Supporting Information

"Direct Aldol Reactions Catalyzed by Intramolecularly Folded Prolinamide Dendrons: Dendrimer Effects on the Stereoselectivity"

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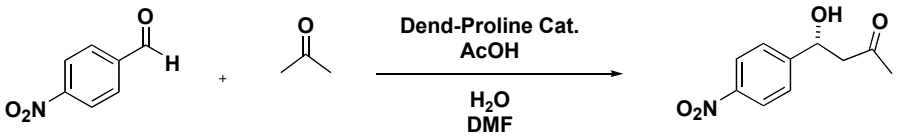
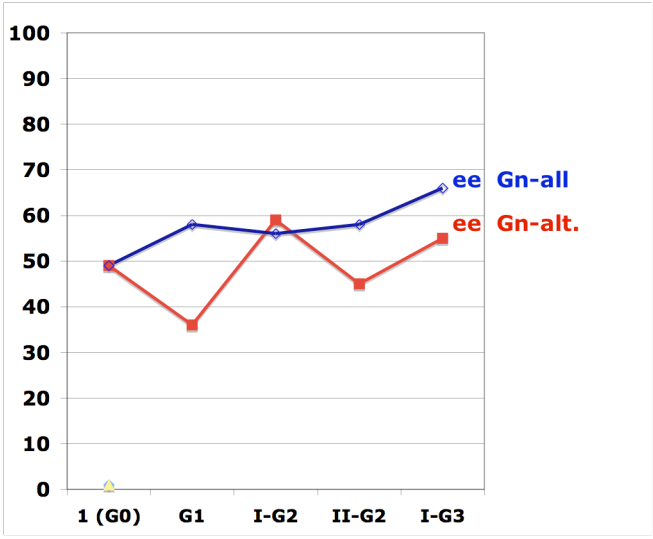
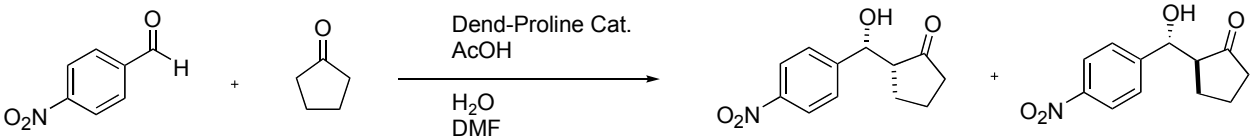
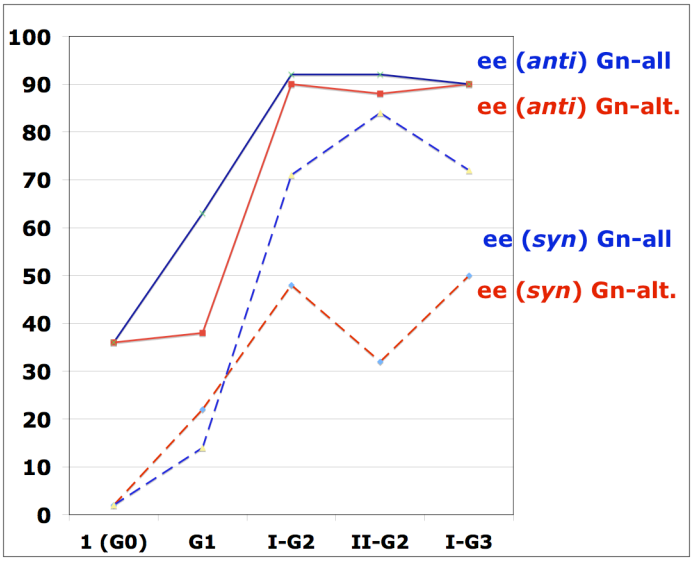
A. Selectivity Trends: Plots of enantioselectivity versus dendron generation.







syn *anti*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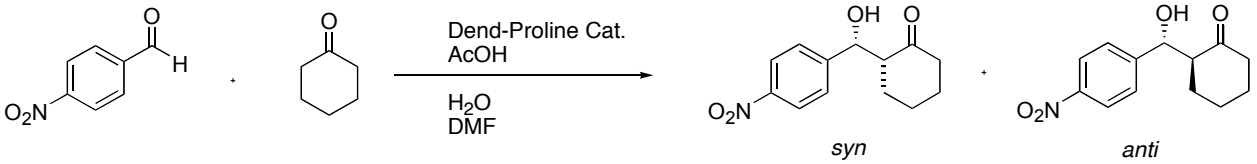
90
80
70
60
50
40
30
20
10
0
1 (G0)
G1
I-G2
II-G2
I-G3
ee (anti) Gn-all
ee (anti) Gn-alt.
ee (syn) Gn-all
ee (syn) Gn-alt.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H
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H2O
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O2N
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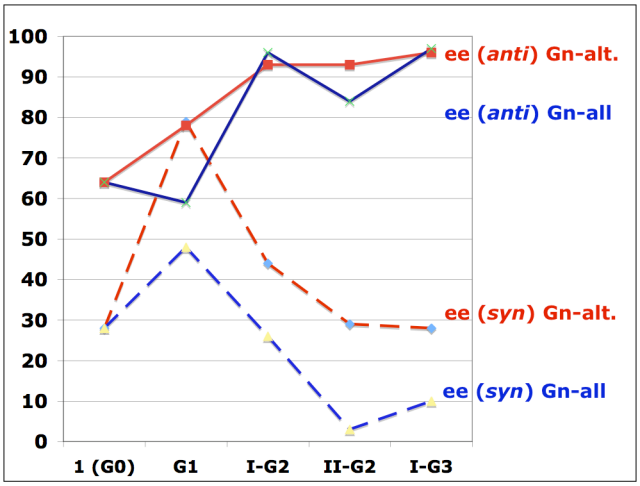
O
O2N
anti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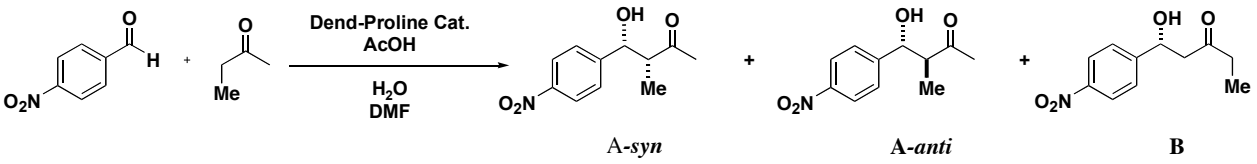
0
1 (G0)
G1
I-G2
II-G2
I-G3
ee (anti) Gn-alt.
ee (anti) Gn-all
ee (syn) Gn-alt.
ee (syn) Gn-all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DMF
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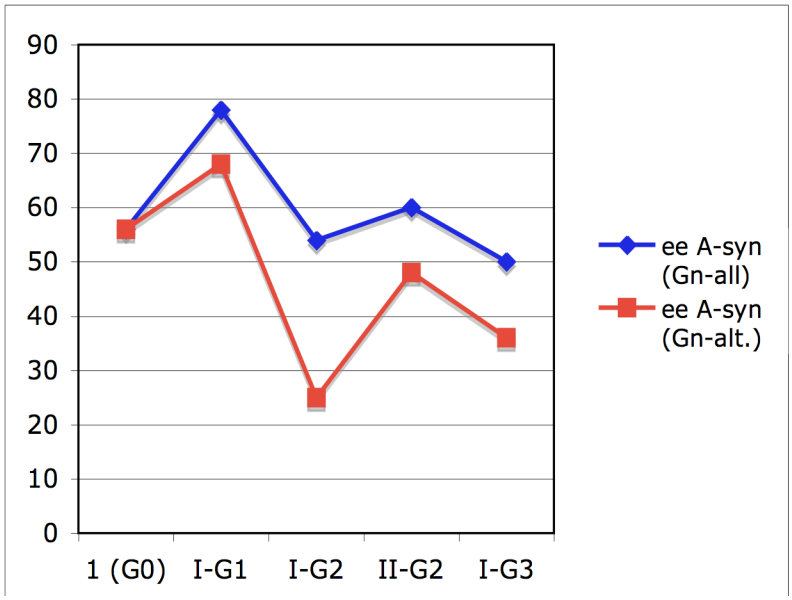
A-anti
OH
O
O2N
Me
B


90
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70
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30
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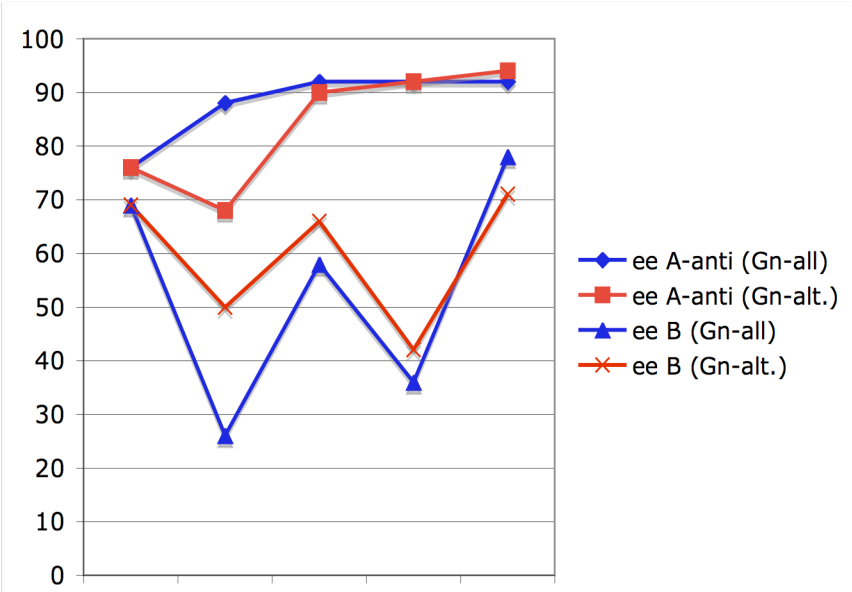
10
0
1 (G0)
I-G1
I-G2
II-G2
I-G3
ee A-syn (Gn-all)
ee A-syn (Gn-alt.)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90
80
70
60
50
40
30
20
10
0
ee A-anti (Gn-all)
ee A-anti (Gn-alt.)
ee B (Gn-all)
ee B (Gn-alt.)

Experimental section.

B. General Methods. Melting Points were determined in open capillaries and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Model 1600 instrument. Fourier transform-infrared (FTIR) were performed on FTIR spectrometer (Thermo Nicolet, Madison, WI). ^{1}H NMR were recorded at 400 or 500 MHz and ^{13}C NMR spectra at 100 or 125 MHz on a Bruker DPX-400 or DPX-500 instrument as indicated. EI or FAB mass spectra were recorded at The Ohio State University Chemical Instrumentation Center. Matrix-assisted laser desorption ionization-time of flight MS (MALDI-TOF MS) spectrometry was performed using 2,5-dihydroxybenzoic acid as the matrix in tetrahydrofuran (THF). All reactions were performed in oven or flame dried glassware under a nitrogen atmosphere unless otherwise noted. N,N-Dimethylformamide (DMF) was dried by distillation from activated 4 Å molecular sieves; Tetrahydrofuran (THF) was distilled from sodium/benzophenone ketyl; dichloromethane was distilled from calcium hydride; pyridine was distilled from calcium hydride; triethylamine was distilled from calcium hydride; chloroform was distilled from calcium carbonate. Boc-Pro-OH

was purchased from Novabiochem and used without further purification. Chromatographic separations were performed on silica gel 60 (230-400 mesh, 60 Å) using the indicated solvents.

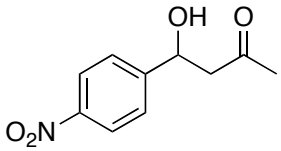
C. General Procedure for Aldol Reaction: To a solution of catalyst (as indicated in the table, mmol) in DMF (0.5 mL, 1.0M) were added AcOH (1 eq. per prolinamide catalytic unit) and freshly distilled ketone (27 eq). After stirring at rt for 15 min, water (90 µl, 5.0 mmol, 10 eq) and 4-nitrobenzaldehyde (76 mg, 0.5 mmol) were added. The resulting mixture was stirred at rt for the indicated time. The reaction was treated with saturated aqueous ammonium chloride (1 mL). This mixture was diluted with water (20 mL) and extracted with ethyl acetate (3 x 10 mL). The combined organic layers were washed with water (10 mL), brine (10 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (20-40% EtOAc/pet ether) to give pure aldol products.

D. Representative Procedure for Aldol Reaction between Cyclohexanone and 4-nitrobenzaldehyde Catalyzed by G3-I-All-Cat (5): To a solution of G3-I-All-Cat **(5)** (13 mg, 0.005 mmol) in anhydrous DMF (0.2 mL) were added AcOH (2.3 µl, 0.04 mmol) and freshly distilled cyclohexanone (0.56 mL, 5.4 mmol). After stirring at rt for 15 min, water (36 µl, 2.0 mmol) and 4-nitrobenzaldehyde (30 mg, 0.2 mmol) were added. The resulting mixture was stirred at rt for 42 h. The reaction was treated with saturated aqueous ammonium chloride (1 mL). This mixture was diluted with water (10 mL) and extracted with ethyl acetate (3 x 10 mL). The combined organic layers were washed with water (10 mL), brine (10 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (20-40% EtOAc/pet ether) to give pure aldol products, 2-[Hydroxy-(4-nitrophenyl)-methyl]-

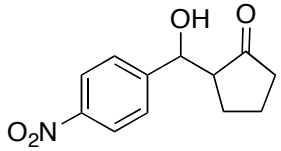
cyclohexanone (49.5 mg, 0.1985 mmol, 99%), as a white solid. The diastereoselectivity was determined by ^{1}H NMR analysis to be 21:1 (*anti:syn*). The enantioselectivity was determined by chiral HPLC (Daicel Chiralpak IA, 20% *i*-PrOH/hexane, UV 254 nm, Flow rate 1.0 mL/min). 97% ee for *anti* isomer (major), t_R 19.3 min, (minor) t_R 13.8 min. 10% ee for *syn* isomer (major), t_R 10.1 min, (minor) t_R 13.5 min.

E. ^{1}H NMR and chiral HPLC data for aldol adducts.

Aldol adducts are all known compounds.[1,2,3]

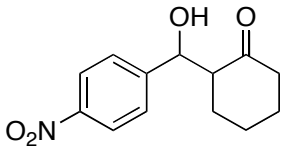


4-Hydroxy-4-(4-nitrophenyl)-butan-2-one (14): ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.20 (s, 3H), 2.84 (m, 2H), 3.58 (s, 1H), 5.25 (m, 1H), 7.53 (d, *J*= 8.0 Hz, 2H), 8.21 (d, *J* = 8.0 Hz, 2H); Chiral HPLC data: Daicel Chiralpak AS-H, 30% *i*-PrOH/hexane, UV 254 nm, Flow rate 1.0 mL/min, Retention times: t_R 12.3 min and t_R 16.3 min.

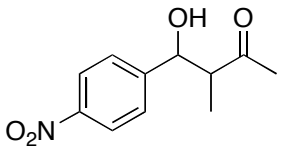


2-[Hydroxy-(4-nitrophenyl)-methyl]-cyclopentanone (15): (*anti* isomer) ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.46-1.58 (m, 1H), 1.65-1.78 (m, 2H), 1.95-2.02 (m, 1H), 2.19-2.29 (m, 1H), 2.32-2.47

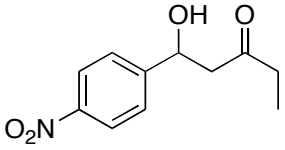
(m, 2H), 4.70 (s, 1H), 4.82 (d, J = 9.2 Hz, 1H), 7.50 (d, J = 8.8 Hz, 2H), 8.17(d, J = 9.0 Hz, 2H); Chiral HPLC data: Daicel Chiralpak IA, 5% *i*-PrOH/hexane, UV 254 nm, Flow rate 1.0 mL/min, Retention times: t_R 57.1 min and t_R 63.2 min; (*syn* isomer) ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.62-1.75 (m, 2H), 1.88-2.04 (m, 2H), 2.08-2.17 (m, 1H), 2.32-2.40 (m, 1H), 2.43-2.48 (m, 1H), 2.69 (s, 1H), 5.40 (d, J = 2.8 Hz, 1H), 7.50 (d, J = 8.8 Hz, 2H), 8.18 (d, J = 8.8 Hz, 2H); Chiral HPLC data: Daicel Chiralpak IA, 5% *i*-PrOH/hexane, UV 254 nm, Flow rate 1.0 mL/min, Retention times: t_R 30.6 min and t_R 49.4 min.



2-[Hydroxy-(4-nitrophenyl)-methyl]-cyclohexanone (16): (*anti* isomer) ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.30-1.42 (m, 1H), 1.48-1.71 (m, 3H), 1.78-1.84 (m, 1H), 2.06-2.13 (m, 1H), 2.30-2.39 (m, 1H), 2.45-2.51 (m, 1H), 2.54-2.60 (m, 1H), 4.04 (s, 1H), 4.88 (d, J = 8.0 Hz, 1H), 7.49 (d, J = 8.4 Hz, 2H), 8.19 (d, J = 8.5 Hz, 2H); Chiral HPLC data: Daicel Chiralpak IA, 20% *i*-PrOH/hexane, UV 254 nm, Flow rate 1.0 mL/min, Retention times: t_R 12.4 min and t_R 17.6 min; (*syn* isomer) ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.4 4-1.77 (m, 4H), 1.84 (d, J = 11.5 Hz, 1H), 2.05-2.13 (m, 1H), 2.33-2.50 (m, 2H), 2.61 (dd, J = 12.9 Hz, 5.5 Hz, 1H), 3.14 (s, 1H), 5.46 (d, J = 2.0 Hz, 1H), 7.47 (d, J = 8.9 Hz, 2H), 8.18 (d, J = 9.0 Hz, 2H); Chiral HPLC data: Daicel Chiralpak IA, 20% *i*-PrOH/hexane, UV 254 nm, Flow rate 1.0 mL/min, Retention times: t_R 9.2 min and t_R 12.2 min.

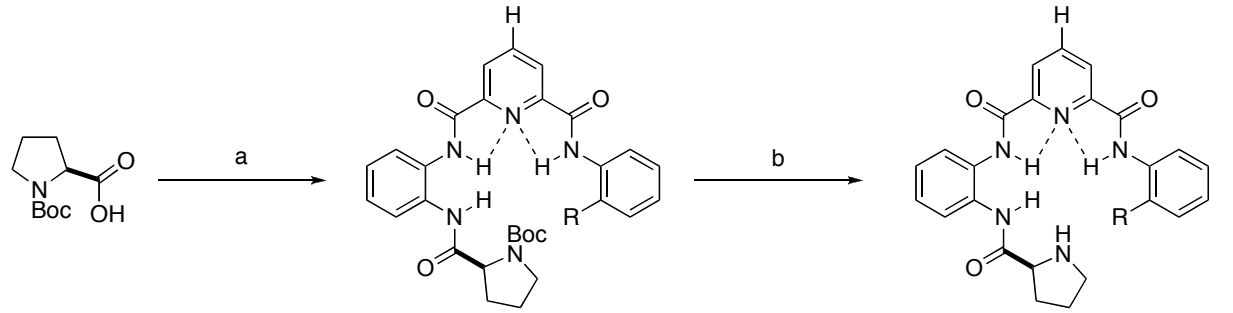


4-Hydroxy-3-methyl-4-(4-nitrophenyl)-butan-2-one (12): (*anti* isomer) ^{1}H NMR (400 MHz, toluene-d_8) δ 0.69 (d, J = 7.1 Hz, 3H), 1.91 (s, 3H), 2.46-2.54 (m, 1H), 2.87 (d, J = 4.1 Hz, 1H), 4.53 (dd, J = 8.3 Hz, 3.1 Hz, 1H), 7.05 (d, J = 8.4 Hz, 2H), 7.97 (d, J = 8.9 Hz, 2H); Chiral HPLC data: Daicel Chiralpak IA, 5% *i*-PrOH/hexane, UV 254 nm, Flow rate 1.0 mL/min, Retention times: t_R 50.6 min and t_R 55.9 min; (*syn* isomer) ^{1}H NMR (400 MHz, toluene-d_8) δ 0.84 (d, J = 7.1 Hz, 3H), 1.82 (s, 3H), 2.18 (d, J = 3.4 Hz, 1H), 3.21 (d, J = 2.5 Hz, 1H), 4.93 (d, J = 2.7 Hz, 1H), 7.05 (d, J = 9.1 Hz, 2H), 7.97 (d, J = 8.9 Hz, 2H); Chiral HPLC data: Daicel Chiralpak IA, 5% *i*-PrOH/hexane, UV 254 nm, Flow rate 1.0 mL/min, Retention times: t_R 27.6 min and t_R 43.4 min.



1-Hydroxy-1-(4-nitrophenyl)-pentan-3-one (13): ^{1}H NMR (400 MHz, toluene-d_8) δ 1.00 (t, J = 7.4 Hz, 3H), 2.00 (q, J = 7.5 Hz, 2H), 2.22-2.25 (m, 2H), 3.46 (s, 1H), 4.95 (d, J = 9.3 Hz, 1H), 7.14 (d, J = 8.6 Hz, 2H), 8.01 (d, J = 9.1 Hz, 2H); Chiral HPLC data: Daicel Chiralpak AS-H, 30% *i*-PrOH/hexane, UV 254 nm, Flow rate 1.0 mL/min, Retention times: t_R 9.8 min and t_R 16.3 min.

F. Reaction Schemes:



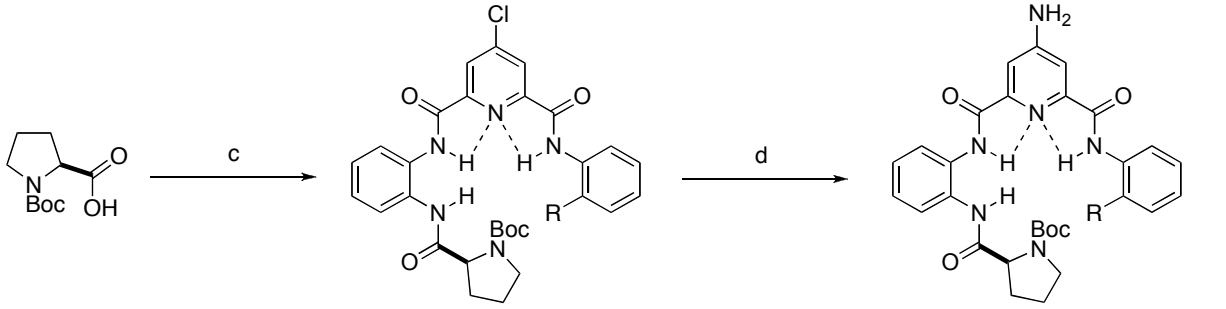
Boc-G1-**H**-Alt (R = H) **20**

Boc-G1-**H**-All (R = prolinamide) **30**

G1-**H**-Alt-Cat (R = H) **6**

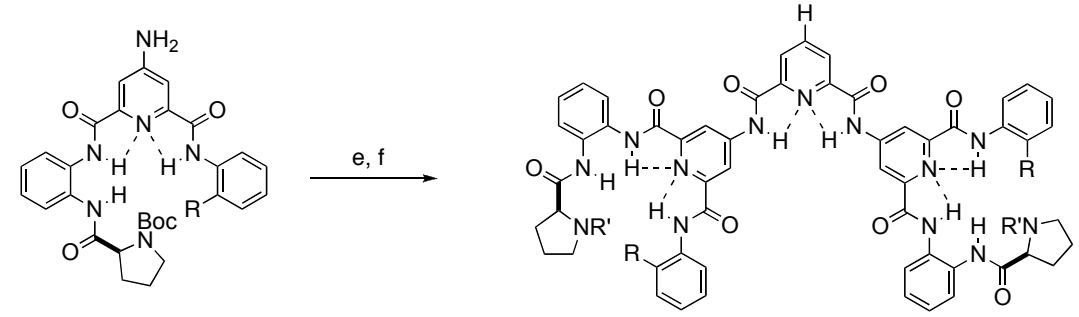
G1-**H**-All-Cat (R = prolinamide) **2**

Scheme 1: Synthesis of Boc-G1-H-(Alt/All) (a) 1) Ethyl chloroformate, Et_3N, THF, 0°C; 2) *o*-phenylenediamine, THF, -20°C; 3) aniline (for R = H); 4) 2,6-pyridinedicarbonyl dichloride, Et_3N, CH_2Cl_2, 0°C, 48% for **20,** 81% for **30**; (b) TFA, anisole, CH_2Cl_2, quant.



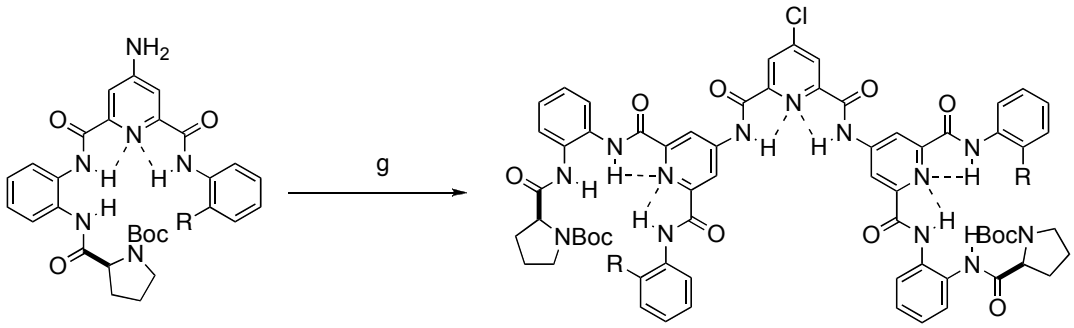
Boc-G1-**Cl**-Alt (R = H) **21**
Boc-G1-**Cl**-All (R = prolinamide) **31**
Boc-G1-**NH_2**-Alt (R = H) **22**
Boc-G1-**NH_2**-All (R = prolinamide) **32**

Scheme 2: Synthesis of Boc-G1-NH_2-(Alt/All) (c) 1) Ethyl chloroformate, Et_3N, THF, 0°C; 2) *o*-phenylenediamine, THF, -20°C; 3) aniline (for R = H); 4) 4-chloro-2,6-pyridinedicarbonyl dichloride, Et_3N, CH_2Cl_2, 0°C, 59% for **21**, 89% for **31**; (d) 1) NaN_3, DMF, 50°C; 2) Pd/C, H_2, EtOH, 78% for **22**, 88% for **32** (2 steps).



