Supporting Information

Expansion of Antibacterial Spectrum of Muraymycins toward *Pseudomonas aeruginosa*

Yusuke Takeoka,[1] Tetsuya Tanino,[2] Mitsuaki Sekiguchi,[1] Shuji Yonezawa,[1] Masahiro Sakagami,[1] Fumiyo Takahashi,[1] Hiroko Togame,[1] Yoshikazu Tanaka,[1] Hiroshi Takemoto,[1] Satoshi Ichikawa,[2,3]* and Akira Matsuda[2]

[1]Shionogi Innovation Center for Drug Discovery, Shionogi & Co., LTD., Kita-21, Nishi-11 Kita-ku, Sapporo 001-0021, Japan

[2]Faculty of Pharmaceutical Sciences, Hokkaido University, Kita-12, Nishi-6, Kita-ku, Sapporo 060-0812, Japan

[3]Center for Research and Education on Drug Discovery, Hokkaido University, Kita-12, Nishi-6, Kita-ku, Sapporo 060-0812, Japan

Corresponding Author: To whom correspondence should be addressed. Tel: (+81) 11-706-3229. Fax: (+81) 11-706-4980. ichikawa@pharm.hokudai.ac.jp.

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1. Synthesis of compounds

General experimental methods. ^{1}H NMR spectra were reported in parts per million (δ) relative to tetramethylsilane (0.00 ppm) as internal standard otherwise noted. Coupling constant (*J*) was reported in herz (Hz). Abbreviations of multiplicity were as follows; s: singlet, d; doublet, t: triplet, q: quartet, m: multiplet, br: broad. Data were presented as follows; chemical shift (multiplicity, integration, coupling constant). Purity of all compounds tested for MraY inhibitory and antibacterial activity was checked by HPLC analysis resulting >90%.

Compound 11. Compound **20** (40 mg, 0.034 mmol) and 10% $Pd(OH)_2/C$ (5 mg) in MeOH (1 mL) were vigorously stirred under a H_2 atmosphere at room temperature for 5 h. The insoluble was filtered off through Celite pad, and the filtrate was concentrated *in vacuo*. The residue was suspended in AcOEt, and the insoluble was filtered off through a short silica gel pad. The filtrate was concentrated *in vacuo*. The residue was treated with 80% aqueous TFA (2 mL) at room temperature for 8 h. The solution was concentrated *in vacuo*, and the residue was triturated from AcOEt to afford a white solid. The solid was purified by C18 reversed phase column chromatography (1.5×10 cm, 80% aqueous MeOH containing 0.5% TFA) to afford **12** (30 mg, 96% over two steps from **20**) as a white solid.^{1}H NMR (CD_3OD, 500 MHz) δ 7.64 (d, 1H, H-6, $J_{6,5}$ = 8.1 Hz), 5.75 (d, 1H, H-1′), 5.70 (d, H- 5, $J_{5,6}$ = 8.1 Hz), 5.18 (s, 1H, H-1″), 4.56 (d, 1H, H-5′, $J_{5',4'}$ = 5.7 Hz), 4.27 (m, 2H, H-2′ and 4′), 4.21 (t, 1H, H-3′, $J_{3',4'}$ = 5.7 Hz), 4.02 (m, 3H, H-2″, 3″ and 4″), 3.82 (m, 2H, H-6′ and H-2-pentadecylGly), 3.47 (m, 1H, H-10′a), 3.34 (m, 1H, 10′b), 3.21 (m, 2H, H-8′a and 5″a), 3.05 (m, 1H, 5″b), 2.95 (m, 1H, H-8′b), 1.93 (m, 2H, H-9′), 1.84 (m, 2H, $CH_3(CH_2)_{13}CH_2CH$), 1.26 (m, 26H, $CH_3(CH_2)_{13}CH_2CH$), 0.87 (t, 3H, $CH_3(CH_2)_{13}CH_2CH$, *J* = 6.9 Hz); ESIMS-LR *m/z* 771 [(M − H)$^-$]; ESIMS-HR calcd for $C_{36}H_{63}N_6O_{12}$ 771.4509, found 771.4535.

Compound 12. Compound **20** (14.6 mg, 0.013 mmol) and 10 % $Pd(OH)_2/C$ (5 mg) in MeOH (1 mL) were vigorously stirred under a H_2 atmosphere at room temperature for 5 h. The insoluble was filtered off through Celite pad, and the filtrate was concentrated *in vacuo*. The residue was suspended in AcOEt and the insoluble was filtered off through a short silica gel pad and the filtrate was concentrated *in vacuo*. The residue in CH_2Cl_2 (1 mL) and Et_3N (2.0 μL, 0.014 mmol) was treated with acetic anhydride (1.18 μL, 0.013 mmol) at 0 °C, and the mixture was stirred at room temperature for 48 h. The reaction mixture was partitioned between AcOEt and 1 M aqueous HCl. The organic phase was washed with H_2O, saturated aqueous $NaHCO_3$, and saturated aqueous NaCl, dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was treated with 80% aqueous TFA (2 mL) at room temperature for 8 h. The solution was concentrated *in vacuo*, and the residue was triturated from Et_2O to afford a white solid. The solid was purified by C18 reverse phase column chromatography (1.5×10 cm, 80% aqueous MeOH containing 0.5% TFA) to afford **12** (10.1 mg, 98% over three steps from **20**) as a white solid. ^{1}H NMR (CD_3OD, 500 MHz) δ 7.64 (d, 1H, H-6, $J_{6,5}$ = 8.0 Hz), 5.75 (d, 1H, H-1′), 5.70 (d, 1H, H-5, $J_{5,6}$ = 8.0 Hz), 5.18 (s, 1H, H-1″), 4.56 (s, 1H, H-4′, $J_{4',5'}$ = 5.7 Hz), 4.23 (s, 1H, H-2′

and H-3′), 4.20 (m, 1H, H-5′), 4.13 (dd, 1H, H-2-pentadecylGly, J = 5.1, 9.2 Hz), 4.05 (m, 3H, H-2″, 3″ and 4″), 3.83 (m, 1H, H-6′), 3.29-3.03 (m, 6H, H-8′, 10′ and 5″), 1.98 (m, 2H, H-9′), 1.85 (m, 2H, $CH_3(CH_2)_{12}CH_2CH_2CH$), 1.74 (m, 2H, $CH_3(CH_2)_{12}CH_2CH_2CH$), 1.34 (m, 24H, $CH_3(CH_2)_{12}CH_2CH_2CH$), 0.87 (t, 3H, $CH_3(CH_2)_{12}CH_2CH_2CH$); ESIMS-LR *m/z* 815 [(M + H)$^+$]; ESIMS-HR calcd for $C_{38}H_{67}N_6O_{13}$ 815.4761, found 815.4769.

Compound 13. In a manner similar to the synthesis of **12**, compound **13** (9.6 mg, 88% over three steps) was prepared with benzoic anhydride (2.82 mg, 0.013 mmol). ^{1}H NMR (CD_3OD, 500 MHz) δ 7.87 (d, 2H, aromatic, J = 7.5 Hz), 7.64 (d, 1H, H-6, $J_{6,5}$ = 8.0 Hz), 7.53 (t, 1H, aromatic, J = 6.9 Hz), 7.47 (t, 1H, aromatic, J = 7.5 Hz), 5.75 (d, 1H, H-1′), 5.69 (d, H-5, $J_{5,6}$ = 8.0 Hz), 5.17 (s, 1H, H-1″), 4.56 (d, 1H, H-5′, $J_{5',4'}$ = 5.7 Hz), 4.40 (dd, 1H, H-2-pentadecylGly, J = 5.7, 9.2 Hz), 4.25 (m, 2H, H-3′ and 5′), 4.20 (m, 1H, H-2′), 4.05 (m, 3H, H-2″, 4″ and 6′), 3.85 (s, 1H, H-3″), 3.67 (m, 2H, H-10′), 3.22 (m, 1H, 5″a), 2.90 (m, 3H, H-8′ and 5″b), 1.87 (m, 4H, H-9′ and $CH_3(CH_2)_{13}CH_2CH$), 1.36 (m, 26H, $CH_3(CH_2)_{13}CH_2CH$), 0.87 (t, 3H, $CH_3(CH_2)_{13}CH_2CH$, J = 6.9 Hz); ESIMS-LR *m/z* 877 [(M + H)$^+$]; ESIMS-HR calcd for $C_{43}H_{69}N_6O_{13}$ 877.4918, found 877.4919.

Compound 14. Compound **20** (20.6 mg, 0.018 mmol) and 10 % $Pd(OH)_2$/C (5.0 mg) in MeOH (1 mL) were vigorously stirred under a H_2 atmosphere at room temperature for 5 h. The insoluble was filtered off through Celite pad, and the filtrate was concentrated *in vacuo*. The residue was suspended in AcOEt and the insoluble was filtered off through a short silica gel pad, and the filtrate was concentrated *in vacuo* to afford the crude amine. A mixture of picolinic acid (2.18 mg, 0.018 mmol), Et_3N (4.9 μL, 0.036 mmol) and *N*-hydroxysuccimide (4.05 mg, 0.036 mmol) in THF (1 mL) was treated with 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDCI, 5.46 mg, 0.036 mmol) at 0 °C for 1 h. The crude amine in CH_2Cl_2 (1 mL) was added to the solution, which was stirred at 0 °C for 1 h and at room temperature for 48 h. The reaction mixture was partitioned between AcOEt and 1 M aqueous HCl. The organic phase was washed with saturated H_2O, aqueous $NaHCO_3$, and saturated aqueous NaCl, dried with Na_2SO_4, filtered and concentrated *in vacuo*. The residue was treated with 80% aqueous TFA (2 mL) at room temperature for 8 h. The solution was concentrated *in vacuo*, and the residue was triturated from Et_2O to afford a white solid. The solid was purified by C18 reversed phase column chromatography (1.5×10 cm, 80% aqueous MeOH containing 0.5% TFA) to afford **14** (15.2 mg, 88% over three steps from **20**) as a white solid. ^{1}H NMR (CD_3OD, 500 MHz) δ 8.66 (d, 1H, aromatic, J = 4.5 Hz), 8.09 (d, 1H, aromatic, J = 7.4 Hz), 7.96 (t, 1H, aromatic, J = 7.4 Hz), 7.66 (d, 1H, H-6, $J_{6,5}$ = 8.0 Hz), 7.56 (t, 1H, aromatic, J = 7.4 Hz), 5.76 (s, 1H, H-1′), 5.71 (d, H-5, $J_{5,6}$ = 8.0 Hz), 5.17 (s, 1H, H-1″), 4.56 (s, 1H, H-5′), 4.47 (dd, 1H, H-2-pentadecylGly, J = 5.2, 8.6 Hz), 4.26 (m, 2H, H-2′ and 4′), 4.20 (m, 1H, H-3′), 4.04 (m, 3H, H-2″, 3″ and 4″), 3.90 (s, 1H, H-6′), 3.33 (m, 2H, H-10′), 3.20 (m, 2H, H-8′a and 5″a), 3.13 (m, 2H, H-8′b and 5″b), 1.88 (m, 4H, H-9′ and $CH_3(CH_2)_{12}CH_2CH_2CH$), 1.36 (m, 24H, $CH_3(CH_2)_{12}CH_2CH_2CH$), 1.24 (m, 24H, $CH_3(CH_2)_{12}CH_2CH_2CH$), 0.88 (t, 3H, $CH_3(CH_2)_{13}CH_2CH$, J = 8.7 Hz); ESIMS-LR *m/z* 878 [M$^+$]; ESIMS-HR calcd for $C_{42}H_{68}N_7O_{13}$ 878.4870, found 878.4882.

Compound 15. In a manner similar to the synthesis of **14**, compound **15** (14.3 mg, 83% over three steps) was prepared from **20** (20.6 mg, 0.018 mmol) and nicotinic acid (2.18 mg, 0.018 mmol). ^{1}H NMR (CD_3OD, 500 MHz) δ 9.08 (s, 1H, aromatic), 8.72 (s, 1H, aromatic), 8.40 (d, 1H, aromatic, J = 8.0 Hz), 7.63 (m, 2H, H-6 and aromatic), 5.72 (s, 1H, H-1′), 5.71 (d, H-5, $J_{5,6}$ = 8.0 Hz), 5.17 (s, 1H, H-1″), 4.56 (s, 1H, H-5′, $J_{5',4'}$ = 5.2 Hz), 4.39 (dd, 1H, H-2-pentadecylGly, J = 7.6, 9.1 Hz), 4.25 (m, 1H, H-2′ and 4′), 4.21 (m, 1H, H-3′), 4.03 (m, 3H, H-2″, 3″ and 4″), 3.97 (s, 1H, H-6′), 3.34 (m, 2H, H-10′), 2.86 (m, 2H, H-8′a and 5″a), 3.10 (m, 2H, H-8′b and 5″b), 1.88 (m, 4H, H-9′ and $CH_3(CH_2)_{13}CH_2CH$), 1.25 (m, 26H, $CH_3(CH_2)_{13}CH_2CH$), 0.87 (t, 3H, $CH_3(CH_2)_{13}CH_2CH$, J = 7.5 Hz); ESIMS-LR *m/z* 878 [M^+]; ESIMS-HR calcd for $C_{42}H_{68}N_7O_{13}$ 878.4870, found 878.4887.

Compound 16. In a manner similar to the synthesis of **14**, compound **16** (14.3 mg, 83% over three steps) was prepared from **20** (20.6 mg, 0.018 mmol) and isonicotinic acid (2.18 mg, 0.018 mmol). ^{1}H NMR (CD_3OD, 500 MHz) δ 8.76 (d, 1H, aromatic, J = 5.2 Hz), 7.96 (d, 1H, aromatic, J = 6.3 Hz), 7.64 (d, 1H, H-6, $J_{6,5}$ = 8.1 Hz), 5.72 (s, 1H, H-1′), 5.71 (d, H-5, $J_{5,6}$ = 8.1 Hz), 5.17 (s, 1H, H-1″), 4.56 (s, 1H, H-5′, $J_{5',4'}$ = 5.2 Hz), 4.39 (dd, 1H, H-2-pentadecylGly, J = 5.7, 9.1 Hz), 4.26 (m, 2H, H-2′ and 4′), 4.20 (m, 1H, H-3′), 4.04 (m, 3H, H-2″, 3″ and 4″), 3.99 (s, 1H, H-6′), 3.32 (m, 2H, H-10′), 3.28 (m, 2H, H-8′a and 5″a), 3.16 (m, 2H, H-8′b and 5″b), 1.88 (m, 4H, H-9′ and $CH_3(CH_2)_{13}CH_2CH$), 1.26 (m, 26H, $CH_3(CH_2)_{13}CH_2CH$), 0.87 (t, 3H, $CH_3(CH_2)_{13}CH_2CH$, J = 6.9 Hz); ESIMS-LR *m/z* 878 [M^+]; ESIMS-HR calcd for $C_{42}H_{68}N_7O_{13}$ 878.4870, found 878.4873.

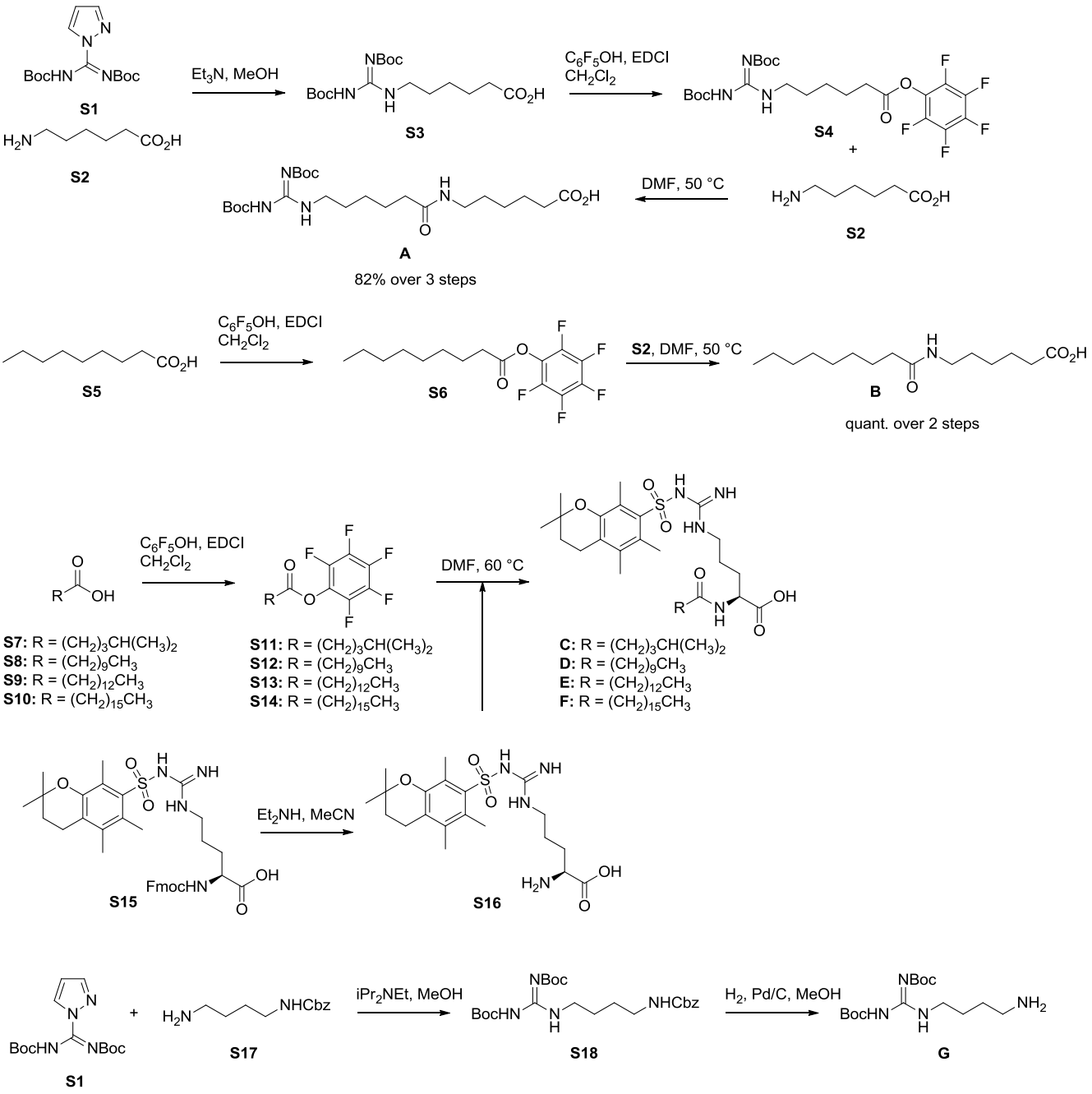
Compound 17. In a manner similar to the synthesis of **14**, compound **17** (13.5 mg, 87% over three steps) was prepared from **20** (20.6 mg, 0.018 mmol) and pyrazine-2-carboxylic acid (2.18 mg, 0.018 mmol). ^{1}H NMR (CD_3OD, 500 MHz) δ 9.23 (s, 1H, aromatic), 8.79 (s, 1H, aromatic), 8.71 (s, 1H, aromatic), 7.64 (d, 1H, H-6, $J_{6,5}$ = 8.1 Hz), 5.75 (s, 1H, H-1′), 5.71 (d, H-5, $J_{5,6}$ = 8.1 Hz), 5.16 (s, 1H, H-1″), 4.55 (d, 1H, H-5′, $J_{5',4'}$ = 4.9 Hz), 4.47 (dd, 1H, H-2-pentadecylGly, J = 5.4, 8.5 Hz), 4.25 (m, 2H, H-2′ and 4′), 4.21 (m, 1H, H-3′), 4.04 (m, 3H, H-2″, 3″ and 4″), 3.92 (s, 1H, H-6′), 3.32 (m, 2H, H-10′), 3.15 (m, 2H, H-8′a and 5″a), 3.11 (m, 2H, H-8′b and 5″b), 1.87 (m, 4H, H-9′ and $CH_3(CH_2)_{13}CH_2CH$), 1.23 (m, 26H, $CH_3(CH_2)_{13}CH_2CH$), 0.87 (t, 3H, $CH_3(CH_2)_{13}CH_2CH$, J = 6.5 Hz); ESIMS-LR *m/z* 879 [M^+]; ESIMS-HR calcd for $C_{41}H_{67}N_8O_{13}$ 879.4822, found 879.4837.

Compound 18. In a manner similar to the synthesis of **14**, compound **18** (12.9 mg, 83% over three steps) was prepared from **20** (20.6 mg, 0.018 mmol) and pyridazine-4-carboxylic acid (2.18 mg, 0.018 mmol). ^{1}H NMR (CD_3OD, 500 MHz) δ 9.57 (s, 1H, aromatic), 9.37 (s, 1H, aromatic, J = 4.9 Hz), 8.10 (s, 1H, aromatic, J = 4.9 Hz), 7.63 (d, 1H, H-6, $J_{6,5}$ = 8.1 Hz), 5.73 (s, 1H, H-1′), 5.69 (d, H-5, $J_{5,6}$ = 8.1 Hz), 5.16 (s, 1H, H-1″), 4.56 (d, 1H, H-5′, $J_{5',4'}$ = 5.4 Hz), 4.38 (t, 1H, H-2-pentadecylGly, J = 5.8 Hz), 4.26 (m, 2H, H-2′ and 4′), 4.19 (m, 1H, H-3′), 4.03 (m, 3H, H-2″, 3″ and 4″), 3.93 (s, 1H, H-6′), 3.32 (m, 2H, H-10′), 3.19 (m, 2H, H-8′a and 5″a), 3.16 (m, 2H, H-8′b and 5″b), 1.88 (m, 4H, H-9′ and $CH_3(CH_2)_{13}CH_2CH$), 1.35 (m, 26H, $CH_3(CH_2)_{13}CH_2CH$), 0.87 (t, 3H, $CH_3(CH_2)_{13}CH_2CH$, J = 8.4 Hz);

ESIMS-LR *m/z* 879 [M^+]; ESIMS-HR calcd for $C_{41}H_{67}N_8O_{13}$ 879.4822, found 879.4838.

