Electronic Supplementary Information

Steps towards sustainable solid phase peptide synthesis: use and recovery of *N*-octyl pyrrolidone.

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In vitro metabolism of NOP

Table S1. NOP metabolites identified in rat and human liver microsomes by HPLC-HRMS

Compound ID	Formula	RT (min)	Ion	Observed mass (*m/z*)	Mass error (ppm)	Metabolic Reaction	% of Parent response	Found in
NOP	$C_{12}H_{23}NO$	5.56	$[M+H]^+$	198.1849	-1.8	--	100	HLM/RLM
M1	$C_{12}H_{21}NO_2$	3.19	$[M+H]^+$	212.1642	-1.6	+O – H2	83.5	HLM/RLM
M2	$C_{12}H_{21}NO_2$	2.36	$[M+H]^+$	212.1645	-0.2	+O – H2	6.0	HLM/RLM
M3	$C_{12}H_{21}NO_2$	2.44	$[M+H]^+$	212.1642	-1.5	+O – H2	3.4	HLM/RLM
M4	$C_{12}H_{21}NO_2$	2.51	$[M+H]^+$	212.1641	-2.0	+O – H2	7.7	HLM/RLM
M5	$C_{12}H_{21}NO_2$	2.56	$[M+H]^+$	212.1641	-2.3	+O – H2	5.0	HLM
M6	$C_{12}H_{23}NO_2$	3.16	$[M+Na]^+$	236.1615	-2.5	+O	8.1	HLM/RLM
M7	$C_{12}H_{23}NO_2$	3.24	$[M+Na]^+$	236.1616	-1.9	+O	17.1	HLM/RLM
M8	$C_{12}H_{23}NO_2$	3.28	$[M+H]^+$	212.1640	-2.7	+O – H2	6.3	HLM/RLM
M9	$C_{12}H_{23}NO_2$	4.40	$[M+H]^+$	214.1795	-3.0	+O	18.3	HLM/RLM
M10	$C_{12}H_{23}NO_2$	4.54	$[M+H]^+$	214.1796	-2.5	+O	28.9	HLM/RLM
M11	$C_{12}H_{23}NO_2$	4.75	$[M+H]^+$	214.1796	-2.7	+O	6.7	HLM

Figure S1. HPLC-HRMS trace of a RLM incubation of N-octyl pyrrolidone (NOP) at t=3h.
Parent compound NOP and metabolites are reported together with their RT. At RT = 3.18 min, the most abundant metabolite (**M1**, with a mass shift of + 14 with respect to NOP) and two minor metabolites (**M6** and **M7**, with a mass shift of + 16 with respect to NOP) co-elute. Extracted Ion Chromatograms (XIC) of co-eluting metabolites **M1**, **M6** and **M7** are reported in Figure S2.

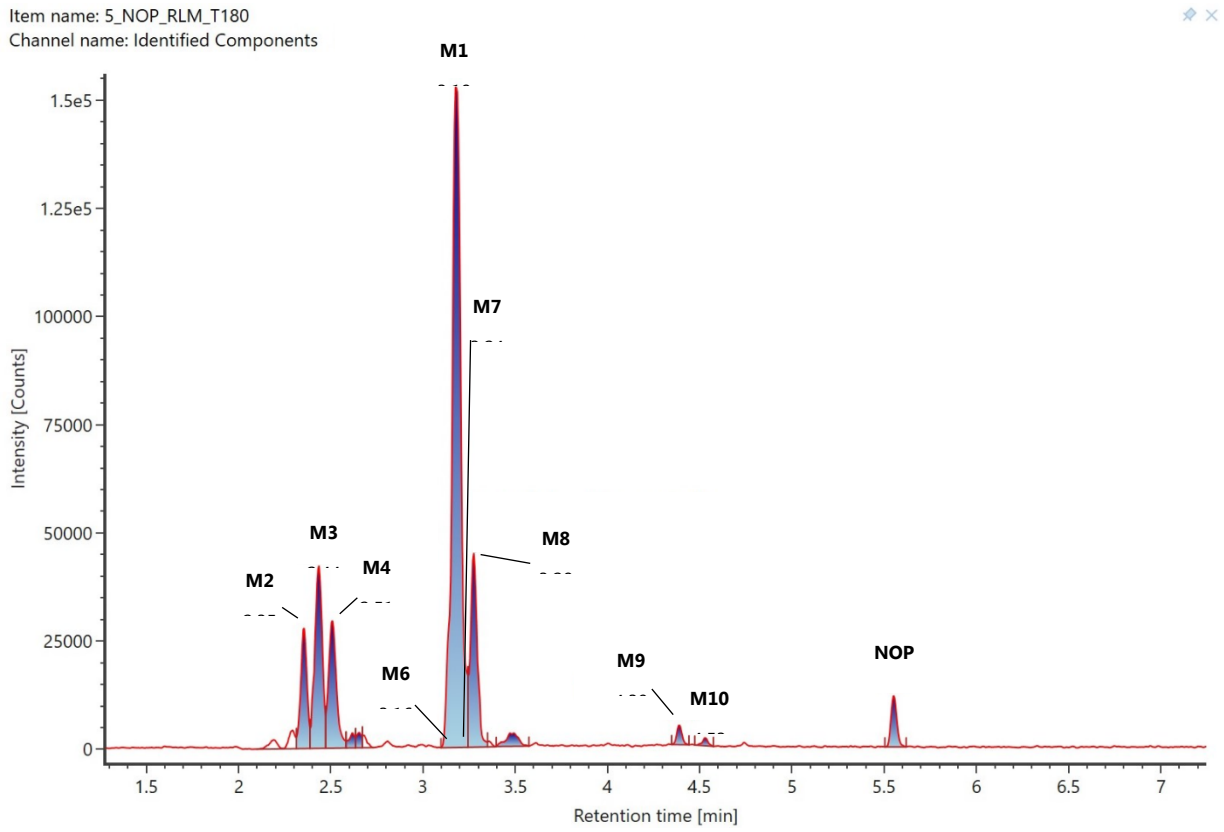


Figure S2. Extracted Ion Chromatogram (XIC) of co-eluting metabolites **M1**, **M6** and **M7** in RLM at t=3h

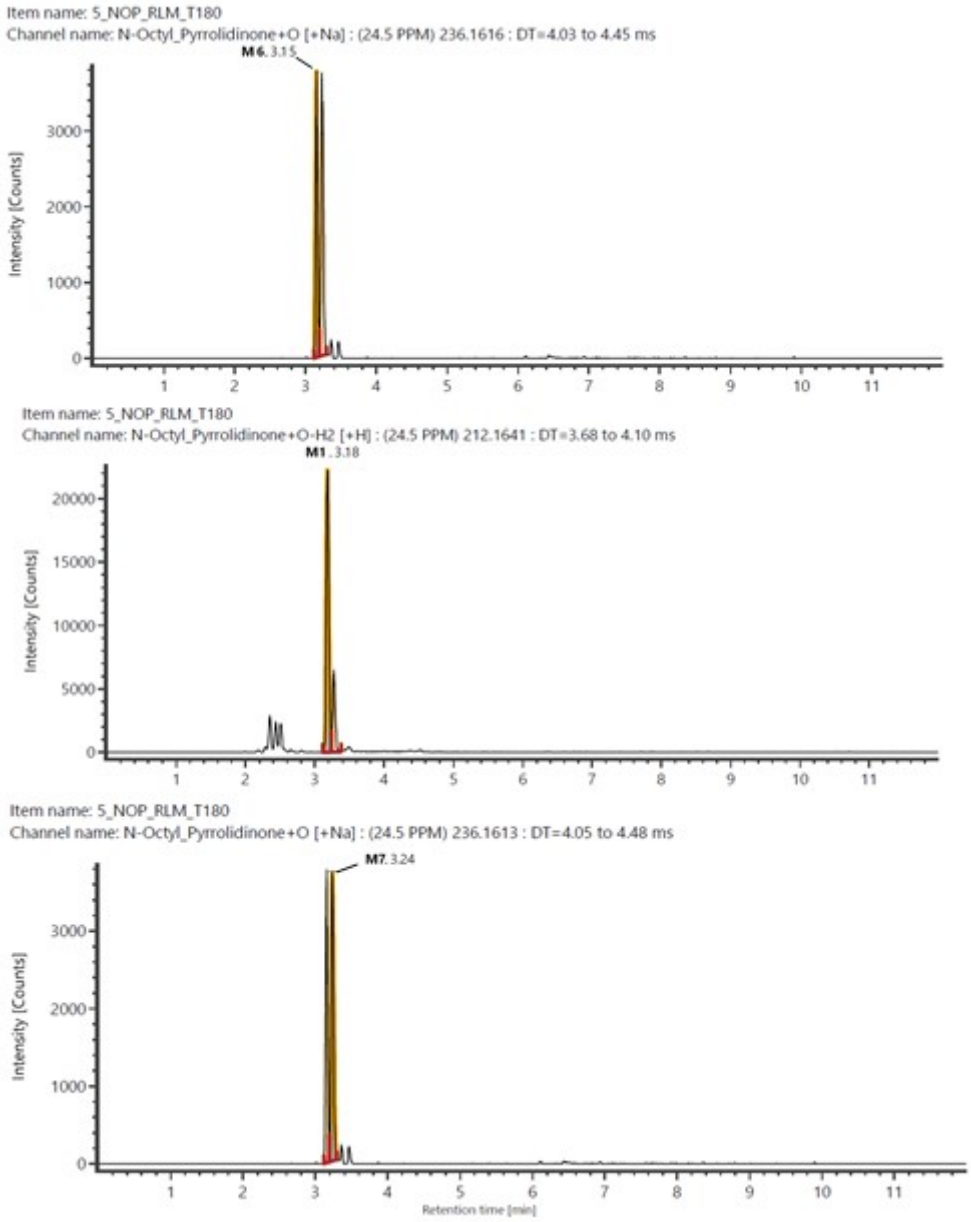


Figure S3. Extracted Ion Chromatogram (XIC) of co-eluting metabolites **M1**, **M6** and **M7** in HLM at t=3h

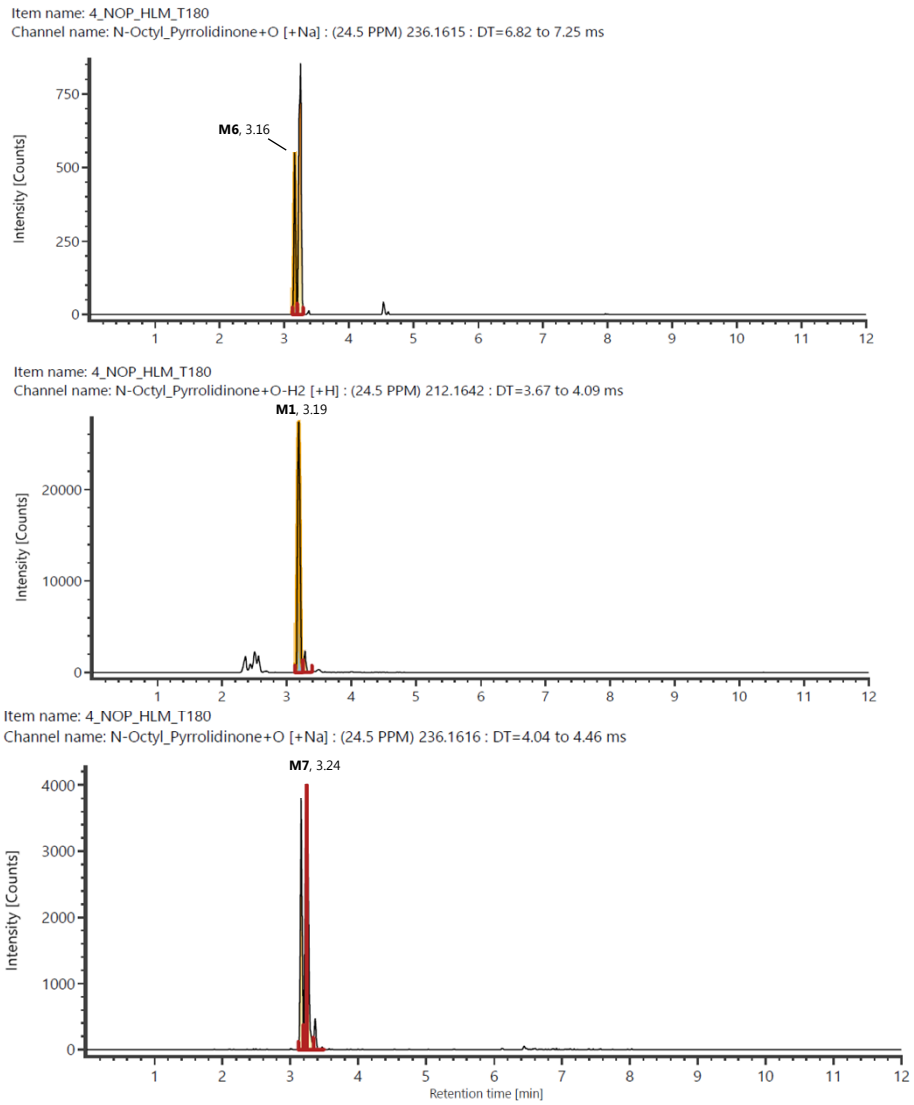


Figure S4. a. Low (upper) and high (lower) energy (HDMS^E) mass spectra for metabolite **M1** (RT = 3.18 min) in RLM (incubation time: t=3h)

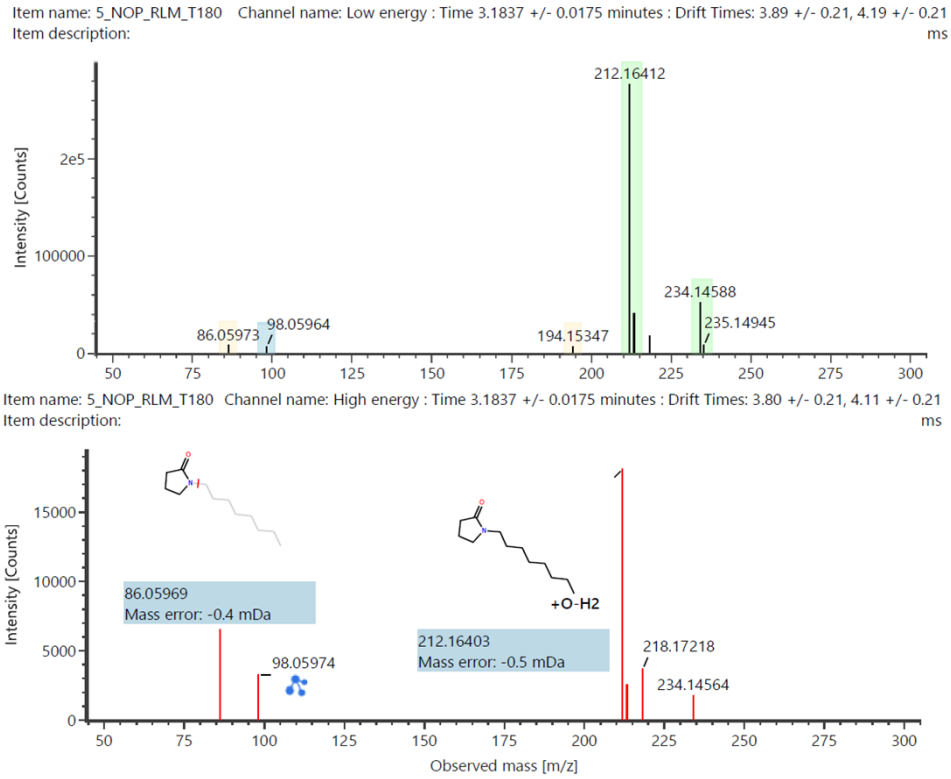


Figure S4. b. Low (upper) and high (lower) energy (HDMS^E) mass spectra for metabolite **M1** (RT = 3.19 min) in HLM (incubation time: t=3h)

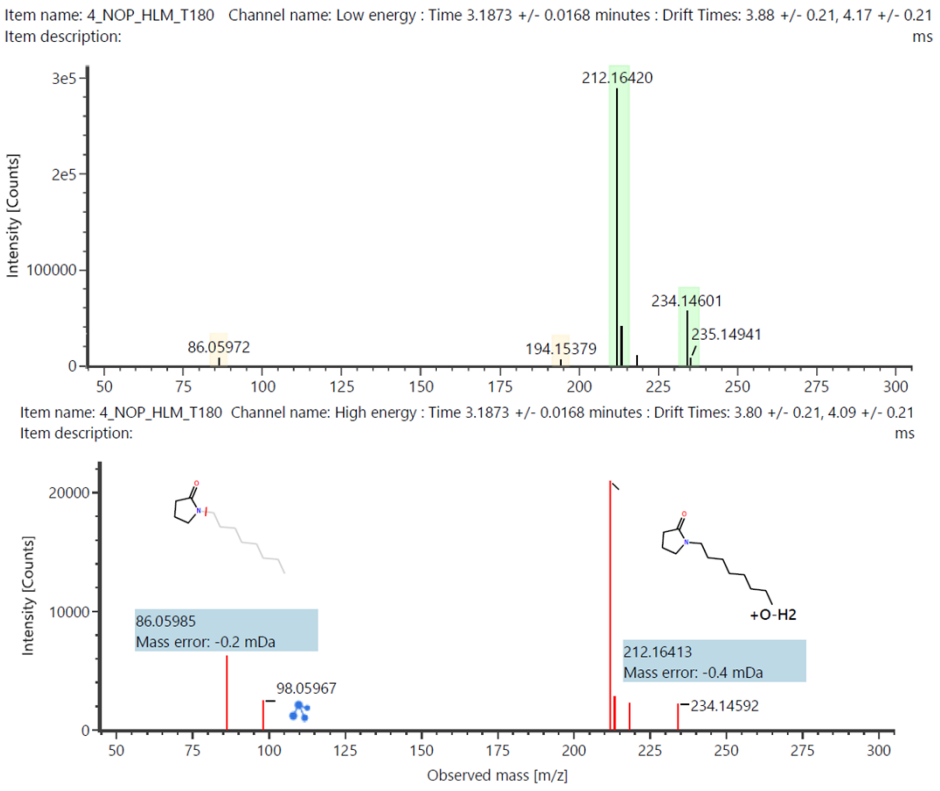


Figure S5. a. Low (upper) and high (lower) energy (HDMS^E) mass spectra for metabolite **M2** (RT = 2.35 min) in RLM (incubation time: t=3h)

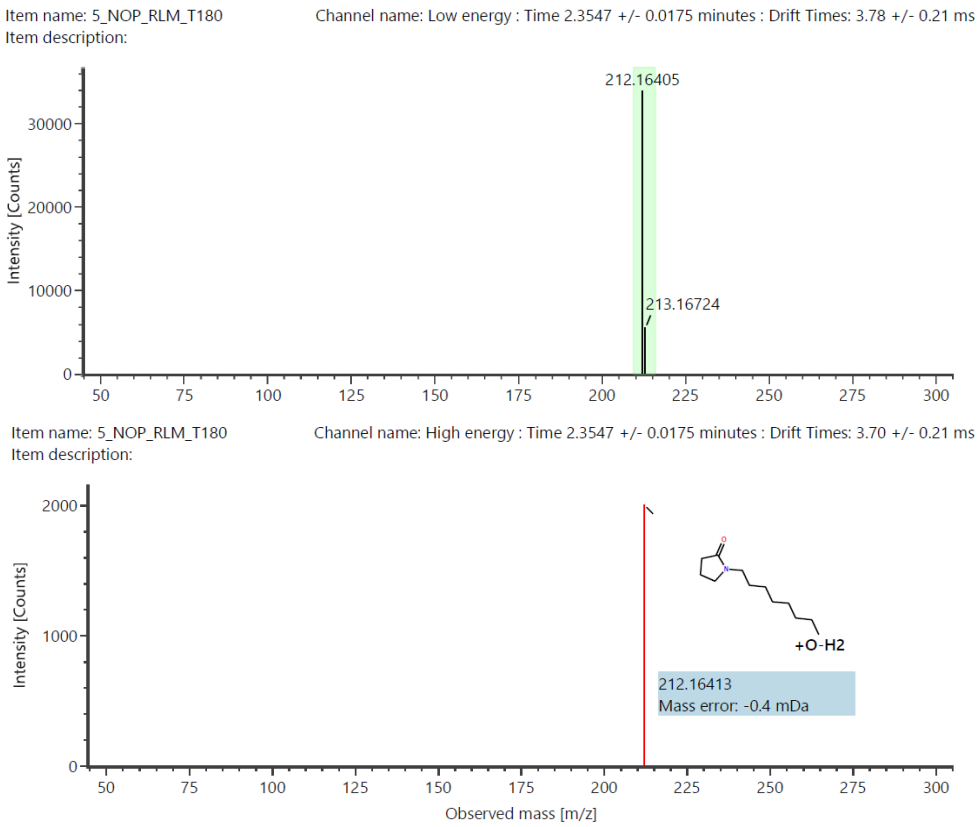


Figure S5. b. Low (upper) and high (lower) energy (HDMS^E) mass spectra for metabolite **M2** (RT = 2.36 min) in HLM (incubation time: t=3h)

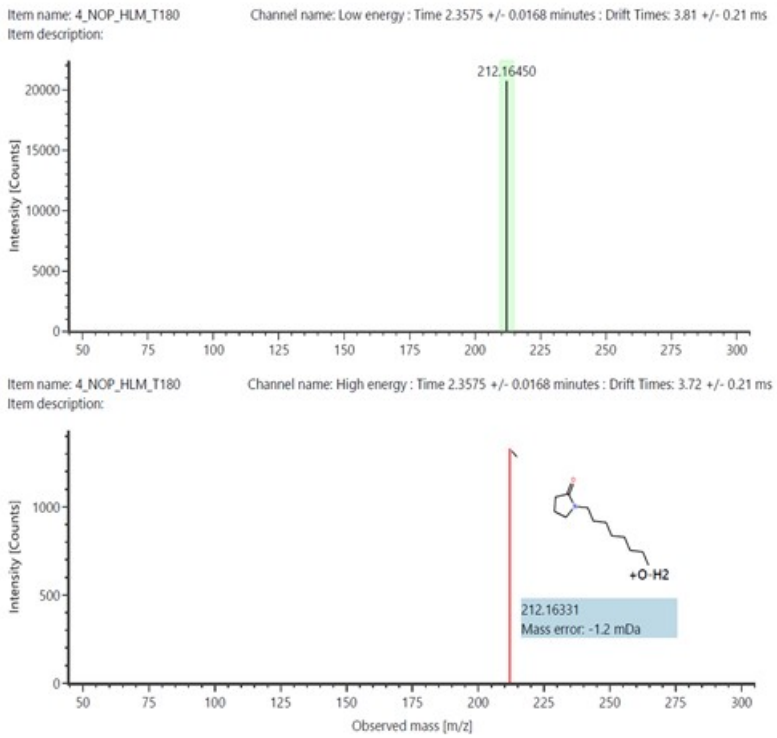


Figure S6. a. Low (upper) and high (lower) energy (HDMS^E) mass spectra for metabolite **M3** (RT = 2.44 min) in RLM (incubation time: t=3h)

