Electronic Supplementary Material (ESI) for RSC Medicinal Chemistry.

Supplementary Information

Argininamide-Type Neuropeptide Y Y_1 Receptor Antagonists: The Nature of N^{ω}-Carbamoyl Substituents Determines Y_1R Binding Mode and Affinity

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1. Figures S1-S2

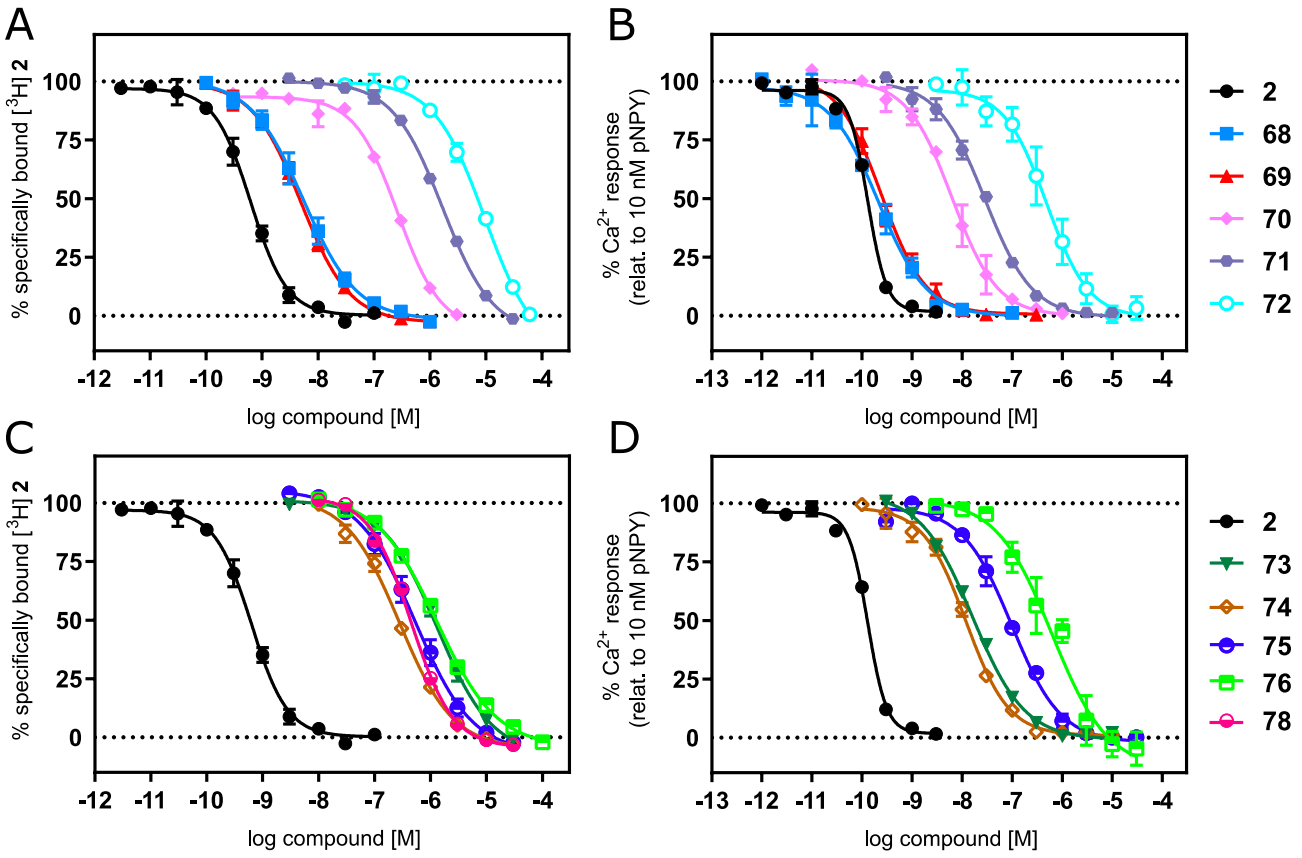


Figure S1. (A, C) Displacement curves of [^{3}H]**2** (c = 0.15 nM) obtained from competition binding studies with **68-72** (A), **73-76**, **78** (C) and reference compound **2** at Y_1R-expressing SK-N-MC cells. (B, D) Concentration dependent inhibition curves obtained from the Fura-2 Ca^{2+} assay at intact HEL cells. The intracellular Ca^{2+} mobilization was induced by 10 nM pNPY after preincubation of the cells with **68-72** (B), **73-76** (D), respectively, for 15 min or the reference compound **2** for 20 min. (A-D) Data of compound **2** were taken from Keller et. al.[1]

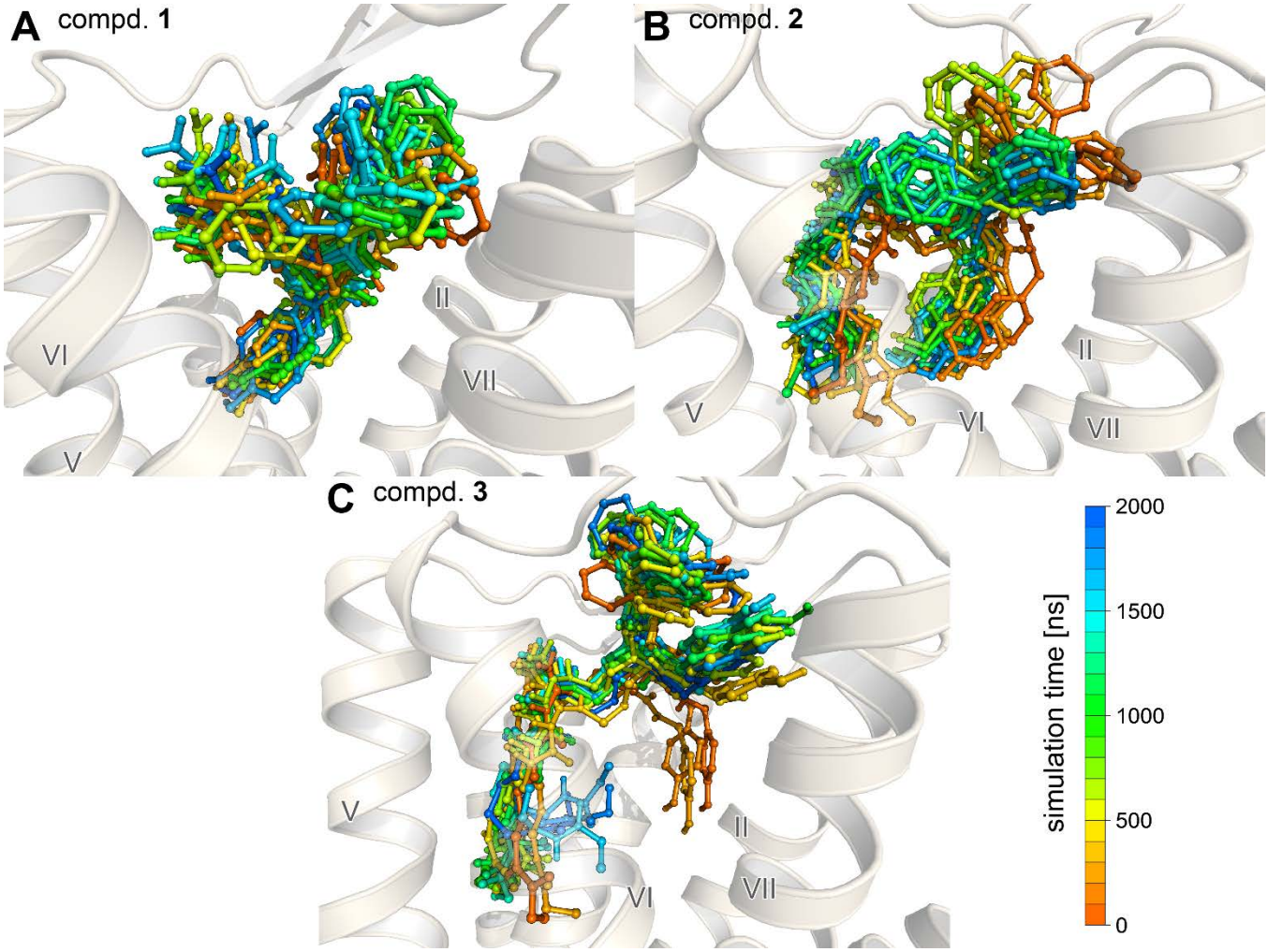


Figure S2. Time-course illustrations of the 2-µs MD simulations of the Y_1R (inactive state, PDB ID: 5ZBQ[2]) bound to **1** (A), **2** (B) or **3** (C) showing superimposed snap shots collected every 100 ns.

2. Table S1

Table S1 Slope factors (Hill slope) of compounds **53-76** and **78** determined by equilibrium competition binding with [^{3}H]**2** and in the Fura-2 Ca^{2+} assay, respectively.

compd.	slope ± SEM[a] (competition binding)	slope ± SEM[b] (Fura-2 Ca^{2+})	compd.	slope ± SEM[a] (competition binding)	slope ± SEM[b] (Fura-2 Ca^{2+})
53	-1.05 ± 0.07	n.d.	**66**	-1.17 ± 0.08	-1.17 ± 0.11
54	-1.06 ± 0.03	n.d.	**67**	-0.97 ± 0.05	-1.30 ± 0.21
55	-0.97 ± 0.10	n.d.	**68**	-1.02 ± 0.09	-0.96 ± 0.07
56	-1.27 ± 0.10	-2.36 ± 0.09**	**69**	-1.00 ± 0.07	-1.07 ± 0.24
57	-1.25 ± 0.06*	-1.92 ± 0.09**	**70**	-1.03 ± 0.14	-1.13 ± 0.30
58	-1.08 ± 0.08	-2.17 ± 0.15**	**71**	-1.00 ± 0.04	-1.02 ± 0.05
59	-1.17 ± 0.03*	-1.74 ± 0.22*	**72**	-0.98 ± 0.07	-1.19 ± 0.12
60	-1.03 ± 0.09	-1.79 ± 0.29	**73**	-0.91 ± 0.16	-0.99 ± 0.07
61	-1.02 ± 0.01	-0.79 ± 0.07	**74**	-0.90 ± 0.03*	-0.83 ± 0.01**
62	-1.01 ± 0.08	-1.39 ± 0.21	**75**	-0.89 ± 0.06	-0.86 ± 0.12
63	-1.10 ± 0.18	-1.27 ± 0.16	**76**	-0.82 ± 0.08	-1.00 ± 0.11
64	-0.89 ± 0.05	-0.69 ± 0.07*	**78**	-1.17 ± 0.03*	n.d.
65	-0.81 ± 0.07	-0.83 ± 0.04			

[a]Slope factors of the four-parameter logistic fit (GraphPad Prism 8) obtained from analysis of radioligand competition binding data. Mean values ± SEM from at least three independent experiments performed in triplicate. [b]Slope factors of the four-parameter logistic fit (GraphPad Prism 8) obtained from analysis of the Fura-2 Ca^{2+} data. Mean values ± SEM from at least three independent experiments performed in singlet. *Slope significantly different from unity, $P \leq 0.05$ (one sample, two-tailed t-test). **Slope significantly different from unity, $P \leq 0.01$ (one sample, two-tailed t-test). n.d.: not determined.

3. Synthesis Protocols and Analytical Data of Compounds 23-34, 38-39, 41-42, 53-76 and 78

Succinimidyl 2-methylpropionate (23).[3] A solution of DCC (0.89 g, 4.31 mmol) in CH_2Cl_2 (1 mL) and of 2-methylpropionic acid (**10**) (369 µL, 3.98 mmol) in CH_2Cl_2 (1 mL) were dropped to an ice-cold solution of **22** (0.46 g, 4.00 mmol) in CH_2Cl_2 (6 mL) and DMF (0.4 mL). The reaction mixture was stirred on an ice bath for 2 h and then at rt overnight. Afterwards, the reaction mixture was filtered and the solid washed (3x) with CH_2Cl_2. The filtrate was washed with a saturated solution of $NaHCO_3$ (100 mL) and the organic phase dried over Na_2SO_4. The solvent was removed by evaporation, the residue was taken up in CH_2Cl_2 and crystallization, initiated by the addition of light petroleum, afforded **23** (0.22 g, 1.19 mmol, 30%) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 1.32 (d, *J* 7.0 Hz, 6H), 2.82 (s, 4H, interfering with the next signal), 2.88 (septet, 1H, *J* 7.0 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 18.9, 25.7, 31.8, 169.4, 172.2. HRMS (APCI): m/z $[M+H]^+$ calc. for $[C_8H_{12}NO_4]^+$ 186.0766, found 186.0765. $C_8H_{11}NO_4$ (185.18).

Succinimidyl 2,2-dimethylpropionate (24).[4] A solution of DCC (1.13 g, 5.48 mmol) in CH_2Cl_2 (1 mL) and of 2,2-dimethylpropionic acid (**11**) (0.50 g, 4.90 mmol) in CH_2Cl_2 (1 mL) were dropped to an ice-cold solution of **22** (0.46 g, 4.00 mmol) in CH_2Cl_2 (6 mL) and DMF (0.4 mL). The reaction mixture was stirred on an ice bath for 2 h and then at rt overnight. Afterwards, the reaction mixture was filtered and the solid washed (3x) with CH_2Cl_2. The filtrate was washed with a saturated solution of $NaHCO_3$ (100 mL), and the organic phase dried over Na_2SO_4. The solvent was removed by evaporation, the residue was taken up in CH_2Cl_2 and crystallization, initiated by the addition of light petroleum, afforded **24** (0.28 g, 1.41 mmol, 35%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.37 (s, 9H), 2.78-2.84 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) 25.7, 27.1, 38.5, 169.3, 173.5. HRMS (APCI): m/z $[M+H]^+$ calc. for $[C_9H_{14}NO_4]^+$ 200.0923, found 200.0918. $C_9H_{13}NO_4$ (199.21).

Succinimidyl N-Boc-glycinate (25).[5] DCC (0.61 g, 2.97 mmol) was dissolved in CH_2Cl_2 and dropped to an ice-cold solution of **22** (0.34 g, 2.97 mmol) and N-Boc-glycinate (**12**) (0.40 g, 2.28 mmol) in CH_2Cl_2 (10 mL). The reaction mixture was stirred on an ice bath for 2 h. Afterwards, the reaction mixture was filtered and the solid washed (3x) with CH_2Cl_2. The filtrate was washed with a saturated solution of $NaHCO_3$ (2x 75 mL), and the organic phase dried over Na_2SO_4. The solvent was evaporation at reduced pressure and **25** (0.53 g,

1.95 mmol, 86%) was obtained as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 1.39 (s, 9H), 2.81 (s, 4H), 4.09 (d, *J* 6.2 Hz, 2H), 7.48 (t, *J* 6.1 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-d_6): δ (ppm) 25.4, 28.1, 39.8, 78.8, 155.6, 166.9, 170.0. HRMS (APCI): m/z $[M+NH_4]^+$ calc. for $[C_{11}H_{20}N_3O_6]^+$ 290.1352, found 290.1350. $C_{11}H_{16}N_2O_6$ (272.26).

Succinimidyl benzoate (26).[6] DCC (1.10 g, 5.33 mmol) was dissolved in THF (10 mL) and dropped to an ice-cold solution of **22** (0.82 g, 3.13 mmol) and benzoic acid (**13**) (0.50 g, 4.09 mmol) in THF (30 mL). The reaction mixture was stirred on an ice bath for 2 h and then at rt overnight. Afterwards, the reaction mixture was filtered, the solid washed (2x) with THF (5 mL) and the organic solvent dried over Na_2SO_4 and evaporated at reduced pressure. The crude product was purified by column chromatography (eluent: CH_2Cl_2/MeOH 97:3) to obtain **26** (0.59 g, 2.69 mmol, 86%) as white solid. ^{1}H NMR (300 MHz, DMSO-d_6): δ (ppm) 2.90 (s, 4H), 7.62-7.70 (m, 2H), 7.80-7.88 (m, 1H), 8.07-8.14 (m, 2H). ^{13}C NMR (75 MHz, DMSO-d_6): δ (ppm) 25.4, 124.4, 129.45, 129.88, 135.5, 161.7, 170.2. HRMS (APCI): m/z $[M+H]^+$ calc. for $[C_{11}H_{10}NO_4]^+$ 220.0610, found 220.0608. $C_{11}H_9NO_4$ (219.20).

Succinimidyl phenylacetate (27).[7] A solution of DCC (0.84 g, 4.07 mmol) in DMF (1 mL) and of 2-phenylacetic acid (**14**) (0.50 g, 3.67 mmol) in DMF (1 mL) were dropped to an ice-cold solution of **22** (0.36 g 7.12 mmol) in DMF (4 mL). The reaction mixture was stirred on an ice bath for 2 h and then at rt overnight. Afterwards, the reaction mixture was filtered and the solid washed (5x) with DMF (1 mL). The organic phase was poured in saturated $NaHCO_3$ solution (75 mL), and the aqueous phase extracted with ethyl acetate (3x 75 mL). The combined organic phases were washed (2x) with water, dried over $MgSO_4$, and evaporated under reduced pressure. The crude product was purified by column chromatography (eluent: light petroleum/ethyl acetate 1:2) to obtain **27** (0.61 g, 2.62 mmol, 84%) as white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 2.81 (s, 4H), 3.94 (s, 2H), 7.28-7.41 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 25.7, 37.7, 127.9, 129.0, 129.4, 131.5, 166.9, 169.1. HRMS (APCI): m/z $[M+H]^+$ calc. for $[C_{12}H_{12}NO_4]^+$ 234.0766, found 234.0765. $C_{12}H_{11}NO_4$ (233.22).

Succinimidyl diphenylacetate (28).[8] DCC (1.08 g, 5.23 mmol) was dissolved in CH_2Cl_2 (1 mL) and dropped to an ice-cold solution of **22** (0.36 g, 3.1 mmol) and diphenylacetic acid (**15**) (0.20 g, 0.94 mmol) in CH_2Cl_2 (10 mL). The reaction mixture was stirred on an ice bath for 2 h. Afterwards, the reaction mixture was filtered and the solid washed (3x) with CH_2Cl_2. The filtrate was washed with a saturated solution of $NaHCO_3$ (3x 100 mL) and the organic phase dried over Na_2SO_4. The solvent was evaporated at reduced pressure and the crude product was purified by column chromatography (eluent light petroleum/ethyl acetate 2:1 to 1:1) to obtain **28** (0.50 g, 1.62 mmol, 72%) as a white sodlid. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.66 (s, 4H), 5.25 (s, 1H), 7.18-7.31 (m, 10H). ^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) 25.7, 54.1, 128.00, 128.79, 128.96, 136.8, 168.2, 169.0. HRMS (APCI): m/z $[M+N]^+$ calc. for $[C_{18}H_{16}NO_4]^+$ 310.1079, found 310.1075. $C_{18}H_{15}NO_4$ (309.32).

Succinimidyl cyclopropanecarboxylat (29).[9] A solution of DCC (0.93 g, 4.51 mmol) in CH_2Cl_2 (1 mL) and of cyclopropane carboxylic acid (**16**) (324 µL, 4.07 mmol) in CH_2Cl_2 (1 mL) were dropped to an ice-cold solution of **22** (0.48 g, 4.17 mmol) in CH_2Cl_2 (6 mL) and DMF (0.4 mL). The reaction mixture was stirred on an ice bath for 2 h and then at rt overnight. Afterwards, the reaction mixture was filtered and the solid washed (3x) with CH_2Cl_2. The filtrate was washed with a saturated solution of $NaHCO_3$ (100 mL), and the organic phase dried over Na_2SO_4. The solvent was removed by evaporation, the residue was taken up in CH_2Cl_2 and crystallization, initiated by the addition of light petroleum, afforded **29** (0.33 g, 1.80 mmol, 43%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.05-1.24 (m, 4H), 1.81-194 (m, 1H), 2.80 (s, 4H). ^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) 10.3, 10.6, 25.6, 169.4, 170.3. HRMS (APCI): m/z $[M+H]^+$ calc. for $[C_8H_{10}NO_4]^+$ 184.0610, found 184.0606. $C_8H_9NO_4$ (183.16).

Succinimidyl cyclobutanecorboxylat (30).[10] A solution of DCC (0.81 g, 3.93 mmol) in ethyl acetate (1 mL) and of cyclobutanecarboxylic acid (**17**) (335 µL, 3.50 mmol) in ethyl acetate (1 mL) were dropped to an ice-cold solution of **22** (0.35 g, 3.04 mmol) in ethyl acetate (6 ml) and DMF (0.4 mL). The reaction mixture was stirred on an ice bath for 2 h and then at rt overnight. Afterwards, the reaction mixture was filtered and the solid washed (3x) with CH_2Cl_2. The filtrate was washed with a saturated solution of $NaHCO_3$ (100 mL), and the organic phase dried over Na_2SO_4. The solvent was removed by evaporation, the residue was taken up in CH_2Cl_2 and crystallization, initiated by the addition of light petroleum, afforded **30** (0.22 g, 1.11 mmol, 37%) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 1.93-2.14 (m, 2H), 2.30-2.53 (m, 4H), 2.78-2.89 (m, 4H),

3.37-3.51 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 18.9, 25.5, 25.8, 35.2, 169.5, 170.7. HRMS (APCI): m/z $[M+H]^+$ calc. for $[C_9H_{12}NO_4]^+$ 198.0766, found 198.0764. $C_9H_{11}NO_4$ (197.19).

Succinimidyl cyclopentanecarboxylat (31). A solution of DCC (0.70 g, 3.39 mmol) in ethyl acetate (1 mL) and of cyclopentanecarboxylic acid (**18**) (333 µL, 3.07 mmol) in ethyl acetate (1 mL) were dropped to an ice-cold solution of **22** (0.35 g, 3.04 mmol) in ethyl acetate (6 ml) and DMF (0.4 mL). The reaction mixture was stirred on an ice bath for 2 h and then at rt overnight. Afterwards, the reaction mixture was filtered and the solid washed (3x) with CH_2Cl_2. The filtrate was washed with a saturated solution of $NaHCO_3$ (100 mL), and the organic phase dried over Na_2SO_4. The solvent was removed by evaporation, the residue was taken up in CH_2Cl_2 and crystallization, initiated by the addition of light petroleum, afforded **31** (0.33 g, 1.56 mmol, 51%) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 1.58-1.79 (m, 4H), 1.89-2.09 (m, 4H), 2.78-2.88 (m, 4H), 2.97-3.11 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 25.7, 26.0, 30.3, 40.7, 169.5, 172.0. HRMS (APCI): m/z $[M+NH_4]^+$ calc. for $[C_{10}H_{17}N_2O_4]^+$ 229.1188, found 229.1187. $C_{10}H_{13}NO_4$ (211.22).

Succinimidyl cyclohexanecarboxylat (32).[10, 11] A solution of DCC (0.77 g, 3.73 mmol) in ethyl acetate (1 mL) and of cyclohexanecarboxylic acid (**19**) (0.36 g, 2.81 mmol) in ethyl acetate (1 mL) were dropped to an ice-cold solution of **22** (0.41 g, 3.56 mmol) in ethyl acetate (6 ml) and DMF (0.4 mL). The reaction mixture was stirred on an ice bath for 2 h and then at rt overnight. Afterwards, the reaction mixture was filtered and the solid washed (3x) with CH_2Cl_2. The filtrate was washed with a saturated solution of $NaHCO_3$ (100 mL), and the organic phase dried over Na_2SO_4. The solvent was removed by evaporation, the residue was taken up in CH_2Cl_2 and crystallization, initiated by the addition of light petroleum, afforded **32** (0.40 g, 1.67 mmol, 59%) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6): δ (ppm) 1.19-1.62 (m, 7H), 1.64-1.75 (m, 2H), 1.86-1.96 (m, 2H), 2.80 (s, 4H). ^{13}C NMR (75 MHz, DMSO-d_6): δ (ppm) 24.3, 25.0, 25.5, 28.4, 39.4, 170.3, 170.9. HRMS (APCI): m/z $[M+NH_4]^+$ calc. for $[C_{11}H_{19}N_2O_4]^+$ 243.1345, found 243.1346. $C_{11}H_{15}NO_4$ (225.24).

Succinimidyl cyclohexylacetate (33). A solution of DCC (0.58 g, 2.81 mmol) in CH_2Cl_2 (1 mL) and of cyclohexylacetic acid (**20**) (0.36 g, 2.53 mmol) in CH_2Cl_2 (1 mL) were dropped to an ice-cold solution of **22** (0.29 g, 2.52 mmol) in CH_2Cl_2 (6 mL) and DMF (0.4 mL). The reaction mixture was stirred on an ice bath for 2 h and then at rt overnight. Afterwards, the reaction mixture was filtered and the solid washed (3x) with CH_2Cl_2. The filtrate was washed with a saturated solution of $NaHCO_3$ (100 mL), and the organic phase dried over Na_2SO_4. The solvent was removed by evaporation, the residue was taken up in CH_2Cl_2 and crystallization, initiated by the addition of light petroleum, afforded **33** (0.25 g, 1.04 mmol, 41%) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 0.99-1.33 (m, 5H), 1.62-1.92 (m, 6H), 2.46 (d, *J* 6.7 Hz, 2H), 2.83 (s, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 25.8, 26.1, 26.2, 33.0, 35.1, 38.8, 168.1, 169.5. HRMS (APCI): m/z $[M+NH_4]^+$ calc. for $[C_{12}H_{21}N_2O_4]^+$ 257.1501, found 257.1506. $C_{12}H_{17}NO_4$ (239.27).

Succinimidyl trifluoroacetate (34).[12] **22** (0.35 g, 3.04 mmol) was dissolved in THF (6 mL), trifluoroacetic acid anhydride (**21**) (0.90 mL, 6.38 mmol) was added dropwise and the solution stirred at rt for 3 h. After evaporation of the solvent, toluene (3 mL) was added and evaporated (3x) to obtain **34** (0.64 g, 3.04 mmol, 100%) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6): δ (ppm) 2.59 (s, 4H). $C_6H_4F_3NO_4$ (211.10).

N-*tert*-Butoxycarbonyl-N′-[2(*tert*-butoxycarbonylamino)ethyl]aminocarbonyl-S-methylisothiourea (38).[1, 13] A solution of *tert*-butyl (2-aminoethyl)carbamate (**36**) (0.62 g, 3.87 mmol) and DIPEA (1.91 mL, 11.2 mmol) in anhydrous CH_2Cl_2 (7 mL) was added dropwise to an ice-cold solution of triphosgene (0.57 g, 1.92 mmol) in anhydrous CH_2Cl_2 (5 mL). The reaction mixture was stirred at rt for 30 min, N-Boc-S-methyl-isothiourea (**35**) (0.79 g, 4.93 mmol) was added, and after 1.5 h, the solvent was removed by evaporation at reduced pressure. The crude product was purified by column chromatography (eluent CH_2Cl_2/ethyl acetate 98:2 to 90:10) to obtain **38** (1.03 g, 2.74 mmol, 71%) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6): δ (ppm) 1.37 (s, 9H), 1.44 (s, 9H), 2.28 (s, 3H), 2.97-3.11 (m, 4H), 6.82 (t, *J* 5.2 Hz, 1H), 7.72 (t, *J* 5.3 Hz, 1H), 12.32 (br s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6): δ (ppm) 13.5, 27.5, 28.1, 39.5, 39.8, 77.6, 82.1, 150.1, 155.6, 161.5, 164.8. HRMS (ESI): m/z $[M+H]^+$ calc. for $[C_{15}H_{29}N_4O_5S]^+$ 377.1859, found 377.1866. $C_{15}H_{28}N_4O_5S$ (376.47).

N-*tert*-Butoxycarbonyl-N′-[3(*tert*-butoxycarbonylamino)propyl]aminocarbonyl-S-methylisothiourea (39).[13] A solution of *tert*-butyl (3-aminopropyl)carbamate (**37**) (5.00 g, 28.7 mmol) and DIPEA (14.7 mL, 86.1 mmol) in anhydrous CH_2Cl_2 (50 mL) was added dropwise to an ice-cold solution of triphosgene (4.26 g, 14.4 mmol) in anhydrous CH_2Cl_2 (45 mL). The reaction mixture was stirred at rt for 30 min, N-Boc-S-methyl-isothiourea (**35**) (6.55 g, 34.4 mmol) was added, and after 2 h, the solvent was removed by evaporation at

reduced pressure. The crude product was purified by column chromatography (eluent CH_2Cl_2/ethyl acetate 98:2 to 96:4; eluent light petroleum/ethyl acetate 87:13 to 82:18) to obtain **39** (5.56g, 14.2 mmol, 50%) as a yellowish oil. ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 1.37 (s, 9H), 1.44 (s, 9H), 1.50-1.60 (m, 2H), 2.28 (s, 3H), 2.87-2.97 (m, 2H), 2.99-3.07 (m, 2H), 6.76 (t, *J* 6.8 Hz, 1H)), 7.73 (t, *J* 5.8 Hz, 1H), 12.39 (br s, 1H). ^{13}C NMR (101 MHz, DMSO-d_6): δ (ppm) 13.6, 27.6, 28.2, 29.5, 37.1, 37.7, 77.4, 82.1, 150.2, 155.6, 161.9, 164.8. HRMS (ESI): m/z $[M+H]^+$ calc. for $[C_{16}H_{30}N_4O_5SNa]^+$ 413.1835, found 413.1832. $C_{16}H_{30}N_4O_5S$ (390.50).

(R)-Nα-Diphenylacetyl-Nω-(aminoethyl)aminocarbonyl(4-hydroxybenzyl)argininamide bis(hydrotrifluoroacetate) (41).[1] (R)-N′-(4-*tert*-Butoxybenzyl)-Nα-(2,2-diphenylacetyl)ornithinamide (**40**) (1.31 g, 3.49 mmol) and N-*tert*-butoxycarbonyl-N′-[2(*tert*-butoxycarbonylamino)ethyl]aminocarbonyl-S-methylisothiourea (**38**) (1.50 g, 3.08 mmol) were dissolved in CH_2Cl_2 (30 mL). $HgCl_2$ (1.26 g, 4.62 mmol) and DIPEA (1.31 mL, 7.70 mmol) were added and the mixture was stirred at rt for 1 h to afford the crude product that was purified by column chromatography (eluent CH_2Cl_2/ethyl acetate 1:1). The purified product was dissolved in CH_2Cl_2 (7.5 mL), the reaction mixture was cooled to 0°C and TFA (7.5 mL) was added. After 1 h, the mixture was allowed to come to rt and stirred overnight. The solvent was evaporated, and the crude product purified by HPLC (gradient: 0-35 min, A/B 85:15–38:62, t_R = 16 min) to obtain **41** (372.11 mg, 47 mmol, 68%) as a white fluffy solid. ^{1}H NMR (600 MHz, DMSO-d_6): δ (ppm) 1.36-1.50 (m, 2H), 1.51-1.58 (m, 1H), 1.64-1.72 (m, 1H), 2.93 (br s, 2H), 3.18-3.26 (m, 2H), 3.33-3.38 (m, 2H), 4.09-4.20 (m, 2H), 4.30-4.36 (m, 1H), 5.13 (s, 1H), 6.65-6.69 (m, 2H), 6.98-7.02 (m, 2H), 7.20-7.25 (m, 2H), 7.26-7.31 (m, 8H), 7.61 (br s, 1H), 7.89 (br s, 3H), 8.36 (t, *J* 5.7 Hz, 1H), 8.42-8.65 (br s, 2H, interfering with the next signal), 8.49 (d, *J* 8.1 Hz, 1H), 9.05 (br s, 1H), 9.33 (br s, 1H), 10.81 (br s, 1H). ^{13}C NMR (151 MHz, DMSO-d_6): δ (ppm) 24.6, 29.4, 37.2, 38.5, 40.4, 41.6, 52.3, 55.9, 115.0, 117.0 (q, *J* 297.1 Hz) (TFA), 126.57, 126.61, 128.17, 128.21, 128.40, 128.50, 128.52, 129.13, 140.3, 140.5, 153.7, 154.4, 156.3, 158.9 (q, *J* 31.6 Hz) (TFA), 170.97, 171.04. HRMS (ESI): m/z $[M+H]^+$ calc. for $[C_{30}H_{38}N_7O_4]^+$ 560.2985, found 560.2986. $C_{30}H_{37}N_7O_4 \times C_4H_2F_6O_4$ (559.67 + 228.05).

