Supporting Information

Trifluoromethyl-substituted pyridyl- and pyrazolylboronic acids and esters: synthesis and Suzuki-Miyaura cross-coupling reactions

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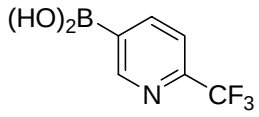
Contents

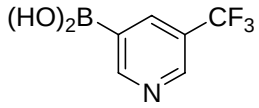
General details of equipment and techniques used are the same as those we have reported previously.[1] All reactions were carried out under an argon atmosphere, glassware was either flame dried or dried in the oven prior to use. All reactions were set up outside of a glovebox, including the weighing of solid substrates. $Pd(PPh)_3Cl_2$ was supplied from Vertellus Specialties UK Ltd or prepared in house,[2] $Pd(OAc)_2$ was purchased from Aldrich, $Pd_2(dba)_3$ was purchased from Alfa Aesar. *t*-Bu_3P and D-*t*-BPF were purchased from Strem, PCy_3 was purchased from Molekula. All other reagents employed were of standard reagent grade, purchased from either Aldrich or Alfa Aesar and used without further purification. Anhydrous solvents were dried through a HPLC column on an Innovative Technology Inc. solvent purification system. All other solvents in this work were used without prior purification. Column chromatography was carried out using 40-60 μm mesh silica (Fluorochem). Thin-layer chromatography (TLC) was performed on 20 mm precoated plates of silica gel (Merck, silica gel $60F_{254}$), visualisation was made using ultraviolet light (254 nm). NMR spectra were recorded on Bruker Avance-400 [^{1}H NMR (400 MHz), ^{13}C NMR (100 MHz), ^{11}B NMR (128 MHz)], Varian 500 [^{13}C NMR (125 MHz)], Varian VNMRS 700 [^{13}C NMR (175 MHz)] or Varian 200 [^{19}F NMR (188 MHz)] instruments, using deuterated solvent as a lock. Chemical shifts are quoted in ppm, relative to tetramethylsilane (TMS), using TMS or the residual solvent as internal reference for ^{1}H and ^{13}C NMR, and $CFCl_3$ as internal reference for ^{19}F NMR. Melting points were determined on a Stuart Scientific SMP3 melting point apparatus and are uncorrected. Electron Impact (EI) mass spectra were recorded on a Thermo-Finnigan Trace with positive ionisation mode. Electrospray (ES^+) mass spectra were recorded on a Micromass LCT mass spectrometer. Elemental analyses were obtained on an Exeter analytical Inc. CE-440 elemental analyser.

6-(Trifluoromethyl)-3-pyridylboronic acid (3)



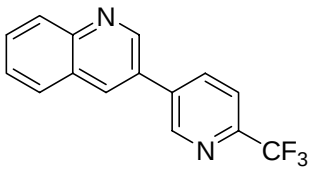
n-Butyllithium (2.5 M in hexane, 19.5 cm^3, 49 mmol) was added to a mixture of 5-bromo-2-(trifluoromethyl)pyridine **1** (10.0 g, 44 mmol) and triisopropylborate (12.3 cm^3, 53 mmol) in anhydrous THF (80 cm^3) at –78 °C under argon. The reaction was stirred at –78 °C for 3 h before warming gradually to –10 °C when the reaction was quenched with deionised water (100 cm^3). The organic solvent was removed in vacuo. The resulting aqueous phase was treated with solid NaOH to obtain pH 10, then washed with diethyl ether (50 cm^3) and acidified to pH 5 using acetic acid. The solution was extracted with EtOAc (200 cm^3) and evaporated to dryness in vacuo to yield **3** as a white solid (8.04 g, 95%): mp 255 °C (decomp.); ^{1}H NMR (400 MHz, DMSO-d_6, DCl) δ 8.98 (1H, s), 8.35 (1H, d, *J* = 7.8 Hz), 7.82 (1H, d, *J* = 7.8 Hz); ^{13}C NMR (125 MHz, DMSO-d_6, DCl) δ 155.3, 144.6, 120.5 (1C, q, *J* = 3 Hz), (*C*F_3 and *C*-CF_3 peaks not observed); ^{11}B NMR (128 MHz, DMSO-d_6, DCl) δ 29.2; ^{19}F NMR (188 MHz, DMSO-d_6, DCl) δ -66.2. Crystals of **3** suitable for X-ray structure determination were grown on slow recrystallisation from EtOAc. (See Figure S1).

5-(Trifluoromethyl)-3-pyridylboronic acid (4)



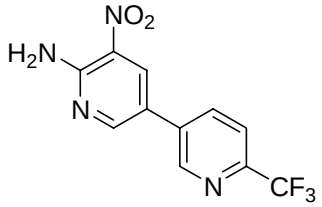
The procedure is described in the text.

3-[6-(Trifluoromethyl)pyridin-3-yl]quinoline (12)



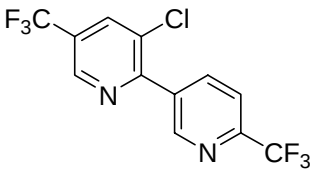
Compound **3** (216 mg, 1.13 mmol), 3-bromoquinoline **5** (0.14 cm^3, 1.0 mmol), $Pd(PPh_3)_2Cl_2$ (35.0 mg, 0.050 mmol), 1,4-dioxane (7 cm^3) and Na_2CO_3 (1 M, 3 cm^3); reaction time 22 h reflux; eluent petroleum ether (bp 40–60 °C): EtOAc 1:1 v/v and subsequent recrystallisation from cyclohexane gave **12** as a white crystalline solid (259 mg, 94%): mp 173.0-174.7 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.16 (1H, d, *J* = 2.5 Hz), 9.07 (1H, d, *J* = 2.0 Hz), 8.37 (1H, d, *J* = 2.1 Hz), 8.18 − 8.16 (2H, m), 7.93 (1H, d, *J* = 8.0 Hz), 7.85 (1H, d, *J* = 8.0 Hz), 7.84 − 7.80 (1H, m), 7.66 − 7.64 (1H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.0, 148.7, 148.1, 147.7 (1C, q, *J* = 35 Hz), 136.6, 136.0, 134.4, 130.7, 129.6, 129.3, 128.3, 127.8, 127.7, 121.6 (1C, q, *J* =274 Hz), 120.9 (1C, q, *J* = 3 Hz); ^{19}F NMR (188 MHz, $CDCl_3$) δ -68.3; MS (ES^+) *m/z* 275.0 ($[M+1]^+$, 100%). Anal. Calcd. for $C_{15}H_9F_3N_2$: C, 65.69; H, 3.31; N, 10.21. Found: C, 65.62; H, 3.31; N, 10.18%.

5-[6-(Trifluoromethyl)pyridin-3-yl]-2-amino-3-nitropyridine (13)



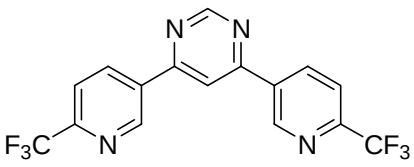
Compound **3** (216 mg, 1.13 mmol), 2-amino-5-bromo-3-nitro-pyridine **6** (218 mg, 1.0 mmol), $Pd(PPh_3)_2Cl_2$ (35.0 mg, 0.050 mmol), 1,4-dioxane (7 cm^3) and Na_2CO_3 (1 M, 3 cm^3); reaction time 17 h reflux; eluent EtOAc and subsequent recrystallisation from toluene gave **13** as a yellow solid (214 mg, 75%): mp 124.2-126.5 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.24 (1H, d, *J* = 1.7 Hz), 9.00 (1H, d, *J* = 2.3 Hz), 8.89 (1H, d, *J* = 2.2 Hz), 8.53 (1H, dd, *J* = 8.2 Hz, *J* = 2.2 Hz), 8.29 (2H, br s, NH_2), 8.06 (1H, d, *J* = 8.2 Hz); ^{13}C NMR (125 MHz, DMSO-d_6) δ 154.8, 153.5, 147.6, 144.9 (1C, q, *J* = 34 Hz), 135.3, 134.8, 133.1, 126.8, 121.8 (1C, q, *J* = 273 Hz), 120.8 (1C, q, *J* = 3 Hz), 120.1; ^{19}F NMR (188 MHz, $CDCl_3$) δ -68.3; MS (EI) *m/z* 284.0 (M^+, 100%). Anal. Calcd. for $C_{11}H_7F_3N_4O_2$: C, 46.49; H, 2.48; N, 19.71. Found: C, 46.57; H, 2.47; N, 19.73%.

3-Chloro-5-(trifluoromethyl)-2-[6-(trifluoromethyl)pyridin-3-yl]pyridine (14)



Compound **3** (383 mg, 2.0 mmol), 2,3-dichloro-5-(trifluoromethyl)pyridine **7** (0.14 cm^3, 1.0 mmol), $Pd(PPh_3)_2Cl_2$ (35.0 mg, 0.050 mmol), 1,4-dioxane (7 cm^3) and Na_2CO_3 (1 M, 3 cm^3); reaction time 4 h reflux; eluent DCM:Et_2O 95:5 v/v, gave a yellow oil which after Kügelrohr distillation, gave **14** as a white crystalline solid (298 mg, 92%): mp 90.9-93.2 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.14 (1H, d, *J* = 1.4 Hz), 8.90 (1H, s), 8.31 (1H, dd, *J* = 8.1 Hz, *J* = 2.0 Hz), 8.11 (1H, d, *J* = 1.8 Hz), 7.83 (1H, d, *J* = 8.1 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.7, 150.6, 148.7 (1C, q, *J* = 35 Hz), 145.0 (1C, q, *J* = 4 Hz), 138.5, 135.8 (1C, q, *J* = 4 Hz), 135.6, 130.9, 127.6 (1C, q, *J* = 34 Hz), 122.5 (1C, q, *J* = 272 Hz), 121.5 (1C, q, *J* = 273 Hz), 120.0 (1C, q, *J* = 3 Hz); ^{19}F NMR (188 MHz, $CDCl_3$) δ -62.9, -68.5; MS (ES^+) *m/z* 327.1 ($[M+1]^+$, 100%). Anal. Calcd. for $C_{12}H_5ClF_6N_2$: C, 44.13; H, 1.54; N, 8.58. Found: C, 44.26; H, 1.49; N, 8.71%.

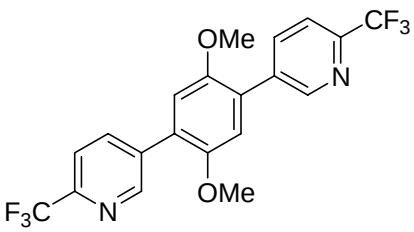
4,6-Bis[6-(trifluoromethyl)pyridin-3-yl]pyrimidine (15)



Compound **3** (601 mg, 3.2 mmol), 4,6-dichloropyrimidine **8** (224 mg, 1.5 mmol), $Pd(PPh_3)_2Cl_2$ (53.0 mg, 0.075 mmol), *t*-Bu_3P (0.02 cm^3, 0.075 mmol), 1,4-dioxane (7 cm^3) and Na_2CO_3 (1 M, 6 cm^3); reaction time 21 h reflux; eluent hexane:EtOAc 1:1 v/v, and subsequent recrystallisation from cyclohexane gave a crystalline yellow solid **15** (456 mg, 81%): mp 156.9-158.6 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.47 (1H, d, *J* = 1.3 Hz), 9.45 (2H, d, *J* = 1.9 Hz), 8.68 (2H, dd, *J* = 8.3, 1.5 Hz), 8.23 (1H, d, *J* = 1.3 Hz), 7.89 (2H, d, *J* = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.9, 160.1, 150.4 (1C, q, *J* = 35 Hz), 148.8, 136.5, 134.9, 121.4 (1C, q, *J* = 274

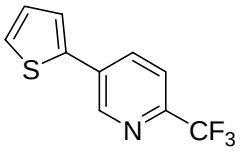
Hz), 120.9, 113.6; ^{19}F NMR (376 MHz, $CDCl_3$) δ -68.5; MS (ES^+) *m/z* 371.2 ($[M+1]^+$, 35%). Anal. Calcd. for $C_{16}H_8F_6N_4$: C, 51.90; H, 2.18; N, 15.13. Found: C, 51.86; H, 2.16; N, 15.18%.

2-(Trifluoromethyl)-5-{4-[6-(trifluoromethyl)pyridin-3-yl]-2,5-dimethoxyphenyl}pyridine (16)



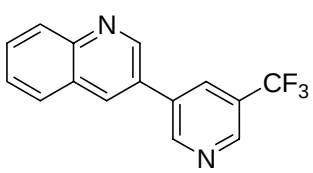
Compound **3** (400 mg, 2.1 mmol), 1,4-dibromo-2,5-dimethoxybenzene **9** (296 mg, 1.0 mmol), $Pd(PPh_3)_2Cl_2$ (35.0 mg, 0.05 mmol), 1,4-dioxane (7 cm^3) and Na_2CO_3 (1 M, 3 cm^3); reaction time 1 h reflux; recrystallisation from toluene gave a white crystalline solid **16** (331 mg, 77%): mp 224.7-226.9 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.92 (2H, s), 8.09 (2H, dd, *J* = 8.1, 1.8 Hz), 7.76 (2H, d, *J* = 8.1 Hz), 7.01 (2H, s), 3.84 (6H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.2, 150.5, 146.9 (2C, q, *J* = 35 Hz), 138.1, 136.7, 127.1, 121.8 (2C, q, *J* = 274 Hz), 120.0 (2C, q, *J* = 3 Hz), 114.4, 56.5; ^{19}F NMR (188 MHz, $CDCl_3$) δ -68.3; MS (ES^+) *m/z* 429.2 ($[M+1]^+$, 100%), Anal. Calcd. for $C_{20}H_{14}F_6N_2O_2$: C, 56.08; H, 3.29; N, 6.54. Found: C, 56.21; H, 3.28; N, 6.56%.

2-(Trifluoromethyl)-5-(thiophen-2-yl)pyridine (17)



Compound **3** (216 mg, 1.13 mmol), 2-bromothiophene **10** (0.1 cm^3, 1.0 mmol), $Pd(PPh_3)_2Cl_2$ (35.0 mg, 0.05 mmol), 1,4-dioxane (7 cm^3) and Na_2CO_3 (1 M, 3 cm^3); reaction time 3 h reflux; eluent Et_2O:DCM 1:9 v/v, gave a beige crystalline solid **17** (221 mg, 93%): mp 65.2-66.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.97 (1H, d, *J* = 2.0 Hz), 8.02 (1H, dd, *J* = 8.1 Hz, *J* = 2.3 Hz), 7.69 (1H, d, *J* = 8.1 Hz), 7.46 − 7.44 (2H, m), 7.18 − 7.16 (1H, m); ^{13}C NMR (175 MHz, $CDCl_3$) δ 147.1, 146.6 (1C, q, *J* = 35 Hz), 138.8, 133.9, 133.3, 128.8, 127.6, 125.8, 121.7 (1C, q, *J* = 273 Hz), 120.7 (1C, q, *J* = 3 Hz); ^{19}F NMR (188 MHz, $CDCl_3$) δ -68.2; MS (ES^+) *m/z* 230.4 ($[M+1]^+$, 100%). Anal. Calcd. for $C_{10}H_6F_3NS$: C, 52.40; H, 2.64; N, 6.11. Found: C, 52.66; H, 2.65; N, 6.09%.

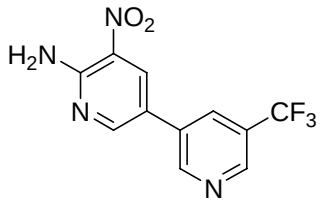
3-[5-(Trifluoromethyl)pyridin-3-yl]quinoline (18)



Compound **4** (216 mg, 1.13 mmol), 3-bromoquinoline **5** (0.14 cm^3, 1.0 mmol), $Pd(PPh_3)_2Cl_2$ (35.0 mg, 0.050 mmol), 1,4-dioxane (7 cm^3) and Na_2CO_3 (1 M, 3 cm^3); reaction time 22 h reflux; eluent EtOAc and subsequent recrystallisation from cyclohexane gave **18** as a white crystalline solid (268 mg, 98%): mp 164.9-166.3 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.170 (1H, s), 9.166 (1H, s), 8.97 (1H, s), 8.38 (1H, d, *J* = 2.1 Hz), 8.24 (1H, s), 8.19 (1H, d, *J* = 8.5 Hz), 7.94 (1H, d, *J* = 8.1Hz), 7.83 – 7.78 (1H, m), 7.65 (1H, t, *J* = 7.1 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.7, 148.9, 148.1, 146.1 (1C, q, *J* = 4 Hz), 134.4, 134.0, 131.7 (1C, q, *J* = 4 Hz), 130.7, 129.6, 129.2,

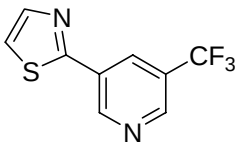
128.3, 127.84, 127.76 (1C, q, *J* = 33 Hz), 127.2 (1C, q, *J* = 33 Hz), 123.5 (1C, q, *J* = 271 Hz); ^{19}F NMR (188 MHz, $CDCl_3$) δ –62.9; MS (ES^+) *m/z* 275.0 ($[M+1]^+$, 100%). Anal. Calcd. for $C_{15}H_9F_3N_2$: C, 65.69; H, 3.31; N, 10.21. Found: C, 65.57; H, 3.28; N, 10.16%.

5-[5-(Trifluoromethyl)pyridin-3-yl]-2-amino-3-nitropyridine (19)



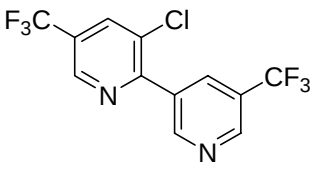
Compound **4** (216 mg, 1.13 mmol), 2-amino-5-bromo-3-nitro-pyridine **6** (218 mg, 1.0 mmol), $Pd(PPh_3)_2Cl_2$ (35.0 mg, 0.050 mmol), 1,4-dioxane (7 cm^3) and Na_2CO_3 (1 M, 3 cm^3); reaction time 17 h reflux; eluent EtOAc gave **19** as a yellow solid (220 mg, 78%): mp 247.2-250.0 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.26 (1H, d, *J* = 2.0 Hz), 8.94 (1H, s), 8.93 (1H, d, *J* = 2.2 Hz), 8.85 (1H, d, *J* = 2.2 Hz), 8.6 (1H, s), 8.18 (2H, br s, NH_2); ^{13}C NMR (125 MHz, DMSO-d_6) δ 154.8, 153.5, 151.0, 144.7 (1C, q, *J* = 4 Hz), 133.2, 131.8, 130.8 (1C, q, *J* = 3 Hz), 126.8, 125.4 (1C, q, *J* = 32 Hz), 123.7 (1C, q, *J* = 271 Hz), 120.0; ^{19}F NMR (188 MHz, $CDCl_3$) δ -62.8; MS (EI) *m/z* 284.0 (M^+, 100%). Anal. Calcd. for $C_{11}H_7F_3N_4O_2$: C, 46.49; H, 2.48; N, 19.71. Found: C, 46.43; H, 2.49; N, 19.50%.

3-(Trifluoromethyl)-5-(thiazol-2-yl)pyridine (20)



Compound **4** (324 mg, 1.7 mmol), 2-bromothiazole **11** (0.14 cm^3, 1.5 mmol), $Pd(PPh_3)_2Cl_2$ (52.0 mg, 0.075 mmol), 1,4-dioxane (7 cm^3) and Na_2CO_3 (1 M, 3 cm^3); reaction time 20.5 h reflux; eluent Et_2O:DCM 1:9 v/v, gave a white crystalline solid **20** (175 mg, 51%): mp 69.2-71.9 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.32 (1H, d, *J* = 2.0 Hz), 8.90 (1H, d, *J* = 1.3 Hz), 8.50 − 8.49 (1H, m), 7.96 (1H, d, *J* = 3.3 Hz), 7.48 (1H, d, *J* = 3.3 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.0, 150.7 (1C, q, *J* = 2 Hz), 147.3 (1C, q, *J* = 4 Hz), 144.6, 130.7 (1C, q, *J* = 3 Hz), 129.7, 127.2 (1C, q, *J* = 34 Hz), 123.3 (1C, q, *J* = 273 Hz), 120.7; ^{19}F NMR (188 MHz, $CDCl_3$) δ -63.0; MS (ES^+) *m/z* 231.4 ($[M+1]^+$, 100%). Anal. Calcd. for $C_9H_5F_3N_2S$: C, 46.96; H, 2.19; N, 12.17. Found: C, 47.16; H, 2.25; N, 12.08%.

3-Chloro-5-(trifluoromethyl)-2-[5-(trifluoromethyl)pyridin-3-yl]pyridine (21)

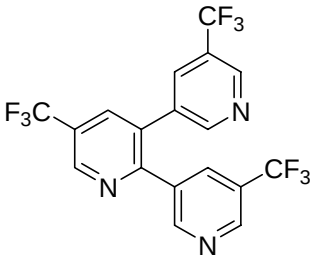


Compound **4** (192 mg, 1.0 mmol), 2,3-dichloro-5-(trifluoromethyl)pyridine **7** (0.14 cm^3, 1.0 mmol), $Pd(PPh_3)_2Cl_2$ (35.0 mg, 0.050 mmol), 1,4-dioxane (7 cm^3) and Na_2CO_3 (1 M, 3 cm^3); reaction time 3 h reflux; eluent gradient DCM:EtOAc, 1:0 to 0:1 v/v, gave a yellow oil which with subsequent distillation of the crude fraction, using Kügelrohr apparatus, gave **21** as a white crystalline solid (244 mg, 75%): mp 47.5-48.7 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.26 (1H, d, *J* = 2.0 Hz), 9.00 (1H, d, *J* 1.3 Hz), 8.91 (1H, s), 8.39 − 8.38 (1H, m), 8.12 (1H, d, *J* = 2.0 Hz); ^{13}C

NMR (125 MHz, $CDCl_3$) δ 155.5, 153.4, 147.4 (1C, q, *J* = 4 Hz), 145.0 (1C, q, *J* = 4 Hz), 135.9 (1C, q, *J* = 3 Hz), 134.2 (1C, q, *J* = 4 Hz), 132.9, 130.9, 127.6 (1C, q, *J* = 33 Hz), 126.6 (1C, q, *J* = 33 Hz), 124.0 (1C, q, *J* = 271 Hz), 121.9 (1C, q, *J* = 271 Hz); ^{19}F NMR (188 MHz, $CDCl_3$) δ -62.8, -62.9; MS (ES^+) *m/z* 327.1 ($[M+1]^+$, 100%). Anal. Calcd. for $C_{12}H_5ClF_6N_2$: C, 44.13; H, 1.54; N, 8.58. Found: C, 44.06; H, 1.51; N, 8.62%.

Compound **4** (383 mg, 2.0 mmol), 2,3-dichloro-5-(trifluoromethyl)pyridine **7** (0.14 cm^3, 1.0 mmol), $Pd(PPh_3)_2Cl_2$ (35.0 mg, 0.050 mmol), 1,4-dioxane (7 cm^3) and Na_2CO_3 (1 M, 3 cm^3); reaction time 28.5 h reflux; eluent hexane:EtOAc, 1:1 v/v, gave a yellow oil which with subsequent distillation using Kügelrohr apparatus, gave **21** as a white crystalline solid (270 mg, 83%) spectroscopically identical with the sample previously prepared. A minor product was also isolated after column chromatography and distilled using a Kügelrohr apparatus to give a colourless oil which was identified as **22** from ^{1}H NMR, COSY and ^{19}F NMR spectra.

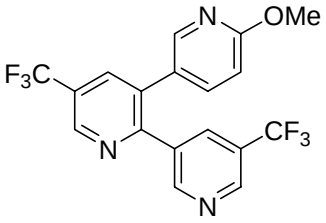
5-(Trifluoromethyl)-2,3-bis[5-(trifluoromethyl)pyridin-3-yl]pyridine (22)



Compound **4** (401 mg, 2.1 mmol), 2,3-dichloro-5-(trifluoromethyl)pyridine **7** (0.14 cm^3, 1.0 mmol), $Pd(PPh_3)_2Cl_2$ (35.0 mg, 0.050 mmol), *t*-Bu_3P (0.02 cm^3, 0.050 mmol), 1,4-dioxane (7 cm^3) and Na_2CO_3 (1 M, 3 cm^3); TLC monitored, after 28 h reflux a second amount of $Pd(PPh_3)_2Cl_2$ (35.0 mg, 0.050 mmol) was added, and left at reflux for a further 27 h; total reaction time 55 h reflux; eluent gradient hexane:EtOAc, 1:1 v/v, recrystallisation from petroleum ether (bp 40–60 °C) gave **22** a white crystalline solid (255 mg, 58%): mp 73.7-75.8 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.11 (1H, s), 8.92 (1H, s), 8.86 (1H, s), 8.66 (1H, d, *J* = 1.7 Hz), 8.64 (1H, d, *J* = 1.8 Hz), 8.08 (1H, d, *J* = 1.9 Hz), 8.04 (1H, s), 7.81 (1H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.2, 153.6, 153.0, 147.2 (1C, q, *J* = 4 Hz), 147.0 (1C, q, *J* = 4 Hz), 146.8 (1C, q, *J* = 4 Hz), 136.2 (1C, q, *J* = 3 Hz), 134.7 (1C, q, *J* = 3 Hz), 133.7 (1C, q, *J* = 4 Hz), 133.7, 133.4, 131.8, 127.2 (1C, q, *J* = 34 Hz), 127.0 (1C, q, *J* = 34 Hz), 126.8 (1C, q, *J* = 34 Hz), 123.1 (2C, q, *J* = 273 Hz), 122.9 (1C, q, *J* = 273 Hz); ^{19}F NMR (188 MHz, $CDCl_3$) δ -62.7, -63.1, -63.2; MS (ES^+) *m/z* 437.9 (M^+, 100%). Anal. Calcd. for $C_{18}H_8F_9N_3$: C, 49.44; H, 1.84; N, 9.61. Found: C, 49.56; H, 1.82; N, 9.56%.

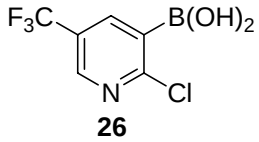
A second product was identified as **21** (117 mg, 36%) spectroscopically identical to the sample previously prepared.

5-(Trifluoromethyl)-2-[5-(trifluoromethyl)pyridin-3-yl]-3-(6-methoxypyridin-3-yl)pyridine (24)

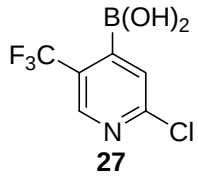


2-Methoxy-5-pyridylboronic acid **23** (53 mg, 0.35 mmol), **21** (100 mg, 0.31 mmol), $Pd(PPh_3)_2Cl_2$ (11 mg, 0.016 mmol), *t*-Bu_3P (0.004 cm^3, 0.016 mmol), 1,4-dioxane (5 cm^3) and Na_2CO_3 (1 M, 1 cm^3); reaction time 2.5 h reflux; eluent hexane:EtOAc, 1:1 v/v, and subsequent Kügelrohr distillation gave **24** a colorless oil (93 mg, 75%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.98 (1H, d, *J* = 1.3 Hz), 8.81 (1H, d, *J* = 1.0 Hz), 8.70 (1H, d, *J* = 1.8 Hz), 8.10 (1H, s), 8.02 (1H, d, *J* = 2.5 Hz), 7.98 (1H, d, *J* = 2.0 Hz), 7.34 (1H, dd, *J* = 8.7, 2.5 Hz), 6.73 (1H, d, *J* = 8.6 Hz), 3.92 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.4, 156.0, 153.7, 147.3, 146.4, (1C, q, *J* = 4 Hz), 146.0 (1C, q, *J* = 4 Hz), 139.2, 136.0 (1C, q, *J* = 4 Hz), 134.6, 134.5 (1C, q, *J* = 4 Hz), 133.6, 126.8 (1C, q, *J* = 3 Hz), 126.5 (1C, q, *J* = 4 Hz), 126.1, 123.3 (1C, q, *J* = 273 Hz), 121.9 (1C, q, *J* = 273 Hz), 111.6, 53.8; ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.7, -63.1; MS (ES^+) *m/z* 400.2 ($[M+1]^+$, 100%). Anal. Calcd. for $C_{18}H_{11}F_6N_3O$: C, 54.14; H, 2.78; N, 10.52. Found: C, 53.90; H, 2.92; N, 10.41%.

2-Chloro-5-(trifluoromethyl)-3-pyridylboronic acid (26) and 2-chloro-5-(trifluoromethyl)-4-pyridylboronic acid (27)



26



27

A solution consisting of diisopropylamine (2.1 cm^3, 15 mmol), and anhydrous THF (15 cm^3) was cooled to −10 °C and *n*-butyllithium (2.5 M in hexanes, 6.0 cm^3, 15 mmol) was added dropwise, and then stirred at 0 °C for 30 min. The lithium diisopropylamine solution was cooled to −78 °C and a solution of 2-chloro-5-(trifluoromethyl)pyridine **25** (1.82 g, 10 mmol) in anhydrous THF (10 cm^3) was added dropwise over 15 min. The reaction mixture was stirred for a further 2 h at −78 °C, before adding triisopropylborate (3.5 cm^3, 15 mmol) dropwise. After stirring at −78 °C for 0.5 h the reaction mixture was warmed to −10 °C and quenched with deionised water (20 cm^3). Et_2O (20 cm^3) was added and the aqueous phase separated and taken to pH 10 with $NaOH_{(s)}$. The aqueous phase was then acidified with glacial acetic acid, at pH 6 the solution turned opaque, the aqueous solution was further acidified to pH 5 then extracted with EtOAc (100 cm^3). In attempts to decolourise, the organic phase was treated with carbon and filtered through a celite pad. The organic solvent was removed in vacuo resulting in an orange solid. The crude product was then purified by column chromatography, eluent EtOAc to EtOAc:MeOH 1:1 v/v to yield **27** as a cream solid (0.94 g, 42%), followed by **26**, an off-white solid, (0.58 g, 25%).

26: mp 138.9-141.1 °C; ^{1}H NMR (400 MHz, DMSO-d_6, DCl) δ 8.68 (1H. s), 8.12 (1H, d, *J* = 2.2 Hz); ^{13}C NMR (175 MHz, DMSO-d_6, DCl) δ 156.6, 146.8 (1C, q, *J* = 5 Hz) 140.4 (1C, q, *J* = 4 Hz),

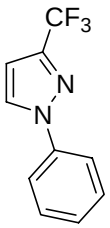
124.0 (1C, q, J = 33 Hz), 123.8 (1C, q, J = 269 Hz), (*C*-B not observed); ^{19}F NMR (376 MHz, DMSO-d_6, DCl) δ -61.2.

27: mp 147.9-149.2 °C; ^{1}H NMR (400 MHz, DMSO-d_6, DCl) δ 8.61 (1H, s), 7.54 (1H, s); ^{13}C NMR (100 MHz, DMSO-d_6, DCl) δ 153.6 (1C, q, J = 2 Hz), 146.8 (1C, q, J = 5 Hz), 127.4, 126.6 (1C, q, J = 31 Hz), 124.1 (1C, q, J = 272 Hz), (*C*-B not observed); ^{19}F NMR (376 MHz, DMSO-d_6, DCl) δ -59.0. Anal. Calcd. for $C_6H_4BClF_3NO_2$: C, 31.98; H, 1.79; N, 6.22. Found: C, 32.39; H, 1.88; N, 6.10%. Crystals for X-ray analysis were grown from ethyl acetate (see Figures S2 and S3).

Typical Procedure for the preparation of 29a-c

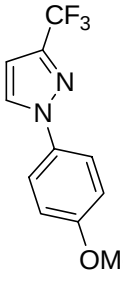
A flame-dried round-bottomed flask, purged with argon was charged with Cu_2O (5 mol%), salicylaldoxime (20 mol%), 3-(trifluoromethyl)pyrazole **28** (1.0 equiv.), anhydrous Cs_2CO_3 (2.0 equiv.) and iodo(hetero)aryl (1.5 equiv.). Degassed acetonitrile (20 cm^3) was added to the reaction flask and the reaction mixture was stirred at reflux for 18 h. The reaction mixture was cooled to room temperature, diluted with DCM and filtered through a celite pad and further washed with DCM (~100 cm^3). The filtrate was concentrated in vacuo, the residue was further purified by column chromatography on silica gel.

3-(Trifluoromethyl)-1-phenyl-1*H*-pyrazole (29a)[3]



3-(Trifluoromethyl)pyrazole **28** (2.0 g, 14.7 mmol), iodobenzene (2.5 cm^3, 22.0 mmol), Cu_2O (106 mg, 0.74 mmol), salicylaldoxime (398 mg, 2.9 mmol), anhydrous Cs_2CO_3 (9.6 g, 29.4 mmol) and acetonitrile (20 cm^3); reaction time 18 h reflux; eluent petroleum ether (bp 40–60 °C):DCM, 100:0 to 1:1 v/v. The crude product a yellow oil was further distilled using Kügelrohr apparatus (69–75 °C/0.6–0.75 mbar) to give **29a** as a pale yellow oil (2.92 g, 94%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95 (1H, d, J = 2.0 Hz), 7.70 (2H, d, J = 8.5 Hz), 7.49 (2H, t, J = 7.7 Hz), 7.37 (1H, t, J = 7.4 Hz), 6.72 (1H, d, J = 2.6 Hz); ^{13}C NMR (175 MHz, $CDCl_3$) δ 144.1 (1C, q, J = 38 Hz), 139.6, 129.7, 128.4, 127.9, 121.4 (1C, q, J = 268 Hz), 120.1, 106.1; ^{19}F NMR (188 MHz, $CDCl_3$) δ -62.5; MS (EI) *m/z* 212.0 (M^+, 100%). HRMS (EI) calcd for $C_{10}H_7F_3N_2$ 212.0561, found 212.0561.

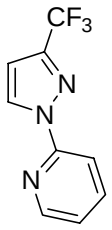
3-(Trifluoromethyl)-1-(4-methoxyphenyl)-1*H*-pyrazole (29b)[4]



3-(Trifluoromethyl)pyrazole **28** (2.0 g, 14.7 mmol), 4-iodoanisole (5.15 g, 22.0 mmol), Cu_2O (106 mg, 0.74 mmol), salicylaldoxime (398 mg, 2.9 mmol), anhydrous Cs_2CO_3 (9.6 g, 29.4 mmol) and acetonitrile (20 cm^3); reaction 19.5 h reflux; eluent DCM:petroleum ether (bp 40–60 °C) 1:9 v/v to give **29b** as a pale yellow oil (3.48 g,

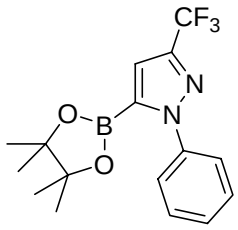
98%); ^{1}H NMR (400 MHz, acetone-d_6) δ 8.37 (1H, dd, *J* = 2.5, 1.0 Hz), 7.76 (2H, d, *J* = 9.2 Hz), 7.07 (2H, d, *J* = 9.2 Hz), 6.85 (1H, dd, *J* = 2.5, 0.4 Hz), 3.84 (3H, s); ^{13}C NMR (100 MHz, acetone-d_6) δ 160.3, 143.7 (1C, q, *J* = 38 Hz), 134.0, 130.3, 122.7 (1C, q, *J* = 267 Hz), 122.1, 115.6, 106.0 (1C, q, *J* = 2 Hz), 56.0; ^{19}F NMR (188 MHz, $CDCl_3$) δ -62.4; MS (EI) *m/z* 242.0 (M^+, 100%), 226.9 ($[M-CH_3]^+$, 80%). Anal. Calcd. for $C_{11}H_9F_3N_2O$: C, 54.55; H, 3.75; N, 11.57. Found: C, 54.90; H, 3.80; N, 11.96%.

3-(Trifluoromethyl)-1-(pyridin-2-yl)-1*H*-pyrazole (29c)



3-(Trifluoromethyl)pyrazole **28** (2.0 g, 14.7 mmol), 2-iodopyridine (2.3 cm^3, 22.0 mmol), Cu_2O (106 mg, 0.74 mmol), salicylaldoxime (398 mg, 2.9 mmol), anhydrous Cs_2CO_3 (9.6 g, 29.4 mmol) and acetonitrile (20 cm^3); reaction 22 h reflux; eluent EtOAc:petroleum ether (bp 40–60 °C) 1:9 v/v to give **29c** as a white crystalline solid (2.95 g, 94%); mp 81.2-82.6 °C. ^{1}H NMR (400 MHz, acetone-d_6) δ 8.79 − 8.77 (1H, m), 8.52 (1H, ddd, *J* = 4.9, 1.7, 1.0), 8.09 − 8.01 (2H, m), 7.45 (1H, ddd, *J* = 8.0, 3.6, 1.6 Hz), 6.93 (1H, dd, *J* = 2.7, 0.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.9, 148.3, 144.9 (1C, q, *J* = 38 Hz), 139.1, 128.5, 122.7, 121.2 (1C, q, *J* = 267 Hz), 113.1, 106.0 (1C, q, *J* = 2 Hz); ^{19}F NMR (188 MHz, $CDCl_3$) δ -63.0; MS (EI) *m/z* 212.9 (M^+, 100%). Anal. Calcd. for $C_9H_6F_3N_3$: C, 50.71; H, 2.84; N, 19.71. Found: C, 50.60; H, 2.88; N, 19.75%.

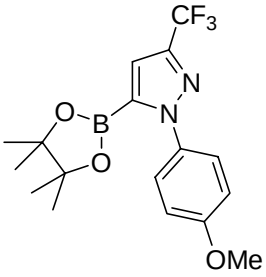
3-(Trifluoromethyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-phenyl-1*H*-pyrazole (30a)



n-Butyllithium (2.5 M in hexane, 1.4 cm^3, 3.5 mmol) was added dropwise to a solution of 3-(trifluoromethyl)-1-phenyl-1*H*-pyrazole **29a** (617 mg, 2.9 mmol) in anhydrous THF (20 cm^3) at –78 °C under argon. The reaction mixture was stirred for 45 min at –78 °C. 2-Isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.62 cm^3, 3.1 mmol) was added dropwise to the reaction mixture at –78 °C, and the mixture was stirred for 1.5 h. The mixture was warmed to room temperature over 1 h and glacial acetic acid (0.18 cm^3, 3.2 mmol) was added. The mixture was filtered through a celite pad which was washed with EtOAc (1 × 100 cm^3). The organic solvent was removed in vacuo and the crude product distilled to remove any unreacted starting material and boron-containing species, the remaining pale-brown solid was confirmed to be **30a** (906 mg, 92%); mp 77.7-79.3 °C. ^{1}H NMR (400 MHz, acetone-d_6) δ 7.65 − 7.62 (2H, m), 7.54 − 7.48 (3H, m), 7.19 (1H, s), 1.29 (12H, s); ^{13}C NMR (100 MHz, acetone-d_6) δ 143.8 (1C, q, *J* = 38 Hz), 141.6, 129.54, 129.53, 125.9, 122.8 (1C, q, *J* = 266 Hz), 115.8 (1C, q, *J* = 2 Hz), 85.7, 25.0, (*C*-B not observed); ^{11}B NMR (128 MHz, acetone-d_6) δ 27.9; ^{19}F NMR (188 MHz, acetone-d_6) δ -62.5; MS (EI) *m/z* 337.8 ($[M(\mathbf{30a})]^+$, 80%), 211.9

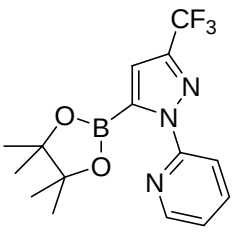
([M(**29a**)]$^+$, 60%). Anal. Calcd. for $C_{16}H_{18}BF_3N_2O_2$: C, 56.83; H, 5.37; N, 8.28. Found: C, 56.72; H, 5.37; N, 8.07%.

