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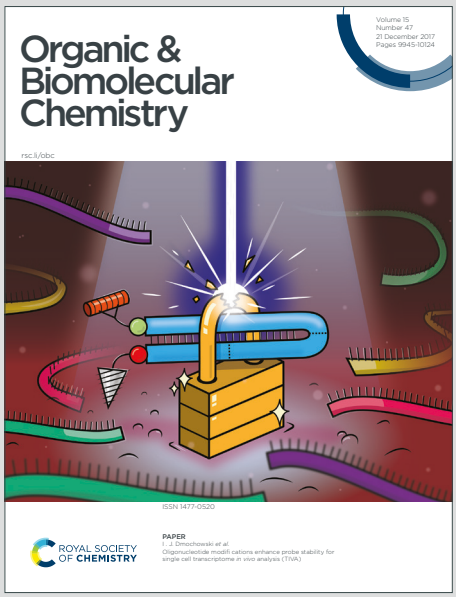

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ARTICLE

A Rink-Amide Soluble Support: High Purity Conotoxins and Other Peptides Accessed with Minimal Reagents

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The use of peptides as therapeutics has been growing due to their biocompatibility. Solid phase peptide synthesis typically used to access these peptides requires excess reagents and/or microwave irradiation to drive reactions to completion because the reaction medium is heterogeneous. Reported herein is a soluble polynorbornene support containing rink amide attached sites for synthesizing oligopeptides and conotoxins in high purity using only 1.2 to 2 equivalents of coupling reagents. The support can be isolated as a precipitate from the reaction medium by adding ether. The loading capacity of the support can be easily determined by spectroscopy and can also be tuned by varying the monomer ratio. This support is promising for accessing peptides as the methodology uses minimal reagents and by-products can be easily separated.

Introduction

the growing use of oligopeptides as therapeutics.[1, 2] Solid phase peptide synthesis (SPPS) provides quick access to a large variety of peptides.[3-5] The method is extremely attractive as it can be automated and does not require chromatographic separation after each step. The efficiency of solid phase peptide synthesis has been further enhanced using automated continuous flow techniques that provide peptides in minutes.[6-9] The only caveat in using SPPS is that typically excess coupling reagents and amino acids are used to drive the peptide coupling reactions to completion in a short span of time. A methodology that provides high purity peptides without the use of excess reagents is highly attractive for accessing peptides with minimal waste. This concept of using soluble supports for peptide synthesis is often referred to as liquid phase peptide synthesis (LPPS). LPPS using salts,[10] fluorous,[11-13] ionic liquid,[14-17] hydrophobic[18-20] as well as polymeric supports[21-25] that are soluble in the reaction medium have led to a considerable decrease in the equivalents of coupling reagents used for peptide synthesis. The growing peptide can be readily isolated from these supports *via* techniques such as cooling, precipitation or extraction. This methodology has also been used for oligosachharide[26] and oligonucleotide[27] synthesis. Among the polymeric supports, polyethylene glycol (PEG)[28-30] has been found to be highly efficient as it provides a polar medium for the growing peptide during synthesis. The PEG supports can load one or two peptides at their termini (Figure 1a). Therefore, they are used in stoichiometric amount and there is limited scope for tuning the amino-acid loading on the support analogous to SPPS. Recently, soluble polystyrene supports have been used to synthesize pentapeptides, oligonucleotides and oligosaccharides.[31] Our group has developed soluble polynorbornene[32, 33] and oligostyrene[34] supports for synthesizing penta-octapeptides in moderate yield. A competing cyclization reaction was found to lower the yields for the peptides using these supports. Therefore, the yields for octapeptides were low and larger oligopeptides were not synthesized using these supports. We report herein a polynorbornene support with a rink-amide attachment site (Figure 1b). The support is found to be superior to our earlier supports in terms of yields for larger peptides and solubility in the reaction medium after octapeptide synthesis. The support also provides access to peptides with the amide linkage at the C-terminus. Peptide synthesis could be accomplished using only 1.2 to 2 equiv of coupling reagents at room temperature.

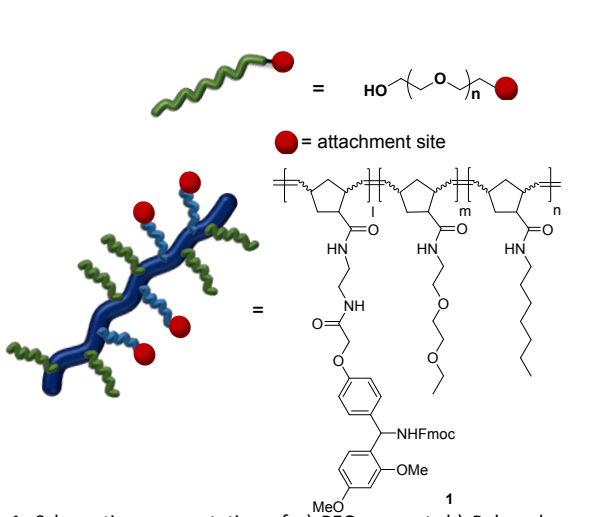

Figure 1. Schematic representation of a) PEG support; b) Polynorbornene support for peptide synthesis.

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Results and Discussion

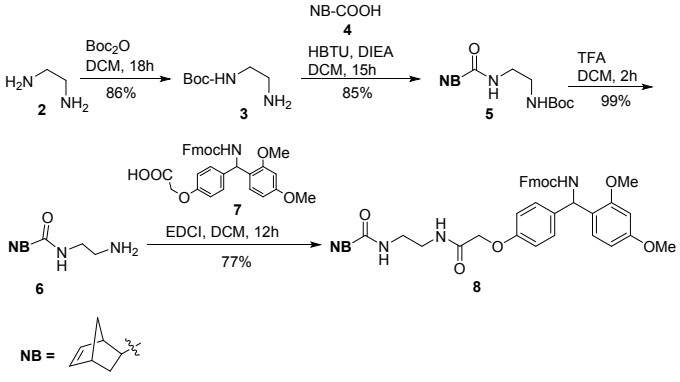
The support **1** was designed such that the rink-amide attachment site is interspersed with alkyl and oligoether chains. These groups not only act as spacers but also help enhance solubility of the growing peptide on the support. The rink amide attached monomer was synthesized from diamine **2**, which was treated with boc anhydride to give monoprotected amine **3** in 86% yield (Scheme 1).[35] Amine **3** was coupled with norbornene-*exo*-acid **4** using *O*-(benzotriazole1-yl)-1,1,3,3-tetramethyl-uroniumhexaflorophosphate (HBTU) to afford the amide **5** in 85% yield. The boc group was cleaved using TFA and the resulting amine **6** was coupled with the acid **7** using 1-ethyl- 3-(3-dimethylaminopropyl carbodiimide hydrochloride (EDCI) and catalytic 4-dimethylaminopyridine (DMAP) to give monomer **8** in 77% yields. Monomers **9** and **10** were prepared following the procedure reported earlier by our group.[32]

Monomers **8-10** were copolymerized *via* the ring-opening metathesis polymerization (ROMP) reaction in the presence of the Grubbs' third generation initiator to access the polymer support (Scheme 2a). The synthesis is highly modular as the loading capacity (mmol of attachment site/g of polymer) can be easily varied by changing the monomer ratio during polymerization. Supports **1a-d** with loading capacities of 0.3 – 0.7 mmol/g, were synthesized, in 75-92% yields. The polymer was highly soluble in solvents such as dichloromethane and DMF and insoluble in hexane, ethyl acetate and diethyl ether. Support **1a** (0.7 mmol/g) was used for attachment of a variety of neutral, acidic and basic amino acids (Scheme 2b). After the reaction, the amino acid attached support was precipitated with diethyl ether to afford loaded supports **11a-l**. The removal of unreacted amino acids during the washing step was ascertained by checking the supernatant using thin layer chromatography (Figure S34). As the support was soluble in chloroform, its loading capacity could be determined using ^{1}H NMR spectroscopy in the presence of a standard 1,1,2,2-tetrachloroethane (TCE). The NMR spectra of compounds **11a-l** also indicated absence of unreacted amino acids. However, the peaks corresponding to the base diisopropylethyl amine were observed.

