Highly efficient synthesis of DNA-binding polyamides using a convergent fragment-based approach

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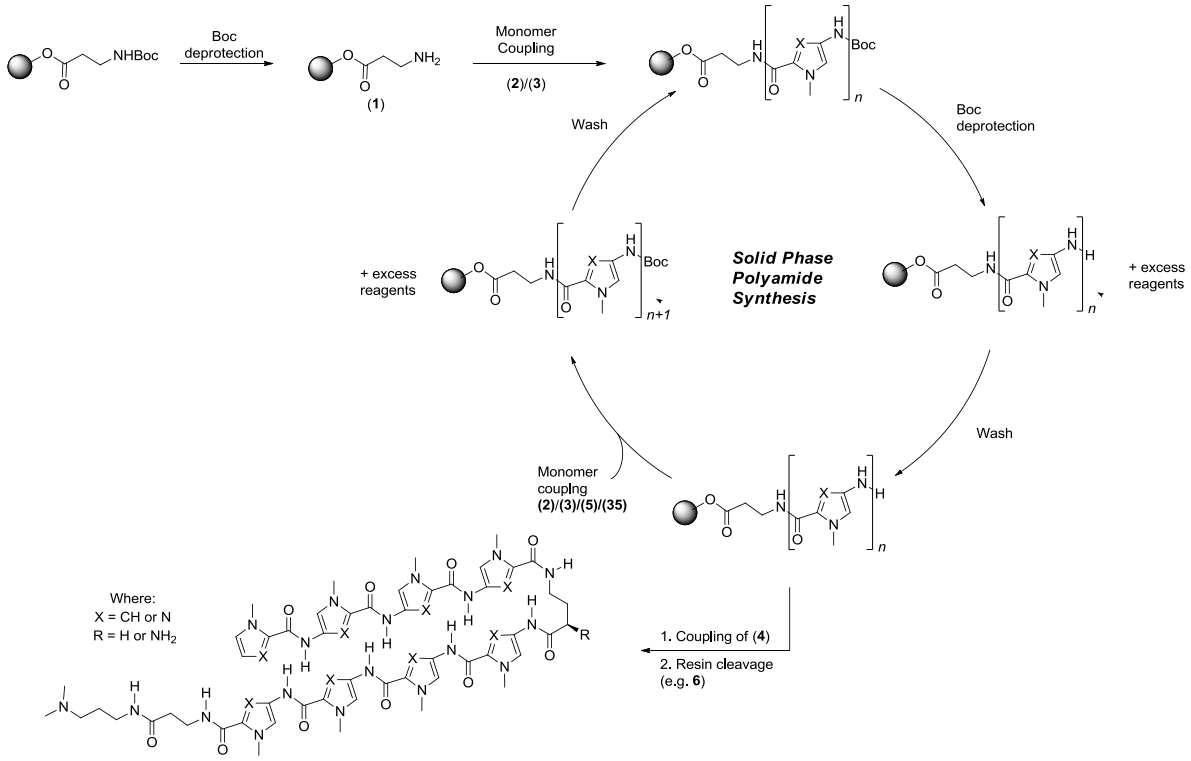
Contents

1.0 Abbreviations

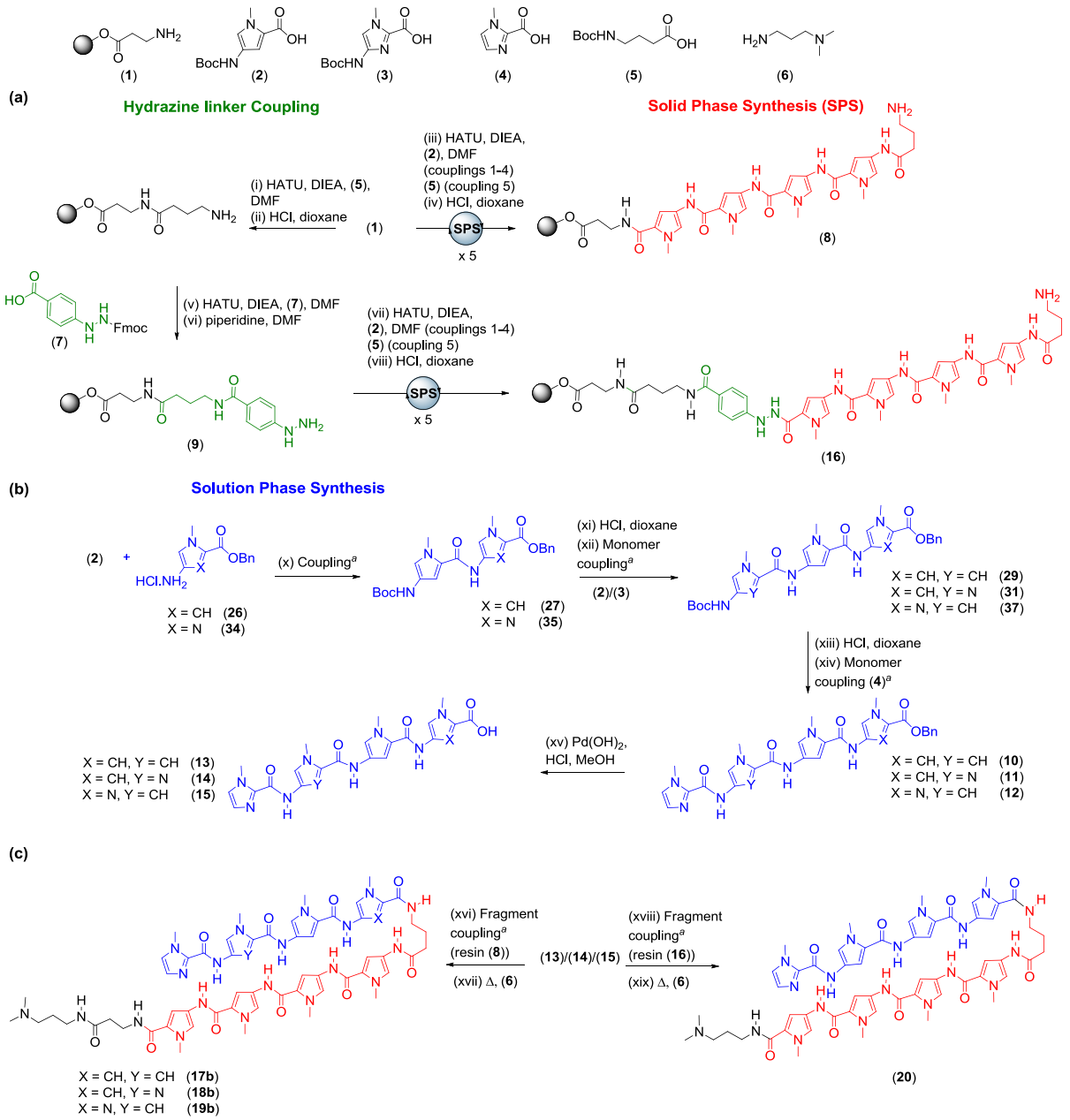
BTC, bis(trichloromethyl)carbonate; DCC, N,N'-dicyclohexylcarbodiimide; DCM, dichloromethane; DCU, dicyclohexylurea; DIEA, N-diisopropylethylamine; DMF, N,N’-dimethylformamide; Fmoc-D-Dab(Boc)-OH, N-α-(9-fluorenylmethyloxycarbonyl)-N-γ-t-butyloxycarbonyl-D-2,4-diaminobutyric acid; GABA, γ-aminobutyric acid; HATU, 2-(1H-7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyl uronium hexafluorophosphate; HBA, 4-(2-Fmoc-hydrazino)benzoic acid; HOAt, Hydroxy-7-azabenzotriazole; TFA, trifluoroacetic acid; THF, tetrahydrofuran; TPW, TFA:phenol:water (92.5 mL: 5 g: 2.5 mL).

2.0 **Traditional Solid Phase Synthesis of Polyamides**



Scheme S1 (Schematic representation of solid phase polyamide synthesis using existing Boc-based methodology. Stepwise Boc-deprotection of resin-bound amine and coupling of the next monomer requires a total of 18 steps to form a standard 8 ring hairpin polyamide.)

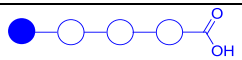
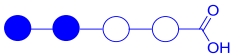
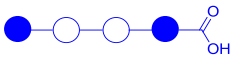
3.0 Convergent Synthesis Approach of this Study



Scheme S2: Schematic representation of our new convergent synthetic approach. (**a**) Solid phase synthesis of C-terminal tetramers (8 and 16, shown in red). (**b**) Solution phase synthesis of N-terminal tetramers (13-15, shown in blue). (**c**) Ligation of the two respective "halves" (13-15) and (8 and 16) and cleavage from the resin afforded full length PAs.

4.0 Solution Phase Tetramer Synthesis

Table 1: Isolated yields of pyrrole/imidazole acid tetramers **13-15** prepared by solution-phase synthesis.

Entry	Compound Number	Tetramer	Yield (%)[a]	Purity (%)[b]
1	**13**		73	89
2	**14**		80	95
3	**15**		59	93

[a]Isolated yield after 7 steps.[b] Purity determined by analytical RP-HPLC at 310 nm. Imidazole units are denoted as solid circles, and pyrrole units as open circles.

5.0 Experimental Section

5.1 General

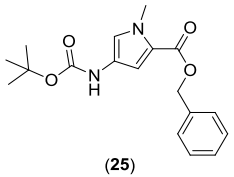
All reagents were either HPLC or peptide synthesis grade and used as supplied. DIEA, HATU and TFA were purchased from Alfa Aesar. BTC, DCC, DCM, DMF, HBA and THF were purchased from Sigma Aldrich. GABA was obtained from NovaBioChem. Fmoc-D-Dab(Boc)-OH was purchased from Fluorochem. Boc-β-Ala PAM resin (0.26 mmol/G loading) was purchased from Peptides International. 1-Methyl-1H-imidazole-2-carboxylic acid was purchased from Maybridge Chemicals.

Boc-Py-OH and Boc-Im-OH were prepared according to the literature.[1]

Analytical and semi-preparative RP-HPLC were performed at room temperature on an ULTIMAT 3000 Instrument (DIONEX). UV absorbance was measured using a photodiode array detector at 310nm. A Phenomenex Gemini-NX 5µm C18 110Å packed column with dimensions 150 x 4.60 mm was used for analytical HPLC. For semi-preparative HPLC, a Phenomenex Gemini- NX 5u C18 110A AXIA Packed column with dimensions 250 x 21.20 mm was used. LC-MS was performed using a Xevo QTof mass spectrometer (Waters) coupled to an Acquity LC system (Waters) using an Acquity UPLC BEH C18 column (2.1 x 50 mm, Waters).

5.2 Solution phase synthesis of polyamide tetramers

Benzyl 4-((tert-butoxycarbonyl)amino)-1-methyl-1H-pyrrole-2-carboxylate (25)



(**25**)

To a solution of 4-((tert-butoxycarbonyl)amino)-1-methyl-1H-pyrrole-2-carboxylic acid (1.00 g; 4.16 mmol) in ethanol/water (3:1 v/v, 20 mL) was added a solution of caesium carbonate (0.678 g; 2.08 mmol) in water (5 mL). The reaction mixture was stirred at room temperature for 2 hours. The solution was then filtered and the solvent removed under vacuum, then distilled azeotropically to dryness with ethanol to give the caesium salt of (**2**) as an off-white/pale yellow solid. This was then dissolved in dry DMF (10 mL) and benzyl bromide (0.718 g; 4.2 mmol) was added dropwise at room temperature with constant stirring. The reaction was then heated to 40°C and stirred overnight. The reaction was quenched by the addition of ice water

(45 mL). The crude product was isolated by centrifugation and decanting of the supernatant. Any remaining water was removed azeotropically with ethanol to yield (**25**) as an off-white solid (0.736 g; 54 %) which required no further purification.

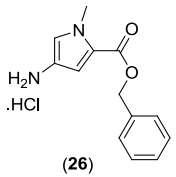
^{1}H NMR (300 MHz; $CDCl_3$) δ 1.49 (s, 9 H), 3.86 (s, 3 H), 5.25 (s, 2 H), 6.38 (s, 1 H), 6.70 (d, *J* = 2.1 Hz, 1 H), 7.08 (s, 1 H), 7.28-7.42 (m, 5 H).

^{13}C NMR (75 MHz; $CDCl_3$) δ 28.4 (3C), 36.7, 65.5, 80.2, 108.3, 119.8, 120.1, 122.2, 128.0 (3C), 128.5 (2C), 136.4, 153.3, 160.8.

HRMS (ESI +ve mode) 331.1658 calculated for $C_{18}H_{23}N_2O_4^+$ $[M+H]^+$ found 331.1660.

Data in agreement to literature.[21]

Benzyl 4-amino-1-methyl-1H-pyrrole-2-carboxylate hydrochloride (26):



(**26**)

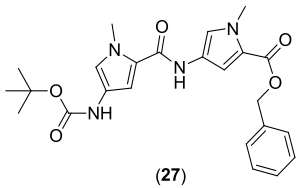
To a solid sample of (**25**) (0.200 g; 0.6 mmol) was added 4 M HCl in dioxane (2 mL; 8 mmol). The mixture was stirred at room temperature for 2 hours and reaction was confirmed complete by analytical RPHPLC. The product was precipitated with hexane then isolated by centrifugation and removal of the supernatant. The crude material was washed twice more with hexane, then suspended in water (5 mL) and lyophilised to dryness, giving the product as an off-white solid (0.160 g; quantitative), which was of sufficient purity to carry forward.

^{1}H NMR (300 MHz; d_4-methanol) δ 3.94 (s, 3 H), 5.28 (s, 2 H), 6.94 (d, J = 2.1 Hz, 1 H), 7.18 (d, J = 2.0 Hz, 1 H), 7.28-7.45 (m, 5 H).

^{13}C NMR (75 MHz; d_4-methanol) δ 37.5, 67.1, 112.5, 114.5, 123.6, 124.7, 129.3 (3C), 129.6 (2C), 137.6, 161.5.

HRMS (ESI +ve mode) 231.1134 calculated for $[M+H]^+$, found 231.1125.

Benzyl 4-(4-((tert-butoxycarbonyl)amino)-1-methyl-1H-pyrrole-2-carboxamido)-1-methyl-1H-pyrrole-2-carboxylate (27):



(**27**)

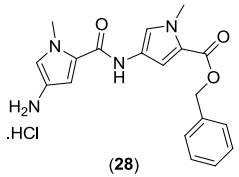
To a solution of Boc-Py-OH (**2**) (0.087 g; 0.365 mmol) and HATU (0.139 g; 0.365mmol) in DMF (5 mL; peptide grade) was added DIEA (500 µL; 3 mmol). The mixture was stirred at room temperature for 30 minutes. This was then added to a separate solution of (**26**) (0.100 g; 0.375 mmol) and DIEA (500 µL; 3 mmol) in DMF (5 mL; peptide grade). The mixture was stirred for 2 hours at room temperature and the reaction was shown to be complete by analytical RPHPLC. The product was precipitated by the addition of acidified water (pH 3; 40 mL) and isolated by centrifugation and removal of the supernatant. The resulting solid was washed twice more with acidified water, then suspended in water (8 mL) and lyophilised to dryness. The product was collected as an off-white solid (0.162 mg; 98 %) and was of sufficient purity to continue.

^{1}H NMR (300 MHz; d_6-DMSO) δ 1.44 (s, 9 H), 3.79 (s, 3 H), 3.83 (s, 3 H), 5.23 (s, 2 H), 6.82 (s, 1 H), 6.88 (s, 1 H), 6.95 (s, 1 H), 7.28-7.44 (m, 5 H), 7.46 (s, 1 H), 9.09 (s, 1 H), 9.82 (s, 1 H).

^{13}C NMR (75 MHz; d_6-DMSO) δ 28.2 (3C), 36.1, 36.2, 64.8, 78.3, 103.8, 108.6, 117.2, 118.4, 121.0, 122.4, 122.5, 123.1, 127.8 (2C), 128.0 (2C), 128.5, 136.6, 152.8, 158.4, 160.1.

HRMS (ESI +ve mode) 453.2138 calculated for $C_{24}H_{29}N_4O_5^+$ $[M+H]^+$, found 453.2120.

Benzyl 4-(4-amino-1-methyl-1H-pyrrole-2-carboxamido)-1-methyl-1H-pyrrole-2-carboxylate hydrochloride (28):



(**28**)

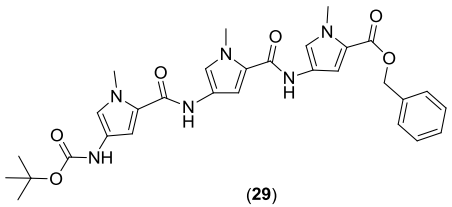
To a solid sample of (**27**) (0.150 g; 0.33 mmol) was added 4 M HCl in dioxane (4 mL; 16 mmol). The mixture was stirred for 2 hours at room temperature. Reaction completion was confirmed by analytical RPHPLC. The product was precipitated by addition of hexane (40 mL) and isolated by centrifugation and removal of the supernatant. The product was washed twice more with hexane, then suspended in water (5 mL) and lyophilised to dryness, yielding (**28**) as red solid (0.127 g; 99 %).

^{1}H NMR (500 MHz; d_6-DMSO) δ 3.86 (s, 3 H), 3.89 (s, 3 H), 5.25 (s, 2 H), 6.99 (d, J = 1.9 Hz, 1 H), 7.03 (d, J = 1.9 Hz, 1 H), 7.12 (d, J = 1.8 Hz, 1 H), 7.33-7.45 (m, 5 H), 7.50 (d, J = 1.9 Hz, 1 H), 10.14 (s, 1 H), 10.19 (s, 2 H).

^{13}C NMR (75 MHz; d_6-DMSO) δ 36.2, 36.5, 64.9, 107.2, 108.6, 113.0, 118.5, 121.0, 121.7, 122.6, 124.5, 127.8 (2C), 127.9, 128.5 (2C), 136.5, 157.6, 160.0.

HRMS (ESI +ve mode) 353.1614 calculated for $C_{19}H_{21}N_4O_3^+$ [M+H]+ found 353.1609.

Benzyl 4-(4-(4-((tert-butoxycarbonyl)amino)-1-methyl-1H-pyrrole-2-carboxamido)-1-methyl-1H-pyrrole-2-carboxamido)-1-methyl-1H-pyrrole-2-carboxylate (29):



(**29**)

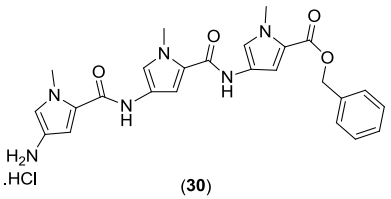
To a solution of Boc-Py-OH (**2**) (0.048 g; 0.2 mmol) and HATU (0.076 g; 0.2 mmol) in DMF (peptide grade; 4 mL) was added DIEA (200 µL; 1.2 mmol). The mixture was stirred at room temperature for 30 minutes. A separate solution of (**28**) (0.080 g; 0.21mmol) with DIEA (100 µL; 0.57 mmol) in DMF (peptide grade; 3 mL) was then added and the reaction stirred at room temperature overnight. Reaction was confirmed complete by analytical RPHPLC as indicated by the disappearance of starting material. The product was precipitated by addition of acidified water (pH 3; 40 mL) and isolated by centrifugation and removal of the supernatant. The crude material was washed three times by suspension in 0.25 M HCl followed by centrifugation to remove the supernatant. The residual solid was suspended in water and lyophilised to dryness, giving the product as a pale brown solid (0.104 g; 90 %), which was used without further purification.

^{1}H NMR (400 MHz; d_6-DMSO) δ 1.44 (s, 9H, *t*-Bu), 3.80 (s, 3H, NCH_3), 3.83 (s, 3H, NCH_3), 3.84 (s, 3H, NCH_3), 5.24 (s, 2H, CH_2Ph), 6.82 (s, 1H), 6.88 (s, 1H), 6.96 (d, J = 2 Hz, 1 H), 7.06 (d, J = 1.6 Hz, 1H), 7.20 (d, J = 1.6 Hz, 1H), 7.30-7.45 (m, 5H, benzyl protons), 7.47 (d, J = 1.6 Hz, 1 H), 9.06 (s, 1H), 9.84 (s, 1H), 9.88 (s, 1H).

^{13}C NMR (100 MHz; d_6-DMSO) δ 28.2 (3C), 36.0 (2C), 36.1, 64.8, 78.4, 103.8, 104.8, 108.6, 117.0, 118.4, 118.5, 120.9, 122.3 (2C), 122.4, 122.8, 123.1, 127.8 (2C), 127.9, 128.4 (2C), 136.6, 152.9, 158.4, 158.5, 160.1.

HRMS (ESI +ve mode) 575.2618 calculated for $C_{30}H_{35}N_6O_6^+$ $[M+H]^+$, found 575.2623.

Benzyl 4-(4-(4-amino-1-methyl-1H-pyrrole-2-carboxamido)-1-methyl-1H-pyrrole-2-carboxamido)-1-methyl-1H-pyrrole-2-carboxylate hydrochloride (30):



(**30**)

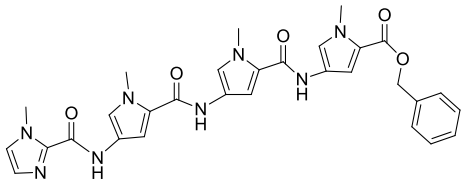
To a solid sample of (**29**) (0.2 g; 0.35 mmol) was added 4M HCl in 1,4-dioxane (10 ml; 40 mmol). The mixture was stirred at room temperature for 3 hours. Complete reaction was confirmed by TLC as indicated by the absence of starting material. The product was precipitated by addition of ether (30 mL) and isolated by centrifugation and removal of the supernatant. The crude mixture was washed twice more by sonication in ether, then centrifugation and removal of the supernatant. The resulting solid was suspended in water (15 mL) and lyophilised to dryness, giving the pure product as a red solid (0.179 g; quantitative).

^{1}H NMR (300 MHz; d_6-DMSO) δ 3.83 (s, 6H, 2 x NMe), 3.88 (s, 3H, NMe), 5.23 (s, 2H, CH_2Ph), 6.96 (s, 1H), 7.07(s, 1H), 7.10 (s, 1H), 7.24 (s, 1H), 7.31-7.45 (m, 5H, benzyl protons), 7.47 (s, 1H), 9.94 (s, 1H), 10.11 (s, *br*, 4H).

^{13}C NMR (100 MHz; d_6-DMSO) δ 36.1, 36.2, 36.6, 64.8, 104.8, 107.2, 108.6, 113.0, 118.4, 118.7, 121.0, 121.6, 121.8, 122.5, 123.0, 124.8, 127.8 (2C), 127.9, 128.5 (2C), 136.5, 157.7, 158.4, 160.1.

HRMS (ESI +ve mode) 475.2094 calculated for $C_{25}H_{27}N_6O_4^+$ $[M+H]^+$, found 475.2098.

Benzyl 1-methyl-4-(1-methyl-4-(1-methyl-4-(1-methyl-1H-imidazole-2-carboxamido)-1H-pyrrole-2-carboxamido)-1H-pyrrole-2-carboxamido)-1H-pyrrole-2-carboxylate (10):



(**10**)

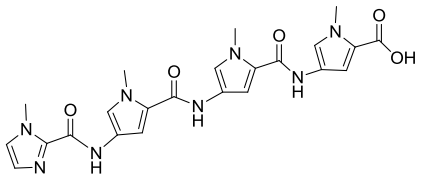
To a solution of (**4**) (0.095 g; 0.75 mmol) with HOAt (0.102 g; 0.75 mmol) in DMF (10 mL) was added DCC (0.146 g; 0.71 mmol) and the mixture was stirred at room temperature for 2 hours. The solid DCU was then removed by filtration and the filtrate added to a stirred solution of (**30**) (0.394 g; 0.77 mmol) and DIEA (700 μL; 4 mmol) in DMF (peptide grade; 10 mL) and the reaction was stirred at room temperature overnight. Complete reaction was confirmed by analytical RPHPLC. The product was precipitated with acidified water (pH 3; 80 mL) and isolated by centrifugation and removal of the supernatant. The product was washed by adding portions of aqueous HCl (0.25 M; 30 mL) and agitating before centrifugation and removal of the supernatant. The resulting solid was suspended in water (5 mL) and lyophilised to dryness, giving the product as an off-white solid (0.380 g; 92 %).

^{1}H NMR (400 MHz; d_6-DMSO) δ 3.91 (s, 3 H), 3.91 (s, 3 H), 3.92 (s, 3 H), 4.06 (s, 3 H), 5.31 (s, 2 H), 7.03 (d, J = 1.9 Hz, 1 H), 7.14 (d, J = 1.8 Hz, 1 H), 7.20 (d, J = 0.8 Hz, 1 H), 7.22 (d, J = 1.8 Hz, 1 H), 7.29 (d, J = 1.7 Hz, 1 H), 7.36 (d, J = 1.7 Hz, 1 H), 7.4-7.52 (m, 6 H), 7.54 (d, J = 1.9 Hz, 1 H), 9.97 (s, 1 H), 10.02 (s, 1 H), 10.58 (s, 1 H).

^{13}C NMR (125 MHz; d_6-DMSO) δ 35.2, 36.1 (3C), 64.8, 104.8, 104.9, 108.6, 118.4, 118.6, 118.7, 121.0, 121.2, 122.2, 122.4, 123.1 (2C), 126.0, 126.3, 127.8 (2C), 127.9, 128.5 (2C), 136.6, 138.5, 155.3, 158.4, 158.4, 160.1.

HRMS (ESI +ve mode) 583.2417 calculated for $C_{30}H_{31}N_8O_5^+$ $[M+H]^+$ found 583.2419.

1-methyl-4-(1-methyl-4-(1-methyl-4-(1-methyl-1H-imidazole-2-carboxamido)-1H-pyrrole-2-carboxamido)-1H-pyrrole-2-carboxamido)-1H-pyrrole-2-carboxylic acid (13):



(**13**)

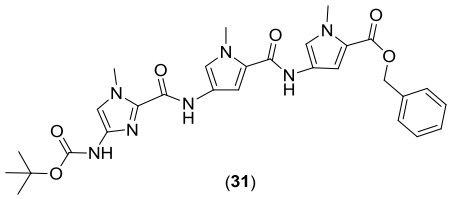
To a solution of (**10**) (0.095 g; 0.16 mmol) in methanol (60 mL) was added palladium hydroxide on carbon (0.029 g; 20 wt. % loading) and aqueous HCl (0.5 M; 0.55 mL; 1.7 equivalents). The mixture was shaken at 50 PSI pressure of hydrogen for 5 hours, and deemed complete by analytical RPHPLC as indicated by the consumption of starting material. The solution was filtered through Celite and methanol removed under vacuum and the resulting residue was suspended in water (2 mL) and lyophilised to dryness, giving the product as an off-white solid (0.079 g; 99 %), which was used without any further purification.

^{1}H NMR (400 MHz; d_6-DMSO) δ 3.83 (s, 3 H), 3.85 (s, 3 H), 3.87 (s, 3 H), 4.00 (s, 3 H), 6.85 (d, *J* = 1.6 Hz, 1 H), 7.07 (d, *J* = 1.6 Hz, 1 H), 7.15 (s, 1 H), 7.16 (d, *J* = 1.6 Hz, 1 H), 7.24 (d, *J* = 1.6 Hz, 1 H), 7.31 (d, *J* = 1.6 Hz, 1 H), 7.42 (d, *J* = 1.6 Hz, 1 H), 7.46 (s, 1 H), 9.89 (s, 1 H), 9.96 (s, 1 H), 10.53 (s, 1 H).

^{13}C NMR (125 MHz; d_6-DMSO) δ 35.2, 36.0, 36.1 (2C), 104.8, 104.9, 108.4, 118.5, 118.7, 119.5, 120.2, 121.2, 122.2, 122.6, 122.7, 123.1, 125.9, 126.3, 138.5, 155.3, 158.4 (2C), 161.9.

HRMS (ESI +ve mode) 493.1948 calculated for $C_{23}H_{25}N_8O_5^+$ $[M+H]^+$ found 493.1939.

Benzyl 4-(4-(4-((tert-butoxycarbonyl)amino)-1-methyl-1H-imidazole-2-carboxamido)-1-methyl-1H-pyrrole-2-carboxamido)-1-methyl-1H-pyrrole-2-carboxylate (31):



(**31**)

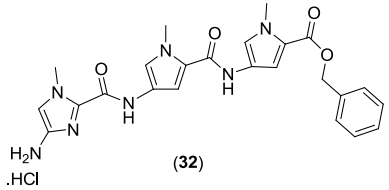
To a solution of Boc-Im-OH (**3**) (0.096 g; 0.39 mmol) and HOAt (0.054 g; 0.39 mmol) in DMF (peptide grade; 2.5 mL) was added DCC (0.078 g; 0.378 mmol). The mixture was stirred for 2 hours at room temperature. The solid DCU was removed by filtration and the filtrate added to a second solution of (**28**) (0.155 g; 0.40 mmol) in DMF (peptide grade; 2.5 mL) with DIEA (320 µL; 1.8 mmol). The reaction was stirred for 5 hours at room temperature. Complete reaction was confirmed by analytical RPHPLC and the product precipitated with acidified water (pH 3; 35 mL) and collected by centrifugation and removal of the supernatant. The crude material was washed twice more with acidified water, then suspended in water and lyophilised to dryness. The crude material was isolated as a light brown solid (0.198 g; 91 %) and was of sufficient purity. An analytical sample was acquired by silica gel column chromatography (50 % EtOAc in hexane) as a pale orange solid.

^{1}H NMR (300 MHz; d_6-DMSO) δ 1.45 (s, 9 H), 3.85 (s, 3 H), 3.85 (s, 3 H), 3.94 (s, 3 H), 5.25 (s, 2 H), 6.97 (d, J = 1.7 Hz, 1 H), 7.16 (d, J = 1.7 Hz, 1 H) 7.21 (s, 1 H), 7.27 (d, 1.5 Hz, 1 H), 7.30-7.46 (m, 5 H), 7.49 (d, J = 1.5 Hz, 1 H), 9.33 (s, 1 H), 9.92 (s, 1 H), 9.97 (s, 1 H).

^{13}C NMR (75 MHz; d_6-DMSO) δ 28.1 (3C), 34.9, 36.2 (2C), 64.9, 79.0, 104.9, 108.6, 113.6, 118.4, 118.8, 121.0, 121.3, 122.7, 123.0, 127.8 (2C), 128.0, 128.5 (2C), 134.1, 136.4, 136.6, 153.0, 155.8, 158.4, 160.1.

HRMS (ESI +ve mode) 576.2571 calculated for $C_{29}H_{34}N_7O_6^+$ $[M+H]^+$ found 576.2598.

Benzyl 4-(4-(4-amino-1-methyl-1H-imidazole-2-carboxamido)-1-methyl-1H-pyrrole-2-carboxamido)-1-methyl-1H-pyrrole-2-carboxylate hydrochloride (32):



(**32**)

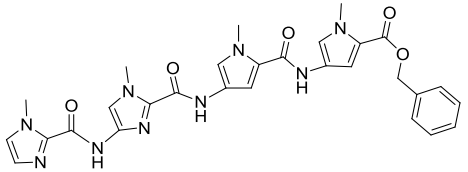
To a solid sample of (**31**) (0.248 g; 0.35 mmol) was added 4M HCl in 1,4-dioxane (5 ml; 20 mmol). The mixture was stirred at room temperature overnight. The crude product was precipitated with the addition of hexane (40 mL) and isolated by centrifugation and removal of the supernatant. The crude material was washed twice more with hexane before being suspended in water (5 mL) and lyophilised to dryness, giving the product as a pale red solid (0.217 g; 98 %).

^{1}H NMR (500 MHz; d_6-DMSO) δ 3.86 (s, 3 H), 3.86 (s, 3 H), 3.97 (s, 3H), 5.26 (s, 2 H), 6.98 (d, J = 2.0 Hz, 1 H), 7.12 (s, 1 H), 7.18 (d, J = 1.9 Hz, 1 H), 7.29 (d, J = 1.8 Hz, 1 H), 7.34-7.46 (m, 5 H), 7.49 (d, J = 1.9 Hz, 1 H), 9.95 (s, 1 H), 10.31 (s, 1 H).

^{13}C NMR (125 MHz; d_6-DMSO) δ 35.3, 36.1, 36.2, 64.8, 105.0, 108.6, 114.0, 118.4, 119.0, 121.0, 121.2, 122.7, 123.0, 127.8 (2C), 127.9, 128.5 (2C), 134.3, 135.3, 136.6, 155.1, 158.3, 160.1.

HRMS (ESI+) 476.2046 calculated for $C_{24}H_{26}N_7O_4^+$ $[M+H]^+$ found 476.2048.

Benzyl 1-methyl-4-(1-methyl-4-(1-methyl-4-(1-methyl-1H-imidazole-2-carboxamido)-1H-imidazole-2-carboxamido)-1H-pyrrole-2-carboxamido)-1H-pyrrole-2-carboxylate (11):



(**11**)

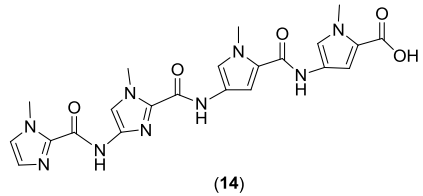
To a solution of (**4**) (0.025 g; 0.20 mmol) with HOAt (0.027 g; 0.20 mmol) in DMF (2 mL) was added DCC (0.039 g; 0.19 mmol). The mixture was shaken for 2 hours at room temperature. The solid DCU was then removed by filtration and the filtrate added to a stirred solution of (**32**) (0.120 g; 0.23 mmol) and DIEA (500 µL; 3 mmol) in DMF (peptide grade; 2 mL). The mixture was stirred at room temperature for two hours. The reaction was confirmed complete by analytical RPHPLC. The product was precipitated by the addition of acidified water (pH 3; 40 mL) and collected by centrifugation and removal of the supernatant. The crude material was washed twice more by addition of acidified water and centrifugation and removal of the supernatant. The resulting solid was suspended in water (5 mL) and lyophilised to dryness, giving (**11**) as a brown solid (0.100 g; 90 %) which was used without further purification.

^{1}H NMR (500 MHz; d_6-DMSO) δ 3.86 (s, 3 H), 3.86 (s, 3 H) 4.02 (s, 6 H), 5.26 (s, 2 H), 6.99 (d, *J* = 1.9 Hz, 1 H), 7.09 (d, *J* = 1.0 Hz, 1 H), 7.18 (d, *J* = 1.8 Hz, 1 H) 7.29 (d, *J* = 1.8 Hz, 1 H), 7.34-7.46 (m, 5 H), 7.46 (d, *J* = 0.7 Hz, 1 H), 7.50 (d, *J* = 1.9 Hz, 1 H), 7.58 (s, 1 H), 9.76 (s, 1 H), 9.96 (s, 1 H), 10.38 (s, 1 H).

^{13}C NMR (75 MHz; d_6-DMSO) δ 35.1, 35.2, 36.1 (2C), 64.8, 104.9, 108.6, 114.0, 118.4, 118.8, 121.0, 121.4, 122.7, 123.0, 127.1, 127.7, 127.8 (2C), 127.9, 128.5 (2C), 134.4, 134.6, 136.6, 137.8, 155.5, 155.7, 158.4, 160.1.

HRMS (ESI+) 584.2370 calculated for $C_{29}H_{30}N_9O_5^+$ $[M+H]^+$ found 584.2393.

1-methyl-4-(1-methyl-4-(1-methyl-4-(1-methyl-1H-imidazole-2-carboxamido)-1H-imidazole-2-carboxamido)-1H-pyrrole-2-carboxamido)-1H-pyrrole-2-carboxylic acid (14):



(**14**)

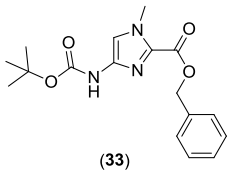
To a solution of (**11**) (0.140 g; 0.24 mmol) in methanol (60 mL) was added palladium hydroxide on carbon (0.040 g; 20 wt. % loading) and aqueous HCl (1 M; 1 mL; 4.2 equivalents). The mixture was shaken at 50 PSI pressure of hydrogen overnight and confirmed complete by analytical RPHPLC. The solution was filtered through Celite and methanol removed under vacuum. The resulting solid was suspended in water (2 mL) and lyophilised to dryness, giving the product as an off-white solid (0.111 g; 94 %), which was used without any further purification.

^{1}H NMR (300 MHz; d_6-DMSO) δ 3.81 (s, 3H), 3.84 (s, 3 H), 4.00 (s, 6 H), 6.84 (d, J = 1.9 Hz, 1 H), 7.10 (s, 1 H), 7.15 (d, J = 1.7 Hz, 1 H), 7.26 (d, J = 1.5 Hz, 1 H), 7.41 (d, J = 1.8 Hz, 1 H), 7.46 (s, 1 H), 7.57 (s, 1 H), 9.82 (s, 1 H), 9.92 (s, 1 H), 10.36 (s, 1 H).

^{13}C NMR (125 MHz; d_6-DMSO) δ 35.1, 35.2, 36.1 (2C), 104.8, 108.4, 114.1, 118.7, 119.5, 120.3, 121.4, 122.6, 122.9, 127.1, 127.4, 134.4, 134.6, 137.7, 155.5, 155.6, 158.4, 161.9.

HRMS (ESI +ve mode) 494.1900 calculated for $C_{22}H_{24}N_9O_5^+$ $[M+H]^+$ found 494.1893.

Benzyl 4-((tert-butoxycarbonyl)amino)-1-methyl-1H-imidazole-2-carboxylate (33):



(**33**)

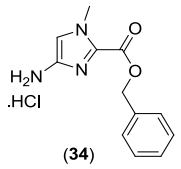
To a stirred solution of Boc-Im-OH (**3**) (0.350 g; 1.45 mmol) in ethanol/water (3:1 v/v, 7 mL) was added a solution of caesium carbonate (0.236 g; 0.725 mmol) in water (2 mL) drop-wise. The reaction mixture was then stirred at room temperature for 2 hours. The reaction mixture was then filtered and the solvent removed under vacuum, then distilled azeotropically to dryness with ethanol, giving the caesium salt of (**3**) as a pale yellow solid. The crude solid was then dissolved in DMF (3.5 mL; dry) and benzyl bromide (180 µL; 1.5 mmol) was added dropwise at room temperature with constant stirring. The temperature was raised to 40 °C and stirred overnight. The reaction was quenched by the addition of ice water (45 mL) and the crude solid isolated by centrifugation and removal of the supernatant. Any remaining water was removed azeotropically with ethanol to yield the crude product as a brown solid (0.401 g; 84 %). An analytical sample was obtained as a pale orange crystalline solid by re-crystallisation from ethanol/hexane.

^{1}H NMR (300 MHz; $CDCl_3$) δ 1.47 (s, 9 H), 3.92 (s, 3 H), 5.31 (s, 2 H), 7.24 (s, 1H), 7.27-7.40 (m, 5 H), 7.52 (s, 1 H).

^{13}C NMR (75 MHz; $CDCl_3$) δ 28.2 (3C), 35.9, 66.8, 80.9, 113.4, 128.3 (2C), 128.5 (2C), 131.1, 135.4, 138.0, 152.7, 158.4, 162.7.

HRMS (ESI +ve mode) 332.1610 calculated for $C_{17}H_{22}N_3O_4^+$ $[M+H]^+$ found 332.1610.

Benzyl 4-amino-1-methyl-1H-imidazole-2-carboxylate hydrochloride (34):



(**34**)

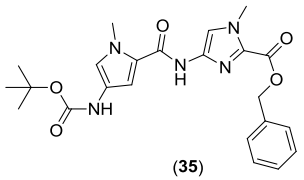
To a solid sample of compound (**33**) (0.200 g; 0.6 mmol) was added 4M HCl in dioxane (2 mL; 8 mmol). The reaction mixture was stirred at room temperature for 2 hours. The reaction was deemed complete by RPHPLC analysis. The product was precipitated by addition of hexane and isolated by centrifugation and removal of the supernatant. The product was washed twice more with hexane, then suspended in water (2 mL) and lyophilised to dryness, yielding (**34**) as an orange solid (0.162 g; quantitative).

^{1}H NMR (300 MHz; *d*$_4$-Methanol) δ 4.06 (s, 3H), 5.44 (s, 2 H), 6.96 (s, 1 H), 7.36-7.52 (m, 5 H).

^{13}C NMR (75 MHz; *d*$_4$-Methanol) δ 37.6, 69.4, 111.1, 127.5, 129.8 (2C), 130.0 (3C), 136.2, 140.7, 155.5.

HRMS (ESI +ve mode) 232.1086 calculated for $C_{12}H_{14}N_3O_2^+$ $[M+H]^+$ found 232.1085.

Benzyl 4-(4-((tert-butoxycarbonyl)amino)-1-methyl-1H-pyrrole-2-carboxamido)-1-methyl-1H-imidazole-2-carboxylate (35):



(**35**)

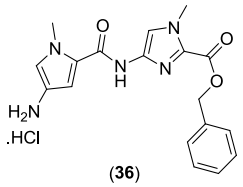
To a solution of (**2**) (0.284 g; 1.18 mmol) in DMF (5mL; peptide grade) was added DCC (0.227 g; 1.1 mmol) and HOAt (0.161 g; 1.18 mmol). The reaction mixture was stirred at room temperature for 2 hours. The solid DCU was removed by filtration and the filtrate added to a solution of (**34**) (0.210 g; 0.79 mmol) with DIEA (2.7 mL; 15.5 mmol) in DMF (5 mL; peptide grade). The reaction was heated in a microwave at 60 °C for 1 hour. The crude product was precipitated by the addition of acidified water (pH 3; 50 mL) and isolated by centrifugation and decanting of the supernatant. The solid material was washed twice with portions of acidified water before being suspended in water (5 mL) and lyophilised to dryness, to yield the crude material as a yellow/brown solid. The product was purified by silica gel chromatography (30 % ethyl acetate in hexane) to give the pure material as a pale yellow solid (0.241 g; 68%).

^{1}H NMR (300 MHz; d_6-DMSO) δ 1.43 (s, 9 H), 3.80 (s, 3 H), 3.94 (s, 3 H), 5.29 (s, 2 H), 6.92 (s, 1 H), 6.98 (s, 1 H), 7.32-7.50 (m, 5 H), 7.66 (s, 1 H), 9.04 (s, 1 H), 10.63 (s, 1 H).

^{13}C NMR (75 MHz; d_6-DMSO) δ 28.1 (3C), 35.4, 36.2, 66.1, 78.2, 105.1, 115.6, 118.2, 121.7, 122.3, 128.3, 128.5 (2C), 128.6 (2C), 130.5, 135.7, 137.9, 152.8, 158.2, 158.6.

HRMS (ESI +ve mode) 454.2090 calculated for $C_{23}H_{28}N_5O_5^+$ $[M+H]^+$ found 454.2089.