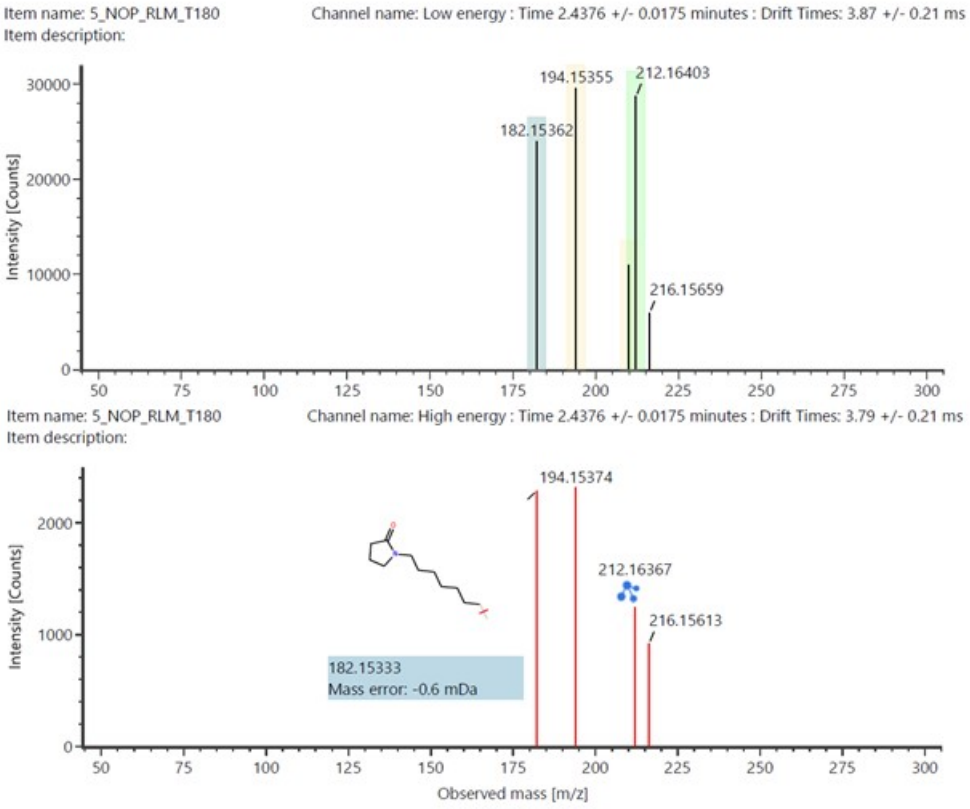


Figure S6. b. Low energy mass spectrum for metabolite **M3** (RT = 2.44 min) in HLM (incubation time: t=3h). Due to the low intensity of parent ion no high energy fragmentation was collected

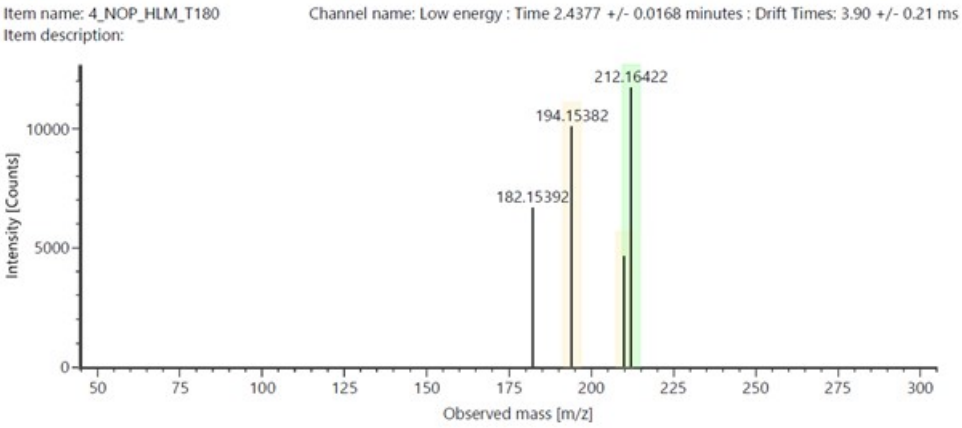


Figure S7. a. Low (upper) and high (lower) energy (HDMS^E) mass spectra for metabolite **M4** (RT = 2.51 min) in RLM (incubation time: t=3h)

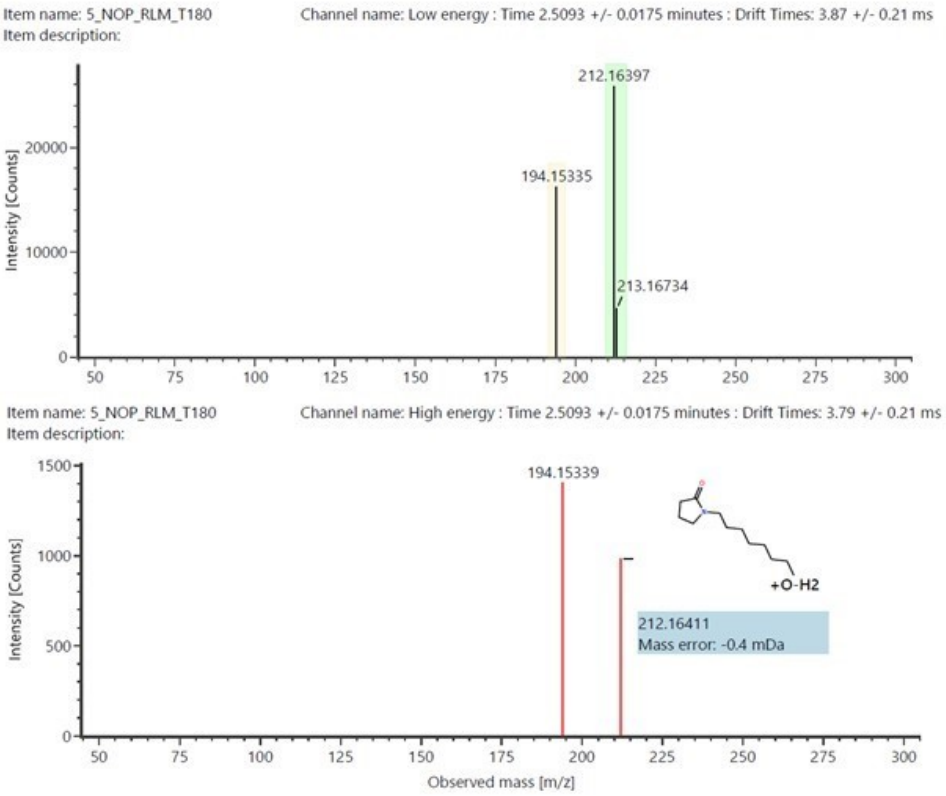


Figure S7. b. Low (upper) and high (lower) energy (HDMS^E) mass spectra for metabolite **M4** (RT = 2.51 min) in HLM (incubation time: t=3h)

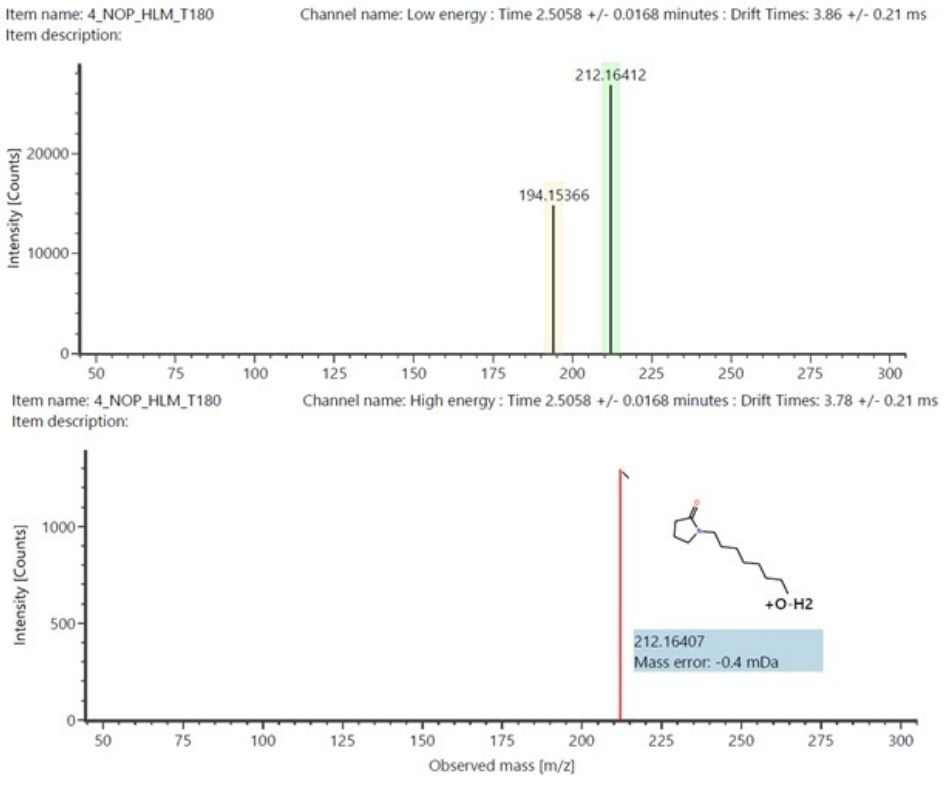


Figure S8. Low energy mass spectrum for metabolite **M5** (RT = 2.56 min) in HLM (incubation time: t=3h). Due to the low intensity of parent ion, no high energy fragmentation was collected

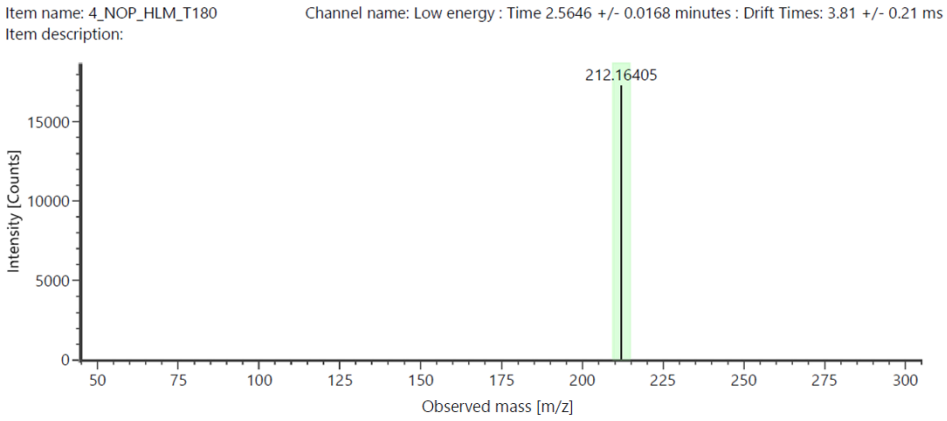


Figure S9. a. Low (upper) and high (lower) energy (HDMS^E) mass spectra for metabolite **M6** (RT = 3.16 min) in RLM (incubation time: t=3h)

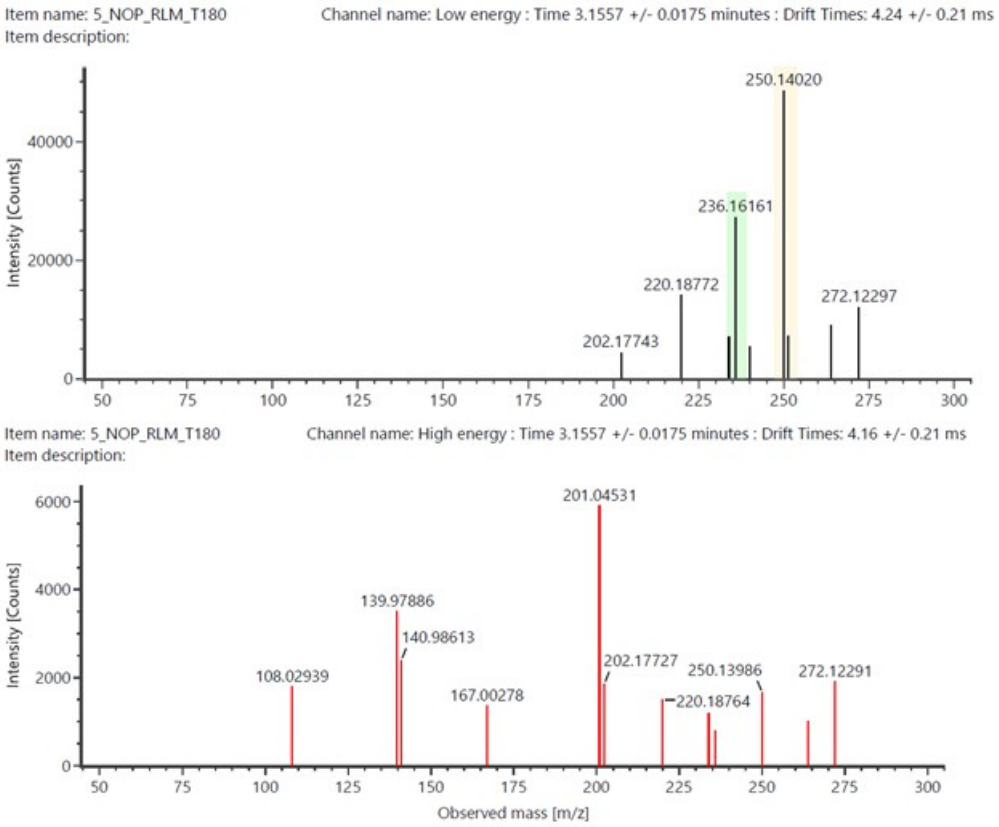


Figure S9. b. Low (upper) and high (lower) energy (HDMS^E) mass spectra for metabolite **M6** (RT = 3.16 min) in HLM (incubation time: t=3h). Due to the low intensity of parent ion, no high energy fragmentation was collected

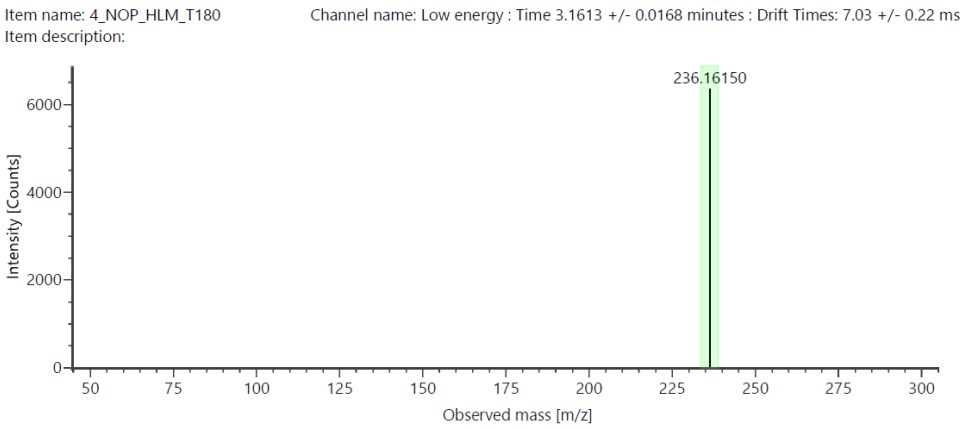


Figure S10. a. Low (upper) and high (lower) energy (HDMS^E) mass spectra for metabolite **M7** (RT = 3.24 min) in RLM (incubation time: t=3h)

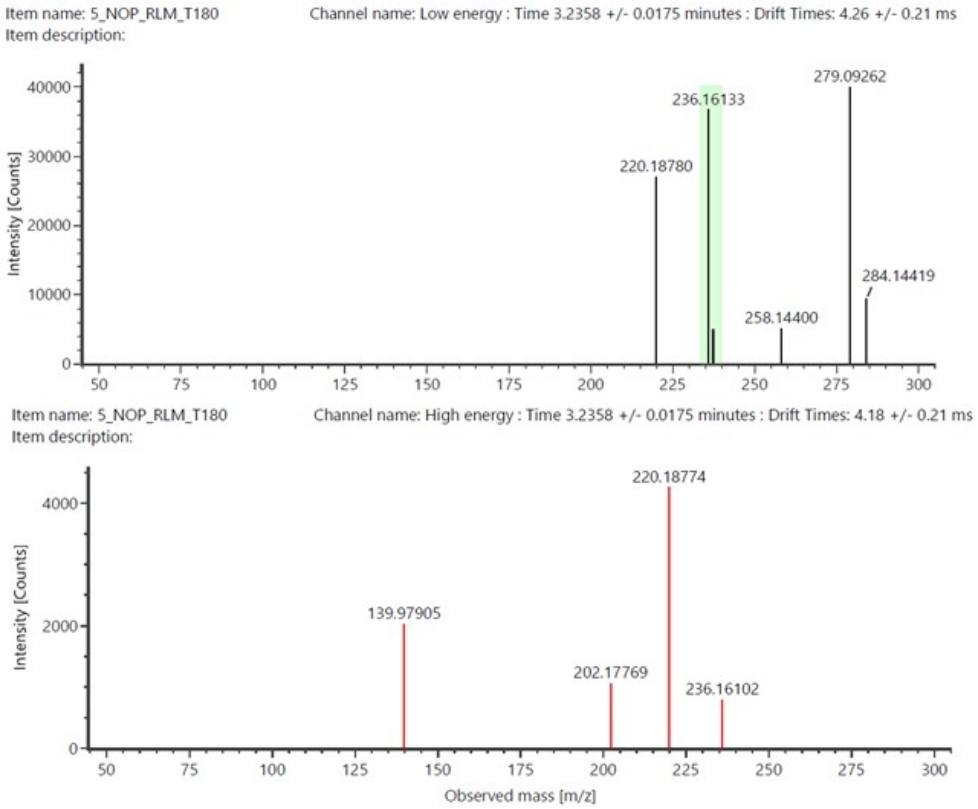


Figure S10. b. Low (upper) and high (lower) energy (HDMS^E) mass spectra for metabolite **M7** (RT = 3.24 min) in HLM (incubation time: t=3h)

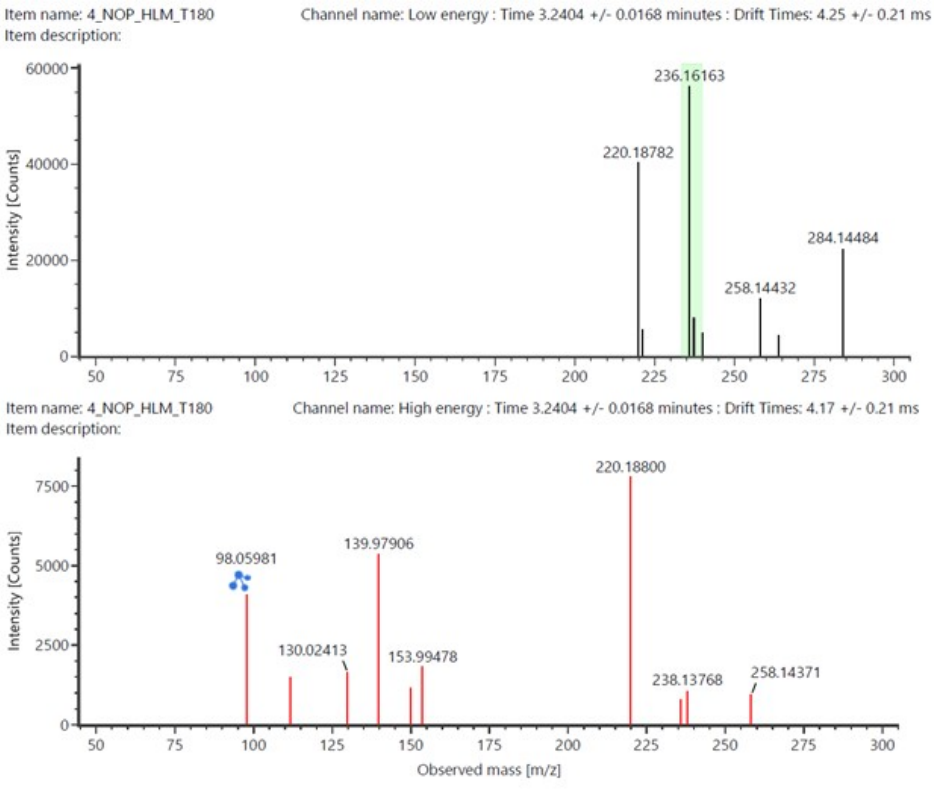


Figure S11. a. Low (upper) and high (lower) energy (HDMS^E) mass spectra for metabolite **M8** (RT = 3.28 min) in RLM (incubation time: t=3h)

