

Synthesis of Functionalized Pyridines via a Regioselective Oxazoline Promoted C-H Amidation Reaction

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1. General Considerations

All reactions were conducted in flame-dried glassware under ambient conditions unless otherwise stated.

Infrared (IR) spectra were recorded on a Perkin Elmer Paragon 100 FTIR spectrophotometer, ν_{max} in cm^{-1} . Samples were recorded neat or as thin films using sodium chloride plates as a dichloromethane solution. Bands are characterised as broad (br), strong (s), medium (m), or weak (w).

^1H NMR spectra were recorded on a Bruker AVIII HD 400 (400 MHz), Bruker AVI 400 (400 MHz), Bruker AMX-400 (400 MHz) or DPX-400 (400 MHz) supported by an Aspect 3000 data system. Chemical shifts are reported in parts per million (ppm) from tetramethylsilane with the residual protic solvent resonance as the internal standard (CHCl_3 : δ 7.26, DMSO: δ 2.50) unless otherwise stated. Data are reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), coupling constants (Hz), assignments).

^{13}C NMR spectra were recorded on a Bruker AVIII HD 400 (100.6 MHz), Bruker AVI 400 (100.6 MHz), Bruker AMX-400 (100.6 MHz) or DPX-400 (100.6 MHz) with complete proton decoupling. Chemical shifts are reported in ppm from tetramethylsilane with the solvent as the internal reference (CHCl_3 : δ 77.16, DMSO: δ 39.52) unless otherwise stated.

^{19}F NMR spectra were recorded on a Bruker AVIII HD 400 (235.1 MHz) or Bruker AMX-400 (235.1 MHz).

High-resolution mass spectra (HRMS) recorded for accurate mass analysis, were performed on either a MicroMass LCT operating in Electrospray mode (TOF ES^+) or a MicroMass Prospec operating in FAB (FAB^+), EI (EI^+) or CI (CI^+) mode.

Thin layer chromatography (TLC) was performed on aluminium backed plates pre-coated with silica (0.2 mm, Merck DC-alufolien Kieselgel 60 F254) which were developed using standard visualizing agents: UV light or potassium permanganate. Flash chromatography was performed on silica-gel (BDH Silica Gel 60 43-60). Melting points were recorded on a Gallenkamp melting point apparatus and are uncorrected. All solvents and reagents were purified using standard laboratory techniques according to methods published in "Purification of Laboratory Chemicals" by Perrin, Armarego and Perrin (Pergamon Press, 1966).

2. Substrate Synthesis

General Procedure A: To a dried round bottomed flask was added pyridine ester (1.0 eq.) and heated to 55 °C with stirring. Upon reaching the desired temperature ethanolamine (1.5 eq.) was added slowly via syringe and the reaction was stirred for 3 h before cooling to room temperature, and stirring for a further 18 hours. The crude reaction mixture was then purified by flash column

chromatography on silica gel eluting with dichloromethane and methanol (1% MeOH to 20% MeOH) or ethyl acetate (100%) to afford the amide products.

NB: When the required pyridine ester was not commercially available, esterification was carried out to the ethyl ester from the parent carboxylic acid using one of the following procedures. The products were used directly without characterisation or purification.

Esterification procedure 1: To a stirred solution of carboxylic acid (1.0 eq.) in dry dichloromethane (0.2 M) at 0 °C was added oxalyl chloride (3.0 eq.) and DMF (few drops). The reaction was allowed to warm to room temperature and stirred for a period of 3 hours before removing the solvent *in vacuo*. The crude residue was then dissolved in dry dichloromethane (0.2 M) and cooled to 0 °C using an ice bath. Triethylamine (3.0 eq.) was then added, followed by ethanol (3.0 eq.) via syringe. The reaction was allowed to warm to room temperature and stir overnight. The reaction was then diluted with a saturated solution of NaHCO₃ (aq.) and dichloromethane, and transferred to a separating funnel. The layers were partitioned and the aqueous layer was further extracted with dichloromethane. The combined organic layers were washed with brine, dried over anhydrous MgSO₄, filtered and the solvent was removed *in vacuo* to afford the crude ester product.

Esterification procedure 2: To a stirred solution of carboxylic acid (1.0 eq.) in MeCN (0.6 M) was added CDI (1.1 eq.). The reaction mixture was allowed to stir for a period of 2 hours at room temperature before ethanol (2.5 eq.) was added via syringe. The reaction was then stirred overnight at room temperature, before diluting with dichloromethane and transferring to a separating funnel. The organic phase was then subsequently washed with a saturated solution of NaHCO₃ (aq.) and deionised water. The organic layer was dried over anhydrous MgSO₄, filtered and the solvent was removed *in vacuo* to afford the crude ester product.

General Procedure B: To a dried round bottomed flask was added amide (1.0 eq.) and dry dichloromethane (0.6 M). With stirring NEt₃ (1.9 eq.) was then added, followed by DMAP (0.2 eq.) and *p*-TsCl (1.7 eq.). The reaction mixture was allowed to stir at room temperature overnight, before being diluted with dichloromethane and water. The mixture was then transferred to a separating funnel and the layers partitioned. The aqueous layer was further extracted with dichloromethane. The combined organic layers were dried over anhydrous MgSO₄, filtered and the solvent was removed *in vacuo*. The crude residue was then subjected to cyclisation conditions B (i) or B (ii) to afford the oxazoline products after purification.

NaOH and MeOH Cyclisation B(i): The crude residue was dissolved in MeOH (0.5 M) and NaOH pellets (3.0 eq.) were added in one portion. The reaction mixture was stirred at room temperature

for 2 – 3 h before removing the solvent *in vacuo*. The residue was dissolved in dichloromethane and water, and transferred to a separating funnel. The layers were partitioned and the aqueous layer was further extracted with dichloromethane and ethyl acetate. The combined organic layers were dried over anhydrous MgSO_4 , filtered and the solvent was removed *in vacuo*. The residue was purified by flash column chromatography on silica gel eluting with petroleum ether (40/60) and ethyl acetate (0% ethyl acetate to 100% ethyl acetate) to afford the oxazoline products.

K₂CO₃ and MeCN Cyclisation B(ii): The crude residue was dissolved in MeCN (0.5 M) and K_2CO_3 (3.0 eq.) was added in one portion. The reaction mixture was stirred at 85 °C for 5 h before cooling to room temperature and removing the solvent *in vacuo*. The residue was dissolved in dichloromethane and water, and transferred to a separating funnel. The layers were partitioned and the aqueous layer was further extracted with dichloromethane and ethyl acetate. The combined organic layers were dried over anhydrous MgSO_4 , filtered and the solvent was removed *in vacuo*. The residue was purified by flash column chromatography on silica gel eluting with petroleum ether (40/60) and ethyl acetate (0% ethyl acetate to 100% ethyl acetate) to afford the oxazoline products.

3. C-H Amidation General Procedure

General Procedure C: C-H Amidation of 2-Substituted Pyridines

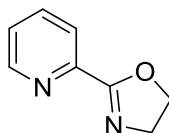
Schlenk tube procedure C (i): To a dried Schlenk tube was added oxazoline (1.2 eq.), $[\text{Cp}^*\text{RhCl}_2]_2$ (2.5 mol %), AgSbF_6 (10 mol %), $\text{PhI}(\text{OAc})_2$ (1.5 eq.) and trifluoroacetamide (1.0 eq.). The tube was fitted with a rubber septum, and placed under an atmosphere of nitrogen, followed by the addition of dry dichloromethane via syringe (0.1 M). The septum was replaced by a Teflon screwcap under nitrogen flow. The reaction mixture was stirred at 40 – 45 °C for 18 – 20 h. After cooling to room temperature the solvent was removed *in vacuo* and the residue was purified by flash column chromatography on silica gel eluting with petroleum ether (40/60) followed by dichloromethane to afford the aminated products.

Reflux apparatus procedure C (ii): To a dried round bottomed flask equipped with a stirrer bar and reflux condenser was added oxazoline (1.2 eq.), $[\text{RhCp}^*\text{Cl}_2]_2$ (2.5 mol %), AgSbF_6 (10 mol %), $\text{PhI}(\text{OAc})_2$ (1.5 eq.) and trifluoroacetamide (1.0 eq.). The system was evacuated and refilled with nitrogen (3 times), followed by the addition of dry dichloromethane via syringe (0.1 M). The reaction mixture was stirred at reflux (40 – 45 °C) for 18 – 20 h. After cooling to room temperature the solvent was removed *in vacuo* and the residue was purified by flash column chromatography on

silica gel eluting with petroleum ether (40/60) followed by dichloromethane to afford the aminated products.

4. Data for substrates 1a to 9 and 12 to 20c

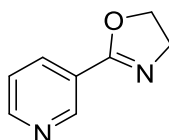
*Synthesis of 2-(pyridine-2-yl)-4,5-dihydrooxazole 1a*¹



Following general procedure B, using of *N*-(2-hydroxyethyl)picolinamide (1.10 g, 6.62 mmol), *p*-TsCl (2.15 g, 11.3 mmol), NEt₃ (1.27 g, 12.6 mmol), DMAP (162 mg, 1.32 mmol) and dichloromethane (11.0 mL), then following general procedure B(i), using NaOH pellets (800 mg, 19.9 mmol) and methanol (13.5 mL), the oxazoline product was afforded as a yellow oil (625 mg, 64%).

¹H NMR (400 MHz, CDCl₃): δ 8.48 (1H, ddd, *J* = 5.0, 1.5, 1.0 Hz, CH_{ar}), 7.82 (1H, dd, *J* = 8.0, 1.0 Hz, CH_{ar}), 7.56 (1H, td, *J* = 8.0, 1.5 Hz, CH_{ar}), 7.17 (1H, ddd, *J* = 8.0, 5.0, 1.0 Hz, CH_{ar}), 4.30 (2H, t, *J* = 9.5 Hz, CH₂), 3.90 (2H, t, *J* = 9.5 Hz, CH₂); ¹³C NMR (100.6 MHz, CDCl₃): δ 163.4, 149.3, 146.3, 136.3, 125.2, 123.4, 67.8, 54.7.

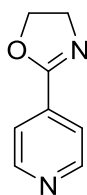
*Synthesis of 2-(pyridin-3-yl)-4,5-dihydrooxazole 1b*¹



Following general procedure B, using of *N*-(2-hydroxyethyl)nicotinamide (687 mg, 4.13 mmol), *p*-TsCl (1.34 g, 7.03 mmol), NEt₃ (794 mg, 7.85 mmol), DMAP (101 mg, 0.826 mmol) and dichloromethane (7.0 mL), then following general procedure B(i), using NaOH pellets (500 mg, 12.4 mmol) and methanol (8.3 mL), the oxazoline product was afforded as a tan solid (338 mg, 55%).

M.p.: 66 – 67 °C (lit. 66 - 68 °C)²; ¹H NMR (400 MHz, CDCl₃): δ 9.02 (1H, dd, *J* = 2.0, 1.0 Hz, CH_{ar}), 8.56 (1H, dd, *J* = 5.0, 2.0 Hz, CH_{ar}), 8.07 (1H, dt, *J* = 8.0, 2.0 Hz, CH_{ar}), 7.21 (1H, ddd, *J* = 8.0, 5.0, 1.0 Hz, CH_{ar}), 4.31 (2H, t, *J* = 9.5 Hz, CH₂), 3.94 (2H, t, *J* = 9.5 Hz, CH₂); ¹³C NMR (100.6 MHz, CDCl₃): δ 162.5, 151.8, 149.3, 135.3, 123.7, 123.0, 67.6, 54.8.

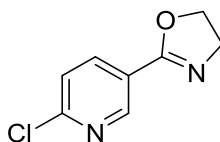
*Synthesis of 2-(pyridine-4-yl)-4,5-dihydrooxazole 1c*¹



Following general procedure B, using of *N*-(2-hydroxyethyl)isonicotinamide (1.0 g, 6.02 mmol), *p*-TsCl (1.95 g, 10.2 mmol), NEt₃ (1.16 g, 11.4 mmol), DMAP (147 mg, 1.20 mmol) and dichloromethane (10 mL), then following general procedure B(i), using NaOH pellets (722 mg, 18.1 mmol) and methanol (12 mL), the oxazoline product was afforded as a pale yellow solid (533 mg, 60%).

M.p.: 109 – 110 °C (lit. 109-111 °C)³; ¹H NMR (400 MHz, CDCl₃): δ 8.69 (2H, dd, *J* = 4.5, 1.5 Hz, CH_{ar}), 7.76 (2H, dd, *J* = 4.5, 1.5 Hz, CH_{ar}), 4.45 (2H, t, *J* = 9.5 Hz, CH₂), 4.08 (2H, t, *J* = 9.5 Hz, CH₂); ¹³C NMR (100.6 MHz, CDCl₃): δ 163.3, 150.4, 135.2, 122.0, 68.1, 55.1.

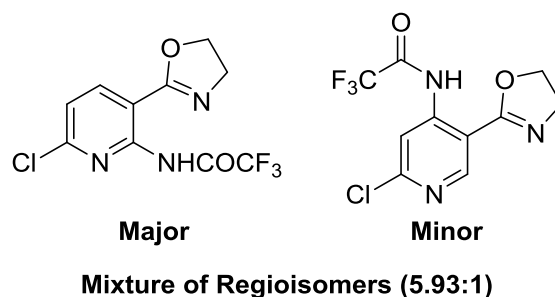
Synthesis of 2-(6-chloropyridin-3-yl)-4,5-dihydrooxazole **1d**



Following general procedure B, using of 6-chloro-*N*-(2-hydroxyethyl)nicotinamide (2.51 g, 12.5 mmol), *p*-TsCl (4.05 g, 21.3 mmol), NEt₃ (2.41 g, 23.8 mmol), DMAP (306 mg, 2.50 mmol) and dichloromethane (21 mL), then following general procedure B(ii), using K₂CO₃ (5.19 g, 37.5 mmol) and MeCN (25 mL), the oxazoline product was afforded as a colourless solid (2.01 g, 88%).

M.p.: 81 – 82 °C; FTIR: ν_{max} / cm⁻¹ (neat) 3039 (w), 2878 (w), 1655 (s), 1581 (m), 1455 (m), 1350 (m), 1120 (s), 1069 (s), 737 (s); ¹H NMR (400 MHz, CDCl₃): δ 8.90 (1H, app. d, *J* = 2.0 Hz, CH_{ar}), 8.16 (1H, dd, *J* = 8.0, 2.0 Hz, CH_{ar}), 7.37 (1H, dd, *J* = 8.0, 1.0 Hz, CH_{ar}), 4.46 (2H, t, *J* = 9.5 Hz, CH₂), 4.07 (2H, t, *J* = 9.5 Hz, CH₂); ¹³C NMR (100.6 MHz, CDCl₃): δ 162.0, 154.1, 149.6, 138.3, 124.2, 123.0, 68.1, 55.1; HRMS: *m/z* [M]⁺ C₈H₇³⁵ClN₂O calcd. 182.0241, found 182.0239.

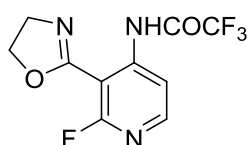
Synthesis of *N*-(6-chloro-3-(4,5-dihydrooxazol-2-yl)pyridine-2-yl)-2,2,2-trifluoroacetamide and *N*-(2-chloro-5-(4,5-dihydrooxazol-2-yl)pyridine-4-yl)-2,2,2-trifluoroacetamide **2**



Following general procedure C(ii), using trifluoroacetamide (516 mg, 4.56 mmol) and 2-(2-chloropyridin-3-yl)-4,5-dihydrooxazole (1.00 g, 5.48 mmol) with $[\text{Cp}^*\text{RhCl}_2]_2$ (70 mg, 0.11 mmol), AgSbF_6 (157 mg, 0.456 mmol) and $\text{PhI}(\text{OAc})_2$ (2.20 g, 6.84 mmol) in dichloromethane (46 mL), regioisomeric mixture **2** was isolated as a colourless solid (1.07 g, 80%).

FTIR: $\nu_{\text{max}}/\text{cm}^{-1}$ 1753 (m), 1598 (m), 1570 (m), 1400 (m), 1264 (m), 1135 (s), 1056 (m), 920 (m), 828 (m); ^1H NMR (400 MHz, CDCl_3) major isomer: δ 13.43 (1H, s, NH), 8.10 (1H, d, $J = 8.0$ Hz, CH_{ar}), 7.20 (1H, d, $J = 8.0$ Hz, CH_{ar}), 4.49 (2H, t, $J = 9.5$ Hz, CH_2), 4.19 (2H, t, $J = 9.5$ Hz, CH_2); ^1H NMR (400 MHz, CDCl_3) minor isomer: δ 13.79 (1H, s, NH), 8.81 (1H, s, CH_{ar}), 8.60 (1H, s, CH_{ar}), 4.50 (2H, t, $J = 9.5$ Hz, CH_2), 4.16 (2H, t, $J = 9.5$ Hz, CH_2); ^{19}F NMR (376.5 MHz, CDCl_3) major isomer: δ -76.3; ^{19}F NMR (376.5 MHz, CDCl_3) minor isomer: δ -76.2; ^{13}C NMR (100.6 MHz, CDCl_3) major isomer: δ 162.7, 154.1 (q, $J = 38.5$ Hz), 152.8, 149.7, 140.0, 120.3, 115.5 (q, $J = 282.0$ Hz), 108.9, 67.7, 54.5; HRMS: m/z $[\text{MH}]^+$ $\text{C}_{10}\text{H}_8^{35}\text{ClF}_3\text{N}_3\text{O}_2$ calcd. 294.0252, found 294.0252.

Synthesis of *N*-(3-(4,5-dihydrooxazol-2-yl)-2-fluoropyridin-4-yl)-2,2,2-trifluoroacetamide **3**

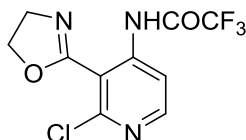


Following general procedure C(i), using trifluoroacetamide (23 mg, 0.20 mmol) and 2-(2-fluoropyridin-3-yl)-4,5-dihydrooxazole (40 mg, 0.24 mmol) with $[\text{Cp}^*\text{RhCl}_2]_2$ (3 mg, 0.005 mmol), AgSbF_6 (7 mg, 0.02 mmol) and $\text{PhI}(\text{OAc})_2$ (97 mg, 0.30 mmol) in dichloromethane (2 mL), product **3** was isolated as a colourless solid (33 mg, 59%).

M.p.: 102 – 103 °C; FTIR: $\nu_{\text{max}}/\text{cm}^{-1}$ (neat) 3242 (m), 3097 (m), 2968 (w), 1633 (s), 1567 (s), 1207 (s), 1157 (s), 1056 (s), 876 (s), 844 (s); ^1H NMR (400 MHz, CDCl_3): δ 14.35 (1H, s, NH), 8.50 (1H, d, $J = 6.0$ Hz, CH_{ar}), 8.27 (1H, d, $J = 6.0$ Hz, CH_{ar}), 4.54 (2H, t, $J = 10.0$ Hz, CH_2), 4.13 (2H, t, $J = 10.0$ Hz, CH_2); ^{19}F NMR (376.5 MHz, CDCl_3): δ -57.8, -76.1; ^{13}C NMR (100.6 MHz, CDCl_3): δ 162.9 (d, $J = 7.0$ Hz), 160.5, 156.3 (q, $J = 39.0$ Hz), 150.9 (d, $J = 18.0$ Hz), 148.4 (d, $J = 5.0$ Hz), 115.6 (q, $J = 288.5$ Hz), 112.6 (d, $J =$

4.5 Hz), 97.6 (d, $J = 29.0$ Hz), 67.8, 53.1; HRMS: m/z $[MH]^+$ $C_{10}H_8F_4N_3O_2$ calcd. 278.0547, found 278.0551.

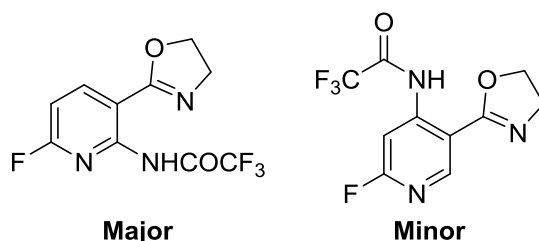
Synthesis of N-(2-chloro-3-(4,5-dihydrooxazol-2-yl)pyridine-4-yl)-2,2,2-trifluoroacetamide 4



Following general procedure C(i), using trifluoroacetamide (23 mg, 0.20 mmol) and 2-(2-chloropyridin-3-yl)-4,5-dihydrooxazole (44 mg, 0.24 mmol) with $[Cp^*RhCl_2]_2$ (3 mg, 0.005 mmol), $AgSbF_6$ (7 mg, 0.02 mmol) and $PhI(OAc)_2$ (97 mg, 0.30 mmol) in dichloromethane (2 mL), product **4** was isolated as a colourless solid (38 mg, 64%).

M.p.: 92 – 93 °C; FTIR: ν_{max}/cm^{-1} (neat) 3151 (w), 2981 (w), 2896 (w), 1731 (s), 1573 (s), 1355 (s), 1296 (m), 1191 (m), 1144 (s), 936 (m), 885 (m), 844 (m); 1H NMR (400 MHz, $CDCl_3$): δ 13.64 (1H, s, NH), 8.49 (1H, d, $J = 5.5$ Hz, CH_{ar}), 8.40 (1H, d, $J = 5.5$ Hz, CH_{ar}), 4.55 (2H, t, $J = 9.5$ Hz, CH_2), 4.15 (2H, t, $J = 9.5$ Hz, CH_2); ^{19}F NMR (376.5 MHz, $CDCl_3$): δ – 76.2; ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 163.2, 156.0 (q, $J = 38.5$ Hz), 151.6, 151.4, 146.5, 115.5 (q, $J = 288.5$ Hz), 113.2, 110.5, 67.9, 53.4; HRMS: m/z $[MH]^+$ $C_{10}H_8^{35}ClF_3N_3O_2$ calcd. 294.0252, found 294.0250.

Synthesis of N-(3-(4,5-dihydrooxazol-2-yl)-6-fluoropyridin-2-yl)-2,2,2-trifluoroacetamide and N-(5-(4,5-dihydrooxazol-2-yl)-2-fluoropyridin-4-yl)-2,2,2-trifluoroacetamide 5



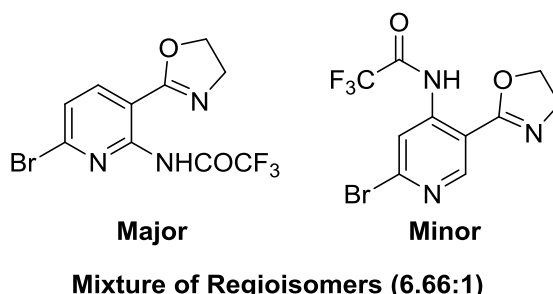
Mixture of Regioisomers (5.32:1)

Following general procedure C(i), using trifluoroacetamide (23 mg, 0.20 mmol) and 2-(6-fluoropyridin-3-yl)-4,5-dihydrooxazole (40 mg, 0.24 mmol) with $[Cp^*RhCl_2]_2$ (3 mg, 0.005 mmol), $AgSbF_6$ (7 mg, 0.02 mmol) and $PhI(OAc)_2$ (97 mg, 0.30 mmol) in dichloromethane (2 mL), regioisomeric mixture **5** was isolated as a colourless solid (39 mg, 71%).

FTIR: ν_{max}/cm^{-1} (neat) 3246 (m), 3132 (m), 3097 (m), 2968 (w), 1633 (s), 1570 (s), 1551 (s), 1333 (s), 1204 (s), 1154 (s), 1056 (s), 1008 (s), 876 (s), 835 (s); 1H NMR (400 MHz, $CDCl_3$) major isomer: δ 13.55 (1H, s, NH), 8.27 (1H, t, $J = 8.0$ Hz, CH_{ar}), 6.80 (1H, dd, $J = 8.0$ Hz, 3.0 Hz, CH_{ar}), 4.49 (2H, t, $J = 9.5$ Hz,

CH_2), 4.19 (2H, t, $J = 9.5$ Hz, CH_2); ^1H NMR (400 MHz, CDCl_3) minor isomer: δ 13.89 (1H, s, NH), 8.71 (1H, s, CH_{ar}), 8.19 (1H, s, CH_{ar}), 4.49 (2H, t, $J = 9.5$ Hz, CH_2), 4.19 (2H, t, $J = 9.5$ Hz, CH_2); ^{19}F NMR (376.5 MHz, CDCl_3) major isomer: δ – 59.3, – 76.3; ^{19}F NMR (376.5 MHz, CDCl_3) minor isomer: δ – 59.5, – 76.2; ^{13}C NMR (100.6 MHz, CDCl_3) major and minor isomers: δ 167.3, 164.8, 164.4, 163.0, 162.6, 162.0, 154.0, 149.6, 149.5, 149.3, 142.9 (d, $J = 9.0$ Hz), 140.0, 120.3, 119.8, 117.0, 116.8, 114.1, 114.0, 111.2, 107.8 (d, $J = 5.0$ Hz), 105.2 (d, $J = 37.0$ Hz), 99.9 (d, $J = 44.0$ Hz), 67.7, 67.4, 54.4, 54.1 – complex ^{13}C due to mixture of regioisomers and ^{19}F coupling; HRMS: m/z $[\text{MH}]^+$ $\text{C}_{10}\text{H}_8\text{F}_4\text{N}_3\text{O}_2$ calcd. 278.0547, found 278.0549.

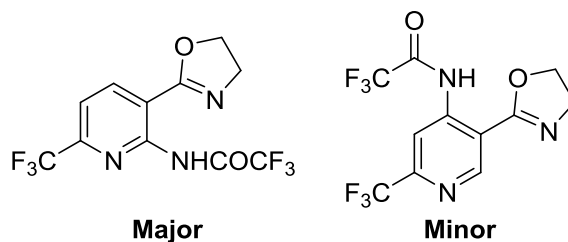
Synthesis of N-(6-bromo-3-(4,5-dihydrooxazol-2-yl)pyridine-2-yl)-2,2,2-trifluoroacetamide and N-(2-bromo-5-(4,5-dihydrooxazol-2-yl)pyridine-4-yl)-2,2,2-trifluoroacetamide 6



Following general procedure C(i), using trifluoroacetamide (23 mg, 0.20 mmol) and 2-(6-bromopyridin-3-yl)-4,5-dihydrooxazole (55 mg, 0.24 mmol) with $[\text{Cp}^*\text{RhCl}_2]_2$ (3 mg, 0.005 mmol), AgSbF_6 (7 mg, 0.02 mmol) and $\text{PhI}(\text{OAc})_2$ (97 mg, 0.30 mmol) in dichloromethane (2 mL), regioisomeric mixture **6** was isolated as a colourless solid (55 mg, 80%).

FTIR: $\nu_{\text{max}}/\text{cm}^{-1}$ (neat) 3101 (w), 2991 (w), 2887 (w), 1750 (m), 1639 (m), 1607 (m), 1568 (m), 1268 (m), 1193 (m), 1125 (s), 1054 (m), 911 (m), 833 (m); ^1H NMR (400 MHz, CDCl_3) major isomer: δ 13.39 (1H, s, NH), 7.97 (1H, d, $J = 8.0$ Hz, CH_{ar}), 7.36 (1H, d, $J = 8.0$ Hz, CH_{ar}), 4.49 (2H, t, $J = 9.5$ Hz, CH_2), 4.17 (2H, t, $J = 9.5$ Hz, CH_2); ^1H NMR (400 MHz, CDCl_3) minor isomer: δ 13.76 (1H, s, NH), 8.76 (1H, s, CH_{ar}), 8.75 (1H, s, CH_{ar}), 4.50 (2H, t, $J = 9.5$ Hz, CH_2), 4.16 (2H, t, $J = 9.5$ Hz, CH_2); ^{19}F NMR (376.5 MHz, CDCl_3) major isomer: δ – 76.4; ^{19}F NMR (376.5 MHz, CDCl_3) minor isomer: δ – 76.2; ^{13}C NMR (100.6 MHz, CDCl_3) major isomer: δ 162.8, 154.1 (q, $J = 38.5$ Hz), 149.6, 143.4, 139.5, 124.2, 115.5 (q, $J = 289.5$ Hz), 109.2, 67.7, 54.5; HRMS: m/z $[\text{MH}]^+$ $\text{C}_{10}\text{H}_8^{79}\text{BrF}_3\text{N}_3\text{O}_2$ calcd. 337.9747, found 337.9747.

Synthesis of N-(3-(4,5-dihydrooxazol-2-yl)-6-(trifluoromethyl)pyridine-2-yl)-2,2,2-trifluoroacetamide and N-(5-(4,5-dihydrooxazol-2-yl)-2-(trifluoromethyl)pyridine-4-yl)-2,2,2-trifluoroacetamide 7

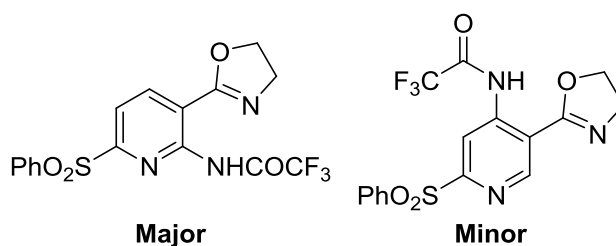


Mixture of Regioisomers (8.34:1)

Following general procedure C(i), using trifluoroacetamide (23 mg, 0.20 mmol) and 2-(6-(trifluoromethyl)pyridine-3-yl)-4,5-dihydrooxazole (52 mg, 0.24 mmol) with $[\text{Cp}^*\text{RhCl}_2]_2$ (3 mg, 0.005 mmol), AgSbF_6 (7 mg, 0.02 mmol) and $\text{PhI}(\text{OAc})_2$ (97 mg, 0.30 mmol) in dichloromethane (2 mL), regioisomeric mixture **7** was isolated as a colourless solid (51 mg, 78%).

FTIR: $\nu_{\text{max}}/\text{cm}^{-1}$ (neat) 3242 (m), 3126 (m), 3097 (m), 2968 (w), 2927 (w), 1633 (s), 1567 (s), 1551 (s), 1337 (s), 1311 (s), 1204 (s), 1150 (s), 1053 (s), 1034 (s), 1008 (s), 876 (s), 838 (s); ^1H NMR (400 MHz, CDCl_3) major isomer: δ 13.42 (1H, s, NH), 8.36 (1H, d, $J = 8.0$ Hz, CH_{ar}), 7.55 (1H, d, $J = 8.0$ Hz, CH_{ar}), 4.53 (2H, t, $J = 9.5$ Hz, CH_2), 4.24 (2H, t, $J = 9.5$ Hz, CH_2); ^1H NMR (400 MHz, CDCl_3) minor isomer: δ 13.88 (1H, s, NH), 9.14 (1H, s, CH_{ar}), 8.96 (1H, s, CH_{ar}), 4.53 (2H, t, $J = 9.5$ Hz, CH_2), 4.24 (2H, t, $J = 9.5$ Hz, CH_2); ^{19}F NMR (376.5 MHz, CDCl_3) major isomer: δ - 68.5, - 76.4; ^{19}F NMR (376.5 MHz, CDCl_3) minor isomer: δ - 68.5, - 76.2; ^{13}C NMR (100.6 MHz, CDCl_3) major and minor isomers: δ 162.5, 154.3, 153.9, 150.9, 150.1, 149.2, 148.8, 145.5, 139.6, 131.1, 130.2, 128.9, 124.9, 122.1, 119.9, 119.4, 117.0, 116.3, 116.2, 114.1, 112.9, 110.9, 67.9, 67.6, 54.7, 54.3 – complex ^{13}C due to mixture of regioisomers and ^{19}F coupling; HRMS: m/z $[\text{MH}]^+$ $\text{C}_{11}\text{H}_8\text{F}_6\text{N}_3\text{O}_2$ calcd. 328.0515, found 328.0516.

*Synthesis of N-(3-(4,5-dihydrooxazol-2-yl)-6-(phenylsulfonyl)pyridine-2-yl)-2,2,2-trifluoroacetamide and N-(5-(4,5-dihydrooxazol-2-yl)-2-(phenylsulfonyl)pyridine-4-yl)-2,2,2-trifluoroacetamide **8***

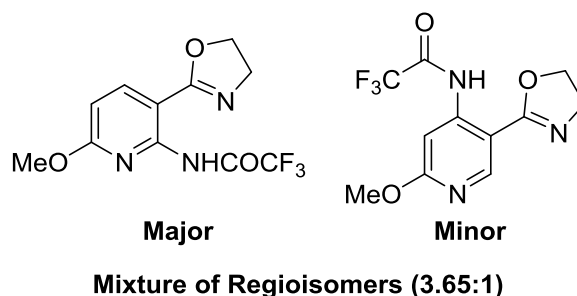


Mixture of Regioisomers (5.98:1)

Following general procedure C(i), using trifluoroacetamide (23 mg, 0.20 mmol) and 2-(6-(phenylsulfonyl)pyridine-3-yl)-4,5-dihydrooxazole (69 mg, 0.24 mmol) with $[\text{Cp}^*\text{RhCl}_2]_2$ (3 mg, 0.005 mmol), AgSbF_6 (7 mg, 0.02 mmol) and $\text{PhI}(\text{OAc})_2$ (97 mg, 0.30 mmol) in dichloromethane (2 mL), regioisomeric mixture **8** was isolated as a colourless solid (57 mg, 72%).

FTIR: $\nu_{\max}/\text{cm}^{-1}$ (neat) 3073 (w), 2987 (w), 2919 (w), 1750 (m), 1643 (m), 1568 (m), 1411 (m), 1318 (m), 1257 (m), 1190 (m), 1133 (s), 1051 (s); ^1H NMR (400 MHz, CDCl_3) major isomer: δ 13.37 (1H, s, NH), 8.36 (1H, d, $J = 8.0$ Hz, CH_{ar}), 8.29 – 8.24 (2H, m, CH_{ar}), 8.01 (1H, d, $J = 8.0$ Hz, CH_{ar}), 7.66 – 7.49 (3H, m, CH_{ar}), 4.50 (2H, t, $J = 9.5$ Hz, CH_2), 4.20 (2H, t, $J = 9.5$ Hz, CH_2); ^1H NMR (400 MHz, CDCl_3) minor isomer: δ 13.87 (1H, s, NH), 9.35 (1H, s, CH_{ar}), 9.05 (1H, s, CH_{ar}), 8.10 – 8.06 (2H, m, CH_{ar}), 7.66 – 7.49 (3H, m, CH_{ar}), 4.50 (2H, t, $J = 9.5$ Hz, CH_2), 4.20 (2H, t, $J = 9.5$ Hz, CH_2); ^{19}F NMR (376.5 MHz, CDCl_3) major isomer: δ – 76.4; ^{19}F NMR (376.5 MHz, CDCl_3) minor isomer: δ – 76.2; ^{13}C NMR (100.6 MHz, CDCl_3) major and minor isomers: δ 162.3, 159.2, 153.8 (q, $J = 38.5$ Hz), 151.2, 150.0, 145.9, 140.0, 139.8, 138.4, 137.8, 134.3, 134.2, 133.7, 130.1, 129.4, 129.3, 129.1, 129.0, 116.9, 114.0, 113.0, 112.4, 111.8, 110.2, 67.9, 67.7, 54.7, 54.3 –complex ^{13}C due to mixture of regioisomers; HRMS: m/z $[\text{MH}]^+$ $\text{C}_{16}\text{H}_{13}\text{F}_3\text{N}_3\text{O}_4\text{S}$ calcd. 400.0573, found 400.0574.

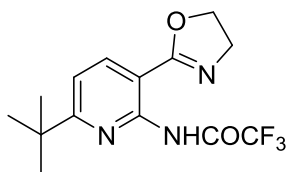
Synthesis of N-(3-(4,5-dihydrooxazol-2-yl)-6-methoxypyridin-2-yl)-2,2,2-trifluoroacetamide and N-(5-(4,5-dihydrooxazol-2-yl)-2-methoxypyridin-4-yl)-2,2,2-trifluoroacetamide 9



Following general procedure C(i), using trifluoroacetamide (23 mg, 0.20 mmol) and 2-(6-methoxypyridin-3-yl)-4,5-dihydrooxazole (43 mg, 0.24 mmol) with $[\text{Cp}^*\text{RhCl}_2]_2$ (3 mg, 0.005 mmol), AgSbF_6 (7 mg, 0.02 mmol) and $\text{PhI}(\text{OAc})_2$ (97 mg, 0.30 mmol) in dichloromethane (2 mL), regioisomeric mixture **9** was isolated as a colourless solid (18 mg, 31%).

FTIR: $\nu_{\max}/\text{cm}^{-1}$ (neat) 2987 (w), 2952 (w), 1737 (m), 1627 (m), 1479 (m), 1371 (m), 1318 (m), 1138 (s), 1131 (s), 1034 (s), 933 (m), 826 (s); ^1H NMR (400 MHz, CDCl_3) major isomer: δ 13.45 (1H, s, NH), 8.00 (1H, d, $J = 8.5$ Hz, CH_{ar}), 6.56 (1H, d, $J = 8.5$ Hz, CH_{ar}), 4.42 (2H, t, $J = 9.0$ Hz, CH_2), 4.13 (2H, t, $J = 9.0$ Hz, CH_2), 4.05 (3H, s, CH_3); ^1H NMR (400 MHz, CDCl_3) minor isomer: δ 13.70 (1H, s, NH), 8.64 (1H, s, CH_{ar}), 7.95 (1H, s, CH_{ar}), 4.45 (2H, t, $J = 9.0$ Hz, CH_2), 4.14 – 4.08 (2H, m, CH_2), 3.99 (3H, s, CH_3); ^{19}F NMR (376.5 MHz, CDCl_3) major isomer: δ – 76.3; ^{19}F NMR (376.5 MHz, CDCl_3) minor isomer: δ – 76.2; ^{13}C NMR (100.6 MHz, CDCl_3) major isomer: δ 164.8, 163.5, 154.3 (q, $J = 37.5$ Hz), 149.4, 139.9, 115.7 (q, $J = 289.5$ Hz), 106.6, 102.7, 67.3, 54.5, 54.3; HRMS: m/z $[\text{MH}]^+$ $\text{C}_{11}\text{H}_{11}\text{F}_3\text{N}_3\text{O}_3$ calcd. 290.0747, found 290.0747.

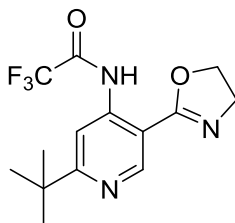
Synthesis of *N*-(6-(*tert*-butyl)-3-(4,5-dihydrooxazol-2-yl)pyridine-2-yl)-2,2,2-trifluoroacetamide and *N*-(2-(*tert*-butyl)-5-(4,5-dihydrooxazol-2-yl)pyridine-4-yl)-2,2,2-trifluoroacetamide **12**



Following general procedure C(ii), using trifluoroacetamide (154 mg, 1.36 mmol) and 2-(6-*tert*-butylpyridin-3-yl)-4,5-dihydrooxazole (333 mg, 1.63 mmol) with [Cp*RhCl₂]₂ (21 mg, 0.034 mmol), AgSbF₆ (47 mg, 0.14 mmol) and PhI(OAc)₂ (657 mg, 2.04 mmol) in 1,2-dichloroethane (13.6 mL), product **12** was isolated as a colourless solid (28 mg, 7%). NB: Reaction performed at 80 °C.

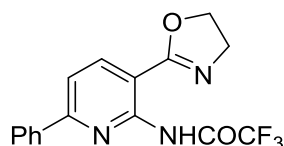
M.p.: 103 – 104 °C; FTIR: ν_{max} / cm⁻¹ (neat) 2941 (m), 2855 (m), 1643 (s), 1543 (s), 1322 (s), 1079 (s), 857 (m), 762 (s); ¹H NMR (400 MHz, CDCl₃): δ 13.17 (1H, s, NH), 8.07 (1H, d, *J* = 8.0 Hz, CH_{ar}), 7.19 (1H, d, *J* = 8.0 Hz, CH_{ar}), 4.45 (2H, t, *J* = 9.5 Hz, CH₂), 4.16 (2H, t, *J* = 9.5 Hz, CH₂), 1.39 (9H, s, C(CH₃)₃); ¹⁹F NMR (376.5 MHz, CDCl₃): δ - 76.3; ¹³C NMR (100.6 MHz, CDCl₃): δ 172.4, 163.4, 154.1 (q, *J* = 37.5 Hz), 149.0, 138.0, 115.8 (q, *J* = 290.0 Hz), 115.1, 107.4, 67.3, 54.5, 38.4, 29.9; HRMS: *m/z* [MH]⁺ C₁₄H₁₇F₃N₃O₂ calcd. 316.1267, found 316.1269.

The alternative regioisomer was isolated as a colourless solid (23 mg, 5%).



M.p.: 111 – 112 °C; FTIR: ν_{max} / cm⁻¹ (neat) 2966 (w), 2912 (w), 2862 (w), 1643 (s), 1603 (m), 1543 (s), 1275 (s), 1147 (s), 1076 (s), 890 (m); ¹H NMR (400 MHz, CDCl₃): δ 13.65 (1H, s, NH), 9.00 (1H, s, CH_{ar}), 8.63 (1H, s, CH_{ar}), 4.47 (2H, t, *J* = 9.5 Hz, CH₂), 4.15 (2H, t, *J* = 9.5 Hz, CH₂), 1.39 (9H, s, C(CH₃)₃); ¹⁹F NMR (376.5 MHz, CDCl₃): δ - 76.2; ¹³C NMR (100.6 MHz, CDCl₃): δ 174.8, 163.8, 156.4 (q, *J* = 38.0 Hz), 149.6, 144.3, 115.6 (q, *J* = 288.5 Hz), 109.4, 107.5, 67.2, 54.2, 38.4, 30.0; HRMS: *m/z* [MH]⁺ C₁₄H₁₇F₃N₃O₂ calcd. 316.1267, found 316.1267.

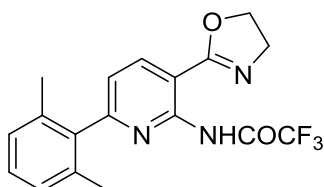
Synthesis of *N*-(3-(4,5-dihydrooxazol-2-yl)-6-phenylpyridin-2-yl)-2,2,2-trifluoroacetamide **13**



Following general procedure C(i), using trifluoroacetamide (23 mg, 0.20 mmol) and 2-(6-phenylpyridin-3-yl)-4,5-dihydrooxazole (54 mg, 0.24 mmol) with $[\text{Cp}^*\text{RhCl}_2]_2$ (3 mg, 0.005 mmol), AgSbF_6 (7 mg, 0.02 mmol) and $\text{PhI}(\text{OAc})_2$ (97 mg, 0.30 mmol) in dichloromethane (2 mL), product **13** was isolated as a colourless amorphous solid (11 mg, 15%).

FTIR: $\nu_{\text{max}}/\text{cm}^{-1}$ (neat) 2976 (w), 2959 (w), 2916 (w), 1643 (m), 1607 (m), 1546 (s), 1318 (m), 1272 (s), 1143 (m), 1079 (m); ^1H NMR (400 MHz, CDCl_3): δ 13.38 (1H, s, NH), 8.26 – 8.10 (3H, m, CH_{ar}), 7.66 (1H, d, $J = 8.0$ Hz, CH_{ar}), 7.53 – 7.42 (3H, m, CH_{ar}), 4.48 (2H, t, $J = 9.5$ Hz, CH_2), 4.20 (2H, t, $J = 9.5$ Hz, CH_2); ^{19}F NMR (376.5 MHz, CDCl_3): δ – 76.3; ^{13}C NMR (100.6 MHz, CDCl_3): δ 163.3, 158.5, 154.4 (q, $J = 37.5$ Hz), 149.9, 138.7, 137.5, 130.5, 129.1, 127.6, 115.8 (q, $J = 289.5$ Hz), 115.5, 108.6, 67.5, 54.6; HRMS: m/z $[\text{MH}]^+$ $\text{C}_{16}\text{H}_{13}\text{F}_3\text{N}_3\text{O}_2$ calcd. 336.0954, found 336.0953.

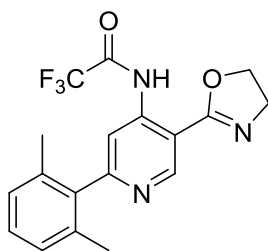
*Synthesis of N-(3-(4,5-dihydrooxazol-2-yl)-6-(2,6-dimethylphenyl)pyridine-2-yl)-2,2,2-trifluoroacetamide and N-(5-(4,5-dihydrooxazol-2-yl)-2-(2,6-dimethylphenyl)pyridine-4-yl)-2,2,2-trifluoroacetamide **14***



Following general procedure C(ii), using trifluoroacetamide (36 mg, 0.32 mmol) and 2-(6-(2,6-dimethylphenyl)pyridine-3-yl)-4,5-dihydrooxazole (98 mg, 0.39 mmol) with $[\text{Cp}^*\text{RhCl}_2]_2$ (5 mg, 0.008 mmol), AgSbF_6 (11 mg, 0.032 mmol) and $\text{PhI}(\text{OAc})_2$ (155 mg, 0.48 mmol) in dichloromethane (3 mL), product **14** was isolated as a colourless solid (15 mg, 13%).

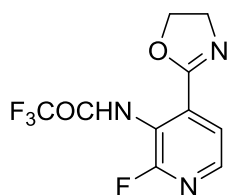
M.p.: 121 – 122 °C; FTIR: $\nu_{\text{max}}/\text{cm}^{-1}$ (neat) 1731 (m), 1646 (m), 1614 (m), 1557 (m), 1361 (m), 1150 (s), 1140 (s), 1054 (m), 783 (m); ^1H NMR (400 MHz, CDCl_3): δ 13.23 (1H, s, NH), 8.24 (1H, d, $J = 8.0$ Hz, CH_{ar}), 7.21 – 7.15 (2H, m, CH_{ar}), 7.10 (2H, d, $J = 8.0$ Hz, CH_{ar}), 4.50 (2H, t, $J = 9.5$ Hz, CH_2), 4.21 (2H, t, $J = 9.5$ Hz, CH_2), 2.18 (6H, s, CH_3); ^{19}F NMR (376.5 MHz, CDCl_3): δ – 76.3; ^{13}C NMR (100.6 MHz, CDCl_3): δ 163.3, 161.7, 154.4 (q, $J = 38.0$ Hz), 149.6, 139.0, 137.8, 136.2, 128.5, 128.1, 121.4, 115.8 (q, $J = 290.0$ Hz), 108.9, 67.5, 54.7, 20.7; HRMS: m/z $[\text{MH}]^+$ $\text{C}_{18}\text{H}_{17}\text{F}_3\text{N}_3\text{O}_2$ calcd. 364.1267, found 364.1273.

The alternative regioisomer was also isolated as a colourless solid (3 mg, 2%).



M.p.: 155 – 156 °C; FTIR: ν_{max} / cm^{-1} (neat) 3008 (w), 2969 (w), 2923 (w), 1735 (m), 1635 (m), 1603 (m), 1571 (s), 1368 (m), 1222 (m), 1143 (s), 1076 (s); ^1H NMR (400 MHz, CDCl_3): δ 13.76 (1H, s, NH), 9.16 (1H, s, CH_{ar}), 8.50 (1H, s, CH_{ar}), 7.21 (1H, dd, J = 8.0, 7.0 Hz, CH_{ar}), 7.12 (1H, app. s, CH_{ar}), 7.10 (1H, app. s, CH_{ar}), 4.52 (2H, t, J = 9.5 Hz, CH_2), 4.20 (2H, t, J = 9.5 Hz, CH_2), 2.07 (6H, s, CH_3); ^{19}F NMR (376.5 MHz, CDCl_3): δ – 76.1; ^{13}C NMR (100.6 MHz, CDCl_3): δ 164.7, 163.8, 156.4 (q, J = 38.5 Hz), 150.6, 144.2, 139.7, 135.6, 128.5, 127.8, 115.6 (q, J = 290.0 Hz), 114.6, 108.4, 67.3, 54.3, 20.3; HRMS: m/z $[\text{MH}]^+$ $\text{C}_{18}\text{H}_{17}\text{F}_3\text{N}_3\text{O}_2$ calcd. 364.1267, found 364.1274.

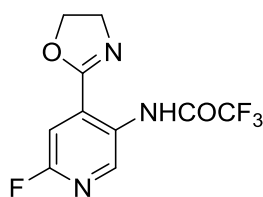
Synthesis of N-(4-(4,5-dihydrooxazol-2-yl)-2-fluoropyridin-3-yl)-2,2,2-trifluoroacetamide and Synthesis of N-(4-(4,5-dihydrooxazol-2-yl)-6-fluoropyridin-3-yl)-2,2,2-trifluoroacetamide **15**



Following general procedure C(i), using trifluoroacetamide (23 mg, 0.20 mmol) and 2-(2-fluoropyridin-4-yl)-4,5-dihydrooxazole (40 mg, 0.24 mmol) with $[\text{Cp}^*\text{RhCl}_2]_2$ (3 mg, 0.005 mmol), AgSbF_6 (7 mg, 0.02 mmol) and $\text{PhI}(\text{OAc})_2$ (97 mg, 0.30 mmol) in dichloromethane (2 mL), product **15** was isolated as a colourless solid (30 mg, 53%).

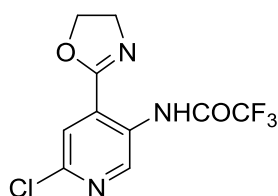
M.p.: 94 – 95 °C; FTIR: ν_{max} / cm^{-1} (neat) 3242 (m), 3094 (m), 2971 (w), 1633 (s), 1570 (s), 1554 (s), 1340 (s), 1207 (s), 1154 (s), 1053 (s), 869 (s), 838 (s); ^1H NMR (400 MHz, CDCl_3): δ 11.53 (1H, s, NH), 8.20 (1H, dd, J = 5.0, 1.0 Hz, CH_{ar}), 7.62 (1H, app. d, J = 5.0 Hz, CH_{ar}), 4.50 (2H, t, J = 10.0 Hz, CH_2), 4.20 (2H, t, J = 10.0 Hz, CH_2); ^{19}F NMR (376.5 MHz, CDCl_3): δ – 64.2, – 75.6; ^{13}C NMR (100.6 MHz, CDCl_3): δ 162.2 (d, J = 4.5 Hz), 156.7 (d, J = 244.5 Hz), 154.8 (q, J = 38.5 Hz), 144.6 (d, J = 14.5 Hz), 129.0 (d, J = 4.5 Hz), 120.3 (d, J = 4.5 Hz), 118.7 (d, J = 30.5 Hz), 115.8 (q, J = 288.5 Hz), 67.7 (s), 55.0 (s); HRMS: m/z $[\text{MH}]^+$ $\text{C}_{10}\text{H}_8\text{F}_4\text{N}_3\text{O}_2$ calcd. 278.0547, found 278.0549.

The alternative regioisomer was also isolated as a colourless solid (3 mg, 4%).



M.p.: 71 – 72 °C; FTIR: ν_{max} / cm^{-1} (neat) 3038 (m), 2987 (m), 1725 (s), 1611 (m), 1542 (s), 1321 (m), 1289 (m), 1150 (s), 970 (m); ^1H NMR (400 MHz, CDCl_3): δ 13.10 (1H, s, NH), 9.59 (1H, s, CH_{ar}), 7.40 (1H, d, J = 3.0 Hz, CH_{ar}), 4.52 (2H, t, J = 10.0 Hz, CH_2), 4.25 (2H, t, J = 10.0 Hz, CH_2); ^{19}F NMR (376.5 MHz, CDCl_3): δ – 70.4, – 75.8; ^{13}C NMR (100.6 MHz, CDCl_3): δ 162.5 (d, J = 3.5 Hz), 160.0 (d, J = 237.5 Hz), 155.4 (q, J = 38.0 Hz), 140.4 (d, J = 15.5 Hz), 131.3 (d, J = 5.0 Hz), 125.9 (d, J = 8.0 Hz), 115.8 (q, J = 288.5 Hz), 108.7 (d, J = 42.0 Hz), 67.6, 54.9; HRMS: m/z $[\text{MH}]^+$ $\text{C}_{10}\text{H}_8\text{F}_4\text{N}_3\text{O}_2$ calcd. 278.0547, found 278.0546.

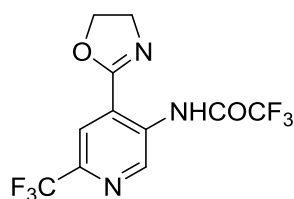
Synthesis of N-(6-chloro-4-(4,5-dihydrooxazol-2-yl)pyridine-3-yl)-2,2,2-trifluoroacetamide 16



Following general procedure C(i), using trifluoroacetamide (23 mg, 0.20 mmol) and 2-(2-chloropyridin-4-yl)-4,5-dihydrooxazole (44 mg, 0.24 mmol) with $[\text{Cp}^*\text{RhCl}_2]_2$ (3 mg, 0.005 mmol), AgSbF_6 (7 mg, 0.02 mmol) and $\text{PhI}(\text{OAc})_2$ (97 mg, 0.30 mmol) in dichloromethane (2 mL), product **16** was isolated as a colourless solid (34 mg, 58%).

M.p.: 98 – 99 °C; FTIR: ν_{max} / cm^{-1} (neat) 3097 (w), 2921 (w), 2882 (w), 1726 (s), 1589 (m), 1565 (m), 1522 (m), 1307 (s), 1143 (s), 1123 (s), 944 (s), 741 (s); ^1H NMR (400 MHz, CDCl_3): δ 13.18 (1H, s, NH), 9.73 (1H, s, CH_{ar}), 7.75 (1H, s, CH_{ar}), 4.51 (2H, t, J = 9.5 Hz, CH_2), 4.24 (2H, t, J = 9.5 Hz, CH_2); ^{19}F NMR (376.5 MHz, CDCl_3): δ – 75.8; ^{13}C NMR (100.6 MHz, CDCl_3): δ 162.6, 155.5 (q, J = 38.5 Hz), 147.1, 142.4, 132.2, 123.4, 122.9, 115.7 (q, J = 288.5 Hz), 67.6, 54.8; HRMS: m/z $[\text{MH}]^+$ $\text{C}_{10}\text{H}_8^{35}\text{ClF}_3\text{N}_3\text{O}_2$ calcd. 294.0252, found 294.0252.

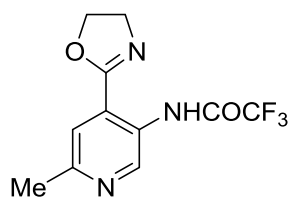
Synthesis of N-(4-(4,5-dihydrooxazol-2-yl)-6-(trifluoromethyl)pyridine-3-yl)-2,2,2-trifluoroacetamide 17



Following general procedure C(i), using trifluoroacetamide (23 mg, 0.20 mmol) and 2-(2-(trifluoromethyl)pyridine-4-yl)-4,5-dihydrooxazole (52 mg, 0.24 mmol) with $[\text{Cp}^*\text{RhCl}_2]_2$ (3 mg, 0.005 mmol), AgSbF_6 (7 mg, 0.02 mmol) and $\text{PhI}(\text{OAc})_2$ (97 mg, 0.30 mmol) in dichloromethane (2 mL), product **17** was isolated as a colourless solid (63 mg, 96%).

M.p.: 52 – 53 °C; FTIR: $\nu_{\text{max}}/\text{cm}^{-1}$ (neat); 3012 (w), 2991 (w), 2916 (w), 1729 (m), 1575 (m), 1322 (m), 1200 (m), 1125 (s), 1100 (s), 947 (s), 915 (s); ^1H NMR (400 MHz, CDCl_3): δ 13.45 (1H, s, NH), 10.07 (1H, s, CH_{ar}), 8.11 (1H, s, CH_{ar}), 4.55 (2H, t, $J = 9.5$ Hz, CH_2), 4.27 (2H, t, $J = 9.5$ Hz, CH_2); ^{19}F NMR (376.5 MHz, CDCl_3): δ – 67.7, – 75.8; ^{13}C NMR (100.6 MHz, CDCl_3): δ 162.8, 155.9 (q, $J = 38.5$ Hz), 144.2 (q, $J = 35.5$ Hz), 142.7, 135.4, 121.3 (q, $J = 274.0$ Hz), 119.9, 119.4 (app d, $J = 2.5$ Hz), 115.6 (q, $J = 285.5$ Hz), 67.7, 54.9; HRMS: m/z $[\text{MH}]^+$ $\text{C}_{11}\text{H}_8\text{F}_6\text{N}_3\text{O}_2$ calcd. 328.0515, found 328.0514.

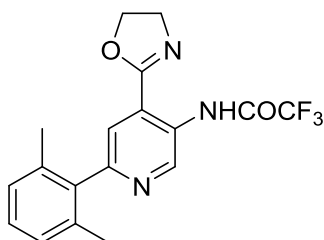
*Synthesis of N-(4-(4,5-dihydrooxazol-2-yl)-6-methylpyridin-3-yl)-2,2,2-trifluoroacetamide **18***



Following general procedure C(i), using trifluoroacetamide (23 mg, 0.20 mmol) and 2-(2-methylpyridin-4-yl)-4,5-dihydrooxazole (39 mg, 0.24 mmol) with $[\text{Cp}^*\text{RhCl}_2]_2$ (3 mg, 0.005 mmol), AgSbF_6 (7 mg, 0.02 mmol) and $\text{PhI}(\text{OAc})_2$ (97 mg, 0.30 mmol) in dichloromethane (2 mL), product **18** was isolated as a colourless solid (35 mg, 64%).

M.p.: 101 – 102 °C; FTIR: $\nu_{\text{max}}/\text{cm}^{-1}$ (neat) 3016 (w), 2966 (w), 1714 (m), 1603 (m), 1525 (m), 1318 (m), 1275 (s), 1147 (s), 954 (m), 754 (s); ^1H NMR (400 MHz, CDCl_3): δ 13.11 (1H, s, NH), 9.82 (1H, s, CH_{ar}), 7.58 (1H, s, CH_{ar}), 4.48 (2H, t, $J = 9.5$ Hz, CH_2), 4.20 (2H, t, $J = 9.5$ Hz, CH_2), 2.59 (3H, s, CH_3); ^{19}F NMR (376.5 MHz, CDCl_3): δ – 75.8; ^{13}C NMR (100.6 MHz, CDCl_3): δ 163.5, 155.3 (q, $J = 38.0$ Hz), 155.1, 141.9, 130.6, 121.4, 121.0, 115.9 (q, $J = 288.5$ Hz), 67.3, 54.8, 24.1; HRMS: m/z $[\text{MH}]^+$ $\text{C}_{11}\text{H}_{11}\text{F}_3\text{N}_3\text{O}_2$ calcd. 274.0798, found 274.0801.

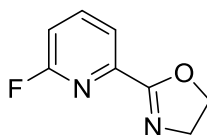
*Synthesis of N-(4-(4,5-dihydrooxazol-2-yl)-6-(2,6-dimethylphenyl)pyridine-3-yl)-2,2,2-trifluoroacetamide **19***



Following general procedure C(ii), using trifluoroacetamide (30 mg, 0.26 mmol) and 2-(2-(2,6-dimethylphenyl)pyridine-4-yl)-4,5-dihydrooxazole (80 mg, 0.32 mmol) with $[\text{Cp}^*\text{RhCl}_2]_2$ (4 mg, 0.007 mmol), AgSbF_6 (9 mg, 0.03 mmol) and $\text{PhI}(\text{OAc})_2$ (128 mg, 0.40 mmol) in dichloromethane (2 mL), product **19** was isolated as a colourless solid (67 mg, 70%).

M.p.: 149 – 150 °C; FTIR: $\nu_{\text{max}}/\text{cm}^{-1}$ (neat) 2995 (w), 2887 (w), 1728 (s), 1607 (m), 1489 (m), 1286 (s), 1193 (s), 1150 (s), 940 (s), 755 (s); ^1H NMR (400 MHz, CDCl_3): δ 13.30 (1H, s, NH), 10.07 (1H, s, CH_{ar}), 7.70 (1H, s, CH_{ar}), 7.21 (1H, dd, $J = 8.0, 7.0$ Hz, CH_{ar}), 7.12 (1H, app. s, CH_{ar}), 7.10 (1H, app. s, CH_{ar}), 4.48 (2H, t, $J = 9.5$ Hz, CH_2), 4.24 (2H, t, $J = 9.5$ Hz, CH_{ar}), 2.05 (6H, s, CH_3); ^{19}F NMR (376.5 MHz, CDCl_3): δ – 75.8; ^{13}C NMR (100.6 MHz, CDCl_3): δ 163.6, 156.5, 155.5 (q, $J = 38.0$ Hz), 142.5, 139.3, 136.1, 131.3, 128.4, 127.8, 122.8, 121.0, 115.9 (q, $J = 288.5$ Hz), 67.3, 54.8, 20.4; HRMS: m/z $[\text{MH}]^+$ $\text{C}_{18}\text{H}_{17}\text{F}_3\text{N}_3\text{O}_2$ calcd. 364.1267, found 364.1271.

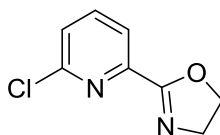
Synthesis of 2-(6-fluoropyridin-2-yl)-4,5-dihydrooxazole **20a**



Following general procedure B, using of 6-fluoro-*N*-(2-hydroxyethyl)picolinamide (1.24 g, 6.73 mmol), *p*-TsCl (2.18 g, 11.5 mmol), NEt_3 (1.29 g, 12.8 mmol), DMAP (164 mg, 1.35 mmol) and dichloromethane (11.2 mL), then following general procedure B(ii), using K_2CO_3 (2.79 g, 20.2 mmol) and MeCN (13.5 mL), the oxazoline product was afforded as a tan solid (970 mg, 87%).

M.p.: 59 – 60 °C; FTIR: $\nu_{\text{max}}/\text{cm}^{-1}$ (neat) 3083 (w), 3057 (w), 2971 (w), 1649 (m), 1460 (m), 1365 (m), 1236 (s), 1111 (s), 978 (s), 824 (s); ^1H NMR (400 MHz, CDCl_3): δ 7.95 – 7.79 (2H, m, CH_{ar}), 7.04 (1H, ddd, $J = 7.5, 3.0, 1.0$ Hz, CH_{ar}), 4.50 (2H, t, $J = 9.5$ Hz, CH_2), 4.11 (2H, t, $J = 9.5$ Hz, CH_2); ^{19}F NMR (376.5 MHz, CDCl_3): δ – 65.3; ^{13}C NMR (100.6 MHz, CDCl_3): δ 163.5 (d, $J = 148.0$ Hz), 161.8, 145.2 (d, $J = 13.5$ Hz), 141.8 (d, $J = 7.5$ Hz), 121.3 (d, $J = 4.0$ Hz), 112.2 (d, $J = 36.5$ Hz), 68.5, 55.3; HRMS: m/z $[\text{MH}]^+$ $\text{C}_8\text{H}_8\text{FN}_2\text{O}$ calcd. 167.0615, found 167.0612.

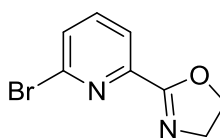
Synthesis of 2-(6-chloropyridin-2-yl)-4,5-dihydrooxazole **20b**



Following general procedure B, using of 6-chloro-*N*-(2-hydroxyethyl)picolinamide (300 mg, 1.50 mmol), *p*-TsCl (486 mg, 2.55 mmol), NEt₃ (288 mg, 2.85 mmol), DMAP (37 mg, 0.30 mmol) and dichloromethane (2.5 mL), then following general procedure B(ii), using K₂CO₃ (622 mg, 4.50 mmol) and MeCN (3 mL), the oxazoline product was afforded as a colourless solid (160 mg, 58%).

M.p.: 79 – 80 °C; FTIR: ν_{max} / cm⁻¹ (neat) 3050 (w), 2875 (w), 1631 (m), 1561 (m), 1432 (m), 1370 (m), 1104 (s), 1069 (s), 807 (s), 737 (s); ¹H NMR (400 MHz, CDCl₃): δ 7.97 (1H, d, *J* = 7.5 Hz, CH_{ar}), 7.75 (1H, t, *J* = 7.5 Hz, CH_{ar}), 7.45 (1H, d, *J* = 7.5 Hz, CH_{ar}), 4.54 (2H, t, *J* = 10.0 Hz, CH₂), 4.13 (2H, t, *J* = 10.0 Hz, CH₂); ¹³C NMR (100.6 MHz, CDCl₃): δ 162.9, 151.6, 147.2, 139.3, 126.6, 122.4, 68.6, 55.2; HRMS: *m/z* [MH]⁺ C₈H₈N₂O³⁵Cl calcd. 183.0325, found 183.0322.

Synthesis of 2-(6-bromopyridin-2-yl)-4,5-dihydrooxazole **20c**

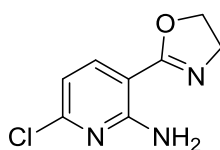


Following general procedure B, using of 6-bromo-*N*-(2-hydroxyethyl)picolinamide (200 mg, 0.816 mmol), *p*-TsCl (264 mg, 1.39 mmol), NEt₃ (157 mg, 1.55 mmol), DMAP (20 mg, 0.16 mmol) and dichloromethane (1.4 mL), then following general procedure B(ii), using K₂CO₃ (338 mg, 2.45 mmol) and MeCN (1.6 mL), the oxazoline product was afforded as a tan solid (970 mg, 87%).

M.p.: 104 – 105 °C; FTIR: ν_{max} / cm⁻¹ (neat) 3043 (w), 2929 (w), 1640 (m), 1554 (m), 1436 (m), 1362 (m), 1245 (m), 1096 (s), 1065 (s), 944 (s), 799 (s), 733 (s), 639 (s); ¹H NMR (400 MHz, CDCl₃): δ 8.00 (1H, dd, *J* = 7.5, 1.0 Hz, CH_{ar}), 7.67 – 7.57 (2H, m, CH_{ar}), 4.53 (2H, t, *J* = 9.5 Hz, CH₂), 4.13 (2H, t, *J* = 9.5 Hz, CH₂); ¹³C NMR (100.6 MHz, CDCl₃): δ 162.8, 147.6, 142.1, 139.0, 130.4, 122.8, 69.0, 55.2; HRMS: *m/z* [MH]⁺ C₈H₈⁷⁹BrN₂O calcd. 226.9820, found 226.9824.

5. Post C-H Amidation Functionalization and data for substrates 21 to 28

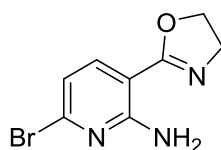
Synthesis of 6-chloro-3-(4,5-dihydrooxazol-2-yl)pyridin-2-amine **21**



To a round bottomed flask was added *N*-(6-chloro-3-(4,5-dihydrooxazol-2-yl)pyridine-2-yl)-2,2,2-trifluoroacetamide (2.22 g, 7.56 mmol) and methanol (76 mL). NaOH pellets (907 mg, 22.7 mmol) were then added and the reaction mixture was stirred at room temperature for 18 hours. The reaction mixture was concentrated, dissolved in ethyl acetate and deionised water and transferred to a separating funnel. The layers were partitioned and the aqueous layer was further extracted with ethyl acetate. The combined organic layers were dried over anhydrous MgSO_4 , filtered and the solvent was removed *in vacuo* to afford the aniline product **21** as a colourless solid (1.33 g, 89%). (NB: Trace amounts of the regioisomer were present in the isolated sample).

FTIR: ν_{max} / cm^{-1} (neat) 3330 (m), 3144 (m), 2984 (w), 2944 (w), 1643 (s), 1550 (s), 1440 (m), 1464 (m), 1357 (m), 1068 (s), 1029 (s), 929 (s), 765 (s); ^1H NMR (400 MHz, d^6 -DMSO): δ 8.25 (1H, br s, NH), 7.85 (1H, d, $J = 8.0$ Hz, CH_{ar}), 7.59 (1H, br s, NH), 6.64 (1H, d, $J = 8.0$ Hz, CH_{ar}), 4.34 (2H, t, $J = 9.5$ Hz, CH_2), 4.02 (2H, t, $J = 9.5$ Hz, CH_2); ^{13}C NMR (100.6 MHz, d^6 -DMSO): δ 162.1, 158.0, 151.2, 140.3, 110.5, 102.2, 66.3, 54.4; HRMS: m/z $[\text{MH}]^+$ $\text{C}_8\text{H}_9^{35}\text{ClN}_3\text{O}$ calcd. 198.0429, found 198.0426.

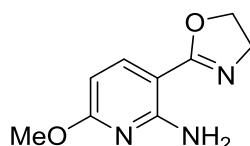
Synthesis of 6-bromo-3-(4,5-dihydrooxazol-2-yl)pyridin-2-amine **22**



To a round bottomed flask was added *N*-(6-bromo-3-(4,5-dihydrooxazol-2-yl)pyridine-2-yl)-2,2,2-trifluoroacetamide (1.03 g, 3.01 mmol) and methanol (31 mL). NaOH pellets (369 mg, 9.22 mmol) were then added and the reaction mixture was stirred at room temperature for 18 hours. The reaction mixture was concentrated, dissolved in ethyl acetate and deionised water and transferred to a separating funnel. The layers were partitioned and the aqueous layer was further extracted with ethyl acetate. The combined organic layers were dried over anhydrous MgSO_4 , filtered and the solvent was removed *in vacuo* to afford the aniline product **22** as colourless solid (664 mg, 89%). (NB: Trace amounts of the regioisomer were present in the isolated sample).

FTIR: ν_{max} / cm^{-1} (neat) 3340 (m), 3266 (w), 3149 (m), 2928 (w), 2878 (w), 1645 (m), 1608 (m), 1551 (s), 1461 (m), 1424 (m), 1370 (m), 1283 (s), 1260 (s), 1072 (s), 915 (s), 767 (s); ^1H NMR (400 MHz, d^6 -DMSO): δ 7.74 (1H, d, $J = 8.0$ Hz, CH_{ar}), 6.78 (1H, d, $J = 8.0$ Hz, CH_{ar}), 4.34 (2H, t, $J = 9.5$ Hz, CH_2), 4.02 (2H, t, $J = 9.5$ Hz, CH_2); ^{13}C NMR (100.6 MHz, d^6 -DMSO): δ 162.2, 158.0, 142.6, 139.9, 114.4, 102.4, 66.3, 54.5; HRMS: m/z $[\text{MH}]^+$ $\text{C}_8\text{H}_9^{79}\text{BrN}_3\text{O}$ calcd. 241.9924, found 241.9925.

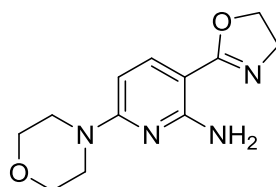
Synthesis of 3-(4,5-dihydrooxazol-2-yl)-6-methoxypyridin-2-amine **23**



To a round bottomed flask was added 6-chloro-3-(4,5-dihydrooxazol-2-yl)pyridin-2-amine (50 mg, 0.25 mmol) and methanol (2.5 mL). NaOH pellets (101 mg, 2.50 mmol) were added in one portion. The reaction was stirred and heated at reflux for a period of 24 hours. The reaction mixture was allowed to cool to room temperature, and ethyl acetate and deionised water were added. The mixture was transferred to a separating funnel and the layers were partitioned. The aqueous layer was further extracted with ethyl acetate. The combined organic layers were dried over anhydrous MgSO_4 , filtered and the solvent was removed *in vacuo* to afford the product **23** as a colourless solid (47 mg, 98%). (NB: Trace amounts of the regioisomer were present in the isolated sample).