(R)-Nα-Diphenylacetyl-Nω-(aminopropyl)aminocarbonyl(4-hydroxybenzyl)argininamide bis(hydrotrifluoroacetate) (42).[14] (R)-N′-(4-*tert*-Butoxybenzyl)-Nα-(2,2-diphenylacetyl)ornithinamide (**40**) (150 mg, 0.31 mmol) and N-*tert*-butoxycarbonyl-N′-[3(*tert*-butoxycarbonylamino)propyl]aminocarbonyl-S-methylisothiourea (**39**) (132 mg, 0.34 mmol) were dissolved in CH_2Cl_2 (30 mL). $HgCl_2$ (126 mg, 0.46 mmol) and DIPEA (100 mg, 0.76 mmol) were added and the mixture was stirred at rt overnight to afford the crude product that was purified by column chromatography (eluent CH_2Cl_2/ethyl acetate 10:1 to 1:1). The purified product was dissolved in a mixture (10.5 mL) of CH_2Cl_2, TFA and water (1:1:0.1). Afterwards, CH_2Cl_2 (20 mL) was added, the organic solvent evaporated (2x) at reduced pressure, and the crude product purified by HPLC (gradient: 0-35 min, A/B 85:15–38:62, t_R = 19 min) to obtain **42** (112 mg, 0.14 mmol, 45%) as a white fluffy solid. ^{1}H NMR (600 MHz, DMSO-d_6): δ (ppm) 1.36-1.50 (m, 2H), 1.50-1.60 (m, 1H), 1.63-1.79 (m, 3H), 2.77-2.88 (m, 2H), 3.14-3.26 (m, 4H), 4.10-4.21 (m, 2H), 4.29-4.38 (m, 1H), 5.13 (s, 1H), 6.64-6.71 (m, 2H), 6.98-7.03 (m, 2H), 7.18-7.24 (m, 2H), 7.26-7.34 (m, 8H), 7.67 (br s, 1H), 7.87 (br s, 3H), 8.37 (t, *J* 5.5 Hz, 1H), 8.41-8.61 (m, 3H), 9.03 (br s, 1H), 9.36 (br s, 1H), 10.78 (br s, 1H). ^{13}C NMR (151 MHz, DMSO-d_6): δ (ppm) 24.6, 27.3, 29.4, 36.5, 36.7, 40.4, 41.7, 52.4, 56.0, 115.0, 117.0 (q, *J* 298.4 Hz) (TFA), 126.59, 126.62, 128.18, 128.22, 128, 4, 128.52, 128.57, 129.2, 140.3, 140.5, 153.8, 154.1, 156.3, 159.2 (q, *J* 32.1 Hz) (TFA), 171.04, 171.08. HRMS (ESI): m/z $[M+H]^+$ calc. for $[C_{31}H_{40}N_7O_4]^+$ 574.3142, found 574.3142. $C_{31}H_{39}N_7O_4 \times C_4H_2F_6O_4$ (573.70 + 228.05).

(R)-Nα-Diphenylacetyl-Nω-(acetylaminoethyl)aminocarbonyl(4-hydroxybenzyl)argininamide hydrotrifluoroacetate (53). Compound **53** was prepared using *General Procedure A*, the reactants **41** (34.6 mg, 43.9 µmol), succinimidyl acetate (**43**) (7.3 mg, 32.5 µmol), DIPEA (29 µL, 166 µmol) and the solvent DMF (300 µL). Purification by preparative HPLC (gradient: 0-35 min, A/B 85:15–45:55, t_R = 20 min) afforded **53** (22.4 mg, 31.3 µmol, 71%) as a white fluffy solid. ^{1}H NMR (600 MHz, DMSO-d_6): δ (ppm) 1.36-1.50 (m, 2H), 1.51-1.61 (m, 1H), 1.64-1.72 (m, 1H), 1.80 (s, 3H), 3.10-3.27 (m, 6H), 4.09-4.20 (m, 2H), 4.31-4.37 (m, 1H), 5.13 (s, 1H), 6.65-6.71 (m, 2H), 6.98-7.03 (m, 2H), 7.19-7.25 (m, 2H), 7.26-7.33 (m, 8H), 7.50-7.56 (m, 1H), 7.90-8.00 (m, 1H), 8.36 (t, *J* 5.8 Hz , 1H), 8.43 (br s, 2H, interfering with two surrounding signals), 8.49 (d, *J* 8.1 Hz, 1H), 8.96 (br s, 1H), 9.31 (br s, 1H), 10.25 (br s, 1H). ^{13}C NMR (151 MHz, DMSO-d_6): δ (ppm) 22.6, 24.6, 29.4, 38.1, 39.1, 40.3, 41.6, 52.3, 55.9, 115.0, 115.7 (TFA), 117.6 (TFA), 126.57, 126.61, 128.17, 128.21, 128.42, 128.50, 128.53, 129.1, 140.3, 140.5, 153.6, 153.9, 156.3, 158.9 (q, *J* 33.2 Hz) (TFA), 169.6, 170.99,

171.03. RP-HPLC (Method A, 220 nm): 100% (t_R = 11.8 min, k = 3.5). HRMS (ESI): m/z $[M+H]^+$ calc. for $[C_{32}H_{40}N_7O_5]^+$ 602.3085, found 602.3092. $C_{32}H_{39}N_7O_5 \times C_2HF_3O_2$ (601.71 + 114.02).

(R)-Nᵅ-Diphenylacetyl-Nᵚ-(acetylylaminopropyl)aminocarbonyl(4-hydroxybenzyl)argininamide hydrotrifluoroacetate (54). Compound **54** was prepared using *General Procedure A*, the reactants **42** (26.3 mg, 32.8 µmol), succinimidyl acetate (**43**) (5.1 mg, 32 µmol), DIPEA (22 µL, 126 µmol) and the solvent DMF (300 µL). Purification by preparative HPLC (gradient: 0-35 min, A/B 85:15–45:55, t_R = 20 min) afforded **54** (15.7 mg, 18.6 µmol, 57%) as a white fluffy solid. ^{1}H NMR (600 MHz, DMSO-d_6): δ (ppm) 1.36-1.50 (m, 2H), 1.52-1.60 (m, 3H), 1.64-1.72 (m, 1H), 1.80 (s, 3H), 3.03-3.08 (m, 2H), 3.08-3.13 (m, 2H), 3.16-3.24 (m, 2H), 4.10-4.20 (m, 2H), 4.31-4.37 (m, 1H), 5.13 (s, 1H), 6.66-6.69 (m, 2H), 6.98-7.02 (m, 2H), 7.19-7.25 (m, 2H), 7.26-7.31 (m, 8H), 7.49 (t, *J* 5.1 Hz, 1H), 7.88 (t, *J* 5.4 Hz, 1H), 8.36 (t, *J* 5.8 Hz, 1H), 8.40 (br s, 2H, interfering with two surrounding signals), 8.49 (d, *J* 8.0 Hz, 1H), 8.94 (br s, 1H), 9.30 (br s, 1H), 10.16 (br s, 1H). ^{13}C NMR (151 MHz, DMSO-d_6): δ (ppm) 22.6, 24.6, 29.2, 29.4, 36.0, 37.0, 40.3, 41.6, 52.3, 55.9, 115.0, 115.4 (TFA), 117.4 (TFA), 126.57, 126.60, 128.17, 128.20, 128.42, 128.50, 128.53, 129.1, 140.3, 140.5, 153.6, 153.7, 156.3, 158.7 (q, *J* 34.0 Hz) (TFA), 169.3, 170.99, 171.03. RP-HPLC (Method A, 220 nm): 100% (t_R = 11.9 min, k = 3.6). HRMS (ESI): m/z $[M+H]^+$ calc. for $[C_{33}H_{42}N_7O_5]^+$ 616.3242 ;found 616.3250. $C_{33}H_{41}N_7O_5 \times C_2HF_3O_2$ (615.74 + 114.02).

(R)-Nᵅ-Diphenylacetyl-Nᵚ-(propionylaminopropyl)aminocarbonyl(4-hydroxybenzyl)argininamide hydrotrifluoroacetate (55). Compound **55** was prepared using *General Procedure A*, the reactants **42** (26.3 mg, 32.8 µmol), succinimidyl propionate (**44**) (6.1 mg, 35.6 µmol), DIPEA (22 µL, 126 µmol) and the solvent DMF (300 µL). Purification by preparative HPLC (gradient: 0-35 min, A/B 85:10–45:55, t_R = 22 min) afforded **55** (17.5 mg, 23.5 µmol, 72%) as a white fluffy solid. ^{1}H NMR (600 MHz, DMSO-d_6): δ (ppm) 0.99 (t, 3H, *J* 7.6 Hz), 1.36-1.50 (m, 2H), 1.50-1.60 (m, 3H), 1.64-1.72 (m, 1H), 2.07 (q, *J* 7.6 Hz, 2H), 3.04-3.13 (m, 4H), 3.16-3.23 (m, 2H), 4.10-4.20 (m, 2H), 4.31-4.37 (m, 1H), 5.13 (s, 1H), 6.66-6.70 (m, 2H), 6.99-7.02 (m, 2H), 7.19-7.25 (m, 2H), 7.26-7.31 (m, 8H), 7.50 (br s, 1H), 7.80 (t, *J* 5.5 Hz, 1H), 8.36 (t, *J* 5.8 Hz, 1H), 8.41 (br s, 2H, interfering with two surrounding signals), 8.49 (d, *J* 8.1 Hz, 1H), 8.95 (br s, 1H), 9.31 (br s, 1H, interfering with previous signal), 10.21 (br s, 1H). ^{13}C NMR (151 MHz, DMSO-d_6): δ (ppm) 10.0, 24.6, 28.5, 29.28, 29.42, 35.9, 37.0, 40.3, 41.6, 52.3, 55.9, 115.0, 115.5 (TFA), 117.5 (TFA), 126.57, 126.60, 128.16, 128.20, 128.42, 128.50, 128.53, 129.1, 140.3, 140.5, 153.63, 153.71, 156.3, 158.8 (q, *J* 33.6 Hz) (TFA), 170.99, 171.03, 170.07. RP-HPLC (Method A, 220 nm): 99% (t_R = 12.4 min, k = 3.8). HRMS (ESI): m/z $[M+H]^+$ calc. for $[C_{34}H_{44}N_7O_5]^+$ 630.3398, found 630.3403. $C_{34}H_{43}N_7O_5 \times C_2HF_3O_2$ (629.76 + 114.02).

(R)-Nᵅ-Diphenylacetyl-Nᵚ-(2-fluoroacetylaminoethyl)aminocarbonyl(4-hydroxybenzyl)argininamide hydrotrifluoroacetate (56). Compound **56** was prepared using *General Procedure C* and the reactants **41** (99.71 mg, 126.6 µmol), 2-fluoroacetic acid (**46**) (28.99 mg, 371.5 µmol), DIPEA (55 µL, 315.7 µmol), DCC (39.44 mg, 191.2 µmol). Purification by preparative HPLC (gradient: 0-35 min, A/B 85:15–38:62, t_R = 21 min) afforded **56** (26.6 mg, 36.3 µmol, 29%) as a white fluffy solid. ^{1}H NMR (600 MHz, DMSO-d_6): δ (ppm) 1.36-1.49 (m, 2H), 1.50-1.58 (m, 1H), 1.64-1.71 (m, 1H), 3.17-3.26 (m, 6H), 4.09-4.18 (m, 2H), 4.30-4.35 (m, 1H), 4.78 (d, *J* 47.1 Hz, 2H), 5.12 (s, 1H), 6.65-6.68 (m, 2H), 6.98-7.01 (m, 2H), 7.18-7.24 (m, 2H), 7.27-7.30 (m, 8H), 7.56 (br s, 1H), 8.26 (t, *J* 5.0 Hz, 1H), 8.35 (t, *J* 5.8 Hz, 1H), 8.44 (br s, 2H, interfering with two surrounding signals), 8.48 (d, *J* 8.1 Hz, 1H), 8.97 (br s, 1H), 9.31 (br s, 1H), 10.36 (br s, 1H). ^{13}C NMR (150 MHz, DMSO-d_6): δ (ppm) 24.6, 29.4, 37.8, 38.8, 40.4, 41.6, 52.3, 55.9, 80.0 (d, *J* 180.4 Hz), 115.0, 116.0 (TFA), 118.0 (TFA), 126.58, 126.62, 128.17, 128.22, 128.43, 128.51, 128.54, 129.1, 140.3, 140.5, 153.7, 154.0, 156.3, 159.0 (q, *J* 32.2 Hz) (TFA), 167.5 (d, *J* 18.2 Hz), 171.01, 171.05. RP-HPLC (Method A, 220 nm): 98% (t_R = 12.6 min, k = 3.9). HRMS (ESI): m/z $[M+H]^+$ calc. for $[C_{32}H_{39}FN_7O_5]^+$ 620.2991, found 620.2999. $C_{32}H_{38}FN_7O_5 \times C_2HF_3O_2$ (619.70 + 114.02).

(R)-Nᵅ-Diphenylacetyl-Nᵚ-(2,2-difluoroacetylaminoethyl)aminocarbonyl(4-hydroxybenzyl)argininamide hydrotrifluoroacetate (57). Compound **57** was prepared using *General Procedure C* and the reactants **41** (66.4 mg, 84.3 µmol), 2,2-difluoroacetic acid (**47**) (15 µL, 238.4 µmol), DIPEA (36 µL, 206.7 µmol), DCC (26.3 mg, 127.5 µmol). Purification by preparative HPLC (gradient: 0-35 min, A/B 85:15–38:62, t_R = 21 min) afforded **57** (10.0 mg, 13.3 µmol, 16%) as a white fluffy solid. ^{1}H NMR (600 MHz, DMSO-d_6): δ (ppm) 1.35-1.48 (m, 2H), 1.49-1.57 (m, 1H), 1.63-1.70 (m, 1H), 3.17-3.27 (m, 6H), 4.08-4.19 (m, 2H), 4.30-4.35 (m, 1H), 5.12 (s, 1H), 6.19 (t, *J* 53.7 Hz, 1H), 6.64-6.69 (m, 2H), 6.97-7.00 (m, 2H), 7.18-7.24 (m, 2H), 7.25-7.31 (m, 8H), 7.58 (br s, 1H), 8.35 (t, *J* 5.7 Hz, 1H), 8.44 (br s, 2H, interfering with two surrounding

signals), 8.48 (d, *J* 8.1 Hz, 1H), 8.86 (t, *J* 5.1 Hz, 1H), 8.94 (br s, 1H), 9.30 (br s, 1H), 10.23 (br s, 1H). ^{13}C NMR (150 MHz, DMSO-d_6): δ (ppm) 24.6, 29.4, 38.2, 38.4, 40.3, 41.6, 52.3, 55.9, 108.5 (t, *J* 247.2 Hz), 115.0, 116.1 (TFA), 118.1 (TFA), 126.56, 126.60, 128.16, 128.20, 128.41, 128.49, 128.52, 129.1, 140.3, 140.5, 153.6, 153.9, 156.3, 158.6 (q, *J* 31.4 Hz) (TFA), 162.6 (t, *J* 25.1 Hz), 170.97, 171.02. RP-HPLC (Method A, 220 nm): 98% (t_R = 12.8 min, *k* = 4.0). HRMS (ESI): m/z [M+H]$^+$ calc. for $[C_{32}H_{38}F_2N_7O_5]^+$ 638.2902, found 638.2905. $C_{32}H_{37}F_2N_7O_5 \times C_2HF_3O_2$ (637.69 + 114.02).

(R)-Nα-Diphenylacetyl-Nω-(trifluoroacetylaminoethyl)aminocarbonyl(4-hydroxybenzyl)argininamide hydrotrifluoroacetate (58). Compound **58** was prepared using *General Procedure A*, the reactants **41** (30 mg, 38.1 µmol), succinimidyl trifluoroacetate (**34**) (20 mg, 88.3 µmol), DIPEA (20 µL, 114.8 µmol) and the solvent DMF (100 µL). Purification by preparative HPLC (gradient: 0-30 min, A/B 85:15–38:62, t_R = 19) afforded **58** (6.24 mg, 8.1 µmol, 21%) as a white fluffy solid. ^{1}H NMR (600 MHz, DMSO-d_6): δ (ppm) 1.36-1.49 (m, 2H), 1.50-1.58 (m, 1H), 1.63-1.71 (m, 1H), 3.17-3.23 (m, 2H), 3.24-3.28 (m, 2H), 3.29-3.32 (m, 2H), 4.08-4.21 (m, 2H), 4.30-4.37 (m, 1H), 5.12 (s, 1H), 6.66-6.69 (m, 2H), 6.98-7.02 (m, 2H), 7.20-7.25 (m, 2H), 7.27-7.30 (m, 8H), 7.61 (t, *J* 5.5 Hz, 1H), 8.36 (t, *J* 5.9 Hz ,1H), 8.44 (br s, 2H, interfering with two surrounding signals), 8.48 (d, *J* 8.1 Hz, 1H), 8.91 (br s, 1H), 9.30 (br s, 1H), 9.48 (t, *J* 5.2 Hz, 1H), 10.17 (br s, 1H). ^{13}C NMR (150 MHz, DMSO-d_6): δ (ppm) 24.6, 29.4, 36.5, 38.1, 38.9, 40.4, 41.6, 52.3, 56.0, 114.96 (TFA), 115.03, 116.9 (TFA), 117.1 (q, *J* 298.6 Hz), 126.58, 126.61, 128.17, 128.21, 128.42, 128.51, 128.56, 129.1, 140.3, 140.5, 153.7, 154.2, 156.5, 156.8 (the last signals belong to a quartet that is not fully resolved), 158.8 (q, *J* 31.7 Hz) (TFA), 171.04, 171.07. RP-HPLC (Method A, 220 nm): 98% (t_R = 13.6 min, *k* = 4.3). HRMS (ESI): m/z [M+H]$^+$ calc. for $[C_{32}H_{37}F_3N_7O_5]^+$ 656.2803, found 656.2814. $C_{32}H_{36}F_3N_7O_5 \times C_2HF_3O_2$ (655.68 + 114.02).

(R)-Nα-Diphenylacetyl-Nω-(2-chloroacetylaminoethyl)aminocarbonyl(4-hydroxybenzyl)argininamide hydrotrifluoroacetate (59). Compound **59** was prepared using *General Procedure B* and the reactants **41** (106.74 mg, 135.5 µmol), 2-chloroacetic acid (**48**) (37.4 mg, 395.8 µmol), DCC (38 mg, 184.2 µmol). Purification by preparative HPLC (gradient: 0-30 min, A/B 85:15–38:62, t_R = 18 min) afforded **59** (16.61 mg, 22.14 µmol, 16%) as a white fluffy solid. ^{1}H NMR (600 MHz, DMSO-d_6): δ (ppm) 1.37-1.50 (m, 2H), 1.51-1.58 (m, 1H), 1.64-1.73 (m, 1H), 3.17-3.24 (m, 6H), 4.05 (s, 2H), 4.10-4.20 (m, 2H), 4.31-4.36 (m, 1H), 5.13 (s, 1H), 6.65-6.70 (m, 2H), 6.98-7.02 (m, 2H), 7.19-7.25 (m, 2H), 7.26-7.32 (m, 8H), 7.56 (br s, 1H), 8.31-8.35 (m, 1H), 8.36 (t, *J* 5.8 Hz, 1H), 8.45 (br s, 2H, interfering with two surrounding signals), 8.49 (d, *J* 8.1 Hz, 1H), 8.96 (br s, 1H), 9.31 (br s, 1H), 10.32 (br s, 1H). ^{13}C NMR (150 MHz, DMSO-d_6): δ (ppm) 24.6, 29.4, 38.6, 38.7, 40.3, 41.6, 42.6, 52.3, 55.9, 115.01, 115.9 (TFA), 117.9 (TFA), 126.56, 126.61, 128.16, 128.21, 128.42, 128.50, 128.53, 129.13, 140.3, 140.5, 153.6, 153.9, 156.3, 158.8 (q, *J* 32.5 Hz) (TFA), 166.3, 170.98, 171.03. RP-HPLC (Method A, 220 nm): 100% (t_R = 12.8 min, *k* = 4.0). HRMS (ESI): m/z [M+H]$^+$ calc. for $[C_{32}H_{39}ClN_7O_5]^+$ 636.2696, found 636.2699. $C_{32}H_{38}ClN_7O_5 \times C_2HF_3O_2$ (636.15 + 114.02).

(R)-Nα-Diphenylacetyl-Nω-(2-bromoacetylaminoethyl)aminocarbonyl(4-hydroxybenzyl)argininamide hydrotrifluoroacetate (60). Compound **60** was prepared using *General Procedure B* and the reactants **41** (93.44 mg, 118.6 µmol), 2-bromoacetic acid (**49**) (37.5 mg, 269.9 µmol), DCC (31.1 mg, 150.7 µmol). Purification by preparative HPLC (gradient: 0-30 min, A/B 85:15–38:62, t_R = 19 min) afforded **60** (15.40 mg, 19.4 µmol, 16%) as a white fluffy solid. ^{1}H NMR (600 MHz, DMSO-d_6): δ (ppm) 1.37-1.50 (m, 2H), 1.51-1.58 (m, 1H), 1.64-1.73 (m, 1H), 3.17-3.24 (m, 6H), 3.85 (s, 2H), 4.10-4.20 (m, 2H), 4.31- 4.36 (m, 1H), 5.13 (s, 1H), 6.65-6.70 (m, 2H), 6.98-7.02 (m, 2H), 7.19-7.25 (m, 2H), 7.26-7.32 (m, 8H), 7.56 (br s, 1H), 8.31-8.35 (m, 1H), 8.36 (t, *J* 5.8 Hz, 1H), 8.45 (br s, 2H, interfering with two surrounding signals), 8.49 (d, *J* 8.1 Hz, 1H), 8.97 (br s, 1H), 9.31 (br s, 1H), 10.32 (br s, 1H). ^{13}C NMR (150 MHz, DMSO-d_6): δ (ppm) 24.6, 29.40, 29.44, 38.66, 38.73, 40.4, 41.6 52.3, 55.9, 115.0, 126.56, 126.61, 128.16, 128.21, 128.42, 128.50, 128.52, 129.13, 140.3, 140.5, 153.6, 153.9, 156.3, 158.8 (q, *J* 32.9 Hz), 166.5, 170.97, 171.03. RP-HPLC (Method A, 220 nm): 99% (t_R = 12.9 min, *k* = 4.0). HRMS (ESI): m/z [M+H]$^+$ calc. for $[C_{32}H_{39}BrN_7O_5]^+$ 680.2191, found 680.2193. $C_{32}H_{38}BrN_7O_5 \times C_2HF_3O_2$ (680.60 + 114.02).

(R)-Nα-Diphenylacetyl-Nω-(glycinylaminoethyl)aminocarbonyl(4-hydroxybenzyl)argininamide bis(hydrotrifluoroacetate) (61). Compound **61** was prepared using *General Procedure A*, the reactants **41** (41.4 mg, 52.6 µmol), succinimidyl N-Boc-glycinate (**25**) (17.6 mg, 64.6 µmol), DIPEA (35 µL, 200.9 µmol) and the solvent DMF (1 mL) Additionally, the crude product was poured into a solution of 100 mL water (5% acetonitrile, 0.5% TFA). After lyophilization, the crude product was dissolved in a mixture (2 mL) of CH_2Cl_2

and TFA (1:1) and stirred at rt for 2 h. The solvent was evaporated, and the crude product purified by preparative HPLC (gradient: 0-30 min, A/B 85:15–40:60, t_R = 15 min) which afforded **61** (20.5 mg, 24.4 µmol, 46%) as a white fluffy solid. ^{1}H NMR (600 MHz, DMSO-d_6): δ (ppm) 1.36-1.50 (m, 2H), 1.51-1.58 (m, 1H), 1.64-1.72 (m, 1H), 3.17-3.26 (m, 6H), 3.53 (s, 2H), 4.09-4.19 (m, 2H), 4.31-4.36 (m, 1H), 5.13 (s, 1H), 6.66-6.70 (m, 2H), 6.98-7.02 (m, 2H), 7.19-7.25 (m, 2H), 7.26-7.31 (m, 8H), 7.64 (br s, 1H), 8.08 (br s, 3H), 8.36 (t, *J* 5.7 Hz, 1H), 8.42-8.56 (m, 4H), 9.02 (br s, 1H), 9.34 (br s, 1H), 10.73 (br s, 1H). ^{13}C NMR (150 MHz, DMSO-d_6): δ (ppm) 24.6, 29.4, 38.3, 38.7, 40.0, 40.3, 41.6, 52.3, 55.9, 115.0, 116.1 (TFA), 118.0 (TFA), 126.58, 126.61, 128.17, 128.21, 128.41, 128.51, 128.54, 129.1, 140.3, 140.5, 153.7, 154.1, 156.3, 158.9 (q, *J* 31.7 Hz) (TFA), 166.2, 171.01, 171.06. RP-HPLC (Method A, 220 nm): 96% (t_R = 10.9 min, *k* = 3.2). HRMS (ESI): m/z $[M+H]^+$ calc. for $[C_{32}H_{41}N_8O_5]^+$ 617.3194, found 617.3205. $C_{32}H_{40}N_8O_5 \times C_4H_2F_6O_4$ (616.31 + 228.04).

(R)-N$^\alpha$-Diphenylacetyl-N$^\omega$-(2-hydroxyacetylaminoethyl)aminocarbonyl(4-hydroxybenzyl)argininamide hydrotrifluoroacetate (62). Under assay conditions, **60** is stable for 24 h. Degradation of compound **60** led to a 1:1 mixture of **60** and **62** after 6 months. Purification by preparative HPLC (gradient: 0-30 min, A/B 85:15–38:62, t_R = 15 min) afforded **62** as a white fluffy solid. ^{1}H NMR (600 MHz, DMSO-d_6): δ (ppm) 1.35-1.49 (m, 2H), 1.50-1.58 (m, 1H), 1.64-1.72 (m, 1H), 3.17-3.25 (m, 6H), 3.81 (s, 2H), 4.09-4.20 (m, 2H), 4.31-4.36 (m, 1H), 5.12 (s, 1H), 5.50 (br s, 1H), 6.50-6.70 (m, 2H), 6.98-7.02 (m, 2H), 7.20-7.25 (m, 2H), 7.26-7.30 (m, 8H), 7.52 (br s, 1H), 7.88 (t, *J* 5.2 Hz, 1H), 8.36 (t, *J* 5.8 Hz, 1H), 8.40 (br s, 2H, interfering with two surrounding signals), 8.48 (d, *J* 8.1 Hz, 1H), 8.89 (br s, 1H), 9.29 (br s, 1H), 9.89 (br s, 1H). ^{13}C NMR (150 MHz, DMSO-d_6): δ (ppm) 24.6, 29.4, 37.7, 39.1, 40.3, 41.6 52.3, 55.9, 61.4, 115.0, 126.57, 126.61, 128.16, 128.20, 128.41, 128.49, 128.50, 129.1, 140.3, 140.4, 153.5, 153.8, 156.3, 158.3 (q, *J* 31.6 Hz) (TFA), 170.95, 171.00, 172.3. RP-HPLC (Method A, 220 nm): 96% (t_R = 11.5 min, *k* = 3.5). HRMS (ESI): m/z $[M+H]^+$ calc. for $[C_{32}H_{40}N_7O_6]^+$ 618.3035, found 618.3038. $C_{32}H_{39}N_7O_5 \times C_2HF_3O_2$ (617.71 + 114.02).

(R)-N$^\alpha$-Diphenylacetyl-N$^\omega$-(acrylaminoethyl)aminocarbonyl(4-hydroxybenzyl)argininamide hydrotrifluoroacetate (63). Compound **63** was prepared using *General Procedure B* and the reactants **41** (97.33 mg, 123.5 µmol), acrylic acid (**52**) (20 µL, 291.4 µmol), DCC (25 mg, 121.2 µmol). Purification by preparative HPLC (gradient: 0-30 min, A/B 85:15–40:60, t_R = 18 min) afforded **63** (9.0 mg, 12.4 µmol, 10%) as a white fluffy solid. ^{1}H NMR (600 MHz, DMSO-d_6): δ (ppm) 1.36-1.50 (m, 2H), 1.50-1.58 (m, 1H), 1.63-1.72 (m, 1H), 3.18-3.23 (m, 4H), 3.23-3.27 (m, 2H), 4.09-4.20 (m, 2H), 4.30-4.36 (m, 1H), 5.16 (s, 1H), 5.59 (dd, ^2J 2.1 Hz, ^3J 10.1 Hz, 1H), 6.08 (dd, ^2J 2.1 Hz, ^3J 17.1Hz, 1H), 6.20 (dd, ^2J 10.1 Hz, ^3J 17.1 Hz, 1H), 6.65-6.70 (m, 2H), 6.98-7.03 (m, 2H), 7.19-7.25 (m, 2H), 7.26-7.32 (m, 8H), 7.56 (br s, 1H), 8.23 (t, *J* 5.3 Hz, 1H), 8.36 (t, *J* 5.8 Hz, 1H), 8.44 (br s, 2H, interfering with two surrounding signals), 8.49 (d, *J* 8.1 Hz, 1H), 8.96 (br s, 1H), 9.31 (br s, 1H), 10.18 (br s, 1H). ^{13}C NMR (150 MHz, DMSO-d_6): δ (ppm) 24.6, 29.4, 38.1, 39.0, 40.3, 41.6, 52.3, 55.9, 115.0, 125.3, 126.56, 126.60, 128.16, 128.20, 128.41, 128.49, 128.52, 129.1, 131.6, 140.3, 140.5, 153.6, 153.9, 156.3, 158.4 (q, *J* 32.1 Hz) (TFA), 165.0, 170.97, 171.02. RP-HPLC (Method A, 220 nm): 98% (t_R = 12.4 min, *k* = 3.8). HRMS (ESI): m/z $[M+H]^+$ calc. for $[C_{33}H_{40}N_7O_5]^+$ 614.3085, found 614.3089. $C_{33}H_{39}N_7O_5 \times C_2HF_3O_2$ (613.72 + 114.02).

