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Improving resins for solid phase synthesis: incorporation of 1-[2-(2-methoxyethoxy)ethoxy]-4-vinyl-benzene

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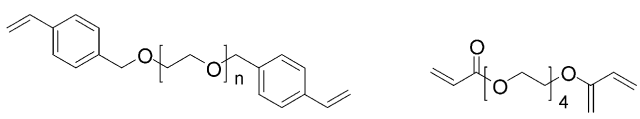
Abstract—The preparation, characterisation and application of a series of non-grafted polystyrene (PS) resins containing a styrenic methoxypoly(ethylene glycol) (MPEG) derivative is presented. These novel PS-MPEG resins were designed to balance swelling and solvation with improved handling. The monomer, 1-[2-(2-methoxyethoxy)ethoxy]-4-vinyl-benzene, contained an inert phenyl ether linkage designed to provide broad chemical compatibility and stability, yet imparting all the favourable properties of the PEG group into the new resin, whilst maintaining a high loading capacity. The synthetic performance of the new resins compared very favourably to those of TentaGel™, ArgoGel™ and aminomethyl PS.

1. Introduction

Since Merrifield's pioneering work[1] on peptide synthesis, considerable efforts have been directed towards the development of new supports for solid phase synthesis with differing compositions and properties, ranging from novel beads to new methods of bead encapsulation and handling.[2–4]

Polystyrene (PS)-based resins are currently the most widely used supports in solid phase synthesis.[5,6] However, such resins suffer from an incompatibility with polar solvents which induces restricted swelling and as a consequence permits only limited accessibility of reagents into the beads.[7] One method of manipulating the hydrophobic nature of PS is to graft a hydrophilic poly(ethylene glycol) (PEG) moiety onto the polymer backbone, and hence generate a highly solvatable environment.[8] TentaGel™ is a well-known example of this type of material, in which a PS resin has been derivatised with ethylene oxide to give a long PEG chain grafted to the PS resin, such that approximately 75% of the resin by mass is PEG.[9] The resin's compatibility with polar solvents and the high quality ^{1}H and ^{13}C NMR spectra that can be obtained on these bead types are important advantages. However, one significant drawback of this resin type is the inherently low resin substitution due to the mass of the PEG attached to the beads reducing the substitution of the initial resin loading significantly, while the degree of swelling is also often too large to be useful for solid phase organic synthesis. There are also potential problems with the long PEG chain complexing Lewis acids as well as problems of PEG leakage following cleavage and the not inconsiderable cost of the grafted PS-PEG supports. An alternative approach to post polymerisation grafting is inclusion of vinyl-functionalised PEG or tetrahydrofuran[10] monomers in the copolymer formulation. One important class are the gel-type polystyrenes which have been lightly cross-linked by PEG derivatives (Fig. 1) introduced by Itsuno,[11] Pillai,[12] Meldal[13,14] and Kurth,[15] amongst others allowing tailoring of resin swelling. The advantage of co-polymerisation of PEG derivatives in suspension polymerisation is that it should afford highly predictable



n=1, 2, 4, 6, 8.7, and 34

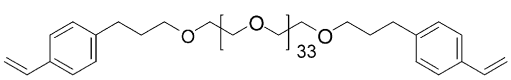


Figure 1. Several PEG derivative cross-linkers.

Keywords: styrenic methoxypoly(ethylene glycol) (MPEG); monomer; resins; solid supports; solid phase synthesis.
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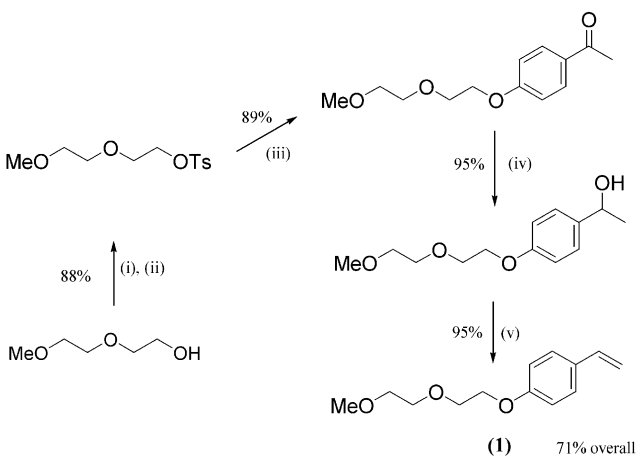
and reproducible loadings as long as issues such as relative reaction coefficients and water partitioning are taken into account. The physical properties of the resulting resin network are influenced by the nature of the cross-link junction, the PEG length and the percentage of the incorporated monomer.[16,17] These resins swell, for example, dramatically in non polar solvents since they are still predominantly hydrophobic in nature, although the cross-linker is highly polar. A major problem faced with many supports is their excessive swelling which complicates resin handling and synthesis due to the large volumes of solvent needed for washing and the large volumes of reagents needed to promote efficient synthesis. Another drawback with these resins is that they often contain chemically labile benzylic ether linkages.