Compound 19. In a manner similar to the synthesis of **14**, compound **19** (14.2 mg, 87% over three steps) was prepared from **20** (20.6 mg, 0.018 mmol) and quinoline-2-carboxylic acid (2.18 mg, 0.018 mmol). ^{1}H NMR (CD_3OD, 500 MHz) δ 8.46 (d, 1H, aromatic, *J* = 8.1 Hz), 8.18 (d, 2H, aromatic, *J* = 8.1 Hz), 7.98 (d, 1H, aromatic, *J* = 8.1 Hz), 7.67 (t, 1H, aromatic, *J* = 8.1 Hz), 7.64 (d, 1H, H-6, $J_{6,5}$ = 7.2 Hz), 5.75 (s, 1H, H-1′), 5.70 (d, H-5, $J_{5,6}$ = 7.2 Hz), 5.16 (s, 1H, H-1″), 4.56 (m, 2H, H-5′ and H-2-pentadecylGly), 4.25 (m, 2H, H-2′ and 4′), 4.21 (m, 1H, H-3′), 4.03 (m, 3H, H-2″, 3″ and 4″), 3.89 (s, 1H, H-6′), 3.34 (m, 2H, H-10′), 3.26 (m, 2H, H-8′a and 5″a), 3.15 (m, 2H, H-8′b and 5″b), 1.88 (m, 4H, H-9′ and $CH_3(CH_2)_{13}CH_2CH$), 1.23 (m, 26H, $CH_3(CH_2)_{13}CH_2CH$), 0.86 (t, 3H, $CH_3(CH_2)_{13}CH_2CH$, *J* = 7.8 Hz); ESIMS-LR *m/z* 928 [M^+]; ESIMS-HR calcd for $C_{46}H_{70}N_7O_{13}$ 928.5026, found 928.5038.

SCHEME S1



6-[6-(*N*,*N′*-di-*tert*-Butoxycarbonylguanidino)hexanoylamino]hexanoic acid (A). A mixture of **S1** (233 mg, 0.75 mmol), **S2** (65.6 mg, 0.50 mmol), and Et_3N (209 μL, 1.5 mmol) in MeOH (5 mL) was stirred at room temperature for 18 h. The mixture was partitioned between AcOEt and 1 M aqueous HCl, and the organic phase was washed with saturated aqueous NaCl, dried with Na_2SO_4, filtered and concentrated *in vacuo*. The residue was dissolved in a small portion of $CHCl_3$, which was passed through a silica gel pad to give **S3** (210 mg). A solution of **S3** in CH_2Cl_2 (2 mL) was treated with pentafluorophenol (138 mg, 0.75 mmol) and EDCI (144 mg, 0.75 mmol), and the mixture was stirred at room temperature for 1.5 h. The mixture was diluted with AcOEt, which was washed with H_2O and saturated aqueous NaCl. The organic layer was dried with Na_2SO_4, filtered and concentrated *in vacuo*

to give **S4**. A mixture of **S4** and **S2** (66 mg, 0.5 mmol) in DMF (0.4 mL) was heated at 50 °C for 2 h. The mixture was diluted with AcOEt, which was washed with 1 M aqueous HCl, saturated aqueous NaCl, dried with Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (0-5% MeOH–$CHCl_3$) to afford **A** (200 mg, 82% over three steps) as a colorless syrup. ^{1}H NMR (CD_3OD, 500 MHz) δ 1.33-1.42 (m, 4H, H-4, H-11), 1.47-1.54 (m, 13H, *tert*-Bu), 1.58-1.68 (m, 4H, H-3, H-5, H-10, H-12,) 2.17-2.29 (m, 4H, H-2, H-9), 3.14-3.21 (m, 2H, H-13), 3.26-3.31 (m, 2H, H-6). ESIMS-LR *m/z* 487 [$(M + H)^+$]; ESIMS-HR calcd for $C_{23}H_{43}N_4O_7$ 487.3132, found 487.3122.

6-Nonanoylaminohexanoic acid (B). In a manner similar to the synthesis of **A**, **B** (234 mg, quant. over two steps) was prepared from **S5** (79.1 mg, 0.50 mmol). ^{1}H NMR (CD_3OD, 500MHz) δ 0.90 (t, 3H, $CH_3(CH_2)_5CH_2CH_2CO$, *J* = 7.0 Hz), 1.25-1.40 (m, 12H, $CH_3(CH_2)_5CH_2CH_2CO$, H-4), 1.48-1.66 (m, 6H, H-3, H-5, $CH_3(CH_2)_5CH_2CH_2CO$), 2.16 (t, 2H, $CH_3(CH_2)_5CH_2CH_2CO$, *J* = 7.5 Hz), 2.29 (t, 2H, H-2, $J_{2,3}$ = 7.7 Hz), 3.16 (t, 2H, H-6, $J_{6,5}$ = 7.1 Hz). ESIMS-LR *m/z* 294 [$(M + Na)^+$]; ESIMS-HR calcd for $C_{15}H_{29}NNaO_3$ 294.2045, found 294.2038.

***N*$^{\alpha}$-(5-Methylhexanolyl)-5-[3-*N*-(2,2,5,7,8-pentamethylchromane-6-sulfonyl)]-L-arginine (C).** A solution of **S7** (130 mg, 1.00 mmol) in CH_2Cl_2 (1 mL) was treated with pentafluorophenol (184 mg, 1.00 mmol) and EDCI (249 mg, 1.00 mmol), and the mixture was stirred at room temperature for 1 h. The mixture was diluted with AcOEt, which was washed with H_2O and saturated aqueous NaCl. The organic layer was dried with Na_2SO_4, filtered and concentrated *in vacuo* to give **S11**. A solution of **S15** (441 mg, 0.66 mmol) in MeCN (0.6 mL) was treated with Et_2NH (0.6 mL) at room temperature for 1 h. The mixture was concentrated *in vacuo* to give **S16**. A mixture of **S11** and **S16** in DMF (1.5 mL) was heated at 60 °C for 3 h. The mixture was diluted with AcOEt, which was washed with 1 M aqueous HCl and saturated aqueous NaCl, dried with Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (0-15% MeOH–$CHCl_3$) to afford **C** (215 mg, 78% over three steps) as a colorless syrup. ^{1}H NMR (CD_3OD, 500 MHz) δ 0.89 (d, 6H, $(CH_3)_2CHCH_2CH_2CH_2CO$, *J* = 6.6 Hz), 1.18-1.24 (m, 2H, $(CH_3)_2CHCH_2CH_2CH_2CO$), 1.31 (s, 6H, chromanyl-2,2-Me_2), 1.50-1.69 (m, 6H, $(CH_3)_2CHCH_2CH_2CH_2CO$, $(CH_3)_2CHCH_2CH_2CH_2CO$, H-3a, H-4), 1.81-1.88 (m, 3H, H-3b, chromanyl-H-3), 2.10 (s, 3H, chromanyl-8-Me), 2.20 (t, 2H, $(CH_3)_2CHCH_2CH_2CH_2CO$, *J* = 7.1 Hz), 2.55 (s, 3H, chromanyl-5-Me or chromanyl-7-Me), 2.56 (s, 3H, chromanyl-5-Me or chromanyl-7-Me), 2.67 (t, 2H, chromanyl-H-4, $J_{\text{chromanyl-4,3}}$ = 6.9 Hz), 3.05-3.25 (m, 2H, H-5), 4.26-4.32 (m, 1H, H-2). ESIMS-LR *m/z* 553 [$(M + H)^+$]; ESIMS-HR calcd for $C_{27}H_{45}N_4O_6S$ 553.3060, found 553.3051.

***N*$^{\alpha}$-Undecanoly-5-[3-*N*-(2,2,5,7,8-pentamethylchromane-6-sulfonyl)]-L-arginine (D).** In a manner similar to the synthesis of **C**, **D** (1.06 g, 87% over three steps) was prepared from **S8** (466 mg, 2.50 mmol). ^{1}H NMR (CD_3OD, 500 MHz) δ 0.89 (t, 3H, $CH_3(CH_2)_7CH_2CH_2CO$, *J* = 7.0 Hz), 1.27-1.32 (m, 20H, $CH_3(CH_2)_7CH_2CH_2CO$, chromanyl-2,2-Me_2), 1.50-1.70 (m, 5H, $CH_3(CH_2)_7CH_2CH_2CO$, H-3a,

H-4), 1.80-1.88 (m, 3H, H-3b, chromanyl-H-3), 2.10 (s, 3H, chromanyl-8-Me), 2.21 (t, 2H, $CH_3(CH_2)_7CH_2CH_2CO$, J = 7.5 Hz,), 2.55 (s, 3H, chromanyl-5-Me or chromanyl-7-Me), 2.56 (s, 3H, chromanyl-5-Me or chromanyl-7-Me), 2.67 (t, 2H, chromanyl-H-4, $J_{\text{chromanyl-4, 3}}$ = 6.8 Hz), 3.14-3.22 (m, 2H, H-5), 4.31 (dd, 1H, H-2, $J_{2,3}$ = 8.4, 4.8 Hz). ESIMS-LR *m/z* 609 [$(M + H)^+$]; ESIMS-HR calcd for $C_{31}H_{53}N_4O_6S$ 609.3686, found 609.3680.

N^{α}-Tetradecanoly-5-[3-*N*-(2,2,5,7,8-pentamethylchromane-6-sulfonyl)]-L-arginine (E). In a manner similar to the synthesis of **C**, **E** (110 mg, 68% over three steps) was prepared from **S9** (114 mg, 0.50 mmol). ^{1}H NMR (CD_3OD, 500 MHz) δ 0.89 (t, 3H, $CH_3(CH_2)_{10}CH_2CH_2CO$, J = 7.0 Hz), 1.27-1.32 (m, 26H, $CH_3(CH_2)_{10}CH_2CH_2CO$, chromanyl-2,2-$Me_2$), 1.50-1.70 (m, 5H, $CH_3(CH_2)_{10}CH_2CH_2CO$, H-3a, H-4), 1.83 (m, 3H, H-3b, chromanyl-H-3), 2.10 (s, 3H, chromanyl-8-Me), 2.22 (t, 2H, $CH_3(CH_2)_{10}CH_2CH_2CO$, J = 7.8 Hz), 2.55 (s, 3H, chromanyl-5-Me or chromanyl-7-Me), 2.56 (s, 3H, chromanyl-5-Me or chromanyl-7-Me), 2.66 (t, 2H, chromanyl-H-4, $J_{\text{chromanyl-4,3}}$ = 6.9 Hz), 3.12-3.22 (m, 2H, H-5), 4.25-4.32 (m, 1H, H-2). ESIMS-LR *m/z* 651 [$(M + H)^+$]; ESIMS-HR calcd for $C_{34}H_{59}N_4O_6S$ 651.4155, found 651.4148.

N^{α}-Heptadecanoly-5-[3-*N*-(2,2,5,7,8-pentamethylchromane-6-sulfonyl)]-L-arginine (F). In a manner similar to the synthesis of **C**, **F** (110 mg, 68% over three steps) was prepared from **S9** (114 mg, 0.50 mmol). ^{1}H NMR (CD_3OD, 500 MHz) δ 0.89 (t, 3H, $CH_3(CH_2)_{13}CH_2CH_2CO$, J = 7.0 Hz), 1.26-1.33 (m, 34H, $CH_3(CH_2)_{13}CH_2CH_2CO$, chromanyl-2,2-$Me_2$, H-4), 1.60-1.64 (m, 5H, $CH_3(CH_2)_{13}CH_2CH_2CO$, H-3a, H-4), 1.80-1.88 (m, 3H, H-3b, chromanyl-H-3), 2.10 (s, 3H, chromanyl-8-Me), 2.21 (t, 2H, $CH_3(CH_2)_{13}CH_2CH_2CO$, J = 7.4 Hz), 2.55 (s, 3H, chromanyl-5-Me or chromanyl-7-Me), 2.56 (s, 3H, chromanyl-5-Me or chromanyl-7-Me), 2.67 (t, 2H, chromanyl-H-4, $J_{\text{chromanyl-4,3}}$ = 6.9 Hz), 3.12-3.20 (m, 2H, H-5), 4.30 (dd, 1H, H-2, $J_{2,3}$ = 8.6, 4.9 Hz). ESIMS-LR *m/z* 694 [$(M + H)^+$]; ESIMS-HR calcd for $C_{37}H_{65}N_4O_6S$ 693.4625, found 693.4613.

***N*-4-Benzyloxycarbonylaminobutyl-*N*,*N′*-di-*tert*-Butoxycarbonylguanidine (S18).** A mixture of **S1** (74.5 mg, 0.24 mmol), **S17** (51.7 mg, 0.50 mmol), and *i*Pr_2NEt (70 μL, 0.4 mmol) in MeOH (2 mL) was stirred at room temperature for 5 h. The mixture was partitioned between AcOEt and 1 M aqueous HCl, and the organic phase was washed with saturated aqueous NaCl, dried with Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (5-40% AcOEt–hexane) to afford **S18** (81 mg, 85%) as a colorless syrup. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.48 (s, 9H, *tert*-Bu), 1.49 (s, 9H, *tert*-Bu), 1.53-1.64 (m, 4H, H-2, H-3), 3.25 (q, 2H, H-4, $J_{4,3}$ = 6.4 Hz), 3.41 (q, 2H, H-1, $J_{1,2}$ = 6.4 Hz), 5.03-5.09 (m, 3H, N*H*, $COOCH_2Ph$), 7.28-7.36 (m, 5H, N*H*, $COOCH_2$*Ph*), 8.34 (s, 1H, N*H*(C=NBoc)NHBoc), 11.48 (s, 1H, NH(C=NBoc)N*H*Boc). ESIMS-LR *m/z* 465 [$(M + H)^+$]; ESIMS-HR calcd for $C_{23}H_{37}N_4O_6$ 465.2713, found 465.2727.

Compound 21. A mixture of **30** (25 mg, 0.026 mmol) and NH_4Cl (41 mg, 0.77 mmol) in MeOH (1 mL) were treated with activated Zn powder (85% purity, 30 mg, 0.41 mmol) at room temperature for 6

h. The insoluble was filtered off through Celite pad, and the filtrate was concentrated *in vacuo* to give a crude amine (12.7 mg). A mixture of the amine, EDCI (4.3 mg, 0.037 mmol) and HOBt (6.2 mg, 0.032 mmol) in CH_2Cl_2 (0.25 mL) was treated with **A** (12.6 mg, 0.026 mmol) for 15 h. The mixture was partitioned between AcOEt and 1 M aqueous HCl, and the organic phase was washed with saturated *aq.* NaCl, dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was treated with 80% aqueous TFA (2 mL) at room temperature for 7 h. The solution was concentrated *in vacuo*, and the residue was purified by C18 reversed phase column chromatography (0-60% aqueous MeCN containing 0.1% TFA) to afford **21** (4.0 mg, 19% over three steps from **30**) as a white solid. ^{1}H NMR (D_2O, 500 MHz) δ 1.27-1.40 (m, 4H, H-15′, H-22′), 1.49-1.66 (m, 8H, H-14′, H-16′, H-21′, H-23′), 1.84-1.96 (m, 2H, H-9′), 2.21-2.29 (m, 4H, H-13′, H-20′), 3.10-3.37 (m, 10H, H-8′, H-10′, H-17′, H-24′, H-5″), 3.99 (s, 1H, H-6′), 4.16-4.22 (m, 3H, H-2″,H-3″, H-4″), 4.31 (dd, 1H, H-4′, $J_{4',5'}$ = 3.7, $J_{4',3'}$ = 7.6 Hz), 4.35 (dd, 1H, H-3′, $J_{3',2'}$ = 5.4, $J_{3',4'}$ = 7.6 Hz), 4.46 (dd, 1H, H-2′, $J_{2',1'}$ = 3.0, $J_{2',3'}$ = 5.4 Hz), 4.62-4.64 (m, 1H, H-5′), 5.23 (d, 1H, H-1″, $J_{1'',2''}$ = 1.7 Hz), 5.83 (d, 1H, H-1′, $J_{1',2'}$ = 3.0 Hz), 5.91 (d, 1H, H-5, $J_{5,6}$ = 8.1 Hz), 7.73 (d, 1H, H-6, $J_{6,5}$ = 8.1 Hz). ESIMS-LR *m/z* 774 [(M + H)$^+$]; ESIMS-HR calcd for $C_{32}H_{56}N_9O_{13}$ 774.3998, found 774.3994.

Compound 22. In a manner similar to the synthesis of **21**, **22** (7.6 mg, 33% over three steps) was prepared from **30** (25 mg, 0.026 mmol) and **B** (12.2 mg, 0.026 mmol). ^{1}H NMR (D_2O, 500 MHz) δ 0.86 (t, 3H, C*H*$_3$(CH$_2$)$_5$CH$_2$CH$_2$CO, *J* = 7.0 Hz), 1.25-1.40 (m, 12H, CH$_3$(C*H*$_2$)$_5$CH$_2$CH$_2$CO, H-15′), 1.48-1.63 (m, 6H, CH$_3$(CH$_2$)$_5$C*H*$_2$CH$_2$CO, H-14′, H-16′), 1.84-1.96 (m, 2H, H-9′), 2.21-2.25 (m, 4H, CH$_3$(CH$_2$)$_5$C*H*$_2$CH$_2$CO, H-13′), 3.10-3.40 (m, 8H, H-8′, H-10′, H-17′, H-5″), 4.00 (d, 1H, H-6′, $J_{6',5'}$ = 1.0 Hz), 4.15-4.21 (m, 3H, H-2″, H-3″, H-4″), 4.31 (dd, 1H, H-4′, $J_{4',5'}$ = 3.7, $J_{4',3'}$ = 7.6 Hz), 4.35 (dd, 1H, H-3′, $J_{3',2'}$ = 5.4, $J_{3',4'}$ = 7.6 Hz), 4.45 (dd, 1H, H-2′, $J_{2',1'}$ = 3.0, $J_{2',3'}$ = 5.4 Hz), 4.62-4.64 (m, 1H, H-5′), 5.23 (d, 1H, H-1″, $J_{1'',2''}$ = 1.7 Hz), 5.83 (d, 1H, H-1′, $J_{1',2'}$ = 3.0 Hz), 5.92 (d, 1H, H-5, $J_{5,6}$ = 8.1 Hz), 7.73 (d, 1H, H-6, $J_{6,5}$ = 8.1 Hz). ESIMS-LR *m/z* 759 [(M + H)$^+$]; ESIMS-HR calcd for $C_{34}H_{59}N_6O_{13}$ 759.4140, found 759.4132.

Compound 23. In a manner similar to the synthesis of **21**, **23** (3.1 mg, 15% over three steps) was prepared from **30** (25 mg, 0.026 mmol) and **C** (14.6 mg, 0.026 mmol). ^{1}H NMR (D_2O, 500 MHz) δ 0.86 (d, 6H, (C*H*$_3$)$_2$CHCH$_2$CH$_2$CH$_2$CO, *J* = 6.9 Hz), 1.14-1.20 (m, 2H, (CH$_3$)$_2$CHC*H*$_2$CH$_2$CH$_2$CO), 1.50-1.90 (m, 8H, (CH$_3$)$_2$CHCH$_2$C*H*$_2$CH$_2$CO, H-9′, H-14′, H-15′), 1.87-1.94 (m, 1H, (CH$_3$)$_2$C*H*CH$_2$CH$_2$CH$_2$CO), 2.28-2.32 (m, 2H, (CH$_3$)$_2$CHCH$_2$CH$_2$C*H*$_2$CO), 3.09-3.40 (m, 8H, H-8′, H-10′, H-16′, H-5″), 3.99 (br s, 1H, H-6′), 4.15-4.23 (m, 4H, H-13′, H-2″, H-3″, H-4″), 4.29-4.37 (m, 2H, H-3′, H-4′), 4.45 (dd, 1H, H-2′, $J_{2',1'}$ = 2.9, $J_{2',3'}$ = 5.1 Hz), 4.62-4.65 (m, 1H, H-5′), 5.23 (br s, 1H, H-1″), 5.84 (d, 1H, H-1′, $J_{1',2'}$ = 2.9 Hz), 5.92 (d, 1H, H-5, $J_{5,6}$ = 8.1 Hz), 7.74 (d, 1H, H-6, $J_{6,5}$ = 8.1 Hz). ESIMS-LR *m/z* 774 [(M + H)$^+$]; ESIMS-HR calcd for $C_{32}H_{56}N_9O_{13}$ 774.3998, found 774.9987.

Compound 24. In a manner similar to the synthesis of **21**, **24** (3.1 mg, 17% over three steps) was prepared from **30** (25 mg, 0.026 mmol) and **D** (15.8 mg, 0.026 mmol). ^{1}H NMR (D_2O, 500 MHz) δ

0.87 (t, 3H, C*H*$_3$(CH$_2$)$_7$CH$_2$CH$_2$CO, *J* = 7.0 Hz), 1.22-1.32 (m, 14H, CH$_3$(C*H*$_2$)$_7$CH$_2$CH$_2$CO), 1.55-1.95 (m, 8H, CH$_3$(CH$_2$)$_7$C*H*$_2$CH$_2$CO, H-9′, H-14′, H-15′), 2.26-2.36 (m, 2H, CH$_3$(CH$_2$)$_7$CH$_2$C*H*$_2$CO), 3.08-3.38 (m, 8H, H-8′, H-10′, H-16′, H-5″), 3.98 (d, 1H, H-6′, $J_{6',5'}$ = 1.2 Hz), 4.15-4.23 (m, 4H, H-13′, H-2″, H-3″, H-4″), 4.31 (dd, 1H, H-4′, $J_{4',5'}$ = 3.7, $J_{4',3'}$ = 7.6 Hz), 4.34 (dd, 1H, H-3′, $J_{3',2'}$ = 5.3, $J_{3',4'}$ = 7.6 Hz), 4.45 (dd, 1H, H-2′, $J_{2',1'}$ = 3.0, $J_{2',3'}$ = 5.3 Hz), 4.62-4.65 (m, 1H, H-5′), 5.24 (d, 1H, H-1″, $J_{1'',2''}$ = 1.7 Hz), 5.84 (d, 1H, H-1′, $J_{1',2'}$ = 3.0 Hz,), 5.92 (d, 1H, H-5, $J_{5,6}$ = 8.2 Hz), 7.74 (d, 1H, H-6, $J_{6,5}$ = 8.2 Hz). ESIMS-LR *m/z* 830 [(M + H)$^+$]; ESIMS-HR calcd for C$_{36}$H$_{64}$N$_9$O$_{13}$ 830.4624, found 830.4617.

