Ambient Temperature Nitrogen Directed Difluoroalkynylborane Carboni-Lindsey Cycloaddition Reactions

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Contents

General Procedures

Cycloaddition reactions were conducted in non flame-dried glassware open to air unless otherwise specified. Flash chromatography was performed on silica gel (Fluorochem Davisil silica gel 43-60 or Fischer Scientific Florisil® general purpose grade). Thin layer chromatography was performed on aluminium backed plates pre-coated with silica (0.2 mm, Merck DC-alufolien Kieselgel 60 F254) and were developed using standard visualizing agents: Ultraviolet light or potassium permanganate.

$^{1}H/^{13}C$ NMR spectra were recorded on Bruker AC-250 or AV1-250 instruments or AMX-400 or AV1-400 instruments or DRX-500 instrument. ^{1}H: Chemical shifts are reported in ppm with the solvent resonance as the internal standard ($CHCl_3$: δ 7.27 ppm). Data are reported as follows: chemical shift, multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, br=broad, m=multiplet), integration, coupling constants (*J*) in Hz, and assignment. ^{13}C NMR spectra were acquired with complete proton decoupling. Chemical shifts are reported in ppm with the solvent resonance as the internal standard ($CDCl_3$: δ 77.0 ppm). Infrared (FTIR) spectra were recorded on a Perkin Elmer Paragon 100 FTIR spectrophotometer, l max in cm^{-1}. Bands are characterized as broad (br), strong (s), medium (m) and weak (w). Samples were recorded as thin films using sodium chloride plates as a DCM solution. Low resolution mass spectra were recorded on Micromass Autospec operating in E.I mode. High-resolution mass spectra (HRMS) recorded for accurate mass analysis, were performed on either a MicroMass LCT operating in Electrospray mode (TOF ES+ or ES-) or a MicroMass Autospec operating in EI (EI+) mode. Melting points were performed on recrystallised solids and 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). Potassium alkynyltrifluoroborates,[1] tetrazines[2] and triazine[3] were prepared according to literature procedures or were purchased from commercial sources.

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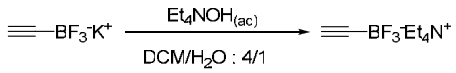
[1] a) Molander, G.; Katona, B.W.; Machrouhi, F. *J. Org. Chem.* **2002**, *67*, 8416. b) Yamamoto, Y.; Hattori, K.; Ishii, J.; Nishiyama, H. *Tetrahedron*. **2006**, *62*, 4294.

[2] a) Boger, D.; Coleman, R.S.; Panek, J. S.; Huber, F.X.; Sauer, J. *J. Org. Chem.* **1985,** *50*, 5377. b) Coburn, M.D.; Buntain, G.A.; Harris, B.W.; Hiskey, M.A.; Lee, K.Y.; Ott, D.G., *J Heterocycl. Chem.* **1991**, *28*, 2049. c) Latosh, N.I.; Rusinov, G.L.; Ganebnykh, I.N.; Chupakhin, O.N. *Russ. J. Org. Chem.* **1999**, *35*, 1363.

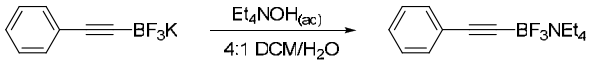
[3] Sauer, J.; Heldmann, D.K.; Pabst, G.R.; *Eur. J. Org. Chem*. **1999**, 1, 313.

General procedure for the synthesis of tetraethylammonium alkynyltrifluoroborate salts as exemplified by the synthesis of tetraethylammonium ethynyltrifluoroborate



A 25% by volume solution of tetraethylammonium hydroxide in water (5 mL, 8.8 mmol) was added to a suspension of potassium ethynyltrifluoroborate (1.0 g, 7.6 mmol) in a 4:1 mixture of DCM and water (25 mL). The biphasic mixture was stirred for 30 minutes, by this time all of the starting material had dissolved. The organic layer was separated and the aqueous layer washed with DCM (2 x 50 mL). The combined organic fractions were dried over $MgSO_4$ and the solvent evaporated to give tetraethylammonium ethynyltrifluoroborate (1.47 g, 86%) as a colourless solid. M.p. 211-213 °C (dec.). ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.32-1.39 (12H, t, J = 7.5 Hz), 1.83 (1H, br s, C-H), 3.28-3.37 (8H, q, J = 7.5 Hz, CH_2). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 7.5, 52.5, 77.2. ^{19}F NMR (235.1 MHz, $CDCl_3$): δ -134.8. FTIR: 3624 (w), 3260 (m), 2995 (m), 2053 (m), 1631 (w), 1487 (s), 1397 (s) cm^{-1}. HRMS (ESI) [M^-] calcd for C_2HBF_3: 93.0119. Found: 93.0123.

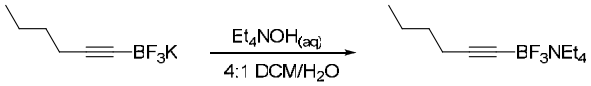
Synthesis of tetraethylammonium (phenylethynyl)trifluoroborate.



Following the general procedure, a 25% by volume solution of tetraethylammonium hydroxide in water (2.9 mL, 5.0 mmol) was added to a suspension of potassium (phenylethynyl)trifluoroborate (1.0 g, 4.8 mmol) in a 4:1 mixture of DCM and water (25 mL). Tetraethylammonium (phenylethynyl)trifluoroborate (1.41 g, 98%) was isolated as colourless solid. M.p. 123-124 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.25 (12H, t, J = 7.5 Hz, CH_3), 3.25 (8H, q, J = 7.5 Hz, CH_2), 7.16-7.24 (3H, m, CH), 7.32-7.40 (2H, m, CH). ^{13}C NMR (62.8 MHz, $CDCl_3$): δ 7.4, 52.4, 90.4 (br), 125.5, 127.1, 128.2, 131.5. ^{19}F NMR (235.1 MHz, $CDCl_3$): δ -133.8. FTIR: 2984 (w), 2939 (w),

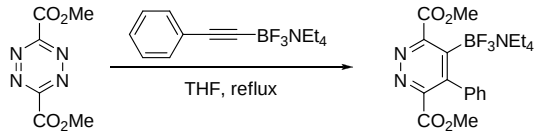
1489 (m), 1442 (w), 1396 (m), 1371 (w), 1225 (m), 1176 (m), 1009 (s), 988 (s) cm^{-1}. HRMS (ESI) [M^-] calcd for $C_8H_5BF_3$: 169.0436. Found: 169.0432.

Synthesis of tetraethylammonium (hex-1-ynyl)trifluoroborate.



Following the general procedure, a 25% by volume solution of tetraethylammonium hydroxide in water (3.2 mL, 5.7 mmol) was added to a suspension of potassium (1-hexyn-1-yl)trifluoroborate (1.0 g, 5.3 mmol) in a 4:1 mixture of DCM and water (25 mL). Tetraethylammonium trifluoro(hex-1-ynyl)borate (1.4 g, 88%) was isolated as a low melting colourless solid. ^{1}H NMR (250 MHz, $CDCl_3$): δ 0.88 (3H, t, J = 7.0 Hz, CH_3), 1.30-1.54 (16H, m, CH_3, CH_2), 2.13 (2H, t, J = 7.0 Hz, CH_2), 3.34 (8H, q, J = 7.0 Hz, CH_2). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 7.4, 13.7, 19.3, 22.1, 31.7, 52.4, 90.5 (br). ^{19}F NMR (235.1 MHz, $CDCl_3$): δ -133.0. FTIR: 3601 (w), 2956 (m), 2932 (m), 2360 (w), 1485 (m), 1460 (m), 1365 (m), 1174 (w), 1092 (s), 998 (s) cm^{-1}. HRMS (ESI) [M^-] calcd for $C_6H_9BF_3$: 149.0751. Found: 149.0749.

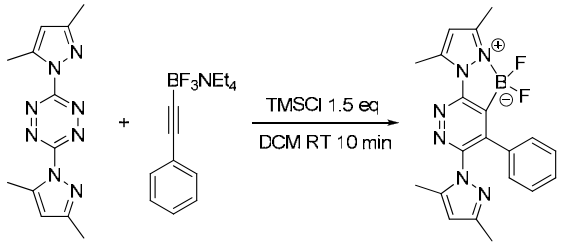
Synthesis of tetraethylammonium dimethyl 4-(trifluoroborate)-5-phenyl-pyridazine-3,6-dicarboxylate.



A solution of dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate (50 mg, 0.25 mmol) and tetraethylammonium (phenylethynyl)trifluoroborate (75 mg, 0.25 mmol) in THF (2 mL) was heated at reflux for 1 hour. The volatiles were removed in vacuo to give the title product tetraethylammonium dimethyl 4-(trifluoroborate)-5-phenylpyridazine-3,6-dicarboxylate (117 mg, 99%) as a yellow oil. Due to the unstable nature of the

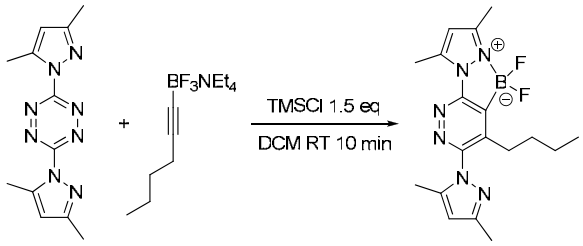
product to column chromatography no further purification was attempted. ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.07 (12H, t, *J* = 7.5 Hz), 3.00 (8H, q, *J* = 7.5 Hz, CH_2), 3.55 (3H, s, CH_3), 3.89 (3H, s, CH_3), 7.29 (5H, br, CH). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 7.2, 52.2, 52.4, 52.5, 127.3, 127.7, 128.8, 137.5, 143.9, 154.3, 159.8, 167.1, 169.0. ^{19}F NMR (235.1 MHz, $CDCl_3$): δ -134.0. FTIR: 2997 (w), 2951 (w), 1740 (s), 1536 (w), 1489 (m), 1444 (m), 1397 (m), 1356 (m), 1307 (w), 1205 (m), 1174 (m), 1104 (m), 1052 (s) cm^{-1}. HRMS (ESI) [M$^-$] calcd for $C_{14}H_{11}BN_2O_4F_3$: 339.0764. Found: 339.0748.

General procedure for TMSCl-promoted cycloadditions as exemplified by the synthesis of 13.



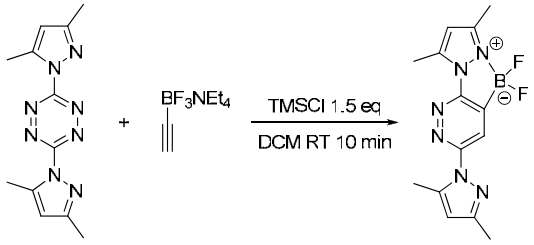
To a solution of 3,6-bis(3,5-dimethyl-1*H*-pyrazol-1-yl)-1,2,4,5-tetrazine (50 mg, 0.185 mmol) and tetraethylammonium (phenylethynyl)trifluoroborate (83 mg, 0.277 mmol) in DCM (1 mL) was added dropwise distilled TMSCl (35 µL, 0.277 mmol). A vigorous reaction took place with production of nitrogen. The reaction was stirred at room temperature until the red colour of the tetrazine had faded (~10 min). The solvent was then evaporated and the residue dry loaded and purified chromatographically over silica gel (gradient; starting with petroleum ether, ending with 50% ethyl acetate in petroleum ether). Compound **13** was isolated as a colourless solid (73 mg, 99%). M.p: 161.0-161.8 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ 2.01 (3H, s, CH_3), 2.20 (3H, s, CH_3), 2.53 (3H, s, CH_3), 2.96 (3H, s, CH_3), 5.90 (1H, s, CH), 6.31 (1H, s, CH), 7.34 (5H, s, Ar). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 11.2, 11.3, 12.8, 13.5, 107.0, 112.3, 128.4, 128.5, 129.3, 133.8, 141.2, 142.4, 143.9, 148.5, 150.2, 153.6, 158.1. ^{19}F NMR (235.1 MHz, $CDCl_3$): δ -150.8. FTIR: 2928 (w), 1575 (m), 1560 (m), 1498 (m), 1474 (m), 1420 (s), 1263 (w), 1114 (s) cm^{-1}. HRMS: (ESI) [MH$^+$] calcd for $C_{20}H_{20}BN_6F_2$: 393.1811, found 393.1826.

Synthesis of 12.



Following the general procedure, a solution of 3,6-bis(3,5-dimethyl-1*H*-pyrazol-1-yl)-1,2,4,5-tetrazine (50 mg, 0.185 mmol) and tetraethylammonium (hex-1-ynyl)trifluoroborate (77 mg, 0.277 mmol) in DCM (1 mL) was treated with TMSCl (35 µL, 0.277 mmol). Chromatographic purification over silica gel (gradient; starting with petroleum ether, ending with 50% ethyl acetate in petroleum ether). Compound **12** was isolated as a colourless solid (62 mg, 89%). M.p: 118.0-118.6 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ 0.82 (3H, t, J = 7.0 Hz, CH_3), 1.19-1.34 (2H, m, CH_2), 1.34-1.49 (2H, m, CH_2), 2.30 (3H, s, CH_3), 2.32 (3H, s, CH_3), 2.54 (3H, s, CH_3), 2.82-2.93 (5H, m, CH_3 + CH_2), 6.05 (1H, s, CH), 6.27 (1H, s, CH). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 11.2, 11.8, 12.7, 13.5, 13.6, 22.6, 30.4, 31.2, 106.8, 112.0, 141.5, 142.2, 147.2, 148.3, 150.1, 155.1, 157.5. ^{19}F NMR (235.1 MHz, $CDCl_3$): δ -154.2. FTIR: 2959 (m), 2931 (m), 2872 (w), 2562 (w), 1474 (m), 1418 (s), 1110 (s) cm^{-1}. HRMS: (ESI) [MH^+] calcd for $C_{18}H_{24}BN_6F_2$: 373.2124, found 373.2105.

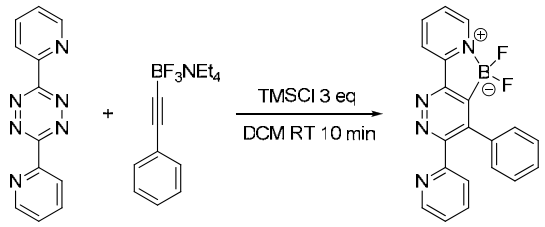
Synthesis of 14



Following the general procedure, a solution of 3,6-bis(3,5-dimethyl-1*H*-pyrazol-1-yl)-1,2,4,5-tetrazine (50 mg, 0.185 mmol) and tetraethylammonium ethynyltrifluoroborate (62 mg, 0.277 mmol) in DCM (1 mL) was treated with TMSCl (35 µL, 0.277 mmol). Chromatographic purification over silica gel (gradient; starting with petroleum ether, ending with ethyl acetate). Compound **14** was isolated as a

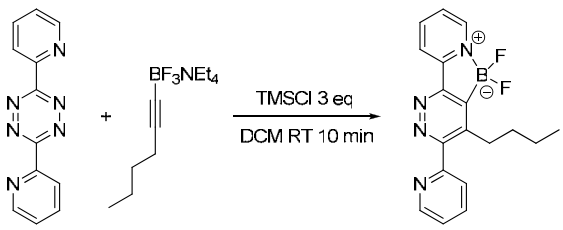
colourless solid (44 mg, 75 %). M.p: 213.0-214.0 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ 2.32 (3H, s, CH_3), 2.53 (3H, s, CH_3), 2.72 (3H, s, CH_3), 2.92 (3H, s, CH_3), 6.07 (1H, s, CH), 6.27 (1H, s, CH), 8.42 (1H, s, CH) ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 11.2, 12.7, 13.6, 14.8, 110.1, 112.0, 125.4, 141.8, 142.2, 148.1, 151.3, 155.9, 156.6. ^{19}F NMR (235.1 MHz, $CDCl_3$): δ -154.8. FTIR: 2360 (s), 2341 (m), 1577 (m), 1425(s), 1291 (m), 1103 (s) cm^{-1}. HRMS: (EI) [MH^+] calcd for $C_{14}H_{15}BN_6F_2$: 316.1419, found 316.1419.

Synthesis of 16.



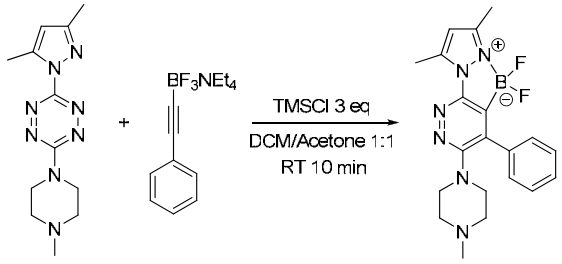
Following the general procedure, a solution of 3,6-di-2-pyridyl-1,2,4,5-tetrazine (43 mg, 0.185 mmol) and tetraethylammonium (phenylethynyl)trifluoroborate (83mg, 0.277 mmol) in DCM (1 mL) was treated with TMSCl (70 µL, 0.554 mmol). The solvent was evaporated and the residue filtered over a small pad of florisil (eluant: ethyl acetate). Compound **16** was isolated as a colourless solid (57 mg, 85 %). M.p: 216.0-217.0 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.22-7.45 (6H, m, Ar), 7.68-7.82 (3H, m, Ar), 8.36 (1H, dt, *J* = 8.0 Hz, 1.0 Hz, Ar), 8.51 (1H, d, *J* = 5.0 Hz, Ar), 8.67 (1H, d, *J* = 5.0 Hz, Ar), 8.72 (1H, d, *J* = 8.0 Hz, Ar). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 120.3, 123.3, 125.2, 126.7, 128.2, 128.3, 129.4, 136.4, 136.5, 142.0, 143.2, 144.7, 149.1, 152.5, 156.3, 157.9, 159.7. ^{19}F NMR (235.1 MHz, $CDCl_3$): δ -154.0. FTIR: 3060 (m), 2360 (w), 2227 (w), 1627 (s), 1587 (m), 1492 (s), 1382 (s), 1159 (s), 1092 (s) cm^{-1}. HRMS: (ESI) [MH^+] calcd for $C_{20}H_{14}BN_4F_2$: 359.1280, found 359.1274.

