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Synthetic Approaches to the Bifunctional Chelators for Radionuclides Based On Pyridine-Containing Azacrown Compounds

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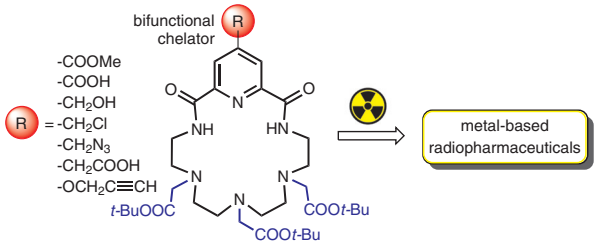

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Abstract Synthetic ways to introduce functional groups (CO_2Me, CO_2H, OCH_2CO_2H, $OCH_2C{\equiv}CH$, CH_2OH, CH_2Cl, CH_2N_3) into the pyridine ring of pyridine-containing azacrown compounds are described. These groups were introduced at position-4 of the pyridine ring, while keeping the macrocyclic carboxylate groups available for metal chelation. The derivatives were obtained by macrocyclization reaction of 4-substituted, trimethyl pyridine-2,4,6-tricarboxylate or by modification of methyl ester group in pyridine fragment of macrocycles. Obtained derivatives can be applied for preparing radiotherapeutic agents by conjugation to different vector biomolecules for targeted drug delivery to cancer cells without damaging healthy tissue.

Key words bifunctional chelators, azacrown compounds, macrocyclization, radiopharmaceuticals, bioconjugation

Nuclear medicine is a powerful tool with the ability to both image disease and subsequently treat the diseased state without harming the surrounding healthy tissue.[1–4] Ligands that are typically used to construct radiopharmaceuticals are bifunctional chelators (BFCs), which are simply chelators with reactive functional groups that can be covalently coupled to targeting vectors (e.g., peptides, nucleotides, antibodies, nanoparticles).[5–10]

BFCs serve as linkers between the radionuclide and targeting biomolecule and therefore play a crucial role in the success of targeted radionuclide therapy. The BFC is expected to impart high in vivo stability to the radiolabeled biomolecule translating to minimum radiation dose to non-target organs. The choice of BFC is therefore governed by the thermodynamic and kinetic stability of the radiometal complexes.[6,11–14] Fast room temperature radiolabeling becomes an important property when working with BFC-conjugates of heat sensitive molecules such as antibodies and their derivatives, or when working with short half-life isotopes such as $^{212/213}$Bi, ^{68}Ga, ^{44}Sc, and ^{62}Cu.[15–20]

DOTA (1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid) (Figure 1) is one of the current 'gold standards' for a number of isotopes, including ^{111}In, ^{177}Lu, $^{86/90}$Y, ^{225}Ac, and $^{44/47}$Sc, and it is likely the most commonly used chelator to this day.[5,21] But it inconveniently requires elevated temperatures for radiolabeling with essentially all radiometals.[22–24] DTPA (diethylenetriaminepentaacetic acid) (Figure 1) is one of the oldest and most pervasive acyclic chelators used in radiochemistry, and like most acyclic chelators it can be radiolabeled with many radiometal ions at room temperature in a matter of minutes.[25] As a first generation radiometal chelator, it suffers from stability issues in

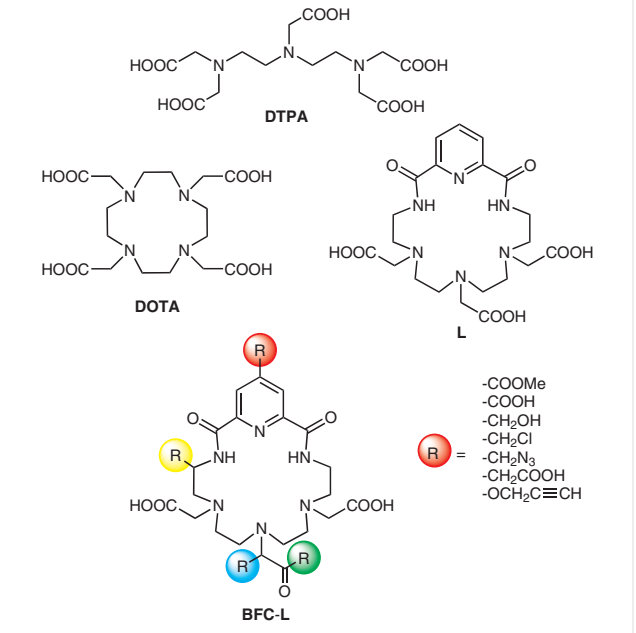

Figure 1 Structures of DTPA, DOTA, **L**, and bifunctional derivatives of **L**

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vivo with many radiometal ions and is universally not as stable as the macrocycles, making its use obsolete in recent years.[26–28]

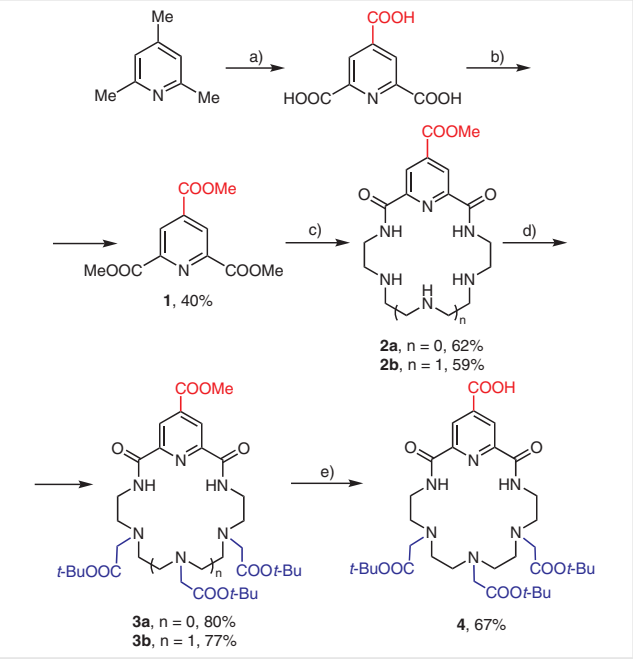
In our earlier studies, the synthesis of the new derivatives of pyridine containing azacrown compounds and their complex formation with heavy metal ions have been reported.[29,30] The rigid structure of pyridine-2,6-dicarboxamide fragment provides fast kinetics of complex formation, the introduction of additional coordination groups improves the binding properties of macrocycles. These chelators have also been tested as chelating agent for radionuclides.

