

Exploration of Novel Cationic Amino Acid-Enriched Short Peptides: Design, SPPS, Biological Evaluation and *in Silico* Study

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Abbreviations

Ala	Alanine
Arg	Arginine
Cys	Cysteine
ESI	Electron spray ionization
Fmoc	Fluorenylmethyloxycarbonyl
Gly	Glycine
His	Histidine
Trt	Tryl
Ile	Isoleucine
Leu	Leucine
MHz	Mega Hertz
Mmol	Milli mole
MS	Mass Spectroscopy
MTCC	Microbial Type Culture Collection
µg/mL	Microgram per milli liter
Pbf	2,2,4,6,7-Pentamethyldihydrobenzofurane
Pro	Proline
Val	Valine
Ser	Serine
tBu	Tertiary Butyl
Tyr	Tyrosine
TIS	Triisopropyl Silane
v/v	Volume by volume

Characterization data:

H-Gly-Cys-Pro-His-Arg-Cys-OH (7a): Yield - 89%; mp: 230-234 °C; ¹H NMR (500 MHz,) δ 14.36 (s, 1H), 8.96 (s, 1H), 8.79 (d, J = 6.7 Hz, 1H), 8.36 (d, J = 11.8 Hz, 1H), 8.10 (d, J = 5.4 Hz, 4H), 7.76 (d, J = 30.4 Hz, 1H), 7.35 (s, 2H), 4.69 (s, 1H), 4.61 (d, J = 5.2 Hz, 1H), 4.43 (d, J = 3.7 Hz, 1H), 4.33 (d, J = 3.4 Hz, 2H), 3.68 (d, J = 7.1 Hz, 4H), 3.10 (d, J = 3.5 Hz, 4H), 2.98 (m, 1H), 2.88 – 2.87 (dd, J = 14.3, 7.7 Hz, 1H), 2.80 -2.78 (dd, J = 8.2, 5.3 Hz, 2H), 2.60 (s, 2H), 2.41 (d, J = 7.5 Hz, 1H), 2.03 (d, J = 6.1 Hz, 1H), 1.88 (s, 1H), 1.84 (d, J = 5.4 Hz, 1H), 1.77 (s, 1H), 1.74 (d, J = 5.5 Hz, 2H), 1.53 (d, J = 4.1 Hz, 4H); ¹³C NMR (126 MHz, DMSO) δ 171.60, 171.29, 169.76, 168.22, 165.93, 159.00, 156.94, 133.72, 129.14, 117.05, 64.94, 59.69, 54.50, 53.20, 52.32, 51.52, 47.32, 40.45, 29.21, 29.13, 26.88, 25.62, 25.51, 24.93, 24.43; HRMS (ESI⁺) calculated for C₁₃H₁₉NO₂ [M+Na]⁺: 694.2530, found: 694.2521.

H-Ala-Cys-Pro-His-Arg-Cys-OH (7b): Yield - 85%; mp: 225-229 °C; ¹H NMR (500 MHz,) δ 14.32 (s, 1H), 8.96 (s, 1H), 8.71 (d, J = 6.7 Hz, 1H), 8.34 (dd, J = 18.1, 7.5 Hz, 1H), 8.14 (s, 2H), 8.07 (d, J = 6.2 Hz, 1H), 7.75 (s, 1H), 7.31 (s, 2H), 4.59 (d, J = 6.0 Hz, 2H), 4.39 (d, J = 3.7 Hz, 1H), 4.28 (s, 2H), 3.87 (s, 2H), 3.64 (s, 4H), 3.34 (d, J = 6.6 Hz, 1H), 3.06 (s, 4H), 2.94 (dd, J = 14.0, 7.5 Hz, 1H), 2.86 – 2.80 (m, 1H), 2.78 – 2.72 (m, 2H), 2.59 (s, 1H), 2.37 (t, J = 7.5 Hz, 1H), 2.00 (s, 1H), 1.85 – 1.79 (m, 2H), 1.70 (d, J = 4.9 Hz, 2H), 1.48 (s, 2H), 1.28 (d, J = 5.9 Hz, 3H), 1.04 (t, J = 6.4 Hz, 1H); ¹³C NMR (126 MHz,) δ 171.63, 171.30, 169.78, 169.52, 168.17, 158.85, 156.96, 133.74, 129.14, 117.08, 64.97, 59.70, 54.52, 53.55, 52.34, 51.53, 48.06, 47.27, 40.47, 29.19, 26.90, 25.53, 24.95, 24.51, 17.14, 15.19; HRMS (ESI⁺) calculated for C₁₃H₁₉NO₂ [M+Na]⁺: 708.2682, found: 708.2653.

H-Val-Cys-Pro-His-Arg-Cys-OH (7c): Yield - 80%; mp: 222-226 °C; ¹H NMR (500 MHz,) δ 14.24 (s, 1H), 8.94 (s, 1H), 8.78 (d, J = 6.6 Hz, 1H), 8.35 (dd, J = 21.2, 7.6 Hz, 2H), 8.19 (s, 2H), 8.11 (d, J = 6.2 Hz, 1H), 7.81 (d, J = 15.7 Hz, 1H), 7.35 (s, 2H), 4.69 – 4.56 (m, 2H), 4.43 (d, J = 3.8 Hz, 1H), 4.32 (s, 2H), 3.69 (d, J = 6.3 Hz, 4H), 3.37 (d, J = 6.6 Hz, 1H), 3.10 (s, 4H), 2.98 (dd, J = 14.1, 7.3 Hz, 1H), 2.87 (d, J = 7.9 Hz, 1H), 2.84 – 2.73 (m, 2H), 2.66 (s, 2H), 2.42 (s, 1H), 2.04 (d, J = 5.6 Hz, 2H), 1.89 (d, J = 5.6 Hz, 1H), 1.86 – 1.80 (m, 1H), 1.75 (dd, J = 11.2, 5.7 Hz, 2H), 1.56 (s, 1H), 1.52 (d, J = 5.7 Hz, 2H), 0.90 (d, J = 3.7 Hz, 6H); ¹³C NMR (126 MHz,) δ 171.65, 171.31, 169.78, 168.23, 167.92, 158.99, 156.99, 133.73, 129.18, 117.10, 59.68, 57.20, 54.54, 53.62, 52.35, 51.58, 47.34, 40.46, 29.93, 29.21, 25.53, 25.26, 24.96, 24.53, 18.25, 17.66; HRMS (ESI⁺) calculated for C₁₃H₁₉NO₂ [M+Na]⁺: 736.2999, found: 736.2985.