Synthesis of 17.



Following the general procedure, a solution of 3,6-di-2-pyridyl-1,2,4,5-tetrazine (43 mg, 0.185 mmol) and tetraethylammonium (hex-1-ynyl)trifluoroborate (77 mg, 0.277 mmol) in DCM (1 mL) was treated with TMSCl (70 µL, 0.554 mmol). The solvent was evaporated and the residue filtered over a small pad of florisil (eluant: ethyl acetate). Compound **17** was isolated as a colourless solid (52 mg, 84 %). M.p: 120.7-121.5 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ 0.83 (3H, t, *J* = 7.0 Hz, CH_3), 1.22-1.40 (2H, m, CH_2), 1.50-1.63 (2H, m, CH_2), 3.08-3.20 (2H, m, CH_2), 7.42 (1H, td, *J* = 6.5, 1.5 Hz, Ar), 7.80 (1H, t, *J* = 6.5 Hz, Ar), 7.85- 8.02 (2H, m, Ar), 8.37 (1H, td, *J* = 8.0, 1.5 Hz, Ar), 8.60-8.80 (3H, m Ar). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 13.6, 22.8, 31.5, 32.4, 120.1, 123.5, 124.9, 126.3, 136.8, 141.9, 144.4, 146.1, 148.6, 152.9, 156.7, 157.4, 160.5. ^{19}F NMR (235.1 MHz, $CDCl_3$): δ -157.0. FTIR: 2958 (m), 2870 (w), 2360 (s), 2341 (m), 1628 (m), 1490 (s), 1388 (s), 1114 (s) cm^{-1}. HRMS: (ESI) [MH^+] calcd for $C_{18}H_{18}BN_4F_2$: 339.1593, found 339.1591.

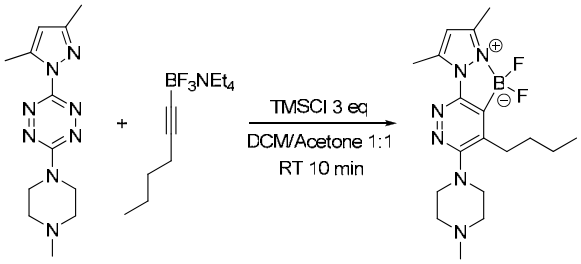
Synthesis of 19.



Following the general procedure, a solution of 3-(3,5-dimethyl-1*H*-pyrazol-1-yl)-6-(4-methyl-1-piperazinyl)-1,2,4,5-tetrazine (51 mg, 0.185 mmol) and tetraethyl-ammonium (phenylethynyl)trifluoroborate (83 mg, 0.277 mmol) in a 1:1 mixture of DCM/acetone (2 mL) was added TMSCl (70 µL, 0.554 mmol). Chromatographic purification over silica gel (gradient; starting with acetone, ending acetone/Et_3N 95:5). Compound **19** was isolated as a colourless solid (67 mg, 91 %). M.p: 213.4-214.2 °C (dec.). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.29 (3H, s, CH_3), 3.35-2.42 (4H, m, CH_2), 2.47 (3H, s, CH_3), 2.89 (3H, s, CH_3), 3.19-3.30 (4H, m, CH_2), 6.21 (1H, s, CH_3), 7.42 (1H, t, *J* = 7.5 Hz), 7.49 (2H, t, *J* = 7.5 Hz), 7.78 (2H, d, *J* = 7.5 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 11.0, 12.6, 46.0, 48.9, 54.6, 111.4, 127.9, 128.7, 128.9, 136.2, 138.1, 141.0, 146.8, 155.3, 160.5. ^{19}F NMR (235.1 MHz, $CDCl_3$): δ -151.0. FTIR: 2938 (m),

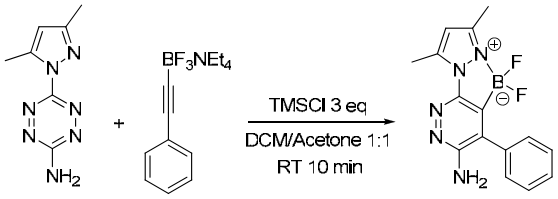
2845 (m), 2799 (m), 2360 (m), 1573 (m), 1416 (s), 1261 (s), 1117 (s), 1007 (m) cm^{-1}. HRMS: (ESI) [MH^+] calcd for $C_{20}H_{24}BN_6F_2$: 397.2124, found 397.2118.

Synthesis of 20.



Following the general procedure, a solution of 3-(3,5-dimethyl-1*H*-pyrazol-1-yl)-6-(4-methyl-1-piperazinyl)-1,2,4,5-tetrazine (51 mg, 0.185 mmol) and tetraethyl-ammonium (hex-1-ynyl)trifluoroborate (77 mg, 0.277 mmol) in a 1:1 mixture of DCM/acetone (2 mL) was added TMSCl (70 µL, 0.554 mmol). Chromatographic purification over silica gel (gradient; starting with acetone, ending acetone/Et_3N 95:5). Compound **20** was isolated as a colourless solid (54 mg, 80 %). M.p: 80.8-82.2 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ 0.98 (3H, t, J = 7.0 Hz, CH_3), 1.35-1.53 (2H, m, CH_2), 1.68-1.84 (2H, m, CH_2), 2.40 (3H, s, CH_3), 2.51 (3H, s, CH_3), 2.60-2.70 (4H, m, CH_2), 2.72-2.82 (2H, m, CH_2), 2.87 (3H, s, CH_3), 3.28-3.38 (4H, m, CH_2), 6.20 (1H, s, CH). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 11.0, 12.6, 13.8, 23.1, 30.5, 31.5, 46.0, 50.6, 55.0, 111.4, 141.2, 143.3, 146.9, 155.5, 163.2. ^{19}F NMR (235.1 MHz, $CDCl_3$): δ -153.8. FTIR: 2959 (m), 2934 (m), 2846 (w), 2793 (w), 2360 (m), 2341 (w), 1568 (w), 1411 (s), 1108 (m) cm^{-1}. HRMS: (ESI) [MH^+] calcd for $C_{18}H_{28}BN_6F_2$: 377.2437, found 377.2425.

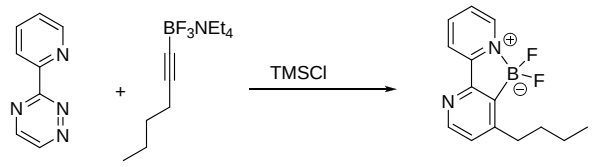
Synthesis of 22.



Following the general procedure, a solution of 3-amino-6-(3,5-dimethylpyrazol-1-yl)-1,2,4,5-tetrazine (37 mg, 0.185 mmol) and tetraethylammonium

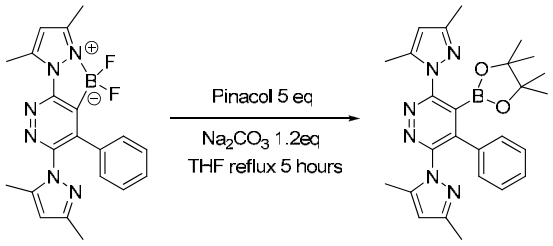
(phenylethynyl)trifluoroborate (83 mg, 0.277 mmol) in a 1:1 mixture of DCM/acetone (2 mL) was added TMSCl (70 µL, 0.554 mmol). Chromatographic purification over florisil (gradient; starting with petroleum ether, ending with ethyl acetate). Compound **22** was isolated as a colourless solid (40 mg, 69 %). M.p: 201.8-202.6 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ 2.47 (3H, s, CH_3), 2.87 (3H, s, CH_3), 5.06 (2H, br s, NH_2), 6.21 (1H, s, CH), 7.43-7.60 (3H, m, Ar), 7.61-7.70 (2H, m, Ar). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 11.0, 12.5, 111.2, 128.5, 129.2, 129.3, 133.2, 133.9, 140.7, 146.4, 153.7, 157.1. ^{19}F NMR (235.1 MHz, $CDCl_3$): δ -151.8. FTIR: 3480 (w), 3385 (w), 2360 (m), 1592 (m), 1427 (s), 1113 (s) cm^{-1}. HRMS: (ESI) [MH^+] calcd for $C_{15}H_{15}BN_5F_2$: 314.1389, found 314.1394.

Synthesis of 24.



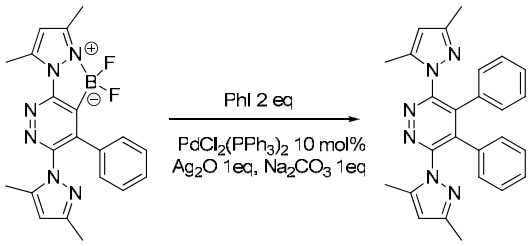
A flame dried flask fitted with a reflux condenser was charged with 3-(2-pyridyl)-1,2,4-triazine (30 mg, 0.185 mmol) and tetraethylammonium (hex-1-ynyl)trifluoroborate (258 mg, 0.925 mmol). The mixture was dissolved in dry DCM (2 mL) and to this was added dropwise distilled TMSCl (106 µL, 0.832 mmol). The mixture was stirred at room temperature for 10 minutes and then heated to reflux for 10 minutes. Chromatographic purification over silica gel (gradient; starting with petroleum ether, ending with ethyl acetate). Product **24** was isolated as a yellow oil (28 mg, 67 %). ^{1}H NMR (250 MHz, $CDCl_3$): δ.0.97 (3H, t, J = 7.5 Hz, CH_3), 1.35-1.53 (2H, m, CH_2), 1.65-1.82 (2H, m, CH_2), 2.84 (2H, t, J = 7.5 Hz, CH_2), 7.18 (1H, d, J = 5.5 Hz, Ar), 7.59-7.68 (1H, m, Ar), 8.24 (1H, td, J = 7.5, 1.5 Hz, Ar), 8.33 (1H, d, J = 8.0 Hz, Ar), 8.49 (1H, d, J = 5.0 Hz, Ar), 8.60 (1H, d, J = 5.0 Hz, Ar). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 13.9, 22.5, 32.5, 34.7, 119.1, 125.0, 126.1, 141.3, 144.1, 149.9, 154.9, 155.2, 156.3. ^{19}F NMR (235.1 MHz, $CDCl_3$): δ -159.1. FTIR: 3055 (w), 2957 (s), 2931 (s), 2863 (m), 1628 (s), 1583 (s), 1571 (s), 1491 (s), 1476 (s), 1380 (m), 1260 (m), 1099 (s), 1000(s) cm^{-1}. HRMS: (ESI) [MH^+] calcd for $C_{14}H_{16}BN_2F_2$: 261.1372, found 261.1375.

Synthesis of 25.



A flame dried flask fitted with a reflux condenser was charged with **13** (100 mg, 0.25 mmol), pinacol (150 mg, 1.27 mol) and Na_2CO_3 (32mg, 0.30 mmol) in dry THF (1 mL). The mixture heated at reflux for 5 hours. The solvent was evaporated and the excess pinacol removed by kugelrohr distillation. The residue was purified by chromatographic purification over florisil (gradient; starting with petroleum ether, ending with petroleum ether/ethyl acetate 1:1). Product **25** was isolated as a colourless solid (82 mg, 68 %) and showed satisfactory spectroscopic and analytical data.[4]

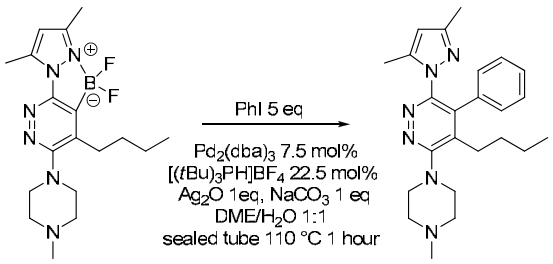
Synthesis of 26.



A flask fitted with a refluxed condenser was charged with **13** (39 mg, 0.1 mmol), $PdCl_2(PPh_3)_2$ (7 mg, 0.01 mmol), Ag_2O (23mg, 0.1 mmol), Na_2CO_3 (11mg, 0.1 mmol) and iodobenzene (40 mg, 0.2 mmol) in a 1:1 mixture of DME/H_2O (1 mL). The reaction was heated to 80 ^oC for 4 hours, cooled to room temperature and dry loaded onto silica gel. Chromatographic purification (gradient; starting with petroleum ether, ending with petrol/ethyl acetate 1/1). Product **26** was isolated as a yellow solid (25 mg, 60 %) and showed satisfactory spectroscopic and analytical data.[4]

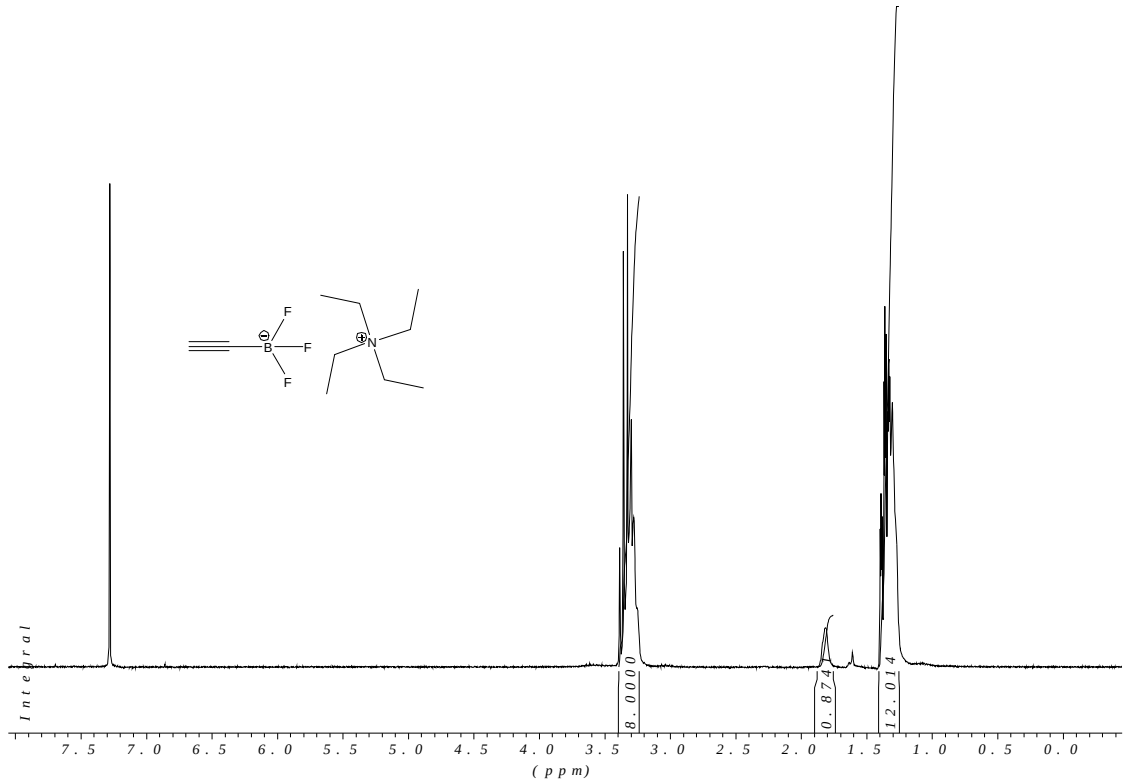
[4] Helm, M. D.; Moore, J. E.; Plant, A.; Harrity, J. P. A. *Angew. Chem. Int. Ed.* **2005**, *44*, 3889.

Synthesis of 27.

