Supplementary Material (ESI) for Organic & Biomolecular Chemistry

Electronic Supplementary Information

An Investigation Into the Anti-HIV Activity of 2',3'-didehydro-2',3'-dideoxyuridine (d4U) and 2',3'-dideoxyuridine (ddU) Phosphoramidate 'ProTide' Derivatives

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Experimental

General

All experiments involving water-sensitive compounds were carried out under dry conditions. The solvents used were dry and used as purchased from Aldrich. All the glassware was oven-dried at 130°C for several hours and allowed to cool under a steam of dry nitrogen.

Thin-Layer Chromatography (TLC) was performed using precoated, aluminium-backed silica gel plates (60 F-54, 0.2mm thickness; supplied by E Merck AG, Darmstad, Germany). Visualisation of the plates was achieved using an ultra-violet (UV) lamp.

Glass columns were slurry-packed in the appropriate eluant under pressure with silica gel, 60A, 40-60μm, (Phase Separations Ltd, Deeside, Clwyd, UK). Samples were applied as a concentrated solution in the same eluant or pre-absorbed on silica gel. Fractions

containing the product were identified by TLC, pooled and the solvent was removed *in vacuo*.

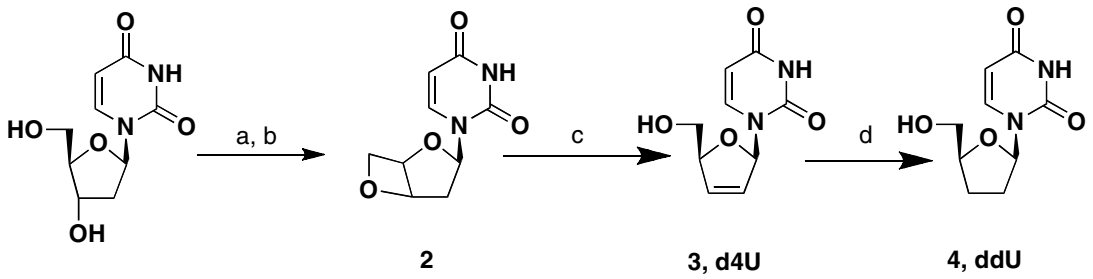
^{1}H, ^{13}C NMR spectra were recorded on a Bruker Avance 500 MHz spectrometer and autocalibrated to the deuterated solvent reference peak. The following abbreviations are used in the assignment of NMR signals: *s* (singlet), *d* (doublet), *t* (triplet), *q* (quartet), *m* (multiplet).

HPLC analytical investigations were conducted on a Varian Prostar instrument (LC work station, Varian prostar 355 LC detector) using a Polaris C18-A 10µm column; eluant was performed using a mobile phase consisting of a water/aetonitrile gradient.

Low resolution mass spectra were run on a microTOFLC Bruker Daltonics spectrometer in electropositive mode.

Chemistry

Synthesis of d4U and ddU



Reagents and Conditions: (a) $MeSO_2Cl$, Pyr, RT (b) Aq.NaOH, MeOH, Reflux (c) NaH, DMF, 100 ¼C (d) H_2, 10% Pd/C, overnight

1-[2,6-dioxa-bicyclo[3.2.0]hept-3-yl]-1*H*-pyrimidine-2,4-dione (2). To a stirred solution of 2'-deoxyuridine (2.00g, 21.91mmol) in anhydrous pyridine (30mL), methanesulfonyl chloride (2.55mL, 65.73mmol) was added drop-wise at 0°C under N_2, and the resulting solution was stirred for a further 30min at room temperature. The solvent was removed *in vacuo* and the residue was washed with ice-cold water (15mL). The resulting brownish solid and aqueous sodium hydroxide (4.4g, 109mmol) in 100mL

of methanol were heated under gentle reflux (88°C) for 2hr. The resulting solution was cooled, neutralized with 35ml of 2N HCl (pH ~ 7) and then concentrated to dryness under reduced pressure. The residue was then extracted with boiling acetone (100mL x 4) and the solvent from the combined extracts was removed under high vacuum giving a crude product which was then purified by flash column chromatography using 5% methanol in dichloromethane as an eluant. This gave the desired compound as a white solid (1.28g, 51%). **^{1}H NMR** (d_6-DMSO): δ 11.24 (1H, *bs*, NH), 7.88 (1H, *d*, *J* = 8.08Hz, H-6), 6.09 (1H, *d*, *J* = 8.10Hz, H-1'), 5.64 (1H, *d*, *J* = 8.08Hz, H-5), 4.26 (1H, *bs*, H-3'), 4.06 (1H, *q*, *J* = 10.29Hz, H-4'), 3.87 (2H, *dd*, *J* = 5.15Hz, *J* = 11.01Hz, H-5'), 2.58-2.64 (2H, *m*, H-2'). **^{13}C NMR** (d_6-DMSO; 500 MHz): δ 163.16 (C=O), 150.51 (C=O), 141.30 (C-6), 101.48 (C-5), 83.95 (C-4'), 83.84 (C-1'), 68.45 (C-3'), 42.14 (C-5'), 40.58 (C-2').

1-(5-Hydroxymethyl-2,5-dihydro-furan-2-yl)1*H*-pyrimidine-2,4-dione (3, d4U). Sodium hydride (60% dispersion in mineral oil: 0.75g, 44.28 mmol) was added to a stirred solution of 1-[2,6-dioxa-bicycol[3.2.0]hept-3-yl]-1H-pyrimidine-2,4-dione(**2**) (0.97g, 14.28mmol) in anhydrous *N,N*-dimethylformamide (25ml) at room temperature and under N_2. After 5mins, the reaction mixture was heated in an oil bath at 100°C for 4hr. After another 2hrs, when TLC [DCM:MeOH, 9:1] revealed that no starting material remained, the mixture was cooled and the solvent was removed *in vacuo*. The resulting residue was dissolved in methanol (20mL), cooled at 0°C and neutralized (pH~7) by cautious addition of HCl (1N). The solvent was removed under reduced pressure and the crude was purified by flash chromatography using as an eluant DCM:MEOH (9/1). The appropriate fractions were combined and the solvent was removed *in vacuo* affording a brownish solid (0.42g, 43%). **^{1}H NMR** (d_6-DMSO): δ 11.29 (1H, *bs*, NH), 7.74 (1H, *d*, *J* = 8.08Hz, H-6), 6.82 (1H, *m*, H-1'), 6.40 (1H, *t*, *J* = 1.78Hz, H-2'), 5.92 (1H, *t*, *J* = 1.78Hz, H-3'), 5.59 (1H, *d*, *J* = 8.08Hz, H-5), 4.97 (1H, *t*, *J* = 5.39Hz, 5'-OH), 4.78 (2H, *m*, H-4'), 3.59 (2H, *dd*, *J* = 4.95Hz, *J* = 8.59Hz, H-5'). **^{13}C NMR** (d_6-DMSO): δ 163.20 (C=O), 150.77 (C=O), 141.07 (C-6), 135.05 (C-3'), 125.73 (C-2'), 101.52 (C-5), 89.08 (C-1'), 87.38 (C-4'), 62.24 (C-5'). **HPLC** (H_2O/CH_3CN from 100/0 to 0/100 in 20min): RT 7.95 min. **ESI MS** m/z (positive) 233.081 [M+Na].

1-(5-Hydroxymethyl-tetrahydro-furan-2-yl)-1*H*-pyrimidine-2,4-dione (4, ddU). 2',3'-didehydro-2',3'-dideoxyuridine (3.2g, 15.22mmol, 1eq.) was dissolved in MeOH (100mL) and 10% Pd/C (0.809mg) was added. Hydrogen gas was introduced into the reaction flask, and the contents were left stirring at room temperature for 5.5hrs. The reaction mixture was filtered through a Celite pad and the solvent was removed. The residue was purified by chromatography using MeOH in chloroform (4:96) as an eluant and the appropriate fractions were collected and the solvent was removed to give the desired product as a white solid in a 75.86% yield (2.45g). **^{1}H NMR** (d_6-DMSO): δ 11.27 (1H, *bs*, NH), 7.94 (1H, *d*, *J* = 8.17Hz, H-6), 5.94 (1H, *q*, *J* = 6.82Hz, H-1'), 5.58 (1H, *d*, *J* = 8.17Hz, H-5), 5.05 (1H, *t*, *J* = 5.35Hz, 5'-OH), 4.02 (1H, *m*, H-4'), 3.50-3.70 (2H, *m*, H-5'), 1.91-1.98 (2H, *m*, H-2'), 1.82 (2H, *m*, H-3'). **^{13}C NMR** (d_6-DMSO): δ 163.22 (C=O), 150.40 (C=O), 140.58 (C-6), 101.01 (C-5), 85.13 (C-1'), 81.52 (C-4'), 62.04 (C-5'), 31.79 (C-2'), 24.82 (C-3').

Synthesis of d4U and ddU Phosphoramidates

(*S*)-methyl 2-((((2*S*,5*R*)-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-2,5-dihydrofuran-2-yl)methoxy)(phenoxy)phosphorylamino)propanoate (1a). Prepared from d4U (3, 100mg, 0.475mmol, 1eq.), ^{t}BuMgCl (1.0M, 0.62mL, 0.617mM, 1.3eq.) and phenyl-L-alanine methyl ester phosphorochloridate (263.8mg, 0.95mM, 2eq.) in THF (7mL). Column chromatography using DCM:MeOH (97:3) as an eluant to afford 82mg of the title compound as a yellowish oil (39%).**^{31}P NMR** ($CDCl_3$): δ 3.50, 3.40. **^{1}H NMR** ($CDCl_3$): δ 8.03 (1H, *bs*, NH), 7.41 (1H, *d*, *J* = 8.65Hz, H-6), 7.06-7.29 (5H, *m*, Ph), 6.92 (1H, *m*, H-1'), 6.23 (1H, *d*, *J* = 8.65Hz, H-5), 5.85 (1H, *m*, H-2'), 5.63 (1H, *m*, H-3'), 5.02 (1H, *m*, H-4'), 4.54 (1H, *s*, NH), 4.27-4.32 (1H, *dd*, *J* = 11.41Hz , H-5'), 4.17-4.21 (1H, *dd*, *J* = 11.41Hz, H-5'), 3.96 (1H, *m*, CH), 3.62-3.70 (3H, *m*, OC$\underline{H}_3$), 1.31 (3H, *m*, CH_3).

(*S*)-methyl 2-((((2*S*,5*R*)-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-2,5-dihydrofuran-2-yl)methoxy)(naphthalen-1-yloxy)phosphorylamino)-propanoate (1b). Prepared from d4U (3, 100mg, 0.475mmol, 1eq.), ^{t}BuMgCl (1.0M, 0.62mL, 0.617mM, 1.3eq.) and 1-naphthyl L-alanine methyl ester phosphorochloridate (311mg,

0.95mM, 2eq.) in THF (7mL). Column chromatography using DCM:MeOH (98:2) as an eluant to afford 51.2mg (21%) of the title compound as a yellowish oil. **^{31}P NMR** ($CDCl_3$): δ 3.25, 2.78. **^{1}H NMR** ($CDCl_3$): δ 8.62 (1H, *bs*, NH), 7.79 (1H, *t*, *J* = 8.75Hz, H-6), 7.12-7.66 (7H, *m*, Ar), 6.89 (1H, *m*, H-1'), 5.81 (1H, m, H2'), 5.68 (1H, m, H-3'), 5.47 (1H, *q*, *J* = 8.75Hz, H-5), 4.92 (1H, *m*, H-4'), 4.34 (1H, *bs*, NH), 3.95 (2H, m, H-5'), 3.62 (1H, *m*, CH), 3.40 (3H, *s*, CH_3), 1.20 (3H, *dd*, *J* = 7.01Hz, *J* = 11.32Hz, CH_3). **ESI MS** m/z (positive) 524.167 [M+Na]. **HPLC** (H_2O/CH_3CN from 100/0 to 0/100 in 20min): Rt 9.71, 9.95 min (1:2).

(*S*)-ethyl 2-((((2*S*,5*R*)-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-2,5-dihydrofuran-2-yl)methoxy)(phenoxy)phosphorylamino)propanoate (1c). Prepared from d4U (3, 100mg, 0.475mmol, 1eq.), ^{t}BuMgCl (1.0M, 0.62mL, 0.617mM, 1.3eq.) and phenyl-L-alanine ethyl ester phosphorochloridate (208mg, 0.95mM, 2eq.) in THF (7mL). Column chromatography using DCM:MeOH (97:3) as an eluant to afford 55.8mg of the title compound as a white solid (43%). **^{31}P NMR** ($CDCl_3$): δ 2.90, 2.50. **^{1}H NMR** ($CDCl_3$): δ 8.87 (1H, *bs*, NH), 7.40 (1H, *d*, *J* = 8.08Hz, H-6), 7.05-7.27 (5H, m, Ar), 6.93 (1H, *m*, H-1'), 6.25 (1H, *m*, H-2'), 5.31 (1H, *m*, H-3'), 5.54 (1H, *d*, *J* = 8.08Hz, H-5), 4.95 (1H, *s*, NH), 4.23 (2H, *m*, CH_2), 4.08 (2H, *m*, H-5'), 3.93 (1H, *m*, CH), 1.22 (3H, *q*, *J* = 7.03Hz, CH_3), 1.16 (3H, *m*, CH_3). **^{13}C NMR** ($CDCl_3$): δ 140.10 (C6), 133.63, 133.37 (C3'), 129.84, 129.80 (C3''), 127.24, 126.99 (C2'), 125.16 (C4''), 119.95, 119.91, 119.88, 119.84 (C2''), 102.77, 102.59 (C5), 89.92 (C1'), 84.93, 84.86, 84.79 (C4'), 77.28, 77.03, 76.77 (C5'), 61.78, 61.73 ($\underline{C}H_2$), 50.32, 50.19 ($\underline{C}H$), 21.05, 20.91 ($\underline{C}H_3$), 14.11 ($\underline{C}H_3$).

(*S*)-ethyl 2-((((2*S*,5*R*)-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-2,5-dihydrofuran-2-yl)methoxy)(naphthalen-1-yloxy)phosphorylamino)-propanoate (1d). Prepared from d4U (3, 100mg, 0.475mmol, 1eq.), ^{t}BuMgCl (1.0M, 0.62mL, 0.617mM, 1.3eq.) and 1-naphthyl L-alanine ethyl ester phosphorochloridate (325mg, 0.95mM, 2eq.) in THF (7mL). Column chromatography using DCM:MeOH (96:4) as an

eluant. The compound in this case was not completely pure, so a preparative TLC with DCM:MeOH (97:3) was used for further purification. The pure final compound was obtained in 23% yield (56mg) as a white solid. **^{31}P NMR** ($CDCl_3$): δ 3.30, 2.83. **^{1}H NMR** ($CDCl_3$): δ 8.31 (1H, *bs*, NH), 7.91 (1H, *d*, *J* = 8.75Hz, H-6), 7.29-7.65 (7H, *m*, Naph), 6.88 (1H, *m*, H-1'), 6.24 (1H, m, H-2'), 5.82 (1H, m, H-3'), 5.42 (1H, *d*, *J* = 8.75Hz, H-5), 4.97 (1H, m, H-4'), 4.11 (2H, m, CH_2), 3.97 (2H, m, H-5'), 3.76 (1H, t, *J* = 9.22Hz, CH), 1.29 (3H, d, *J* = 7.38Hz, CH_3), 1.14 (3H, m, CH_3). **^{13}C NMR** ($CDCl_3$): δ 171.50 (CO-ester), 163.50 (C=O), 150.81 (C=O), 144.12 (C6), 126.12, 125.34, 125.06, 125.02, 124.89, 124.77, 124.67, 123.67, 123.15, 119.25 (10C-naphthyl), 100.90, 100.73 (C5), 80.08 (C1'), 82.96 (C4'), 65.20, 65.16 (C5'), 59.93, 58.86 (CH_2-ester), 48.42 (CH), 19.28 (CH_3), 12.19 (CH_3).

(*S*)-isopropyl 2-((((2*S*,5*R*)-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-2,5-dihydrofuran-2-yl)methoxy)(phenoxy)phosphorylamino)propanoate (1e). Prepared from d4U (3, 100mg, 0.475mmol, 1eq.), ^{t}BuMgCl (1.0M, 0.62mL, 0.617mM, 1.3eq.) and phenyl L-alanine isopropyl ester phosphorochloridate (290.4mg, 0.95mM, 2eq.) in THF (7mL). Column chromatography using DCM:MeOH (97:3) as an eluant to afford 130mg (57%) of the title compound as a white solid. **^{31}P NMR** ($CDCl_3$): δ 2.98, 2.62. **^{1}H NMR** ($CDCl_3$): δ 9.19 (1H, *d*, *J* = 8.41Hz, NH), 7.50 (1H, *q*, *J* = 8.40Hz, H-6), 7.09-7.37 (5H, *m*, Phe), 6.34 (1H, *t*, *J* = 5.89Hz, H-1'), 8.91 (1H, *m*, H-2'), 5.84 (1H, *m*, H-3'), 5.62 (1H, *q*, *J* = 8.40Hz, H-5), 5.31 (1H, *m*, NH), 5.02 (2H, *m*, CH & H-3'), 4.28-4.40 (2H, m, CH & H-4'), 3.79-3.85 (2H, m, H-5'), 1.34 (3H, *dd*, *J* = 7.07Hz, *J* = 16.64Hz, CH_3), 1.22 (6H, *m*, 2xCH_3). **HPLC** (H_2O/CH_3CN from 100/0 to 0/100 in 20min): Rt 9.67, 9.89 min (2:3). **ESI MS** m/z (positive) 502.178 [M+Na].

(*S*)-isopropyl 2-((((2*S*,5*R*)-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-2,5-dihydrofuran-2-yl)methoxy)(naphthalen-1-yloxy)phosphorylamino)-propanoate (1f). Prepared from d4U (3, 100mg, 0.475mmol, 1eq.), ^{t}BuMgCl (1.0M, 0.62mL, 0.617mM, 1.3eq.) and 1-naphthyl L-alanine isopropyl ester phosphorochloridate (338mg, 0.95mM, 2eq.) in THF (7mL). Column chromatography using DCM:MeOH (98:2) as an

eluant to afford 220mg (87%) of the title compound as a white solid. **^{31}P NMR** ($CDCl_3$): δ 3.47, 3.05. ^{1}H NMR ($CDCl_3$): δ 9.45 (1H, *d*, *J* = 14.81Hz, NH), H-6), 7.74 (1H, *d, J* = 8.081Hz, H-6), 7.20-8.01 (7H, *m*, Naph), 7.15 (1H, *m*, H-1'), 6.89 (1H, *t*, *J* = 1.77Hz, H-2'), 6.19 (1H, *dd*, *J* = 6.01Hz, *J* = 18.64Hz, H-3'), 5.42 (1H, *d*, *J* = 8.08Hz, H-5), 2.92 (2H, m, H-4' & NH), 4.24 (1H, m, CH), 3.88-4.11 (2H, *m*, H-5'), 1.25 (3H, d, *J* = 6.84Hz, CH3), 1.08 (9H, *m*, 2xCH_3). **HPLC** (H_2O/CH_3CN from 100/0 to 0/100 in 20min): Rt 10.91, 11.03 min (1:2). **ESI MS** m/z (positive) 552.138 [M+Na].

(*S*)-*tert*-butyl 2-((((2*S*,5*R*)-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-2,5-dihydrofuran-2-yl)methoxy)(phenoxy)phosphorylamino)propanoate (1g). Prepared from d4U (3, 100mg, 0.475mmol, 1eq.), ^{t}BuMgCl (1.0M, 0.62mL, 0.617mM, 1.3eq.) and phenyl L-alanine *tert*-butyl ester phosphorochloridate (453.6mg, 0.95mM, 2eq.) in THF (7mL). Column chromatography using DCM:MeOH (97:3) as an eluant to afford 42.8mg (18%) of the title compound as a white solid. **^{31}P NMR** ($CDCl_3$): δ 2.20, 1.89. **^{1}H NMR** ($CDCl_3$): δ 8.29 (1H, *bs*, NH), 6.62 (1H, *dd*, *J* = 8.75Hz, H-6), 6.27-6.49 (5H, *m*, Ph), 6.13 (1H, *m*, H-1'), 5.45 (1H, *t*, *J* = 6.64Hz, H-2'), 4.89-5.05 (1H, *dd*, *J* = 5.32Hz, *J* = 39.02Hz, H-3'), 4.73 (1H, *q*, *J* = 8.75Hz, *J* = 18.94Hz, H-5), 4.14 (1H, *m*, H-4'), 3.54 (1H, *m*, CH), 3.46 (1H, *bs*, NH), 2.77-3.01 (1H, m, H-5'), 0.55 (9H, *d*, *J* = 8.46Hz, 3xCH_3), 0.48 (3H, *dd*, CH_3). **^{13}C NMR** ($CDCl_3$): δ 171.70 (CO-ester), 149.83 (C=O), 149.65 (C1''), 139.59, 139.28 (C6), 132.76, 132.57 (C3'), 128.97, 128.94 (C3''), 126.36, 126.13 (C2'), 124.25 (C4''), 119.13, 119.03, 119.04, 119.00 (C2''), 101.94, 101.74 (C5), 89.04 (88.84 (C1'), 84.10, 84.03, 83.99, 83.92 (C4'), 81.44 (C-ester), 76.43, 76.18, 75.92 (C5'), 49.94, 49.85 (CH-amino acid), 20.37, 20.17, 20.13 (3x$\underline{C}H_3$), 14.40 ($\underline{C}H_3$).

(*S*)-*tert*-butyl 2-((((2*S*,5*R*)-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-2,5-dihydrofuran-2-yl)methoxy)(naphthalen-1-yloxy)phosphorylamino)-propanoate (1h). Prepared from d4U (3, 100mg, 0.475mmol, 1eq.), ^{t}BuMgCl (1.0M, 0.62mL, 0.617mM, 1.3eq.) and 1-naphthyl L-alanine *tert*-butyl ester phosphorochloridate (500mg, 0.95mM, 2eq.) in THF (7mL). Column chromatography using DCM:MeOH (98:2) as an eluant to afford 54mg (21%) of the title compound as a white solid. **^{31}P NMR** ($CDCl_3$): δ

3.48, 3.08. **^{1}H NMR** ($CDCl_3$): δ 8.62 (1H, *bs*, NH), 7.62 (1H, *d, J* = 8.08Hz, H-6), 7.13-7.53 (7H, *m*, Naph), 6.90 (1H, *d*, *J* = 23.56Hz, H-1'), 6.20 (1H, *d*, *J* = 24.26Hz, H-2'), 5.63-5.72 (1H, *d*, *J* = 46.11Hz, H-3'), 5.45 (1H, *d*, *J* = 8.08Hz, H-5), 5.17 (1H, *m*, NH), 4.92 (1H, *m*, CH), 4.25 (1H, *m*, H-4'), 3.19-3.43 (2H, *m*, H-5'), 1.31 (9H, *d*, *J* = 12.88Hz, 3xCH3), 1.19 (3H, *m*,CH_3). **HPLC** (H_2O/CH_3CN from 100/0 to 0/100 in 20min): Rt 11.67, 11.95 min (1:1). **ESI MS** m/z (positive) 566.169 [M+Na].

(*S*)-benzyl 2-((((2*S*,5*R*)-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-2,5-dihydrofuran-2-yl)methoxy)(phenoxy)phosphorylamino)propanoate (1i). Prepared from d4U (3, 100mg, 0.475mmol, 1eq.), ^{t}BuMgCl (1.0M, 0.62mL, 0.617mM, 1.3eq.) and phenyl L-alanine benzyl ester phosphorochloridate (466mg, 0.95mM, 2eq.) in THF (7mL). Column chromatography using DCM:MeOH (97:3) as an eluant gave 180mg (31%) of the title compound as a white solid. **^{31}P NMR** ($CDCl_3$): δ 2.80, 2.33. **^{1}H NMR** ($CDCl_3$): δ 8.60 (1H, *s*, NH), 7.36 (1H, *d*, *J* = 8.08Hz, H-6), 7.03-7.31 (10H, *m*, 2Ph), 6.91 (1H, *m*, H-1'), 6.24 (1H, *d*, *J* = 5.93Hz, H-2'), 5.74 (1H, *d*, *J* = 7.92Hz, H-3'), 5.51 (1H, *d*, *J* = 8.08Hz, H-5), 5.08 (2H, *d*, *J* = 3.43Hz, CH_2), 4.91 (1H, *m*, H-4'), 4.10-4.30 (2H, *m*, H-5'), 3.97 (1H, *m*, NH), 3.61 (1H, *t*, CH), 1.25 (3H, *d*, *J* = 7.10Hz, CH_3).

(*S*)-benzyl 2-((((2*S*,5*R*)-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-2,5-dihydrofuran-2-yl)methoxy)(naphthalen-1-yloxy)phosphorylamino)-propanoate (1j). Prepared from d4U (3, 100mg, 0.475mmol, 1eq.), ^{t}BuMgCl (1.0M, 0.62mL, 0.617mM, 1.3eq.) and 1-naphthyl L-alanine benzyl ester phosphorochloridate (383mg, 0.95mM, 2eq.) in THF (7mL). Column chromatography using DCM:MeOH (98:2) as an eluant to afford 58mg (21%) of the title compound as a white solid. **^{31}P NMR** ($CDCl_3$): δ 3.23, 2.65. **^{1}H NMR** ($CDCl_3$): δ 8.22 (1H, *bs,* NH), 7.56 (1H, *d*, *J* = 8.08Hz, H-6), 7.11-7.52 (12H, *m*, Ar), 6.89 (1H, *d*, *J* = 7.31Hz, H-1'), 6.15 (1H, *dd*, *J* = 5.36Hz, *J* = 28.62Hz, H-2'), 5.64-5.73 (1H, *dd*, H-3'), 4.40 (1H, *d*, *J* = 8.08Hz, H-5), 5.05 (2H, *s*, CH_2), 4.36 (1H, *t*, *J* = 9.15Hz, H-4'), 4.24 (1H, m, CH), 4.06 (1H, m, NH), 3.47-3.76 (2H, *m*, H-5'), 1.23 (3H, *dd*, *J* = 7.02Hz, *J* = 17.43Hz, CH_3). **HPLC** (H_2O/CH_3CN from 100/0 to 0/100 in 20min): Rt 12.19 min. **ESI MS** m/z (positive) 600.151 [M+Na].

(*S*)-methyl 2-((((2*S*,5*R*)-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-tetrahydrofuran-2-yl)methoxy)(phenoxy)phosphorylamino)propanoate (2a). Prepared from ddU (4, 100mg, 0.471mmol, 1 eq.), ^{t}BuMgCl (1.0M, 0.7mL, 0.61mM, 1.3eq.) and phenyl L-alanine methyl ester phosphorochloridate (214mg, 0.94mM, 2eq.) in THF (7mL). Column chromatography using DCM:MeOH (97:3) as an eluant to afford 43.2mg (20%) of the title compound as a white solid. **^{31}P NMR** ($CDCl_3$): δ 2.70, 2.92. **^{1}H NMR** ($CDCl_3$): δ 9.27 (1H, *s*, NH), 7.66 (1H, *q*, *J* = 8.10Hz, H-6), 7.06-7.24 (5H, *m*, Ph), 6.00 (1H, *m*, H-1'), 6.23 (1H, *q*, *J* = Hz, H-5), 4.34 (1H, *m*, H-4'), 4.14-4.26 (1H, *m*, H-5'), 3.89-4.06 (1H, *m*, CH), 3.62 (3H, *s*, CH_3), 3.41 (1H, *q*, *J* = 7.59Hz, NH), 2.24-2.43 (1H, *m*, H-2'), 2.03 (1H, *m*, H-3'), 1.76-1.75 (1H, *m*, H-2'), 1.32 (3H, *t*, *J* = 7.22Hz, CH_3). **^{13}C NMR** ($CDCl_3$): δ 174.00, 173.85 (CO-ester), 163.43, 163.41 (C=O), 150.60, 150.55 (C1''), 150.38 (C=O), 139.79, 139.78 (C6), 129.81, 129.78 (C3''), 125.15, 125.13 (C4''), 120.04, 120.02, 120.00, 119.98 (C2''), 102.11, 102.05 (C5), 86.36, 86.10 (C4), 79.01, 78.97, 87.94, 78.90 (C1'), 77.30, 77.05, 76.79 (C5'), 52.59, 52.58 (CH_3O), 50.34, 50.16 (CH), 32.27, 32.20 (C2'), 25.30, 25.17 (C3'), 15.26 (CH3). **HPLC** (H_2O/CH_3CN from 100/0 to 0/100 in 20min): Rt 8.65 min. **ESI MS** m/z (positive) 476.178 [M+Na].

(*S*)-methyl 2-((((2*S*,5*R*)-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-tetrahydrofuran-2-yl)methoxy)(naphthalen-1-yloxy)phosphorylamino)-propanoate (2b). Prepared from ddU (4, 100mg, 0.471mmol, 1 eq.), ^{t}BuMgCl (1.0M, 0.7mL, 0.61mM, 1.3eq.) and 1-naphthyl L-alanine methyl ester phosphorochloridate (403mg, 0.94mM, 2eq.) in THF (7mL). Column chromatography using DCM:MeOH (97:3) as an eluant to afford 73.5mg (31%) of the title compound as a white solid. **^{31}P NMR** ($CDCl_3$): δ 3.76, 3.83. **^{1}H NMR** ($CDCl_3$): δ 8.09 (1H, *bs*, NH), 7.76 (1H, *d*, *J* = 8.10Hz, H-6), 7.34-7.60 (7H, *m*, Naph), 5.73 (1H, *m*, H-1'), 5.39 (1H, *d*, *J* = 8.10Hz, H-5), 4.33 (1H, *m*, H-4'), 4.18 (1H, *m*, NH), 4.10 (1H, *m*, CH), 3.52 (2H, *m*, H-5'), 2.21-2.29 (1H, *m*, H-2'), 1.91 (1H, *m*, H-3'), 1.78-1.89 (1H, *m*, H-2'), 1.27 (3H, *t*, *J* = 8.78Hz, CH_3).

(*S*)-ethyl 2-((((2*S*,5*R*)-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-tetrahydrofuran-2-yl)methoxy)(phenoxy)phosphorylamino)propanoate (2c). Prepared from ddU (4, 100mg, 0.471mmol, 1 eq.), ^{t}BuMgCl (1.0M, 0.7mL, 0.61mM, 1.3eq.) and phenyl L-alanine ethyl ester phosphorochloridate (208mg, 0.94mM, 2eq.) in THF (7mL). Column chromatography using DCM:MeOH (97:3) as an eluant to afford 48.3mg (22%) of the title compound as a white solid. **^{31}P NMR** ($CDCl_3$): δ 2.81, 3.14. **^{1}H NMR** ($CDCl_3$): δ 9.50 (1H, *bs*, NH), 7.58 (1H, *d*, *J* = 8.10, Hz, H-6), 7.03-7.23 (5H, *m*, Ph), 6.00 (1H, *m*, H-1'), 5.56 (1H, *d*, *J* = 8.10Hz, H-5), 4.33 (1H, *m*, H-4'), 4.16-4.23 (1H, *m*, H-5'), 4.10 (1H, *m*, CH), 3.96 (2H, *m*, CH_2), 3.41 (1H, *q*, *J* = Hz, NH), 2.24-2.38 (1H, *m*, H-2'), 2.01 (1H, *m*, H-3'), 1.77-1.93 (1H, *m*, H-2'), 1.27 (3H, *t*, *J* = 6.52Hz, CH_3), 1.14 (3H, *m*, CH_3). **^{13}C NMR** ($CDCl_3$): δ 173.58, 173.52, 173.45, 173.40 (CO-ester), 163.54, 163.52 (C=O), 150.62, 150.57 (C=O), 150.44 (C1''), 139.77 (C6), 129.79, 129.76, 129.62 (C3''), 125.12, 125.09, 124.77 (C4''), 120.13, 120.05, 120.01, 119.98 (C2''), 102.12, 102.06 (C5), 86.32, 86.08 (C1'), 78.99, 78.96, 78.93, 78.89 (C4'), 67.30, 67.26, 67.02 (C5'), 61.66, 61.49 (CH_2), 50.65, 50.40, 50.21 (CH), 32.27, 32.20 (C2'), 25.30, 25.17 (C3'), 20.99, 20.95, 20.90 (CH_3-amino acid), 14.11, 14.09 (CH_3-ester). **HPLC** (H_2O/CH_3CN from 100/0 to 0/100 in 20min): Rt 8.85 min. **ESI MS** m/z (positive) 490.195 [M+Na].