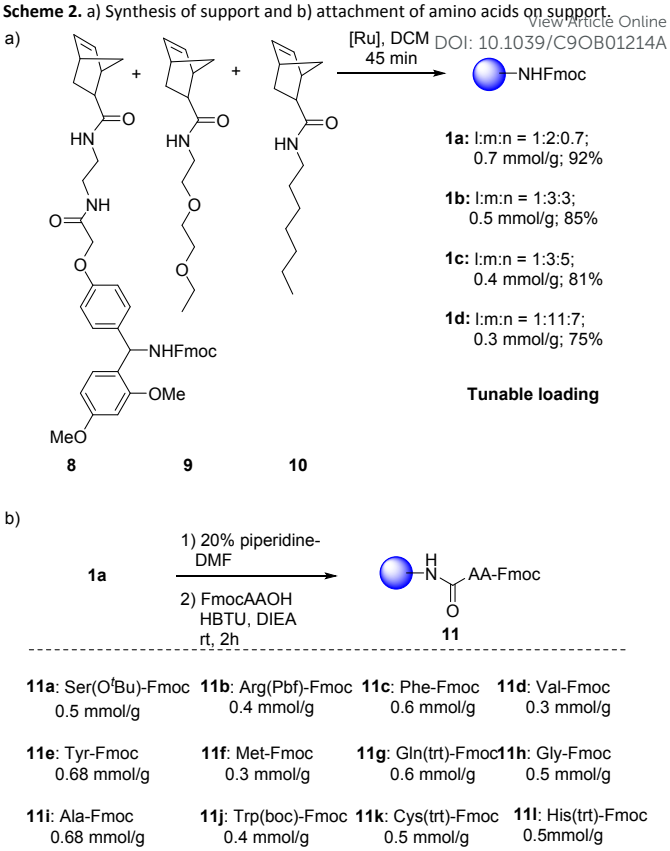
Peptides were synthesized using support **1** as shown in Scheme 3. The Fmoc group was deprotected using piperidine/DMF. Subsequently, the reaction mixture was washed using hexane, re-dissolved in dichloromethane and precipitated with diethyl ether. The precipitate was treated with the requisite amino acid, *O*-(benzotriazole1-yl)-1,1,3,3-tetramethyluroniumhexa-florophosphate (HBTU) and diisopropylethyl amine (DIEA) in dichloromethane.

A small volume (2 mL) of dichloromethane was used for the coupling reactions as the support was highly soluble in the reaction medium (Figure 2a). The coupling reactions were monitored by ninhydrin test. After completion of the reaction, separation of the peptide from the unreacted amino acids and by-products was very facile as the support was highly insoluble in diethyl ether (Figure 2b). The sequence of deprotection and coupling was repeated until the target peptide was obtained. The peptide was cleaved from the support using a mixture of TFA, TIS and water. After removal of TFA from the reaction mixture, water was added to extract peptide **12**. The peptides were purified by semi-preparative HPLC (Table S1).

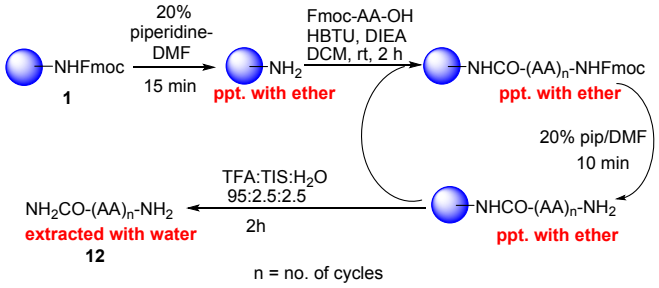
Scheme 1. Synthesis of rink-amide monomer



Scheme 2. a) Synthesis of support and b) attachment of amino acids on support.



Scheme 3. Peptide synthesis



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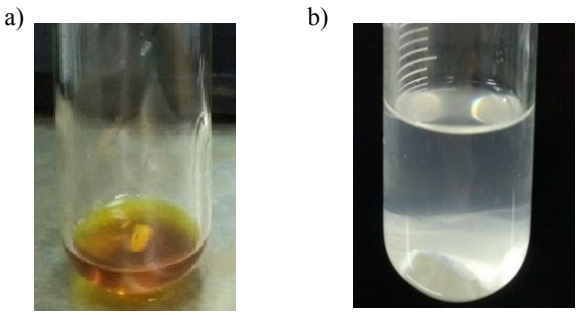

Figure 2. Support **1** a) dissolved in dichloromethane; b) precipitated with diethyl ether.

Following the protocol shown in Scheme 3, a variety of peptides were synthesized (Table 1). The smaller tripeptides **12b** and **12c** were chosen as cysteine and histidine are known to epimerize during peptide synthesis. The peptides **12d-12f** contain residues such as proline, tryptophan and histidine that are not easy to couple. Only 1.2 equivalents of amino acids and coupling reagents were used for synthesis of tri- to octapeptides **12a-12f** in 65-88% yields. The solubility of the support was found to be good during peptide synthesis. The HPLC chromatogram of the crude peptides showed the desired peptide as the major peak (Figures S35 & S36) and minor impurities. The isolated yields of the peptides after purification using reversed phase HPLC were also very high (56-70%).

The methodology was extended to synthesize conotoxins **12g-i** that have been previously synthesized on SPPS supports using automated continuous flow.[8] The synthesis of these cysteine rich peptides is non-trivial. Our support afforded the desired peptides in high yields (63-88%) using only 2 equivalents of coupling reagents and amino acids. None of the coupling steps were repeated in order to obtain the desired peptide. The HPLC chromatogram of the crude peptides (Figure 3, S37-S39) were comparable to those obtained using the automated SPPS method with excess equivalents of coupling reagents.[8] The isolated yields of the conotoxins after purification was also good (53-56%). It is notable that the synthesis could be accomplished using support **1a** that has a high loading capacity of 0.7 mmol/g. In SPPS, typically such large loading capacities are not efficient for the synthesis of larger peptides because the accessibility of reagents is reduced. Our support being highly solvated in the reaction medium shows better reactivity. The synthesis of the decapeptide **12j** is known to be challenging due to its propensity to aggregate during peptide synthesis.[8] Supports **1a**, **1b** and **1d** were used to synthesize this peptide The yield for peptide **12j** correlated with the loading capacity of the supports (entries 10-12, Figure S40). The desired peptide could be obtained in the best yield (43%) using support **1d** with a loading capacity of 0.3 mmol/g. Lastly, the synthesis of hexadecapeptide **12k** was attempted using support **1d** and only 2 equiv. of coupling reagents. As earlier, none of the coupling steps were repeated. The total synthesis time for the crude hexadecapeptide including reaction time and work-up is 40 h. Purification by HPLC afforded the desired peptide in 14% yield.

Table 1. Peptides and conotoxins synthesized using support **1**

No.	Support	Peptide **10**	AA, eq.	Yield
1	**1a**	**12a:** AFV	1.2	85 (70)[a]
2	**1a**	**12b:** GCF	1.2	72 (65)[a]
3	**1a**	**12c:** FHL	1.2	69 (64)[a]
4	**1a**	**12d:** AFIA	1.2	85 (56)[a]
5	**1a**	**12e:** AFWMHYAF	1.2	65 (57)[a]
6	**1a**	**12f:** AFAIAPGF	1.2	69 (56)[a]
7	**1a**	**12g:** GCPWQPYC	2	88 (54)[a]
8	**1a**	**12h:** TCFGCTPCC	2	65 (56)[a]
9	**1a**	**12i:** CCPPALWCC	2	63 (53)[a]
10	**1a**	**12j:** WFTTLISTIM	2	41 (29)[a]
11	**1b**	**12j:** WFTTLISTIM	2	44 (31)[a]
12	**1d**	**12j:** WFTTLISTIM	2	49 (43)[a]
13	**1d**	**12k**:GCCGAFACRFGCTPCC	2	35 (14%)

a] Isolated yield.

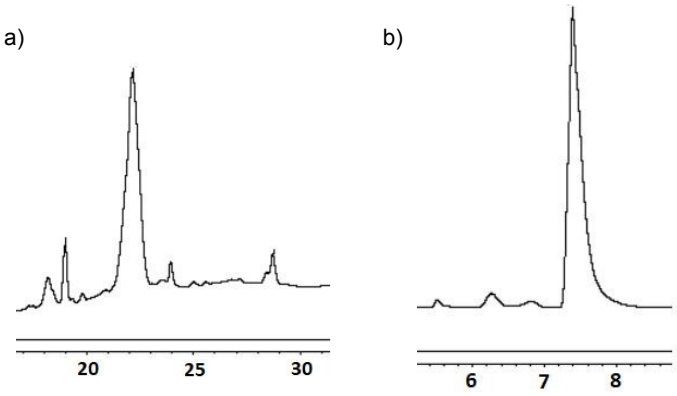

Figure 3. HPLC chromatograms of crude conotoxins a) **12g**; b) **12h**

Conclusions

A non-crosslinked polynorbornene support containing the rink-amide attachment site and oligoether/alkyl chains has been used for synthesizing peptides. Peptide coupling reactions were efficiently carried out on the support using significantly lower equivalents of coupling reagents as compared to solid phase synthesis. The solubility of the support also enabled determination of loading capacity using non-destructive techniques such as NMR spectroscopy. The support was used for synthesizing a variety of oligopeptides in good isolated yields. During peptide synthesis, the support could be easily precipitated using ether. The volumes of solvent required were

not very high. Conotoxins and difficult deca/hexadecapeptides were also synthesized in yields comparable to reported methods. Ongoing efforts are focused on automating the process to expand the scope of this methodology. Automation would not only improve the efficiency of this method, but would also make it a very attractive alternative to SPPS because it minimizes the loss of expensive coupling reagents and amino acids.