FTIR: ν_{max} / cm^{-1} (neat) 3330 (w), 3148 (w), 2984 (w), 1639 (m), 1589 (m), 1553 (m), 1460 (m), 1297 (s), 1261 (s), 1061 (m), 1022 (m), 765 (s); ^1H NMR (400 MHz, d^6 -DMSO): δ 7.75 (1H, d, J = 8.5 Hz, CH_{ar}), 5.99 (1H, d, J = 8.5 Hz, CH_{ar}), 4.28 (2H, t, J = 9.5 Hz, CH_2), 3.97 (2H, t, J = 9.5 Hz, CH_2); ^{13}C NMR (100.6 MHz, d^6 -DMSO): δ 164.5, 162.9, 157.9, 140.1, 97.3, 95.7, 65.9, 54.2, 53.0; HRMS: m/z $[\text{MH}]^+$ $\text{C}_9\text{H}_{12}\text{N}_3\text{O}_2$ calcd. 194.0924, found 194.0923.

Synthesis of 3-(4,5-dihydrooxazol-2-yl)-6-morpholinopyridin-2-amine **24**

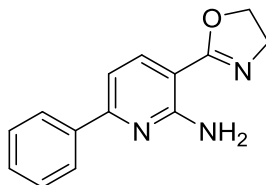


To a round bottomed flask containing 6-chloro-3-(4,5-dihydrooxazol-2-yl)pyridin-2-amine (50 mg, 0.25 mmol) and K_2CO_3 (173 mg, 1.25 mmol). The flask was placed under an atmosphere of nitrogen followed by the addition of DMF (2.5 mL) and morpholine (44 mg, 0.50 mmol). The reaction mixture was then stirred and heated at 120 °C for a period of 48 hours. The reaction mixture was cooled to room temperature and concentrated. The reaction mixture was dry loaded onto silica gel and purified by flash column chromatography eluting with petroleum ether (40/60) and ethyl acetate (0% to 40% ethyl acetate) to afford the product **24** as a colourless solid (39 mg, 63%).

FTIR: ν_{max} / cm^{-1} (neat) 3461 (w), 3376 (w), 3258 (w), 2980 (w), 2883 (w), 1632 (m), 1603 (s), 1368 (m), 1278 (s), 1111 (m), 1061 (w), 765 (s); ^1H NMR (400 MHz, CDCl_3): δ 7.74 (1H, d, J = 8.5 Hz, CH_{ar}), 5.94 (1H, d, J = 8.5 Hz, CH_{ar}), 4.28 (2H, t, J = 9.5 Hz, CH_2), 4.03 (2H, t, J = 9.5 Hz, CH_{ar}), 3.82 – 3.70 (4H,

m, CH₂), 3.63 – 3.49 (4H, m, CH₂); ¹³C NMR (100.6 MHz, CDCl₃): δ 164.2, 157.9, 151.0, 139.5, 108.4, 95.2, 66.9, 66.2, 54.8, 45.1; HRMS: *m/z* [MH]⁺ C₁₂H₁₇N₄O₂ calcd. 249.1346, found 249.1349.

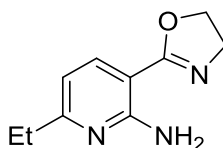
Synthesis of 3-(4,5-dihydrooxazol-2-yl)-6-phenylpyridin-2-amine 25



To a round bottomed flask equipped with a reflux condenser was added 6-bromo-3-(4,5-dihydrooxazol-2-yl)pyridin-2-amine (61 mg, 0.25 mmol), phenyl boronic acid (79 mg, 0.65 mmol) and PdCl₂(dppf).CH₂Cl₂ (21 mg, 0.025 mmol). The reaction system was evacuated and refilled with nitrogen (3 cycles) followed by the addition of the degassed solvents ethanol (0.5 mL) and 1,4-dioxane (5 mL). Degassed aqueous Na₂CO₃ (2M, 0.76 mL) was then added. The reaction mixture was then stirred and heated at 80 °C for a period of 18 hours. The reaction mixture was then cooled to room temperature and concentrated. The residue was dissolved in NaOH aqueous solution (10% (w/v)) and ethyl acetate (sonication was necessary to completely dissolve the residue). The mixture was transferred to a separating funnel and the layers were partitioned. The aqueous layer was further extracted with ethyl acetate. The combined organic layers were dried over anhydrous MgSO₄, filtered and the solvent was removed *in vacuo*. The residue was purified by flash column chromatography eluting with petroleum ether (40/60) and ethyl acetate (0% to 30% ethyl acetate) to afford the product **25** as a yellow solid (35 mg, 58%).

M.p.: 131 – 132 °C; FTIR: *v*_{max}/ cm⁻¹ (neat) 3354 (m), 3280 (w), 3159 (w), 3019 (w), 2972 (w), 2908 (w), 2871 (w), 1638 (s), 1615 (s), 1575 (s), 1555 (s), 1454 (s), 1364 (s), 1253 (s), 1059 (s), 1029 (s), 942 (m), 918 (m); ¹H NMR (400 MHz, CDCl₃): δ 8.06 – 7.96 (3H, m, CH_{ar}), 7.51 – 7.34 (3H, m, CH_{ar}), 7.08 (1H, d, *J* = 8.0 Hz, CH_{ar}), 4.36 (2H, t, *J* = 9.5 Hz, CH₂), 4.12 (2H, t, *J* = 9.5 Hz, CH₂); ¹³C NMR (100.6 MHz, CDCl₃): δ 163.8, 158.7, 158.0, 139.1, 138.8, 129.4, 128.7, 127.2, 109.4, 103.4, 66.5, 55.1; HRMS: *m/z* [MH]⁺ C₁₄H₁₄N₃O calcd. 240.1131, found 240.1130.

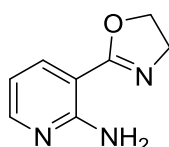
Synthesis of 3-(4,5-dihydrooxazol-2-yl)-6-ethylpyridin-2-amine 26



To a round bottomed flask was added 6-chloro-3-(4,5-dihydrooxazol-2-yl)pyridin-2-amine (50 mg, 0.25 mmol) and $\text{Fe}(\text{acac})_3$ (13 mg, 0.038 mmol). The flask was placed under an atmosphere of nitrogen followed by the addition of dry THF (2.27 mL) and NMP (0.23 mL). Ethylmagnesium bromide (0.28 mL, 2.7 M in diethyl ether, 0.75 mmol) was added to the stirred solution dropwise, resulting in colour changes of red to brown to violet. Upon complete addition the reaction mixture was stirred at room temperature for a period of 2 hours. The reaction was then quenched by the addition of saturated NH_4Cl aq. solution. NaOH aqueous solution (10% (w/v)) was then added followed by ethyl acetate, and the mixture was transferred to a separating funnel. The layers were partitioned and the aqueous layer was further extracted with ethyl acetate. The combined organic layers were dried over anhydrous MgSO_4 , filtered and the solvent was removed *in vacuo*. The residue was purified by flash column chromatography eluting with petroleum ether (40/60) and ethyl acetate (0% to 40% ethyl acetate) to afford the product **26** as a yellow solid (27 mg, 57%).

M.p.: 102 – 103 °C; FTIR: $\nu_{\text{max}}/\text{cm}^{-1}$ (neat) 3323 (w), 3263 (w), 3132 (w), 2972 (w), 1638 (s), 1615 (m), 1585 (s), 1454 (s), 1364 (s), 1257 (s), 1066 (s), 1032 (s), 935 (s), 814 (s), 798 (s); ^1H NMR (400 MHz, CDCl_3): δ 7.84 (1H, d, J = 8.0 Hz, CH_{ar}), 6.48 (1H, d, J = 8.0 Hz, CH_{ar}), 4.32 (2H, t, J = 9.5 Hz, CH_2), 4.07 (2H, t, J = 9.5 Hz, CH_2), 2.64 (2H, q, J = 7.5 Hz, CH_2), 1.25 (3H, t, J = 7.5 Hz, CH_3); ^{13}C NMR (100.6 MHz, CDCl_3): δ 165.9, 163.0, 157.9, 138.4, 110.7, 102.3, 66.4, 55.0, 31.6, 13.7; HRMS: m/z $[\text{MH}]^+$ $\text{C}_{10}\text{H}_{14}\text{N}_3\text{O}$ calcd. 192.1131, found 192.1131.

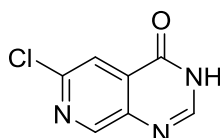
Synthesis of 3-(4,5-dihydrooxazol-2-yl)pyridine-2-amine **27**



To a round bottomed flask equipped with a stirrer bar and a reflux condenser was added 6-chloro-3-(4,5-dihydrooxazol-2-yl)pyridin-2-amine (50 mg, 0.25 mmol), ammonium formate (315 mg, 5.0 mmol) and ethanol (2.5 mL). The flask was placed under an atmosphere of nitrogen followed by the addition of Pd/C (3 mg, 0.03 mmol). The reaction was then stirred and heated at 100 °C for a period of 2 hours. The reaction was then cooled to room temperature and filtered through a plug of Celite, rinsing with methanol. The filtrate was concentrated and the residue was purified by flash column chromatography on silica gel eluting with petroleum ether (40/60) and ethyl acetate (0% to 60% ethyl acetate) to afford the product **27** as a colourless solid (28 mg, 69%).

M.p.: 116 – 117 °C; FTIR: ν_{max} / cm^{-1} (neat) 3317 (m), 3260 (m), 3129 (m), 2978 (w), 2871 (w), 1645 (m), 1618 (m), 1571 (m), 1478 (m), 1451 (m), 1374 (m). 1257 (s), 1069 (s), 1032 (s), 945 (s), 774 (s); ^1H NMR (400 MHz, CDCl_3): δ 8.12 (1H, dd, J = 5.0, 2.0 Hz, CH_{ar}), 7.92 (1H, dd, J = 7.5, 2.0 Hz, CH_{ar}), 6.60 (1H, dd, J = 7.5, 5.0 Hz, CH_{ar}), 4.34 (2H, t, J = 9.5 Hz, CH_2), 4.09 (2H, t, J = 9.5 Hz, CH_2); ^{13}C NMR (100.6 MHz, CDCl_3): δ 163.7, 158.2, 151.2, 138.1, 112.4, 104.9, 66.5, 55.0; HRMS: m/z $[\text{MH}]^+$ $\text{C}_8\text{H}_{10}\text{N}_3\text{O}$ calcd. 164.0818, found 164.0819.

Synthesis of 6-chloropyrido[3,4-d]pyrimidin-4(3H)-one **28**

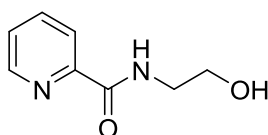


2-((6-Chloropyrido[3,4-d]pyrimidin-4-yl)amino)ethanol (54 mg, 0.24 mmol) was suspended in 6 M HCl aq. (1.70 mL), and heated to 100 – 105 °C for 2 hours. The reaction was then allowed to cool to room temperature, and then further cooled to 0 °C with an ice/water bath. The reaction mixture was basified to pH 11 with aqueous ammonia solution (35%), and allowed to stir for 15 minutes. NaOH aqueous solution (10% (w/v)) was then added and the reaction mixture was concentrated. The mixture was re-suspended in dichloromethane and methanol and dry loaded onto silica gel. The reaction was purified by flash column chromatography on silica gel eluting with dichloromethane and methanol (0% to 20% methanol) to afford the quinazolinone product **28** as a colourless solid (22 mg, 51%).

M.p.: > 250 °C (lit. 318 - 226 °C)⁴; ^1H NMR (400 MHz, d^6 -DMSO): δ 12.75 (1H, s, NH), 8.90 (1H, d, J = 0.5 Hz, CH_{ar}), 8.24 (1H, s, N=CH), 7.97 (1H, d, J = 0.5 Hz, CH_{ar}); ^{13}C NMR (100.6 MHz, d^6 -DMSO): δ 158.9, 151.0, 147.7, 146.2, 142.9, 130.6, 118.5.

6. Data for all other substrates

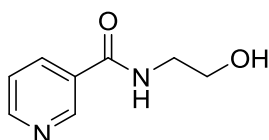
Synthesis of *N*-(2-hydroxyethyl)picolinamide⁵



Following general procedure A, using ethyl-2-picolinate (1.00 g, 6.62 mmol) and ethanolamine (607 mg, 9.93 mmol) the amide product was afforded as a colourless oil (1.11 g, 100%).

^1H NMR (400 MHz, CDCl_3): δ 8.47 (1H, ddd, J = 5.0, 1.5, 1.0 Hz, CH_{ar}), 8.44 (1H, s, NH), 8.10 (1H, dt, J = 8.0, 1.0 Hz, CH_{ar}), 7.77 (1H, td, J = 8.0, 1.5 Hz, CH_{ar}), 7.36 (1H, ddd, J = 8.0, 5.0, 1.0 Hz, CH_{ar}), 3.89 (1H, s, OH), 3.78 (2H, app. q, J = 10.0 Hz, CH_2), 3.59 (2H, app. q, J = 10.0 Hz, CH_2); ^{13}C NMR (100.6 MHz, CDCl_3): δ 165.4, 149.7, 148.2, 137.5, 126.3, 122.3, 61.9, 42.4.

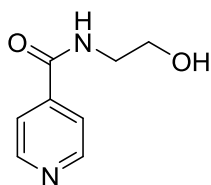
*Synthesis of N-(2-hydroxyethyl)nicotinamide*⁵



Following general procedure A, using ethyl nicotinate (1.00 g, 6.62 mmol) and ethanolamine (607 mg, 9.93 mmol) the amide product was afforded as a colourless solid (732 mg, 67%).

M.p.: 92 – 93 °C (lit. 92 °C)⁶; ^1H NMR (400 MHz, $\text{DMSO}-d^6$): δ 9.01 (1H, dd, J = 2.0, 1.0 Hz, CH_{ar}), 8.69 (1H, dd, J = 5.0, 1.5 Hz, CH_{ar}), 8.66 (1H, t, J = 5.0 Hz, NH), 8.19 (1H, ddd, J = 8.0, 2.0, 1.5 Hz, CH_{ar}), 7.49 (1H, ddd, J = 8.0, 5.0, 1.0 Hz, CH_{ar}), 3.52 (2H, t, J = 6.0 Hz, CH_2), 3.37 – 3.32 (3H, m, CH_2 and OH); ^{13}C NMR (100.6 MHz, d^6 -DMSO): δ 164.9, 151.7, 148.4, 134.9, 130.0, 123.4, 59.6, 42.2.

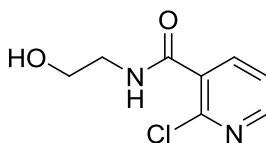
*Synthesis of N-(2-hydroxyethyl)isonicotinamide*⁵



Following general procedure A, using ethyl isonicotinate (1.00 g, 6.62 mmol) and ethanolamine (607 mg, 9.93 mmol) the amide product was afforded as a colourless solid (1.04 g, 95%).

M.p.: 131 – 132 °C (lit. 133 - 134 °C)⁷; ^1H NMR (400 MHz, d^6 -DMSO): δ 8.75 (1H, s, NH), 8.72 (2H, dd, J = 4.5, 1.5 Hz, CH_{ar}), 7.76 (2H, dd, J = 4.5, 1.5 Hz, CH_{ar}), 4.77 (1H, s, OH), 3.53 (2H, t, J = 5.5 Hz, CH_2), 3.35 (2H, app. q, J = 5.5 Hz, CH_2); ^{13}C NMR (100.6 MHz, d^6 -DMSO): δ 164.8, 150.2, 141.5, 121.3, 59.5, 42.3.

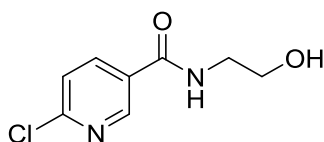
Synthesis of 2-chloro-N-(2-hydroxyethyl)nicotinamide



Following general procedure A, using ethyl 2-chloro nicotinate (2.00 g, 10.8 mmol) and ethanolamine (987 mg, 16.2 mmol) the amide product was afforded as a colourless solid (1.14 g, 53%).

M.p.: 75 – 76 °C; FTIR: ν_{max} / cm^{-1} (neat) 3261 (m), 3070 (w), 2941 (w), 1640 (s), 1589 (s), 1546 (s), 1401 (s), 1057 (s), 740 (m); ^1H NMR (400 MHz, d^6 -DMSO): δ 8.58 (1H, br s, NH), 8.45 (1H, dd, J = 5.0, 2.0 Hz, CH_{ar}), 7.89 (1H, dd, J = 7.5, 2.0 Hz, CH_{ar}), 7.48 (1H, dd, J = 7.5, 5.0 Hz, CH_{ar}), 4.76 (1H, t, J = 5.5 Hz, OH), 3.52 (2H, app. q, J = 6.0 Hz, CH_2), 3.31 (2H, app. q, J = 6.0 Hz, CH_2); ^{13}C NMR (100.6 MHz, d^6 -DMSO): δ 165.3, 150.2, 146.6, 138.1, 133.3, 123.0, 59.6, 42.0; HRMS: m/z $[\text{MH}]^+$ $\text{C}_8\text{H}_{10}^{35}\text{ClN}_2\text{O}_2$ calcd. 201.0425, found 201.0428.

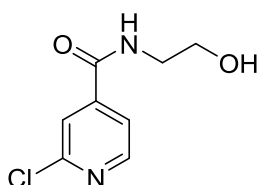
Synthesis of 6-chloro-*N*-(2-hydroxyethyl)nicotinamide



Following general procedure A, using ethyl 6-chloro nicotinate (4.00 g, 21.6 mmol) and ethanolamine (1.97 g, 32.3 mmol) the amide product was afforded as a colourless solid (2.60 g, 60%).

M.p.: 100 – 101 °C; FTIR: ν_{max} / cm^{-1} (neat) 3363 (m), 3277 (m), 3044 (w), 2930 (w), 2873 (w), 1640 (s), 1586 (m), 1542 (s), 1456 (s), 1371 (m), 1169 (m), 1109 (s), 1059 (m), 1034 (s), 1018 (s), 851 (s); ^1H NMR (400 MHz, d^6 -DMSO): δ 8.83 (1H, dd, J = 2.5, 0.5 Hz, CH_{ar}), 8.72 (1H, t, J = 5.0 Hz, NH), 8.24 (1H, dd, J = 8.0, 2.5 Hz, CH_{ar}), 7.63 (1H, dd, J = 8.0, 0.5 Hz, CH_{ar}), 4.76 (1H, t, J = 5.5 Hz, OH), 3.52 (2H, app. q, J = 6.0 Hz, CH_2), 3.34 (2H, app. q, J = 6.0 Hz, CH_2); ^{13}C NMR (100.6 MHz, d^6 -DMSO): δ 163.8, 152.4, 149.0, 138.6, 129.4, 124.1, 59.5, 42.0; HRMS: m/z $[\text{MH}]^+$ $\text{C}_8\text{H}_{10}^{35}\text{ClN}_2\text{O}_2$ calcd. 201.0425, found 201.0426.

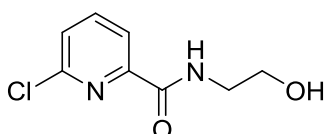
Synthesis of 2-chloro-*N*-(2-hydroxyethyl)isonicotinamide



Following general procedure A, using ethyl 2-chloro isonicotinate (5.00 g, 26.9 mmol) and ethanolamine (2.47 g, 40.4 mmol) the amide product was afforded as a colourless solid (5.23 g, 97%).

M.p.: 138 – 139 °C; FTIR: $\nu_{\text{max}}/\text{cm}^{-1}$ (neat) 3416 (m), 3281 (m), 3069 (m), 2946 (w), 1652 (s), 1557 (s), 1539 (s), 1327 (s), 1305 (s), 1207 (m), 1119 (m), 1059 (s), 1027 (m), 882 (s); ^1H NMR (400 MHz, d^6 -DMSO): δ 8.85 (1H, t, $J = 5.0$ Hz, NH), 8.56 (1H, dd, $J = 5.0, 1.0$ Hz, CH_{ar}), 7.88 (1H, dd, $J = 1.5, 1.0$ Hz, CH_{ar}), 7.78 (1H, dd, $J = 5.0, 1.5$ Hz, CH_{ar}), 4.77 (1H, t, $J = 5.5$ Hz, OH), 3.52 (2H, app. q, $J = 6.0$ Hz, CH_2), 3.41 – 3.29 (2H, m, CH_2 – signal not resolved due to overlap with residual H_2O); ^{13}C NMR (100.6 MHz, d^6 -DMSO): δ 163.3, 150.8, 150.7, 145.1, 122.0, 120.9, 59.4, 42.4; HRMS: m/z $[\text{MH}]^+$ $\text{C}_8\text{H}_{10}^{35}\text{ClN}_2\text{O}_2$ calcd. 201.0425, found 201.0426.

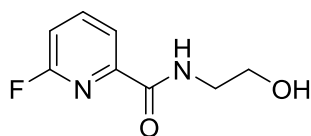
Synthesis of 6-chloro-*N*-(2-hydroxyethyl)picolinamide



Following general procedure A, using ethyl 6-chloro picolinate (1.00 g, 5.39 mmol) and ethanolamine (494 mg, 8.09 mmol) the amide product was afforded as a colourless solid (1.05 g, 97%).

M.p.: 55 – 56 °C; FTIR: $\nu_{\text{max}}/\text{cm}^{-1}$ (neat) 3416 (m), 3296 (m), 2955 (m), 1646 (s), 1567 (s), 1529 (s), 1431 (s), 1311 (m), 1217 (m), 1147 (m), 1131 (m), 1068 (s), 1049 (s), 816 (s); ^1H NMR (400 MHz, d^4 -MeOD): δ 8.04 (1H, dd, $J = 7.5, 1.0$ Hz, CH_{ar}), 7.95 (1H, t, $J = 7.5$ Hz, CH_{ar}), 7.59 (1H, dd, $J = 7.5, 1.0$ Hz, CH_{ar}), 3.73 (1H, t, $J = 5.5$ Hz, CH_2), 3.54 (1H, t, $J = 5.5$ Hz, CH_2); ^{13}C NMR (100.6 MHz, d^4 -MeOD): δ 165.3, 151.6, 151.4, 141.8, 128.4, 122.0, 61.5, 43.0; HRMS: m/z $[\text{MH}]^+$ $\text{C}_8\text{H}_{10}^{35}\text{ClN}_2\text{O}_2$ calcd. 201.0425, found 201.0427.

Synthesis of 6-fluoro-*N*-(2-hydroxyethyl)picolinamide



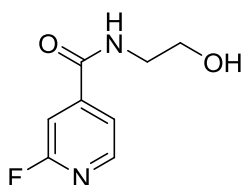
Following general procedure A, using ethyl 6-fluoro picolinate (2.40 g, 14.2 mmol) and ethanolamine (1.30 g, 21.3 mmol) the amide product was afforded as a yellow amorphous solid (2.36 g, 90%).

NB: Ethyl 6-fluoro picolinate was synthesised from the corresponding carboxylic acid using esterification procedure 1

FTIR: $\nu_{\text{max}}/\text{cm}^{-1}$ (neat) 3397 (m), 3274 (m), 3082 (w), 2959 (s), 1646 (s), 1535 (s), 1447 (s), 1330 (m), 1239 (s), 1068 (s), 1049 (s), 942 (s); ^1H NMR (400 MHz, d^6 -DMSO): δ 8.55 (1H, br s, NH), 8.18 (1H, dd, $J = 16.0, 8.0$ Hz, CH_{ar}), 7.97 (1H, dd, $J = 7.5, 2.5$ Hz, CH_{ar}), 7.41 (1H, dd, $J = 8.0, 2.5$ Hz, CH_{ar}), 4.78 (1H, t, $J = 5.5$ Hz, OH), 3.52 (2H, q, $J = 6.0$ Hz, CH_2), 3.36 (2H, q, $J = 6.0$ Hz, CH_2); ^{19}F NMR (376.5 MHz, d^6 -

DMSO): δ – 68.2; ^{13}C NMR (100.6 MHz, d^6 -DMSO): δ 161.7 (d, J = 240.0 Hz), 160.5, 148.6 (d, J = 11.5 Hz), 143.8 (d, J = 8.0 Hz), 120.0, 112.7 (d, J = 36.5 Hz), 59.5, 41.7; HRMS: m/z $[\text{MH}]^+$ $\text{C}_8\text{H}_{10}\text{FN}_2\text{O}_2$ calcd. 185.0721, found 185.0718.

Synthesis of 2-fluoro-N-(2-hydroxyethyl)isonicotinamide

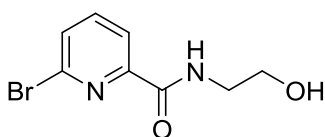


Following general procedure A, using ethyl 2-fluoro isonicotinate (1.40 g, 8.28 mmol) and ethanolamine (759 mg, 12.4 mmol) the amide product was afforded as a colourless solid (1.33 g, 87%).

NB: Ethyl 2-fluoro isonicotinate was synthesised from the corresponding carboxylic acid using esterification procedure 1

M.p.: 99 – 100 °C; FTIR: ν_{max} / cm^{-1} (neat) 3336 (m), 3093 (w), 2945 (w), 1640 (m), 1550 (s), 1401 (s), 1315 (s), 1237 (m), 1073 (s), 764 (s), 651 (s); ^1H NMR (400 MHz, d^6 -DMSO): δ 8.82 (1H, br s, NH), 8.38 (1H, d, J = 5.0 Hz, CH_{ar}), 7.73 (1H, d, J = 5.0 Hz, CH_{ar}), 7.53 (1H, s, CH_{ar}), 4.77 (1H, t, J = 5.5 Hz, OH), 3.53 (2H, app. q, J = 6.0 Hz, CH_2), 3.34 (2H, app. q, J = 6.0 Hz, CH_2); ^{19}F NMR (376.5 MHz, d^6 -DMSO): δ – 68.0; ^{13}C NMR (100.6 MHz, d^6 -DMSO): δ 163.5 (d, J = 236.0 Hz), 163.4 (d, J = 3.5 Hz), 148.4 (d, J = 15.0 Hz), 147.7 (d, J = 7.5 Hz), 119.9 (d, J = 4.0 Hz), 107.6 (d, J = 39.0 Hz), 59.4, 42.4; HRMS: m/z $[\text{MH}]^+$ $\text{C}_8\text{H}_{10}\text{FN}_2\text{O}_2$ calcd. 185.0721, found 185.0720.

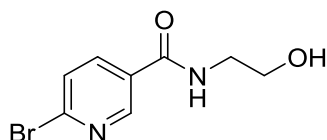
*Synthesis of 6-bromo-N-(2-hydroxyethyl)picolinamide*⁸



Following general procedure A, using ethyl 6-bromo 2-pyridine carboxylate (1.00 g, 4.35 mmol) and ethanolamine (398 mg, 6.52 mmol) the amide product was afforded as a beige solid (967 mg, 91%).

M.p.: 79 – 80 °C; ^1H NMR (400 MHz, d^6 -DMSO): δ 8.52 (1H, app. s, NH), 8.04 (1H, dd, J = 7.5, 1.0 Hz, CH_{ar}), 7.94 (1H, t, J = 7.5 Hz, CH_{ar}), 7.85 (1H, dd, J = 7.5, 1.0 Hz, CH_{ar}), 4.81 (1H, br s, OH), 3.53 (2H, br s, CH_2), 3.38 (2H, app. q, J = 6.0 Hz, CH_2); ^{13}C NMR (100.6 MHz, d^6 -DMSO): δ 162.4, 151.3, 141.0, 140.2, 130.8, 121.4, 59.5, 41.7.

Synthesis of 6-bromo-N-(2-hydroxyethyl)nicotinamide

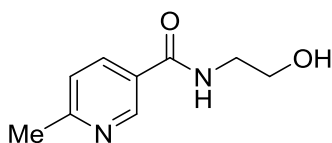


Following general procedure A, using ethyl 6-bromo nicotinate (1.29 g, 5.60 mmol) and ethanolamine (513 mg, 8.41 mmol) the amide product was afforded as a colourless solid (795 mg, 58%).

NB: Ethyl 6-bromo nicotinate was synthesised from the corresponding carboxylic acid using esterification procedure 2

M.p.: 118 – 119 °C; FTIR: ν_{max} / cm^{-1} (neat) 3360 (m), 3273 (m), 3042 (w), 2942 (w), 2871 (w), 1638 (s), 1578 (s), 1541 (s), 1458 (m), 1370 (m), 1086 (s), 1036 (s), 848 (s), 660 (s); ^1H NMR (400 MHz, d^6 -DMSO): δ 8.80 (1H, d, J = 2.5 Hz, CH_{ar}), 8.73 (1H, t, J = 5.0 Hz, NH), 8.12 (1H, dd, J = 8.0, 2.5 Hz, CH_{ar}), 7.78 (1H, d, J = 8.0 Hz, CH_{ar}), 4.75 (1H, t, J = 5.5 Hz, OH), 3.51 (2H, app. q, J = 6.0 Hz, CH_2), 3.33 (2H, app. q, J = 6.0 Hz, CH_2); ^{13}C NMR (100.6 MHz, d^6 -DMSO): δ 163.9, 149.4, 143.8, 138.2, 129.7, 127.8, 59.5, 42.3; HRMS: m/z $[\text{MH}]^+$ $\text{C}_8\text{H}_{10}^{79}\text{BrN}_2\text{O}_2$ calcd. 244.9920, found 244.9922.

Synthesis of *N*-(2-hydroxyethyl)-6-methylnicotinamide

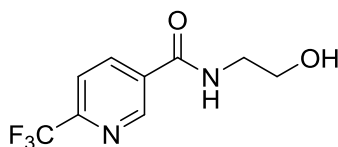


Following general procedure A, using ethyl 6-methyl nicotinate (1.30 g, 7.69 mmol) and ethanolamine (704 mg, 11.5 mmol) the amide product was afforded as an amorphous colourless solid (988 mg, 71%).

NB: Ethyl 6-methyl nicotinate was synthesised from the corresponding carboxylic acid using esterification procedure 2

FTIR: ν_{max} / cm^{-1} (neat) 3304 (m), 3070 (m), 2972 (m), 1632 (s), 1604 (s), 1554 (s), 1292 (s), 1214 (m), 1053 (s), 877 (m), 862 (m), 655 (s); ^1H NMR (400 MHz, d^6 -DMSO): δ 8.88 (1H, d, J = 2.0 Hz, CH_{ar}), 8.55 (1H, t, J = 5.0 Hz, NH), 8.07 (1H, dd, J = 8.0, 2.0 Hz, CH_{ar}), 7.33 (1H, d, J = 8.0 Hz, CH_{ar}), 4.74 (1H, br s, OH), 3.50 (2H, app. d, J = 3.5 Hz, CH_2), 3.31 (2H, m, CH_2 – peak cannot be fully resolved due to overlap with H_2O signal); ^{13}C NMR (100.6 MHz, d^6 -DMSO): δ 164.9, 160.7, 147.9, 135.2, 127.2, 122.6, 59.7, 42.1, 24.0; HRMS: m/z $[\text{MH}]^+$ $\text{C}_9\text{H}_{13}\text{N}_2\text{O}_2$ calcd. 181.0972, found 181.0974.

Synthesis of *N*-(2-hydroxyethyl)-6-(trifluoromethyl)nicotinamide

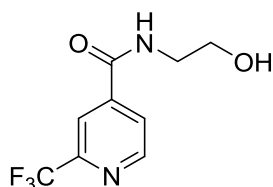


Following general procedure A, using ethyl 6-(trifluoromethyl) nicotinate (1.50 g, 6.84 mmol) and ethanolamine (627 mg, 10.3 mmol) the amide product was afforded as a colourless solid (1.45 g, 90%).

NB: Ethyl 6-(trifluoromethyl) nicotinate was synthesised from the corresponding carboxylic acid using esterification procedure 1

M.p.: 113 – 114 °C; FTIR: ν_{max} / cm^{-1} (neat) 3426 (m), 3277 (m), 3101 (w), 2946 (w), 1646 (s), 1542 (m), 1450 (m), 1330 (s), 1185 (m), 1166 (s), 1125 (s), 1087 (s), 1059 (s), 1046 (m), 857 (m); ^1H NMR (400 MHz, d^6 -DMSO): δ 9.15 (1H, app. s, CH_{ar}), 8.89 (1H, s, NH), 8.46 (1H, dd, J = 8.0, 1.5 Hz, CH_{ar}), 8.05 (1H, d, J = 8.0 Hz, CH_{ar}), 4.79 (1H, s, OH), 3.54 (2H, m, CH_2), 3.37 (2H, app. dd, J = 11.5, 6.0 Hz, CH_2); ^{19}F NMR (376.5 MHz, d^6 -DMSO): δ – 66.6; ^{13}C NMR (100.6 MHz, d^6 -DMSO): δ 164.2, 149.5, 148.4 (q, J = 34.0 Hz), 137.8, 133.6, 121.9 (q, J = 274.0 Hz), 121.0, 59.9, 42.8; HRMS: m/z $[\text{MH}]^+$ $\text{C}_9\text{H}_{10}\text{F}_3\text{N}_2\text{O}_2$ calcd. 235.0689, found 235.0692.

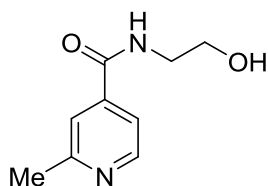
Synthesis of *N*-(2-hydroxyethyl)-2-(trifluoromethyl)isonicotinamide



Following general procedure A, using ethyl 2-(trifluoromethyl) isonicotinate (924 mg, 4.22 mmol) and ethanolamine (386 mg, 6.33 mmol) the amide product was afforded as a colourless solid (846 mg, 86%).

NB: Ethyl 2-(trifluoromethyl) isonicotinate was synthesised from the corresponding carboxylic acid using esterification procedure 1

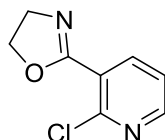
M.p.: 126 - 127 °C; FTIR: ν_{max} / cm^{-1} (neat) 3369 (w), 3276 (w), 3091 (w), 2980 (w), 1646 (m), 1550 (m), 1304 (m), 1143 (s), 1086 (s), 1061 (s), 904 (m), 854 (m); ^1H NMR (400 MHz, d^6 -DMSO): δ 9.00 (1H, br s, NH), 8.92 (1H, d, J = 5.0 Hz, CH_{ar}), 8.26 (1H, app. s, CH_{ar}), 8.09 (1H, dd, J = 5.0, 1.0 Hz, CH_{ar}), 4.79 (1H, br s, OH), 3.58 – 3.52 (2H, m, CH_2), 3.41 – 3.34 (2H, m, CH_2); ^{19}F NMR (376.5 MHz, d^6 -DMSO): δ – 66.6; ^{13}C NMR (100.6 MHz, d^6 -DMSO): δ 163.4, 151.1, 147.1 (q, J = 34.0 Hz), 143.6, 125.1, 121.6 (q, J = 274.0 Hz), 118.3, 59.4, 42.5; HRMS: m/z $[\text{MH}]^+$ $\text{C}_9\text{H}_{10}\text{F}_3\text{N}_2\text{O}_2$ calcd. 235.0689, found 235.0691.

Synthesis of N-(2-hydroxyethyl)-2-methylisonicotinamide

Following general procedure A, using ethyl 2-methyl isonicotinate (857 mg, 5.07 mmol) and ethanolamine (460 mg, 7.60 mmol) the amide product was afforded as a yellow amorphous solid (714 mg, 78%).

NB: Ethyl 2-methyl isonicotinate was synthesised from the corresponding carboxylic acid using esterification procedure 1

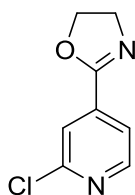
FTIR: ν_{max} / cm^{-1} (neat) 3258 (m), 3076 (w), 2941 (w), 1635 (s), 1546 (s), 1314 (s), 1076 (s), 894 (m), 858 (m); ^1H NMR (400 MHz, d^6 -DMSO): δ 8.66 (1H, t, $J = 5.0$ Hz, NH), 8.56 (1H, d, $J = 5.0$ Hz, CH_{ar}), 7.63 (1H, app. s, CH_{ar}), 7.55 (1H, dd, $J = 5.0, 1.0$ Hz, CH_{ar}), 4.75 (1H, t, $J = 5.5$ Hz, OH), 3.52 (2H, q, $J = 6.0$ Hz, CH_2), 3.41 – 3.27 (2H, m, CH_2), 2.53 (3H, s, CH_3); ^{13}C NMR (100.6 MHz, d^6 -DMSO): δ 165.0, 158.6, 149.5, 141.8, 120.6, 118.4, 59.5, 42.2, 24.1; HRMS: m/z $[\text{MH}]^+$ $\text{C}_9\text{H}_{13}\text{N}_2\text{O}_2$ calcd. 181.0972, found 181.0972.

Synthesis of 2-(2-chloropyridin-3-yl)-4,5-dihydrooxazole

Following general procedure B, using of 6-chloro-*N*-(2-hydroxyethyl)nicotinamide (300 mg, 1.50 mmol), *p*-TsCl (486 mg, 2.55 mmol), NEt_3 (288 mg, 2.85 mmol), DMAP (37 mg, 0.30 mmol) and dichloromethane (2.5 mL), then following general procedure B(ii), using K_2CO_3 (622 mg, 4.50 mmol) and MeCN (3 mL), the oxazoline product was afforded as a yellow solid (172 mg, 63%).

M.p.: 90 – 91 $^\circ\text{C}$; FTIR: ν_{max} / cm^{-1} (neat) 3072 (w), 2981 (w), 1658 (m), 1633 (m), 1586 (m), 1400 (s), 1368 (m), 1270 (m), 1119 (s), 1030 (s), 936 (s), 901 (s), 819 (s); ^1H NMR (400 MHz, CDCl_3): δ 8.43 (1H, dd, $J = 5.0, 2.0$ Hz, CH_{ar}), 8.09 (1H, dd, $J = 7.5, 2.0$ Hz, CH_{ar}), 7.28 (1H, dd, $J = 7.5, 5.0$ Hz, CH_{ar}), 4.44 (2H, t, $J = 9.5$ Hz, CH_2), 4.10 (2H, t, $J = 9.5$ Hz, CH_2); ^{13}C NMR (100.6 MHz, CDCl_3): δ 161.7, 151.0, 149.8, 140.1, 124.4, 122.0, 67.9, 55.5; HRMS: m/z $[\text{M}]^+$ $\text{C}_8\text{H}_7^{35}\text{ClN}_2\text{O}$ calcd. 182.0241, found 182.0239.

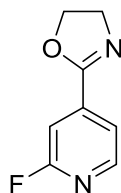
*Synthesis of 2-(2-chloropyridin-4-yl)-4,5-dihydrooxazole*⁹



Following general procedure B, using of 2-chloro-*N*-(2-hydroxyethyl)isonicotinamide (5.0 g, 24.9 mmol), *p*-TsCl (8.07 g, 42.4 mmol), NEt₃ (4.79 g, 47.4 mmol), DMAP (610 mg, 4.98 mmol) and dichloromethane (42 mL), then following general procedure B(i), using NaOH pellets (3.0 g, 74.8 mmol) and methanol (50 mL), the oxazoline product was afforded as a colourless solid (3.69 g, 81%).

M.p.: 89 – 90 °C; ¹H NMR (400 MHz, CDCl₃): δ 8.41 (1H, dd, *J* = 5.0, 1.0 Hz, CH_{ar}), 7.76 (1H, s, CH_{ar}), 7.65 (1H, dd, *J* = 5.0, 1.0 Hz, CH_{ar}), 4.42 (2H, t, *J* = 10.0 Hz, CH₂), 4.05 (2H, t, *J* = 10.0 Hz, CH₂); ¹³C NMR (100.6 MHz, CDCl₃): δ 161.9, 152.1, 150.1, 138.1, 122.9, 120.7, 68.2, 55.2.

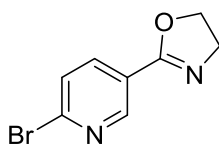
Synthesis of 2-(2-fluoropyridin-4-yl)-4,5-dihydrooxazole



Following general procedure B, using of 2-fluoro-*N*-(2-hydroxyethyl)isonicotinamide (200 mg, 1.09 mmol), *p*-TsCl (352 mg, 1.85 mmol), NEt₃ (209 mg, 2.06 mmol), DMAP (27 mg, 0.22 mmol) and dichloromethane (1.8 mL), then following general procedure B(i), using K₂CO₃ (450 mg, 3.26 mmol) and MeCN (2.2 mL), the oxazoline product was afforded as a colourless solid (128 mg, 71%).

M.p.: 99 – 100 °C; FTIR: ν_{max}/ cm⁻¹ (neat) 3058 (w), 2980 (w), 1651 (m), 1604 (m), 1550 (m), 1413 (s), 1389 (s), 1194 (m), 1081 (m), 945 (m), 854 (s), 702 (m); ¹H NMR (400 MHz, CDCl₃): δ 8.29 (1H, d, *J* = 5.0 Hz, CH_{ar}), 7.72 – 7.64 (1H, m, CH_{ar}), 7.41 (1H, *J* = 1.0 Hz, CH_{ar}), 4.48 (2H, t, *J* = 9.5 Hz, CH₂), 4.11 (2H, t, *J* = 9.5 Hz, CH₂); ¹⁹F NMR (376.5 MHz, CDCl₃): δ – 66.9; ¹³C NMR (100.6 MHz, CDCl₃): δ 164.1 (d, *J* = 239.0 Hz), 162.0 (d, *J* = 4.0 Hz), 148.3 (d, *J* = 15.0 Hz), 140.5 (d, *J* = 8.5 Hz), 119.9 (d, *J* = 4.5 Hz), 108.5 (d, *J* = 40.0 Hz), 68.3, 55.2; HRMS: *m/z* [M]⁺ C₈H₇FN₂O calcd. 166.0537, found 166.0535.

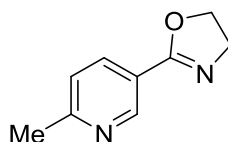
Synthesis of 2-(6-bromopyridin-3-yl)-4,5-dihydrooxazole



Following general procedure B, using of 6-bromo-*N*-(2-hydroxyethyl)nicotinamide (458 mg, 1.87 mmol), *p*-TsCl (606 mg, 3.18 mmol), NEt₃ (360 mg, 3.55 mmol), DMAP (46 mg, 0.37 mmol) and dichloromethane (3.2 mL), then following general procedure B(ii), using K₂CO₃ (775 mg, 5.61 mmol) and MeCN (3.8 mL), the oxazoline product was afforded as a yellow solid (314 mg, 74%).

M.p.: 114 – 115 °C; FTIR: ν_{max} / cm⁻¹ (neat) 3079 (w), 2955 (w), 1652 (m), 1578 (m), 1448 (m), 1253 (m), 1096 (s), 1069 (s), 935 (s), 737 (s), 680 (m); ¹H NMR (400 MHz, CDCl₃): δ 8.86 (1H, d, *J* = 2.0 Hz, CH_{ar}), 8.04 (1H, dd, *J* = 8.5, 2.0 Hz, CH_{ar}), 7.53 (1H, d, *J* = 8.5 Hz, CH_{ar}), 4.44 (2H, t, *J* = 9.5 Hz, CH₂), 4.05 (2H, t, *J* = 9.5 Hz, CH₂); ¹³C NMR (100.6 MHz, CDCl₃): δ 161.9, 149.8, 144.9, 137.8, 127.9, 123.3, 68.0, 55.1; HRMS: *m/z* [M]⁺ C₈H₈⁷⁹BrN₂O calcd. 226.9815, found 226.9816.

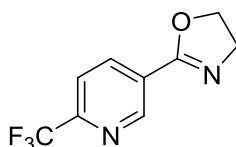
Synthesis of 2-(6-methylpyridin-3-yl)-4,5-dihydrooxazole



Following general procedure B, using of *N*-(2-hydroxyethyl)-6-methylnicotinamide (695 mg, 3.86 mmol), *p*-TsCl (1.25 g, 6.56 mmol), NEt₃ (742 mg, 7.33 mmol), DMAP (94 mg, 0.77 mmol) and dichloromethane (6.5 mL), then following general procedure B(ii), using K₂CO₃ (463 mg, 11.6 mmol) and MeCN (8 mL), the oxazoline product was afforded as a beige solid (400 mg, 64%).

M.p.: 56 – 57 °C; FTIR: ν_{max} / cm⁻¹ (neat) 3035 (w), 2933 (w), 1640 (s), 1597 (m), 1378 (s), 1261 (s), 1077 (s), 940 (s), 842 (m), 733 (s), 690 (s); ¹H NMR (400 MHz, CDCl₃): δ 8.92 (1H, d, *J* = 2.0 Hz, CH_{ar}), 7.98 (1H, dd, *J* = 8.0, 2.0 Hz, CH_{ar}), 7.10 (1H, d, *J* = 8.0 Hz, CH_{ar}), 4.33 (2H, t, *J* = 9.5 Hz, CH₂), 3.95 (2H, t, *J* = 9.5 Hz, CH₂), 2.50 (3H, s, CH₃); ¹³C NMR (100.6 MHz, CDCl₃): δ 162.8, 161.3, 148.8, 135.7, 122.8, 121.0, 67.6, 54.8, 24.6; HRMS: *m/z* [MH]⁺ C₉H₁₀N₂O calcd. 162.0788, found 162.0785.

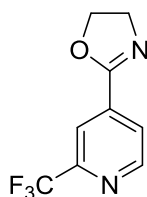
Synthesis of 2-(6-(trifluoromethyl)pyridine-3-yl)-4,5-dihydrooxazole



Following general procedure B, using of *N*-(2-hydroxyethyl)-6-(trifluoromethyl)nicotinamide (500 mg, 2.14 mmol), *p*-TsCl (694 mg, 3.64 mmol), NEt₃ (411 mg, 4.07 mmol), DMAP (52 mg, 0.43 mmol) and dichloromethane (3.6 mL), then following general procedure B(i), using NaOH pellets (257 mg, 6.42 mmol) and methanol (4.3 mL), the oxazoline product was afforded as a colourless solid (363 mg, 79%).

M.p.: 72 – 73 °C; FTIR: ν_{max} / cm^{-1} 3054 (w), 2988 (w), 1655 (m), 1335 (m), 1116 (s), 1092 (s), 1073 (s), 1014 (m), 936 (m), 858 (m), 686 (m); ^1H NMR (400 MHz, CDCl_3): δ 9.22 (1H, s, CH_{ar}), 8.37 (1H, dd, J = 8.0, 1.0 Hz, CH_{ar}), 7.72 (1H, d, J = 8.0 Hz, CH_{ar}), 4.48 (2H, t, J = 9.5 Hz, CH_2), 4.10 (2H, t, J = 9.5 Hz, CH_2); ^{19}F NMR (376.5 MHz, CDCl_3): δ – 68.2; ^{13}C NMR (100.6 MHz, CDCl_3): δ 161.6, 150.0 (q, J = 35.0 Hz), 149.7, 137.1, 126.6, 121.4 (q, J = 274.0 Hz), 120.2, 68.2, 55.2; HRMS: m/z $[\text{MH}]^+$ $\text{C}_9\text{H}_8\text{F}_3\text{N}_2\text{O}$ calcd. 217.0583, found 217.0582.

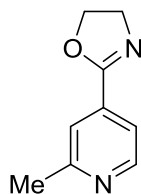
Synthesis of 2-(2-(trifluoromethyl)pyridine-4-yl)-4,5-dihydrooxazole



Following general procedure B, using of *N*-(2-hydroxyethyl)-2-(trifluoromethyl)isonicotinamide (626 mg, 2.67 mmol), *p*-TsCl (866 mg, 4.54 mmol), NEt_3 (513 mg, 5.07 mmol), DMAP (65 mg, 0.53 mmol) and dichloromethane (4.5 mL), then following general procedure B(i), using NaOH pellets (320 mg, 8.01 mmol) and methanol (5 mL), the oxazoline product was afforded as a colourless solid (444 mg, 77%).

M.p.: 49 – 50 °C; FTIR: ν_{max} / cm^{-1} (neat) 2991 (w), 2905 (w), 1653 (m), 1607 (m), 1314 (m), 1250 (m), 1111 (s), 1079 (s), 940 (s), 879 (s); ^1H NMR (400 MHz, CDCl_3): δ 8.83 (1H, d, J = 5.0 Hz, CH_{ar}), 8.19 (1H, app. s, CH_{ar}), 7.98 (1H, dd, J = 5.0, 1.0 Hz, CH_{ar}), 4.52 (2H, t, J = 9.5 Hz, CH_{ar}), 4.14 (2H, t, J = 9.5 Hz, CH_{ar}); ^{19}F NMR (376.5 MHz, CDCl_3): δ – 68.1; ^{13}C NMR (100.6 MHz, CDCl_3): δ 162.1, 150.7, 149.1 (q, J = 35.0 Hz), 137.0, 124.7, 121.4 (q, J = 274.0 Hz), 119.2 (app d, J = 2.5 Hz), 68.5, 55.4; HRMS: m/z $[\text{MH}]^+$ $\text{C}_9\text{H}_8\text{F}_3\text{N}_2\text{O}$ calcd. 217.0583, found 217.0584.

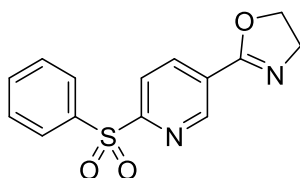
Synthesis of 2-(2-methylpyridin-4-yl)-4,5-dihydrooxazole



Following general procedure B, using of *N*-(2-hydroxyethyl)-2-methylisonicotinamide (507 mg, 2.81 mmol), *p*-TsCl (912 mg, 4.78 mmol), NEt_3 (540 mg, 5.34 mmol), DMAP (69 mg, 0.56 mmol) and dichloromethane (4.7 mL), then following general procedure B(i), using NaOH pellets (337 mg, 8.43 mmol) and methanol (5.6 mL), the oxazoline product was afforded as a tan solid (373 mg, 82%).

M.p.: 58 – 59 °C; FTIR: $\nu_{\text{max}}/\text{cm}^{-1}$ (neat) 2984 (w), 2919 (w), 1650 (m), 1610 (m), 1479 (m), 1375 (s), 1211 (s), 1083 (s), 954 (s); ^1H NMR (400 MHz, CDCl_3): δ 8.57 (1H, d, J = 5.0 Hz, CH_{ar}), 7.65 (1H, app. s, CH_{ar}), 7.56 (1H, dd, J = 5.0, 1.0 Hz, CH_{ar}), 4.45 (2H, t, J = 9.5 Hz, CH_2), 4.08 (2H, t, J = 9.5 Hz, CH_2), 2.59 (3H, s, CH_3); ^{13}C NMR (100.6 MHz, CDCl_3): δ 163.4, 159.3, 149.7, 135.4, 121.6, 119.1, 68.0, 55.2, 24.5; HRMS: m/z $[\text{MH}]^+$ $\text{C}_9\text{H}_{11}\text{N}_2\text{O}$ calcd. 163.0866, found 163.0866.

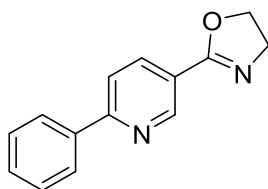
Synthesis of 2-(6-(phenylsulfonyl)pyridine-3-yl)-4,5-dihydrooxazole



To a round bottomed flask was added 2-(2-chloropyridin-3-yl)-4,5-dihydrooxazole (200 mg, 1.10 mmol), benzenesulfinic acid sodium salt (271 mg, 1.65 mmol), tetrabutyl ammonium chloride (92 mg, 0.33 mmol) and DMA (1.60 mL). The reaction mixture was stirred and heated at 100 °C for a period of 24 hours. After cooling to room temperature, deionised water was added (4 mL) and the mixture was stirred for 10 minutes. The observable thick colourless slurry was collected by vacuum filtration, washing with a little deionised water. After drying under vacuum the oxazoline product was afforded as a colourless solid (131 mg, 41%).

M.p.: 189 – 190 °C; FTIR: $\nu_{\text{max}}/\text{cm}^{-1}$ (neat) 3096 (w), 3062 (w), 2908 (w), 1645 (m), 1578 (w), 1307 (m), 1173 (m), 1076 (m), 1019 (w), 761 (s), 687 (s), 607 (s); ^1H NMR (400 MHz, CDCl_3): δ 9.19 – 9.18 (1H, m, CH_{ar}), 8.42 (1H, dd, J = 8.0, 2.0 Hz, CH_{ar}), 8.24 (1H, dd, J = 8.0, 0.5 Hz, CH_{ar}), 8.09 – 8.06 (2H, m, CH_{ar}), 7.69 – 7.59 (1H, m, CH_{ar}), 7.59 – 7.49 (2H, m, CH_{ar}), 4.47 (2H, t, J = 9.5 Hz, CH_2), 4.10 (2H, t, J = 9.5 Hz, CH_2); ^{13}C NMR (100.6 MHz, CDCl_3): δ 161.3, 160.4, 150.1, 138.6, 137.6, 134.0, 129.2, 129.1, 126.8, 121.8, 68.1, 55.2; HRMS: m/z $[\text{MH}]^+$ $\text{C}_{14}\text{H}_{13}\text{N}_2\text{O}_3\text{S}$ calcd. 289.0641, found 289.0645.

Synthesis of 2-(6-phenylpyridin-3-yl)-4,5-dihydrooxazole

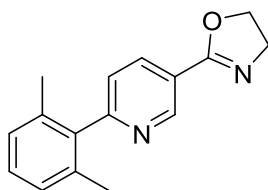


A round bottomed flask equipped with a stirrer bar was added 2-(2-chloropyridin-3-yl)-4,5-dihydrooxazole (183 mg, 1.00 mmol), $\text{PhB}(\text{OH})_2$ (146 mg, 1.2 mmol), $\text{Pd}(\text{OAc})_2$ (5 mg, 2.0 mol %, 0.02 mmol), XPhos (12 mg, 2.4 mol %, 0.024 mmol) and $\text{CsOH}\cdot\text{H}_2\text{O}$ (285 mg, 1.7 mmol). The flask was sealed and placed under an atmosphere of nitrogen, followed by the addition of the degassed

solvents, *n*-BuOH (5.6 mL) and H₂O (1.36 mL). The reaction mixture was then stirred at room temperature for a period of 2 hours. The reaction mixture was then transferred to a separating funnel and the layers were partitioned. The aqueous layer was further extracted with ethyl acetate. The combined organic layers were dried over anhydrous MgSO₄, filtered and the solvent was removed *in vacuo*. The residue was purified by flash column chromatography on silica gel eluting with petroleum ether (40/60) and ethyl acetate (0% ethyl acetate to 100% ethyl acetate) to afford the oxazoline product as a colourless solid (185 mg, 83%).

M.p.: 131 – 132 °C; FTIR: ν_{max} / cm⁻¹ (neat) 3086 (w), 2982 (w), 1649 (m), 1595 (w), 1558 (w), 1370 (m), 1263 (m), 1079 (m), 935 (m), 744 (s), 690 (s); ¹H NMR (400 MHz, CDCl₃): δ 9.20 (1H, d, *J* = 2.0 Hz, CH_{ar}), 8.25 (1H, dd, *J* = 8.5, 2.0 Hz, CH_{ar}), 8.07 – 8.01 (2H, m, CH_{ar}), 7.77 (1H, dd, *J* = 8.5 Hz, 1.0 Hz, CH_{ar}), 7.52 – 7.40 (3H, m, CH_{ar}), 4.45 (2H, t, *J* = 9.5 Hz, CH₂), 4.08 (2H, t, *J* = 9.5 Hz, CH₂); ¹³C NMR (100.6 MHz, CDCl₃): δ 162.9, 159.6, 149.5, 138.6, 136.4, 129.7, 129.0, 127.3, 122.2, 119.9, 67.8, 55.1; HRMS: *m/z* [MH]⁺ C₁₄H₁₃N₂O calcd. 225.1022, found 225.1021.

Synthesis of 2-(6-(2,6-dimethylphenyl)pyridine-3-yl)-4,5-dihydrooxazole

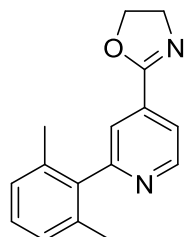


A round bottomed flask equipped with a stirrer bar was added 2-(2-chloropyridin-3-yl)-4,5-dihydrooxazole (120 mg, 0.660 mmol), 2,6-dimethylphenyl boronic acid (148 mg, 0.990 mmol), XPhosPdG2 (26 mg, 5 mol %, 0.033 mmol) and CsOH.H₂O (188 mg, 1.12 mmol). The flask was sealed and placed under an atmosphere of nitrogen, followed by the addition of the degassed solvents, 1,2-DME (3.73 mL) and H₂O (0.91 mL). The reaction mixture was then stirred at 80 °C for a period of 18 hours. The reaction mixture was then cooled to room temperature, and transferred to a separating funnel. Ethyl acetate was added and the layers were partitioned. The aqueous layer was further extracted with ethyl acetate. The combined organic layers were dried over anhydrous MgSO₄, filtered and the solvent was removed *in vacuo*. The residue was purified by flash column chromatography on silica gel eluting with petroleum ether (40/60) and ethyl acetate (0% ethyl acetate to 80% ethyl acetate) to afford the oxazoline product as a colourless oil (99 mg, 59%).

FTIR: ν_{max} / cm⁻¹ 3016 (w), 2966 (w), 2909 (w), 1646 (s), 1600 (m), 1461 (m), 1375 (s), 1257 (s), 1083 (s), 1018 (s), 936 (s), 765 (s); ¹H NMR (400 MHz, CDCl₃): δ 9.25 (1H, dd, *J* = 2.0, 1.0 Hz, CH_{ar}), 8.28 (1H, dd, *J* = 8.0, 2.0 Hz, CH_{ar}), 7.29 (1H, dd, *J* = 8.0, 1.0 Hz, CH_{ar}), 7.19 (1H, t, *J* = 7.0 Hz, CH_{ar}), 7.09 (2H, d, *J*

= 7.0 Hz, CH_{ar}), 4.48 (2H, t, J = 9.5 Hz, CH_2), 4.10 (2H, t, J = 9.5 Hz, CH_2), 2.03 (6H, s, CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 163.0, 162.7, 149.5, 139.9, 135.9, 135.7, 128.3, 127.7, 124.2, 122.0, 67.9, 55.1, 20.3; HRMS: m/z $[MH]^+$ $C_{16}H_{17}N_2O$ calcd. 253.1335, found 253.1337.

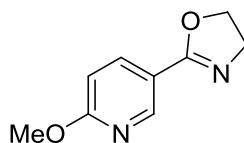
Synthesis of 2-(2-(2,6-dimethylphenyl)pyridine-4-yl)-4,5-dihydrooxazole



A round bottomed flask equipped with a stirrer bar was added 2-(2-chloropyridin-4-yl)-4,5-dihydrooxazole (120 mg, 0.660 mmol), 2,6-dimethylphenyl boronic acid (148 mg, 0.990 mmol), XPhosPdG2 (26 mg, 5 mol %, 0.033 mmol) and $CsOH \cdot H_2O$ (188 mg, 1.12 mmol). The flask was sealed and placed under an atmosphere of nitrogen, followed by the addition of the degassed solvents, 1,2-DME (3.73 mL) and H_2O (0.91 mL). The reaction mixture was then stirred at 80 °C for a period of 18 hours. The reaction mixture was then cooled to room temperature, and transferred to a separating funnel. Ethyl acetate was added and the layers were partitioned. The aqueous layer was further extracted with ethyl acetate. The combined organic layers were dried over anhydrous $MgSO_4$, filtered and the solvent was removed *in vacuo*. The residue was purified by flash column chromatography on silica gel eluting with petroleum ether (40/60) and ethyl acetate (0% ethyl acetate to 80% ethyl acetate) to afford the oxazoline product as a colourless oil (125 mg, 75%).

FTIR: ν_{max}/cm^{-1} 3019 (w), 2980 (w), 1650 (m), 1596 (m), 1400 (m), 1225 (m), 1079 (m), 947 (s), 772 (s), 751 (s); 1H NMR (400 MHz, $CDCl_3$): δ 8.81 (1H, dd, J = 5.0, 1.0 Hz, CH_{ar}), 7.75 (1H, dd, J = 5.0, 1.5 Hz, CH_{ar}), 7.74 – 7.73 (1H, m, CH_{ar}), 7.18 (1H, dd, J = 8.0, 7.0 Hz, CH_{ar}), 7.10 (1H, app. s, CH_{ar}), 7.08 (1H, app. s, CH_{ar}), 4.46 (2H, t, J = 9.5 Hz, CH_2), 4.09 (2H, t, J = 9.5 Hz, CH_2), 2.03 (6H, s, CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 163.2, 160.8, 150.3, 140.0, 135.8, 135.6, 128.1, 127.7, 122.8, 120.0, 68.0, 55.2, 20.3; HRMS: m/z $[MH]^+$ $C_{16}H_{17}N_2O$ calcd. 253.1335, found 253.1337.

Synthesis of 2-(6-methoxypyridin-3-yl)-4,5-dihydrooxazole

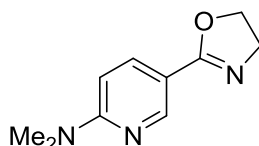


To a round bottomed flask was added 2-(2-chloropyridin-3-yl)-4,5-dihydrooxazole (1.09 g, 5.97 mmol), NaOH pellets (717 mg, 17.9 mmol) and methanol (12 mL). The reaction mixture was stirred

at room temperature for 6 hours. The reaction mixture was then concentrated, dissolved in dichloromethane and water, and transferred to a separating funnel. The layers were partitioned and the aqueous layer was further extracted with dichloromethane. The combined organic layers were dried over anhydrous MgSO_4 , filtered and the solvent was removed *in vacuo* to afford the oxazoline product as a colourless amorphous solid (845 mg, 79%).

FTIR: $\nu_{\text{max}}/\text{cm}^{-1}$ (neat) 2944 (w), 1655 (m), 1600 (m), 1495 (s), 1284 (s), 1072 (s); ^1H NMR (400 MHz, CDCl_3): δ 8.59 (1H, app. d, $J = 2.0$ Hz, CH_{ar}), 7.97 (1H, dd, $J = 8.5, 2.0$ Hz, CH_{ar}), 6.64 (1H, dd, $J = 8.5, 1.0$ Hz, CH_{ar}), 4.29 (2H, t, $J = 9.5$ Hz, CH_2), 3.91 (2H, t, $J = 9.5$ Hz, CH_2), 3.86 (3H, s, OMe); ^{13}C NMR (100.6 MHz, CDCl_3): δ 165.7, 162.7, 147.5, 138.1, 117.3, 110.6, 67.5, 54.8, 53.7; HRMS: m/z $[\text{MH}]^+$ $\text{C}_9\text{H}_{11}\text{N}_2\text{O}_2$ calcd. 179.0821, found 179.0814.

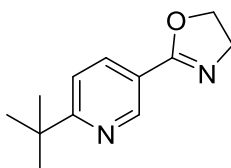
Synthesis of 5-(4,5-dihydrooxazol-2-yl)-N,N-dimethylpyridin-2-amine



To a sealed tube equipped with a stirrer bar was added 2-(2-chloropyridin-3-yl)-4,5-dihydrooxazole (85 mg, 0.47 mmol) and PhMe (3.88 mL). Dimethylamine (3.95 mL, 2.0 M in THF, 7.90 mmol) was then added via syringe, followed by sealing the tube with a Teflon lined cap. The reaction mixture was stirred and heated to 120 °C for a period of 36 hours. After cooling to room temperature, the reaction mixture was concentrated and the residue was dry loaded onto silica gel and purified by flash column chromatography on silica gel, eluting with 20% methanol in dichloromethane to afford the oxazoline product as a yellow solid (35 mg, 39%).

M.p.: 138 – 139 °C; FTIR: $\nu_{\text{max}}/\text{cm}^{-1}$ (neat) 3044 (w), 2971 (w), 1643 (m), 1598 (s), 1516 (s), 1311 (s), 1254 (s), 1077 (m), 933 (s); ^1H NMR (400 MHz, CDCl_3): δ 8.67 (1H, app. s, CH_{ar}), 7.94 (1H, dd, $J = 9.0, 2.0$ Hz, CH_{ar}), 6.48 (1H, d, $J = 9.0$ Hz, CH_{ar}), 4.37 (2H, t, $J = 9.0$ Hz, CH_2), 3.99 (2H, t, $J = 9.0$ Hz, CH_2), 3.13 (6H, s, NMe_2); ^{13}C NMR (100.6 MHz, CDCl_3): δ 163.9, 160.3, 148.9, 136.9, 111.6, 104.9, 67.4, 54.8, 38.2; HRMS: m/z $[\text{MH}]^+$ $\text{C}_{10}\text{H}_{14}\text{N}_3\text{O}$ calcd. 192.1121, found 192.1133.

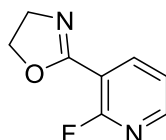
Synthesis of 2-(6-(tert-butyl)pyridine-3-yl)-4,5-dihydrooxazole



To a round bottomed flask was added 2-(2-chloropyridin-3-yl)-4,5-dihydrooxazole (700 mg, 3.83 mmol) and copper (I) iodide (365 mg, 50 mol %, 1.92 mmol). The flask was then placed under an atmosphere of nitrogen followed by the addition of THF (6.4 mL). The reaction was stirred and cooled to 0 °C using an ice/water bath. *Tert*-butyl magnesium chloride (4.0 mL, 1.42 M in THF, 5.75 mmol) was then added dropwise, upon complete addition the ice/water bath was removed and the reaction mixture was stirred at room temperature overnight. The reaction was quenched by the addition of saturated NH₄Cl (aq.) solution (approx. 10 mL) and stirred for 10 – 15 mins. The reaction mixture was then transferred to a separating funnel where ethyl acetate and aqueous ammonia solution (35 %) were added. The layers were partitioned and the aqueous layer was further extracted with ethyl acetate. The combined organic layers were dried over anhydrous MgSO₄, filtered and the solvent was removed *in vacuo*. The residue was purified by flash column chromatography on silica gel eluting with petroleum ether (40/60) and ethyl acetate (0% ethyl acetate to 60% ethyl acetate) to afford the oxazoline product as a yellow amorphous solid (334 mg, 43%).

FTIR: ν_{max} / cm⁻¹ (neat) 2966 (w), 2912 (w), 1639 (s), 1593 (m), 1486 (m), 1368 (m), 1261 (s), 1129 (m), 1076 (s), 940 (s); ¹H NMR (400 MHz, CDCl₃): δ 9.05 (1H, dd, *J* = 2.0, 0.5 Hz, CH_{ar}), 8.11 (1H, dd, *J* = 8.0, 2.0 Hz, CH_{ar}), 7.36 (1H, dd, *J* = 8.0, 0.5 Hz, CH_{ar}), 4.42 (2H, t, *J* = 9.5 Hz, CH₂), 4.04 (2H, t, *J* = 9.5 Hz, CH₂), 1.36 (9H, s, C(CH₃)₃); ¹³C NMR (100.6 MHz, CDCl₃): δ 172.4, 163.1, 148.4, 135.9, 121.0, 118.7, 67.7, 55.0, 37.9, 30.2; HRMS: *m/z* [MH]⁺ C₁₂H₁₇N₂O calcd. 205.1335, found 205.1338.

Synthesis of 2-(2-fluoropyridin-3-yl)-4,5-dihydrooxazole

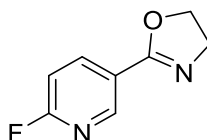


To a stirred solution of 2-fluoro-3-pyridine carboxylic acid (500 mg, 3.54 mmol) in dry dichloromethane (17 mL) at 0 °C was added oxalyl chloride (1.35 g, 10.6 mmol) and DMF (few drops). The reaction was allowed to warm to room temperature and stirred for a period of 3 hours before removing the solvent *in vacuo*. The crude residue was then dissolved in dry dichloromethane (17 mL) and cooled to 0 °C using an ice bath. Triethylamine (1.07 g, 10.6 mmol) was then added, followed by ethanolamine (260 mg, 4.25 mmol) via syringe. The reaction was allowed to warm to room temperature and stir overnight. The reaction was then dry loaded onto silica gel and purified by flash column chromatography on silica gel eluting with dichloromethane and methanol (0 to 2% methanol) to afford the amide product (316 mg, 1.72 mmol). Without further purification or

characterisation, the amide was carried forward to yield the oxazoline. Following general procedure B, using *p*-TsCl (557 mg, 2.92 mmol), NEt₃ (331 mg, 3.27 mmol), DMAP (42 mg, 0.34 mmol) and dichloromethane (2.9 mL) then following general procedure B(ii), using K₂CO₃ (713 mg, 5.16 mmol) and MeCN (3.5 mL), the oxazoline product was afforded as a colourless solid (181 mg, 31% over two steps).

M.p.: 60 – 61 °C; FTIR: ν_{max} / cm⁻¹ 3072 (w), 2987 (w), 1646 (m), 1608 (m), 1447 (m), 1434 (m), 1264 (m), 1040 (s), 942 (m); ¹H NMR (400 MHz, CDCl₃): δ 8.33 – 8.27 (2H, m, CH_{ar}), 7.29 – 7.24 (1H, m, CH_{ar}), 4.44 (2H, t, *J* = 9.5 Hz, CH₂), 4.12 (2H, t, *J* = 9.5 Hz, CH₂); ¹⁹F NMR (376.5 MHz, CDCl₃): δ – 62.4; ¹³C NMR (100.6 MHz, CDCl₃): δ 161.1 (d, *J* = 248.0 Hz), 160.1 (d, *J* = 9.5 Hz), 150.1 (d, *J* = 15.0 Hz), 141.9 (d, *J* = 2.0 Hz), 121.4 (d, *J* = 5.0 Hz), 111.6 (d, *J* = 25.5 Hz), 55.5, 67.7; HRMS: *m/z* [MH]⁺ C₈H₈FN₂O calcd. 167.0615, found 167.0613.