Benzyl 4-(4-amino-1-methyl-1H-pyrrole-2-carboxamido)-1-methyl-1H-imidazole-2-carboxylate hydrochloride (36):



(**36**)

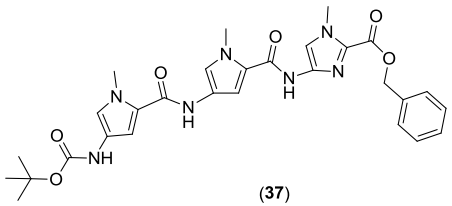
To a solid sample of compound (**35**) (0.200 g; 0.18 mmol) was added 4 M HCl in dioxane (4 mL; 16 mmol). The mixture was stirred at room temperature for 2 hours, after which time the formation of a cloudy white precipitate was observed. The product was collected by addition of hexane and isolated by centrifugation and removal of the supernatant. The crude material was washed twice more with hexane. The resulting solid was suspended in water (4 mL) and lyophilised, giving (**36**) as a very pale yellow solid (0.171.8 g; quantitative).

^{1}H NMR (300 MHz; d_6-DMSO) δ 3.87 (s, 3 H), 3.94 (s, 3 H), 5.29 (s, 2 H), 7.14 (d, J = 1.5 Hz, 1 H), 7.18 (d, J = 1.7 Hz, 1 H), 7.32-7.48 (m, 5 H), 7.69 (s, 1 H), 10.19 (s, 3 H), 10.88 (s, 1 H).

^{13}C NMR (75 MHz; d_6-DMSO) δ 35.5, 36.8, 66.2, 108.3, 113.2, 115.7, 122.5, 123.6, 128.3, 128.5 (2C), 128.6 (2C), 130.5, 135.6, 137.3, 157.9, 158.0.

HRMS (ESI+) 354.1566 calculated for $C_{18}H_{20}N_5O_3^+$ $[M+H]^+$ found 354.1564.

Benzyl 4-(4-(4-((tert-butoxycarbonyl)amino)-1-methyl-1H-pyrrole-2-carboxamido)-1-methyl-1H-pyrrole-2-carboxamido)-1-methyl-1H-imidazole-2-carboxylate (37):



(**37**)

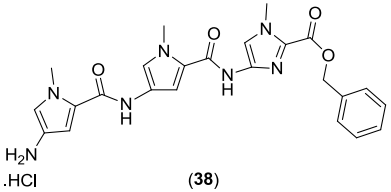
To a solution of (**2**) (0.035 g; 0.145 mmol) and HATU (0.055 g; 0.145 mmol) in DMF (1 mL; peptide grade) was added DIEA (400 µL; 2.3 mmol). The reaction mixture was stirred at room temperature for 30 minutes. The activated ester was added to a stirred solution of (**36**) (0.058 g; 0.15 mmol) in DMF (1 mL; peptide grade) and the mixture stirred at room temperature for 2 hours. Reaction was deemed complete by analytical RPHPLC as indicated by absence of starting material, and the product precipitated by the addition of acidified water (pH 3; 35 mL) and isolated by centrifugation and decanting off the supernatant. The solid material was washed twice more with portions of acidified water before being suspended in water (5 mL) and lyophilised to dryness, giving the crude product as a light brown solid (0.078 g; 94 %) which was used without further purification. An analytical sample was acquired by silica gel column chromatography (40 % EtOAc in hexane) as an off-white powder.

^{1}H NMR (300 MHz; d_6-DMSO) δ 1.44 (s, 9 H), 3.79 (s, 3 H), 3.83 (s, 3 H), 3.94 (s, 3 H), 5.30 (s, 2 H), 6.83 (s, 1 H), 6.88 (s, 1 H), 7.07 (d, J = 1.5 Hz, 1 H), 7.32 (d, J = 1.4 Hz, 1 H), 7.34-7.47 (m, 5 H), 7.68 (s, 1 H), 9.07 (s, 1 H), 9.84 (s, 1 H), 10.69 (s, 1 H).

^{13}C NMR (75 MHz; d_6-DMSO) δ 28.2 (3C), 35.5, 36.0, 36.2, 66.1, 78.2, 103.9, 105.8, 115.7, 117.0, 119.7, 121.6, 122.2, 122.3, 122.7, 128.3, 128.5 (2C), 128.6 (2C), 130.5, 135.7, 137.9, 152.8, 158.2, 158.5, 158.7.

HRMS (ESI +ve mode) 576.2571 calculated for $C_{29}H_{34}N_7O_6^+$ $[M+H]^+$ found 576.2598.

Benzyl 4-(4-(4-amino-1-methyl-1H-pyrrole-2-carboxamido)-1-methyl-1H-pyrrole-2-carboxamido)-1-methyl-1H-imidazole-2-carboxylate hydrochloride (38):



(**38**)

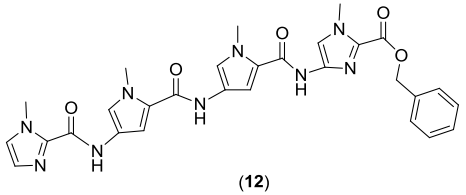
To a solid sample of (**37**) (0.200 g; 0.35 mmol) was added 4 M HCl in dioxane (4 mL; 16 mmol) and the mixture was stirred at room temperature for 2 hours. Reaction was confirmed to be complete by analytical RPHPLC as indicated by absence of starting material. The product was precipitated with hexane then isolated by centrifugation and removal of the supernatant. The crude material was washed twice more with hexane, then suspended in water (5 mL) and lyophilised to dryness, giving the product as an off-white solid (0.179 g; quantitative).

^{1}H NMR (400 MHz; d_6-DMSO) δ 3.90 (s, 3 H), 3.93 (s, 3 H), 4.00 (s, 3 H), 5.35 (s, 2 H), 7.01 (d, J = 1.9 Hz, 1 H), 7.13 (d, J = 2.5 Hz, 1 H), 7.14 (d, J = 2.1 Hz, 1 H), 7.39 (d, J = 1.6 Hz, 1 H), 7.41-7.52 (m, 5 H), 7.73 (s, 1 H), 9.88 (s br, 2 H), 10.08 (s, 1 H), 10.75 (s, 1 H).

^{13}C NMR (75 MHz; d_6-DMSO) δ 35.5, 36.3, 36.6, 66.1, 105.7, 107.0, 112.9, 115.7, 119.8, 121.5, 121.6, 121.8, 124.9, 128.3, 128.5 (2C), 128.6 (2C), 130.5, 135.7, 137.9, 157.7, 158.2, 158.6.

HRMS (ESI +ve mode) 476.2046 calculated for $C_{24}H_{26}N_7O_4^+$ $[M+H]^+$, found 476.2058.

Benzyl 1-methyl-4-(1-methyl-4-(1-methyl-4-(1-methyl-1H-imidazole-2-carboxamido)-1H-pyrrole-2-carboxamido)-1H-pyrrole-2-carboxamido)-1H-imidazole-2-carboxylate (12):



(**12**)

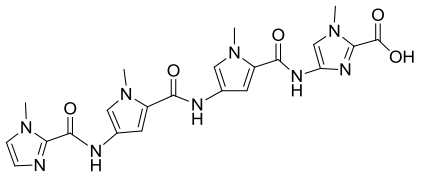
To a solution of (**4**) (0.053 g; 0.42 mmol) and HOAt (0.057 g; 0.42 mmol) in DMF (dry; 6 mL) was added DCC (0.085 g; 0.41 mmol) and the reaction mixture was stirred at room temperature for 2 hours. The solid DCU was then removed by filtration and the filtrate added to a stirred solution of (**38**) (0.220 g; 0.43 mmol) and DIEA (0.75 mL; 4.3 mmol) in DMF (dry; 6 mL). The reaction mixture was stirred at room temperature overnight. The reaction was confirmed to be complete by analytical RPHPLC as indicated by the absence of starting material. The crude product was precipitated by the addition of acidified water (pH 3; 40 mL) and was collected by centrifugation and removal of the supernatant. The crude solid was washed twice more with acidified water before being suspended in water (5 mL) and lyophilised to dryness, giving the product as a pale brown powder (0.225 g; 94 %) which was used without further purification. An analytical specimen was obtained by semi-preparative HPLC purification as a fluffy, off-white solid.

^{1}H NMR (300 MHz; d_6-DMSO) δ 3.89 (s, 6 H), 4.00 (s, 3 H), 4.05 (s, 3 H), 5.35 (s, 2 H), 7.14 (d, *J* = 1.7 Hz, 1 H), 7.20-7.21 (m, 2 H), 7.35 (d, *J* = 1.6 Hz, 1 H), 7.40 (d, *J* = 1.7 Hz, 1 H), 7.42-7.51 (m, 6 H), 7.74 (s, 1 H), 10.01 (s, 1 H), 10.60 (s, 1 H), 10.76 (s, 1 H).

^{13}C NMR (125 MHz; d_6-DMSO) δ 35.3, 35.5, 36.1, 36.3, 66.1, 104.9, 105.8, 115.7, 118.7, 119.8, 121.1, 121.7, 122.1, 123.1, 125.4, 126.2, 128.3, 128.5 (2C), 128.6 (2C), 130.5, 135.7, 137.9, 138.3, 154.8, 158.2, 158.5, 158.7.

HRMS (ESI +ve mode) 584.2370 calculated for $C_{29}H_{30}N_9O_5^+$ $[M+H]^+$, found 584.2398.

1-methyl-4-(1-methyl-4-(1-methyl-4-(1-methyl-1H-imidazole-2-carboxamido)-1H-pyrrole-2-carboxamido)-1H-pyrrole-2-carboxamido)-1H-imidazole-2-carboxylic acid (15):



(**15**)

To a solution of (**12**) (0.100 g; 0.17 mmol) in methanol (60 mL) was added palladium hydroxide on carbon (0.030 g; 20 wt. % loading) and aqueous HCl (1 M; 0.3 mL; 1.7 equivalents). The mixture was shaken at 50 PSI pressure of hydrogen for 5 hours. Analytical HPLC showed the reaction stalled at approximately 50 % conversion. A further addition of palladium hydroxide on carbon (0.030 g; 20 wt. % loading) and aqueous HCl (1M; 0.5 mL; 2.9 equivalents) was made and the pressure returned to 50 psi and the reaction left overnight. The solution was filtered through Celite and methanol removed under vacuum to give a solid which was suspended in water (2 mL) and lyophilised to dryness, giving the product as a yellow/brown solid (0.084 g; 99

%), which was used without any further purification. Compound (**15**) was found to readily decarboxylate when stored at RT, however the compound was stable when stored at -20 °C after lyophilisation.

^{1}H NMR (500 MHz; d_6-DMSO) δ 3.86 (s, 3 H), 3.87 (s, 3 H), 3.94 (s, 3 H), 4.01 (s, 3 H), 7.07 (d, J = 0.8 Hz, 1 H), 7.11 (d, J = 1.8 Hz, 1 H), 7.18 (d, J = 1.8 Hz, 1 H), 7.31 (d, J = 1.7 Hz, 1 H), 7.37 (d, J = 1.6 Hz, 1 H), 7.41 (s, 1 H), 7.63 (s, 1 H), 9.98 (s, 1 H), 10.46 (s, 1 H), 10.65 (s, 1 H).

^{13}C NMR (125 MHz; d_6-DMSO) δ 35.1, 35.5, 36.1, 36.2, 105.0, 105.7, 115.1, 118.6, 119.6, 121.3, 121.8, 122.1, 123.0, 126.3, 126.7, 131.7, 137.4, 138.7, 155.9, 158.5, 158.7, 160.0.

HRMS (ESI +ve mode) 494.1900 calculated for $C_{22}H_{24}N_9O_5^+$ $[M+H]^+$, found 494.1876.

5.3 Manual solid phase synthesis protocol

5.3.1 General preparation of resin and coupling protocol for solid phase synthesis of polyamides

Boc-β-Alanine-PAM resin (100 mg; 0.026 mmol) was placed in a fritted glass reaction vessel, washed with DMF (5 x 1 min) and then drained. The Boc group was removed using a TFA:phenol:water mixture (92.5:5:2.5) twice (1 x 1 min, and 1 x 5 min) with shaking. The resin was washed with DMF (4 x 1 min), followed by another washing step (DMF for DCC\HOAt and HATU couplings, THF for BTC couplings) for 1 min before the vessel was drained. The activated monomer was added (followed by DIEA if required) and the reaction was mixed resulting in the formation of a slurry. The couplings were conducted for the allotted time (dependant on sequence and coupling method), before being drained and washed with DMF (4 x 1 min).

To ensure complete deprotection of the amine, the resin bound material was treated with 3 consecutive treatments of TPW mixture. The timings for these treatments are dependent upon which monomer the Boc group is located and are as follows:

Boc-pyrrole, GABA and Fmoc-D-Dab(Boc)-OH building blocks – 1 minute, 3 minutes, 3 minutes respectively.

Boc-imidazole building blocks – 1 minute, 3 minutes, 20 minutes for successive rounds of coupling.

5.3.2 General cleavage protocol and isolation of polyamide

Polyamides were cleaved from the resin by placing them into a sealed container with the appropriate cleavage amine and heating to 55 °C for 16 hours. The resin was removed by filtration through cotton wool and washed with 1 mL of DCM. The crude material was precipitated by addition of cold diethyl

ether and isolated by centrifugation and decanting off the supernatent. The polyamide was washed twice more by dissolving in DCM (1 ml) and re-precipitating with diethyl ether to yield the crude material.

5.3.3 HPLC analysis and purification of polyamides

Analytical HPLC retention times were acquired using 0.1 % TFA in water as buffer A and 0.1 % TFA in acetonitrile as buffer B with a flow rate of 0.5 mL/minute, starting at 15 % B and holding for 5 minutes before increasing to 60 % B over 20 minutes. Unless otherwise stated, polyamides were purified by semi-preparative HPLC with a gradient starting at 17.5 % B and holding for 5 minutes before increasing to 30 % B over 30 minutes and a constant flow rate of 10.6 mL/minute.

5.4 General activation protocols for polyamide synthesis

5.4.1 Activation with HATU

General procedure for 100 mg of β-ala-PAM resin (0.26 meq/g): Monomer (4.0 equivalents; 0.104 mmol) and HATU (3.6 equivalents; 0.3744 mmol; 36 mg) were dissolved in dry DMF (1 mL). Upon addition of DIEA (150 μL; 0.9 mmol) the solution was left to activate for 2 minutes, before being added to the resin.

5.4.2 Activation with DCC/HOAt

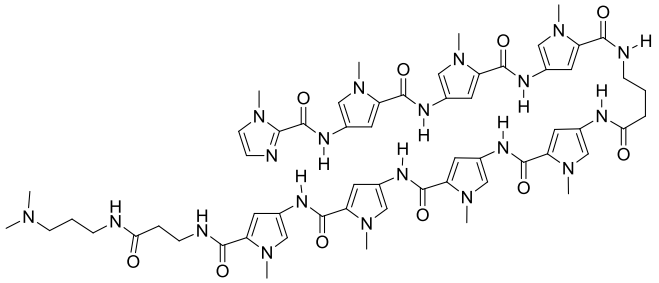
General procedure for 100 mg of β-ala-PAM resin (0.26 meq/g): Monomer (4.0 equivalents; 0.104 mmol) was added to DCC (19.31 mg; 0.0936 mmol; 3.6 equivalents) and HOAt (13.45 mg; 0.0988 mmol; 3.8 equivalents) in dry DMF (1 mL) and activated for 2 hours with constant shaking. The DCU that precipitates is filtered off and the solution added to resin followed by addition of DIEA (150 μL; 0.9 mmol).

5.4.3 Activation with BTC

General procedure for 100 mg of β-ala-PAM resin (0.26 meq/g): To a solution of monomer (4.0 equivalents; 0.104 mmol) and BTC (9.6 mg; 0.0324 mmol; 1.2 equivalents) in dry THF (1 mL) was added 2,3,5-collidine (50 μL; 0.38 mmol). This resulted in the formation of a white emulsion, which was allowed to mix for 2 minutes. The activated monomer was then added to the resin with DIEA (150 μL; 0.9mmol).[3]

5.5 Synthesis of polyamides 17a-19a through solid phase synthesis

5.5.1 Synthesis of polyamide (17a)



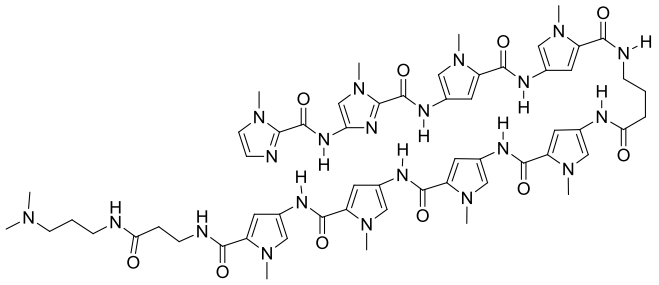
(17a)

Polyamide (**17a**) was synthesised on 50 mg of Boc-β-ala-PAM resin as shown in Scheme S3 using the following reagents and times: (i) TPW; (ii) BocPyOH, HATU, DIEA, 40 minutes; (iii) TPW; (iv) BocPyOH, HATU, DIEA, 40 minutes; (v) TPW; (vi) BocPyOH, HATU, DIEA, 40 minutes; (vii) TPW; (viii) BocPyOH, HATU, DIEA, 60 minutes; (ix) TPW; (x) GABA, HATU, DIEA, 60 minutes; (xi) TPW; (xii) BocPyOH, HATU, DIEA, 60 minutes; (xiii) TPW; (xiv) BocPyOH, HATU, DIEA, 90 minutes; (xv) TPW; (xvi) BocPyOH, HATU, DIEA, 120 minutes; (xvii) TPW; (xviii) ImOH, DCC, HOAt, DIEA, 90 minutes. This was cleaved from the resin under standard cleavage conditions (See section 2.3.2, page S22) to give the crude material in 68 % purity. After purification by semi-preparative HPLC the pure material was isolated as a fluffy white solid (1.9 mg; 12 % recovery).

Analytical HPLC t_r = 14.4 minutes.

HRMS (ESI +ve mode) 1221.5819 calculated for $C_{59}H_{73}N_{20}O_{10}^{+}$ $[M+H]^{+}$, found 1221.5776.

5.5.2 Synthesis of polyamide (18a)



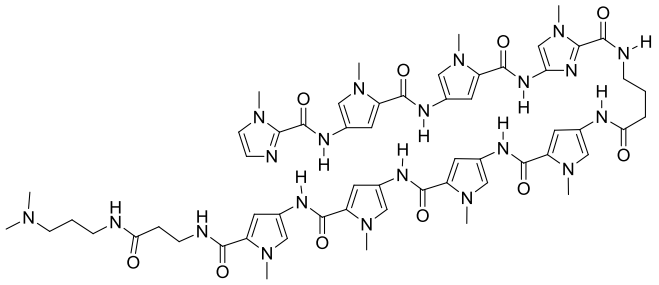
(18a)

Polyamide (**18a**) was synthesised on 50 mg of Boc-β-ala-PAM resin as shown in Scheme S3 using the following reagents and times: (i) TPW; (ii) BocPyOH, HATU, DIEA, 40 minutes; (iii) TPW; (iv) BocPyOH, HATU, DIEA, 40 minutes; (v) TPW; (vi) BocPyOH, HATU, DIEA, 40 minutes; (vii) TPW; (viii) BocPyOH, HATU, DIEA, 60 minutes; (ix) TPW; (x) GABA, HATU, DIEA, 60 minutes; (xi) TPW; (xii) BocPyOH, HATU, DIEA, 60 minutes; (xiii) TPW; (xiv) BocPyOH, HATU, DIEA, 90 minutes; (xv) TPW; (xvi) BocImOH, DCC, HOAt, DIEA, 120 minutes; (xvii) TPW; (xviii) ImOH, DCC, HOAt, DIEA, 90 minutes. This was cleaved from the resin under standard cleavage conditions (See section 2.3.2, page S22) to give the crude material in 76 % purity. After purification by semi-preparative HPLC the pure material was isolated as a fluffy white solid (1.6 mg; 10 % recovery).

Analytical HPLC t_r = 14.2 minutes.

HRMS (ESI +ve mode) 1222.5771 calculated for $C_{59}H_{73}N_{20}O_{10}^{+}$ $[M+H]^{+}$, found 1222.5826.

5.5.3 Synthesis of polyamide (19a)

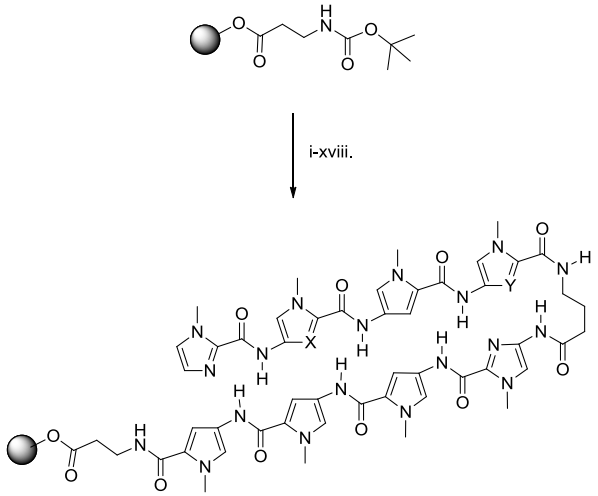


(19a)

Polyamide (**19a**) was synthesised on 50 mg of Boc-β-ala-PAM resin as shown in Scheme S3 using the following reagents and times: (i) TPW; (ii) BocPyOH, HATU, DIEA, 40 minutes; (iii) TPW; (iv) BocPyOH, HATU, DIEA, 40 minutes; (v) TPW; (vi) BocPyOH, HATU, DIEA, 40 minutes; (vii) TPW; (viii) BocPyOH, HATU, DIEA, 60 minutes; (ix) TPW; (x) GABA, HATU, DIEA, 60 minutes; (xi) TPW; (xii) BocImOH, DCC, HOAt, DIEA, 60 minutes; (xiii) TPW; (xiv) BocPyOH, BTC/Collidine, DIEA, 90 minutes; (xv) TPW; (xvi) BocPyOH, HATU, DIEA, 120 minutes; (xvii) TPW; (xviii) ImOH, DCC, HOAt, DIEA, 90 minutes. This was cleaved from the resin under standard cleavage conditions to give the crude material in 78 % purity. After purification by semi-preparative HPLC the pure material was isolated as a fluffy white solid (1.7 mg; 11 % recovery).

Analytical HPLC t_r = 14.6 minutes.

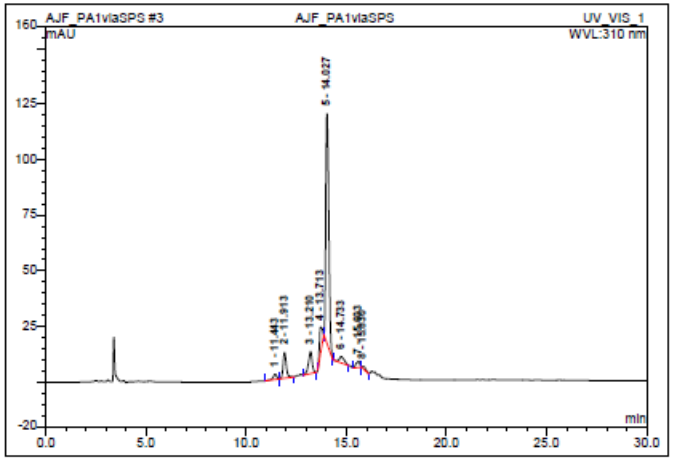
HRMS (ESI +ve mode) 1222.5771 calculated for $C_{59}H_{73}N_{20}O_{10}^{+}$ $[M+H]^{+}$, found 1221.5746.



Scheme S3: Synthesis of PAs **17a-19a**. Steps (i)-(xviii) are stated in the respective polyamide experimental.

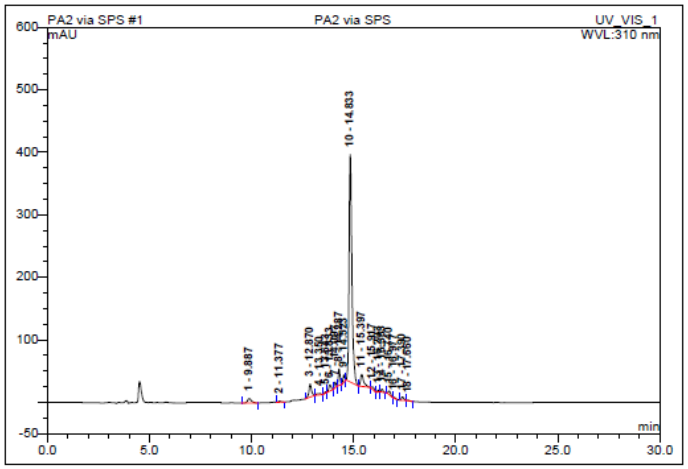
5.5.4 Characterisation of Polyamides 17a-19a

5.5.4.1 Crude HPLC data



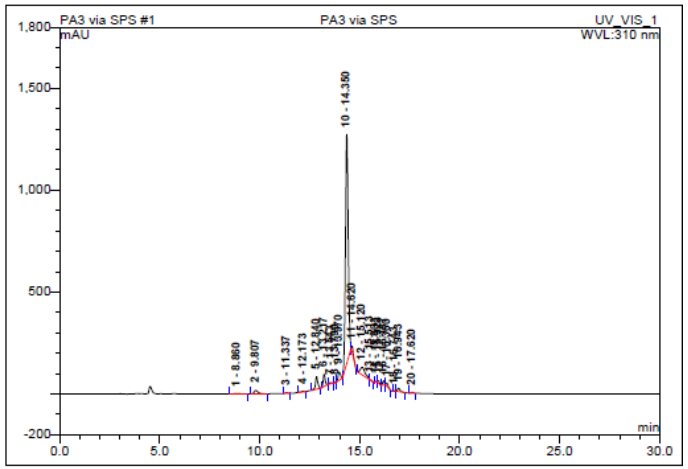
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	11.44	n.a.	2.476	0.509	1.93	n.a.	BMB
2	11.91	n.a.	11.560	2.127	8.07	n.a.	BMB
3	13.21	n.a.	9.924	2.110	8.01	n.a.	BMB
4	13.71	n.a.	11.497	1.837	6.97	n.a.	BMB
5	14.03	n.a.	103.313	18.060	68.53	n.a.	bMB
6	14.73	n.a.	2.905	0.868	3.29	n.a.	BMB
7	15.60	n.a.	2.814	0.595	2.26	n.a.	BMb
8	15.83	n.a.	1.017	0.244	0.93	n.a.	bMB
Total:			145.505	26.351	100.00	0.000	

Figure S1: Crude HPL chromatogram of polyamide (**17a**).



No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	9.89	n.a.	7.076	1.508	1.96	n.a.	BMB
2	11.38	n.a.	1.687	0.248	0.32	n.a.	BMB
3	12.87	n.a.	20.964	3.094	4.02	n.a.	BMB
4	13.35	n.a.	2.253	0.540	0.70	n.a.	bMB
5	13.64	n.a.	1.805	0.224	0.29	n.a.	BMB
6	13.83	n.a.	9.652	1.329	1.73	n.a.	bMB
7	14.10	n.a.	9.245	0.862	1.12	n.a.	BMb
8	14.29	n.a.	26.364	2.658	3.46	n.a.	bMB
9	14.52	n.a.	11.266	1.058	1.38	n.a.	BMb
10	14.83	n.a.	363.674	58.703	76.34	n.a.	bMB
11	15.40	n.a.	19.191	3.513	4.57	n.a.	BMB
12	15.92	n.a.	3.775	0.617	0.80	n.a.	BMB
13	16.20	n.a.	3.017	0.273	0.36	n.a.	BMb
14	16.38	n.a.	4.515	0.502	0.65	n.a.	bMB
15	16.74	n.a.	5.990	0.776	1.01	n.a.	BMB

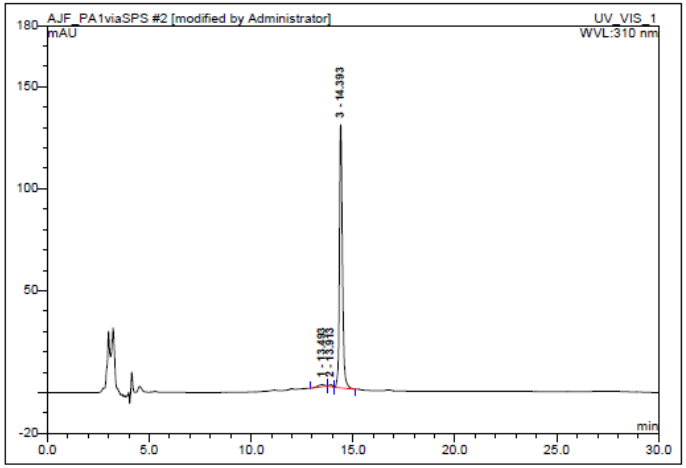
Figure S2: Crude HPL chromatogram of polyamide (**18a**).



No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	8.86	n.a.	1.615	0.540	0.23	n.a.	BMB
2	9.81	n.a.	16.797	3.830	1.67	n.a.	BMB
3	11.34	n.a.	3.366	0.405	0.18	n.a.	BMB
4	12.17	n.a.	3.217	0.705	0.31	n.a.	BMB
5	12.84	n.a.	61.889	8.371	3.64	n.a.	BMB
6	13.22	n.a.	60.562	7.243	3.15	n.a.	BMB
7	13.54	n.a.	5.610	0.703	0.31	n.a.	bMB
8	13.79	n.a.	2.027	0.148	0.06	n.a.	BMB
9	13.97	n.a.	40.012	5.540	2.41	n.a.	BMB
10	14.35	n.a.	1124.147	179.724	78.15	n.a.	BMb
11	14.62	n.a.	27.920	2.782	1.21	n.a.	bMB
12	15.12	n.a.	38.007	10.744	4.67	n.a.	BMB
13	15.51	n.a.	0.109	0.428	0.19	n.a.	BMB
14	15.80	n.a.	3.076	0.233	0.10	n.a.	BMb
15	15.92	n.a.	10.864	1.257	0.55	n.a.	bMB

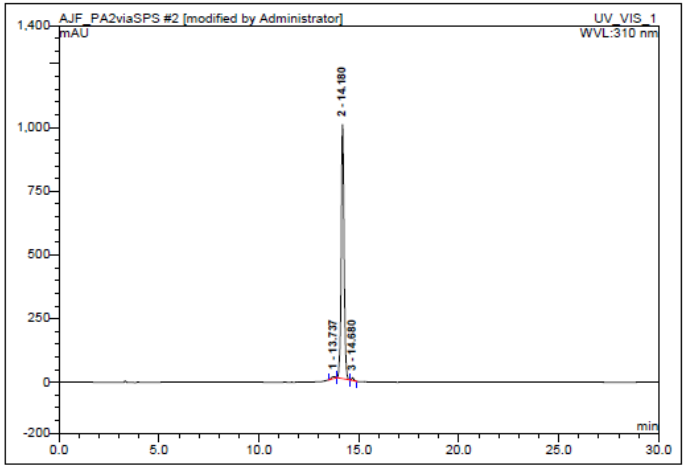
Figure S3: Crude HPL chromatogram of polyamide (**19a**).

5.5.4.2 Analytical HPLC traces of polyamides purified by semi-preparative HPLC



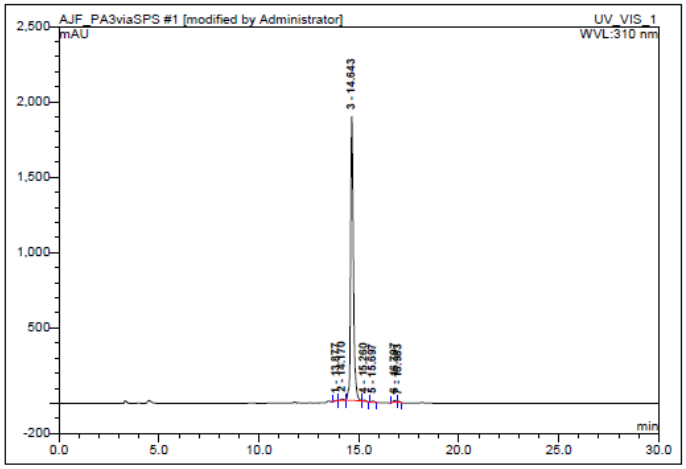
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	13.49	n.a.	0.945	0.367	1.59	n.a.	BMb
2	13.91	n.a.	1.009	0.174	0.76	n.a.	bMB
3	14.39	n.a.	129.097	22.476	97.65	n.a.	BMB
Total:			131.051	23.018	100.00	0.000	

Figure S4: HPL chromatogram of polyamide (**17a**).



No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	13.74	n.a.	6.707	1.619	0.97	n.a.	BMb
2	14.18	n.a.	996.583	164.141	98.25	n.a.	bMB
3	14.68	n.a.	10.225	1.305	0.78	n.a.	BMB
Total:			1013.515	167.065	100.00	0.000	

Figure S5: HPL chromatogram of polyamide (**18a**).



No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	13.88	n.a.	3.500	0.660	0.21	n.a.	BMb*
2	14.17	n.a.	8.772	1.572	0.51	n.a.	bMB
3	14.64	n.a.	1883.578	303.373	97.77	n.a.	BMB
4	15.26	n.a.	6.234	1.139	0.37	n.a.	BMB
5	15.70	n.a.	9.575	1.287	0.41	n.a.	BMB
6	16.80	n.a.	10.965	1.722	0.56	n.a.	BMb
7	16.98	n.a.	4.463	0.544	0.18	n.a.	bMB
Total:			1927.087	310.297	100.00	0.000	

Figure 6: HPL chromatogram of polyamide (**19a**).

5.5.4.3 HRMS data of polyamides 17a-19a purified by semi-preparative HPLC.

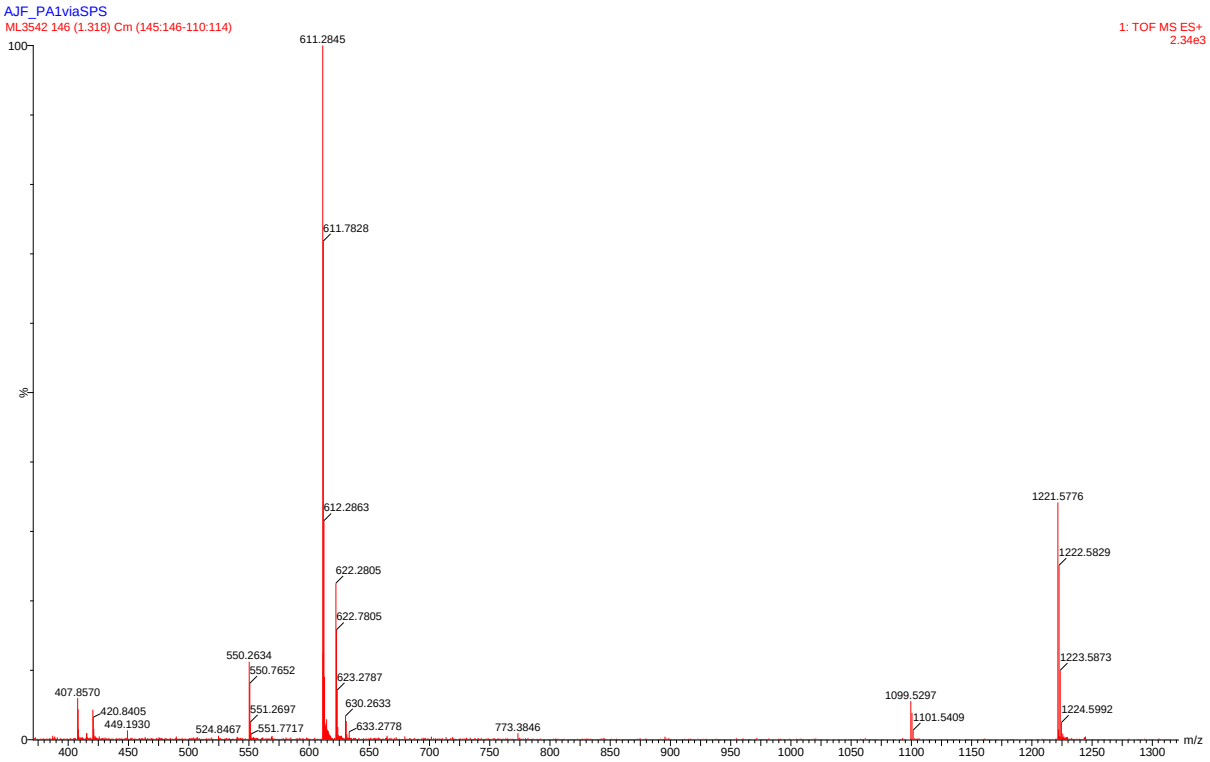


Figure S7: HRMS of polyamide (**17a**). Key peaks shown are $[M+H]^+$ at 1221.5776, $[M+2H]^{2+}$ at 611.2845, $[M+H+Na]^{2+}$ at 622.2805.

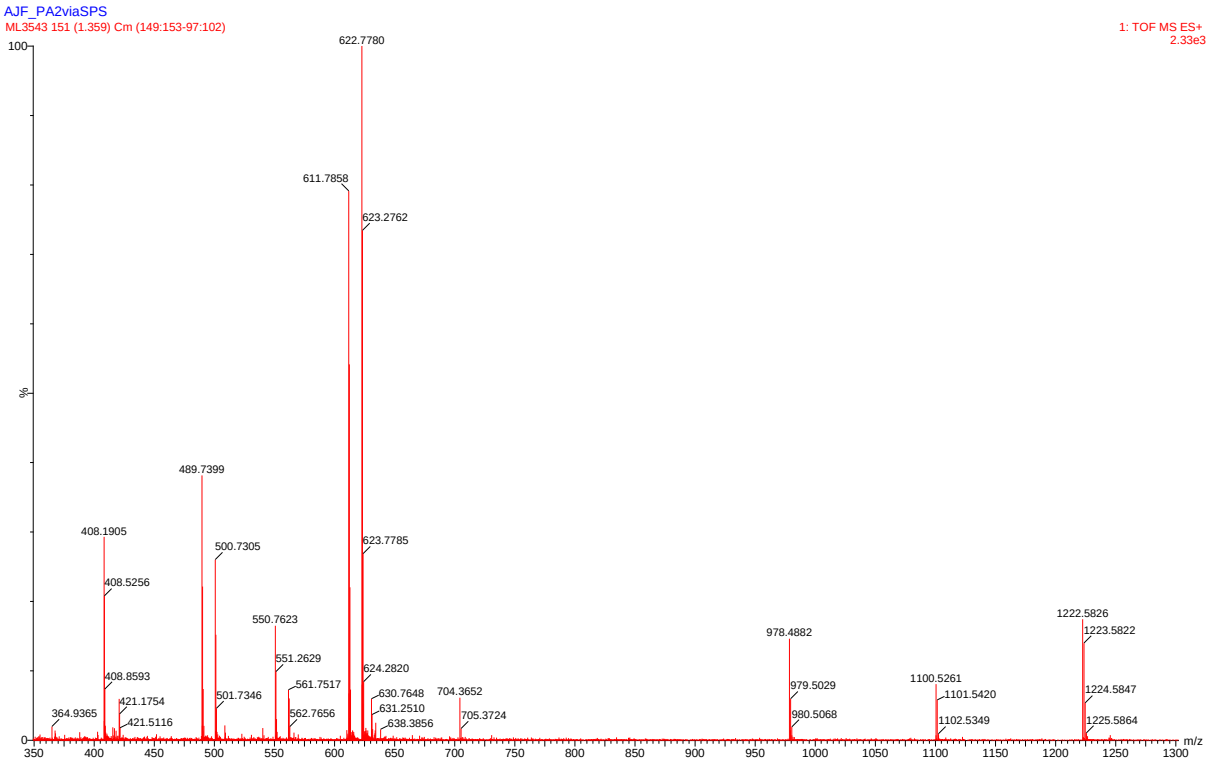


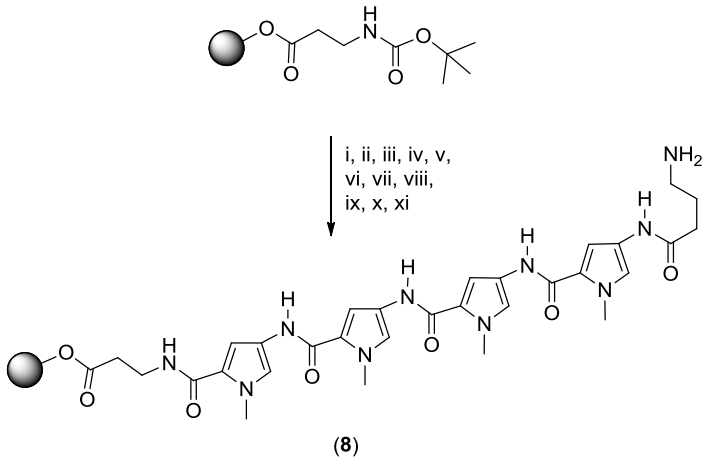
Figure S8: HRMS of polyamide (**18a**). Key peaks shown are $[M+H]^+$ at 1222.5826, $[M+2H]^{2+}$ at 611.7858, $[M+H+Na]^{2+}$ at 622.7780.

Figure S9: HRMS of polyamide (**19a**). Key peaks shown are $[M+H]^+$ at 1222.5746, $[M+2H]^{2+}$ at 611.7834, $[M+H+Na]^{2+}$ at 622.7799.

5.6 Synthesis of polyamides using a half-half coupling protocol

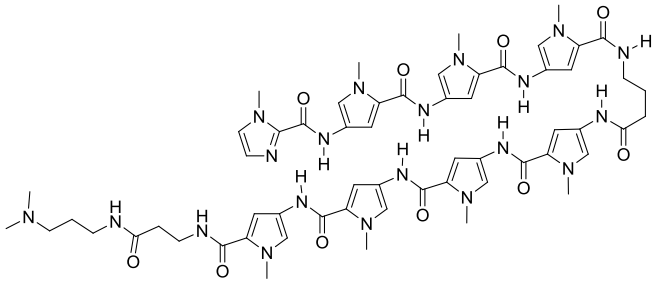
5.6.1 Preparation of resin bound tetramer

The first four pyrrole units were coupled to the resin using the protocols described above. Reaction times and conditions are shown in Scheme S4.



Scheme S4: Synthesis of polyamide tetramer on Boc-β-Ala PAM resin. (i) TPW; (ii) BocPyOH, HATU, DIEA, 40 minutes; (iii) TPW; (iv) BocPyOH, HATU, DIEA, 40 minutes; (v) TPW; (vi) BocPyOH, HATU, DIEA, 40 minutes; (vii) TPW; (viii) BocPyOH, HATU, DIEA, 60 minutes; (ix)TPW; (x) GABA, HATU, DIEA, 60 minutes; (xi) TPW.

5.6.2 Synthesis of polyamide (17b)



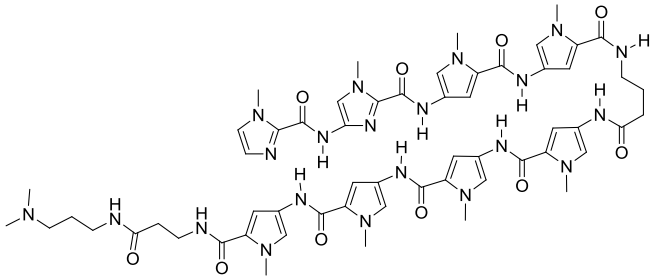
(17b)

Resin-bound tetramer (**8**) (20 mg; 5.2 μmol) was swollen in DMF for 2 hours. The resin was then drained and washed three times with DMF. The tetramer (**13**) (10 mg; 20.3 μmol) was pre-activated with HATU (7 mg; 18.4 μmol) and DIEA (50 μL; 0.3 mmol) in DMF (600 μL) for 30 minutes before being added to the resin, and then shaken for 4 hours. The reaction mixture was then drained from the vessel and the resin washed three times with DMF, then DCM, then twice with methanol before being flushed with nitrogen for 5 minutes. **(17b)** was cleaved from the resin with N^1,N^1-dimethylpropane-1,3-diamine (500 μL) under standard cleavage conditions with the crude material being 90 % pure by HPLC at 310 nm (Figure S10). This was purified by semipreparative HPLC to give the product as a fluffy white solid (1.9 mg; 30 % recovery).