Experimental

General Methods

All reagents for synthesis were purchased from commercial suppliers and used without further purification unless stated otherwise. All air-sensitive reactions were performed using oven-dried glassware in an inert atmosphere of nitrogen. Syringe or cannula was used to transfer air-sensitive solvents and solutions. Dichloromethane and *N*,*N*-diisopropylethylamine (DIEA) were distilled over calcium hydride. All dry solvents were

stored over 4 Å molecular sieves prior to use. All monomers were synthesized in solution using HBTU and EDCI (1-Ethyl-3-(3-dimethylaminopropyl) carbodiimide as coupling reagents and *N*,*N*-diisopropylethylamine as a base. Rink amide was commercially obtained from aapptec chemicals. Analytical thin layer chromatography (TLC) was performed on Merck precoated silica gel 60 F_{254}TLC plates. Eluting solvents are reported as volume percents. Compounds were visualized using UV light and ninhydrin, iodine & $KMnO_4$ stains. Flash column chromatography was performed using silica gel (100-200 mesh). All NMR spectra were recorded using $CDCl_3$, D_2O or DMSO-d_6 as a solvent. The NMR spectra were referenced using residual solvent peaks as the standard. Chemical shifts (δ) are denoted in parts per million, coupling constants (*J*) are reported in hertz (Hz), and spin multiplicities are reported as singlet (s), doublet (d), triplet (t), quartet (q), quintet (quint), apparent quintet (app. quint.), multiplet (m). High-resolution mass spectra (HRMS) were recorded on the MICRO-Q-TOF mass spectrometer using the ESI technique. All IR spectra were recorded in the form of KBr pellet. IR spectra peaks are reported in wavenumbers (cm^{-1}) as strong (s), medium (m) and broad (br). Semi-preparative RP-HPLC was carried out on an LC-20A HPLC system using water (0.1%TFA) and acetonitrile (0.1% TFA) as the mobile phase and a prep C-18,5µm, 10 × 250 mm column as the stationary phase. Peptides were injected at a concentration of 10 mg/mL, and a flow rate of 4.5 mL/min was used for semipreparative RP-HPLC. Peptide elution was monitored at 190 - 254 nm.

***N*-tert-butoxycarbonyl-1,2-ethanediamine 3**: To a solution of ethylene diamine **2** (18 mL, 0.26 mmol, 10 equiv) in CH_2Cl_2 (50 mL) at 0 °C, was added a solution of boc anhydride (5.7 g, 0.03 mmol, 1 equiv) in CH_2Cl_2 (10 mL) over a period of 10 min. The reaction was allowed to stir at RT under nitrogen for 18 h. The reaction mixture was concentrated. A 20% aqueous solution of Na_2CO_3 (30 mL) was added to the residue and the solution was extracted with CH_2Cl_2 (3 × 20 mL). The organic layer was washed with a 20% aqueous solution of Na_2CO_3 (30 mL). The organic layer was dried over sodium sulphate, filtered and concentrated in vacuo to give the mono-boc protected amine **3** (3.59 g, 86%) as a semi solid, which was used for the next reaction without further purification. TLC R_f = 0.2, $CH_2Cl_2$with Et_3N (1%). **^{1}H NMR** (400 MHz, $CDCl_3$, 25 °C): δ = 5.09 (s, 1H; NH_{Boc}), 3.18-3.10 (m, 2H; CH_2NH), 2.77 (t, *J* = 6Hz, 2H; CH_2NH_2), 2.27 (bs, 2H; NH_2), 1.41 (s, 9H; C$H_{3(Boc)}$); **^{13}CNMR** (100 MHz $CDCl_3$,25˚C): δ = 156.4, 79.2, 43.2, 41.8, 28.5; **IR** (KBr Pellet): ν = 3362 (br), 2985 (s), 1686 (s), 1595 (m), 1533 (s), 1279 (s), 1176 (s), 986 (s) cm^{-1}; **LRMS (ESI)$^+$:** calcd for $C_7H_{16}N_2NaO_2$ (MNa^+) 183.11, found 183.12.

Monomer with boc-protected spacer 5: To a solution of norbornene-*exo*-acid **4**[32] (1.00 g, 0.007 mmol, 1 equiv) and boc-protected amine **3** (1.40 g, 0.009 mmol, 1.2 equiv) in CH_2Cl_2 (30 mL) at 0 °C, was added EDCI (2.0 g, 0.01 mmol, 1.5 equiv), DIEA (2.5 mL, 0.02 mmol, 2 equiv). The reaction mixture was allowed to warm to room temperature and stirred for 15 h. Subsequently, the reaction mixture was concentrated in vacuo. Ethyl acetate (50 mL) was added and the reaction mixture was washed with H_2O (2 × 100 mL). The organic layer was dried over anhydrous sodium sulphate, filtered and concentrated in vacuo to give the crude compound. Purification using flash column chromatography (gradient 10-40% EtOAc/Hexane) afforded amide **5** (1.5 g, 85%) as a white solid. TLC R_f = 0.3 in 40% EtOAc/Hexane. **^{1}H NMR** (400 MHz, $CDCl_3$, 25 °C): δ = 6.39 (bs, 1H; N*H*), 6.15-6.05 (2H; C*H*=C*H*), 3.38-3.22 (4H; NHCH_2), 2.95 - 2.86 (2H; CH_{nb}), 2.03 (1H; C$H_{(nb)}$), 1.88(d, *J* = 9.6Hz, 1H; CH_{2nb}), 1.66 (d, *J* = 7.6Hz, 1H; CH_{nb}), 1.43(9H; CH_{3Boc}), 1.37-1.22 (3H; CH_{2nb}& solvent); **^{13}C NMR** (100 MHz $CDCl_3$, 25 ˚C): δ = 176.2, 156.8, 138.0, 135.8, 79.5, 46.9, 46.2, 44.5, 41.4, 40.7, 40.1, 30.3, 28.2; **IR** (KBr Pellet): ν = 3340 (br), 2978 (m), 2939 (m), 1692 (s), 1649 (s), 1540 (s), 1447 (w), 1365 (m), 1279 (m), 1247 (m), 1176 (m) cm^{-1}; **HRMS (ESI)$^+$:** calcd for $C_{15}H_{24}N_2NaO_3$ (MNa^+) 303.1679, found 303.1676.

Monomer with amine spacer 6: TFA (2.5 mL, 33 mmol, 20 equiv) was slowly added over a period of 10 min using a syringe to a solution of boc-protected amine **5** (0.46 g, 1.65 mmol, 1 equiv) in CH_2Cl_2 (2.5 mL) at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 1h. The excess TFA was removed under a stream of nitrogen to give free amine **6** (0.49 g, 99%). The compound was used in the next step without further purification.

Rink amide attached monomer 8: To a solution of amine **6** (0.82 g, 2.8 mmol, 1 equiv) and rink amide **7** (1.5 g, 2.8 mmol, 1.2 equiv) in CH_2Cl_2 (25 mL) at 0 °C, was added EDCI (1.4 g, 3.4 mmol, 1.2 equiv) and DIEA (1.5 mL, 3.4mmol, 3 equiv). The reaction mixture was allowed to warm to room temperature and stirred for 12 h. Subsequently, the reaction mixture was diluted with CH_2Cl_2 (100 mL) and washed with water (2 × 20 mL). The organic layer was dried over anhydrous sodium sulphate, filtered and concentrated in vacuo to give the crude compound. Purification using flash column chromatography (5% MeOH/DCM) afforded monomer **8** (0.8 g, 67%) as a white solid.

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TLC R_f= 0.4 in 5% MeOH/CH_2Cl_2. **^{1}H NMR** (400 MHz,$CDCl_3$, 25 °C): δ = 7.76 (d, *J* = 7.2Hz, 2H; H_{ArFmoc}), 7.58 (d, *J* = 6.8Hz, 1H; H_{Fmoc}), 7.45 – 7.27 (4H; $_{ArFmoc}$), 7.24 – 7.03 (4H; $H_{ArFmoc,}$&H_{att}), 6.83 (d, *J* = 8.4Hz, 2H; $H_{Ar(att)}$), 6.51 – 6.42 (m, 2H, $H_{Ar(att)}$), 6.18 – 6.05 (3H; C*H*=C*H*, & CH_{Fmoc}), 5.81 (d, *J* = 8.8 Hz, 1H; CH_{Fmoc}), 4.49 – 4.38 (C$H_{2Fmoc,}$ & O-CH_2), 3.80 (s, 3H; O-CH_3), 3.73 (s, 3H; O-CH_3), 3.52 –2.90 (4H; CH_2NH), 2.92 – 2.85 (2H; CH_{nb}), 2.01 – 1.94 (m, 1H; CH_{nb}), 1.90 – 1.83 (m, 1H; CH_{nb}), 1.65 (d, *J* = 8Hz, 1H; CH_{2nb}), 1.35 – 1.25 (3H; CH_{2nb}), **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 175.4, 169.6, 160.7, 144.1, 141.5, 138.0, 136.0, 132.3, 129.7, 128.2, 127.8, 127.1, 125.2, 120.1, 114.5, 104.3, 99.6, 67.4, 66.8, 55.62, 55.55, 54.9, 54.9, 50.1, 47.5, 46.3, 44.9, 42.8, 40.0, 39.6, 29.9; **IR** (KBr Pellet): ν = 3327 (br), 3063 (br), 2971 (m), 1660 (s), 1648 (m), 1537 (s), 1451 (m), 1212 (m) cm^{-1}; **HRMS (ESI)$^+$:** calcd for $C_{42}H_{43}N_3NaO_7$(MNa^+) 724.2993, found 724.2992.