(R)-N$^\alpha$-Diphenylacetyl-N$^\omega$-(3-chloropropanoylaminoethyl)aminocarbonyl(4-hydroxybenzyl)argininamide hydrotrifluoroacetate (64). Compound **64** was prepared using *General Procedure B* and the reactants **41** (101.15 mg, 128.4 µmol), 3-chloropropionic acid (**50**) (20.31 mg, 187.2 µmol), DCC (33.02 mg, 160 µmol). Purification by preparative HPLC (gradient: 0-35 min, A/B 85:15–38:62, t_R = 21 min) afforded **64** (9.16 mg, 12.0 µmol, 9%) as a white fluffy solid. ^{1}H NMR (600 MHz, DMSO-d_6): δ (ppm) 1.36-1.50 (m, 2H), 1.51-1.59 (m, 1H), 1.64-1.72 (m, 1H), 2.56 (t, *J* 6.4 Hz, 2H), 3.14-3.23 (m, 6H), 3.77 (t, *J* 6.4 Hz, 2H), 4.09-4.20 (m, 2H), 4.31-4.37 (m, 1H), 5.13 (s, 1H), 6.65-6.70 (m, 2H), 6.98-7.02 (m, 2H), 7.19-7.26 (m, 2H), 7.26-7.32 (m, 8H), 7.51 (br s, 1H), 8.12 (br s, 1H), 8.36 (t, *J* 5.8 Hz, 1H), 8.44 (br s, 2H, interfering with two surrounding signals), 8.49 (d, *J* 8.1 Hz, 1H), 8.97 (br s, 1H), 9.32 (br s, 1H), 10.34 (br s, 1H). ^{13}C NMR (150 MHz, DMSO-d_6): δ (ppm) 24.6, 29.4, 38.1, 38.3, 39.1, 40.3, 40.9, 41.6, 52.3, 55.9, 115.0, 116.0 (TFA), 118.0 (TFA), 126.56, 126.60, 128.16, 128.20, 128.41, 128.49, 128.52, 129.13, 140.3, 140.5, 153.6, 153.9, 156.3, 158.7 (q, *J* 31.6 Hz) (TFA), 169.2, 170.98, 171.03. RP-HPLC (Method A, 220 nm): 96% (t_R = 12.8 min, *k* = 4.0). HRMS (ESI): m/z $[M+H]^+$ calc. for $[C_{33}H_{41}ClN_7O_5]^+$ 650.2852, found 650.2854. $C_{33}H_{40}ClN_7O_5 \times C_2HF_3O_2$ (650.18 + 114.02).

(R)-N$^\alpha$-Diphenylacetyl-N$^\omega$-(3-bromopropanoylaminoethyl)aminocarbonyl(4-hydroxybenzyl)argininamide hydrotrifluoroacetate (65). Compound **65** was prepared using *General Procedure B* and the reactants **41** (97.3 mg, 123.5 µmol), 3-bromopropionic acid (**51**) (80 mg, 522.9 µmol), DCC (30 mg, 145.4

μmol). Purification by preparative HPLC (gradient: 0-35 min, A/B 85:15–38:62, t_R = 21 min) afforded **65** (12.0 mg, 14.8 μmol, 12%) as a white fluffy solid. ^{1}H NMR (600 MHz, DMSO-d_6): δ (ppm) 1.35-1.49 (m, 2H), 1.49-1.57 (m, 1H), 1.63-1.71 (m, 1H), 2.67 (t, *J* 6.5 Hz, 2H), 3.14-3.22 (m, 6H), 3.63 (t, *J* 6.5 Hz, 2H), 4.09-4.20 (m, 2H), 4.31-4.36 (m, 1H), 5.13 (s, 1H), 6.66-6.69 (m, 2H), 6.99-7.02 (m, 2H), 7.20-7.25 (m, 2H), 7.26-7.31 (m, 8H), 7.48-7.52 (m, 1H), 8.10-8.13 (m, 1H), 8.36 (t, *J* 5.8 Hz, 1H), 8.42 (br s, 2H, interfering with two surrounding signals), 8.48 (d, *J* 8.48 Hz, 1H), 8.93 (br s, 1H), 9.30 (br s, 1H), 10.14 (br s, 1H). ^{13}C NMR (150 MHz, DMSO-d_6): δ (ppm) 24.6, 29.36, 29.40, 38.1, 38.5, 38.9, 40.3, 41.6 52.3, 55.9, 115.0, 126.57, 126.60, 128.16, 128.20, 128.41, 128.49, 128.51, 129.1, 140.3, 140.5, 153.6, 153 .8, 156.3, 158.6 (q, *J* 33.4 Hz) (TFA), 169.5, 170.96, 171.02. RP-HPLC (Method A, 220 nm): 97% (t_R = 13.0 min, *k* = 4.1). HRMS (ESI): m/z $[M+H]^+$ calc. for $[C_{32}H_{41}BrN_7O_5]^+$ 694.2347, found 694.2355. $C_{33}H_{40}BrN_7O_5 \times C_2HF_3O_2$ (694.63 + 114.02).

(R)-N$^\alpha$-Diphenylacetyl-N$^\omega$-(2-methylpropionylaminoethyl)aminocarbonyl(4-hydroxybenzyl)arginininamide hydrotrifluoroacetate (66). Compound **66** was prepared using *General Procedure A*, the reactants **41** (30.98 mg, 39.3 μmol), succinimidyl 2-methylpropionate (**23**) (7.76 mg, 41.9 μmol), DIPEA (20 μL, 114.8 μmol) and the solvent DMF (100 μL). Purification by preparative HPLC (gradient: 0-30 min, A/B 85:15–38:62, t_R = 17 min) afforded **66** (24.54 mg, 33.0 μmol, 84%) as a white fluffy solid. ^{1}H NMR (600 MHz, DMSO-d_6): δ (ppm) 0.99 (d, *J* 6.9 Hz, 6H), 1.36-1.50 (m, 2H), 1.51-1.58 (m, 1H), 1.64-1.72 (m, 1H), 2.32 (septet, *J* 6.9 Hz, 1H), 3.12-3.18 (m, 4H), 3.18-3.23 (m, 2H), 4.10-4.20 (m, 2H), 4.31-4.36 (m, 1H), 5.13 (s, 1H), 6.66-6.70 (m, 2H), 6.99-7.02 (m, 2H), 7.19-7.25 (m, 2H), 7.26-7.30 (m, 8H), 7.49 (br s, 1H), 7.81-7.84 (m, 1H), 8.36 (t, *J* 5.8 Hz, 1H), 8.44 (br s, 2H, interfering with two surrounding signals), 8.49 (d, *J* 8.1 Hz, 1H), 8.97 (br s, 1H), 9.31 (br s, 1H), 10.33 (br s, 1H). ^{13}C NMR (151 MHz, DMSO-d_6): δ (ppm) 19.5, 24.6, 29.4, 34.1, 38.0, 39.1, 40.3, 41.6, 52.3, 55.9, 115.0, 115.7 (TFA), 117.7 (TFA), 126.56, 126.60, 128.16, 128.20, 128.41, 128.49, 128.52, 129.13, 140.3, 140.5, 153.6, 153.9, 156.3, 158.8 (q, *J* 33.1 Hz) (TFA), 170.97, 171.03, 173.0. RP-HPLC (Method B, 220 nm): 99% (t_R = 15.8 min, *k* = 4.5). HRMS (ESI): m/z $[M+H]^+$ calc. for $[C_{34}H_{44}N_7O_5]^+$ 630.3398, found 630.3410. $C_{34}H_{43}N_7O_5 \times C_2HF_3O_2$ (629.76 + 114.02).

(R)-N$^\alpha$-Diphenylacetyl-N$^\omega$-(2,2-dimethylpropionylaminoethyl)aminocarbonyl(4-hydroxybenzyl)arginininamide hydrotrifluoroacetate (67). Compound **67** was prepared using *General Procedure A*, the reactants **41** (31.06 mg, 39.4 μmol), succinimidyl 2,2-dimethylpropionate (**24**) (14.09 mg, 70.7 μmol), DIPEA (20 μL, 114.8 μmol) and the solvent DMF (100 μL). Purification by preparative HPLC (gradient: 0-30 min, A/B 90:10–30:70, t_R = 19 min) afforded **67** (26.60 mg, 35.1 μmol, 89%) as a white fluffy solid. ^{1}H NMR (600 MHz, DMSO-d_6): δ (ppm) 1.08 (s, 9H), 1.36-1.50 (m, 2H), 1.50-1.59 (m, 1H), 1.63-1.72 (m, 1H), 3.13-3.23 (m, 6H), 4.09-4.20 (m, 2H), 4.31-4.37 (m, 1H), 5.13 (s, 1H), 6.65-6.70 (m, 2H), 6.98-7.02 (m, 2H), 7.19-7.25 (m, 2H), 7.26-7.32 (m, 8H), 7.47 (br s, 1H), 7.52-7.57 (m, 1H), 8.36 (t, *J* 5.8 Hz, 1H), 8.43 (br s, 2H, interfering with two surrounding signals), 8.49 (d, *J* 8.0 Hz, 1H), 8.97 (s, 1H), 9.31 (br s, 1H), 10.38 (s, 1H). ^{13}C NMR (150 MHz, DMSO-d_6): δ (ppm) 24.6, 27.4, 29.4, 38.0, 38.5, 39.01, 40.3, 41.6, 52.3, 55.9, 115.0, 115.7 (TFA), 117.7 (TFA), 126.57, 126.60, 128.16, 128.20, 128.41, 128.50, 128.53, 129.13, 140.3, 140.5, 153.7, 154.0, 156.3, 158.9 (q, *J* 32.8 Hz) (TFA), 170.98, 171.03, 177.9. RP-HPLC (Method B, 220 nm): 99% (t_R = 17.5 min, *k* = 5.1). HRMS (ESI): m/z $[M+H]^+$ calc. for $[C_{35}H_{46}N_7O_5]^+$ 644.3555, found 644.3570. $C_{35}H_{45}N_7O_5 \times C_2HF_3O_2$ (643.79 + 114.02).

(R)-N$^\alpha$-Diphenylacetyl-N$^\omega$-(cyclopropoylaminoethyl)aminocarbonyl(4-hydroxybenzyl)argininamide hydrotrifluoroacetate (68). Compound **68** was prepared using *General Procedure A*, the reactants **41** (30.81 mg, 39.1 μmol), succinimidyl cyclopropanecarboxylat (**29**) (11.13 mg, 60.8 μmol), DIPEA (20 μL, 114.8 μmol) and the solvent DMF (100 μL). Purification by preparative HPLC (gradient: 0-30 min, A/B 85:15–38:62, t_R = 17 min) afforded **68** (19.36 mg, 26.1 μmol, 67%) as a white fluffy solid.^{1}H NMR (600 MHz, DMSO-d_6): δ (ppm) 0.61-0.69 (m, 4H), 1.38-1.57 (m, 4H), 1.63-1.71 (m, 1H), 3.14-3.23 (m, 6H), 4.09-4.20 (m, 2H), 4.31-4.36 (m, 1H), 5.13 (s, 1H), 6.66-6.69 (m, 2H), 6.99-7.01 (m, 2H), 7.20-7.25 (m, 2H), 7.27-7.30 (m, 8H), 7.54 (br s, 1H), 8.17 (s, 1H), 8.36 (t, *J* 5.8 Hz, 1H), 8.44 (br s, 2H, interfering with two surrounding signals), 8.49 (d, *J* 8.1 Hz, 1H) , 8.97 (s, 1H), 9.31 (s, 1H), 10.20 (s, 1H). ^{13}C NMR (151 MHz, DMSO-d_6): δ (ppm) 6.3, 13.6, 24.6, 29.4, 38.2, 39.3, 40.3, 41.6, 52.3, 55.9, 115.0, 116.1 (TFA), 118.1 (TFA), 126.56, 126.60, 128.16, 128.20, 128.41, 128.49, 128.52, 129.1, 140.3, 140.5, 153.6, 153.9, 156.3, 158.6 (q, *J* 32.7 Hz) (TFA), 170.97, 171.02, 173.0. RP-HPLC (Method B, 220 nm): 99% (t_R = 17.0 min, *k* = 4.9). HRMS (ESI): m/z $[M+H]^+$ calc. for $[C_{34}H_{42}N_7O_5]^+$ 628.3244, found 628.3255. $C_{34}H_{41}N_7O_5 \times C_2HF_3O_2$ (627.75 + 114.02).

(R)-Nα-Diphenylacetyl-Nω-(cyclobutoylaminoethyl)aminocarbonyl(4-hydroxybenzyl)argininamide hydrotrifluoroacetate (69). Compound **69** was prepared using *General Procedure A*, the reactants **41** (30.27 mg, 38.4 µmol), succinimidyl cyclobutanecorboxylat (**30**) (11.46 mg, 63.1 µmol), DIPEA (20 µL, 114.8 µmol) and the solvent DMF (100 µL). Purification by preparative HPLC (gradient: 0-30 min, A/B 85:15–38:62, t_R = 18 min) afforded **69** (20.90 mg, 27.7 µmol, 72%) as a white fluffy solid. ^{1}H NMR (600 MHz, DMSO-d_6): δ (ppm) 1.35-1.50 (m, 2H), 1.50-1.58 (m, 1H), 1.64-1.77 (m, 2H), 1.82-1.90 (m, 1H), 1.96-2.02 (m, 2H), 2.07-2.15 (m, 2H), 2.96 (q, *J* 8.5 Hz, 1H), 3.12-3.17 (m, 4H), 3.18-3.23 (m, 2H), 4.10-4.20 (m, 2H), 4.31-4.36 (m, 1H), 1.53 (s, 1H), 6.66-6.69 (m, 2H), 6.99-7.02 (m, 2H), 7.20-7.25 (m, 2H), 7.27-7.30 (m, 8H), 7.51 (br s, 1H), 7.74 (br s, 1H), 8.36 (t, *J* 5.8 Hz, 1H), 8.43 (br s, 2H, interfering with two surrounding signals), 8.49 (d, *J* 8.1 Hz, 1H), 8.96 (br s, 1H), 9.31 (br s, 1H), 10.24 (br s, 1H). ^{13}C NMR (151 MHz, DMSO-d_6): δ (ppm) 17.7, 24.7, 29.4, 36.5, 38.1, 38.7, 39.1, 40.3, 41.6, 52.3, 55.9, 115.0, 115.6 (TFA), 117.6 (TFA), 126.56, 126.60, 128.16, 128.20, 128.41, 128.49, 128.52, 129.13, 140.3, 140.5, 153.6, 153.9, 156.3, 158.7 (q, *J* 33.6 Hz) (TFA), 170.97, 171.02, 174.3. RP-HPLC (Method B, 220 nm): 96% (t_R = 16.4 min, *k* = 4.7). HRMS (ESI): m/z [M+H]$^+$ calc. for $[C_{35}H_{44}N_7O_5]^+$ 642.3398, found 642.3406. $C_{35}H_{43}N_7O_5 \times C_2HF_3O_2$ (641.77 + 114.02).

(R)-Nα-Diphenylacetyl-Nω-(cyclopentoylaminoethyl)aminocarbonyl(4-hydroxybenzyl)arginina-mide hydrotrifluoroacetate (70). Compound **70** was prepared using *General Procedure A*, the reactants **41** (30.82 mg, 39.1 µmol), succinimidyl cyclopentanecarboxylat (**31**) (10.13 mg, 48.0 µmol), DIPEA (20 µL, 114.8 µmol) and the solvent DMF (100 µL). Purification by preparative HPLC (gradient: 0-30 min, A/B 85:15–38:62, t_R = 19 min) afforded **70** (15.90 mg, 20.7 µmol, 53%) as a white fluffy solid. ^{1}H NMR (600 MHz, DMSO-d_6): δ (ppm) 1.35-1.64 (m, 10H), 1.65-1.75 (m, 3H), 3.13 (m, 4H), 3.18-3.23 (m, 2H), 4.09-4.19 (m, 2H), 4.31 (m, 1H), 5.13 (s, 1H), 6.65-6.70 (m, 2H), 6.98-7.02 (m, 2H), 7.20-7.25 (m, 2H), 7.26-7.31 (m, 8H), 7.50 (br s, 1H), 7.86 (br s, 1H), 8.36 (t, *J* 5.8 Hz, 1H), 8.44 (br s, 2H, interfering with two surrounding signals), 8.49 (d, *J* 8.1 Hz, 1H), 8.96 (br s, 1H), 9.32 (br s, 1H), 10.27 (br s, 1H). ^{13}C NMR (151 MHz, DMSO-d_6): δ (ppm) 24.6, 25.6, 29.4, 29.9, 38.1, 39.1, 40.3, 41.6, 44.3, 52.3, 55.9, 115.0, 115.7 (TFA), 117.6 (TFA), 126.56, 126.60, 128.15, 128.20, 128.41, 128.49, 128.52, 129.13, 140.3, 140.5, 153.6, 153.9, 156.3, 158.6 (q, *J* 33.2 Hz) (TFA), 170.97, 171.02, 175.7. RP-HPLC (Method B, 220 nm): 99% (t_R = 17.0 min, *k* = 4.9). HRMS (ESI): m/z [M+H]$^+$ calc. for $[C_{36}H_{46}N_7O_5]^+$ 656.3555, found 656.3571. $C_{36}H_{45}N_7O_5 \times C_2HF_3O_2$ (655.80 + 114.02).

(R)-Nα-Diphenylacetyl-Nω-(cyclohexoylaminoethyl)aminocarbonyl(4-hydroxybenzyl)argininamide hydrotrifluoroacetate (71). Compound **71** was prepared using *General Procedure A*, the reactants **41** (29.0 mg, 36.8 µmol), succinimidyl cyclohexanecarboxylat (**32**) (11.3 mg, 54.0 µmol), DIPEA (20 µL, 114.8 µmol) and the solvent DMF (100 µL). Purification by preparative HPLC (gradient: 0-30 min, A/B 85:15–38:62, t_R = 20.0 min) afforded **71** (17.45 mg, 22.3 µmol, 60.6%) as a white fluffy solid. ^{1}H NMR (600 MHz, DMSO-d_6): δ (ppm) 1.10-1.22 (m, 3H), 1.26-1.35 (m, 2H), 1.36-1.50 (m, 2H), 1.51-1.62 (m, 2H), 1.64-1.71 (m, 5H), 2.02-2.08 (m, 1H), 3.11-3.17 (m, 4H), 3.18-3.23 (m, 2H), 4.10-4.19 (m, 2H), 4.31-4.36 (m, 1H), 5.13 (s, 1H), 6.66-6.69 (m, 2H), 6.99-7.02 (m, 2H), 7.19-7.25 (m, 2H), 7.26-7.31 (m, 8H), 7.47 (br s, 1H), 7.75-7.80 (m, 1H), 8.36 (t, *J* 5.8 Hz, 1H), 8.43 (br s, 2H, interfering with two surrounding signals), 8.49 (d, *J* 8.1 Hz, 1H), 8.95 (br s, 1H), 9.31 (br s, 1H), 10.25 (br s, 1H). ^{13}C NMR (150 MHz, DMSO-d_6): δ (ppm) 24.6, 25.3, 25.5, 29.2, 29.4, 37.9, 39.3, 40.3, 41.6, 44.1, 52.3, 55.9, 115.0, 115.6 (TFA), 117.6 (TFA), 126.57, 126.60, 128.16, 128.20, 128.41, 128.49, 128.52, 129.1, 140.3, 140.5, 153.6, 153.9, 156.3, 158.7 (q, *J* 32.4 Hz) (TFA), 170.97, 171.02, 175.6. RP-HPLC (Method B, 220 nm): 99% (t_R = 18.0 min, *k* = 5.2). HRMS (ESI): m/z [M + H]$^+$ calc. for $[C_{37}H_{48}N_7O_5]^+$ 670.3711, found 670.3722. $C_{37}H_{47}N_7O_5 \times C_2HF_3O_2$ (669.83 + 114.02).

(R)-Nα-Diphenylacetyl-Nω-(cyclohexylacetylaminoethyl)aminocarbonyl(4-hydroxybenzyl)arginina-mide hydrotrifluoroacetate (72). Compound **72** was prepared using *General Procedure A*, the reactants **41** (30.6 mg, 38.8 µmol), succinimidyl cyclohexylacetate (**33**) (12.7 mg, 56.9 µmol), DIPEA (20 µL, 114.8 µmol) and the solvent DMF (100 µL). Purification by preparative HPLC (gradient: 0-30 min, A/B 85:15–38:62, t_R = 21 min) afforded **72** (15.8 mg, 19.8 µmol, 51%) as a white fluffy solid. ^{1}H NMR (600 MHz, DMSO-d_6): δ (ppm) 0.82-0.92 (m, 2H), 1.06-1.21 (m, 3H), 1.37-1.50 (m, 2H), 1.50-1.74 (m, 8H), 1.93 (d, *J* 6.9 Hz, 2H), 3.15 (br s, 4H), 3.18-3.22 (m, 2H), 4.09-4.20 (m, 2H), 4.31-4.36 (m, 1H), 5.13 (s, 1H), 6.65-6.70 (m, 2H), 6.97-7.03 (m, 2H), 7.19-7.25 (m, 2H), 7.26-7.31 (m, 8H), 7.48 (br s, 1H), 7.87 (br s, 1H), 8.36 (t, *J* 5.8 Hz, 1H), 8.44 (br s, 2H, interfering with two surrounding signals), 8.49 (d, *J* 8.1 Hz, 1H), 8.96 (br s, 1H), 9.31 (br s, 1H), 10.25 (s, 1H). ^{13}C NMR (151 MHz, DMSO-d_6): δ (ppm) 24.6, 25.6, 25.8, 29.4, 32.5, 34.6, 37.9, 39.3, 40.3, 41.6, 43.4, 52.3, 55.9, 115.0, 126.56, 126.59, 128.15, 128.19, 128.40, 128.49, 128.52, 129.1, 140.3, 140.5, 153.6, 153.9, 156.3, 158.7

(q, *J* 34.5 Hz) (TFA), 170.96, 171.02, 171.7. RP-HPLC (Method B, 220 nm): 100% (t_R = 16.0 min, k = 4.6). HRMS (ESI): m/z $[M+H]^+$ calc. for $[C_{38}H_{50}N_7O_5]^+$ 684.3868, found 684.3887. $C_{38}H_{49}N_7O_5 \times C_2HF_3O_2$ (683.85 + 114.02).

(R)-Nα-Diphenylacetyl-Nω-(benzoylaminoethyl)aminocarbonyl(4-hydroxybenzyl)argininamide hydrotrifluoroacetate (73). Compound **73** was prepared using *General Procedure A*, the reactants **41** (30.74 mg, 39.0 µmol), succinimidyl benzoate (**26**) (13 mg, 59.3 µmol), DIPEA (20 µL, 114.8 µmol) and the solvent DMF (100 µL). Purification by preparative HPLC (gradient: 0-30 min, A/B 85:15–40:60, t_R = 21 min) afforded **73** (12.0 mg, 15.4 µmol, 39%) as a white fluffy solid. ^{1}H NMR (600 MHz, DMSO-d_6): δ (ppm) 1.36-1.50 (m, 2H), 1.51-1.59 (m, 1H), 1.64-1.73 (m, 1H), 3.17-3.24 (m, 2H), 3.28-3.33 (m, 2H), 3.34-3.42 (m, 2H, overlaid with water), 4.09-4.20 (m, 2H), 4.31-4.36 (m, 1H), 5.13 (s, 1H), 6.65-6.70 (m, 2H), 6.98-7.03 (m, 2H), 7.19-7.25 (m, 2H), 7.26-7.31 (m, 8H), 7.43-7.48 (m, 2H), 7.50-7.55 (m, 1H), 7.58-7.64 (m, 1H), 7.82-7.87 (m, 2H), 8.36 (t, *J* 5.7 Hz, 1H), 8.44 (br s, 2H, interfering with two surrounding signals), 8.49 (d, *J* 8.0 Hz, 1H), 8.56 (t, *J* 5.5 Hz, 1H), 8.96 (br s, 1H), 9.32 (br s, 1H), 10.24 (br s, 1H). ^{13}C NMR (150 MHz, DMSO-d_6): δ (ppm) 24.6, 29.4, 38.8, 39.0, 40.3, 41.6, 52.3, 55.9, 115.0, 126.56, 126.60, 127.20, 128.16, 128.20, 128.24, 128.41, 128.49, 128.52, 129.1, 131.2, 134.4, 140.3, 140.5, 153.6, 153.9, 156.3, 158.8 (q, *J* 31.5 Hz) (TFA), 166.6, 170.98, 171.03. RP-HPLC (Method A, 220 nm): 99% (t_R = 13.7 min, k = 4.3). HRMS (ESI): m/z $[M+H]^+$ calc. for $[C_{37}H_{42}N_7O_5]^+$ 664.3242, found 664.3250. $C_{37}H_{41}N_7O_5 \times C_2HF_3O_2$ (663.78 + 114.02).

(R)-Nα-Diphenylacetyl-Nω-(4-fluorobenzoylaminoethyl)aminocarbonyl(4-hydroxybenzyl)argininamide hydrotrifluoroacetate (74). Compound **74** was prepared using *General Procedure A*, the reactants **41** (30.95 mg, 39.3 µmol), succinimidyl 4-fluorobenzoate (**45**) (10.21 mg, 23.4 µmol), DIPEA (20 µL, 114.8 µmol) and the solvent DMF (100 µL). Purification by preparative HPLC (gradient: 0-30 min, A/B 80:20–50:50, t_R = 20 min) afforded **74** (13.8 mg, 17.3 µmol, 44%) as a white fluffy solid. ^{1}H NMR (600 MHz, DMSO-d_6): δ (ppm) 1.36-1.49 (m, 2H), 1.51-1.58 (m, 1H), 1.64-1.72 (m, 1H), 3.17-3.23 (m, 2H), 3.27-3.32 (m, 2H), 3.35-3.40 (m, 2H), 4.09-4.20 (m, 2H), 4.31-4.36 (m, 1H), 5.13 (s, 1H), 6.66-6.69 (m, 2H), 6.99-7.01 (m, 2H), 7.19-7.25 (m, 2H), 7.26-7.30 (m, 10H), 7.30-7.31 (m, 1H), 7.64 (br s, 1H), 7.89-7.93 (m, 2H), 8.36 (t, *J* 5.8 Hz, 1H), 8.44 (br s, 2H, interfering with two surrounding signals), 8.49 (d, *J* 8.1 Hz, 1H), 8.60 (t, *J* 5.5 Hz, 1H), 8.96 (br s, 1H), 9.31 (br s, 1H). ^{13}C NMR (150 MHz, DMSO-d_6): δ (ppm) 24.6, 29.4, 38.8, 39.0, 40.3, 41.6, 52.3, 55.9, 115.0, 115.14 (d, *J* 21.7 Hz), 126.55, 126.59, 128.14, 128.19, 128.40, 128.48, 128.51, 129.1, 129.8 (d, *J* 9.0 Hz), 130.9 (d, *J* 3.0 Hz), 140.3, 140.4, 153.6, 153.9, 156.3, 158.4 (q, *J* 30.7 Hz) (TFA), 163.8 (d, *J* 248.3 Hz), 165.5, 170.97, 171.01. RP-HPLC (Method C, 220 nm): 98% (t_R = 22.9 min, k = 6.9). HRMS (ESI): m/z $[M+H]^+$ calc. for $[C_{37}H_{41}FN_7O_5]^+$ 682.3148, found 682.3157. $C_{37}H_{40}FN_7O_5 \times C_2HF_3O_2$ (681.77 + 114.0 2).

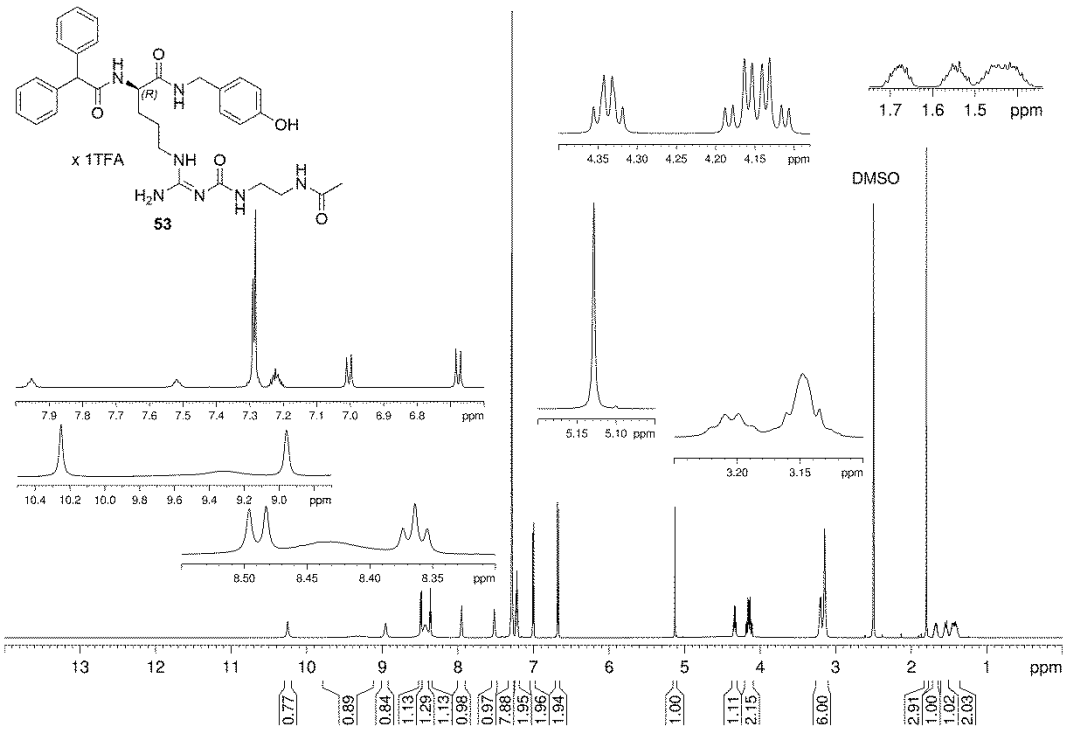
(R)-Nα-Diphenylacetyl-Nω-(phenylacetylaminoethyl)aminocarbonyl(4-hydroxybenzyl)argininamide hydrotrifluoroacetate (75). Compound **75** was prepared using *General Procedure A*, the reactants **41** (30.18 mg, 38.3 µmol), succinimidyl phenylacetate (**27**) (10.39 mg, 44.6 µmol), DIPEA (20 µL, 114.8 µmol) and the solvent DMF (100 µL). Purification by preparative HPLC (gradient: 0-30 min, A/B 85:15–38:62, t_R = 19 min) afforded **75** (19.64 mg, 24.8 µmol, 65%) as a white fluffy solid. ^{1}H NMR (600 MHz, DMSO-d_6): δ (ppm) 1.36-1.51 (m, 2H), 1.51-1.59 (m, 1H), 1.64-1.73 (m, 1H), 3.14-3.24 (m, 6H), 3.40 (s, 2H), 4.09-4.20 (m, 2H), 4.30-4.38 (m, 1H), 5.13 (s, 1H), 6.66-6.69 (m, 2H), 6.98-7.02 (m, 2H), 7.19-7.31 (m, 15H), 7.53 (br s, 1H), 8.15 (br s, 1H), 8.36 (t, *J* 5.7 Hz, 1H), 8.44 (br s, 2H, interfering with two surrounding signals), 8.49 (d, *J* 8.0 Hz, 1H), 8.95 (br s, 1H), 9.31 (br s, 1H), 10.27 (br s, 1H). ^{13}C NMR (151 MHz, DMSO-d_6): δ (ppm) 24.6, 29.4, 38.2, 39.1, 40.3, 41.6, 42.4, 52.3, 55.9, 115.0, 115.8 (TFA), 117.8 (TFA), 126.3, 126.57, 126.60, 128.16, 128.20, 128.41, 128.50, 128.52, 128.99 (two carbon signals), 129.13, 136.3, 140.3, 140.5, 153.6, 153.9, 156.3, 158.7 (q, *J* 33.6 Hz) (TFA), 170.5, 170.98, 171.03. RP-HPLC (Method B, 220 nm): 99% (t_R = 17.0 min, k = 4.9). HRMS (ESI): m/z $[M+H]^+$ calc. for $[C_{38}H_{44}N_7O_5]^+$ 678.3398, found 678.3414. $C_{38}H_{43}N_7O_5 \times C_2HF_3O_2$ (677.81 + 114.02).