Ligand **L** (Figure 1) possessing three acetate pendant arms forms the most stable complex with Bi^{3+} (lgK = 21) through the studied ligands. The complex **L**·Bi^{3+} is stable even in 100 times volume excess of fetal serum during at least 3 hours. The complex **L**·Bi^{3+} demonstrates fast clearance in vivo.[31] The results of in vitro serum stability and in vivo biodistribution studies suggest that the novel ligand **L** can be promising as BFC for the preparation of radiopharmaceutical with short half-life ^{213}Bi. Thus, it is essential to have in hand a family of **L** derivatives with different reactive functions in order to allow covalent coupling of the free ligand or its metal complexes to bioactive molecules, biomolecules, macromolecules, or nanosystems.

There are several possible approaches to the conjugation of chelator to a targeting moiety. The most common conjugation strategy is to substitute one acetate donor.[26,32] This strategy has been used for a long time in the field of DOTA bioconjugates.[33–38] However, in some cases, this approach can affect the denticity of the ligand, the overall charge of the complex and may decrease in vitro and in vivo stabilities of the resulting metal complexes.[39] Three other approaches can be exploited, which do not affect on the coordination ability of macrocyclic moiety. In the presented approaches in Figure 1, the functional group can be attached to (i) one of the pyridine carbon,[40–42] (ii) one of the carbons of the ethylene group of the macrocyclic chelator backbone,[43–47] and (iii) one of the α-positions to the carboxylic groups.[32,40,48–51] In our research, the 4-position of the pyridine ring was chosen for modification due to big synthetic facilities in obtaining the acyclic pyridine precursors. Also, we assumed that in this case the functional group should be sufficiently far away from the coordination cage to limit any interference with the coordination cage.

Synthetic methodology for building the skeletal backbone of pyridine-azacrown compound is the double amidation reaction[29,52–54] with high efficiency in the crucial macrocyclization step. Herein, we wish to demonstrate that this approach provides an easy access to new BFCs. Also, in this paper we suggest the ways for the further modification of the substituted pyridine ring in pyridine-azacrown ethers without destruction of macrocyclic unit. The BFCs, described in this report, display ester, carboxylic acid, alcohol, propargyl, chloride, or azide functions to be eventually used for conjugation and leave the carboxylate groups of macrocyclic moiety available for metal chelation.

Scheme 1 demonstrates the synthesis of a pyridine containing azacrown ethers **3a**,**b** with a methyl ester substituent in the 4-position of the pyridine ring. The aromatic ester was chosen because it can be easily transformed into a carboxylic acid, an amide, an alcohol, or into other compounds in good yields under mild conditions. Moreover, methyl ester can be selectively cleaved in the presence of *tert*-butyl esters using alkaline conditions of hydrolysis.



Scheme 1 *Reagents and conditions*: (a) CrO_3, H_2SO_4, 80 °C; (b) 1) $SOCl_2$, reflux, 2) MeOH, reflux; (c) triethylenetetramine, MeOH, RT (**2a**), tetraethylenepentamine, MeOH, RT (**2b**); (d) *tert*-butyl bromoacetate, K_2CO_3, MeCN, reflux; (e) 1 M NaOH, MeOH, RT

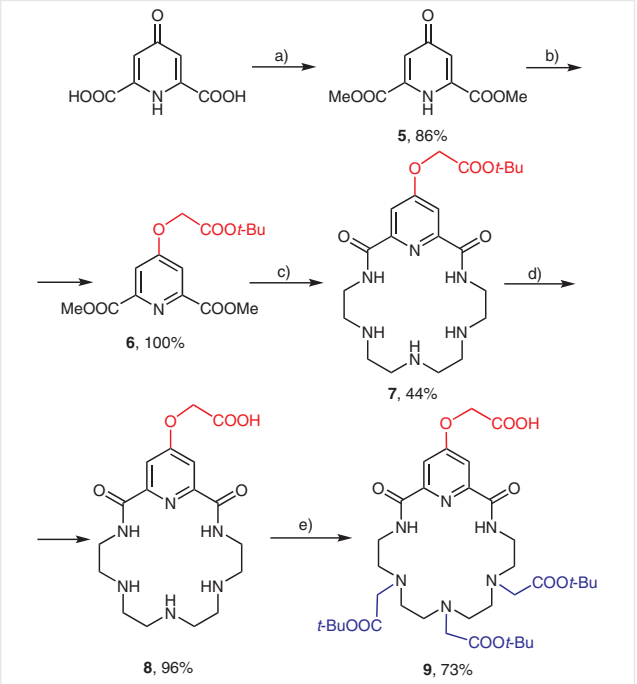
The trimethyl pyridine-2,4,6-tricarboxylate (**1**) was prepared from commercial 2,4,6-collidine in three steps according to the reported procedure[53] (Scheme 1): an oxidation by chromium oxide in sulfuric acid to pyridine-2,4,6-tricarboxylic acid, which was then transferred to the corresponding trimethyl ester **1** through the stage of the formation of acid chloride by action of thionyl chloride (overall yield is 40%).

The macrocyclization reaction between ester **1** and polyamines was carried out similarly to the synthesis of the unfunctionalized pyridine-azacrown compounds without use of any template agents and high-dilution technique. We used triethylenetetramine or tetraethylenepentamine to prepare 15- and 18-membered azacrown compounds in good overall yields (yields of **2a** and **2b** are 62% and 59% respectively).

It should be noted that the presence of additional ester groups in the 4-position of the pyridine ring did not have a noticeable negative effect on the process of macrocyclization if the yields of **2a**,**b** are compared with those of analogous unsubstituted pyridine containing azamacrocyclic compounds described earlier.[29] We propose that the pyridine nitrogen atom affects the formation of the macrocycle due to the formation of hydrogen bonds with polyamine. In any case, this does not exclude the possibility of side reactions occurring in the ester group located in the 4-position of the pyridine ring.

At the next stage, chelating groups were introduced into the macrocycle structure by alkylation of N-atoms with *tert*-butyl bromoacetate in acetonitrile. Hydrolysis of methyl ester was carried out selectively in methanol solution of 1 M NaOH at room temperature, since *tert*-butyl and amide groups were not affected under such conditions (yield 67%).