(*S*)-*tert*-butyl 2-((((2*S*,5*R*)-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-tetrahydrofuran-2-yl)methoxy)(phenoxy)phosphorylamino)propanoate (2d). Prepared from ddU (4, 100mg, 0.471mmol, 1 eq.), ^{t}BuMgCl (1.0M, 0.7mL, 0.61mM, 1.3eq.) and phenyl L-alanine *tert*-butyl ester phosphorochloridate (300mg, 0.94mM, 2eq.) in THF (7mL). Column chromatography using DCM:MeOH (97:3) as an eluant to afford 49.2mg (21%) of the title compound as a white solid. **^{31}P NMR** ($CDCl_3$): δ 3.00, 3.08. **^{1}H NMR** ($CDCl_3$): δ 9.53 (1H, *bs*, NH), 7.64 (1H, *d*, *J* = 8.10Hz, H-6), 7.13-7.31 (5H, *m*, Ph), 6.07 (1H, *m*, H-1'), 5.61 (1H, *d*, *J* = 8.10Hz, H-5), 4.43 (1H, *m*, H-4'), 3.90-4.23 (2H, *m*, H-5'), 3.47 (1H, *s*, NH), 2.31-2.41 (1H, *m*, H-2'), 2.07 (1H, *m*, H-3'), 1.87-1.99 (1H, *m*, H-2'), 1.46 (9H, *q*, *J* = 1.92Hz, 3xCH_3), 1.32 (3H, *d*, *J* = 1.28Hz, CH_3). **^{13}C NMR** ($CDCl_3$): δ 172.69, 172.62, 172.55 (CO-ester), 163.49 (C=O), 150.66, 150.61 (C=O),

150.44 (C1''), 139.74 (C6), 129.78, 129.75, 129.61 (C3''), 125.05 (C4''), 120.06, 120.04, 120.02, 120.00 (C2''), 102.12, 102.08 (C5), 86.31, 86.08 (C1'), 78.98, 78.91 (C4'), 67.22, 67.18, 66.97, 66.93 (C5'), 65.82 (CH_2), 50.89, 50.74, 50.67 (CH), 32.31, 32.22 (C2'), 27.92, 27.91 (3xCH3), 25.35, 25.17 (C3'), 21.17, 21.13, 21.07, 21.03 (CH_3-amino acid), 14.11, 14.09 (CH_3-ester). **HPLC** (H_2O/CH_3CN from 100/0 to 0/100 in 20min): Rt 10.19 min. **ESI MS** m/z (positive) 518.227 [M+Na].

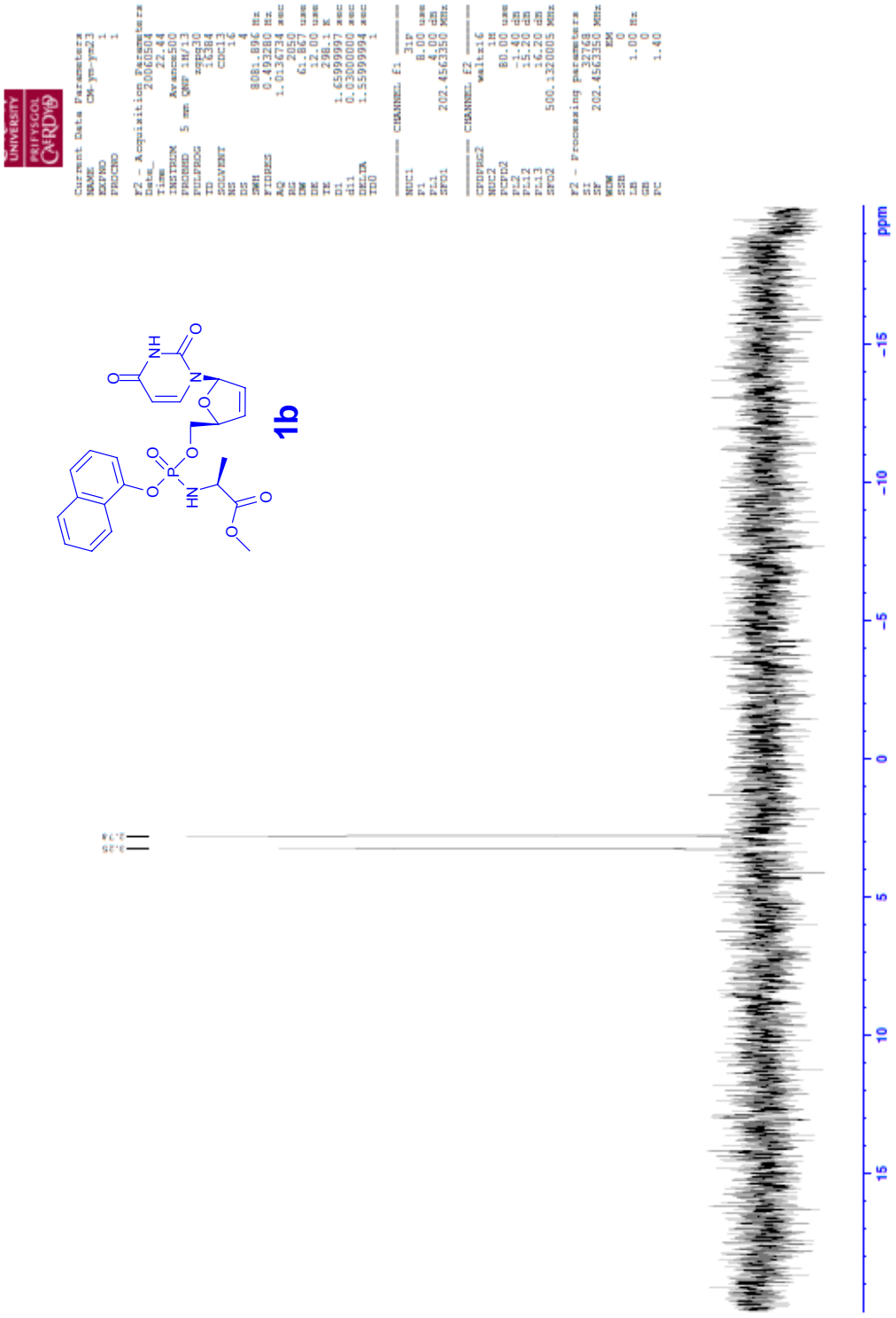
(*S*)-benzyl 2-((((2*S*,5*R*)-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-tetrahydrofuran-2-yl)methoxy)(phenoxy)phosphorylamino)propanoate (2e). Prepared from ddU (4, 100mg, 0.471mmol, 1 eq.), ^{t}BuMgCl (1.0M, 0.7mL, 0.61mM, 1.3eq.) and phenyl L-alanine benzyl ester phosphorochloridate (332mg, 0.94mM, 2eq.) in THF (7mL). Column chromatography using DCM:MeOH (97:3) as an eluant to afford 53.4g (21%)of the title compound as a white solid. **^{31}P NMR** ($CDCl_3$): δ 2.62, 2.83. **^{1}H NMR** ($CDCl_3$): δ 9.05 (1H, *bs*, NH), 7.53 (1H, *d*, *J* = 8.09Hz, H-6), 7.03-7.31 (10H, *m*, Ph), 5.98 (1H, *m*, H-1'), 5.56 (1H, *d*, *J* = 8.09Hz, H-5), 5.03 (2H, *s*, CH_2), 4.30 (1H, *m*, H-4'), 4.18 (2H, *m*, H-5'), 4.10 (1H, *m*, CH), 3.86 (1H, *m*, NH), 2.25-2.36 (1H, *m*, H-2'), 1.99 (1H, *m*, H-3'), 1.79-1.96 (1H, *m*, H-2'), 1.32 (3H, *t*, *J* = 6.95Hz , CH_3). **^{13}C NMR** ($CDCl_3$): δ 173.38 (CO-ester), 163.26 (C=O), 150.51, 150.30 (C=O), 150.27 (C1''), 139.74 (C6), 135.16, 129.82, 129.78, 128.68, 128.65, 128.60, 128.53, 128.29, 128.27, 125.16, (10C-Ar), 102.10, 102.02 (C5), 86.31, 86.09 (C1'), 78.93, 78.87 (C4'), 67.34, 67.27, 67.23, 67.06, 67.02 (C5'), 50.75, 50.48, 50.29 (CH_2), 32.25, 32.17 (CH), 25.23, 25.16 (C2'), 21.02, 20.96, 20.91, 20.86 (C3'), 14.18 (CH_3-ester).

(*S*)-benzyl 2-((((2*S*,5*R*)-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-tetrahydrofuran-2-yl)methoxy)(naphthalen-1-yloxy)phosphorylamino)-propanoate (2f). Prepared from ddU (4, 100mg, 0.471mmol, 1 eq.), ^{t}BuMgCl (1.0M, 0.7mL, 0.61mM, 1.3eq.) and 1-naphthyl L-alanine benzyl ester phosphorochloridate (379mg, 0.94mM, 2eq.) in THF (7mL). Column chromatography using DCM:MeOH (97:3) as an eluant to afford 44.3mg (16%) of the title compound as a white solid. **^{31}P NMR** ($CDCl_3$): δ 3.08, 3.38. **^{1}H NMR** ($CDCl_3$): δ 9.38 (1H, *bs*, NH), 7.98 (1H, *d*, *J* = 8.08Hz, H-6),

7.22-7.71 (12H, *m*, Ar), 5.91 (1H, *m*, H-1'), 5.39 (1H, *d*, *J* = 8.08Hz, H-5), 4.98 (1H, *s*, NH), 4.27 (1H, *m*, H-4'), 4.06 (1H, *m*, CH), 3.96-4.20 (2H, *m*, H-5'), 3.40 (2H, *s*, NH), 2.17-2.22 (1H, *m*, H-2'), 1.81 (1H, *m*, H-3'), 1.64-1.72 (1H, m, H-2'), 1.27 (3H, m, CH_3). **^{13}C NMR** ($CDCl_3$): δ 173.45, 173.40, 173.23, 173.18 (CO-ester), 163.40 (C=O), 150.38 (C=O), 134.77, 134.74, 128.67, 128.61, 128.58, 128.48, 128.40, 128.29, 128.22, 128.13, 127.97, 126.97 (12C-Ar), 102.16, 102.10 (C5), 86.18, 85.90 (C1'), 78.71, 78.66, 78.60 (C4'), 77.33, 77.08, 76.83 (C5'), 67.51, 67.47, 67.33, 67.29 (CH_2), 50.56, 50.42 (CH), 32.04, 31.85 (C2'), 25.26, 25.15 (C3'), 15.27 (CH_3-amino acid). **HPLC** (H_2O/CH_3CN from 100/0 to 0/100 in 20min): Rt 11.05 min. **ESI MS** m/z (positive) 602.230 [M+Na].

(*S*)-benzyl 2-((((2*S*,5*R*)-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-tetrahydrofuran-2-yl)methoxy)(4-methoxynaphthalen-1-yloxy)phosphoryl-amino)propanoate (2g). Prepared from ddU (4, 100mg, 0.471mmol, 1 eq.), ^{t}BuMgCl (1.0M, 0.7mL, 0.61mM, 1.3eq.) and 1-naphthyl L-alanine benzyl ester phosphorochloridate (408mg, 0.94mM, 2eq.) in THF (7mL). Column chromatography using DCM:MeOH (97:3) as an eluant to afford 51.2mg (18%) of the title compound as a white solid. **^{31}P NMR** ($CDCl_3$): δ 3.41, 3.43. **^{1}H NMR** ($CDCl_3$): δ 8.87 (1H, *d*, NH), 7.91 (1H, *d*, *J* = 8.09Hz, H-6), 7.23-7.51 (11H, *m*, Ar), 5.93 (1H, *d*, *J* = 9.71Hz, H-1'), 5.41 (1H, *d*, *J* = 8.09Hz, H-5), 5.01 (2H, *s*, CH_2), 4.26 (1H, *m*, H-4'), 4.03-4.23 (2H, *m*, H-5'), 3.87 (1H, *m*, CH), 3.82 (1H, *m*, NH), 2.16-2.23 (1H, *m*, H-2'), 1.66-1.73 (1H, *m*, H-3'), 1.19-1.59 (1H, *m*, H-2'), 1.22 (2H, *dd*, *J* = 7.09Hz, *J* = 10.41Hz, CH_3). **^{13}C NMR** ($CDCl_3$): δ 173.41, 173.40, 173.39 (CO-ester), 163.00 (C=O), 152.73 (C=O), 150.18, 139.59, 139.50, 128.27, 128.62, 128.59, 128.49, 128.28, 128.21, 127.06, 127.01, 126.33, 115.03, 102.81, 102.72 (Ar), 102.15, 102.08 (C5), 86.20, 85.95 (C1'), 78.73, 78.67 (C4'), 77.28, 77.03, 76.78 (C5'), 67.46, 67.42, 67.33, 67.24 (CH_2), 55.75 ($\underline{C}H_3OAr$), 50.55, 50.41 (CH), 32.03, 31.91 (C2'), 25.27, 25.16 (C3'), 21.09, 21.05, 20.97 (CH_3-amino acid). **HPLC** (H_2O/CH_3CN from 100/0 to 0/100 in 20min): Rt 11.32 min. **ESI MS** m/z (positive) 632.243 [M+Na].

Ammonium((2*S*,5*R*)-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-2,5-dihydrofuran-2-yl)methyl phosphate. Under an argon atmosphere, to a suspension of 2',3'didehydro-2',3'-dideoxyuridine (640mg, 1.1mmol) in triethyl phosphate (5mL), $POCl_3$ (0.32mL, 1.50mmol) was added to 0°C. the reaction was stirred at the same temperature, i.e. 0°C, for 2hr. After this time TLC (EtOAc:MeOH, 9:1 and iPrOH:NH_3:H_2O, 7:1:2) showed the disappearance of the starting material. A solution of NH_4CO_3 (0.4M) was then added until the effervescence stopped. After 10minutes the mixture was concentrated under reduced pressure, the residue was dissolved in water (10mL) and filtered off. The filtrate was subsequently purified by column chromatography (iPrOH:NH_3:H_2O; 9:1:2). The appropriate fractions were collected and the solvent was removed *in vacuo* to yield a white salt (100mg). **^{31}P NMR** (D_2O): δ 1.46. **^{1}H NMR** (D_2O): δ 7.73 (1H, *d*, *J* = 8.08Hz, H-6), 6.90 (1H, *d*, H-1'), 6.43 (1H, *m*, H-2'), 5.92 (1H, *m*, H-3'), 5.82 (1H, *d*, *J* = 8.08Hz, H-5), 5.05 (1H, *m*, H-4'), 3.92 (2H, *m*, H-5'). ^{13}C NMR (D_2O): δ 166.46 (C=O), 152.13 (C=O), 65.74 (C-5'), 142.90 (C-6), 134.07 (C-2'), 125.08 (C-3'), 102.11 (C-5), 90.20 (C-1'), 86.00 (C-4'), 65.78 (C5'). **HPLC** (H_2O/CH_3CN from 100/0 to 0/100 in 20min): Rt 1.60 min.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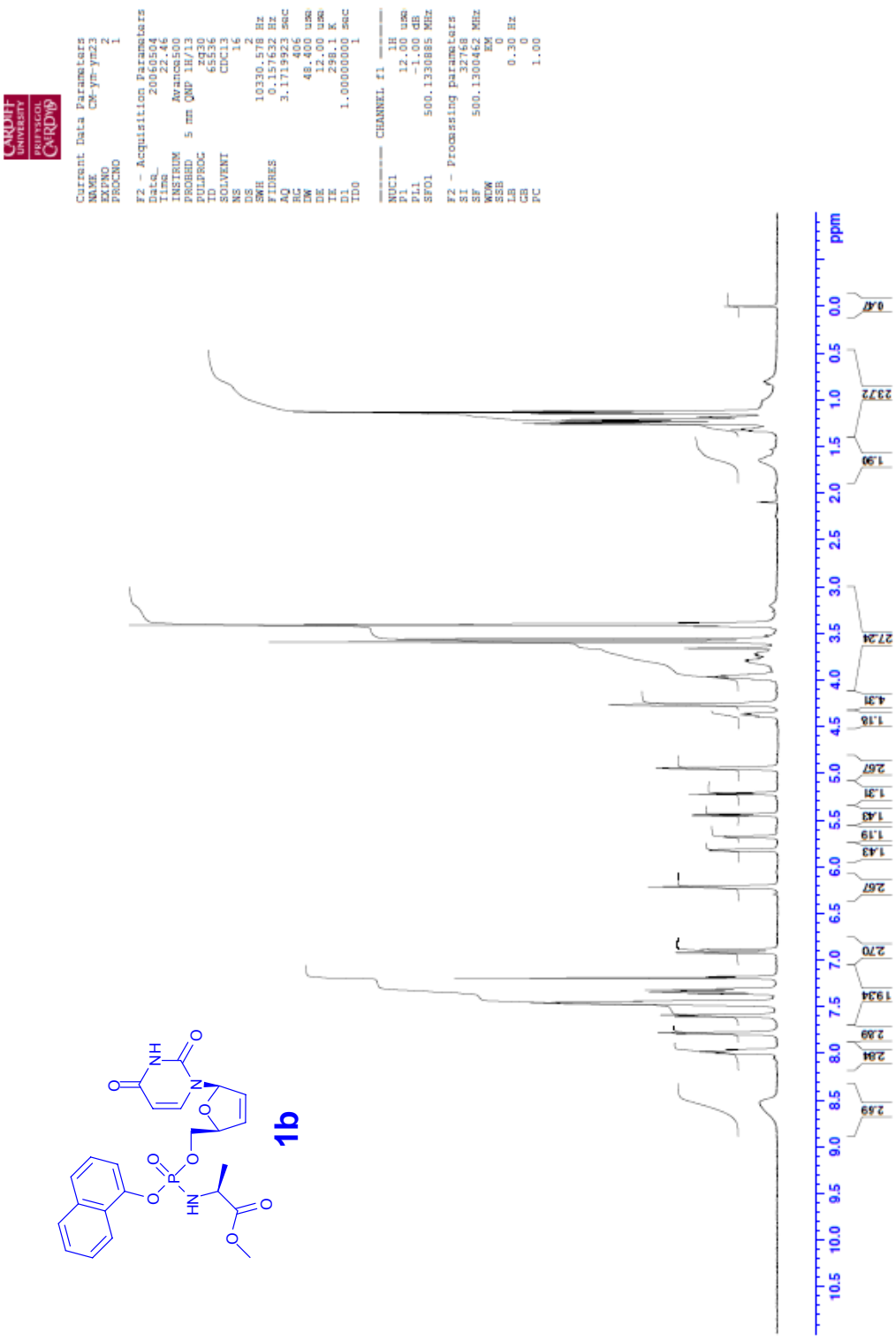
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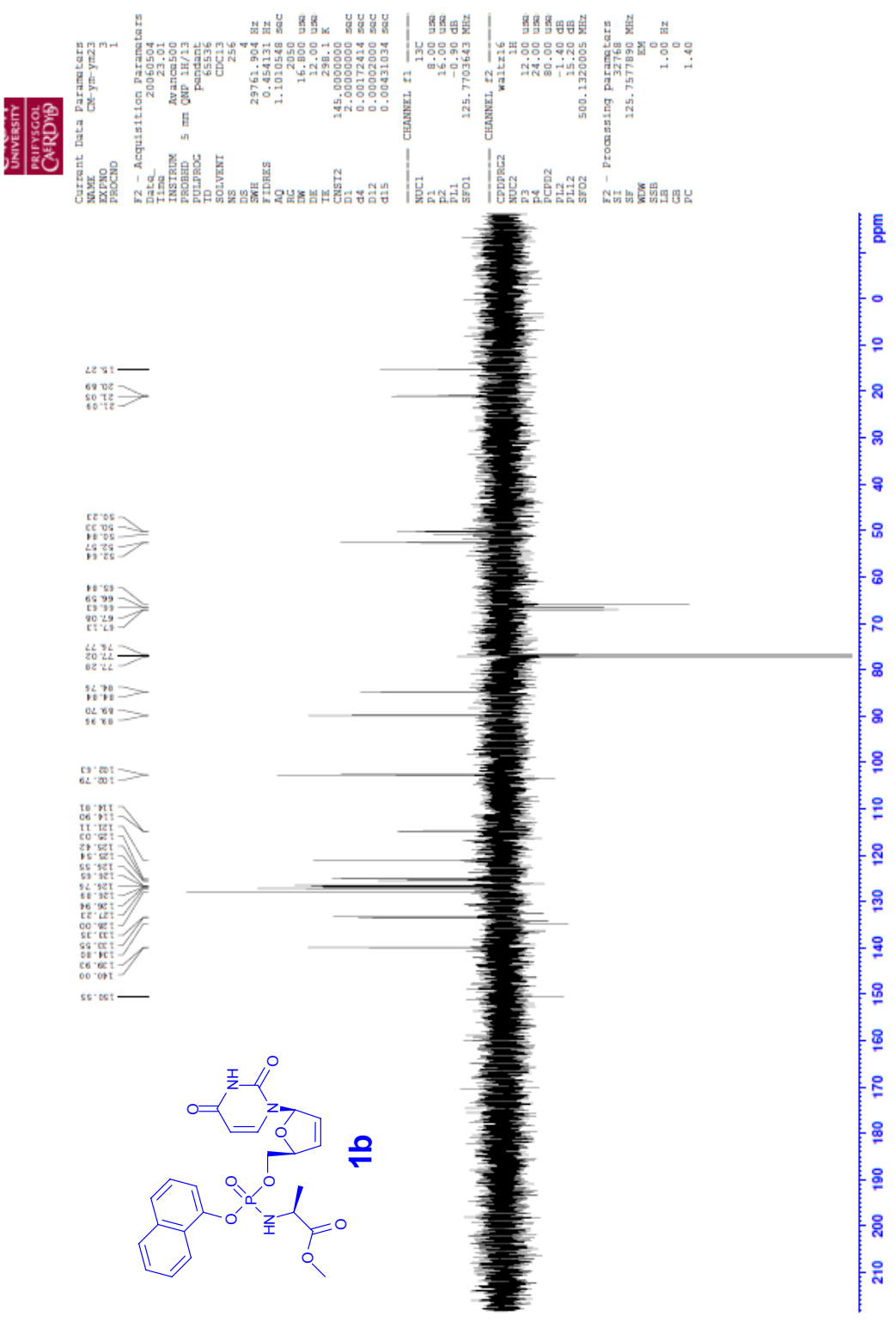
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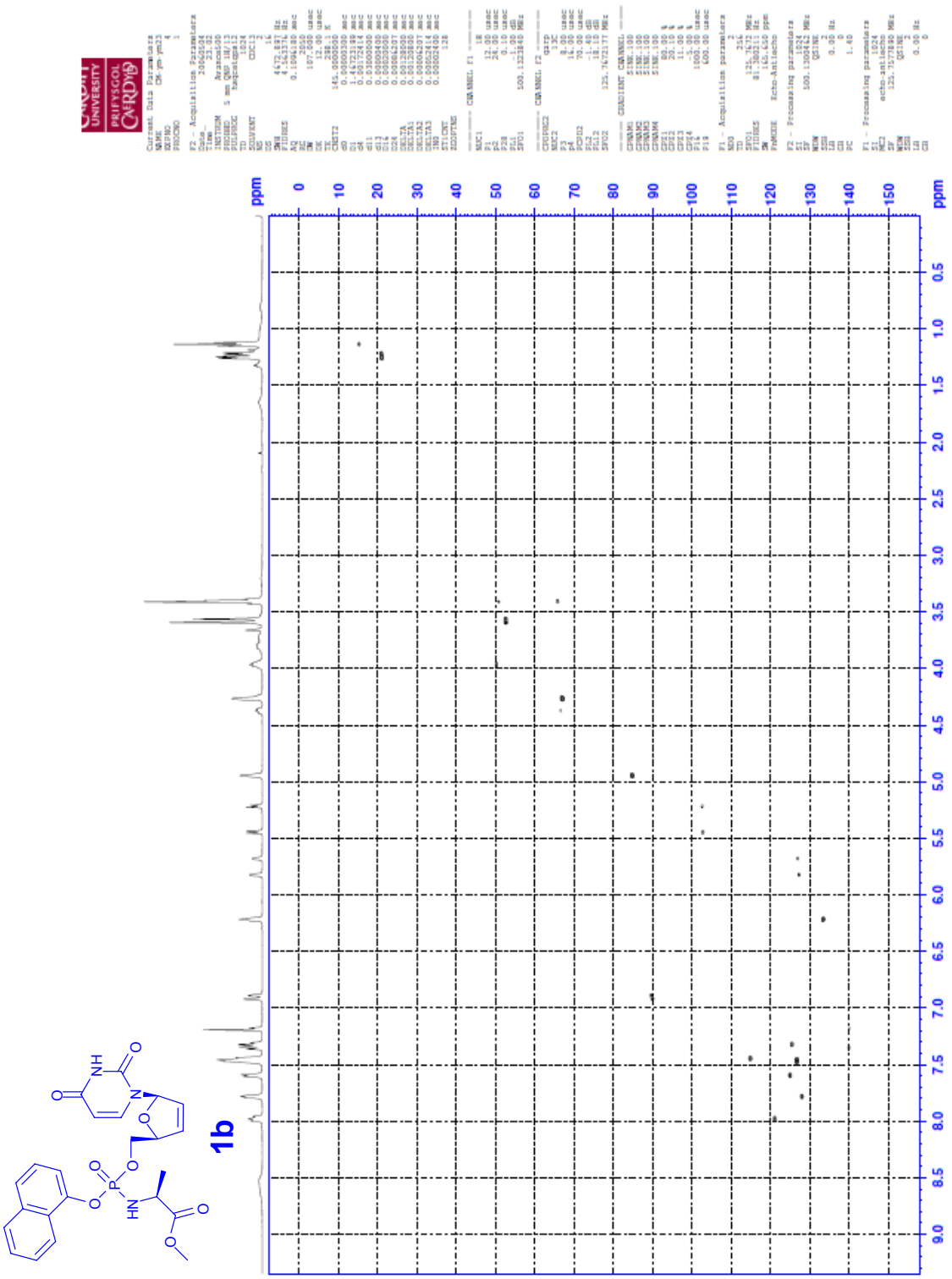
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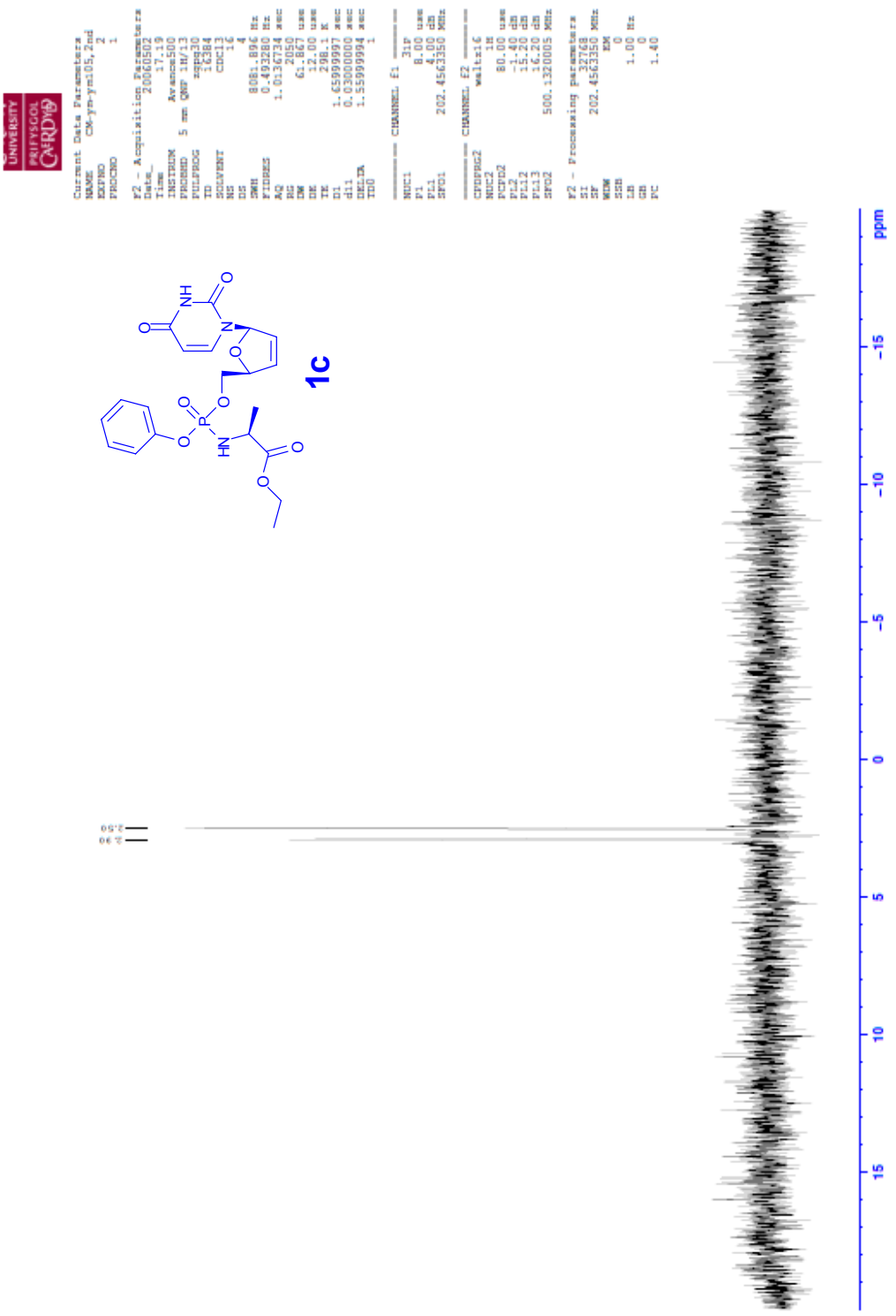
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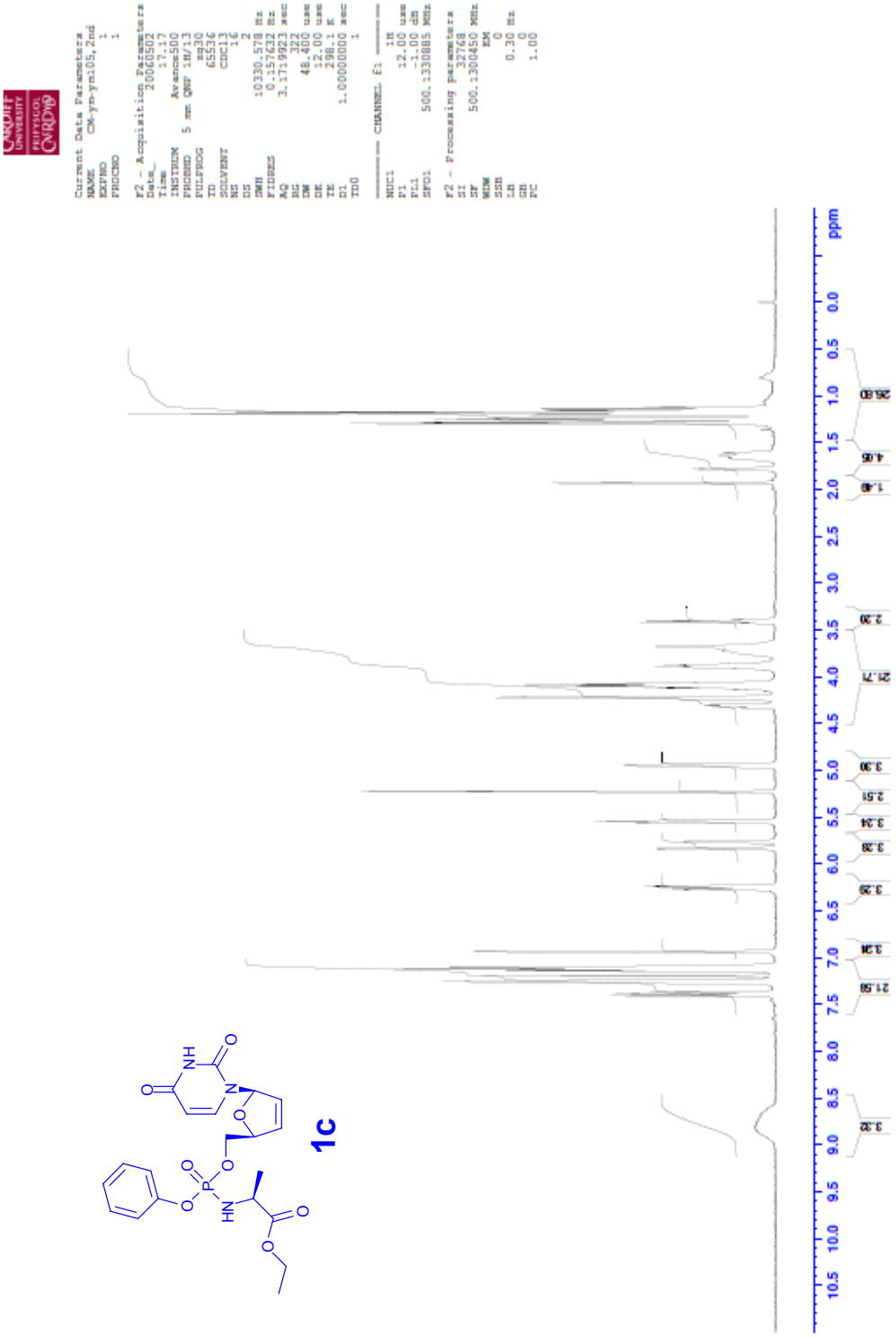
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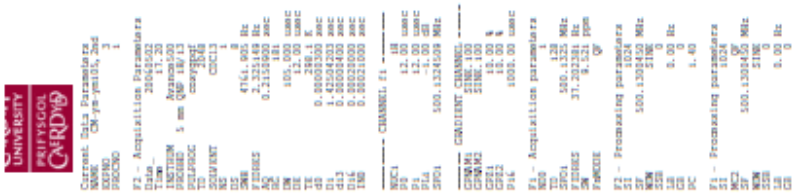

