SUPPORTING INFORMATION

Structure-activity relationship studies of the aromatic positions in cyclopentapeptide CXCR4 antagonists

Jignesh Mungalpara,‡[a] Zack G. Zachariassen,‡[a] Stefanie Thiele,[b] Mette M. Rosenkilde,[b] and Jon Våbenø*[a]

[a] *Department of Pharmacy, Faculty of Health Sciences, UiT The Arctic University of Norway, Breivika, NO-9037 Tromsø, Norway. Fax: +47 77 64 61 51; Tel: +47 77 62 09 09; E-mail: jon.vabeno@uit.no.*

[b] *Laboratory for Molecular Pharmacology, Department of Neuroscience and Pharmacology, Faculty of Health and Medical Sciences, The Panum Institute, University of Copenhagen, Blegdamsvej 3, DK-2200 Copenhagen, Denmark.*

‡ These authors contributed equally to this work.

Table of contents

Table S1. Antagonistic potency of **2** and the analogues **4**–**22** on human CXCR4.

No.	Compound[a]	log EC_{50} ± SEM[b]	EC_{50} (μM)
2[c]	FC131	–6.40 ± 0.04	0.40
4	[Phg[3]]FC131	> –4	>100
5	[Phe[3]]FC131	> –4	>100
6	[Cha[3]]FC131	> –4	>100
7	[Hph[3]]FC131	–4.51 ± 0.30	31
8	[Hch[3]]FC131	–4.54 ± 0.14	29
9	[Bsa[3]]FC131	–4.71 ± 0.07	19
10	[1-Nal[3]]FC131	–5.25 ± 0.08	5.6
11	[Pph[3]]FC131	> –4	>100
12	[Bph[3]]FC131	> –4	>100
13[c]	[Ala[3]]FC131	> –4	>100
14[c]	[D-Phe[5]]FC131	–6.07 ± 0.05	0.85
15	[Aic[5]]FC131	–4.13 ± 0.19	74
16	[D-Tic[5]]FC131	–4.60 ± 0.02	25
17[d]	[*trans*-Ppr[5]]FC131	–4.46 ± 0.14	35
18[e]	[*cis*-Ppr[5]]FC131	–4.43 ± 0.18	37
19	[D-Pic[5]]FC131	> –4	>100
20	[D-Pro[5]]FC131	> –4	>100
21[c]	[D-Ala[5]]FC131	–4.29 ± 0.08	51
22	[Gly[5]]FC131	–5.29 ± 0.16	5.1

[a] 1-Nal = 3-(1-naphthyl)alanine; Aic = 2-aminoindan-2-carboxylic acid; Bph = 4-benzoylphenylalanine; Bsa = β-styrylalanine; Cha = 3-cyclohexylalanine; Hch = 2-amino-4-cyclohexylbutanoic acid; Hph = 2-amino-4-phenylbutanoic acid; Phg = phenylglycine; Pic = pipecolic acid; Pph = 4-phenylphenylalanine; Ppr = 3-phenyl-Pro; Tic = tetrahydroisoquinoline-3-carboxylic acid. [b] Inhibition of C-X-C chemokine ligand 12 (CXCL12) induced activation of human CXCR4. Values represent the mean of at least three independent experiments performed in duplicate. [c] Known compounds; see main text. [d] Tested as a 47:53 mixture of the two diastereomers. [e] Tested as a 68:32 mixture of the two diastereomers.

Table S2. Yields and HRMS data for compounds 4-22.

Compd	Sequence	Yield[a] (%)	Mol Formula	$[M+H]^+$ calcd	$[M+H]^+$ obsd[b]
4	cyclo(-Arg^1-Arg^2-Phg^3-Gly^4-D-Tyr^5-) × 2 TFA	8.5	$C_{31}H_{43}N_{11}O_6$	666.3471	666.3469
5	cyclo(-Arg^1-Arg^2-Phe^3-Gly^4-D-Tyr^5-) × 2 TFA	24	$C_{32}H_{45}N_{11}O_6$	680.3627	680.3627
6	cyclo(-Arg^1-Arg^2-Cha^3-Gly^4-D-Tyr^5-) × 2 TFA	28	$C_{32}H_{51}N_{11}O_6$	686.4097	686.4096
7	cyclo(-Arg^1-Arg^2-Hph^3-Gly^4-D-Tyr^5-) × 2 TFA	6.5	$C_{33}H_{47}N_{11}O_6$	694.3784	694.3786
8	cyclo(-Arg^1-Arg^2-Hch^3-Gly^4-D-Tyr^5-) × 2 TFA	29	$C_{33}H_{53}N_{11}O_6$	700.4253	700.4253
9	cyclo(-Arg^1-Arg^2-Bsa^3-Gly^4-D-Tyr^5-) × 2 TFA	5.7	$C_{34}H_{47}N_{11}O_6$	706.3784	706.3784
10	cyclo(-Arg^1-Arg^2-1-Nal^3-Gly^4-D-Tyr^5-) × 2 TFA	29	$C_{36}H_{47}N_{11}O_6$	730.3784	730.3786
11	cyclo(-Arg^1-Arg^2-Pph^3-Gly^4-D-Tyr^5-) × 2 TFA	28	$C_{38}H_{49}N_{11}O_6$	756.3940	756.3944
12	cyclo(-Arg^1-Arg^2-Bph^3-Gly^4-D-Tyr^5-) × 2 TFA	18	$C_{39}H_{49}N_{11}O_7$	784.3889	784.3891
13	cyclo(-Arg^1-Arg^2-Ala^3-Gly^4-D-Tyr^5-) × 2 TFA	34	$C_{26}H_{41}N_{11}O_6$	604.3314	604.3314
14	cyclo(-Arg^1-Arg^2-2-Nal^3-Gly^4-D-Phe^5-) × 2 TFA	19	$C_{36}H_{47}N_{11}O_5$	714.3834	714.3840
15	cyclo(-Arg^1-Arg^2-2-Nal^3-Gly^4-Aic^5-) × 2 TFA	26	$C_{37}H_{47}N_{11}O_5$	726.3834	726.3834
16	cyclo(-Arg^1-Arg^2-2-Nal^3-Gly^4-D-Tic^5-) × 2 TFA	28	$C_{37}H_{47}N_{11}O_5$	726.3834	726.3831
17	cyclo(-Arg^1-Arg^2-2-Nal^3-Gly^4-*trans*-Ppr^5-) × 2 TFA	34	$C_{38}H_{49}N_{11}O_5$	740.3991	740.3987
18	cyclo(-Arg^1-Arg^2-2-Nal^3-Gly^4-*cis*-Ppr^5-) × 2 TFA	9.8	$C_{38}H_{49}N_{11}O_5$	740.3991	740.3985
19	cyclo(-Arg^1-Arg^2-2-Nal^3-Gly^4-D-Pic^5-) × 2 TFA	17	$C_{33}H_{47}N_{11}O_5$	678.3834	678.3841
20	cyclo(-Arg^1-Arg^2-2-Nal^3-Gly^4-D-Pro^5-) × 2 TFA	28	$C_{32}H_{45}N_{11}O_5$	664.3678	664.3674
21	cyclo(-Arg^1-Arg^2-2-Nal^3-Gly^4-D-Ala^5-) × 2 TFA	18	$C_{30}H_{43}N_{11}O_5$	638.3521	638.3529
22	cyclo(-Arg^1-Arg^2-2-Nal^3-Gly^4-Gly^5-) × 2 TFA	28	$C_{29}H_{41}N_{11}O_5$	624.3365	624.3374

[a]Calculated from resin. [b]HRMS ESI+.

^{1}H and ^{13}C NMR data

cyclo(-Arg^{1}-Arg^{2}-Phg^{3}-Gly^{4}-D-Tyr^{5}-) × 2 TFA (4). **^{1}H NMR** (400 MHz, CD_3OD): δ 7.48 – 7.30 (m, 5H), 7.05 (d, *J* = 8.4 Hz, 2H), 6.72 (d, *J* = 8.4 Hz, 2H), 5.56 (s, 1H), 4.40 – 4.31 (m, 2H), 4.08 (d, *J* = 15.1 Hz, 1H), 4.00 (dd, *J* = 11.2, 3.8 Hz, 1H), 3.60 (d, *J* = 15.1 Hz, 1H), 3.23 – 3.09 (m, 2H), 3.08 – 2.77 (m, 4H), 2.03 – 1.77 (m, 2H), 1.62 – 1.34 (m, 4H), 1.34 – 1.06 (m, 2H). **^{13}C NMR** (100 MHz, CD_3OD): δ 172.6, 172.4, 172.2, 171.0, 170.6, 157.2, 157.2, 155.9, 135.0, 130.1, 128.2, 128.0, 127.2, 127.1, 115.0, 57.7, 56.6, 53.9, 53.1, 44.5, 42.7, 40.6, 40.1, 35.9, 28.3, 27.8, 24.8.

cyclo(-Arg^{1}-Arg^{2}-Phe^{3}-Gly^{4}-D-Tyr^{5}-) × 2 TFA (5). **^{1}H NMR** (400 MHz, CD_3OD): δ 7.29 – 7.16 (m, 5H), 7.02 (d, *J* = 6.5 Hz, 2H), 6.71 (d, *J* = 6.5 Hz, 2H), 4.50 – 4.41 (m, 1H), 4.34 – 4.28 (m, 1H), 4.23 – 4.16 (m, 1H), 4.07 – 4.04 (m, 1H), 4.01 (d, *J* = 15.7 Hz, 1H), 3.68 (d, *J* = 15.7 Hz, 1H), 3.21 – 3.06 (m, 4H), 3.05 – 2.96 (m, 2H), 2.94 – 2.83 (m, 2H), 1.89 – 1.78 (m, 1H), 1.77 – 1.66 (m, 2H), 1.47 – 1.26 (m, 3H), 1.19 – 1.07 (m, 2H). **^{13}C NMR** (100 MHz, CD_3OD): δ 174.6, 174.6, 174.5, 172.6, 171.9, 158.6, 158.6, 157.3, 138.7, 131.4, 130.2, 129.5, 128.5, 127.7, 116.4, 58.1, 57.4, 55.7, 55.0, 43.3, 41.8, 41.6, 36.7, 36.4, 29.3, 29.0, 26.2, 26.1.

cyclo(-Arg^{1}-Arg^{2}-Cha^{3}-Gly^{4}-D-Tyr^{5}-) × 2 TFA (6). **^{1}H NMR** (400 MHz, CD_3OD): δ 7.03 (d, *J* = 8.4 Hz, 2H), 6.72 (d, *J* = 8.4 Hz, 2H), 4.42 – 4.22 (m, 3H), 4.10 (dd, *J* = 11.2, 3.7 Hz, 1H), 3.86 (dd, *J* = 32.3, 15.9 Hz, 2H), 3.27 – 3.13 (m, 2H), 3.03 (t, *J* = 6.7 Hz, 2H), 2.95 – 2.85 (m, 2H), 1.94 – 1.80 (m, 3H), 1.79 – 1.51 (m, 9H), 1.48 – 1.37 (m, 1H), 1.37 – 1.05 (m, 6H), 1.03 – 0.87 (m, 2H). **^{13}C NMR** (100 MHz, CD_3OD): δ 174.3, 173.1, 173.1, 171.5, 170.6, 157.2, 157.2, 155.9, 130.1, 127.1, 115.0, 56.8, 53.7, 53.6, 52.8, 41.8, 40.4, 40.2, 36.7, 35.3, 34.2, 33.1, 32.4, 27.7, 27.6, 26.1, 25.9, 25.8, 25.0, 24.9.

cyclo(-Arg^{1}-Arg^{2}-Hph^{3}-Gly^{4}-D-Tyr^{5}-) × 2 TFA (7). **^{1}H NMR** (400 MHz, CD_3OD): δ 7.33 – 7.16 (m, 5H), 7.08 (d, *J* = 8.2 Hz, 2H), 6.74 (d, *J* = 8.2 Hz, 2H), 4.45-4.30 (m, 2H), 4.19 – 4.02 (m, 3H), 3.73 (d, *J* = 16.0 Hz, 1H), 3.09 – 2.97 (m, 2H), 2.92 (d, *J* = 7.9 Hz, 2H), 2.68 (dd, *J* = 16.1, 8.8 Hz, 2H), 2.29 – 2.08 (m, 2H), 2.09 –1.96 (m, 2H), 1.83 (m, 2H), 1.69 – 1.47 (m, 2H), 1.43 – 1.26 (m, 2H), 1.18 (m, 2H). **^{13}C NMR** (100 MHz, CD_3OD): δ 175.0, 174.6, 174.5, 172.8, 172.0, 158.6, 157.3, 142.3, 131.5, 129.5, 129.5, 128.6, 127.2, 116.4, 58.2, 55.8, 55.5, 54.6, 46.1, 43.2, 41.9, 41.6, 36.6, 33.3, 32.4, 29.2, 29.0, 26.4, 26.1.

cyclo(-Arg^{1}-Arg^{2}-Hch^{3}-Gly^{4}-D-Tyr^{5}-) × 2 TFA (8). **^{1}H NMR** (400 MHz, CD_3OD): δ 7.03 (d, *J* = 8.5 Hz, 2H), 6.71 (d, *J* = 8.5 Hz, 2H), 4.38 – 4.28 (m, 2H), 4.13 – 4.05 (m, 2H), 3.91 (d, *J* = 16.0 Hz, 1H), 3.78 (d, *J* = 16.0 Hz, 1H), 3.27 – 3.13 (m, 2H), 3.03 (t, *J* = 6.8 Hz, 2H), 2.93 – 2.86 (m, 2H), 1.91 – 1.75 (m, 4H), 1.74 – 1.50 (m, 8H), 1.28 – 1.08 (m, 9H), 0.95 – 0.80 (m, 2H). **^{13}C NMR** (100 MHz, CD_3OD): δ 175.6, 174.7, 174.5, 173.0, 172.1, 158.7, 158.7, 157.4, 131.6, 128.7, 116.5, 58.2, 56.9, 55.4, 55.1, 43.4, 41.9, 41.7, 38.8, 36.9, 34.9, 34.6, 34.5, 29.3, 29.1, 28.4, 27.8, 27.5, 26.5, 26.4.

cyclo(-Arg^{1}-Arg^{2}-Bsa^{3}-Gly^{4}-D-Tyr^{5}-) × 2 TFA (9). **^{1}H NMR** (400 MHz, CD_3OD): δ 7.36 – 7.24 (m, 4H), 7.22 – 7.17 (m, 1H), 7.04 (d, *J* = 8.0 Hz, 2H), 6.71 (d, *J* = 8.0 Hz, 2H), 6.48 (d, *J* = 15.7 Hz, 1H), 6.24 – 6.13 (m, 1H), 4.38 – 4.24 (m, 3H), 4.09 (dd, *J* = 11.3, 3.2 Hz, 1H), 4.04 (d, *J* = 15.9 Hz, 1H), 3.69 (d, *J* = 15.9 Hz, 1H), 3.10 – 2.97 (m, 4H), 2.91 (d, *J* = 8.1 Hz, 2H), 2.76 (t, *J* = 7.2 Hz, 2H), 1.90 – 1.63 (m, 3H), 1.51 (m, 3H), 1.21 – 1.08 (m, 2H). **^{13}C NMR** (100 MHz, CD_3OD): δ 173.2, 173.1, 173.1, 171.3, 170.6, 157.2, 157.1, 155.8, 137.1, 133.0, 130.0, 128.2, 127.2, 127.0, 125.7, 124.9, 115.0, 56.6, 54.5, 54.5, 53.4, 42.0, 40.4, 40.1, 35.3, 35.3, 32.9, 28.0, 27.9, 27.6, 27.5, 24.9, 24.8.

cyclo(-Arg^{1}-Arg^{2}-1-Nal^{3}-Gly^{4}-D-Tyr^{5}-) × 2 TFA (10). **^{1}H NMR** (400 MHz, CD_3OD): δ 8.15 (d, *J* = 8.4 Hz, 1H), 7.87 (d, *J* = 8.0 Hz, 1H), 7.81 – 7.70 (m, 1H), 7. 52 (dt, *J* = 14.7 Hz, 2H), 7.41-7.37 (m, 2H), 7.03 (d, *J* = 8.5 Hz, 2H), 6.71 (d, *J* = 8.5 Hz, 2H), 4.64 (t, *J* = 7.5 Hz, 1H), 4.35 (t, *J* = 8.1 Hz, 1H), 4.14 (t, *J* = 7.6 Hz, 1H), 4.10 – 3.98 (m, 2H), 3.68 – 3.57 (m, 3H), 3.18 – 3.01 (m, 4H), 2.90 (d, *J* = 8.7 Hz, 2H), 1.88 – 1.78 (m, 1H), 1.76 – 1.67 (m, 2H), 1.50 – 1.26 (m, 3H), 1.21 – 1.09 (m, 2H). **^{13}C NMR** (100 MHz, CD_3OD): δ 173.2, 173.1, 173.1, 171.3, 170.5, 157.2, 157.1, 155.8, 134.0, 133.2, 131.9, 130.0, 128.5, 127.3, 127.2, 127.2, 125.9, 125.3, 124.9, 123.1, 115.0, 56.5, 55.3, 54.5, 53.5, 42.1, 40.4, 40.1, 35.4, 35.4, 32.2, 27.9, 27.5, 24.8, 24.7.

cyclo(-Arg^{1}-Arg^{2}-Pph^{3}-Gly^{4}-D-Tyr^{5}-) × 2 TFA (11). **^{1}H NMR** (400 MHz, CD_3OD): δ 7.55 (m, 4H), 7.40 (t, *J* = 7.6 Hz, 2H), 7.31 (d, *J* = 7.7 Hz, 3H), 7.03 (d, *J* = 8.4 Hz, 2H), 6.71 (d, *J* = 8.4 Hz, 2H), 4.50 (t, *J* = 7.7 Hz, 1H), 4.34 (m, 1H), 4.24 (m, 1H), 4.10 – 3.98 (m, 2H), 3.71 (d, *J* = 15.7 Hz, 1H), 3.27 – 3.07 (m, 4H), 3.02 (t, *J* = 6.5 Hz, 2H), 2.97 – 2.83 (m, 2H), 1.92 – 1.70 (m, 3H), 1.50 – 1.35 (m, 3H), 1.19 – 1.06 (m, 2H). **^{13}C NMR** (100 MHz, CD_3OD): δ 173.2, 173.2, 173.1, 171.4, 170.5, 157.2, 157.1, 155.9, 140.5, 139.5, 136.5, 130.0, 129.4, 128.5, 127.1, 126.9, 126.6, 126.4, 115.0, 56.7, 56.1, 54.2, 53.6, 42.0, 40.4, 40.2, 35.4, 34.7, 28.0, 27.6, 24.9, 24.8.