3-(Trifluoromethyl)-1-(4-methoxyphenyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (30b)



n-Butyllithium (2.5 M in hexane, 4.0 cm^3, 10.0 mmol) was added dropwise to a solution of 3-(trifluoromethyl)-1-(4-methoxyphenyl)-1*H*-pyrazole **29b** (2.0 g, 8.3 mmol) in anhydrous THF (20 cm^3) at –78 °C under argon. The reaction mixture was stirred for 30 min at –78 °C. 2-Isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1.9 cm^3, 9.1 mmol) was added dropwise to the reaction mixture at –78 °C, and the mixture was stirred for 1.5 h. The mixture was warmed to room temperature over 1 h and glacial acetic acid (0.52 cm^3, 9.1 mmol) was added. The mixture was filtered through a celite pad which was washed with EtOAc (1 × 100 cm^3). The organic solvent was removed in vacuo, recrystallisation of the crude product from hexane with external cooling precipitated **30b** as an off-white crystalline solid (2.99 g, 98%): mp 97.8-99.7 °C. ^{1}H NMR (400 MHz, acetone-d$_6$) δ 7.52 (2H, d, *J* = 9.1 Hz), 7.11 (1H, s), 7.06 (2H, d, *J* = 9.1 Hz), 3.88 (3H, s), 1.28 (12H, s); ^{13}C NMR (100 MHz, acetone-d$_6$) δ 160.9, 143.3 (1C, q, *J* = 36 Hz), 135.0, 127.2, 122.8 (1C, q, *J* = 266 Hz), 115.4, 114.6, 85.7, 56.0, 25.0, (*C*-B not observed); ^{11}B NMR (128 MHz, acetone-d$_6$) δ 27.9; ^{19}F NMR (188 MHz, acetone-d$_6$) δ -62.5; MS (EI) *m/z* 368.0 (M$^+$, 100%). Anal. Calcd. for $C_{17}H_{20}BF_3N_2O_3$: C, 55.46; H, 5.48; N, 7.61. Found: C, 55.27; H, 5.44; N, 7.46%. Crystals of **30b** suitable for X-ray analysis were grown on slow recrystallisation from hexane. (See Figure S4).

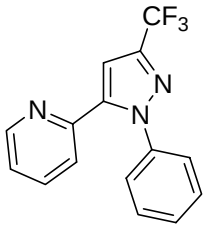
3-(Trifluoromethyl)-1-(pyridin-2-yl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (30c)



n-Butyllithium (2.5 M in hexane, 3.3 cm^3, 8.4 mmol) was added dropwise to a solution of 3-(trifluoromethyl)-1-(pyridin-2yl)-1*H*-pyrazole **29c** (1.5 g, 7.0 mmol) in anhydrous THF (50 cm^3) at –78 °C under argon. The reaction mixture was stirred for 45 min at –78 °C. 2-Isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1.6 cm^3, 7.7 mmol) was added dropwise to the reaction mixture at –78 °C, and the mixture was stirred for 1.5 h. The mixture was warmed to room temperature over 1 h and glacial acetic acid (0.44 cm^3, 7.7 mmol) was added. The mixture was filtered through a celite pad which was washed with EtOAc (1 × 100 cm^3). The organic solvent was removed in vacuo and the crude product distilled to remove any unreacted starting material and boron-containing species, the remaining colorless opaque oil was confirmed to be **30c** (1.98 g, 84%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 (1H, ddd, *J* = 4.9, 1.8, 0.9 Hz), 8.00 (1H, dt, *J* = 8.2, 0.9 Hz), 7.85 (1H, ddd, *J* = 8.3,

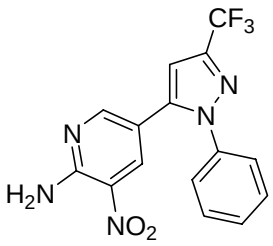
7.4, 1.8 Hz), 7.26 (1H, ddd, *J* = 7.5, 5.0, 1.0 Hz), 6.83 (1H, s), 1.42 (12H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.8, 146.7, 145.1 (1C, q, *J* = 38 Hz), 139.3, 122.5, 121.1 (1C, q, *J* = 267 Hz), 113.2, 111.5 (1C, q, *J* = 2 Hz), 84.6, 24.8, (*C*-B not observed); ^{11}B NMR (128 MHz, $CDCl_3$) δ 28.1; ^{19}F NMR (188 MHz, $CDCl_3$) δ -62.6; MS (EI) *m/z* 323.9 ($[M-CH_3]^+$, 100%). Anal. Calcd. for $C_{15}H_{17}BF_3N_3O_2$: C, 53.13; H, 5.05; N, 12.39. Found: C, 53.40; H, 5.09; N, 12.29%.

2-[3-(Trifluoromethyl)-1-phenyl-1*H*-pyrazol-5-yl]pyridine (35)



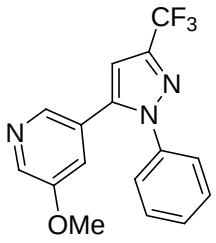
Compound **30a** (279 mg, 0.83 mmol), 2-bromopyridine **31** (0.07 cm^3, 0.75 mmol), Pd(dppf)Cl_2·DCM (61 mg, 0.075 mmol), 1,4-dioxane (7 cm^3), K_3PO_4 (477 mg, 2.3 mmol) and HCOOK (32 mg, 0.38 mmol); reaction time 4.5 h at 80 °C; eluent gradient petroleum ether (bp 40–60 °C) to EtOAc:petroleum ether (bp 40–60 °C) 1:3 v/v gave **35** as a light yellow oil (167 mg, 77%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.58 (1H, d, *J* = 4.1 Hz), 7.61 (1H, td, *J* = 7.8, 1.8 Hz), 7.40 – 7.30 (5H, m), 7.24 (1H, ddd, *J* = 7.6, 4.9, 1.1 Hz), 7.15 (1H, dt, *J* = 7.9, 1.0), 7.03 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.1, 148.4, 144.0, 143.3 (1C, q, *J* = 39 Hz), 139.7, 136.6, 129.2, 128.8, 125.7, 123.7, 123.5, 121.3 (1C, q, *J* = 269 Hz), 106.8 (1C, q, *J* = 2 Hz); ^{19}F NMR (188 MHz, $CDCl_3$) δ -62.7; MS (EI) *m/z* 288.0 ($[M-H]^+$, 100%), 289.1 (M^+, 40%). Anal. Calcd. for $C_{15}H_{10}F_3N_3$: C, 62.28; H, 3.48; N, 14.53. Found: C, 62.30; H, 3.68; N, 14.37%.

5-[3-(Trifluoromethyl)-1-phenyl-1*H*-pyrazol-5-yl]-3-nitropyridin-2-amine (36)



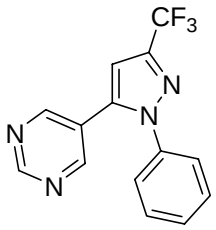
Compound **30a** (279 mg, 0.83 mmol), 2-amino-5-bromo-3-nitropyridine **6** (164 mg, 0.75 mmol), Pd(dppf)Cl_2·DCM (61 mg, 0.075 mmol), 1,4-dioxane (7 cm^3), K_3PO_4 (477 mg, 2.3 mmol) and HCOOK (32 mg, 0.38 mmol); reaction time 4 h at 80 °C; eluent gradient petroleum ether (bp 40–60 °C) to EtOAc:petroleum ether (bp 40–60 °C) 1:3 v/v gave **36** as a yellow solid (215 mg, 82%): mp 166.6-168.1 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (1H, d, *J* = 2.2 Hz), 8.18 (1H, d, *J* = 2.2 Hz), 7.47 – 7.42 (3H, m), 7.37 – 7.32 (2H, m), 6.81 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.7, 152.8, 143.6 (1C, q, *J* = 38 Hz), 139.7, 138.5, 134.5, 129.7, 129.3, 127.4, 125.7, 121.0 (1C, q, *J* = 260 Hz), 115.6, 105.5 (1C, q, *J* = 2 Hz); ^{19}F NMR (188 MHz, $CDCl_3$) δ -62.8; MS (EI) *m/z* 348.8 (M^+, 100%). Anal. Calcd. for $C_{15}H_{10}F_3N_5O_2$: C, 51.58; H, 2.89; N, 20.05. Found: C, 51.47; H, 2.91; N, 20.15%. Crystals suitable for X-ray structural analysis were grown from EtOAc/hexane. (See Figure S5).

3-[3-(Trifluoromethyl)-1-phenyl-1*H*-pyrazol-5-yl]-5-methoxypyridine (37)



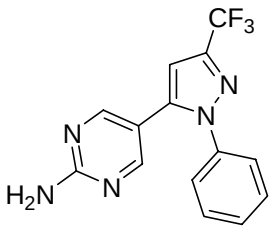
Compound **30a** (279 mg, 0.83 mmol), 3-bromo-5-methoxypyridine **32** (141 mg, 0.75 mmol), Pd(dppf)Cl_2·DCM (61 mg, 0.075 mmol), 1,4-dioxane (7 cm^3), K_3PO_4 (477 mg, 2.3 mmol) and HCOOK (32 mg, 0.38 mmol); reaction time 4 h at 80 °C; eluent gradient petroleum ether (bp 40–60 °C) to EtOAc:petroleum ether (bp 40–60 °C) 1:3 v/v gave **37** as a pale pink oil (192 mg, 80%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (1H, d, *J* = 2.8 Hz), 8.12 (1H, d, *J* = 1.7 Hz), 7.41 – 7.37 (3H, m), 7.33 – 7.29 (2H, m), 6.92 (1H, dd, *J* = 2.8, 1.8 Hz), 6.83 (1H, s), 3.69 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.3, 143.5 (1C, q, *J* = 39 Hz), 141.5, 141.3, 138.9, 138.4, 129.6, 129.1, 125.8, 121.1 (1C, q, *J* = 267 Hz), 120.1, 106.2, 55.7 (one C not observed); ^{19}F NMR (188 MHz, $CDCl_3$) δ -62.7; MS (EI) *m/z* 319.0 (M^+, 80%), 317.9 ($[M-H]^+$, 100%). Anal. Calcd. for $C_{16}H_{12}F_3N_3O$: C, 60.19; H, 3.79; N, 13.16. Found: C, 59.89; H, 3.94; N, 13.53%.

5-[3-(Trifluoromethyl)-1-phenyl-1*H*-pyrazol-5-yl]pyrimidine (38)



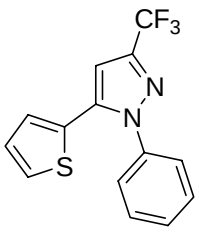
Compound **30a** (279 mg, 0.83 mmol), 5-bromopyrimidine **33** (119 mg, 0.75 mmol), Pd(dppf)Cl_2·DCM (61 mg, 0.075 mmol), 1,4-dioxane (7 cm^3), K_3PO_4 (477 mg, 2.3 mmol) and HCOOK (32 mg, 0.38 mmol); reaction time 3 h at 80 °C; eluent gradient petroleum ether (bp 40–60 °C) to EtOAc:petroleum ether (bp 40–60 °C) 1:3 v/v gave **38** as a pale orange crystalline solid (161 mg, 74%): mp 117.3-118.8 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.17 (1H, s), 8.60 (2H, s), 7.46 – 7.42 (3H, m), 7.33 – 7.28 (2H, m), 6.91 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.6, 156.0, 144.1 (1C, q, *J* = 39 Hz), 138.4, 138.2, 129.9, 129.7, 125.8, 124.1, 121.1 (1C, q, *J* = 267 Hz), 106.6 (1C, q, *J* = 2 Hz); ^{19}F NMR (188 MHz, $CDCl_3$) δ -62.8; MS (EI) *m/z* 290.0 (M^+, 90%), 289.0 ($[M-H]^+$, 100%). Anal. Calcd. for $C_{14}H_9F_3N_4$: C, 57.93; H, 3.13; N, 19.30. Found: C, 57.93; H, 3.24; N, 19.42%.

5-[3-(Trifluoromethyl)-1-phenyl-1*H*-pyrazol-5-yl]pyrimidin-2-amine (39)



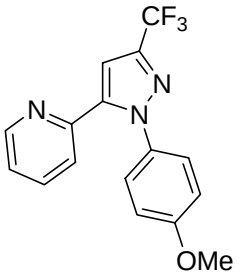
Compound **30a** (279 mg, 0.83 mmol), 2-amino-5-bromopyrimidine **34** (131 mg, 0.75 mmol), Pd(dppf)Cl_2·DCM (61 mg, 0.075 mmol), 1,4-dioxane (7 cm^3), K_3PO_4 (477 mg, 2.3 mmol) and HCOOK (32 mg, 0.38 mmol); reaction time 5 h at 80 °C; eluent gradient petroleum ether (bp 40–60 °C) to EtOAc:petroleum ether (bp 40–60 °C) 1:1 v/v gave **39** as a white solid (153 mg, 67%): mp 172.3-174.3 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (2H, s), 7.46 – 7.40 (3H, m), 7.37 – 7.32 (2H, m), 6.74 (1H, s), 5.28 (2H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.5, 157.9, 143.7 (1C, q, *J* = 38 Hz), 139.5, 138.9, 129.7, 129.2, 125.8, 121.2 (1C, q, *J* = 264 Hz), 114.2, 105.2 (1C, q, *J* = 2 Hz); ^{19}F NMR (188 MHz, $CDCl_3$) δ -62.8; MS (EI) *m/z* 305.0 (M^+, 100%). HRMS (EI) calcd for $C_{14}H_{10}F_3N_5$ 305.0994, found 305.0994.

3-(Trifluoromethyl)-1-phenyl-5-(thiophen-2-yl)-1*H*-pyrazole (40)



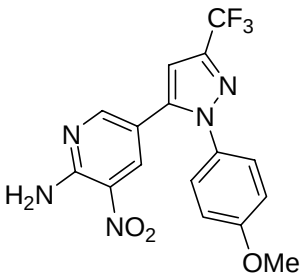
Compound **30a** (279 mg, 0.83 mmol), 2-bromothiophene **10** (0.07 cm^3, 0.75 mmol), Pd(dppf)Cl_2·DCM (61 mg, 0.075 mmol), 1,4-dioxane (7 cm^3), K_3PO_4 (477 mg, 2.3 mmol) and HCOOK (32 mg, 0.38 mmol); reaction time 5 h at 80 °C; eluent gradient petroleum ether (bp 40–60 °C) to petroleum ether (bp 40–60 °C):DCM 1:1 v/v gave **40** as a pale yellow solid (178 mg, 81%): mp 78.7-80.4 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 – 7.39 (5H, m), 7.32 (1H, dd, *J* = 5.1, 1.2 Hz), 6.96 (1H, dd, *J* = 5.1, 3.7 Hz), 6.86 (1H, dd, *J* = 3.7, 1.2 Hz), 6.80 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.1 (1C, q, *J* = 38 Hz), 138.9, 138.7, 129.7, 129.3, 129.2, 128.1, 127.50, 127.45, 126.3, 121.3 (1C, q, *J* = 267 Hz), 105.3 (1C, q, *J* = 2 Hz); ^{19}F NMR (188 MHz, $CDCl_3$) δ -62.8; MS (EI) *m/z* 293.9 (M^+, 100%). Anal. Calcd. for $C_{14}H_9F_3N_2S$: C, 57.14; H, 3.08; N, 9.52. Found: C, 57.01; H, 3.11; N, 9.67%.

2-[3-(Trifluoromethyl)-1-(4-methoxyphenyl)-1*H*-pyrazol-5-yl]pyridine (41)



Compound **30b** (304 mg, 0.83 mmol), 2-bromopyridine **31** (0.07 cm^3, 0.75 mmol), Pd(dppf)Cl_2·DCM (61 mg, 0.075 mmol), 1,4-dioxane (7 cm^3), K_3PO_4 (477 mg, 2.3 mmol) and HCOOK (32 mg, 0.38 mmol); reaction time 5.5 h at 80 °C; eluent EtOAc:petroleum ether (bp 40–60 °C) 1:4 v/v gave **41** as an off-white crystalline solid (150 mg, 63%): mp 107.6-109.4 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.59 (1H, ddd, *J* = 4.9, 1.7, 1.0 Hz), 7.60 (1H, td, *J* = 7.8, 1.8 Hz), 7.27 – 7.20 (m, 3H), 7.12 (1H, dt, *J* = 8.0, 1.0 Hz), 7.03 (1H, s), 6.88 (2H, d, *J* = 9.0 Hz), 3.82 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.7, 149.9, 148.3, 143.9, 142.9 (1C, q, *J* = 38 Hz), 136.4, 132.7, 126.9, 123.4, 123.3, 121.2 (1C, q, *J* = 267 Hz), 114.3, 106.3 (1C, q, *J* = 2 Hz), 55.50.; ^{19}F NMR (188 MHz, $CDCl_3$) δ -62.7; MS (EI) *m/z* 318.0 ($[M-H]^+$, 100%), 319.1 (M^+, 40%). Anal. Calcd. for $C_{16}H_{12}F_3N_3O$: C, 60.19; H, 3.79; N, 13.16. Found: C, 59.89; H, 3.78; N, 13.12%.

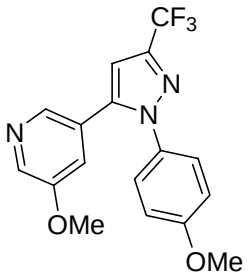
5-[3-(Trifluoromethyl)-1-(4-methoxyphenyl)-1*H*-pyrazol-5-yl]-3-nitropyridin-2-amine (42)



Compound **30b** (304 mg, 0.83 mmol), 2-amino-5-bromo-3-nitropyridine **6** (164 mg, 0.75 mmol), Pd(dppf)Cl_2·DCM (61 mg, 0.075 mmol), 1,4-dioxane (7 cm^3), K_3PO_4 (477 mg, 2.3 mmol) and HCOOK (32 mg, 0.38 mmol); reaction time 5 h at 80 °C; eluent EtOAc:petroleum ether (bp 40–60 °C) 1:3 v/v gave **42** as a yellow solid (225 mg, 79%): mp 190.9-193.1 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (1H, d, *J* = 2.2 Hz), 8.18 (1H, d, *J* = 2.2 Hz), 7.26 (2H, d, *J* = 9.0 Hz), 6.93 (2H, d, *J* = 9.0 Hz), 6.79 (1H, s), 3.84 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.3, 154.9, 152.9, 143.3 (1C, q, *J* = 39 Hz), 139.9, 134.7, 131.6, 127.6,

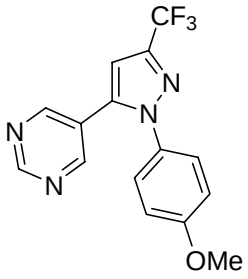
127.2, 121.2 (1C, q, J = 267 Hz), 115.9, 114.9, 105.3 (1C, q, J = 2 Hz), 55.7; ^{19}F NMR (188 MHz, $CDCl_3$) δ -62.8; MS (EI) *m/z* 378.9 (M^+, 100%). Anal. Calcd. for $C_{16}H_{12}F_3N_5O_3$: C, 50.67; H, 3.19; N, 18.46. Found: C, 50.38; H, 3.20; N, 18.51%.

3-[3-(Trifluoromethyl)-1-(4-methoxyphenyl)-1*H*-pyrazol-5-yl]-5-methoxypyridine (43)



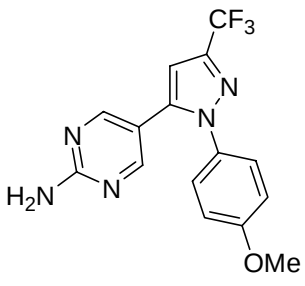
Compound **30b** (304 mg, 0.83 mmol), 3-bromo-5-methoxypyridine **32** (141 mg, 0.75 mmol), Pd(dppf)Cl_2·DCM (61 mg, 0.075 mmol), 1,4-dioxane (7 cm^3), K_3PO_4 (477 mg, 2.3 mmol) and HCOOK (32 mg, 0.38 mmol); reaction time 5 h at 80 °C; eluent gradient petroleum ether (bp 40–60 °C) to EtOAc:petroleum ether (bp 40–60 °C) 1:3 v/v gave **43** as a pink oil, which solidified and was recrystallised from hexane (214 mg, 82%): mp 88.2-90.2 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 (1H, d, J = 2.8 Hz), 8.10 (1H, d, J = 1.7 Hz), 7.21 (2H, d, J = 9.1 Hz), 6.95 (1H, dd, J = 2.8, 1.8 Hz), 6.87 (2H, d, J = 9.0 Hz), 6.79 (1H, s), 3.79 (3H, s), 3.72 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.9, 155.2, 143.1 (1C, q, J = 28 Hz), 141.3, 141.1, 137.9, 131.8, 127.0, 125.8, 121.1 (1C, q, J = 267 Hz), 120.1, 114.5, 105.7 (1C, q, J = 2 Hz), 55.53, 55.52; ^{19}F NMR (188 MHz, $CDCl_3$) δ -62.6; MS (EI) *m/z* 349.0 (M^+, 100%), 348.0 ($[M-H]^+$, 90%). Anal. Calcd. for $C_{17}H_{14}F_3N_3O_2$: C, 58.45; H, 4.04; N, 12.03. Found: C, 58.40; H, 4.08; N, 12.06%.

5-[3-(Trifluoromethyl)-1-(4-methoxyphenyl)-1*H*-pyrazol-5-yl]pyrimidine (44)



Compound **30b** (304 mg, 0.83 mmol), 5-bromopyrimidine **33** (119 mg, 0.75 mmol), Pd(dppf)Cl_2·DCM (61 mg, 0.075 mmol), 1,4-dioxane (7 cm^3), K_3PO_4 (477 mg, 2.3 mmol) and HCOOK (32 mg, 0.38 mmol); reaction time 3 h at 80 °C; eluent gradient petroleum ether (bp 40–60 °C) to EtOAc:petroleum ether (bp 40–60 °C) 1:3 v/v gave **44** as a pale orange solid (143 mg, 60%): mp 94.4-95.9 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.14 (1H, s), 8.58 (2H, s), 7.20 (2H, d, J = 9.1 Hz), 6.90 (2H, d, J = 9.0 Hz), 6.87 (1H, s), 3.80 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.4, 158.4, 155.9, 143.6 (1C, q, J = 39 Hz), 138.2, 131.3, 127.2, 124.1, 121.0 (1C, q, J = 268 Hz), 115.0, 106.1 (1C, q, J = 2 Hz), 55.7; ^{19}F NMR (188 MHz, $CDCl_3$) δ -62.7; MS (EI) *m/z* 319.9 (M^+, 100%). Anal. Calcd. for $C_{15}H_{11}F_3N_4O$: C, 56.25; H, 3.46; N, 17.49. Found: C, 56.33; H, 3.59; N, 17.09%.

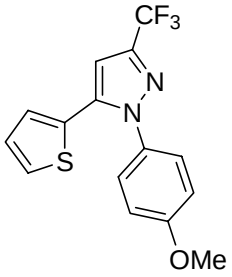
5-[3-(Trifluoromethyl)-1-(4-methoxyphenyl)-1*H*-pyrazol-5-yl]pyrimidin-2-amine (45)



Compound **30b** (304 mg, 0.83 mmol), 2-amino-5-bromopyrimidine **33** (131 mg, 0.75 mmol), Pd(dppf)Cl_2·DCM (61 mg, 0.075 mmol), 1,4-dioxane (7 cm^3), K_3PO_4 (477 mg, 2.3 mmol) and HCOOK (32 mg, 0.38

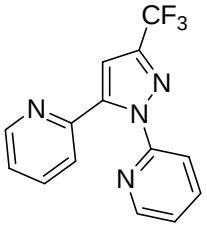
mmol); reaction time 5 h at 80 °C; eluent gradient petroleum ether (bp 40–60 °C) to EtOAc:petroleum ether (bp 40–60 °C) 1:1 v/v gave **45** as a white solid (180 mg, 72%): mp 171.3-173.3 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (2H, s), 7.23 (2H, d, *J* = 9.0 Hz), 6.89 (2H, d, *J* = 9.0 Hz), 6.70 (1H, s), 5.61 (2H, s), 3.80 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.5, 160.0, 157.8, 143.2 (1C, q, *J* = 38 Hz), 139.6, 131.8, 127.2, 121.2 (1C, q, *J* = 268Hz), 114.8, 114.0, 104.7 (1C, q, *J* = 2 Hz), 55.6; ^{19}F NMR (188 MHz, $CDCl_3$) δ -62.7; MS (EI) *m/z* 334.8 (M^+, 100%). HRMS (EI) calcd for $C_{15}H_{12}F_3N_5O$ 335.0994, found 335.0994. Anal. Calcd. for $C_{15}H_{12}F_3N_5O$: C, 53.73; H, 3.61; N, 20.89. Found: C, 53.48; H, 3.77; N, 20.32%.

3-(Trifluoromethyl)-1-(4-methoxyphenyl)-5-(thiophen-2-yl)-1*H*-pyrazole (46)



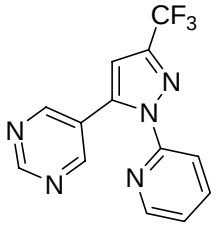
Compound **30b** (304 mg, 0.83 mmol), 2-bromothiophene **10** (0.07 cm^3, 0.75 mmol), Pd(dppf)Cl_2·DCM (61 mg, 0.075 mmol), 1,4-dioxane (7 cm^3), K_3PO_4 (477 mg, 2.3 mmol) and HCOOK (32 mg, 0.38 mmol); reaction time 5 h at 80 °C; eluent gradient petroleum ether (bp 40–60 °C) to petroleum ether (bp 40–60 °C):DCM 1:1 v/v gave **46** as a pale yellow solid (206 mg, 85%): mp 107.5-109.1 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 – 7.29 (3H, m), 6.97 − 6.93 (3H, m), 6.88 (1H, dd, *J* = 3.6, 1.0), 6.79 (1H, s), 3.86 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.4, 143.0 (1C, q, *J* = 38 Hz), 139.1, 132.0, 130.0, 128.0, 128.0, 127.6, 127.5, 121.3 (1C, q, *J* = 268 Hz), 114.5, 104.8 (1C, q, *J* = 2 Hz), 55.7; ^{19}F NMR (188 MHz, $CDCl_3$) δ -62.8; MS (EI) *m/z* 323.9 (M^+, 100%). Anal. Calcd. for $C_{15}H_{11}F_3N_2OS$: C, 55.55; H, 3.42; N, 8.64. Found: C, 55.33; H, 3.43; N, 8.55%.

2-[3-(Trifluoromethyl)-1-(pyridin-2-yl)-1*H*-pyrazol-5-yl]pyridine (47)



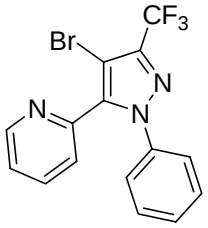
Compound **30c** (280 mg, 0.83 mmol), 2-bromopyridine **31** (0.07 cm^3, 0.75 mmol), Pd(dppf)Cl_2·DCM (61 mg, 0.075 mmol), 1,4-dioxane (7 cm^3), K_3PO_4 (477 mg, 2.3 mmol) and HCOOK (32 mg, 0.38 mmol); reaction time 4.5 h at 80 °C; eluent EtOAc:petroleum ether (bp 40–60 °C) 1:1 v/v gave **47** as a yellow oil (35 mg, 16%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.48 (1H, ddd, *J* = 4.8, 1.6, 0.9 Hz), 8.26 (1H, ddd, *J* = 4.8, 1.7, 0.7 Hz), 7.89 – 7.82 (1H, td, *J* = 8.0, 2.0 Hz), 7.75 – 7.67 (2H, m), 7.41 (1H, dt, *J* = 7.9, 1.0 Hz), 7.26 (2H, m), 6.96 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.2, 149.5, 149.1, 148.2, 144.4, 143.7 (1C, q, *J* = 39 Hz), 138.8, 136.5, 123.7, 123.6, 123.4, 121.2 (1C, q, *J* = 268 Hz), 119.1, 107.2 (1C, q, *J* = 2 Hz); ^{19}F NMR (188 MHz, $CDCl_3$) δ -62.9; MS (EI) *m/z* 220.7 ($[M-CF_3]^+$, 90%), 289.0 ($[M-H]^+$, 50%), 290.1 (M^+, 30%). HRMS (ES^+) calcd for $C_{14}H_{10}F_3N_4$ 291.0852, found 291.0852. Anal. Calcd. for $C_{14}H_9F_3N_4$: C, 57.93; H, 3.13; N, 19.30. Found: C, 57.03; H, 3.35; N, 18.39%.

5-[3-(Trifluoromethyl)-1-(pyridin-2-yl)-1*H*-pyrazol-5-yl]pyrimidine (48)



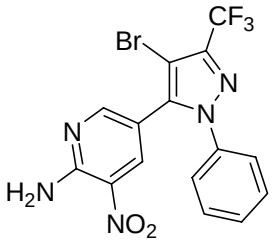
Compound **30c** (280 mg, 0.83 mmol), 5-bromopyrimidine **33** (119 mg, 0.75 mmol), Pd(dppf)Cl_2·DCM (61 mg, 0.075 mmol), 1,4-dioxane (7 cm^3), K_3PO_4 (477 mg, 2.3 mmol) and HCOOK (32 mg, 0.38 mmol); reaction time 4.5 h at 80 °C; eluent EtOAc:petroleum ether (bp 40–60 °C) 1:1 v/v gave **48** as an white solid (65 mg, 30%): mp 116.5-117.2 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.21 (1H, s), 8.76 (2H, s), 8.21 (1H, ddd, *J* = 4.8, 1.7, 0.9), 7.95 – 7.87 (m, 2H), 7.29 (1H, ddd, *J* = 6.9, 4.9, 1.5), 6.85 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.4, 156.6, 151.6, 147.9, 144.23 (1C, q, *J* = 38 Hz), 139.4, 138.9, 125.7, 123.7, 120.9 (1C, q, *J* = 267 Hz), 117.4, 108.6 (1C, q, *J* = 2 Hz); ^{19}F NMR (188 MHz, $CDCl_3$) δ -63.1; MS (EI) *m/z* 290.0 ($[M-H]^+$, 100%). Anal. Calcd. for $C_{13}H_8F_3N_5$: C, 53.61; H, 2.77; N, 24.05. Found: C, 53.44; H, 2.83; N, 23.91%.

2-[4-Bromo-3-(trifluoromethyl)-1-phenyl-1*H*-pyrazol-5-yl]pyridine (49)



Bromine (0.02 cm^3, 0.48 mmol) was added to a solution of compound **35** (92 mg, 0.32 mmol) in glacial acetic acid (5 cm^3). The mixture was heated to 100 °C for 17 h. The reaction mixture was allowed to cool slightly before quenching with deionised water (10 cm^3), the mixture was then neutralised with NaOH solution (1 M). A saturated solution of $Na_2S_2O_3$ (40 cm^3) was added and the product then extracted with EtOAc (2 × 75 cm^3). The organic phase was dried over Na_2SO_4, filtered and evaporated to dryness in vacuo. Following column chromatography, eluent DCM, **49** was isolated as a white solid (78 mg, 66%): mp 106.4-108.2 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.61 (1H, d, *J* = 4.2 Hz), 7.77 (1H, td, *J* = 7.7, 1.6 Hz), 7.47 (1H, d, *J* = 7.8 Hz), 7.32 − 7.30 (4H, m), 7.26 − 7.23 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.3, 147.2, 142.3, 141.4 (1C, q, *J* = 37 Hz), 139.4, 136.7, 129.2, 128.8, 125.9, 125.0, 124.1, 120.8 (1C, q, *J* = 269 Hz), 94.1 (1C, q, *J* = 1.4 Hz); ^{19}F NMR (188 MHz, $CDCl_3$) δ -62.9; MS (EI) *m/z* 365.9 ($[M(^{79}Br)-H]^+$, 90%), 367.8 ($[M(^{81}Br)-H]^+$, 100%), 369.0 ($[M(^{81}Br)]^+$, 15%). Anal. Calcd. for $C_{15}H_9BrF_3N_3$: C, 48.94; H, 2.46; N, 11.41. Found: C, 48.22; H, 2.49; N, 11.20%. HRMS (EI) calcd for $C_{15}H_9BrF_3N_3$ 366.9932, found 366.9932.

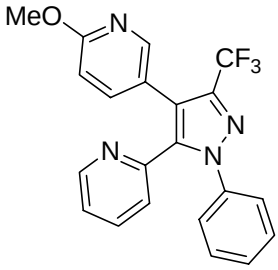
5-[4-Bromo-3-(trifluoromethyl)-1-phenyl-1*H*-pyrazol-5-yl]-3-nitropyridin-2-amine (50)



Bromine (0.012 cm^3, 0.24 mmol) was added to a solution of compound **36** (55 mg, 0.16 mmol) in glacial acetic acid (5 cm^3). The mixture was heated to 100 °C for 18 h. The reaction mixture was allowed to cool slightly before quenching with deionised water (25 cm^3), the mixture was then neutralised with a saturated solution of $NaHCO_3$. A saturated solution of $Na_2S_2O_3$ (50 cm^3) was added and the product then extracted with DCM (3 × 50 cm^3). The organic phase was dried

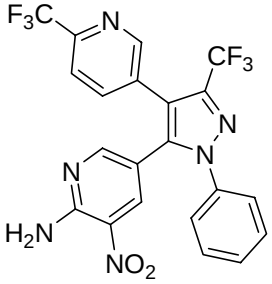
over Na_2SO_4, filtered and evaporated to dryness in vacuo. The crude product was passed through a silica pad and then recrystallised from cyclohexane to yield **50** as a yellow crystalline solid (58 mg, 86%): mp 183.9-185.6 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 (1H, d, *J* = 2.2 Hz), 8.20 (1H, d, *J* = 2.2 Hz), 7.44 – 7.40 (3H, m), 7.31 – 7.27 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.9, 153.2, 141.8 (1C, q, *J* = 37 Hz), 138.7, 138.5, 136.4, 129.8, 129.6, 127.6, 125.5, 120.6 (1C, q, *J* = 267 Hz), 113.8, 94.3 (1C, q, *J* = 1 Hz); ^{19}F NMR (188 MHz, $CDCl_3$) δ -63.0; MS (EI) *m/z* 426.8 ([M(^{79}Br)$^+$, 100%), 427.8 ([M(^{81}Br)–H]$^+$, 40%), 428.8 ([M(^{81}Br)]$^+$, 95%). Anal. Calcd. for $C_{15}H_9BrF_3N_5O_2$: C, 42.08; H, 2.12; N, 16.36. Found: C, 41.96; H, 2.14; N, 15.97%.

2-[3-(Trifluoromethyl)-4-(6-methoxypyridin-3-yl)-1-phenyl-1*H*-pyrazol-5-yl]pyridine (51)



Compound **49** (120 mg, 0.33 mmol), 2-methoxy-5-pyridylboronic acid (55 mg, 0.36 mmol), $Pd(PPh_3)_4$ (5 mol%, 19 mg, 0.016 mmol) and degassed1,4-dioxane (4 cm^3) were added sequentially to a reaction flask, under an argon atmosphere, the mixture was placed stirred at room temperature for 20 min. Degassed Na_2CO_3 (1 M, 1.0 cm^3, 1.0 mmol) was added and the reaction mixture heated to reflux. After 6 h at reflux the reaction was complete, the mixture was cooled slightly before adding EtOAc (50 cm^3) and brine (50 cm^3). The organic phase was extracted and dried over Na_2SO_4, filtered and evaporated to dryness in vacuo. The crude product was purified by column chromatography, eluent EtOAc, followed by recrystallisation from hexane/DCM to yield **51** as light yellow/orange, rectangular crystals (104 mg, 80%): mp 127.8-130.1 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.53 (1H, ddd, *J* = 4.9, 1.8, 1.0 Hz), 8.06 (1H, d, *J* = 2.2 Hz), 7.59 – 7.51 (2H, m), 7.34 – 7.28 (5H, m, 5H), 7.20 (1H, ddd, *J* = 7.7, 4.9, 1.2 Hz), 7.06 (1H, dt, *J* = 7.8, 1.1 Hz), 6.71 (1H, dd, *J* = 8.6, 0.8 Hz), 3.92 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.8, 150.2, 148.3, 147.9, 141.2, 141.6 (1C, q, *J* = 36 Hz), 140.5 (1C, q, *J* = 1 Hz), 139.4, 136.6, 129.1, 128.5, 126.0, 125.3, 123.7, 121.6 (1C, q, *J* = 268 Hz), 119.2, 118.6, 110.6, 53.6; ^{19}F NMR (188 MHz, $CDCl_3$) δ -60.1; MS (EI) *m/z* 395.0 ([M−H]$^+$, 100%), 396.1 (M$^+$, 25%). Anal. Calcd. for $C_{21}H_{15}F_3N_4O$: C, 63.63; H, 3.81; N, 14.14. Found: C, 63.60; H, 3.86; N, 14.33%. Crystals, obtained as described above, were suitable for X-ray structure determination. (See Figure S6).

5-[3-(Trifluoromethyl)-4-(6-(trifluoromethyl)pyridin-3-yl)-1-phenyl-1*H*-pyrazol-5-yl]-3-nitropyridin-2-amine (52)



Compound **50** (43 mg, 0.10 mmol), 6-(trifluoromethyl)-3-pyridylboronic acid **3** (21 mg, 0.11 mmol), $Pd(PPh_3)_4$ (5 mol%, 5.8 mg, 0.005 mmol) and degassed 1,4-dioxane (10 cm^3) were added sequentially to a reaction flask, under an argon atmosphere, the mixture was placed stirred at room

temperature for 10 min. Degassed Na_2CO_3 (1 M, 0.30 cm^3, 0.30 mmol) was added and the reaction mixture heated to reflux. After 3.5 h at reflux the reaction was complete, the reaction solvent was removed in vacuo before EtOAc (50 cm^3) and brine (50 cm^3) were added to the reaction mixture. The organic phase was extracted and solvent removed in vacuo, the crude product was filtered through a silica pad, washing with EtOAc. The combined organic solvent was removed in vacuo and the crude product was purified by column chromatography, eluent DCM to yield **52** as a yellow solid (15 mg, 30%): mp 164.9 °C darkens, >200 °C decomp.; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 (1H, d, *J* = 1.8 Hz), 8.04 (1H, d, *J* = 2.2 Hz), 7.97 (1H, d, *J* = 2.2 Hz), 7.88 (1H, dd, *J* = 8.0, 1.7 Hz), 7.75 (1H, d, *J* = 8.0 Hz), 7.48 – 7.43 (3H, m), 7.37 – 7.31 (2H, m), 6.01 (2H, broad s); ^{13}C NMR (175 MHz, $CDCl_3$) δ 155.8, 153.1, 150.8, 147.9 (1C, q, *J* = 33 Hz), 141.5 (1C, q, *J* = 37 Hz), 139.1, 138.7, 138.1, 136.3, 129.9, 129.7, 129.2, 127.5, 125.8, 121.4 (1C, q, *J* = 271 Hz), 121.1 (1C, q, *J* = 270 Hz), 120.5 (1C, q, *J* = 2 Hz), 116.9, 113.6; ^{19}F NMR (188 MHz, $CDCl_3$) δ -60.0, -68.4; MS (ES^+) *m/z* 495.1 ($[M+H]^+$, 100%). HRMS (ES^+) calcd for $C_{21}H_{13}F_6N_6O_2$ 495.09987, found 495.09995.