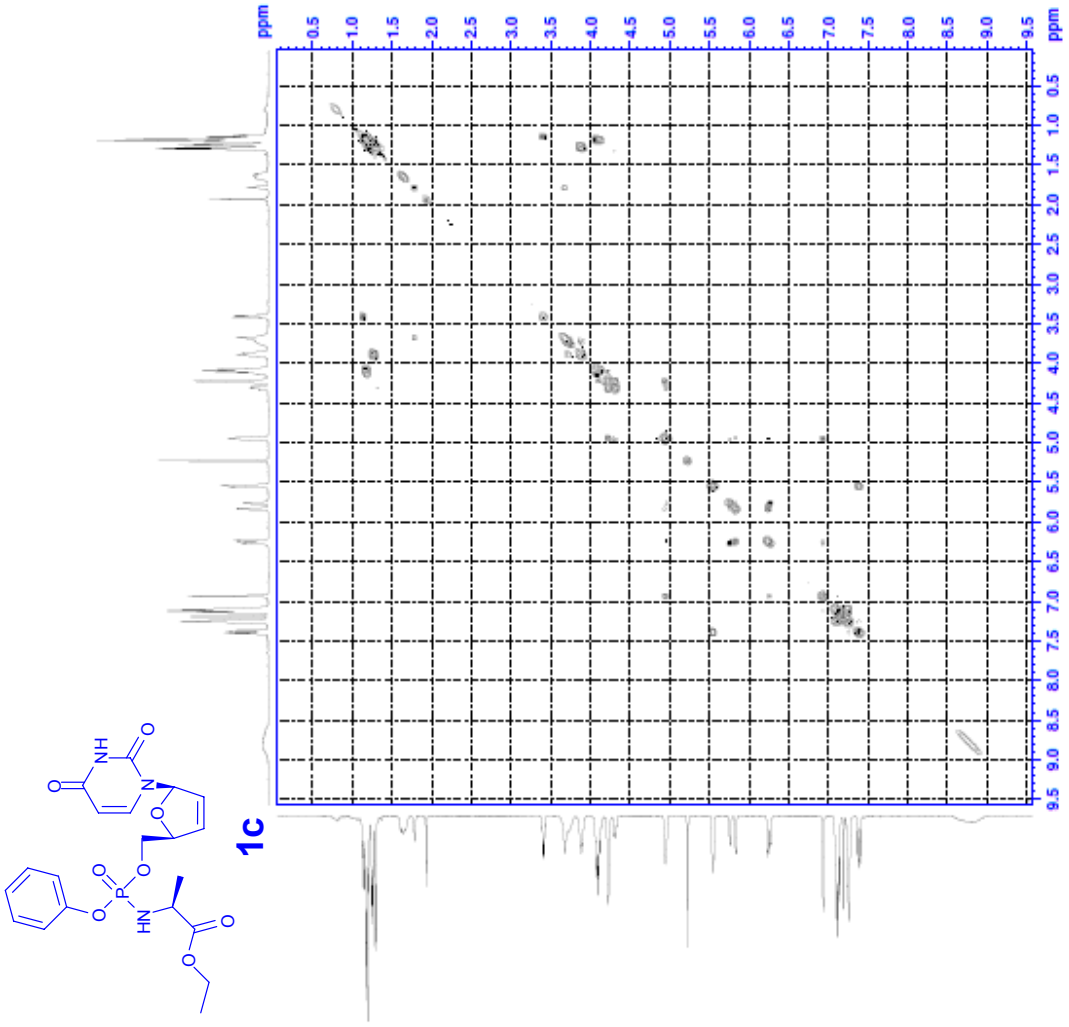
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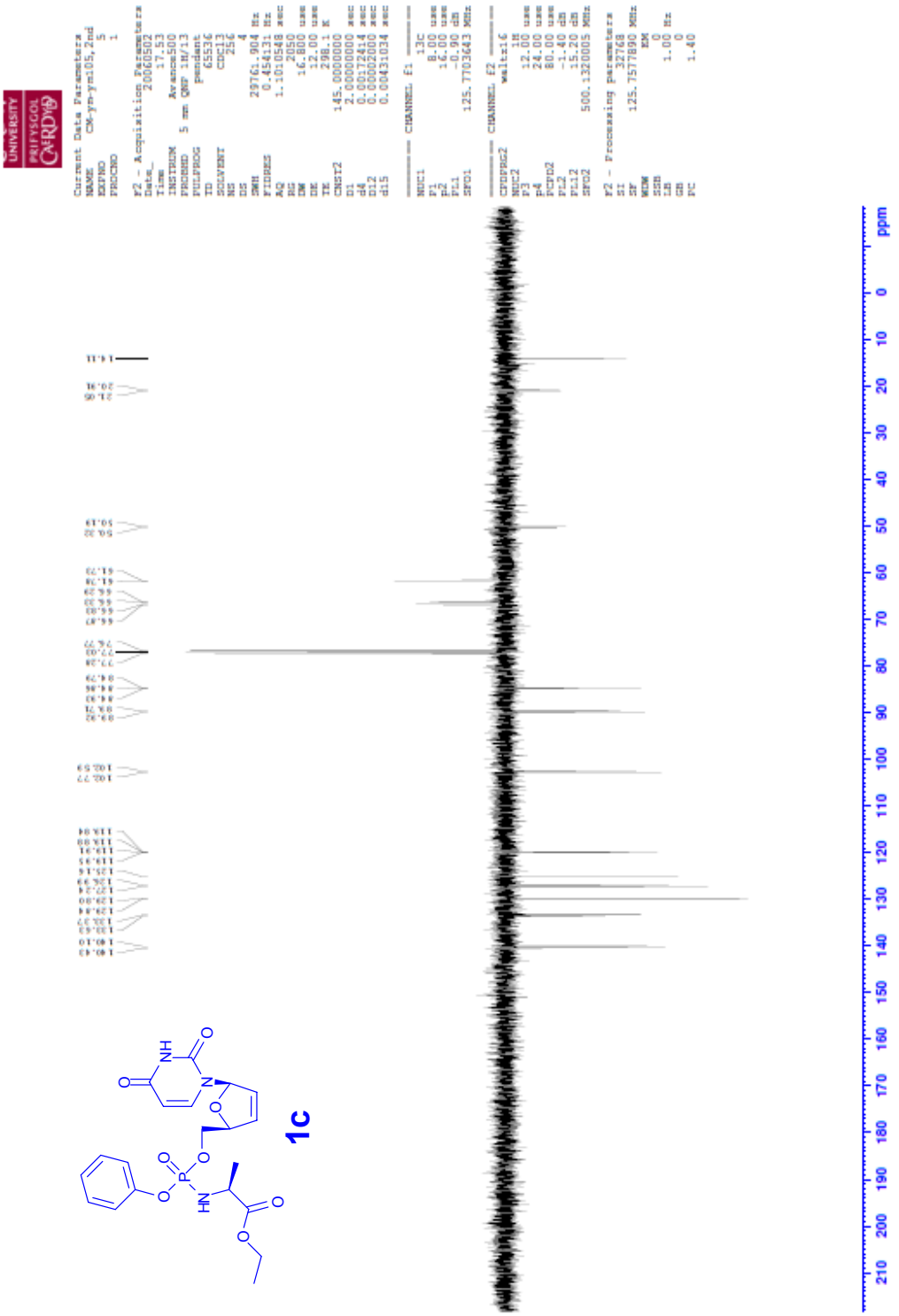
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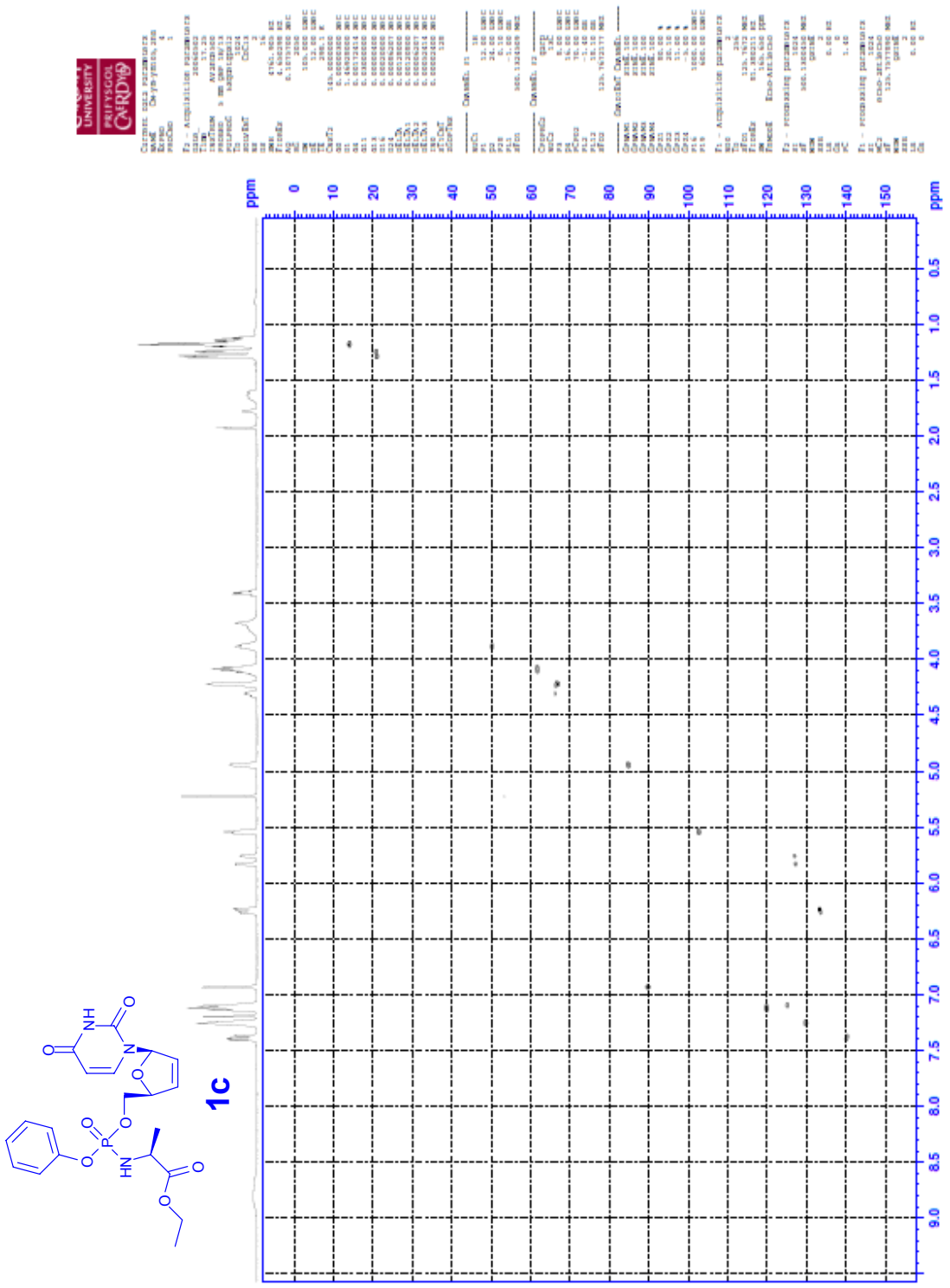
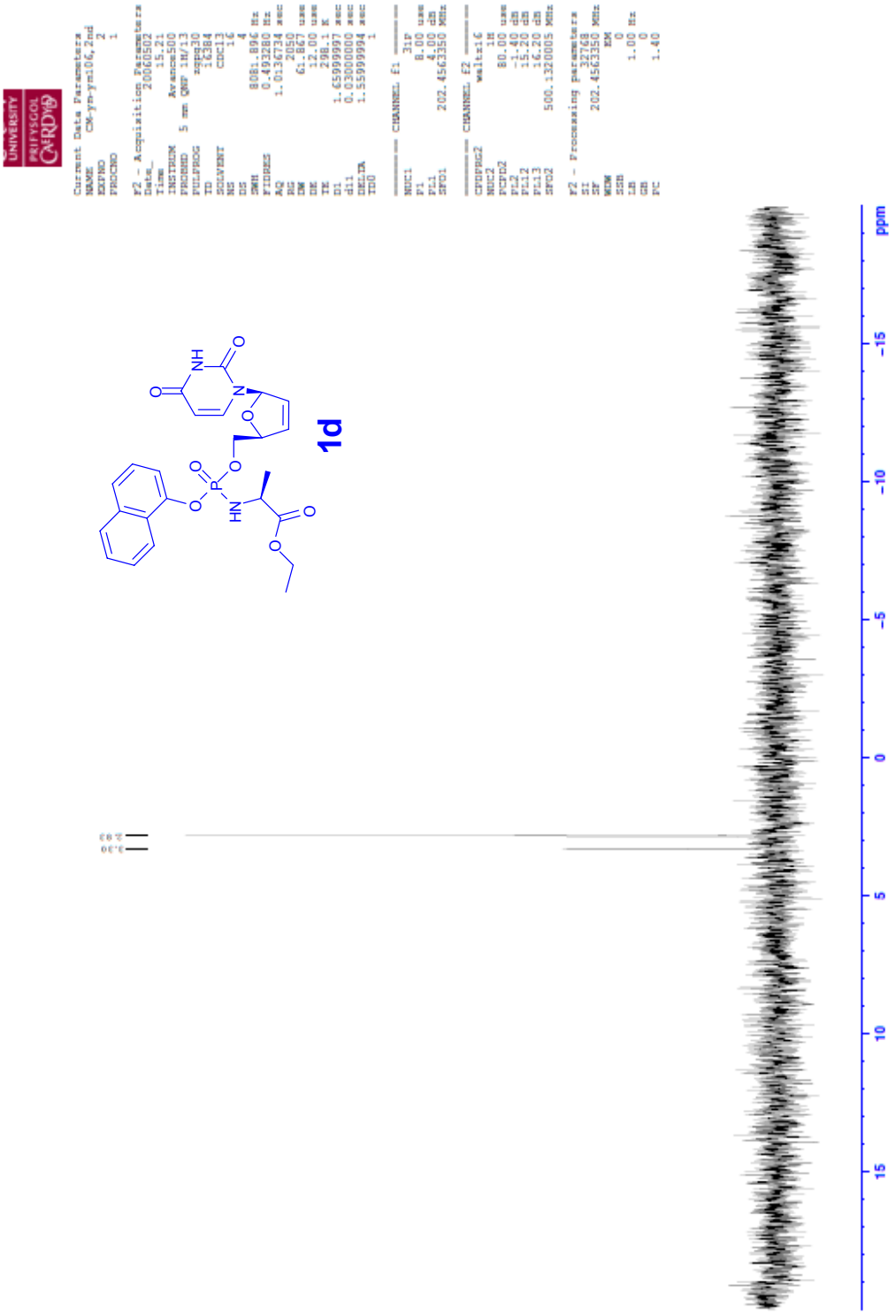
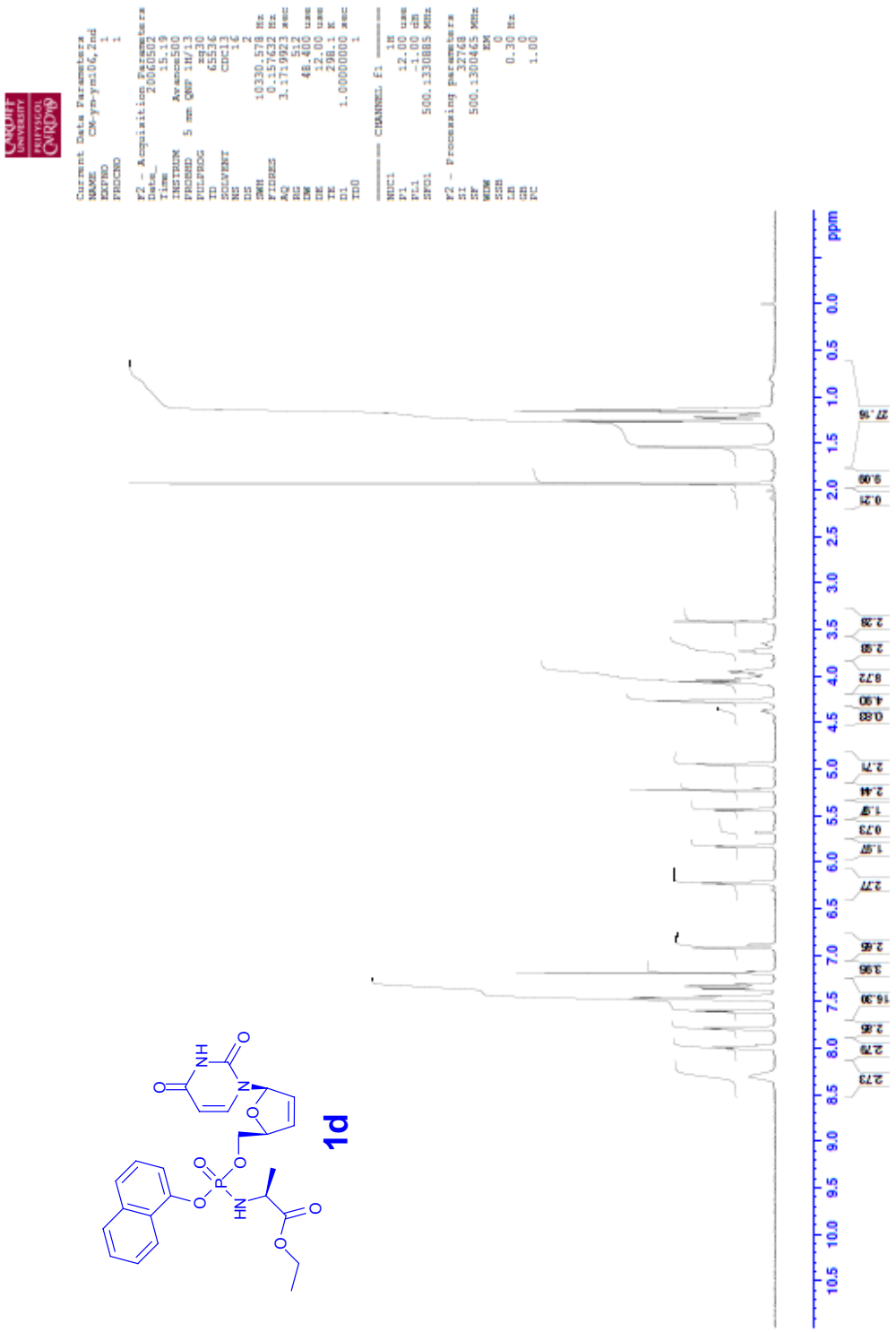
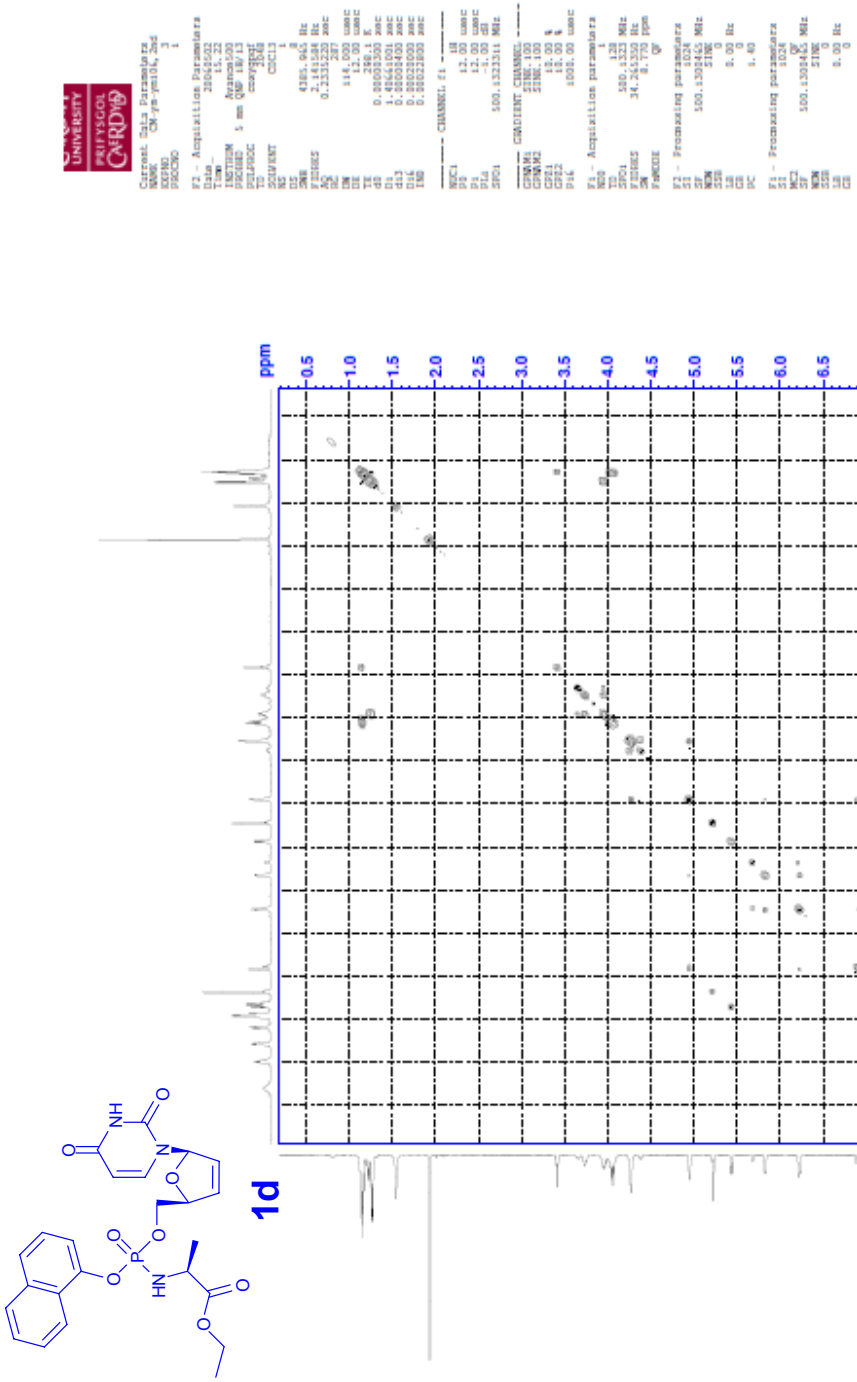

1c
ppm
ppm


1d
ppm


1d
ppm


1d
ppm
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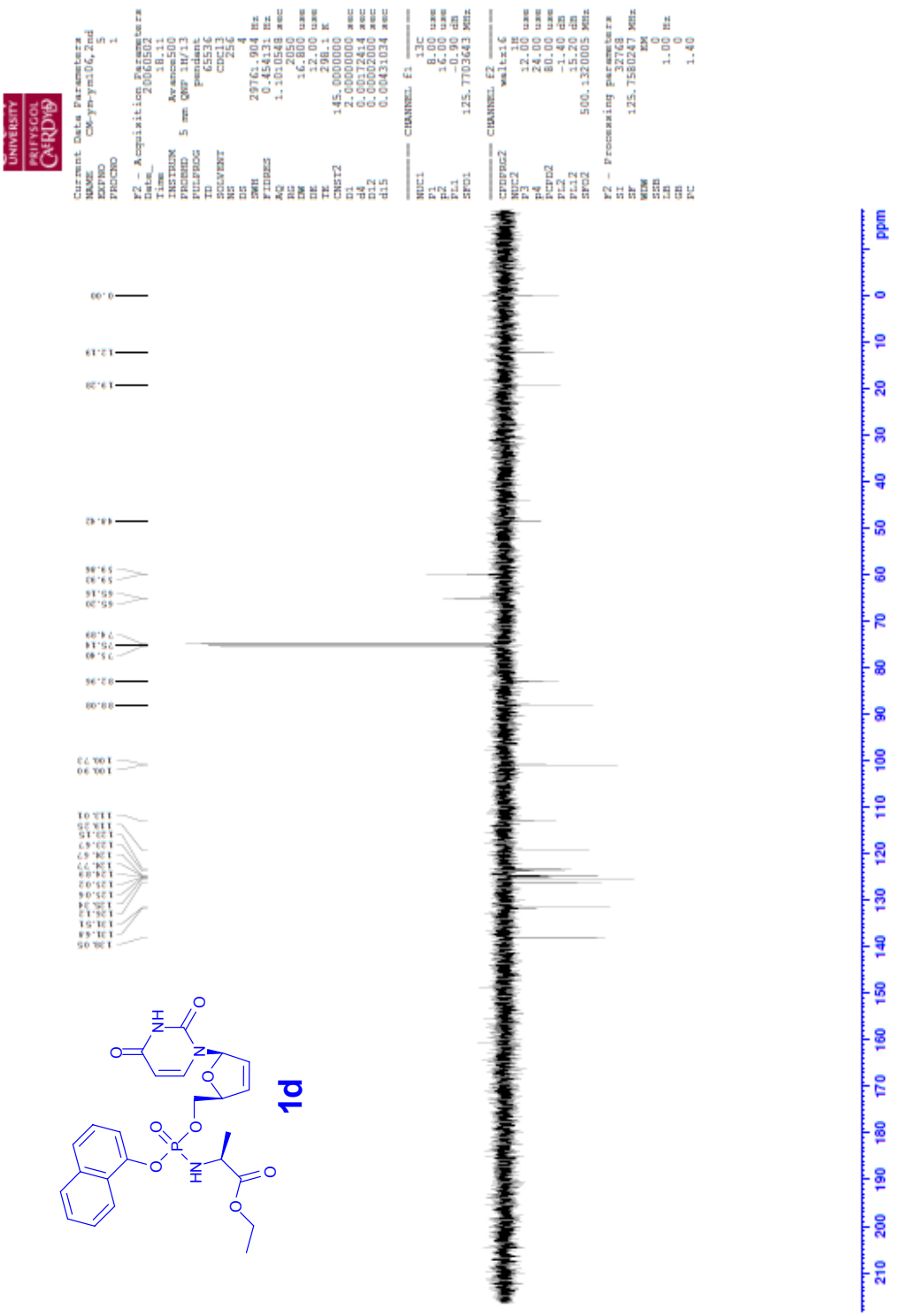
1d
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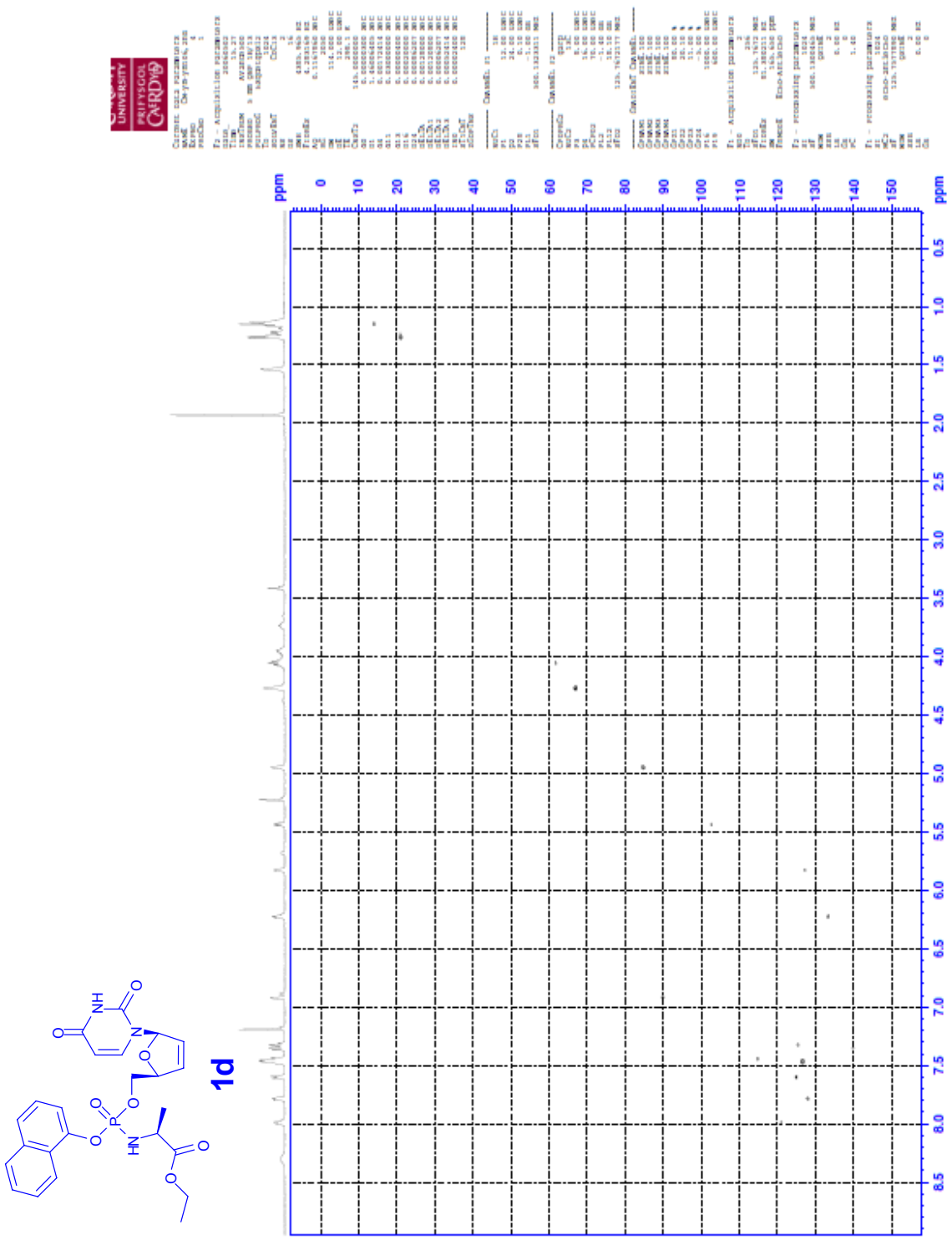
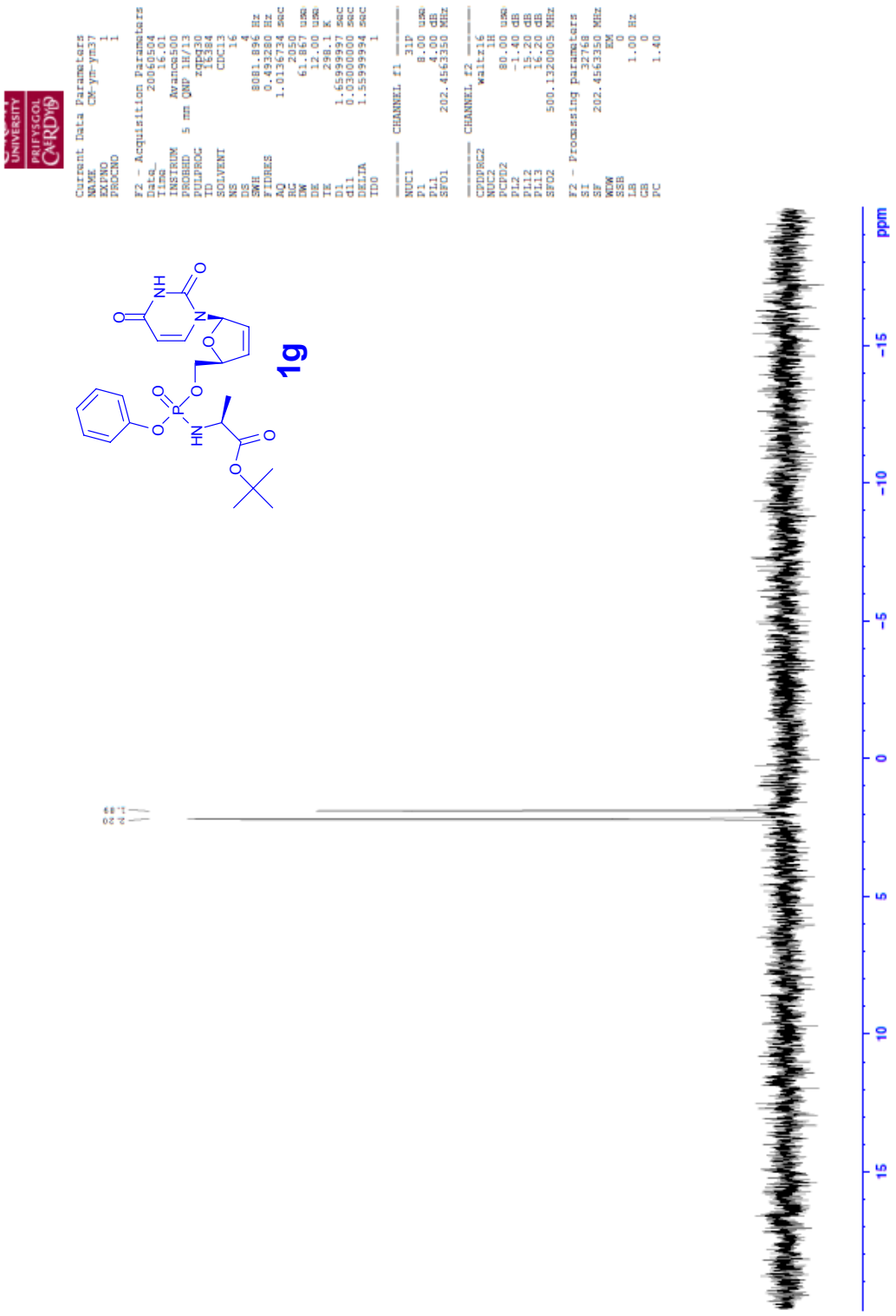
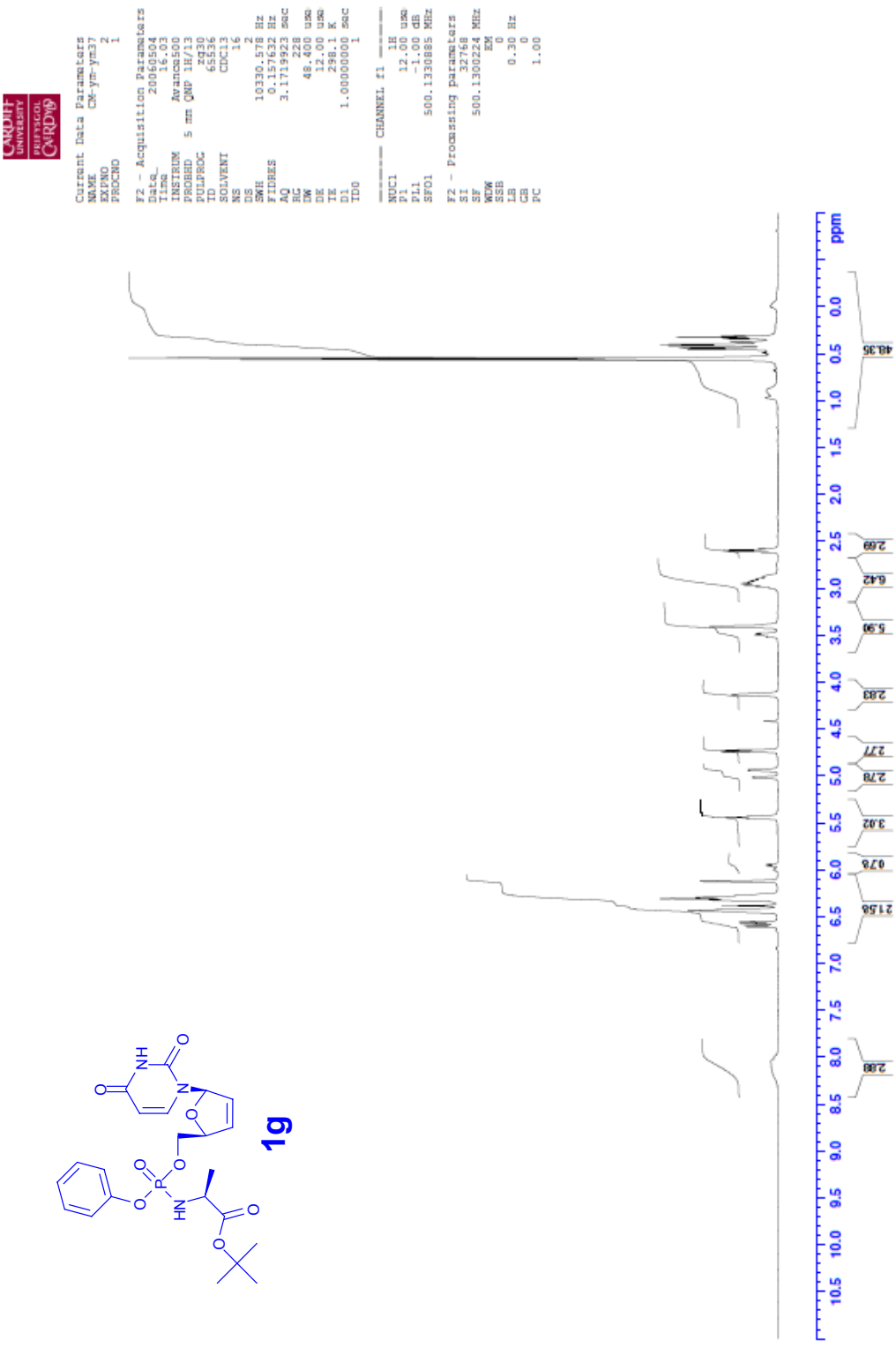
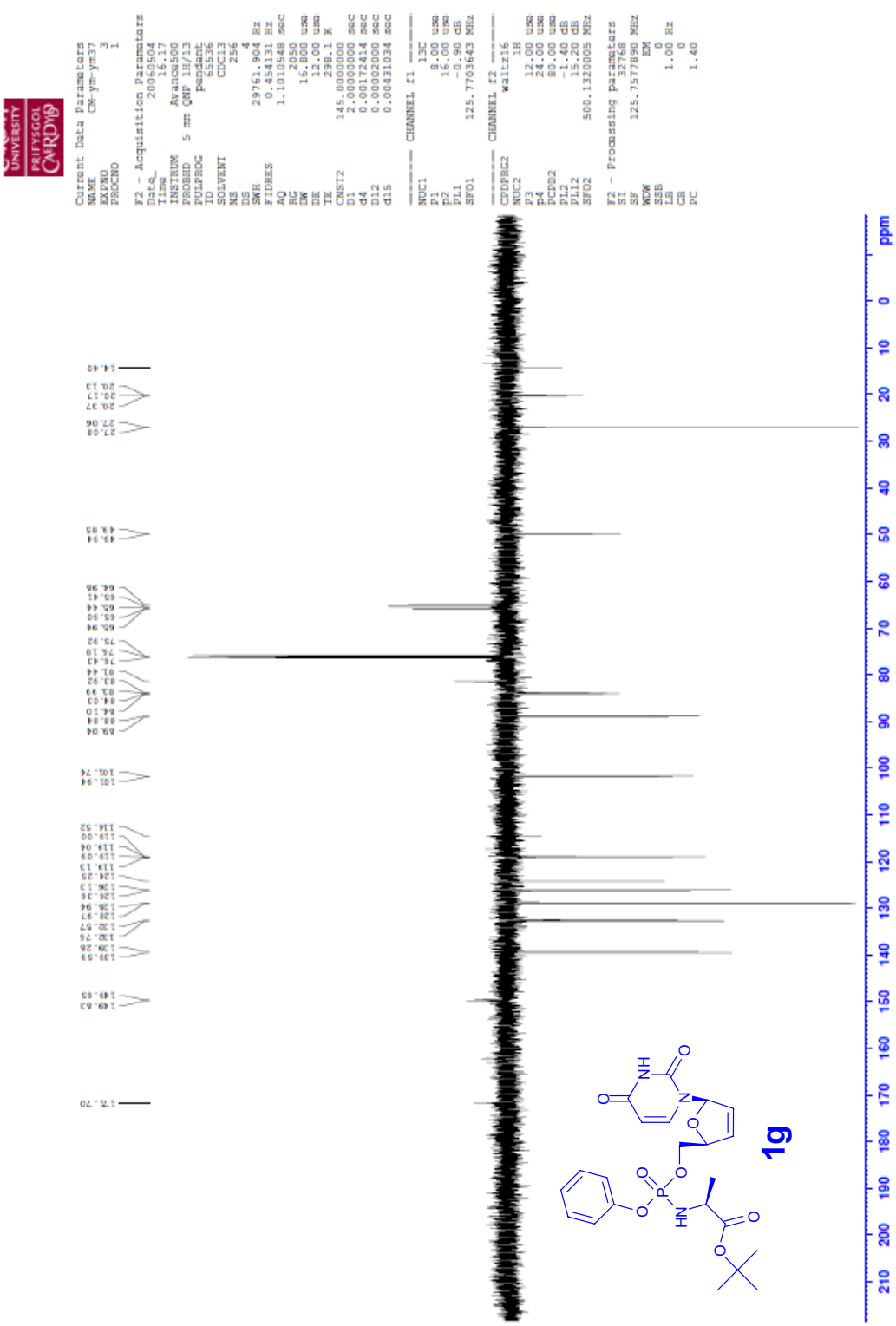