cyclo(-Arg^1-Arg^2-Bph^3-Gly^4-D-Tyr^5-) × 2 TFA (12). **^{1}H NMR** (400 MHz, CD_3OD): δ 7.77 – 7.66 (m, 4H), 7.62 (m, 1H), 7.51 (t, *J* = 4.0, 8.0 Hz, 2H), 7.39 (d, *J* = 8.0 Hz, 2H), 7.00 (d, *J* = 8.0 Hz, 2H), 6.70 (d, *J* = 8.0 Hz, 2H), 4.53 (t, *J* = 7.8 Hz, 1H), 4.31 (dd, *J* = 9.6, 6.7 Hz, 1H), 4.19 (t, *J* = 7.5 Hz, 1H), 4.11 – 4.00 (m, 2H), 3.65 (d, *J* = 15.7 Hz, 1H), 3.17 – 3.03 (m, 3H), 3.05 – 2.95 (m, 3H), 2.92 – 2.81 (m, 2H), 1.88 – 1.77 (m, 1H), 1.78 – 1.63 (m, 2H), 1.46 – 1.26 (m, 3H), 1.18 – 1.05 (m, 2H). **^{13}C NMR** (100 MHz, CD_3OD): δ 198.7, 174.9, 174.7, 174.5, 172.9, 172.2, 158.8, 158.8, 157.5, 144.7, 139.0, 137.5, 134.1, 131.7, 131.5, 131.2, 130.7, 129.7, 128.7, 116.6, 58.4, 57.1, 56.0, 55.1, 43.5, 42.0, 41.8, 36.9, 36.8, 36.5, 29.6, 29.2, 26.4, 26.4.

cyclo(-Arg^1-Arg^2-Ala^3-Gly^4-D-Tyr^5-)× 2 TFA (13). **^{1}H NMR** (400 MHz, CD_3OD): δ ^{1}H NMR (400 MHz, CD_3OD) δ 7.06 (d, *J* = 8.4 Hz, 2H), 6.73 (d, *J* = 8.4 Hz, 2H), 4.42 – 4.15 (m, 3H), 4.13 (dd, *J* = 11.4, 3.8 Hz, 1H), 4.03 (d, *J* = 15.8 Hz, 1H), 3.73 (d, *J* = 15.8 Hz, 1H), 3.28 – 3.17 (m, 2H), 3.08 – 2.99 (m, 2H), 2.96 – 2.88 (m, 2H), 1.99 – 1.74 (m, 3H), 1.69 – 1.44 (m, 3H), 1.41 (d, *J* = 7.1 Hz, 3H), 1.33 – 0.94 (m, 2H). **^{13}C NMR** (100 MHz, CD_3OD): δ 175.9, 174.7, 174.6, 172.7, 172.2, 158.7, 157.4, 131.6, 128.5, 116.5, 58.3, 55.4, 54.9, 51.7, 43.3, 41.9, 41.7, 36.8, 29.3, 29.1, 26.4, 26.3, 15.8.

cyclo(-Arg^1-Arg^2-2-Nal^3-Gly^4-D-Phe^5-) × 2 TFA (14). **^{1}H NMR** (400 MHz, CD_3OD): δ 7.83 – 7.74 (m, 3H), 7.70 (s, 1H), 7.49 – 7.36 (m, 3H), 7.30 – 7.16 (m, 5H), 4.60 (dd, *J* = 9.0,6.7 Hz, 1H), 4.43 (t, *J* = 8.05 Hz, 1H), 4.16 (t, *J* = 7.62 Hz, 1H), 4.09-4.00 (m, 2H), 3.70 (d, *J* = 15.71 Hz, 1H), 3.37 – 3.33 (m, 2H), 3.04 – 2.93 (m, 6H), 1.86 – 1.74 (m, 1H), 1.75 – 1.64 (m, 2H), 1.49 – 1.38 (m, 1H), 1.37 – 1.17 (m, 2H), 1.16 – 1.04 (m, 2H). **^{13}C NMR** (100 MHz, CD_3OD): δ 174.6, 174.5, 174.3, 172.7, 171.9, 158.5, 158.5, 137.8, 136.2, 134.9, 133.8, 130.4, 129.6, 129.1, 128.9, 128.9, 128.6, 128.6, 128.5, 128.4, 127.9, 127.2, 126.7, 57.7, 57.2, 55.8, 55.1, 43.5, 41.7, 41.5, 37.6, 36.7, 29.3, 28.9, 26.2, 26.0.

cyclo(-Arg^1-Arg^2-2-Nal^3-Gly^4-Aic^5-) × 2 TFA (15). **^{1}H NMR** (400 MHz, CD_3OD): δ 7.85 – 7.75 (m, 3H), 7.72 (s, 1H), 7.49 – 7.38 (m, 3H), 7.27 – 7.15 (m, 4H), 4.71 (m, 1H), 4.49 – 4.37 (m, 1H), 3.96-3.88 (m, 1H), 3.86 – 3.75 (m, 2H), 3.57 (d, *J* = 14.0 Hz, 1H), 3.46 – 3.32 (m, 3H), 3.28 – 3.07 (m, 4H), 3.00 – 2.88 (m, 2H), 1.93 – 1.72 (m, 4H), 1.67 – 1.46 (m, 2H), 1.36 – 1.24 (m, 1H), 1.24 – 1.10 (m, 1H). **^{13}C NMR** (100 MHz, CD_3OD): δ 174.5, 172.9, 172.6, 172.1, 170.1, 157.1, 157.0, 140.6, 138.7, 134.9, 133.5, 132.4, 127.7, 127.5, 127.2, 127.1, 127.0, 126.8, 126.5, 125.8, 125.3, 124.2, 124.1, 67.3, 56.5, 55.0, 53.0, 43.4, 42.4, 41.4, 40.3, 40.3, 36.3, 28.5, 26.9, 24.9, 24.8.

cyclo(-Arg¹-Arg²-2-Nal³-Gly⁴-D-Tic⁵-) × 2 TFA (16). **^{1}H NMR** (400 MHz, CD_3OD): δ 7.82 – 7.72 (m, 3H), 7.73 (s, 1H), 7.47 – 7.31 (m, 3H), 7.27 – 7.17 (m, 4H), 4.72 (t, *J* = 8.00 Hz, 1H), 4.65 (d, *J* = 14.5 Hz, 1H), 4.52 (d, *J* = 14.5 Hz, 1H), 4.39 – 4.25 (m, 3H), 4.21 – 4.11 (m, 2H), 3.33 (d, *J* = 8.02 Hz, 2H), 3.19 (t, *J* = 6.43 Hz, 2H), 3.07 – 3.02 (m, 2H), 2.91 – 2.83 (m, 2H), 2.08 – 1.96 (m, 1H), 1.77 – 1.61 (m, 5H), 1.31 – 1.16 (m, 1H), 1.15 – 1.06 (m, 1H). **^{13}C NMR** (100 MHz, CD_3OD) δ 175.4, 175.3, 174.2, 172.5, 170.4, 158.7, 158.4, 136.4, 135.4, 134.9, 134.9, 133.8, 129.2, 128.9, 128.6, 128.5, 128.3, 128.3, 128.2, 127.2, 127.0, 126.7, 58.8, 57.1, 56.2, 54.8, 46.4, 42.7, 41.8, 41.7, 36.1, 31.8, 29.5, 29.4, 26.6, 25.9.

cyclo(-Arg¹-Arg²-2-Nal³-Gly⁴-*trans*-Ppr⁵-) × 2 TFA (17). Obtained as a mixture of the two diastereomers in a ratio of 47:53 (as determined by analytical HPLC) after purification, and not characterized by NMR.

cyclo(-Arg¹-Arg²-2-Nal³-Gly⁴-*cis*-Ppr⁵-) × 2 TFA (18). Obtained as a mixture of the two diastereomers in a ratio of 68:32 (as determined by analytical HPLC) after purification, and not characterized by NMR.

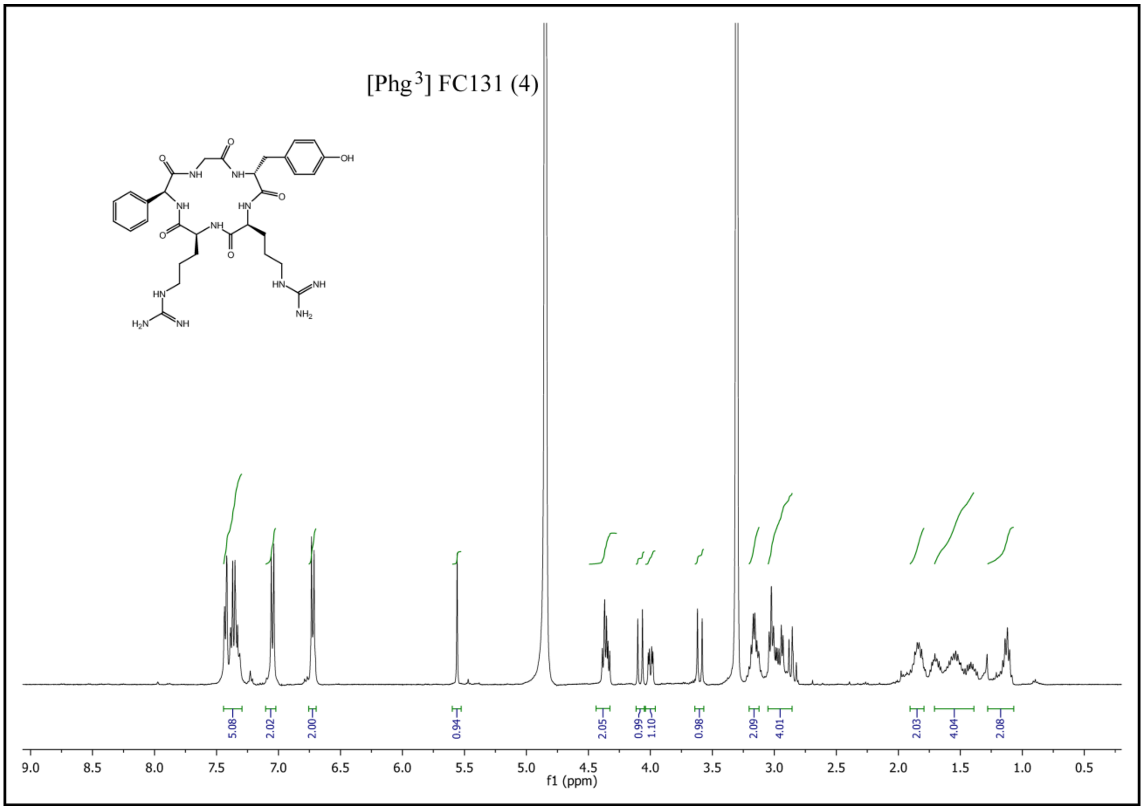
cyclo(-Arg¹-Arg²-2-Nal³-Gly⁴-D-Pic⁵-) × 2 TFA (19). **^{1}H NMR** (400 MHz, CD_3OD): δ 7.87 – 7.77 (m, 3H), 7.75 (s, 1H), 7.52 – 7.37 (m, 3H), 4.73 (t, *J* = 7.96 Hz, 1H), 4.38 – 4.26 (m, 2H), 4.27 – 4.17 (m, 2H), 3.93 (d, *J* = 16,4 Hz, 1H), 3.65 – 3.56 (m, 2H), 3.38 (d, *J* = 8.10 Hz, 2H), 3.21 (t, *J* = 6.44 Hz, 2H), 2.95 (m, 2H), 2.24 – 2.14 (m, 2H), 2.11 – 1.94 (m, 4H), 1.82 – 1.58 (m, 6H), 1.34 – 1.11 (m, 2H). **^{13}C NMR** (100 MHz, CD_3OD): δ 175.6, 175.2, 174.6, 173.6, 172.1, 157.9, 157.2, 135.5, 134.3, 133.3, 129.4, 129.0, 128.7, 128.5, 128.3, 127.7, 127.2, 58.6, 57.1, 56.1, 55.1, 54.4, 44.6, 44.0, 41.5, 41.3, 37.0, 28.3, 28.3, 26.2, 25.7, 24.9, 20.4.

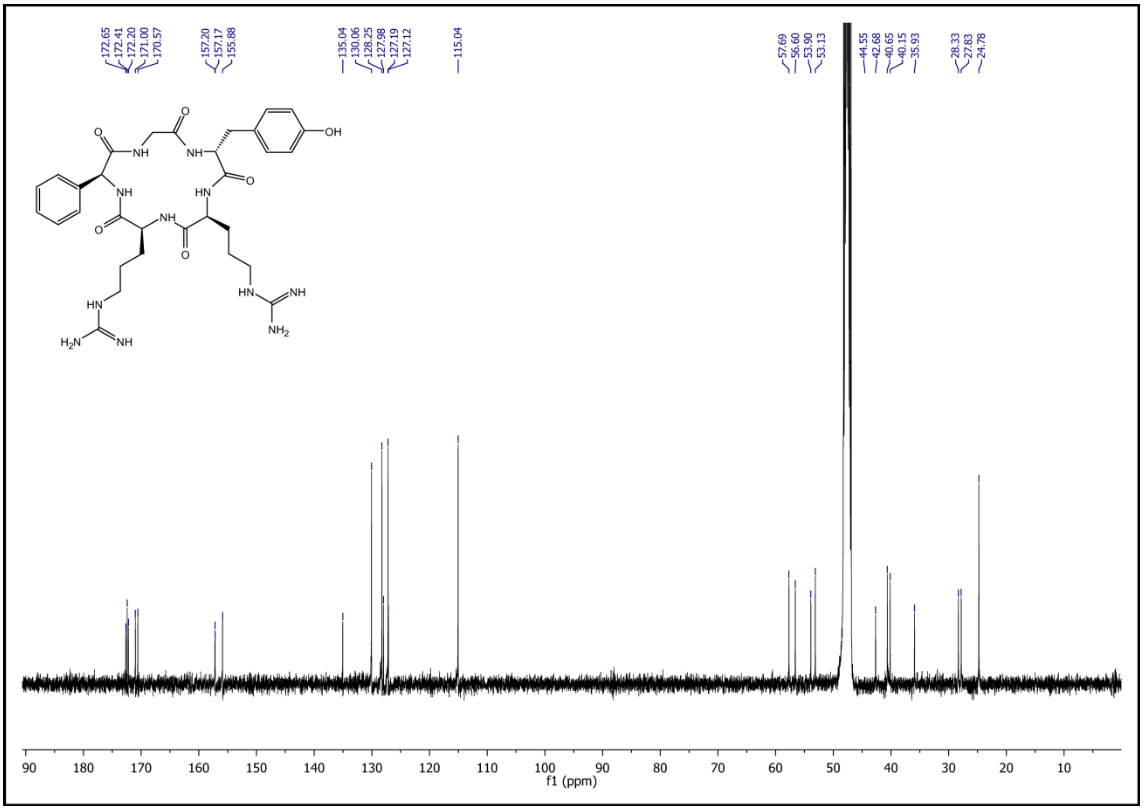
cyclo(-Arg¹-Arg²-2-Nal³-Gly⁴-D-Pro⁵-) × 2 TFA (20). **^{1}H NMR** (400 MHz, CD_3OD): δ 7.88 – 7.80 (m, 3H), 7.77 (s, 1H), 7.53-7.43 (m, 3H), 4.75 (t, *J* = 8.0 Hz, 1H), 4.41 – 4.28 (m, 2H), 4.28 – 4.17 (m, 2H), 3.90 (d, *J* = 16.4 Hz, 1H), 3.66 – 3.56 (m, 2H), 3.39 (d, *J* = 12.4 Hz, 2H), 3.22 (t, *J* = 6.4 Hz, 2H), 2.99 – 2.92 (m, 2H), 2.28 – 2.11 (m, 2H), 2.15 – 1.92 (m, 3H), 1.83 – 1.63 (m, 5H), 1.33 – 1.08 (m, 2H). **^{13}C NMR** (100 MHz, CD_3OD): δ 174.3, 174.0, 172.9, 172.8, 171.1, 168.1, 157.2, 157.0, 135.0, 133.5, 132.4, 127.7, 127.4, 127.2, 127.1, 126.9, 125.8, 125.3, 61.1, 55.9, 54.6, 54.5, 53.5, 46.0, 41.2, 40.4, 34.5, 28.1, 27.9, 25.2, 25.2, 24.5.