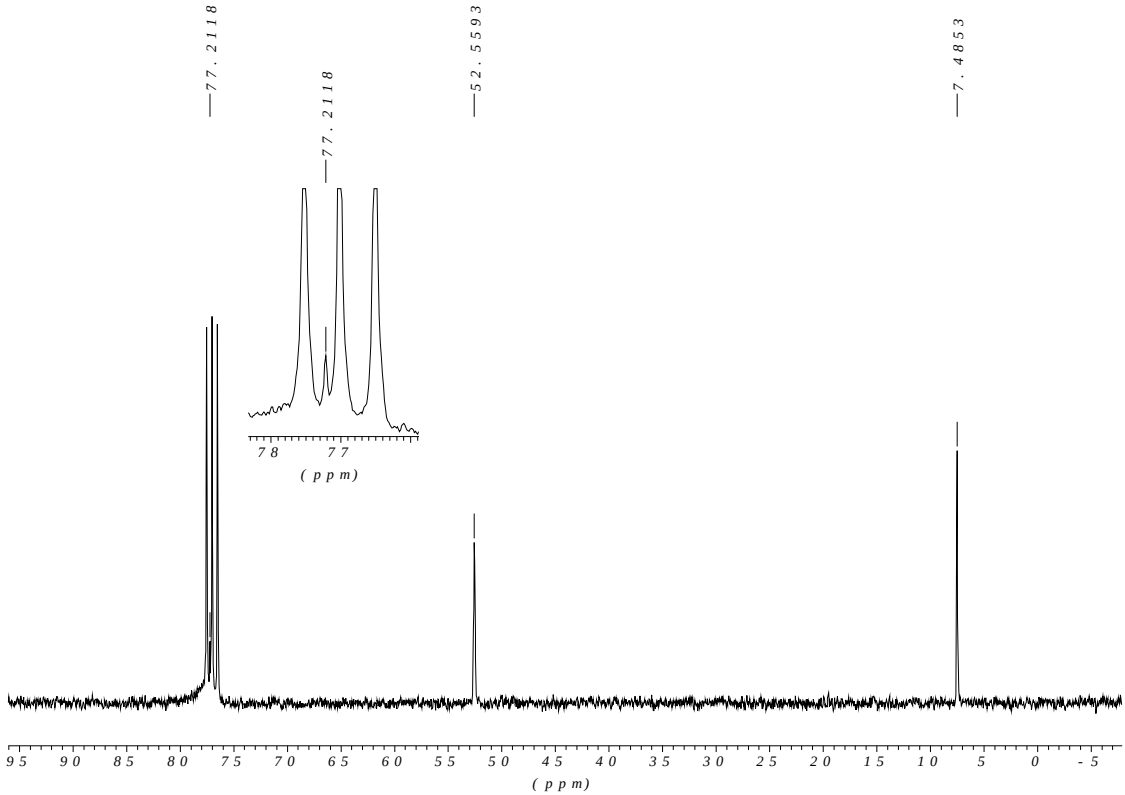


A microwave vial was charged with **20** (19 mg, 0.05 mmol), $Pd_2(dba)_3$ (7 mg, 7.5 µmol), Ag_2O (12 mg, 0.05 mmol), Na_2CO_3 (6mg, 0.05 mmol) and iodobenzene (50 mg, 0.245 mmol) in a 1:1 mixture of DME/H_2O (1 mL). The vial was flushed with argon, *t*-$Bu_3P.HBF_4$ (5 mg, 0.018 mmol) was added before the flask was sealed and introduced into a preheated silicon oil bath at 110 ^oC. After one hour at this temperature the reaction was allowed to cool to room temperature and was dry loaded onto silica gel. Chromatographic purification (gradient; starting with petroleum ether, ending with ethyl acetate/Et_3N 95/5). Product **27** was isolated as a colourless solid (14 mg, 68 %). M.p: 212-213 °C. ^1H NMR (250 MHz, CD_3OD): δ 0.75 (3H, t, J = 7.0 Hz, CH_3), 1.07-1.24 (2H, m, CH_2), 1.26-1.42 (2H, m, CH_2), 2.06 (3H, s, CH_3), 2.08 (3H, s, CH_3), 2.44 (3H, s, CH_3), 2.68-2.80 (6H, m, CH_2), 3.43-3.51 (4H, m, CH_2), 5.85 (1H, s, CH), 7.13-7.23 (2H, m, Ar), 7.30-7.40 (3H, m, Ar). ^{13}C NMR (62.9 MHz, CD_3OD): δ 9.8, 11.5, 12.3, 22.2, 27.7, 30.0, 44.7, 50.1, 54.5, 105.5, 127.8, 128.2, 128.5, 132.5, 137.9, 141.3, 141.8, 149.4, 150.9, 164.5. FTIR: 2931 (m), 2845 (w), 2792 (m), 2361 (m), 2342 (m), 1459 (m), 1406 (s), 1366 (m), 1287 (w), 1254 (w) cm^{-1}. HRMS: (ESI) [MH^+] calcd for $C_{24}H_{33}N_6$: 405.2767, found 405.2762.

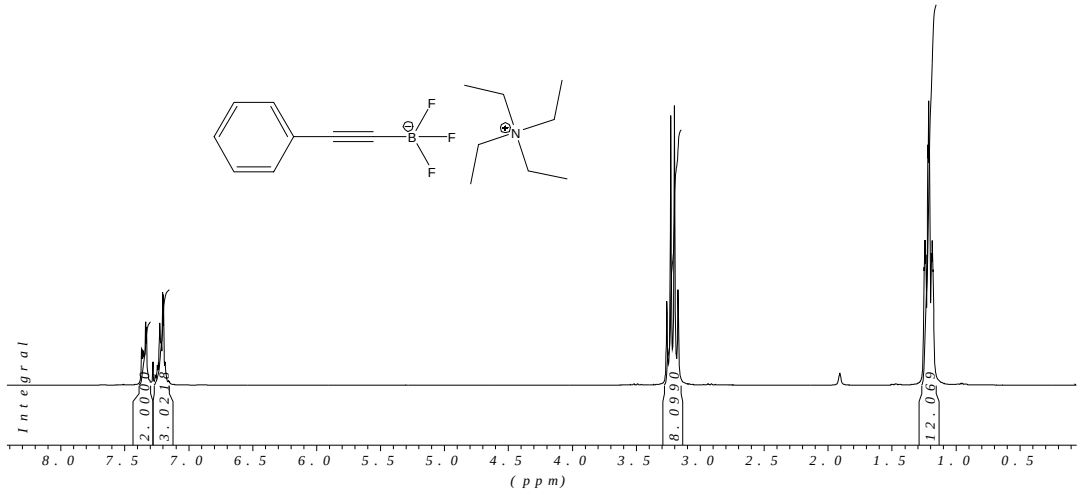
^{1}H NMR spectrum of tetraethylammonium ethynyltrifluoroborate



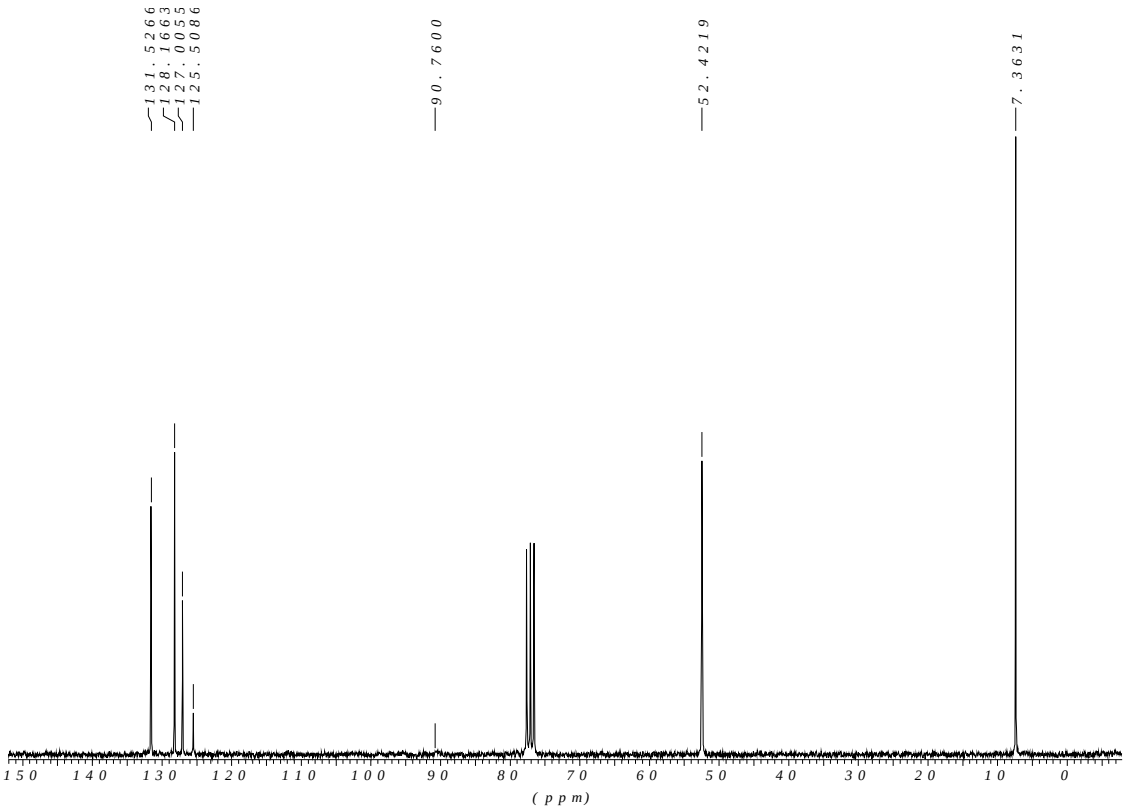
^{13}C NMR spectrum of tetraethylammonium ethynyltrifluoroborate



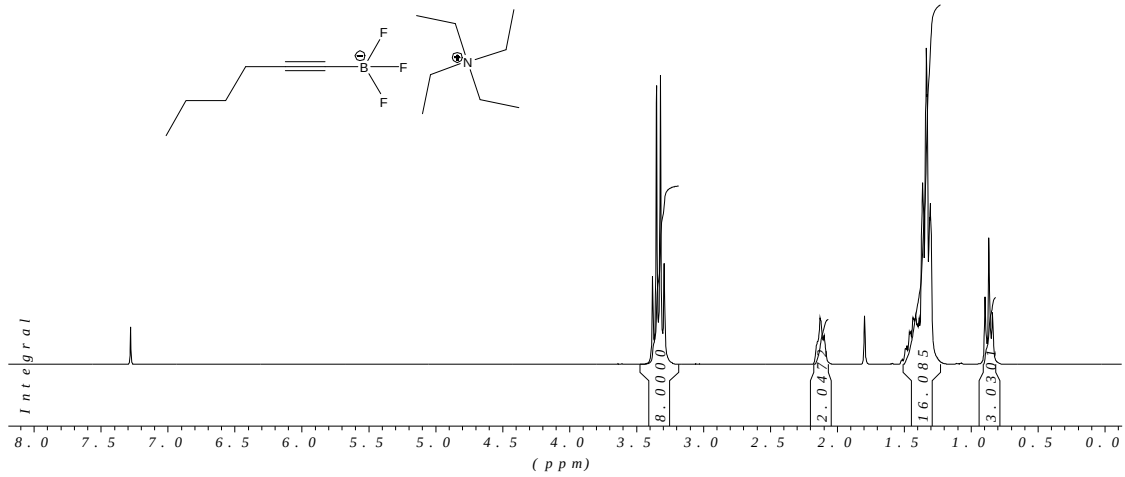
^{1}H NMR spectrum of tetraethylammonium (phenylethynyl)trifluoroborate



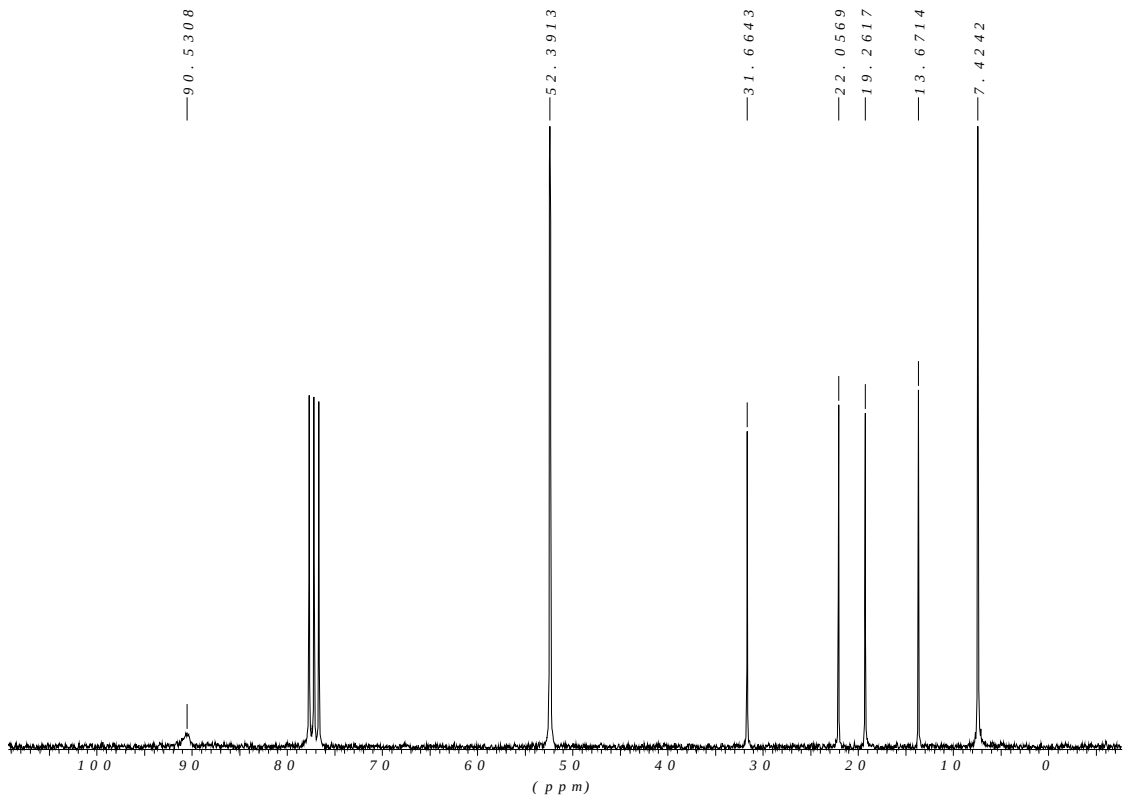
^{13}C NMR spectrum of tetraethylammonium (phenylethynyl)trifluoroborate



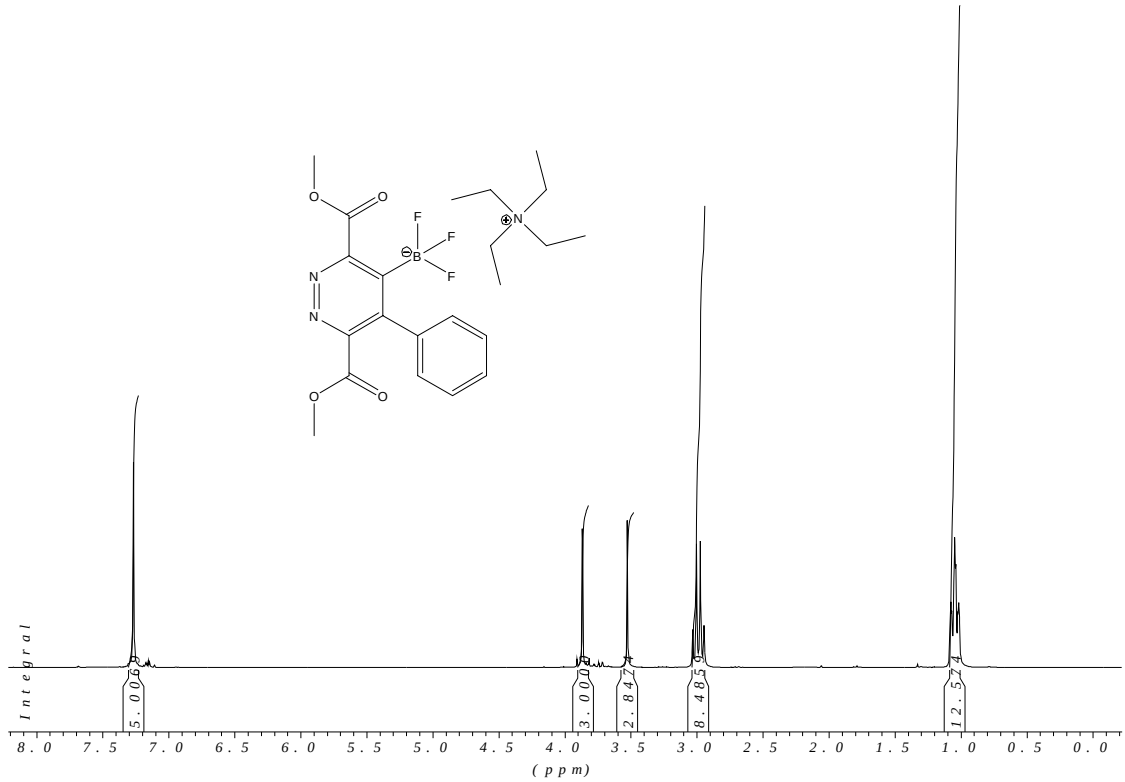
^{1}H NMR spectrum of tetraethylammonium (hex-1-ynyl)trifluoroborate