Synthesis of 2-(6-fluoropyridin-3-yl)-4,5-dihydrooxazole



To a stirred solution of 2-fluoro-5-pyridine carboxylic acid (500 mg, 3.54 mmol) in dry dichloromethane (17 mL) at 0 °C was added oxalyl chloride (1.35 g, 10.6 mmol) and DMF (few drops). The reaction was allowed to warm to room temperature and stirred for a period of 3 hours before removing the solvent *in vacuo*. The crude residue was then dissolved in dry dichloromethane (17 mL) and cooled to 0 °C using an ice bath. Triethylamine (1.07 g, 10.6 mmol) was then added, followed by ethanolamine (260 mg, 4.25 mmol) via syringe. The reaction was allowed to warm to room temperature and stir overnight. The reaction was then dry loaded onto silica gel and purified by flash column chromatography on silica gel eluting with dichloromethane and methanol (0 to 5% methanol) to afford the amide product (287 mg, 1.56 mmol). Without further purification or characterisation, the amide was carried forward to yield the oxazoline. Following general procedure B, using *p*-TsCl (506 mg, 2.65 mmol), NEt₃ (300 mg, 2.96 mmol), DMAP (38 mg, 0.31 mmol) and dichloromethane (2.6 mL) then following general procedure B(ii), using K₂CO₃ (647 mg, 4.68 mmol) and MeCN (3.1 mL), the oxazoline product was afforded as a colourless solid (191 mg, 32% over two steps).

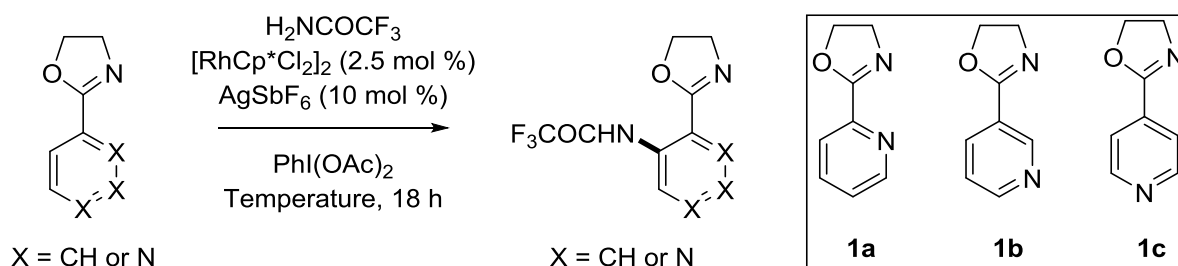
M.p.: 72 – 73 °C; FTIR: ν_{max} / cm⁻¹ 3052 (w), 2967 (w), 1653 (m), 1594 (m), 1383 (s), 1079 (s), 935 (s), 853 (m), 834 (m); ¹H NMR (400 MHz, CDCl₃): δ 8.76 (1H, d, *J* = 2.5 Hz, CH_{ar}), 8.32 (1H, ddd, *J* = 8.5, 7.0, 2.5 Hz, CH_{ar}), 6.97 (1H, dd, *J* = 8.5, 2.5 Hz, CH_{ar}), 4.46 (2H, t, *J* = 9.5 Hz, CH₂), 4.07 (2H, t, *J* = 9.5 Hz, CH-

2); ^{19}F NMR (376.5 MHz, CDCl_3): δ – 63.7; ^{13}C NMR (100.6 MHz, CDCl_3): δ 165.1 (d, J = 244.0 Hz), 161.2, 148.3 (d, J = 16.0 Hz), 141.2 (d, J = 9.0 Hz), 122.3, 109.6 (d, J = 37.5 Hz), 68.1, 55.1; HRMS: m/z $[\text{MH}]^+$ $\text{C}_8\text{H}_8\text{FN}_2\text{O}$ calcd. 167.0615, found 167.0615.

7. Details of Initial Optimization Studies

Reactions were performed following general procedure C(i) on a 0.2 mmol scale with substrates **1a** –

1c. Trace reaction product was observed by LCMS in entries 6 to 8.

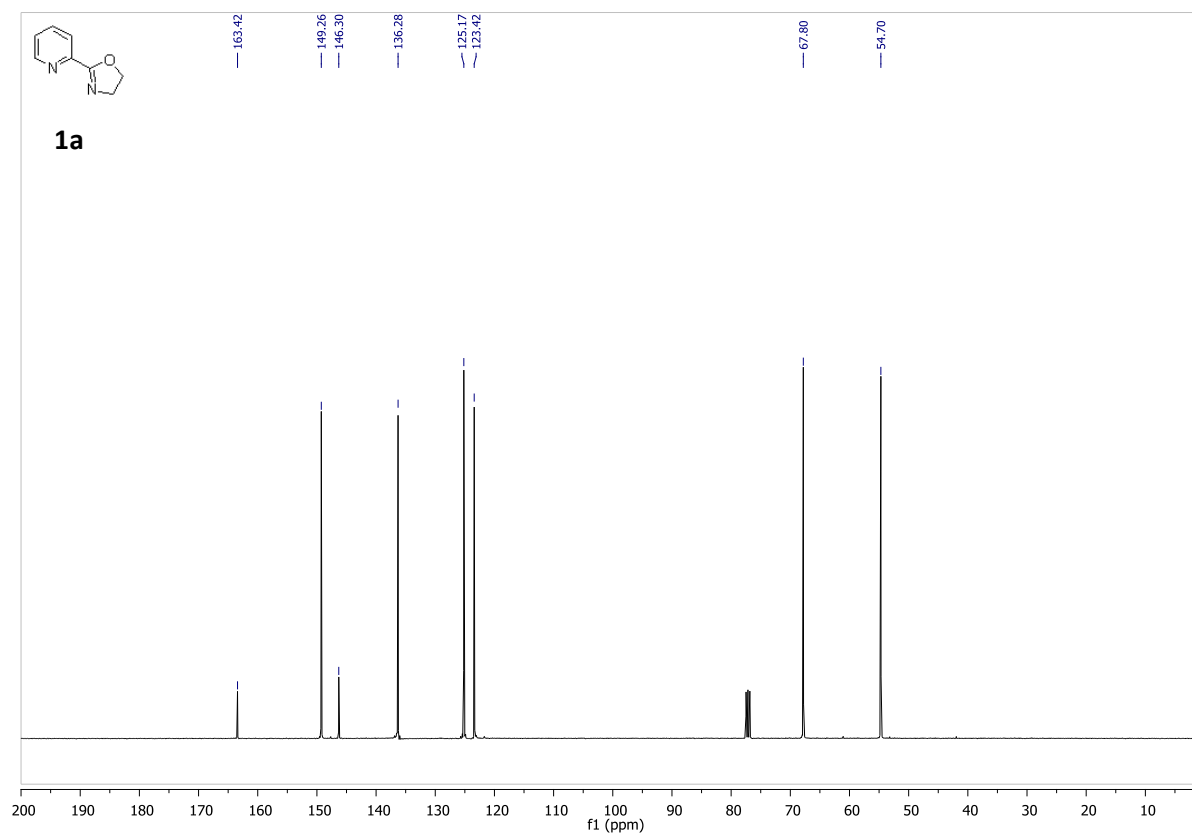
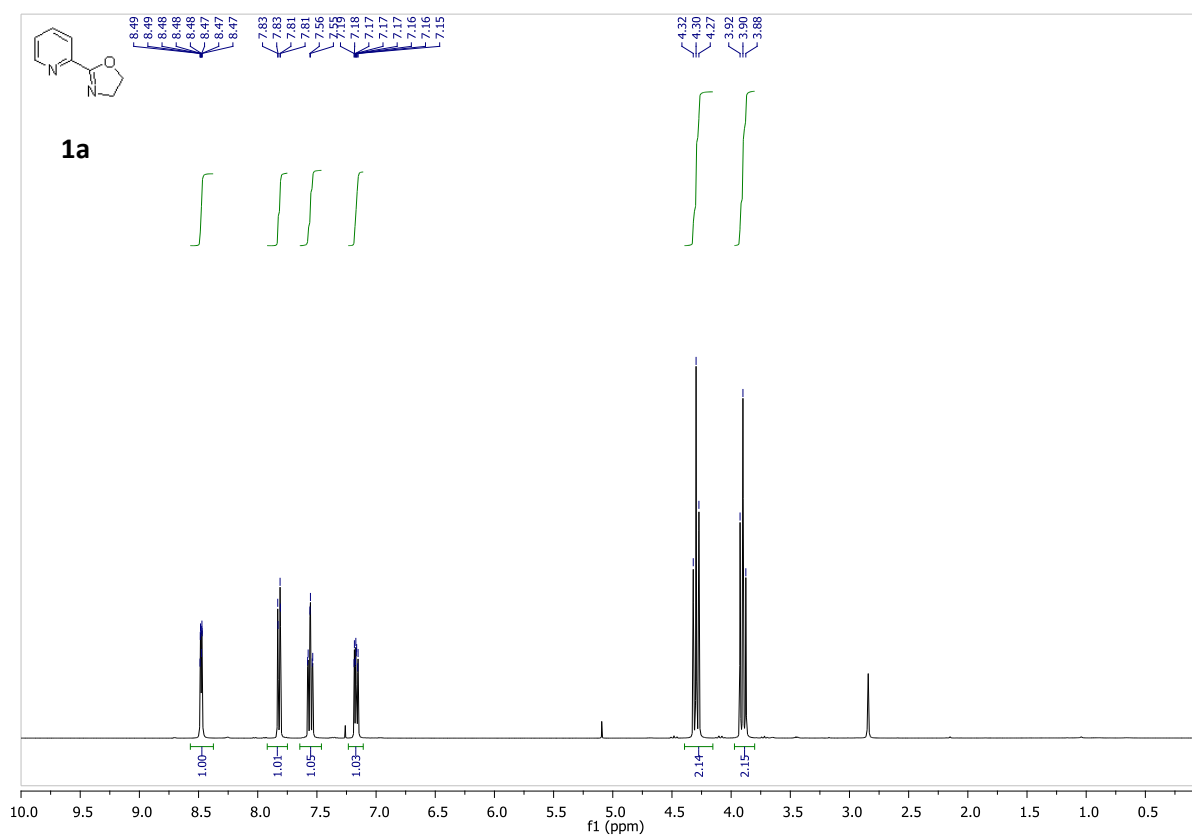


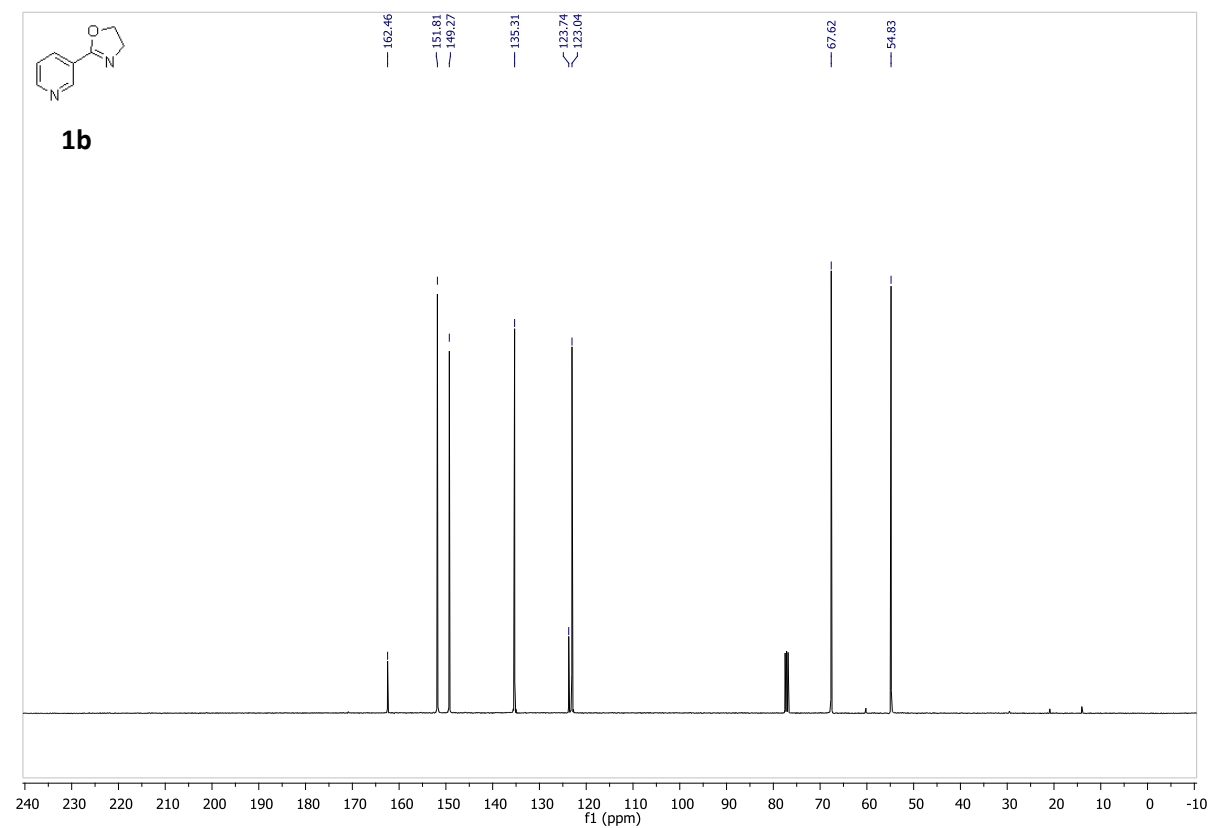
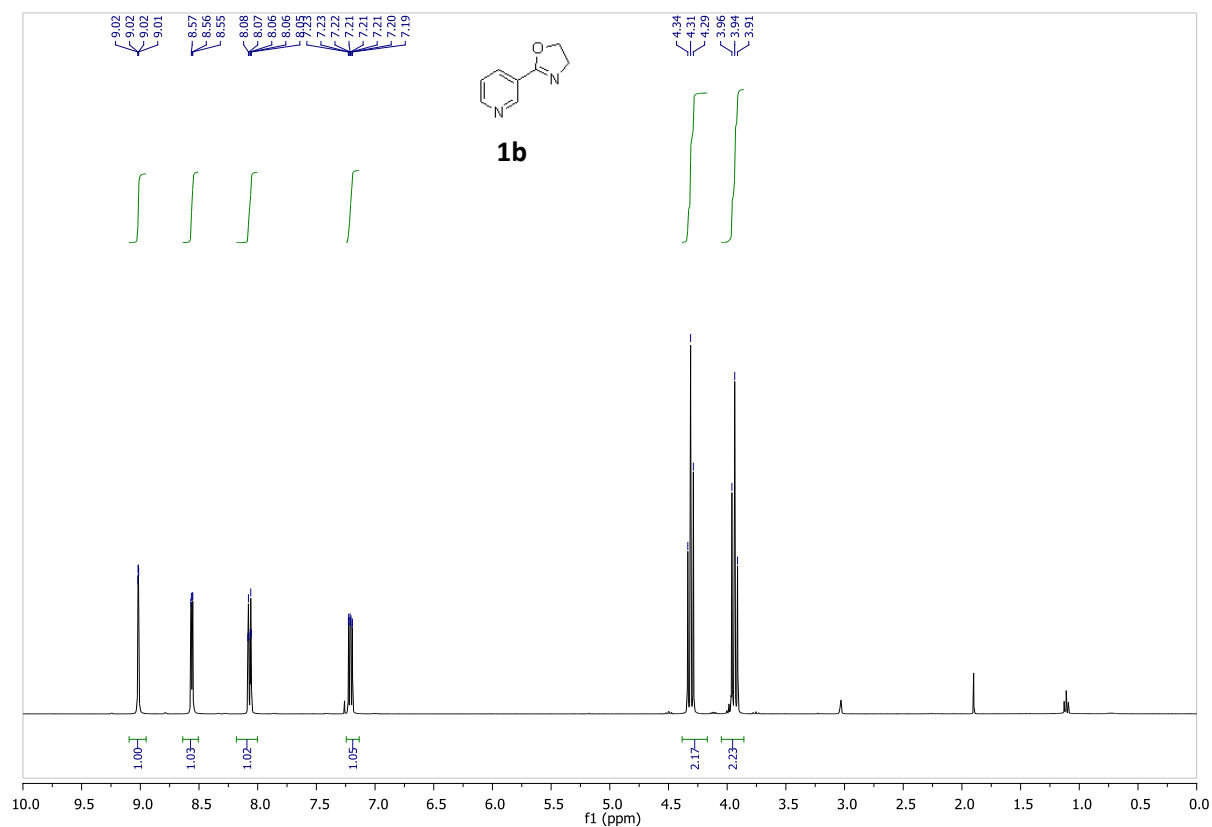
Entry	Substrate	Solvent	Temperature	Time	Additive	Result
1	1a	CH_2Cl_2	40 °C	18 h	-	0%
2	1b	CH_2Cl_2	40 °C	18 h	-	0%
3	1c	CH_2Cl_2	40 °C	18 h	-	0%
4	1a	1,2-DCE	100 °C	18 h	-	0%
5	1b	1,2-DCE	100 °C	18 h	-	0%
6	1c	1,2-DCE	100 °C	18 h	-	Trace
7	1c	1,2-DCE	100 °C	48 h	-	Trace
8	1c	1,2-DCE	120 °C	18 h	-	Trace
9	1c	1,2-DCE	100 °C	22 h	CuSO_4 (1.2 eq.)	0%
10	1c	1,2-DCE	100 °C	22 h	CuSO_4 (1.2 eq.) (Pre-stir with C)	0%

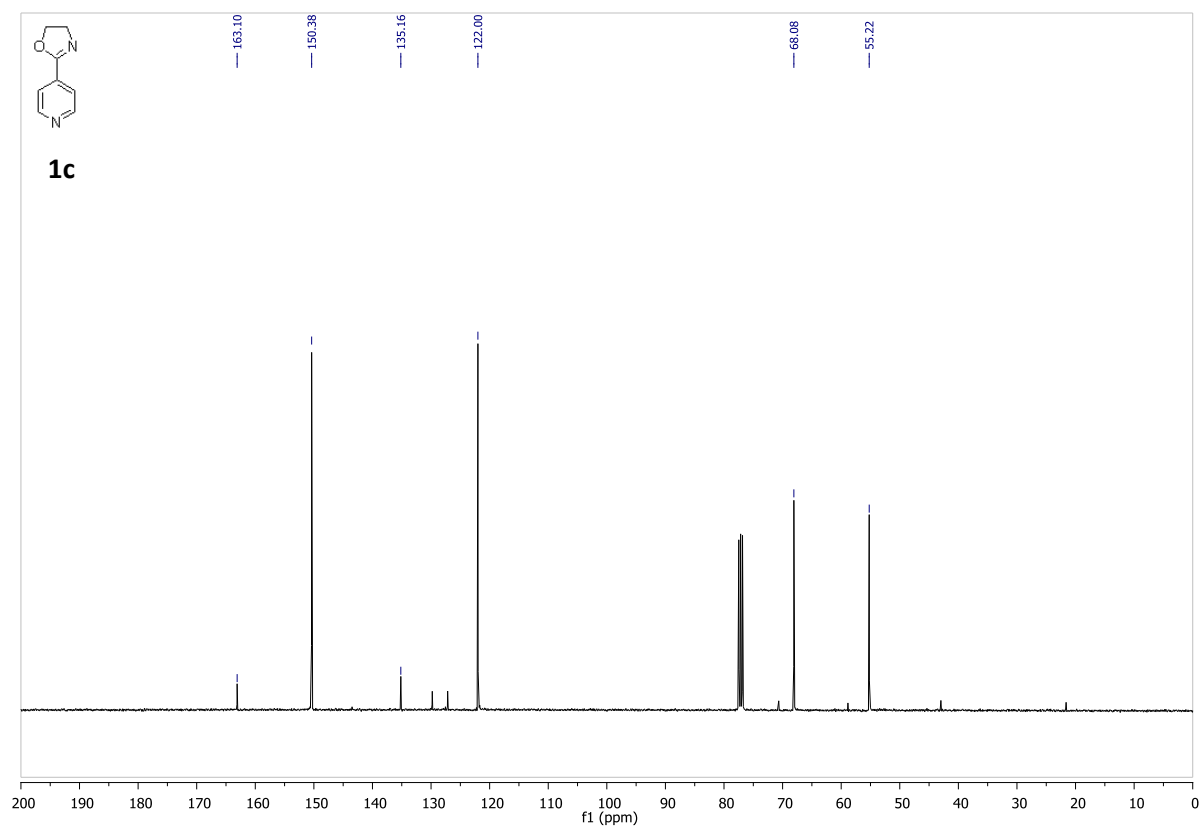
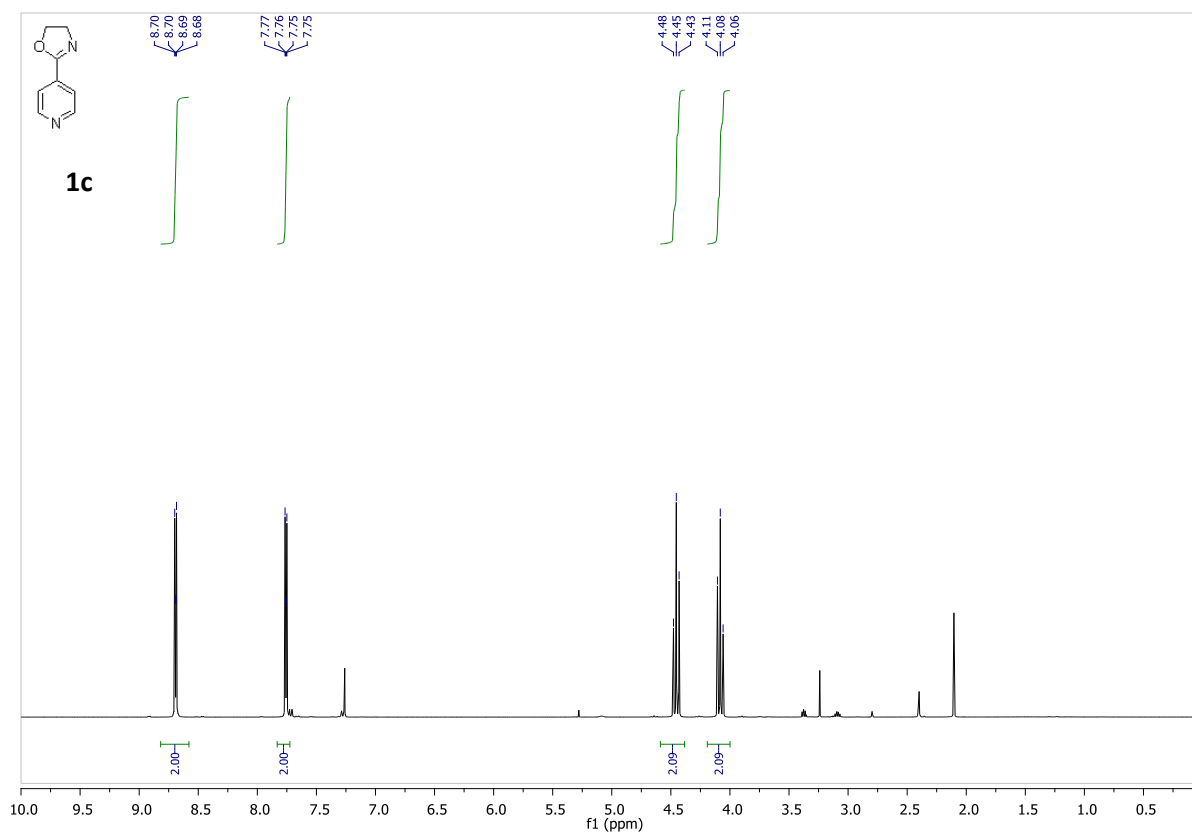
8. Deuterium Labelling Experiments

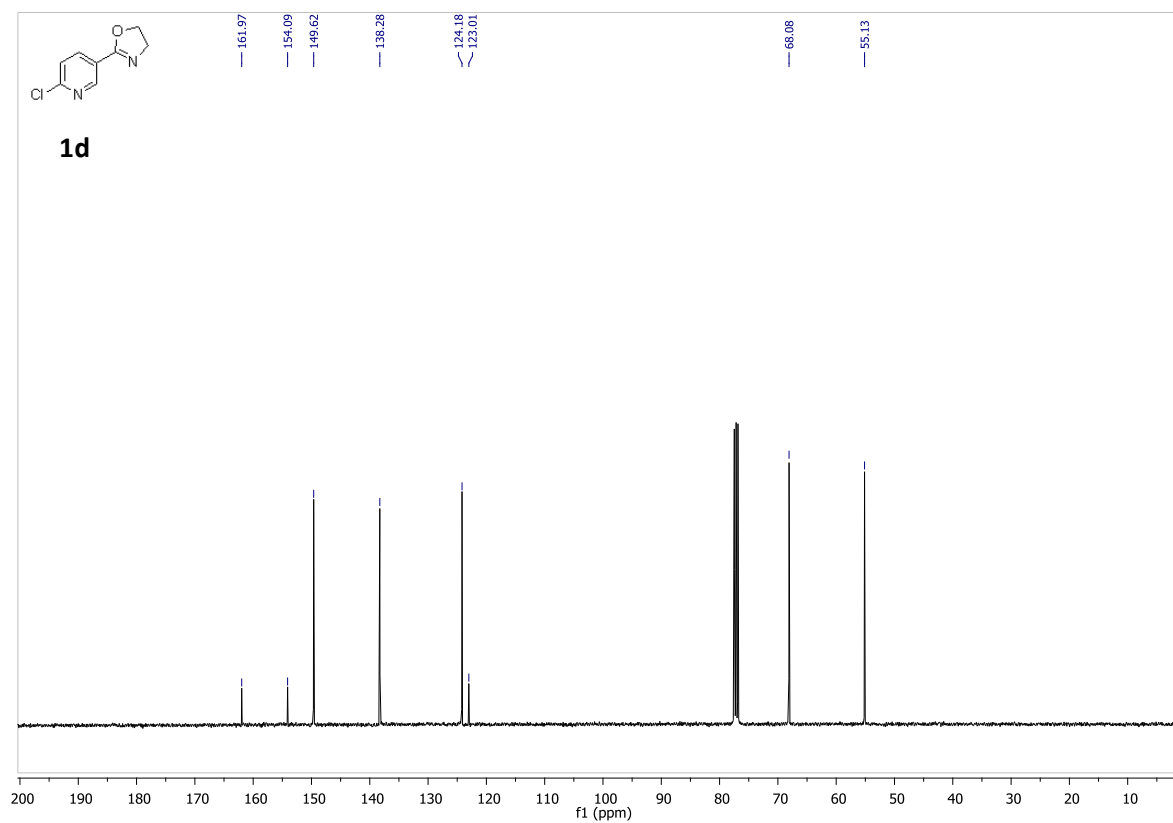
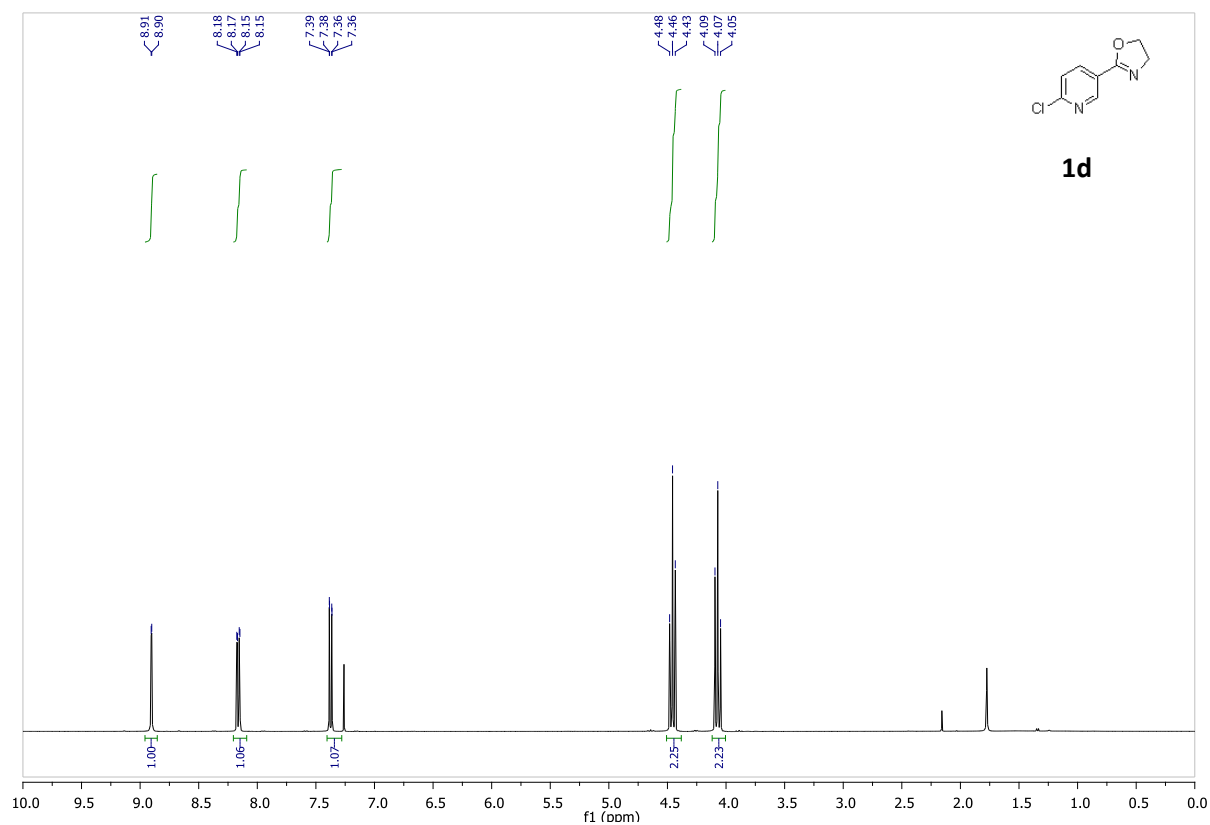
General procedure D: To a dried Schlenk tube was added oxazoline (1.2 eq.), $[\text{Cp}^*\text{RhCl}_2]_2$ (2.5 mol %), AgSbF_6 (10 mol %), $\text{PhI}(\text{OAc})_2$ (1.5 eq.) and trifluoroacetamide (1.0 eq.). The tube was fitted with a rubber septum, and placed under an atmosphere of nitrogen, followed by the addition of dry dichloromethane and deuterated methanol (9:1 respectively, 0.1 M). The septum was replaced by a Teflon screwcap under nitrogen flow. The reaction mixture was stirred at 40 – 45 °C for 18 – 20 h. After cooling to room temperature the solvent was removed in *vacuo* and the residue was purified by flash column chromatography on silica gel eluting with petroleum ether (40/60) followed by dichloromethane to afford the reaction products.

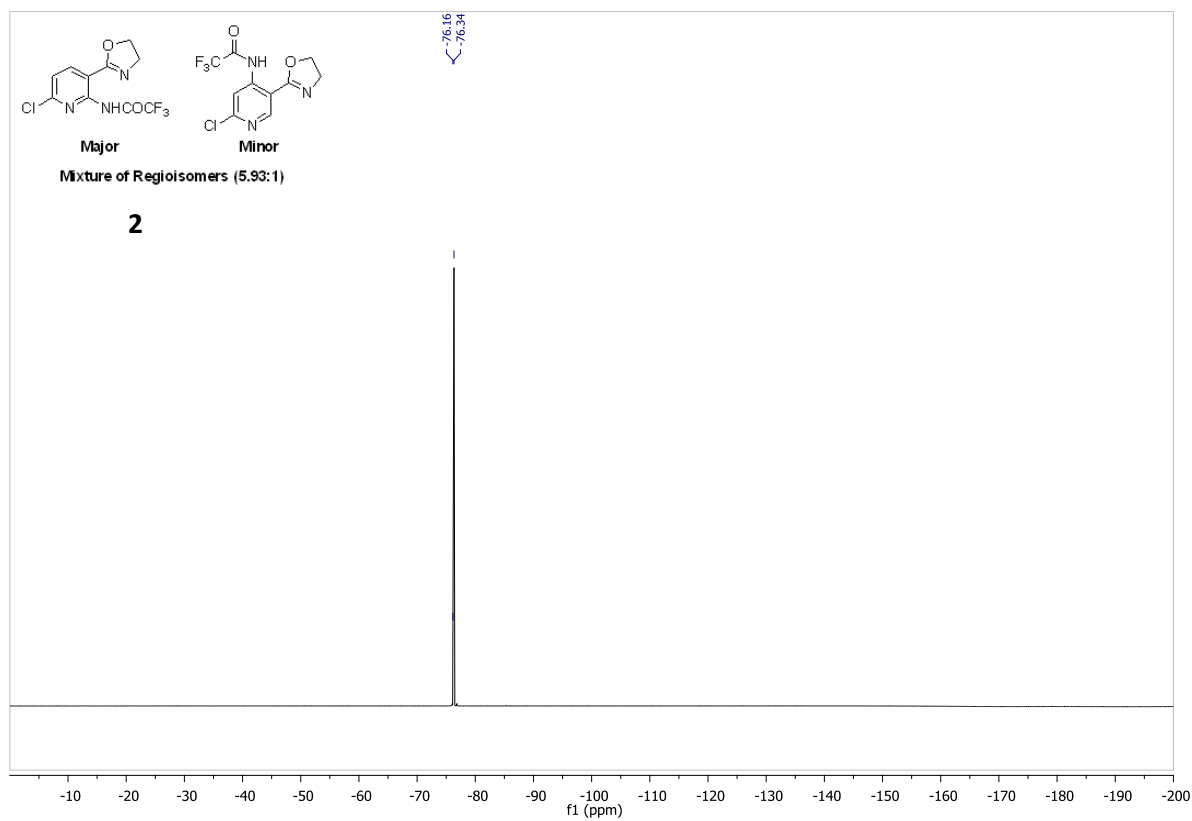
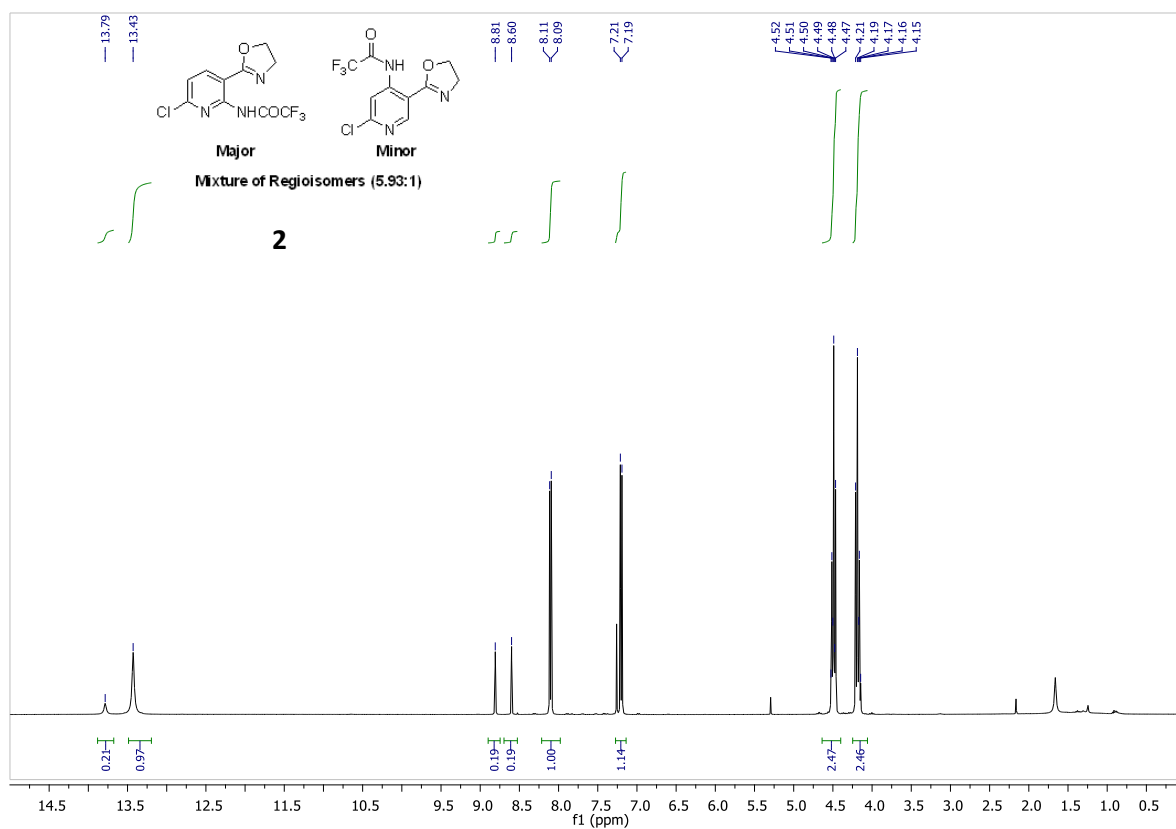
Deuterium incorporation experiments were performed with substrates **20a**, **20b** and **20c** on a 0.20 mmol scale. In all cases no deuterium incorporation was observed. The starting material was recovered following purification of the reaction mixture.

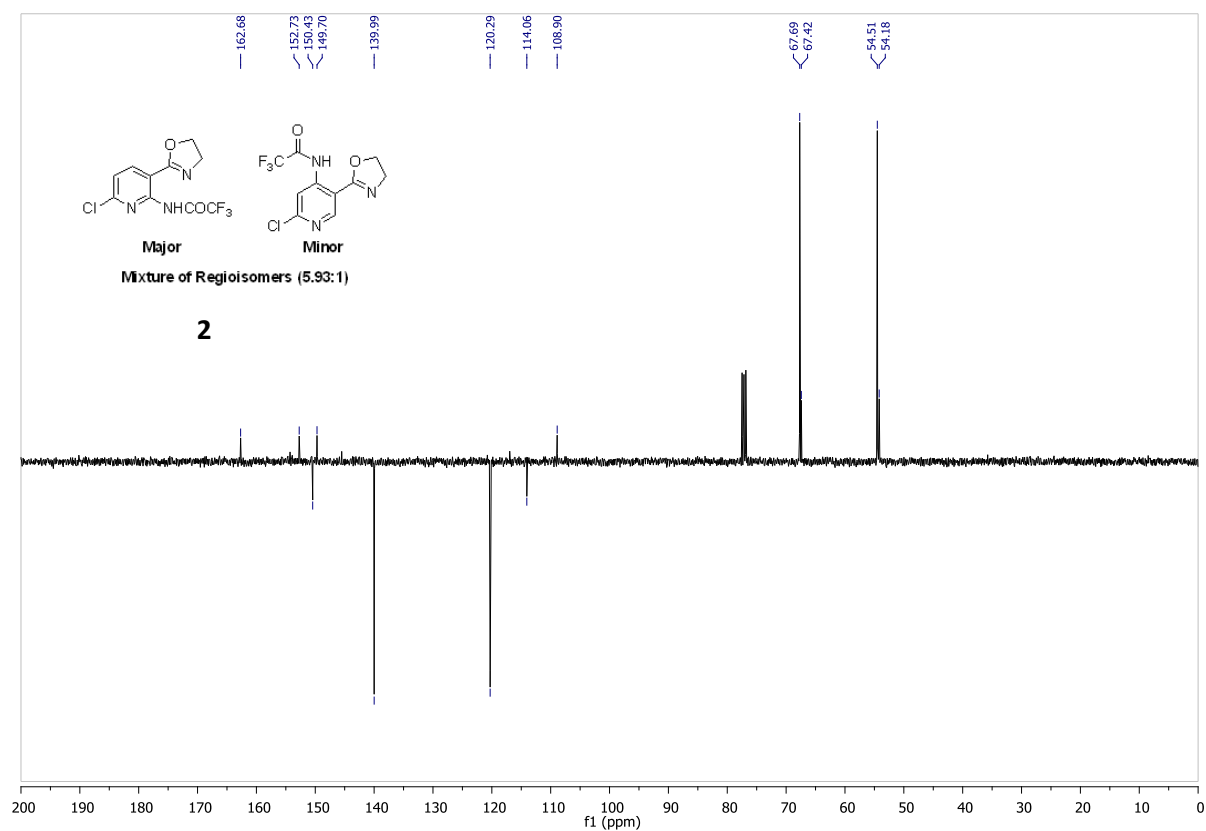
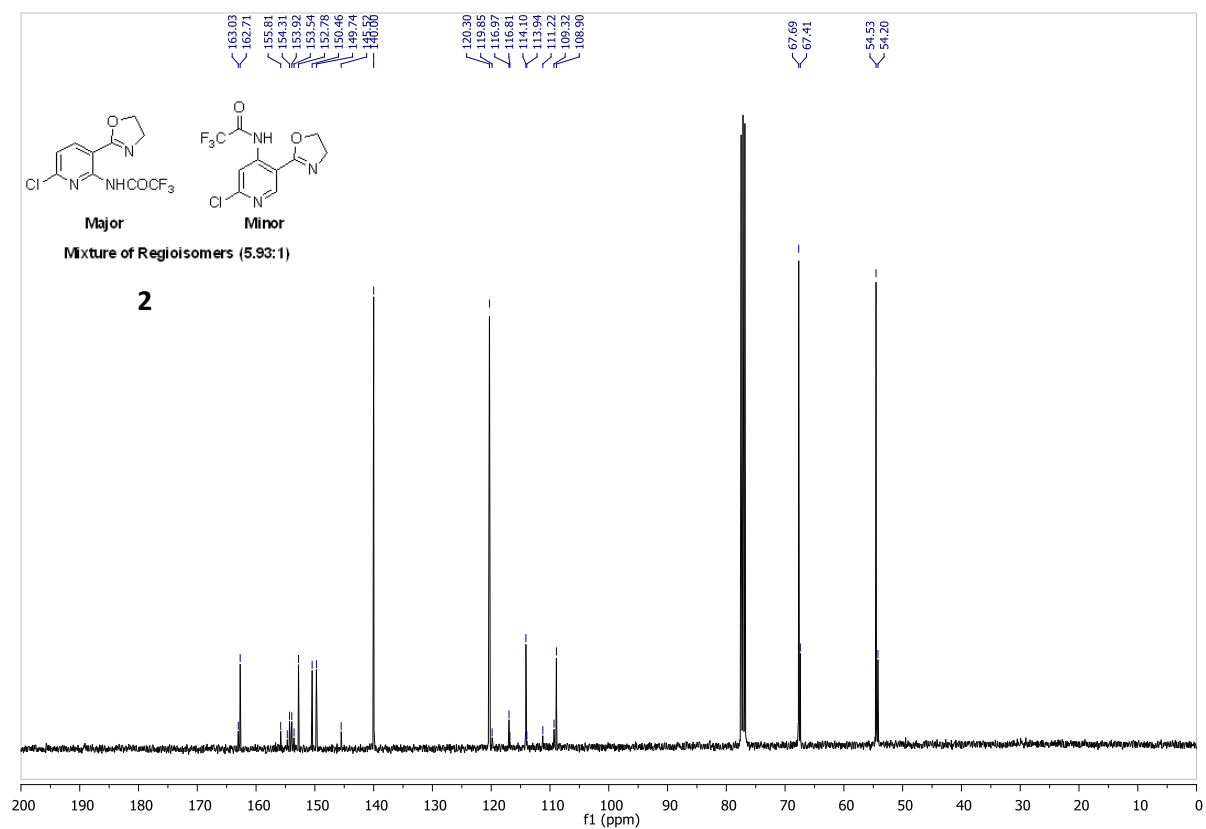
9. Spectral Data

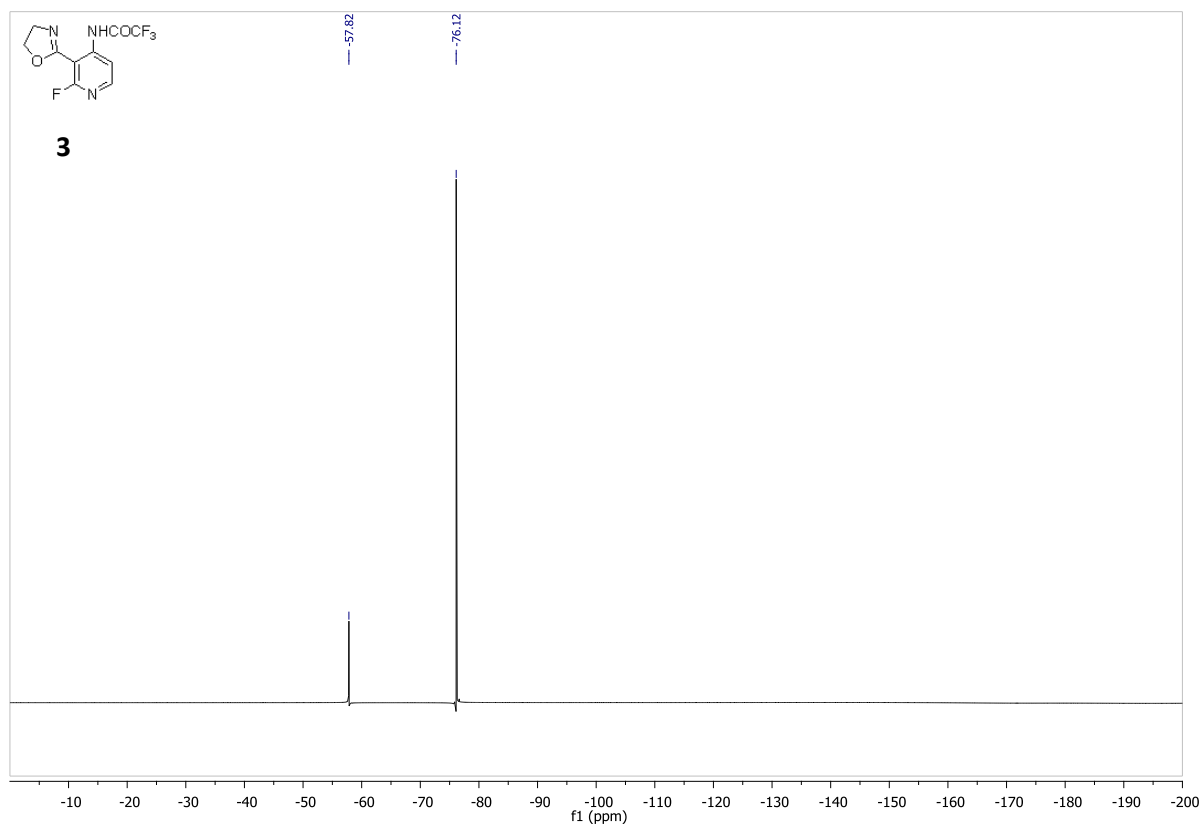
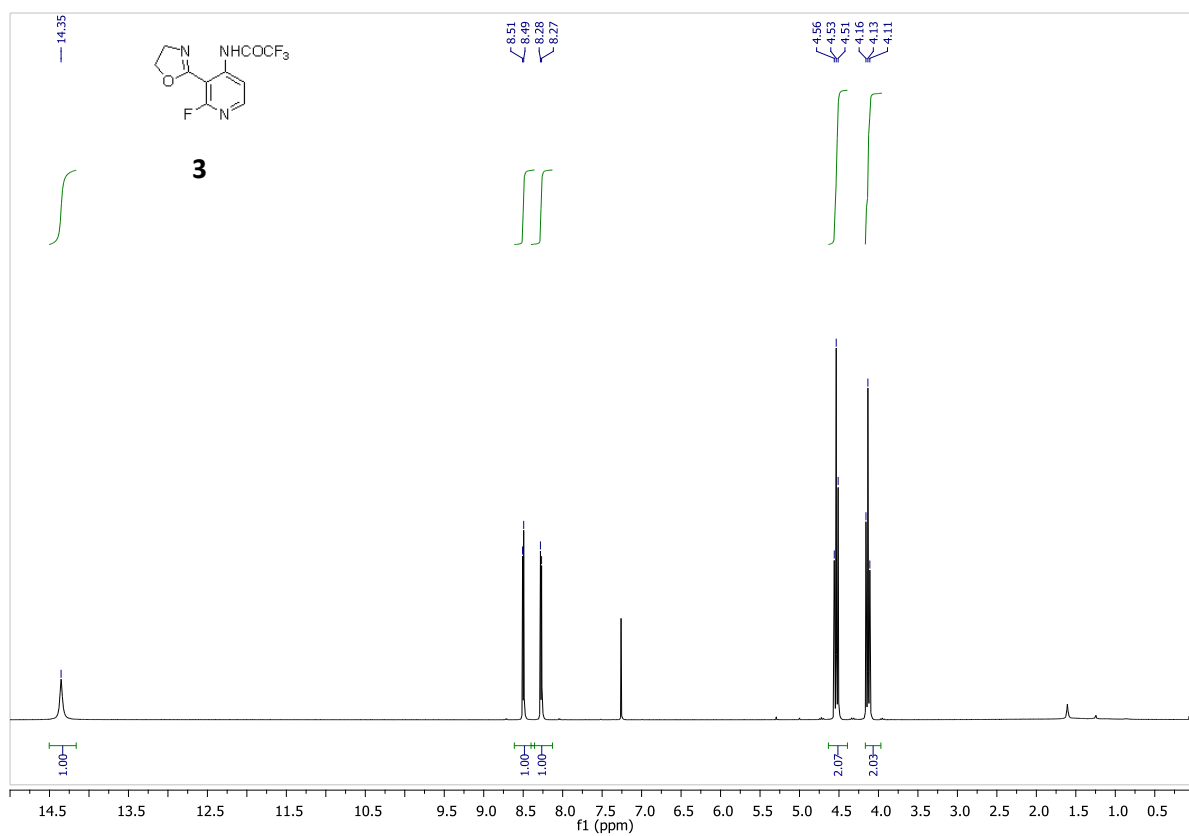


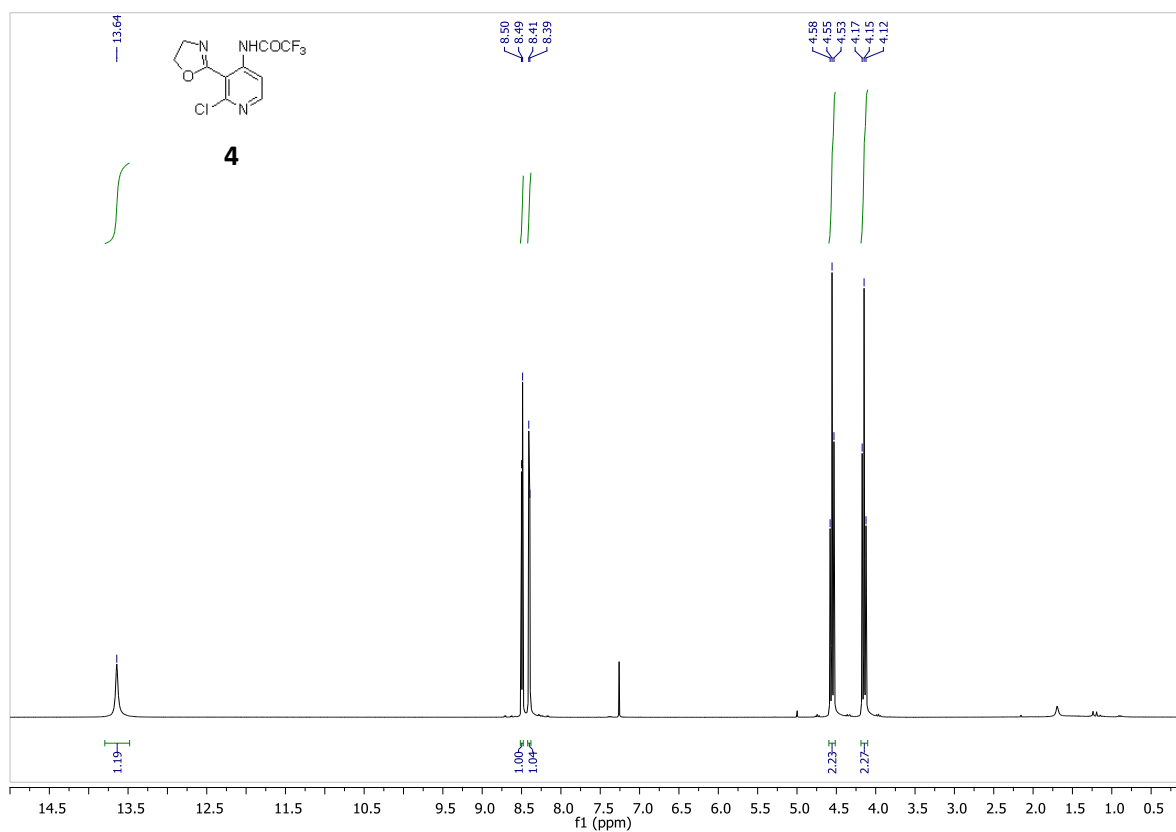
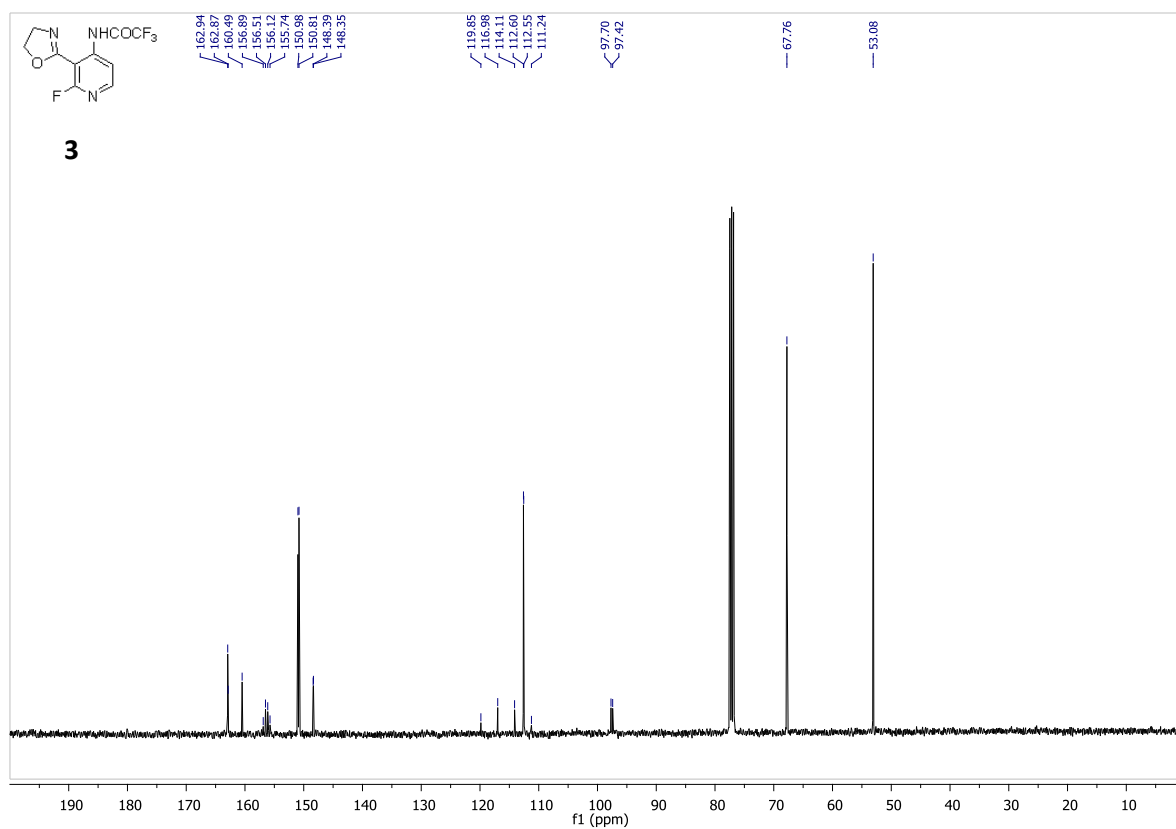


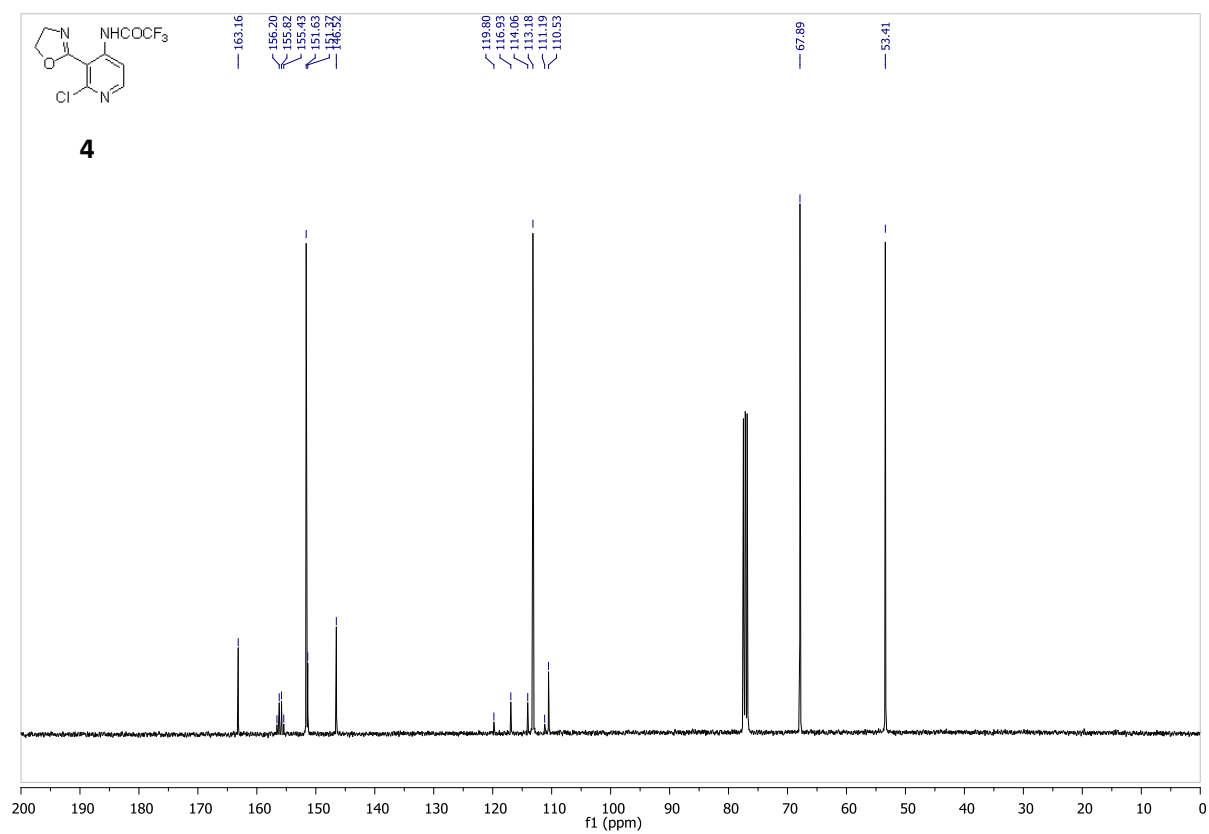
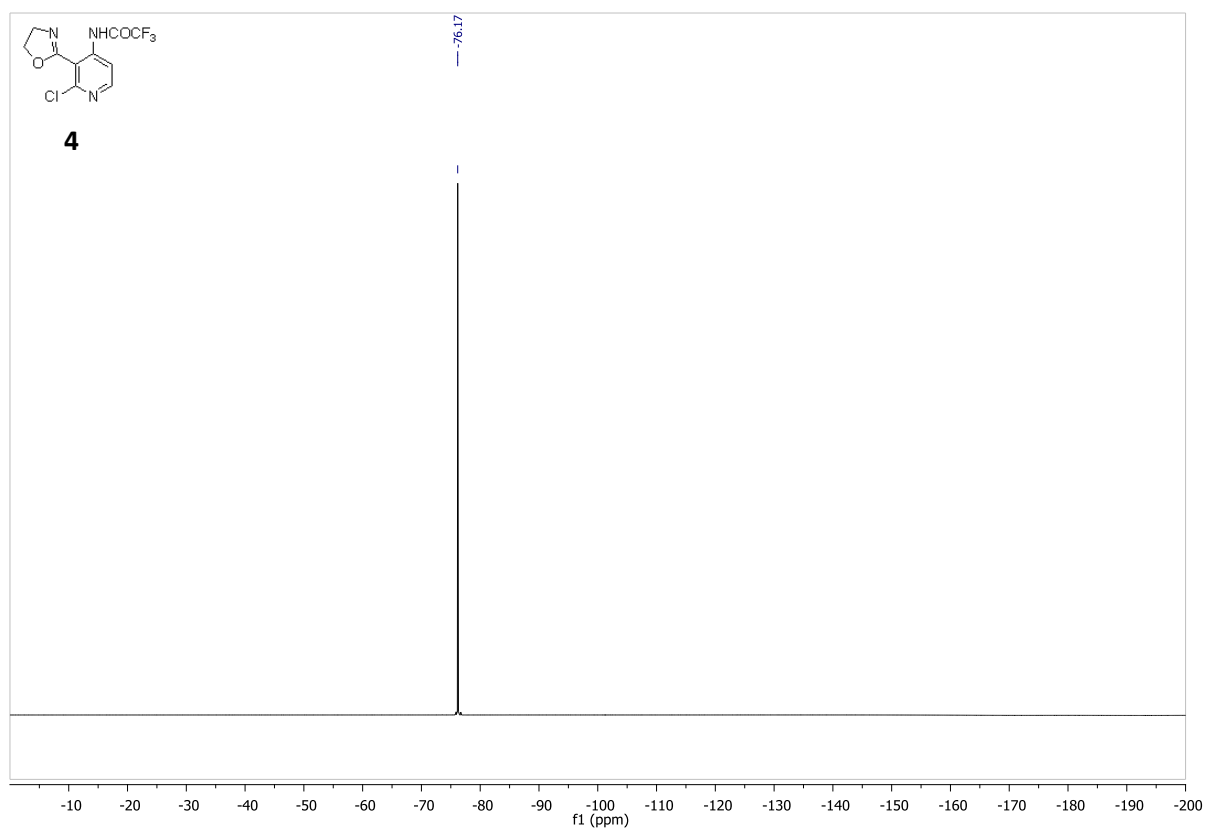


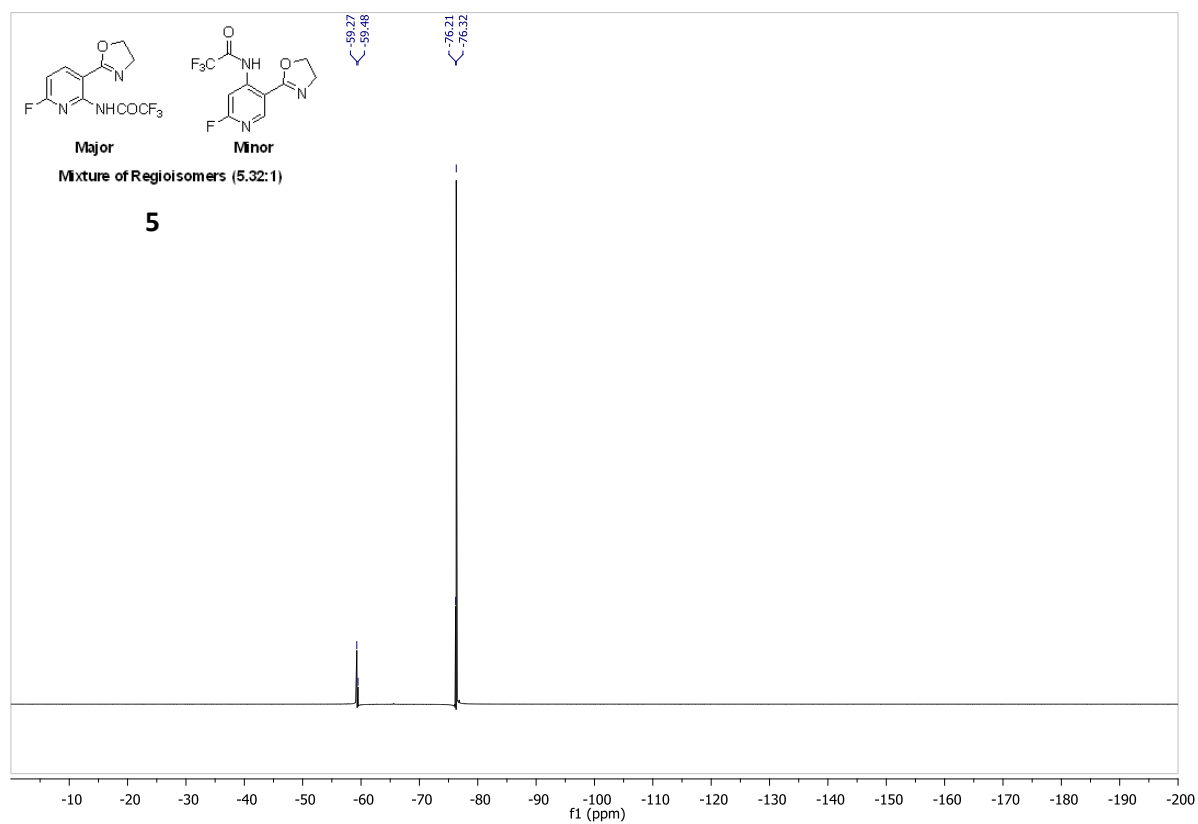
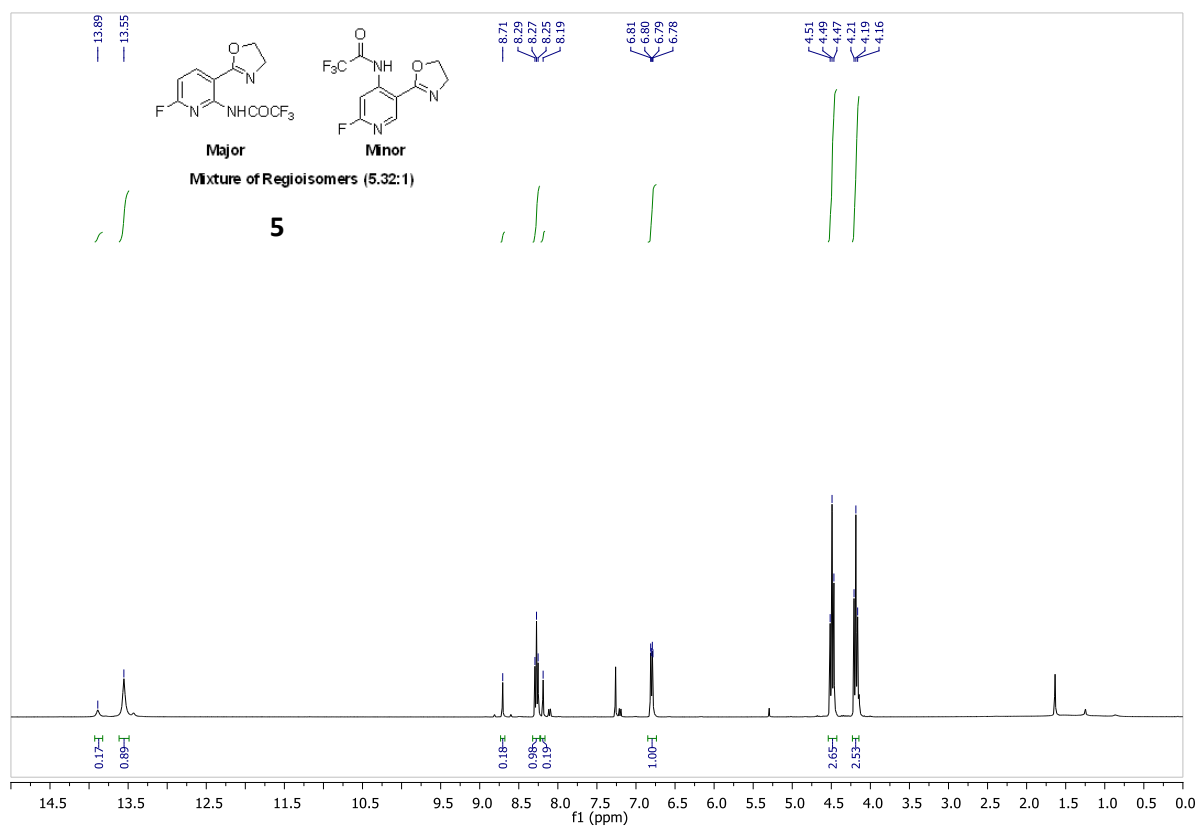