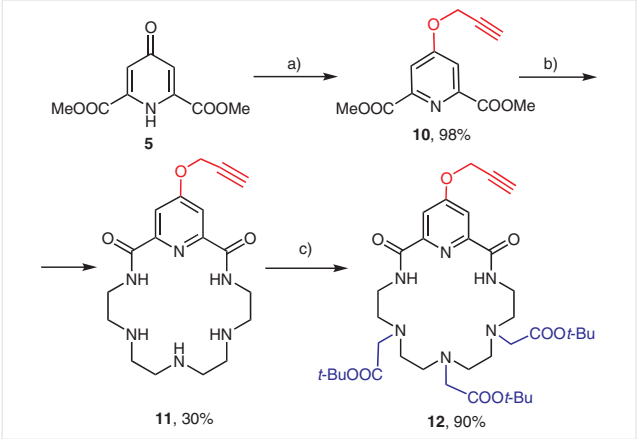
It is known that spacing between the radiometal chelate and the targeting vector affects the pharmacodynamics, affinity, and mode of excretion of the bioconjugate.[55] For obtaining the chelators with longer distance between macrocycle and COOH groups, the synthesis presented in Scheme 2 is proposed. Chelidamic acid was used as the starting compound, from which diester **5** was obtained with 86% yield.[56] The dimethyl chelidamate (**5**) in solution exists in two tautomeric forms (NH and OH), while the alkylation with *tert*-butyl bromoacetate quantitatively proceeds at the oxygen atom to form compound **6**.[57]



Scheme 2 *Reagents and conditions*: (a) 1) $SOCl_2$, reflux, 2) MeOH, reflux; (b) *tert*-butyl bromoacetate, K_2CO_3, MeCN, reflux; (c) tetraethylenepentamine, MeOH, RT; (d) H_2O, reflux; (e) *tert*-butyl bromoacetate, K_2CO_3, MeCN, reflux.

Macrocyclization gives azacrown compound **7** in 44% yield, the following hydrolysis of *tert*-butyl ester in boiling water without the addition of acid as catalyst results in **8** in high yield (Scheme 2). This convenient way to remove *tert*-butyl protection group was developed by us earlier,[30,58] it avoids the use of ion-exchange resin or other difficult methods for the purification of the target product. At the final stage, the chelating groups are introduced to obtain a bifunctional derivative **9** in 73% yield.

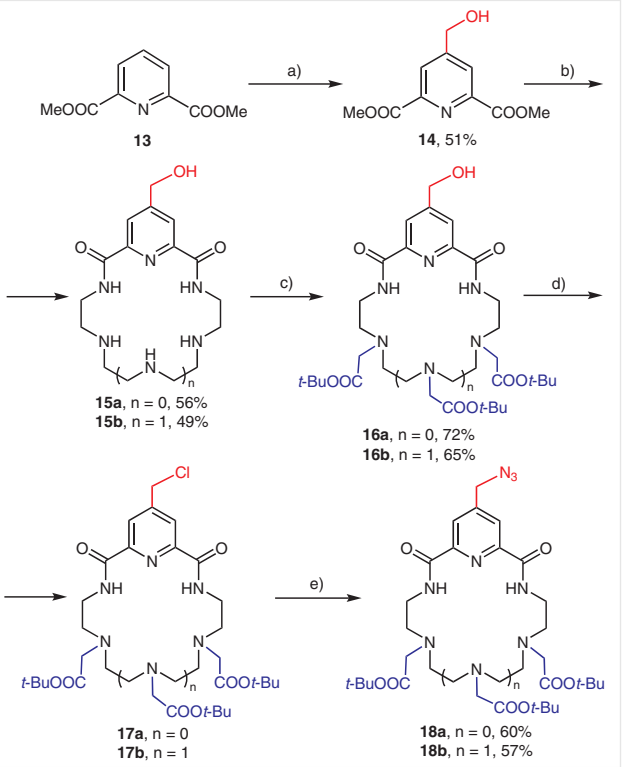
In order to prepare a bifunctional derivative available for a click chemistry approach, in particular for the 1,3-dipolar Huisgen cycloaddition between alkyne and azide functions,[59–63] we envisioned a synthetic way to a propargyl derivative **12** (Scheme 3). It includes alkylation of dimethyl chelidamate (**5**) with propargyl bromide resulting in **10**,[64] following macrocyclization giving **11** and alkylation with chelating *tert*-butyl acetate groups (Scheme 3).



Scheme 3 *Reagents and conditions*: (a) propargyl bromide, K_2CO_3, MeCN, reflux; (b) tetraethylenepentamine, MeOH, RT; (c) *tert*-butyl bromoacetate, K_2CO_3, MeCN, reflux.

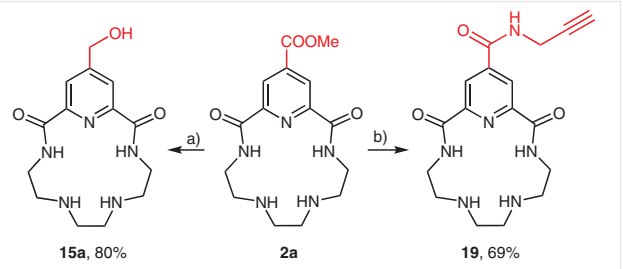
The alcohol group is of great practical interest, since it can be easily modified by replacing it with a halide and azide groups, which can be used for covalent binding of a chelator to various molecules.[17,65,66]

To introduce the hydroxymethyl group at the 4-position of the pyridine ring, in accordance with the literature method,[67] dimethyl 2,6-pyridinedicarboxylate (**13**) prepared from the corresponding acid[68] was oxidized using Fenton's reagent [H_2O_2, $Fe(ClO_4)_2$] in methanol in the presence of perchloric acid (Scheme 4). In this case, methanol plays the role of both a solvent and a reagent. After macrocyclization of the precursor **14** with polyamines and the introduction of chelating groups by alkylation with *tert*-butyl bromoacetate, the hydroxyl group of **15a**,**b** was replaced by chloride through the reaction with thionyl chloride. At the last stage, the obtained crude chloride products **17a**,**b** were reacted with sodium azide in acetonitrile to give the targeted azide derivatives **18a**,**b** in 60% and 57% yield, respectively.



Scheme 4 *Reagents and conditions*: (a) MeOH, H_2O_2, $Fe(ClO_4)_2$, $HClO_4$, H_2O; (b) triethylenetetramine, MeOH, RT (**15a**), tetraethylenepentamine, MeOH, RT (**15b**); (c) *tert*-butyl bromoacetate, K_2CO_3, MeCN, reflux; (d) $SOCl_2$, $CHCl_3$, RT; (e) NaN_3, NEt_3, MeCN, reflux.