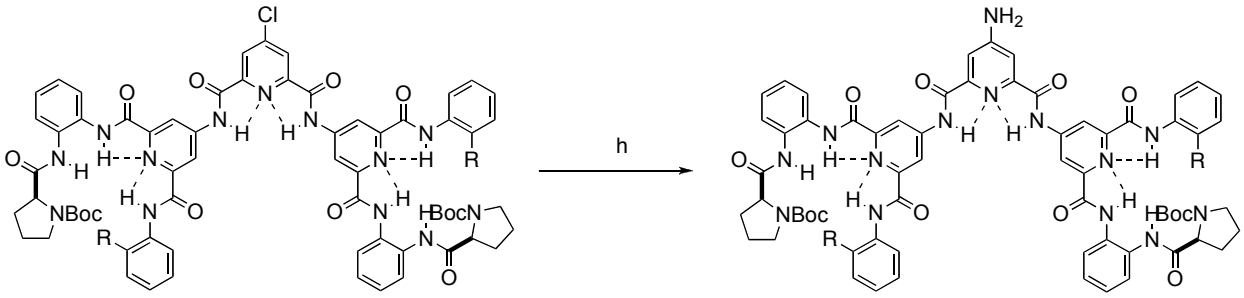
Boc-G1-**NH_2**-Alt (R = H) **22**
Boc-G1-**NH_2**-All (R = prolinamide) **32**
Boc-G2-I-**H**-Alt (R = H, R' = Boc) **23**
Boc-G2-I-**H**-All (R = prolinamide, R' = Boc) **33**
G2-I-**H**-Alt-Cat (R = H, R' = H) **7**
G2-I-**H**-All-Cat (R = prolinamide, R' = H) **3**

Scheme 3: Synthesis of G2-I-H-(Alt/All)-Cat (e) 2,6-pyridinedicarbonyl dichloride, pyridine, DMAP, CH_2Cl_2, 0°C, 86% for **23**, 84% for **33**; (f) **23** or **33**, TFA, anisole, CH_2Cl_2, quant.



Boc-G1-**NH_2**-Alt (R = H) **22**
Boc-G1-**NH_2**-All (R = prolinamide) **32**
Boc-G2-I-**Cl**-Alt (R = H) **24**
Boc-G2-I-**Cl**-All (R = prolinamide) **34**

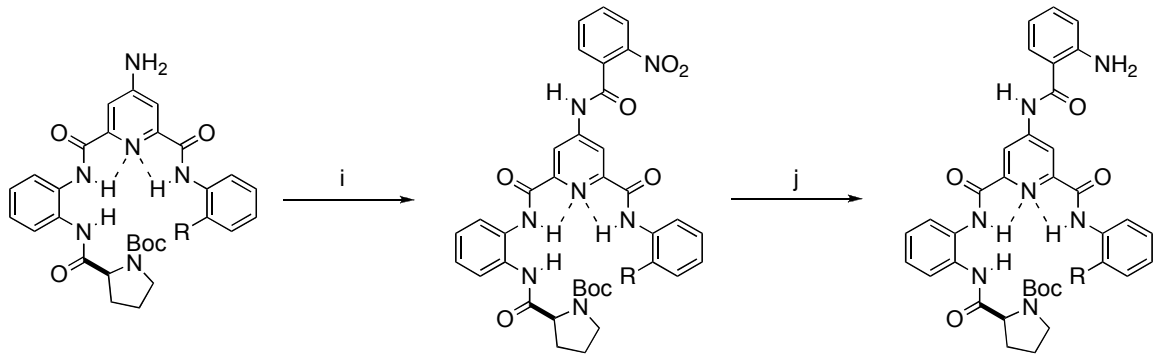
Scheme 4: Synthesis of Boc-G2-I-Cl-(Alt/All) (g) 4-chloro-2,6-pyridinedicarbonyl dichloride, pyridine, DMAP, CH_2Cl_2, 0°C, 91% for **24**, 75% for **34**.



Boc-G2-I-**Cl**-Alt (R = H) **24**
Boc-G2-I-**Cl**-All (R = prolinamide) **34**

Boc-G2-I-**NH_2**-Alt (R = H) **25**
Boc-G2-I-**NH_2**-All (R = prolinamide) **35**

Scheme 5: Synthesis of Boc-G2-I-NH_2-(Alt/All) (h) 1) NaN_3, DMF, 50°C; 2) Pd/C, H_2, EtOH, 27% for **25**, 67% for **35** (2 steps).

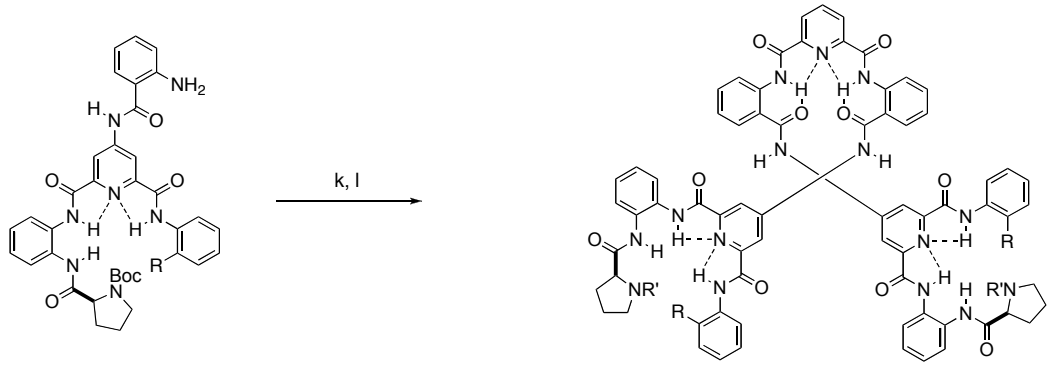


Boc-G1-**NH_2**-Alt (R = H) **22**
Boc-G1-**NH_2**-All (R = prolinamide) **32**

Boc-G1-TU-**NO_2**-Alt (R = H) **26**
Boc-G1-TU-**NO_2**-All (R = prolinamide) **36**

Boc-G1-TU-**NH_2**-Alt (R = H) **27**
Boc-G1-TU-**NH_2**-All (R = prolinamide) **37**

Scheme 6: Synthesis of Boc-G1-TU-NH_2-(Alt/All) (i) 2-nitrobenzoylchloride, pyridine, DMAP, CH_2Cl_2, 0°C, 48% for **36**; (j) Pd/C, H_2, EtOH, 93% for **27** (2 steps), 85% for **37**.

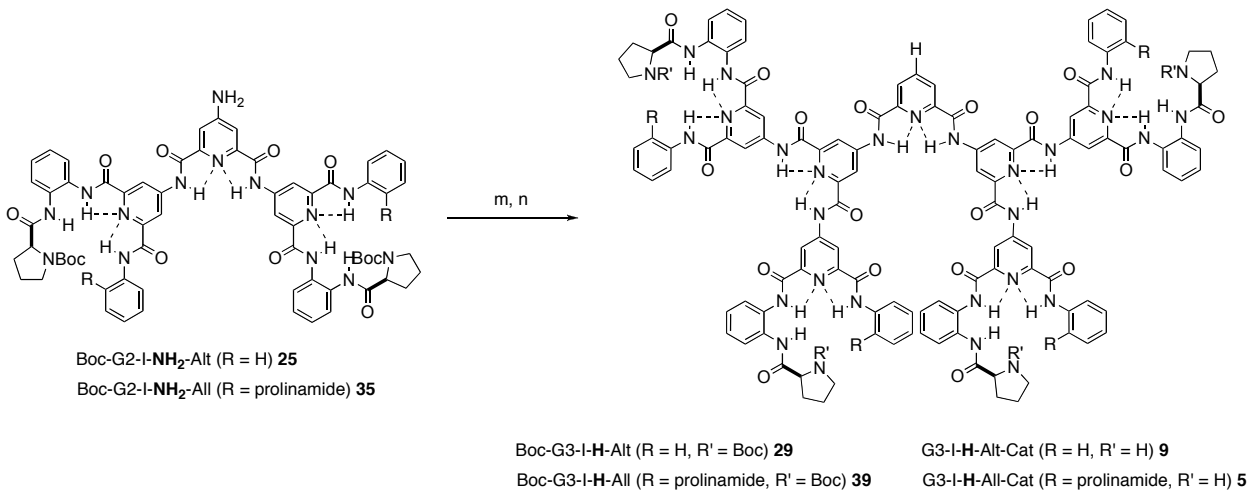


Boc-G1-TU-**NH_2**-Alt (R = H) **27**
Boc-G1-TU-**NH_2**-All (R = prolinamide) **37**

Boc-G2-II-**H**-Alt (R = H, R' = Boc) **28**
Boc-G2-II-**H**-All (R = prolinamide, R' = Boc) **38**

G2-II-**H**-Alt-Cat (R = H, R = H) **8**
G2-II-**H**-All-Cat (R = prolinamide, R' = H) **4**

Scheme 7: Synthesis of Boc-G2-II-H-(Alt/All) (k) 2,6-pyridinedicarbonyl dichloride, pyridine, DMAP, CH_2Cl_2, 0°C, 74% for **28**, 56% for **38**; (l) **28** or **38**, TFA, anisole, CH_2Cl_2, quant.



Scheme 8: Synthesis of Boc-G3-I-H-(Alt/All) (m) 2,6-pyridinedicarbonyl dichloride, pyridine, DMAP, CH_2Cl_2, 0ºC, 29% for **29**, 69% for **39**; (n) **29** or **39**, TFA, anisole, CH_2Cl_2, quant.

G. Experimental procedures for the synthesis of compounds 1-41:

Cbz-(S)-*N*-phenylpyrrolidine-2-carboxamide and (S)-*N*-phenylpyrrolidine-2-carboxamide **(1)** were prepared by the procedure of Gong et al.[2]

Boc-G1-H-Alt (20): To a solution of Boc-Pro-OH (2.15 g, 10.0 mmol) in anhydrous THF (50 mL) was added Et_3N (2.79 mL, 20.0 mmol) at room temperature under N_2 atmosphere. The reaction mixture was stirred for 30 min and cooled to 0°C. Ethyl chloroformate (0.956 mL, 10.0 mmol) was added to the reaction mixture dropwise and the reaction was stirred and warmed to rt over 3 h. The reaction was cooled to -20°C, and then *o*-phenylenediamine (973 mg, 9.0 mmol) in anhydrous THF (4.5 mL) was added to the reaction mixture quickly. The resulting mixture was stirred while warming to rt gradually over 12 h. After the complete consumption of diamine starting material (~12 h), the reaction was cooled to 0°C. Aniline (0.5 mL, 5.5 mmol) and an additional amount of Et_3N (4.18 mL, 30.0 mmol) were added. To this reaction mixture, was added a solution of 2,6-pyridinedicarbonyl dichloride (2.04 g, 10.0 mmol) in CH_2Cl_2 (10 mL)

dropwise over 5 min. The resulting reaction mixture was stirred while warming to rt over 12 h. The solvent was removed *in vacuo*. The residue was redissolved in $CHCl_3$ (50 mL) and washed with cold 1M HCl (30 mL). The aqueous layer was back-extracted with $CHCl_3$ (2 x 20 mL). The combined organics were treated with solid $NaHCO_3$ until pH ~7, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (0%-50% EtOAc/ether) to give Boc-G1-H-Alt (**20**) (2.3 g, 4.34 mmol, 48% based on diamine) as a white solid. mp 130-135 °C ($CHCl_3$); ^{1}H NMR (400 MHz, 80°C, DMSO-d_6) δ 1.21 (s, 9H), 1.59-1.72 (m, 2H), 1.84-1.92 (m, 1H), 2.04-2.11 (m, 1H), 3.00-3.07 (m, 1H), 3.13-3.19 (m, 1H), 4.25 (dd, *J* = 8.6 Hz, 5.0 Hz, 1H), 7.17 (t, *J* = 7.2 Hz, 1H), 7.28-7.33 (m, 2H), 7.40 (t, *J* = 7.9 Hz, 2H), 7.49 (d, *J* = 7.1 Hz, 1H), 7.81 (d, *J* = 7.7 Hz, 1H), 7.93 (d, *J* = 8.6 Hz, 2H), 8.29 (t, *J* = 7.3 Hz, 1H), 8.38-8.43 (m, 2H), 9.85 (s, 1H), 10.62 (s, 1H), 11.03 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 23.0, 27.5, 30.1, 46.1, 60.2, 78.3, 120.4, 123.8, 124.2, 124.5, 124.7, 125.19, 125.21, 125.3, 128.2, 130.2, 130.5, 137.7, 139.6, 148.3, 148.4, 152.93, 160.9, 161.0, 172.3; IR (KBr) 3450, 3308, 2976, 1684, 1601, 1533, 1449, 1390, 1305, 1233, 1162 cm^{-1}. HRMS calcd for $C_{29}H_{31}N_5O_5$ (M+Na) 552.2223, found 552.2213.

G1-Alt-Cat (6): To a solution of Boc-G1-H-Alt (**20**) (1.69 g, 3.19 mmol) in CH_2Cl_2 (4.9 mL) was added anisole (1.7 mL, 16.0 mmol) at rt. The mixture was cooled to 0°C and TFA (4.9 mL, 63.8 mmol) was added dropwise over 5 min. The reaction was stirred while warming to rt gradually over 12 h. The volatiles were removed *in vacuo*. To the residue was added diethyl ether (15 mL) and the solid precipitate was isolated by filtration. The precipitate was redissolved in $CHCl_3$ (30 mL), washed with saturated aqueous $NaHCO_3$ (20 mL), dried over Na_2SO_4 and concentrated *in vacuo* to give G1-Alt-Cat (**6**) (1.35 mg, 3.14 mmol, 99%) as a white solid. mp

170-172 °C ($CHCl_3$); ^{1}H NMR (400 MHz, 80°C, DMSO-d_6) δ 1.45-1.55 (m, 2H), 1.70-1.78 (m, 1H), 1.86-1.95 (m, 1H), 2.62-2.68 (m, 1H), 2.71-2.77 (m, 1H), 2.96 (brs, 1H), 3.72 (dd, *J* = 9.0 Hz, 5.3 Hz, 1H), 7.19 (t, *J* = 7.4 Hz, 1H), 7.26-7.34 (m, 2H), 7.43 (t, *J* = 8.6 Hz, 2H), 7.70 (dd, *J* = 7.7 Hz, 2.5 Hz, 1H), 7.77 (dd, *J* = 7.2 Hz, 2.0 Hz, 1H), 7.93 (dd, *J* = 8.8 Hz, 1.0 Hz, 2H), 8.32 (t, *J* = 7.9 Hz, 1H), 8.40 (dd, *J* = 7.8 Hz, 1.3 Hz, 1H), 8.44 (dd, *J* = 7.6 Hz, 1.3 Hz, 1H), 10.14 (s, 1H), 10.72 (s, 1H), 11.05 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 25.2, 30.0, 46.1, 60.4, 120.7, 122.8, 124.0, 124.4, 124.6, 124.7, 125.8, 126.0, 128.2, 128.9, 131.6, 137.6, 139.5, 148.3, 148.5, 161.1, 161.3, 174.2; IR (KBr) 3237, 3058, 2960, 2861, 1692, 1670, 1643, 1598, 1504, 1446, 1324, 1300, 1222, 1138, 1105, 1070 cm^{-1}; HRMS calcd for $C_{24}H_{23}N_5O_3$ (M+Na) 452.1699, found 452.1694.

Boc-G1-Cl-Alt (21): To a solution of Boc-Pro-OH (1.57 g, 8.07 mmol) in anhydrous THF (80 mL) was added Et_3N (1.69 mL, 12.1 mmol) at room temperature under N_2 atmosphere. The reaction mixture was stirred for 30 min and cooled to 0°C. Ethyl chloroformate (0.772 mL, 8.07 mmol) was added to the reaction mixture dropwise and the reaction was stirred and warmed to rt over 3 h. After the reaction was cooled to -20°C, and then *o*-phenylenediamine (786 mg, 7.27 mmol) in anhydrous THF (7.3 mL) was added to the reaction mixture quickly. The resulting mixture was stirred while warming to rt gradually over 12 h. After the complete consumption of diamine starting material (~12 h), the reaction was cooled to 0°C. Aniline (0.589 mL, 6.46 mmol) and an additional amount of Et_3N (3.37 mL, 24.2 mmol) were added. To this reaction mixture, was added a solution of 4-chloro-2,6-pyridinedicarbonyl dichloride (1.77 g, 7.27 mmol) in CH_2Cl_2 (7.3 mL) dropwise over 5 min. The resulting reaction mixture was stirred while warming to rt over 12 h. The solvent was removed *in vacuo*. The residue was redissolved in

$CHCl_3$ (50 mL) and washed with cold 1M HCl (30 mL). The aqueous layer was back-extracted with $CHCl_3$ (2 x 20 mL). The combined organics were treated with solid $NaHCO_3$ until pH ~7, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (0%-50% EtOAc/ether) to give Boc-G1-H-Alt (**21**) (2.13 g, 3.78 mmol, 59% based on aniline) as a white solid. mp 135-140 °C ($CHCl_3$); ^{1}H NMR (400 MHz, 80°C, DMSO-d_6) δ 1.22 (s, 9H), 1.61-1.73 (m, 2H), 1.87-1.94 (m, 1H), 2.04-2.12 (m, 1H), 3.03-3.07 (m, 1H), 3.14-3.19 (m, 1H), 4.25 (dd, *J* = 9.0 Hz, 4.9 Hz, 1H), 7.19 (t, *J* = 7.5 Hz, 1H), 7.31-7.34 (m, 2H), 7.41 (t, *J* = 7.9 Hz, 2H), 7.52 (d, *J* = 5.8 Hz, 1H), 7.78 (d, *J* = 8.2 Hz, 1H), 7.91 (d, *J* = 8.2 Hz, 2H), 8.36 (d, J = 1.9 Hz, 1H), 8.39 (d, *J* = 2.0 Hz, 1H), 9.82 (s, 1H), 10.63 (s, 1H), 11.05 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 23.1, 27.6, 30.2, 46.1, 60.2, 78.4, 120.4, 124.1, 124.2, 124.3, 124.4, 125.2, 125.5, 128.2, 129.8, 130.6, 137.4, 146.5, 150.0, 150.2, 153.0, 159.8, 159.9, 172.3; IR (KBr) 3461, 3236, 3076, 2969, 2861, 1687, 1602, 1539, 1481, 1441, 1392, 1361, 1325, 1231, 1159, 1123, 1083 cm^{-1}; HRMS calcd for $C_{29}H_{30}ClN_5O_5$ (M+Na) 586.1833, found 586.1841.

Boc-G1-NH_2-Alt (22): Boc-G1-Cl-Alt (**21**) (656 mg, 1.16 mmol) was dissolved in anhydrous DMF (5.8 mL). To this solution was added NaN_3 (754 mg, 11.6 mmol). After stirring at 50°C for 48 h, the solvent was removed under reduced pressure. The residue was redissolved in water (40 mL) and $CHCl_3$ (20 mL). The organic layer was extracted and washed with brine (20 mL) and dried over Na_2SO_4. After concentration *in vacuo*, the residue was redissolved in anhydrous EtOH (6 mL). 10% Pd/C (66 mg) was added to this mixture and the reaction was hydrogenated under H_2 at atmospheric pressure for 12 h. The catalyst was removed by filtration through a pad of celite. The solvent was removed *in vacuo* and the residue was purified by column

chromatography on silica gel (0-30% EtOAc/ether) to give Boc-G1-NH_2-Alt (**22**) (495 mg, 0.91 mmol, 78% over 2 steps) as an off-white solid. mp 152-155 °C ($CHCl_3$); ^{1}H NMR (400 MHz, 80°C, DMSO-d_6) δ 1.26 (s, 9H), 1.59-1.73 (m, 2H), 1.82-1.90 (m, 1H), 2.03-2.12 (m, 1H), 3.03-3.07 (m, 1H), 3.13-3.19 (m, 1H), 4.24 (dd, *J* = 9.0 Hz, 5.0 Hz, 1H), 6.63 (s, 2H), 7.13 (t, *J* = 7.0 Hz, 1H), 7.24-7.33 (m, 2H), 7.36 (t, *J* = 7.8 Hz, 2H), 7.41-7.45 (m, 1H), 7.52 (dd, *J* = 7.9 Hz, 2.5 Hz, 1H), 7.78 (d, *J* = 8.0 Hz, 2H), 7.93 (d, *J* = 7.8 Hz, 1H), 9.83 (s, 1H), 10.50 (s, 1H), 10.85 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 23.0, 27.5, 30.2, 46.1, 60.2, 78.4, 108.6, 108.7, 120.1, 123.4, 124.3, 124.9, 125.1, 125.2, 128.1, 130.2, 130.7, 138.0, 148.8, 149.0, 153.0, 157.0, 161.8, 161.9, 172.3; IR (KBr) 3443, 3345, 3058, 2978, 2879, 2360, 1688, 1594, 1537, 1454, 1392, 1368, 1317, 1233, 1160, 1120 cm^{-1}; HRMS calcd for $C_{29}H_{32}N_6O_5$ (M+Na) 567.2332, found 567.2327.

Boc-G2-I-H-Alt (23): To a solution of Boc-G1-NH_2-Alt (**22**) (735 mg, 1.35 mmol) in dry CH_2Cl_2 (20 mL) were added DMAP (50 mg, 0.41 mmol) and pyridine (10 mL). The reaction mixture was cooled to 0°C in an ice bath. To this mixture was added a solution of 2,6-pyridinedicarbonyl dichloride (138 mg, 0.68 mmol) in CH_2Cl_2 (0.7 mL) dropwise over 5 min. The reaction was stirred while warming to rt gradually over 12 h. The reaction was diluted with CH_2Cl_2 (20 mL) and washed with cold 1 M HCl (30 mL). The aqueous layer was back-extracted with $CHCl_3$ (2 x 20 mL). The organic layer was treated with solid $NaHCO_3$ until pH ~7 and dried over Na_2SO_4. After concentration *in vacuo*, the residue was purified by column chromatography on silica gel (1-5% MeOH/$CHCl_3$) to afford Boc-G2-I-H-Alt (**23**) (705 mg, 0.578 mmol, 86%) as an off-white solid. mp (dec) 230 °C ($CHCl_3$); ^{1}H NMR (400 MHz, 80°C, DMSO-d_6) δ 1.24 (s, 18H), 1.59-1.77 (m, 4H), 1.88-1.96 (m, 2H), 2.06-2.15 (m, 2H), 3.04-3.10 (m, 2H), 3.15-3.21

(m, 2H), 4.28 (dd, *J* = 8.5 Hz, 5.3 Hz, 2H), 7.17 (t, *J* = 7.6 Hz, 2H), 7.27-7.36 (m, 4H), 7.40 (t, *J* = 8.1 Hz, 4H), 7.50 (d, *J* = 6.8 Hz, 2H), 7.86 (d, *J* = 8.0 Hz, 2H), 7.98 (d, *J* = 7.8 Hz, 4H), 8.39 (dd, *J* = 9.3 Hz, 7.3 Hz, 1H), 8.53 (d, *J* = 7.5 Hz, 2H), 9.09 (d, *J* = 2.2 Hz, 2H), 9.10 (d, *J* = 2.1 Hz, 2H), 9.90 (s, 2H), 10.69 (s, 2H), 11.16 (s, 2H), 11.61 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 23.0, 27.4, 30.1, 46.3, 60.2, 78.3, 114.8, 120.4, 123.8, 124.2, 125.1, 125.9, 128.1, 130.2, 130.4, 137.6, 139.6, 147.8, 148.1, 149.6, 149.7, 153.0, 160.9, 161.0, 162.5, 172.2; IR (KBr) 3471, 3308, 3076, 2964, 2912, 2870, 1700, 1678, 1593, 1533, 1481, 1443, 1386, 1361, 1305, 1220, 1159, 1125 cm^{-1}; MALDI-TOF MS calcd for $C_{65}H_{65}N_{13}O_{12}$ (M+Na) 1242.477, found 1242.433.

G2-I-Alt-Cat (7): To a solution of Boc-G2-I-H-Alt (**23**) (705 mg, 0.578 mmol) in CH_2Cl_2 (2.6 mL) was added anisole (0.63 mL, 5.7 mmol) at rt. The mixture was cooled to 0°C and TFA (2.60 mL, 23.1 mmol) was added dropwise over 5 min. The reaction was stirred while warming to rt gradually over 12 h. The volatiles were removed *in vacuo*. To the residue was added diethyl ether (10 mL) and the solid precipitate was isolated by filtration. The precipitate was redissolved in a mixture of H_2O (5 mL) and CH_3CN (5 mL). To this mixture was added solid $NaHCO_3$ with stirring until pH ~8. The white solid precipitate was isolated by filteration and dried *in vacuo* over P_2O_5 to give G2-I-H-Alt-Cat (**7**) (580 mg, 0.569 mmol, 98%) as a white solid. mp 263-267 °C ($CHCl_3$); ^{1}H NMR (400 MHz, 80°C, DMSO-d_6) δ 1.68-1.75 (m, 4H), 2.04-2.13 (m, 2H), 2.19-2.28 (m, 2H), 3.07-3.17 (m, 4H), 4.35 (dd, *J* = 8.8 Hz, 6.6 Hz, 2H), 7.22 (t, *J* = 7.5 Hz, 2H), 7.34-7.38 (m, 4H), 7.46 (t, *J* = 8.2 Hz, 4H), 7.73-7.75 (m, 2H), 7.77-7.80 (m, 2H), 7.90 (dd, *J* = 8.8 Hz, 1.1 Hz, 4H), 8.42 (dd, *J* = 8.9 Hz, 7.3 Hz, 1H), 8.55 (d, *J* = 7.9 Hz, 2H), 9.07 (d, *J* = 2.0 Hz, 2H), 9.09 (d, *J* = 2.1 Hz, 2H), 10.08 (s, 2H), 10.79 (s, 2H), 10.82 (s, 2H), 11.64 (s, 2H);

^{13}C NMR (100 MHz, DMSO-d_6) δ 23.3, 29.3, 45.5, 59.5, 115.0, 115.1, 121.2, 124.1, 124.5, 125.3, 125.8, 126.1, 126.3, 128.3, 130.0, 131.1, 137.6, 139.9, 147.9, 148.0, 150.1, 161.4, 161.6, 162.7, 168.1; IR (KBr) 3445, 3282, 3076, 2921, 2354, 1675, 1589, 1529, 1442, 1314, 1202, 1134 cm^{-1}; MALDI-TOF MS calcd for $C_{55}H_{49}N_{13}O_8$ (M+Na) 1042.372, found 1042.473.

Boc-G2-I-Cl-Alt (24): To a solution of Boc-G1-NH_2-Alt (**22**) (545 mg, 1.00 mmol) in dry CH_2Cl_2 (10 mL) were added DMAP (37 mg, 0.30 mmol) and pyridine (3 mL). The reaction mixture was cooled to 0°C in an ice bath. To this mixture was added a solution of 4-chloro-2,6-pyridinedicarbonyl dichloride (102 mg, 0.50 mmol) in CH_2Cl_2 (0.5 mL) dropwise over 5 min. The reaction was stirred while warming to rt gradually over 12 h. The reaction was diluted with CH_2Cl_2 (10 mL) and washed with cold 1 M HCl (10 mL). The aqueous layer was back-extracted with $CHCl_3$ (2 x 10 mL). The combined organic layer was treated with solid $NaHCO_3$ until pH ~7 and dried over Na_2SO_4. After concentration *in vacuo*, the residue was purified by column chromatography on silica gel (1-5% MeOH/$CHCl_3$) to afford Boc-G2-I-Cl-Alt (**24**) (568 mg, 0.453 mmol, 91%) as an off-white solid. mp (dec) 235 °C ($CHCl_3$); ^{1}H NMR (400 MHz, 80°C, DMSO-d_6) δ 1.23 (s, 18H), 1.60-1.75 (m, 4H), 1.87-1.95 (m, 2H), 2.05-2.12 (m, 2H), 3.03-3.20 (m, 4H), 4.27 (dd, J = 8.6 Hz, 4.9 Hz, 2H), 7.18 (t, J = 8.2 Hz, 2H), 7.28-7.36 (m, 4H), 7.41 (t, J = 8.2 Hz, 4H), 7.49 (d, J = 6.6 Hz, 2H), 7.85 (d, J = 7.9 Hz, 2H), 7.97 (d, J = 8.3 Hz, 4H), 8.50 (s, 2H), 9.05 (d, J = 1.5 Hz, 2H), 9.06 (d, J = 1.9 Hz, 2H), 9.89 (s, 2H), 10.68 (s, 2H), 11.11 (s, 2H), 11.61 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 23.1, 27.5, 28.5, 46.1, 60.2, 78.4, 114.84, 114.86, 120.4, 123.9, 124.3, 125.25, 125.28, 125.8, 128.2, 130.2, 130.5, 137.6, 139.6, 146.6, 148.0, 149.4, 149.7, 149.8, 153.0, 160.9, 161.0, 161.5, 172.4; IR (KBr) 3461, 3308, 3085, 2969, 2915, 1598, 1585, 1504, 1441, 1392, 1307, 1239, 1159, 1119 cm^{-1}; MALDI-TOF MS calcd for

$C_{65}H_{64}ClN_{13}O_{12}$ (M+Na) 1276.438, found 1276.343.