Compound 25. In a manner similar to the synthesis of **21**, **25** (3.1 mg, 15% over three steps) was prepared from **30** (25 mg, 0.026 mmol) and **E** (14.6 mg, 0.026 mmol). ^{1}H NMR (D$_2$O, 500 MHz) δ 0.84-0.88 (m, 3H, C*H*$_3$(CH$_2$)$_{10}$CH$_2$CH$_2$CO), 1.23-1.30 (m, 20H, CH$_3$(C*H*$_2$)$_{10}$CH$_2$CH$_2$CO), 1.50-1.95 (m, 8H, CH$_3$(CH$_2$)$_{10}$C*H*$_2$CH$_2$CO, H-9′, H-14′, H-15′), 2.27-2.35 (m, 2H, CH$_3$(CH$_2$)$_{10}$CH$_2$C*H*$_2$CO), 3.08-3.42 (m, 8H, H-8′, H-10′, H-16′, H-5″), 3.98 (s, 1H, H-6′), 4.17-4.25 (m, 4H, H-13′, H-2″, H-3″, H-4″), 4.30-4.37 (m, 2H, H-3′, H-4′), 4.44 (dd, 1H, H-2′, $J_{2',1'}$ = 3.2, $J_{2',3'}$ = 4.4 Hz), 4.62-4.66 (m, 1H, H-5′), 5.24 (br s, 1H, H-1″), 5.84 (d, 1H, H-1′, $J_{1',2'}$ = 3.2 Hz), 5.91 (d, 1H, H-5, $J_{5,6}$ = 8.1 Hz), 7.75 (d, 1H, H-6, $J_{6,5}$ = 8.1 Hz). ESIMS-LR *m/z* 872 [(M + H)$^+$]; ESIMS-HR calcd for C$_{39}$H$_{70}$N$_9$O$_{13}$ 872.5093, found 872.5089.

Compound 26. In a manner similar to the synthesis of **21**, **26** (5.5 mg, 23% over three steps) was prepared from **30** (25 mg, 0.026 mmol) and **F** (18.3 mg, 0.026 mmol). ^{1}H NMR (D$_2$O, 500 MHz) δ 0.86 (t, 3H, C*H*$_3$(CH$_2$)$_{13}$CH$_2$CH$_2$CO, *J* = 6.8 Hz), 1.18-1.32 (m, 26H, CH$_3$(C*H*$_2$)$_{13}$CH$_2$CH$_2$CO), 1.50-1.98 (m, 8H, CH$_3$(CH$_2$)$_{13}$C*H*$_2$CH$_2$CO, H-9′, H-14′, H-15′), 2.22-2.37 (m, 2H, CH$_3$(CH$_2$)$_{13}$CH$_2$C*H*$_2$CO), 3.10-3.42 (m, 8H, H-8′, H-10′, H-16′, H-5″), 3.99 (br s, 1H, H-6′), 4.14-4.25 (m, 4H, H-13′, H-2″, H-3″, H-4″), 4.32-4.46 (m, 3H, H-2′, H-3′, H-4′,), 4.64 (br s, 1H, H-5′), 5.24 (br s, 1H, H-1″), 5.84 (s, 1H, H-1′), 5.90 (d, 1H, H-5, $J_{5,6}$ = 8.2 Hz), 7.75 (d, 1H, H-6, $J_{6,5}$ = 8.2 Hz). ESIMS-LR *m/z* 914 [(M + H)$^+$]; ESIMS-HR calcd for C$_{42}$H$_{76}$N$_9$O$_{13}$ 914.5563, found 914.5557.

Compound 32. A mixture of **S18** (81 mg, 0.17 mmol) and 10% Pd/C in MeOH (2 mL) was vigorously stirred under a hydrogen atmosphere at room temperature for 6 h. The insoluble was filtered off through Celite pad, and the filtrate was concentrated in vacuo to give a crude **G**. A mixture of G, **31** (114 mg, 0.15 mmol), EDCI (37.4 mg, 0.30 mmol), and HOBt (40.5 mg, 0.30 mmol) was stirred at room temperature for 2 h. The mixture was partitioned between AcOEt and 1 M aqueous HCl, and the organic phase was washed with saturated aqueous NaCl, dried (Na$_2$SO$_4$), filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (0-10% MeOH–CHCl$_3$) to afford **32** (148 mg, 89%) as a white foam. ^{1}H NMR (CD$_3$OD, 500 MHz) δ 0.76-0.83 (m, 6H, CH$_2$C*H*$_3$), 1.42-1.65 (m, 41H, C*H*$_2$CH$_3$, acetonide, *tert*-Bu, CONHCH$_2$(C*H*$_2$)$_2$CH$_2$NH(C=N*Boc*)NH*Boc*), 2.98 (dd, 1H, H-5″a, $J_{5''a,4''}$ = 7.1, $J_{5''a,5''b}$ = 13.9 Hz), 3.12-3.40 (m, 5H, H-5″b, CONHC*H*$_2$(CH$_2$)$_2$C*H*$_2$NH(C=NBoc)NHBoc), 4.07-4.13 (m, 1H, H-4″), 4.17 (dd, 1H, H-4′, $J_{4',3'}$ = 4.4,

$J_{4',5'}$ = 8.8 Hz), 4.33-4.45 (m, 3H, H-5′, H-6′, H-3″), 4.66 (d, 1H, H-2″, $J_{2'',3''}$ = 5.9 Hz), 4.88-4.94 (m, 1H, H-3′), 5.04-5.08 (m, 2H, CH_2Ph, H-2′), 5.15 (s, 1H, H-1″), 5.18 (d, 1H, CH_2Ph, J = 12.2 Hz), 5.65 (d, 1H, H-5, $J_{5,6}$ = 7.9 Hz), 5.71 (d, 1H, H-1′, $J_{1',2'}$ = 1.3 Hz), 7.27-7.40 (m, 5H, Ph), 7.64 (d, 1H, H-6, $J_{6,5}$ = 7.9 Hz).

Compound 34. A mixture of **32** (170 mg, 0.15 mmol) and 10% Pd/C (16 mg) in MeOH (0.6 mL) was vigorously stirred under a H_2 atmosphere at room temperature for 6 h. The catalyst was filtered off through Celite pad, and the filtrate was concentrated *in vacuo* to give a crude amine. A solution of the amine and 3-(2,2,2-trichloroethoxycarbonyl)aminopropanal (44.7 mg, 0.18 mmol) and AcOH (86 μL, 1.5 mmol) in CH_2Cl_2 (2 mL) was treated with $NaBH(OAc)_3$ (95.4 mg, 0.45 mmol) at room temperature for 1.5 h. The reaction was quenched by saturated aqueous $NaHCO_3$ (500 μL), and the whole mixture was partitioned between AcOEt and saturated aqueous $NaHCO_3$. The organic phase was washed with saturated aqueous NaCl, dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (0-10% MeOH–$CHCl_3$) to afford **34** (161 mg, 89% over two steps) as a white foam. ^{1}H NMR (CD_3OD, 500 MHz) δ 0.76-0.82 (m, 6H, CH_2CH_3), 1.43-1.74 (m, 43H, CH_2CH_3, acetonide, H-9′, 5″-CH_2NH*Boc*, CONHCH_2(CH_2)$_2$CH_2NH(C=N*Boc*)NH*Boc*), 2.50-2.57 (m, 1H, H-8′a), 2.65-2.72 (m, 1H, H-8′b), 3.03 (dd, 1H, H-5″a, $J_{5''a,4''}$ = 7.3, $J_{5''a,5''b}$ = 14.1 Hz), 3.16 (dd, 1H, H-5″b, $J_{5''b,4''}$ = 5.7, $J_{5''b,5''a}$ = 14.1 Hz), 3.21-3.44 (m, 7H, H-6′, H-10′, CONHCH_2(CH_2)$_2$CH_2NH(C=NBoc)NHBoc), 4.11-4.20 (m, 2H, H-5′, H-4″), 4.42 (dd, 1H, H-4′, $J_{4',3'}$ = 4.2, $J_{4',5'}$ = 9.0 Hz), 4.54 (d, 1H, H-3″, $J_{3'',2''}$ = 6.3 Hz,), 4.64 (d, 1H, H-2″, $J_{2'',3''}$ = 6.3 Hz), 4.76 (s, 2H, CH_2CCl_3), 4.93 (dd, 1H, H-3′, $J_{3',4'}$ = 4.2, $J_{3',2'}$ = 6.3 Hz), 5.08 (s, 1H, H-1″), 5.16 (dd, 1H, H-2′, $J_{2',1'}$ = 1.5, $J_{2',3'}$ = 6.3 Hz), 5.66 (d, 1H, H-5, $J_{5,6}$ = 8.0 Hz), 5.71 (d, 1H, H-1′, $J_{1',2'}$ = 1.5 Hz), 7.66 (d, 1H, H-6, $J_{6,5}$ = 8.0 Hz).

Compound 35. In a manner similar to the synthesis of **32**, **33** (105 mg) was prepared from **31** (94.8 mg, 0.12 mmol) and hexadecylamine (32 mg, 0.13 mmol). This material was directly used for the next step. In a manner similar to the synthesis of **34**, **35** (105 mg, 90% over two steps from **31**) was prepared. ^{1}H NMR (CD_3OD, 500 MHz) δ 0.76-0.92 (m, 9H, CH_2CH_3, CH_3(CH_2)$_{13}$CH_2CH_2NHCO), 1.27-1.69 (m, 49H, CH_3(CH_2)$_{13}$CH_2CH_2NHCO, *tert*-Bu, CH_2CH_3, acetonide, H-9′), 2.51-2.58 (m, 1H, H-8′a), 2.64-2.72 (m, 1H, H-8′b), 3.02 (dd, 1H, H-5″a, $J_{5''a,4''}$ = 7.1, $J_{5''a,5''b}$ = 13.9 Hz), 3.13-3.32 (m, 6H, CH_3(CH_2)$_{13}$CH_2CH_2NHCO, H-6′, H-10′, H-5b″), 4.08-4.14 (m, 1H, H-4″), 4.17 (d, 1H, H-5′, $J_{5',4'}$ = 8.8 Hz), 4.41 (dd, 1H, H-4′, $J_{4',3'}$ = 4.4, $J_{4',5'}$ = 8.8 Hz), 4.54 (d, 1H, H-3″, $J_{3'',2''}$ = 5.9 Hz), 4.65 (d, 1H, H-2″, $J_{2'',3''}$ = 5.9 Hz), 4.76 (s, 2H, CH_2CCl_3), 4.91-4.95 (m, 1H, H-3′), 5.10 (s, 1H, H-1″), 5.16 (dd, 1H, H-2′, $J_{2',3'}$ = 5.4 Hz), 5.66 (d, 1H, H-5, $J_{5,6}$ = 8.1 Hz), 5.72 (s, 1H, H-1′), 7.66 (d, 1H, H-6, $J_{6,5}$ = 8.1 Hz).

Compound 27. In a manner similar to the synthesis of **21**, **27** (11.0 mg, 50% over three steps) was prepared from **34** (31.2 mg, 0.026 mmol) and heptadecanoic acid (7.0 mg, 0.026 mmol). ^{1}H NMR (CD_3OD, 500 MHz) δ 0.90 (t, 3H, CH_3(CH_2)$_{13}$CH_2CH_2CO, J = 7.0 Hz), 1.28-1.33 (m, 26H,

$CH_3(CH_2)_{13}CH_2CH_2CO$), 1.58-1.66 (m, 6H, $CH_3(CH_2)_{13}CH_2CH_2CO$, $CONHCH_2(CH_2)_2CH_2NH(C=NH)NH_2$), 1.84-1.90 (m, 2H, H-9′), 2.21 (t, 2H, $CH_3(CH_2)_{13}CH_2CH_2CO$, J = 8.0 Hz), 2.97 (br s, 2H, $CONHCH_2(CH_2)_2CH_2NH(C=NH)NH_2$), 3.20-3.30 (m, 7H, H-8′, H-10′a, H-5″, $CONHCH_2(CH_2)_2CH_2NH(C=NH)NH_2$), 3.39-3.45 (m, 1H, H-10′b), 4.04-4.14 (m, 5H, H-3′, H-6′, H-2″, H-3″, H-4″), 4.27 (dd, 1H, H-2′, $J_{2',1'}$ = 2.5, $J_{2',3'}$ = 5.4 Hz), 4.30-4.38 (m, 2H, H-4′, H-5′), 5.16 (d, 1H, H-1″, $J_{1'',2''}$ = 3.5 Hz), 5.72 (d, 1H, H-5, $J_{5,6}$ = 8.0 Hz), 5.81 (d, 1H, H-1′, $J_{1',2'}$ = 2.5 Hz), 7.75 (d, 1H, H-6, $J_{6,5}$ = 8.0 Hz). ESIMS-LR *m/z* 870 [$(M + H)^+$]; ESIMS-HR calcd for $C_{41}H_{76}N_9O_{11}$ 870.5664, found 870.5659.

Compound 28. In a manner similar to the synthesis of **21**, **28** (7.4 mg, 29% over three steps) was prepared from **35** (28.9 mg, 0.026 mmol) and N^a-Boc-L-Arg(Pbf)-OH (15.8 mg, 0.029 mmol). ^{1}H NMR (CD_3OD, 500 MHz) δ 0.90 (t, 3H, $CH_3(CH_2)_{13}CH_2CH_2NHCO$, J = 7.0 Hz), 1.27-1.40 (m, 26H, $CH_3(CH_2)_{13}CH_2CH_2NHCO$), 1.56-1.61 (m, 2H, $CH_3(CH_2)_{13}CH_2CH_2NHCO$ or H-15′), 1.62-1.72 (m, 2H, $CH_3(CH_2)_{13}CH_2CH_2NHCO$ or H-15′), 1.83-1.95 (m, 4H, H-9′, H-14′), 3.22-3.40 (m, 10H, $CH_3(CH_2)_{13}CH_2CH_2NHCO$, H-8′, H-10′, H-16′, H-5″), 3.88 (t, 1H, H-13′, $J_{13',14'}$ = 6.8 Hz), 4.04-4.14 (m, 4H, H-6′, H-2″, H-3″, H-4″), 4.19 (dd, 1H, H-4′, $J_{4',5'}$ = 3.3, $J_{4',3'}$ = 7.2 Hz), 4.27 (dd, 1H, H-2′, $J_{2',1'}$ = 2.7, $J_{2',3'}$ = 5.4 Hz), 4.29-4.33 (m, 2H, H-3′, H-5′), 5.15 (d, 1H, H-1″, $J_{1'',2''}$ = 2.7 Hz), 5.73 (d, 1H, H-5, $J_{5,6}$ = 8.1 Hz), 5.80 (d, 1H, H-1′, $J_{1',2'}$ = 2.7 Hz), 7.71 (d, 1H, H-6, $J_{6,5}$ = 8.1 Hz). ESIMS-LR *m/z* 885 [$(M + H)^+$]; ESIMS-HR calcd for $C_{41}H_{77}N_{10}O_{11}$ 885.5773, found 885.5768.

Compound 29. In a manner similar to the synthesis of **21**, **29** (7.7 mg, 21% over three steps) was prepared from **34** (31.2 mg, 0.026 mmol) and **F** (19.8 mg, 0.029 mmol). ^{1}H NMR (CD_3OD, 500 MHz) δ 0.90 (t, 3H, $CH_3(CH_2)_{13}CH_2CH_2CONH$, J = 7.2 Hz), 1.25-1.40 (m, 26H, $CH_3(CH_2)_{13}CH_2CH_2CONH$), 1.55-1.90 (m, 12H, $CH_3(CH_2)_{13}CH_2CH_2CONH$, $CONHCH_2(CH_2)_2CH_2NH(C=NH)NH_2$, H-9′, H-14′, H-15′), 2.22-2.32 (m, 2H, $CH_3(CH_2)_{13}CH_2CH_2CONH$), 2.94-3.02 (m, 2H, $CONHCH_2(CH_2)_2CH_2NH(C=NH)NH_2$), 3.18-3.33 (m, 10H, $CONHCH_2(CH_2)_2CH_2NH(C=NH)NH_2$, H-8′, H-10′, H-16′, H-5″), 4.06-4.16 (m, 5H, H-6′, H-13′, H-2″, H-3″, H-4″), 4.19 (dd, 1H, H-3′, $J_{3',2'}$ = 5.4, $J_{3',4'}$ = 8.9 Hz), 4.28 (dd, 1H, H-2′, $J_{2',1'}$ = 2.7, $J_{2',3'}$ = 5.4 Hz), 4.31-4.37 (m, 2H, H-4′, H-5′), 5.16 (d, 1H, H-1″, $J_{1'',2''}$ = 3.0 Hz), 5.74 (d, 1H, H-5, $J_{5,6}$ = 8.2 Hz), 5.82 (d, 1H, H-1′, $J_{1',2'}$ = 2.7 Hz), 7.73 (d, 1H, H-6, $J_{6,5}$ = 8.2 Hz). ESIMS-LR *m/z* 1026 [$(M + H)^+$]; ESIMS-HR calcd for $C_{47}H_{88}N_{13}O_{12}$ 1026.6675, found 1026.6663.

2. Fluorescence based MraY assay

Reactions were carried out in 384-well microplate. Reaction mixtures contained, in a final volume of 20 μL, 50 mM Tris-HCl (pH 7.6), 50 mM KCl, 25 mM $MgCl_2$, 0.2% Triton X-100, 8% glycerol, 100 μM C_{55}-P and 100 μM UDP-MurNAc-dansylpentapeptide. The reaction was initiated by the addition of *Staphylococcus aureus* MraY enzyme (11 ng/5 μL/well). After 3-4 h incubation at room temperature, the formation of dansylated lipid I was monitored by fluorescence enhancement (excitation at 355 nm, emission at 535 nm) by using the EnVision™ 2103 Multilabel Plate Reader. The

inhibitory effects of the each compound were determined in the MraY assays described above. The mixtures contained 2% dimethyl sulfoxide in order to increase the solubility of the compounds.