Here we now report on the preparation, characterisation and application of a series of new, non-grafted PS-MPEG resins, containing the styrene MPEG derivative (**1**) (Scheme 1) in which solvent compatibility and improved reaction kinetics were engineered into the supports without the need for excessive solvent swelling character.



Scheme 1. (i) TsCl (1.5 equiv.), NEt_3 (1.5 equiv.), DMAP (cat.), DCM, 0°C to ambient temperature, 24 h; (ii) Amberlite IRA 96 (Scavenging) (3 equiv.), ambient temperature, overnight; (iii) *p*-hydroxy-acetophenone (1.2 equiv.), K_2CO_3 (1.2 equiv.), CH_3CN, reflux, 24 h; (iv) $NaBH_4$ (1 equiv.), THF/EtOH 1:1, ambient temperature, 3 h; (v) Pyridinium tosylate (cat.), toluene, reflux, overnight.

2. Results and discussion

2.1. Preparation of the monomer (1)

Monomer (**1**), 1-[2-(2-methoxyethoxy)ethoxy]-4-vinylbenzene, was prepared on a large-scale (up to 500 g), as shown in Scheme 1, following a procedure for the preparation of α,ω-bis(*p*-vinylphenyl)oligo(oxyethylenes) described by Inokuma.[18] Monomer (**1**) was obtained by the sequence of tosylation of diethylene glycol monomethyl ether, Williamson ether formation, reduction and dehydration in an overall yield of 71%. A scavenging resin was used for the purification on a large scale. This monomer contained a stable phenyl ether linkage designed to provide broad chemical compatibility.

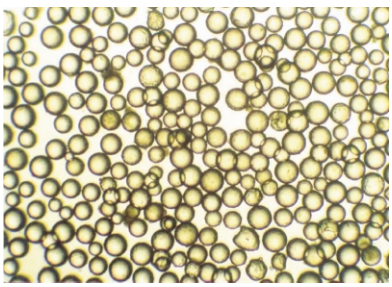


Figure 2. PS-MPEG Resin beads (125–250 μm) with 7% monomer (**1**) and 2% DVB in DMF.

2.2. Preparation of the PS-MPEG resin beads

The resins were obtained by suspension copolymerisation[19–21] using a multi-parallel polymerisation reactor designed in our laboratories,[22] and gave good quality beaded materials as shown in Figure 2. Various mole fractions (from 5 to 43%) of the monomer (**1**) were incorporated into the resin beads along with styrene, 4-vinyl benzylchloride (to give a loading of 1 mmol/g) and divinylbenzene (tech. grade, 80%) (from 2 to 8%), and a selection of the resins made is given in Table 1.

2.3. Resin properties

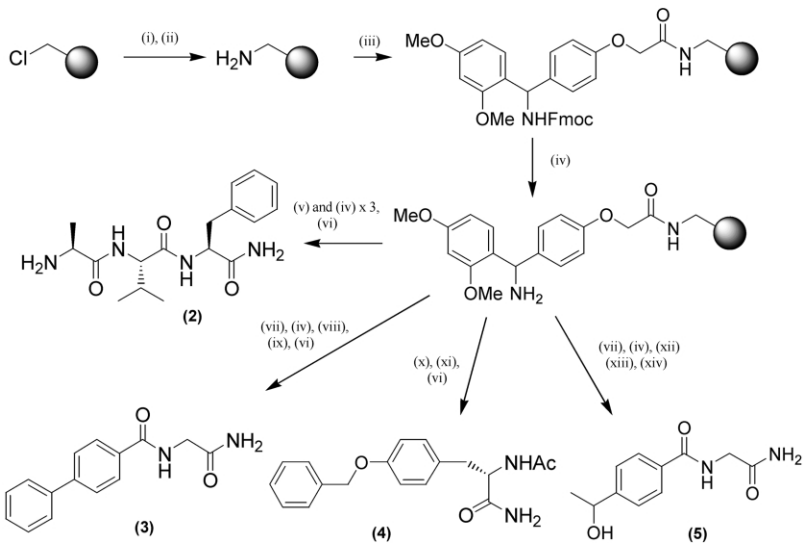
Swelling studies and reactions on the resins were performed and compared with three commonly used supports of the same bead size (125–250 μm): 2% cross-linked aminomethyl polystyrene (made in-house, 1 mmol/g), TentaGel™ (0.25 mmol/g) and ArgoGel™ (0.35 mmol/g) resins. The swelling profiles of the resins are given in Table 2. Resin swelling was found to be broadly dependent on the percentage of the PEG monomer (**1**) incorporated with a 7% level of incorporation observed to impart comparable swelling to TentaGel™ resin. The chemical and physical stability of these PS-MPEG copolymers was observed to be very good. Thus when the resins were treated for 12 h at room temperature with a variety of acids (TFA, 6M HCl), bases (piperidine, 2M NaOH), the beads were stable (chemically and physically) with no PEG fragments being observed by MS. The resins were robust toward mechanical shaking and gentle magnetic stirring over a 24-hour period.

