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Supporting Information

Synthesis of Functionalized Guanidino Amino Acids

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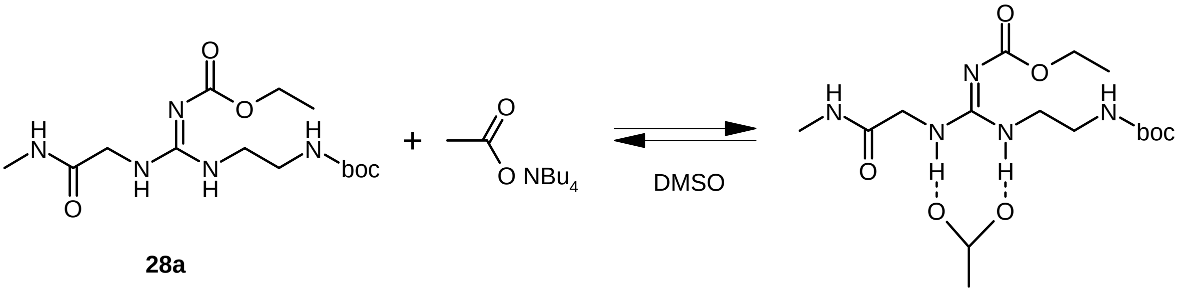
1) NMR titration of guanidine 28a with acetate ions in DMSO



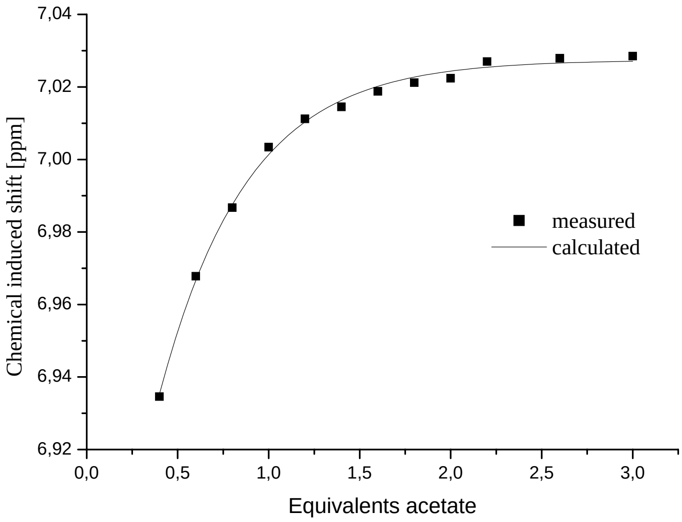
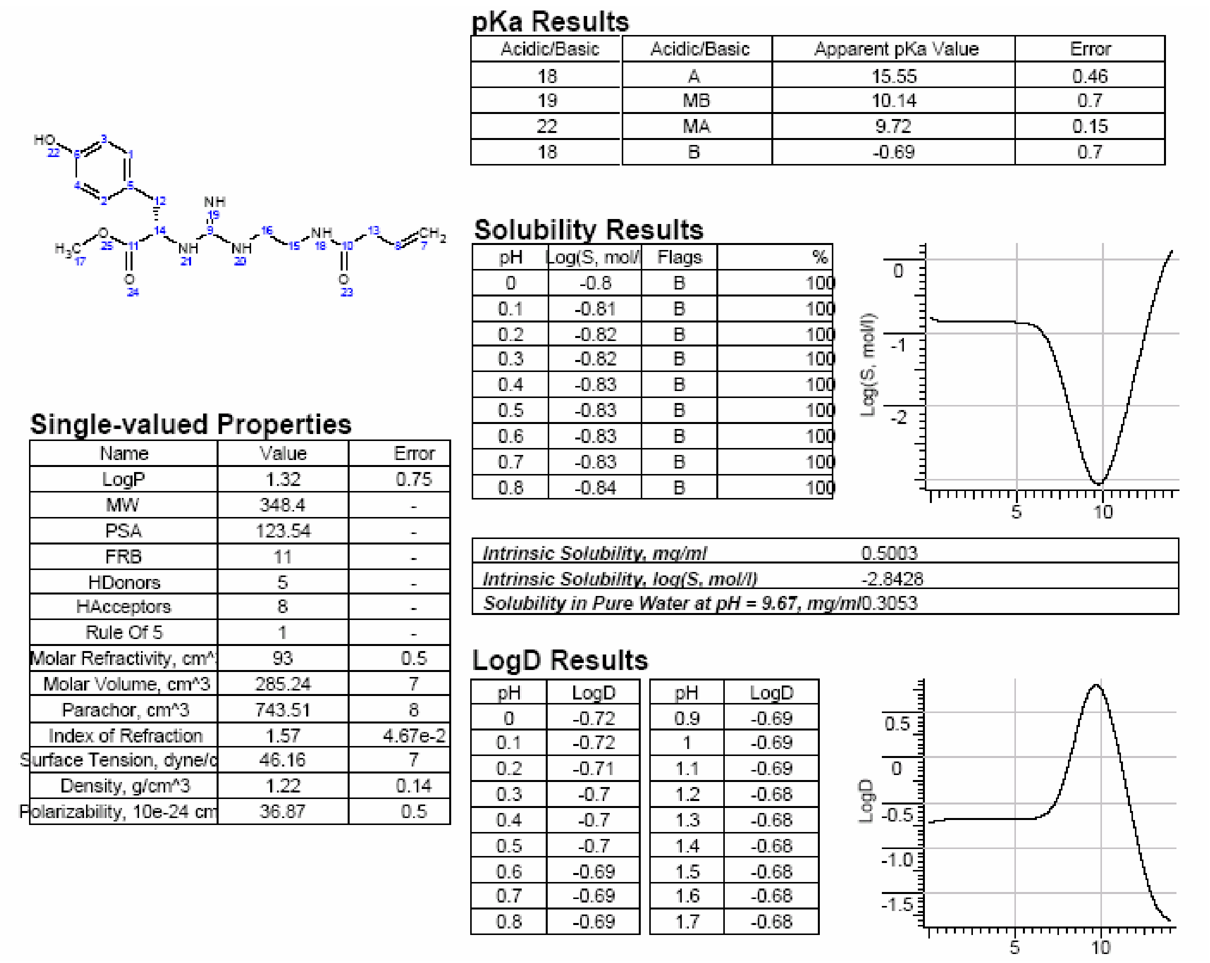


Figure S-1. NMR-titration curve of **28a** (2 mM) of **15** with Bu_4NOAc in DMSO-D_6, monitoring the chemically induced shift of the guanidine NH protons.

2) Estimation of properties of compounds **37-H**, **38-H** and **40-H**



pKa Results

Acidic/Basic	Acidic/Basic	Apparent pKa Value	Error
18	A	15.55	0.46
19	MB	10.14	0.7
22	MA	9.72	0.15
18	B	-0.69	0.7

Single-valued Properties

Name	Value	Error
LogP	1.32	0.75
MW	348.4	-
PSA	123.54	-
FRB	11	-
HDonors	5	-
HAcceptors	8	-
Rule Of 5	1	-
Molar Refractivity, cm^	93	0.5
Molar Volume, cm^3	285.24	7
Parachor, cm^3	743.51	8
Index of Refraction	1.57	4.67e-2
Surface Tension, dyne/c	46.16	7
Density, g/cm^3	1.22	0.14
Polarizability, 10e-24 cm	36.87	0.5

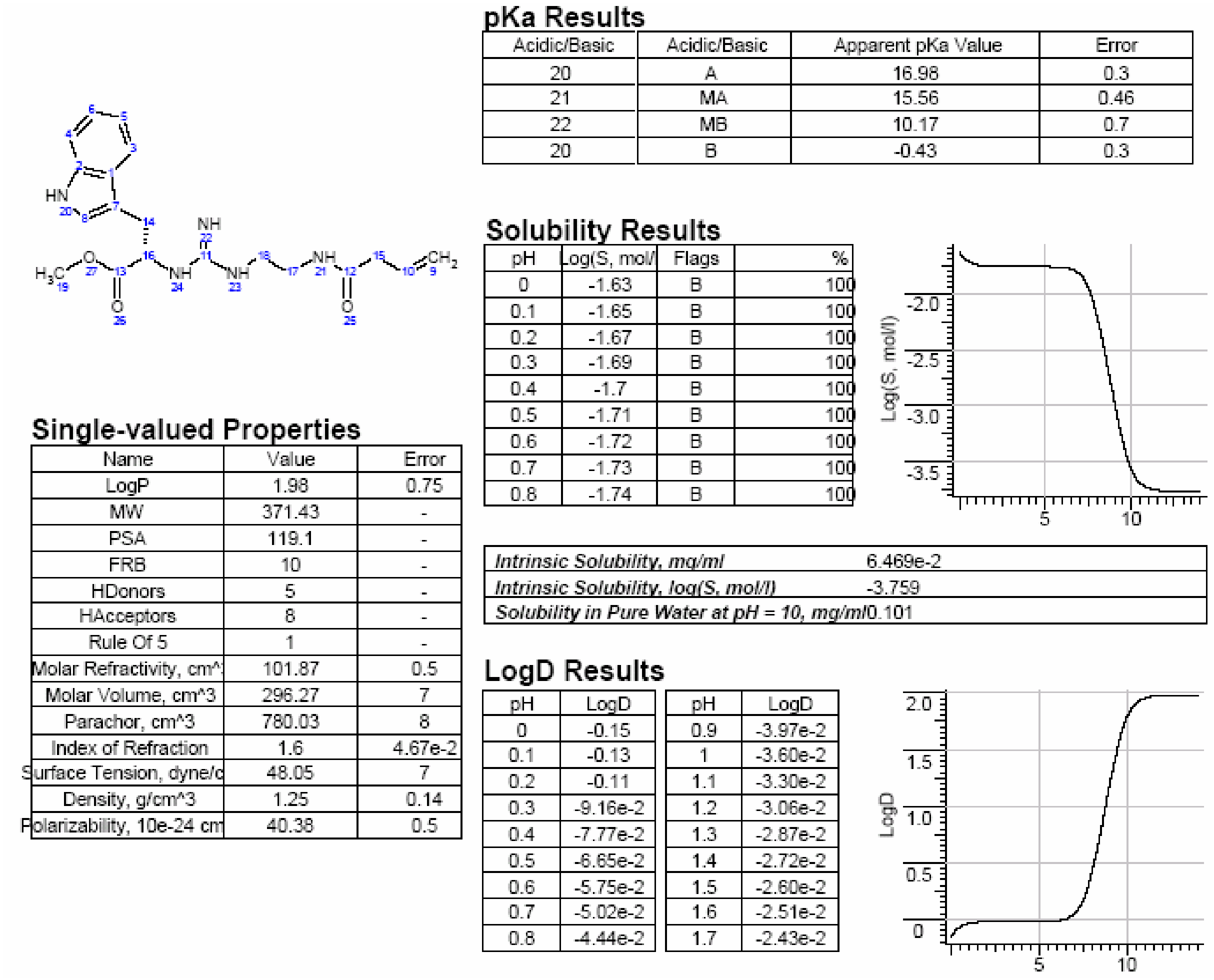
Solubility Results

pH	Log(S, mol/	Flags	%
0	-0.8	B	100
0.1	-0.81	B	100
0.2	-0.82	B	100
0.3	-0.82	B	100
0.4	-0.83	B	100
0.5	-0.83	B	100
0.6	-0.83	B	100
0.7	-0.83	B	100
0.8	-0.84	B	100

Intrinsic Solubility, mg/ml	0.5003
Intrinsic Solubility, log(S, mol/l)	-2.8428
Solubility in Pure Water at pH = 9.67, mg/ml	0.3053

LogD Results

pH	LogD	pH	LogD
0	-0.72	0.9	-0.69
0.1	-0.72	1	-0.69
0.2	-0.71	1.1	-0.69
0.3	-0.7	1.2	-0.68
0.4	-0.7	1.3	-0.68
0.5	-0.7	1.4	-0.68
0.6	-0.69	1.5	-0.68
0.7	-0.69	1.6	-0.68
0.8	-0.69	1.7	-0.68



pKa Results

Acidic/Basic	Acidic/Basic	Apparent pKa Value	Error
20	A	16.98	0.3
21	MA	15.56	0.46
22	MB	10.17	0.7
20	B	-0.43	0.3

Single-valued Properties

Name	Value	Error
LogP	1.98	0.75
MW	371.43	-
PSA	119.1	-
FRB	10	-
HDonors	5	-
HAcceptors	8	-
Rule Of 5	1	-
Molar Refractivity, cm^	101.87	0.5
Molar Volume, cm^3	296.27	7
Parachor, cm^3	780.03	8
Index of Refraction	1.6	4.67e-2
Surface Tension, dyne/c	48.05	7
Density, g/cm^3	1.25	0.14
Polarizability, 10e-24 cm	40.38	0.5

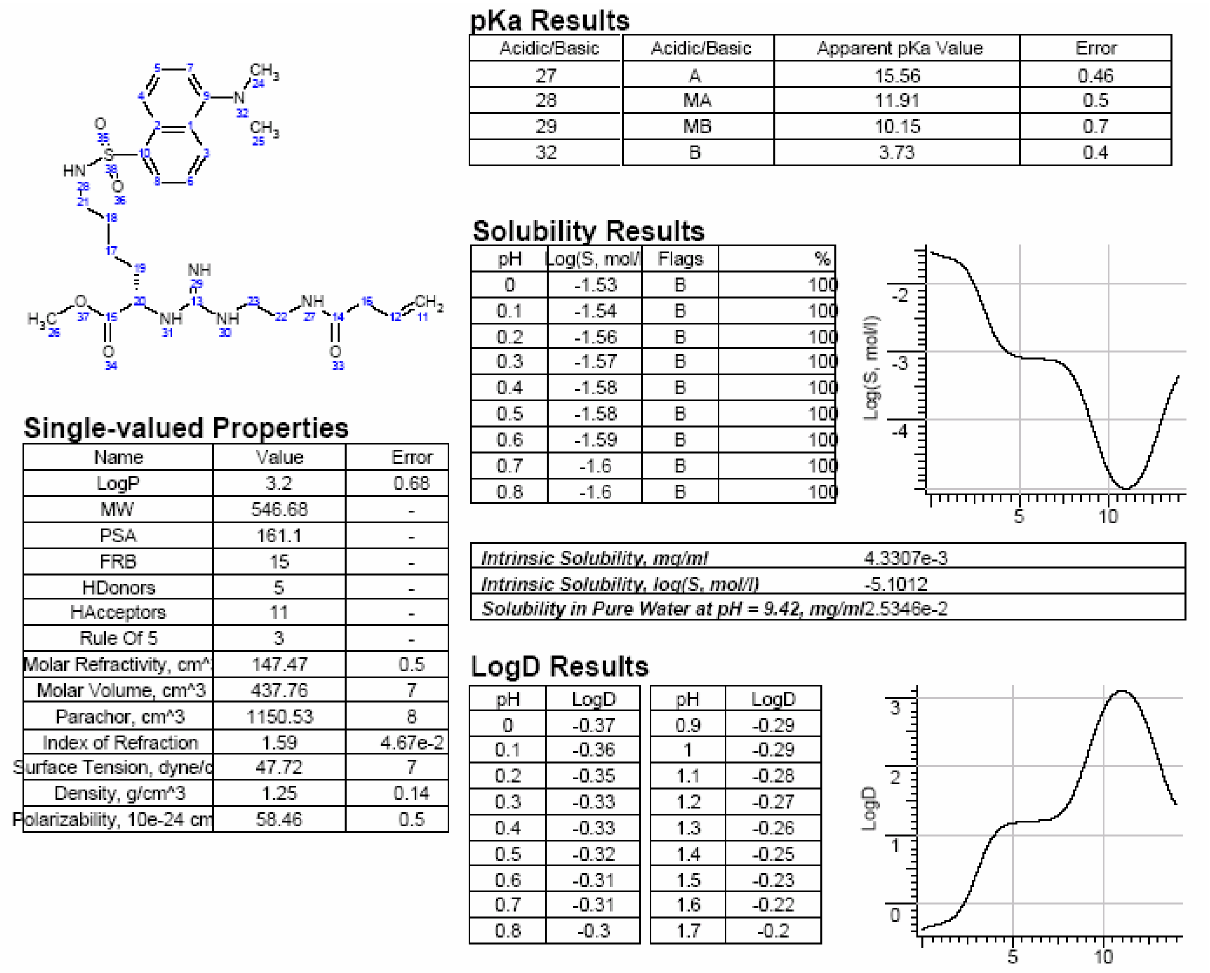
Solubility Results

pH	Log(S, mol/	Flags	%
0	-1.63	B	100
0.1	-1.65	B	100
0.2	-1.67	B	100
0.3	-1.69	B	100
0.4	-1.7	B	100
0.5	-1.71	B	100
0.6	-1.72	B	100
0.7	-1.73	B	100
0.8	-1.74	B	100

Intrinsic Solubility, mg/ml	6.469e-2
Intrinsic Solubility, log(S, mol/l)	-3.759
Solubility in Pure Water at pH = 10, mg/ml	0.101

LogD Results

pH	LogD	pH	LogD
0	-0.15	0.9	-3.97e-2
0.1	-0.13	1	-3.60e-2
0.2	-0.11	1.1	-3.30e-2
0.3	-9.16e-2	1.2	-3.06e-2
0.4	-7.77e-2	1.3	-2.87e-2
0.5	-6.65e-2	1.4	-2.72e-2
0.6	-5.75e-2	1.5	-2.60e-2
0.7	-5.02e-2	1.6	-2.51e-2
0.8	-4.44e-2	1.7	-2.43e-2



pKa Results

Acidic/Basic	Acidic/Basic	Apparent pKa Value	Error
27	A	15.56	0.46
28	MA	11.91	0.5
29	MB	10.15	0.7
32	B	3.73	0.4

Solubility Results

pH	Log(S, mol/	Flags	%
0	-1.53	B	100
0.1	-1.54	B	100
0.2	-1.56	B	100
0.3	-1.57	B	100
0.4	-1.58	B	100
0.5	-1.58	B	100
0.6	-1.59	B	100
0.7	-1.6	B	100
0.8	-1.6	B	100

Intrinsic Solubility, mg/ml	4.3307e-3
Intrinsic Solubility, log(S, mol/l)	-5.1012
Solubility in Pure Water at pH = 9.42, mg/ml	2.5346e-2

Single-valued Properties

Name	Value	Error
LogP	3.2	0.68
MW	546.68	-
PSA	161.1	-
FRB	15	-
HDonors	5	-
HAcceptors	11	-
Rule Of 5	3	-
Molar Refractivity, cm^	147.47	0.5
Molar Volume, cm^3	437.76	7
Parachor, cm^3	1150.53	8
Index of Refraction	1.59	4.67e-2
Surface Tension, dyne/c	47.72	7
Density, g/cm^3	1.25	0.14
Polarizability, 10e-24 cm	58.46	0.5

LogD Results

pH	LogD	pH	LogD
0	-0.37	0.9	-0.29
0.1	-0.36	1	-0.29
0.2	-0.35	1.1	-0.28
0.3	-0.33	1.2	-0.27
0.4	-0.33	1.3	-0.26
0.5	-0.32	1.4	-0.25
0.6	-0.31	1.5	-0.23
0.7	-0.31	1.6	-0.22
0.8	-0.3	1.7	-0.2

