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A new approach in the solid-phase synthesis of polyamine derivatives: construction of polyamine backbones from the center

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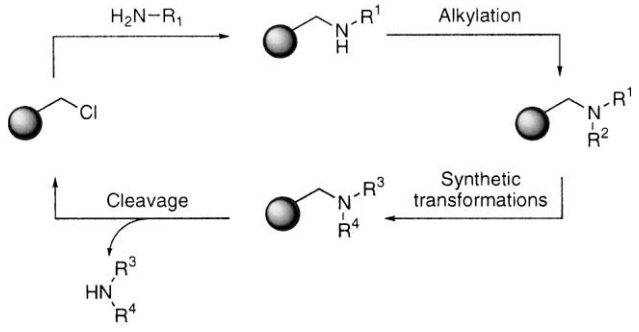
Abstract—A new and divergent approach for the solid-phase synthesis of polyamines and polyamine derivatives is shown. Monoprotected diamines are coupled to the Merrifield resin and alkylated at the resin-bound benzylic amine with masked ω-aminoalkyl groups. Selective deprotection of either of the two terminal amino functions allows the specific prolongation or derivatization of the resin-bound triamines at the two ends of the molecules. © 2001 Elsevier Science Ltd. All rights reserved.

1. Introduction

Linear polymethylene polyamines, particularly putrescine, spermidine, and spermine and also more uncommon representatives, are widely distributed throughout the animal and plant kingdom. They occur either in free form as protonated bases or conjugated to other biomolecules, and they exhibit in either forms, a variety of biological activities.[1] Just to mention a few of the biological effects of such compounds, they play important roles in DNA stabilization[2] and modification,[3] affect protein synthesis,[4] are involved in the modification of neuroreceptors and their associated ion channels,[5] and interact with phospholipids in biological membranes.[6] It is not surprising thus, that polyamines as well as their analogs and derivatives are considered as therapeutic leads for the treatment of a variety of diseases, and that new and efficient methods for their synthesis are searched for.

The synthesis of polyamines in solution is a laborious task since it involves extensive use of protective group strategy,[7] which can, however, be brought to almost perfection,[8] and requires tedious and often difficult purification steps due to the polarity of the compounds. An improvement represents the recently developed solid-phase syntheses of polyamines and polyamine derivatives,[9,10] which particularly facilitate the workup and purification operations. However, the solid-phase approaches for the synthesis of polyamine backbones published so far[10] suffer from three major shortcomings: (i) the resins used as yet are rather expensive, (ii) they do not tolerate a broad range of synthetic manipulations, and (iii) they allow solely a consecutive one-dimensional elongation of the polyamines. Particularly the latter point is disadvantageous with respect to the synthesis of larger libraries of polyamine derivatives. We thus elaborated a new method for the divergent solid-phase synthesis of polyamine derivatives, based on the inexpensive and robust Merrifield resin. Merrifield resins, derivatized with primary amines, should be readily alkylated at the benzylic N-atom, and the resulting modified amines are easily cleaved off the polymer by treatment with 1-chloroethyl chloroformate (ACE-Cl) and subsequent hydrolysis with MeOH[11] (Scheme 1). The possibility of alkylation of the resin-bound amino group adds a second spatial dimension to the construction of a solid-supported polyamine, thus allowing the independent modification of such molecules at both ends.



Scheme 1.

2. Results and discussion

Merrifield resin (200–400 mesh, 1% divinylbenzene, 0.9 mmol/g loading capacity) was derivatized by the action of excess of monoprotected diamines **1**–**3** in 1-methyl-2-pyrrolidone (NMP) at 50°C (Scheme 2). The reaction was complete within 24 h, and the loading was quantitative (0.7–0.8 mmol/g) as it was determined by liberation and

