Supporting information

For

Structure Enabled Design of BAZ2-ICR, a Chemical Probe Targeting the Bromodomains of BAZ2A and BAZ2B

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Catalyzed C-C bond forming reaction

General Experimental

Unless otherwise stated, reagents and solvents were purchased from commercial suppliers and used without further purification. Chromatography solvents were HPLC grade and were used without further purification. All reactions were carried out in oven-dried flasks under a positive pressure of N_2, and air- and moisture-sensitive reagents transferred *via* syringe. Brine refers to saturated aqueous solution of NaCl. The term concentrated *in vacuo* refers to rotary evaporation.

Normal phase thin layer chromatography was conducted on standard commercial aluminium sheets pre-coated with a 0.2 mm layer of silica gel (Merck 60-254), and normal phase flash column chromatography was performed on silica gel 40 – 63 μm (Fluka 40 or Geduran 60) or on pre-packed Biotage SNAP columns. Purification by reversed-phase HPLC were performed onto a Phenomenex Gemini column (5 μm, 250 x 10 mm, C18, Phenomenex, Torrance, USA). Chromatographic separation at room temperature was carried out using a 1200 Series Preparative HPLC (Agilent, Santa Clara, USA). UV-Vis spectra were acquired at 254 nm and 280 nm on a 1200 Series Prep Scale diode array detector (Agilent, Santa Clara, USA). Collection was triggered by timed fractions, and collected on a 1200 Series Fraction Collector (Agilent, Santa Clara, USA). Raw data were processed using Agilent Chemstation Software. Or onto a Phenomenex Luna column (10 μm, 250 x 21.2 mm, C18, Phenomenex, Torrance, USA). Chromatographic separation at room temperature was carried out using a Gilson GX-281 Liquid Handler system combined with a Gilson 322 HPLC pump (Gilson, Middleton, USA). UV-Vis spectra were acquired at 254 nm on a Gilson 156 UV-Vis detector (Gilson, Middleton, USA). Collection was triggered by UV signal, and collected using a Gilson GX-281 Liquid Handler system (Gilson, Middleton, USA). Raw data were processed using Gilson Trilution Software.

^{1}H NMR spectra were recorded on a Bruker Avance 500 MHz spectrometer using an internal deuterium lock. Chemical shifts were measured in parts per million (ppm) relative to

tetramethylsilane (TMS, δ = 0) and were referenced to the following residual solvent signals: $CHCl_3$ (δ 7.26), CD_2HOD (δ 3.32), DHO (δ 4.79) and $(CD_3)(CD_2H)SO$ (δ 2.50). Data are presented in the following format: chemical shift (integration, multiplicity, coupling constants (*J* in Hz, order corresponds to order of multiplicities reported), assignment).

^{13}C NMR spectra were recorded on a Bruker Avance 500 MHz spectrometer using an internal deuterium lock. Chemical shifts were measured in parts per million (ppm) relative to tetramethylsilane (TMS, δ = 0) and were referenced to the following residual solvent signals: $CHCl_3$ (δ 77.16), CD_2HOD (δ 49.00) and $(CD_3)(CD_2H)SO$ (δ 39.52). Data are presented in the following format: chemical shift (multiplicity, coupling constants (*J* in Hz, order corresponds to order of multiplicities reported)).

LCMS analyses and high resolution mass spectrometry were performed on an Agilent 1200 series HPLC and diode array detector coupled to a 6210 time of flight mass spectrometer with dual multimode APCI/ESI source. Samples were supplied as approximately 1 mg/mL solutions in MeOH or $CHCl_3$ with 0.5-10 μL injected on a partial loop fill.

The purities of compounds were measured by analytical liquid chromatography using diode array detector at 254 nm and were ≥95%, unless stated otherwise in a few cases. Analytical separation was carried out at 30 °C on either a Merck Chromolith SpeedROD column (RP-18e, 50 x 4.6 mm) using a flow rate of 2 mL/min or a Merck Purospher STAR column (RP-18e, 30 x 4 mm) using a flow rate of 1.5 mL/min. Detection was at 254 nm. Molecular weight scan range was 85 – 950, 160 – 950 or 160 – 1700. HRMS references: **caffeine** $[M+H]^+$ 195.08765; **reserpine** $[M+H]^+$ 609.28066 or **hexakis (2,2-difluroethoxy)phosphazene** $[M+H]^+$ 622.02896; and **hexakis(1*H*,1*H*,3*H*-tetrafluoropentoxy)phosphazene** $[M+H]^+$ 922.00980.

The gradients for each method were as follows, with MeOH as eluent A and 0.1% formic acid in water as eluent B.

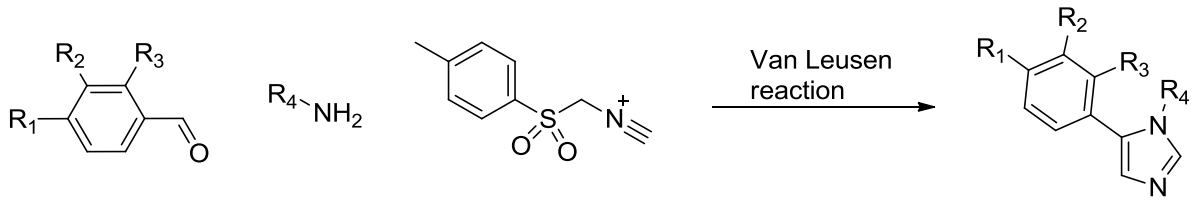
Fast4min:

Time / min	**A (%)**	**B (%)**
0	10	90
2.5	90	10
3.5	90	10
3.8	10	90
4	10	90

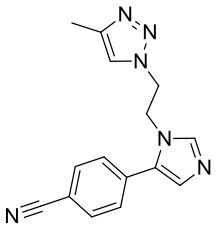
Melting points were determined on a Reichert Thermovar melting point apparatus and are uncorrected. IR analyses were carried out on a Bruker Alpha-P FT-IR spectrometer and absorptions are specified in wavenumbers (cm^{-1}).

Synthetic procedures

Van Leusen reaction.[1]



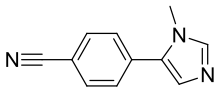
Synthesis of 4-(1-(2-(4-methyl-1*H*-1,2,3-triazol-1-yl)ethyl)-1*H*-imidazol-5-yl)benzonitrile (6)



To a solution of 2-(4-methyl-1*H*-1,2,3-triazol-1-yl)ethanamine (100 mg, 0.790 mmol) and 4-formylbenzonitrile (74 mg, 0.560 mmol) in EtOH (3 mL) was added glacial AcOH (0.06 mL) and the mixture was heated to reflux for 4 h. After cooling to room temperature, the solvent was removed *in vacuo* and the residue was taken up in DMF (5 mL). K_2CO_3 (155 mg, 1.12 mmol) and TosMIC (164 mg, 0.840 mmol) were added and the mixture was heated to 95 °C for 24 h. EtOAc (20 mL) and brine (20 mL) were added, the aqueous layer was extracted with EtOAc (20 mL) and the combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. The crude material was purified by flash column chromatography (0-20% MeOH in EtOAc) to yield the title compound **(6)** as a yellow oil (103 mg, 0.370 mmol, 66%). R_f = 0.1 (15% MeOH in EtOAc); ^{1}H NMR (500 MHz, MeOD) δ 2.18 (3H, d, *J* = 1.0 Hz, C$\underline{H}_3$-10), 4.54 (2H, dd, *J* = 5.5, 7.3 Hz, C$\underline{H}_2$-7), 4.67 (2H, dd, *J* = 4.0, 5.5 Hz, C$\underline{H}_2$-6), 7.07 (1H, d, *J* = 1.0 Hz, H-4), 7.28 (1H, d, *J* = 1.0 Hz, H-8), 7.47 (2H, dat, *J* = 2.0, 2.0, 8.5 Hz, H-12, H-16), 7.70 (1H, d, *J* = 1.0 Hz, H-2), 7.78 (2H, dat, *J* = 2.0, 2.0, 8.5 Hz, H-13, H-15); ^{13}C NMR (126 MHz, MeOD) δ 10.4 (C-10), 46.5 (C-6), 51.5 (C-7), 112.8 (C$\underline{N}$), 119.4 (C-11), 123.9 (C-8), 129.7 (C-4), 130.3 (C-12, C-16), 133.1 (C-14), 133.8 (C-13, C-15), 134.9 (C-5), 141.2 (C-2), 144.4

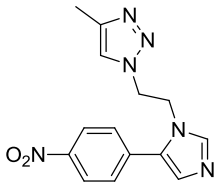
(C-9); IR (film) 3093, 2226, 1609, 1222, 855, 842, 821, 813, 567, 555, cm^{-1}; LCMS (Fast4min) t_r = 0.82 min, *m/z* 279 $[M + H]^+$; purity (AUC) > 95%; HRMS (ESI) *m/z* calcd for $C_{15}H_{15}N_6$ $[M + H]^+$ 279.1353, found $[M + H]^+$ 279.1358.

Synthesis of 4-(1-methyl-1H-imidazol-5-yl)benzonitrile (9)



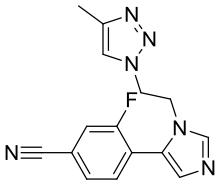
To a solution of methylaminium chloride (1.27 g, 18.81 mmol, 1.0 equiv) and 4-formylbenzonitrile (2.75 g, 20.97 mmol, 1.1 equiv) in ethanol (40 mL) was added glacial acetic acid (2.4 mL, 42.0 mmol, 2.2 equiv.) and the mixture was refluxed for 6 h. After cooling to room temperature, the solvent was removed *in vacuo* and the residue was taken up in DMF (30 mL). K_2CO_3 (9.29 g, 67.2 mmol, 3.6 equiv.) and TOSMIC (5.9 g, 30.2 mmol, 1.6 equiv.) were added and the mixture was heated to 95 °C for 18 h. Ethyl acetate (100 mL) and brine (50 mL) were added, and the aqueous layer was extracted with ethyl acetate (50 mL). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo* . The crude mixture was purified by flash column chromatography (0-10 % MeOH in DCM) to give 4-(1-methyl-1*H*-imidazol-5-yl)benzonitrile **(9)** as a colourless oil (330 mg, 10%). R_f = 0.4 (15% MeOH in EtOAc) blue spot under UV. ^{1}H NMR (500 MHz, MeOD-d_4) δ 7.82 (2H, dat, *J* = 2.0, 2.0, 8.5 Hz, ArH), 7.77 (1H, brs, ArH), 7.69 (2H, dat, *J* = 2.0, 2.0, 8.5 Hz, ArH), 7.21 (1H, d, *J* = 1 Hz, ArH), 3.78 (3H, s, CH_3) ppm; ^{13}C NMR (126 MHz, MeOD-d_4) δ 141.9, 135.7, 133.8, 133.5, 129.8, 129.5, 119.5, 112.5, 33.4 ppm; IR (film) 3091, 2227, 1610, 1491, 1128, 833, 554 cm^{-1}; LCMS (Fast4min) t_r = 0.59 min, *m/z* 184 $[M + H]^+$; purity (AUC) > 95%; HRMS for $[M + H^+]$ $C_{11}H_{10}N_3$ calcd, 184.0869; found, 184.0879.

Synthesis of 4-methyl-1-(2-(5-(4-nitrophenyl)-1*H*-imidazol-1-yl)ethyl)-1*H*-1,2,3-triazole (14)



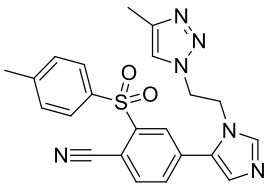
To a solution of 2-(4-methyl-1*H*-1, 2, 3-trizol-1-yl)ethanamine (153 mg, 1.21 mmol, 1.0 equiv) and 4-nitrobenzaldehyde (211 mg, 1.40 mmol, 1.2 equiv) in ethanol (3 mL) was added glacial acetic acid (0.14 mL) and the mixture was refluxed for 3 h. After cooling to room temperature, the solvent was removed *in vacuo* and the residue was taken up in DMF (4 mL). K_2CO_3 (368 mg, 2.66 mmol, 2.2 equiv) and TOSMIC (352 mg, 1.80 mmol, 1.5 equiv) were added and the mixture was heated to 95 °C for 22.5 h. Ethyl acetate (20 mL) and brine (20 mL) were added and the aqueous layer was extracted with ethyl acetate (20 mL). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. The crude mixture was purified by flash column chromatography (0-20 % MeOH in EtOAc) to give 4-methyl-1-(2-(5-(4-nitrophenyl)-1*H*-imidazol-1-yl)ethyl)-1*H*-1,2,3-triazole **(14)** as a brown oil (46 mg, 13 %). ^{1}H NMR (500 MHz, MeOD-d_4) δ 8.29 (2H, dat, *J* =2.5, 2.5, 9.0, ArH), 7.70 (1H, d, J = 1.0 Hz, ArH), 7.54 (2H, dat, J = 2.0, 2.0, 9.0 Hz, ArH), 7.29 (1H, d, *J* = 1.0, ArH), 7.13 (1H, d, *J* = 1.0, ArH), 4.71 (2H, dd, *J* = 4.0, 5.5 Hz, CH_2), 4.55 (2H, dd, *J* = 5.5, 7.0 Hz, CH_2), 2.16 (3H, d, J = 1.0 Hz, CH_3) ppm; ^{13}C NMR (126 MHz, MeOD) δ 148.7, 144.4, 141.5, 136.7, 132.7, 130.4, 130.1, 125.0, 123.9, 51.4, 46.6, 10.3 ppm; IR (film) 3086, 2233, 1414, 1223, 1118, 751, 659 cm^{-1}; LCMS (Fast4min) t_r = 1.04 min, *m/z* 299 $[M + H]^+$; purity (AUC) > 95%; HRMS for $[M + H^+]$ $C_{14}H_{15}N_6O_2$ calcd, 299.1251; found, 299.1247.

Synthesis of 3-fluoro-4-(1-(2-(4-methyl-1*H*-1,2,3-triazol-1-yl)ethyl)-1*H*-imidazol-5-yl)benzonitrile (15)



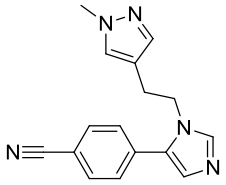
To a solution of 2-(4-methyl-1*H*-1, 2, 3-triazol-1-yl)ethanamine (156 mg, 1.24 mmol, 1.0 equiv) and 3-fluoro-4-formylbenzonitrile (207 mg, 1.39 mmol, 1.1 equiv) in ethanol (3 mL) was added glacial acetic acid (0.14 mL), and the mixture was refluxed for 3 h. After cooling to room temperature, the solvent was removed *in vacuo* and the residue was taken up in DMF (4 mL). K_2CO_3 (361 mg, 2.61 mmol, 2.1 equiv) and TOSMIC (352 mg, 1.80 mmol, 1.5 equiv) were added and the mixture was heated to 95 °C for 15 h. Ethyl acetate (20 mL) and brine (20 mL) were added and the aqueous layer was extracted with ethyl acetate (20 mL). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. The crude mixture was purified by flash column chromatography (0-20 % MeOH in EtOAc) to give 3-fluoro-4-(1-(2-(4-methyl-1*H*-1,2,3-triazol-1-yl)ethyl)-1*H*-imidazol-5-yl)benzonitrile **(15)** as a brown oil (110 mg, 30 %). R_f = 0.2 (10% MeOH in EtOAc); ^{1}H NMR (500 MHz, MeOD-d_4) δ 7.76 (1H, d, *J* = 1.0 Hz, ArH), 7.71 (2H, dat, *J* = 2.0, 2.0, 8.5 Hz, ArH), 7.38 (at, *J* = 7.5, 7.5 Hz, ArH), 7.29 (1H, d, *J* = 1.0 Hz, ArH), 7.07 (1H, brs, ArH), 4.55-4.59 (2H, m, CH_2), 4.53-4.55 (2H, m, CH_2), 2.18 (3H, d, *J* = 1.0 Hz, CH_3); ^{13}C NMR (126 MHz, MeOD-d_4) δ 160.4 (d, *J* = 248.6 Hz), 144.5, 141.2, 133.9 (d, *J* = 2.7 Hz), 130.9 (d, *J* = 1.9 Hz), 129.8 (d, *J* = 4.6 Hz), 129.8, 127.0, 126.9, 123.8, 121.0 (d, 25.5 Hz), 115.1 (d, *J* = 10.5 Hz), 51.8, 46.8 (d, *J* = 3.6 Hz), 10.4 ppm; LCMS (Fast4min) t_r = 0.89 min, *m/z* 297 $[M + H]^+$; purity (AUC) > 95%; HRMS for $[M + H^+]$ $C_{15}H_{14}FN_6$ calcd, 297.1258; found, 297.1257.

Synthesis of 4-(1-(2-(4-methyl-1*H*-1,2,3-triazol-1-yl)ethyl)-1*H*-imidazol-5-yl)-2-(4-methylphenylsulfonyl)benzonitrile (16) This molecule was isolated as impurity from the Van Leusen reaction.



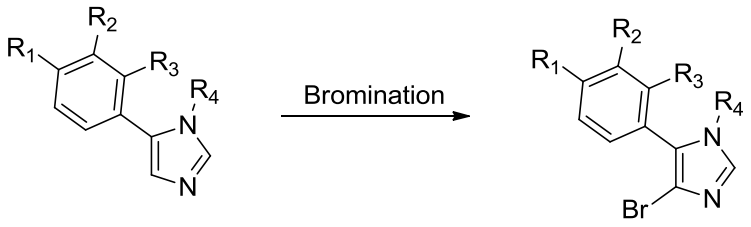
To a solution of 2-(4-methyl-1*H*-1, 2, 3-triazol-1-yl)ethanamine (154 mg, 1.22 mmol, 1.0 equiv) and 2-fluoro-4-formylbenzonitrile (200 mg, 1.34 mmol, 1.1 equiv) in ethanol (3 mL) was added glacial acetic acid (0.14 mL), and the mixture was refluxed for 3 h. After cooling to room temperature, the solvent was removed *in vacuo* and the residue was taken up in DMF (4 mL). K_2CO_3 (369 mg, 2.67 mmol, 2.2 equiv) and TOSMIC (357 mg, 1.83 mmol, 1.5 equiv) were added and the mixture was heated to 95 °C for 22.5 h. Ethyl acetate (20 mL) and brine (20 mL) were added, and the aqueous layer extracted with ethyl acetate (20 mL). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. The crude mixture was purified by flash column chromatography (0-20 % MeOH in EtOAc) to give 4-(1-(2-(4-methyl-1*H*-1,2,3-triazol-1-yl)ethyl)-1*H*-imidazol-5-yl)-2-(4-methylphenylsulfonyl)benzonitrile **(16)** as a brownish oil (193 mg, 53 %). R_f = 0.1 (10% MeOH in EtOAc); ^{1}H NMR (500 MHz, MeOD-d_4) δ 8.22 (1H, d, J = 2.0 Hz, ArH), 8.00 (2h, dat, J = 2.0, 2.0, 8.5 Hz, 2 x ArH), 7.94 (1H, d, J = 7.5 Hz, ArH), 7.81 (1H, brs, ArH), 7.70 (1H, dd, J = 2.0, 8.0 Hz, ArH), 7.45-7.47 (2H, m, 2 x ArH), 7.29 (1H, d, J = 1.0 Hz, ArH), 7.23 (1H, brs, ArH), 4.72 (2H, dd, J = 5.0, 7.0 Hz, CH_2), 4.58 (2 H, dd, J = 5.0, 7.0 Hz, CH_2), 2.45 (1H, s, CH_3), 2.12 (3H, d, J = 1.0 Hz, CH_3) ppm; ^{13}C NMR (126 MHz, MeOD-d_4) δ 147.3, 145.5, 144.5, 137.8, 137.6, 133.9, 131.3, 131.1, 129.9, 129.7, 126.3, 123.9, 119.0, 116.6, 110.7, 51.7, 46.7, 21.7, 10.3 ppm; IR (film) 2959, 2228, 1597, 1153, 560, 541 cm^{-1}; LCMS (Fast4min) t_r = 1.99 min, m/z 433 $[M + H]^+$; purity (AUC) > 86%; HRMS for $[M + H^+]$ $C_{22}H_{21}N_6O_2S$ calcd, 433.1441; found, 433.1425.

Synthesis of 4-(1-(2-(1-methyl-1*H*-pyrazol-4-yl)ethyl)-1*H*-imidazol-5-yl)benzonitrile (17)

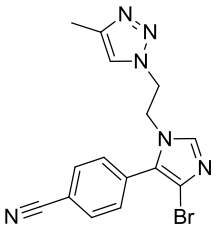


To a solution of 2-(1-methyl-1*H*-pyrazol-4-yl)ethanamine (85 mg, 0.679 mmol, 1.0 equiv) and 4-formylbenzonitrile (90 mg, 1.01 mmol, 1.0 equiv) in ethanol (3 mL) was added glacial acetic acid (0.08 mL), and the mixture was refluxed for 4 h. After cooling to room temperature, the solvent was removed *in vacuo* and the residue was taken up in DMF (5 mL). K_2CO_3 (200 mg, 1.45 mmol, 2.1 equiv) and TOSMIC (200 mg, 1.02 mmol, 1.5 equiv) were added and the mixture was heated to 95 °C for 22.5 h. Ethyl acetate (20 mL) and brine (20 mL) were added and the aqueous layer was extracted with ethyl acetate (20 mL). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo* . The crude mixture was purified by flash column chromatography (1-9 % MeOH in DCM) to give 4-(1-(2-(1-methyl-1*H*-pyrazol-4-yl)ethyl)-1*H*-imidazol-5-yl)benzonitrile **(17)** as a reddish brown oil (100 mg, 53 %). ^{1}H NMR (500 MHz, MeOD-d_4) δ 7.77 (2H, dat, J = 1.5, 1.5, 8.5 Hz, ArH), 7.74 (1H, d, J = 1.5 Hz, ArH), 7.53 (2H, dat, J = 1.5, 1.5, 8.5 Hz, ArH), 7.10 (1H, d, J = 1.0 Hz, ArH), 6.98 (b1H, rs, ArH), 4.30 (2H, t, J = 7.0 Hz, CH_2), 3.73 (3H, s, CH_3), 2.71 (2H, t, J = 7.0 Hz, CH_2) ppm; ^{13}C NMR (126 MHz, MeOD-d_4) δ 141.2, 139.5, 135.8, 133.8, 132.9, 130.9, 130.0, 130.0, 119.5, 117.9, 112.5, 47.9, 38.7, 26.7 ppm; LCMS (Fast4min) t_r = 1.30 min, *m/z* 278 $[M + H]^+$; purity (AUC) > 95%; HRMS for $[M + H^+]$ $C_{16}H_{16}N_5$ calcd, 278.1400; found, 278.1412.

Bromination reaction

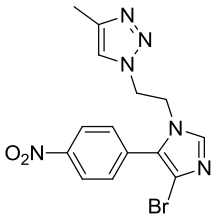


Synthesis of 4-(4-bromo-1-(2-(4-methyl-1*H*-1,2,3-triazol-1-yl)ethyl)-1*H*-imidazol-5-yl)benzonitrile (18)



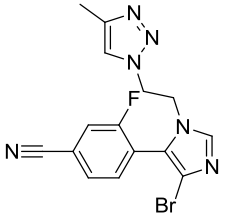
To a solution of 4-(1-(2-(4-methyl-1*H*-1,2,3-triazol-1-yl)ethyl)-1*H*-imidazol-5-yl) benzonitrile **(6)** (287 mg, 1.03 mmol) in DMF (44 mL) at 0 °C was added DBDMH (148 mg, 0.517 mmol). The mixture was allowed to warm to room temperature, and after stirring for 20 h, brine (100 mL) and EtOAc (50 mL) were added and the organic layer was dried ($MgSO_4$) and concentrated *in vacuo*. The crude material was purified by flash column chromatography (0-20% MeOH in CH_2Cl_2) to yield the title compound **(18)** as a pale yellow solid (221 mg, 0.619 mmol, 60%). m.p.: 174-176 °C; R_f = 0.5 (10% MeOH in CH_2Cl_2); ^{1}H NMR (500 MHz, MeOD) δ 7.84 (2H, dat, *J* = 2.0, 2.0, 8.5 Hz, H-13, H-15), 7.67 (1H, s, H-2), 7.47 (2H, dat, *J* = 2.0, 2.0, 8.5 Hz, H-12, H-16), 7.36 (1H, d, *J* = 1.0 Hz, H-8), 4.57 (2H, dd, *J* = 3.5, 5.5 Hz, C$\underline{H}_2$-6), 4.49 (2H, dd, *J*= 5.5, 7.0 Hz, C$\underline{H}_2$-7), 2.21 (3H, d, *J* = 1.0 Hz, C$\underline{H}_3$-10) ppm; ^{13}C NMR (126 MHz, MeOD) δ 144.1 (C-9), 139.0 (C-2), 133.2 (C-13, C-15), 132.7 (C-11), 131.2 (C-12, C-16), 128.9 (C-5), 123.0 (C-8), 118.7 (C$\underline{\equiv}$N), 116.1 (C-4), 113.1 (C-14), 50.5 (C-7), 46.6 (C-6), 10.5 (C-10) ppm; IR (solid) 3080, 2227, 1490, 1247, 842, 796, 567; LCMS (Fast4min) t_r = 2.35 min, *m/z* 359 $[M + H]^+$; purity (AUC) = 94%; HRMS (ESI) *m/z* calcd for $C_{15}H_{14}BrN_6$ $[M + H]^+$ 357.0458, found $[M + H]^+$ 357.0469.

Synthesis of 1-(2-(4-bromo-5-(4-nitrophenyl)-1*H*-imidazol-1-yl)ethyl)-4-methyl-1*H*-1,2,3-triazole (19)



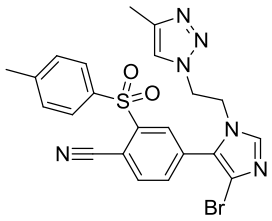
To a solution of 4-methyl-1-(2-(5-(4-nitrophenyl)-1*H*-imidazol-1-yl)ethyl)-1*H*-1,2,3-triazole **(14)** (46 mg, 0.154 mmol, 1.0 equiv) in DMF (5 mL) at 0 °C was added DBDMH (28 mg, 0.0980 mmol, 0.6 equiv). The mixture was allowed to warm to room temperature, and after stirring for 24 h, brine (20 mL) and EtOAc (10 mL) were added. The organic layer was separated, dried ($MgSO_4$) and concentrated *in vacuo.* The crude material was purified by flash column chromatography, (0-20% MeOH in CH_2Cl_2) to yield 1-(2-(4-bromo-5-(4-nitrophenyl)-1*H*-imidazol-1-yl)ethyl)-4-methyl-1*H*-1,2,3-triazole **(19)** (20 mg, 35%). ^{1}H NMR (500 MHz, MeOD-d_4) δ 8.32 (2H, dat, *J* = 2.0, 2.0, 8.5 Hz, ArH), 7.47 (2H, dat, *J* = 2.5, 2.5, 9.0 Hz, ArH), 7.33 (s, 1H), 6.92 (d, J = 0.5 Hz, 1H), 4.53 (2H, dd, *J* = 5.0, 6.5 Hz, CH_2), 4.39 (2H, dd, *J* = 5.5 Hz, 7.0 Hz, CH_2), 2.26 (3H, d, *J* = 0.5 Hz, CH_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ 147.9, 144.0, 138.4, 134.1, 130.8, 127.6, 124.4, 121.9, 117.2, 49.9, 46.1, 10.8; LCMS (Fast4min) t_r = 2.30 min, *m/z* 377 $[M + H]^+$; purity (AUC) > 95%; HRMS for $[M + H^+]$ $C_{14}H_{14}BrN_6O_2$ calcd, 377.0356; found, 377.0343.

Synthesis of 4-(4-bromo-1-(2-(4-methyl-1H-1,2,3-triazol-1-yl)ethyl)-1H-imidazol-5-yl)-3-fluorobenzonitrile (20)



To a solution of 3-fluoro-4-(1-(2-(4-methyl-1*H*-1,2,3-triazol-1-yl)ethyl)-1*H*-imidazol-5-yl)benzonitrile **(15)** (95 mg, 0.321 mmol, 1.0 equiv) in DMF (15 mL) at 0 °C was added DBDMH (53.2 mg, 0.186 mmol, 0.6 equiv). The mixture was allowed to warm to room temperature, and after stirring for 24 h, brine (30 mL) and EtOAc (50 mL) were added. The organic layer was separated, dried ($MgSO_4$) and concentrated *in vacuo.* The crude material was purified by flash column chromatography, (0-20% MeOH in CH_2Cl_2) to yield 4-(4-bromo-1-(2-(4-methyl-1*H*-1,2,3-triazol-1-yl)ethyl)-1*H*-imidazol-5-yl)-3-fluorobenzonitrile **(20)** (63 mg, 52 %) as yellowish crystals on slow evaporation from methanol. R_f = 0.7 (DCM/MeOH: 9/1); ^{1}H NMR (500 MHz, MeOD-d_4) δ 7.74 (1H, dd, J = 1.5, 9.5 Hz, ArH), 7.71 (1H, s, ArH), 7.69 (1H, dd, J = 1.5, 8.0 Hz, ArH), 7.41 (1H, at, J = 8.0, 8.0 Hz, ArH), 7.39 (1H, d, J = 1.0 Hz, ArH), 4.52 (4H, br s, $2CH_2$), 2.22 (3H, d, J = 1.0 Hz, CH_3) ppm; ^{13}C NMR (126 MHz, MeOD-d_4) δ 160.6 (d, J = 251.2 Hz), 144.6, 140.4, 135.2 (d, J = 2.8 Hz), 129.8 (d, J = 4.7 Hz), 124.4, 123.8, 121.7 (d, J = 15.7 Hz), 121.3 (d, J = 26.7 Hz), 118.1 (d, J = 2.6 Hz), 117.4, 116.3 (d, J = 10.1 Hz), 51.4, 47.5 (d, J = 3.1 Hz), 10.4 ppm; IR (solid) 3139, 2234, 1245, 754 cm^{-1}; LCMS (Fast4min) t_r = 2.19 min, *m/z* 375 $[M + H]^+$; purity (AUC) > 95%; HRMS for $[M + H^+]$ $C_{15}H_{13}BrFN_6$ calcd, 375.0364; found, 375.0352.

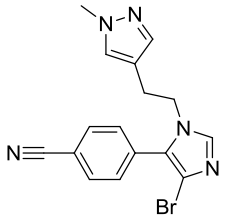
Synthesis of 4-(4-bromo-1-(2-(4-methyl-1*H*-1,2,3-triazol-1-yl)ethyl)-1*H*-imidazol-5-yl)-2-(4-methylphenylsulfonyl)benzonitrile (21) This molecule was isolated as impurity from the bromination of the mixture from Van Leusen reaction.



To a solution of the inseparable mixture from **(16)** (189 mg, 0.638 mmol, 1.0 equiv) in DMF (5 mL) at 0 °C was added DBDMH (102 mg, 0.357 mmol, 0.6 equiv). The mixture was allowed to warm to room temperature, and after stirring for 24 h, brine (30 mL) and EtOAc

(50 mL) were added. The organic layer was separated, dried ($MgSO_4$) and concentrated *in vacuo.* The crude material was purified by flash column chromatography, (0-20% MeOH in CH_2Cl_2) to yield 4-(4-bromo-1-(2-(4-methyl-1*H*-1,2,3-triazol-1-yl)ethyl)-1*H*-imidazol-5-yl)-2-(4-methylphenylsulfonyl)benzonitrile **(21)** as yellowish crystals from slow evaporation from methanol (126 mg, 67 %, 85% purity). R_f = 0.7 (10% MeOH in CH_2Cl_2); ^{1}H NMR (500 MHz, MeOD-d_4) δ 8.23 (1H, d, *J* = 1.5 Hz, ArH), 8.00 (1H, d, *J* = 8.0 Hz, ArH), 7.97 (2H, dat, *J* = 2.0, 2.0, 8.5 Hz, 2 x ArH), 7.77 (1H, s, ArH), 7.70 (1H, dd, *J* = 1.5, 8.0 Hz, ArH), 7.44 (2H, brd, *J* = 8.0 Hz, 2 x ArH), 7.36 (1H, d, *J* = 1.0 Hz, ArH), 4.65 (2H, dd, *J* = 5.0, 7.0 Hz, CH_2), 4.55 (2H, dd, *J* = 5.0, 7.0 Hz, CH_2), 2.41 (3H, s, CH_3), 2.17 (3H, d, *J* = 1.0 Hz, CH_3) ppm; NMR (126 MHz, MeOD-d_4) δ 147.4, 145.3, 144.7, 140.9, 137.7, 137.6, 135.6, 134.2, 131.7, 131.3, 129.8, 128.5, 123.8, 117.3, 116.5, 111.4, 51.4, 47.6, 14.5, 10.4, IR (solid) 3095, 2230, 1327, 1243, 1158, 753, 562, 543 cm^{-1}; LCMS (Fast4min) t_r = 2.49 min, *m/z* 513 $[M + H]^+$; purity (AUC) > 95%; HRMS for $[M + H^+]$ $C_{22}H_{20}BrN_6O_2S$ calcd, 511.0546; found, 511.052.

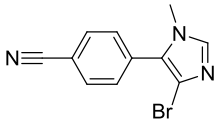
Synthesis of 4-(4-bromo-1-(2-(1-methyl-1*H*-pyrazol-4-yl)ethyl)-1*H*-imidazol-5-yl)benzonitrile (22)



To a solution of 4-(1-(2-(1-methyl-1*H*-pyrazol-4-yl)ethyl)-1*H*-imidazol-5-yl)benzonitrile **(17)** (755 mg, 2.72 mmol, 1.0 equiv) in DMF (50 mL) at 0 °C was added DBDMH (398 mg, 1.39 mmol, 0.51 equiv). The mixture was allowed to warm to room temperature and after stirring for 24 h, brine (100 mL) and EtOAc (50 mL) were added. The organic layer was separated, dried ($MgSO_4$) and concentrated *in vacuo.* The crude material was purified by flash column chromatography, (0-15% MeOH in EtOAc) to yield 4-(4-bromo-1-(2-(1-methyl-1*H*-pyrazol-4-yl)ethyl)-1*H*-imidazol-5-yl)benzonitrile **(22)** (782 mg, 81%) as an orange oil. ^{1}H NMR (500

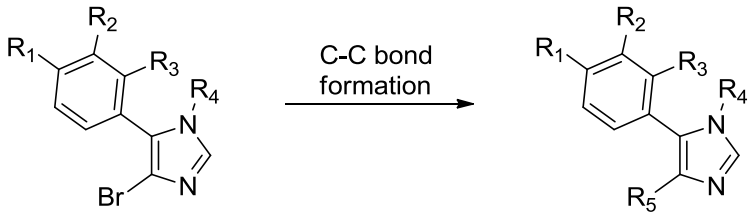
MHz, MeOD-d_4) δ 7.84 (2H, dat, J = 2.0, 2.0, 8.5 Hz, ArH), 7.73 (1H, s, ArH), 7.50 (2H, dat, J = 2.0, 2.0, 8.5 Hz, ArH), 7.11 (1H, brs, ArH), 6.98 (1H, brs, ArH), 4.20 (2H, t, J = 6.5 Hz, CH_2), 3.75 (3H, s, CH_3), 2.66 (2H, t, J = 6.5 Hz, CH_2) ppm; ^{13}C NMR (126 MHz, MeOD-d_4) δ 139.9, 139.5, 134.3, 133.7, 131.9, 130.9, 129.8, 119.3, 117.7, 115.6, 113.4, 48.7, 38.7, 26.4 ppm; LCMS (Fast4min) t_r = 2.32 min, m/z 358 $[M + H]^+$; purity (AUC) > 95%; HRMS for $[M + H^+]$ $C_{16}H_{15}BrN_5$ calcd, 356.0505; found, 356.0507.

Synthesis of 4-(4-bromo-1-methyl-1*H*-imidazol-5-yl)benzonitrile (23)

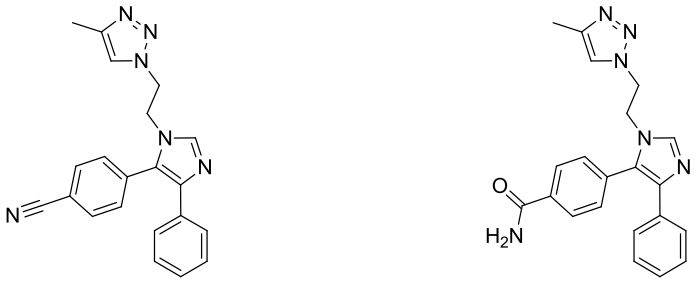


To a cooled solution of 4-(1-methyl-1*H*-imidazol-5-yl)benzonitrile **(9)** (316 mg, 1.72 mmol, 1.0 equiv) in DMF (50 mL) was added DBDMH (283 mg, 0.990 mmol, 0.57 equiv.). The mixture was then allowed to warm to room temperature and after stirring for 20 h, brine (100 mL) and EtOAc (50 mL) were added and the organic layer was dried ($MgSO_4$) and concentrated *in vacuo*. The crude material was purified by Snap column chromatography (0-20% MeOH in CH_2Cl_2) to yield 4-(4-bromo-1-methyl-1*H*-imidazol-5-yl)benzonitrile **(23)** as a pale yellow amorphous solid (257 mg, 0.981 mmol, 57%). R_f =0.7 (10% MeOH in DCM). ^{1}H NMR (500 MHz, MeOD-d_4) δ 7.87 (2H, dat, J = 2.0, 2.0, 9.0 Hz, ArH), 7.77 (1H, s, ArH), 7.68 (2H, dat, J = 2.0, 2.0, 9.0 Hz, ArH), 3.67 (3H, s, CH_3) ppm; ^{13}C NMR (126 MHz, MeOD-d_4) δ 140.5, 134.1, 133.7, 131.9, 130.2, 119.3, 115.4, 113.5, 34.0 ppm; IR (solid) 3114, 2228, 1610, 1491, 1460, 1240, 960, 845, 571, 561 cm^{-1}; LCMS (Fast4min) t_r = 2.30 min, m/z 262 $[M + H]^+$; purity (AUC) > 95%; HRMS (ESI) m/z calcd for $C_{11}H_9BrN_3$ $[M + H]^+$ 261.9974, found $[M + H]^+$ 261.9996.

Catalyzed C-C bond forming reaction



Synthesis of 4-(1-(2-(4-methyl-1*H*-1,2,3-triazol-1-yl)ethyl)-4-phenyl-1*H*-imidazol-5-yl)benzonitrile (1) and 4-(1-(2-(4-methyl-1*H*-1,2,3-triazol-1-yl)ethyl)-4-phenyl-1*H*-imidazol-5-yl)benzamide (24)



Method A (Reflux Conditions)

A mixture of 4-(4-bromo-1-(2-(4-methyl-1*H*-1,2,3-triazol-1-yl)ethyl)-1*H*-imidazol-5-yl)benzonitrile **(18)** (15 mg, 0.0420 mmol), phenylboronic acid (10 mg, 0.0820 mmol), $PdCl_2$(dppf) (3 mg, 0.004 mmol), $BnEt_3NCl$ (1 mg, 0.004 mmol), CsF (19 mg, 0.130 mmol), toluene (1 mL) and water (1 mL) was stirred at reflux for 24 h. Phenylboronic acid (5 mg, 0.04 mmol), $PdCl_2$(dppf) (3 mg, 0.004 mmol), $BnEt_3NCl$ (1 mg, 0.004 mmol), and CsF (10 mg, 0.066 mmol) were added and the mixture heated for a further 48 h. The mixture was filtered through celite, and phenylboronic acid (10 mg, 0.082 mmol), $PdCl_2$(dppf) (3 mg, 0.004 mmol), $BnEt_3NCl$ (1 mg, 0.004 mmol), and CsF (19 mg, 0.13 mmol) were added. After a further 24 h, the mixture was cooled to room temperature and extracted with EtOAc (4 × 20 mL), and the combined organic layers were washed with brine (50 mL), dried ($MgSO_4$) and concentrated *in vacuo* to yield **(1)** as an off-white solid (7 mg, 0.02 mmol, 47%).

Method B (Microwave Conditions)

A mixture of 4-(4-bromo-1-(2-(4-methyl-1*H*-1,2,3-triazol-1-yl)ethyl)-1*H*-imidazol-5-yl)benzonitrile **(18)** (30 mg, 0.0840 mmol), $Pd(PPh_3)_4$ (5 mg, 0.004 mmol), Na_2CO_3 (18 mg, 0.17 mmol), phenylboronic acid (13 mg, 0.11 mmol), 1,4-dioxane (1 mL) and water (1 mL) was heated to 140 °C in a Biotage Initiator 2.5 Microwave for 30 min. The crude material was purified by Isolute Flash SCX-2 column (100% MeOH to 2 M NH_3 in MeOH) followed by flash column chromatography (0-20% MeOH in CH_2Cl_2) to yield 4-(1-(2-(4-methyl-1*H*-1,2,3-triazol-1-yl)ethyl)-4-phenyl-1*H*-imidazol-5-yl)benzonitrile **(1)** as an off-white solid (11 mg, 0.03 mmol, 37%) and 4-(1-(2-(4-methyl-1*H*-1,2,3-triazol-1-yl)ethyl)-4-phenyl-1*H*-imidazol-5-yl)benzamide **(24)** as a white solid (9 mg, 0.02 mmol, 29%, ≥90% purity).