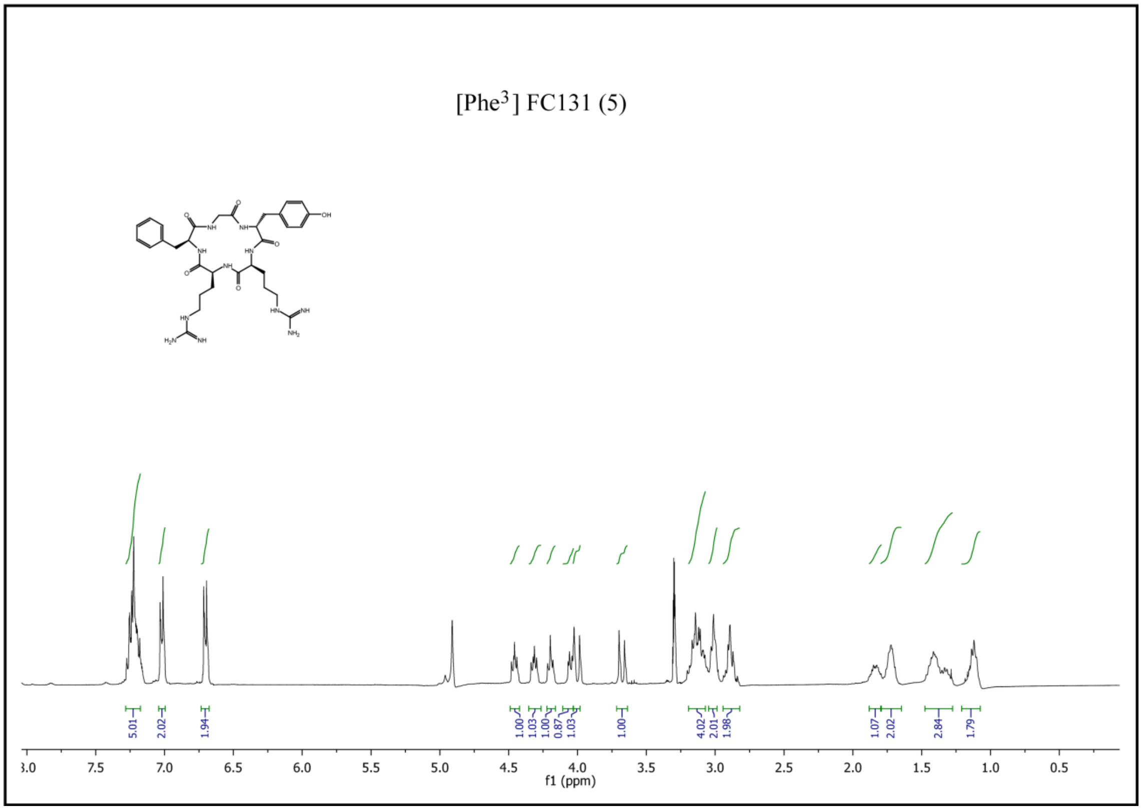
cyclo(-Arg^{1}-Arg^{2}-2-Nal^{3}-Gly^{4}-D-Ala^{5}-) × 2 TFA (21). **^{1}H NMR** (400 MHz, CD_3OD): δ 7.80 – 7.73 (m, 3H), 7.66 (s, 1H), 7.46 – 7.33 (m, 3H), 4.61 (dd, J = 9.1, 6.3 Hz, 1H), 4.38 – 4.30 (m, 1H), 4.30 – 4.22 (m, 1H), 4.05 (t, J = 7.7 Hz, 1H), 3.94 (d, J = 15.7 Hz, 1H), 3.67 (d, J = 15.8 Hz, 1H), 3.35 – 3.14 (m, 4H), 2.98 – 2.88 (m, 2H), 1.96 – 1.85 (m, 1H), 1.76 – 1.54 (m, 5H), 1.35 – 1.31 (m, 1H), 1.27 (d, J = 6.9 Hz, 3H), 1.24 – 1.13 (m, 1H). **^{13}C NMR** (100 MHz, CD_3OD): δ 175.7, 174.9, 174.8, 173.3, 172.0, 158.8, 158.7, 136.3, 135.1, 134.1, 129.3, 129.2, 128.9, 128.7, 127.4, 126.9, 56.9, 56.8, 55.3, 50.9, 44.3, 41.0, 41.9, 37.8, 29.3, 29.2, 26.7, 26.3, 16.7.

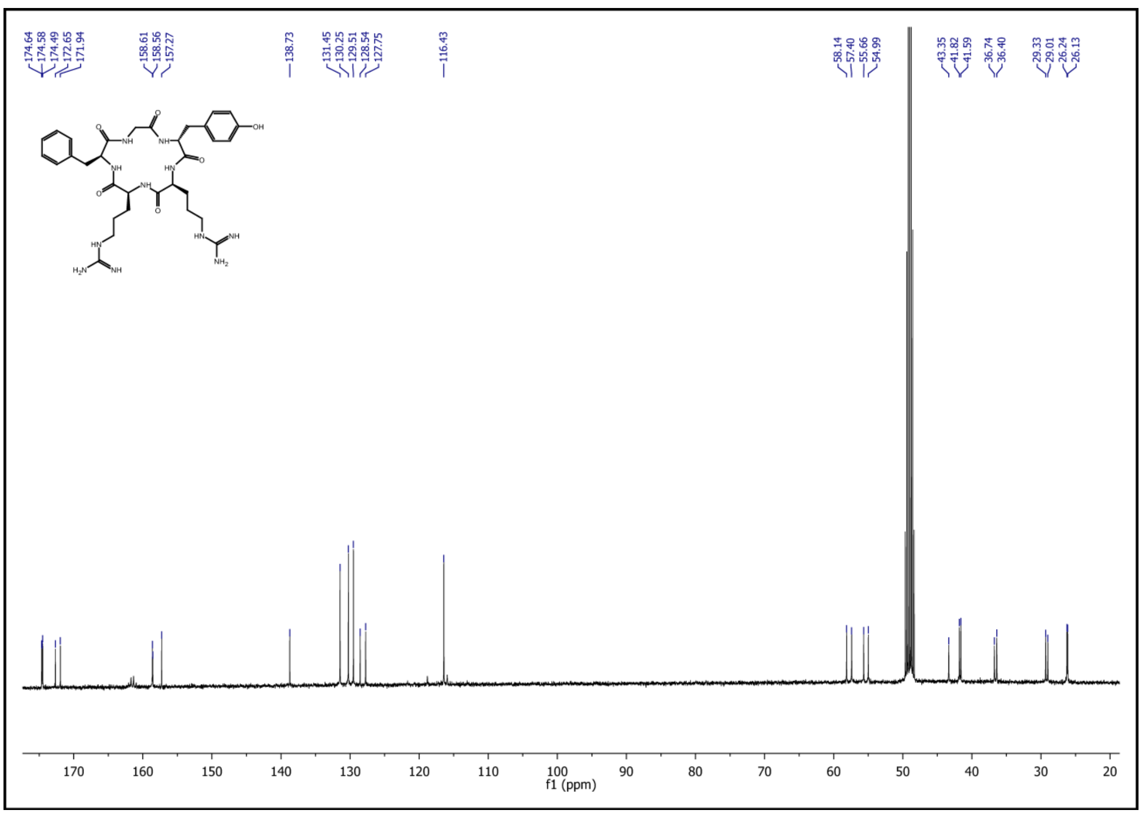
cyclo(-Arg^{1}-Arg^{2}-2-Nal^{3}-Gly^{4}-Gly^{5}-) × 2 TFA (22). **^{1}H NMR** (400 MHz, CD_3OD): δ 7.82 – 7.72 (m, 3H), 7.61 (s, 1H), 7.46 – 7.33 (m, 3H), 4.47 (dd, J = 10.3, 4.8 Hz, 1H), 4.22 – 4.13 (m, 2H), 4.09 – 3.98 (m, 2H), 3.77 (d, J = 15.1 Hz, 1H), 3.58 (d, J = 16.4 Hz, 1H), 3.38 (dd, J = 13.7, 4.9 Hz, 1H), 3.24 – 3.15 (m, 3H), 2.89 – 2.80 (m, 2H), 1.93 – 1.76 (m, 2H), 1.73 – 1.50 (m, 3H), 1.49 – 1.37 (m, 1H), 1.37 – 1.19 (m, 2H). **^{13}C NMR** (100 MHz, CD_3OD): δ 175.1, 174.4, 174.2, 173.0, 172.7, 158.8, 158.6, 136.6, 135.1, 134.1, 129.5, 129.4, 128.9, 128.6, 128.6, 127.5, 126.9, 56.7, 56.5, 55.7, 55.7, 44.7, 43.6, 41.9, 41.8, 37.7, 31.0, 28.7, 26.8, 26.3.

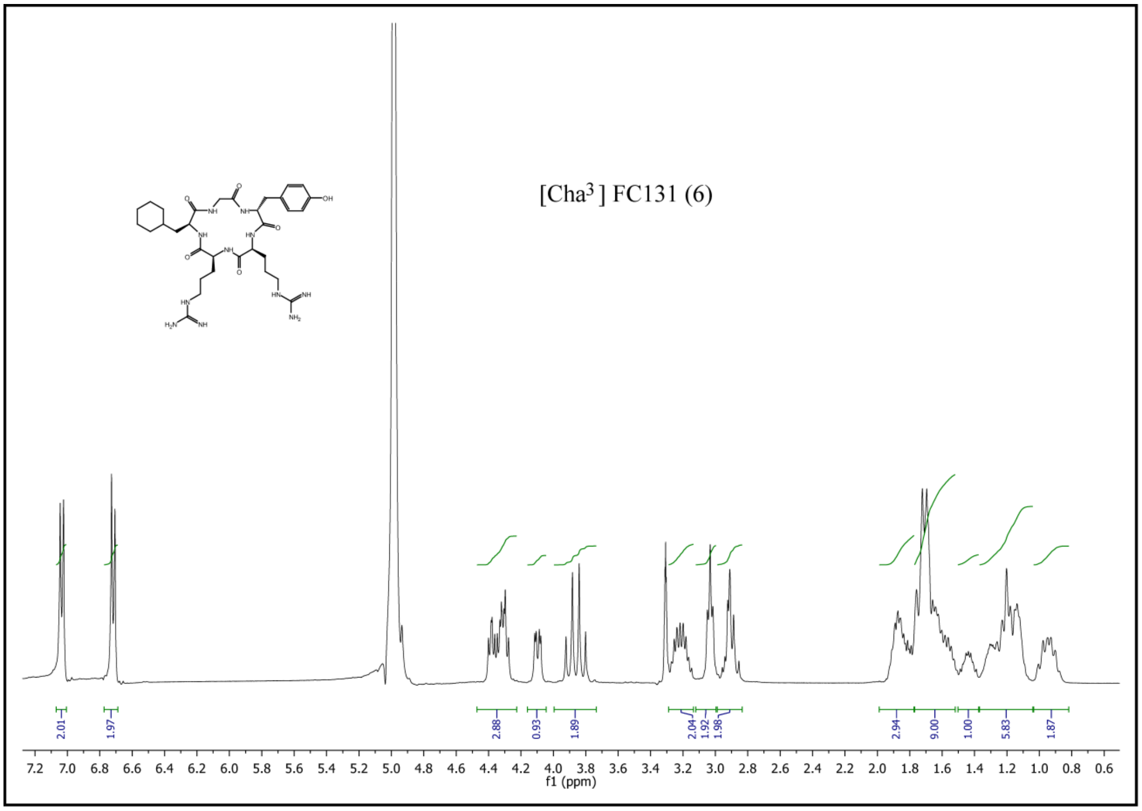
^{1}H and ^{13}C NMR spectra

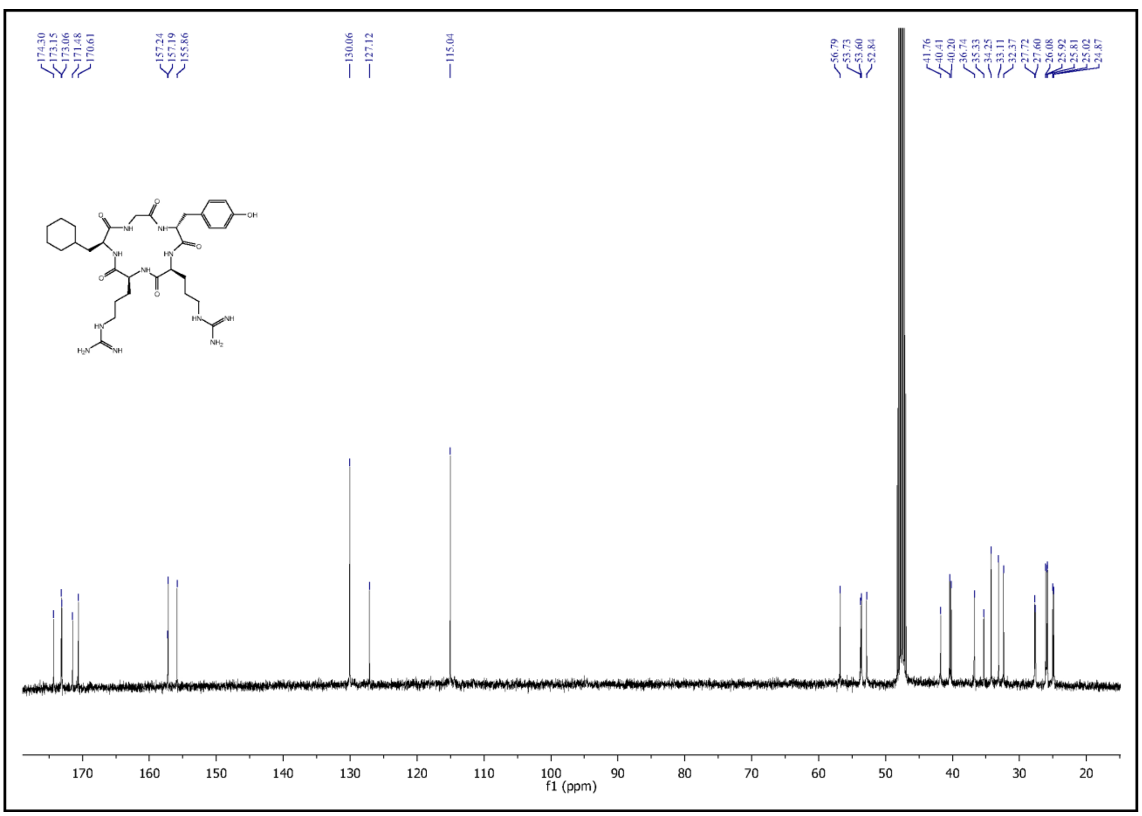




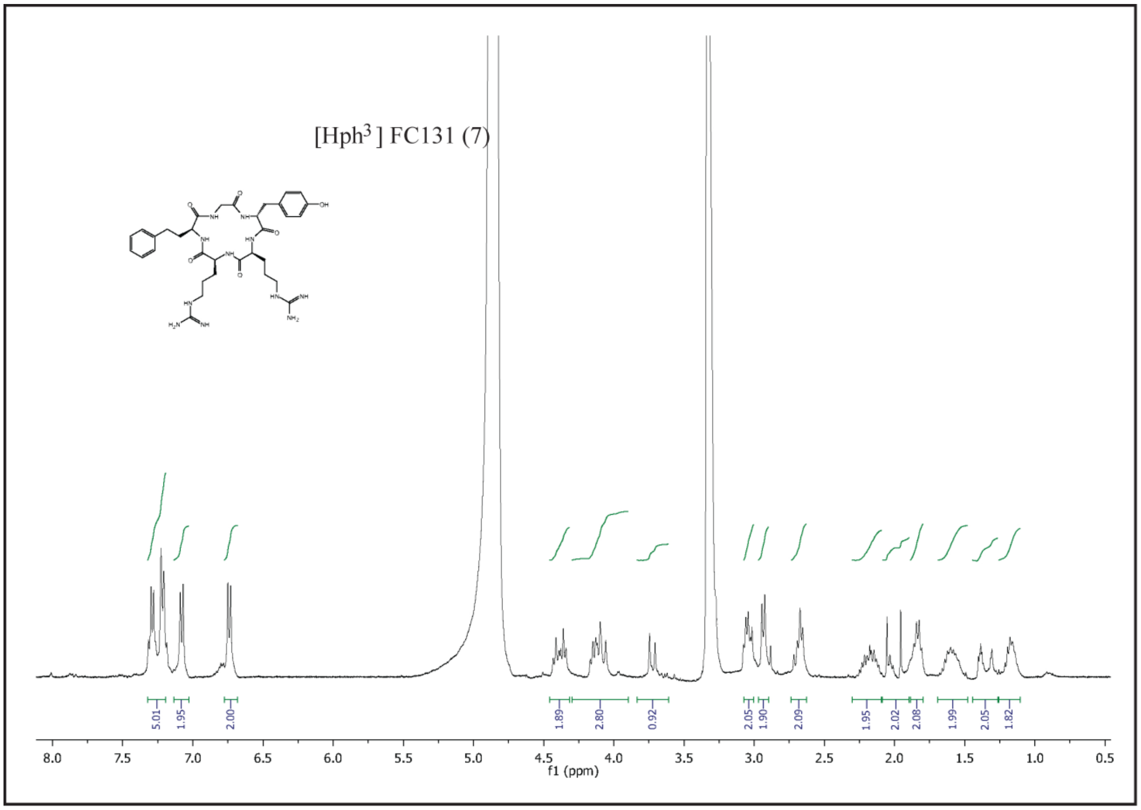

[Phe3] FC131 (5)
f1 (ppm)

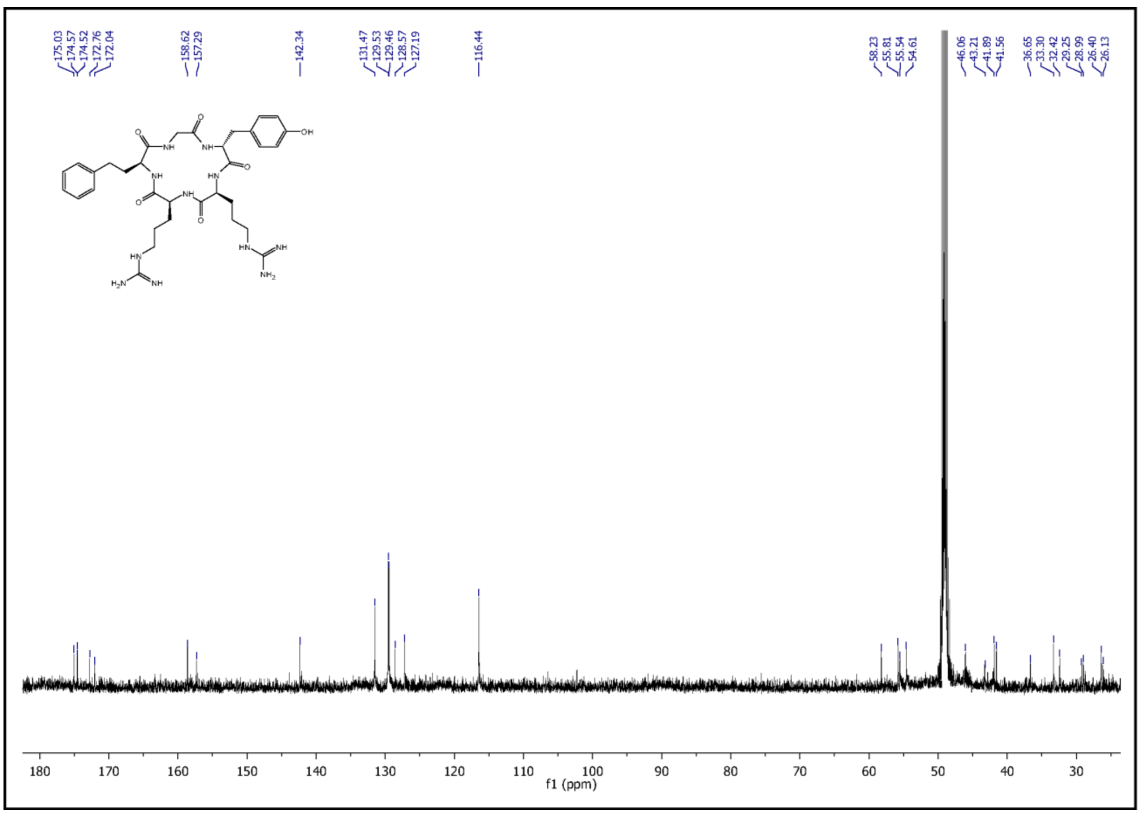

f1 (ppm)