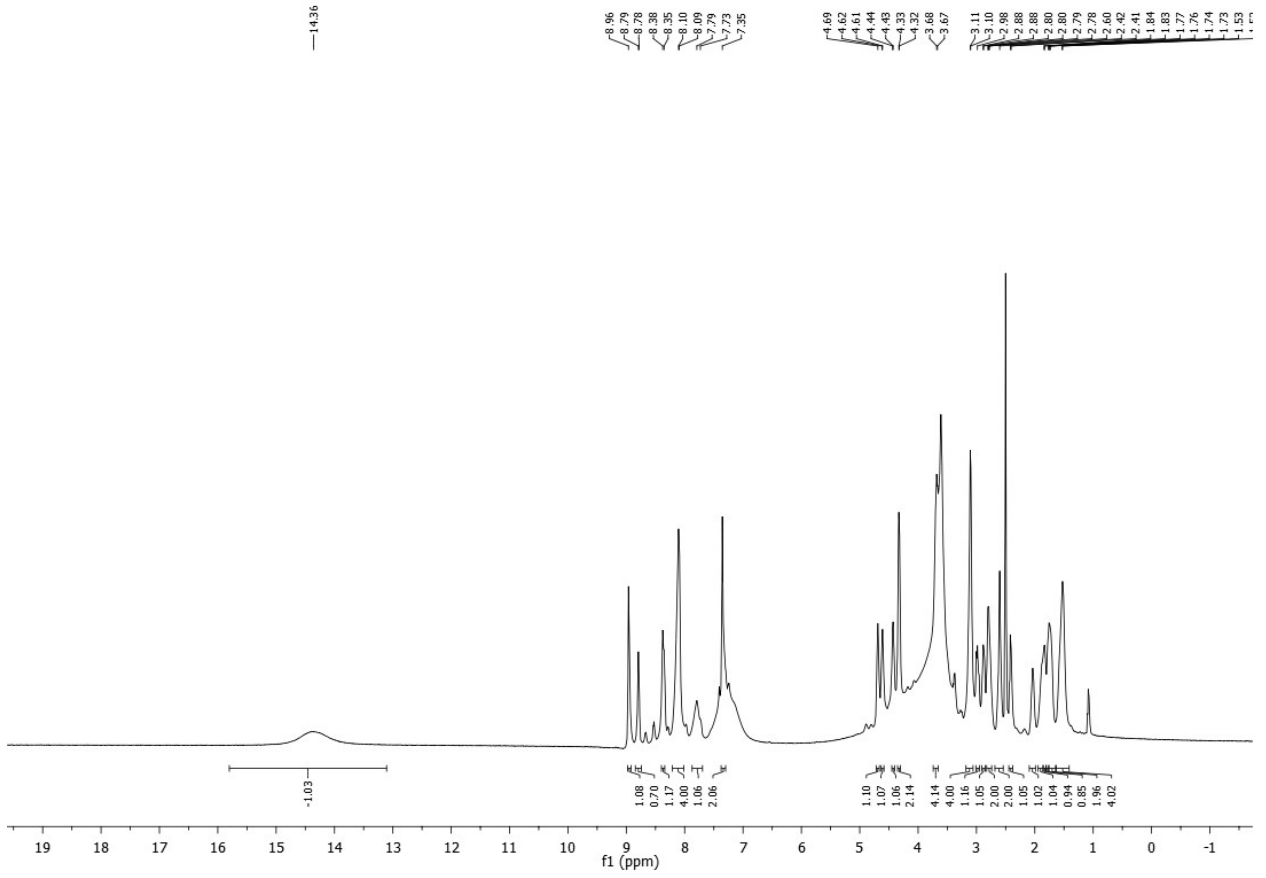
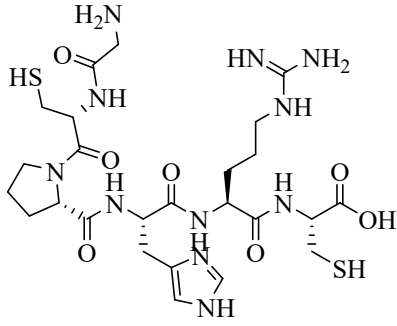
H-Leu-Cys-Pro-His-Arg-Cys-OH (7d): Yield - 80%; mp: 218-222 °C; ¹H NMR (500 MHz,) δ 14.36 (s, 1H), 8.95 (s, 1H), 8.87 (d, J = 6.8 Hz, 1H), 8.34 (dd, J = 20.0, 7.6 Hz, 1H), 8.19 (s, 2H), 7.71 (s, 1H), 7.32 (t, J = 15.6 Hz, 4H), 7.24 (d, J = 5.6 Hz, 1H), 4.66 (d, J = 5.9 Hz, 2H), 4.61 (d, J = 5.7 Hz, 2H), 4.43 (d, J = 3.8 Hz, 1H), 4.33 (s, 2H), 3.83 (s, 1H), 3.69 (s, 1H), 3.64 (d, J = 5.3 Hz, 1H), 3.37 (dd, J = 13.5, 6.7 Hz, 1H), 3.10 (s, 4H), 2.99 (dd, J = 14.6, 7.5 Hz, 1H), 2.87 (d, J = 8.2 Hz, 1H), 2.82-2.79 (m, 1H), 2.64 (s, 1H), 2.42 (t, J = 7.9 Hz, 1H), 2.04 (d, J = 6.2 Hz, 1H), 1.94-1.87 (m, 1H), 1.82 (dd, J = 11.7, 6.1 Hz, 1H), 1.75 (dd, J = 15.9, 10.0 Hz, 2H), 1.61 (dd, J = 13.0, 6.6 Hz, 1H), 1.52 (s, 4H), 1.08 (t, J = 7.0 Hz, 1H), 0.87 (s, 6H); ¹³C NMR (126 MHz,) δ 171.64, 171.32, 169.79, 169.04, 168.16, 156.92, 144.19, 117.41, 117.09, 115.07, 64.97, 59.70,

