Electronic Supporting Information

2,2,2-Trifluoroethanol as a Tool to Control Nucleophilic Peptide Arylation

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Materials and general methods

All chemicals and solvents were analytical grade and used without further purification. Liquid chromatography-mass spectrometry (LC/MS; ESI+ mode) analyses were performed on a Acquity UPLC BEH C18 column (1.7 μm 2.1 mm x 50 mm) using a Waters Acquity UPLC system equipped with a photodiode array detector, providing absorbance data from 210 nm to 400 nm. A gradient with eluent I (0.1% HCOOH in water) and eluent II (0.1% HCOOH in acetonitrile) rising linearly from 5 to 95% of II during t=0.2–4.0 min was applied at a flow rate of 0.6 ml/min after 0.2 min of 95% solvent I initial equilibration. High-resolution QToF-LC/MS and QToF-MS/MS analyses were performed in a Acquity UPLC BEH C18 column (1.7 μm, 2.1 mm x 50 mm) using a Waters Acquity UPLC system coupled to Micromass QToF Premier mass spectrometer, also equipped with a photodiode array detector providing absorbance data from 210 nm to 400 nm. A gradient with eluent I (0.1% HCOOH in water) and eluent II (0.1% HCOOH in acetonitrile) rising linearly from 0 to 99% of II during t=0.0–5.0 min was applied at a flow rate of 0.6 ml/min. ^{19}F NMR spectra studies were recorded at 376MHz in a Bruker Advance spectrometer at 298 K, using 8 scans with a relaxation delay of 1s. All data has been processed using Mestrenova® software.

Peptides (pep**1-4)** were prepared using conventional Fmoc/tBu SPSS procedures. Full experimental details and characterisation of **pep1-4** are given in -

D. Gimenez, C.A Mooney, A. Dose, G. Sandford, C.R. Coxon and S.L. Cobb, "Application of Pentafluoropyridine and Related Polyfluorinated Reagents in the Preparation of Modified Peptide Systems". ***OB-ART-02-2017-000283***.

Model peptide tagging and stapling with perfluoroaromatics:

General procedure for solution phase peptide tagging and stapling

Solid crude peptides **pep1-3** (2 mg, approx. 2.5 µmol) were dissolved in the DMF or TFE (0.5 mL) in a 1.5 mL plastic Eppendorf tube, to which a Cs_2CO_3 or DIPEA stock solution (50 mM in appropriate solvent, 0.5 mL) was added. Pentafluoropyridine (1) or hexafluorobenzene (3) was added in 5 equivalents and the tube was shaken vigorously at room temperature for 4.5 h. After removal of volatiles under vacuum, all products were redissolved in an 8:1:1 mixture of DMF/H_2O/MeCN (1mL) and characterised by LC/MS (ESI+). When formation of novel compounds was observed, 10-fold scaled reactions were employed in all cases for product isolation and purification in order to afford a complete characterisation. Scaled reactions were run under exactly the same conditions but in argon-flushed syringes, to avoid air bubbles where volatile aromatic compounds could concentrate. LC/MS data for crude reactions is provided next.

LC/MS analysis of small scale reactions **1-22**

Effect of the solvent: DMF vs. TFE, using DIPEA. Entries **1-12** from **Table 1 (main article)**

Entry 1: Ac-YCGGGCAL- NH_2 + HEXAFLUOROBENZENE in DMF/DIPEA:

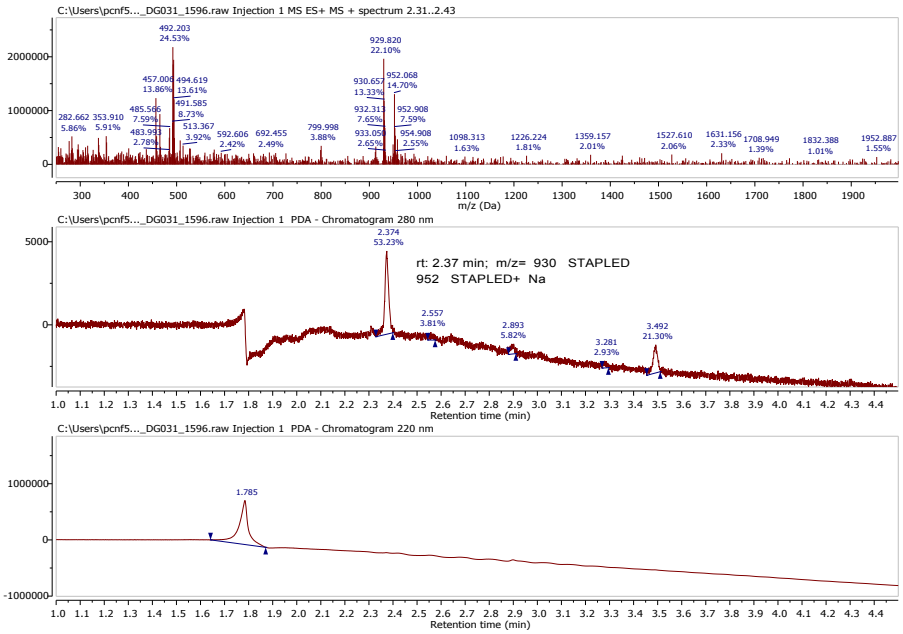


Figure SI01. LC/MS traces at λ= 280 (middle panel) and λ= 220 nm (lower panel) of crude reaction of peptide **pep1** with hexafluorobenzene when using DIPEA as a base in DMF.

Entry 2: Ac-YSGGGSAL-NH_2 + HEXAFLUOROBENZENE in DMF/DIPEA:

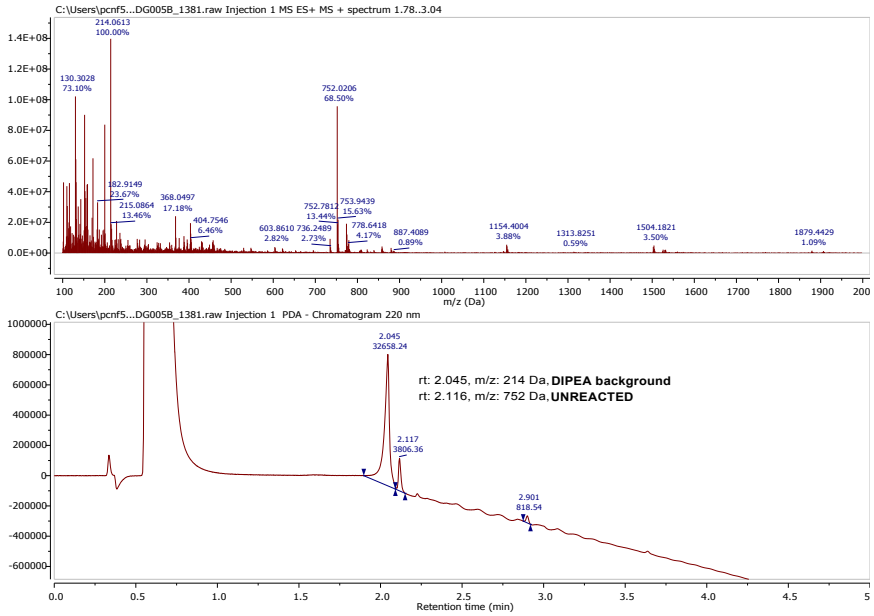


Figure SI02. LC/MS traces at λ=220 nm of crude reaction of peptide **pep2** with hexafluorobenzene when using DIPEA as a base in DMF.

Entry 3: Ac-YKGGGKAL- NH_2 + HEXAFLUOROBENZENE in DMF/DIPEA:

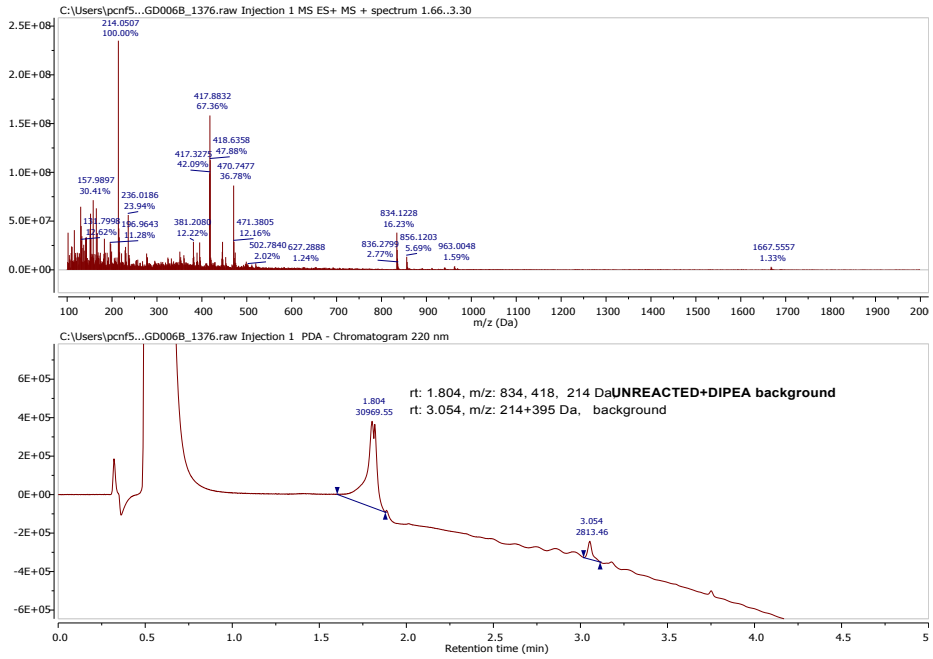
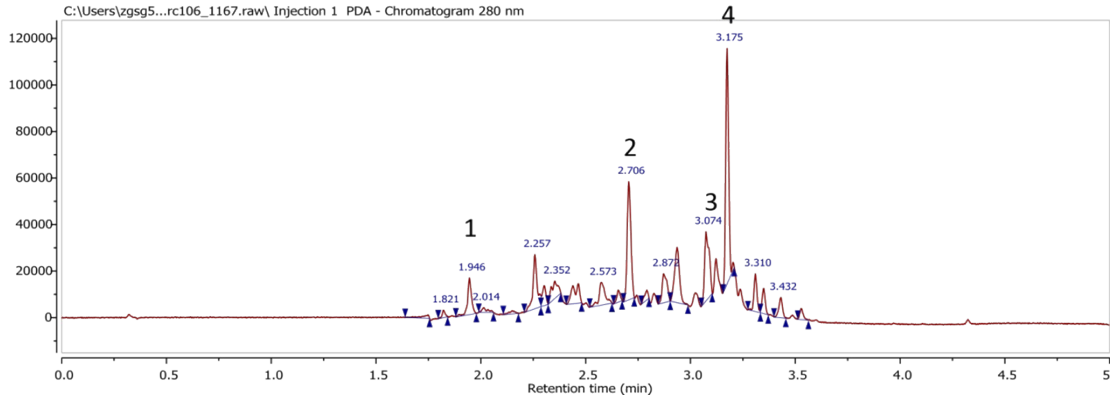


Figure SI03. LC/MS traces λ=220 nm of crude reaction of peptide **pep3** with hexafluorobenzene when using DIPEA as a base in DMF.

Entry 4: Ac-YCGGGCAL- NH_2 + PENTAFLUOROPYRIDINE in DMF/DIPEA:



Peak	Retention time	*m/z*	Identity
1	1.946	820	Starting peptide $[M+MeCN]^+$
2	2.706	1082	Double ArF addition $[M+2ArF]^+$
3	3.074	1138	$[M+2ArF+TFA]^{2+}$
4	3.175	1231	Triple ArF addition $[M+3ArF]^+$

Figure SI04. LC/MS traces at λ=280 nm of crude reaction of peptide **pep1** with pentafluoropyridine when using DIPEA as a base in DMF.

Entry 5: Ac-YSGGGSAL- NH_2 + PENTAFLUOROPYRIDINE in DMF/DIPEA:

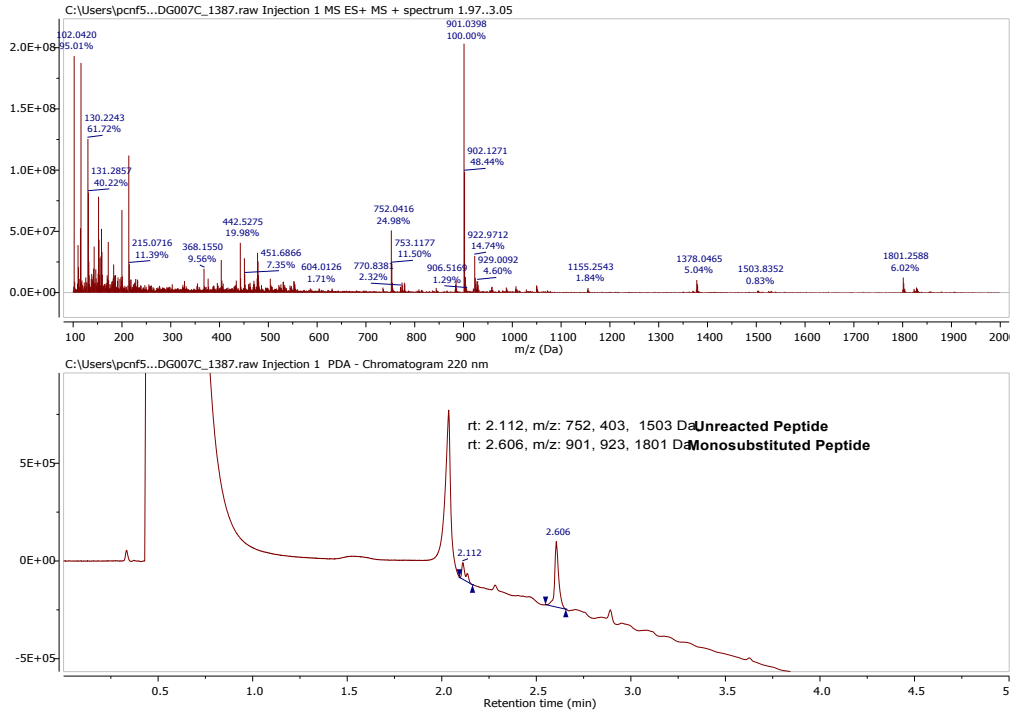


Figure SI05. LC/MS traces at λ=220 nm of crude reaction of peptide **pep2** with pentafluoropyridine when using DIPEA as a base in DMF.

Entry 6: Ac-YKGGGKAL- NH_2 + PENTAFLUOROPYRIDINE in DMF/DIPEA:

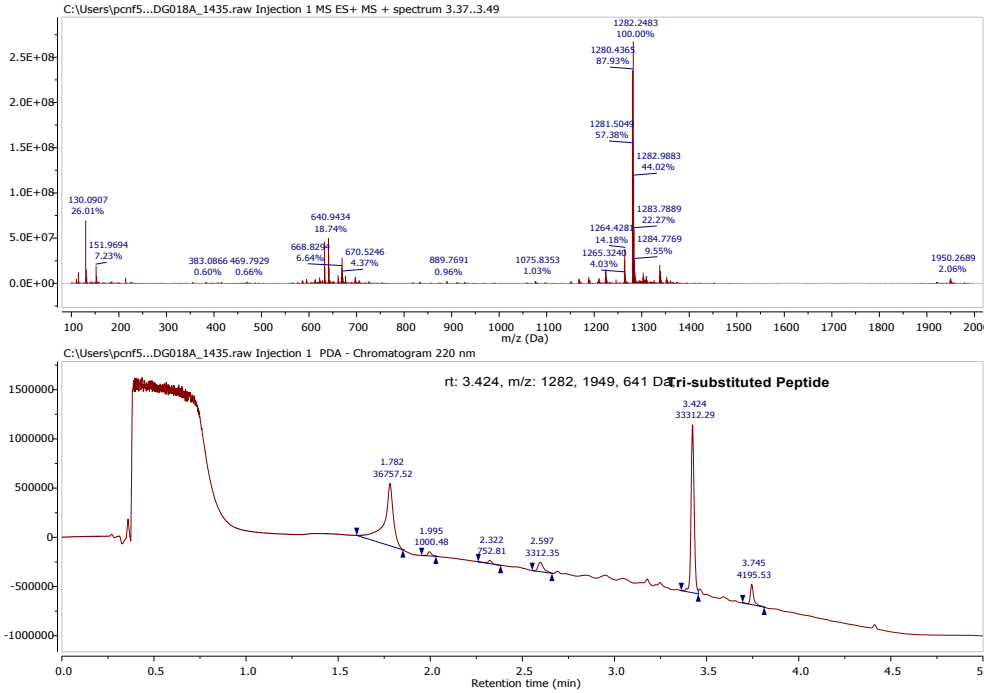


Figure SI6. LC/MS traces at λ=220 nm of crude reaction of peptide **pep3** with pentafluoropyridine when using DIPEA as a base in DMF.

Entry 7: Ac-YCGGGCAL- NH_2 + HEXAFLUOROBENZENE in TFE/DIPEA:

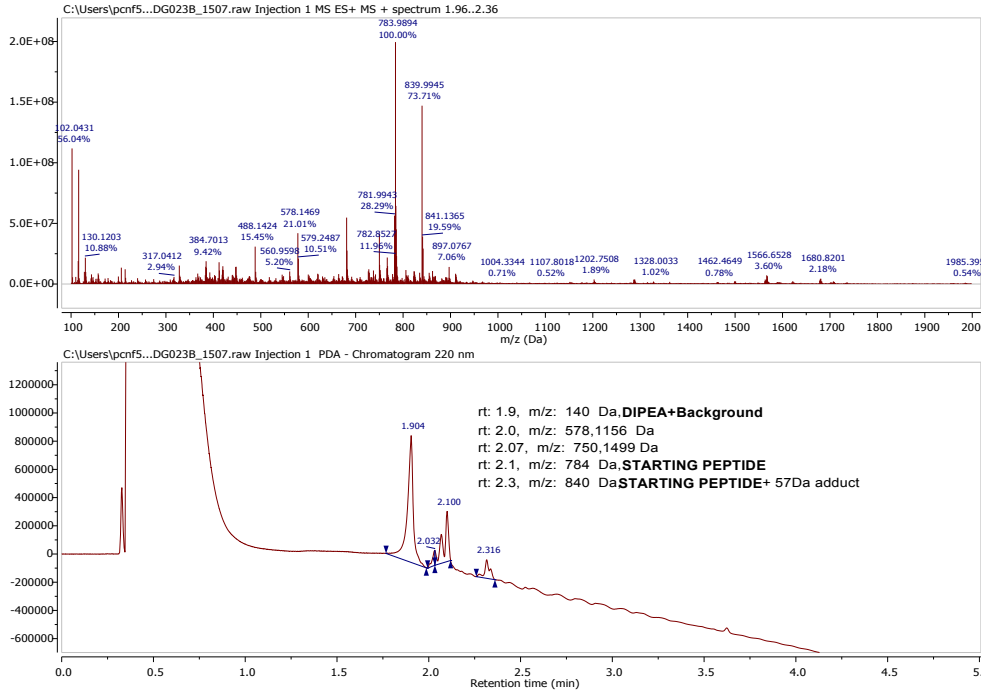


Figure SI7. LC/MS traces at λ=220 nm of crude reaction of peptide **pep1** with hexafluorobenzene when using DIPEA as a base in TFE.

Entry 8: Ac-YSGGGSAL- NH_2 + HEXAFLUOROBENZENE in TFE/DIPEA:

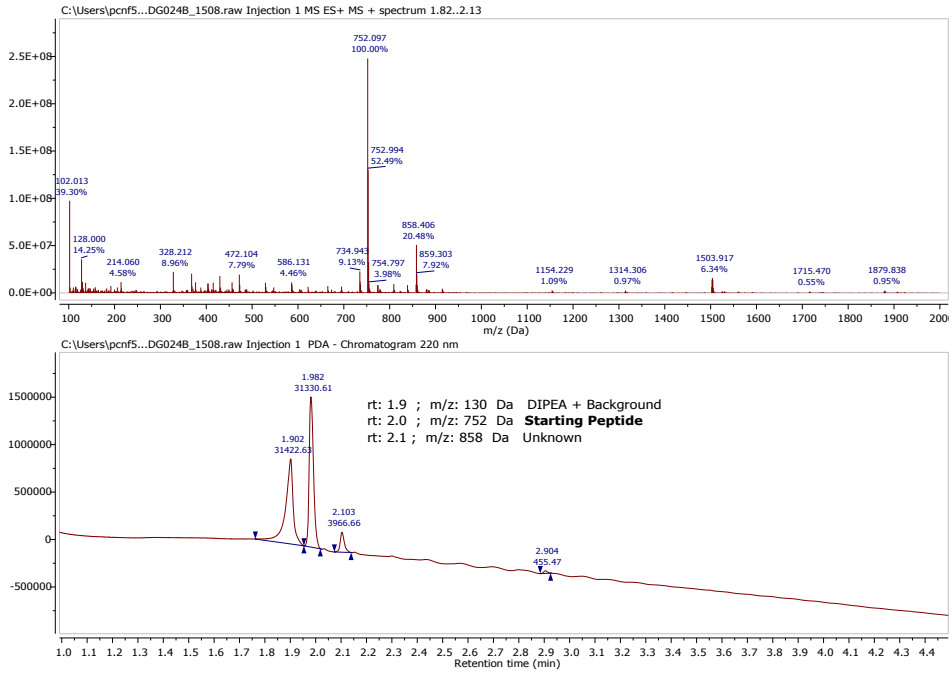


Figure SI8. LC/MS traces at λ=220 nm of crude reaction of peptide **pep2** with hexafluorobenzene when using DIPEA as a base in TFE.