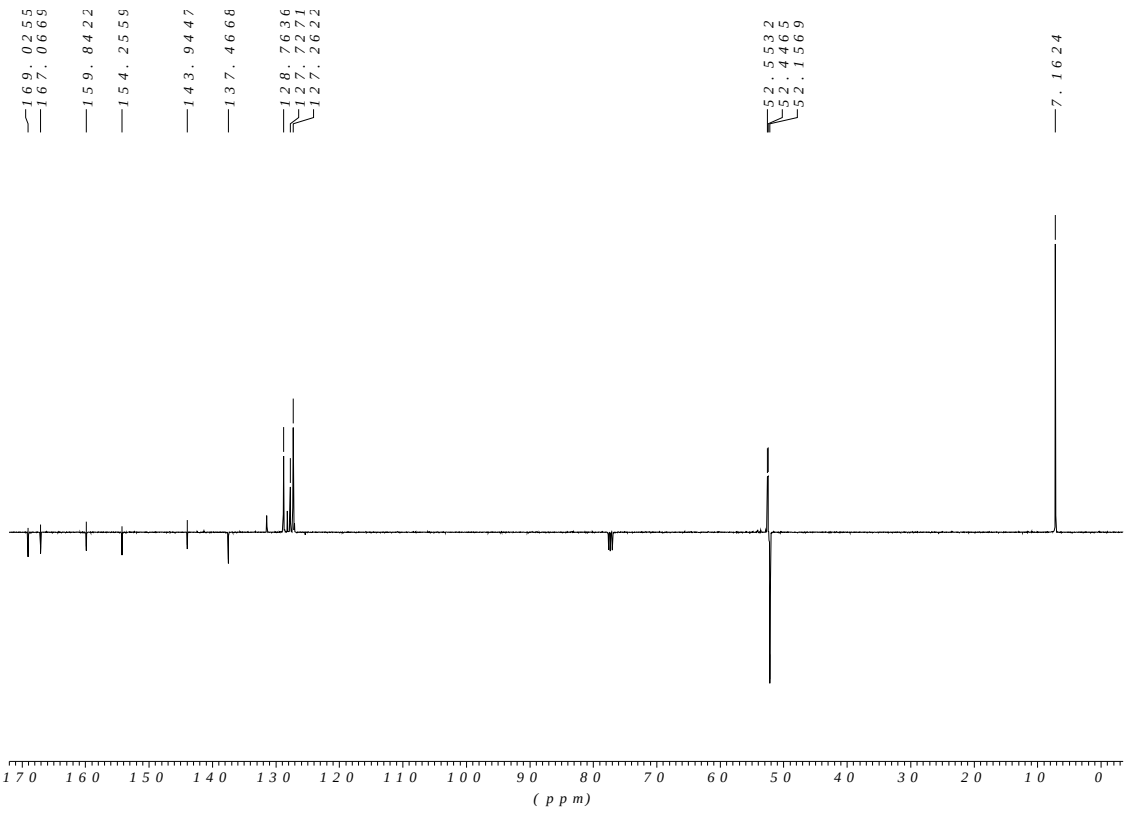
^{13}C NMR spectrum of tetraethylammonium (hex-1-ynyl)trifluoroborate



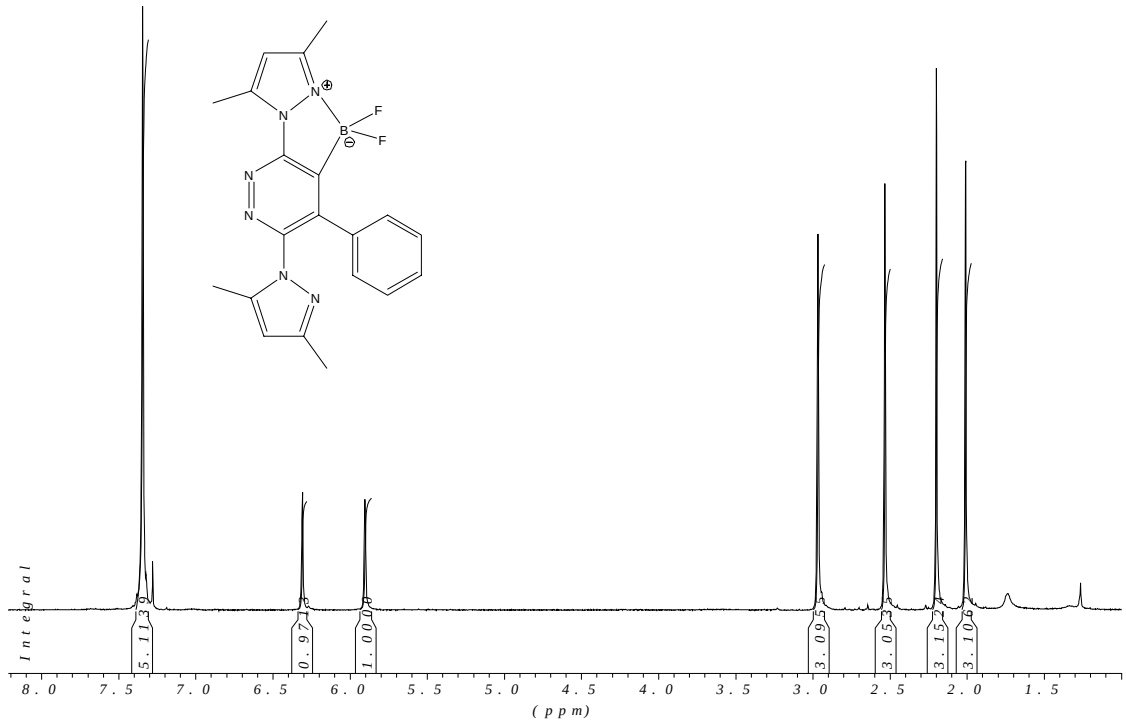
^{1}H NMR spectrum of tetraethylammonium dimethyl 4-(trifluoroborate)-5-phenyl-pyridazine-3,6-dicarboxylate



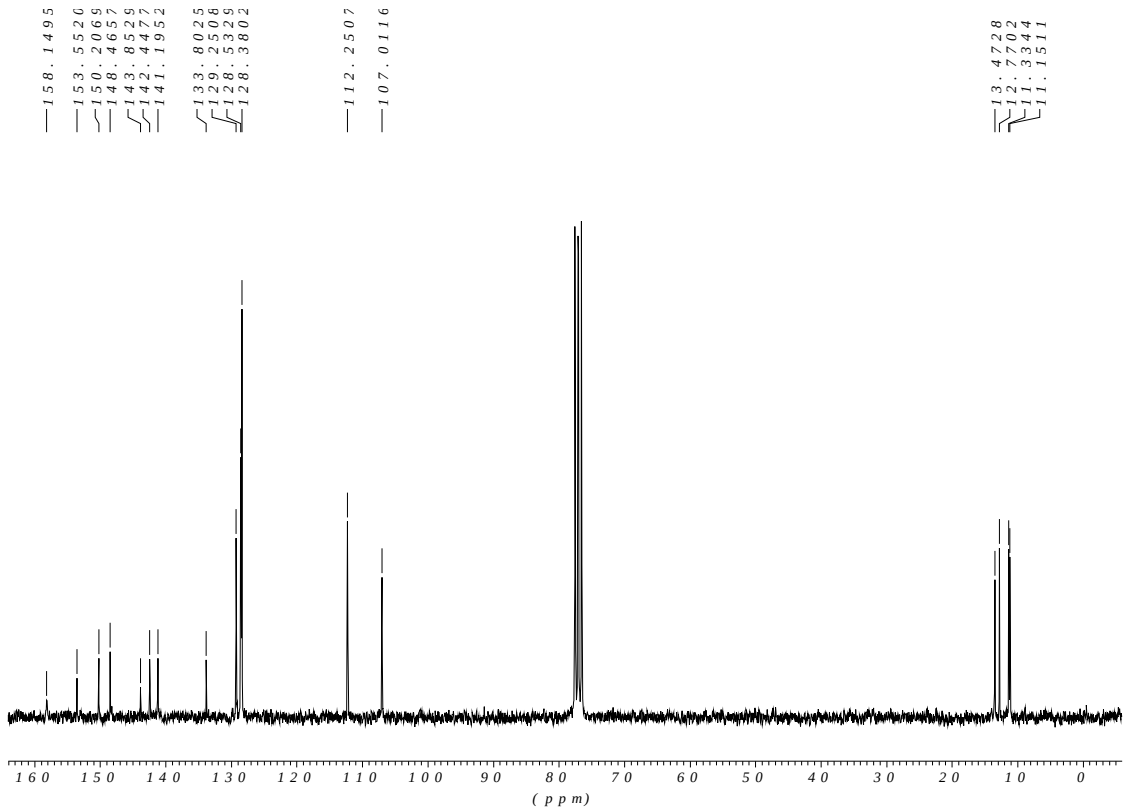
^{13}C NMR spectrum of tetraethylammonium dimethyl 4-(trifluoroborate)-5-phenyl-pyridazine-3,6-dicarboxylate