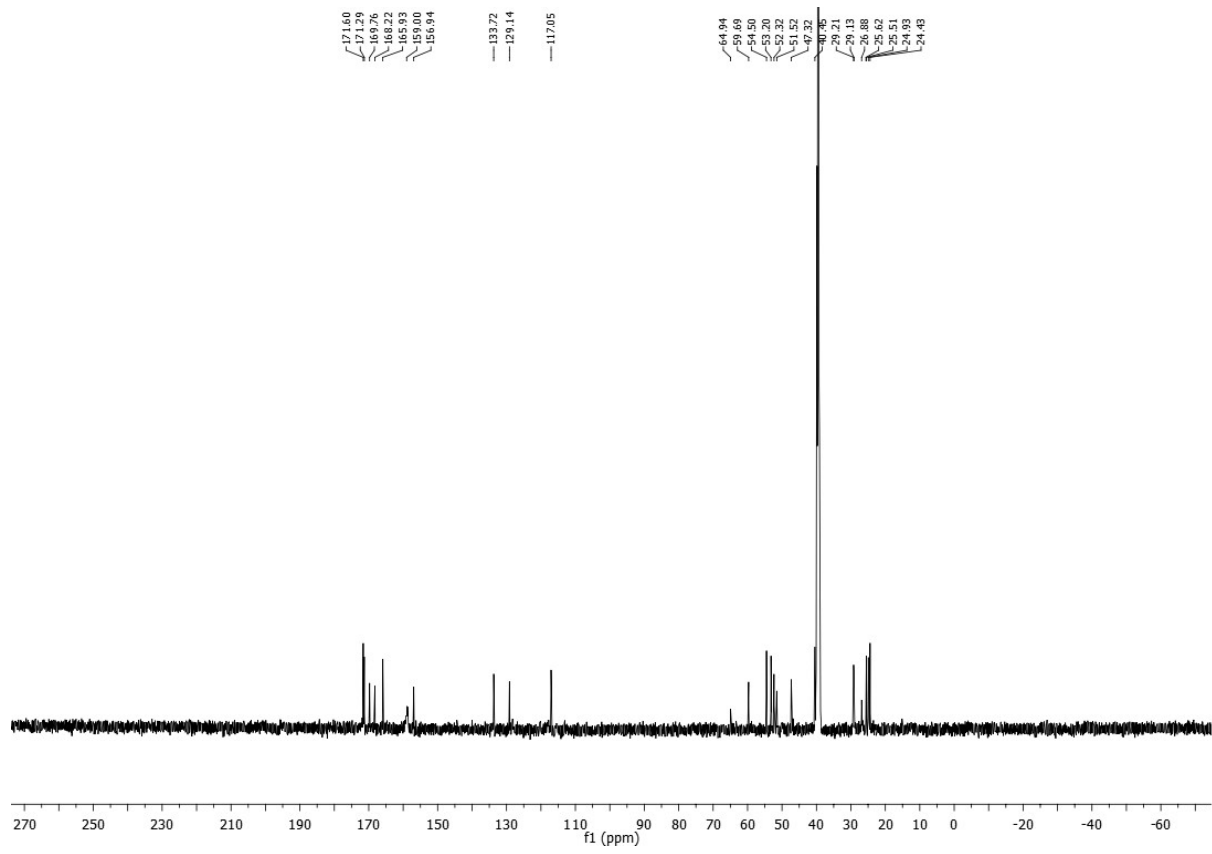
54.54, 53.56, 52.36, 51.58, 50.79, 47.31, 40.49, 40.19, 29.23, 25.54, 25.37, 24.95, 24.47, 23.57, 22.65, 21.84, 15.19; HRMS (ESI⁺) calculated for C₁₃H₁₉NO₂ [M+H]⁺: 728.3336, found: 728.3307.

H-Pro-Cys-Pro-His-Arg-Cys-OH (7e): Yield - 80%; mp: 218-222 °C; ¹H NMR (500 MHz,) δ 14.35 (s, 1H), 9.68 (s, 1H), 8.92 (s, 1H), 8.54 (d, *J* = 19.5 Hz, 1H), 8.36 (s, 1H), 8.09 (d, *J* = 58.8 Hz, 1H), 7.82 (s, 1H), 7.35-7.29 (m, 4H), 7.24 (s, 1H), 4.83 (s, 1H), 4.61 (d, *J* = 5.2 Hz, 2H), 4.52 (s, 1H), 4.43 (d, *J* = 1.8 Hz, 1H), 4.33 (s, 2H), 4.26 (s, 1H), 3.69 (s, 1H), 3.61 (s, 1H), 3.38 (dd, *J* = 13.7, 6.8 Hz, 1H), 3.21 (s, 2H), 3.12 (s, 1H), 3.10 (s, 2H), 3.00 (d, *J* = 7.1 Hz, 1H), 2.85 (d, *J* = 8.8 Hz, 1H), 2.76 (d, *J* = 30.8 Hz, 1H), 2.66 (s, 1H), 2.40 (s, 1H), 2.31 (d, *J* = 4.7 Hz, 1H), 2.05 (s, 1H), 1.85 (d, *J* = 4.6 Hz, 4H), 1.77 (d, *J* = 7.3 Hz, 1H), 1.75 (s, 2H), 1.56 (s, 1H), 1.51 (d, *J* = 4.5 Hz, 2H); ¹³C NMR (126 MHz,) δ 171.61, 171.28, 169.78, 168.19, 159.10, 156.98, 144.15, 117.75, 117.07, 115.40, 59.70, 58.85, 54.52, 53.81, 52.33, 51.55, 45.73, 40.44, 40.02, 29.49, 29.12, 26.77, 25.49, 25.28, 24.90, 24.83, 24.49, 23.51; HRMS (ESI⁺) calculated for C₁₃H₁₉NO₂ [M+H]⁺: 712.3023, found: 712.3036.