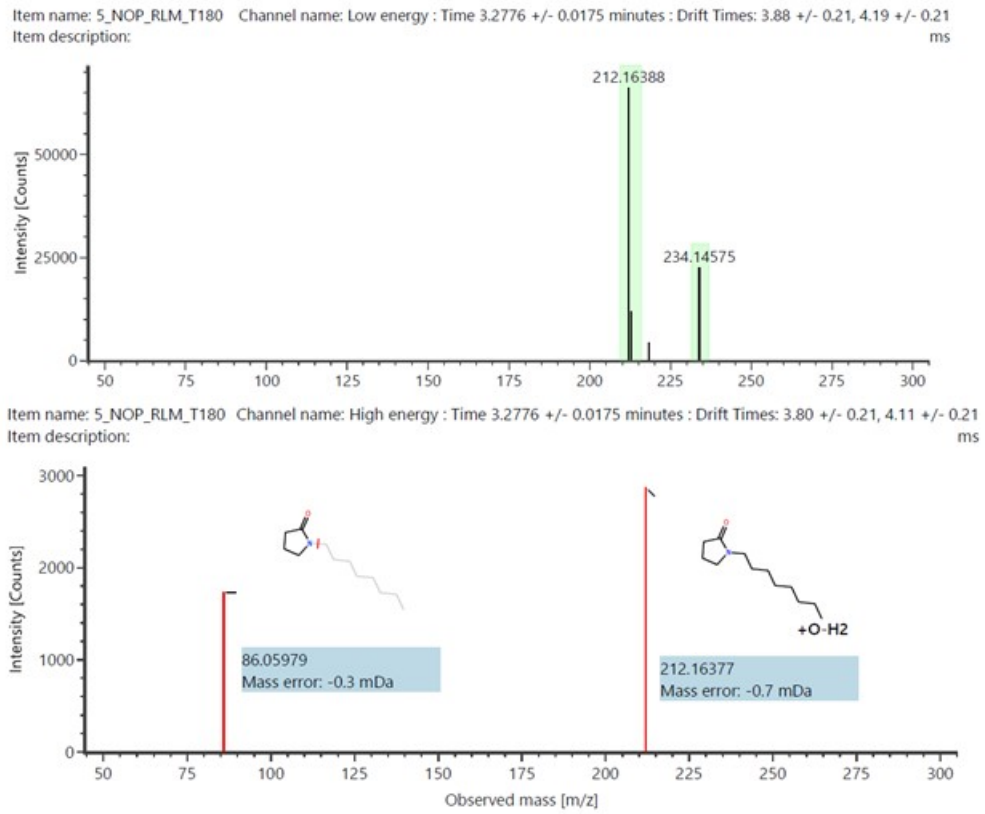


Figure S11. b. Low (upper) and high (lower) energy (HDMS^E) mass spectra for metabolite **M8** (RT = 3.28 min) in HLM (incubation time: t=3h). Due to the low intensity of parent ion, no high energy fragmentation was collected

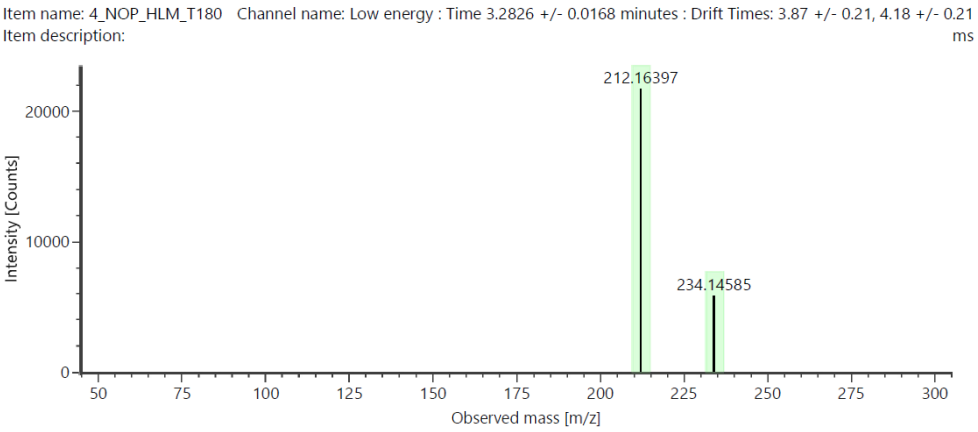


Figure S12. a. Low (upper) and high (lower) energy (HDMS^E) mass spectra for metabolite **M9** (RT = 4.40 min) in RLM (incubation time: t=3h)

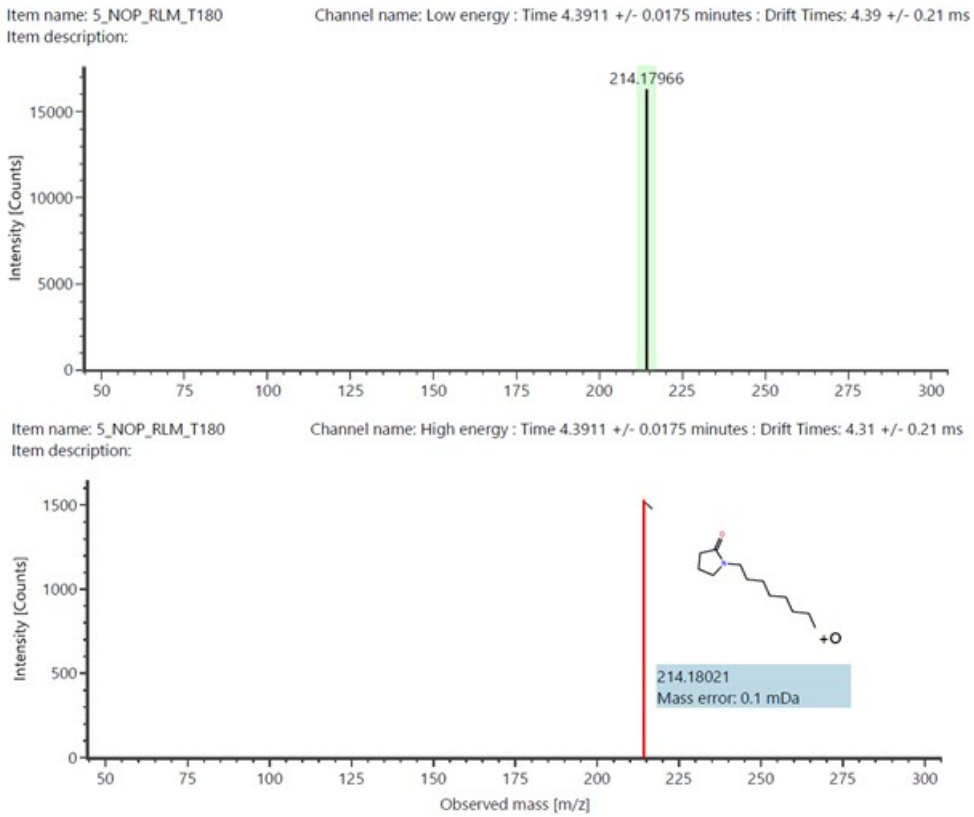


Figure S12. b. Low (upper) and high (lower) energy (HDMS^E) mass spectra for metabolite **M9** (RT = 4.40 min) in HLM (incubation time: t=3h)

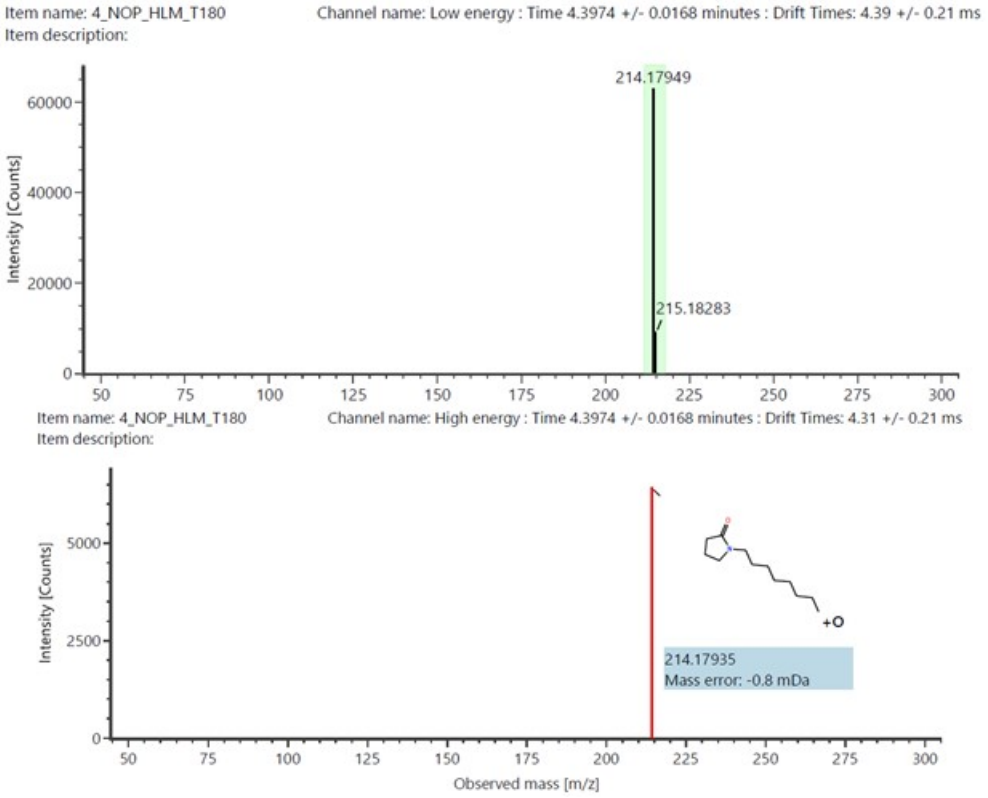


Figure S13. a. Low energy mass spectrum for metabolite **M10** (RT = 4.53 min) in RLM (incubation time: t=3h). Due to the low intensity of parent ion, no high energy fragmentation was collected

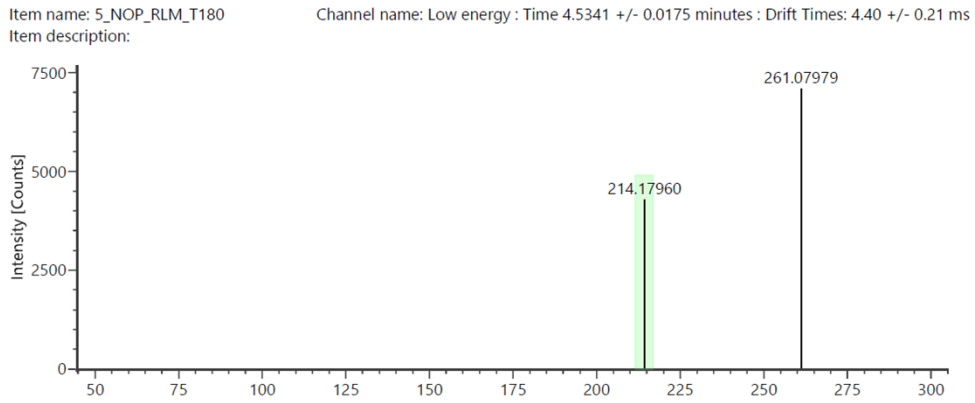


Figure S13. b. Low (upper) and high (lower) energy (HDMS^{E}) mass spectra for metabolite **M10** (RT = 4.54 min) in HLM (incubation time: t=3h)

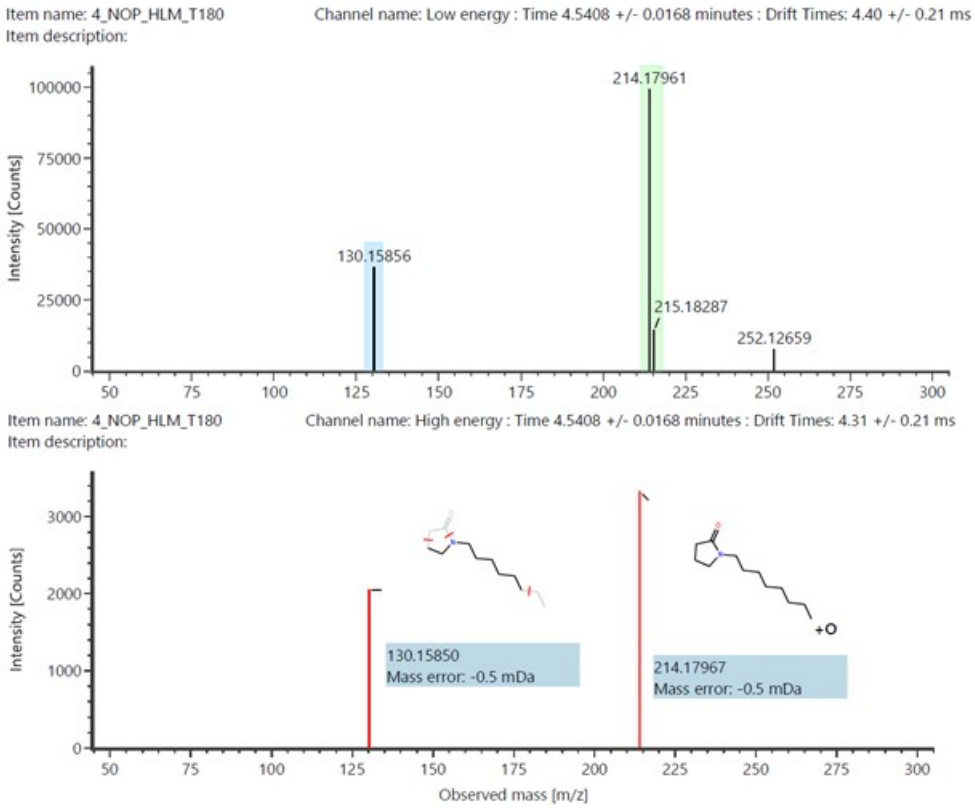


Figure S14. Low (upper) and high (lower) energy (HDMS^E) mass spectra for metabolite **M11** (RT = 4.75 min) in HLM (incubation time: t=3h). Due to the low intensity of parent ion, no high energy fragmentation was collected

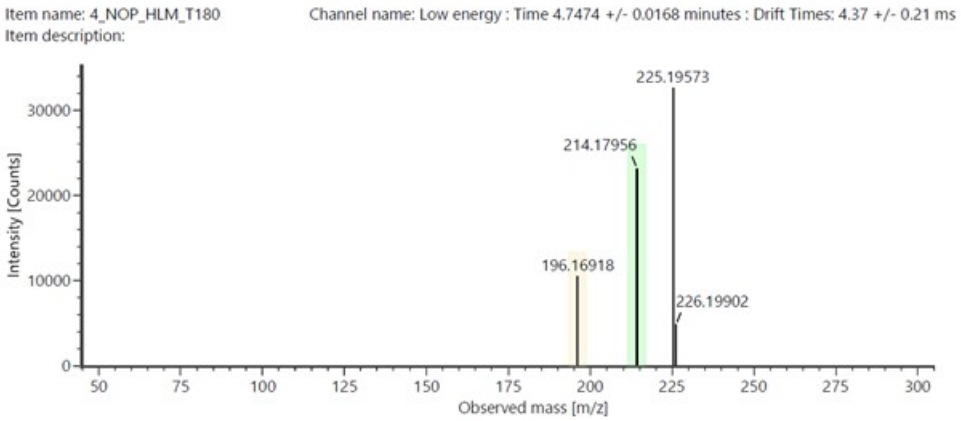
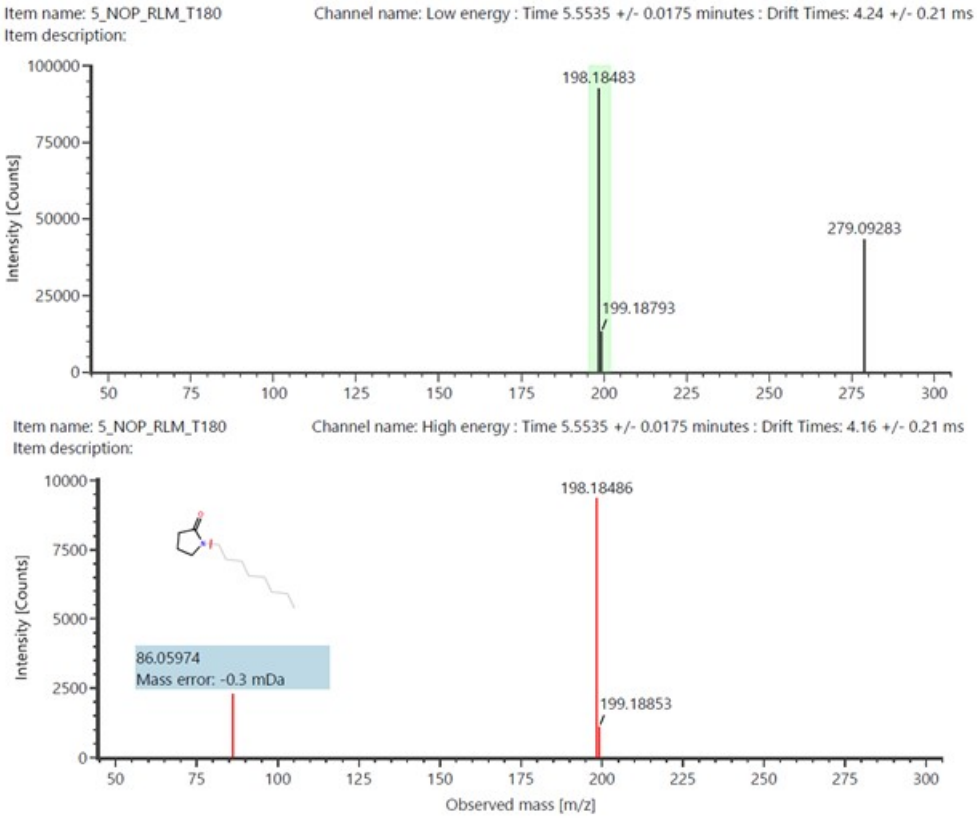


Figure S15. Low (upper) and high (lower) energy (HDMS^E) mass spectra for metabolite parent compound NOP (RT = 5.55 min) in RLM (incubation time: t=3h)



Solubility tests

Table S2. Solubilization efficacy of Fmoc-AA(PG)-OH amino acids and coupling reagents mixtures in green solvents[a]

	Mixture Fmoc-AA(PG)-OH + coupling reagents (A-E)														
Solvent	Gly +A	Gly +B	Gly +C	Gly +D	Gly +E	Ala +A	Ala +B	Ala +C	Ala +D	Ala +E	Aib +A	Aib +B	Aib +C	Aib +D	Aib +E
NOP															
NCP															
NBnP															

	Mixture Fmoc-AA(PG)-OH + coupling reagents (A-E)														
Solvent	Phe +A	Phe +B	Phe +C	Phe +D	Phe +E	Pro +A	Pro +B	Pro +C	Pro +D	Pro +E	Tyr (tBu) +A	Tyr (tBu) +B	Tyr (tBu) +C	Tyr (tBu) +D	Tyr (tBu) +E
NOP															
NCP															
NBnP															

	Mixture Fmoc-AA(PG)-OH + coupling reagents (A-E)														
Solvent	Thr (tBu) +A	Thr (tBu) +B	Thr (tBu) +C	Thr (tBu) +D	Thr (tBu) +E	Lys (Boc) +A	Lys (Boc) +B	Lys (Boc) +C	Lys (Boc) +D	Lys (Boc) +E	Cys (Trt) +A	Cys (Trt) +B	Cys (Trt) +C	Cys (Trt) +D	Cys (Trt) +E
NOP															
NCP															0.1 M
NBnP													0.1 M	0.1 M	0.1 M

Legend: OxymaPure®/DIC (A), COMU/DIPEA (B), PyBOP/DIPEA (C), PyOxyma/DIPEA (D), HOBt/DIC (E); green=soluble; yellow=moderately soluble; red=insoluble; PG: protecting groups

[a]Solubilisation monitored at 0.2 M concentration unless 0.1 M is specified.

Representative examples of solubility of Fmoc-amino acids in pyrrolidones in presence of selected coupling reagent combinations

Figure S16. Fmoc-Aib-OH (1 eq) after 5 minutes stirring in 1 mL NOP (left), NCP (center) or NBnP (right) mixed with a) DIC/Oxyma Pure® (1 eq); b) HOBt/DIC (1 eq); c) COMU/DIPEA (1 eq)

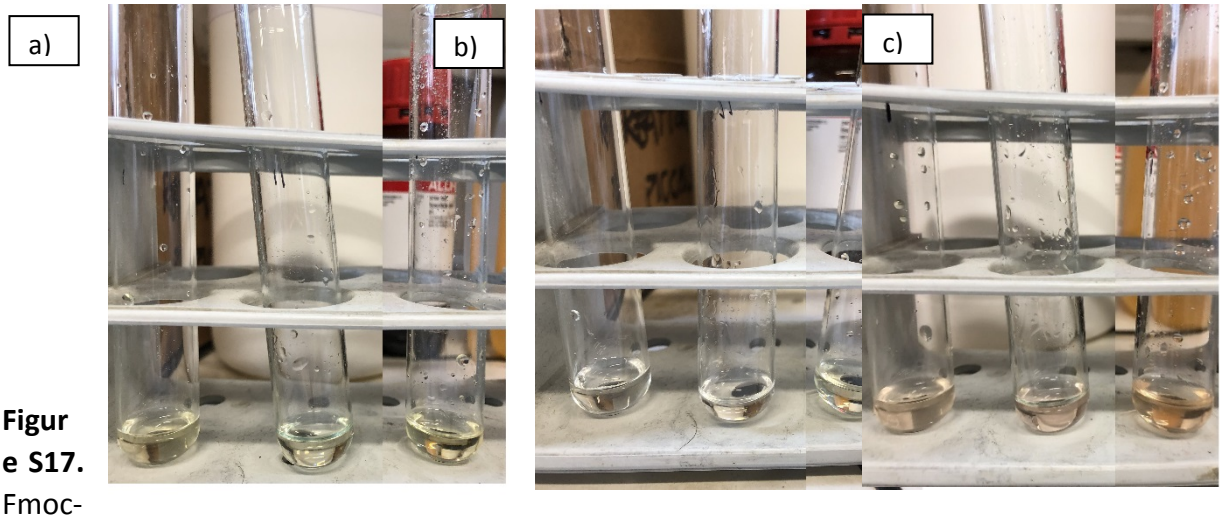


Figure S17. Fmoc-Phe-OH (1 eq) after 5 minutes stirring in 1 mL NOP (left), NCP (center) or NBnP (right) mixed with a) DIC/Oxyma Pure® (1 eq); b) HOBt/DIC (1 eq); c) COMU/DIPEA (1 eq)