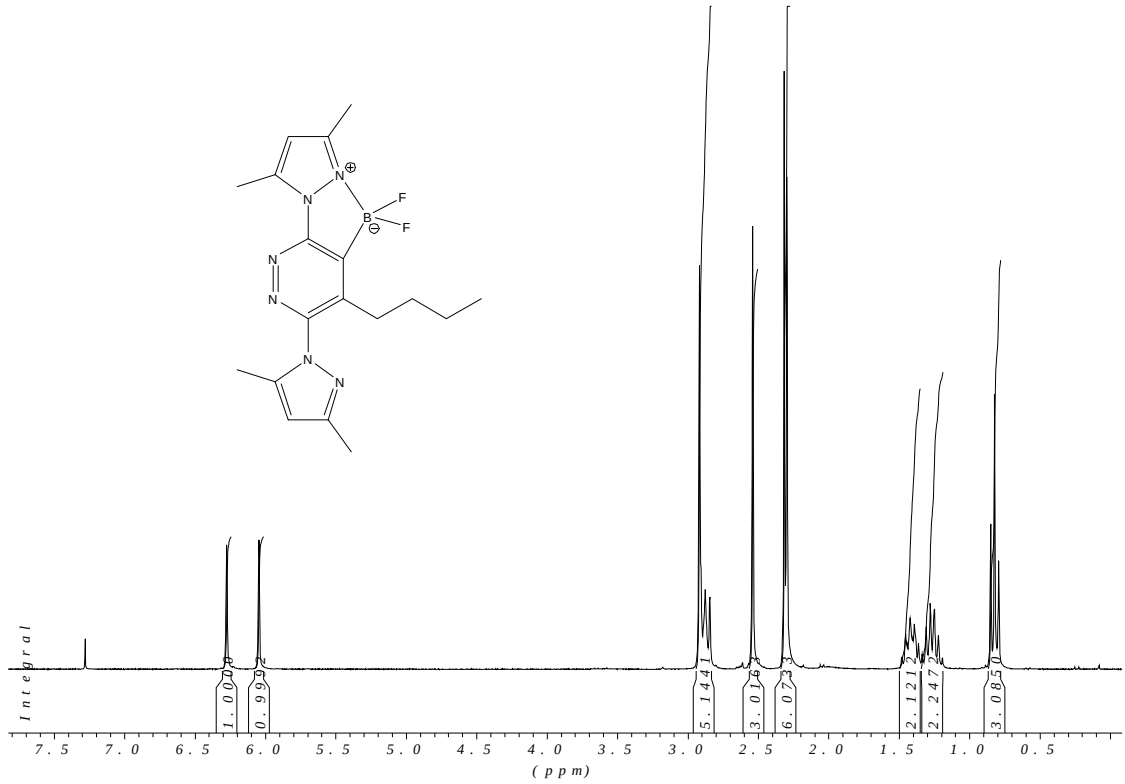
^{1}H NMR spectrum of **13**



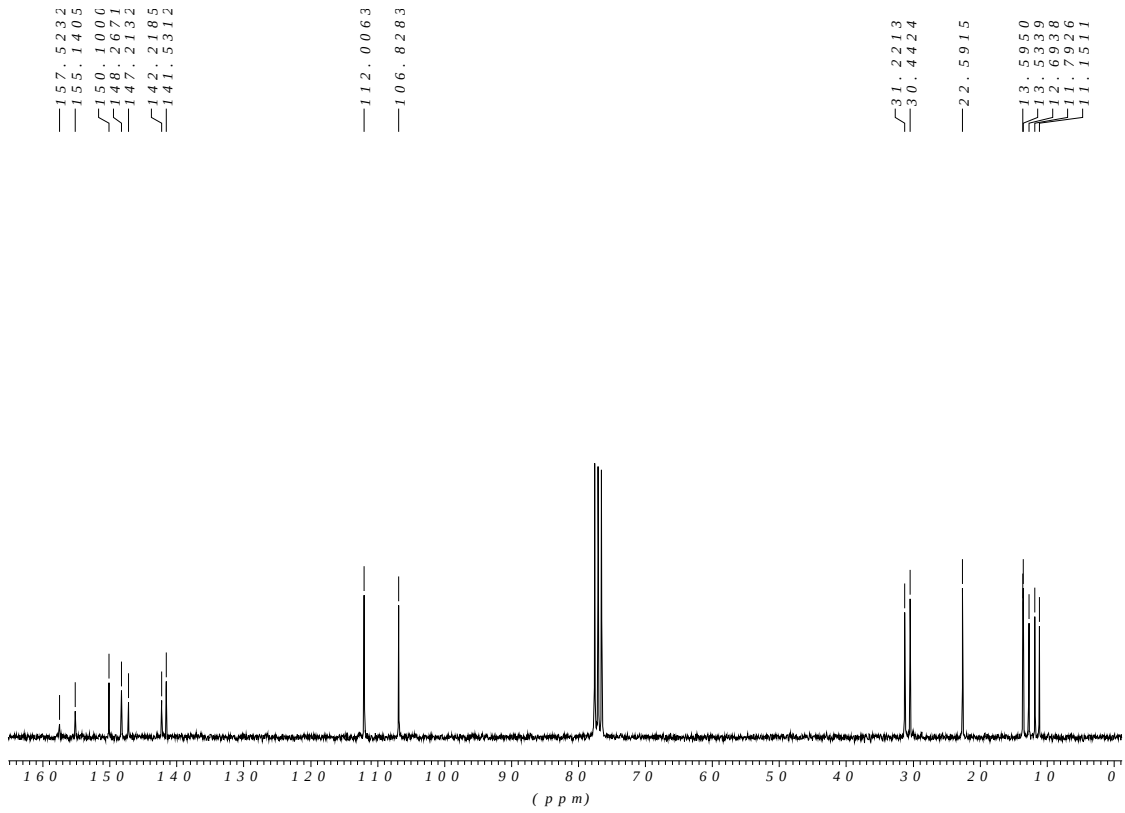
^{13}C NMR spectrum of **13**



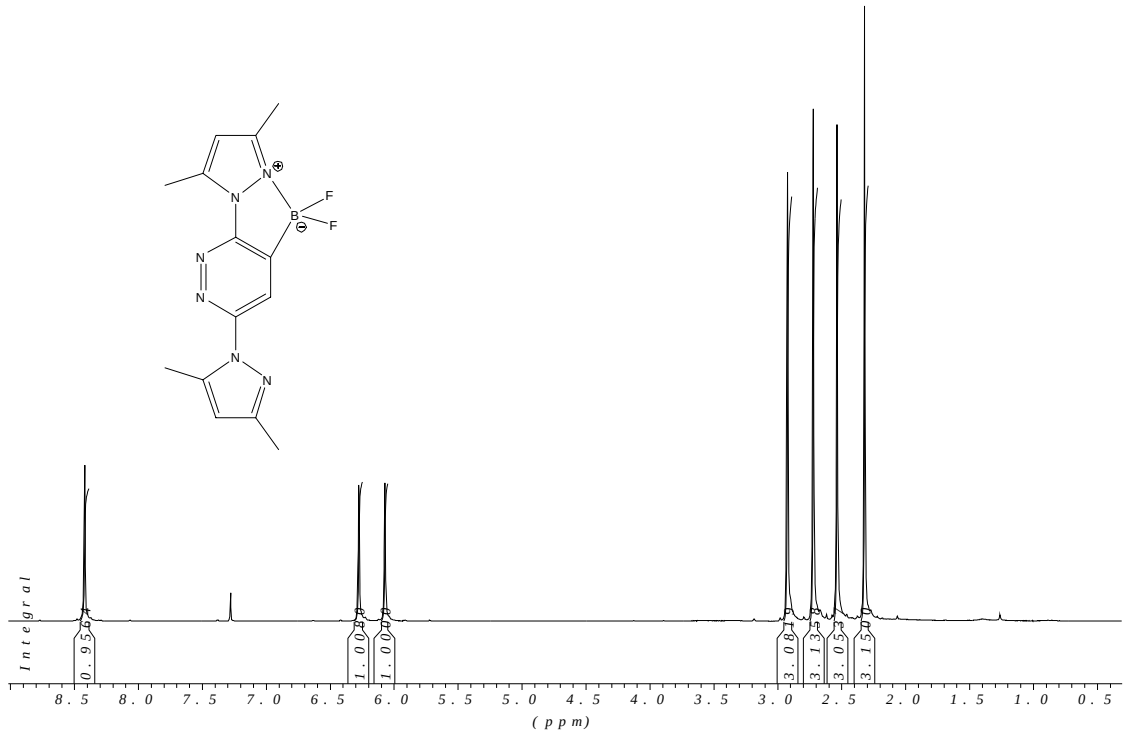
^{1}H NMR spectrum of **12**



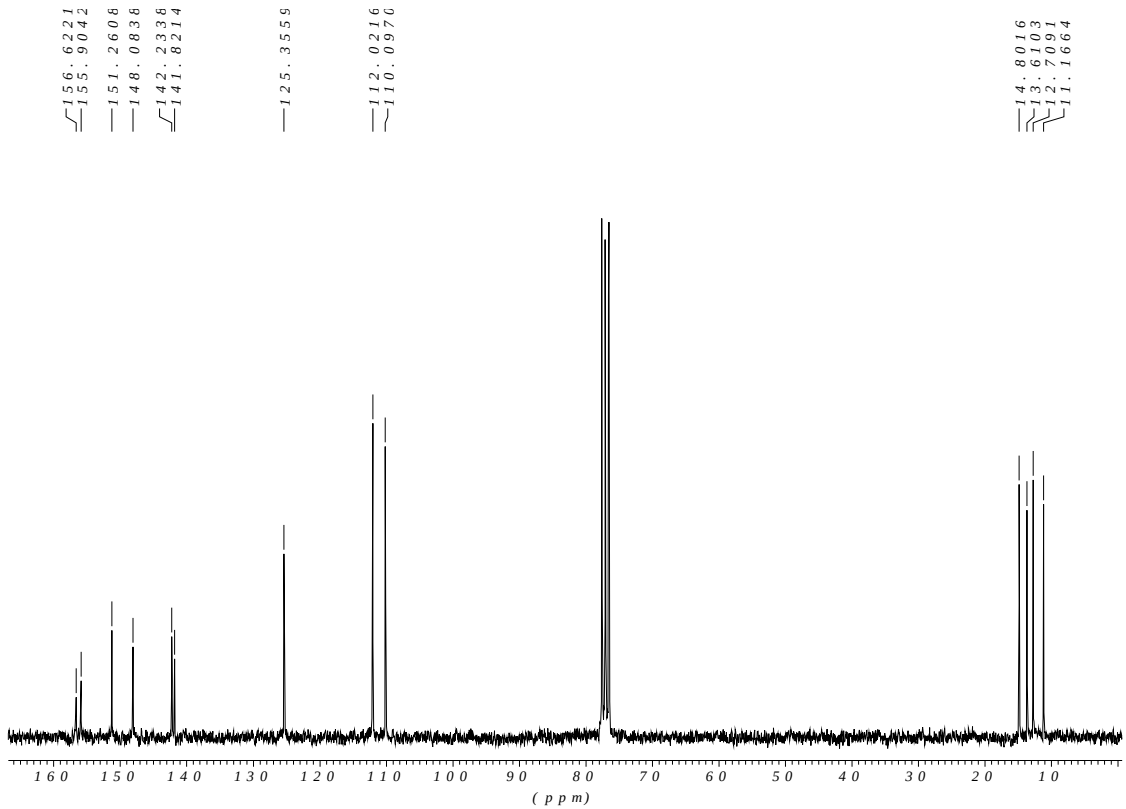
^{13}C NMR spectrum of **12**



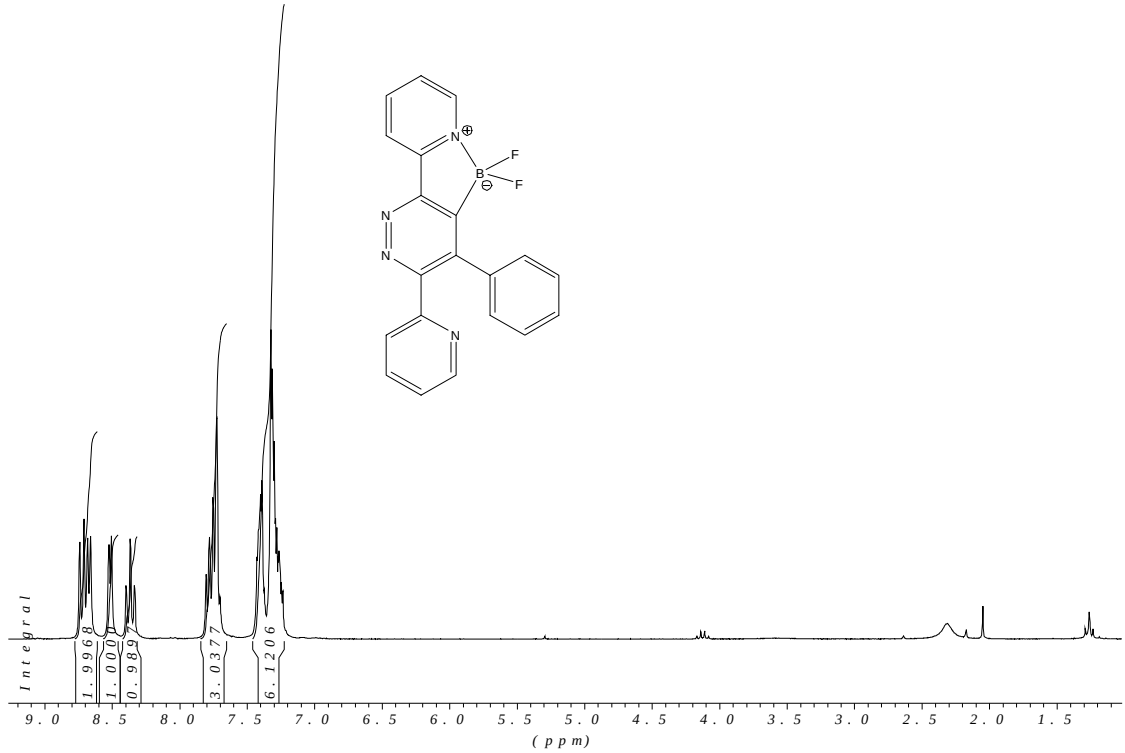
^{1}H NMR spectrum of **14**



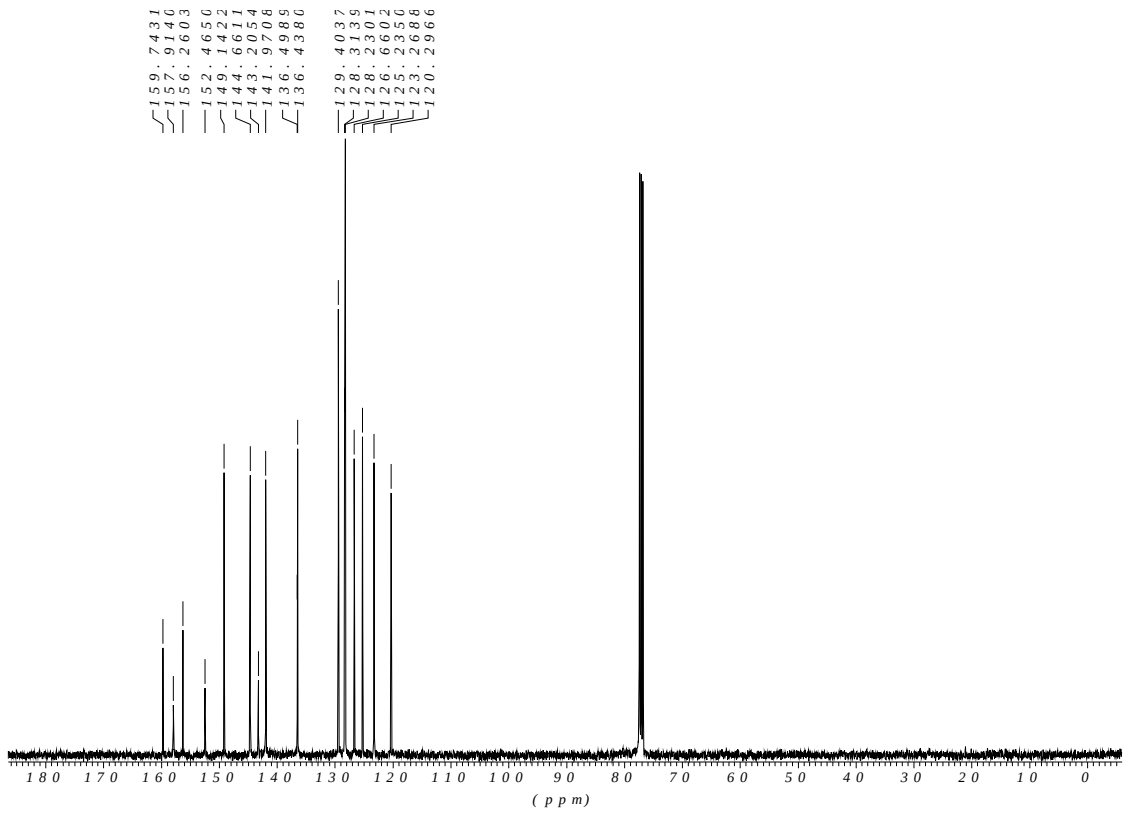
^{13}C NMR spectrum of **14**



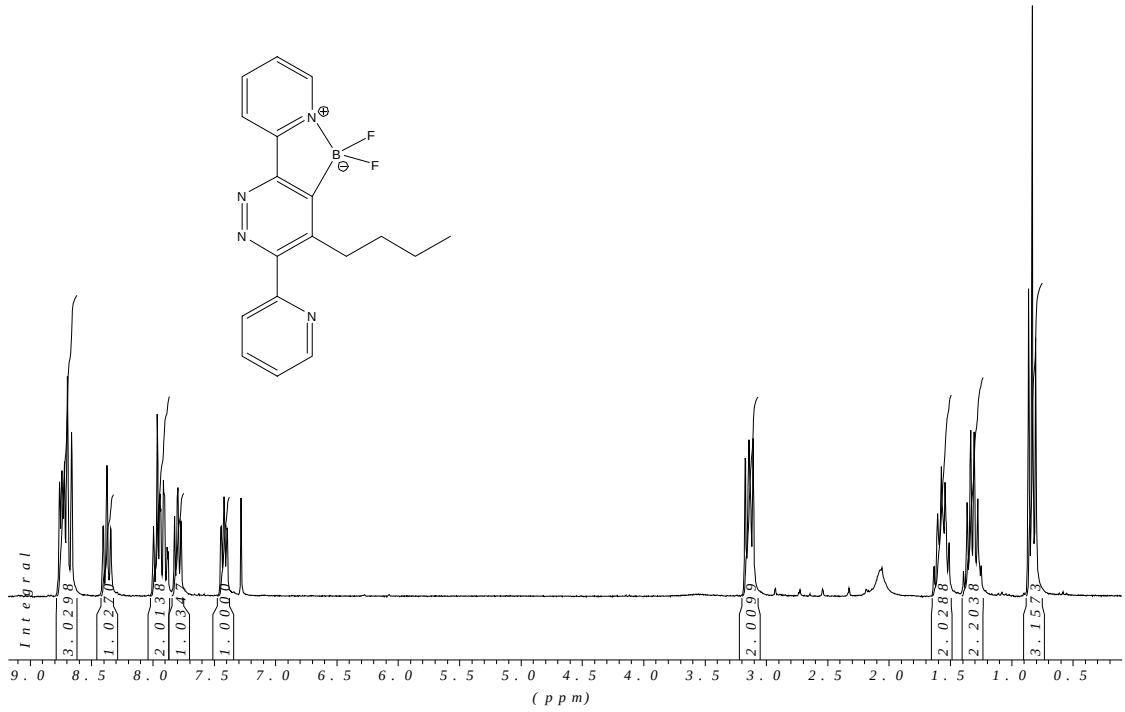
^{1}H NMR spectrum of **16**



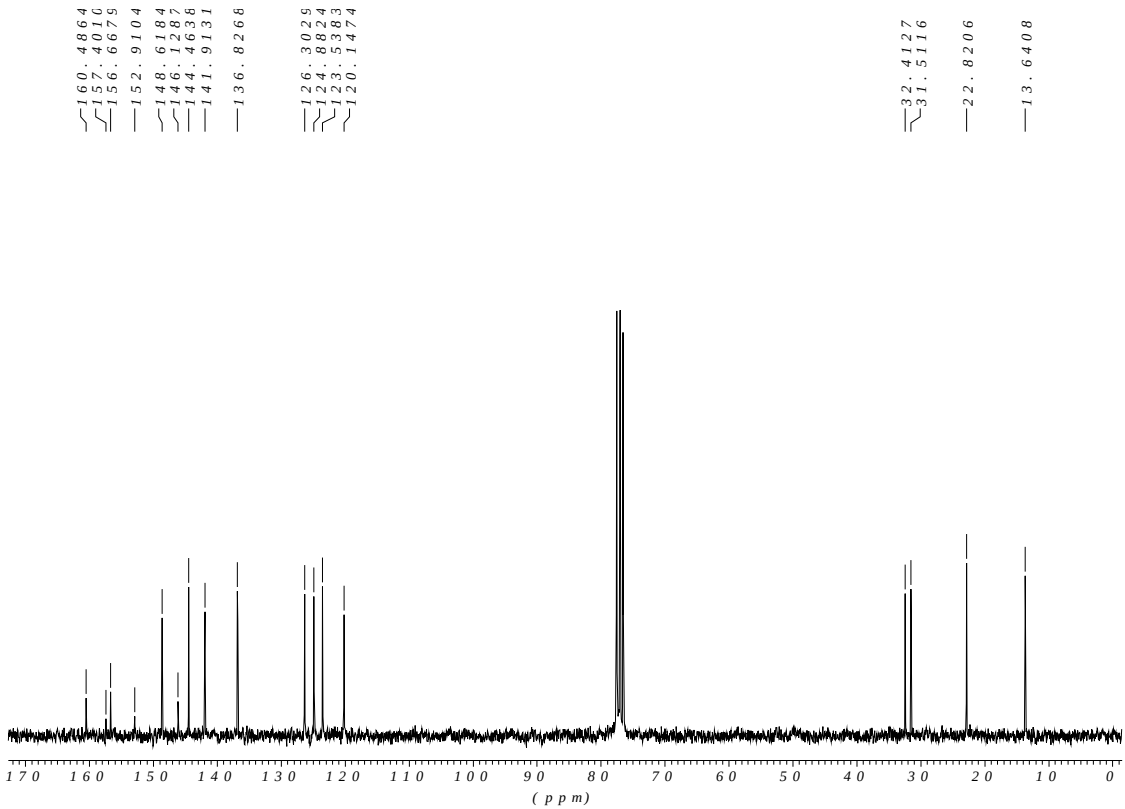
^{13}C NMR spectrum of **16**



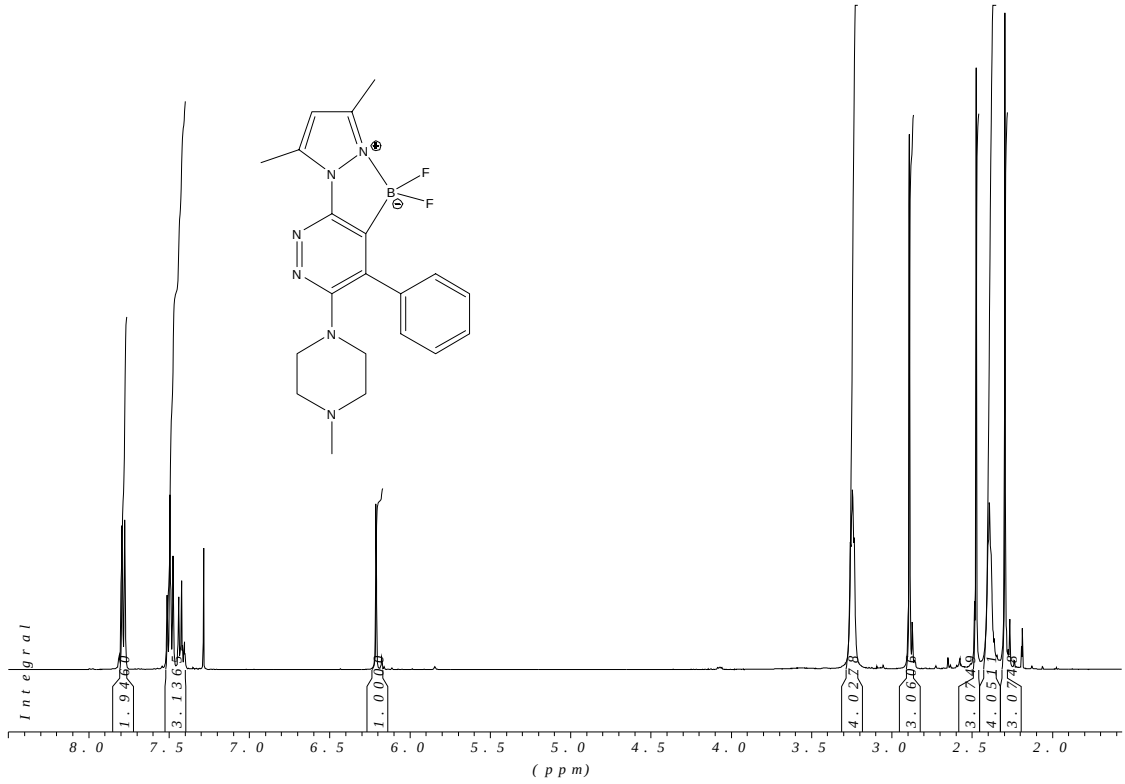