1d


1g
ppm
15
10
5
0
-5
-10
-15


CARDIFF UNIVERSITY
PRIFYSGOL CAERDYDD
Current Data Parameters
NAME CM-ym-ym37
EXPNO 2
PROCNO 1
F2 - Acquisition Parameters
Date_ 20060504
Time 16.03
INSTRUM Avance500
PROBHD 5 mm QNP 1H/13
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 10330.578 Hz
FIDRES 0.157632 Hz
AQ 3.1719923 sec
RG 228
DW 48.400 usec
DE 12.00 usec
TE 298.1 K
D1 1.00000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 1H
P1 12.00 usec
PL1 -1.00 dB
SFO1 500.1330885 MHz
F2 - Processing parameters
SI 32768
SF 500.1300224 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
ppm
48.35
2.09
6.42
5.90
2.83
2.77
2.78
3.02
0.78
2158
2.00
19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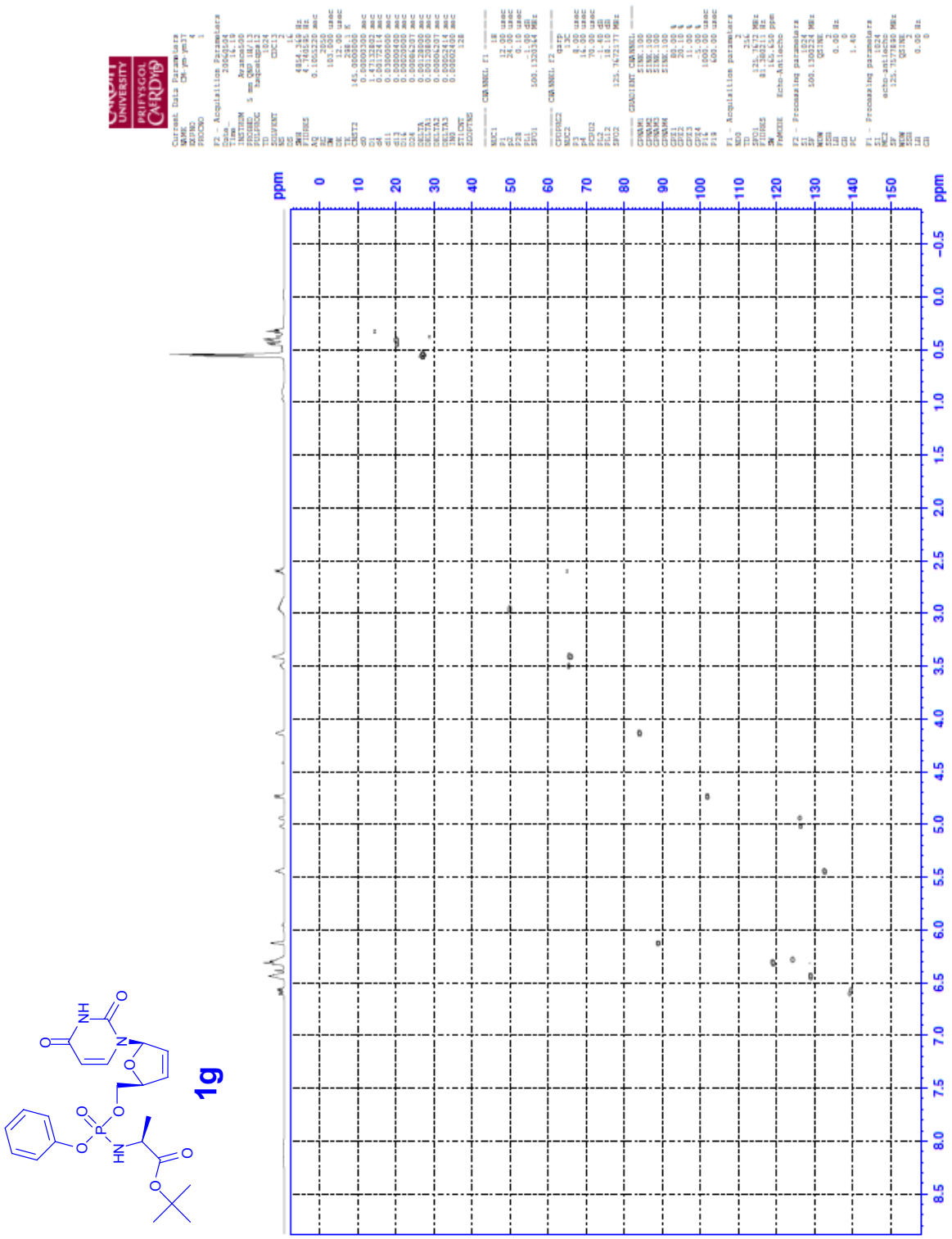
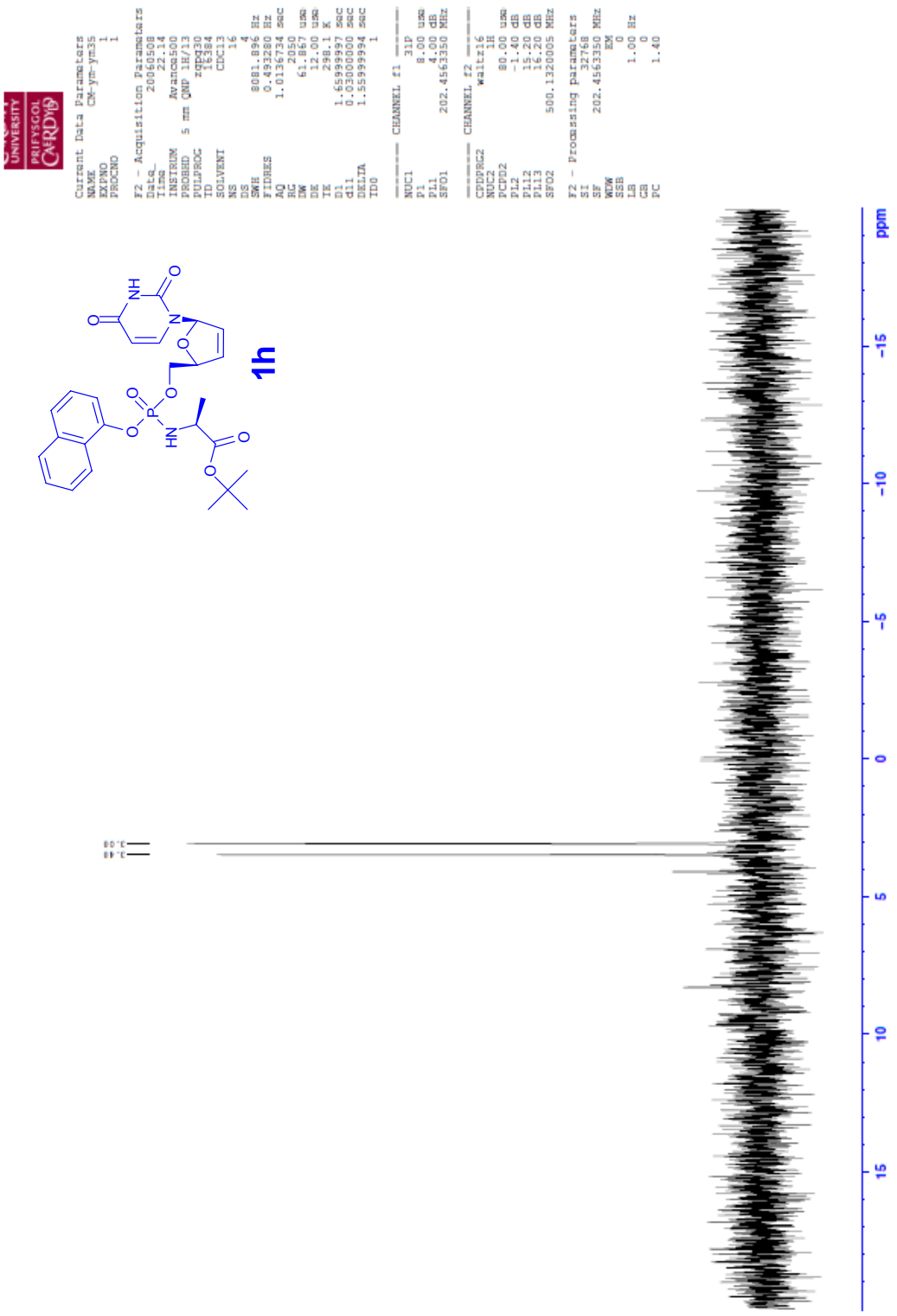
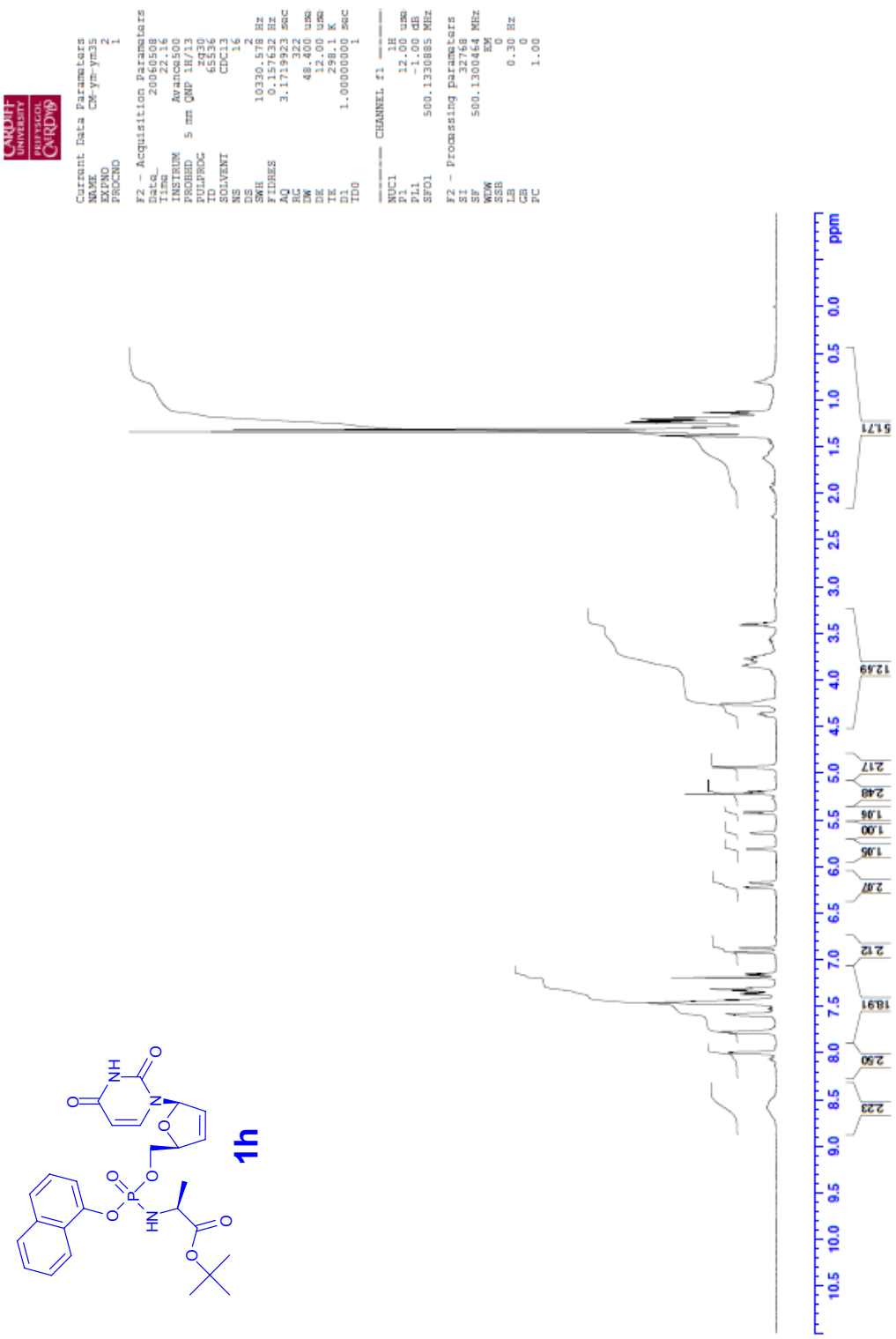
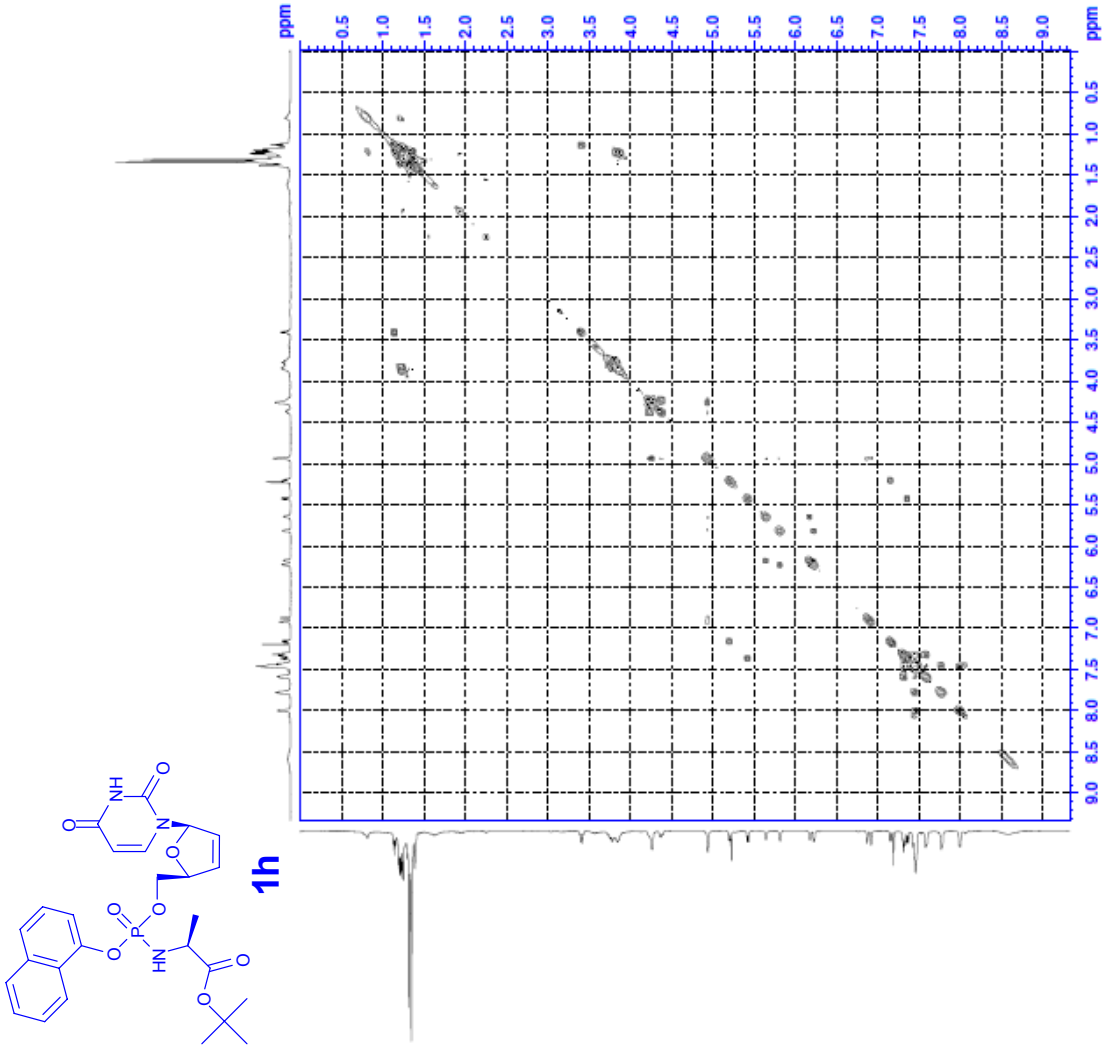
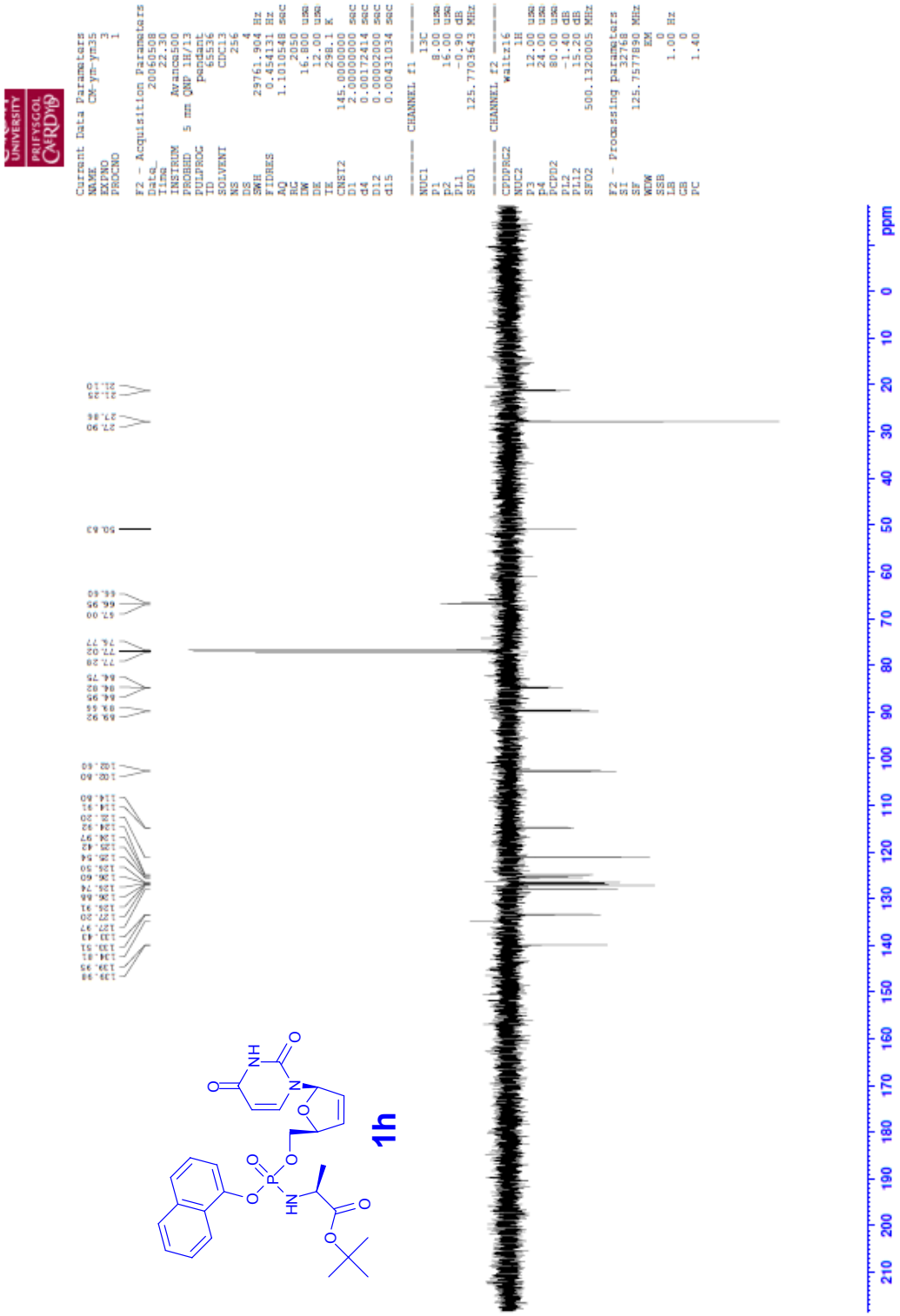
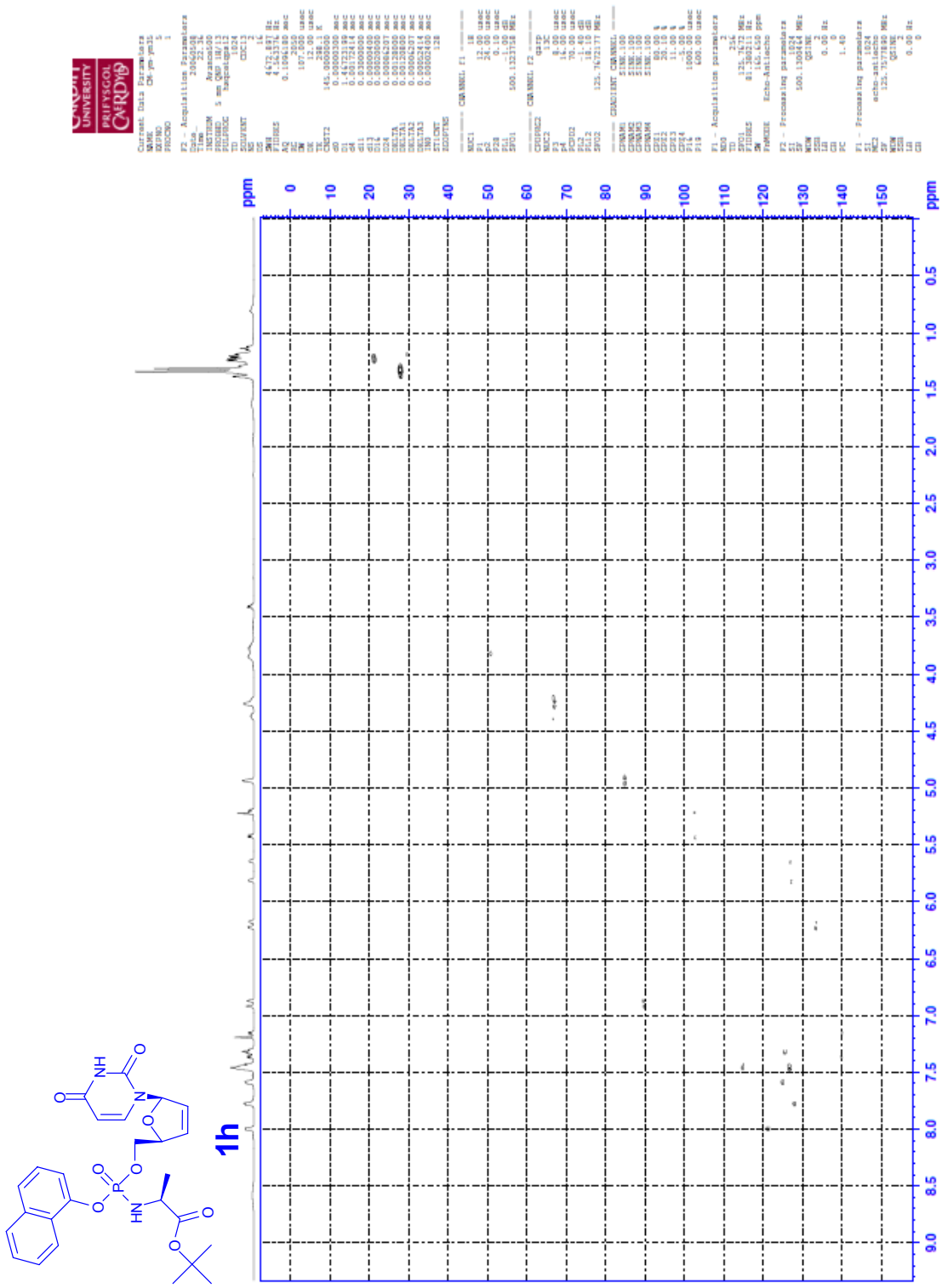