X-ray Crystallography

Full crystallographic data (except structure factors) is provided in the CIF format and has been deposited at the Cambridge Crystallographic Data Centre, deposition numbers CCDC-699539 (**3**), CCDC-699843 (**27**), 699540 (**30b**), 699541 (**36**) and 699542 (**51**).

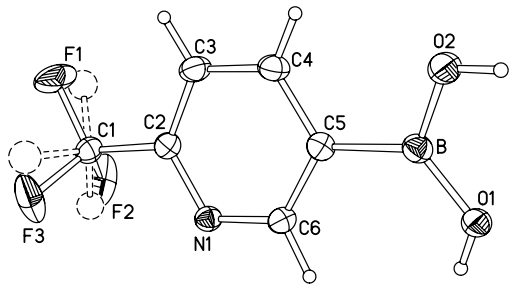


Figure S1. X-ray molecular structure of **3**. The rotational disorder of the CF_3 group was modelled as two orientations with the probabilities of 85% (solid) and 15% (dashed). Here and in the figures below atomic displacement ellipsoids are drawn at the 50% probability level.

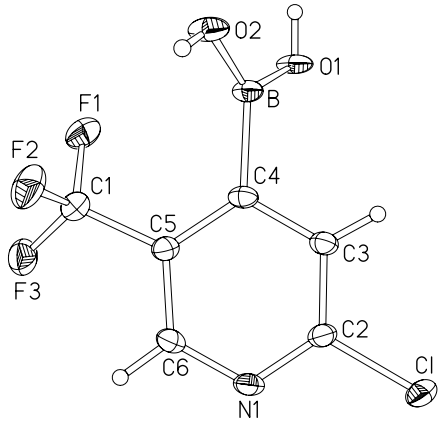


Figure S2. X-ray molecular structure of **27**.

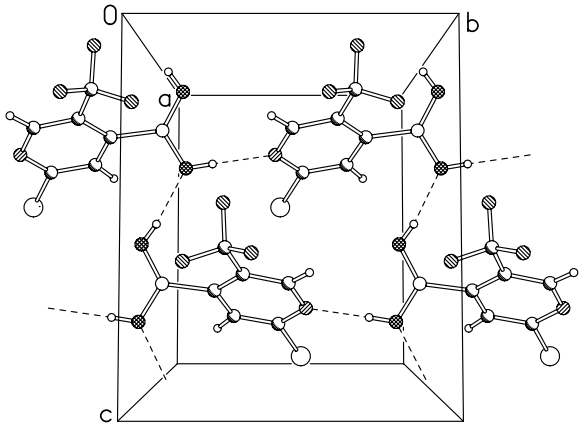


Figure S3. Hydrogen bonding in the crystal of **27**.

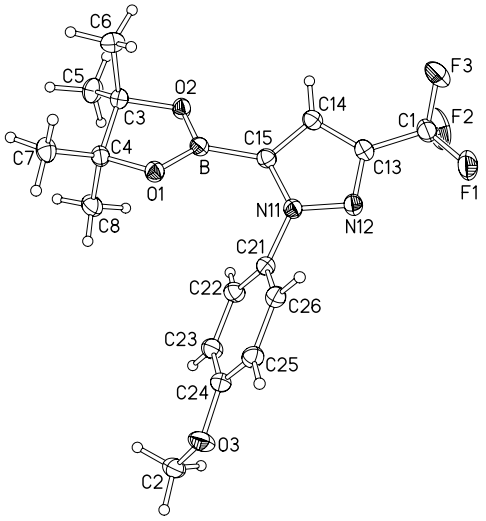


Figure S4. X-ray molecular structure of **30b**.

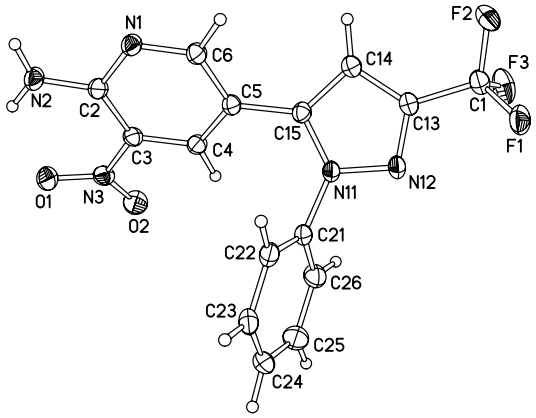


Figure S5. X-ray molecular structure of **36**

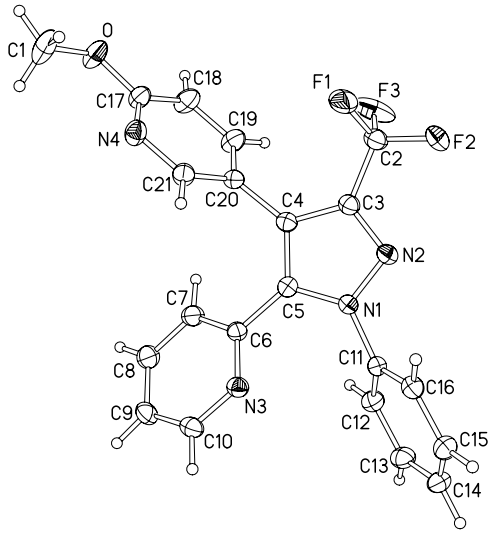
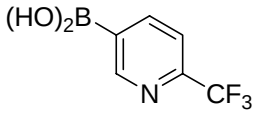
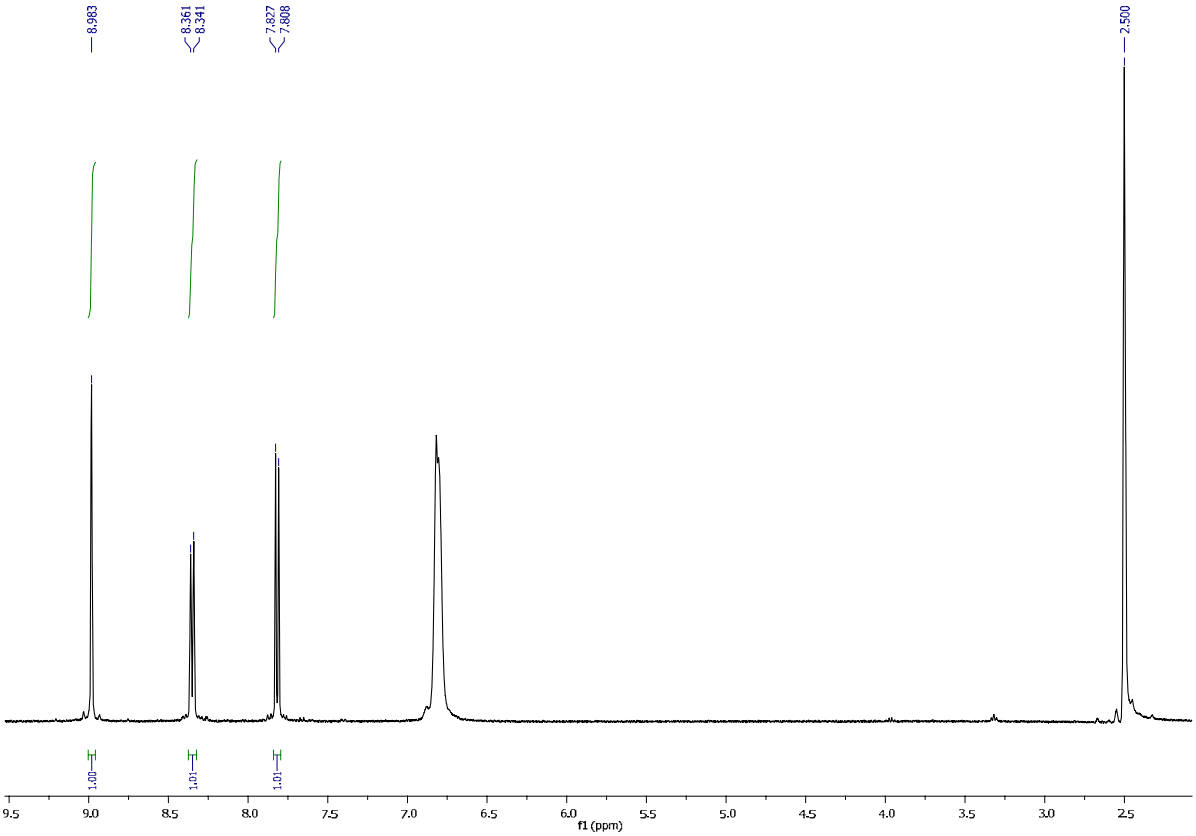


Figure S6. X-ray molecular structure of **51**.

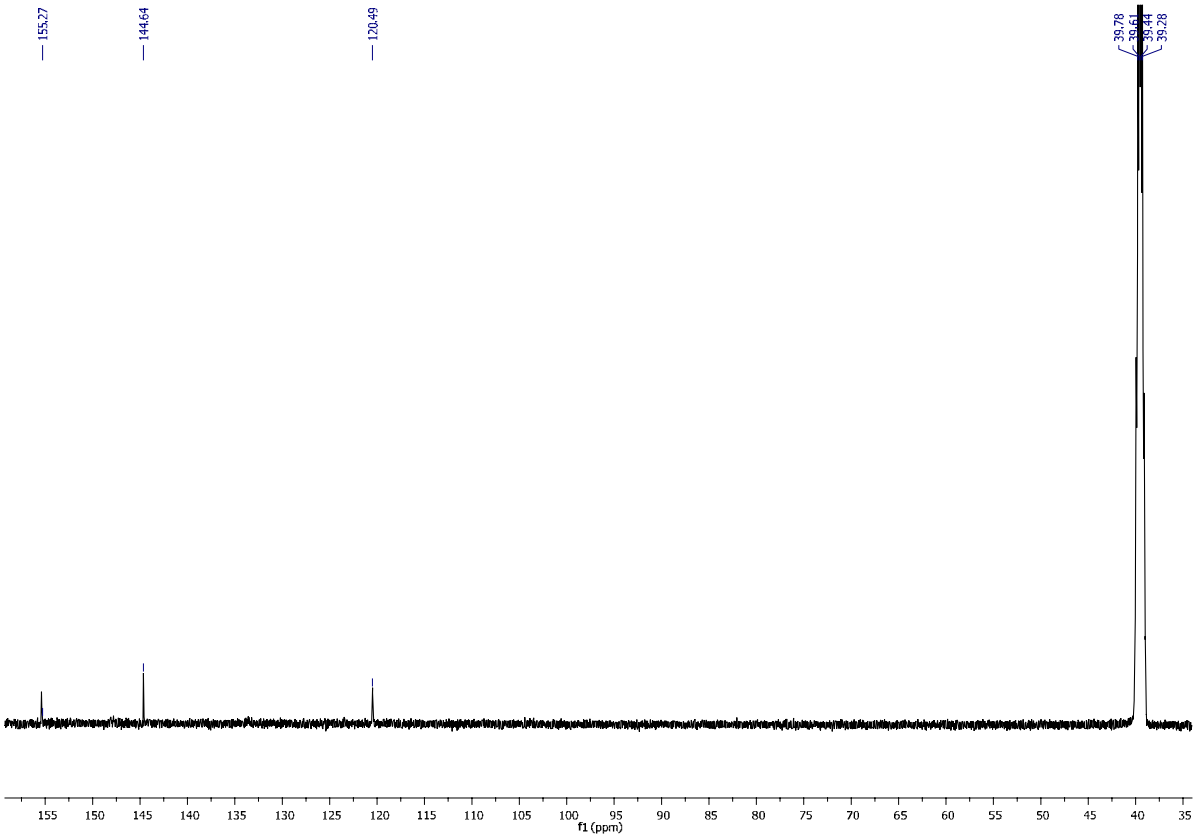


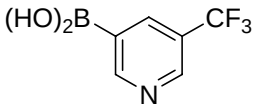
6-(Trifluoromethyl)-3-pyridylboronic acid (3)

^{1}H NMR (400 MHz, DMSO-d_6, DCl)



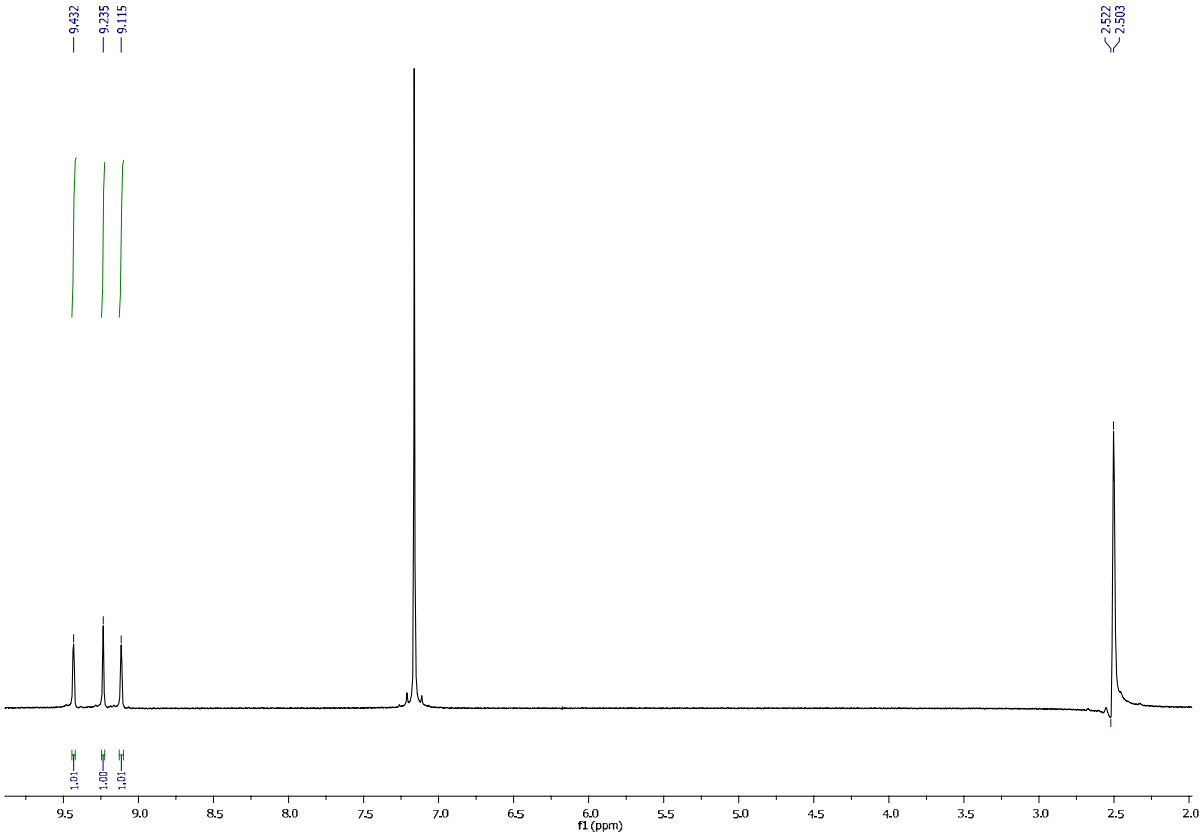
^{13}C NMR (125 MHz, DMSO-d_6, DCl)



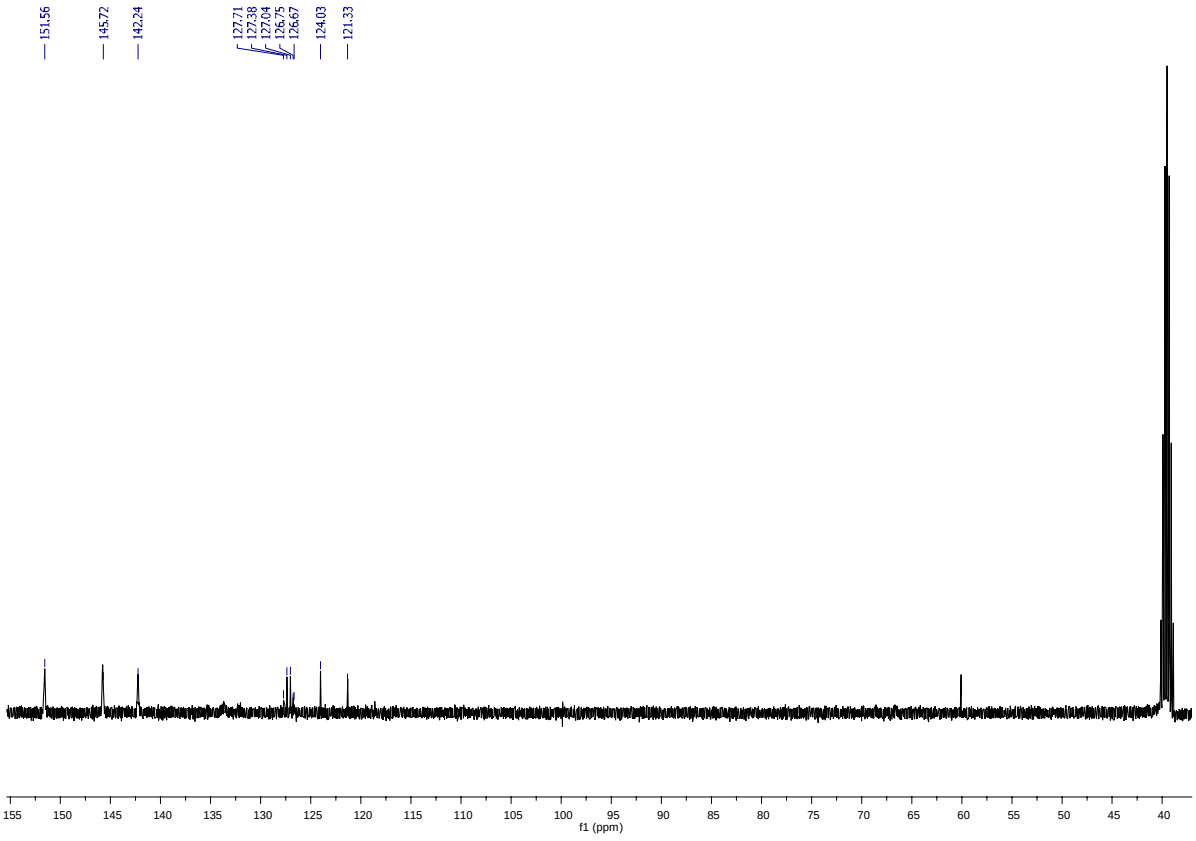


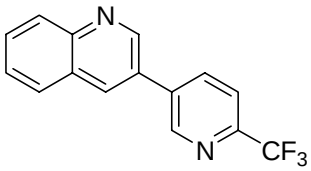
5-(Trifluoromethyl)-3-pyridylboronic acid (4)

^{1}H NMR (400 MHz, DMSO-d_6, DCl)



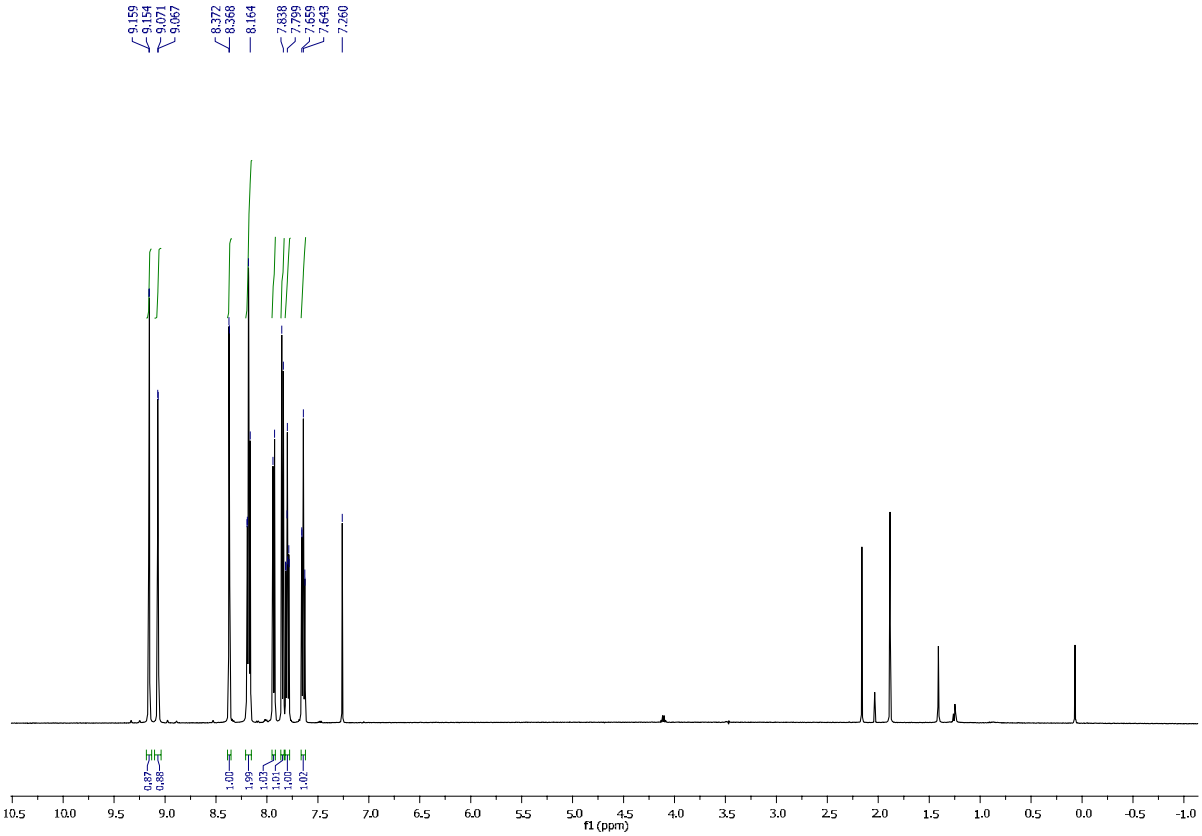
^{13}C NMR (100 MHz, DMSO-d_6, DCl)



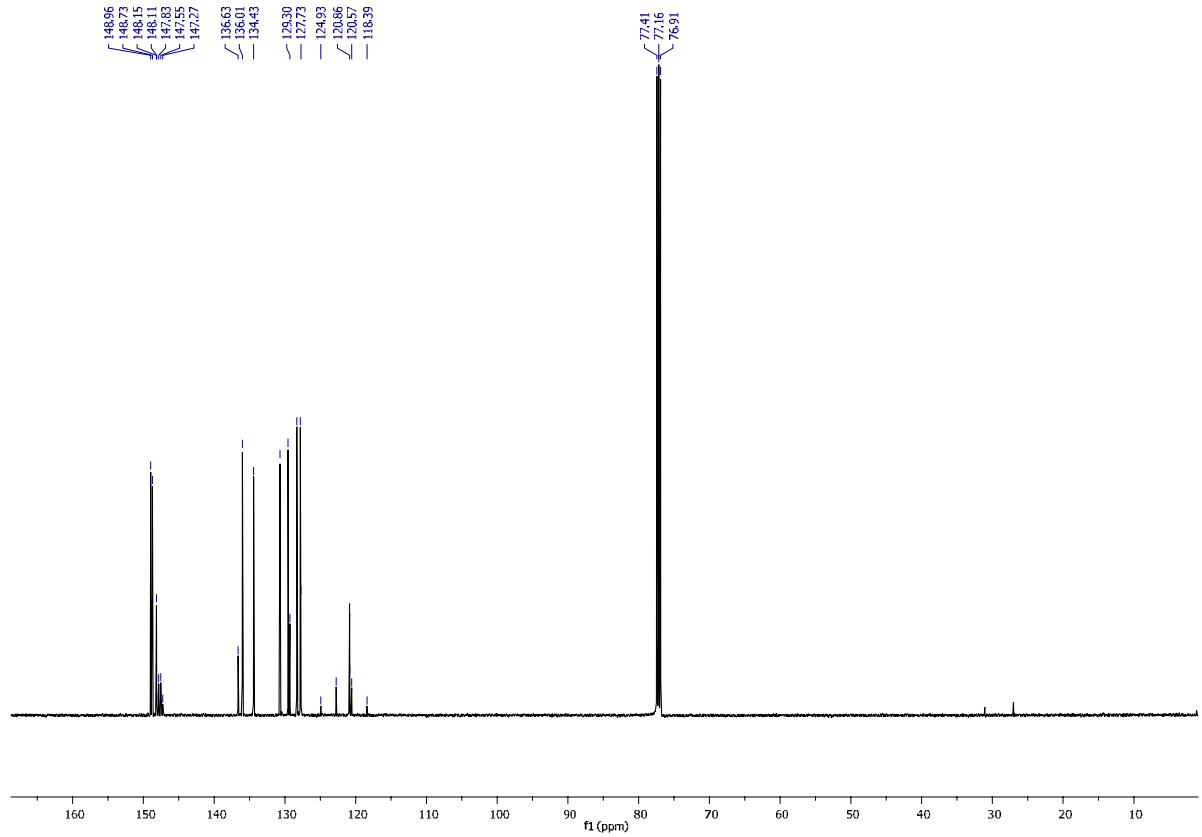


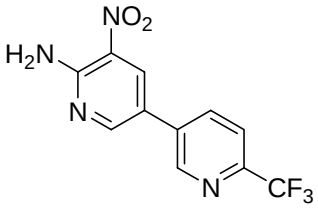
3-[6-(Trifluoromethyl)pyridin-3-yl]quinoline (12)

^{1}H NMR (500 MHz, $CDCl_3$)



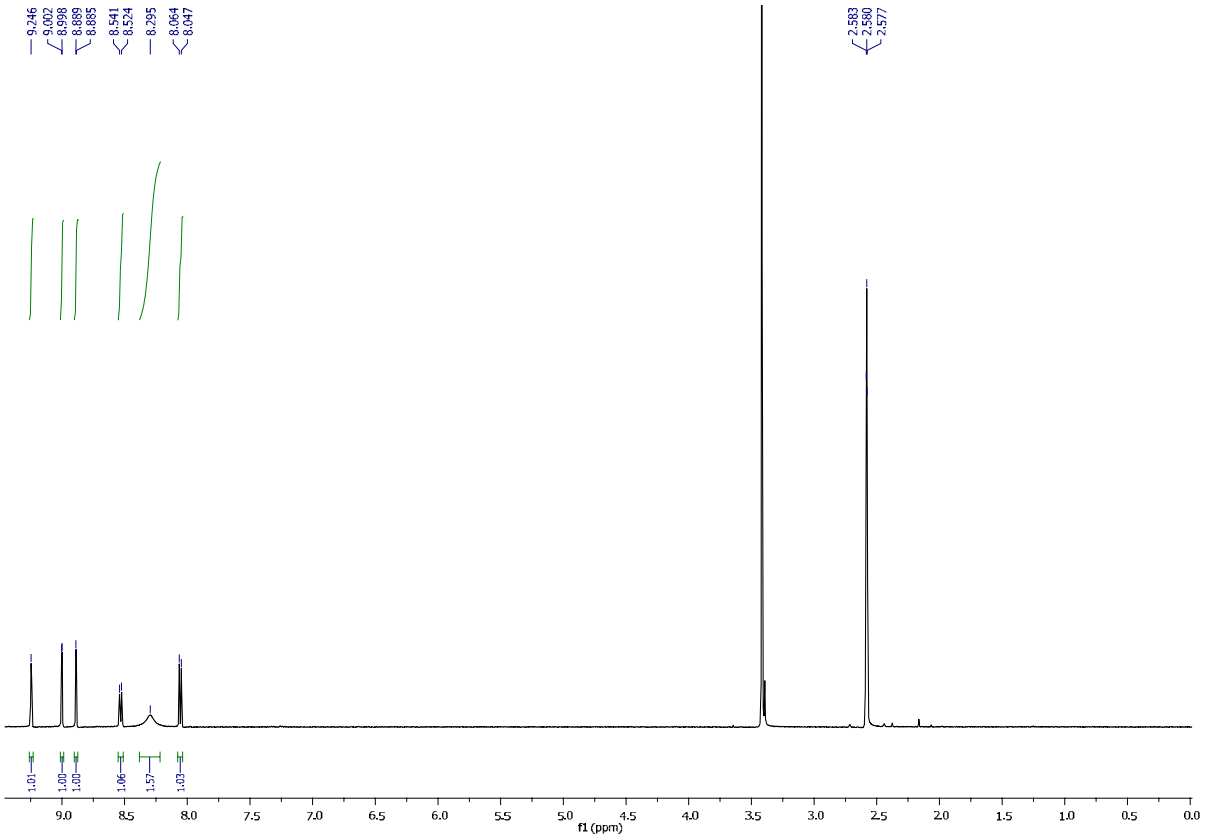
^{13}C NMR (125 MHz, $CDCl_3$)



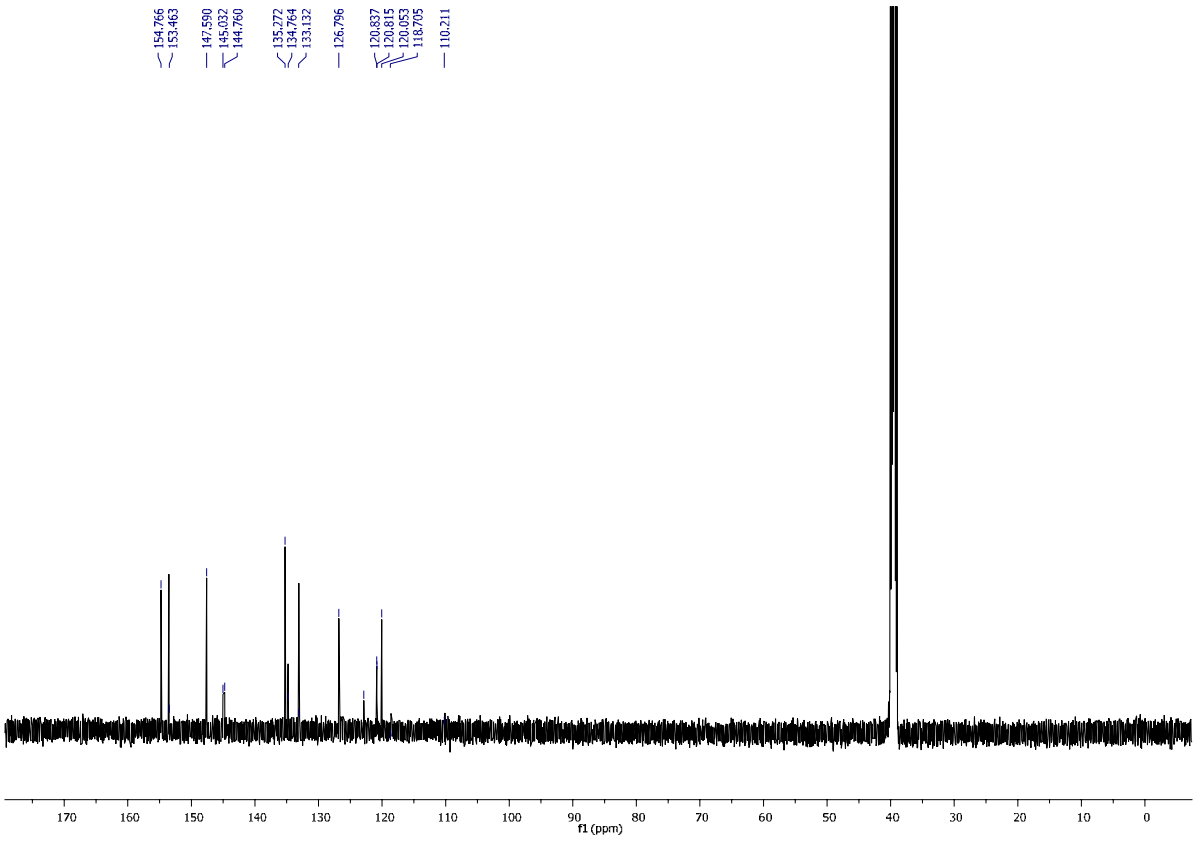


5-[6-(Trifluoromethyl)pyridin-3-yl]-2-amino-3-nitropyridine (13)

^{1}H NMR (500 MHz, DMSO-d_6)

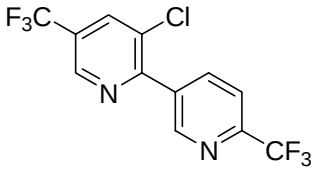


^{13}C NMR (125 MHz, DMSO-d_6)

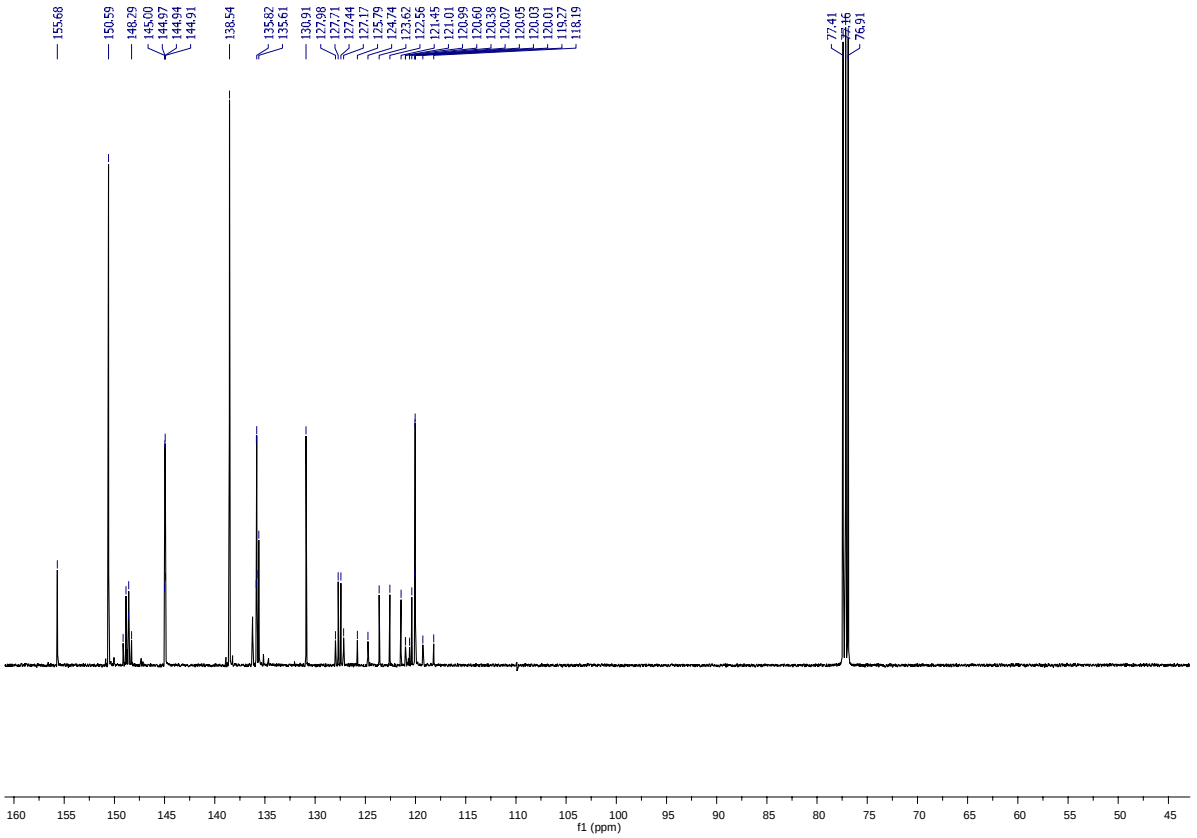


3-Chloro-5-(trifluoromethyl)-2-[6-(trifluoromethyl)pyridin-3-yl]pyridine (14)

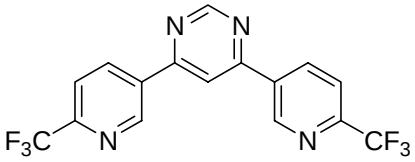
^{1}H NMR (400 MHz, $CDCl_3$)



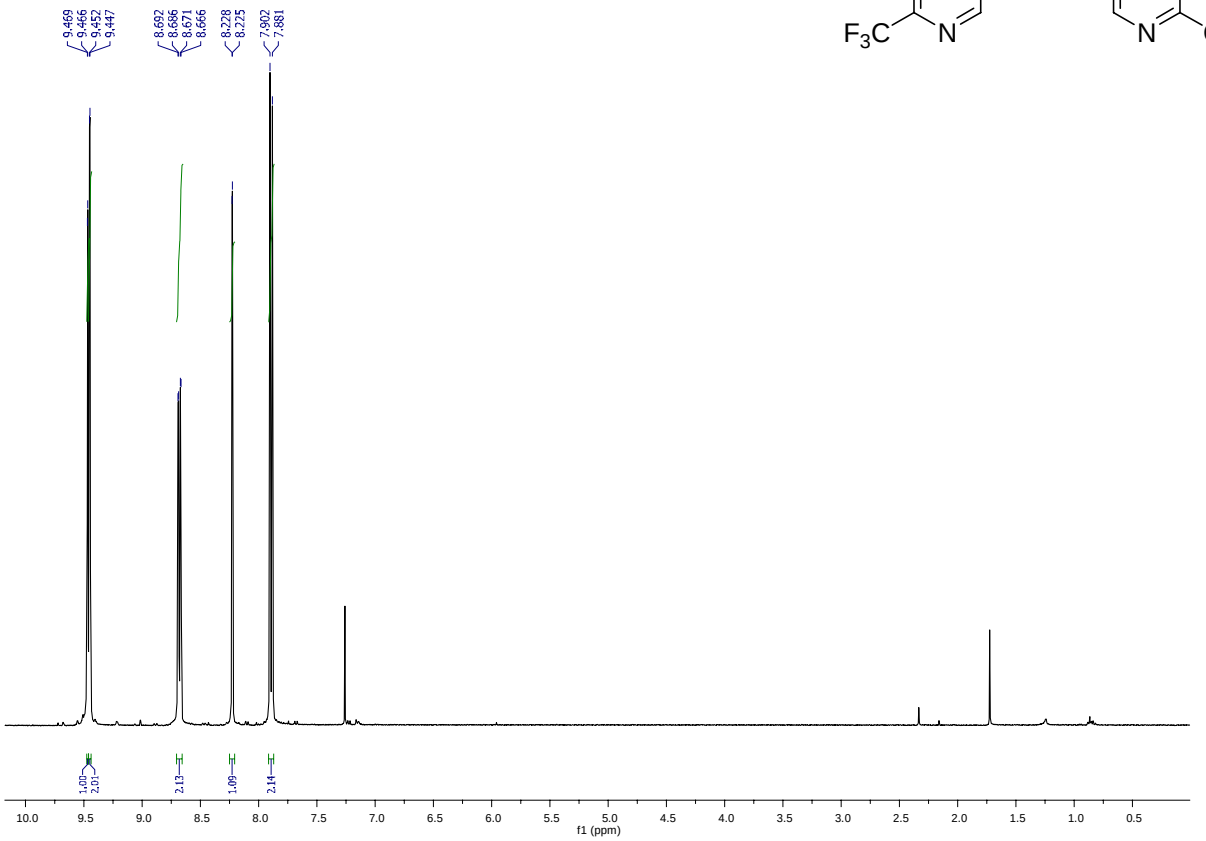
^{13}C NMR (125 MHz, $CDCl_3$)