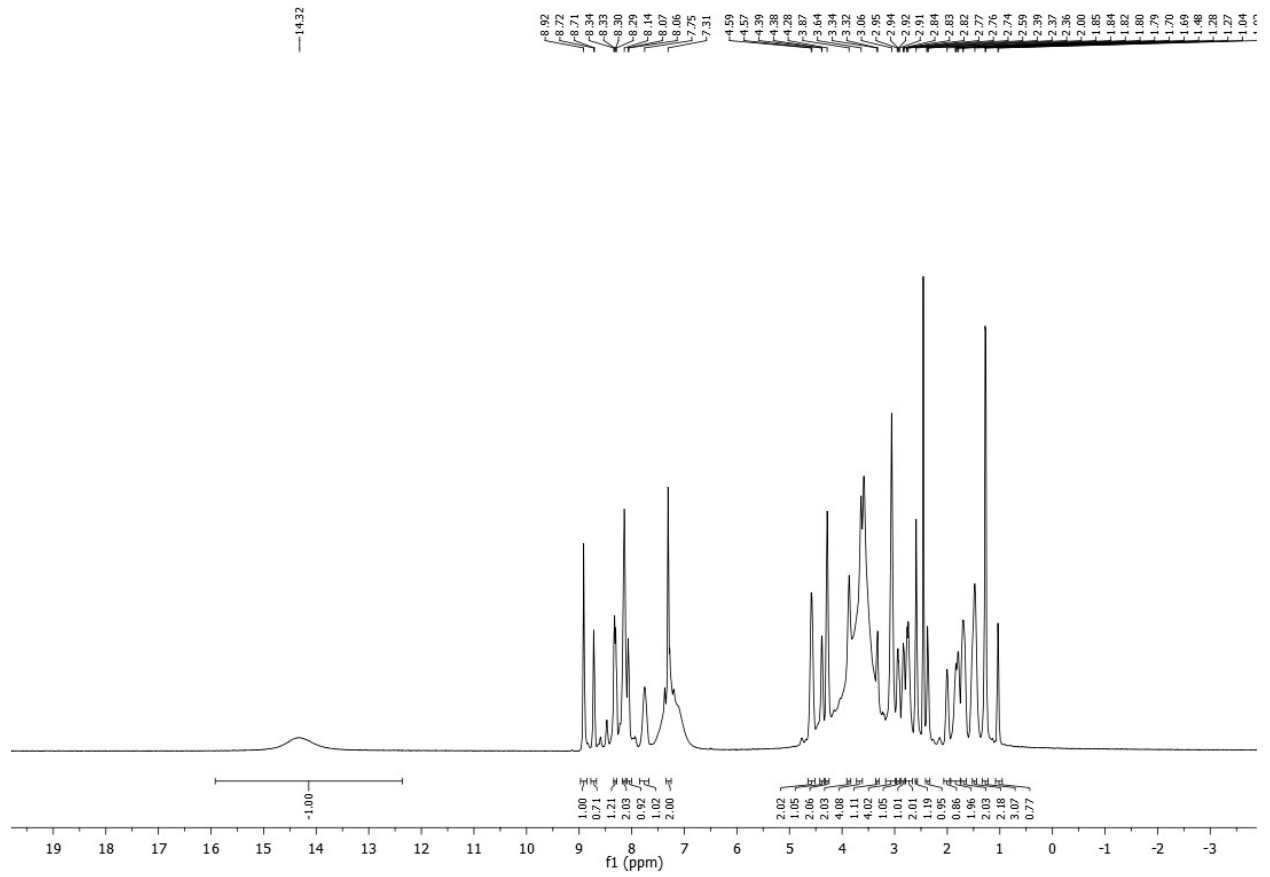
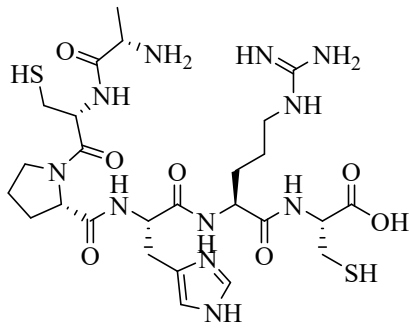
H-Tyr-Cys-Pro-His-Arg-Cys-OH (7f): Yield - 80%; mp: 218-222 °C; ¹H NMR (500 MHz,) δ 14.31 (s, 1H), 8.91 (d, *J* = 25.2 Hz, 1H), 8.38 (d, *J* = 40.0 Hz, 1H), 8.19 (s, 2H), 8.09 (s, 1H), 7.78 (s, 1H), 7.31 (s, 3H), 7.24 (s, 2H), 6.98 (s, 2H), 6.67 (s, 2H), 4.83 (s, 1H), 4.62 (s, 2H), 4.43 (s, 1H), 4.33 (s, 1H), 4.01 (s, 4H), 3.63 (s, 4H), 3.42 (s, 1H), 3.10 (s, 4H), 3.00 (d, *J* = 5.0 Hz, 2H), 2.94 (d, *J* = 20.0 Hz, 2H), 2.79 (d, *J* = 5.0 Hz, 1H), 2.41 (s, 1H), 2.03 (s, 1H), 1.74 (d, *J* = 25.0 Hz, 4H), 1.51 (d, *J* = 15.0 Hz, 4H); ¹³C NMR (126 MHz,) δ 171.61, 171.29, 169.76, 167.98, 159.01, 156.62, 144.14, 130.49, 129.09, 128.13, 124.51, 117.68, 117.05, 115.27, 59.62, 54.51, 53.37, 53.19, 52.32, 51.57, 47.19, 40.46, 36.00, 29.16, 29.09, 26.86, 25.48, 25.41, 24.91, 24.83, 24.30, 24.21; HRMS (ESI⁺) calculated for C₁₃H₁₉NO₂ [M+H]⁺: 778.3129, found: 778.3115.