General Procedure for polymerization using Grubb's third generation initiator

A solution of monomers **8-10** in dichloromethane was deoxygenated using a stream of N_2 gas for 2-3 min. A deoxygenated solution of Grubb's third generation initiator in dichloromethane was added to this solution. The reaction mixture was allowed to stir at room temperature for 45 min. Ethylvinyl ether (1 mL) was added and the reaction mixture was allowed to stir for an additional 30 min. The mixture was concentrated in vacuo to 1 mL. Diethylether (10 mL) was added to precipitate the polymer support. The supernatant was decanted and the residue was dissolved in dichloromethane (3 mL). Re-precipitation with diethyl ether (8 mL) and isolation *via* centrifugation afforded polymer support **1** as a white solid.

General Procedure for determination of loading capacity and l: m: n ratio of polymers by ^{1}H NMR Spectroscopy:

The number of attachments sites in the polymer was determined by ^{1}H NMR spectroscopy in presence of a known amount of a 1,1,2,2-tetrachloroethane (TCE). Integration of the peak at δ = 5.95 ppm corresponding to TCE was compared with the peak at δ = 7.73 ppm for the Fmoc protons of the attachment site to determine the number of attachment sites in polymer **10**. The l:m:n ratio of monomers in the polymer was determined by the integration of Fmoc protons at the attachment site (δ =7.73 ppm), methyl protons of the alkyl chain (δ =0.85 ppm), and the olefinic protons (δ = 5.27 - 5.16).

Polymer 1a: A solution of Grubbs' third generation initiator (2.4 mg, 0.028 mmol, 1 equiv) in CH_2Cl_2 (4 mL) and a solution of monomer **10** (53 mg, 0.28 mmol, 100 equiv), monomer **9** (29 mg, 0.14 mmol, 50 equiv) and monomer **8** (80 mg, 0.14 mmol, 50 equiv) in CH_2Cl_2 (10 mL) were used to afford polymer **1a** (125 mg, 92%). Loading = 0.7 mmol/g. l:m:n ratio = 1:2.2:0.7. **^{1}H NMR** (400 MHz, $CDCl_3$, 25°C):δ **=** 7.74 (2H;$H_{Ar(}$Fmoc), 7.57 (1.6H; $H_{Ar(Fmoc)}$), 7.41 - 7.21 (2.3H; $H_{Ar(Fmoc)}$), 7.13 (3.1H, $H_{Ar(}$Fmoc)), 6.83 (1.9H, $H_{Ar(att)}$), 6.46 (2.1H, $H_{Ar(att)}$), 6.04 (1.6H, $H_{Ar(att)}$), 5.48 - 5.01 (8.2H; C*H*=C*H*), 4.50 -4.30 (3.3H; C$H_{2(Fmoc),}$C$H_{(Fmoc(att)}$), 4.20 (1H; H_{Fmoc}), 3.89 – 3.62 (5.1H; CH_3O), 3.60 - 2.82 (23.8H; C$H_{2deg,}$ C$H_2$$NH_{att,}$ CH_{nb}), 2.63 (2.9H; CH_{nb}), 2.40 – 1.71 (19.3H; C$H_{2alk,deg}$), 1.71 – 1.30 (7.8H; C$H_{2nb,\ alk,}$ & $_{deg}$), 1.31 – 1.02 (26.2H; C$H_{2deg,\ nb,}$ $_{alk}$ CH_{3deg} & solvent), 0.85 (7.7H; CH_{3alk}).

Polymer 1b: A solution of deoxygenated Grubbs' third generation initiator (2.4 mg, 0.028 mmol, 1 equiv) in CH_2Cl_2 (4 mL) and a solution of monomer **10** (100 mg, 0.42 mmol, 150 equiv), monomer **9** (72 mg, 0.42 mmol, 100 equiv) and monomer **8** (100 mg, 0.14 mmol, 50 equiv) in CH_2Cl_2 were used to afford polymer **1b** (200mg, 85%). Loading = 0.5mmol/g. l:m:n ratio = 1:3.1:3.2. **^{1}H NMR** (400 MHz, $CDCl_3$, 25 °C): δ **=** 7.75 (2H; $H_{Ar(}$Fmoc)),7.58 (1.6H; $H_{Ar(}$Fmoc)), 7.43 – 7.34 (2.1H; H_{Fmoc}), 7.19 – 7.09 (3.3H; $H_{Ar(Fmoc)}$ &$H_{Ar(att)}$), 6.84 (2.2H; $H_{Ar(att)}$), 6.47 (2.4H; $H_{Ar(att)}$), 5.50-5.10 (21.4H; C*H*=C*H*), 4.51 - 4.31 (3.8H; C$H_{2(Fmoc),}$OCH_{2att}), 4.29 – 4.13 (1H; CH_{Fmoc}),3.81 – 3.70 (5.6H; CH_3O), 3.61 – 2.82 (67.4H; C$H_{2deg,}$ $NH_{att,}$ C$H_{nb,}$ &$_{alk}$), 2.79 – 2.50 (7.9H; CH_{nb} &CH_{2deg}), 2.59 – 1.72 (42.6H; CH_{2alk}, & CH_{nb}), 1.70 – 1.34 (25.5H; C$H_{2alk,deg,\ nb}$, & solvent), 1.34 – 1.0 (57.5H; CH_{2nb}, CH_{3deg} & solvent), 0.87 (12.3H; CH_{3alk}).

Polymer 1c: A solution of deoxygenated Grubbs' third generation initiator (2.4 mg, 0.028 mmol, 1 equiv) in CH_2Cl_2 (4 mL) and a solution of monomer **10** (100 mg, 0.42 mmol, 150 equiv), monomer **9** (108 mg, 0.42 mmol, 150 equiv) and monomer **8** (100 mg, 0.14 mmol, 50 equiv) in CH_2Cl_2 were used to afford polymer **1c** in (230mg, 85%). Loading = 0.4 mmol/g. l: m:n ratio = 1: 3.2: 4.7. **^{1}H NMR** (400 MHz, $CDCl_3$, 25 °C): δ **=** 7.75 (2H;$H_{Ar(}$Fmoc)), 7.58 (1.8H; $H_{Ar(}$Fmoc), 7.51 – 7.42 (2.5H; $H_{Ar(}$Fmoc)), 7.32 – 7.21 (3.3H; $H_{Ar(Fmoc)}$&$H_{Ar(att)}$), 6.83 (2.2H; $H_{Ar(att)}$), $H_{Ar(att)}$), 6.51 – 6.40 (2H; $H_{Ar(att)}$), 6.09 - 6.00 (2.4H; $H_{Ar(att)}$), 5.48 - 5.05 (15H; C*H*=C*H*), 4.50 – 4.32 (3.5H; C$H_{2Ar(Fmoc)}$ & OC$H_{2(att)}$), 4.29 - 4.19 (1H; CH_{Fmoc}), 3.82 - 3.59 (5.0H; CH_3O), 3.52 - 2.82 (46.1H; C$H_{2deg,\ alk,}$&solvent), 2.79 –2.50 (6H; C$H_{nb,\ alk,}$ & CH_2NH), 2.40 – 1.71 (22.7H; CH_{2deg},& $_{alk}$), 1.60 – 1.32 (28.8H; CH_{2alk} & solvent), 1.32 – 1.0 (39.8H; C$H_{3deg,}$ C$H_{2alk,nb}$ &solvent), 0.87 (9.5H; CH_{3alk}).

Polymer 1d: A solution of deoxygenated Grubbs' third generation initiator (2.4 mg, 0.028 mmol, 1 equiv) in CH_2Cl_2 (4 mL) and a solution of monomer **10** (301 mg, 1 mmol, 450 equiv), monomer **9** (180 mg, 0.71 mmol, 250 equiv) and monomer **8** (100 mg, 0.14 mmol, 50 equiv) in CH_2Cl_2 were used to afford polymer **1d** in (230mg, 75%). Loading = 0.3 mmol/g. l:m:n ratio = 1:11.53:7.38. **^{1}H NMR** (400 MHz, $CDCl_3$, 25 °C): δ **=** 7.75 (2H;$H_{Ar(}$Fmoc)), 7.58 (1.4H; $H_{Ar(}$Fmoc)), 7.44 – 7.31 (2.8H; H_{Fmoc}), 7.2 – 7.06 (3.5 H; $H_{Ar(Fmoc)}$ &$H_{Ar(att)}$), 6.85 (2.3H; $H_{Ar(att)}$), 6.46 (2.6H; $H_{Ar(att)}$),6.46 (2.5H; H_{Ar}), 5.49 - 5.02 (36.6H; C*H*=C*H*), 4.50 -4.38 (3.4H; C$H_{2(Fmoc)}$&C$H_{(Fmoc}$), 3.82 – 3.70 (5.7H; CH_3O), 3.69 – 2.89 (109.9H; C$H_{nb,}$ C$H_{2deg,}$ C$H_2$$NH_{att}$&solvent), 2.66 (12.7H; CH_{nb}& CH_{2deg}), 2.40 – 1.79 (106.8H; C$H_{2alk,\ nb}$, & solvent), 1.70 – 1.32 (45.9H; C$H_{2deg,alk}$ & solvent), 1.31 – 1.0 (122.2H; C$H_{2nb,alk,deg}$,C$H_{3deg,}$ &solvent), 0.87 (31.0H; CH_{3alk}).