1g

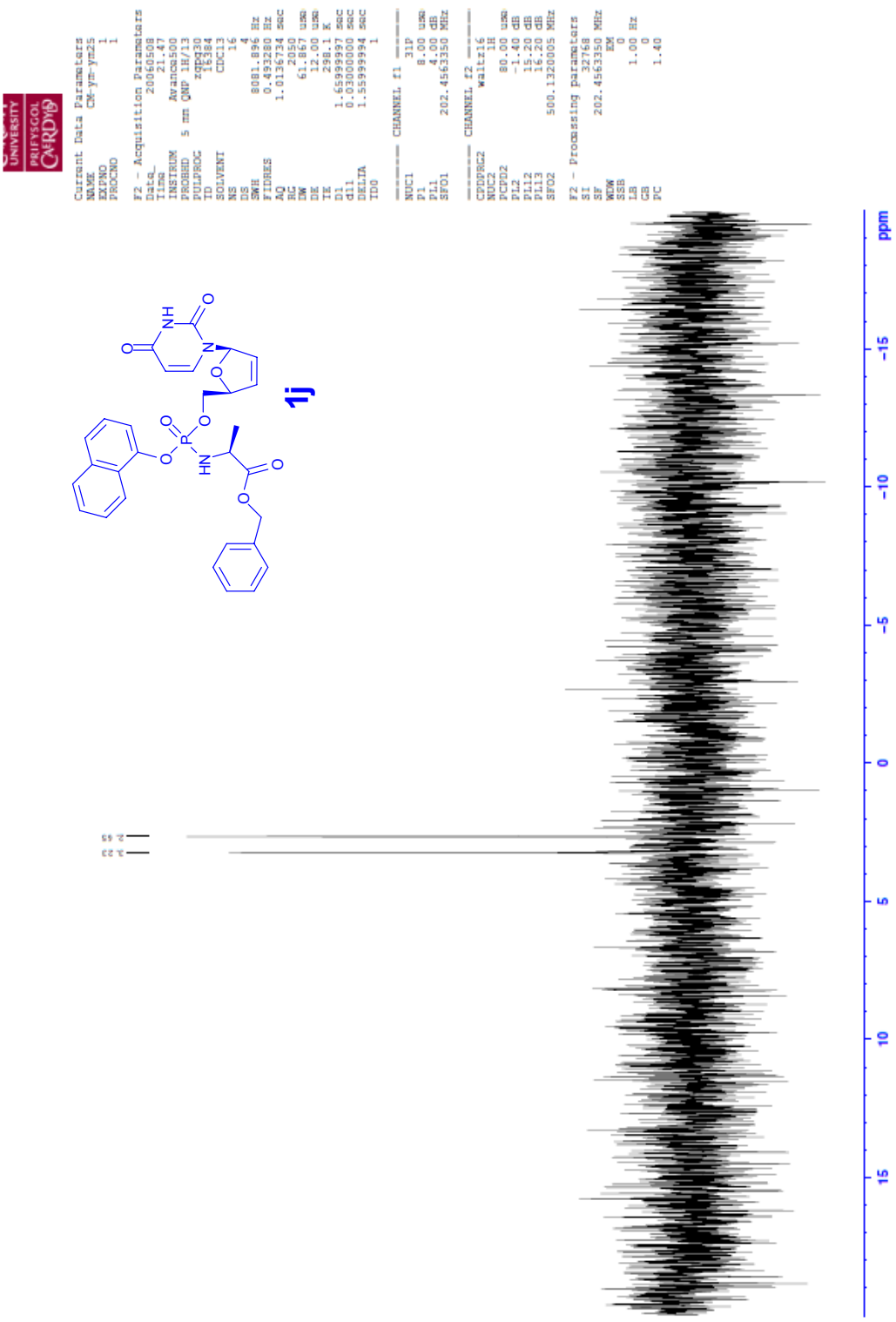

1h
ppm
15
10
5
0
-5
-10
-15

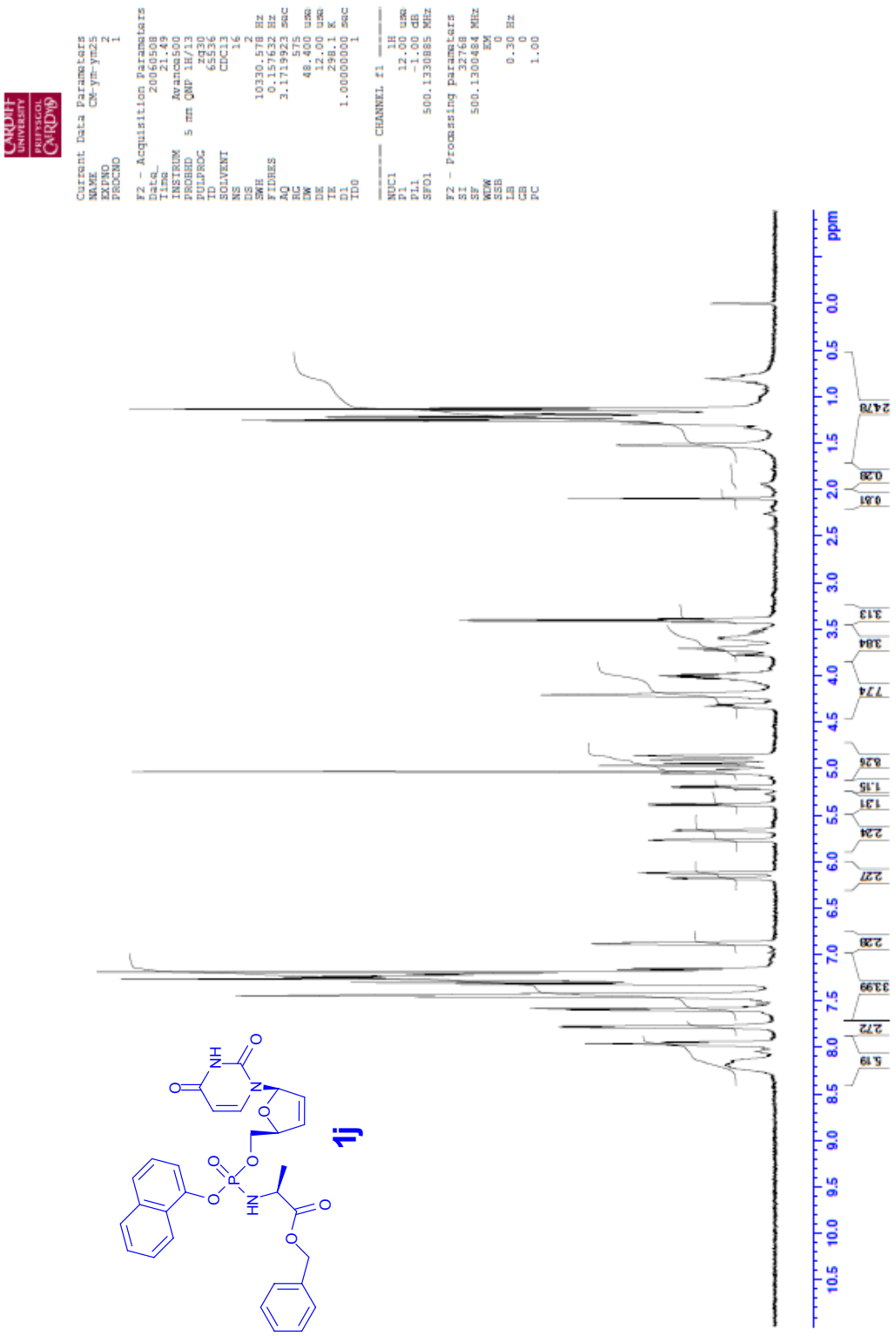

Current Data Parameters
NAME CM-ym-ym35
EXPNO 2
PROCNO 1
F2 - Acquisition Parameters
Date_ 20060508
Time 22.16
INSTRUM Avance500
PROBHD 5 mm QNP 1H/13
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 10330.578 Hz
FIDRES 0.157632 Hz
AQ 3.1719923 sec
RG 322
DW 48.400 usec
DE 12.00 usec
TE 298.1 K
D1 1.00000000 sec
TD0 1
CHANNEL f1
NUC1 1H
P1 12.00 usec
PL1 -1.00 dB
SFO1 500.1330885 MHz
F2 - Processing parameters
SI 32768
SF 500.1300464 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
ppm
5.71
12.49
2.17
2.48
1.06
1.00
1.05
2.07
2.12
18.91
2.50
2.23
1h

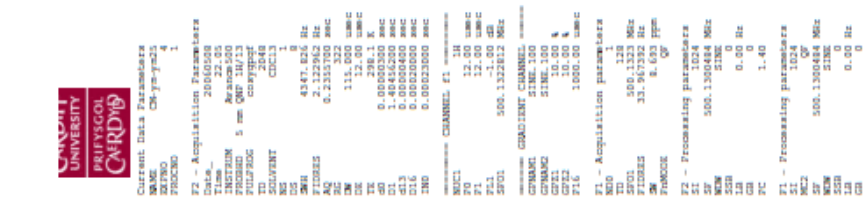

ppm
1h

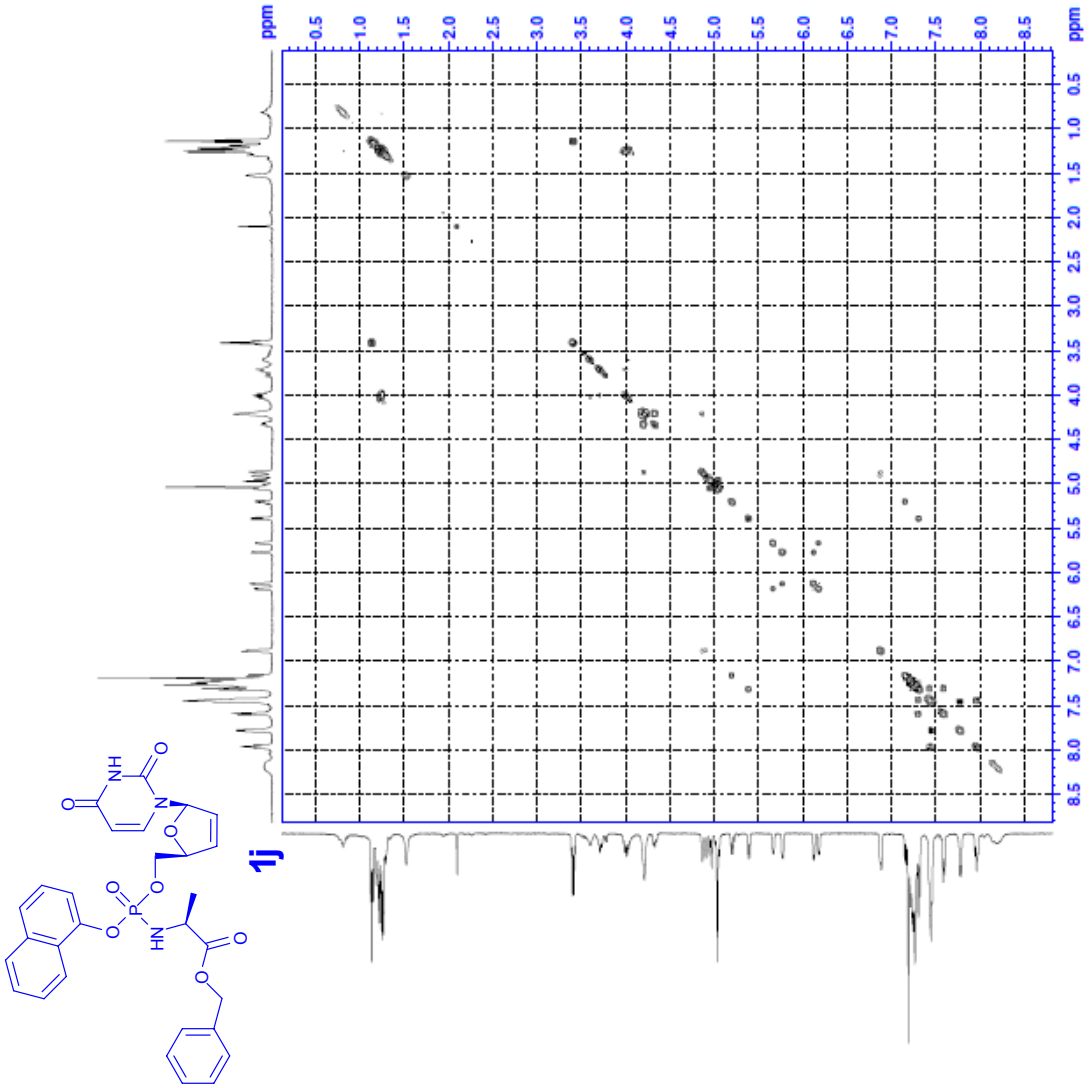

1h
ppm

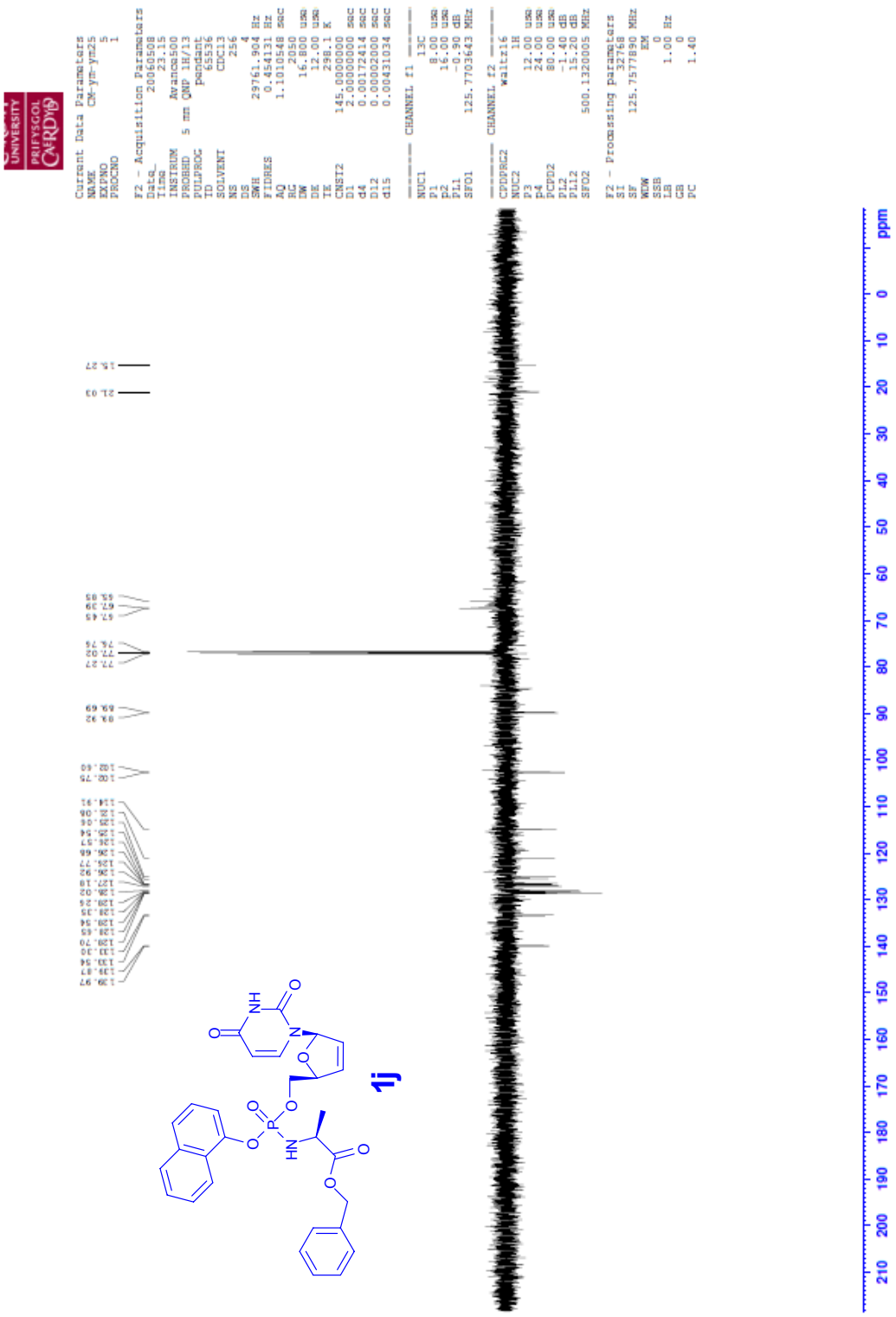

1h
ppm
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
8.5
9.0
NH
O
N
O
O
P
O
O
HN
O
O

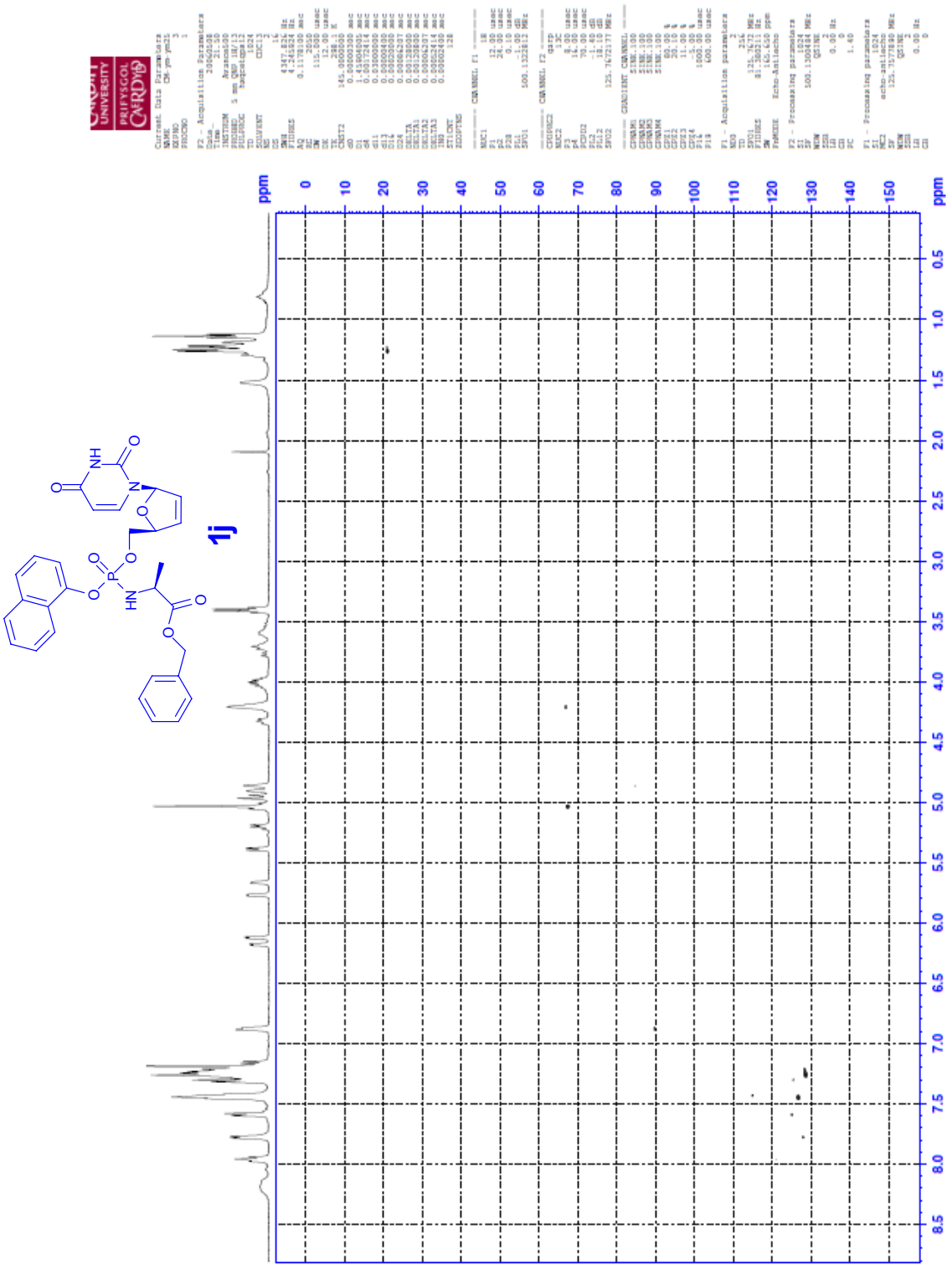

1j
ppm
15
10
5
0
-5
-10
-15

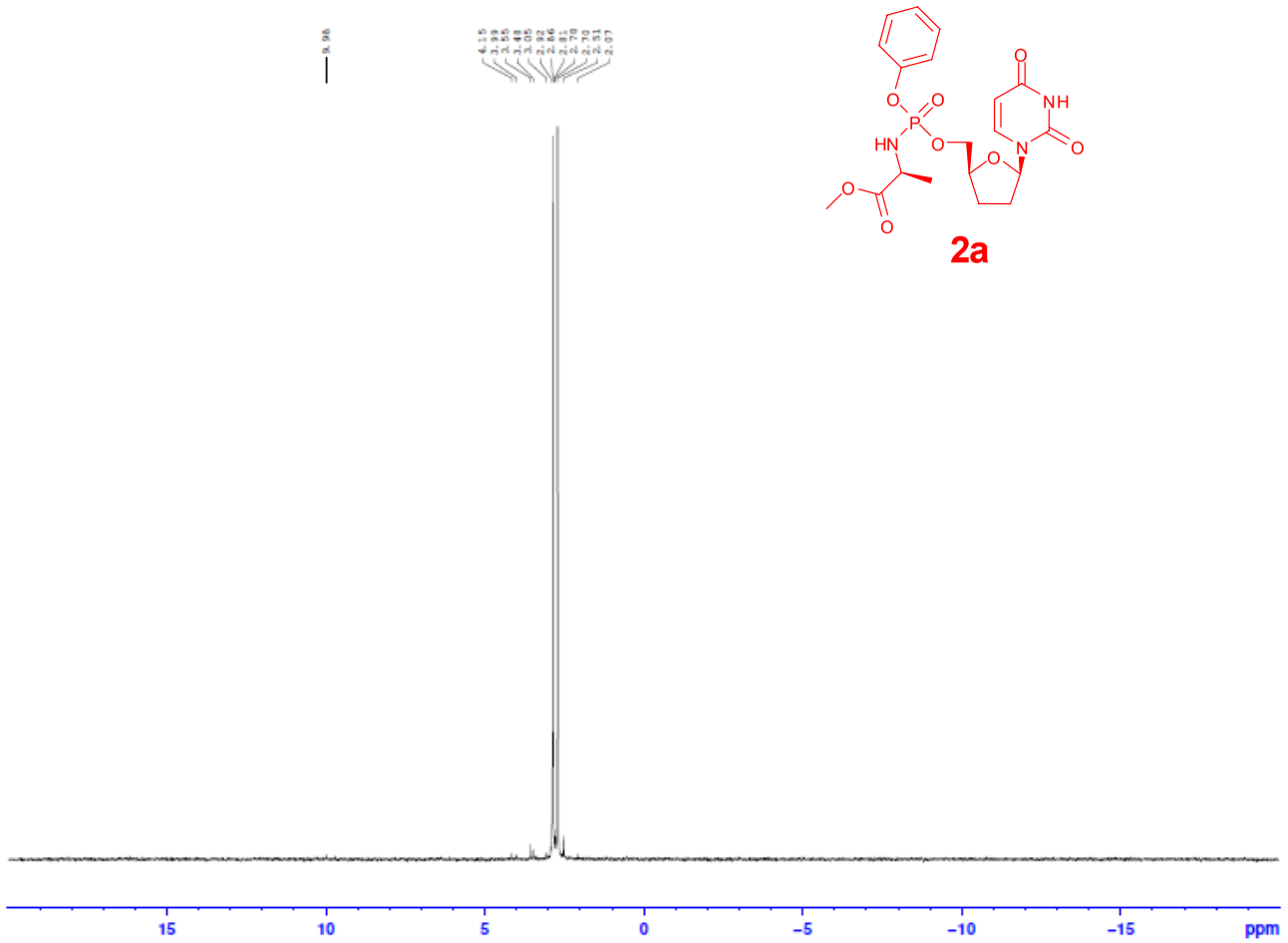

Current Data Parameters
NAME CM-ym-ym25
EXPNO 2
PROCNO 1
F2 - Acquisition Parameters
Data_ 20060508
Time 21.49
INSTRUM Avance500
PROBHD 5 mm QNP 1H/13
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 10330.578 Hz
FIDRES 0.157632 Hz
AQ 3.1719923 sec
RG 48.400
DW 48.400 usec
DE 12.00 usec
TE 298.1 K
D1 1.00000000 sec
TD0 1
CHANNEL f1
NUC1 1H
P1 12.00 usec
PL1 -1.00 dB
SFO1 500.1330885 MHz
F2 - Processing parameters
SI 32768
SF 500.1300484 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
ppm
1j