(R)-Nα-Diphenylacetyl-Nω-(diphenylacetylaminoethyl)aminocarbonyl(4-hydroxybenzyl)argininamide hydrotrifluoroacetate (76). Compound **76** was prepared using *General Procedure A*, the reactants **41** (35.81 mg, 45.5 µmol), succinimidyl diphenylacetate (**28**) (26 mg, 84.1 µmol), DIPEA (25 µL, 143.5 µmol) and the solvent DMF (100 µL). Purification by preparative HPLC (gradient: 0-30 min, A/B 85:15–38:62, t_R = 16 min) afforded **76** (15 mg, 17.3 µmol, 38%) as a white fluffy solid. ^{1}H NMR (600 MHz, DMSO-d_6): δ (ppm) 1.37-1.48 (m, 2H), 1.50-1.58 (m, 1H), 1.64-1.73 (m, 1H), 3.14-3.24 (m, 6H), 4.07-4.20 (m, 2H), 4.29-4.37 (m, 1H), 4.90 (s, 1H), 5.12 (s, 1H), 6.65-6.68 (m, 2H), 6.98-7.01 (m, 2H), 7.18-7.24 (m, 4H), 7.26-7.29 (m, 16H),

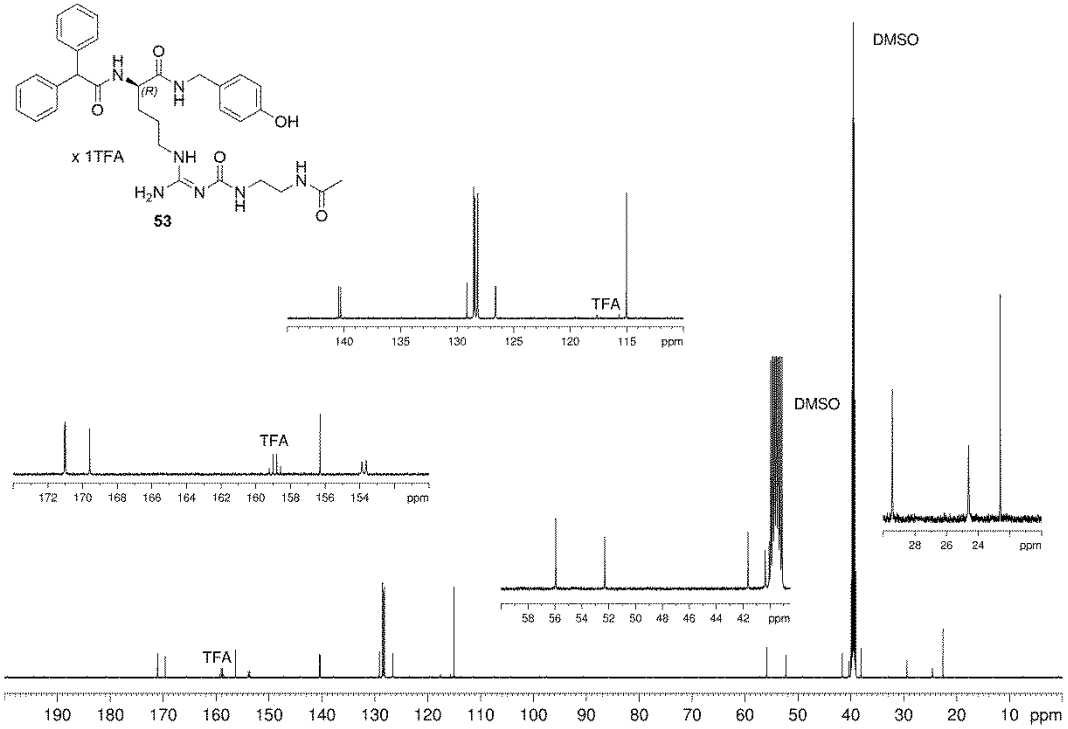
7.49 (br s, 1H), 8.34-8.38 (m, 2H), 8.42 (br s, 2H, interfering with two surrounding signals), 8.49 (d, *J* 8.1 Hz, 1H), 8.92 (br s, 1H), 9.30 (br s, 1H), 10.18 (br s, 1H). ^{13}C NMR (150 MHz, DMSO-d_6): δ (ppm) 24.6, 29.4, 38.3, 39.0, 40.4, 41.6, 52.3, 55.9, 56.6, 115.0, 116.1 (TFA), 118.1 (TFA), 126.55, 126.58 (two carbon signals), 128.14, 128.17, 128.18, 128.27, 128.34, 128.39 (2 carb.), 128.46, 128.47, 128.49, 129.11, 140.3 (2 carb.), 140.4, 153.6, 153.9, 156.3, 158.6 (q, *J* 30.5 Hz) (TFA), 170.95, 171.01, 171.37. one aromatic carbon was not resolved. RP-HPLC (Method B, 220 nm): 98% (t_R = 19.6 min, k = 5.8). HRMS (ESI): m/z $[M+H]^+$ calc. for $[C_{44}H_{48}N_7O_5]^+$ 754.3711, found 754.3715. $C_{44}H_{47}N_7O_5 \times C_2HF_3O_2$ (753.90 + 114.02).

(R)-N$^{\alpha}$-Diphenylacetyl-N$^{\omega}$-(4-((1E,3E)-4-(4-(dimethylamino)phenyl)buta-1,3-dienyl)-2,6-dimethylpyridinioethyl)aminocarbonyl(4-hydroxybenzyl)argininamide hydrotrifluoroacetate trifluoroacetate (78). DIPEA (2.80 µL, 16 µmol) was added to a solution of compound **41** (3.19 mg, 4.04 µmol) in DMF (50 µL). After 5 min, the fluorescent dye Py-5 (**77**) (5.74 mg, 15.6 µmol) was added, and the reaction mixture was shaken for 3 h in the dark. Purification by preparative HPLC (gradient: 0-30 min, A/B 85:15–38:62, t_R = 20 min) afforded **78** (0.94 mg, 0.90 µmol, 22%) as a red solid. RP-HPLC (*Method A*, 220 nm): 95% (t_R = 14.0 min, k = 4.4). HRMS (ESI): m/z $[M+H]^+$ calc. for $[C_{44}H_{48}N_7O_5]^+$ 821.4497, found 821.4509. $C_{49}H_{57}N_8O_4^+ \times C_2HF_3O_2 \times C_2F_3O_2^-$ (822.05 + 114.02 + 113.02).

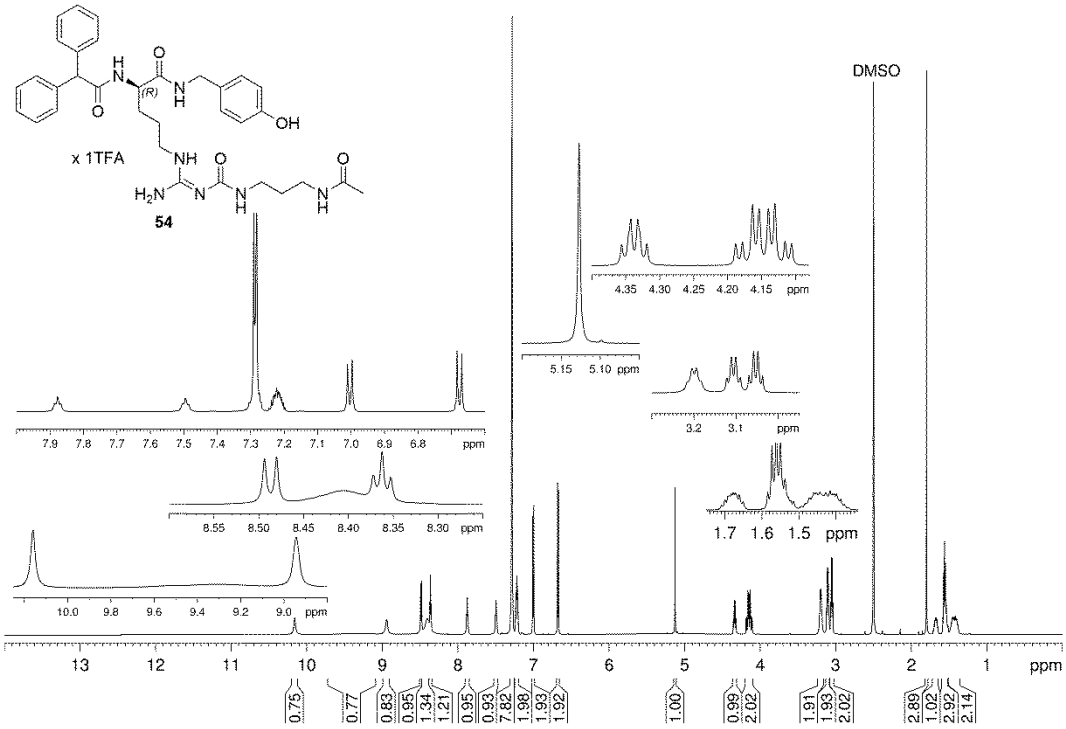
4. ^{1}H-NMR und ^{13}C-NMR Spectra of Compounds 53-76