2.4. Resin based synthesis

The novel PS-MPEG resins were used as solid supports for a range of chemistries including, peptide synthesis, Suzuki[23] coupling, Mitsunobu[24] condensations and reduction in methanol as shown in Scheme 2. Thus the chloromethyl resins were converted into the corresponding aminomethylated materials[25] to give loadings[26] ranging from 0.63 to

Table 1. Preparation of the resin beads

Entry	DVB (%)	Monomer (**1**) (%)	Loading (mmol/g)	Yield (%)
1	8	12	–	60
2	3	5	1.0	90
3	2	7	1.0	64
4	2	14	1.0	60
5	2	24	0.90	78
6	2	43	0.96	71



Scheme 2. (i) Potassium phthalamide (5 equiv.), DMF 120°C, 18 h; (ii) hydrazine (10 equiv.), EtOH reflux, 5 h; (iii) Fmoc-Rink-linker (1.5 equiv.), HOBt (1.5 equiv.), DIC (1.5 equiv.), DCM, 4 h; (iv) 20% piperidine/DMF, (2×20 min); (v) Fmoc-AA-OH (2 equiv.), DIC (2 equiv.), HOBt (3 equiv.), DCM, 3 h; (vi) TFA/H_2O (95:5) (1 or 2 h); (vii) Fmoc-Gly-OH (5 equiv.), HOBt (5 equiv.), DCM, 3 h; (viii) 4-iodobenzoic acid (5 equiv.), DIC (5 equiv.), HOBt (5 equiv.), DCM, 5 h; (ix) phenylboronic acid (2 equiv.), Cs_2CO_3 (2 equiv.), $Pd(PPh_3)_4$ (0.1 equiv.), DMF, 90°C, 24 h; (x) Ac-Tyr-OH (5 equiv.), DIC (5 equiv.), HOBt (5 equiv.), DCM, 3 h; (xi) $PhCH_2OH$ (10 equiv.), PPh_3 (5 equiv.), DEAD (5 equiv.), THF, 12 h; (xii) 4-acetylbenzoic acid (5 equiv.), DIC (5 equiv.), HOBt (5 equiv.), DCM, overnight; (xiii) $NaBH_4$ (5 equiv.), MeOH, overnight; (xiv) TFA/DCM (50/50), (2×30 min). DIC=diisopropylcarbodiimmide, HOBt=1-hydroxybenzotriazole.

0.77 mmol/g. These resins were then loaded with the Fmoc-Rink linker[27] and in parallel used to prepare a model tripeptide, a biaryl compound, an arylether, and an alchol via ketone reduction. The results of these investigations are shown in Tables 3 and 4.

During the synthesis of peptide (**2**) the biaryl derivative (**3**) and the arylether derivative (**4**) (Table 3), the PS-MPEG resin containing 7% of the monomer (**1**) gave the best results in terms of the overall yields and purities of the final products **2**-**4** amongst the various resins tested including those containing higher levels of the PEG derivative. This resin was comparable, if not better, than TentaGel™ and AM-PS resins.

The reduction of a ketone in methanol, a much more polar

Table 2. Resin swelling (mL/g) of various non-grafted resins compared to TentaGel™ and ArgoGel™ (±0.2 mL/g)

Mon. (1) (%)	Dry vol.	DCM	Dioxane	THF	DMF	DME	Toluene	MeOH	2-PrOH	H_2O
0	1.8	5.4	4.8	6.0	4.6	4.6	5.2	2.4	2.2	2.0
7	2.0	8.2	7.0	8.4	5.8	5.8	6.6	2.8	2.6	2.4
14	2.0	7.6	6.8	7.2	5.8	5.8	7.0	2.8	2.6	2.6
24	2.0	8.0	6.8	6.8	6.6	6.6	7.6	2.8	2.8	2.4
43	2.0	8.2	8.2	8.2	8.0	8.6	9.4	3.0	2.8	2.8
TentaGel™	2.0	5.5	3.9	3.9	4.0	4.0	5.2	3.0	3.0	3.0
ArgoGel™	2.0	8.6	6.4	6.4	7.0	6.0	6.2	4.9	4.9	4.0

Table 3. Comparison of PS-MPEG resins for the synthesis of peptide (**2**), biaryl derivative (**3**) and arylether derivative (**4**)

Resin[a]	Loading[b] (mmol/g)	Peptide (**2**)		Biaryl derivative (**3**)		Arylether derivative (**4**)	
		Yield[c] (%)	Purity[d] (%)	Yield[c] (%)	Purity[e] (%)	Yield[c] (%)	Purity[e] (%)
7[f]	0.77	80	94	97	99	88	80
14[f]	0.63	50	94	80	95	67	77
24[f]	0.70	65	85	74	63	70	77
43[f]	0.67	58	89	84	84		
TentaGel™	0.25	43	83	94	84	65	68
AM-PS (1%)	1.13	72	95	71	97	43	51
AM-PS (2%)	1.0	56	95				

[a] Beads size 125–75 μm.
[b] Loading of the amino resin.
[c] Yield relative to the loading of amino resin.
[d] Determined by HPLC, λ=220 nm.
[e] Determined by HPLC, λ=254 nm.
[f] Percentage of monomer (**1**).