In current research, we demonstrated that selective reduction of the methyl ester group with $NaBH_4$ is possible in the presence of the amide groups in macrocycle **2a** (Scheme 5). Thus, the reduction of **2a** with $NaBH_4$ in methanol gave hydroxyl derivative **15a** in high yield (80%). Besides, reaction of the ester derivative **2a** with an excess (9 equiv) of neat propargylamine yielded the derivative **19**.



Scheme 5 *Reagents and conditions*: (a) $NaBH_4$, MeOH, RT; (b) propargylamine, RT.

In conclusion, we have reported the synthesis of a series of bifunctional derivatives of pyridine-azacrown compounds bearing a free reactive functional group at the 4-position of the pyridine ring. The synthetic methodology developed herein provides a simple route to BFCs in high yields in the crucial macrocyclization step and suitable overall yields. Thanks to their free CO_2Me, CO_2H, C≡CH, OH, Cl, or N_3 groups, all the novel derivatives may undergo coupling reactions with a wide range of biological vectors to create bioconjugates capable of targeted drug delivery to cancer cells without damaging healthy tissue. The creation of the effective chelators for short half-life radionuclides is an extremely urgent task. Therefore, the obtained bifunctional derivatives have good prospects for practical application in the field of radiopharmaceuticals, since in vitro and in vivo studies of **L** have shown advantages over known analogues. Therefore, in the future, we plan to develop the synthesis of conjugates from the obtained BFCs of **L** with biomolecules and study their properties, in particular radionuclide labeling with ^{213}Bi, thermodynamic and kinetic stability, as well as biodistribution. In conclusion, it should be emphasized that the described approach to the synthesis of BFCs based on 15- and 18-membered pyridine-azacrown compounds can be considered as promising for preparing other macrocycles containing pyridine ring, since it was shown that the presence of various functional groups in 4-position of the pyridine ring does not interfere the macrocyclization reaction resulting in the desired derivatives. This greatly expands the possibilities of using this approach in the future.

All commercially available reagents were used without further purification. The progress of reactions was followed with TLC using silica gel (Macherey-Nagel, Alurgam Xtra Sil G/UV_{254}, 0.20 mm silica gel 60) and Al_2O_3 (Merck, 60 F_{254}, neutral). Trimethyl pyridine-2,4,6-tricarboxylate (**1**),[53] dimethyl chelidamate (**5**),[56] dimethyl 4-(2-*tert*-butoxy-2-oxoethoxy)pyridine-2,6-dicarboxylate (**6**),[57] dimethyl 4-(prop-2-ynyloxy)pyridine-2,6-dicarboxylate (**10**),[64] dimethyl 2,6-pyridinedicarboxylate (**13**),[68] and dimethyl 4-(hydroxymethyl)pyridine-2,6-dicarboxylate (**14**)[67] were synthesized following the literature procedures.

^1H and ^{13}C NMR spectra were recorded at 25 °C on Bruker Avance 400, Bruker Avance 500, and Bruker Avance 600 MHz spectrometers. Chemical shifts for ^1H and ^{13}C are reported in parts per million (δ) relative to deuterated solvent as an internal reference ($CDCl_3$ ^1H δ = 7.27 and ^{13}C δ = 77.00; D_2O δ = 4.75; CD_3CN ^1H δ = 1.94; DMSO-d_6 ^1H δ = 2.50 and ^{13}C δ = 39.51). Coupling constants (*J*) are given in hertz (Hz). Spectral assignments were based in part on the two-dimensional NMR experiments (^1H COSY, HSQC, and HMBC). Numbering of hydrogen and carbon nuclei used to describe the ^1H and ^{13}C NMR spectra is given in the Supporting Information. Electrospray ionization mass spectrometry (ESI-MS) analyses were performed using a Finnigan LCQ Advantage mass spectrometer equipped with an octopole ion-trap mass-analyzer, an MS Surveyor pump, a Surveyor auto sampler, a Schmidlin-Lab nitrogen generator (Germany), and Finnigan X-Calibur 1.3 software for data collecting and processing. Direct infusion of the sample solution was used. Positive electrospray ionization was achieved using an ionization voltage at 4.5 kV at a temperature of 200 °C. Electrospray full scan spectra in the range *m*/*z* 100–2000 were obtained by infusion at 0.05 mL·min^{-1} of 50 μM aqueous solutions of the compounds. Melting points were determined on a Mel-temp II apparatus in open capillary tubes. IR spectra were recorded from KBr

pellets on Magna IR (Nicolet) and Tensor 37 (Bruker) Fourier spectrometers. Elemental analyses were carried out on a Carlo Erba 1108 elemental analyzer.

Compound 2a

Compound **2a** was prepared according to a modified procedure.[29] A solution of triethylenetetramine (289 mg, 1.97 mmol) in MeOH (50 mL) was quickly added to a solution of triester **1** (500 mg, 1.97 mmol) in MeOH (100 mL) at RT. The mixture was stirred for 7 days and then the solvent was evaporated in vacuum. The crude product was recrystallized from MeCN to give **2a** as a beige solid; yield: 411 mg (62%); mp 205 °C (dec.).

^{1}H NMR (600.22 MHz, $CDCl_3$): δ = 2.84 (s, 4 H, H7), 2.95 (t, *J* = 5.7 Hz, 4 H, H6), 3.50 (q, *J* = 5.7 Hz, 4 H, H5), 3.99 (s, 3 H, H9), 8.74 (s, 2 H, H2), 9.11 (br s, 2 H, NH).

^{13}C NMR (150.93 MHz, $CDCl_3$): δ = 39.0 (C-5), 47.5 (C-6), 49.7 (C-7), 52.9 (C-9), 123.2 (C-2), 141.1 (C-1), 149.8 (C-3), 162.1 (C-4), 164.5 (C-8).

MS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{21}N_5O_4$ + H$^+$: 336.2; found: 336.4.

Anal. Calcd for $C_{15}H_{21}N_5O_4{\cdot}H_2O$: C, 53.33; H, 6.29; N, 13.33. Found: C, 53.33; H, 6.51; N, 12.98.

Compound 2b

Compound **2b** was obtained analogously to **2a** by using of triester **1** (500 mg, 1.97 mmol) and tetraethylenepentamine (374 mg, 1.97 mmol) in MeOH (150 mL). The crude product was recrystallized from MeCN to give **2b** as a beige solid; yield: 441 mg (59%); mp 204–207 °C.