Entry 9: Ac-YKGGGKAL- NH_2 + HEXAFLUOROBENZENE in TFE/DIPEA:

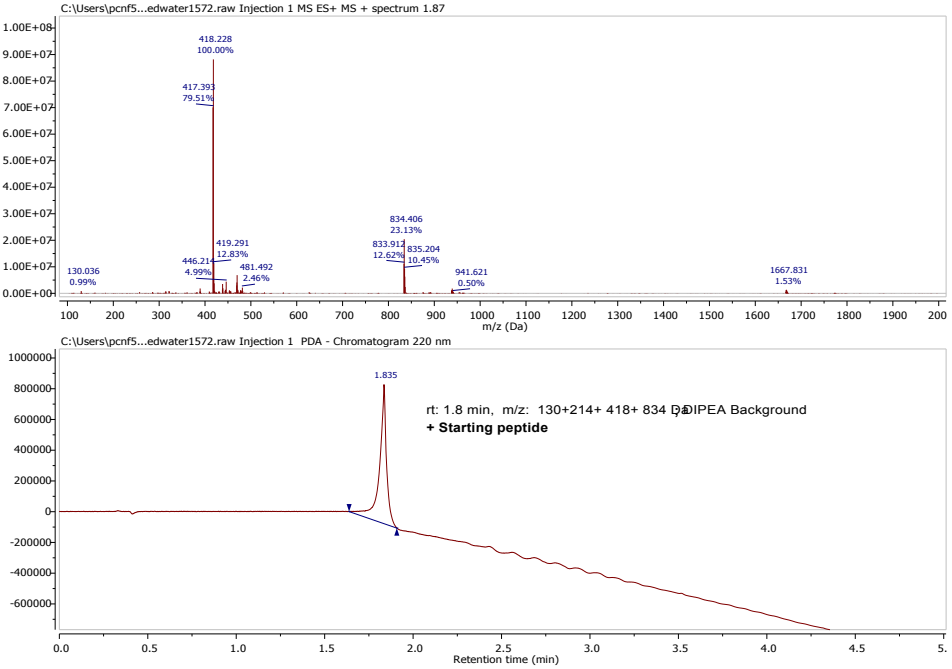
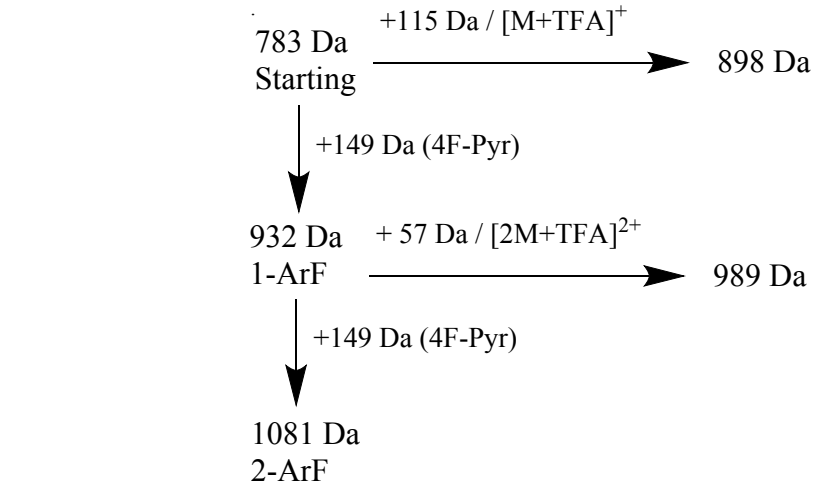


Figure SI9. LC/MS traces at λ=220 nm of crude reaction of peptide **pep3** with hexafluorobenzene when using DIPEA as a base in TFE.

Entry 10: Ac-YCGGGCAL- NH_2 + PENTAFLUOROPYRIDINE in TFE/DIPEA:



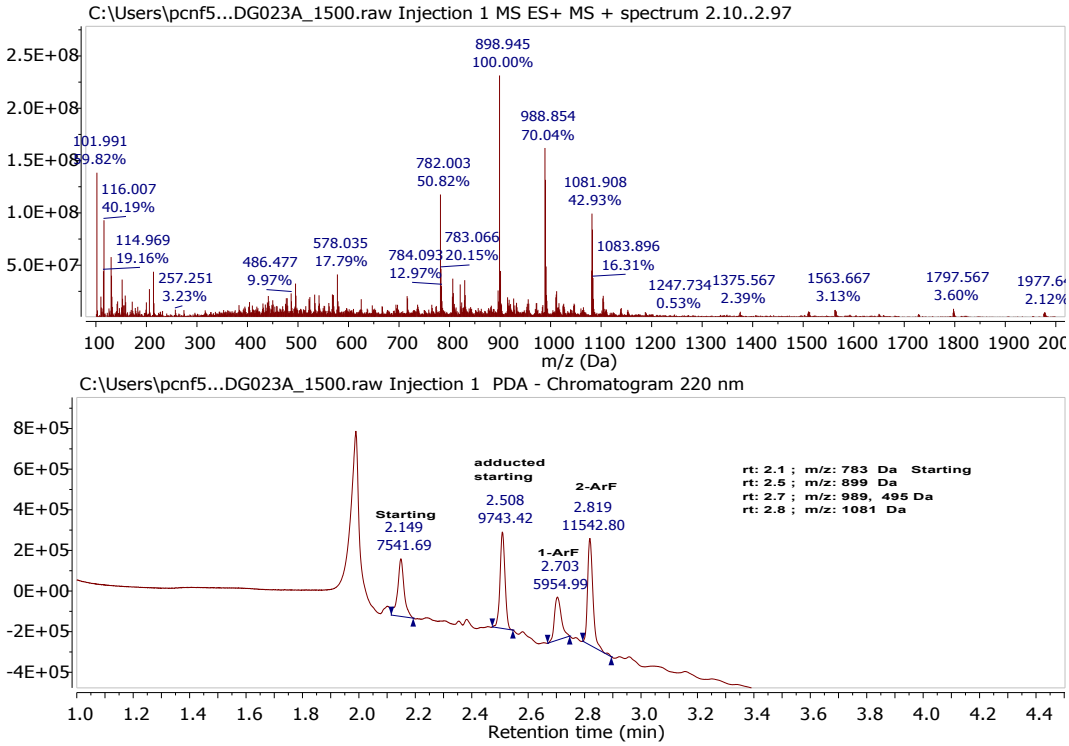


Figure SI10. LC/MS traces at λ=220 nm of crude reaction of peptide **pep1** with pentafluoropyridine when using DIPEA as a base in TFE. Upper figure showing the scheme corresponding to adduct formation on the basis of the observed masses.

Entry 11: Ac-YSGGGSAL- NH_2 + PENTAFLUOROPYRIDINE in TFE/DIPEA:

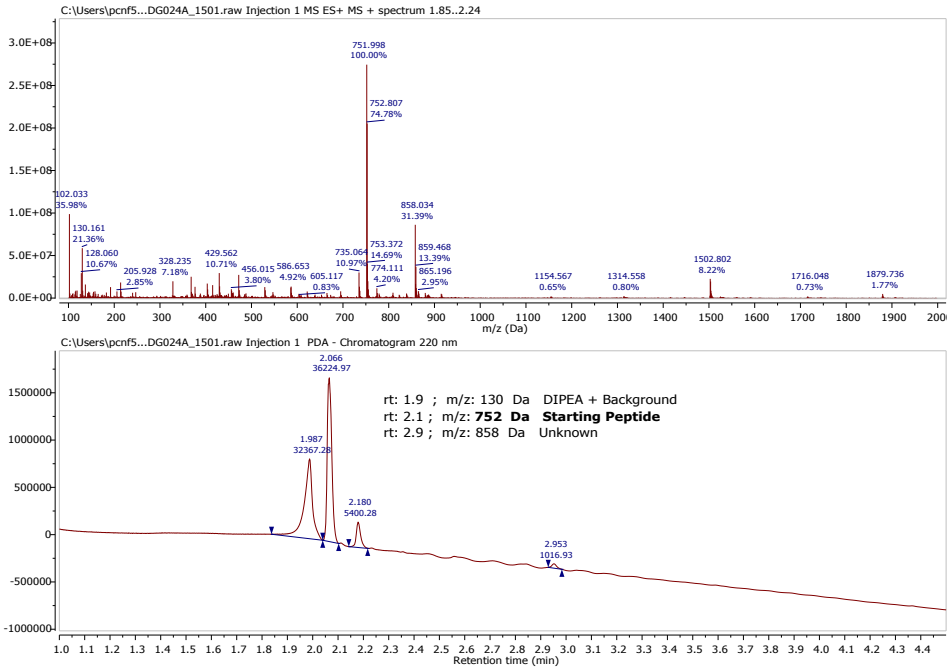


Figure SI11. LC/MS traces at λ=220 nm of crude reaction of peptide **pep2** with pentafluoropyridine when using DIPEA as a base in TFE.

Entry 12: Ac-YKGGGKAL- NH_2 + PENTAFLUOROPYRIDINE in TFE/DIPEA:

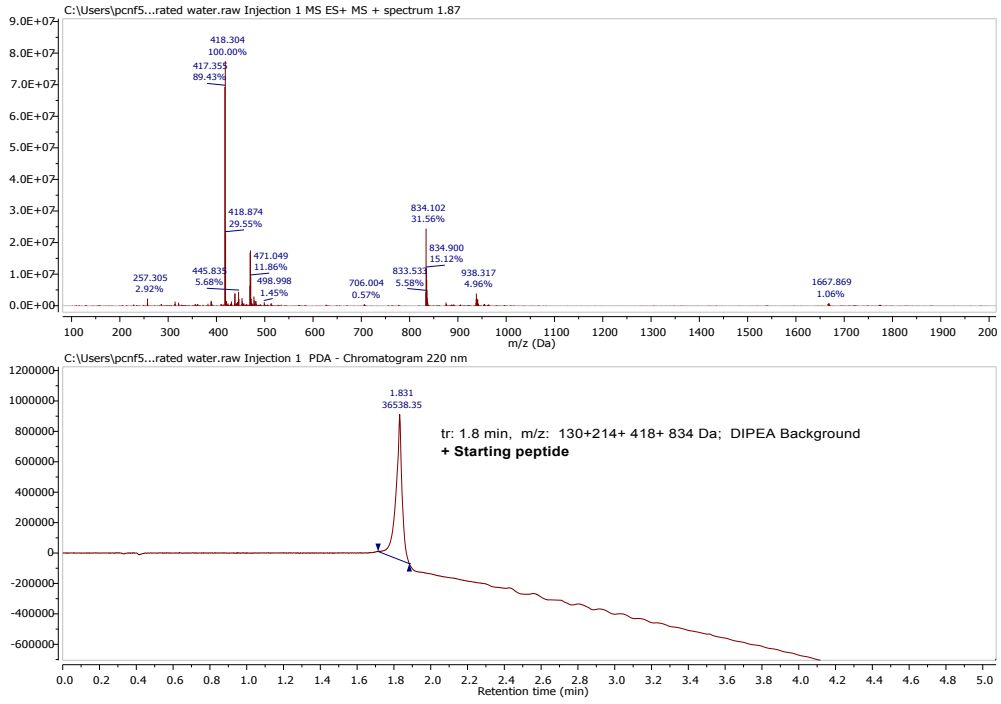


Figure SI12. LC/MS traces at λ=220 nm of crude reaction of peptide **pep3** with pentafluoropyridine when using DIPEA as a base in TFE

Effect of the base: DIPEA vs Cs_2CO_3. **Entries 13-18** from **Table 1** (main article)

Entry 13: Ac-YCGGGCAL- NH_2 + HEXAFLUOROBENZENE in TFE/Cs_2CO_3:

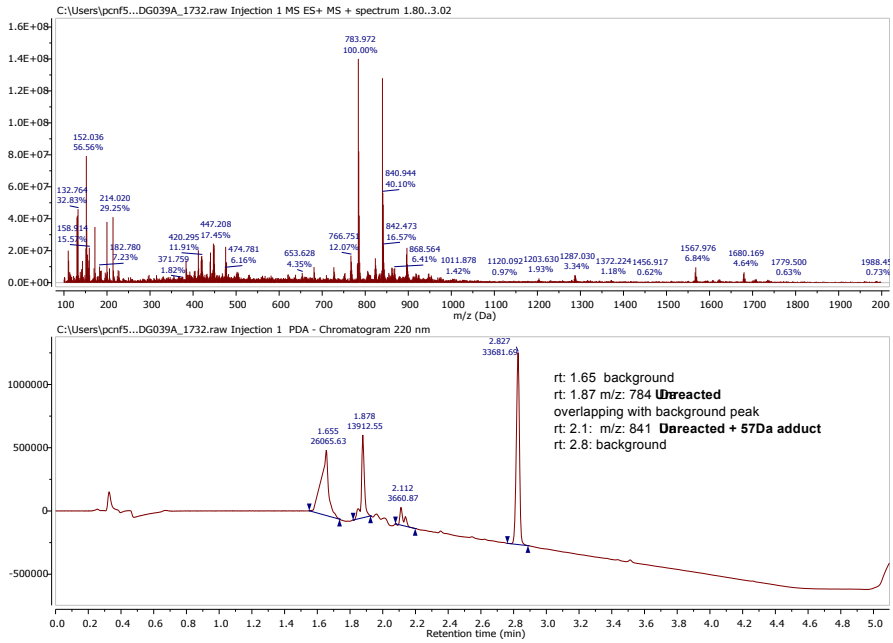


Figure SI13. LC/MS traces at λ=220 nm of crude reaction of peptide **pep1** with hexafluorobenzene when using Cs_2CO_3 as a base in TFE.

Entry 14: Ac-YSGGGSAL- NH_2 + HEXAFLUOROBENZENE in TFE/Cs_2CO_3:

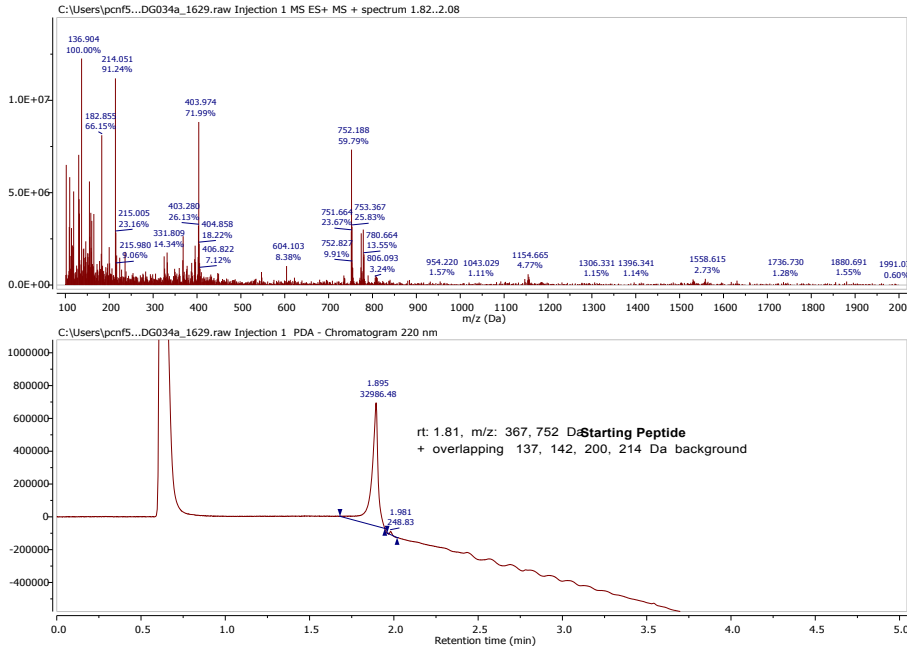


Figure SI14. LC/MS traces at λ=220 nm of crude reaction of peptide **pep2** with hexafluorobenzene when using Cs_2CO_3 as a base in TFE.

Entry 15: Ac-YKGGGKAL- NH_2 + HEXAFLUOROBENZENE in TFE/Cs_2CO_3:

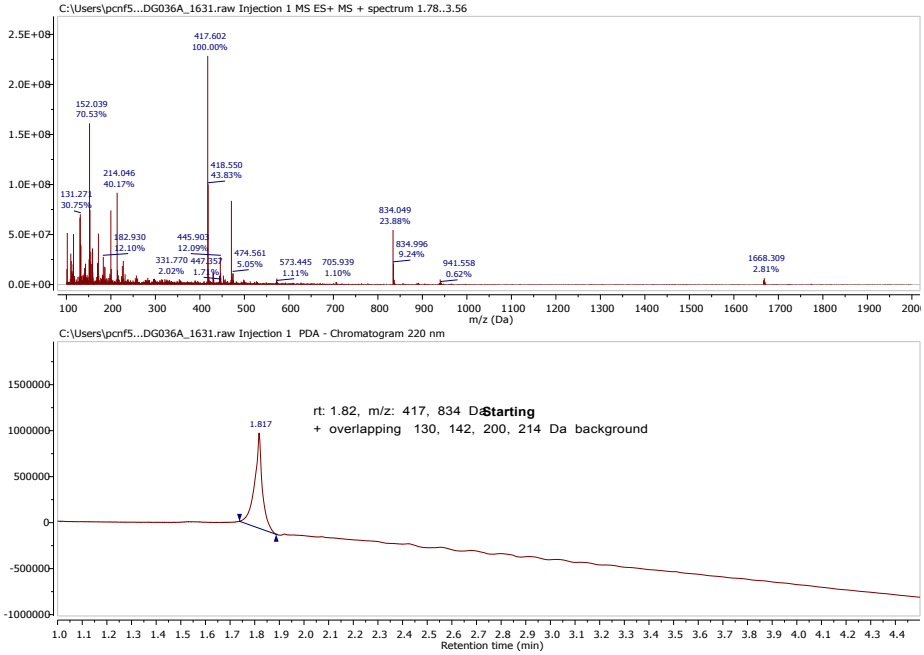
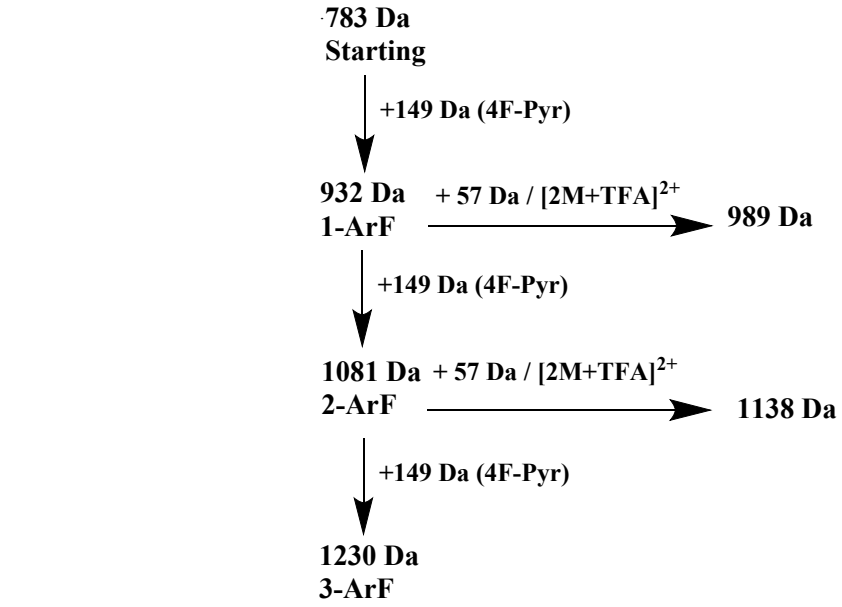


Figure SI15. LC/MS traces at λ=220 nm of crude reaction of peptide **pep3** with hexafluorobenzene when using Cs_2CO_3 as a base in TFE.