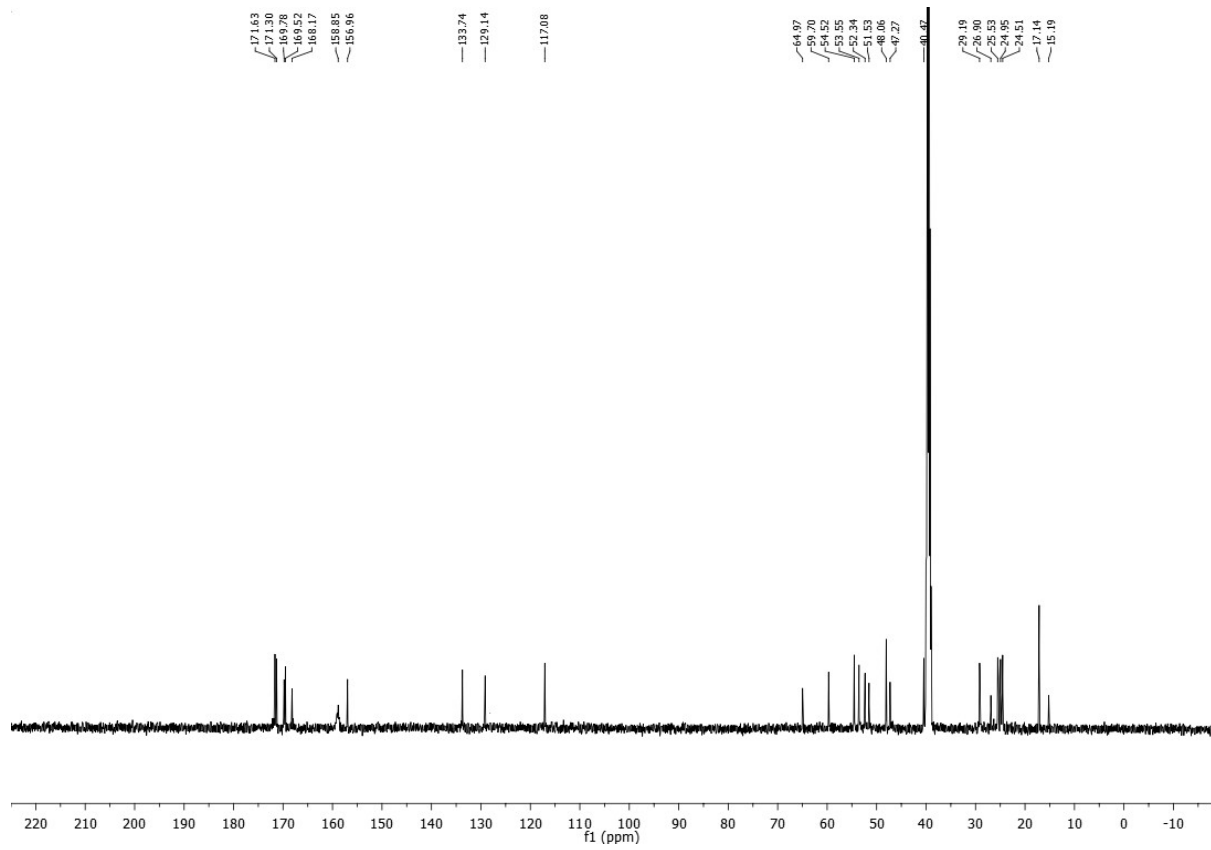
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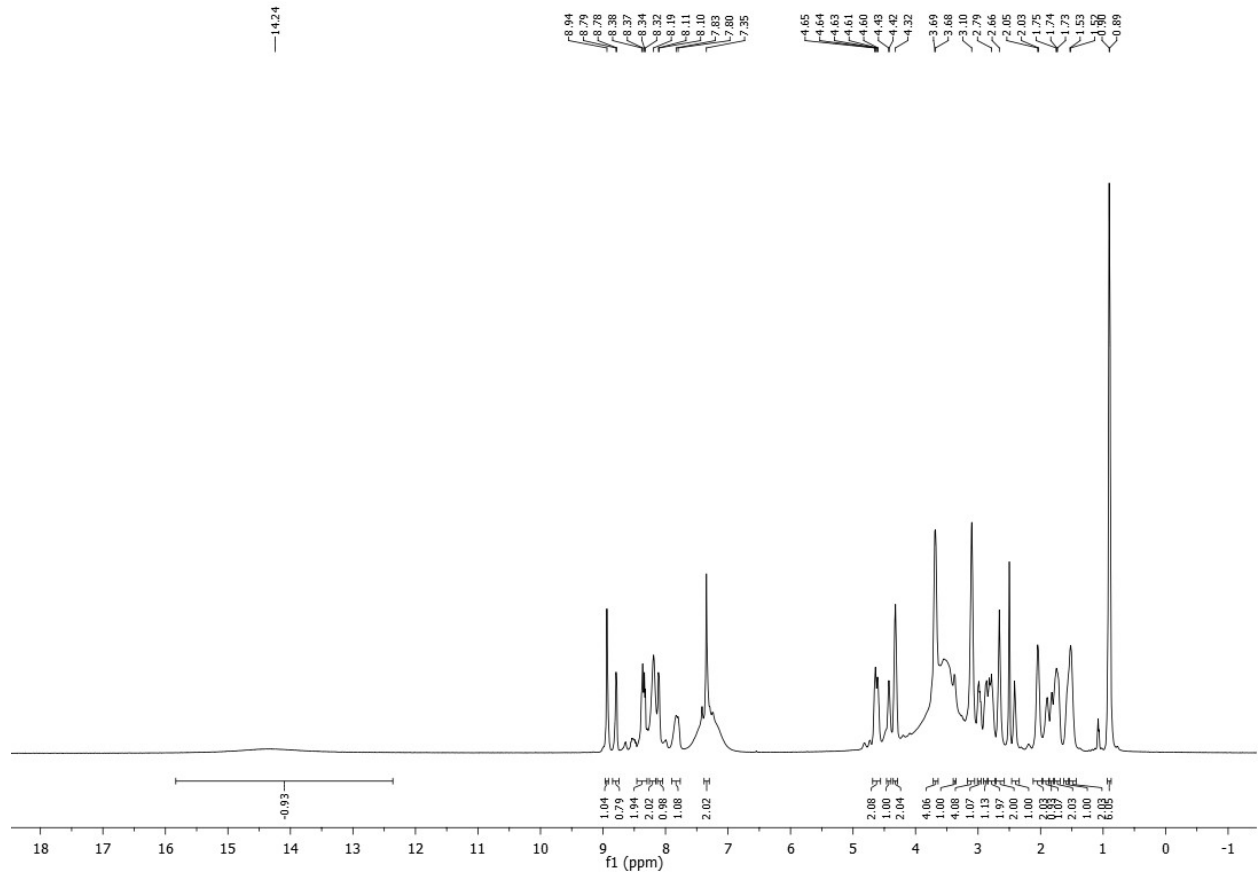
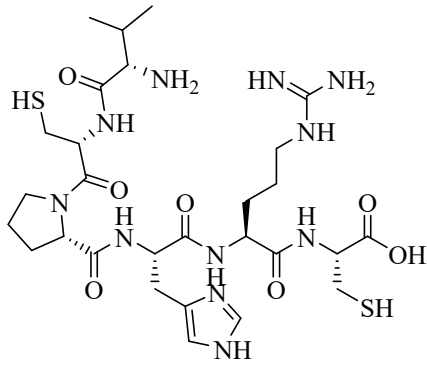