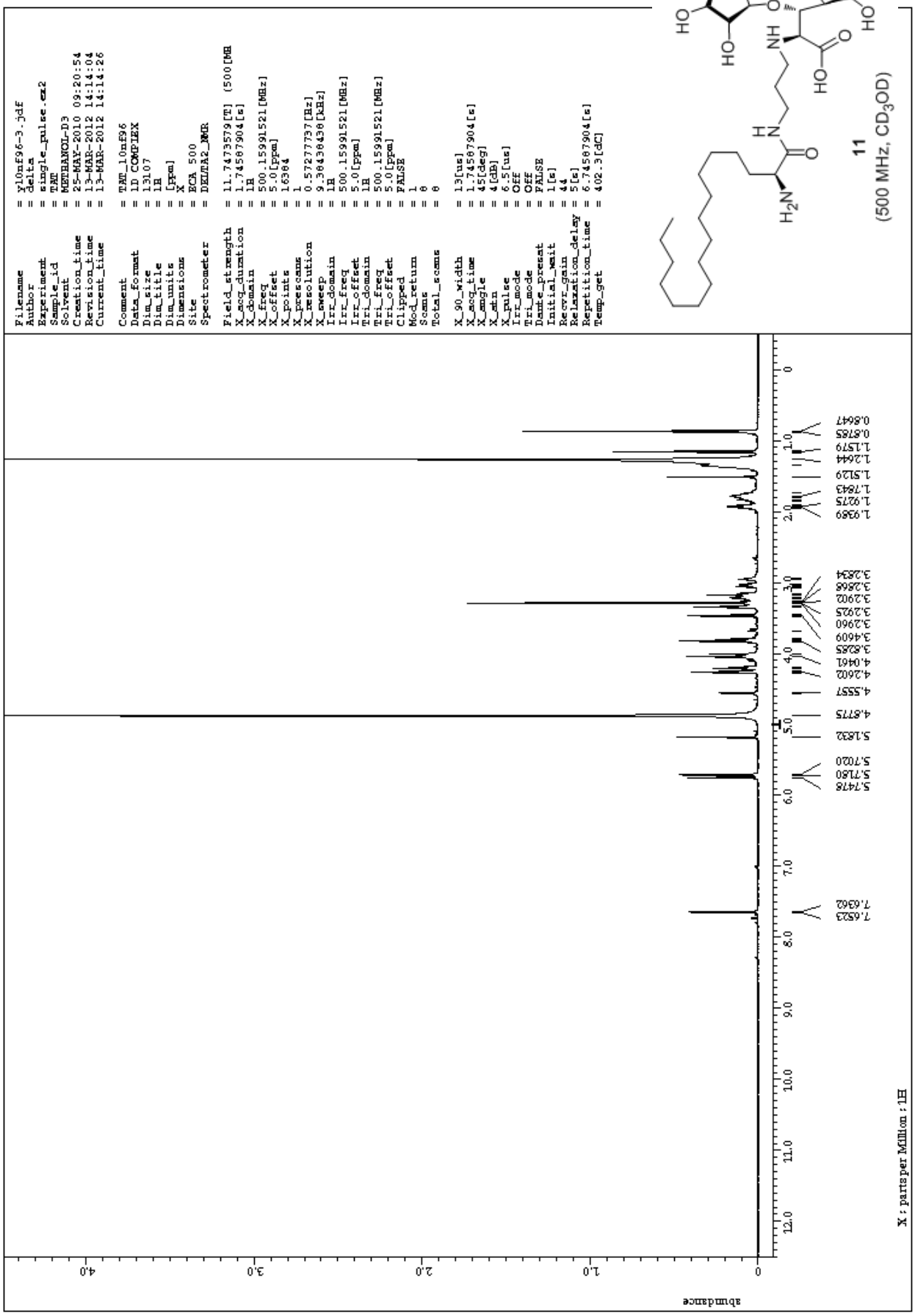
3. Antibacterial Activity Evaluation

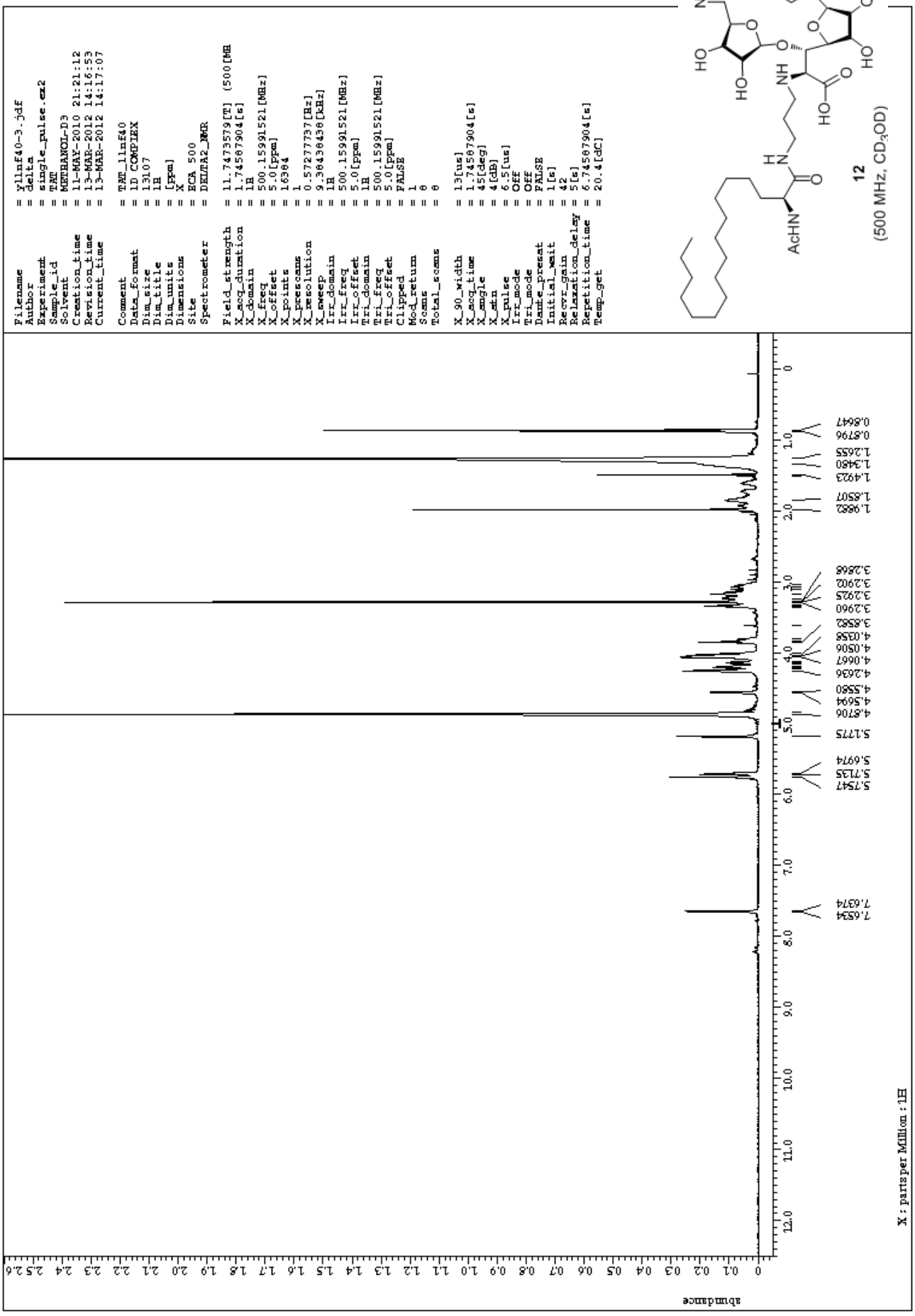
P. aeruginosa ATCC 25619 was purchased from ATCC (American Type Culture Collection). *P. aeruginosa* SR 27156 was a clinical isolate collected from hospitals of Japan. *P. aeruginosa* PAO1, and *P. aeruginosa* YY165 (*⊿*mexB) were kindly provided by Shionogi & Co., Ltd. (Osaka, Japan) (For details, see *Nippon Kagaku Ryoho Gakkai Zasshi* **2005**, 53(S-1), 80-91). MICs were determined by a microdilution broth method as recommended by the CLSI (Clinical and Laboratory Standards Institute) with cation-adjusted Mueller-Hinton broth (CA-MHB). Serial two-fold dilutions of each compound were made in appropriate broth, and the plates were inoculated with 5×10^4 CFU of each strain in a volume of 0.1mL Plates were incubated at 35 °C for 20 h and then MICs were scored.

4. *In vitro* metabolic stability testing

Rat liver microsomes were prepared from male rats by the established method (See Matsubara T, Otsubo S, Yoshihara E. Liver microsomal cytochrome P-450-dependent *O*-dealkylation reaction in various animals. *Jpn. J. Pharmacol.* **1983**, *33*, 1065–1075). Pooled human liver microsomes were purchased from XenoTech LLC (Lenexa, KS). Metabolic stability of compounds by rat and human liver microsomes was conducted in duplicate. Rat and human liver microsomes were incubated at 37 °C in Tris-HCl buffer (pH 7.4) containing 50 mM Tris-HCl, 150 mM KCl, 10 mM $MgCl_2$, 1 mM β-NADPH and 2 μM compounds. The protein concentration was 0.5 mg/mL, and the final volume was 0.2 mL. Incubations were terminated by addition of two-fold volume of ice-cold acetonitrile/methanol (1:1, v/v) after 0 and 30 minutes of incubation. Samples were centrifuged at 3000 rpm for 10 min. Percentage of the remaining material was determined by LC-MS/MS analysis of the supernatants.