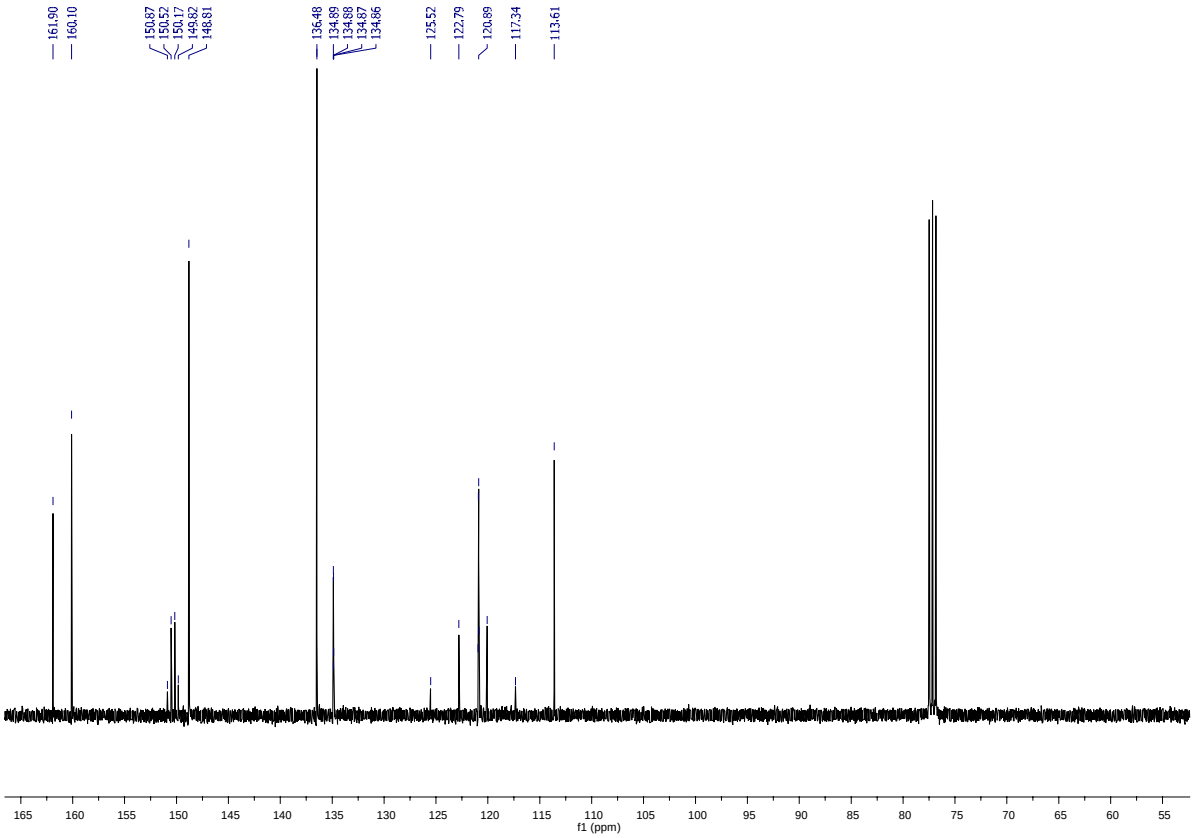
4,6-Bis[6-(trifluoromethyl)pyridin-3-yl]pyrimidine (15)



^{1}H NMR (400 MHz, $CDCl_3$)

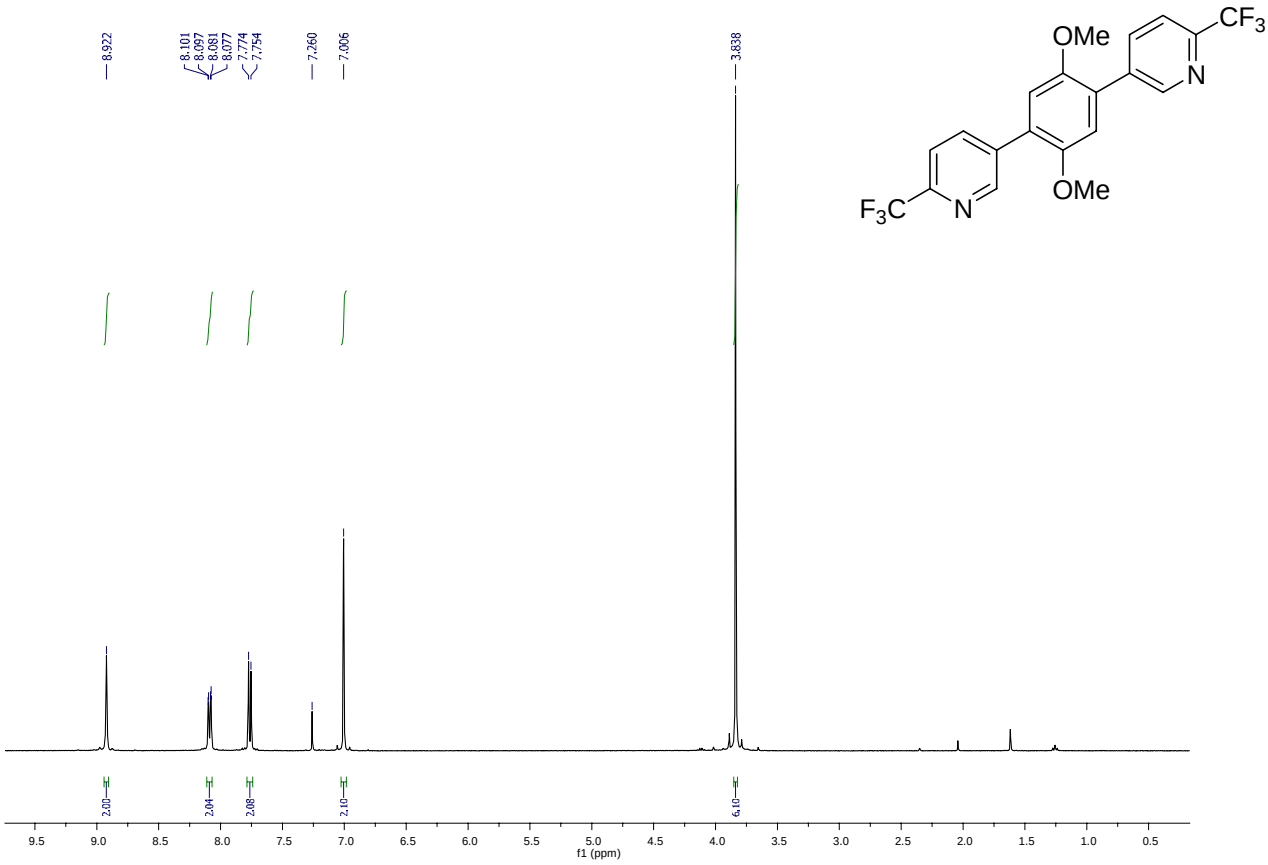


^{13}C NMR (100 MHz, $CDCl_3$)

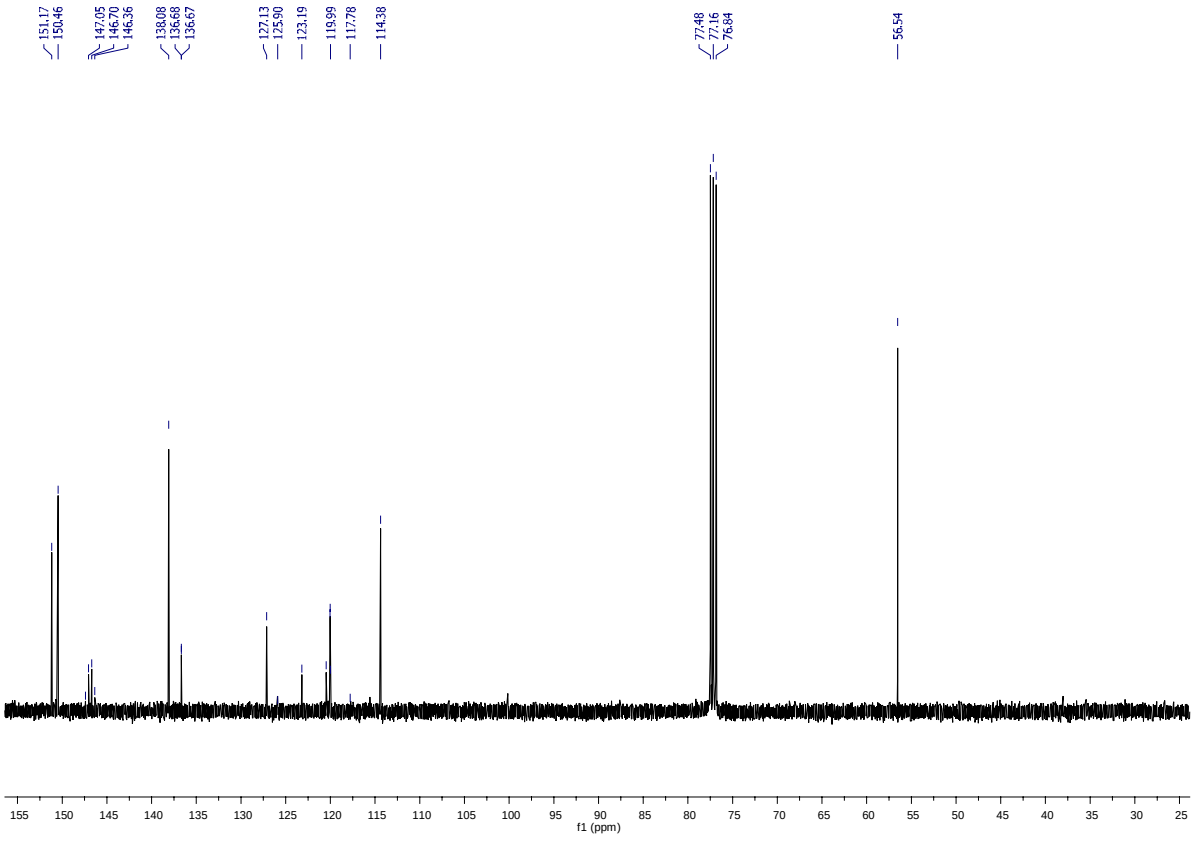


2-(Trifluoromethyl)-5-{4-[6-(trifluoromethyl)pyridin-3-yl]-2,5-dimethoxyphenyl}pyridine (16)

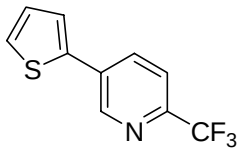
^{1}H NMR (400 MHz, $CDCl_3$)



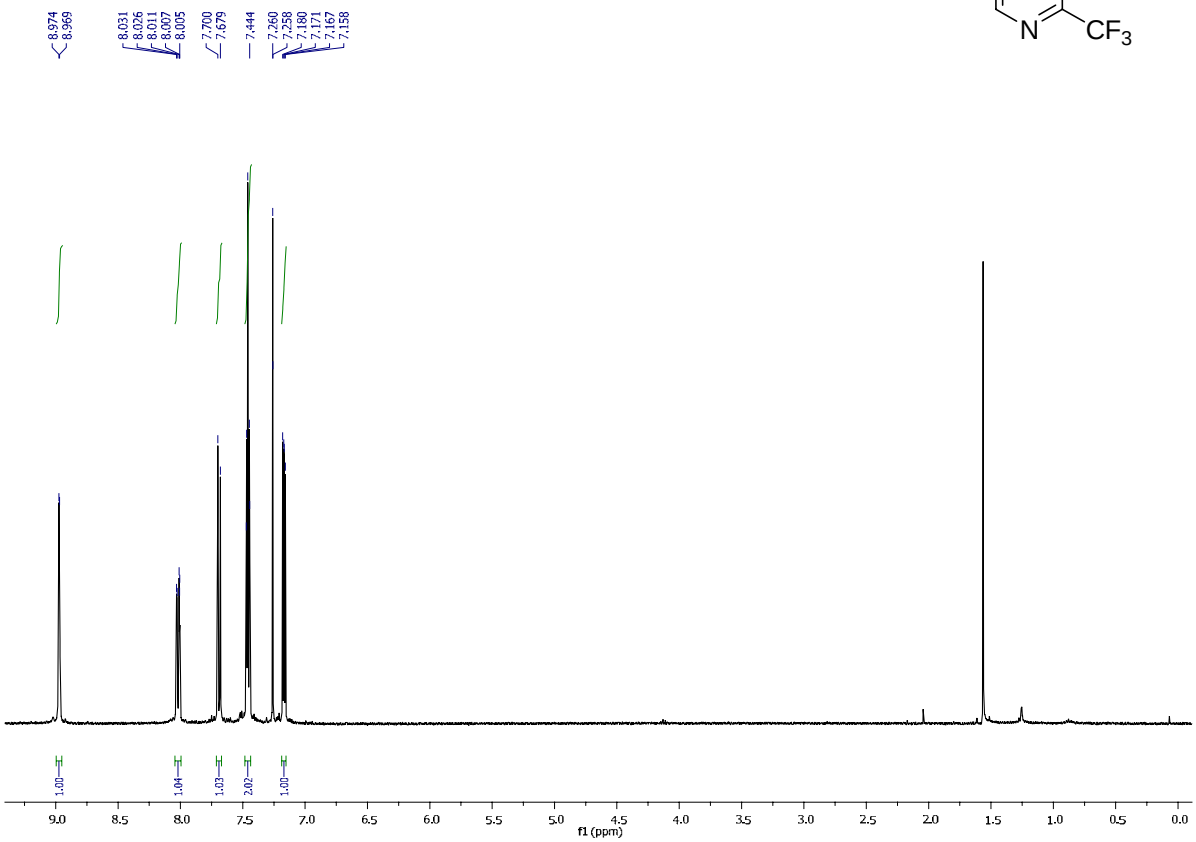
^{13}C NMR (100 MHz, $CDCl_3$)



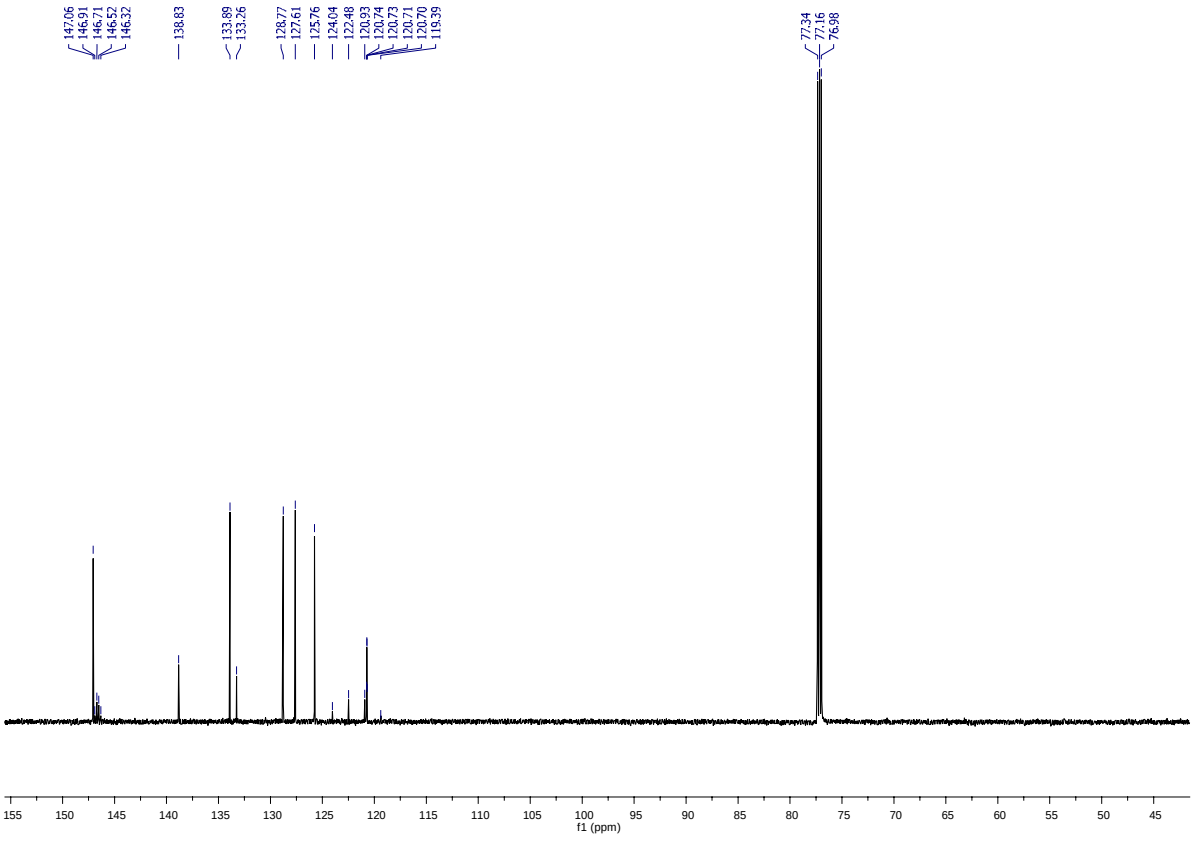
2-(Trifluoromethyl)-5-(thiophen-2-yl)pyridine (17)

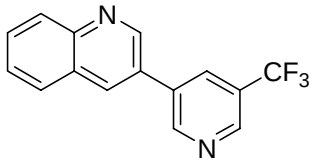


^{1}H NMR (400 MHz, $CDCl_3$)



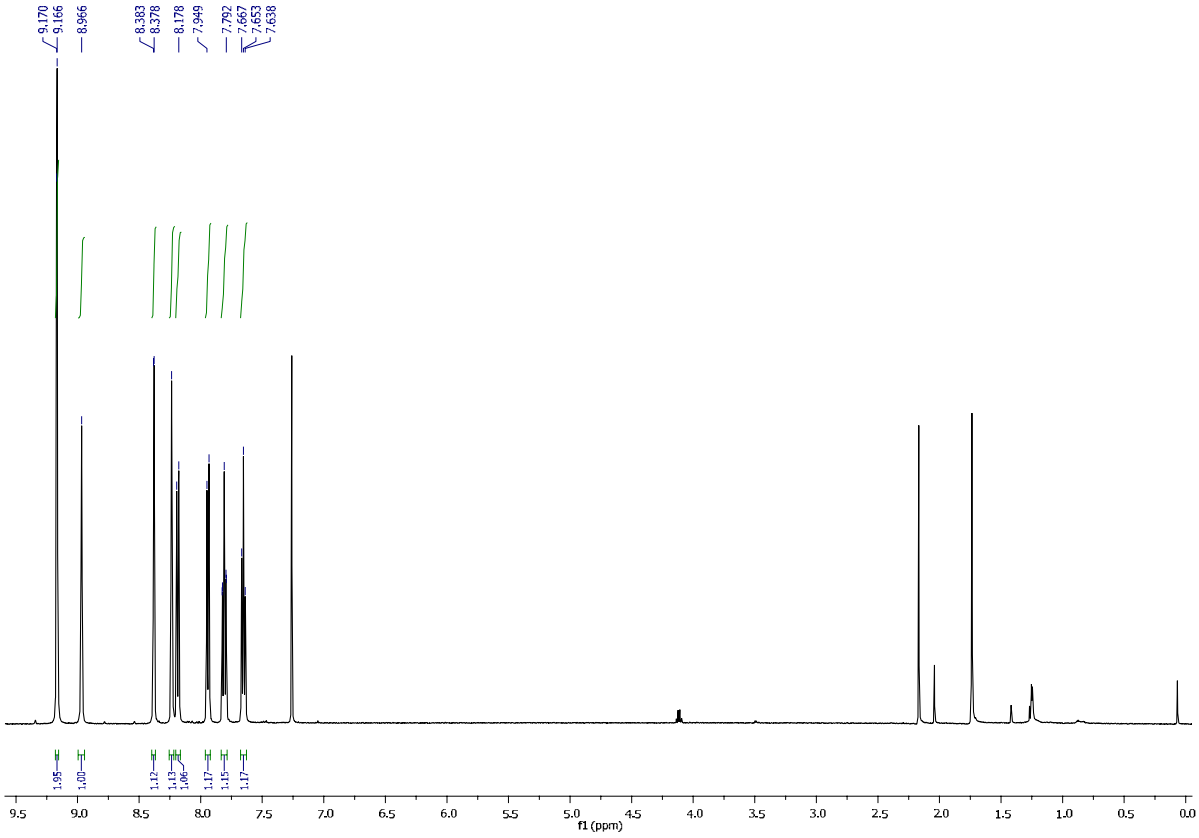
^{13}C NMR (175 MHz, $CDCl_3$)



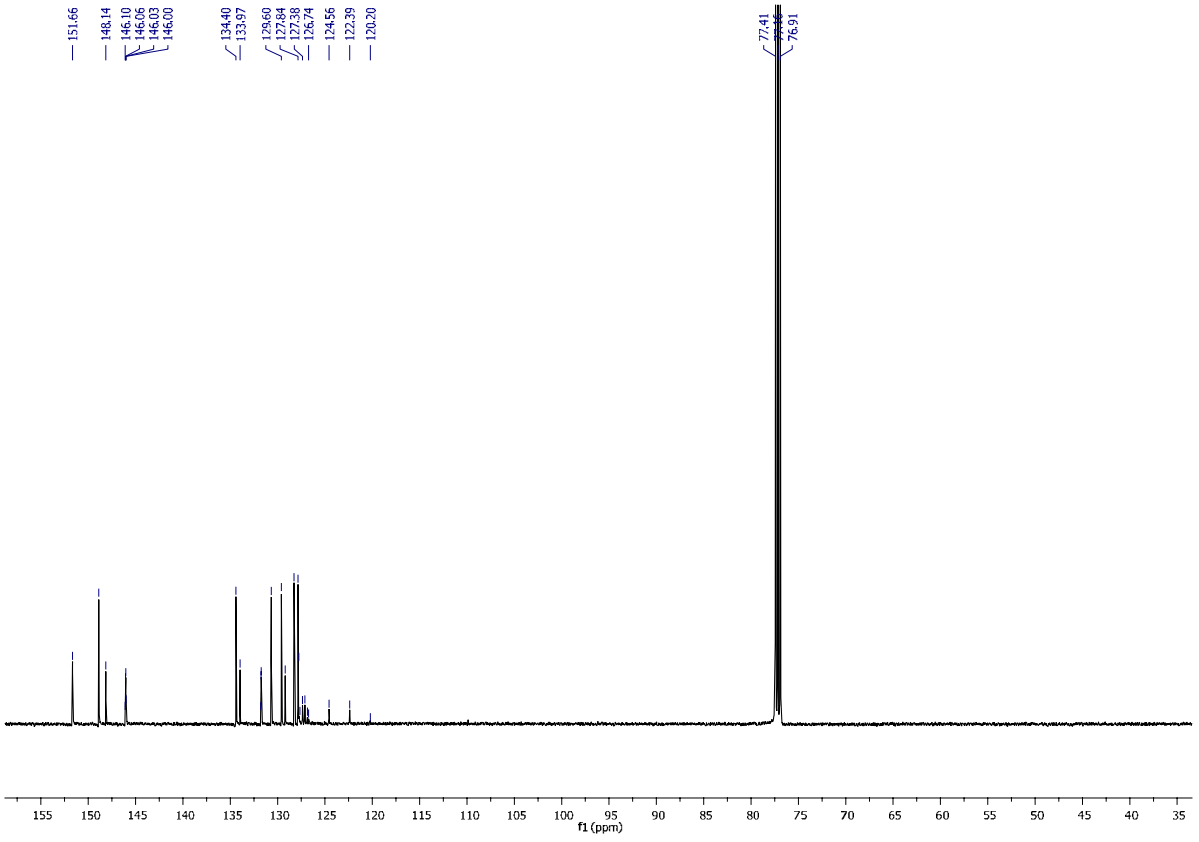


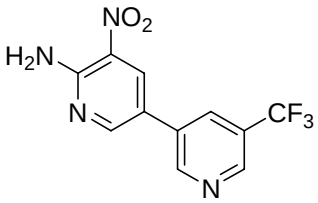
3-[5-(Trifluoromethyl)pyridin-3-yl]quinoline (18)

^{1}H NMR (500 MHz, $CDCl_3$)



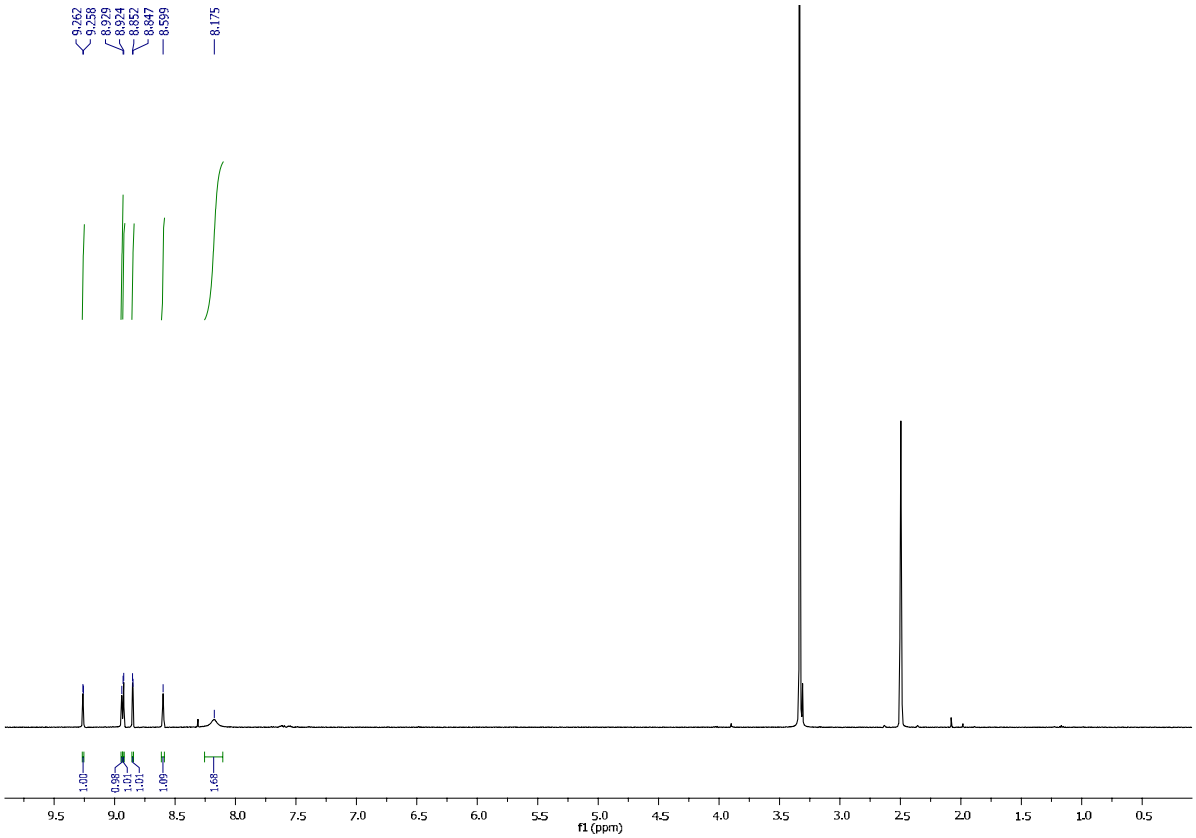
^{13}C NMR (125 MHz, $CDCl_3$)



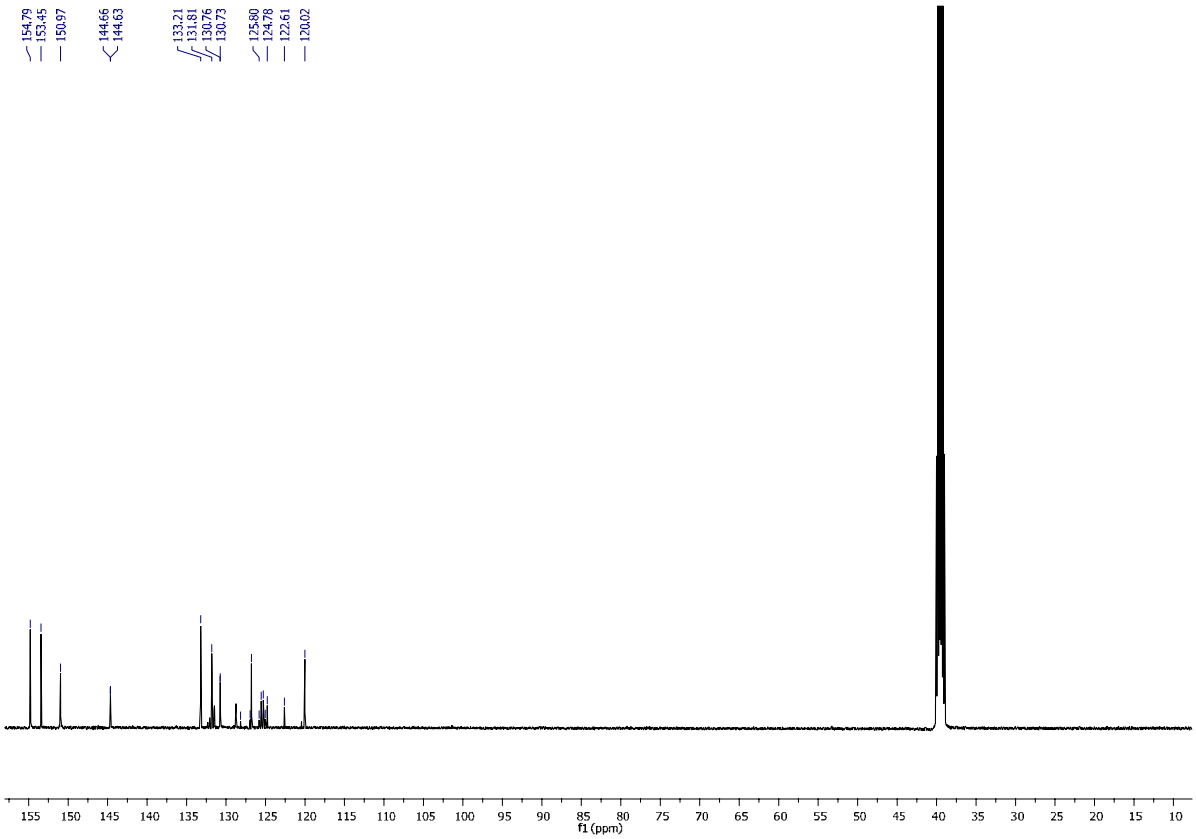


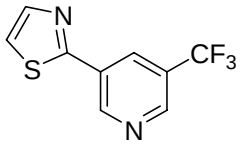
5-[5-(Trifluoromethyl)pyridin-3-yl]-2-amino-3-nitropyridine (19)

^{1}H NMR (500 MHz, DMSO-d$_6$)



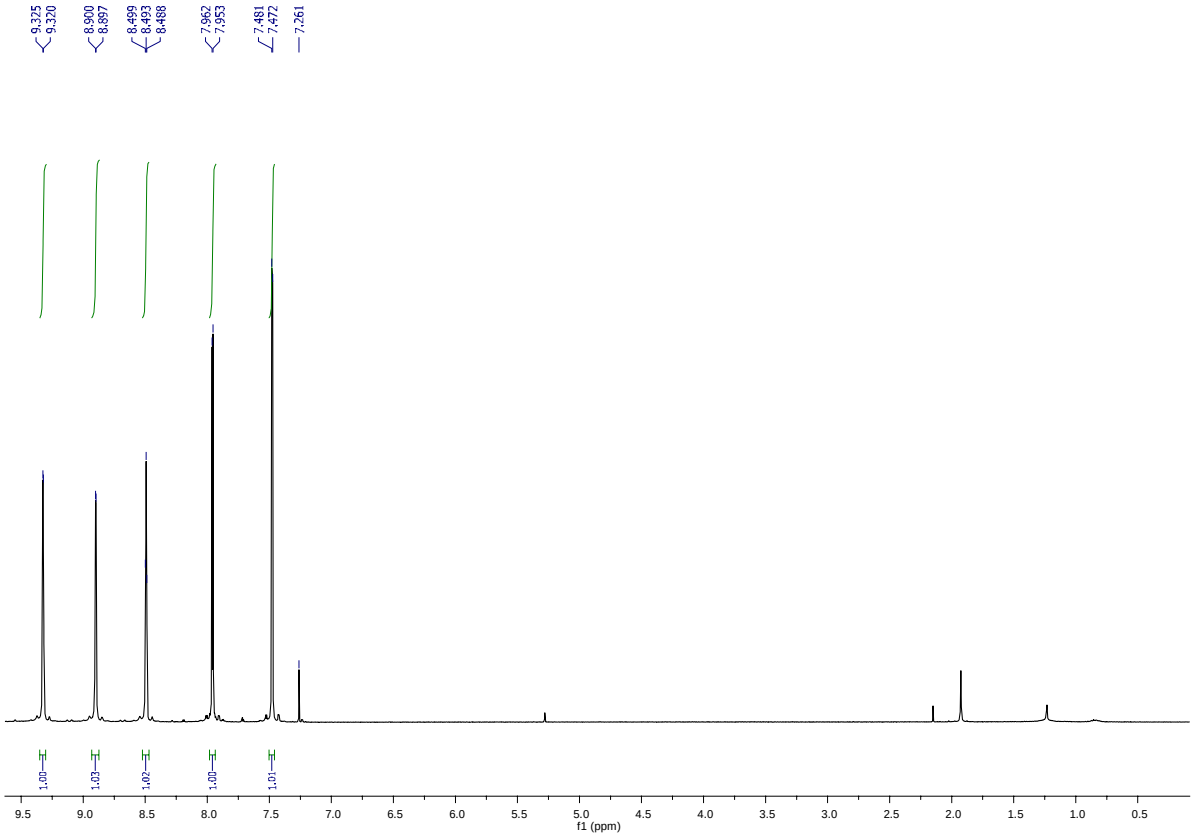
^{13}C NMR (125 MHz, DMSO-d$_6$)



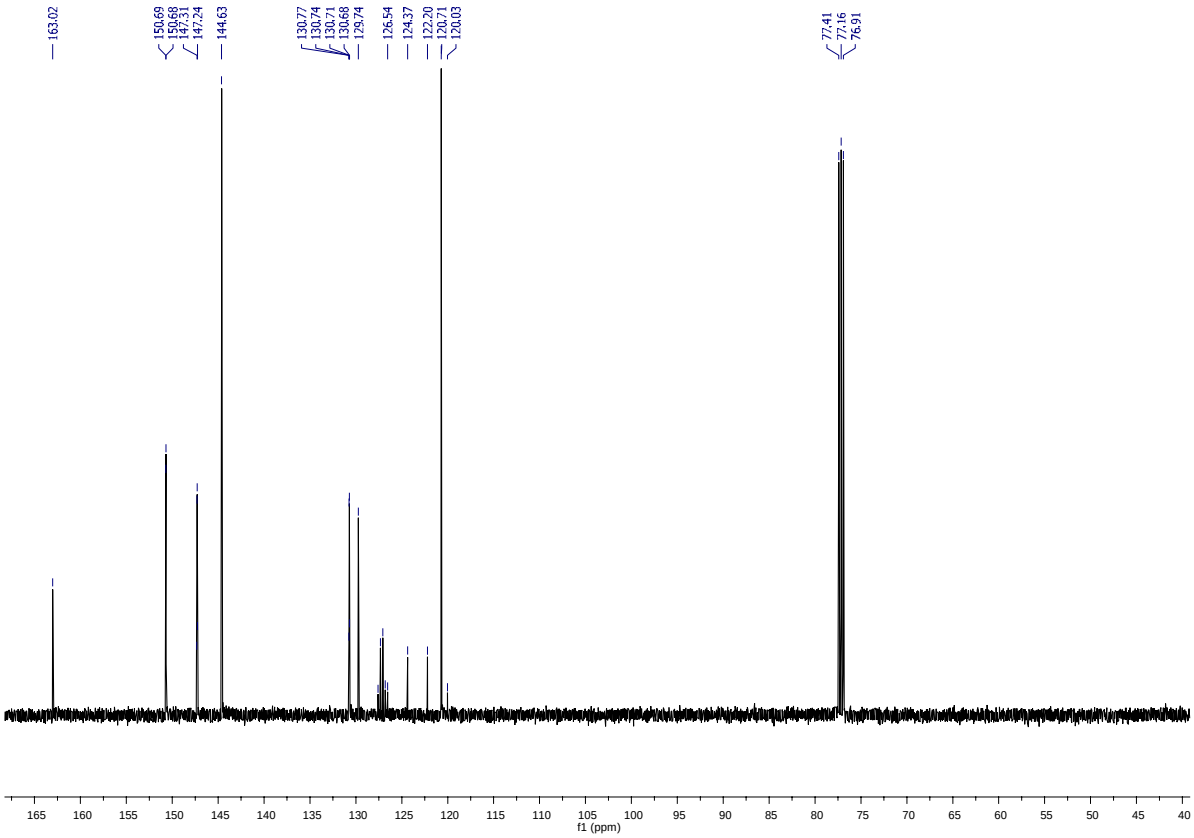


3-(Trifluoromethyl)-5-(thiazol-2-yl)pyridine (20)

^{1}H NMR (400 MHz, $CDCl_3$)

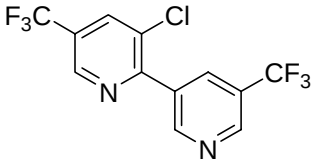


^{13}C NMR (125 MHz, $CDCl_3$)

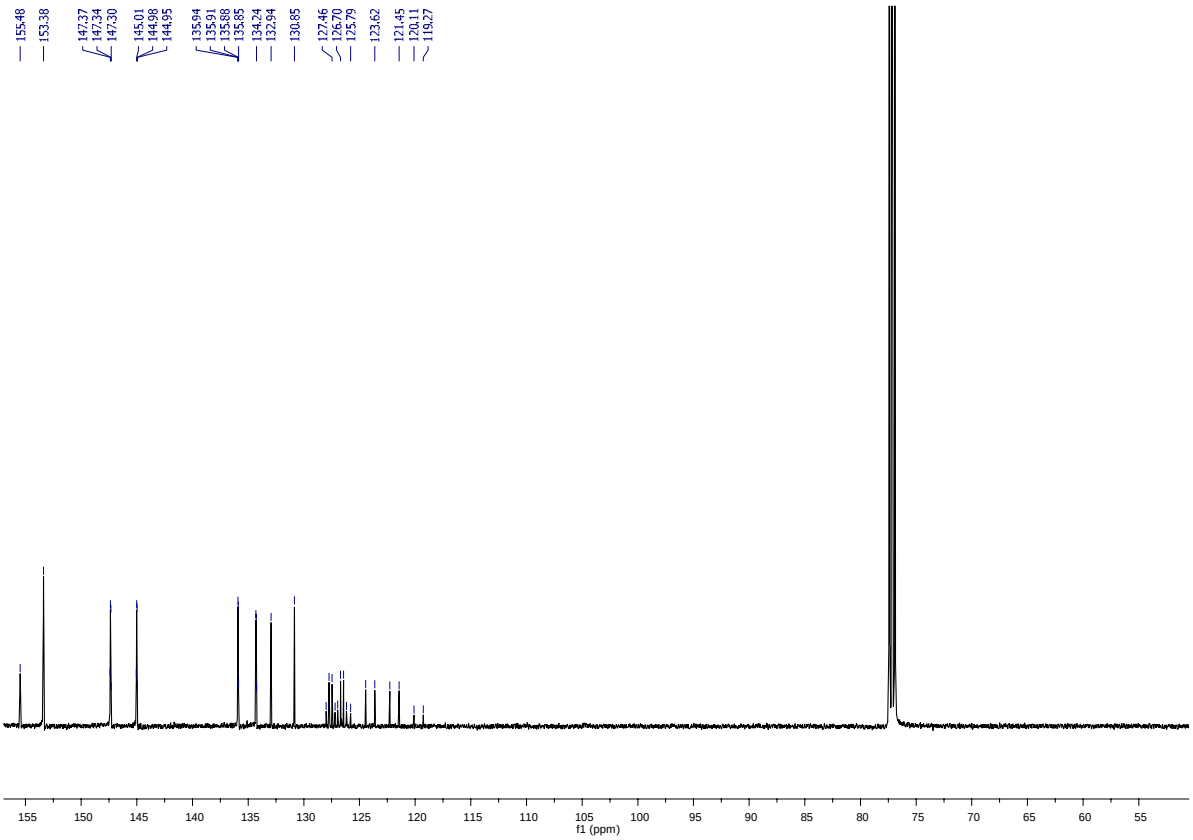


3-Chloro-5-(trifluoromethyl)-2-[5-(trifluoromethyl)pyridin-3-yl]pyridine (21)