3) Emission spectra of compounds **37-H**, **38-H** and **40-H**

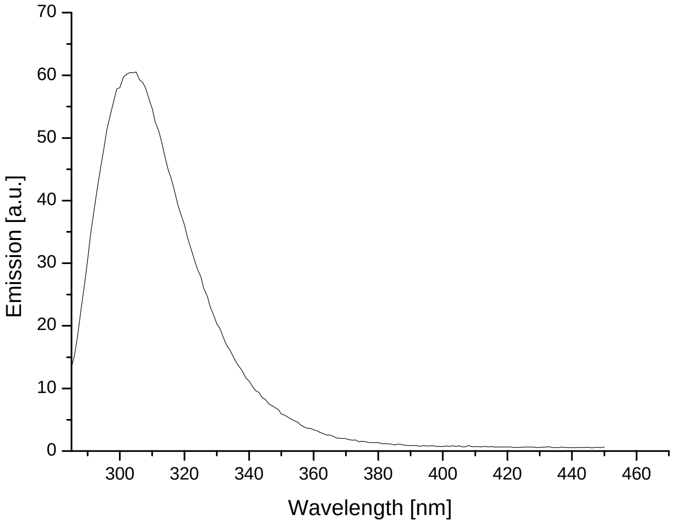


Figure S-2. Emission spectra of **37-H** in water (c = 10^{-4} M; excitation at 274 nm)

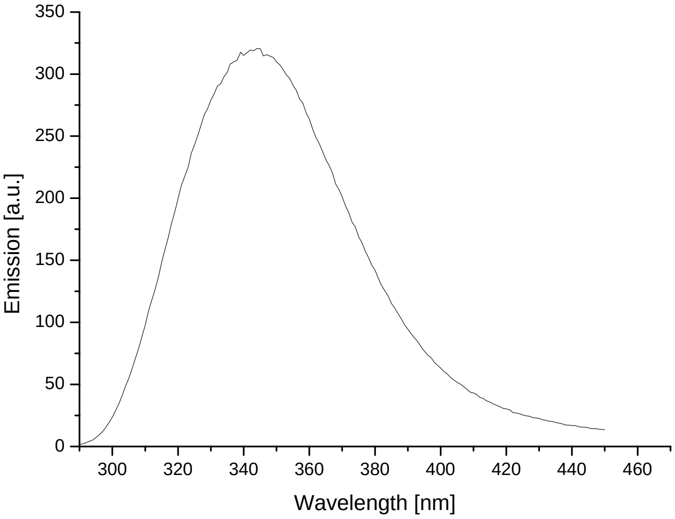


Figure S-3. Emission spectra of **38-H** in MeOH ($5x10^{-5}$ M; excitation 280 nm)

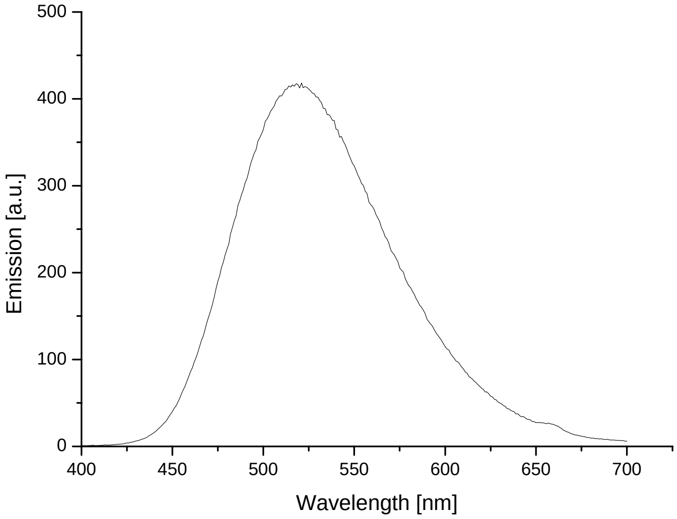


Figure S-4. Emission spectra of **40-H** in MeOH c = $5x10^{-5}$ M; excitation 330 nm)

4) Spectrophotometric titrations of compounds **37-H**, **38-H** and **40-H**

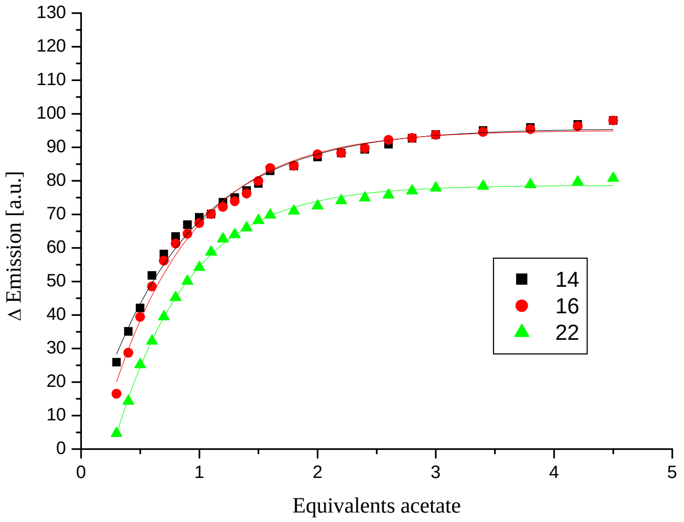


Figure S-5. Emission titration of a 2.02 10^{-4} M solution of compounds **37-H** (black), **38-H** **(**red) and **40-H** (green) with Bu_4NOAc in DMSO.

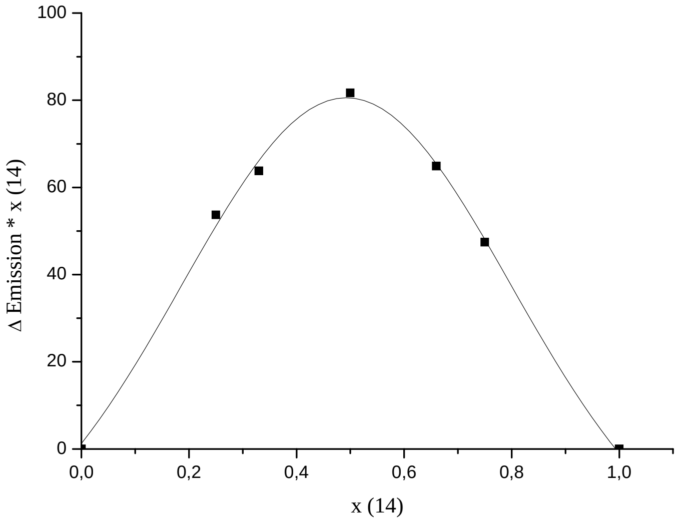


Figure S-6. Job´s plot analysis of the binding of **37-H** and Bu_4NOAc in DMSO.

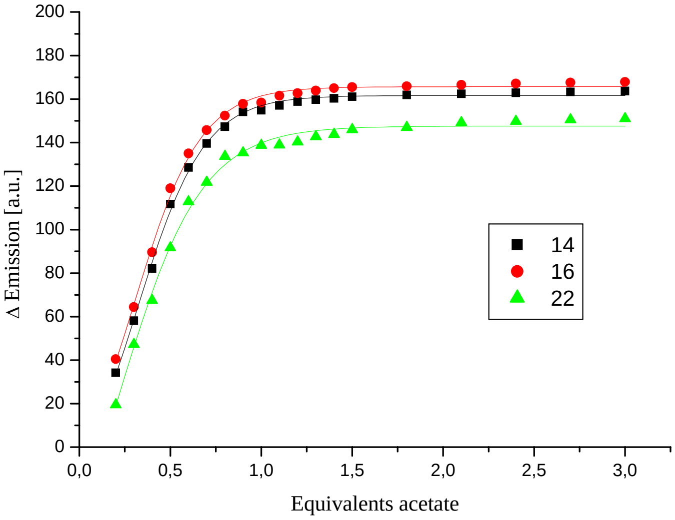


Figure S-7. Emission titration of a 2.45 10^{-4} M solution of **37-H (**black), **38-H** (red) and **40-H** (green) with Bu_4NOAc in MeOH.

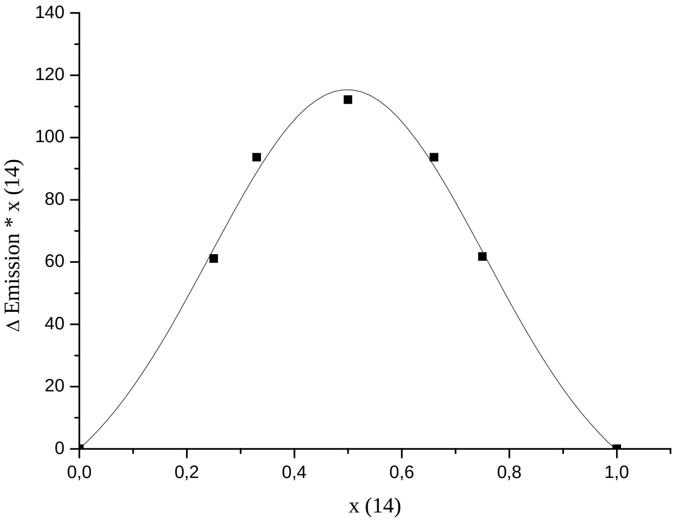


Figure S-8. Job´s plot analysis of the binding of **37-H** and Bu_4NOAc in MeOH.

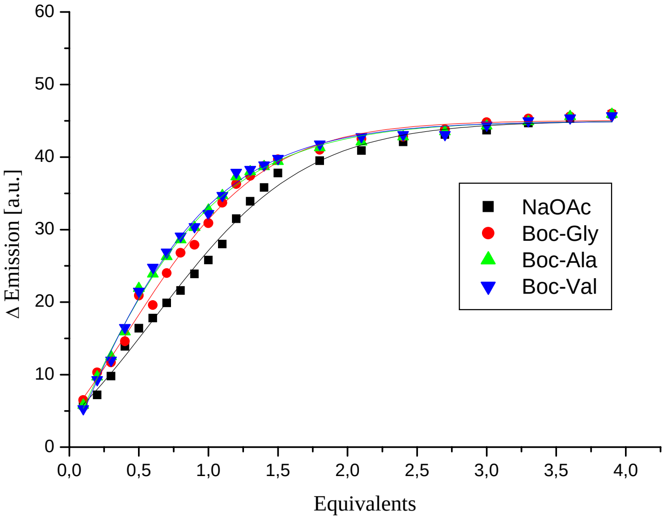


Figure S-9. Emission titration of a 2.6 10^{-4} M solution of **37-H in** H_2O (Tris, pH = 7.0, 50 mM) with different carboxylate salts.

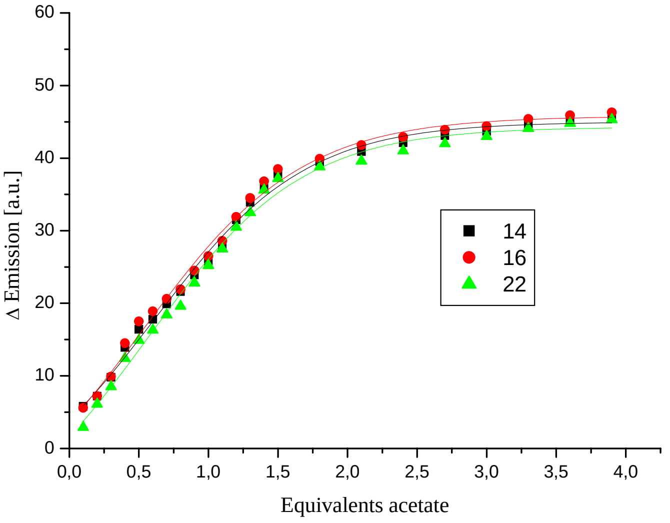


Figure S-10. Emission titration of a 2.6 10^{-4} M solution of **37-H (**black), **38-H** (red) and **40-H** (green) with NaOAc in H_2O (Tris, pH = 7.0, 50 mM).

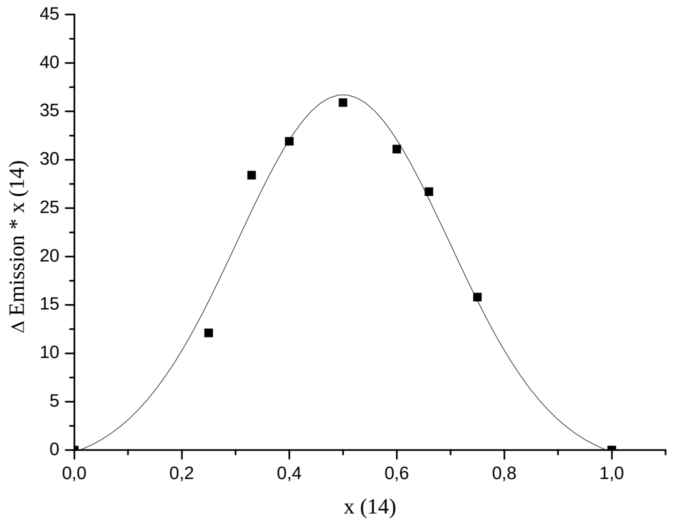


Figure S-11. Job´s plot analysis of the binding of **37-H** and NaOAc in H_2O (Tris, pH = 7.0, 50 mM).

A 1:1 mixture of guanidine amino acid **37-H** and sodium acetate in DMSO was diluted several times and absorption and emission spectra were recorded. While the absorption decreases linearly with concentration (following the Beer-Lambert law), the change in emission intensity is non linear. If proton transfer would have been occurred, the equilibrium between **37-H** and the acetate anion is determined by their pK values, which are independent from the concentration. Therefore the emission intensity must change linearly with dilution if proton transfer occurs, which is not observed. If a binding equilibrium between **37-H** and acetate exist, the equilibrium changes with concentration of the binding partners (because the equilibrium constant K is a constant) leading to non-linear change of emission intensity, which the experiment confirms.

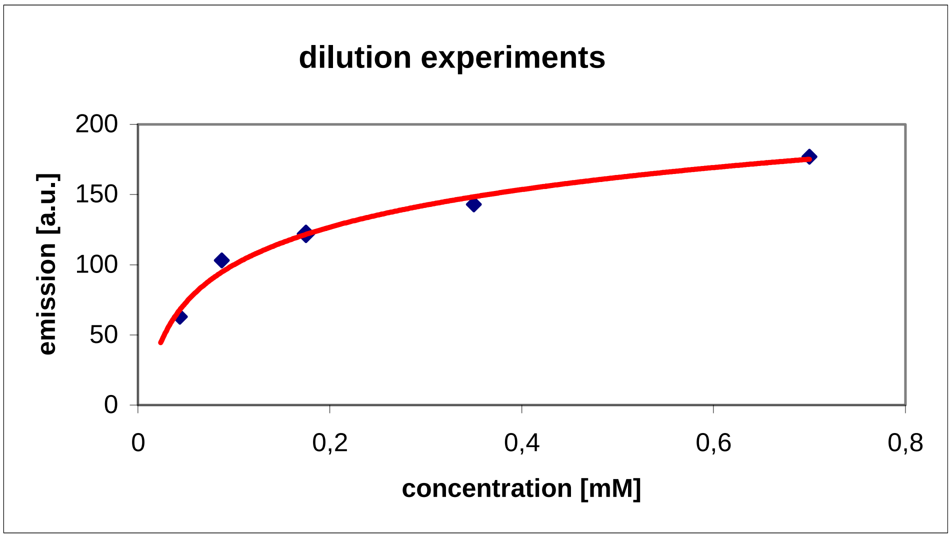


Figure S-12. Change in emission intensity by dilution of a solution of a 1:1 mixture of **37-H** and acetate in DMSO.

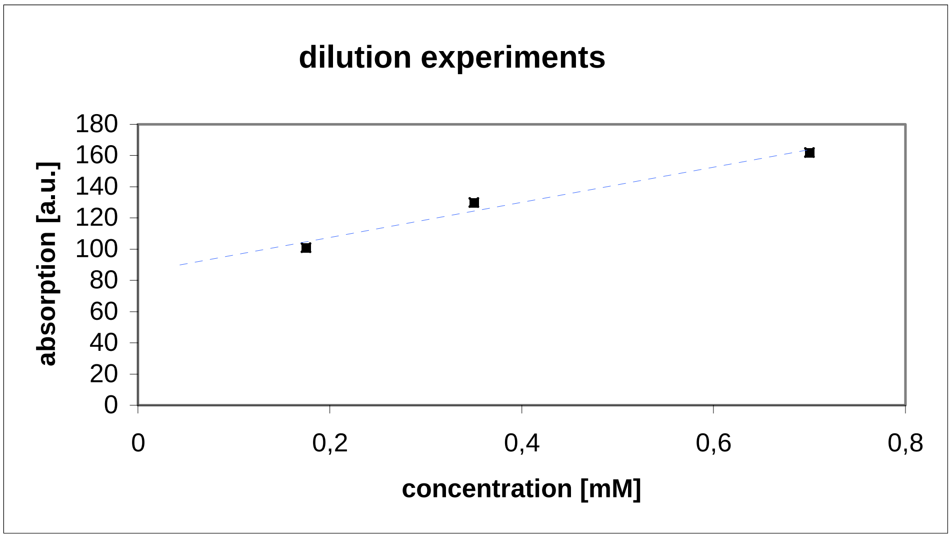


Figure S-13. Change in absorption intensity by dilution of a solution of a 1:1 mixture of **37-H** and acetate in DMSO.

6) Isothermal calorimetric titration of **37-H** with sodium acetate in aqueous buffer

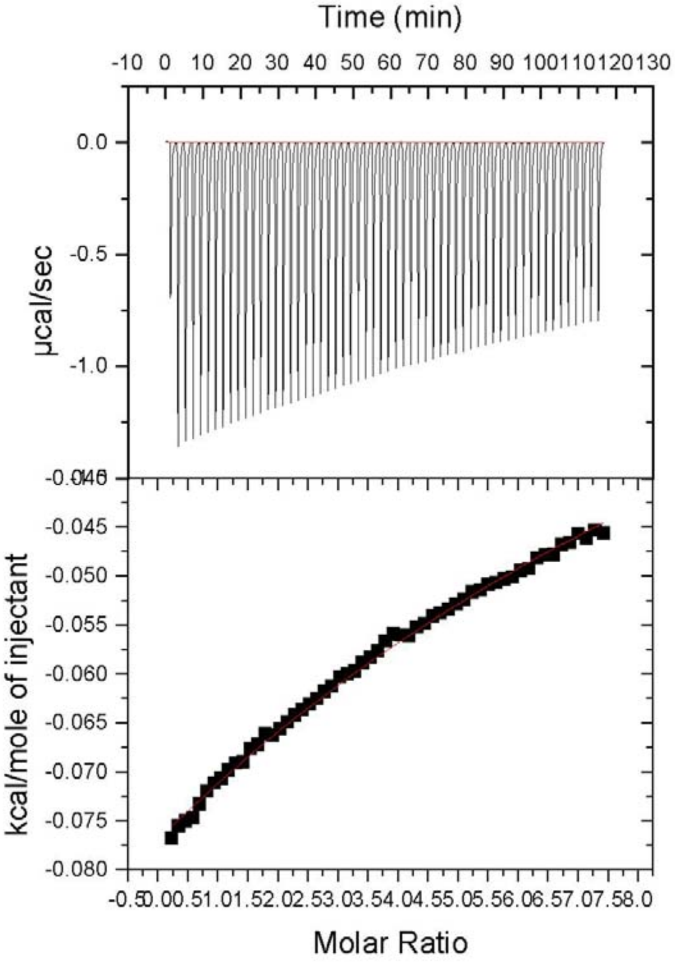


Figure S-14. Isothermal titration calorimetry of **37-H** and sodium acetate in buffered water (Tris, pH 7.0); lg*K* = 4.1 (+/-0.2); ΔH = - 7.4 (+/-0.3) kcal/mol; ΔS = 22 cal/mol K.