Analytical HPLC t_r = 14.8 minutes.

HRMS (ESI +ve mode) 1221.5819 calculated for $C_{59}H_{73}N_{20}O_{10}^+$ $[M+H]^+$, found 1221.5808.

5.6.3 Synthesis of polyamide (18b)



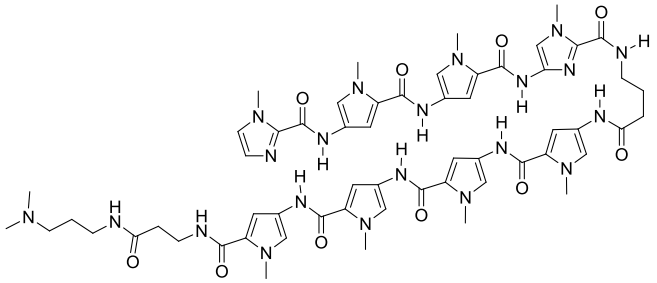
(18b)

Resin-bound tetramer (**8**) (20 mg; 5.2 µmol) was swollen in DMF for 2 hours. The resin was then drained and washed three times with DMF. The tetramer (**14**) (10 mg; 20.3 µmol) was pre-activated with HATU (7 mg; 18.4 µmol) and DIEA (50 µL; 0.3mmol) in DMF (600 µL) for 30 minutes before being added to the resin, and then shaken for 4 hours. The reaction mixture was then drained from the vessel and the resin washed three times with DMF, then DCM, then twice with methanol before being flushed with nitrogen for 5 minutes. Crude (**18b**) was cleaved from the resin using N^1,N^1-dimethylpropane-1,3-diamine (500 µL) under standard cleavage conditions and the resulting crude product was found to be 88 % pure by HPLC at 310 nm (Figure S11). This was purified by semi-preparative HPLC to give the product as a fluffy white solid (1.9 mg; 30 % recovery).

Analytical HPLC t_r = 14.4 minutes.

HRMS (ESI +ve mode) 1222.5771 calculated for $C_{58}H_{72}N_{21}O_{10}^+$ $[M+H]^+$, found 1222.5734.

5.6.4 Synthesis of polyamide (19b)



(19b)

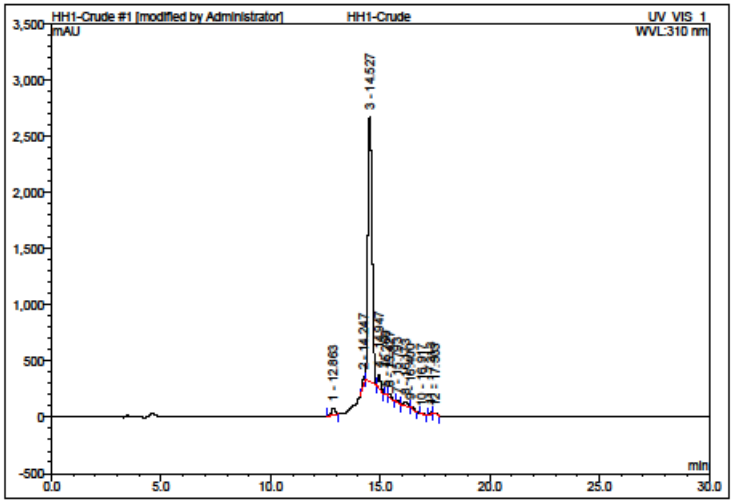
Resin-bound tetramer (**8**) (20 mg; 5.2 μmol) was swollen in DMF for 2 hours. The resin was then drained and washed three times with DMF. The tetramer (**15**) (15 mg; 30.4 μmol) was pre-activated with DCC (5 mg; 24.2 μmol) and HOAt (4 mg; 30 μmol) in DMF (600 μL) for 2 hours before being filtered through a cotton wool plug and added to the resin with DIEA (50 μL; 0.3 mmol), and then shaken for 4 hours. The reaction mixture was then drained from the vessel and the resin washed three times with DMF, then DCM, then twice with methanol before being flushed with nitrogen for 5 minutes. Crude (**19b**) was cleaved from the resin with N^1,N^1-dimethylpropane-1,3-diamine (500 μL) under standard cleavage conditions and the resulting crude product was found to be 85 % pure by HPLC at 310 nm (Figure S12). This was purified by semi-preparative HPLC to give the product as a fluffy white solid (1.7 mg; 28 % recovery).

Analytical HPLC t_r = 14.8 minutes.

HRMS (ESI +ve mode) 1222.5771 calculated for $C_{58}H_{72}N_{21}O_{10}^+$ $[M+H]^+$, found 1222.5726.

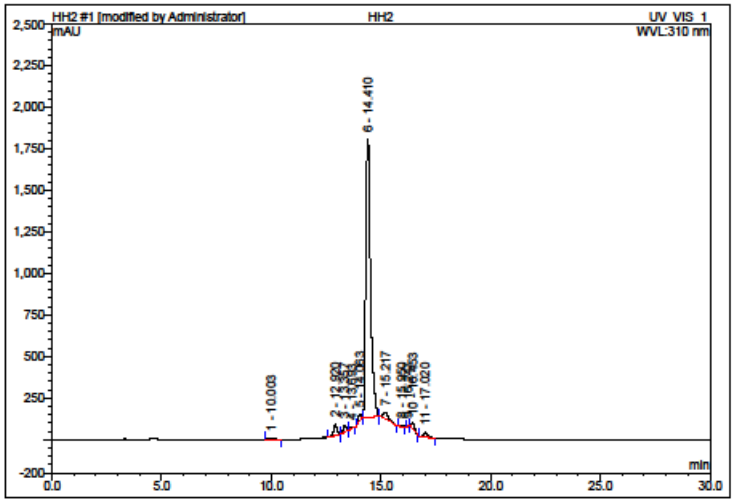
5.7 Characterisation of half-half polyamides

5.7.1 Crude HPLC traces



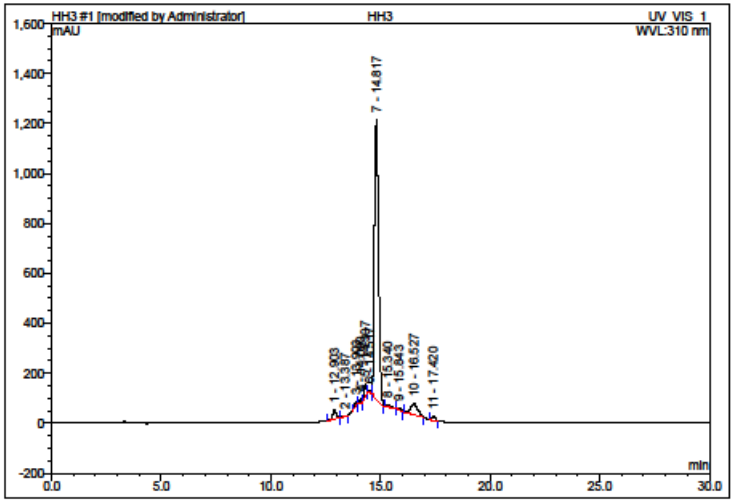
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	12.86	n.a.	63.550	11.939	2.02	n.a.	BMB
2	14.25	n.a.	78.470	9.246	1.57	n.a.	BMb
3	14.53	n.a.	2364.344	531.680	90.14	n.a.	bMB
4	14.95	n.a.	124.296	18.546	3.14	n.a.	BMB
5	15.26	n.a.	6.335	0.570	0.10	n.a.	BMB
6	15.43	n.a.	14.872	2.531	0.43	n.a.	BMB
7	15.79	n.a.	15.845	2.429	0.41	n.a.	BMB
8	16.17	n.a.	31.638	6.139	1.04	n.a.	BMB
9	16.40	n.a.	0.345	1.994	0.34	n.a.	BMB
10	16.92	n.a.	8.358	1.203	0.20	n.a.	BMB
11	17.31	n.a.	17.178	2.268	0.38	n.a.	BMb
12	17.50	n.a.	8.331	1.274	0.22	n.a.	bMB
Total:			2733.561	589.819	100.00	0.000	

Figure S10: Crude HPLC trace of (**17b**).



No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	10.00	n.a.	9.004	2.563	0.53	n.a.	BMB
2	12.92	n.a.	67.478	12.740	2.64	n.a.	BMB
3	13.36	n.a.	38.717	6.607	1.37	n.a.	BMb*
4	13.69	n.a.	10.219	1.729	0.36	n.a.	bMB
5	14.06	n.a.	34.156	5.979	1.24	n.a.	BMb
6	14.41	n.a.	1670.592	425.407	88.02	n.a.	bMb
7	15.22	n.a.	39.451	12.941	2.68	n.a.	bMB
8	15.95	n.a.	10.618	1.869	0.39	n.a.	BMB
9	16.25	n.a.	8.949	1.022	0.21	n.a.	BMb
10	16.45	n.a.	42.506	6.602	1.37	n.a.	bMB
11	17.02	n.a.	25.982	5.836	1.21	n.a.	BMB
Total:			1957.673	483.295	100.00	0.000	

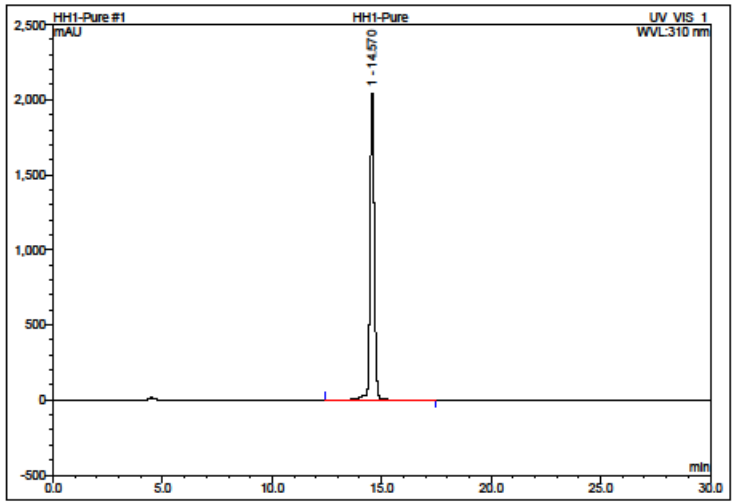
Figure S11: Crude HPLC trace of (**18b**).



No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	12.90	n.a.	35.705	6.830	2.43	n.a.	BMB
2	13.39	n.a.	2.779	0.575	0.20	n.a.	BMB
3	13.90	n.a.	16.160	2.785	0.99	n.a.	BMb*
4	14.09	n.a.	16.399	1.534	0.55	n.a.	bMB
5	14.31	n.a.	53.190	6.219	2.21	n.a.	BMb
6	14.52	n.a.	10.414	0.904	0.32	n.a.	bMB
7	14.82	n.a.	1119.056	238.907	85.03	n.a.	BMB
8	15.34	n.a.	11.442	2.567	0.91	n.a.	BMB
9	15.84	n.a.	5.010	1.032	0.37	n.a.	BMB
10	16.53	n.a.	44.909	17.033	6.06	n.a.	BMB
11	17.42	n.a.	14.810	2.569	0.91	n.a.	BMB
Total:			1329.874	280.954	100.00	0.000	

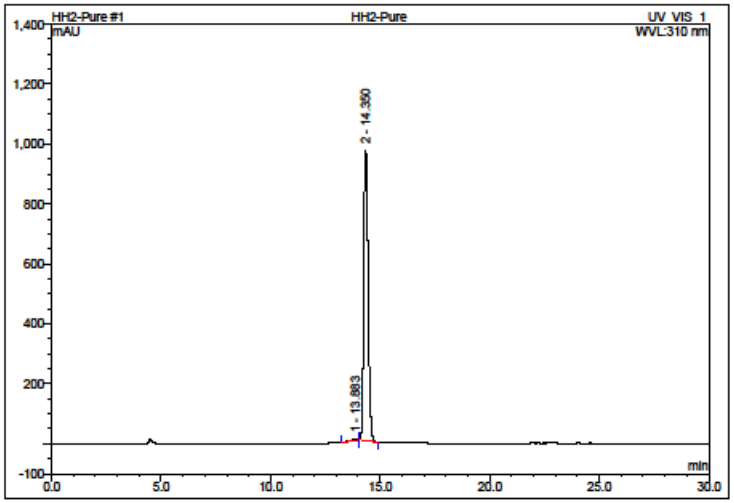
Figure S12: Crude HPLC trace of (**19b**).

5.7.2 Analytical HPLC traces of polyamides purified by semi-preparative HPLC



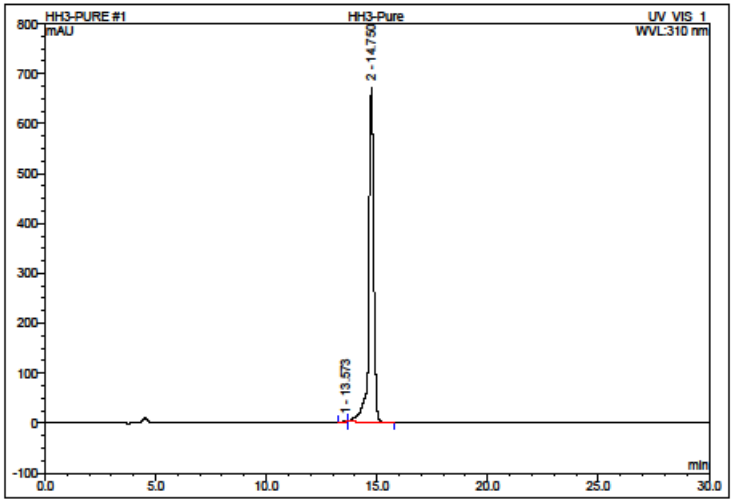
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	14.57	n.a.	2042.803	464.128	100.00	n.a.	BMB
Total:			2042.803	464.128	100.00	0.000	

Figure S13: Pure HPLC trace of (**17b**).



No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	13.88	n.a.	3.583	1.420	0.62	n.a.	BMb
2	14.35	n.a.	966.215	227.542	99.38	n.a.	bMB
Total:			969.798	228.962	100.00	0.000	

Figure S14: Pure HPLC trace of (**18b**).



No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	13.57	n.a.	0.654	0.122	0.07	n.a.	BMb
2	14.75	n.a.	670.697	174.333	99.93	n.a.	bMB
Total:			671.351	174.455	100.00	0.000	

Figure S15: Pure HPLC trace of (**19b**).

5.7.3 HRMS data of crude polyamides 17b-19b.

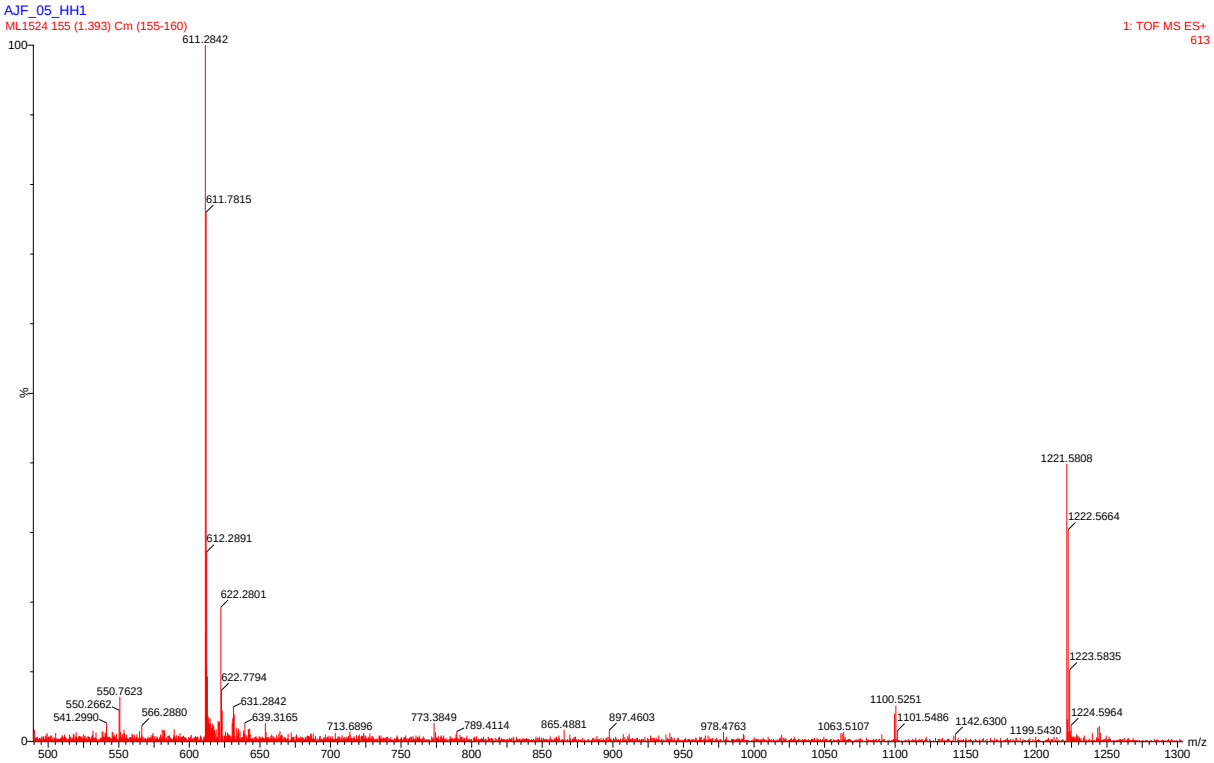


Figure S16: HRMS for (**17b**). Key peaks shown are $[M+H]^+$ at 1221.808, $[M+2H]^{2+}$ at 611.2842, $[M+H+Na]^{2+}$ at 622.2801.

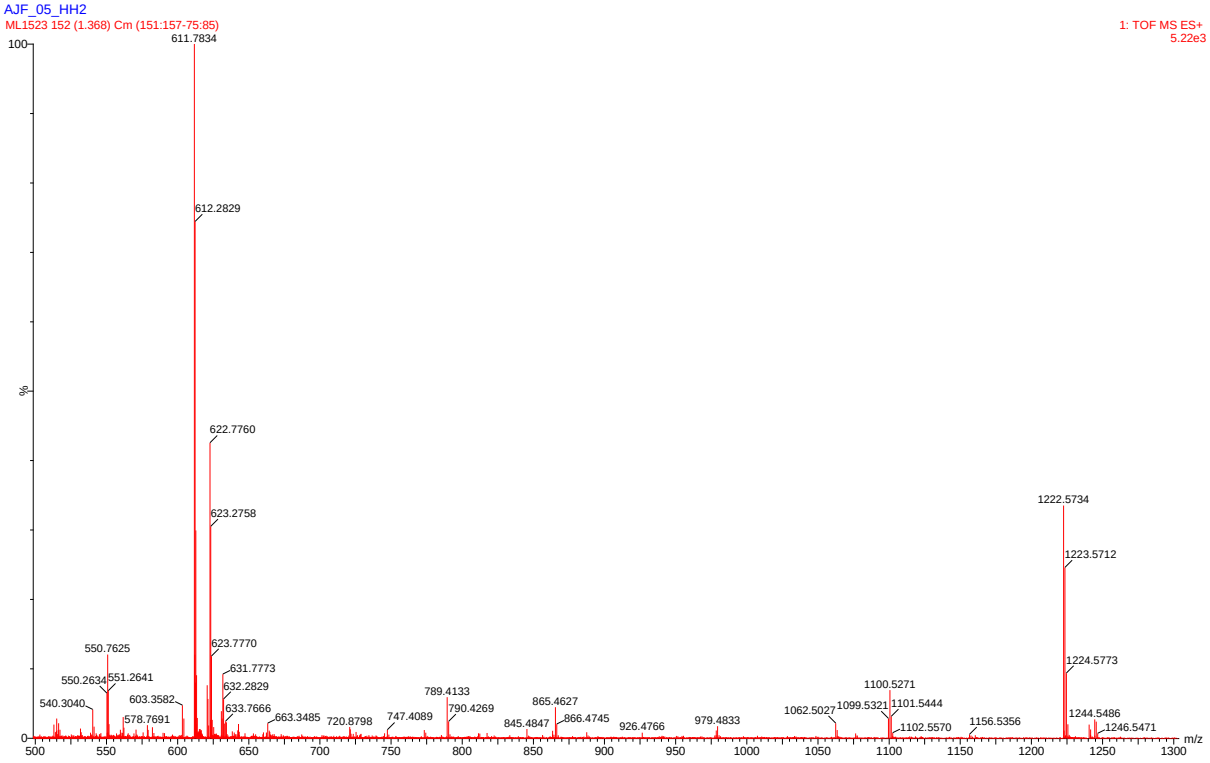


Figure S17: HRMS of (**18b**). Key peaks shown are $[M+H]^+$ at 1222.5734, $[M+2H]^{2+}$ at 611.7834, $[M+H+Na]^{2+}$ at 622.7760.

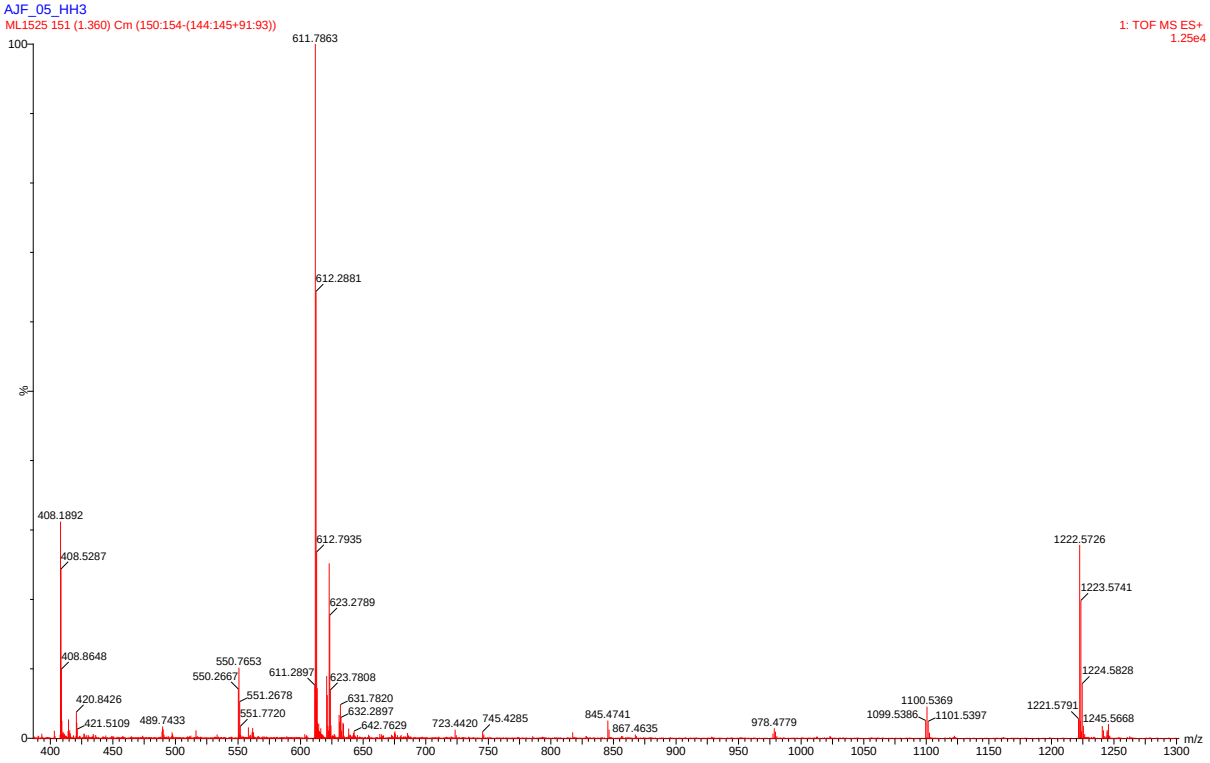
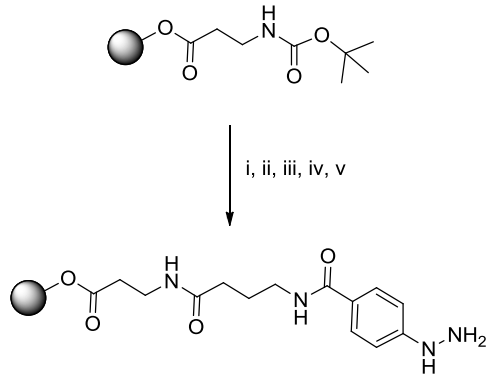


Figure S18: HRMS of (**19b**). Key peaks shown are $[M+H]^+$ at 1222.5726, $[M+2H]^{2+}$ at 611.7863, $[M+3H]^{3+}$ at 408.1892.

5.8 Synthesis of polyamides using a hydrazine linker

5.8.1 Resin Preparation

The preparation of Boc-β-ala PAM resin is outlined in Scheme S5. The resin bound amine was deprotected through treatment with TPW solution for 1 minute, then 5 minutes with fresh reagent, after which GABA (4.0 equivalents) was preactivated with HATU (3.6 equivalents) and DIEA (9 equivalents) in DMF (dry; 1 mL) for 2 minutes before being added to the resin and shaken for 40 minutes at room temperature. The resin was then drained and washed successively with DMF (3x) and DCM (3x) before being swollen in DMF for 5 minutes. The amine was deprotected by treatment with TPW for 1 minute, then 2 x 3 minutes (fresh reagent each time), before being washed with DMF (4x) and dry DMF. The HBA monomer (4.0 equivalents) was preactivated with HATU (3.6 equivalents) and DIEA (9.0 equivalents) in DMF (dry; 1 mL) for 5 minutes, then was added to resin and shaken for 40 minutes. Once drained, the resin was washed again with DMF (4x).

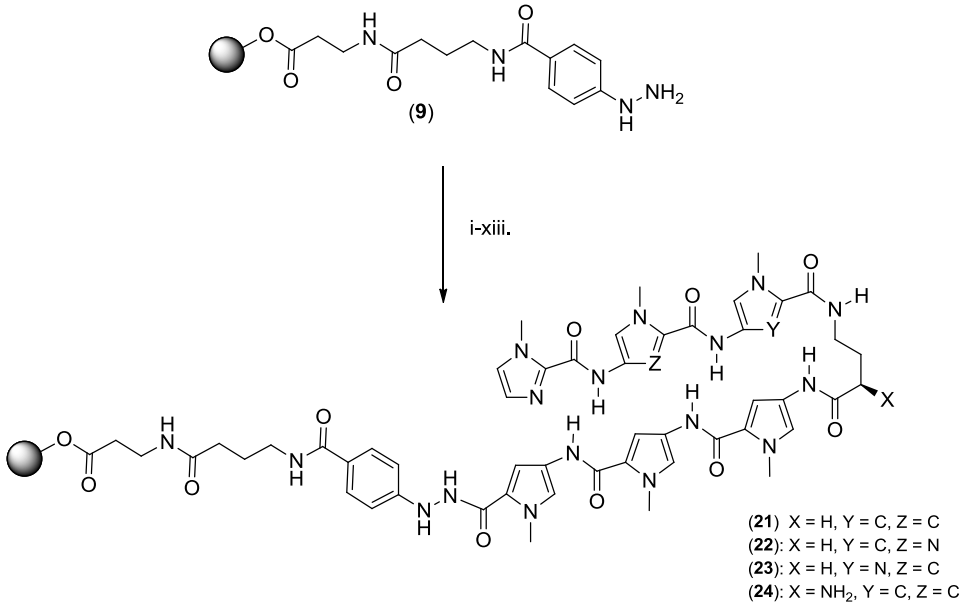


(**9**)

Scheme S5: Preparation of Boc-β-ala PAM resin. (i) TPW; (ii) GABA, HATU, DIEA; (iii) TPW; (iv) HBA, HATU, DIEA; (v) 20 % piperidine in DMF (V/V).

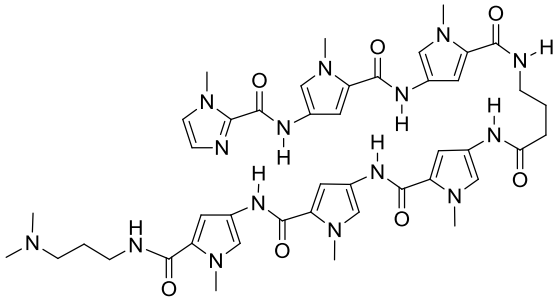
5.8.2 Synthesis of polyamides using the PAM-hydrazine hybrid resin

Polyamides were synthesised using the same activation strategies described earlier in Section 5.4. The initial Fmoc deprotection was carried out by two treatments of shaking with a 20 % piperidine in DMF solution (v/v) for 2 x 10 minutes (fresh reagent each time). The resin was then washed with DMF (4x), then dry DMF. Polyamides (**21-24**) were then synthesised according to Scheme S6.



Scheme S6: Synthesis of PAs **21-24**. Steps (i)-(xiii) are stated in the respective polyamide experimental.

*5.8.2.1 Synthesis of (**21**)*



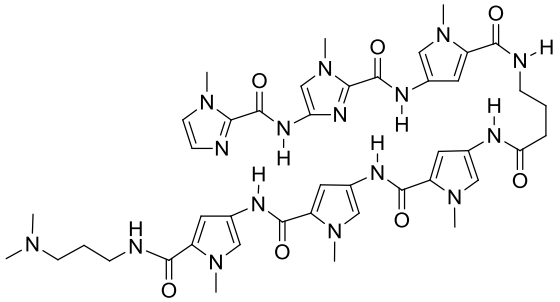
(21)

Polyamide (**21**) was synthesised on 50 mg of resin (**9**) as shown in Scheme S6 using the following reagents and times: (i) BocPyOH, HATU, DIEA, 40 minutes; (ii) TPW; (iii) BocPyOH, HATU, DIEA, 40 minutes; (iv) TPW; (v) BocPyOH, HATU, DIEA, 40 minutes; (vi) TPW; (vii) GABA, HATU, DIEA, 60 minutes; (viii) TPW; (ix) BocPyOH, HATU, DIEA, 60 minutes; (x) TPW; (xi) BocPyOH, HATU, DIEA, 90 minutes; (xii) TPW; (xiii) ImOH, DCC/HOAt, DIEA, 60 minutes. This was cleaved from the resin under standard cleavage conditions to give the crude material in 68 % purity. After purification by semi-preparative HPLC the pure material was isolated as a fluffy white solid (1.3 mg; 11 % recovery).

Analytical HPLC t_r = 13.6 minutes.

HRMS (ESI+) 906.4487 calculated for $C_{44}H_{56}N_{15}O_7^+$, $[M+H]^+$, found 906.4487.

*5.8.2.2 Synthesis of (**22**)*



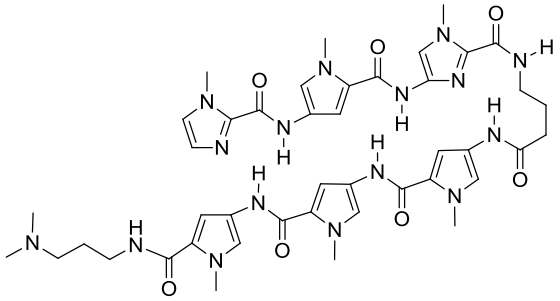
(22)

Polyamide (**22**) was synthesised on 50 mg of resin (**9**) (Scheme S6) using the following reagents and times: (i) BocPyOH, HATU, DIEA, 40 minutes; (ii) TPW; (iii) BocPyOH, HATU, DIEA, 40 minutes; (iv) TPW; (v) BocPyOH, HATU, DIEA, 40 minutes; (vi) TPW; (vii) GABA, HATU, DIEA, 60 minutes; (viii) TPW; (ix) BocPyOH, HATU, DIEA, 60 minutes; (x) TPW; (xi) BocImOH, DCC/HOAt, DIEA, 60 minutes; (xii) TPW; (xiii) ImOH, DCC/HOAt, DIEA, 60 minutes. This was cleaved under standard cleavage conditions to give the crude material in 70 % purity by HPLC at 310 nm. After purification by semi-preparative HPLC the pure material was isolated as a fluffy white solid (1.3 mg; 11 % recovery).

Analytical HPLC t_r = 14.0 minutes.

HRMS (ESI+) 907.4440 calculated for $C_{43}H_{55}N_{16}O_7^+$, $[M+H]^+$, found 907.4456.

*5.8.2.3 Synthesis of (**23**)*



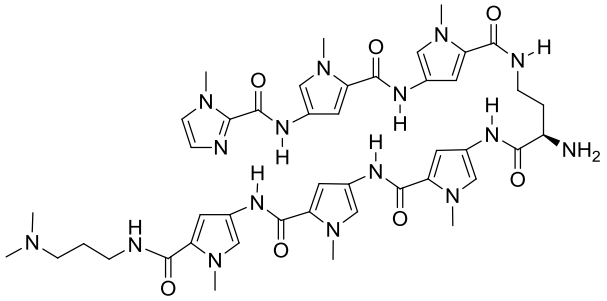
(23)

Polyamide (**23**) was synthesised on 50 mg of resin (**9**) (Scheme S6) using the following reagents and times: (i) BocPyOH, HATU, DIEA, 40 minutes; (ii) TPW; (iii) BocPyOH, HATU, DIEA, 40 minutes; (iv) TPW; (v) BocPyOH, HATU, DIEA, 40 minutes; (vi) TPW; (vii) GABA, HATU, DIEA, 60 minutes; (viii) TPW; (ix) BocImOH, DCC/HOAt, DIEA, 60 minutes; (x) TPW; (xi) BocPyOH, BTC/collidine, DIEA, 90 minutes; (xii) TPW; (xiii) ImOH, DCC/HOAt, DIEA, 60 minutes. This was cleaved under standard cleavage conditions to give the crude material in 74 % purity by HPLC at 310 nm. After purification by semi-preparative HPLC the pure material was isolated as a fluffy white solid (1.4 mg; 12 % recovery).

Analytical HPLC t_r = 13.3 minutes.

HRMS (ESI +ve mode) 907.4440 calculated for $C_{43}H_{55}N_{16}O_7^+$, $[M+H]^+$, found 907.4449.

*5.8.2.4 Synthesis of (**24**)*



(24)

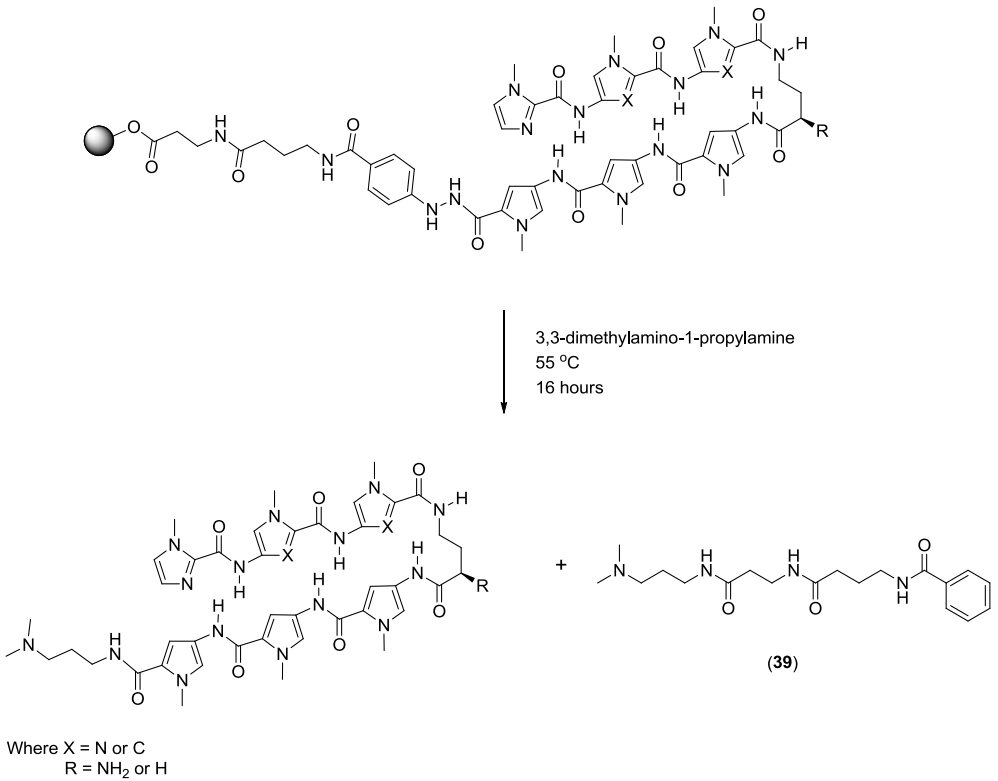
Polyamide (**24**) was synthesised on 50 mg of resin (**9**) (Scheme S6) using the following reagents and times: (i) BocPyOH, HATU, DIEA, 40 minutes; (ii) TPW; (iii) BocPyOH, HATU, DIEA, 40 minutes; (iv) TPW; (v) BocPyOH, HATU, DIEA, 40 minutes; (vi) TPW; (vii) Fmoc-D-Dab(Boc)-OH, HATU, DIEA, 60 minutes; (viii) TPW; (ix) BocPyOH, HATU, DIEA, 60 minutes; (x) TPW; (xi) BocPyOH, HATU, DIEA, 90 minutes; (xii) TPW; (xiii) ImOH, DCC/HOAt, DIEA, 60 minutes. This was cleaved under standard cleavage conditions to give the crude material in 79 % purity by HPLC at 310 nm. After purification by semi-preparative HPLC the pure material was isolated as a fluffy white solid (1.6 mg; 13 % recovery).

Analytical HPLC t_r = 12.1 minutes.

HRMS (ESI +ve mode) 921.4596 calculated for $C_{44}H_{57}N_{16}O_7^+$, $[M+H]^+$, found 921.4561.

5.8.3 Cleavage of polyamides using the hydrazine resin

Polyamides (**21-24**) were cleaved from the resin under standard cleavage conditions and found to yield only the shortened polyamide through cleavage at the hydrazide (Scheme S7). The tail was also found to cleave from the resin under these conditions to give compound (**39**) shown in Scheme S7 which was characterised by HRMS (363.2396 calculated for $C_{19}H_{31}N_4O_3^+$ $[M+H]^+$, found 363.2400 - Figure S19). This confirmed that oxidation of the hydrazinyl group prior to resin cleavage was not essential in order to obtain the shortened polyamide.



Scheme S7: Illustration of products resulting from cleavage of hydrazine resin.

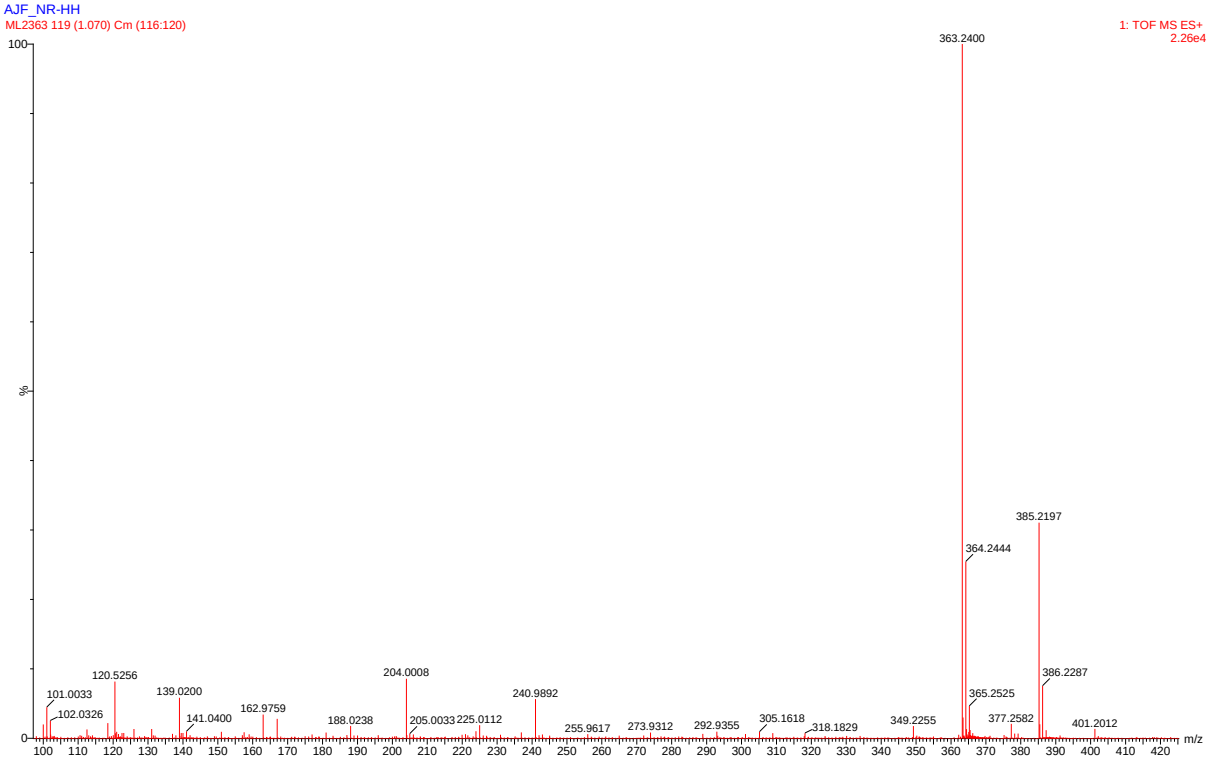
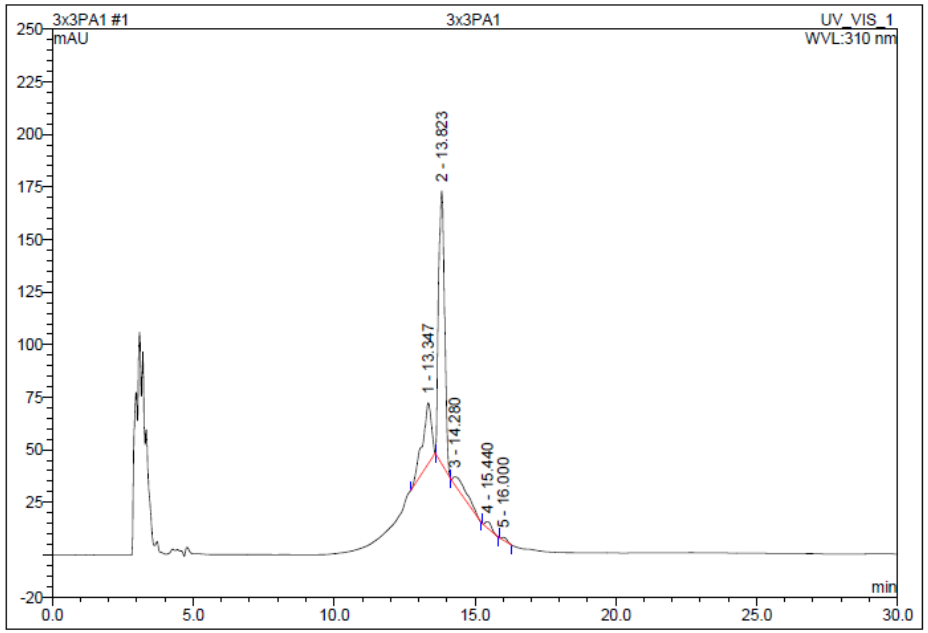


Figure S19: MS of cleavage by-product (**39**). Key peaks shown are $[M+H]^+$ at 363.2400, $[M+Na]^+$ at 385.2197.