^{1}H NMR (400 MHz, $CDCl_3$)

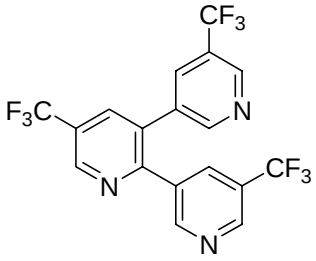


^{13}C NMR (125 MHz, $CDCl_3$)

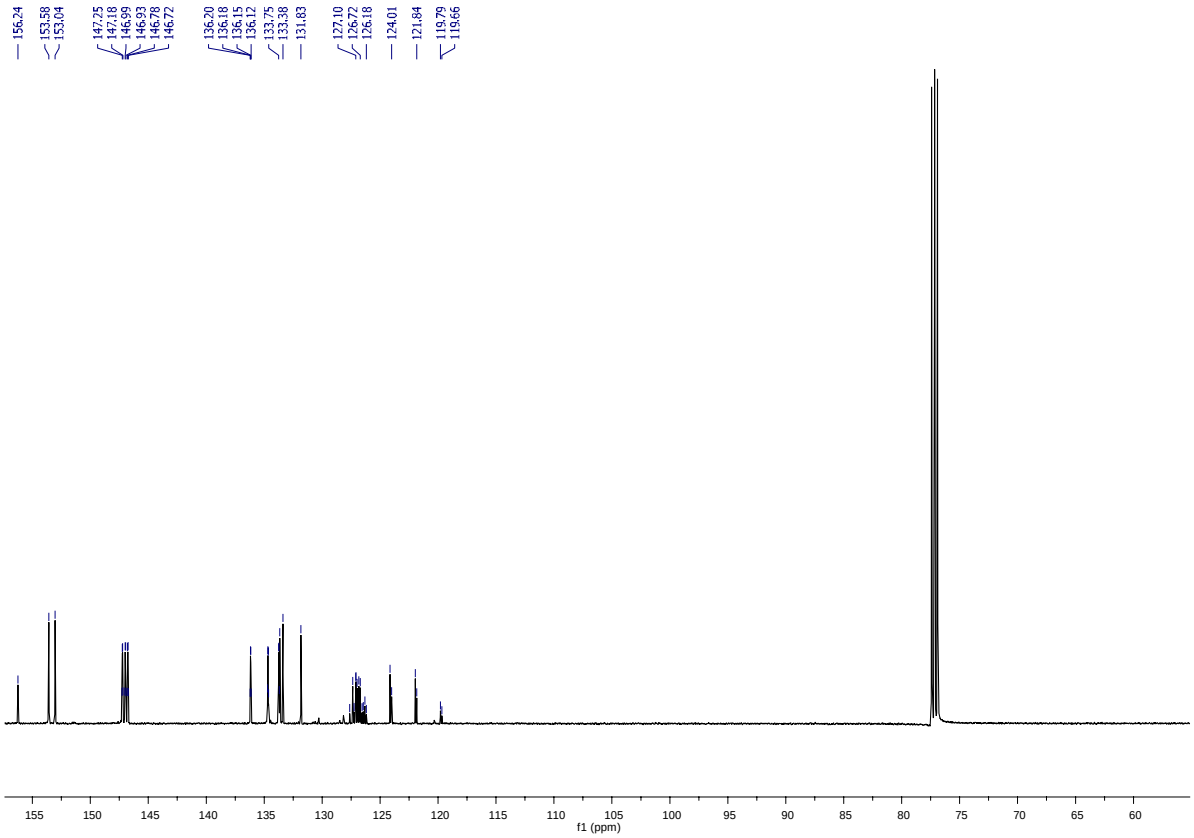


5-(Trifluoromethyl)-2,3-bis[5-(trifluoromethyl)pyridin-3-yl]pyridine (22)

^{1}H NMR (500 MHz, $CDCl_3$)

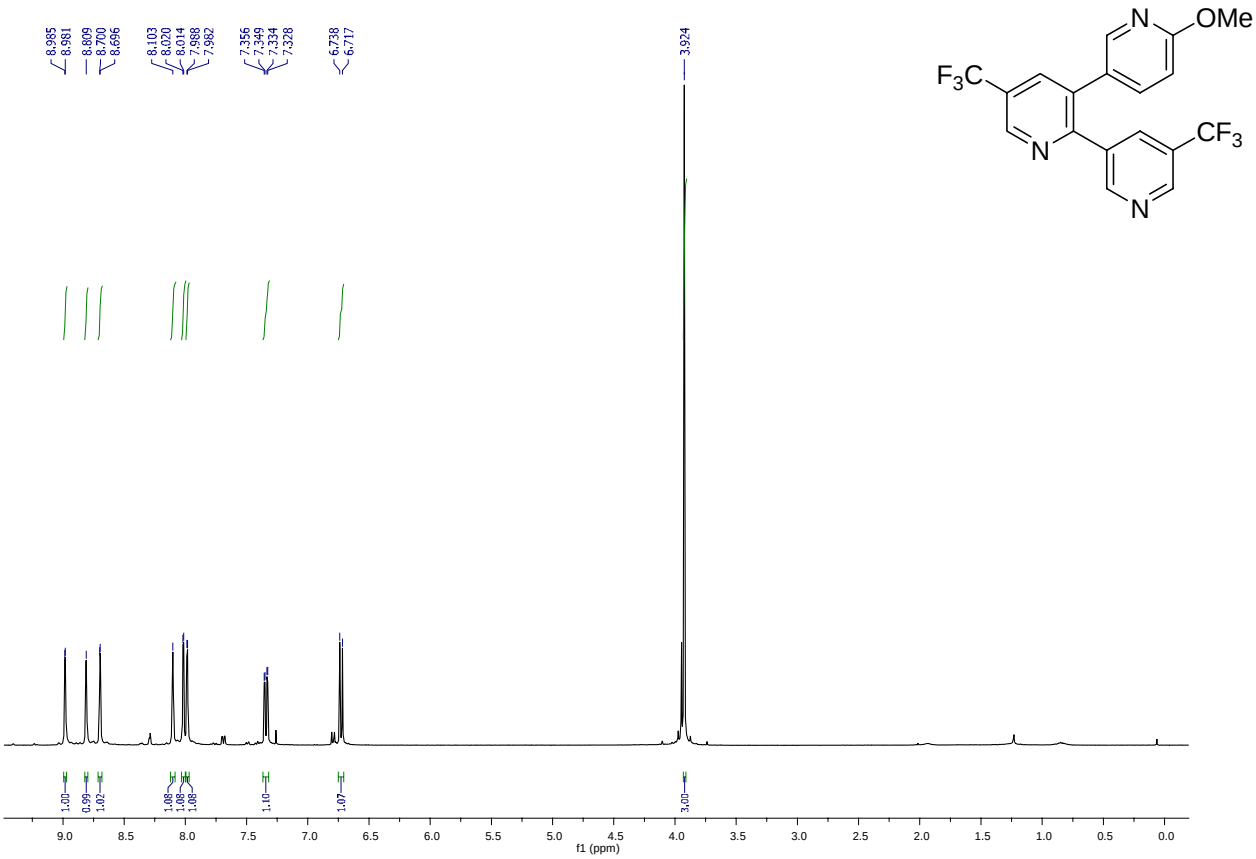


^{13}C NMR (125 MHz, $CDCl_3$)

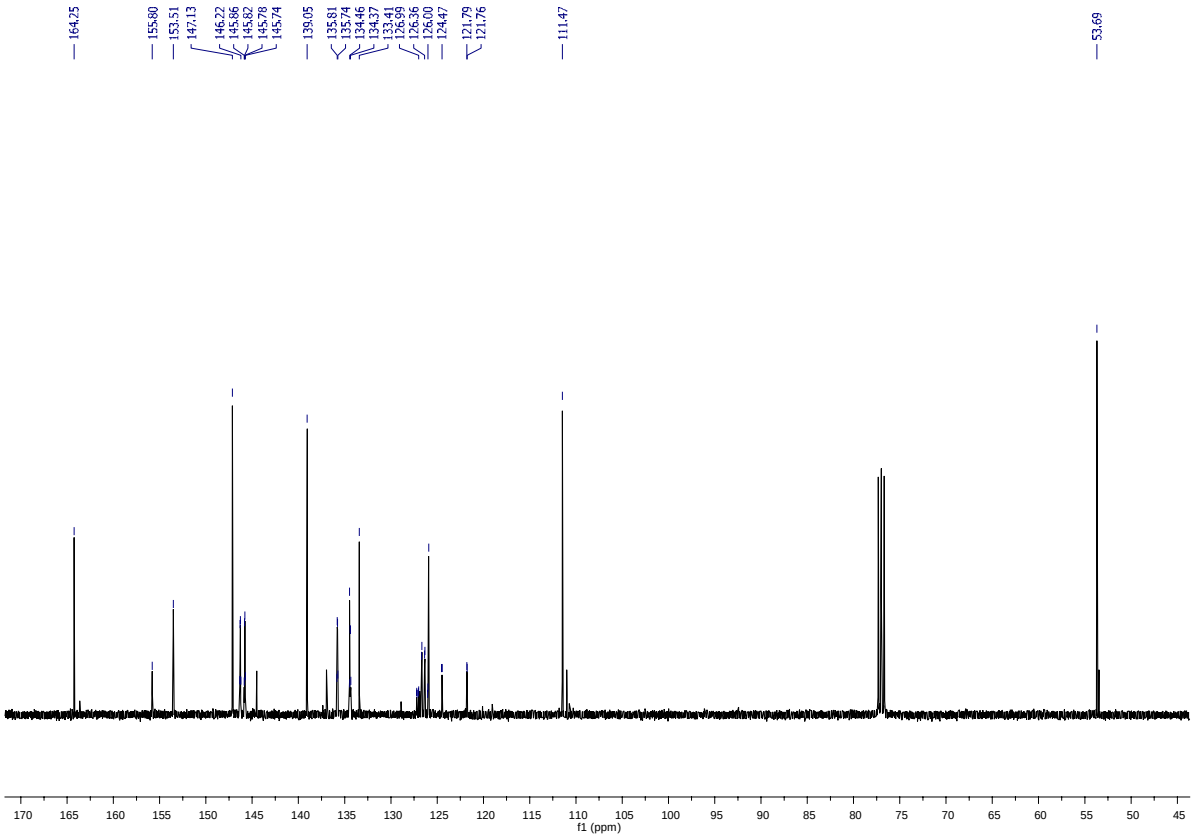


5-(Trifluoromethyl)-2-[5-(trifluoromethyl)pyridin-3-yl]-3-(6-methoxypyridin-3-yl)pyridine (24)

^{1}H NMR (400 MHz, $CDCl_3$)

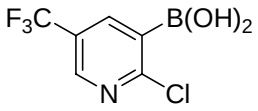


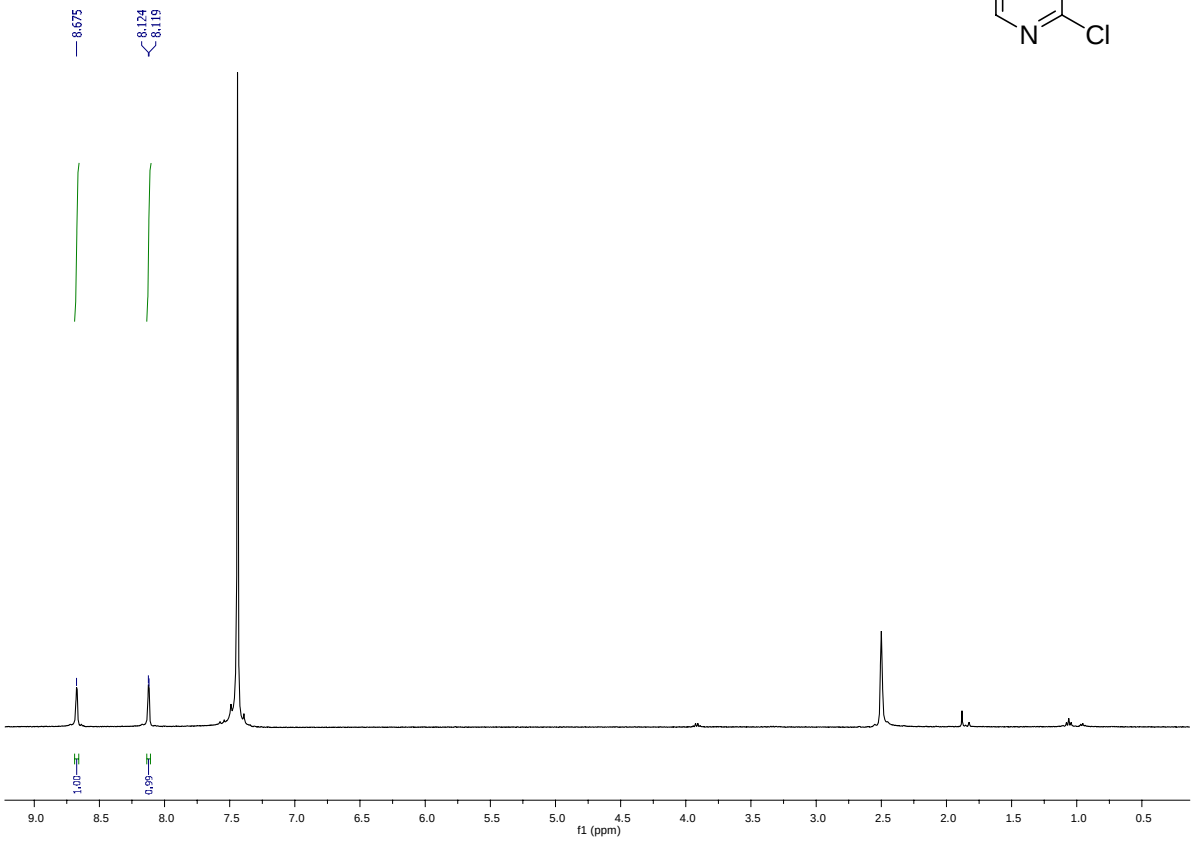
^{13}C NMR (100 MHz, $CDCl_3$)



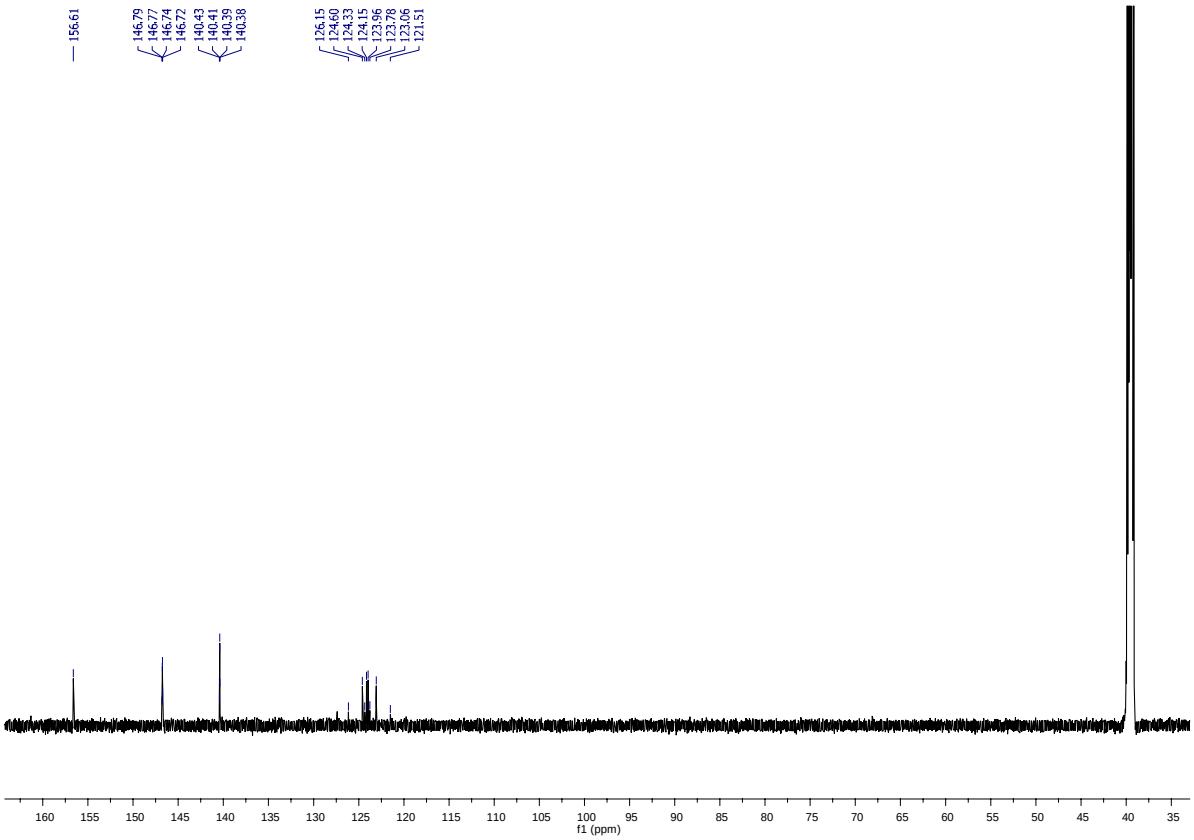
2-Chloro-5-(trifluoromethyl)-3-pyridylboronic acid (26)

^{1}H NMR (400 MHz, DMSO-d_6, DCl)

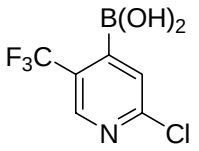




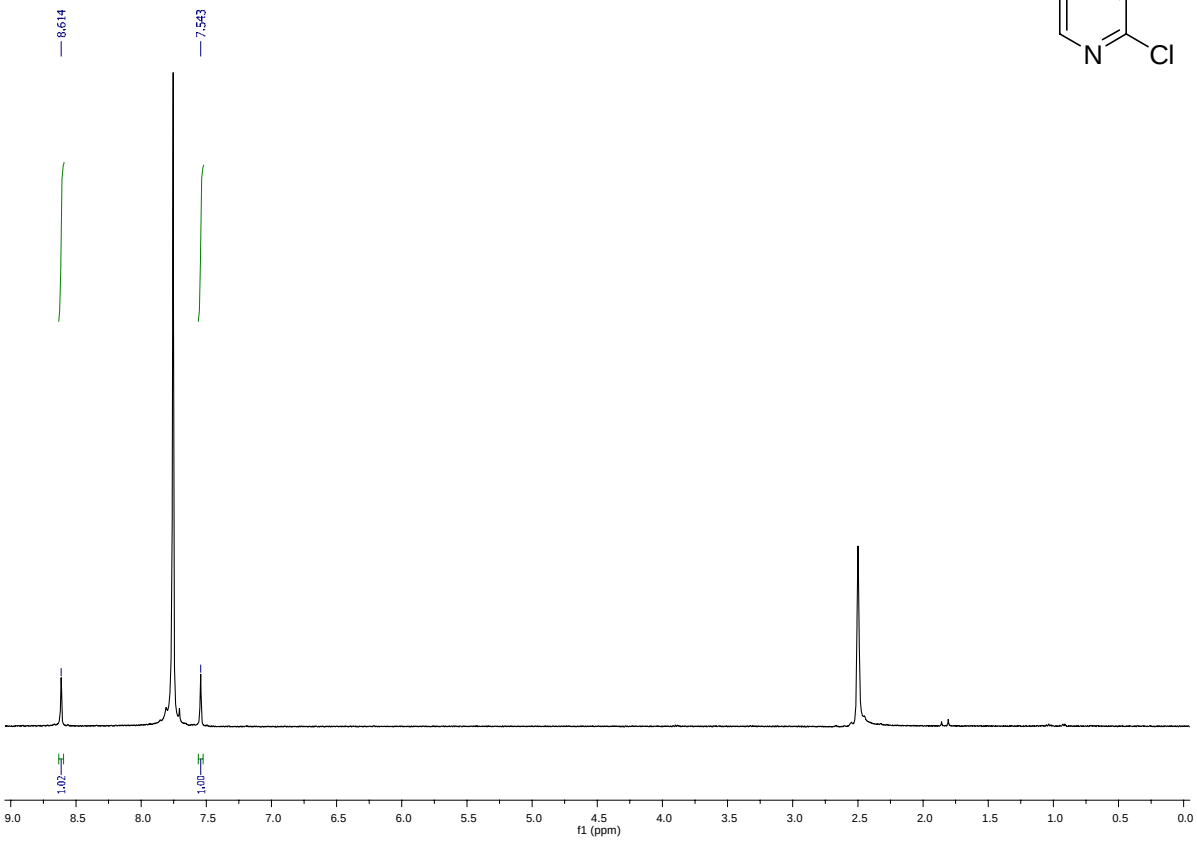
^{13}C NMR (175 MHz, DMSO-d_6, DCl)



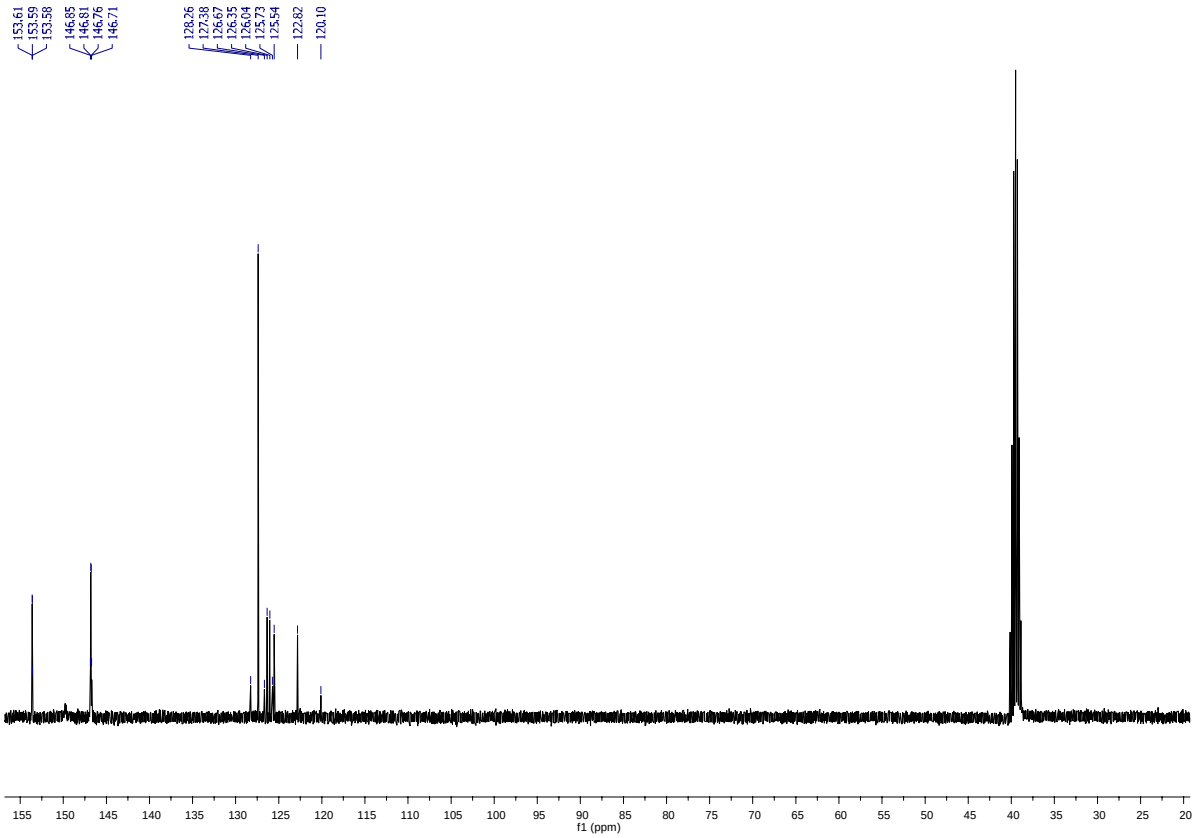
2-Chloro-5-(trifluoromethyl)-4-pyridylboronic acid (27)



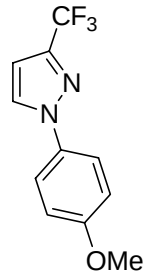
^{1}H NMR (400 MHz, DMSO-d_6, DCl)



^{13}C NMR (100 MHz, DMSO-d_6, DCl)

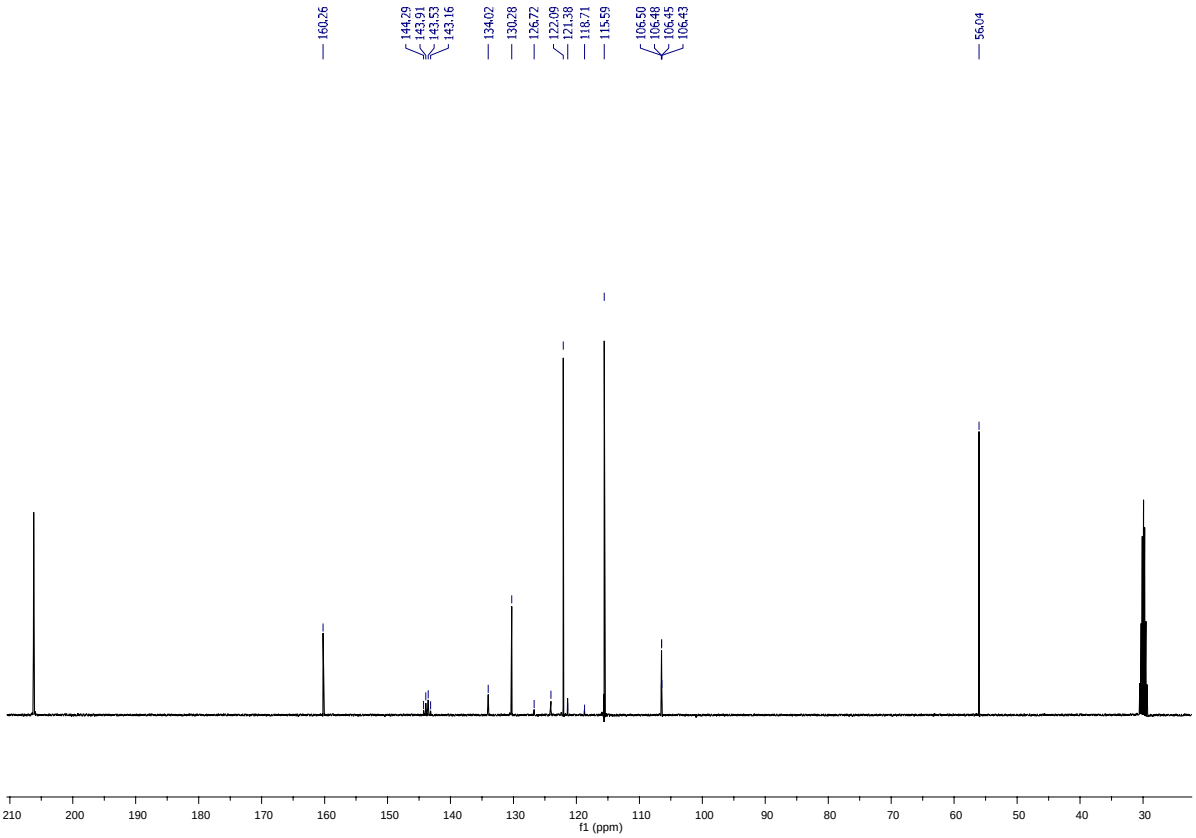


3-(Trifluoromethyl)-1-(4-methoxyphenyl)-1*H*-pyrazole (29b)

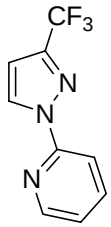


^{1}H NMR (400 MHz, acetone-d_6)

^{13}C NMR (100 MHz, acetone-d_6)

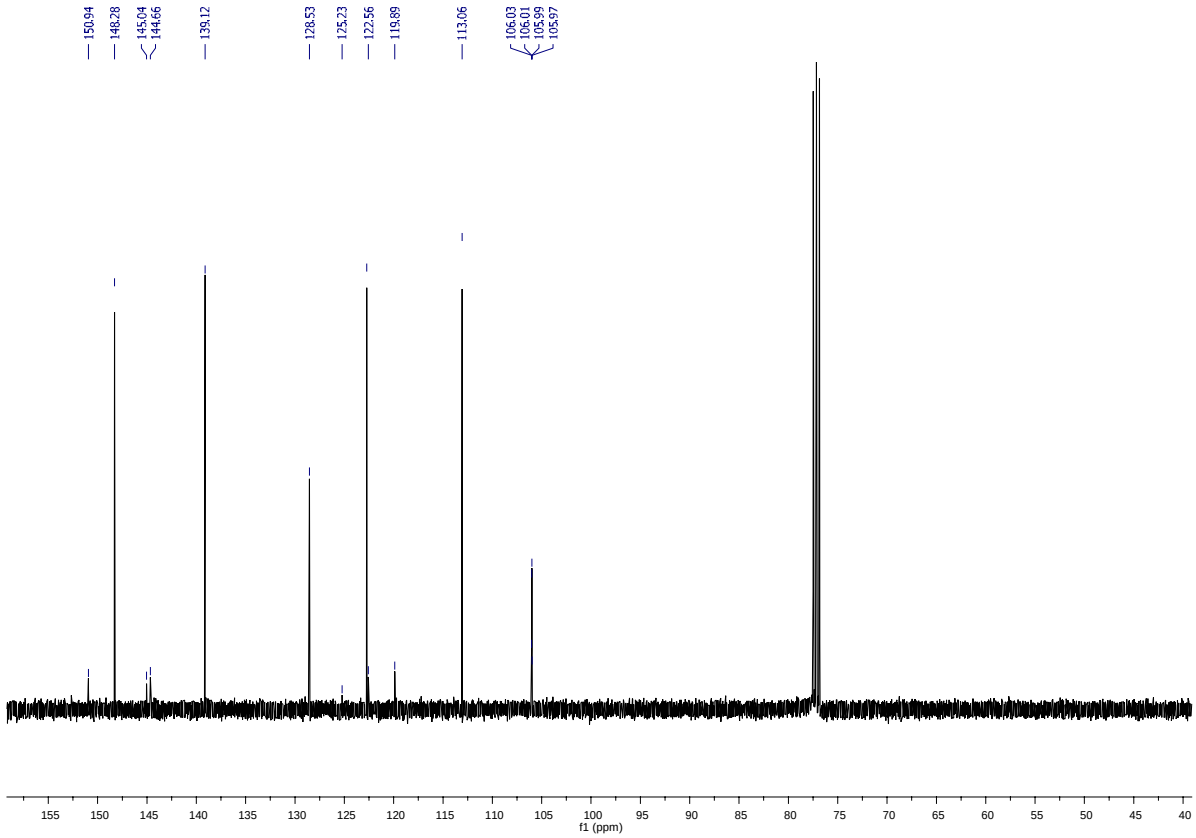


3-(Trifluoromethyl)-1-(pyridin-2-yl)-1*H*-pyrazole (29c)



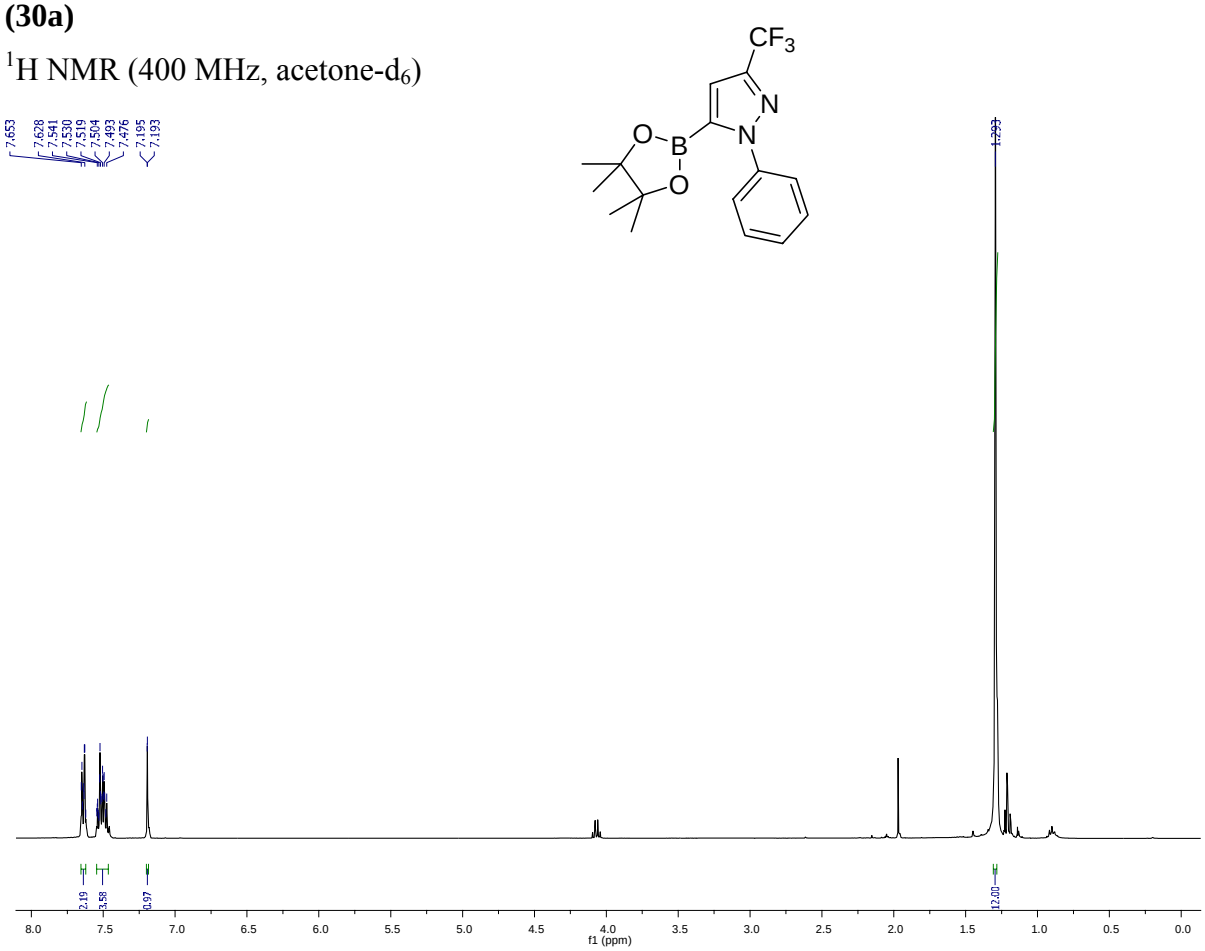
^{1}H NMR (400 MHz, acetone-d_6)

^{13}C NMR (100 MHz, $CDCl_3$)

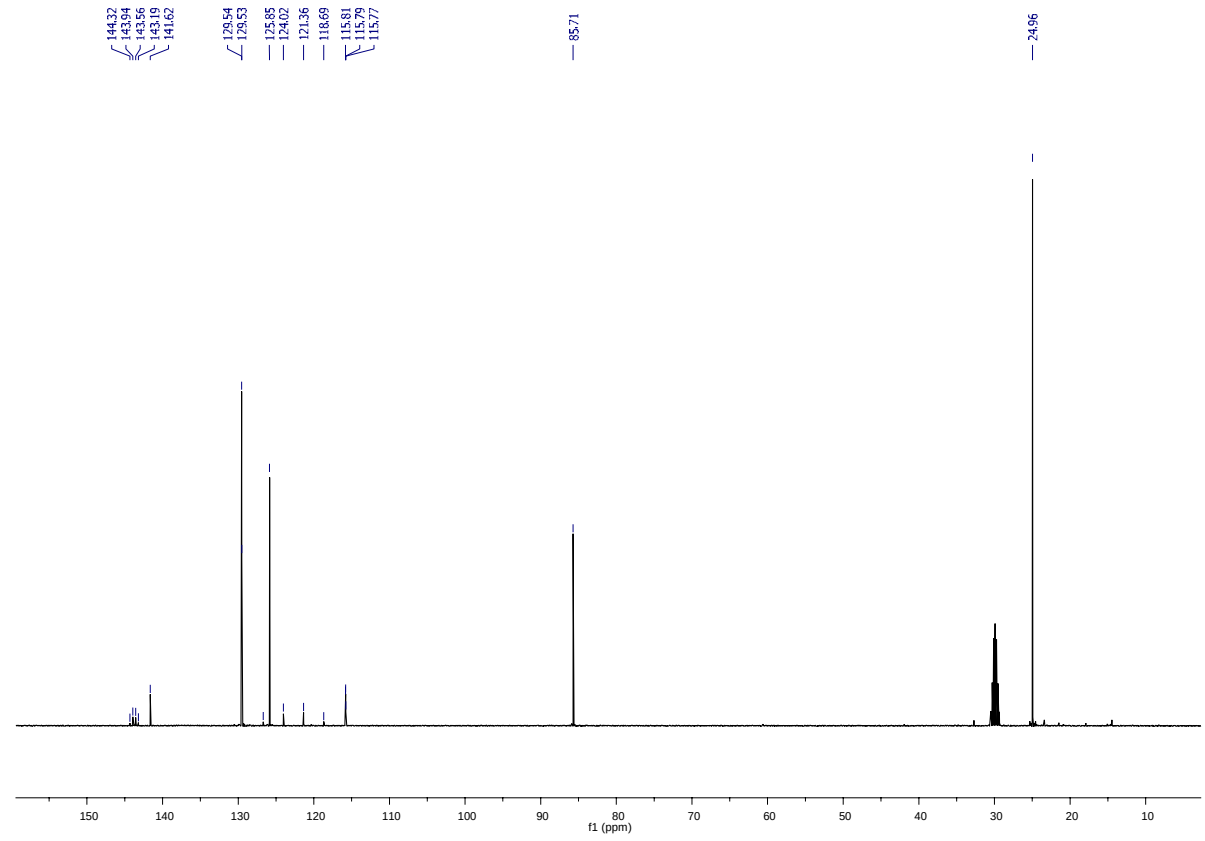


3-(Trifluoromethyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-phenyl-1*H*-pyrazole (30a)