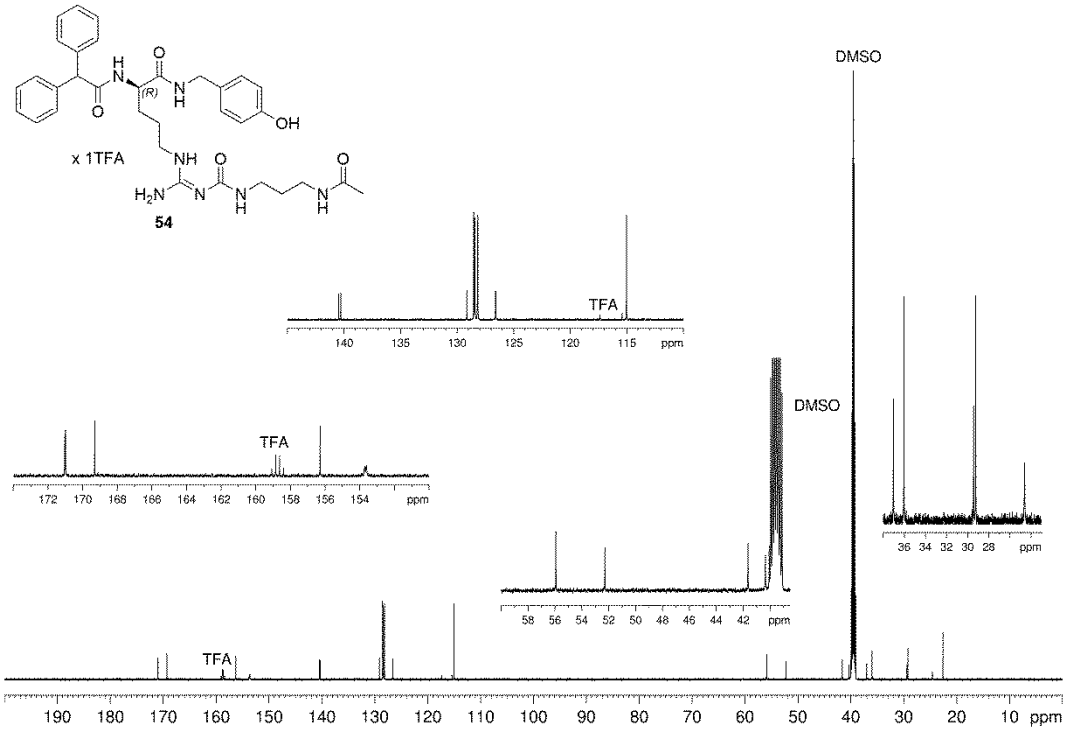
^{1}H-NMR of compound **53**



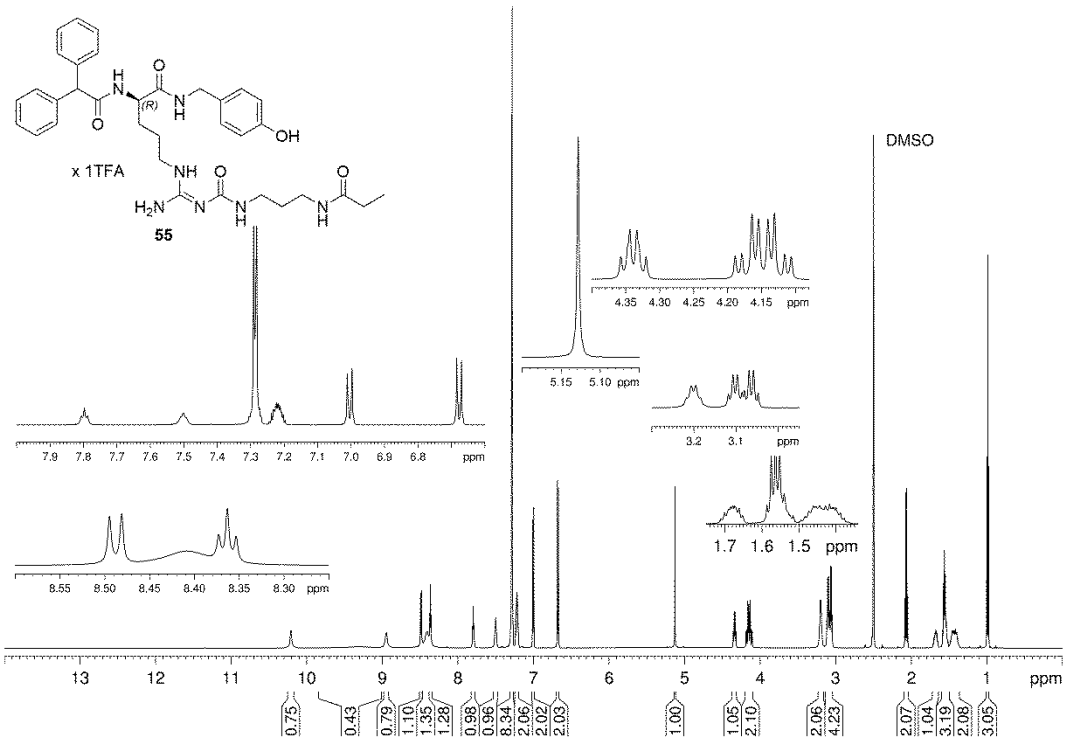
^{13}C-NMR of compound **53**



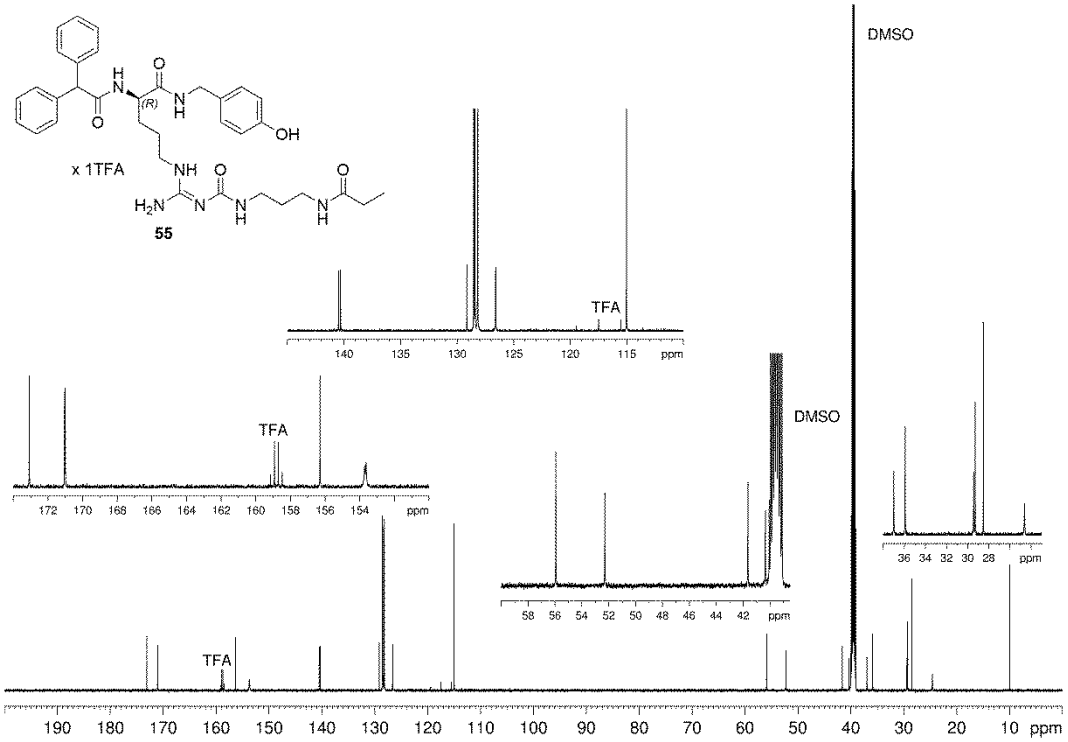
^{1}H-NMR of compound **54**



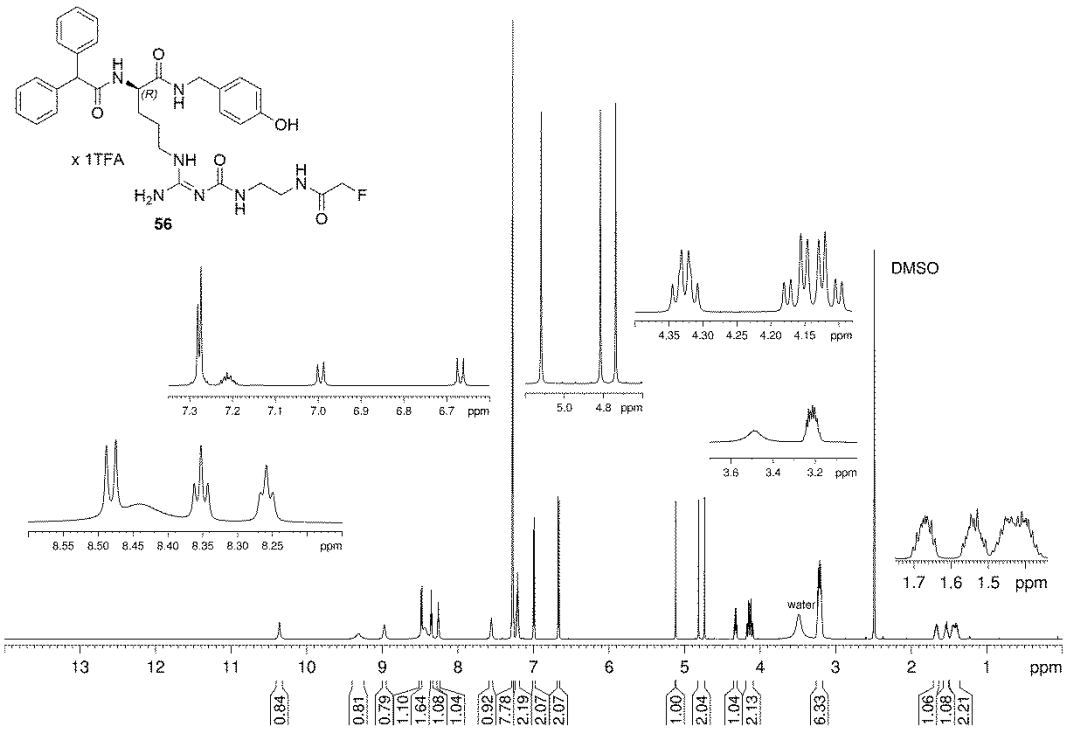
^{13}C-NMR of compound **54**



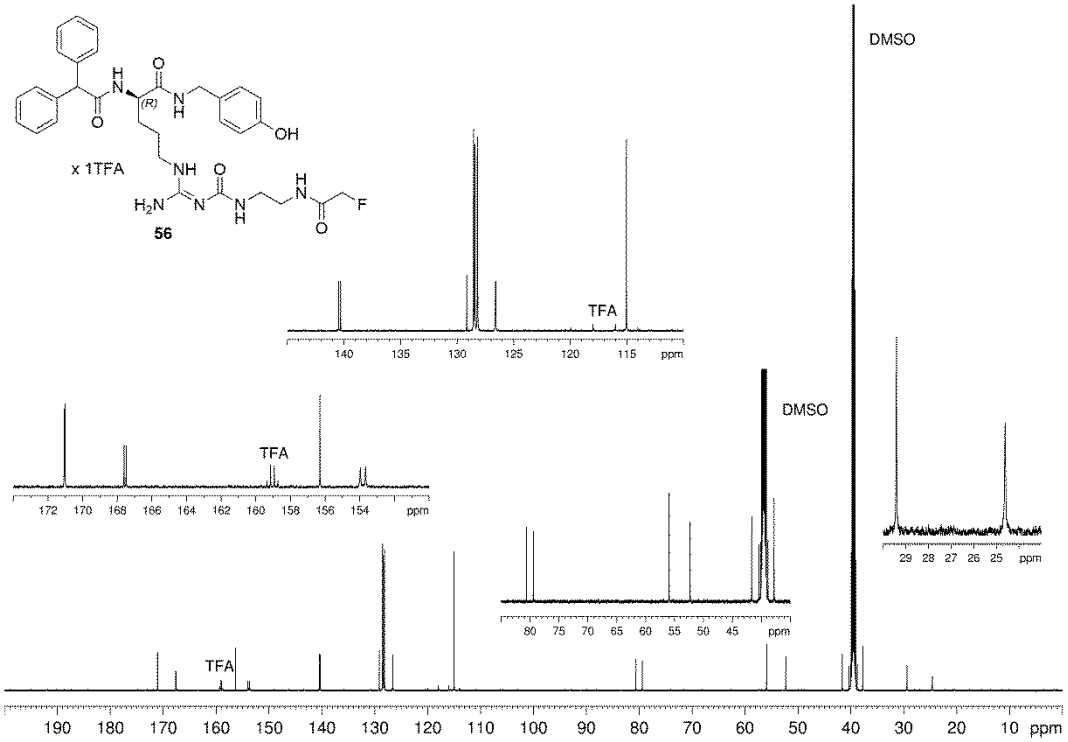
^{1}H-NMR of compound **55**



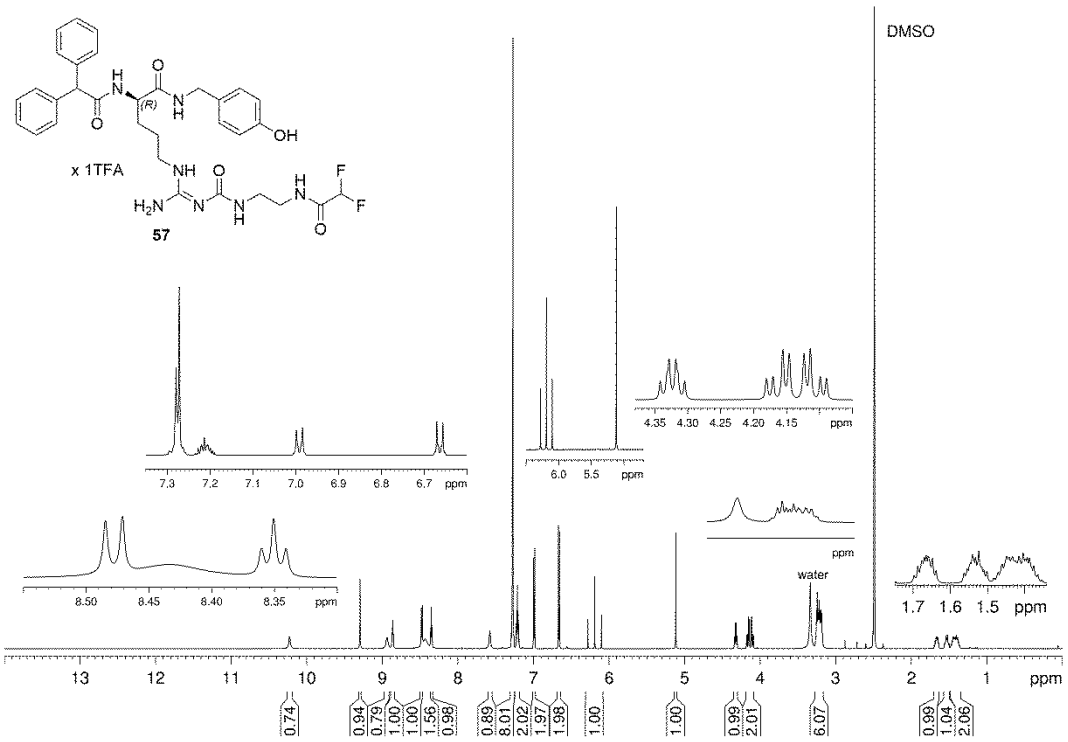
^{13}C-NMR of compound **55**



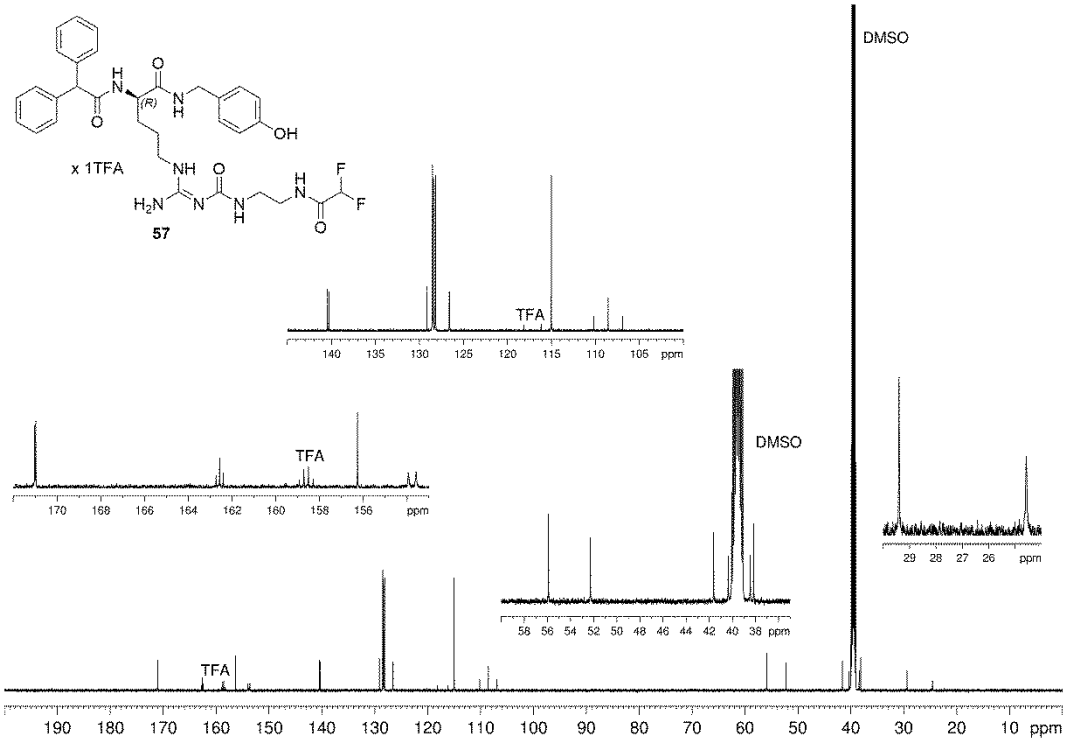
^{1}H-NMR of compound **56**



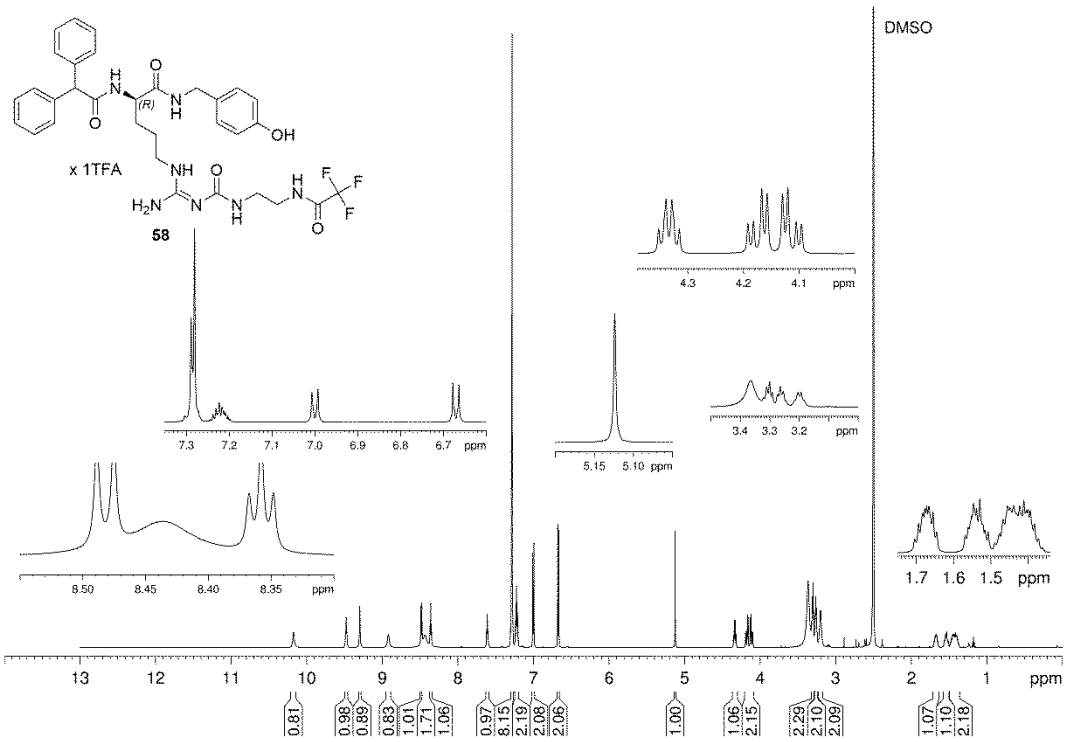
^{13}C-NMR of compound **56**



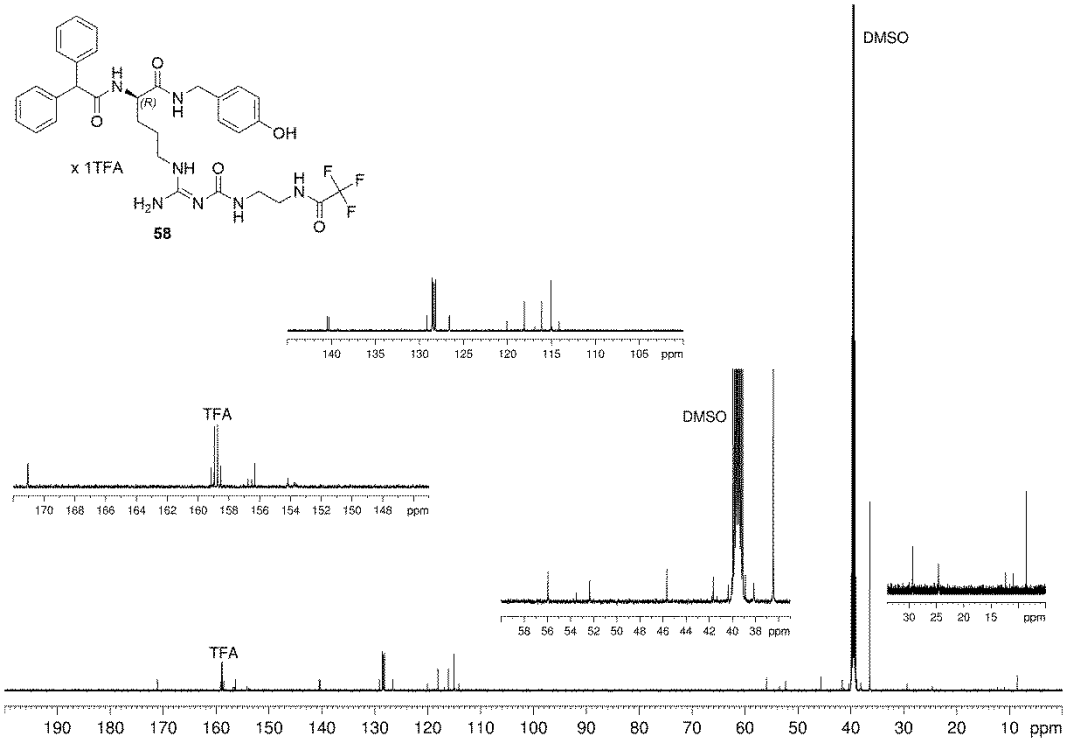
^{1}H-NMR of compound **57**



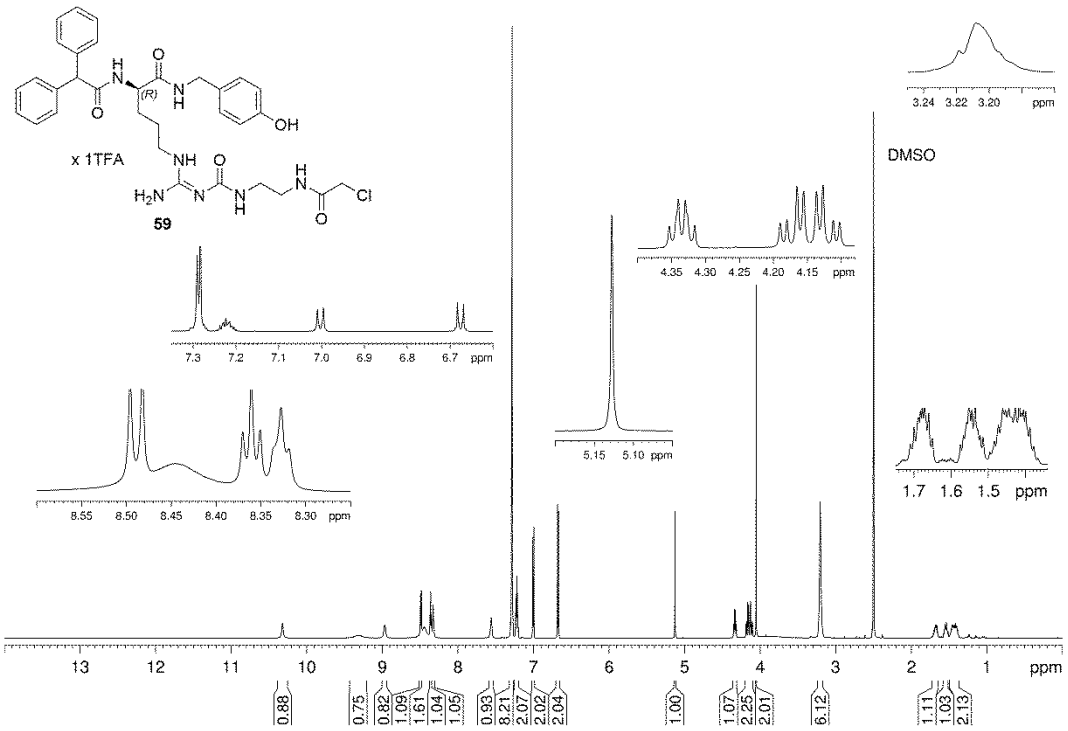
^{13}C-NMR of compound **57**



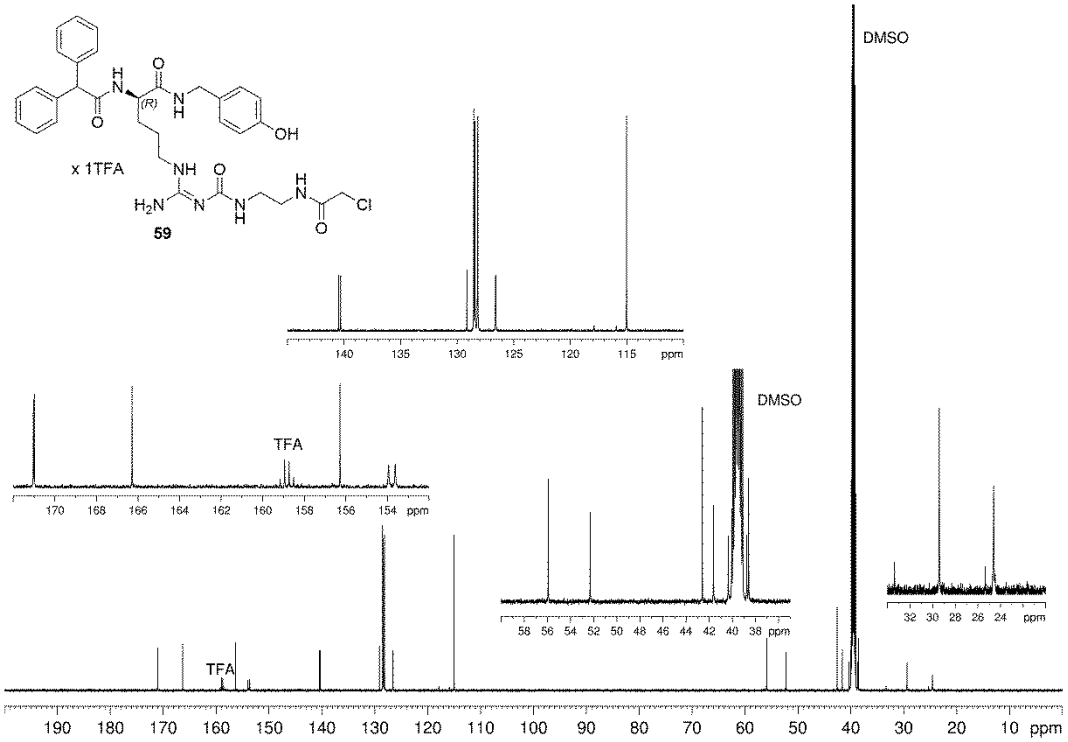
^{1}H-NMR of compound **58**



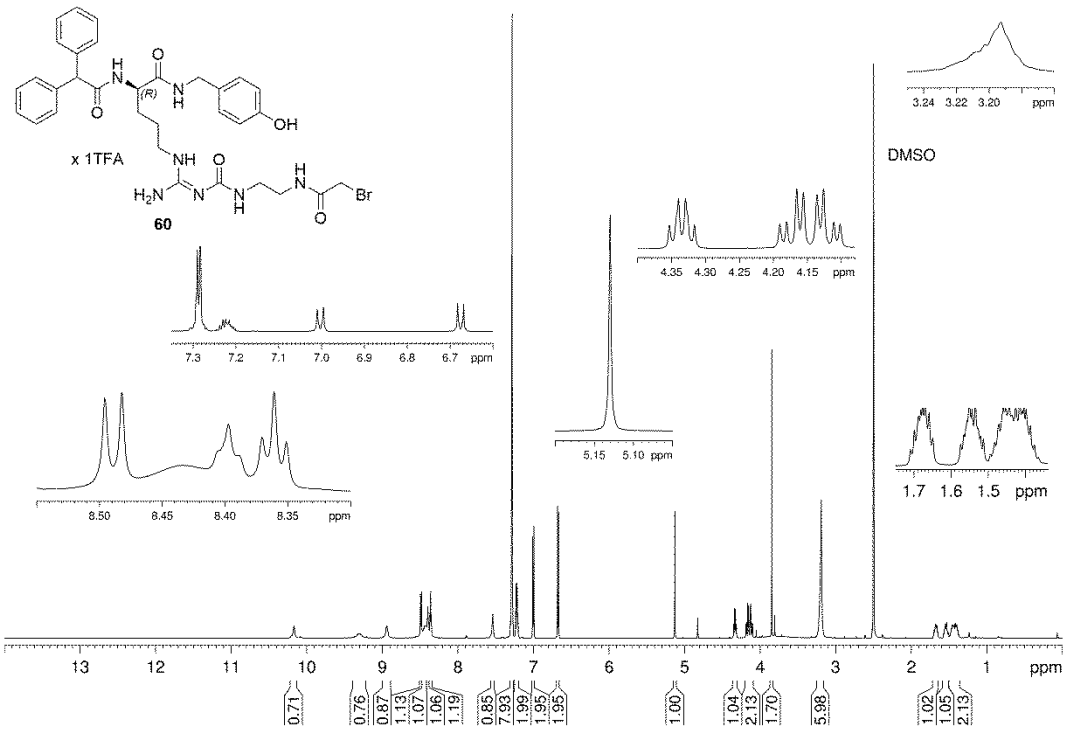
^{13}C-NMR of compound **58**



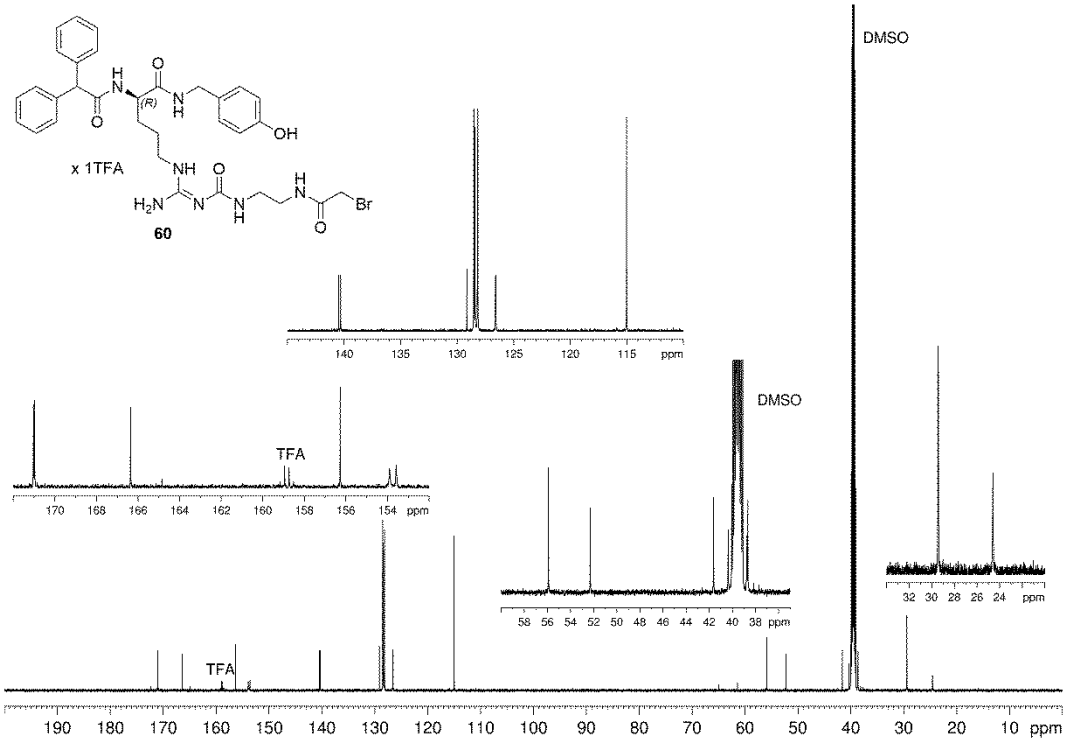
^{1}H-NMR of compound **59**



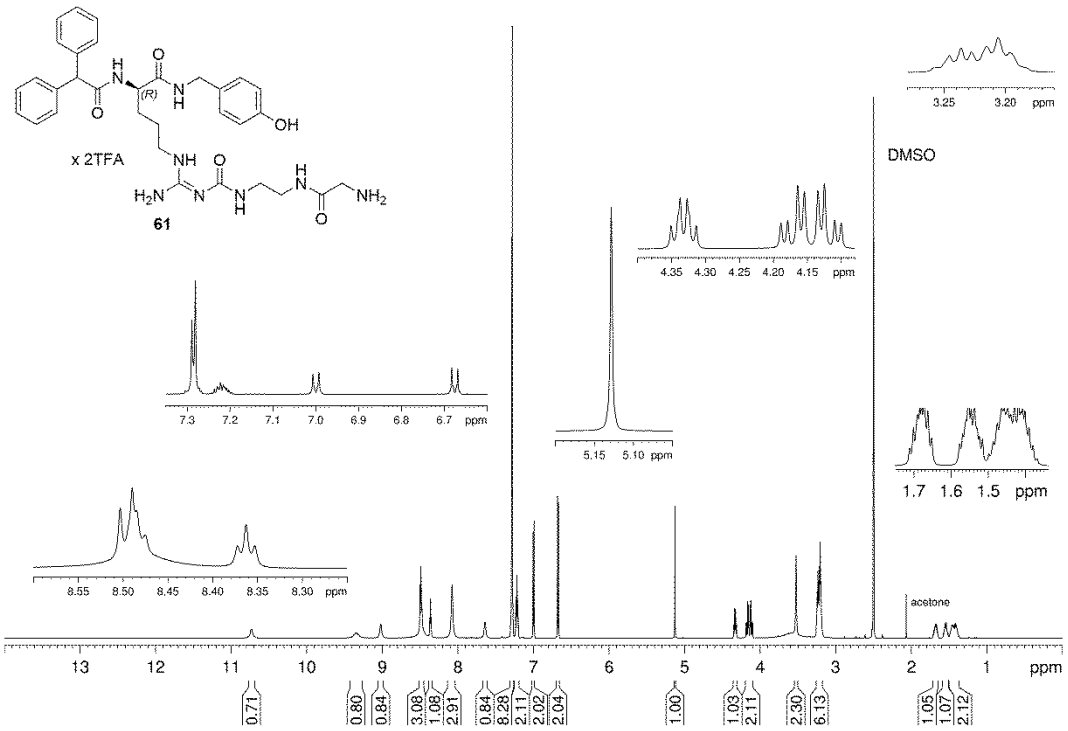
^{13}C-NMR of compound **59**



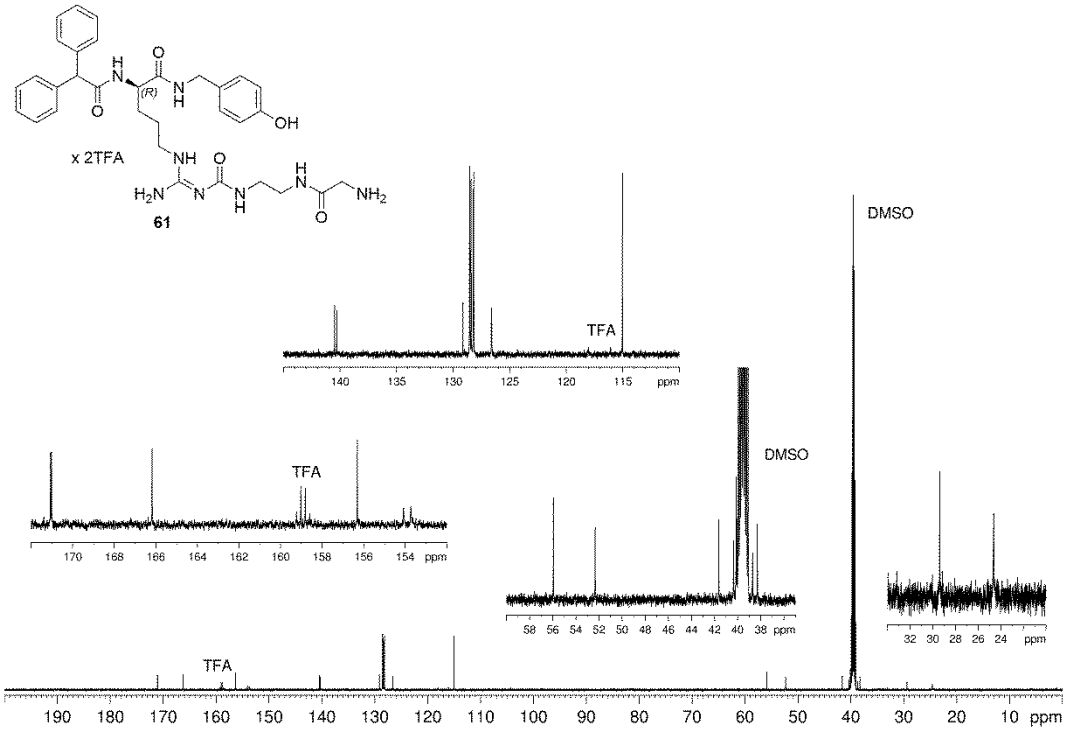
^{1}H-NMR of compound **60**



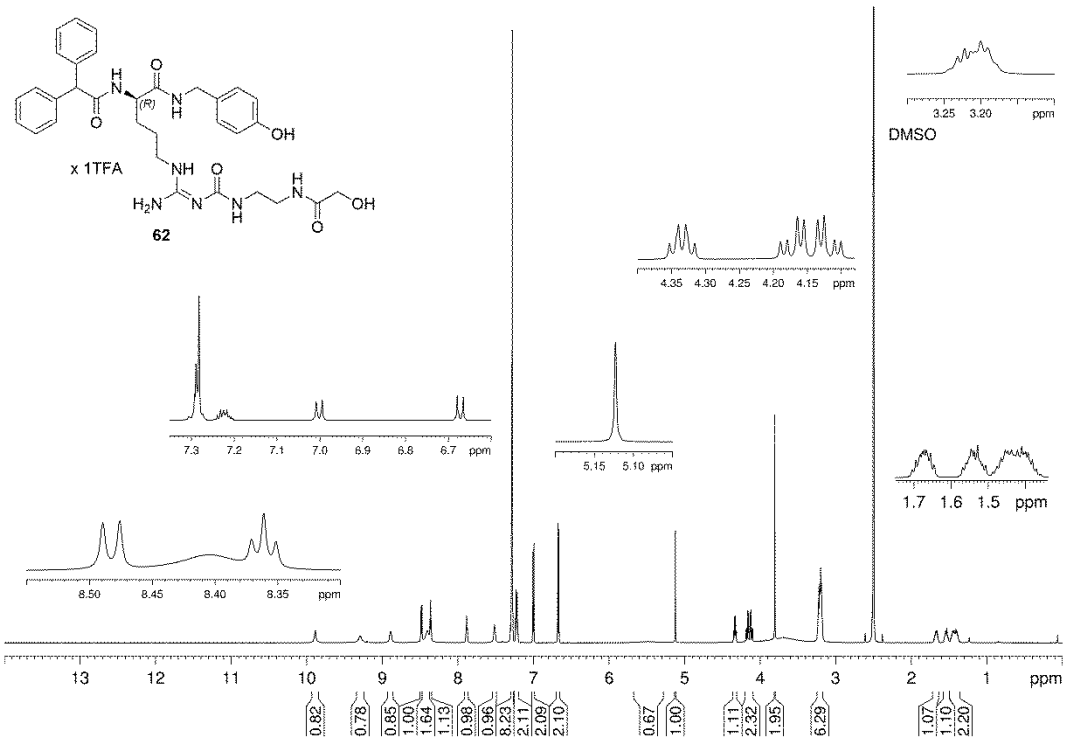
^{13}C-NMR of compound **60**



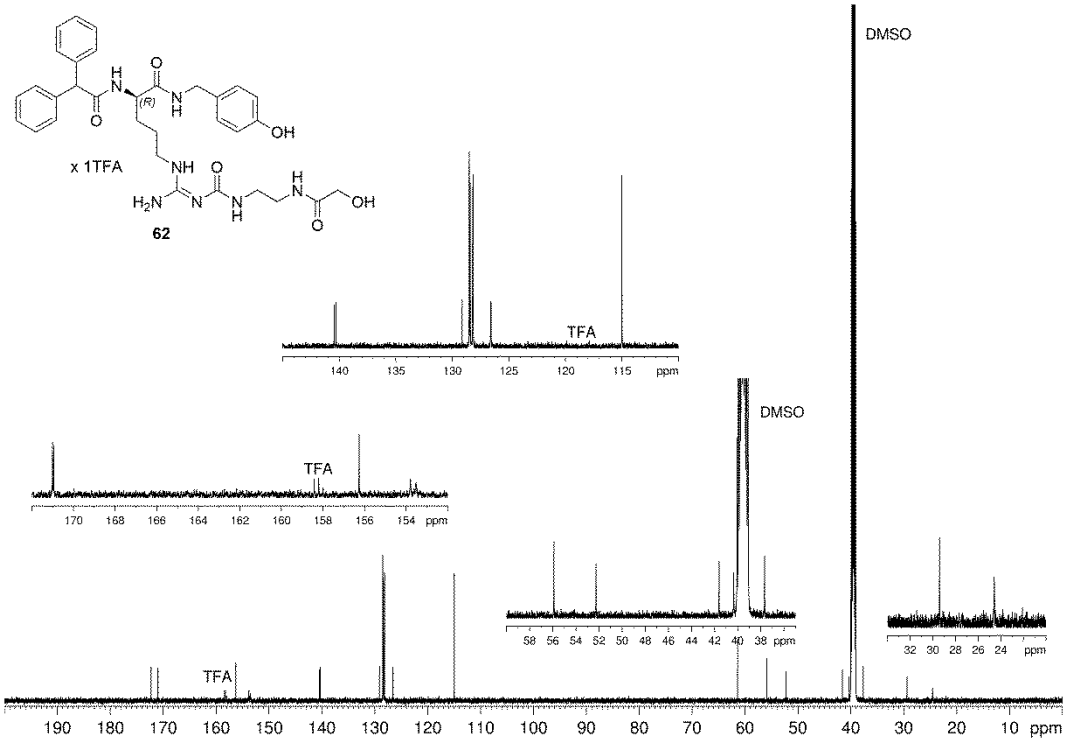
^{1}H-NMR of compound **61**



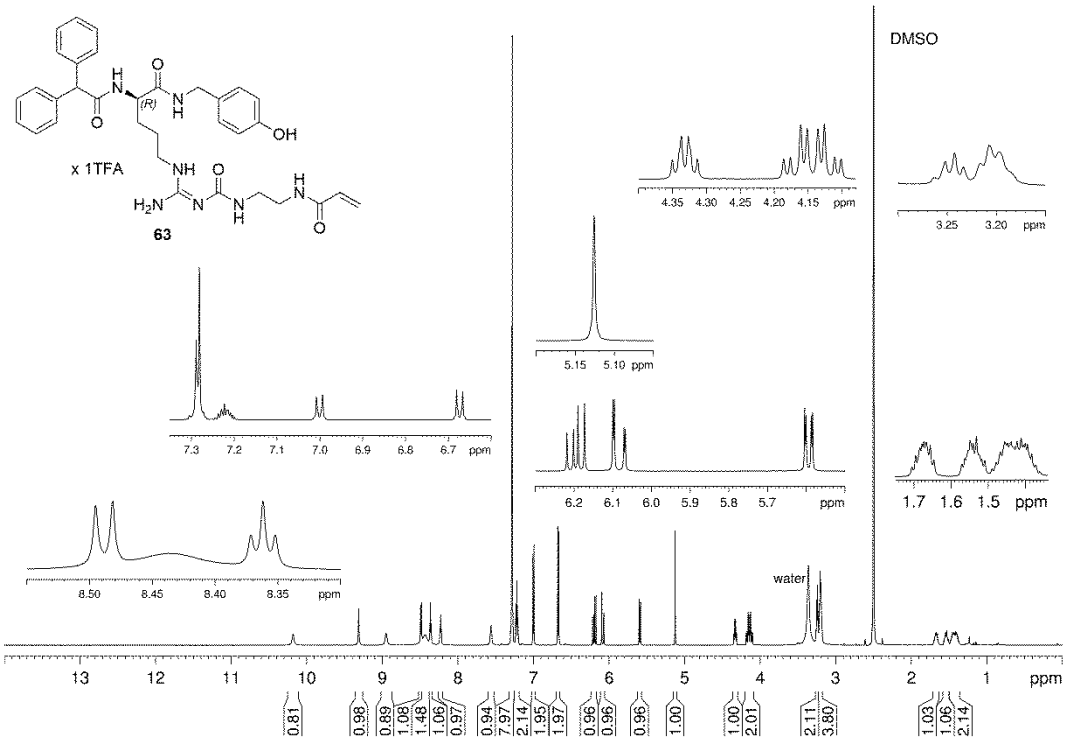
^{13}C-NMR of compound **61**



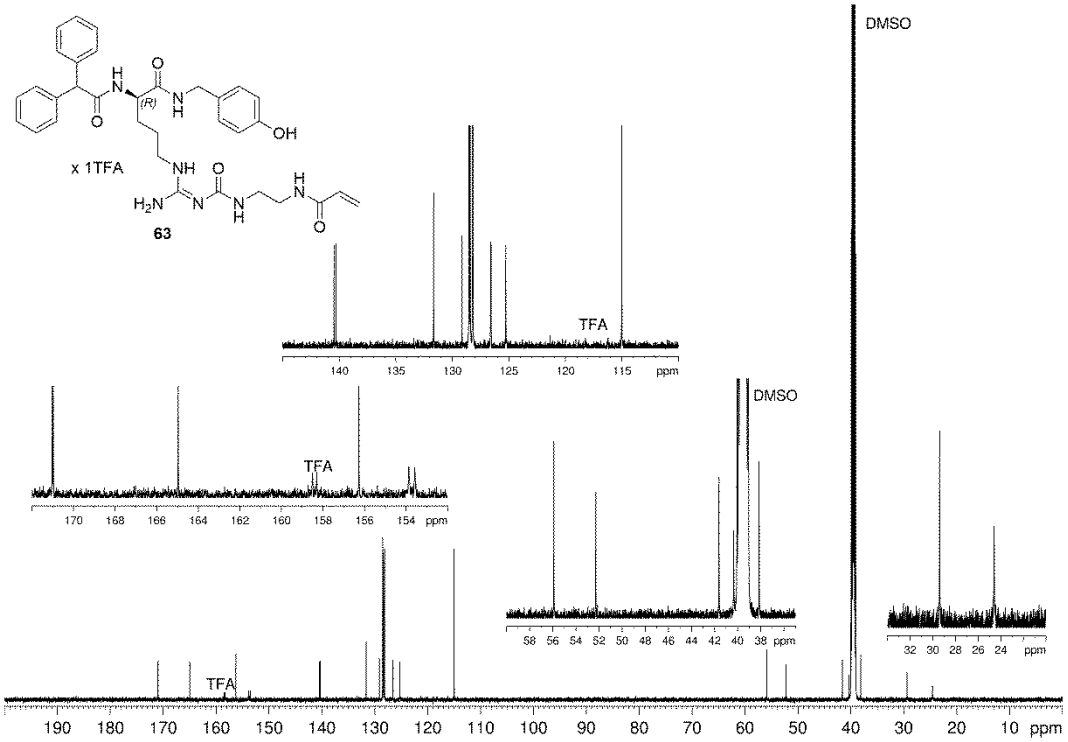
^{1}H-NMR of compound **62**



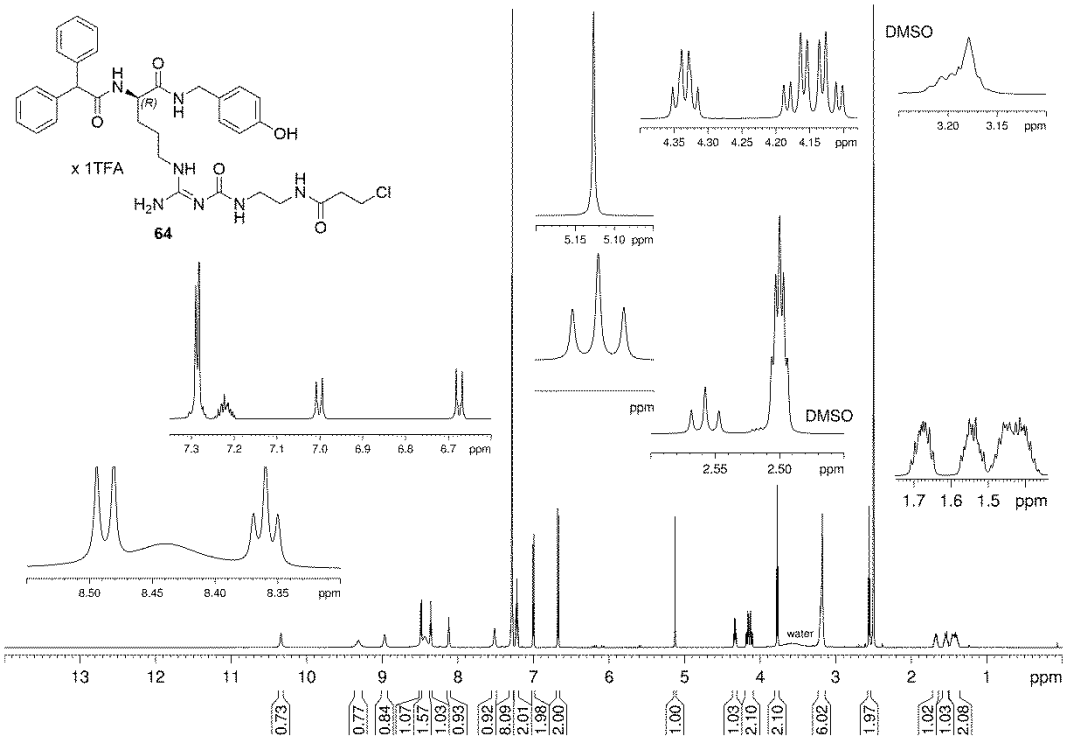
^{13}C-NMR of compound **62**



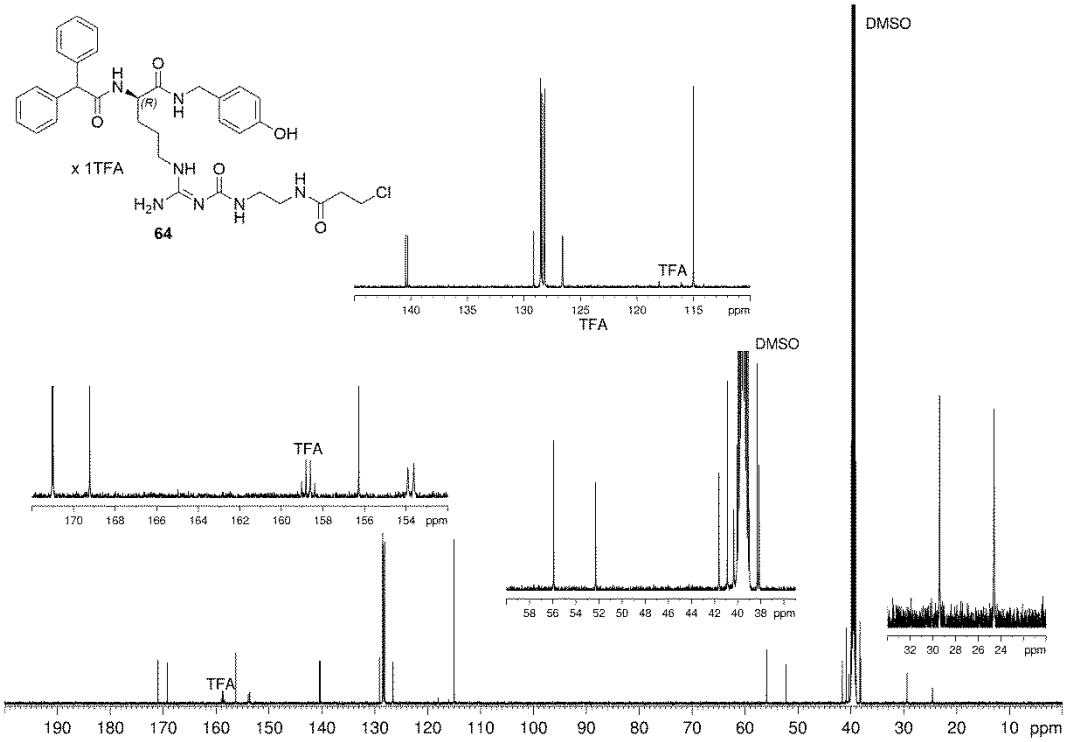
^{1}H-NMR of compound **63**



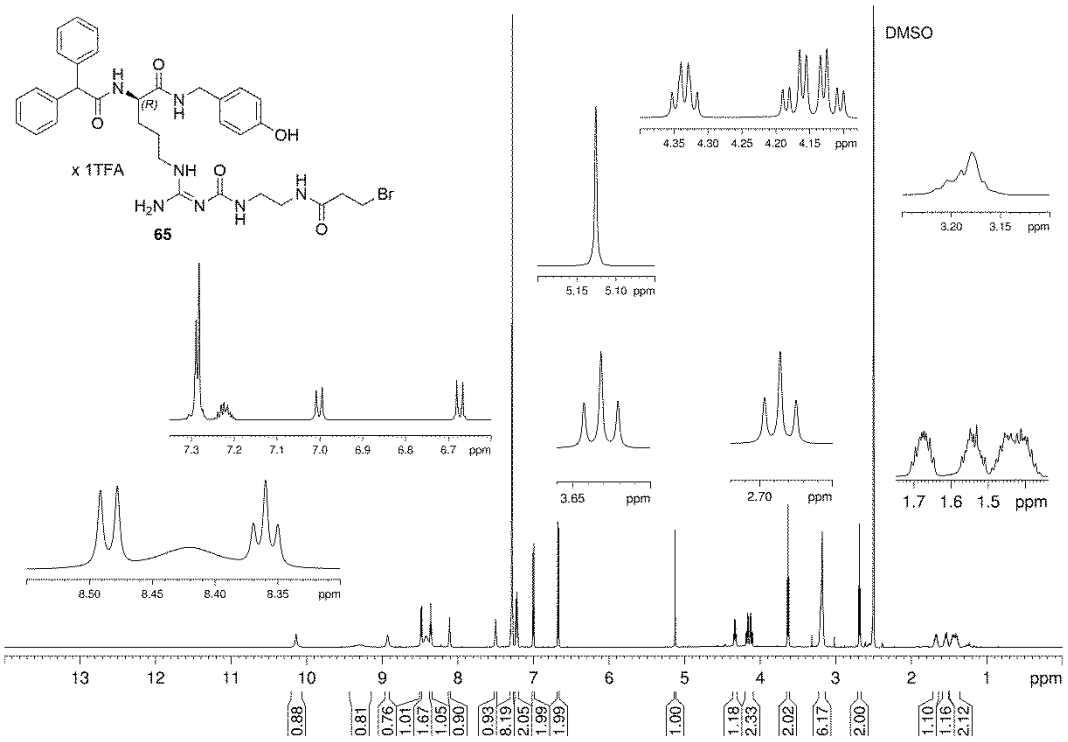
^{13}C-NMR of compound **63**