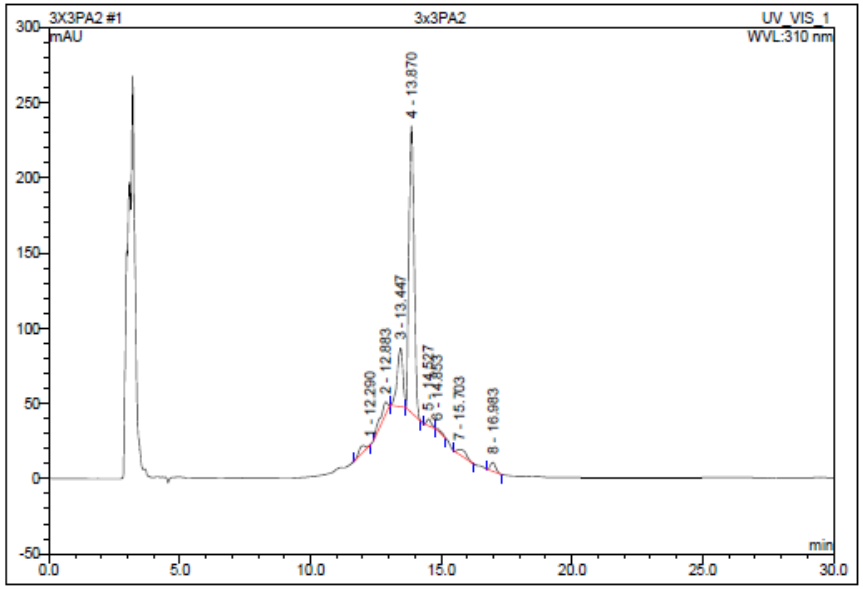
5.9 HPLC analysis and purification of polyamides prepared on the hydrazine hybrid resin

5.9.1 Crude HPLC traces of polyamides (21-24)



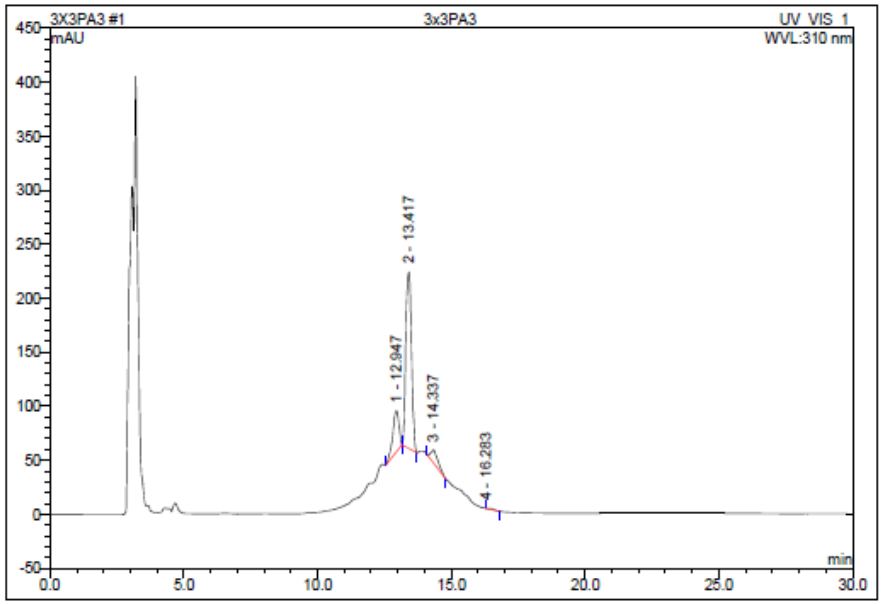
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	13.35	n.a.	28.905	10.746	22.69	n.a.	BMb
2	13.82	n.a.	129.914	32.087	67.76	n.a.	bMB
3	14.28	n.a.	3.731	3.384	7.15	n.a.	BMB
4	15.44	n.a.	2.958	0.804	1.70	n.a.	BMB
5	16.00	n.a.	1.237	0.335	0.71	n.a.	BMB
Total:			166.746	47.356	100.00	0.000	

Figure S20: Crude HPLC trace of (**21**).



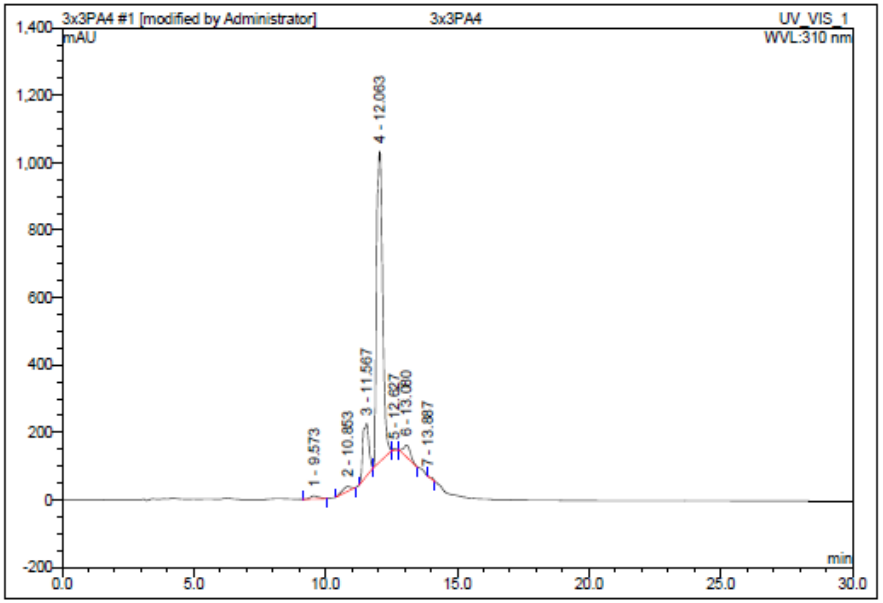
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	12.29	n.a.	0.000	1.364	2.21	n.a.	BMB
2	12.88	n.a.	7.986	3.110	5.04	n.a.	BMb
3	13.45	n.a.	38.907	9.712	15.72	n.a.	bMb
4	13.87	n.a.	190.527	43.410	70.28	n.a.	bMB
5	14.53	n.a.	4.510	0.912	1.48	n.a.	BMB
6	14.85	n.a.	0.934	0.318	0.51	n.a.	BMB
7	15.70	n.a.	3.275	1.575	2.55	n.a.	BMB
8	16.98	n.a.	5.969	1.362	2.21	n.a.	BMB
Total:			252.107	61.764	100.00	0.000	

Figure S21: Crude HPLC trace of (**22**).



No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	12.95	n.a.	38.087	10.170	18.59	n.a.	BMb
2	13.42	n.a.	163.592	40.583	74.19	n.a.	bMB
3	14.34	n.a.	12.016	3.754	6.86	n.a.	BMB
4	16.28	n.a.	0.001	0.196	0.36	n.a.	BMB
Total:			213.697	54.702	100.00	0.000	

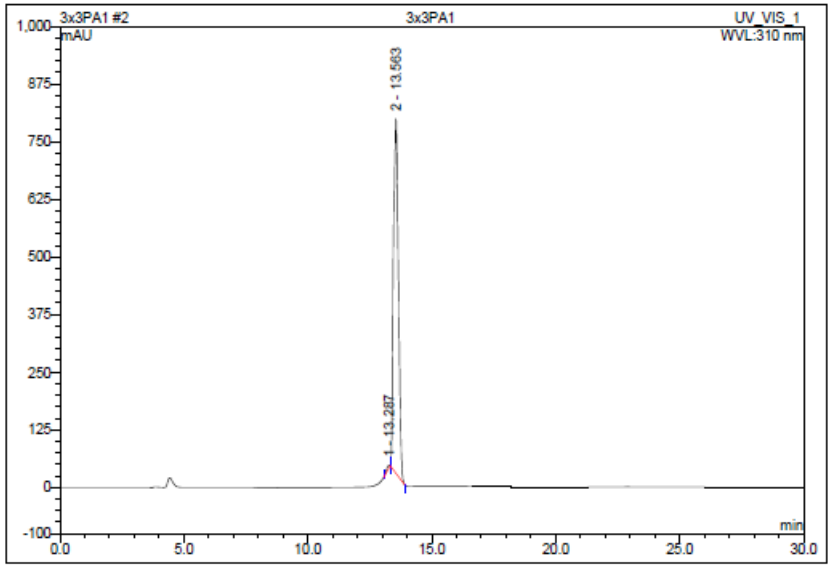
Figure S22: Crude HPLC trace of (**23**).



No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	9.57	n.a.	9.043	3.374	1.09	n.a.	BMB
2	10.85	n.a.	14.942	5.699	1.85	n.a.	BMB
3	11.57	n.a.	155.360	41.977	13.61	n.a.	BMb*
4	12.06	n.a.	920.604	245.036	79.47	n.a.	bMb*
5	12.63	n.a.	5.028	0.672	0.22	n.a.	bMb
6	13.08	n.a.	35.035	10.993	3.57	n.a.	bMB
7	13.89	n.a.	0.003	0.581	0.19	n.a.	BMB
Total:			1140.015	308.333	100.00	0.000	

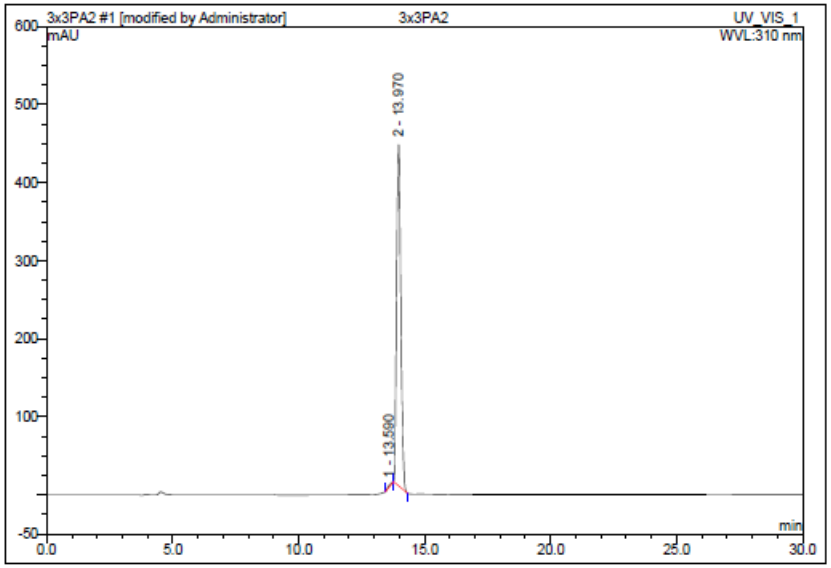
Figure S23: Crude HPLC trace of (**24**).

5.9.2 HPLC traces of polyamides (21-24) after semi-preparative HPLC purification



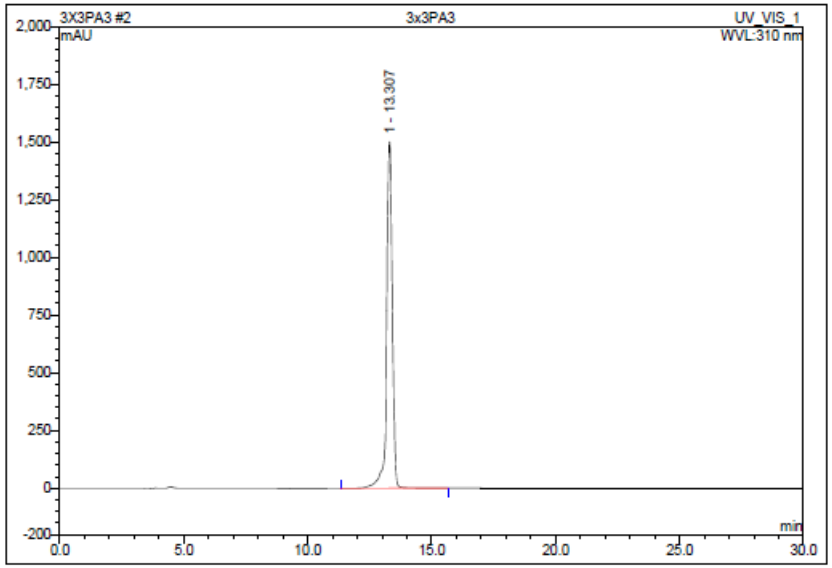
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	13.29	n.a.	5.288	1.200	0.67	n.a.	BMb
2	13.56	n.a.	768.649	177.340	99.33	n.a.	bMB
Total:			773.937	178.540	100.00	0.000	

Figure S24: Pure HPLC trace of (**21**).



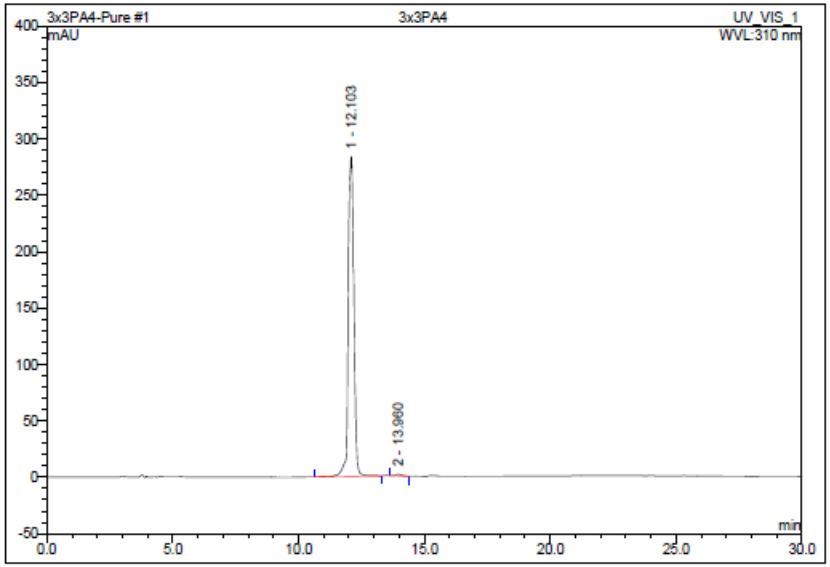
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	13.59	n.a.	2.446	0.436	0.51	n.a.	BMb*
2	13.97	n.a.	436.836	85.026	99.49	n.a.	bMB*
Total:			439.283	85.462	100.00	0.000	

Figure S25: Pure HPLC trace of (**22**).



No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	13.31	n.a.	1500.087	400.172	100.00	n.a.	BMB
Total:			1500.087	400.172	100.00	0.000	

Figure S26: Pure HPLC trace of (**23**).



No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	12.10	n.a.	283.566	73.475	99.52	n.a.	BMB
2	13.96	n.a.	1.404	0.353	0.48	n.a.	BMB
Total:			284.970	73.828	100.00	0.000	

Figure S27: Pure HPLC trace of (**24**).

5.9.3 Crude HRMS data of polyamides (21-24)

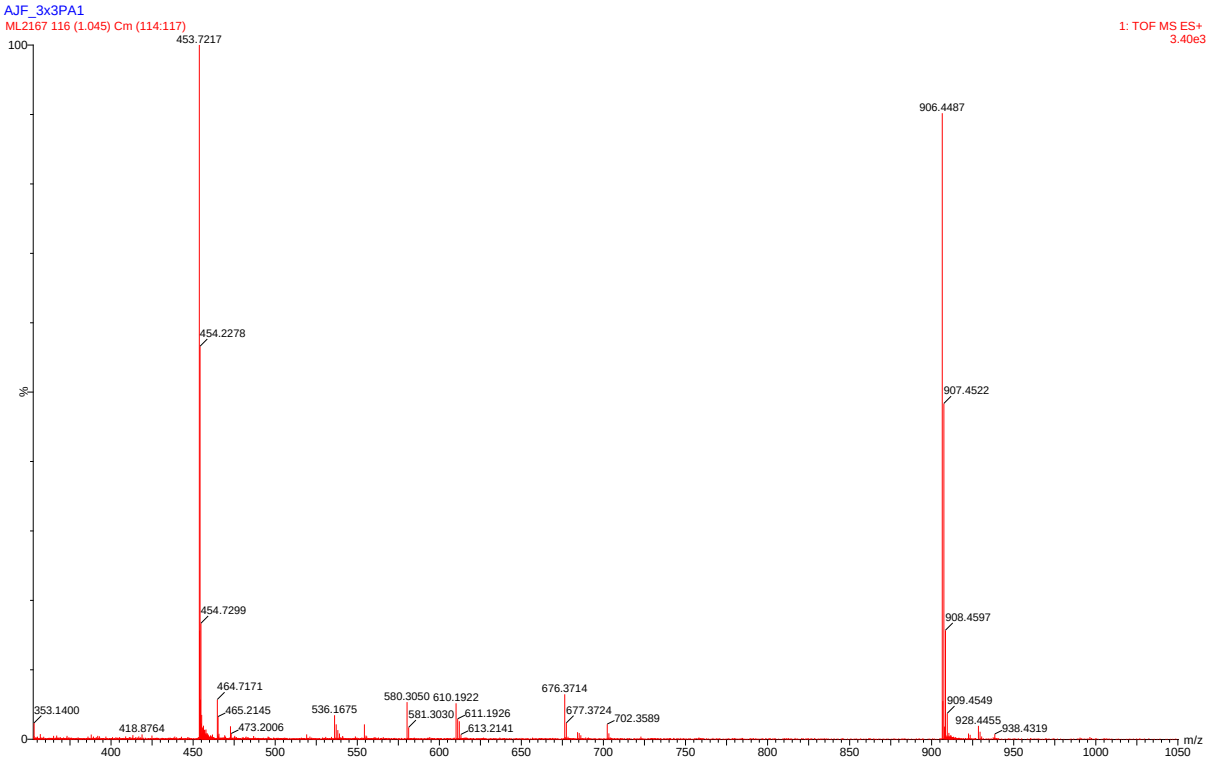


Figure S28: HRMS of (**21**). Key peaks shown are $[M+H]^+$ at 906.4487, $[M+2H]^{2+}$ at 453.7217.

Figure S29: HRMS of (**22**). Key peaks shown are $[M+H]^+$ at 907.4456, $[M+2H]^{2+}$ at 454.2199.

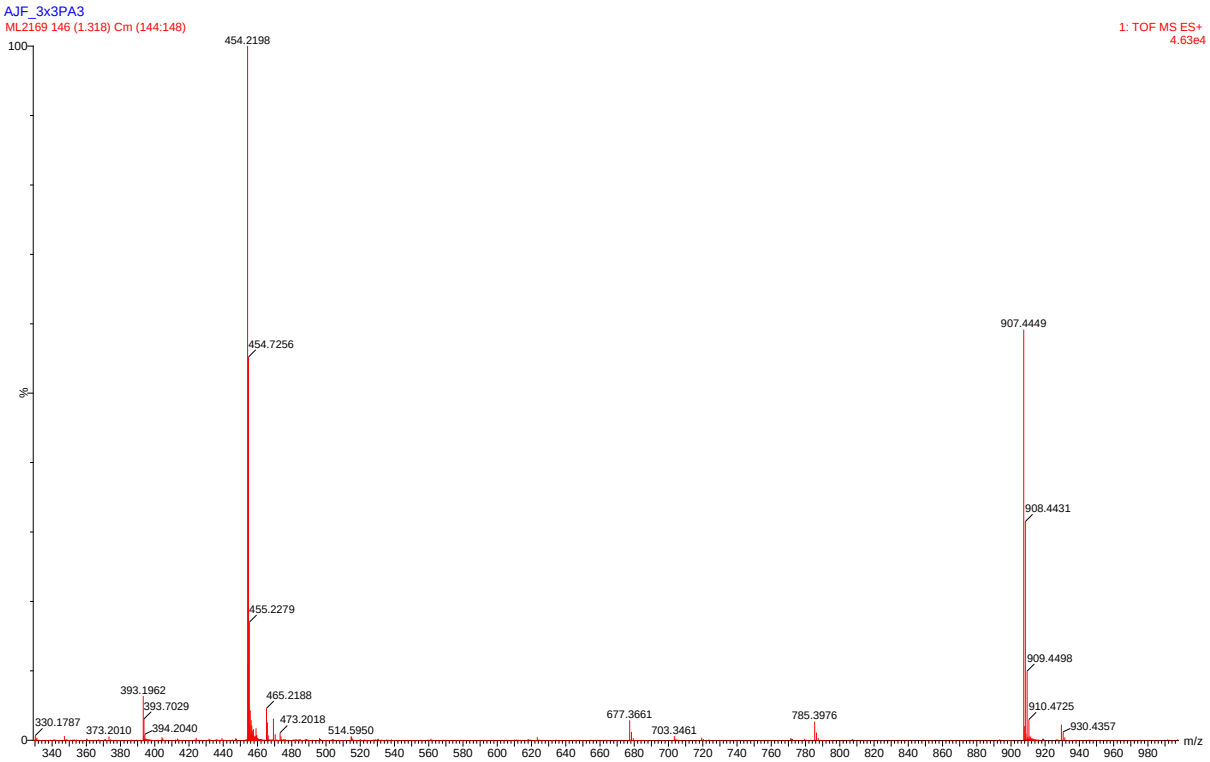


Figure S30: HRMS of (**23**). Key peaks shown are $[M+H]^+$ at 907.4449, $[M+2H]^{2+}$ at 454.2198.

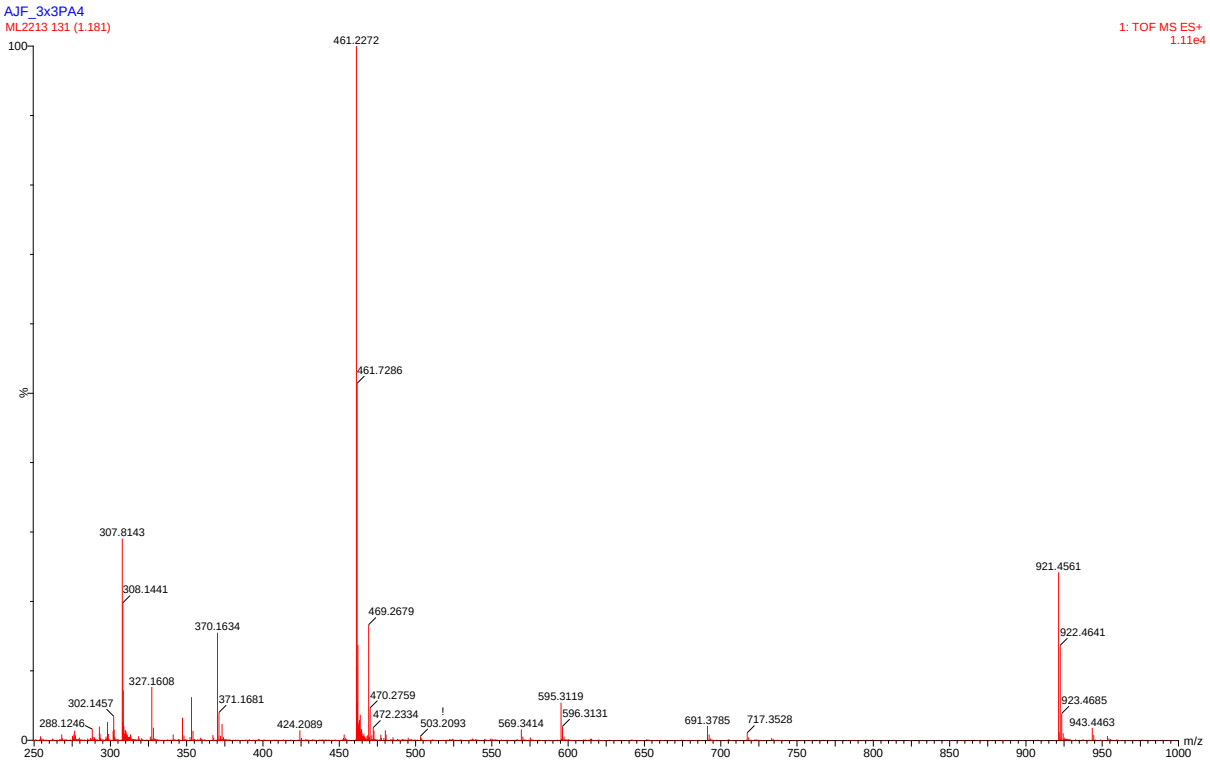
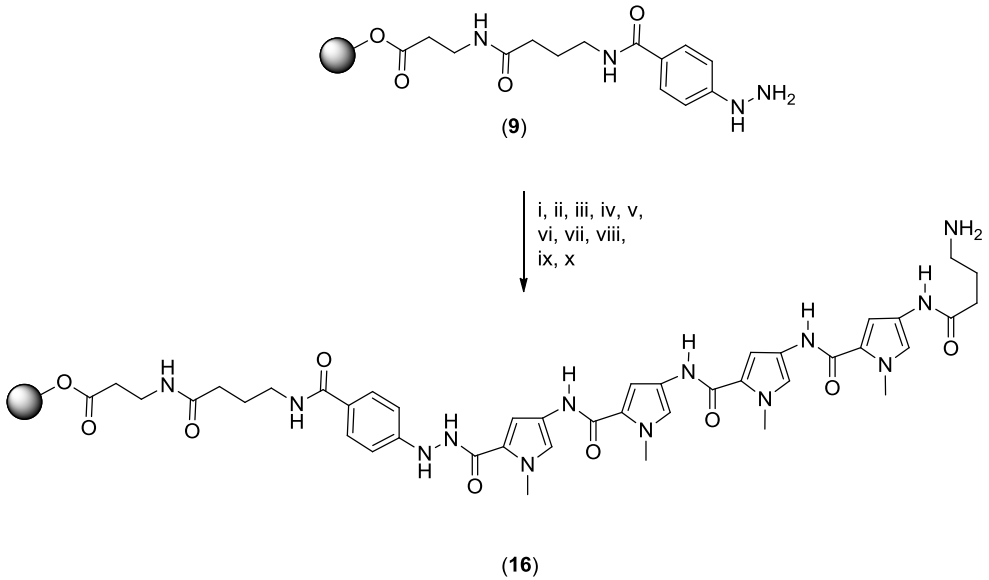


Figure S31: HRMS of (**24**). Key peaks shown are $[M+H]^{+}$ at 921.4561, $[M+2H]^{2+}$ at 461.2272, $[M+3H]^{3+}$ at 307.8143.

5.10 Preparation of polyamides using the half-half coupling method on the hydrazine resin

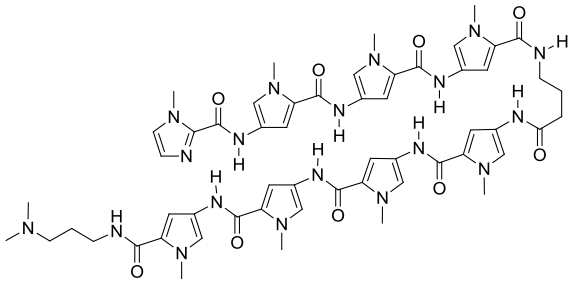
5.10.1 Preparation of resin-bound tetramer (16)

The resin bound tetramer was synthesised as in Scheme S8, utilising a hydrazine resin (Scheme S5).



Scheme S8: Synthesis of polyamide tetramer on new resin. (i) BocPyOH, HATU, DIEA, 40 minutes; (ii) TPW; (iii) BocPyOH, HATU, DIEA, 40 minutes; (iv) TPW; (v) BocPyOH, HATU, DIEA, 40 minutes; (vi) TPW; (vii) BocPyOH, HATU, DIEA, 60 minutes; (viii)TPW; (ix) GABA, HATU, DIEA, 60 minutes; (x) TPW.

5.10.2 Synthesis of (20)

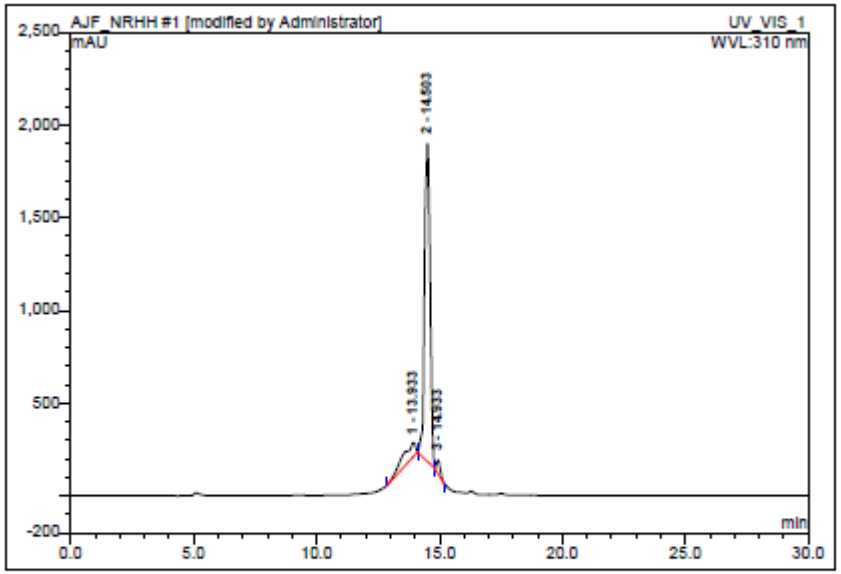


Resin-bound tetramer (**16**) (20 mg; 5.2 μmol, Scheme S8) was swollen in DMF for 2 hours. The resin was then drained and washed three times with DMF. The tetramer (**13**) (10 mg; 20.3 μmol) was pre-activated with HATU (7 mg; 18.4 μmol) and DIEA (50 μL; 0.3mmol) in DMF (600 μL) for 30 minutes before being added to the resin, and then shaken for 4 hours. The reaction mixture was then drained from the vessel and the resin washed three times with DMF, then DCM, then twice with methanol before being flushed with nitrogen for 5 minutes. Polyamide (**20**) was cleaved from the resin with N^1,N^1-dimethylpropane-1,3-diamine (500 μL) under standard cleavage conditions and the resulting crude product was found to be 87 % pure by HPLC at 310 nm. This was purified by semi-preparative HPLC to give the product as a fluffy white solid (1.2 mg; 20 % recovery).

Analytical HPLC t_r = 14.7 minutes.

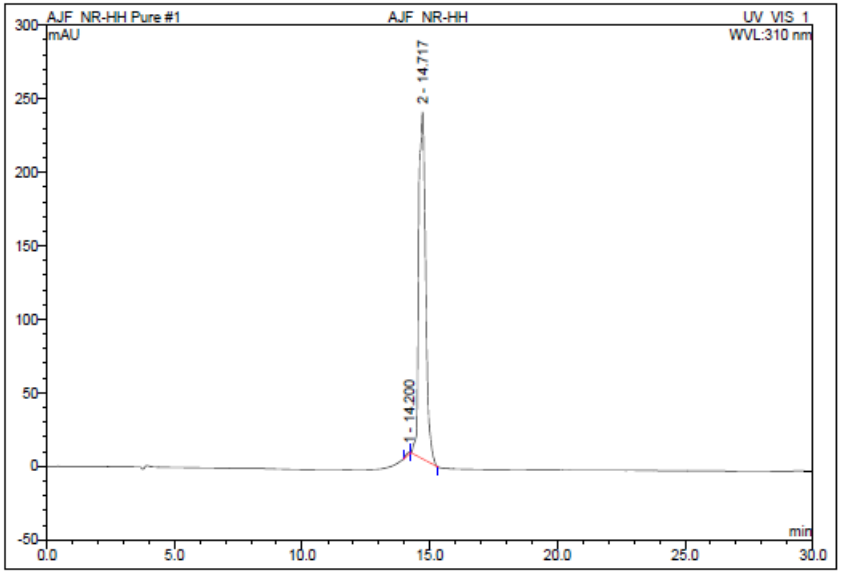
HRMS (ESI+) 1150.5447 calculated for $C_{56}H_{68}N_{19}O_9^+$ $[M+H]^+$, found 1150.5410.

5.11 Characterisation of (20)



No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	13.93	n.a.	75.759	52.581	10.13	n.a.	BMb
2	14.50	n.a.	1716.468	453.502	87.36	n.a.	bMB
3	14.93	n.a.	72.975	13.019	2.51	n.a.	BMB
Total:			1865.202	519.102	100.00	0.000	

Figure S32: Crude HPLC trace of (**20**).



No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	14.20	n.a.	1.219	0.290	0.39	n.a.	BMb
2	14.72	n.a.	235.834	74.061	99.61	n.a.	bMB
Total:			237.053	74.352	100.00	0.000	

Figure S33: Pure HPLC trace of (**20**).

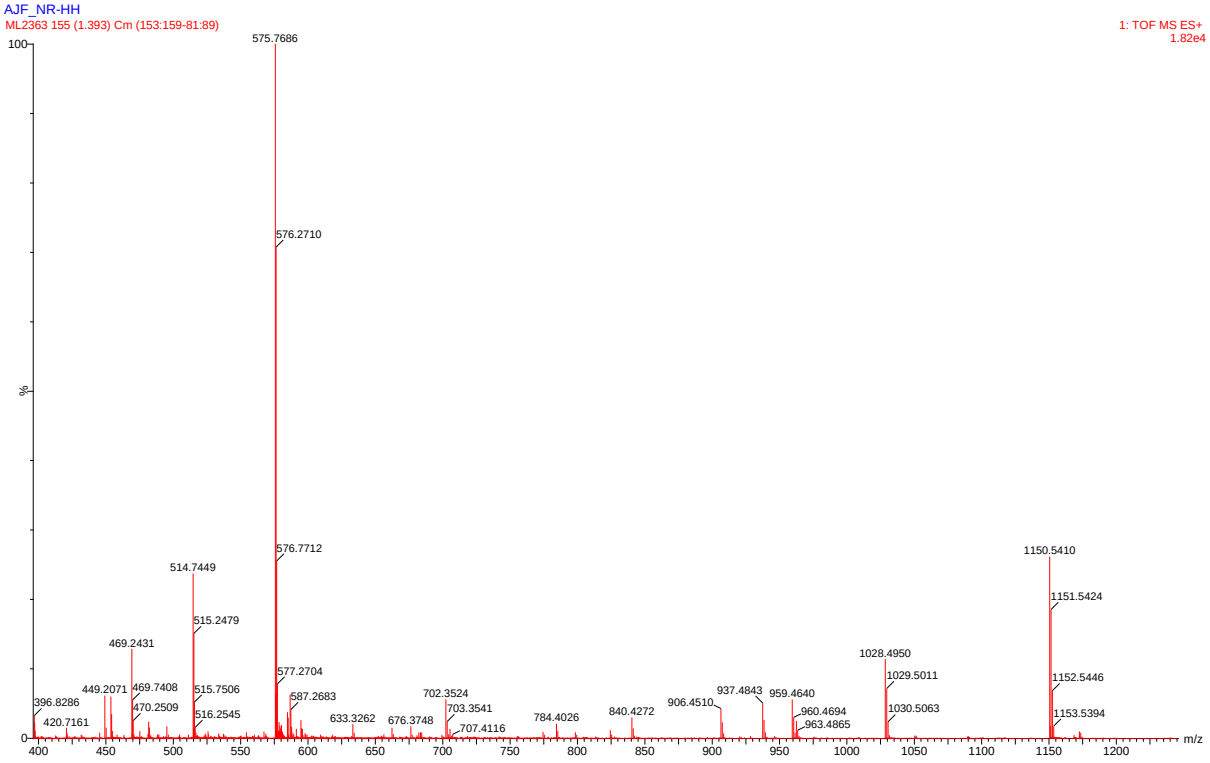
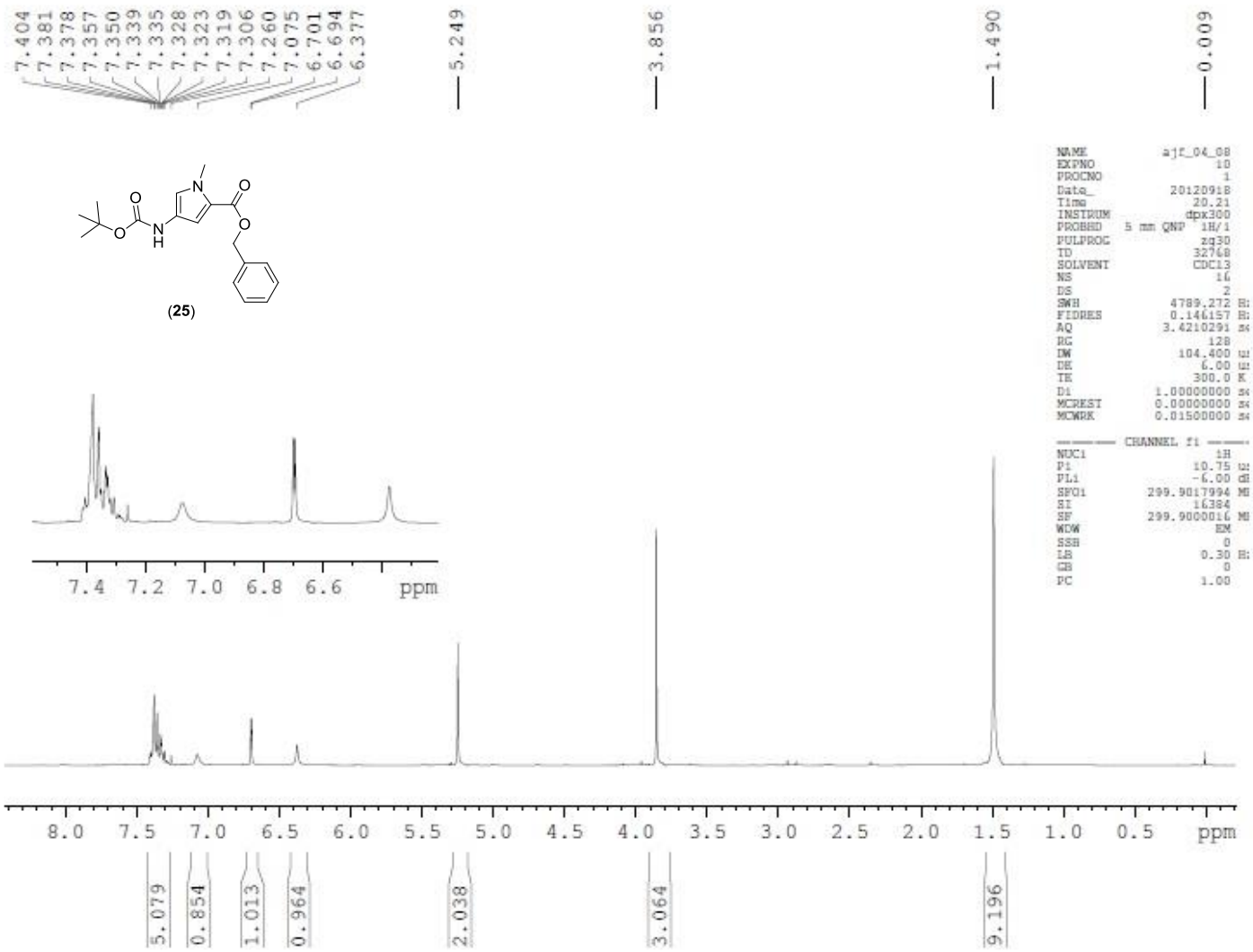


Figure S34: HRMS of crude (**20**). Key peaks shown are $[M+H]^+$ at 1150.5410, $[M+2H]^{2+}$ at 575.7686.