ppm
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
8.5
1j

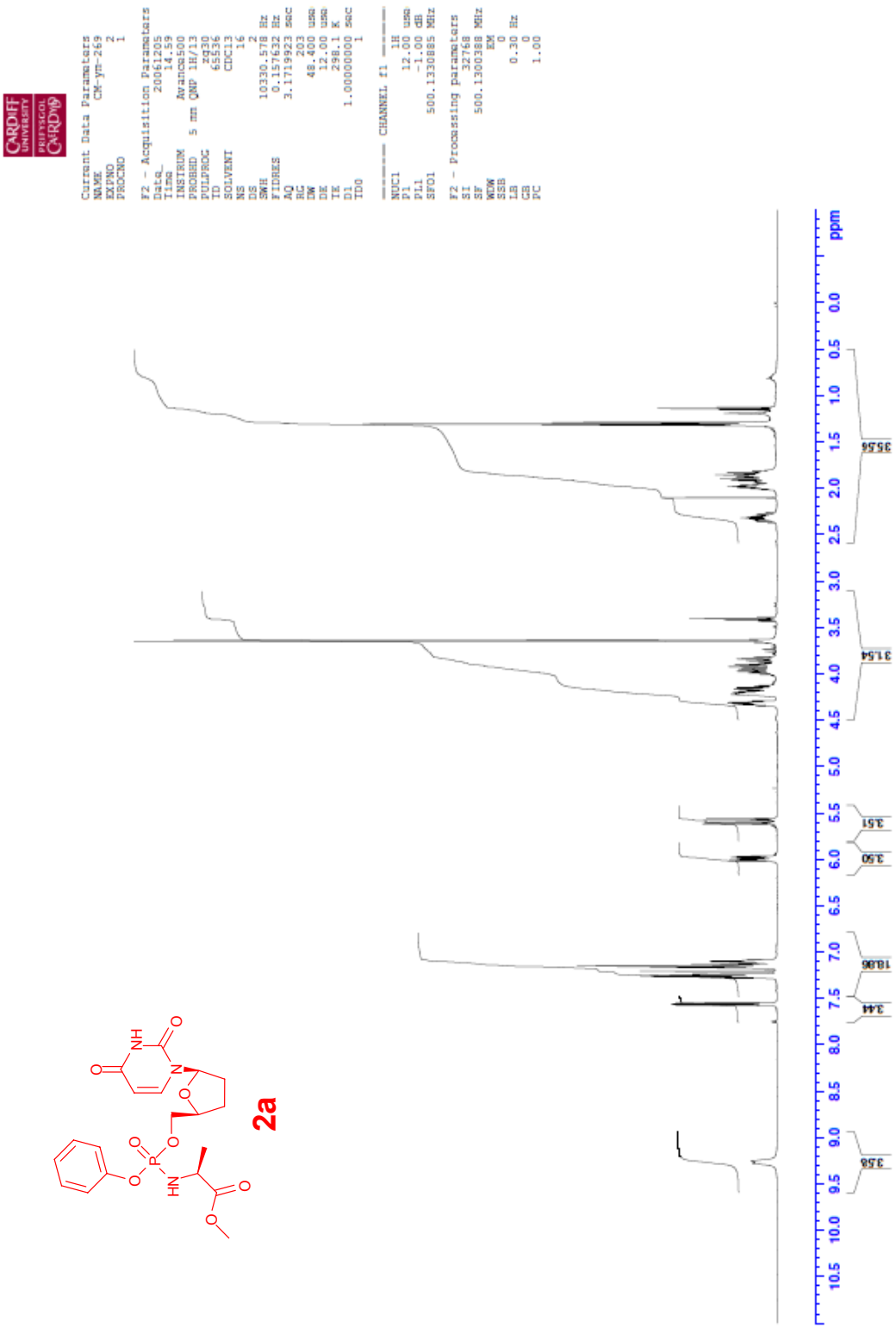

1j
ppm

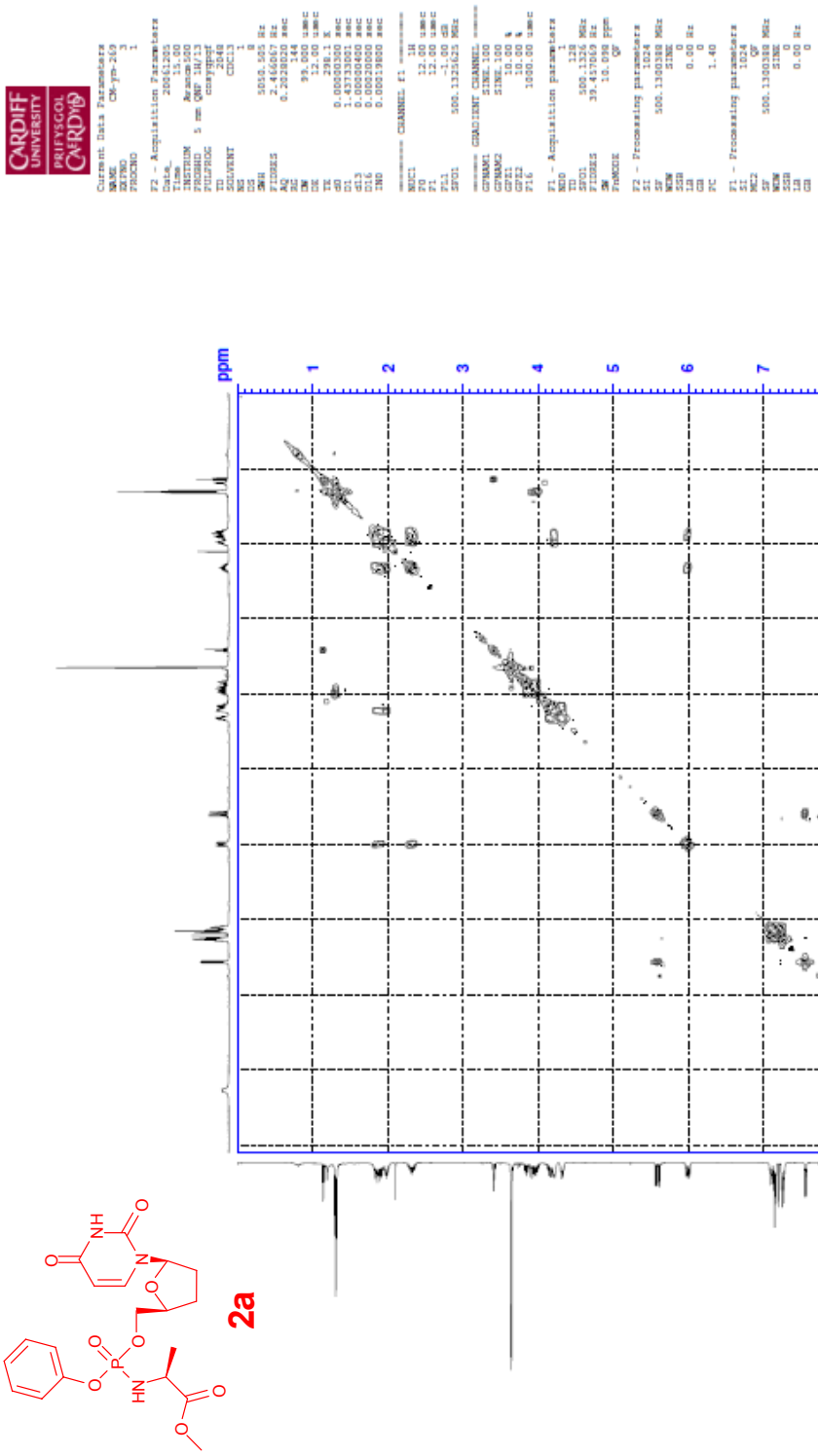

1j
ppm
ppm

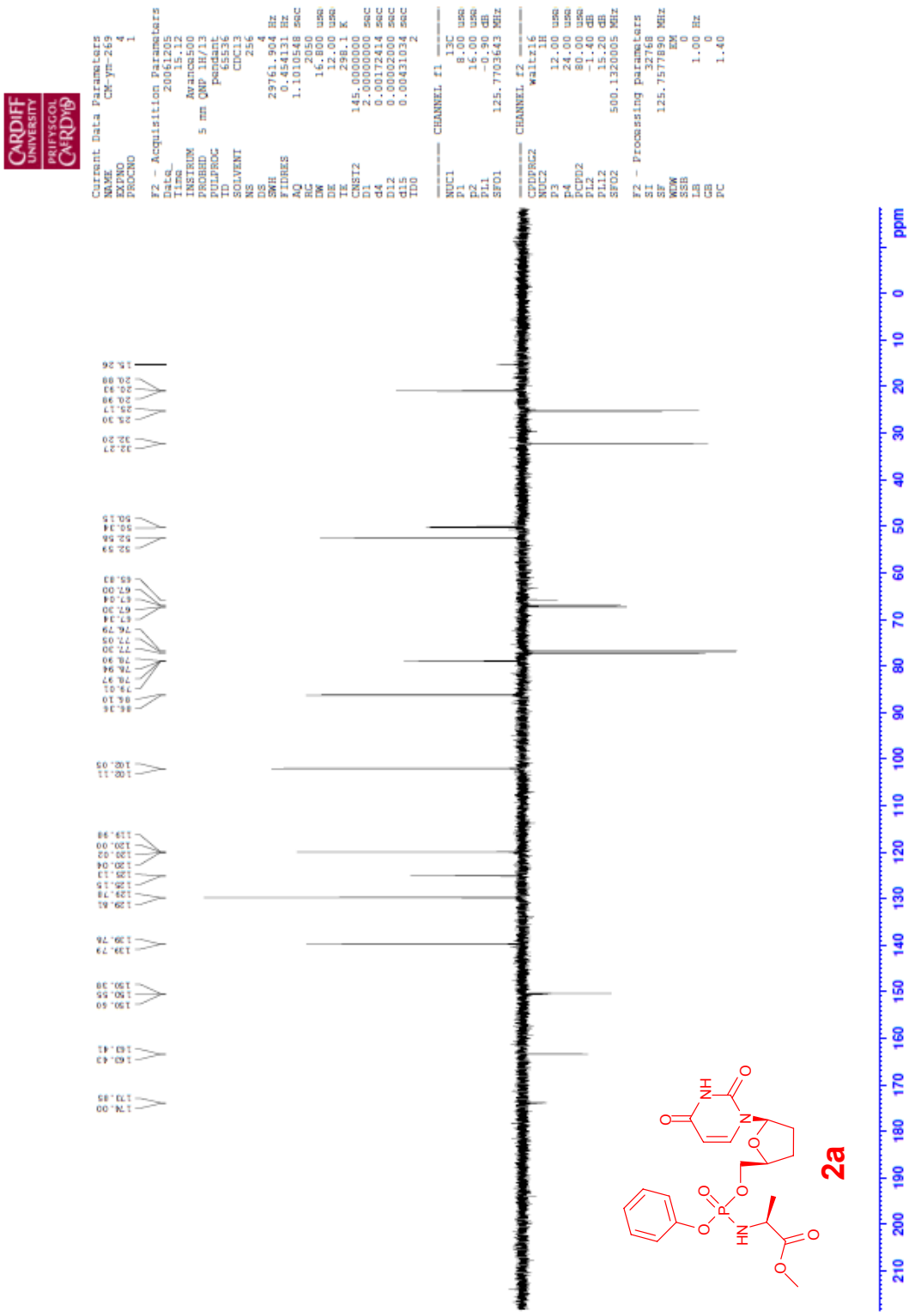


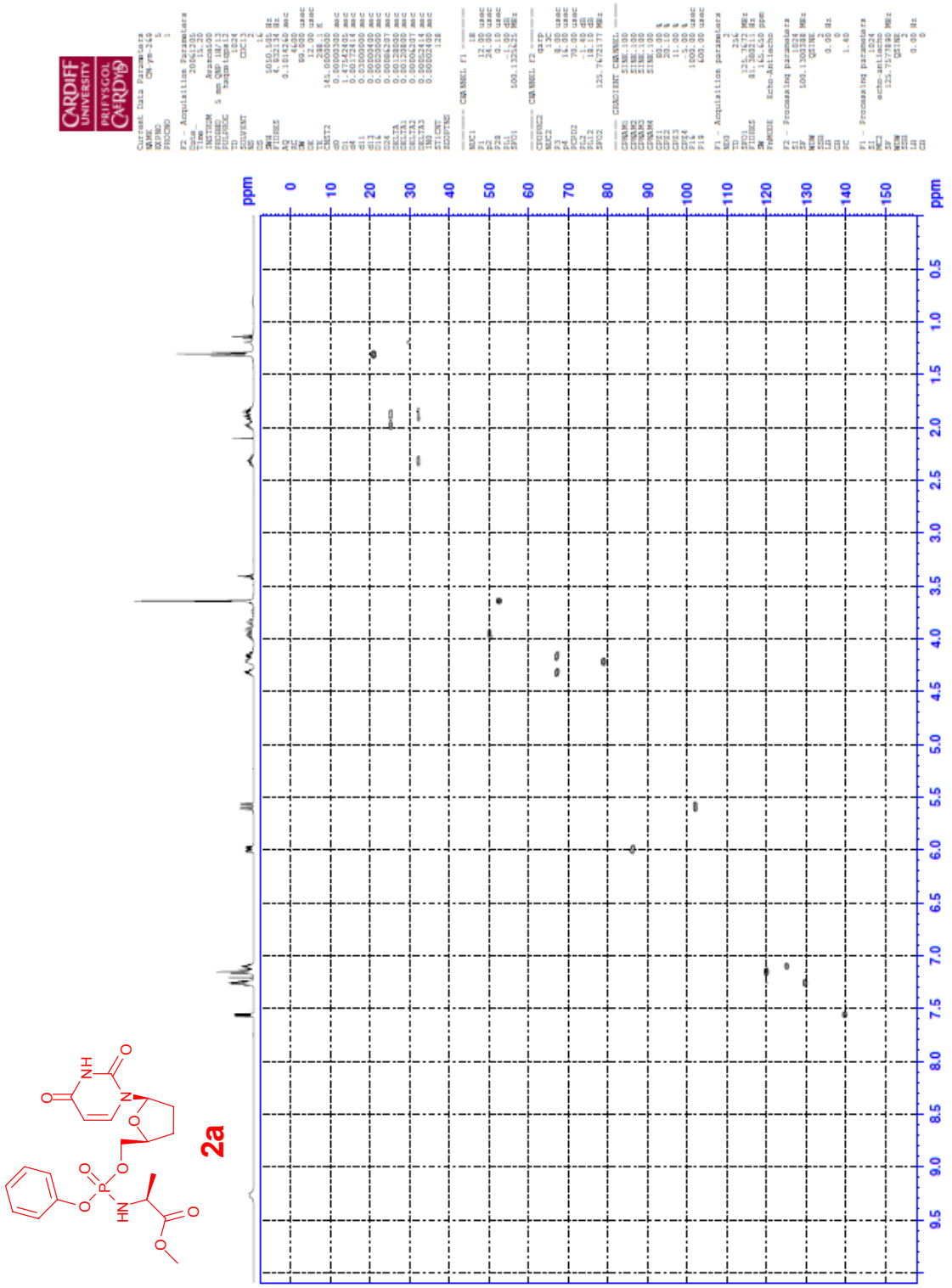
2a

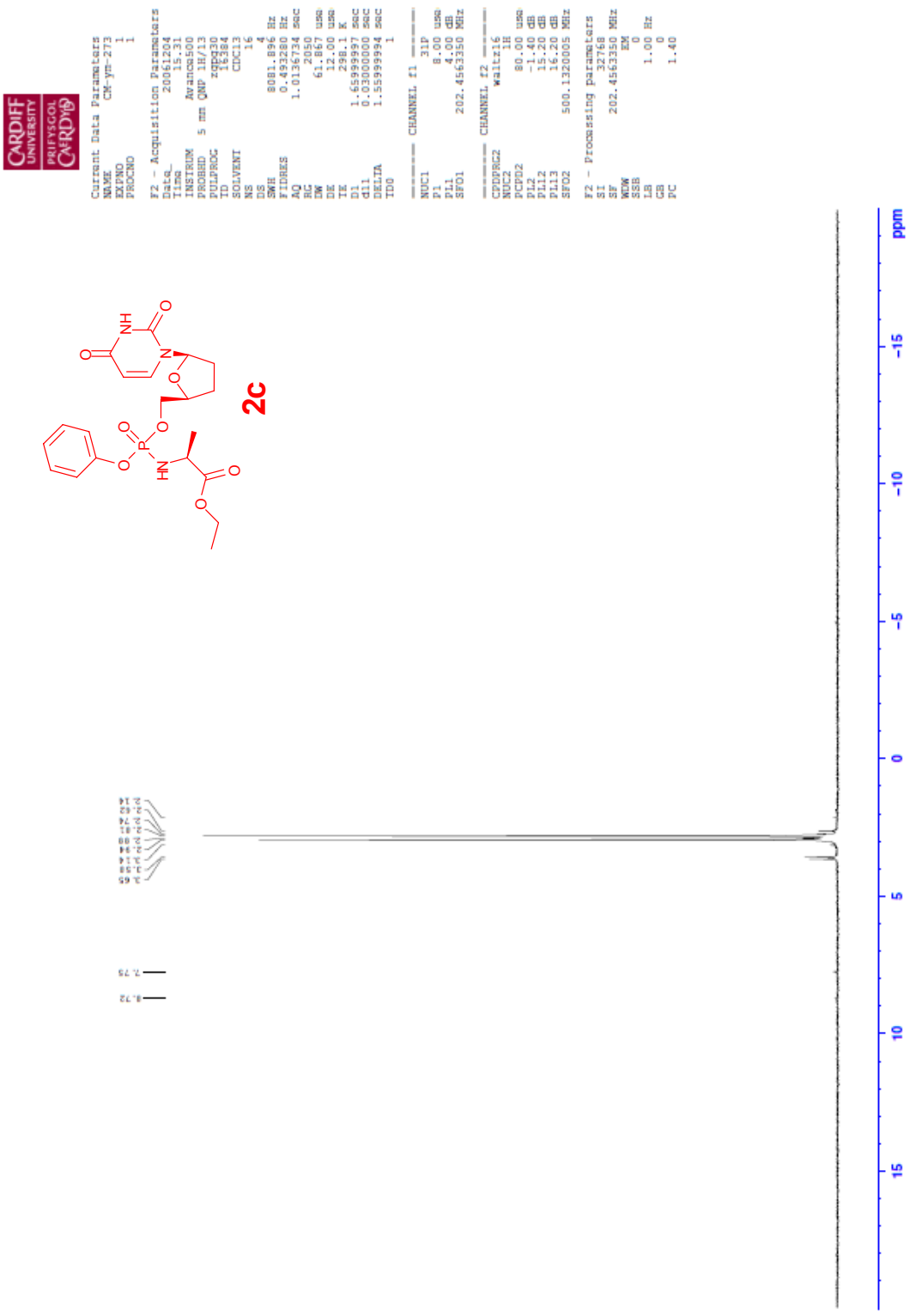
```
Current Data Parameters
NAME                  CM-ym-269
EXPNO                         1
PROCNO                        1

F2 - Acquisition Parameters
Data_                  20061205
Time                      14.47
INSTRUM                Avance500
PROBHD    5 mm QNP 1H/13
PULPROG                  zgpg30
TD                        16384
SOLVENT                   CDCl3
NS                           16
DS                            4
SWH                    8081.896 Hz
FIDRES                 0.493280 Hz
AQ                     1.0136734 sec
RG                         2050
DW                       61.867 usec
DE                       12.00 usec
TE                       298.1 K
D1                     1.65999997 sec
d11                    0.03000000 sec
DELTA                  1.55999994 sec
TD0                           1

======== CHANNEL f1 ========
NUC1                        31P
P1                         8.00 usec
PL1                        4.00 dB
SFO1                202.4563350 MHz

======== CHANNEL f2 ========
CPDPRG2                 waltz16
NUC2                        1H
PCPD2                     80.00 usec
PL2                       -1.40 dB
PL12                      15.20 dB
PL13                      16.20 dB
SFO2                500.1320005 MHz

F2 - Processing parameters
SI                         32768
SF                  202.4563350 MHz
WDW                           EM
SSB                            0
LB                          1.00 Hz
GB                             0
PC                          1.40
```

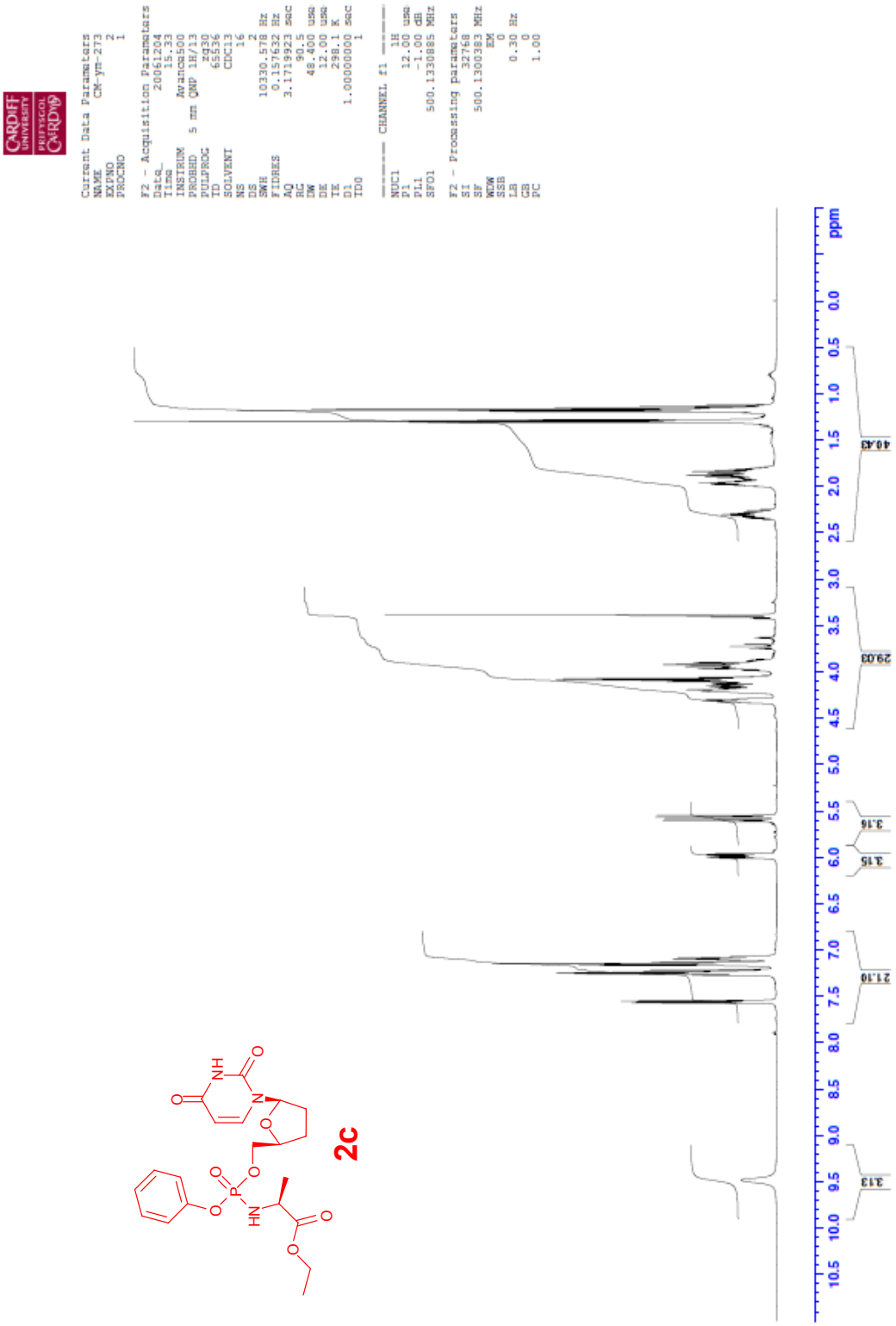

Current Data Parameters
NAME CM-ym-269
EXPNO 2
PROCNO 1
F2 - Acquisition Parameters
Date_ 20091205
Time 14.55
INSTRUM Avance500
PROBHD 5 mm QNP 1H/13
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 10330.578 Hz
FIDRES 0.157632 Hz
AQ 3.1719923 sec
RG 203
DW 48.400 usec
DE 12.00 usec
TE 298.1 K
D1 1.00000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 1H
P1 12.00 usec
PL1 -1.00 dB
SFO1 500.1330885 MHz
F2 - Processing parameters
SI 32768
SF 500.1300388 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
3.58
31.54
3.51
3.50
18.86
3.44
3.58
ppm
2a

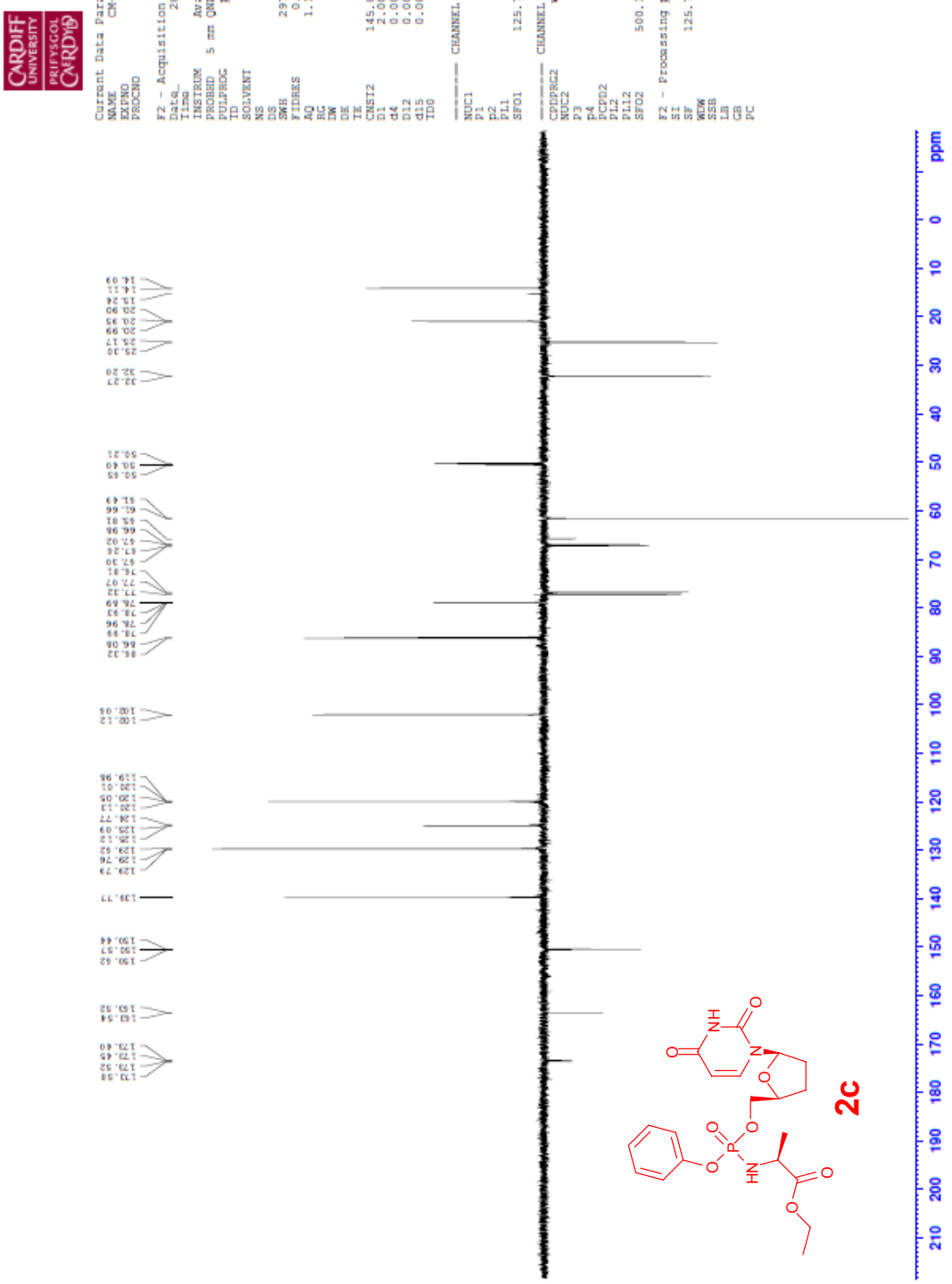

ppm
1
2
3
4
5
6
7
8
9
10
2a

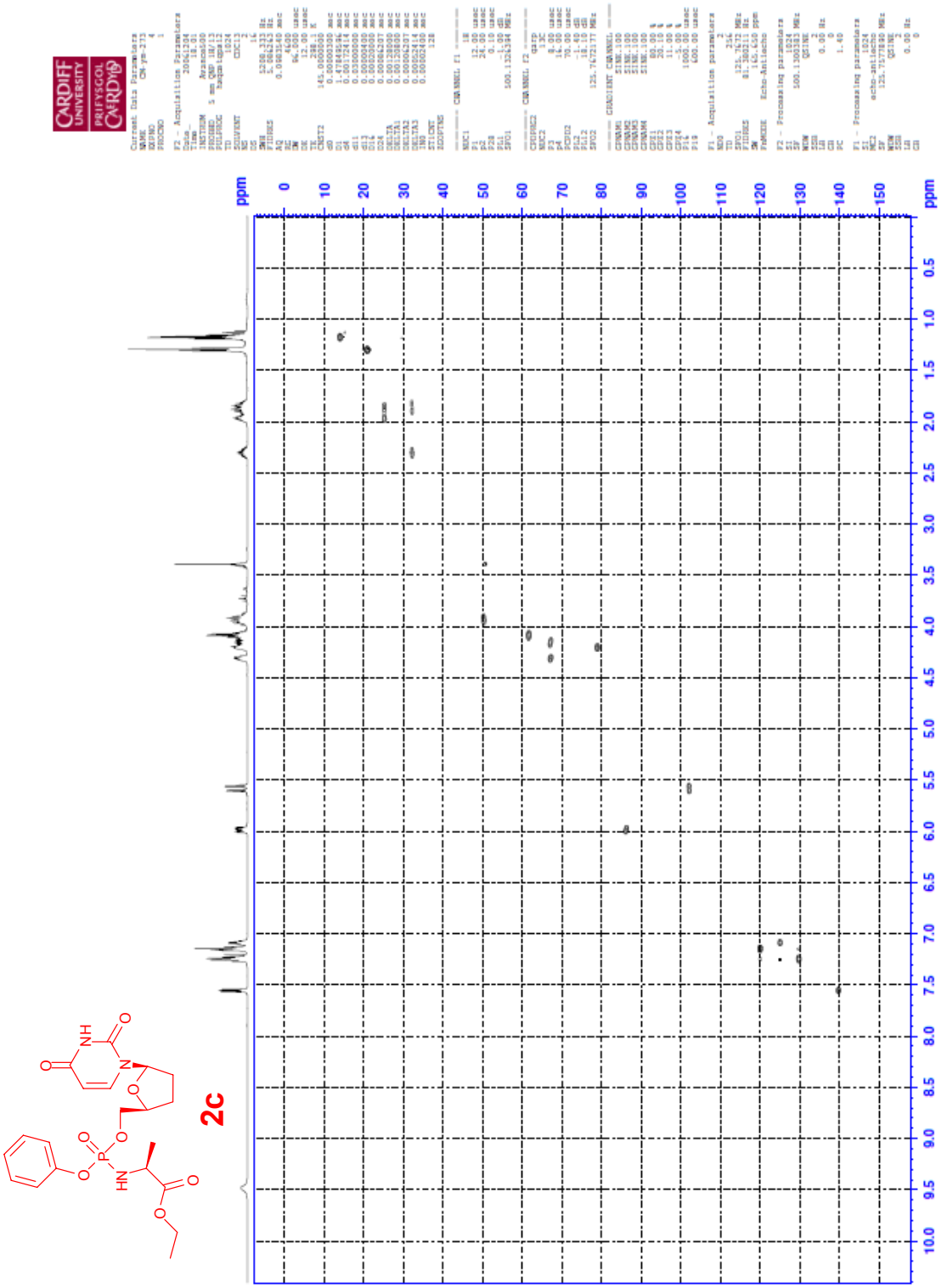

2a
ppm

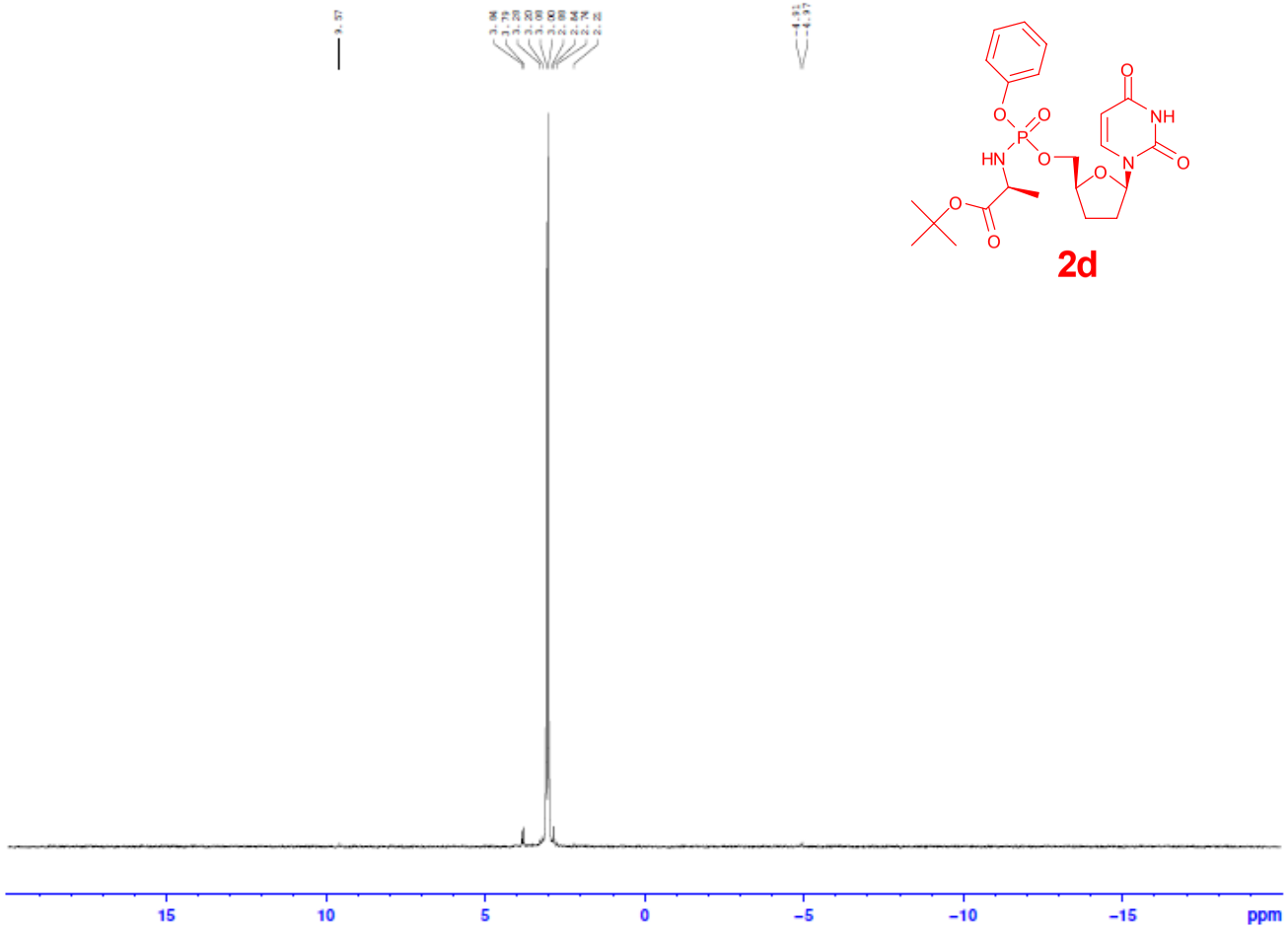

2a
ppm


CARDIFF UNIVERSITY
PRIFYSGOL CAERDYDD
Current Data Parameters
NAME CM-ys-273
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20061204
Time 15.31
INSTRUM Avance500
PROBHD 5 mm QNP 1H/13
PULPROG zgpg30
TD 65384
SOLVENT CDCl3
NS 16
DS 4
SWH 8081.896 Hz
FIDRES 0.493280 Hz
AQ 1.0136734 sec
RG 2050
DW 61.867 usec
DE 12.00 usec
TE 298.1 K
D1 1.65999997 sec
d11 0.03000000 sec
DELTA 1.55999994 sec
TD0 1
CHANNEL f1
NUC1 31P
P1 8.00 usec
PL1 4.00 dB
SFO1 202.4563350 MHz
CHANNEL f2
CPDPRG2 waltz16
NUC2 1H
PCPD2 80.00 usec
PL2 -1.40 dB
PL12 15.20 dB
PL13 16.20 dB
SFO2 500.1320005 MHz
F2 - Processing parameters
SI 32768
SF 202.4563350 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
2c
ppm

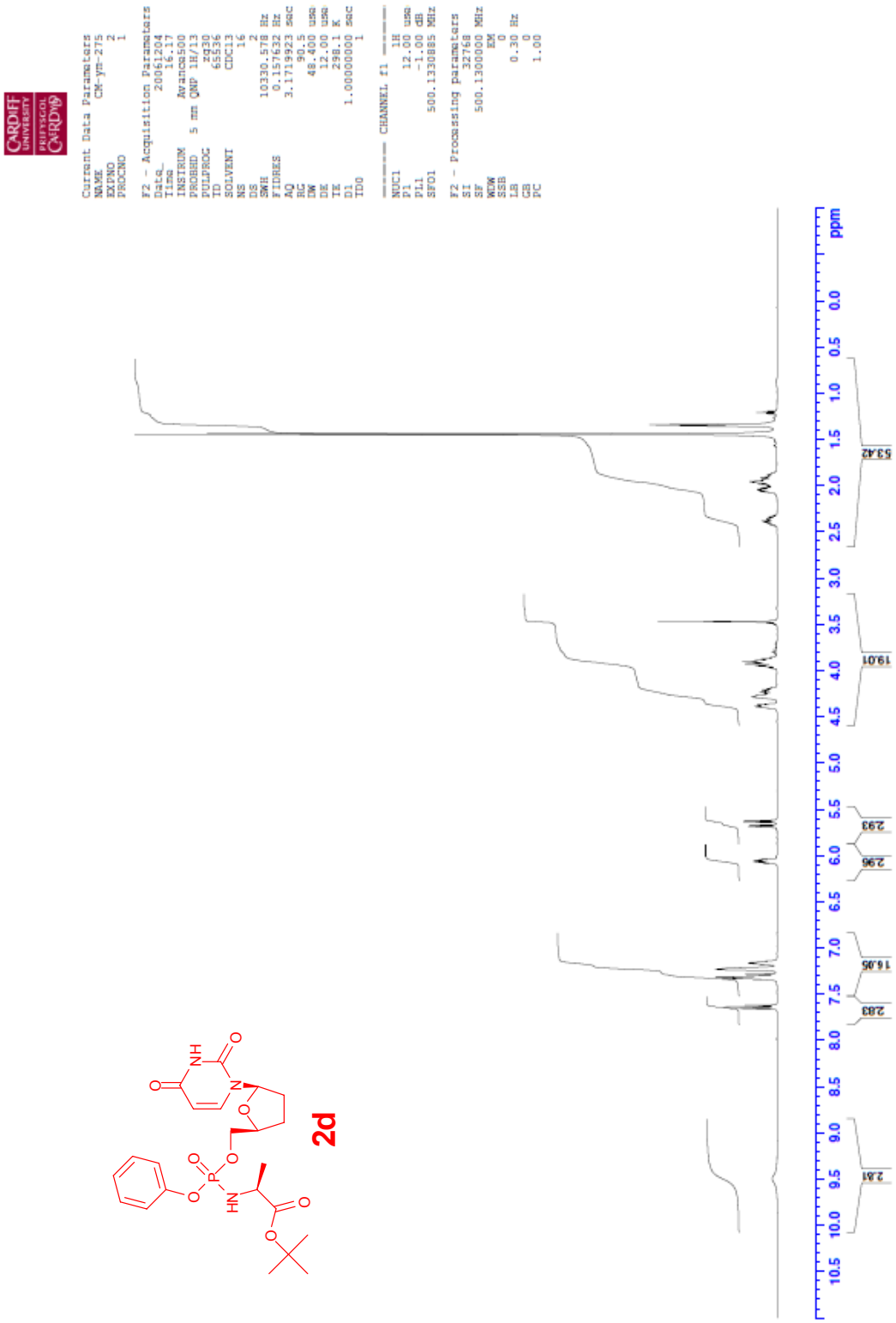

Current Data Parameters
NAME CM-ym-273
EXPNO 2
PROCNO 1
F2 - Acquisition Parameters
Date_ 20061204
Time 11.33
INSTRUM Avance500
PROBHD 5 mm QNP 1H/13
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 10330.578 Hz
FIDRES 0.157632 Hz
AQ 3.1719923 sec
RG 90.5
DW 48.400 usec
DE 12.00 usec
TE 298.1 K
D1 1.00000000 sec
TD0 1
CHANNEL f1
NUC1 1H
P1 12.00 usec
PL1 -1.00 dB
SFO1 500.1330885 MHz
F2 - Processing parameters
SI 32768
SF 500.1300383 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
10.43
29.03
3.16
3.15
21.10
3.13
ppm
2c