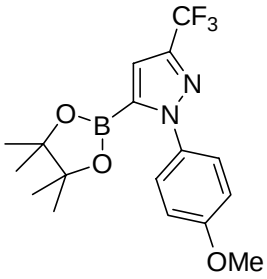
^{1}H NMR (400 MHz, acetone-d$_6$)



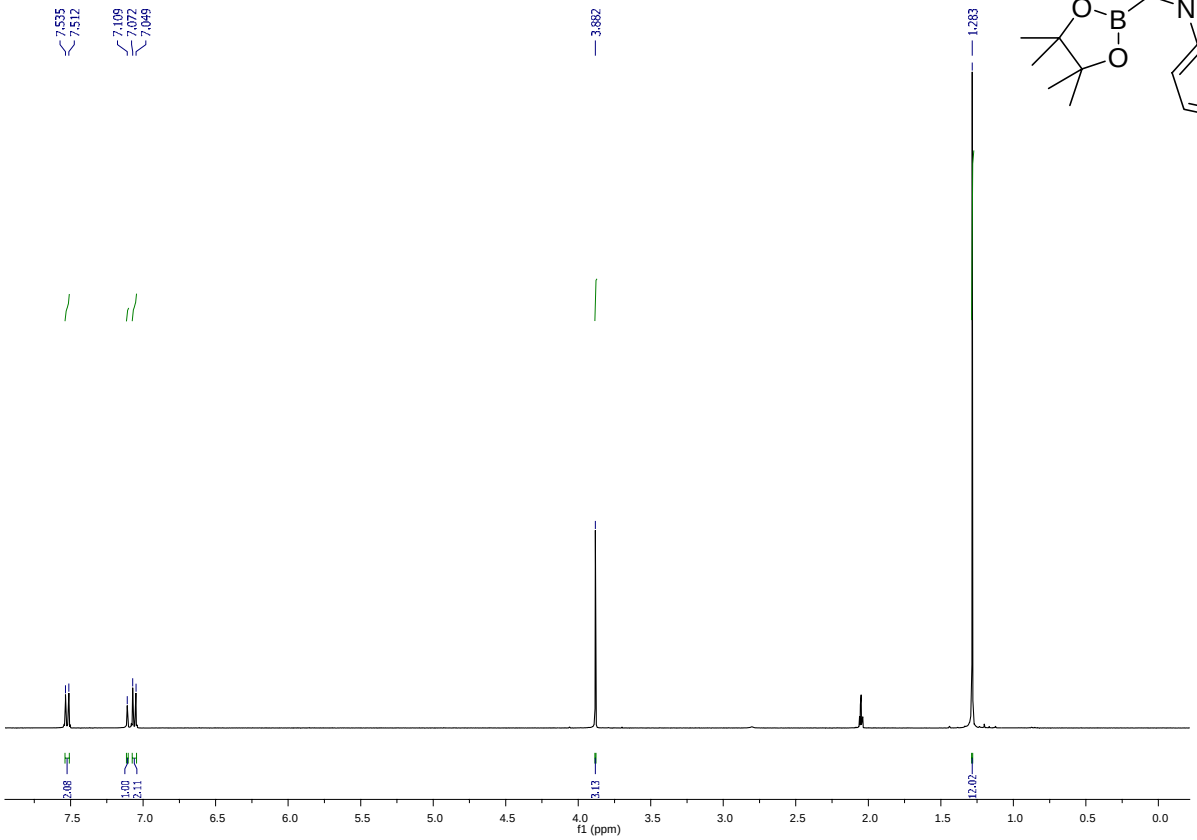
^{13}C NMR (100 MHz, acetone-d$_6$)



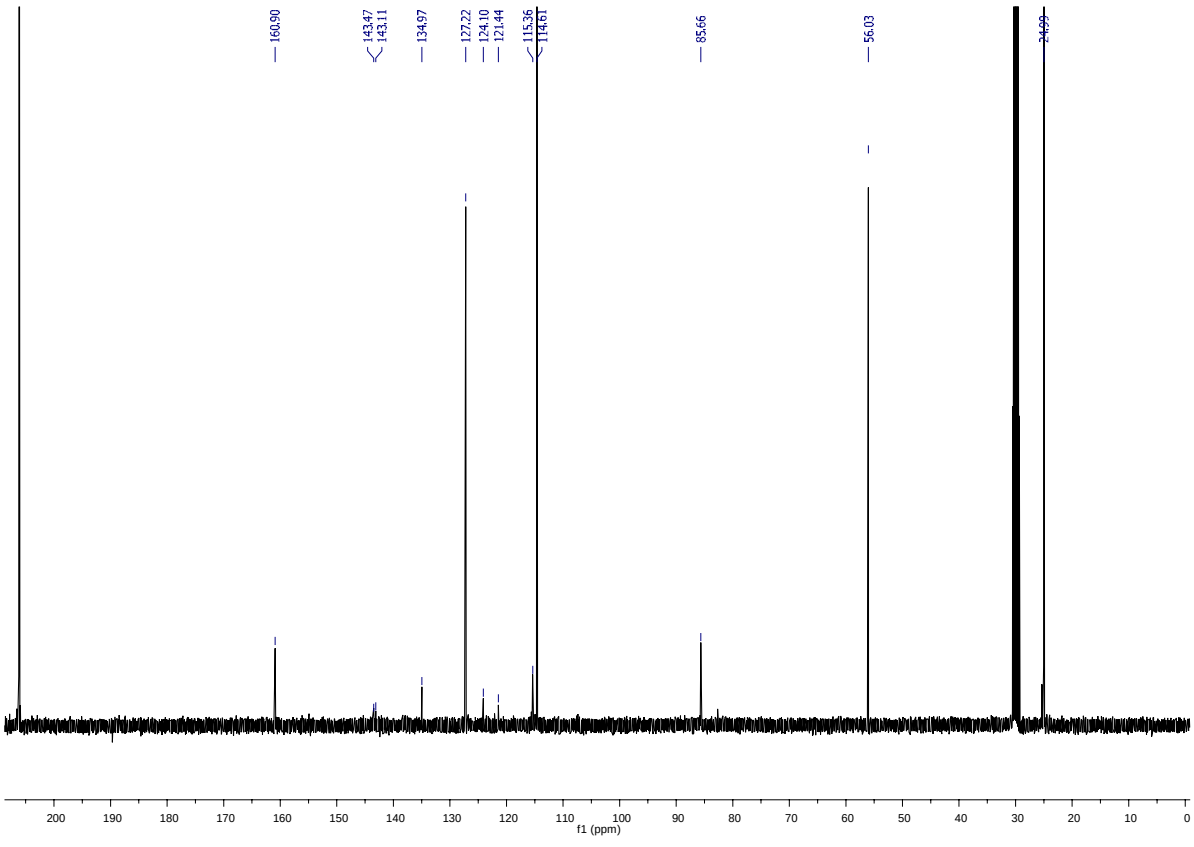
3-(Trifluoromethyl)-1-(4-methoxyphenyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (30b)



^{1}H NMR (400 MHz, acetone-d$_6$)

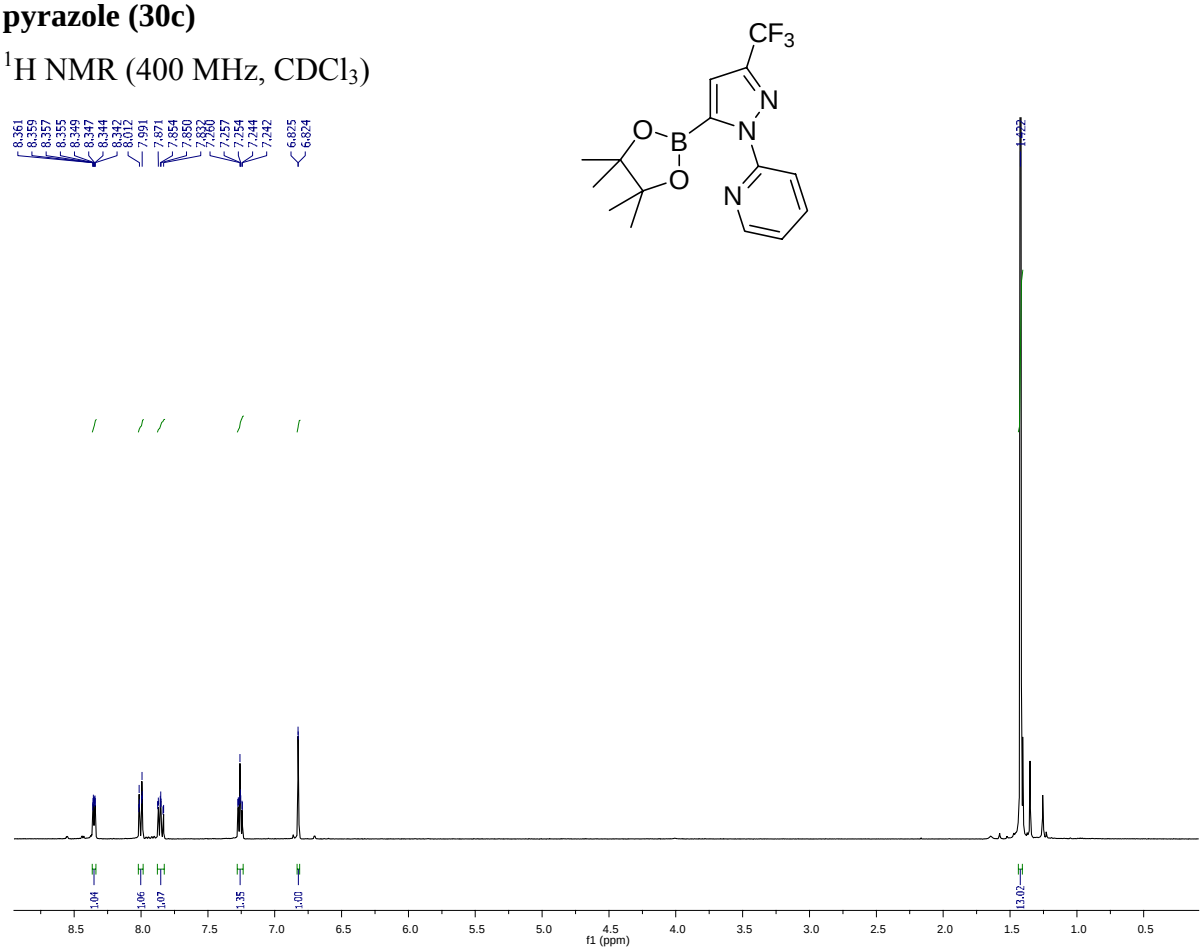


^{13}C NMR (100 MHz, acetone-d$_6$)

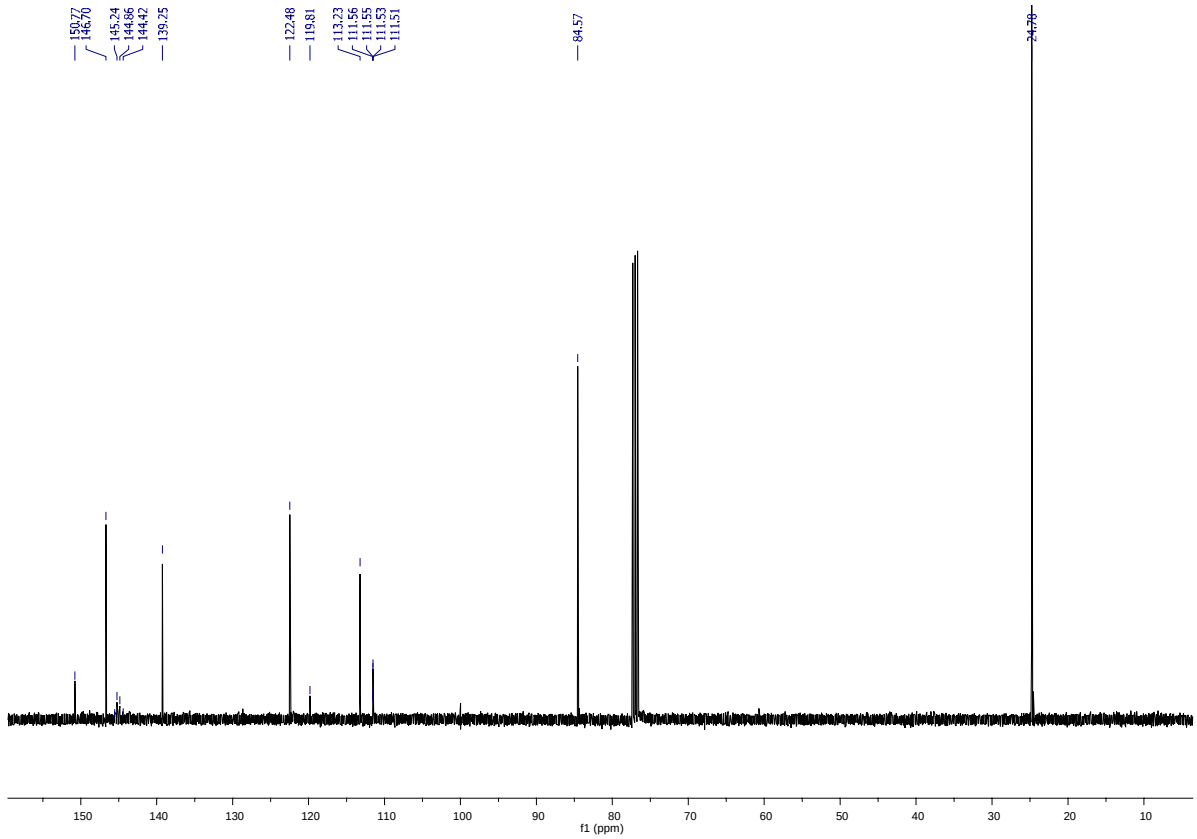


3-(Trifluoromethyl)-1-(pyridin-2-yl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (30c)

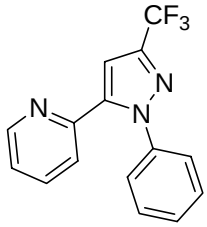
^{1}H NMR (400 MHz, $CDCl_3$)



^{13}C NMR (100 MHz, $CDCl_3$)

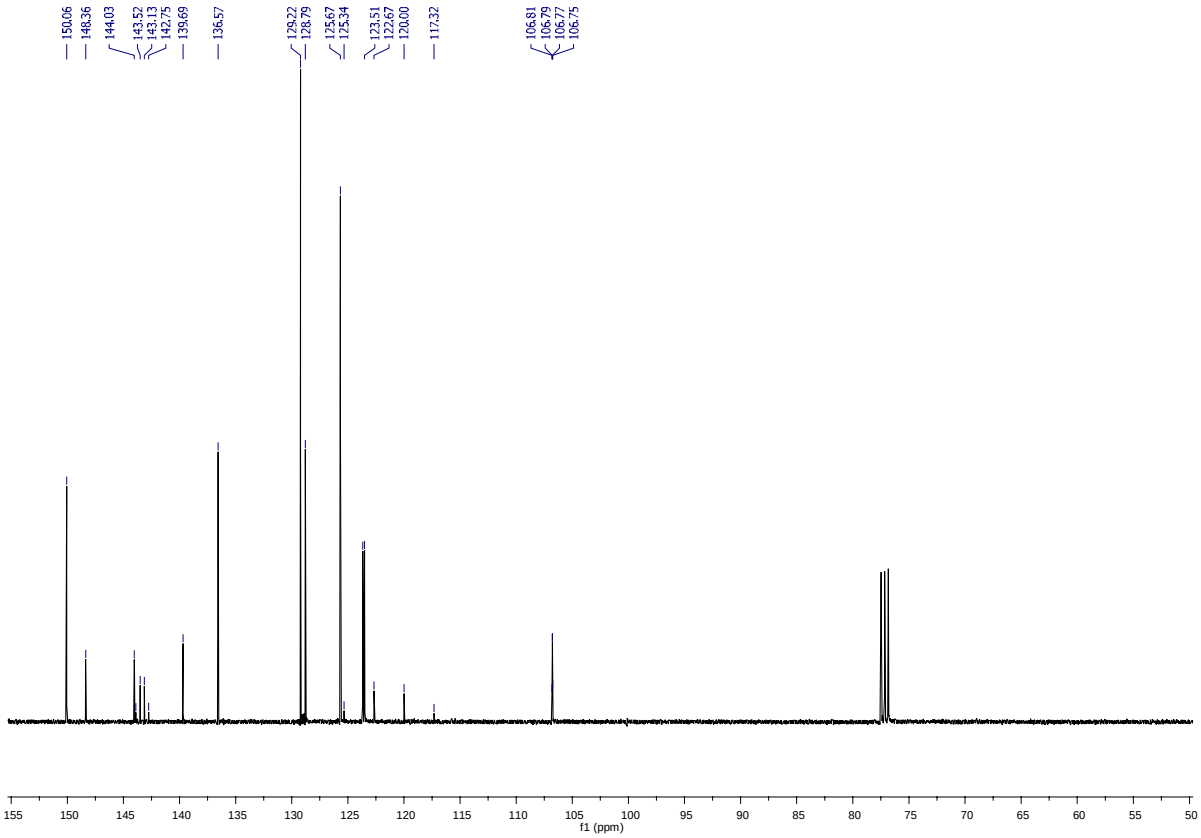


2-[3-(Trifluoromethyl)-1-phenyl-1*H*-pyrazol-5-yl]pyridine (35)



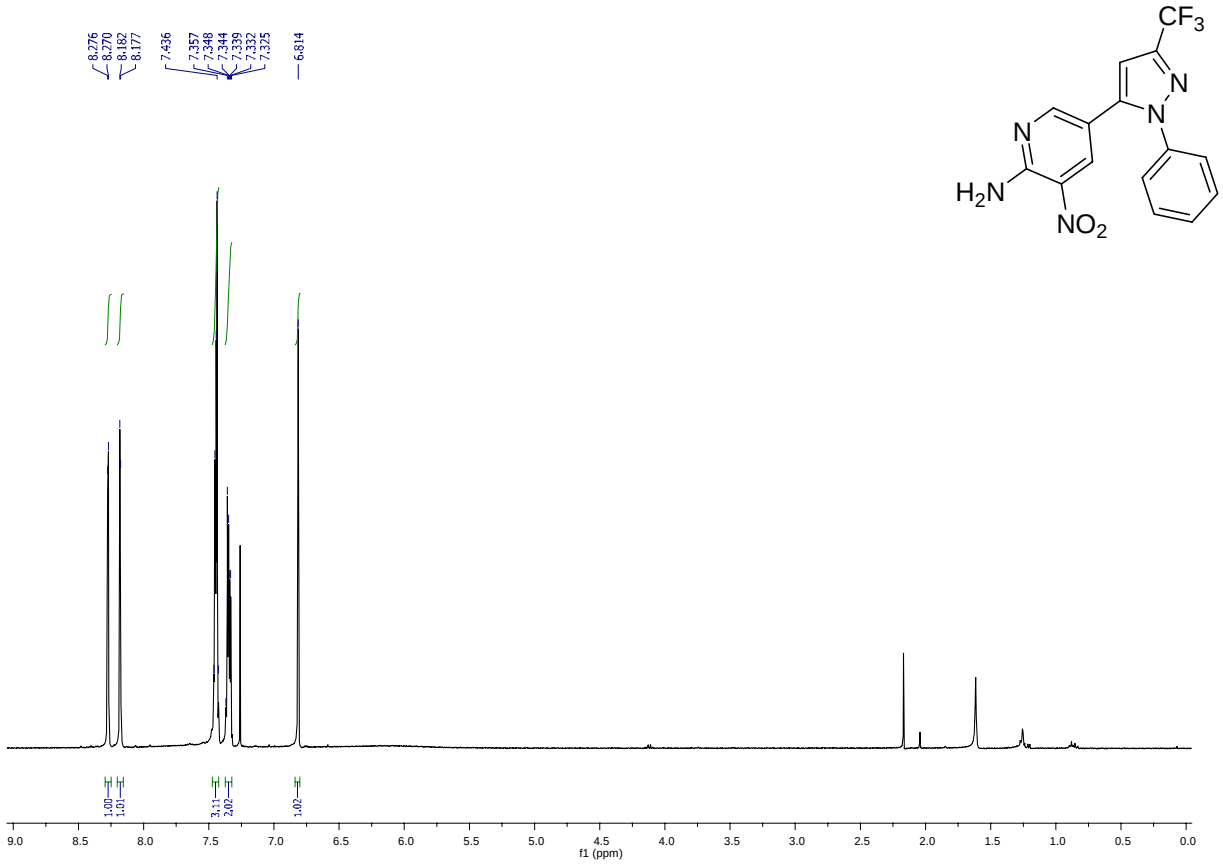
^{1}H NMR (400 MHz, $CDCl_3$)

^{13}C NMR (100 MHz, $CDCl_3$)

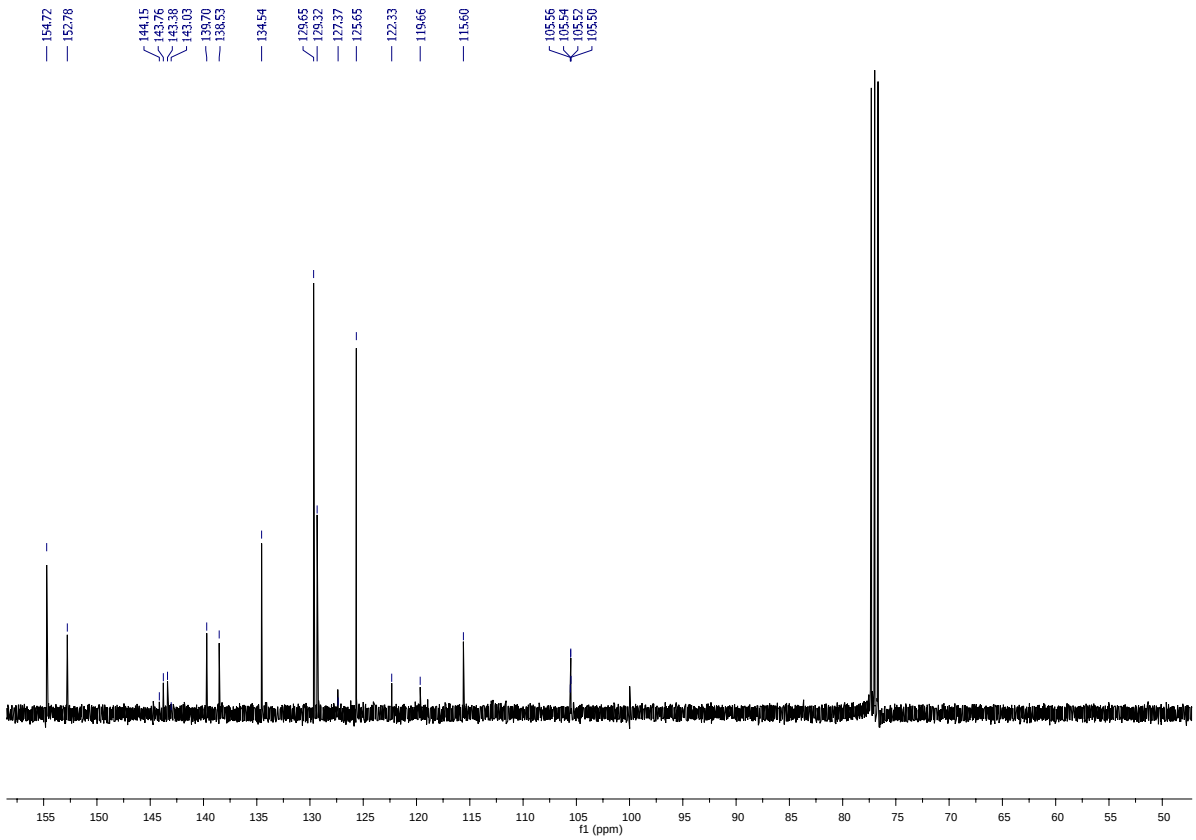


5-[3-(Trifluoromethyl)-1-phenyl-1*H*-pyrazol-5-yl]-3-nitropyridin-2-amine (36)

^{1}H NMR (400 MHz, $CDCl_3$)

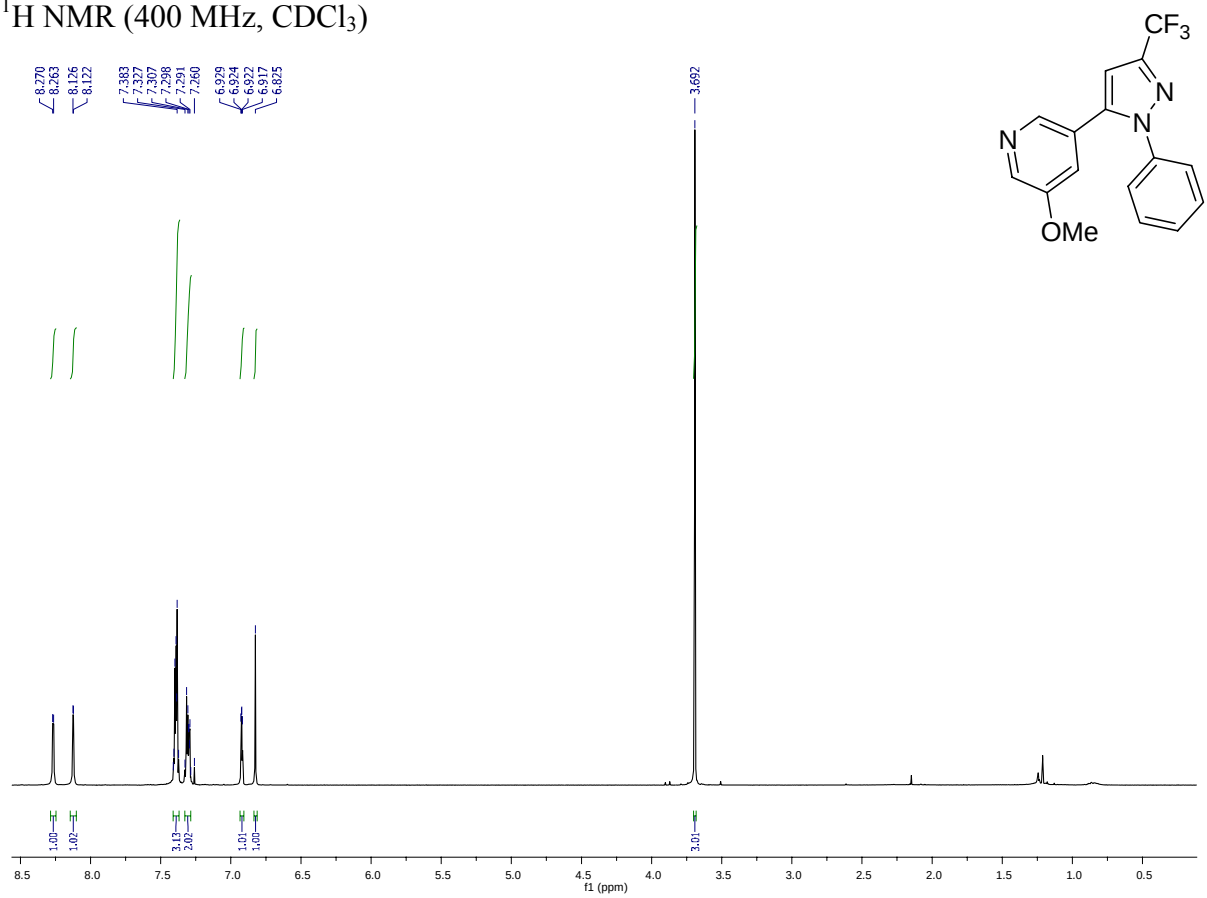


^{13}C NMR (100 MHz, $CDCl_3$)

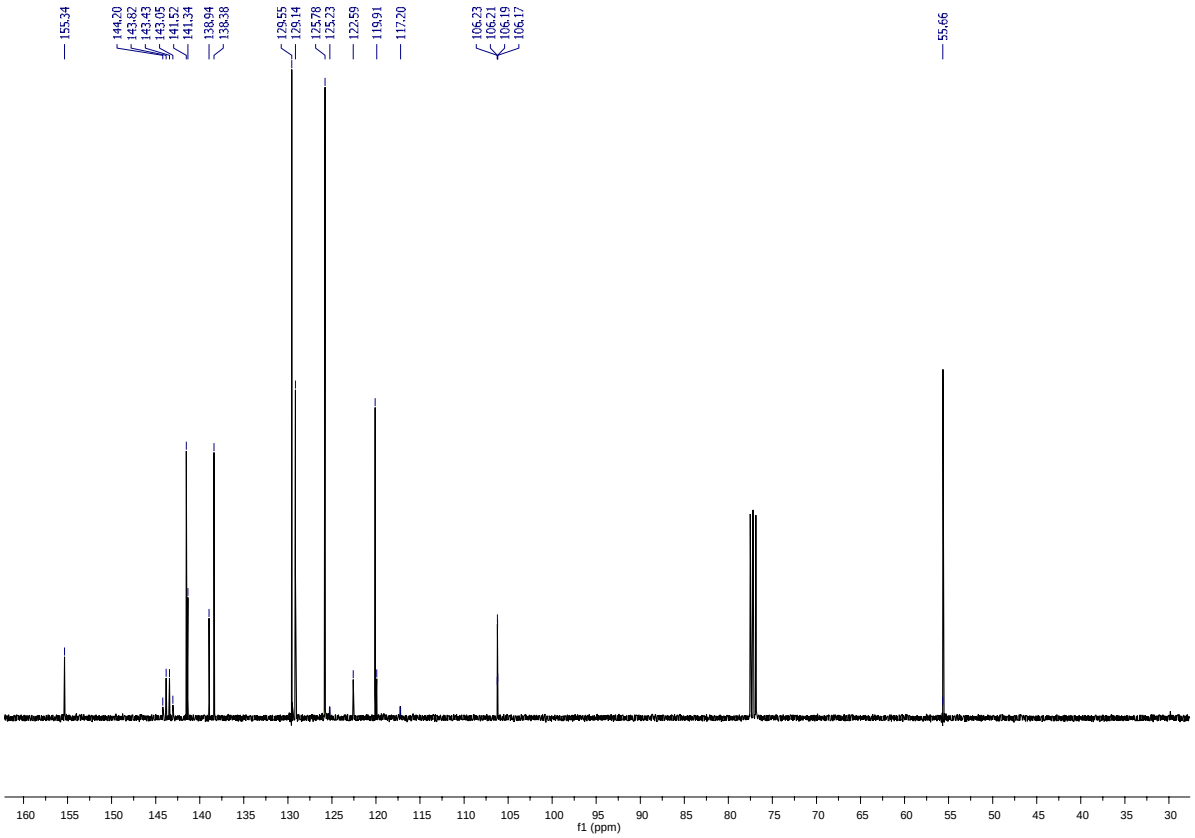


3-[3-(Trifluoromethyl)-1-phenyl-1*H*-pyrazol-5-yl]-5-methoxypyridine (37)

^{1}H NMR (400 MHz, $CDCl_3$)

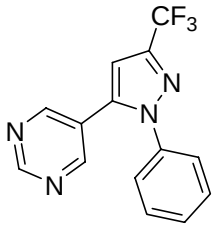


^{13}C NMR (100 MHz, $CDCl_3$)

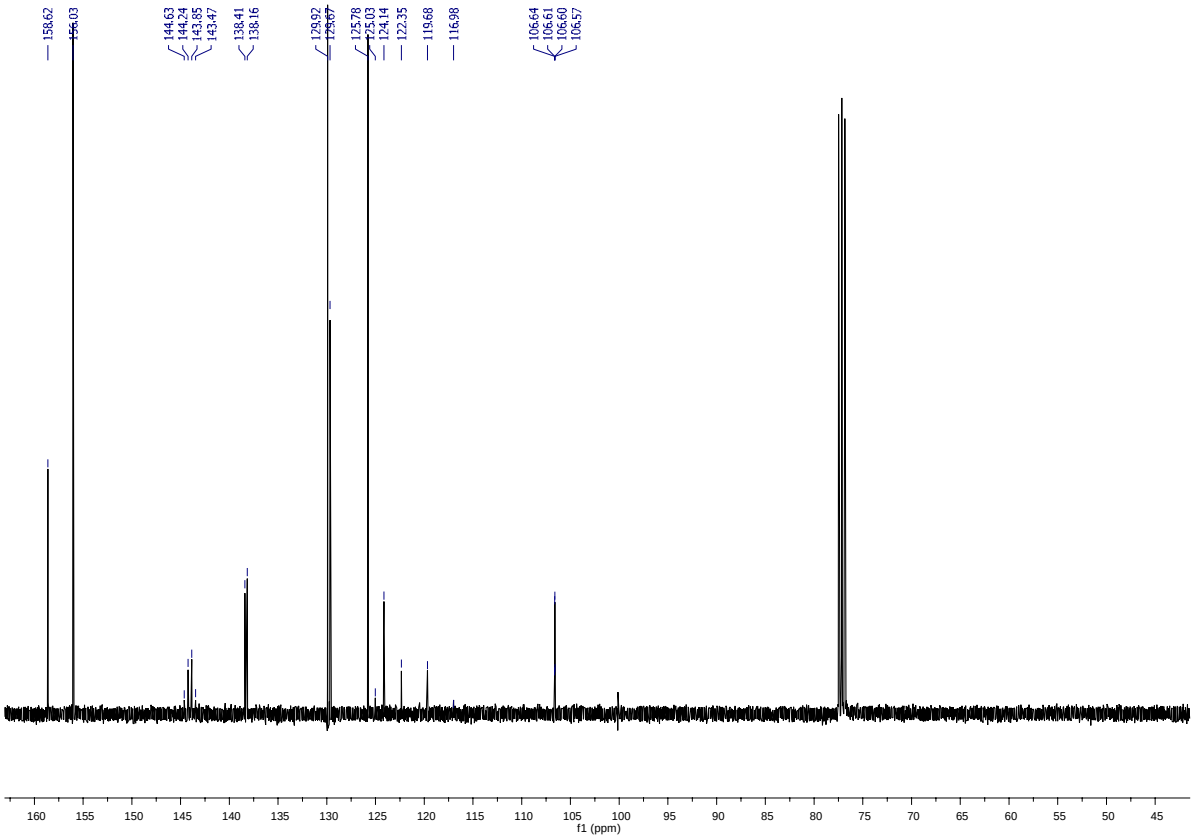


5-[3-(Trifluoromethyl)-1-phenyl-1*H*-pyrazol-5-yl]pyrimidine (38)

^{1}H NMR (400 MHz, $CDCl_3$)

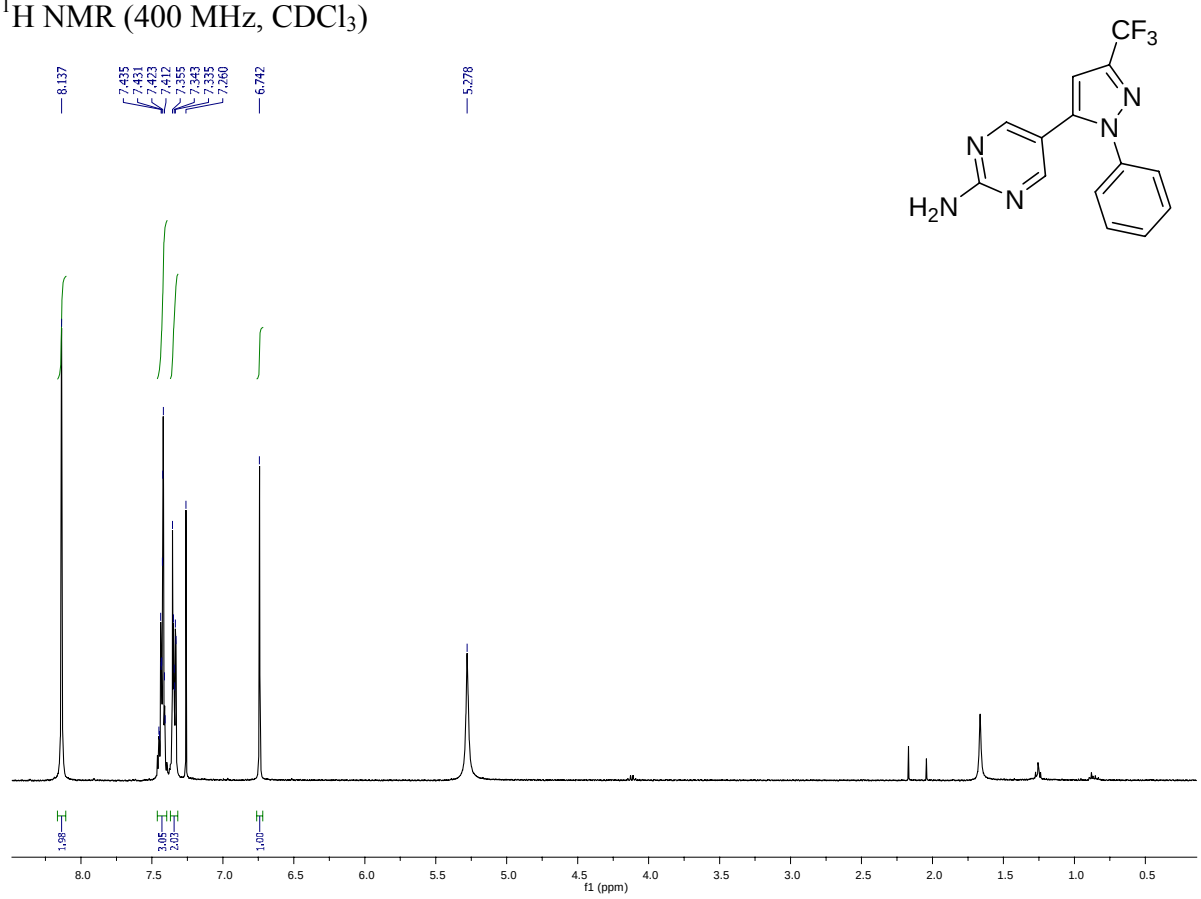


^{13}C NMR (100 MHz, $CDCl_3$)