7) Synthesis and characterisation of compounds

General methods. Melting points (mp) are uncorrected; All ^{1}H- and ^{13}C-NMR spectra were measured in DMSO-d_6 at 300 K with TMS as internal reference at 300 or 75.5 MHz, resp., if not stated otherwise. Characterisation of NMR signals: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, bs = broad singlet, dd = double doublet. Integration is determined as the relative number of atoms. Thin Layer Chromatography (TLC) was performed on alumina plates coated with silica gel (layer thickness 0.2 nm). Visualisation was accomplished by UV-light (λ = 254 nm) and staining with ninhydrine in MeOH. Column Chromatography (CC) was performed on silica gel (70-230 mesh). All solvents were purified before use by standard laboratory procedures.

N-(Methoxycarbonylmethyl) N´-(ethoxycarbonyl)thiourea (**20**). Ethoxycarbonyl isothiocyanat **19** (2.32 g, 17.7 mmol) was added to a solution of glycine methylester (**18**) (3.33 g, 26.5 mmol) and NEt_3 (3.05 g, 4.1 mL, 30.1 mmol) in dichloromethane (40 mL) and stirred at room temp. for 5 h. After addition of water (30 mL) the phases were separated and the organic phase was washed twice with water (30 mL). The organic phase was dried (anhydrous Na_2SO_4) and the solvent was removed under reduced pressure. The crude product was purified by CC (EtOAc; R_f = 0.6) to give **20** (3.34 g, 86 %) as a pale yellow solid; mp: 81 °C. - IR (KBr): 2950 cm^{-1}, 2910, 1719, 1537, 1384, 1147. - ^{1}H NMR ($CDCl_3$): δ = 1.29 (t, J = 7.0 Hz, 3 H), 3.78 (s, 3 H), 4.23 (q, J = 7.0 Hz, 2 H), 4.41 (d, J = 4.9 Hz, 2 H), 8.46 (bs, 1 H), 10.13 (bs, 1 H). - ^{13}C NMR ($CDCl_3$): δ = 14.2 (+), 46.9 (-), 52.6 (+), 62.9 (-), 152.7 (C_{quat}), 168.9 (C_{quat}), 179.8 (C_{quat}). - MS (EI, 70 eV): m/z (%) = 220.1 (100) [M^+], 188.0 (50) [M – CH_3OH], 160.0 (33) [M – CH_3OH – C_2H_4], 132.0 (17) [M – $CH_3CH_2CO_2NH$]. – Elemental analysis calcd. (%) for $C_7H_{12}N_2O_4S$ (220.24): C 38.17, H 5.50, N 12.73; found C 38.11, H 5.43, N 12.78.

[2-(1-Ethoxycarbonyl-5-oxo-4,5-dihydro 1H-imidazol-2-ylamino)-ethyl] carbamic acid tert-butyl ester (22). Thiourea **20** (88 mg, 0.39 mmol) was added to a solution of 1-(*tert*-butyloxycarbonyl) ethyldiamine (92 mg, 0.58 mmol) and NEt_3 (79 mg, 0.11 mL, 0.78 mmol) in DMF (20 mL). Hg(II) chloride (125 mg, 0.46 mmol) was added in one portion and the reaction mixture was stirred for 15 h at room temp. The mixture was filtered over Celite and the solvent was removed under reduced pressure. The crude product was purified by CC (EtOAc; R_f = 0.5) to yield **22** (99 mg, 81 %) as a white solid; mp: 81 °C. - IR (KBr): 3389 cm^{-1}, 3325, 2976, 2924, 1750, 1688, 1533, 1474, 1251. - ^{1}H NMR: δ = 1.19 (t, J = 7.1 Hz, 3 H), 1.35 (s, 9 H), 3.11 (q, *J* = 5.8 Hz, 2 H), 3.50 (t, *J* = 5.8 Hz, 2 H), 3.96 – 4.08 (m, 4 H), 6.87 (t, *J* = 6.0 Hz, 1 H), 8.92 (bs, 1 H). - ^{13}C NMR (DMSO-d$_6$): δ = 14.3 (+), 28.1 (+, 3 C), 37.5 (-), 38.9 (-), 47.4 (-), 60.1 (-), 77.5 (C$_{quat}$), 161.1 (C$_{quat}$), 162.3 (C$_{quat}$), 171.9 (C$_{quat}$). - MS (EI, 70 eV): m/z (%) = 314.1 (9) [M$^+$], 269.1 (4) [M$^+$ - C_2H_5O], 241.0 (14) [M$^+$ - C_4H_9O], 213.0 (11) [M$^+$ - $C_4H_9CO_2$]. - Elemental analysis calcd. (%) for $C_{13}H_{22}N_4O_5$ (314.16): C 49.66, H 7.06, N 17.83; found C 49.59, H 7.09, N 17.96.

[N´-(2-tert-Butoxycarbonylamino-ethyl) N´´-ethoxycarbonyl guanidino] acetic acid (**25a**). Thiourea **24a** (300 mg, 1.45 mmol) was added to a solution of 1-(*tert*-butyloxycarbonyl) ethyldiamine (348 mg, 2.17 mmol) and NEt_3 (323 mg, 0.44 mL, 3.19 mmol) in DMF (20 mL). Hg(II) chloride (472 mg, 1.74 mmol) was added in one portion and the reaction mixture was stirred for 15 h at room temp. The mixture was filtered over Celite and the solvent was removed under reduced pressure. The crude product was dissolved in H_2O (25 mL) and acidified with 5 % $KHSO_4$ to pH = 2-3. The aqueous layer was extracted with EtOAc (3 x 50 mL). The combined organic layers were dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude product was purified by CC (EtOAc; R_f = 0.2) to give **24a** (366 mg, 76 %) as a white solid; mp: 93 °C. - ^{1}H NMR: δ = 1.21 (t, *J* = 7.1 Hz, 3 H), 1.38 (s, 9 H), 2.97 (m, 2 H), 3.09 (m, 2 H), 3.75 (d, *J* = 5.2 Hz, 2 H), 4.12 (q, *J* = 7.1 Hz, 2 H), 6.82 (t, *J* = 5.5 Hz, 1 H), 7.95 (t, *J* = 5.8 Hz, 1 H), 8.11 (t, *J* = 5.2 Hz), 10.05 (bs, 1 H). - ^{13}C NMR (DMSO-d$_6$): δ = 14.1 (+), 28.1 (+), 38.7 (-), 39.7 (-), 42.4 (-), 61.1 (-), 77.6 (C$_{quat}$), 152.8 (C$_{quat}$), 154.3 (C$_{quat}$), 155.5 (C$_{quat}$), 168.5 (C$_{quat}$). - MS (EI, 70 eV): m/z (%) = 332.1 (5) [M$^+$], 276.0 (10) [M$^+$ - C_4H_8], 259.0 (20) [M$^+$ - C_4H_8O], 231.1 (5) [M$^+$ - $C_4H_8CO_2$], 203.0 (40) [M$^+$ - Boc – C_2H_4]. – $C_{13}H_{24}N_4O_6$ (332.36).

3-Ethoxycarbonylthiourea propionic acid (**24b**). Ethoxycarbonyl isothiocyanat **19** (981 mg, 0.845 mL, 7.48 mmol) in dioxane (20 mL) was added to solution of β-Ala-OH **23b** (1 g, 11.22 mmol) in 10 mL of H_2O and 5 mL of 1N NaOH. The mixture was stirred at room temp. for 12 h and the organic solvent was removed under reduced pressure. The water phase was acidified with 5 % $KHSO_4$ solution to pH = 2. After addition of EtOAc (25 mL) the phases were separated and the water phase was extracted with EtOAc (2 x 40 mL). The combined organic phases were dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude product was purified by CC (EtOAc; R_f = 0.45) to yield **24b** (1.22 g, 74 %) as a white solid; mp: 78 °C. - IR (KBr): 3183 cm^{-1}, 2973, 2915, 1720, 1548, 1416, 1259, 1151. - ^{1}H NMR: δ = 1.21 (t, *J* = 7.1 Hz, 3 H), 2.52 - 258 (m, 2 H), 3.71 – 3.78 (m, 2 H), 4.14 (q, *J* =

7.1 Hz, 2 H), 9.92 – 10.08 (m, 1 H), 10.95 (s, 1 H), 12.37 (bs, 1 H). - ^{13}C NMR (DMSO-d_6): δ = 14.0 (+), 32.3 (-), 40.2 (-), 61.6 (-), 153.3 (C_{quat}), 172.8 (C_{quat}), 179.4 (C_{quat}). - MS (CI - MS, NH_3): m/z (%) = 220.9 (100) [MH^+]. - Elemental analysis calcd. (%) for $C_7H_{12}N_2O_4S$ (220.24): C 38.17, H 5.49, N 12.72; found C 38.15, H 5.21, N 12.73.

[N´-(2-tert-Butoxycarbonylaminoethyl) N´´-ethoxycarbonyl guanidino] propionic acid (**25c**). Thiourea **24b** (300 mg, 1.36 mmol) was added to a solution of 1-(*tert*-butyloxycarbonyl) ethyldiamine (327 mg, 2 mmol) and NEt_3 (303 mg, 0.4 mL, 2.99 mmol) in DMF (20 mL). Hg(II) chloride (442 mg, 1.63 mmol) was added in one portion and the reaction mixture was stirred for 15 h at room temp. The mixture was filtered over Celite and the solvent was removed under reduced pressure. The crude product was dissolved in H_2O (25 mL) and acidified with 5 % $KHSO_4$ to pH = 2-3. The aqueous layer was extracted with EtOAc (3 x 50 mL). The combined organic layers were dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude product was purified by CC (EtOAc; R_f = 0.25) to give **25c** (350 mg, 74 %), as a white solid; mp: 95 °C. - IR (KBr): 3325 cm^{-1}, 2980, 1690, 1644, 1536, 1367, 1243, 1173, 1018, 979, 769. - ^{1}H NMR: δ = 1.18 (t, J = 7.1 Hz, 3 H), 1.37 (s, 9 H), 2.23 – 2.28 (m, 2 H), 2.94 – 3.08 (m, 4 H), 3.29 – 3.38 (m, 2 H), 4.09 (q, J = 7.1 Hz, 2 H), 6.78 (bs, 1 H), 7.92 – 7.98 (m, 2 H), 9.92 (bs, 1 H). - ^{13}C NMR (DMSO-d_6): δ = 14.1 (+), 28.1 (+), 35.0 (-), 35.5 (-), 38.6 (-), 39.4 (-), 61.0 (-), 77.5 (C_{quat}), 152.6 (C_{quat}), 154.3 (C_{quat}), 155.5 (C_{quat}), 170.5 (C_{quat}). - MS (CI - MS, NH_3): m/z (%) = 364.0 (3) [MNH_4^+], 347.0 (100) [MH^+], 290.9 (26) [MH^+ - C_4H_8], 247.0 (5) [MH^+ - Boc]. – $C_{14}H_{26}N_4O_6$ (346.19).

[N´-(2-Allyloxycarbonylamino-ethyl) N´´ethoxycarbonyl guanidino]methyl acetamide (**28b**). Thiourea **27** (360 mg, 1.64 mmol) was added to a solution of 1-allyloxycarbonyl ethylenediamine (580 mg, 2.37 mmol) and NEt_3 (830 mg, 1.1 mL, 8.2 mmol) in DMF (20 mL). Hg(II) chloride (535 mg, 1.97 mmol) was added in one portion and the reaction mixture was stirred for 15 h at room temp. The mixture was filtered over Celite and the solvent was removed under reduced pressure. The crude product was dissolved in H_2O (25 mL) and acidified with 5 % $KHSO_4$ to pH = 2-3. The aqueous layer was extracted with EtOAc (3 x 50 mL). The combined organic layers were dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude product was purified by CC (EtOAc; R_f = 0.1) to yield **28b** (428 mg, 79 %) as a white solid, mp: 102 °C. - IR (KBr): 3323 cm^{-1}, 3085, 2982, 2948, 1721, 1655, 1456, 1251, 1151, 1108, 1027, 914, 874, 769, 688. - ^{1}H NMR: δ = 1.21 (t, J = 7.1 Hz, 3 H), 2.60 (d, J = 5.0 Hz, 2 H), 2.98 – 3.18 (m, 4 H), 3.75 (d, J = 5.0 Hz, 2 H), 4.12 (q, J = 7.1

Hz, 2 H), 4.46 (d, 5.2 Hz), 5.17 (dd, *J* = 1.7 Hz, 9.3 Hz, 1 H), 5.27 (dd, *J* = 1.7 Hz, 16.2 Hz, 1 H), 5.83 – 5.97 (m, 1 H), 7.23 (t, *J* = 5.5 Hz, 1 H), 8.03 (bs, 1 H), 8.67 (bs, 1 H). - ^{13}C NMR (DMSO-d$_6$): δ = 14.2 (+), 25.3 (+), 38.5 (-), 39.7 (-), 42.6 (-), 61.0 (-), 64.3 (-), 117.0 (-), 133.5 (+), 152.8 (C$_{quat}$), 154.3 (C$_{quat}$), 155.9 (C$_{quat}$), 168.6 (C$_{quat}$). - MS (ESI, dichloromethane/MeOH + 10 mmol/L NH_4OAc): m/z (%) = 330.1 (100) [MH$^+$], 299.0 (5) [MH$^+$ - CH_3NH_2], 284.0 (25) [MH$^+$ - EtOH]. – $C_{13}H_{23}N_5O_5$ (329.36).

[N´-(2-Acetylaminoethyl) N´´-ethoxycarbonylguanidino] methyl acetamide (**29**). Compound **28b** (77 mg, 0.23 mmol) and Ac_2O (60 mg, 50 µL, 0.58 mmol) were dissolved in 10 mL of dichloromethane. $Pd(PPh_3)_4$ (13 mg, 5 mol%) and immediately Bu_3SnH (81 mg, 74 µL, 0.28 mmol) were added to the solution. The reaction mixture was stirred at room temp. for 1 h. The solvent was evaporated and the crude product was purified by CC (EtOAc; R_f = 0.25) to give **29** (49 mg, 75 %) as a colourless oil. IR (KBr): 3312 cm^{-1}, 3071, 2972, 2939, 1719, 1641, 1367, 1134, 1108, 1007, 923, 856, 774. - ^{1}H NMR: δ = 1.17 (t, *J* = 7.1 Hz, 3 H), 1.81 (s, 3 H), 2.61 (d, *J* = 4.7 Hz, 2 H), 2.98 – 3.18 (m, 4 H), 3.75 (d, *J* = 5.2 Hz, 2 H), 3.91 (q, *J* = 7.1 Hz, 2 H), 7.04 (bs, 1 H), 7.89 (bs, 1 H), 8.07 (bs, 1 H), 9.23 (bs, 1 H). - MS (ESI, dichloromethane/MeOH + 10 mmol/L NH_4OAc): m/z (%) = 310.0 (10) [MNa$^+$], 288.0 (100) [MH$^+$], 241.8 (55) [MH$^+$ - EtOH]. – $C_{11}H_{21}N_5O_4$ (287.32).

[N´-(2-Allyloxycarbonylaminoethyl) N´´-ethoxycarbonylguanidino] methyl benzylamide (**30**). Compound **25b** (220 mg, 0.70 mmol) was dissolved in 8 mL of dichloromethane, $SOCl_2$ (833 mg, 0.51 mL, 7.0 mmol) and 2 drops of DMF were added and the reaction mixture was stirred at room temp. for 2 h. The solvent was evaporated and the product was dried under high vacuum for 1 h. The acid chloride was dissolved in 10 mL of dichloromethane, benzylamine (75 mg, 80 µL, 0.7 mmol) and NEt_3 (71 mg, 0.1 mL, 0.7 mmol) were added and the reaction mixture was stirred at room temp. for 18 h. The solvent was evaporated and the crude product was purified by CC (EtOAc; R_f = 0.15) to yield **30** (174 mg, 62 %) as a light brown oil. ^{1}H NMR: δ = 1.18 (t, *J* = 7.0 Hz, 3 H), 2.98 – 3.18 (m, 4 H), 3.73 (d, *J* = 5.1 Hz, 2 H), 4.12 (q, *J* = 7.1 Hz, 2 H), 4.46 (d, 5.1 Hz), 4.58 (s, 2 H), 5.18 (dd, *J* = 1.7 Hz, 9.3 Hz, 1 H), 5.29 (dd, J = 1.7 Hz, 16.2 Hz, 1 H), 5.82 – 5.96 (m, 1 H), 7.13 – 7.31 (m, 6 H), 8.03 (bs, 1 H), 8.67 (bs, 1 H). - MS (ESI, dichloromethane/MeOH + 10 mmol/L NH_4OAc): m/z (%) = 406.1 (100) [MH$^+$]. – $C_{19}H_{27}N_5O_5$ (405.20).

(S)-6-(5-Dimethylaminonaphthalene-1-sulfonylamino)-2-(tert-butoxycarbonyl)amino hexanoic acid methyl ester (39-Boc). N-boc Lysine methyl ester (400 mg, 1.54 mmol) was dissolved in 14 mL of dichloromethane. After addition of dansyl chloride (415 mg, 1.54 mmol) and NEt_3 (467 mg, 0.64 mL, 4.62 mmol), the solution was stirred at room temp. for 15 h. The solution was evaporated after filtration and the crude product was purified by CC (EtOAc; R_f = 0.55) to give **39-Boc** (631 mg, 83 %) as a yellow solid; mp: 108 °C. - ^{1}H-NMR ($CDCl_3$): δ = 1.31 – 1.73 (m, 15 H), 2.83 – 2.98 (m, 8 H), 3.70 (s, 3 H), 4.10 – 4.23 (m, 1 H), 4.79 (t, *J* = 6.0 Hz, 1 H), 4.95 (d, J = 8.0 Hz, 1 H), 7.22 (d, J = 7.7 Hz), 7.51 – 7.61 (m, 2 H), 8.21 – 8.34 (m, 2 H), 8.58 (d, J = 8.0 Hz). - ^{13}C- NMR ($CDCl_3$): δ = 22.2 (-), 28.3 (+), 29.0 (-), 32.2 (-), 42.9 (-), 45.4 (+), 52.3 (+), 53.0 (+), 115.2 (+), 118.8 (+), 123.2 (+), 128.4 (+), 129.7 (+), 130.4 (+), 134.7 (C_{quat}), 152.0 (C_{quat}), 155.6 (C_{quat}). - MS (ESI, dichloromethane/MeOH + 10 mmol/L NH_4OAc): m/z (%) = 494.4 (100) [MH^+], 438.3 (20) [MH^+ - C_4H_8], 394.3 (5) [MH^+ - Boc]. - Elemental analysis calcd. (%) for $C_{24}H_{35}N_3O_6S$ (493.22): C 58.39, H 7.15, N 8.52; found C 58.26, H 7.29, N 8.46.