4-(1-(2-(4-Methyl-1*H*-1,2,3-triazol-1-yl)ethyl)-4-phenyl-1*H*-imidazol-5-yl)benzonitrile (1)

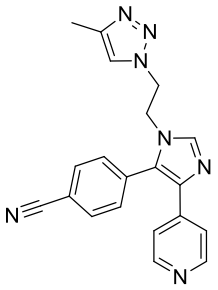
m.p.: 65-74 °C; R_f = 0.3 (10% MeOH in CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76 (2H, dat, J = 1.5, 1.5, 8.5 Hz, ArH), 7.54 (1H, s, ArH), 7.34 (2H, dat, J = 1.5, 1.5, 8.5 Hz, ArH), 7.31-7.32 (2H, m, 2 x ArH), 7.20-7.23 (3H, m, 3 x ArH), 6.93 (1H, d, J = 0.5 Hz, ArH), 4.41 (4H, br s, 2 x CH_2), 2.28 (3H, s, CH_3) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ 143.9, 139.6, 137.7, 134.4, 133.1, 132.6, 131.3, 128.5, 127.5, 127.0, 126.1, 121.8, 118.0, 113.1, 49.8, 45.1, 10.7 ppm; IR (solid) 3298, 2934, 1633, 1529, 1218, 697 cm^{-1}; LCMS (Fast4min) t_r = 2.13 min, *m/z* 355 $[M + H]^+$; purity (AUC) > 95%; HRMS (ESI) *m/z* calcd for $C_{21}H_{19}N_6$ $[M + H]^+$ 355.1666, found $[M + H]^+$ 355.1668.

4-(1-(2-(4-Methyl-1*H*-1,2,3-triazol-1-yl)ethyl)-4-phenyl-1*H*-imidazol-5-yl)benzamide (24)

m.p.: > 230 °C (decomposition); R_f = 0.8 (15% MeOH in CH_2Cl_2); ^{1}H NMR (500 MHz, MeOD) δ 7.96 (2H, br d, 2 x ArH), 7.61 (1H, s, ArH), 7.40 (1H, br s, ArH), 7.32 (2H, br d, J = 8.5 Hz, 2 x ArH), 7.28 (2H, br dd, J = 1.5, 8.0 Hz, 2 x ArH), 7.14-7.20 (3H, m, 3 x ArH), 4.46-4.52 (4H, m, 2 x CH_2), 2.22 (3H, s, CH_3) ppm; ^{13}C NMR (126 MHz, MeOD) δ 171.5, 144.6, 139.9, 139.2, 135.5, 135.0, 134.4, 132.1, 129.5, 129.2, 129.0, 128.3, 128.0, 123.9, 51.2, 46.2, 10.4

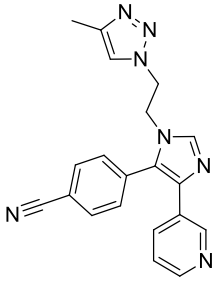
ppm; IR (solid) 3155, 2922, 1661, 1617, 1387, 777, 698 cm^{-1}; LCMS (Fast4min) t_r = 1.62 min, *m/z* 373 $[M + H]^+$; purity (AUC) > 95%; HRMS (ESI) *m/z* calcd for $C_{21}H_{20}N_6NaO$ $[M + Na]^+$ 395.1591, found $[M + Na]^+$ 395.1602.

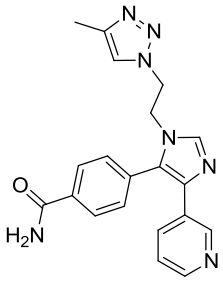
Synthesis of 4-(1-(2-(4-methyl-1*H*-1,2,3-triazol-1-yl)ethyl)-4-(pyridin-4-yl)-1*H*-imidazol-5-yl)benzonitrile (2)



To a solution of 4-(4-bromo-1-(2-(4-methyl-1*H*-1,2,3-triazol-1-yl)ethyl)-1*H*-imidazol-5-yl)benzonitrile **(18)** (30 mg, 0.0840 mmol) and $Pd(PPh_3)_4$ (13 mg, 0.011 mmol) in 1,4-dioxane (4 mL) was added 4-(tributylstannyl)pyridine (0.08 mL, 0.200 mmol) and the mixture was heated to 150 °C in a Biotage Initiator 2.5 Microwave for 1.5 h. The crude material was purified by Isolute Flash SCX-2 column (100% MeOH to 2 M NH_3 in MeOH) followed by flash column chromatography (0-20% MeOH in CH_2Cl_2) to yield the title compound **(2)** as a yellow oil (14 mg, 0.039 mmol, 46%, ≥90% purity). R_f = 0.5 (15% MeOH in CH_2Cl_2); ^{1}H NMR (500 MHz, MeOD) δ 8.51 (2H, d, *J* = 7.5 Hz, 2 x ArH), 7.95 (2H, dat, *J* = 1.5, 1.5, 8.5 Hz, 2 x ArH), 7.86 (1H, s, ArH), 7.71 (2H, br d, *J* = 7.0 Hz, 2 x ArH), 7.52 (1H, d, *J* = 0.5 Hz, ArH), 7.50 (2H, dat, *J* = 1.5, 1.5, 8.5 Hz, 2 x ArH), 4.58 (2H, dd, *J* = 5.0, 7.5 Hz, CH_2), 4.50 (2H, dd, *J* = 5.0, 7.5 Hz, CH_2), 2.25 (3H, d, *J* = 0.5 Hz, CH_3) ppm; ^{13}C NMR (126 MHz, MeOD) δ 150.6, 144.8, 143.9, 141.5, 134.8, 2 x 134.7, 134.0, 132.7, 124.0, 123.4, 119.0, 115.3, 51.0, 46.5, 10.4 ppm; IR (oil) 2923, 1665, 1634, 1432, 1177, 1126, 834, 799, 721 cm^{-1}; LCMS (Fast4min) t_r = 1.20 min, *m/z* 356 $[M + H]^+$; purity (AUC) > 95%; HRMS (ESI) *m/z* calcd for $C_{20}H_{18}N_7$ $[M + H]^+$ 356.1618, found $[M + H]^+$ 356.1616.

Synthesis of 4-(1-(2-(4-methyl-1*H*-1,2,3-triazol-1-yl)ethyl)-4-(pyridin-3-yl)-1*H*-imidazol-5-yl)benzonitrile (3) and 4-(1-(2-(4-methyl-1*H*-1,2,3-triazol-1-yl)ethyl)-4-(pyridin-3-yl)-1*H*-imidazol-5-yl)benzamide (25)





A mixture of 4-(4-bromo-1-(2-(4-methyl-1*H*-1,2,3-triazol-1-yl)ethyl)-1*H*-imidazol-5-yl)benzonitrile **(18)** (30 mg, 0.0840 mmol), $Pd(PPh_3)_4$ (5 mg, 0.004 mmol), Na_2CO_3 (18 mg, 0.17 mmol), pyridin-3-ylboronic acid (13 mg, 0.110 mmol), 1,4-dioxane (1 mL) and water (1 mL) was heated to 140 °C in a Biotage Initiator 2.5 Microwave for 30 min. The crude material was purified by Isolute Flash SCX-2 column (100% MeOH to 2 M NH_3 in MeOH) followed by flash column chromatography (0-20% MeOH in CH_2Cl_2) to yield 4-(1-(2-(4-methyl-1*H*-1,2,3-triazol-1-yl)ethyl)-4-(pyridin-3-yl)-1*H*-imidazol-5-yl)benzonitrile **(3)** as an off-white solid (4.2 mg, 0.012 mmol, 14%, ≥90% purity) and 4-(1-(2-(4-methyl-1*H*-1,2,3-triazol-1-yl)ethyl)-4-(pyridin-3-yl)-1*H*-imidazol-5-yl)benzamide **(25)** as a white solid (16.8 mg, 0.0450 mmol, 54%, ≥90%).

4-(1-(2-(4-methyl-1*H*-1,2,3-triazol-1-yl)ethyl)-4-(pyridin-3-yl)-1*H*-imidazol-5-yl)benzonitrile (3)

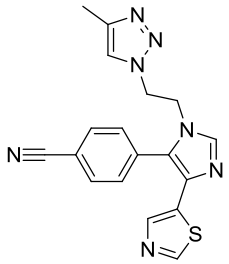
m.p.: 69-74 °C; R_f = 0.7 (15% MeOH in CH_2Cl_2); ^{1}H NMR (500 MHz, MeOD) δ 8.40 (1H, dd, *J* = 1.0, 2.0, Hz, ArH), 8.35 (1H, dd, *J* = 1.5, 5.0 Hz, ArH), 7.85 (2H, dat, *J* = 1.5, 1.5, 8.0 Hz, 2 x ArH), 7.75 (1H, s, ArH), 7.73 (1H, ddd, *J* = 1.5, 2.0, 8.0 Hz, ArH), 7.45 (1H, d, *J* = 1.0 Hz, ArH), 7.42 (2H, dat, *J* = 1.5, 1.5, 8.0 Hz, 2 x ArH), 7.33 (1H, ddd, *J* = 1.0, 5.0, 8.0 Hz, ArH), 4.51-4.55 (4H, m, 2 x CH_2),2.23 (3H, d, *J* = 1.0 Hz, CH_3) ppm; ^{13}C NMR (126 MHz, MeOD) δ 148.5, 148.4, 144.6, 140.4, 136.8, 136.5, 134.9, 2 x 134.3, 2 x 132.8, 131.5, 129.6, 125.1, 123.9, 119.1, 114.2, 49.8, 46.4, 10.4 ppm; IR (solid) 2925, 2229, 1610, 1504, 1365, 847,

710, 575 cm^{-1}; LCMS (Fast4min) t_r = 1.46 min, *m/z* 356 $[M + H]^+$; purity (AUC) = 83%; HRMS (ESI) *m/z* calcd for $C_{20}H_{17}N_7Na$ $[M + Na]^+$ 378.1438, found $[M + Na]^+$ 378.1432.

4-(1-(2-(4-Methyl-1*H*-1,2,3-triazol-1-yl)ethyl)-4-(pyridin-3-yl)-1*H*-imidazol-5-yl)benzamide (25)

m.p.: 105-110 °C; R_f = 0.2 (15% MeOH in CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.43 (1H, dd, *J* = 0.5, 2.0 Hz, ArH), 8.32 (1H, dd, *J* = 1.5, 5.0 Hz, ArH), 8.00 (2H, dat, *J* = 1.5, 1.5, 8.5 Hz, 2 x ArH), 7.75 (1H, ddd, *J* = 1.5, 2.0, 8.0 Hz, ArH), 7.71 (1H, s, ArH), 7.46 (1H, d, *J* = 0.5 Hz, ArH), 7.35 (2H, dat, *J* = 1.5, 1.5, 8.5 Hz, 2 x ArH), 7.30 (1H, ddd, *J* = 1.0, 5.0, 8.0 Hz, ArH), 4.53-4.55 (2H, m, CH_2), 4.49-4.52 (2H, m, CH_2), 2.25 (3H, d, *J* = 1.0 Hz, CH_3) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.2, 148.2, 148.1, 144.6, 140.0, 136.2, 135.9, 133.5, 2 x 132.0, 131.8, 130.4, 2 x 129.8, 125.0, 123.9, 121.8, 51.2, 46.3, 10.4 ppm; IR (solid) 2921, 2854, 2190, 2170, 1668, 1614, 1374, 781, 711 cm^{-1}; LCMS (Fast4min) t_r = 1.06 min, *m/z* 374 $[M + H]^+$; purity (AUC) > 95%; HRMS (ESI) *m/z* calcd for $C_{20}H_{19}N_7NaO$ $[M + Na]^+$ 396.1543, found $[M + Na]^+$ 396.1545.

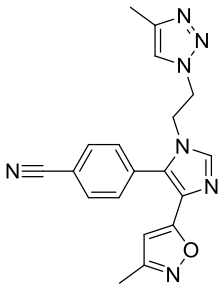
Synthesis of 4-(1-(2-(4-methyl-1*H*-1,2,3-triazol-1-yl)ethyl)-4-(thiazol-5-yl)-1*H*-imidazol-5-yl)benzonitrile (4)



4-(4-Bromo-1-(2-(4-methyl-1*H*-1,2,3-triazol-1-yl)ethyl)-1*H*-imidazol-5-yl)benzonitrile **(18)** (28 mg, 0.0780 mmol, 1.0 equiv), $Pd(PPh_3)_4$ (13.6 mg, 0.0120 mmol, 0.15 equiv) and 5-(tributylstannyl)thiazole (57 mg, 0.152 mmol, 1.9 equiv) were added to a solution of 1,4-dioxane (4 mL) and the resulting mixture heated to 150 °C in a Biotage Initiator 2.5

microwave for 1.5 h. The crude material was purified by Isolute Flash SCX-2 column (100 % MeOH to 2M NH_3 in MeOH). The resulting mixture was further purified by preparative HPLC (formic acid buffer) and the solvent removed *in vacuo* to give 4-(1-(2-(4-methyl-1*H*-1,2,3-triazol-1-yl)ethyl)-4-(thiazol-5-yl)-1*H*-imidazol-5-yl)benzonitrile **(4)** (15 mg, 53%) as a white solid. ^{1}H NMR (500 MHz, Acetone-d_6) δ 8.69 (1H, d, J = 1.0 Hz, 1H), 7.92 (2H, dat, J = 1.5, 1.5, 8.5 Hz, ArH), 7.57 (2H, dat, J = 1.5, 1.5, 8.5 Hz, ArH), 7.59 (1H, s, ArH), 7.41 (1H, d, J = 0.5 Hz, ArH), 7.56 (1H, s, ArH), 4.59 (2H, dd, J = 4.0, 6.0 Hz, CH_2), 4.51 (2H, dd, J = 5.0, 7.0 Hz, CH_2), 2.20 (3H, d, J = 1.0 Hz, CH_3) ppm; ^{13}C NMR (126 MHz, Acetone-d_6) δ 154.0, 151.9, 143.5, 142.0, 139.2, 139.0, 134.5, 133.7, 132.6, 132.0, 122.8, 118.8, 113.8, 50.4, 45.9, 10.7 ppm; IR (solid) 3154, 2229, 1450, 819, 779, 663, 603 cm^{-1}; LCMS (Fast4min) t_r = 1.89 min, *m/z* 362 $[M + H]^+$; purity (AUC) > 95%; HRMS for $C_{18}H_{15}N_7S$ calcd, 362.1182; found, 362.1169.

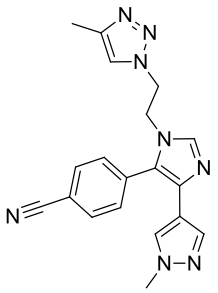
Synthesis of 4-(1-(2-(4-methyl-1*H*-1,2,3-triazol-1-yl)ethyl)-4-(3-methylisoxazol-5-yl)-1*H*-imidazol-5-yl)benzonitrile (5)

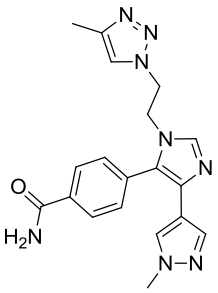


At 0 °C, to a solution of 4-(4-ethynyl-1-(2-(4-methyl-1*H*-1,2,3-triazol-1-yl)ethyl)-1*H*-imidazol-5-yl)benzonitrile **(27)**, acetaldoxime (70.8 mg, 1.20 mmol, 5.0 equiv.), and triethylamine (1 ml) in anhydrous THF (1 ml) was added sodium hypochlorite (2 ml, 13% active chlorine). The reaction mixture was then warmed up to 50 °C. After 15 hs, the reaction mixture was cooled to room temperature and partitioned between DCM (2 ml) and water (2 ml), the aqueous layer was then re-extracted with DCM (2 x 2 ml) and the combined organic layers

were washed with water (2 ml), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by preparative TLC (20% MeOH in EtOAc) to afford the expected 4-(1-(2-(4-methyl-1*H*-1,2,3-triazol-1-yl)ethyl)-4-(3-methylisoxazol-5-yl)-1*H*-imidazol-5-yl)benzonitrile **(5)** (4 mg, 3%, ≥60% purity) as yellowish oil. R_f = 0.3 (10% MeOH in EtOAc)); ^{1}H NMR (500 MHz, MeOD-d_4) δ 7.88 (2H, dat, *J* = 1.5, 1.5, 8.5 Hz, ArH), 7.76 (1H, s, ArH), 7.48 (2H, dat, *J* = 1.5, 1.5, 8.5 Hz, ArH), 7.43 (1H, d, *J* = 1.0 Hz, ArH), 6.20 (1H, s, ArH), 4.52-4.54 (2H, m, CH_2), 4.49-4.51 (2H, m, CH_2), 2.24 (3H, d, *J* = 0.5 Hz, CH_3), 2.21 (3H, s, CH_3) ppm; LCMS (Fast4min) t_r = 1.88 min, *m/z* 360 $[M + H]^+$; purity (AUC) > 95%; HRMS for $[M + H^+]$ $C_{19}H_{18}N_7O$ calcd, 360.1567; found, 360.1550.

Synthesis of 4-(1-(2-(4-methyl-1*H*-1,2,3-triazol-1-yl)ethyl)-4-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-imidazol-5-yl)benzonitrile (7) and 4-(1-(2-(4-methyl-1*H*-1,2,3-triazol-1-yl)ethyl)-4-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-imidazol-5-yl)benzamide (26)





Method A (Reflux Conditions)

A mixture of 4-(4-bromo-1-(2-(4-methyl-1*H*-1,2,3-triazol-1-yl)ethyl)-1*H*-imidazol-5-yl)benzonitrile **(18)** (50 mg, 0.140 mmol), 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (58 mg, 0.280 mmol), $PdCl_2$(dppf) (10 mg, 0.014 mmol), $BnEt_3NCl$ (3 mg, 0.013 mmol), CsF (65 mg, 0.43 mmol), toluene (2 mL) and water (2 mL) was stirred at reflux for 42 h. 1-Methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (58 mg, 0.28 mmol), $PdCl_2$(dppf) (10 mg, 0.014 mmol), $BnEt_3NCl$ (3 mg, 0.013 mmol) and CsF (65 mg, 0.43 mmol) were added and the mixture was stirred for a further 3 days. $PdCl_2$(dppf) (20

mg, 0.028 mmol) was added and the mixture stirred for a further 4 days. The crude material was purified by Isolute Flash SCX-2 column (100% MeOH to 2 M NH_3 in MeOH) followed by flash column chromatography (0-20% MeOH in CH_2Cl_2) to yield **7** as a light brown oil (2.8 mg, 0.0078 mmol, 6%, ≥90% purity).

Method B (Microwave Conditions)

A mixture of 4-(4-bromo-1-(2-(4-methyl-1*H*-1,2,3-triazol-1-yl)ethyl)-1*H*-imidazol-5-yl)benzonitrile **(18)** (30 mg, 0.0840 mmol), $Pd(PPh_3)_4$ (5 mg, 0.004 mmol), Na_2CO_3 (18 mg, 0.17 mmol), 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (21 mg, 0.100 mmol), 1,4-dioxane (1 mL) and water (1 mL) was heated to 140 °C in a Biotage Initiator 2.5 Microwave for 30 min. The crude material was purified by Isolute Flash SCX-2 column (100% MeOH to 2 M NH_3 in MeOH) followed by flash column chromatography (0-20% MeOH in CH_2Cl_2) to yield 4-(1-(2-(4-methyl-1*H*-1,2,3-triazol-1-yl)ethyl)-4-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-imidazol-5-yl)benzonitrile **(7)** as a light brown oil (1.7 mg, 0.0047 mmol, 6%, ≥90% purity) and 4-(1-(2-(4-methyl-1*H*-1,2,3-triazol-1-yl)ethyl)-4-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-imidazol-5-yl)benzamide **(26)** as a white solid (12 mg, 0.032 mmol, 38%, ≥90% purity).

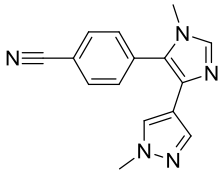
4-(1-(2-(4-Methyl-1*H*-1,2,3-triazol-1-yl)ethyl)-4-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-imidazol-5-yl)benzonitrile (7)

R_f = 0.7 (15% MeOH in CH_2Cl_2); ^{1}H NMR (500 MHz, MeOD) δ 7.86 (2H, dat, *J* = 1.5, 1.5, 8.5 Hz, 2 x ArH), 7.61 (1H, s, ArH), 7.45 (2H, dat, *J* = 1.5, 1.5, 8.5 Hz, 2 x ArH), 7.43 (1H, br s, ArH), 7.41 (1H, d, *J* = 0.5 Hz, ArH), 7.25 (1H, d, *J* = 0.5 Hz, ArH), 4.45-4.51 (4H, m, 2 x CH_2), 3.80 (3H, s, CH_3), 2.23 (3H, d, *J* = 0.5 Hz, CH_3) ppm; ^{13}C NMR (126 MHz, MeOD) δ 144.6, 139.5, 137.8, 135.4, 2 x 134.1, 132.8, 2 x 129.4, 126.9, 123.9, 119.3, 117.0, 113.9, 51.3, 46.3, 10.3 ppm; IR (oil) 2922, 2852, 1743, 842 cm^{-1}; LCMS (Fast4min) t_r = 1.61 min, *m/z* 359 $[M + H]^+$; purity (AUC) = 95%; HRMS (ESI) *m/z* calcd for $C_{19}H_{18}N_8Na$ $[M + Na]^+$ 381.1547, found $[M + Na]^+$ 381.1557.

4-(1-(2-(4-Methyl-1*H*-1,2,3-triazol-1-yl)ethyl)-4-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-imidazol-5-yl)benzamide (26)

m.p.: 234-239 °C; R_f = 0.4 (15% MeOH in CH_2Cl_2); ^{1}H NMR (500 MHz, 1:1 MeOD / $CDCl_3$) δ 8.00 (2H, dat, *J* = 2.0, 2.0, 8.5 Hz, 2 x ArH), 7.43 (1H, s, ArH), 7.35 (1H, br s, ArH), 7.34 (2H, dat, *J* = 2.0, 2.0, 8.5 Hz, 2 x ArH), 7.22 (2H, dd, *J* = 1.0, 6.0 Hz, 2 x ArH), 4.42-4.44 (2H, m, CH_2), 4.38-4.40 (2H, m, CH_2), 3.78 (3H, s, CH_3), 2.24 (3H, d, *J* = 0.5 Hz, CH_3) ppm; ^{13}C NMR (126 MHz, 1:1 MeOD / $CDCl_3$) δ 170.7, 144.1, 138.1, 137.1, 134.9, 133.2, 132.6, 131.3, 129.2, 128.5, 126.6, 123.1, 116.6, 50.6, 45.5, 38.8, 10.5 ppm; IR (solid) 2921, 1657, 1616, 1403, 1379, 1255, 663, 522 cm^{-1}; LCMS (Fast4min) t_r = 1.05 min, *m/z* 377 $[M + H]^+$; purity (AUC) > 95%; HRMS (ESI) *m/z* calcd for $C_{19}H_{20}N_8ONa$ $[M + Na]^+$ 399.1652, found $[M + Na]^+$ 399.1643.

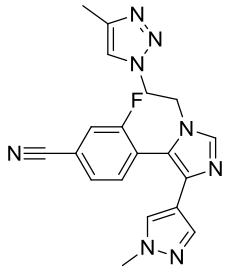
Synthesis of 4-(1-methyl-4-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-imidazol-5-yl)benzonitrile (8)



4-(4-Bromo-1-methyl-1*H*-imidazol-5-yl)benzonitrile **(23)** (74 mg, 0.282 mmol, 1.0 equiv), $Pd(PPh_3)_4$ (25 mg, 0.0220 mmol, 0.08 equiv) and 1-methyl-4-(tributylstannyl)-1*H*-pyrazole (220 mg, 0.593 mmol, 2.1 equiv) were added to a solution of dioxane (2.5 mL) and the resulting was degassed by bubbling Ar for 5 min prior the mixture was heated to 150 °C in a Biotage Initiator 2.5 microwave for 1.5 h. The resulting mixture was purified by preparative TLC (10% MeOH in DCM) to give 4-(1-methyl-4-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-imidazol-5-yl)benzonitrile **(8)** (40 mg, 54%) as a pale yellow oil. R_f =0.7 (20% MeOH in DCM). ^{1}H NMR (500 MHz, MeOD-d_4) δ 7.87 (2H, dat, *J* = 1.5, 1.5, 8.5 Hz, ArH), 7.77 (1H, brs, ArH), 7.61 (2H, dat, *J* = 1.5, 1.5, 8.5 Hz, ArH), 7.49 (1H, brs, ArH), 7.32 (1H, d, *J* = 1.0 Hz, ArH), 3.81 (1H, s, CH_3), 3.58 (1H, s, CH_3) ppm; ^{13}C NMR (126 MHz, MeOD-d_4) δ 140.1, 139.5, 137.9,

136.1, 133.9, 132.6, 129.9, 129.4, 119.4, 117.3, 113.6, 38.8, 32.9 ppm; IR (film) 2943, 2227, 1608, 1499, 1250, 925, 846, 750, 662, 575 cm^{-1}; LCMS (Fast4min) t_r = 1.28 min, *m/z* 264 $[M + H]^+$; purity (AUC) > 95%; LCMS (Fast4min) t_r = 1.28 min, *m/z* 264 $[M + H]^+$; purity (AUC) > 95%; HRMS (ESI) *m/z* calcd for $C_{15}H_{13}N_5Na$ $[M + Na]^+$ 286.1063, found $[M + Na]^+$ 286.1058.

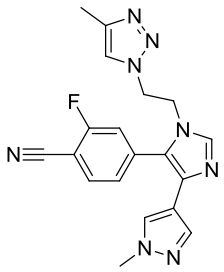
Synthesis of 3-fluoro-4-(1-(2-(4-methyl-1*H*-1,2,3-triazol-1-yl)ethyl)-4-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-imidazol-5-yl)benzonitrile (10)



4-(4-Bromo-1-(2-(4-methyl-1*H*-1,2,3-triazol-1-yl)ethyl)-1*H*-imidazol-5-yl)-3-fluorobenzonitrile **(20)** (8 mg, 0.0210 mmol, 1.0 equiv), $Pd(PPh_3)_4$ (4 mg, 0.0033 mmol, 0.16 equiv) and 1-methyl-4-(tributylstannyl)-1H-pyrazole (20 mg, 0.054 mmol, 2.6 equiv) were added to a solution of 1,4-dioxane (1.5 mL) and the resulting mixture was heated to 150 °C in a Biotage Initiator 2.5 microwave for 1.5 h. The resulting mixture was purified by preparative R-HPLC (formic acid buffer) and the solvent was removed *in vacuo* to give 3-fluoro-4-(1-(2-(4-methyl-1H-1,2,3-triazol-1-yl)ethyl)-4-(1-methyl-1H-pyrazol-4-yl)-1H-imidazol-5-yl)benzonitrile **(10)** (4 mg, 50%) as a cream amorphous solid. ^{1}H NMR (500 MHz, MeOD-d_4) δ 8.25 (1H, brs, protonated), 7.77 (1H, dd, *J* = 1.5, 9.0 Hz, ArH), 7.69 (1H, dd, *J* = 1.5, 8.0 Hz, ArH), 7.68 (1H, brs, ArH), 7.43 (1H, d, *J* = 8.0 Hz, ArH), 7.41 (1H, d, *J* = 7.5 Hz, ArH), 7.40 (1H, d, *J* = 0.5 Hz, ArH), 7.26 (1H, d, *J* = 0.5 Hz, ArH), 4.53 (2H, dd, *J* = 5.0, 10.0 Hz, CH_2), 4.43 (2H, brs, CH_2), 3.80 (3H, s, CH_3), 2.23 (3H, d, *J* = 0.5 Hz, CH_3) ppm; ^{13}C NMR (126 MHz, MeOD-d_4) δ 166.6, 161.2 (d, *J* = 248.8 Hz), 144.6, 140.1, 137.6, 135.6 (d, *J* = 2.0 Hz), 134.8, 130.2 (d, *J* = 4.2 Hz), 129.4, 123.9, 121.6, 121.4, 120.5, 116.7, 116.2 (d, *J* = 9.3 Hz), 51.4, 46.5 (d, *J* = 1.7 Hz), 38.8, 10.4 ppm; IR (solid) 2929, 2235, 1412, 754 cm^{-1}; LCMS (Fast4min) t_r =

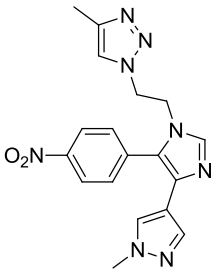
1.61 min, *m/z* 377 $[M + H]^+$; purity (AUC) > 95%; HRMS for $[M+H^+]$ $C_{19}H_{18}FN_8$ calcd, 377.1633; found, 377.1622.

Synthesis of 2-fluoro-4-(1-(2-(4-methyl-1*H*-1,2,3-triazol-1-yl)ethyl)-4-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-imidazol-5-yl)benzonitrile (11)



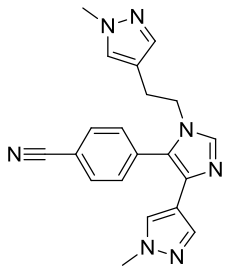
The inseparable mixture from (**21**) (101 mg, 0.0210 mmol, 1.0 equiv), $Pd(PPh_3)_4$ (30 mg, 0.0260 mmol, 0.09 equiv) and 1-methyl-4-(tributylstannyl)-1H-pyrazole (215 mg, 0.579 mmol, 2.07 equiv) were added to a solution of 1,4-dioxane (4 mL) and the resulting mixture was heated to 150 °C in a Biotage Initiator 2.5 microwave for 1.5 h. The resulting mixture was purified by preparative R-HPLC (0.1% formic acid buffer) to give 2-fluoro-4-(1-(2-(4-methyl-1*H*-1,2,3-triazol-1-yl)ethyl)-4-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-imidazol-5-yl)benzonitrile **(11)** (11 mg, 10 %) as a colourless oil. ^{1}H NMR (500 MHz, MeOD-d_4) δ 9.15 (1H, s, protonated), 7.97 (1H, dd, *J* = 6.5, 8.0 Hz, ArH), 7.68 (1H, d, *J* = 0.5 Hz, ArH), 7.66 (1H, brs, ArH), 7.50 (1H, d, *J* = 1.0 Hz, ArH), 7.41 (1H, dd, *J* = 1.5, 9.5 Hz, ArH), 7.37 (1H, dd, *J* = 1.5, 8.0 Hz, ArH), 4.68-4.73 (4H, m, $2CH_2$), 3.86 (3H, s, CH_3), 2.28 (3H, d, *J* = 0.5, CH_3) ppm; ^{13}C NMR (126 MHz, MeOD-d_4) δ 164.4 (d, *J* = 259.6 Hz), 144.8, 138.5, 137.3, 136.3, 133.2 (d, *J* = 9.0 Hz), 131.2, 129.1 (d, *J* = 3.6 Hz), 127.4, 126.6, 124.6, 120.3 (d, *J* = 22.1 Hz), 114.0, 108.7, 104.8 (d, *J* =15.6 Hz), 50.5, 48.5, 39.3, 10.3 ppm; IR (film) 3020, 2220, 1458, 623 cm^{-1}; LCMS (Fast4min) t_r = 1.63 min, *m/z* 377 $[M + H]^+$; purity (AUC) > 95%; HRMS for $[M+H^+]$ $C_{19}H_{18}FN_8$ calcd, 377.1633; found, 377.1620.

Synthesis of 4-methyl-1-(2-(4-(1-methyl-1*H*-pyrazol-4-yl)-5-(4-nitrophenyl)-1*H*-imidazol-1-yl)ethyl)-1*H*-1,2,3-triazole (12)



1-(2-(4-Bromo-5-(4-nitrophenyl)-1*H*-imidazol-1-yl)ethyl)-4-methyl-1*H*-1,2,3-triazole **(19)** (20 mg, 0.0530 mmol, 1.0 equiv), $Pd(PPh_3)_4$ (9.5 mg, 0.008 mmol, 0.15 equiv) and 1-methyl-4-(tributylstannyl)-1H-pyrazole (38 mg, 0.103 mmol, 1.9 equiv) were added to a solution of 1,4-dioxane (4 mL) and the resulting mixture was heated to 150 °C in a Biotage Initiator 2.5 microwave for 4.5 h. A second aliquot of $Pd(PPh_3)_4$ (9.5 mg, 0.008 mmol, 0.15 equiv) and 1-methyl-4-(tributylstannyl)-1*H*-pyrazole (44 mg, 0.119 mmol, 2.25 equiv) was added and the reaction mixture was heated to 150 °C in a Biotage Initiator 2.5 microwave for 1.5 h. The resulting mixture was purified by preparative R-HPLC (0.1% formic acid buffer) to afford 4-methyl-1-(2-(4-(1-methyl-1*H*-pyrazol-4-yl)-5-(4-nitrophenyl)-1*H*-imidazol-1-yl)ethyl)-1*H*-1,2,3-triazole **(12)** (5 mg, 25%) as a brown residue. ^{1}H NMR (500 MHz, MeOD-d_4) δ 9.01 (s, 1H), 8.41 (2H, dat, *J*= 2.0, 2.0, 9.0 Hz, ArH), 8.07 (1H, s, ArH), 7.61 (2H, dat, *J* = 2.0, 2.0, 9.0 Hz, ArH),7.61 (1H, br s, ArH), 7.58 (1H, d, *J* = 0.5 Hz, ArH), 7.46 (1H, d, *J* = 1.0 Hz, ArH) 4.69 (2H, dd, *J* = 3.5, 6.5 Hz, CH_2), 4.64 (2H, dd, *J* = 3.5, 6.5 Hz, CH_2), 3.84 (s, CH_3), 2.25 (3H, d, *J* = 1.0 Hz, CH_3) ppm; ^{13}C NMR (126 MHz, MeOD-d_4) δ 164.4, 150.6, 144.9, 138.4, 137.3, 133.5, 132.7, 130.9, 128.2, 125.7, 124.1, 109.3, 50.3, 48.4, 39.2, 10.4 ppm; IR (film) 2928, 1599, 1519, 1345, 855 cm^{-1}; LCMS (Fast4min) t_r = 1.62 min, *m/z* 379 $[M + H]^+$; purity (AUC) > 95%; HRMS for $[M+H^+]$ $C_{18}H_{19}N_8O_2$ calcd, 379.1625; found, 379.1614.

Synthesis of 4-(4-(1-methyl-1*H*-pyrazol-4-yl)-1-(2-(1-methyl-1*H*-pyrazol-4-yl)ethyl)-1*H*-imidazol-5-yl)benzonitrile BAZ2-ICR (13)

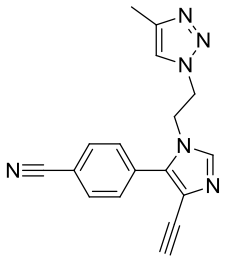


4-(4-Bromo-1-(2-(1-methyl-1*H*-pyrazol-4-yl)ethyl)-1*H*-imidazol-5-yl)benzonitrile **(22)** (44 mg, 0.124 mmol, 1.0 equiv), $Pd(PPh_3)_4$ (30 mg, 0.027 mmol, 0.21 equiv) and 1-methyl-4-(tributylstannyl)-1*H*-pyrazole (0.11 mL, 92 mg, 0.248 mmol, 2.0 equiv) were added to a solution of 1,4-dioxane (2 mL) and the resulting mixture was heated to 150 °C in a Biotage Initiator 2.5 microwave for 1.5 h. The resulting mixture was purified by preparative R-HPLC (0.1% formic acid buffer) and the solvent was removed *in vacuo* to give 4-(4-(1-methyl-1*H*-pyrazol-4-yl)-1-(2-(1-methyl-1*H*-pyrazol-4-yl)ethyl)-1*H*-imidazol-5-yl)benzonitrile **(13)** (20 mg, 45 %) as a clear pale yellow oil. R_f = 0.2 (20% MeOH in CH_2Cl_2); ^{1}H NMR (500 MHz, MeOD-d_4) δ 8.09 (1H, brs, protonated), 8.07 (1H, s, ArH), 7.88 (2H, dat, *J* = 1.5, 1.5, 8.5 Hz, ArH), 7.0 (2H, dat, *J* = 1.5, 1.5, 8.5 Hz, ArH), 7.50 (1H, brs, ArH), 7.32 (1H, d, *J* = 0.5 Hz, ArH), 7.19 (1H, brs, ArH), 7.03 (1H, brs, ArH), 4.15 (2H, t, *J* = 6.5 Hz, CH_2), 3.81 (3H, s, CH_3), 3.78 (3H, s, CH_3), 2.71 (2H, t, *J* = 6.5 Hz, CH_2) ppm; ^{13}C NMR (126 MHz, MeOD-d_4) δ 139.6, 138.7, 137.9, 135.1, 134.1, 132.8, 131.3, 131.1, 129.8, 127.5, 119.3, 117.8, 115.2, 114.1, 48.3, 38.9, 38.7, 26.4 ppm; IR (film) 2941, 2228, 1954, 1607, 1496, 847, 666 cm^{-1}; LCMS (Fast4min) t_r = 1.66 min, *m/z* 358 $[M + H]^+$; purity (AUC) > 95%; HRMS for $[M + H^+]$ $C_{20}H_{20}N_7$ calcd, 358.1775; found, 358.1777.

Neutral form ^{1}H NMR (500 MHz, MeOD-d_4) δ 7.86 (2H, dat, *J* = 1.5, 1.5, 8.5 Hz, ArH), 7.73 (1H, s, ArH), 7.47 (2H, dat, *J* = 1.5, 1.5, 8.5 Hz, ArH), 7.44 (1H, brs, ArH), 7.27 (1H, d, *J* = 0.5 Hz, ArH), 7.14 (1H, brs, ArH), 7.01 (1H, brs, ArH), 4.10 (2H, t, *J* = 7.0 Hz, CH_2), 3.80

(3H, s, CH_3), 3.77 (3H, s, CH_3), 2.67 (2H, t, *J* = 6.5 Hz, CH_2) ppm; ^{13}C NMR (126 MHz, MeOD-d_4) δ 139.6, 139.5, 137.8, 136.2, 134.0, 133.1, 132.7, 131.0, 129.3, 127.1, 119.4, 118.0, 117.2, 113.6, 47.7, 38.8, 38.7, 26.6 ppm.

Synthesis of 4-(4-ethynyl-1-(2-(4-methyl-1*H*-1,2,3-triazol-1-yl)ethyl)-1*H*-imidazol-5-yl)benzonitrile (27)



A mixture of 4-(4-bromo-1-(2-(4-methyl-1*H*-1,2,3-triazol-1-yl)ethyl)-1*H*-imidazol-5-yl)benzonitrile **(18)** (87 mg, 0.244 mmol, 1.0 equiv), ethynyltributylstannane (0.15 ml, 0.518 mmol, 2.1 equiv), $Pd(PPh_3)_4$ (24 mg, 0.0210 mmol, 0.09 equiv), 1,4-dioxane (3 mL) was heated to 150 °C in a Biotage Initiator 2.5 Microwave for 1.5h. The crude material was then purified by Isolute Flash SCX-2 column (100% MeOH to 2 M NH_3 in MeOH) followed by flash column chromatography (0-30% MeOH in EtOAc) to yield 4-(4-ethynyl-1-(2-(4-methyl-1*H*-1,2,3-triazol-1-yl)ethyl)-1*H*-imidazol-5-yl)benzonitrile **(27)** (72 mg, 98 %, ≥90% purity) as colorless oil. R_f = 0.9 (DCM/MeOH: 4/1); ^{1}H NMR (500 MHz, MeOD-d_4) δ 7.83 (2H, dat, *J* = 2.0, 2.0, 8.5 Hz, ArH), 7.66 (1H, s, ArH), 7.53 (2H, dat, *J* = 2.0, 2.0, 8.5 Hz, ArH), 7.33 (1H, d, *J* = 1.0 Hz, ArH), 4.62 (2H, dd, *J* = 5.0, 7.0 Hz, CH2), 4.52 (2H, dd, *J* = 5.0, 7.0 Hz, CH_2), 3.48 (1H, s, CH), 2.19 (3H, d, *J* = 1.0 Hz, CH_3) ppm; ^{13}C NMR (126 MHz, MeOD-d_4) δ 144.5, 140.3, 136.2, 133.6, 132.2, 131.3, 127.7, 123.8, 119.3, 113.6, 80.8, 77.3, 51.3, 46.8, 10.3 ppm; IR (film) 2957, 2926, 2229, 1609, 1494, 1219, 846, 754, 663 cm^{-1}; LCMS (Fast4min) t_r = 1.64 min, *m/z* 303 $[M + H]^+$; purity (AUC) > 95%; HRMS for $[M + H^+]$ $C_{17}H_{15}N_6$ calcd, 303.1353; found, 303.1364.

20% of reduced product was observed.

Protein expression and purification.

BAZ2A and BAZ2B have been expressed and purified as described previously.[2]

Crystallization.

All crystallization experiments were performed using sitting-drop vapour diffusion method at 4 ˚C. Initial apo crystals of BAZ2B were obtained using the protein concentration of 10-20 mg/ml in the buffer containing 25 mM HEPES, pH 7.5, 150 mM NaCl, 0.5 mM TCEP, and the crystallization reagent containing 30%-36% low molecular weight PEG smears, 0.1 M MES pH 6.0-6.5. Soaking was performed in the drop overnight using the solution prepared from the reservoir solution supplemented with 20% ethylene glycol and 6 mM X1 or X6 inhibitors.

Data collection and structural determination.

Inhibitor-soaked crystals of BAZ2B were flash-cooled in liquid nitrogen, and diffraction data were collected in-house using Rigaku FR-E Superbright. The data were processed with MOSFLM[3] and subsequently scaled using SCALA[4] from CCP4 suite.[5] Molecular replacement was performed for structure solutions using Phaser program[6] and the BAZ2B coordinates (pdb id: 4NR9) as a search model. All structures were subjected to iterative cycles of manual model building in COOT[7] alternated with refinement using REFMAC.[8] TLS definitions used in the late refinement step were calculated using TLSMD server.[9] Geometric correctness of all structures was validated with MOLPROBITY.[10] Statistics for data collection and structure refinement are summarized in **Supplementary Table 1**.