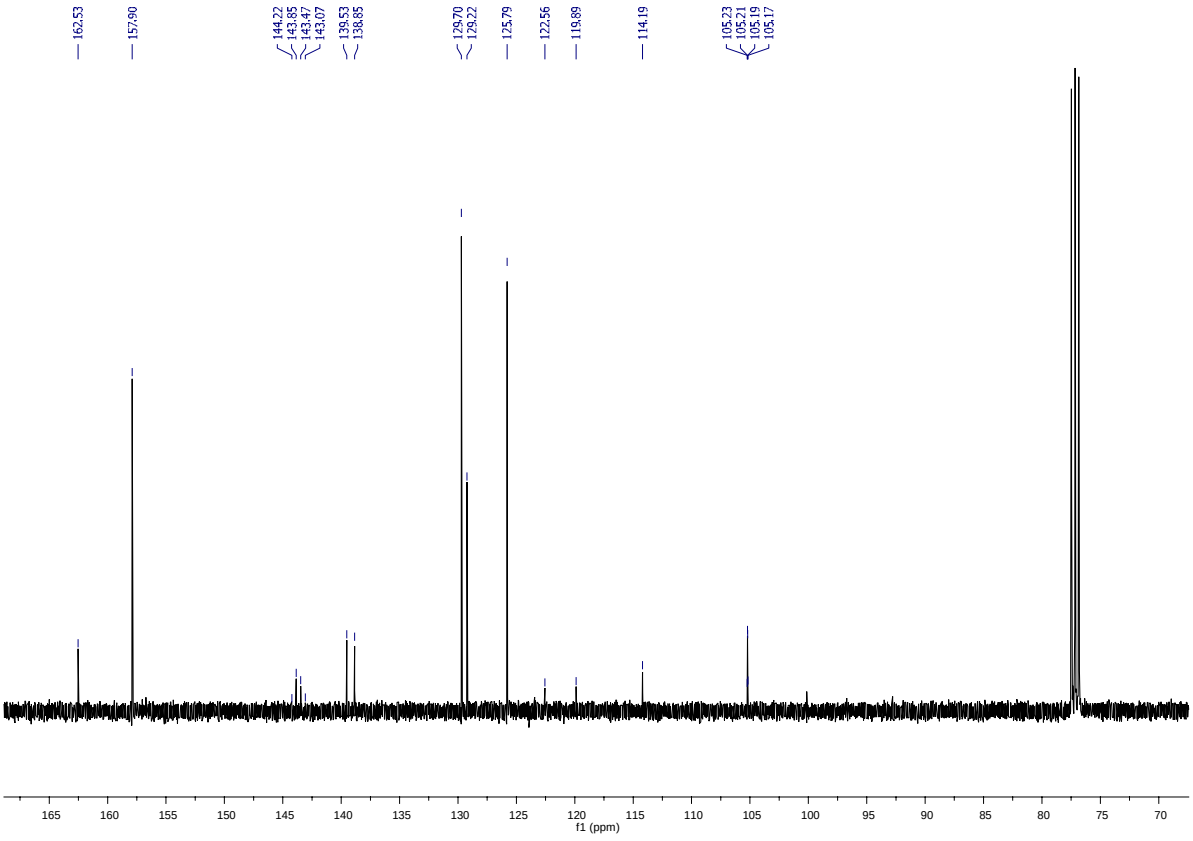


5-(3-(Trifluoromethyl)-1-phenyl-1*H*-pyrazol-5-yl)pyrimidin-2-amine (39)

^{1}H NMR (400 MHz, $CDCl_3$)

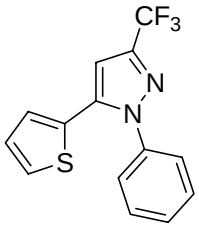


^{13}C NMR (100 MHz, $CDCl_3$)

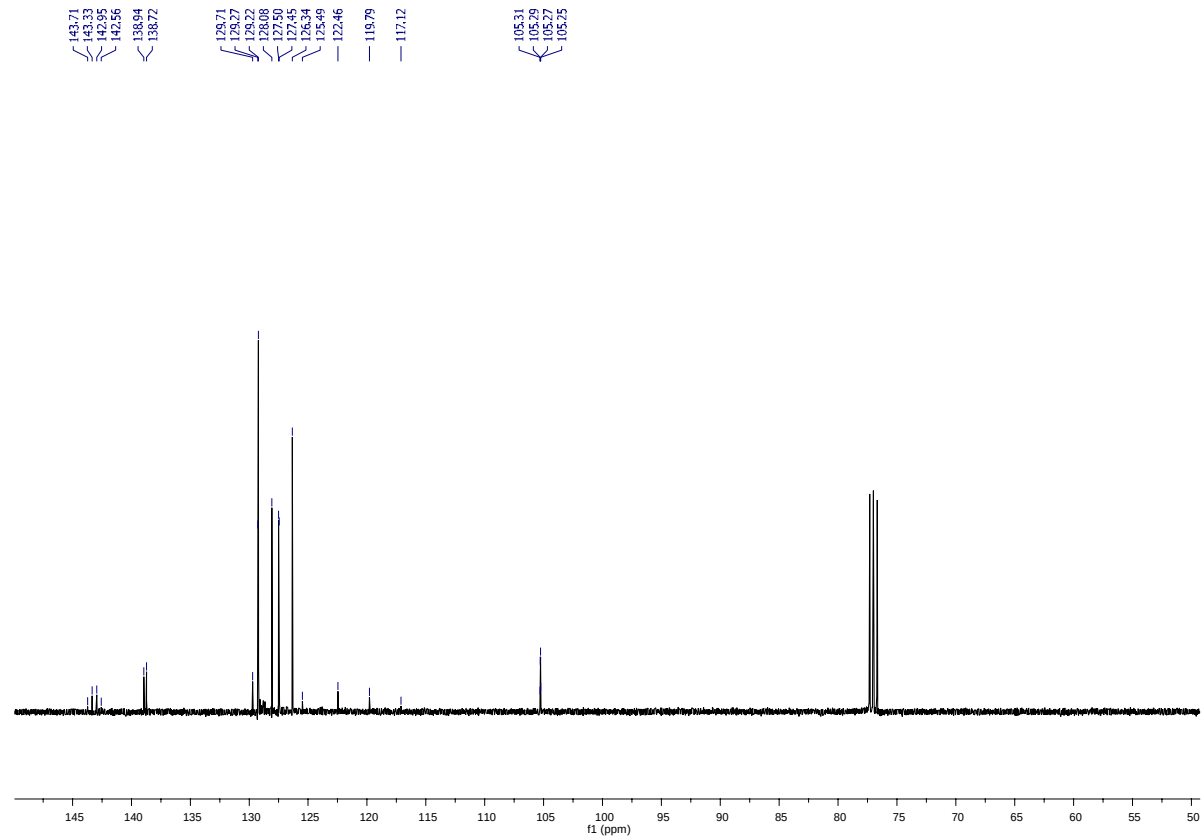


3-(Trifluoromethyl)-1-phenyl-5-(thiophen-2-yl)-1*H*-pyrazole (40)

^{1}H NMR (400 MHz, $CDCl_3$)

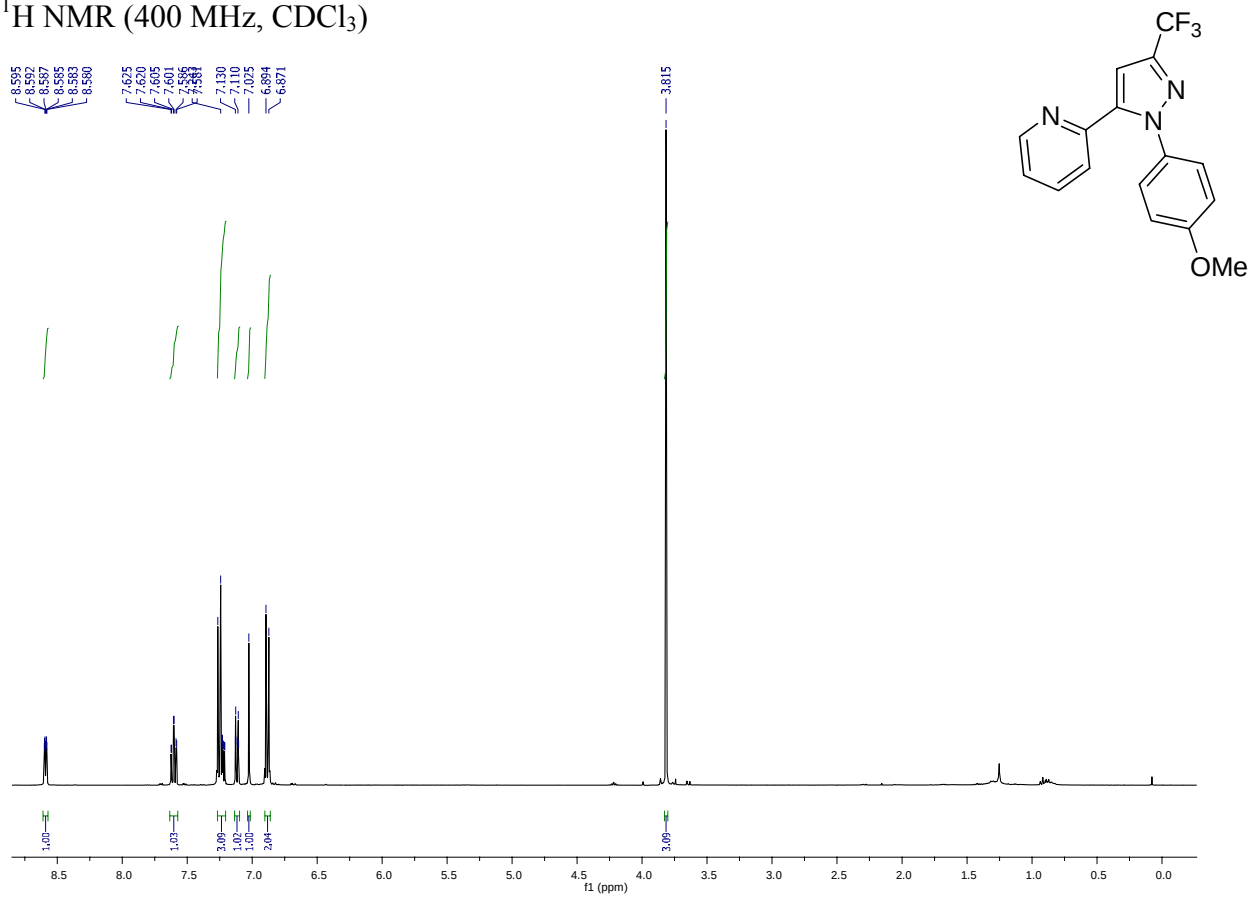


^{13}C NMR (100 MHz, $CDCl_3$)

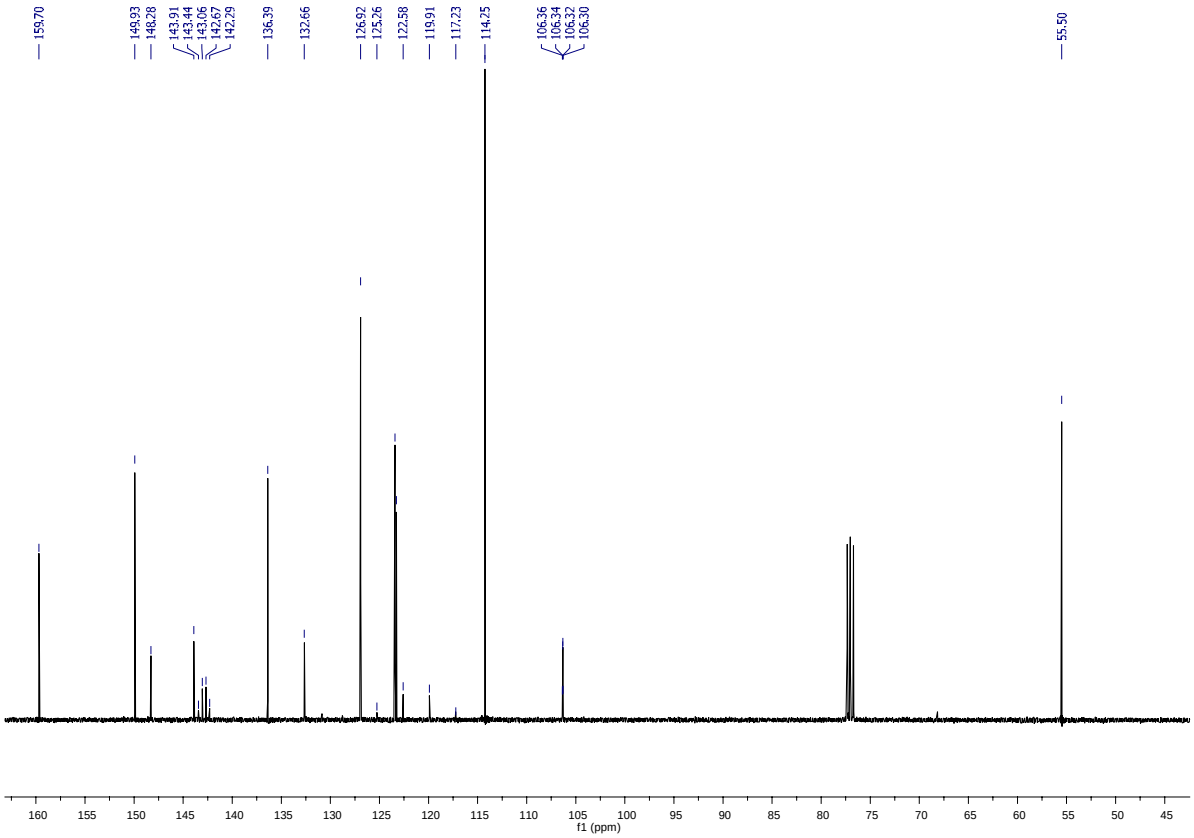


2-[3-(Trifluoromethyl)-1-(4-methoxyphenyl)-1*H*-pyrazol-5-yl]pyridine (41)

^{1}H NMR (400 MHz, $CDCl_3$)

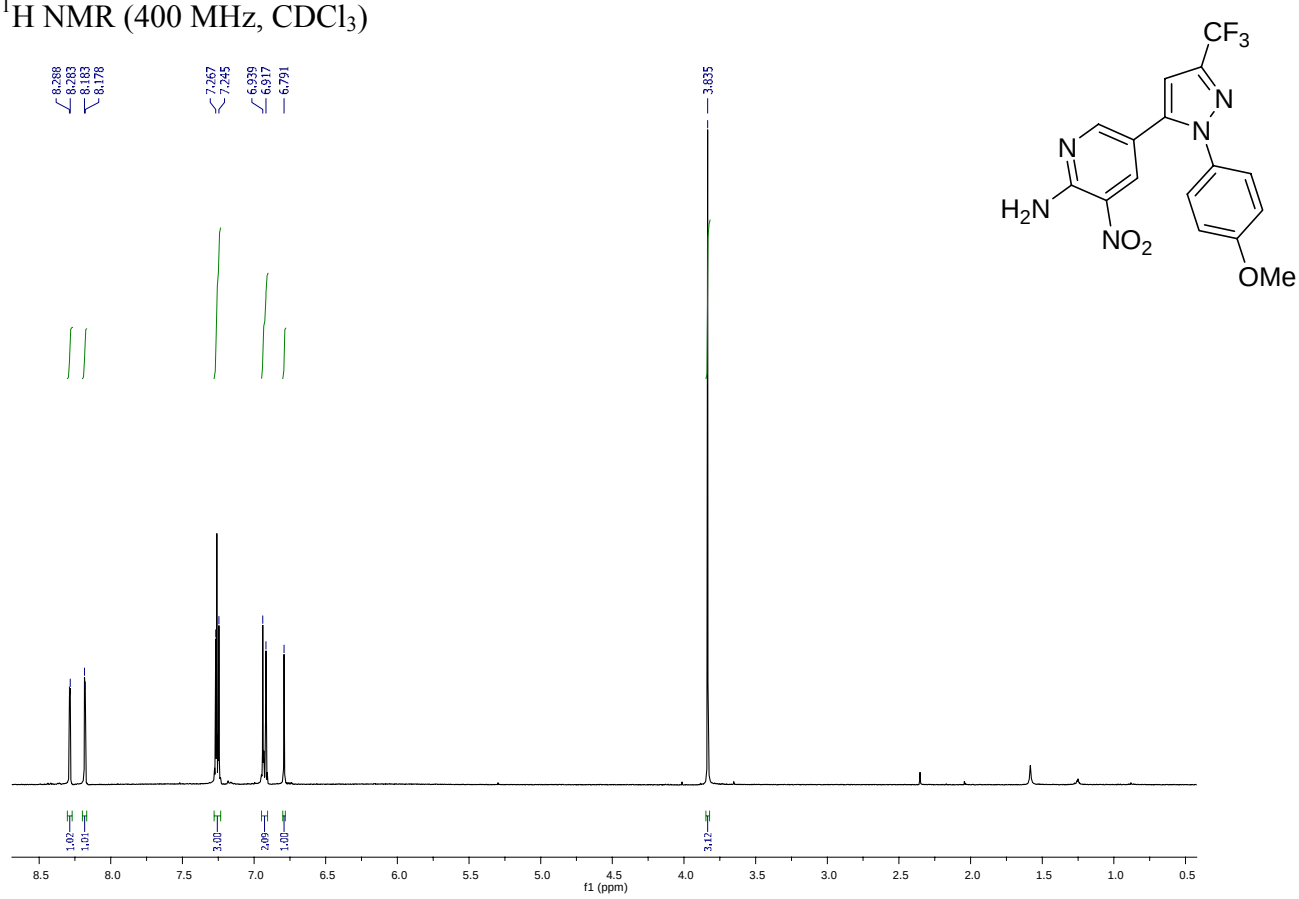


^{13}C NMR (100 MHz, $CDCl_3$)

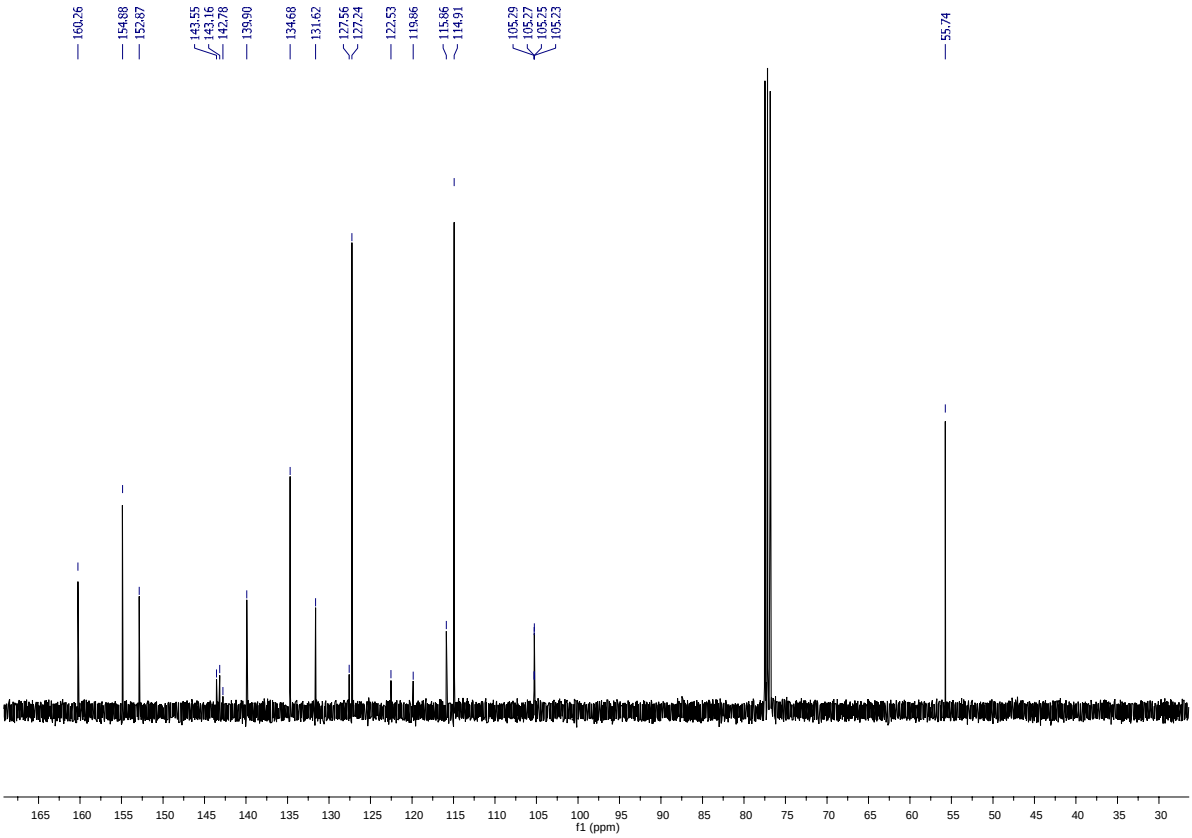


5-[3-(Trifluoromethyl)-1-(4-methoxyphenyl)-1*H*-pyrazol-5-yl]-3-nitropyridin-2-amine (42)

^{1}H NMR (400 MHz, $CDCl_3$)

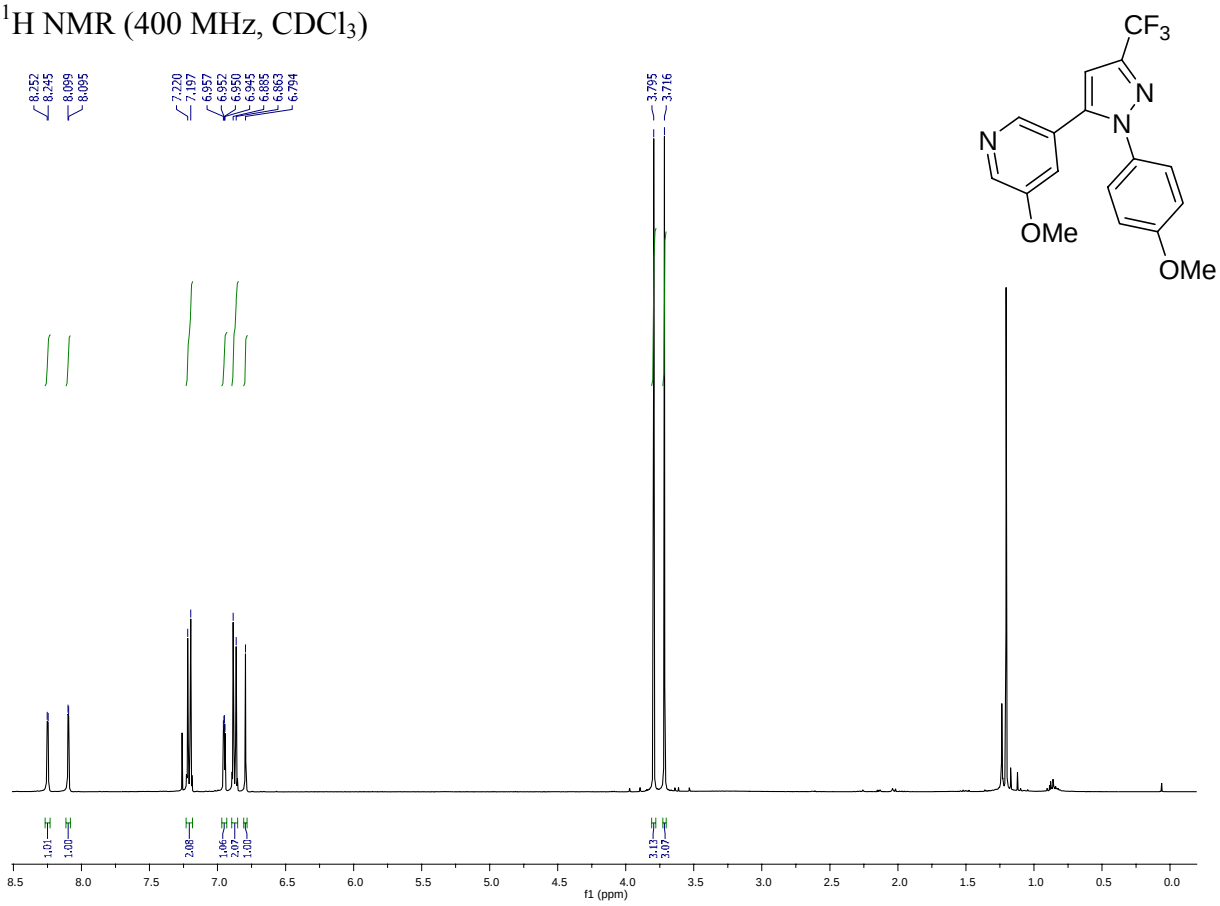


^{13}C NMR (100 MHz, $CDCl_3$)

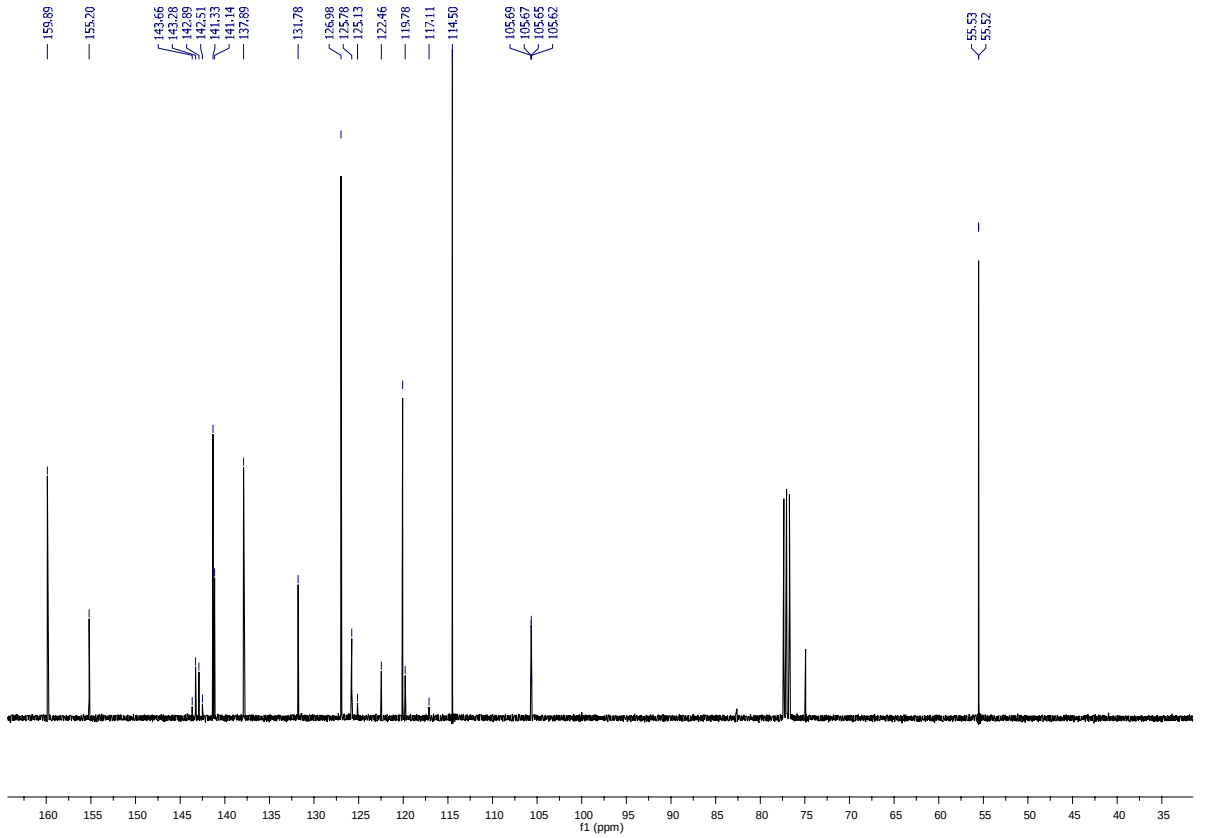


3-[3-(Trifluoromethyl)-1-(4-methoxyphenyl)-1*H*-pyrazol-5-yl]-5-methoxypyridine (43)

^{1}H NMR (400 MHz, $CDCl_3$)

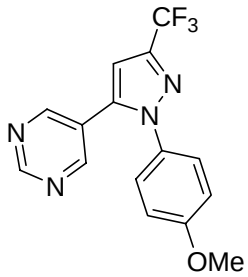


^{13}C NMR (100 MHz, $CDCl_3$)

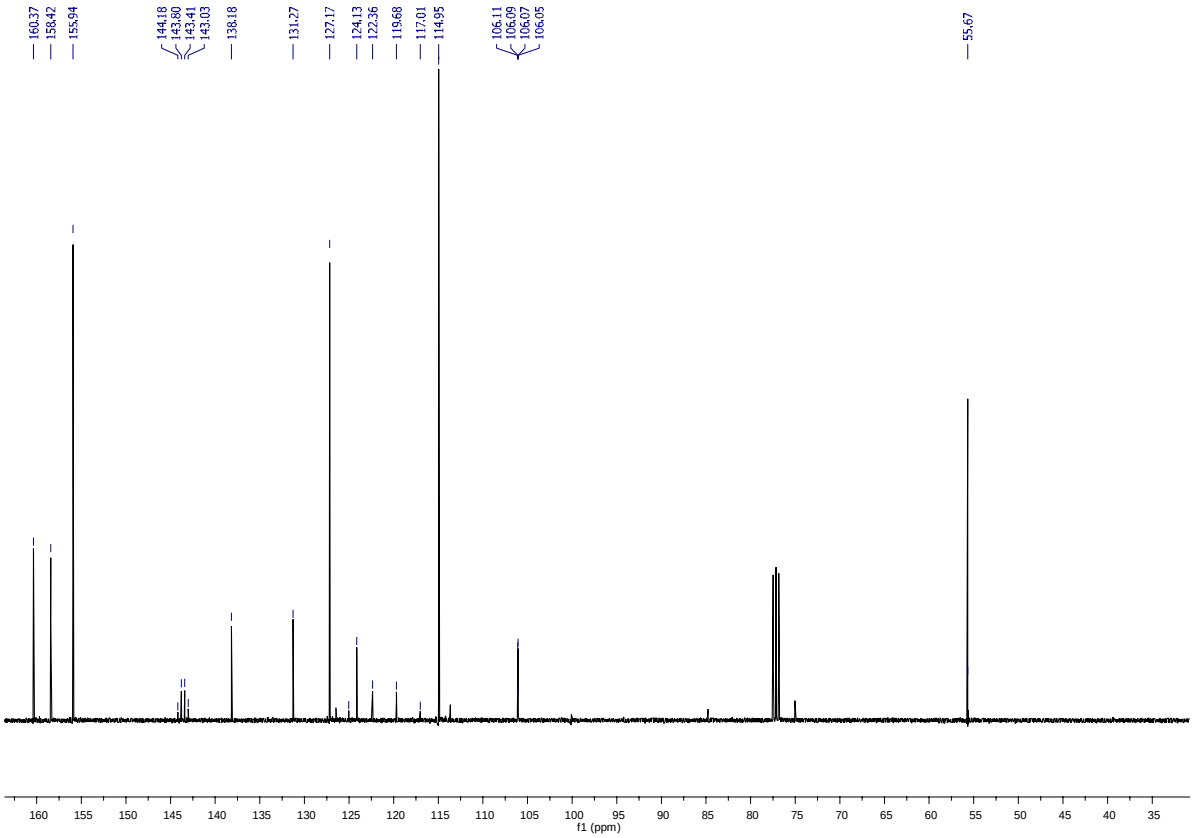


5-[3-(Trifluoromethyl)-1-(4-methoxyphenyl)-1*H*-pyrazol-5-yl]pyrimidine (44)

^{1}H NMR (400 MHz, $CDCl_3$)

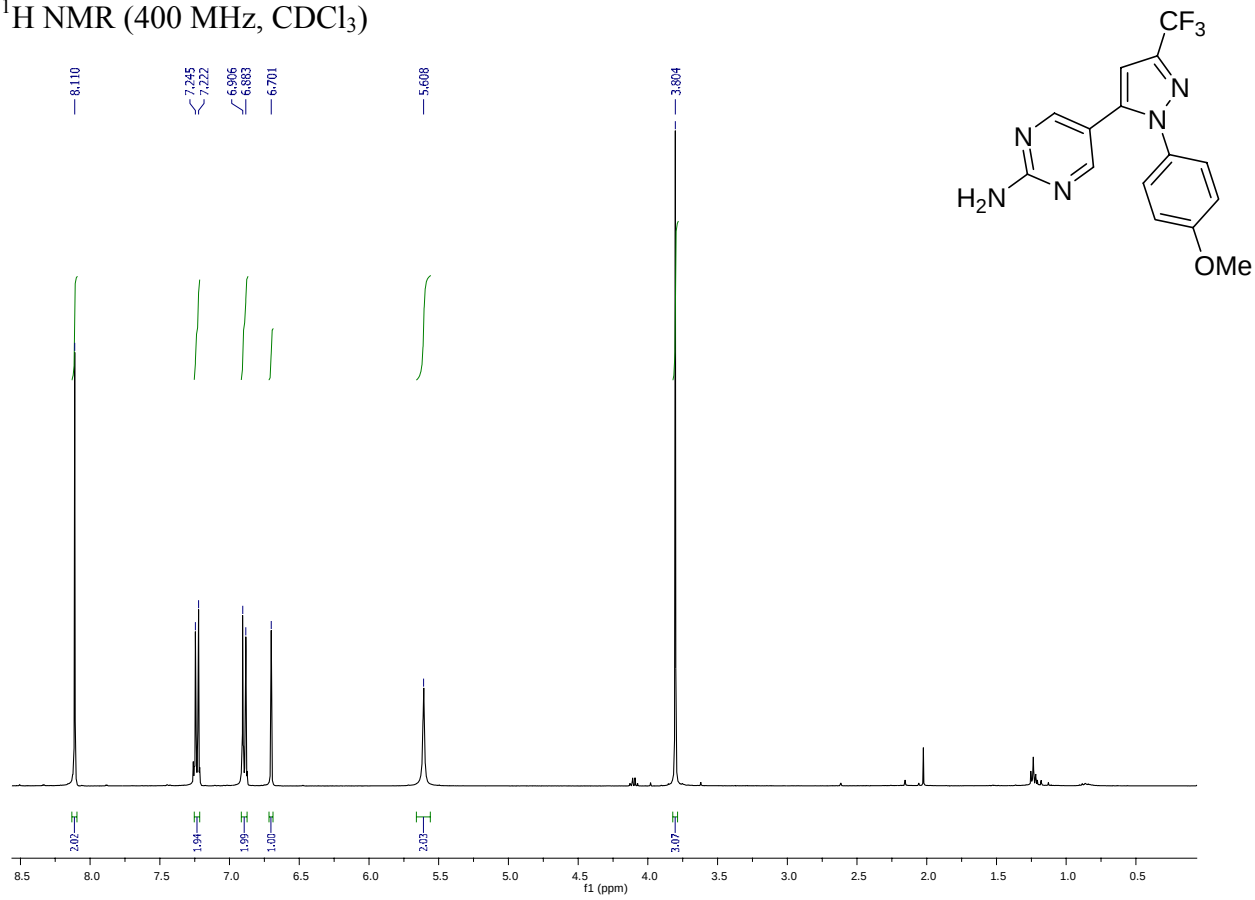


^{13}C NMR (100 MHz, $CDCl_3$)

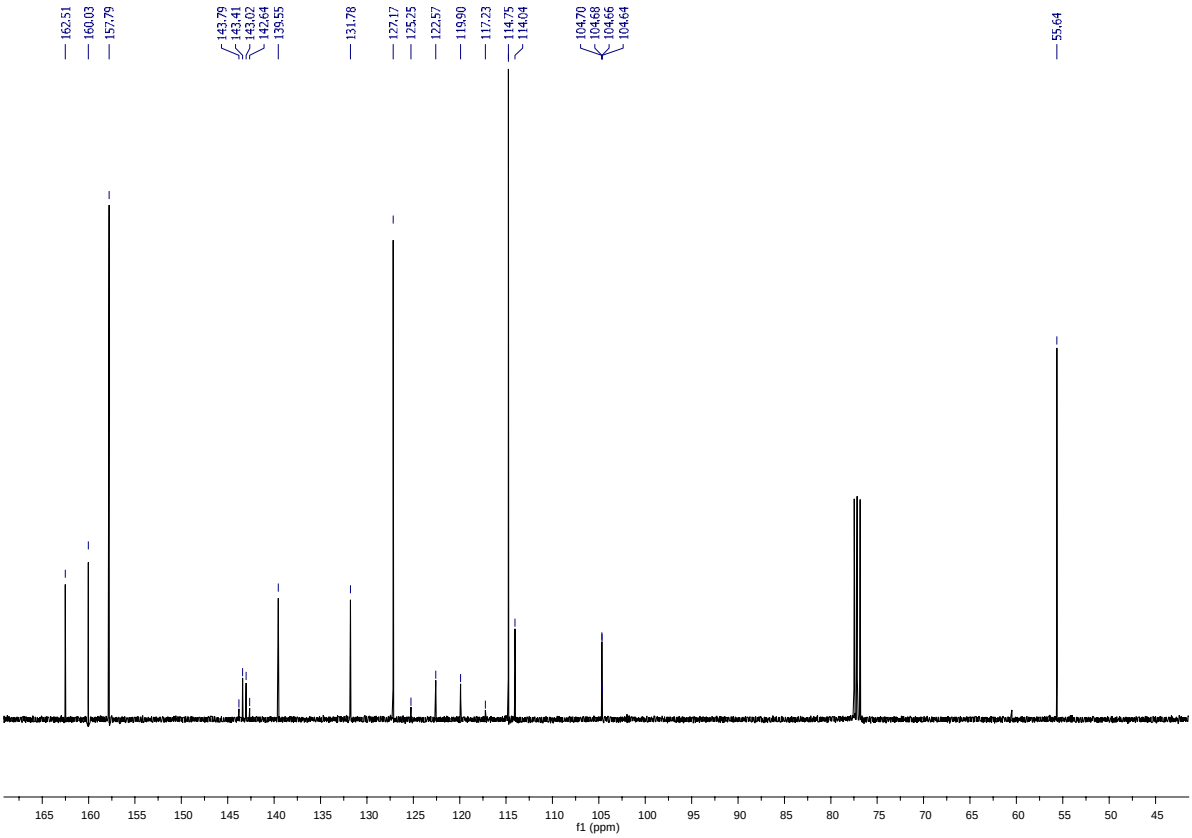


5-[3-(Trifluoromethyl)-1-(4-methoxyphenyl)-1*H*-pyrazol-5-yl]pyrimidin-2-amine (45)

^{1}H NMR (400 MHz, $CDCl_3$)

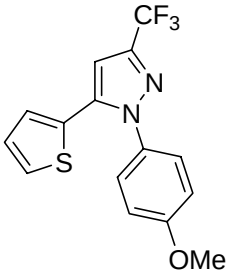


^{13}C NMR (100 MHz, $CDCl_3$)

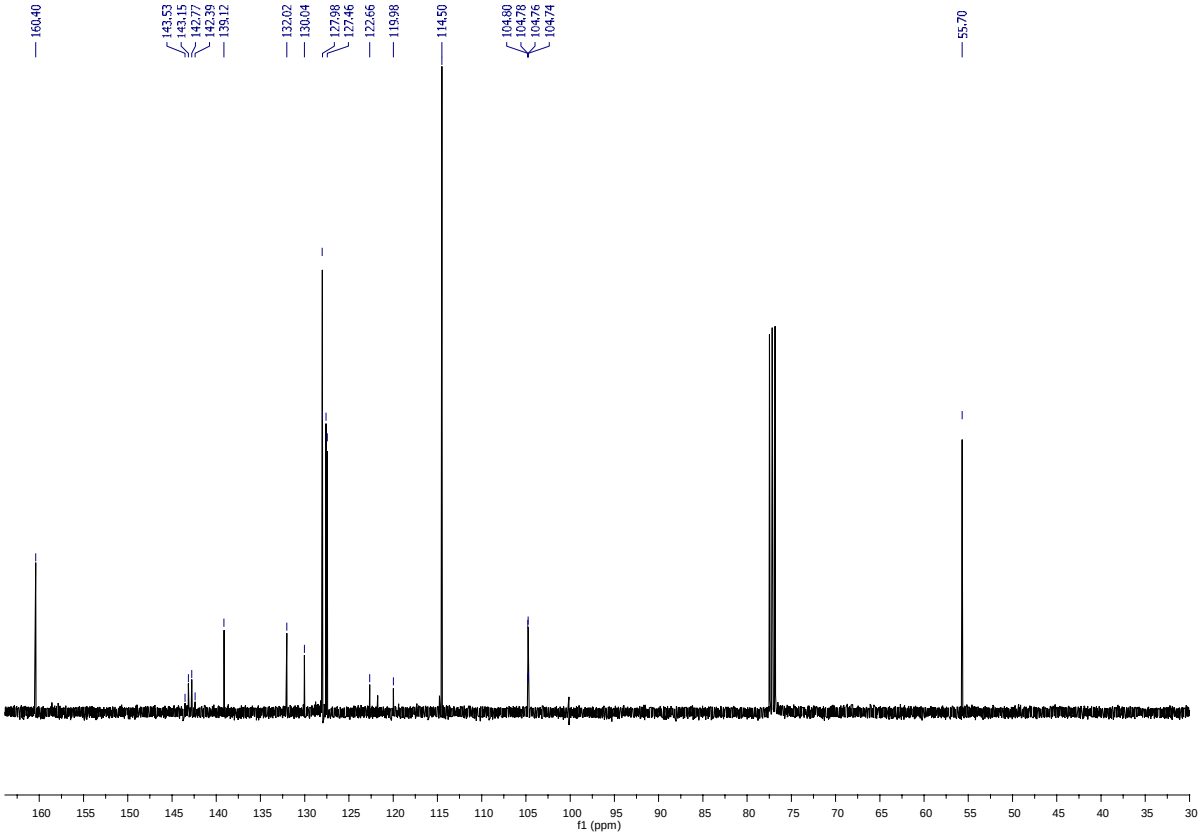


3-(Trifluoromethyl)-1-(4-methoxyphenyl)-5-(thiophen-2-yl)-1*H*-pyrazole (46)