(S)-6-(5-Dimethylaminonaphthalene-1-sulfonylamino)-2-amino hexanoic acid methyl ester hydrochloride (39-H). Compound **39-Boc** (631 mg, 1.28 mmol) was dissolved in 8 mL dichloromethane and 15 mL of HCl saturated ether was added. The reaction mixture was stirred at room temp. for 1 h. The solvent was evaporated and the product was dried in high vacuum yielding **39-H** (906 mg, 100 %) as a yellow solid. IR (KBr): 3406 cm^{-1}, 3192, 2951, 1701, 1637, 1516, 1449, 1437, 1322, 1259, 1143, 794, 586. - ^{1}H-NMR ($CDCl_3$): δ = 1.30 – 1.52 (m, 4 H), 1.61 – 1.72 (m, 2 H), 2.73 – 2.91 (m, 8 H), 3.72 (s, 3 H), 3.81 – 3.99 (m, 2 H) , 7.20 (d, J = 7.9 Hz), 7.51 – 7.61 (m, 2 H), 8.21 – 8.34 (m, 2 H), 8.59 (d, J = 8.0 Hz). - MS (ESI, dichloromethane/MeOH + 10 mmol/L NH_4OAc): m/z (%) = 787.6 (8) [$2MH^+$], 394.3 (100) [MH^+]. – $C_{19}H_{28}N_3O_4SCl$ (429.15).

(S)-2-[N´-(2-Acetylaminoethyl) N´,N´´-di-(-(tert-butoxycarbonyl)guanidino]-3-(4-hydroxyphenyl) propionic acid methyl ester (**41-Boc**). Compound **37-Boc** (345 mg, 0.61 mmol) and Ac_2O (156 mg, 0.144 mL, 1.53 mmol) were dissolved in 15 mL of dichloromethane. $Pd(PPh_3)_4$ (35 mg, 5 mol%) and Bu_3SnH (195 mg, 0.177 mL, 0.67 mmol) were added and the reaction mixture was stirred at room temp. for 45 min. The solvent was evaporated and the crude product was purified by CC (EtOAc; R_f = 0.5) to give **41-Boc** (266 mg, 84 %) as a colourless oil. IR (KBr): 3256 cm^{-1}, 3008, 2988, 2923, 1722, 1623, 1455, 1367, 1278, 1189, 1007, 984, 845, 734. - ^{1}H-NMR ($CDCl_3$): δ = 1.41 (s, 9 H,), 1.45 (s, 9 H), 1.87 (s, 3 H,), 2.80 – 3.19 (m, 6 H), 3.71 (s, 3 H), 4.05 – 4.22 (m, 1 H), 6.81 (d, J = 8.0 Hz, 2 H), 6.93 (t, *J* = 5.3 Hz, 1 H), 7.06 (d, *J* = 8.0 Hz, 2 H), 10.01 (bs, 1 H). - MS (ESI, dichloromethane/MeOH + 10 mmol/L NH_4OAc): m/z (%) = 523.3 (100) [MH^+], 467.2 (10) [MH^+ - C_4H_8], 423.3 (10) [MH^+ - Boc]. – $C_{25}H_{38}N_4O_8$ (522.27).

Lithium (S)-2-[N´-(2-acetylamino-ethyl) N´,N´´-di-[(tert-butoxycarbonyl)guanidino]-3-(4-hydroxyphenyl) propionic acid (**42-Boc**). Compound **41-Boc** (266 mg, 0.51 mmol) was dissolved in 10 mL of MeOH:H_2O (3:1) and LiOH x H_2O (21 mg, 0.51 mmol) was added. The reaction mixture was stirred at room temp. for 18 h. The solvents were removed and the product was dried in high vacuum. Compound **42-Boc** (242 mg, 92 %) was obtained as a pale yellow solid; mp: 123 °C. - ^{1}H-NMR: δ = 1.41 (s, 9 H), 1.45 (s, 9 H), 1.89 (s, 3 H), 2.84 – 3.29 (m, 6 H), 4.05 – 4.14 (m, 1 H), 6.81 (d, J = 8.0 Hz, 2 H), 6.91 (t, J = 5.3 Hz, 1 H), 7.06 (d, J = 8.0 Hz, 2 H), 10.45 (bs, 1 H). - MS (ESI, dichloromethane/MeOH + 10 mmol/L NH_4OAc): m/z (%) = 507.6 (100) [M-H^+]. – $C_{24}H_{35}N_4O_8Li$ (514.26).

Lithium (S)-2-[N´-(2-Allyloxycarbonylamino-ethyl) N´,N´´-di-[(tert-butoxycarbonyl)-guanidino]-3-(4-hydroxyphenyl) propionic acid (**43-Boc**). Compound **37-Boc** (190 mg, 0.34 mmol) was dissolved in 10 mL of MeOH:H_2O (3:1) and LiOH x H_2O (14 mg, 0.34 mmol) was added. The reaction mixture was stirred at room temp. for 15 h. The solvents were removed and the product was dried in high vacuum. Compound **43-Boc** (189 mg, 100 %) was obtained as a pale red solid; mp: 89 °C. - ^{1}H-NMR: δ = 1.39 (s, 9 H, Boc), 1.44 (s, 9 H), 2.81 – 3.34 (m, 6 H), 3.89 – 4.03 (m, 1 H), 4.53 (d, 5.2 Hz), 5.17 (dd, *J* = 1.7 Hz, 9.3 Hz, 1 H), 5.28 (dd, *J* = 1.7 Hz, 16.2 Hz, 1 H), 5.83 – 5.97 (m, 1 H), 6.78 – 6.91 (m, 3 H), 6.99 – 7.06 (m, 2 H), 9.81 (bs, 1 H). - MS (ESI, dichloromethane/MeOH + 10 mmol/L NH_4OAc): m/z (%) = 549.26 (100) [M – H^+]. – $C_{26}H_{37}N_4O_9Li$ (556.27).