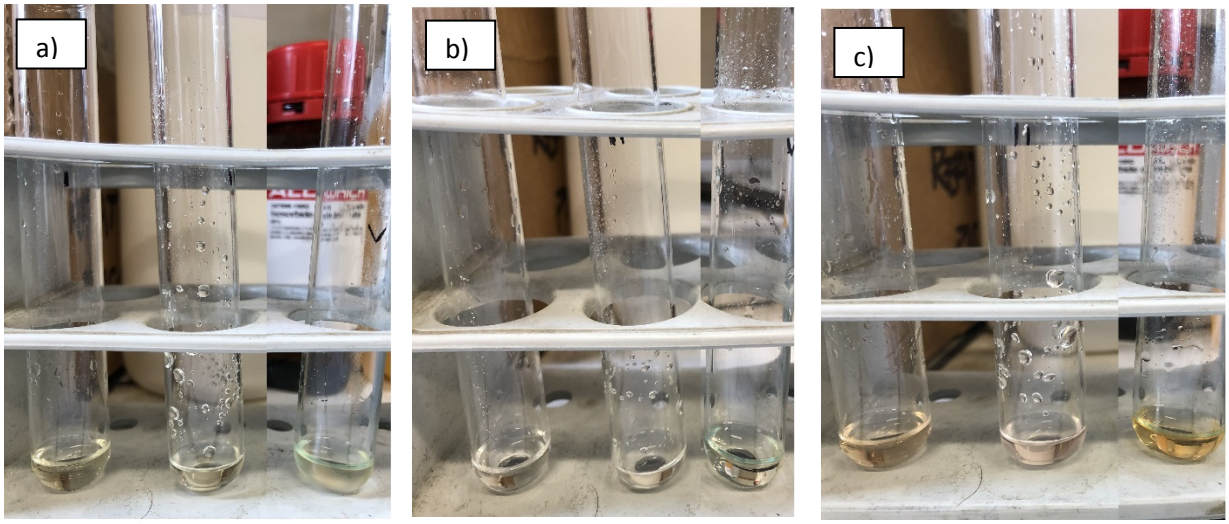
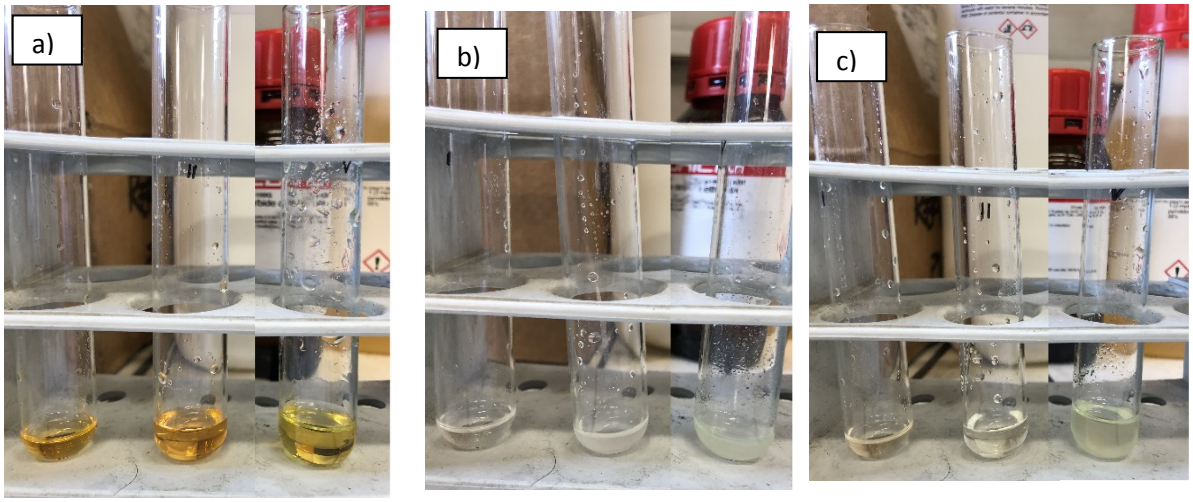


Figure S18. Fmoc-Cys(Trt)-OH (1 eq) after 5 minutes stirring in 1 mL NOP (left), NCP (center) or NBnP (right) alone (a) or mixed with b) DIC/Oxyma Pure® (1 eq); c) COMU/DIPEA (1 eq). In cases a) and c), the mixture in NBnP was further diluted to 0.1M to allow complete dissolution, as reported in the main text



Swelling tests

Table S3. Physical parameters of resins evaluated for swelling tests

Resin	**Bead size** (μm)	**Bead size** (mesh)	**Loading** (mmol·g^{-1})	**Cross-linking** (%)
PS-Wang	75-150	100-200	1.1	1
PS-Trt-Cl	37-75	200-400	1.85	1
PS-RinkAmide	500-560	35-37	0.4-0.7	1
TG-Wang	90	170	0.20	-
TG-RinkAmide	100-200	75-150	0.23	-
CM-Wang	150-500	35-100	0.5-1.2	-
CM-RinkAmide	150-500	35-100	0.4-0.6	-

Table S4. Calculations of standard deviations for the swelling measurements of the reported resins

PS-Wang resin					
	Swell 1	Swell 2	Swell 3	Swelling (mean value)	Standard deviation
DMF	5,6	5,5	5,6	5,6	0,05
NOP	5,4	5,6	5,6	5,5	0,09
NCP	5,1	5	5,2	5,1	0,08
NBnP	2,3	2,1	2,4	2,3	0,12
NBP	4,3	4,4	4,7	4,5	0,17
NOP/DMC 80:20	5,1	5,3	5,2	5,2	0,08
DMC	3,2	3,4	3,2	3,3	0,09

PS-Trt-Cl resin					
	Swell 1	Swell 2	Swell 3	Swelling (mean value)	Standard deviation
DMF	3,1	3,3	3,3	3,2	0,12
NOP	3,4	3,5	3,2	3,4	0,12
NCP	3,5	3,6	3,6	3,6	0,05
NBnP	1,4	1,7	1,6	1,6	0,12
NBP	5	4,9	5	5,0	0,05
NOP/DMC 80:20	3,1	3,1	2,9	3,0	0,09
DMC	3,3	3,2	3,5	3,3	0,12

PS-Rink Amide resin					
	Swell 1	Swell 2	Swell 3	Swelling (mean value)	Standard deviation
DMF	3,3	3	3,4	3,2	0,17
NOP	1,4	1,7	1,6	1,6	0,12
NCP	1,5	1,5	1,6	1,5	0,05
NBnP	1,5	1,7	1,6	1,6	0,08
NBP	2,1	2	2	2,0	0,05

TG-Wang resin					
	Swell 1	Swell 2	Swell 3	Swelling (mean value)	Standard deviation
DMF	6,2	5,8	6,1	6,0	0,17
NOP	1,7	1,6	1,8	1,7	0,08
NCP	2,3	2,6	2,5	2,5	0,12
NBnP	1,1	1,4	1,4	1,3	0,14

TG-Rink Amide					
	Swell 1	Swell 2	Swell 3	Swelling (mean value)	Standard deviation
DMF	6,3	6	6,4	6,2	0,17
NOP	4,2	4,5	4,1	4,3	0,17
NCP	3,3	3,4	3,4	3,4	0,05
NBnP	4,2	3,9	3,9	4,0	0,14

CM-Wang resin					
	Swell 1	Swell 2	Swell 3	Swelling (mean value)	Standard deviation
DMF	4,3	4,5	4,5	4,4	0,09
NOP	1,4	1,2	1,5	1,4	0,12
NCP	1,5	1,7	1,7	1,6	0,09
NBnP	1,6	1,4	1,5	1,5	0,08

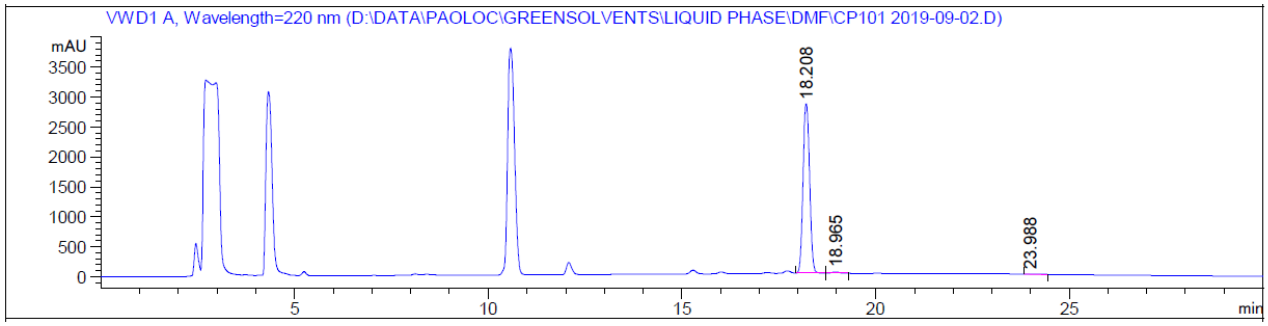
CM-Rink Amide					
	Swell 1	Swell 2	Swell 3	Swelling (mean value)	Standard deviation
DMF	8,0	7,7	7,8	7,8	0,12
NOP	3,5	3,3	3,5	3,4	0,09
NCP	6,0	6,1	6,1	6,1	0,05
NBnP	6,7	6,9	6,6	6,7	0,12

Coupling reactions in solution phase

Chromatograms referred to selected entries of Table 6 (main text) are reported below.

Peaks of target Z-Phg-Pro-NH_2, Z-D-Phg-Pro-NH_2 and starting Z-Phg-OH (if still present) are considered in the spectra.

Figure S19. Chromatogram of Z-Phg-Pro-NH_2, liquid phase synthesis in DMF with COMU/DIPEA

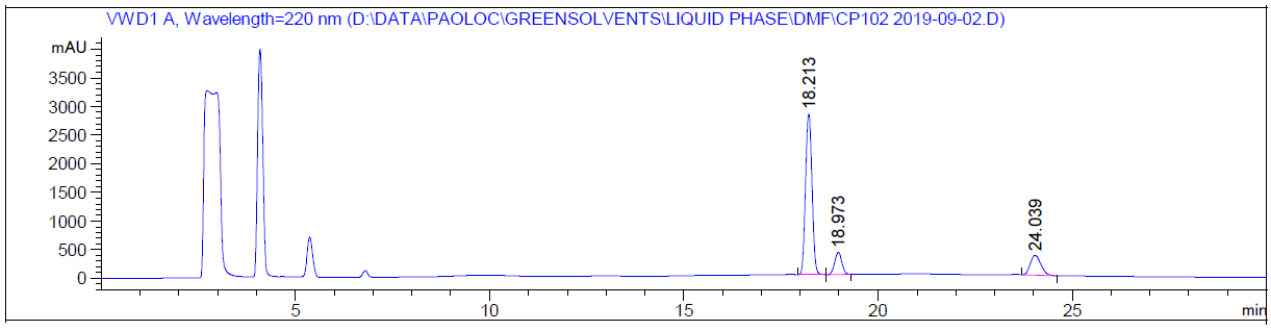


Signal 2: VWD1 A, Wavelength=220 nm

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	18.208	BB	0.1883	3.30223e4	2827.07617	98.9838
2	18.965	BB	0.1985	300.55829	23.94113	0.9009
3	23.988	BBA	0.3489	38.46123	1.77398	0.1153
Totals :				3.33614e4	2852.79128	

Product	Rt (min)	Area (%)
Z-Phg-Pro-NH_2	18.208	99.0
Z-D-Phg-Pro-NH_2	18.965	0.9
Z-Phg-OH	23.988	0.1

Figure S20. Chromatogram of Z-Phg-Pro-NH_2, liquid phase synthesis in DMF with HOBt/DIC



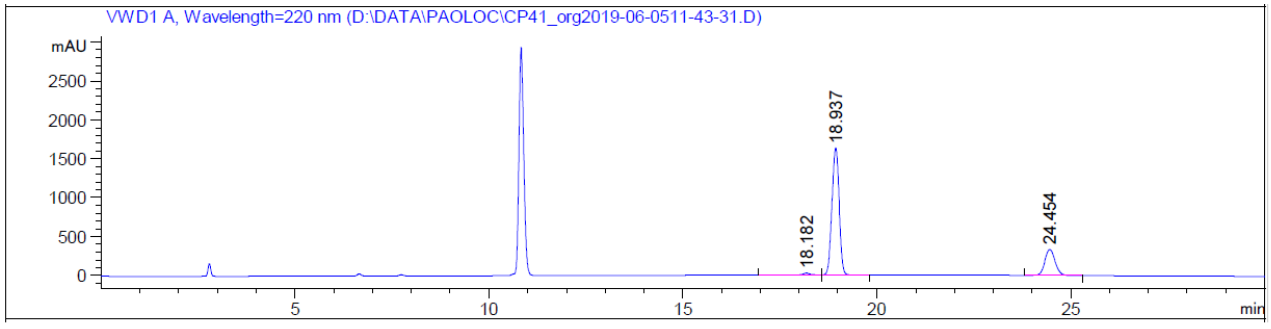

```
Signal 2: VWD1 A, Wavelength=220 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  18.213 BB    0.1856 3.26085e4  2805.47949  73.9204
   2  18.973 BB    0.1995 4973.25342  388.14386  11.2739
   3  24.039 BBA   0.3013 6531.19727  344.37027  14.8056

Totals :                 4.41129e4  3537.99362
```

Product	Rt (min)	Area (%)
Z-Phg-Pro-NH_2	18.213	73.9
Z-D-Phg-Pro-NH_2	18.973	11.3
Z-Phg-OH	24.039	14.8

Figure S21. Chromatogram of Z-D-Phg-Pro-NH_2, liquid phase synthesis in DMF with DIC/OxymaPure®



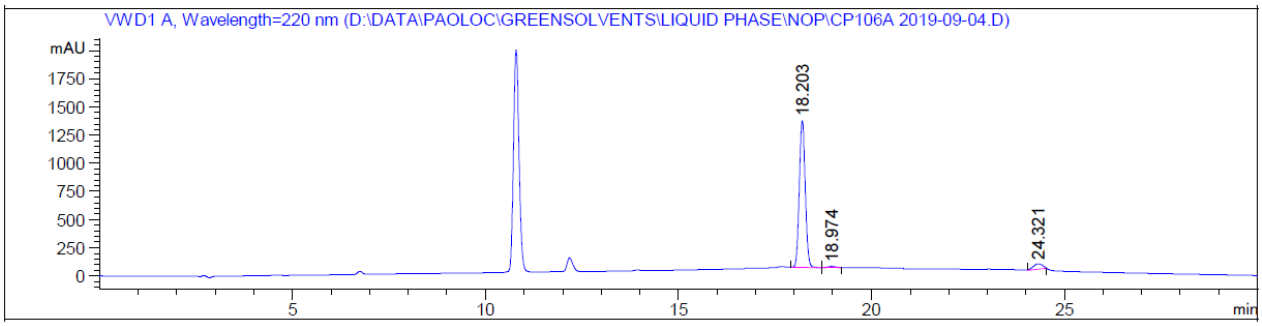

```
Signal 2: VWD1 A, Wavelength=220 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  18.182 BB    0.1921  327.00656   24.44429   1.1886
   2  18.937 BB    0.2025 2.10566e4  1632.74902  76.5341
   3  24.454 BB    0.2857 6129.09180  334.60367  22.2774

Totals :                 2.75127e4  1991.79698
```

Product	Rt (min)	Area (%)
Z-Phg-Pro-NH_2	18.182	1.2
Z-D-Phg-Pro-NH_2	18.937	76.5
Z-Phg-OH	24.454	22.2

Figure S22. Chromatogram of Z-Phg-Pro-NH_2, liquid phase synthesis in NOP with DIC/OxymaPure®

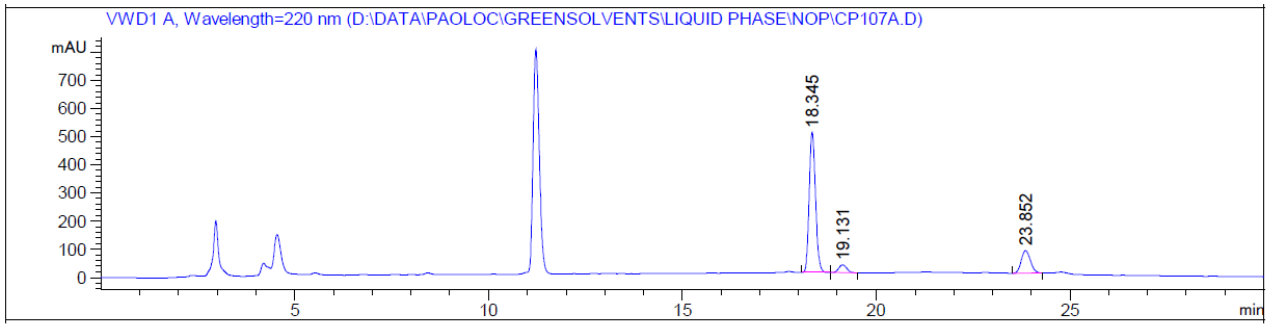


Signal 2: VWD1 A, Wavelength=220 nm

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	18.203	BB	0.1686	1.39291e4	1303.77344	93.7300
2	18.974	BB	0.1951	139.24954	11.35123	0.9370
3	24.321	MM	0.2738	792.52600	48.23468	5.3330
Totals :				1.48608e4	1363.35934	

Product	Rt (min)	Area (%)
Z-Phg-Pro-NH_2	18.203	93.7
Z-D-Phg-Pro-NH_2	18.974	0.9
Z-Phg-OH	24.321	5.3

Figure S23. Chromatogram of Z-Phg-Pro-NH_2, liquid phase synthesis in NOP with COMU/DIPEA

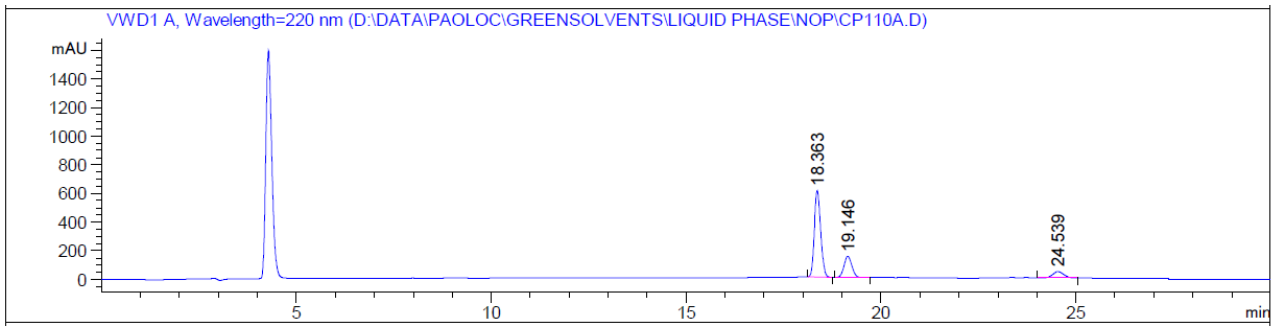


Signal 2: VWD1 A, Wavelength=220 nm

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	18.345	BB	0.1737	5635.76367	499.20959	76.7876
2	19.131	BB	0.2220	395.47168	27.45575	5.3883
3	23.852	BB	0.2567	1308.18469	80.03396	17.8241
Totals :				7339.42004	606.69930	

Product	Rt (min)	Area (%)
Z-Phg-Pro-NH_2	18.208	99.0
Z-D-Phg-Pro-NH_2	18.965	0.9
Z-Phg-OH	23.988	0.1

Figure S24. Chromatogram of Z-Phg-Pro-NH_2, liquid phase synthesis in NOP with PyBOP/HOBt/DIPEA

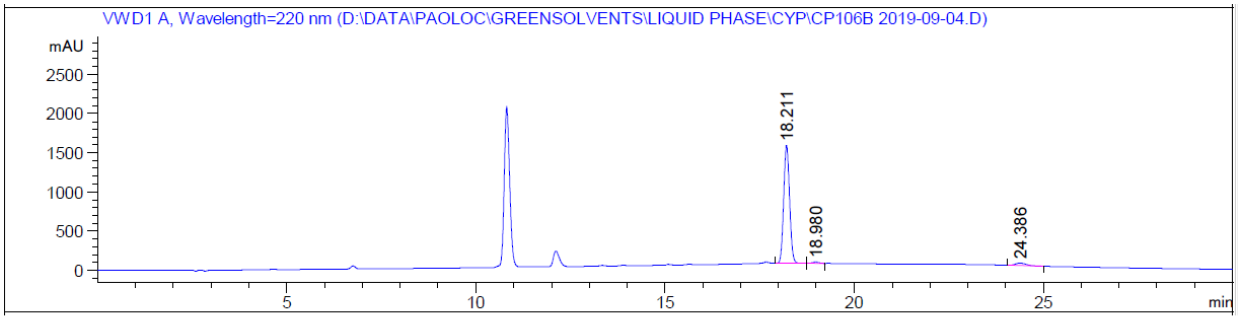


Signal 2: VWD1 A, Wavelength=220 nm

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	18.363	BB	0.1741	6843.63623	604.44281	69.6726
2	19.146	BB	0.2204	2084.97290	147.93764	21.2263
3	24.539	BB	0.3056	893.96100	45.42034	9.1011
Totals :				9822.57013	797.80079	

Product	Rt (min)	Area (%)
Z-Phg-Pro-NH_2	18.363	69.7
Z-D-Phg-Pro-NH_2	19.146	21.2
Z-Phg-OH	24.539	9.1

Figure S25. Chromatogram of Z-Phg-Pro-NH_2, liquid phase synthesis in NCP with DIC/OxymaPure®

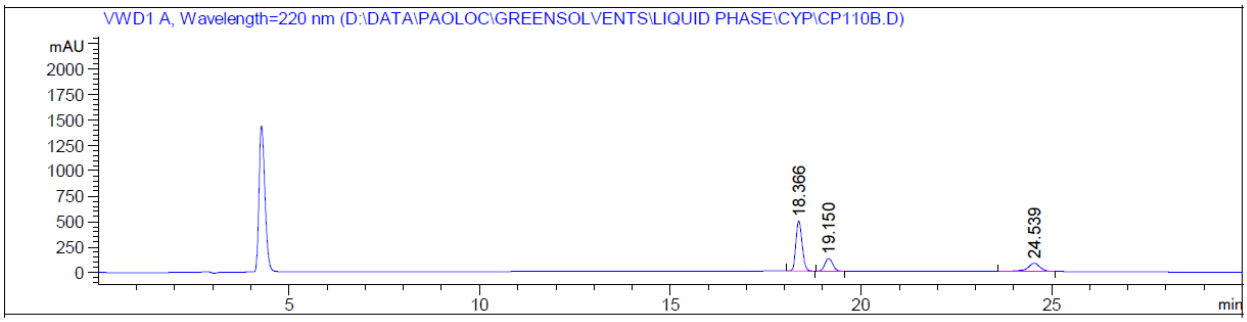


Signal 2: VWD1 A, Wavelength=220 nm

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	18.211	BB	0.1702	1.62625e4	1503.28638	95.1064
2	18.980	BB	0.1958	181.97142	14.75985	1.0642
3	24.386	BBA	0.3154	654.79907	32.72625	3.8294
Totals :				1.70993e4	1550.77247	

Product	Rt (min)	Area (%)
Z-Phg-Pro-NH_2	18.211	95.1
Z-D-Phg-Pro-NH_2	18.980	1.1
Z-Phg-OH	24.386	3.8