Boc-G2-I-NH_2-Alt (25): Boc-G2-Cl-Alt (**24**) (542 mg, 0.433 mmol) was dissolved in anhydrous DMF (4.3 mL). To this solution was added NaN_3 (281 mg, 4.33 mmol). After stirring at 50°C for 48 h, the solvent was removed under reduced pressure. The residue was redissolved in water (40 mL) and $CHCl_3$ (20 mL). The organic layer was extracted and washed with brine (20 mL) and dried over Na_2SO_4. After concentration *in vacuo*, the residue was redissolved in anhydrous EtOH (4.3 mL). 10% Pd/C (54 mg) was added to this mixture and the reaction was hydrogenated under H_2 at atmospheric pressure for 12 h. The catalyst was removed by filtration through a pad of celite. The solvent was removed *in vacuo* and the residue was purified by column chromatography on silica gel (5-10% MeOH/$CHCl_3$ to give Boc-G2-NH_2-Alt (**25**) (136 mg, 0.110 mmol, 27% over 2 steps) as an off-white solid. mp (dec) 240 °C ($CHCl_3$); ^{1}H NMR (400 MHz, 80°C, DMSO-d_6) δ 1.24 (s, 18H), 1.61-1.76 (m, 4H), 1.88-1.95 (m, 2H), 2.06-2.13 (m, 2H), 3.04-3.20 (m, 4H), 4.27 (dd, J = 8.7 Hz, 5.0 Hz, 2H), 6.83 (s, 2H), 7.19 (t, J = 7.4 Hz, 2H), 7.29-7.37 (m, 4H), 7.41 (t, J = 7.7 Hz, 4H), 7.50 (d, J = 6.9 Hz, 2H), 7.67 (s, 2H), 7.86 (d, J = 7.4 Hz, 2H), 7.98 (d, J = 8.2 Hz, 4H), 9.04 (d, J = 2.0 Hz, 2H), 9.05 (d, J = 2.3 Hz, 2H), 9.89 (s, 2H), 10.70 (s, 2H), 11.08 (s, 2H), 11.48 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 23.0, 27.5, 28.5, 46.1, 60.2, 78.4, 110.0, 114.8, 120.4, 123.9, 124.3, 125.26, 125,29, 128.2, 130.3, 130.5, 137.7, 148.3, 148.4, 149.6, 149.7, 153.0, 157.0, 161.0, 161.1, 163.5, 172.3; IR (KBr) 3461, 3345, 2978, 2924, 2360, 1670, 1602, 1567, 1522, 1446, 1401, 1159, 1119 cm^{-1}; MALDI-TOF MS calcd for $C_{65}H_{66}N_{14}O_{12}$ (M+Na) 1257.488, found 1257.556.

Boc-II-G1-NO_2-Alt (26): To a solution of Boc-G1-NH_2-Alt (**22**) (297 mg, 0.545 mmol) in dry

CH_2Cl_2 (5.5 mL) were added DMAP (15 mg, 0.123 mmol) and pyridine (2.8 mL). The reaction mixture was cooled to 0°C in an ice bath. To this mixture was added a solution of 2-nitrobenzoyl chloride (102 mg, 0.55 mmol) in CH_2Cl_2 (0.5 mL) dropwise over 5 min. The reaction was stirred while warming to rt gradually over 12 h. The reaction was diluted with CH_2Cl_2 (10 mL) and washed with cold 1 M HCl (10 mL). The aqueous layer was back-extracted with $CHCl_3$ (2 x 10 mL). The combined organic layer was treated with solid $NaHCO_3$ until pH ~7 and dried over Na_2SO_4. After concentration *in vacuo*, the crude residue was directly used in the next step. A small amount of the crude material was purified by preparative TLC on silica gel (5% MeOH/$CHCl_3$) to afford analytically pure Boc-II-G1-NO_2-Alt (**26**) as an off-white solid. mp (dec) 180 °C ($CHCl_3$); ^{1}H NMR (400 MHz, 80°C, DMSO-d_6) δ 1.27 (s, 9H), 1.61-1.75 (m, 2H), 1.87-1.95 (m, 1H), 2.06-2.15 (m, 1H), 3.01-3.11 (m, 1H), 3.16-3.22 (m, 1H), 4.27 (dd, *J* = 8.5 Hz, 5.0 Hz, 1H), 7.18 (t, *J* = 7.0 Hz, 1H), 7.27-7.37 (m, 2H), 7.41 (t, *J* = 7.9 Hz, 2H), 7.50 (d, *J* = 7.5 Hz, 1H), 7.81-7.88 (m, 3H), 7.94 (t, *J* = 8.1 Hz, 3H), 8.21 (d, *J* = 8.1 Hz, 1H), 8.67 (d, *J* = 2.2 Hz, 1H), 8.69 (d, *J* = 2.1 Hz, 1H), 9.83 (s, 1H), 10.62 (s, 1H), 11.02 (s, 1H), 11.33 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 23.0, 27.5, 30.2, 46.1, 60.2, 78.4, 114.0, 120.3, 123.8, 123.9, 124.3, 125.21, 125.24, 125.3, 128.2, 128.8, 130.22, 130.24, 130.5, 131.1, 131.2, 133.8, 137.7, 146.0, 148.5, 149.7, 149.8, 153.0, 160.8, 160.9, 164.9, 172.3; IR (KBr) 3470, 3318, 3237, 3085, 2978, 2924, 1710, 1674, 1589, 1522, 1477, 1441, 1392, 1347, 1293, 1249, 1159, 1123, 1070 cm^{-1}; HRMS calcd for $C_{36}H_{35}N_7O_8$ (M+Na) 716.2445, found 716.2439.

Boc-II-G1-NH_2-Alt (27): Crude Boc-II-G1-NO_2-Alt (**26**) (442 mg, 0.545 mmol) was dissolved in anhydrous EtOH (5.5 mL). 10% Pd/C (44 mg) was added to this mixture and the reaction was hydrogenated under H_2 at atmospheric pressure for 12 h. The catalyst was removed by filtration

through a pad of celite. The solvent was removed *in vacuo* and the residue was purified by column chromatography on silica gel (10-15% THF/$CHCl_3$ to give Boc-II-G1-NH_2-Alt (**27**) (336 mg, 0.506 mmol, 93% over 2 steps) as an off-white solid. mp (dec) 190 °C ($CHCl_3$); ^{1}H NMR (400 MHz, 80°C, DMSO-d_6) δ 1.26 (s, 9H), 1.61-1.76 (m, 2H), 1.86-1.94 (m, 1H), 2.05-2.15 (m, 1H), 3.06-3.12 (m, 1H), 3.16-3.22 (m, 1H), 4.27 (dd, *J* = 8.5 Hz, 5.0 Hz, 1H), 6.41 (s, 2H), 6.63-6.67 (m, 1H), 6.84 (dd, *J* = 8.4 Hz, 1.1 Hz, 1H), 7.17-7.20 (m, 1H), 7.25-7.37 (m, 3H), 7.38-7.43 (m, 2H), 7.49 (d, *J* = 7.5 Hz, 1H), 7.80 (dd, *J* = 8.1 Hz, 1.6 Hz, 1H), 7.82 (d, *J* = 7.8 Hz, 1H), 7.96 (dd, *J* = 8.8 Hz, 1.0 Hz, 2H), 8.82 (d, *J* = 2.1 Hz, 1H), 8.84 (d, *J* = 2.0 Hz, 1H), 9.83 (s, 1H), 10.61 (s, 1H), 11.01 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 23.0, 27.5, 28.5, 46.1, 60.2, 78.4, 110.0, 114.8, 120.4, 123.9, 124.3, 125.19, 125.24, 128.2, 130.3, 130.5, 137.7, 148.3, 148.4, 149.6, 149.7, 153.0, 157.0, 161.0, 161.1, 163.5, 172.3; IR (KBr) 3461, 3318, 3076, 2978, 2933, 1674, 1584, 1522, 1446, 1396, 1293, 1235, 1159, 1114 cm^{-1}; HRMS calcd for $C_{36}H_{37}N_7O_6$ (M+Na) 686.2703, found 686.2705.

Boc-G2-II-H-Alt (28): To a solution of Boc-II-G1-NH_2-Alt (**27**) (272 mg, 0.410 mmol) in dry CH_2Cl_2 (4.1 mL) were added DMAP (10 mg, 0.082 mmol) and pyridine (1.6 mL). The reaction mixture was cooled to 0°C in an ice bath. To this mixture was added a solution of 2,6-pyridinedicarbonyl dichloride (44 mg, 0.21 mmol) in CH_2Cl_2 (0.2 mL) dropwise over 5 min. The reaction was stirred while warming to rt gradually over 12 h. The reaction was diluted with CH_2Cl_2 (10 mL) and washed with cold 1 M HCl (10 mL. The aqueous layer was back-extracted with $CHCl_3$ (2 x 10 mL). The organic layer was treated with solid $NaHCO_3$ until pH ~7 and dried over Na_2SO_4. After concentration *in vacuo*, the residue was purified by column chromatography on silica gel (10-25% THF/$CHCl_3$) to afford Boc-G2-II-H-Alt (**28**) (220 mg, 0.151 mmol, 74%)

as an off-white solid. mp (dec) 230 °C ($CHCl_3$); ^{1}H NMR (400 MHz, 80°C, DMSO-d_6) δ 1.24 (s, 18H), 1.58-1.73 (m, 4H), 1.84-1.92 (m, 2H), 2.02-2.11 (m, 2H), 3.00-3.09 (m, 2H), 3.12-3.19 (m, 2H), 4.25 (dd, *J* = 8.6 Hz, 5.0 Hz, 2H), 7.14 (t, *J* = 7.5 Hz, 2H), 7.19 (t, *J* = 7.2 Hz, 2H), 7.30 (td, *J* = 7.8 Hz, 1.6 Hz, 2H), 7.37 (td, *J* = 7.8 Hz, 1.7 Hz, 2H), 7.40-7.82 (m, 8H), 7.76 (d, *J* = 8.1 Hz, 2H). 7.84 (d, *J* = 8.3 Hz, 2H), 7.94 (d, *J* = 7.9 Hz, 4H), 8.34 (dd, *J* = 9.3 Hz, 6.4 Hz, 1H), 8.40-8.43 (m, 4H), 8.50 (d, *J* = 2.1 Hz, 2H), 8.58 (d, *J* = 2.0 Hz, 2H), 9.85 (s, 2H), 10.44 (s, 2H), 10.77 (s, 2H), 10.88 (s, 2H), 12.14 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 23.0, 27.5, 30.4, 46.1, 60.2, 78.3, 114.5, 114.6, 120.2, 121.7, 122.8, 123.1, 123.6, 124.4, 124.7, 125.0, 125.1, 125.3, 128.1, 128.5 130.1, 130.5, 131.8, 137.1, 137.8, 139.9, 148.5, 148.6, 149.0, 149.2, 153.0, 160.7, 161.0, 166.8, 172.4; IR (KBr) 3452, 3318, 2978, 2924, 1710, 1674, 1589, 1531, 1443, 1396, 1302, 1240, 1164, 1123, 1083 cm^{-1}; MALDI-TOF MS calcd for $C_{79}H_{75}N_{15}O_{14}$ (M+Na) 1480.551, found 1480.549.

G2-II-H-Alt-Cat (8): To a solution of Boc-G2-II-H-Alt (**28**) (400 mg, 0.274 mmol) in $CHCl_3$ (5 mL) and THF (5 mL) was added anisole (106 μL, 0.979 mmol) at rt. The mixture was cooled to 0°C and TFA (1.06 mL, 13.7 mmol) was added dropwise over 5 min. The reaction was stirred while warming to rt gradually over 12 h. The volatiles were removed *in vacuo*. To the residue was added diethyl ether (15 mL) and the solid precipitate was isolated by filtration The precipitate was redissolved in a mixture of H_2O (3 mL) and CH_3CN (3 mL). To this mixture was added solid $NaHCO_3$ with stirring until pH ~8. The white solid precipitate was isolated by filteration and dried *in vacuo* over P_2O_5 to give G2-II-H-Alt-Cat (**8**) (166 mg, 0.270 mmol, 99%) as a white solid. mp 245-250 °C ($CHCl_3$); ^{1}H NMR (400 MHz, 80°C, DMSO-d_6) δ 1.63-1.78 (m, 4H), 2.05-2.14 (m, 2H), 2.27-2.37 (m, 2H), 3.09-3.23 (m, 4H), 4.46 (t, *J* = 7.6 Hz, 5.0 Hz, 2H),

7.18-7.23 (m, 4H), 7.31-7.39 (m, 4H), 7.43-7.50 (m, 6H) 7.69 (dd, *J* = 7.9 Hz, 1.8 Hz, 2H), 7.81 (td, *J* = 7.6 Hz, 1.2 Hz, 4H), 7.97 (dd, *J* = 8.7 Hz, 1.1 Hz, 4H), 8.35 (dd, *J* = 9.0 Hz, 6.7 Hz, 1H), 8.41-8.44 (m, 4H), 8.53 (d, *J* = 2.1 Hz, 2H), 8.62 (d, *J* = 2.1 Hz, 2H), 9.13 (brs, 2H), 10.58 (s, 2H), 10.79 (s, 4H), 10.84 (s, 2H), 12.19 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 23.0, 27.5, 30.2, 46.1, 60.2, 78.4, 114.0, 120.3, 123.8, 123.9, 124.3, 125.2, 125.3, 128.2, 128.8, 130.2, 130.5, 131.1, 131.2, 133.8, 137.7, 146.0, 148.5, 149.7, 149.8, 153.0, 160.8, 160.9, 164.9, 172.3; IR (KBr) 3443, 3255, 3031, 2951, 1674, 1589, 1535, 1446, 1400, 1352, 1307, 1226, 1199, 1132, 1079 cm^{-1}; MALDI-TOF MS calcd for $C_{69}H_{59}N_{15}O_{10}$ (M+Na) 1280.446, found 1280.468

Boc-G3-I-H-Alt (29): To a solution of Boc-G2-NH_2-Alt (**25**) (438 mg, 0.355 mmol) in dry CH_2Cl_2 (3.6 mL) were added DMAP (4 mg, 0.036 mmol) and pyridine (1.8 mL). The reaction mixture was cooled to 0°C in an ice bath. To this mixture was added a solution of 2,6-pyridinedicarbonyl dichloride (36.9 mg, 0.178 mmol) in CH_2Cl_2 (0.2 mL) dropwise over 5 min. The reaction was stirred while warming to rt gradually over 12 h. The reaction was diluted with CH_2Cl_2 (5 mL) and washed with cold 1 M HCl. The aqueous layer was back-extracted with $CHCl_3$ (2 x 10 mL). The combined organic layer was treated with solid $NaHCO_3$ until pH ~7 and dried over Na_2SO_4. After concentration *in vacuo*, the residue was purified by column chromatography on silica gel (1-5% MeOH/$CHCl_3$) to afford Boc-G3-I-H-Alt (**29**) (134 mg, 0.0515 mmol, 29%) as an off-white solid. mp (dec) 240 °C ($CHCl_3$); ^{1}H NMR (400 MHz, 80°C, DMSO-d_6) δ 1.25 (s, 36H), 1.61-1.76 (m, 8H), 1.88-1.96 (m, 4H), 2.05-2.14 (m, 4H), 3.07-3.12 (m, 4H), 3.15-3.21 (m, 4H), 4.27 (dd, *J* = 9.1 Hz, 4.9 Hz, 4H), 7.17 (t, *J* = 7.7 Hz, 4H), 7.28-7.35 (m, 8H), 7.40 (t, *J* = 7.9 Hz, 8H), 7.50 (d, *J* = 6.9 Hz, 4H), 7.86 (d, *J* = 7.3 Hz, 4H), 7.98 (d, *J* = 9.2 Hz, 8H), 8.44 (t, *J* = 7.4 Hz, 1H), 8.57 (d, *J* = 7.9 Hz, 2H), 9.09 (dd, *J* = 13.0 Hz, 2.3

Hz, 8H), 9.18 (s, 4H), 9.85 (s, 4H), 10.68 (s, 4H), 11.09 (s, 4H), 11.65 (s, 2H), 11.67 (s, 4H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 22.7, 27.2, 29.9, 45.8, 60.0, 78.1, 114.7, 116.0, 120.1, 123.5, 124.0, 124.88, 124.91, 125.7, 127.8, 130.04, 130.11, 130.12, 130.17, 137.4, 147.6, 147.9, 148.0 148.9, 149.4, 149.5, 152.72, 152.74, 152.76, 160.7, 160.8, 162.3, 162.4, 170.0; IR (KBr) 3460, 3308, 3066, 2977, 2914, 2842, 1678, 1584, 1526, 1441, 1405, 1342, 1306, 1226, 1159, 1122 cm^{-1}; MALDI-TOF MS calcd for $C_{137}H_{133}N_{29}O_{26}$ (M+Na) 2622.987, found 2623.025.

G3-I-Alt-Cat (9): To a solution of Boc-G3-I-H-Alt (**29**) (100 mg, 0.0384 mmol) in CH_2Cl_2 (0.75 mL) was added anisole (83 μL, 0.77 mmol) at rt. The mixture was cooled to 0°C and TFA (237 μL, 3.07 mmol) was added dropwise over 5 min. The reaction was stirred while warming to rt gradually over 12 h. The volatiles were removed *in vacuo*. To the residue was added diethyl ether (5 mL) and the solid precipitate was isolated by filtration. The precipitate was redissolved in a mixture of H_2O (1 mL) and CH_3CN (1 mL). To this mixture was added solid $NaHCO_3$ with stirring until pH ~8. The white solid precipitate was isolated by filteration and dried *in vacuo* over P_2O_5 to give G3-I-Alt-Cat (**9**) (84 mg, 0.382 mmol, 99%) as a white solid. mp (dec) 290 °C ($CHCl_3$); ^{1}H NMR (400 MHz, 80°C, DMSO-d_6) δ 1.67-1.75 (m, 8H), 2.04-2.12 (m, 4H), 2.18-2.27 (m, 4H), 3.06-3.16 (m, 8H), 4.33 (dd, J = 7.4 Hz, 7.0 Hz, 4H), 7.22 (t, J = 7.6 Hz, 4H), 7.34-7.38 (m, 8H), 7.45 (t, J = 8.0 Hz, 8H), 7.71-7.78 (m, 8H), 7.89 (d, J = 8.4 Hz, 8H), 8.42 (t, J = 8.6 Hz, 1H), 8.55 (d, J = 8.2 Hz, 2H), 9.10 (s, 8H), 9.18 (s, 4H), 10.04 (brs, 4H), 10.78 (s, 4H), 10.81 (s, 4H), 11.67 (s, 2H), 11.69 (s, 4H); ^{13}C NMR (100 MHz, DMSO-d_6) d 23.1, 29.1, 45.5, 59.5, 115.0, 115.1, 116.3, 121.0, 124.0, 124.5, 125.3, 125.6, 126.0, 128.1, 130.1, 130.9, 137.5, 147.9, 148.0, 148.3, 149.2, 149.8, 150.1, 161.4, 161.5, 162.6, 162.8, 167.83, 167.86, 167.88; IR (KBr) 3443, 3237, 3022, 2960, 1678, 1576, 1517, 1447, 1411, 1348, 1317, 1222,

1133, 1000 cm^{-1}; MALDI-TOF MS calcd for $C_{117}H_{101}N_{29}O_{18}$ (M+Na) 2222.777, found 2222.823.

Boc-G1-H-All (30): To a solution of Boc-Pro-OH (2.15 g, 10.0 mmol) in anhydrous THF (50 mL) was added Et_3N (2.79 mL, 20.0 mmol) at room temperature under N_2 atmosphere. The reaction mixture was stirred for 30 min and cooled to 0°C. Ethyl chloroformate (0.956 mL, 10.0 mmol) was added to the reaction mixture dropwise and the reaction was stirred and warmed to rt over 3 h. The reaction was cooled to -20°C, and then *o*-phenylenediamine (973 mg, 9.0 mmol) in anhydrous THF (4.5 mL) was added to the reaction mixture quickly. The resulting mixture was stirred while warming to rt gradually over 12 h. After the complete consumption of diamine starting material (~12 h), the reaction was cooled to 0°C. An additional amount of Et_3N (4.18 mL, 30.0 mmol) was added. To this reaction mixture, was added a solution of 2,6-pyridinedicarbonyl dichloride (1.02 g, 5.0 mmol) in CH_2Cl_2 (5 mL) dropwise over 5 min. The resulting reaction mixture was stirred while warming to rt over 12 h. The solvent was removed *in vacuo*. The residue was redissolved in $CHCl_3$ (50 mL) and washed with cold 1M HCl (30 mL). The aqueous layer was back-extracted with $CHCl_3$ (2 x 20 mL). The combined organics were treated with solid $NaHCO_3$ until pH ~7, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (0%-50% EtOAc/ether) to give Boc-G1-H-All (**30**) (5.41 g, 7.29 mmol, 81% based on diamine) as a white solid. mp 155-158 °C ($CHCl_3$); ^{1}H NMR (400 MHz, 80°C, DMSO-d_6) δ 1.23 (s, 18H), 1.53-1.70 (m, 4H), 1.82-1.90 (m, 2H), 1.97-2.06 (m, 2H), 3.09-3.22 (m, 4H), 4.18 (dd, J = 8.5 Hz, 4.4 Hz, 2H), 7.28-7.33 (m, 4H), 7.63-7.65 (m, 2H), 7.81-7.83 (m, 2H), 8.34 (dd, J = 8.7 Hz, 6.9Hz, 1H), 8.43 (d, J = 7.5 Hz, 2H), 9.5 (s, 2H), 10.88 (s, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 23.0, 27.5, 30.1, 46.1,

60.3, 78.3, 124.3, 124.7, 124.8, 124.9, 125.3, 129.7, 130.6, 130.5, 139.6, 148.2, 153.1, 161.2, 171.6; IR (KBr) 3478, 3263, 3075, 2967, 2914, 2870, 2350, 1691, 1602, 1526, 1491, 1450, 1391, 1360, 1306, 1253, 1159, 1118, 1003 cm^{-1}. HRMS calcd for $C_{39}H_{47}N_7O_8$ (M+Na) 764.3384, found 764.3380.

G1-All-Cat (2): To a solution of Boc-G1-All-H (**30**) (3.7 g, 5.0 mmol) in CH_2Cl_2 (20 mL) was added anisole (2.7 mL, 25 mmol) at rt. The mixture was cooled to 0°C and TFA (7.43 mL, 100 mmol) was added dropwise over 5 min. The reaction was stirred while warming to rt gradually over 12 h. The volatiles were removed *in vacuo*. To the residue was added diethyl ether (25 mL) and the solid precipitate was isolated by filtration. The precipitate was redissolved in $CHCl_3$ (100 mL), washed with saturated aqueous $NaHCO_3$ (50 mL), dried over Na_2SO_4 and concentrated *in vacuo* to give G1-All-Cat (**2**) (2.6 g, 4.8 mmol, 96%) as a white solid. mp 115-118 °C ($CHCl_3$); ^{1}H NMR (400 MHz, 80°C, DMSO-d_6) δ 1.46-1.53 (m, 4H), 1.67-1.74 (m, 2H), 1.83-1.92 (m, 2H), 2.57-2.62 (m, 2H), 2.70-2.75 (m, 2H), 2.99 (brs, 2H), 3.64 (dd, J = 8.9 Hz, 5.3 Hz, 2H), 7.21-7.33 (m, 4H), 7.63-7.60 (dd, J = 7.8 Hz, 1.4 Hz, 2H), 7.9 (dd, J = 8.0 Hz, 1.4 Hz, 2H), 8.34 (dd, J = 8.6 Hz, 6.8Hz, 1H), 8.42 (d, J = 7.2 Hz, 2H), 10.04 (brs, 2H), 10.93 (brs, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 25.1, 29.7, 45.9, 60.4, 69.4, 122.2, 123.8, 124.4, 126.0, 128.1, 132.4, 139.5, 148.1, 161.5, 173.4; IR (KBr) 3464, 3346, 3256, 2959, 2869, 2356, 1682, 1592, 1516, 1480, 1300, 1226, 1135, 1106 cm^{-1}; HRMS calcd for $C_{29}H_{31}N_7O_4$ (M+Na) 564.2332, found 564.2335.

Boc-G1-Cl-All (31): To a solution of Boc-Pro-OH (2.15g, 10.0 mmol) in anhydrous THF (50 mL) was added Et_3N (2.79 mL, 20.0 mmol) at room temperature under N_2 atmosphere. The

reaction mixture was stirred for 30 min and cooled to 0°C. Ethyl chloroformate (0.956 mL, 10.0 mmol) was added to the reaction mixture dropwise and the reaction was stirred and warmed to rt over 3 h. The reaction was cooled to -20°C, and then *o*-phenylenediamine (973 mg, 9.0 mmol) in anhydrous THF (4.5 mL) was added to the reaction mixture quickly. The resulting mixture was stirred while warming to rt gradually over 12 h. After the complete consumption of diamine starting material (~12 h), the reaction was cooled to 0°C. An additional amount of Et_3N (4.18 mL, 30.0 mmol) was added. To this reaction mixture, was added a solution of 4-chloro-2,6-pyridinedicarbonyl dichloride (1.02 g, 5.0 mmol) in CH_2Cl_2 (5 mL) dropwise over 5 min. The resulting reaction mixture was stirred while warming to rt over 12 hr. The solvent was removed *in vacuo*. The residue was redissolved in $CHCl_3$ (50 mL) and washed with cold 1M HCl (30 mL). The aqueous layer was back-extracted with $CHCl_3$ (2 x 20 mL). The combined organics were treated with solid $NaHCO_3$ until pH ~7, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (0%-50% EtOAc/ether) to give Boc-G1-Cl-All (**31**) (6.21 g, 8.0 mmol, 89% based on diamine) as a white solid. mp 174-178 °C ($CHCl_3$); ^{1}H NMR (400 MHz, 80°C, DMSO-d_6) δ 1.23 (s, 18H), 1.57-1.71 (m, 4H), 1.84-1.92 (m, 2H), 1.98-2.06 (m, 2H), 3.09-3.23 (m, 4H), 4.19 (dd, J = 8.4 Hz, 4.4 Hz, 2H), 7.29-7.34 (m, 4H), 7.64-7.66 (m, 2H), 7.76-7.79 (m, 2H), 8.41 (s, 2H), 9.51 (s, 2H), 10.88 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 23.0, 27.5, 30.1, 46.1, 60.2, 78.4, 78.7, 124.3, 124.4, 124.9, 125.6, 129.3, 130.8, 146.6, 149.9, 153.1, 160.1, 171.5; IR (KBr) 3492, 3241, 3068, 2973, 2921, 2869, 2349, 1690, 1600, 1534, 1482, 1452, 1395, 1317, 1255, 1162, 1118, 1010 cm^{-1}; HRMS calcd for $C_{39}H_{46}ClN_7O_8$ (M+Na) 798.2994, found 798.2996.