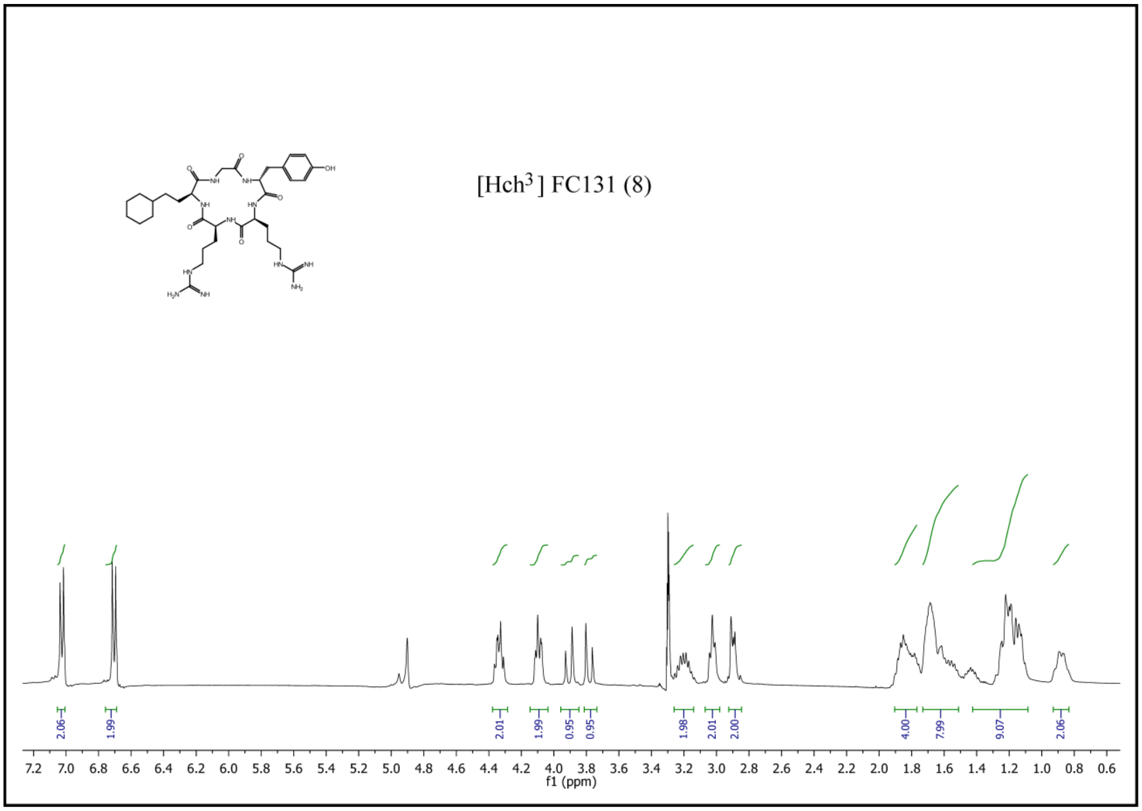

[Cha3] FC131 (6)
f1 (ppm)

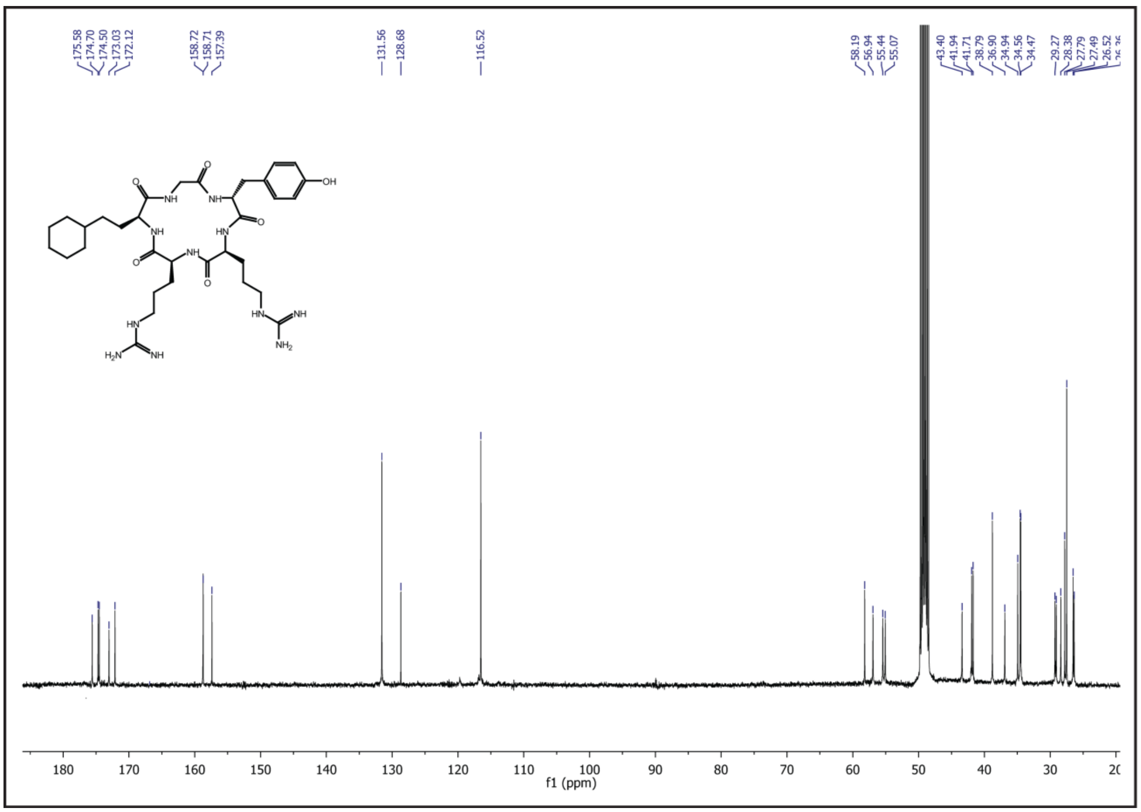

f1 (ppm)

Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry

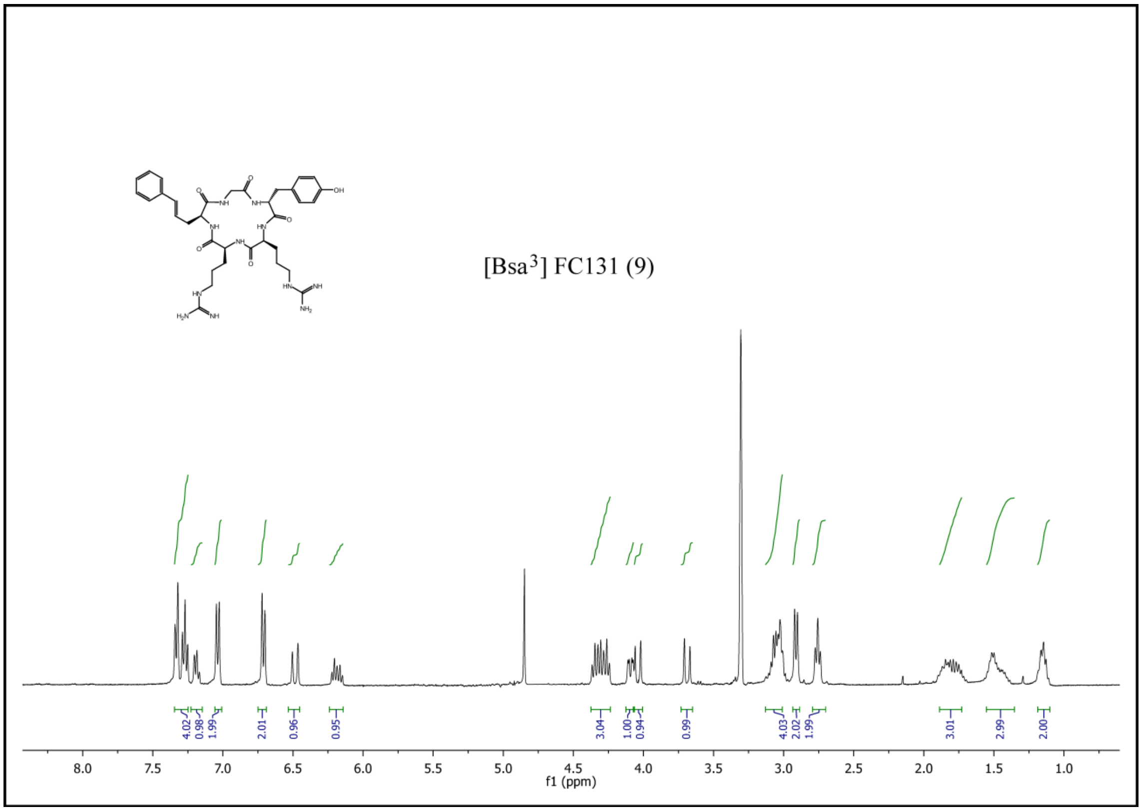


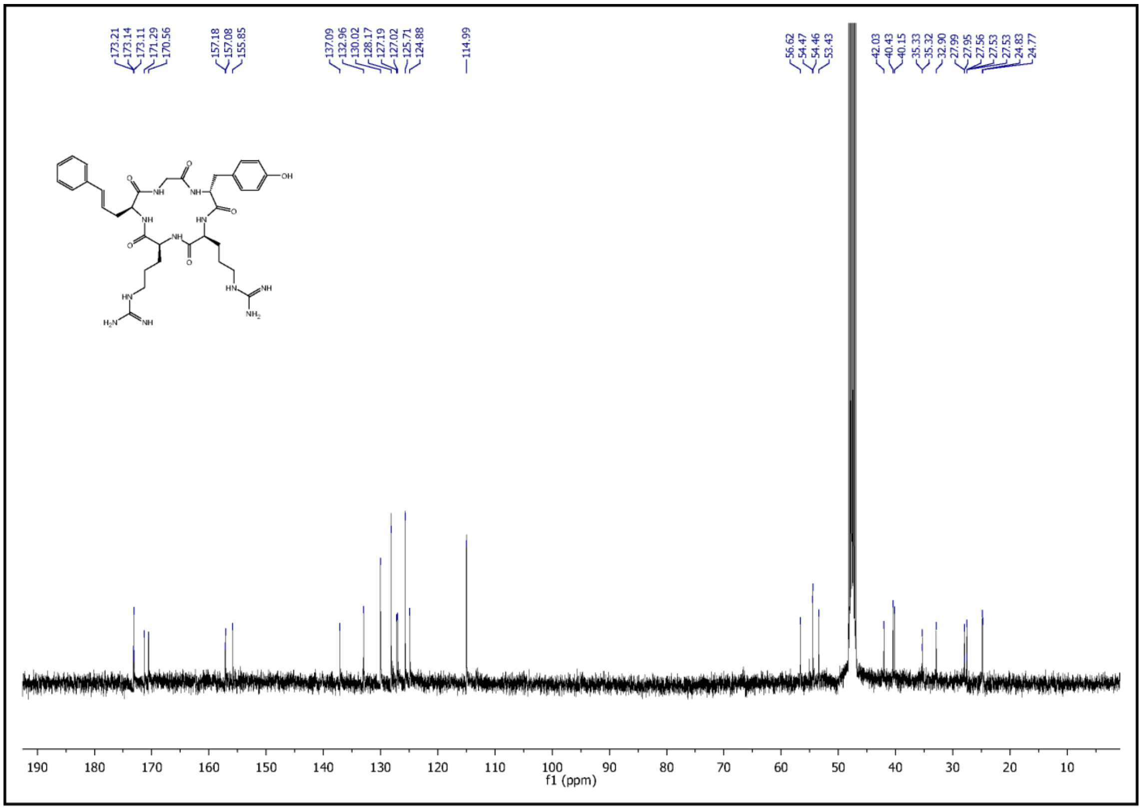


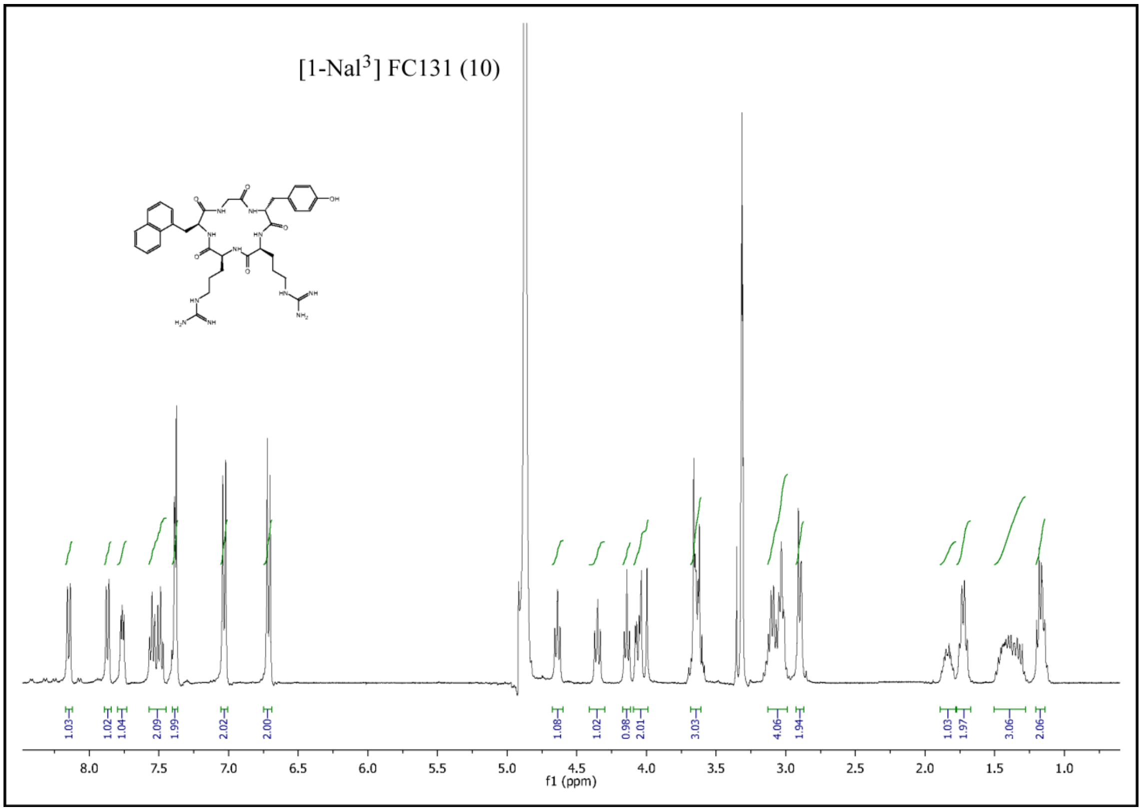

[Hch3] FC131 (8)
f1 (ppm)

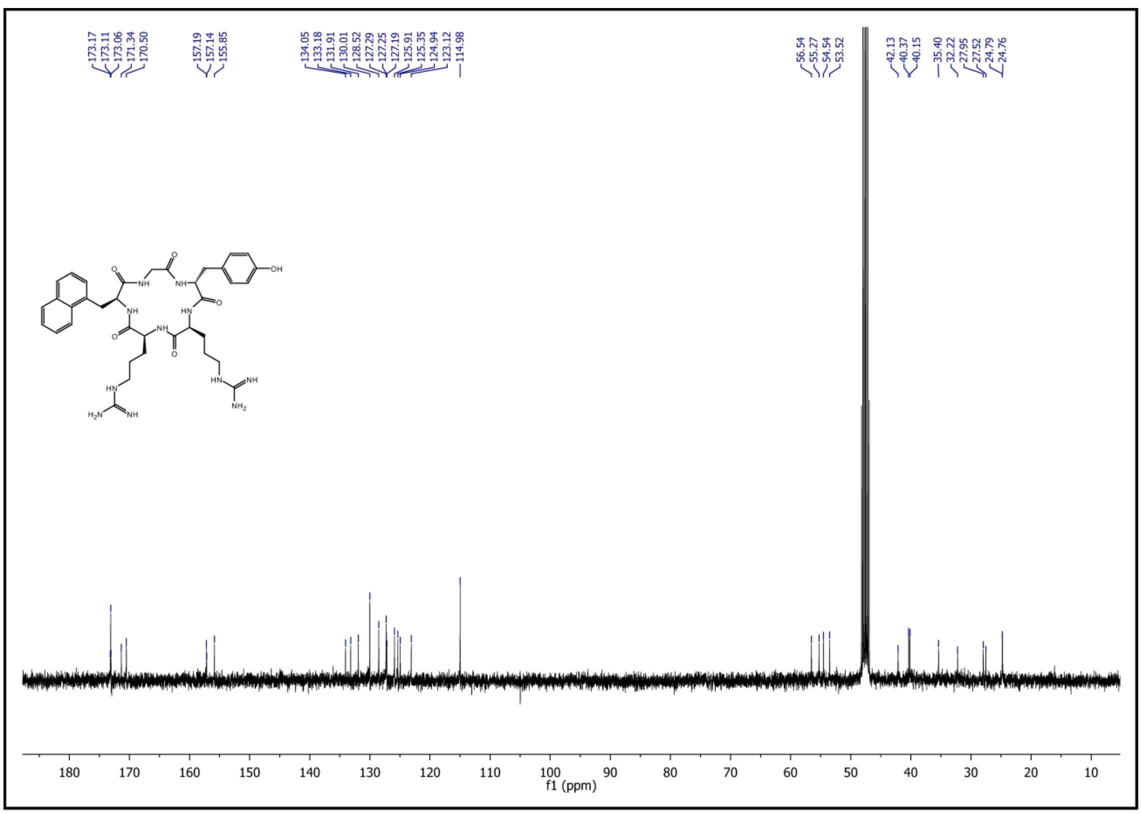

f1 (ppm)

Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry

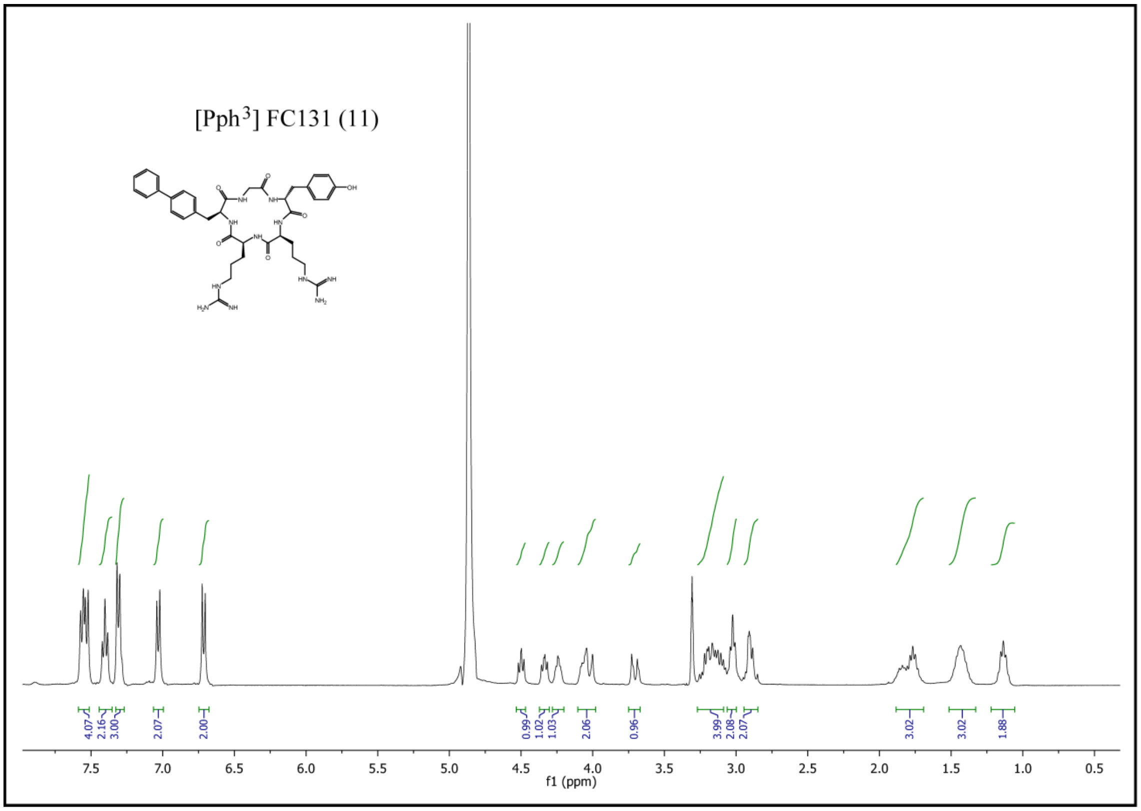


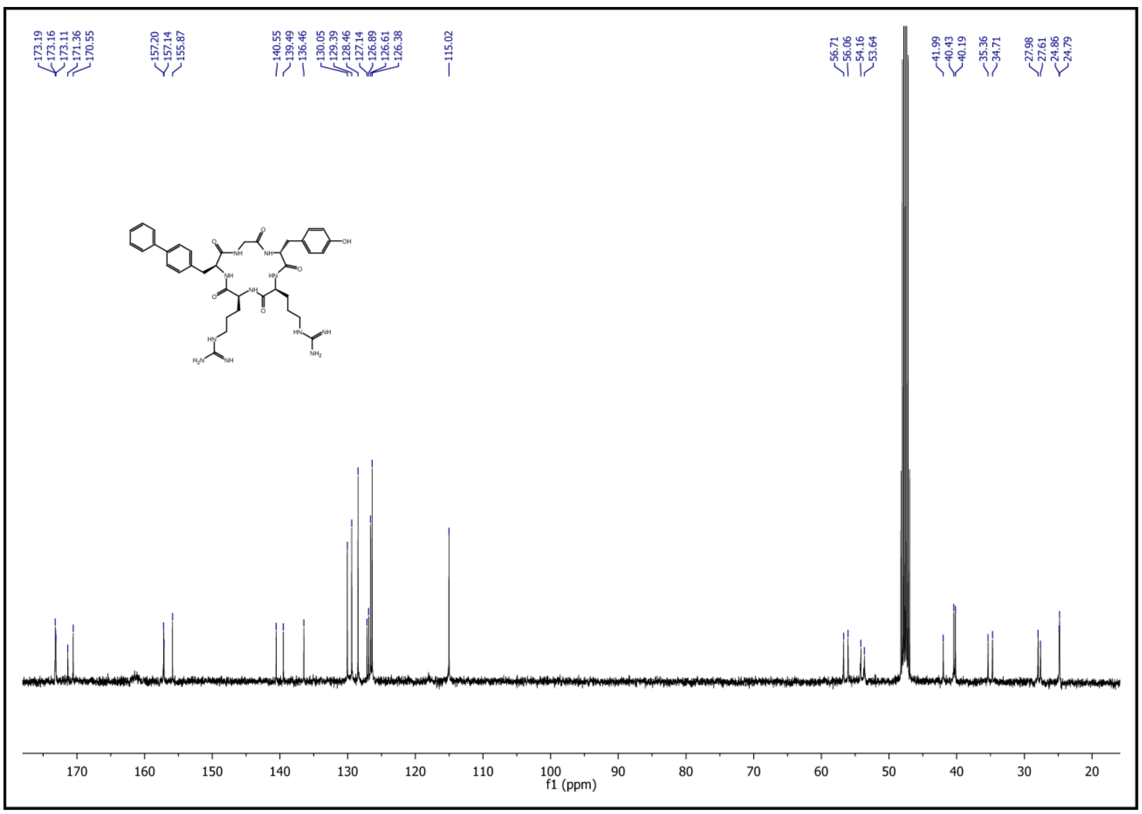



[1-Nal³] FC131 (10)
f1 (ppm)

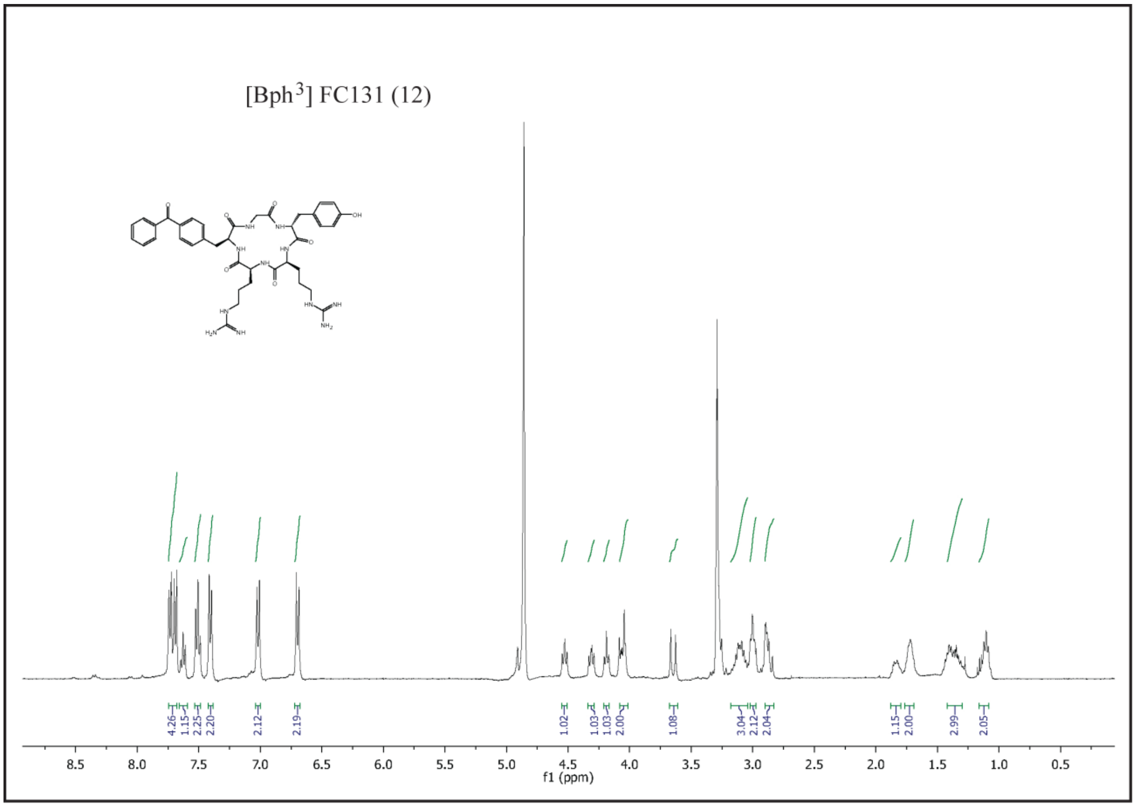

f1 (ppm)

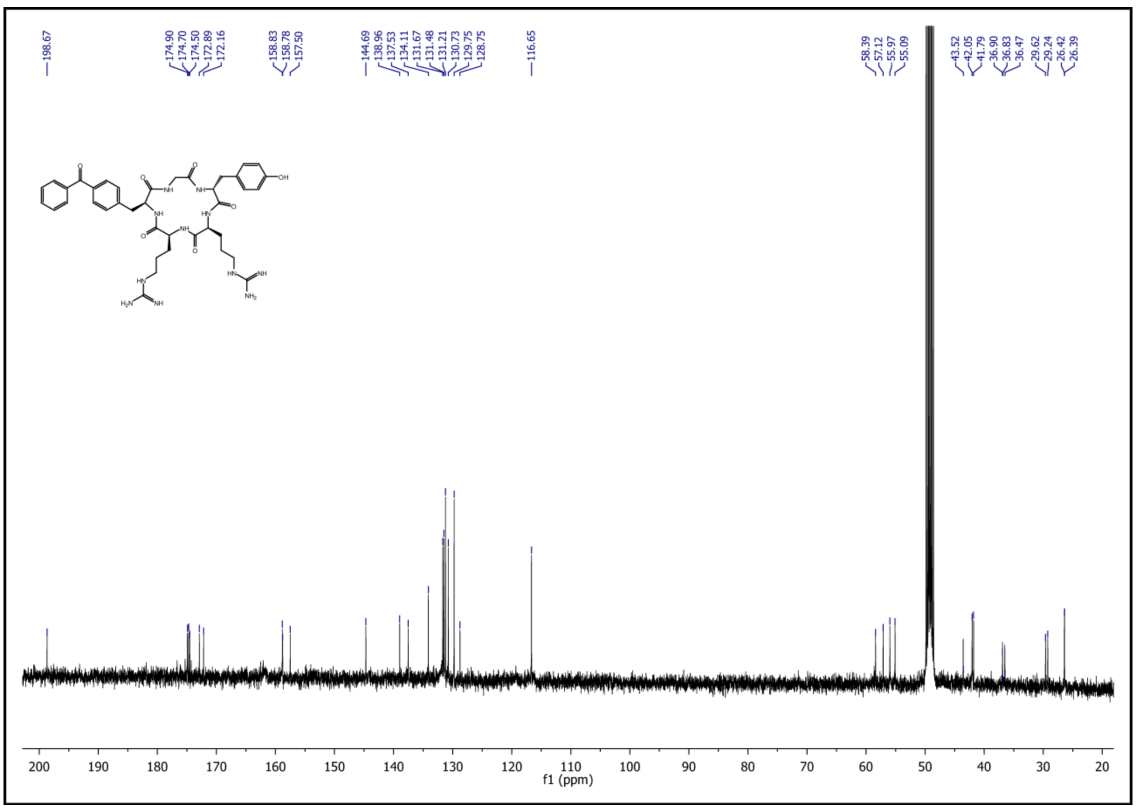
Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry

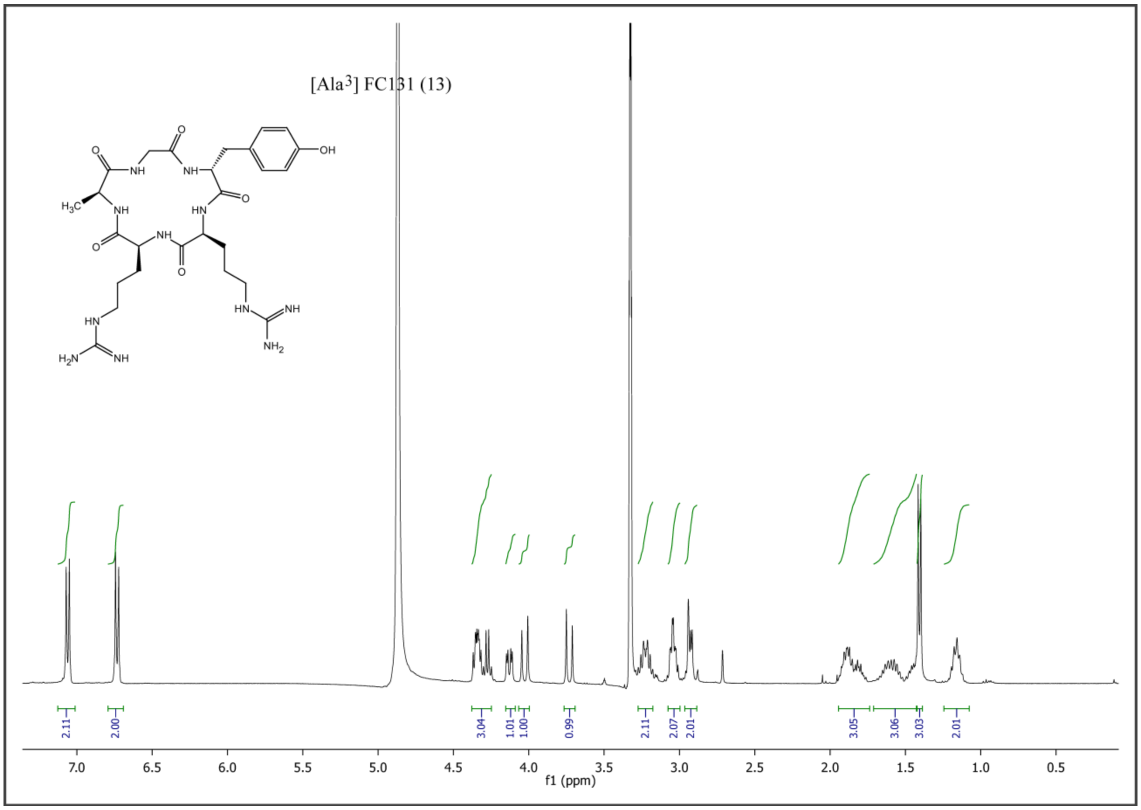


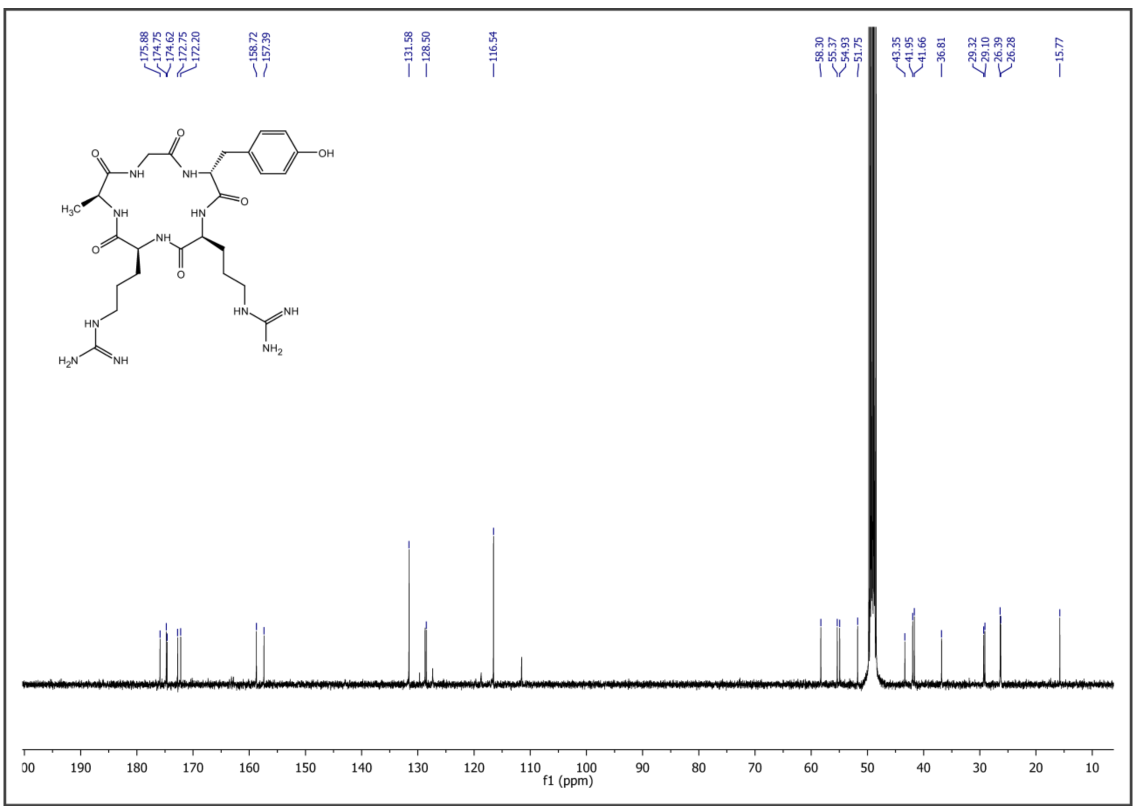


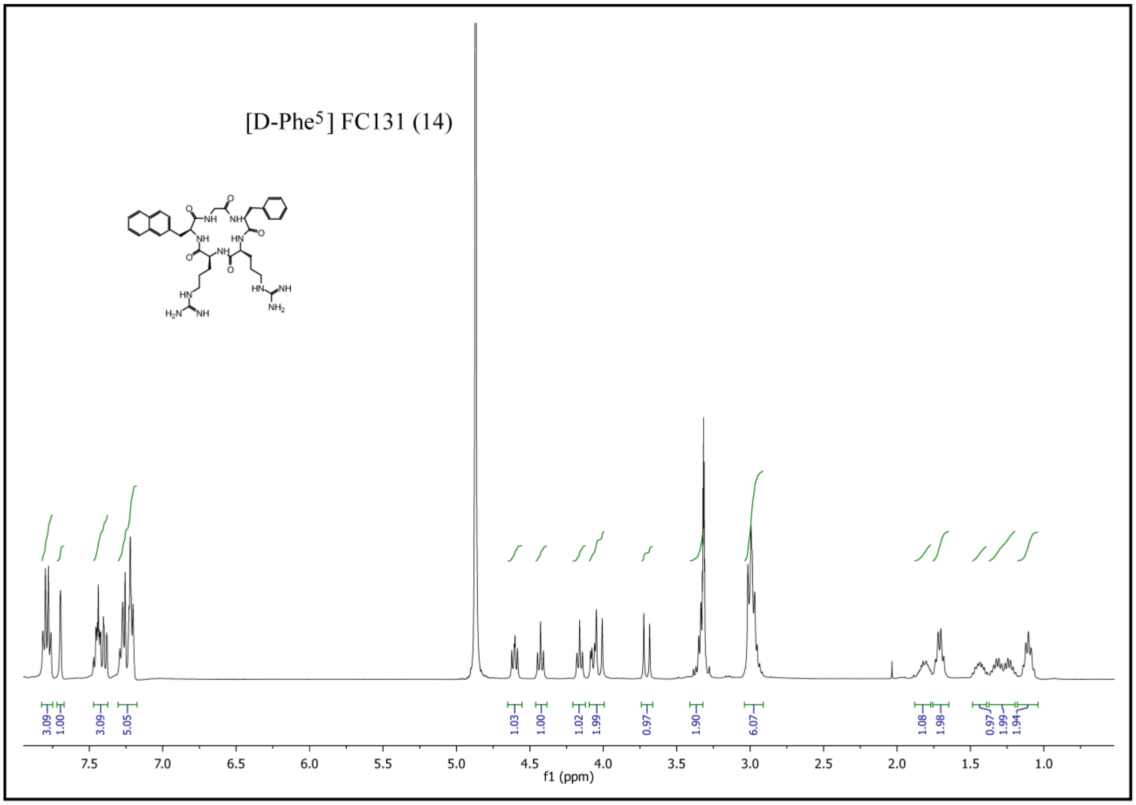
[Bph³] FC131 (12)