6.0 NMR Spectra



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PROCNO 1
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Time 20.21
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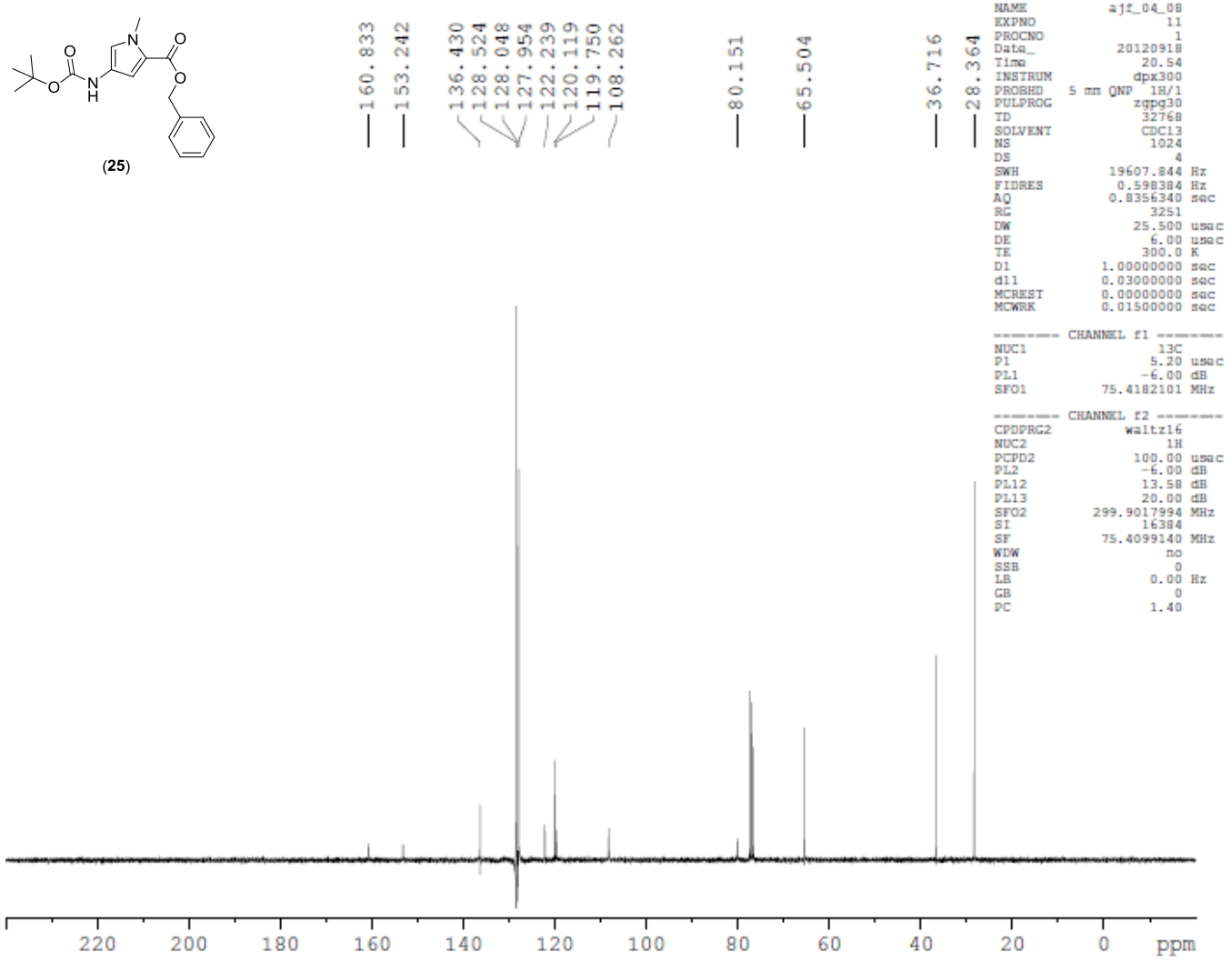
PROBHD 5 mm QNP 1H/1
PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 16
DS 2
SWH 4789.272 Hz
FIDRES 0.146157 Hz
AQ 3.4210291 sec
RG 128
DW 104.400 usec
DE 6.00 usec
TE 300.0 K
D1 1.00000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec
CHANNEL f1
NUC1 1H
P1 10.75 usec
PL1 -6.00 dB
SFO1 299.9017994 MHz
SI 16384
SF 299.9000016 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00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128.524
128.048
127.954
122.239
120.119
119.750
108.262
80.151
65.504
36.716
28.364
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PROCNO 1
Date_ 20120918
Time 20.54
INSTRUM dpx300
PROBHD 5 mm QNP 1H/1
PULPROG zgpg30
TD 32768
SOLVENT CDCl3
NS 1024
DS 4
SWH 19607.844 Hz
FIDRES 0.598384 Hz
AQ 0.8356340 sec
RG 3251
DW 25.500 usec
DE 6.00 usec
TE 300.0 K
D1 1.00000000 sec
d11 0.03000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec
CHANNEL f1
NUC1 13C
P1 5.20 usec
PL1 -6.00 dB
SFO1 75.4182101 MHz
CHANNEL f2
CPDPRG2 waltz16
NUC2 1H
PCPD2 100.00 usec
PL2 -6.00 dB
PL12 13.58 dB
PL13 20.00 dB
SFO2 299.9017994 MHz
SI 16384
SF 75.4099140 MHz
WDW no
SSB 0
LB 0.00 Hz
GB 0
PC 1.40
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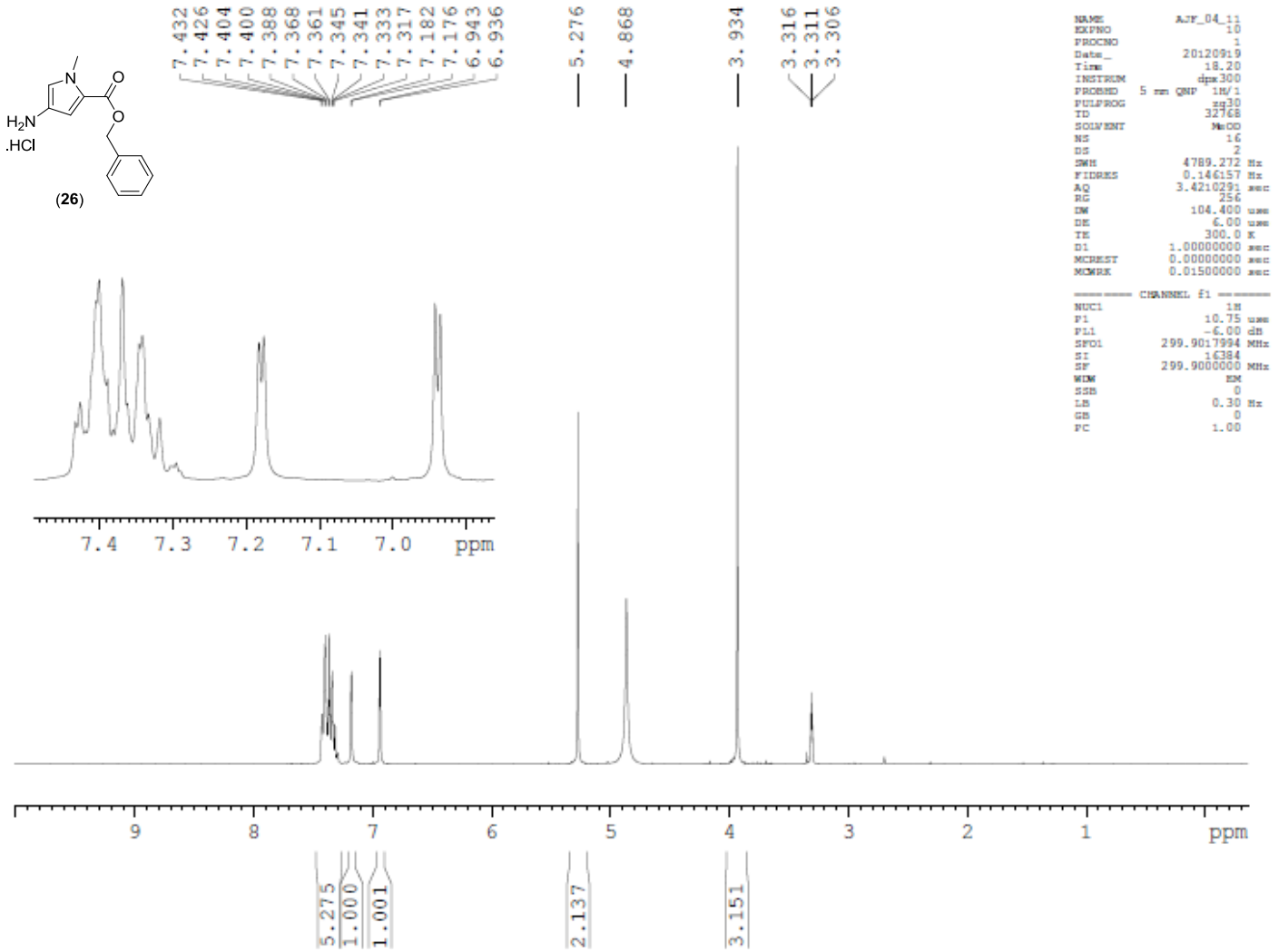
200
180
160
140
120
100
80
60
40
20
0
ppm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7.426
7.404
7.400
7.388
7.368
7.361
7.345
7.341
7.333
7.317
7.182
7.176
6.943
6.936
5.276
4.868
3.934
3.316
3.311
3.306
H_2N
.HCl
(26)
7.4
7.3
7.2
7.1
7.0
ppm
9
8
7
6
5
4
3
2
1
ppm
5.275
1.000
1.001
2.137
3.151
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PROCNO 1
Date_ 20120919
Time 18.20
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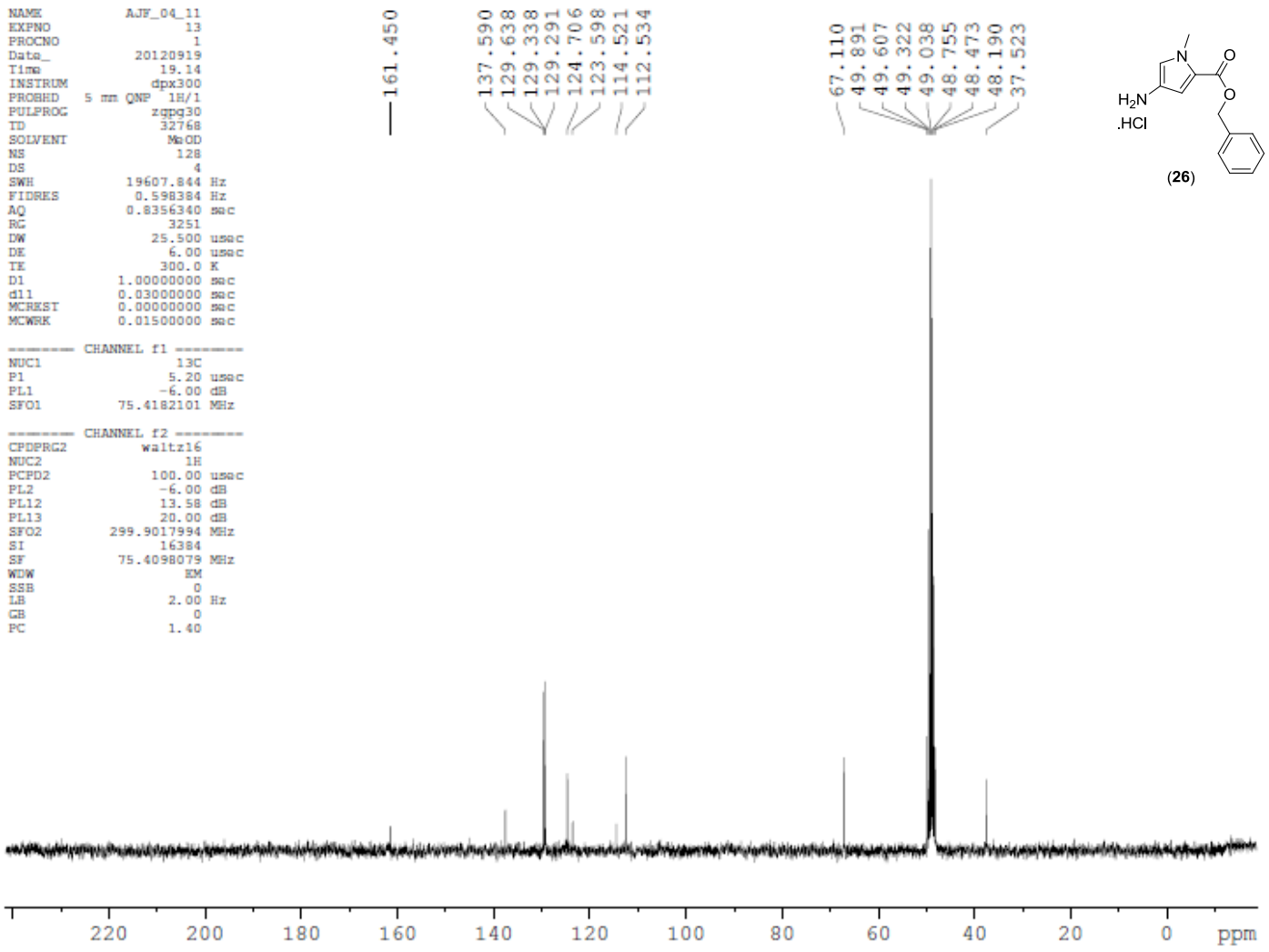
PROBHD 5 mm QNP 1H/1
PULPROG zg30
TD 32768
SOLVENT MeOD
NS 16
DS 2
SWH 4789.272 Hz
FIDRES 0.146157 Hz
AQ 3.4210291 sec
RG 256
DW 104.400 usec
DE 6.00 usec
TE 300.0 K
D1 1.00000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec
CHANNEL f1
NUC1 1H
P1 10.75 usec
PL1 -6.00 dB
SFO1 299.9017994 MHz
SI 16384
SF 299.9000000 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00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PROCNO 1
Date_ 20120919
Time 19.14
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PROBHD 5 mm QNP 1H/1
PULPROG zqpg30
TD 32768
SOLVENT MeOD
NS 128
DS 4
SWH 19607.844 Hz
FIDRES 0.598384 Hz
AQ 0.8356340 sec
RG 3251
DW 25.500 usec
DE 6.00 usec
TE 300.0 K
D1 1.00000000 sec
d11 0.03000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec
CHANNEL f1
NUC1 13C
P1 5.20 usec
PL1 -6.00 dB
SFO1 75.4182101 MHz
CHANNEL f2
CPDPRG2 waltz16
NUC2 1H
PCPD2 100.00 usec
PL2 -6.00 dB
PL12 13.58 dB
PL13 20.00 dB
SFO2 299.9017994 MHz
SI 16384
SF 75.4098079 MHz
WDW EM
SSB 0
LB 2.00 Hz
GB 0
PC 1.40
161.450
137.590
129.638
129.338
129.291
124.706
123.598
114.521
112.534
67.110
49.891
49.607
49.322
49.038
48.755
48.473
48.190
37.523
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O
O
H_2N
.HCl
(26)
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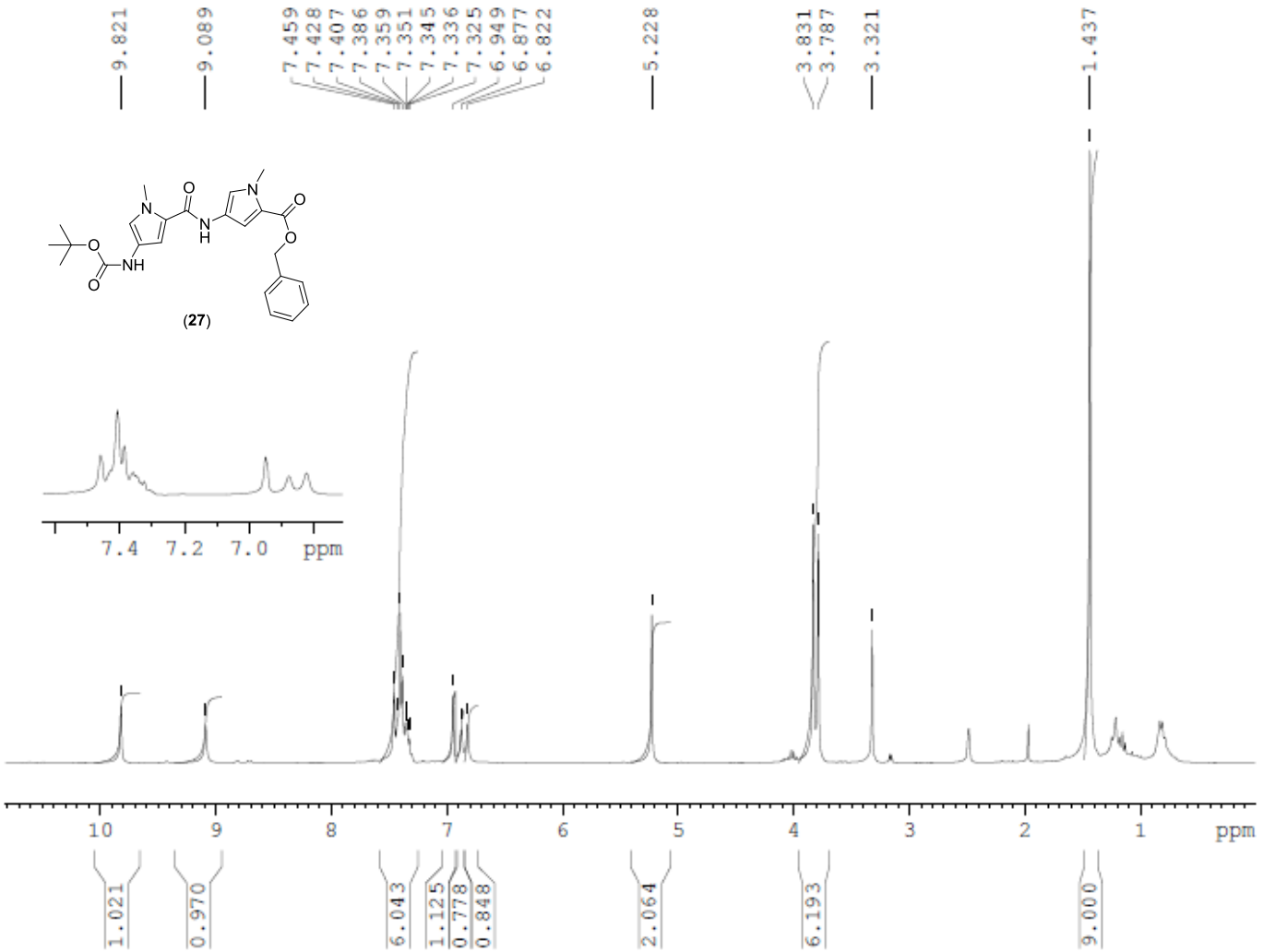
200
180
160
140
120
100
80
60
40
20
0
ppm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7.407
7.386
7.359
7.351
7.345
7.336
7.325
6.949
6.877
6.822
5.228
3.831
3.787
3.321
1.437
(27)
7.4
7.2
7.0
ppm
10
9
8
7
6
5
4
3
2
1
ppm
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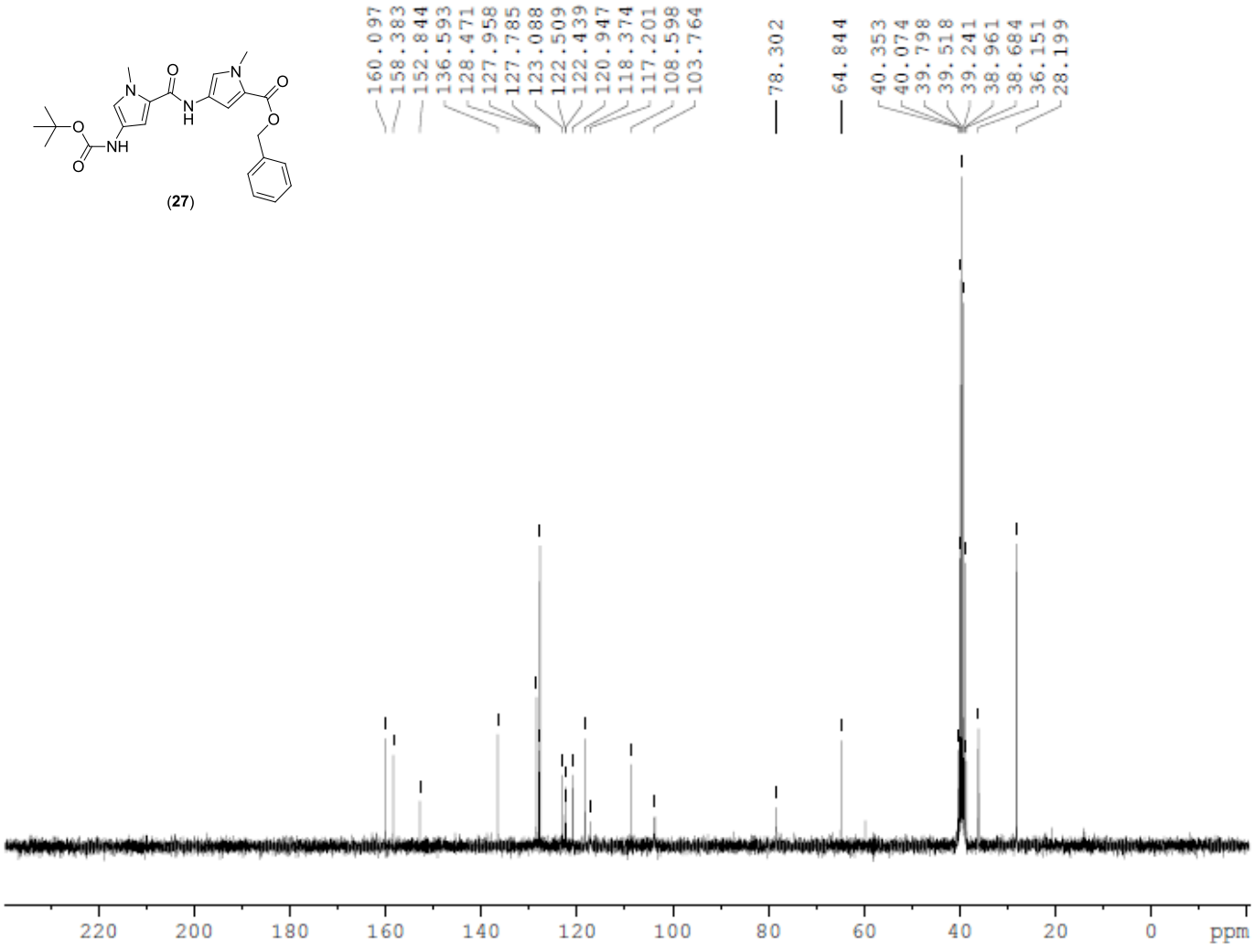
0.970
6.043
1.125
0.778
0.848
2.064
6.193
9.000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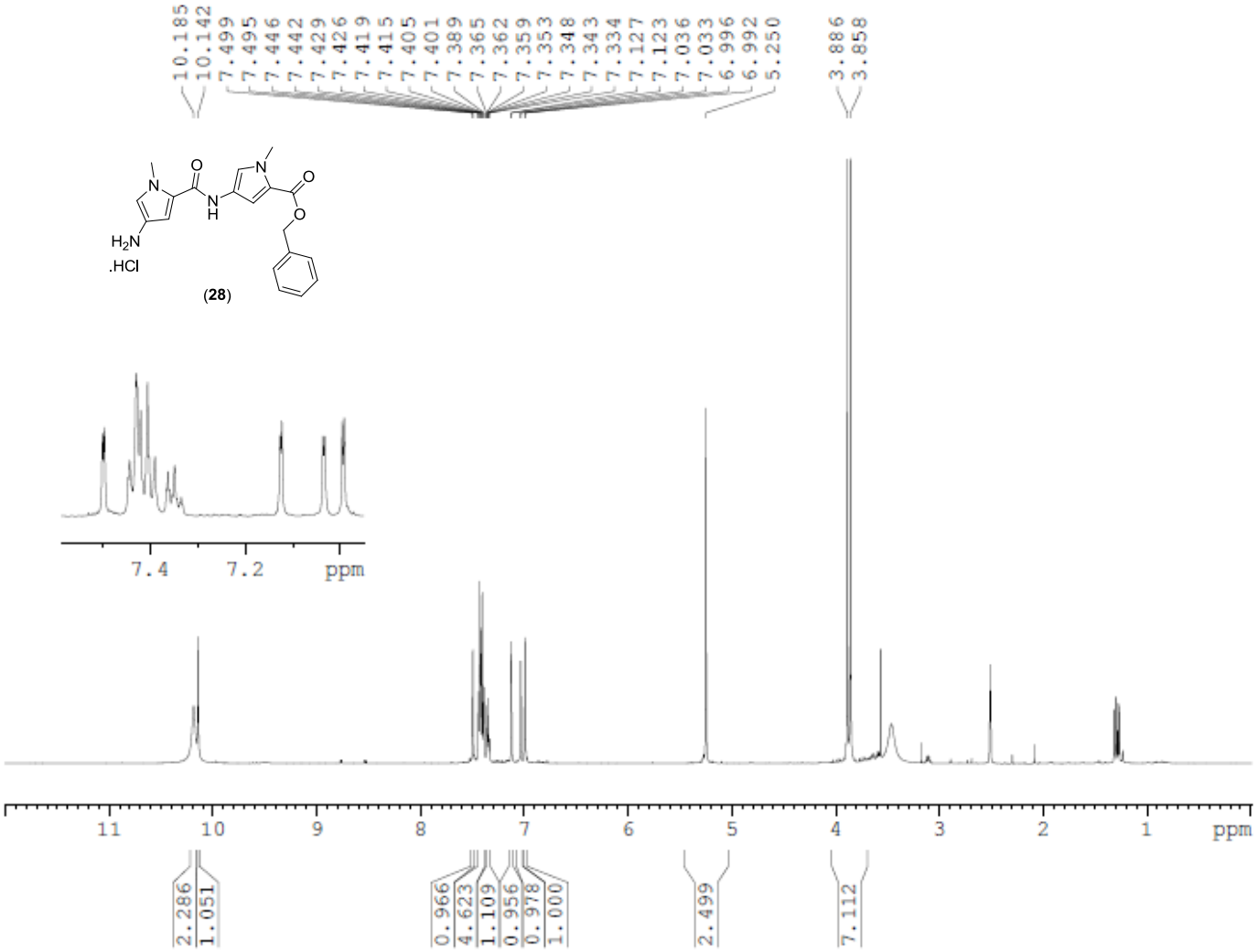
127.958
127.785
123.088
122.509
122.439
120.947
118.374
117.201
108.598
103.764
78.302
64.844
40.353
40.074
39.798
39.518
39.241
38.961
38.684
36.151
28.199
220
200
180
160
140
120
100
80
60
40
20
0
ppm

(**27**)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7.495
7.446
7.442
7.429
7.426
7.419
7.415
7.405
7.401
7.389
7.365
7.362
7.359
7.353
7.348
7.343
7.334
7.127
7.123
7.036
7.033
6.996
6.992
5.250
3.886
3.858
H2N
.HCl
(28)
7.4
7.2
ppm
11
10
9
8
7
6
5
4
3
2
1
ppm
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1.051
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4.623
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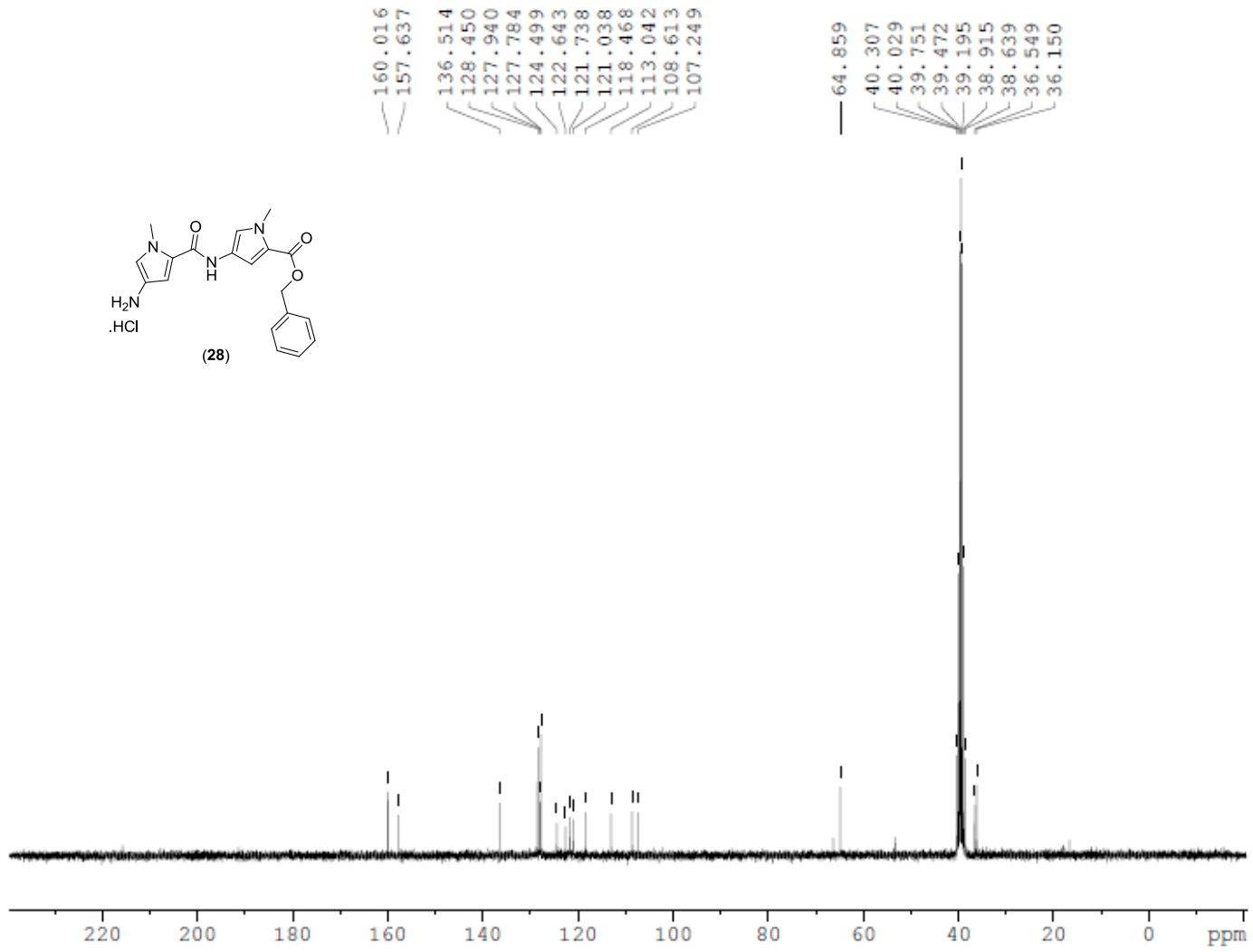
0.956
0.978
1.000
2.499
7.112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122.643
121.738
121.038
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113.042
108.613
107.249
64.859
40.307
40.029
39.751
39.472
39.195
38.915
38.639
36.549
36.150
H2N
.HCl
(28)
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200
180
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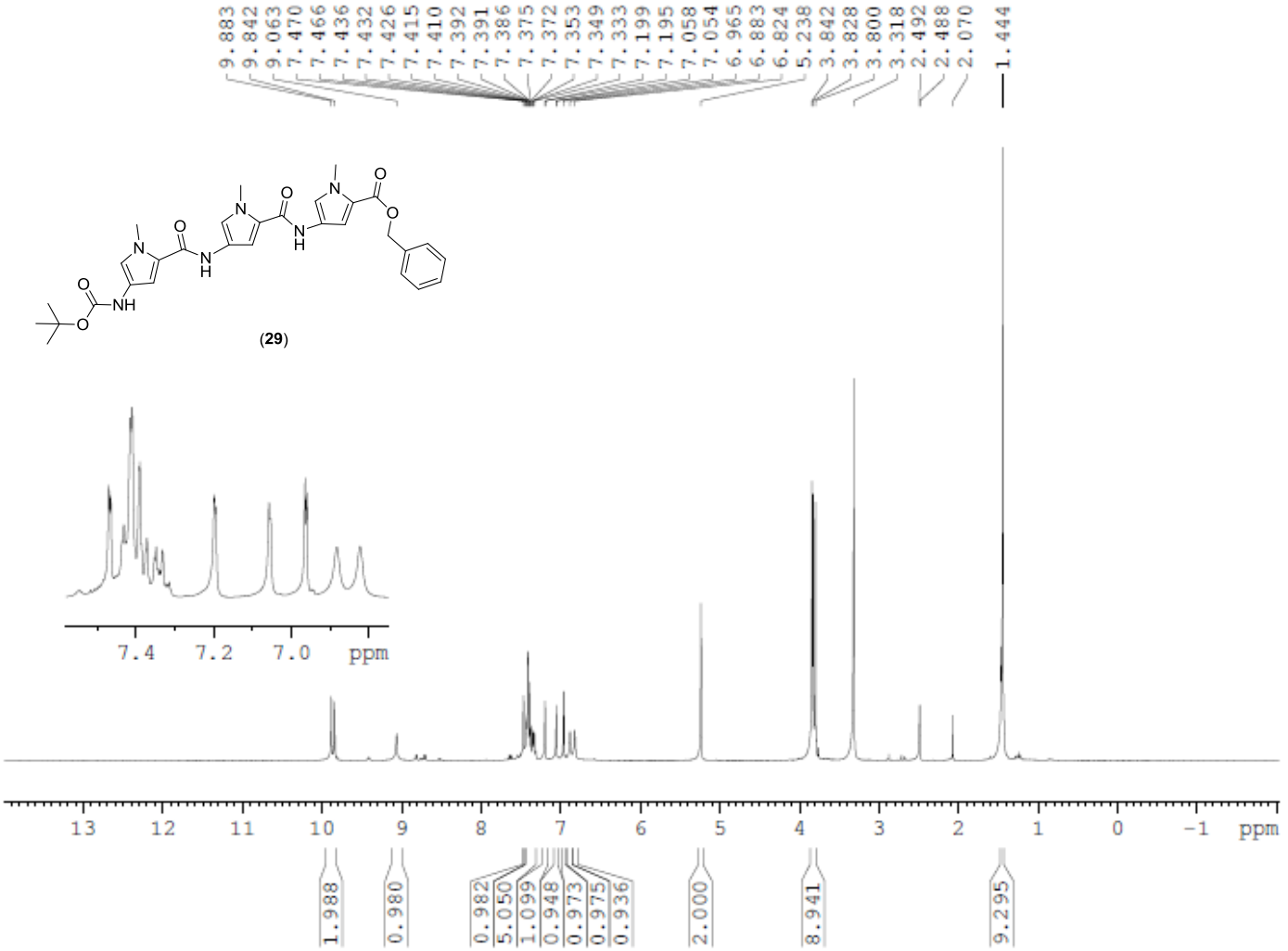
140
120
100
80
60
40
20
0
ppm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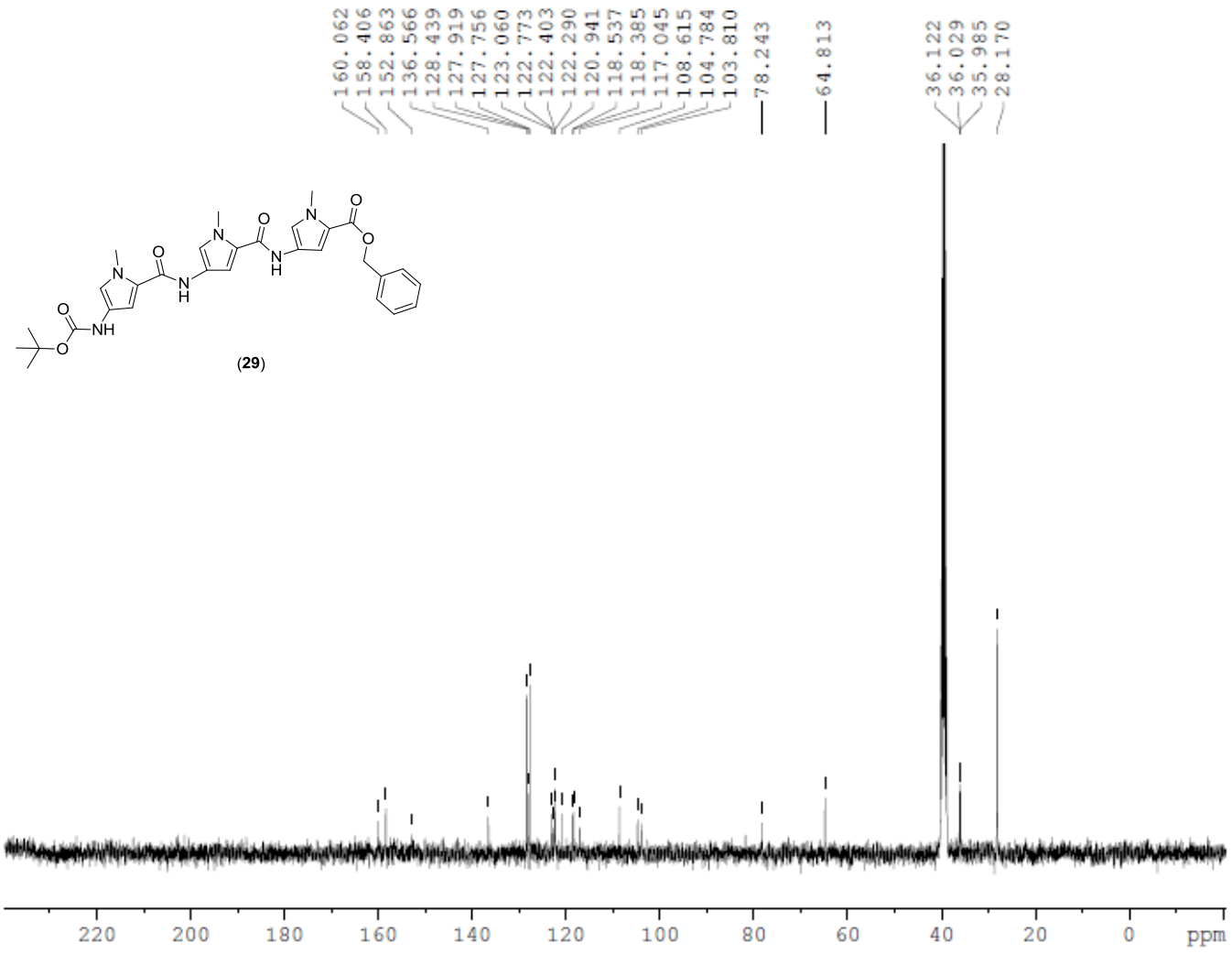
9.063
7.470
7.466
7.436
7.432
7.426
7.415
7.410
7.392
7.391
7.386
7.375
7.372
7.353
7.349
7.333
7.199
7.195
7.058
7.054
6.965
6.883
6.824
5.238
3.842
3.828
3.800
3.318
2.492
2.488
2.070
1.444
(29)
7.4
7.2
7.0
ppm
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
ppm
1.988
0.980
0.982
5.050
1.099
0.948
0.973
0.975
0.936
2.000
8.941
9.295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152.863
136.566
128.439
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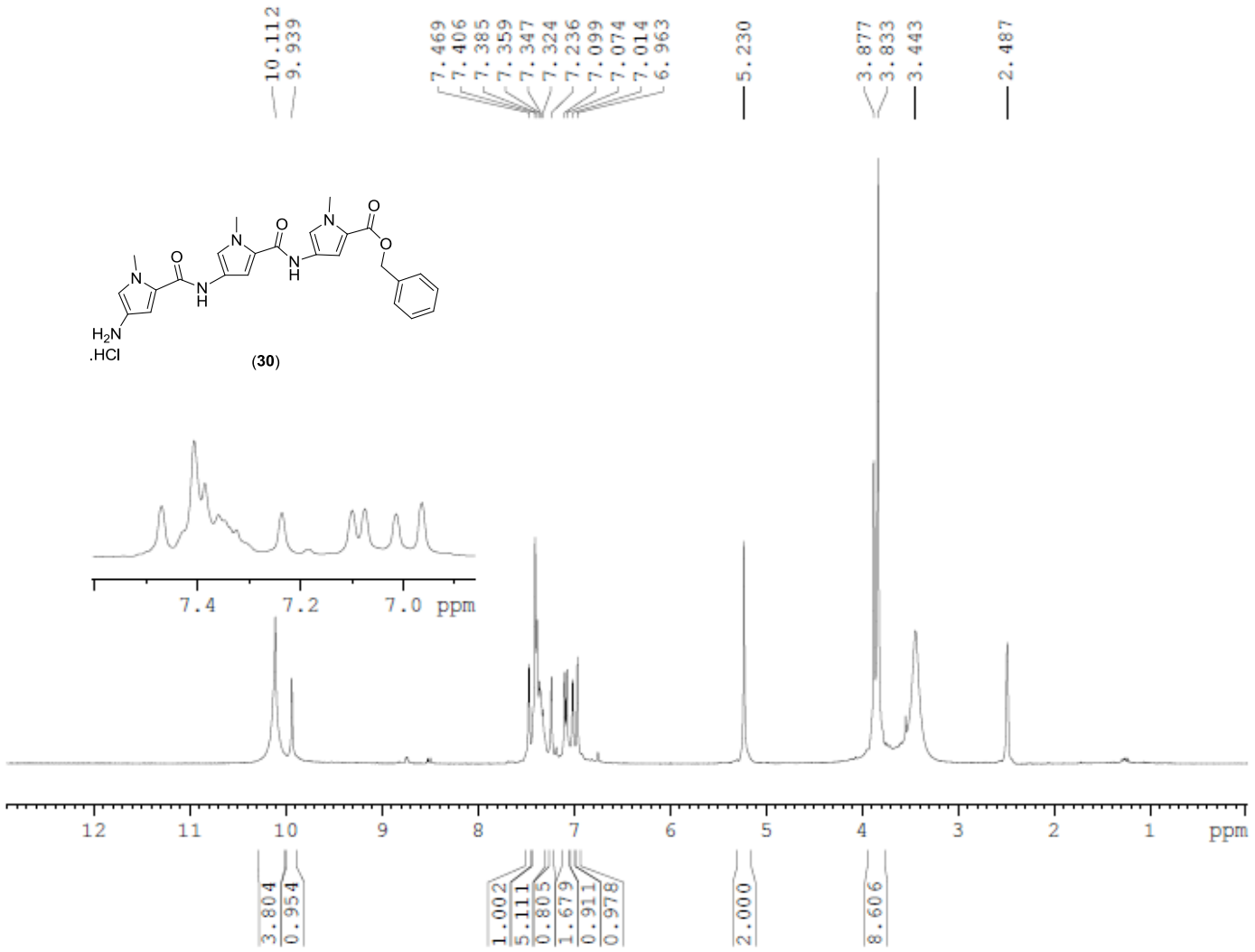
123.060
122.773
122.403
122.290
120.941
118.537
118.385
117.045
108.615
104.784
103.810
78.243
64.813
36.122
36.029
35.985
28.170
220
200
180
160
140
120
100
80
60
40
20
0
ppm