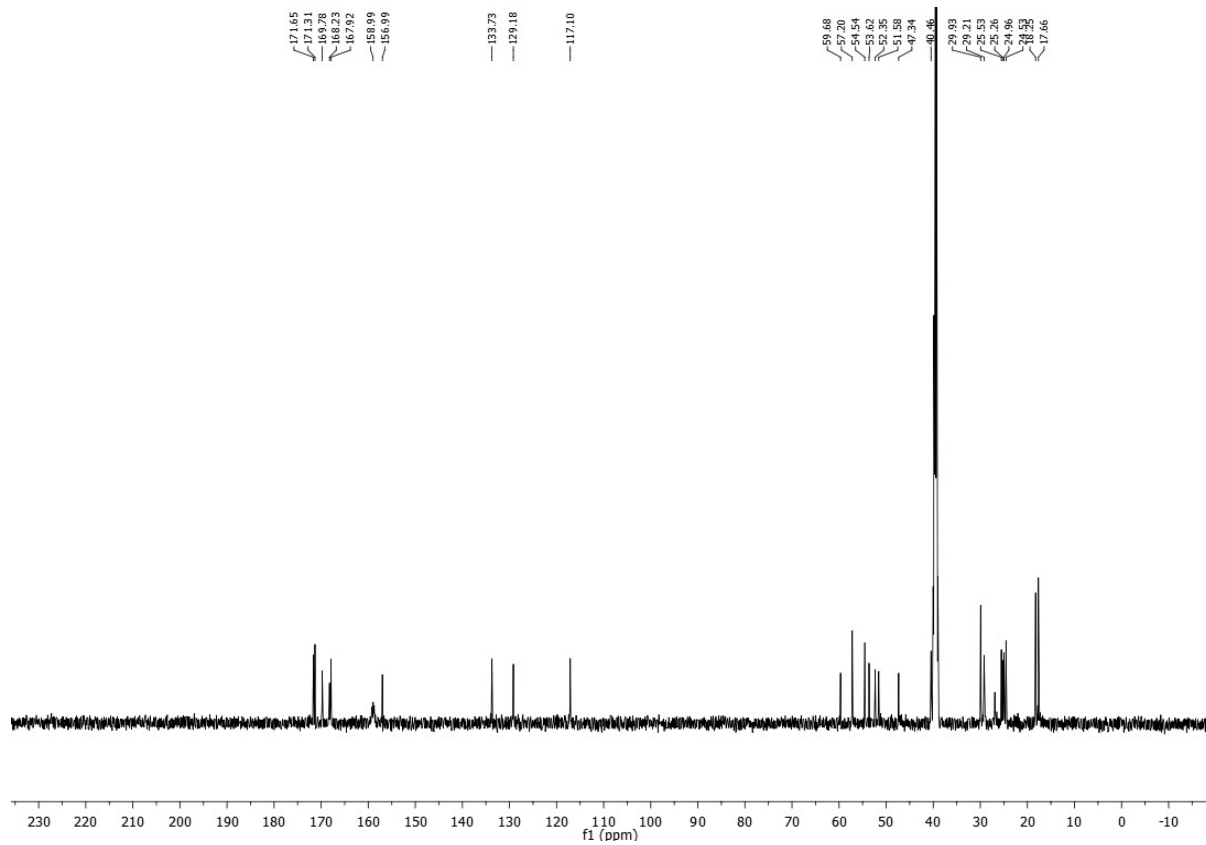
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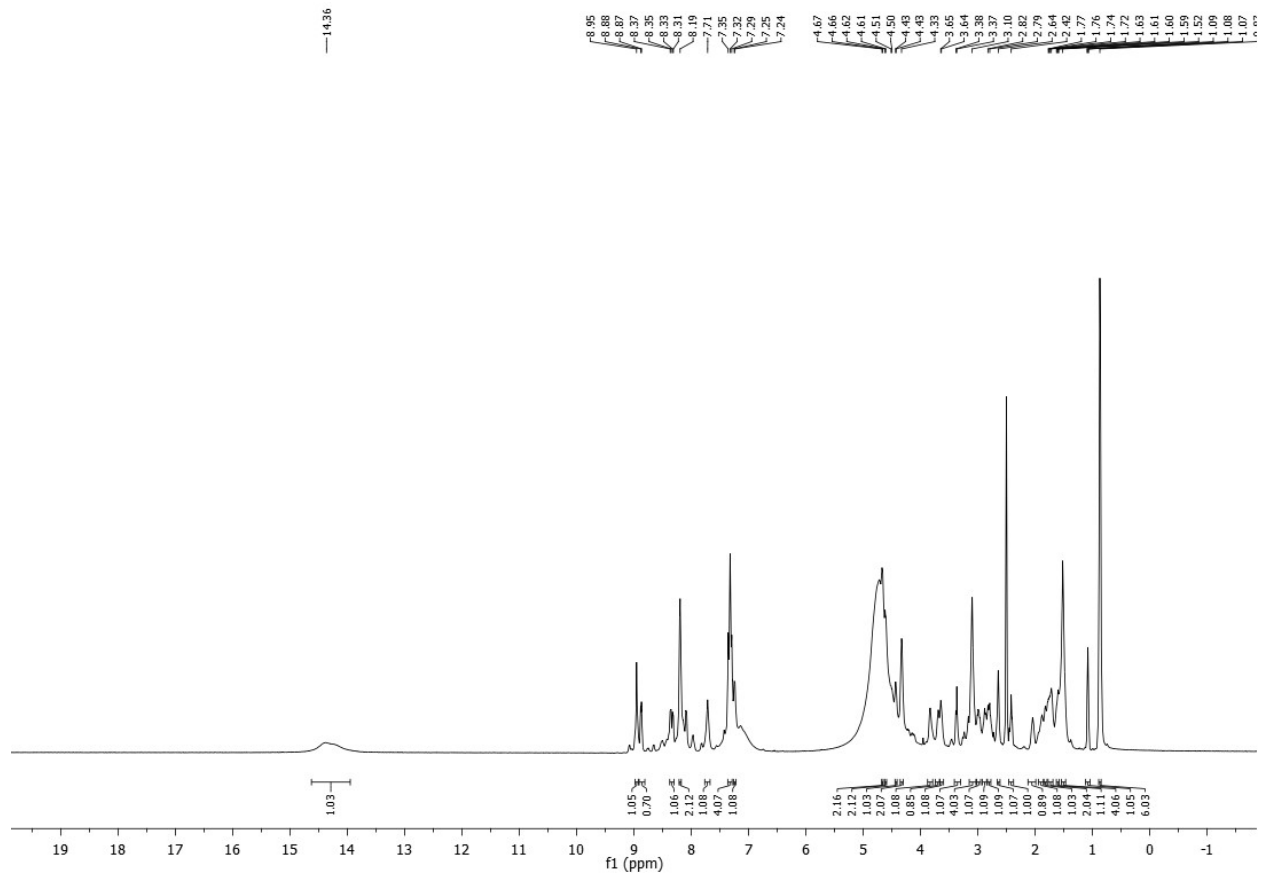
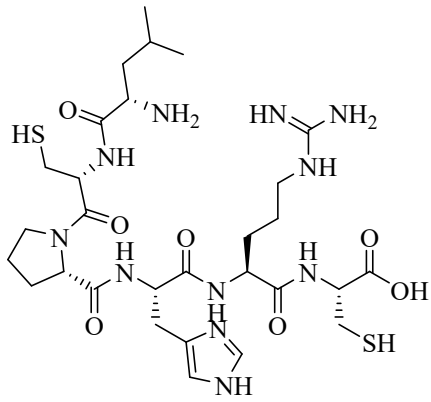