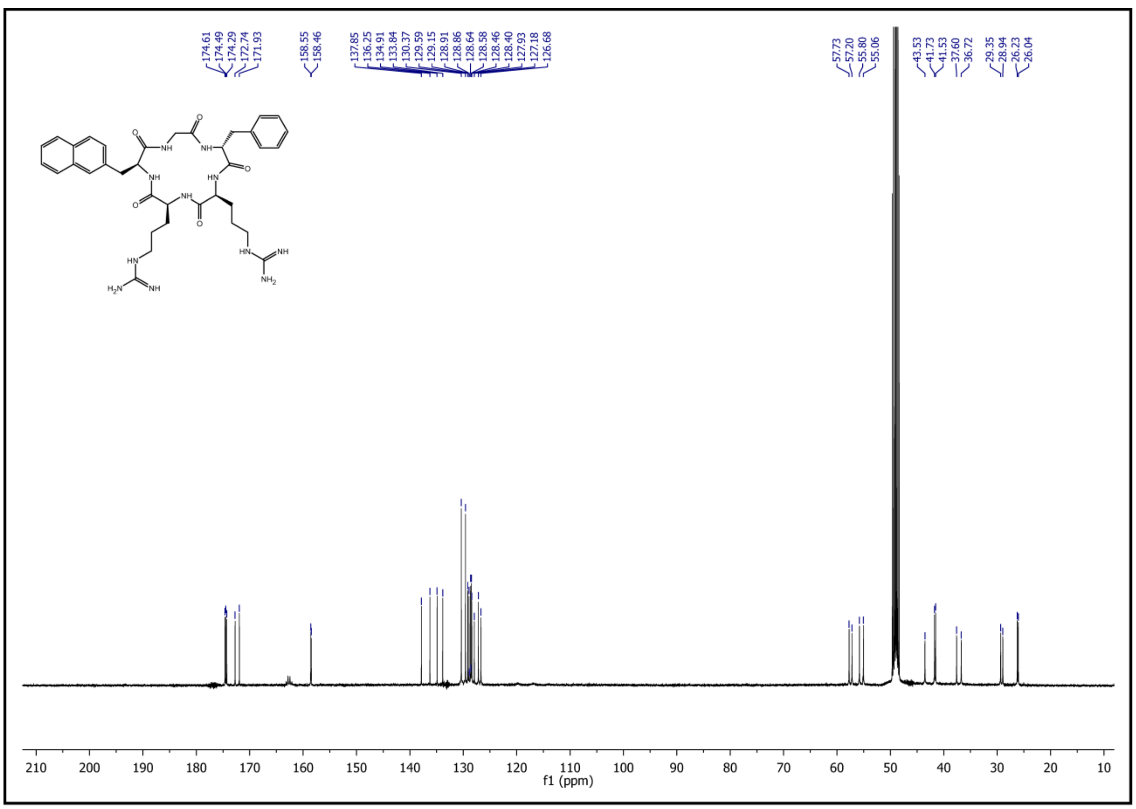


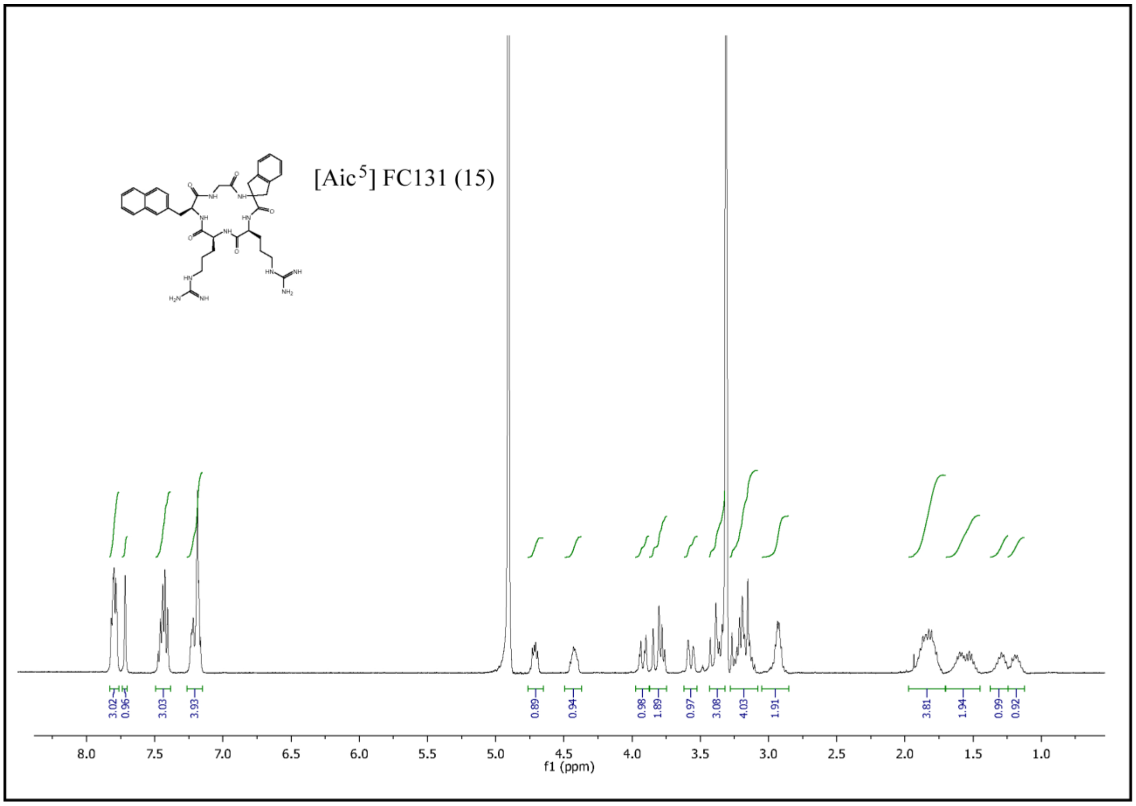


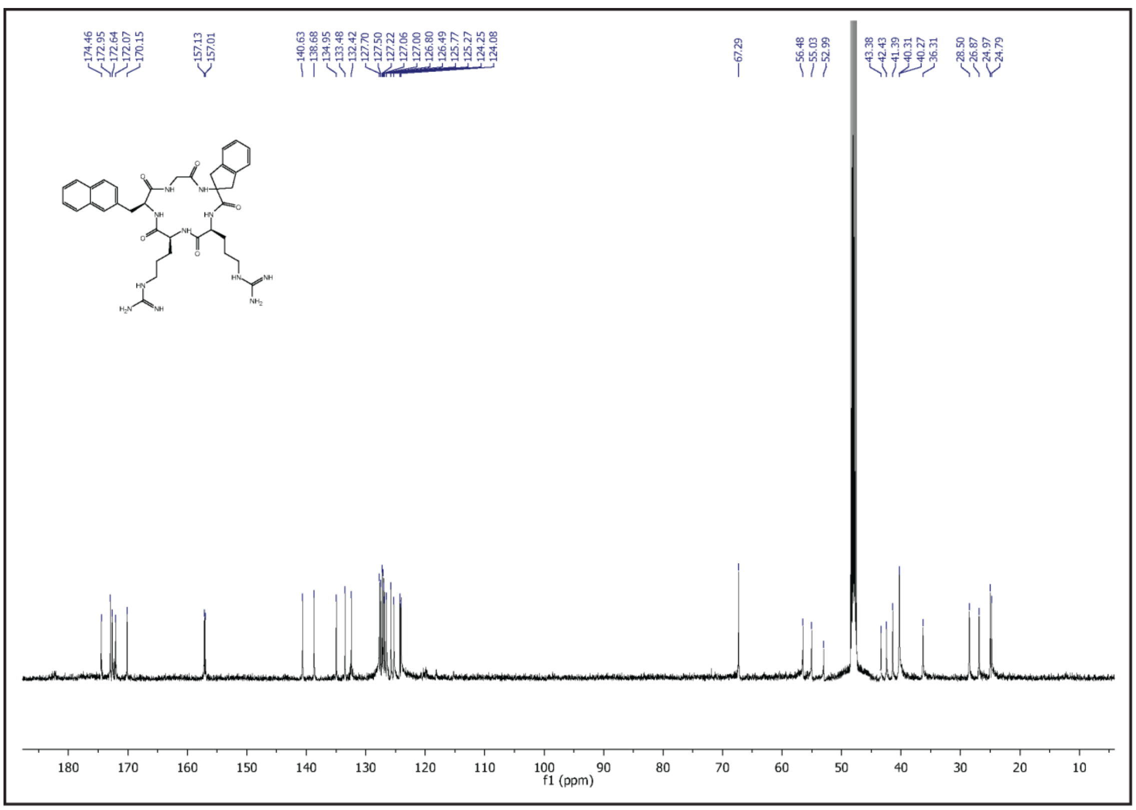

[Ala3] FC131 (13)
f1 (ppm)

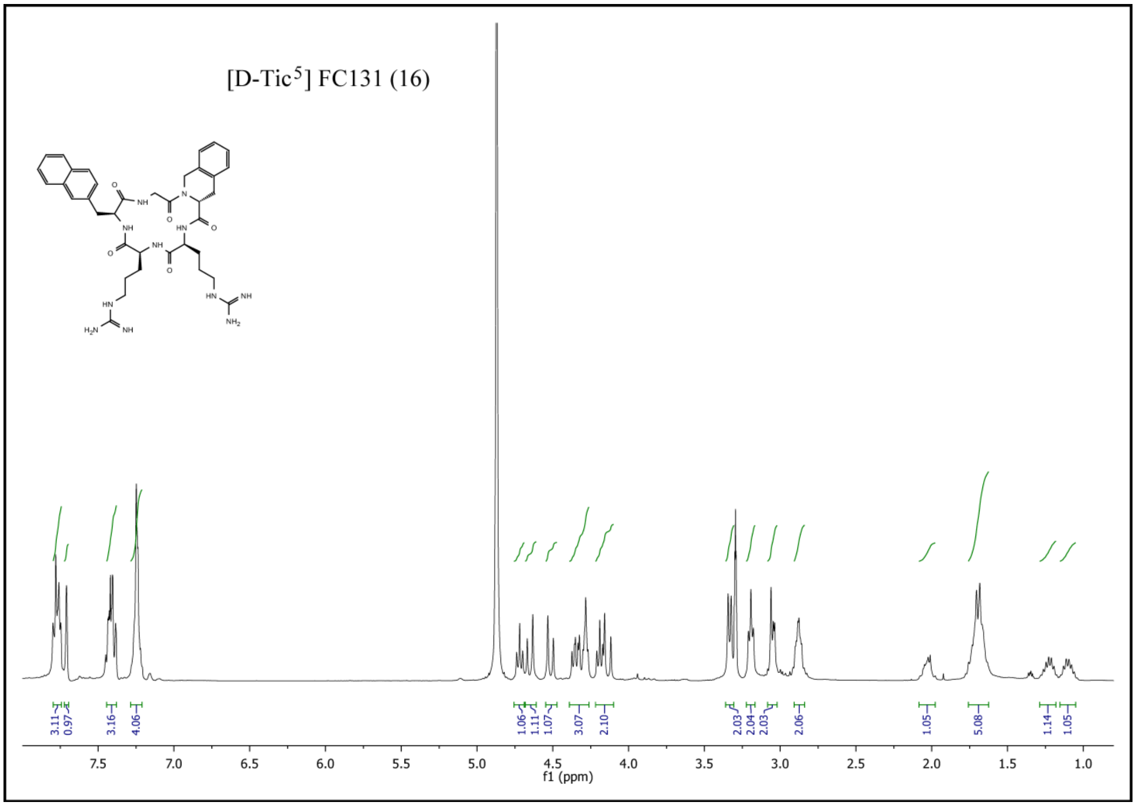

f1 (ppm)

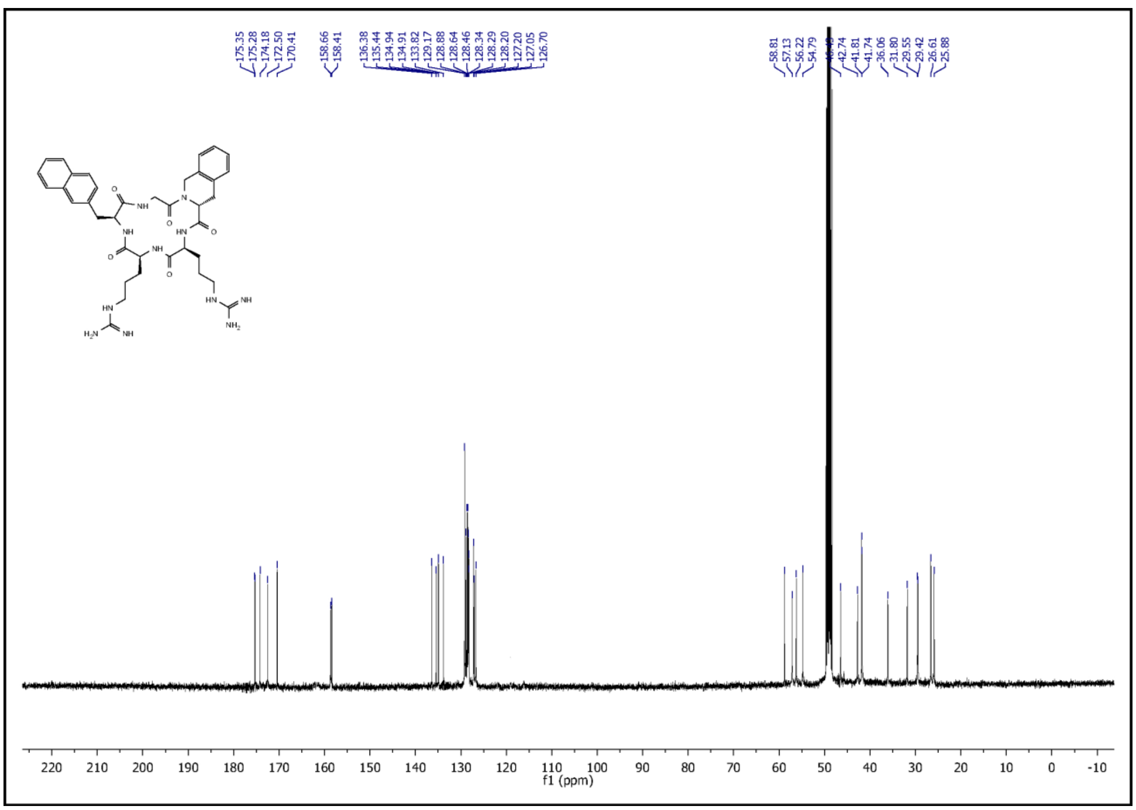

[D-Phe5] FC131 (14)
f1 (ppm)

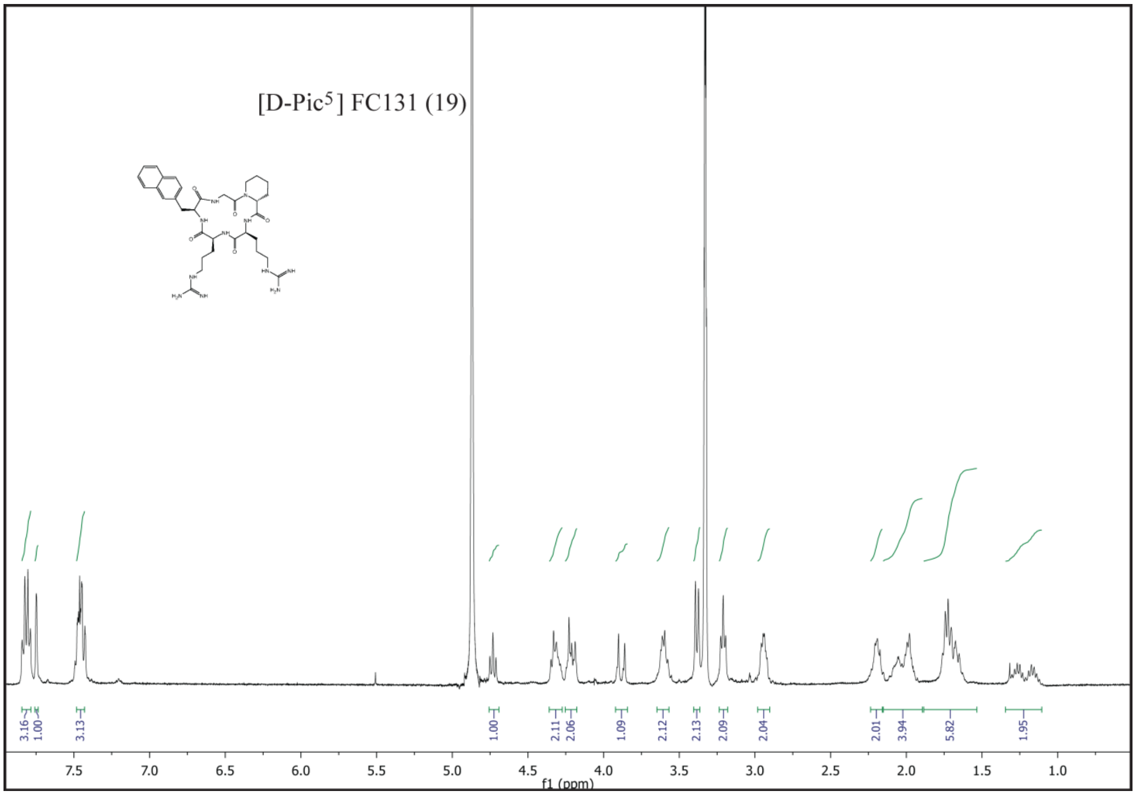

f1 (ppm)