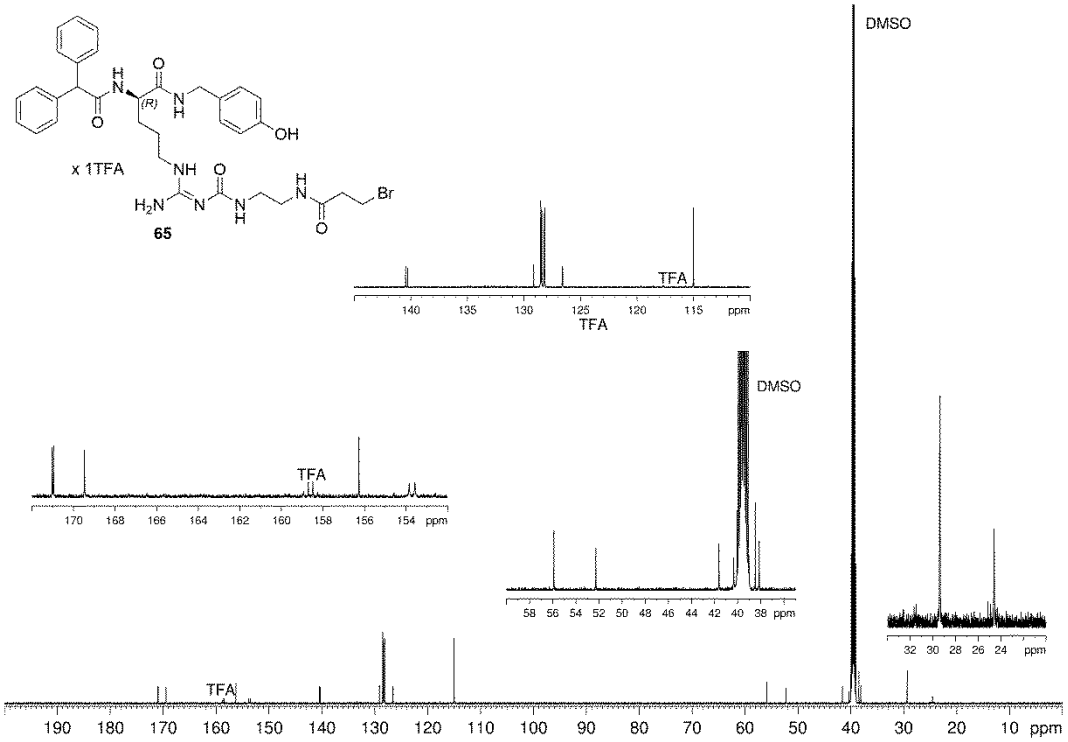
^{1}H-NMR of compound **64**



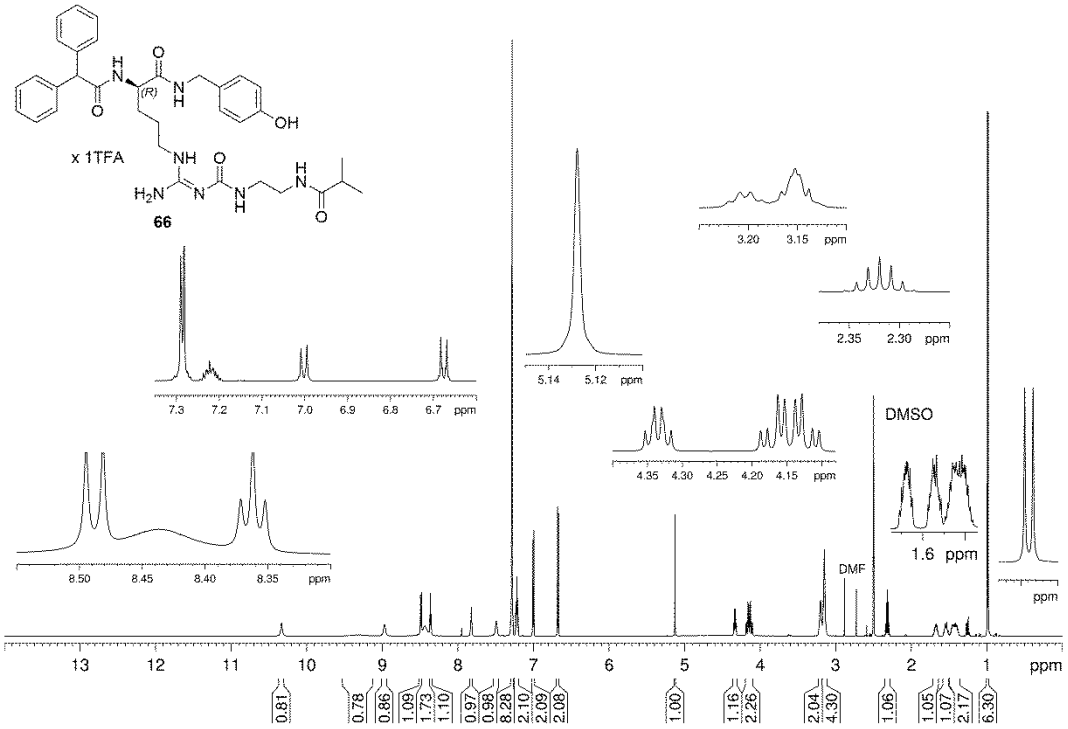
^{13}C-NMR of compound **64**



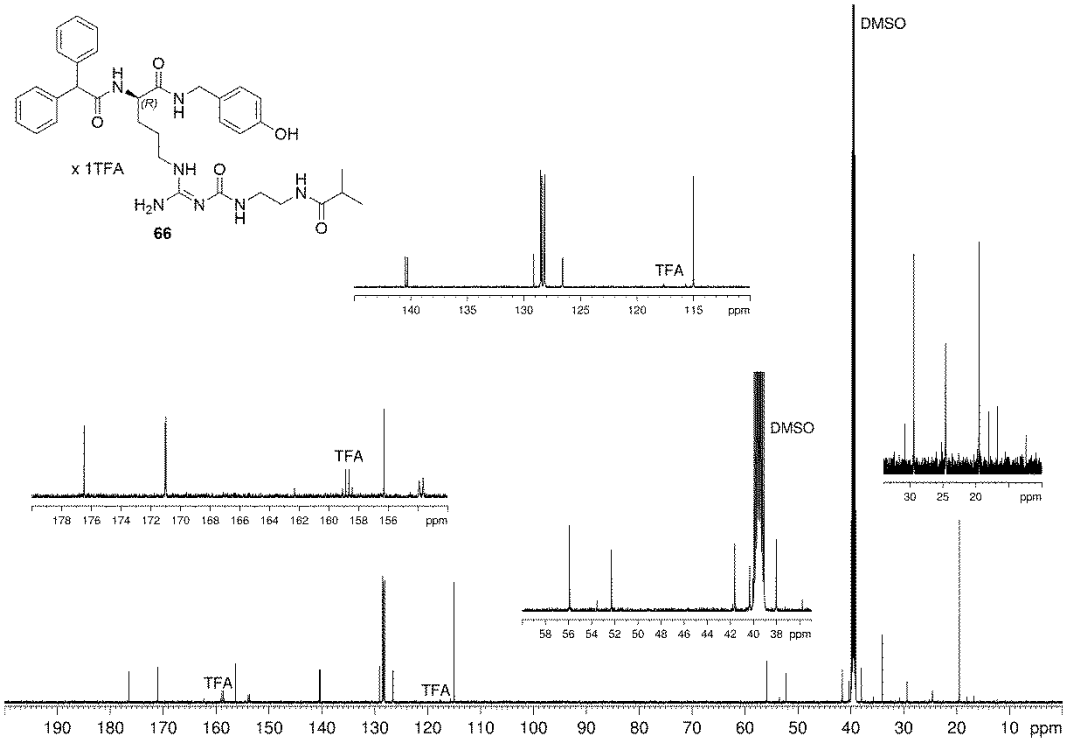
^{1}H-NMR of compound **65**



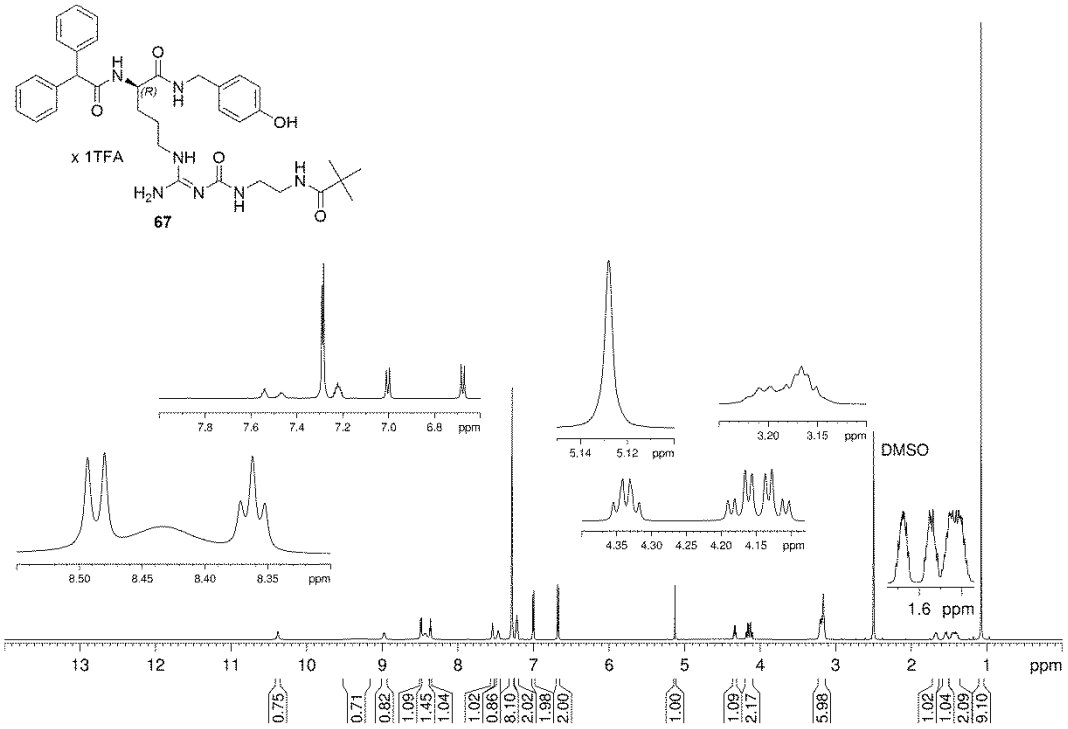
^{13}C-NMR of compound **65**



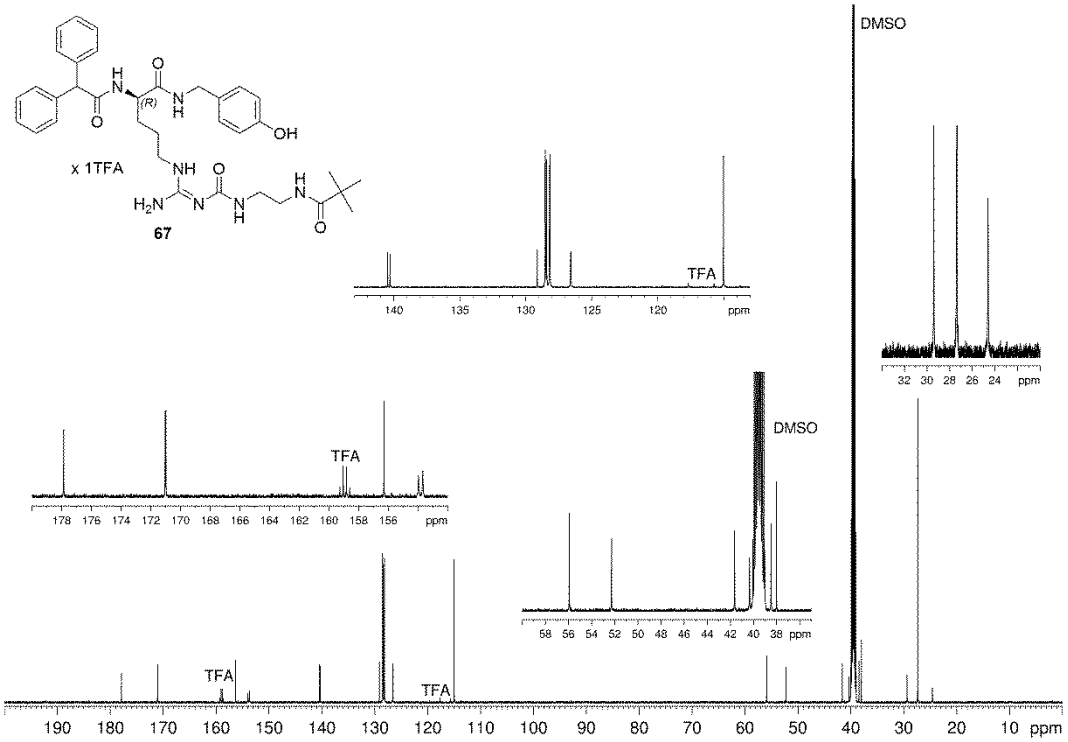
^{1}H-NMR of compound **66**



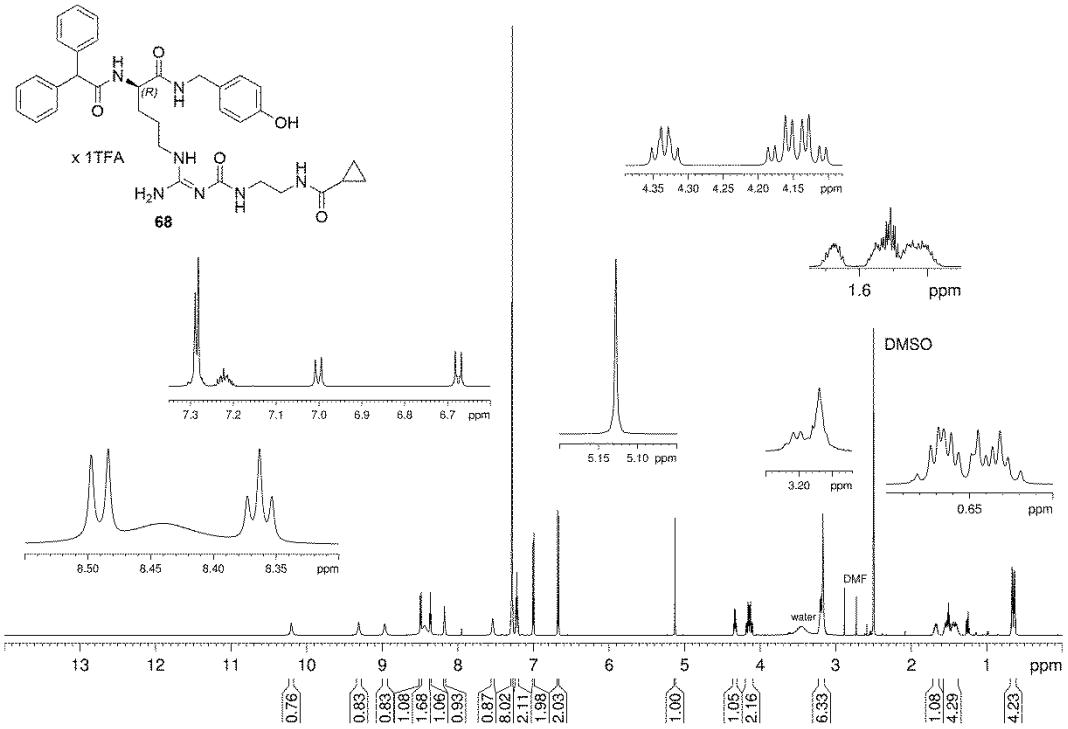
^{13}C-NMR of compound **66**



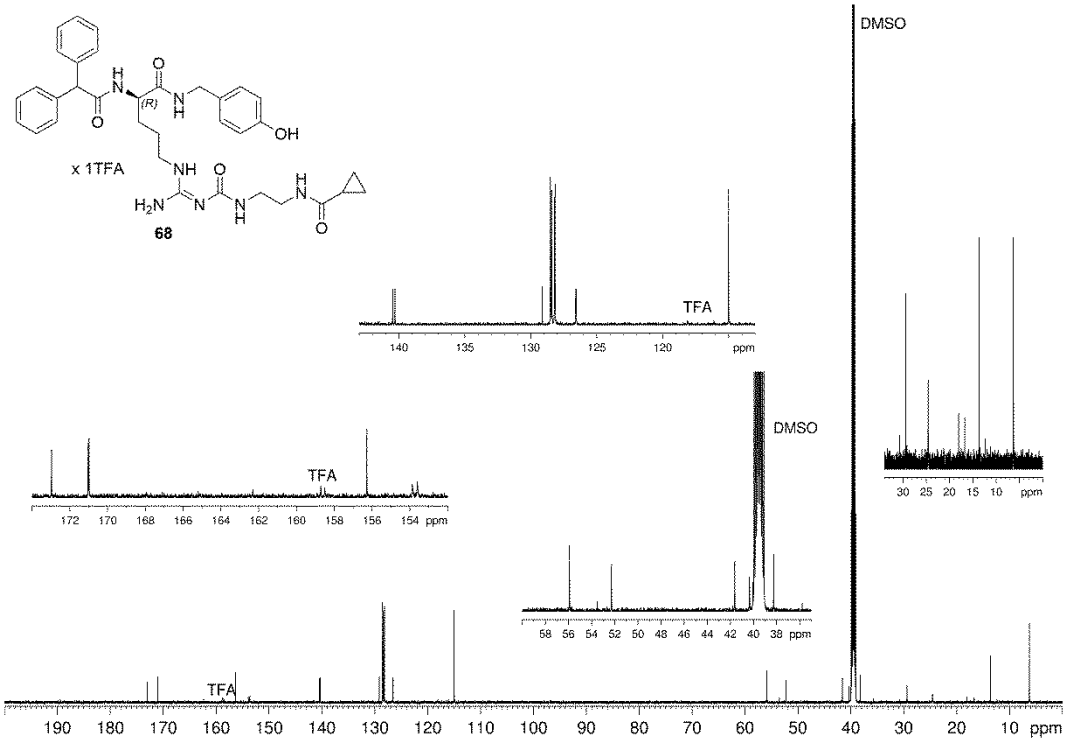
^{1}H-NMR of compound **67**



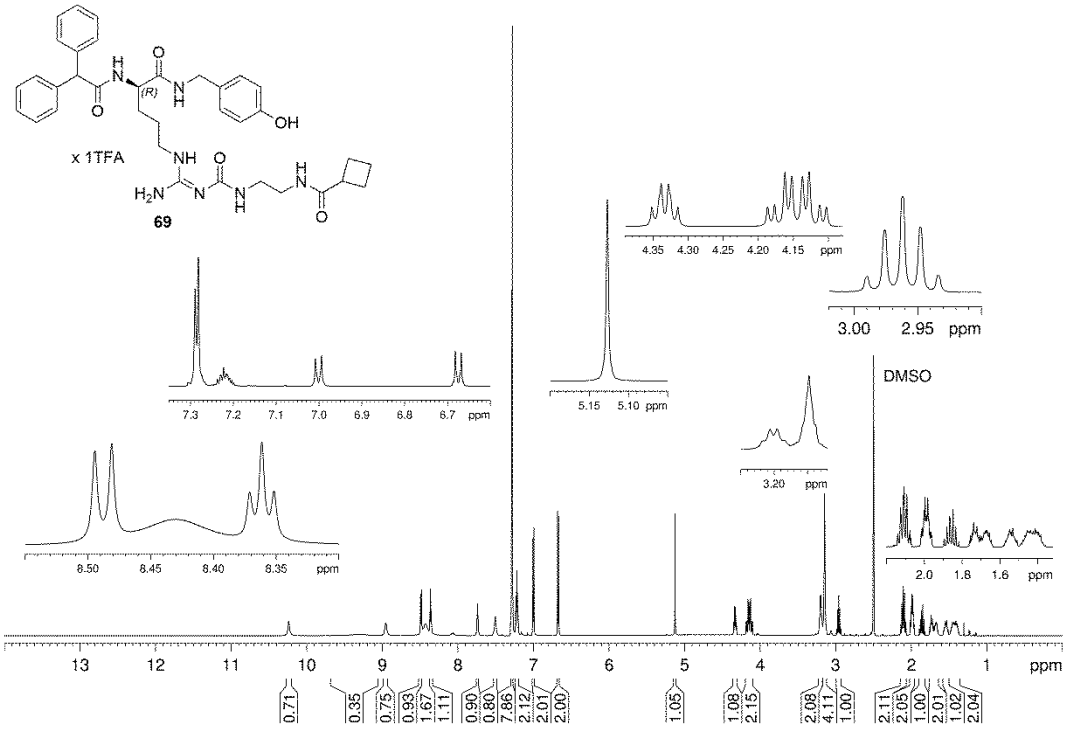
^{13}C-NMR of compound **67**



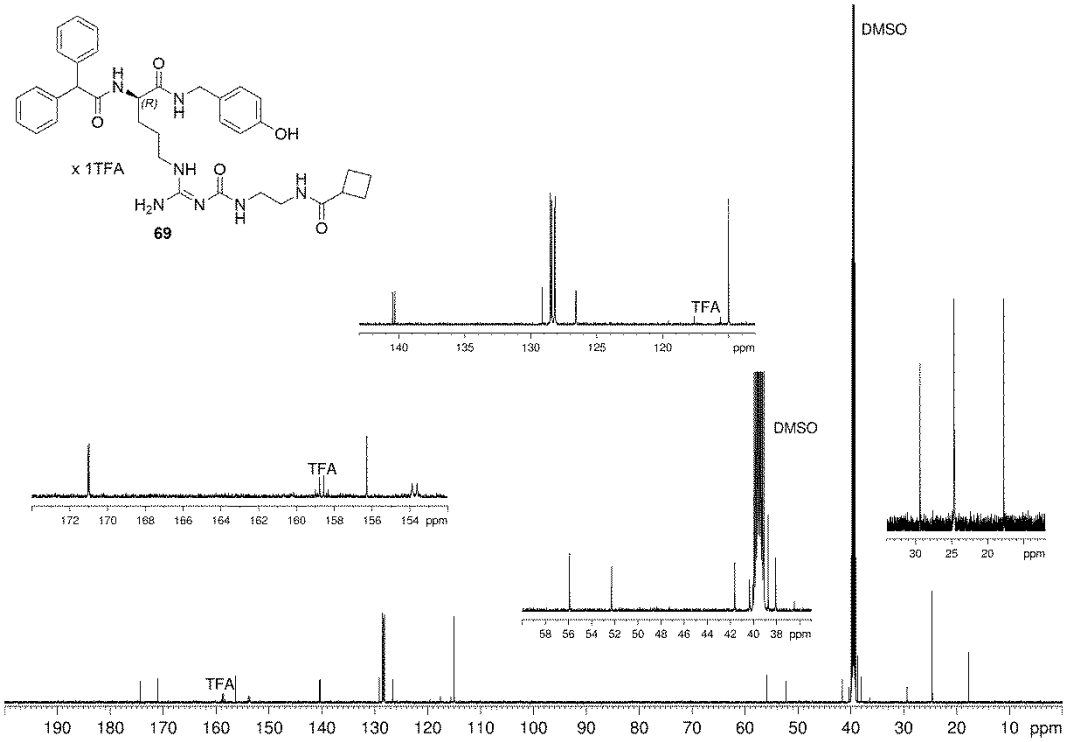
^{1}H-NMR of compound **68**



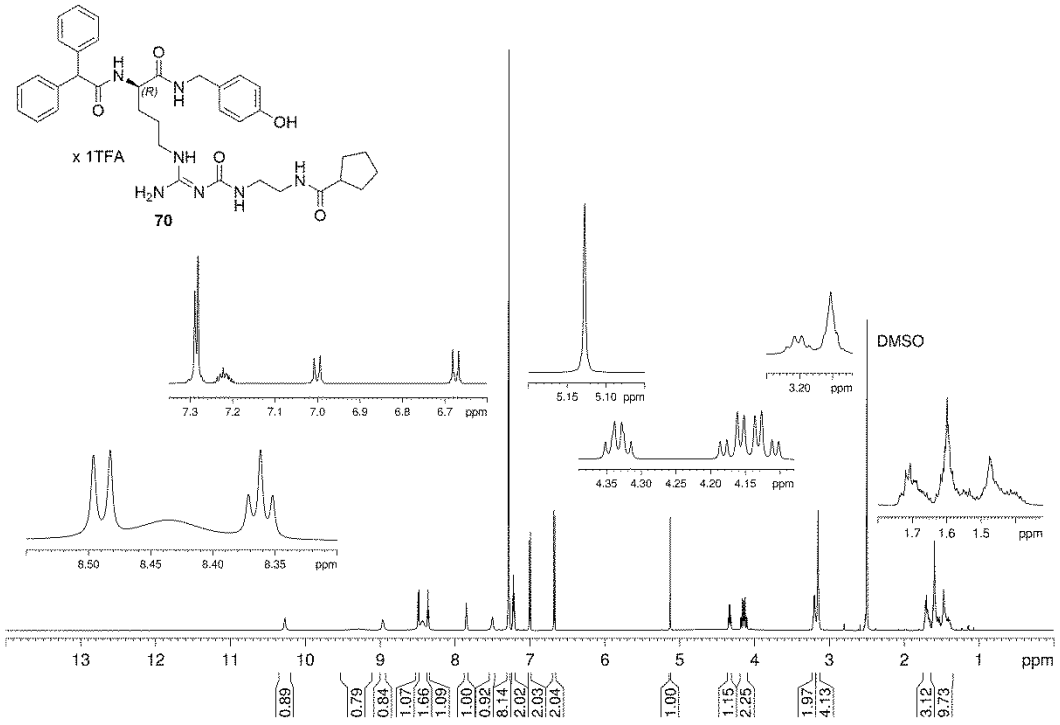
^{13}C-NMR of compound **68**



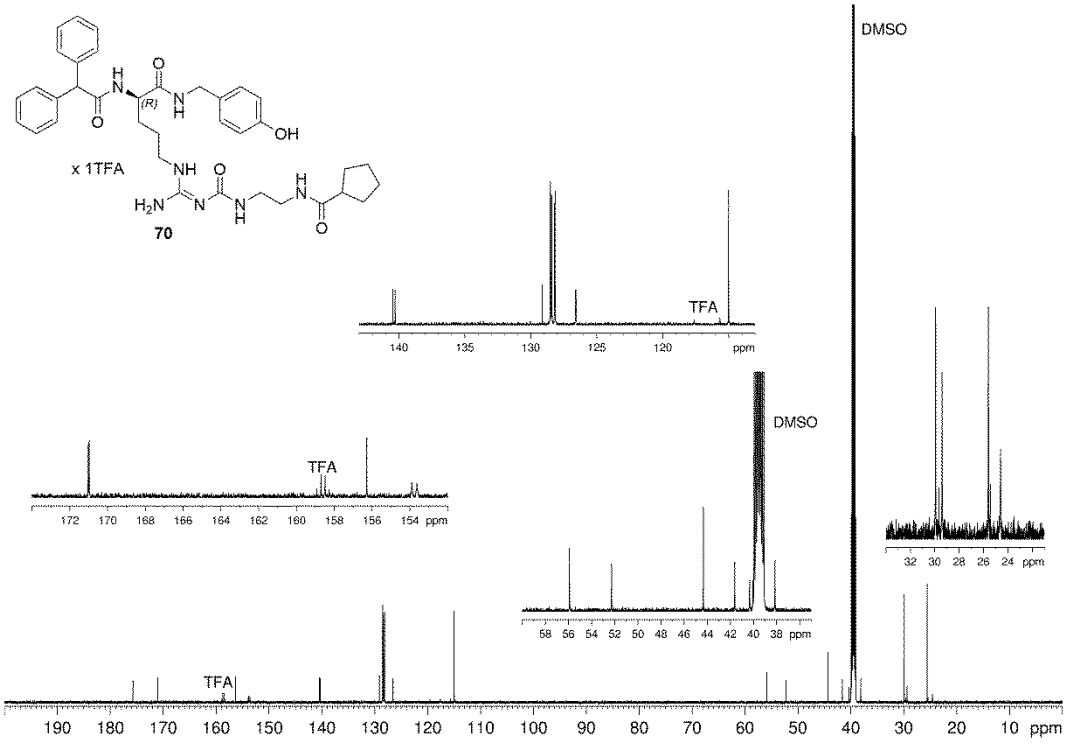
^{1}H-NMR of compound **69**



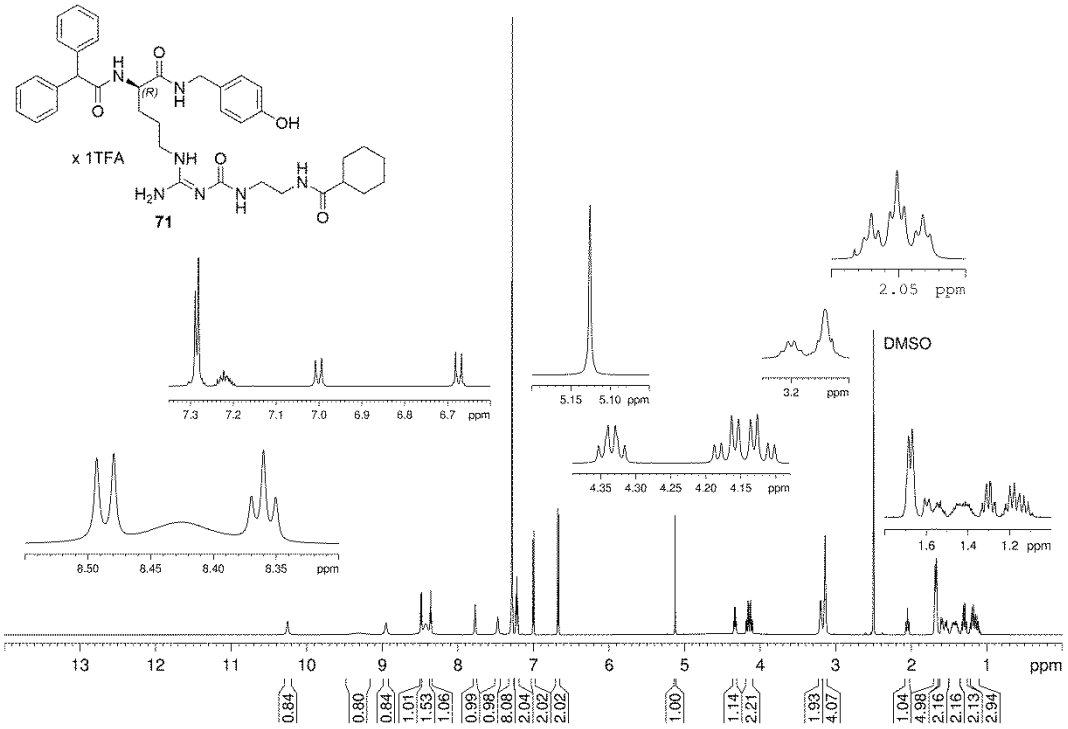
^{13}C-NMR of compound **69**



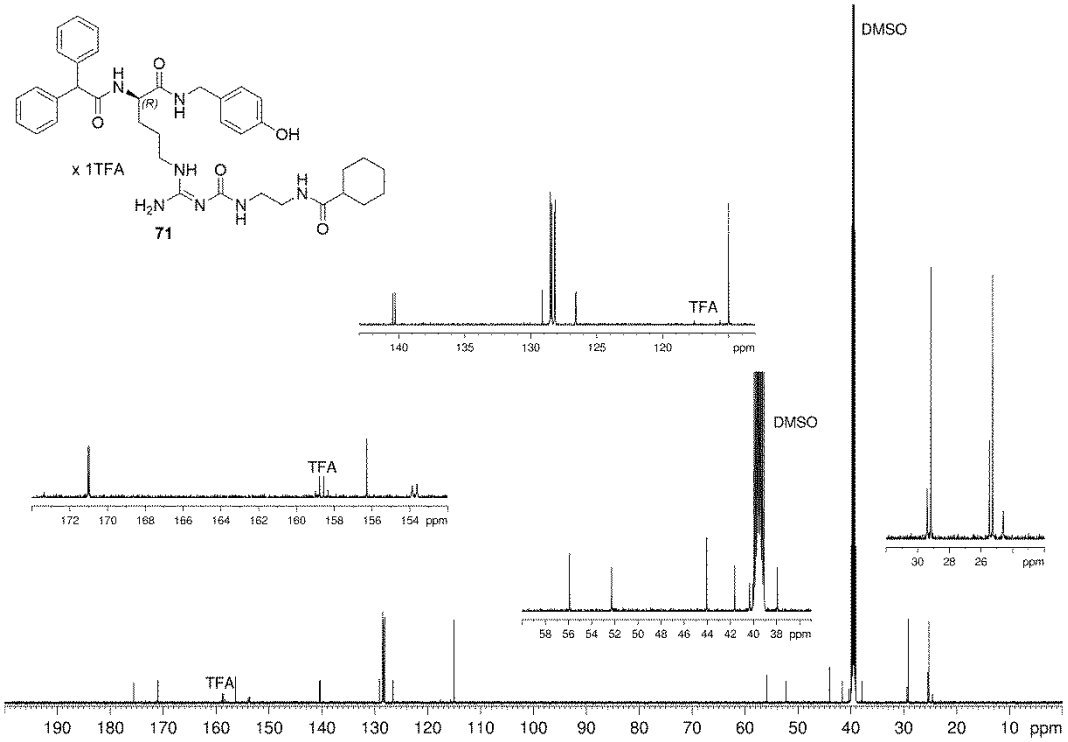
^{1}H-NMR of compound **70**



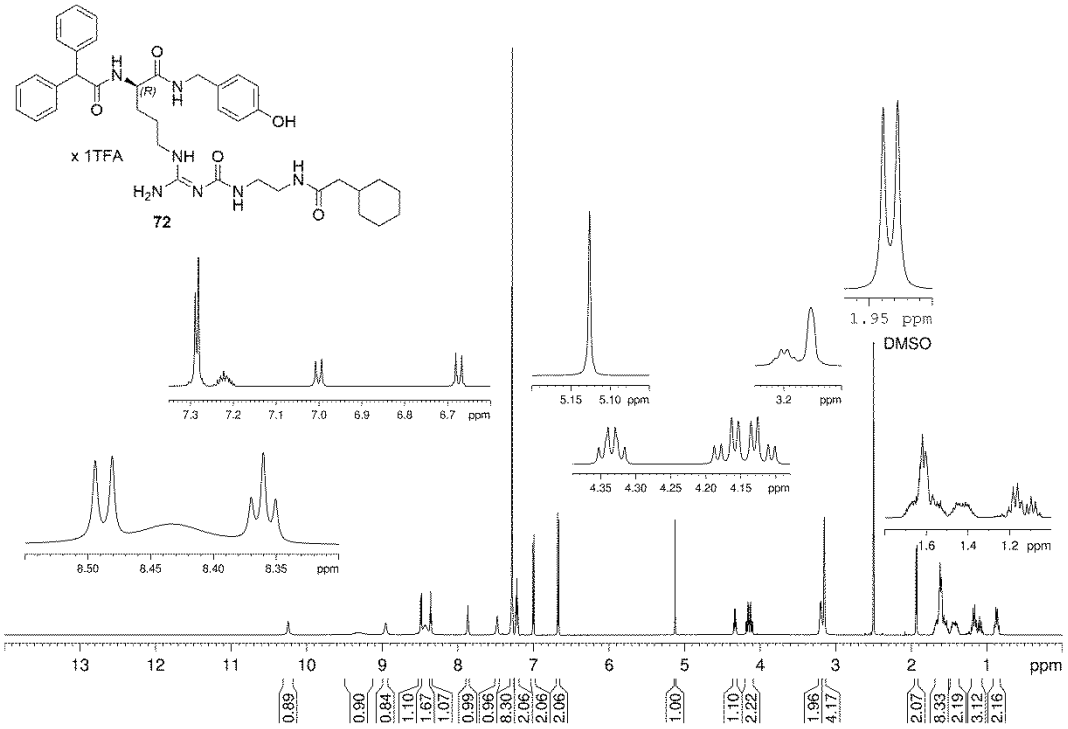
^{13}C-NMR of compound **70**



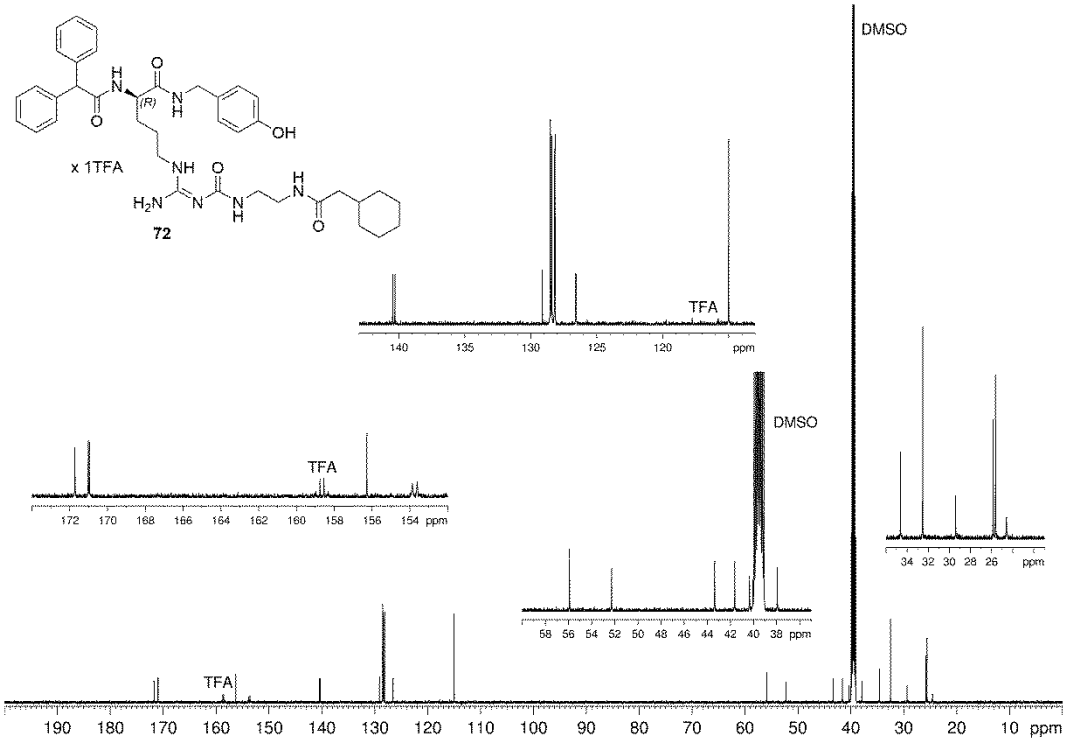
^{1}H-NMR of compound **71**



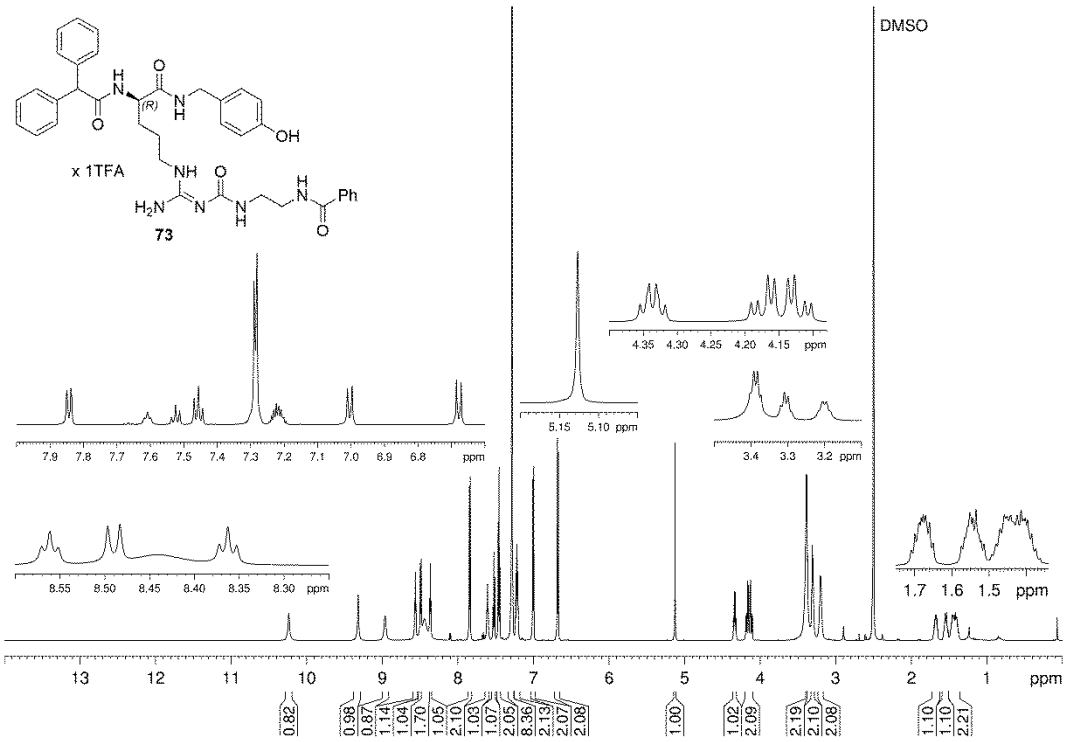
^{13}C-NMR of compound **71**



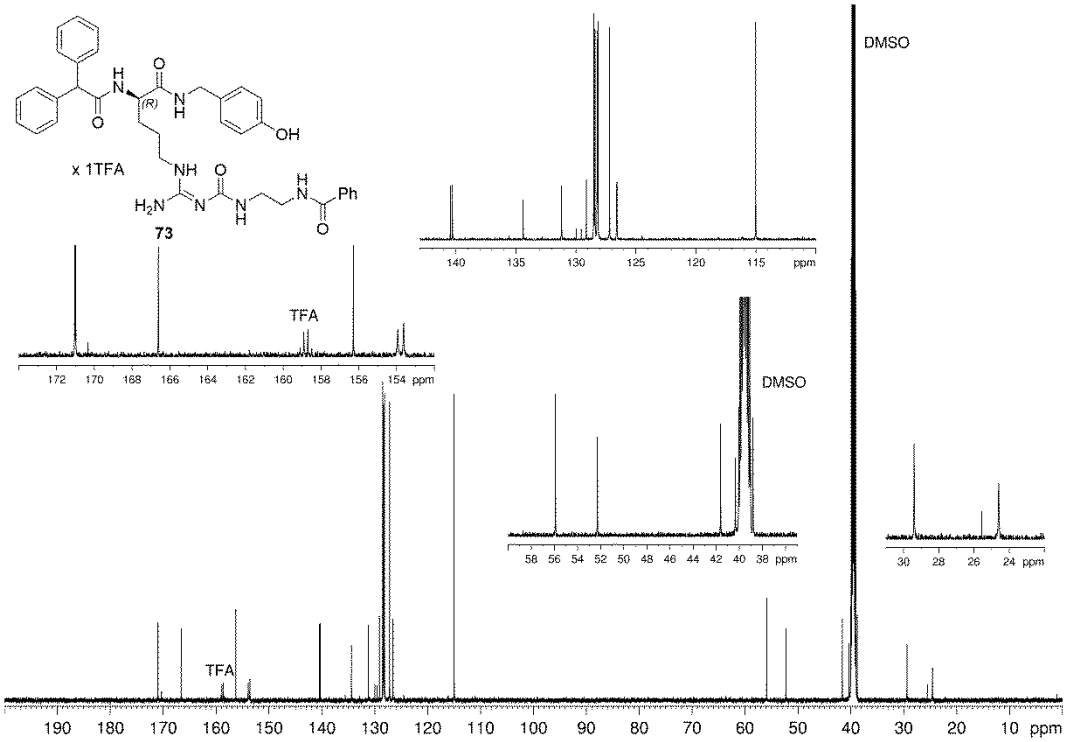
^{1}H-NMR of compound **72**



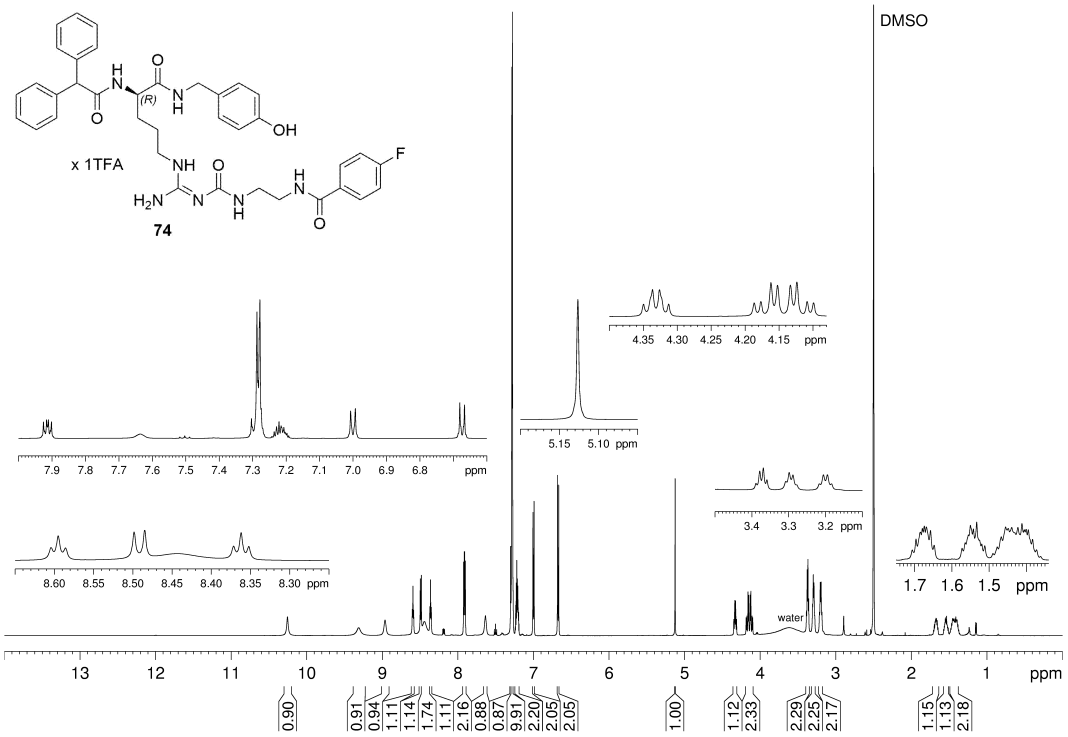
^{13}C-NMR of compound **72**



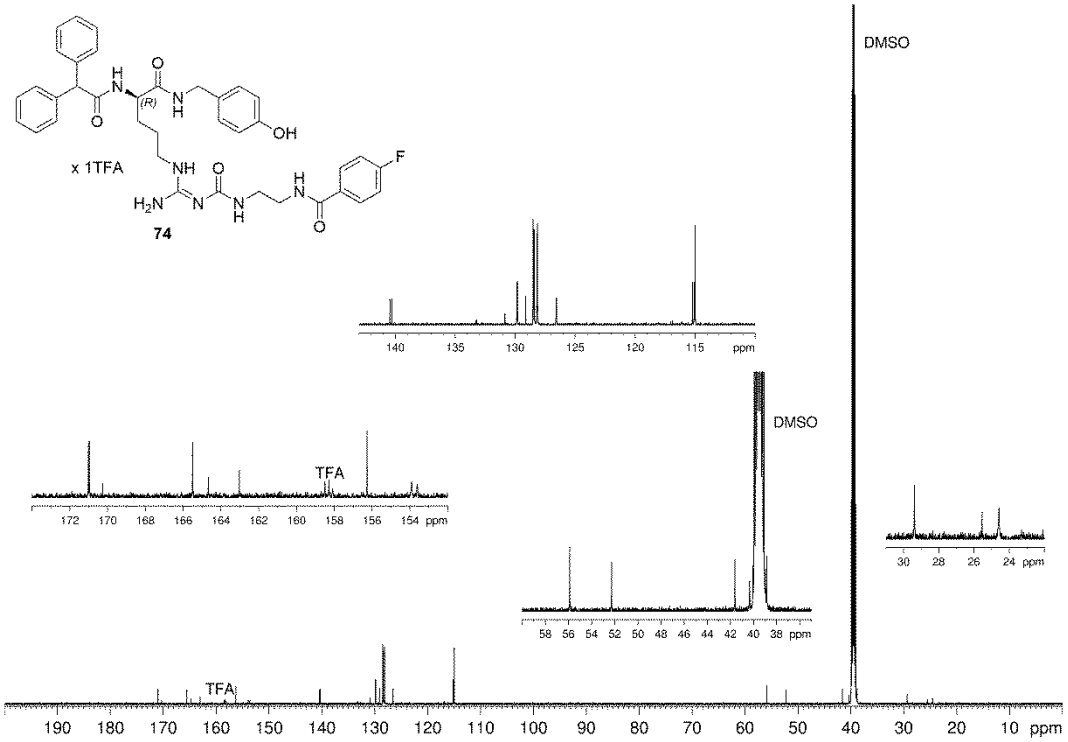
^{1}H-NMR of compound **73**



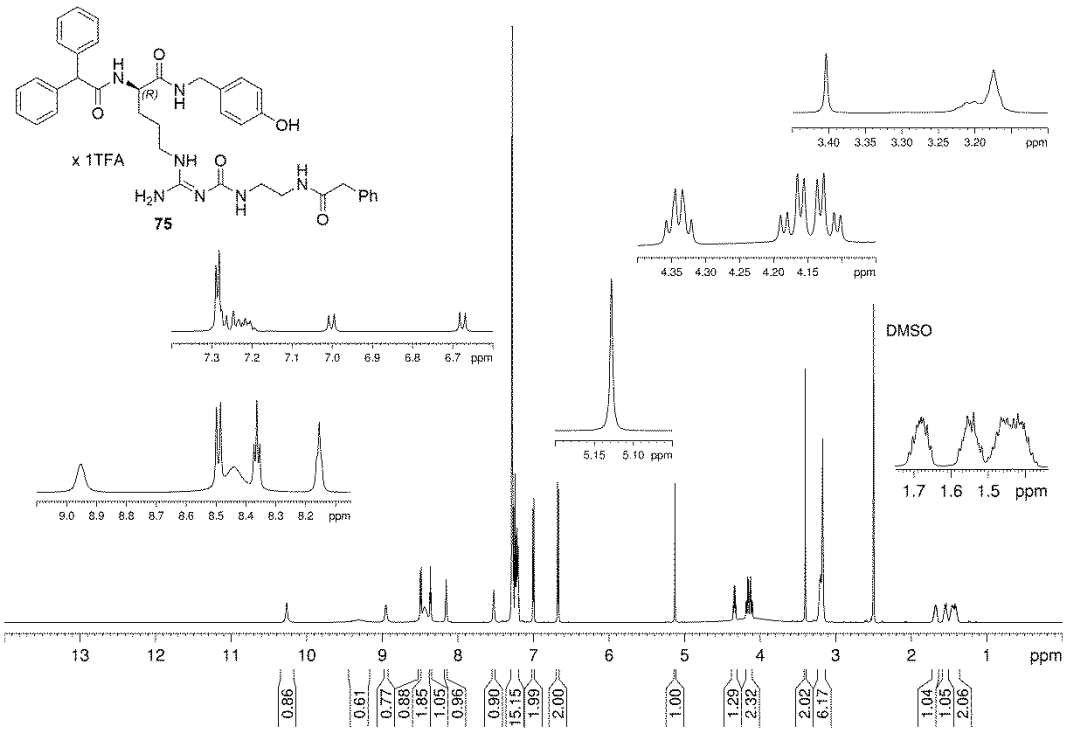
^{13}C-NMR of compound **73**



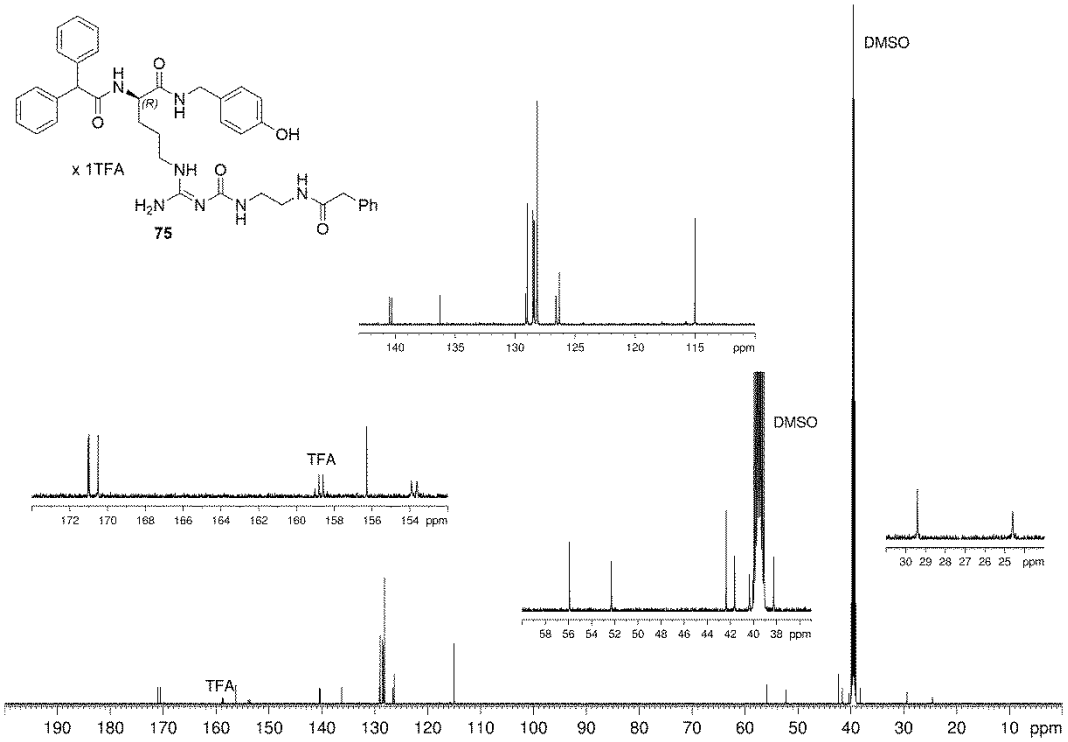
^{1}H-NMR of compound **74**



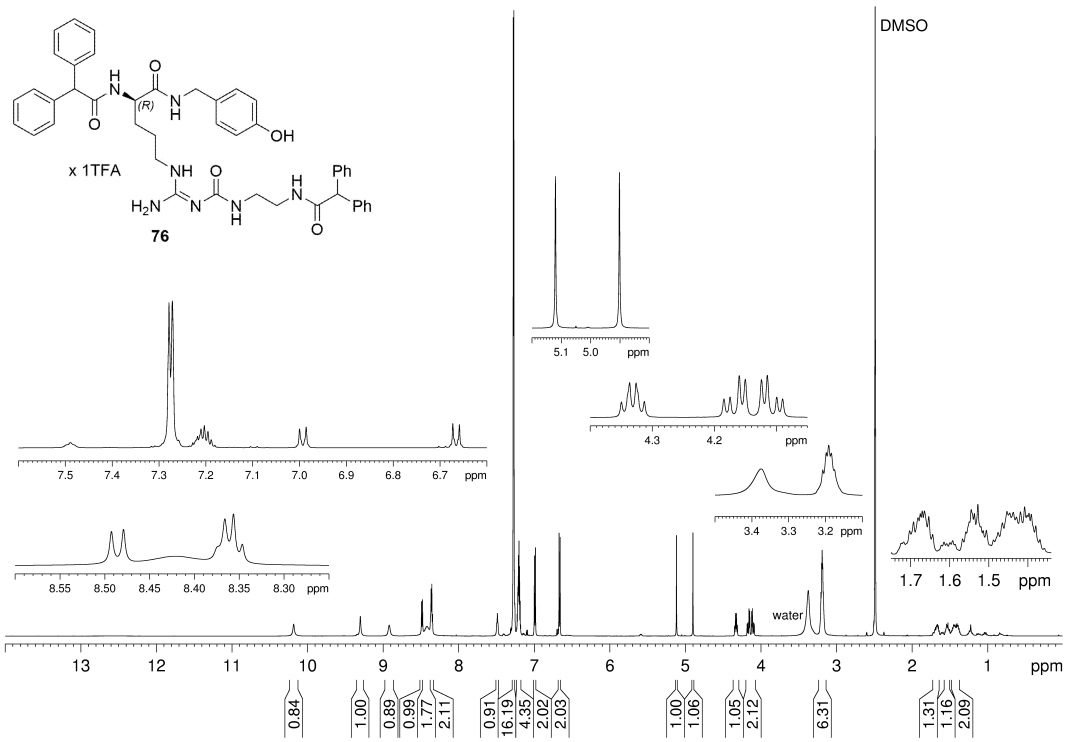
^{13}C-NMR of compound **74**



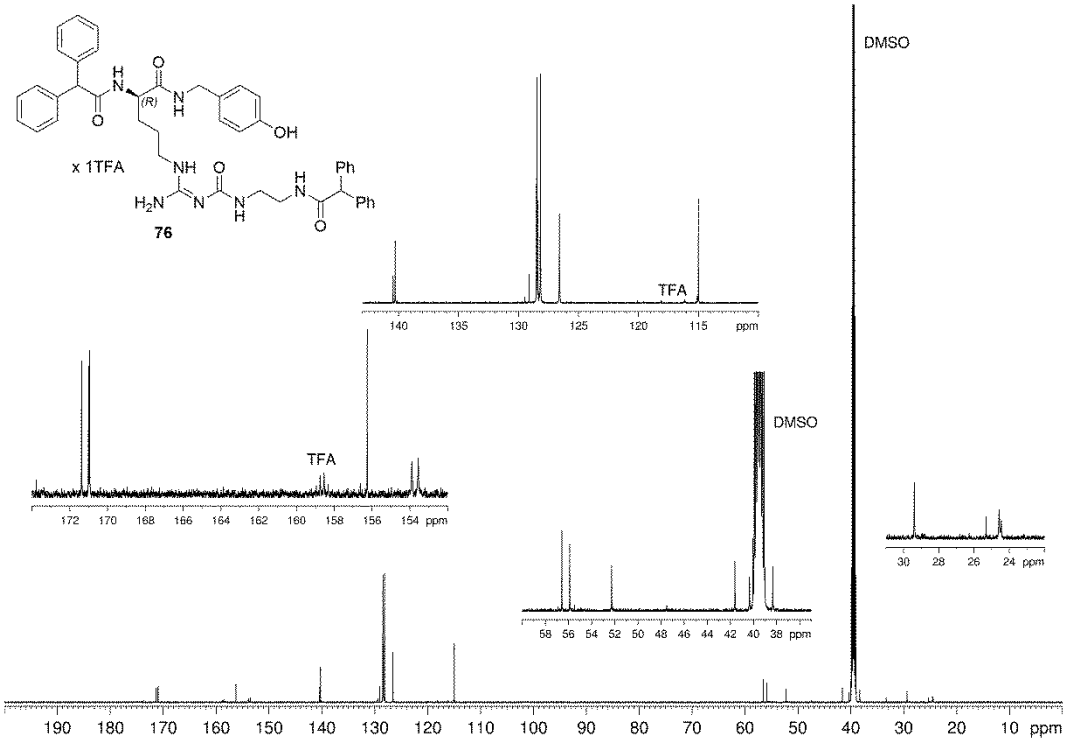