^{1}H NMR (600.22 MHz, $CDCl_3$): δ = 2.76 (t, *J* = 4.6 Hz, 4 H, H8), 2.88 (t, *J* = 4.6 Hz, 4 H, H7), 2.92 (t, *J* = 5.0 Hz, 4 H, H6), 3.65 (q, *J* = 5.0 Hz, 4 H, H5), 4.01 (s, 3 H, H10), 8.43 (br s, 2 H, NH), 8.90 (s, 2 H, H2).

^{13}C NMR (150.93 MHz, $CDCl_3$): δ = 38.8 (C-5), 49.1 (C-6, C-7), 49.9 (C-8), 53.0 (C-10), 124.5 (C-2), 140.5 (C-1), 150.4 (C-3), 162.7 (C-4), 164.6 (C-9).

MS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{26}N_6O_4$ + H$^+$: 379.2; found: 379.6.

Anal. Calcd for $C_{17}H_{26}N_6O_4$: C, 53.96; H, 6.93; N, 22.21. Found: C, 53.82; H, 7.08; N, 22.31.

Compound 3a

A solution of *tert*-butyl bromoacetate (174 μL, 1.19 mmol) in MeCN (10 mL) was added to a mixture of **2a** (200 mg, 0.60 mmol) and K_2CO_3 (329 mg, 2.39 mmol) in MeCN (20 mL) and refluxed for 20 h. The solvent was evaporated under vacuum and the residue was dissolved in H_2O and extracted with $CHCl_3$. The crude product obtained by concentration of the combined organic extracts was purified by column chromatography (Al_2O_3, EtOAc). The product was obtained as a yellow oil; yield: 269 mg (80%).

^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 1.38 (s, 18 H, H13), 2.90 (s, 4 H, H7), 3.01 (t, *J* = 5.7 Hz, 4 H, H6), 3.25 (s, 4 H, H10), 3.50 (q, *J* = 5.1 Hz, 4 H, H5), 3.99 (s, 3 H, H9), 8.75 (s, 2 H, H2), 9.10 (br s, 2 H, NH).

^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 28.2 (C-13), 36.5 (C-5), 51.3 (C-6), 52.7 (C-10), 52.9 (C-9), 53.7 (C-7), 81.3 (C-12), 123.1 (C-2), 140.9 (C-1), 149.5 (C-3), 162.5 (C-4), 164.5 (C-8), 170.2 (C-11).

MS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{27}H_{41}N_5O_8$ + H$^+$: 564.3; found: 564.3.

Anal. Calcd for $C_{27}H_{41}N_5O_8$: C, 57.53; H, 7.33; N, 12.43. Found: C, 57.48; H, 7.38; N, 12.35.

Compound 3b

Compound **3b** was obtained analogously to **3a** by using of **2b** (350 mg, 0.92 mmol), *tert*-butyl bromoacetate (404 μL, 2.77 mmol), and K_2CO_3 (766 mg, 5.55 mmol) in MeCN (30 mL). The crude product obtained by concentration of the combined organic extracts was purified by column chromatography (Al_2O_3, EtOAc/EtOH 50:1). The product was obtained as a yellow oil; yield: 513 mg (77%).

^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 1.33 (s, 9 H, H16), 1.41 (s, 18 H, H12), 2.78 (br s, 4 H, H8), 2.82 (br s, 8 H, H6,7), 3.26 (s, 2 H, H13), 3.35 (s, 4 H, H9), 3.55 (br s, 4 H, H5), 3.99 (s, 3 H, H18), 8.84 (s, 2 H, H2).

^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 28.1 (C-16), 28.1 (C-12), 37.0 (C-5), 51.6 (C-7), 52.0 (C-6), 52.9 (C-18), 53.5 (C-9), 54.3 (C-13), 54.6 (C-8), 80.8 (C-15), 81.2 (C-11), 123.9 (C-2), 140.4 (C-1), 150.3 (C-3), 162.9 (C-4), 164.7 (C-17), 170.7 (C-14), 171.2 (C-10).

MS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{35}H_{56}N_6O_{10}$ + H$^+$: 721.4; found: 721.4; *m*/*z* [M + Na]$^+$ calcd for $C_{35}H_{56}N_6O_{10}$ + Na$^+$: 743.4; found: 743.2.

Anal. Calcd for $C_{35}H_{56}N_6O_{10}$: C, 58.32; H, 7.83; N, 11.66. Found: C, 58.29; H, 7.85; N, 11.65.

Compound 4

A solution of 1 M NaOH in MeOH (350 μL) was added to a solution of compound **3b** (250 mg, 0.35 mmol) in MeOH (8 mL) and the mixture was stirred at RT for 24 h. At first H_2O (10 mL) and then aq 0.2 M HCl (1.75 mL) were added to the mixture, and product was extracted with $CHCl_3$. The product **4** was purified by column chromatography (SiO_2, $CHCl_3$/EtOH 1:1) and obtained as a white solid; yield: 164 mg (67%); mp 152–154 °C.

IR (KBr): 3351 (NH), 2978–2862 (CH_2), 1730 (C=O, COO*t*Bu), 1675 (amide I), 1532 (amide II), 1155 cm^{-1} (C–O, COO*t*Bu).

^{1}H NMR (500.13 MHz, $CDCl_3$): δ = 1.15 (s, 9 H, H16), 1.39 (s, 18 H, H12), 2.74–3.56 (br s, 16 H, H5,6,7,8), 2.94 (s, 2 H, H13), 3.26 (s, 4 H, H9), 8.85 (s, 2 H, H2), 9.67 (br s, 2 H, NH).

^{13}C NMR (125.76 MHz, $CDCl_3$): δ = 27.6 (C-16), 28.1 (C-12), 36.9 (C-5), 49.1 (C-6), 50.6 (C-9), 52.0 (C-7), 53.7 (C-8), 56.1 (C-13), 81.4 (C-11), 82.5 (C-15), 124.2 (C-2), 146.7 (C-1), 149.8 (C-3), 164.1 (C-4), 168.2 (C-17), 169.7 (C-10), 170.2 (C-14).

MS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{34}H_{54}N_6O_{10}$ + H$^+$: 707.4; found: 707.3; *m*/*z* [M + Na]$^+$ calcd for $C_{34}H_{54}N_6O_{10}$ + Na$^+$: 729.4; found: 729.3; *m*/*z* [M + K]$^+$ calcd for $C_{34}H_{54}N_6O_{10}$ + K$^+$: 745.1; found: 745.3.