NMR methods.

NMR data was collected on a Bruker Avance 500 spectrometer equipped with a 5 mm BBO probe. The ^{1}H spectra were referenced to the internal deuterated solvent. All NMR data were acquired at the temperature of 295 K. All data were acquired using Bruker Topspin 2.1.

The ^{1}H-NMR spectrum was acquired using Bruker standard 1D zg30 or zg pulse sequence. The sweep width was 20.5 ppm, and the FID contained 64k time-domain data points. The ^{1}H-^{1}H NOESY spectrum was acquired using a Bruker noesygpph pulse sequence. 2K data points were collected for 256 t1 increments of 2 or 8 transients each.

The quantitative ^{1}H-NMR spectrum was acquired using a Bruker standard 1D zg pulse sequence with 32 scans. The sweep width was 20.5 ppm, and the FID contained 32k time-domain data points. The relaxation delay is set to 20 seconds. The concentration is quantified using PULCON method with an external reference sample containing 20 mM of Caffeine in D_2O.[11]

Thermodynamic solubility sample preparation: Around 16 mg of compound solid was added to 0.5 mL of D_2O in a 2 mL vial and agitated by a magnetic stirrer bar for 24 hours at room temperature. The solution was then centrifuge for 15 minutes at 14,000 rpm on Eppendorf 5415C centrifuge. 0.45 ml of the supernatant was transferred to a 5 mm NMR tube.

Thermal stability shift assays.

The kinases at 2 µM were mixed with 10 µM inhibitors. The assays and data evaluation for melting temperatures were performed using a Real-Time PCR Mx3005p machine (Stratagene) and the protocols previously described.[12]

Isothermal titration calorimetry.

All calorimetric titration experiments were carried out on VP-ITC (MicroCal) at 15 ˚C. The buffer condition used was 20 mM HEPES, pH 7.5, 150 mM NaCl and 0.5 mM TCEP. Titration was performed by injecting the proteins (200 μM) into a reaction cell containing the inhibitors (15 μM). Integrated heat of the titrations after corrected for the heat of dilution were analysed using the Origin program. The corrected data were fitted to a single binding site model using a nonlinear least-square minimization algorithm, and the binding parameters including reaction enthalpy changes (ΔH), reaction enthalpy changes (TΔS), equilibrium dissociation constants (K_D), stoichiometry (n) were calculated.

PK experiment.

The *in vitro* and *in vivo* experiments were performed as described elsewhere.[13]

FRAP.

FRAP studies were performed using U2OS cells expressing a full-length BAZ2A protein chimerized with an N-terminal eGFP. Six hours after transfection 2.5 μM SAHA was added and 1 μM inhibitor was added 1 hour before imaging, which was carried out 24 hours after transfection. Full details of the FRAP experiment are as described elsewhere.[14]

Table S1: Crystallographic data collection and refinement statistics

Complex	**BAZ2B-1**	**BAZ2B-7**
PDB accession code	**4XUA**	**4XUB**
Data Collection		
Beamline	Rigaku FR-E	Rigaku FR-E
Wavelength (Å)	1.5418	1.5418
Resolution[a] (Å)	33.35-1.75 (1.84-1.75)	33.22-1.98 (2.09-1.98)
Spacegroup	$C\,2\,2\,2_1$	$C\,2\,2\,2_1$
Cell dimensions	a = 81.6, b = 96.0, c = 57.8 Å	a = 81.2, b = 96.7, c = 57.8 Å
	α = β = γ = 90.0°	α = β = γ = 90.0°
No. unique reflections[a]	22,857 (3,222)	16,214 (2,328)
Completeness[a] (%)	98.4 (96.7)	100.0 (100.0)
I/σI[a]	15.2 (2.5)	15.0 (2.1)
R_{merge}[a]	0.053 (0.479)	0.057 (0.738)
Redundancy[a]	5.1 (5.1)	5.1 (5.0)
Refinement		
ligands	**1**	**7**
No. atoms in refinement (P/L/O)[b]	998/ 27/ 255	952/ 27/ 181
R_{fact} (%)	18.0	18.0
R_{free} (%)	21.9	21.5
B_f (P/L/O)[b] (Å^2)	35/ 34/ 47	46/ 33/ 53
rms deviation bond[c] (Å)	0.015	0.016
rms deviation angle[c] (°)	1.6	1.5
Molprobity		
Ramachandran favour	99.2	99.1
Ramachandran allowed	100	100

[a] Values in brackets show the statistics for the highest resolution shells.
[b] P/L/O indicate protein, ligand molecules presented in the active sites, and other (water and solvent molecules), respectively.
[c] rms indicates root-mean-square.

Table S2: Temperature shift data

Target	ΔTm (°C)	Control Inhibitor
ASH1L	-0.5±0.1	
ATAD2A	-0.5±0.3	Yes, undisclosed
BAZ1A	-0.3±0.4	
BAZ1B	-0.3±0.5	
BAZ2A	5.2±0.1	GSK2801
BAZ2B	3.8±0.1	GSK2801
BRD1	0.2±0.1	OF-1
BRD2(1)	-0.1±0.2	JQ1
BRD2(2)	0.2±0.1	JQ1
BRD3(2)	-0.1±0.1	JQ1
BRD4(1)	0.1±0.02	JQ1
BRD4(2)	-0.1±0.15	JQ1
BRD7	0.0±0.2	bromosporine
BRD9	-0.9±0.2	bromosporine
BRDT(2)	0.1±0.18	JQ1
BRDT(1)	0.0±0.1	JQ1
BRPF1A	0.4±0.1	OF-1
BRPF1B	0.0±0.2	OF-1
BRPF3	-0.4±0.3	OF-1
BRWD3(2)	0.2±0.5	
CECR2	2.0±0.18	bromosporine
CREBBP	0.5±0.2	CBP30
EP300	0.6±0.3	CBP30
FALZ	-0.4±0.15	
GCN5L2	-0.4±0.4	
KIAA1240A	0.0±0.18	
LOC93349A*	-0.2±0.4	
MLL	-0.2±0.42	
PB1(1)	0.1±0.2	
PB1(2)	0.3±0.1	Yes, undisclosed
PB1(3)	-0.2±0.3	
PB1(4)	0.2±0.4	
PB1(5)	0.0±0.12	PFI-3
PB1(6)	-0.1±0.2	
PCAF	0.3±0.3	
PHIP(2)	-1.2±0.8	
SMARCA2	0.1±0.2	PFI-3
SMARCA4	-0.1±0.3	PFI-3
SP140	-0.5±0.15	
TAF1(1)	0.0±0.1	

TAF1(2)	-0.2±0.1	bromosporine
TAF1L(1)	-0.4±0.15	Yes, undisclosed
TAF1L(2)	-0.6±0.3	bromosporine
TIF1*	-0.2±0.3	Yes, undisclosed
TIF1	-0.2±0.3	Yes, undisclosed
TRIM28*	-0.9±0.2	
WDR9(2)	-0.6±0.1	

Data represent mean of three independent measurements. * Proteins containing PHD and bromodomain.

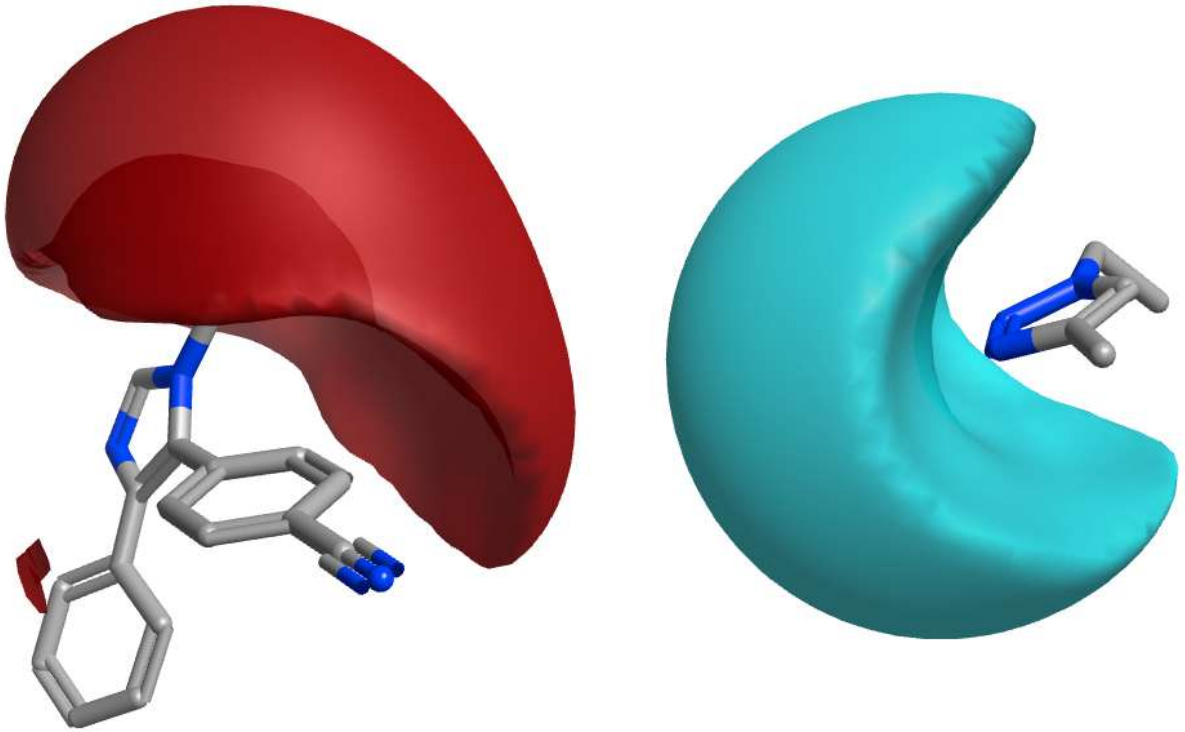


Figure S1: Cresset field analysis. Comparison of the Cresset field strengths around the two sections of compound **1** at equal field strength threshold of 2.0. Red volume indicates regions that are electron poor, and the blue volume areas that are electron rich. It can be seen that the surface of the phenyl ring shows a region that is electron poor and the triazole a region that is electron rich. This suggests that there is a favourable electronic component to the π-stack formation.

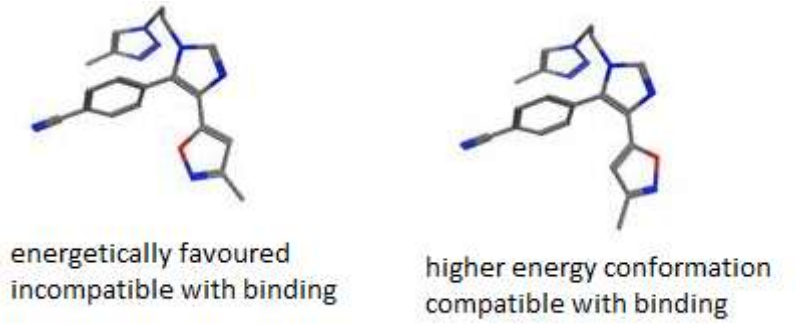
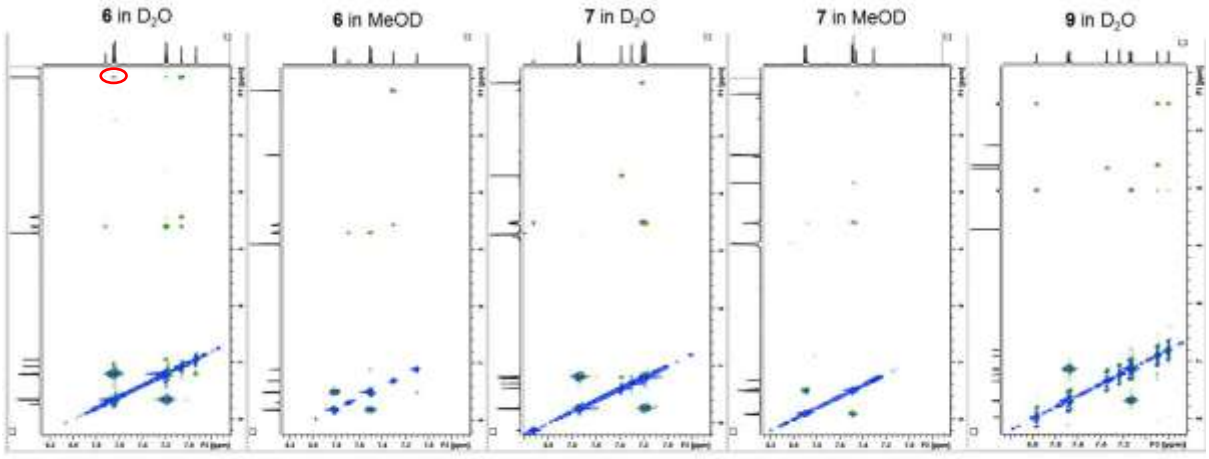
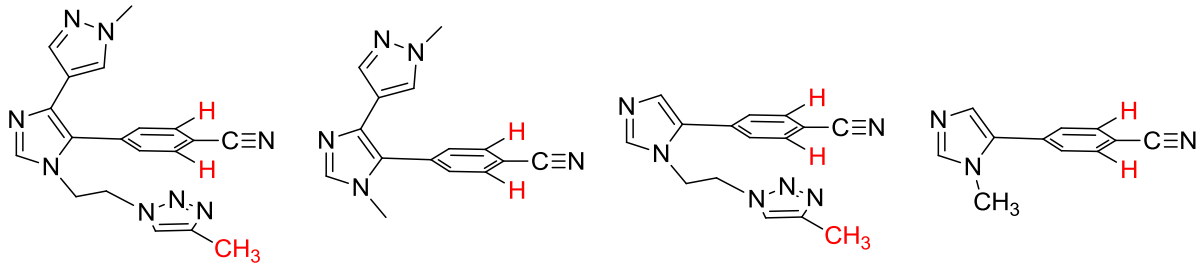


Figure S2: Analysis of the torsion angles that connect the isoxazole of 5 with the central imidazole. The analysis was performed using the conformational analysis tool in MOE. To generate **5**, the three dimensional structure of **7** was extracted from the crystal structure (**Figure 2**) and the methylpyrazole replaced by the isoaxazole. The isoaxzole was allowed to relax while all other atoms were fixed in the bioactive conformation. All other parameters were used at default settings. The conformation predicted to be energetically favoured cannot bind to the protein since the methyl group is pointing in the opposite direction (left). The analysis generated one additional conformation (right). In this conformation, the methyl group points in the correct position for binding to the BAZ2 bromodomains, but the predicted energy is less favourable suggesting that is associated with a significant penalty.



^{1}H-^{1}H NOESY spectra of **6**, **7**, **9** in D_2O and **6**, **7** in MeOD at 295K.



7 **8** **6** **9**

Figure S3: ^{1}H-^{1}H NOESY spectra. Compounds **6**, **7**, **9** in D_2O and **6**, **7** in MeOD at 295K. The correlation between the methyl group and the aromatic protons of compound 6 is indicated by a red circle.

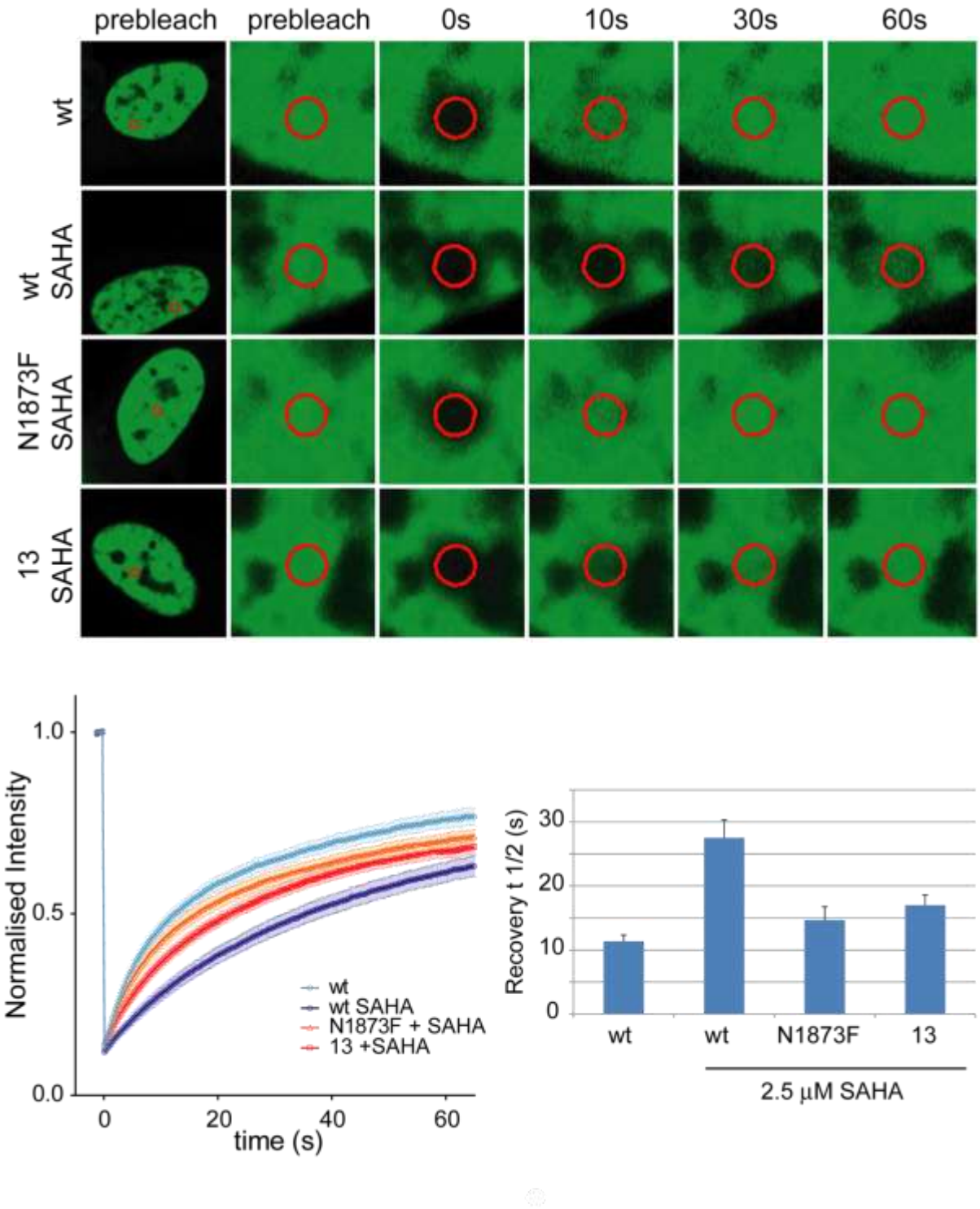


Figure S4: FRAP data. The figure shows representative images of bleached cells (top panel). The bleached area is highlighted by a red circle. The recovery of the fluorescent in the bleached area as a function of time is shown on the lower left panel and the averaged recovery half-lives (t½) are shown on the lower right panel. *P < 0.05, significant difference from wild type treated with SAHA.

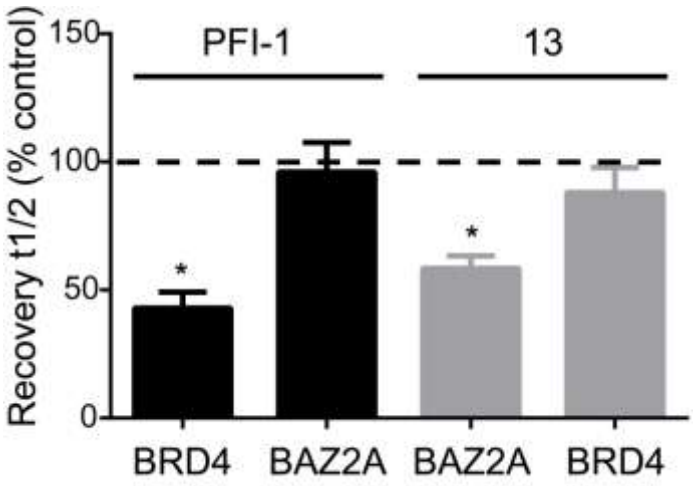


Figure S5. Selectivity of compound 13 and PFI-1 in cells shown by FRAP assay. Half-times of fluorescence recovery (t½) expressed as a percentage of the relevant wild-type control cells without inhibitor. Cells were transfected with GFP-tagged BAZ2A or BRD4 and treated with 1 μM PFI-1 or compound **13**. Light bars depict assay with suberoylanilide hydroxamic acid (SAHA) addition, and dark bars depict assays without SAHA addition (2.5 μM). The dotted line demarks the point equivalent to 100% of the relevant wild-type control cells without inhibitor. Error bars depict the standard error of the mean. Bars marked with an asterisk indicate a significant difference from controls ($P < 0.05$).

Route	Dose (mg/kg)	Animal	Animal Wt (g)	Tmax (h)	Cmax (nmol/L)	AUC (h*nmol/L)	CL (L/h)	CL (ml/min/kg)	Terminal Half-Life (h)	Vss (L)	Vss (L/kg)	F
IV	5	2	26.4	0.083	13843	7614	0.049	30.62	0.944	0.024	0.909	
		3	20.5	0.083	9532	6073	0.047	38.38	0.849	0.024	1.169	
		4	23.3	0.083	10443	5875	0.055	39.68	0.996	0.028	1.196	
PO	5	6	20.9	0.083	6464	4073	0.051	40.21	0.757			
		7	23.1	0.083	6124	5161	0.044	31.74	1.140			0.70
		8	22.2	0.25	4885	4542	0.048	36.06	0.822			

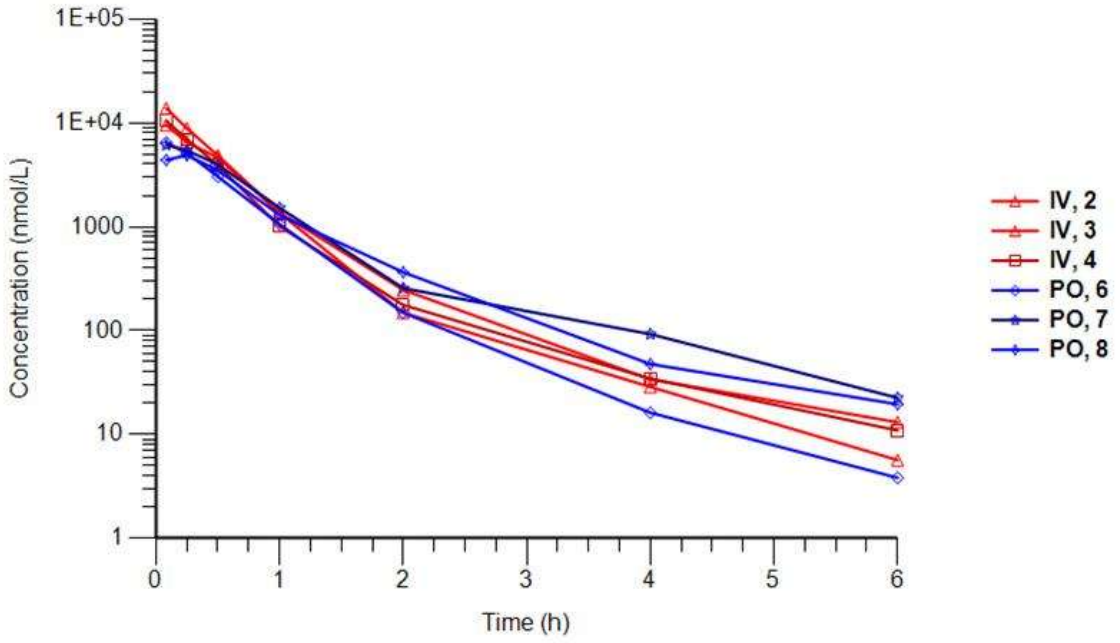


Figure S6: PK data. 3 mice were dosed IV and 3 mice PO. Key parameters and the curves are shown for each animal.

Table 3. *in vitro* pharmacological assay.

Experiment Date	Assay	Catalog Ref	Test Concentration (M)	% Inhibition of Control Specific Binding	% of Control Specific Binding			Reference Compound	IC50 Ref (M)	Ki Ref (M)	nH Ref
					1st	2nd	Mean				
02/12/2014	A1 (h) (antagonist radioligand)	0002	1.0E-05	9	98.6	82.5	90.5	DPCPX	8.1E-10	5.1E-10	1.1
01/12/2014	A2A (h) (agonist radioligand)	0004	1.0E-05	-11	100.3	122.3	111.3	NECA	1.7E-08	1.4E-08	1.0
02/12/2014	A3 (h) (agonist radioligand)	0006	1.0E-05	-11	111.2	110.7	110.9	IB-MECA	1.2E-10	7.3E-11	0.7
02/12/2014	alpha 1 (non-selective) (antagonist radioligand)	0008	1.0E-05	0	103.5	95.9	99.7	prazosin	1.6E-10	4.2E-11	1.0
02/12/2014	alpha 2 (non-selective) (antagonist radioligand)	0011	1.0E-05	18	84.4	80.3	82.4	yohimbine	7.5E-08	3.2E-08	0.8
02/12/2014	beta 1 (h) (agonist radioligand)	0018	1.0E-05	-5	104.5	106.1	105.3	atenolol	2.9E-07	1.6E-07	0.9
02/12/2014	beta 2 (h) (agonist radioligand)	0020	1.0E-05	-7	115.5	98.3	106.9	ICI 118551	6.3E-10	2.1E-10	1.2
02/12/2014	AT1 (h) (antagonist radioligand)	0024	1.0E-05	7	91.3	94.1	92.7	saralasin	7.3E-10	3.6E-10	0.9
02/12/2014	BZD (central) (agonist radioligand)	0028	1.0E-05	-33	140.6	126.1	133.4	diazepam	7.2E-09	6.1E-09	1.1
02/12/2014	B2 (h) (agonist radioligand)	0033	1.0E-05	0	100.4	99.4	99.9	NPC 567	1.6E-08	8.0E-09	0.8
02/12/2014	CB1 (h) (agonist radioligand)	0036	1.0E-05	-11	89.9	132.3	111.1	CP 55940	1.5E-09	1.3E-09	0.8
09/12/2014	CCK1 (CCKA) (h) (agonist radioligand)	0039	1.0E-05	-7	99.8	113.2	106.5	CCK-8s	7.1E-11	5.3E-11	1.2
02/12/2014	D1 (h) (antagonist radioligand)	0044	1.0E-05	0	98.2	101.7	100.0	SCH 23390	5.2E-10	2.1E-10	0.9
02/12/2014	D2S (h) (antagonist radioligand)	0046	1.0E-05	0	106.3	93.3	99.8	(+)butaclamol	2.5E-09	8.4E-10	1.3
02/12/2014	ETA (h) (agonist radioligand)	0054	1.0E-05	0	110.1	90.6	100.3	endothelin-1	1.6E-11	7.8E-12	1.0
01/12/2014	GABA (non-selective) (agonist radioligand)	0057	1.0E-05	-3	105.7	100.5	103.1	GABA	8.6E-08	5.1E-08	2.0
02/12/2014	GAL2 (h) (agonist radioligand)	0410	1.0E-05	-4	104.2	103.9	104.1	galanin	3.4E-10	3.1E-10	0.8
02/12/2014	CXCR2 (IL-8B) (h) (agonist radioligand)	0419	1.0E-05	-11	118.2	103.1	110.7	IL-8	2.5E-10	1.2E-10	1.2
02/12/2014	CCR1 (h) (agonist radioligand)	0361	1.0E-05	2	104.7	90.9	97.8	MIP-1alpha	1.6E-11	1.1E-11	1.9
02/12/2014	H1 (h) (antagonist radioligand)	0870	1.0E-05	-13	119.1	107.5	113.3	pyrilamine	1.5E-09	9.6E-10	0.9
02/12/2014	H2 (h) (antagonist radioligand)	1208	1.0E-05	6	98.6	90.2	94.4	cimetidine	6.3E-07	6.2E-07	0.9
02/12/2014	MC4 (h) (agonist radioligand)	0420	1.0E-05	-9	102.1	114.9	108.5	NDP-alpha -MSH	4.0E-10	3.6E-10	1.2
02/12/2014	MT1 (ML1A) (h) (agonist radioligand)	1538	1.0E-05	15	85.3	85.1	85.2	melatonin	2.5E-10	2.0E-10	1.3
04/12/2014	M1 (h) (antagonist radioligand)	0091	1.0E-05	-11	107.1	115.4	111.2	pirenzepine	2.3E-08	2.0E-08	0.9
02/12/2014	M2 (h) (antagonist radioligand)	0093	1.0E-05	-12	123.0	100.7	111.9	methoctramine	2.3E-08	1.6E-08	0.8
02/12/2014	M3 (h) (antagonist radioligand)	0095	1.0E-05	-6	112.3	99.5	105.9	4-DAMP	9.5E-10	6.8E-10	1.3
01/12/2014	NK2 (h) (agonist radioligand)	0102	1.0E-05	-4	100.1	107.8	103.9	[Nleu10]-NKA (4-10)	1.1E-08	6.1E-09	0.9
02/12/2014	NK3 (h) (antagonist radioligand)	0104	1.0E-05	-3	101.5	104.3	102.9	SB 222200	6.9E-09	3.7E-09	1.0
02/12/2014	Y1 (h) (agonist radioligand)	0106	1.0E-05	8	90.7	93.7	92.2	NPY	1.6E-10	1.1E-10	1.0
01/12/2014	Y2 (h) (agonist radioligand)	0107	1.0E-05	-3	111.5	95.0	103.2	NPY	6.0E-11	2.4E-11	1.2
02/12/2014	NTS1 (NT1) (h) (agonist radioligand)	0109	1.0E-05	-16	113.6	118.2	115.9	neurotensin	2.6E-10	2.1E-10	0.8
02/12/2014	delta 2 (DOP) (h) (agonist radioligand)	0114	1.0E-05	4	98.3	93.8	96.0	DPDPE	2.7E-09	1.6E-09	1.1
02/12/2014	kappa (KOP) (agonist radioligand)	1971	1.0E-05	-10	104.1	116.1	110.1	U 50488	8.7E-10	5.8E-10	1.0
02/12/2014	mu (MOP) (h) (agonist radioligand)	0118	1.0E-05	-5	113.2	95.9	104.5	DAMGO	4.4E-10	1.8E-10	0.8
02/12/2014	NOP (ORL1) (h) (agonist radioligand)	0358	1.0E-05	11	94.2	83.7	89.0	nociceptin	6.6E-10	1.3E-10	1.0
02/12/2014	EP4 (h) (agonist radioligand)	0441	1.0E-05	-1	101.1	100.5	100.8	PGE2	2.8E-10	1.0E-10	0.7
02/12/2014	5-HT1A (h) (agonist radioligand)	0131	1.0E-05	19	89.5	72.5	81.0	8-OH-DPAT	5.6E-10	3.5E-10	1.2
02/12/2014	5-HT1B (antagonist radioligand)	0132	1.0E-05	-23	125.6	120.3	122.9	serotonin	1.2E-08	7.1E-09	1.2
02/12/2014	5-HT2A (h) (antagonist radioligand)	0135	1.0E-05	-5	105.8	103.3	104.5	ketanserin	4.9E-10	2.7E-10	1.2
01/12/2014	5-HT2B (h) (agonist radioligand)	1333	1.0E-05	-9	106.3	111.0	108.7	(±)DOI	4.5E-09	2.3E-09	1.0
02/12/2014	5-HT3 (h) (antagonist radioligand)	0411	1.0E-05	0	106.4	94.5	100.5	MDL 72222	7.1E-09	4.9E-09	1.1
02/12/2014	5-HT5a (h) (agonist radioligand)	0140	1.0E-05	-5	101.1	108.8	105.0	serotonin	6.1E-08	3.1E-08	0.7
02/12/2014	5-HT6 (h) (agonist radioligand)	0142	1.0E-05	-6	104.7	106.5	105.6	serotonin	1.2E-07	5.5E-08	0.8
02/12/2014	5-HT7 (h) (agonist radioligand)	0144	1.0E-05	-8	109.7	106.7	108.2	serotonin	3.1E-10	1.1E-10	0.6
02/12/2014	sst (non-selective) (agonist radioligand)	0149	1.0E-05	-22	127.2	117.6	122.4	somatostatin-14	1.3E-10	8.0E-11	0.8
02/12/2014	VPAC1 (VIP1) (h) (agonist radioligand)	0157	1.0E-05	-13	118.5	107.3	112.9	VIP	1.1E-10	6.3E-11	0.8
02/12/2014	V1a (h) (agonist radioligand)	0159	1.0E-05	3	103.2	91.0	97.1	[d(CH2)51,Tyr(Me)2]-AVP	1.1E-09	7.2E-10	1.0
02/12/2014	Ca2+ channel (L, verapamil site) (phenylalkylamine) (antagonist radioligand)	0163	1.0E-05	-6	110.0	101.5	105.8	D 600	1.7E-08	8.3E-09	0.5
02/12/2014	KV channel (antagonist radioligand)	0166	1.0E-05	-21	117.3	123.7	120.5	alpha -dendrotoxin	6.3E-11	5.0E-11	0.9
02/12/2014	SKCa channel (antagonist radioligand)	0167	1.0E-05	4	92.4	99.9	96.1	apamin	2.0E-11	1.0E-11	1.0
02/12/2014	Na+ channel (site 2) (antagonist radioligand)	0169	1.0E-05	6	103.5	84.5	94.0	veratridine	6.6E-06	5.9E-06	1.3
02/12/2014	Cl- channel (GABA-gated) (antagonist radioligand)	0170	1.0E-05	1	102.2	95.5	98.9	picrotoxinin	8.6E-08	7.1E-08	0.8
02/12/2014	norepinephrine transporter (h) (antagonist radioligand)	0355	1.0E-05	-11	117.1	105.2	111.2	protriptyline	4.7E-09	3.5E-09	1.0
02/12/2014	dopamine transporter (h) (antagonist radioligand)	0052	1.0E-05	-10	111.1	109.7	110.4	BTCP	1.2E-08	6.3E-09	1.1
02/12/2014	5-HT transporter (h) (antagonist radioligand)	0439	1.0E-05	-3	99.1	106.4	102.8	imipramine	2.5E-09	1.2E-09	1.1

References

(1) Van leusen, A. M.; Wildeman, J.; Oldenziel, O. H. Chemistry of Sulfonylmethyl Isocyanides. 12. Base-Induced Cycloaddition of Sulfonylmethyl Isocyanides to Carbon, Nitrogen Double Bonds. Synthesis of 1,5-Disubstituted and 1,4,5-Trisubstituted Imidazoles from Aldimines and Imidoyl Chlorides. *J. Org. Chem.* **1977**, *42*, 1153–1159.

(2) Filippakopoulos, P.; Picaud, S.; Mangos, M.; Keates, T.; Lambert, J. P.; Barsyte-Lovejoy, D.; Felletar, I.; Volkmer, R.; Muller, S.; Pawson, T.; Gingras, A. C.; Arrowsmith, C. H.; Knapp, S. Histone Recognition and Large-Scale Structural Analysis of the Human Bromodomain Family. *Cell* **2012**, *149*, 214–231.

(3) Battye, T. G.; Kontogiannis, L.; Johnson, O.; Powell, H. R.; Leslie, A. G. iMOSFLM: a New Graphical Interface for Diffraction-Image Processing with MOSFLM. *Acta Crystallogr. D Biol. Crystallogr*. **2011**, *67*, 271–281.

(4) Evans, P. Scaling and Assessment of Data Quality. *Acta Crystallogr. D Biol. Crystallogr*. **2006**, *62*, 72–82.

(5) Collaborative Computational Project. The CCP4 Suite: Programs for Protein Crystallography. *Acta Crystallogr. D Biol. Crystallogr*. **1994**, *50*, 760–763.

(6) McCoy, A. J.; Grosse-Kunstleve, R. W.; Adams, P. D.; Winn, M. D.; Storoni, L. C.; Read, R. J. Phaser Crystallographic Software. *J. Appl. Crystallogr*. **2007**, *40*, 658–674.

(7) Emsley, P.; Lohkamp, B.; Scott, W. G.; Cowtan, K. Features and Development of Coot. *Acta Crystallogr. D Biol. Crystallogr*. **2010**, *66*, 486–501.

(8) Murshudov, G. N.; Vagin, A. A.; Dodson, E. J. Refinement of Macromolecular Structures by the Maximum-Likelihood Method. *Acta Crystallogr. D Biol. Crystallogr*. **1997**, *53*, 240–255.

(9) Painter, J.; Merritt, E. A. Optimal Description of a Protein Structure in Terms of Multiple Groups Undergoing TLS Motion. *Acta Crystallogr. D Biol. Crystallogr*. **2006**, *62*, 439–450.

(10) Davis, I. W.; Leaver-Fay, A.; Chen, V. B.; Block, J. N.; Kapral, G. J.; Wang, X.; Murray, L. W.; Arendall, W. B., 3rd; Snoeyink, J.; Richardson, J. S.; Richardson, D. C. MolProbity: All-

atom Contacts and Structure Validation for Proteins and Nucleic Acids. *Nucleic Acids Res.* **2007**, *35*, W375–383.

(11) Wider, G., Dreier, L. Measuring Protein Concentrations by NMR Spectroscopy. *J. Am. Chem. Soc*. **2006**, *28*, 2571–2576.

(12) Fedorov, O.; Niesen, F. H.; Knapp, S. Kinase Inhibitors Selectivity Profiling Using Differential Scanning Fluorometry. *Methods Mol. Biol.* **2012**, *795*, 109–118.

(13) Naud, S.; Westwood, I. M.; Faisal, A.; Sheldrake, P.; Bavetsias, V.; Atrash, B.; Cheung, K.-W. J.; Liu, M.; Hayes, A.; Schmitt, J.; Wood, A.; Choi, V.; Boxall, K.; Mak, G.; Gurden, M.; Valenti, M.; de Haven Brandon, A.; Henley, A.; Baker, R.; McAndrew, C.; Matijssen, B.; Burke, R.; Hoelder, S.; Eccles, S. A.; Raynaud, F. L.; Linardopoulos, S.; van Montfort, R. L. M.; Blagg, J. Structure-Based Design of Orally Bioavailable 1*H*-Pyrrolo[3,2-*c*]pyridine Inhibitors of Mitotic Kinase Monopolar Sprindle 1 (MPS1). *J. Med. Chem*. **2013**, *56*, 10045–10065.

(14) Philpott, M.; Rogers, C. M.; Yapp, C.; Wells, C.; Lambert, J.-P.; Strain-Damerell, C.; Burgess-Brown, N. A.; Gingras, A.-C.; Knapp, S.; Müller, S. Assessing Cellular Efficacy of Bromodomain Inhibitors Using Fluorescence Recovery After Photobleaching. *Epigenetics & Chromatin* **2014**, *7*. doi:10.1186/1756-8935-7-14.

$^{1}H/^{13}C$ NMR Spectra

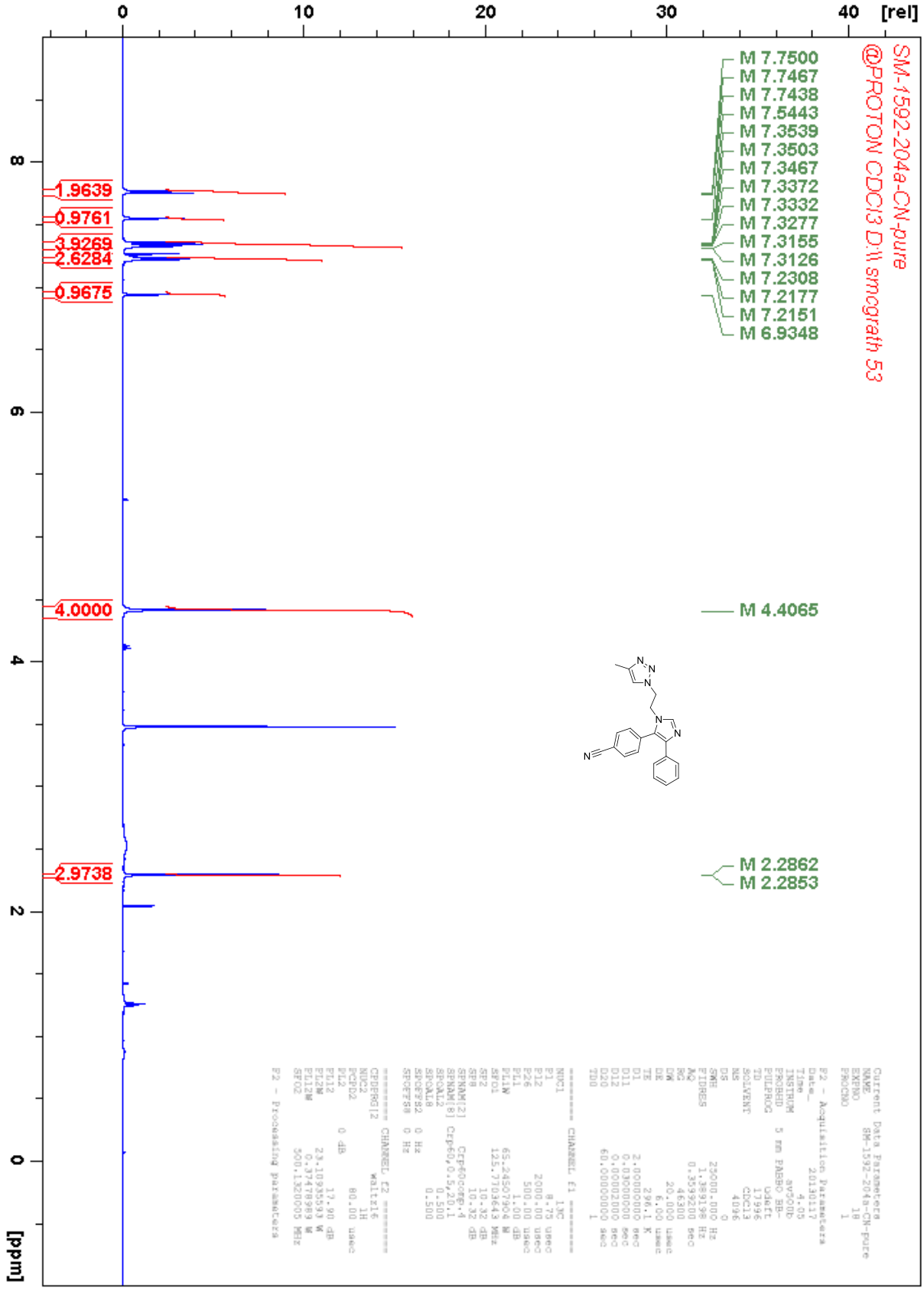


Figure S7. ^{1}H NMR ($CDCl_3$, 500 MHz) of **1**.