(**29**)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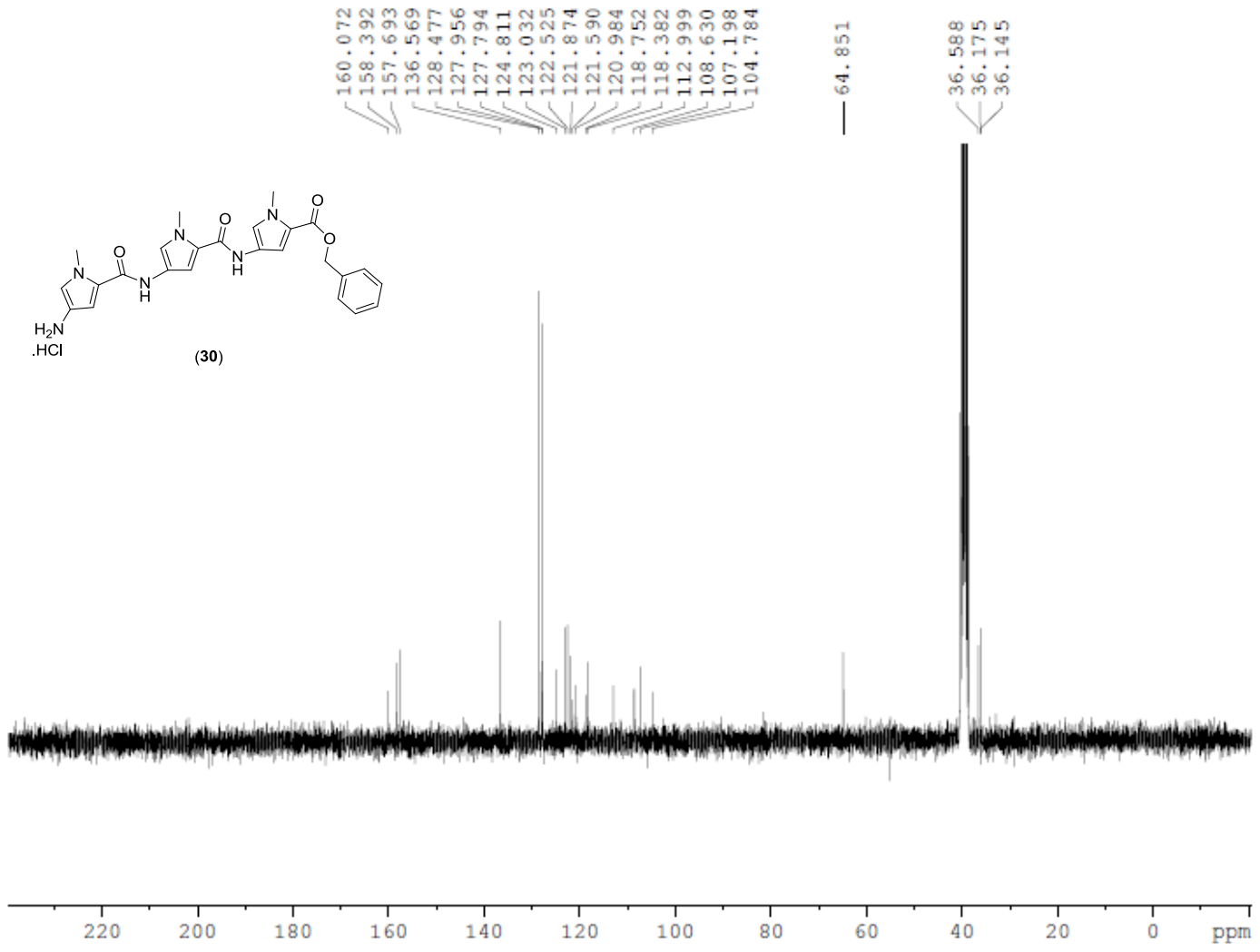
7.469
7.406
7.385
7.359
7.347
7.324
7.236
7.099
7.074
7.014
6.963
5.230
3.877
3.833
3.443
2.487
H2N
.HCl
(30)
7.4
7.2
7.0 ppm
12
11
10
9
8
7
6
5
4
3
2
1
ppm
3.804
0.954
1.002
5.111
0.805
1.679
0.911
0.978
2.000
8.606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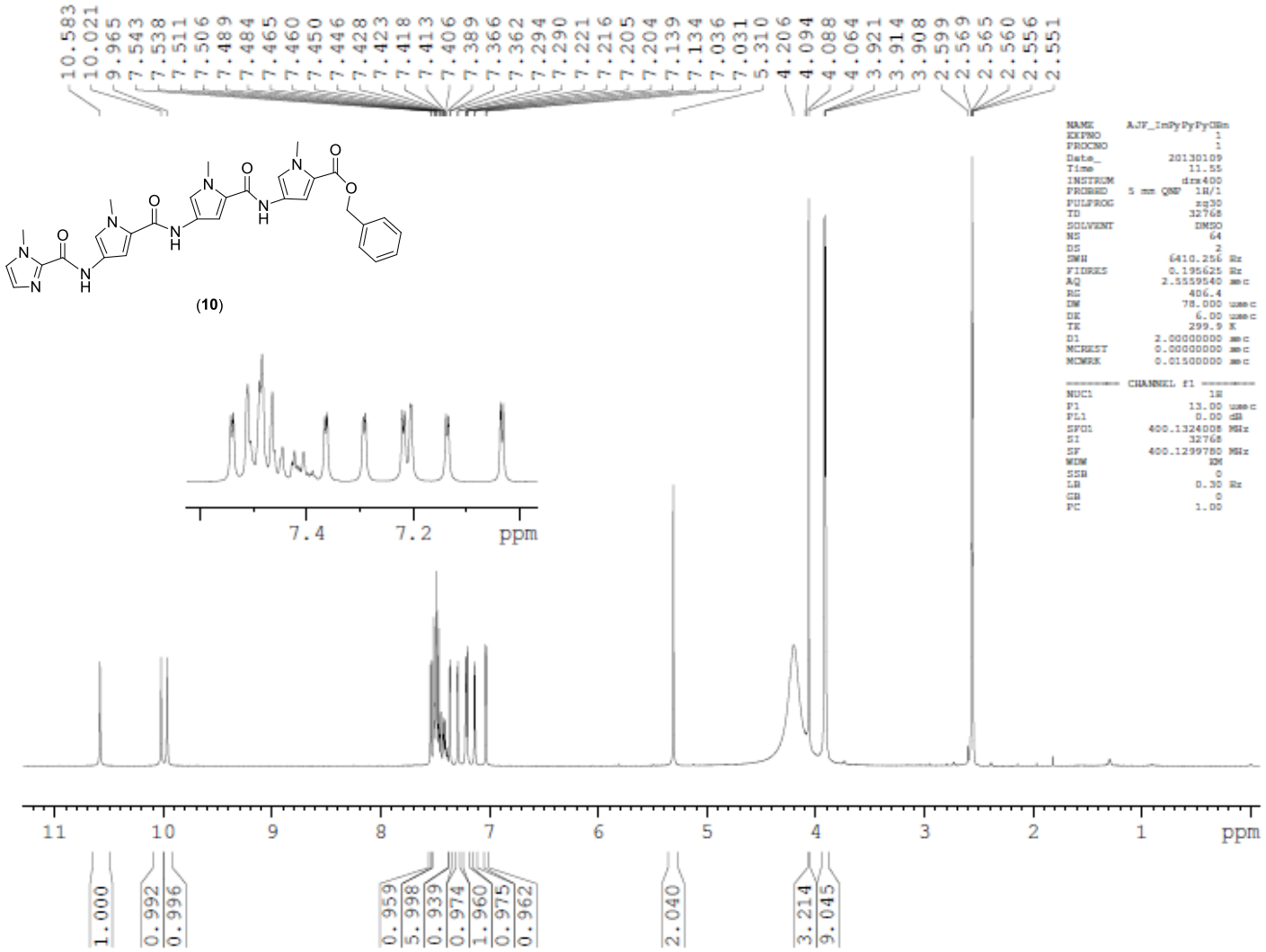
127.956
127.794
124.811
123.032
122.525
121.874
121.590
120.984
118.752
118.382
112.999
108.630
107.198
104.784
64.851
36.588
36.175
36.145
H2N
.HCl
(30)
220
200
180
160
140
120
100
80
60
40
20
0
ppm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9.965
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7.538
7.511
7.506
7.489
7.484
7.465
7.460
7.450
7.446
7.428
7.423
7.418
7.413
7.406
7.389
7.366
7.362
7.294
7.290
7.221
7.216
7.205
7.204
7.139
7.134
7.036
7.031
5.310
4.206
4.094
4.088
4.064
3.921
3.914
3.908
2.599
2.569
2.565
2.560
2.556
2.551
(10)
7.4
7.2
ppm
11
10
9
8
7
6
5
4
3
2
1
ppm
1.000
0.992
0.996
0.959
5.998
0.939
0.974
1.960
0.975
0.962
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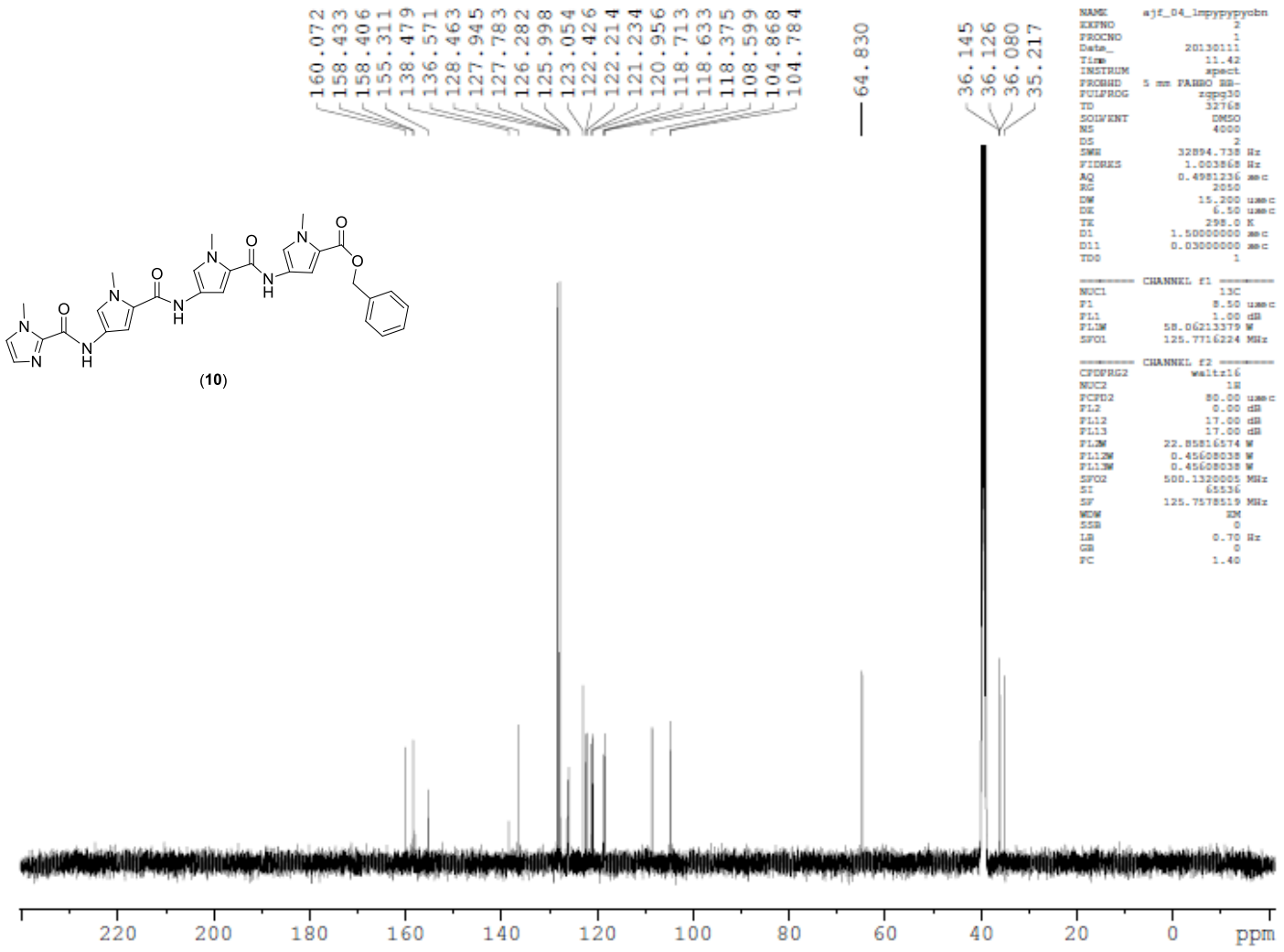
3.214
9.045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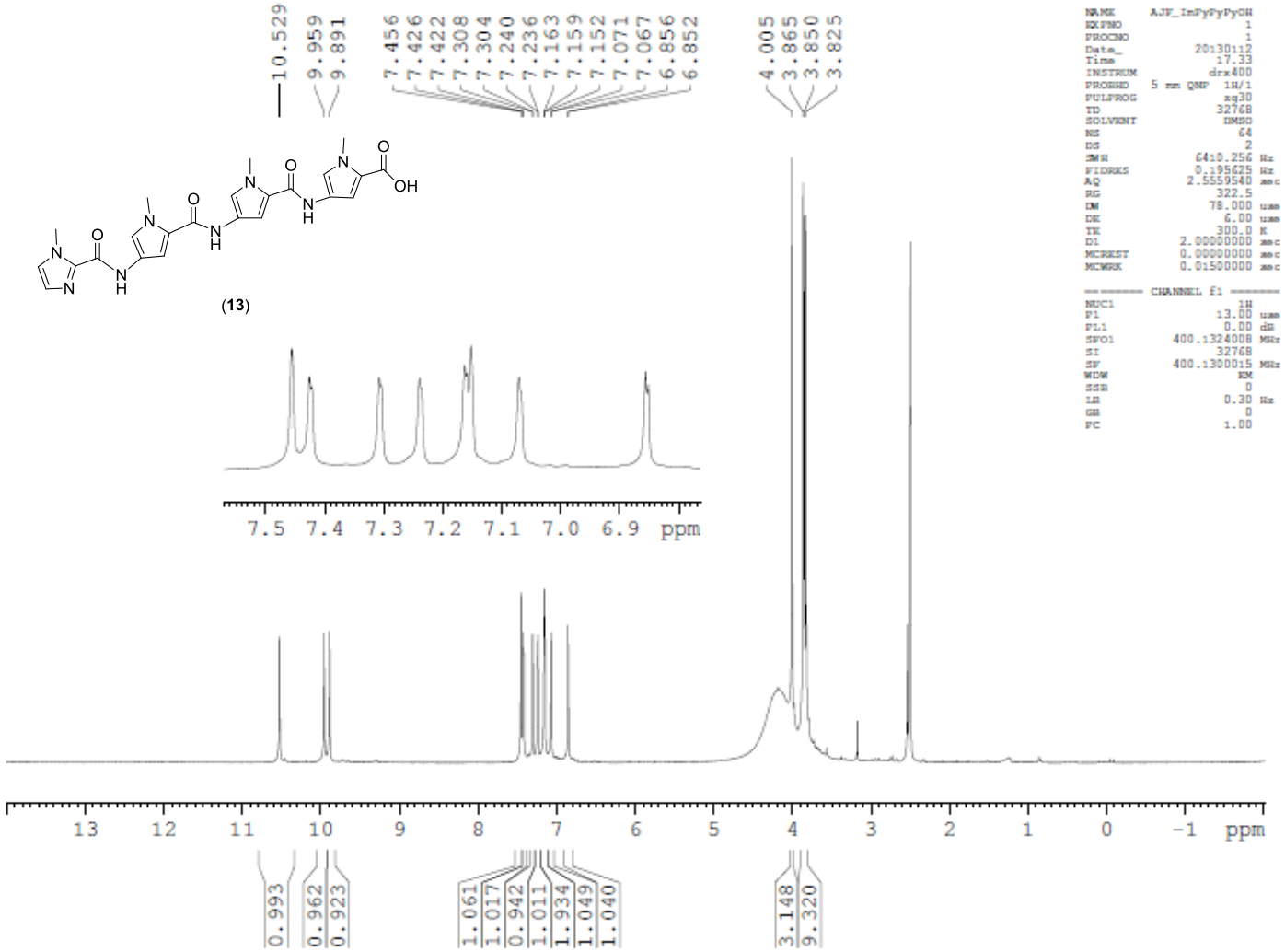
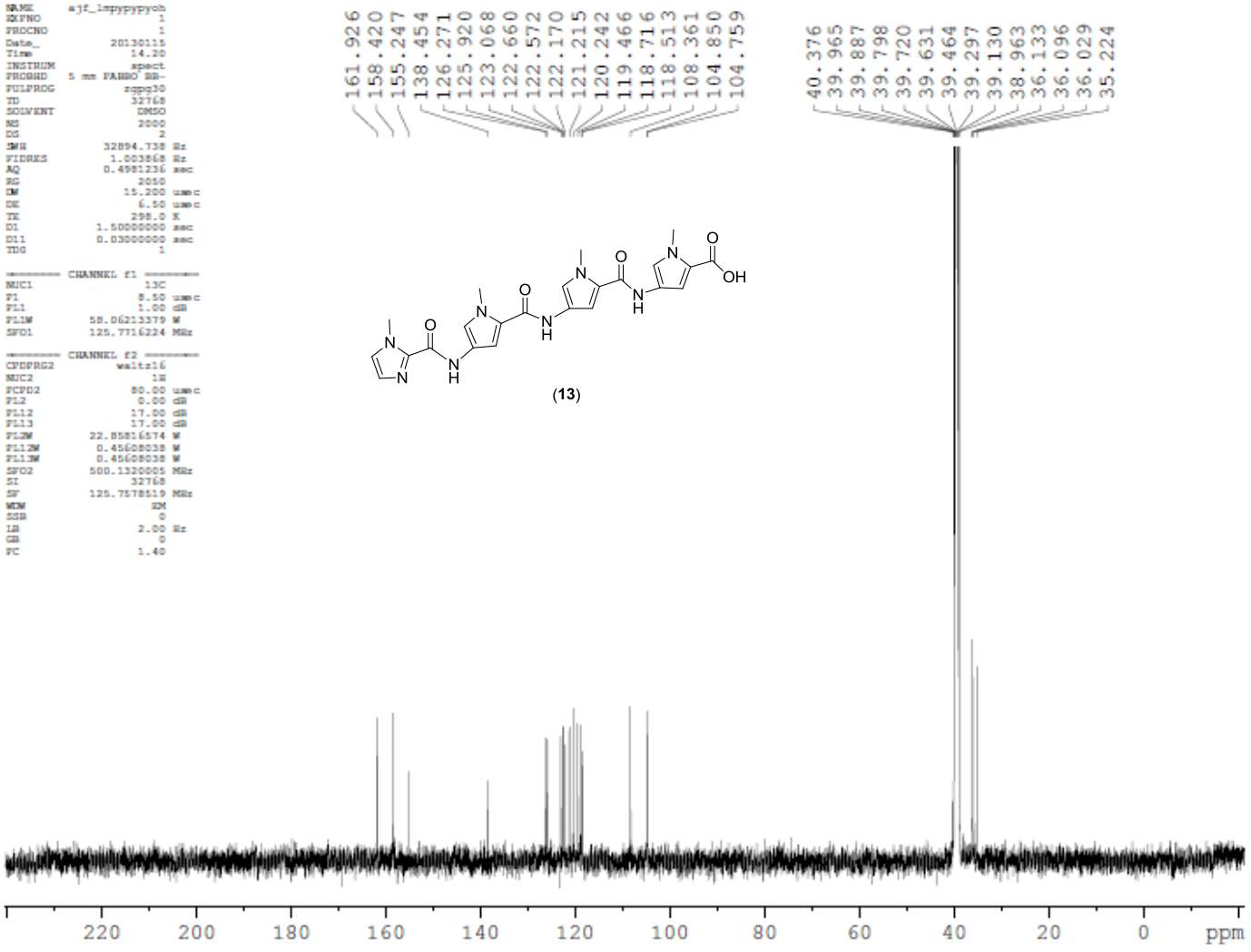
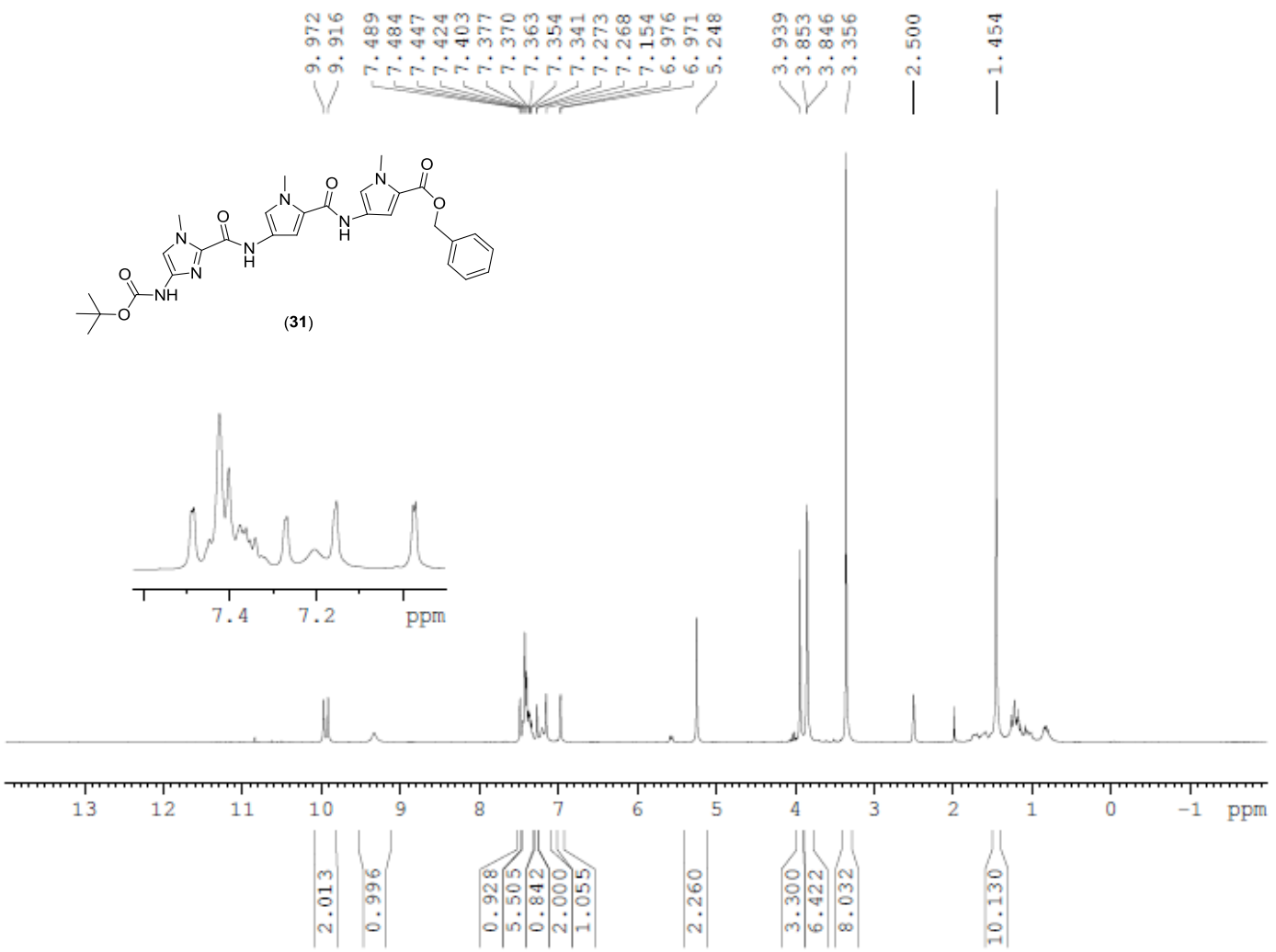
122.214
121.234
120.956
118.713
118.633
118.375
108.599
104.868
104.784
64.830
36.145
36.126
36.080
35.217
220
200
180
160
140
120
100
80
60
40
20
0
ppm

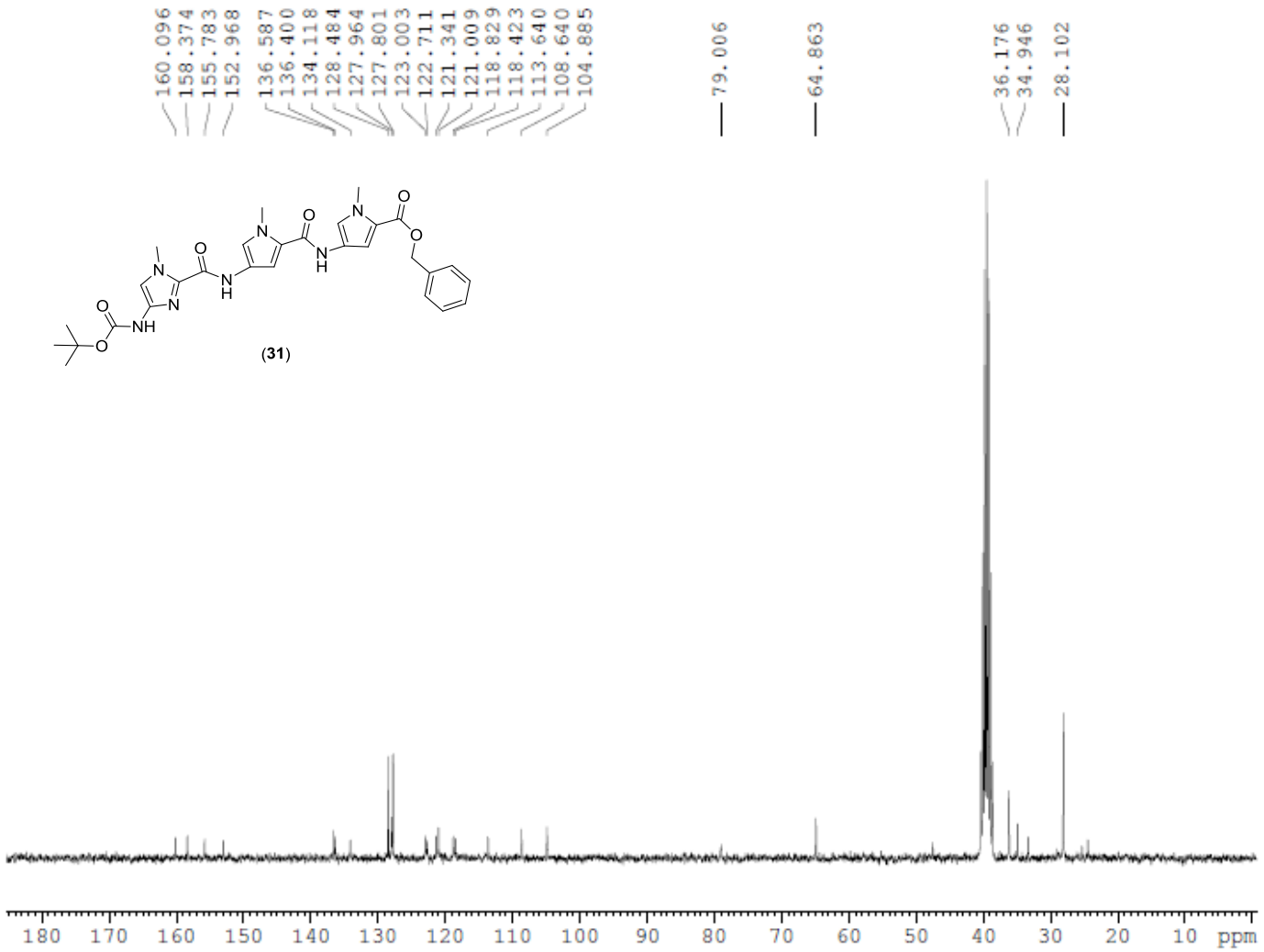
(**10**)

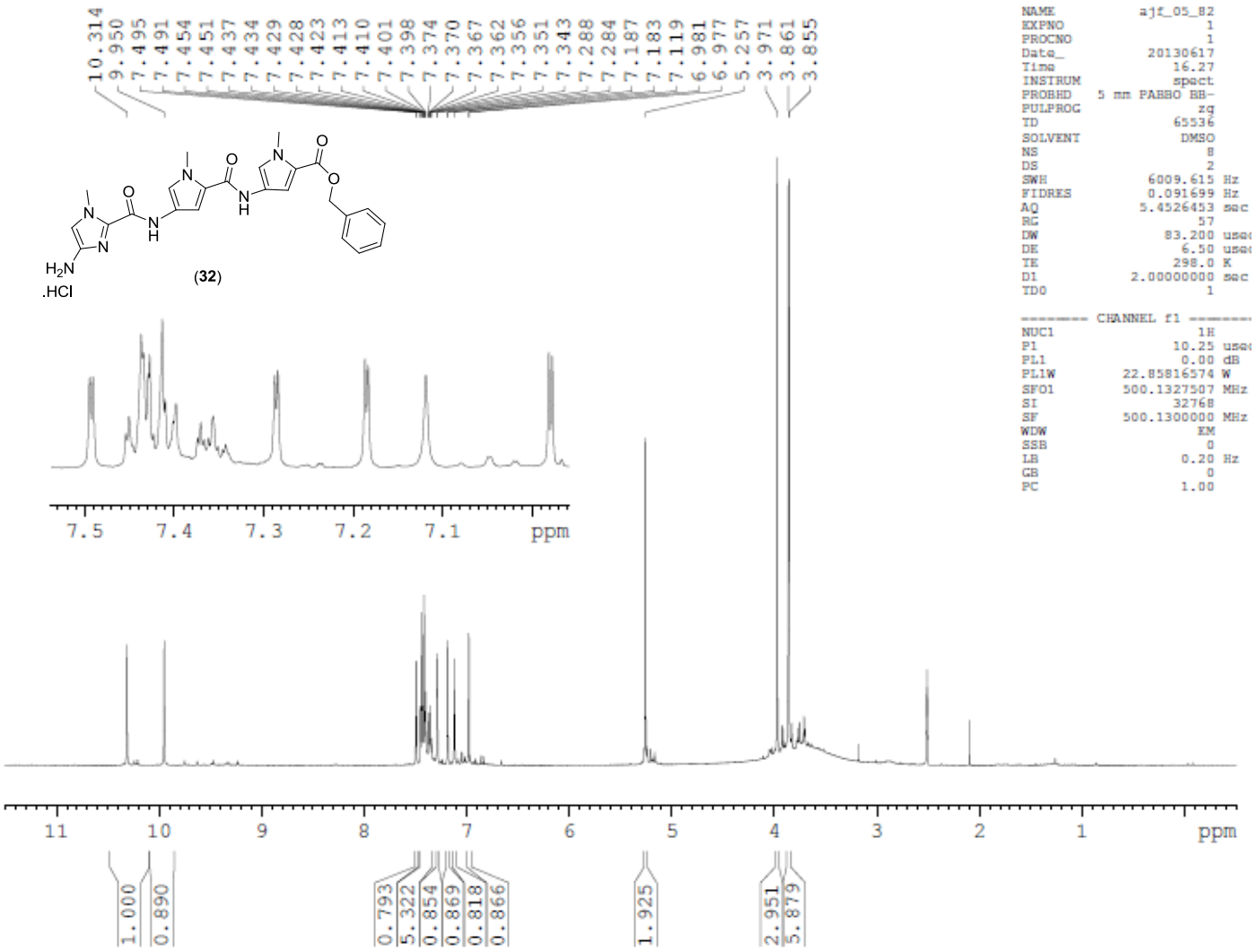


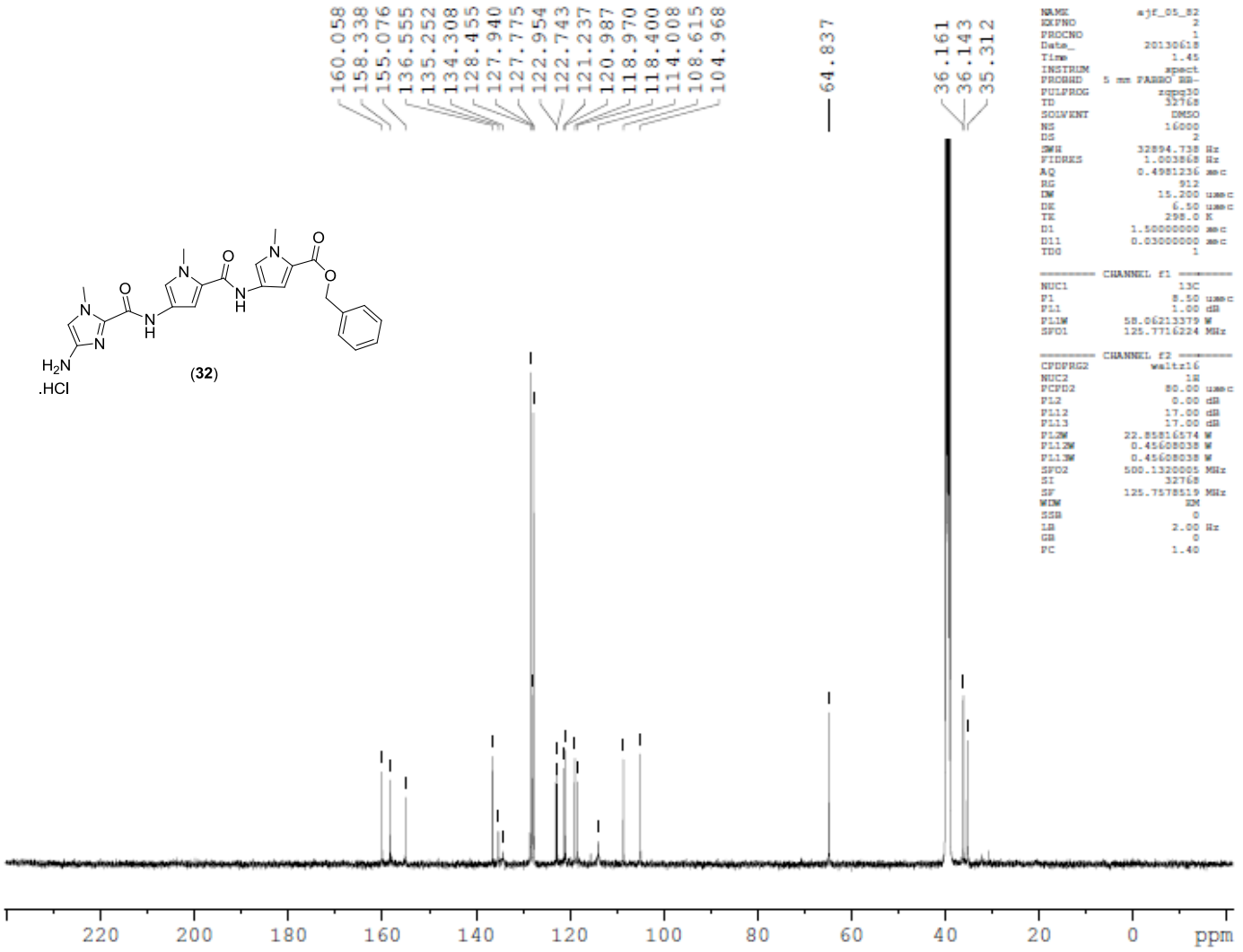
NAME AJE_ImPyPyPyOH
EXPNO 1
PROCNO 1
Date_ 20130112
Time 17.33
INSTRUM drx400
PROBHD 5 mm QNP 1H/1
PULPROG zg30
TD 32768
SOLVENT DMSO
NS 64
DS 2
SWH 6410.256 Hz
FIDRES 0.195625 Hz
AQ 2.5559540 sec
RG 322.5
DW 78.000 usec
DE 6.00 usec
TE 300.0 K
D1 2.00000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec
CHANNEL f1
NUC1 1H
P1 13.00 usec
PL1 0.00 dB
SFO1 400.1324008 MHz
SI 32768
SF 400.1300015 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00

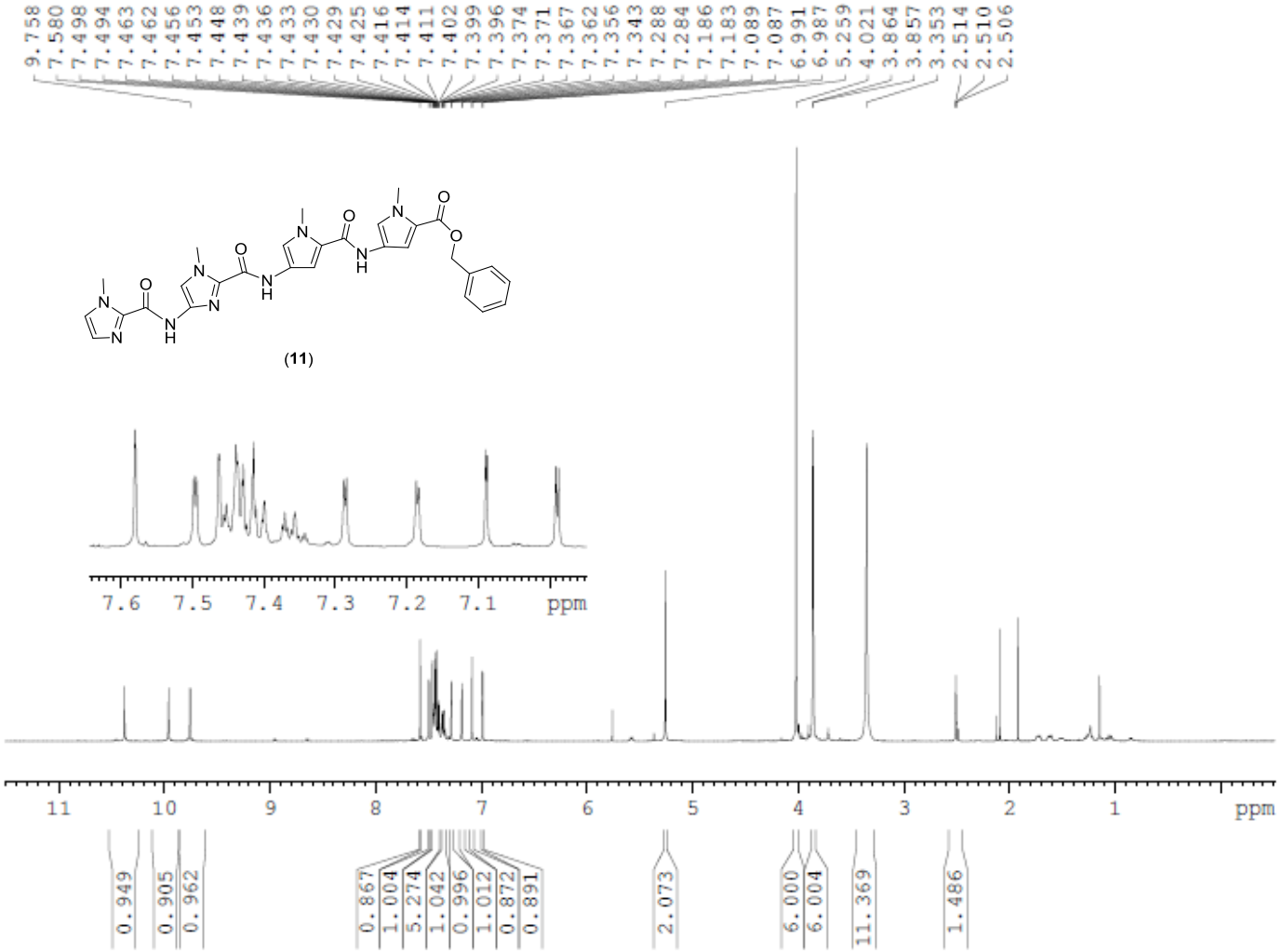

NAME ajf_1mpypypyoh
EXPNO 1
PROCNO 1
Date_ 20130115
Time 14.20
INSTRUM spect
PROBHD 5 mm PABBO BB-
PULPROG zgpg30
TD 32768
SOLVENT DMSO
NS 2000
DS 2
SWH 32894.738 Hz
FIDRES 1.003868 Hz
AQ 0.4981236 sec
RG 2050
DW 15.200 usec
DE 6.50 usec
TE 298.0 K
D1 1.50000000 sec
D11 0.03000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 13C
P1 8.50 usec
PL1 1.00 dB
PL1W 58.06213379 W
SFO1 125.7716224 MHz
======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 80.00 usec
PL2 0.00 dB
PL12 17.00 dB
PL13 17.00 dB
PL2W 22.85816574 W
PL12W 0.45608038 W
PL13W 0.45608038 W
SFO2 500.1320005 MHz
SI 32768
SF 125.7578519 MHz
WDW EM
SSB 0
LB 2.00 Hz
GB 0
PC 1.40
161.926
158.420
155.247
138.454
126.271
125.920
123.068
122.660
122.572
122.170
121.215
120.242
119.466
118.716
118.513
108.361
104.850
104.759
40.376
39.965
39.887
39.798
39.720
39.631
39.464
39.297
39.130
38.963
36.133
36.096
36.029
35.224
(13)
220
200
180
160
140
120
100
80
60
40
20
0
ppm

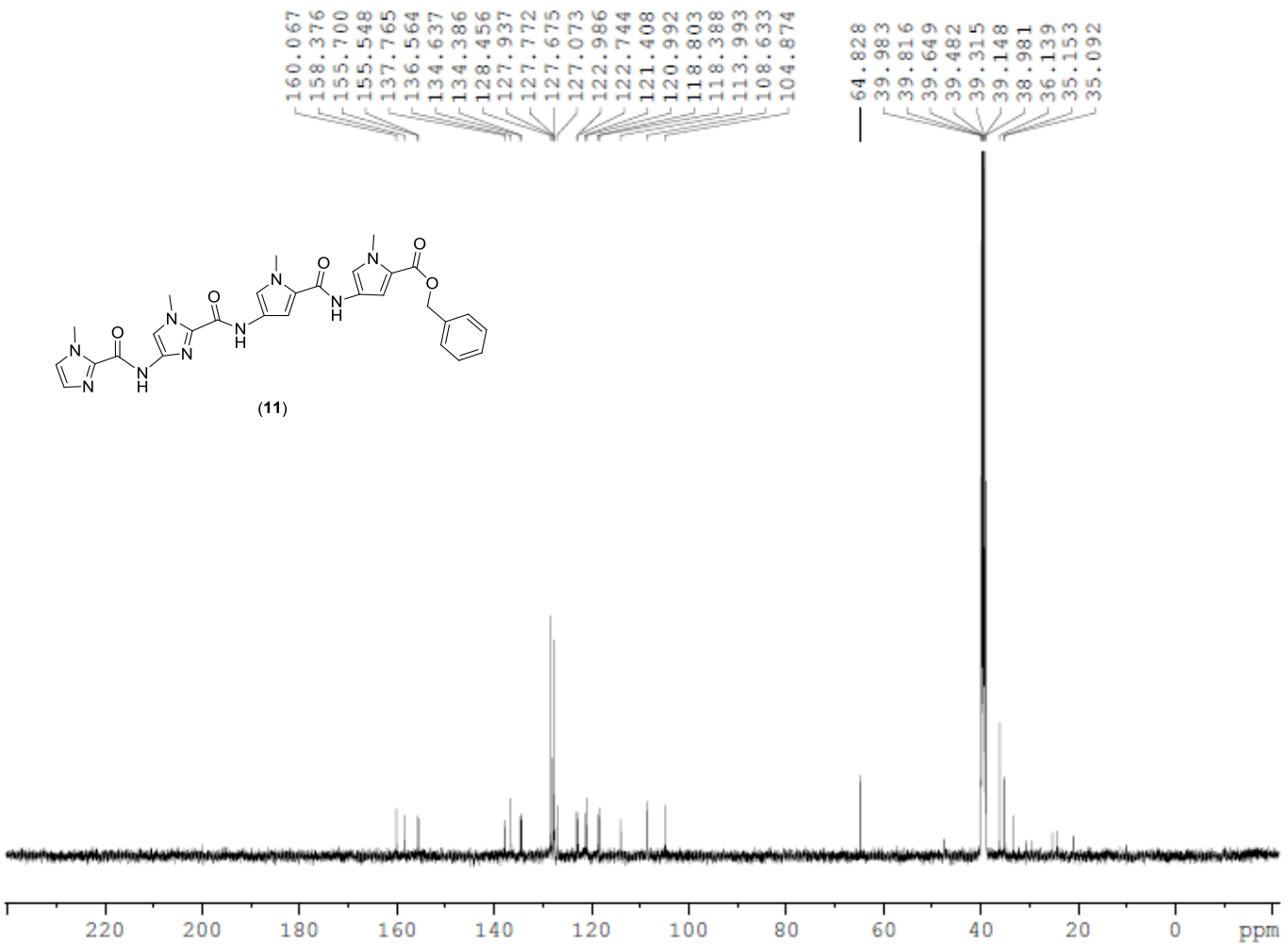

9.972
9.916
7.489
7.484
7.447
7.424
7.403
7.377
7.370
7.363
7.354
7.341
7.273
7.268
7.154
6.976
6.971
5.248
3.939
3.853
3.846
3.356
2.500
1.454
(31)
7.4
7.2
ppm
13
12
11
10
9
8
7
6
5
4
3
2
1
0
−1
ppm
2.013
0.996
0.928
5.505
0.842
2.000
1.055
2.260
3.300
6.422
8.032
10.130


160.096
158.374
155.783
152.968
136.587
136.400
134.118
128.484
127.964
127.801
123.003
122.711
121.341
121.009
118.829
118.423
113.640
108.640
104.885
79.006
64.863
36.176
34.946
28.102
(31)
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