Entry 16: Ac-YCGGGCAL- NH_2 + PENTAFLUOROPYRIDINE in TFE/Cs_2CO_3:



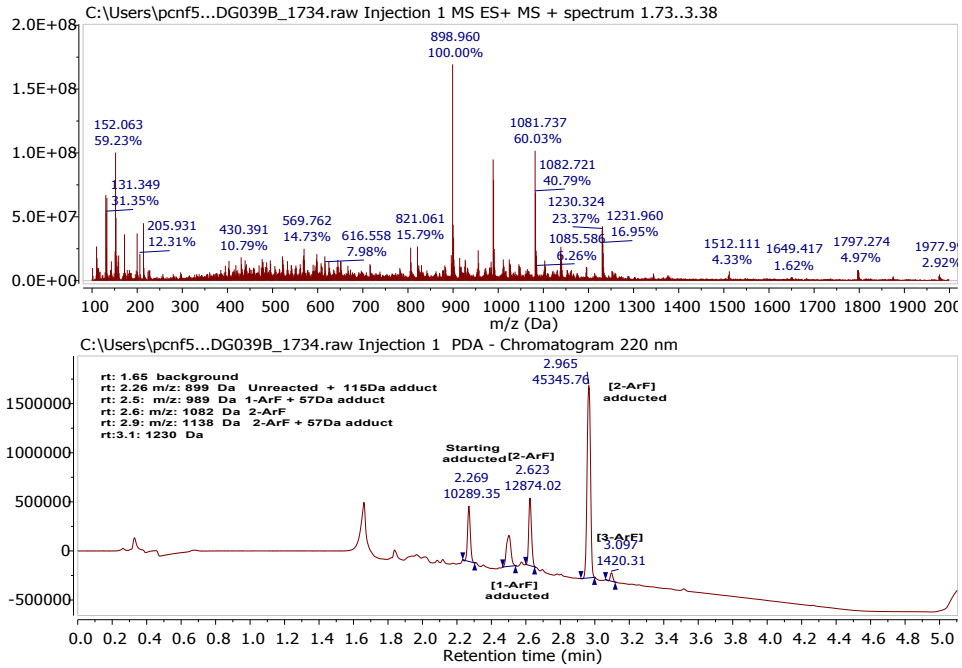


Figure SI16. LC/MS traces at λ=220 nm of crude reaction of peptide **pep1** with pentafluoropyridine when using Cs_2CO_3 as a base in TFE. Upper figure showing the scheme corresponding to adduct formation on the basis of the observed masses.

Entry 17: Ac-YSGGGSAL- NH_2 + PENTAFLUOROPYRIDINE in TFE/Cs_2CO_3

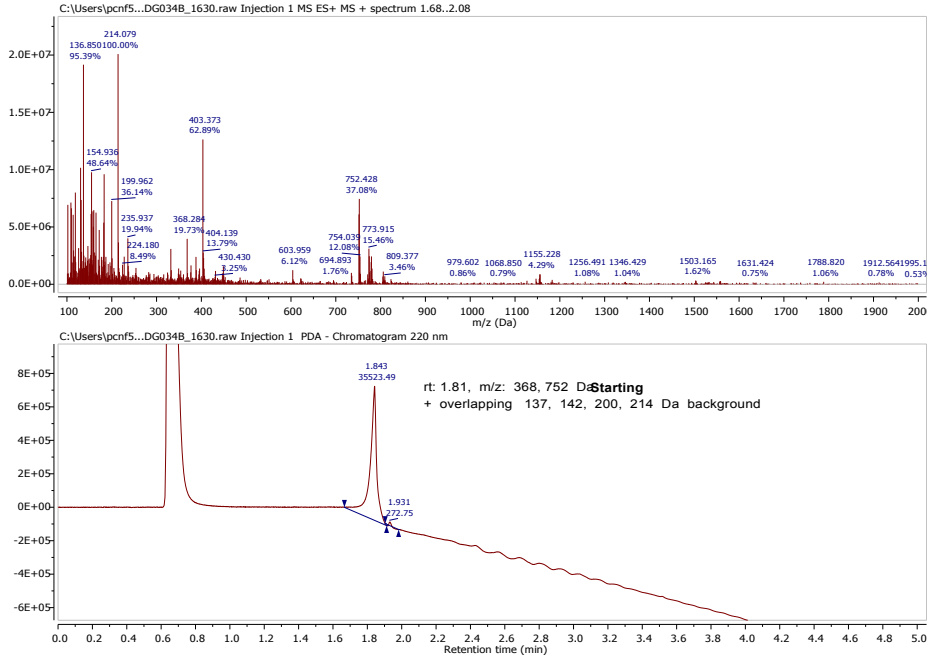


Figure SI17. LC/MS traces at λ=220 nm of crude reaction of peptide **pep2** with pentafluoropyridine when using Cs_2CO_3 as a base in TFE.

Entry 18: Ac-YKGGGKAL- NH_2 + PENTAFLUOROPYRIDINE in TFE/Cs_2CO_3

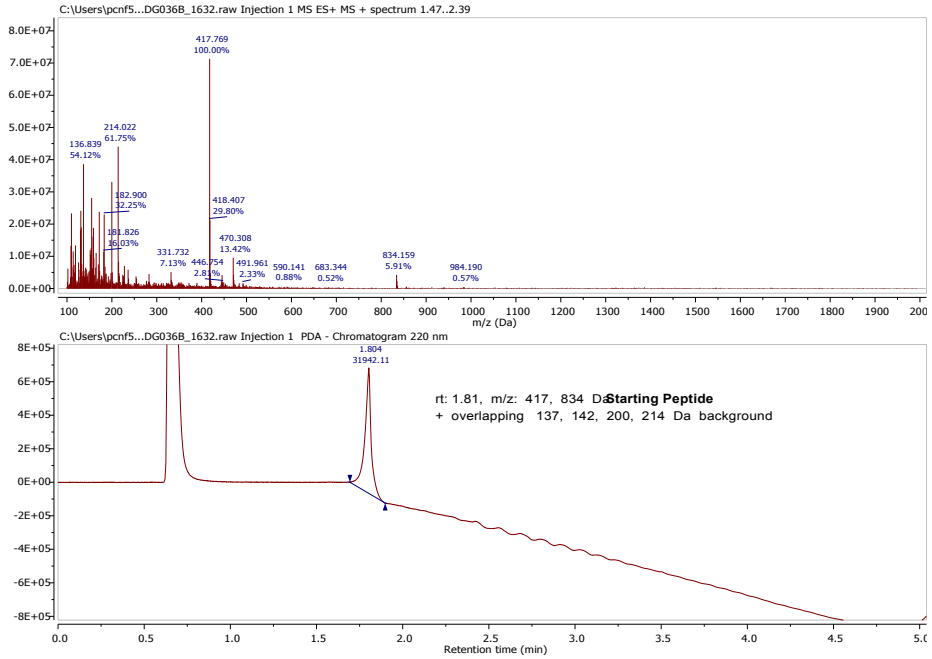


Figure SI18. LC/MS traces at λ=220 nm of crude reaction of peptide **pep3** with pentafluoropyridine when using Cs_2CO_3 as a base in TFE.

Selective tagging of **pep4**. Entries **19-22** from **Table 2** (main article)

Entry 19: Ac- FKACGKGCA - NH_2 + HEXAFLUOROBENZENE in DMF/DIPEA

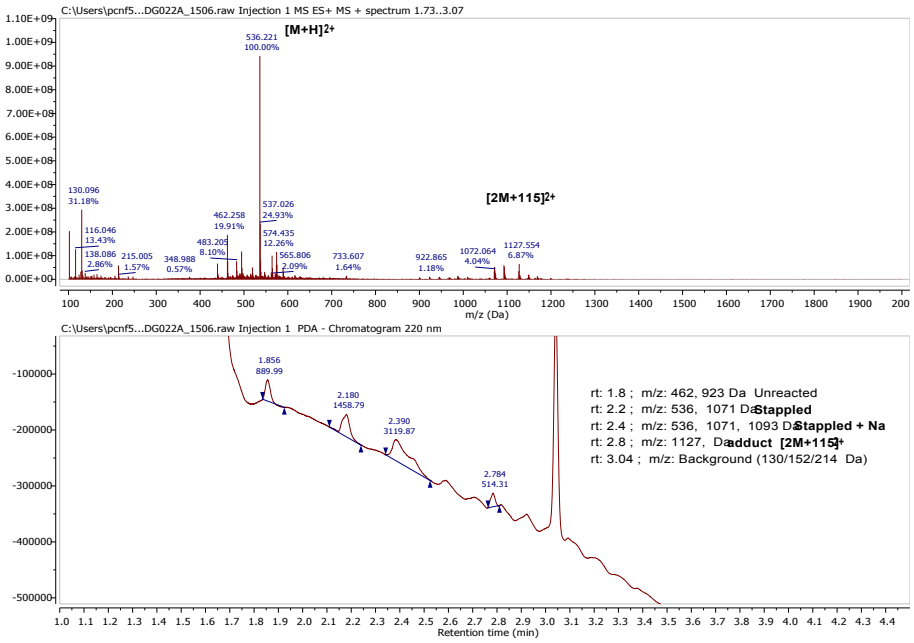


Figure SI19. LC/MS traces at λ=220 nm of crude reaction of peptide **pep4** with hexafluorobenzene when using DIPEA as a base in DMF.

Entry 20: Ac- FKACGKGCA - NH_2 + HEXAFLUOROBENZENE in TFE/DIPEA

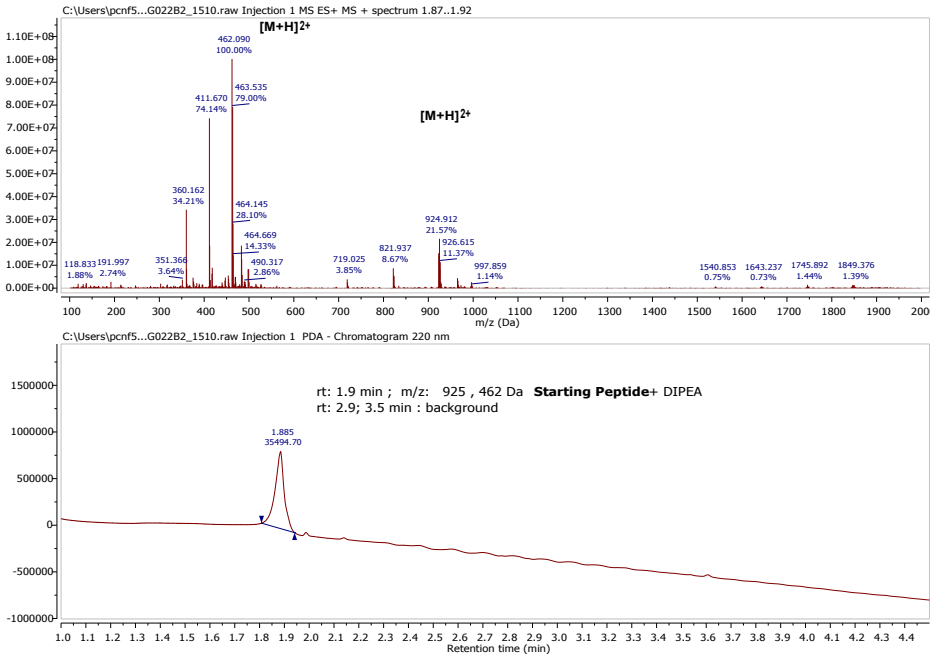


Figure SI20. LC/MS traces at λ=220 nm of crude reaction of peptide **pep4** with hexafluorobenzene when using DIPEA as a base in TFE.

Entry 21: Ac- FKACGKGCA - NH_2 + PENTAFLUOROFYRIDINE in DMF/DIPEA

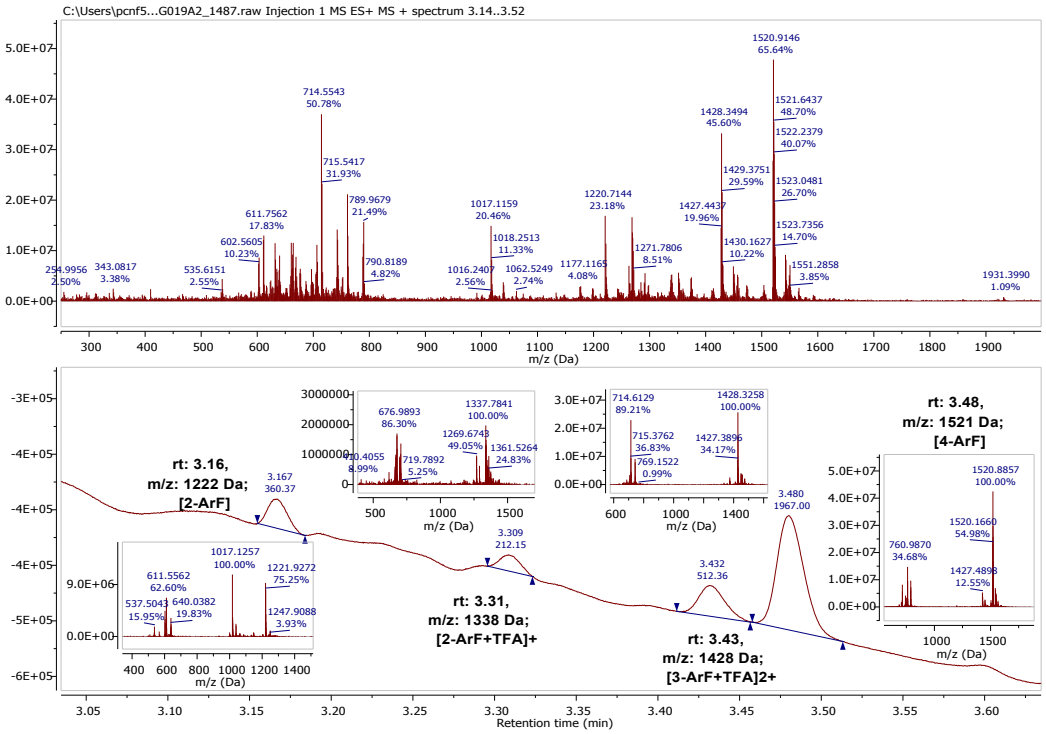


Figure SI21. LC/MS traces at λ=220 nm of crude reaction of peptide **pep4** with pentafluoropyridine when using DIPEA as a base in DMF.

Entry 22: Ac- FKACGKGCA - NH_2 + PENTAFLUOROFYRIDINE in TFE/DIPEA

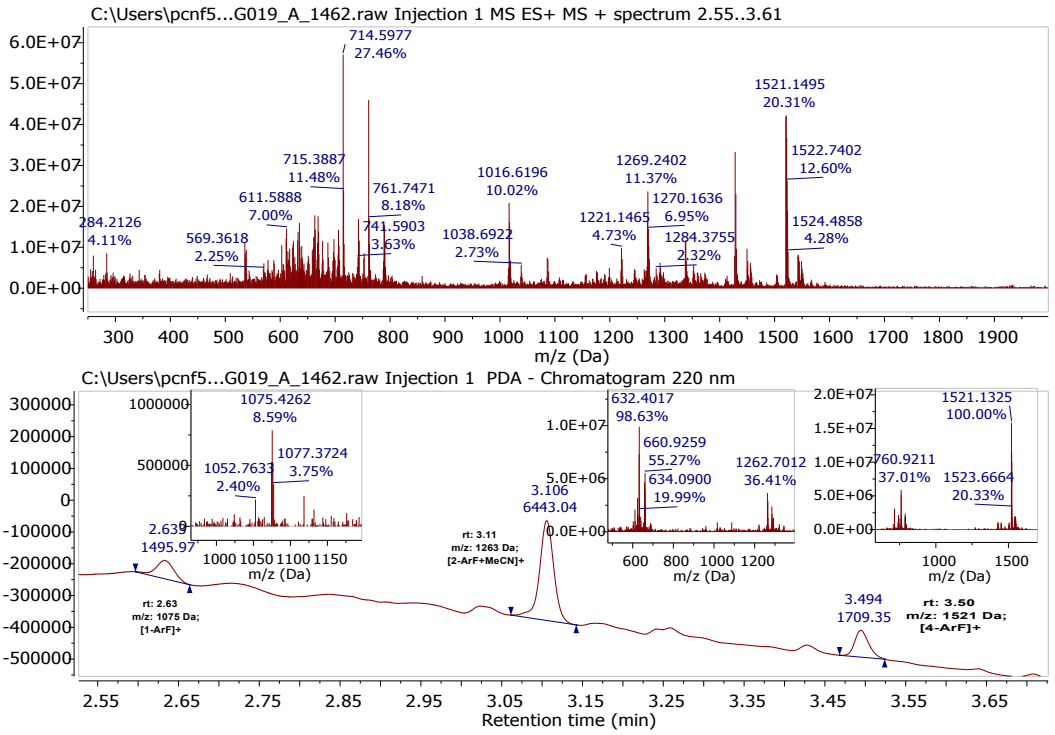


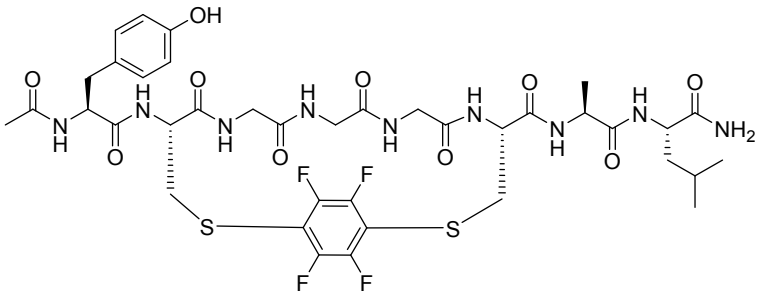
Figure SI22. LC/MS traces at λ=220 nm of crude reaction of peptide **pep4** with pentafluoropyridine when using DIPEA as a base in TFE.

Isolation and characterization of compounds 4-14

General methods:

Products from large-scale reactions were purified and isolated by semi-preparative reverse phase HPLC performed on a Discovery Bio wide pore C_{18}-5 column from Supelco (5 μm, 25 cm × 10 mm), using a Pelkin-Elmer 200 LC pump coupled to a Waters 486 tuneable absorbance detector set at λ=220 nm. A gradient with eluent A (95:5:0.1% H_2O:ACN:TFA) and eluent B (5:95:0.1% H_2O:ACN:TFA) was applied, where solvent B was firstly rose linearly from 0 to 100% during *t*=60 min and finally maintained isocratically for 5 min at a flow rate of 2 mL/min. Purified pooled fractions were then freeze-dried and the identity of the different compounds verified by LC/MS. The desired pure compounds were then further characterised by ^{19}F NMR (2 mg/mL in H_2O/CD_3CN 50:50, unless otherwise stated), high resolution LC/MS-QToF and ion directed tandem mass spectrometry (MS/MS), allowing to obtain the characteristic rupture profile for each product. In MS/MS fragmentation analysis we have made use of the accepted nomenclature for fragment ions firstly proposed by Roepstorff and Fohlman (P. Roepstorff and J. Fohlman, *Biol. Mass Spectrom*. 1984, **11**, 601–601.), and subsequently modified by Johnson et *al*. (R. S. Johnson, S. A. Martin, K. Biemann J. T. Stults and J. T. Watson, *Anal. Chem.*, 1987, **59**, 2621–2625). Note that, in peptides and proteins, ions arising from fragmentation series γ or *b* are expected to be predominant.

Product 4.



QToF LC/MS: Calculated *m/z*: 929.96, observed *m/z*: 931.49 $[M+H^+]^+$. Retention time: 2.400 min. Elemental composition: C_{38} H_{47} F_4 N_9 O_{10} S_2.

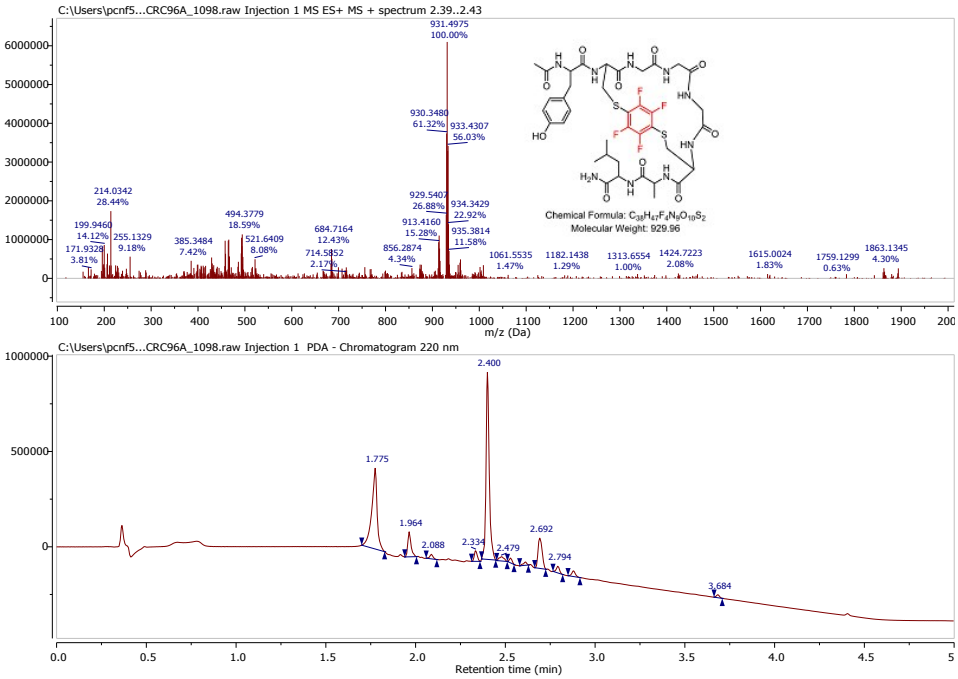


Figure SI23. Structure, high resolution QToF-LC/MS trace at λ=280 nm and composition of isolated compound **4**.