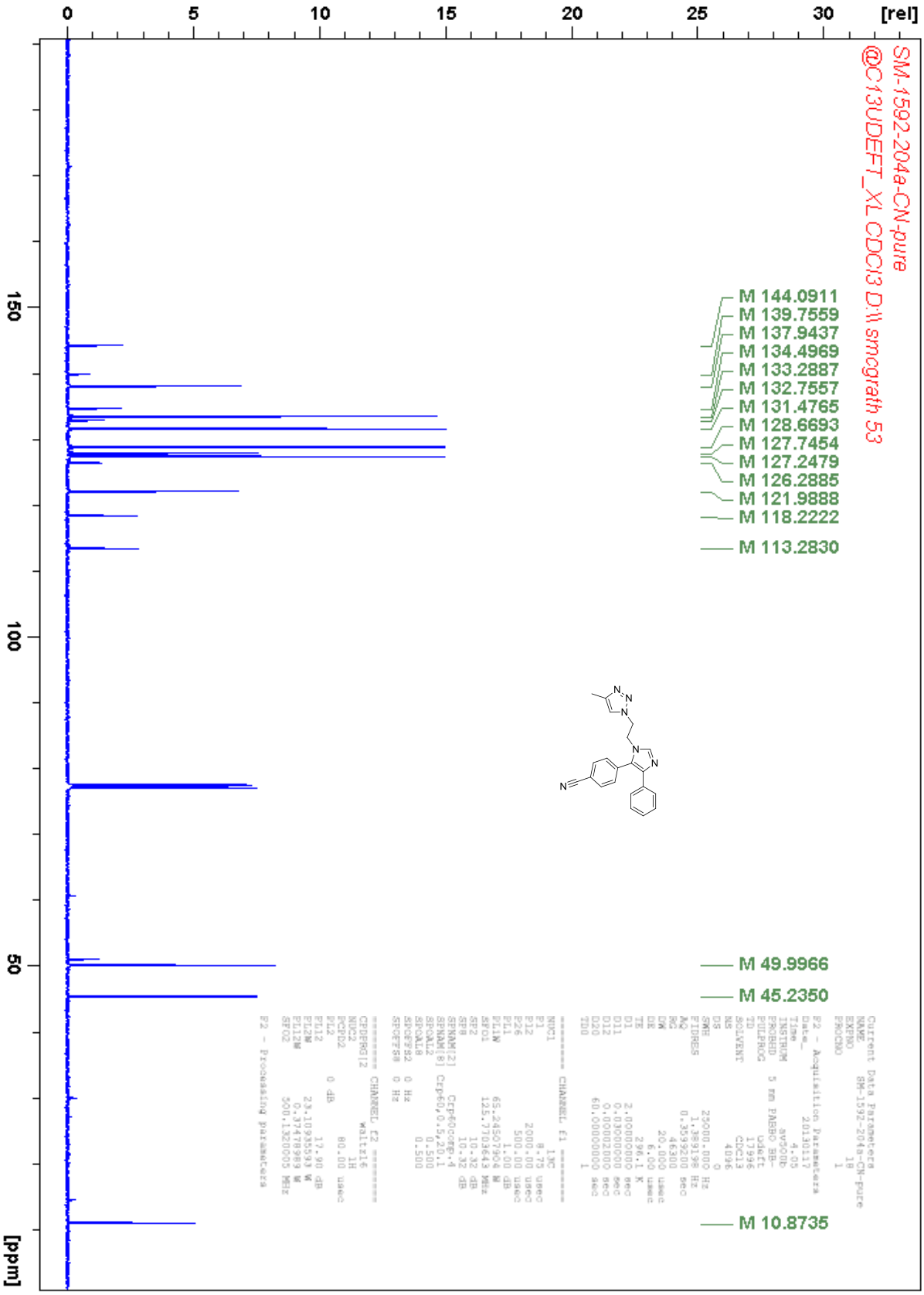


Figure S8. ^{1}H NMR ($CDCl_3$, 500 MHz) of **1**.

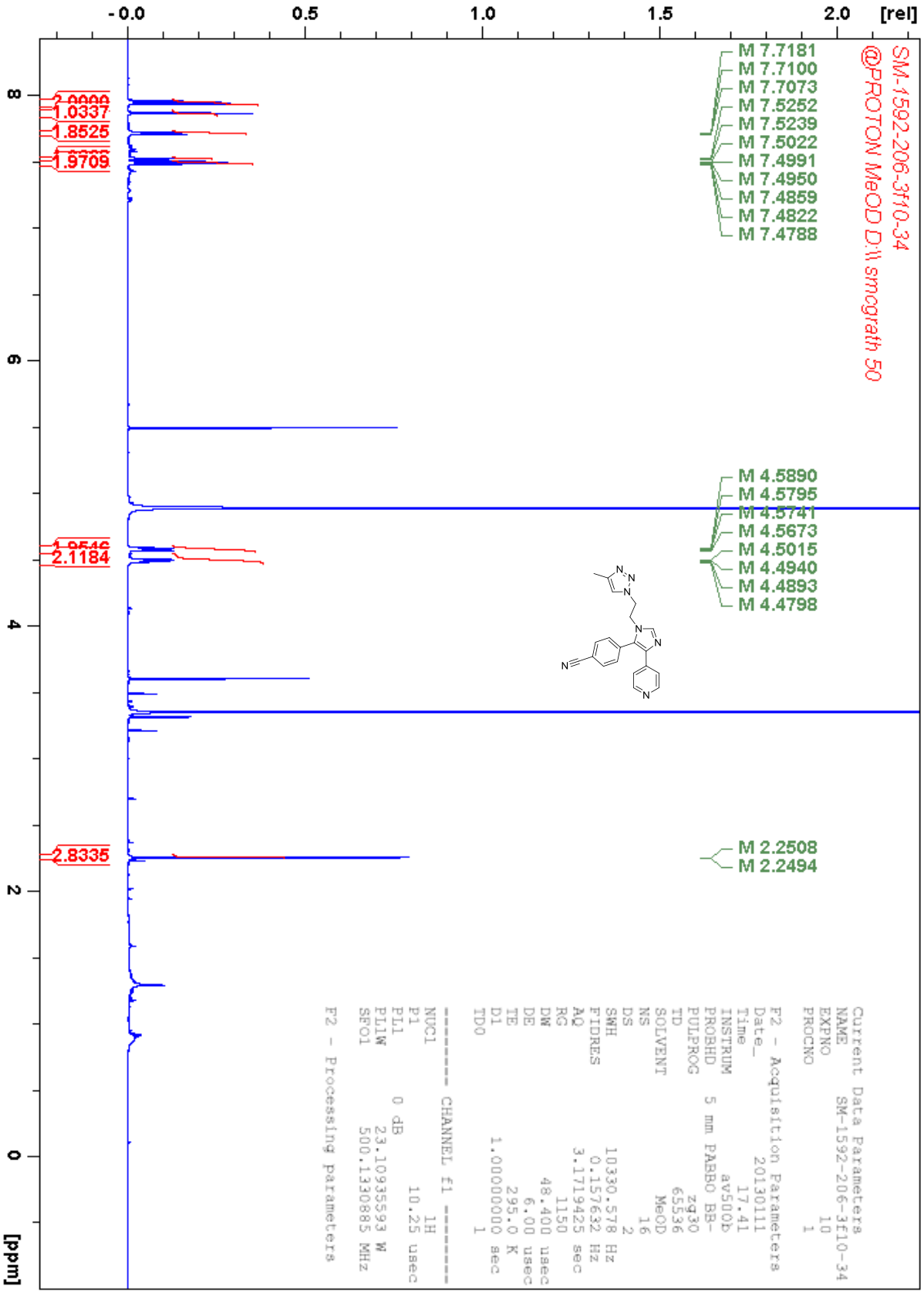


Figure S9. ^{1}H NMR (CD_3OD, 500 MHz) of **2**.

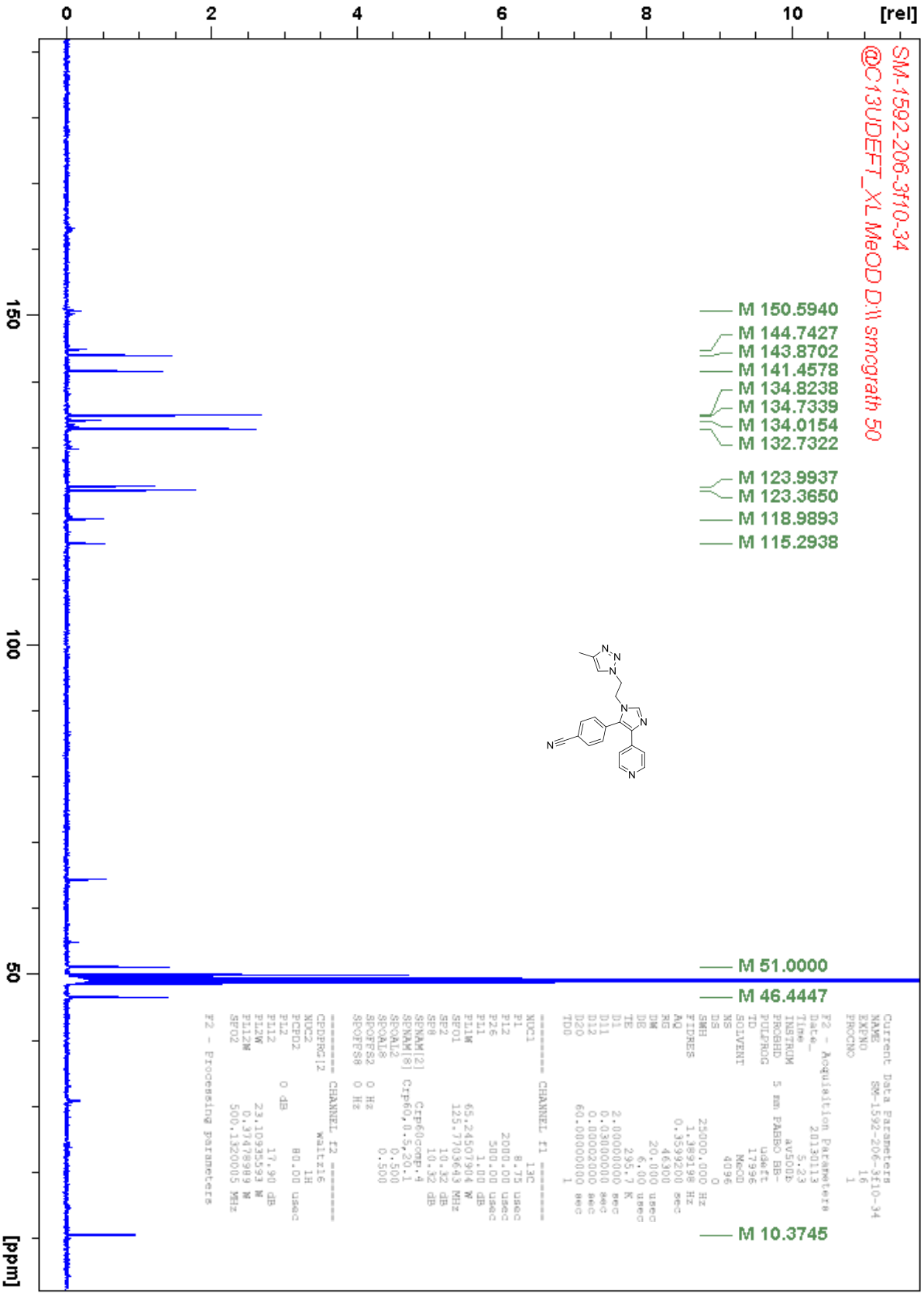


Figure S10. ^{13}C NMR (CD_3OD, 126 MHz) of **2**.

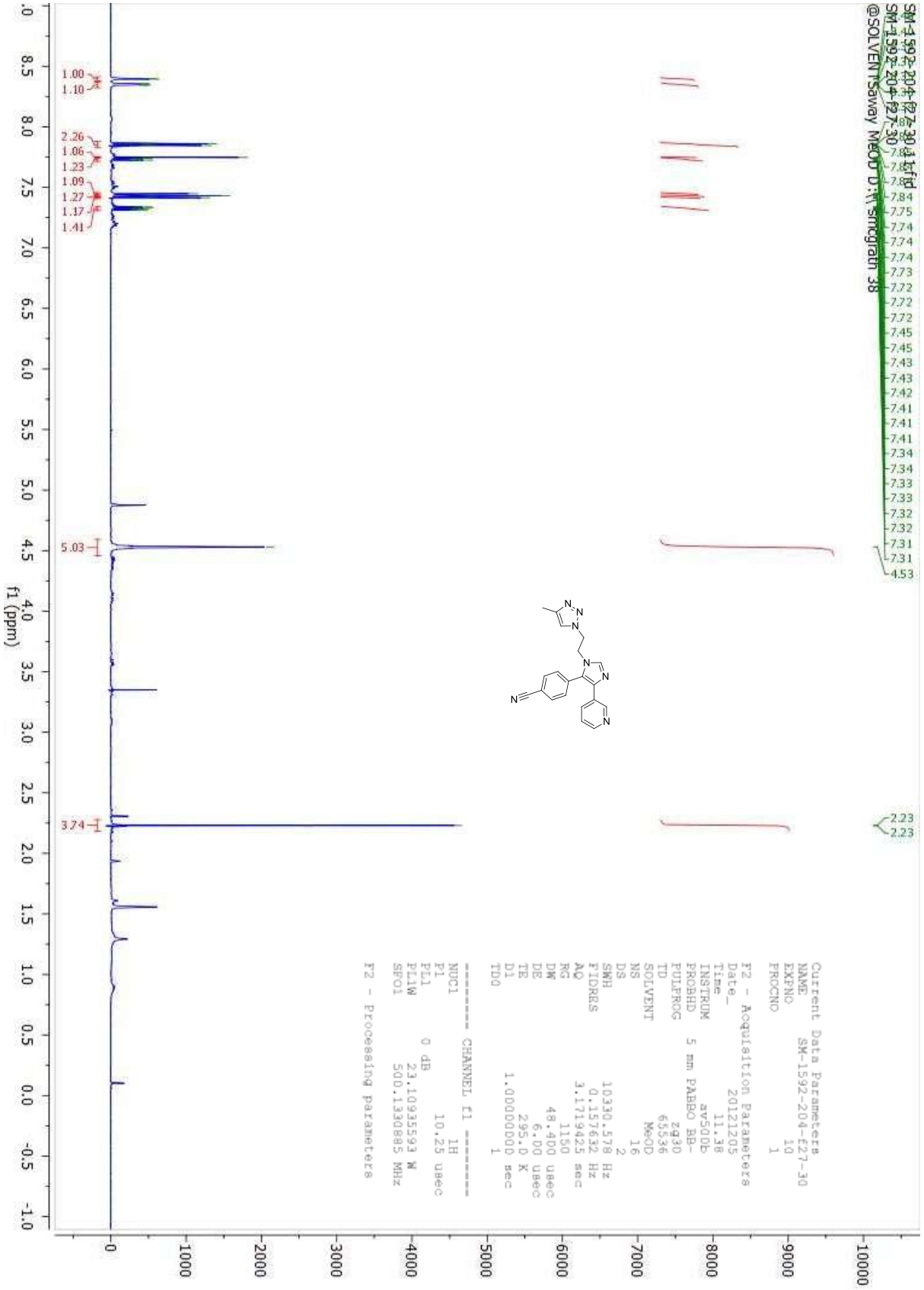


Figure S11. ^{1}H NMR (CD_3OD, 500 MHz) of **3**.

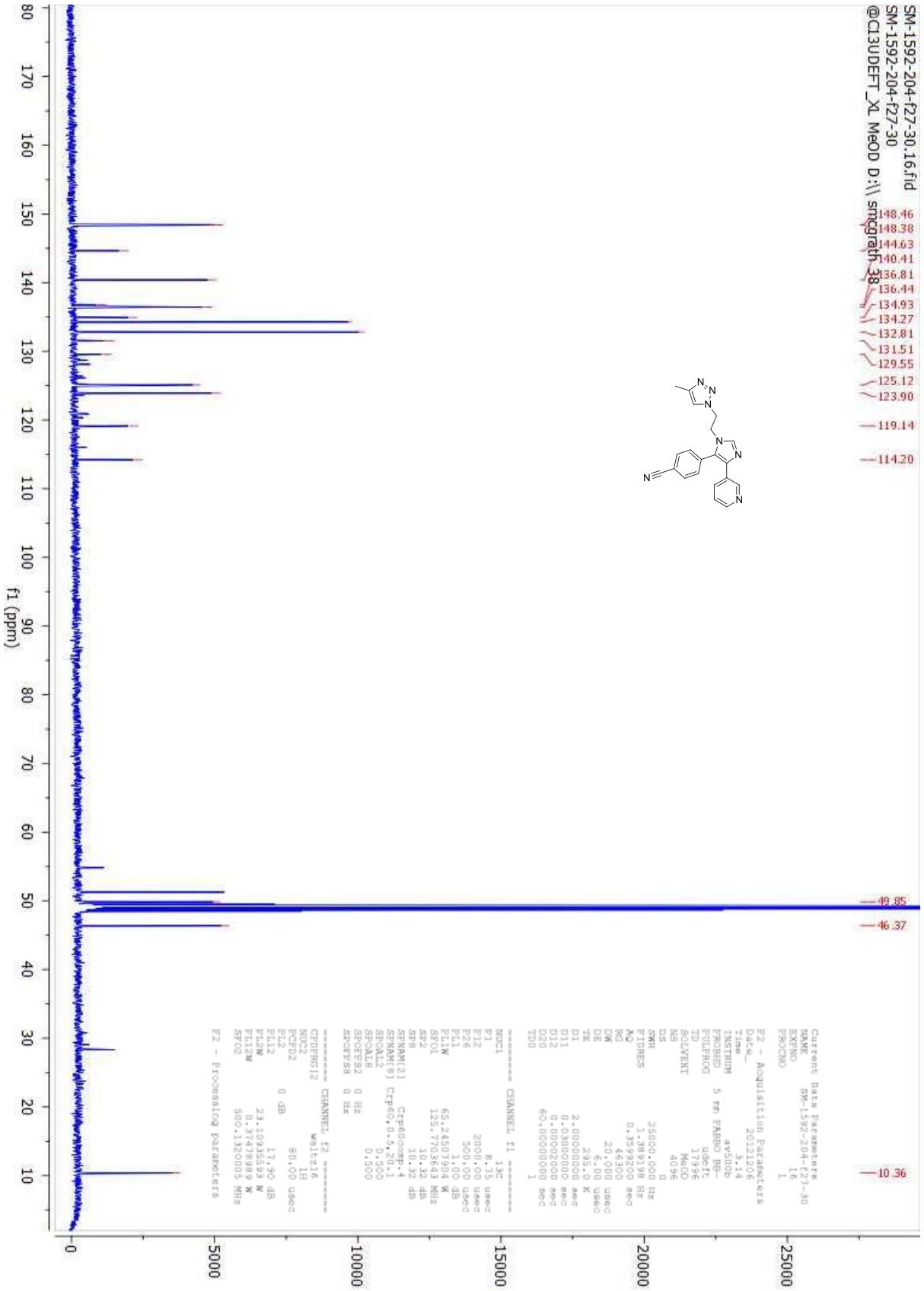


Figure S12. ^{13}C NMR (CD_3OD, 126 MHz) of **3**.

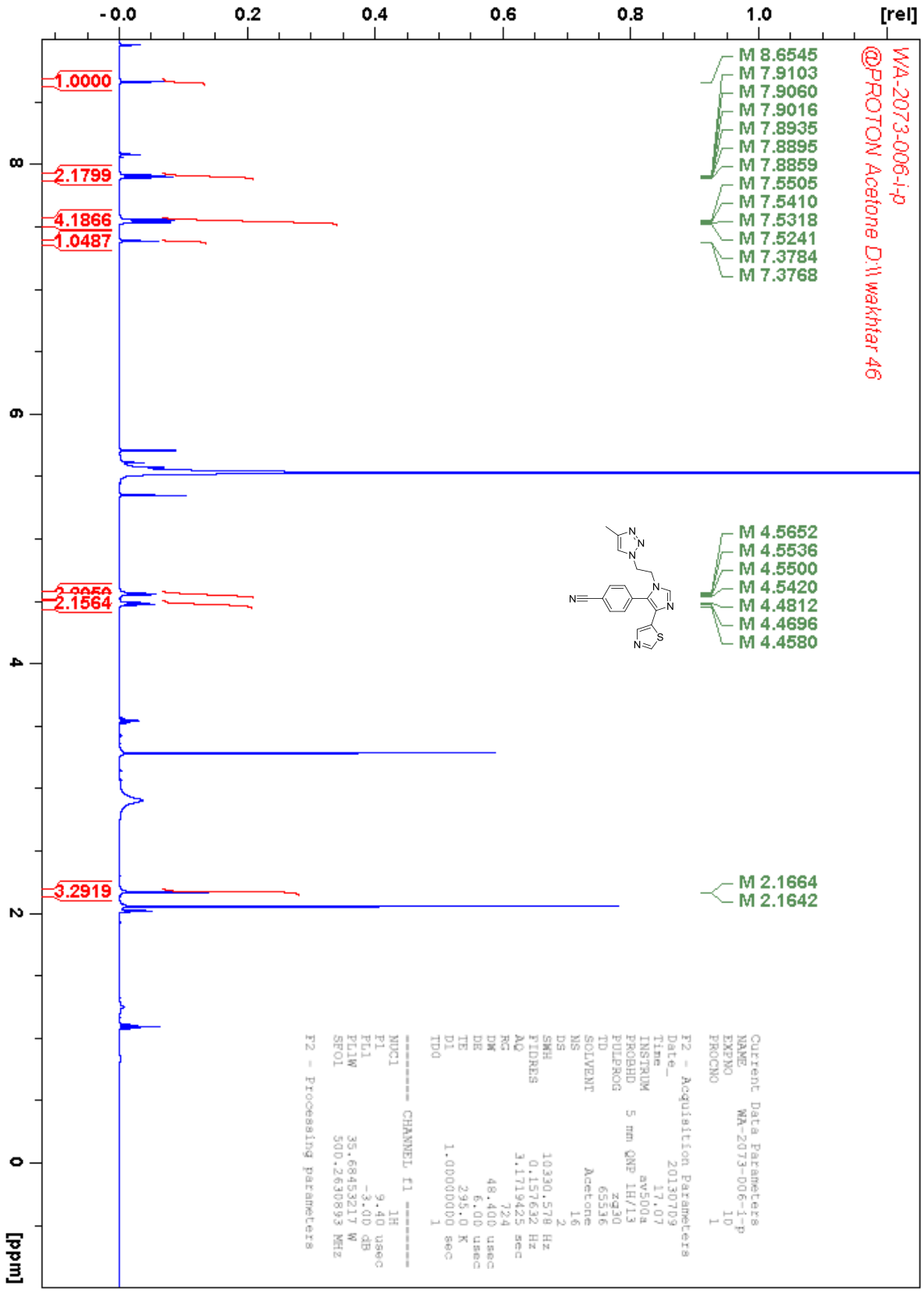


Figure S13. ^{1}H NMR (CD_3COCD_3, 500 MHz) of **4**.

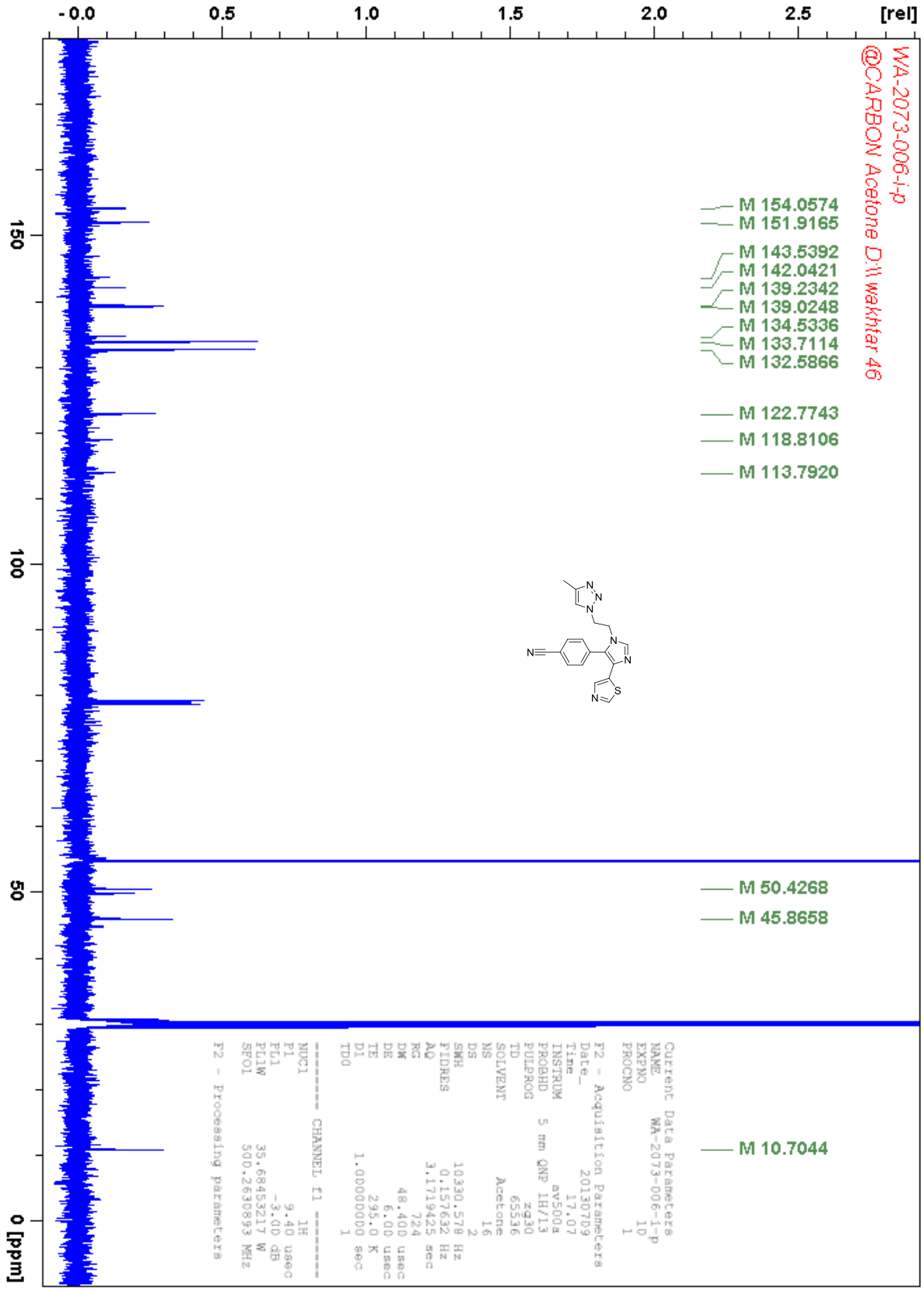


Figure S14. ^{13}C NMR (CD_3COCD_3, 126 MHz) of **4**.

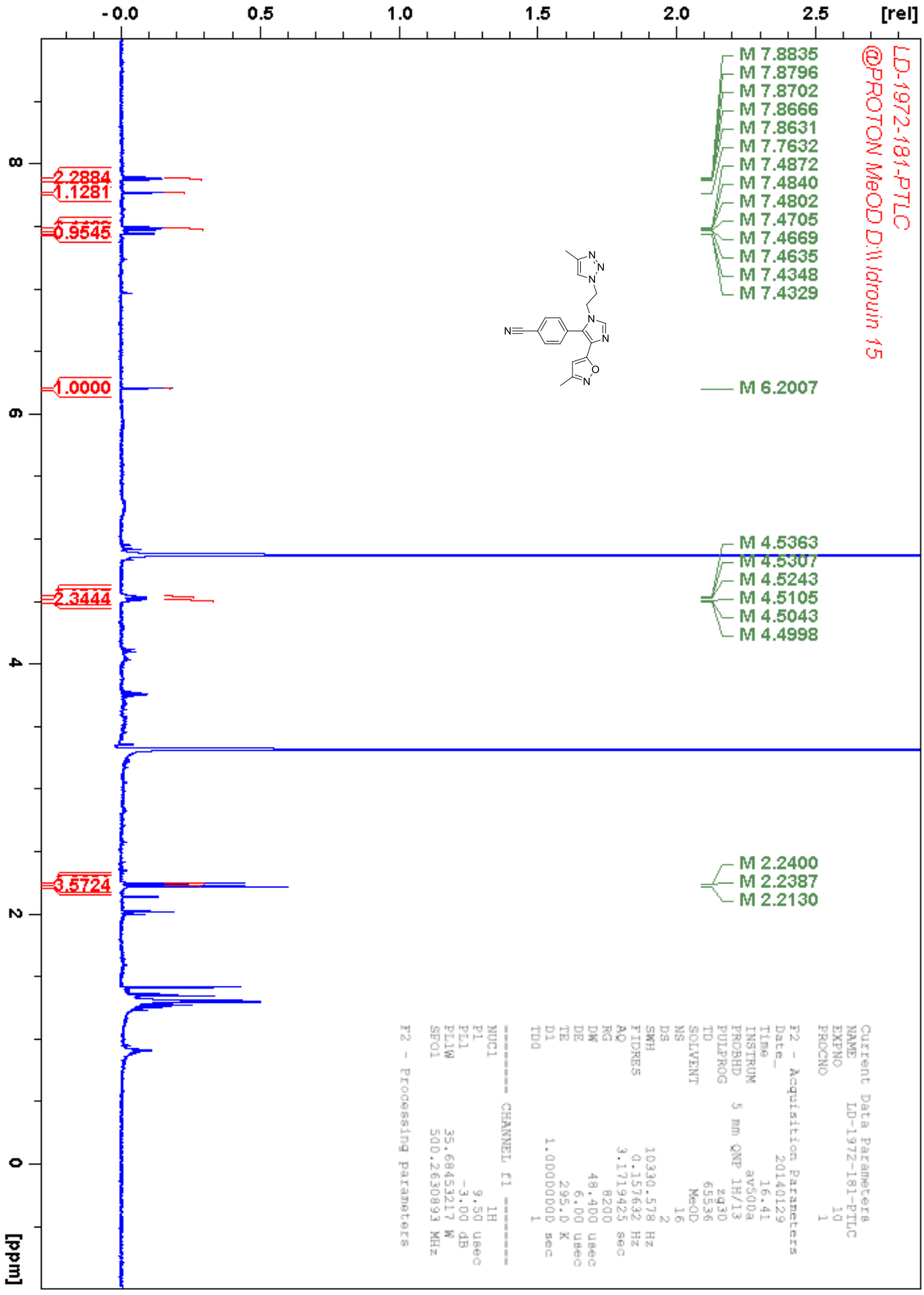


Figure S15. ^{1}H NMR (CD_3OD, 500 MHz) of **5**.

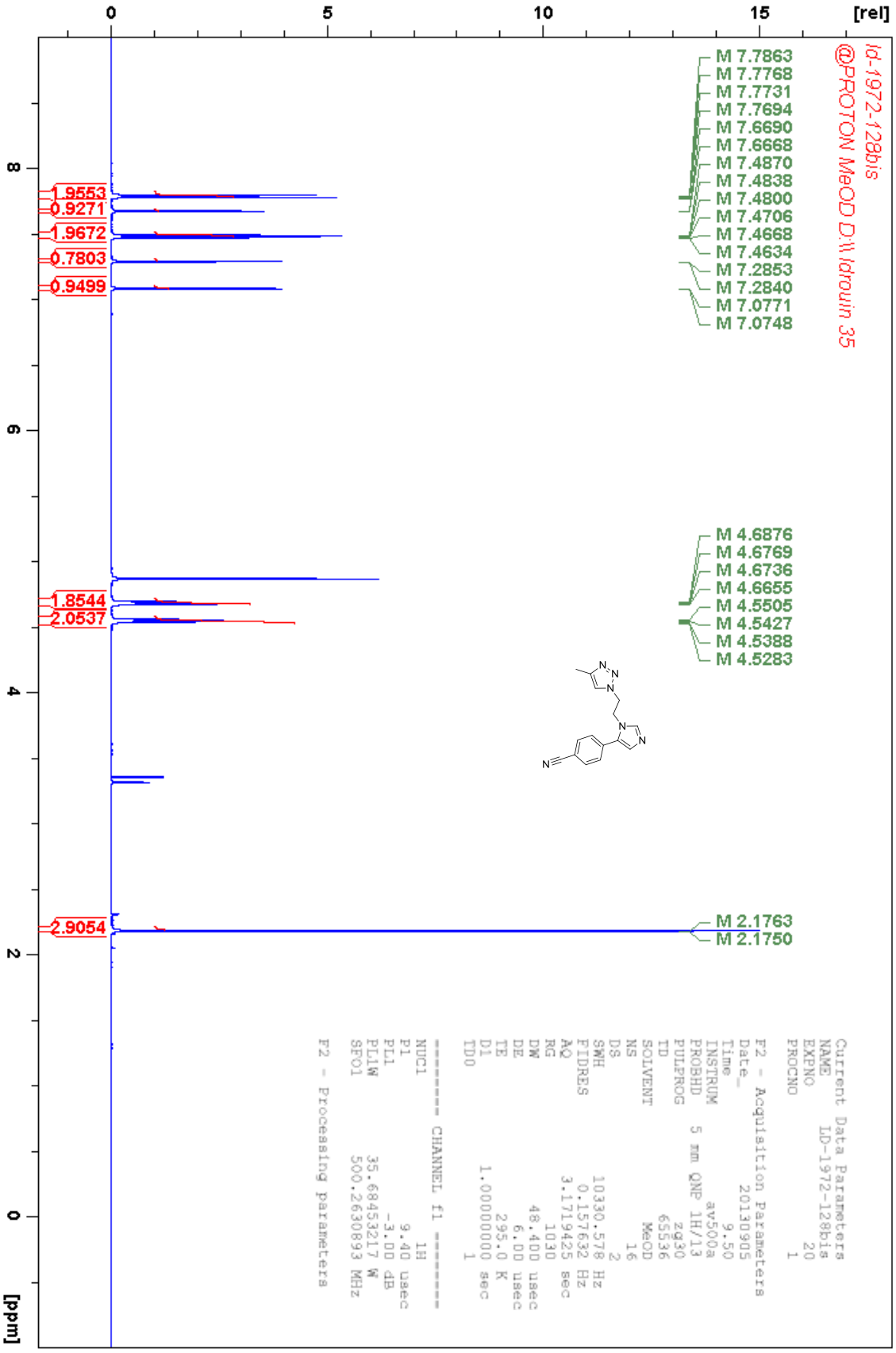


Figure S16. ^{1}H NMR (CD_3OD, 500 MHz) of **6**.

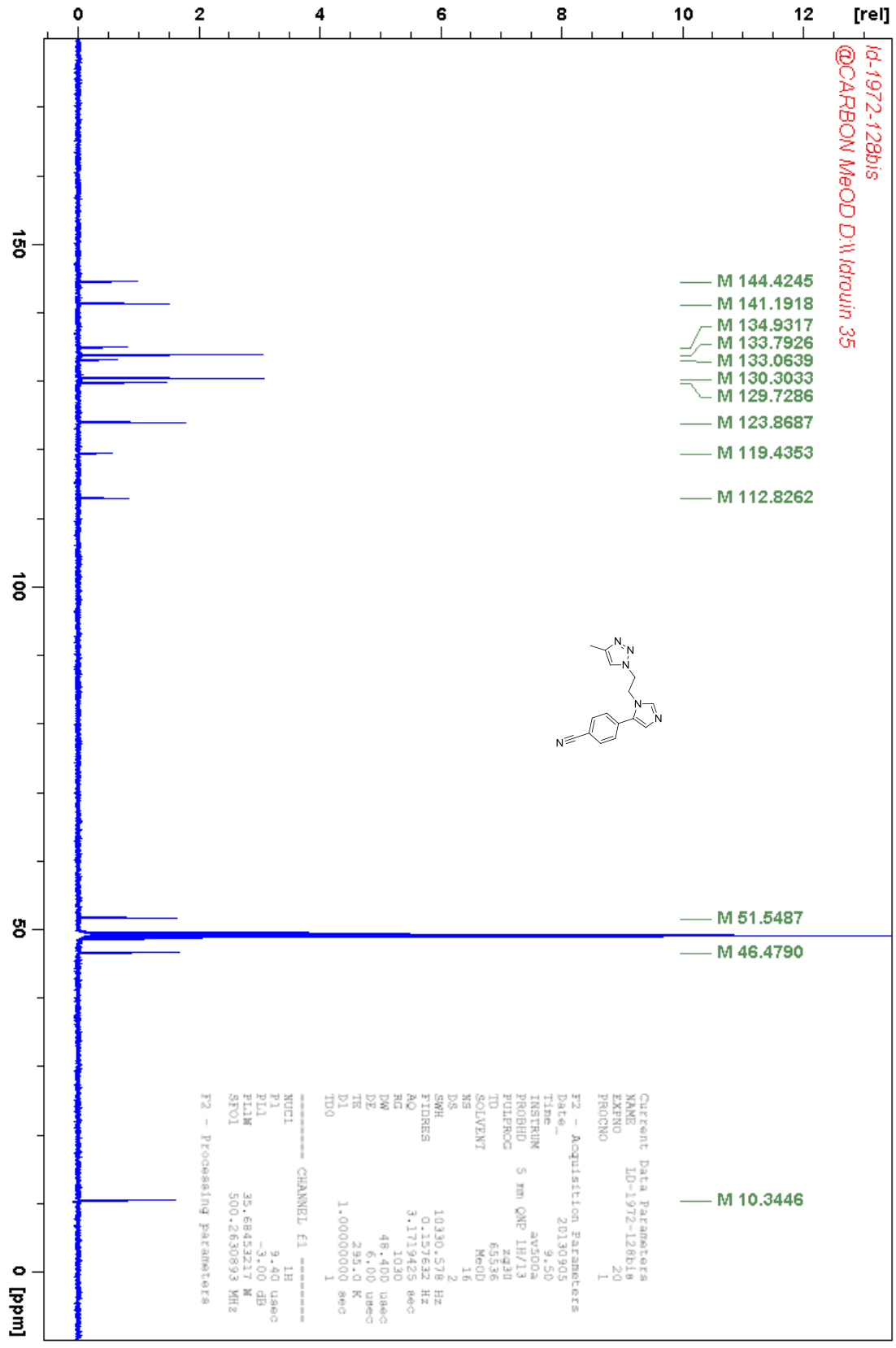


Figure S17. ^{13}C NMR (CD_3OD, 126 MHz) of **6**.

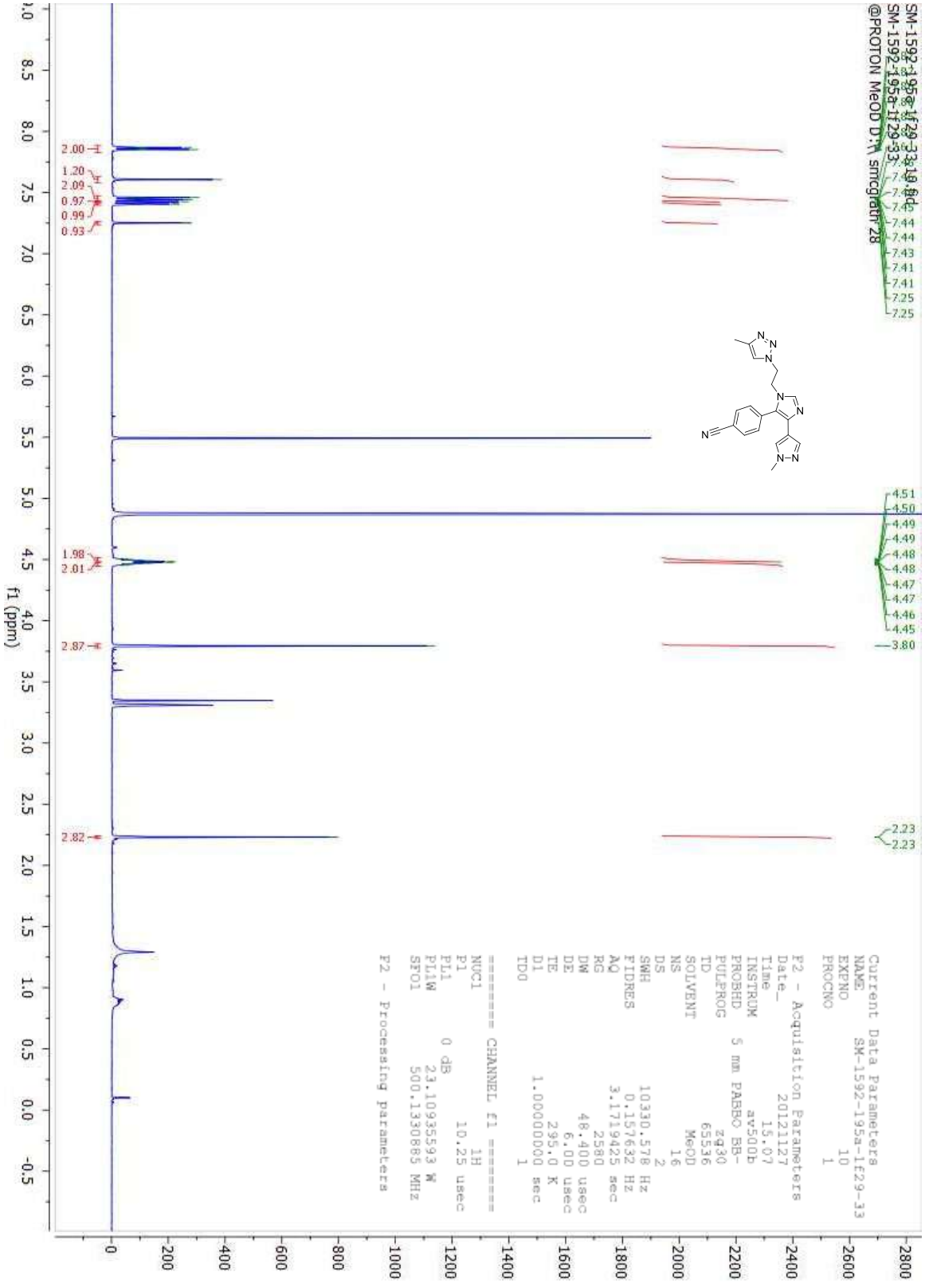


Figure S18. ^{1}H NMR (CD_3OD, 500 MHz) of **7**.