4. ^{1}H NMR spectra of synthesized compounds

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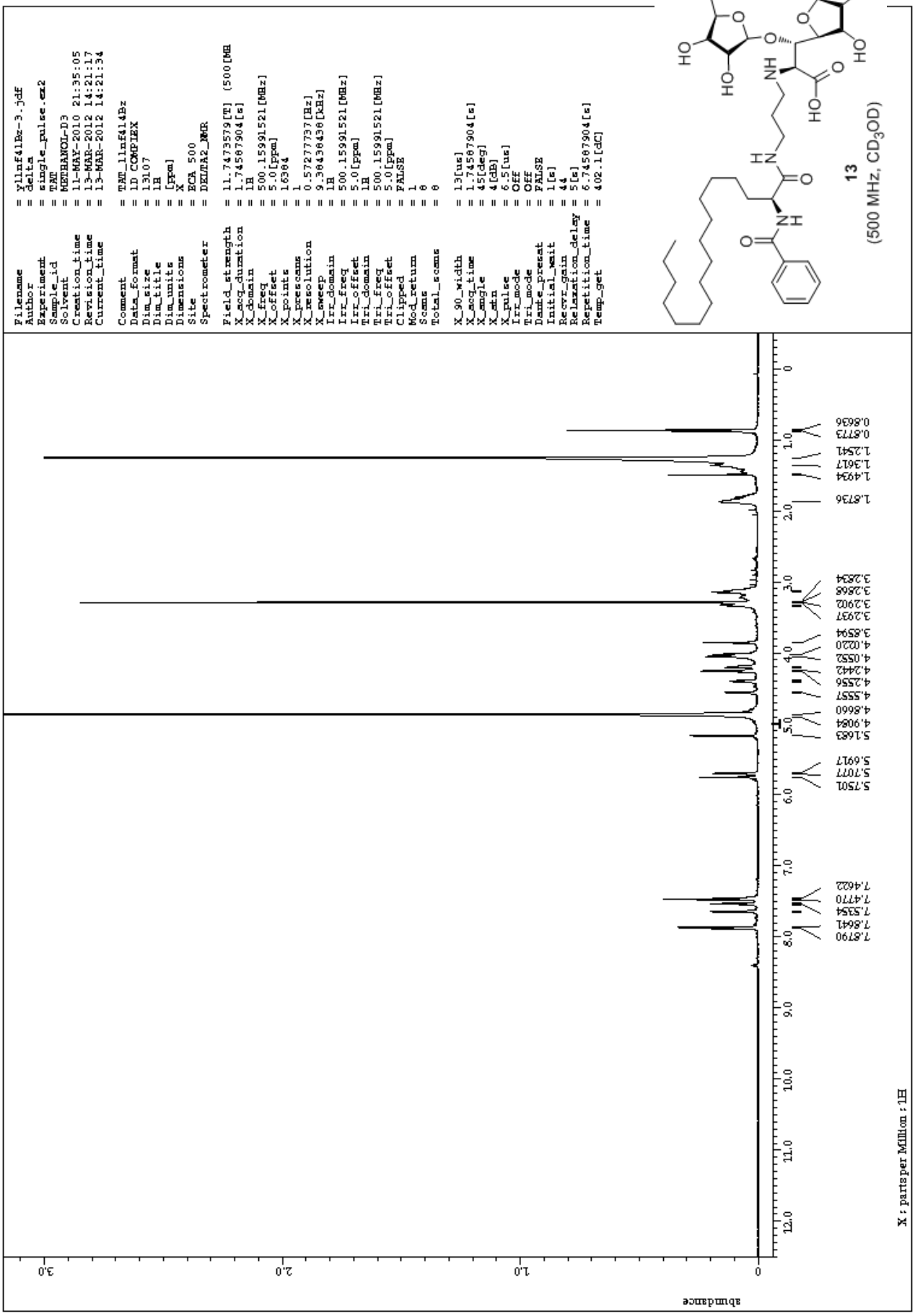
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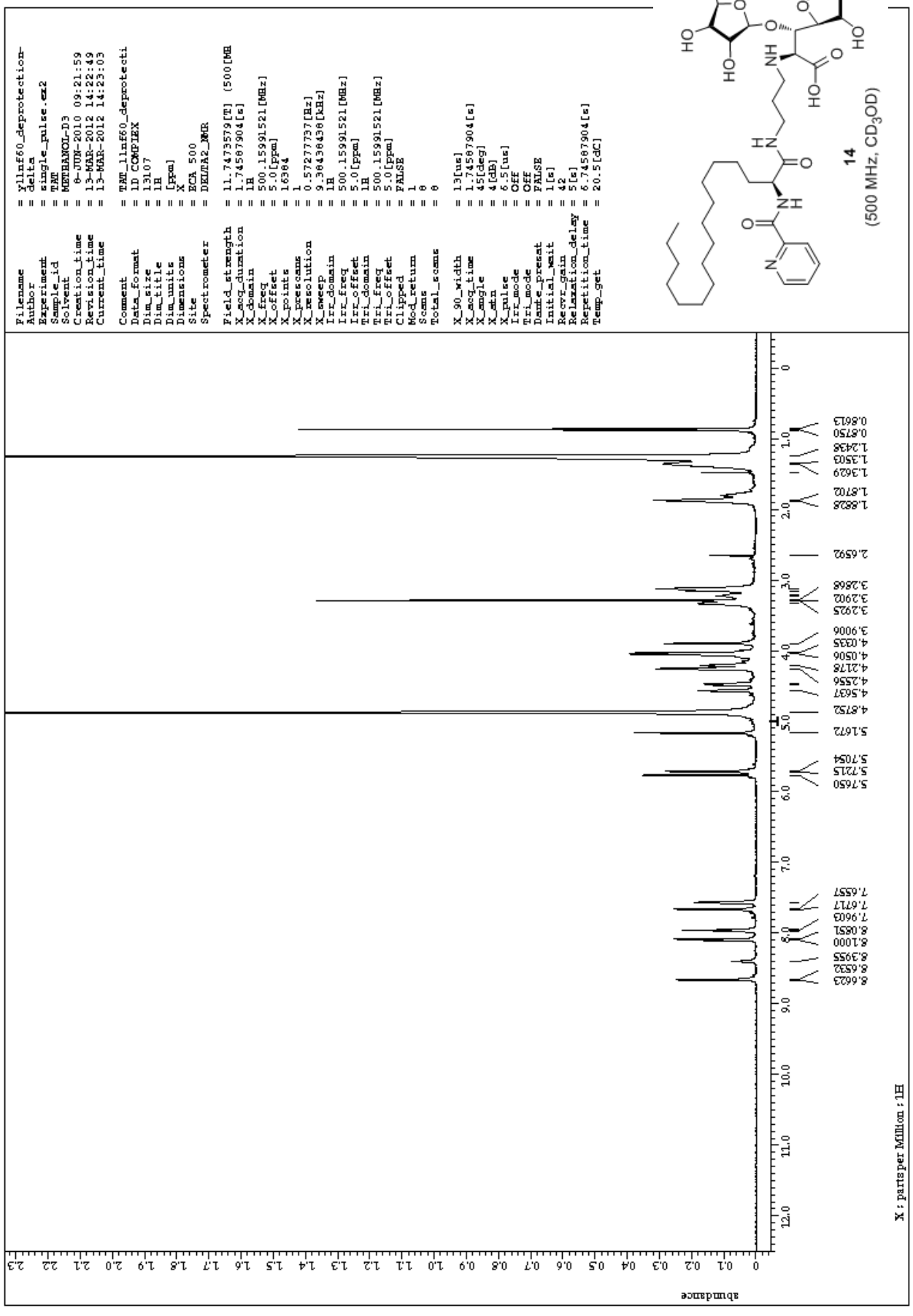
X : parts per Million : 1H
abundance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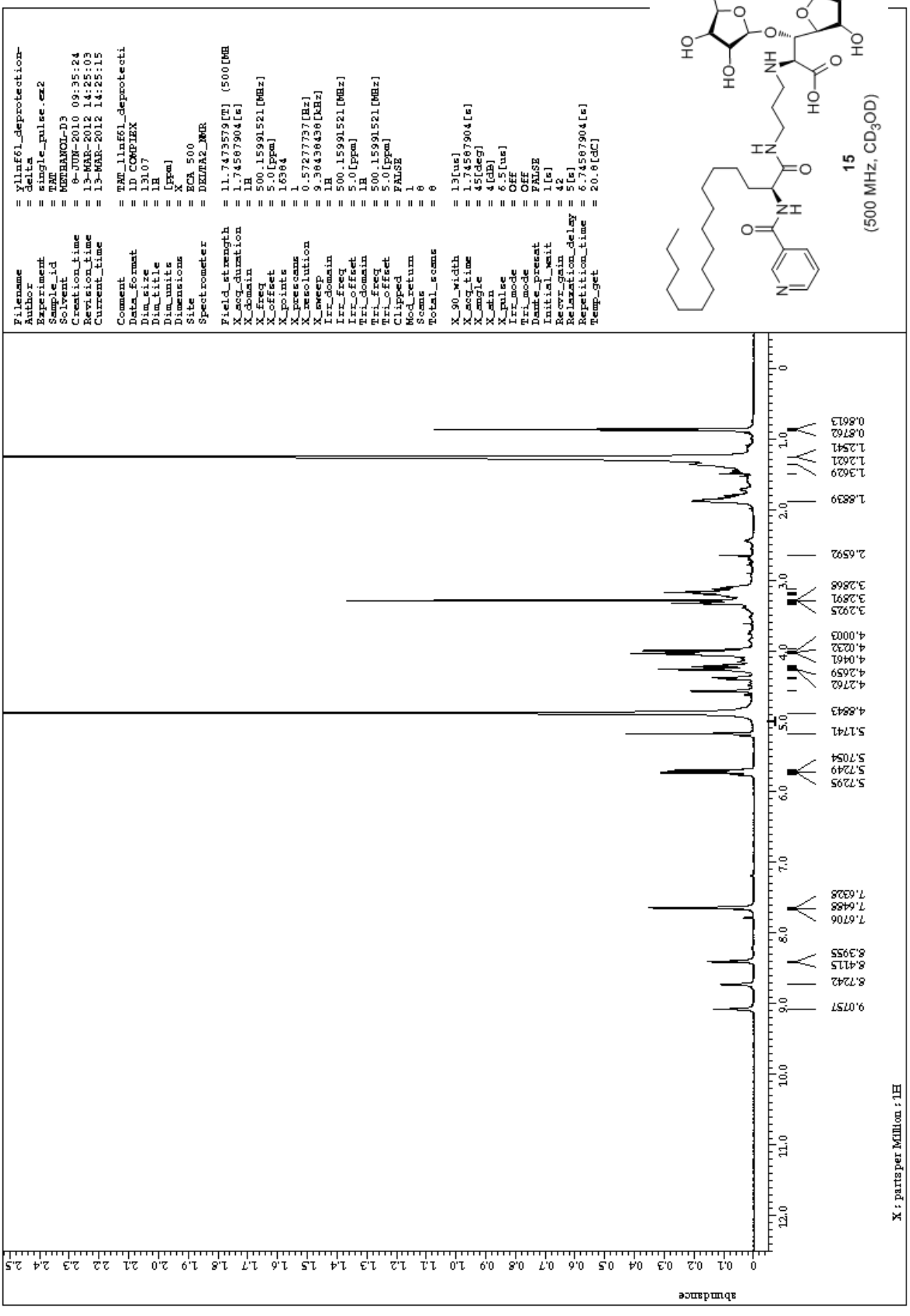
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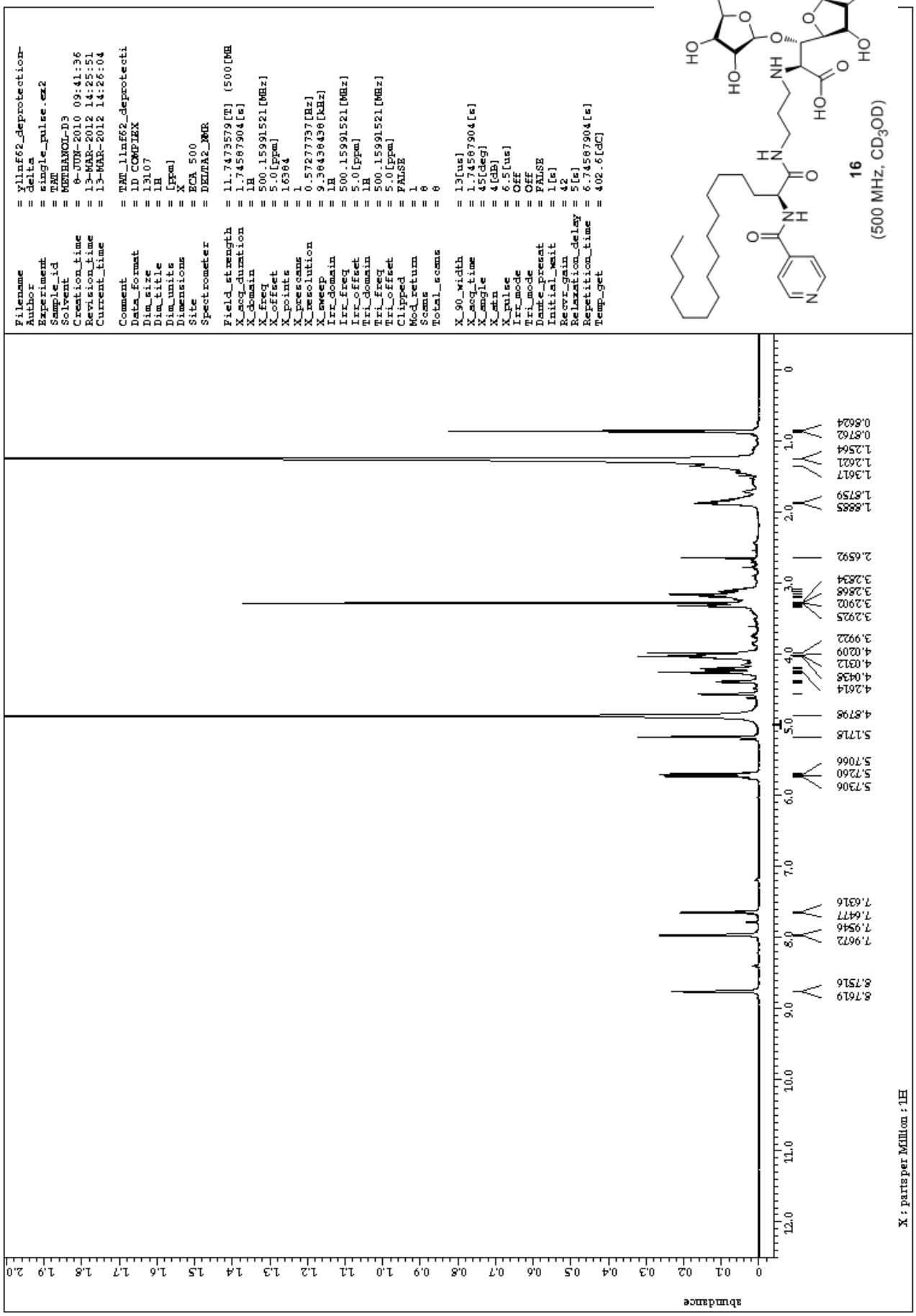
abundance
X : parts per Million : 1H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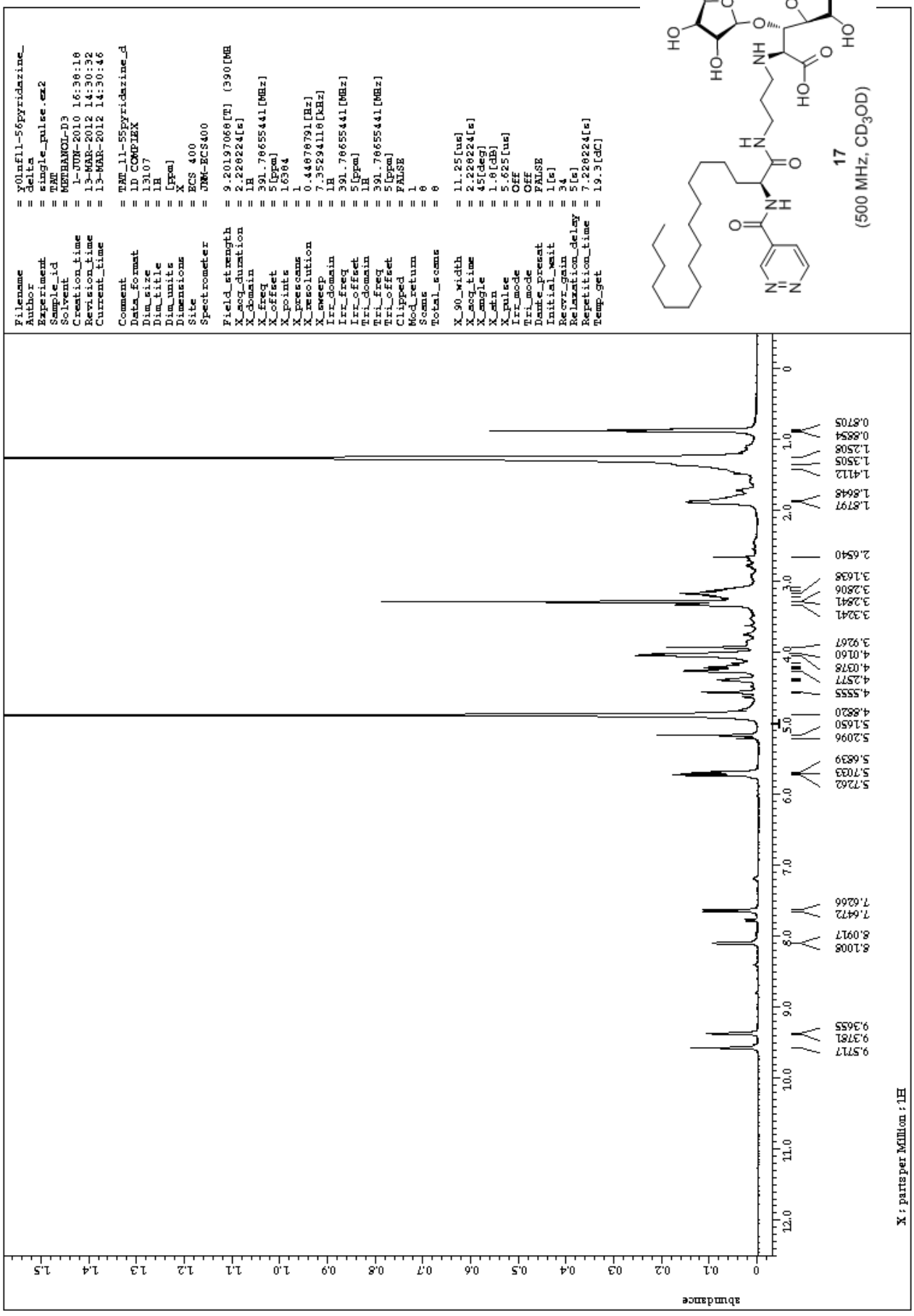
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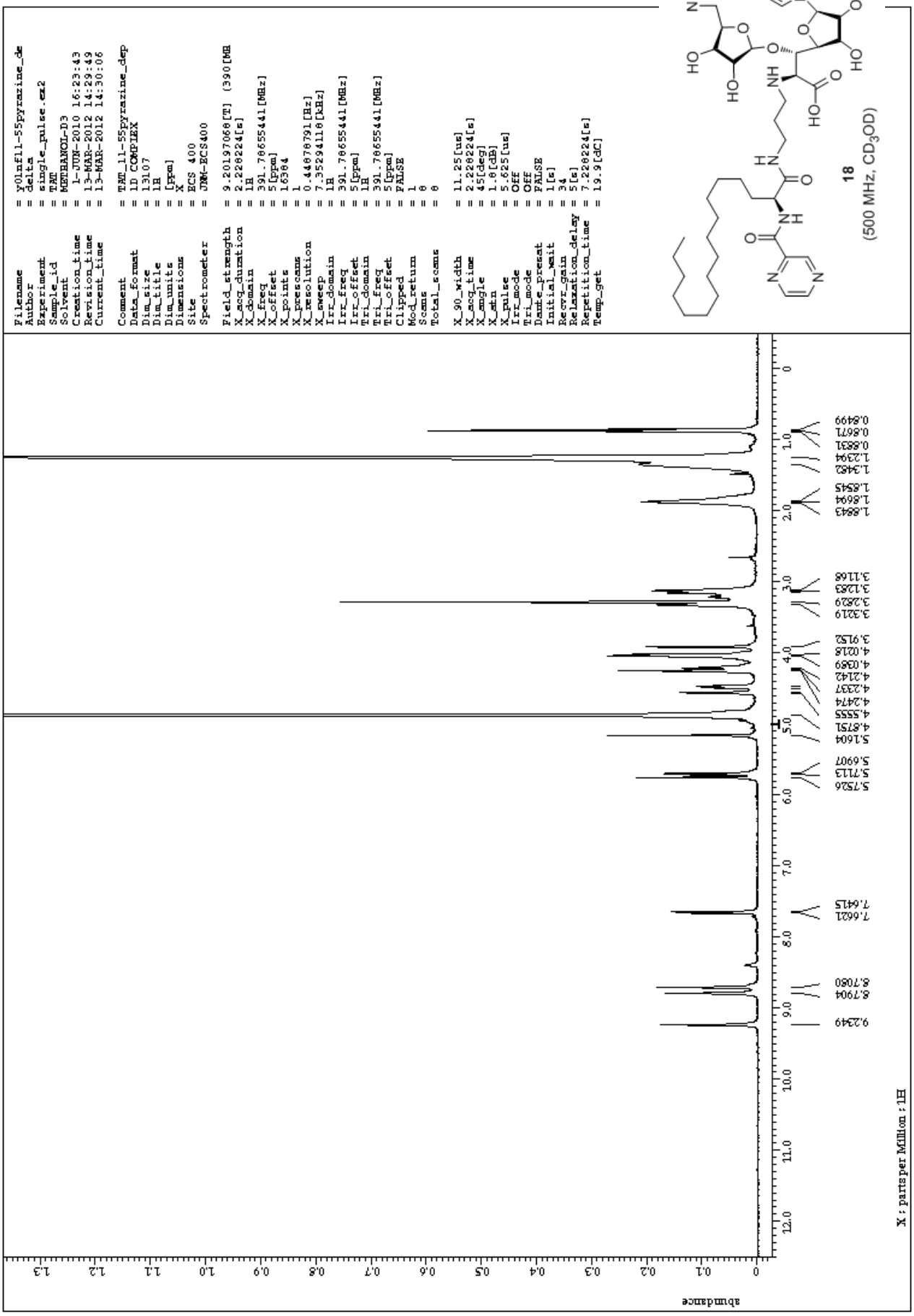
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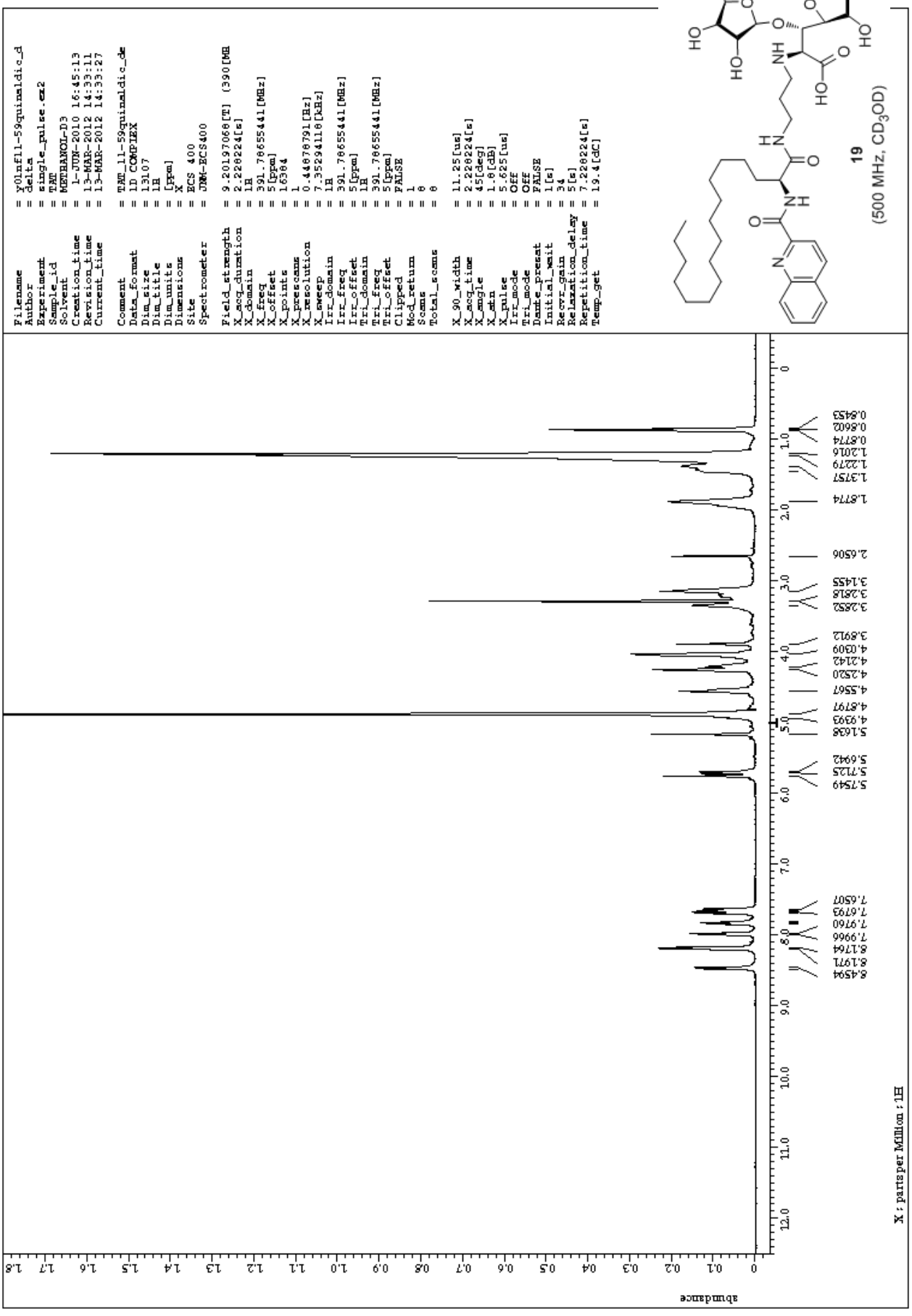
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(500 MHz, CD3OD)
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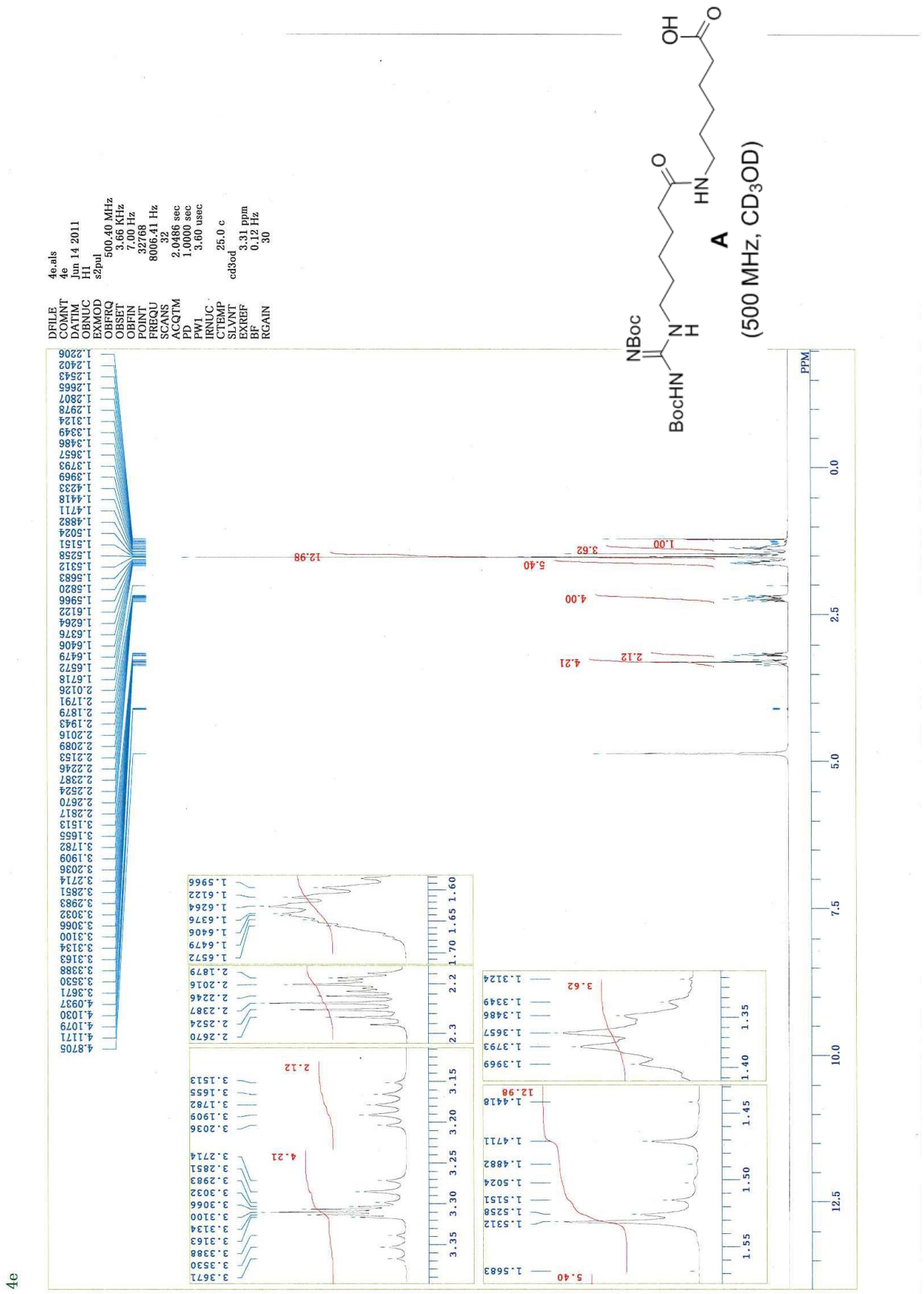
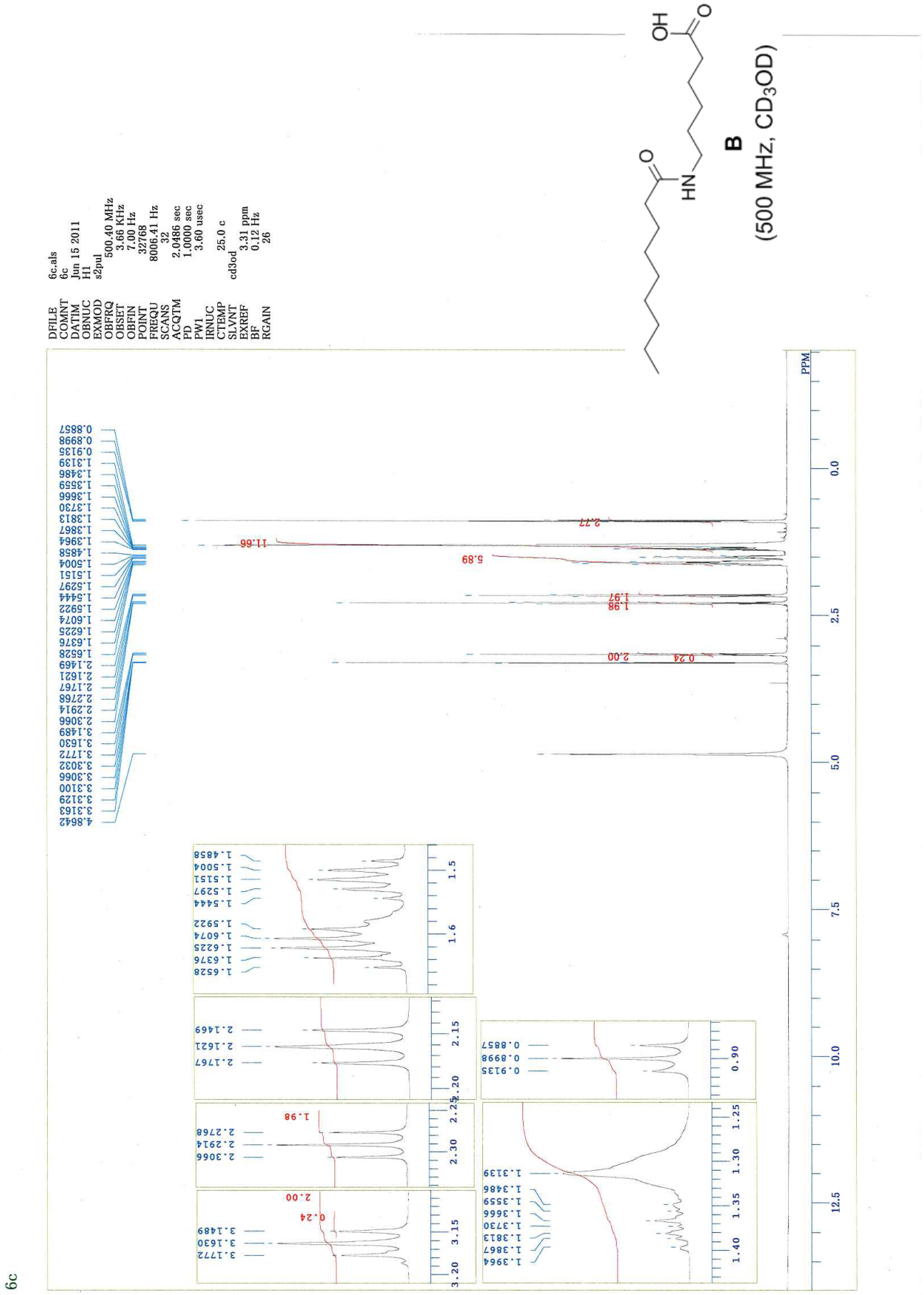
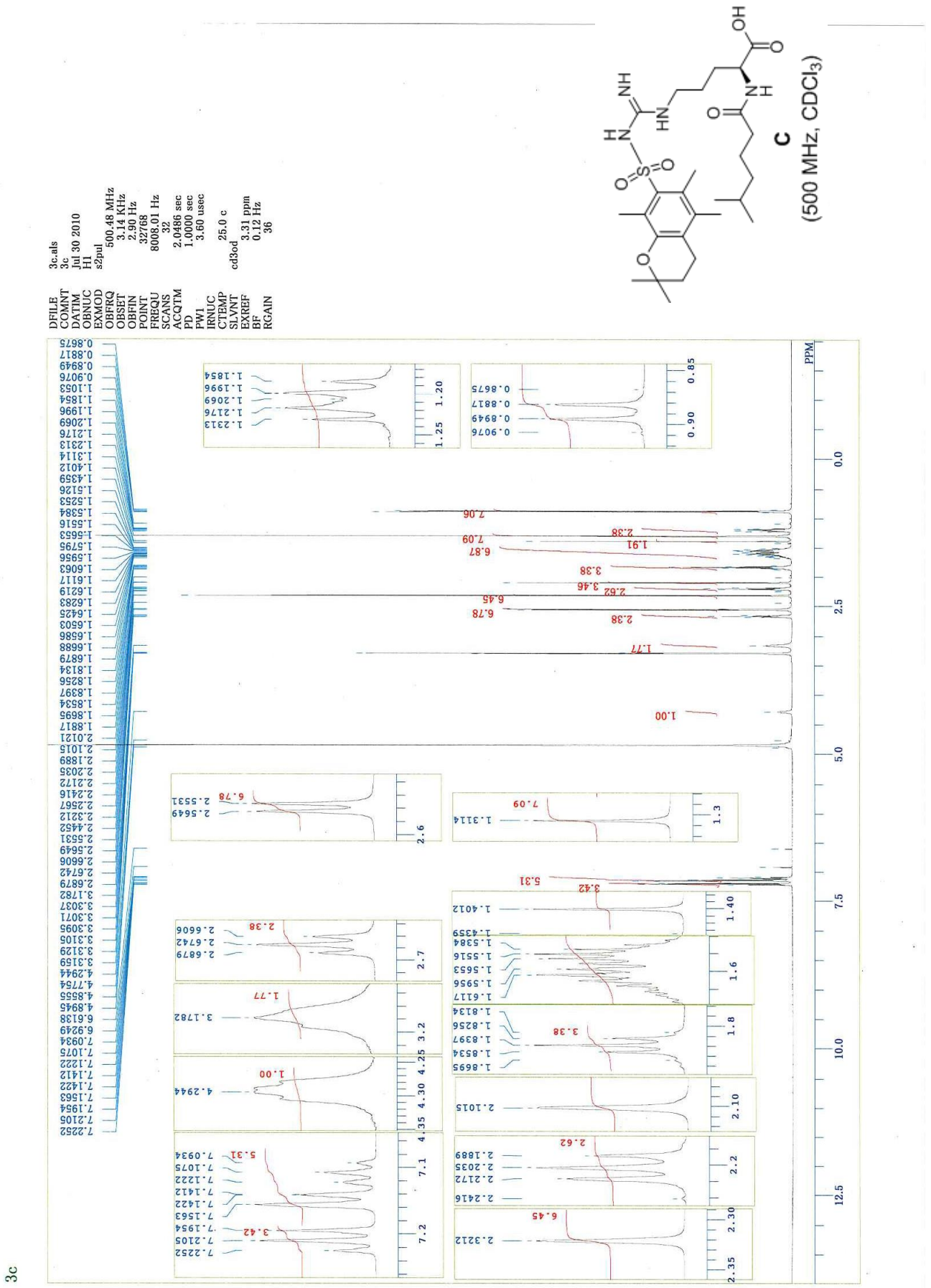
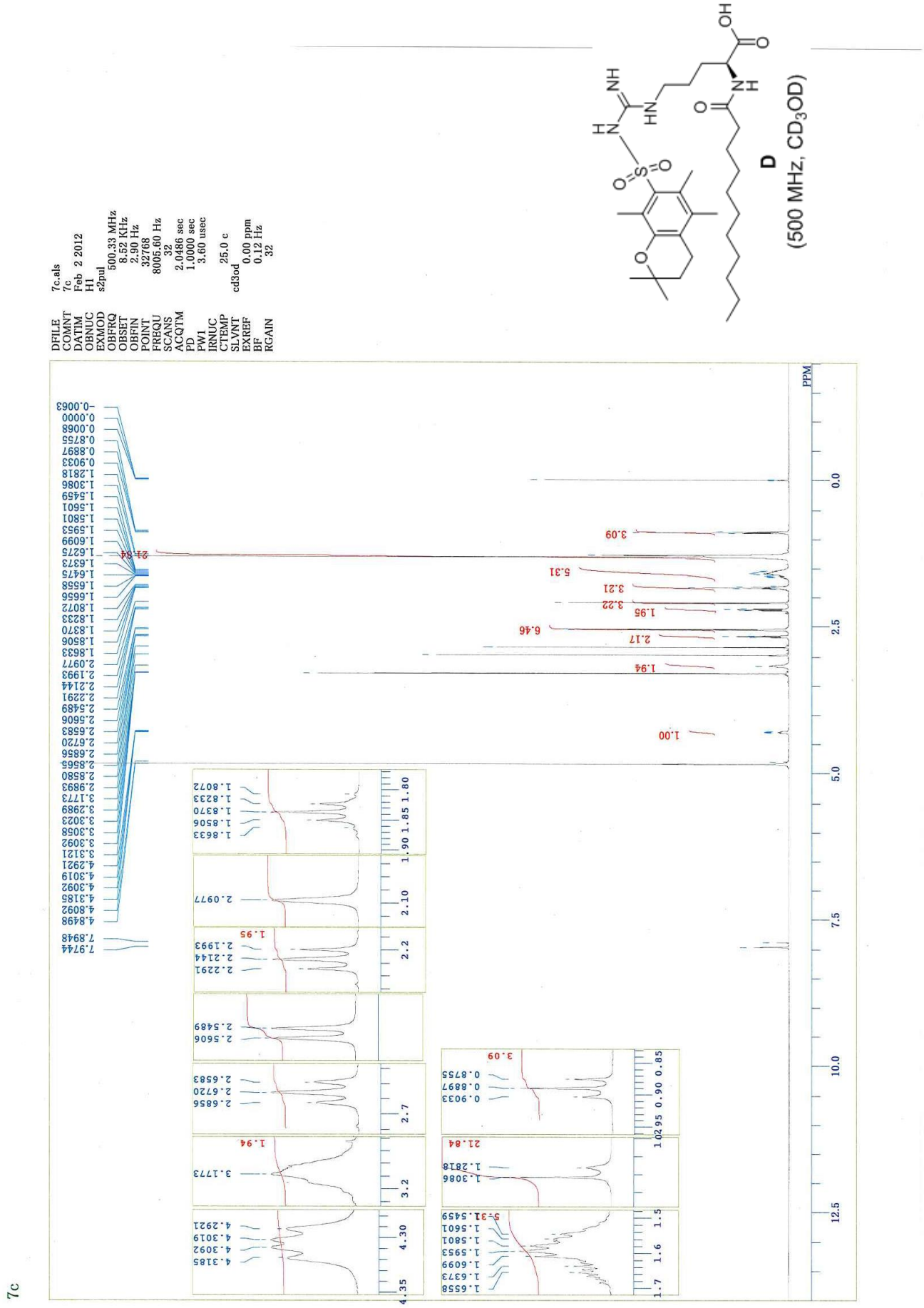
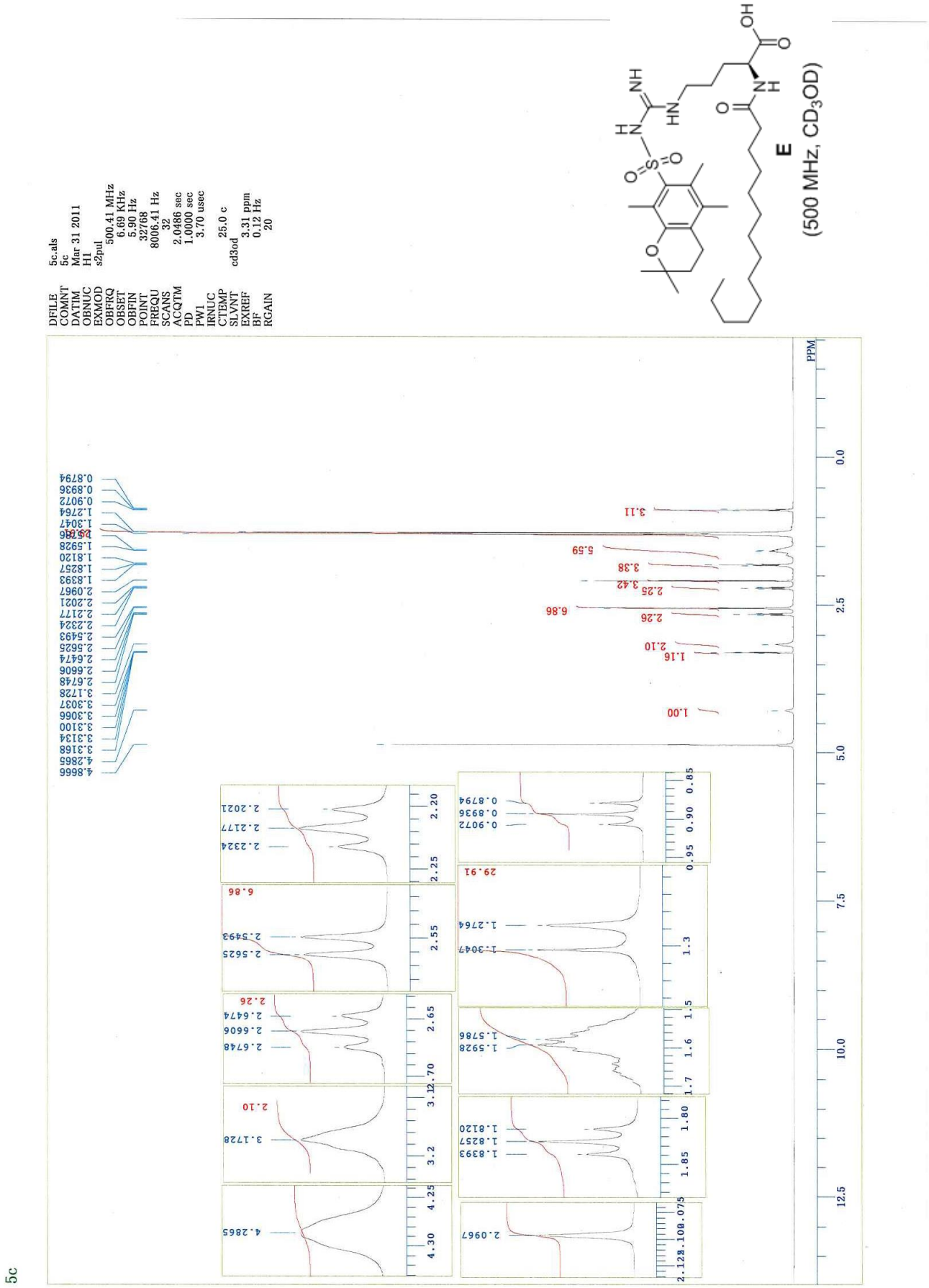
0.8602
0.8453