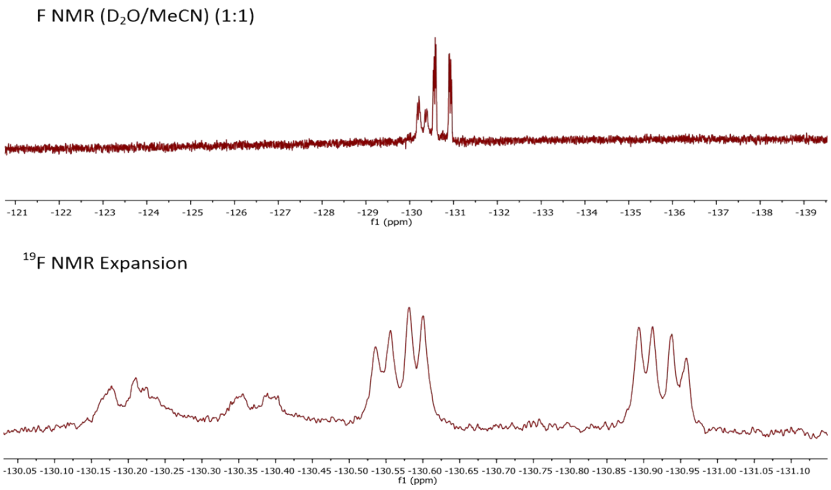
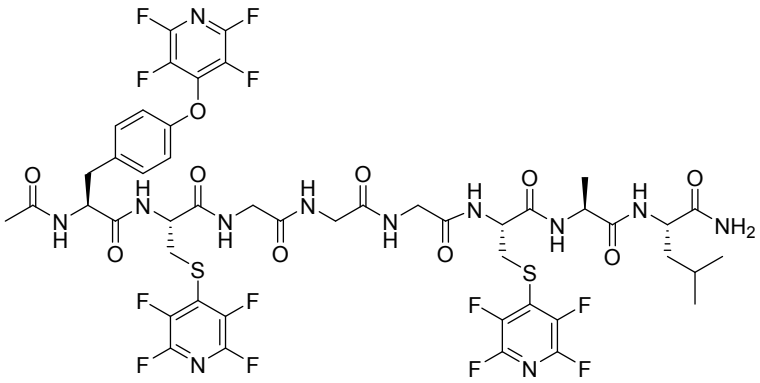


Figure SI24. ^{19}F NMR spectrum of compound **4** as recorded in D_2O/MeCN 1:1 at room temperature.

Product 5.



QToF LC/MS: Calculated *m/z*: 1230.27, observed *m/z*: 1231.28 $[M+H]^+$. Retention time: 3.442 min. Elemental composition: C_{47} H_{46} F_{12} N_{12} O_{10} S_2.

QToF-MS/MS: Calculated *m/z*: 1103.18 $[b7+H]^+$, 1032.81 $[b6+H]^+$, 780.14 $[b5+H]^+$, 722.11 $[b4+H]^+$, 665.09 $[b3+H]^+$, 608.07 $[b2+H]^+$, 356.07 $[b1+H]^+$, 495.15 $[z4+H]^+$ Da.

Observed *m/z*: 1103.22 $[b7+H]^+$, 1032.18 $[b6+H]^+$, 780.17 $[b5+H]^+$, 722.14 $[b4+H]^+$, 665.12 $[b3+H]^+$, 608.13 $[b2+H]^+$, 355.08 $[b1+H]^+$, 495.14 $[z4+H]^+$ Da.

^{19}F NMR (376 MHz, DMSO-d_6) δ -91.20 (m, 2F), -93.42 (m, 4F), -137.49 (m, 4F), -155.63 (m, 2F).

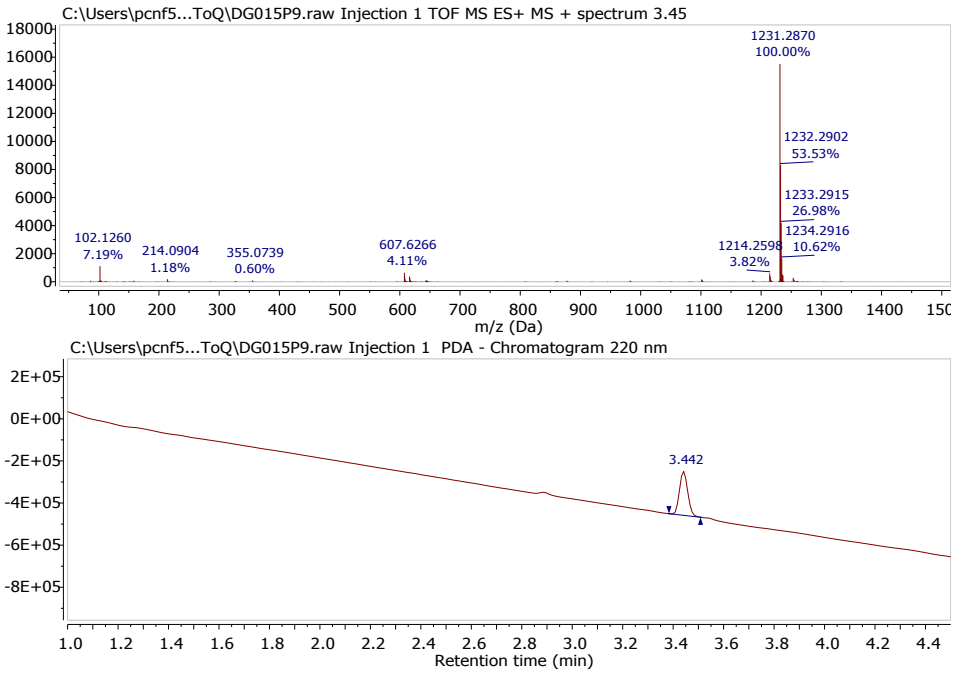


Figure SI25. Structure, high resolution QToF-LC/MS trace at λ=220 nm and composition of isolated compound **5**.

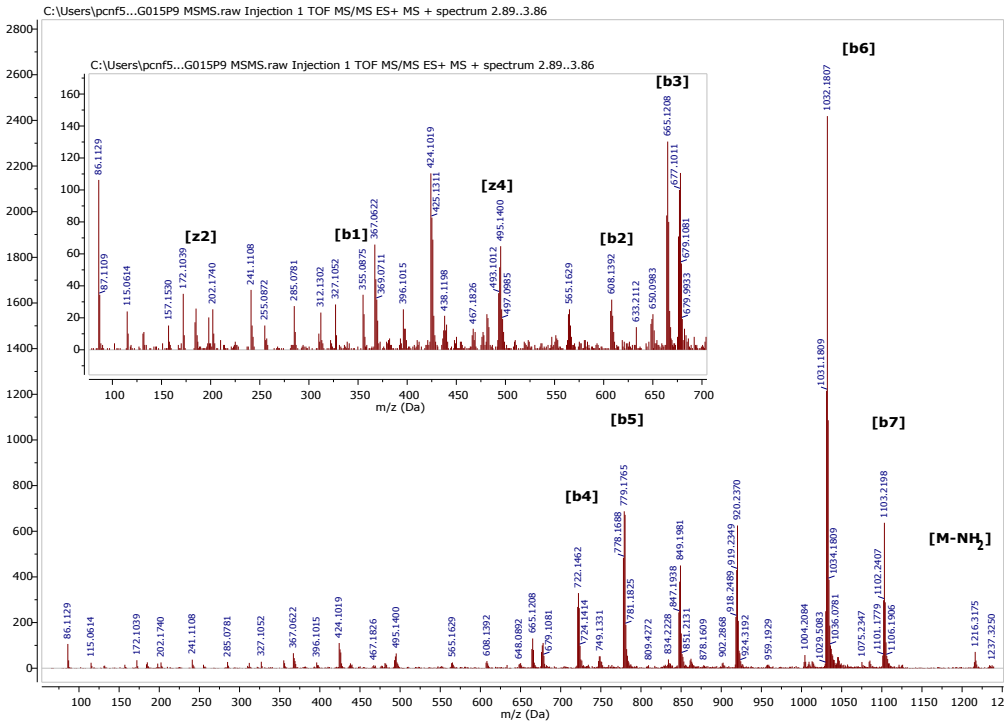


Figure SI26. MS/MS analysis of compound **5** showing its characteristic rupture pattern and the assignation of the main ions observed.

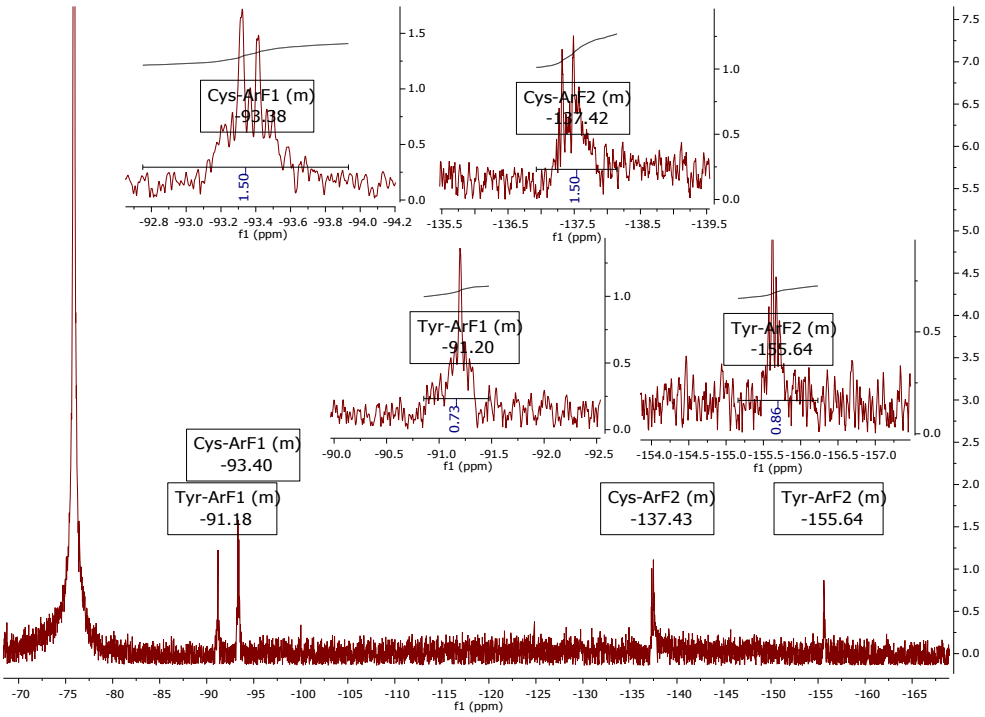
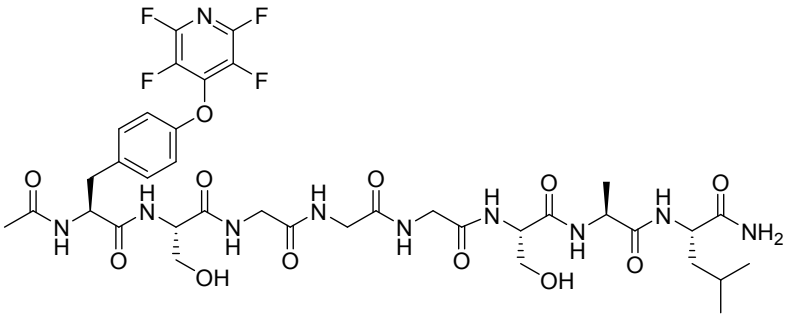


Figure SI27. ^{19}F NMR spectrum of compound **5** as recorded in DMSO-d_6 at room temperature.

Product 6.



QToF LC/MS: Calculated *m/z*: 900.34, observed *m/z*: 901.34 $[M+H]^+$. Retention time: 2.375 min. Elemental composition: C_{37} H_{48} F_4 N_{10} O_{12}.

QToF-MS/MS: Calculated *m/z*: 771.24 $[b7+H]^+$, 700.20 $[b6+H]^+$, 613.17 $[b5+H]^+$, 499.12 $[b3+H]^+$, 442.35 $[b2+H]^+$, 355.07 $[b1+H]^+$, 530.26 $[z7+H]^+$, 443.23 $[z6+H]^+$ Da.

Observed *m/z*: 771.27 $[b7+H]^+$, 700.24 $[b6+H]^+$, 613.19 $[b5+H]^+$, 449.10 $[b3+H]^+$, 442.08 $[b2+H]^+$, 355.11 $[b1+H]^+$, 530.26 $[z7+H]^+$, 442.08 $[z6+H]^+$ Da.

^{19}F NMR (376 MHz, H_2O/MeOD 1:1) δ -91.32 (m, 2F), -155.98 (m, 2F).

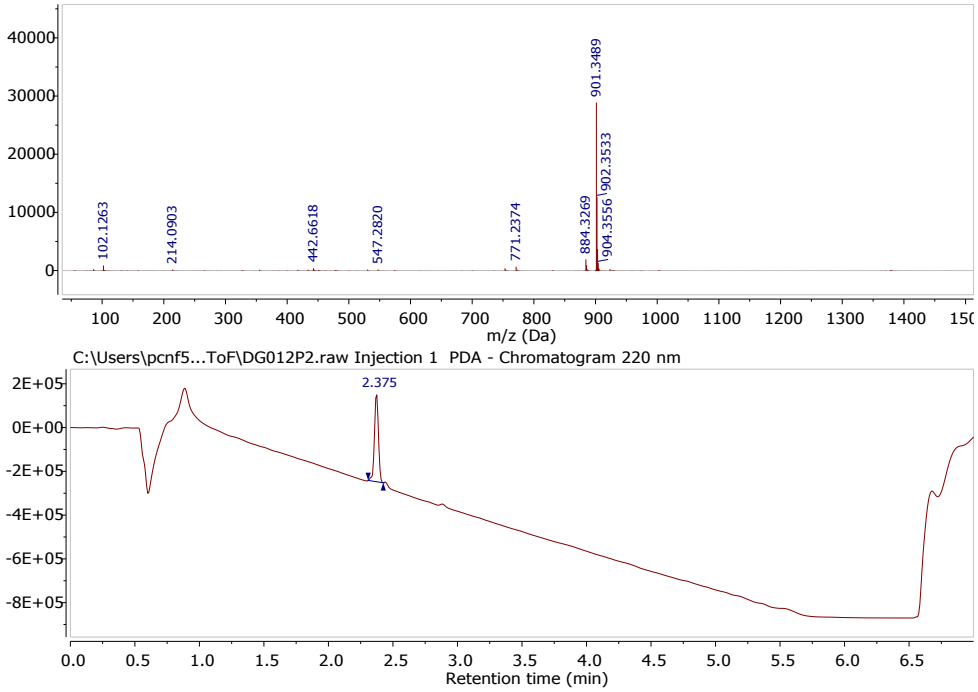


Figure SI28. Structure, high resolution QToF-LC/MS trace at λ=220 nm and composition of isolated compound **6**.

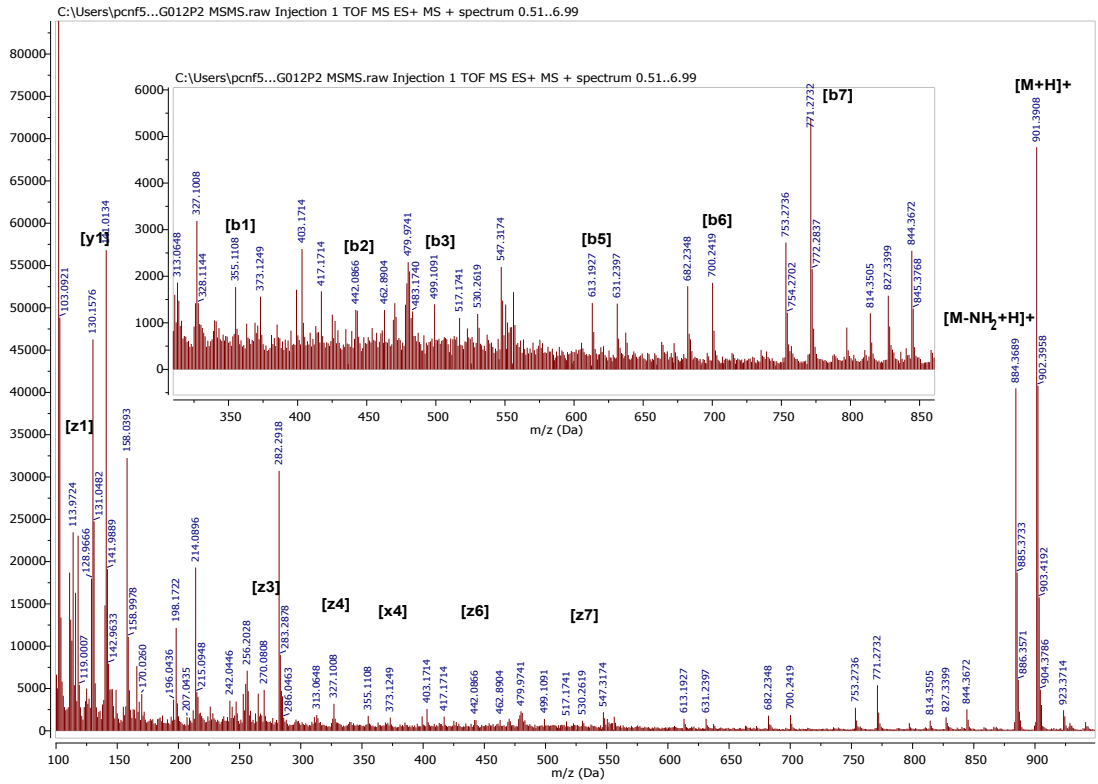


Figure SI29. MS/MS analysis of compound **6** showing its characteristic rupture pattern and the assignation of the main ions observed.

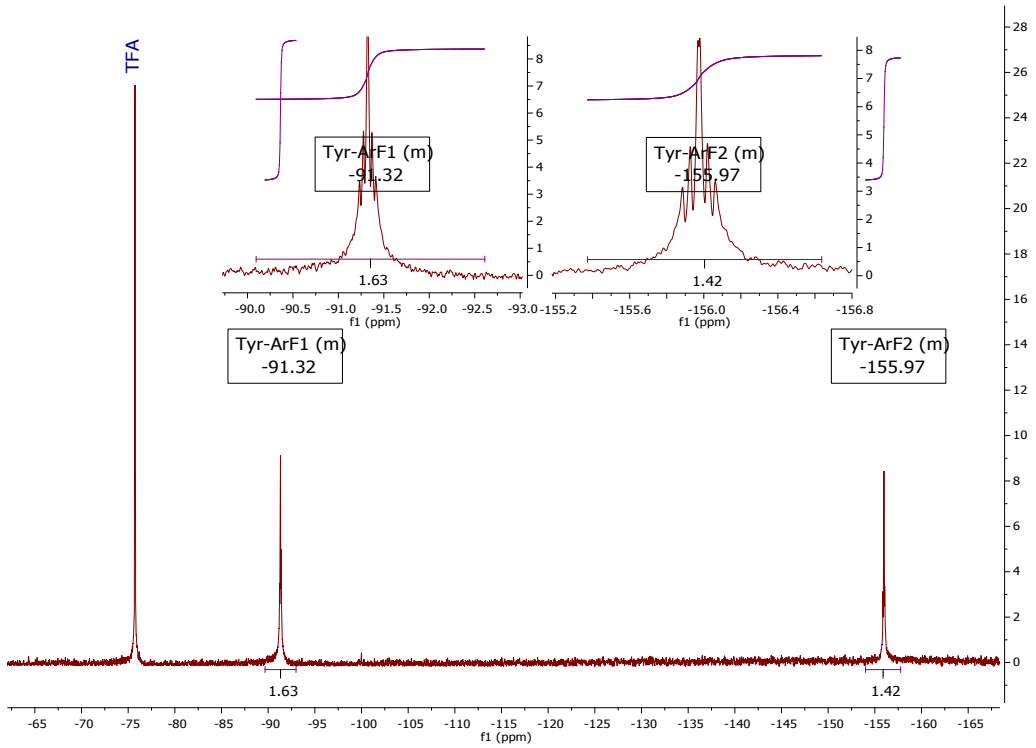
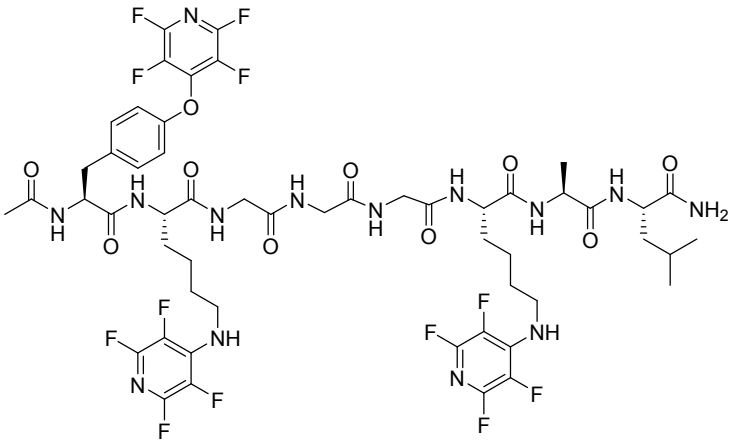


Figure SI30. ^{19}F NMR spectrum of compound **6** as recorded in H_2O/MeOD 1:1 at room temperature.