8) ^{1}H- and ^{13}C-NMR spectra of compounds

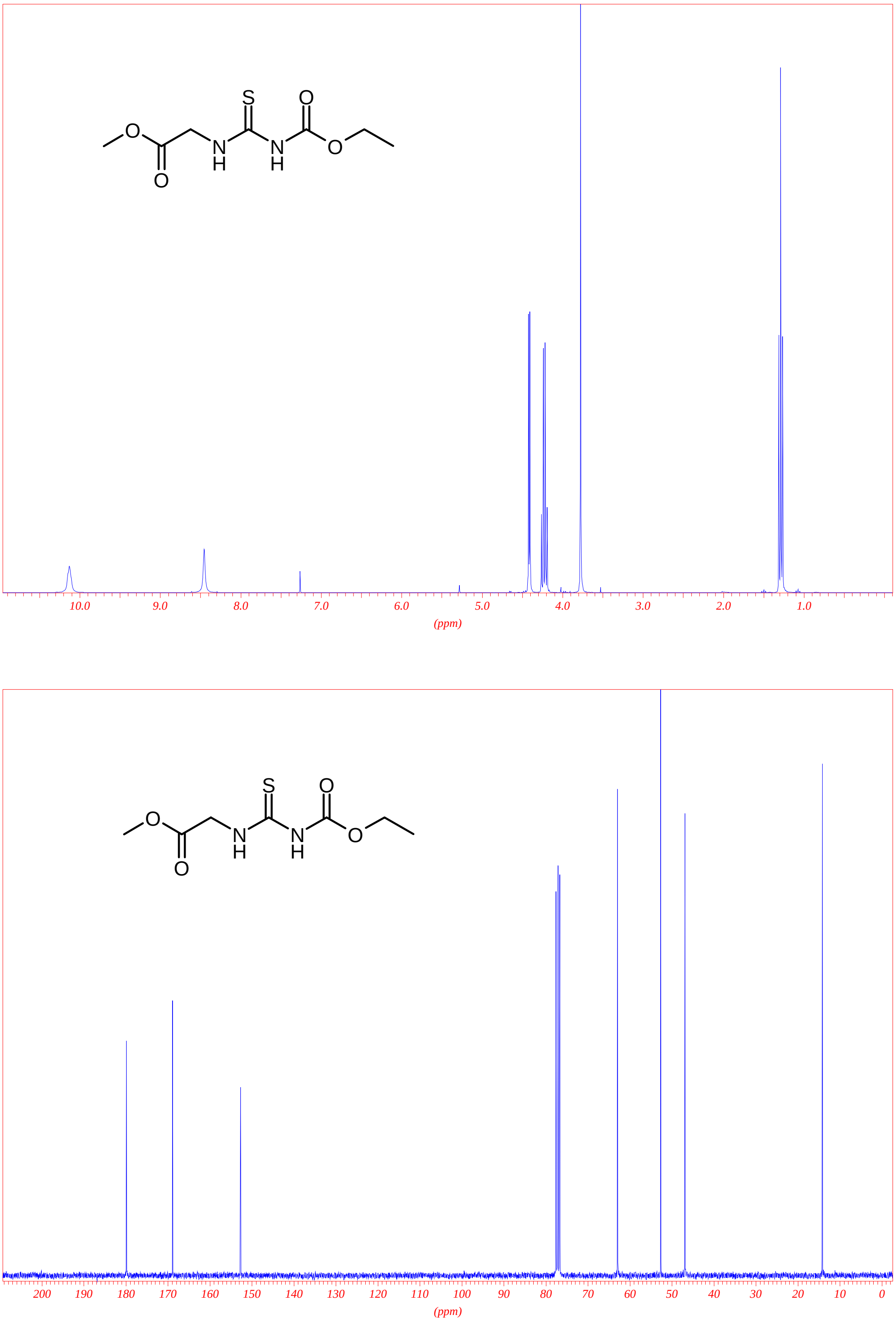


Figure S-15. ^{1}H-NMR and ^{13}C-NMR of compound **20.**

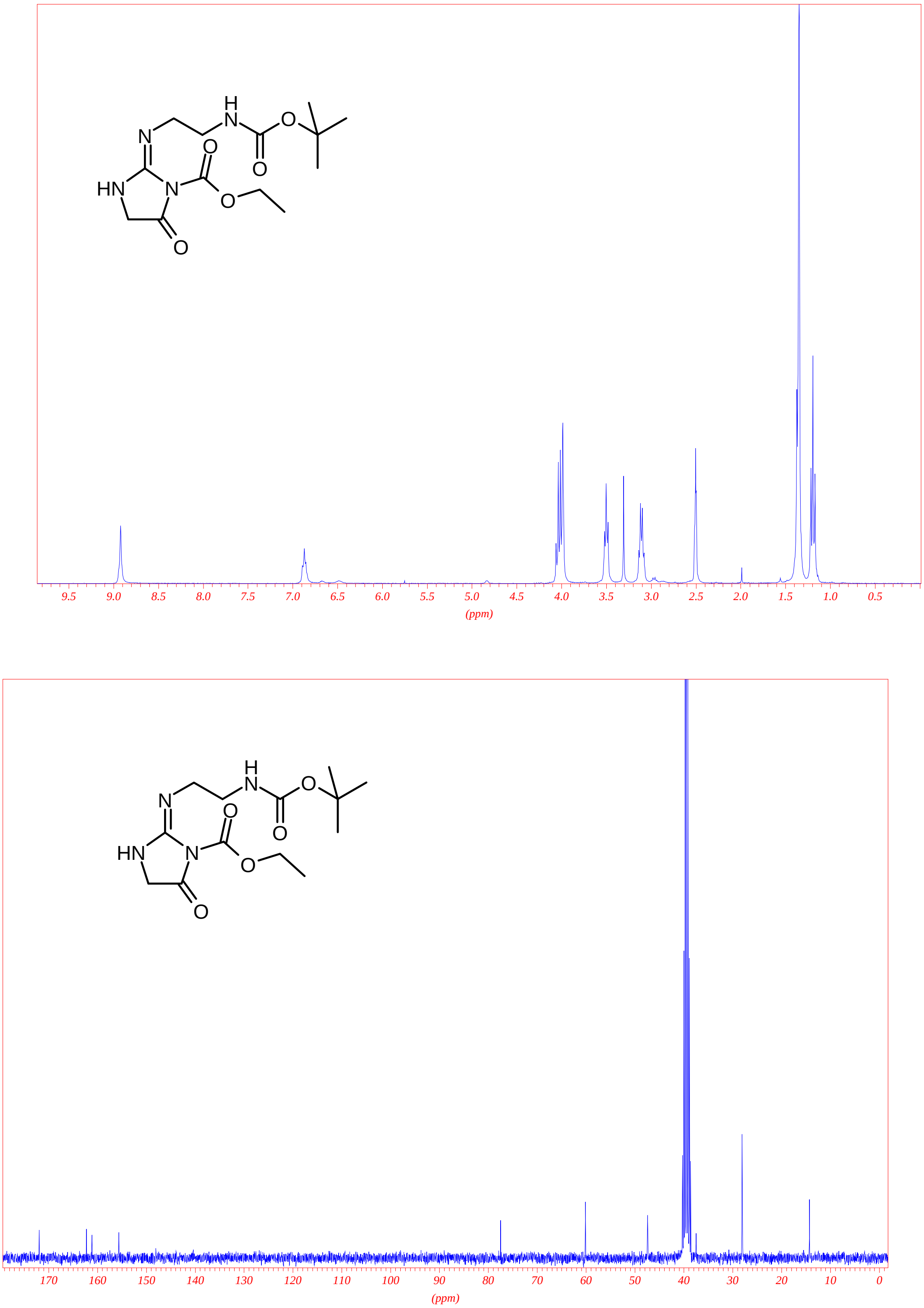


Figure S-16. ^{1}H-NMR and ^{13}C-NMR of compound **22**

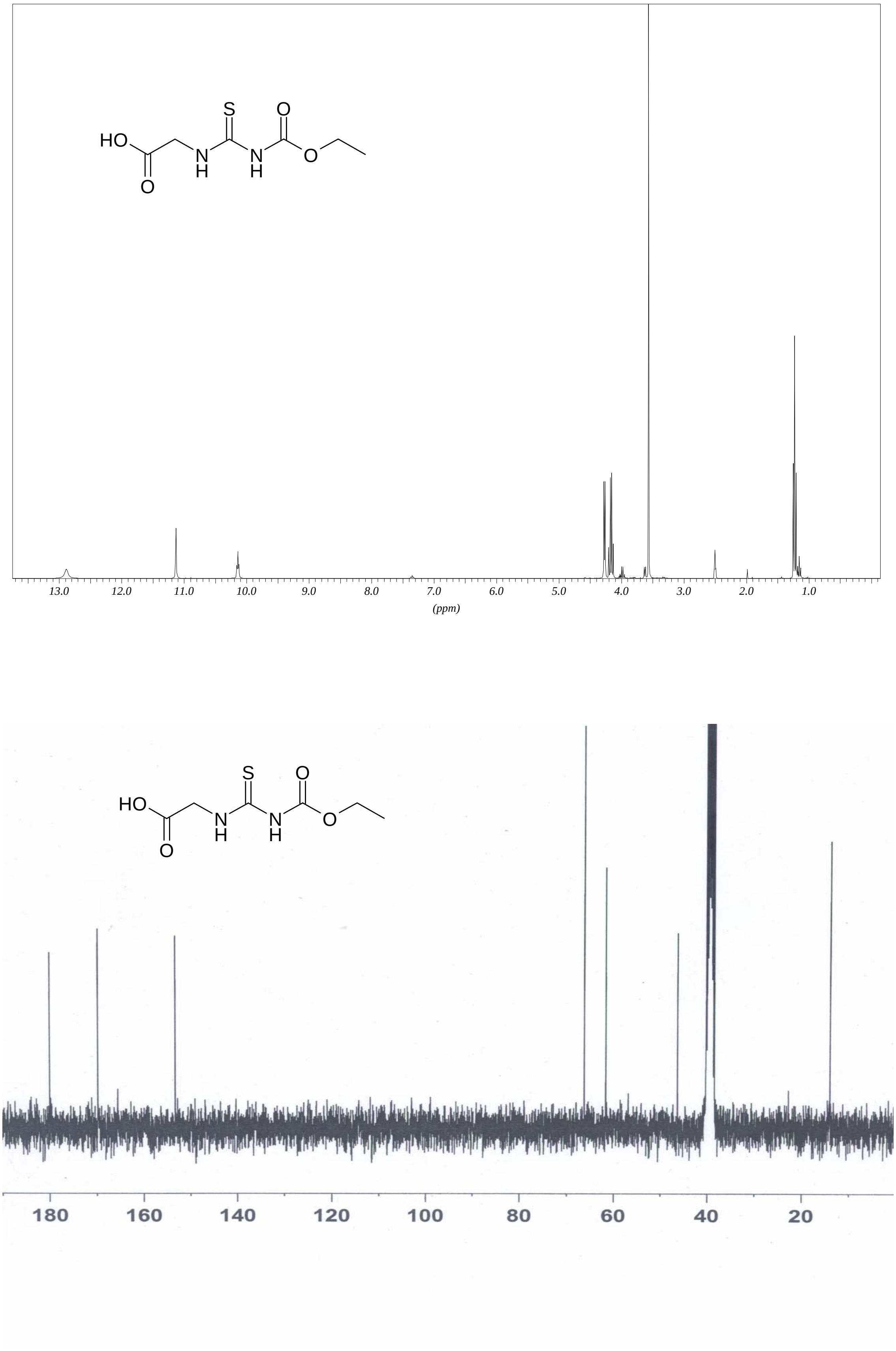


Figure S-17. ^{1}H-NMR and ^{13}C-NMR of compound **24a**

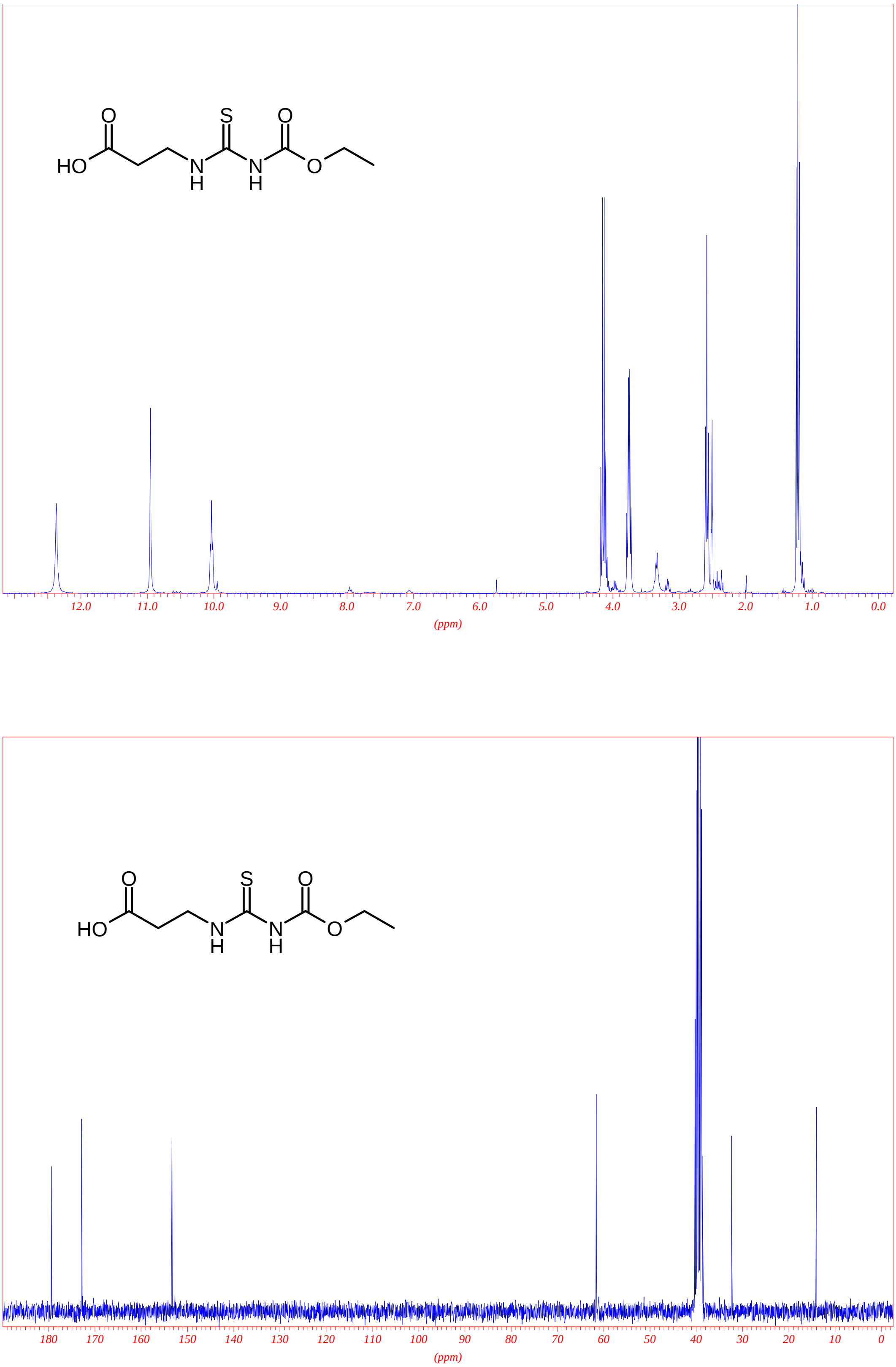


Figure S-18. ^{1}H-NMR and ^{13}C-NMR of compound **24b**

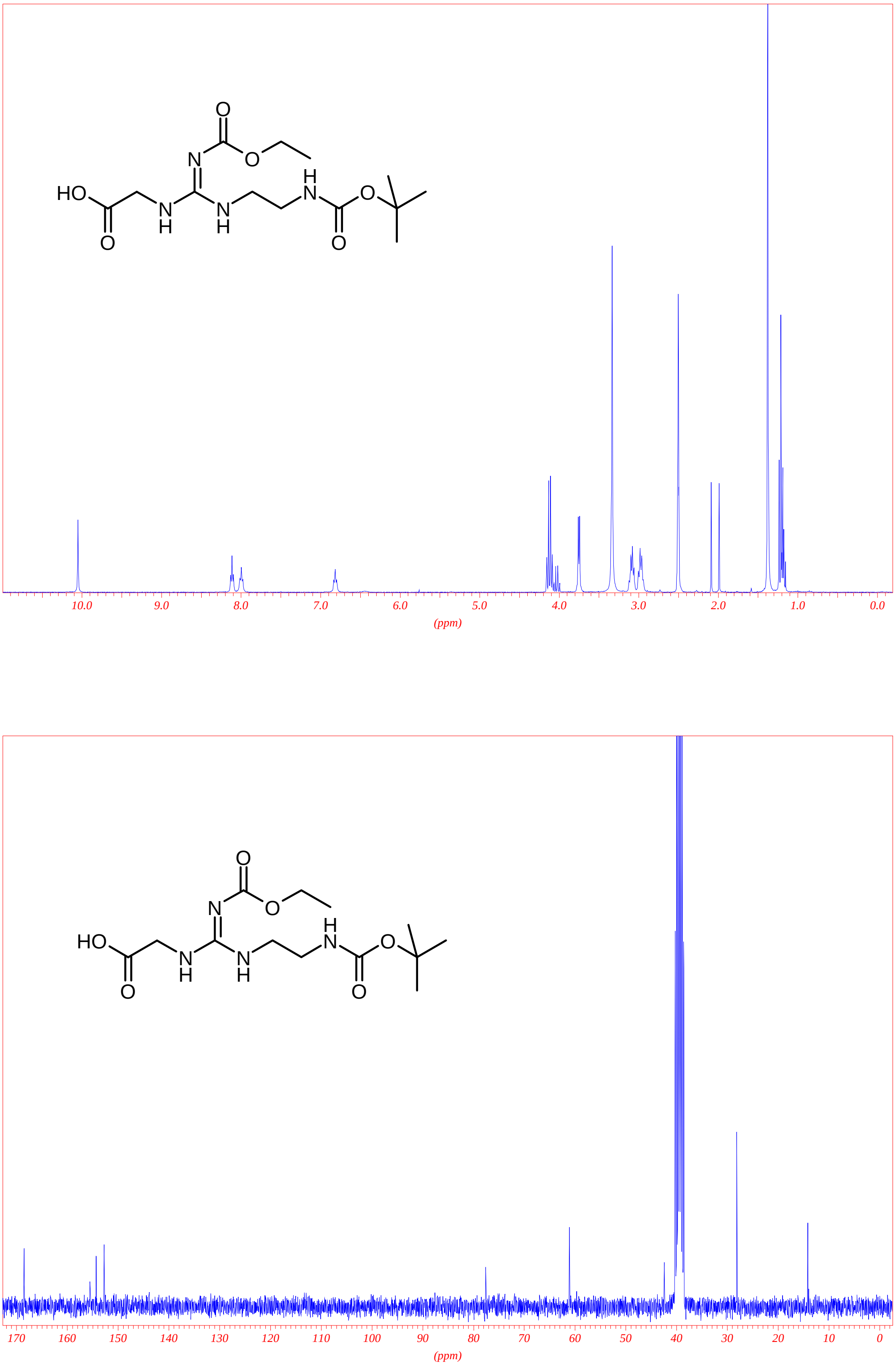


Figure S-19. ^{1}H-NMR and ^{13}C-NMR of compound **25a**