Boc-G1-NH_2-All (32): Boc-G1-Cl-All (**31**) (1.88 g, 2.42 mmol) was dissolved in anhydrous DMF (16.7 mL). To this solution was added NaN_3 (2.17 g, 33.3 mmol). After stirring at 50°C for 48 h, the solvent was removed under reduced pressure. The residue was redissolved in water (50 mL) and $CHCl_3$ (30 mL). The organic layer was extracted and washed with brine (20 mL) and dried over Na_2SO_4. After concentration *in vacuo*, the residue was redissolved in anhydrous EtOH. 10% Pd/C (189 mg) was added to this mixture and the reaction was hydrogenated under H_2 at atmospheric pressure for 12 h. The catalyst was removed by filtration through a pad of celite. The solvent was removed *in vacuo* and the residue was purified by column chromatography on silica gel (1-5% MeOH/$CHCl_3$ to give Boc-G1-NH_2-All (**32**) (1.61 g, 2.13 mmol, 88% over 2 steps) as an off-white solid. mp 176-180 °C ($CHCl_3$); ^{1}H NMR (400 MHz, 80°C, DMSO-d_6) δ 1.24 (s, 18H), 1.53-1.70 (m, 4H), 1.77-1.85 (m, 2H), 1.94-2.00 (m, 2H), 3.09-3.19 (m, 4H), 4.19 (dd, J = 8.6 Hz, 4.5 Hz, 2H), 6.65 (s, 2H), 7.23-7.30 (m, 4H), 7.53 (s, 2H), 7.55-7.58 (m, 2H), 7.78-7.80 (m, 2H), 9.53 (s, 2H), 10.70 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 22.9, 27.5, 30.0, 46.0, 60.2, 78.4, 108.7, 124.4, 124.89, 124.92, 130.14, 130.18, 148.6, 153.0, 157.1, 162.1, 171.6; IR (KBr) 3449, 3353, 3250, 2973, 2921, 2869, 2358, 1695, 1603, 1520, 1482, 1447, 1395, 1365, 1300, 1257, 1162, 1123 cm^{-1}; HRMS calcd for $C_{39}H_{48}N_8O_8$ (M+Na) 779.3487, found 779.3459.

Boc-G2-H-All (33): To a solution of Boc-G1-NH_2-All (**32**) (456 mg, 0.602 mmol) in dry CH_2Cl_2 (3 mL) were added DMAP (15 mg, 0.12 mmol) and pyridine (3 mL). The reaction mixture was cooled to 0°C in an ice bath. To this mixture was added a solution of 2,6-pyridinedicarbonyl dichloride (61 mg, 0.30 mmol) in CH_2Cl_2 (0.3 mL) dropwise over 5 min. The reaction was stirred while warming to rt gradually over 12 h. The reaction was diluted with CH_2Cl_2 (10 mL) and

washed with cold 1 M HCl (10 mL). The aqueous layer was back-extracted with $CHCl_3$ (2 x 10 mL). The combined organic layer was treated with solid $NaHCO_3$ until pH ~7 and dried over Na_2SO_4. After concentration *in vacuo*, the residue was purified by column chromatography on silica gel (10-20% MeOH/ether) to afford Boc-G2-I-H-All (**33**) (414 mg, 0.252 mmol, 84%) as an off-white solid. mp (dec) 210 °C ($CHCl_3$); ^{1}H NMR (400 MHz, 80°C, DMSO-d_6) δ 1.22 (s, 36H), 1.54-1.65 (m, 8H), 1.80-1.88 (m, 4H), 1.95-2.02 (m, 4H), 3.10-3.17 (m, 8H), 4.16 (dd, *J* = 8.6 Hz, 4.6 Hz, 4H), 7.27-7.34 (m, 8H), 7.59-7.61 (m, 4H), 7.83-7.85 (m, 4H), 8.42 (t, *J* = 7.7 Hz, 1H), 8.56 (d, *J* = 7.9 Hz, 2H), 9.07 (s, 4H), 9.58 (s, 4H), 10.89 (s, 4H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 22.9, 27.4, 30.0, 46.0, 60.1, 78.2, 114.9, 124.3, 124.75, 124.84, 125.1, 126.0, 129.8, 130.5, 139.7, 147.8, 148.2, 149.5, 153.0, 161.2, 162.7, 171.5; IR (KBr) 3469, 3299, 3075, 2977, 2923, 2889, 1674, 1602, 1575, 1521, 1477, 1445, 1396, 1360, 1311, 1257, 1163, 1127 cm^{-1}; HRMS calcd for $C_{85}H_{97}N_{17}O_{18}$ (M+Na) 1666.7090, found 1666.7125.

G2-I-All-Cat (3): To a solution of Boc-G2-I-H-All (**33**) (100 mg, 0.061 mmol) in CH_2Cl_2 (0.61 mL) was added anisole (61 μL, 0.56 mmol) at rt. The mixture was cooled to 0°C and TFA (0.61 mL, 7.9 mmol) was added dropwise over 5 min. The reaction was stirred while warming to rt gradually over 12 h. The volatiles were removed *in vacuo*. To the residue was added diethyl ether (5 mL) and the solid precipitate was isolated by filtration. The precipitate was redissolved in a mixture of H_2O (1 mL) and CH_3CN (1 mL). To this mixture was added solid $NaHCO_3$ with stirring until pH ~8. The white solid precipitate was isolated by filteration and dried *in vacuo* over P_2O_5 to give G2-I-H-All-Cat (**3**) (73 mg, 0.059 mmol, 96%) as a white solid. mp (dec) 215 °C ($CHCl_3$); ^{1}H NMR (400 MHz, 80°C, DMSO-d_6) δ 1.66-1.83 (m, 8H), 1.99-2.07 (m, 4H), 2.20-2.29 (m, 4H), 3.12 (t, *J* = 7.5 Hz, 8H), 3.74 (brs, 4H), 4.39 (dd, *J* = 9.2 Hz, 7.0 Hz, 4H),

7.32-7.38 (m, 8H), 7.62-7.65 (m, 4H), 7.68-7.73 (m, 4H), 8.42 (dd, *J* = 8.9 Hz, 7.1 Hz, 1H), 8.56 (d, *J* = 7.7 Hz, 2H), 9.03 (s, 4H), 9.89 (brs, 4H), 10.66 (s, 4H), 11.63 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 22.8, 28.9, 45.2, 59.3, 114.9, 124.7, 125.5, 125.7, 130.0, 130.8, 147.8, 148.0, 149.7, 161.6, 162.7, 167.0; IR (KBr) 3475, 3296, 3081, 2982, 2785, 2355, 1663, 1596, 1569, 1524, 1448, 1412, 1309, 1202, 1134 cm^{-1}; HRMS calcd for $C_{65}H_{65}N_{17}O_{10}$ (M+Na) 1266.4993, found 1266.4965.

Boc-G2-I-Cl-All (34): To a solution of Boc-G1-NH_2-All (**32**) (550 mg, 0.727 mmol) in dry CH_2Cl_2 (3.6 mL) were added DMAP (9 mg, 0.07 mmol) and pyridine (1.8 mL). The reaction mixture was cooled to 0°C in an ice bath. To this mixture was added a solution of 4-chloro-2,6-pyridinedicarbonyl dichloride (87 mg, 0.36 mmol) in CH_2Cl_2 (0.4 mL) dropwise over 5 min. The reaction was stirred while warming to rt gradually over 12 h. The reaction was diluted with CH_2Cl_2 (10 mL) and washed with cold 1 M HCl (10 mL). The aqueous layer was back-extracted with $CHCl_3$ (2 x 10 mL). The combined organic layer was treated with solid $NaHCO_3$ until pH ~7 and dried over Na_2SO_4. After concentration *in vacuo*, the residue was purified by column chromatography on silica gel (1-2% MeOH/$CHCl_3$) to afford Boc-G2-I-Cl-All (**34**) (458 mg, 0.273 mmol, 75%) as an off-white solid. mp 170-174 °C ($CHCl_3$); ^{1}H NMR (400 MHz, 80°C, DMSO-d_6) δ 1.23 (s, 36H), 1.54-1.68 (m, 8H), 1.82-1.89 (m, 4H), 1.96-2.03 (m, 4H), 3.08-3.20 (m, 8H), 4.17 (dd, *J* = 8.5 Hz, 4.5 Hz, 4H), 7.27-7.35 (m, 8H), 7.60-7.62 (m, 4H), 7.84-7.86 (m, 4H), 8.53 (s, 2H), 9.06 (s, 4H), 9.58 (s, 4H), 10.90 (s, 4H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 23.0, 27.5, 30.8, 46.1, 60.2, 78.3, 114.9, 124.4, 124.8, 125.0, 125.3, 125.9, 129.8, 130.5, 146.6, 148.1, 149.5, 149.6, 153.1, 161.2, 161.6, 171.6; IR (KBr) 3483, 3276, 3068, 2977, 2931, 2351, 1673, 1599, 1519, 1480, 1455, 1393, 1368, 1217, 1181, 1126 cm^{-1}; MALDI-TOF MS calcd for

$C_{85}H_{96}ClN_{17}O_{18}$ (M+Na) 1700.669, found 1700.879.

Boc-G2-I-NH_2-All (35): Boc-G2-I-Cl-All (**34**) (458 mg, 0.273 mmol) was dissolved in anhydrous DMF (5.4 mL). To this solution was added NaN_3 (177 mg, 2.73 mmol). After stirring at 50°C for 48 h, the solvent was removed under reduced pressure. The residue was redissolved in water (30 mL) and $CHCl_3$ (20 mL). The organic layer was extracted and washed with brine (20 mL) and dried over Na_2SO_4. After concentration *in vacuo*, the residue was redissolved in anhydrous EtOH (2.7 mL). 10% Pd/C (46 mg) was added to this mixture and the reaction was hydrogenated under H_2 at atmospheric pressure for 12 h. The catalyst was removed by filtration through a pad of celite. The solvent was removed *in vacuo* and the residue was purified by column chromatography on silica gel (1-5% MeOH/$CHCl_3$ to give Boc-G2-I-NH_2-All (**35**) (305 mg, 0.184 mmol, 67% over 2 steps) as an off-white solid. mp (dec) 235 °C ($CHCl_3$); ^{1}H NMR (400 MHz, 80°C, DMSO-d_6) δ 1.23 (s, 36H), 1.53-1.71 (m, 8H), 1.82-1.89 (m, 4H), 1.96-2.05 (m, 4H), 3.10-3.20 (m, 4H), 4.17 (dd, J = 8.6 Hz, 4.5 Hz, 4H), 6.78 (s, 2H), 7.28-7.34 (m, 8H), 7.60-7.63 (m, 4H), 7.68 (s, 2H), 7.84-7.86 (m, 4H), 9.04 (s, 4H), 9.53 (s, 4H), 10.85 (s, 4H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 22.9, 27.4, 29.9, 46.0, 60.2, 78.3, 110.0, 114.7, 124.3, 124.7, 124.9, 125.2, 129.8, 130.4, 148.3, 148.4, 149.4, 153.0, 156.9, 161.2, 163.4, 171.6; IR (KBr) 3484, 3278, 2973, 2928, 2875, 2364, 1681, 1601, 1573, 1519, 1475, 1399, 1362, 1300, 1258, 1162, 1121 cm^{-1}; MALDI-TOF MS calcd for $C_{85}H_{98}N_{18}O_{18}$ (M+Na) 1681.719, found 1681.917.

Boc-II-G1-NO_2-All (36): To a solution of Boc-G1-NH_2-All (**32**) (0.50 g, 0.66 mmol) in dry CH_2Cl_2 (3.3 mL) were added DMAP (16 mg, 0.13 mmol) and pyridine (3.3 mL). The reaction mixture was cooled to 0°C in an ice bath. To this mixture was added a solution of 2-nitrobenzoyl

chloride (122 mg, 0.66 mmol) in CH_2Cl_2 (0.7 mL) dropwise over 5 min. The reaction was stirred while warming to rt gradually over 12 h. The reaction was diluted with CH_2Cl_2 (10 mL) and washed with cold 1 M HCl (15 mL). The aqueous layer was back-extracted with $CHCl_3$ (2 x 10 mL). The combined organic layer was treated with solid $NaHCO_3$ until pH ~7 and dried over Na_2SO_4. After concentration *in vacuo*, the residue was purified by column chromatography on silica gel (1-3% MeOH/$CHCl_3$) to afford Boc-II-G1-NO_2-All (**36**) (289 mg, 0.319 mmol, 48%) as an off-white solid. mp 185 °C ($CHCl_3$); ^{1}H NMR (400 MHz, 80°C, DMSO-d_6) δ 1.26 (s, 18H), 1.55-1.71 (m, 4H), 1.84-1.91 (m, 2H), 1.98-2.07 (m, 2H), 3.12-3.23 (m, 4H), 4.19 (dd, *J* = 8.7 Hz, 4.4 Hz, 2H), 7.23-7.34 (m, 4H), 7.62-7.64 (m, 2H), 7.82-7.84 (m, 2H), 7.87 (td, *J* = 7.6 Hz, 1.7 Hz, 2H), 7.94 (td, *J* = 7.5 Hz, 1.1 Hz, 1H), 8.22 (dd, *J* = 8.2 Hz, 1.0 Hz, 1H), 8.72 (s, 2H), 9.56 (s, 2H), 10.87 (s, 2H), 11.38 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 23.0, 27.5, 30.0, 46.1, 60.3, 78.4, 114.0, 123.9, 124.4, 124.8, 125.0, 125.3, 128.8, 129.8, 130.6, 131.1, 131.2, 133.8, 146.0, 148.6, 149.5, 153.1, 161.2, 165.0, 171.6; IR (KBr) 3447, 3355, 3086, 2978, 2931, 2347, 1681, 1596, 1531, 1481, 1393, 1367, 1349, 1296, 1256, 1160, 1128 cm^{-1}; HRMS calcd for $C_{46}H_{51}N_9O_{11}$ (M+Na) 928.3600, found 928.3609.

Boc-II-G1-NH_2-All (37): Boc-II-G1-NO_2-All (**36**) (289 mg, 0.320 mmol) was dissolved in anhydrous EtOH. 10% Pd/C (29 mg) was added to this mixture and the reaction was hydrogenated under H_2 at atmospheric pressure for 12 h. The catalyst was removed by filtration through a pad of celite. The solvent was removed *in vacuo* and the residue was purified by column chromatography on silica gel (1-3% MeOH/$CHCl_3$) to give Boc-II-G1-NH_2-All (**37**) (237 mg, 0.271 mmol, 85%) as an off-white solid. mp 174-178 °C ($CHCl_3$); ^{1}H NMR (400 MHz, 80°C, DMSO-d_6) δ 1.24 (s, 18H), 1.54-1.70 (m, 4H), 1.79-1.88 (m, 2H), 1.95-2.05 (m, 2H),

3.10-3.20 (m, 4H), 4.16 (dd, *J* = 9.0 Hz, 4.4 Hz, 2H), 6.42 (brs, 2H), 6.65 (td, 7.0 Hz, 1.4 Hz, 1H), 6.84 (dd, *J* = 8.4 Hz, 1.1 Hz, 1H), 7.23-7.34 (m, 5H), 7.59-7.61 (m, 2H), 7.78-7.82 (m, 3H), 8.84 (s, 2H), 9.53 (s, 2H), 10.82 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 23.0, 27.5, 30.0, 46.1, 60.2, 69.5, 78.3, 113.3, 114.4, 116.5, 124.4, 124.7, 124.9, 125.2, 128.5, 129.9, 130.5, 132.6, 149.1, 149.4, 150.2, 153.1, 161.4, 168.3, 171.6; IR (KBr) 3440, 3258, 2973, 2877, 2358, 1677, 1594, 1517, 1478, 1447, 1391, 1361, 1292, 1235, 1157, 1123 cm^{-1}; HRMS calcd for $C_{46}H_{53}N_9O_9$ (M+Na) 898.3864, found 898.3859.

Boc-G2-II-H-All (38): To a solution of Boc-II-G1-NH_2-All (**37**) (596 mg, 0.68 mmol) in dry CH_2Cl_2 (3.4 mL) were added DMAP (17 mg, 0.14 mmol) and pyridine (3.4 mL). The reaction mixture was cooled to 0°C in an ice bath. To this mixture was added a solution of 2,6-pyridinedicarbonyl dichloride (69 mg, 0.34 mmol) in CH_2Cl_2 (0.4 mL) dropwise over 5 min. The reaction was stirred while warming to rt gradually over 12 h. The reaction was diluted with CH_2Cl_2 (10 mL) and washed with cold 1 M HCl (10 mL). The aqueous layer was back-extracted with $CHCl_3$ (2 x 10 mL). The organic layer was treated with solid $NaHCO_3$ until pH ~7 and dried over Na_2SO_4. After concentration *in vacuo*, the residue was purified by column chromatography on silica gel (5-15% MeOH/ether) to afford Boc-G2-II-H-All (**38**) (356 mg, 0.190 mmol, 56%) as an off-white solid. mp (dec) 215 °C ($CHCl_3$); ^{1}H NMR (400 MHz, 80°C, DMSO-d_6) δ 1.21 (s, 36H), 1.50-1.65 (m, 8H), 1.77-1.85 (m, 4H), 1.92-2.01 (m, 4H), 3.05-3.16 (m, 8H), 4.12 (dd, *J* = 9.0 Hz, 4.6 Hz, 4H), 7.19 (t, *J* = 7.8 Hz, 2H), 7.27-7.34 (m, 8H), 7.46 (t, *J* = 8.2 Hz, 2H), 7.57 (d, *J* = 7.8 Hz, 4H), 7.77 (dd, *J* = 4 Hz, 1.5 Hz, 2H), 7.83 (dd, *J* = 3.9 Hz, 1.4 Hz, 4H), 8.28 (d, *J* = 7.5 Hz, 2H), 8.31 (t, *J* = 2.8 Hz, 1H), 8.38 (d, *J* = 1.8 Hz, 2H), 8.57 (s, 4H), 9.57 (s, 4H), 10.70 (s, 4H), 10.87 (s, 2H), 11.95 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 22.9, 27.5, 30.1,

46.0, 60.2, 78.3, 114.6, 122.2, 123.5, 123.9, 124.4, 124.50, 124.56, 124.64, 125.0, 128.5, 130.0, 131.7, 136.7, 138.5, 139.9, 148.4, 148.8, 148.9, 153.0, 160.9, 161.0, 166.9, 171.7; IR (KBr) 3460, 3281, 3075, 2977, 2878, 2359, 1691, 1588, 1526, 1477, 1450, 1395, 1367, 1302, 1254, 1161, 1127, 1087 cm^{-1}; HRMS calcd for $C_{99}H_{107}N_{19}O_{20}$ (M+Na) 1905.7866, found 1905.7880.

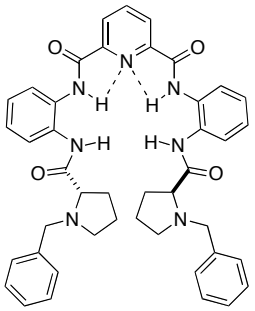
G2-II-All-Cat (4): To a solution of Boc-G2-II-H-All (**38**) (200 mg, 0.107 mmol) in CH_2Cl_2 (1.1 mL) was added anisole (107 μL, 0.989 mmol) at rt. The mixture was cooled to 0°C and TFA (1.1 mL, 1.4 mmol) was added dropwise over 5 min. The reaction was stirred while warming to rt gradually over 12 h. The volatiles were removed *in vacuo*. To the residue was added diethyl ether (10 mL) and the solid precipitate was isolated by filtration. The precipitate was redissolved in a mixture of H_2O (2 mL) and CH_3CN (2 mL). To this mixture was added solid $NaHCO_3$ with stirring until pH ~8. The white solid precipitate was isolated by filteration and dried *in vacuo* over P_2O_5 to give G2-II-H-All-Cat (**4**) (150 mg, 0.102 mmol, 95%) as a white solid. mp (dec) 220 °C ($CHCl_3$); ^{1}H NMR (400 MHz, 80°C, DMSO-d_6) δ 1.65-1.78 (m, 8H), 1.94-2.02 (m, 4H), 2.15-2.24 (m, 4H), 3.03-3.14 (m, 8H), 3.92 (brs, 4H), 4.37 (dd, J = 9.1 Hz, 7.1 Hz, 4H), 7.24 (t, J = 7.9Hz, 2H), 7.33-7.38 (m, 8H), 7.49 (t, 2H), 7.65-7.67 (m, 8H), 7.78 (dd, J = 7.8 Hz, 1.7 Hz, 2H), 8.15 (dd, J = 8.2 Hz, 1.1 Hz, 2H), 8.28 (t, J = 5.6 Hz, 1H), 8.31 (t, J = 8.6 Hz, 2H), 8.34 (d, J = 2.9 Hz, 2H), 8.58 (s, 4H), 9.94 (brs, 4H), 10.46 (s, 4H), 10.96 (s, 2H), 11.79 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 22.9, 28.8, 45.2, 59.3, 114.7, 122.4, 123.5, 124.4, 124.6, 125.0, 125.4, 125.5, 125.6, 128.5, 130.2, 131.6, 136.4, 148.3, 148.5, 149.1, 157.9, 158.1, 161.0, 161.3, 166.9, 167.1; IR (KBr) 3464, 3356, 3256, 3076, 2986, 2752, 2374, 1678, 1583, 1520, 1448, 1403, 1353, 1304, 1202, 1134 cm^{-1}; HRMS calcd for $C_{79}H_{75}N_{19}O_{12}$ (M+Na) 1504.5735, found 1504.5741.

Boc-G3-I-H-All (39): To a solution of Boc-G2-I-NH_2-All (**35**) (152 mg, 0.092 mmol) in dry CH_2Cl_2 (1.0 mL) were added DMAP (2 mg, 0.018 mmol) and pyridine (0.75 mL). The reaction mixture was cooled to 0°C in an ice bath. To this mixture was added a solution of 2,6-pyridinedicarbonyl dichloride (9.4 mg, 0.046 mmol) in CH_2Cl_2 (0.1 mL) dropwise over 5 min. The reaction was stirred while warming to rt gradually over 12 h. The reaction was diluted with CH_2Cl_2 (10 mL) and washed with cold 1 M HCl (5 mL). The aqueous layer was back-extracted with $CHCl_3$ (2 x 10 mL). The combined organic layer was treated with solid $NaHCO_3$ until pH ~7 and dried over Na_2SO_4. After concentration *in vacuo*, the residue was purified by column chromatography on silica gel (1-5% MeOH/$CHCl_3$) to afford Boc-G3-I-H-All (**39**) (110 mg, 0.032 mmol, 69%) as an off-white solid. mp (dec) 245 °C ($CHCl_3$); ^{1}H NMR (400 MHz, 80°C, DMSO-d_6) δ 1.23 (s, 72H), 1.52-1.71 (m, 16H), 1.82-1.89 (m, 8H), 1.95-2.03 (m, 8H), 3.10-3.20 (m, 16H), 4.17 (dd, J = 8.6 Hz, 4.4 Hz, 8H), 7.27-7.35 (m, 16H), 7.60-7.62 (m, 8H), 7.84-7.86 (m, 8H), 8.46 (dd, J = 9.1 Hz, 7.5 Hz, 1H), 8.60 (d, J = 8.0 Hz, 2H), 9.10 (s, 8H), 9.17 (s, 4H), 9.54 (s, 8H), 10.88 (s, 8H), 11.63 (s, 2H), 11.67 (s, 4H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 22.9, 27.4, 29.9, 46.0, 60.2, 78.3, 114.9, 116.4, 124.3, 124.7, 124.9, 125.2, 126.1, 129.8, 130.4, 147.9, 148.2, 148.3, 149.1, 149.5, 153.0, 161.1, 161.2, 162.6, 162.9, 171.6; IR (KBr) 3478, 3281, 2986, 2914, 2842, 2359, 1683, 1597, 1580, 1517, 1477, 1445, 1396, 1360, 1342, 1306, 1163, 1126 cm^{-1}; MALDI-TOF MS calcd for $C_{177}H_{197}N_{37}O_{38}$ (M+Na-$C_{40}O_{16}H_{64}$) 2671.032, found 2671.957.

G3-I-All-Cat (5): To a solution of Boc-G3-I-H-All (**39**) (110 mg, 0.0319 mmol) in CH_2Cl_2 (3.2 mL) was added anisole (276 μL, 2.55 mmol) at rt. The mixture was cooled to 0°C and TFA (393 μL, 5.10 mmol) was added dropwise over 5 min. The reaction was stirred while warming to rt

gradually over 12 h. The volatiles were removed *in vacuo*. To the residue was added diethyl ether (5 mL) and the solid precipitate was isolated by filtration. The precipitate was redissolved in a mixture of H_2O (1 mL) and CH_3CN (1 mL). To this mixture was added solid $NaHCO_3$ with stirring until pH ~8. The white solid precipitate was isolated by filteration and dried *in vacuo* over P_2O_5 to give G3-I-H-All-Cat (**5**) (82 mg, 0.0309 mmol, 97%) as a white solid. mp (dec) 285 °C ($CHCl_3$); ^{1}H NMR (400 MHz, 80°C, DMSO-d_6) δ 1.69-1.76 (m, 16H), 1.99-2.07 (m, 8H), 2.18-2.27 (m, 8H), 3.06-3.12 (m, 16H), 4.38 (t, J = 7.6 Hz, 8H), 7.33-7.38 (m, 16H), 7.72-7.74 (m, 16H), 8.46 (t, J = 8.2 Hz, 1H), 8.59 (d, J = 7.9 Hz, 2H), 9.09 (s, 8H), 9.16 (s, 4H), 10.72 (s, 8H), 11.74 (s, 2H), 11.75 (s, 4H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 23.2, 29.2, 45.4, 59.5, 115.0, 116.5, 124.6, 125.4, 125.9, 126.0, 126.2, 129.9, 131.1, 148.0, 148.1 148.4, 149.2, 149.8, 161.7, 162.8, 163.1, 168.0; IR (KBr) 3455, 3283, 3076, 2923, 2356, 1673, 1601, 1574, 1516, 1453, 1412, 1344, 1384, 1200, 1133 cm^{-1}; MALDI-TOF MS calcd for $C_{137}H_{133}N_{37}O_{22}$ (M+H) 2649.051, found 2649.441.