^{1}H NMR spectrum of **17**



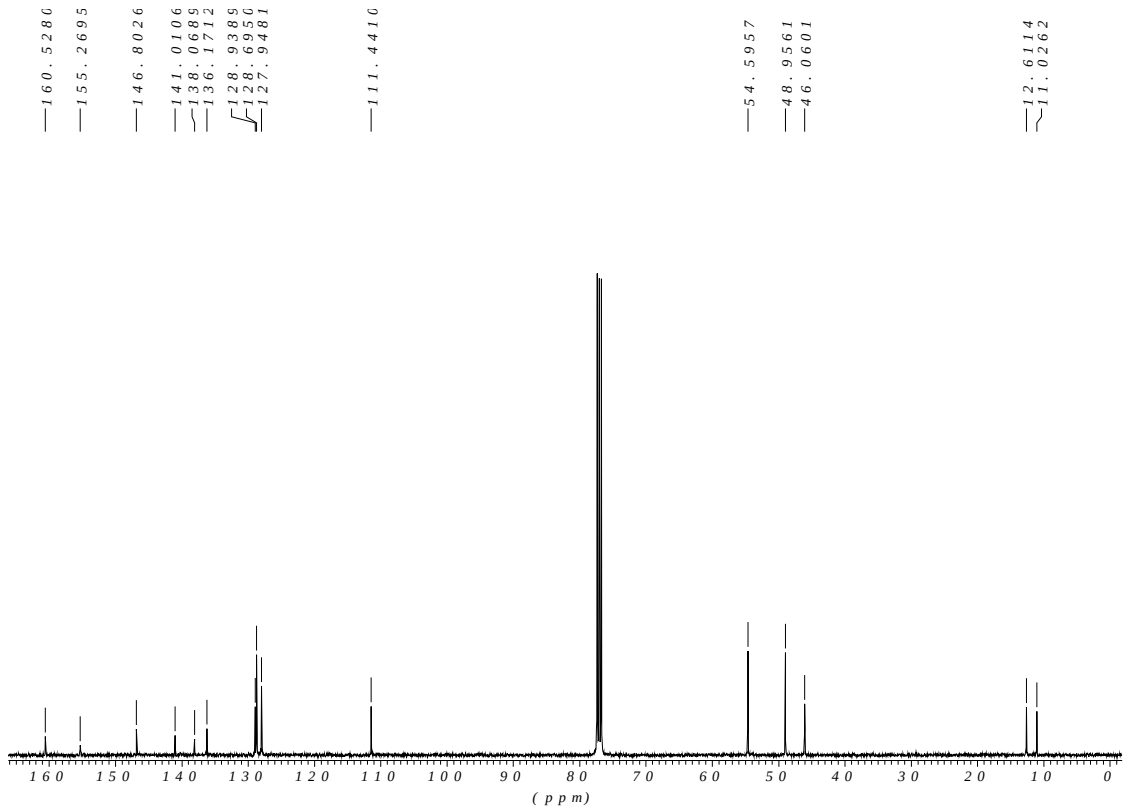
^{13}C NMR spectrum of **17**



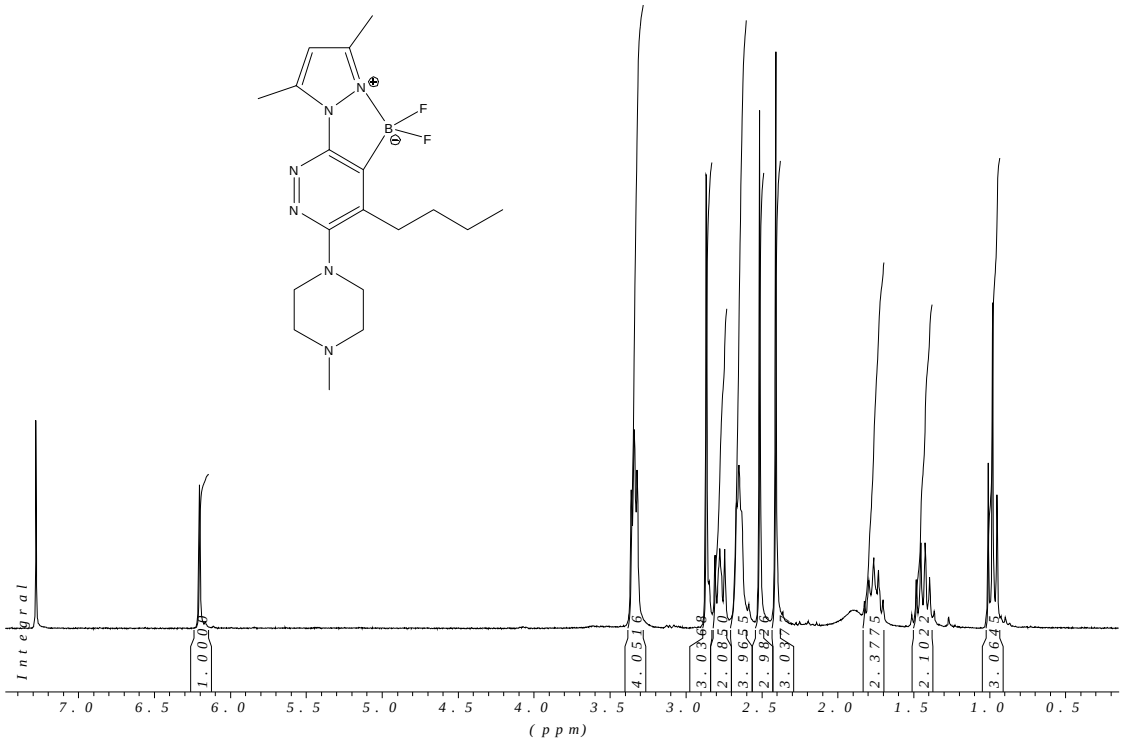
^{1}H NMR spectrum of **19**



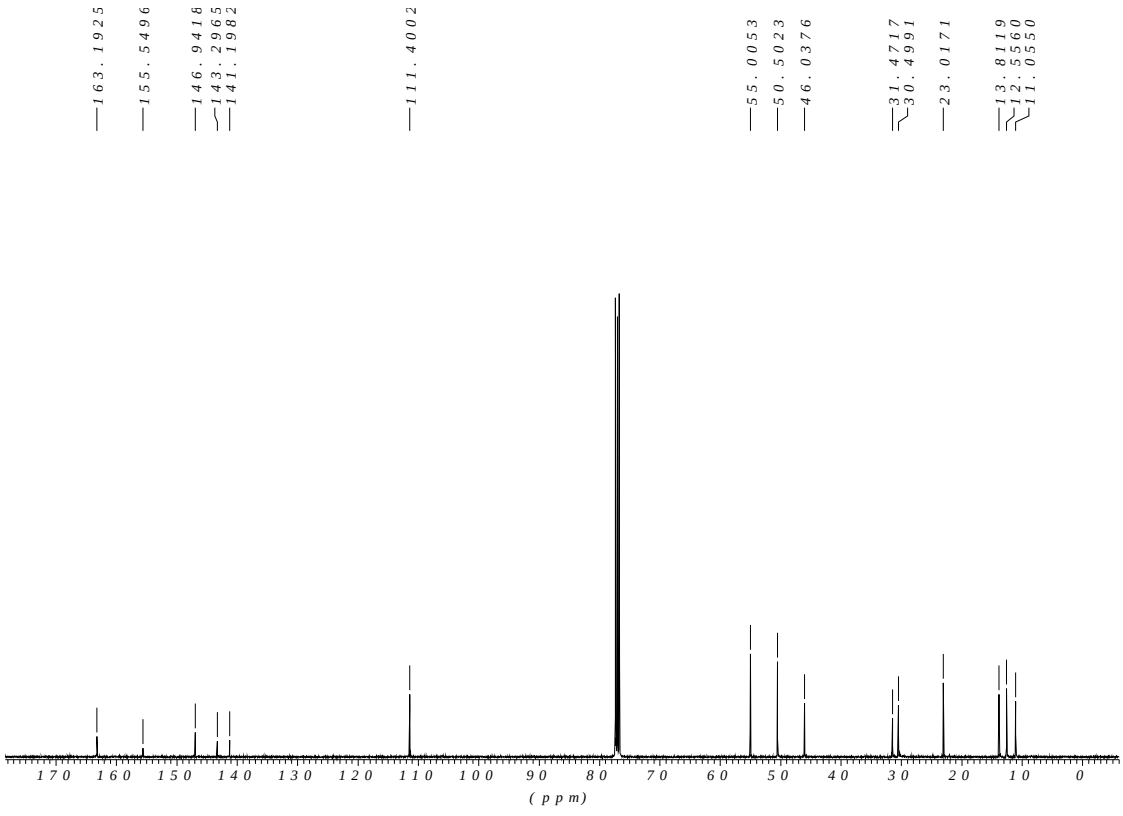
^{13}C NMR spectrum of **19**



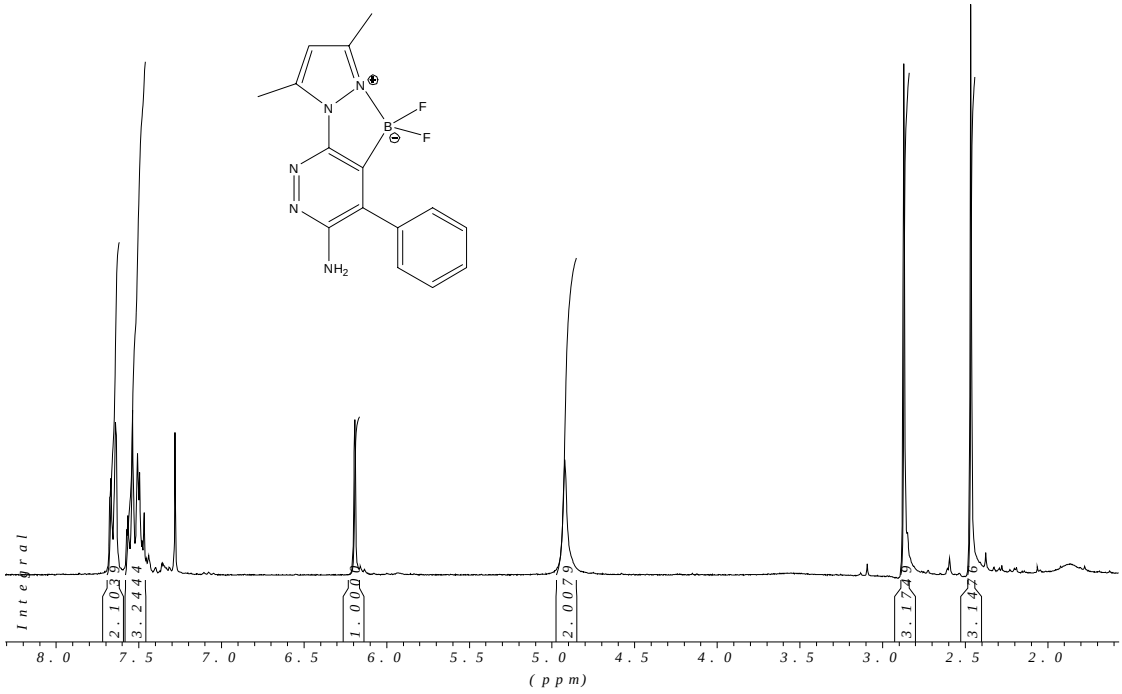
^{1}H NMR spectrum of **20**



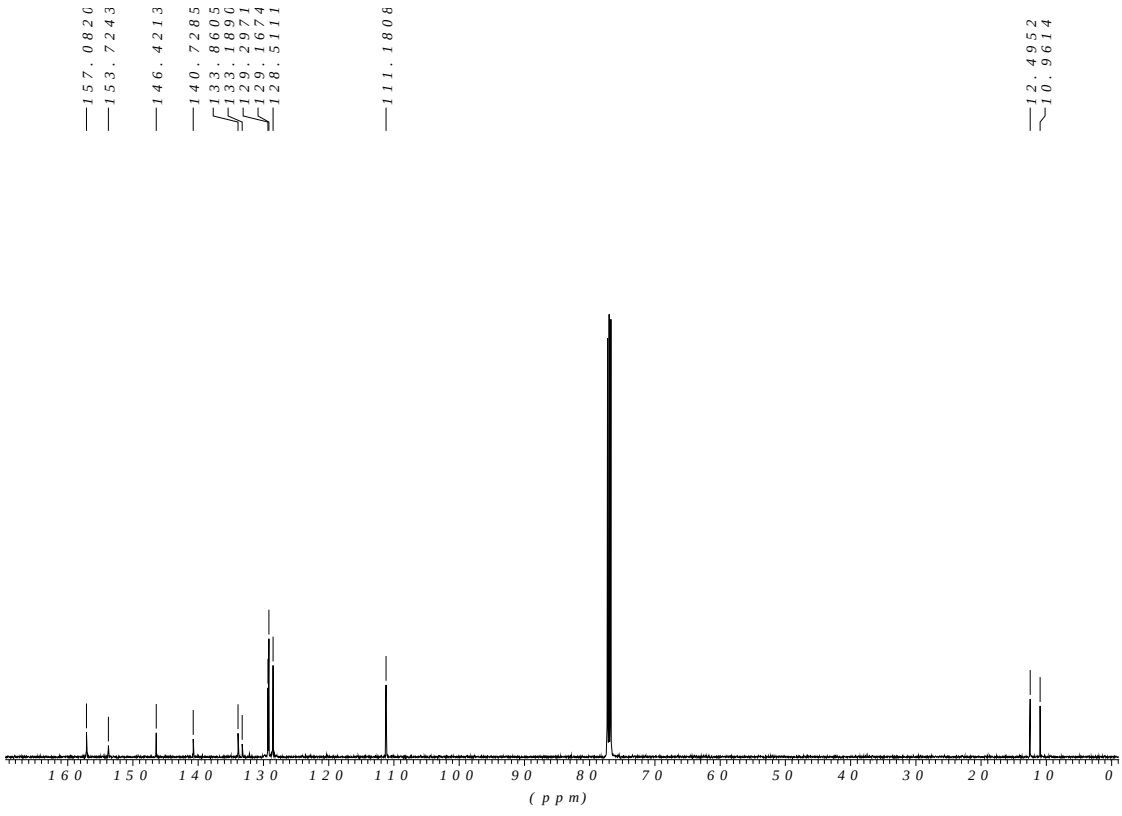
^{13}C NMR spectrum of **20**



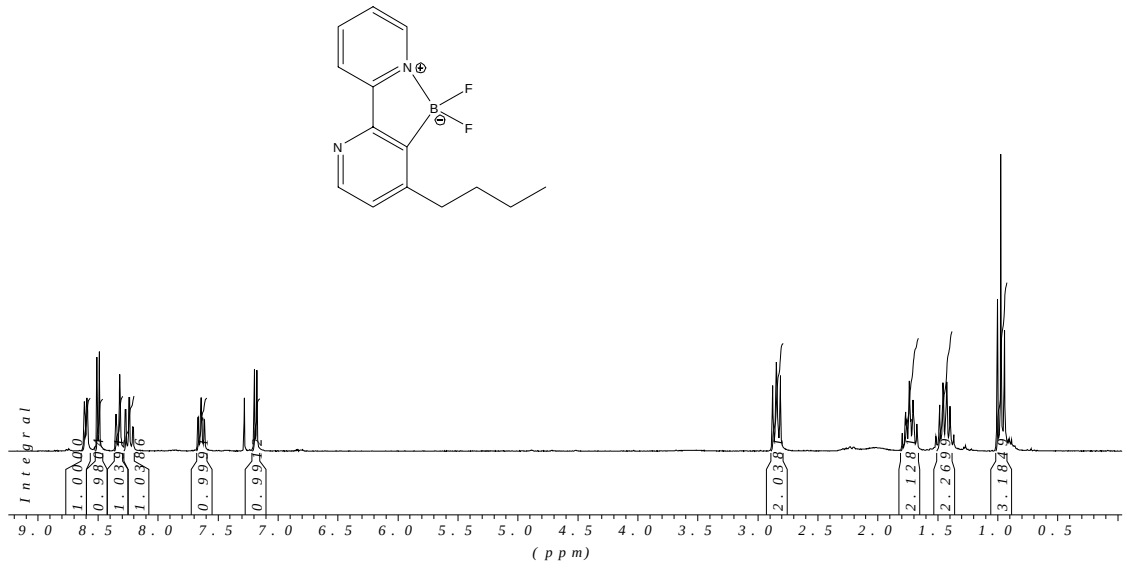
^{1}H NMR spectrum of **22**



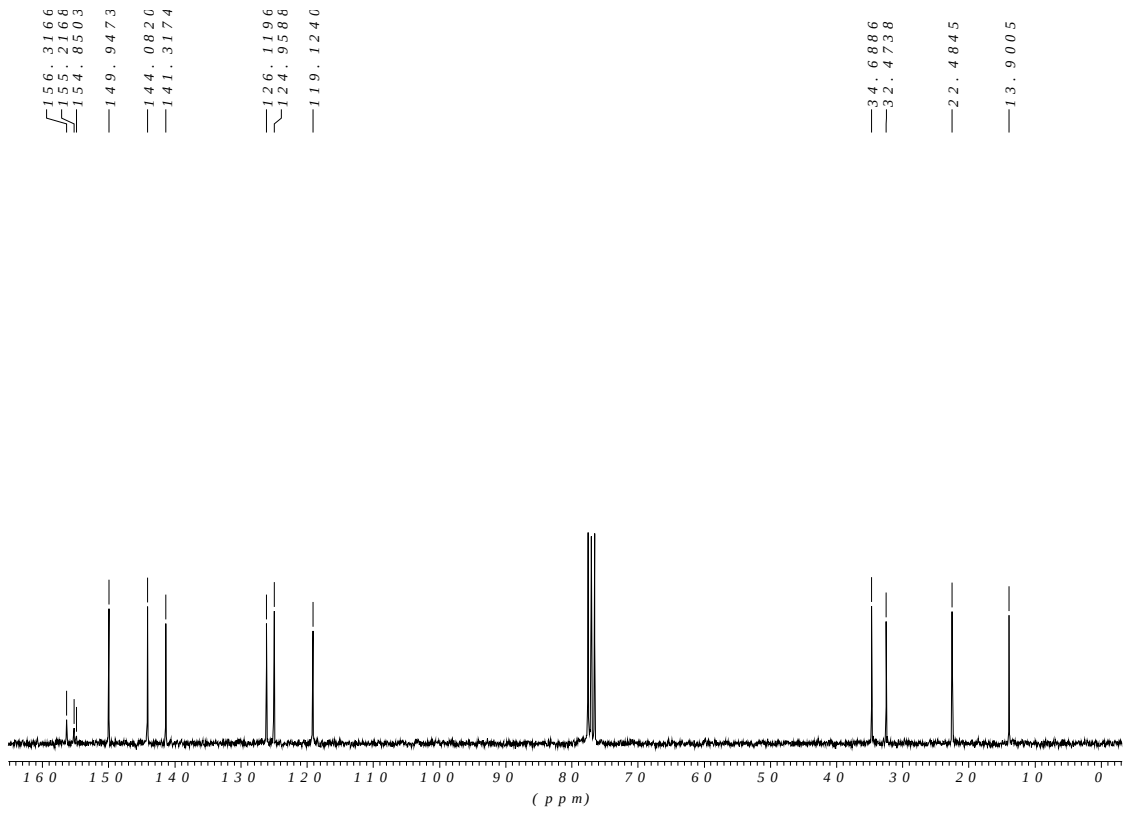
^{13}C NMR spectrum of **22**



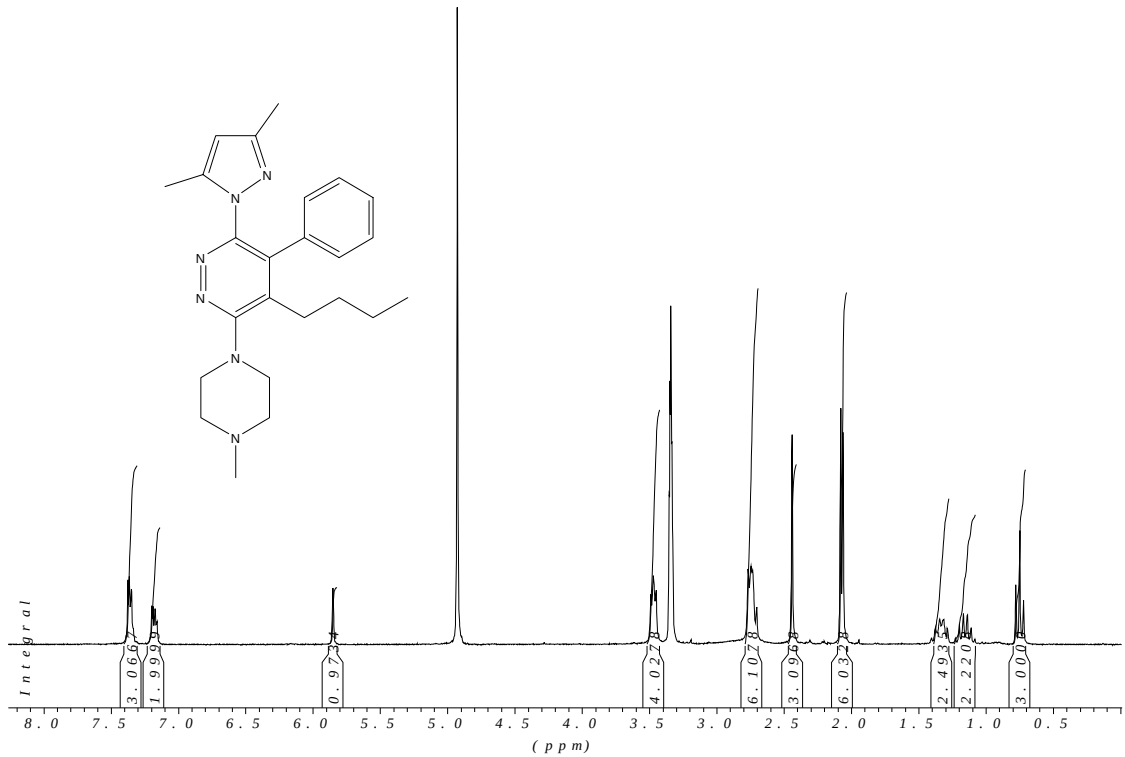
^{1}H NMR spectrum of **24**