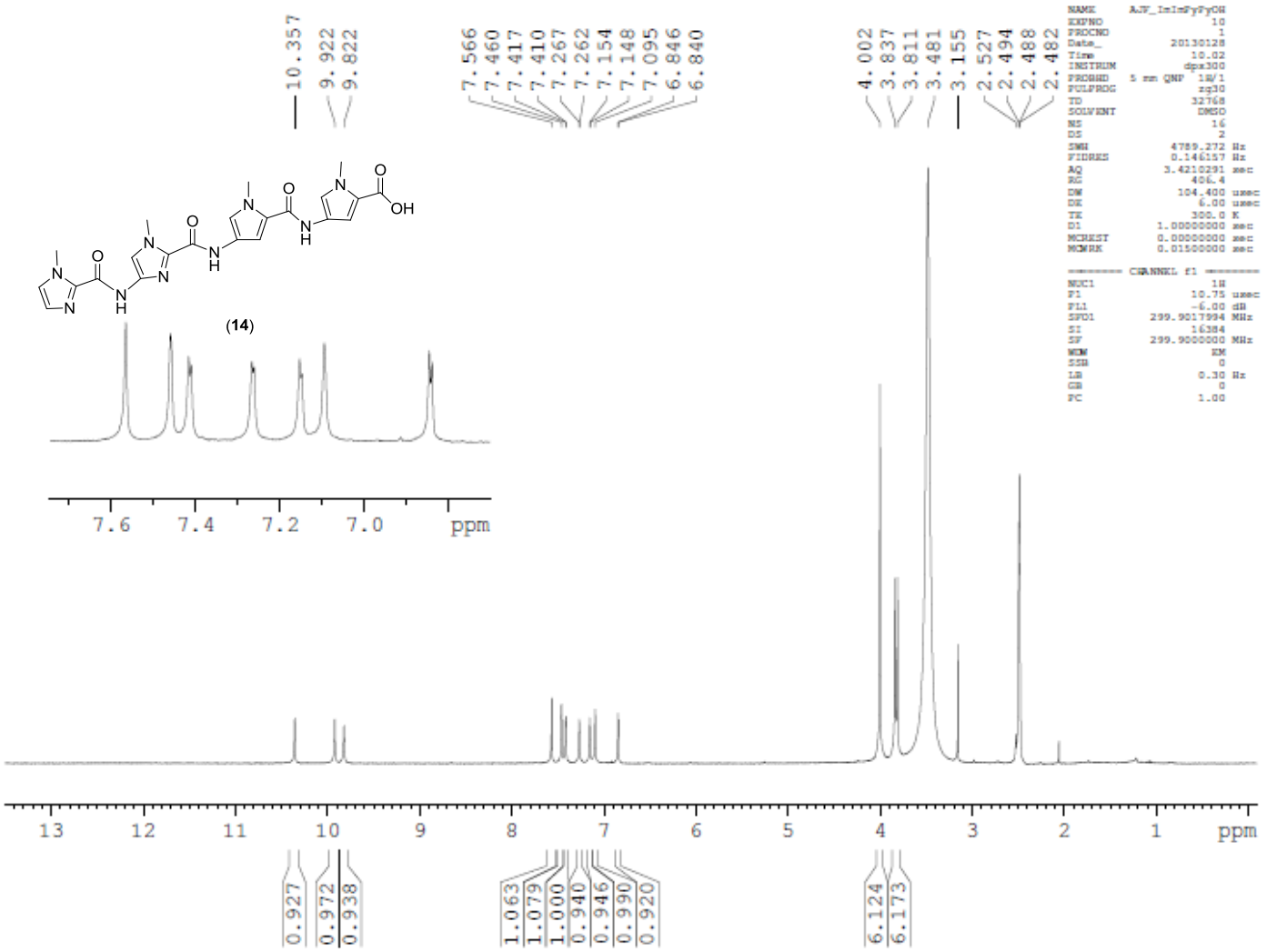

10.314
9.950
7.495
7.491
7.454
7.451
7.437
7.434
7.429
7.428
7.423
7.413
7.410
7.401
7.398
7.374
7.370
7.367
7.362
7.356
7.351
7.343
7.288
7.284
7.187
7.183
7.119
6.981
6.977
5.257
3.971
3.861
3.855
(32)
.HCl
NAME ajf_05_82
EXPNO 1
PROCNO 1
Date_ 20130617
Time 16.27
INSTRUM spect
PROBHD 5 mm PABBO BB-
PULPROG zg
TD 65536
SOLVENT DMSO
NS 8
DS 2
SWH 6009.615 Hz
FIDRES 0.091699 Hz
AQ 5.4526453 sec
RG 57
DW 83.200 use
DE 6.50 use
TE 298.0 K
D1 2.00000000 sec
TD0 1
CHANNEL f1
NUC1 1H
P1 10.25 use
PL1 0.00 dB
PL1W 22.85816574 W
SFO1 500.1327507 MHz
SI 32768
SF 500.1300000 MHz
WDW EM
SSB 0
LB 0.20 Hz
GB 0
PC 1.00
7.5
7.4
7.3
7.2
7.1
ppm
11
10
9
8
7
6
5
4
3
2
1
ppm
1.000
0.890
0.793
5.322
0.854
0.869
0.818
0.866
1.925
2.951
5.879

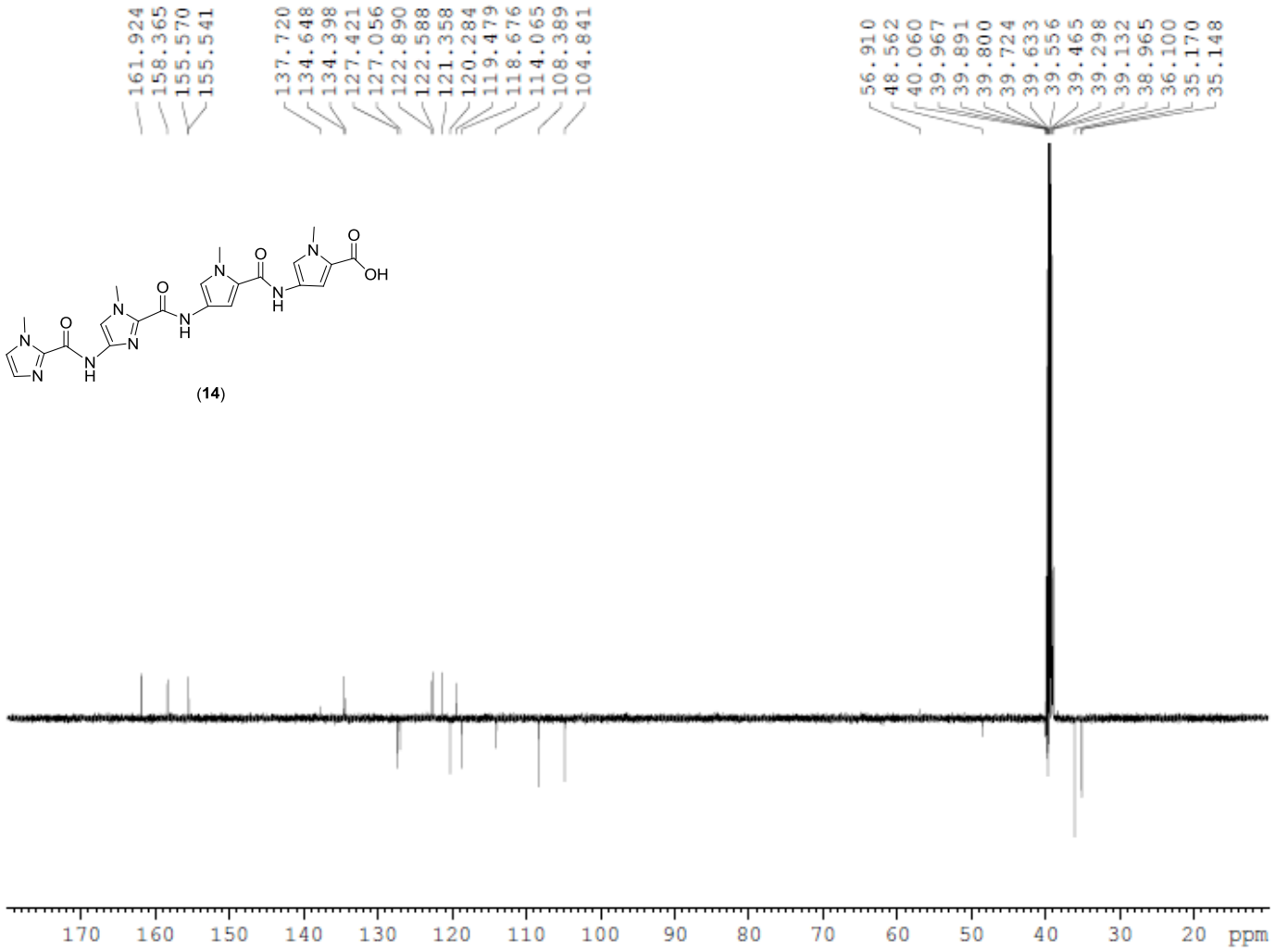

160.058
158.338
155.076
136.555
135.252
134.308
128.455
127.940
127.775
122.954
122.743
121.237
120.987
118.970
118.400
114.008
108.615
104.968
64.837
36.161
36.143
35.312
(32)
.HCl
220
200
180
160
140
120
100
80
60
40
20
0
ppm


9.758
7.580
7.498
7.494
7.463
7.462
7.456
7.453
7.448
7.439
7.436
7.433
7.430
7.429
7.425
7.416
7.414
7.411
7.402
7.399
7.396
7.374
7.371
7.367
7.362
7.356
7.343
7.288
7.284
7.186
7.183
7.089
7.087
6.991
6.987
5.259
4.021
3.864
3.857
3.353
2.514
2.510
2.506
(11)
7.6
7.5
7.4
7.3
7.2
7.1
ppm
11
10
9
8
7
6
5
4
3
2
1
ppm
0.949
0.905
0.962
0.867
1.004
5.274
1.042
0.996
1.012
0.872
0.891
2.073
6.000
6.004
11.369
1.486

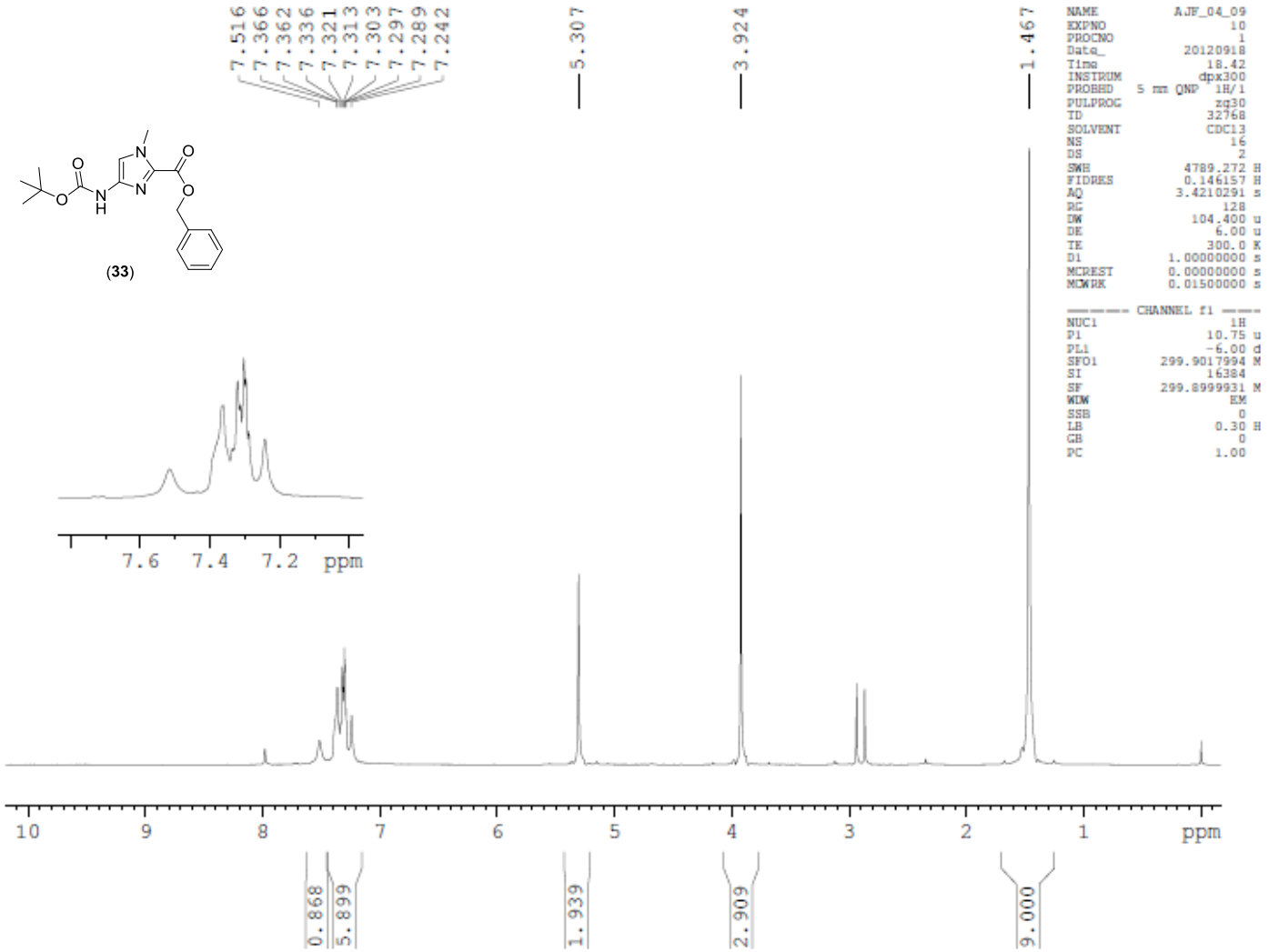

160.067
158.376
155.700
155.548
137.765
136.564
134.637
134.386
128.456
127.937
127.772
127.675
127.073
122.986
122.744
121.408
120.992
118.803
118.388
113.993
108.633
104.874
64.828
39.983
39.816
39.649
39.482
39.315
39.148
38.981
36.139
35.153
35.092
220
200
180
160
140
120
100
80
60
40
20
0
ppm

(**11**)


10.357
9.922
9.822
7.566
7.460
7.417
7.410
7.267
7.262
7.154
7.148
7.095
6.846
6.840
4.002
3.837
3.811
3.481
3.155
2.527
2.494
2.488
2.482
(14)
7.6
7.4
7.2
7.0
ppm
13
12
11
10
9
8
7
6
5
4
3
2
1
ppm
0.927
0.972
0.938
1.063
1.079
1.000
0.940
0.946
0.990
0.920
6.124
6.173

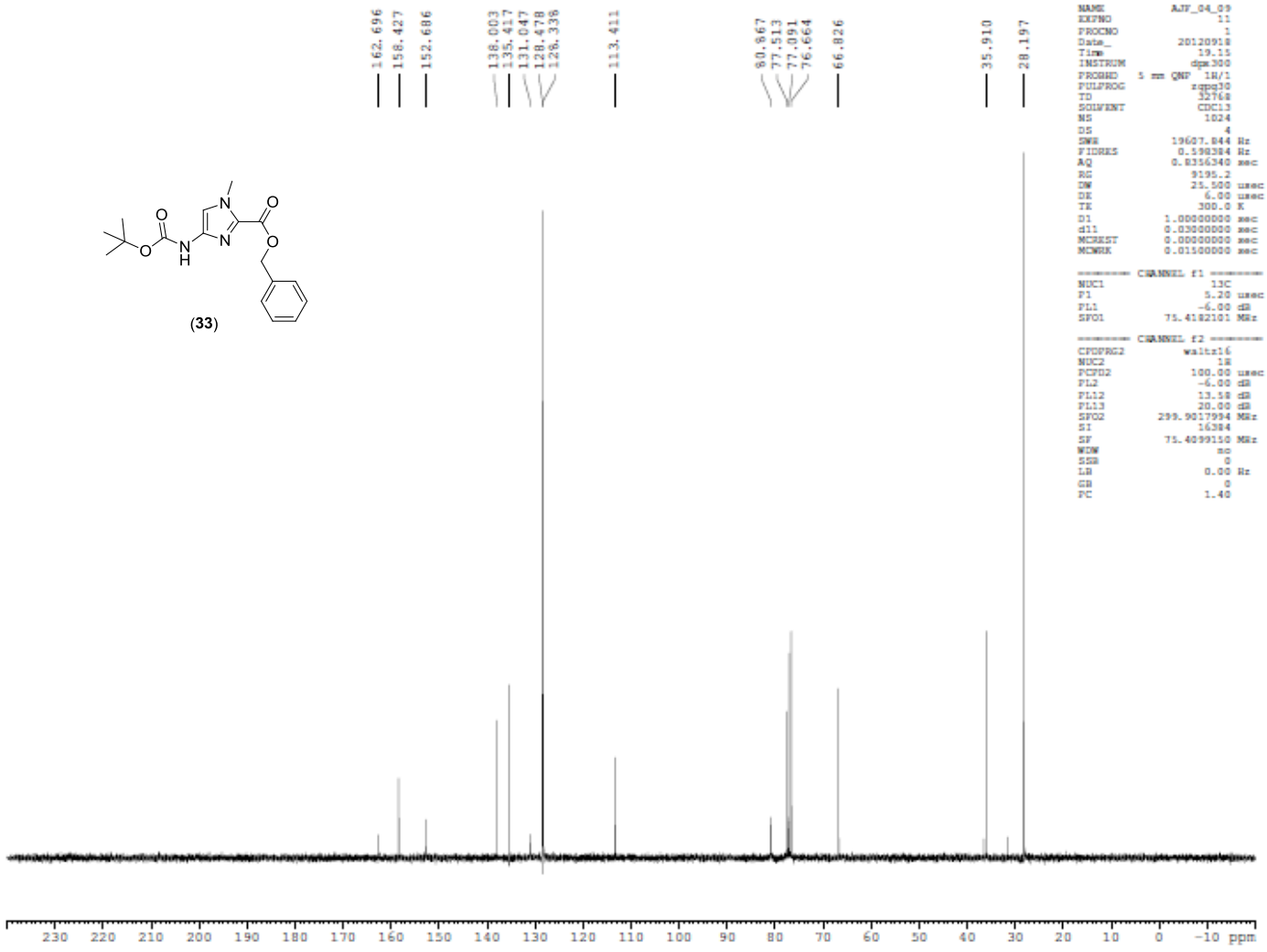

161.924
158.365
155.570
155.541
137.720
134.648
134.398
127.421
127.056
122.890
122.588
121.358
120.284
119.479
118.676
114.065
108.389
104.841
56.910
48.562
40.060
39.967
39.891
39.800
39.724
39.633
39.556
39.465
39.298
39.132
38.965
36.100
35.170
35.148
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm

(**14**)

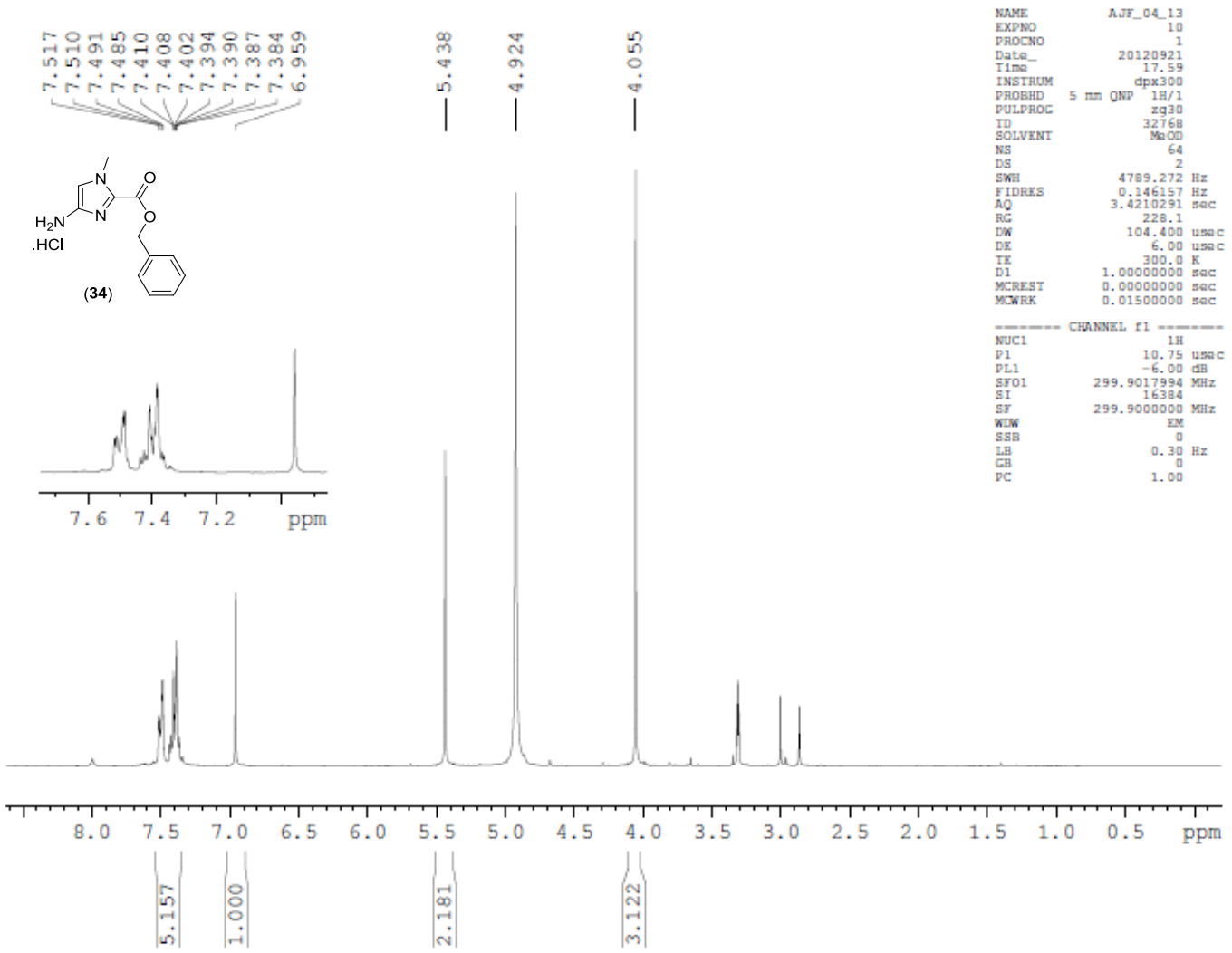


NAME AJF_04_09
EXPNO 10
PROCNO 1
Date_ 20120918
Time 18.42
INSTRUM dpx300
PROBHD 5 mm QNP 1H/1
PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 16
DS 2
SWH 4789.272 H
FIDRES 0.146157 H
AQ 3.4210291 s
RG 128
DW 104.400 u
DE 6.00 u
TE 300.0 K
D1 1.00000000 s
MCREST 0.00000000 s
MCWRK 0.01500000 s

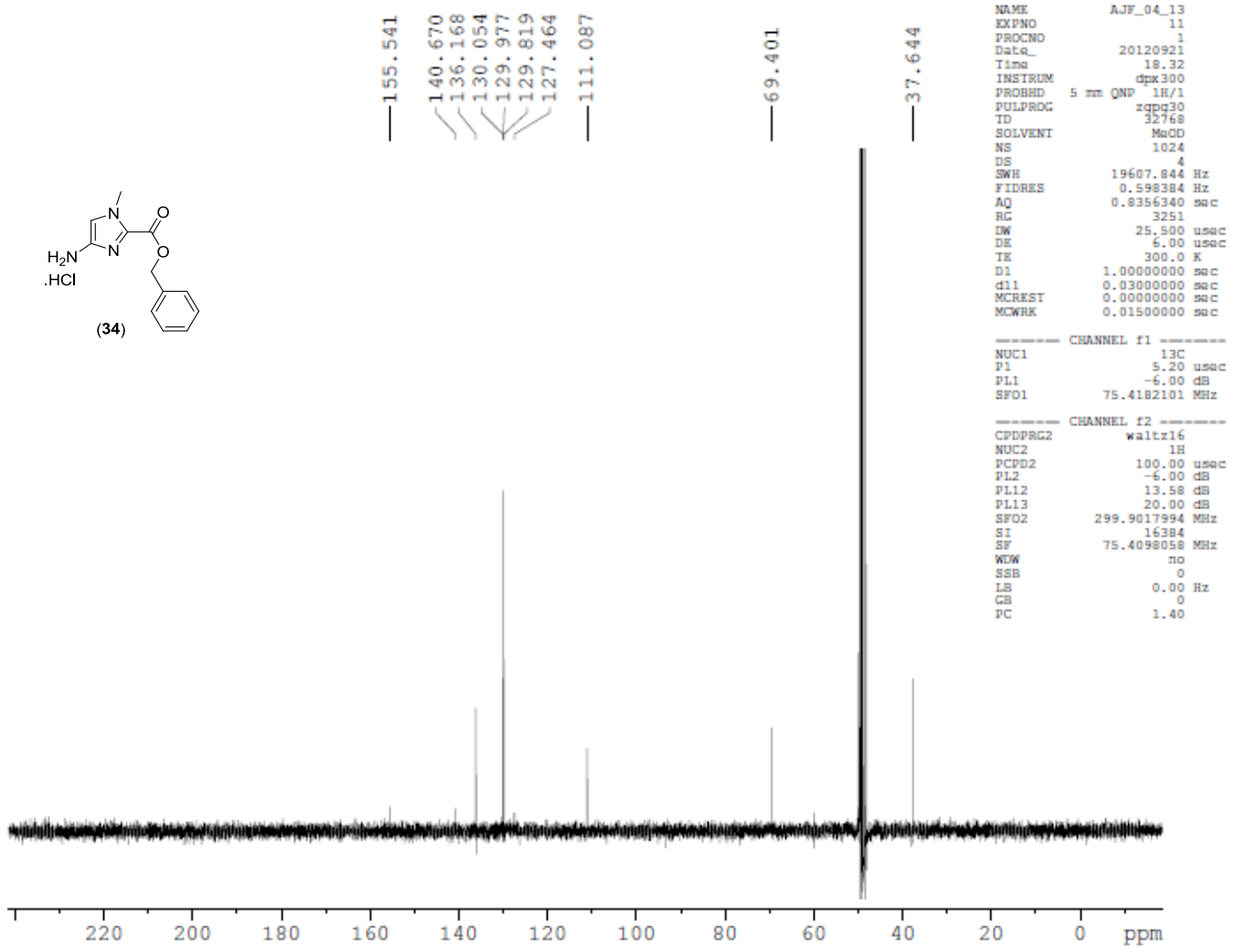
------ CHANNEL f1 ------
NUC1 1H
P1 10.75 u
PL1 -6.00 d
SFO1 299.9017994 M
SI 16384
SF 299.8999931 M
WDW EM
SSB 0
LB 0.30 H
GB 0
PC 1.00

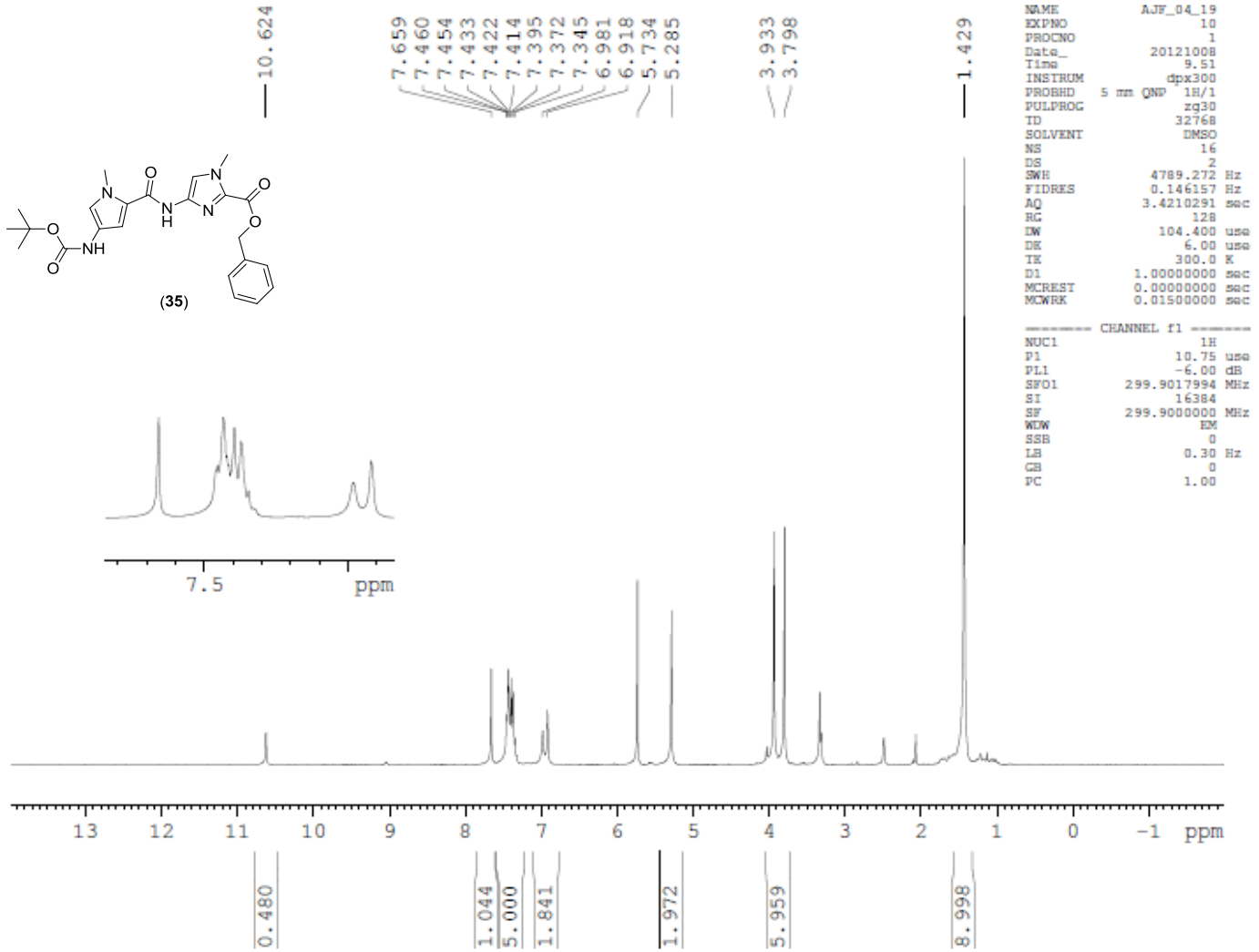

162.696
158.427
152.686
138.003
135.417
131.047
128.478
126.338
113.411
80.867
77.513
77.091
76.664
66.826
35.910
28.197
NAME AJF_04_09
EXPNO 11
PROCNO 1
Date_ 20120918
Time 19.15
INSTRUM dpx300
PROBHD 5 mm QNP 1H/1
PULPROG zgpg30
TD 32768
SOLVENT CDCl3
NS 1024
DS 4
SWH 19607.844 Hz
FIDRES 0.598384 Hz
AQ 0.8356340 sec
RG 9195.2
DW 25.500 usec
DE 6.00 usec
TE 300.0 K
D1 1.00000000 sec
d11 0.03000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec
CHANNEL f1
NUC1 13C
P1 5.20 usec
PL1 -6.00 dB
SFO1 75.4182101 MHz
CHANNEL f2
CPDPRG2 waltz16
NUC2 1H
PCPD2 100.00 usec
PL2 -6.00 dB
PL12 13.58 dB
PL13 20.00 dB
SFO2 299.9017994 MHz
SI 16384
SF 75.4699150 MHz
WDW no
SSB 0
LB 0.00 Hz
GB 0
PC 1.40
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 ppm

(**33**)

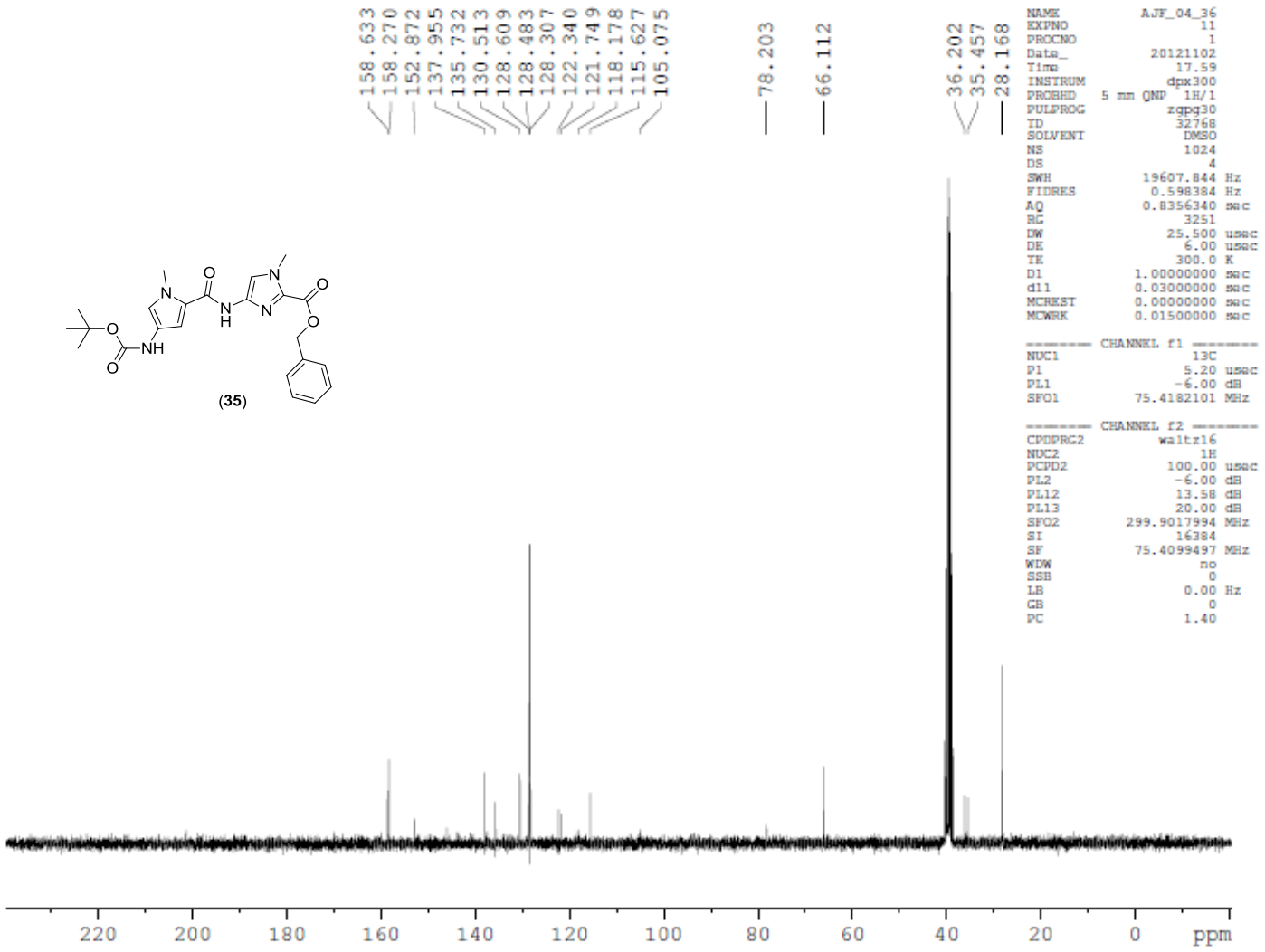


NAME	AJF_04_13
EXPNO	10
PROCNO	1
Date_	20120921
Time	17.59
INSTRUM	dpx300
PROBHD	5 mm QNP 1H/1
PULPROG	zg30
TD	32768
SOLVENT	MeOD
NS	64
DS	2
SWH	4789.272 Hz
FIDRES	0.146157 Hz
AQ	3.4210291 sec
RG	228.1
DW	104.400 usec
DE	6.00 usec
TE	300.0 K
D1	1.00000000 sec
MCREST	0.00000000 sec
MCWRK	0.01500000 sec
========	CHANNEL f1 ========
NUC1	1H
P1	10.75 usec
PL1	-6.00 dB
SFO1	299.9017994 MHz
SI	16384
SF	299.9000000 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00

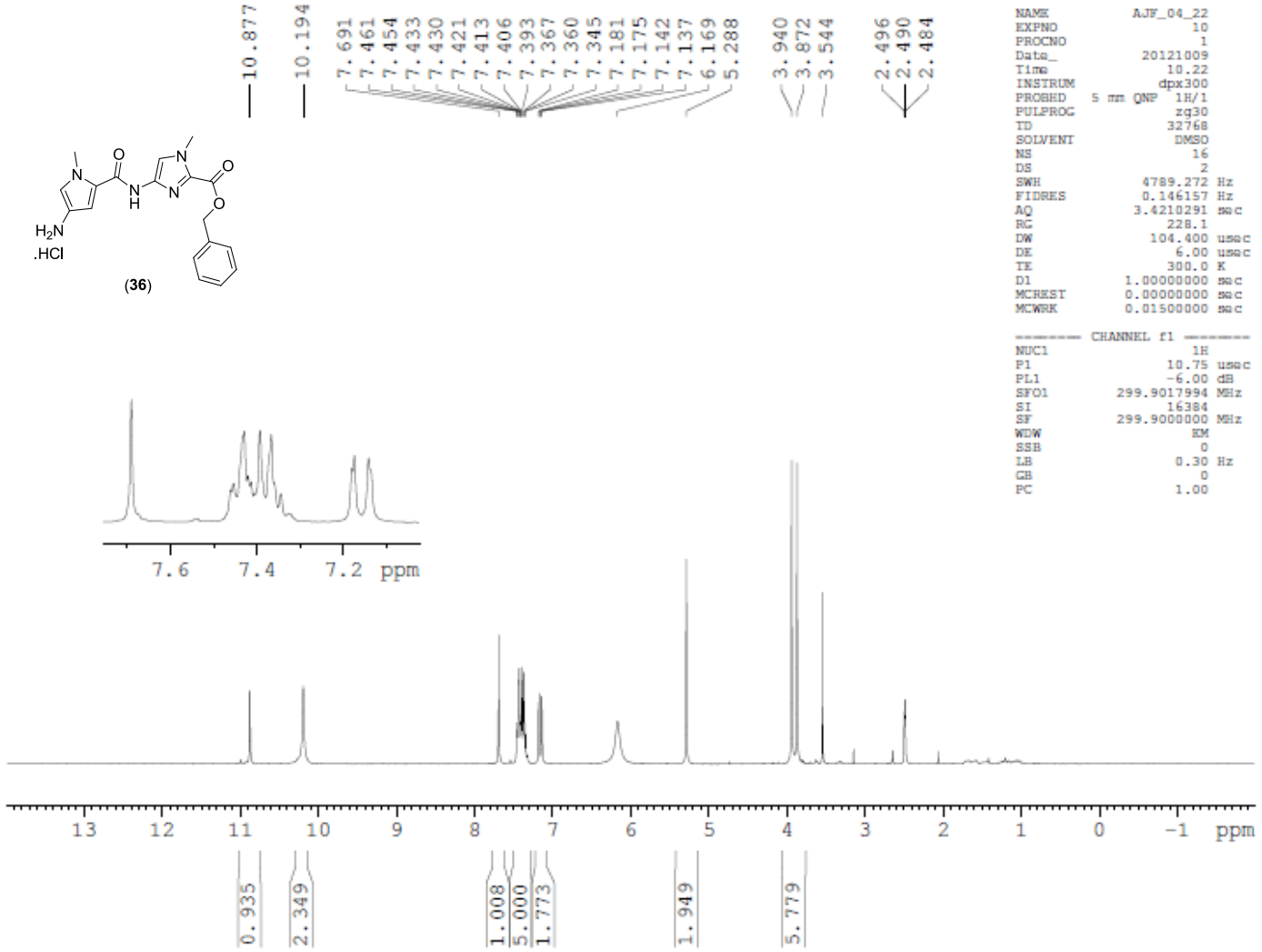

155.541
140.670
136.168
130.054
129.977
129.819
127.464
111.087
69.401
37.644
NAME AJF_04_13
EXPNO 11
PROCNO 1
Date_ 20120921
Time 18.32
INSTRUM dpx300
PROBHD 5 mm QNP 1H/1
PULPROG zgpg30
TD 32768
SOLVENT MeOD
NS 1024
DS 4
SWH 19607.844 Hz
FIDRES 0.598384 Hz
AQ 0.8356340 sec
RG 3251
DW 25.500 usec
DE 6.00 usec
TE 300.0 K
D1 1.00000000 sec
d11 0.03000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec
CHANNEL f1
NUC1 13C
P1 5.20 usec
PL1 -6.00 dB
SFO1 75.4182101 MHz
CHANNEL f2
CPDPRG2 waltz16
NUC2 1H
PCPD2 100.00 usec
PL2 -6.00 dB
PL12 13.58 dB
PL13 20.00 dB
SFO2 299.9017994 MHz
SI 16384
SF 75.4098058 MHz
WDW no
SSB 0
LB 0.00 Hz
GB 0
PC 1.40
H2N
.HCl
(34)
220
200
180
160
140
120
100
80
60
40
20
0
ppm



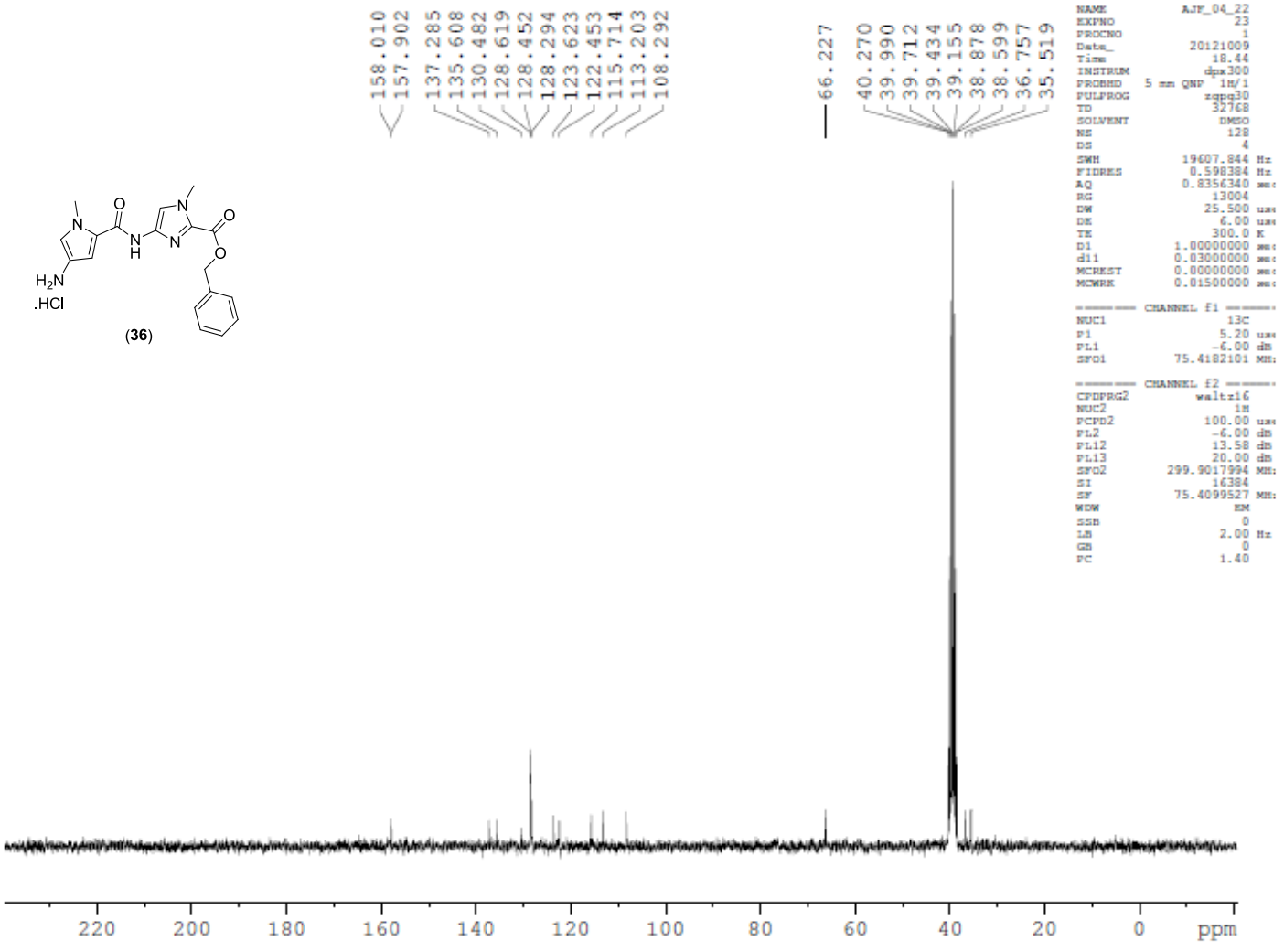
NAME	AJF_04_19
EXPNO	10
PROCNO	1
Date_	20121008
Time	9.51
INSTRUM	dpx300
PROBHD	5 mm QNP 1H/1
PULPROG	zg30
TD	32768
SOLVENT	DMSO
NS	16
DS	2
SWH	4789.272 Hz
FIDRES	0.146157 Hz
AQ	3.4210291 sec
RG	128
DW	104.400 usec
DE	6.00 usec
TE	300.0 K
D1	1.00000000 sec
MCREST	0.00000000 sec
MCWRK	0.01500000 sec
======== CHANNEL f1 ========	
NUC1	1H
P1	10.75 usec
PL1	-6.00 dB
SFO1	299.9017994 MHz
SI	16384
SF	299.9000000 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00