Product 7.



QToF LC/MS: Calculated *m/z*: 1280.44, observed *m/z*: 1281.45 $[M+H]^+$. Retention time: 3.492 min. Elemental composition: C_{53} H_{60} F_{12} N_{14} O_{10}.

QToF-MS/MS:

Calculated *m/z*: 1152.34 $[b7+H]^+$, 1081.30 $[b6+H]^+$, 804.22 $[b5+H]^+$, 691.2337 $[b3+H]^+$, 747.20 $[b4+H]^+$, 911.36 $[z7+H]^+$, 634.28 $[z6+H]^+$, 520.23 $[z4+H]^+$ Da.

Observed *m/z*: 1152.40 $[b7+H]^+$, 1082.36 $[b6+H]^+$, 804.26 $[b5+H]^+$, 690.23 $[b3+H]^+$, 747.24 $[b4+H]^+$, 911.36 $[z7+H]^+$, 634.29 $[z6+H]^+$, 520.23 $[z4+H]^+$ Da.

^{19}F NMR (376 MHz, H_2O/MeOD 1:1) δ -91.66 (m, 2F), -98.17 (m, 4F), -156.29 (m, 4F), -165.54 (m, 2F).

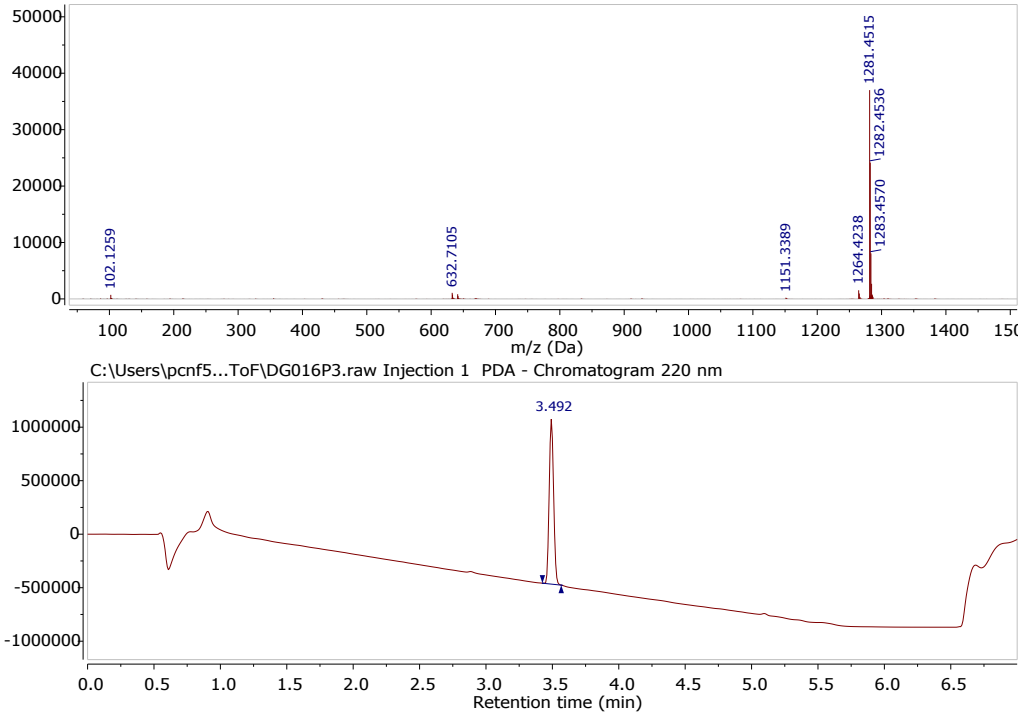


Figure SI31. Structure, high resolution QToF-LC/MS trace at λ=220 nm and composition of isolated compound **7**.

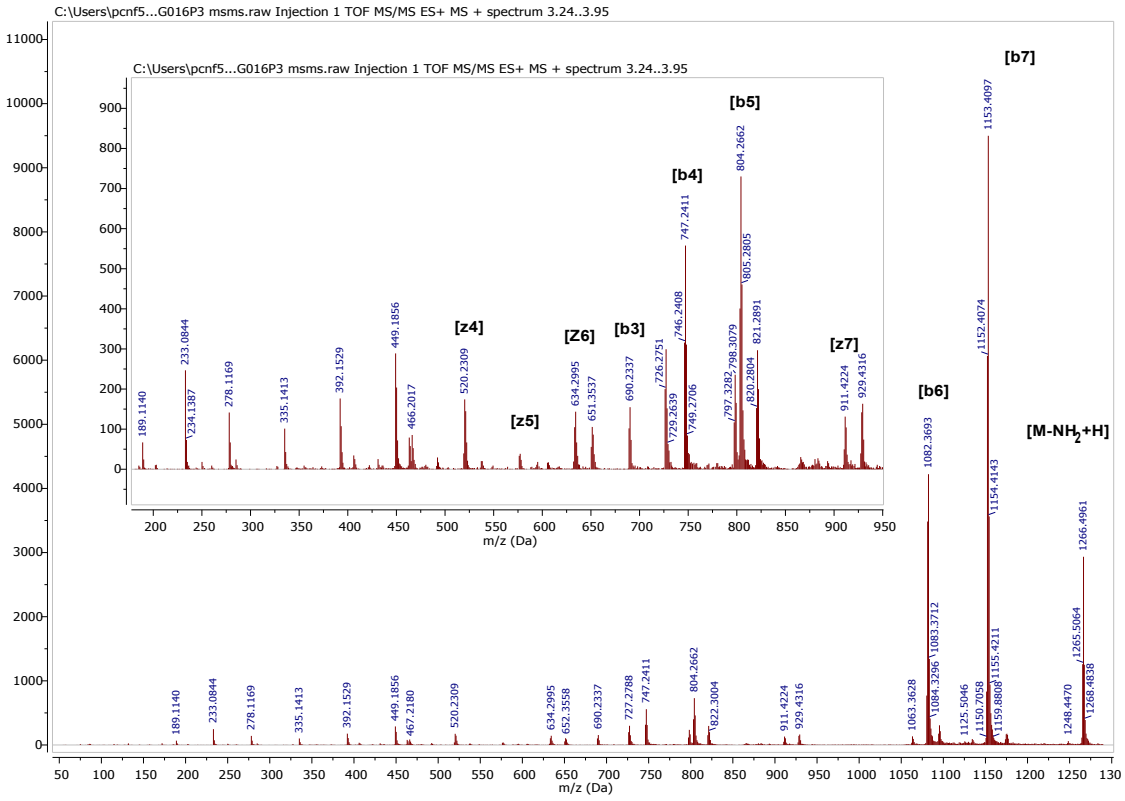


Figure SI32. MS/MS analysis of compound **7** showing its characteristic rupture pattern and the assignation of the main ions observed.

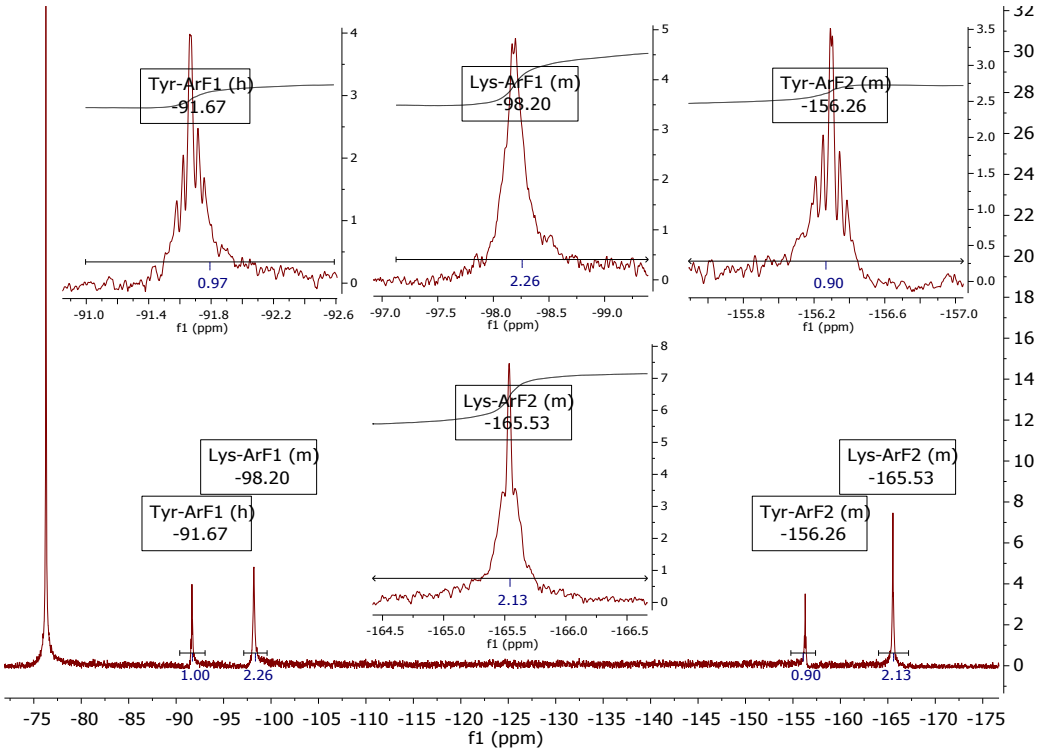
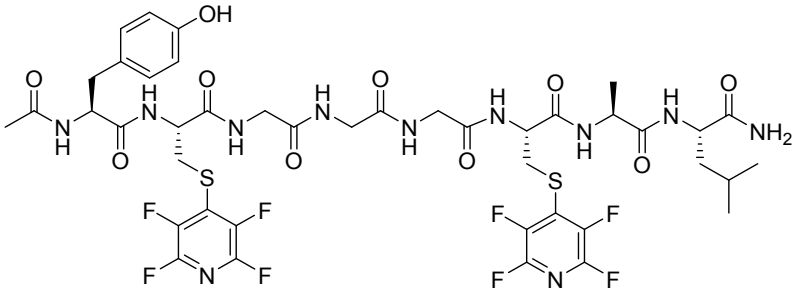


Figure SI33. ^{19}F NMR spectrum of compound **7** as recorded in H_2O/MeOD 1:1 at room temperature.

Product 8.



QToF LC/MS: Calculated *m/z*: 1081.28, observed *m/z*: 1082.19 $[M+H]^+$. Retention time: 3.017 min. Elemental composition: C_{42} H_{47} F_8 N_{11} O_{10} S_2.

QToF-MS/MS:

Calculated *m/z*: 953.18 $[b7+H]^+$, 882.14 $[b6+H]^+$, 630.56 $[b5+H]^+$, 573.51 $[b4+H]^+$, 516.46 $[b3+H]^+$ Da.

Observed *m/z*: 954.22 $[b7+H]^+$, 883.18 $[b6+H]^+$, 630.16 $[b5+H]^+$, 573.16 $[b4+H]^+$, 517.06 $[b3+H]^+$ Da.

^{19}F NMR (376 MHz, H_2O/ MeCN-d_3 1:1) δ -94.02 (m, 2F), -94.16 (m, 2F), -138.01 (m, 2F), -138.32 (m, 2F).

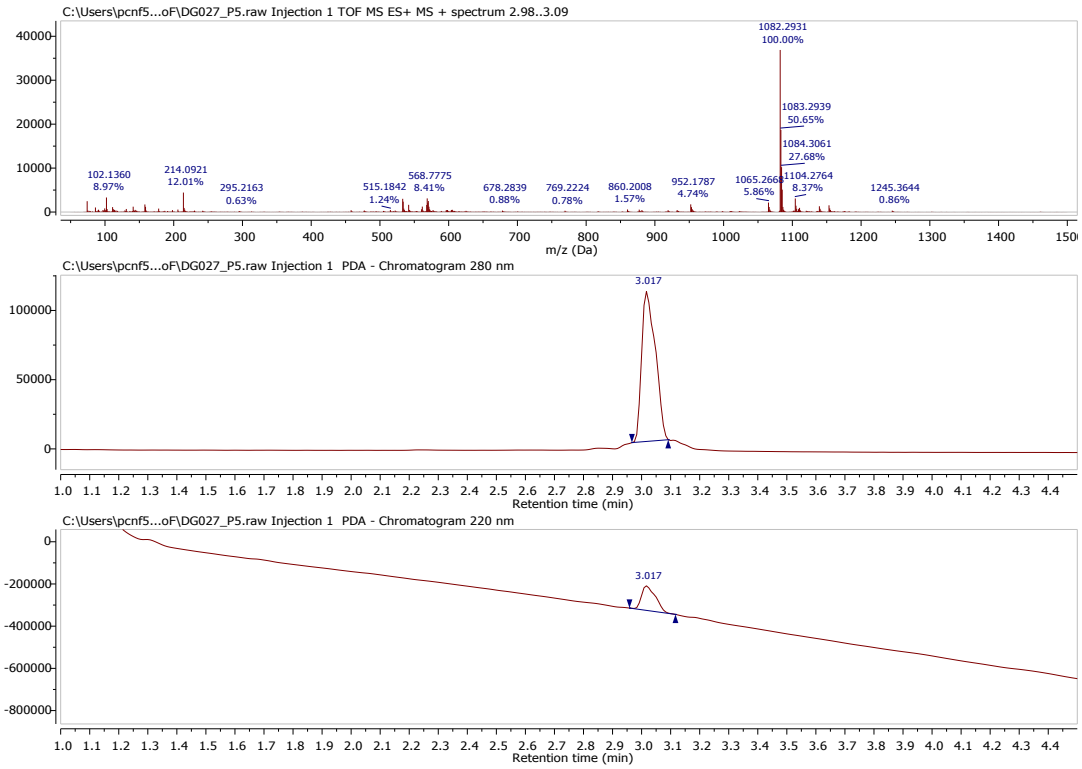


Figure SI34. Structure, high resolution QToF-LC/MS trace and composition of isolated compound **8**.

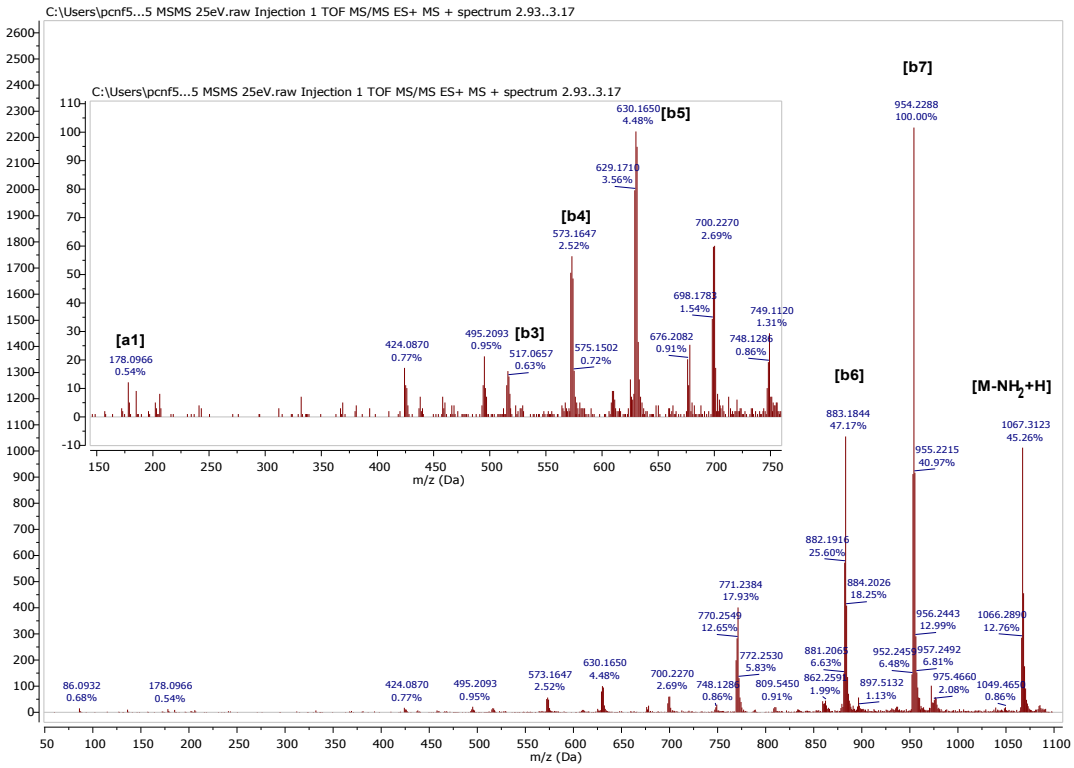


Figure SI35. MS/MS analysis of compound **8** showing its characteristic rupture pattern and the assignation of the main ions observed.

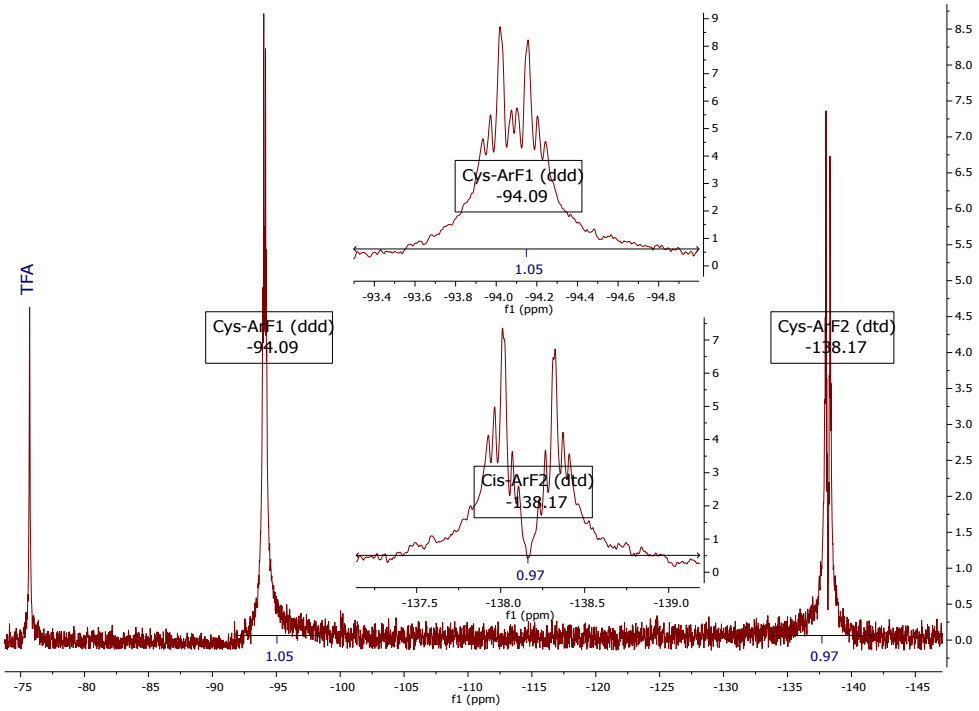
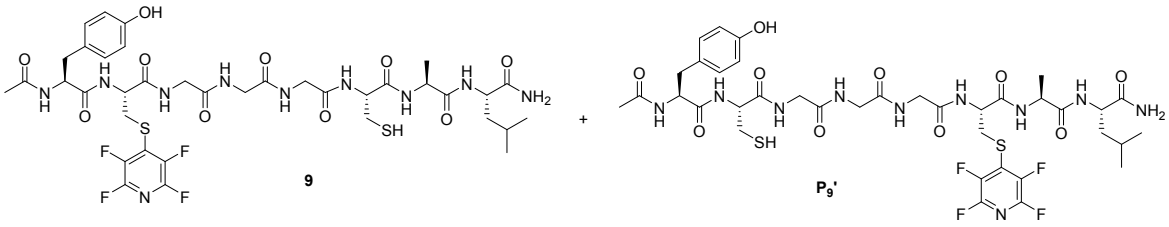


Figure SI36. ^{19}F NMR spectrum of compound **8** as recorded in H_2O/ MeCN-d_3 1:1 at room temperature.