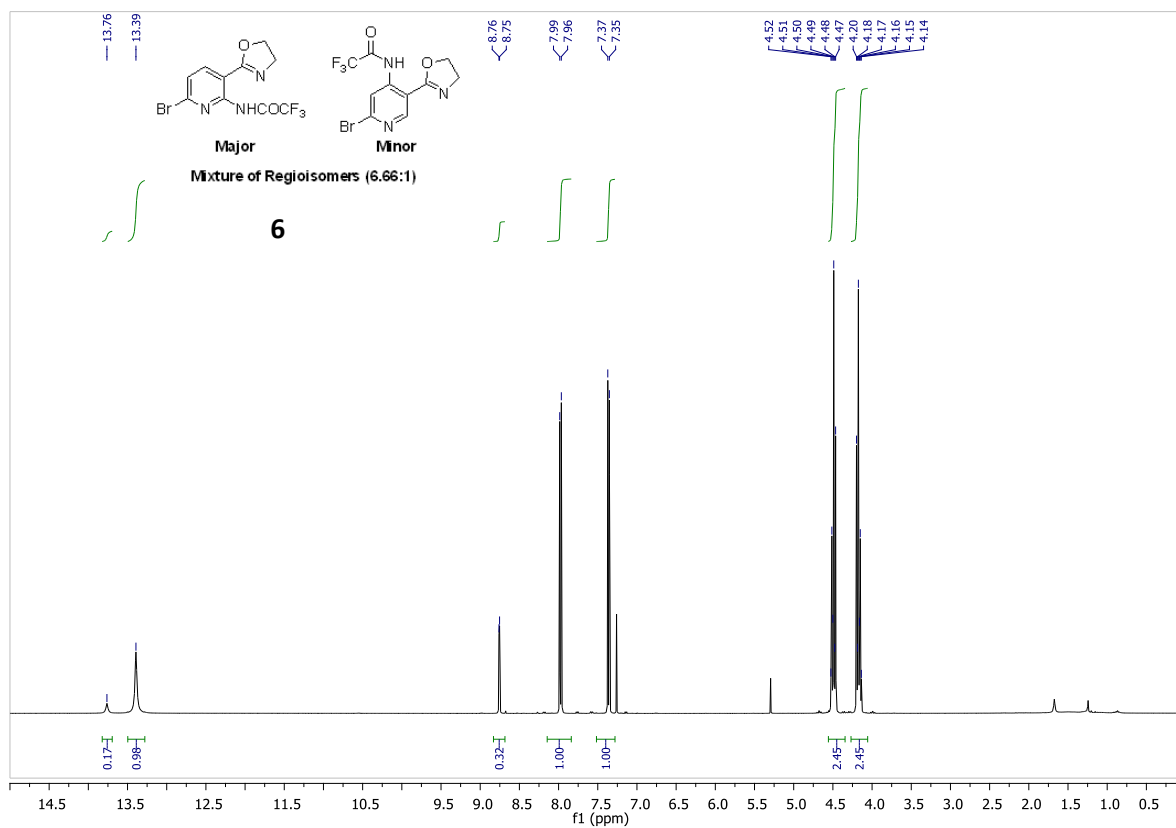
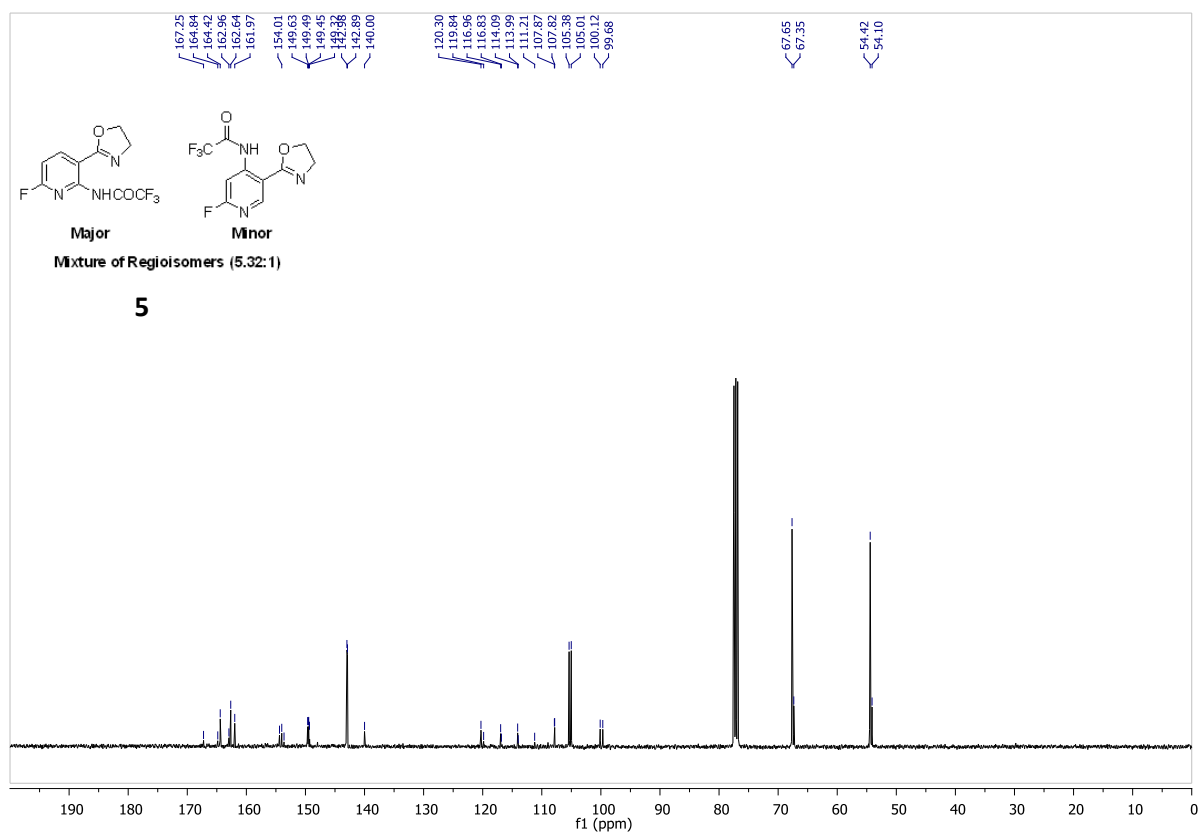


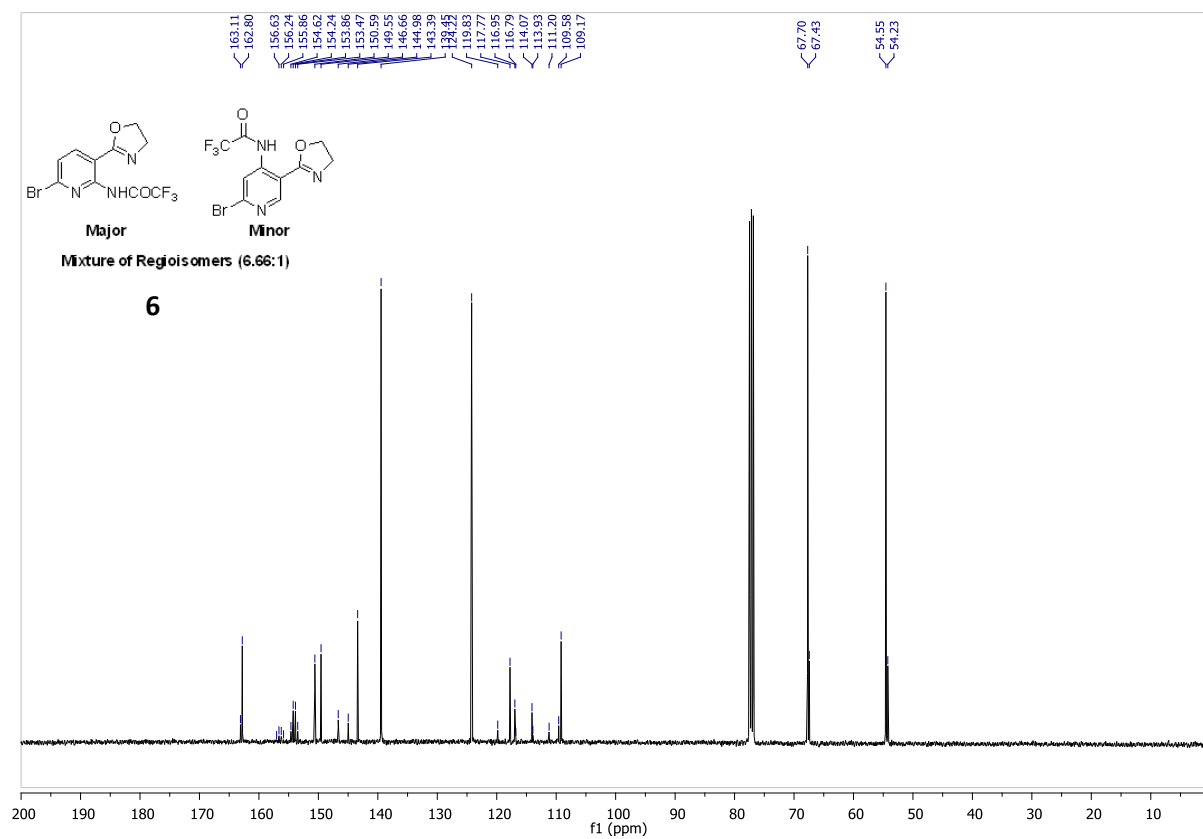
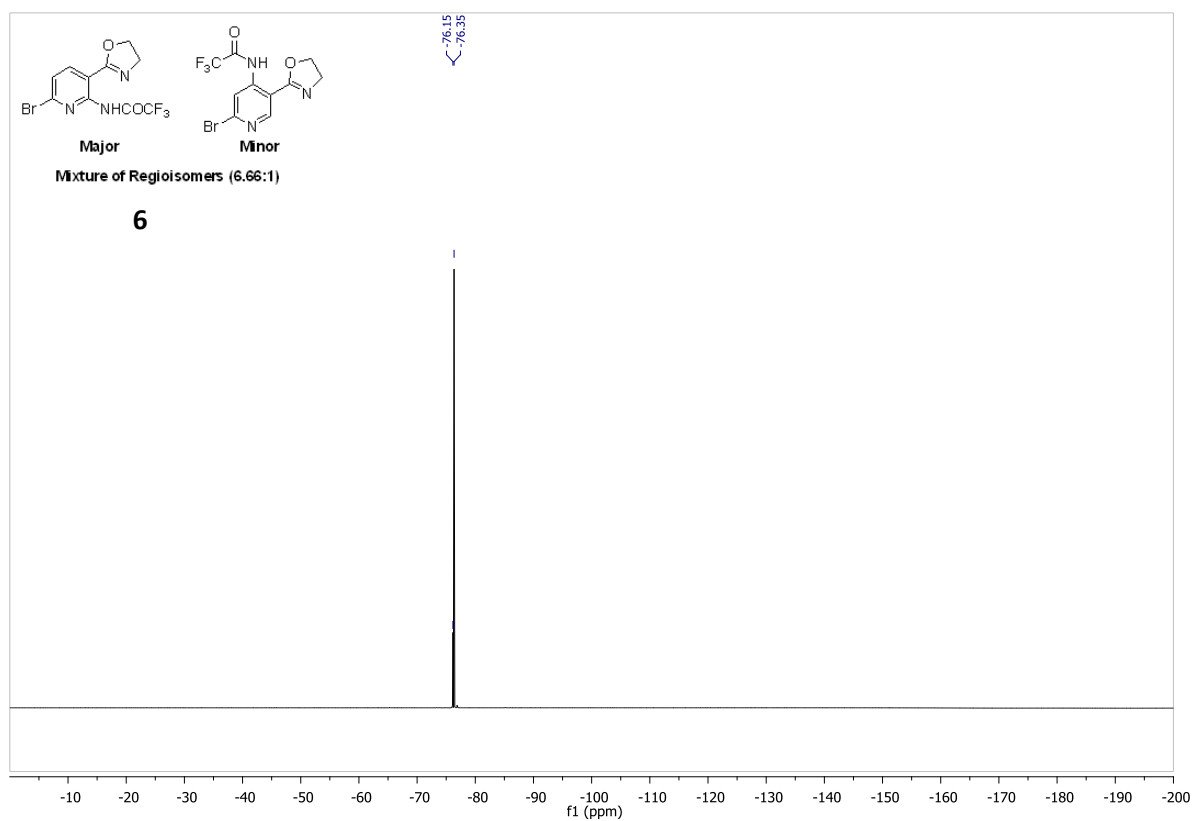


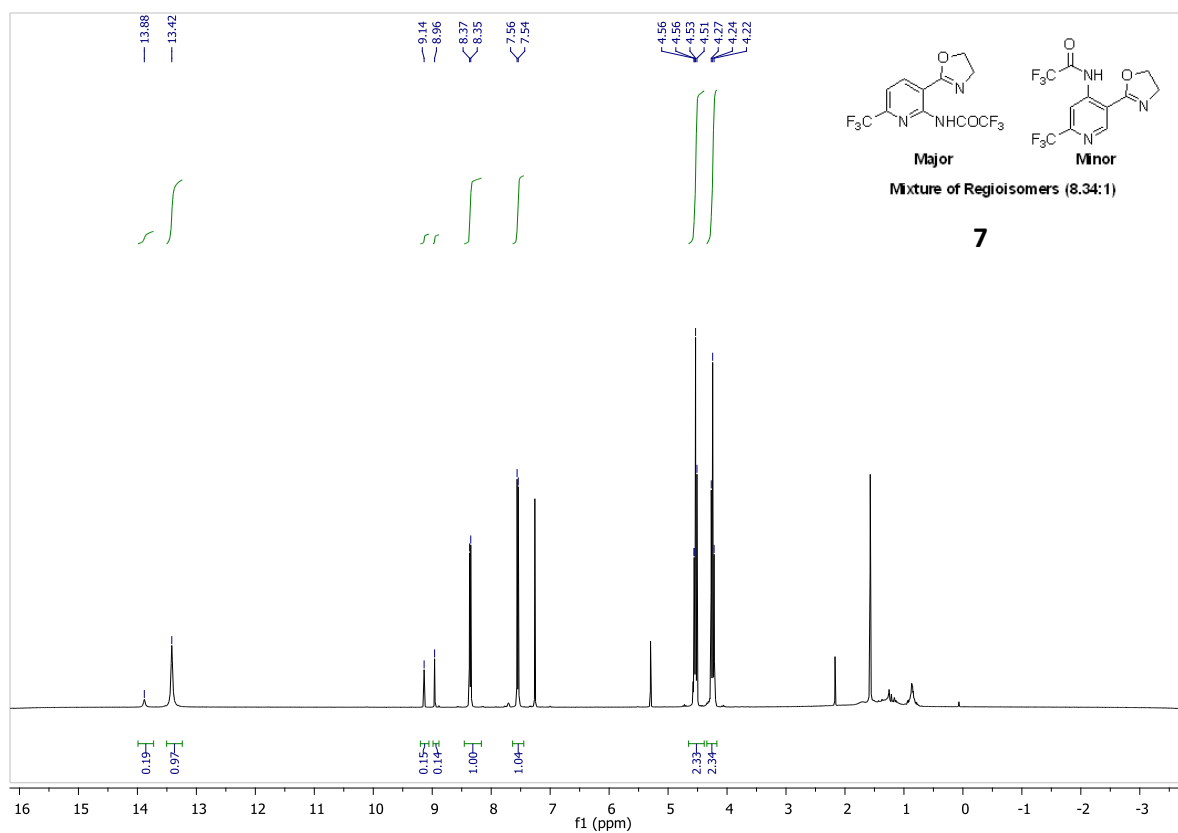
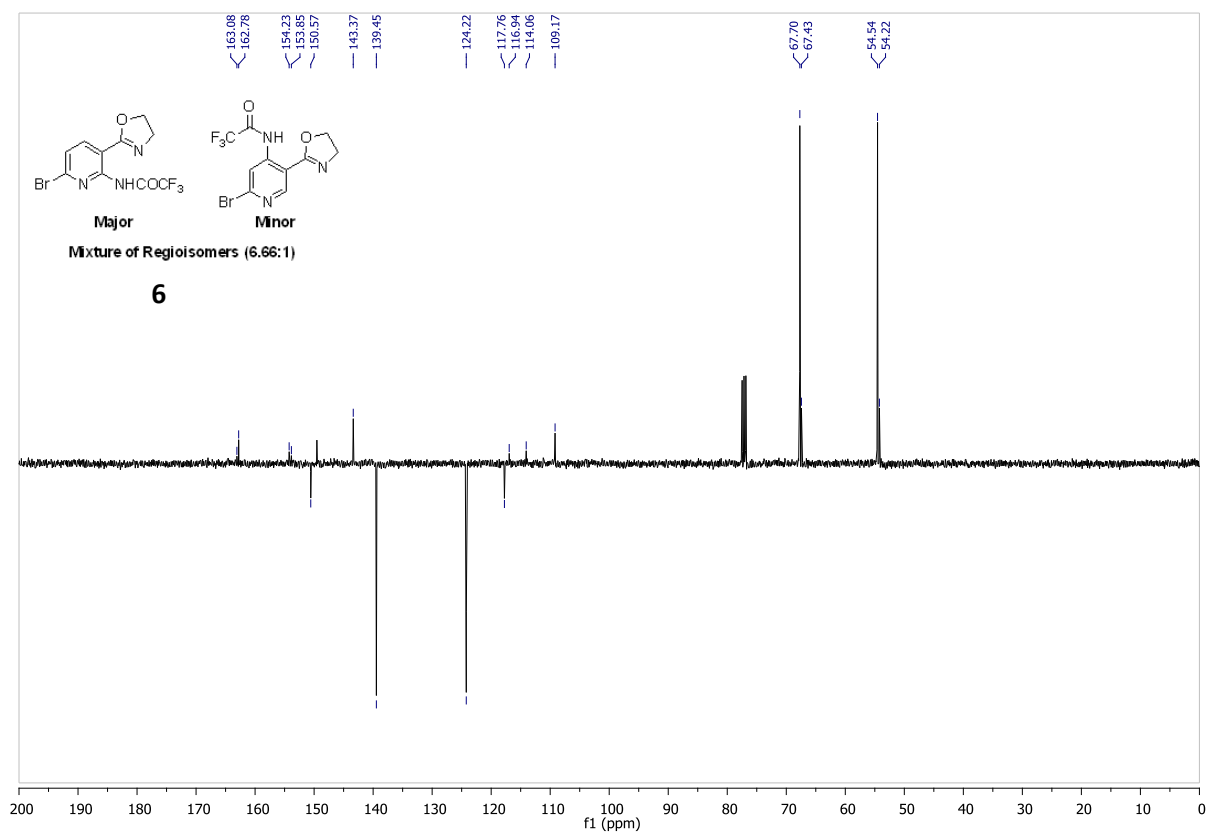


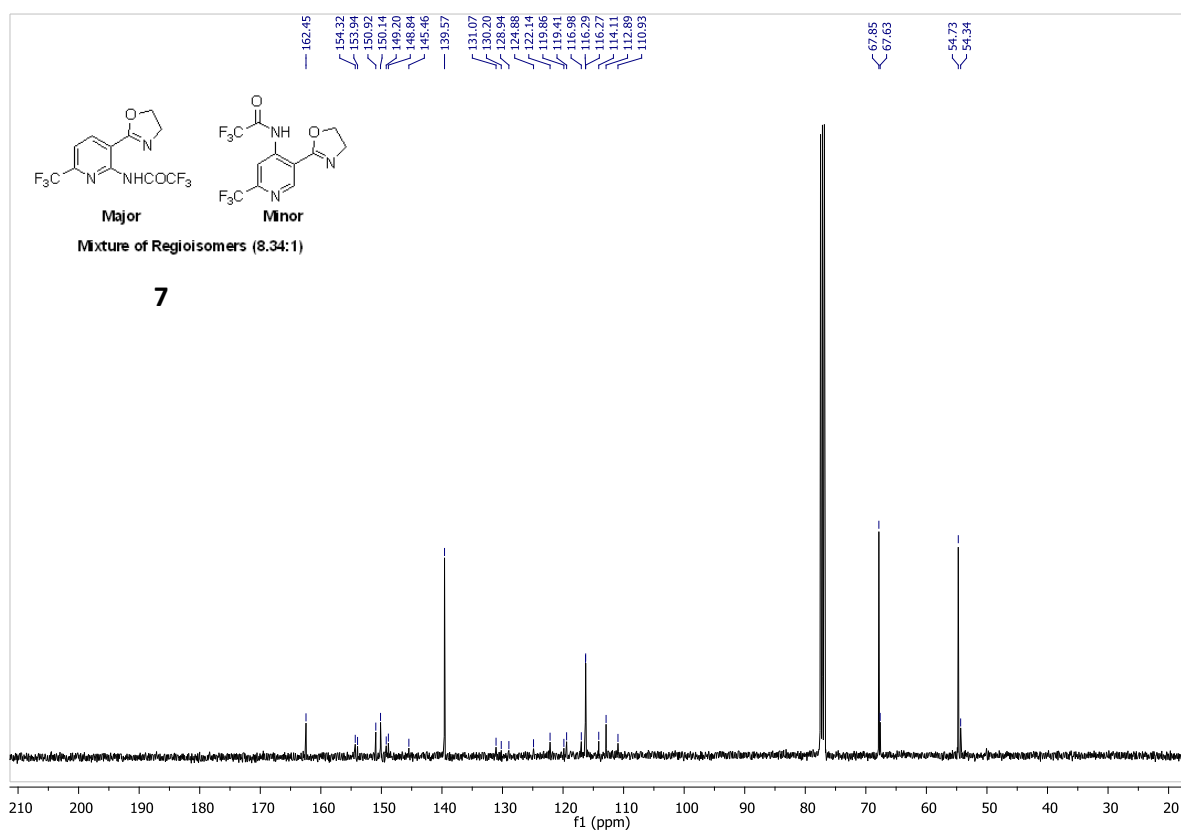
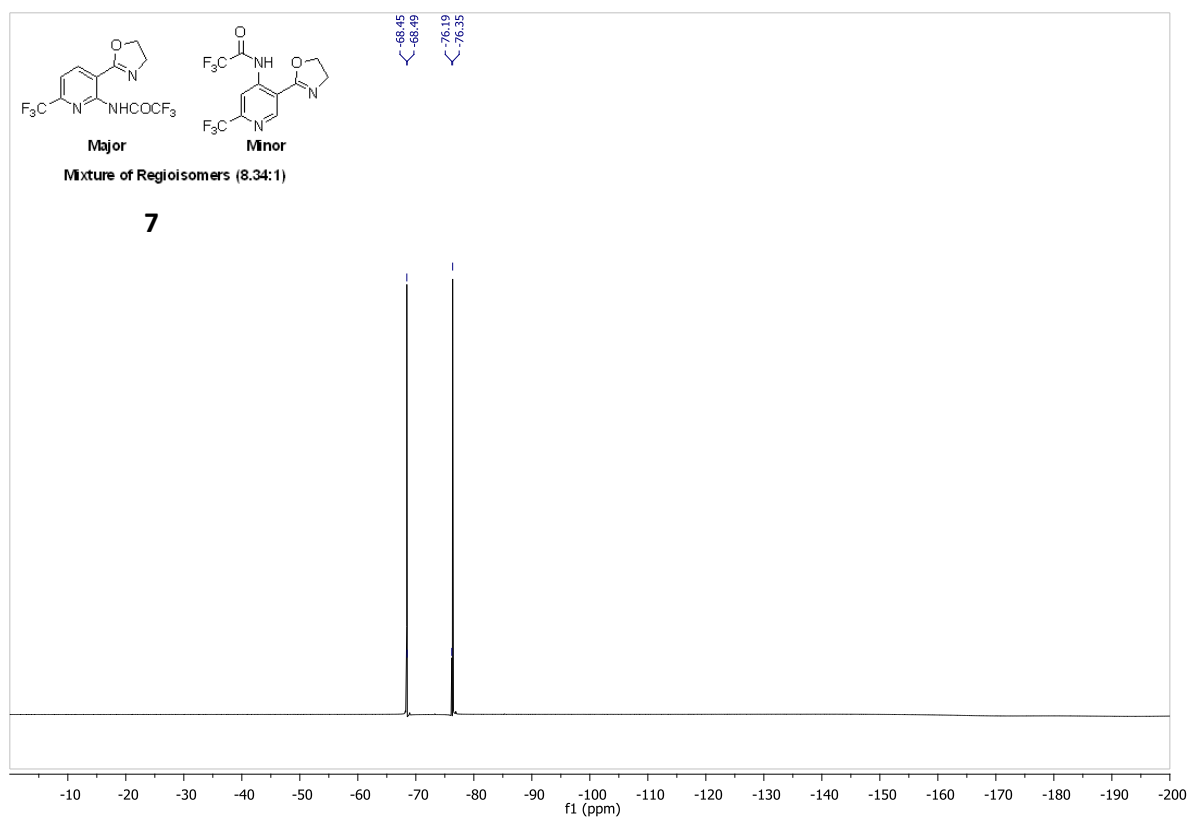


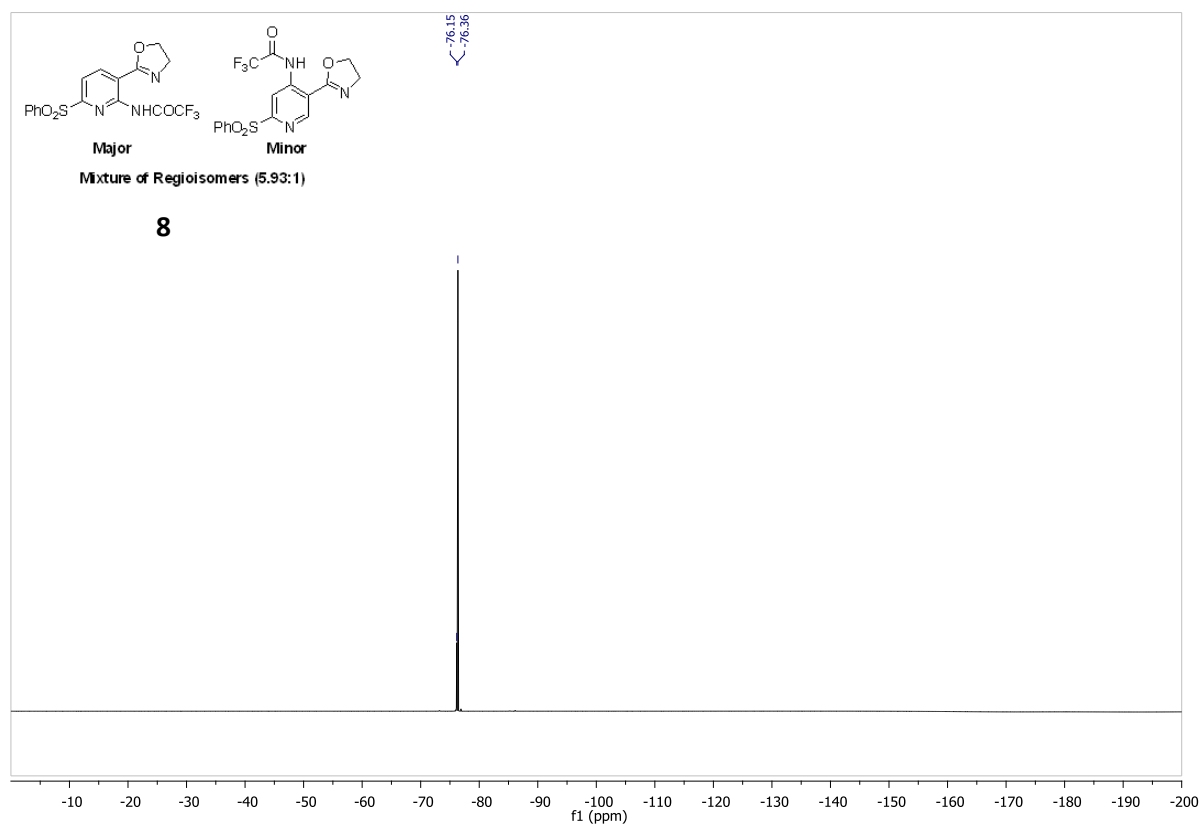
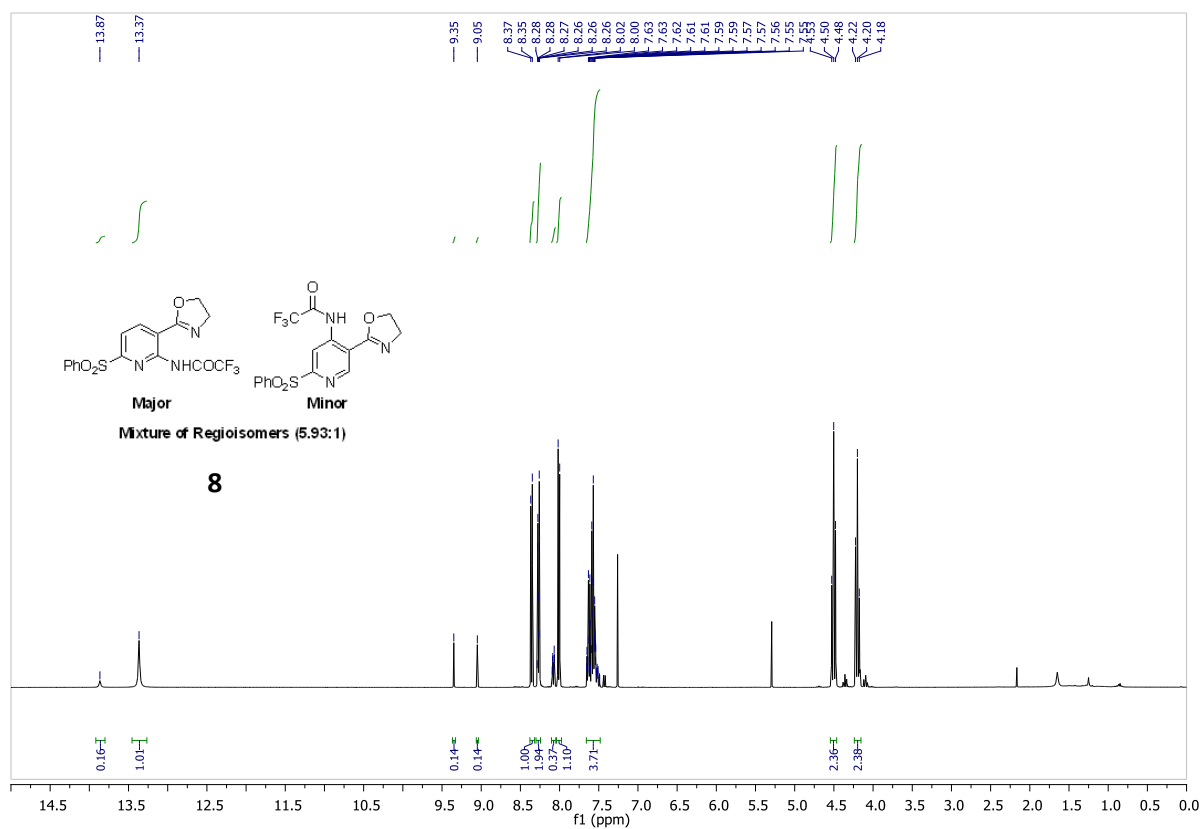


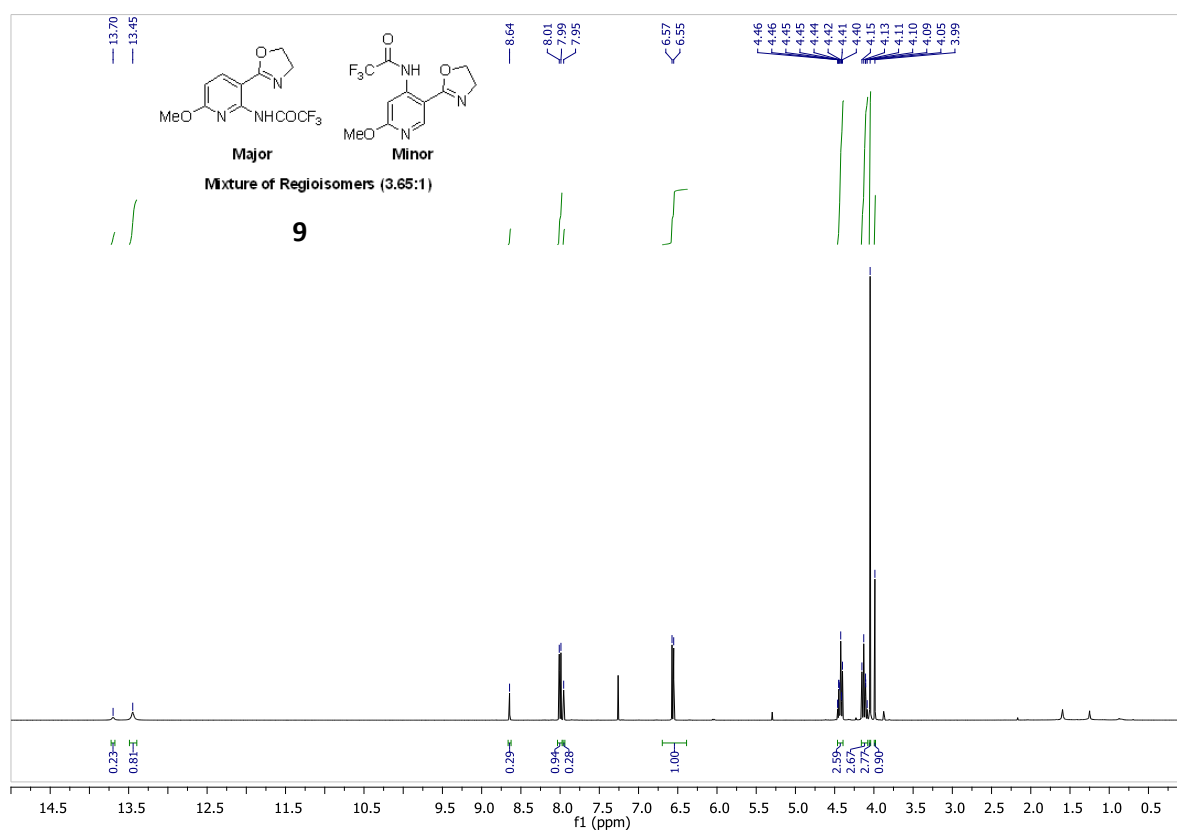
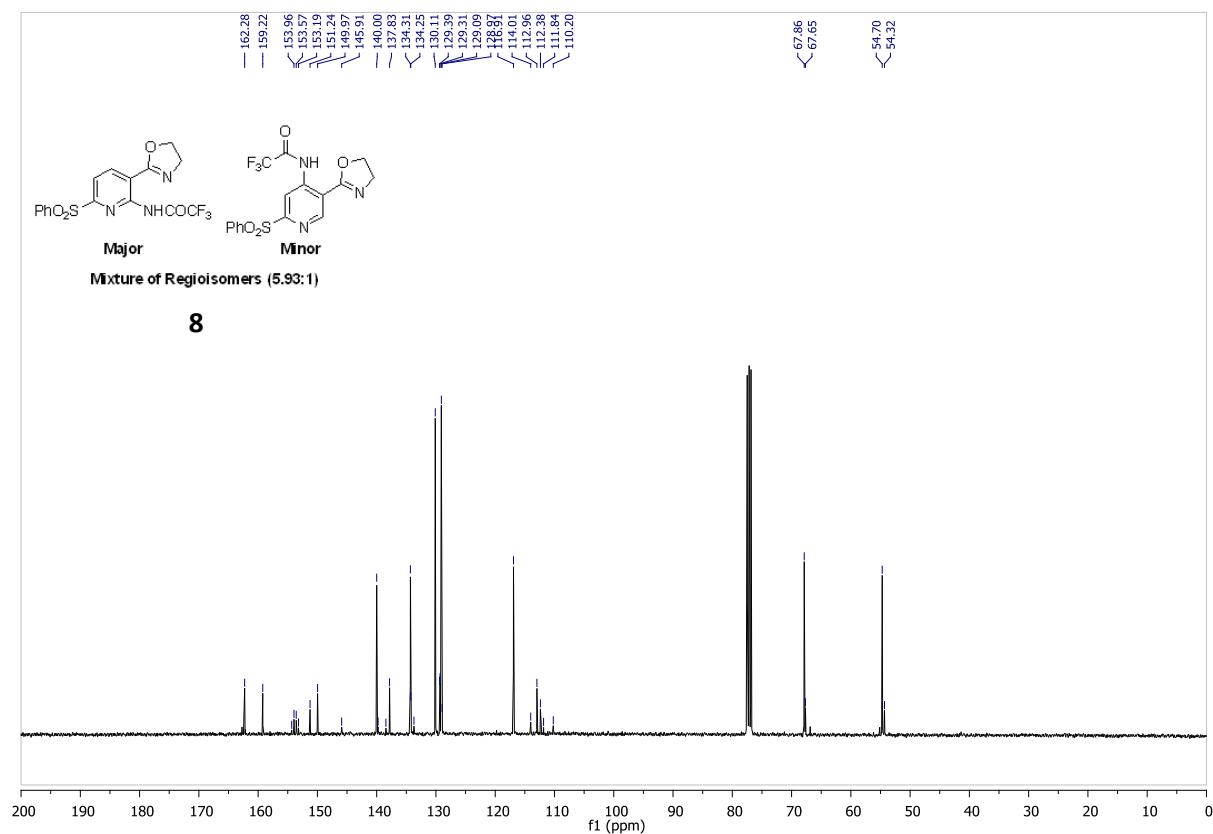


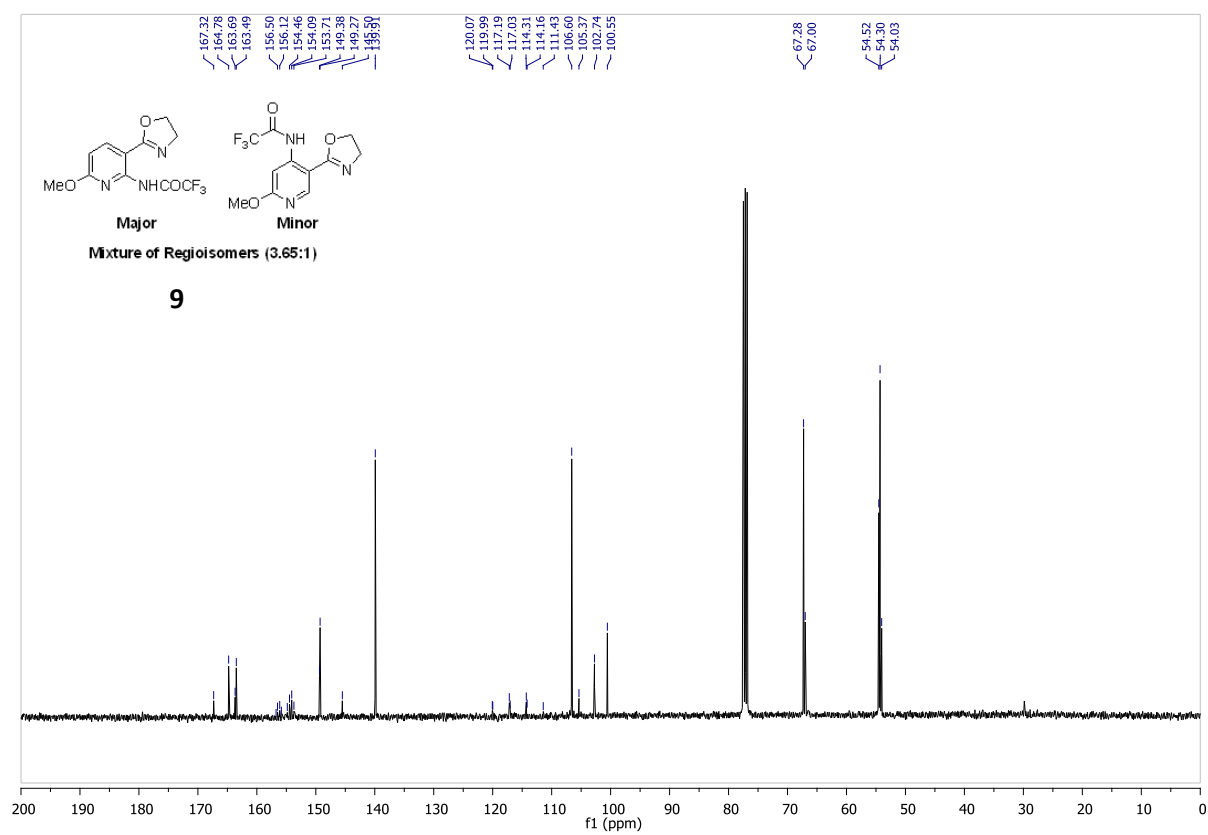
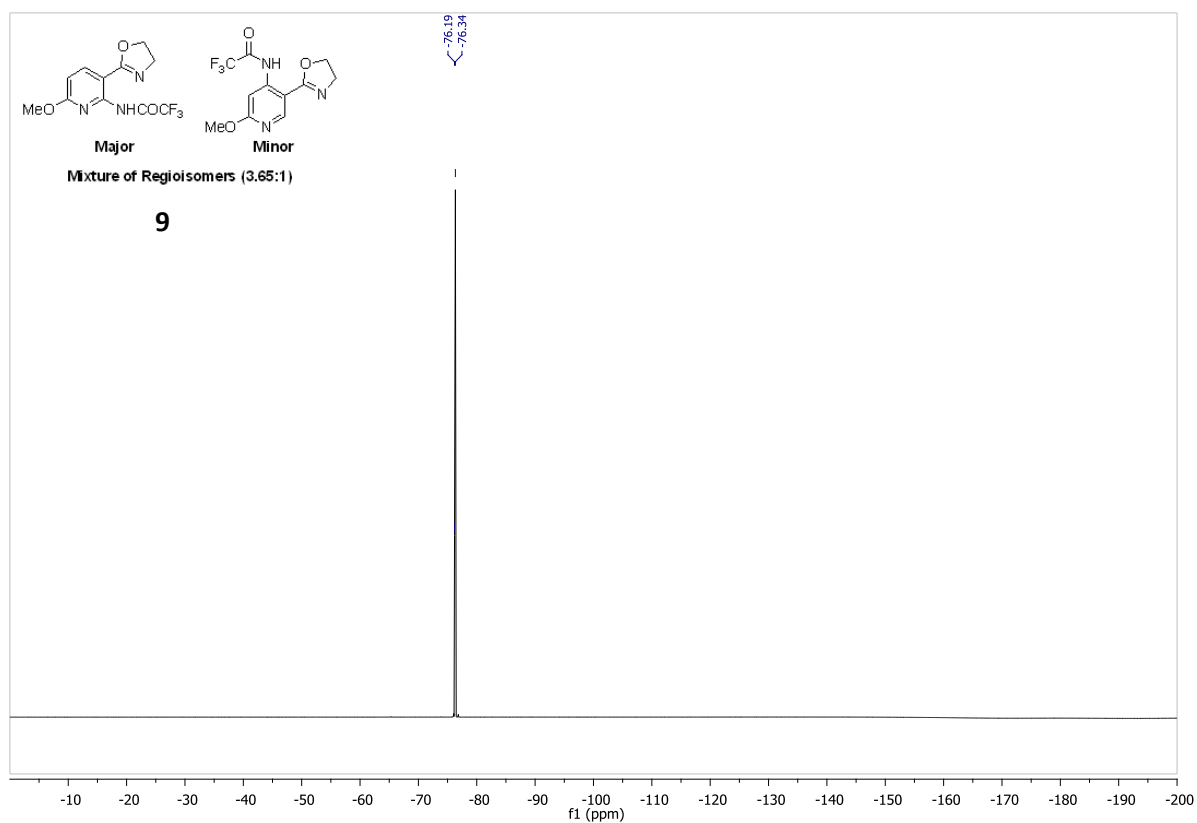


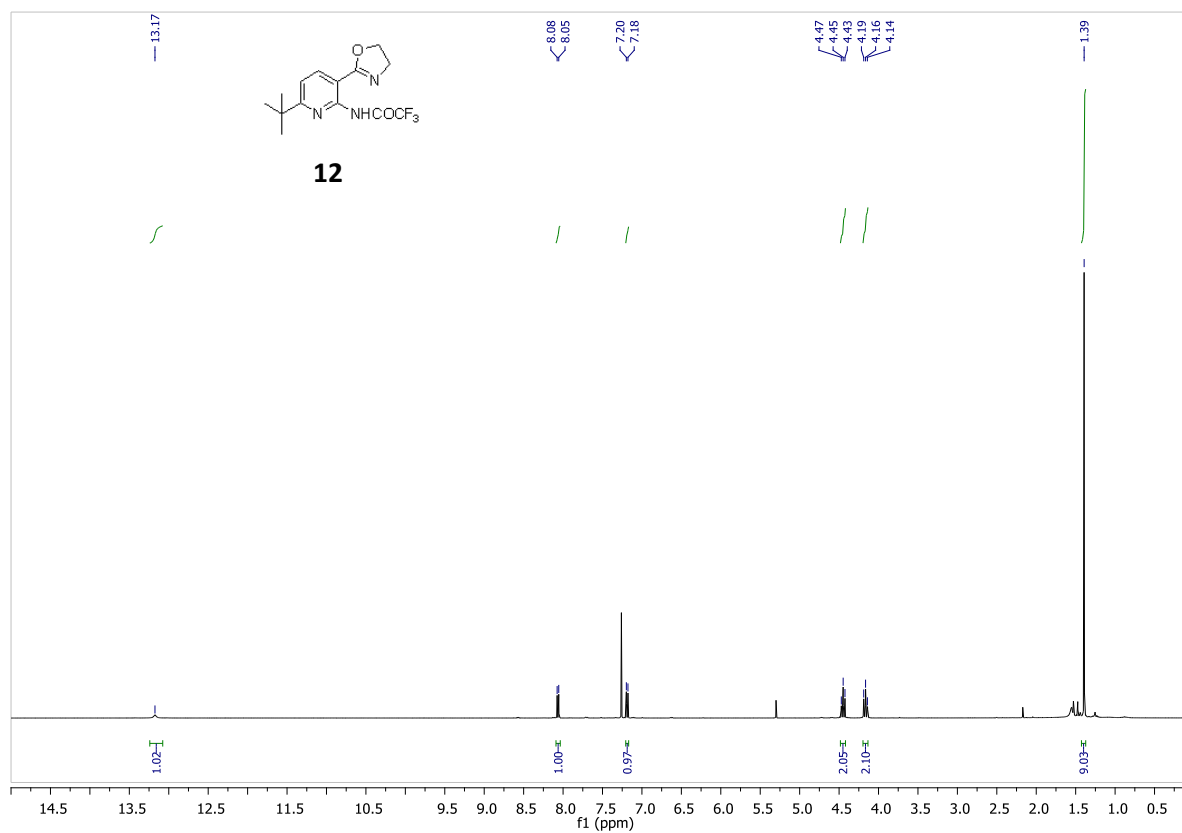
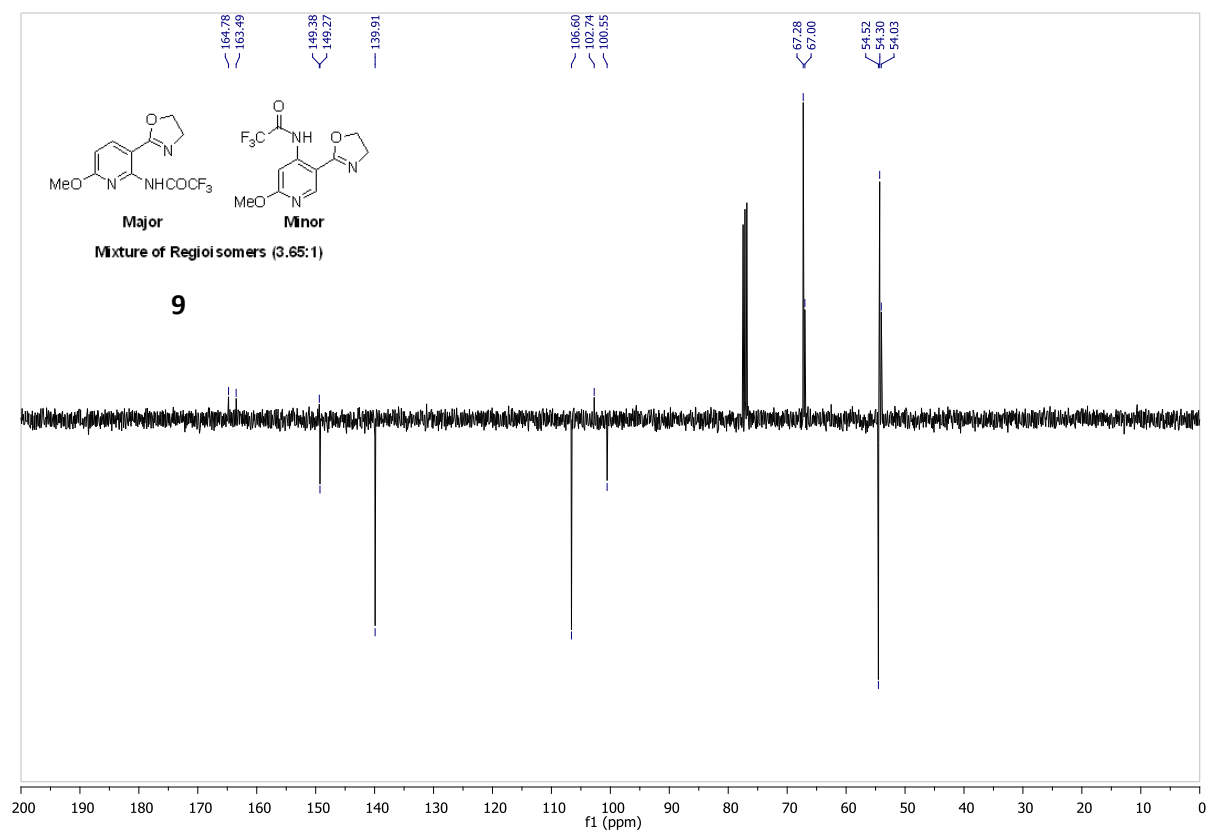


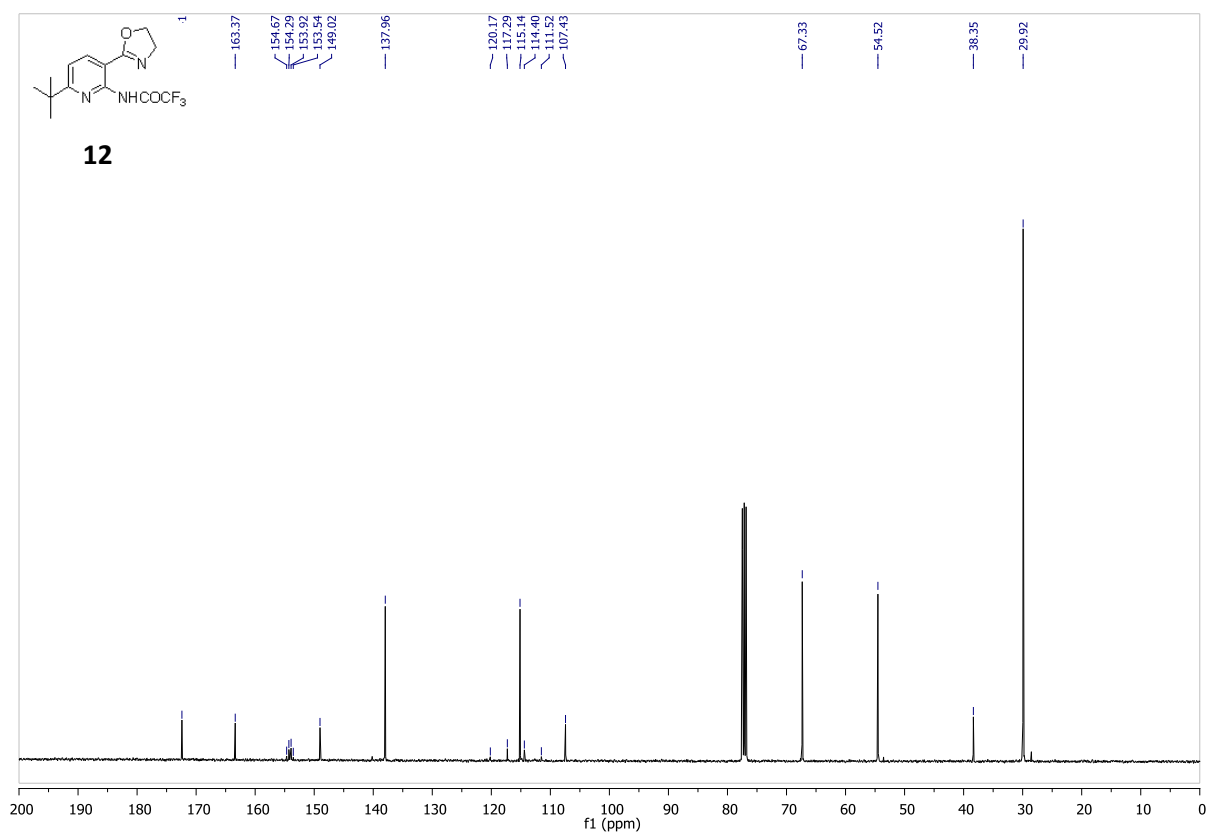
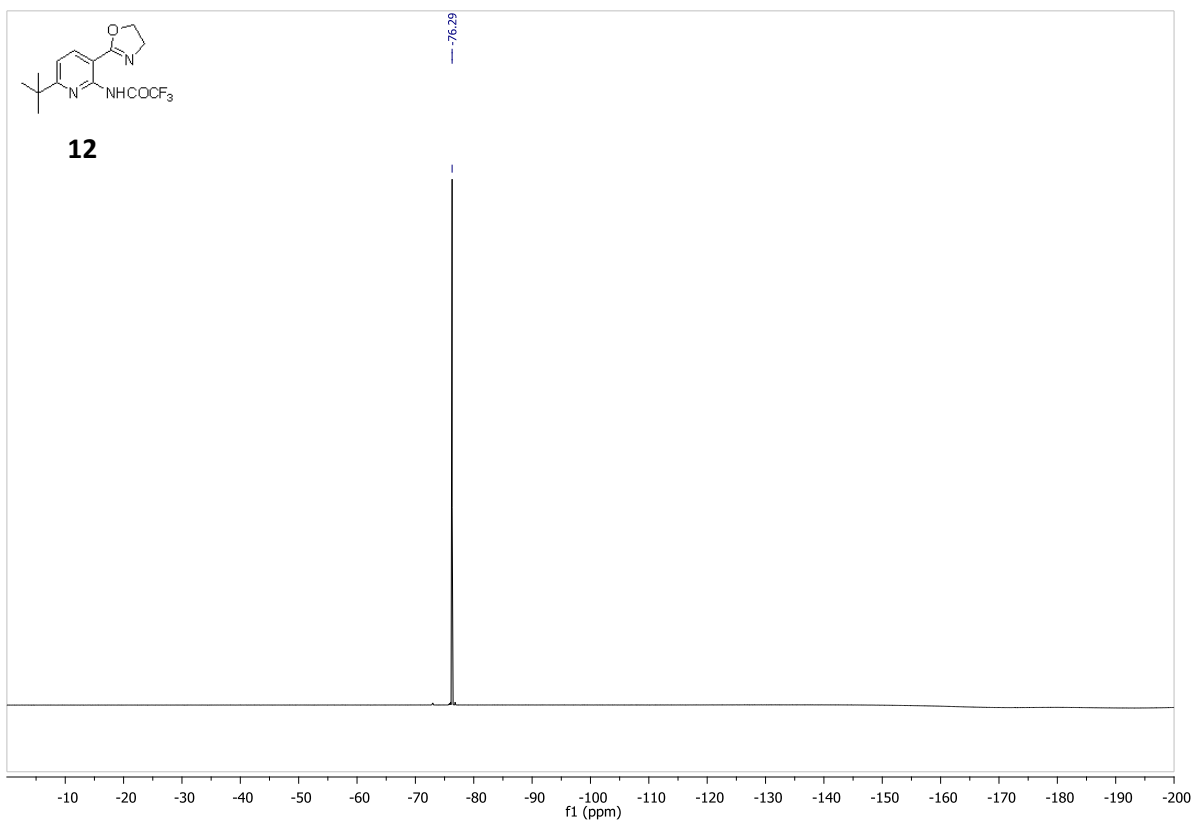


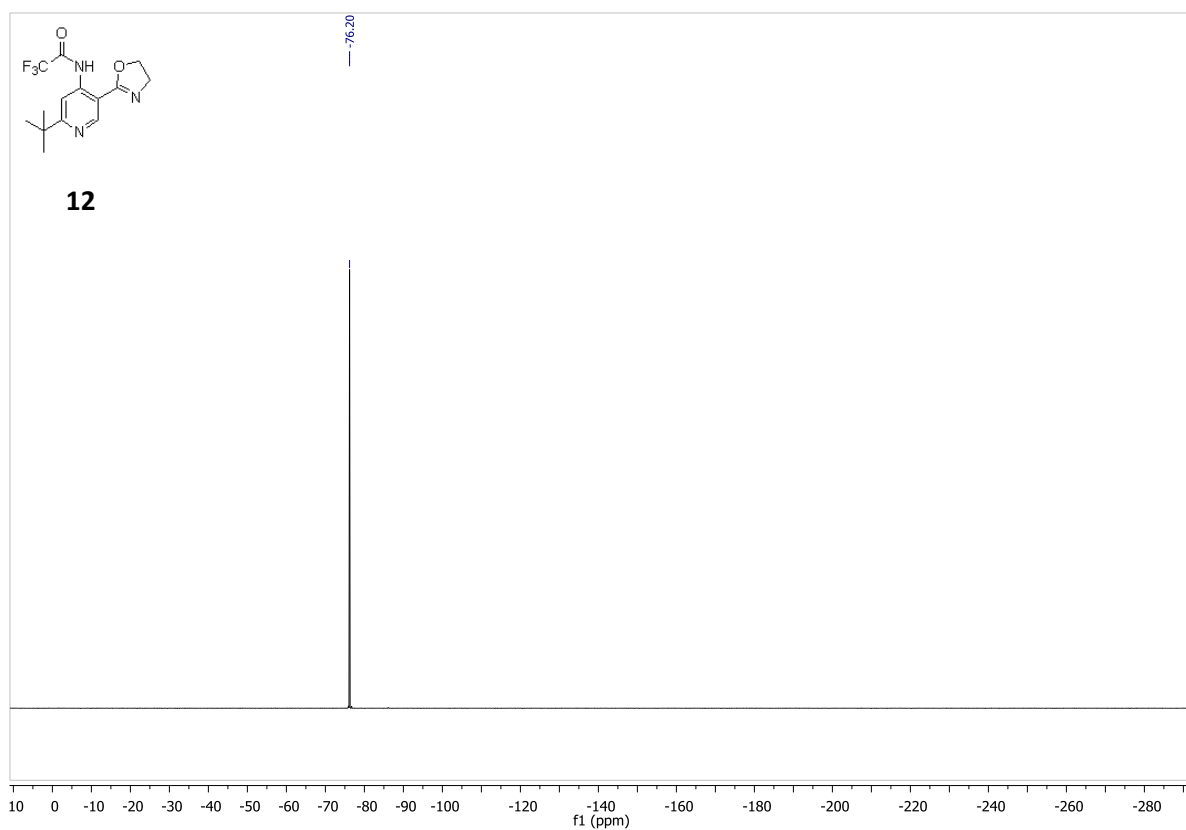
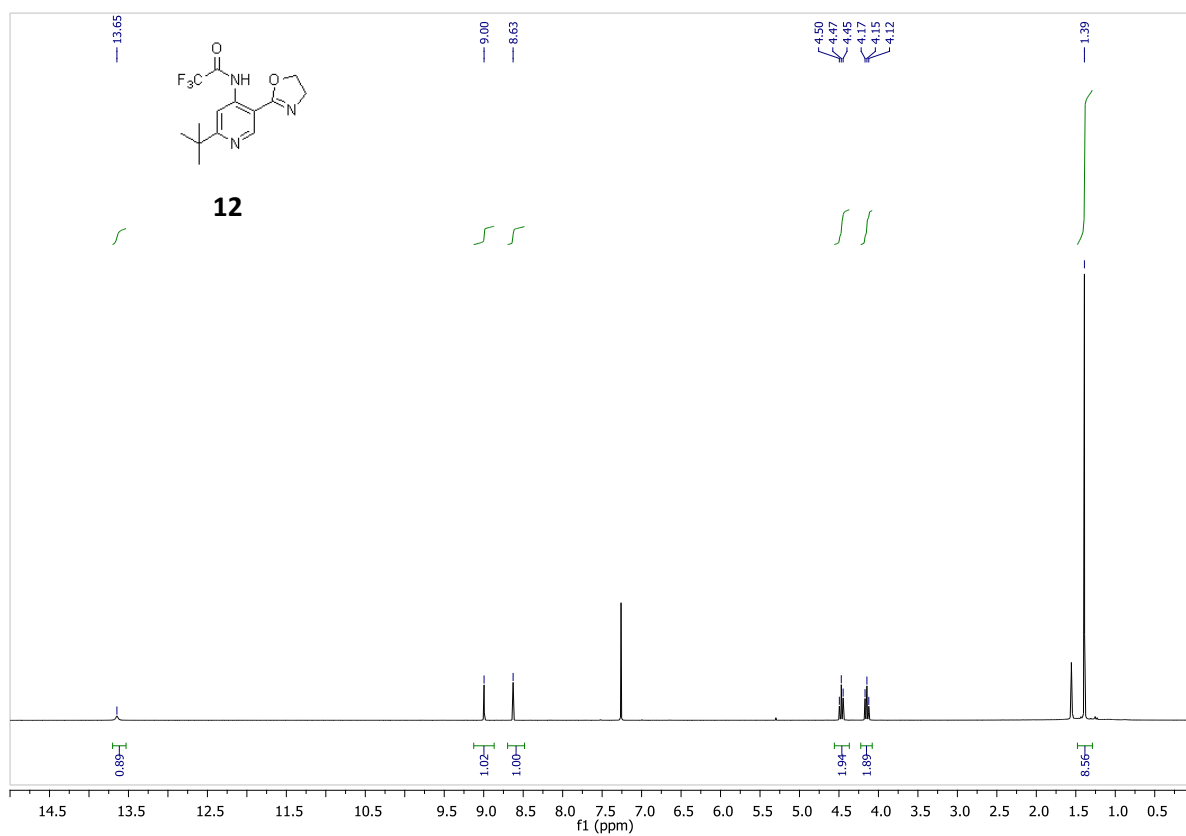


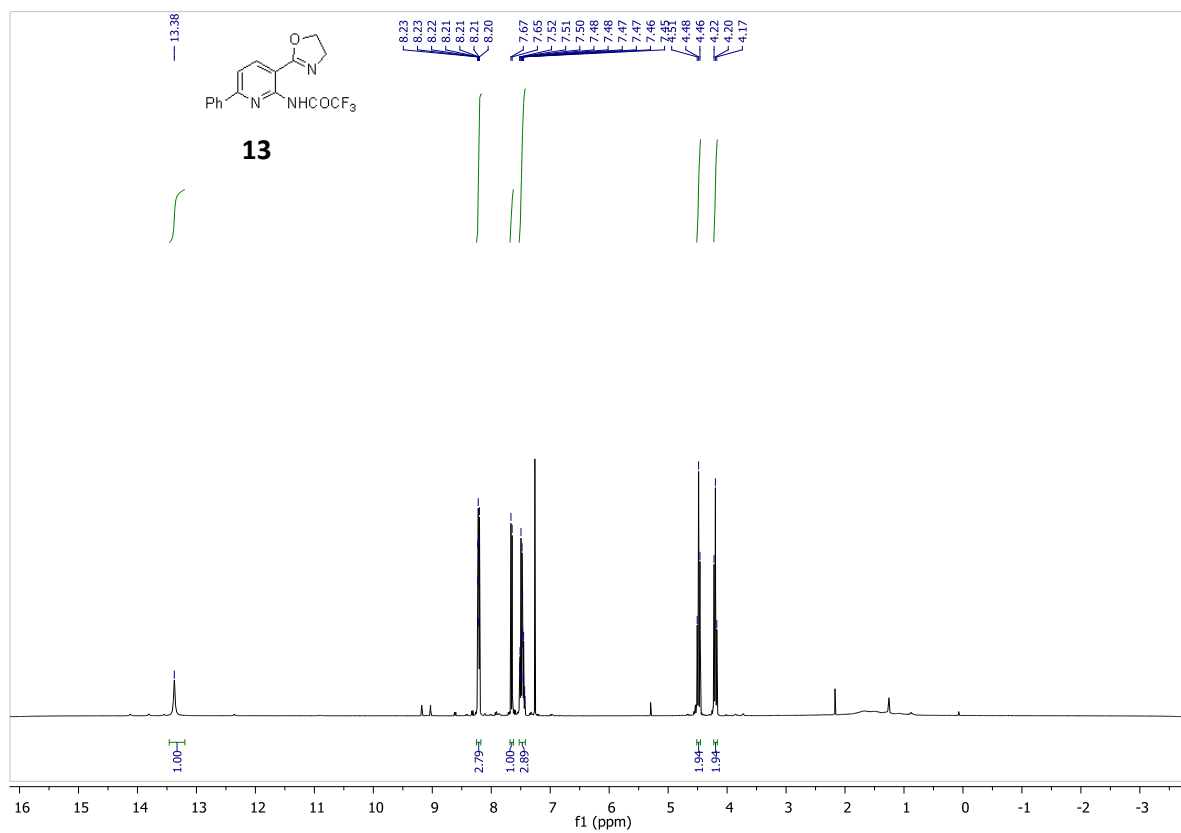
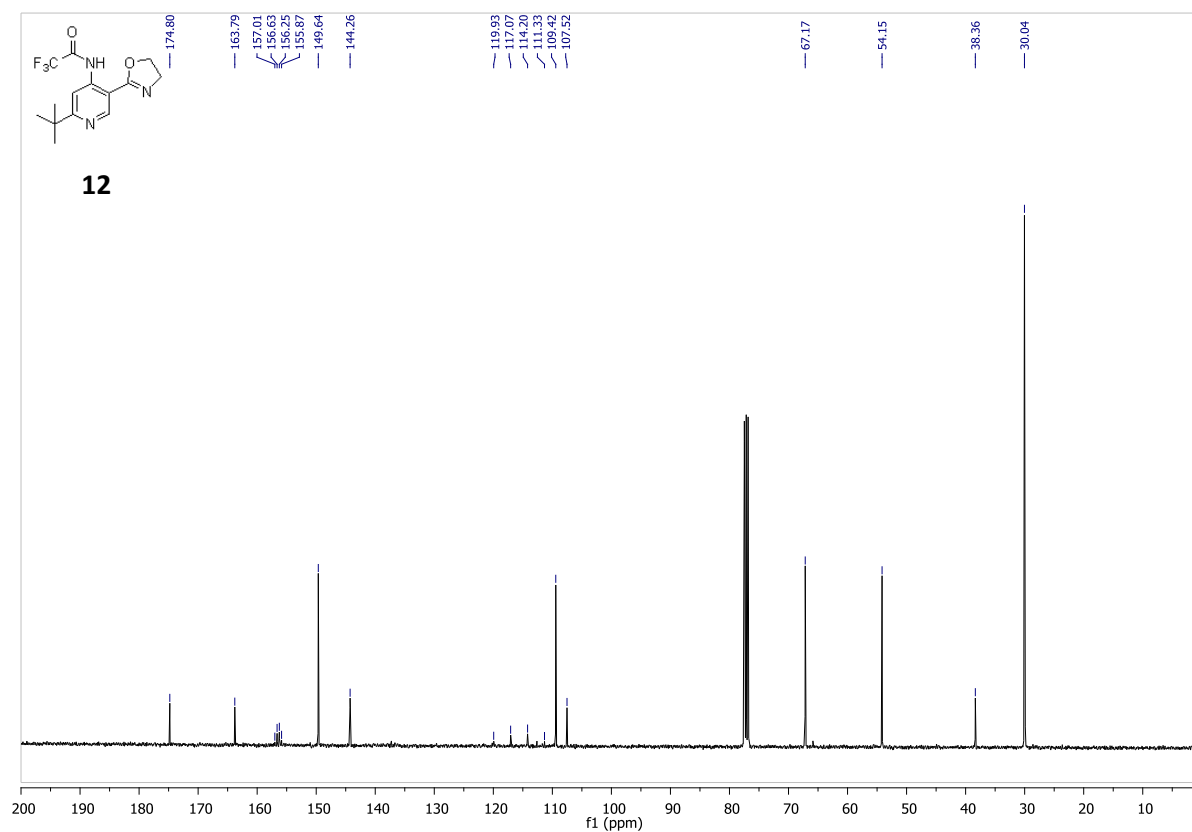


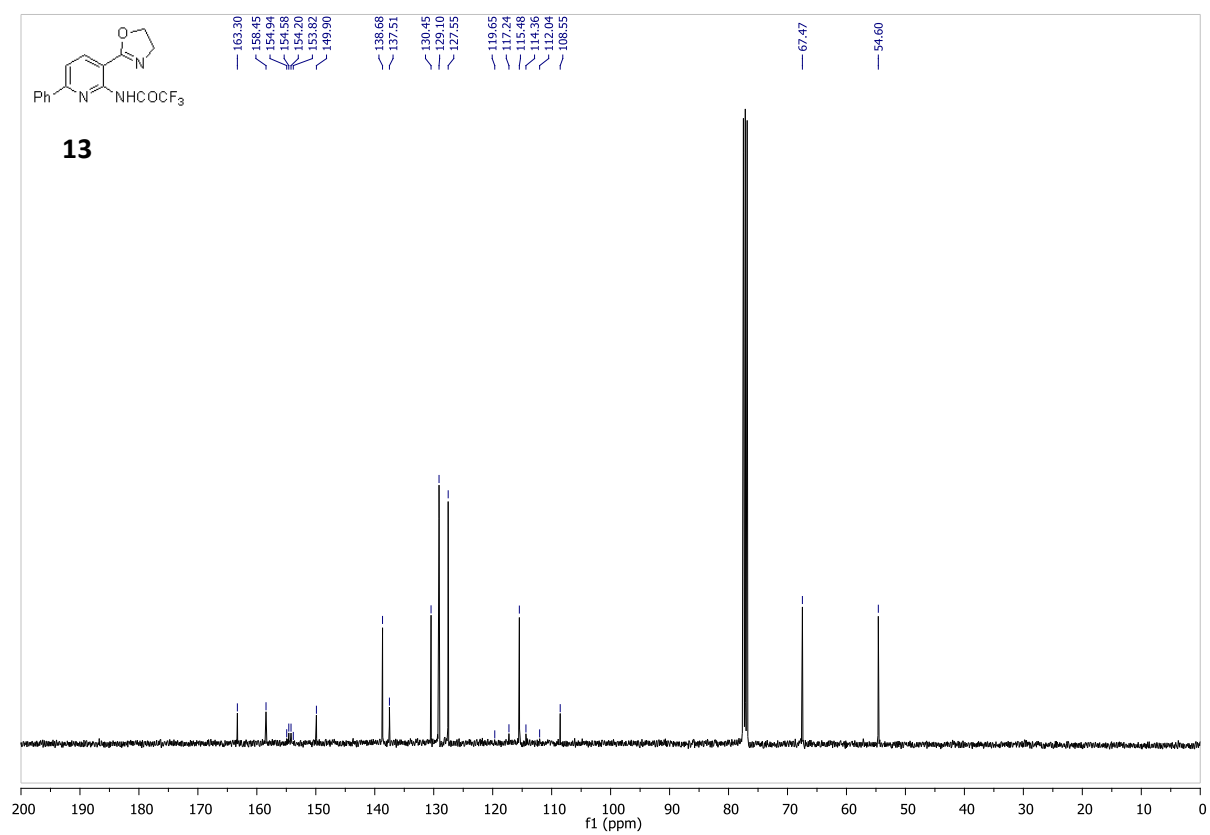
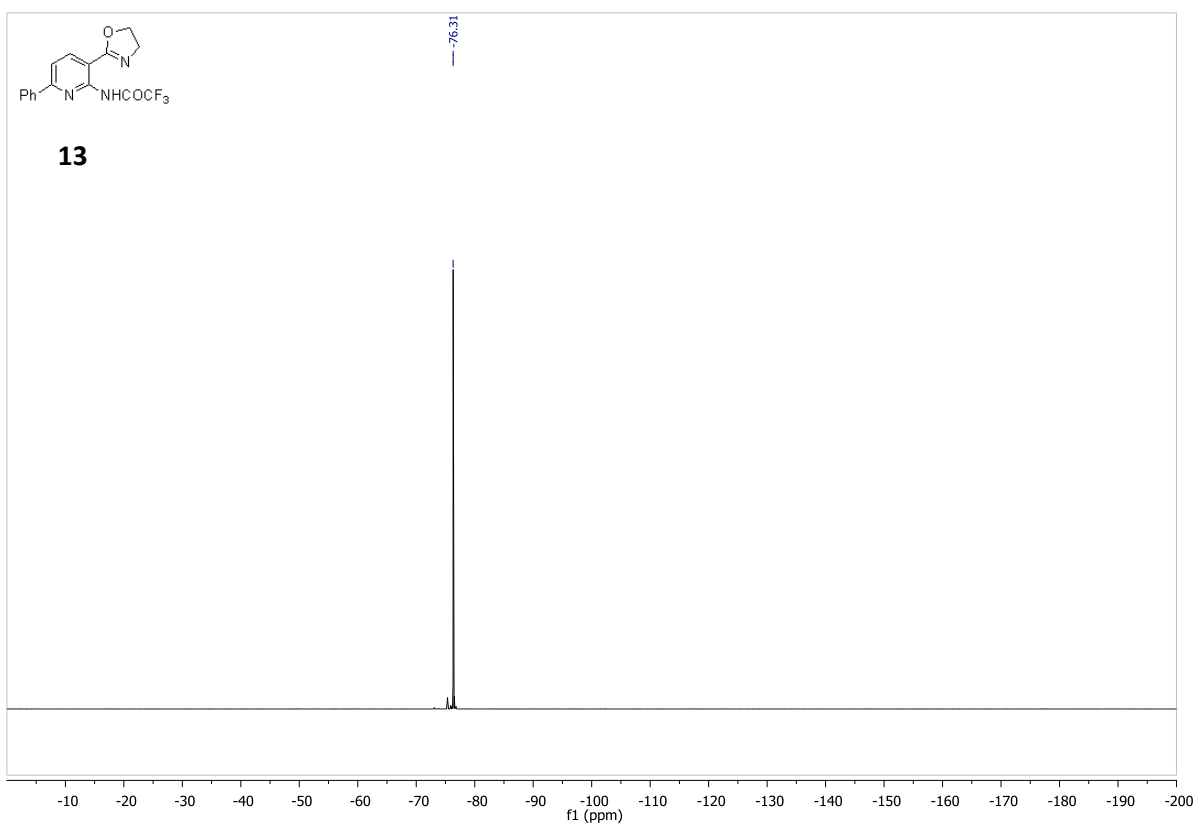