General procedure for attachment of first amino acid to polymer support: Polymer **1a** was treated with 20% piperidine in DMF (1mL) to remove the fmoc group. Subsequently, hexane (5 mL) was added to precipitate the support. The precipitate was isolated by centrifugation and dissolved in dichloromethane (1 mL). Diethylether (8 mL) was added to the solution to precipitate the support. The suspension was

centrifuged and the supernatant was decanted. The residue was dried in vacuo to afford the free amine. Fmoc-AA-OH (2 equiv), HBTU (2equiv) in CH_2Cl_2 (2-3mL) and DIEA (4 equiv) were added to the support containing free amine and the reaction was allowed to stir for 2 h at room temperature. After completion of the reaction, the solvent was concentrated in vacuo to 1 mL. Diethylether was added to precipitate the amino acid attached support. The supernatant was decanted and the precipitate was dissolved in dichloromethane (1mL). Re-precipitation with diethylether (8mL) and isolation of the precipitate by centrifugation afforded amino acid attached polymer **11a**-**11l.**

Serine attached support 11a: Polymer support **1a** (30.0 mg ,0.02 mmol, 1 equiv), Fmoc-L-ser(tbu) (16.1 mg; 0.04 mmol, 2 equiv), HBTU (15.9 mg; 0.04 mmol) and DIEA (14.6 µL, 0.08 mmol) in DCM was used. The reaction was allowed to stir at room temperature for 2h to afford compound **11a** (31.5mg, 69%). Loading = 0.49 mmol/g. **^{1}H NMR** (400 MHz, $CDCl_3$, 25°C): δ =7.74 (2H;H_{Fmoc}), 7.52 (2.5H; H_{Fmoc}), 7.37 (1.6H; H_{fmoc}), 7.14 - 7.01 (4.5 H; $H_{(Fmoc,}$&$_{att}$), 6.89 - 6.68 (4.2H; H_{Fmoc}&$_{Ar(att)}$), 6.48 – 6.30 (4.3H; $H_{Ar(att)}$), 6.23 (2.5H; $H_{Ar(att)}$), 5.49 - 5.13 (15.9H; CH=CH), 4.49 – 4.10 (7.9H; CH_{2Fmoc}, C$H_{Fmoc,}$ OC$H_{2Ar,}$ CH_{ser}&CH_{2ser}), 3.60 - 3.33(23.9H; CH_3O, CH_{nb}), 3.01 – 2.83 (10.7H; C$H_{(nb),}$C$H_{2alk,}$ $_{deg,}$ &CH_2NH), 2.71 – 2.43 (12.7H; CH_{2deg}), 2.39 – 2.20 (14.4H; C$H_{2alk,deg}$,&$_{nb}$), 2.20 – 1.50 (113.9H; C$H_{2alk,\ deg}$,&$_{nb}$), 1.50 – 1.31 (231.8H; C$H_{2alk,\ deg,\ nb}$ & CH_{3Otbu}), 1.31 - 1.21 (55.4H; C$H_{2alk,\ nb}$,& solvent), 0.86 (13.5H; C$H_{3(alk)}$).

Compound 11b: Polymer support **1a** (10 mg ,0.014 mmol, 1 equiv), Fmoc-L-Arg (Pbf) (8.8 mg; 0.013 mmol, 2 equiv), HBTU (5.1 mg; 0.013 mmol) and DIEA (4.75 µl, 0.03 mmol) in DCM was used. The reaction was allowed to stir at room temperature for 2 h to afford compound **11b** (15.4 mg, 89%). Loading = 0.46 mmol/g. **^{1}H NMR** (400 MHz, $CDCl_3$, 25 °C): δ = 7.83 – 7.63 (2.6H; $H_{Ar(Fmoc)}$), 7.62 – 7.40 (2.0H; $H_{Ar(Fmoc)}$), 7.40 – 7.29 (1.6H; $H_{Ar(Fmoc)}$), 7.19 –7.0 (2.1H; C$H_{Ar(Fmoc)}$ & C$H_{Ar(att)}$), 6.78 (2.1H; C$H_{Ar(att)}$), 6.42 – 6.20 (3.9H; $H_{Ar(att)}$), 5.44-5.12 (8.3H; CH=CH), 4.43 - 4.12 (2.3H; CH_{2Fmoc}), 4.12 – 4.10 (0.7H; CH_{Arg}), 3.72 - 3.29 (17.6H; CH_3O, C$H_{2arg,\ deg,}$ CH_{Fmoc} & CH_2NH), 3.28 – 2.81 (13.4H; CH_{2deg}, & CH_2NH), 2.70 – 2.40 (5.9H; CH_{nb}), 2.27 (3.3H; CH_{2deg}), 2.04 (2.5H; CH_{nb}), 2.0 - 1.80 (20.9H; C$H_{2alk,\ nb}$ & $_{deg}$), 1.75 – 1.50 (3.4H; CH_{2alk}), 1.49 – 1.32 (20.5H; C$H_{2arg,\ deg}$ & $_{alk}$), 1.30 – 1.12 (22.9H; C$H_{2\ nb,\ deg,\ alk,}$ C$H_{3deg,\ arg}$ & solvent), 0.85 (7.9H; C$H_{3(alk)}$).

Compound 11c: Polymer support **1a** (12.7 mg ,0.009 mmol, 1 equiv), Fmoc-L-Phe- OH (6.8 mg; 0.017 mmol, 2 equiv), HBTU (5.2 mg; 0.017 mmol) and DIEA (6.19 µl, 0.04 mmol) in DCM was used. The reaction was allowed to stir at room temperature for 2 h to afford compound **11c** (14.6 mg, 76%). Loading = 0.54 mmol/g. **^{1}H NMR** (400 MHz, $CDCl_3$, 25 °C): δ = 7.75 (2H; $H_{Ar(Fmoc)}$), 7.60 – 7.32 (4.8H; $H_{Ar(Fmoc)}$, 7.20 - 6.69 (5.0H; $H_{Ar(Fmoc),}$ &$_{Phe}$), 6.38 (2.1H; H_{Ar}), 6.23 – 6.10 (1.8H; $H_{Ar(att)}$), 5.49 - 5.0 (7.1H; CH=CH), 4.50 – 4.09 (4.6H; C$H_{(Fmoc),}$C$H_{2(Fmoc)}$ & CH_{Phe}), 3.63 – 3.32 (8.8H; C$H_{3OMe,}$ & CH_2NH), 3.29 – 2.82 (15.6H; C$H_{2deg,\ Phe}$ & solvent) 2.74 – 2.49 (3.5H; CH_{nb}), 2.49 – 2.20 (4H; CH_{2deg} & $_{nb}$), 2.14 – 1.52 (44.3H; CH_{2deg} & $_{alk}$), 1.50 – 1.32 (67.4H; C$H_{2alk,\ nb}$ & solvent), 1.31 – 1.10 (17.6H; C$H_{2\ nb,\ alk}$&CH_{3deg}), 0.85 (5.6H; C$H_{3(alk)}$).

Compound 11d: Polymer support **1a** (15 mg ,0.01 mmol, 1 equiv), Fmoc-L -Val-OH (7.1 mg; 0.02 mmol, 2 equiv), HBTU (7.97 mg; 0.02 mmol) and DIEA (7.3 µl, 0.04 mmol) in DCM was used. The reaction was allowed to stir at room temperature for 2 h to afford compound **11d** (10.6 mg, 48%). Loading = 0.34 mmol/g. **^{1}H NMR** (400 MHz, $CDCl_3$, 25 °C): δ = 7.75 (2H; $H_{Ar(Fmoc)}$), 7.61 – 7.50 (2.4H; $H_{Ar(Fmoc)}$), 7.38 (2.2H; $H_{Ar(Fmoc)}$), 7.09 (2.1H; H_{Fmoc}), 6.90 – 6.70 (2.8H; $H_{Ar(att)}$), 6.69 – 6.50 (3H; $H_{Ar(att)}$), 6.49 – 6.20 (4.4H; $H_{Ar(att)}$), 5.49 – 5.20 (11.2H; CH=CH), 4.49 –4.10 (5.5H; ArCH_{2att}, C$H_{2(Fmoc)}$ & C$H_{(Fmoc)}$), 3.62 - 3.32 (14.4H; CH_3O, CH_2NH), 3.23 - 3.11 (9.1H; solvent), 3.09 – 2.82 (6.9H; CH_{nb}, & CH_{2deg}), 2.72 - 2.50 (4.3H; CH_{2deg} & CH_2NH), 2.40 – 2.20 (5.4H; CH_{nb}, CH_{2nb}), 2.20 - 1.89 (50.5H; C$H_{2deg,\ alk}$ & CH_{val}), 1.51 -1.38 (49.2H; C$H_{2alk,}$ & solvent), 1.30 – 1.10 (23.3H; C$H_{3deg,\ val,}$ CH_{2alk} & solvent), 0.86 (9.4H; C$H_{3(alk)}$).