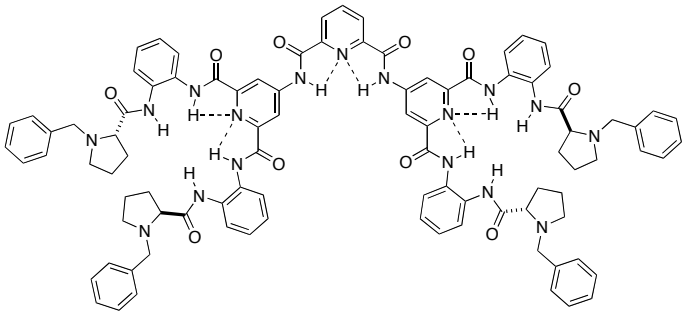
Bis-G1 Bn Amine (40):



To a solution of G1-All-Cat (**2**) (54 mg, 0.1 mmol) in acetonitrile (2 mL) and water (0.5 mL) was sequentially added $NaHCO_3$ (25 mg, 0.3 mmol) at rt and benzyl bromide (24 μL, 0.2 mmol) at 0ºC. The reaction was stirred for 24 h at 5 ºC. After the removal of solvents under reduced

pressure, the crude material was purified by column chromatography on silica gel (20% EtOAc/ether) to give Bis-G1-Bn Amine (**40**) (68 mg, 0.094 mmol, 94%) as a white solid. mp 189-191 ºC ($CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.54-1.65 (m, 4H), 1.77-1.92 (m, 4H), 2.26-2.33 (m, 2H), 2.98-3.06 (m, 4H), 3.53 (d, *J* = 13.3 Hz, 2H), 3.78 (d, *J* = 13.3 Hz, 2H), 6.99-7.00 (m, 6H), 7.10-7.13 (m, 4H), 7.23-7.32 (m, 4H), 7.49 (d, *J* = 8.1 Hz, 2H), 7.88 (d, *J* = 9.6 Hz, 2H), 8.10 (t, *J* = 8.9 Hz, 1H), 8.43 (d, *J* = 9.6 Hz, 2H), 9.68 (s, 2H), 11.13 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 24.20, 30.73, 54.31, 59.89, 67.15, 124.12, 125.11, 125.31, 125.85, 125.94, 127.16, 128.16, 128.52, 129.80, 130.28, 137.89, 139.11, 148.68, 161.84, 174.33; IR (KBr) 3292, 3204, 2941, 2820, 1684, 1640, 1591, 1530, 1486, 1448, 1310 cm^{-1}; HRMS calcd for $C_{43}H_{43}N_7O_4$ (M+Na) 744.3275, found 744.3158.

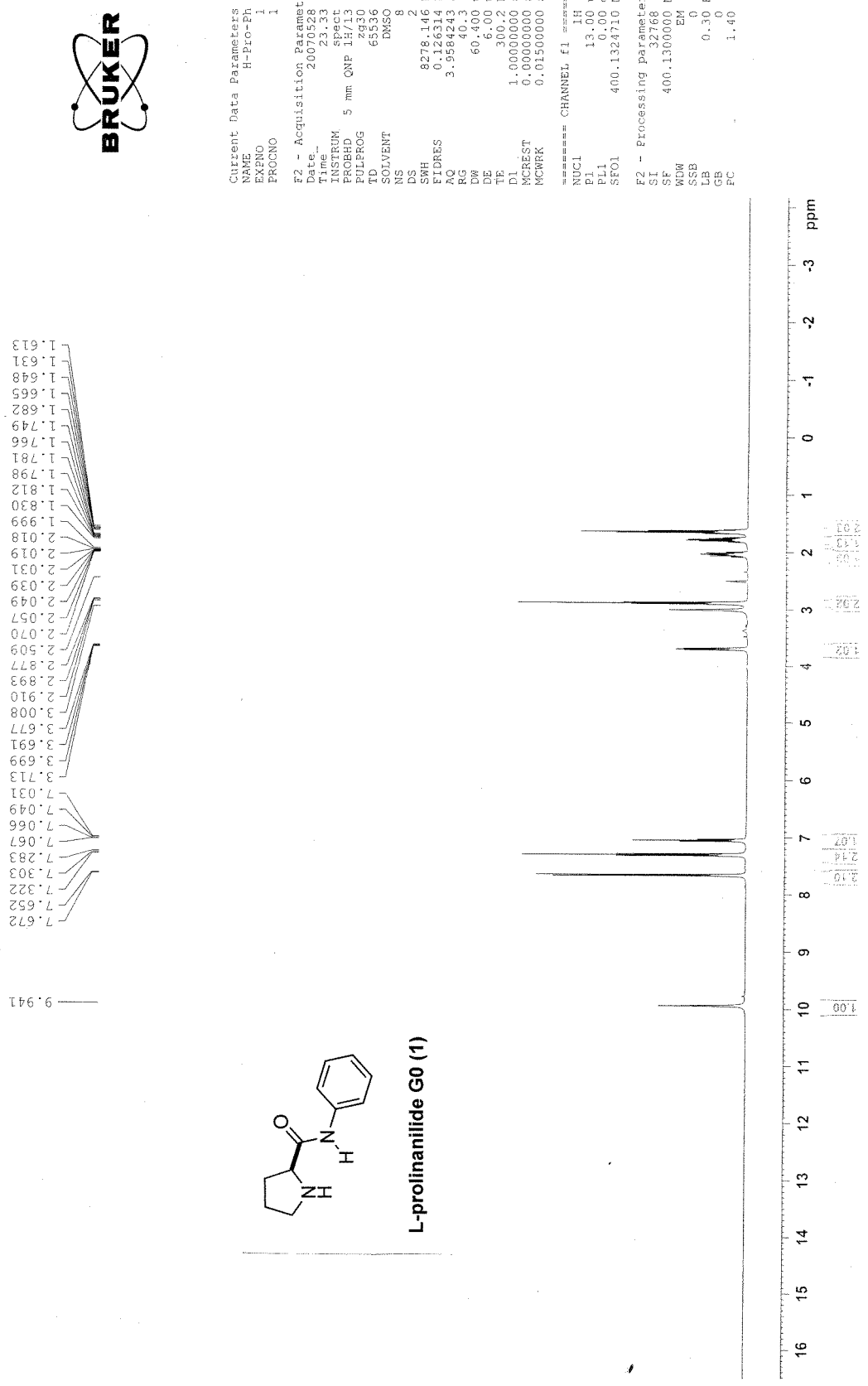
Bis-G2-I-Bn Amine (41):



To a solution of G2-I-All-Cat (**3**) (13.6 mg, 0.011 mmol) in acetonitrile (0.5 mL) and water (0.1 mL) was sequentially added $NaHCO_3$ (9.3 mg, 0.11 mmol) at rt and benzyl bromide (13 μL, 0.11 mmol) at 0ºC. The reaction was stirred for 24 h at 5 ºC. After the removal of solvents under

reduced pressure, the crude material was purified by column chromatography on silica gel (2-4% MeOH/$CHCl_3$) to give Bis-G2-I-Bn Amine (**41**) (12 mg, 0.0074 mmol, 67%) as a white solid. mp 235 ºC (dec) ($CHCl_3$); ^{1}H NMR (DMSO-d_6) δ 1.50-1.62 (m, 8H), 1.70-1.78 (m, 4H), 1.90-2.00 (m, 4H), 2.16-2.24 (m, 4H), 2.75-2.80 (m, 4H), 3.09-3.16 (m, 4H), 3.47 (d, J = 13.2 Hz, 4H), 3.74 (d, J = 13.0 Hz, 4H), 6.98-7.05 (m, 12H), 7.10-7.14 (m, 8H), 7.23-7.33 (m, 8H), 7.61 (d, J = 7.9 Hz, 4H), 7.80 (d, J = 8.4 Hz, 4H), 8.44 (t, J = 7.9 Hz, 1H), 8.57 (d, J = 8.4 Hz, 2H), 9.04 (s, 4H), 9.80 (s, 4H), 11.04 (s, 4H), 11.66 (s, 2H); ^{13}C NMR (DMSO-d_6) δ 23.94, 30.66, 53.85, 59.40, 67.45, 115.40, 123.57, 123.55, 125.16, 126.75, 126.97, 127.12, 128.29, 128.90, 128.81, 132.80, 138.47, 148.53, 149.00, 149.94, 162.32, 163.61, 173.46; IR (KBr) 3474, 3288, 2973, 2816, 1666, 1587, 1527, 1448, 1309 cm^{-1}; MALDI-TOF MS calcd for $C_{93}H_{89}N_{17}O_{10}$ (M) 1604.8097, found 1604.894.

H. ^{1}H-NMR and ^{13}C-NMR spectrum of 1-9 and 40-41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PROCNO 1
F2 - Acquisition Parameters
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Time_ 23.33
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PULPROG zg30
TD 65536
SOLVENT DMSO
NS 8
DS 2
SWH 8278.146 Hz
FIDRES 0.126314 Hz
AQ 3.9584243 sec
RG 40.3
DW 60.400 usec
DE 6.00 usec
TE 300.2 K
D1 1.00000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec
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P1 13.00 usec
PL1 0.00 dB
SFO1 400.1324710 MHz
F2 - Processing parameters
SI 32768
SF 400.1300000 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.40
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7.652
7.322
7.303
7.283
7.067
7.066
7.049
7.031
3.713
3.699
3.691
3.677
3.008
2.910
2.893
2.877
2.509
2.070
2.057
2.049
2.039
2.031
2.019
2.018
1.999
1.830
1.812
1.798
1.781
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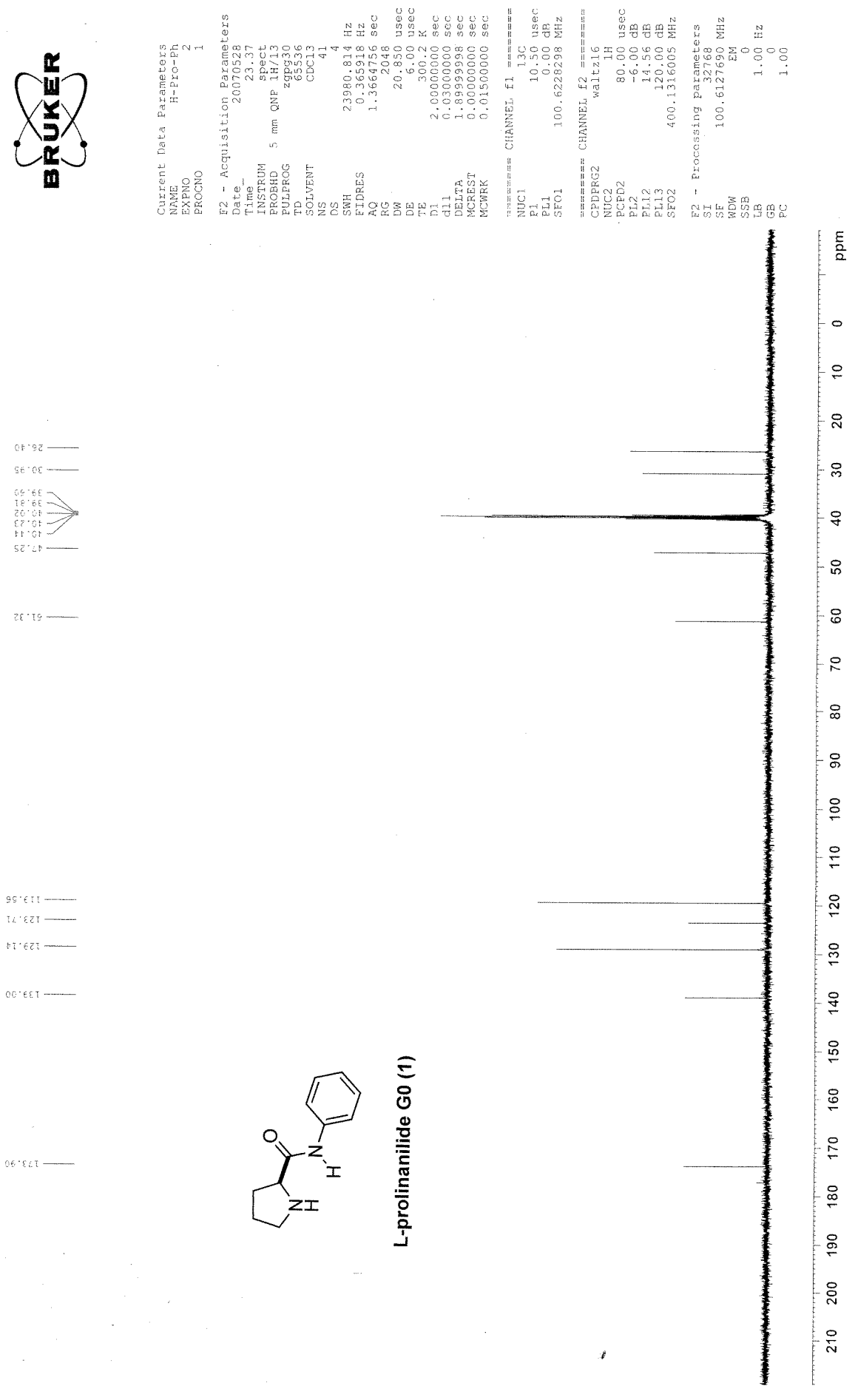
1.749
1.682
1.665
1.648
1.631
1.613
L-prolinanilide G0 (1)
ppm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EXPNO 2
PROCNO 1
F2 - Acquisition Parameters
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Time_ 23.37
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PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 41
DS 4
SWH 23980.814 Hz
FIDRES 0.365918 Hz
AQ 1.3664756 sec
RG 2048
DW 20.850 usec
DE 6.00 usec
TE 300.2 K
D1 2.00000000 sec
d11 0.03000000 sec
DELTA 1.89999998 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec
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PL1 0.00 dB
SFO1 100.6228298 MHz
======== CHANNEL f2 ========
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NUC2 1H
PCPD2 80.00 usec
PL2 -6.00 dB
PL12 14.56 dB
PL13 120.00 dB
SFO2 400.1316005 MHz
F2 - Processing parameters
SI 32768
SF 100.6127690 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.00
173.90
133.00
129.14
123.71
113.56
61.32
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40.23
40.02
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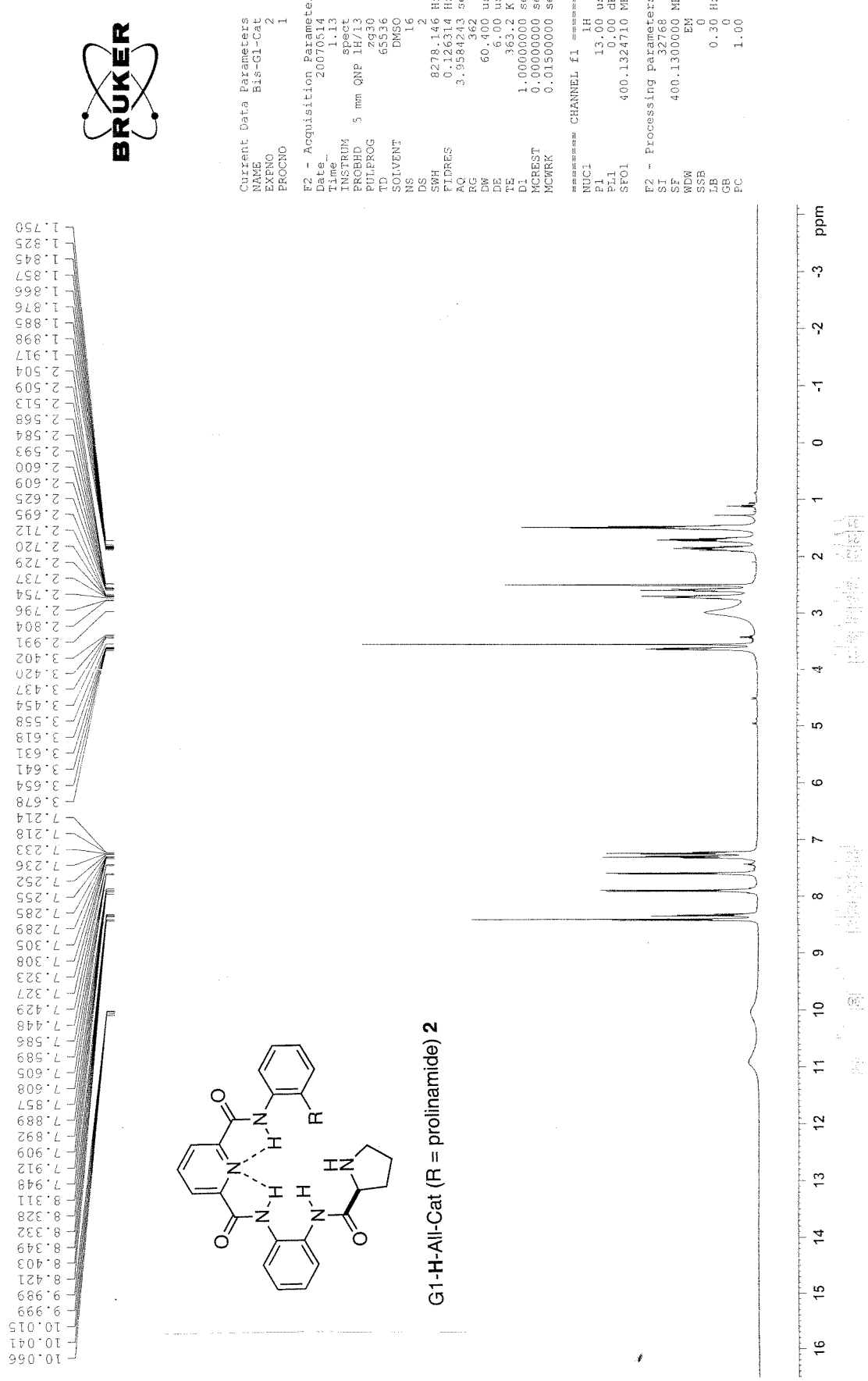
39.60
30.95
26.40
L-prolinanilide G0 (1)
ppm


BRUKER
Current Data Parameters
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EXPNO 2
PROCNO 1
F2 - Acquisition Parameters
Date_ 20070514
Time_ 1.13
INSTRUM spect
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PULPROG zg30
TD 65536
SOLVENT DMSO
NS 16
DS 2
SWH 8278.146 Hz
FIDRES 0.126314 Hz
AQ 3.9584243 sec
RG 362
DW 60.400 usec
DE 6.00 usec
TE 363.2 K
D1 1.00000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec
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NUC1 1H
P1 13.00 usec
PL1 0.00 dB
SFO1 400.1324710 MHz
F2 - Processing parameters
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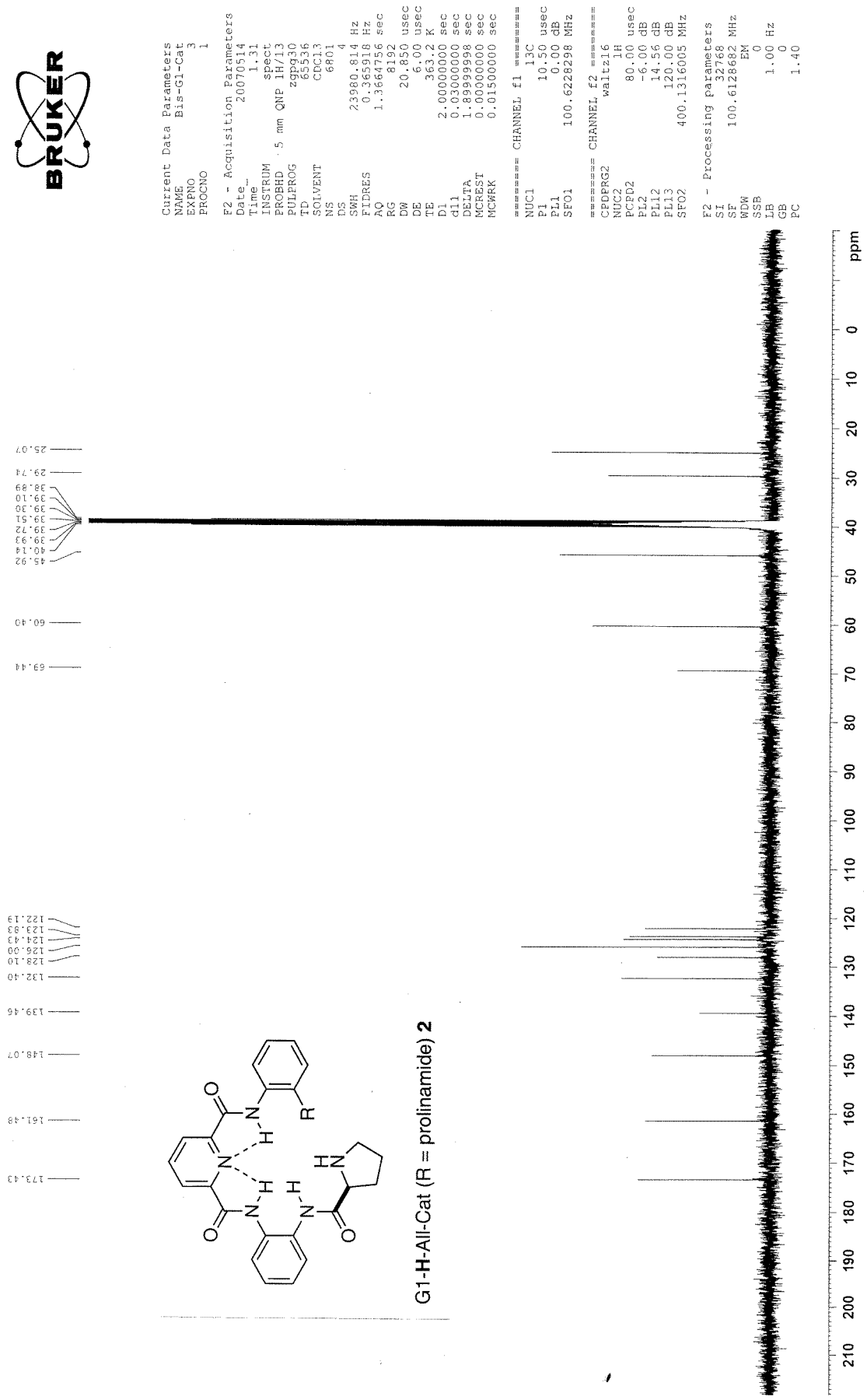
SF 400.1300000 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
G1-H-All-Cat (R = prolinamide) 2
ppm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PROCNO 1
F2 - Acquisition Parameters
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Time_ 1.31
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PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 6801
DS 4
SWH 23980.814 Hz
FIDRES 0.365918 Hz
AQ 1.3664756 sec
RG 8192
DW 20.850 usec
DE 6.00 usec
TE 363.2 K
D1 2.00000000 sec
d11 0.03000000 sec
DELTA 1.89999998 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec
======== CHANNEL f1 ========
NUC1 13C
P1 10.50 usec
PL1 0.00 dB
SFO1 100.6228298 MHz
======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 80.00 usec
PL2 -6.00 dB
PL12 14.56 dB
PL13 120.00 dB
SFO2 400.1316005 MHz
F2 - Processing parameters
SI 32768
SF 100.6128682 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
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29.74
38.89
39.10
39.30
39.51
39.72
39.93
40.14
45.92
60.40
69.44
122.19
123.83
124.43
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132.40
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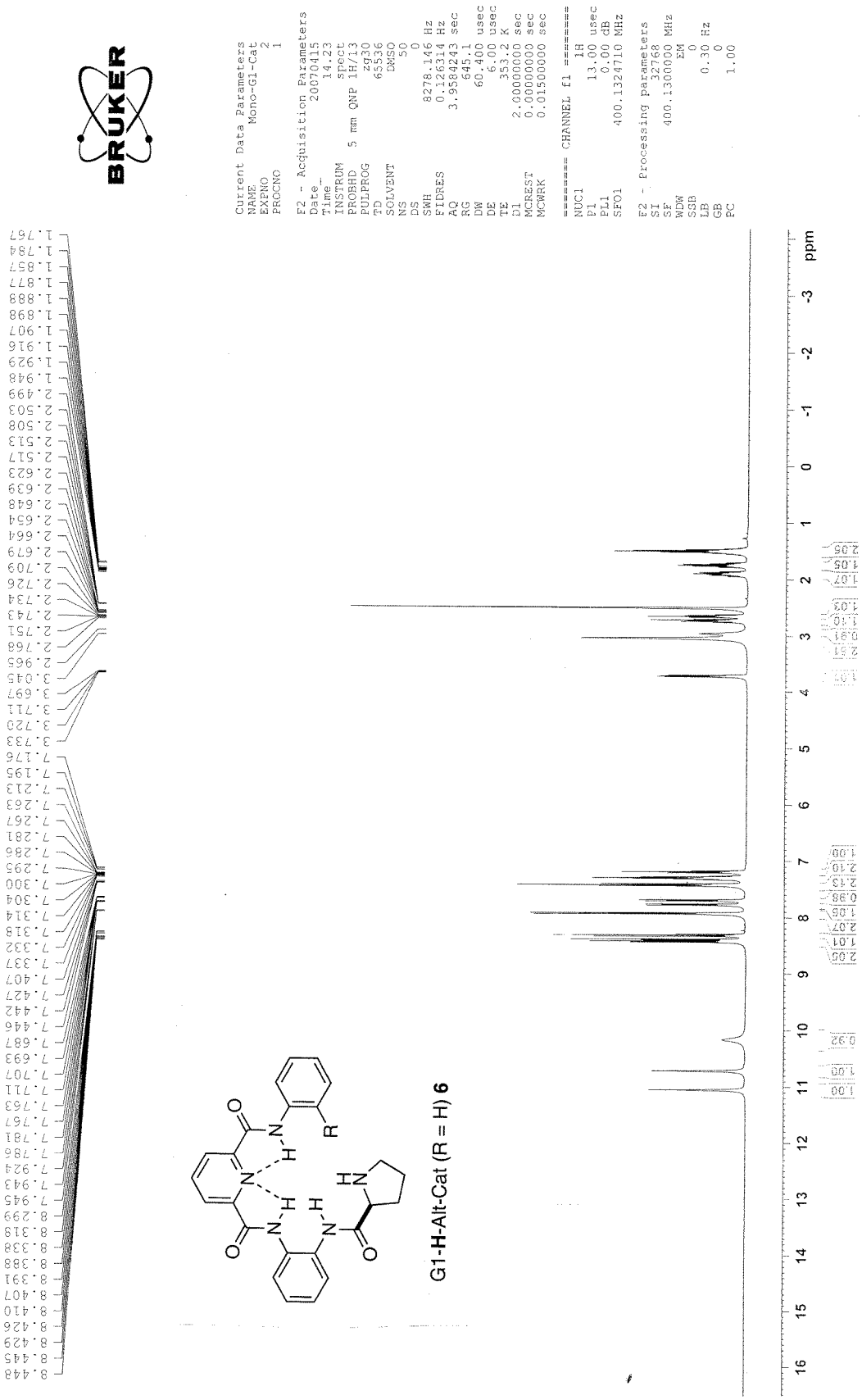
148.07
161.48
173.43
G1-H-All-Cat (R = prolinamide) 2
ppm