Anal. Calcd for $C_{34}H_{54}N_6O_{10}{\cdot}H_2O$: C, 56.34; H, 7.79; N, 11.59. Found: C, 56.19; H, 7.51; N, 11.38.

Compound 7

Compound **7** was obtained analogously to **2a** by using of **6** (500 mg, 1.54 mmol) and tetraethylenepentamine (291 mg, 1.54 mmol) in MeOH (150 mL). The product was purified by column chromatography (Al_2O_3, CH_2Cl_2/MeOH 10:1) and obtained as a yellow oil; yield: 305 mg (44%).

^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 1.48 (s, 9 H, H12), 2.82 (br s, 4 H, H8), 2.89 (br s, 8 H, H6,7), 3.63 (br s, 4 H, H5), 4.68 (s, 2 H, H9), 7.80 (s, 2 H, H2), 8.74 (br s, 2 H, NH).

^{1}H NMR (400.13 MHz, D_2O): δ = 1.4 (s, 9 H, H12), 2.79 (br s, 12 H, H6,7,8), 3.48 (br s, 4 H, H5), 4.69 (s, 2 H, H9), 7.42 (s, 2 H, H2).

^{13}C NMR (100.61 MHz, D_2O): δ = 27.2 (C-12), 38.6 (C-5), 46.5 (C-6), 46.7 (C-7), 47.1 (C-8), 65.7 (C-9), 84.9 (C-11), 110.8 (C-2), 150.0 (C-3), 164.6 (C-4), 166.4 (C-10), 168.7 (C-1).

MS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{34}N_6O_5$ + H$^+$: 451.3; found: 451.3.

Anal. Calcd for $C_{21}H_{34}N_6O_5$: C, 55.98; H, 7.61; N, 18.65. Found: C, 55.97; H, 7.63; N, 18.63.

Compound 8

H_2O (15 mL) was added to the crown compound **7** (200 mg, 0.44 mmol), and the mixture was refluxed for 12 h. The solution was washed with $CHCl_3$ and the aqueous layer was separated and concentrated under vacuum. The product was obtained as a beige solid; yield: 168 mg (96%); mp 285 °C (dec.).

^{1}H NMR (400.13 MHz, D_2O): δ = 2.92 (br s, 4 H, H8), 3.03 (br s, 4 H, H7), 3.06 (br s, 4 H, H6), 3.63 (br s, 4 H, H5), 4.68 (s, 2 H, H9), 7.26 (s, 2 H, H2).

^{13}C NMR (100.61 MHz, D_2O): δ = 36.2 (C-5), 45.3 (C-8), 48.4 (C-6), 48.5 (C-7), 67.3 (C-9), 111.0 (C-2), 149.2 (C-3), 164.4 (C-4), 167.5 (C-1), 176.1 (C-10).

MS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{26}N_6O_5$ + H$^+$: 395.2; found: 395.2.

Anal. Calcd for $C_{17}H_{26}N_6O_5{\cdot}2H_2O$: C, 47.43; H, 7.02; N, 19.52. Found: C, 47.39; H, 7.05; N, 19.50.

Compound 9

Compound **9** was obtained analogously to **3a** by using of **8** (100 mg, 0.25 mmol), *tert*-butyl bromoacetate (111 μL, 0.76 mmol) and K_2CO_3 (210 mg, 1.52 mmol) in MeCN (15 mL). The product was obtained as a yellow oil; yield: 136 mg (73%).

^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 1.43 (s, 18 H, H14), 1.48 (s, 9 H, H18), 2.80 (br s, 4 H, H8), 2.84 (br s, 8 H, H6,7), 3.27 (s, 2 H, H15), 3.36 (s, 4 H, H11), 3.54 (br s, 4 H, H5), 4.63 (s, 2 H, H9), 7.84 (s, 2 H, H2), 8.78 (br s, 2 H, NH).

^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 27.9 (C-18), 28.2 (C-14), 37.8 (C-5), 49.2 (C-6), 50.5 (C-11), 52.0 (C-7), 53.7 (C-8), 56.1 (C-15), 63.7 (C-9), 81.4 (C-13), 82.6 (C-17), 110.7 (C-2), 151.9 (C-3), 164.7 (C-4), 168.9 (C-1), 169.7 (C-12), 170.5 (C-16), 171.0 (C-10).

MS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{35}H_{56}N_6O_{11}$ + H$^+$: 737.4; found: 737.4.

Anal. Calcd for $C_{35}H_{56}N_6O_{11}{\cdot}H_2O$: C, 55.69; H, 7.74; N, 11.13. Found: C, 55.76; H, 7.80; N, 11.10.

Compound 11

Compound **11** was obtained analogously to **2a** by using of **10** (500 mg, 2.01 mmol) and tetraethylenepentamine (380 mg, 2.01 mmol) in MeOH (150 mL). The product was purified by column chromatography (Al_2O_3, CH_2Cl_2/EtOH 10:1) to afford **11** as a white solid; yield: 225 mg (30%); mp 156–159 °C.

^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 2.61 (t, *J* = 2.3 Hz, 1 H, H11), 3.07 (br s, 8 H, H7,8), 3.14 (br s, 4 H, H6), 3.65 (br s, 4 H, H5), 4.85 (d, *J* = 2.3 Hz, 2 H, H9), 7.82 (s, 2 H, H2), 9.51 (br s, 2 H, NH).

^{1}H NMR (400.13 MHz, D_2O): δ = 2.67 (br s, 9 H, H7,8,11), 2.76 (br s, 4 H, H6), 3.47 (br s, 4 H, H5), 4.72 (s, 2 H, H9), 7.36 (s, 2 H, H2).

^{13}C NMR (100.61 MHz, D_2O): δ = 38.8 (C-5), 47.1 (C-6), 47.2 (C-7), 47.5 (C-8), 56.6 (C-9), 76.4 (C-10,11), 110.9 (C-2), 149.8 (C-3), 164.6 (C-4), 166.1 (C-1).

MS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{26}N_6O_3$ + H$^+$: 375.2; found: 375.2.

Anal. Calcd for $C_{18}H_{26}N_6O_3{\cdot}H_2O$: C, 55.09; H, 7.19; N, 21.41. Found: C, 55.11; H, 7.23; N, 21.40.