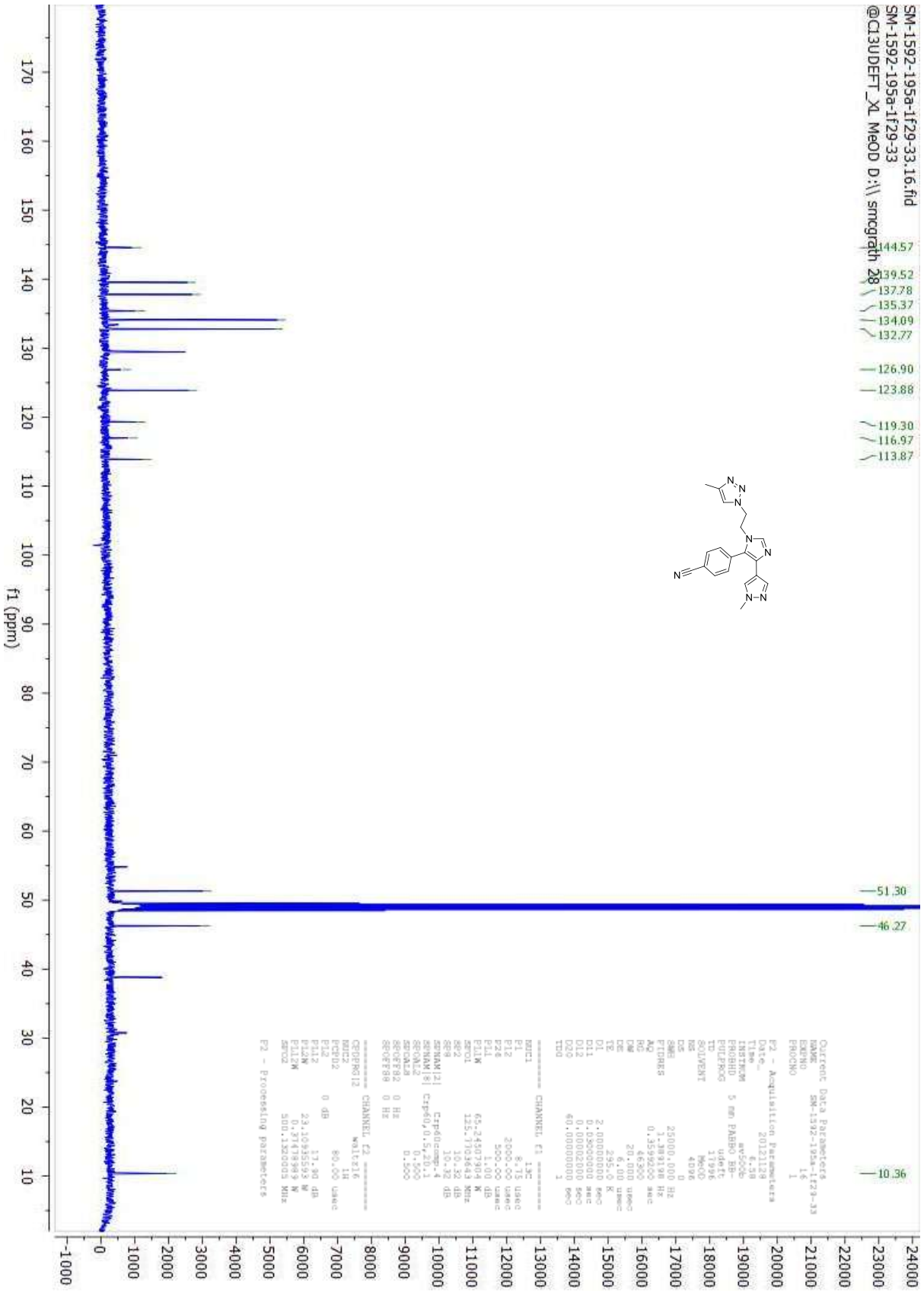


Figure S19. ^{13}C NMR (CD_3OD, 126 MHz) of **7**.

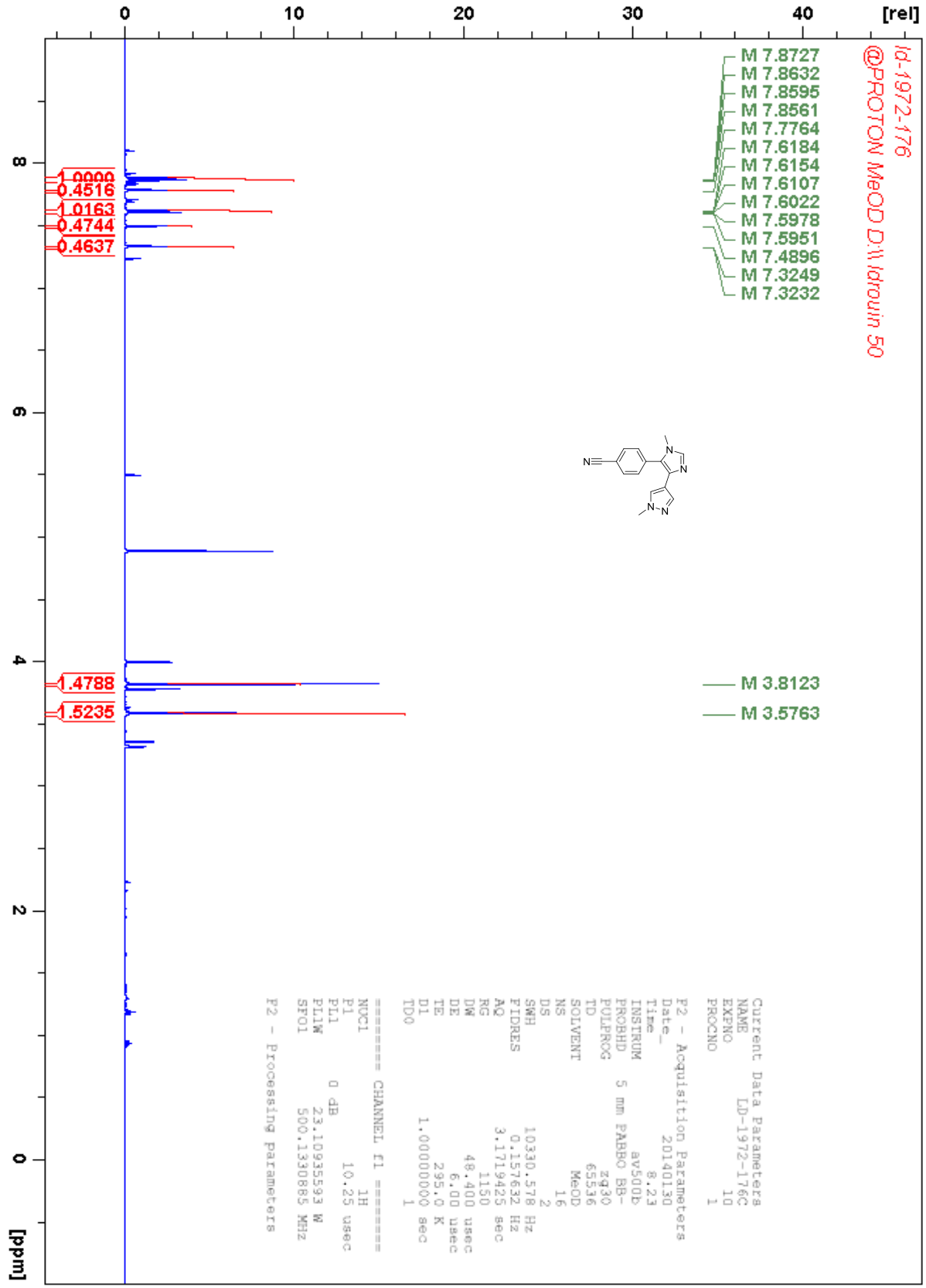


Figure S20. ^{1}H NMR (CD_3OD, 500 MHz) of **8**.

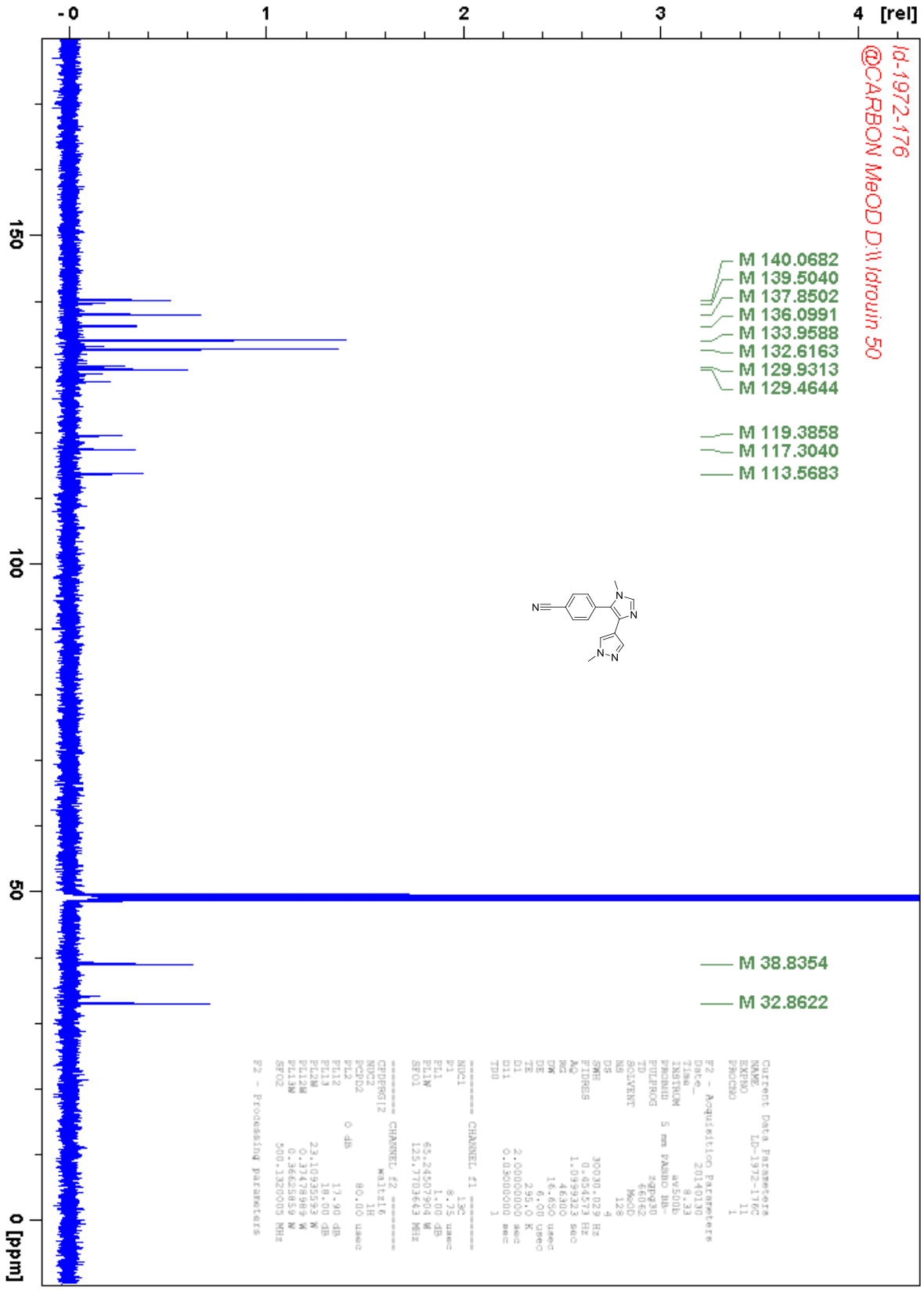


Figure S21. ^{13}C NMR (CD_3OD, 126 MHz) of **8**.

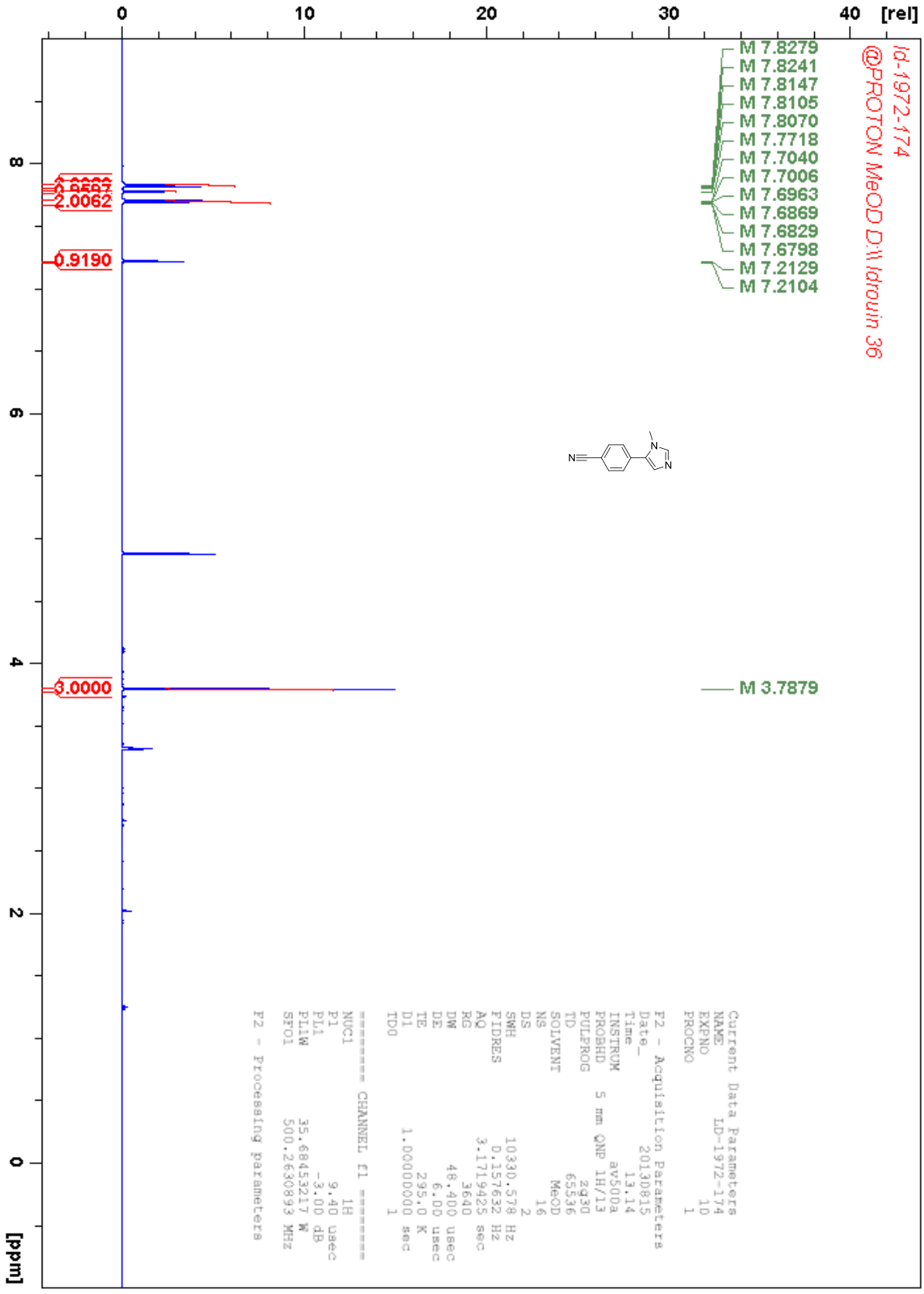


Figure S22. ^{1}H NMR (CD_3OD, 500 MHz) of **9**.

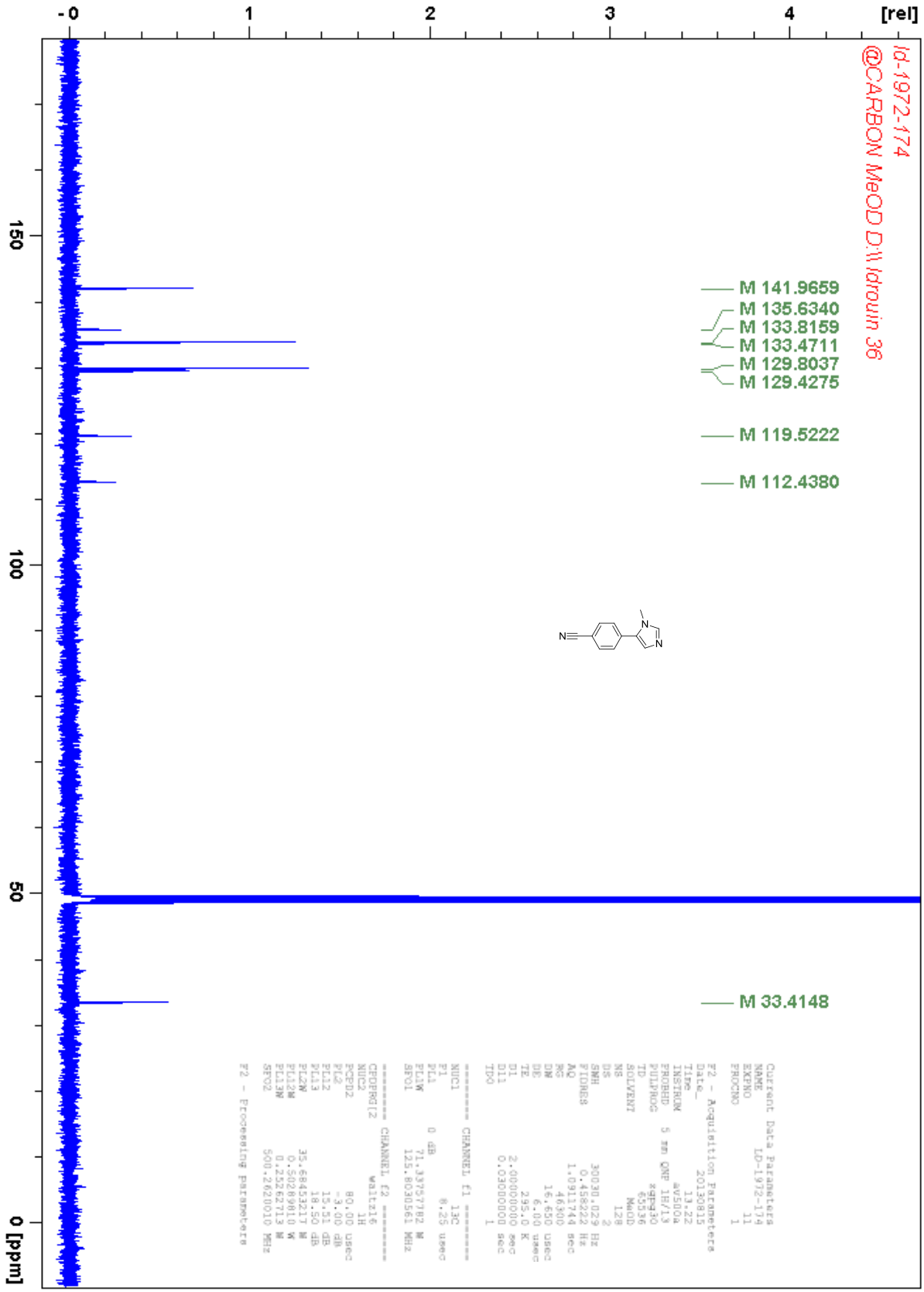


Figure S23. ^{13}C NMR (CD_3OD, 126 MHz) of **9**.

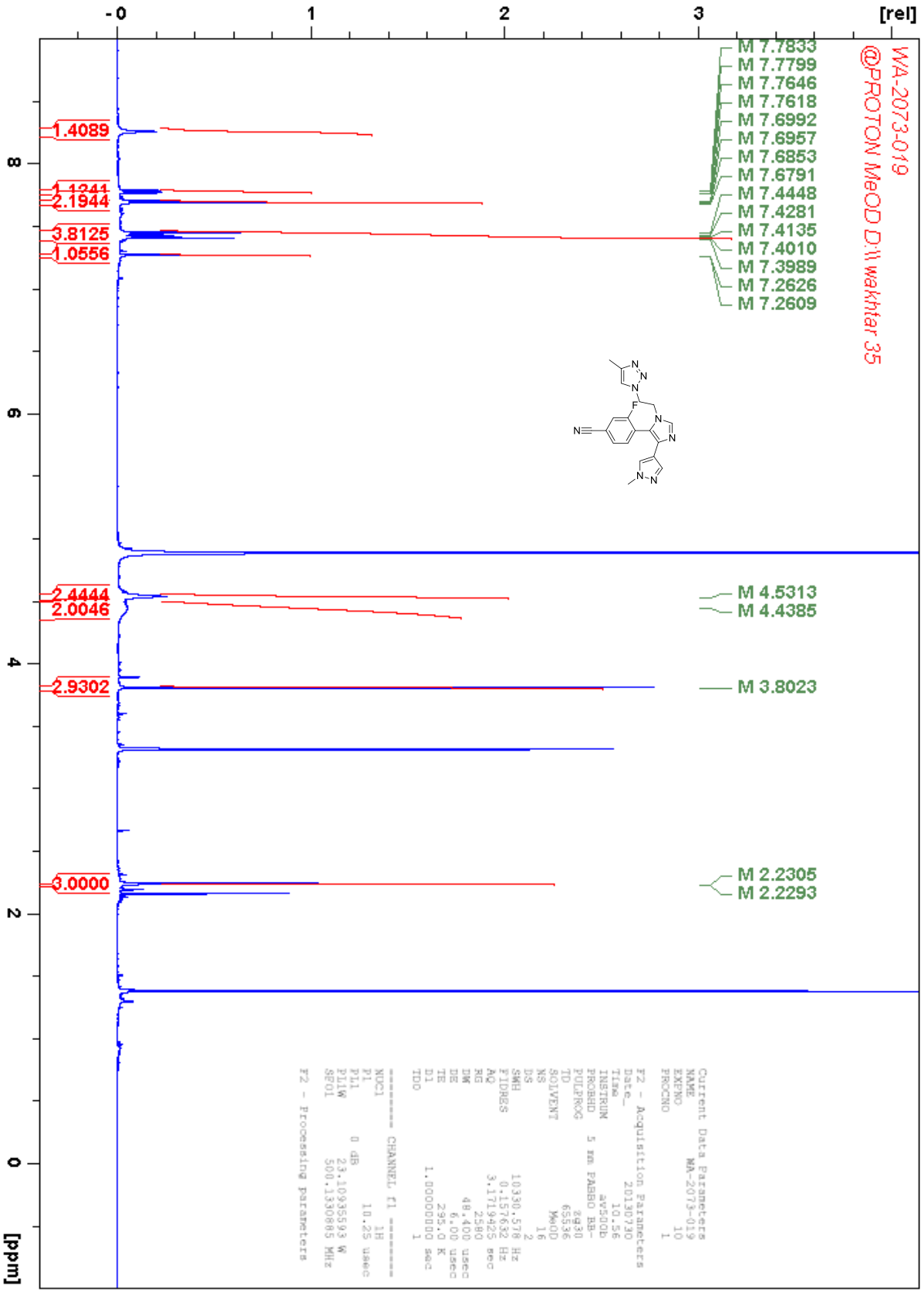


Figure S24. ^{1}H NMR (CD_3OD, 500 MHz) of **10**.

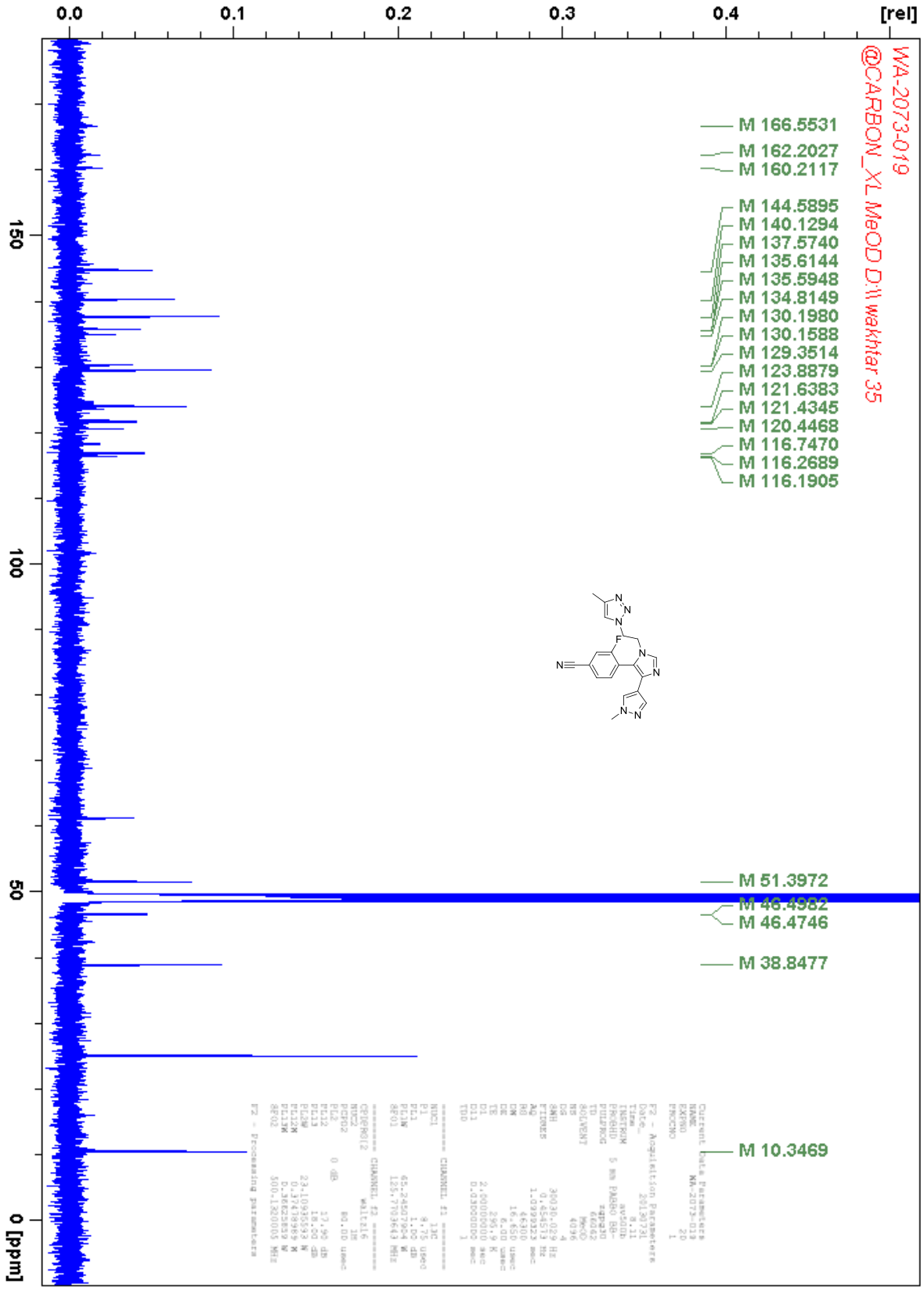


Figure S25. ^{13}C NMR (CD_3OD, 126 MHz) of **10**.

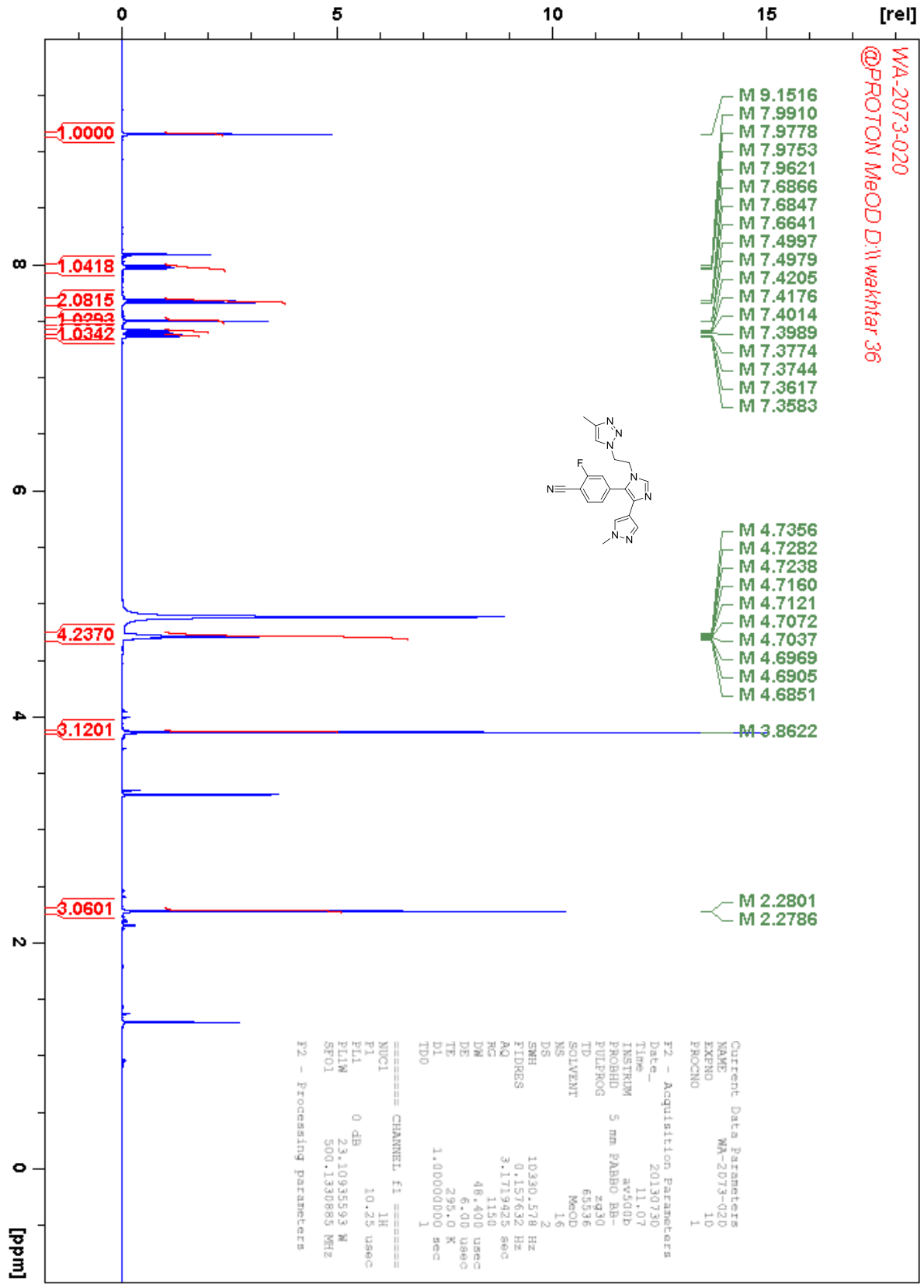


Figure S26. ^{1}H NMR (CD_3OD, 500 MHz) of **11**.

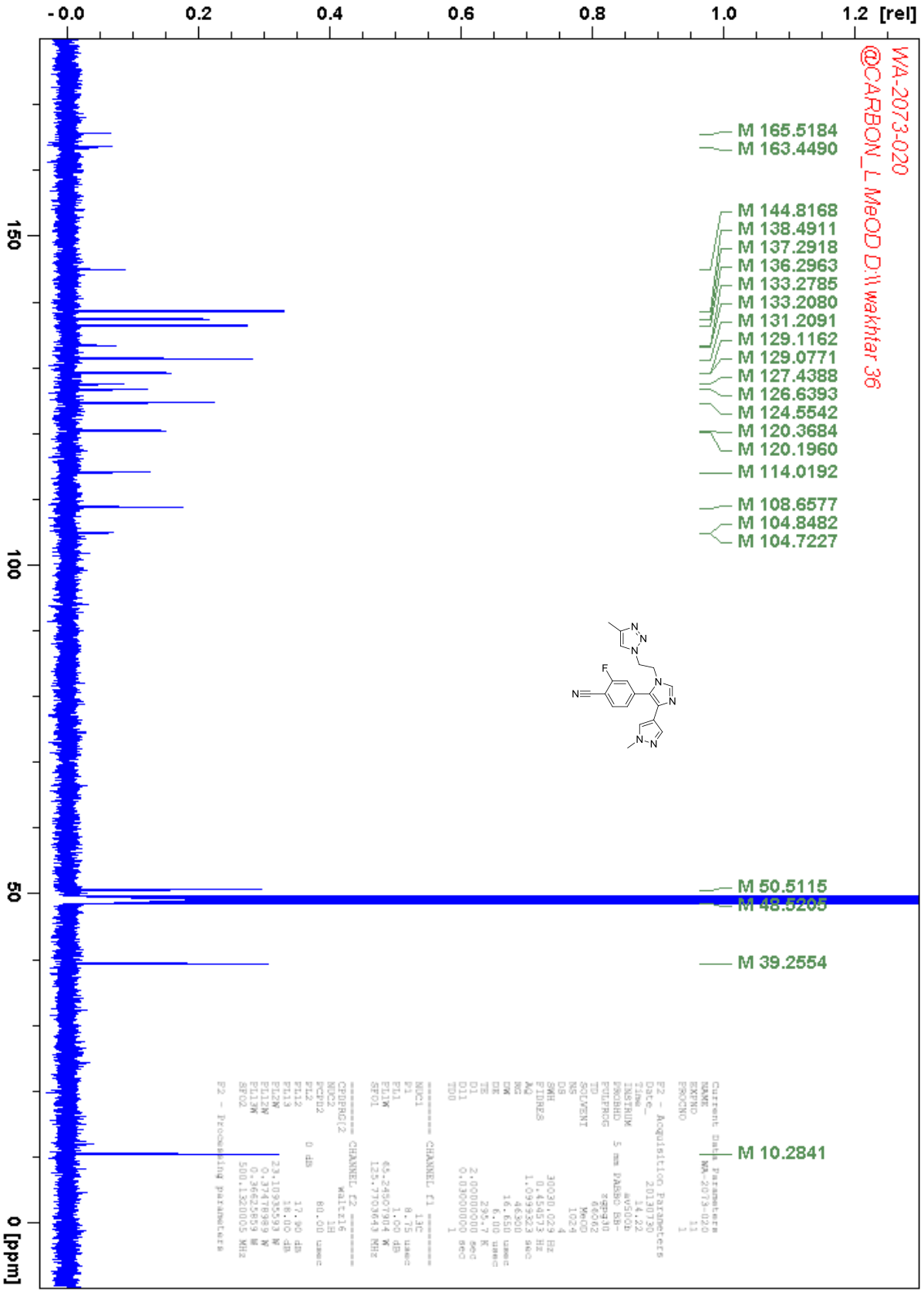


Figure S27. ^{13}C NMR (CD_3OD, 126 MHz) of **11**.

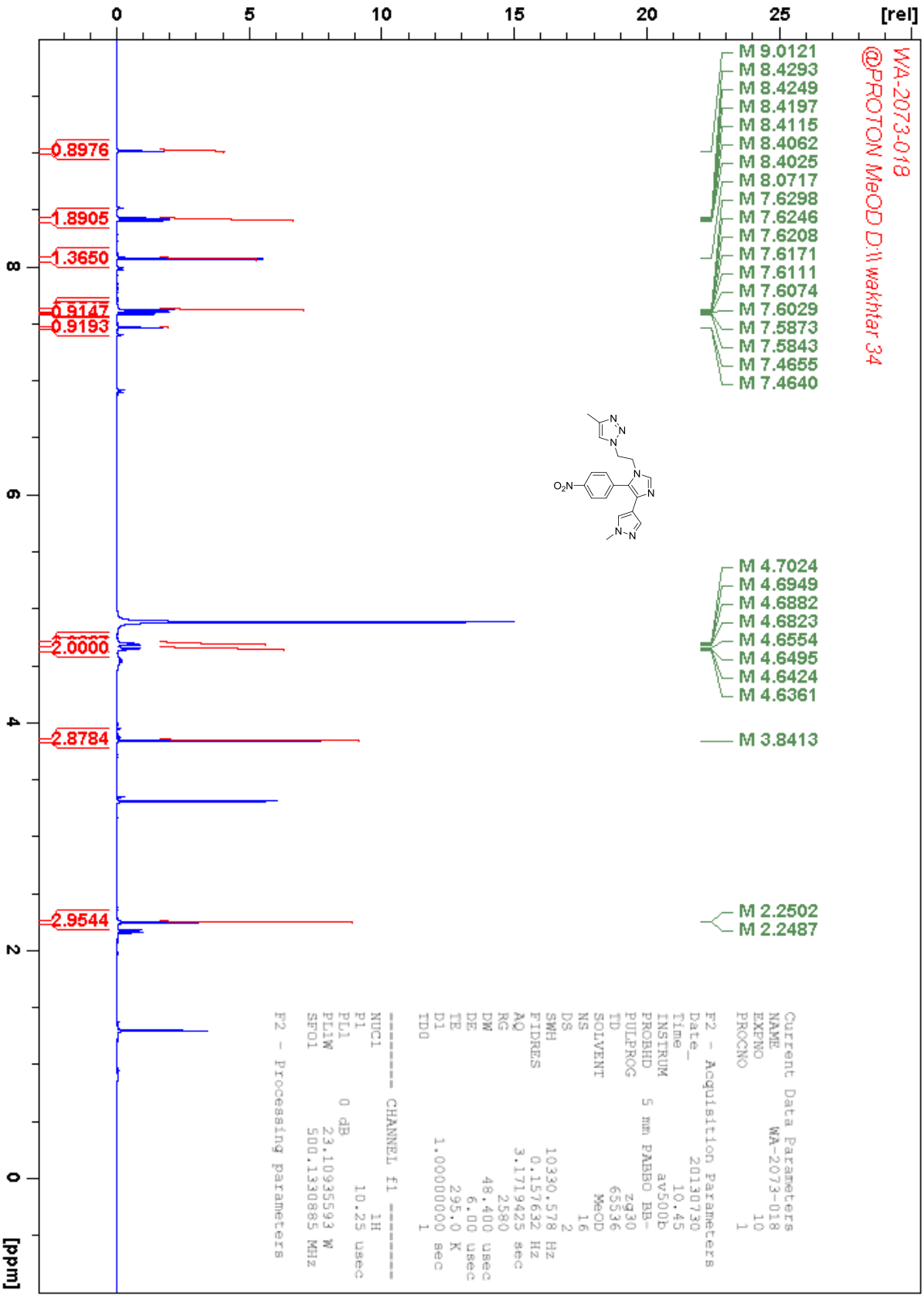


Figure S28. ^{1}H NMR (CD_3OD, 500 MHz) of **12**.