Table 4. Comparison of PS-MPEG resins for the synthesis of alcohol (**5**)

Resin[a]	Loading[b] (mmol/g)	Overall yield[c] (%)	Molar ratio[d]
7[e]	0.77	95	90:10
14[e]	0.63	84	97:3
24[e]	0.70	82	100:0
ArgoGel™	0.50	62	100:0
TentaGel™	0.25	83	100:0
AM-PS (1%)	1.11	90	80:20
AM-PS (2%)	1.0	92	79:21

[a] Beads size 125–75 μm.
[b] Loading of amino resin.
[c] Yield relative to the loading of the amino resin.
[d] Between the product (**5**) and the ketone and calculated by ^{1}H NMR.
[e] Percentage of monomer (**1**).

solvent, was examined to compare this reaction with ArgoGel™ and TentaGel™. As shown in Table 4, all the resins containing the new monomer (**1**) gave better results than standard PS resins, and ArgoGel™ in terms of isolated yields although only the resin containing higher percentages (24%) of (**1**) allowed full reduction of the ketone into the corresponding alcohol (**5**).

In conclusion, a series of novel non-grafted chloromethylated PS-MPEG resins were prepared by copolymerisation. Relative to traditional PEG-grafted resins, the MPEG-based resins had a much higher loading capacity while maintaining broad solvent compatibility. The co-polymers were stable to strongly acidic/basic conditions and a range of physical manipulations. The resin containing 7% of the new monomer (**1**) proved to be highly suitable for peptide synthesis, Suzuki and Mitsunobu couplings, having improved performance over TentaGel™ and Merrifield resins. For reaction in methanol, the resins containing the new monomer (**1**) gave better results than standard PS resins while all MPEG-based resins were better than ArgoGel™ in terms of the isolated yield. These resins thus provide an alternative to conventional PEG grafted supports.

3. Experimental

3.1. General

NMR spectra were recorded using a Bruker AC300 spectrometer operating at 300 MHz for ^{1}H and 75 MHz for ^{13}C, or a Bruker DPX400 spectrometer operating at 400 MHz for ^{1}H and 100 MHz for ^{13}C (δ scale in parts per million). ESI mass spectra were recorded using a VG Platform Quadrupole Electrospray Ionisation mass spectrometer, measuring mono-isotopic masses. Infra-red spectra were recorded on a BIORAD Golden Gate FTS 135. All samples were run as either neat solids or oils. In the case of resin linked compounds, the resins beads were washed with dichloromethane, diethyl ether and then dried in vacuo. Melting points were determined using a Gallenkamp melting point apparatus and are uncorrected. UV–Vis spectra were recorded using an 8452A Diode Array Spectrophotometer. Analytical HPLC was accomplished using a Hewlett–Packard HP1100 Chemstation, using a Phenomenex C_{18} prodigy 5 μm (150 mm×3 mm) column. A gradient from water containing 0.1% trifluoroacetic acid to acetonitrile containing 0.042% trifluoroacetic acid was run over 20 min followed by 5 min at acetonitrile.

Aluminium backed silica plates (0.25 mm layer of silica gel 60 with the florescent indicator Alugram SIL G/UV_{254}) were used for thin layer chromatography (TLC). UV (254 nm) was used to visualize compounds unless stated otherwise. Resin beads were sieved using a Retsch AS 200 control Sieve Shaker. All amino acids used were the natural L configuration. All chemicals and solvents were used from purchase unless otherwise stated.

3.1.1. Synthesis of 2-(2-methoxyethoxy)ethyl 4-methyl-1-benzenesulfonate.[28] To a solution of diethylene glycol monomethyl ether (5 mL, 42 mmol, 1 equiv.) and dry triethylamine (8.48 g, 84 mmol, 2 equiv.) in anhydrous THF (50 mL), *p*-toluene sulfonyl chloride (12 g, 63 mmol, 1.5 equiv.) was slowly added over a 20-minute period at 0°C. The mixture was allowed to warm to room temperature, stirred for 24 h and monitored by TLC. The white solid (Et_3N·HCl) present in the mixture was removed by filtration and the solvent removed in vacuo to give a yellow oil. The product was purified by column chromatography on silica gel using Pet/EtOAc (7:3) as the eluent to give 9.7 of the title product as a yellow oil. Yield 84%.