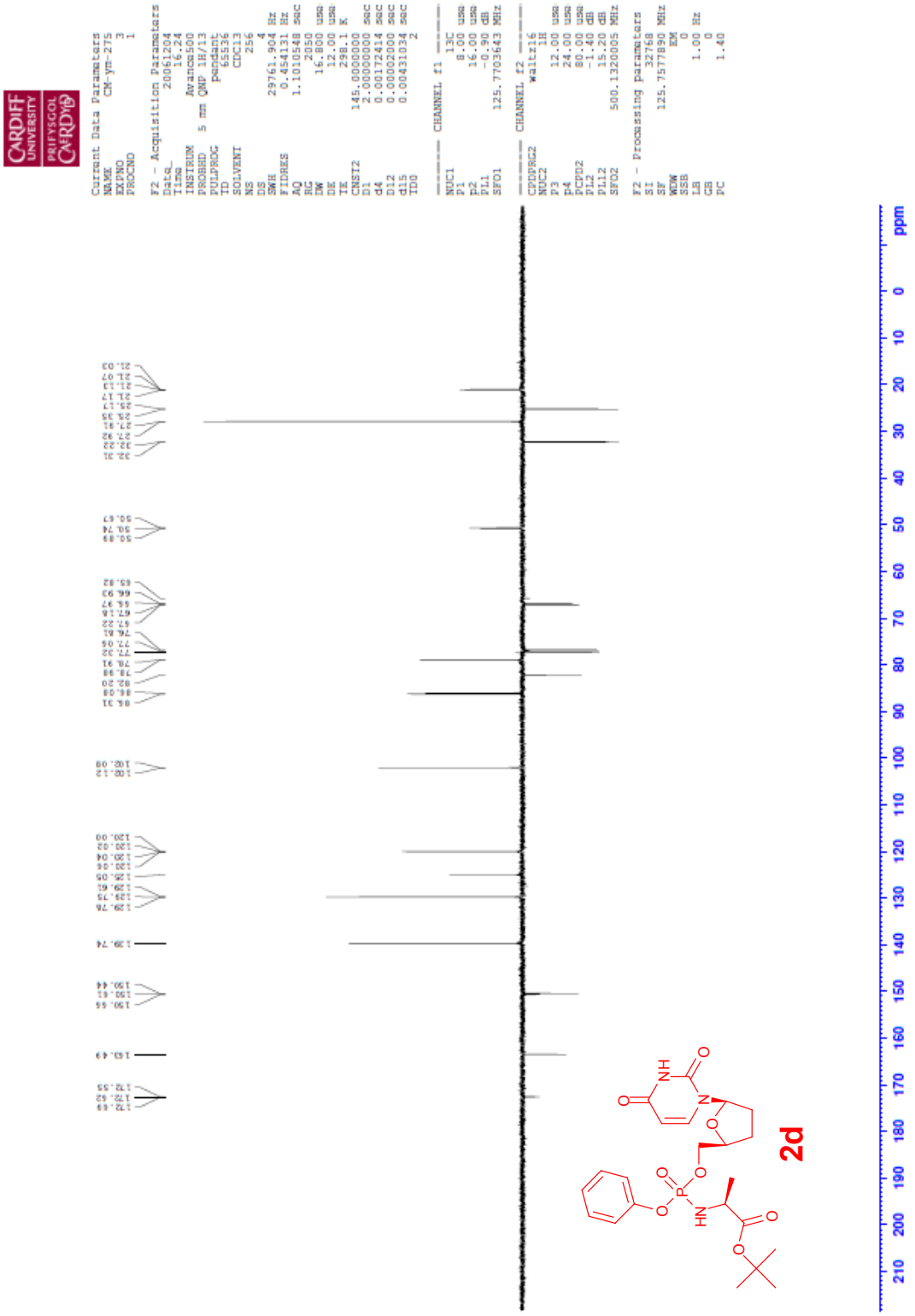

2c
ppm

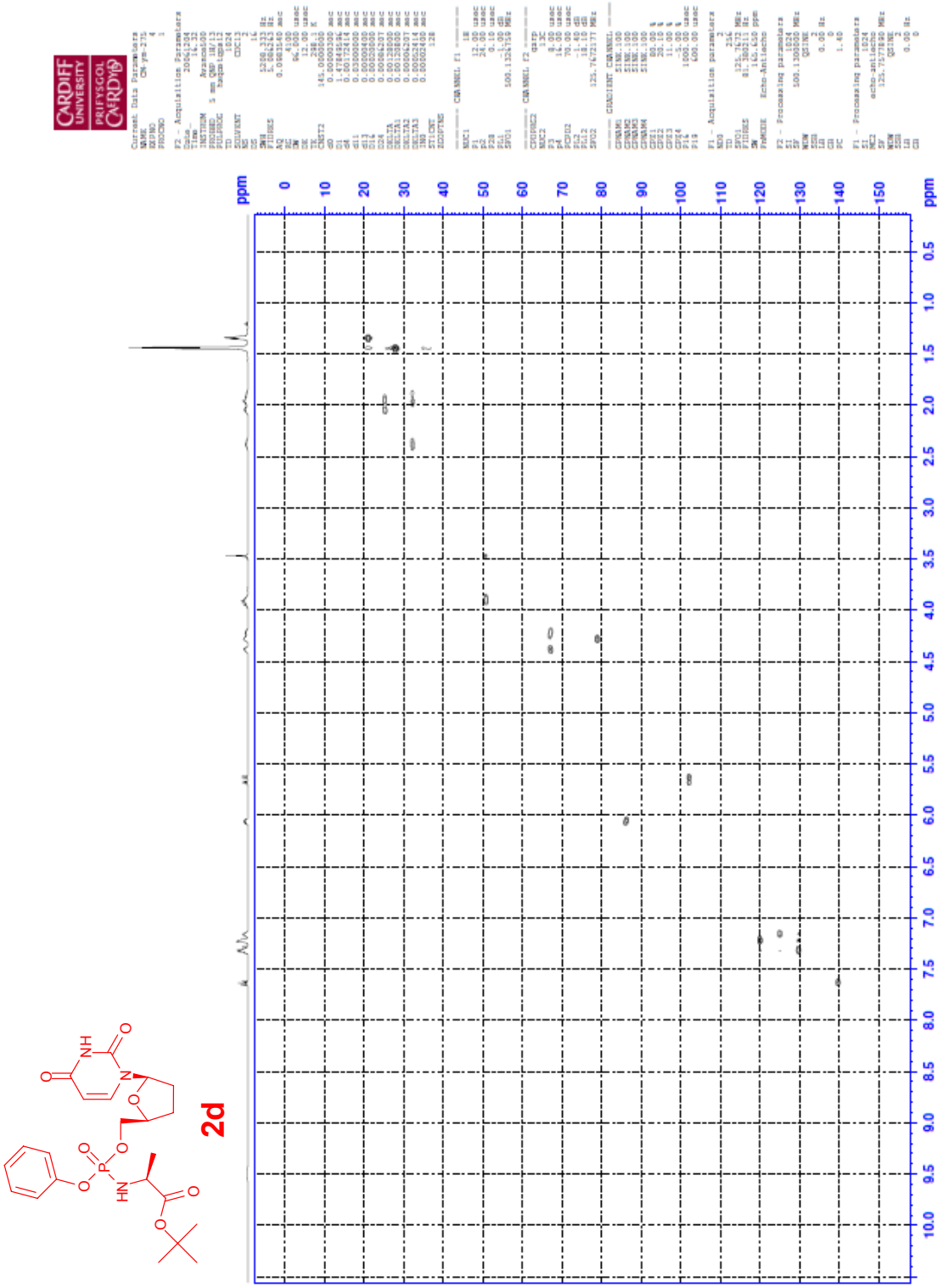

2c
ppm

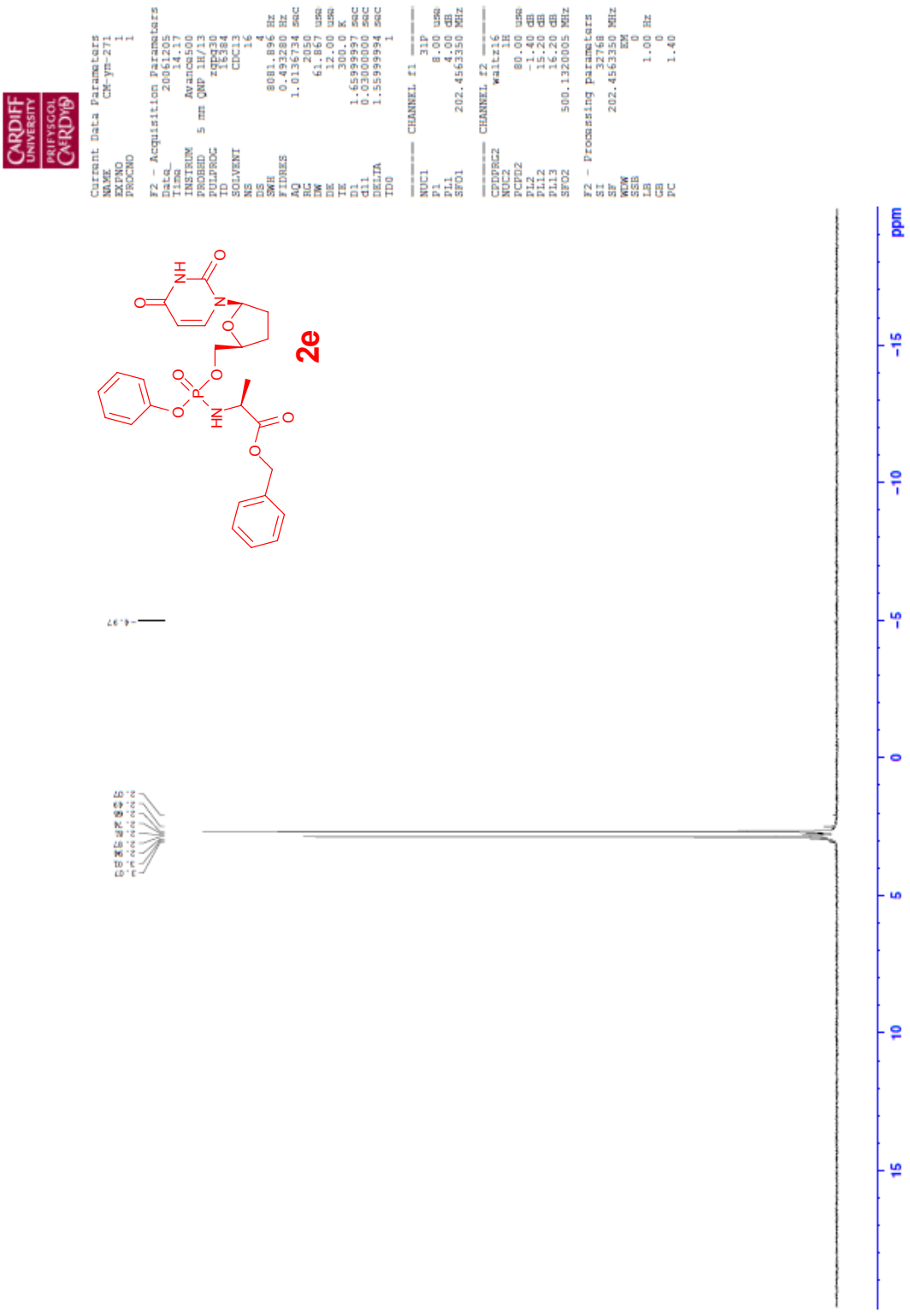


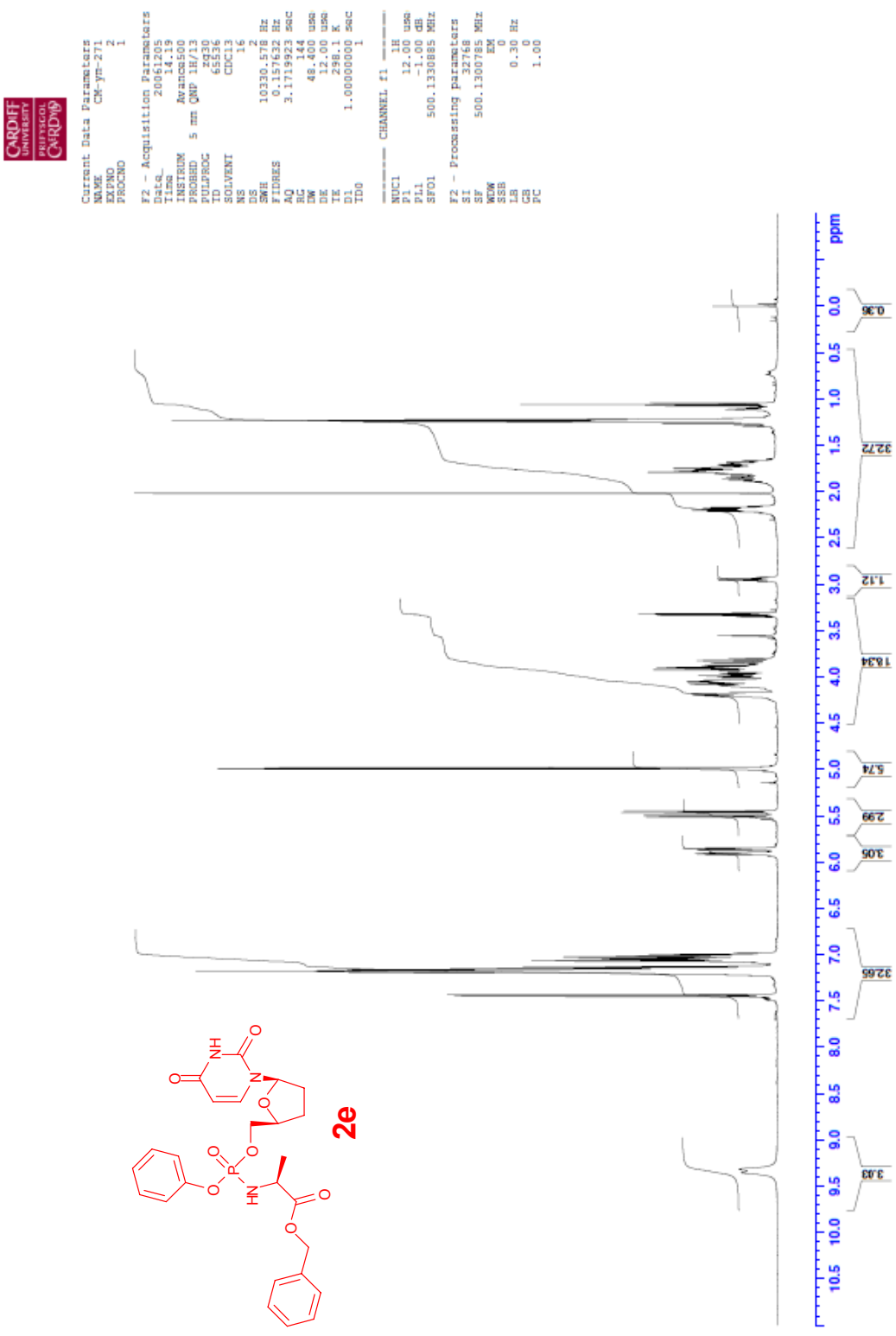

```
Current Data Parameters
NAME                  CM-ym-275
EXPNO                         1
PROCNO                        1

F2 - Acquisition Parameters
Date_              20061204
Time                   15.44
INSTRUM              Avance500
PROBHD    5 mm QNP 1H/13
PULPROG              zgpg30
TD                     16384
SOLVENT                CDCl3
NS                        16
DS                         4
SWH                 8081.896 Hz
FIDRES              0.493280 Hz
AQ                  1.0136734 sec
RG                      2050
DW                    61.867 usec
DE                    12.00 usec
TE                    298.1 K
D1                  1.65999997 sec
d11                 0.03000000 sec
DELTA               1.55999994 sec
TD0                           1

======== CHANNEL f1 ========
NUC1                      31P
P1                      8.00 usec
PL1                     4.00 dB
SFO1             202.4563350 MHz

======== CHANNEL f2 ========
CPDPRG2                waltz16
NUC2                       1H
PCPD2                  80.00 usec
PL2                    -1.40 dB
PL12                   15.20 dB
PL13                   16.20 dB
SFO2             500.1320005 MHz

F2 - Processing parameters
SI                        32768
SF               202.4563350 MHz
WDW                          EM
SSB                           0
LB                     1.00 Hz
GB                            0
PC                     1.40
```

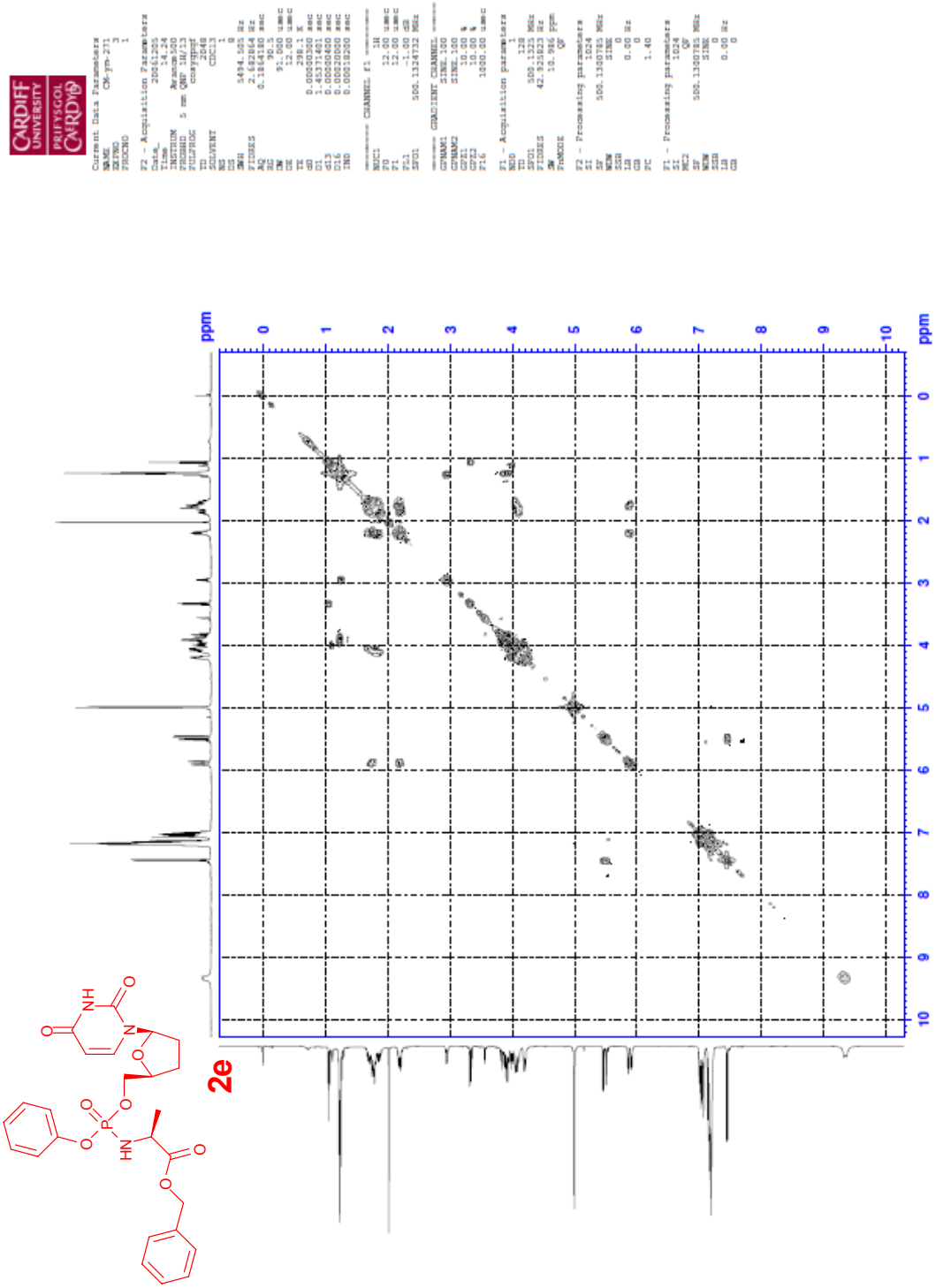

CARDIFF UNIVERSITY
PRIFYSGOL CAERDYDD
Current Data Parameters
NAME CM-ym-275
EXPNO 2
PROCNO 1
F2 - Acquisition Parameters
Date_ 20061204
Time 16.17
INSTRUM Avance500
PROBHD 5 mm QNP 1H/13
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 10330.578 Hz
FIDRES 0.157652 Hz
AQ 3.1719923 sec
RG 90.5
DW 48.400 usec
DE 12.00 usec
TE 298.1 K
D1 1.00000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 1H
P1 12.00 usec
PL1 -1.00 dB
SFO1 500.1330885 MHz
F2 - Processing parameters
SI 32768
SF 500.1300000 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
5342
1901
293
296
1605
283
281
ppm
2d

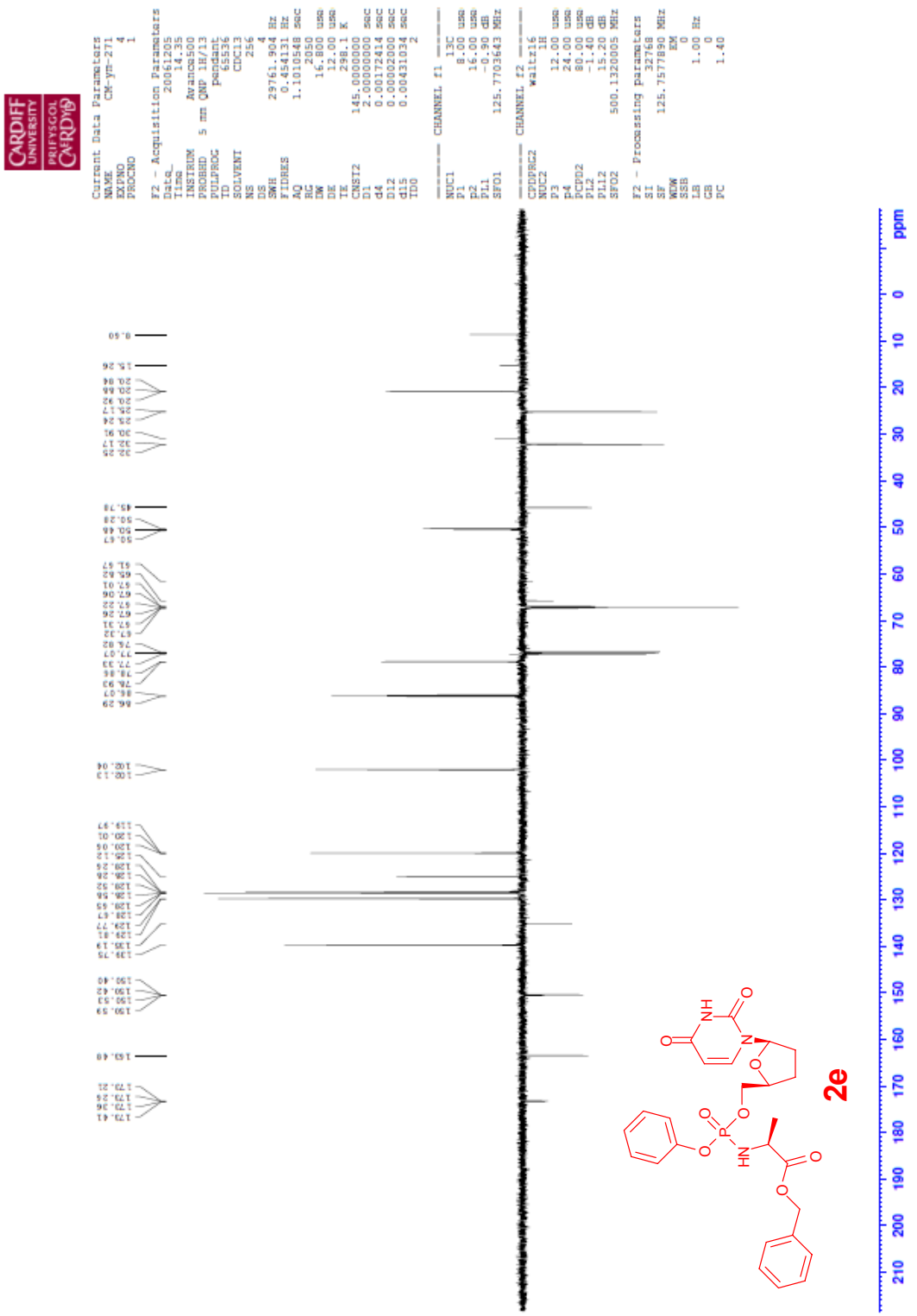

CARDIFF UNIVERSITY
PRIFYSGOL CAERDYDD
Current Data Parameters
NAME CM-yn-275
EXPNO 3
PROCNO 1
F2 - Acquisition Parameters
Date_ 20061204
Time 16.24
INSTRUM Avance500
PROBHD 5 mm QNP 1H/13
PULPROG zgpgdtc
TD 65536
SOLVENT CDCl3
NS 256
DS 4
SWH 29761.904 Hz
FIDRES 0.454131 Hz
AQ 1.1010648 sec
RG 2050
DW 16.800 usec
DE 12.00 usec
TE 298.1 K
CNST2 145.0000000
D1 2.0000000000 sec
d4 0.0017241 sec
D12 0.0000020000 sec
d15 0.0043103 sec
TD0 2
CHANNEL f1
NUC1 13C
P1 8.00 usec
p2 16.00 usec
PL1 -0.90 dB
SFO1 125.7703643 MHz
CHANNEL f2
CPDPRG2 waltz16
NUC2 1H
P3 12.00 usec
p4 24.00 usec
PCPD2 80.00 usec
PL2 -1.40 dB
PL12 15.20 dB
SFO2 500.1320005 MHz
F2 - Processing parameters
SI 32768
SF 125.7577890 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
2d
ppm

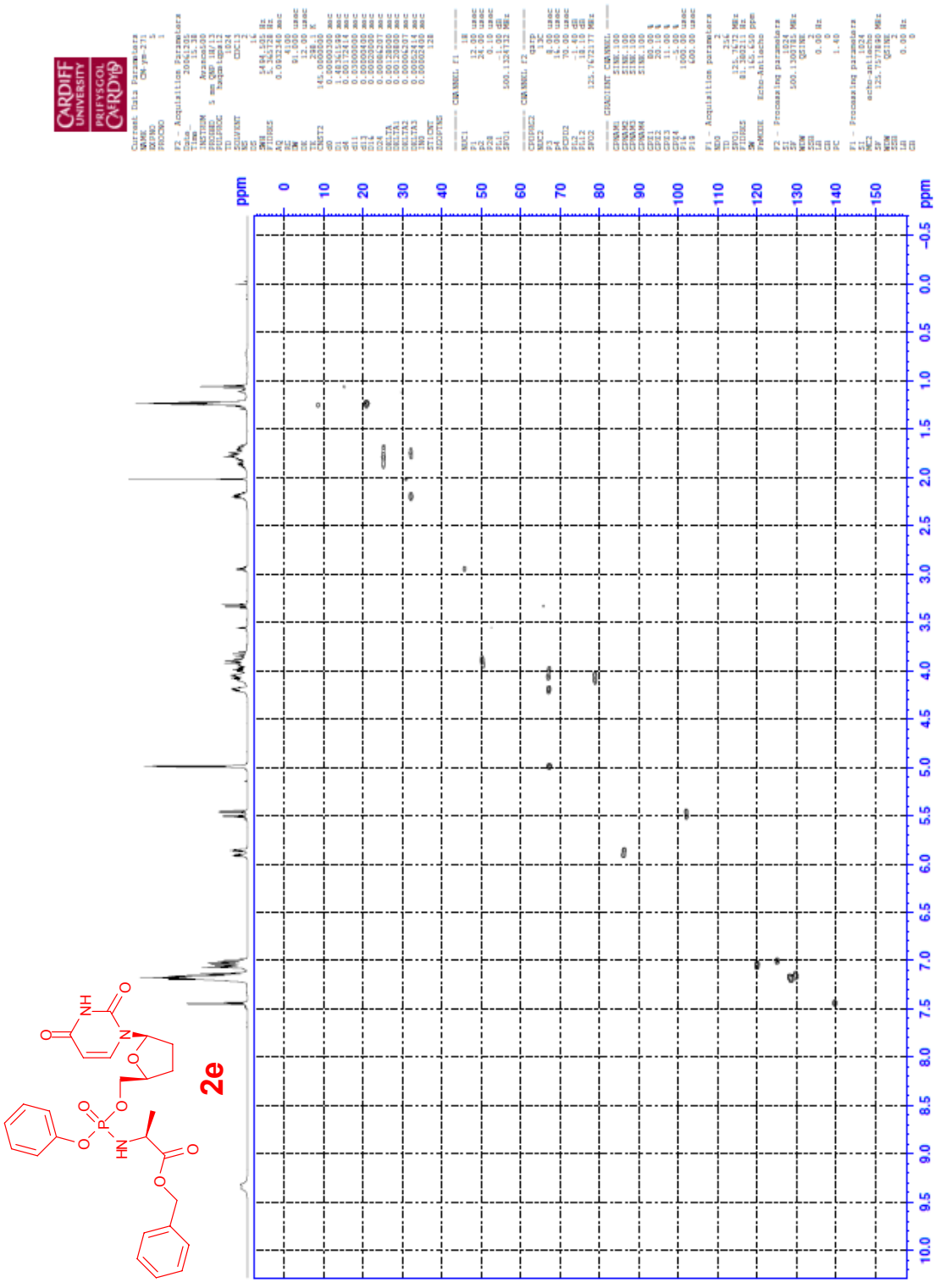

2d

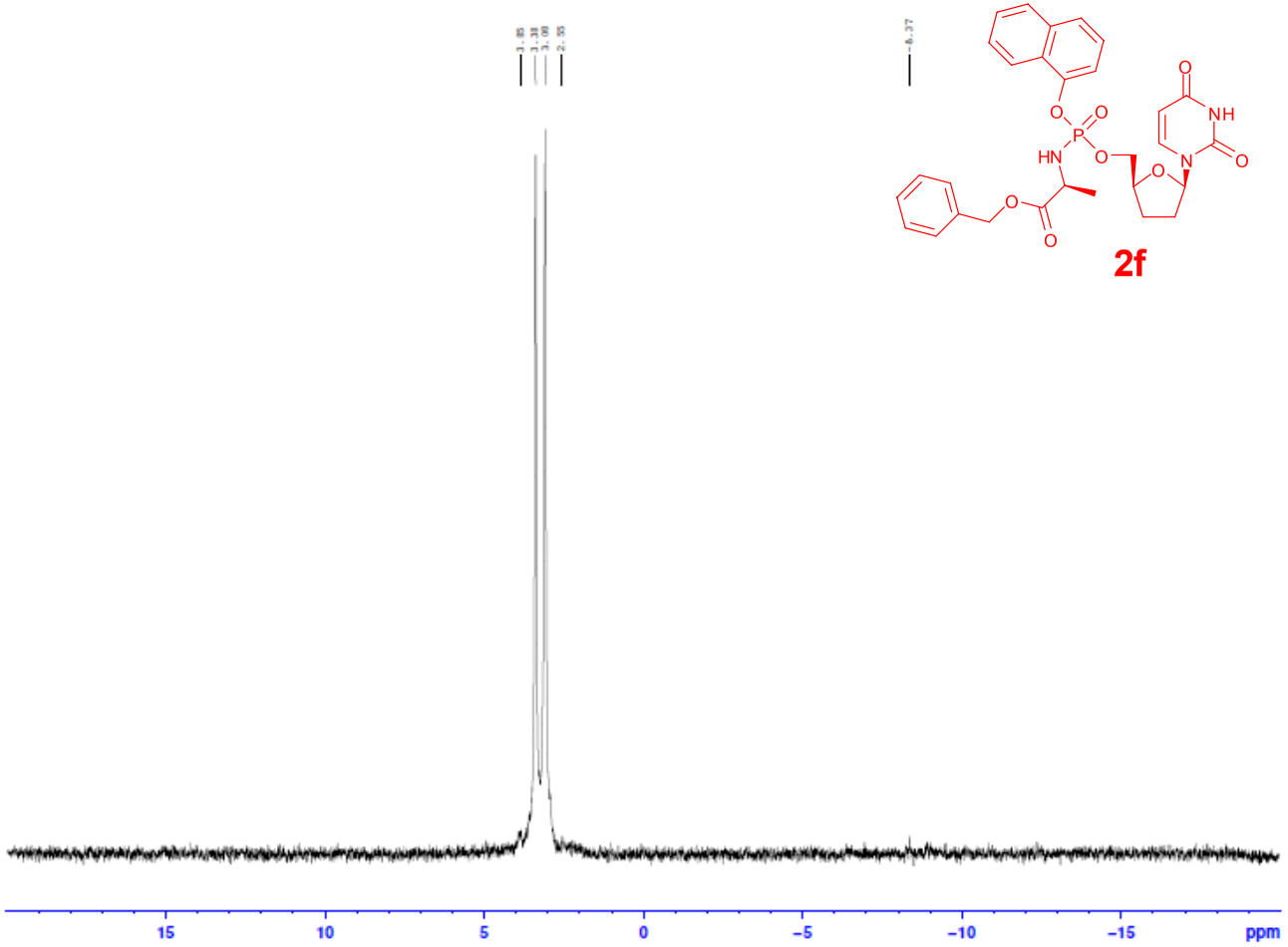

2e
ppm
15
10
5
0
-5
-10
-15


Current Data Parameters
NAME CM-ym-271
EXPNO 2
PROCNO 1
F2 - Acquisition Parameters
Data_ 20061205
Time 14.19
INSTRUM Avance500
PROBHD 5 mm QNP 1H/13
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 10330.578 Hz
FIDRES 0.157622 Hz
AQ 3.1719923 sec
RG 7.14
DW 48.400 usec
DE 12.00 usec
TE 298.1 K
D1 1.00000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 1H
P1 12.00 usec
PL1 -1.00 dB
SFO1 500.1330885 MHz
F2 - Processing parameters
SI 32768
SF 500.1300785 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
ppm
0.36
32.72
11.12
16.34
5.74
2.99
3.05
32.65
3.03
2e