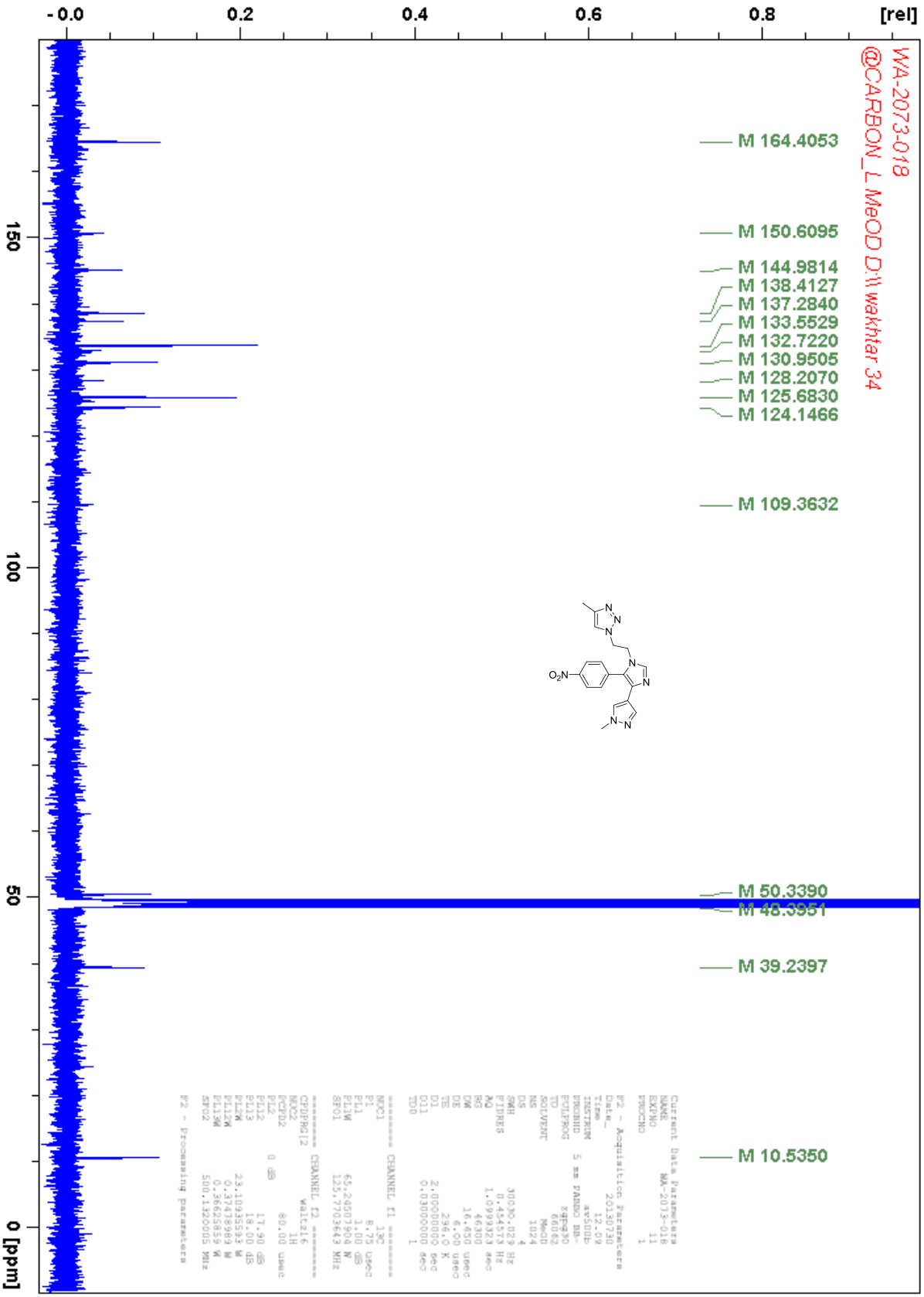


Figure S29. ^{13}C NMR (CD_3OD, 126 MHz) of **12**.

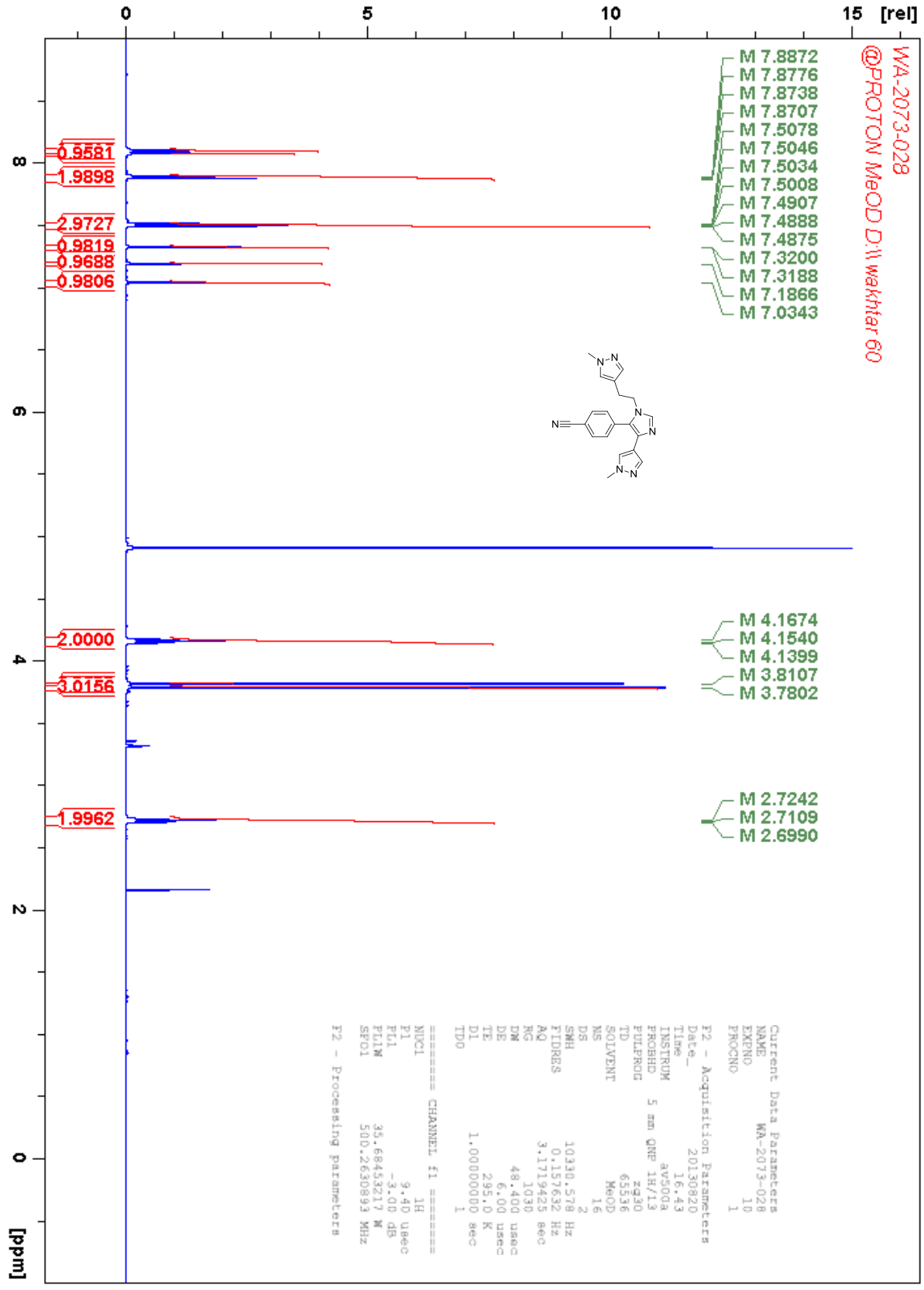


Figure S30. ^{1}H NMR (CD_3OD, 500 MHz) of **BAZ2-ICR (13)**.

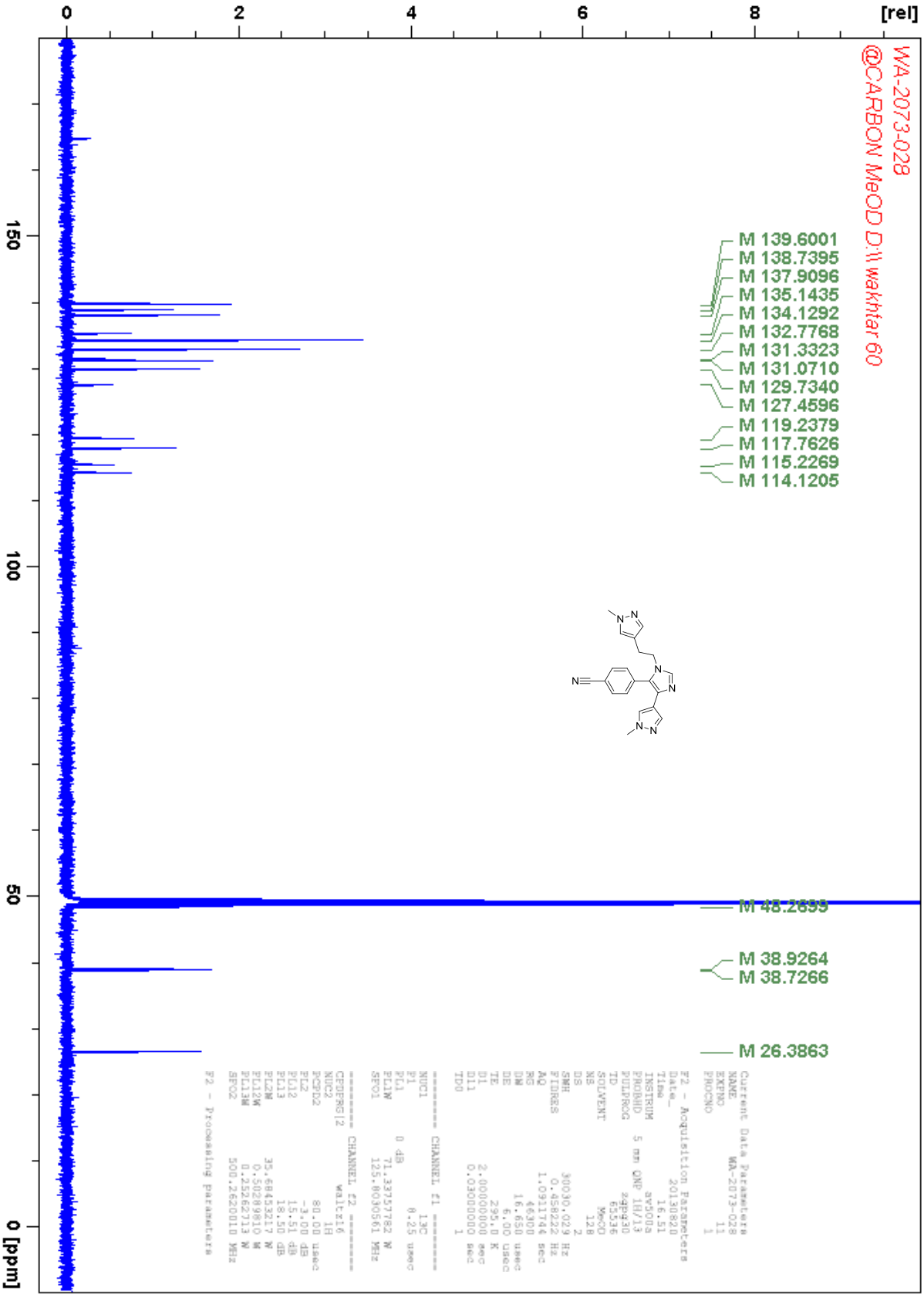


Figure S31. ^{13}C NMR (CD_3OD, 126 MHz) of **BAZ2-ICR (13)**.

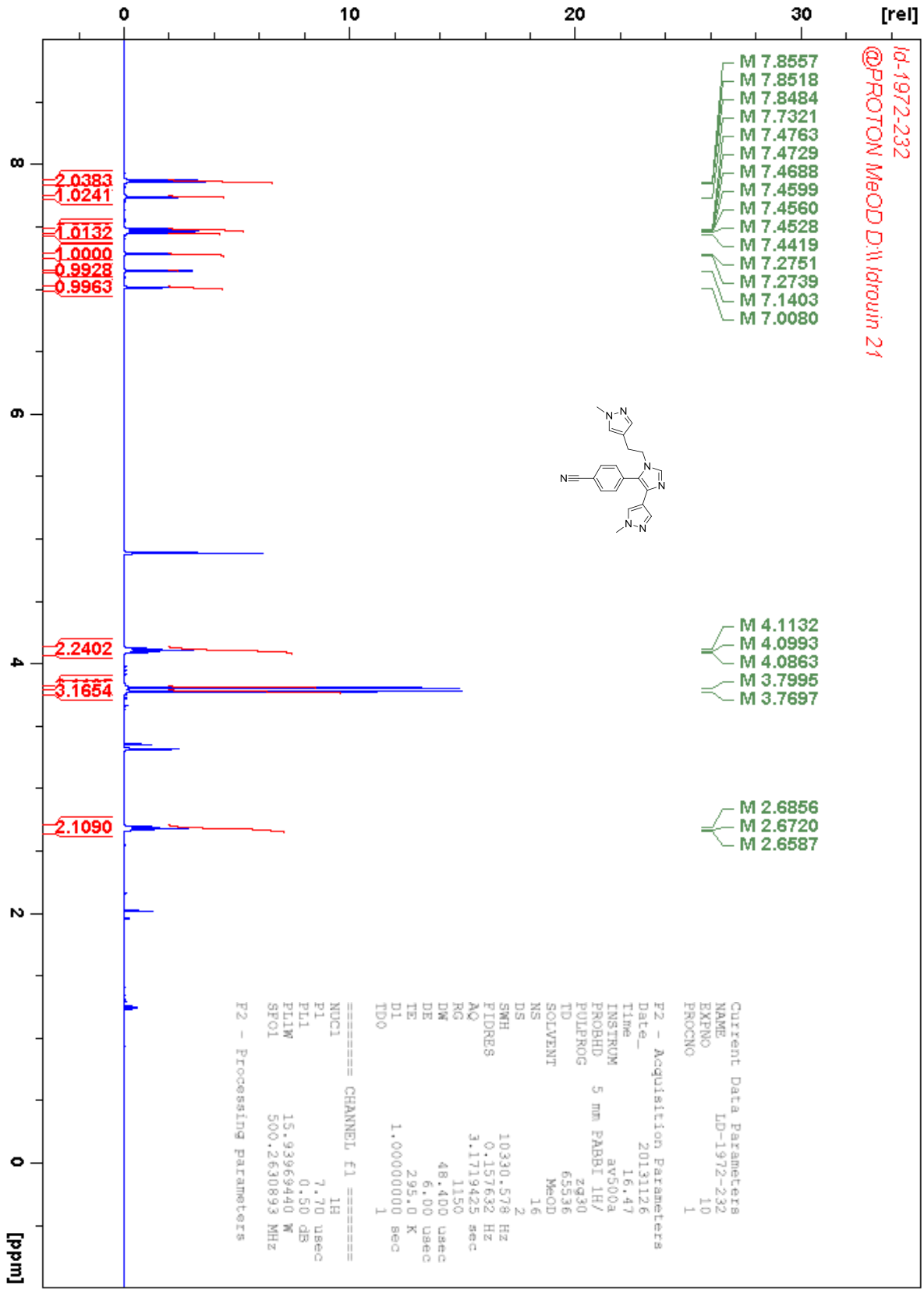


Figure S32. ^{1}H NMR (CD_3OD, 500 MHz) of **BAZ2-ICR (13)** as neutral form.

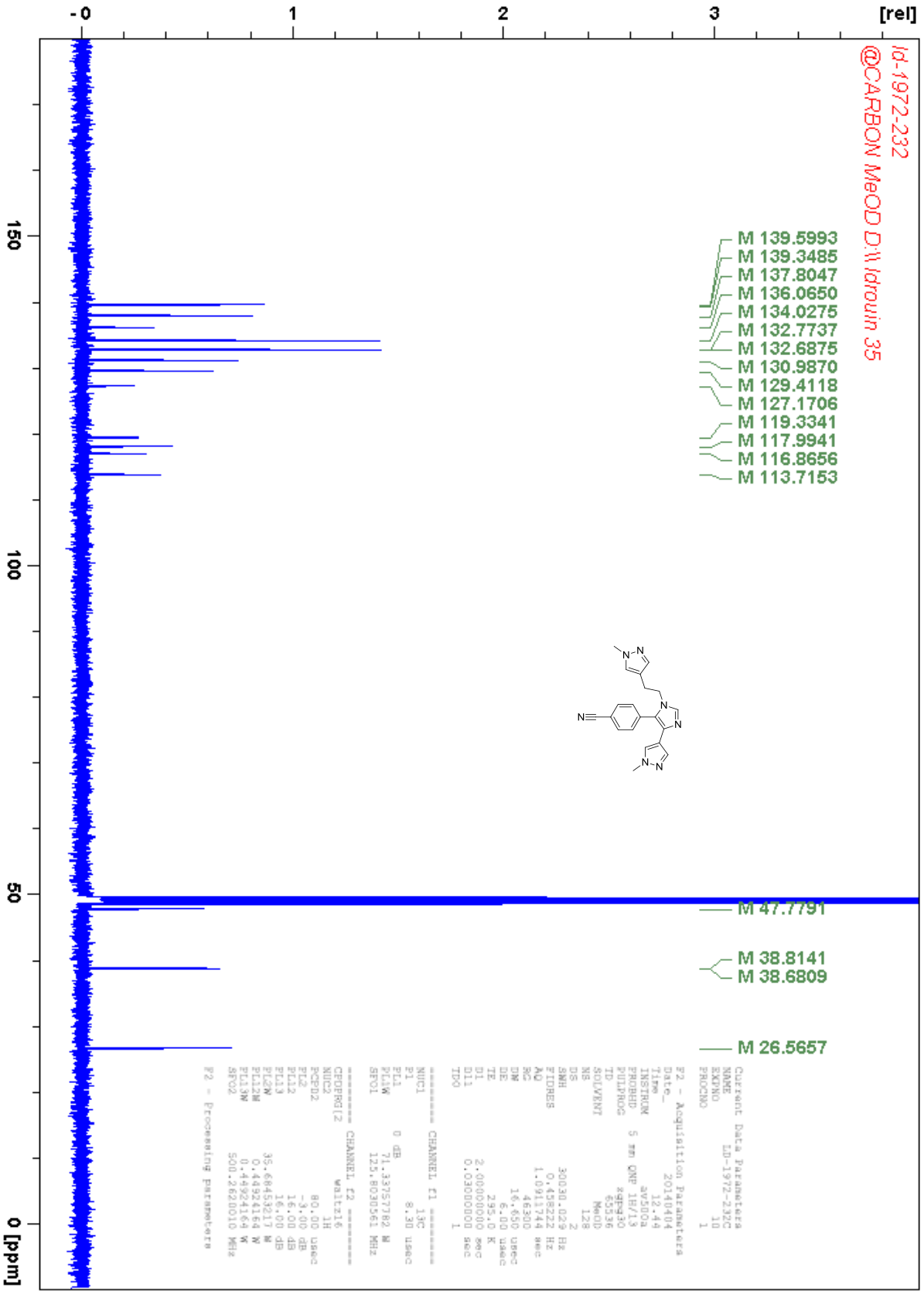


Figure S33. ^{13}C NMR (CD_3OD, 126 MHz) of **BAZ2-ICR (13)** as neutral form.

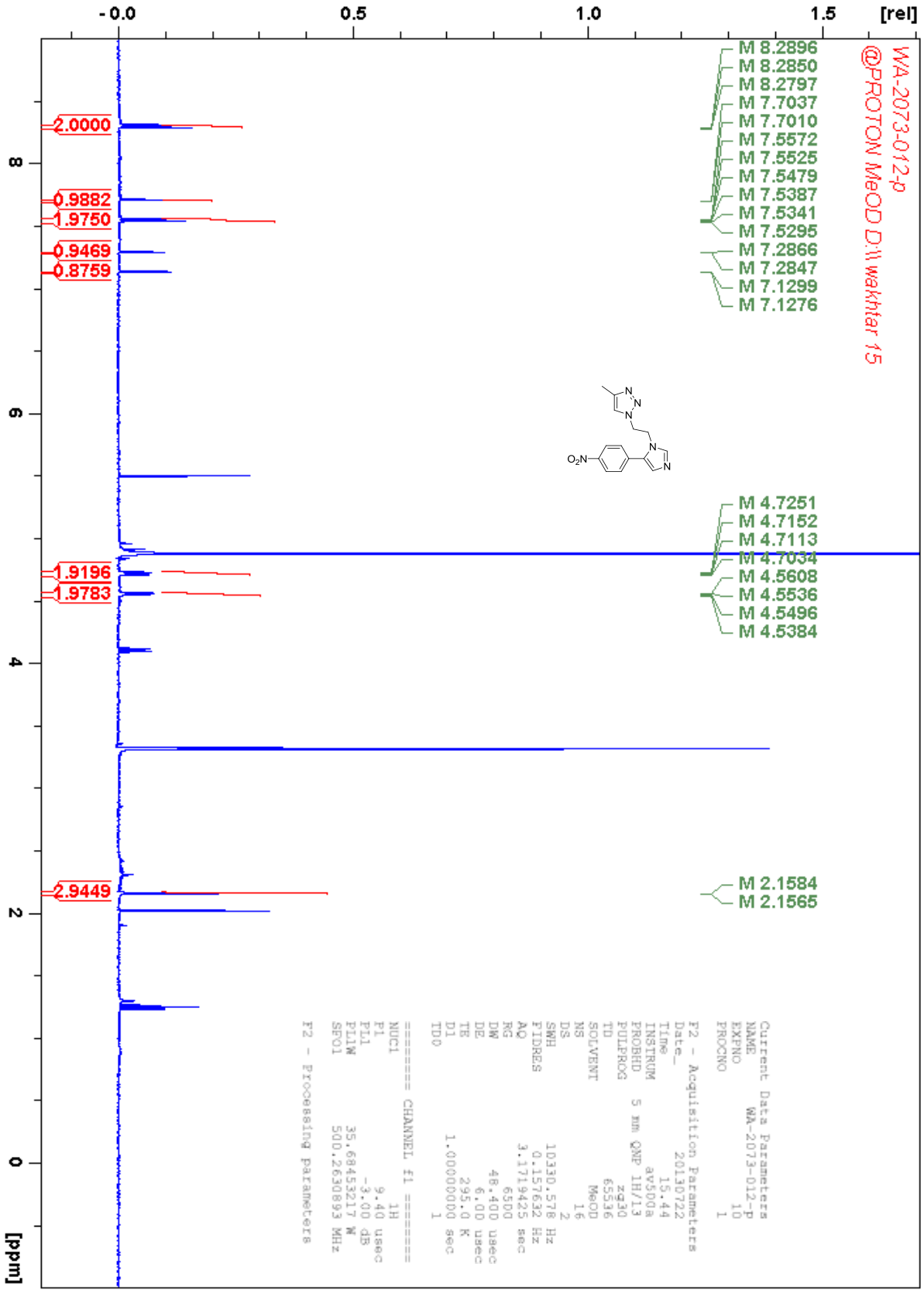


Figure S34. ^{1}H NMR (CD_3OD, 126 MHz) of **14**.

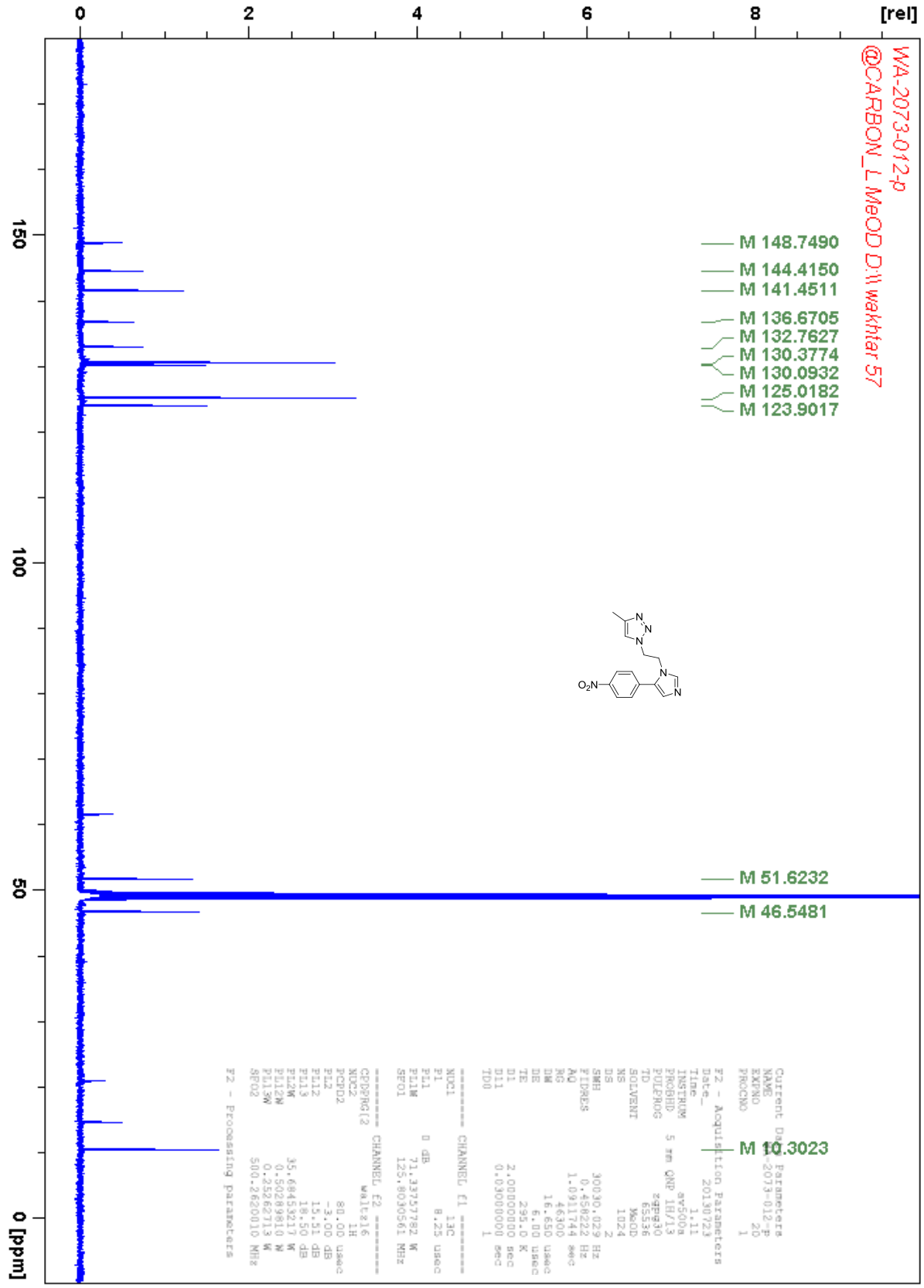


Figure S35. ^{13}C NMR (CD_3OD, 126 MHz) of **14**.

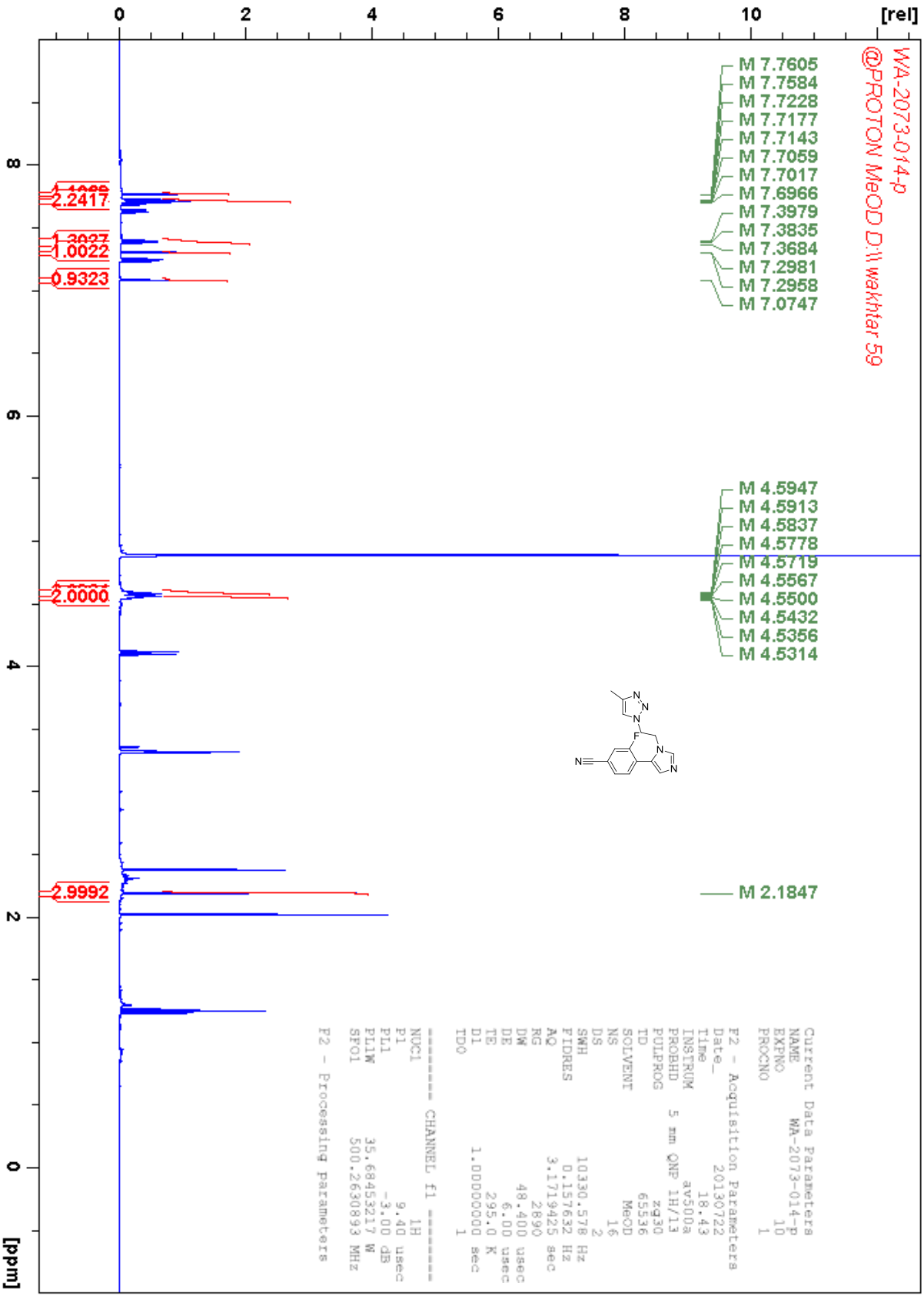


Figure S36. ^{1}H NMR (CD_3OD, 500 MHz) of **15**.

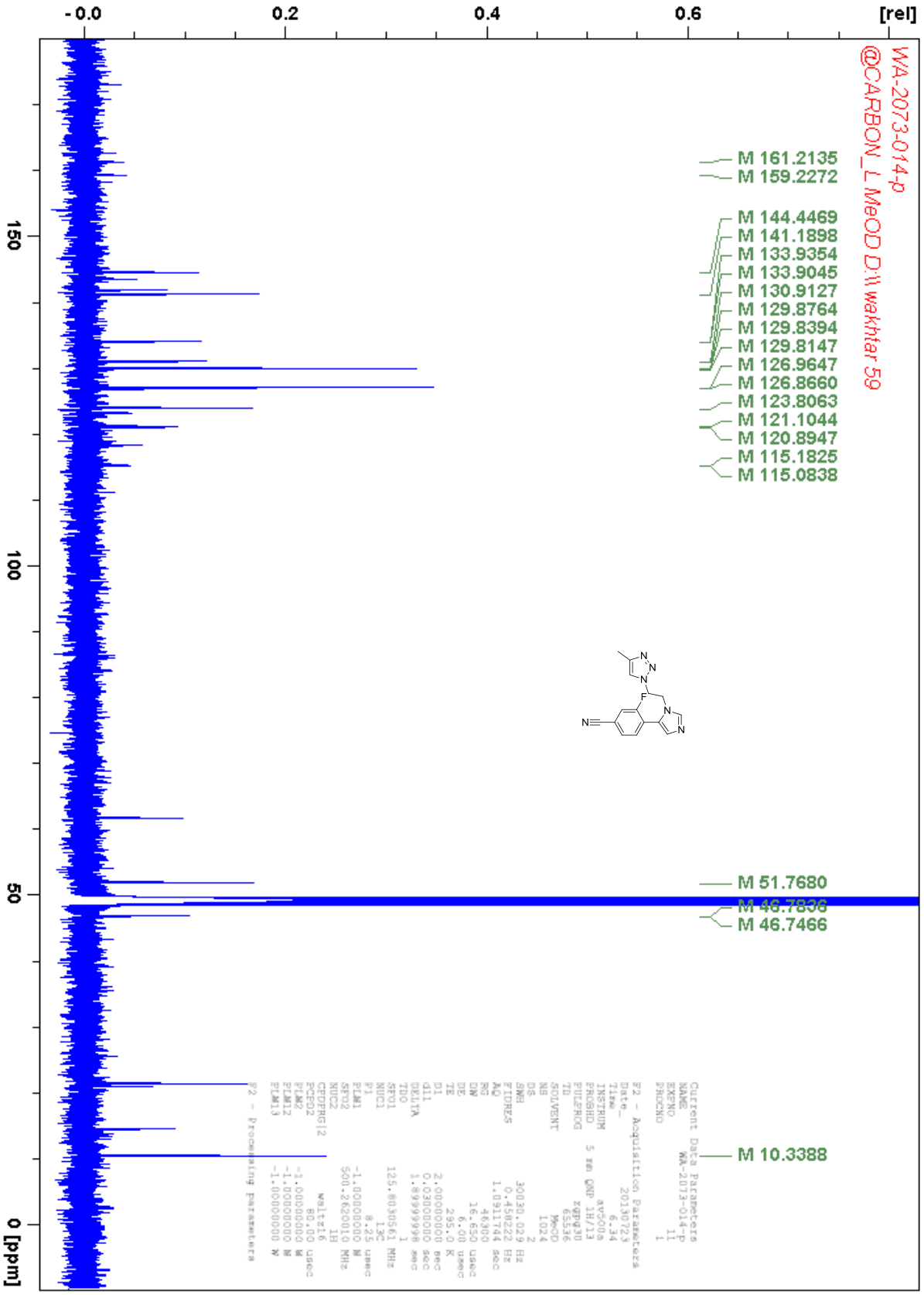


Figure S37. ^{13}C NMR (CD_3OD, 126 MHz) of **15**.

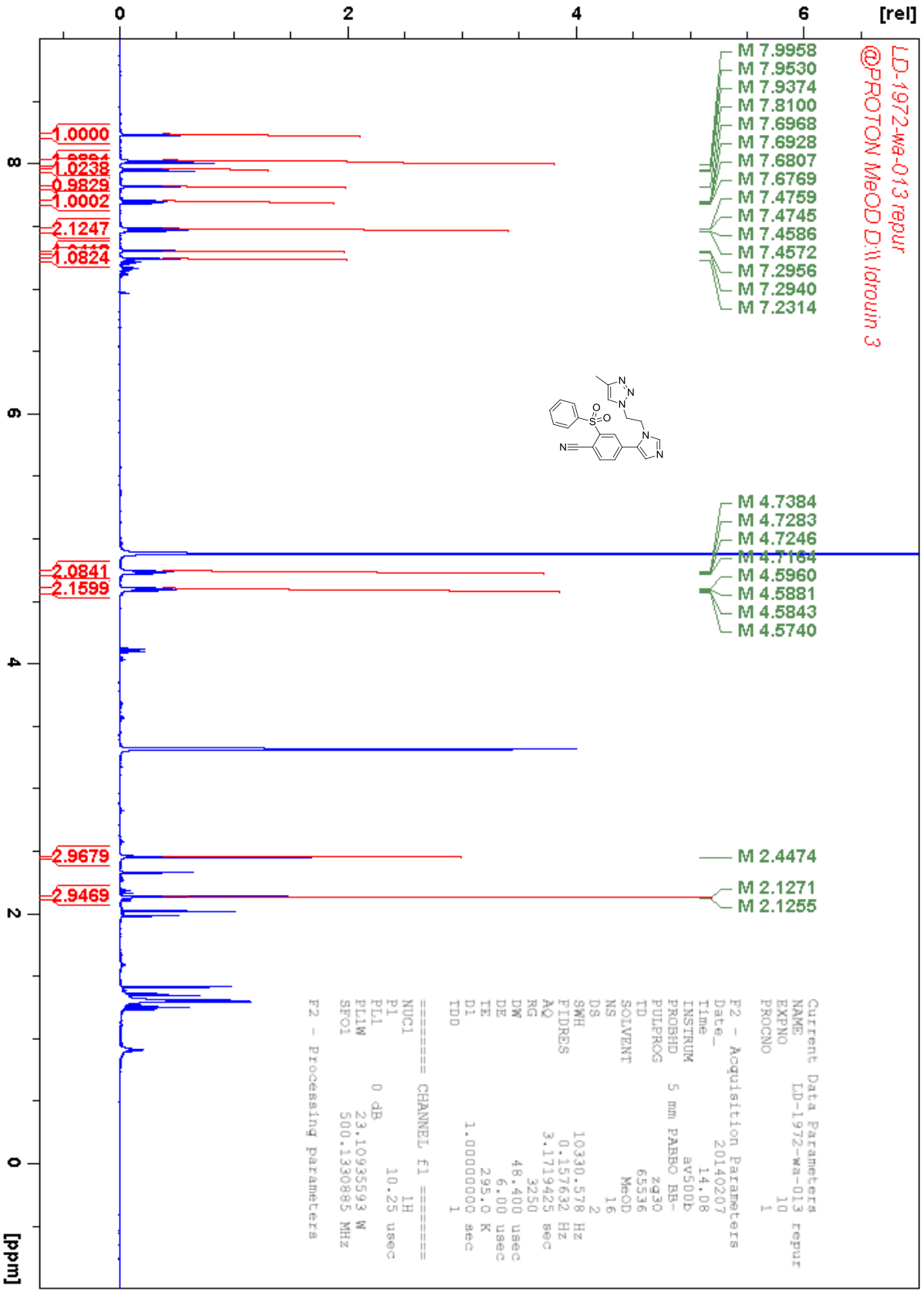


Figure S38. ^{1}H NMR (CD_3OD, 500 MHz) of **16**.

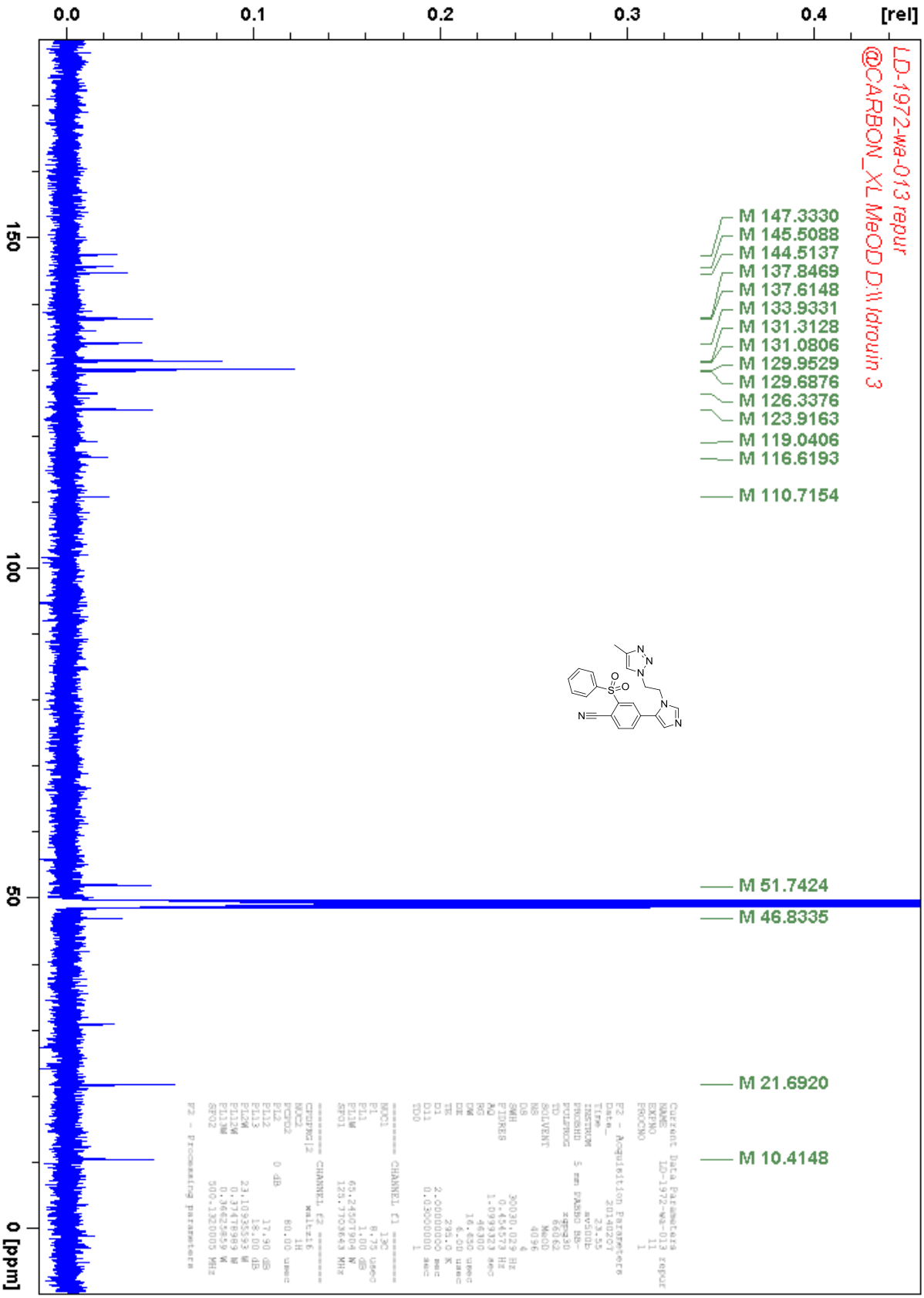


Figure S39. ^{13}C NMR (CD_3OD, 126 MHz) of **16**.