Compound 11e: Polymer **1a** (10.0 mg, 0.01 mmol, 1 equiv), Fmoc-L-Tyr-OH (9.6mg, 0.02 mmol, 2 equiv), HBTU (7.97 mg; 0.02 mmol) and DIEA (7.3 µl, 0.04 mmol) in DCM was used. The reaction was allowed to stir at room temperature for 2 h to afford compound **11e** (18.2 mg, 94%). Loading 0.64 mmol/g. **^{1}H NMR** (400 MHz, $CDCl_3$, 25 °C): δ = 7.73 (2H; $H_{Ar(Fmoc)}$), 7.60 – 7.42 (2.9H; $H_{Ar(Fmoc)}$), 7.37 (2.7H; H_{ArFmoc}), 7.11 – 6.69 (8.3H; $H_{Ar(att),}$ & $H_{Ar(Tyr)}$), 6.51 – 6.12 (9.9H; $H_{Ar(att)}$), 5.49 –5.02 (11.6H; CH = CH), 4.49 - 4.0 (6.3H; C$H_{2(Tyr),\ (Fmoc),}$ CH_{Fmoc}&$_{Tyr}$), 3.62 -3.48 (11.8H; CH_3O, CH_2NH, & OCH_{2Ar}), 3.10 – 2.80 (9.7H; CH_{nb} & CH_{2deg}), 2.61 (4.6H; CH_{nb}), 2.40 – 2.20 (6.2H; CH_{nb} & CH_{2deg}), 2.04 (6.0H; CH_{2alk} $_{\&\ nb}$), 1.81 - 1.62 (56.8H; C$H_{2alk\ \&\ deg}$), 1.50 – 1.30 (108.7H; C$H_{2alk,}$ $_{deg}$ & CH_{3Otbu}), 1.30 – 1.0 (31.4H; C$H_{2alk,\ nb,}$ CH_{3deg} & solvent), 0.85 (8.4H; C$H_{3(alk)}$).

Compound 11f: Polymer **1a** (12.5 mg, 0.008 mmol, 1 equiv), Fmoc-L-Met-OH (6.2 mg, 0.016 mmol, 2 equiv), HBTU (6.3 mg; 0.016 mmol) and DIEA (5.8 µl, 0.033 mmol) in DCM was used. The reaction was allowed to stir at room temperature for 2 h to afford compound **11f** (9.3 mg, 50%). Loading 0.34 mmol/g. **^{1}H NMR** (400 MHz, $CDCl_3$, 25 °C): δ = 7.73 (2H; $H_{Ar(Fmoc)}$), 7.57 (2.2H; $H_{Ar(Fmoc)}$), 7.38 (2.3H; $H_{Ar(Fmoc)}$), 7.12 (2.4H; $H_{Ar(Fmoc)}$), 6.83 (3H; $H_{Ar(att)}$), 6.44 (1.3H; $H_{Ar(att)}$), 6.25 (1.3H; $H_{Ar(att)}$), 5.49 – 5.12 (11H; CH=CH), 4.50 –4.13 (5.7H; C$H_{(Fmoc),\ Met}$ C$H_{2,\ (Fmoc)\ \&\ Met}$), 3.61 - 3.32 (15.7H; CH_3O, CH_2NH & OC$H_{2Ar,}$), 3.09 – 2.79 (7.3H; CH_2NH, CH_{2Met} & CH_{2deg}), 2.62 (4.1H; CH_{nb}, & CH_{2deg}), 2.49 – 2.20 (6.5H; C$H_{2nb\ \&\ alk}$), 2.19 –1.71 (33.4H; C$H_{2alk,\ (deg),(met)}$ & solvent), 1.68 – 1.51 (4.2H; CH_{nb}), 1.50 – 1.31 (67.8H; C$H_{2alk,\ deg,}$ & solvent) ,1.30 – 1.10 (32.4H; C$H_{3met,\ deg}$ & solvent), 0.86 (7.0H; C$H_{3(alk)}$).

Compound 11g: Polymer **1a** (14.7 mg, 0.01 mmol, 1 equiv), Fmoc-L- Gln (Trt)-OH (12.02 mg, 0.02 mmol, 2 equiv), HBTU (7.4 mg; 0.02 mmol) and DIEA (6.8 µl, 0.04 mmol) in DCM was used. The reaction was allowed to stir at room temperature for 2 h to afford compound **11g** (24.2 mg, 90%). Loading = 0.61 mmol/g. **^{1}H NMR** (400 MHz, $CDCl_3$, 25 °C): δ = 7.73 (2.0H; $H_{Ar(Fmoc)}$), 7.57 (1.8H; (2H; $H_{Ar(Fmoc)}$), 7.28 (2.3H; $H_{Ar(Fmoc)}$), 7.24 – 7.13 (3.6H; $H_{Ar(Fmoc)}$ & $H_{Ar(att)}$), 7.11 – 6.90 (0.9H; $H_{Ar(att)}$, 6.7(1.7H; $H_{Ar(att)}$), 6.5 (3.1H; $H_{Ar(Trt)}$), 6.36 (1.3H; $H_{Ar(Trt)}$), 6.19 (0.8H; $H_{Ar(Trt)}$), 5.60 – 5.0 (5.9H; CH=CH), 4.43 – 4.10 (3.2H; C$H_{(Fmoc),}$ C$H_{2(Fmoc)}$), 3.60 – 3.42 (5.7 H; C$H_{2(Gln)}$), 3.10 – 2.82 (3.2H; C$H_{2(nb)}$), 2.70 – 2.50 (1.9H;

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CH_{deg} & $CH_{(nb)}$), 2.28 (2.7H; $CH_{(nb)}$), 2.10 – 1.70 (17.8H; CH_{nb}, $CH_{2(alk,\ deg,\ \&\ Gln)}$), 1.50 – 1.02 (65.5H; $CH_{2alk,}$ $CH_{3(deg)}$ & $CH_{2(nb)}$ & solvent), 0.85 (4.7H; $CH_{3(alk)}$).

Compound 11h: Polymer **1a** (10.2 mg, 0.007 mmol, 1 equiv), Fmoc-L- Gly-OH (4.0 mg, 0.014 mmol, 2 equiv), HBTU (5.1 mg; 0.014 mmol) and DIEA (4.7 µl, 0.027 mmol) in DCM was used. The reaction was allowed to stir at room temperature for 2 h to afford compound **11h** (9.2 mg, 65%). Loading = 0.46 mmol/g. **^{1}H NMR** (400 MHz, $CDCl_3$, 25 °C): δ = 7.80 – 7.65 (2H; $H_{Ar(Fmoc)}$), 7.62– 7.53 (1.9H; $H_{Ar(Fmoc)}$), 7.41 - 7.32 (2.1H; $H_{Ar(Fmoc)}$), 7.10 (1.9H; $H_{Ar(Fmoc)}$), 6.79 (2.2H; $H_{Ar(att)}$), 6.49 - 6.20 (4H; $H_{Ar(att)}$), 5.42 - 5.12 (8.2H; C*H*=C*H*), 4.40 – 4.29 (2.5H; $CH_{(Fmoc),}$ $CH_{2,(Fmoc)}$), 4.29 - 4.10 (1.9H; OCH_{2Ar}), 3.51 - 3.49 (8.2H; CH_3O & CH_2NH), 3.09 – 2.82 (5.3H; $CH_{2deg\ \&\ Gly}$), 2.72 - 2.50 (4.1H; CH_{2deg} & CH_{nb}), 2.40 – 2.19 (4.9H; $CH_{(nb)}$, CH_{2deg}), 2.0 – 1.52 (55H; $CH_{2deg,\ alk,\ nb}$ & solvent), 1.51 – 1.30 (51.5H; $CH_{2alk,\ nb}$ & solvent), 1.25 (23H; CH_{3deg} & CH_{2nb}), 0.85 (7.2H; $CH_{3(alk)}$).

Compound 11i: Polymer **1a** (10.2 mg, 0.007 mmol, 1 equiv), Fmoc-L- Ala-OH (4.2 mg, 0.014 mmol, 2 equiv), HBTU (5.1 mg; 0.014 mmol) and DIEA (4.7 µl, 0.027 mmol) in DCM was used. The reaction was allowed to stir at room temperature for 2 h to afford compound **11i** (11.5 mg, 80%). Loading = 0.61 mmol/g. **^{1}H NMR** (400 MHz, $CDCl_3$, 25 °C): δ = 7.75 (2H; $H_{Ar(Fmoc)}$), 7.65 – 7.52 (2.5H; $H_{Ar(Fmoc)}$), 7.43 - 7.34 (2.3H; $H_{Ar(Fmoc)}$), 7.19 - 7.02 (2.9H; $H_{Ar(Fmoc)}$ & $H_{Ar(att)}$), 6.91 – 6.70 (3.5H; $H_{Ar(att)}$), 6.49 - 6.10(8.9H; CH_{att}, & solvent), 5.49 - 5.03 (11.8H; C*H*=C*H*), 4.50 - 4.09 (7.4H; $CH_{(Ala,\ Fmoc,}$ CH_{2Fmoc} & $OCH_{2Ar(att)}$), 3.62 - 3.42 (11.7; CH_3O & CH_2NH), 2.99 (6.4H; $CH_{2(deg)}$ & $CH_{2(nb)}$), 2.74 – 2.71(5H; CH_{2deg} & CH_{nb}), 2.41 – 1.80 (14.1H; $CH_{2alk,\ deg,}$ &$_{nb}$), 1.70 – 1.52 (41.9H;$CH_{2alk,deg}$ & solvent), 1.51 –1.30 (77.7H; $CH_{2alk,deg,}$ & solvent), 1.30 – 1.12 (22.9H; $CH_{3deg,\ Ala}$ & solvent), 0.86 (7.8H; $CH_{3(alk)}$).