2e
ppm
ppm

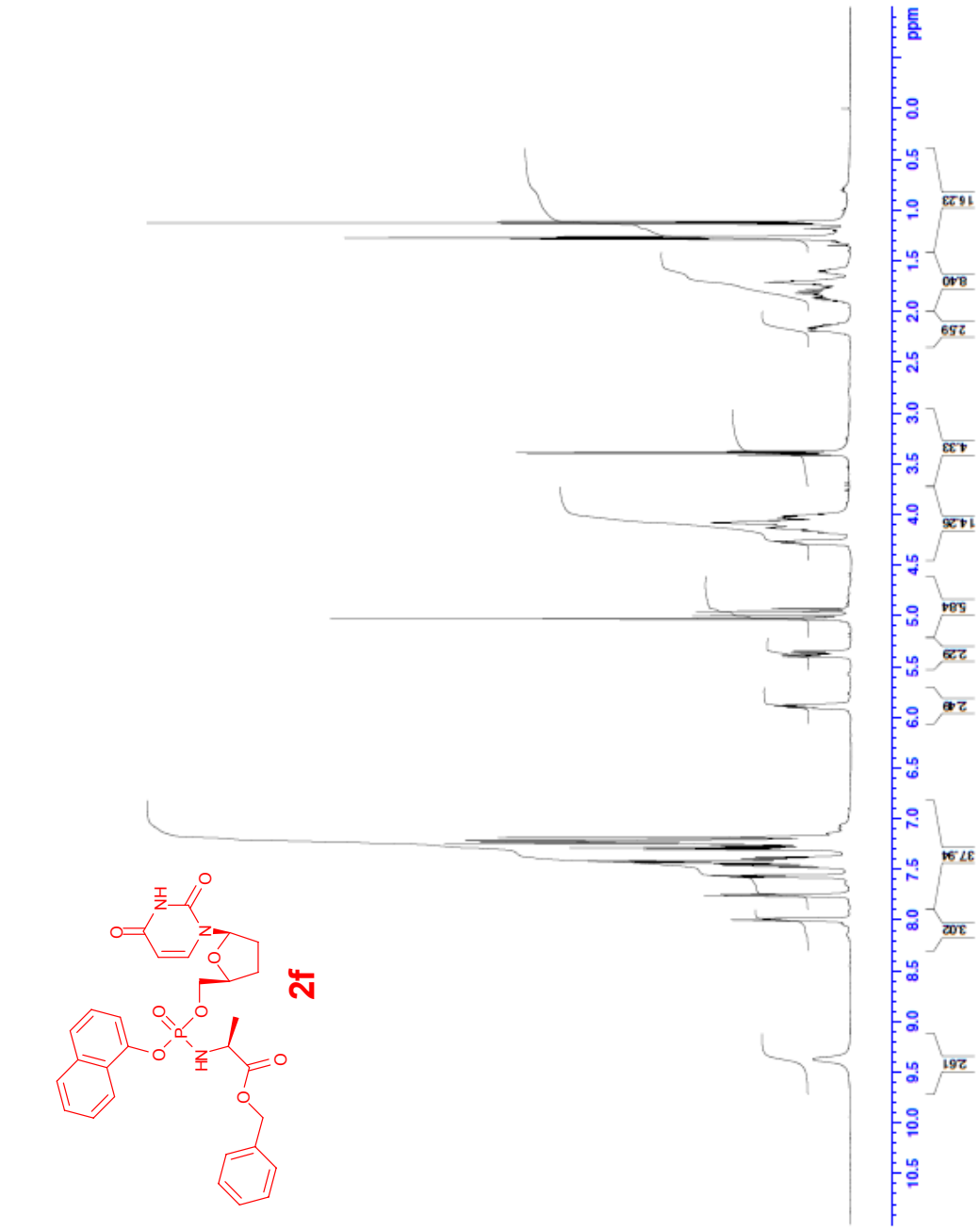

2e
ppm

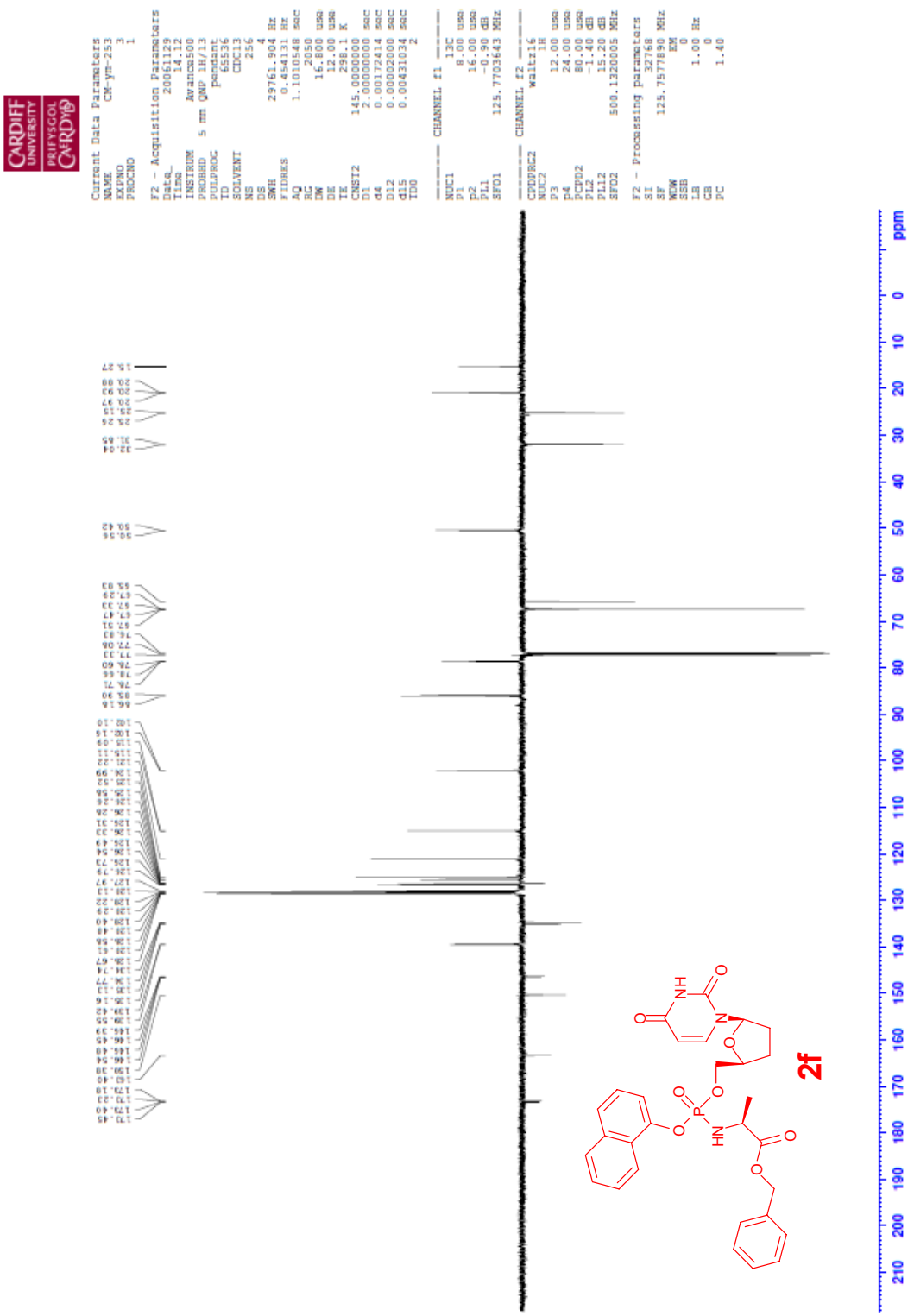

2e
ppm

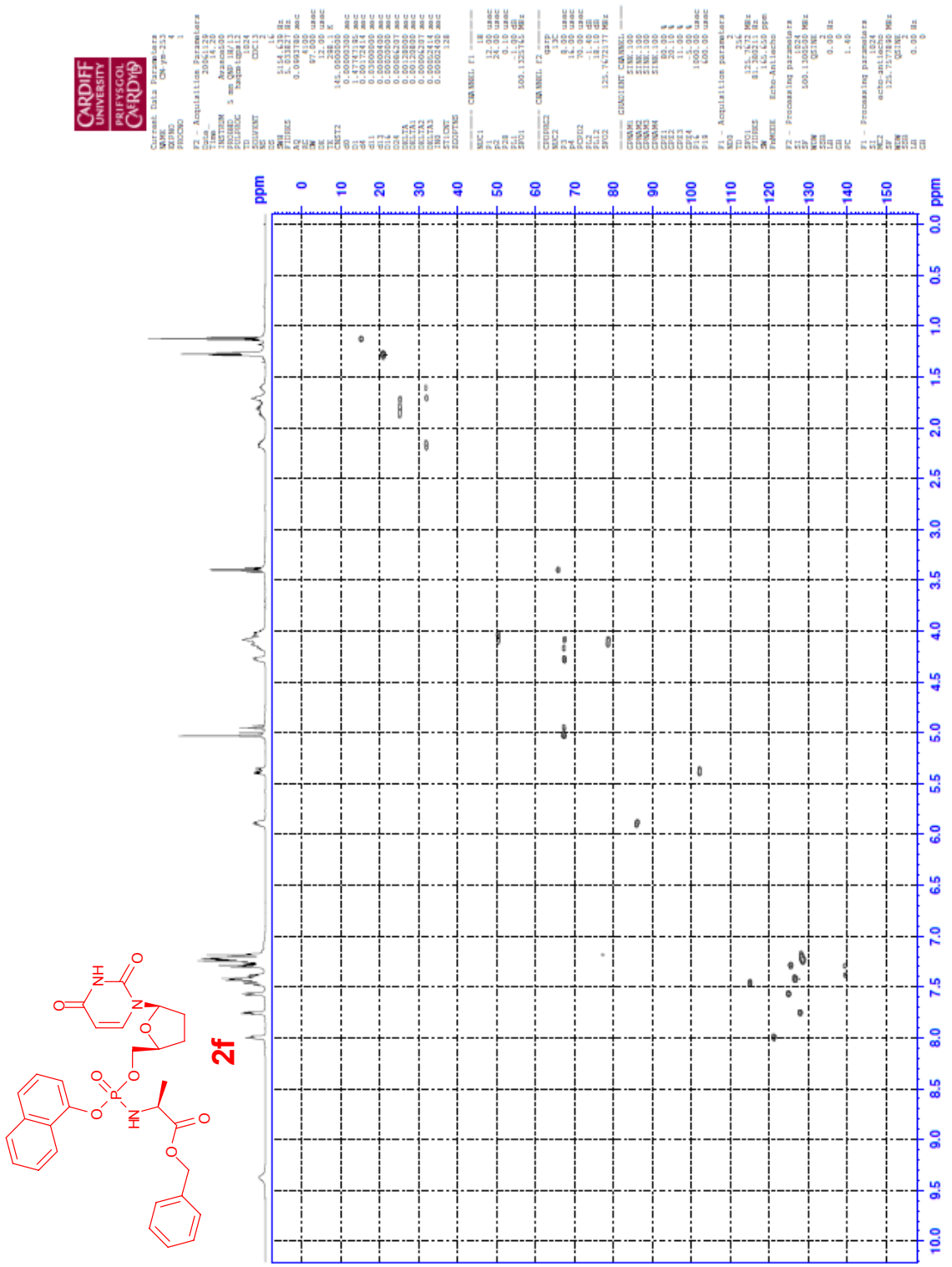


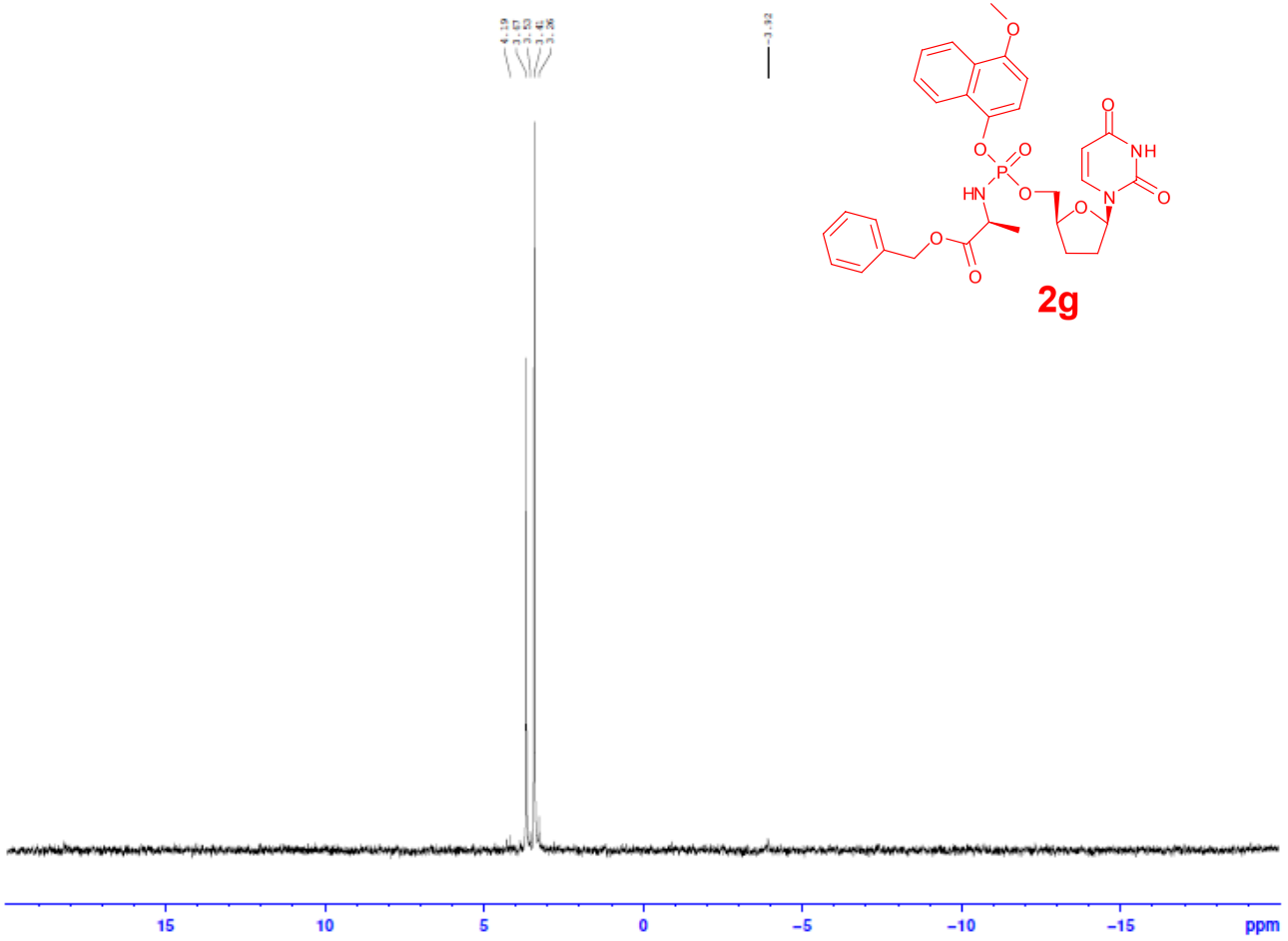
2f

```
Current Data Parameters
NAME                  CM-ym-253
EXPNO                         1
PROCNO                        1

F2 - Acquisition Parameters
Date_                  20061129
Time                      13.26
INSTRUM                Avance500
PROBHD    5 mm QNP 1H/13
PULPROG                  zgpg30
TD                        16384
SOLVENT                   CDCl3
NS                           16
DS                            4
SWH                    8081.896 Hz
FIDRES                 0.493280 Hz
AQ                     1.0136734 sec
RG                         2050
DW                       61.867 usec
DE                       12.00 usec
TE                       298.1 K
D1                     1.65999997 sec
d11                    0.03000000 sec
DELTA                  1.55999994 sec
TD0                           1

======== CHANNEL f1 ========
NUC1                        31P
P1                         8.00 usec
PL1                        4.00 dB
SFO1                202.4563350 MHz

======== CHANNEL f2 ========
CPDPRG2                 waltz16
NUC2                         1H
PCPD2                     80.00 usec
PL2                       -1.40 dB
PL12                      15.20 dB
PL13                      16.20 dB
SFO2                500.1320005 MHz

F2 - Processing parameters
SI                         32768
SF                  202.4563350 MHz
WDW                           EM
SSB                            0
LB                          1.00 Hz
GB                             0
PC                          1.40
```


Current Data Parameters
NAME CM-ym-253
EXPNO 2
PROCNO 1
F2 - Acquisition Parameters
Data_ 20061129
Time 13.28
INSTRUM Avance500
PROBHD 5 mm QNP 1H/13
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 10330.578 Hz
FIDRES 0.157632 Hz
AQ 3.1719923 sec
RG 90.5
DW 48.400 usec
DE 24.00 usec
TE 298.1 K
D1 1.00000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 1H
P1 12.00 usec
PL1 -1.00 dB
SFO1 500.1330885 MHz
F2 - Processing parameters
SI 32768
SF 500.1300500 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
ppm
1.23
0.40
2.59
4.33
1.26
5.84
2.29
2.48
37.94
3.02
2.61
2f

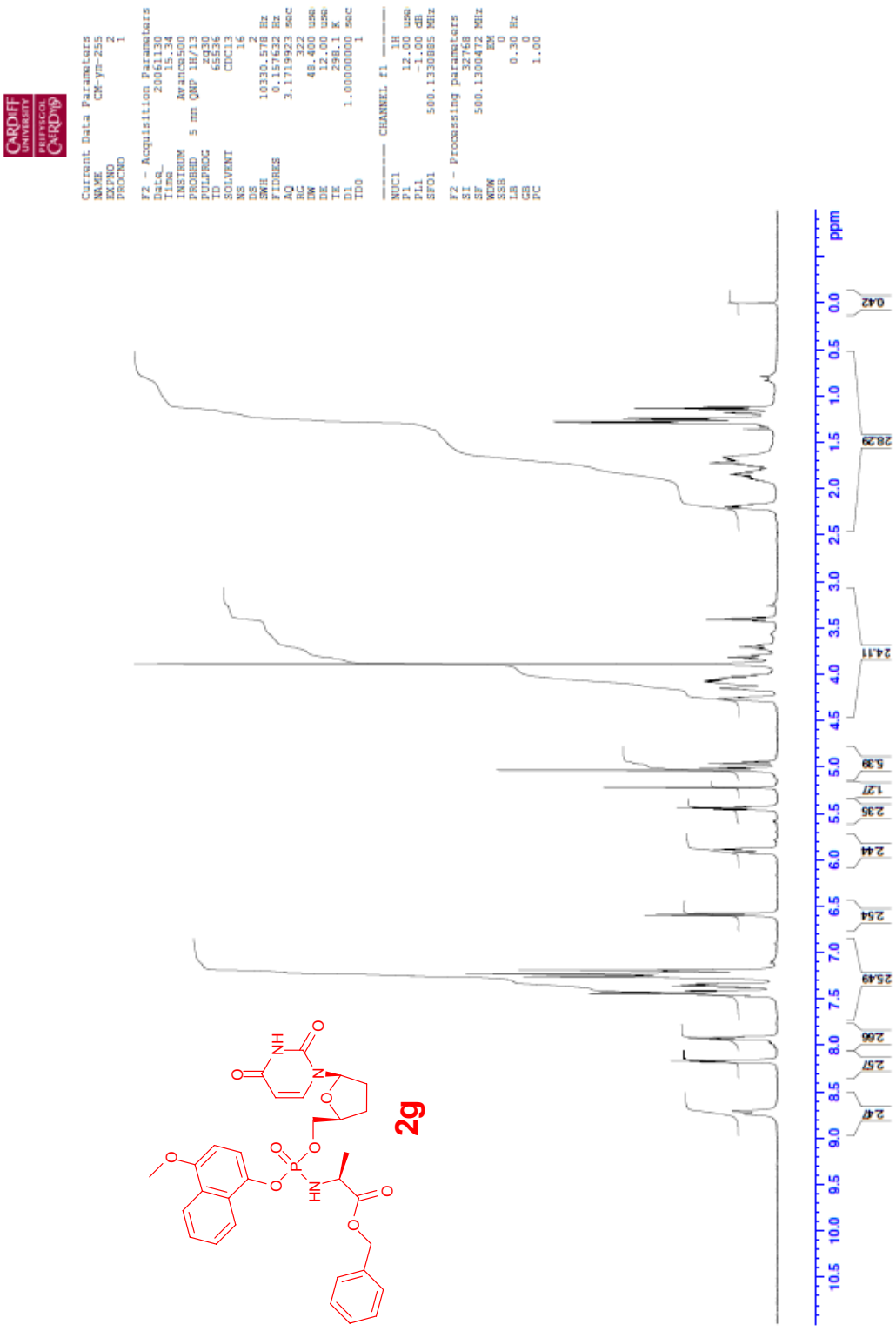

2f
ppm

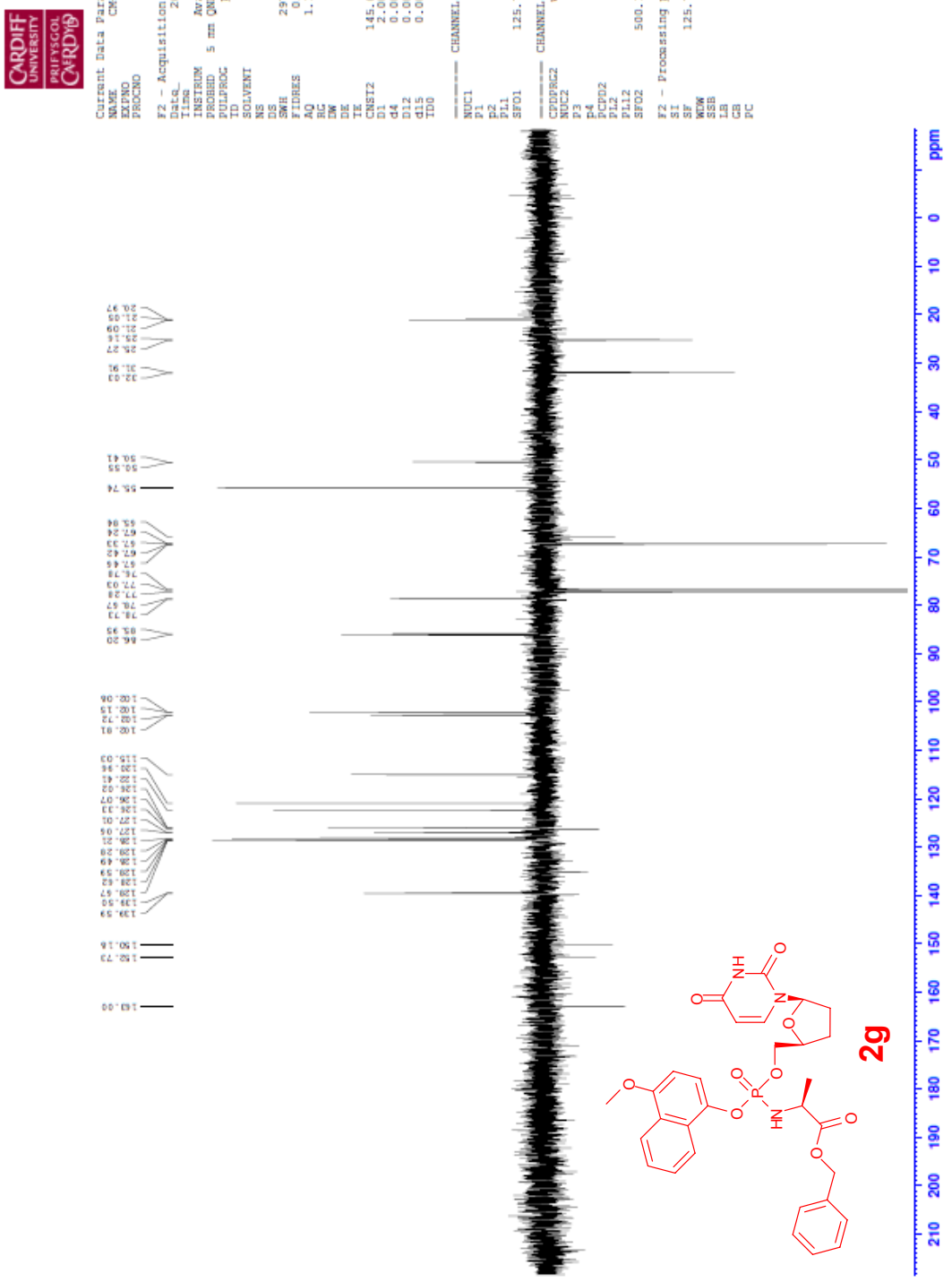

2f

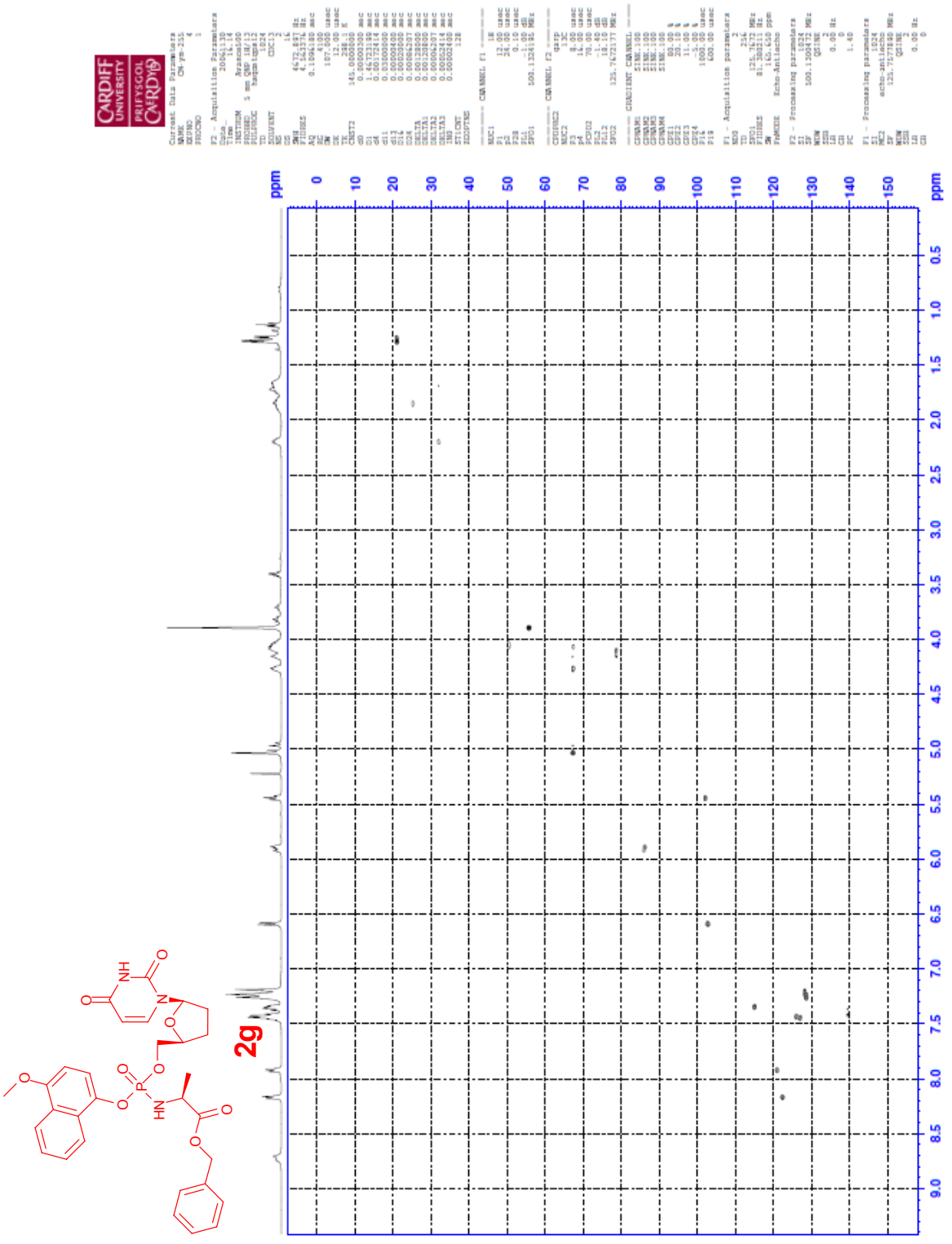


CARDIFF UNIVERSITY
PRIFYSGOL CAERDYDD

```
Current Data Parameters
NAME                  CM-yn-255
EXPNO                         1
PROCNO                        1

F2 - Acquisition Parameters
Date_               20061130
Time                      15.32
INSTRUM                Avance500
PROBHD     5 mm QNP 1H/13
PULPROG                 zgpg30
TD                       16384
SOLVENT                  CDCl3
NS                          16
DS                           4
SWH                   8081.896 Hz
FIDRES                0.493280 Hz
AQ                    1.0136734 sec
RG                        2050
DW                      61.867 usec
DE                      12.00 usec
TE                      298.1 K
D1                    1.65999997 sec
d11                   0.03000000 sec
DELTA                 1.55999994 sec
TD0                           1

====== CHANNEL f1 ======
NUC1                        31P
P1                         8.00 usec
PL1                        4.00 dB
SFO1                202.4563350 MHz

====== CHANNEL f2 ======
CPDPRG2                 waltz16
NUC2                        1H
PCPD2                     80.00 usec
PL2                       -1.40 dB
PL12                      15.20 dB
PL13                      16.20 dB
SFO2                500.1320005 MHz

F2 - Processing parameters
SI                        32768
SF                  202.4563350 MHz
WDW                          EM
SSB                           0
LB                         1.00 Hz
GB                            0
PC                         1.40
```


Current Data Parameters
NAME CM-ym-255
EXPNO 2
PROCNO 1
F2 - Acquisition Parameters
Date_ 20061130
Time 15.34
INSTRUM Avance500
PROBHD 5 mm QNP 1H/13
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 10330.578 Hz
FIDRES 0.157632 Hz
AQ 3.1719923 sec
RG 322
DW 48.400 usec
DE 22.00 usec
TE 298.1 K
D1 1.00000000 sec
TD0 1
CHANNEL f1
NUC1 1H
P1 12.00 usec
PL1 -1.00 dB
SFO1 500.1330885 MHz
F2 - Processing parameters
SI 32768
SF 500.1300472 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
ppm
0.42
2.29
2.41
5.39
1.27
2.35
2.44
2.54
2.49
2.66
2.57
2.47
2g


2g


2g