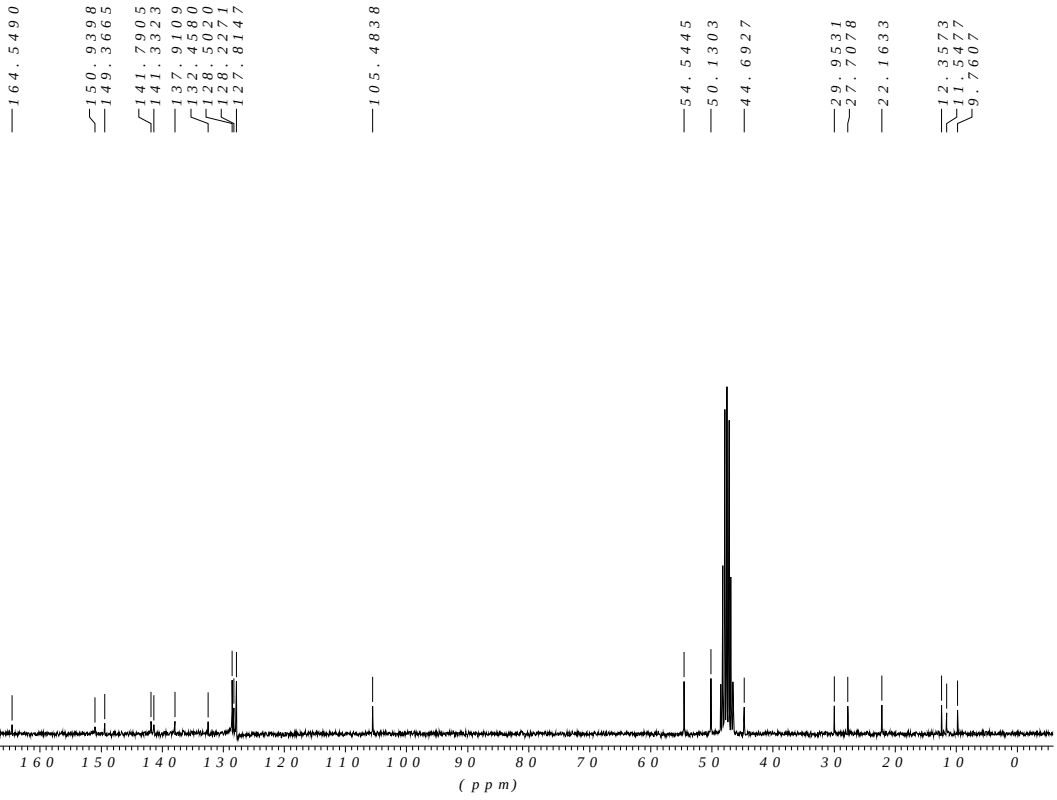
^{13}C NMR spectrum of **24**



^{1}H NMR spectrum of **27**



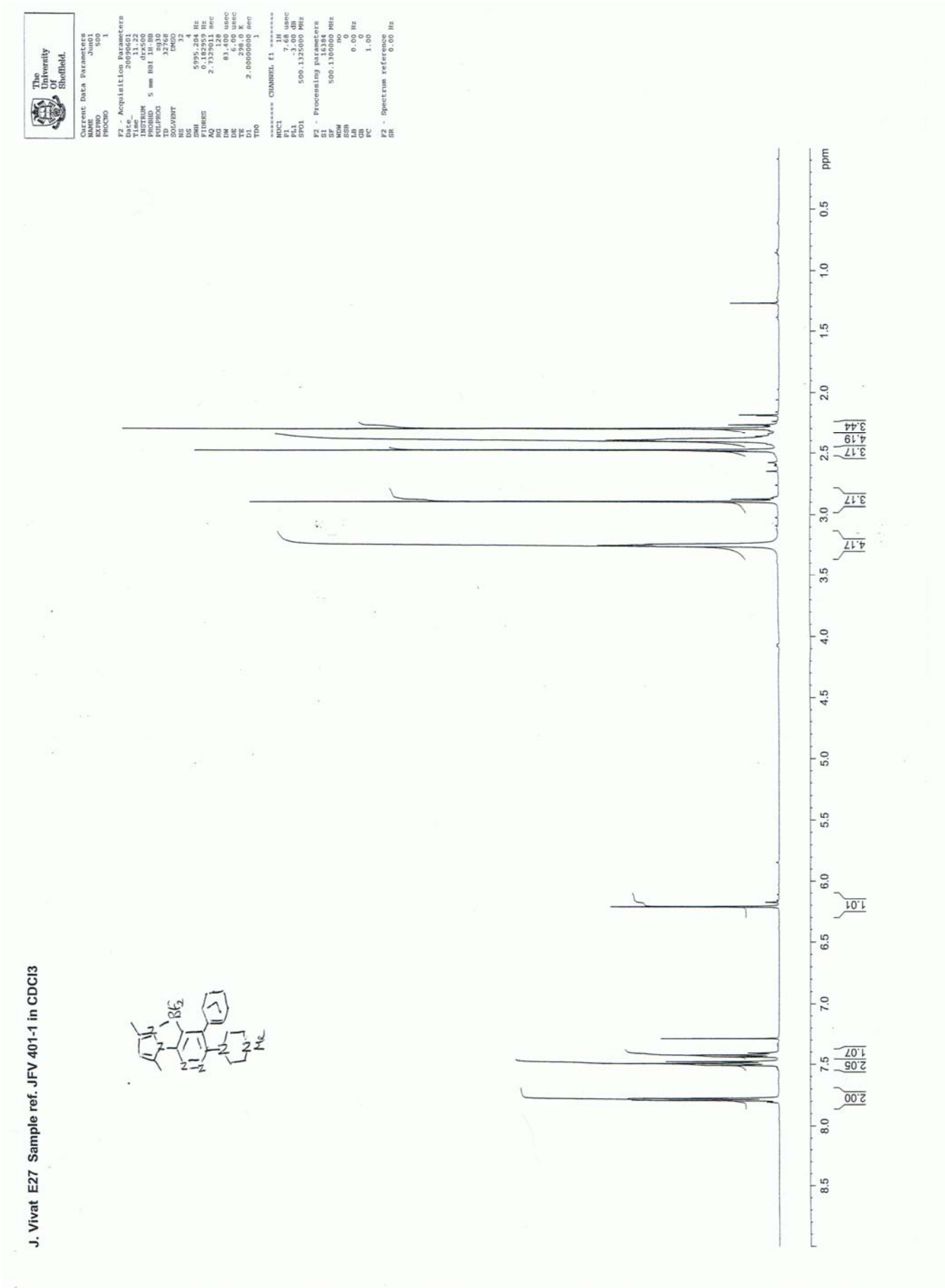
^{13}C NMR spectrum of **27**



Regiochemistry Assignments

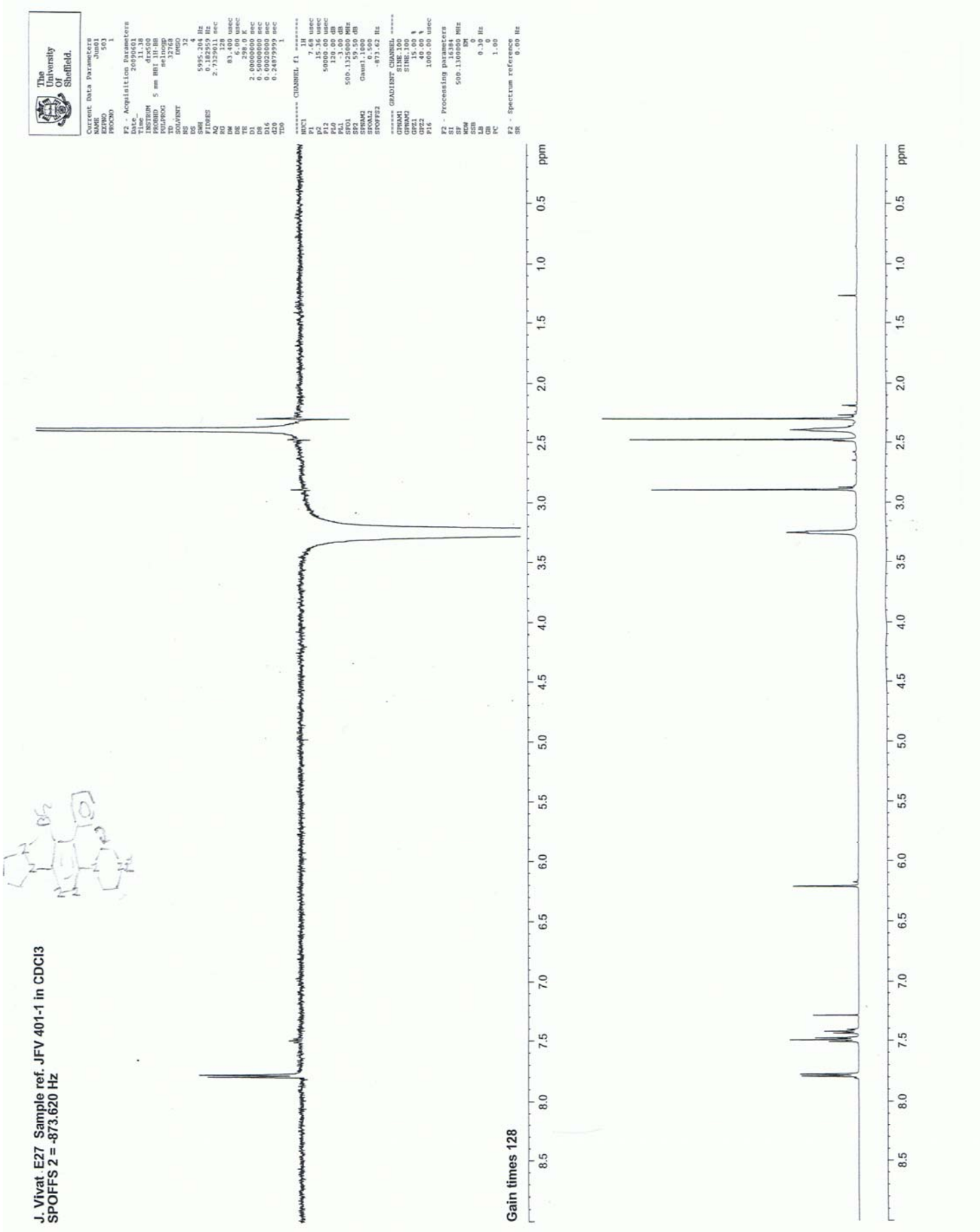
The regiochemistry of compounds **19** and **24** were assigned by nOe spectroscopy (see below). The regiochemistry of compound **22** was assigned by X-ray crystallography. CCDC-750154 contains the supplementary crystallographic data for compound **22**. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. The regiochemistry of compound **20** has been assigned by inference.