Figure S26. Chromatogram of Z-Phg-Pro-NH_2, liquid phase synthesis in NCP with PyBOP/HOBt/DIPEA

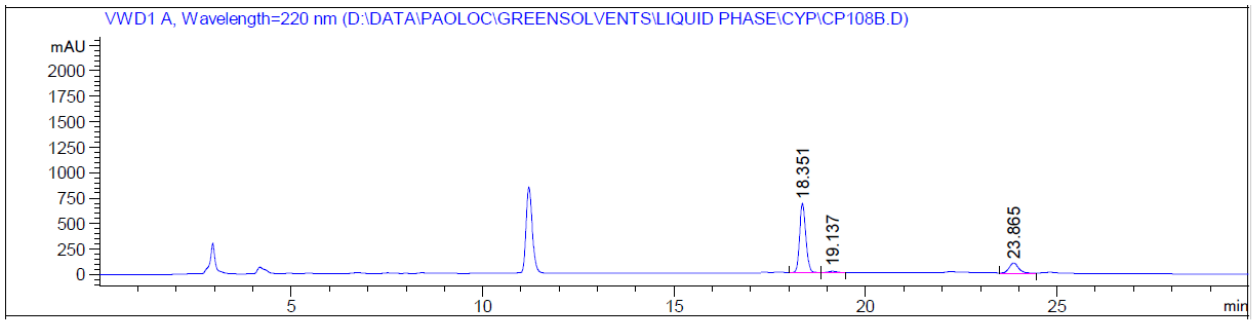


Signal 2: VWD1 A, Wavelength=220 nm

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	18.366	BB	0.1743	5578.51953	491.92984	60.8877
2	19.150	BB	0.2202	1744.89819	124.00921	19.0450
3	24.539	BB	0.3412	1838.56287	80.87137	20.0673
Totals :				9161.98059	696.81042	

Product	Rt (min)	Area (%)
Z-Phg-Pro-NH_2	18.366	60.9
Z-D-Phg-Pro-NH_2	19.150	19.0
Z-Phg-OH	24.539	20.1

Figure S27. Chromatogram of Z-Phg-Pro-NH_2, liquid phase synthesis in NCP with PyOxyma/DIPEA

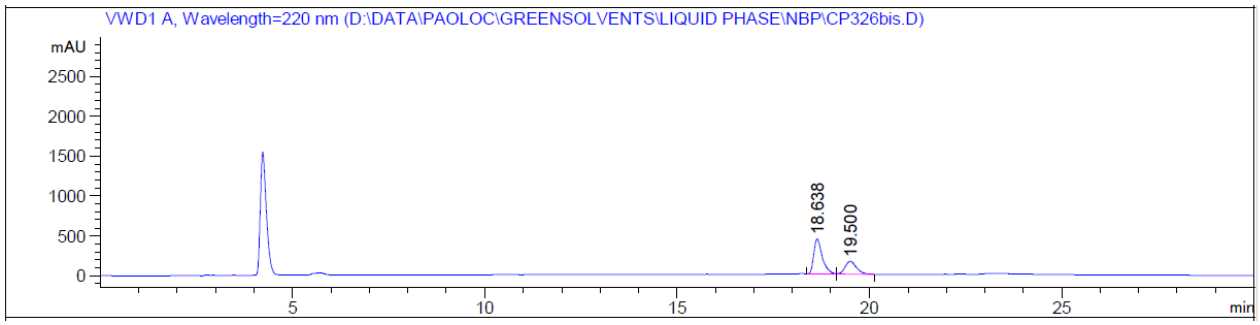


Signal 2: VWD1 A, Wavelength=220 nm

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	18.351	BB	0.1739	7652.02441	676.83398	81.1264
2	19.137	BB	0.2208	181.47392	12.85008	1.9240
3	23.865	BB	0.2590	1598.73096	96.66351	16.9497
Totals :				9432.22929	786.34758	

Product	Rt (min)	Area (%)
Z-Phg-Pro-NH_2	18.351	81.1
Z-D-Phg-Pro-NH_2	19.137	1.9
Z-Phg-OH	23.865	16.9

Figure S28. Chromatogram of Z-Phg-Pro-NH_2, liquid phase synthesis in NBnP with PyBOP/HOBt/DIPEA

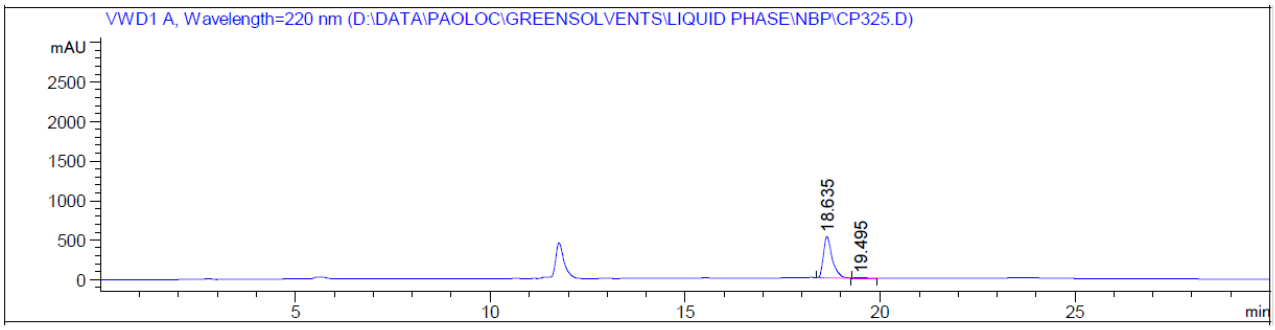


Signal 2: VWD1 A, Wavelength=220 nm

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	18.638	BB	0.2294	6626.39258	435.76483	67.8210
2	19.500	BB	0.3048	3144.01807	157.53407	32.1790
Totals :				9770.41064	593.29890	

Product	Rt (min)	Area (%)
Z-Phg-Pro-NH_2	18.638	67.8
Z-D-Phg-Pro-NH_2	19.500	32.2

Figure S29. Chromatogram of Z-Phg-Pro-NH_2, liquid phase synthesis in NBnP with PyOxyma/DIPEA

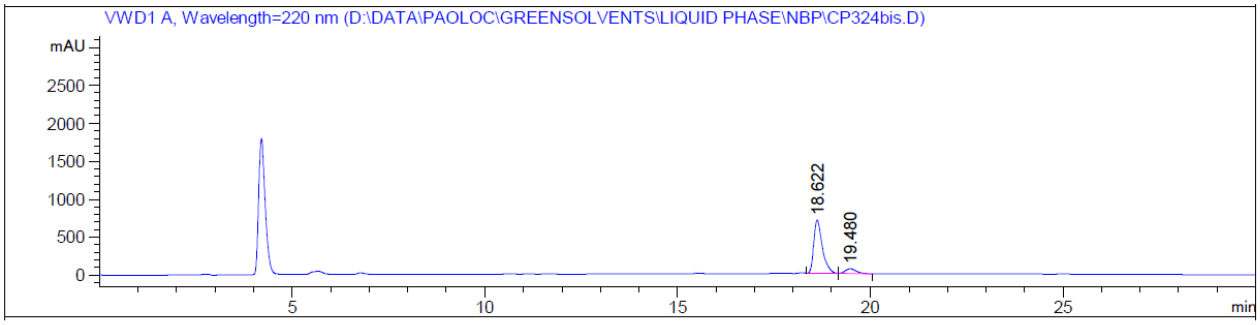


Signal 2: VWD1 A, Wavelength=220 nm

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	18.635	BB	0.2301	8040.38184	520.78162	99.2990
2	19.495	BB	0.2715	56.76353	3.35316	0.7010
Totals :				8097.14536	524.13478	

Product	Rt (min)	Area (%)
Z-Phg-Pro-NH_2	18.635	99.3
Z-D-Phg-Pro-NH_2	19.495	0.7

Figure S30. Chromatogram of Z-Phg-Pro-NH_2, liquid phase synthesis in NBnP with HOBt/DIC



Signal 2: VWD1 A, Wavelength=220 nm

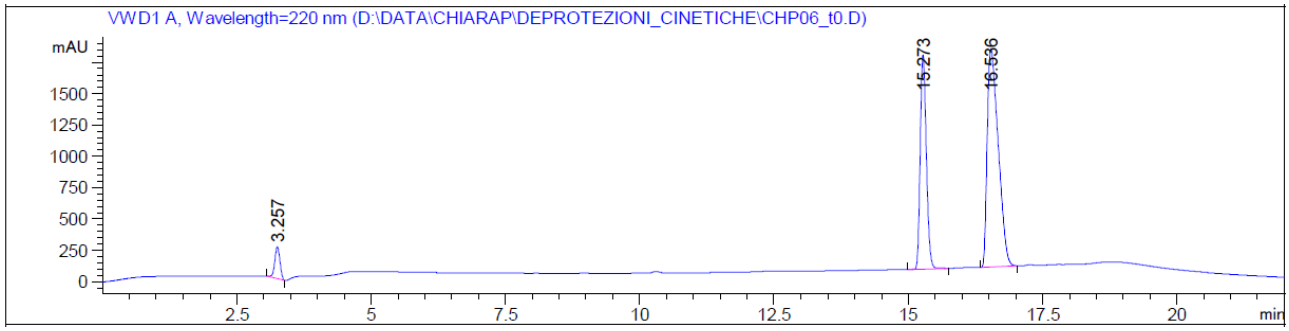
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	18.622	BB	0.2317	1.07921e4	700.55780	89.9444
2	19.480	BB	0.2963	1206.53198	62.74966	10.0556
Totals :				1.19987e4	763.30746	

Product	Rt (min)	Area (%)
Z-Phg-Pro-NH_2	18.622	89.9
Z-D-Phg-Pro-NH_2	19.480	10.1

Deprotection kinetic tests

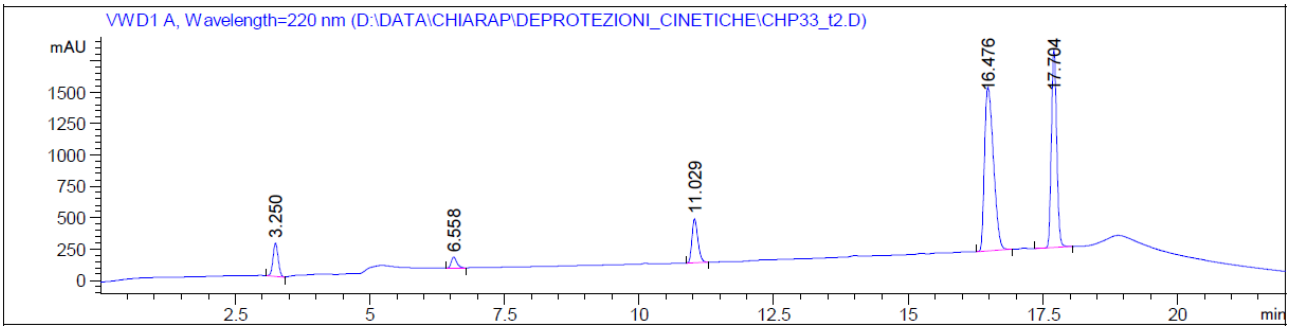
Deprotection kinetic tests in all investigated pyrrolidones revealed complete Fmoc removal in 2 minutes. A selected example in NOP is reported below.

Figure S31. Chromatogram of Fmoc-Phe-OH deprotection in NOP at t=0 (before base addition)



Legend: Piperidine = peak at 3.257 min; Fmoc-Phe-OH = peak at 15.273 min; NOP = peak at 16.536 min

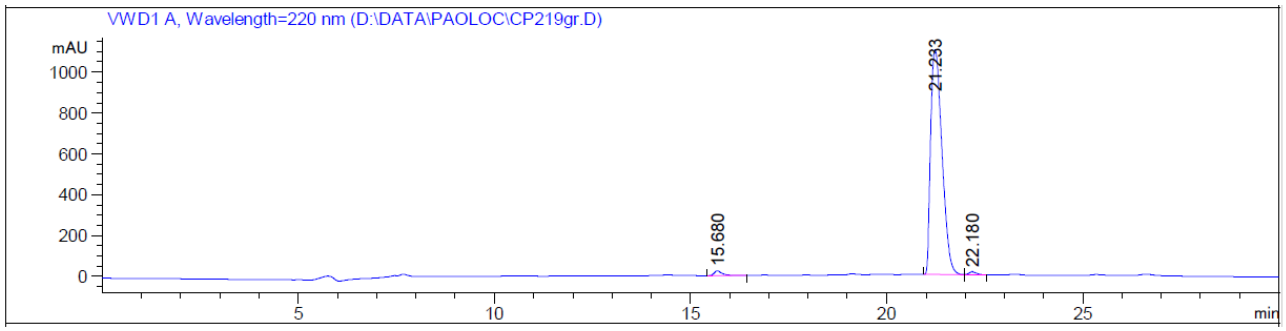
Figure S32. Chromatogram of Fmoc-Phe-OH deprotection in NOP at t=2 minutes



Legend: Piperidine = peak at 3.250 min; H-Phe-OH = peak at 6.558 min; DBF-piperidine adduct = peak at 11.029 min; NOP = peak at 16.476 min; dibenzofulvene (DBF) = peak at 17.704 min

SPPS of Aib-Enkephalin in Green Solvents

Figure S33. Chromatogram of Aib-Enkephalin pentapeptide, manual SPPS in NOP on PS-Wang resin



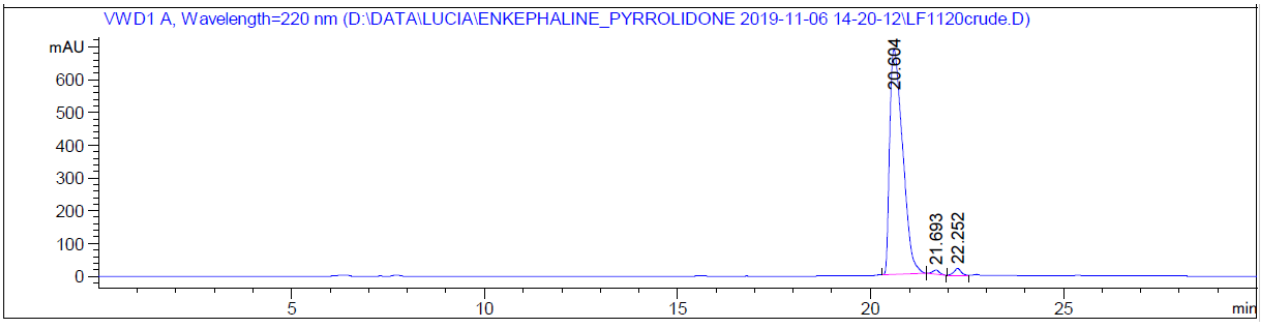

```
Signal 2: VWD1 A, Wavelength=220 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  15.680 BB    0.2123  329.22705   22.81919   1.4622
   2  21.233 BB    0.3216 2.20013e4  1098.72717  97.7158
   3  22.180 BB    0.2012  185.07613   14.09826   0.8220

Totals :                  2.25156e4  1135.64462
```

Peptide	Rt (min)	RRT	Area (%)
Des-Phe	15.680	0.74	1.5
Aib-Enkephalin	21.233	1.00	97.7
Des-Aib	22.180	1.04	0.8

Figure S34. Chromatogram of Aib-Enkephalin pentapeptide, manual SPPS in NOP on PS-Trt-Cl resin



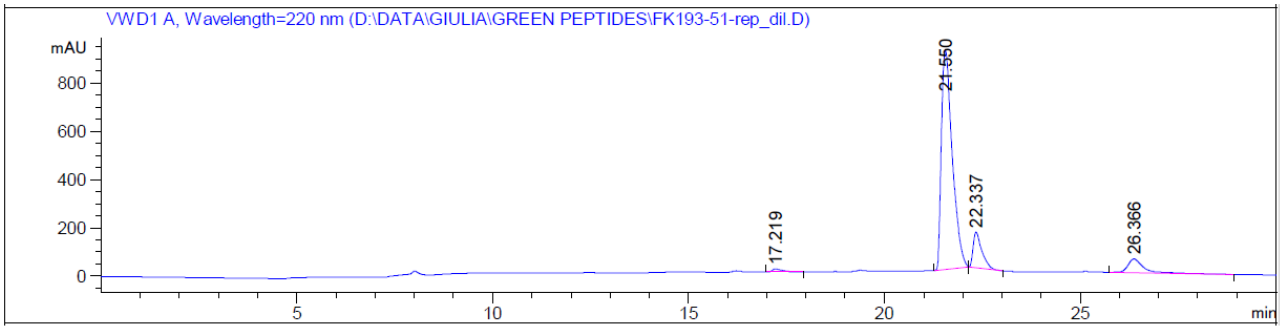

```
Signal 2: VWD1 A, Wavelength=220 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  20.604 BB    0.3613 1.60242e4   689.11395  97.4135
   2  21.693 BB    0.1815  157.17870   13.14057   0.9555
   3  22.252 BB    0.1893  268.28781   21.25153   1.6310

Totals :                  1.64497e4   723.50605
```

Peptide	Rt (min)	RRT	Area (%)
Aib-Enkephalin	20.604	1.00	97.4
Des-Aib	21.693	1.04	1.0
Des-Aib+tBu+TFA	22.252	1.08	1.6

Figure S35. Chromatogram of Aib-Enkephalin pentapeptide, manual SPPS in NCP on PS-Wang resin

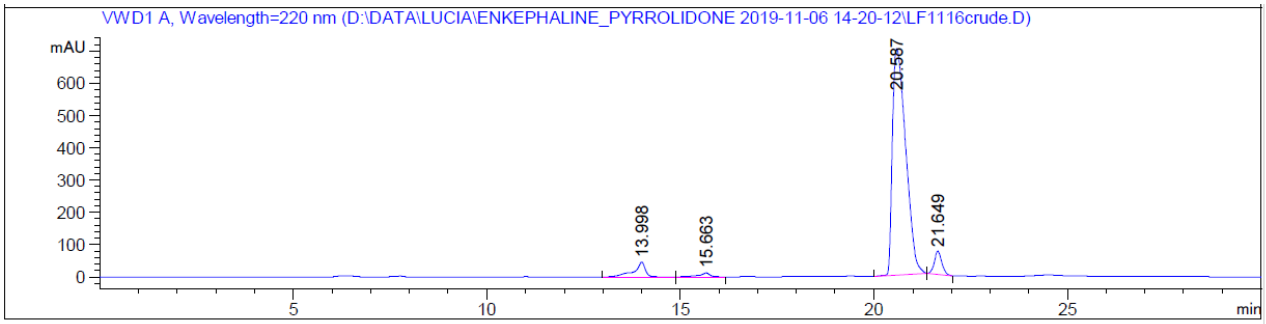


Signal 2: VWD1 A, Wavelength=220 nm

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	17.219	BB	0.2546	222.67754	12.45164	1.0294
2	21.550	BB	0.2902	1.75010e4	910.80939	80.9062
3	22.337	BB	0.2256	2278.07446	147.96461	10.5314
4	26.366	BB	0.4191	1629.48035	56.73232	7.5330
Totals :				2.16313e4	1127.95797	

Peptide	Rt (min)	RRT	Area (%)
Des-Aib-Tyr	17.219	0.80	1.0
Aib-Enkephalin	21.550	1.00	80.9
Des-Aib	22.337	1.04	10.5
Aib-Enkephalin+TFA	26.366	1.23	7.6

Figure S36. Chromatogram of Aib-Enkephalin pentapeptide, manual SPPS in NCP on PS-Trt-Cl resin

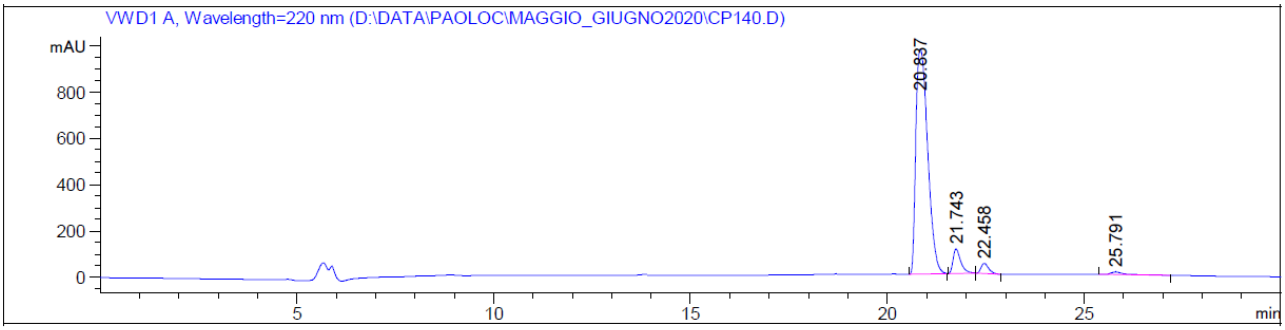


Signal 2: VWD1 A, Wavelength=220 nm

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	13.998	BB	0.2773	912.86908	45.26573	4.8253
2	15.663	BB	0.2435	206.71103	11.85194	1.0927
3	20.587	BB	0.3778	1.68199e4	701.40295	88.9086
4	21.649	BB	0.2063	978.72028	72.14259	5.1734
Totals :				1.89182e4	830.66321	

Peptide	Rt (min)	RRT	Area (%)
Des-Phe-Aib	13.998	0.68	4.8
Des-Phe	15.663	0.76	1.1
Aib-Enkephalin	20.587	1.00	88.9
Des-Aib	21.649	1.04	5.2

Figure S37. Chromatogram of Aib-Enkephalin pentapeptide, manual SPPS in NBP on PS-Wang resin