BRUKER
Current Data Parameters
NAME Mono-G1-Cat
EXPNO 2
PROCNO 1
F2 - Acquisition Parameters
Date_ 20070415
Time 14.23
INSTRUM spect
PROBHD 5 mm QNP 1H/13
PULPROG zg30
TD 65536
SOLVENT DMSO
NS 50
DS 0
SWH 8278.146 Hz
FIDRES 0.126314 Hz
AQ 3.9584243 sec
RG 645.1
DW 60.400 usec
DE 6.00 usec
TE 353.2 K
D1 2.00000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec
======== CHANNEL f1 ========
NUC1 1H
P1 13.00 usec
PL1 0.00 dB
SFO1 400.1324710 MHz
F2 - Processing parameters
SI 32768
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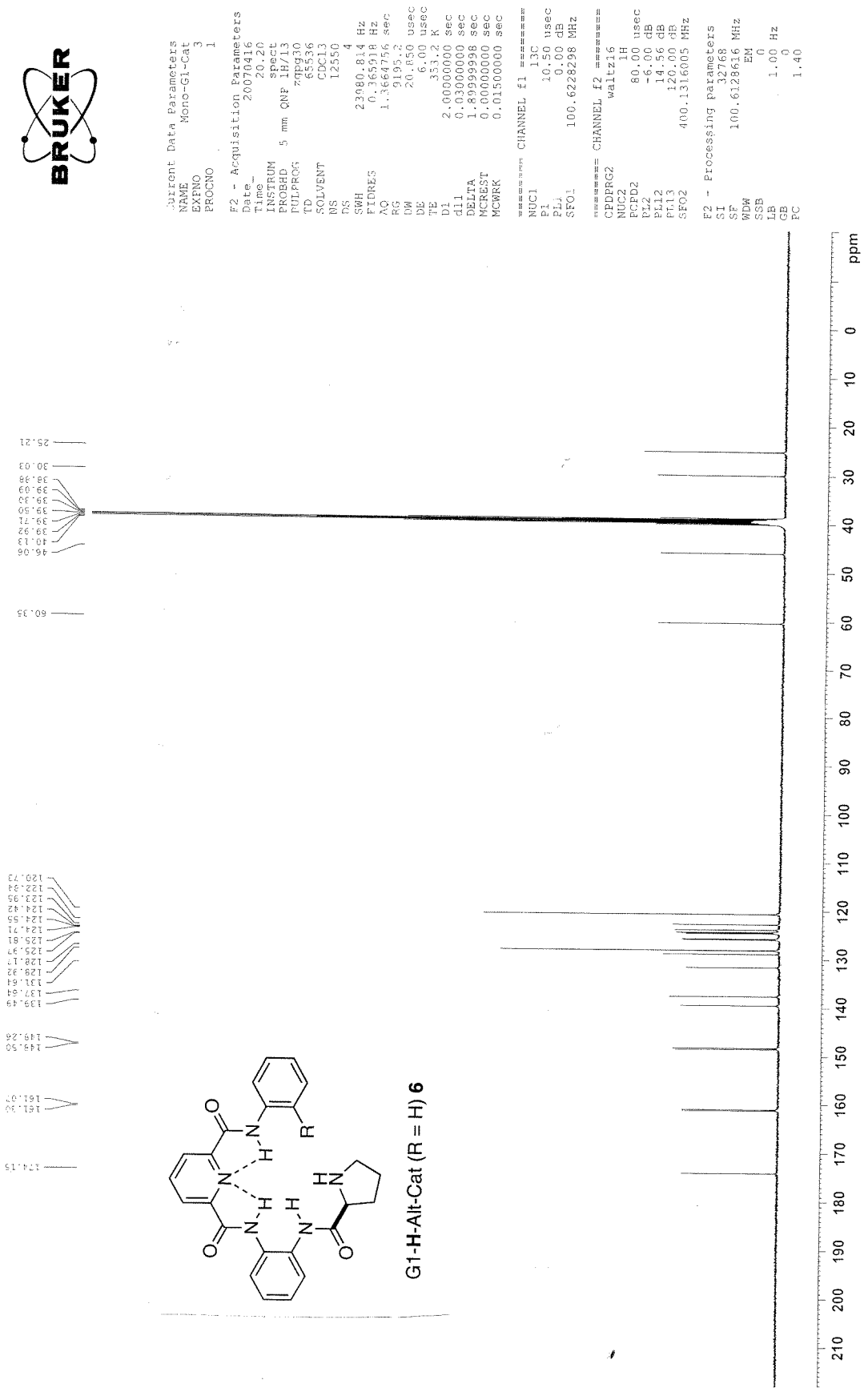
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
G1-H-Alt-Cat (R = H) 6
ppm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EXPNO 3
PROCNO 1
F2 - Acquisition Parameters
Date_ 20070416
Time_ 20.20
INSTRUM spect
PROBHD 5 mm QNP 1H/13
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 12550
DS 4
SWH 23980.814 Hz
FIDRES 0.365918 Hz
AQ 1.3664756 sec
RG 9193.2
DW 20.850 usec
DE 6.00 usec
TE 353.2 K
D1 2.00000000 sec
d11 0.03000000 sec
DELTA 1.89999998 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec
======== CHANNEL f1 ========
NUC1 13C
P1 10.50 usec
PL1 0.00 dB
SFO1 100.6228298 MHz
======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 80.00 usec
PL2 -6.00 dB
PL12 14.56 dB
PL13 120.00 dB
SFO2 400.1316005 MHz
F2 - Processing parameters
SI 32768
SF 100.6128616 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
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30.03
38.98
39.09
39.30
39.50
39.71
39.92
40.13
46.06
60.35
120.73
122.34
123.95
124.42
124.55
124.71
125.81
125.97
128.17
128.32
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149.24
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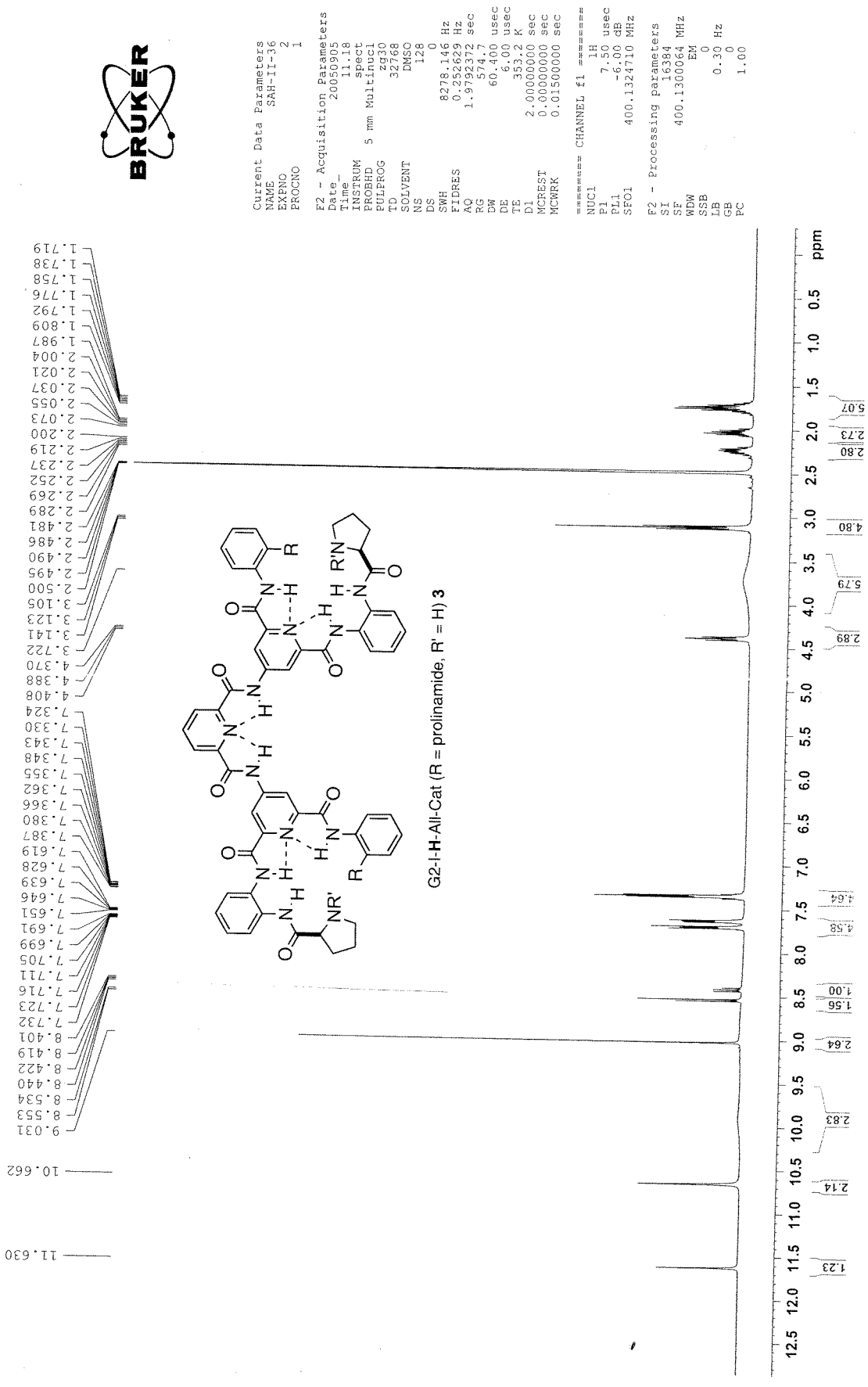
161.30
161.07
174.15
ppm
G1-H-Alt-Cat (R = H) 6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NAME SAH-II-36
EXPNO 2
PROCNO 1
F2 - Acquisition Parameters
Date_ 20050905
Time_ 11.18
INSTRUM spect
PROBHD 5 mm Multinucl
PULPROG zg30
TD 32768
SOLVENT DMSO
NS 128
DS 0
SWH 8278.146 Hz
FIDRES 0.252629 Hz
AQ 1.9792372 sec
RG 574.7
DW 60.400 usec
DE 6.00 usec
TE 353.2 K
D1 2.00000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec
======== CHANNEL f1 ========
NUC1 1H
P1 7.50 usec
PL1 -6.00 dB
SFO1 400.1324710 MHz
F2 - Processing parameters
SI 16384
SF 400.1300064 MHz
WDW EM
SSB 0
LB 0.30 Hz
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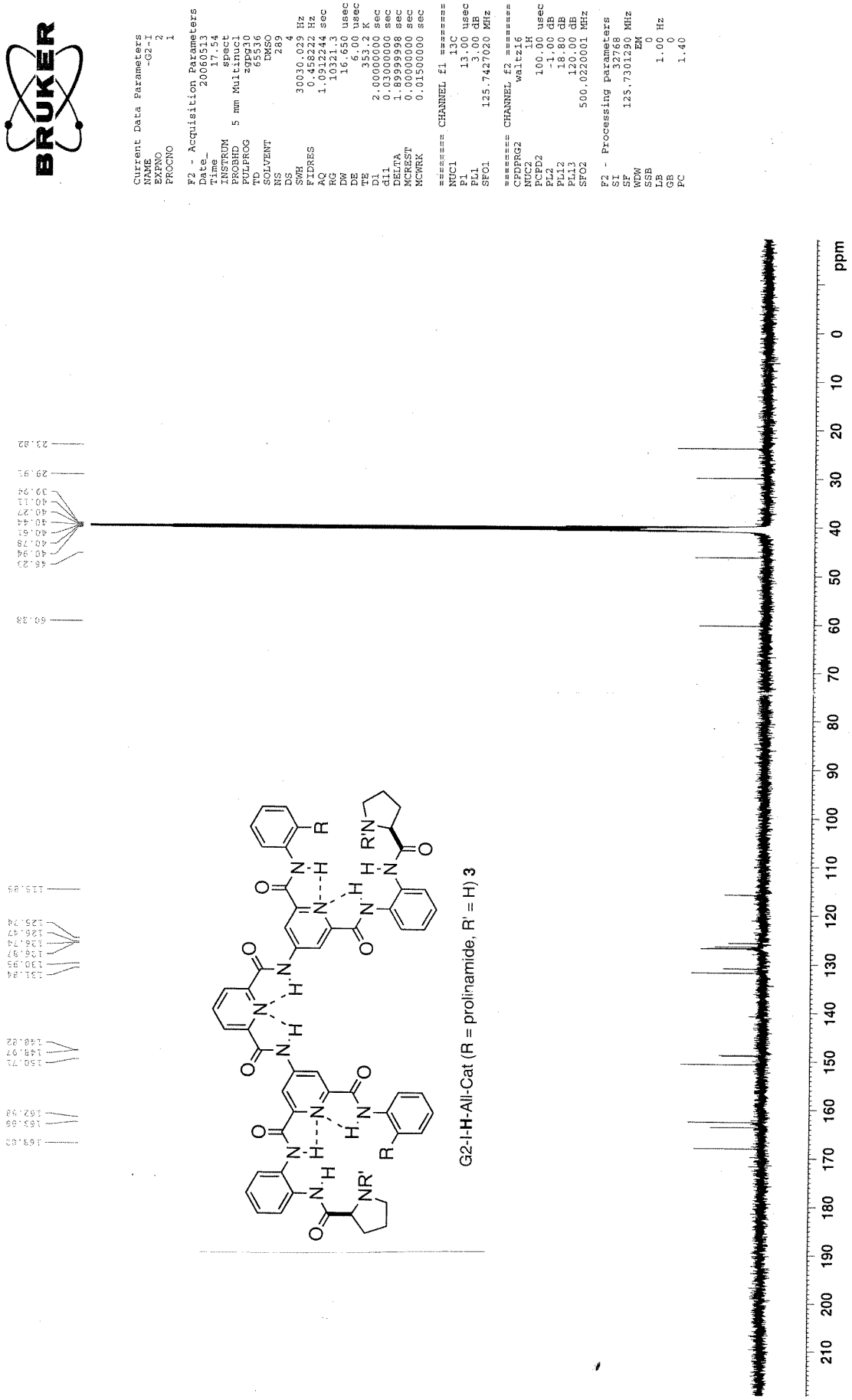
PC 1.00
G2-I-H-All-Cat (R = prolinamide, R' = H) 3
ppm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EXPNO 2
PROCNO 1
F2 - Acquisition Parameters
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Time_ 17.54
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PULPROG zgpg30
TD 65536
SOLVENT DMSO
NS 289
DS 4
SWH 30030.029 Hz
FIDRES 0.458222 Hz
AQ 1.0912244 sec
RG 10321.3
DW 16.650 usec
DE 6.00 usec
TE 353.2 K
D1 2.00000000 sec
d11 0.03000000 sec
DELTA 1.89999998 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec
======== CHANNEL f1 ========
NUC1 13C
P1 13.00 usec
PL1 3.00 dB
SFO1 125.7427020 MHz
======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 100.00 usec
PL2 -1.00 dB
PL12 18.80 dB
PL13 120.00 dB
SFO2 500.0220001 MHz
F2 - Processing parameters
SI 32768
SF 125.7301290 MHz
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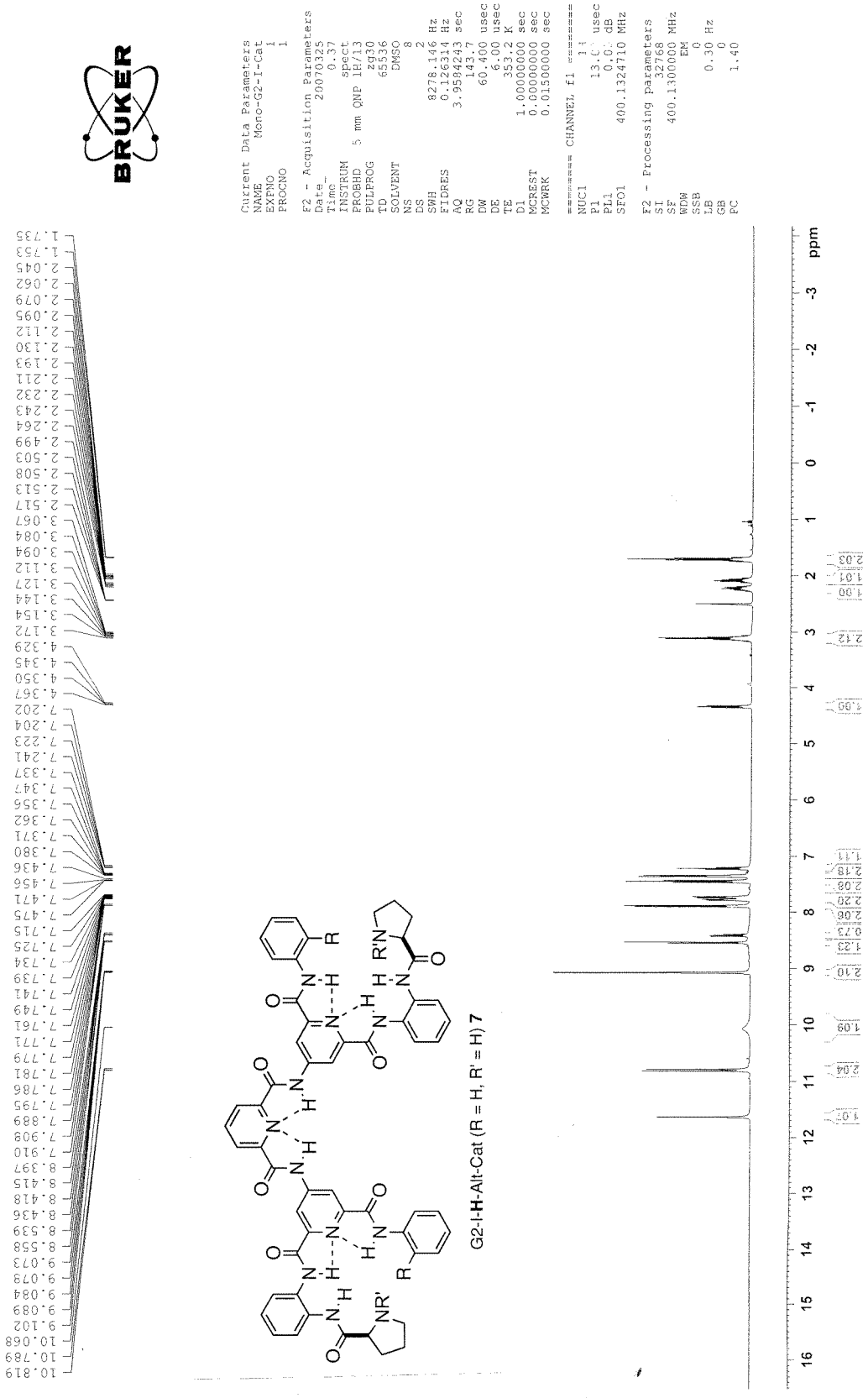
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
G2-I-H-All-Cat (R = prolinamide, R' = H) 3
ppm


BRUKER
Current Data Parameters
NAME Mono-G2-I-Cat
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20070325
Time_ 0.37
INSTRUM spect
PROBHD 5 mm QNP 1H/13
PULPROG zg30
TD 65536
SOLVENT DMSO
NS 8
DS 2
SWH 8278.146 Hz
FIDRES 0.126314 Hz
AQ 3.9584243 sec
RG 143.7
DW 60.400 usec
DE 6.00 usec
TE 353.2 K
D1 1.0000000 sec
MCREST 0.0000000 sec
MCWRK 0.01500000 sec
======== CHANNEL f1 ========
NUC1 1H
P1 13.0 usec
PL1 0.0 dB
SFO1 400.1324710 MHz
F2 - Processing parameters
SI 32768
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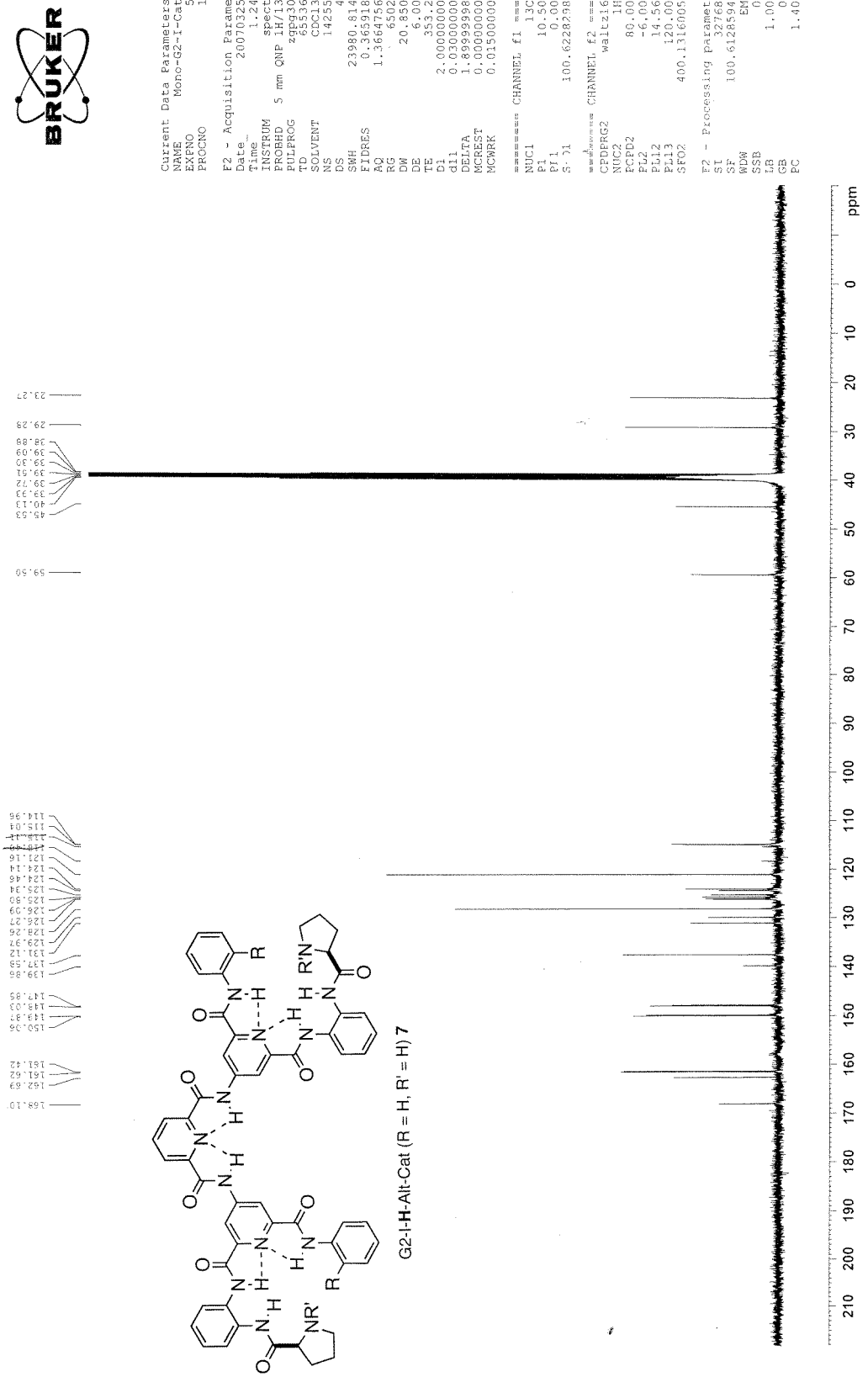
SSB 0
LB 0.30 Hz
GB 0
PC 1.40
G2-I-H-Alt-Cat (R = H, R' = H) 7
ppm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NAME Mono-G2-T-Cat
EXPNO 5
PROCNO 1
F2 - Acquisition Parameters
Date_ 20070325
Time 1.24
INSTRUM spect
PROBHD 5 mm QNP 1H/13
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 14255
DS 4
SWH 23980.814 Hz
FIDRES 0.365918 Hz
AQ 1.3664756 sec
RG 6502
DW 20.850 usec
DE 6.00 usec
TE 353.2 K
D1 2.00000000 sec
d11 0.03000000 sec
DELTA 1.89999998 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec
CHANNEL f1
NUC1 13C
P1 10.50 usec
PL1 0.00 dB
SF01 100.6228298 MHz
CHANNEL f2
CPDPRG2 waltz16
NUC2 1H
PCPD2 80.00 usec
PL2 -6.00 dB
PL12 14.56 dB
PL13 120.00 dB
SFO2 400.1316005 MHz
F2 - Processing parameters
SI 32768
SF 100.6128594 MHz
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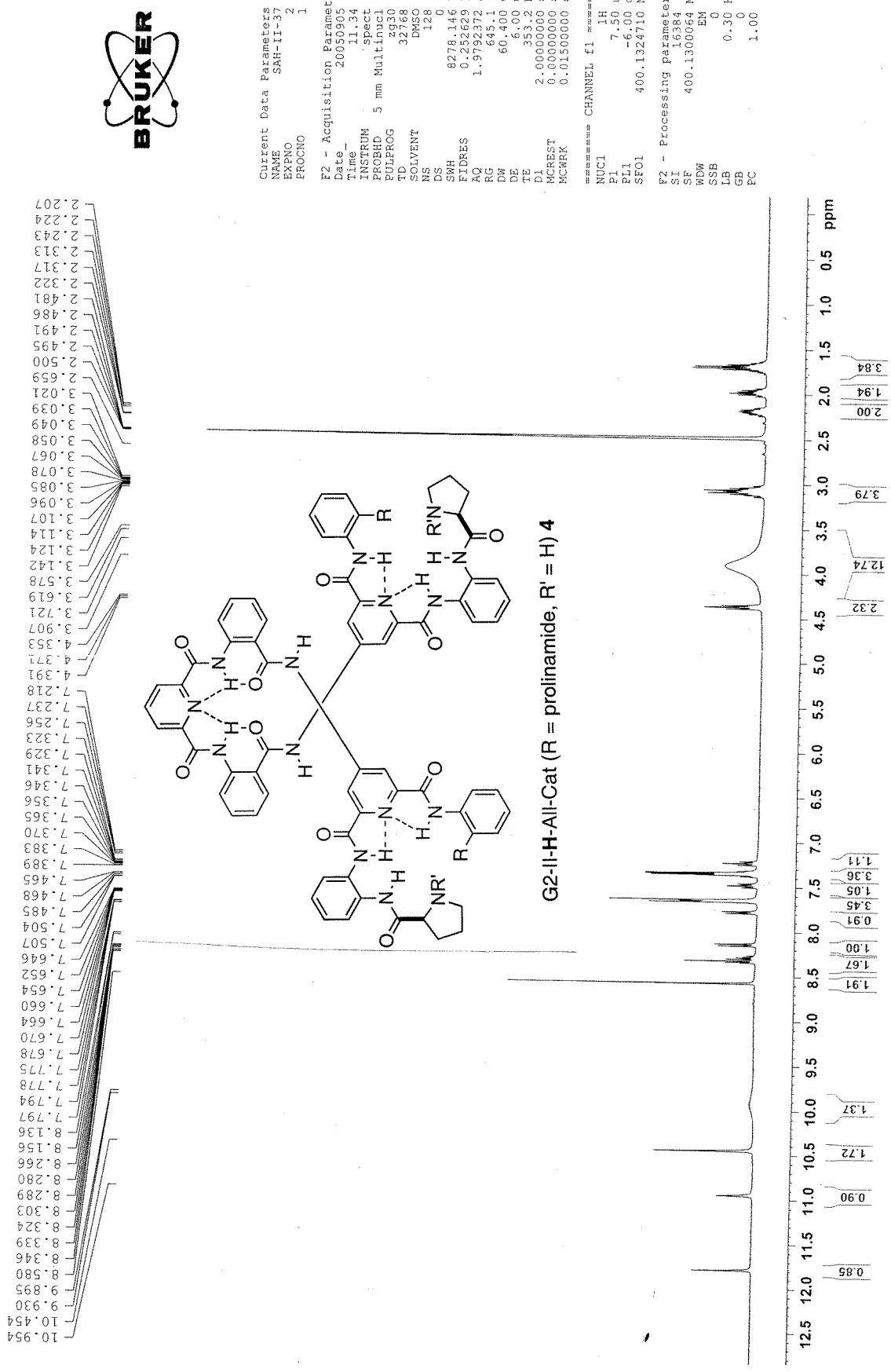
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
G2-I-H-Alt-Cat (R = H, R' = H) 7
ppm