Compound 11j: Polymer **1a** (10.2mg, 0.007 mmol, 1 equiv), Fmoc-L- Trp-(Boc)-OH (7.1 mg, 0.014 mmol, 2 equiv), HBTU (5.1 mg; 0.014 mmol) and DIEA (4.7 µL, 0.027 mmol) in DCM was used. The reaction was allowed to stir at room temperature for 2 h to afford compound **11j** (9.9 mg, 90%). Loading = 0.39 mmol/g. **^{1}H NMR** (400 MHz, $CDCl_3$, 25 °C): δ = 7.73 (2H; $H_{Ar(Fmoc)}$), 7.60 – 7.30 (5.1H; $H_{Ar(Fmoc)}$), 7.09 - 6.80 (2.5H; $H_{Ar(att)}$), 6.80 – 6.62 (2H; H_{ArTrp}), 6.49 – 6.20 (4.4H; $H_{ArTrp\ \&\ att}$), 6.20 – 6.09 (1.5H; H_{ArTrp}), 5.49 – 5.09 (6.8H; C*H*=C*H*), 4.73 - 4.50 (2.1H; $CH_{Fmoc\ \&\ Trp}$), 4.49 – 4.21 (2.7H; CH_{2Fmoc}), 3.60 – 3.32 (9.3H; CH_3O, $OCH_{2Ar,}$ & CH_2NH), 3.09 – 2.79 (4.9H; CH_{2Trp} & CH_{nb}), 2.70 – 2.50 (2.8H; CH_{nb}), 2.39 – 2.19 (3.2H; CH_{2deg}), 2.18 – 1.80 (4.8H; CH_{2deg} &$_{alk}$), 1.75 – 1.52 (45.3H; $CH_{2alk,\ nb}$ & solvent), 1.51 – 1.33 (38.1H; $CH_{2alk,}$ CH_{3Boc} & CH_{nb}), 1.30 – 1.1 (17.4H; CH_{3deg}, CH_{2nb} & solvent), 0.85 (6.2H; $CH_{3(alk)}$).

Compound 11k: Polymer **1a** (10.2 mg, 0.007 mmol, 1 equiv), Fmoc-L-Cys-(Trt)-OH (7.1 mg, 0.014 mmol, 2 equiv), HBTU (5.1 mg; 0.014 mmol) and DIEA (4.7µl, 0.027 mmol) in DCM was used. The reaction was allowed to stir at room temperature for 2h to afford compound **11k** (12.6 mg, 73%). Loading = 0.49 mmol/g. **^{1}H NMR** (400 MHz, $CDCl_3$, 25 °C): δ = 7.73 (2H; H_{ArFmoc}), 7.60–7.42 (1.7H; $H_{Ar(Fmoc)}$),7.40 - 7.30 (5.5H; $H_{Ar(Fmoc)}$ & $_{att}$), 7.21 – 7.10 (6.7H; $H_{ArTrt,\ \&\ att}$), 7.09 – 6.92 (2.3H; H_{ArTrt}), 6.50 – 6.30 (6.8H; H_{ArTrt}), 6.20 – 6.08 (1.7H; H_{ArTrt}), 5.43 – 5.03 (11.6H; C*H*=C*H*), 4.41- 4.05 (4H; $CH_{cys,\ Fmoc}$ & CH_{2Fmoc}), 3.80 – 3.65 (12H; $CH_{2cys,}$ CH_3O, & OCH_{2Ar}), 3.64 – 3.83 (43.7H; CH_2NH, CH_{2nb}&$_{deg}$), 2.61 (5.8H; CH_{nb}), 2.42 – 2.21 (5.8H; $CH_{2deg,\ \&\ alk}$), 2.12 – 1.72 (24.4H; $CH_{nb,}$ & $CH_{2deg,\ alk}$), 1.52 – 1.31 (82.4H; $CH_{2alk,\ nb}$ & solvent), 1.30 – 1.05 (32.6H; CH_{3deg}, CH_{2nb} & solvent), 0.85 (8.5H; $CH_{3(alk)}$).

Compound 11l: Polymer support **1a** (15 mg ,0.01 mmol, 1 equiv), Fmoc-L-His (Trt) (13.01 mg; 0.02 mmol, 2 equiv), HBTU (7.97 mg; 0.02 mmol) and DIEA (7.3 µl, 0.042 mmol) in DCM was used. The reaction was allowed to stir at room temperature for 2 h to afford compound **11l** (21 mg, 75%). Loading = 0.46 mmol/g. **^{1}H NMR** (400 MHz, $CDCl_3$, 25 °C)**:**7.73 (2H;$H_{Ar(Fmoc)}$), 7.51 (2.6H; $H_{Ar(Fmoc)}$), 7.41 – 7.30 (3.8H; $H_{Ar(Fmoc)}$), 7.12 – 6.93 (4H; $H_{Ar(att)}$), 6.83 –6.18 (10.9; $H_{Ar(att)\ \&\ Trt}$), 5.44 - 5.0 (9H; C*H*=C*H*), 4.52 - 4.49 (1.8H; $CH_{His,}$ &$_{Fmoc}$), 4.42 – 4.01 (4.3H; $CH_{2Fmoc\ \&\ His}$), 3.62 – 3.39 (11.1H; CH_{2deg}, OCH_{2Ar}, & CH_3O), 3.10 – 2.81 (6.9H; CH_{2nb}, & CH_2NH), 2.75 – 2.50 (4H; CH_{nb}, & CH_{2deg}), 2.42 – 2.10 (8.3H; C*H*nb, & CH_{2deg}), 2.0 – 1.59 (51.5H; $CH_{2nb,\ alk,}$ & solvent), 1.50 – 1.33 (66.3H; $CH_{2alk,\ nb}$ & solvent), 1.30 – 1.05 (CH_{3deg}, CH_{2alk} & solvent), 0.85 (6.0H; CH_{3alk}).

General procedure for peptide synthesis: The procedure for attachment of the first amino acid was followed. The process of deprotection and coupling was repeated until the desired peptide sequence was obtained. At the end of synthesis, the peptide was cleaved from the support using a mixture of 95:2.5:2.5 (TFA: TIS: H_2O). The reaction was allowed to stir at room temperature for 2h. After removal of TFA, water was added and the solution was lyophilized to afford the crude peptide. Purification by semi-preparative HPLC afforded the desired peptide.

Characterization of peptides synthesized on support 1

Tripeptide AFV 12a: ^{1}H NMR (500 MHz, D_2O, 25 °C): δ = 7.37 - 7 24 (m, 5H; H_{Ar}), 4.62 (app t, *J* = 8.0 Hz, 1H; CH_{Phe}), 4.16 (q, *J* = 7Hz, 1H; CH_{Ala}), 3.75 (d, *J* = 5.5Hz, 1H; CH_{Val}), 3.16 - 3.03 (17H; $CH_{2(Phe)}$ & solvent), 2.20 - 2.10 (m, 1H; CH_{Val}), 1.25 (d, *J* = 7.0, Hz, 3H; CH_{3Ala}), 0.98 – 0.93 (6H; $2CH_{3Val}$); **^{13}C NMR** (125MHz, D_2O, 25 °C): 176.8, 172.1, 169.0, 135.8, 129.2, 128.9, 127.4, 58.2, 55.1, 49.2, 44.5, 36.8, 22.2, 21.4, 17.5, 16.7, 16.6; **IR** (KBr Pellet): ν = 3854 (br), 3732 (br), 3293 (br), 2925 (m), 2857 (w), 2589 (w), 1669 (s), 1645 (s), 1202 (w), 1134, (w), 1031 (m), 837 (w) cm^{-1}; **HRMS (ESI$^+$):** calcd. for $C_{17}H_{26}N_4NaO_3$ (MH^+) 357.1897, found 357.1895.

Tripeptide GCF 12b: ^{1}H NMR (500 MHz, D_2O, 25 °C): δ = 7.41 - 7.26 (m, 5.0H; H_{Ar}), 4.64 (dd, *J* = 9Hz, 6.5Hz, 1H; CH_{Cys}), 4.49 (app t, *J* = 6.5Hz, 1H; CH_{Phe}), 3.84 (d, *J* = 4.5 Hz, 2H; CH_{2Gly}), 3.14 (appt, *J* = 9Hz,2H; CHH_{Cys}), 3.05- 2.89 (2H; CHH_{Phe}); **^{13}C NMR** (125 MHz, D_2O, 25 °C): 171.2, 163.1, 162.9, 136.5, 129.4, 129.3, 128.8, 128.7, 127.2, 54.7, 44.6, 44.5, 40.4, 37.1, 22.3, 22.2, 21.5, 21.4; **IR** (KBr Pellet): ν = 3773 (br), 3394 (br), 2513 (s), 1645 (s), 1448 (m), 1305 (w), 1258 (w), 1202 (m), 1148 (m), 810 (w); **HRMS**

(ESI⁺): calcd. for $C_{14}H_{20}N_4NaO_3S$ (MH^+) 347.1148, found 347.1147.