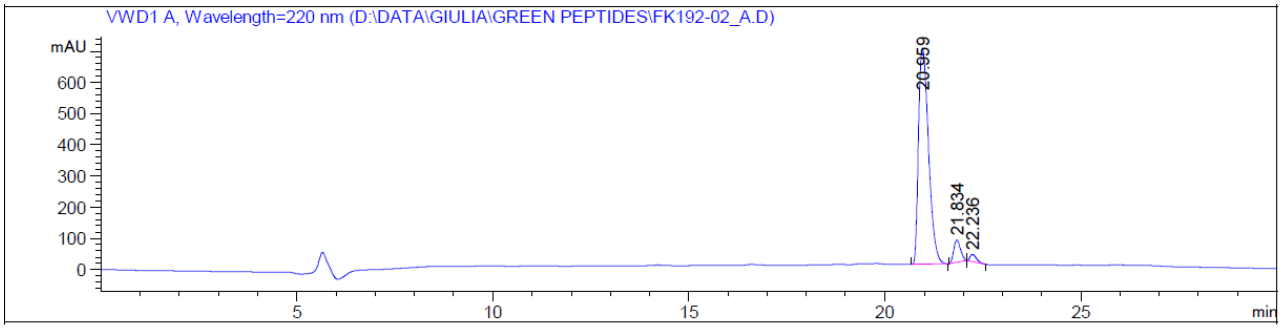


Signal 2: VWD1 A, Wavelength=220 nm

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	20.837	BB	0.3368	2.02126e4	971.16205	89.7160
2	21.743	BB	0.2046	1414.25427	105.33276	6.2773
3	22.458	BB	0.1992	575.41437	43.81619	2.5540
4	25.791	BB	0.3745	327.27429	12.29867	1.4526
Totals :				2.25295e4	1132.60966	

Peptide	Rt (min)	RRT	Area (%)
Aib-Enkephalin	20.837	1.00	89.7
Des-Aib	21.743	1.04	6.3
Des-Aib+tBu+TFA	22.458	1.08	2.6
Aib-Enkephalin+TFA	25.791	1.23	1.4

Figure S38. Chromatogram of Aib-Enkephalin pentapeptide, manual SPPS in NBP on PS-Trt-Cl resin



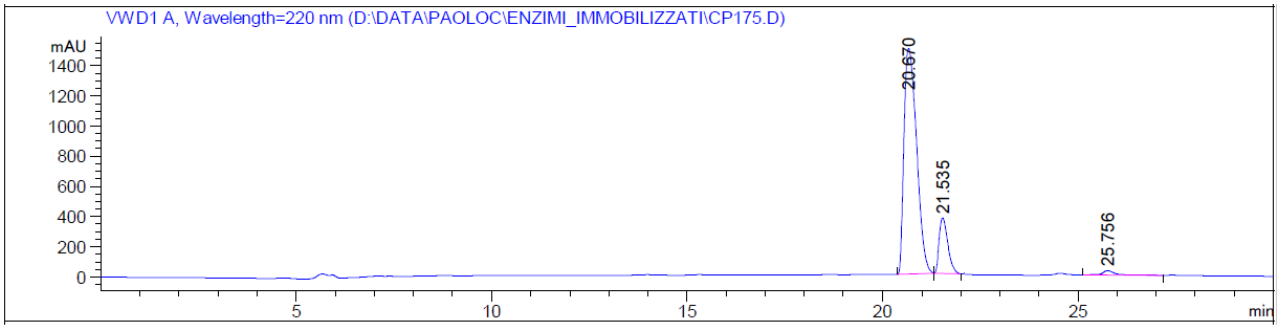

```
Signal 2: VWD1 A, Wavelength=220 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  20.959 BB    0.2817 1.23417e4   693.12585  91.6110
   2  21.834 BB    0.1851  862.24347   72.29428   6.4003
   3  22.236 BB    0.1763  267.91568   23.62984   1.9887

Totals :                 1.34719e4   789.04997
```

Peptide	Rt (min)	RRT	Area (%)
Aib-Enkephalin	20.959	1.00	91.6
Des-Aib	21.834	1.04	6.4
Des-Aib+tBu+TFA	22.236	1.06	2.0

Figure S39. Chromatogram of Aib-Enkephalin pentapeptide, manual SPPS in DMF on PS-Wang resin



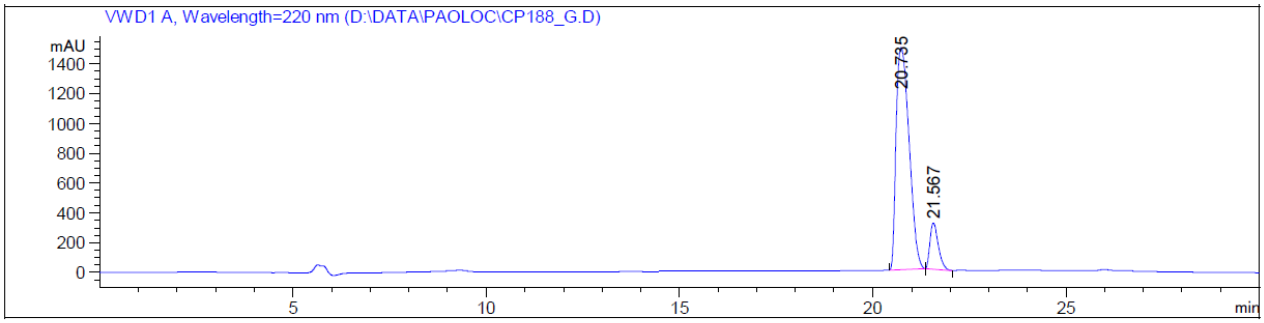

```
Signal 2: VWD1 A, Wavelength=220 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  20.670 BB    0.3657 3.35146e4  1494.20105  84.0369
   2  21.535 BB    0.2424 5678.86670  367.24759  14.2396
   3  25.756 BB    0.3358  687.37134   29.29332   1.7236

Totals :                 3.98808e4  1890.74195
```

Peptide	Rt (min)	RRT	Area (%)
Aib-Enkephalin	20.670	1.00	84.0
Des-Aib	21.535	1.04	14.2
Aib-Enkephalin+TFA	25.756	1.23	1.8

Figure S40. Chromatogram of Aib-Enkephalin pentapeptide, manual SPPS in DMF on PS-Trt-Cl resin



Signal 2: VWD1 A, Wavelength=220 nm

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	20.735	BB	0.3830	3.49027e4	1491.34082	88.1380
2	21.567	BB	0.2361	4697.35010	311.21463	11.8620
Totals :				3.96001e4	1802.55545	

Peptide	Rt (min)	RRT	Area (%)
Aib-Enkephalin	20.735	1.00	88.1
Des-Aib	21.567	1.04	11.9

Figure S41. Mass spectrum of H_2N-Tyr-Aib-Aib-Phe-Leu-COOH (Aib-Enkephalin)

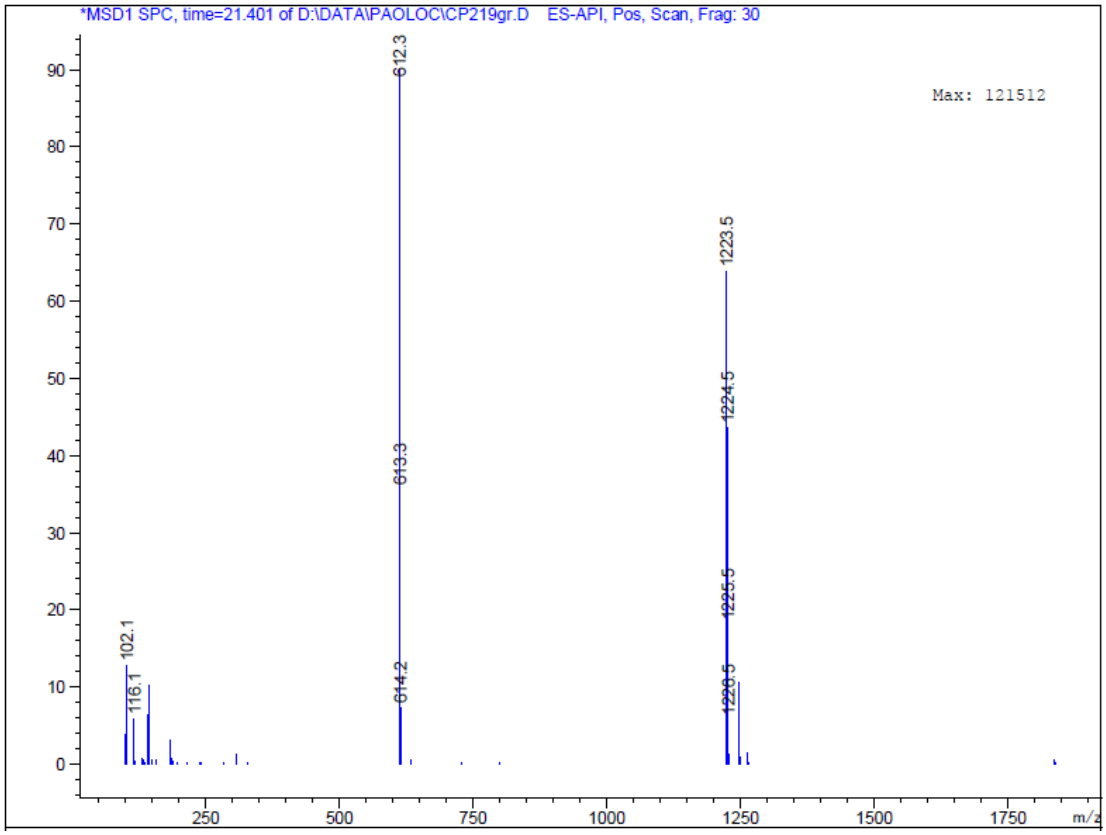


Figure S42. Mass spectrum of H_2N-Tyr-Aib-Aib-Phe-Leu-COOH + TFA (Aib-Enkephalin+TFA)

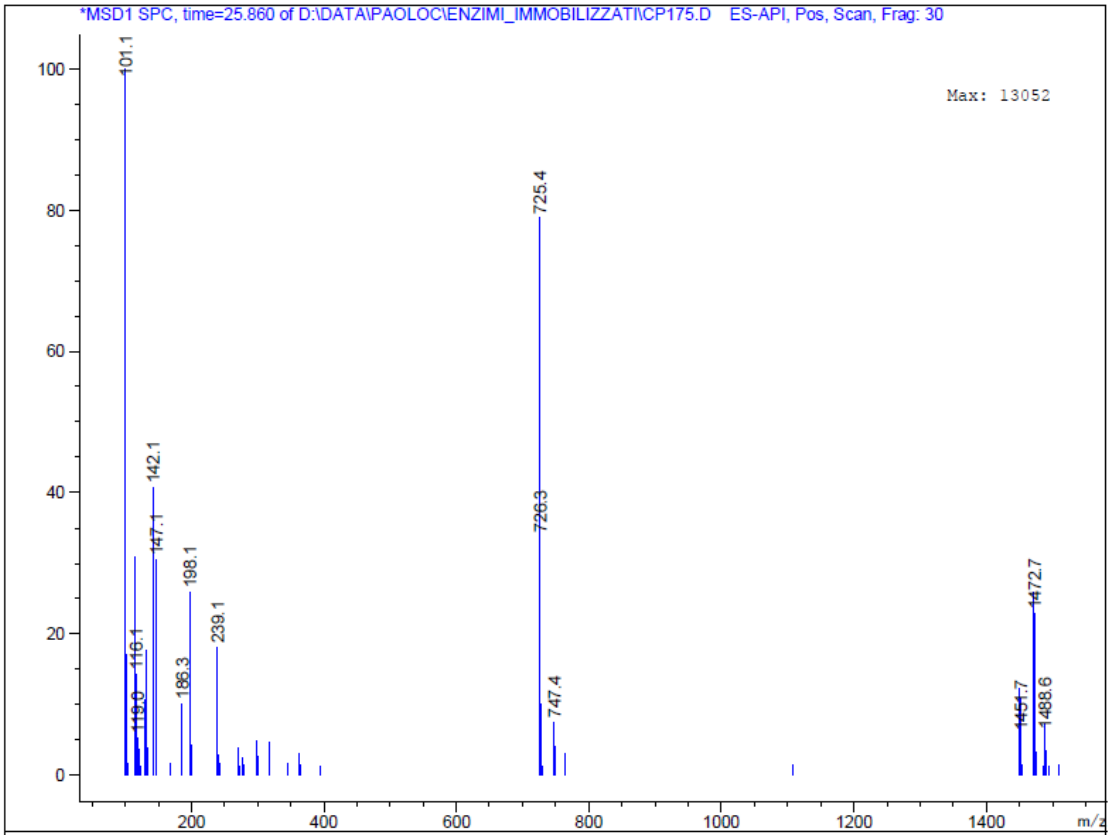


Figure S43. Mass spectrum of H_2N-Tyr-Aib-Phe-Leu-COOH (des-Aib)

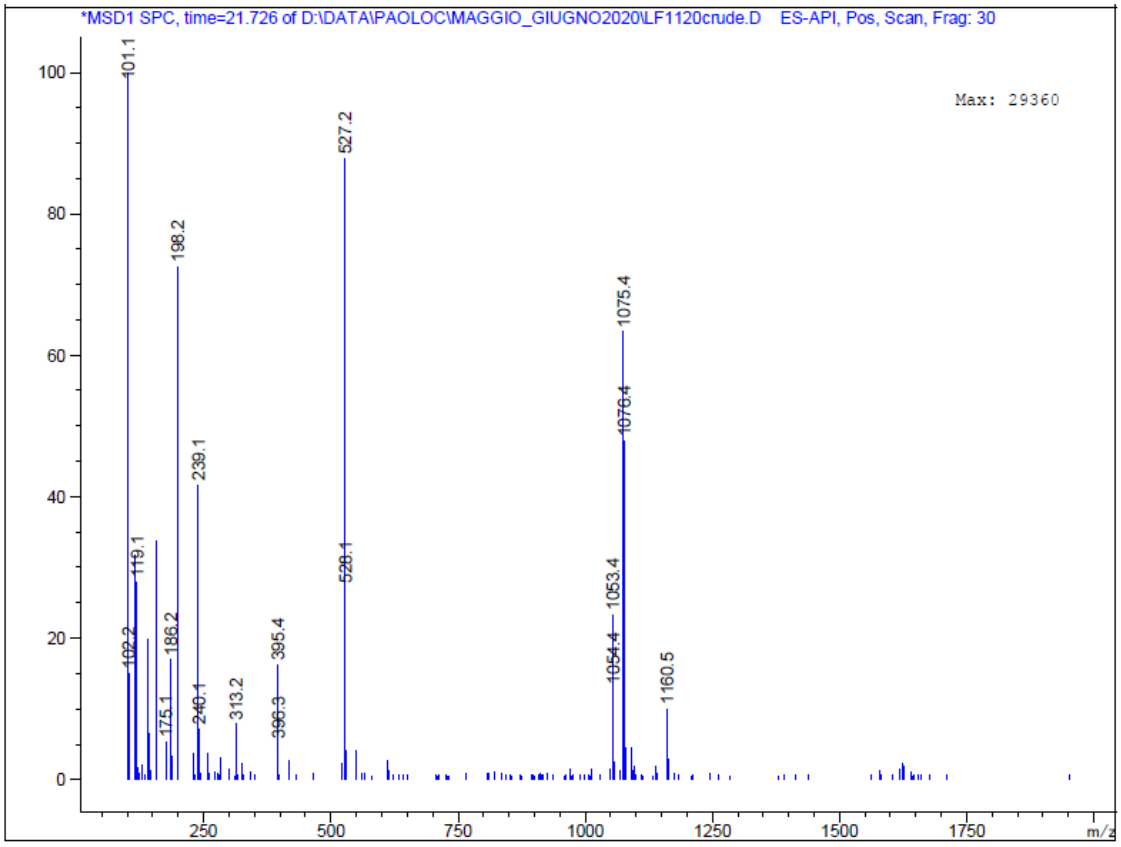


Figure S44. Mass spectrum of H_2N-Tyr-Aib-Phe-Leu-COOH+tBu+TFA (des-Aib+tBu+TFA)

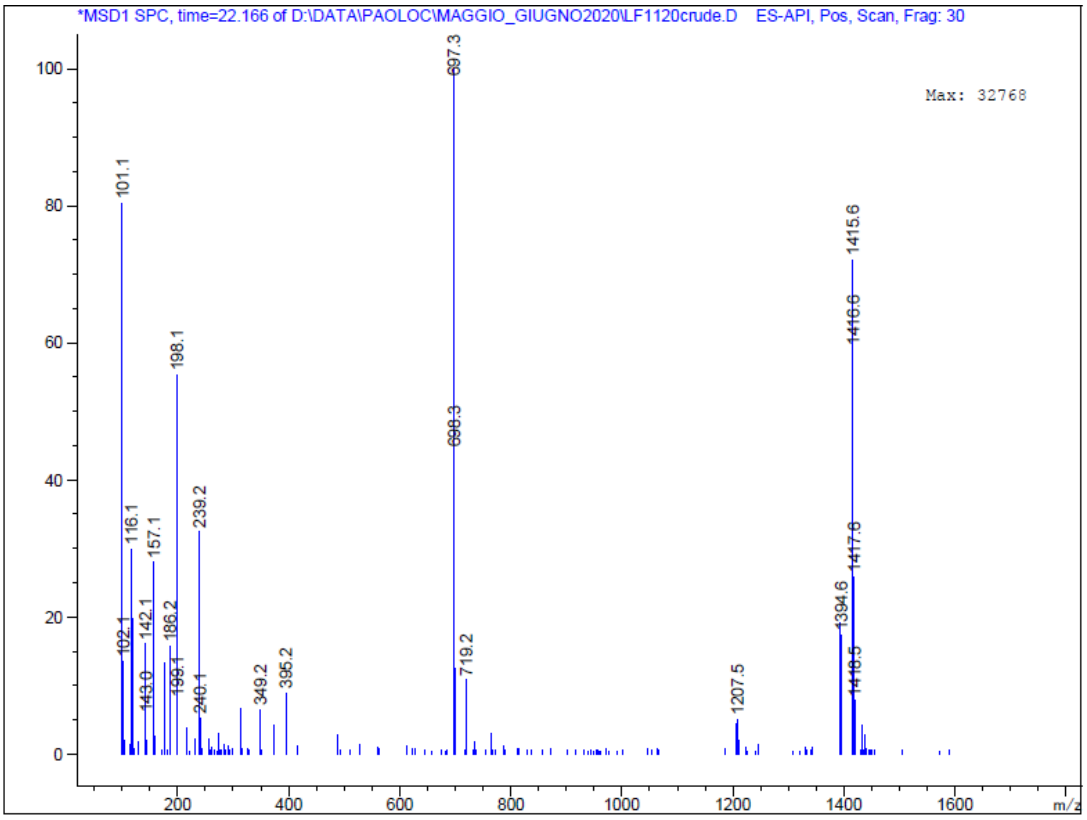


Figure S45. Mass spectrum of H_2N-Tyr-Aib-Aib-Leu-COOH (des-Phe)

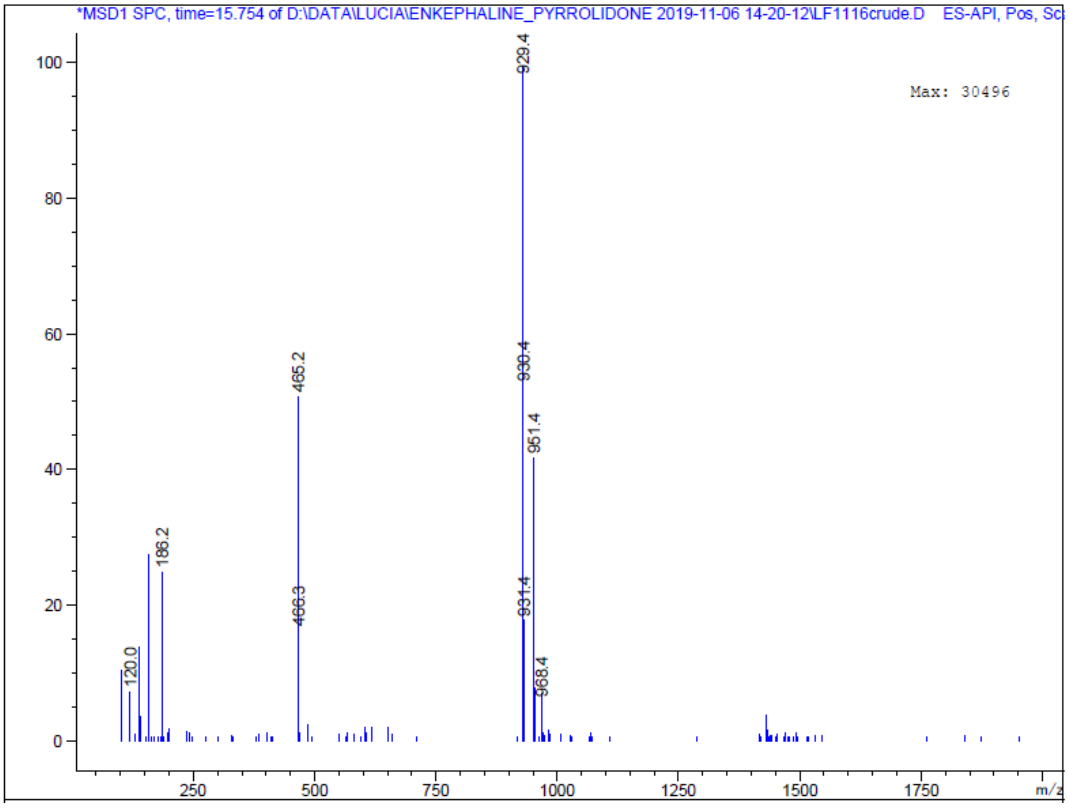


Figure S46. Mass spectrum of H_2N-Aib-Phe-Leu-COOH (des-Aib-Tyr)