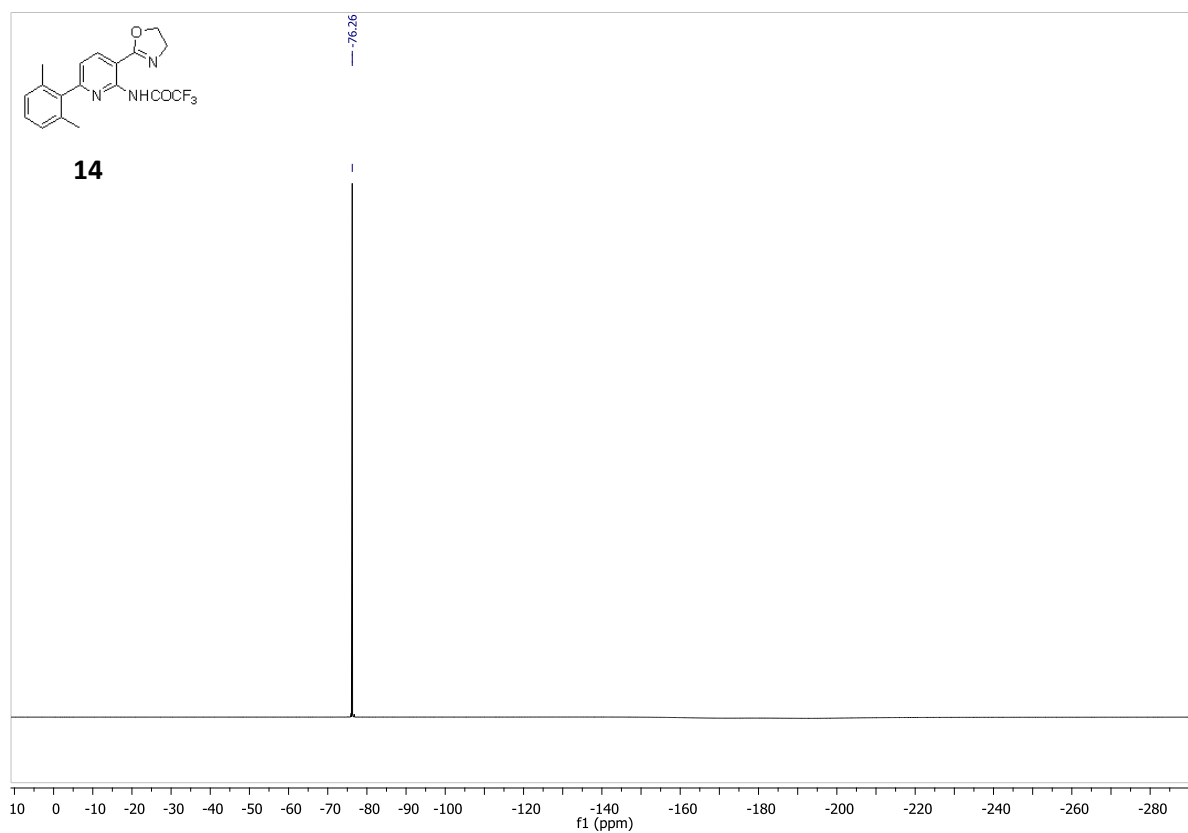
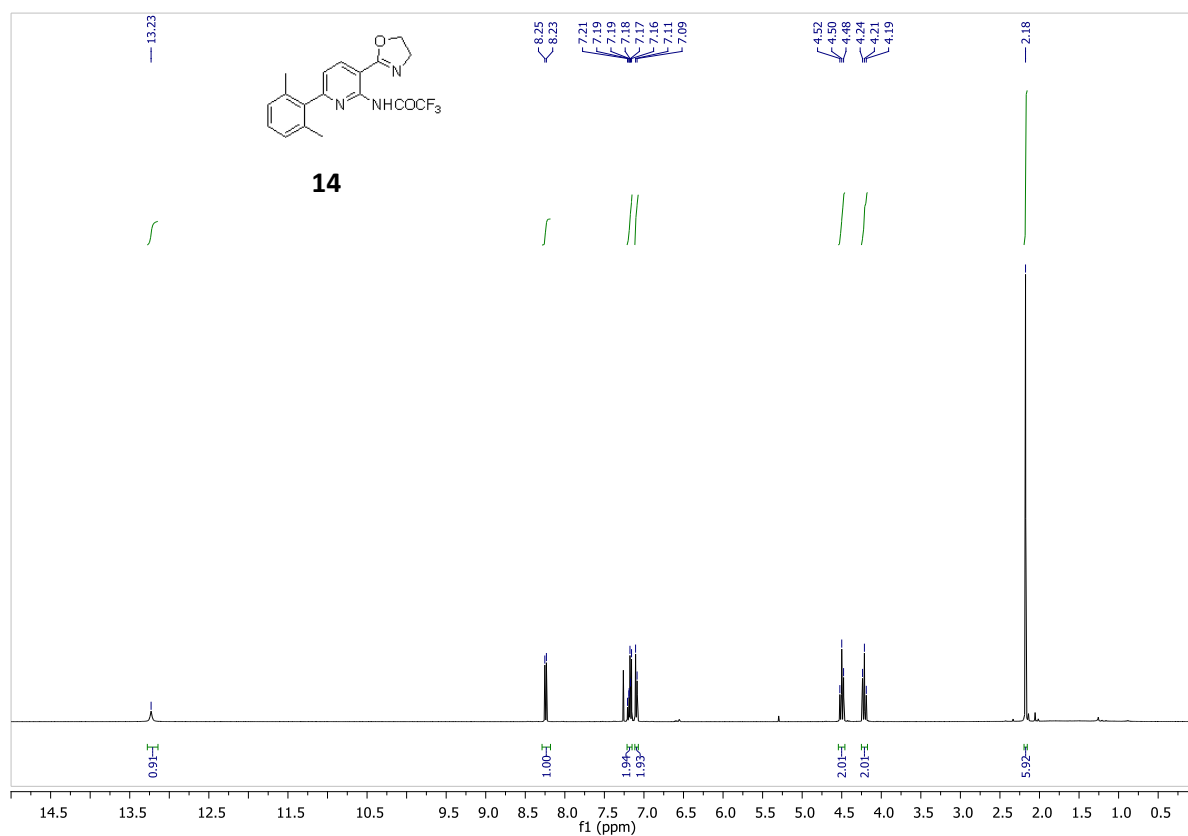


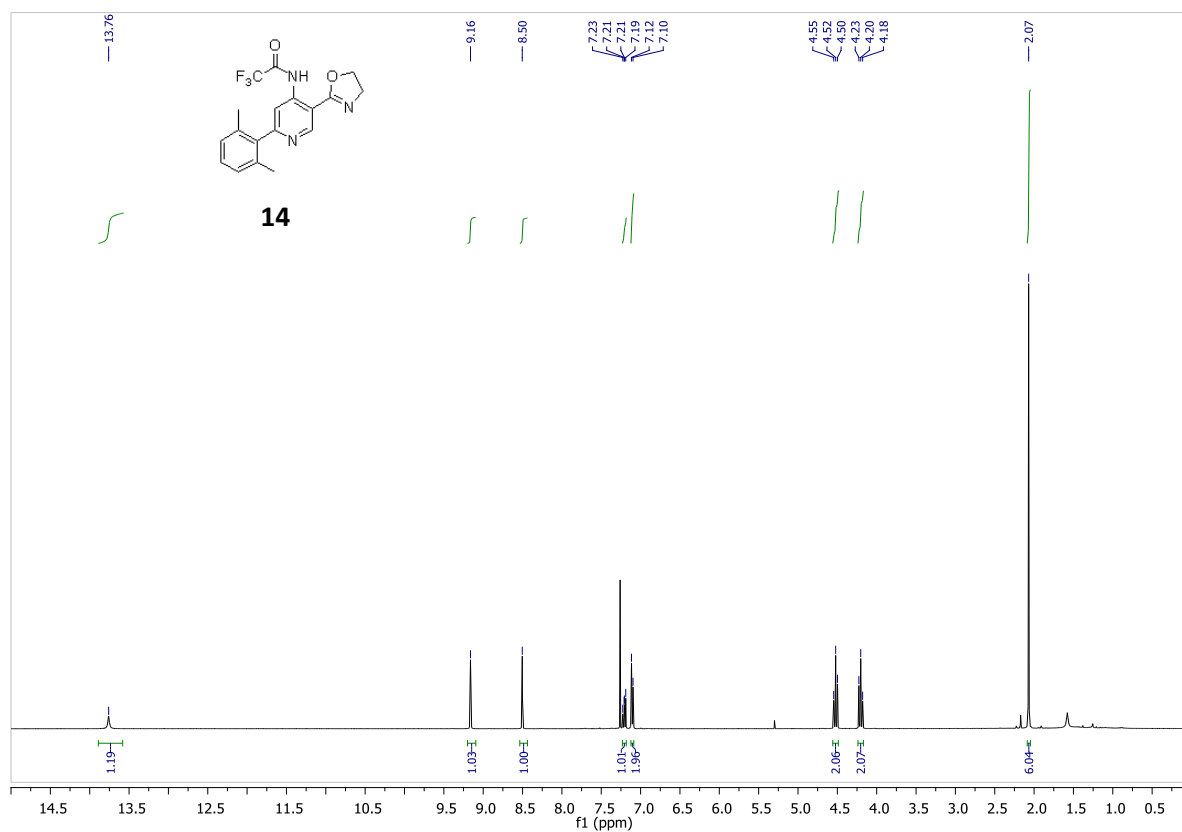
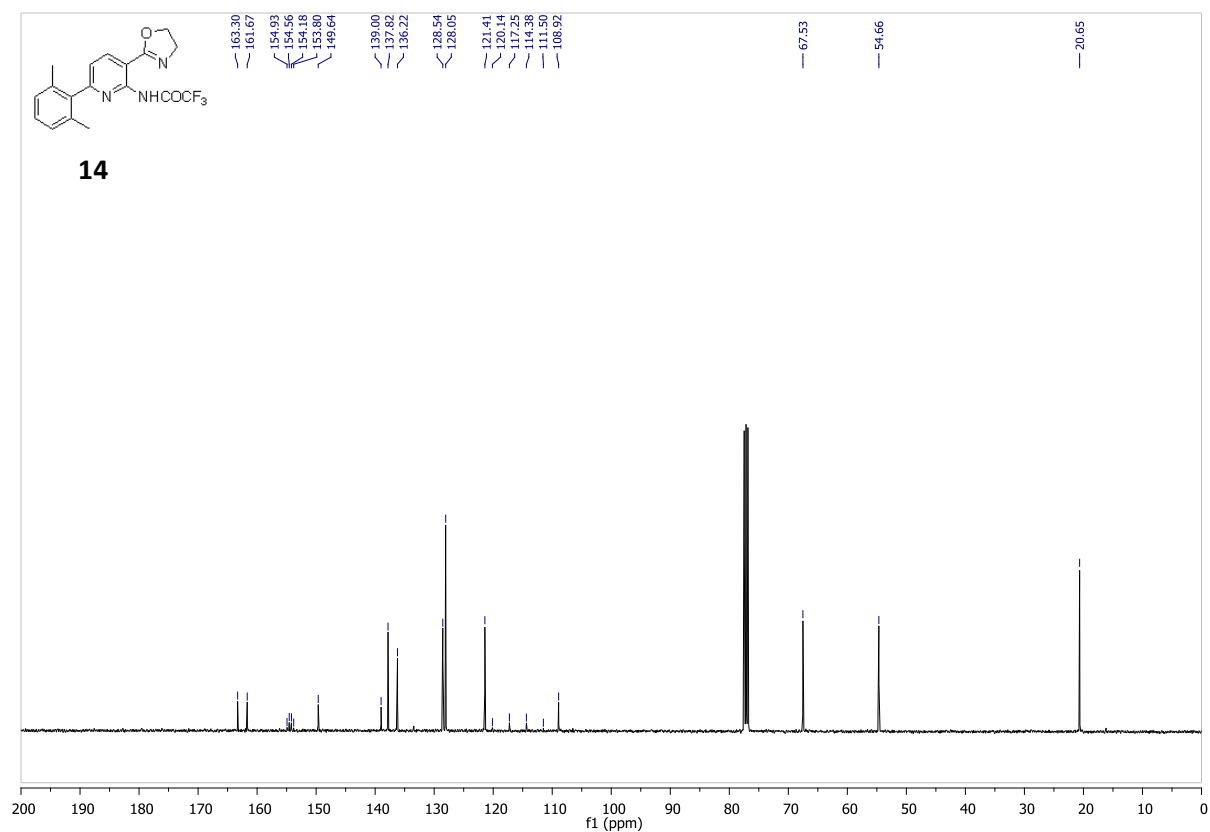


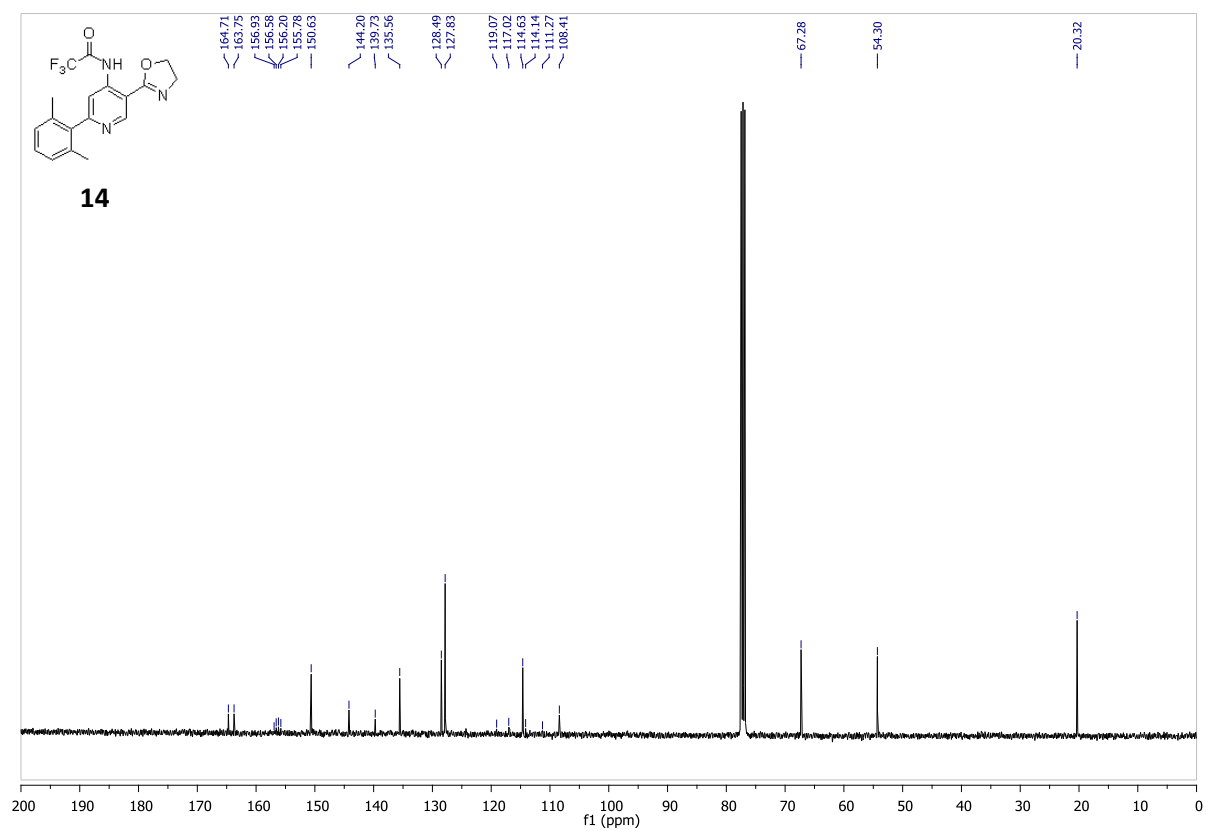
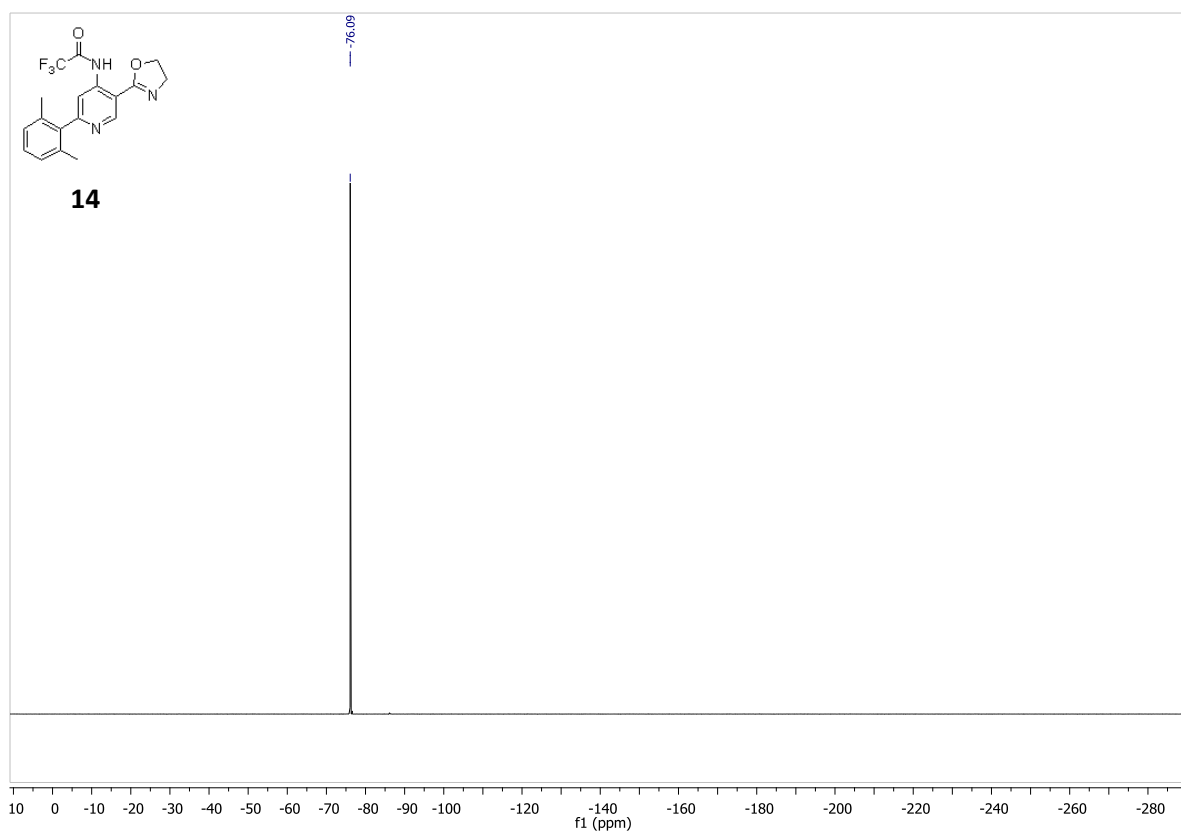


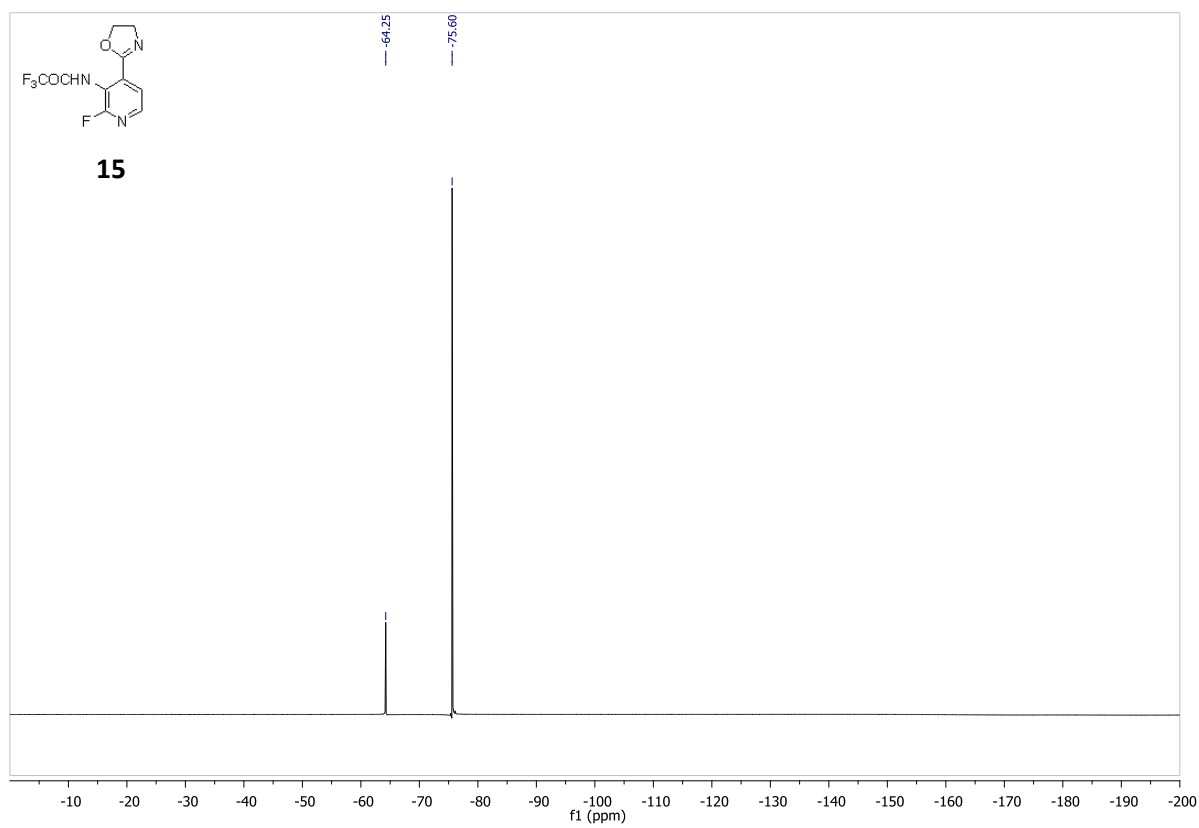
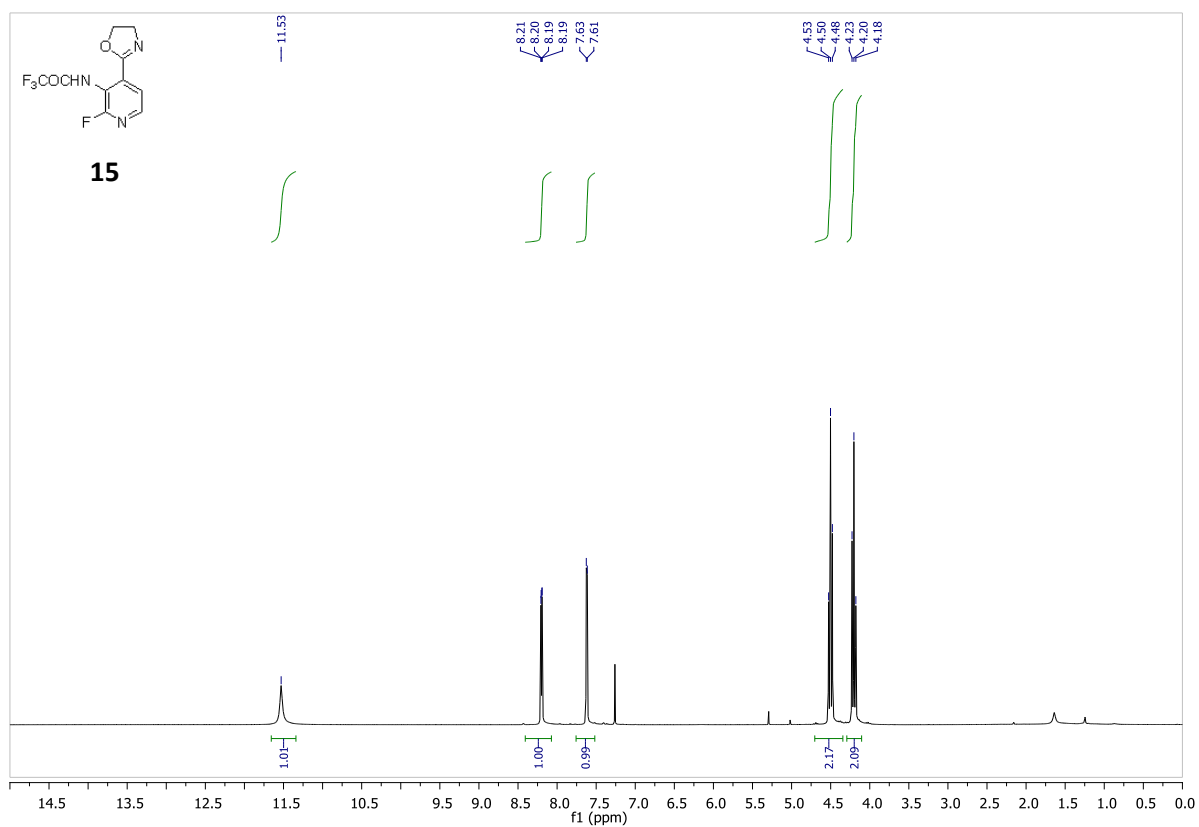


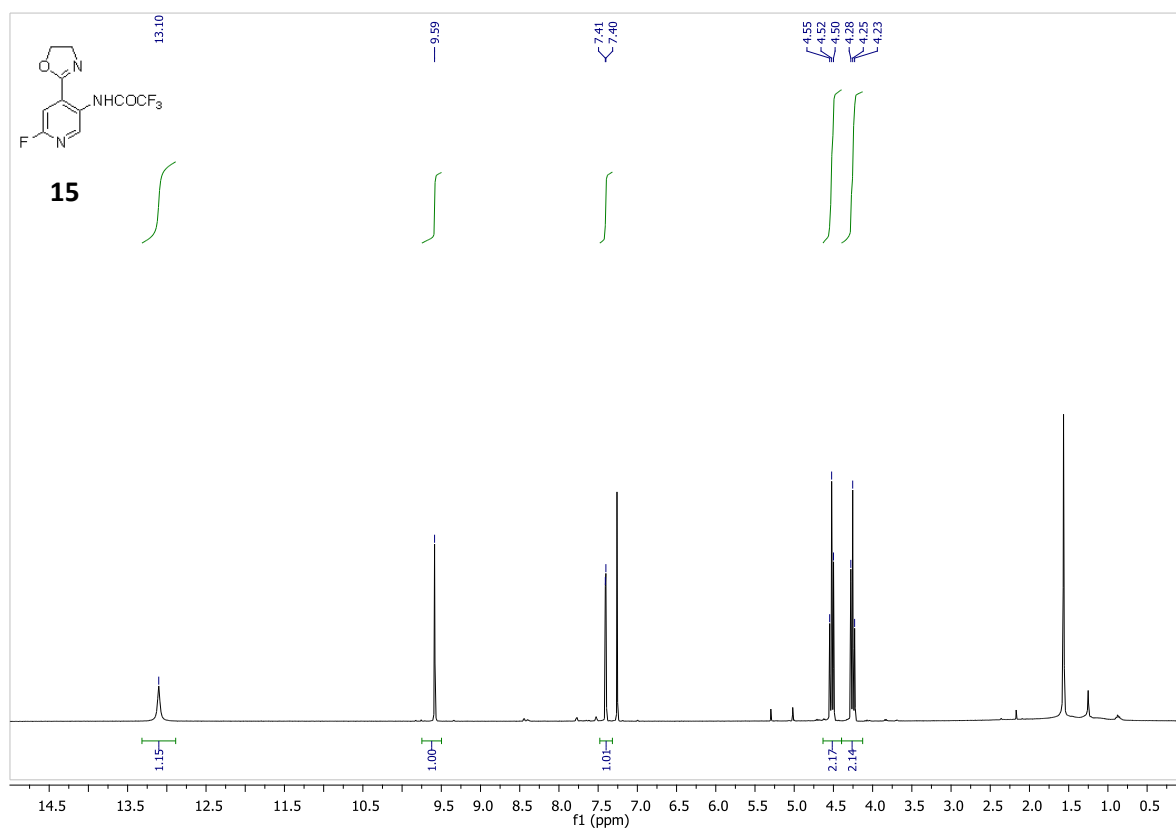
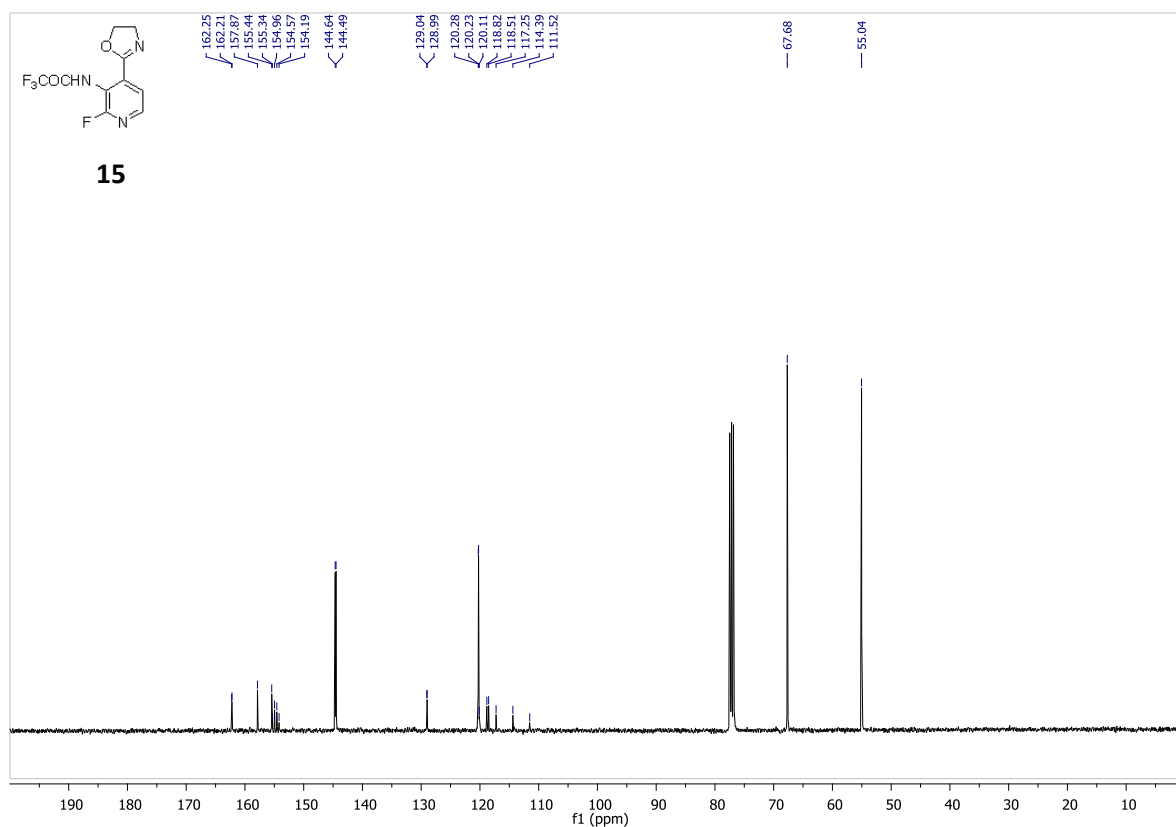


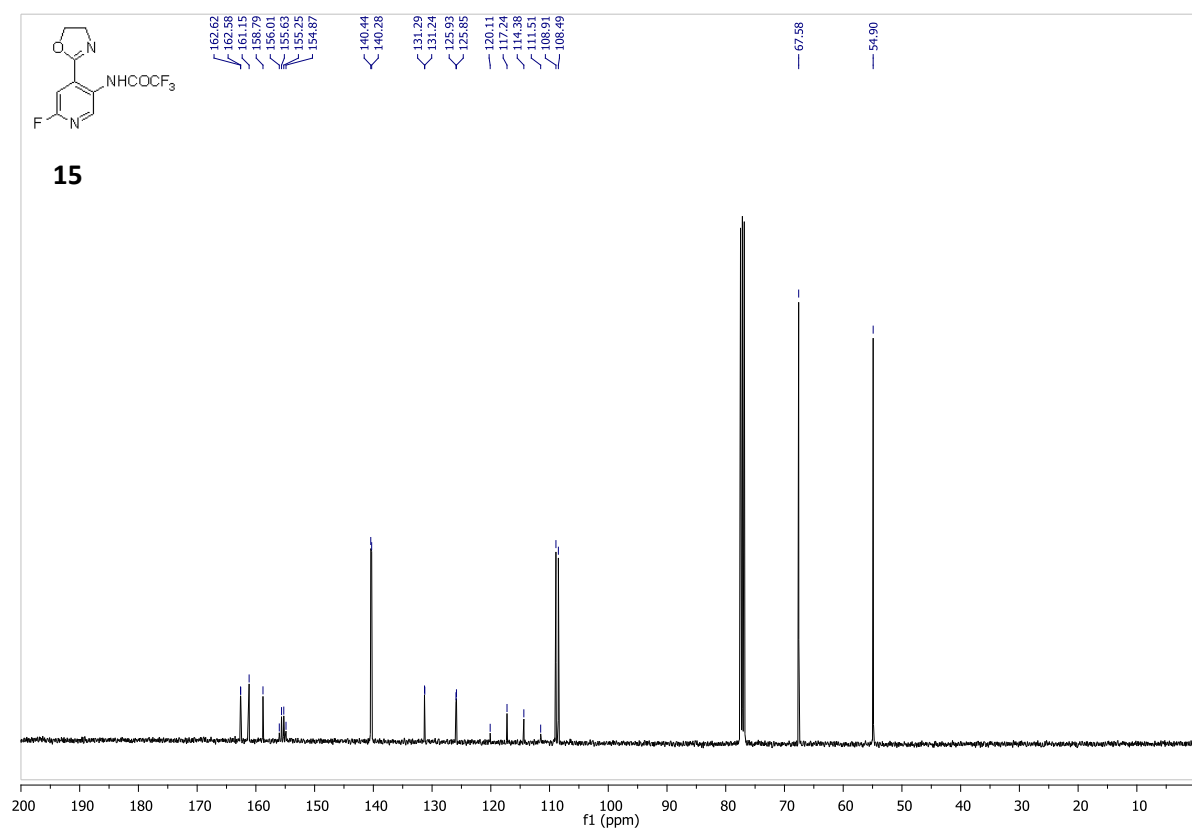
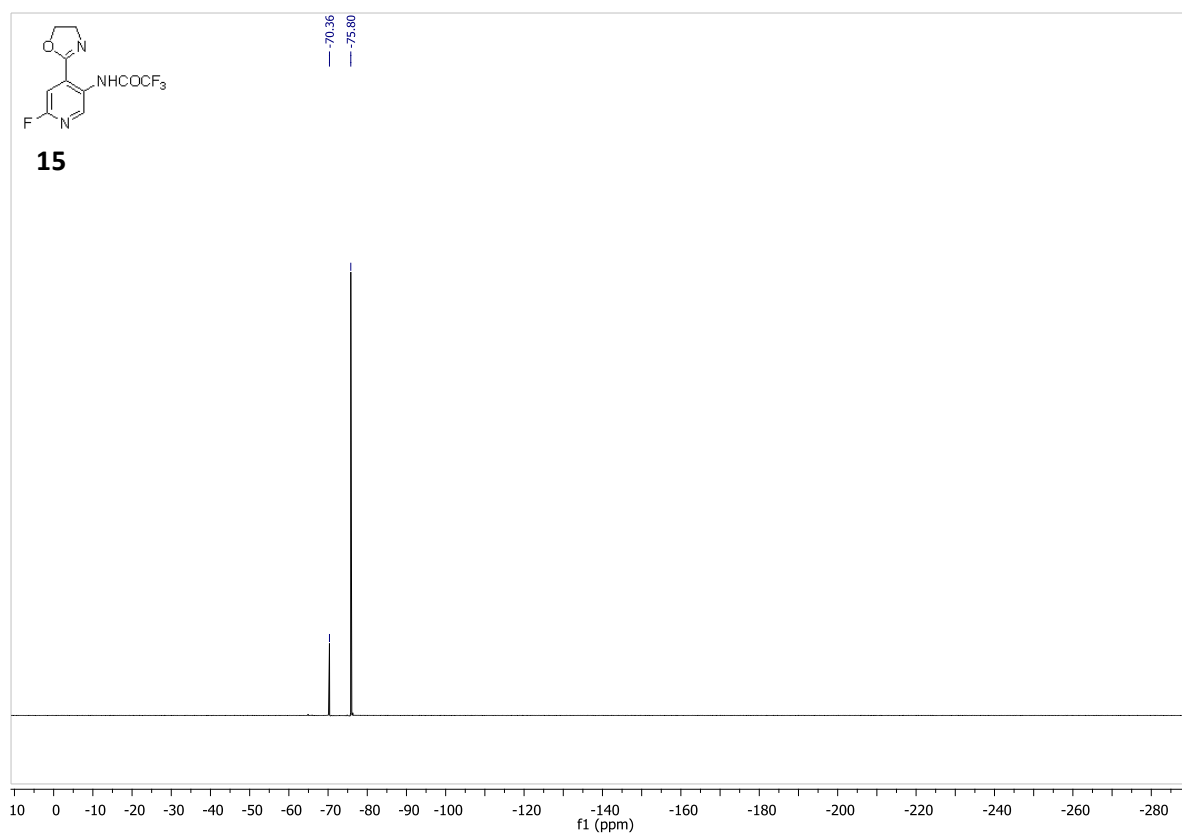


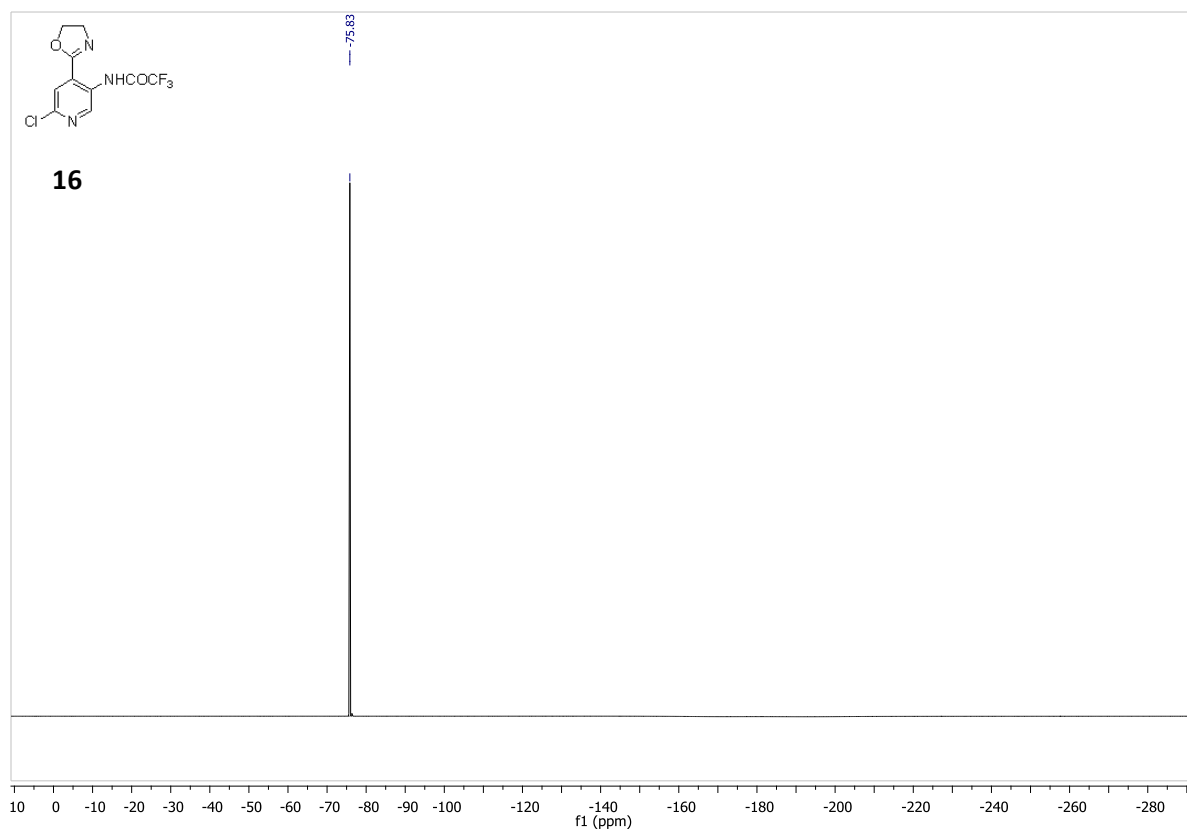
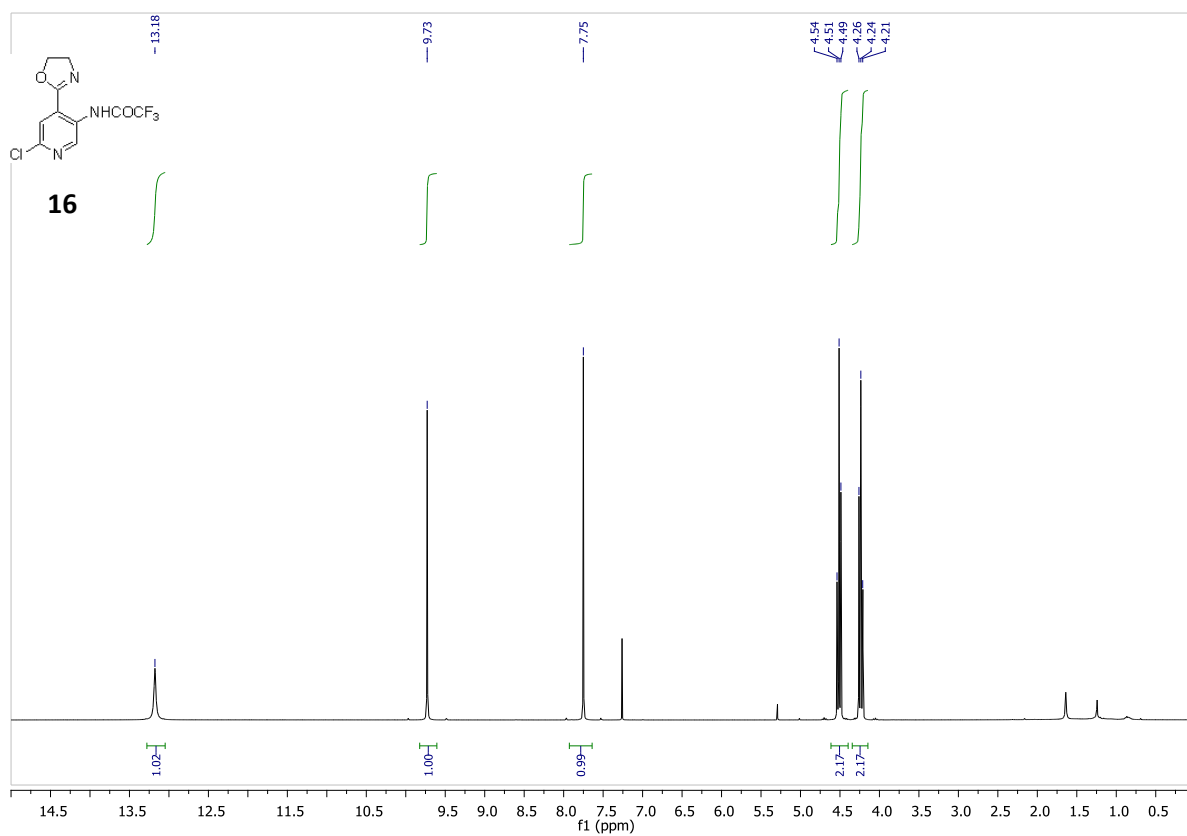


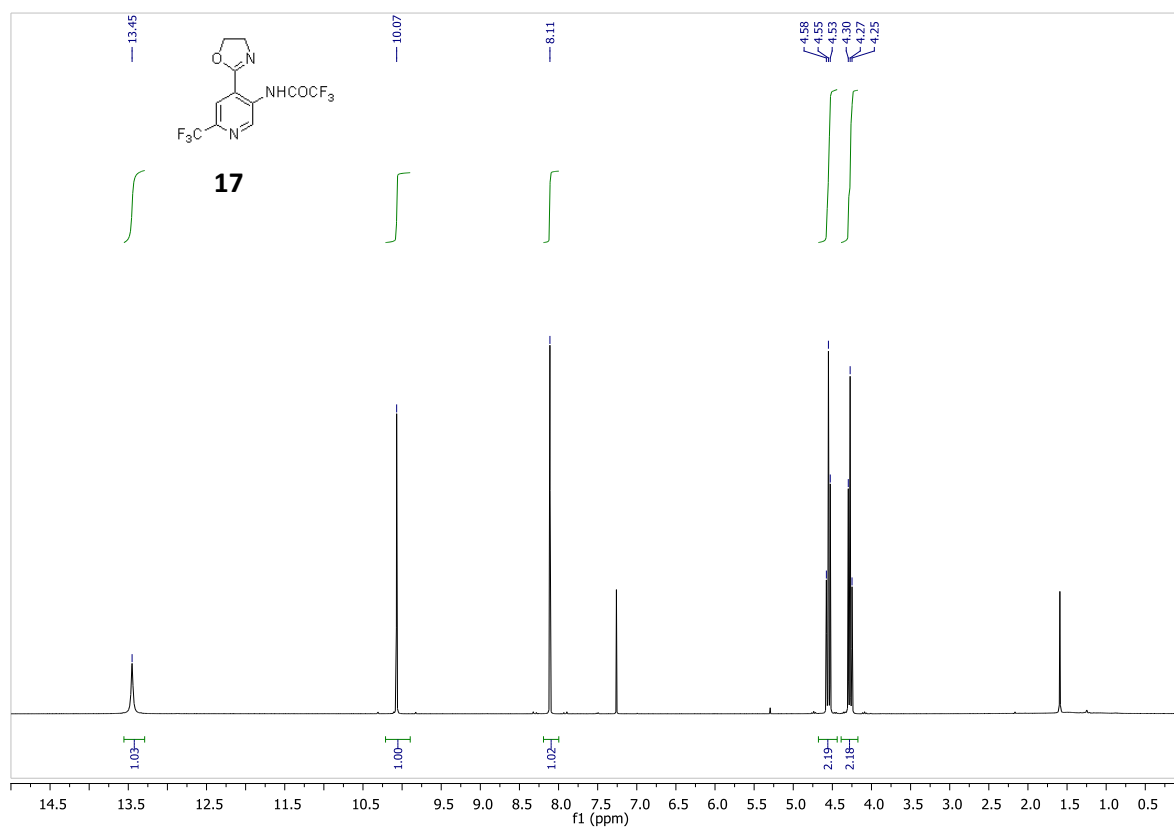
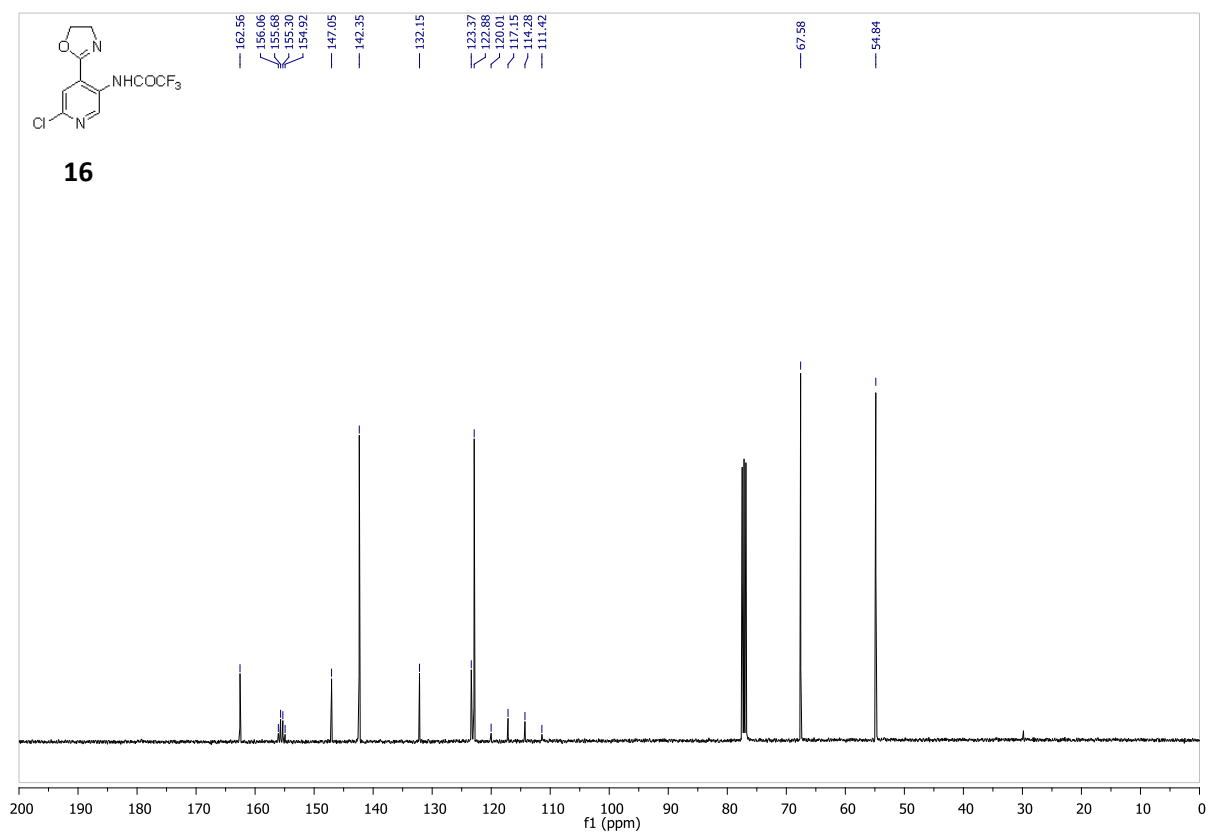


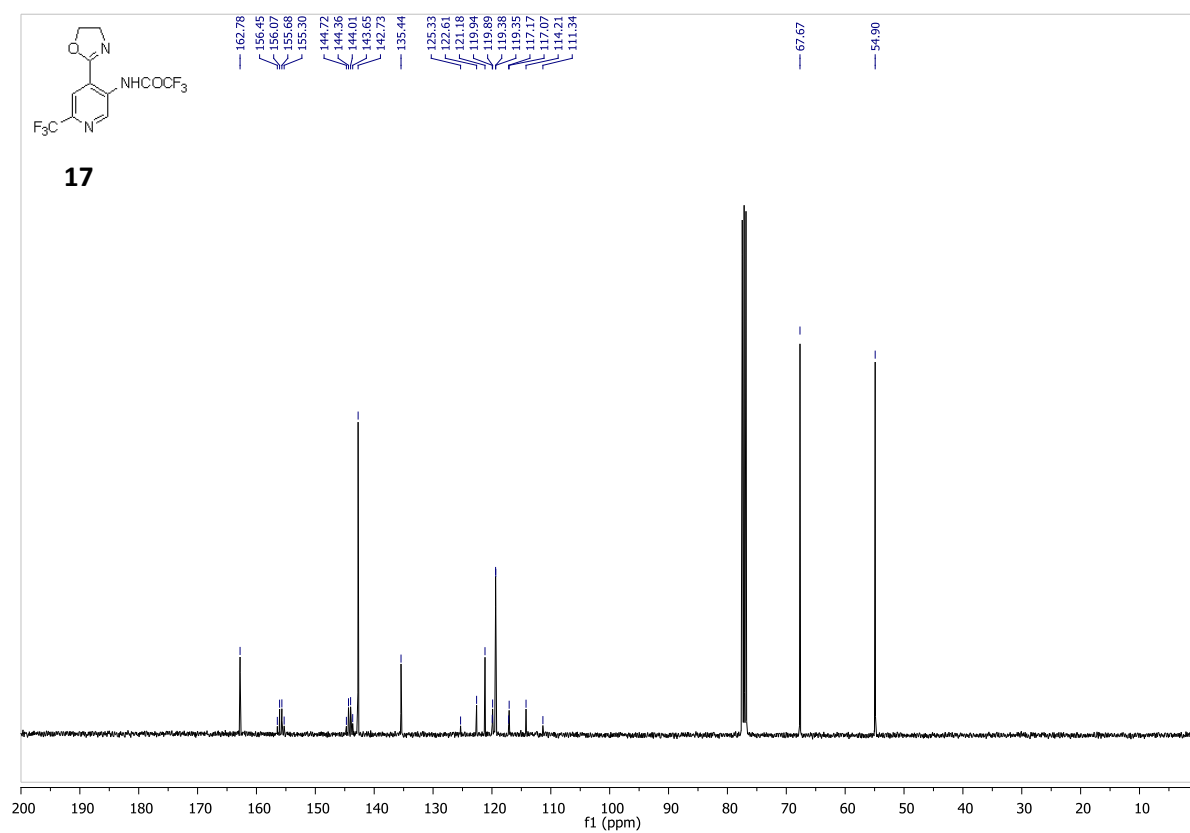
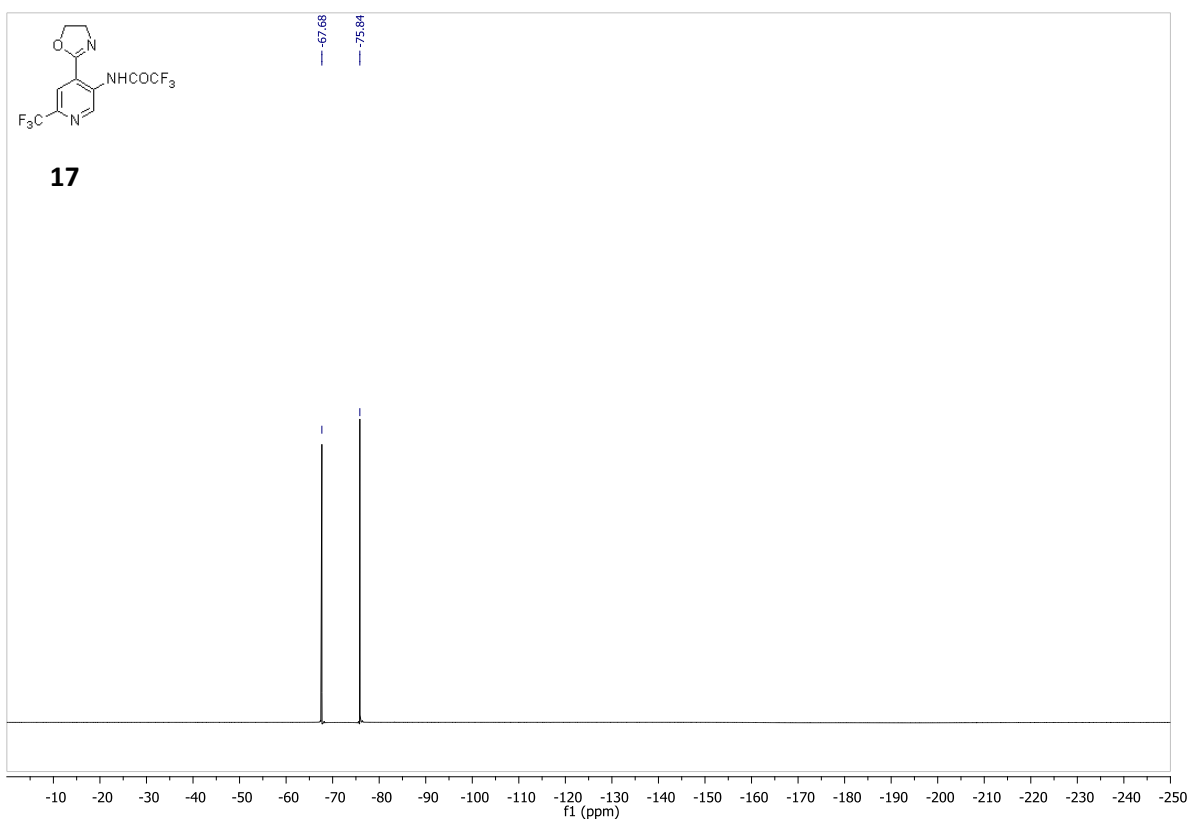


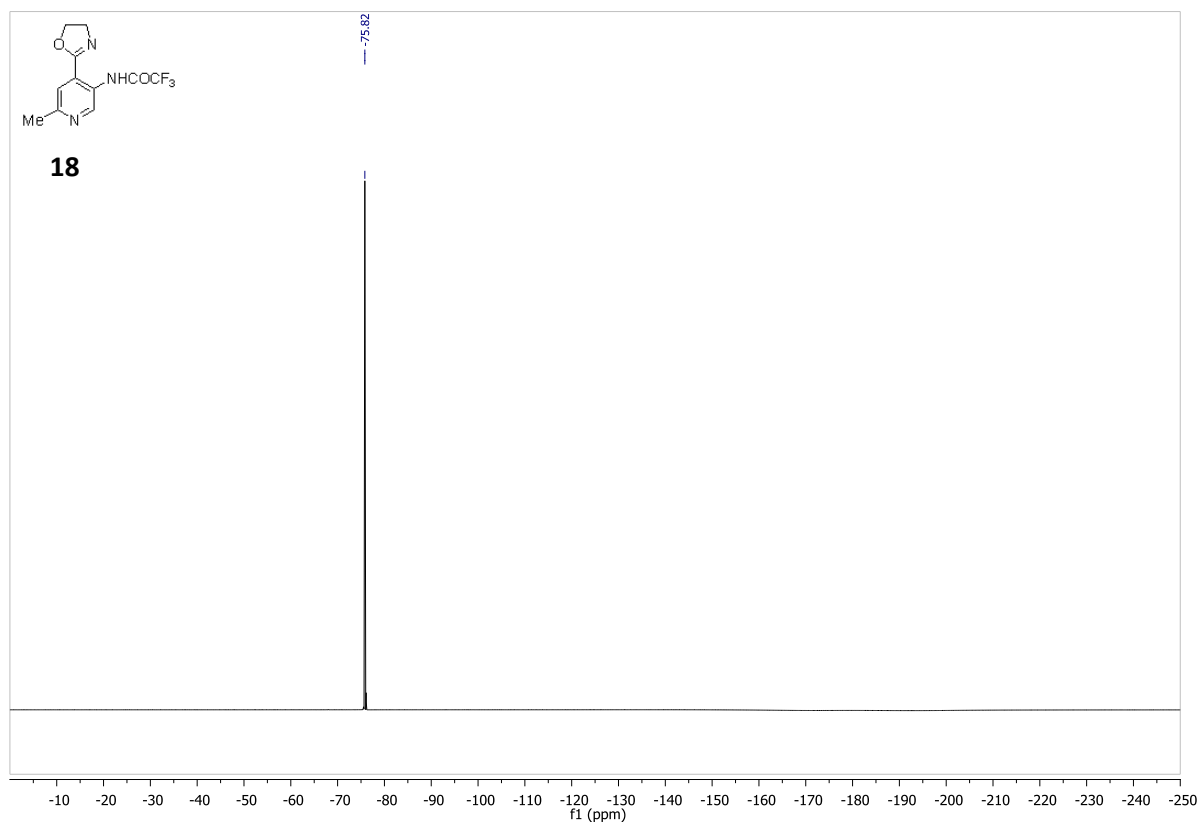
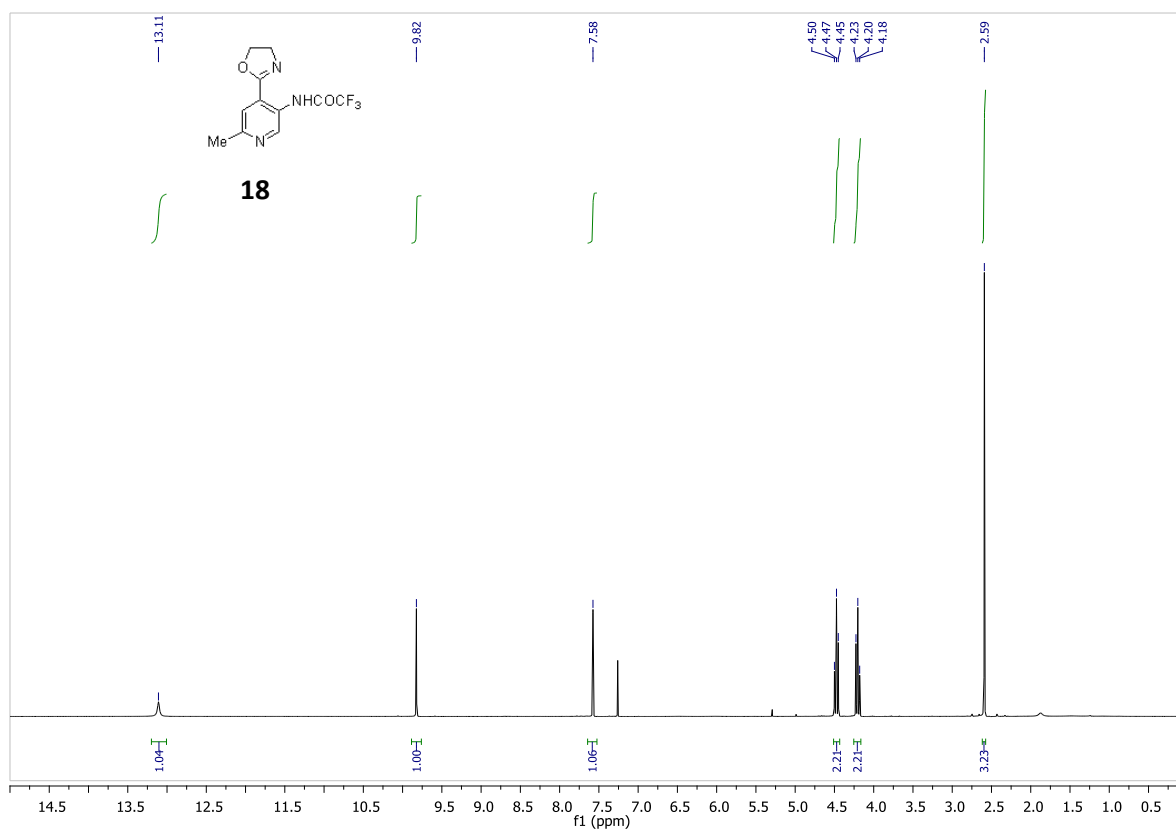


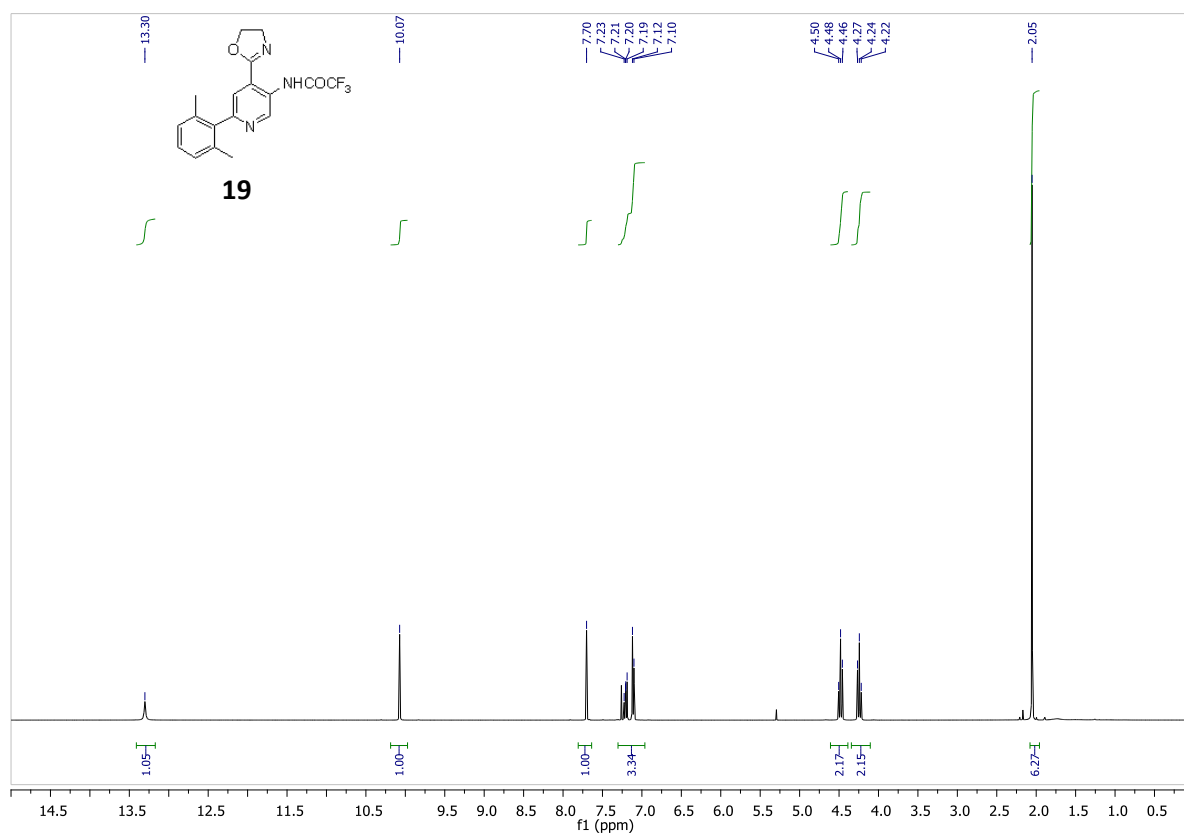
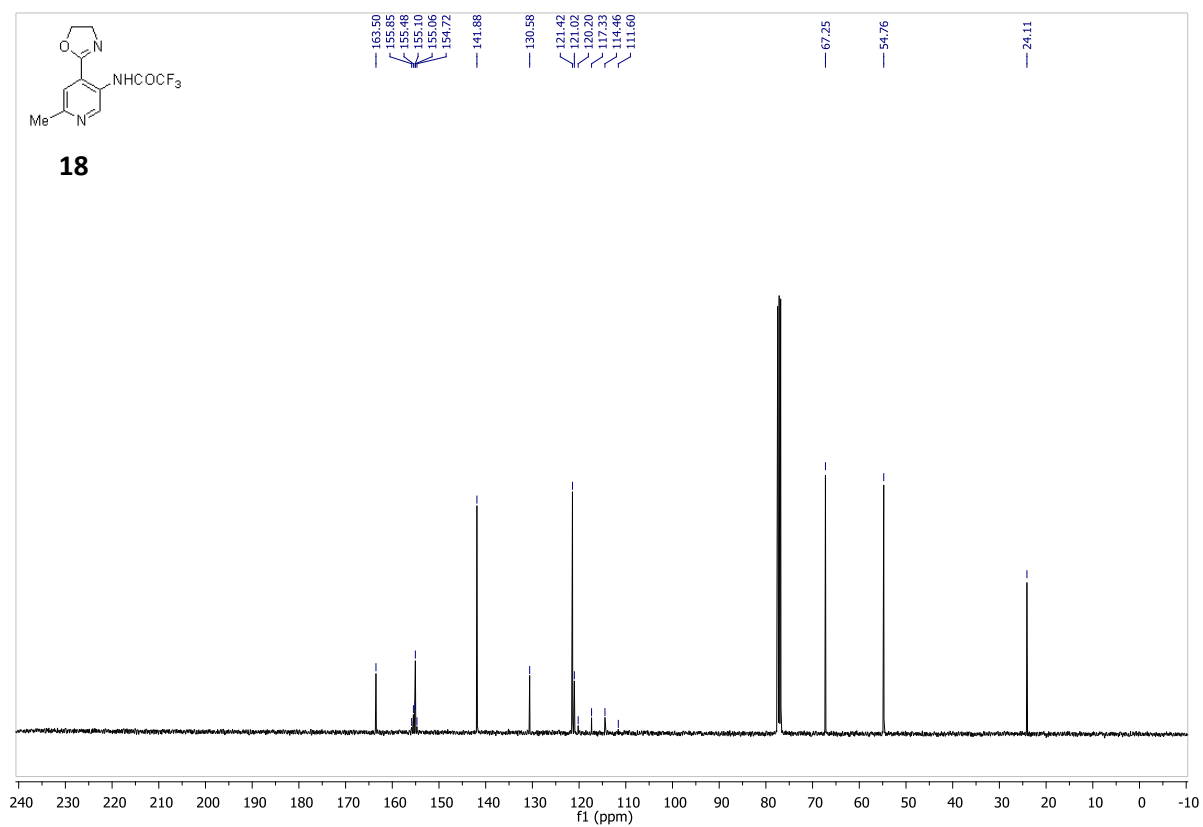