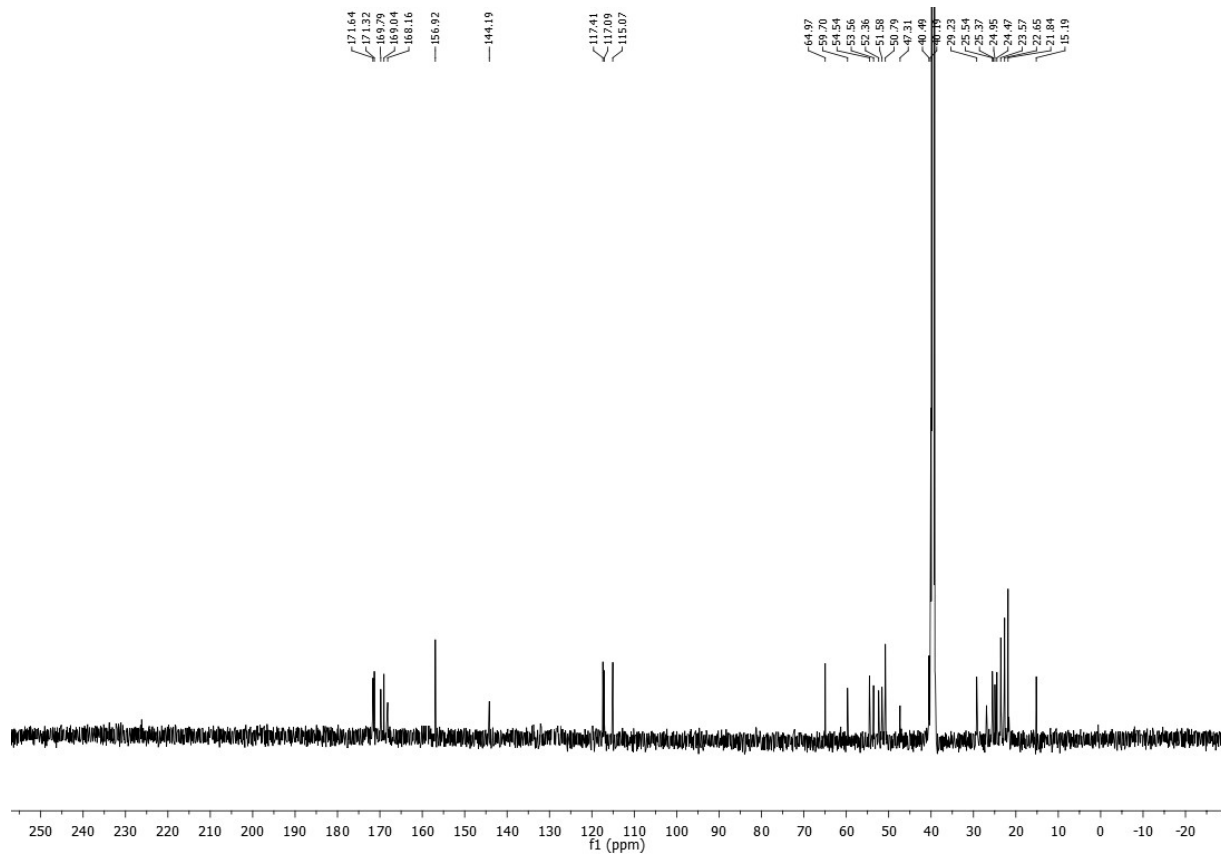
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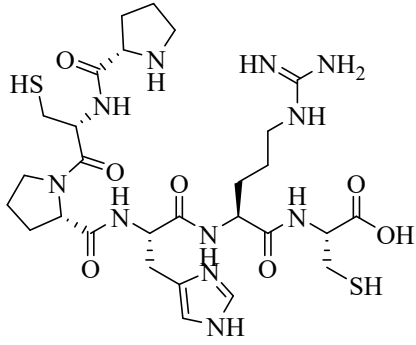