Alternative purification. Polyamine resin Amberlite IRA-96 (3 equiv.) was washed thoroughly with DCM (50 mL), MeOH (30 mL), Et_2O (30 mL) and dried in vacuo. The resin was swollen with THF. Crude 2-(2-methoxyethoxy)ethyl 4-methyl-1-benzensulfonate (**1**) (1 equiv.) was dissolved in THF and added to the resin slurry. The mixture was then shaken overnight. The resin was washed with THF and the solvent was evaporated in vacuo to give compound (**1**). HPLC purity: 93% and yield: 95%

R_f=0.35 (Pet/EtOAc 7:3); IR: ν=2878, 1598, 1451, 1353, 1108 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.80 (d, J=8 Hz, 2H, ArH), 7.34 (d, J=8 Hz, 2H, ArH), 4.18 (m, 2H, CH_2OSO_2), 3.70 (m, 2H, CH_2O), 3.58 (m, 2H, CH_2O), 3.49 (m, 2H, CH_2O), 3.36 (s, 3H, OCH_3), 2.45 (s, 3H, $ArCH_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ=144.9 (0), 133.1 (0), 130.0 (1), 128.0 (1), 71.9 (2), 70.8 (2), 69.4 (2), 68.8 (2), 59.2 (3); 21.8 (3); MS (AP^+): *m*/*z* (%): 275.1 (100) $[M+H]^+$, 297.0 (20) $[M+Na]^+$; RP HPLC (λ=254 nm) 14.6 min.

3.1.2. Synthesis of 1-{4-[2-(2-methoxyethoxy)ethoxy]-phenyl}-ethan-1-one. 2-(2-Methoxyethoxy)ethyl 4-methyl-1-benzenesulfonate (1.01 g) (1.01 g, 3.64 mmol, 1 equiv.) and potassium iodide (20 mg) were dissolved in acetonitrile (15 mL), and stirred for 5 min. A mixture of *p*-hydroxyacetophenone (0.74 g, 5.50 mmol, 1.5 equiv.) and potassium carbonate (0.75 g, 5.50 mmol, 1.5 equiv.) dissolved in acetonitrile (10 mL), was added. The reaction mixture was refluxed for 24 h. The white solid in the mixture was removed by filtration and the solvent was removed in vacuo. The crude product was dissolved in EtOAc (10 mL) and washed with sodium hydroxide (20 mL, 1 mM). The organic layer was dried over sodium sulphate and the solvent removed in vacuo to give 0.76 g of the title compound as a yellow oil that needed no further purification. Yield 89%.

R_f=0.25 (Pet/EtOAc 7:3); IR: ν=2876, 1674, 1599, 1358 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ=7.92 (d, 2H, J=9 Hz, ArH), 6.94 (d, 2H, J=9 Hz, ArH), 4.20 (m, 2H, CH_2OAr), 3.88 (m, 2H, CH_2O), 3.72 (m, 2H, CH_2O), 3.59 (m, 2H, CH_2O), 3.39 (s, 3H, OCH_3), 2.55 (s, 3H, $COCH_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ=197.0 (0); 162.8 (0); 130.7 (0); 130.5 (1); 114.4 (1); 72.0 (2), 71.0 (2), 70.0 (2), 68.0 (2), 59.2 (3); 26.5 (3); MS (ES^+): m/z (%): 239.2 (100) $[M+H]^+$, 256.2 (25), $[M+NH_4]^+$, 261.2 (5), $[M+Na]^+$; HRMS calcd for $C_{13}H_{18}O_4$: 238.1205, found: 238.1204; RP HPLC (ELSD): 8.6 min.

3.1.3. Synthesis of 1-{4-[2-(2-methoxyethoxy)ethoxy]-phenyl}-ethan-1-ol. 1-{4-[2-(2-Methoxyethoxy)ethoxy]-phenyl}-ethan-1-one (1.0 g, 4.20 mmol, 1 equiv.) was dissolved in ethanol (10 mL) and stirred at 0°C. Sodium borohydride (0.16 g, 4.23 mmol, 1 equiv.) was slowly added in portions. The mixture was stirred for 3 h and excess sodium borohydride quenched with 2 M HCl in ethanol. The solvent was removed by distillation, water (30 mL) was added and the compound was extracted with DCM (100 mL). The organic layer was dried with sodium sulphate and the solvent removed in vacuo to give 0.95 g of the title compound as yellow oil. Yield 95%.