BRUKER
Current Data Parameters
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EXPNO 2
PROCNO 1
F2 - Acquisition Parameters
Date_ 20050905
Time 11.34
INSTRUM spect
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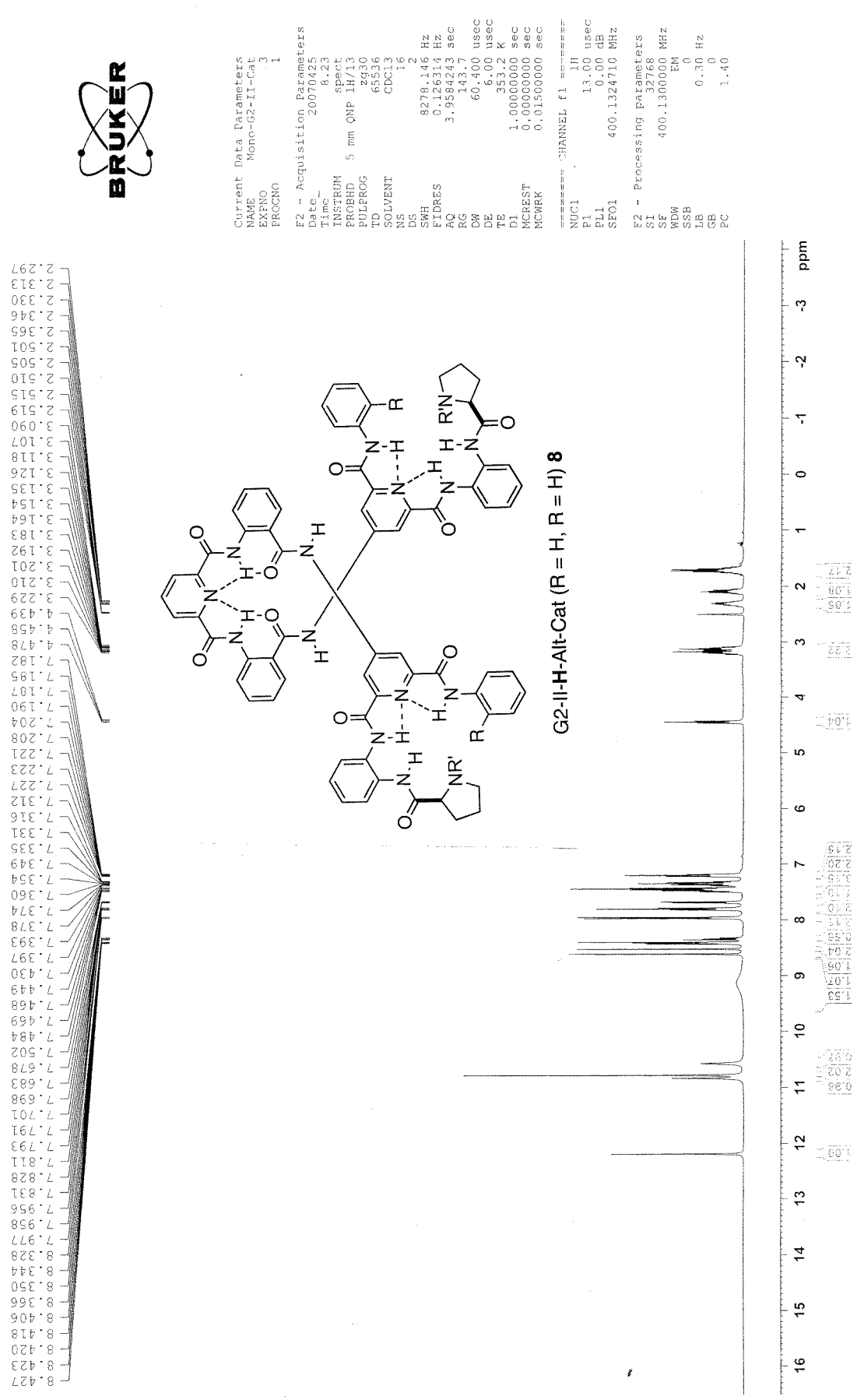
PULPROG zg30
TD 32768
SOLVENT DMSO
NS 128
DS 0
SWH 8278.146 Hz
FIDRES 0.252629 Hz
AQ 1.9792372 sec
RG 645.1
DW 60.400 usec
DE 6.00 usec
TE 353.2 K
D1 2.00000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec
======== CHANNEL f1 ========
NUC1 1H
P1 7.50 usec
PL1 -6.00 dB
SFO1 400.1324710 MHz
F2 - Processing parameters
SI 16384
SF 400.1300064 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
G2-II-H-All-Cat (R = prolinamide, R' = H) 4
ppm

G2-II-**H**-All-Cat (R = prolinamide, R' = H) **4**


BRUKER
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NAME Mono-G2-II-Cat
EXPNO 3
PROCNO 1
F2 - Acquisition Parameters
Date_ 20070425
Time 8.23
INSTRUM spect
PROBHD 5 mm QNP 1H/13
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 8278.146 Hz
FIDRES 0.126314 Hz
AQ 3.9584243 sec
RG 143.7
DW 60.400 usec
DE 6.00 usec
TE 353.2 K
D1 1.00000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec
NUC1 1H
P1 13.00 usec
PL1 0.00 dB
SFO1 400.1324710 MHz
F2 - Processing parameters
SI 32768
SF 400.1300000 MHz
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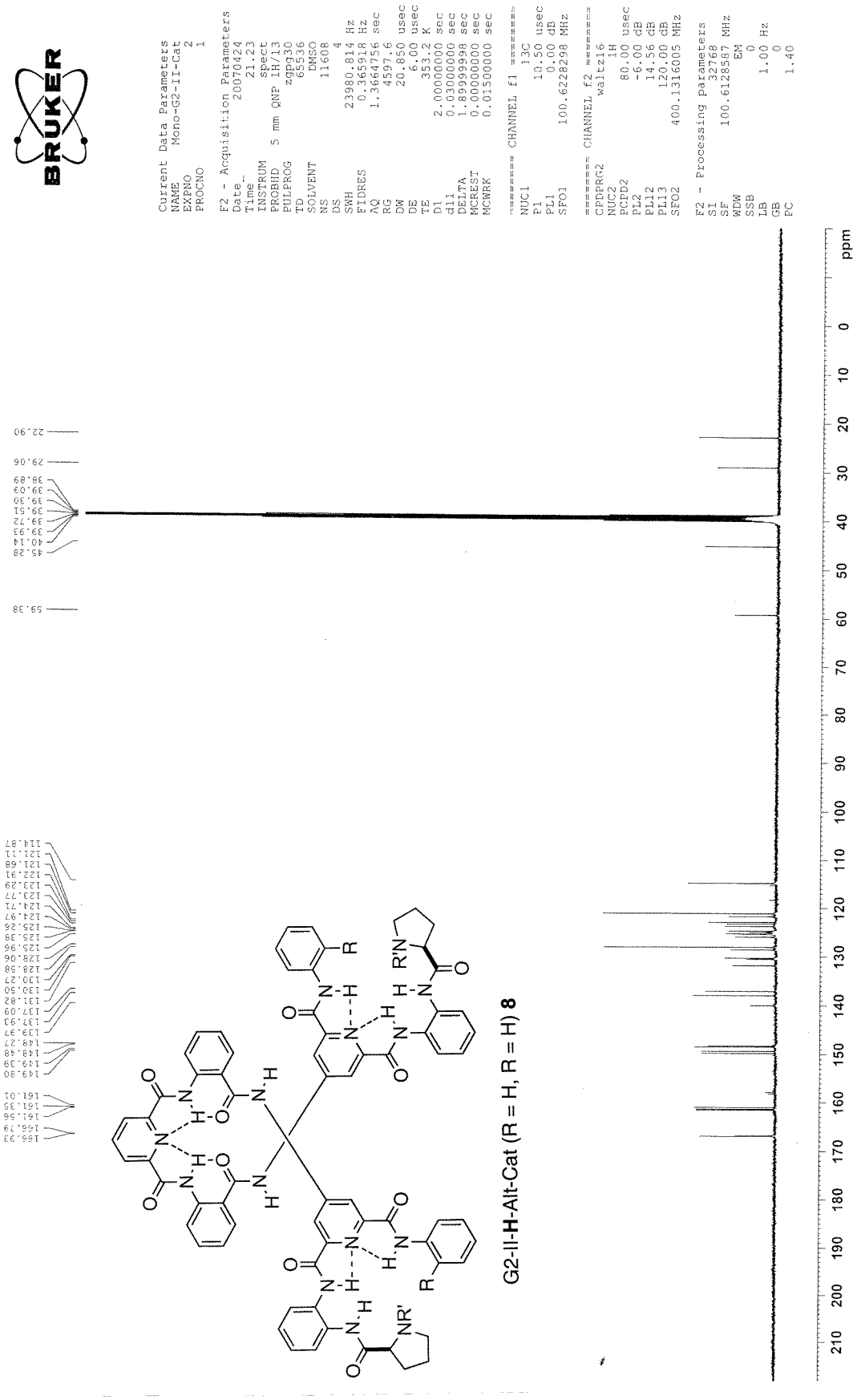
SSB 0
LB 0.30 Hz
GB 0
PC 1.40
G2-II-H-Alt-Cat (R = H, R = H) 8
ppm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EXPNO 2
PROCNO 1
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Date_ 20070424
Time_ 21.23
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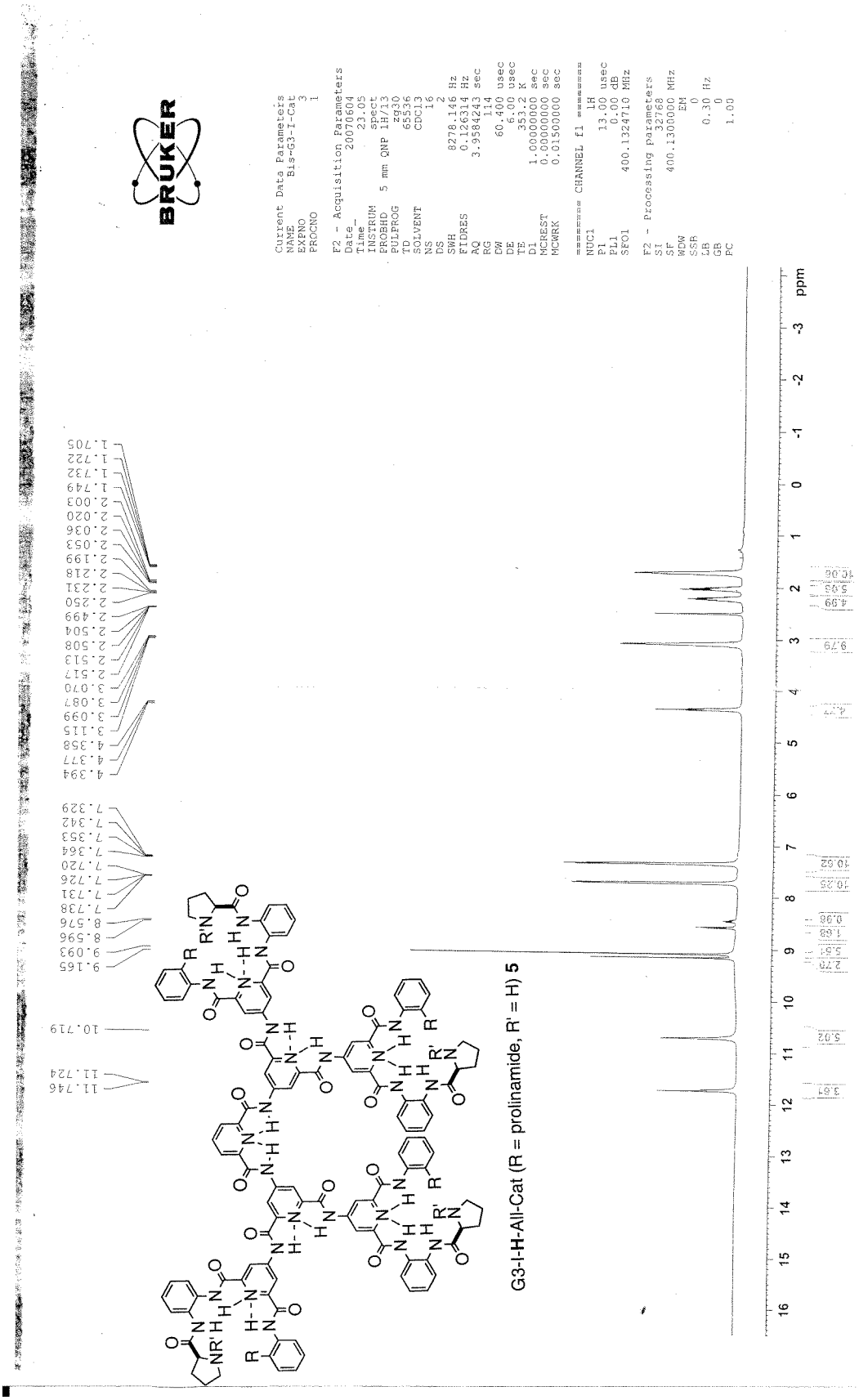
PULPROG zgpg30
TD 65536
SOLVENT DMSO
NS 11608
DS 4
SWH 23980.814 Hz
FIDRES 0.365918 Hz
AQ 1.3664756 sec
RG 4597.6
DW 20.850 usec
DE 6.00 usec
TE 353.2 K
D1 2.00000000 sec
d11 0.03000000 sec
DELTA 1.89999998 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec
======== CHANNEL f1 ========
NUC1 13C
P1 10.50 usec
PL1 0.00 dB
SFO1 100.6228298 MHz
======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 80.00 usec
PL2 -6.00 dB
PL12 14.56 dB
PL13 120.00 dB
SFO2 400.1316005 MHz
F2 - Processing parameters
SI 32768
SF 100.6128587 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
ppm
G2-II-H-Alt-Cat (R = H, R = H) 8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TD 65536
SOLVENT CDCl3
NS 16
DS 2
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FIDRES 0.126314 Hz
AQ 3.9584243 sec
RG 114
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DE 6.00 usec
TE 353.2 K
D1 1.00000000 sec
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MCWRK 0.01500000 sec
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PL1 0.00 dB
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F2 - Processing parameters
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SF 400.1300000 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
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1.722
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1.749
2.003
2.020
2.036
2.053
2.199
2.218
2.231
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2.508
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2.517
3.070
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3.115
4.358
4.377
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7.329
7.342
7.353
7.364
7.720
7.726
7.731
7.738
8.576
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G3-I-H-All-Cat (R = prolinamide, R' = H) 5
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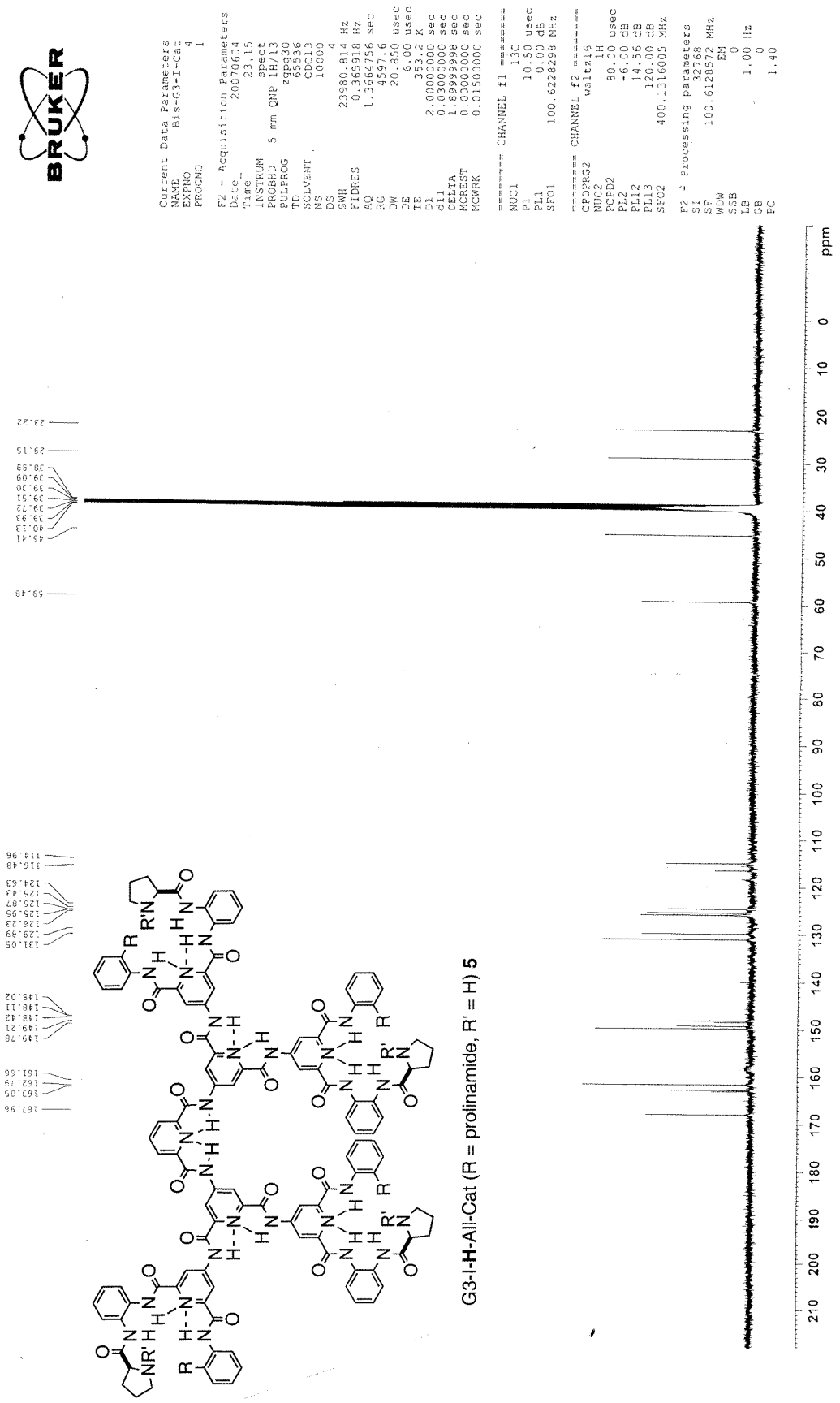
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SOLVENT CDCl3
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TE 353.2 K
D1 2.00000000 sec
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DELTA 1.89999998 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec
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NUC1 13C
P1 10.50 usec
PL1 0.00 dB
SFO1 100.6228298 MHz
======== CHANNEL f2 ========
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NUC2 1H
PCPD2 80.00 usec
PL2 -6.00 dB
PL12 14.56 dB
PL13 120.00 dB
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F2 - Processing parameters
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SF 100.6228572 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
23.22
29.15
38.89
39.09
39.30
39.51
39.72
39.93
40.13
45.41
59.48
116.48
119.96
124.63
125.43
125.87
125.95
126.23
129.89
131.05
148.02
148.11
148.42
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161.66
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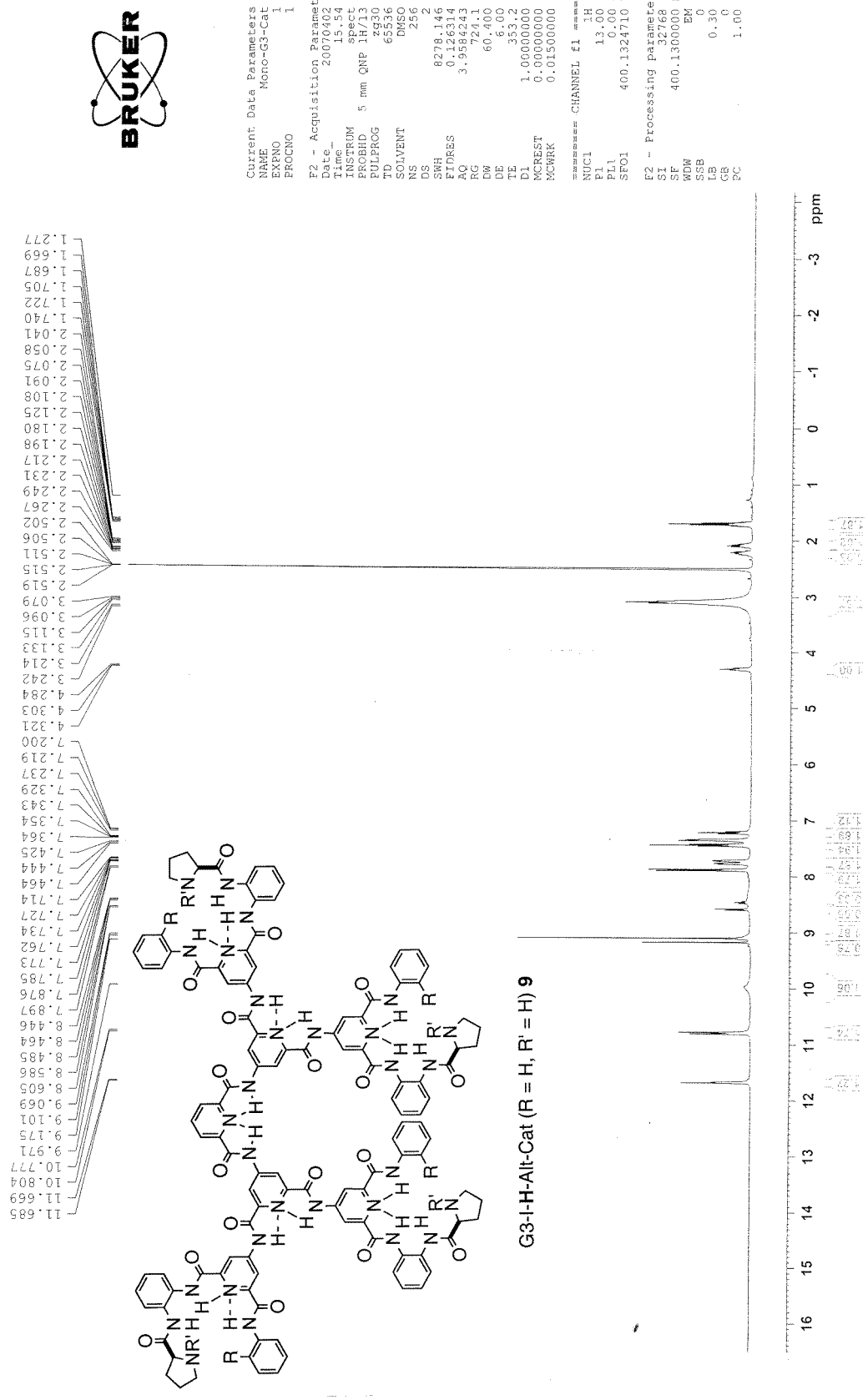
G3-I-H-All-Cat (R = prolinamide, R' = H) 5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SOLVENT DMSO
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FIDRES 0.126314 Hz
AQ 3.9584243 sec
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DW 60.400 usec
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TE 353.2 K
D1 1.00000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec
CHANNEL f1
NUC1 1H
P1 13.00 usec
PL1 0.00 dB
SFO1 400.1324710 MHz
F2 - Processing parameters
SI 32768
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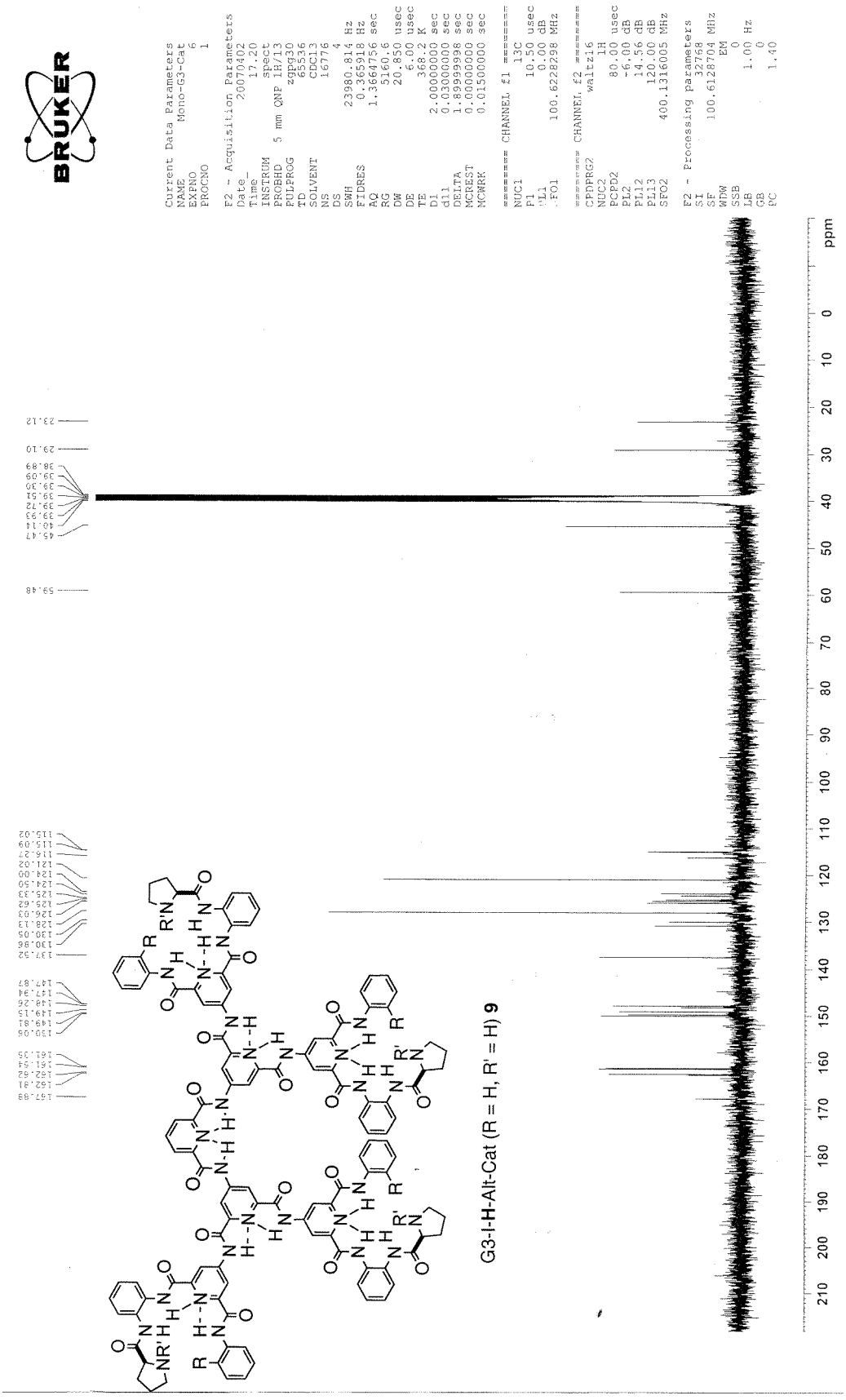
G3-I-H-Alt-Cat (R = H, R' = H) 9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PROCNO 1
F2 - Acquisition Parameters
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PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 16776
DS 4
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FIDRES 0.365918 Hz
AQ 1.3664756 sec
RG 5160.6
DW 20.850 usec
DE 6.00 usec
TE 368.2 K
D1 2.00000000 sec
d11 0.03000000 sec
DELTA 1.89999998 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec
======== CHANNEL f1 ========
NUC1 13C
P1 10.50 usec
PL1 0.00 dB
SFO1 100.6228298 MHz
======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 80.00 usec
PL2 -6.00 dB
PL12 14.56 dB
PL13 120.00 dB
SFO2 400.1316005 MHz
F2 - Processing parameters
SI 32768
SF 100.6128704 MHz
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SSB 0
LB 1.00 Hz
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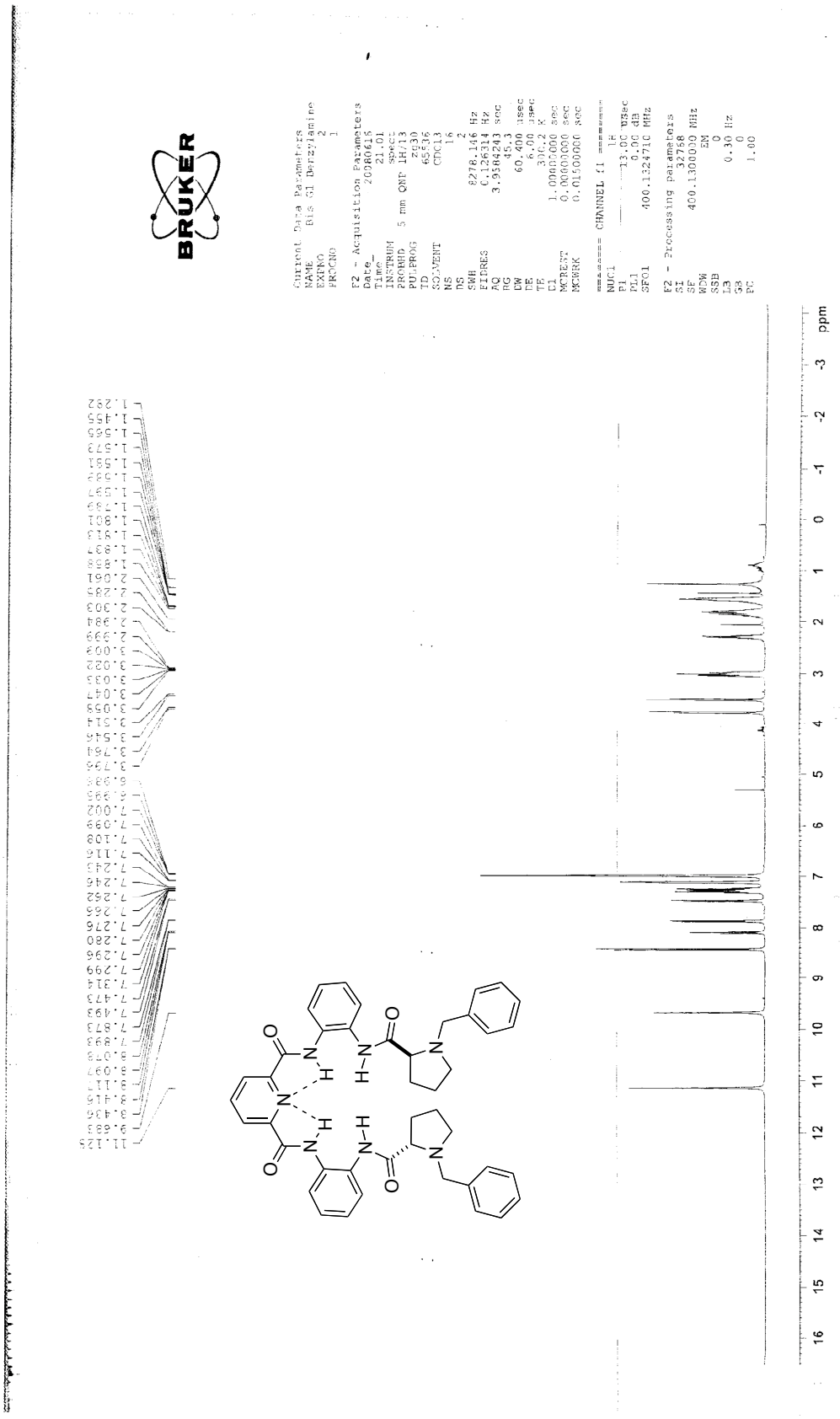
PC 1.40
G3-I-H-Alt-Cat (R = H, R' = H) 9
ppm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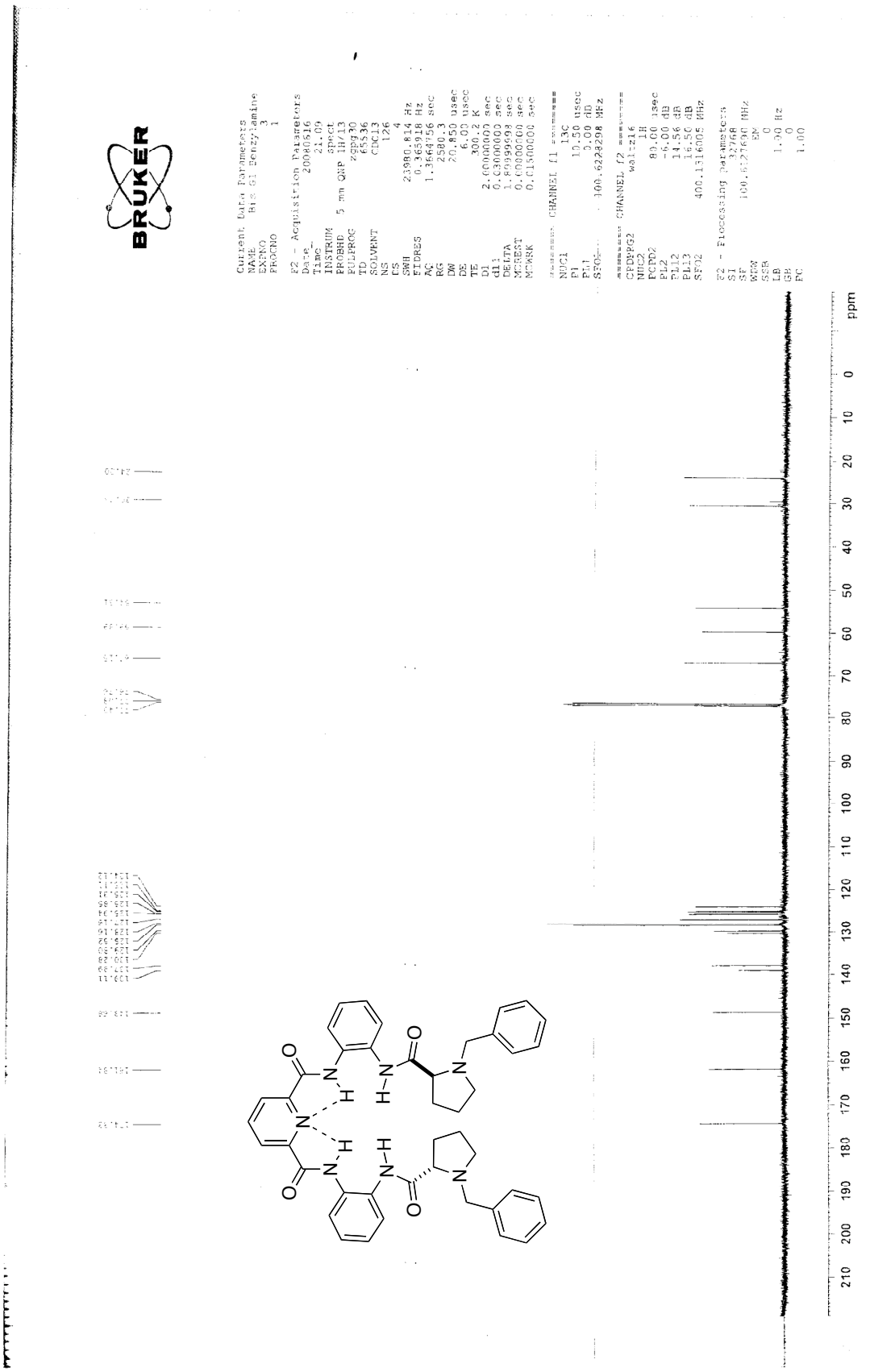