Compound 12

Compound **12** was obtained analogously to **3a** by using of **11** (100 mg, 0.27 mmol), *tert*-butyl bromoacetate (117 μL, 0.80 mmol), and K_2CO_3 (221 mg, 1.60 mmol) in MeCN (15 mL). The product was obtained as a yellow oil; yield: 172 mg (90%).

IR (KBr): 3368 (NH), 2125 (C≡C), 1738 (C=O), 1678 (amide I), 1530 cm^{-1} (amide II).

^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 1.35 (s, 9 H, H19), 1.43 (s, 18 H, H15), 2.58 (t, *J* = 2.54 Hz, 1 H, H11), 2.79 (br s, 4 H, H8), 2.83 (br s, 8 H, H6,7), 3.27 (s, 2 H, H16), 3.36 (s, 4 H, H12), 3.54 (br s, 4 H, H5), 4.85 (d, *J* = 2.54 Hz, 2 H, H9), 7.90 (s, 2 H, H2), 8.82 (s, 2 H, NH).

^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 28.1 (C-19), 28.1 (C-15), 35.9 (C-5), 51.6 (C-9), 51.9 (C-7), 53.4 (C-6), 54.4 (C-16), 54.6 (C-12), 56.1 (C-8), 77.2 (C-11), 80.7 (C-10), 81.1 (C-14,18), 111.0 (C-2), 151.1 (C-3), 163.4 (C-4), 166.1 (C-1), 170.8 (C-17), 171.2 (C-13).

MS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{36}H_{56}N_6O_9$ + H$^+$: 717.4; found: 717.7; *m*/*z* [M + Na]$^+$ calcd for $C_{36}H_{56}N_6O_9$ + Na$^+$: 739.4; found: 739.3.

Anal. Calcd for $C_{36}H_{56}N_6O_9$: C, 60.32; H, 7.87; N, 11.72. Found: C, 60.33; H, 7.91; N, 11.68.

Compound 15a

Method A: Compound **15a** was obtained anlogous to **2a** by using of **14** (500 mg, 2.22 mmol) and triethylenetetramine (325 mg, 2.22 mmol) in MeOH (150 mL). The product was isolated as a beige solid; yield: 683 mg (56%).

Method B: $NaBH_4$ (14 mg, 0.36 mmol) was added to solution of **2a** (100 mg, 0.30 mmol) in anhyd MeOH (10 mL), and the mixture was refluxed for 5 h. H_2O was added to the mixture and the product was extracted with $CHCl_3$. Compound **15a** was obtained by concentration of the combined organic extracts as a beige solid; yield: 73 mg (80%); mp 225–228 °C.

^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 2.88 (s, 4 H, H7), 2.97 (t, *J* = 5.4 Hz, 4 H, H6), 3.51 (q, *J* = 5.4 Hz, 4 H, H5), 4.85 (s, 2 H, H8), 8.19 (s, 2 H, H2), 9.02 (br s, 2 H, NH).

^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 39.0 (C-5), 47.4 (C-6), 49.5 (C-7), 63.4 (C-8), 121.1 (C-2), 148.6 (C-3), 154.8 (C-1), 163.1 (C-4).

MS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{21}N_5O_3$ + H$^+$: 308.2; found: 308.1.

Anal. Calcd for $C_{14}H_{21}N_5O_3{\cdot}H_2O$: C, 51.68; H, 7.13; N, 21.52. Found: C, 51.64; H, 7.16; N, 21.50.

Compound 15b

Compound **15b** was obtained analogously to **2a** by using **14** (500 mg, 2.22 mmol) and tetraethylenepentamine (420 mg, 2.22 mmol) in MeOH (150 mL). The product was obtained as a yellow oil; yield: 436 mg (49%).

^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 2.77 (m, 4 H, H8), 2.87 (m, 8 H, H6,7), 3.34 (br s, 4 H, H5), 4.74 (s, 2 H, H9), 8.18 (s, 2 H, H2), 8.32 (br s, 2 H, NH).

^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 38.7 (C-5), 48.7 (C-6), 48.7 (C-7), 49.2 (C-8), 62.5 (C-9), 122.0 (C-2), 148.7 (C-3), 155.0 (C-1), 163.5 (C-4).

MS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{26}N_6O_3$ + H$^+$: 351.2; found: 351.3.

Anal. Calcd for $C_{16}H_{26}N_6O_3{\cdot}H_2O$: C, 52.16; H, 7.66; N, 22.81. Found: C, 52.20; H, 7.71; N, 22.83.

Compound 16a

Compound **16a** was obtained analogously to **3a** by using of **15a** (300 mg, 0.98 mmol), *tert*-butyl bromoacetate (285 μL, 1.95 mmol), and K_2CO_3 (539 mg, 3.91 mmol) in MeCN (30 mL). The product was purified by column chromatography (Al_2O_3, EtOAc/EtOH 25:1) to give a light-yellow oil; yield: 377 mg (72%).

^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 1.38 (s, 18 H, H12), 2.91 (s, 4 H, H7), 3.01 (t, *J* = 5.4, 5.7 Hz, 4 H, H6), 3.25 (s, 4 H, H9), 3.47 (q, *J* = 5.1 Hz, 4 H, H5), 4.84 (s, 2 H, H8), 8.26 (s, 2 H, H2), 9.08 (br s, 2 H, NH).

^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 28.0 (C-12), 36.4 (C-5), 51.2 (C-6), 52.6 (C-9), 53.5 (C-7), 63.1 (C-8), 81.3 (C-11), 121.2 (C-2), 148.2 (C-3), 151.2 (C-1), 163.6 (C-4), 170.2 (C-10).

MS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{26}H_{41}N_5O_7$ + H$^+$: 536.3; found: 536.1; *m*/*z* [M + Na]$^+$ calcd for $C_{26}H_{41}N_5O_7$ + Na$^+$: 558.3; found: 558.1.

Anal. Calcd for $C_{26}H_{41}N_5O_7$: C, 58.30; H, 7.72; N, 13.07. Found: C, 58.28; H, 7.78; N, 13.05.

Compound 16b

Compound **16b** was obtained analogously to **3a** by using of **15b** (300 mg, 0.86 mmol), *tert*-butyl bromoacetate (374 μL, 2.57 mmol), and K_2CO_3 (709 mg, 5.14 mmol) in MeCN (40 mL). The product was purified by column chromatography (Al_2O_3, EtOAc/EtOH 25:1) and obtained as a light-yellow oil; yield: 386 mg (65%).