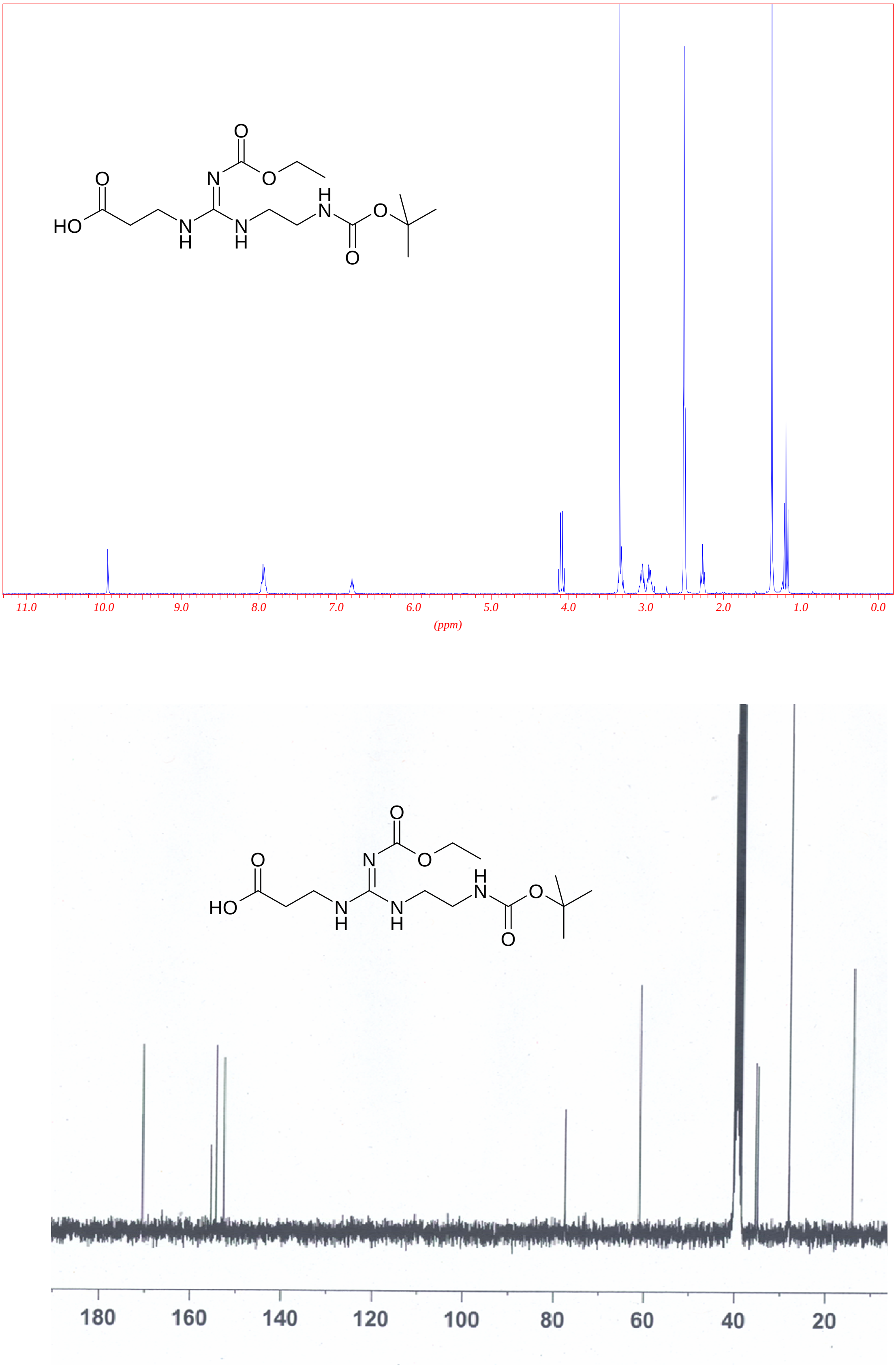


Figure S-20. ^{1}H-NMR and ^{13}C-NMR of compound **25c**

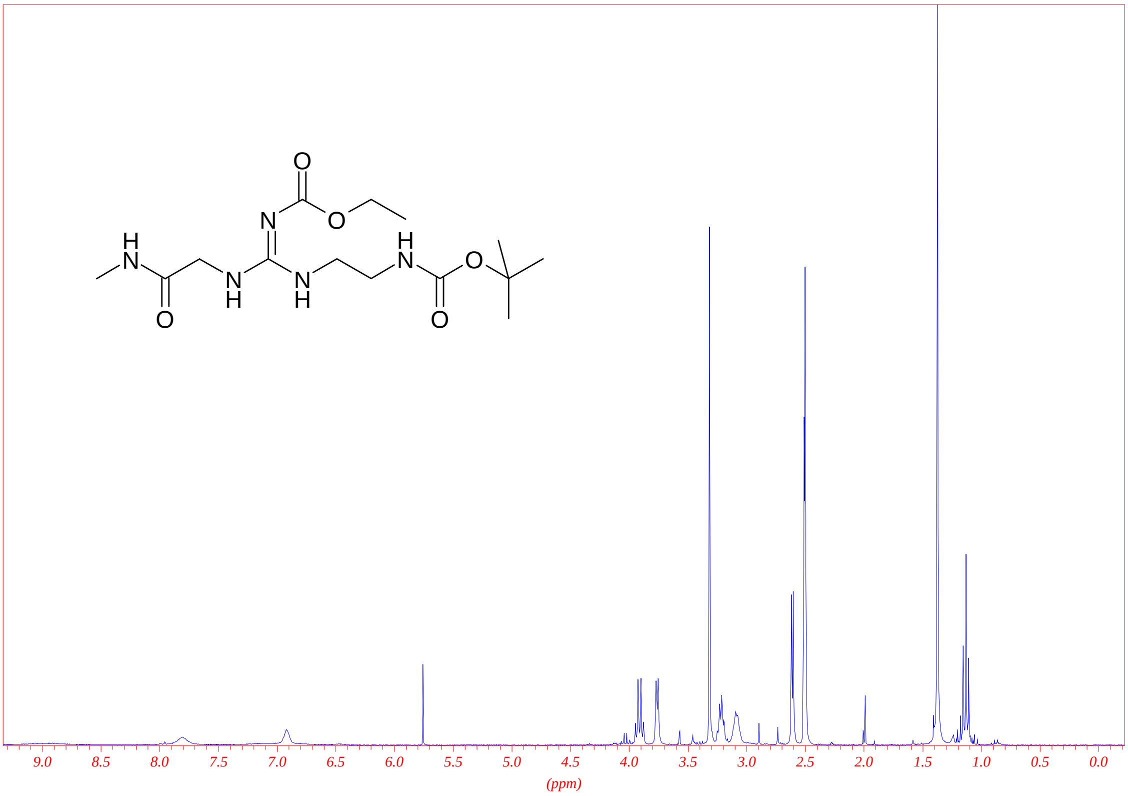


Figure S-21. ^{1}H-NMR of compound **28a**

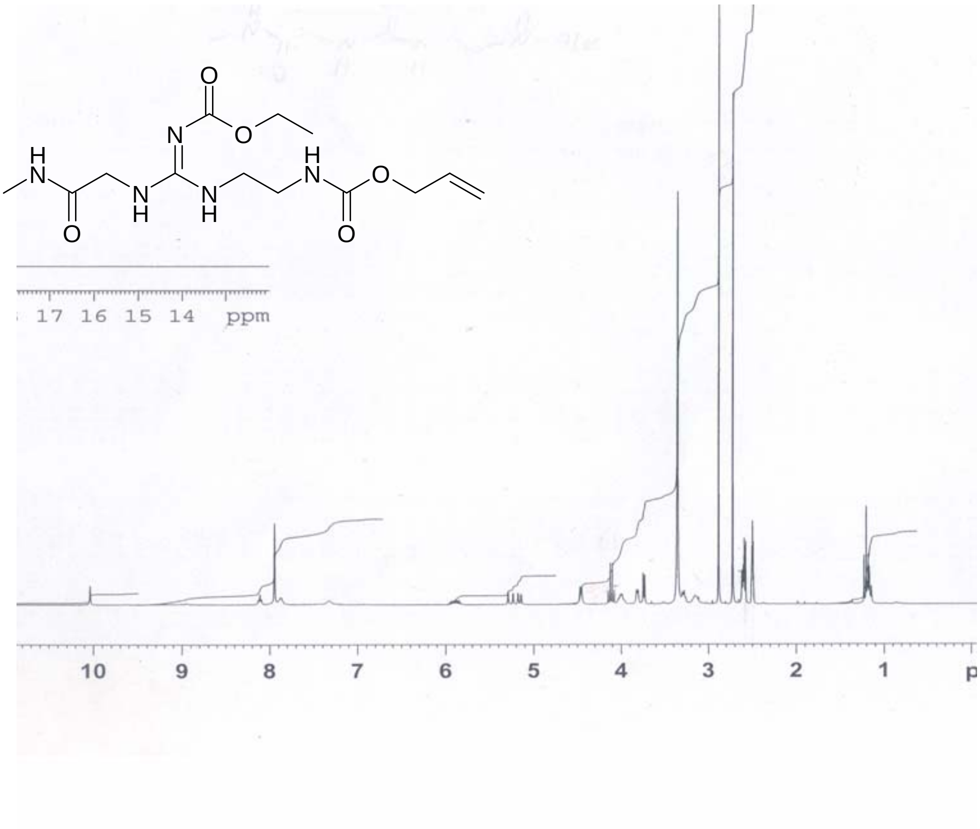


Figure S-22. ^{1}H-NMR of compound **28b**

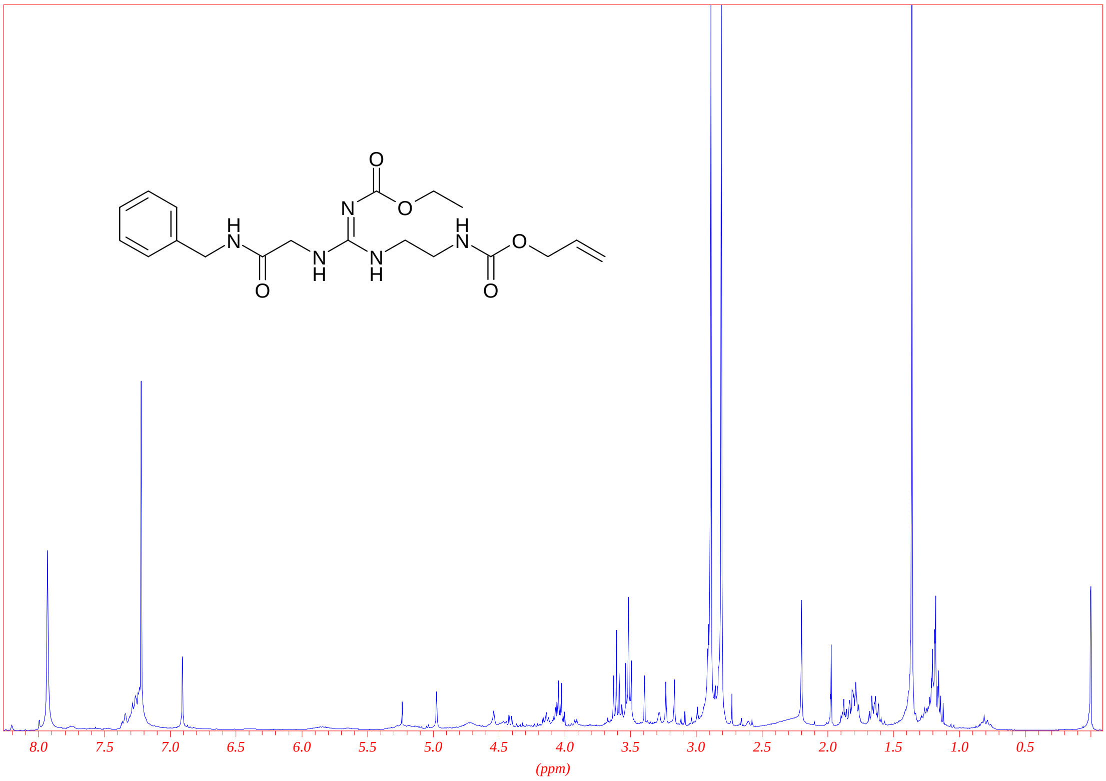


Figure S-23. ^{1}H-NMR of compound **30**

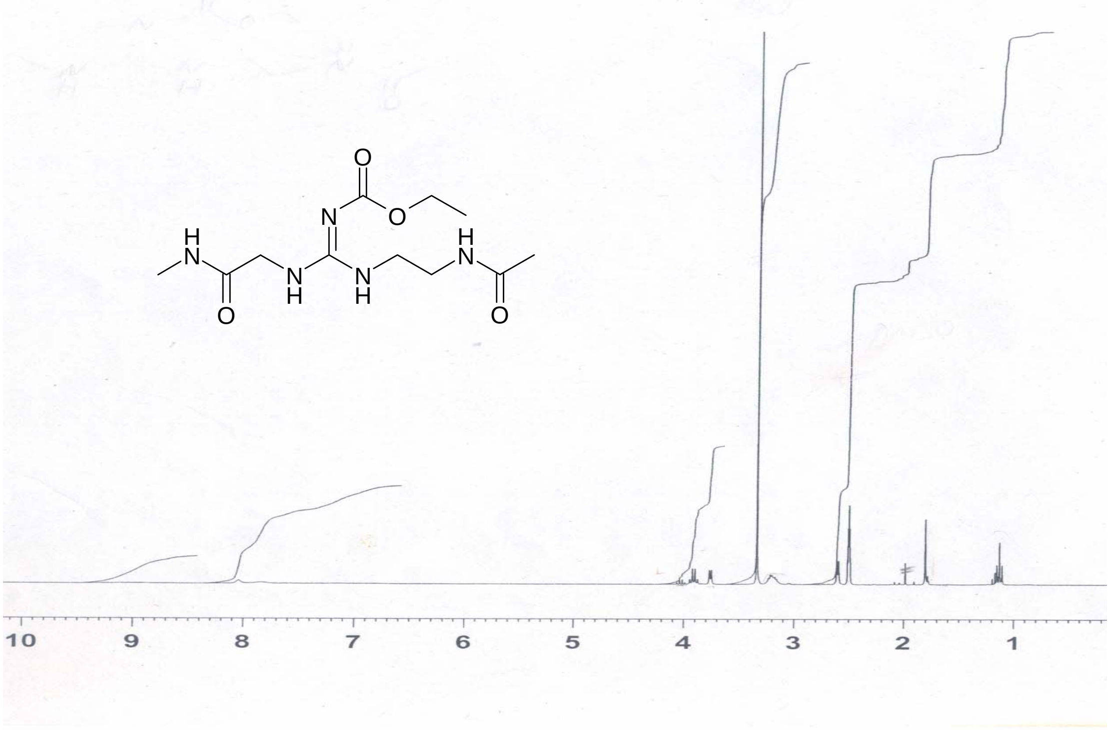


Figure S-24. ^{1}H-NMR of compound **29**

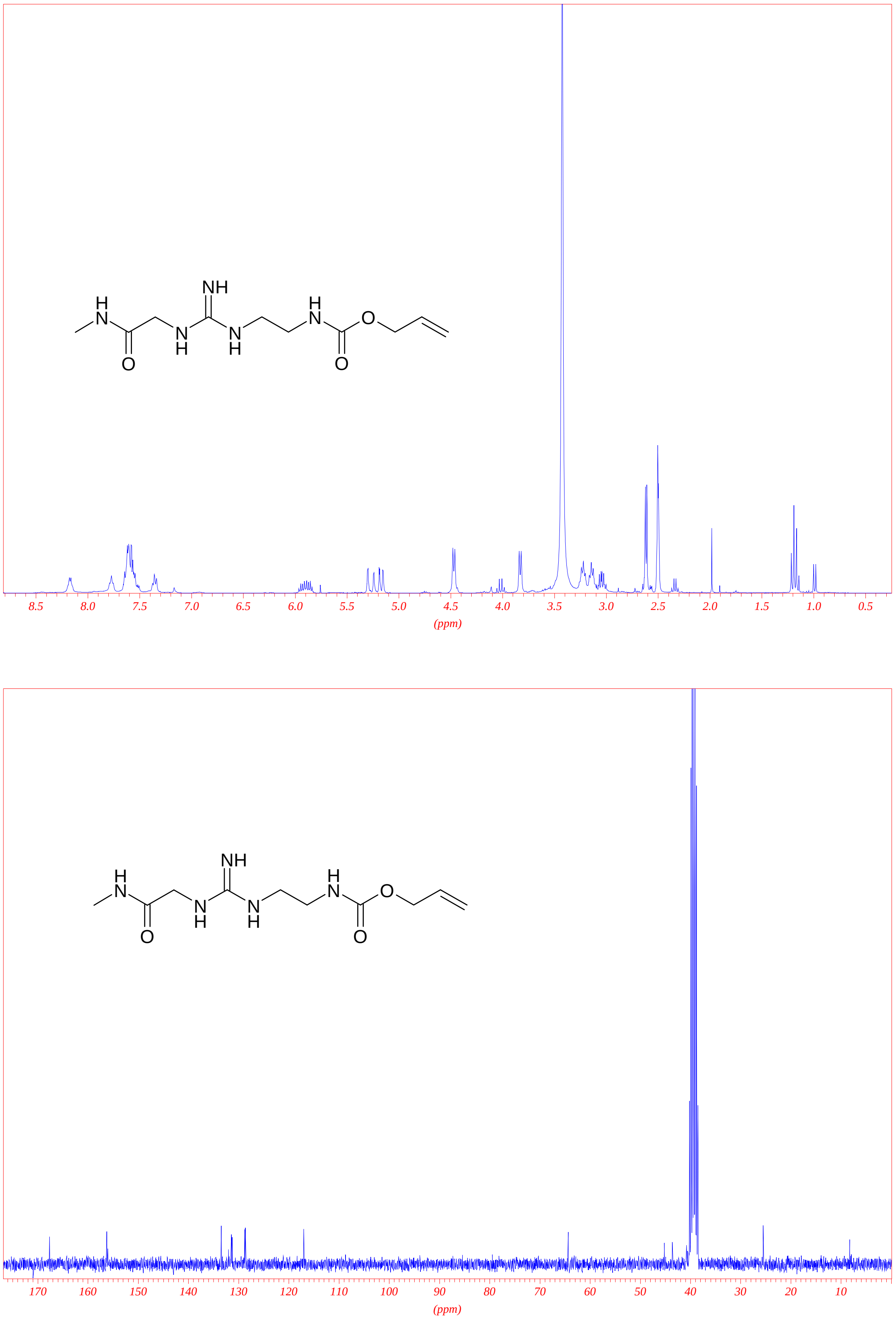
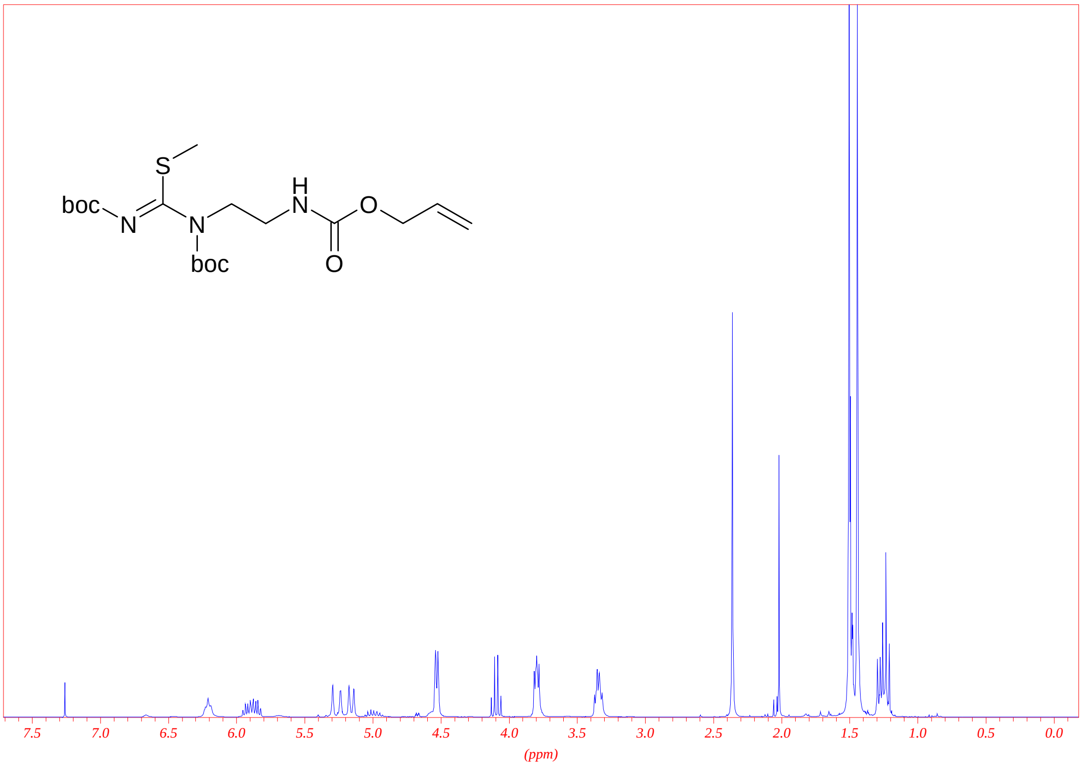