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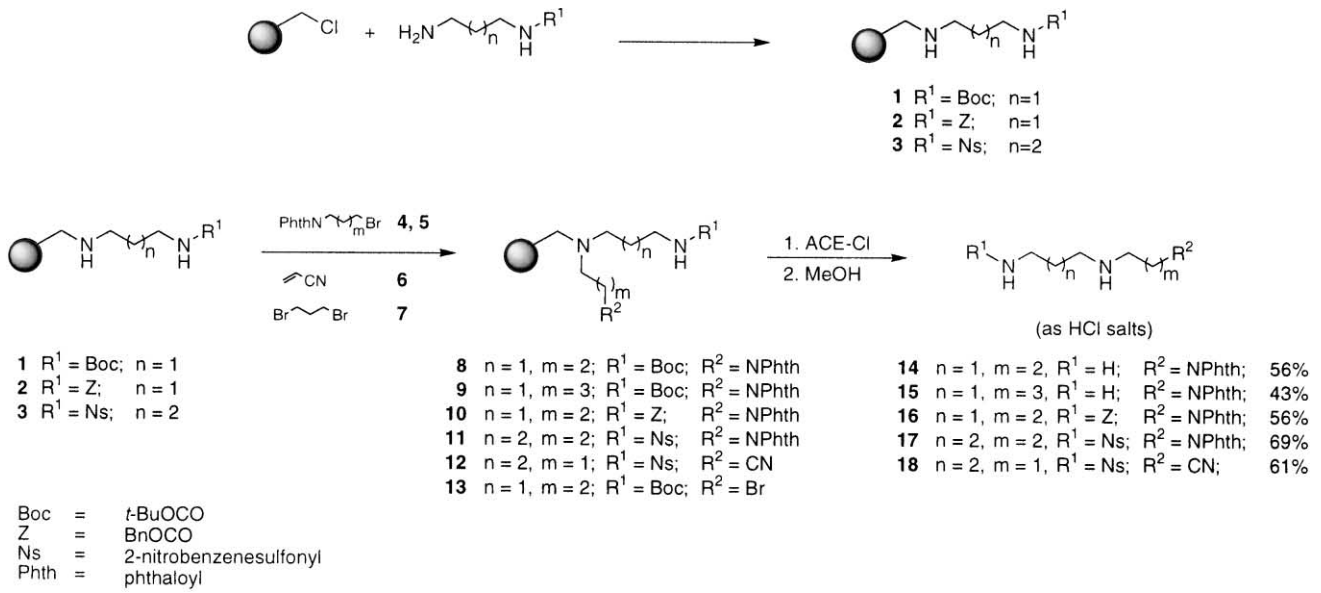


Scheme 2.

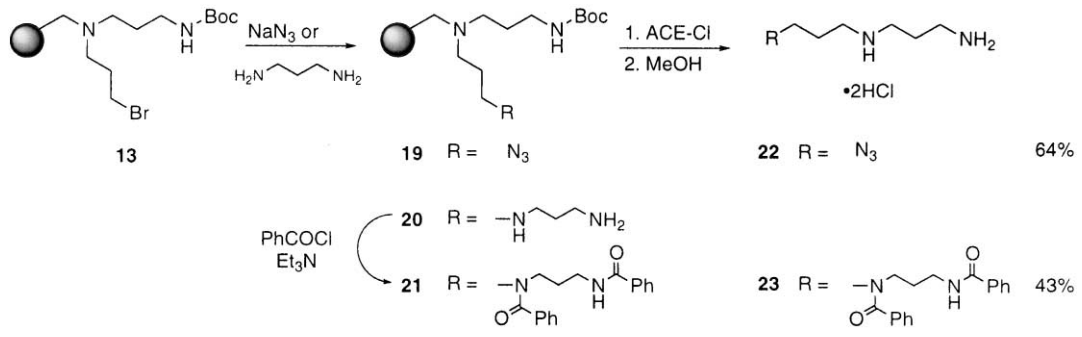
Volhard titration of the benzylic chlorides of the resin prior and after the transformation.[12] Alkylation of the free benzylic N-atoms was then effected by treatment of the resins with ω-phthalimidoalkyl bromides **4**–**5**, and for resin **1** with 1,3-dibromopropane (**7**), affording resins **8**–**11**, **13**. In the case of the ω-phthalimidoalkyl bromides as alkylating species, the progress of the reactions could be followed by IR spectroscopy with the diagnostic absorption at $1/\lambda$ 1772 cm^{-1} for the phthalimide.

Consecutive reaction of the resins **8**–**11** with ACE-Cl and MeOH to remove the modified amine from the resin afforded monoprotected triamines **14** and **15** and α,ω-orthogonally diprotected triamines **16** and **17** in overall 43–69% yield. The products arose as the HCl salts in virtually pure form after simple precipitation from MeOH with Et_2O. The substitution patterns of the compounds show that Boc groups can (and will) be removed simultaneously during the cleavage of the polyamines from the resins. On the other hand, Z, Ns, and phthalimido groups are stable under the cleavage conditions.