^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 1.34 (s, 9 H, H17), 1.42 (s, 18 H, H13), 2.79–2.86 (m, 12 H, H6,7,8), 3.25 (s, 2 H, H14), 3.36 (s, 4 H, H10), 3.54 (br s, 4 H, H5), 4.85 (s, 2 H, H9), 8.37 (s, 2 H, H2), 8.90 (br s, 2 H, NH).

^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 28.0 (C-17), 28.1 (C-13), 36.9 (C-5), 51.6 (C-7), 51.8 (C-6), 53.4 (C-10), 54.4 (C-14), 54.6 (C-8), 63.2 (C-9), 80.8 (C-16), 81.2 (C-12), 122.1 (C-2), 149.0 (C-3), 154.2 (C-1), 164.0 (C-4), 170.8 (C-15), 171.2 (C-11).

MS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{34}H_{56}N_6O_9$ + H$^+$: 693.4; found: 693.2.

Anal. Calcd for $C_{34}H_{56}N_6O_9$: C, 58.94; H, 8.15; N, 12.13. Found: C, 58.90; H, 8.18; N, 12.10.

Compound 18a

$SOCl_2$ (0.5 mL) was added to a solution of **16a** (50 mg, 0.09 mmol) in $CHCl_3$ (5 mL), and the mixture was stirred at RT for 4 h. The solvent was evaporated under vacuum to yield the chloride **17a**. NaN_3 (9 mg, 0.14 mmol) was added to a solution of **17a** in MeCN (5 mL) and NEt_3 (100 μL, 0.72 mmol) was added dropwise to the mixture. The reaction mixture was refluxed for 18 h and concentrated under vacuum. The residue was dissolved in H_2O and extracted with $CHCl_3$. After concentration of the combined organic extracts, the product **18a** was obtained as a yellow oil; yield: 31 mg (60%).

^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 1.41 (s, 18 H, H12), 2.93 (s, 4 H, H7), 3.03 (t, *J* = 5.2 Hz, 4 H, H6), 3.27 (s, 4 H, H9), 3.51 (q, *J* = 5.2 Hz, 4 H, H5), 4.57 (s, 2 H, H8), 8.21 (s, 2 H, H2), 9.12 (br s, 2 H, NH).

^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 27.8 (C-12), 36.5 (C-5), 47.7 (C-8), 50.9 (C-6), 52.5 (C-9), 53.6 (C-7), 81.3 (C-11), 123.2 (C-2), 149.9 (C-3), 152.0 (C-1), 163.4 (C-4), 170.9 (C-10).

MS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{26}H_{40}N_8O_6$ + H$^+$: 561.3; found: 561.2.

Anal. Calcd for $C_{26}H_{40}N_8O_6$: C, 55.70; H, 7.19; N, 19.99. Found: C, 55.75; H, 7.15; N, 19.98.

Compound 18b

Compound **18b** was obtained analogously to **18a** by using of **16b** (200 mg, 0.29 mmol), $SOCl_2$ (1 mL) in $CHCl_3$ (10 mL), NaN_3 (281 mg, 4.33 mmol), and NEt_3 (321 μL, 2.31 mmol) in MeCN (25 mL). The product **18b** was obtained as a yellow oil; yield: 118 mg (57%).

IR (KBr): 3370 (NH), 2106 (N_3), 1730 (C=O), 1674 (amide I), 1532 cm^{-1} (amide II).

^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 1.35 (s, 9 H, H17), 1.43 (s, 18 H, H13), 2.81 (br s, 4 H, H8), 2.85 (br s, 8 H, H6,7), 3.28 (s, 2 H, H14), 3.36 (s, 4 H, H10), 3.57 (br s, 4 H, H5), 4.55 (s, 2 H, H9), 8.29 (s, 2 H, H2), 8.88 (br s, 2 H, NH).

^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 28.0 (C-17), 28.2 (C-13), 36.9 (C-5), 47.8 (C-9), 51.5 (C-7), 52.8 (C-6), 53.3 (C-10), 54.2 (C-14), 56.2 (C-8), 81.2 (C-16), 81.4 (C-12), 123.1 (C-2), 149.8 (C-3), 151.7 (C-1), 163.5 (C-4), 170.6 (C-15), 171.2 (C-11).

MS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{34}H_{55}N_9O_8$ + H$^+$: 718.4; found: 718.3.

Anal. Calcd for $C_{34}H_{55}N_9O_8$: C, 56.89; H, 7.72; N, 17.83. Found: C, 56.96; H, 7.80; N, 17.79.

Compound 19

Crown compound **2a** (115 mg, 0.34 mmol) was dissolved in propargylamine (200 μL), and the mixture was stirred at RT for 6 days. Then MeCN was added to the mixture and the formed precipitate was collected by filtration and dried to afford the product **19** as a beige solid; yield: 85 mg (69%); mp 280 °C (dec.).

^{1}H NMR (400.13 MHz, CD_3CN): δ = 2.50 (t, *J* = 2.5 Hz, 1 H, H11), 2.75 (s, 4 H, H7), 2.87 (t, *J* = 5.7 Hz, 4 H, H6), 3.38 (q, *J* = 5.7 Hz, 4 H, H5), 4.15–4.17 (m, 2 H, H9), 8.47 (s, 2 H, H2), 9.19 (br s, 2 H, NH).

^{1}H NMR (400.13 MHz, DMSO-d_6): δ = 2.7 (s, 4 H, H7), 2.81 (t, *J* = 5.1 Hz, 4 H, H6), 3.16 (t, *J* = 2.2, 2.5 Hz, 1 H, H11), 3.35 (q, *J* = 5.1 Hz, 4 H, H5), 4.10 (q, *J* = 2.2, 2.5 Hz, 2 H, H9), 8.54 (s, 2 H, H2), 9.28 (t, *J* = 4.1, 4.5 Hz, 2 H, NH), 9.28 (t, *J* = 5.1 Hz, 1 H, NH).

^{13}C NMR (100.61 MHz, DMSO-d_6): δ = 29.0 (C-9), 38.7 (C-5), 47.2 (C-6), 49.1 (C-7), 73.4 (C-11), 80.6 (C-10), 121.1 (C-2), 144.6 (C-1), 149.8 (C-3), 162.1 (C-8), 163.4 (C-4).

MS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{22}N_6O_3$ + H$^+$: 359.2; found: 359.2.

Anal. Calcd for $C_{17}H_{22}N_6O_3$·MeOH: C, 55.37; H, 6.71; N, 21.52. Found: C, 55.87; H, 6.52; N, 21.54.

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Supporting Information

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