7d



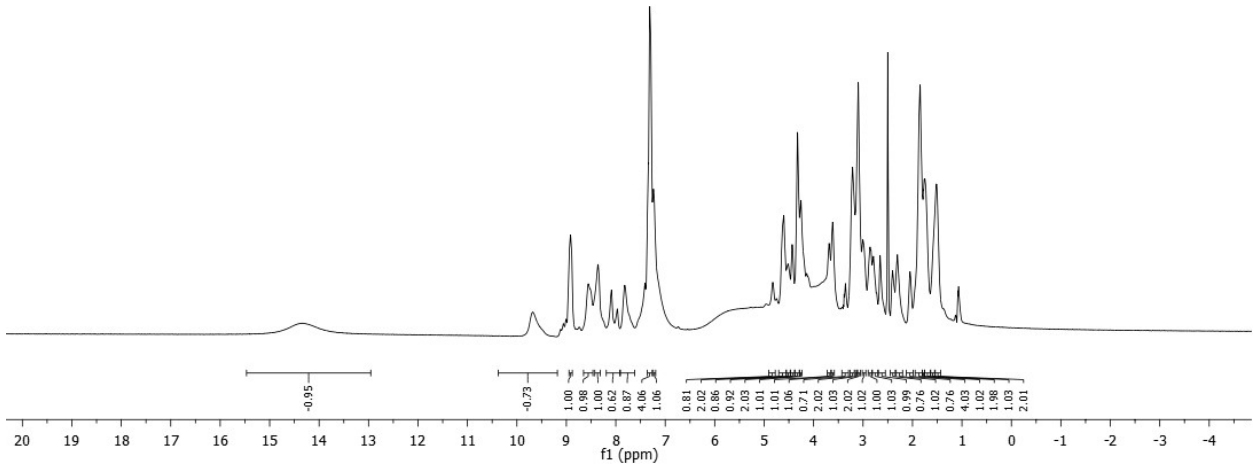


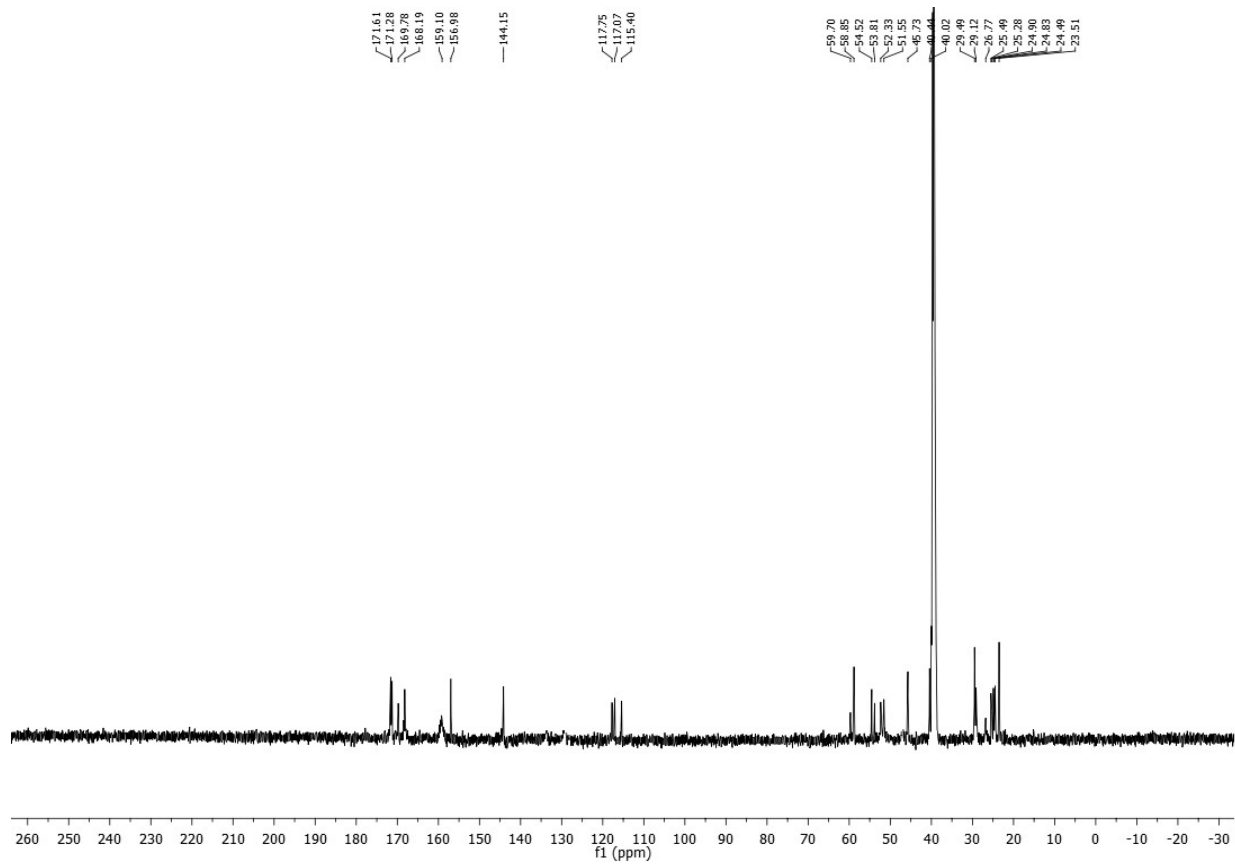
7e



-14.35

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2.40
2.32
2.31
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1.85
1.78
1.76
1.62
1.52
1.51





7f