^{1}H NMR spectrum of **19**



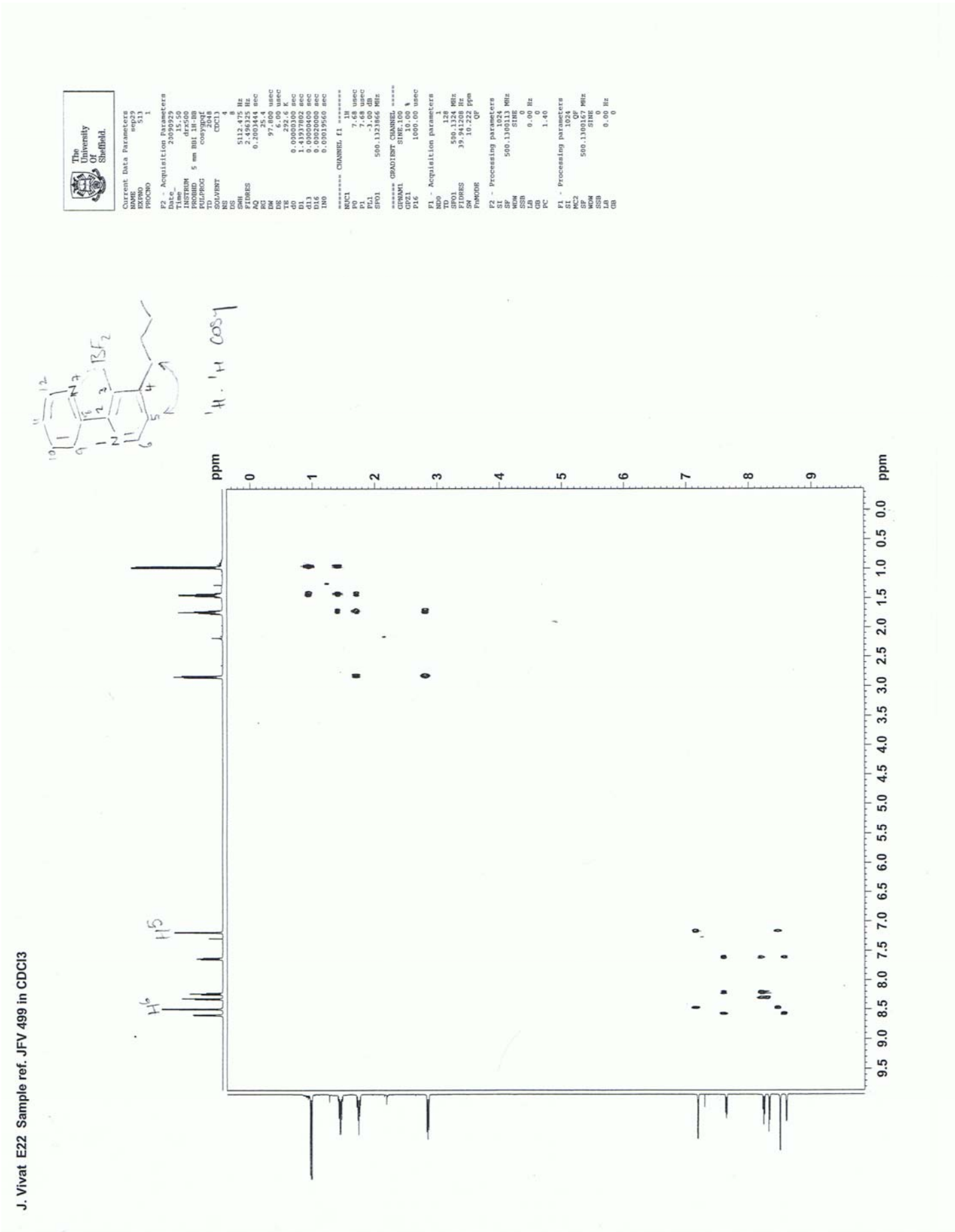
nOe spectrum of **19**

nOe spectrum of **19**

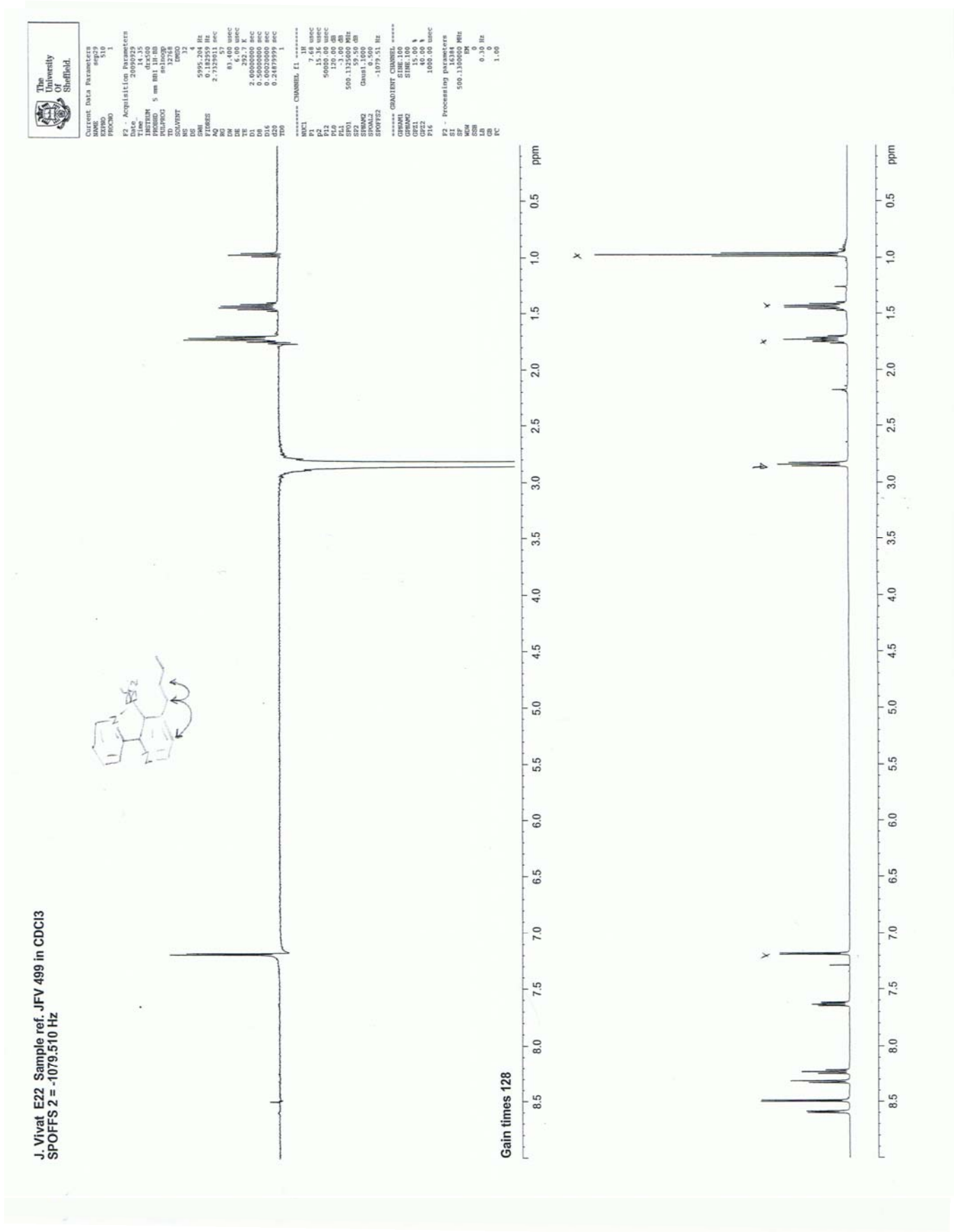


nOe spectrum of **19**

COSY spectrum of **24**

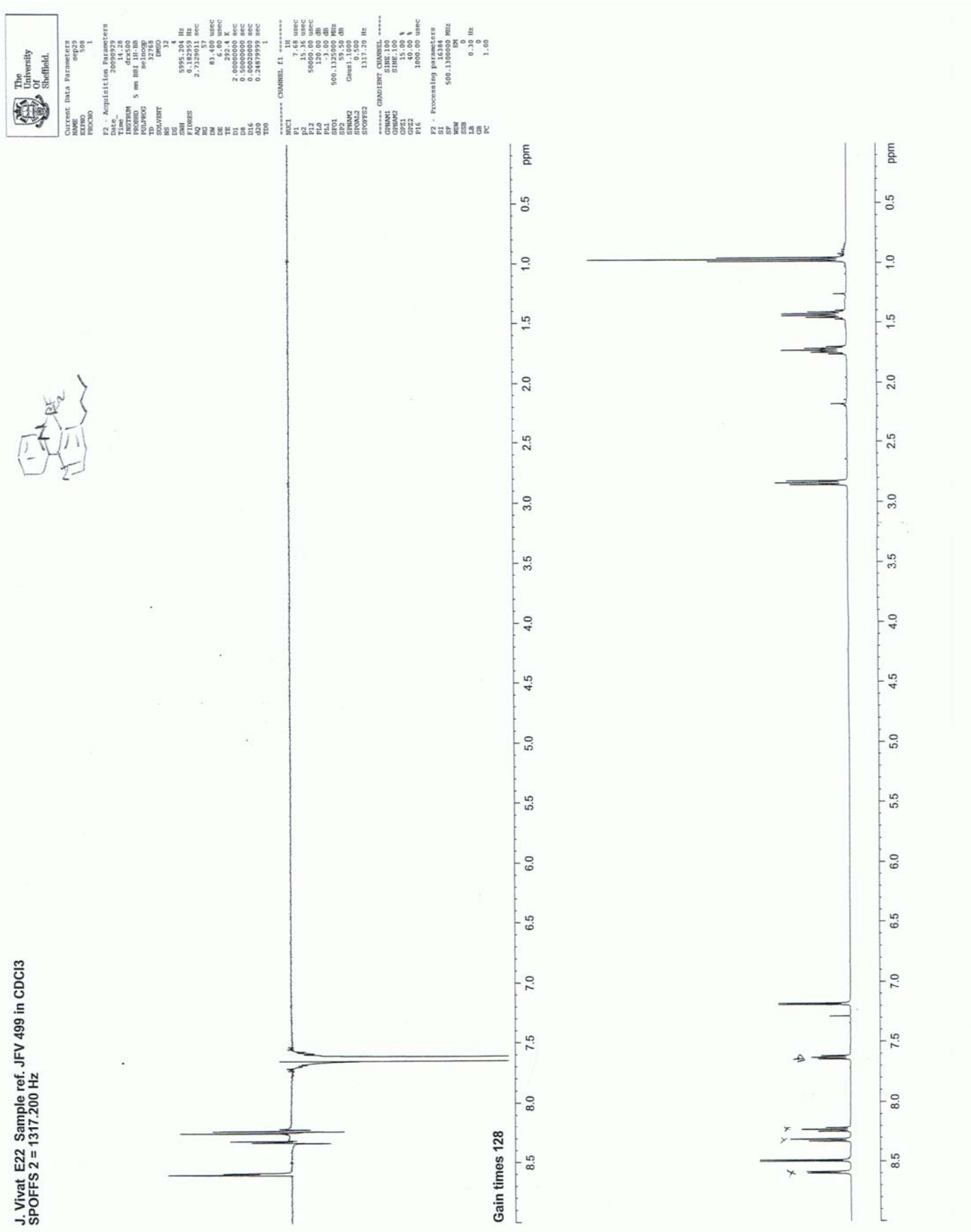


nOe spectrum of **24**

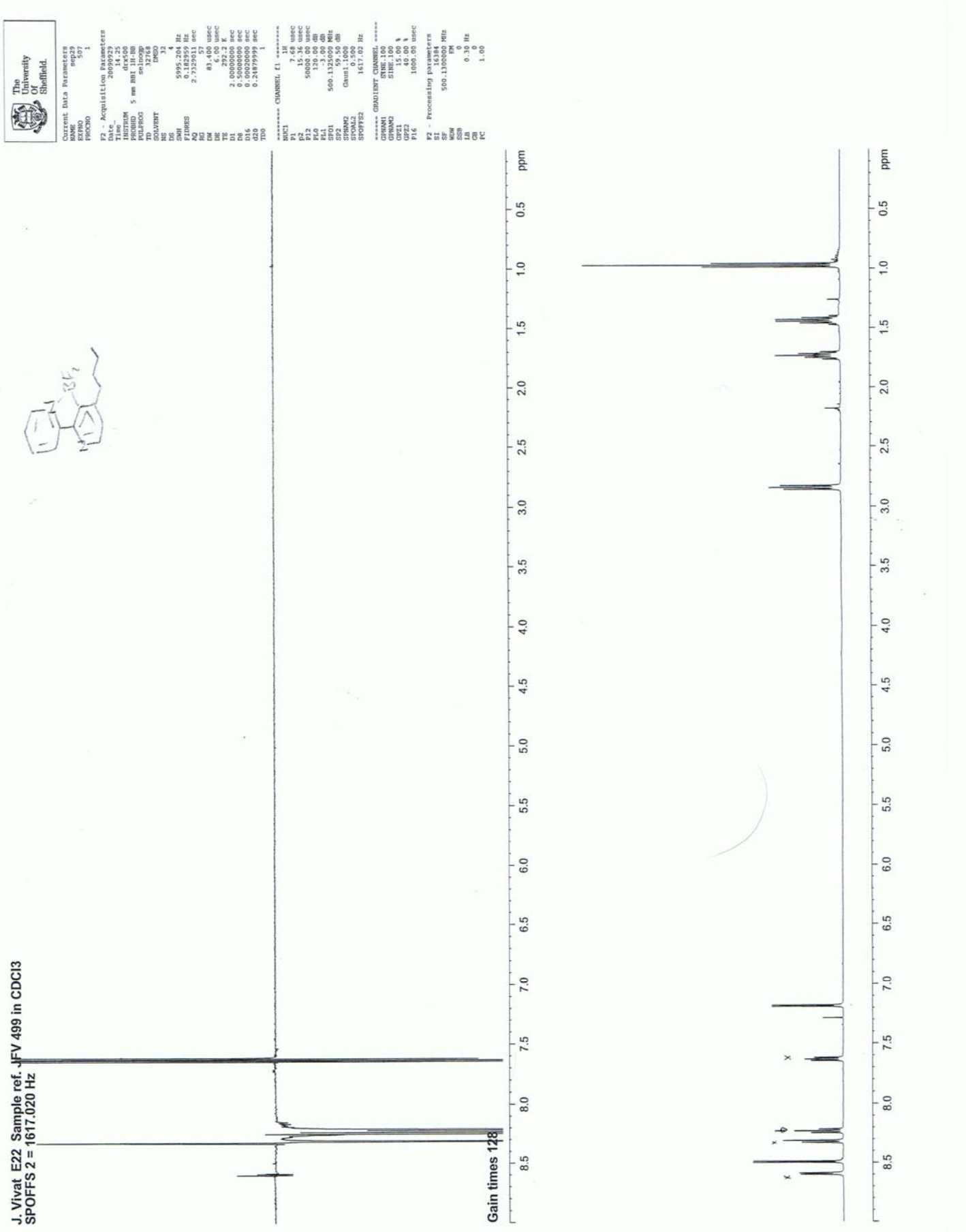


nOe spectrum of **24**

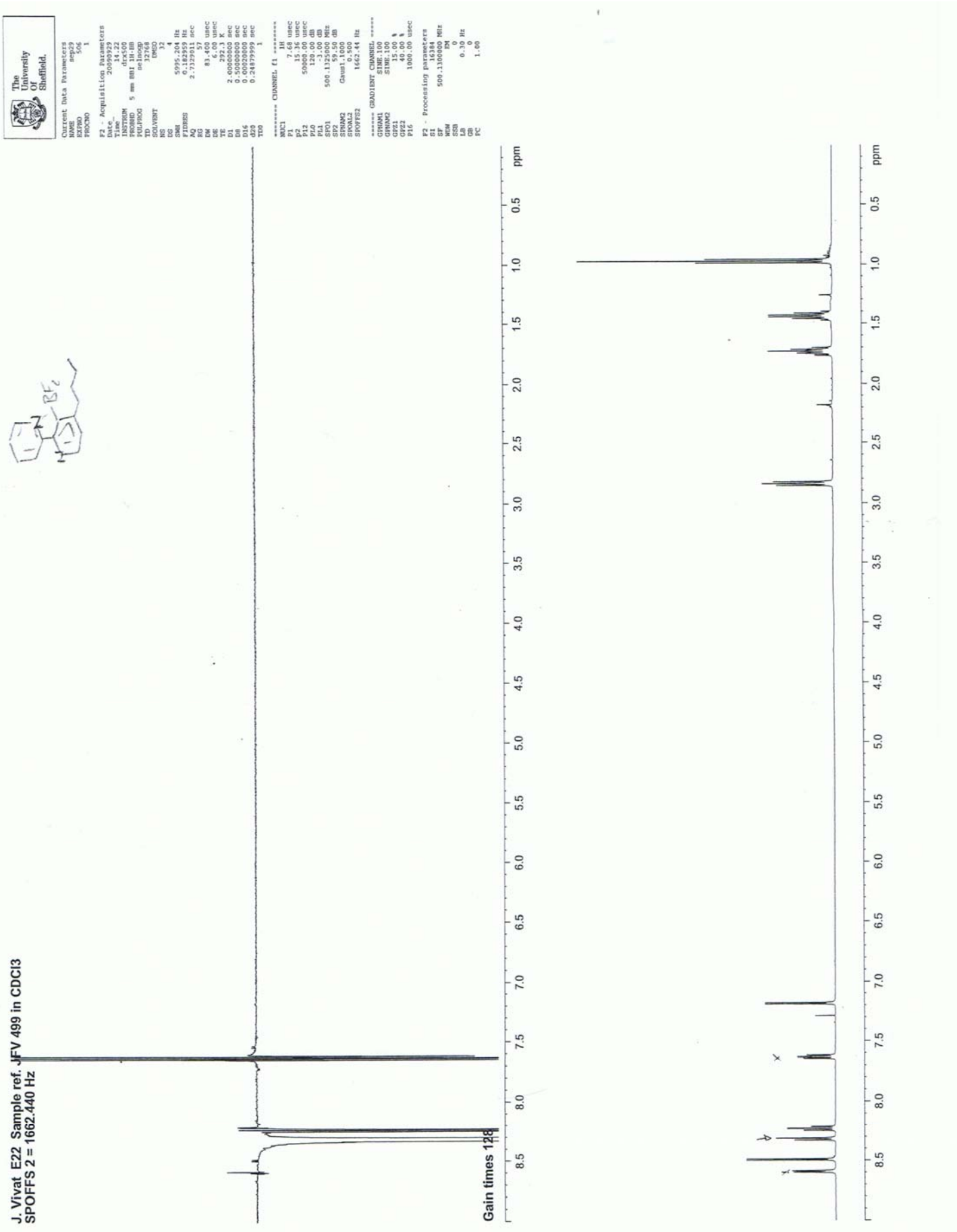
nOe spectrum of **24**



nOe spectrum of **24**



nOe spectrum of **24**



nOe spectrum of **24**