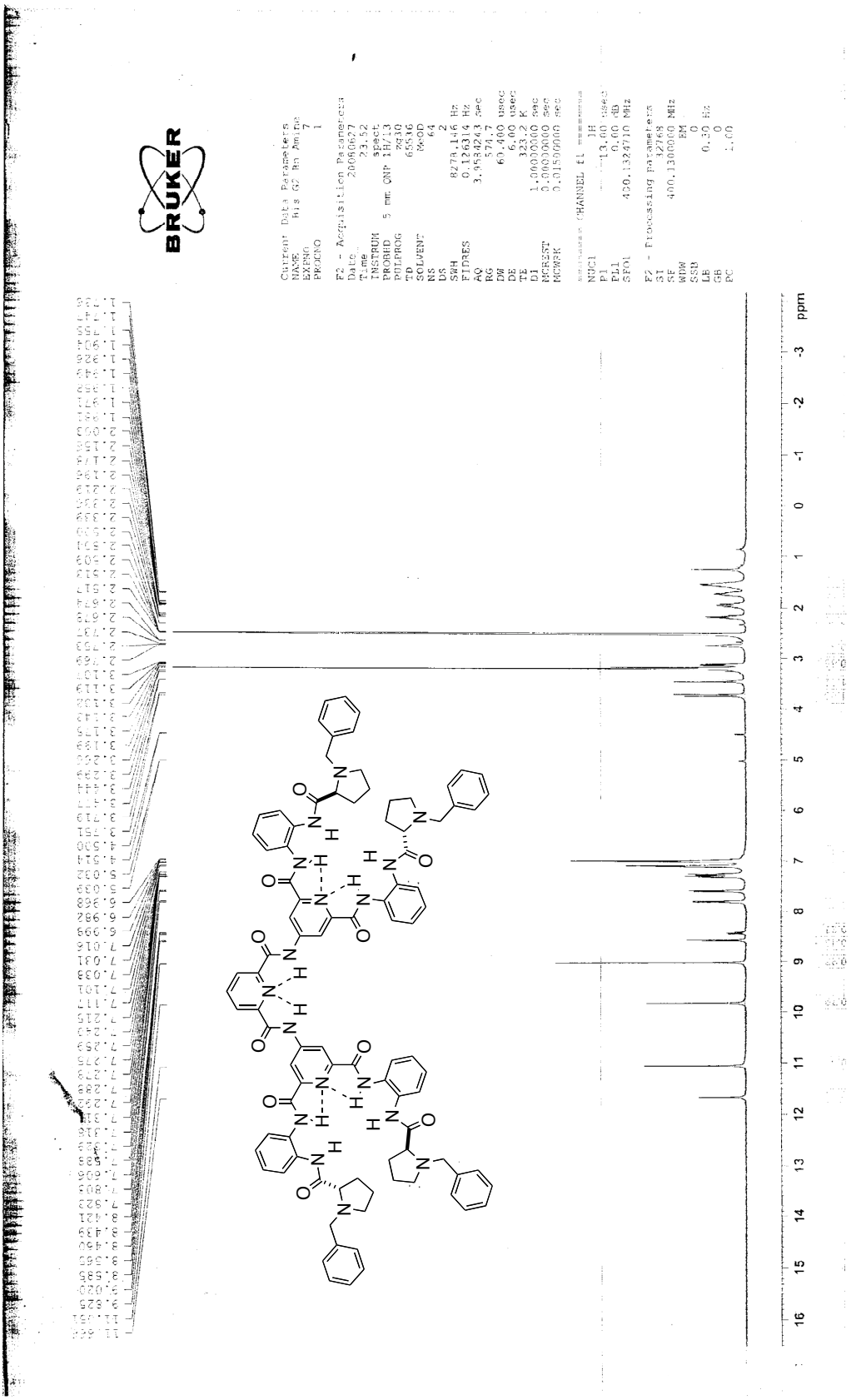
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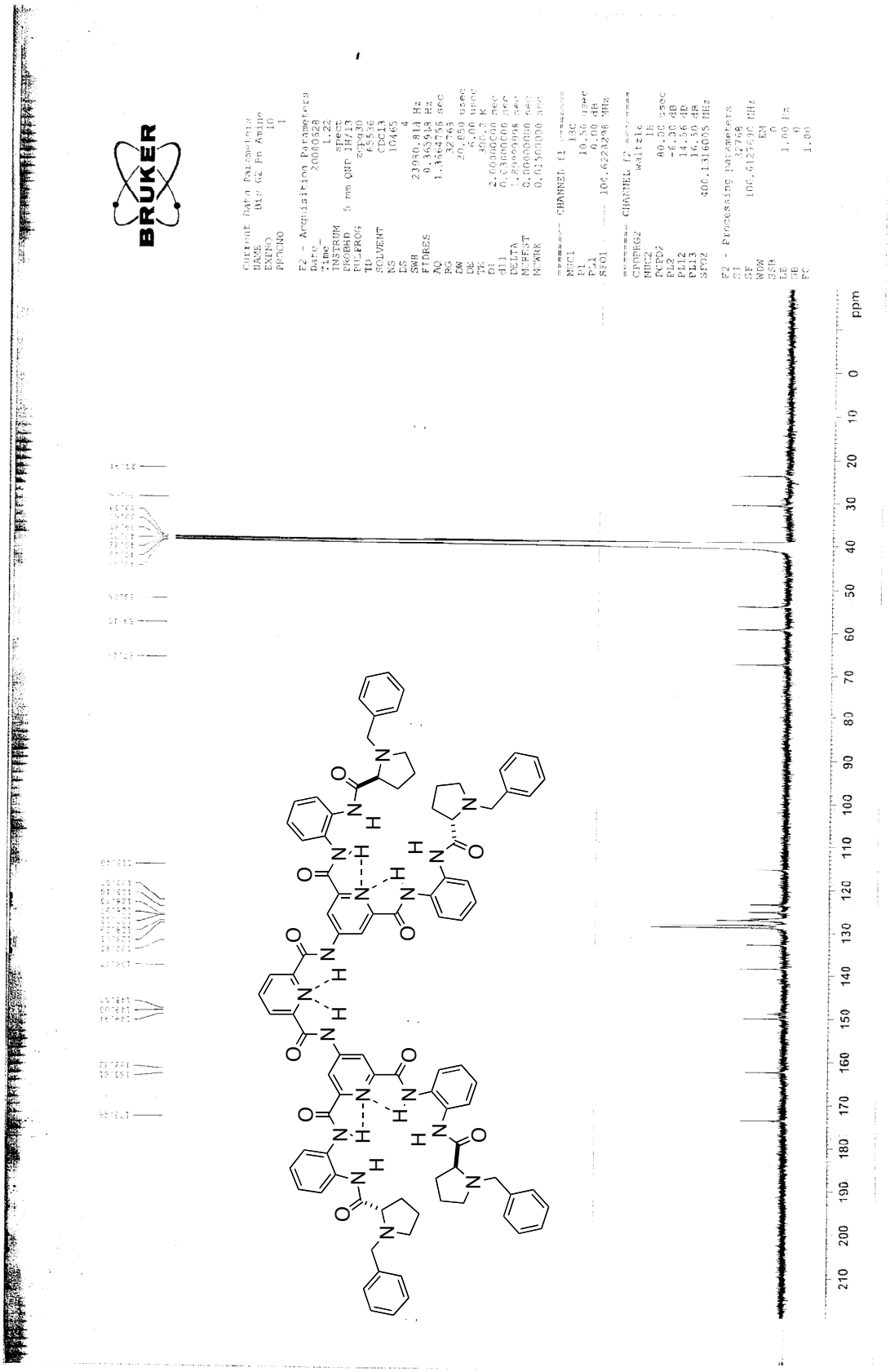
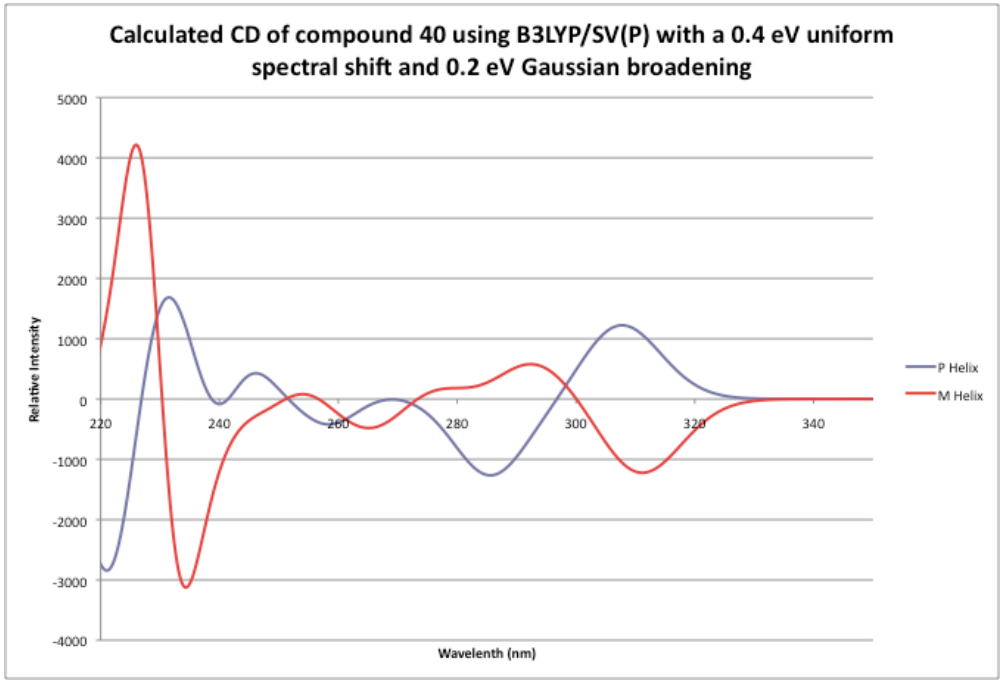

BRUKER
ppm

Computational Methods

The CD spectrum was calculated at the TD-B3LYP/SV(P) level of theory and using the X-ray crystallographic geometry. A 0.2 eV Gaussian line-broadening was applied to each excitation and the spectrum was blue-shifted by 0.4 eV. The spectrum was normalized to match the intensity of the 305 nm peak. This procedure is supported by previous work on theoretical CD predictions, which have demonstrated good agreement with experiment.[4]

The theoretical and experimental spectra are in good agreement, particularly between 280 and 350 nm. The predicted CD underestimates the quantity of negative polarization from 225-275 nm, but qualitatively matches the peak and valley of the experimental spectrum between 220-230 nm. To further validate the assignment of helicity in solution, stochastic sampling methods were used to obtain the *M* helical isomer that best matches the *P* helical crystal structure, while retaining the stereochemistry of the prolinamides. CD spectrum calculations on the *M* helical geometry exhibited a negative excitonic couplet centered at 300 nm, opposite of the experimental and calculated *P* helical sense, supporting the finding that the *P* helical sense is dominant in solution.



X-ray Crystallography Details

G1-all (SI-40)

Parquette 1673

The colorless crystal used for data collection was approximately a square plate.
Examination of the diffraction pattern on a Nonius Kappa CCD diffractometer indicated a monoclinic crystal system. All work was done at 150 K using an Oxford Cryosystems Cryostream Cooler. The data collection strategy was set up to measure a quadrant of reciprocal space with a redundancy factor of 3.9, which means that 90% of the reflections were measured at least 3.9 times. Phi and omega scans with a frame width of 1.0° were used. Data integration was done with Denzo(1), and scaling and merging of the data was done with Scalepack(1). Merging the data and averaging the symmetry equivalent reflections resulted in an Rint value of 0.039.

The structure was solved by the direct methods procedure in SHELXS-97(2). Full-matrix least-squares refinements based on F^2 were performed in SHELXL-97(3), as incorporated in the WinGX package(4). The correct enantiomer was chosen based on the known chiral carbon atoms.

The hydrogen atoms bonded to N(3) and N(6) were refined isotropically. For the hydrogen atoms bonded to N(2) and N(5), only their positional parameters were refined. The remaining hydrogen atoms were included in the model at calculated positions using a riding model with U(H) = 1.2 * Ueq(attached atom). The final refinement cycle was based on 6616 intensities and 501 variables, and resulted in agreement factors of R1(F) = 0.049 and wR2(F^2) = 0.078. For the subset of data with I > 2*sigma(I), the R1(F) value is 0.035 for 5611 reflections. The final difference electron density map contains maximum and minimum peak heights of 0.15 and -0.15 e/Å^3. Neutral atom scattering factors were used and include terms for anomalous dispersion(5).

All four of the N-H groups are involved in intramolecular hydrogen bonds.

References

(1) DENZO: Otwinowski, Z. & Minor, W., Methods in Enzymology, Vol 276: Macromolecular Crystallography, part A, 307-326, (1997), Carter, Jr., C. W. & Sweet, R. M., Eds., Academic Press.

(2) SHELXS-97: Sheldrick, G. M., Acta Cryst., (2008), A64, 112-122.

(3) SHELXL-97: Sheldrick, G. M., Acta Cryst., (2008), A64, 112-122.

(4) WinGX-Version 1.64.05: Farrugia, L. J., J. Appl. Cryst., (1999), 32, 837-838.

(5) International Tables for Crystallography (1992). Volume C.

Dordrecht: Kluwer Academic Publishers.

Crystallographic details for Parquette G1-all (SI-40)

Formula	C43 H43 N7 O4
Formula weight	721.84
Temperature	150(2) K
Wavelength	0.71073 Å
Crystal system	monoclinic
Space group	$P2_1$
Unit cell dimensions	a = 9.7376(1) Å
	b = 18.8927(2) Å
	c = 10.8852(1) Å
	β= 108.797(1)°
Volume	1895.74(3) $Å^3$
Z	2
Density (calculated)	1.265 Mg/m^3
Absorption coefficient	0.083 mm^{-1}
F(000)	764
Crystal size	0.08 x 0.19 x 0.21 mm^3
Theta range for data collection	2.16 to 24.99°
Index ranges	-11<=h<=11, -21<=k<=22, -12<=l<=12
Reflections collected	28888
Independent reflections	6616 [R(int) = 0.039]
Completeness to theta = 24.99°	99.9 %
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	6616 / 1 / 501
Goodness-of-fit on F^2	1.039
Final R indices [I>2sigma(I)]	R1 = 0.0352, wR2 = 0.0734
R indices (all data)	R1 = 0.0486, wR2 = 0.078
Largest diff. peak and hole	0.148 and -0.154 e/$Å^3$

G1-alt (6)

The crystal used for data collection was a colorless chunk. Examination of the diffraction pattern on a Nonius Kappa CCD diffractometer indicated a monoclinic crystal system. All work was done at 150 K using an Oxford Cryosystems Cryostream Cooler. The data collection strategy was set up to measure a quadrant of reciprocal space with a redundancy factor of 4.0, which means that 90% of the reflections were measured at least 4.0 times. Phi and omega scans with a frame width of 2.0˚ were used. Data integration was done with Denzo(1), and scaling and merging of the data was done with Scalepack(1). Merging the data and averaging the symmetry equivalent reflections resulted in an Rint value of 0.040.

The structure was solved by the direct methods procedure in SHELXS-97(2). Full-matrix least-squares refinements based on F^2 were performed in SHELXL-97(3), as incorporated in the WinGX package(4). The correct enantiomer was chosen based on the known chiral carbon atom.

The hydrogen atoms bonded to atoms N(2), N(3), N(4) and N(5) were refined isotropically.
The remaining hydrogen atoms were included in the model at calculated positions using a riding model with U(H) = 1.2 * Ueq(attached atom). The final refinement cycle was based on 4813 intensities and 305 variables, and resulted in agreement factors of R1(F) = 0.056 and wR2(F^2) = 0.081. For the subset of data with I > 2*sigma(I), the R1(F) value is 0.036 for 3866 reflections. The final difference electron density map contains maximum and minimum peak heights of 0.19 and -0.24 e/Å^3. Neutral atom scattering factors were used and include terms for anomalous dispersion(5).

All four of the N-H groups are involved in inter or intramolecular hydrogen bonds (see table).

References

(1) DENZO: Otwinowski, Z. & Minor, W., Methods in Enzymology, Vol 276: Macromolecular Crystallography, part A, 307-326, (1997), Carter, Jr., C. W. & Sweet, R. M., Eds., Academic Press.

(2) SHELXS-97: Sheldrick, G. M., Acta Cryst., (2008), A64, 112-122.

(3) SHELXL-97: Sheldrick, G. M., Acta Cryst., (2008), A64, 112-122.

(4) WinGX-Version 1.64.05: Farrugia, L. J., J. Appl. Cryst., (1999), 32, 837-838.

(5) International Tables for Crystallography (1992). Volume C. Dordrecht: Kluwer Academic Publishers.

Crystallographic details for Parquette G1-alt (6)

Formula	C24 H23 N5 O3
Formula weight	429.47
Temperature	150(2) K
Wavelength	0.71073 Å
Crystal system	monoclinic
Space group	$P2_1$
Unit cell dimensions	a = 9.1013(1) Å
	b = 12.5045(2) Å
	c = 9.5586(2) Å
	β= 98.496(1)°
Volume	1075.90(3) $Å^3$
Z	2
Density (calculated)	1.326 Mg/m^3
Absorption coefficient	0.090 mm^{-1}
F(000)	452
Crystal size	0.27 x 0.27 x 0.38 mm^3
Theta range for data collection	2.70 to 27.47°
Index ranges	-11<=h<=11, -16<=k<=15, -12<=l<=12
Reflections collected	23526
Independent reflections	4813 [R(int) = 0.040]
Completeness to theta = 27.47°	99.8 %
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4813 / 1 / 305
Goodness-of-fit on F^2	1.071
Final R indices [I>2sigma(I)]	R1 = 0.0365, wR2 = 0.0748
R indices (all data)	R1 = 0.0557, wR2 = 0.0807
Largest diff. peak and hole	0.189 and -0.236 e/$Å^3$

J. References

(1) Tang, Z.; Jiang, F.; Yu, L.-T.; Cui, X.; Gong, L.-Z.; Mi, A.-Q.; Jiang, Y.-Z.; Wu, Y.-D. *J. Am. Chem. Soc.* **2003**, *125*, 5262-5263.

(2) Tang, Z.; Jiang, F.; Cui, X; Gong, L.-Z.; Mi, A.-Q.; Jiang, Y.-Z.; Wu, Y.-D. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5755-5760.

(3) Tang, Z.; Yang, Z.-H.; Chen, X.-H.; Cun, L.-F.; Mi, A.-Q.; Jiang, Y.-Z.; Gong, L.-Z. *J. Am. Chem. Soc.* **2005**; *127*, 9285-9289.

(4) (a) Diedrich, C.; Grimme, S. *J. Phys. Chem. A* **2003**, *107*, 2524–2539. (b) Mori, T.; Inoue, Y.; Grimme, S. *J. Org. Chem.* **2006**, *71*, 9797–9806. (c) Crawford, T. D.; Tam, M. C.; Abrams, M. L. *J. Phys. Chem. A* **2007**, *111*, 12057–12068. (d) Stephens, P. J.; Devlin, F. J.; Gasparrini, F.; Ciogli, A.; Spinelli, D.; Cosimelli, B. *J. Org. Chem.* **2007**, *72*, 4707–4715. (e) King, E. D.; Tao, P.; Sanan, T. T.; Hadad, C. M.; Parquette, J. R. *Org. Lett.* **2008**, *10*, 1671-1674.