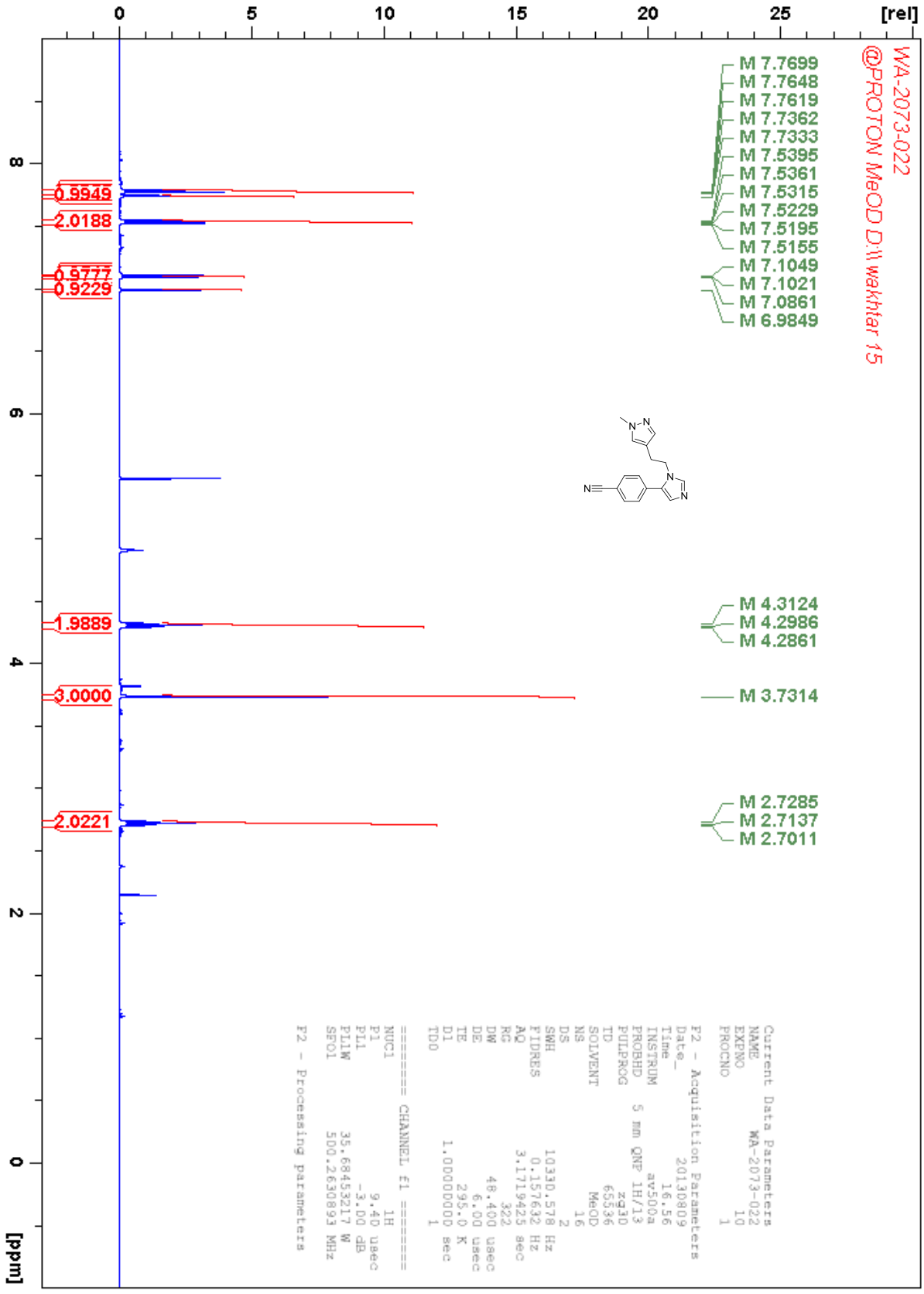


Figure S40. ^{1}H NMR (CD_3OD, 500 MHz) of **17**.

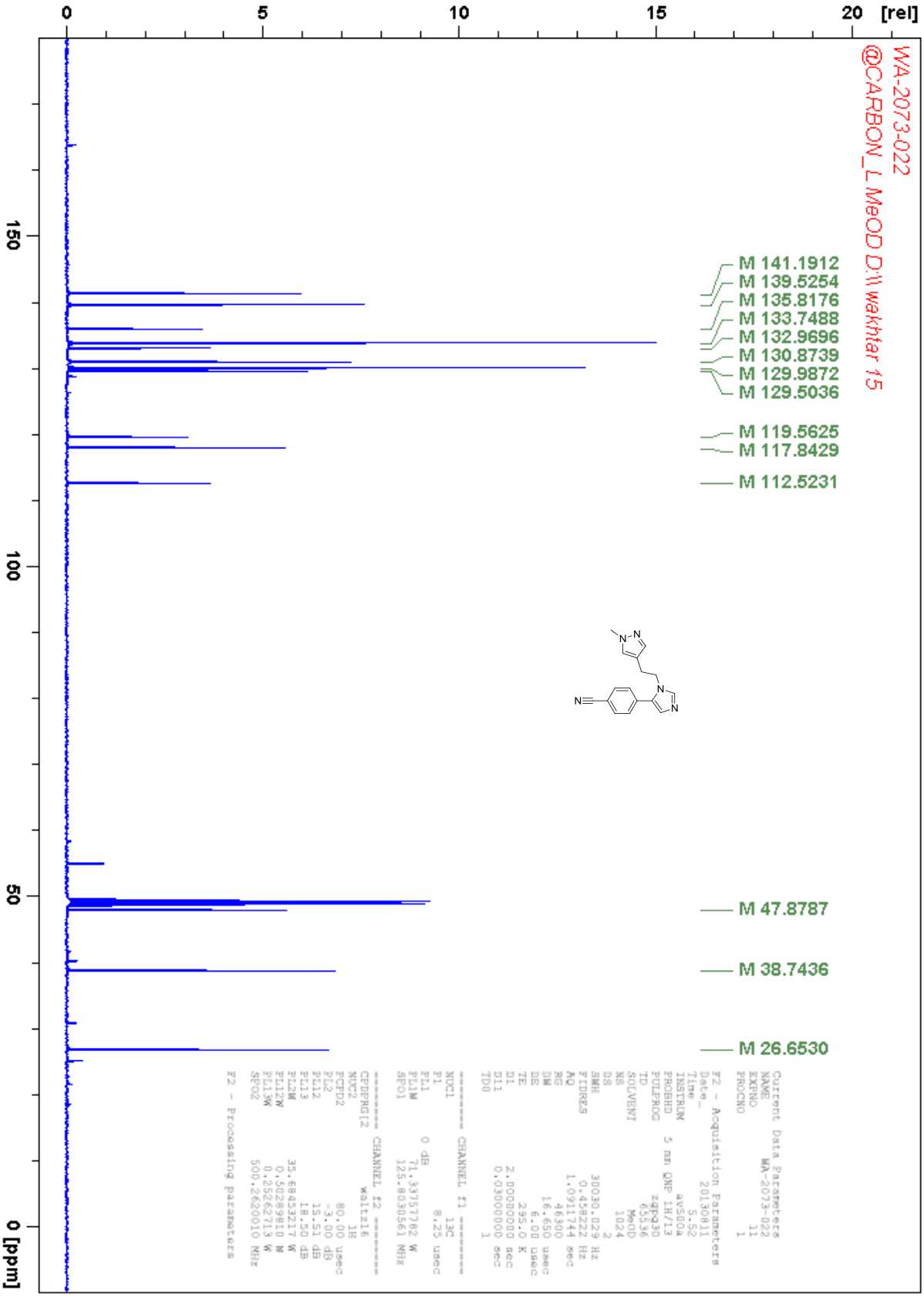


Figure S41. ^{13}C NMR (CD_3OD, 126 MHz) of **17**.

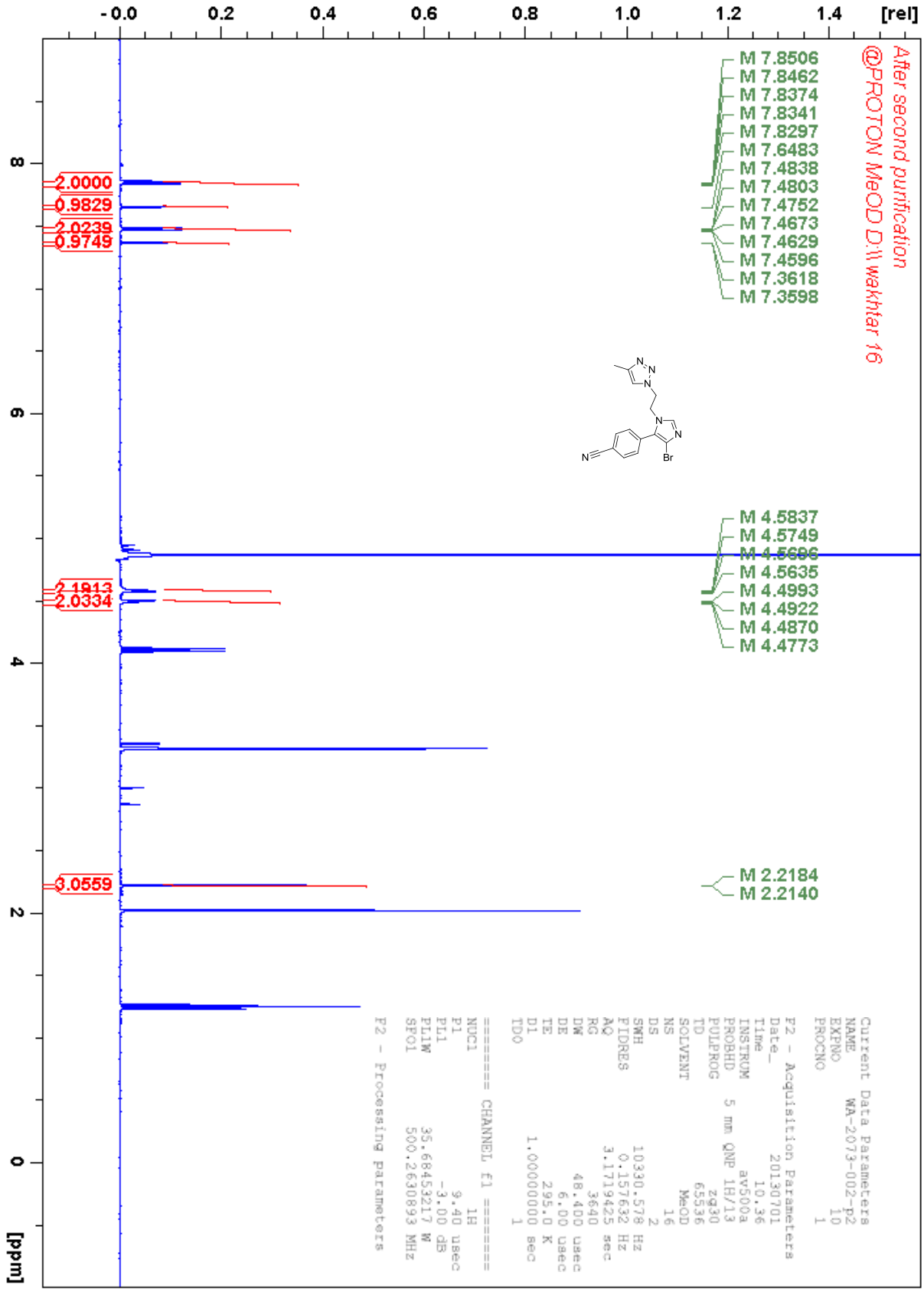


Figure S42. ^{1}H NMR (CD_3OD, 500 MHz) of **18**

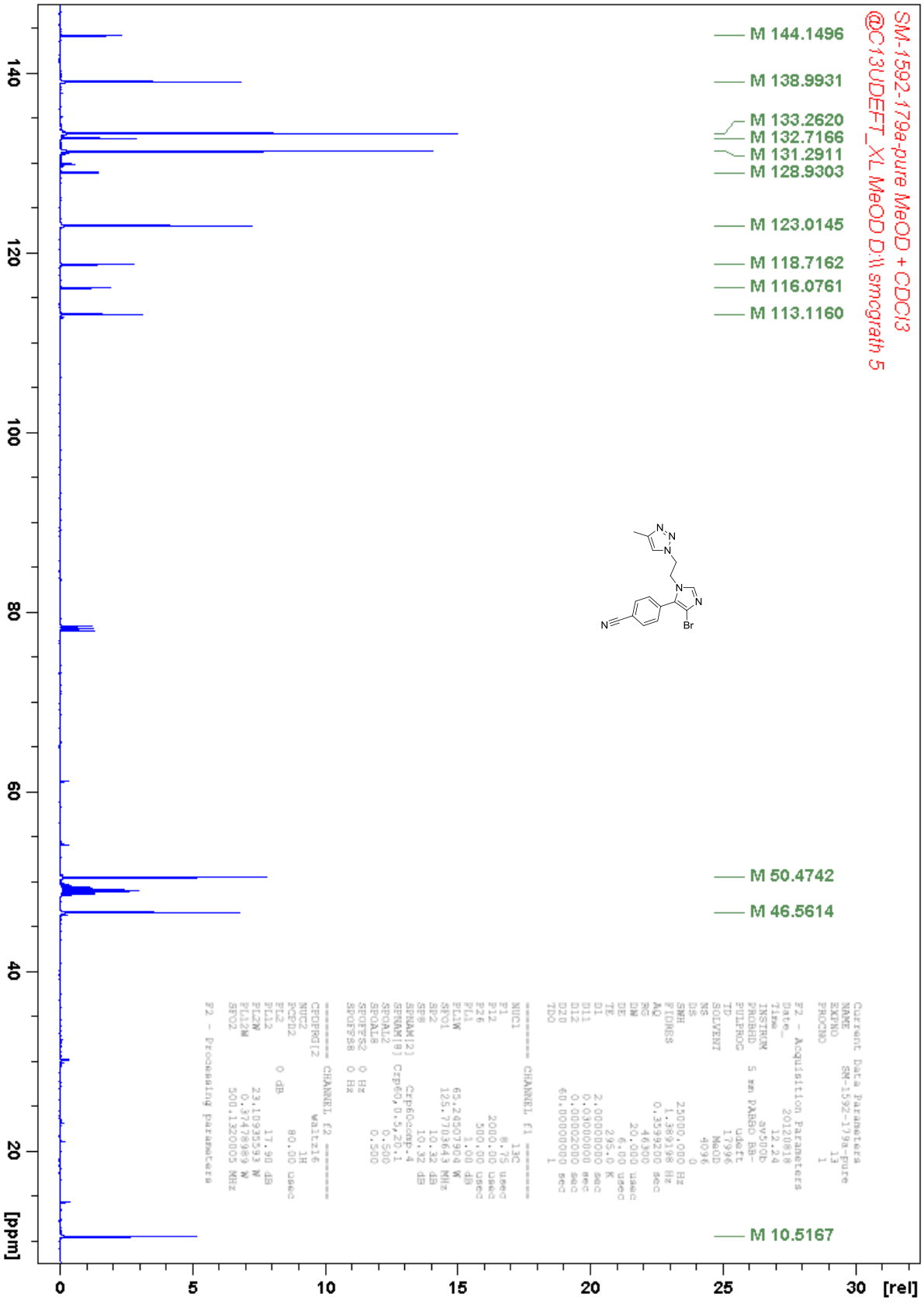


Figure S43. ^{13}C NMR (CD_3OD + $CDCl_3$, 500 MHz) of **18**

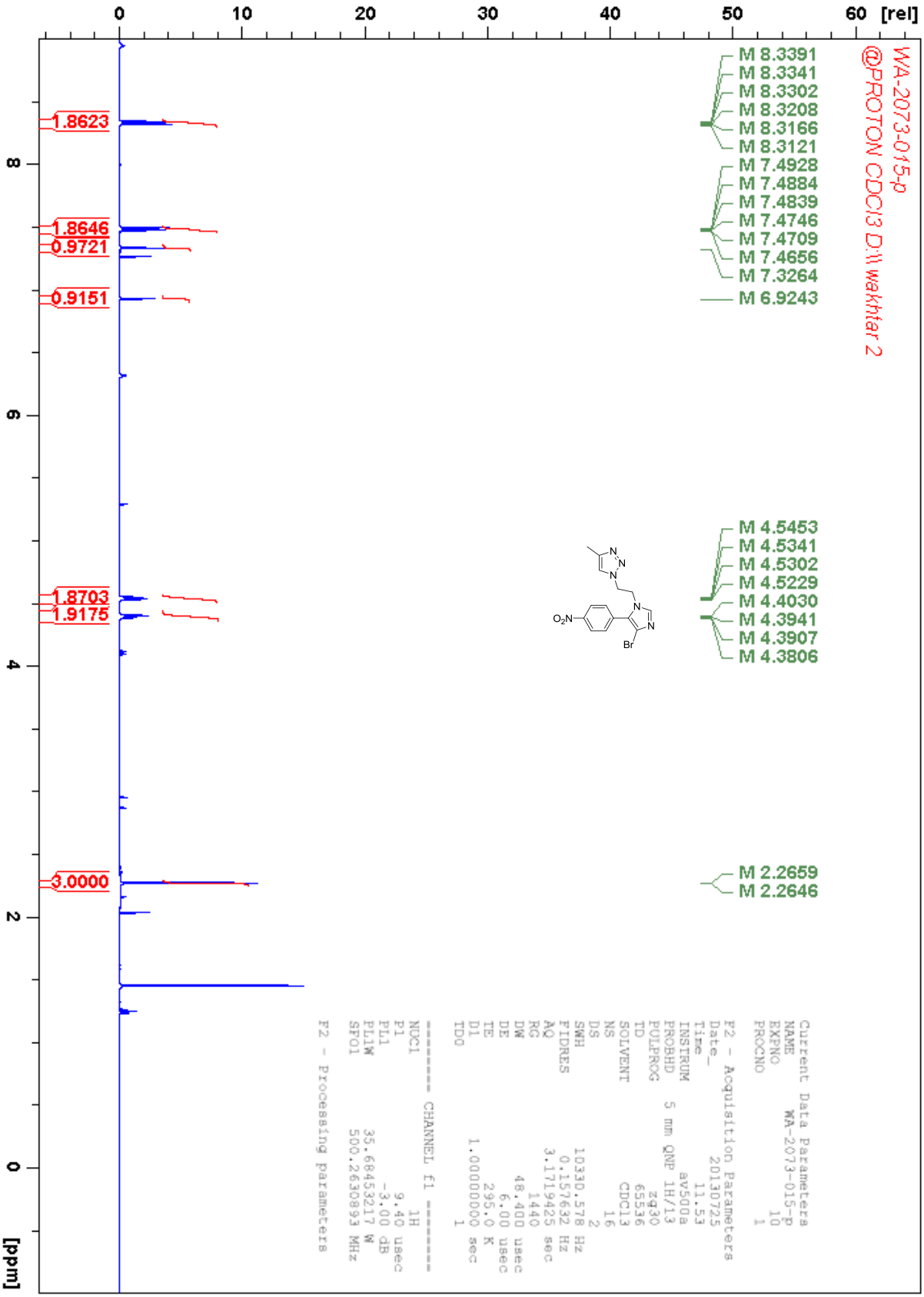


Figure S44. ^{1}H NMR ($CDCl_3$, 500 MHz) of **19.**

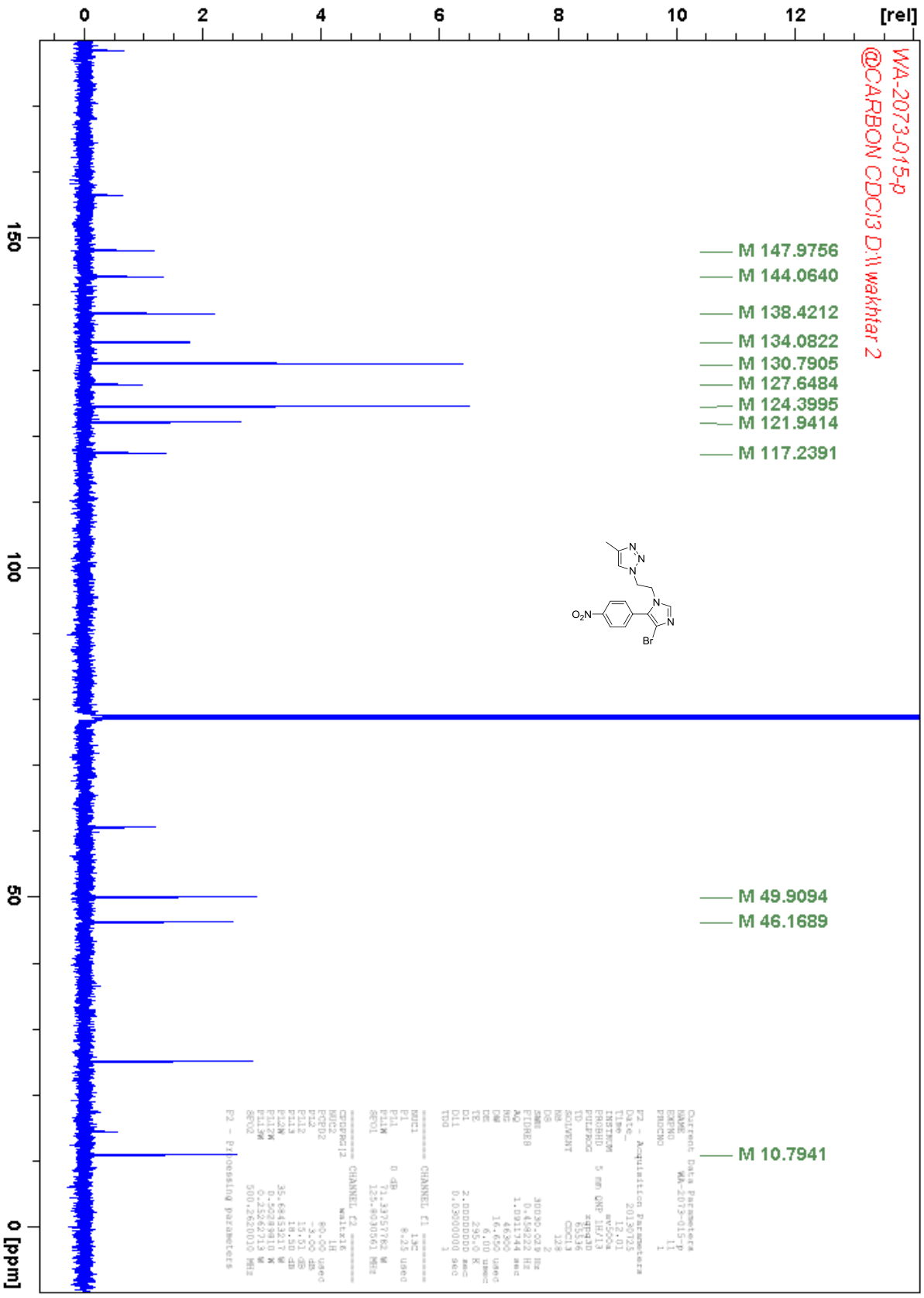


Figure S45. ^{13}C NMR ($CDCl_3$, 126 MHz) of **19**.

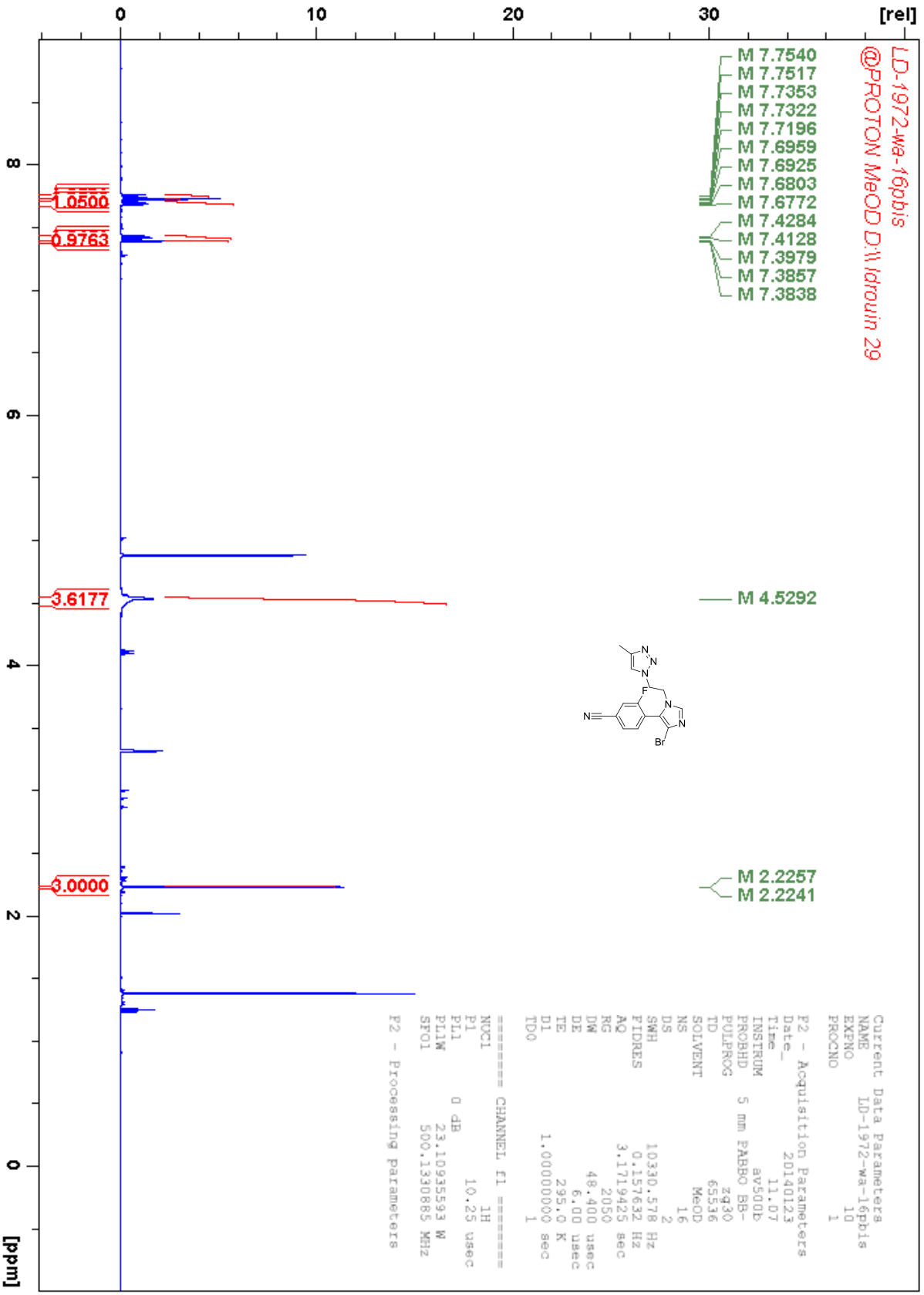


Figure S46. ^{1}H NMR (CD_3OD, 500 MHz) of **20**.

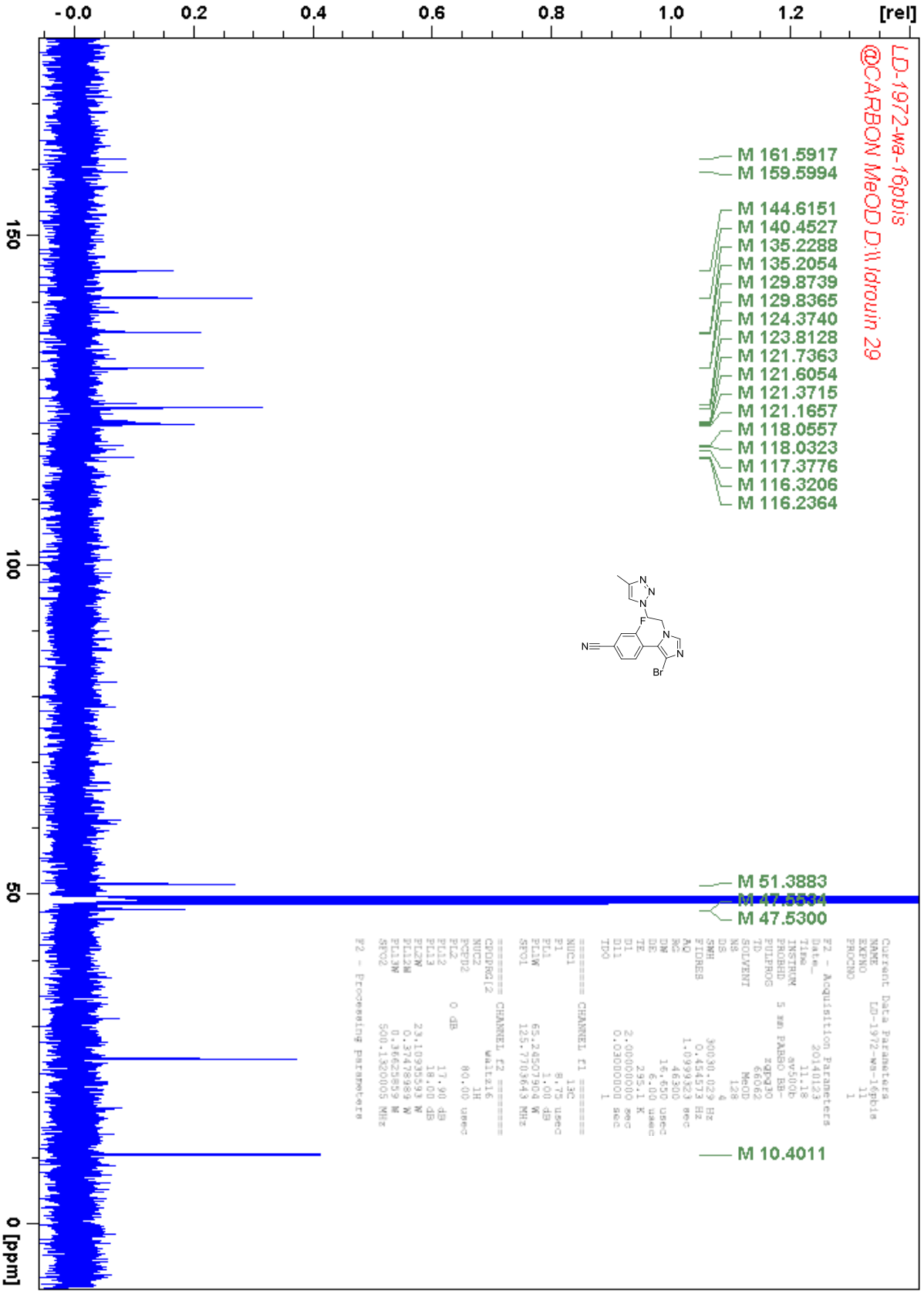


Figure S47. ^{13}C NMR (CD_3OD, 126 MHz) of **20**.

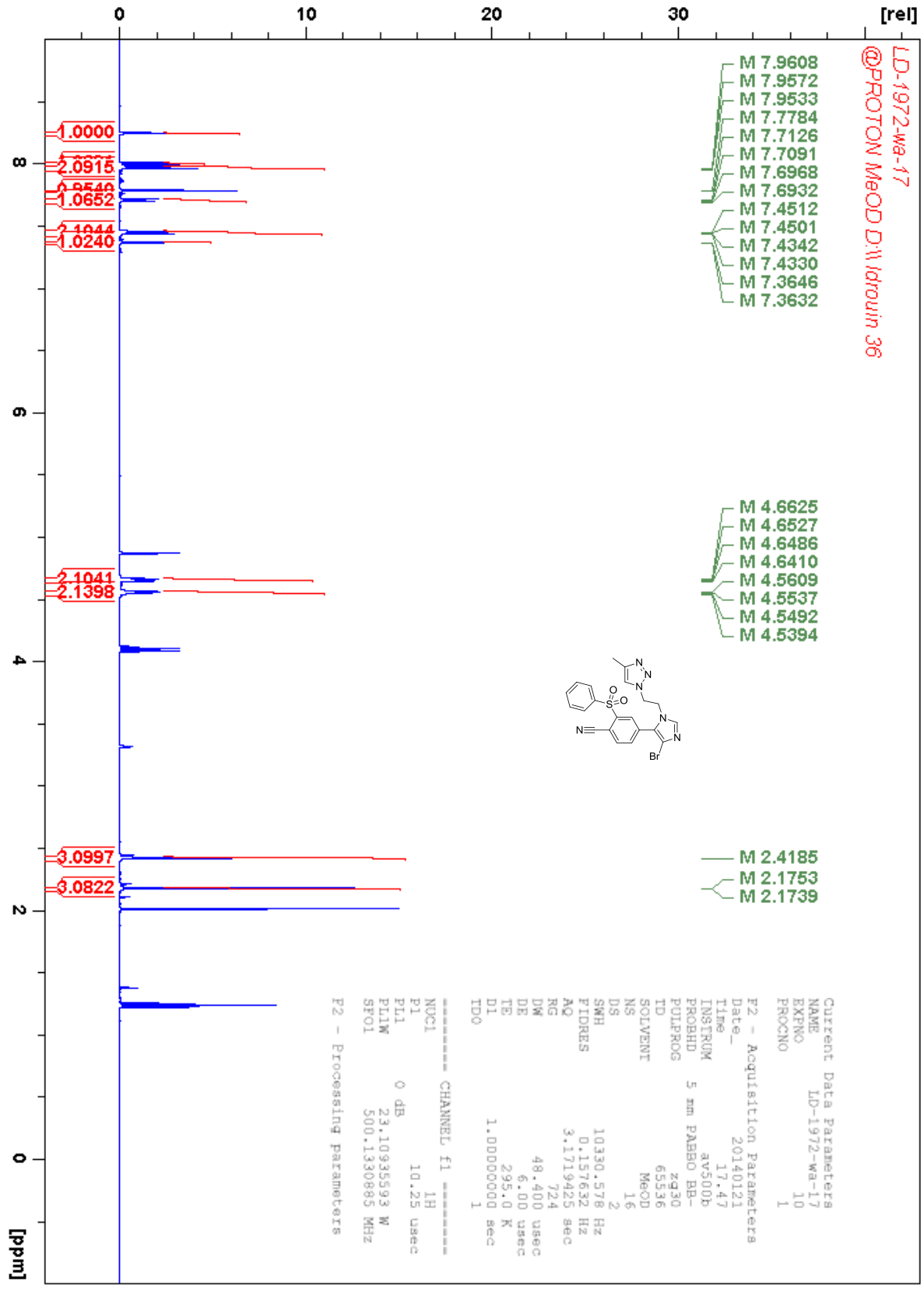


Figure S48. ^{1}H NMR (CD_3OD, 500 MHz) of **21**.

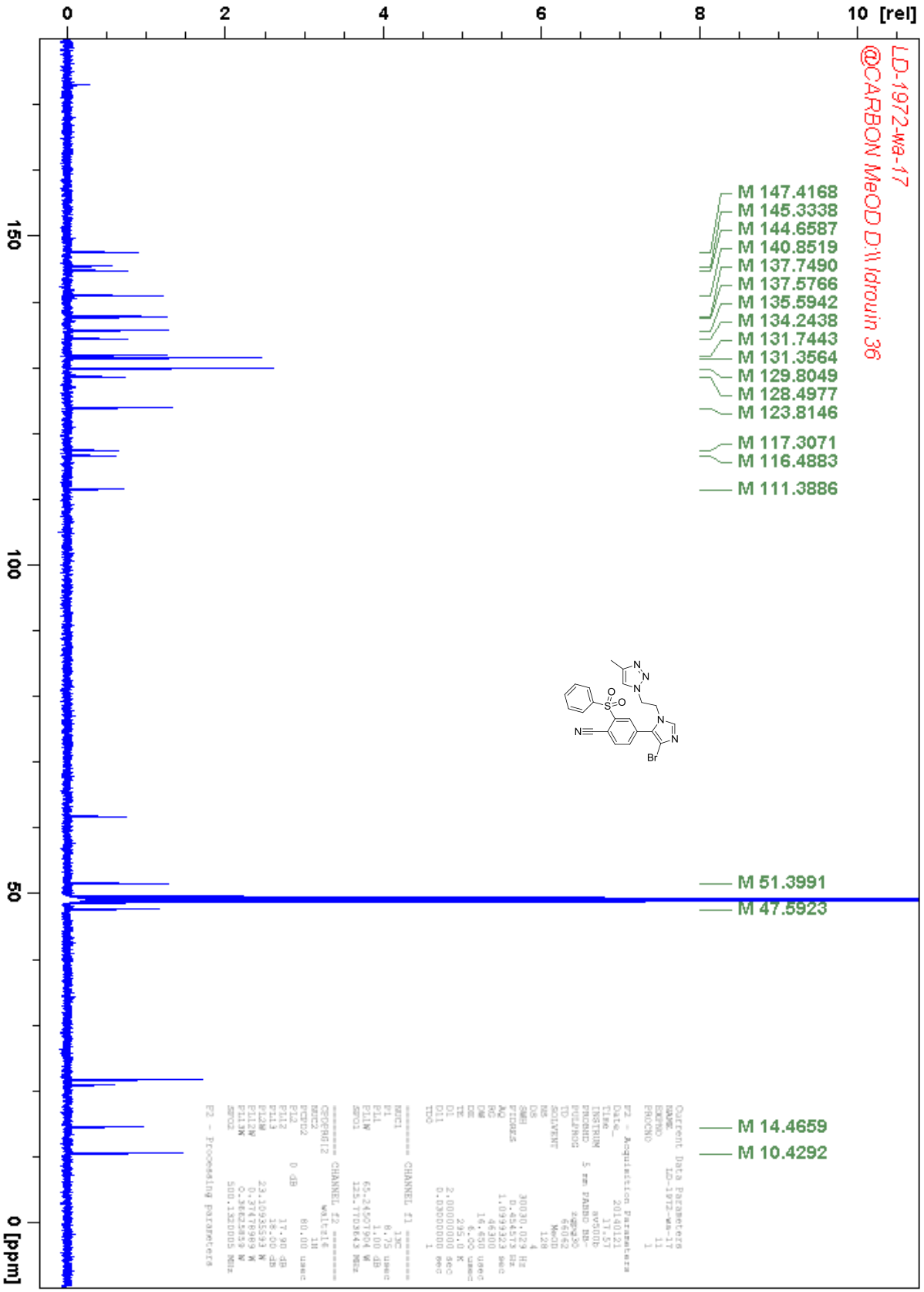


Figure S49. ^{13}C NMR (CD_3OD, 126 MHz) of **21**.

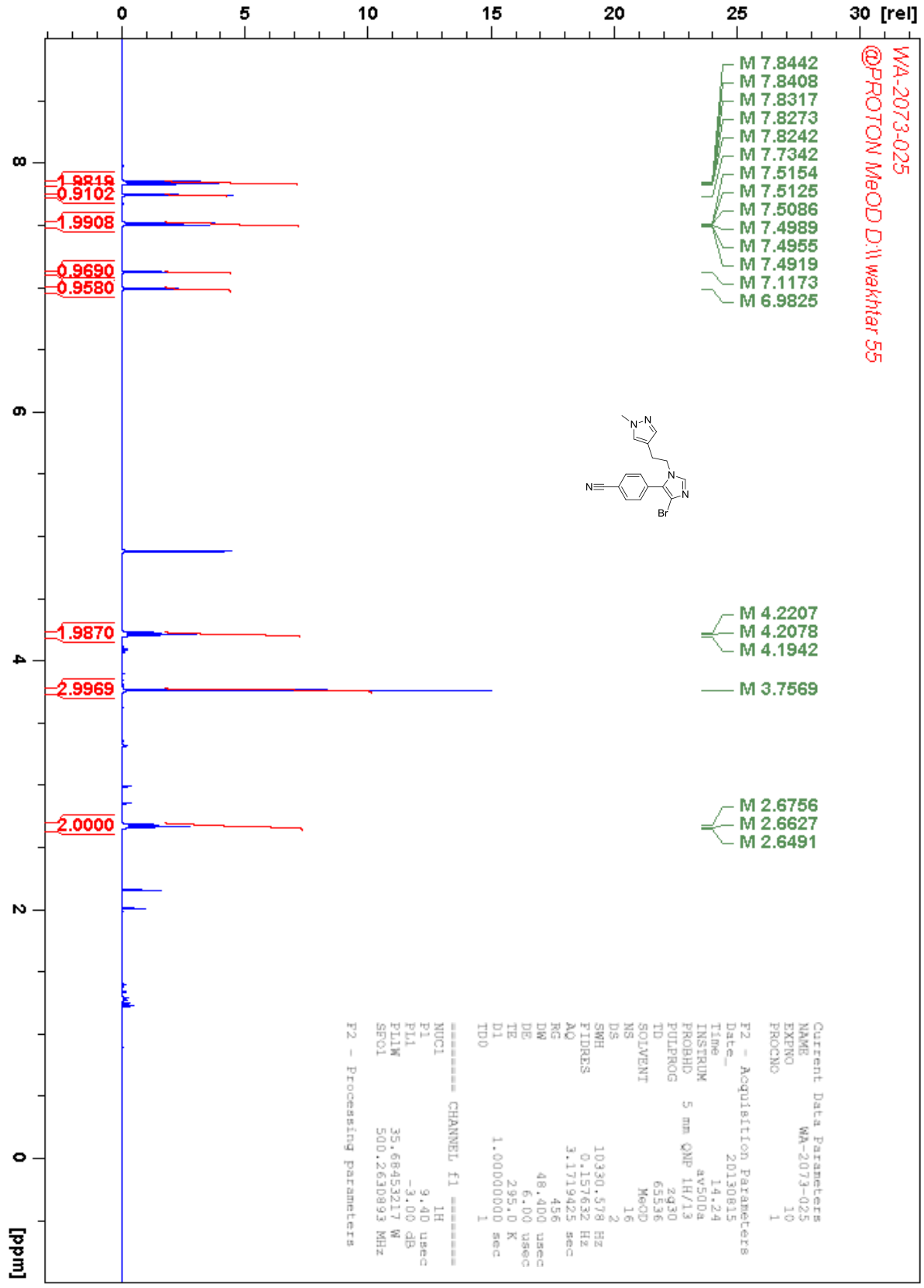


Figure S50. ^{1}H NMR (CD_3OD, 500 MHz) of **22**.