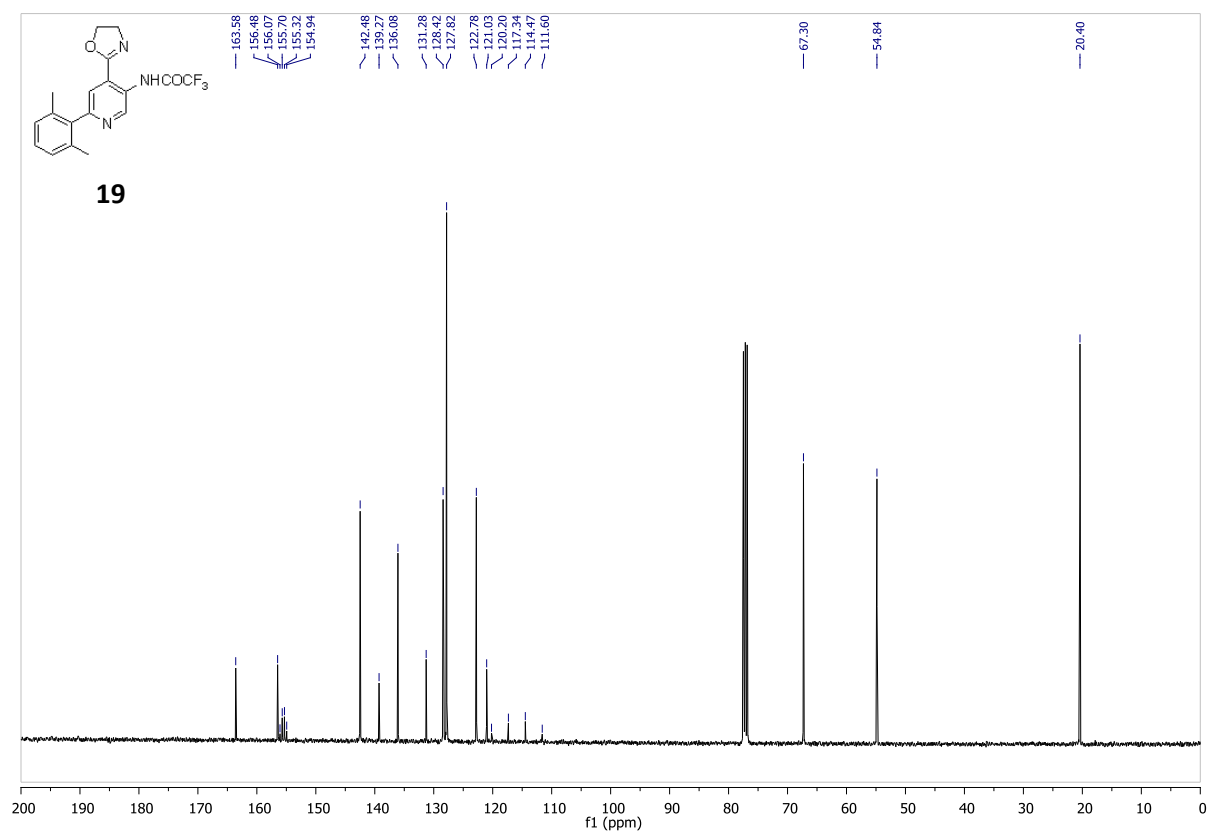
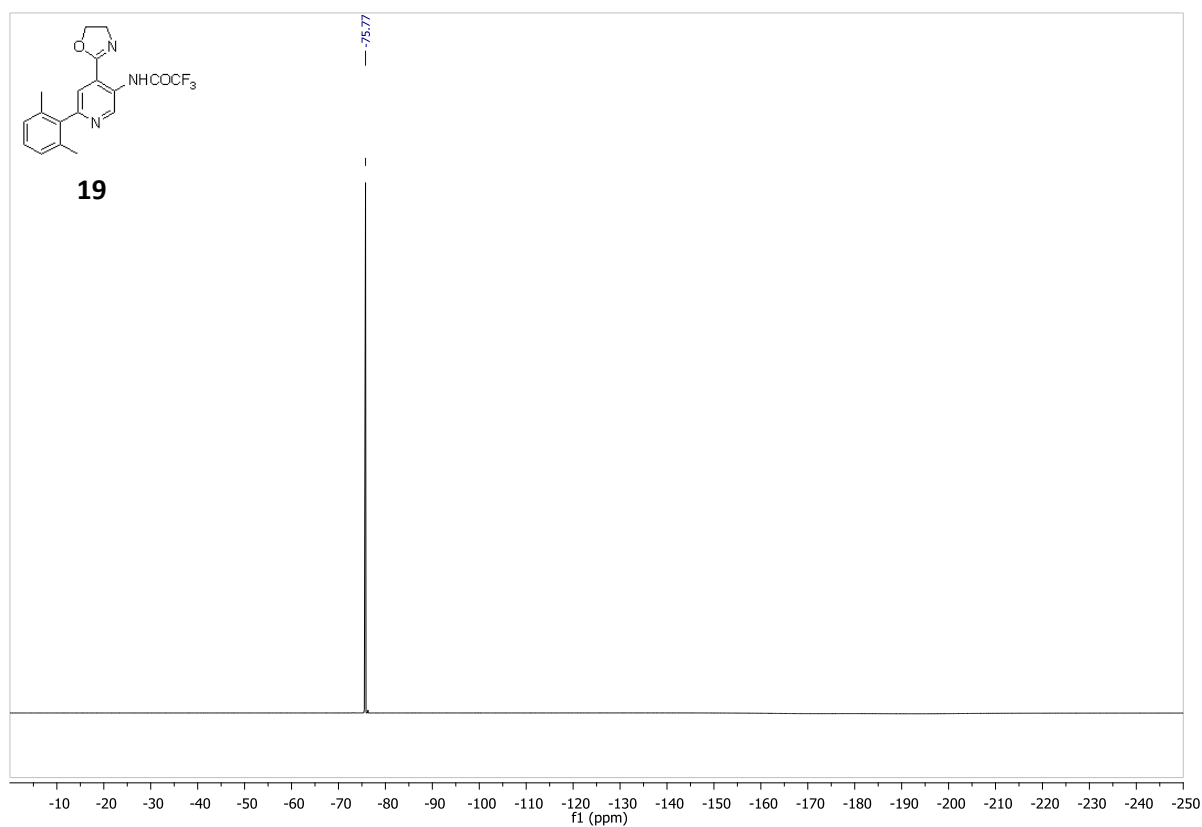


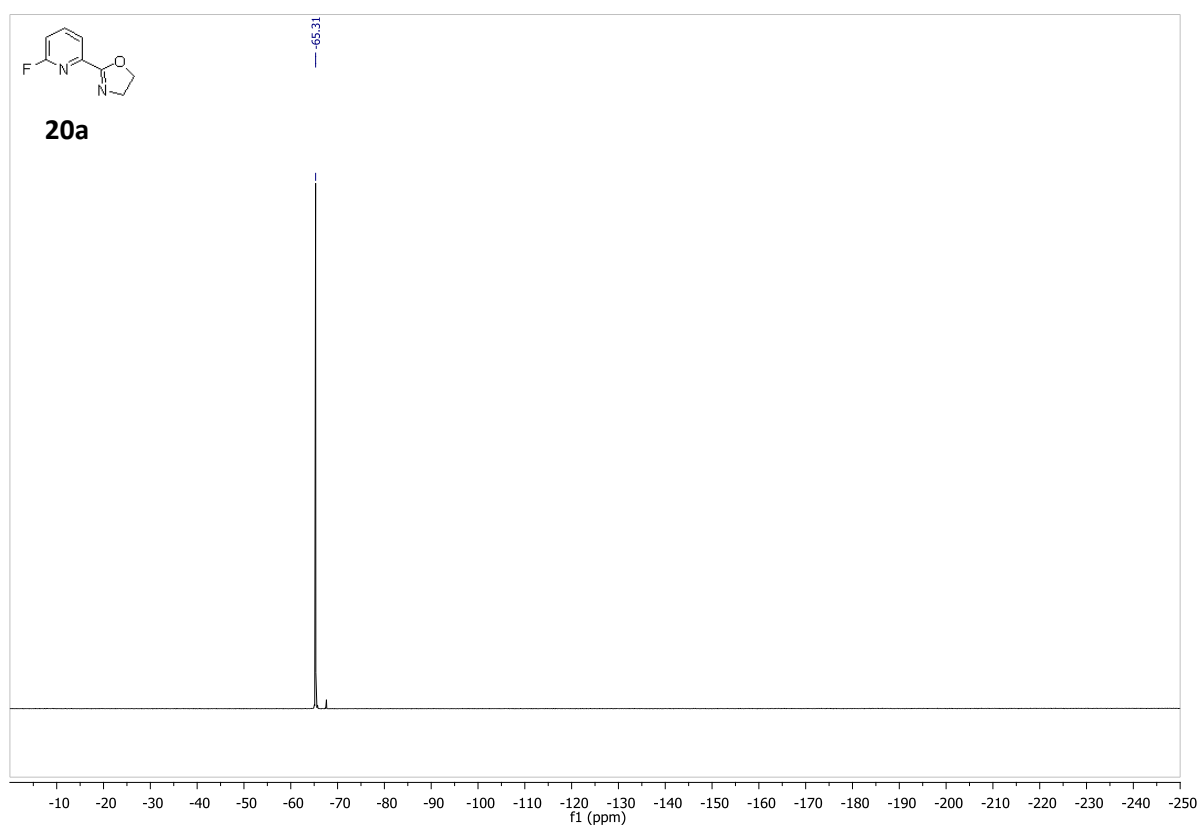
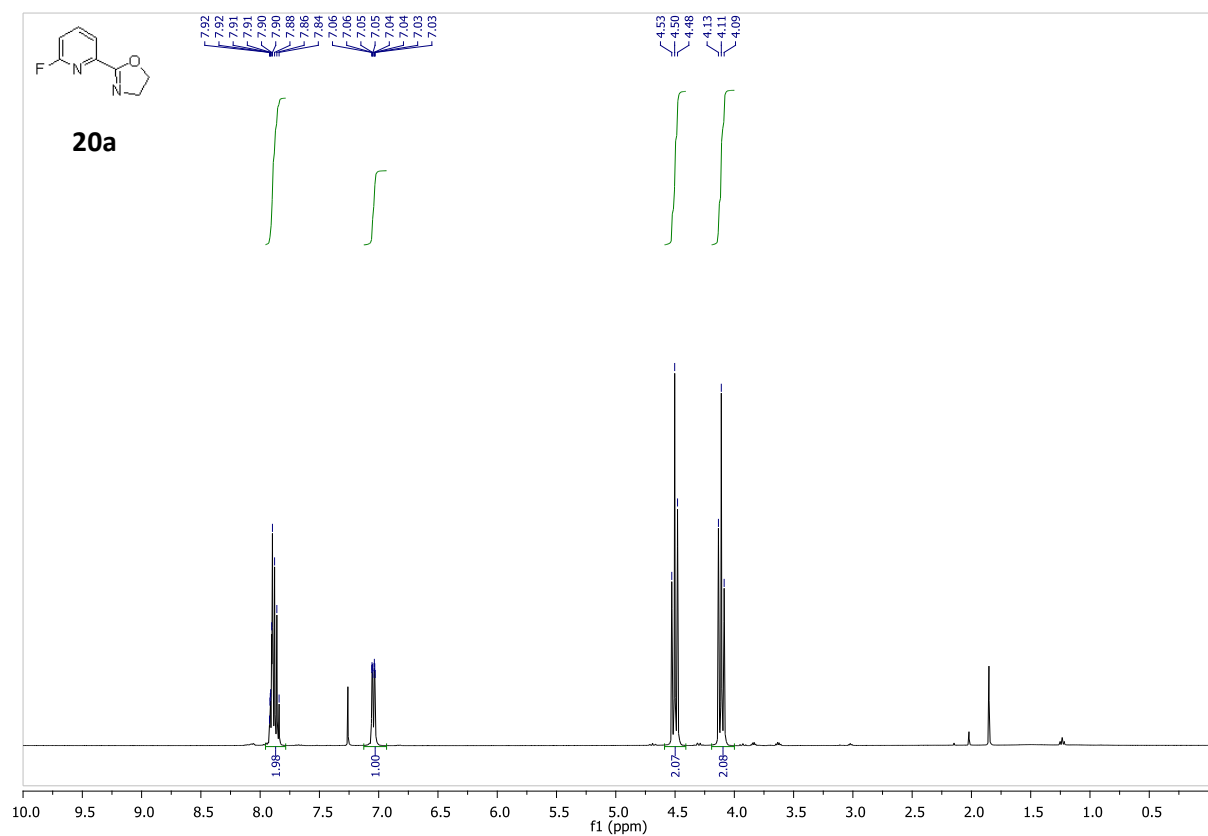


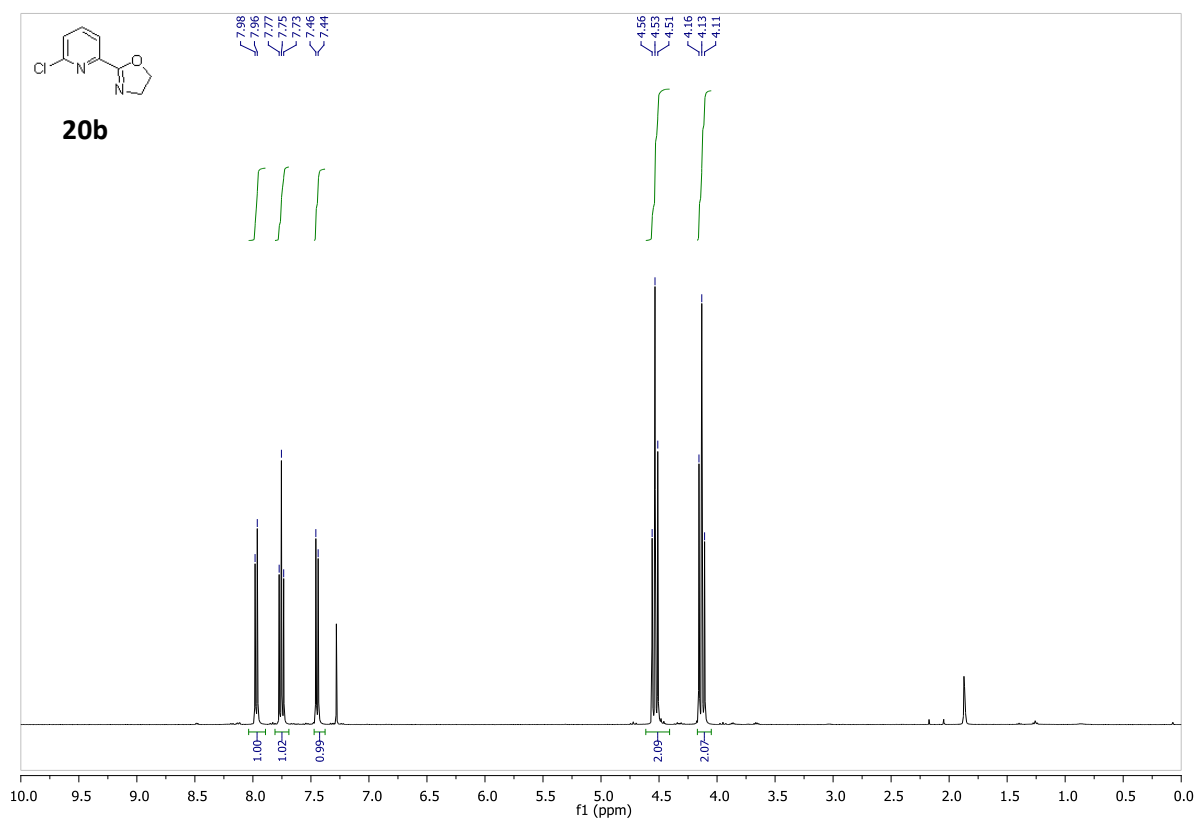
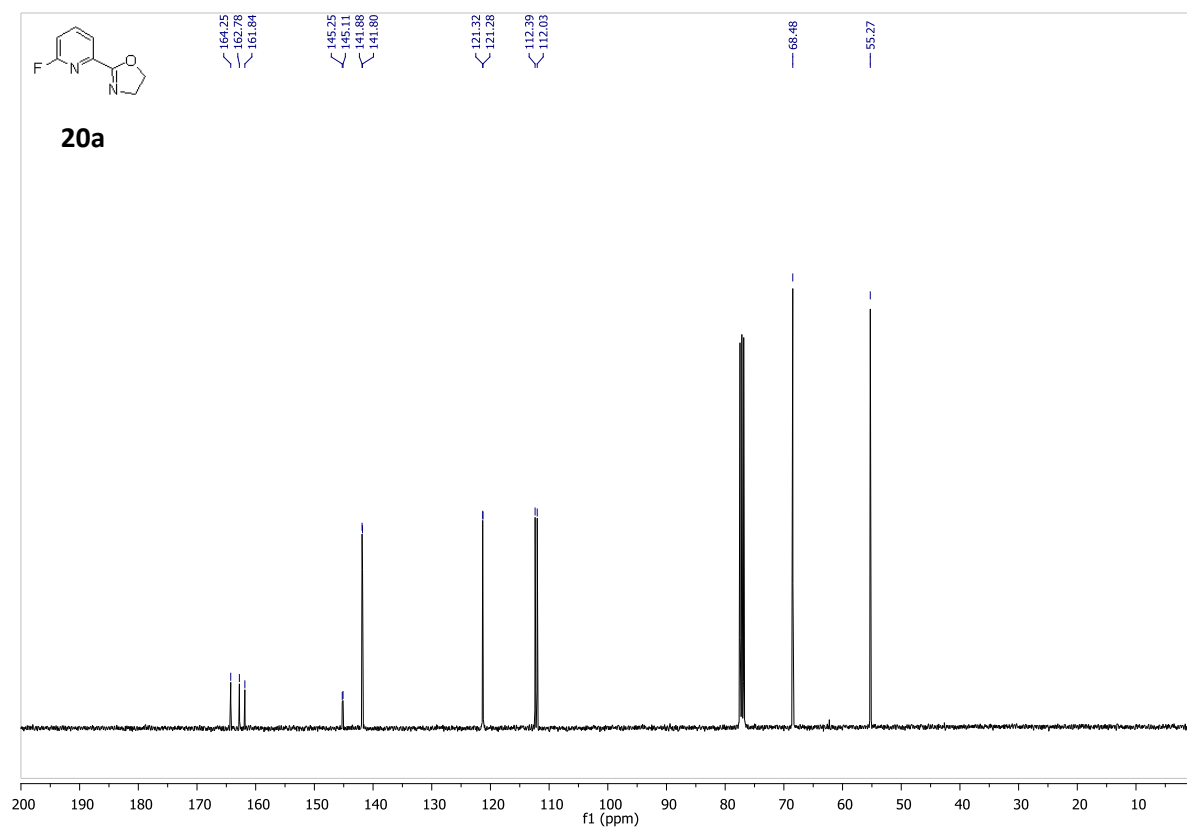


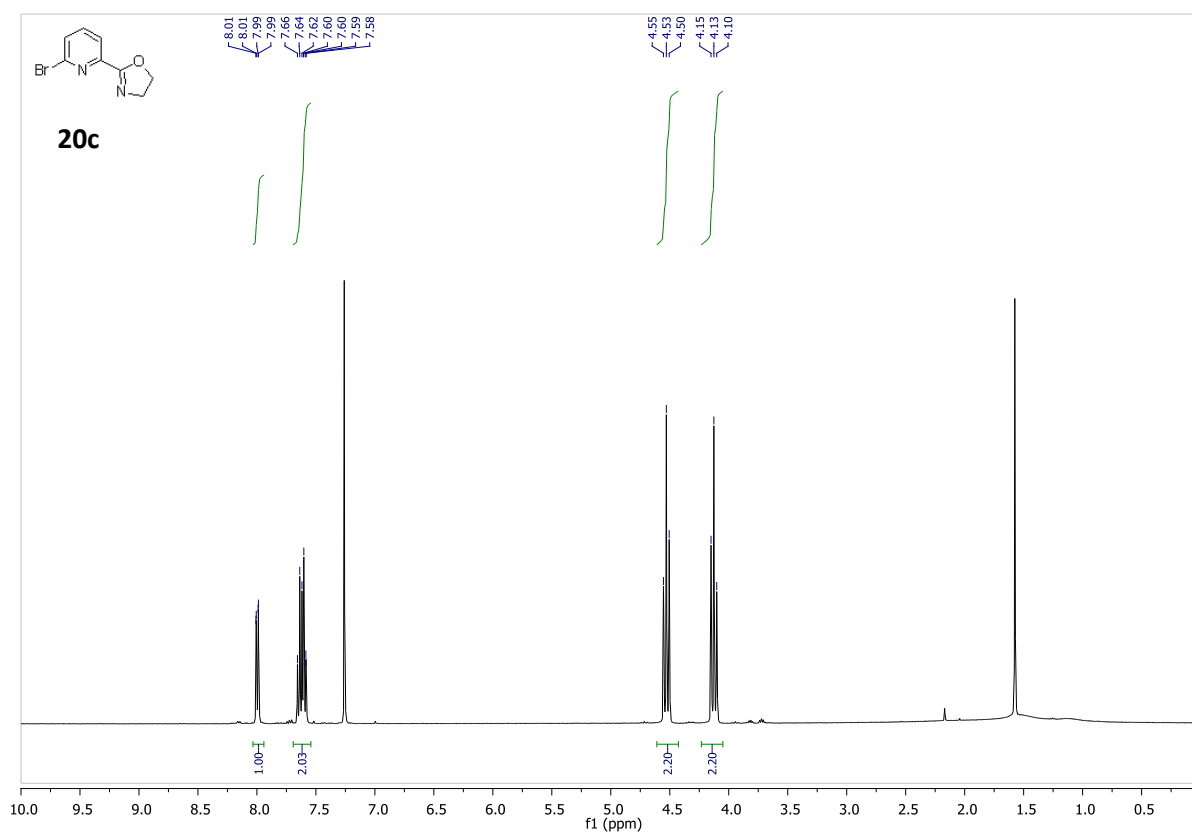
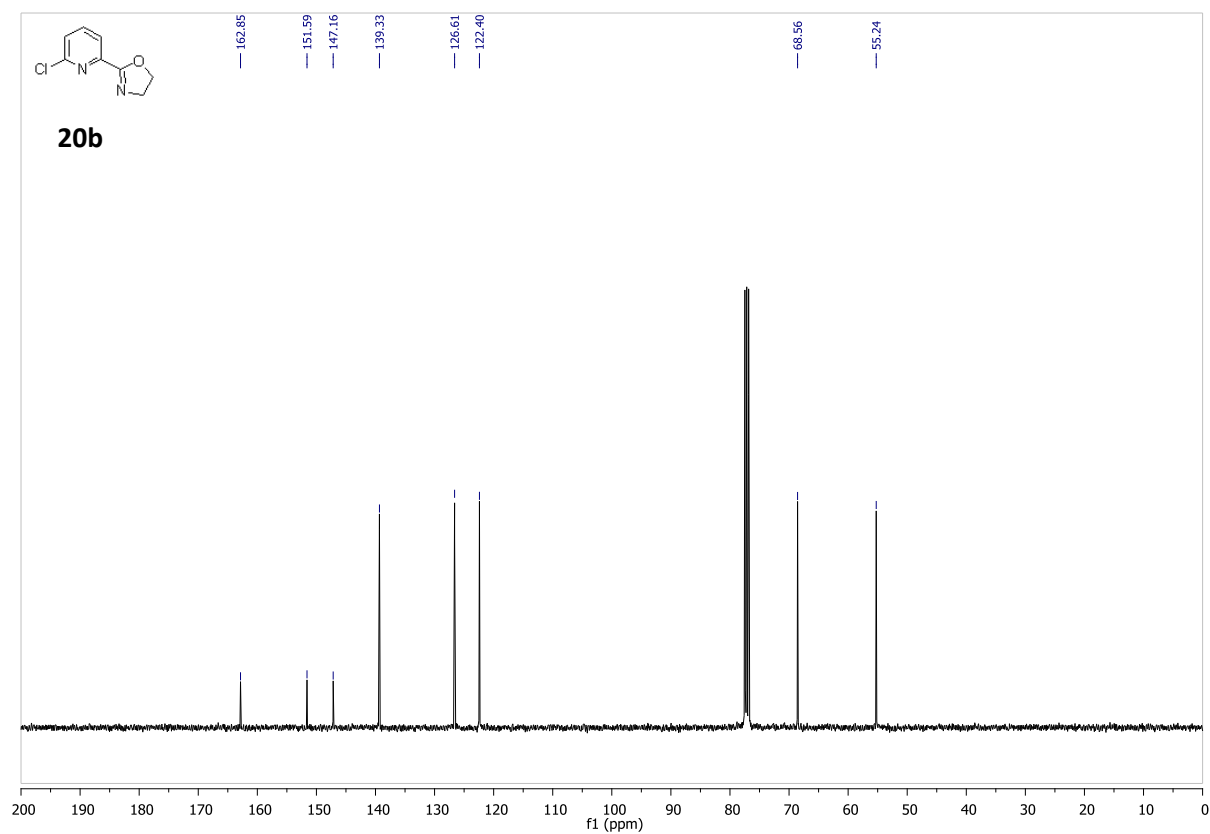


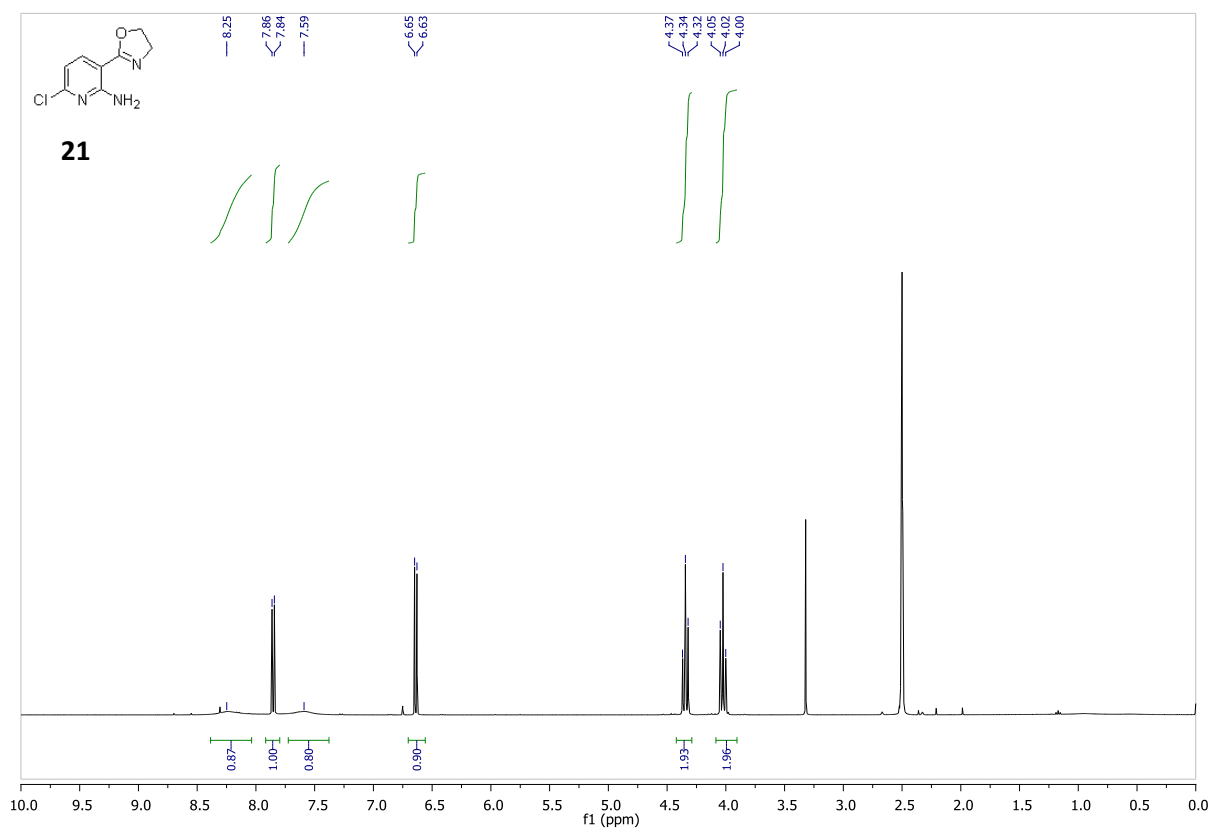
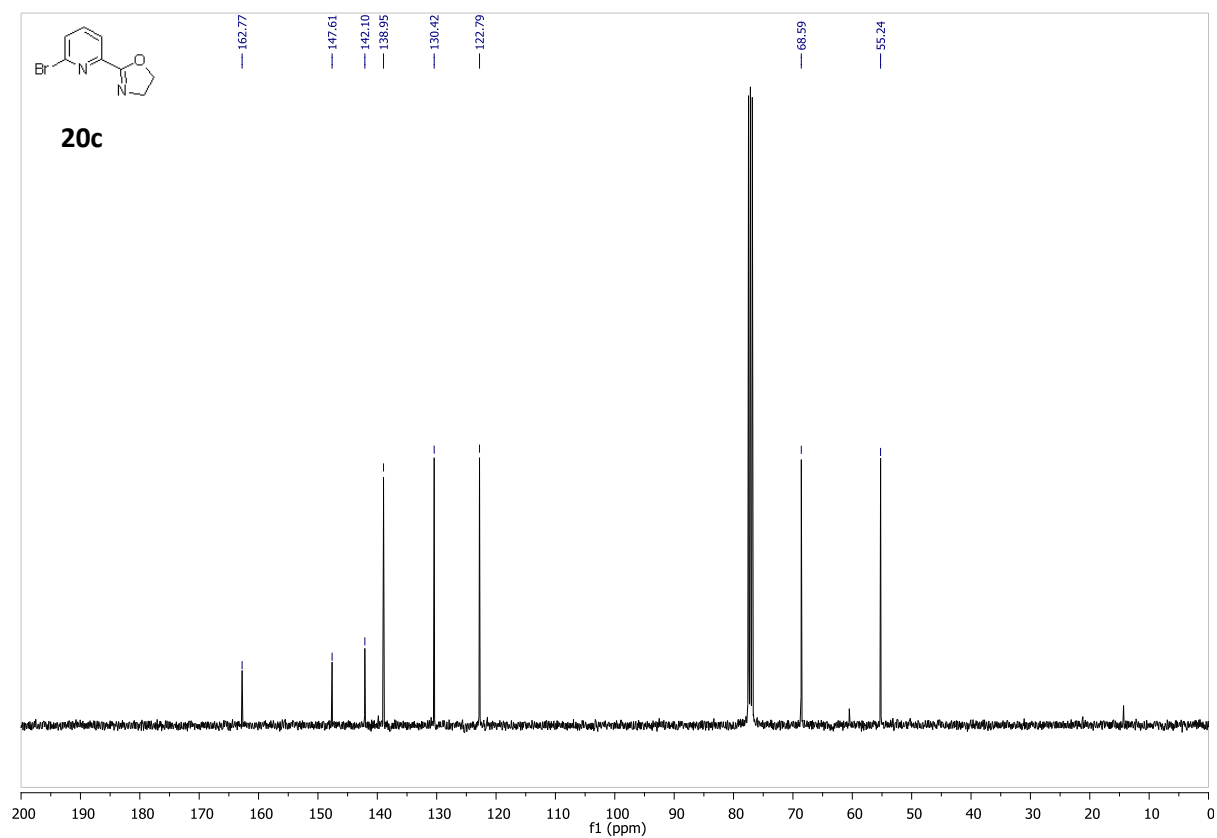


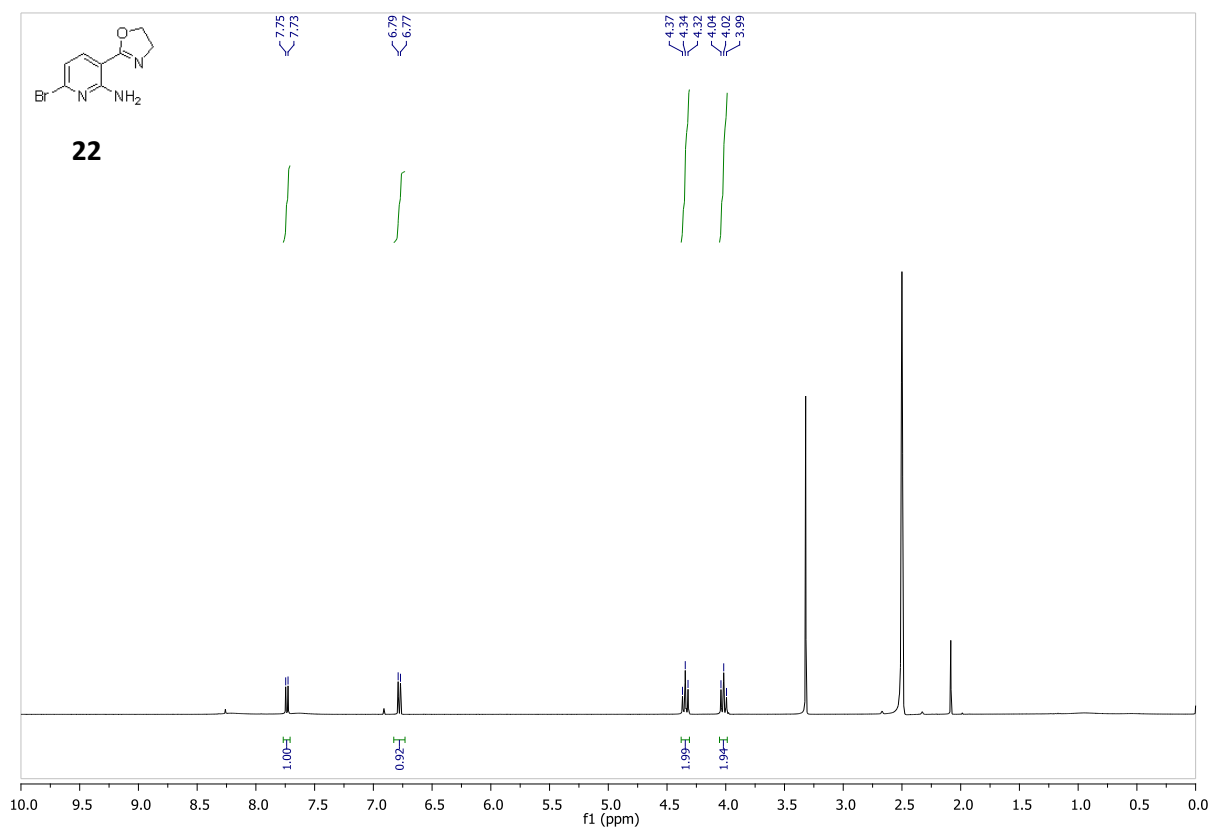
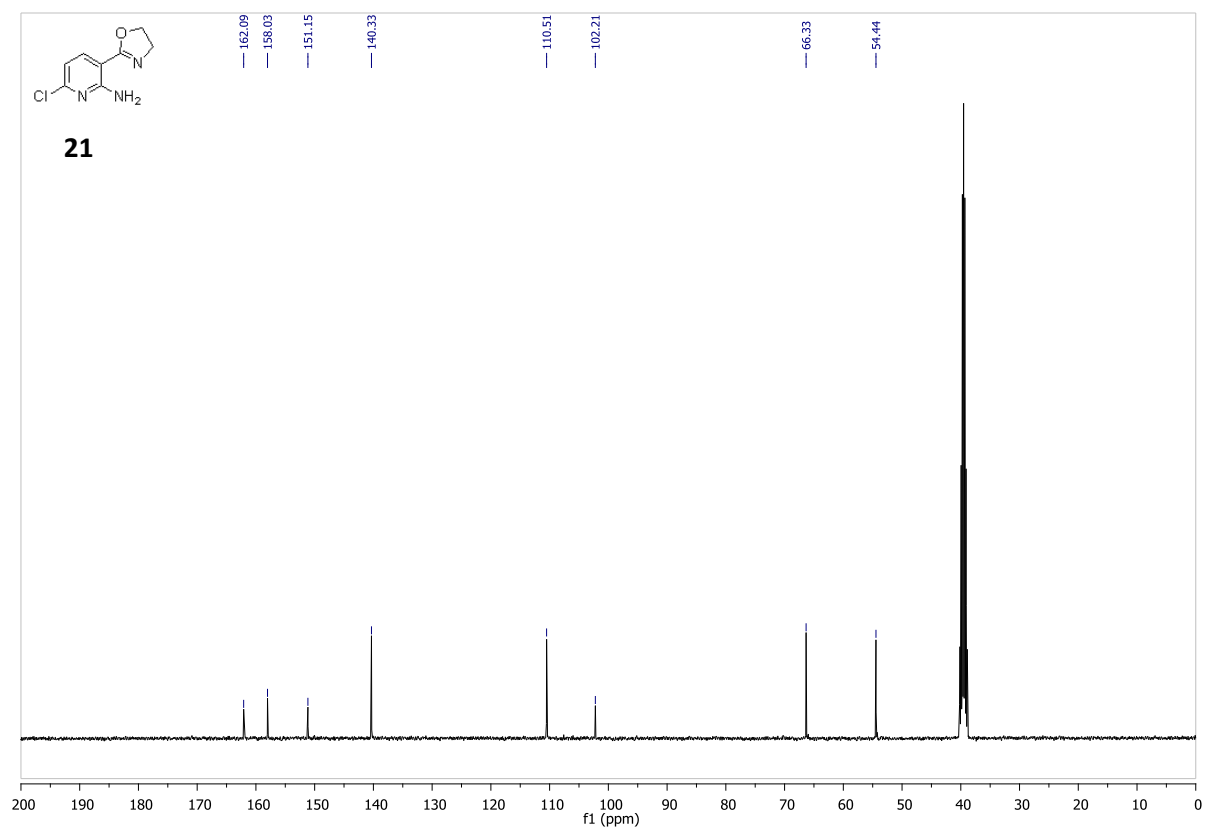


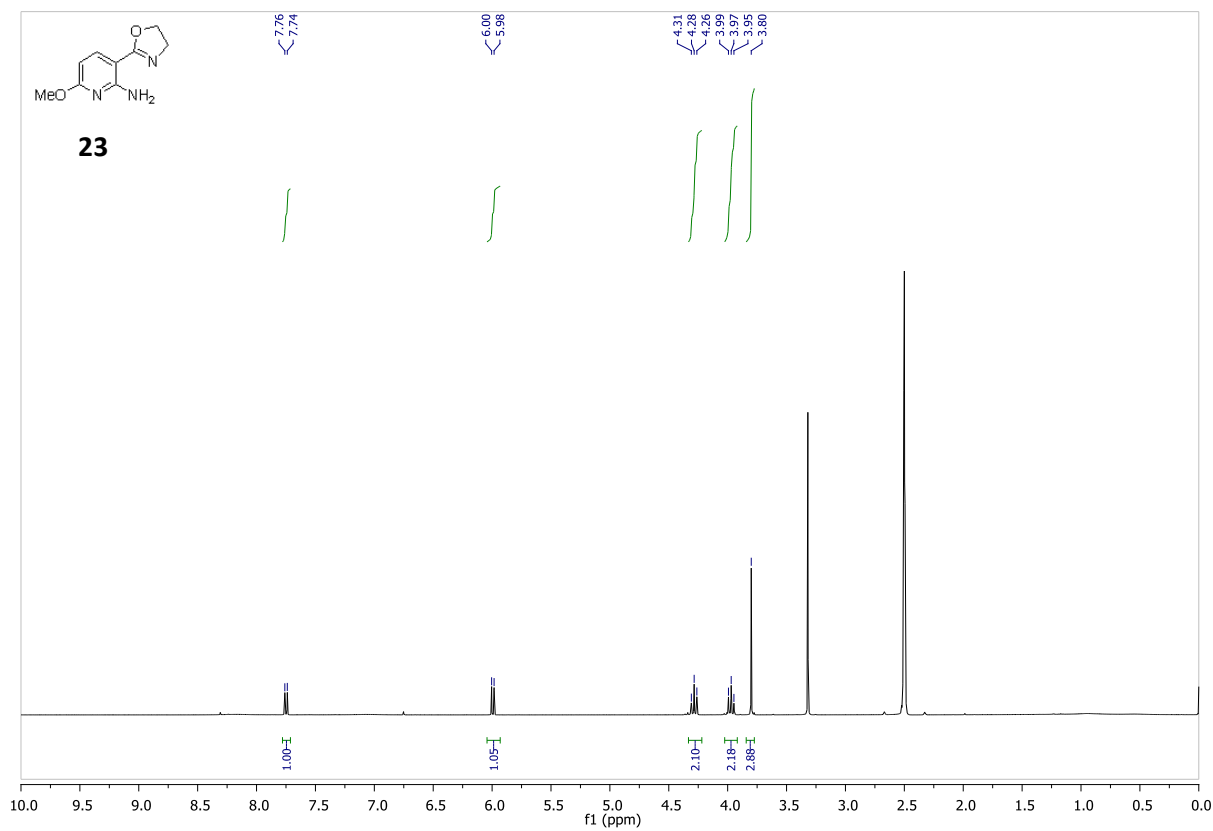
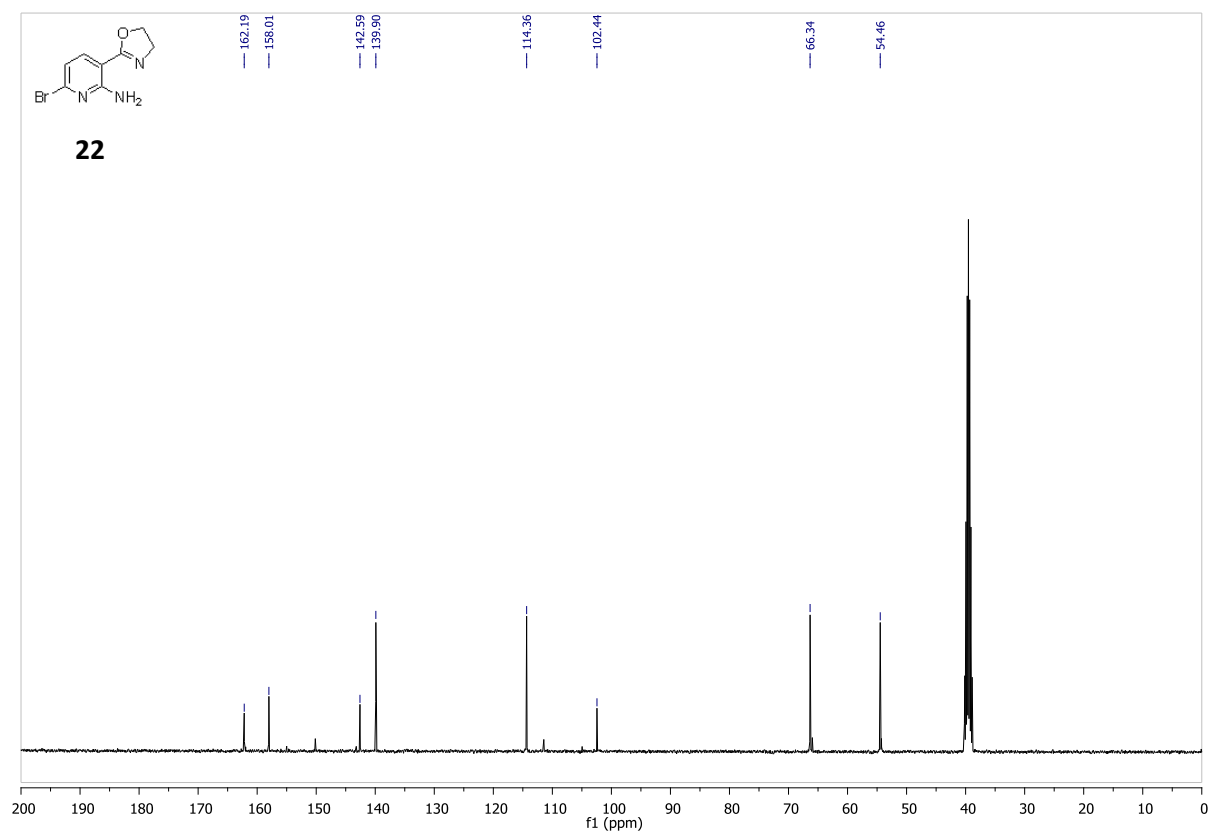


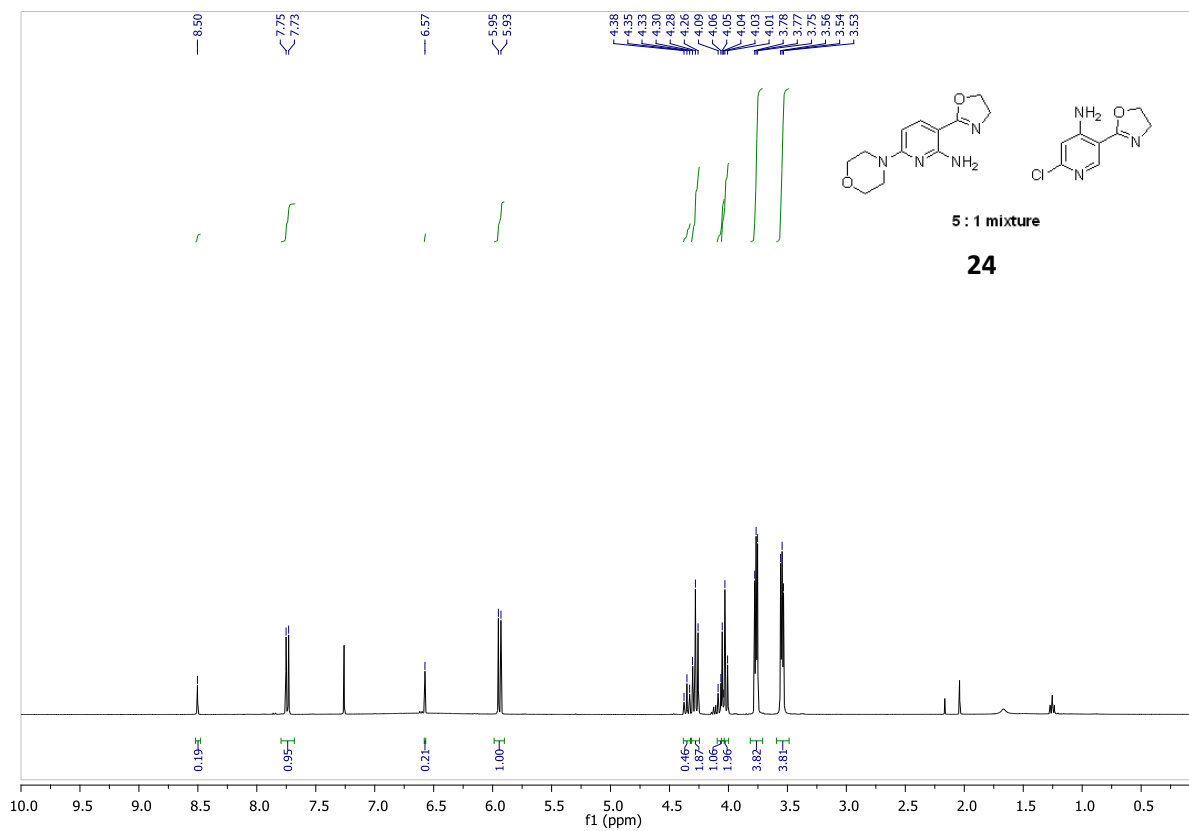
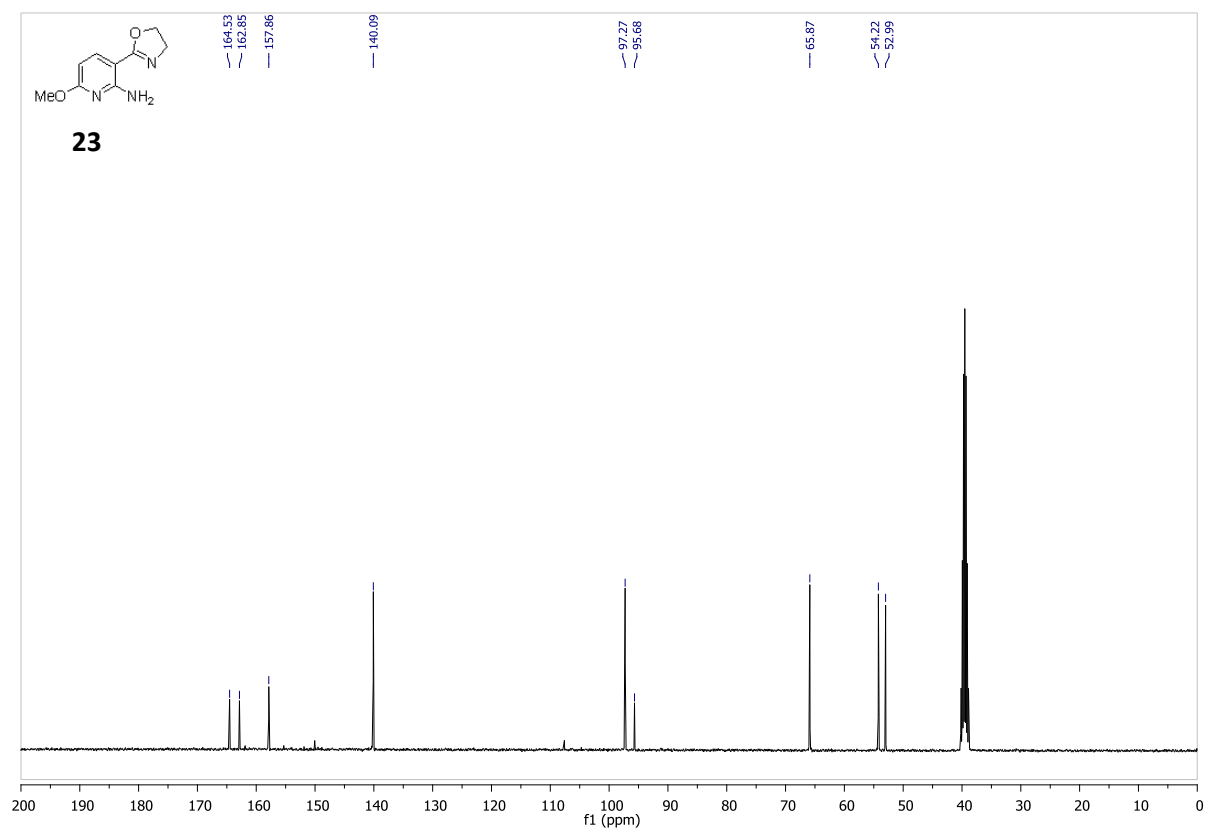


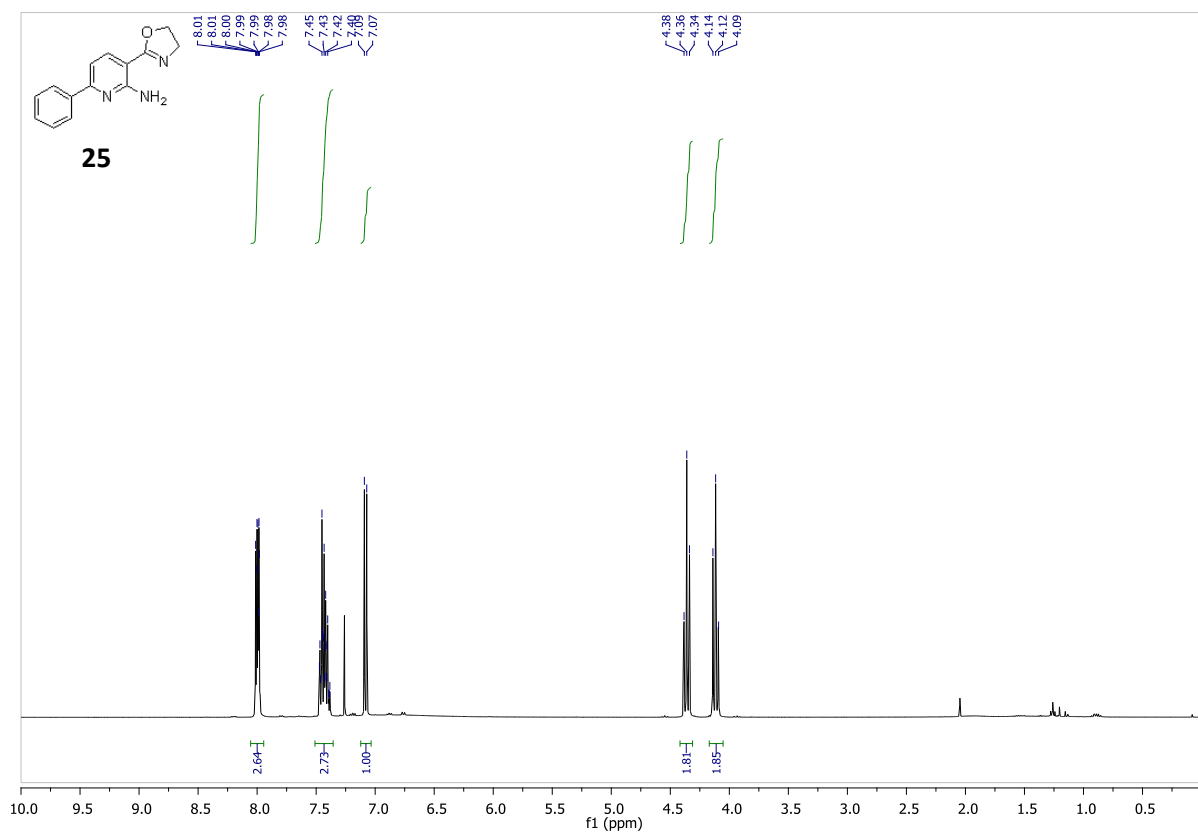
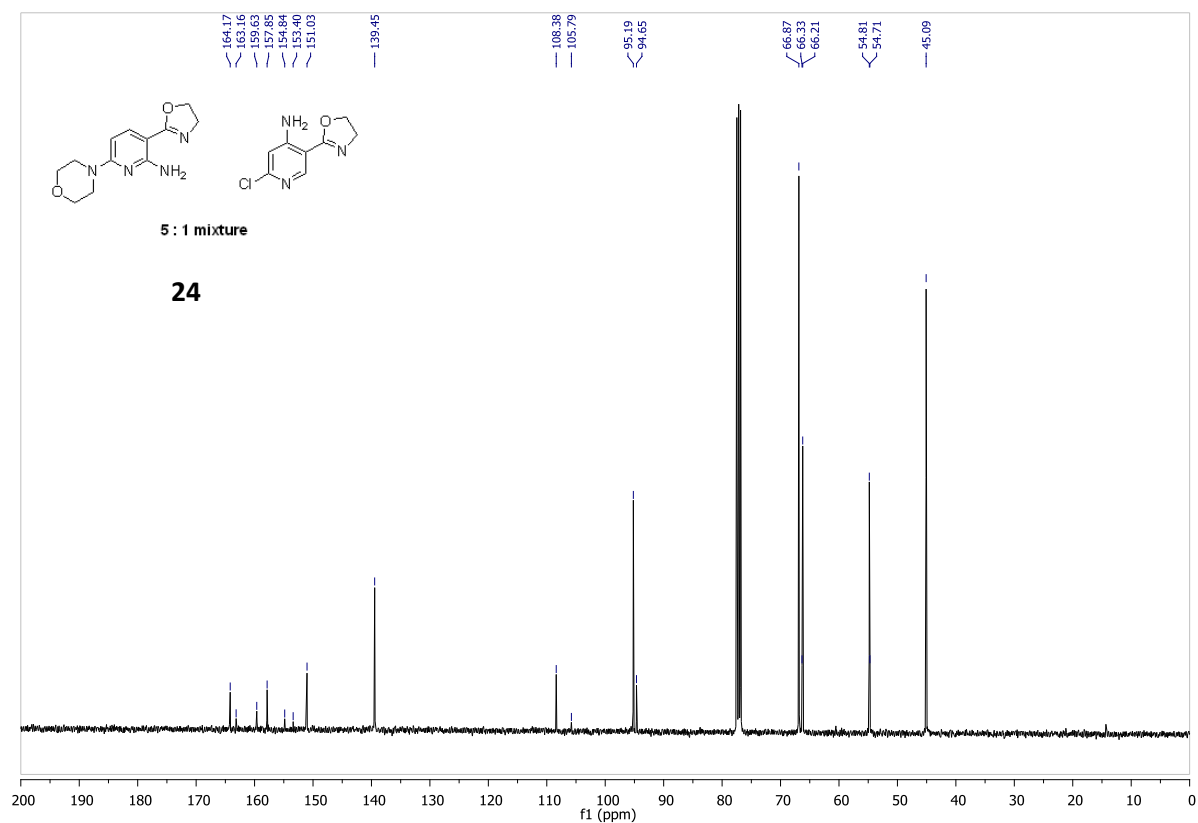


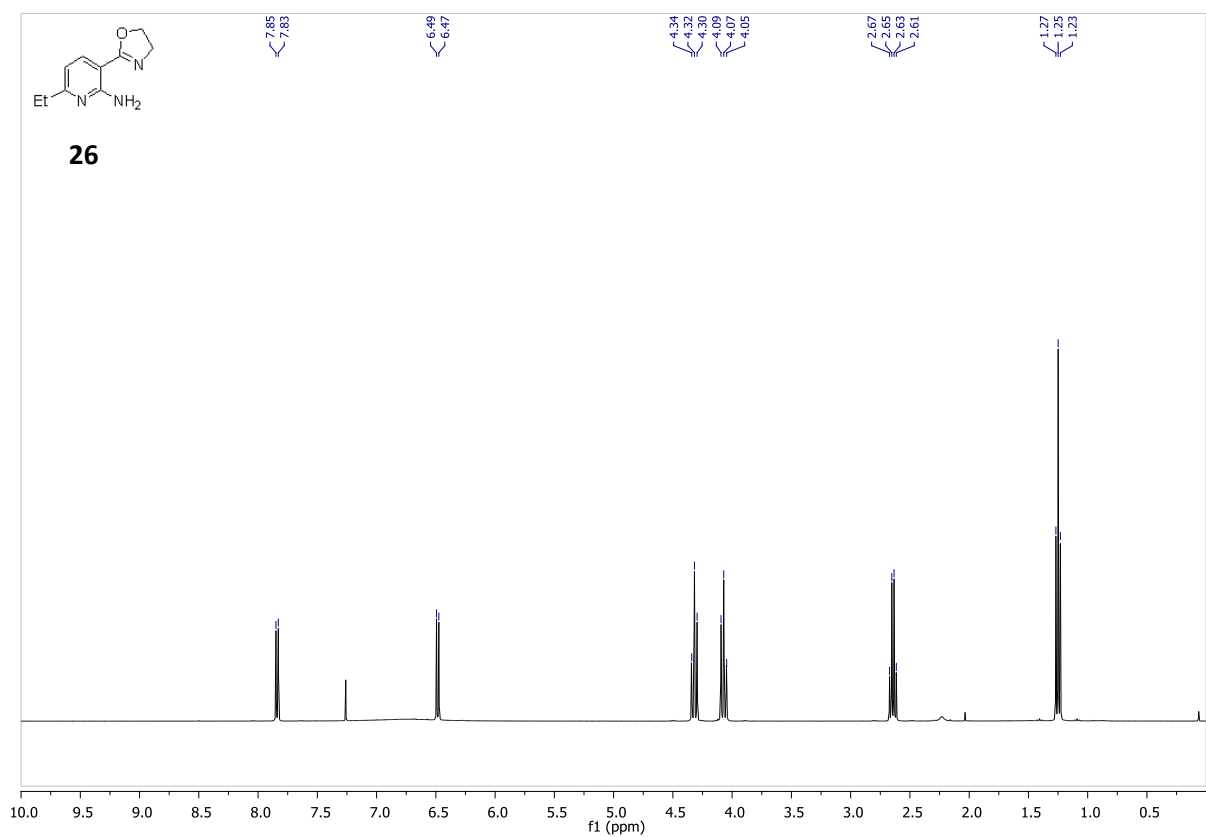
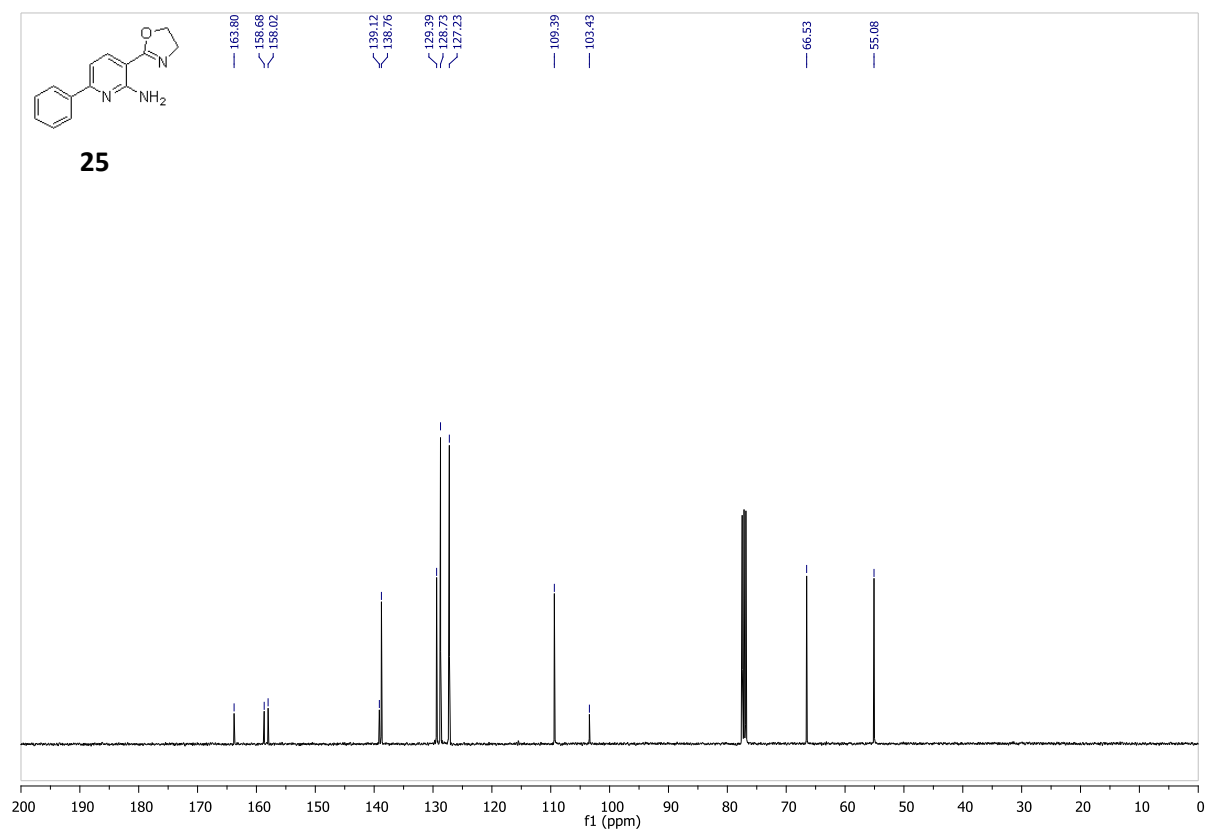


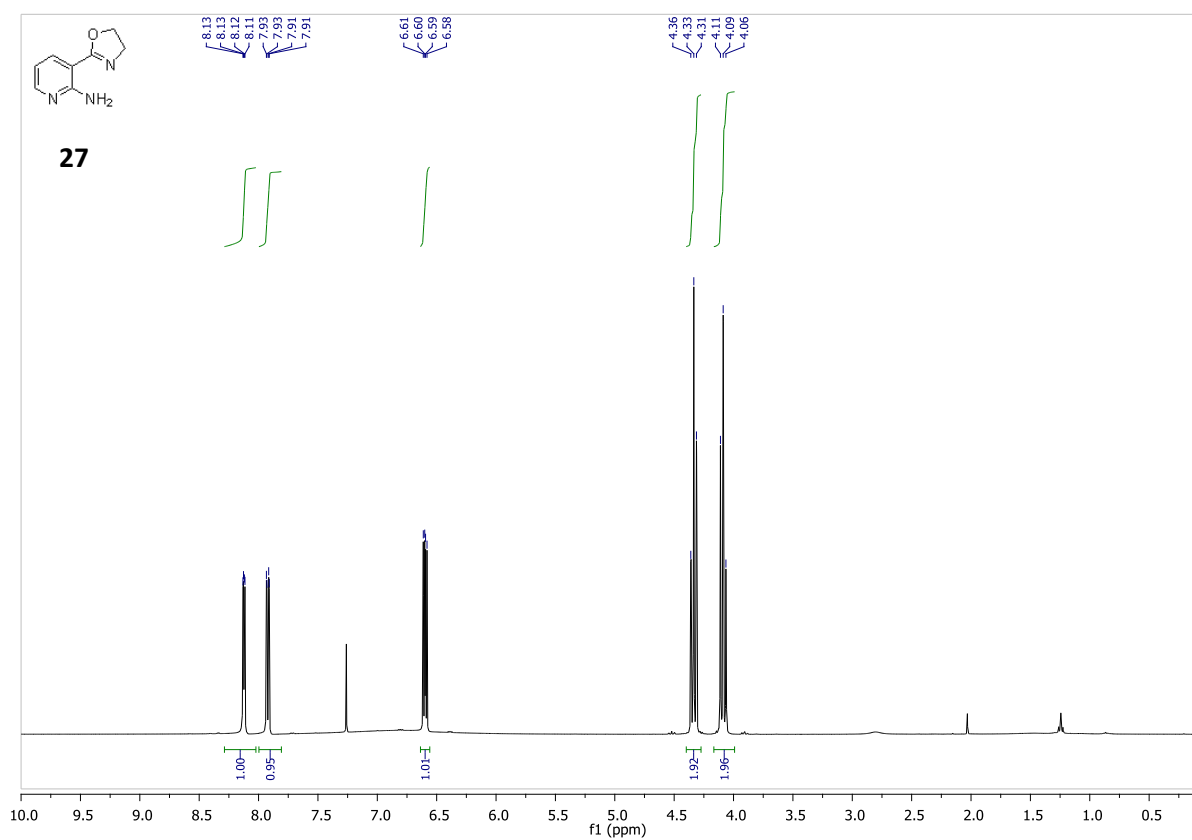
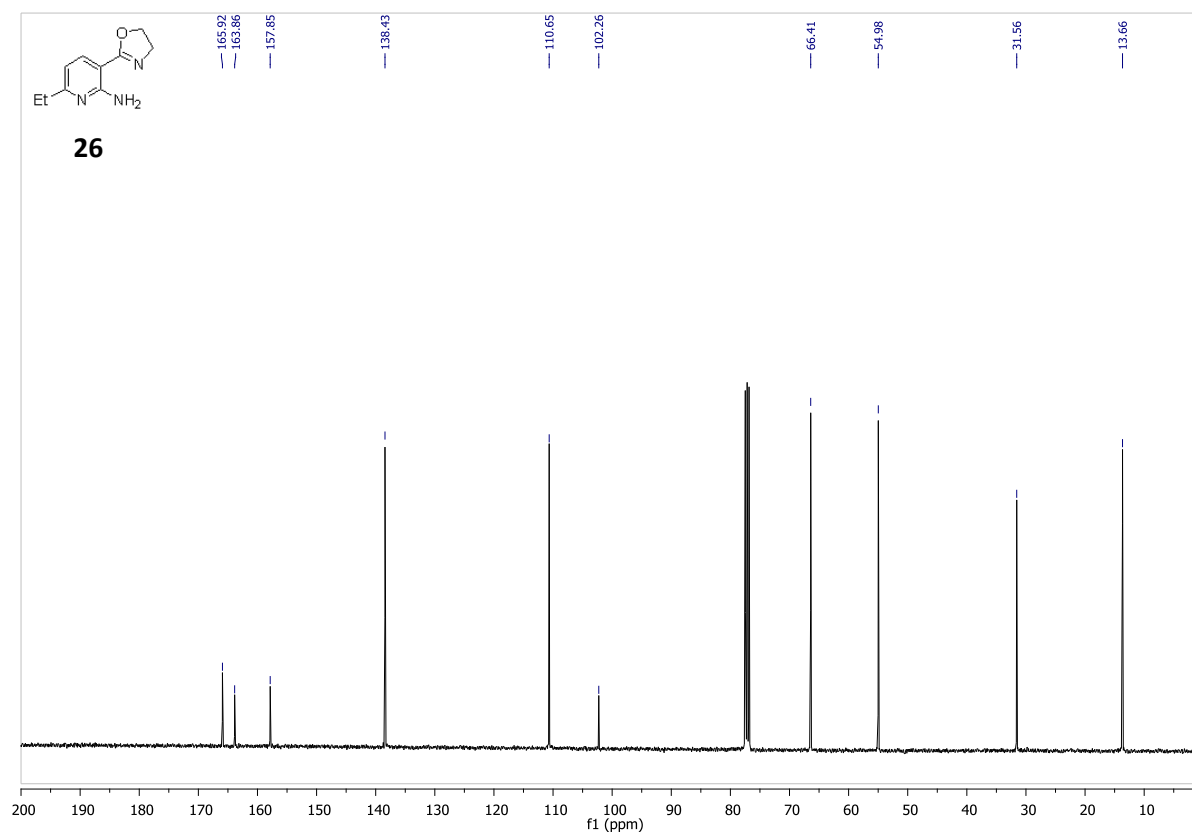