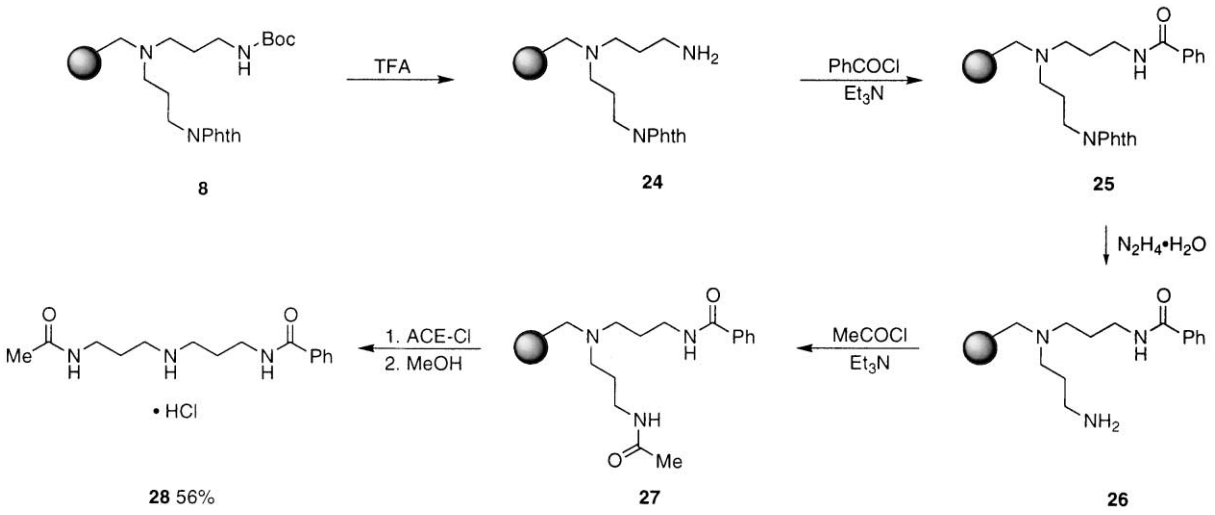
Cyanoethylation of amino-derivatized Merrifield resins did not proceed easily, and it was successfully achieved only with resin **3**. Treatment of this polymer with excess of acrylonitrile, added in two portions, led to resin **12**. The stretching vibration of its nitrile group, however, was hardly identified in the IR spectrum, and thus the alkylation was initially not recognized. The successful alkylation step was verified only after cleavage of the modified amine from the solid support, delivering diprotected triamine **18** in 61% yields. The same reaction sequence, performed with resin **1**, resulted only in marginal amount of the desired polyamine. The reason for the lower reactivity of **1** towards acrylonitrile is not clear.

To demonstrate the potential and divergency of the new methodology, resins **8** and **13** were modified (Scheme 3). Substitution of the bromide of **13** with azide delivered resin **19**, which upon treatment with ACE-Cl/MeOH afforded the mono-masked triamine **22** in 64% yield. Likewise, the reaction of resin **13** with 1,3-diaminopropane as the nucleophile provided resin **20**. Benzoylation of the free amino groups and finally liberation of the polyamine portion as usual gave rise to bis-acylated tetramine **23** (43%). Analogously, further nucleophiles could be used for the elongation of the polyamine on the bromopropyl branch of the molecule, and selective deprotection and modification at the other branch could be effected as shown with resin **8**.

The Boc group at the N-atom of the resin-bound triamine of resin **8** was selectively removed by the action of



Scheme 3.



Scheme 4.

trifluoroacetic acid. This formed resin **24** and opened the possibility for the controlled modification of the polyamine at one end. Such a modification was performed with the acylation of the primary amino group with benzoyl chloride, which delivered resin **25**. Deprotection of the second terminal amino group by removal of the phthalimido moiety under the influence of hydrazine hydrate gave resin **26**, whose free amino group was acetylated with acetyl chloride to deliver resin **27**. Finally, cleavage of the polyamine from the support afforded α-acetyl-ω-benzoyltriamine **28** in 56% yield (Scheme 4).

3. Conclusion

We have demonstrated that linear polyamines and their derivatives can be constructed by solid-phase synthesis on the Merrifield resin in a divergent manner. The attachment of a monoprotected diamine to the solid support, followed by alkylation of the remaining nucleophilic benzylic amine with a masked ω-aminoalkyl electrophile opens the way for the independent modification of a linear polyamine at the two terminal ends. This is exemplified with the preparation of α-acetyl-ω-benzoyltriamine **28**. Alternative modifications, like chain prolongation or acylation with different acyl components should likewise be possible and are presently under investigation.