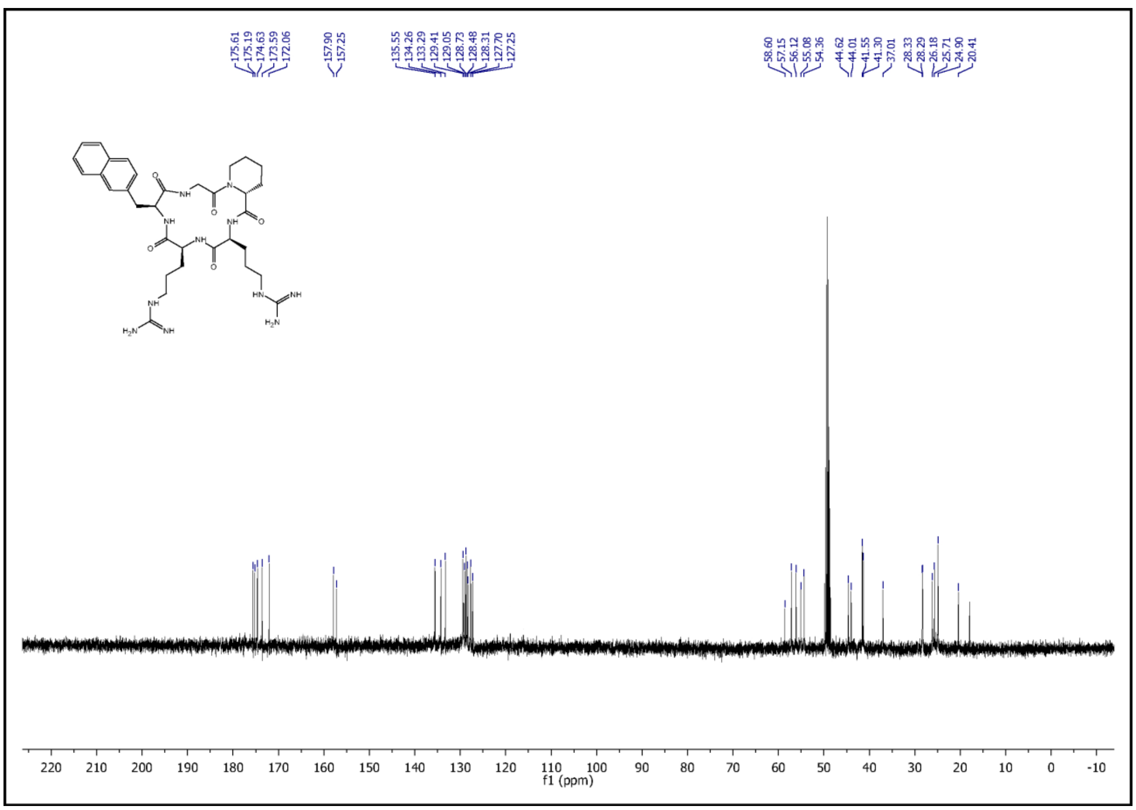

[Aic[5]] FC131 (15)
f1 (ppm)

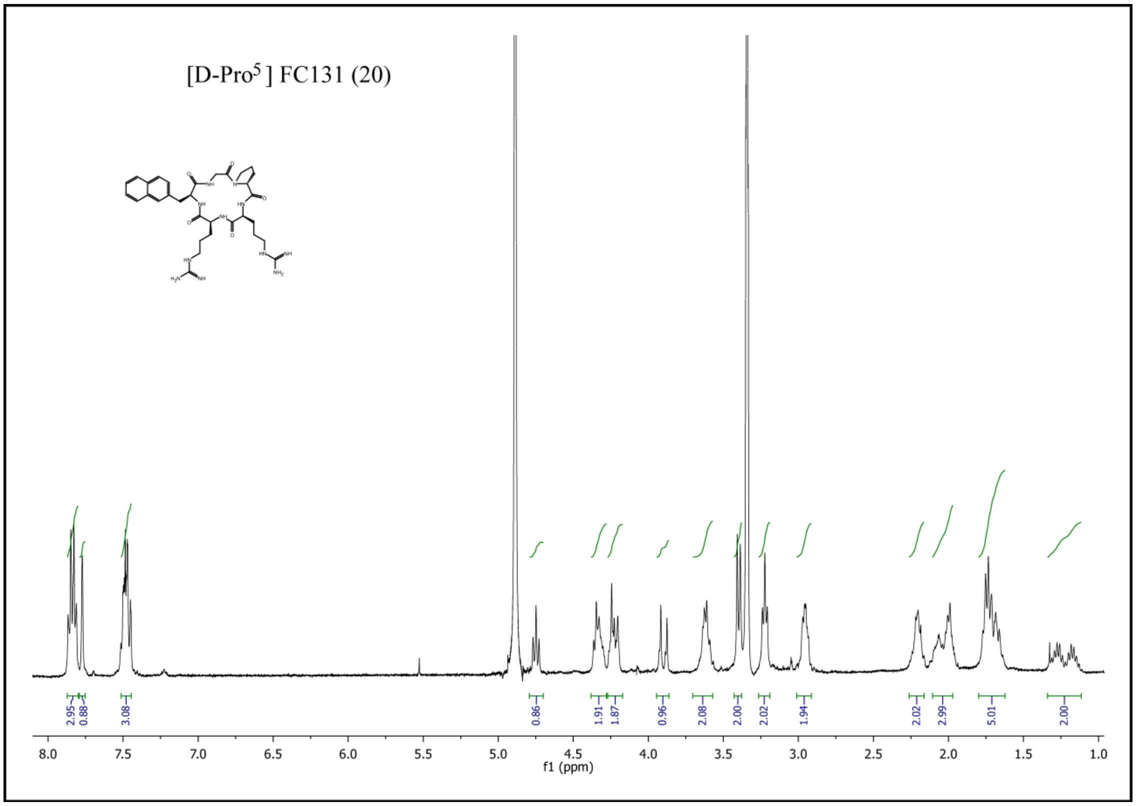

f1 (ppm)

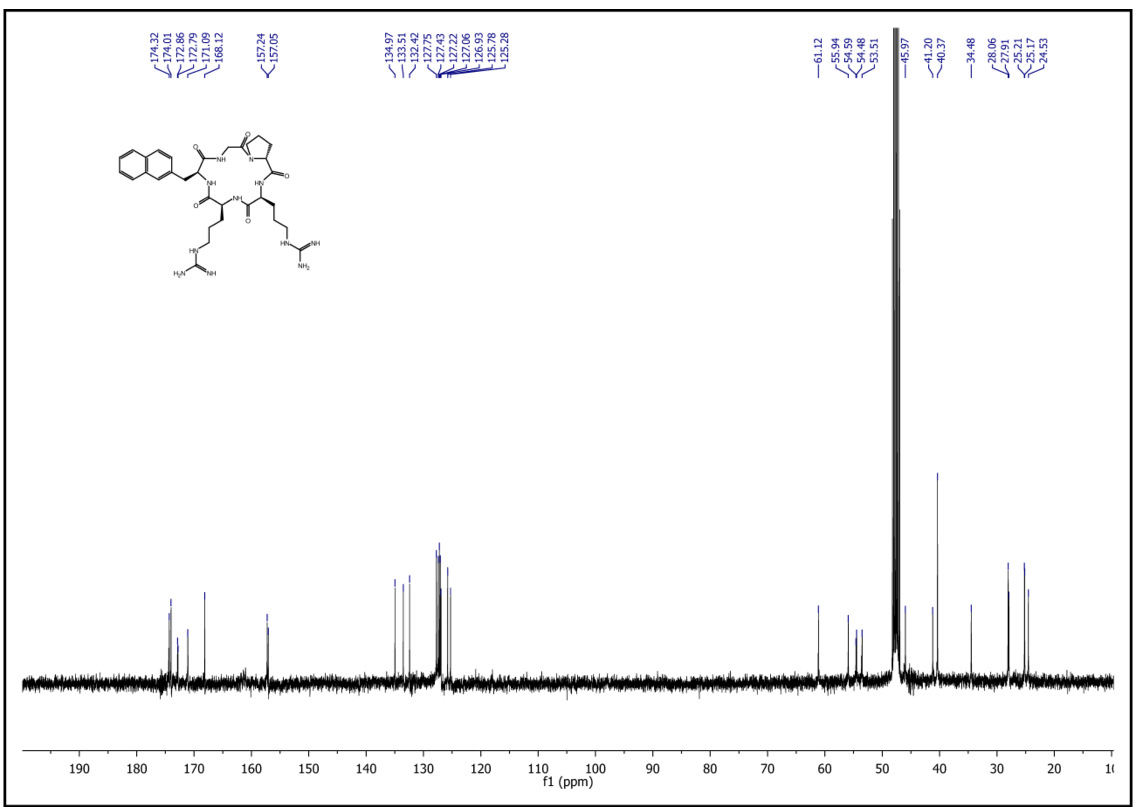

[D-Tic5] FC131 (16)
f1 (ppm)

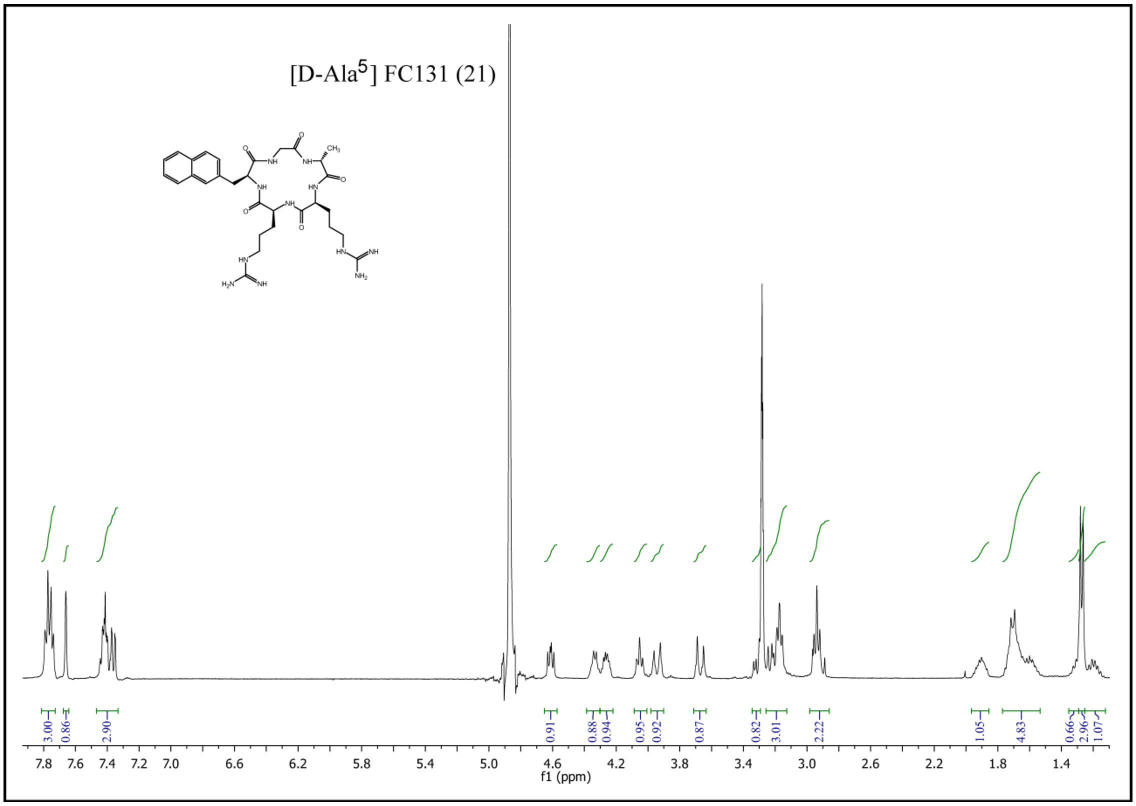

f1 (ppm)

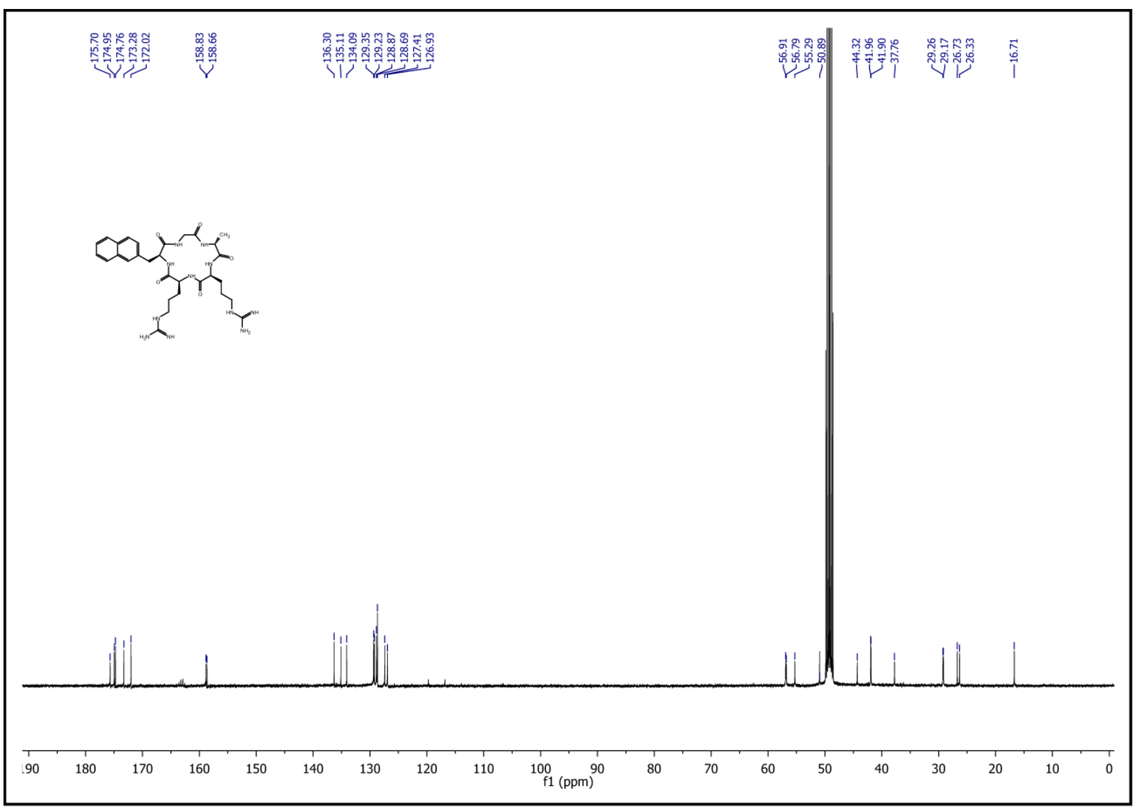

[D-Pic5] FC131 (19)
3.16
1.00
3.13
1.00
2.11
2.06
1.09
2.12
2.13
2.09
2.04
2.01
3.94
5.82
1.95
f1 (ppm)


175.61
175.19
174.63
173.59
172.06
157.90
157.25
135.55
134.26
133.29
129.41
129.05
128.73
128.48
128.31
127.70
127.25
58.60
57.15
56.12
55.08
54.36
44.62
44.01
41.55
41.30
37.01
28.33
28.29
26.18
25.71
24.90
20.41
f1 (ppm)


[D-Pro5] FC131 (20)
f1 (ppm)

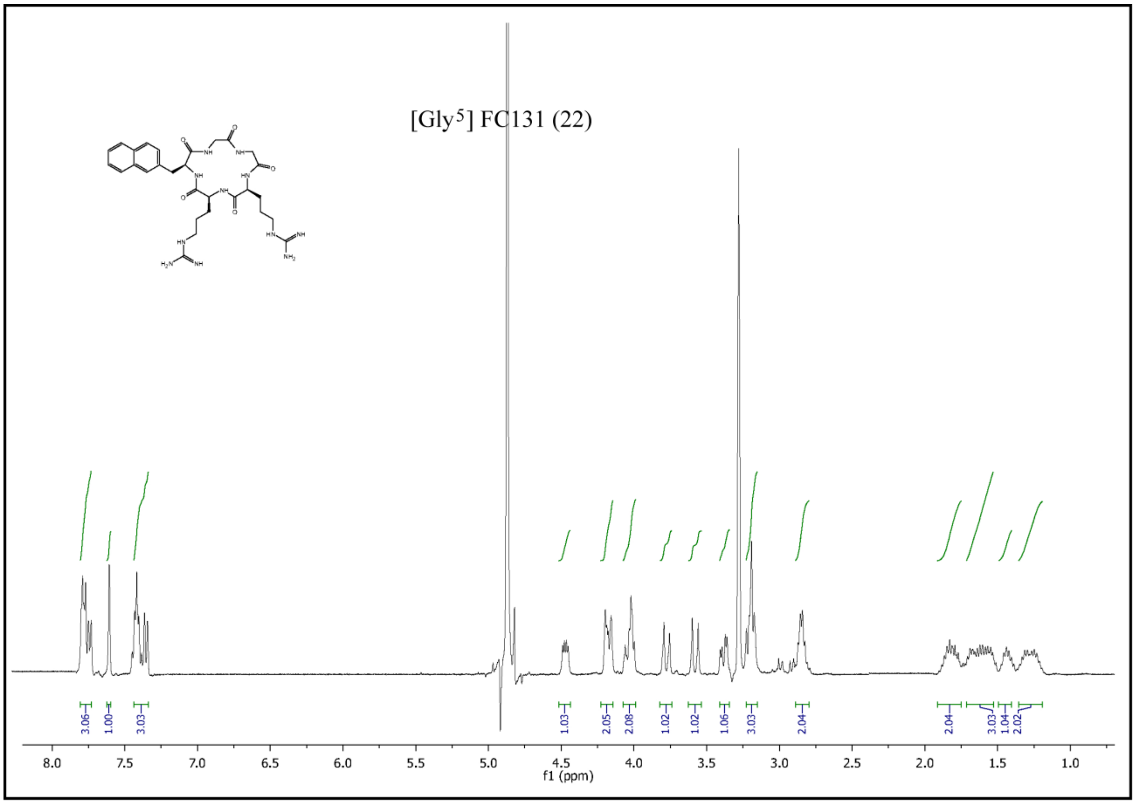

174.32
174.01
172.86
172.79
171.09
168.12
157.24
157.05
134.97
133.51
132.42
127.75
127.43
127.22
127.06
126.93
125.78
125.28
61.12
55.94
54.59
54.48
53.51
45.97
41.20
40.37
34.48
28.06
27.91
25.21
25.17
24.53
f1 (ppm)