Tripeptide FHL 12c: ^{1}H NMR (500 MHz, D_2O, 25 °C): δ = 8.60 (1.0H; H_{His}), 7.40 - 7.34 (3.0H; $H_{Phe\ \&\ His}$), 7.26 - 7.24, (3.0H; $H_{Phe\ \&\ His}$), 4.64(app. *t*, *J* = 7Hz, 1.0H; C$H_{(His)}$), 4.28-4.22 (2H; C$H_{(Phe)}$ & C$H_{(Leu)}$),. 3.23- 3.15 (6H; 2CHH$_{His}$, 2CHHH$_{Phe,}$ & solvent), 1.80 - 1.73 (m, 2H; 2CHHH$_{(Leu)}$), 1.60- 1.57 (m, 1H; C$H_{(Leu)}$),0.95 (d, *J* = 6Hz, 3H; C$H_{3(Leu)}$); 0.92 (d, *J* = 6Hz, 3H; C$H_{3(Leu)}$); **^{13}CNMR** (125Hz, 25 °C): 176.8, 170.2, 168.7, 133.6, 133.5, 129.2, 129.1, 128.0, 127.7, 117.4, 54.1, 52.3, 52.1, 44.5, 39.8, 36.8, 26.7, 22.2, 22.0, 21.4, 20.9; **IR** (KBr Pellet): ν = 3840 (br), 3732 (br), 3447 (br), 2955 (m), 2864 (w), 2530 (w), 1679 (s), 1601 (w), 1578 (w), 1236, (w) 1202 (s), 1135 (m), 1028 (w) cm^{-1}; **HRMS (ESI⁺):** calcd. for $C_{21}H_{31}N_6O_3$ (MH^+) 415.2452, found 415.2458.

Tetrapeptide AFIA 12d: ^{1}H NMR (500 MHz, D_2O, 25 °C): δ = 7.39- 7.26 (m, 5H; H_{Ar}), 4.63 (app. t, *J* = 7.5Hz, 1H; CH_{Phe}), 4.22 (q, *J* = 7.5Hz, 1.0 H; CH_{Ala}), 4.16 (d, *J* = 8.0 Hz, 1H; CH_{Ile}), 4.07 (q, *J* = 7.0 Hz, 1H; CH_{Ala}), 3.13 -3.00 (3H; 2CHH$_{Phe}$ & CHH $_{Ile(a)}$), 1.82-1.73 (m, 1H; CHH$_{Ile(b)}$), 1.44 (d, *J* = 7.0 Hz, 3H; C$H_{3(Ala)}$), 1.36 – 1.29 (5H; C$H_{3(Ala)}$ & solvent), 1.19- 1.09 (m, 1H; C$H_{Ile(b)}$), 0.89 - 0.79 (6H; 2C$H_{3(Ile)}$); **^{13}C NMR** (125 MHz, D_2O, 25 °C): 177.0, 172.9, 172.3, 170.6, 168.7, 136.1, 129.2, 128.8, 127.3, 58.3, 54.8, 49.2, 48.8, 37.0, 36.2, 24.5, 16.7, 14.6, 10.0; **IR** (KBr pellet): ν = 3854 (br), 3747 (br), 3421 (br), 3282 (br), 2964 (w), 2925 (w), 1678 (s), 1543 (m), 1440 (s), 1262 (w), 1206 (w), 1134 (s), 803 (w) cm^{-1}; **HRMS (ESI⁺):** calcd. for $C_{21}H_{34}N_5O_4$ (MH^+) 420.2605, found 420.2604.

Octapeptide AFWMHYAF 12e: ^{1}H NMR (500 MHz, D_2O, 25 °C): δ = 7.60 (d, *J* = 9.5Hz, 2H; CH_{His}), 7.41 (d, *J* = 10Hz, 2H; H_{ArTyr}),7.36- 7.11 (18H; H_{Ar}), 4.56 – 4.51 (2H; CH_{Trp}& $_{His}$), 4.47 – 4.42 (2H; C$H_{(Tyr\ \&Met)}$), 4.36 – 4.30(2H; CH_{Ala}), 4.16 – 4.12 (2H; CH_{Phe}), 4.02 (dd, *J* = 3.23 -3.16 (4H; CHH$_{Phe}$ & CH_aC$H_{b(Phe)}$), 3.30 - 2.8 (10H; CH_{2Met}, CH_aC$H_{b(Phe),\ Trp,\ His,\ Tyr\ \&\ Met)}$), 1.35 - 1.99 (9H; 2C$H_{3(Ala),}$ C$H_{3(Met)}$); **^{13}C NMR** (125 MHz, D_2O, 25 °C): 177.2, 173.4, 172.7, 171.7, 168.6, 165.0, 163.2, 162.3, 136.1, 135.9, 133.5, 129.3, 129.3, 129.0, 128.7, 127.9, 127.2, 126.9, 124.5, 122.0, 119.4, 118.1, 117.8, 114.9,111.9, 108.5, 54.6, 54.4, 54.0, 49.3, 44.5, 37.1, 37.0, 36.7, 31.4, 30.2, 27.0, 22.2, 21.5, 16.6; **IR** (KBr pellet): ν = 3903, (br), 3772, (br), 3455, (br) 3281, (br), 2918, (s), 2513 (w), 2308 (m), 1668 (s), 1440 (w), 1202 (w), 1137 (w), 1042 (m), 801 (w), 700 (w) cm^{-1}; **HRMS (ESI⁺):** calcd. For $C_{55}H_{67}N_{12}O_9S$ (MH^+) 1071.4869, found 1071.4866.

Octapeptide AFAIAPGF 12f: (500 MHz, D_2O, 25 °C): δ = 7.45 - 7.25 (10H; H_{Ar}), 4.69 – 4.65 (m, 1H; CH_{Phe}), 4.63 - 4.59 (m, 1H;CH_{Phe}), 4.37 – 4.31 (m, 1H; CH_{Pro}), 4.34 (q, *J* = 7.0 Hz, 1H; CH_{Ala}), 4.10 (d, *J* = 8Hz, 1H CH_{Ile}), 4.13 – 4.10 (2H; C$H_{2(Gly)}$), 4.07 – 4.0 (m, 1H; CH_{ala}), 3.95 - 3.90 (m, 1H; CH_{ala}), 3.88 - 3.79 (2H; C$H_{2(Pro)}$), 3.78 - 3.65 (4H; C$H_{2Pro\ \&\ impurity}$), 3.24 - 3.12 (m, 2H; CH_{2Phe}), 3.11 – 3.0 (2H; CH_{2Phe}), 2.32 -2.26 (m, 1H; CHaH$_{b(Pro)}$), 2.10 - 1.98 (2H; C$H_{2(Ile)}$), 1.95 – 1.86 (m, 1H; CHa$H_{b(Pro)}$), 1.87 – 1.78 (m, 1H; CHa$H_{b(Pro)}$), 1.37 (d, *J* = 7Hz, 3H; C$H_{3(ala)}$), 1.34 (d, *J* = 7Hz, 3H; C$H_{3(Ala)}$), 1.25 - 1.17 (m, 1H; CH_{Ile}), 0.98 - 0.84 (6H; C$H_{3(Ile)}$); **IR** (KBr pellet): ν = 3905 (br), 3783 (br), 3269 (br), 2922 (m), 2311 (m), 1664 (s), 1425 (s), 1259 (w), 1202 (s), 1137 (w), 1020 (m), 704 (w) cm^{-1}; **HRMS (ESI⁺):** calcd. for $C_{40}H_{58}N_9O_8$ (MH^+) 793.4403, found 793.4405.

Octapeptide GCPWQPYC 12g: HRMS (ESI⁺): calcd. for $C_{43}H_{48}N_{11}O_{10}S_2$ for (MH^+) 952.3804 found 952.3808.

Nonapeptide TCFGCTPCC 12h: HRMS (ESI⁺): calcd. for $C_{36}H_{57}N_{10}O_{11}S_4$ for (MH^+) 933.2978 found 933.2971.

Nonapeptide CCPPALWCC 12i: HRMS (ESI⁺): calcd. for $C_{42}H_{64}N_{11}O_9S_4$ for (MH^+) 994.3629 found 994.3627.

Decapeptide WFTTLISTIM 12j: **HRMS (ESI⁺):** calcd. for $C_{58}H_{91}N_{12}O_{14}S$ for (MH^+) 1211.6493 found 1211.6494.

Hexadecapeptide GCCGAFACRFGCTPCC 12k: LRMS (ESI⁺) was found to be 1597.4806

Conflicts of interest

There are no conflicts to declare.

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