4. Experimental

4.1. General

Unless otherwise stated, starting materials were obtained from commercial suppliers and were used without further purification. As solid support was used, Merrifield peptide resin 200–400 mesh, 1% divinylbenzene, loading 0.9 mmol/g from Advanced ChemTech. For the solid phase reactions was used: PLS 4×6 Organic Synthesiser. IR spectra as KBr presslings; Perkin–Elmer IR 'Spectrum One'; in cm^{-1}. ^1H NMR spectra in DMSO-d_6 or MeOH-d_4; Bruker AC-300 (300 MHz); δ in ppm rel. to DMSO-d_6 (δ 2.50) or MeOH-d_4 (δ 4.87), J in Hz. ^{13}C NMR spectra in DMSO-d_6 or MeOH-d_4; Bruker ARX-300 (75.5 MHz); δ in ppm rel. to DMSO-d_6 (δ 39.51) or MeOH-d_4 (δ 49.15); multiplicities from DEPT-135 and DEPT-90 experiments. Mass spectrometry (MS): Finnigan MAT 90 or Finnigan SSQ 700; electron impact MS (EI MS) at 70 eV; chemical-ionization MS (CI MS) with NH_3 as the reactant gas; molecular ions, quasi-molecular ions, and characteristic fragments either with interpretation or ≥10 rel.%; in *m/z*. Proof of structure and purity of the final polyamine derivatives is provided by their ^1H NMR spectra. Elemental analyses and HRMS is not appropriate for polyamine derivatives since the compounds arise, as free bases, as waxy or glassy solids only, from which the last solvent molecules can hardly be removed. The hydrochloric salts are rather hygroscopic, and the uptake of water falsifies the elemental analyses. The compounds are not stable enough to survive distillation and show heavy fragmentation in EI-MS. HRMS on the molecular ions is thus not possible, and HRMS on fragment ions are not informative enough to prove the overall structures.

4.2. Derivatization of Merrifield resin with monoprotected diamines

4.2.1. Derivatization of Merrifield resin with *tert*-butyl *N*-(3-aminopropyl)carbamate (resin 1). Merrifield resin (20 g, 18 mmol) was swelled in NMP (130 ml). *tert*-Butyl *N*-(3-aminopropyl)carbamate (18.8 g, 108 mmol)[13] was added and the mixture was stirred for 24 h at 50°C. The resin was filtered off, washed successively with DMF, CH_2Cl_2, and MeOH, and dried in vacuo. Loading: 0.8 mmol/g (100%), measured as described below.

4.2.2. Derivatization of Merrifield resin with benzyl *N*-(3-aminopropyl)carbamate (resin 2). Merrifield resin (3 g, 2.4 mmol) was swelled in NMP (30 ml). After addition of benzyl *N*-(3-aminopropyl)carbamate (2.48 g, 12 mmol),[14] the suspension was stirred for 24 h at 50°C. The resin was filtered off, washed with DMF, CH_2Cl_2, and MeOH, and dried in vacuo. Loading: 0.72 mmol/g (100%), measured as described below.

4.2.3. Derivatization of Merrifield resin with 1-amino-4-(2-nitrobenzenesulfonyl)aminobutane (resin 3). Merrifield resin (10 g, 8.8 mmol) was swelled in NMP (70 ml). After addition of 1-amino-4-(2-nitrobenzenesulfonyl)-aminobutane (12.03 g, 44 mmol)[15] and *N*-ethyldiisopropylamine (DIEA) (7.5 ml, 44 mmol), the mixture was stirred for 24 h at 50°C. The resin was filtered off, washed with NMP, DMF, CH_2Cl_2, and MeOH, and dried in vacuo. Loading: 0.76 mmol/g (100%), measured as described below.

4.2.4. Determination of the loading by Volhard titration.[12] Dry resin samples (approx. 100 mg, prior and after loading) were heated with pyridine (2 ml) for 2 h at 98°C. The solutions with the resins were transferred to an Erlenmeyer flask with 50 ml of 20% acetic acid. A Volhard titration for chloride was carried out by addition of saturated ferric ammonium sulfate indicator (five drops), concentrated nitric acid (5 ml), 0.1N $AgNO_3$ (5 ml), and toluene (3 ml), followed by back-titration of the excess Ag^+ with 0.1N KSCN.