R_f=0.2 (Pet/EtOAc 7:3); IR: ν=3422, 2877 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ=7.22 (d, 2H, J=9 Hz, ArH), 6.88 (d, 2H, J=9 Hz, ArH), 4.35 (q, 1H, J=7 Hz, $CHCH_3$), 4.14 (m, 2H, CH_2OAr), 3.85 (m, 2H, CH_2O), 3.72 (m, 2H, CH_2O), 3.58 (m, 2H, CH_2O), 3.39 (s, 3H, OCH_3), 1.40 (d, 3H, J=7 Hz, $CHCH_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ=158.2 (0), 136.5 (0), 127.8 (1), 114.6 (1), 72.0 (1), 71.0 (2), 70.0 (2), 67.0 (2), 64.0 (2), 59.2 (3); 24.3 (3); MS (ES^+): m/z (%): 258.3 (30) $[M+NH_4]^+$, 263.2 (100) $[M+Na]^+$, 279.2 (10) $[M+K]^+$; HRMS calcd for $C_{13}H_{20}O_4$: 240.1362, found: 240.1365; RP HPLC (ELSD): 7.7 min.

3.1.4. Synthesis of 1-[2-(2-methoxyethoxy)ethoxy]-4 vinyl benzene. A solution of 1-{4-[2-(2-methoxyethoxy)-ethoxy]phenyl}-ethan-1-ol (140 mg, 0.57 mmol) and pyridinium tosylate (14 mg, 0.056 mmol) in toluene (30 mL) was refluxed overnight using a Dean–Stark trap. The cooled solution was washed with water (30 mL) and a saturated solution of sodium chloride (30 mL). The toluene layer was dried with sodium sulfate and the solvent removed in vacuo. The product was purified by column chromatography on alumina eluting with Pet/EtOAc (7:3) to give 0.12 g of the title product as a pale yellow oil. Yield 95%.

R_f=0.48 (Pet/EtOAc 7:3) on alumina; IR: ν=2876, 1606, 1509 cm^{-1}; ^1H NMR: (300 MHz, $CDCl_3$): δ=7.33 (d, 2H, J=8 Hz, ArH), 6.87 (d, 2H, J=8 Hz, ArH), 6.65 (dd, 1H, J_{trans}=18 Hz, J_{cis}=11 Hz, $CHCH_2$), 5.60 (d, 1H, J_{trans}=18 Hz, CHH), 5.12 (d, 1H, J_{cis}=11 Hz, $CHCH$), 4.14 (m, 2H, CH_2OAr), 3.86 (m, 2H, OCH_2), 3.72 (m, 2H, OCH_2), 3.58 (m, 2H, OCH_2), 3.39 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ=158.6 (0), 136.4 (0), 130.7 (1), 127.5 (1), 114.7 (1), 111.7 (2), 72.0 (2), 71.0 (2), 70.0 (2), 67.5 (2), 59.2 (3); MS (ES^+): m/z (%): 240.2 (100) $[M+NH_4]^+$, 245.1 (18) $[M+Na]^+$, 261.1 (8) $[M+K]^+$, 286.2 (50) $[M+Na+CH_3CN]^+$); HRMS calcd for $C_{13}H_{18}O_3$: 222.1256, found: 222.1253; RP HPLC (λ=254 nm): 10.8 min.

3.2. Suspension polymerisation[22]

Pre-mixed organic phases (Table 5) were added to the aqueous phase (1.0 g of PVA (polyvinyl alcohol, 87–89% hydrolyzed—M_r 85–146 kDa), 5 g of Na_2SO_4, 200 mL H_2O) while stirring in 500 mL cylindrical reaction vessels, equipped with mechanical stirring connected to a central stirring motor, and purged with N_2. The suspensions were allowed to equilibrate for 30 min, and the temperature raised to 65°C for 16 h. The crude polymers were collected in six polypropylene filtration bags and washed with water, water/THF (1:1), THF, THF/MeOH (1:1), and MeOH. The beads were dried in vacuo and sieved to afford resins in five size ranges (>355, 355–250, 250–125, 125–75, 75–45 μm).

3.2.1. Solid phase synthesis of tripeptide Ala-Val-Phe-NH_2 (2). The Fmoc-Rink linker, *p*-[(*R*,*S*)-α-[1-(9*H*-fluoren-9-yl)-methoxyformamido]-2,4-dimethoxybenzyl]-phenoxy-acetic acid (1.5 equiv.), was coupled onto the aminomethyl resins (75–125 μm) with DIC/HOBt (1.5 equiv.) in DCM and then Fmoc deprotected with 20% piperidine in DMF (2×20 min). H-Rink amide-PS resin (200 mg) was swollen in a minimum amount of DCM/DMF (10:1) for 30 min. The Fmoc-amino acid (2 equiv.) and HOBt (2 equiv.) were dissolved in DCM/DMF (10:1) for 10 min. DIC (3 equiv.) was added and the mixture stirred for 10 min before addition to the resin. The resins were agitated for 3 h to effect coupling. The resins were washed with DMF (×3), DCM (×3), MeOH (×3) and Et_2O (×2) and dried under vacuum for 30 min. Fmoc removal was performed using 20% piperidine in DMF with two sequential treatments of 20 min. The resins were filtered and washed with DMF (×3), DCM (×3), MeOH (×3) and Et_2O (×2) and dried under vacuum. Peptides were cleaved from the resin by treating the resin with TFA/DCM (95:5) (2 mL) for 2 h. The resins were removed by filtration, the filtrates concentrated to ca. 1 mL and added to cold Et_2O (25 mL). The resulting precipitates were collected by centrifugation and washed with Et_2O (25 mL×2).