4e.als
4e
Jun 14 2011
H1
s2pul
500.40 MHz
3.66 KHz
7.00 Hz
32768
8006.41 Hz
32
2.0486 sec
1.0000 sec
3.60 usec
25.0 c
cd3od
3.31 ppm
0.12 Hz
30
NBoc
BocHN
N H
HN
O
OH
A
(500 MHz, CD3OD)
PPM
12.98
5.40
3.62
1.00
4.00
4.21
2.12
4e

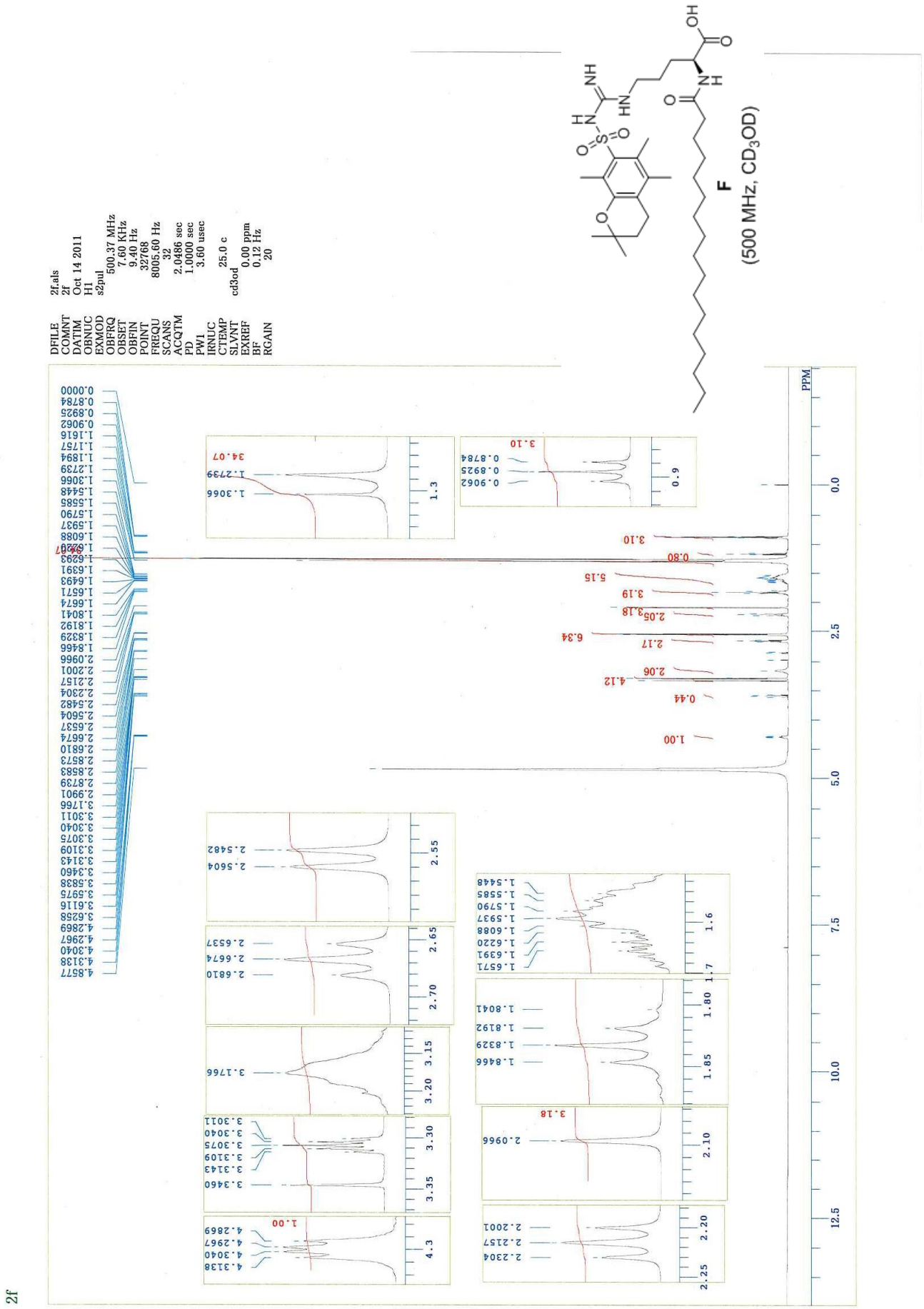

B
(500 MHz, CD3OD)
DFILE 6c.als
COMNT 6c
DATIM Jun 15 2011
OBNUC H1
EXMOD s2pul
OBFRQ 500.40 MHz
OBSET 3.66 KHz
OBFIN 7.00 Hz
POINT 32768
FREQU 8006.41 Hz
SCANS 32
ACQTM 2.0486 sec
PD 1.0000 sec
PW1 3.60 usec
IRNUC
CTEMP 25.0 c
SLVNT cd3od
EXREF 3.31 ppm
BF 0.12 Hz
RGAIN 26
PPM
6c

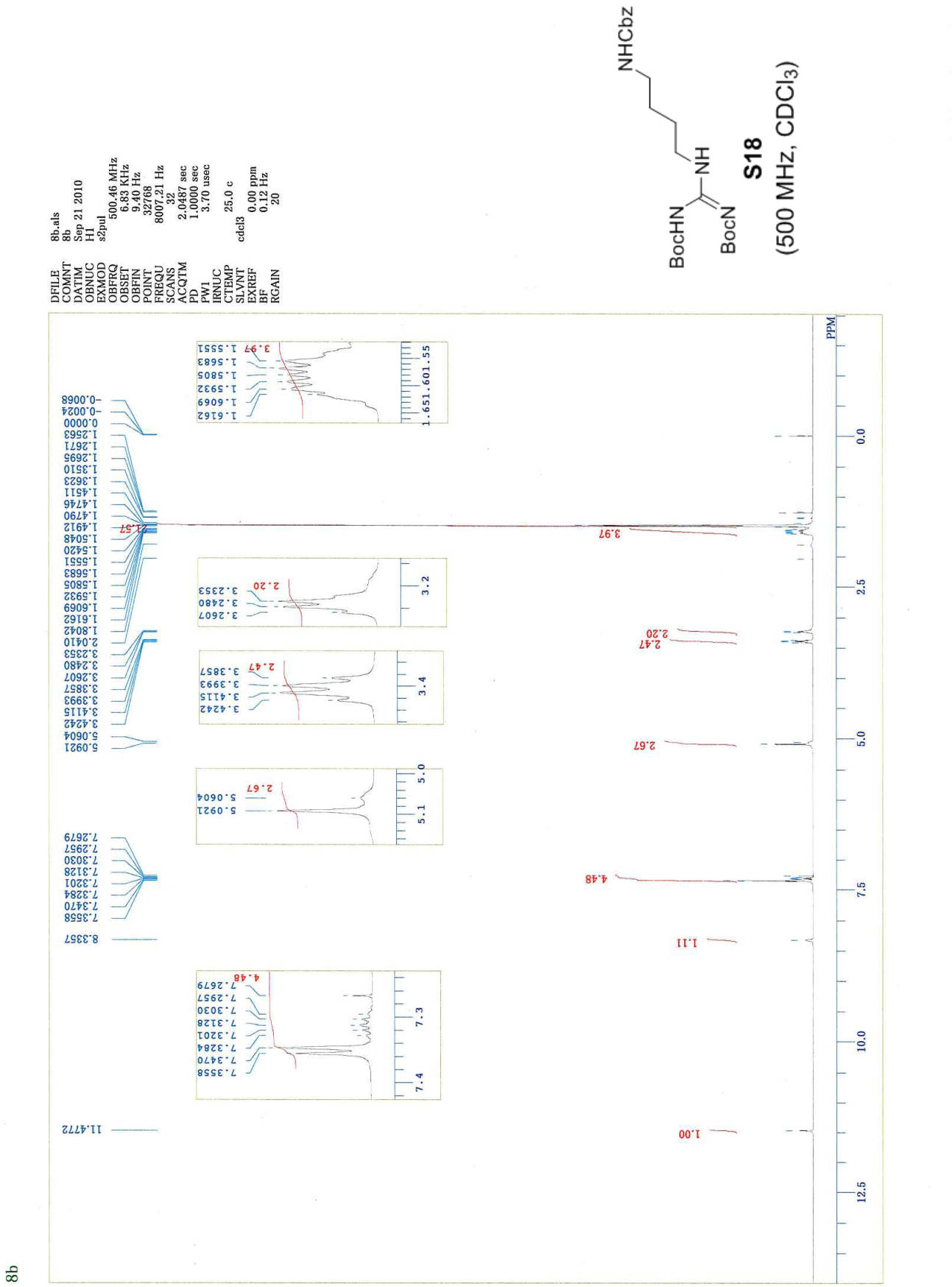

3c
(500 MHz, CDCl3)
c
DFILE 3c.als
COMNT 3c
DATIM Jul 30 2010
OBNUC H1
EXMOD s2pul
OBFRQ 500.48 MHz
OBSET 3.14 KHz
OBFIN 2.90 Hz
POINT 32768
FREQU 8008.01 Hz
SCANS 32
ACQTM 2.0486 sec
PD 1.0000 sec
PW1 3.60 usec
IRNUC
CTEMP 25.0 c
SLVNT cd3od
EXREF 3.31 ppm
BF 0.12 Hz
RGAIN 36
PPM

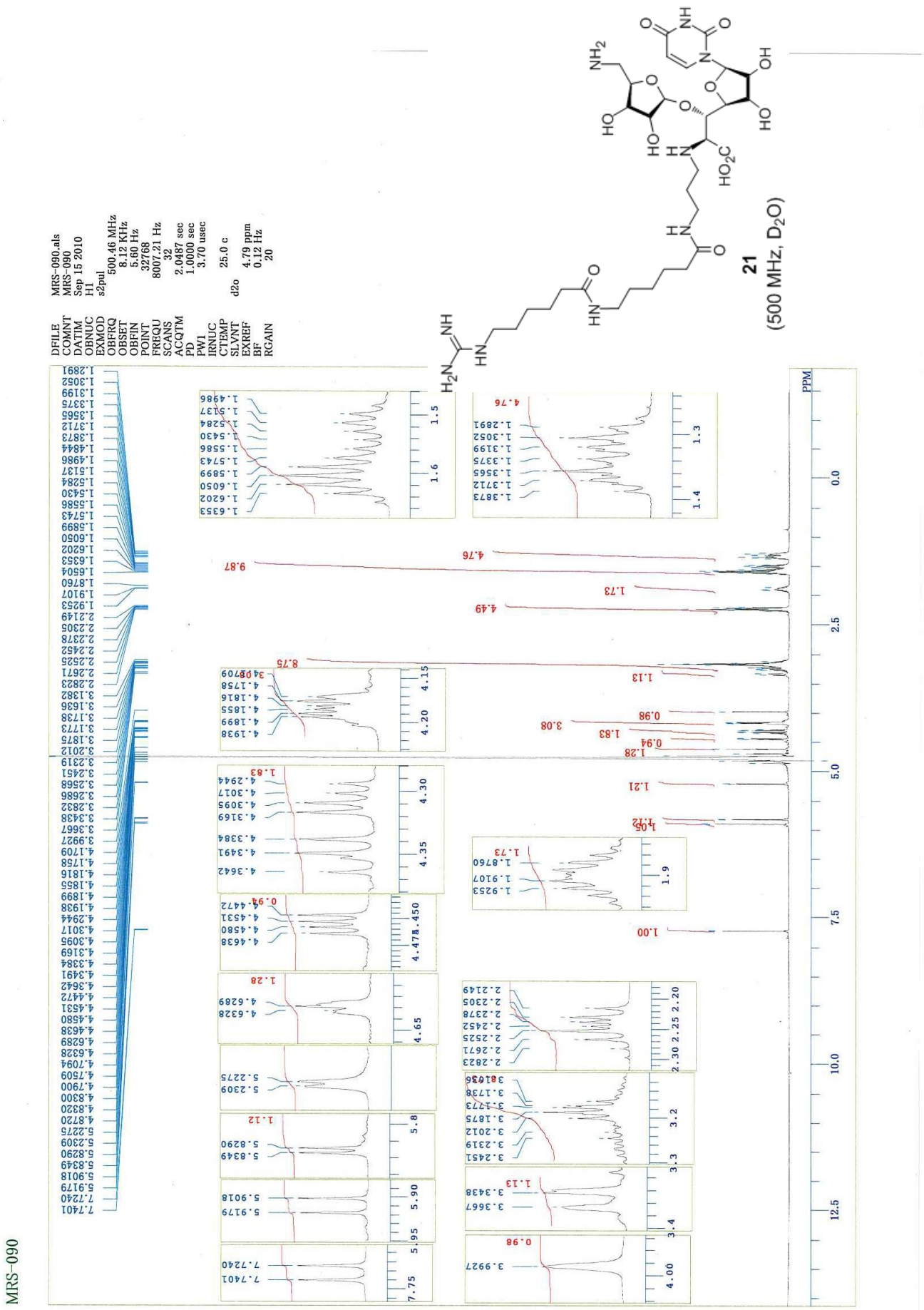

D
(500 MHz, CD3OD)
DFILE 7c.als
COMNT 7c
DATIM Feb 2 2012
OBNUC H1
EXMOD s2pul
OBFRQ 500.33 MHz
OBSET 8.52 KHz
OBFIN 2.90 Hz
POINT 32768
FREQU 8005.60 Hz
SCANS 32
ACQTM 2.0486 sec
PD 1.0000 sec
PW1 3.60 usec
IRNUC
CTEMP 25.0 c
SLVNT cd3od
EXREF 0.00 ppm
BF 0.12 Hz
RGAIN 32
PPM
7c

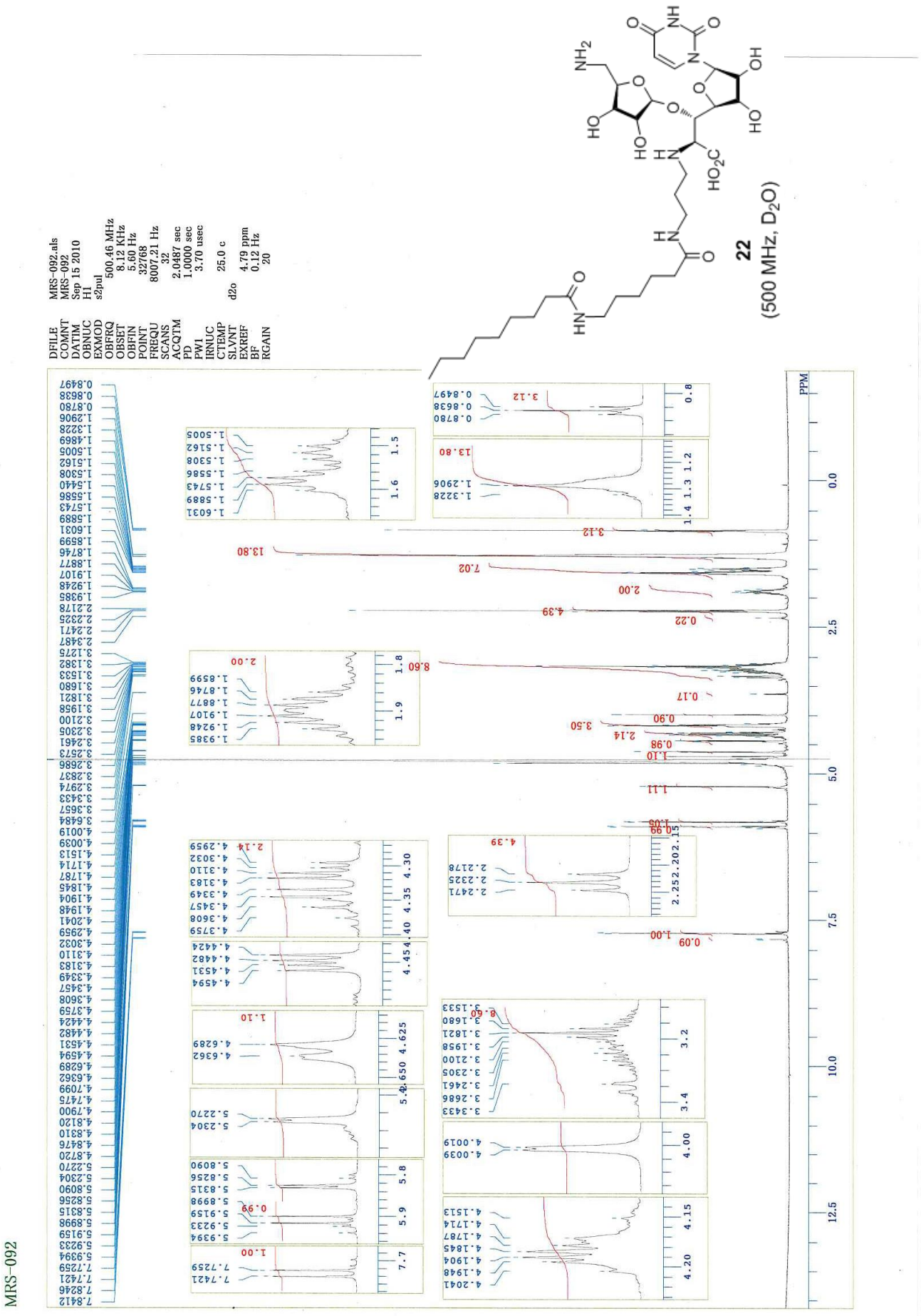

DFILE 5c.als
COMNT 5c
DATIM Mar 31 2011
OBNUC H1
EXMOD s2pul
OBFRQ 500.41 MHz
OBSET 6.69 KHz
OBFIN 5.90 Hz
POINT 32768
FREQU 8006.41 Hz
SCANS 32
ACQTM 2.0486 sec
PD 1.0000 sec
PW1 3.70 usec
IRNUC
CTEMP 25.0 c
SLVNT cd3od
EXREF 3.31 ppm
BF 0.12 Hz
RGAIN 20
E
(500 MHz, CD3OD)
PPM
0.0
2.5
5.0
7.5
10.0
12.5
3.11
5.59
3.38
3.42
2.25
6.86
2.26
2.10
1.16
1.00
4.8666
4.2865
3.3168
3.3134
3.3100
3.3066
3.3037
3.1728
2.6748
2.6606
2.6474
2.5493
2.5625
2.3224
2.2177
2.2021
2.0967
1.8393
1.8257
1.8120
1.5928
1.5786
1.3047
1.2764
0.9072
0.8936
0.8794