Figure S-25. ^{1}H-NMR and ^{13}C-NMR of compound **31**



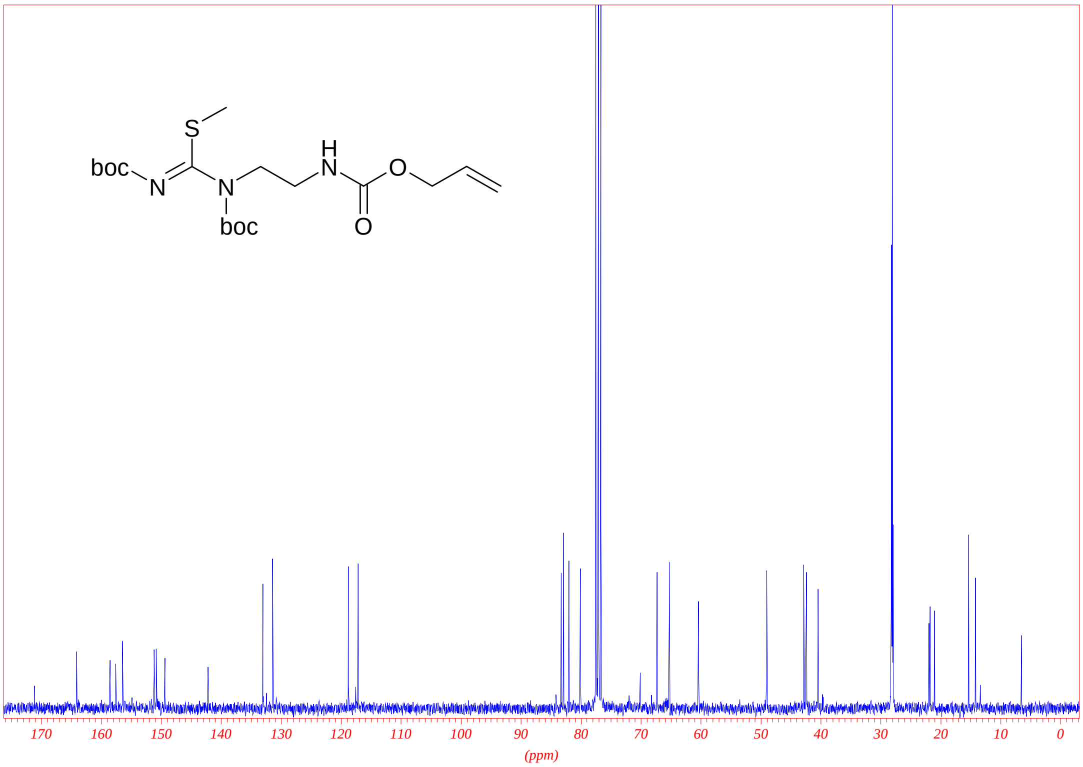


Figure S-26. ¹H-NMR and ¹³C-NMR of compound **34**

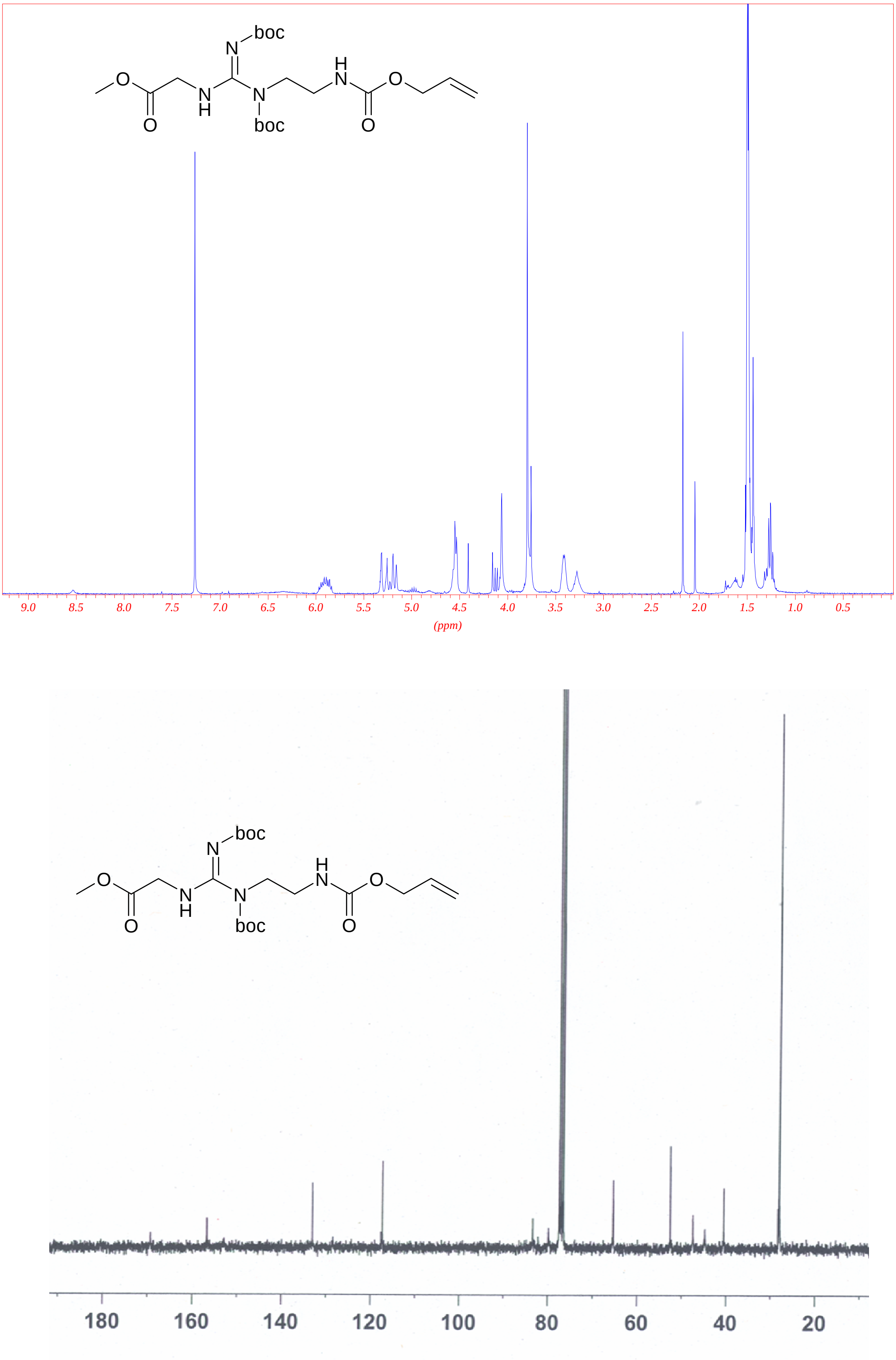


Figure S-27. ^{1}H-NMR and ^{13}C-NMR of compound **35**

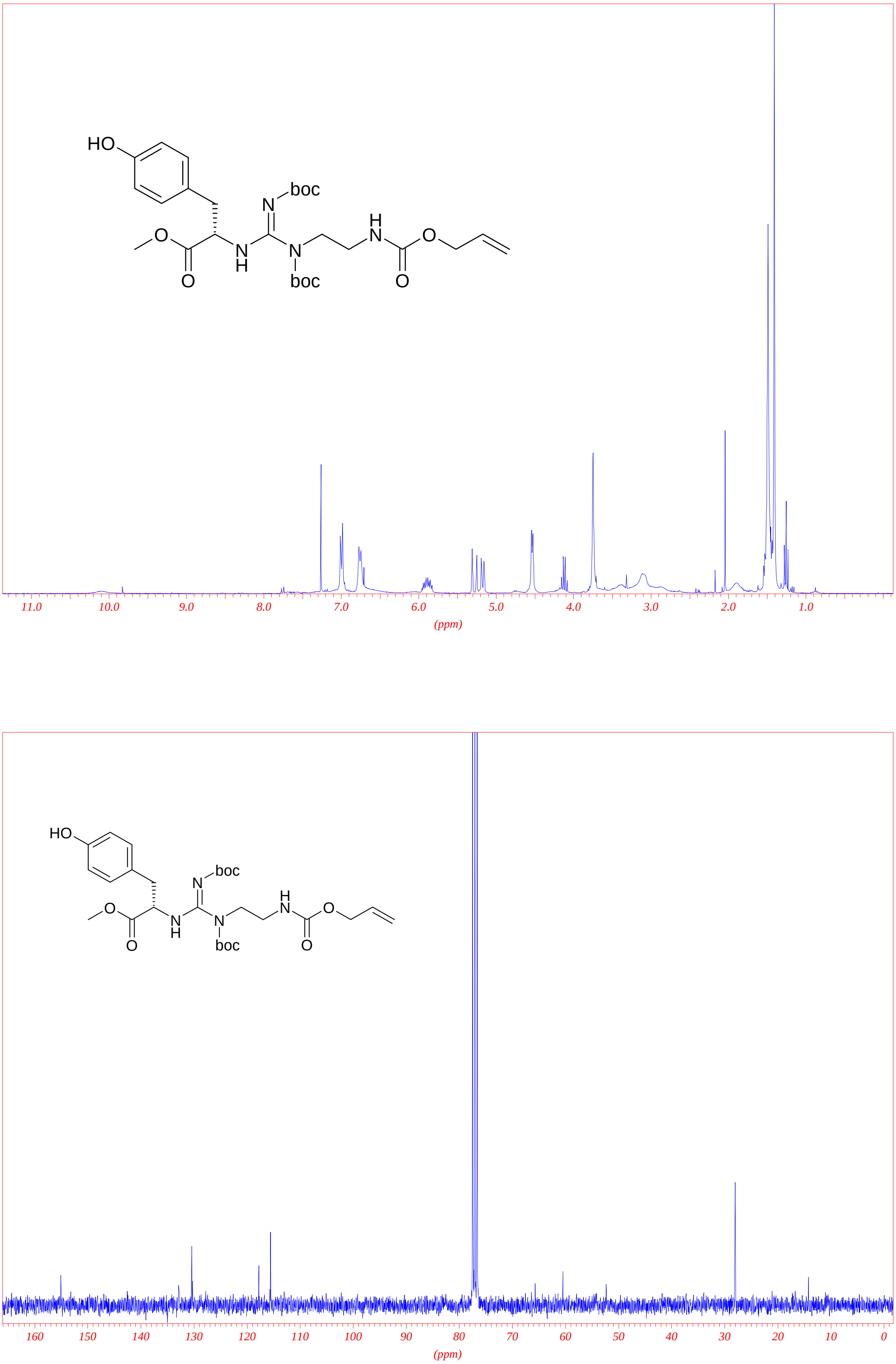


Figure S-28. ^{1}H-NMR and ^{13}C-NMR of compound **37-Boc**

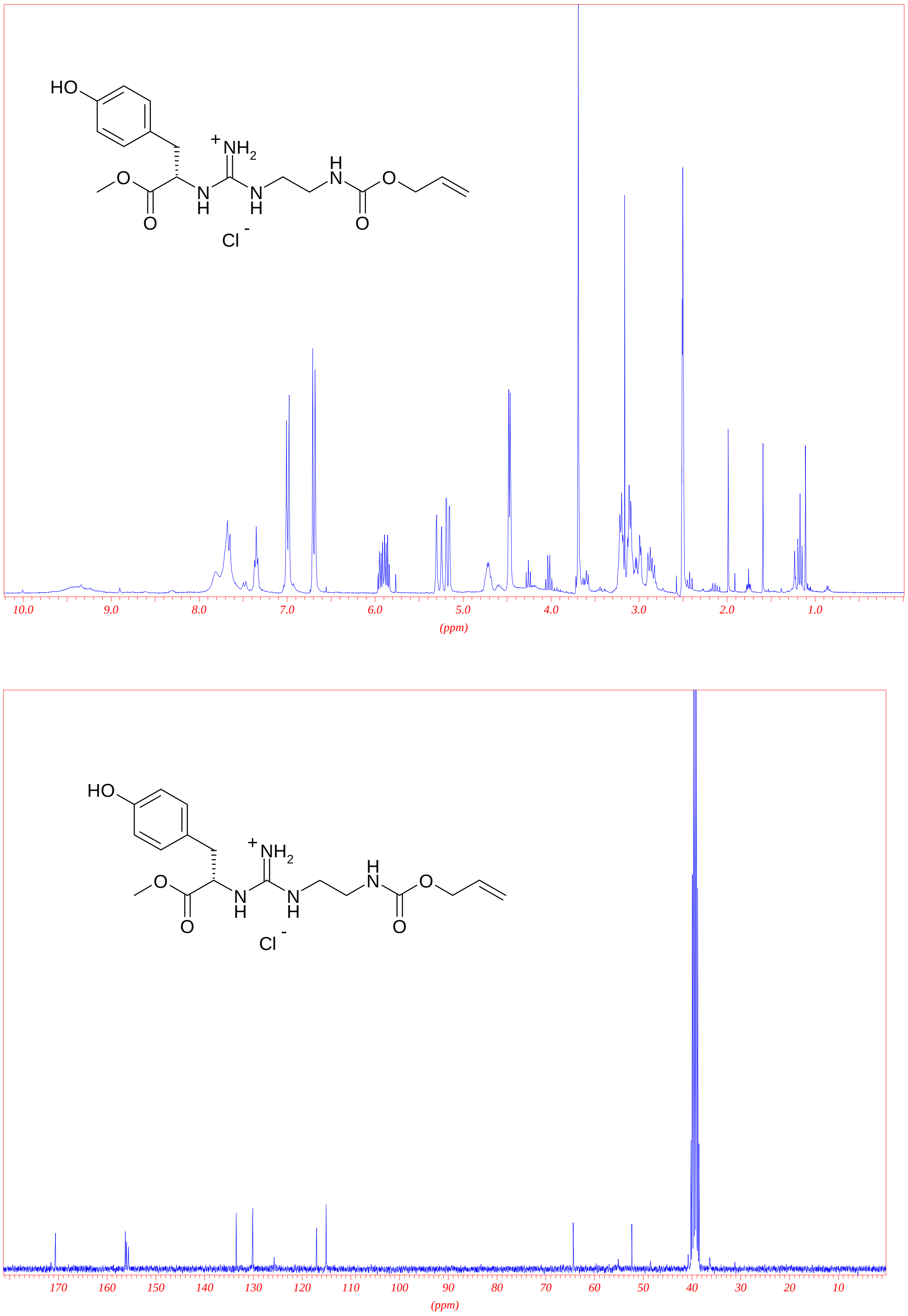


Figure S-29. ^{1}H-NMR and ^{13}C-NMR of compound **37-H**

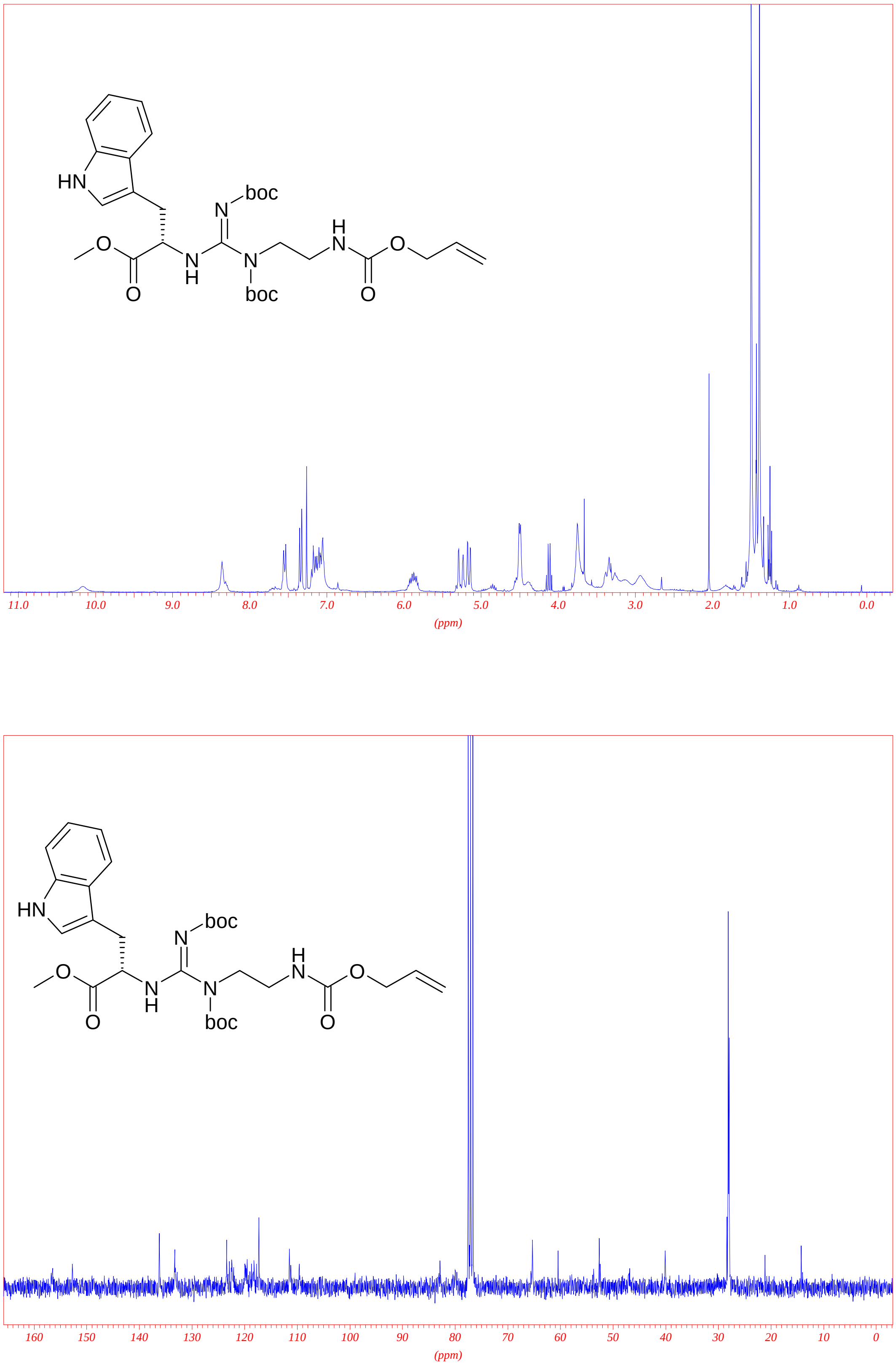


Figure S-30. ^{1}H-NMR and ^{13}C-NMR of compound **38-Boc**

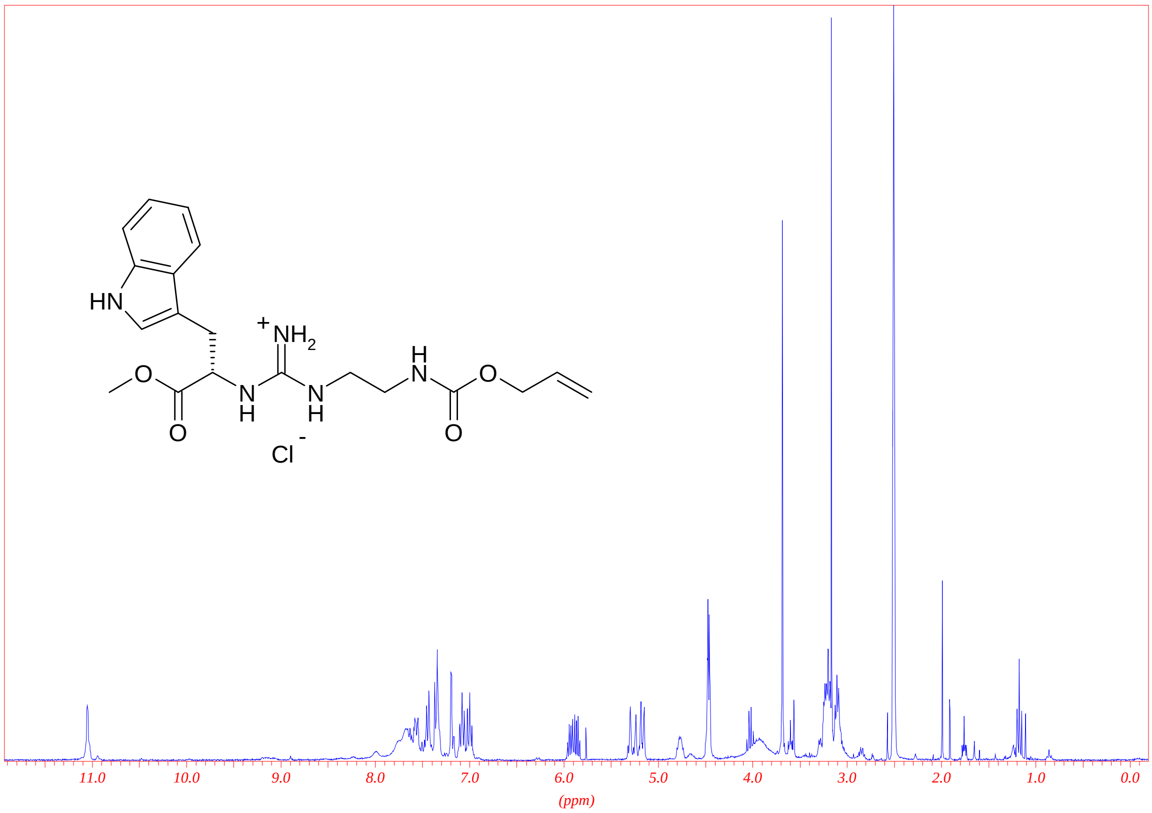


Figure S-31. ^{1}H-NMR of compound **38-H**

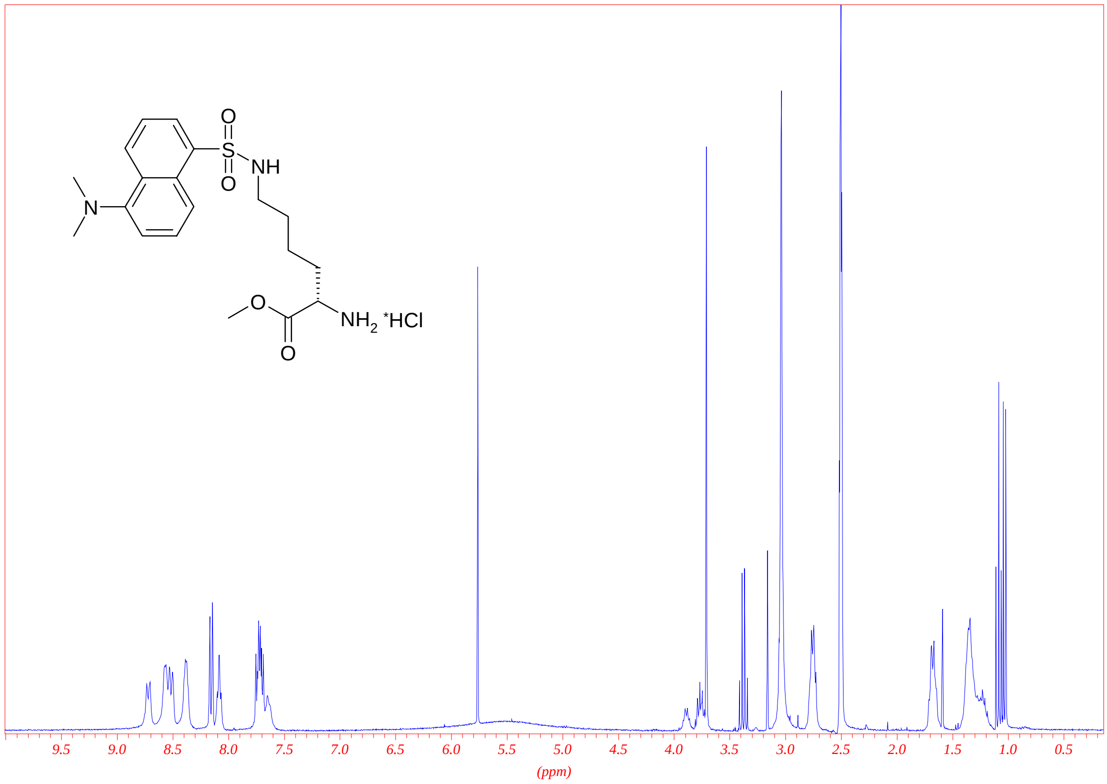


Figure S-32 ^{1}H-NMR of compound **39-H**