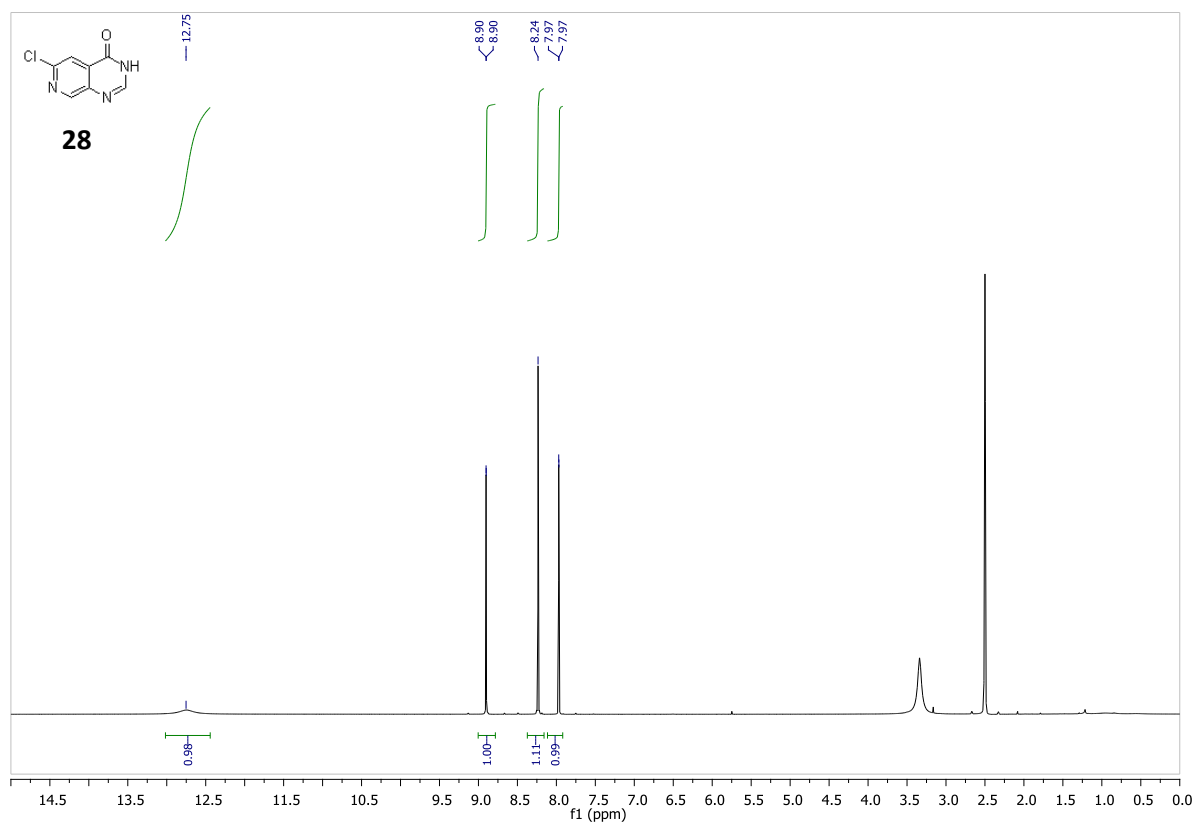
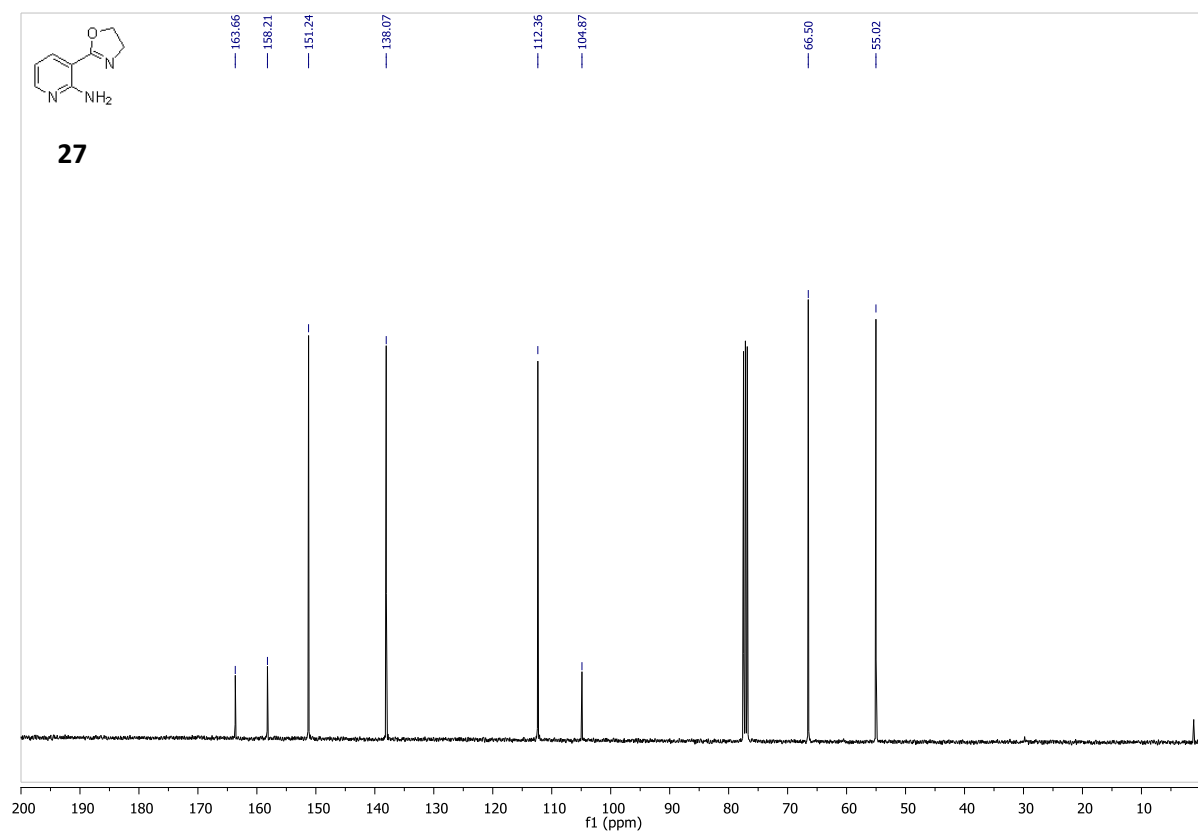


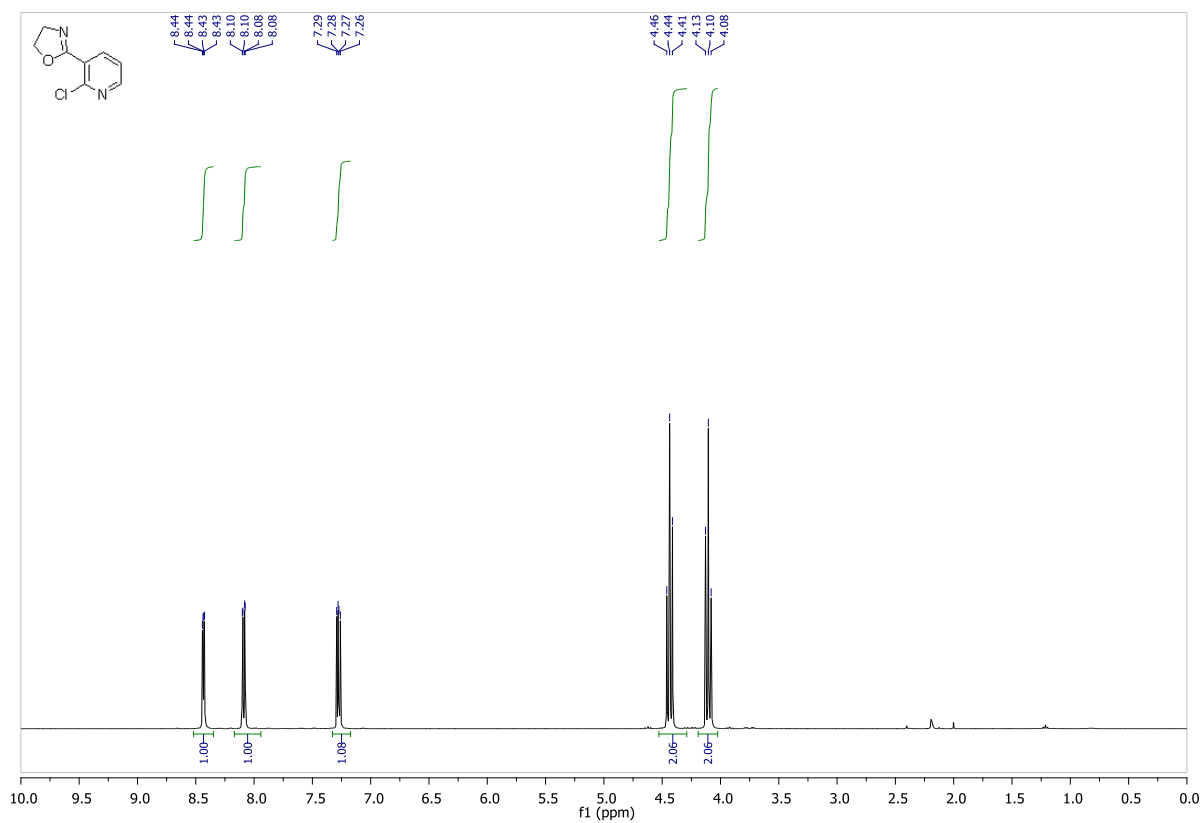
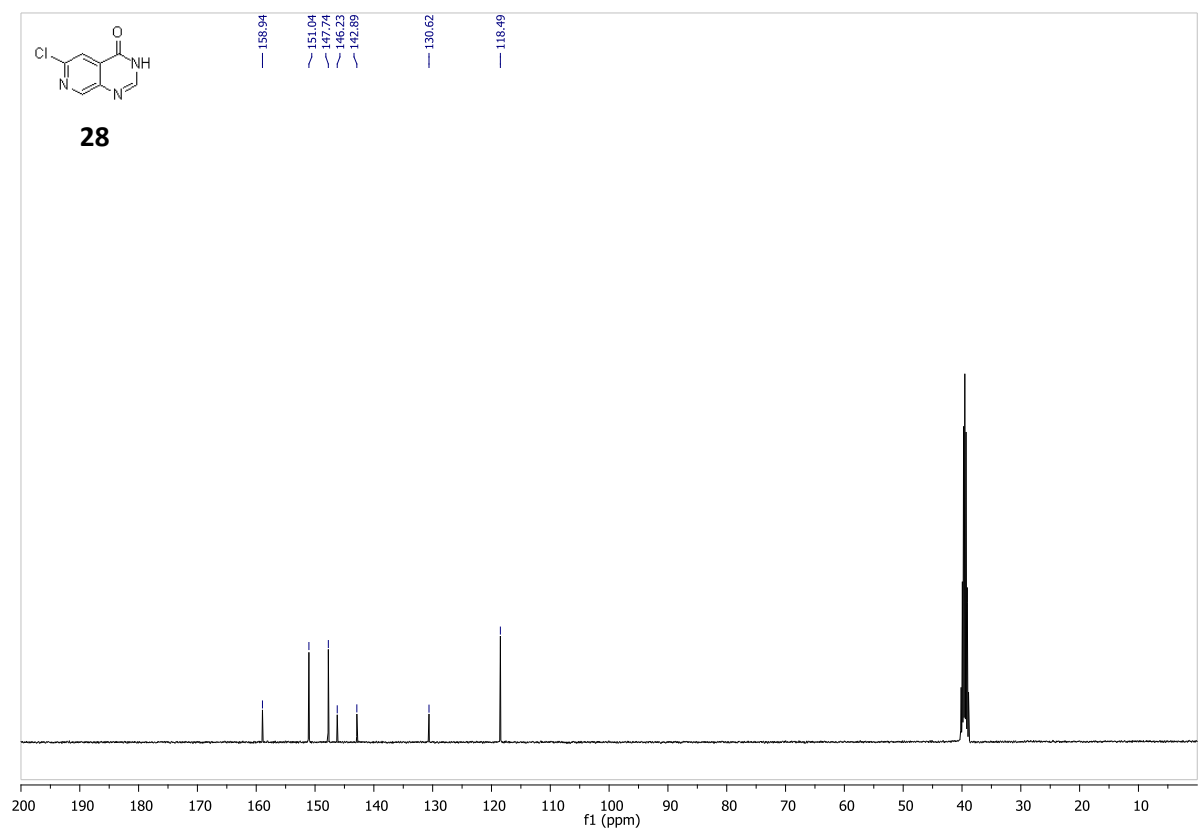


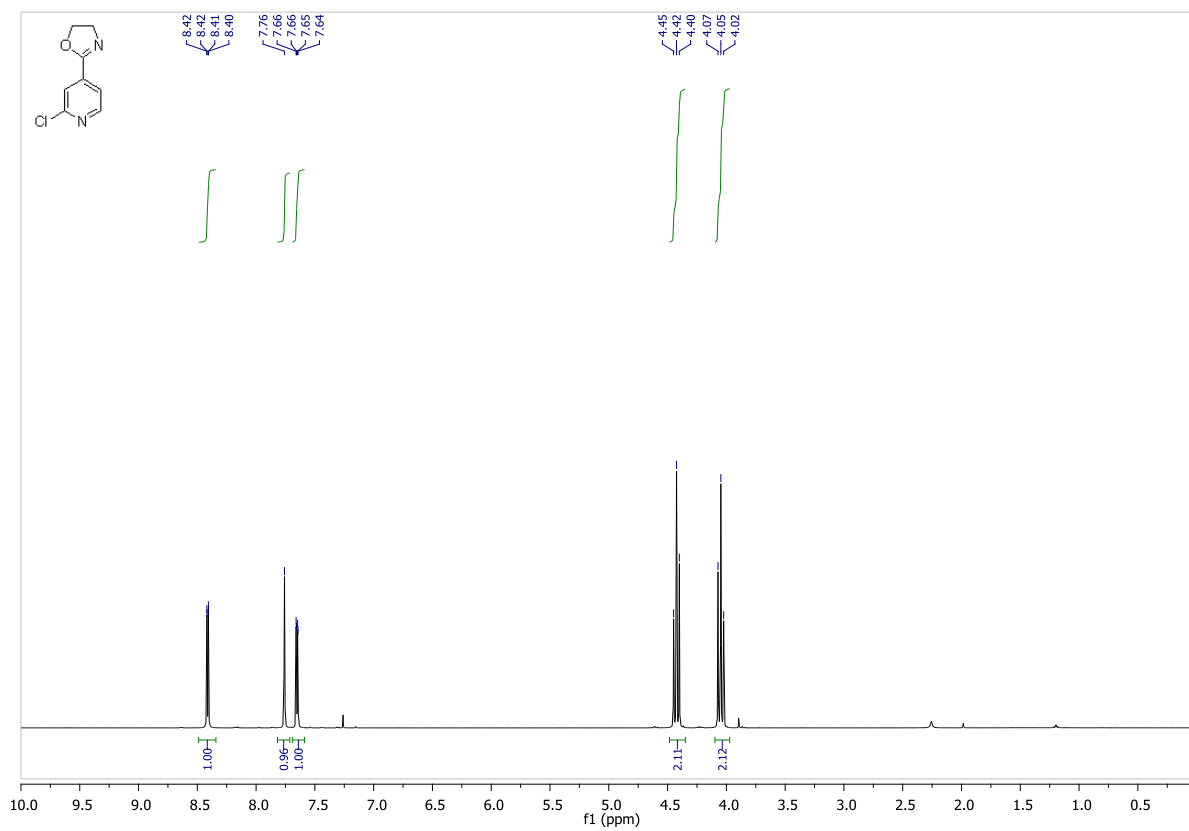
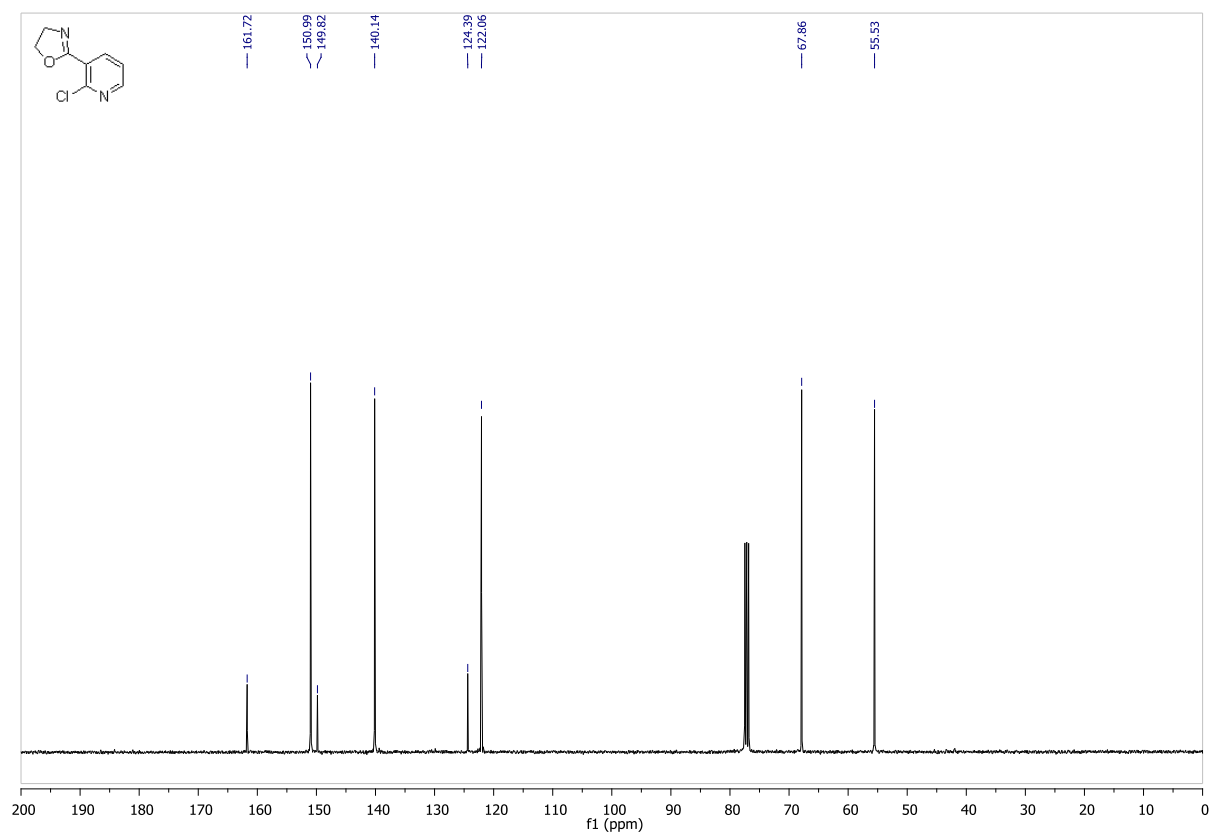


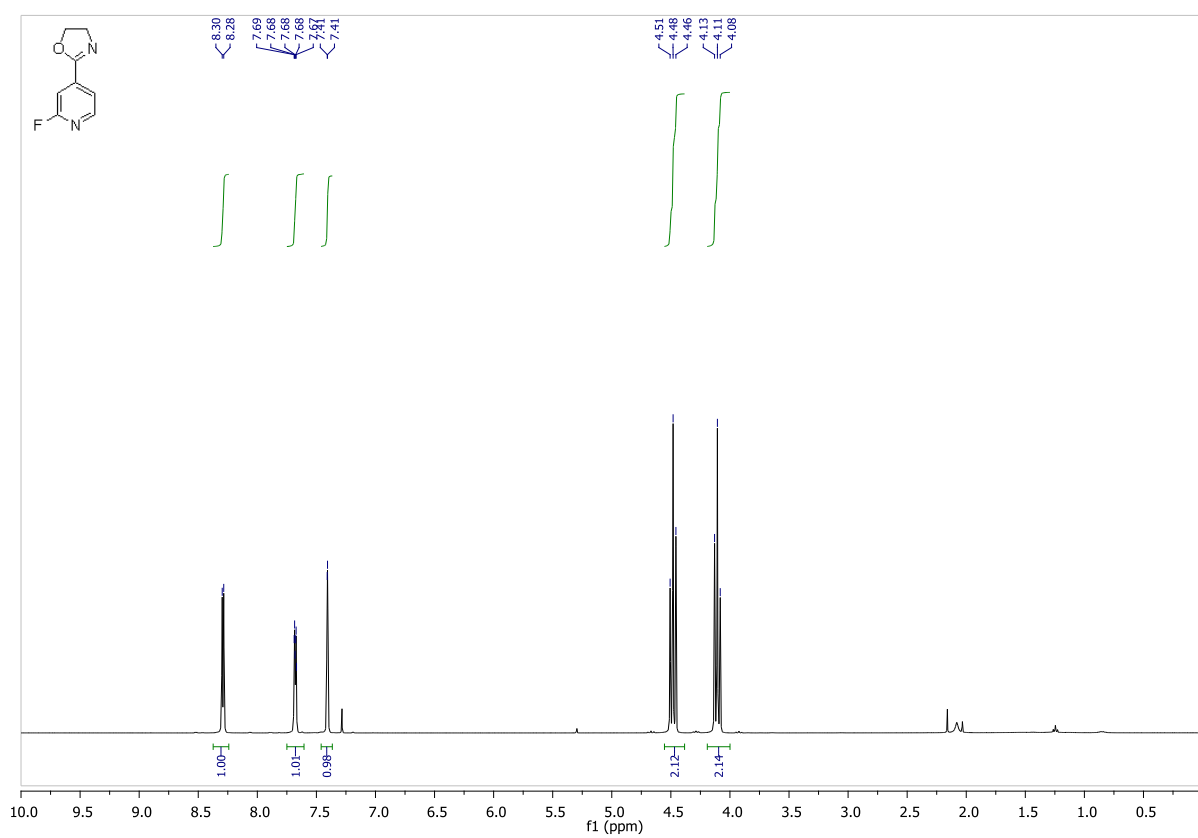
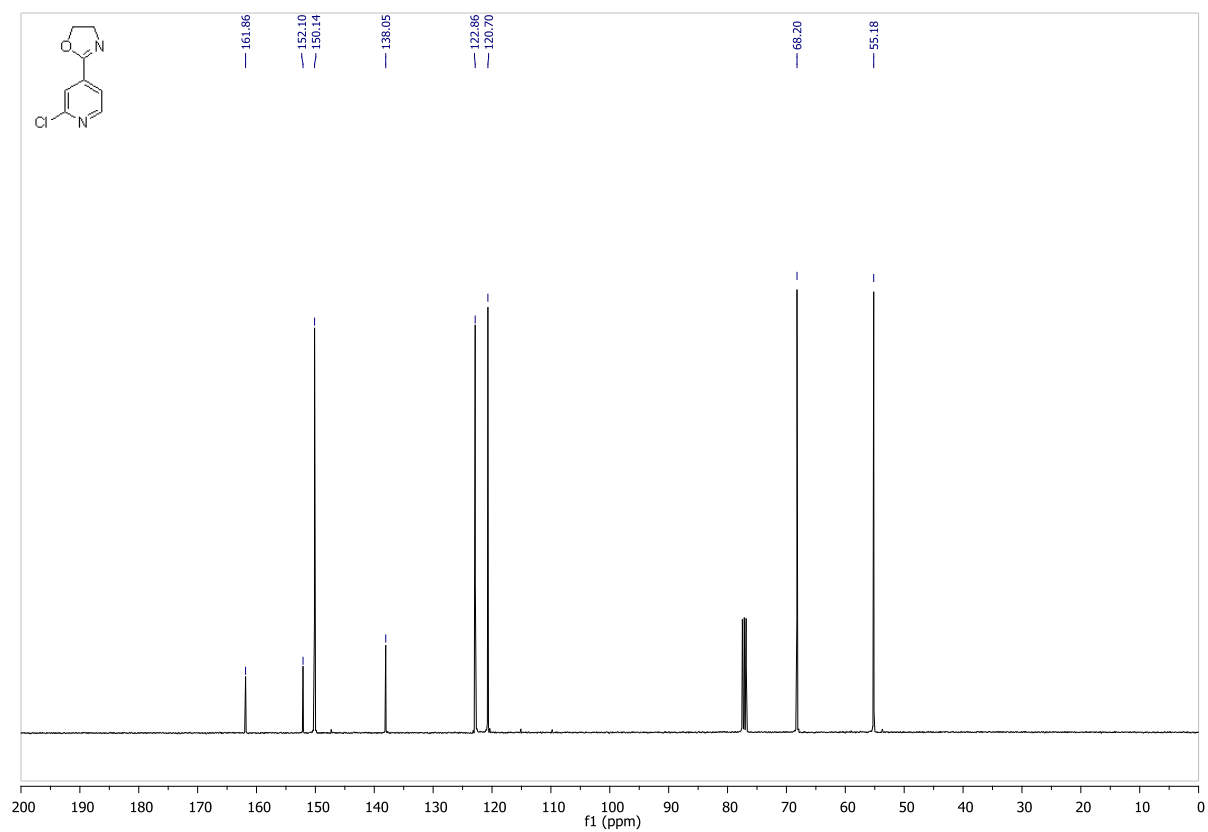


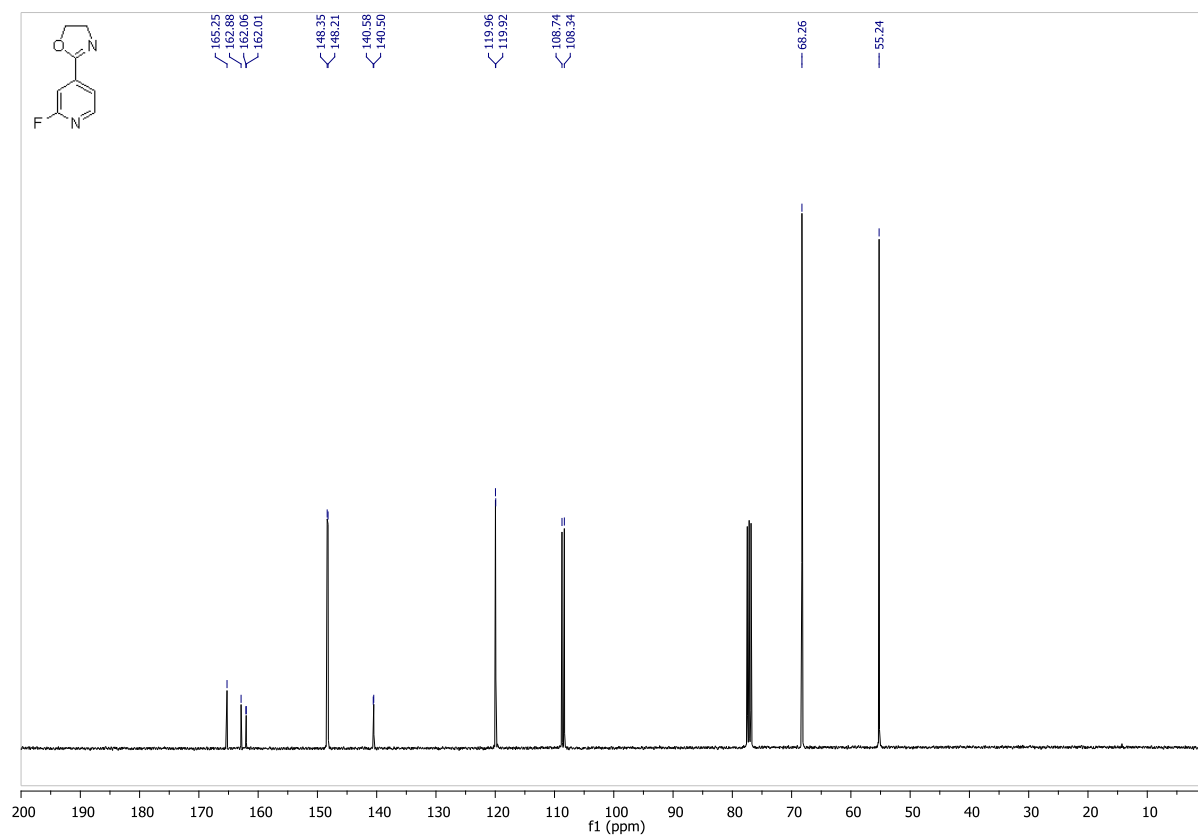
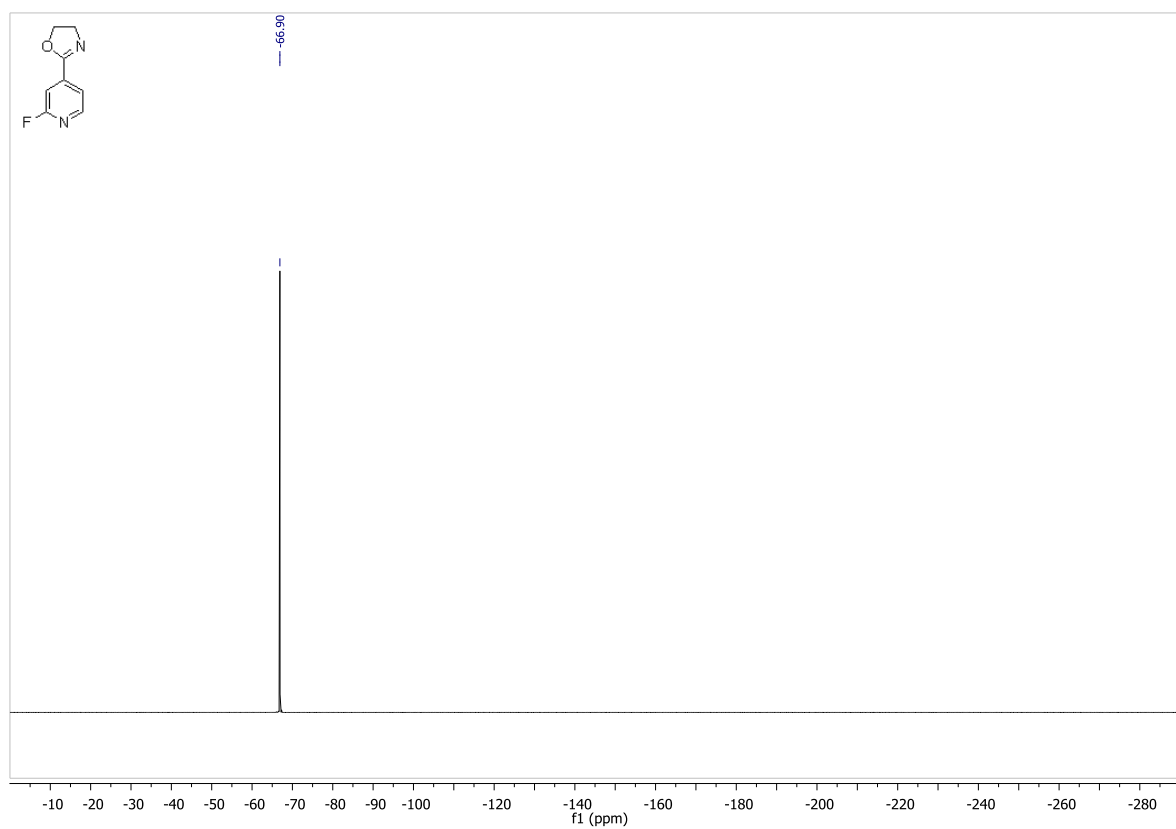


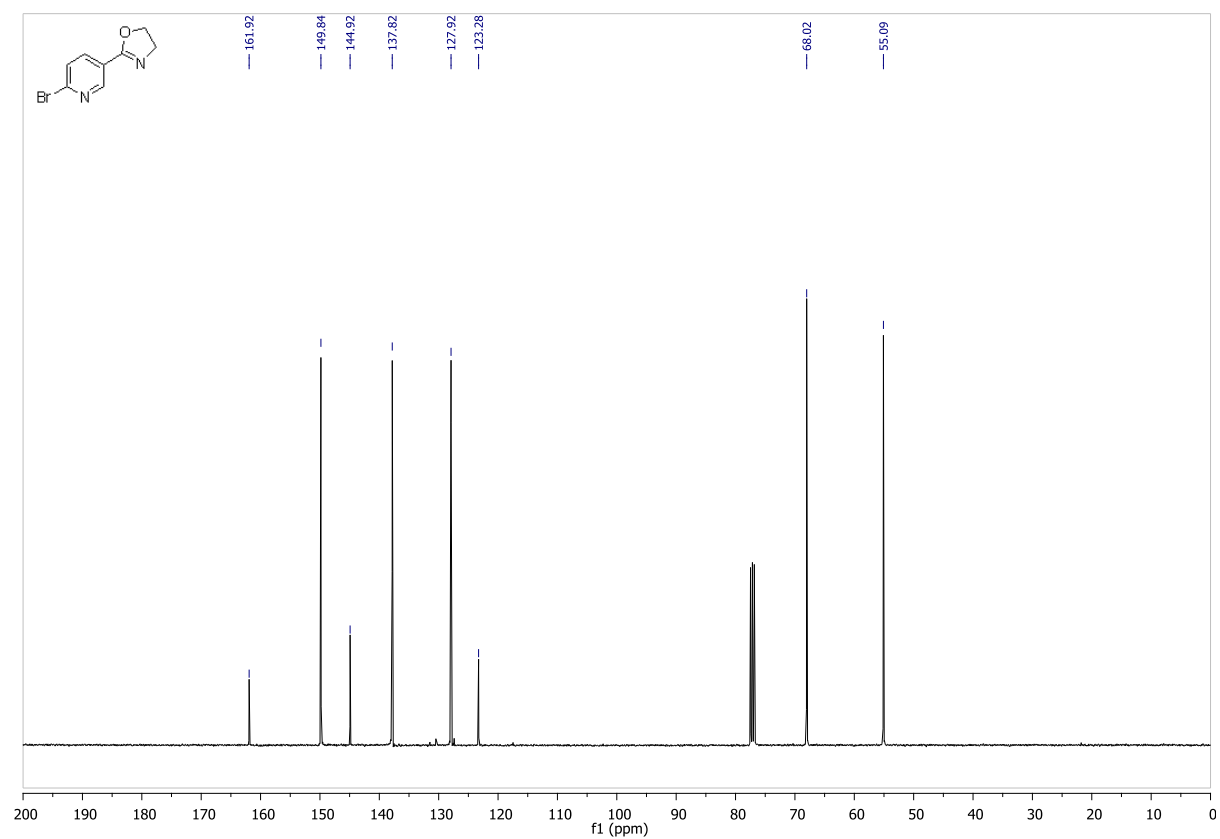
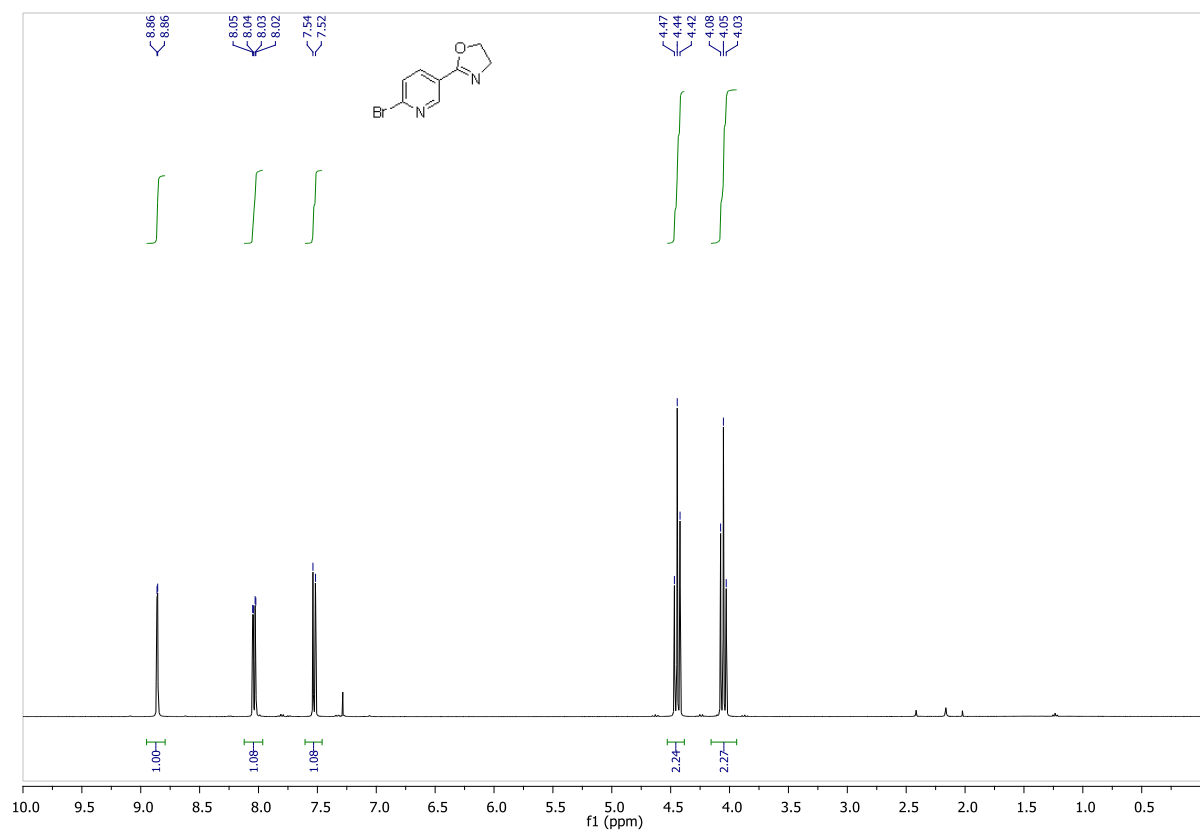


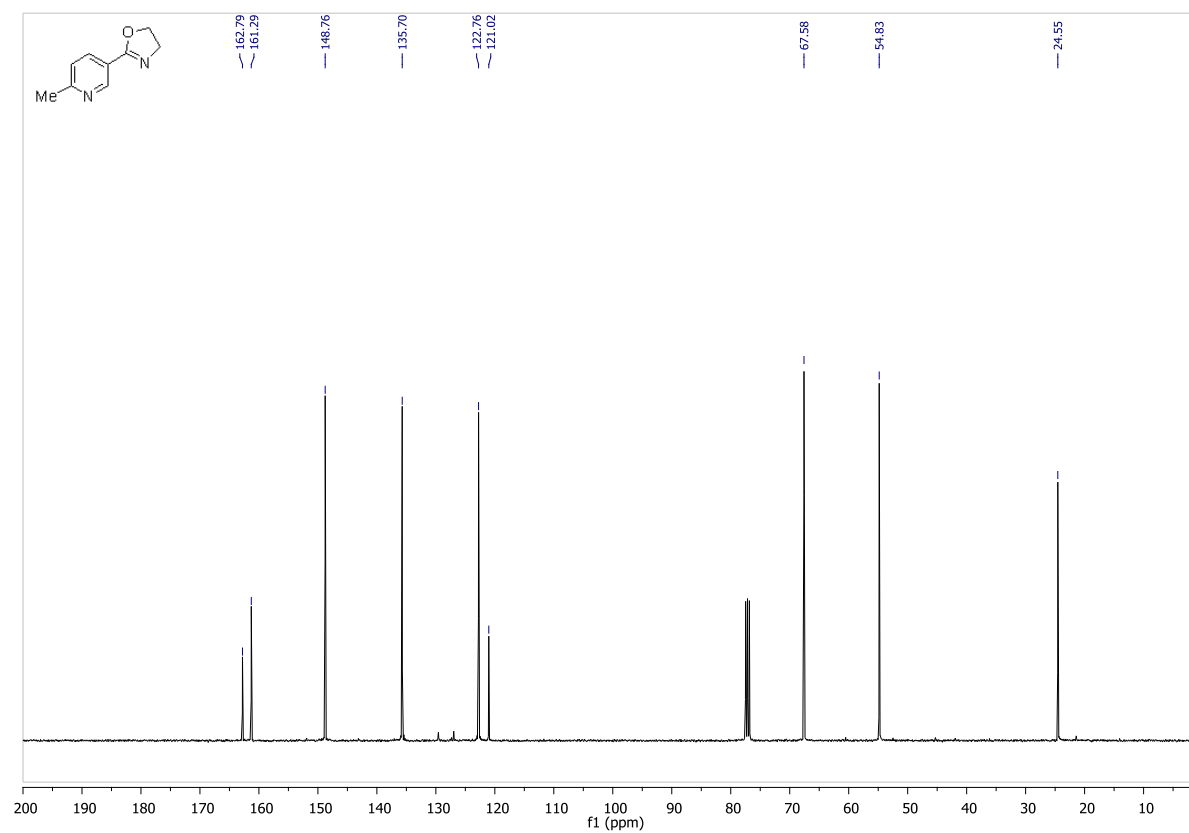
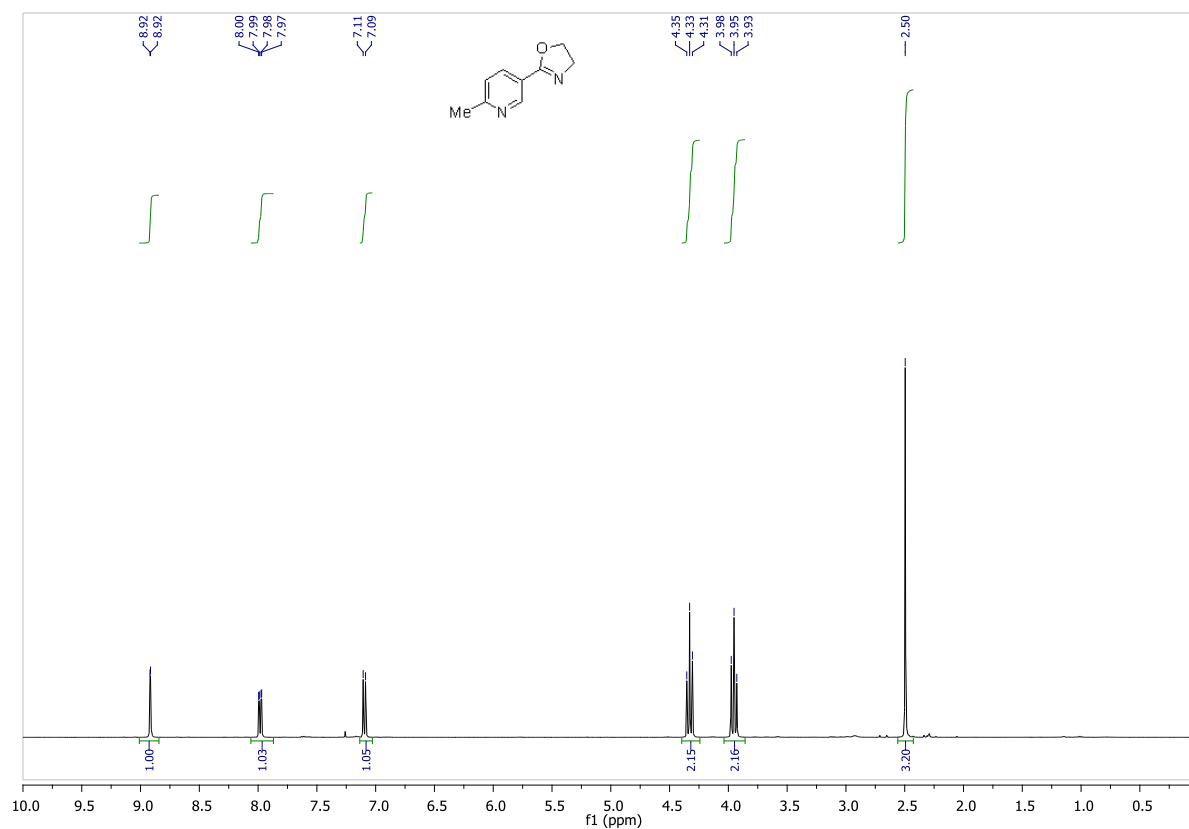


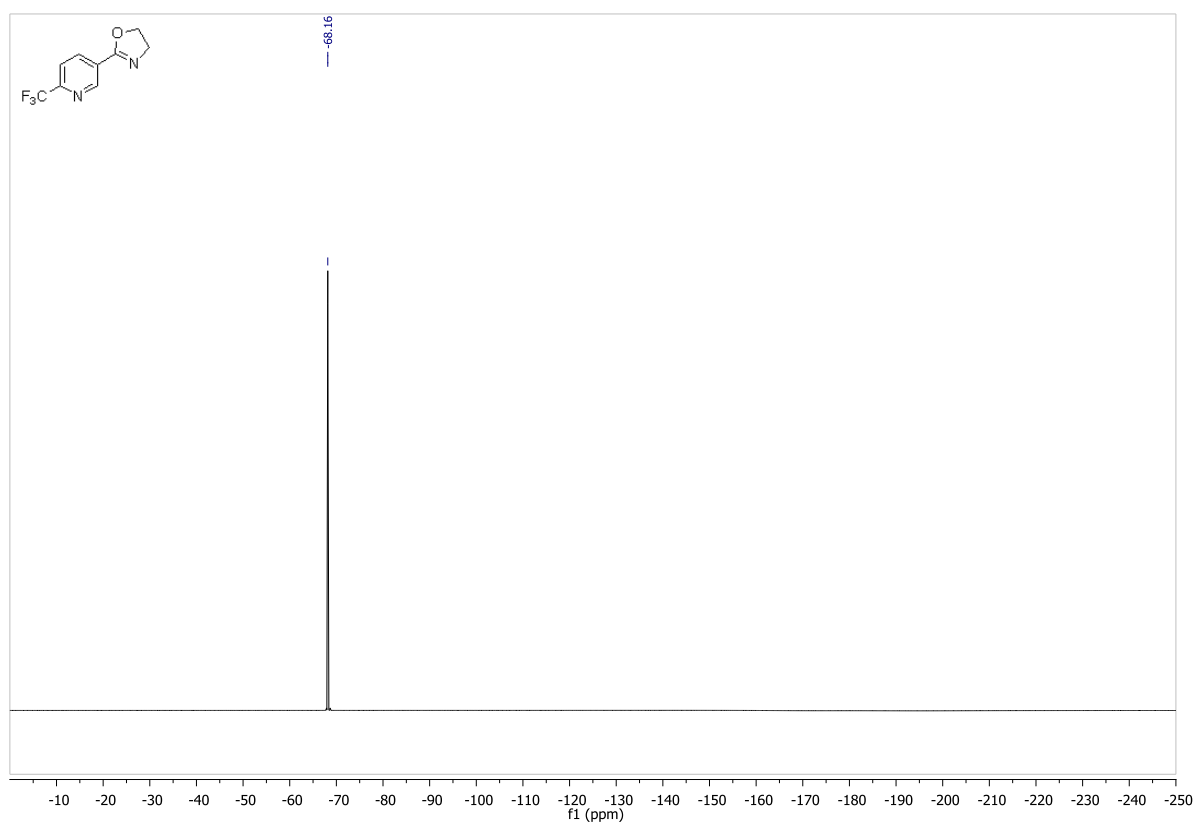
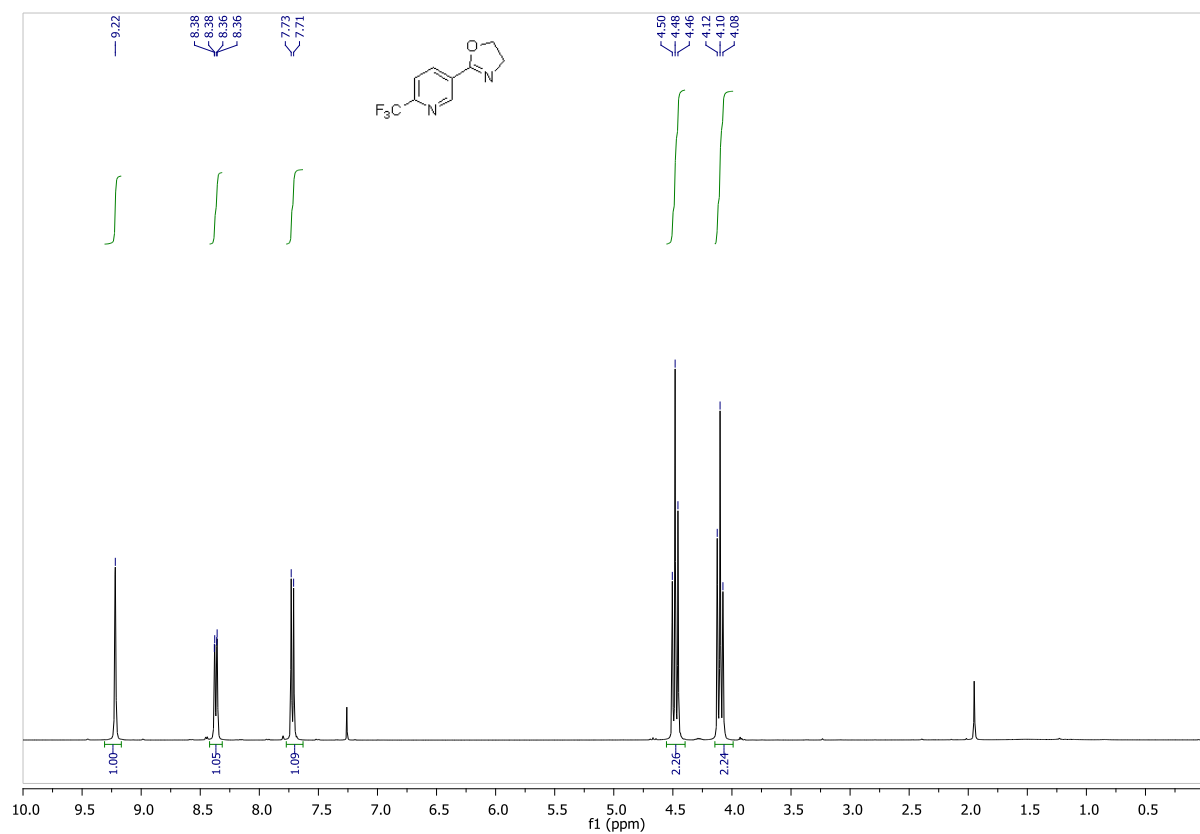


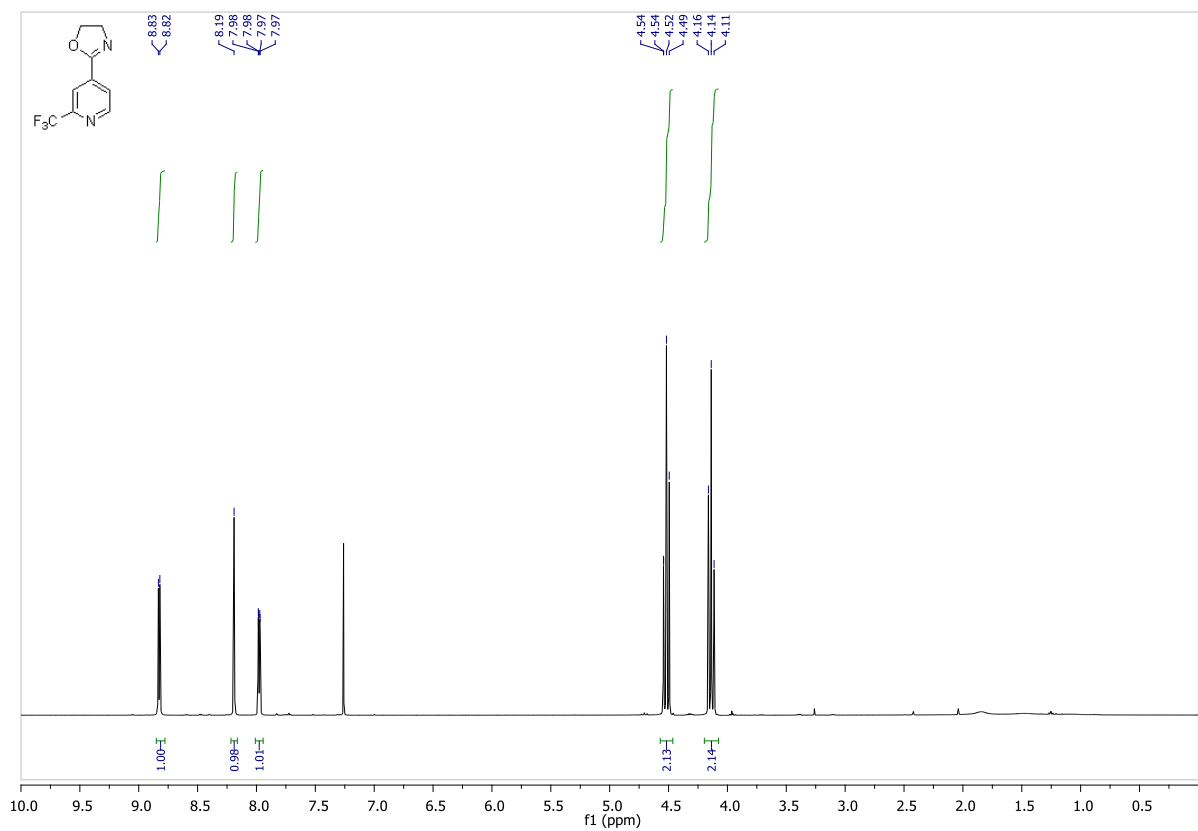
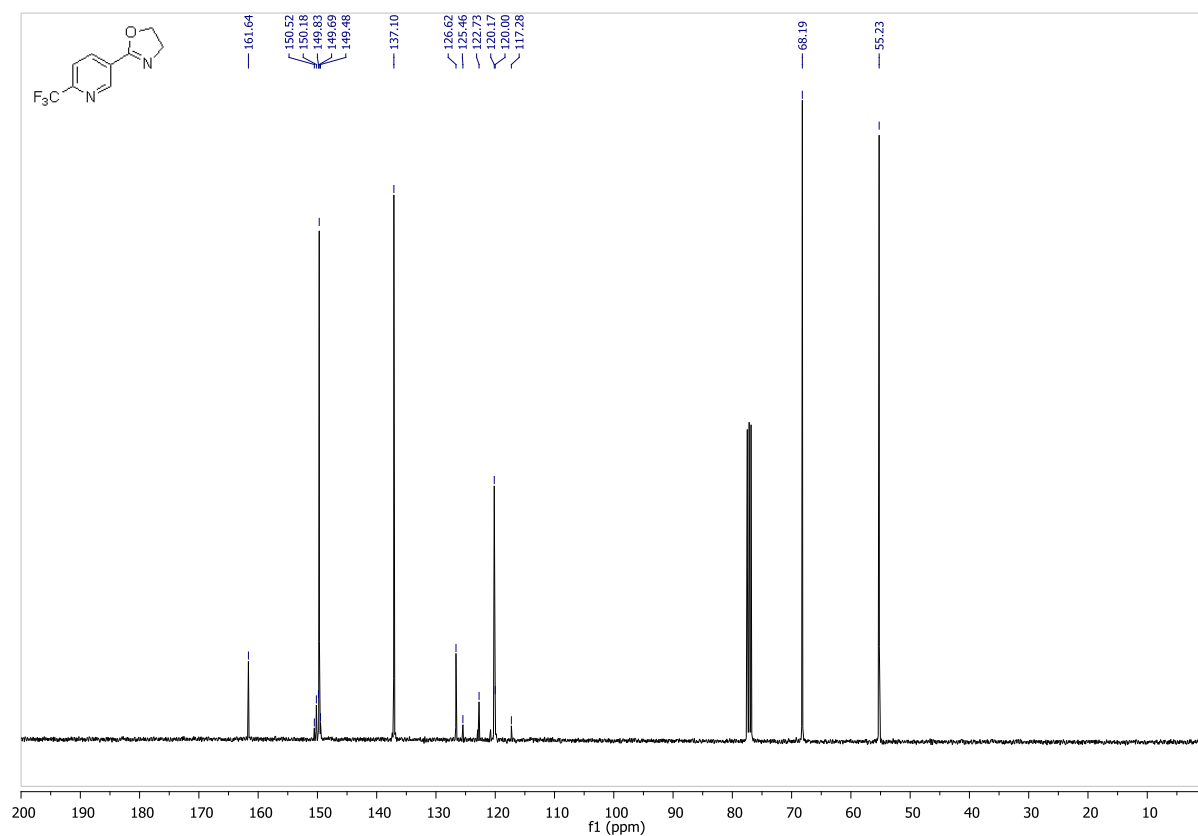


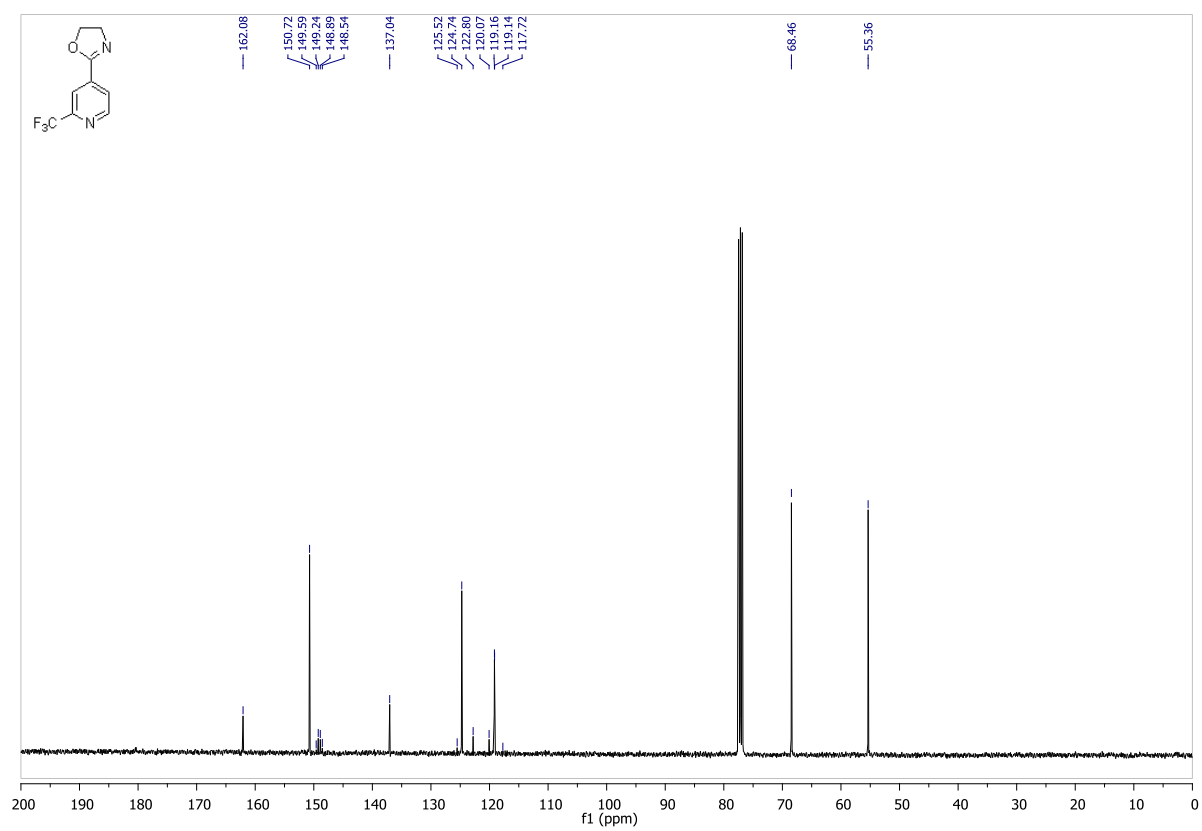
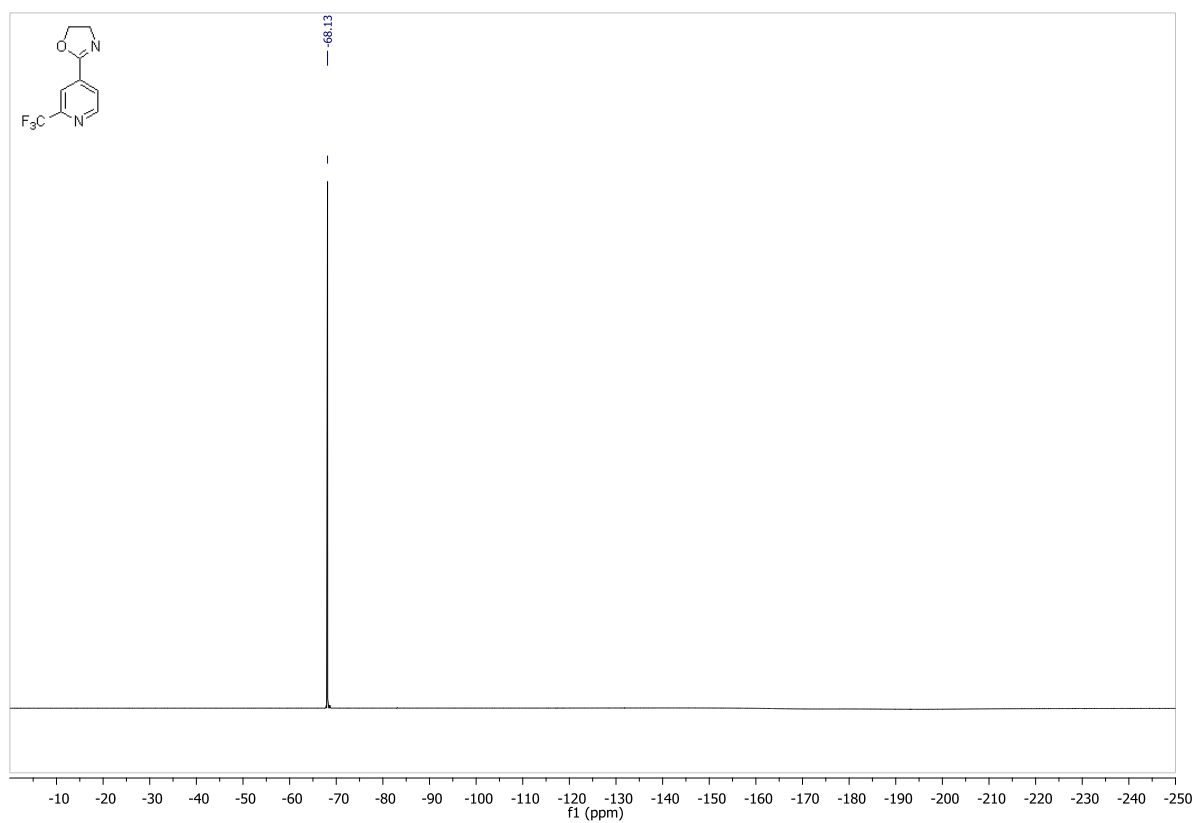


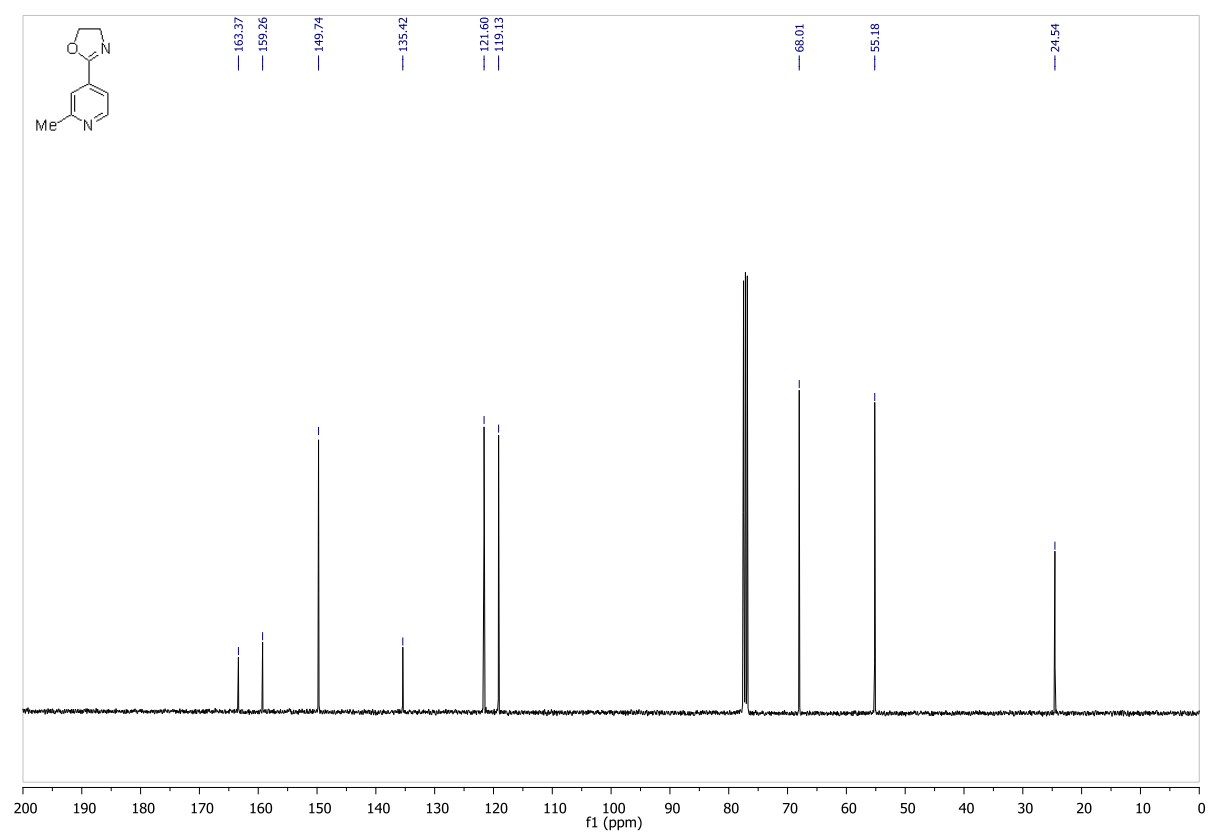
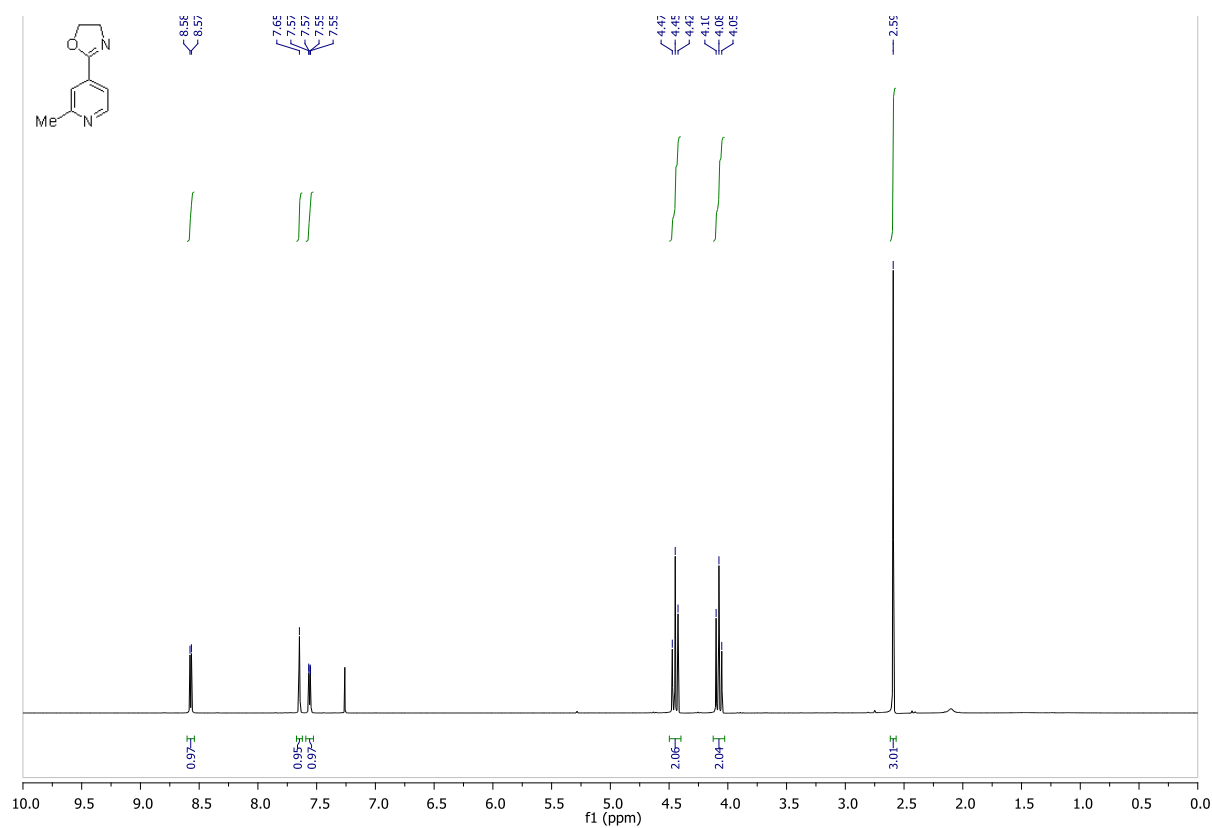


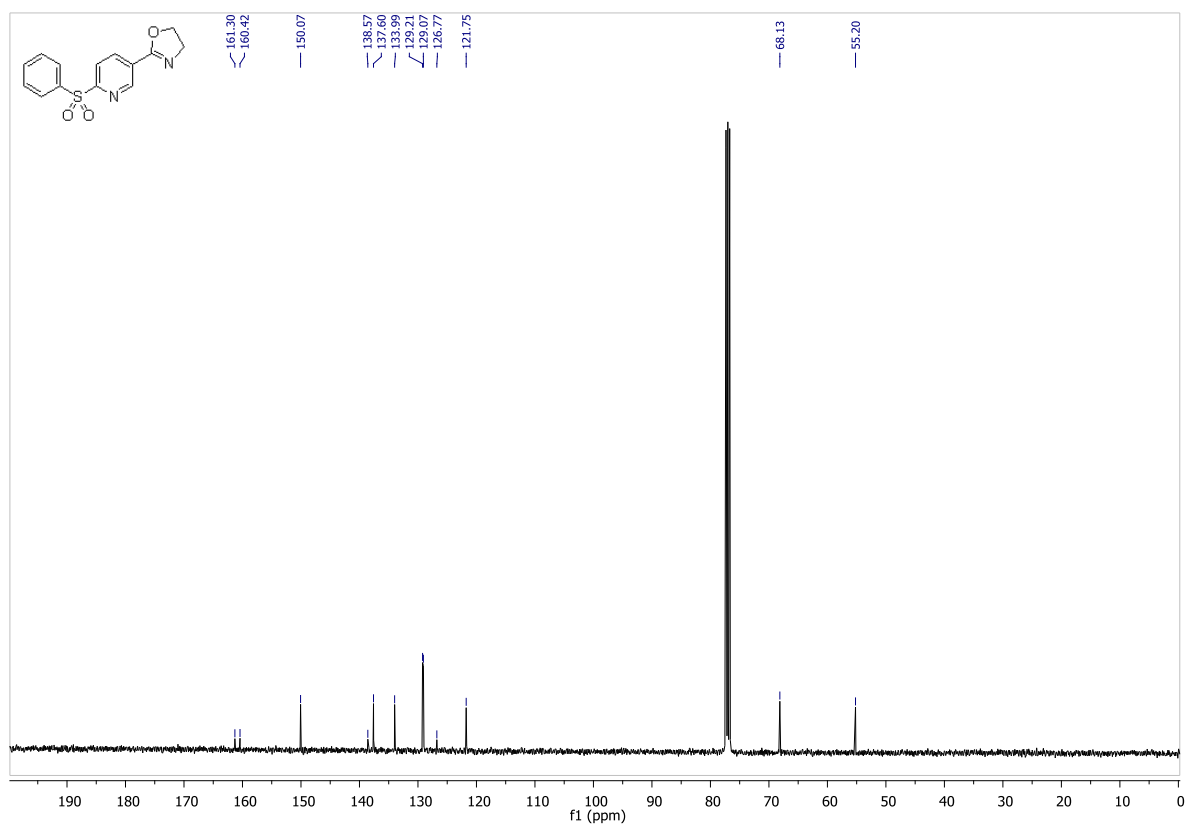
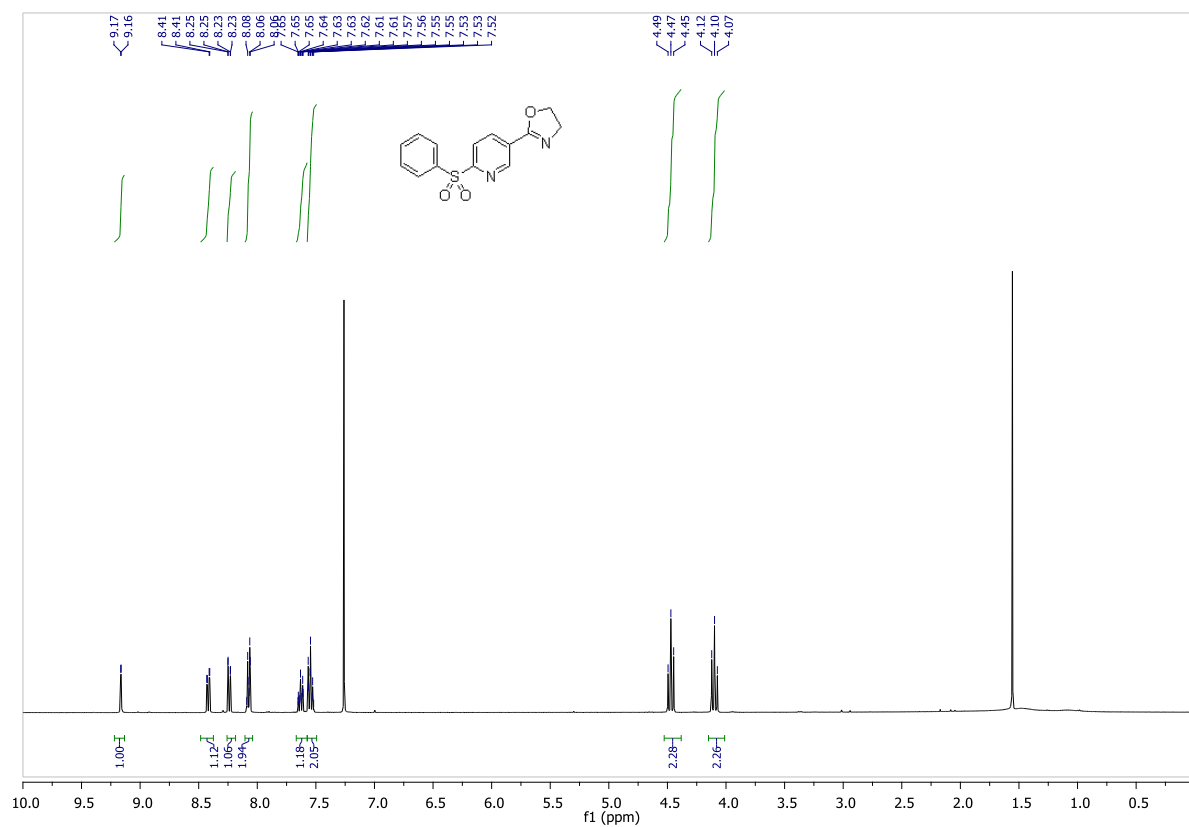