4.3. Alkylation of resins 1–3

4.3.1. Alkylation of resin 1 with *N*-(3-bromopropyl)phthalimide (resin 8). Resin **1** (0.36 mmol) was suspended in NMP (4 ml). *N*-(3-bromopropyl)phthalimide **4** (3.6 mmol, 0.97 g) and DIEA (3.6 mmol, 0.62 ml) were added, and the mixture was agitated for 20 h at 50°C. The resin was filtered off, washed with NMP, DMF, CH_2Cl_2, and MeOH, and dried in vacuo. IR: 3422w, 1772w, 1712s.

4.3.2. Alkylation of resin 1 with *N*-(4-bromobutyl)-phthalimide (resin 9). Resin **1** (0.2 mmol) was suspended in NMP (3 ml). *N*-(4-bromobutyl)phthalimide **5** (2 mmol, 0.56 g) and DIEA (2 mmol, 0.34 ml) were added, and the mixture was agitated for 20 h at 50°C. The resin was filtered off, washed with NMP, DMF, CH_2Cl_2, and MeOH, and dried in vacuo. IR: 3424w, 1771m, 1709s.

4.3.3. Alkylation of resin 2 with *N*-(3-bromopropyl)-phthalimide (resin 10). Resin **2** (0.36 mmol) was suspended in NMP (3 ml). *N*-(3-bromopropyl)phthalimide **4** (3.6 mmol, 0.97 g) and DIEA (3.6 mmol, 0.62 ml) were added, and the mixture was agitated for 20 h at 50°C. The resin was filtered off, washed with NMP, DMF, CH_2Cl_2, and MeOH, and dried in vacuo. IR: 3419w, 1772w, 1710s.

4.3.4. Alkylation of resin 3 with *N*-(3-bromopropyl)-phthalimide (resin 11). Resin **3** (0.38 mmol) was suspended in NMP (3 ml). *N*-(3-bromopropyl)phthalimide **4** (3.8 mmol, 1.02 g) and DIEA (3.8 mmol, 0.65 ml) were added, and the mixture was agitated for 45 h at 80°C. The resin was filtered off, washed with NMP, DMF, CH_2Cl_2, and MeOH, and dried in vacuo. IR: 3357w, 1772m, 1713s, 1542s, 1396s, 1364s, 1345s, 1168s.

4.3.5. Alkylation of resin 3 with acrylonitrile (resin 12). Resin **3** (0.38 mmol) was swelled in NMP (3.5 ml). A first portion of acrylonitrile **6** (3.8 mmol, 0.25 ml) was added and, after agitation for 24 h at 60°C, a second portion (3.8 mmol, 0.25 ml) followed. After stirring for 24 h (60°C), the resin was filtered off, washed with NMP, CH_2Cl_2, and MeOH, and dried in vacuo. IR: 3355w, 2247w, 1539s, 1343s, 1165s.

4.3.6. Alkylation of resin 1 with 1,3-dibromopropane (resin 13). Resin **1** (0.36 mmol) was suspended in NMP (4 ml). 1,3-Dibromopropane (**7**, 3.6 mmol, 0.37 ml) and DIEA (3.6 mmol, 0.62 ml) were added, and the mixture was agitated for 20 h at 50°C. The resin was filtered off, washed with NMP, DMF, CH_2Cl_2, and MeOH, and dried in vacuo.

4.4. Cleavage of the amines from the resins

4.4.1. *N*-(7-Amino-4-azaheptyl)phthalimide dihydrochloride (14). Resin **8** (0.36 mmol) was suspended in 1,2-dichloroethane (3.5 ml) and 1-chloroethyl chloroformate (ACE-Cl, 3.6 mmol, 0.39 ml) was added. After agitation for 3 h at 23°C, the resin was filtered off and washed with CH_2Cl_2. The organic solutions were collected and evaporated to dryness. The residue was dissolved in MeOH, and the resulting solution was refluxed for 3 h. The solvent was removed in vacuo, the residue re-dissolved in MeOH, and precipitated by the addition of Et_2O. After filtration, amine **14** (66 mg, 20 mmol, 56% with respect to resin **1**; 2 steps) was obtained as the HCl salt in virtually pure form. IR: 3479w, 2958s, 2923s, 2754s, 2698s, 2512m, 2412m, 1780m, 1708s, 1608m, 1531m, 1465m, 1446m, 1410m, 1384m, 1333m, 1204m, 1050m, 936m, 880w, 720m, 710s, 623w, 531m. ^{1}H NMR (DMSO-d_6): 9.22 (br s, NH_2); 8.18 (br s, NH_3); 7.92–7.81 (m, 4arom. H); 3.65 (t, J=6.7 Hz, PhthNCH_2); 3.03–2.81 (m, 6H); 2.07–1.90 (m, 4H). ^{13}C NMR (DMSO-d_6): 168.1 (s, 2CO); 134.6 (d, 2arom. C); 131.6 (s, 2arom. C); 123.2 (d, 2arom. C); 44.8, 43.9, 36.2, 35.1, 25.1, 23.8 (6t). CI MS: 263 (17, $[M+2H]^{2+}$), 262 (100, $[M+H]^+$), 244 (10).