Product 9. (Mixture of regioisomers)



QToF LC/MS: Calculated *m/z*: 932.96, observed *m/z*: 989.36 $[2M+TFA+H]^{2+}$. Retention time: 2.842 min. Elemental composition: C_{37} H_{48} F_4 N_{10} O_{10} S_2.

QToF-MS/MS:

Calculated *m/z*: 860.50 $[2(b7/b'7)+TFA+H]^{2+}$, 789.95 $[2(b6/b'6)+TFA+H]^{2+}$, 768.50 $[2(z7/z'7)+TFA+H]^{2+}$, 629.25 $[2b4+TFA+H]^{2+}$, 537.50 $[2b'5+TFA+H]^{2+}$, 515.58 $[2b2+TFA+H]^{2+}$, 480.63 $[2b'5+TFA+H]^{2+}$, 423.61 $[2b'3+TFA+H]^{2+}$, 366.59 $[2b'2+TFA+H]^{2+}$ Da.

Observed *m/z*: 860.29 $[2(b7/b'7)+TFA+H]^{2+}$, 789.25 $[2(b6/b'6)+TFA+H]^{2+}$, 769.24 $[2(z7/z'7)+TFA+H]^{2+}$, 629.17 $[2b4+TFA+H]^{2+}$, 536.23 $[2b'5+TFA+H]^{2+}$, 515.17 $[2b2+TFA+H]^{2+}$, 479.21 $[2b'4+TFA+H]^{2+}$, 422.19 $[2b'3+TFA+H]^{2+}$, 365.17 $[2b'2+TFA+H]^{2+}$ Da.

^{19}F NMR (376 MHz, H_2O/ MeCN-d_3 1:1) δ -94.05 (m, 2F), -94.18 (m, 2F), -138.01 (m, 2F), -138.31 (m, 2F).

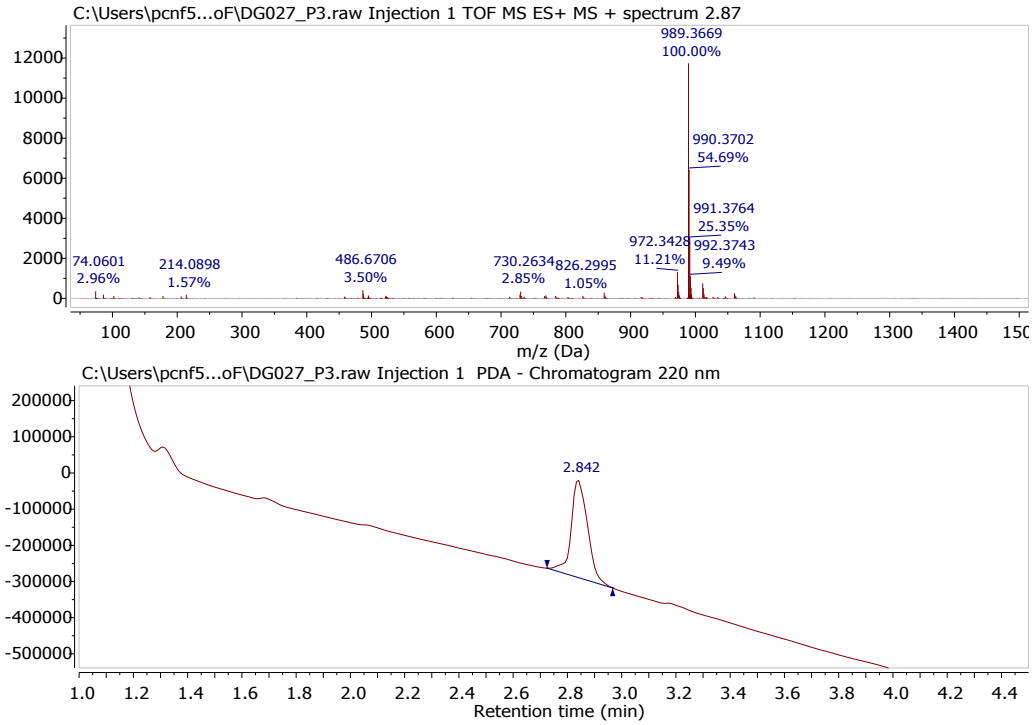


Figure SI37. Structure, high resolution QToF-LC/MS trace at λ=220 nm and composition of isolated compound **9**.

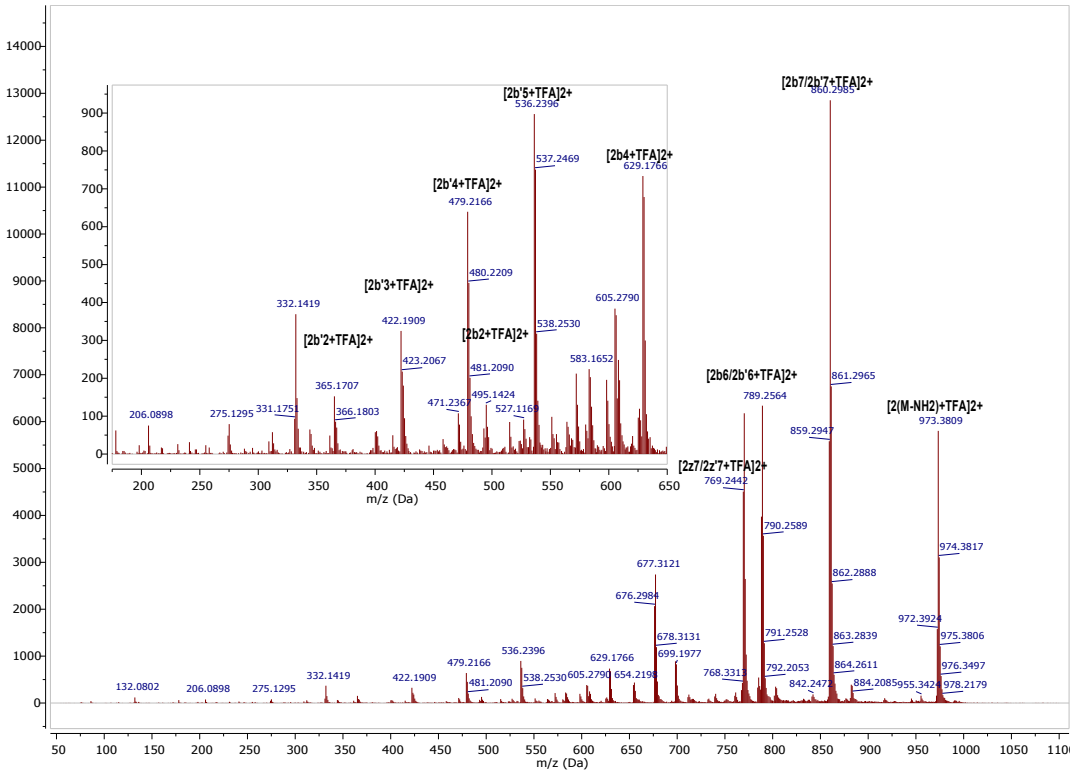


Figure SI38. MS/MS analysis of compound **9** showing its characteristic rupture pattern and the assignation of the main ions observed.

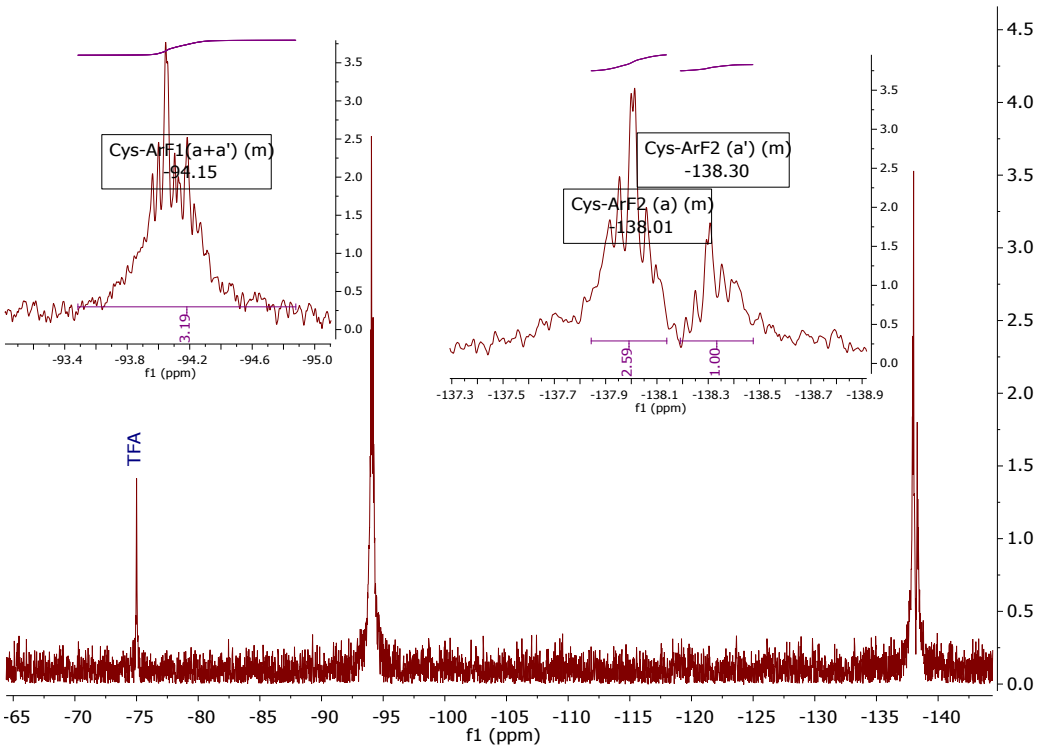
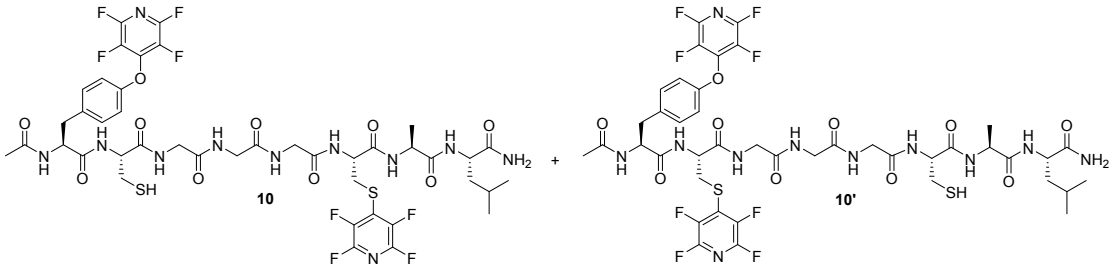


Figure SI39. ^{19}F NMR spectrum of compound **9** as recorded in H_2O/ MeCN-d_3 1:1 at room temperature.

Product 10. (Mixture of regioisomers)



QToF LC/MS: Calculated *m/z*: 1081.28, observed *m/z*: 1138.35 $[2M+TFA+2H^+]^{2+}$. Retention time: 3.300 min. Elemental composition: C_{42} H_{47} F_8 N_{11} O_{10} S_2.

QToF-MS/MS:

Calculated *m/z*: 938.64 $[2(b6/b'6)+TFA+2H]^{2+}$, 919.18 $[(b7/ b'7)+TFA-4fPyr+H]^+$, 848.15 $[b6/b'6+TFA-4fPyr+H]^+$, 778.61 $[2(b'4)+TFA+H]^{2+}$, 722.59 $[2b'3+TFA+H]^{2+}$, 686.60 $[2b5 + TFA +H]^{2+}$, 664.57 $[2b'3+ TFA +H]^{2+}$, 629.62 $[2b4 + TFA +H]^{2+}$, 480.15 $[2b5-4fPyr+H]^+$, 423.13 $[2b4-4fPyr+H]^+$ Da.

Observed *m/z*: 939.24 $[2(b6/b'6)+TFA+H]^{2+}$, 920.56 $[(b7/b'7)+ TFA-4fPyr+H]^+$, 849.17 $[b6/b'6)+TFA-4fPyr+H]^+$, 779.14 $[2b'4+TFA+H]^{2+}$, 723.14 $[2b'3+TFA+H]^{2+}$, 687.23 $[2b5+TFA+H]^{2+}$, 664.12 $[2b'3+TFA+H]^{2+}$, 630.18 $[2b4 +TFA+H]^{2+}$, 481.13 $[2b5-4fPyr+H]^+$, 424.08 $[2b4-4fPyr+H]^+$ Da.

^{19}F NMR (376 MHz, H_2O/ MeCN-d_3 1:1) δ -91.57 (m, 2F), -93.40 (m, 2F), -137.69 (m, 2F), -156.12 (m, 2F).

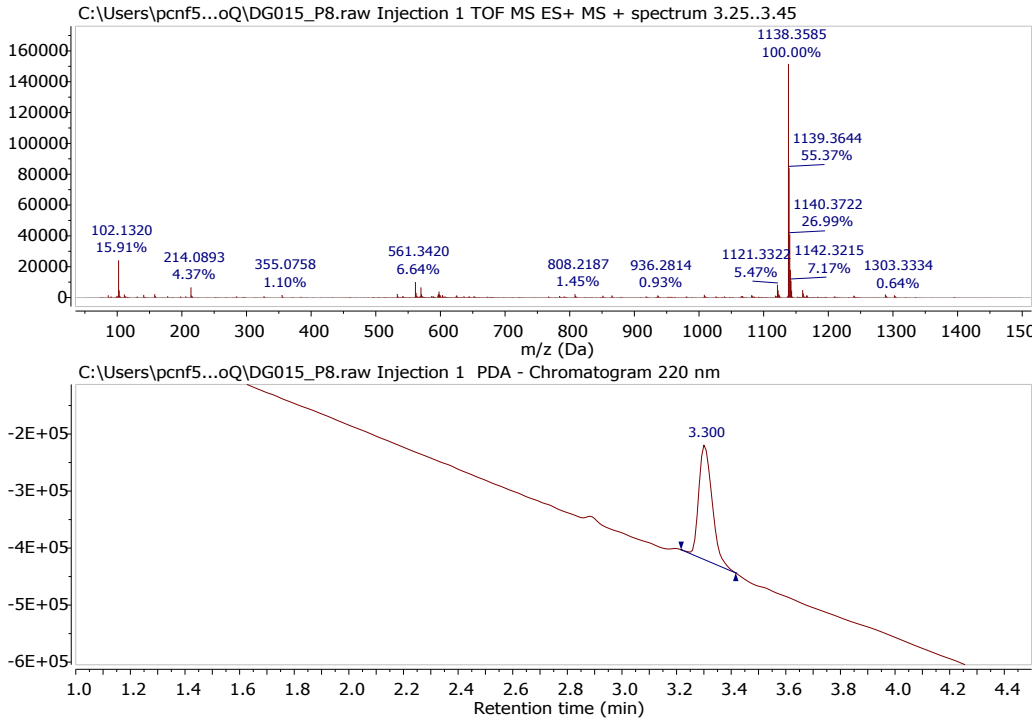


Figure SI40. Structure, high resolution QToF-LC/MS trace at λ=220 nm and composition of isolated compound **10**.

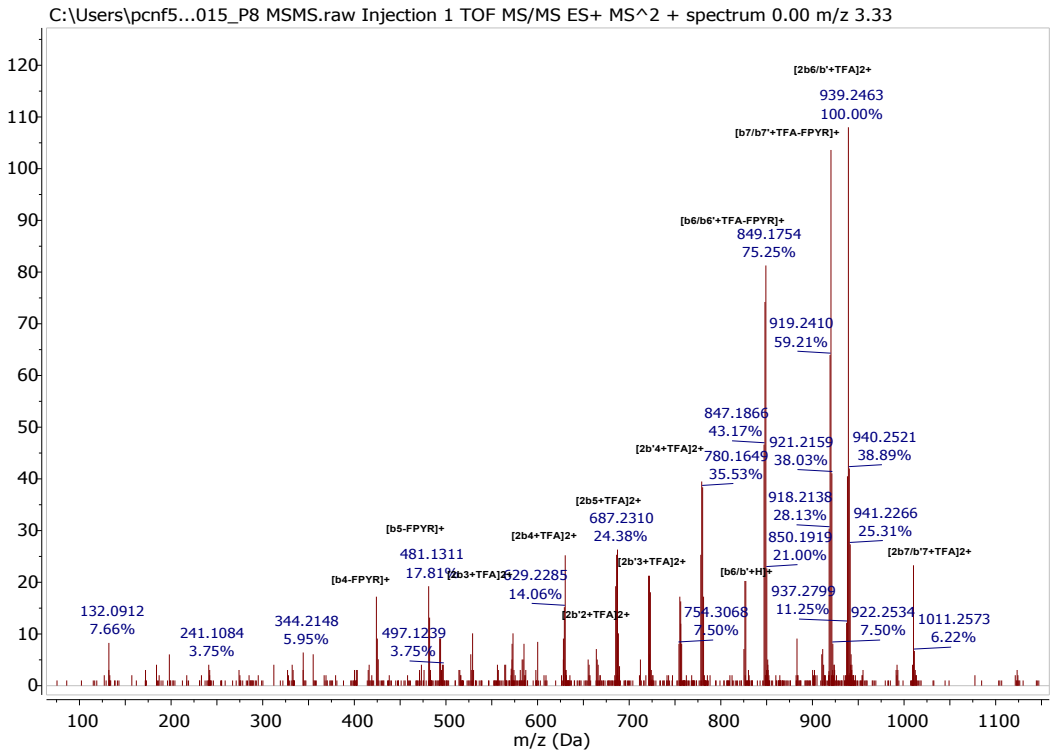


Figure SI41. MS/MS analysis of compound **10** showing its characteristic rupture pattern and the assignation of the main ions observed.

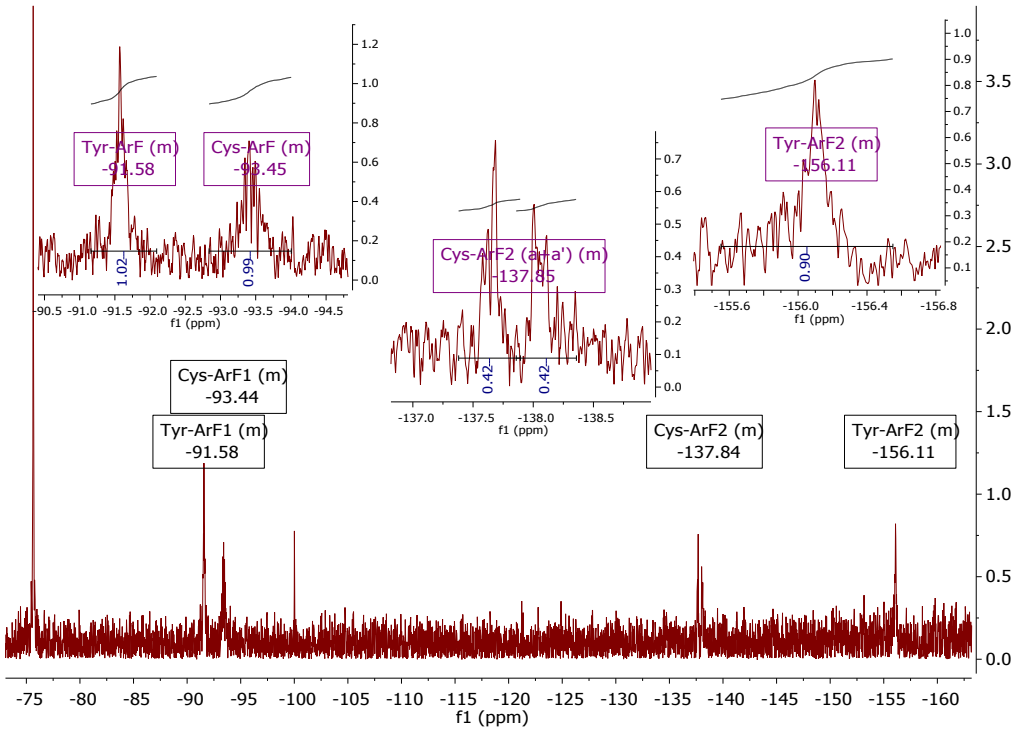
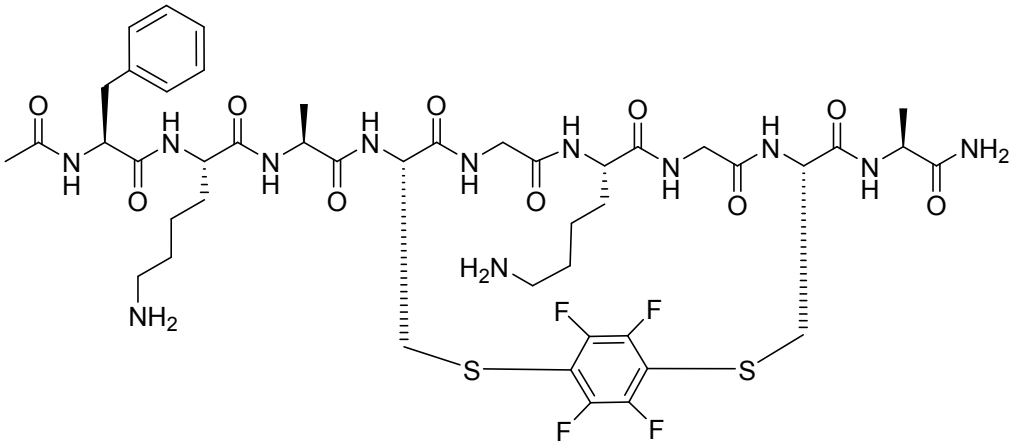


Figure SI42. ^{19}F NMR spectrum of compound **10** as recorded in H_2O/ MeCN-d_3 1:1 at room temperature.