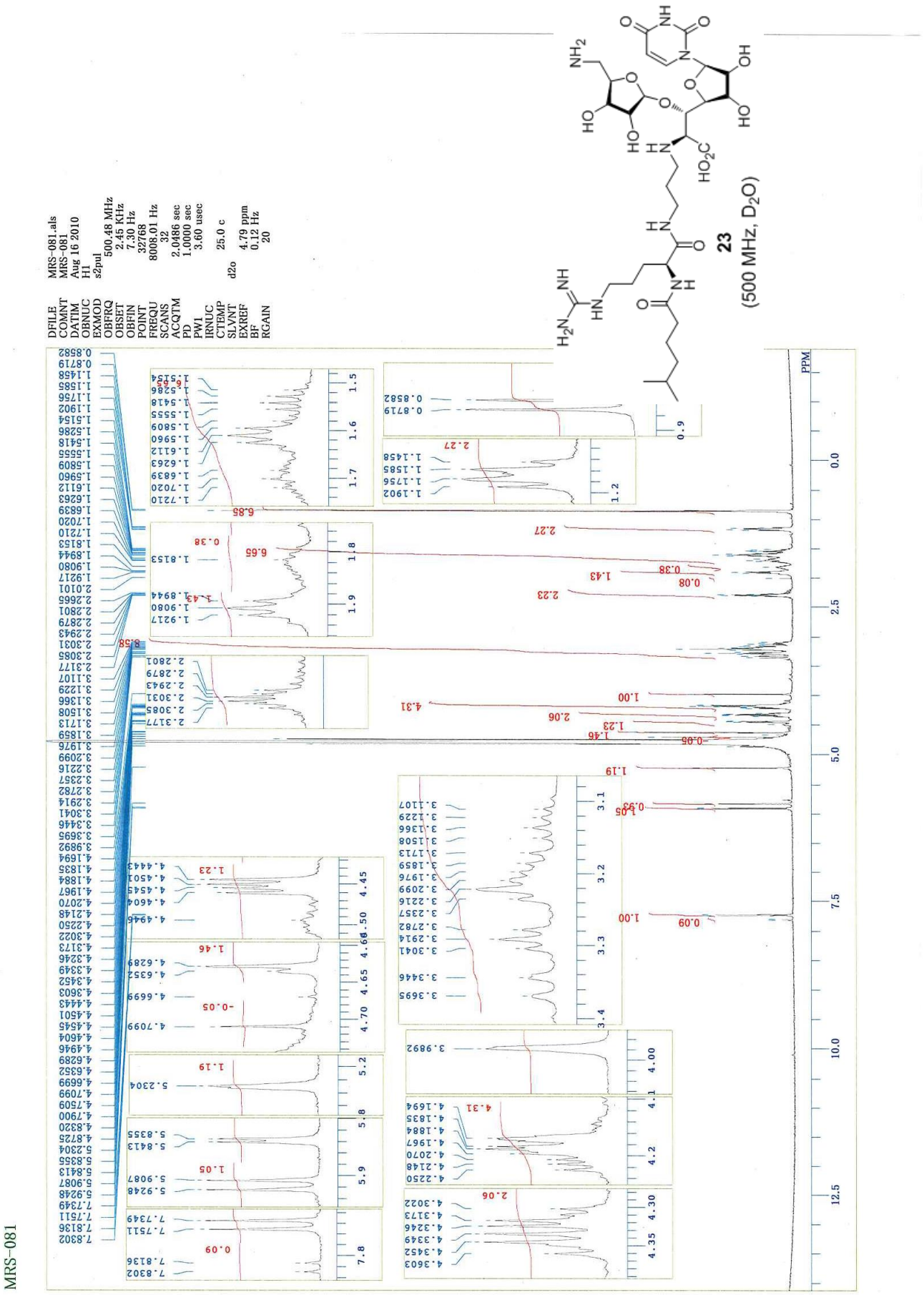
5c

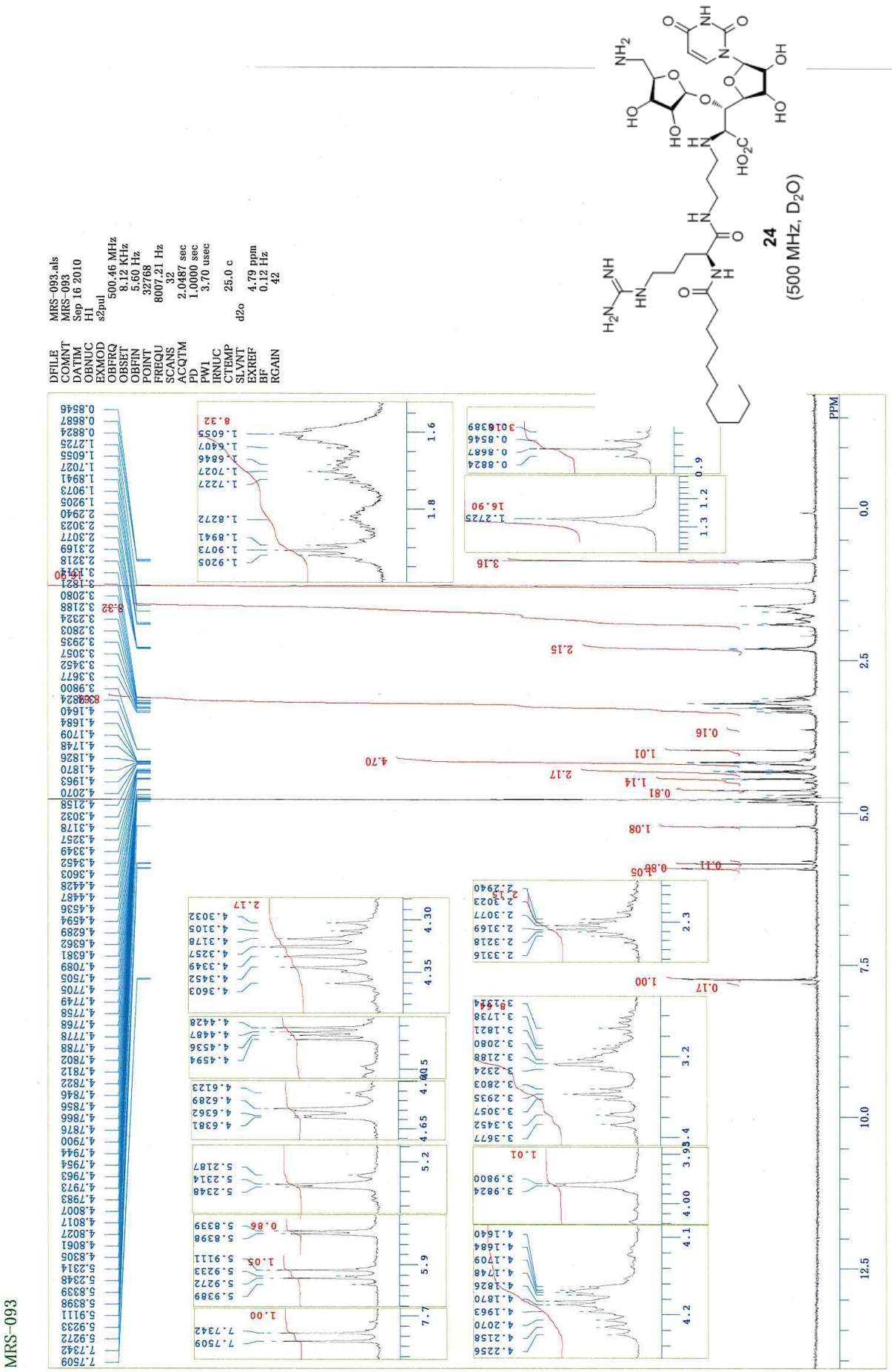

F
(500 MHz, CD_3OD)
2f
PPM

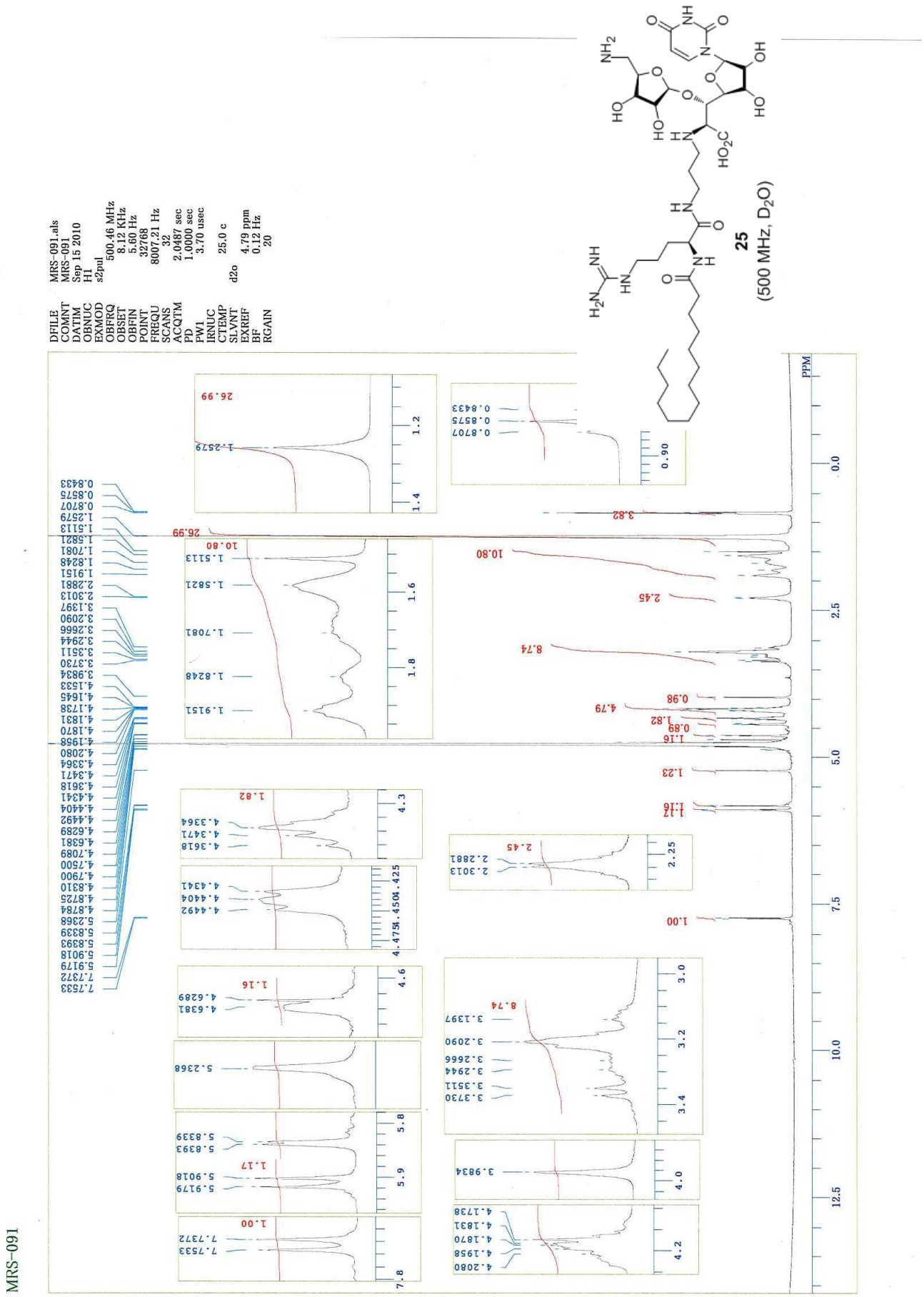

NHCbz
BocHN
NH
BocN
S18
(500 MHz, CDCl3)
8b

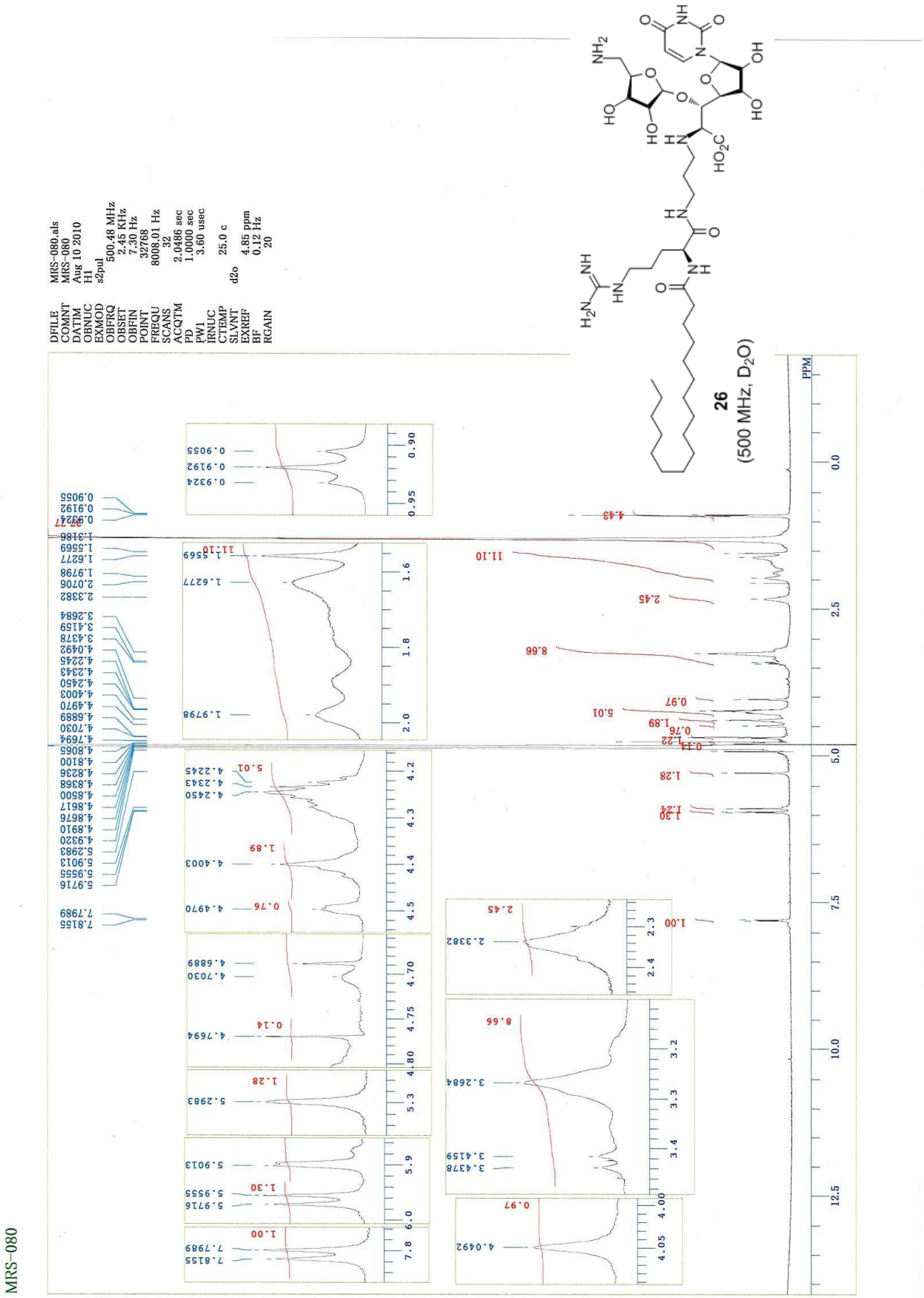

21
(500 MHz, D2O)
MRS-090.als
MRS-090
Sep 15 2010
H1
s2pul
500.46 MHz
8.12 KHz
5.60 Hz
32768
8007.21 Hz
32
2.0487 sec
1.0000 sec
3.70 usec
25.0 c
d2o
4.79 ppm
0.12 Hz
20
DFILE
COMNT
DATIM
OBNUC
EXMOD
OBFRQ
OBSET
OBFIN
POINT
FREQU
SCANS
ACQTM
PD
PW1
IRNUC
CTEMP
SLVNT
EXREF
BF
RGAIN
PPM
MRS-090

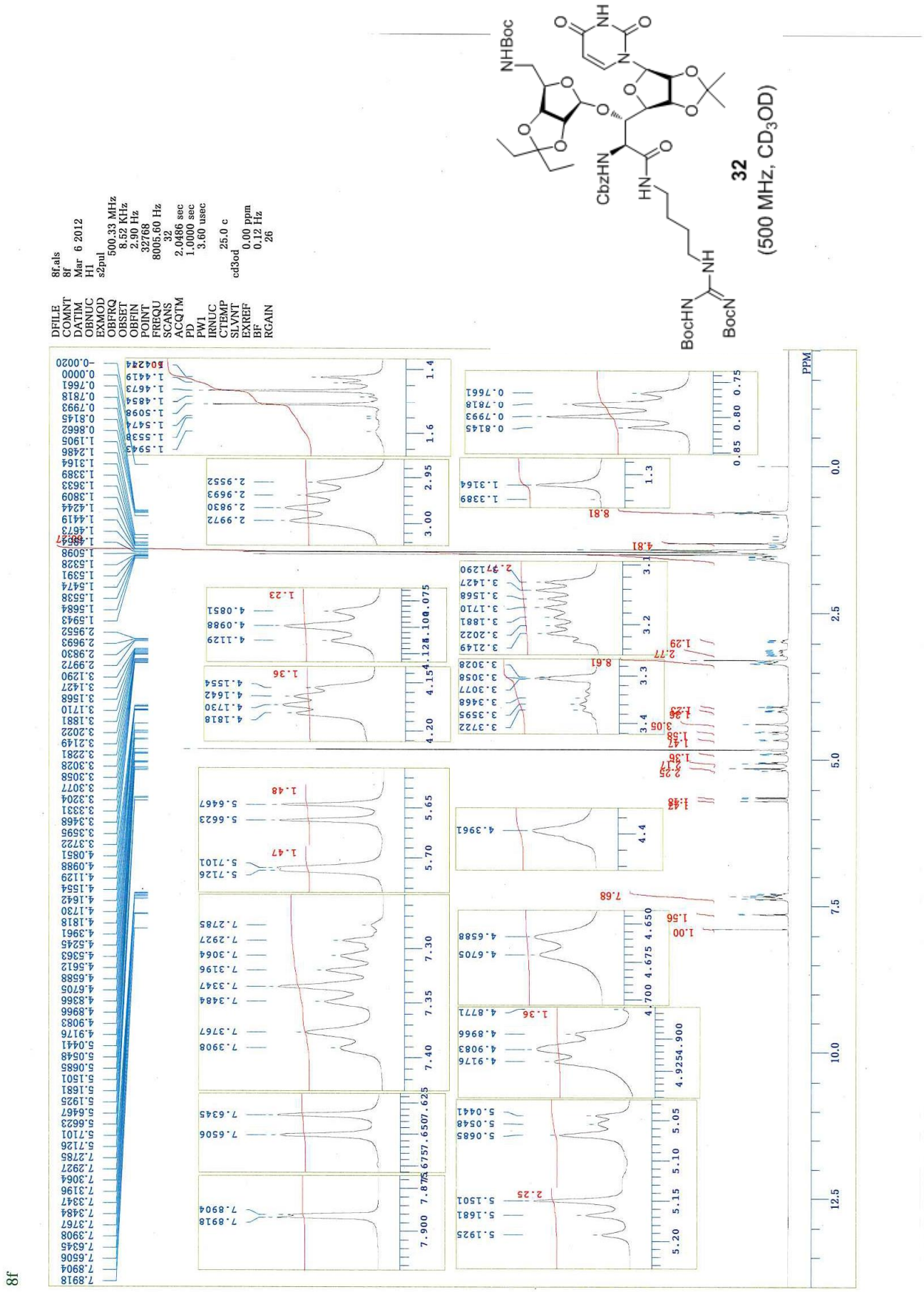

22
(500 MHz, D_2O)
DFILE MRS-092.als
COMNT MRS-092
DATIM Sep 15 2010
OBNUC H1
EXMOD s2pul
OBFRQ 500.46 MHz
OBSET 8.12 KHz
OBFIN 5.60 Hz
POINT 32768
FREQU 8007.21 Hz
SCANS 32
ACQTM 2.0487 sec
PD 1.0000 sec
PW1 3.70 usec
IRNUC
CTEMP 25.0 c
SLVNT d2o
EXREF 4.79 ppm
BF 0.12 Hz
RGAIN 20
MRS-092
PPM


23
(500 MHz, D2O)
MRS-081
DFILE MRS-081.als
COMNT MRS-081
DATIM Aug 16 2010
OBNUC H1
EXMOD s2pul
OBFRQ 500.48 MHz
OBSET 2.45 KHz
OBFIN 7.30 Hz
POINT 32768
FREQU 8008.01 Hz
SCANS 32
ACQTM 2.0486 sec
PD 1.0000 sec
PW1 3.60 usec
IRNUC
CTEMP 25.0 c
SLVNT d2o
EXREF 4.79 ppm
BF 0.12 Hz
RGAIN 20
PPM