4.4.2. *N*-(8-Amino-5-azaoctyl)phthalimide dihydrochloride (15). Analogous to Section 4.4.1, resin **9** (0.2 mmol) was cleaved to yield **15** (30 mg, 0.086 mmol, 43% with respect to resin **1**; 2 steps). IR: 3460w, 2957m, 2779m, 2531w, 1772m, 1710s, 1608w, 1530w, 1465m, 1438m, 1403m, 1377m, 1048m, 722m, 711m, 532w. ^{1}H NMR (DMSO-d_6): 9.08 (br s, NH_2); 8.16 (br s, NH_3); 7.90–7.80 (m, 4arom. H); 3.63–3.54 (m, PhthNCH_2); 3.00–2.78 (m, 6H); 1.96 (*quint*., J=7.5 Hz, 2H); 1.71–1.56 (m, 4H). ^{13}C NMR (DMSO-d_6): 168.1 (s, 2CO); 134.6 (d, 2arom. C); 131.8 (s, 2arom. C); 123.2 (d, 2arom. C); 46.2, 44.0, 37.0, 36.2, 25.4, 23.8, 23.1 (7t). EI MS: 275 (1, $M^{+\cdot}$), 160 (69, $[C_9H_6NO_2]^+$), 104 (15, $[C_7H_4O]^+$), 87 (61, $[C_4H_{11}N_2]^+$), 84 (60, $[C_5H_{10}N]^+$), 76 (27, $[C_6H_4]^+$), 73 (16, $[C_3H_9N_2]^+$), 71 (15, $[C_4H_9N]^+$), 70 (100, $[C_4H_8N]^-$), 58 (28, $[C_3H_8N]^+$), 57 (69, $[C_3H_7N]^+$), 56 (88, $[C_3H_6N]^+$), 51 (10, $[C_4H_3]^+$), 50 (9, $[C_4H_2]^+$).

4.4.3. Benzyl *N*-(7-phthalimido-4-azaheptyl)carbamate hydrochloride (16). Analogous to Section 4.4.1, resin **10** (0.36 mmol) was cleaved to yield **16** (85 mg, 0.20 mmol, 56% with respect to resin **2**; 2 steps). IR: 3347m, 2955m, 2780m, 2746m, 2513m, 2410w, 1775m, 1710s, 1610w, 1536s, 1466m, 1443m, 1400m, 1334m, 1279m, 1257m, 1049m, 1022m, 936w, 880w, 720m, 712m, 621w, 531w. ^{1}H NMR (MeOH-d_4): 8.01–7.85 (m, 4arom. H and NH of carbamate); 7.50–7.35 (m, 5arom. H); 5.16 (s, CH_2O); 3.89

(t, J=6.2 Hz, NCH_2); 3.34 (t, J=6.3 Hz, NCH_2); 3.19–3.06 (m, 4H); 2.25–2.10 (m, 2H); 2.07–1.91 (m, 2H). ^{13}C NMR (MeOH-d_4): 170.0 (s, 2CO); 159.5 (s, CO); 138.4 (s, arom. C); 135.7 (d, 2arom. C); 133.4 (s, 2arom. C); 129.6, 129.2, 129.0 (3d, 3arom. C); 124.4 (d, 2arom. C); 67.8 (t, CH_2Ph); 46.9, 46.7, 38.5, 35.9, 28.2, 26.8 (6t). CI MS: 396 (100, $[M+H]^+$), 288 (20, $[M-PhCH_2O]^+$).