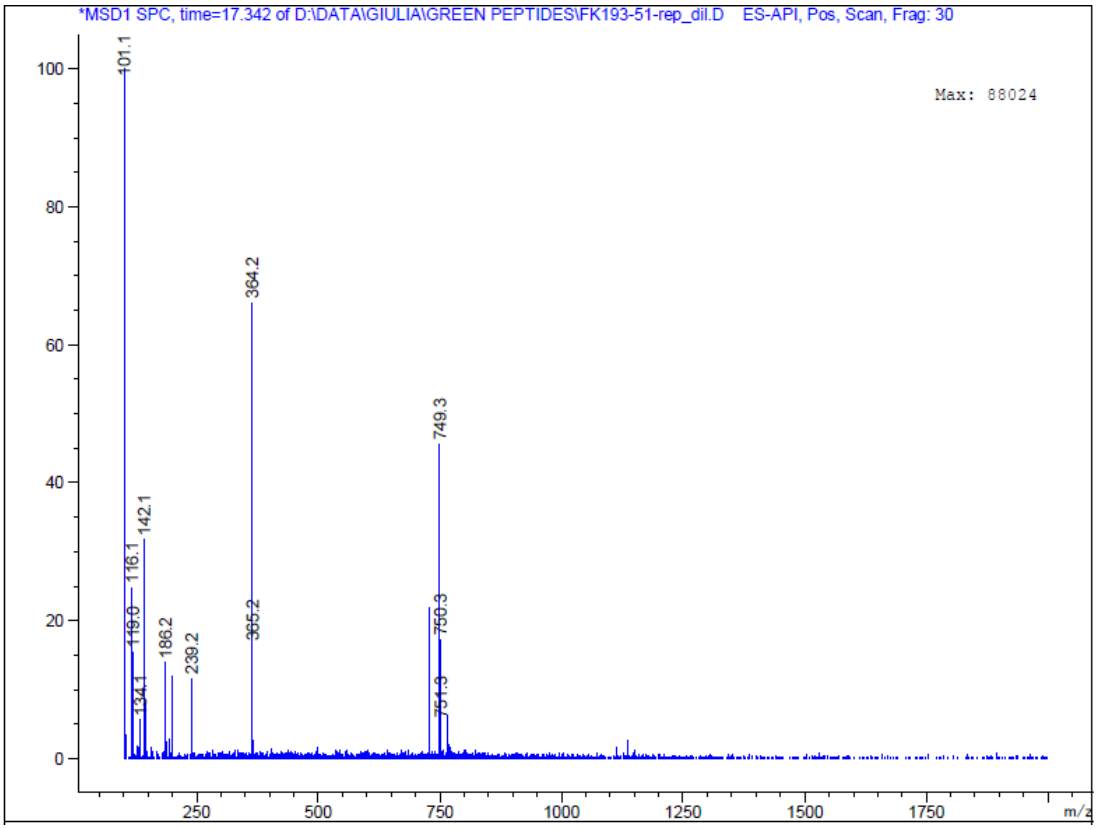
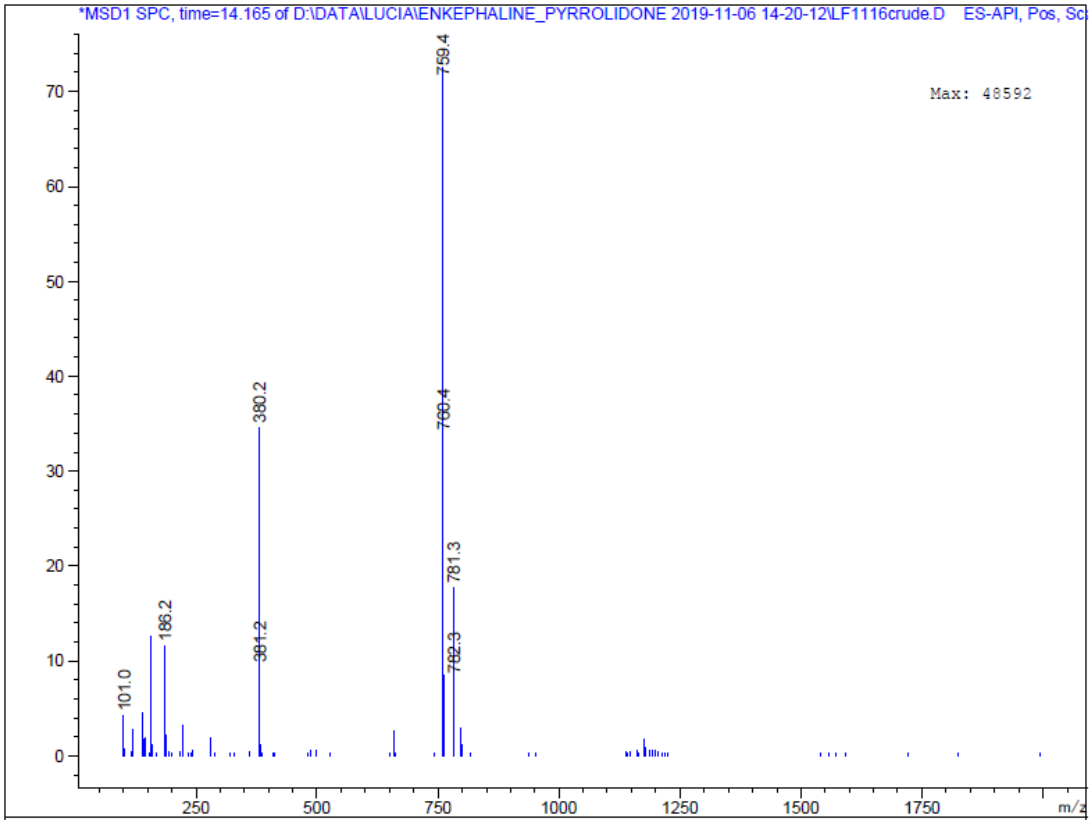
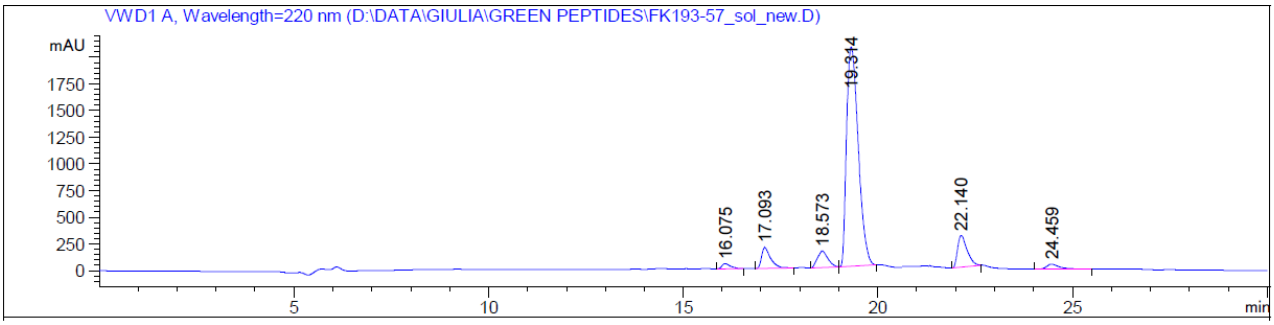


Figure S47. Mass spectrum of H_2N-Tyr-Aib-Leu-COOH (des-Phe-Aib)



SPPS of linear Octreotide in Green Solvents

Figure S48. Chromatogram of linear Octreotide, manual SPPS in DMF

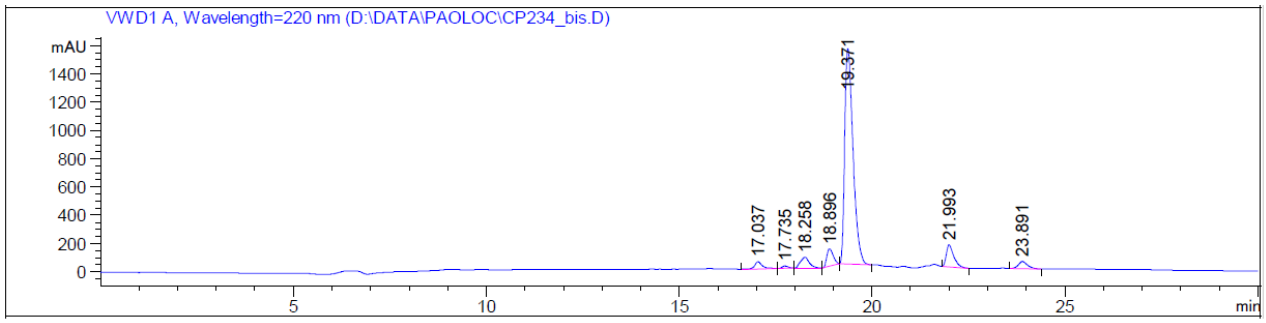


Signal 3: VWD1 A, Wavelength=220 nm

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.075	BB	0.2235	768.38983	50.49308	1.3774
2	17.093	BB	0.2418	3249.43457	197.66211	5.8250
3	18.573	BB	0.2689	2855.27539	154.98911	5.1184
4	19.314	BB	0.3333	4.28366e4	2054.30322	76.7901
5	22.140	BB	0.2549	5004.95947	296.59695	8.9720
6	24.459	BB	0.3338	1069.39221	47.28645	1.9170
Totals :				5.57841e4	2801.33093	

Peptide	Rt (min)	RRT	Area (%)
Cyclized Octreotide N,O shift	16.075	0.83	1.4
Cyclized Octreotide	17.093	0.88	5.8
Linear Octreotide + CO_2	18.573	0.97	5.1
Linear Octreotide	19.314	1.00	76.8
Linear Octreotide + tBu	22.140	1.14	9.0
Linear Octreotide + tBu2	24.459	1.26	1.9

Figure S49. Chromatogram of linear Octreotide, manual SPPS in NBP

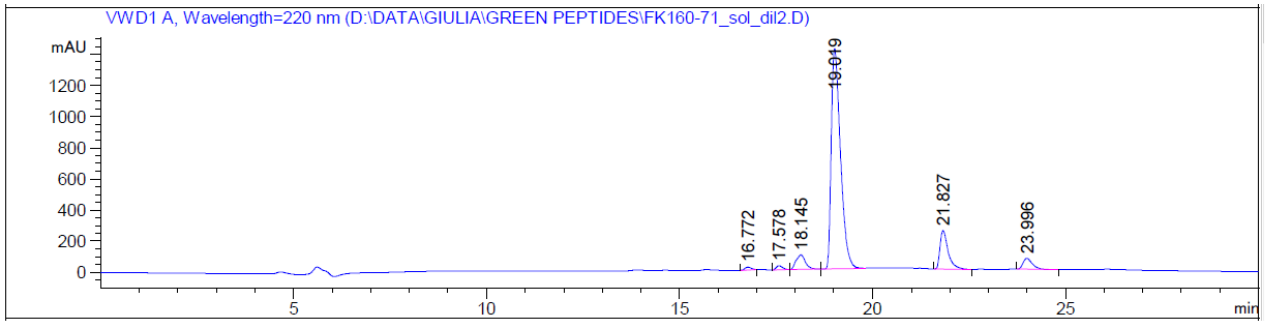


Signal 3: VWD1 A, Wavelength=220 nm

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	17.037	BB	0.2040	725.18536	51.58432	2.4587
2	17.735	BB	0.1741	197.43239	17.70697	0.6694
3	18.258	BB	0.2302	1245.63489	77.20074	4.2233
4	18.896	BB	0.1741	1401.56506	123.80760	4.7520
5	19.371	BB	0.2314	2.29071e4	1523.86560	77.6661
6	21.993	BB	0.2023	2130.73779	157.06062	7.2242
7	23.891	BB	0.2446	886.67169	53.16150	3.0062
Totals :				2.94943e4	2004.38736	

Peptide	Rt (min)	RRT	Area (%)
Cyclized Octreotide	17.037	0.88	2.4
Linear Octreotide N,O-shift 1	17.735	0.92	0.7
Linear Octreotide N,O-shift 2	18.258	0.95	4.2
Linear Octreotide+CO_2	18.896	0.97	4.8
Linear Octreotide	19.371	1.00	77.7
Linear Octreotide+tBu	21.993	1.14	7.2
Linear Octreotide+tBu2	23.891	1.26	3.0

Figure S50. Chromatogram of linear Octreotide, manual SPPS in NOP

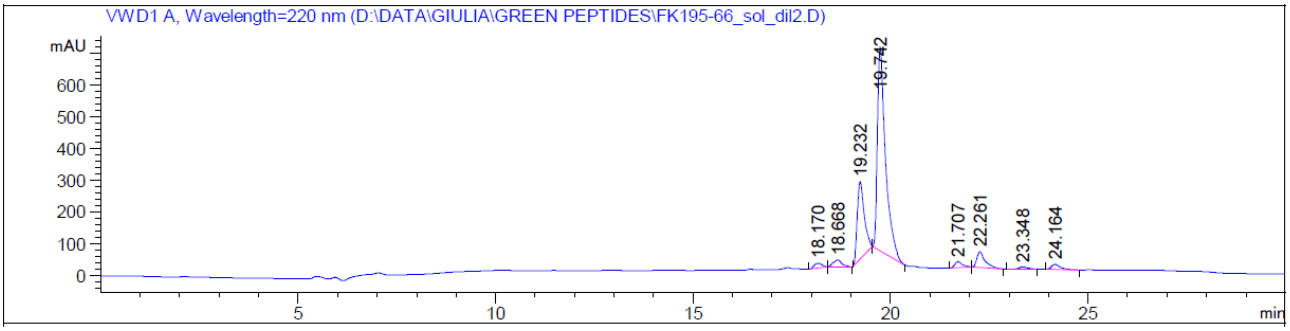


Signal 2: VWD1 A, Wavelength=220 nm

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.772	BB	0.1705	201.14771	18.26477	0.6597
2	17.578	BB	0.1728	302.99942	27.01583	0.9937
3	18.145	BB	0.2352	1585.15430	94.75126	5.1985
4	19.019	BB	0.2611	2.36682e4	1414.98083	77.6199
5	21.827	BB	0.2139	3569.33667	248.07680	11.7057
6	23.996	BB	0.2528	1165.58362	69.82388	3.8225
Totals :				3.04924e4	1872.91337	

Peptide	Rt (min)	RRT	Area (%)
Cyclized Octreotide	16.772	0.88	0.7
Linear Octreotide N,O-shift 1	17.578	0.92	1.0
Linear Octreotide N,O-shift 2	18.145	0.95	5.2
Linear Octreotide	19.019	1.00	77.6
Linear Octreotide+tBu	21.827	1.14	11.7
Linear Octreotide+tBu2	23.996	1.26	3.8

Figure S51. Chromatogram of linear Octreotide, manual SPPS in NOP/DMC 80:20

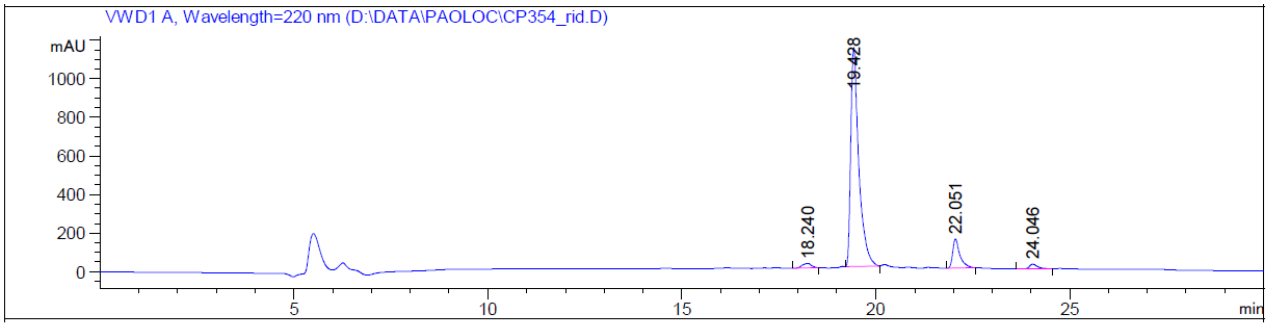


Signal 2: VWD1 A, Wavelength=220 nm

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	18.170	BB	0.2206	201.05826	14.60746	1.4404
2	18.668	BB	0.2137	340.64853	22.36730	2.4404
3	19.232	BB	0.1835	3011.40967	244.75949	21.5734
4	19.742	BB	0.2053	9083.64355	641.24805	65.0743
5	21.707	BB	0.1934	243.02454	18.72661	1.7410
6	22.261	BB	0.2100	720.24097	49.42918	5.1597
7	23.348	BB	0.2255	106.01482	7.04599	0.7595
8	24.164	BB	0.2386	252.84393	15.64409	1.8113
Totals :				1.39589e4	1013.82816	

Peptide	Rt (min)	RRT	Area (%)
Linear Octreotide N,O-shift 1	18.170	0.92	1.4
Linear Octreotide N,O-shift 2	18.668	0.95	2.4
Linear Octreotide+CO_2	19.232	0.97	21.6
Linear Octreotide	19.742	1.00	65.1
Linear Octreotide+Boc	21.707	1.10	1.7
Linear Octreotide+tBu	22.261	1.14	5.2
Linear Octreotide+Boc2	23.348	1.18	0.8
Linear Octreotide+tBu2	24.164	1.26	1.8

Figure S52. Chromatogram of linear Octreotide, automated SPPS in NOP/DMC 80:20



Signal 2: VWD1 A, Wavelength=220 nm

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	18.240	BB	0.2179	385.12341	24.43648	2.0225
2	19.428	BB	0.2146	1.63817e4	1133.47070	86.0280
3	22.051	BB	0.1853	1913.27478	151.52823	10.0475
4	24.046	BB	0.2174	362.18839	24.65477	1.9020
Totals :				1.90423e4	1334.09018	

Peptide	Rt (min)	RRT	Area (%)
Linear Octreotide N,O-shift 2	18.240	0.95	2.0
Linear Octreotide	19.428	1.00	86.0
Linear Octreotide+tBu	22.051	1.14	10.0
Linear Octreotide+tBu2	24.046	1.26	2.0