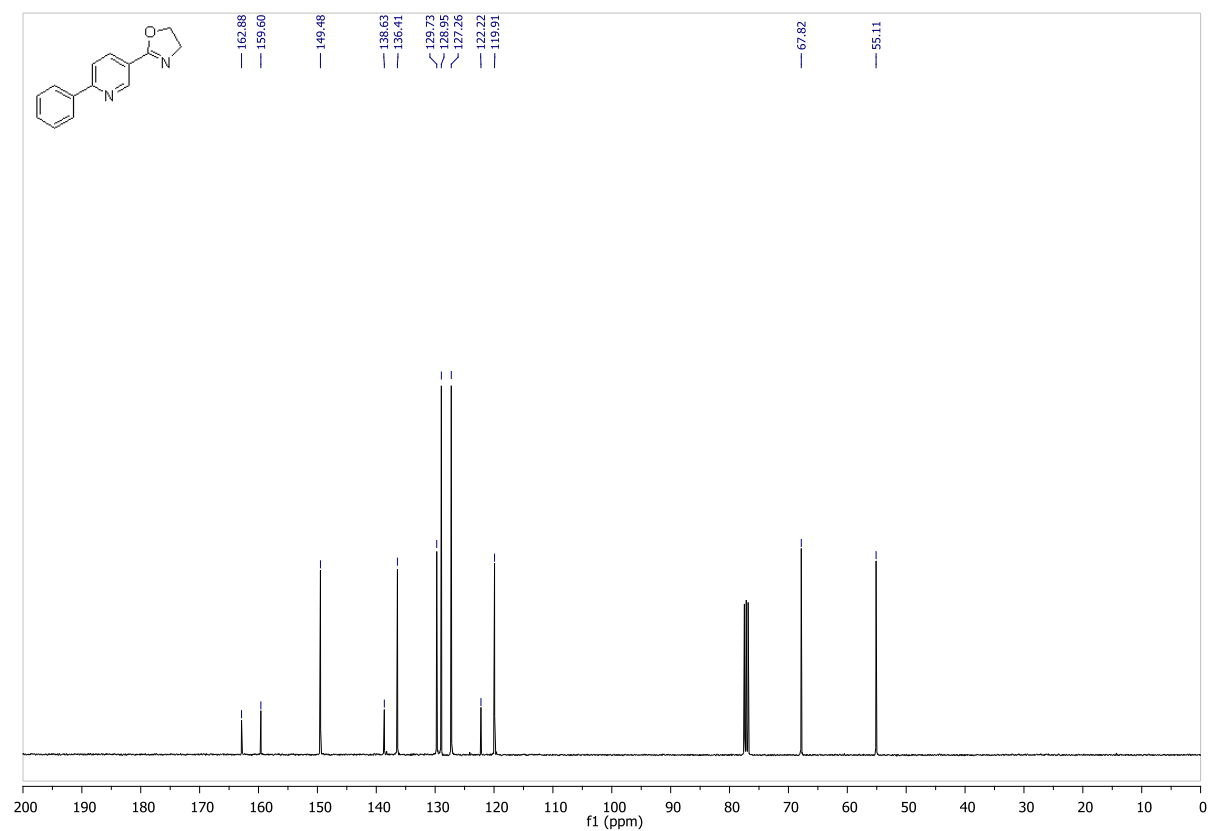
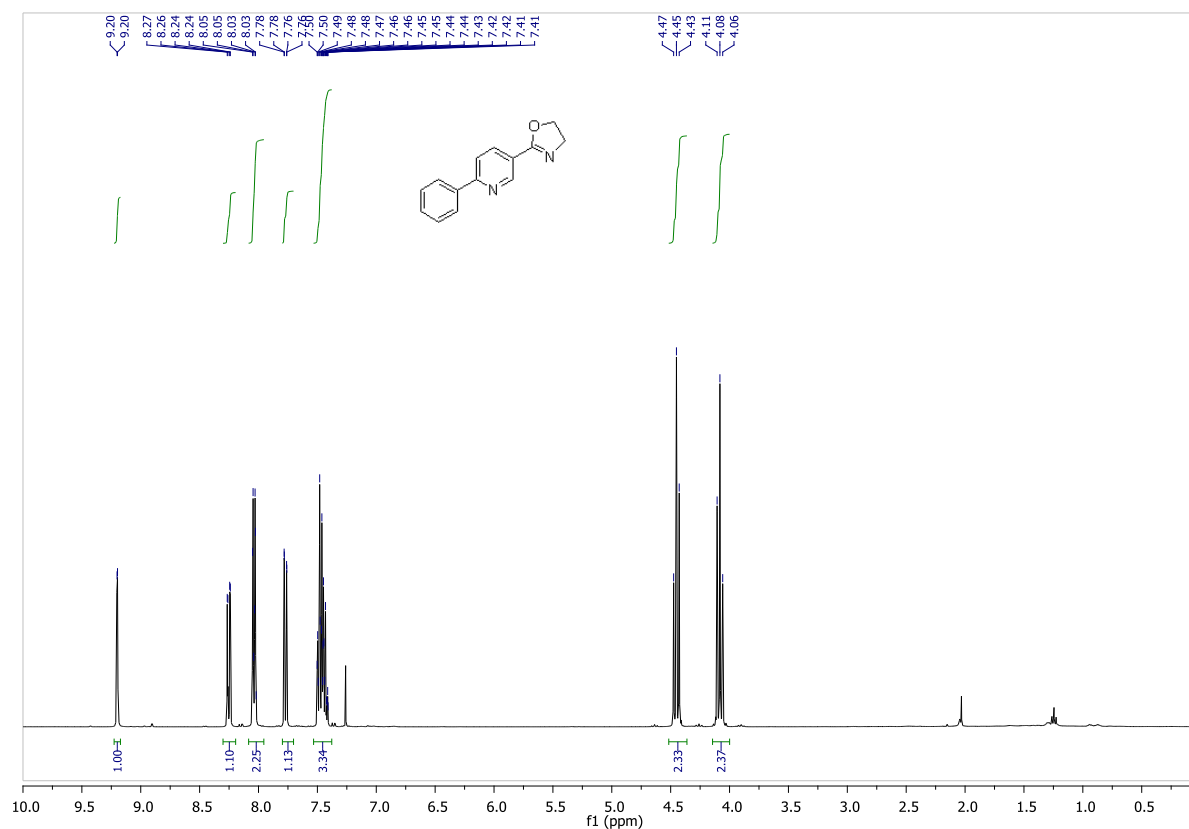


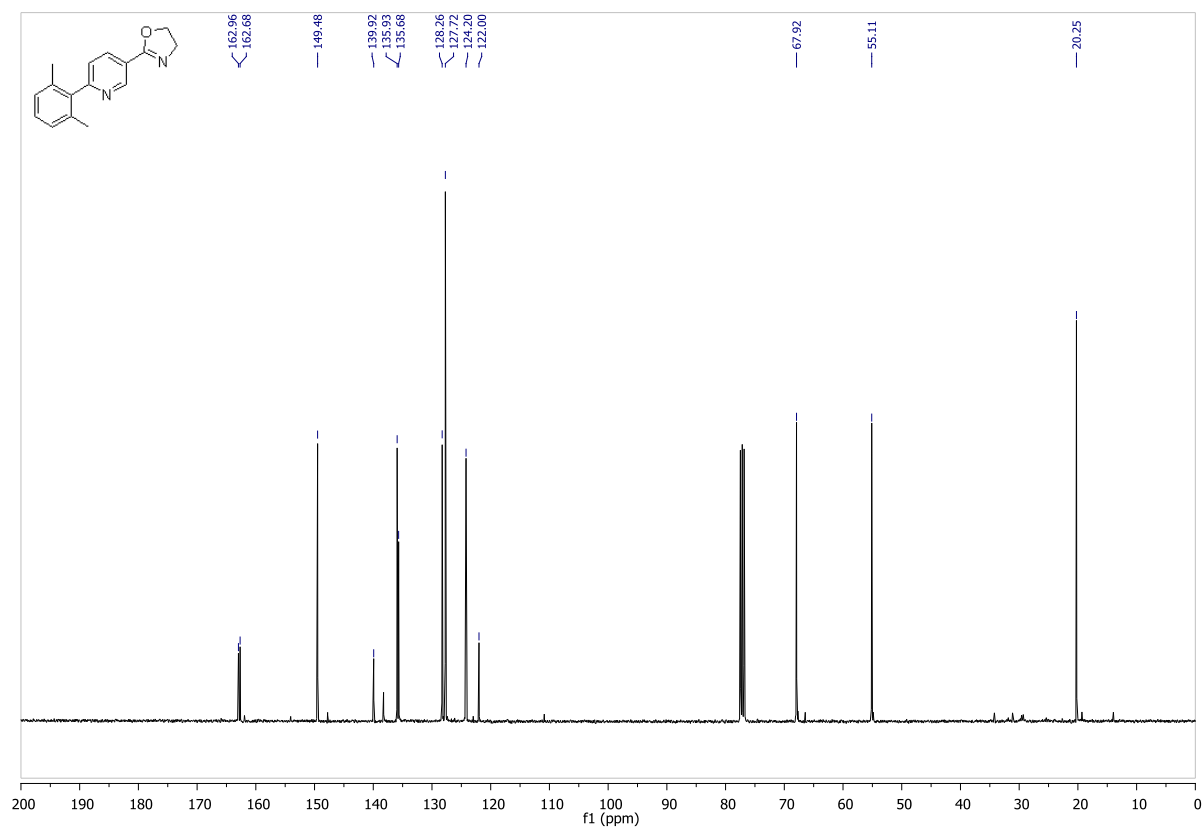
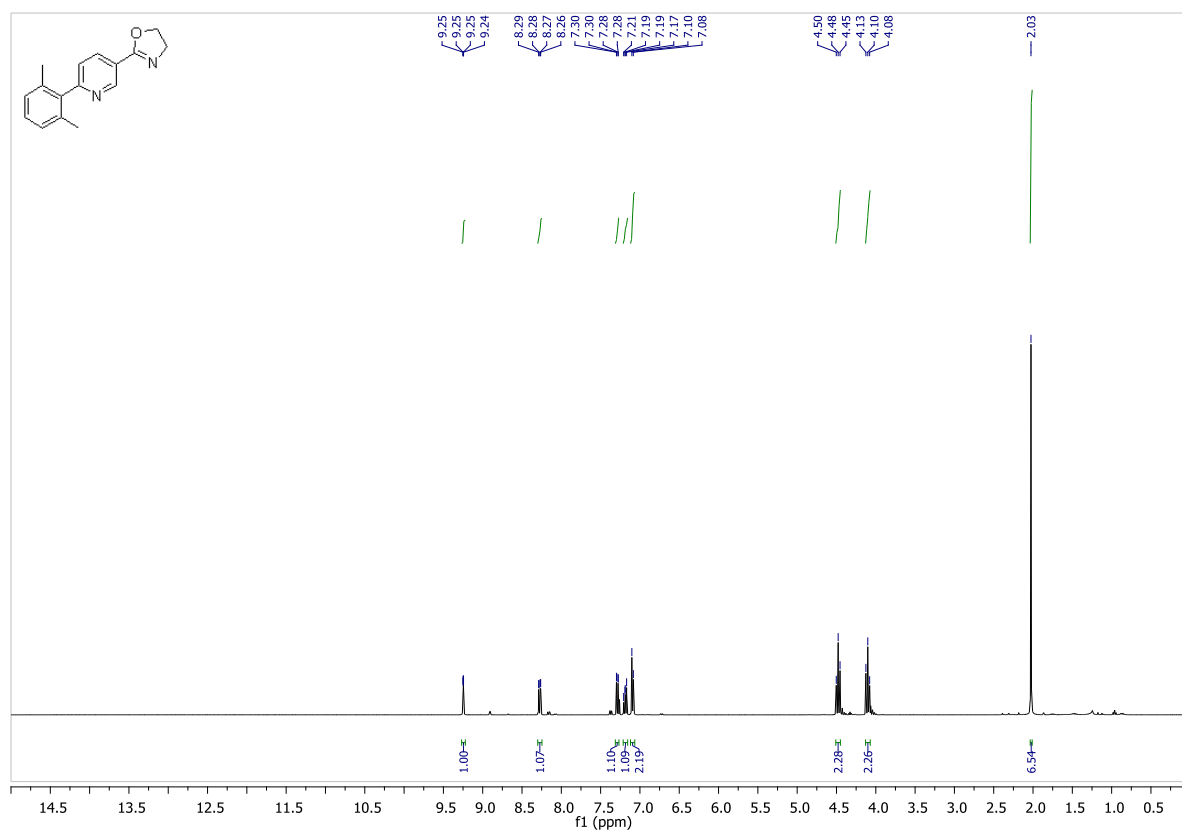


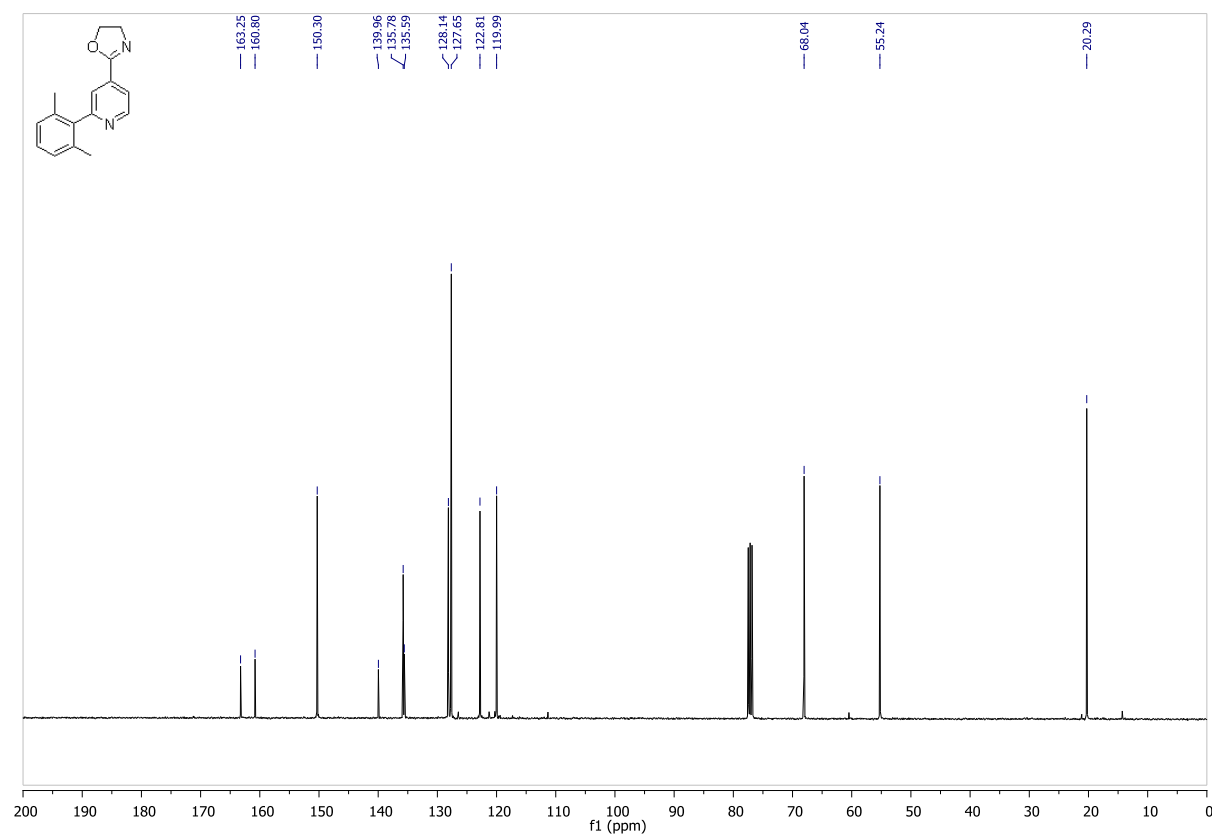
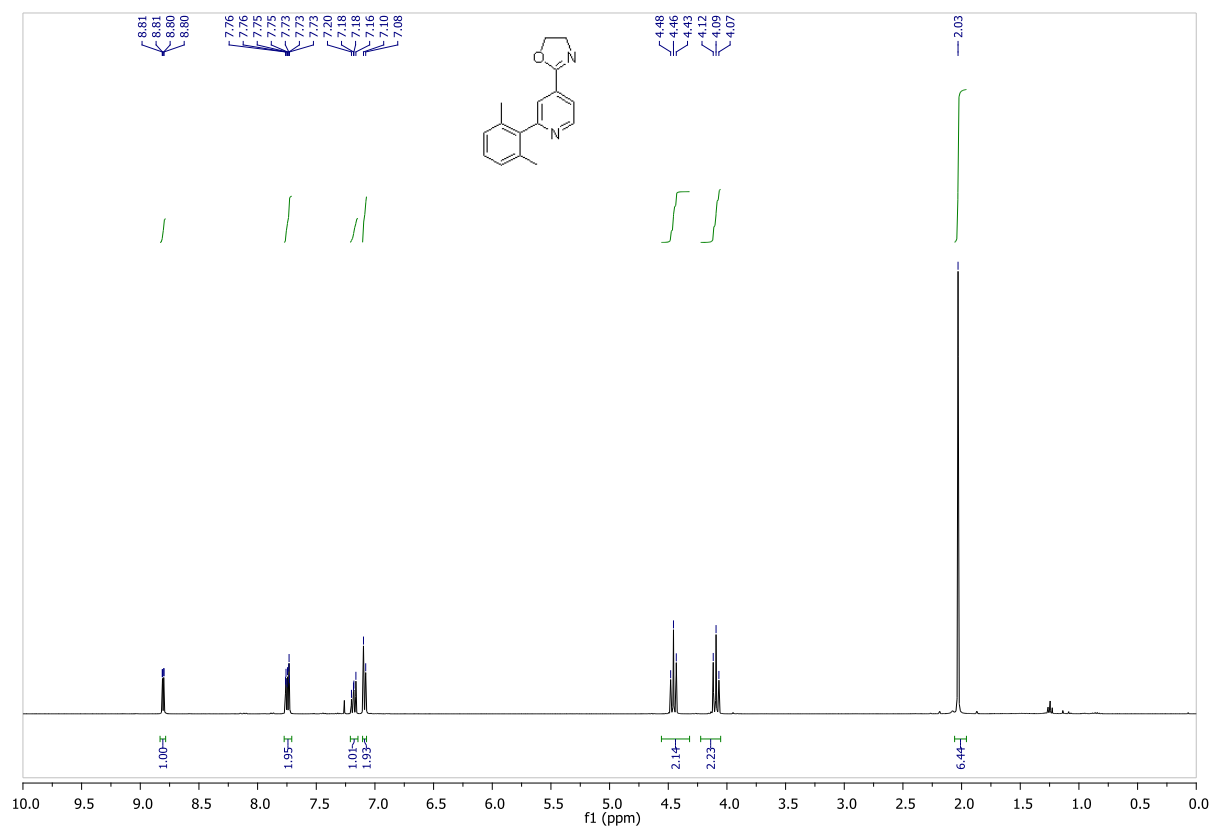


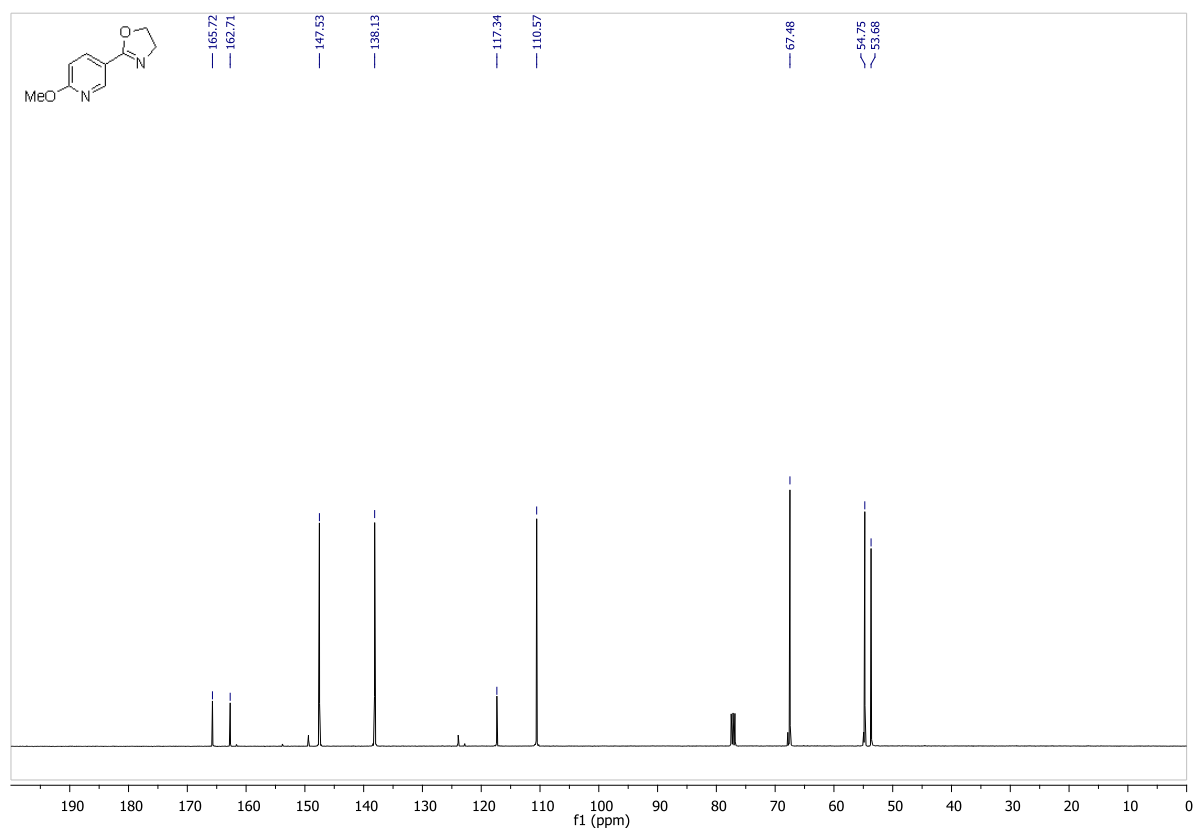
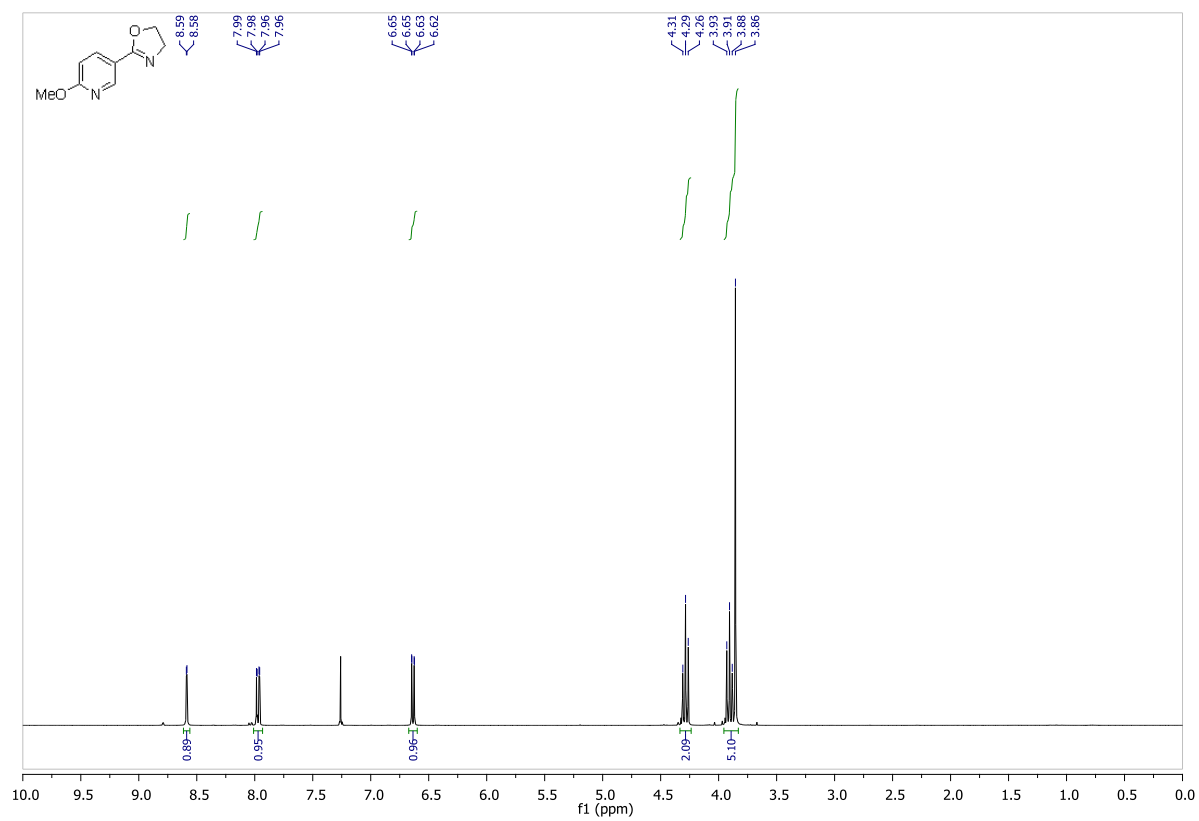


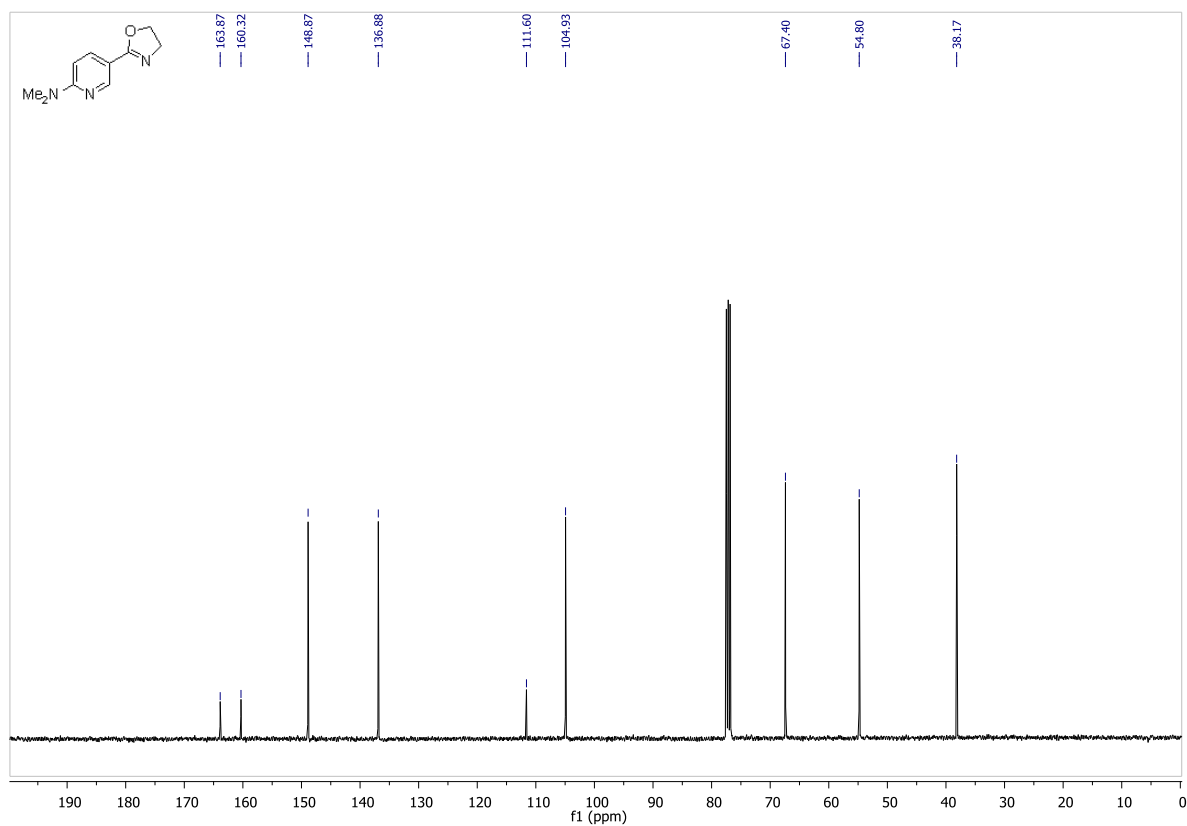
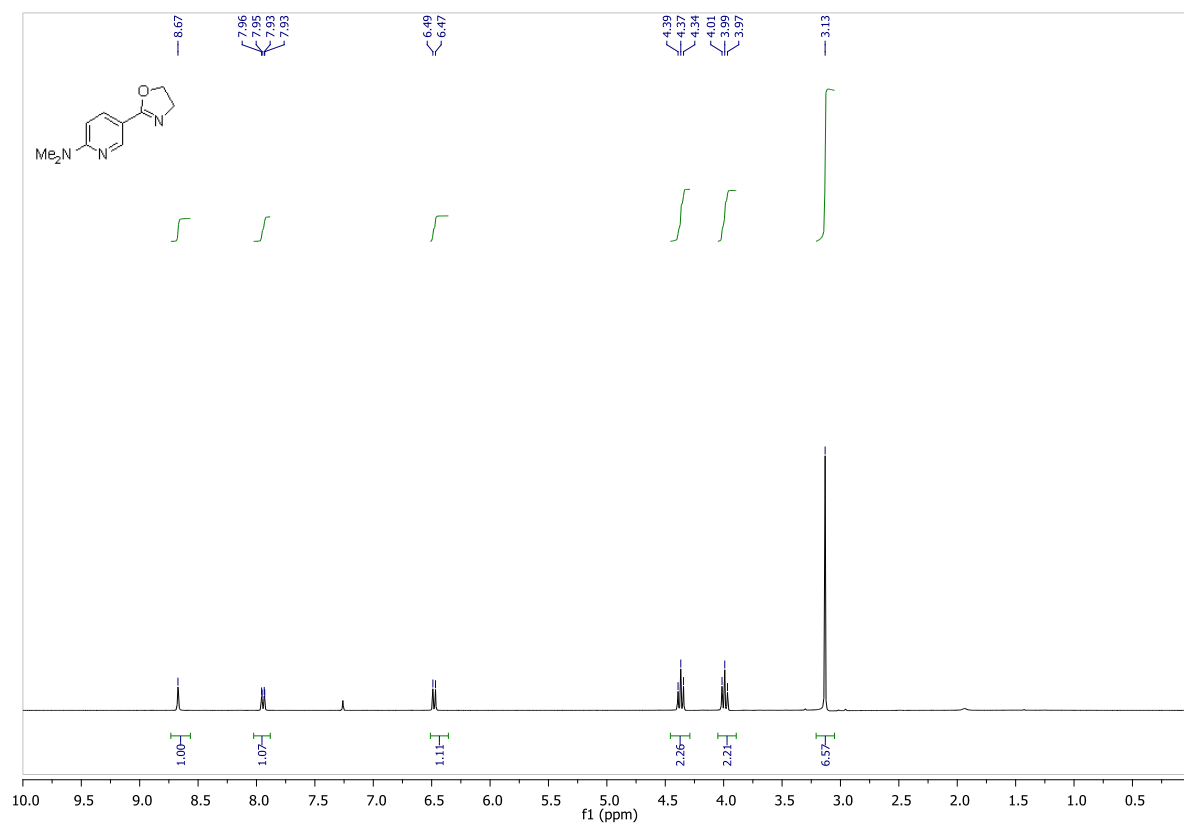


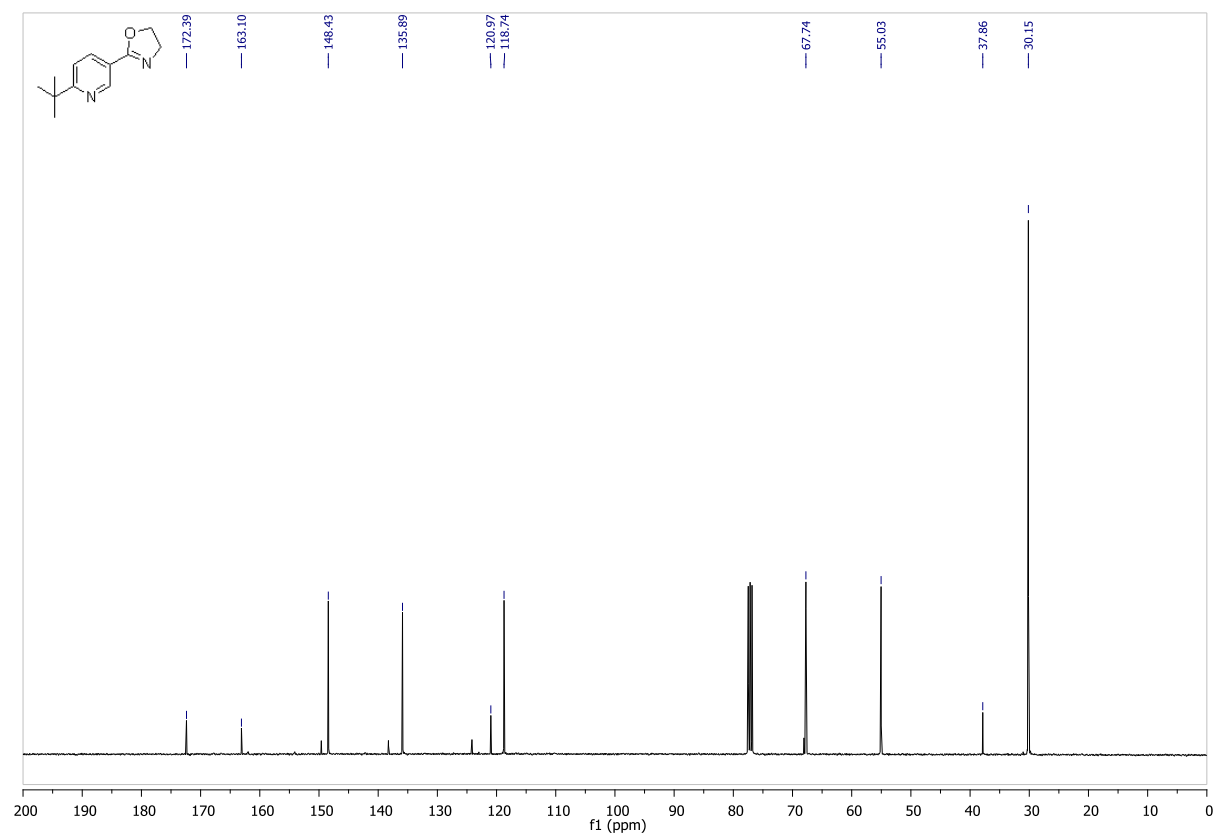
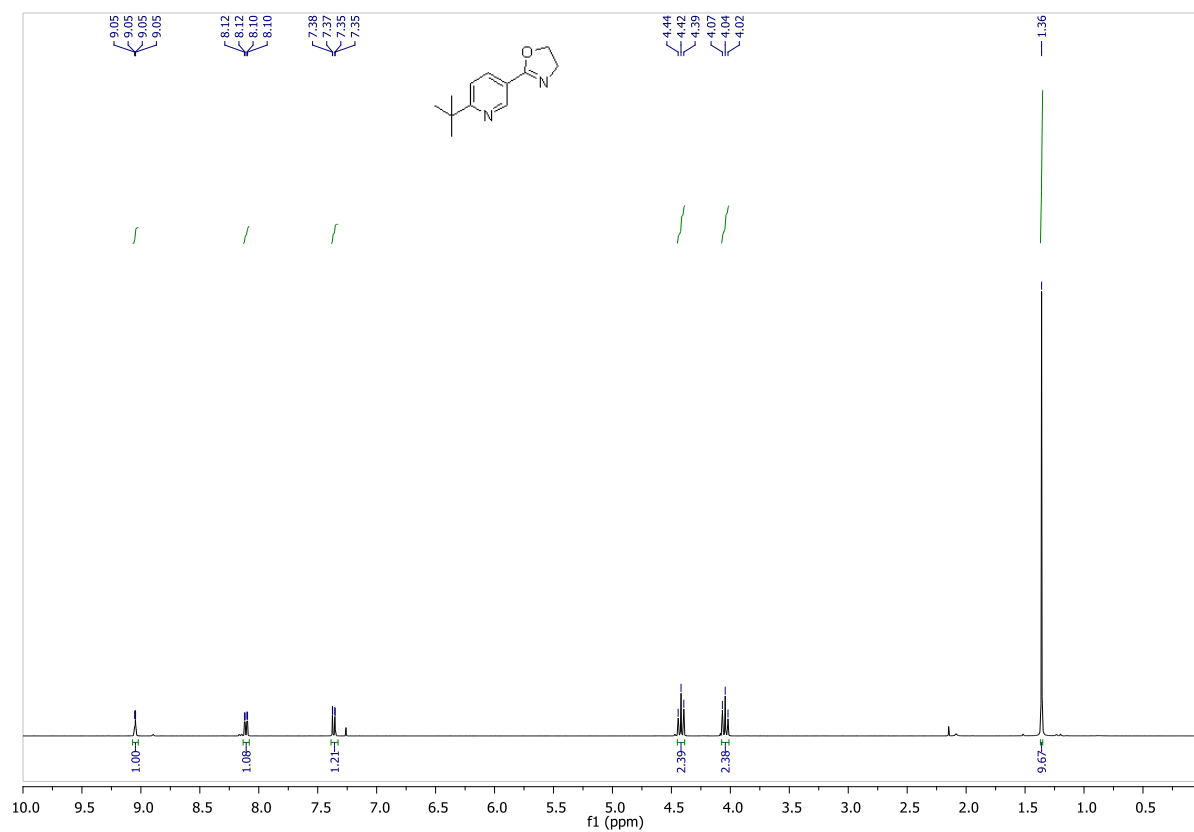


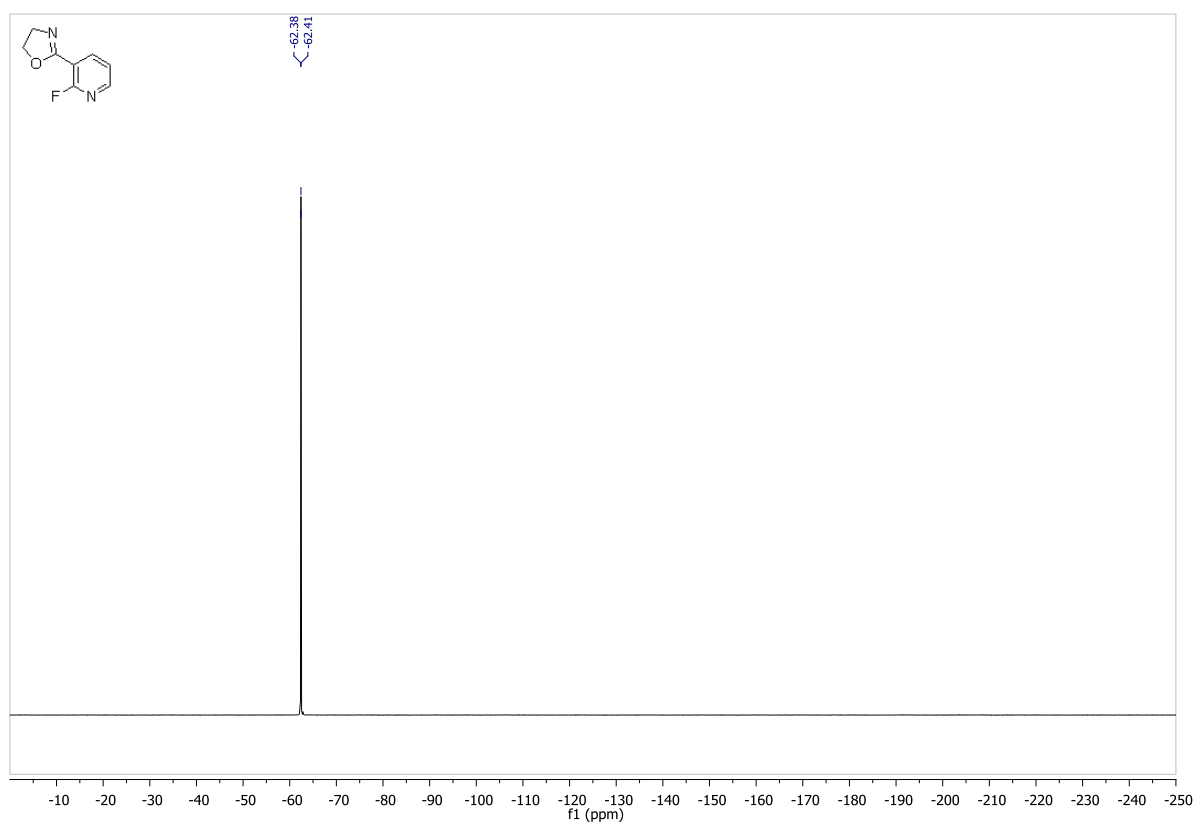
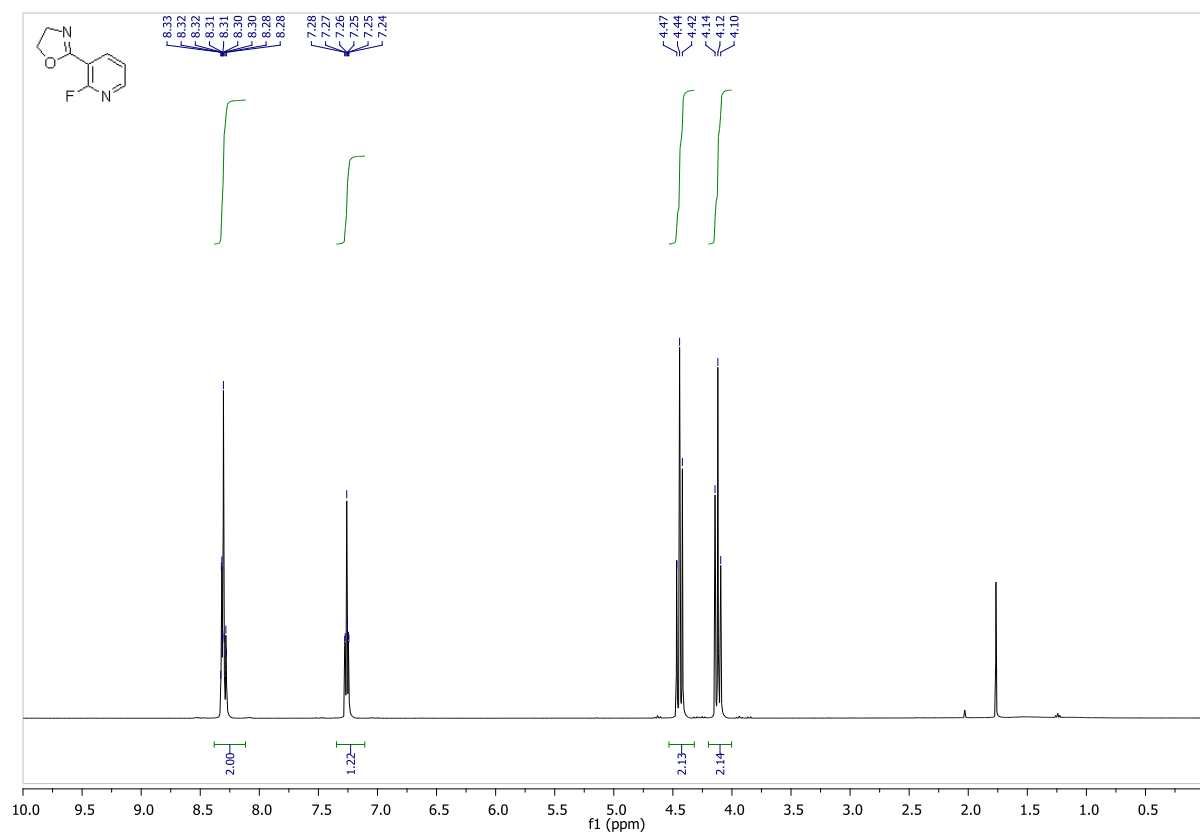


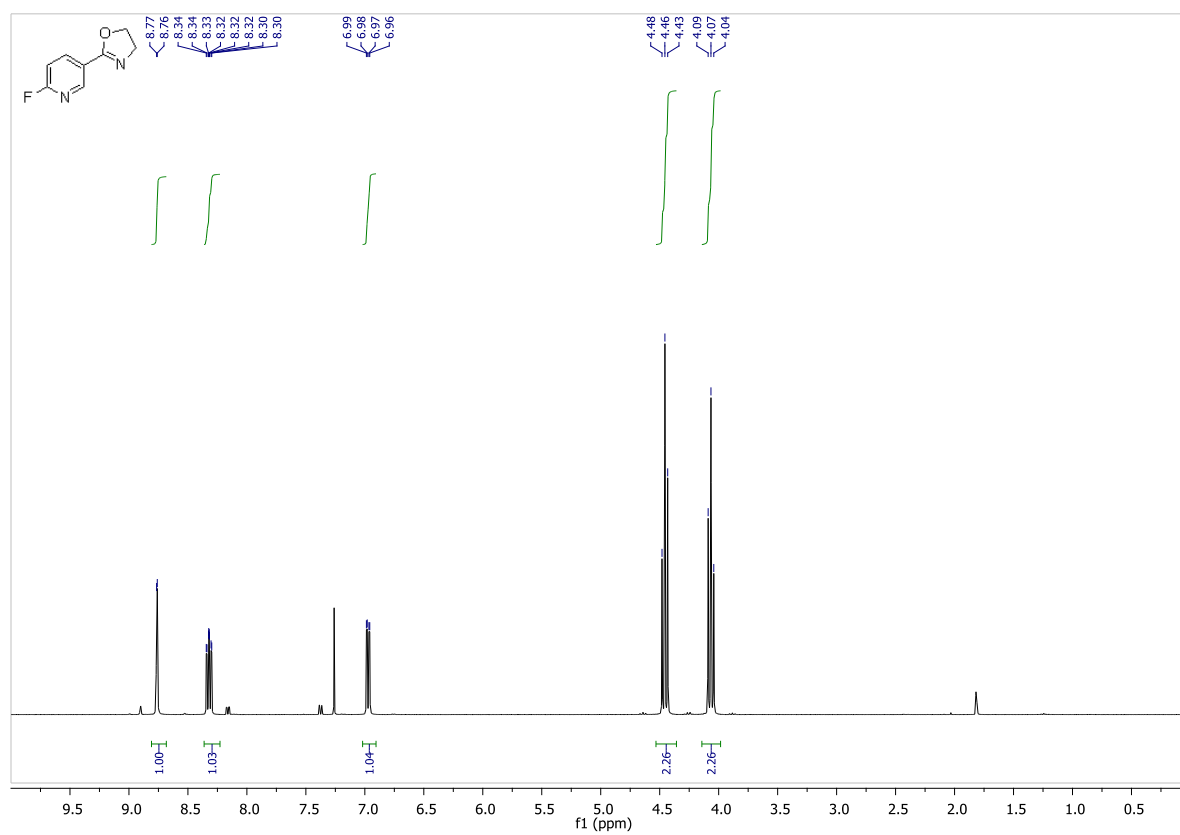
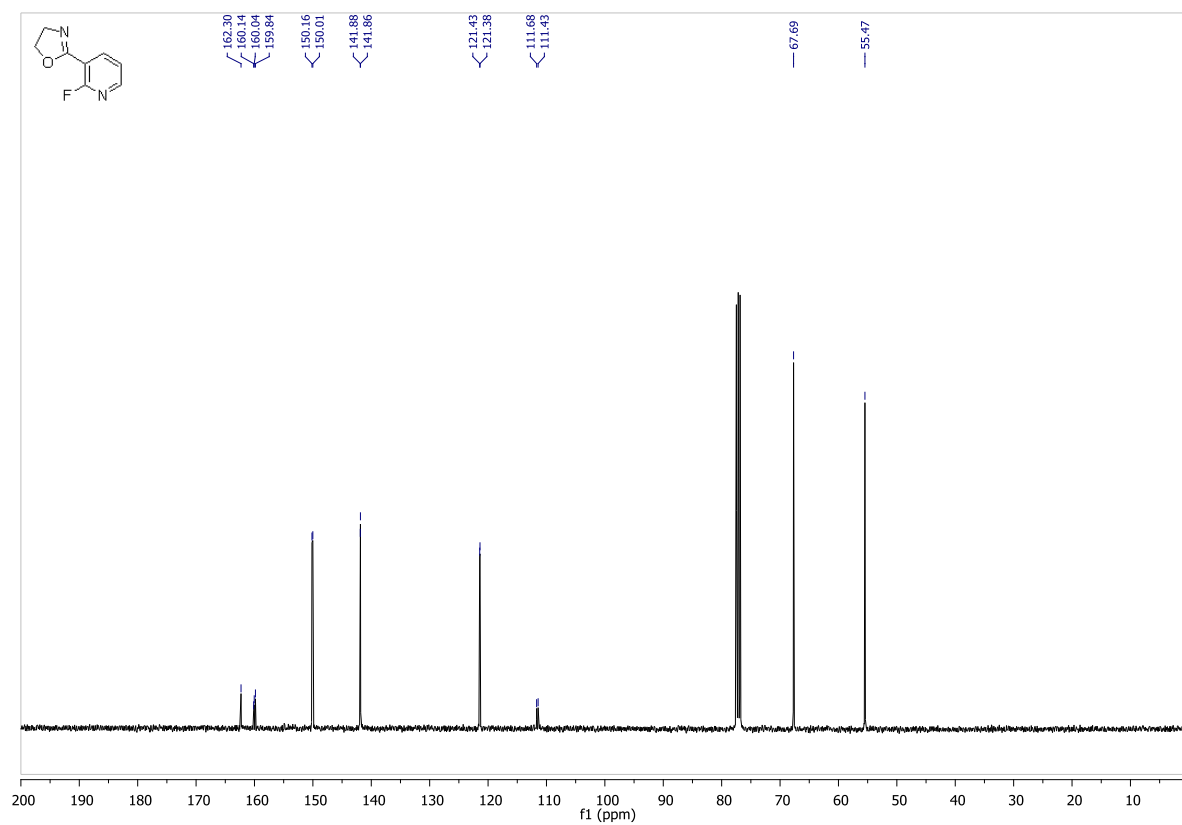


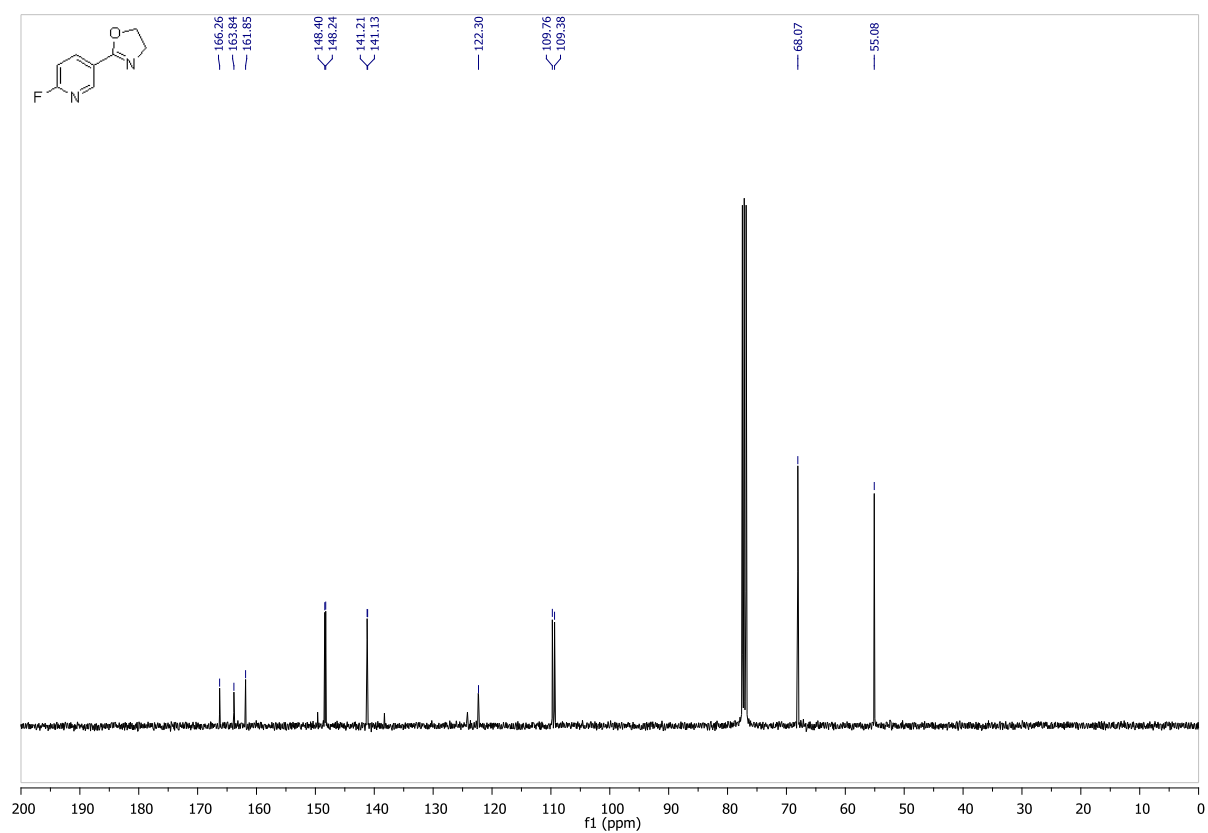
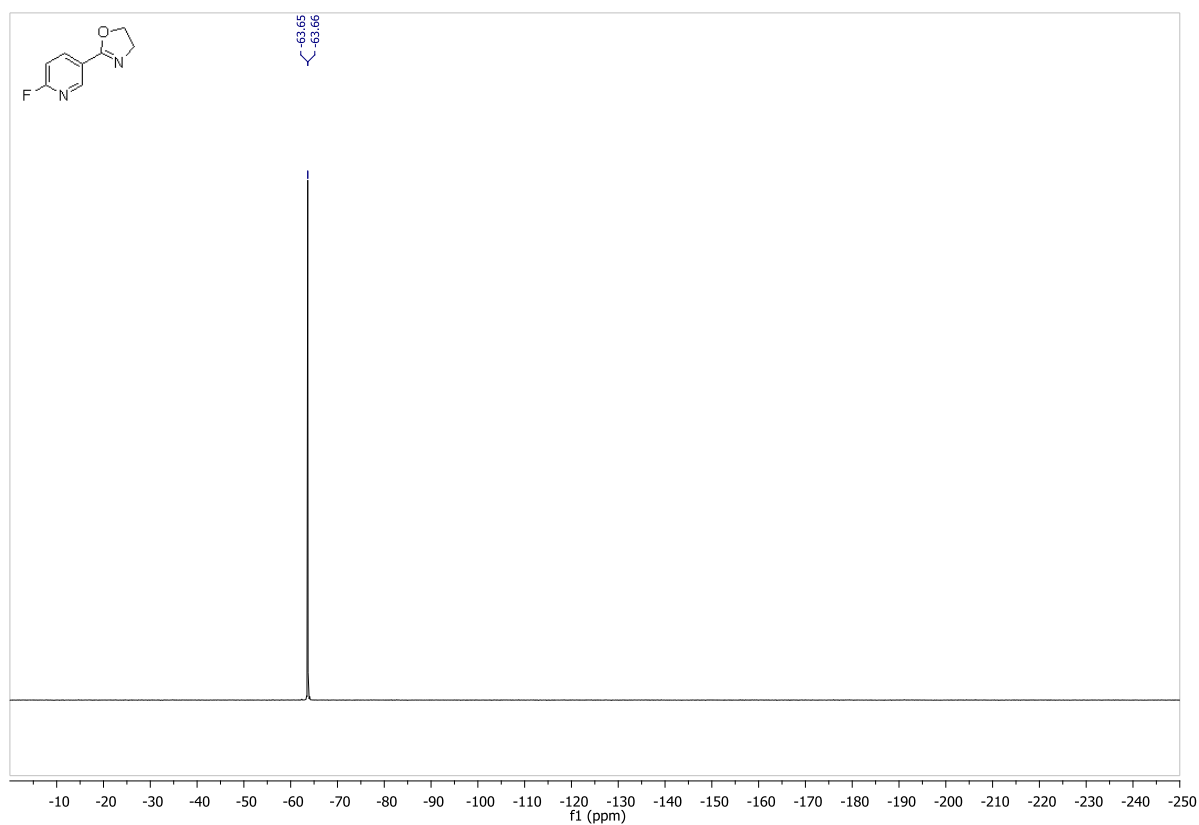


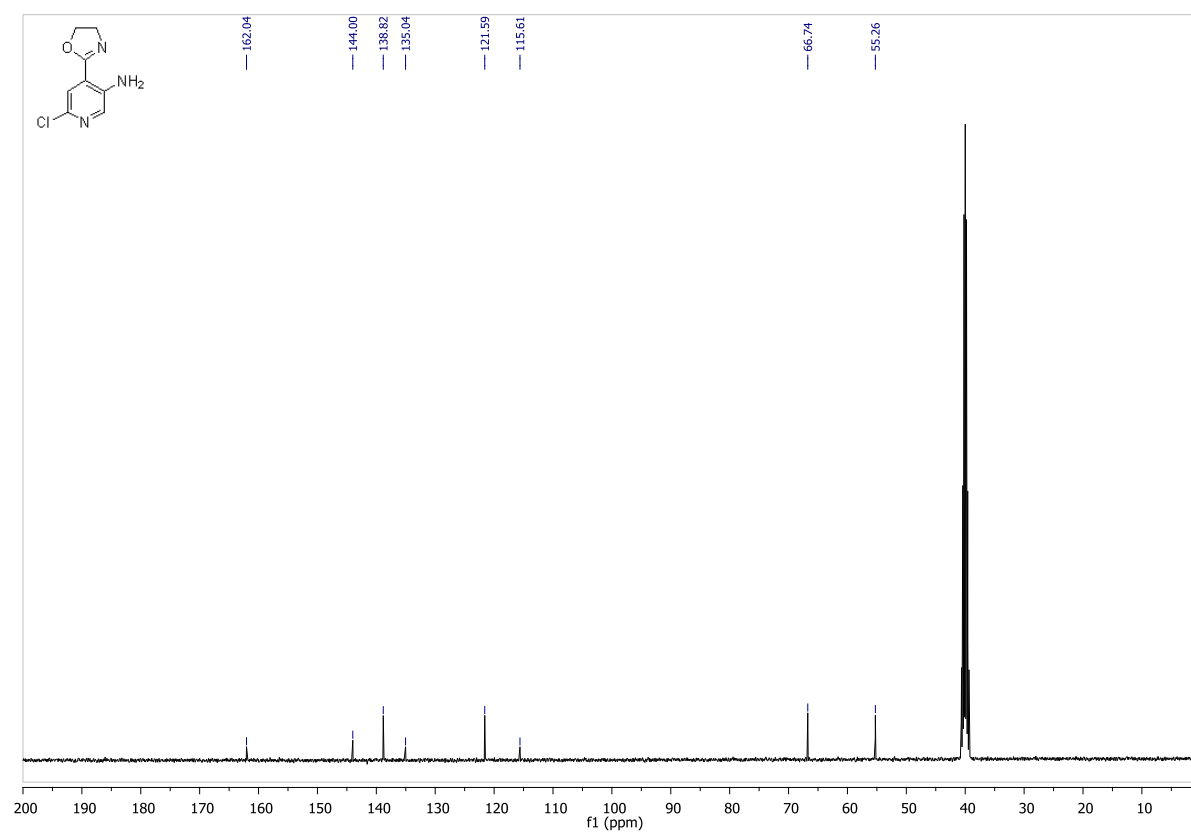
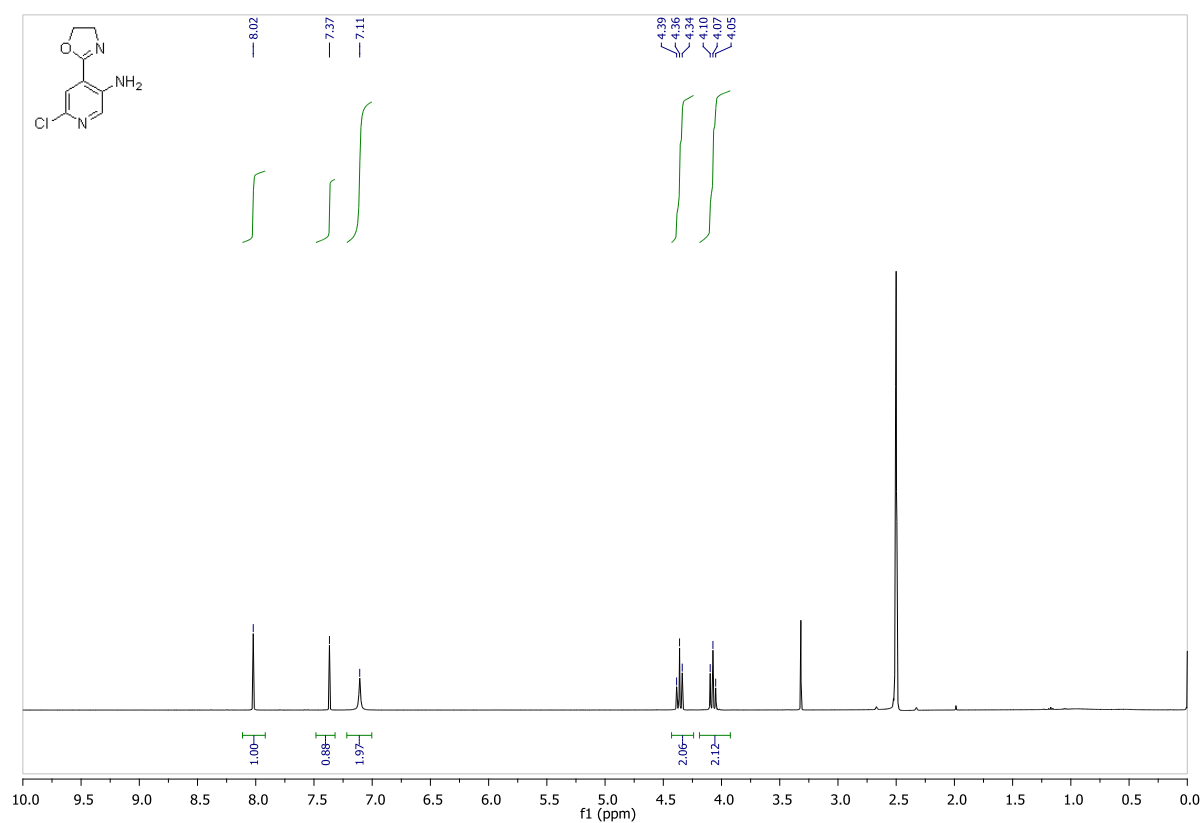


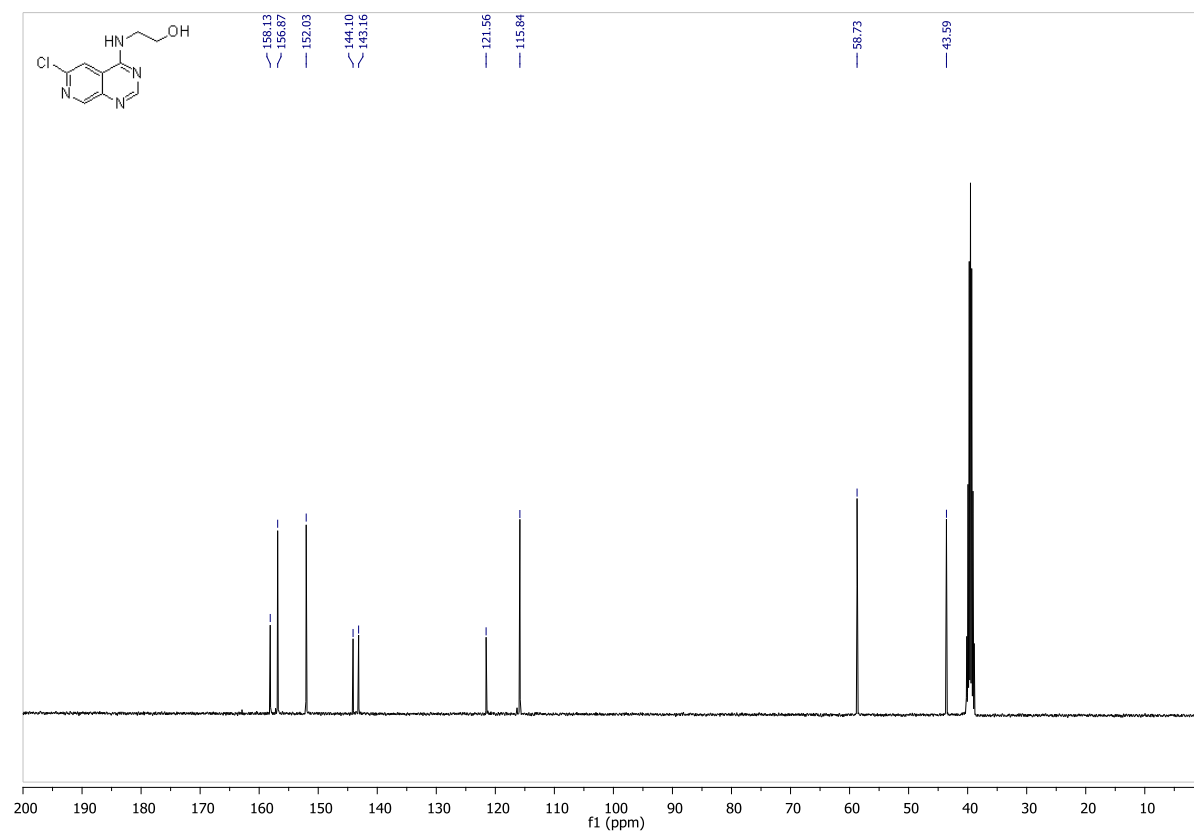
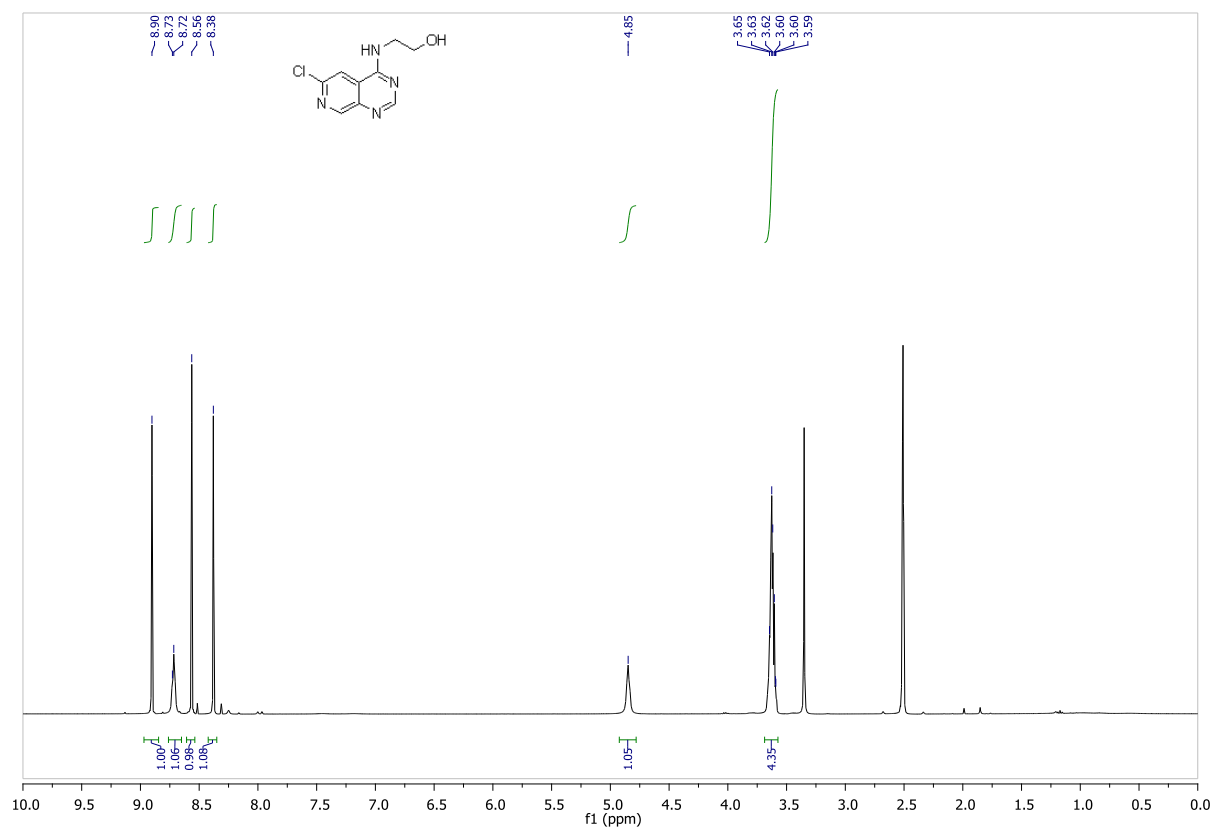












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