4.4.4. *N*-[8-(2-Nitrobenzolsulfonamido)-4-azaoctyl]phthalimide hydrochloride (17). Analogous to Section 4.4.1, resin **11** (0.38 mmol) was cleaved to yield **17** (130 mg, 0.26 mmol, 69% with respect to resin **3**; 2 steps). IR: 3450w, 3197s, 3013s, 2945s, 2869m, 2829s, 2736m, 2676m, 2485w, 1768s, 1709s, 1611m, 1553s, 1468s, 1440s, 1402s, 1366s, 1336s, 1216m, 1187m, 1172s, 1160s, 1085s, 1039s, 976m, 851m, 817m, 803m, 779s, 737s, 653m, 592s, 571m, 533m. ^{1}H NMR (DMSO-d_6): 8.99 (br s, NH_2); 8.24 (t, J=5.8 Hz, $NHSO_2$); 8.07–7.79 (m, 8arom. H), 3.64 (t, J=6.7 Hz, NCH_2); 2.97–2.73 (m, 6H); 2.04–1.91 (m, 2H); 1.68–1.41 (m, 4H). ^{13}C NMR (DMSO-d_6): 168.1 (s, 2CO); 147.9 (s, CNO_2); 134.5 (d, 2arom. C); 134.1 (d, arom. C); 132.9 (s, CSO_2); 132.8 (d, arom. C); 131.8 (s, 2arom. C); 129.6, 124.5 (2d, 2arom. C); 123.2 (d, 2arom. C); 46.3, 44.6, 42.2, 35.0, 26.5, 25.0, 22.8 (7t). CI MS: 461 (100, $[M+H]^+$), 257 (14, $[M-C_{11}H_{11}N_2O_2]^+$).

4.4.5. *N*-[4-(2-Cyanoethylamino)butyl]-2-nitrobenzenesulfonamide hydrochloride (18). Analogous to Section 4.4.1, resin **12** (0.38 mmol) was cleaved to yield **18** (85 mg, 0.23 mmol, 61% with respect to resin **3**; 2 steps). IR: 3450w, 3265s, 2950m, 2780m, 2620m, 2450m, 2260m, 1735m, 1595m, 1540s, 1465m, 1425s, 1360s, 1330s, 1165s, 1125m, 1065m, 955w, 900w, 855m, 780m, 740m, 730m. ^{1}H NMR (DMSO-d_6): 9.39 (br s, NH_2); 8.23 (t, J=5.6 Hz, $NHSO_2$); 8.06–7.82 (m, 4arom. H), 3.25–3.12 (m, NCH_2); 3.06–2.75 (m, 6H); 1.70–1.42 (m, 6H); 1.70–1.42 (m, 4H).^{13}C NMR (DMSO-d_6): 147.7 (s, CNO_2); 133.9 (d, arom. C); 132.7 (s, CSO_2); 132.6, 129.4 (2d, 2arom. C); 124.3 (d, arom. C); 117.7 (s, CN); 46.1, 42.0, 41.9, 26.3, 22.5, 14.2 (6t). CI MS: 327 (100, $[M+H]^+$).

4.5. Modifications of the resins

4.5.1. Substitution of resin 13 with NaN_3 (resin 19). Resin **13** (0.36 mmol) was swelled in NMP (4 ml), and NaN_3 (3.6 mmol, 0.23 g) was added. After agitation for 24 h at 23°C, the resin was filtered off, washed with NMP, CH_2Cl_2, and MeOH, and dried in vacuo. IR: 3427w, 2094m, 1715s.

4.5.2. Substitution of resin 13 with 1,3-diaminopropane (resin 20). Resin **13** (0.37 mmol) was swelled in NMP (4 ml), and 1,3-diaminopropane (3.7 mmol, 0.31 ml) and DIEA (3.7 mmol, 0.63 ml) were added. After agitation for 22 h at 50°C, the resin was filtered off, washed with NMP, CH_2Cl_2, and MeOH, and dried in vacuo.

4.5.3. Acylation of resin 20 with benzoyl chloride (resin 21). Resin **20** (0.37 mmol) was suspended in CH_2Cl_2 (4 ml), and benzoyl chloride (3.7 mmol, 0.43 ml) and Et_3N (3.7 mmol, 0.52 ml) were added dropwise. After agitation for 5 h at 23°C, the resin was filtered off, washed with CH_2Cl_2 and MeOH, and dried in vacuo. The Kaiser[16] test revealed the absence of primary amino groups.

4.5.4. *N*-(3-Azidopropyl)-1,3-diaminopropane dihydrochloride (22). Analogous to Section 4.4.1, resin **19** (0.36 mmol) was cleaved to yield **22** (53 mg, 0.23 mmol, 64% with respect to resin **1**; 3 steps). IR: 3418m, 2958s, 2774s, 2504m, 2417m, 2099s, 1608m, 1529m, 1463m, 1405m, 1352m, 1286m, 1010w, 777w. ^{1}H NMR (DMSO-d_6): 9.35 (br s, NH_2); 8.20 (br s, NH_3); 3.50 (t, J=6.7 Hz, NCH_2); 3.06–2.80 (m, 6H); 2.07–1.85 (m, 4H). ^{13}C NMR (DMSO-d_6): 48.1, 44.4, 44.0, 36.3, 25.1, 23.8 (6t). ESI MS: 158 (83, $[M+H]^+$), 100 (100, $[M+H-C_3H_8N]^+$).