Product 11.



QToF LC/MS: Calculated *m/z*: 1070.41, observed *m/z*: 1071.41 $[M+H]^+$, 536.39 $[M+2H]^{2+}$. Retention time: 1.875 min. Elemental composition: $C_{45}\ H_{62}\ F_4\ N_{12}\ O_{10}\ S_2$.

QToF-MS/MS:

Calculated *m/z*: 881.32 $[y8+H]^+$, 753.23 $[y7+H]^+$, 536.22 $[M+2H]^{2+}$, 492.67 $[b8+2H]^{2+}$, 441.16 $[y8+2H]^{2+}$ Da.

Observed *m/z*: 884.28 $[y8+H]^+$, 757.26 $[y7+H]^+$, 537.72 $[M+2H]^{2+}$, 493.19 $[b8+2H]^{2+}$, 442.66 $[y8+2H]^{2+}$ Da.

^{19}F NMR (376 MHz, H_2O/ MeCN-d_3 1:1) δ -134.53 (m, 4F).

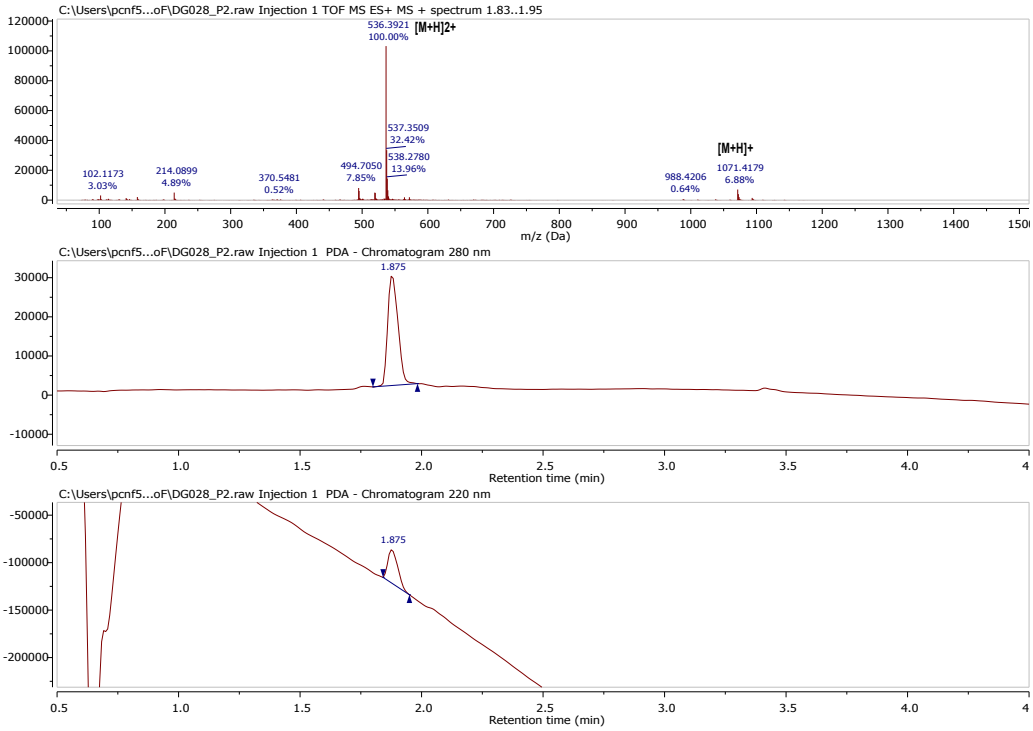


Figure SI43. Structure, high resolution QToF-LC/MS trace at λ=220 nm and composition of isolated compound **11**.

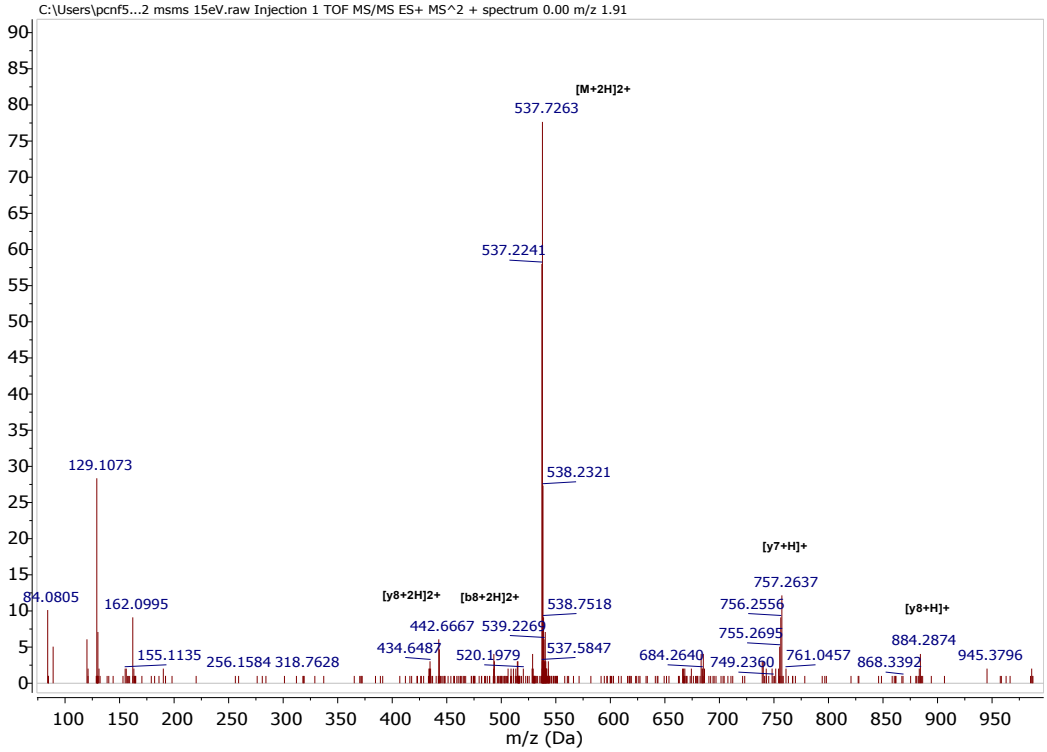


Figure SI44. MS/MS analysis of compound **11** showing its characteristic rupture pattern and the assignation of the main ions observed.

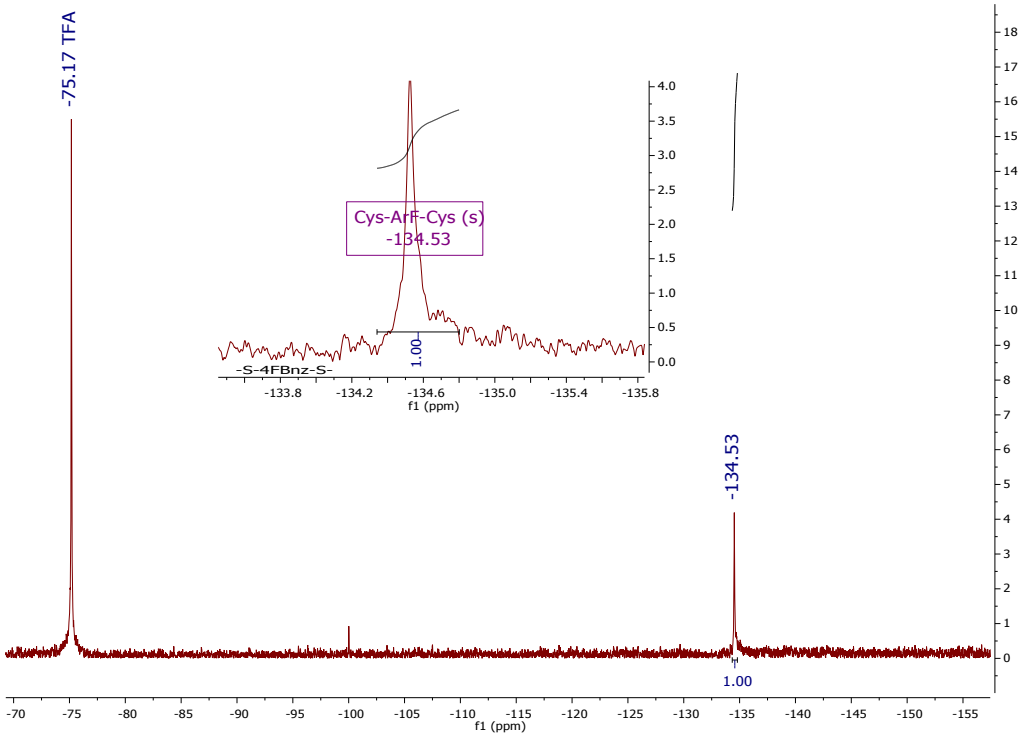
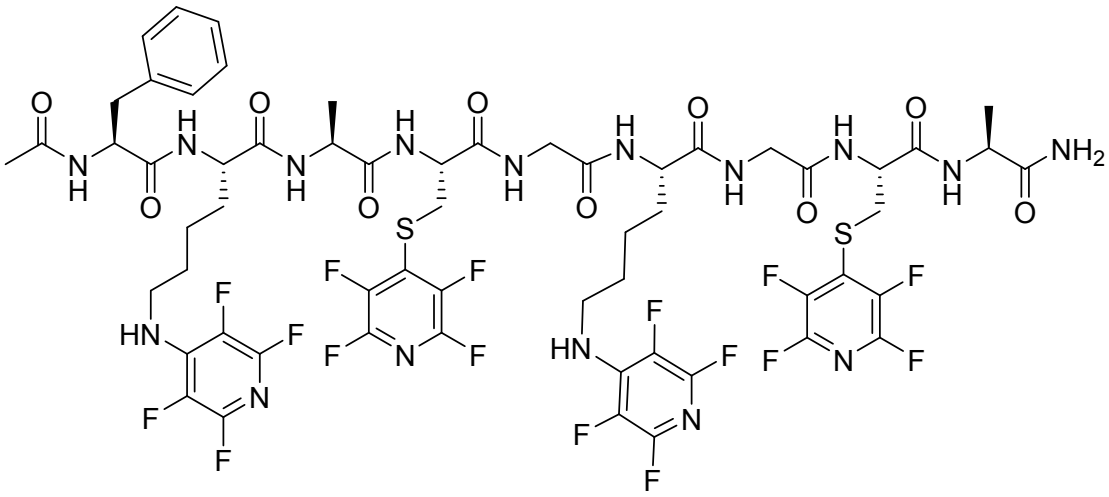


Figure SI45. ^{19}F NMR spectrum of compound **11** as recorded in H_2O/ MeCN-d_3 1:1 at room temperature.

Product 12.



QToF LC/MS: Calculated *m/z*: 1520.39, observed *m/z*: 1521.41 $[M+H]^+$. Retention time: 4.033 min. Elemental composition: $C_{59}\,H_{60}\,F_{16}\,N_{16}\,O_{10}\,S_2$.

QToF MS/MS:

Calculated *m/z*: 753.18 $[M\text{-}NH_2+2H]^{2+}$, 717.66 $[b8+2H]^{2+}$ Da.

Observed 754.18 $[M\text{-}NH_2+2H]^{2+}$, 718.15 $[b8+2H]^{2+}$ Da.

^{19}F NMR (376 MHz, H_2O/ MeCN-d_3 1:1) δ -93.99 (m, 4F), -98.06 (m, 4F), -138.14 (m, 4F), -165.38 (m, 4F).

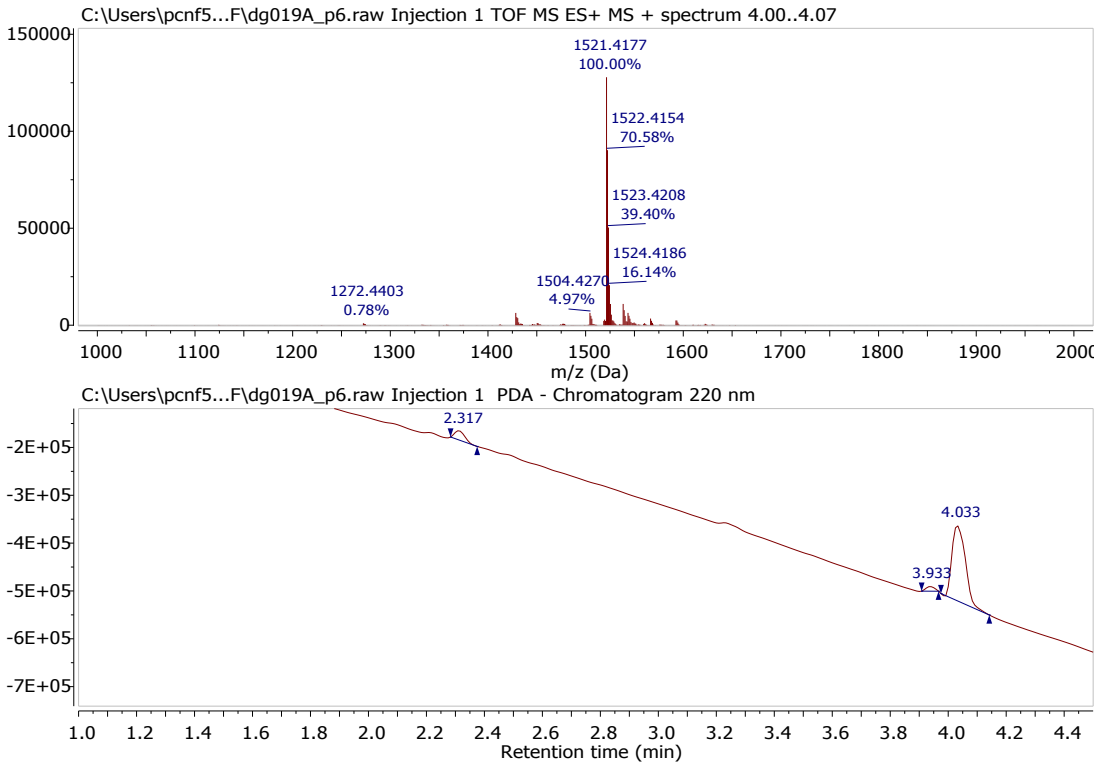


Figure SI46. Structure, high resolution QToF-LC/MS trace at λ=220 nm and composition of isolated compound **12**.

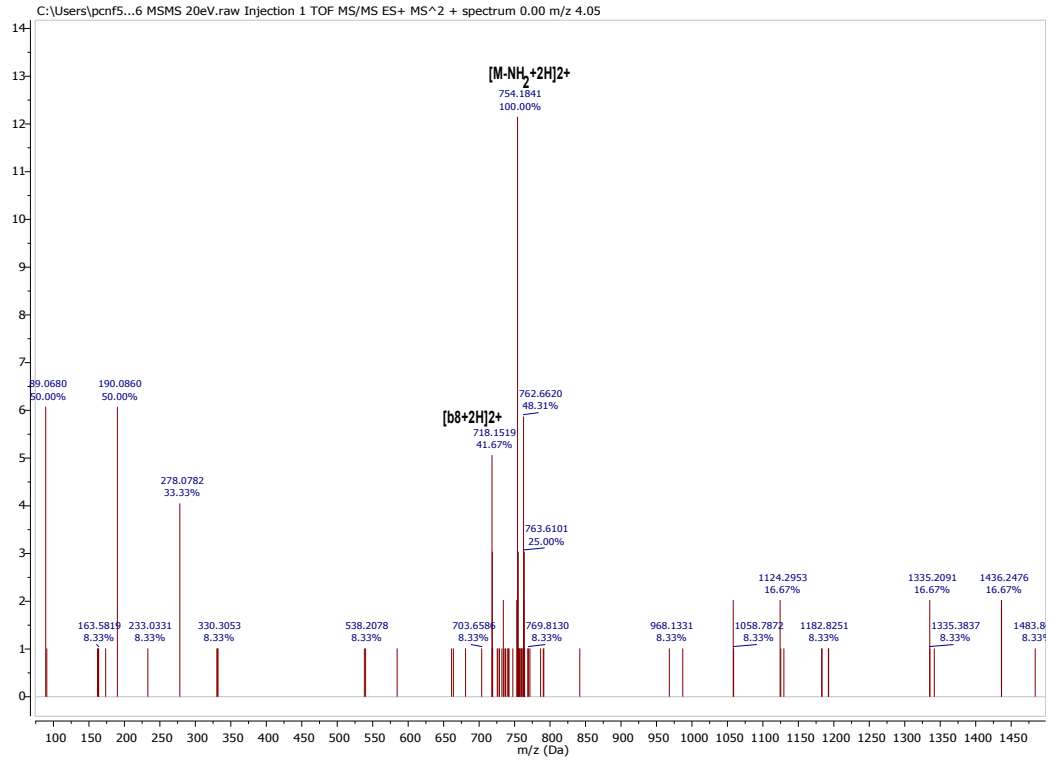


Figure SI47. MS/MS analysis of compound **12** showing its characteristic rupture pattern and the assignation of the main ions observed.

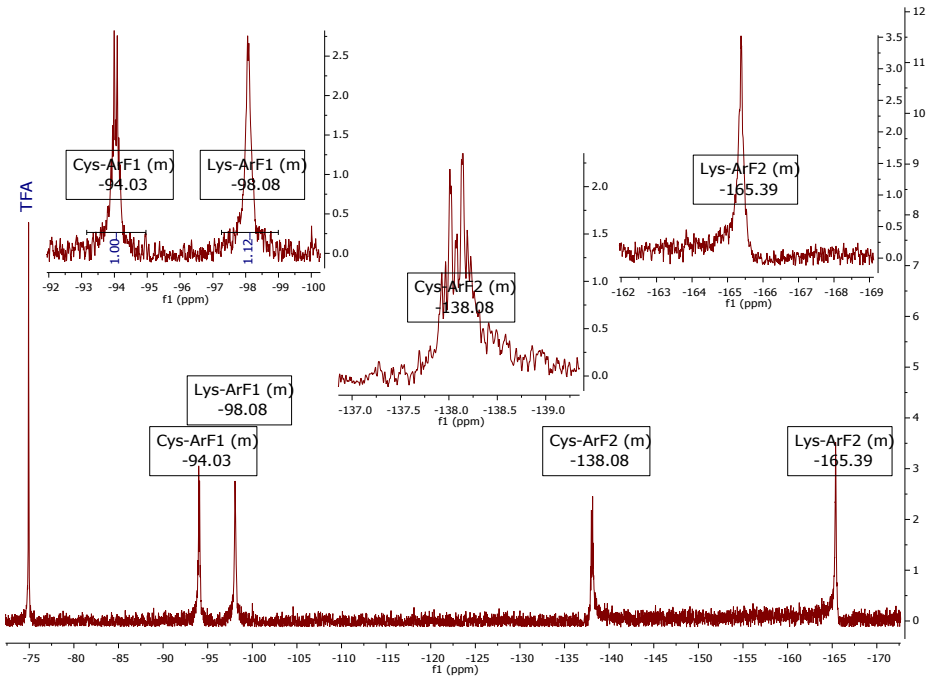
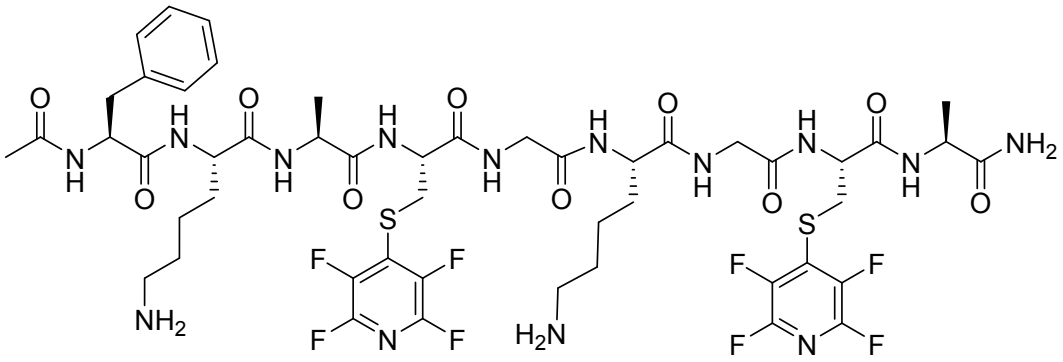


Figure SI48. ^{19}F NMR spectrum of compound **12** as recorded in H_2O/ MeCN-d_3 1:1 at room temperature.