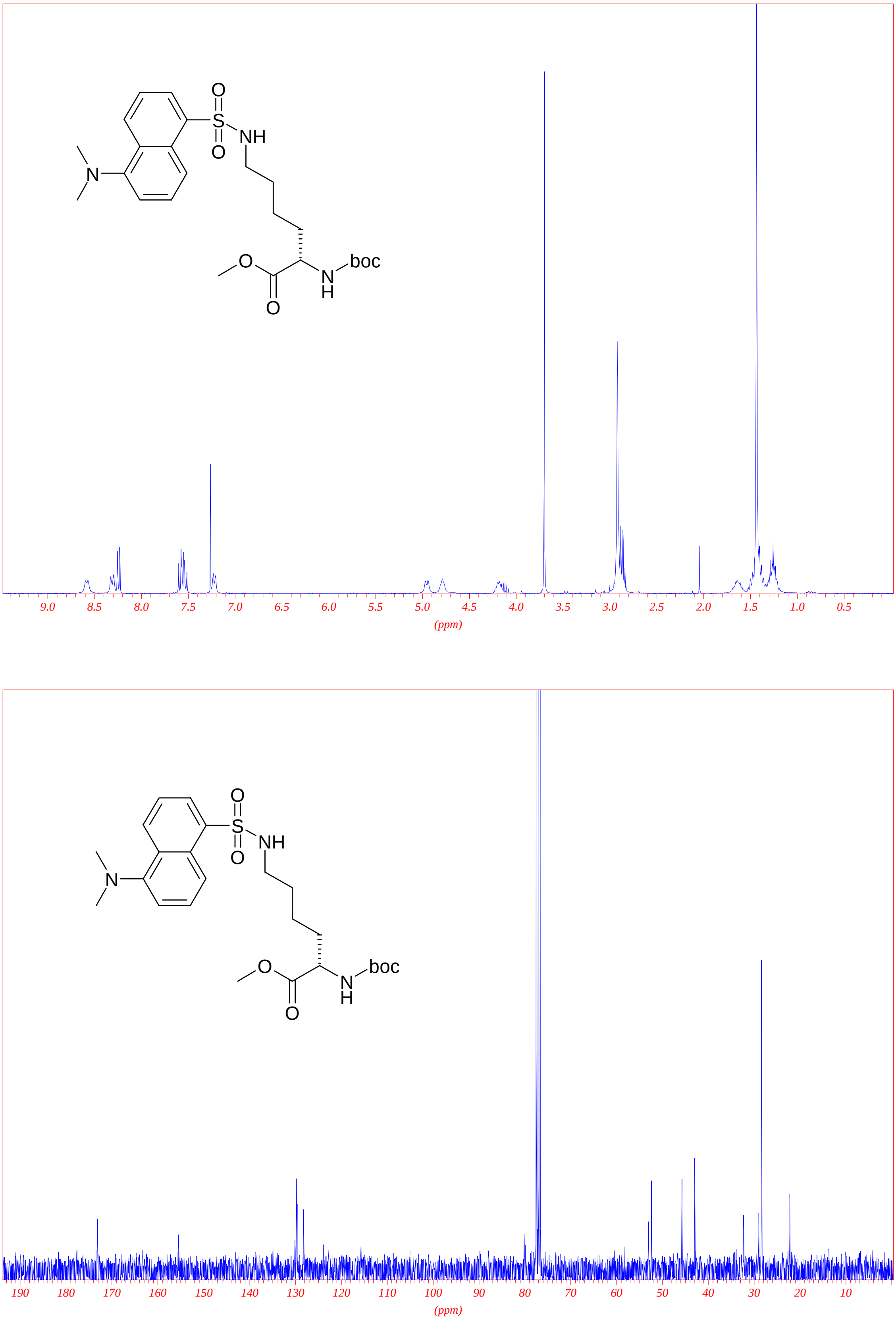


Figure S-33. ^{1}H-NMR and ^{13}C-NMR of compound **39-Boc**

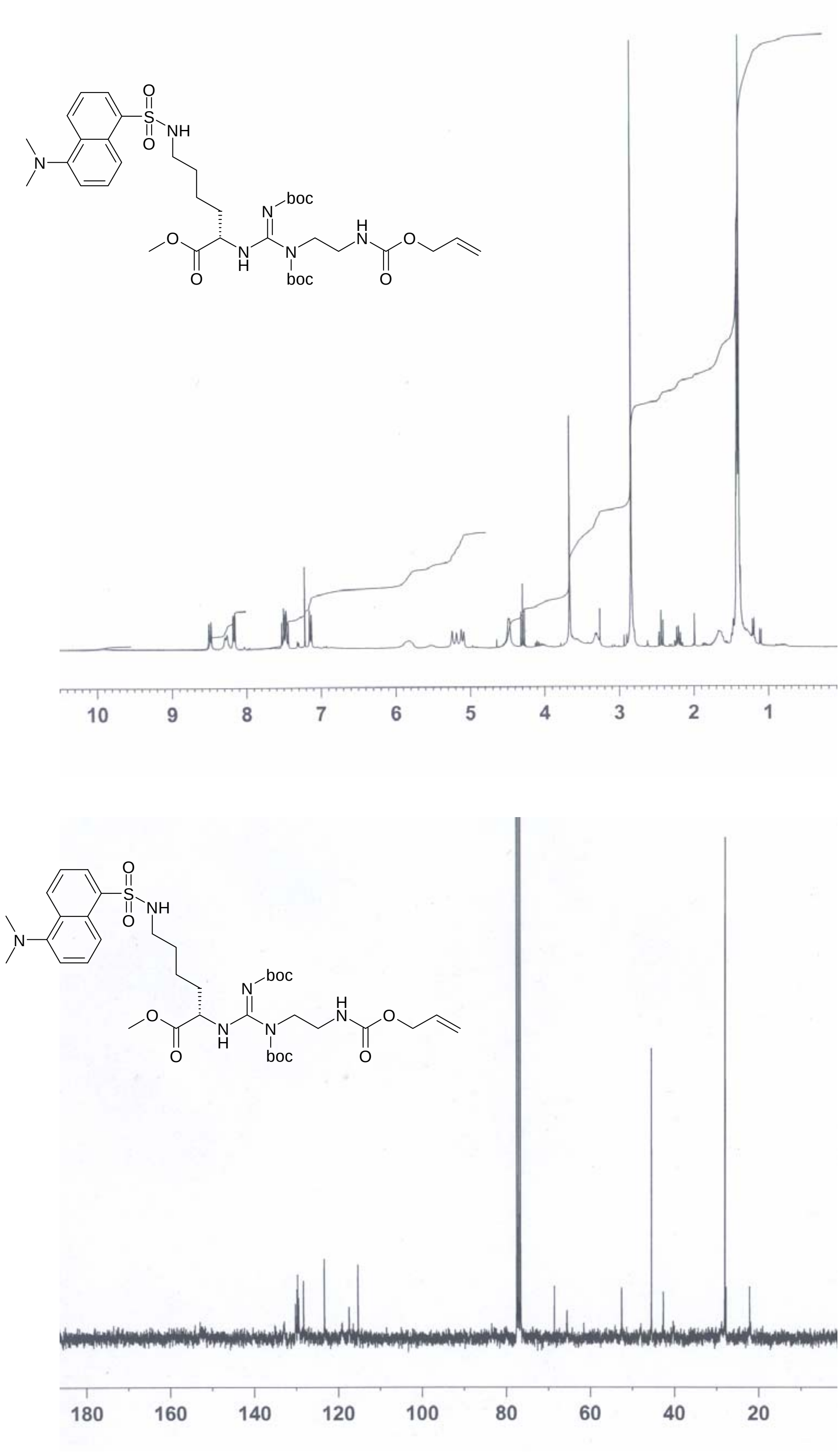


Figure S-34. ^{1}H-NMR and ^{13}C-NMR of compound **40-Boc**

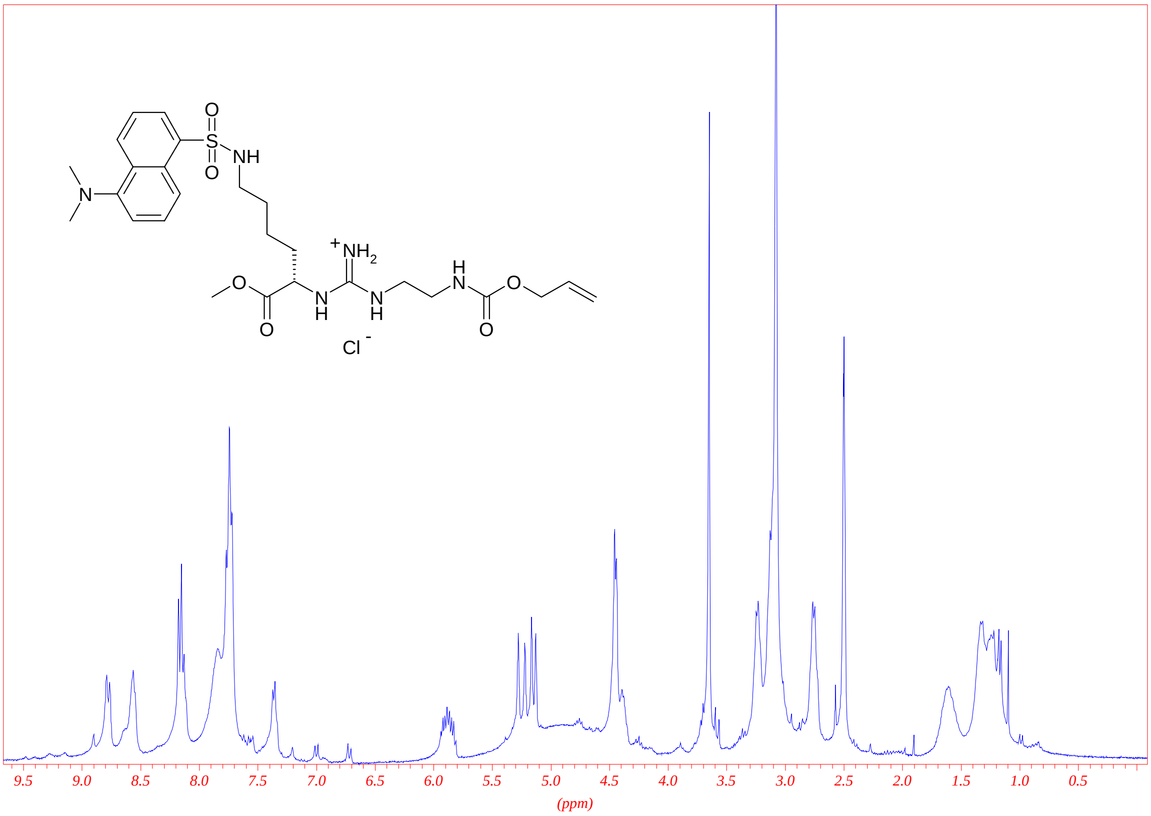


Figure S-35. ^{1}H-NMR of compound **40-H**

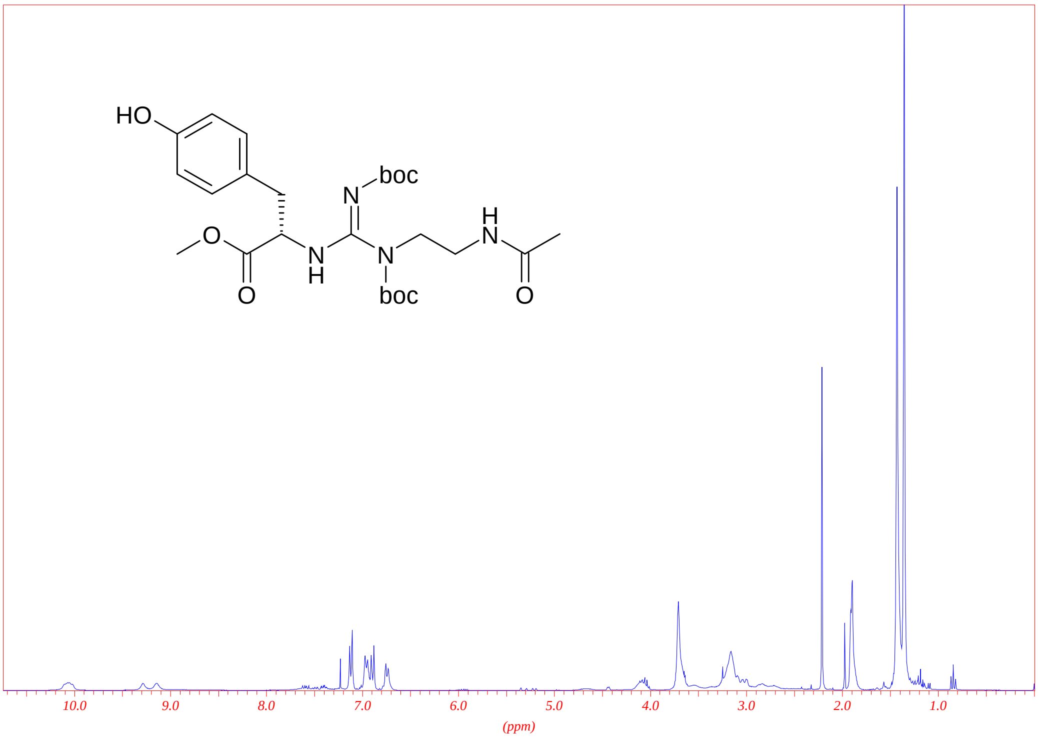


Figure S-36. ^{1}H-NMR of compound **41-Boc**

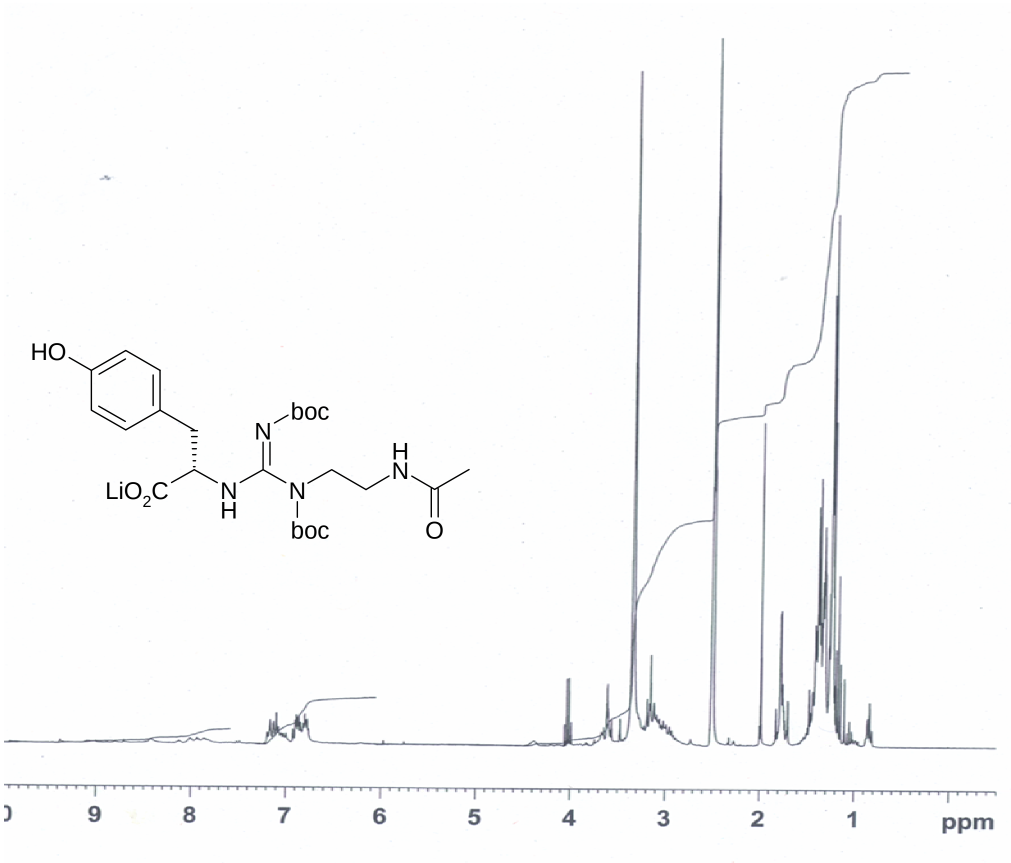


Figure S-37. ^{1}H-NMR of compound **42-Boc**

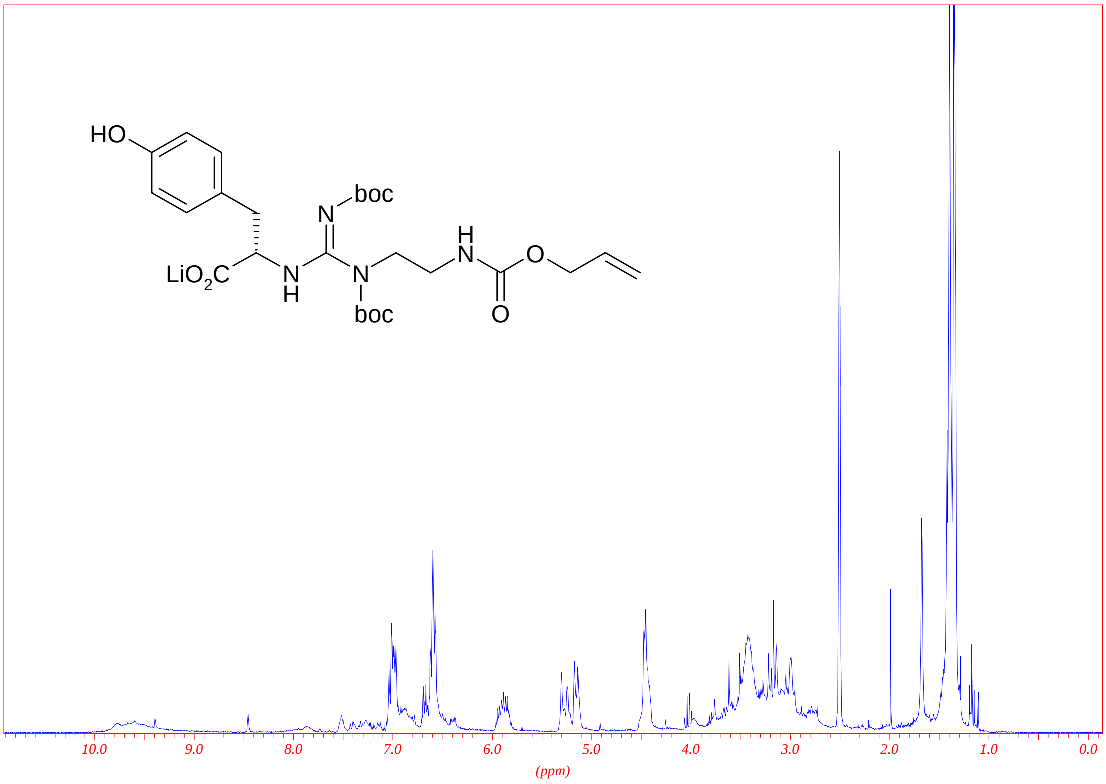


Figure S-38. ^{1}H-NMR of compound **43-Boc**

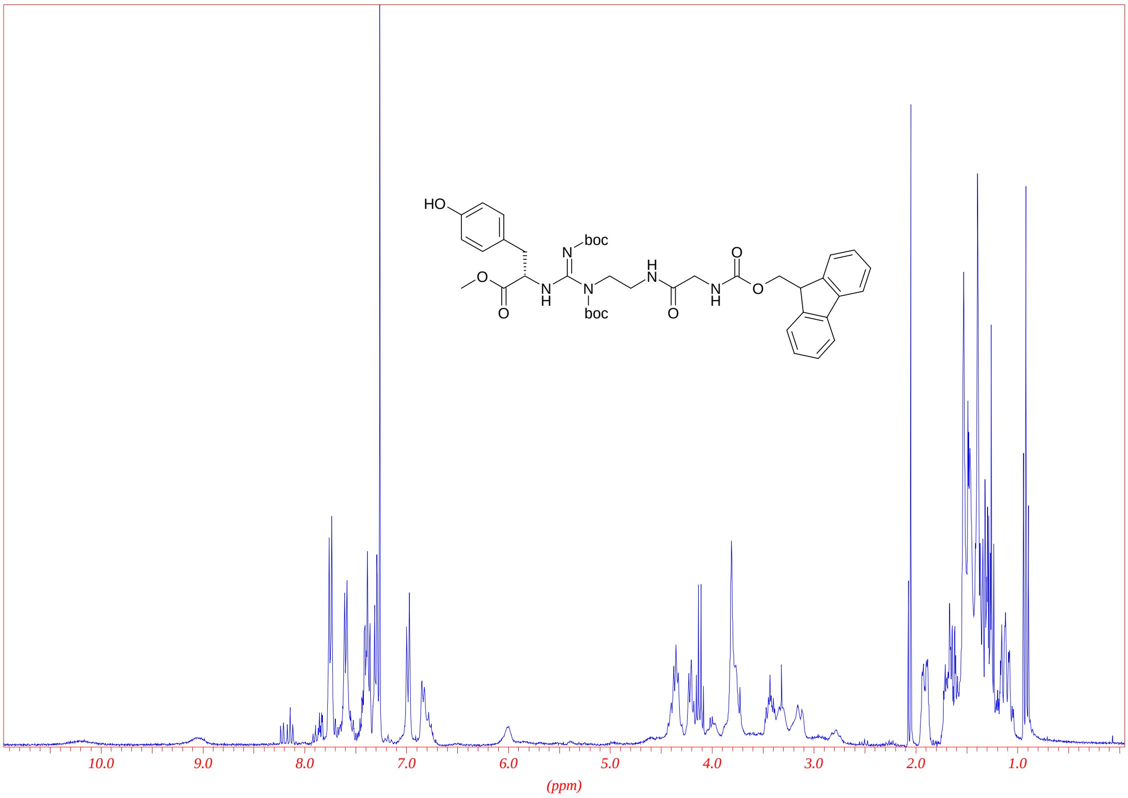


Figure S-39. ^{1}H-NMR of compound **45-Boc**

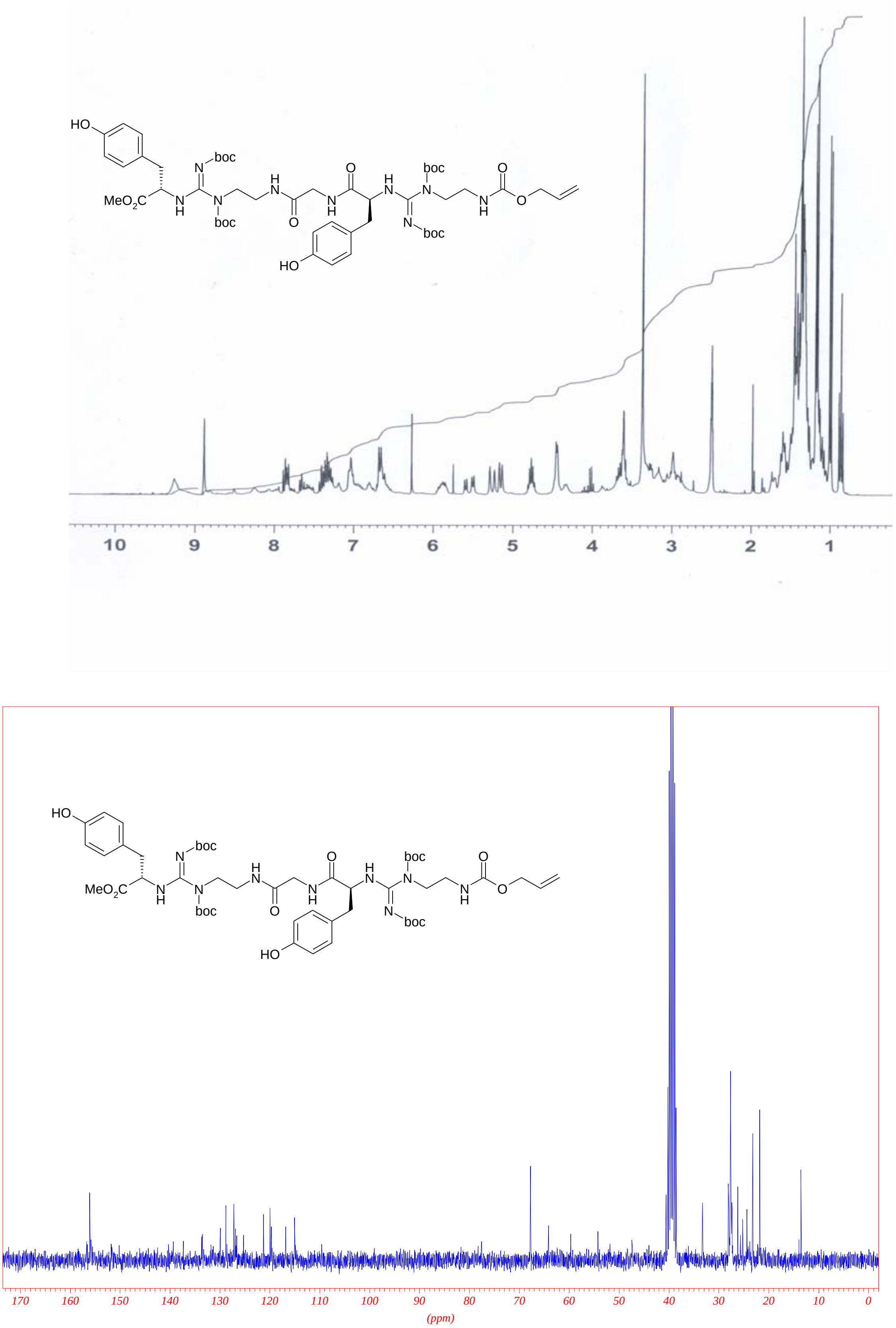


Figure S-40. ^{1}H-NMR and ^{13}C-NMR of compound **47-Boc**