158.633
158.270
152.872
137.955
135.732
130.513
128.609
128.483
128.307
122.340
121.749
118.178
115.627
105.075
78.203
66.112
36.202
35.457
28.168
NAME AJF_04_36
EXPNO 11
PROCNO 1
Date_ 20121102
Time 17.59
INSTRUM dpx300
PROBHD 5 mm QNP 1H/1
PULPROG zgpg30
TD 32768
SOLVENT DMSO
NS 1024
DS 4
SWH 19607.844 Hz
FIDRES 0.598384 Hz
AQ 0.8356340 sec
RG 3251
DW 25.500 usec
DE 6.00 usec
TE 300.0 K
D1 1.00000000 sec
d11 0.03000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec
CHANNEL f1
NUC1 13C
P1 5.20 usec
PL1 -6.00 dB
SFO1 75.4182101 MHz
CHANNEL f2
CPDPRG2 waltz16
NUC2 1H
PCPD2 100.00 usec
PL2 -6.00 dB
PL12 13.58 dB
PL13 20.00 dB
SFO2 299.9017994 MHz
SI 16384
SF 75.4099497 MHz
WDW no
SSB 0
LB 0.00 Hz
GB 0
PC 1.40
220
200
180
160
140
120
100
80
60
40
20
0
ppm

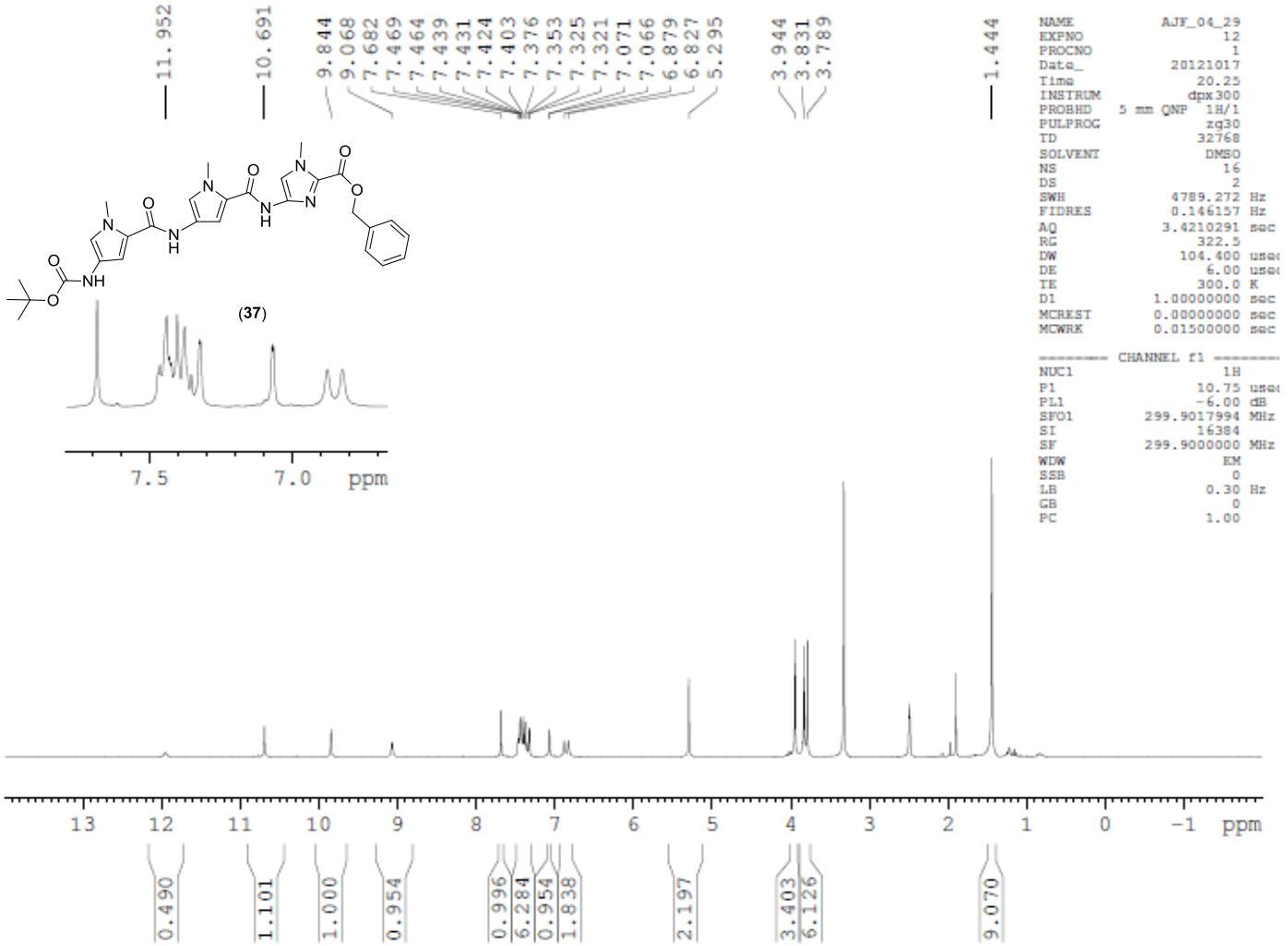
(**35**)

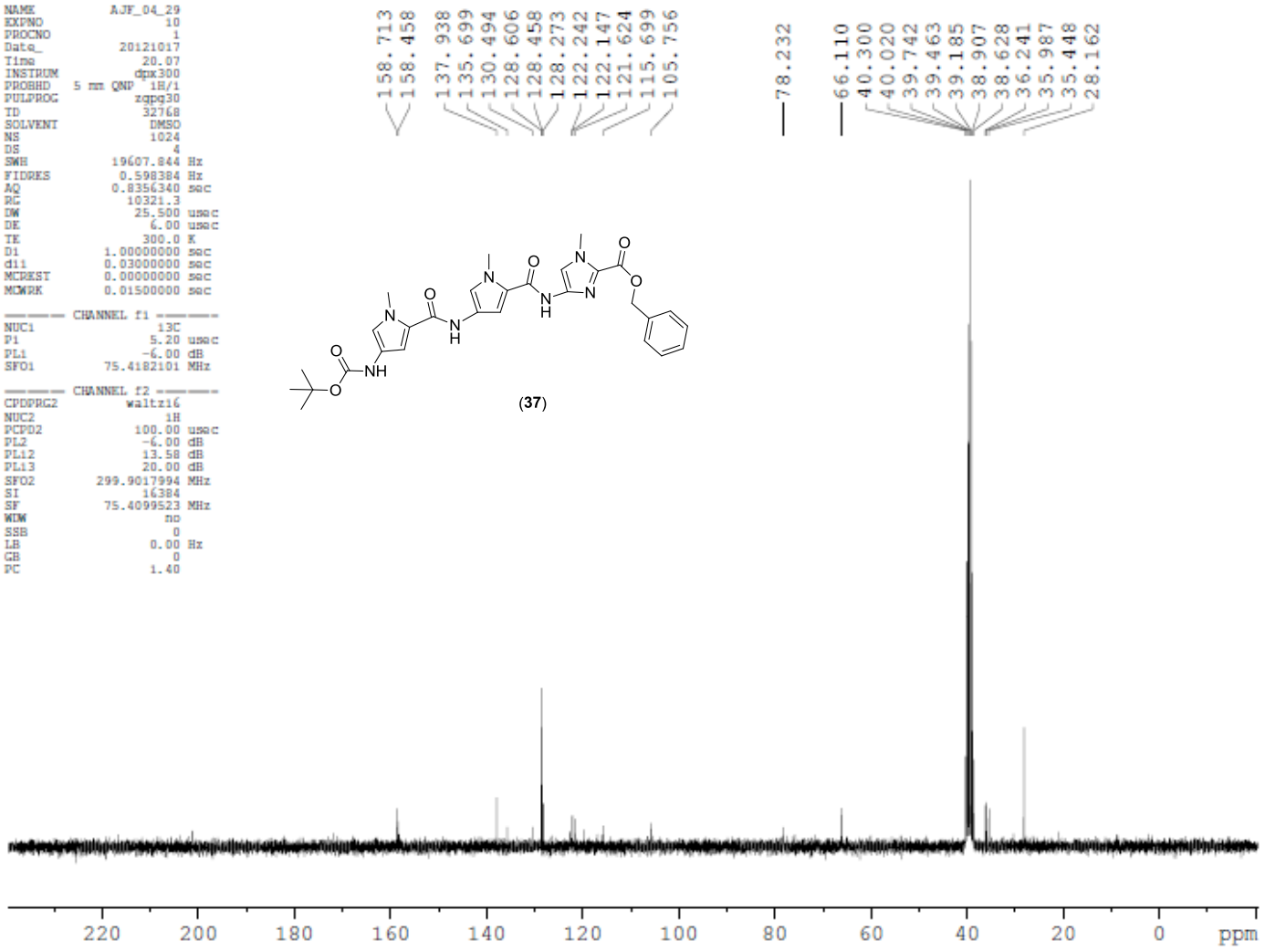

10.877
10.194
7.691
7.461
7.454
7.433
7.430
7.421
7.413
7.406
7.393
7.367
7.360
7.345
7.181
7.175
7.142
7.137
6.169
5.288
3.940
3.872
3.544
2.496
2.490
2.484
NAME AJF_04_22
EXPNO 10
PROCNO 1
Date_ 20121009
Time 10.22
INSTRUM dpx300
PROBHD 5 mm QNP 1H/1
PULPROG zg30
TD 32768
SOLVENT DMSO
NS 16
DS 2
SWH 4789.272 Hz
FIDRES 0.146157 Hz
AQ 3.4210291 sec
RG 228.1
DW 104.400 usec
DE 6.00 usec
TE 300.0 K
D1 1.00000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec
CHANNEL f1
NUC1 1H
P1 10.75 usec
PL1 -6.00 dB
SFO1 299.9017994 MHz
SI 16384
SF 299.9000000 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
7.6
7.4
7.2 ppm
13 12 11 10 9 8 7 6 5 4 3 2 1 0 −1 ppm
0.935
2.349
1.008
5.000
1.773
1.949
5.779

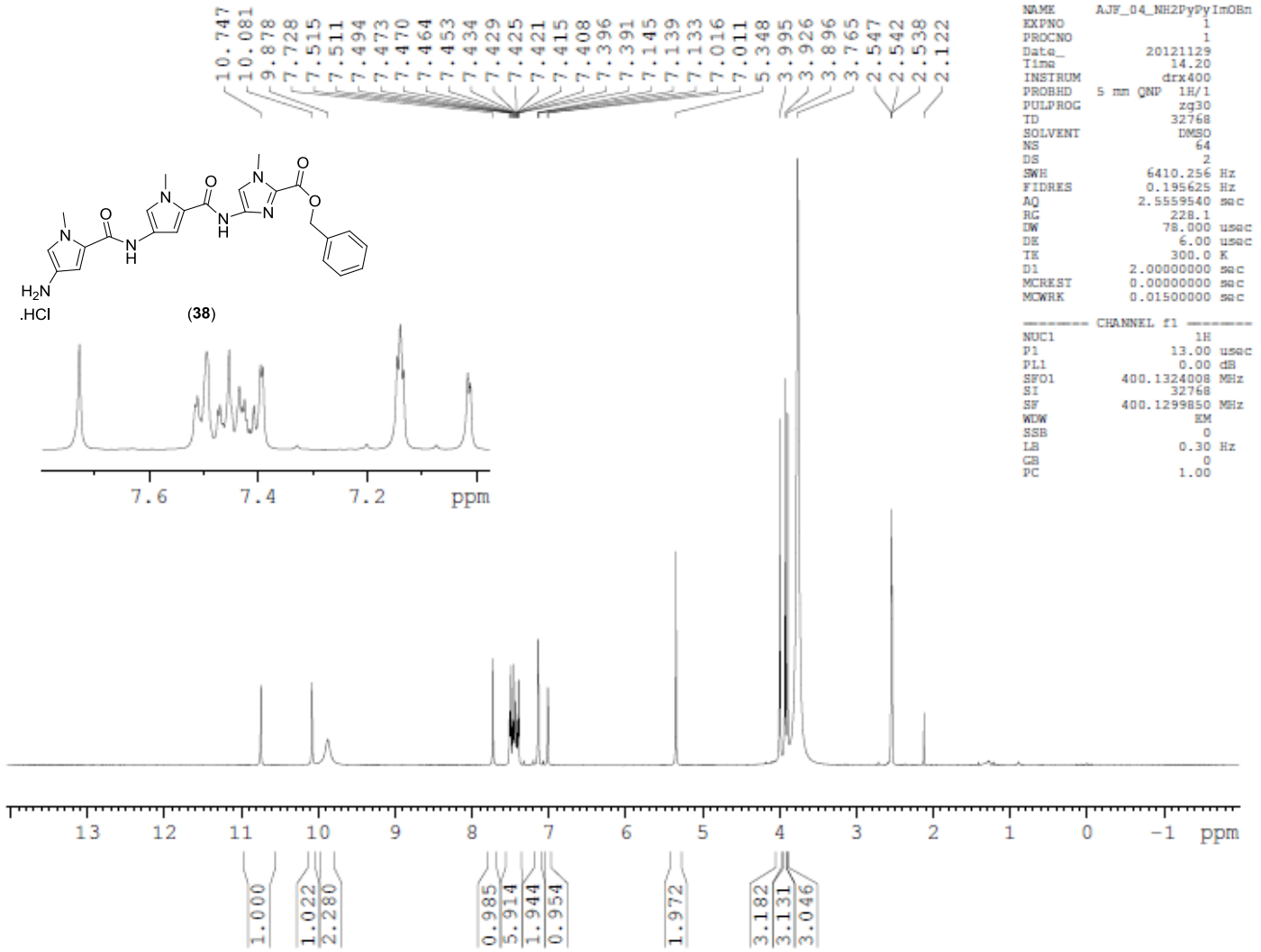
(**36**)

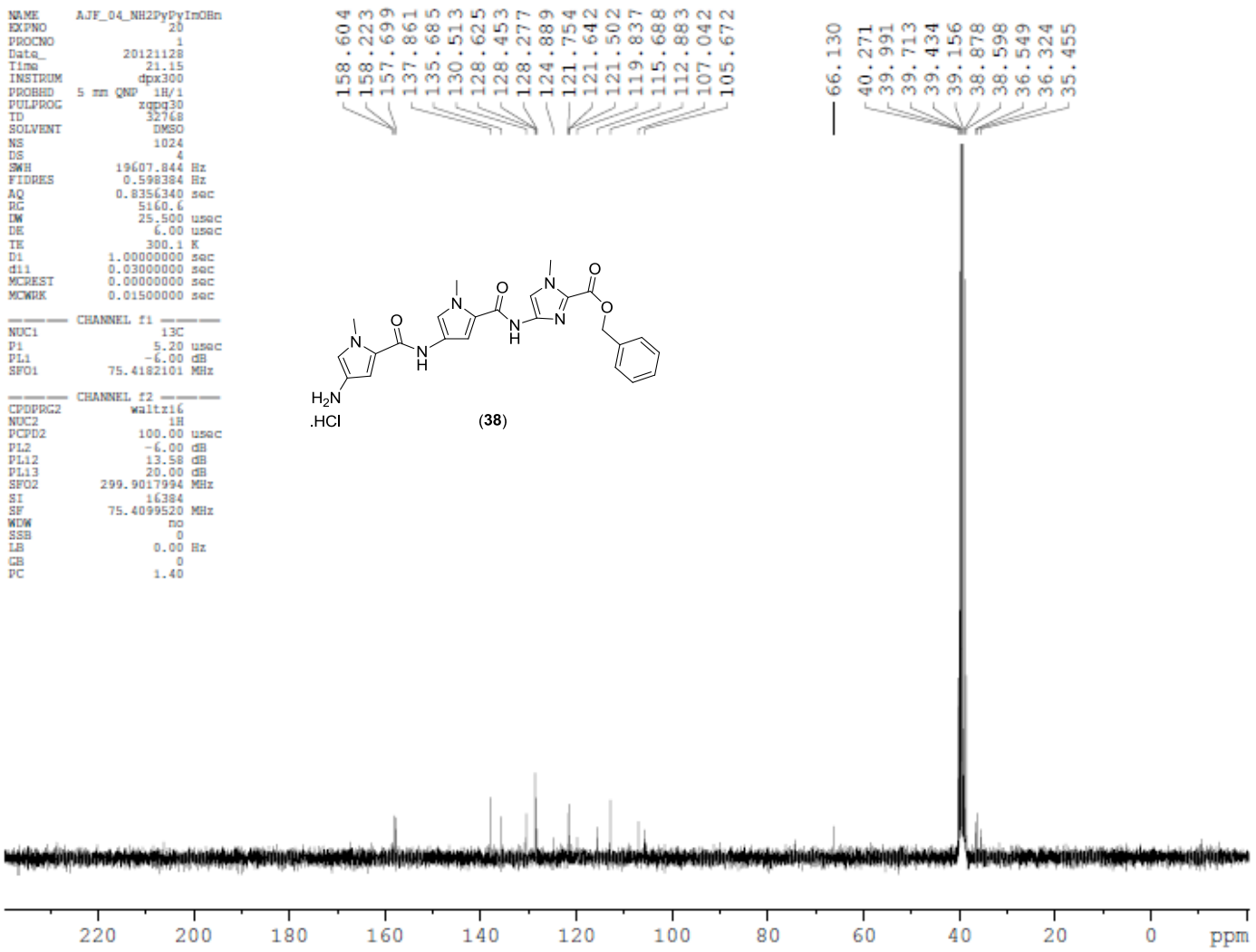

158.010
157.902
137.285
135.608
130.482
128.619
128.452
128.294
123.623
122.453
115.714
113.203
108.292
66.227
40.270
39.990
39.712
39.434
39.155
38.878
38.599
36.757
35.519
NAME AJF_04_22
EXPNO 23
PROCNO 1
Date_ 20121009
Time 18.44
INSTRUM dpx300
PROBHD 5 mm QNP 1H/1
PULPROG zgpg30
TD 32768
SOLVENT DMSO
NS 128
DS 4
SWH 19607.844 Hz
FIDRES 0.598384 Hz
AQ 0.8356340 sec
RG 13004
DW 25.500 usec
DE 6.00 usec
TE 300.0 K
D1 1.00000000 sec
d11 0.03000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec
CHANNEL f1
NUC1 13C
P1 5.20 usec
PL1 -6.00 dB
SFO1 75.4182101 MHz
CHANNEL f2
CPDPRG2 waltz16
NUC2 1H
PCPD2 100.00 usec
PL2 -6.00 dB
PL12 13.58 dB
PL13 20.00 dB
SFO2 299.9017994 MHz
SI 16384
SF 75.4099527 MHz
WDW EM
SSB 0
LB 2.00 Hz
GB 0
PC 1.40
220
200
180
160
140
120
100
80
60
40
20
0
ppm

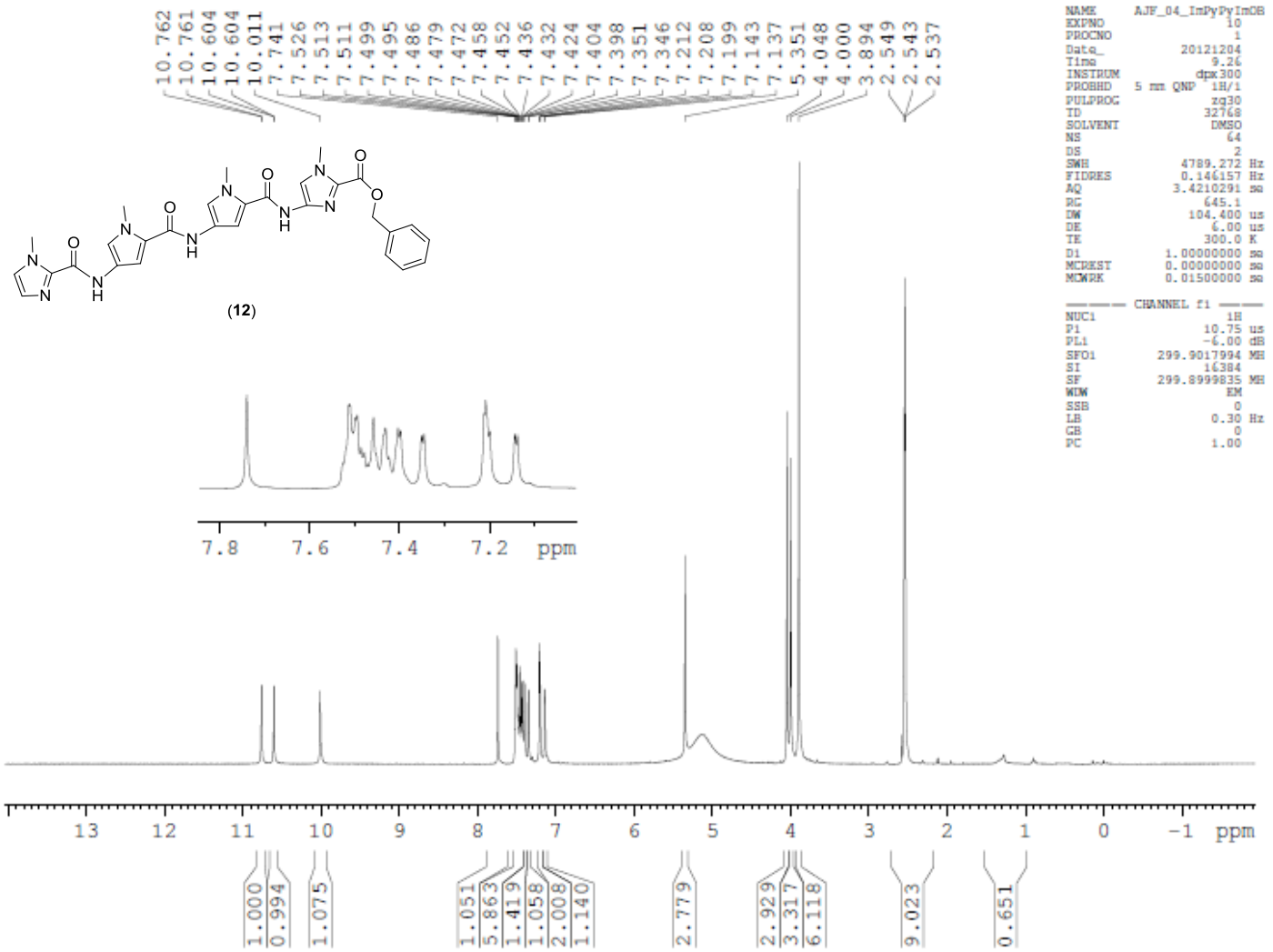
(**36**)

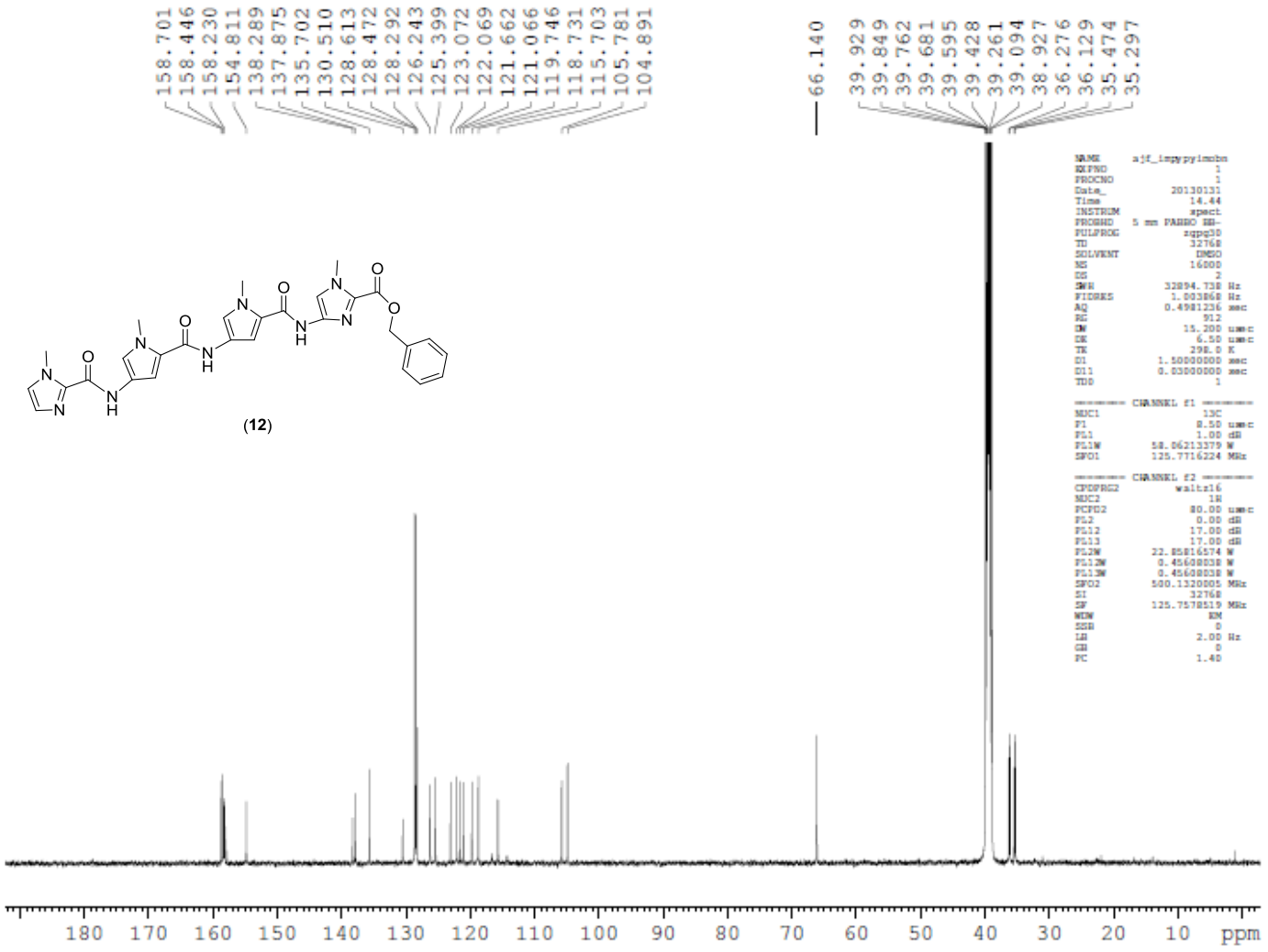

11.952
10.691
9.844
9.068
7.682
7.469
7.464
7.439
7.431
7.424
7.403
7.376
7.353
7.325
7.321
7.071
7.066
6.879
6.827
5.295
3.944
3.831
3.789
1.444
(37)
7.5
7.0
ppm
NAME AJF_04_29
EXPNO 12
PROCNO 1
Date_ 20121017
Time 20.25
INSTRUM dpx300
PROBHD 5 mm QNP 1H/1
PULPROG zg30
TD 32768
SOLVENT DMSO
NS 16
DS 2
SWH 4789.272 Hz
FIDRES 0.146157 Hz
AQ 3.4210291 sec
RG 322.5
DW 104.400 usec
DE 6.00 usec
TE 300.0 K
D1 1.00000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec
CHANNEL f1
NUC1 1H
P1 10.75 usec
PL1 -6.00 dB
SFO1 299.9017994 MHz
SI 16384
SF 299.9000000 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
ppm
0.490
1.101
1.000
0.954
0.996
6.284
0.954
1.838
2.197
3.403
6.126
9.070

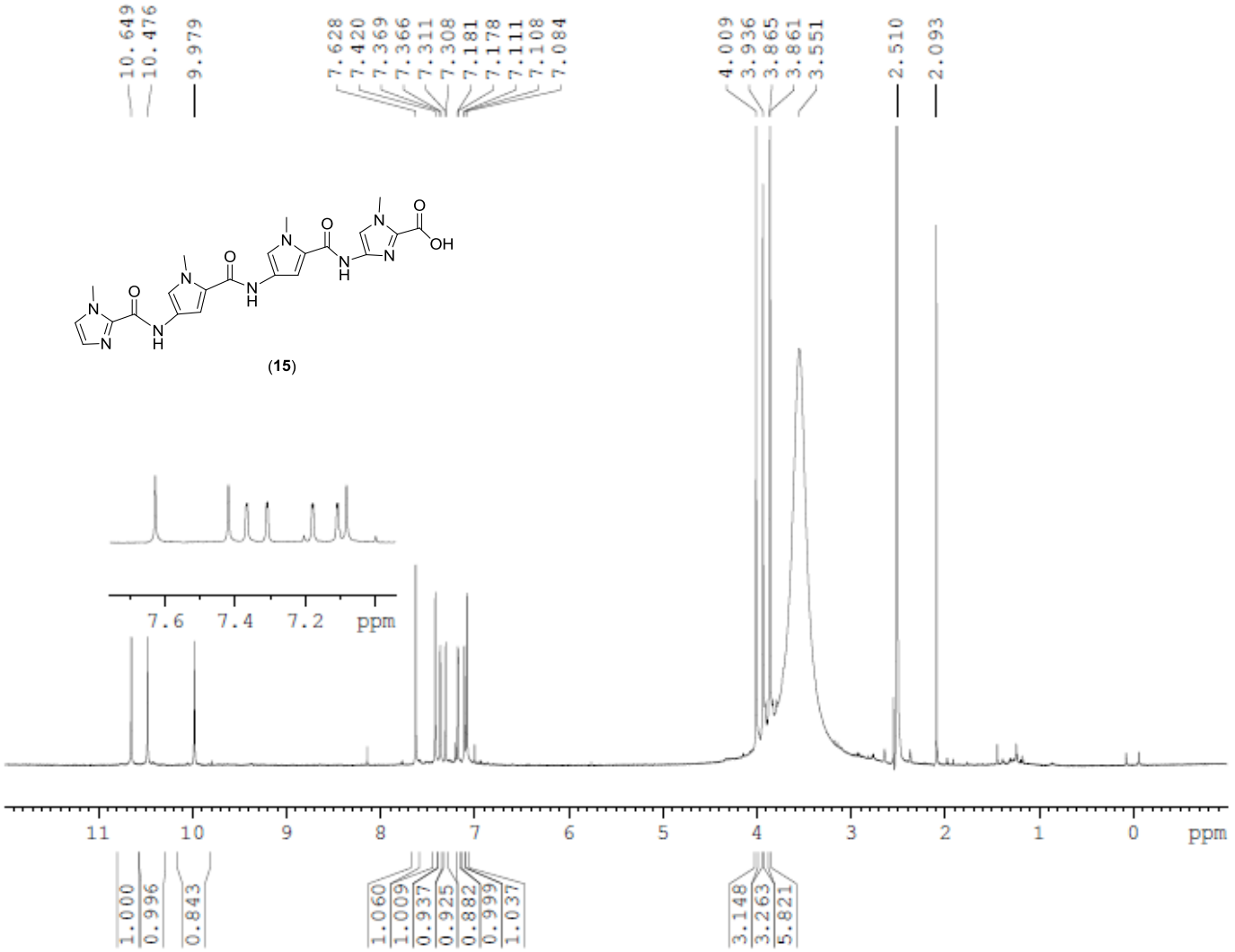

NAME AJF_04_29
EXPNO 10
PROCNO 1
Date_ 20121017
Time 20.07
INSTRUM dpx300
PROBHD 5 mm QNP 1H/1
PULPROG zgpg30
TD 32768
SOLVENT DMSO
NS 1024
DS 4
SWH 19607.844 Hz
FIDRES 0.598384 Hz
AQ 0.8356340 sec
RG 10321.3
DW 25.500 usec
DE 6.00 usec
TE 300.0 K
D1 1.00000000 sec
d11 0.03000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec
CHANNEL f1
NUC1 13C
P1 5.20 usec
PL1 -6.00 dB
SFO1 75.4182101 MHz
CHANNEL f2
CPDPRG2 waltz16
NUC2 1H
PCPD2 100.00 usec
PL2 -6.00 dB
PL12 13.58 dB
PL13 20.00 dB
SFO2 299.9017994 MHz
SI 16384
SF 75.4099523 MHz
WDW no
SSB 0
LB 0.00 Hz
GB 0
PC 1.40
158.713
158.458
137.938
135.699
130.494
128.606
128.458
128.273
122.242
122.147
121.624
115.699
105.756
78.232
66.110
40.300
40.020
39.742
39.463
39.185
38.907
38.628
36.241
35.987
35.448
28.162
(37)
220
200
180
160
140
120
100
80
60
40
20
0
ppm


10.747
10.081
9.878
7.728
7.515
7.511
7.494
7.473
7.470
7.464
7.453
7.434
7.429
7.425
7.421
7.415
7.408
7.396
7.391
7.145
7.139
7.133
7.016
7.011
5.348
3.995
3.926
3.896
3.765
2.547
2.542
2.538
2.122
NAME AJF_04_NH2PyPyImOBn
EXPNO 1
PROCNO 1
Date_ 20121129
Time 14.20
INSTRUM drx400
PROBHD 5 mm QNP 1H/1
PULPROG zg30
TD 32768
SOLVENT DMSO
NS 64
DS 2
SWH 6410.256 Hz
FIDRES 0.195625 Hz
AQ 2.5559540 sec
RG 228.1
DW 78.000 usec
DE 6.00 usec
TE 300.0 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 400.1324008 MHz
SI 32768
SF 400.1299850 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
H2N
.HCl
(38)
7.6
7.4
7.2
ppm
13
12
11
10
9
8
7
6
5
4
3
2
1
0
−1
ppm
1.000
1.022
2.280
0.985
5.914
1.944
0.954
1.972
3.182
3.131
3.046

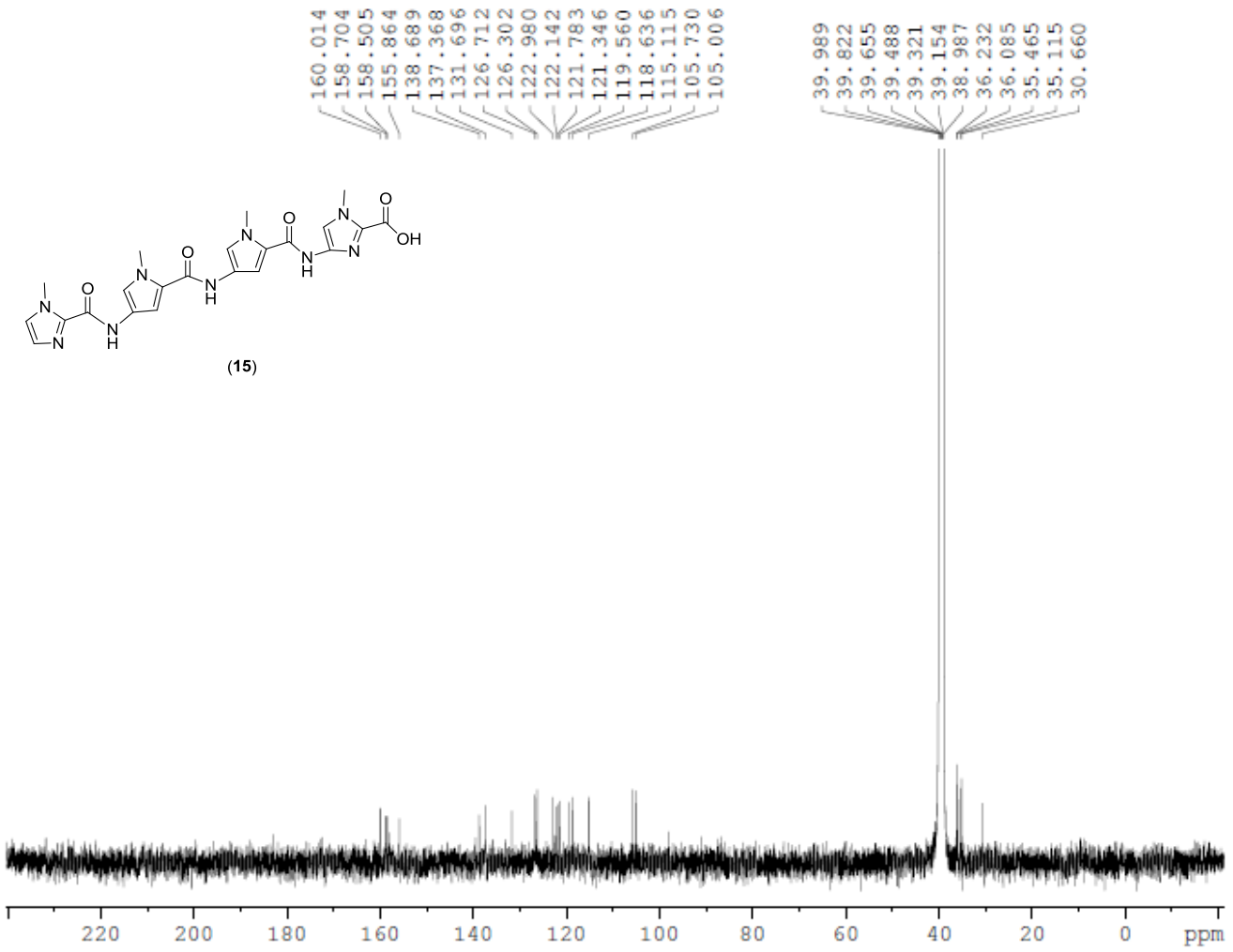

NAME AJF_04_NH2PyPyInOBn
EXPNO 20
PROCNO 1
Date_ 20121128
Time 21.15
INSTRUM dpx300
PROBHD 5 mm QNP 1H/1
PULPROG xqpg30
TD 32768
SOLVENT DMSO
NS 1024
DS 4
SWH 19607.844 Hz
FIDRES 0.598384 Hz
AQ 0.8356340 sec
RG 5160.6
DW 25.500 usec
DE 6.00 usec
TE 300.1 K
D1 1.00000000 sec
d11 0.03000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec
CHANNEL f1
NUC1 13C
P1 5.20 usec
PL1 -6.00 dB
SFO1 75.4182101 MHz
CHANNEL f2
CPDPRG2 waltz16
NUC2 1H
PCPD2 100.00 usec
PL2 -6.00 dB
PL12 13.58 dB
PL13 20.00 dB
SFO2 299.9017994 MHz
SI 16384
SF 75.4099520 MHz
WDW no
SSB 0
LB 0.00 Hz
GB 0
PC 1.40
158.604
158.223
157.699
137.861
135.685
130.513
128.625
128.453
128.277
124.889
121.754
121.642
121.502
119.837
115.688
112.883
107.042
105.672
66.130
40.271
39.991
39.713
39.434
39.156
38.878
38.598
36.549
36.324
35.455
.HCl
(38)
220
200
180
160
140
120
100
80
60
40
20
0
ppm


10.762
10.761
10.604
10.604
10.011
7.741
7.526
7.513
7.511
7.499
7.495
7.486
7.479
7.472
7.458
7.452
7.436
7.432
7.424
7.404
7.398
7.351
7.346
7.212
7.208
7.199
7.143
7.137
5.351
4.048
4.000
3.894
2.549
2.543
2.537
(12)
NAME AJF_04_ImPyPyImOB
EXPNO 10
PROCNO 1
Date_ 20121204
Time 9.26
INSTRUM dpx300
PROBHD 5 mm QNP 1H/1
PULPROG zg30
TD 32768
SOLVENT DMSO
NS 64
DS 2
SWH 4789.272 Hz
FIDRES 0.146157 Hz
AQ 3.4210291 sec
RG 645.1
DW 104.400 usec
DE 6.00 usec
TE 300.0 K
D1 1.00000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec
CHANNEL f1
NUC1 1H
P1 10.75 usec
PL1 -6.00 dB
SFO1 299.9017994 MHz
SI 16384
SF 299.8999835 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
7.8
7.6
7.4
7.2
ppm
13
12
11
10
9
8
7
6
5
4
3
2
1
0
−1
ppm
1.000
0.994
1.075
1.051
5.863
1.419
1.058
2.008
1.140
2.779
2.929
3.317
6.118
9.023
0.651


158.701
158.446
158.230
154.811
138.289
137.875
135.702
130.510
128.613
128.472
128.292
126.243
125.399
123.072
122.069
121.662
121.066
119.746
118.731
115.703
105.781
104.891
66.140
39.929
39.849
39.762
39.681
39.595
39.428
39.261
39.094
38.927
36.276
36.129
35.474
35.297
(12)
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


10.649
10.476
9.979
7.628
7.420
7.369
7.366
7.311
7.308
7.181
7.178
7.111
7.108
7.084
4.009
3.936
3.865
3.861
3.551
2.510
2.093
7.6
7.4
7.2
ppm
11
10
9
8
7
6
5
4
3
2
1
0
ppm
1.000
0.996
0.843
1.060
1.009
0.937
0.925
0.882
0.999
1.037
3.148
3.263
5.821

(**15**)


160.014
158.704
158.505
155.864
138.689
137.368
131.696
126.712
126.302
122.980
122.142
121.783
121.346
119.560
118.636
115.115
105.730
105.006
39.989
39.822
39.655
39.488
39.321
39.154
38.987
36.232
36.085
35.465
35.115
30.660
OH
220
200
180
160
140
120
100
80
60
40
20
0
ppm

(**15**)

7.0 References

1. E. E. Baird and P. B. Dervan, *J. Am. Chem. Soc.*, 1996, **118**, 6141–6146.

2. L. Grehn and U. Ragnarsson, *J. Org. Chem.*, 1981, **46**, 3492–3497.

3. W. Su, S. J. Gray, R. Dondi, and G. A. Burley, *Org. Lett.*, 2009, **11**, 3910–3.