^{1}H-NMR of compound **75**



^{13}C-NMR of compound **75**

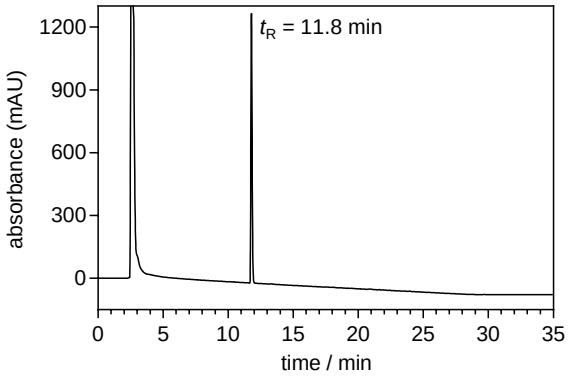


^{1}H-NMR of compound **76**

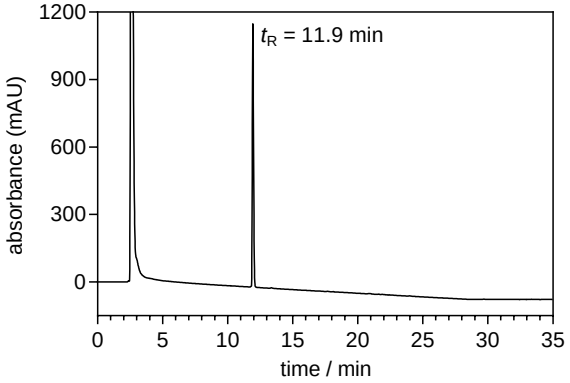


^{13}C-NMR of compound **76**

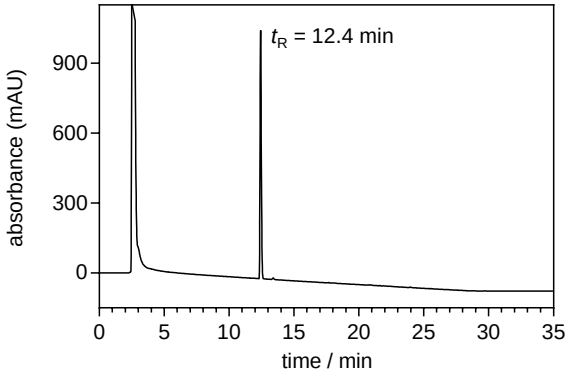
5. RP-HPLC Purity Chromatograms of Compounds 53-76 and 78



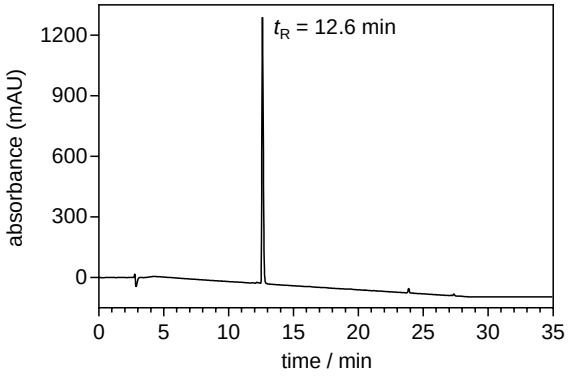
RP-HPLC chromatogram of **53**



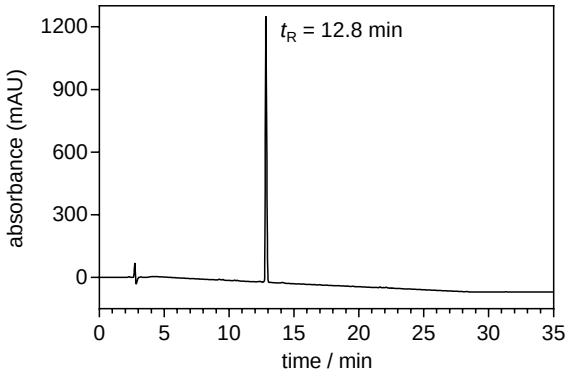
RP-HPLC chromatogram of **54**



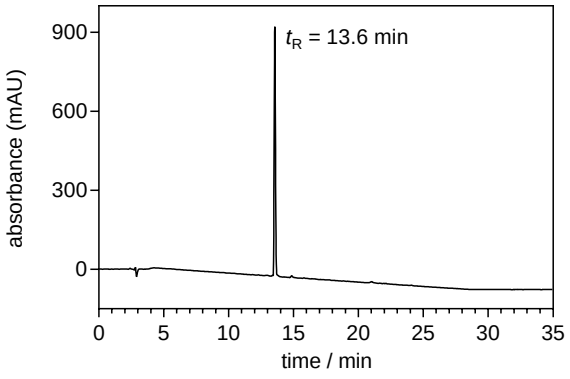
RP-HPLC chromatogram of **55**



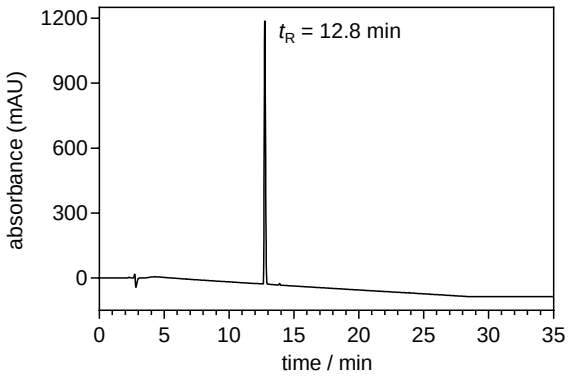
RP-HPLC chromatogram of **56**



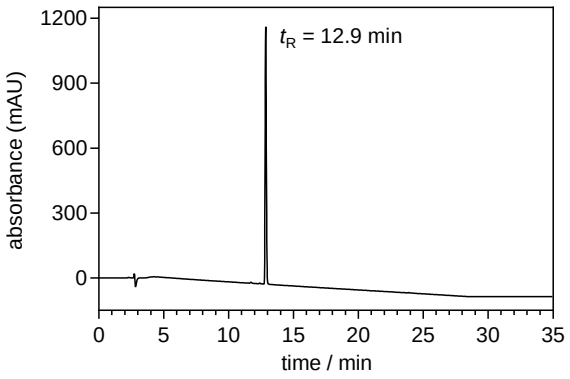
RP-HPLC chromatogram of **57**



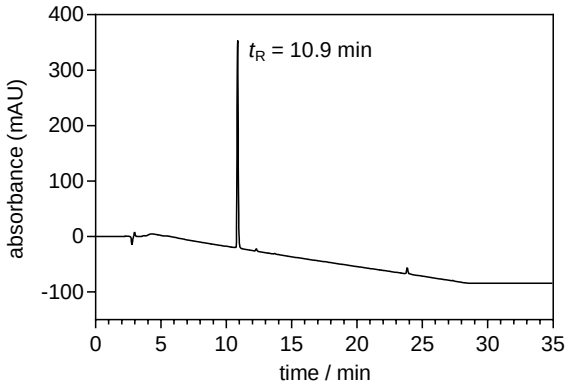
RP-HPLC chromatogram of **58**



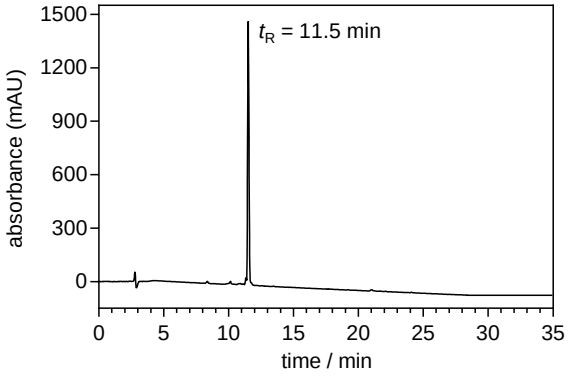
RP-HPLC chromatogram of **59**



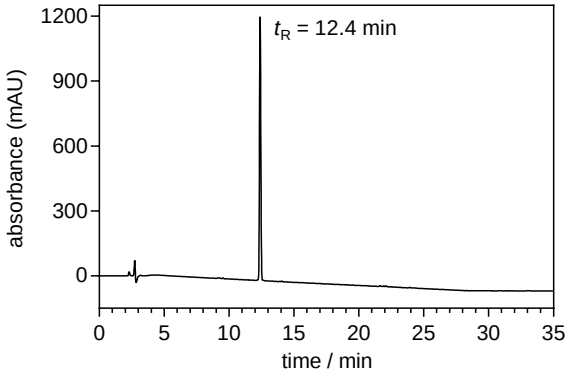
RP-HPLC chromatogram of **60**



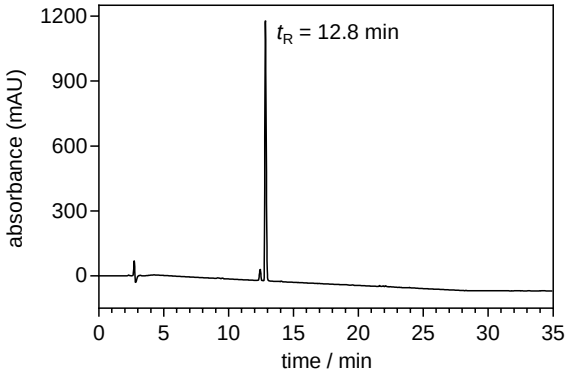
RP-HPLC chromatogram of **61**



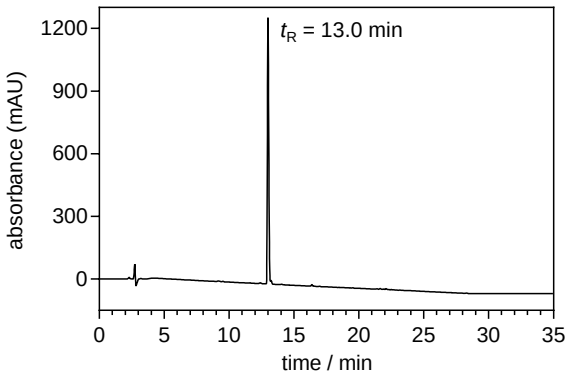
RP-HPLC chromatogram of **62**



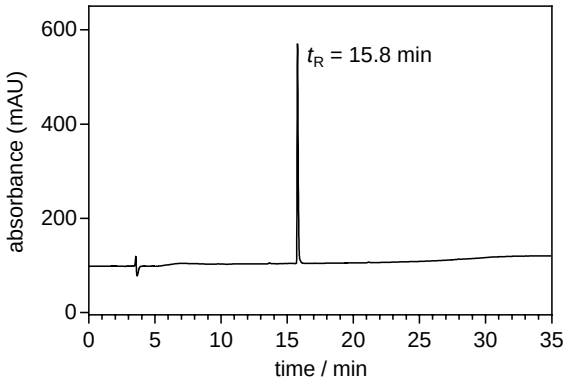
RP-HPLC chromatogram of **63**



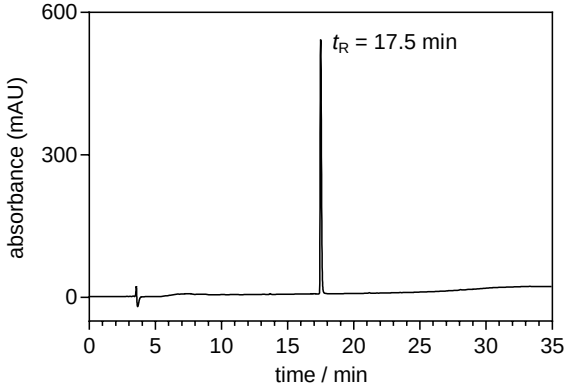
RP-HPLC chromatogram of **64**



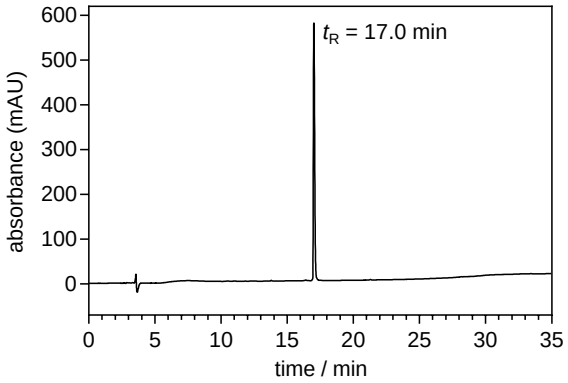
RP-HPLC chromatogram of **65**



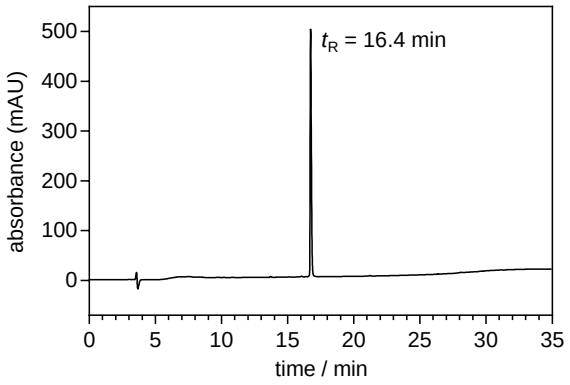
RP-HPLC chromatogram of **66**



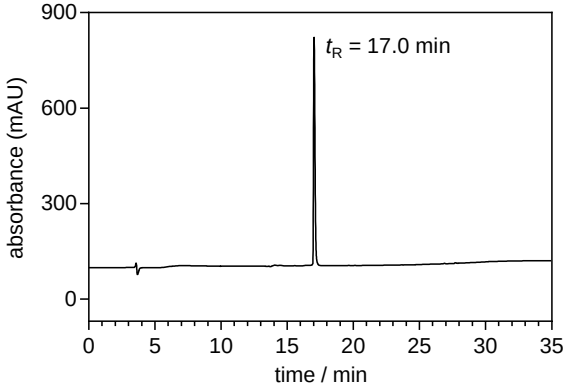
RP-HPLC chromatogram of **67**



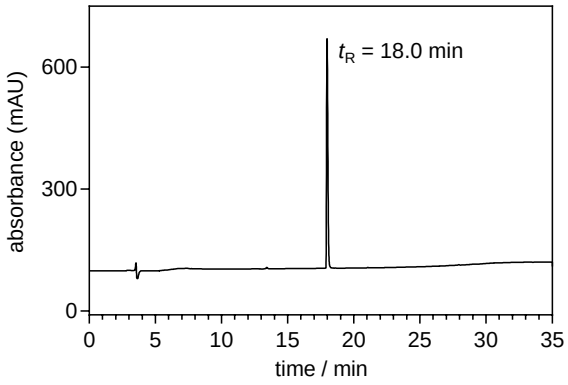
RP-HPLC chromatogram of **68**



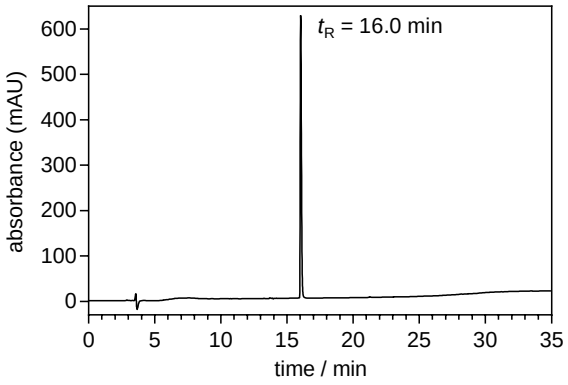
RP-HPLC chromatogram of **69**



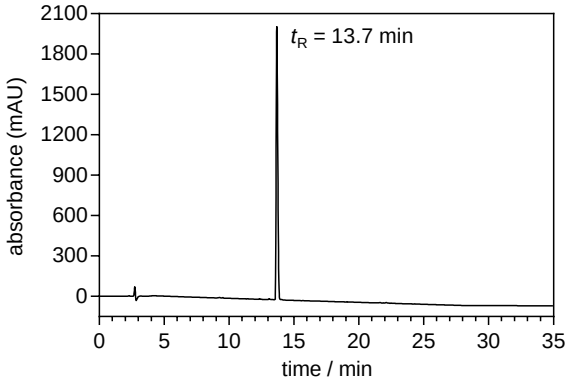