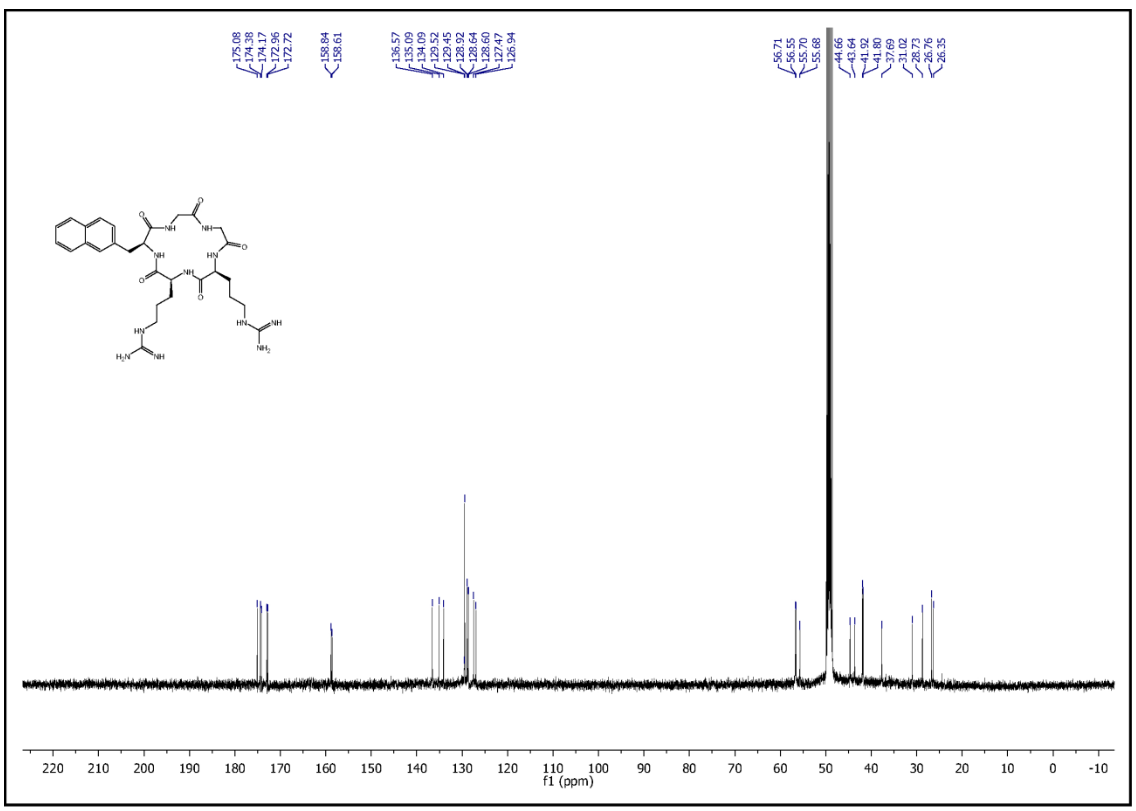

[D-Ala5] FC131 (21)
f1 (ppm)


f1 (ppm)

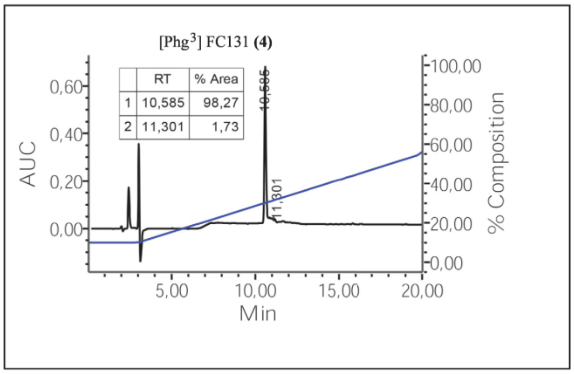
Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry

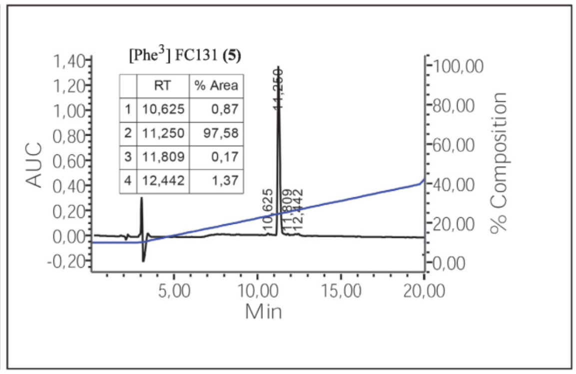
[Gly⁵] FC131 (22)

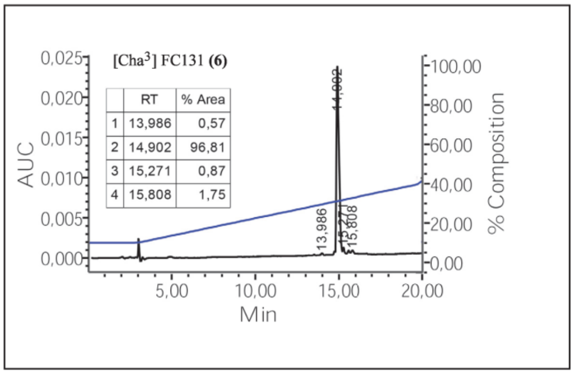


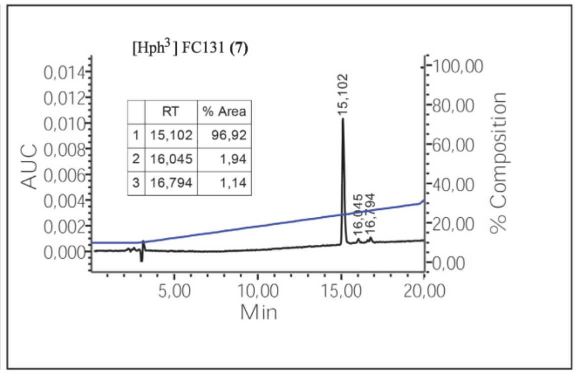


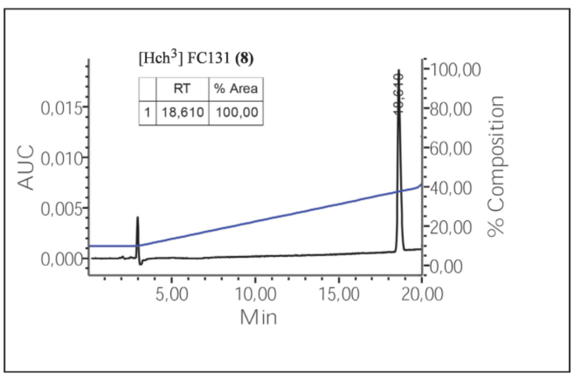
HPLC chromatograms

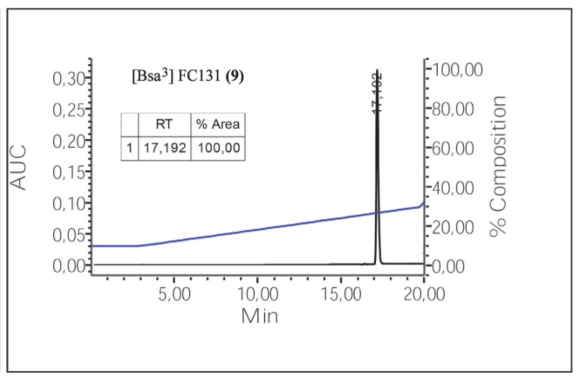


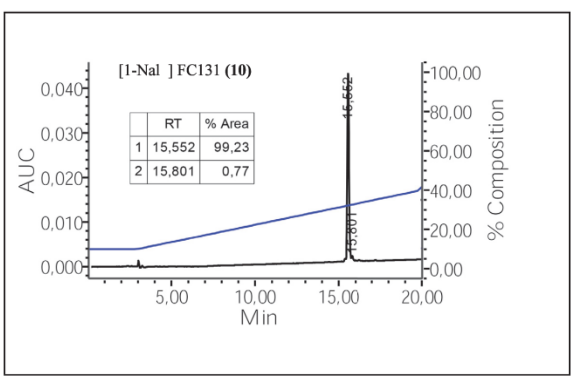


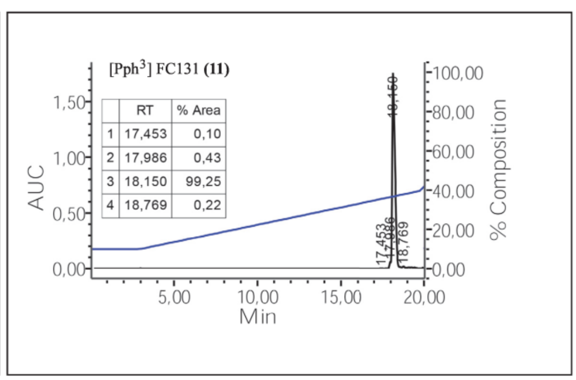


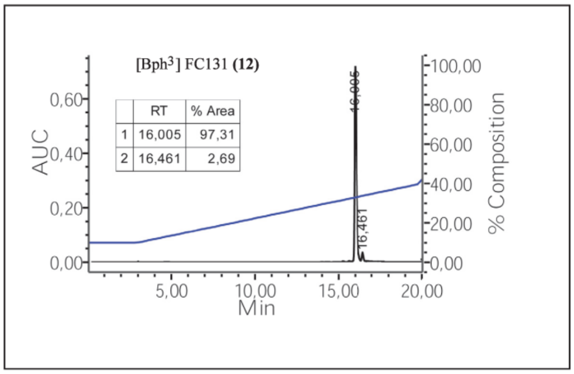


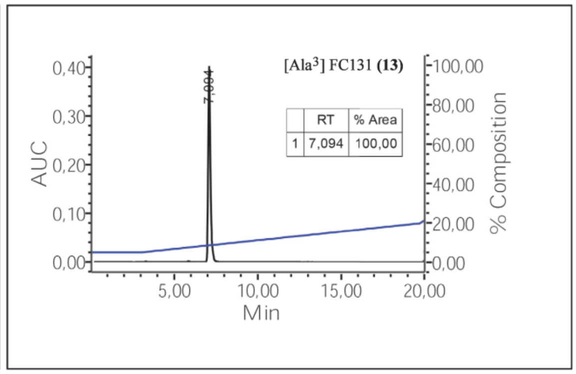


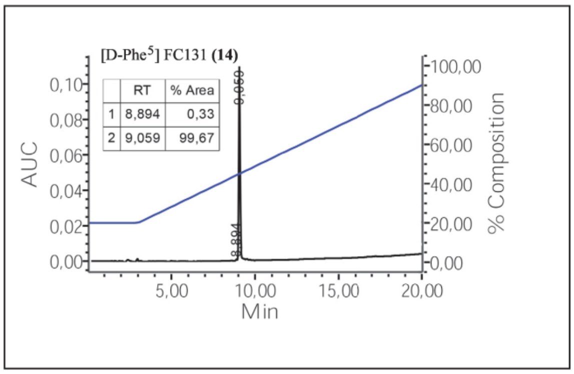


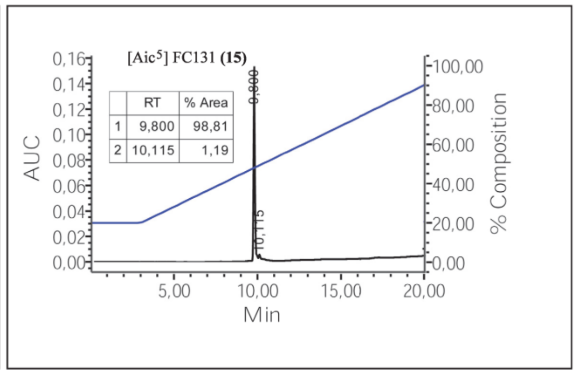


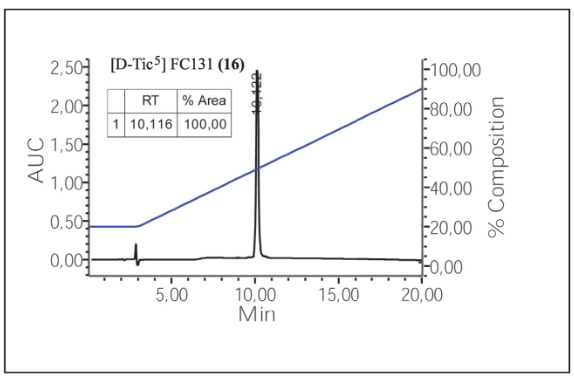


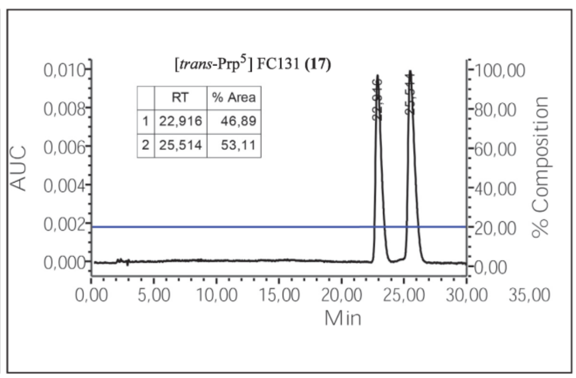

[Bph3] FC131 (12)
RT | % Area
1 | 16,005 | 97,31
2 | 16,461 | 2,69
AUC
% Composition
Min

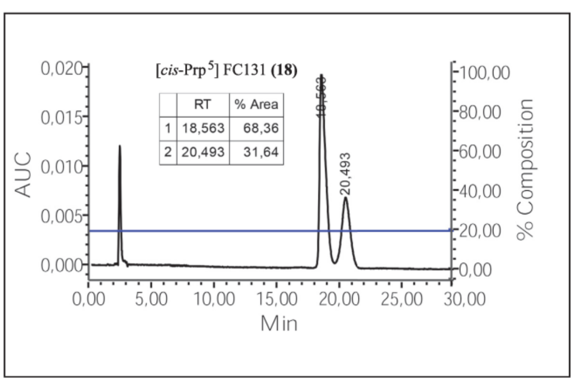

[Ala3] FC131 (13)
RT | % Area
1 | 7,094 | 100,00
AUC
% Composition
Min

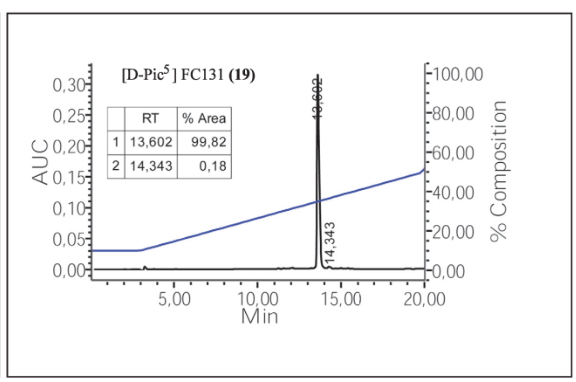

[D-Phe5] FC131 (14)
RT | % Area
1 | 8,894 | 0,33
2 | 9,059 | 99,67
AUC
% Composition
Min

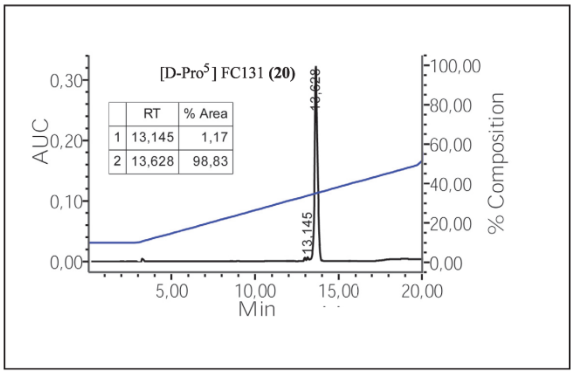

[Aic5] FC131 (15)
RT | % Area
1 | 9,800 | 98,81
2 | 10,115 | 1,19
AUC
% Composition
Min

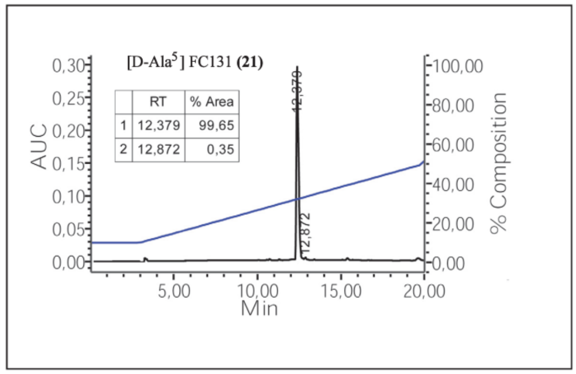

[D-Tic5] FC131 (16)
RT | % Area
1 | 10,116 | 100,00
AUC
% Composition
Min

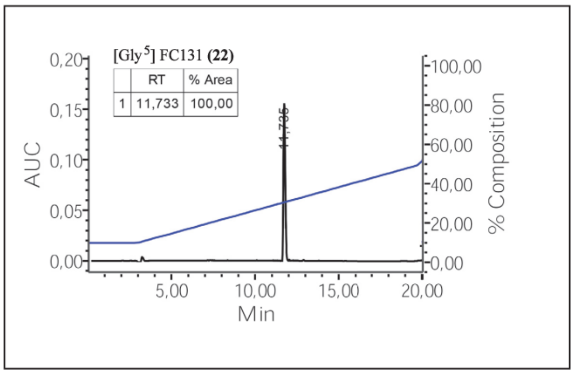

[trans-Prp5] FC131 (17)
RT | % Area
1 | 22,916 | 46,89
2 | 25,514 | 53,11
AUC
% Composition
Min


[cis-Prp5] FC131 (18)
RT | % Area
1 | 18,563 | 68,36
2 | 20,493 | 31,64
AUC
% Composition
Min


[D-Pic5] FC131 (19)
RT | % Area
1 | 13,602 | 99,82
2 | 14,343 | 0,18
AUC
% Composition
Min


[D-Pro5] FC131 (20)
RT | % Area
1 | 13,145 | 1,17
2 | 13,628 | 98,83
AUC
% Composition
Min
13,145
0,00
0,10
0,20
0,30
5,00
10,00
15,00
20,00
100,00
80,00
60,00
40,00
20,00


[D-Ala5] FC131 (21)
RT | % Area
1 | 12,379 | 99,65
2 | 12,872 | 0,35
AUC
% Composition
Min
12,379
12,872


[Gly5] FC131 (22)
RT | % Area
1 | 11,733 | 100,00
AUC
% Composition
Min