Product 13.



QToF LC/MS: Calculated *m/z*: 1222.41, observed *m/z*: 1223.41 $[M+H]^+$, 612.20 $[M+2H]^{2+}$. Retention time: 2.200 min. Elemental composition: C_{49} H_{62} F_8 N_{14} O_{10} S_2.

QToF-MS/MS:

Calculated *m/z*: 1135.35 $[b8+H]^+$, 1033.32 $[y8+H]^+$, 905.23 $[y7+H]^+$, 834.19 $[y6+H]^+$, 612.05 $[M+2H]^{2+}$, 518.16 $[y8+2H]^+$, 389.22 $[b3+H]^+$ Da.

Observed *m/z*: 1130.45 $[b8+H]^+$, 1036.31 $[y8+H]^+$, 908.22 $[y7+H]^+$, 837.18 $[y6+H]^+$, 613.44 $[M+2H]^{2+}$, 518.94 $[y8+2H]^+$, 389.22 $[b3+H]^+$ Da.

^{19}F NMR (376 MHz, H_2O/ MeCN-d_3 1:1) δ -94.01 (m, 4F), -137.98 (m, 4F).

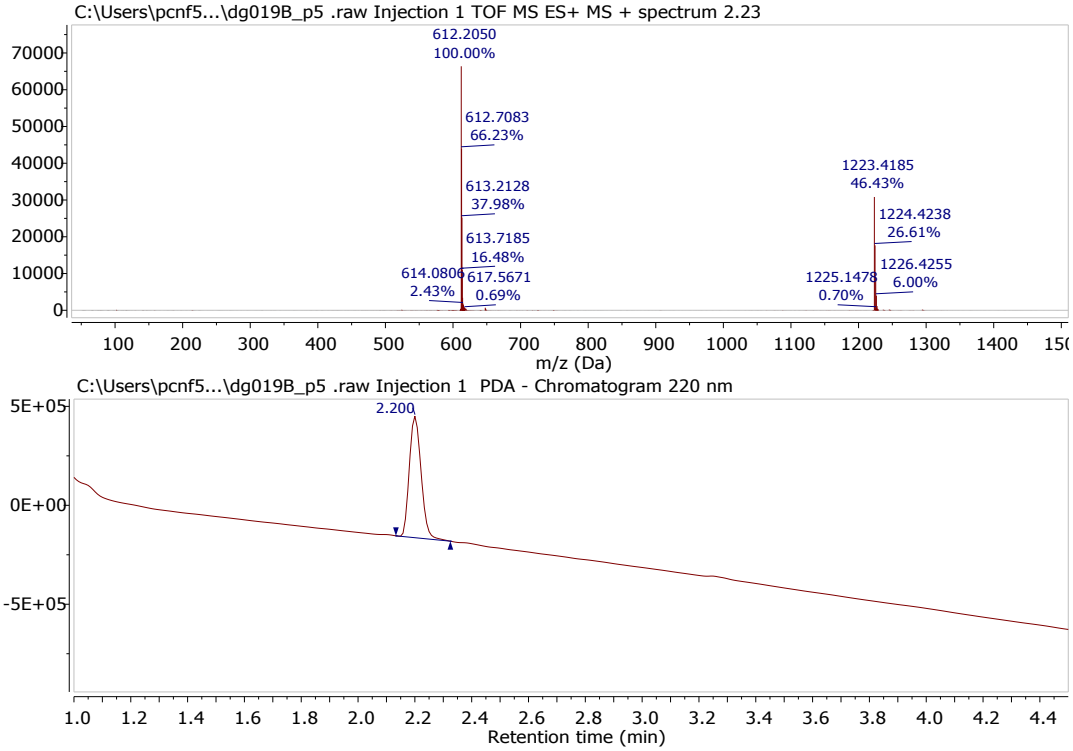


Figure SI49. Structure, high resolution QToF-LC/MS trace at λ=220 nm and composition of isolated compound **13**.

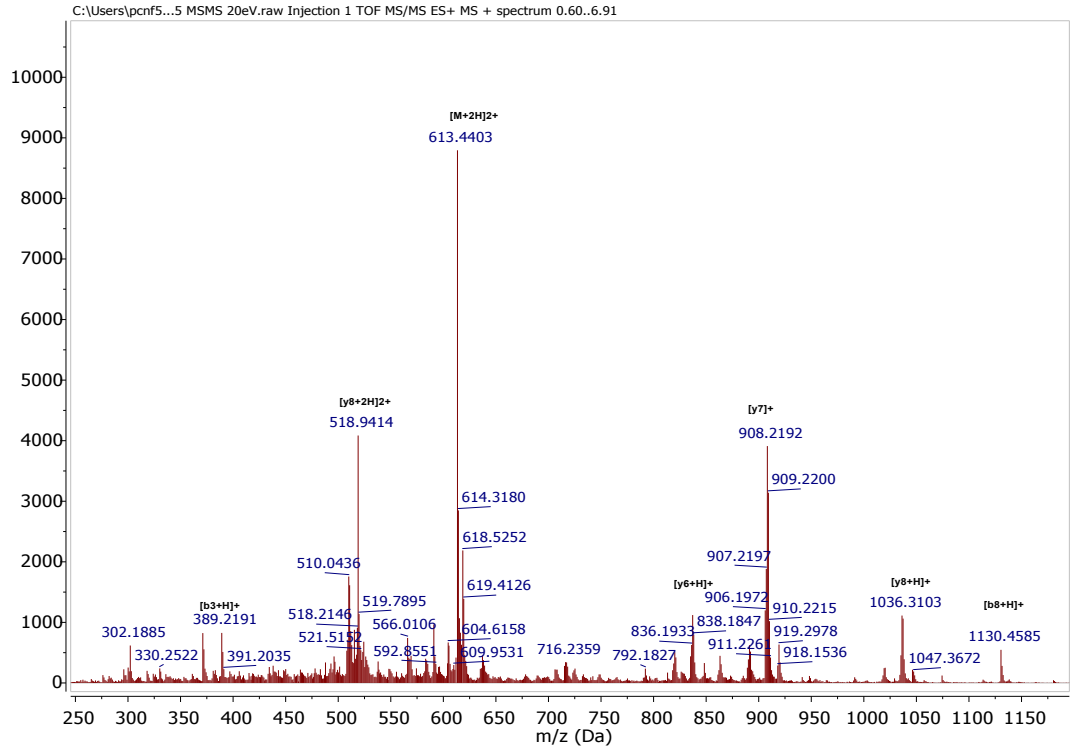


Figure SI50. MS/MS analysis of compound **13** showing its characteristic rupture pattern and the assignation of the main ions observed.

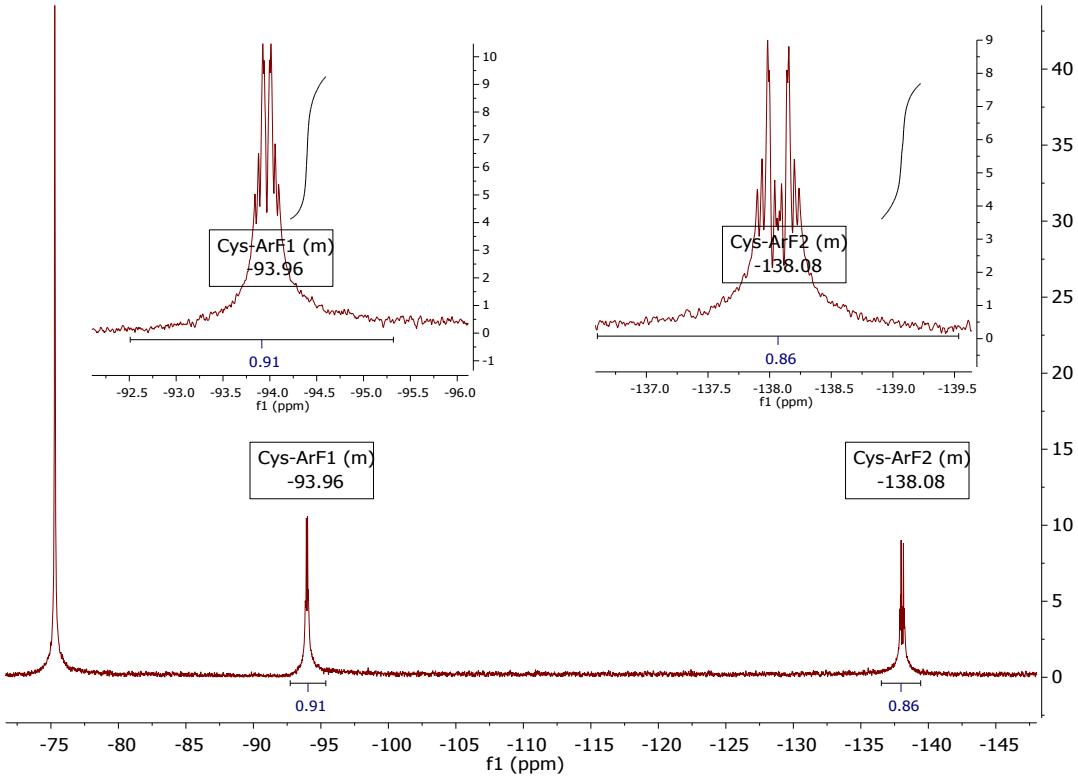
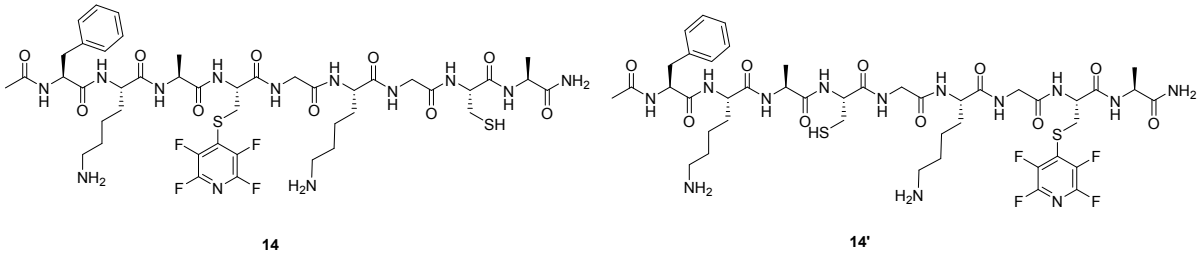


Figure SI51. ^{19}F NMR spectrum of compound **13** as recorded in H_2O/ MeCN-d_3 1:1 at room temperature.

Product 14. (Mixture of regioisomers)



14 14'

QToF LC/MS: Calculated *m/z*: 1073.42, observed *m/z*: 1130.49 $[2M+TFA+H]^{2+}$. Retention time: 2.167 min. Elemental composition: C_{44} H_{63} F_4 N_{13} O_{10} S_2.

QToF-MS/MS:

Calculated *m/z*: 1058.40 $[M-NH_2+H]^+$, 942.83 $[2(y8/y'8)+TFA+2H]^{2+}$, 814.74 $[2(y7/y'7)+TFA+2H]^{2+}$, 743.50 $[2(y6/y'6)+TFA+2H]^{2+}$, 566.25 $[Z'5+H]^+$, 537.71 $[M+2H]^{2+}$, 566.7301 $[z5+TFA+2H]^{2+}$,389.22 $[2b3/b'3+H]^+$ Da.

Observed *m/z*: 1059.40 $[M-NH_2+H]^+$, 943.39 $[2(y8/y'8)+ +TFA+2H]^{2+}$, 815.31 $[2(y7/y'7)+TFA+2H]^{2+}$, 744.25 $[2(y6/y'6)+TFA+2H]^{2+}$, 566.73 $[z5'+H]^+$, 538.69 $[M+2H]^{2+}$, 472.19 $[2z5+TFA+2H]^{2+}$, 389.21 $[b3/b'3+H]^+$ Da.

^{19}F NMR (376 MHz, H_2O/ MeCN-d_3 1:1) δ -93.39 (m, 2F), -138.12 (m, 2F).

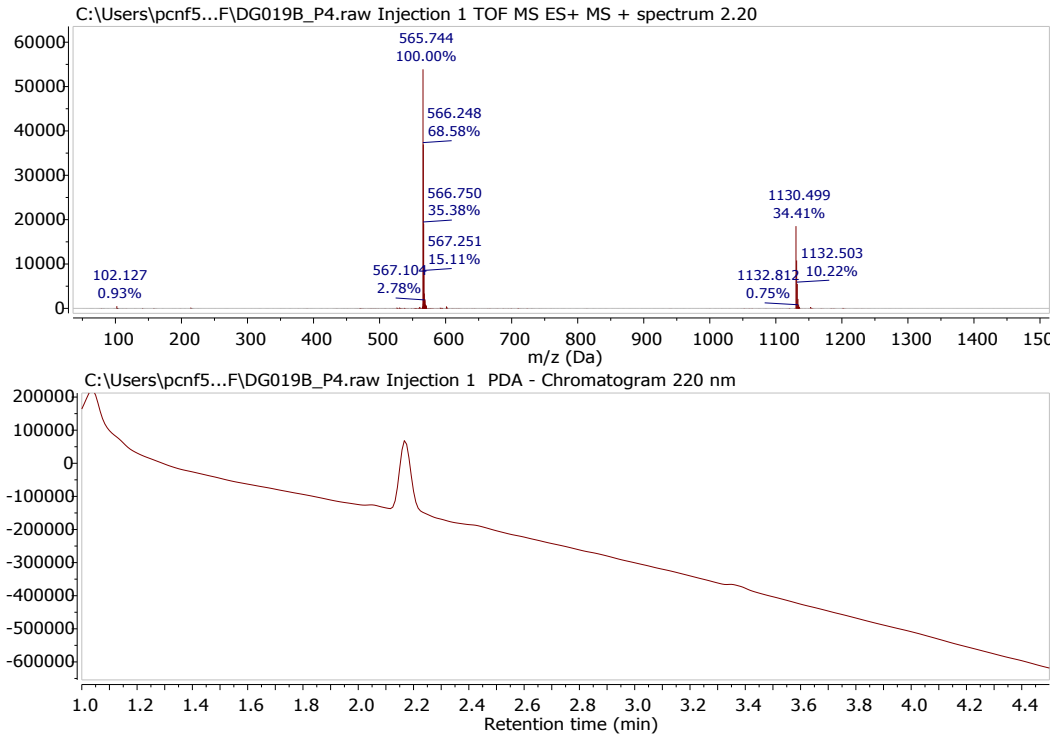


Figure SI52. Structure, high resolution QToF-LC/MS trace at λ=220 nm and composition of isolated compound **14**.

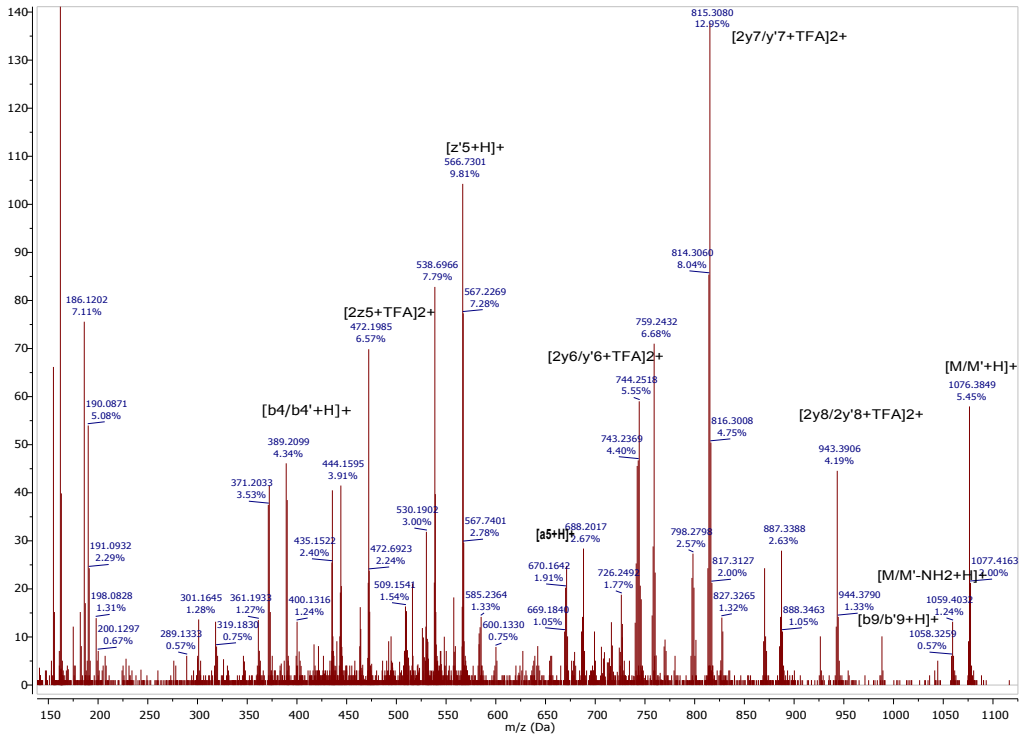


Figure SI53. MS/MS analysis of compound **14** showing its characteristic rupture pattern and the assignation of the main ions observed.

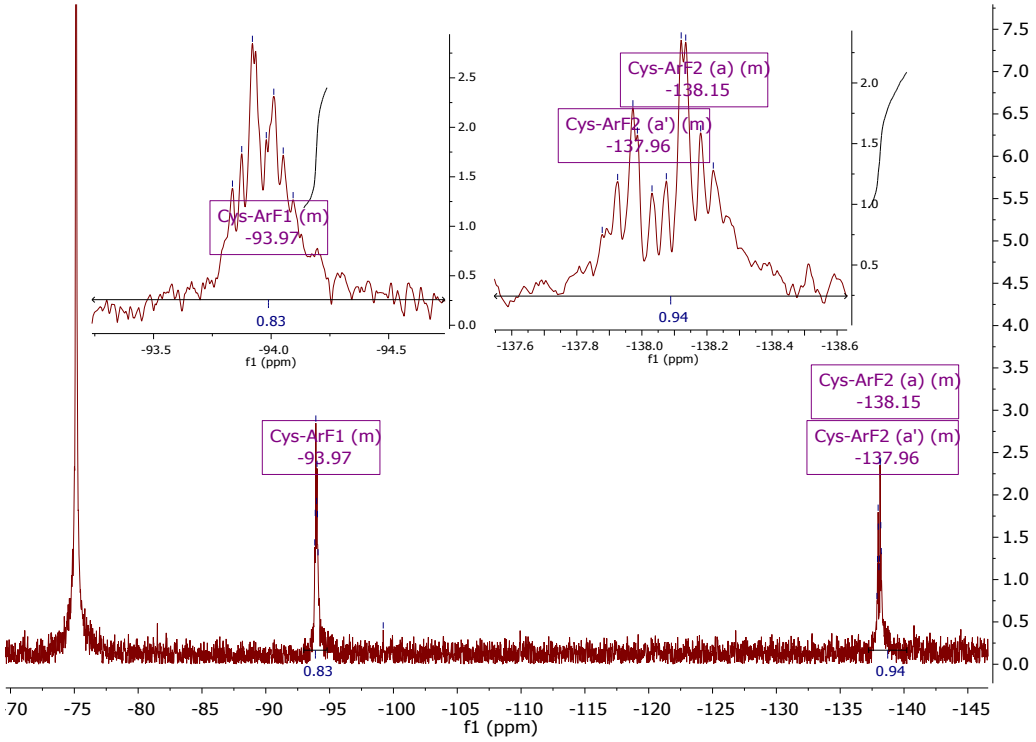


Figure SI54. ^{19}F NMR spectrum of compound **14** as recorded in H_2O/ MeCN-d_3 1:1 at room temperature.