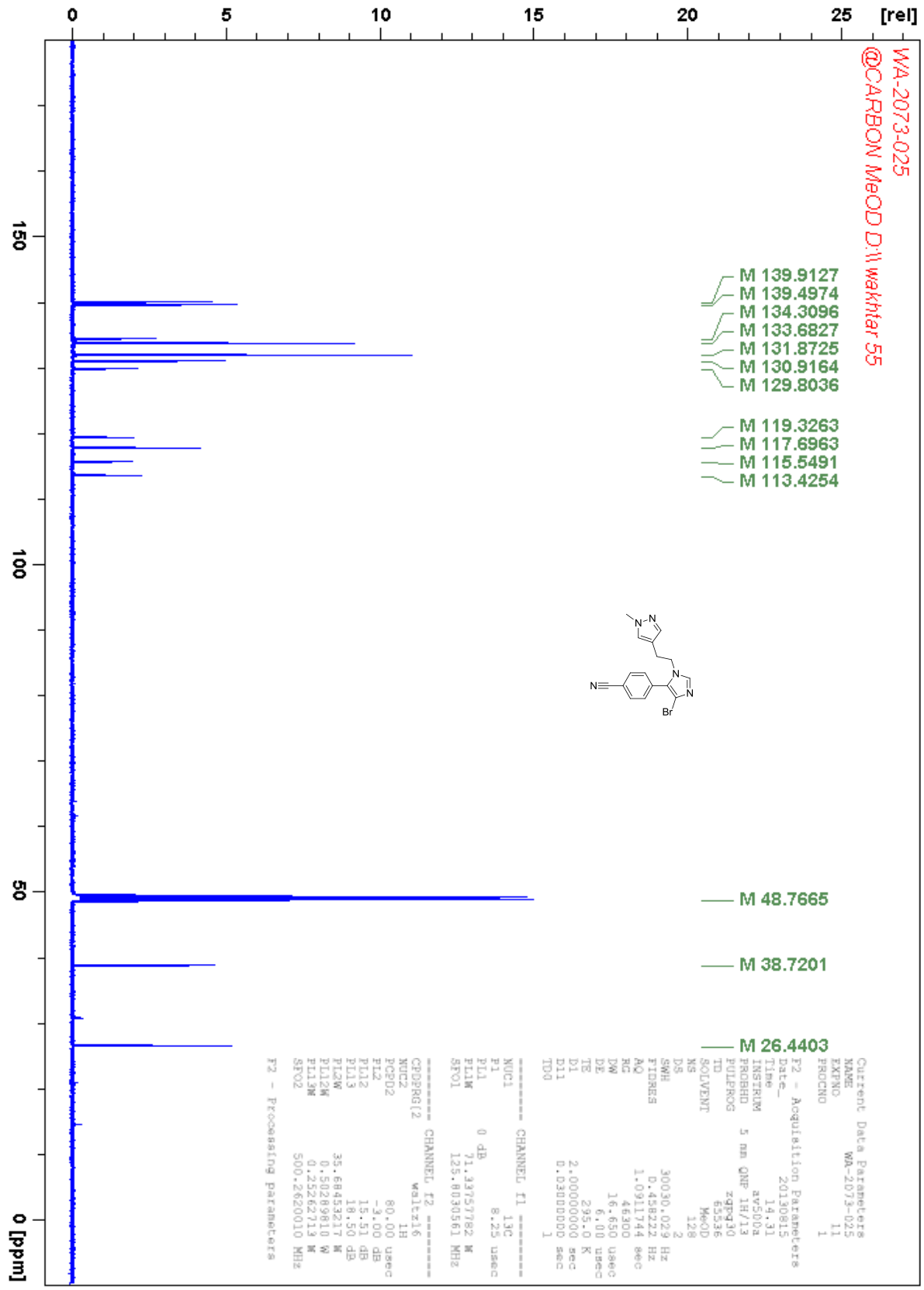


Figure S51. ^{13}C NMR (CD_3OD, 126 MHz) of **22**.

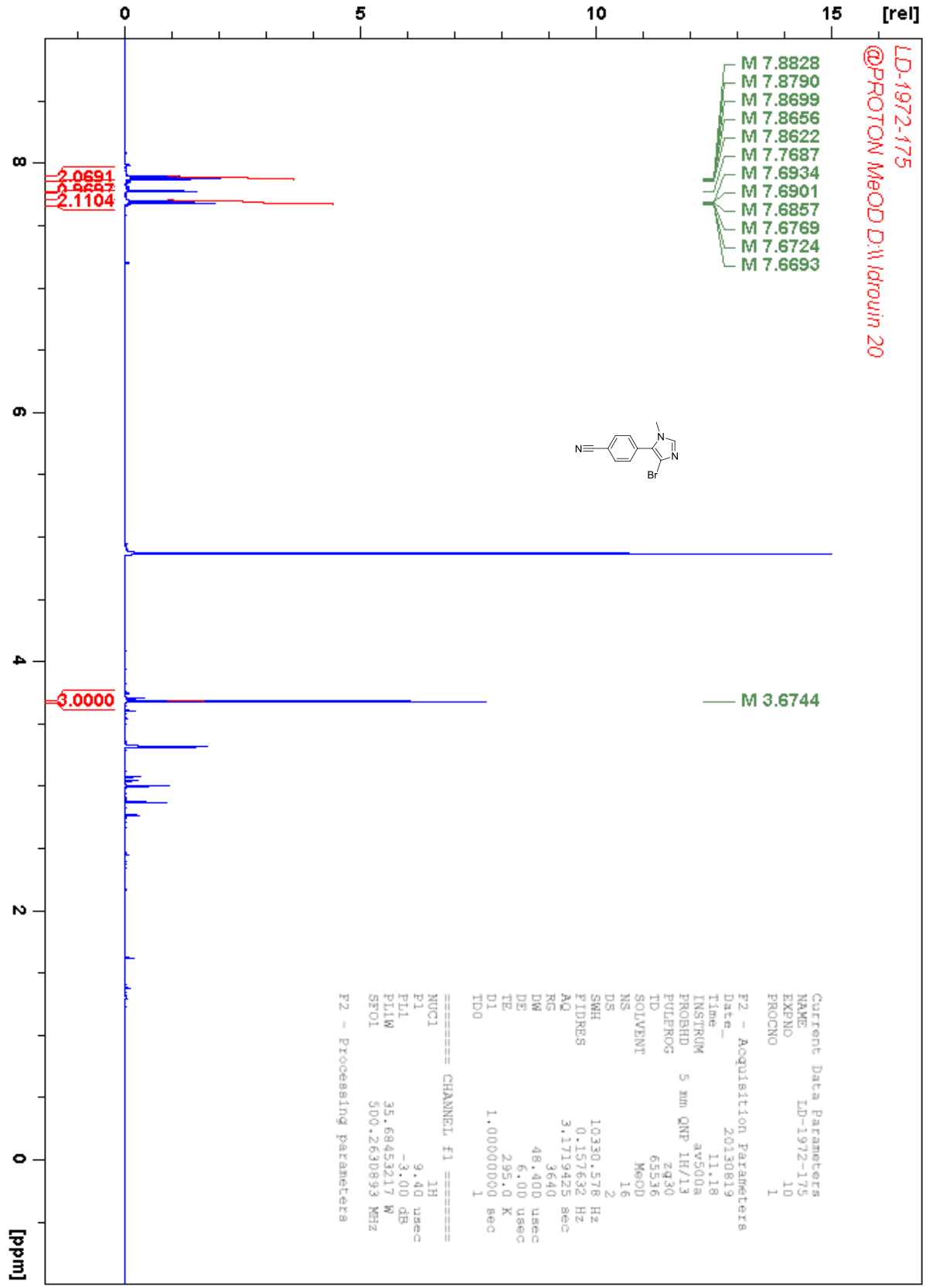


Figure S52. ^{1}H NMR (CD_3OD, 500 MHz) of **23**.

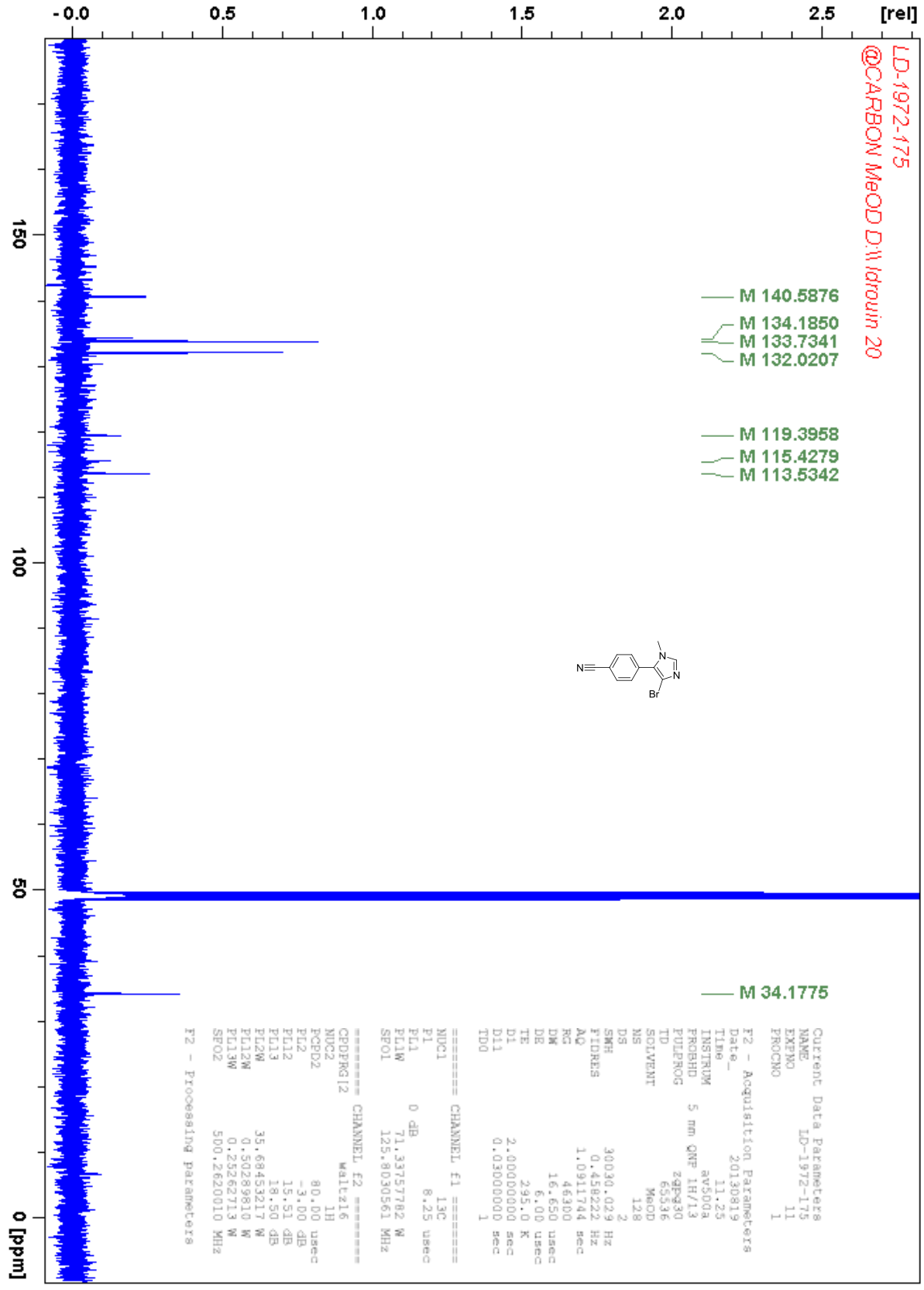


Figure S53. ^{13}C NMR (CD_3OD, 126 MHz) of **23**.

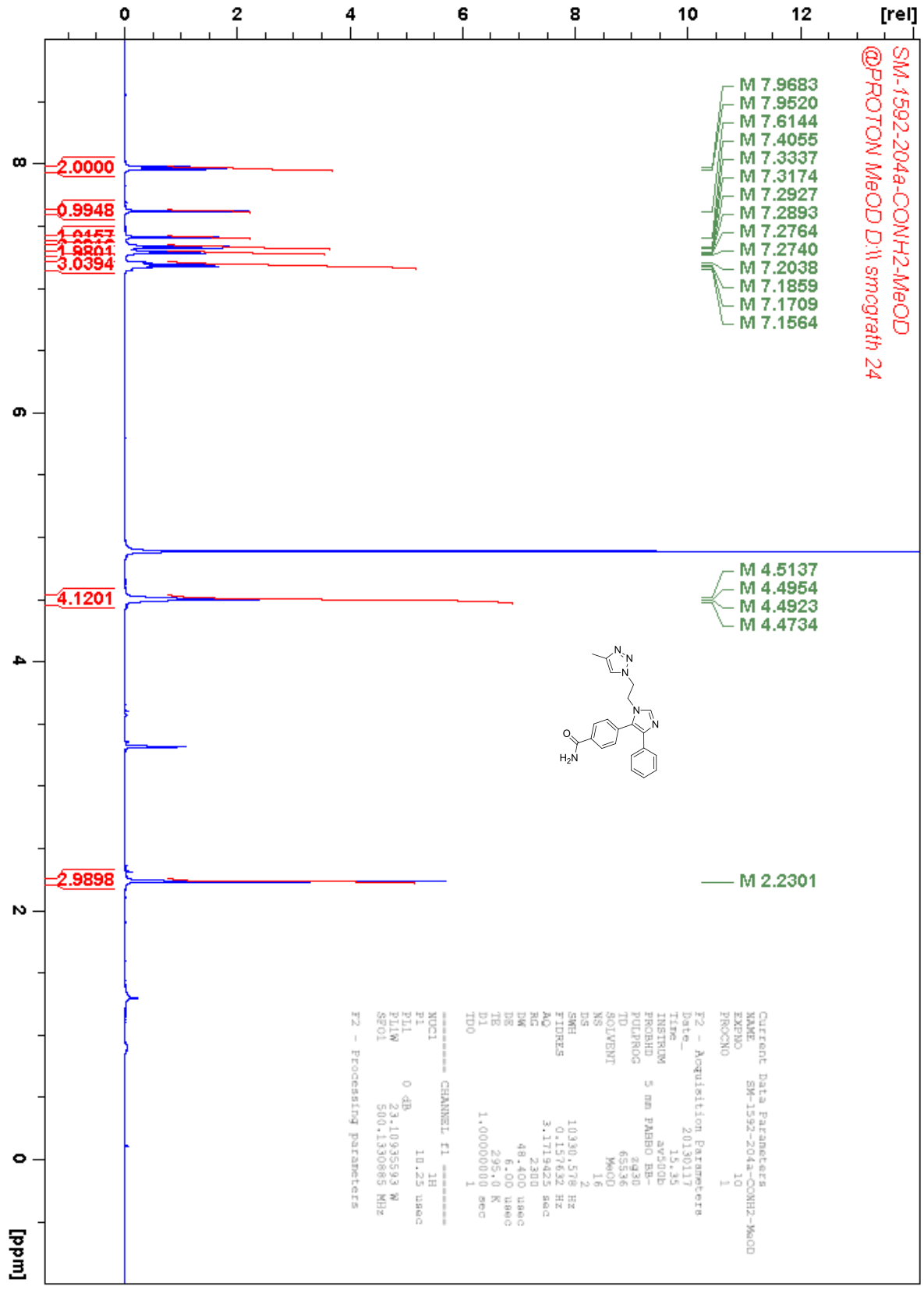


Figure S54. ^{1}H NMR (CD_3OD, 500 MHz) of **24**.

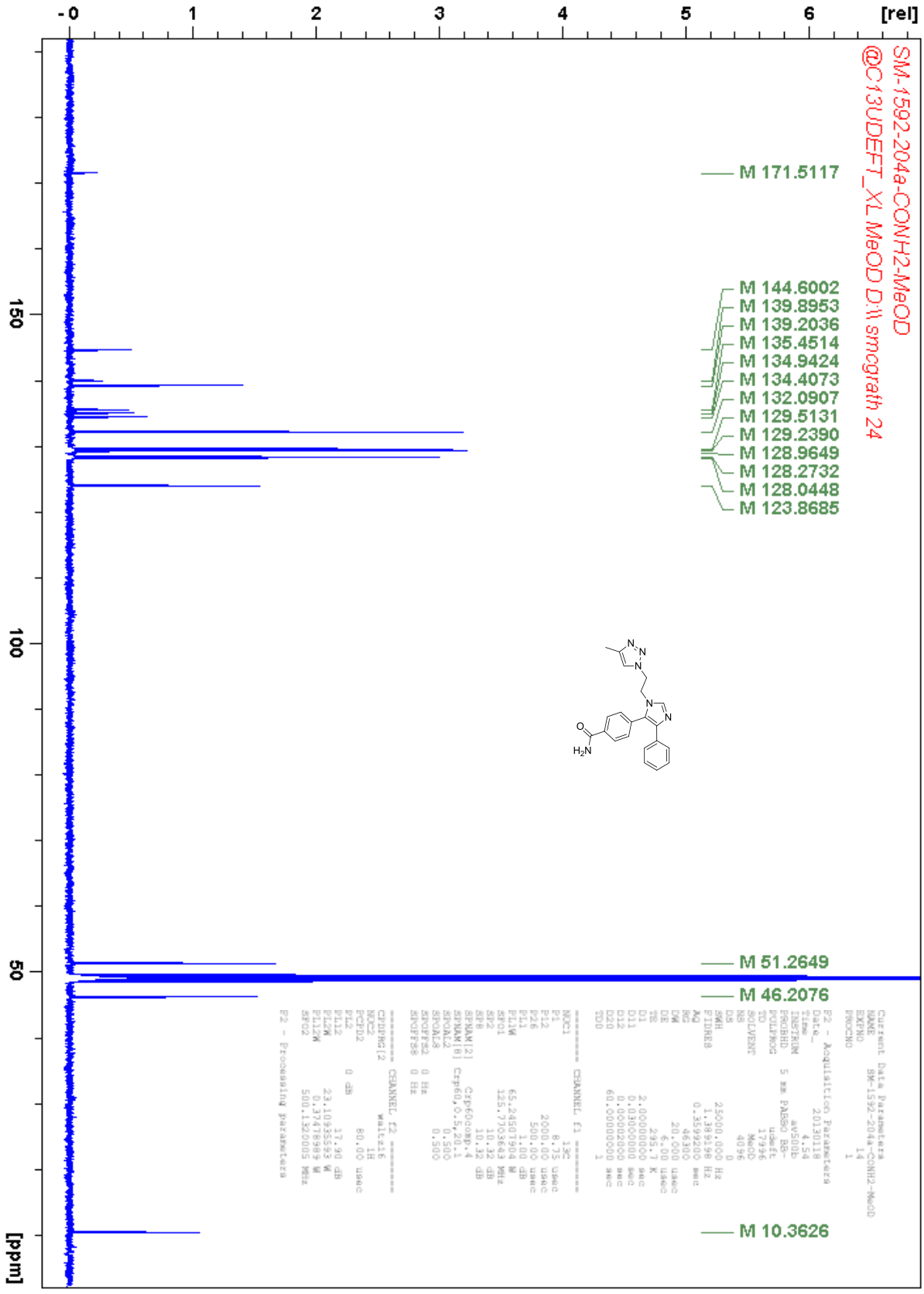


Figure S55. ^{13}C NMR (CD_3OD, 126 MHz) of **24**.

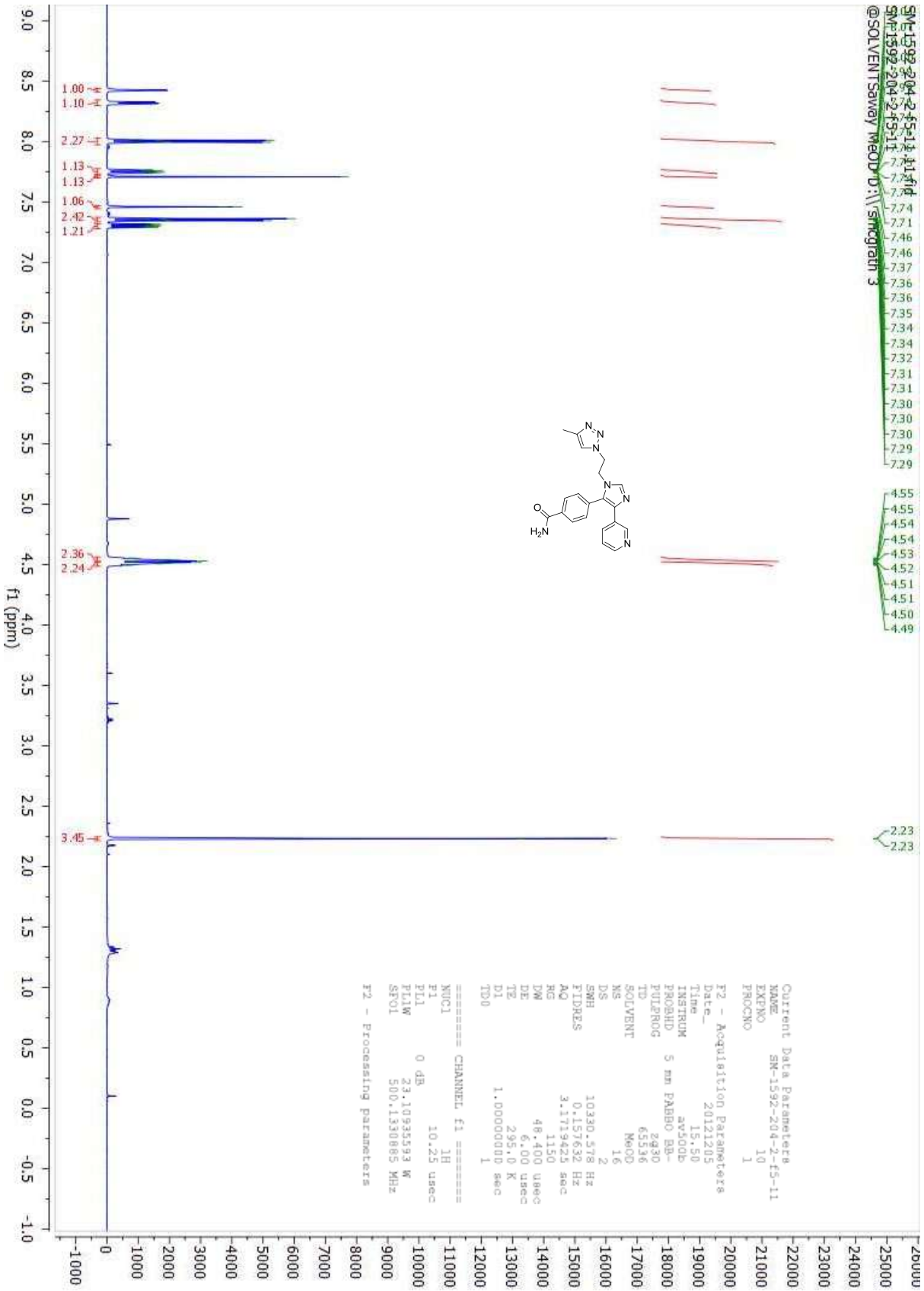


Figure S56. ^{1}H NMR (CD_3OD, 500 MHz) of **25**.

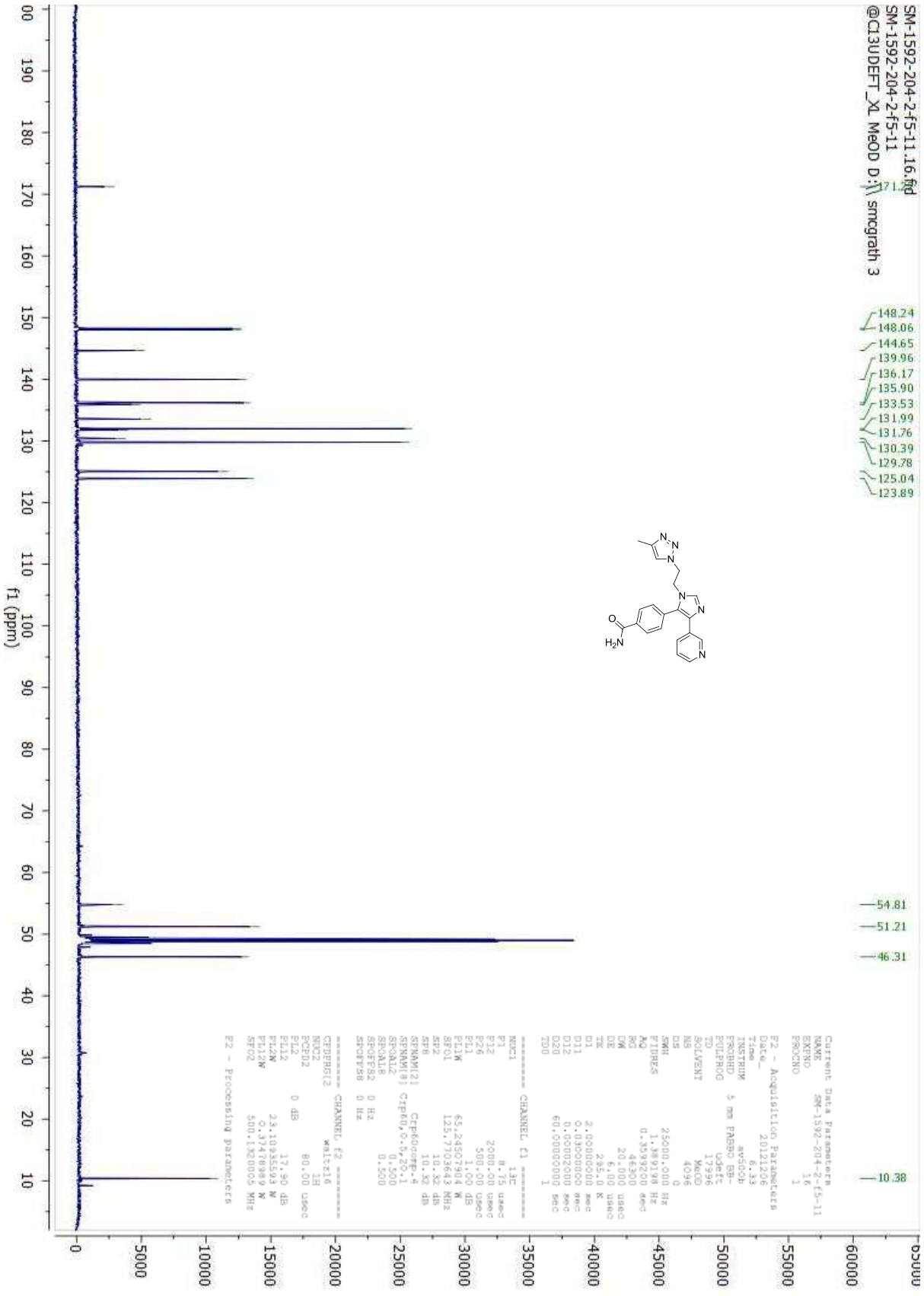


Figure S57. ^{13}C NMR (CD_3OD, 126 MHz) of **25**.

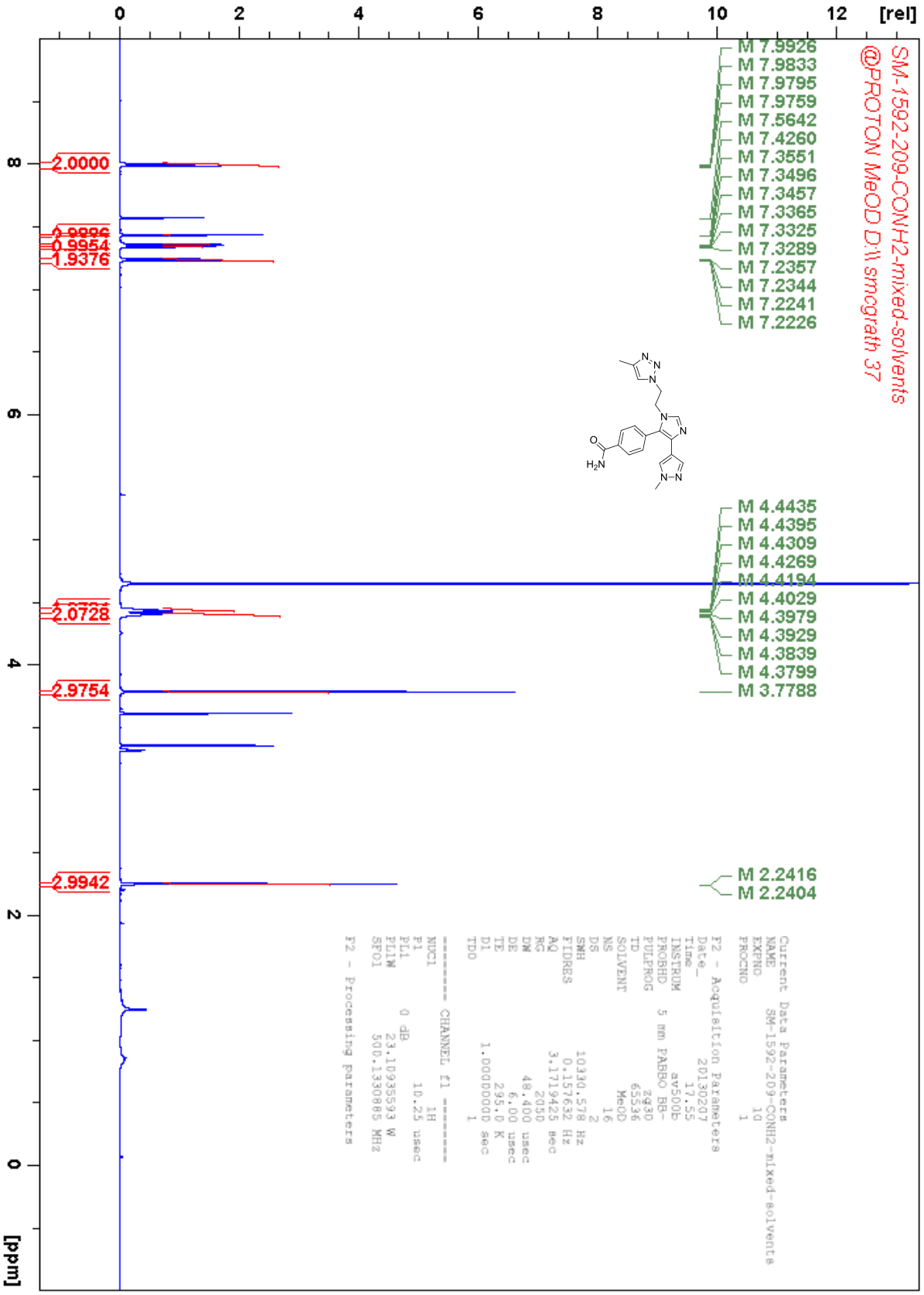


Figure S58. ^{1}H NMR ($CD_3OD/CDCl_3$, 500 MHz) of **26**.

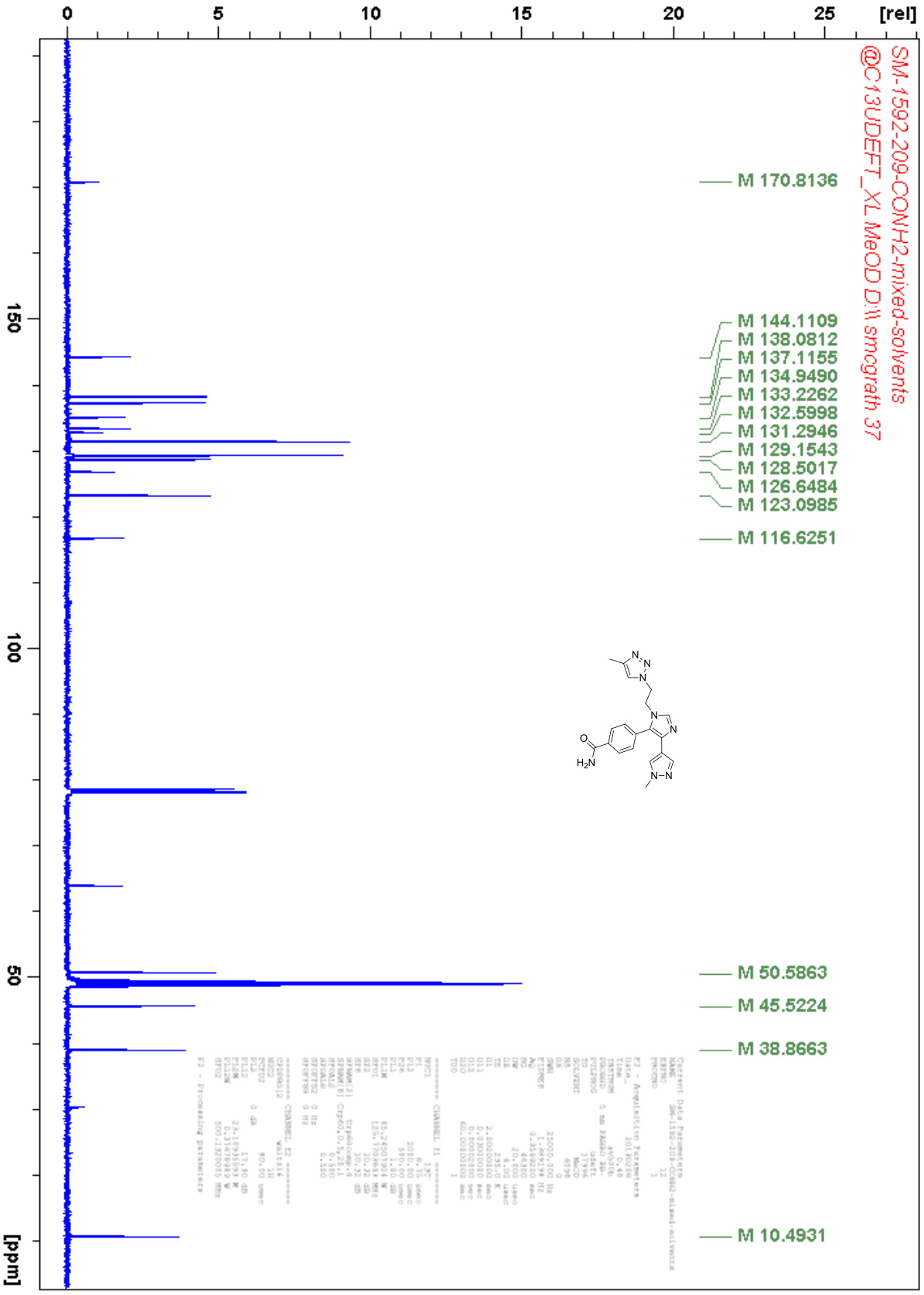


Figure S59. ^{13}C NMR ($CD_3OD/CDCl_3$, 126 MHz) of **26**.

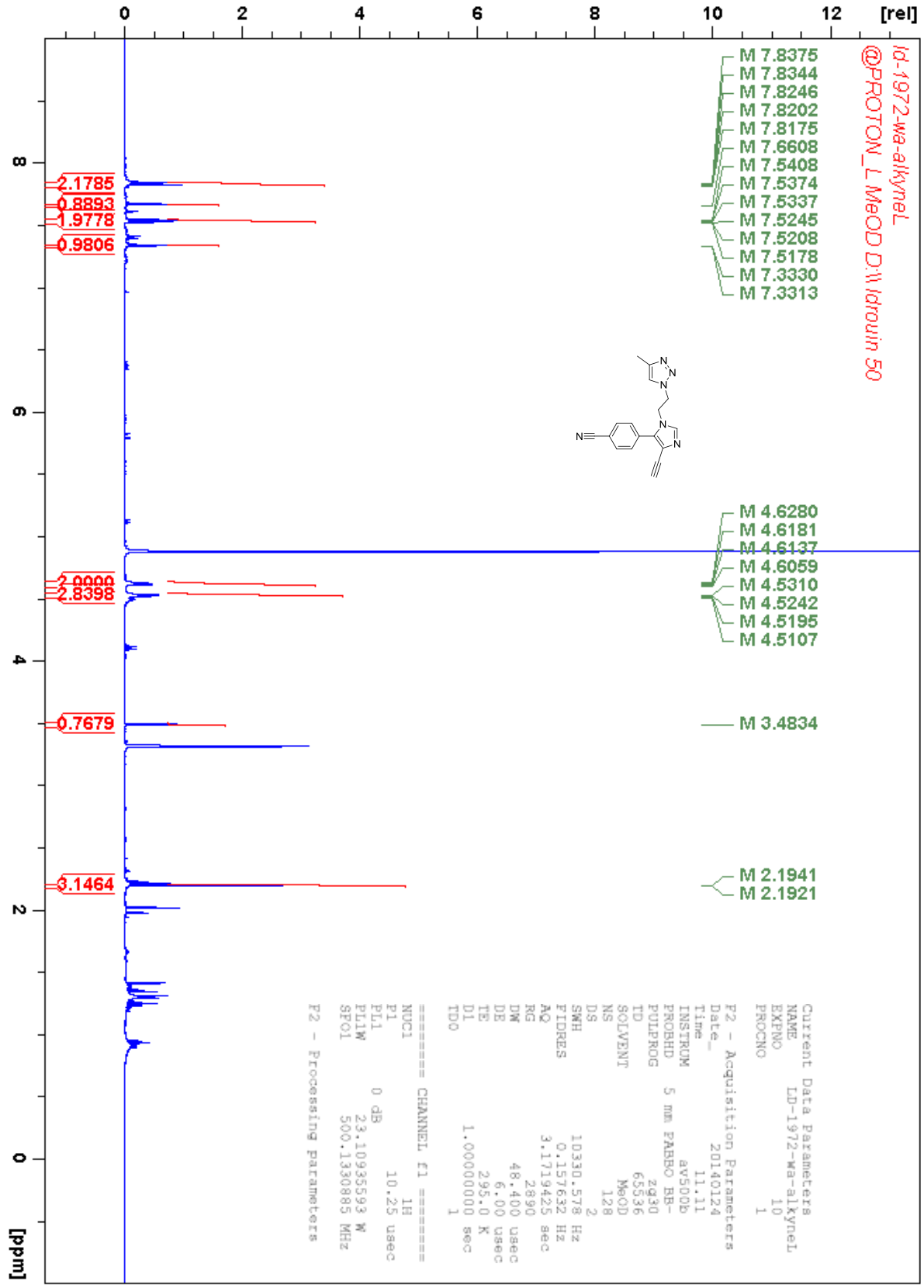


Figure S60. ^{1}H NMR (CD_3OD, 500 MHz) of **27**.

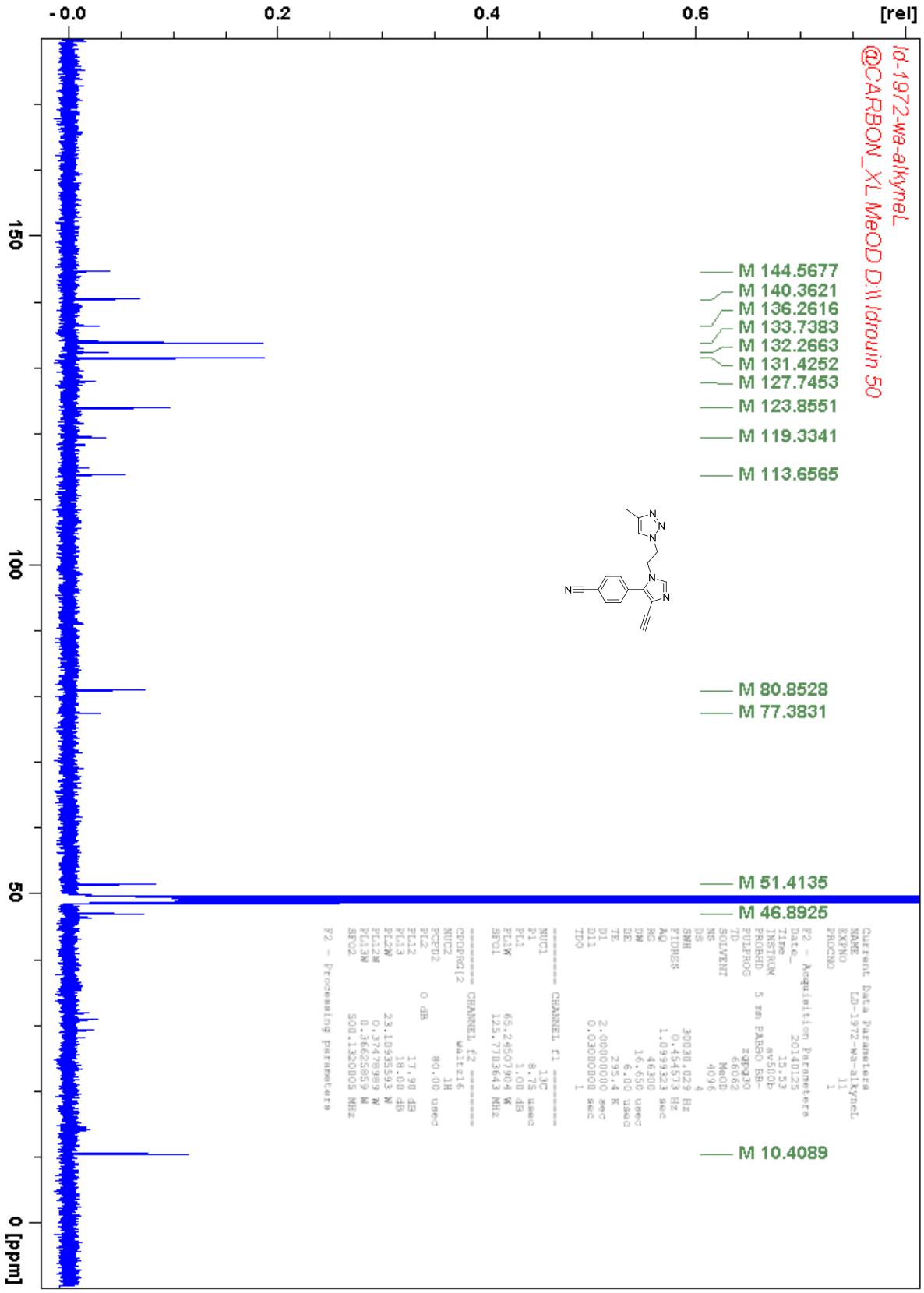


Figure S61. ^{13}C NMR (CD_3OD, 126 MHz) of **27**.