Figure S53. Mass spectrum of linear Octreotide

Figure S54. Mass spectrum of linear Octreotide+CO_2

Figure S55. Mass spectrum of linear Octreotide+tBu

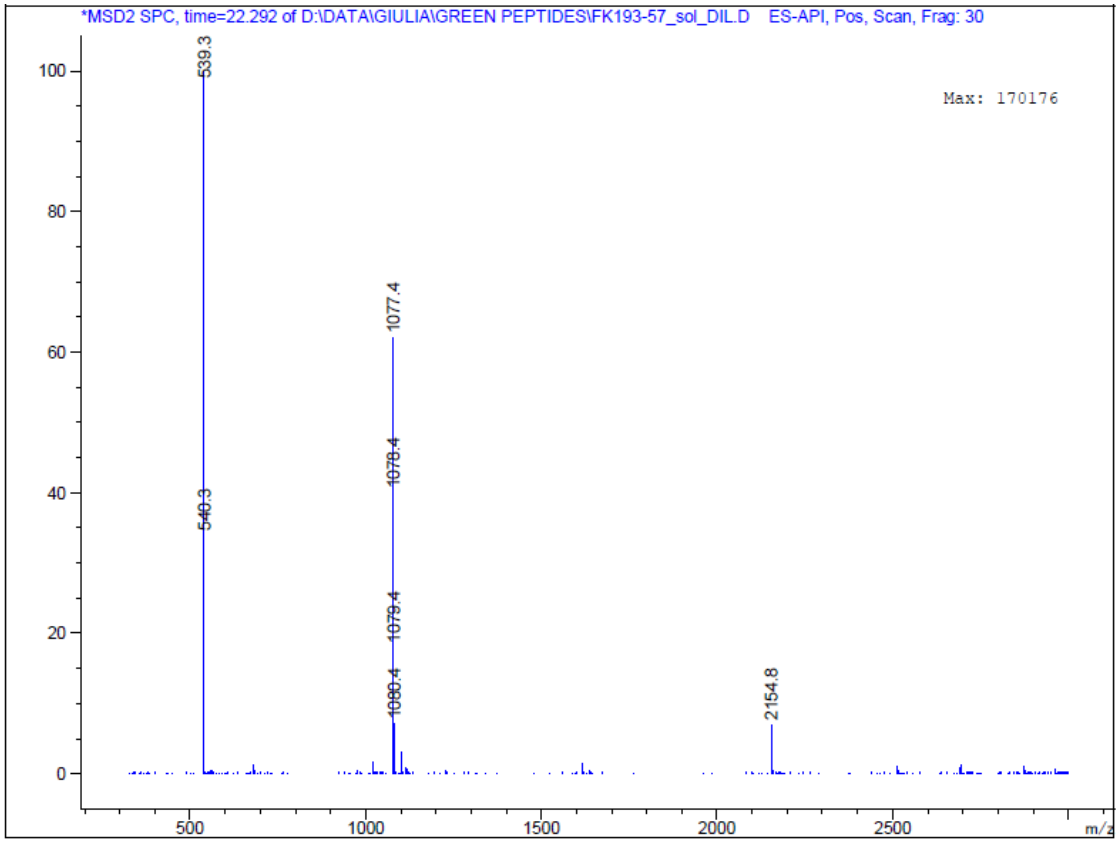


Figure S56. Mass spectrum of linear Octreotide+Boc

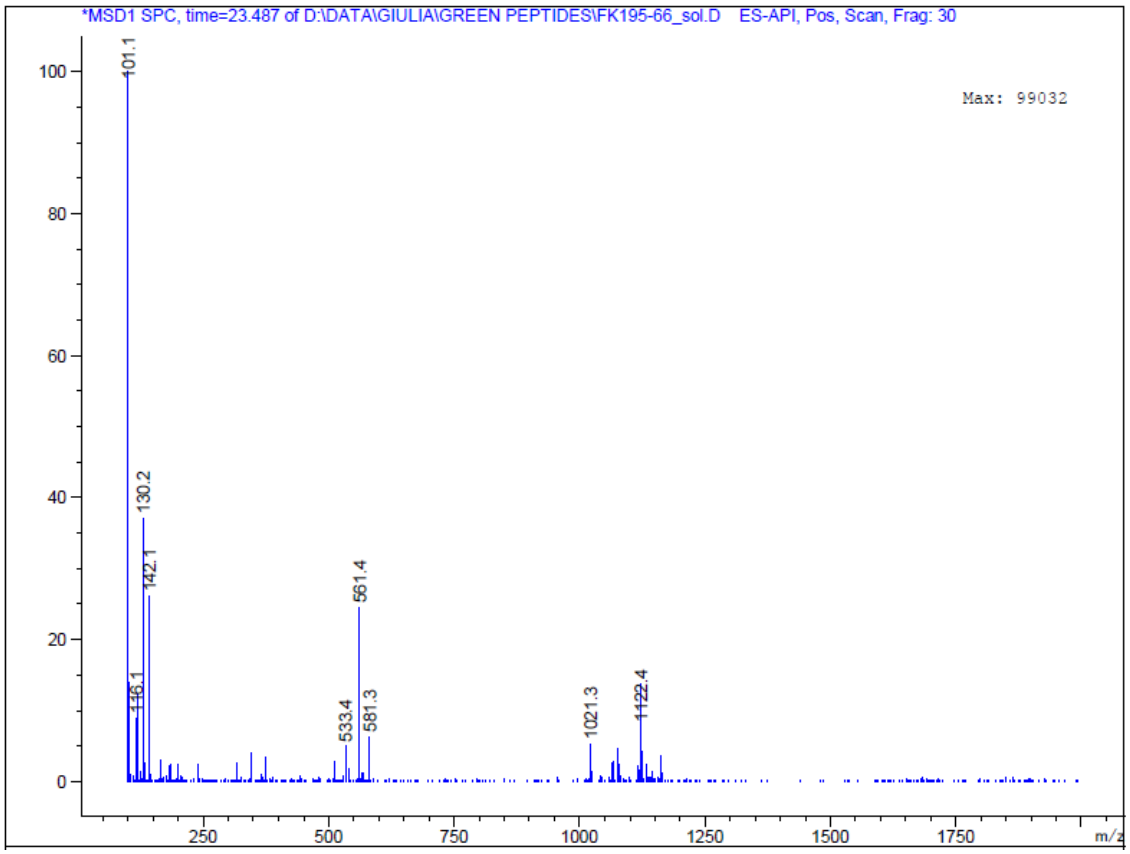
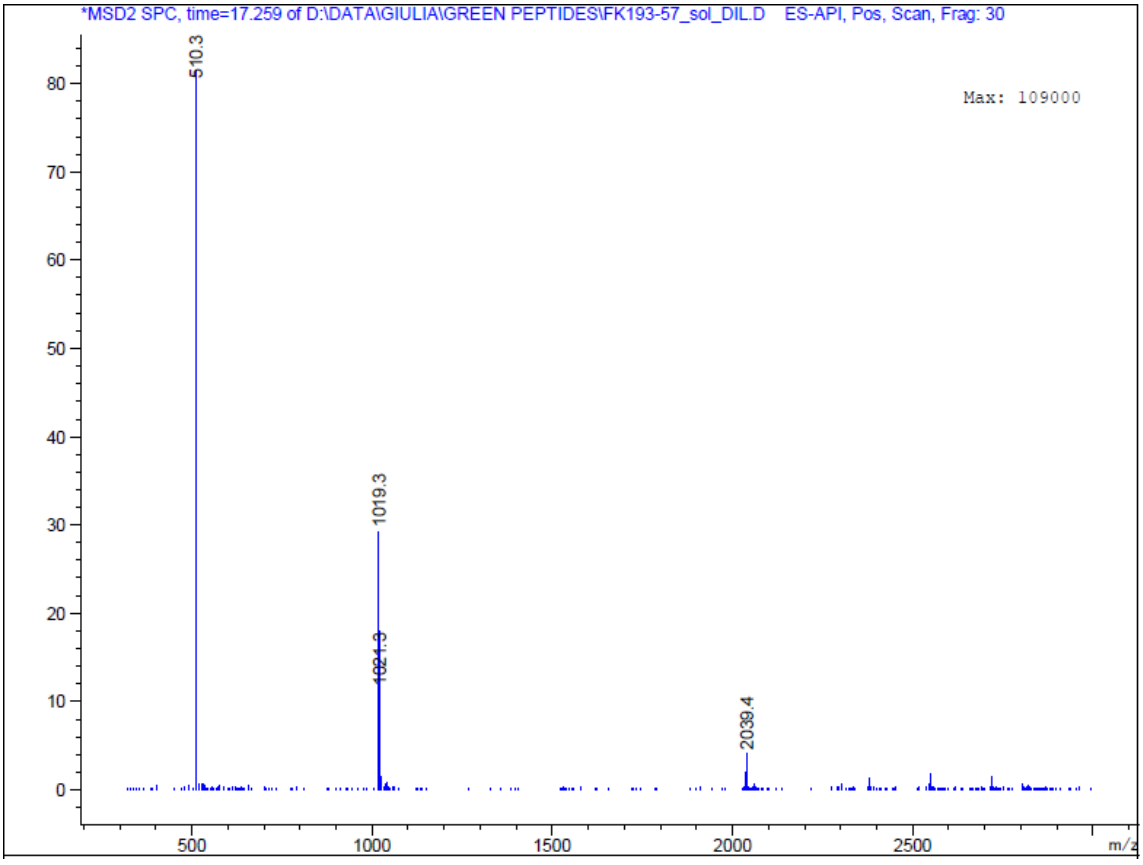


Figure S57. Mass spectrum of cyclic Octreotide



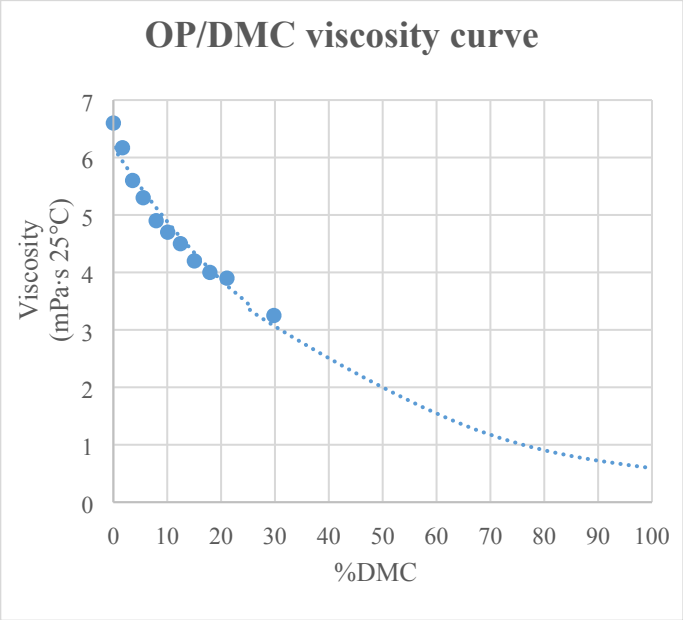
Green solvent mixtures

The viscosity was determined according to the following relation[i]:

$$\text{Viscosity} = \text{shear stress}/\text{shear rate}$$

Table S5. NOP/DMC mixtures viscosity measurements at 25°C and relative plot at different ratios

V% NOP	V% DMC	Viscosity (mPa·s 25°C)
100	0	6,6
98,3	1,7	6,2
96,4	3,6	5,6
94,5	5,5	5,3
92,1	7,9	4,9
89,9	10,1	4,7
87,6	12,4	4,5
85	15,0	4,2
82,1	17,9	4
78,9	21,1	3,9
70,2	29,8	3,3
0	100	0,59



Recycling of linear Octreotide SPPS waste stream

Five cases of linear Octreotide are compared, in order to determine the PMI of each process: i) conventional synthesis in DMF; ii) green synthesis in NOP; iii) green synthesis in NOP/DMC 80:20; iv) green synthesis in NOP with recycling of NOP (85%) and piperidine (95%); v) green synthesis in NOP/DMC 80:20 with recycling of NOP (85%), DMC (95%) and piperidine (95%).
To notice, piperidine involved in the formation of DBF-piperidine adduct was subtracted from the total recoverable piperidine volume.

SPPS of linear Octreotide was conducted applying always the same protocol, as reported in the Experimental Section (main text), apart from the employed solvent. In all five cases the total SPPS solvent consumption is considered to be the same, according to the protocol reported in the Experimental Section (main text). When the mixture NOP/DMC 80:20 was used, the ratio between the two solvents was maintained along all the synthetic steps.

The scale of the linear Octreotide SPPS was 0.22 mmol in all cases. The amount of the crude obtained was considered to be the same in all five cases (0.204 g), based on the amount of crude linear Octreotide isolated using the SPPS in NOP.

Stream of deprotection waste (including washings) and stream of coupling waste (including resin swelling and washings) were collected and distilled separately (see Experimental Section).

PMI calculation for linear Octreotide SPPS

Process Mass Intensity (PMI)[ii] is defined as the ratio between the total mass of materials and the mass of the isolated product and was calculated according to the following equation:

$$PMI = \frac{\sum mass\ of\ materials}{mass\ of\ isolated\ product}$$

Specifically, mass of materials includes:

- Starting materials: Fmoc-AA-OH, DIC, Oxyma Pure®, resin, cleavage cocktail (TFA+scavengers)
- Solvents (DMF or NOP or NOP/DMC 80:20, DCM for pre-cleavage resin washings and Et_2O for crude peptide precipitation)
- Base (piperidine)

Mass of starting materials, base, DCM and Et_2O are unvaried for all SPPS (Table S6), independently from the used solvent, while total mass of the used solvent (DMF or NOP or NOP/DMC 80:20) slightly varies according to their different densities (Table S7).

Total mass of materials employed in cases i), ii) and iv) (without recycling) is reported in Table S8.

Table S6. Overview of starting materials, base, DCM and Et_2O that are unvaried for all SPPS (independently from the used solvent) and their total mass

	MW (g/mol)	d (g/mL)	eq	mmol	Volume (mL)	Mass (g)	repetitions	Total mass (g)
Fmoc-Thr(tBu)-ol-Trt-PS resin			1	0,22		0,2	1	0,2
Coupling								
Fmoc-Cys(Trt)-OH	585,71		3	0,66		0,39	3	1,16
Fmoc-Thr(tBu)-OH	397,43		3	0,66		0,26	1	0,26
Fmoc-Lys(Boc)-OH	468,54		3	0,66		0,31	1	0,31
Fmoc-D-Trp(Boc)-OH	526,28		3	0,66		0,35	1	0,35
Fmoc-Phe-OH	387,43		3	0,66		0,26	1	0,26
Fmoc-D-Phe-OH	387,43		3	0,66		0,26	1	0,26
OxymaPure	142,11		3	0,66		0,09	8	0,75
DIC	126,2	0,815	3	0,66		0,08	8	0,67
Deprotection								
Piperidine	85,15	0,862			0,6	0,52	16	8,28
Cleavage and precipitation								
TFA	114,02	1,489			5,75	8,56	1	8,56
TIPS	158,36	0,773			0,125	0,10	1	0,10
H_2O	18,02	0,997			0,125	0,12	1	0,12
DCM	84,93	1,325			2	2,65	3	7,95
Et_2O	102,17	0,725			25	18,13	1	18,13

	Total	**47,36**

Table S7. Overview of the solvents used for SPPS with DMF, NOP and NOP/DMC 80:20 and their total mass for each SPPS

	MW (g/mol)	d (g/mL)	eq	mmol	Volume (mL)	Mass (g)	repetitions	Total mass (g)
DMF								
DMF swelling	73,09	0,944			2	1,9	1	1,89
DMF couplings	73,09	0,944			2,5	2,36	8	18,88
DMF washings after couplings	73,09	0,944			4,5	4,25	7	29,74
DMF deprotection	73,09	0,944			1,2	1,13	16	18,12
DMF washings after deprotection	73,09	0,944			4,5	4,25	8	33,98
							Total	**102,61**
NOP								
NOP swelling	197,32	0,92			2	1,80	1	1,84
NOP couplings	197,32	0,92			2,5	2,30	8	18,40
NOP washings after couplings	197,32	0,92			4,5	4,14	7	28,98
NOP deprotection	197,32	0,92			1,2	1,10	16	17,66
NOP washings after deprotection	197,32	0,92			4,5	4,14	8	33,12
							Total	**100,00**
NOP/DMC 80:20								
NOP swelling	197,32	0,92			1,6	1,5	1	1,47
NOP couplings	197,32	0,92			2	1,84	8	14,72
NOP washings after couplings	197,32	0,92			3,6	3,31	7	23,18
DMC swelling	90,08	1,07			0,4	0,43	7	3,00
DMC couplings	90,08	1,07			0,5	0,54	7	3,75
DMC washings after couplings	90,08	1,07			0,9	0,96	7	6,74
NOP deprotection	197,32	0,92			0,96	0,8832	16	14,13
NOP washings after deprotection	197,32	0,92			3,6	3,312	8	26,50
DMC deprotection	90,08	1,07			0,24	0,2568	16	4,11
DMC washings after deprotection	90,08	1,07			0,9	0,963	8	7,70
							Total	**105,30**

Table S8. Total mass of materials employed for SPPS without recycling

	SPPS solvents		
	DMF	NOP	NOP/DMC 80:20
∑ starting materials[a] (g)	13,0	13,0	13,0
∑ solvents[b] (g)	128,7	126,1	131,4
∑ base (g)	8,3	8,3	8,3
Total (g)	150,0	147,4	152,7

[a]Starting materials include Fmoc-AA-OH, DIC, Oxyma Pure®, resin, cleavage cocktail (TFA+scavengers)

[b]Solvents include DCM for pre-cleavage resin washings and Et_2O for crude peptide precipitation

When solvents (NOP or NOP/DMC 80:20) and base (piperidine) were recycled (cases iii and v), final PMI was calculated by subtracting the mass of recovery materials from the mass of used materials.

$$PMI\ (for\ SPPS\ with\ recycling) = \frac{\sum mass\ of\ materials - \sum mass\ of\ recovered\ materials}{mass\ of\ isolated\ product}$$

Table S9 depicts the amount of total recovered mass of NOP or NOP/DMC 80:20 and piperidine when the recycling approach was employed. PMI calculations for all SPPS (cases i-v) are reported in Table 9 in the main body text and in Table S10.

Table S9. Total mass of solvents (NOP or NOP/DMC 80:20) and piperidine employed for SPPS and their recovered mass

	SPPS solvent	
	NOP	NOP/DMC 80:20
∑ NOP (g)	100,0	80,0
∑ NOP recycled (g)	85,0	68,0
∑ DMC (g)	-	25,3
∑ DMC recycled (g)	-	24,0
∑ base (g)	8,28	8,3
∑ base recycled (g)	7,72	7,72
Total solvents + base recycled (g)	92,7	99,7

Table S10. PMI for linear Octreotide SPPS processes

	SPPS solvents				
	DMF	NOP	NOP+**recycling**	NOP/DMC 80:20	NOP/DMC 80:20 + **recycling**
∑ starting materials[a] (g)	13.0	13.0	13.0	13.0	13.0
∑ solvents[b] (g)	128.7	126.1	41.1	131.4	39.3
∑ base (g)	8.3	8.3	0.6	8.3	0.6
PMI[c]	735	722	268	748	256

[a]Starting materials include Fmoc-AA-OH, DIC, Oxyma Pure®, resin, cleavage cocktail (TFA + scavengers)
[b]Solvents include DCM for pre-cleavage resin washing and Et_2O for crude peptide precipitation
[c]PMI = Σm (starting materials)+Σm (solvents)+Σm (base)/m (crude linear Octreotide product)

Purities of distilled NOP, DMC (from coupling stream waste), piperidine or DMC/piperidine mixture was assessed > 95% from ^{1}H NMR (Figures S58-59). Recovered NOP, DMC and piperidine was reused as such.

Figure S58. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of NOP recovered from distillation processes

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 3.35 (t, *J* = 7.0 Hz, 2H), 3.24 (t, *J* = 7.4 Hz, 2H), 2.36 (t, *J* = 8.1 Hz, 2H), 2.04 – 1.93 (m, 2H), 1.54 – 1.43 (m, 2H), 1.18 – 1.30 (m, 10H), 0.86 (t, *J* = 6.8 Hz, 3H).

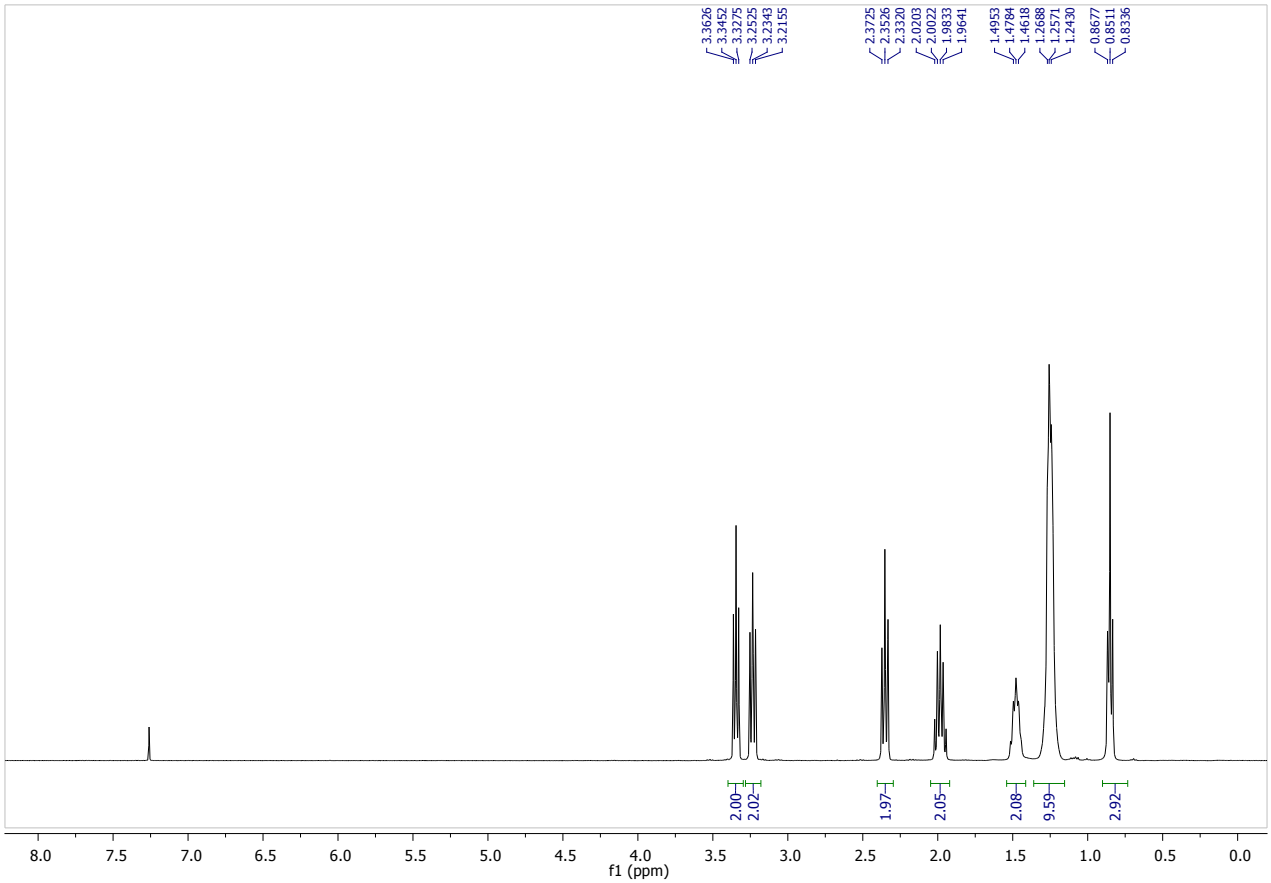
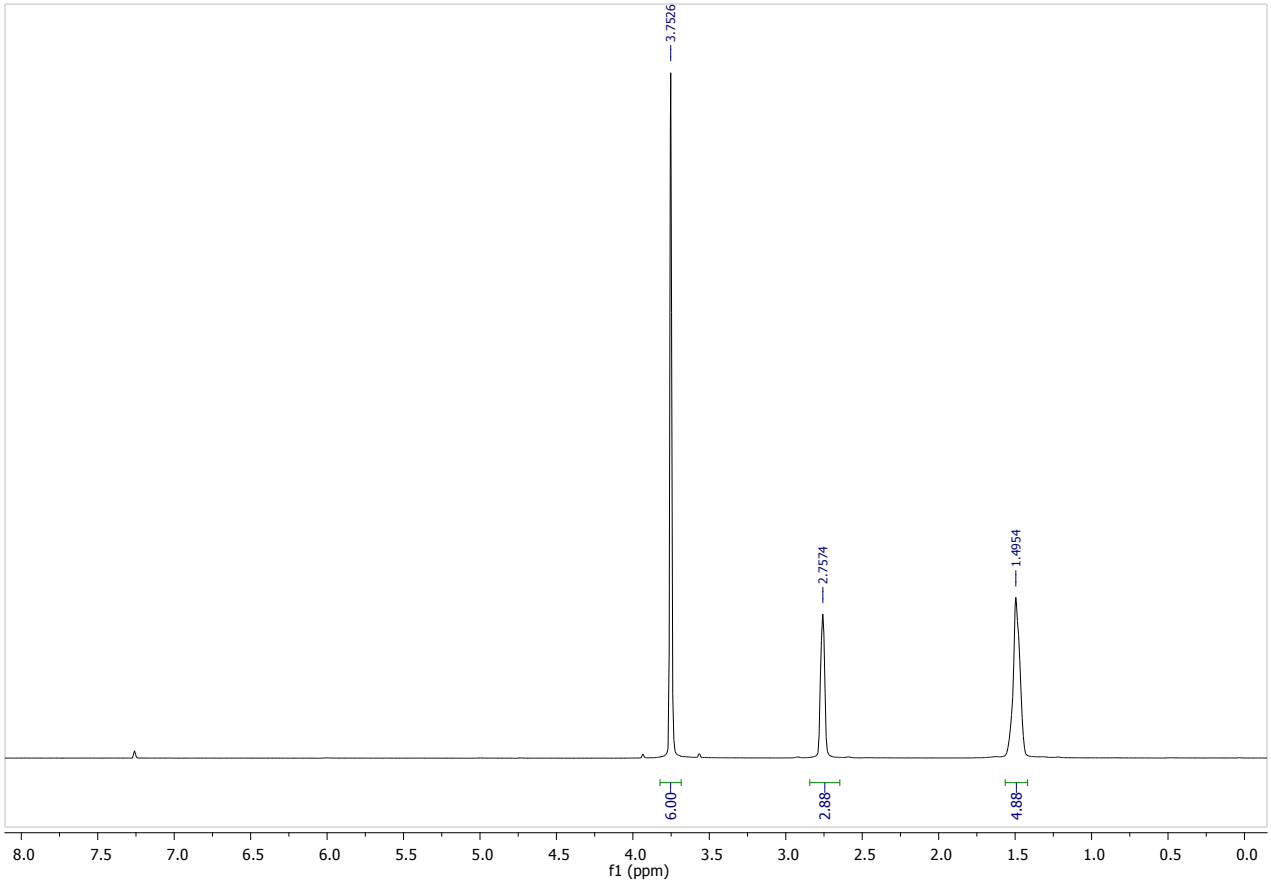


Figure S59. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of piperidine/DMC mixture recovered from distillation process of deprotection waste stream of linear Octreotide SPPS in NOP/DMC

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) DMC: 3.75 (s, 6H); piperidine: 2.76 (s, 4H), 1.50 (s, 6H). DMC and piperidine are in a 1:0.86 V/V ratio corresponding to1:0.75 mol/mol ratio.



[i] G. Schramm, A practical approach to Rheology and Rheometry 2nd Edition by Gebruder HAAKE Gmbh, 2000, p.15
[ii] E. R. Monteith, P. Mampuys, L. Summerton, J. H. Clark, B. U. W. Maes, C. R. McElroy, *Green Chem*., 2020, **22**, 123.