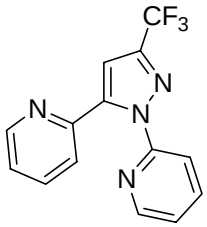
^{1}H NMR (400 MHz, $CDCl_3$)



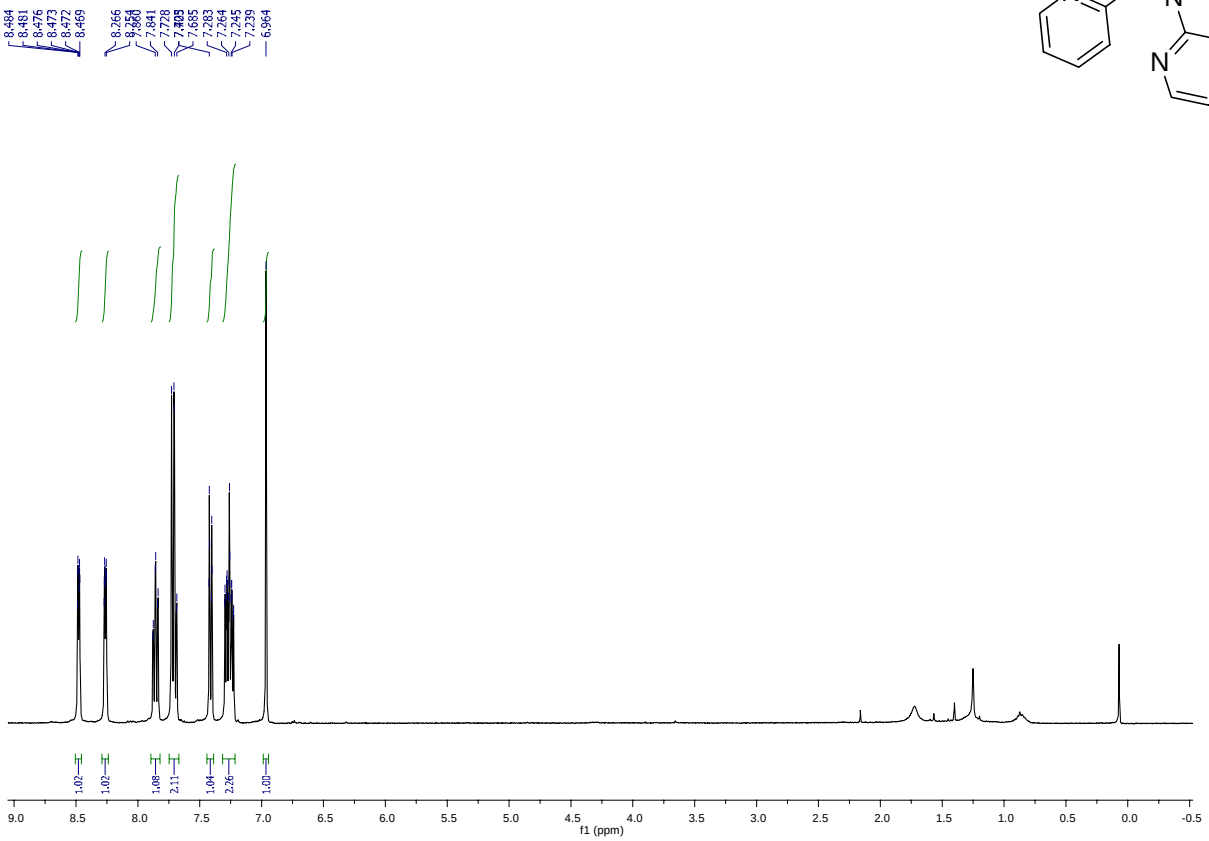
^{13}C NMR (100 MHz, $CDCl_3$)



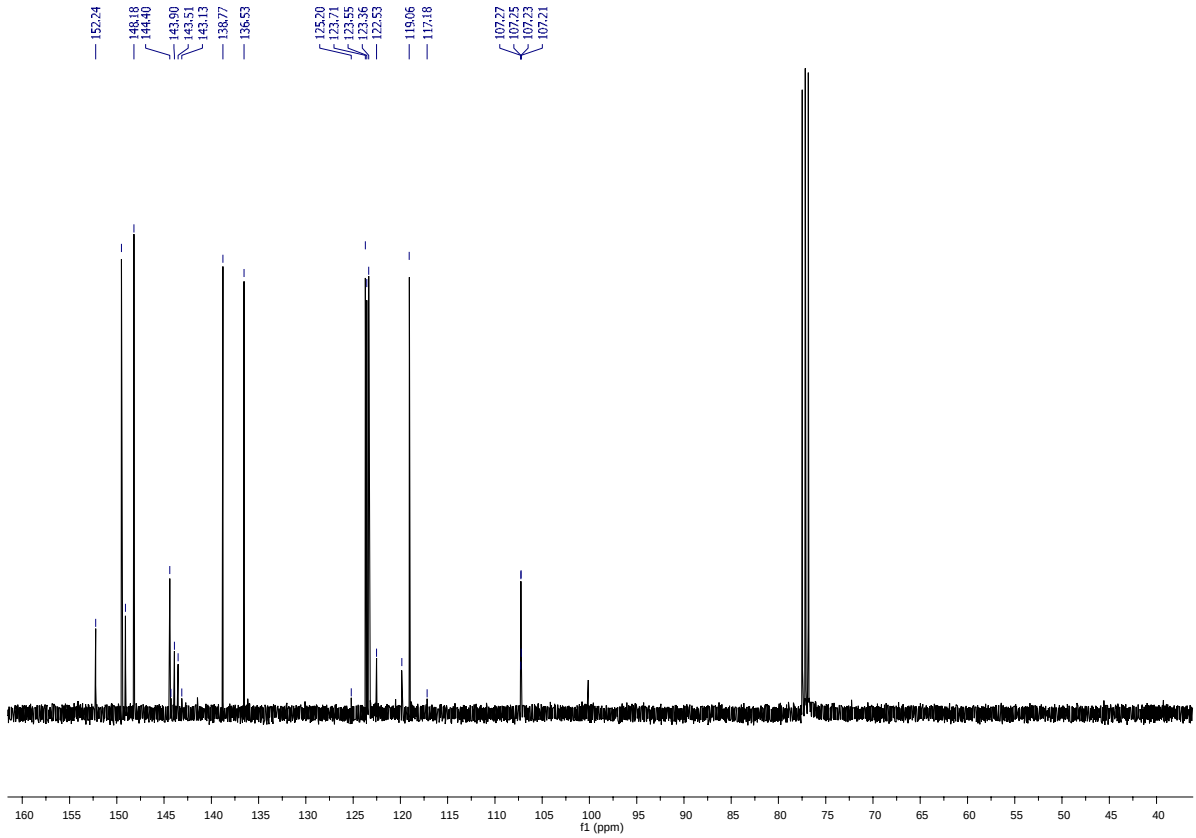
2-(3-[Trifluoromethyl)-1-(pyridin-2-yl)-1*H*-pyrazol-5-yl]pyridine (47)



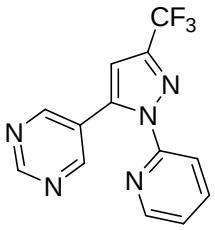
^{1}H NMR (400 MHz, $CDCl_3$)



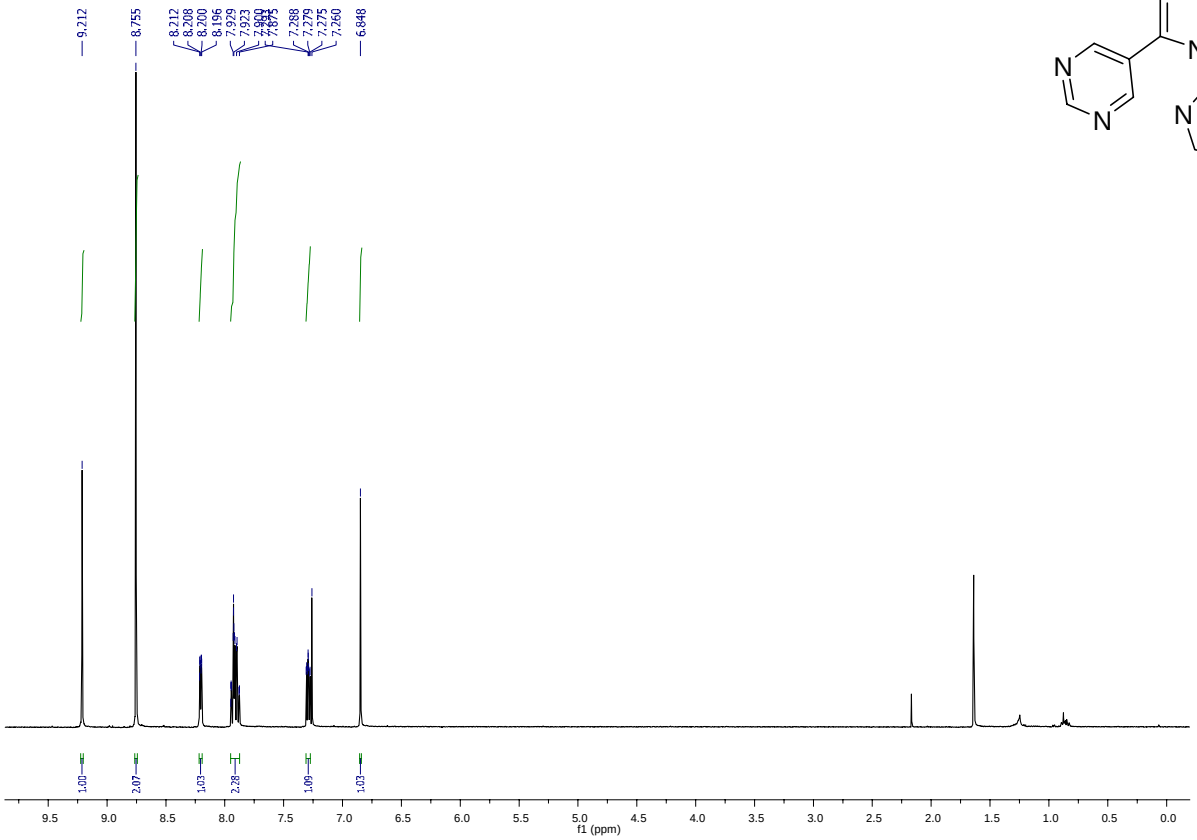
^{13}C NMR (100 MHz, $CDCl_3$)



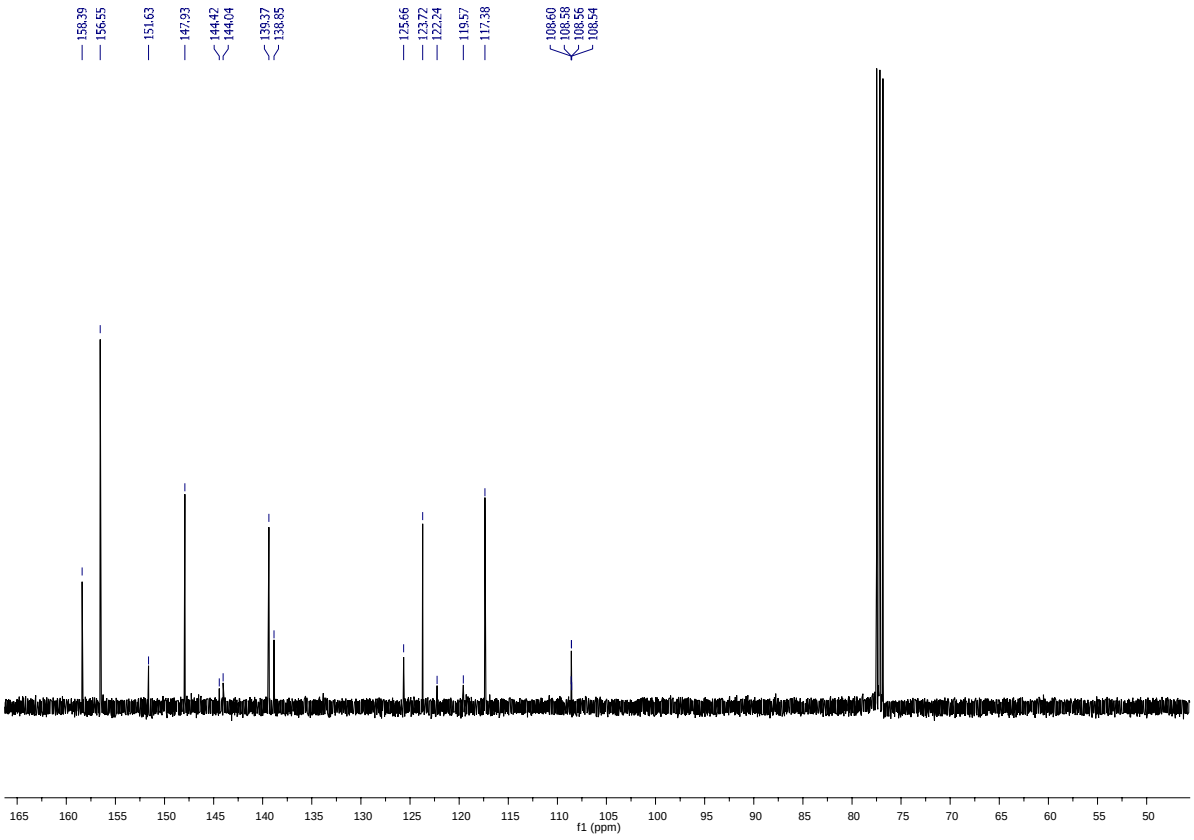
5-[3-(Trifluoromethyl)-1-(pyridin-2-yl)-1*H*-pyrazol-5-yl]pyrimidine (48)



^{1}H NMR (400 MHz, $CDCl_3$)

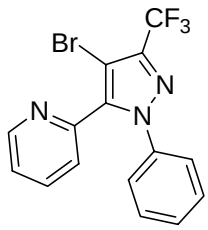


^{13}C NMR (100 MHz, $CDCl_3$)

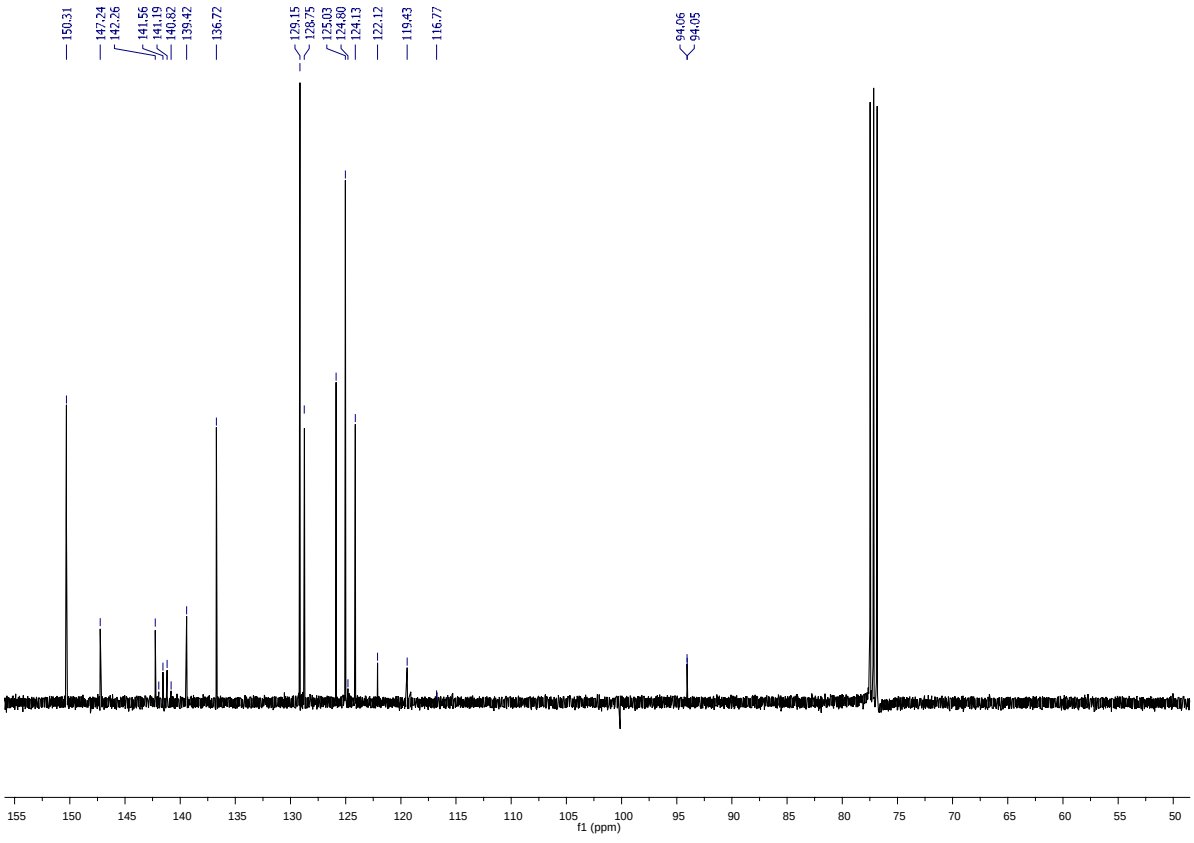


2-[4-Bromo-3-(trifluoromethyl)-1-phenyl-1*H*-pyrazol-5-yl]pyridine (49)

^{1}H NMR (400 MHz, $CDCl_3$)

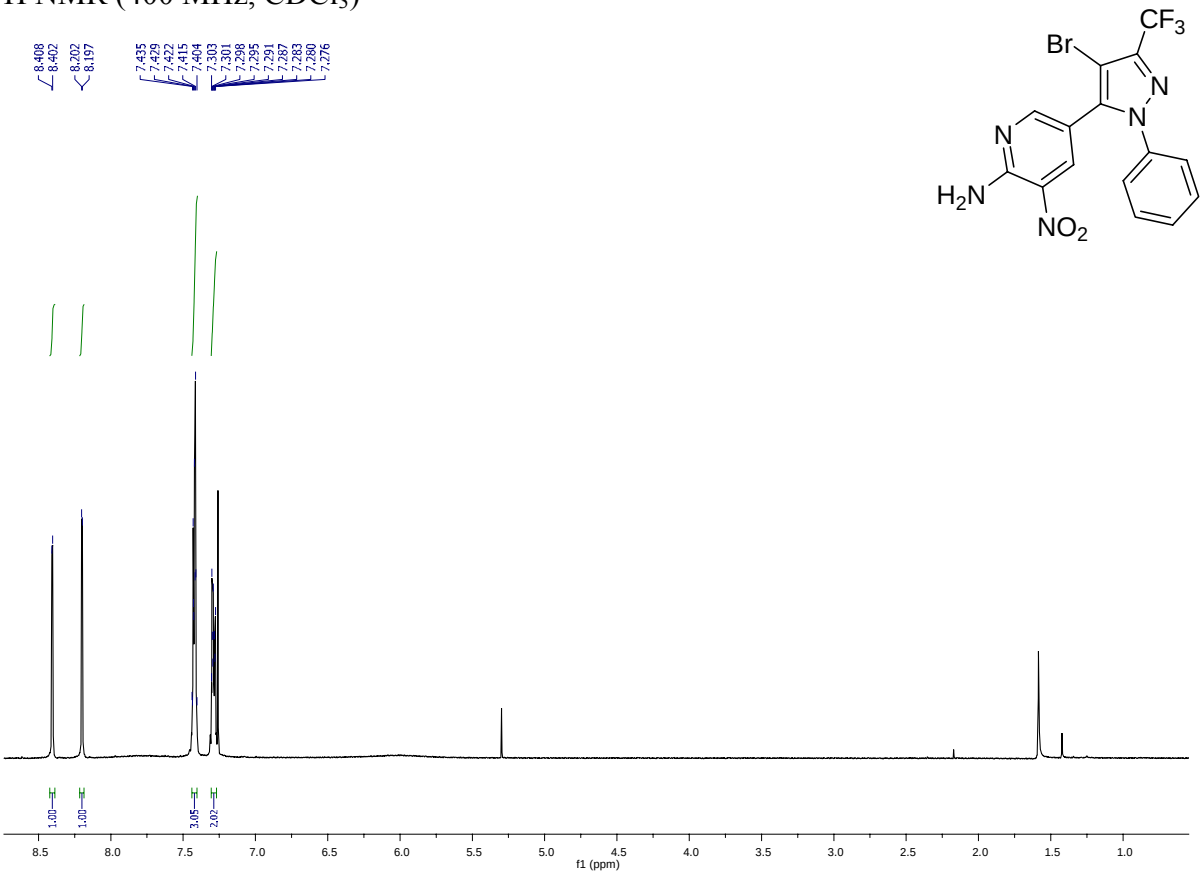


^{13}C NMR (100 MHz, $CDCl_3$)

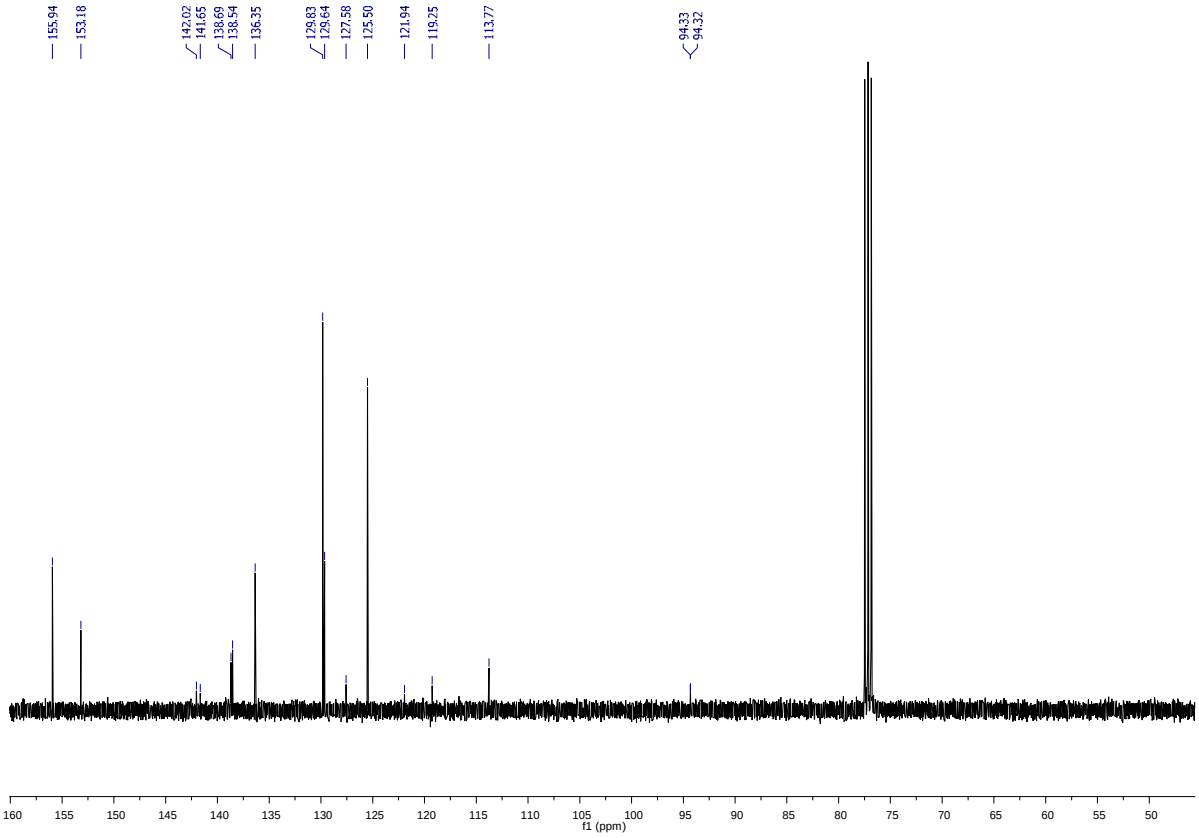


5-[4-Bromo-3-(trifluoromethyl)-1-phenyl-1*H*-pyrazol-5-yl]-3-nitropyridin-2-amine (50)

^{1}H NMR (400 MHz, $CDCl_3$)

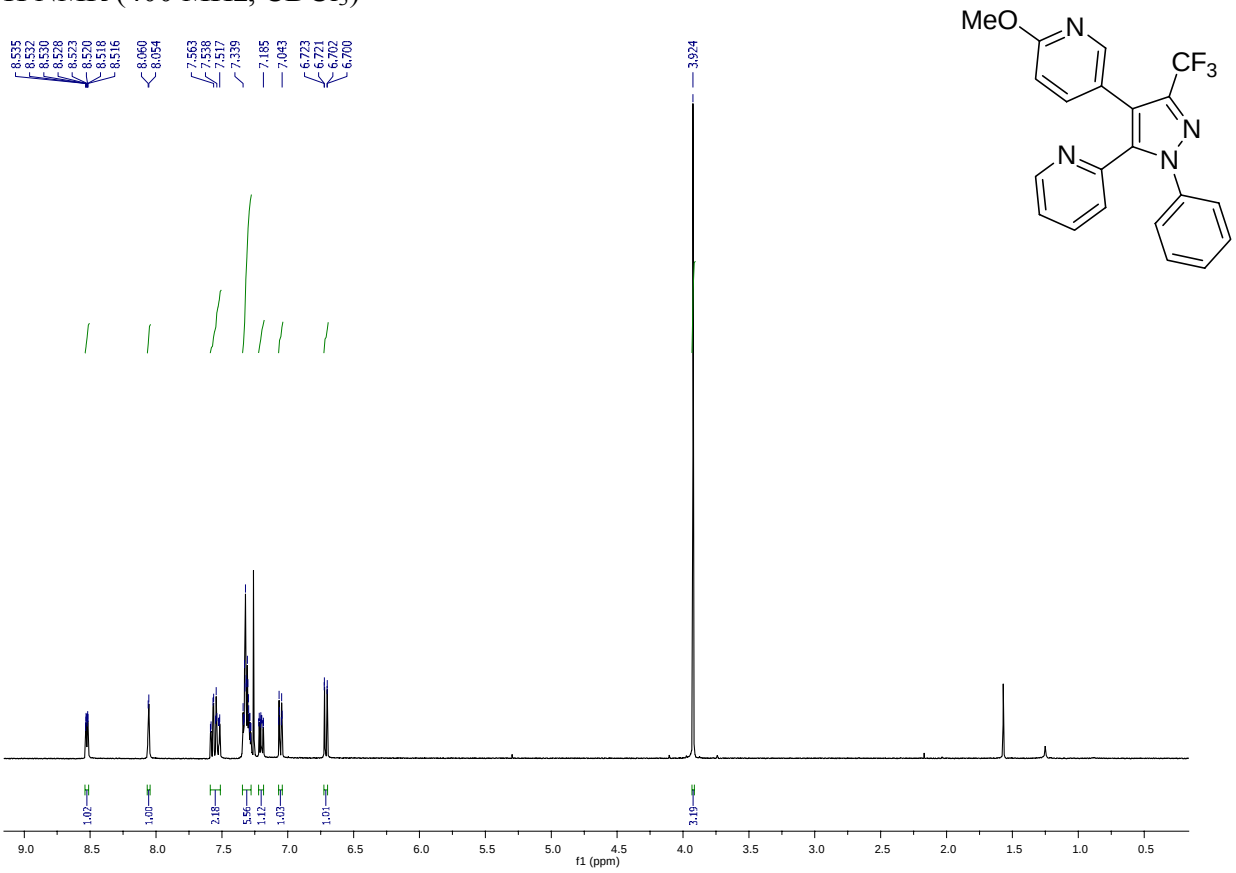


^{13}C NMR (100 MHz, $CDCl_3$)

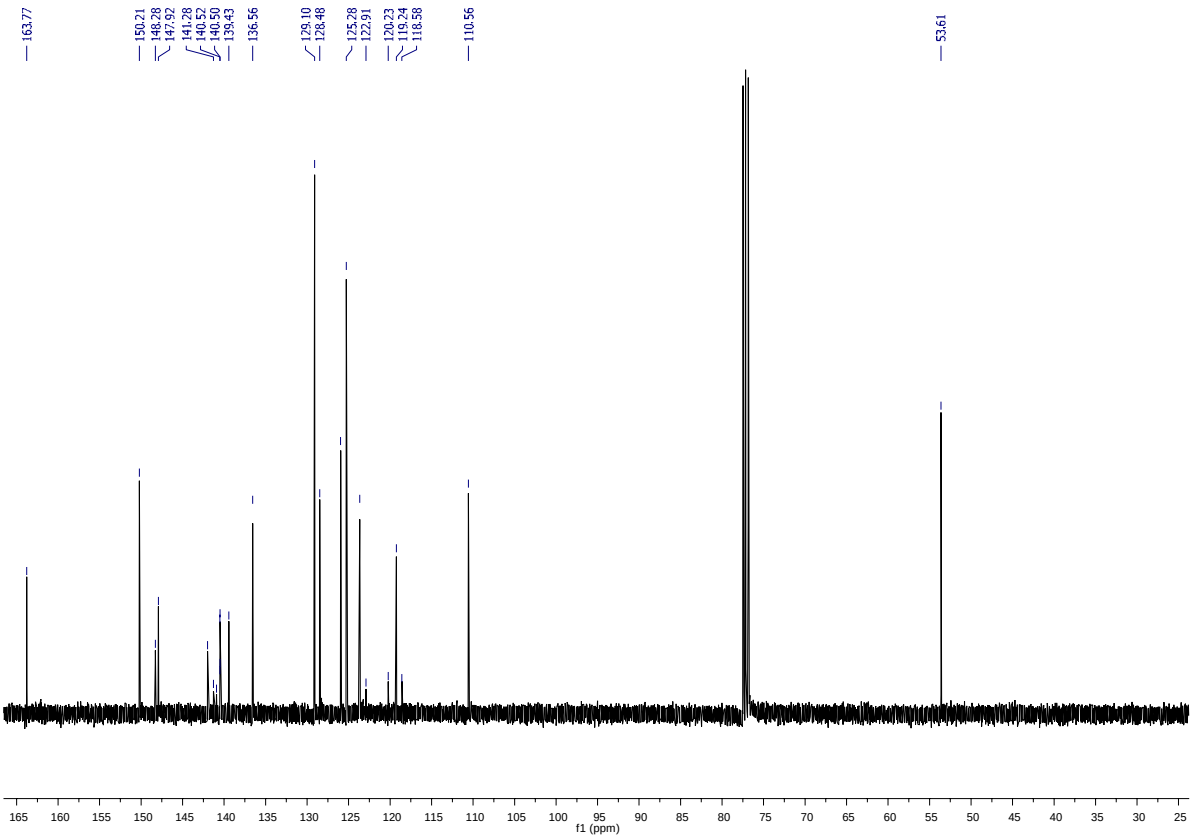


2-[3-(Trifluoromethyl)-4-(6-methoxypyridin-3-yl)-1-phenyl-1*H*-pyrazol-5-yl]pyridine (51)

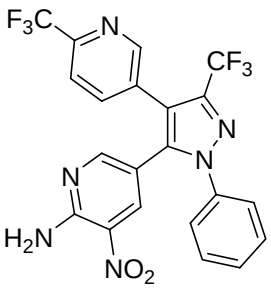
^{1}H NMR (400 MHz, $CDCl_3$)



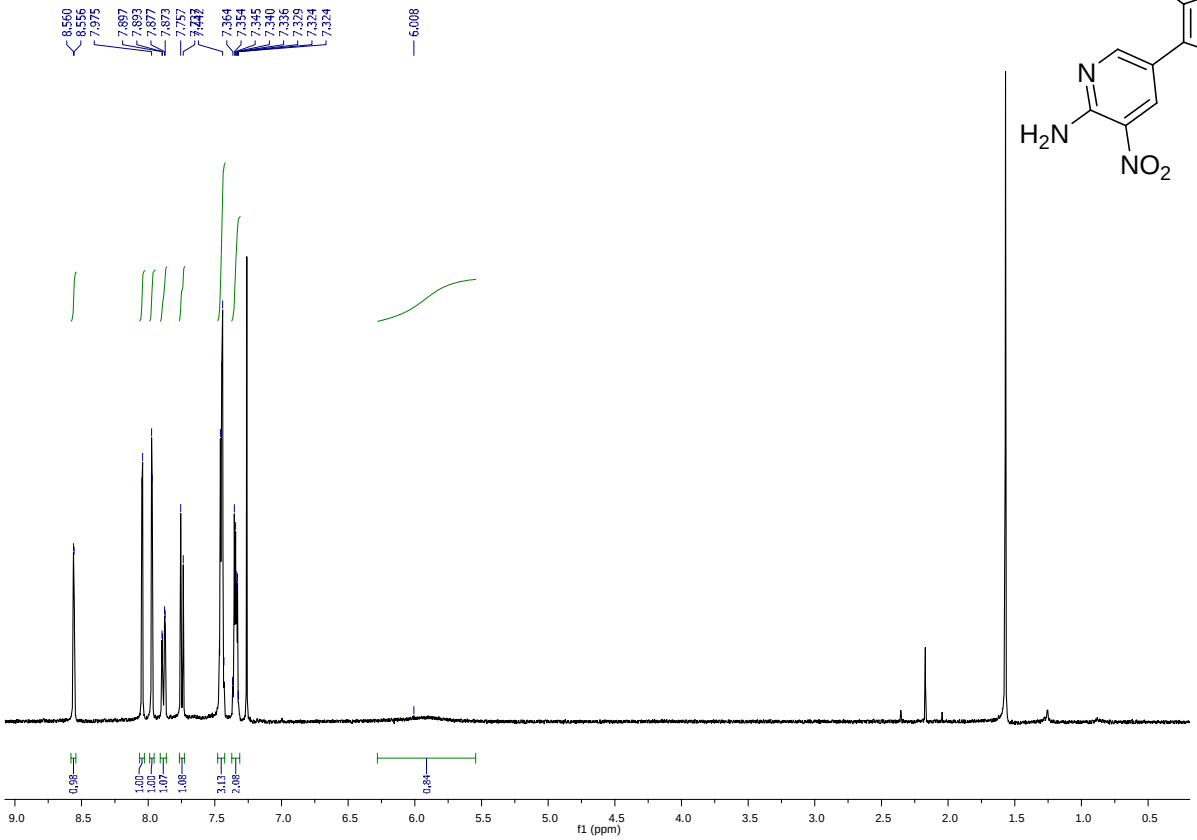
^{13}C NMR (100 MHz, $CDCl_3$)



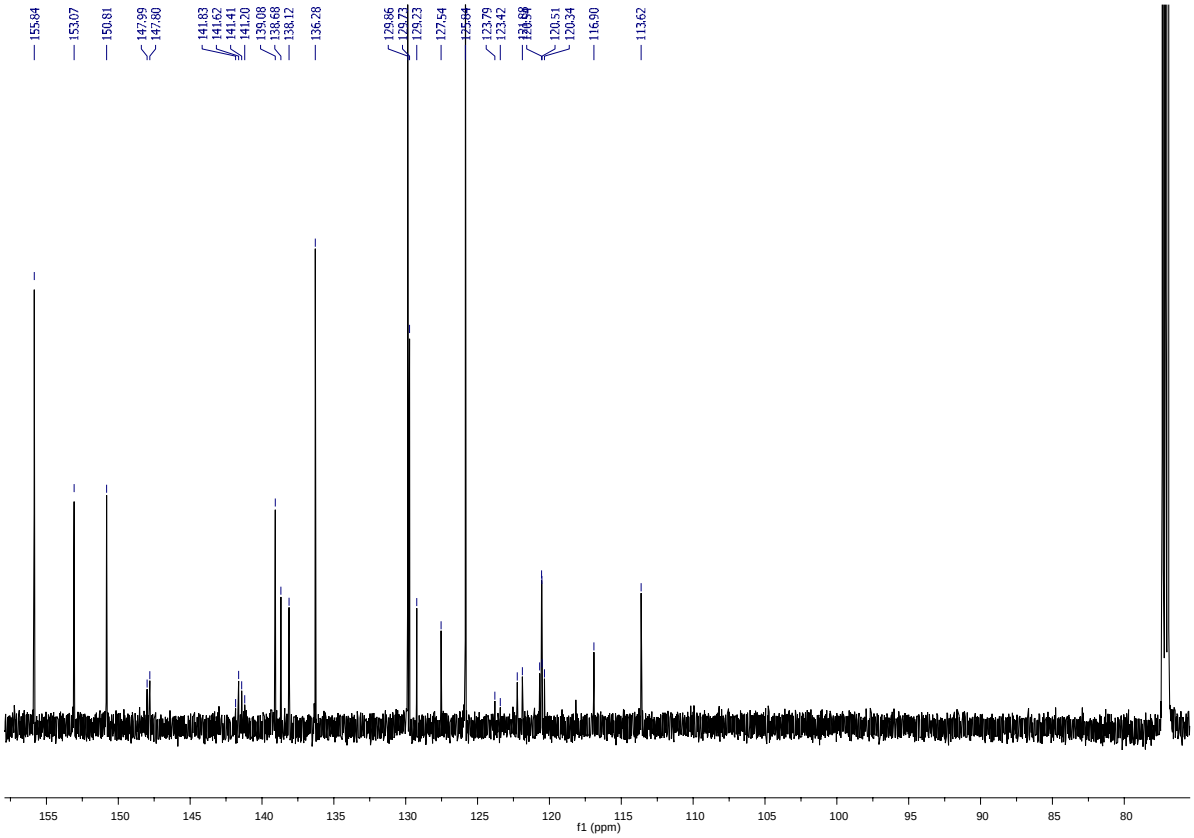
5-[3-(Trifluoromethyl)-4-(6-(trifluoromethyl)pyridin-3-yl)-1-phenyl-1*H*-pyrazol-5-yl]-3-nitropyridin-2-amine (52)



^{1}H NMR (400 MHz, $CDCl_3$)



^{13}C NMR (175 MHz, $CDCl_3$)



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4 Commercially available from Apollo Scientific.