RP-HPLC chromatogram of **70**



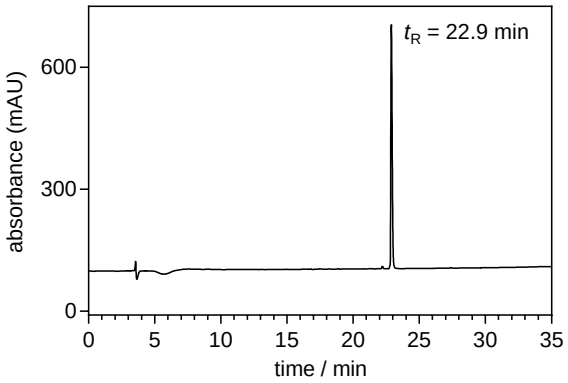
RP-HPLC chromatogram of **71**



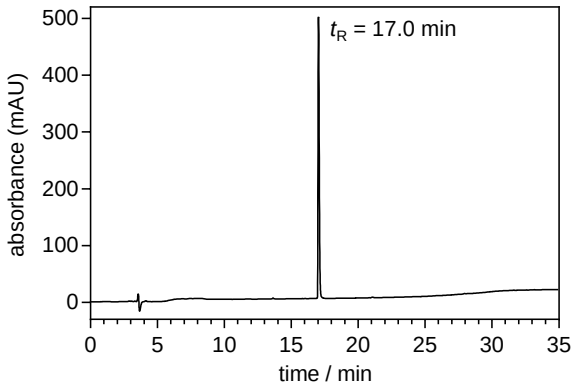
RP-HPLC chromatogram of **72**



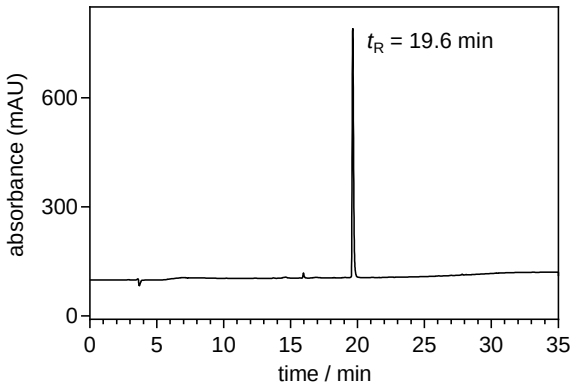
RP-HPLC chromatogram of **73**



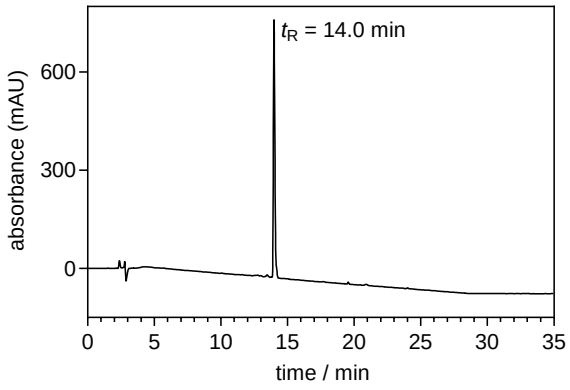
RP-HPLC chromatogram of **74**



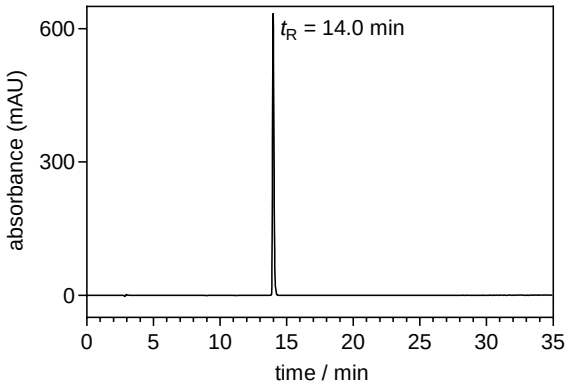
RP-HPLC chromatogram of **75**



RP-HPLC chromatogram of **76**



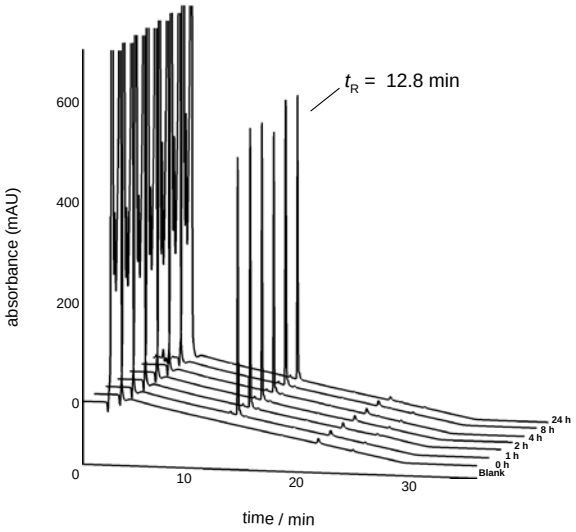
RP-HPLC chromatogram of **78** (220 nm)



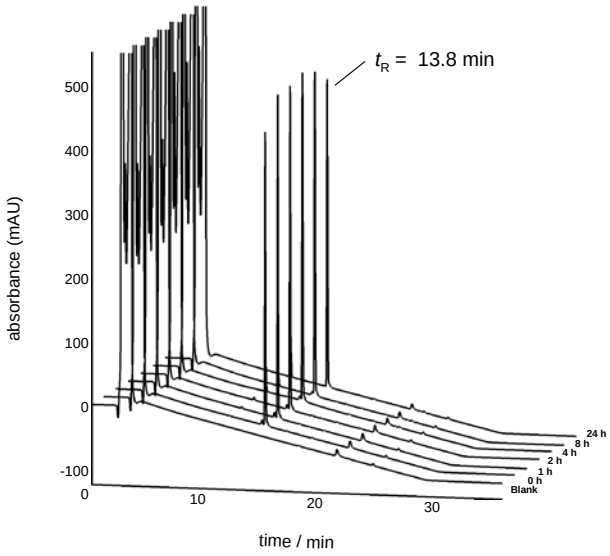
RP-HPLC chromatogram of **78** (480 nm)

6. Investigation of the Chemical Stability of Compounds 56, 58-61, 63 and 68

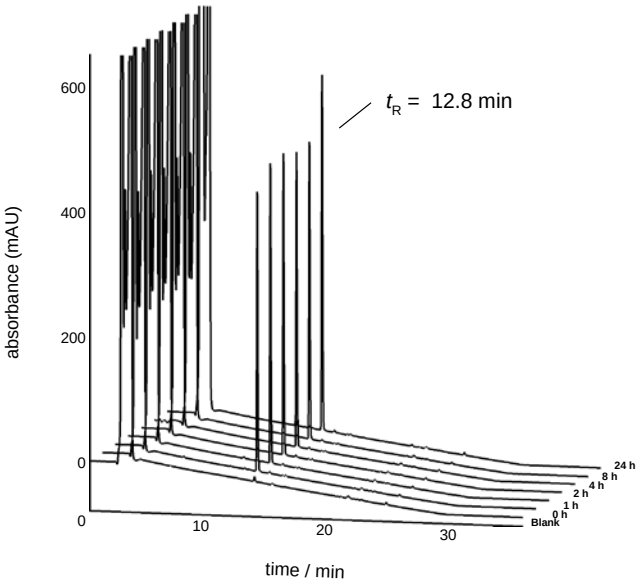
To determine the chemical stability, compounds **56**, **58-61**, **63** and **68** (100 µM) were incubated in buffer (10 mM HEPES, 150 mM NaCl, 5 mM KCl, 2.5 mM $CaCl_2$ x H_20, 1.2 mM KH_2PO_4, 1.2 mM Mg_2SO_4 x H_2O, 25 mM $NaHCO_3$, pH 7) at rt for 24 h. The solution was diluted (1:1) with 10% aq TFA and the stability monitored at 6 time intervals (0 h, 1 h, 2 h, 4 h, 8 h and 24 h) by analytical HPLC analysis (*Method A*, 220 nm).



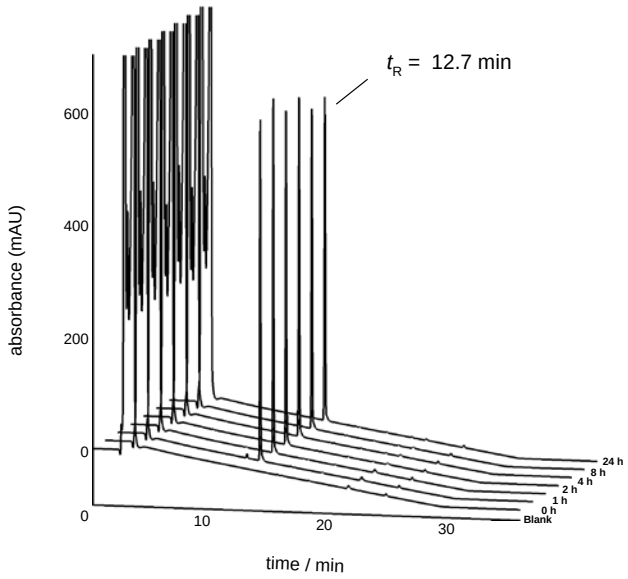
RP-HPLC chromatogram of **56**



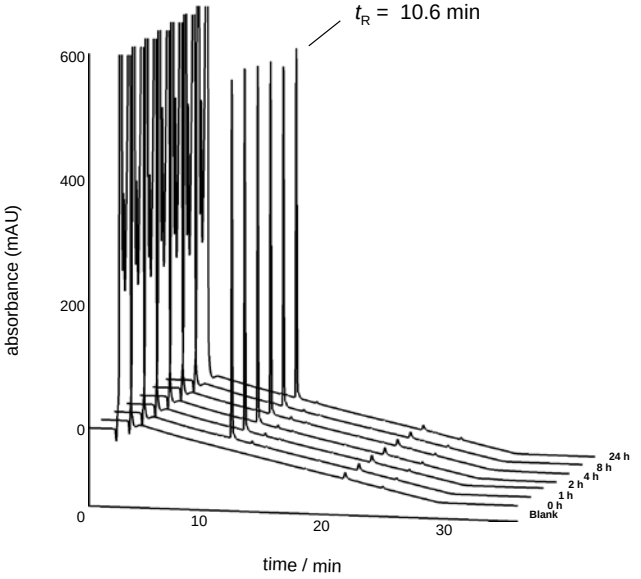
RP-HPLC chromatogram of **58**



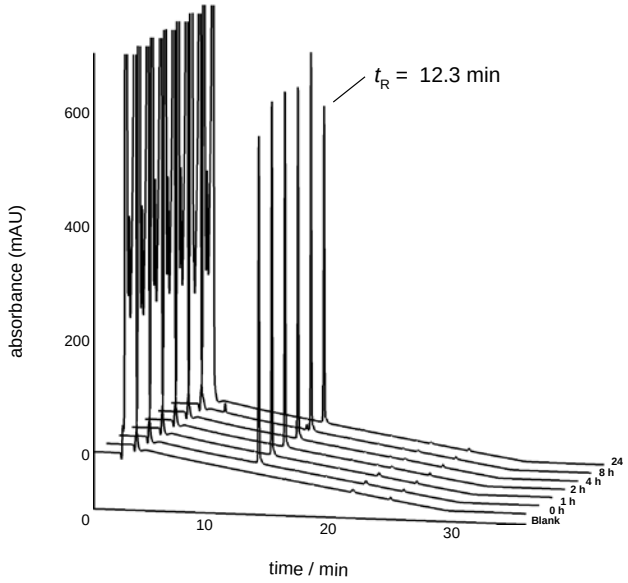
RP-HPLC chromatogram of **59**



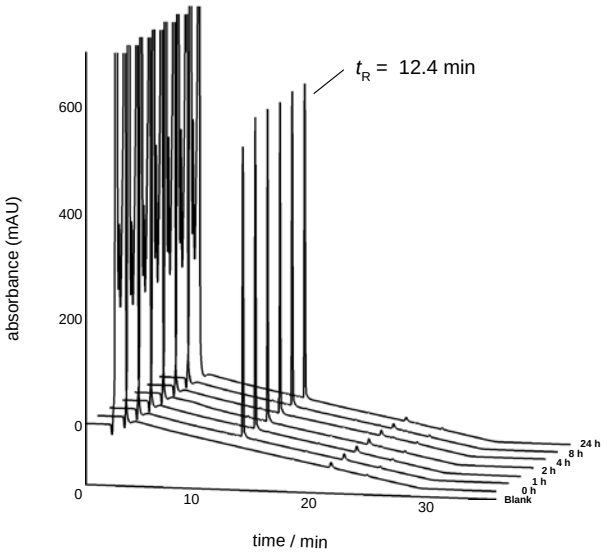
RP-HPLC chromatogram of **60**



RP-HPLC chromatogram of **61**



RP-HPLC chromatogram of **63**



RP-HPLC chromatogram of **68**

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