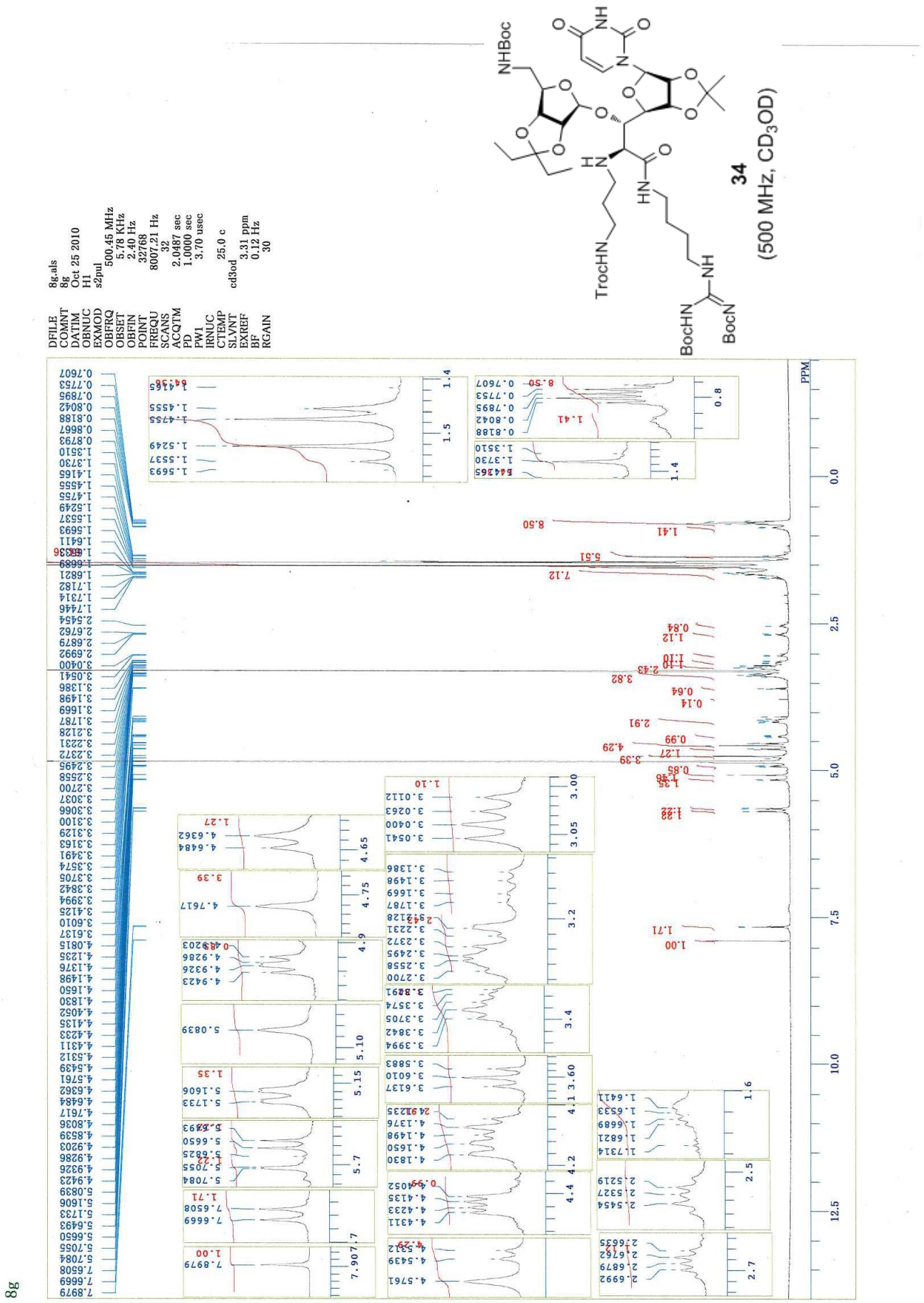

24
(500 MHz, D2O)
MRS-093
PPM

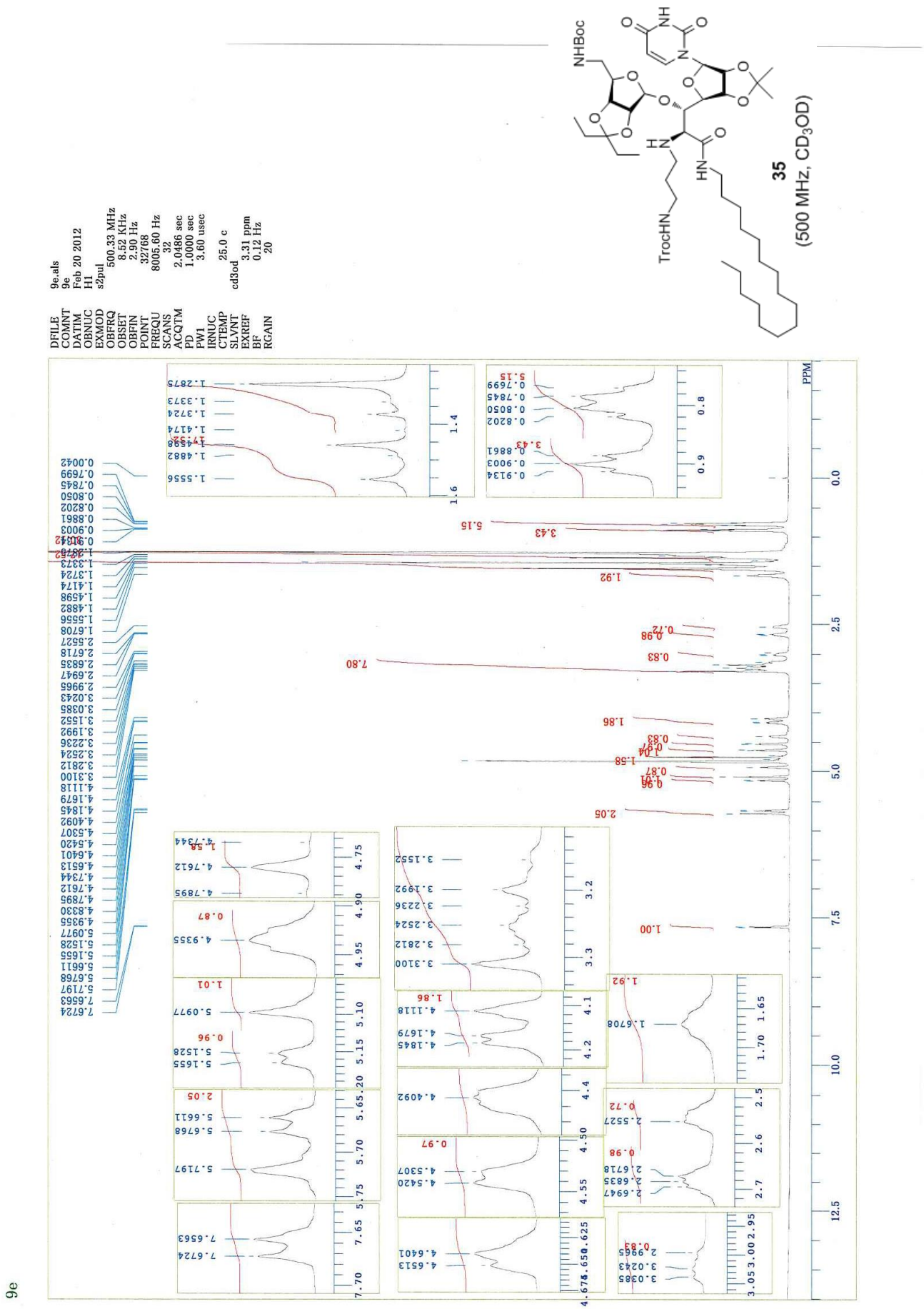

25
(500 MHz, D2O)
DFILE MRS-091.als
COMNT MRS-091
DATIM Sep 15 2010
OBNUC H1
EXMOD s2pul
OBFRQ 500.46 MHz
OBSET 8.12 KHz
OBFIN 5.60 Hz
POINT 32768
FREQU 8007.21 Hz
SCANS 32
ACQTM 2.0487 sec
PD 1.0000 sec
PW1 3.70 usec
IRNUC
CTEMP 25.0 c
SLVNT d2o
EXREF 4.79 ppm
BF 0.12 Hz
RGAIN 20
MRS-091
PPM

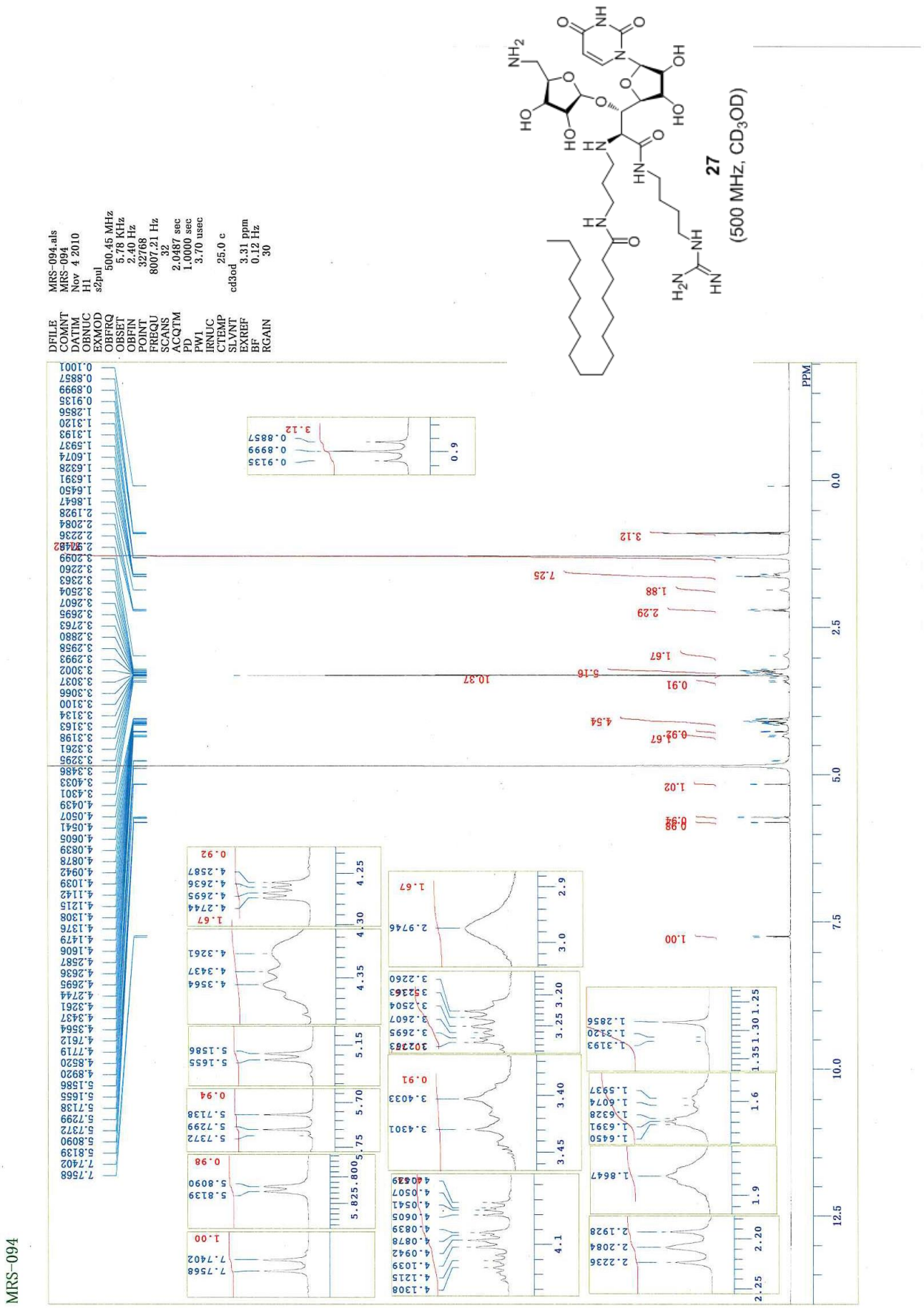

MRS-080
26
(500 MHz, D2O)
PPM
DFILE MRS-080.als
COMNT MRS-080
DATIM Aug 10 2010
OBNUC H1
EXMOD s2pul
OBFRQ 500.48 MHz
OBSET 2.45 KHz
OBFIN 7.30 Hz
POINT 32768
FREQU 8008.01 Hz
SCANS 32
ACQTM 2.0486 sec
PD 1.0000 sec
PW1 3.60 usec
IRNUC
CTEMP 25.0 c
SLVNT d2o
EXREF 4.85 ppm
BF 0.12 Hz
RGAIN 20

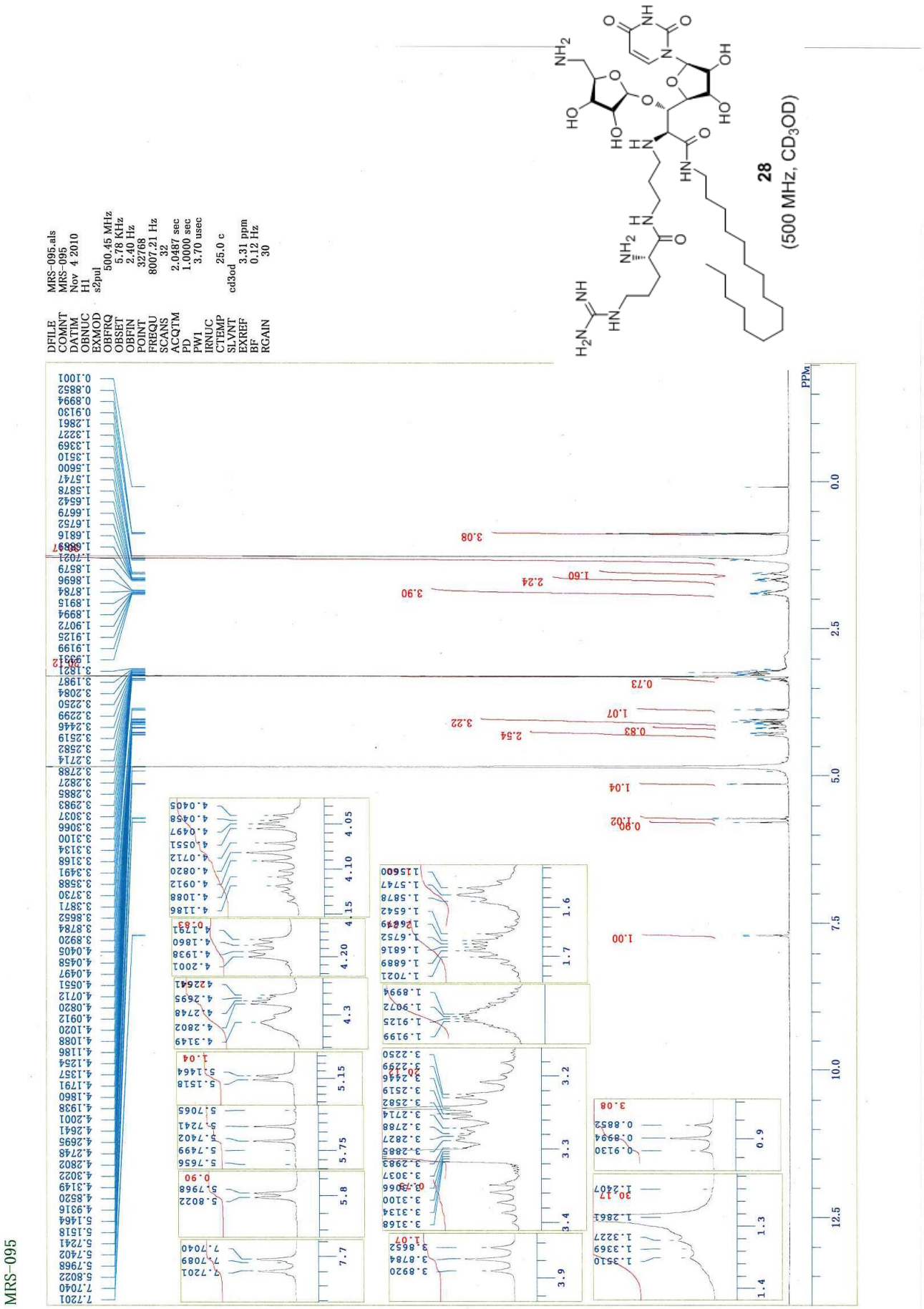

NHBoc
NH
CbzHN
HN
NH
BocHN
BocN
32
(500 MHz, CD3OD)
8f.als
8f
Mar 6 2012
H1
s2pul
500.33 MHz
8.52 KHz
2.90 Hz
32768
8005.60 Hz
32
2.0486 sec
1.0000 sec
3.60 usec
25.0 c
cd3od
0.00 ppm
0.12 Hz
26
DFILE
COMNT
DATIM
OBNUC
EXMOD
OBFRQ
OBSET
OBFIN
POINT
FREQU
SCANS
ACQTM
PD
PW1
IRNUC
CTEMP
SLVNT
EXREF
BF
RGAIN
PPM

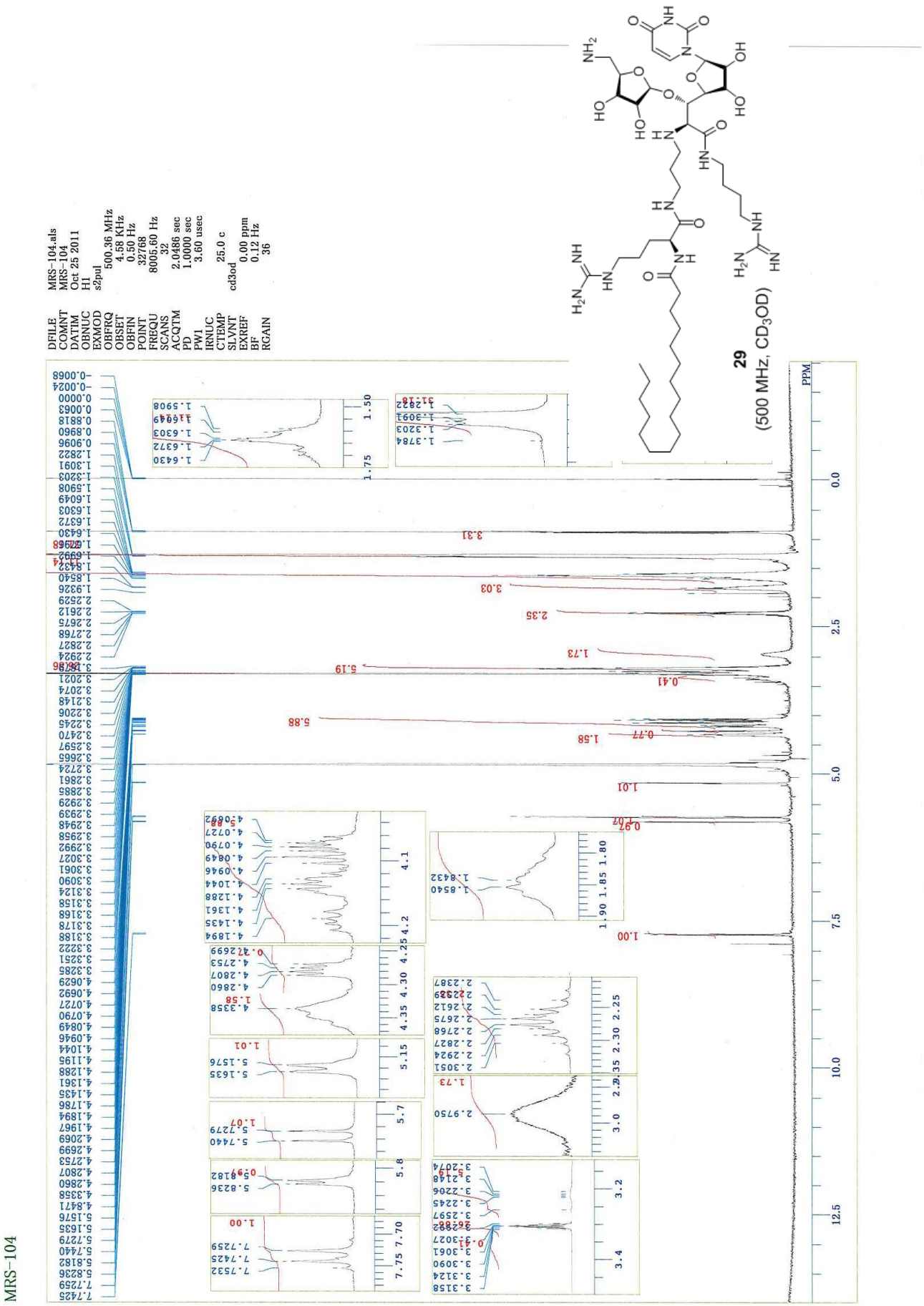
8f


NHBoc
TrocHN
BocHN
BocN
34
(500 MHz, CD3OD)
DFILE 8g.als
COMNT 8g
DATIM Oct 25 2010
OBNUC H1
EXMOD s2pul
OBFRQ 500.45 MHz
OBSET 5.78 KHz
OBFIN 2.40 Hz
POINT 32768
FREQU 8007.21 Hz
SCANS 32
ACQTM 2.0487 sec
PD 1.0000 sec
PW1 3.70 usec
IRNUC
CTEMP 25.0 c
SLVNT cd3od
EXREF 3.31 ppm
BF 0.12 Hz
RGAIN 30
PPM
8g


NHBoc
TrocHN
35
(500 MHz, CD3OD)
9e.als
9e
Feb 20 2012
H1
s2pul
500.33 MHz
8.52 KHz
2.90 Hz
32768
8005.60 Hz
32
2.0486 sec
1.0000 sec
3.60 usec
25.0 c
cd3od
3.31 ppm
0.12 Hz
20
DFILE
COMNT
DATIM
OBNUC
EXMOD
OBFRQ
OBSET
OBFIN
POINT
FREQU
SCANS
ACQTM
PD
PW1
IRNUC
CTEMP
SLVNT
EXREF
BF
RGAIN
PPM
9e


MRS-094
27
(500 MHz, CD3OD)
DFILE MRS-094.als
COMNT MRS-094
DATIM Nov 4 2010
OBNUC H1
EXMOD s2pul
OBFRQ 500.45 MHz
OBSET 5.78 KHz
OBFIN 2.40 Hz
POINT 32768
FREQU 8007.21 Hz
SCANS 32
ACQTM 2.0487 sec
PD 1.0000 sec
PW1 3.70 usec
IRNUC
CTEMP 25.0 c
SLVNT cd3od
EXREF 3.31 ppm
BF 0.12 Hz
RGAIN 30
PPM


28
(500 MHz, CD_3OD)
MRS-095
PPM


MRS-104
29
(500 MHz, CD_3OD)
PPM