Table 5. Composition of the organic phase for suspension polymerization

Entry	Resin cross-linking (%)	Styrene (g)	DVB (g)	Monomer (**1**) (g)	Vinyl benzyl chloride (g)	Toluene[a] (mL)
1	8	27.5	3.6	8.8	0	25
2	3	34.4	1.6	4.0	6.1	20
3	2	13.8	0.45	2.6	3.75	11
4	2	10.9	0.45	4.94	3.75	11
5	2	6.6	0.3	5.78	2.29	8
6	2	3.7	0.27	8.74	2.29	7

[a] Initiator AIBN (1.0%, w/w) was added to the organic phase.

R_f=0.50 (DCM/MeOH 9:1). Mp: 215–216°C; IR: ν=3375–3299, 1671, 1632 cm^{-1}; ^1H NMR (400 MHz,$(CD_3)_2SO$): δ=8.34 (d, J=9 Hz, 1H, NH), 8.10 (d, J=8 Hz, 1H, NH), 7.43 (br, 2H, $CONH_2$), 7.23 (m, 5H, ArH), 7.10 (br, 2H, CH_3CHNH_2), 4.54 (ddd, 1H, J_1=5, 9 and 9 Hz, J_3=9 Hz, C*H*CH_2Ph), 4.23 (m, 1H, C*H*$CH(CH_3)_2$), 3.94 (q, 1H, J=7 Hz, C*H*CH_3), 3.04 (dd, 1H, J=5 and 14 Hz, $CHCH_\alpha H_\beta Ph$), 2.85 (dd, 1H, J=9 and 14 Hz, $CHCH_\alpha H_\beta Ph$), 1.99 (m, 1H, $CHCH(CH_3)_2$), 1.30 (d, 3H, J=7 Hz, CH_3CHNH_2), 0.87 (d, 6H, J=7 Hz, $CH(CH_3)_2$); ^{13}C NMR (100 MHz, $(CD_3)_2SO$): δ=173.1 (0), 170.5 (0), 170.0 (0), 138.2 (0), 129.5 (1), 128.4 (1), 126.6 (1), 58.3 (1), 53.9 (1), 48.5 (1), 38.2 (2), 31.1 (1), 19.6 (3), 18.5 (3), 17.9 (3); MS (ES^+): *m/z* (%): 335.3 (100) $[M+H]^+$, 669.5 (5) $[2M+H]^+$; HRMS ($[M+Na]^+$) calcd for $C_{17}H_{26}N_4O_3Na$: 357.1897, found: 357.1890; RP HPLC (λ=220 nm): 6.5 min.

3.2.2. Solid phase synthesis of *N*-(carbamoylmethyl) biphenyl-4-carboxamide (3). Fmoc-Glycine (5 equiv.) was coupled onto the H-Rink amide resins (300 mg) prepared as above. The loadings of the resins were calculated by a quantitative Fmoc test. After deprotection of the Fmoc group, the resins was swollen in DCM and coupled with 4-iodobenzoic acid (5 equiv.) according to the method described above. The resultant resins were suspended in DMF and Cs_2CO_3 (2 equiv.), $Pd(PPh_3)_4$ (0.1 equiv.) and phenyl boronic acid (1.5 equiv.) were added under N_2. The resulting suspensions were heated at 100°C for 24 h. Resins were filtered and washed with DMF (3×10 mL), DCM (3×10 mL), MeOH, Et_2O and dried in vacuo. The final compound (**3**) was cleaved from the resins with TFA/H_2O (95:5) (3 mL) shaking the suspension for 1 h. The resin was removed by filtration, and the TFA evaporated in vacuo. The crude materials were analysed by HPLC and ES-MS.

Mp: 210–212°C; IR: ν=3382, 3330, 1660, 1633 cm^{-1}; ^1H NMR: (400 MHz, $(CD_3)_2SO$): δ=8.81 (t, 1H, J=6 Hz, CON*H*), 8.09 (d, 2H, J=8 Hz, ArH), 7.89 (d, 2H, J=8 Hz, ArH), 7.85 (d, 2H, J=7 Hz, ArH), 7.61 (t, 2H, J=7 Hz, ArH), 7.52 (t, 1H, J=7 Hz, ArH), 3.96 (d, 2H, J=6 Hz, $COCH_2$); ^{13}C NMR (100 MHz, $(CD_3)_2SO$): δ=169.8 (0), 164.8 (0), 141.5 (0), 137.9 (0), 131.7 (0), 127.8 (1), 126.8 (1), 125.6 (1), 125.2 (1), 41.2 (2); MS (ES^+): *m/z* (%): 255.0 (30) $[M+H]^+$, 318.0 (100) $[M+Na+MeCN]^+$, 531.1 (80) $[2M+Na]^+$, 785.0 (20) $[3M+Na]^+$; HRMS ($[M+Na]^+$) calcd for $C_{15}H_{14}N_2O_2Na$: 277.0950, found: 277.0947; RP HPLC (λ=254 nm): 8.1 min.