4.5.5. *N*-[(11-Amino-4-benzoyl)-4,8-diazaundecyl]benzoylamide dihydrochloride (23). Analogous to Section 4.4.1, resin **21** (0.37 mmol) was cleaved to yield **23** (73 mg, 0.16 mmol, 43% with respect to resin **1**; 4 steps). IR: 3322m, 2923s, 2752s, 2518m, 2416m, 1625s, 1578s, 1538s, 1444s, 1396m, 1307m, 1060w, 696s. ^{1}H NMR (MeOH-d_4): 8.05–7.25 (m, 10arom. H); 3.95–2.85 (m, 12H); 2.40–1.85 (m, 6H). ^{13}C NMR (MeOH-d_4): 175.3, 170.4 (2s, 2CO); 137.1, 135.3 (2s, 2arom. C); 132.9, 131.1, 129.9, 129.7, 128.4, 127.4 (6d, 6arom. H); 49.0, 46.9, 46.1, 43.4, 38.1, 38.0, 29.9, 25.9, 25.4 (9t). ESI MS: 397 (100, $[M+H]^+$).

4.5.6. Removing of the Boc protective group from resin 8 (resin 24). To resin **8** (0.36 mmol), swelled in CH_2Cl_2 (4 ml), was added, trifluoracetic acid (7.2 mmol, 0.55 ml). After agitation for 12 h at 23°C, the resin was filtered off, washed with CH_2Cl_2, CH_2Cl_2/DIEA (1:1), CH_2Cl_2, and MeOH, and dried in vacuo.

4.5.7. Benzoylation of resin 24 (resin 25). Resin **24** (0.36 mmol) was acylated with benzoyl chloride analogous to Section 4.5.3. The Kaiser16 test revealed the absence of primary amino groups. IR: 3422w, 1772m, 1714s, 1663m.

4.5.8. Removing of the phthalimide protective group from resin 25 (resin 26). Resin **25** (0.36 mmol) was swelled in NMP (3.5 ml), and $N_2H_4{\cdot}H_2O$ (36 mmol, 1.75 ml) was added. The mixture was agitated for 3 h at 80°C, the resin was filtered off, washed with NMP, dioxane, dioxane/H_2O (1:1), H_2O, EtOH, and MeOH, and dried in vacuo. IR: 3364w, 1660m.

4.5.9. Acetylation of resin 26 (resin 27). Resin **26** (0.36 mmol) was acylated with acetyl chloride analogous to Section 4.5.3. The Kaiser test[16] revealed the absence of primary amino groups.

4.5.10. *N*-(7-Acetyl-4-azaheptyl)benzoylamide hydrochloride (28). Analogous to Section 4.4.1, resin **27** (0.36 mmol) was cleaved to yield **28** (62 mg, 0.20 mmol, 56% with respect to resin **1**; 6 steps). IR: 3314m, 3066m, 3035m, 2956s, 2780s, 2736m, 2552w, 2457w, 1638s, 1604m, 1579m, 1536s, 1483m, 1465m, 1316m, 714m, 692m, 670w. ^{1}H NMR (DMSO-d_6): 8.90 (br s, NH_2); 8.72 (br t, J=5.8 Hz, NHCO); 8.06 (br t-like m, NHCO); 7.91–7.85 (m, 2arom. H); 7.56–7.42 (m, 3arom. H); 3.40–3.30 (sym. m, 4lines, CH_2NH); 3.14–3.06 (sym. m, 4lines, CH_2NH); 2.99–2.79 (m, 2CH_2NH_2); 2.00–1.70 (m,

$2CH_2CH_2CH_2$); 1.81 (s, CH_3).^{13}C NMR (DMSO-d_6): 169.7 (s, $COCH_3$); 166.6 (s, COPh); 134.4 (s, arom. C); 131.4 (d, arom. C); 128.4, 127.4 (2d, 4arom. C); 44.9, 44.8, 36.4, 35.9, 26.1, 26.1 (6t); 22.7 (q, *Me*CO). ESI MS: 278 (100, $[M+H]^+$), 162 (13, $[M-C_5H_{11}N_2O]^+$).

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