3.2.3. Solid phase synthesis of 2-(acetylamino)-3-[4-(benzyloxy)phenyl]propanamide (4). *N*-Acetyltyrosine (5 equiv.) was coupled onto the resin Rink linker (300 mg) as above. A solution of PPh_3 (5 equiv.) and benzyl alcohol (10 equiv.) in dry THF (3 mL) was added to the dried resin and DEAD (5 equiv.) was added in four portions over 5 min. The resins were shaken overnight, washed with THF, DCM and Et_2O and dried in vacuo. Compound (**4**) was cleaved from the resins with TFA/H_2O (95:5) (3 mL) and shaking the suspension for 1 h. The crude materials were analysed by HPLC and ES-MS.

IR: ν=3373, 3317, 1660, 1639, 1510 cm^{-1}; ^1H NMR: (400 MHz, $(CD_3)_2SO$): δ=8.06 (d, 1H, J=8 Hz, CON*H*), 7.48 (m, 5H, ArH), 7.25 (d, 2H, J=8 Hz, ArH), 7.09 (br s, 2H, $CONH_2$), 7.01 (d, 2H, J=8 Hz, ArH), 5.16 (s, 2H, OCH_2Ph), 4.34 (m, 1H, CONHC*H*), 3.02 (dd, 1H, J=5 and 14 Hz, $CH_\alpha H_\beta Ph$), 2.78 (dd, 1H, J=9 and 14 Hz, $CH_\alpha H_\beta$-Ph), 1.85 (s, 3H, $COCH_3$); ^{13}C NMR (100 MHz, $(CD_3)_2SO$): δ=173.8 (0), 169.4 (0), 157.3 (0), 137.7 (0), 130.7 (0), 130.5 (1), 128.8 (1), 114.8 (1), 69.6 (2), 54.5 (1), 37.3 (2), 23.0 (3); MS (ES^+): *m/z* (%): 313.2 (70) $[M+H]^+$, 335.0 (10) $[M+Na]^+$, 625.3 (10) $[2M+H]^+$, 647.3 (10) $[2M+Na]^+$; HRMS ($[M+H]^+$) calcd for $C_{18}H_{21}N_2O_3$: 313.1553, found: 313.1547; RP HPLC (λ=254 nm): 8.6 min.

3.2.4. Solid phase synthesis of *N*-(carbamoylmethyl)-4-(1-hydroxyethyl)-benzamide (5). Fmoc-Glycine (5 equiv.) was coupled onto the H-Rink amide resins (400 mg) prepared as above. After deprotection of the Fmoc group, the resins was swollen in DCM and coupled with 4-acetylbenzoic acid (5 equiv.) according to the method described above. The resultant resins were suspended in MeOH (4 mL) and $NaBH_4$ (5 equiv.) was added. The resulting suspensions were shaken overnight at room temperature. Resins were filtered and washed with MeOH (3×10 mL), DMF (3×10 mL), DCM (3×10 mL) and dried in vacuo. The final compound (**5**) was cleaved from the resins with TFA/DCM (1:1, v/v) (5 mL) shaking the suspension for 30 min. The resin was removed by filtration, and the TFA evaporated in vacuo, and the materials analysed by HPLC and ES-MS.

Mp: 153–155°C; IR: ν=3312, 3213, 2974, 1672, 1642, 1542, 1503, 1301, 1091 cm^{-1}; ^1H NMR: (400 MHz, $(CD_3)_2SO$): δ=8.61 (t, 1H, J=6 Hz, CON*H*), 7.87 (d, 2H, J=8.5 Hz, ArH), 7.46 (d, 2H, J=8.5 Hz, ArH), 7.38 (s, 1H, CON*H*), 7.01 (s, 1H, CON*H*), 4.81 (q, 1H, J=6.5 Hz, OCH), 3.84 (d, 2H, J=6 Hz, $COCH_2$), 1.37 (d, 3H, J=6.5 Hz, CH_3); ^{13}C NMR (100 MHz, $(CD_3)_2SO$): δ=172.0 (0), 167.2 (0), 151.7 (0), 133.4 (0), 128.1 (1), 126.0 (1), 68.7 (1), 43.4 (2), 26.8 (3); MS (ES^+): *m/z* (%): 223.1 (13) $[M+H]^+$, 245.0 (100) $[M+Na]^+$, 246.0 (11) $[M+Na+H]^+$, 467.2 (22) $[2M+Na]^+$; HRMS ($[M+Na]^+$) calcd for $C_{11}H_{14}N_2O_3Na$: 245.0896, found: 245.0896.

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