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Functionalized N-Aryl-Substituted Cyclens by Nucleophilic Aromatic Substitution

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Abstract: The reaction of trifold protected cyclen with fluorinated dinitroarenes yields aryl-substituted or aryl-bridged cyclen derivatives in good yield. The two arene nitro groups, necessary for the nucleophilic aromatic substitution, are subsequently selectively reduced to amines and further functionalized by amide formation. As an example, a cyclen derivative bearing a heterocyclic oligoamide with potential DNA binding ability was prepared.

Keywords: Azamacrocycles, DNA binding, ionophore, nucleophilic aromatic substitution

INTRODUCTION

Metal complexes with open coordination sites have found wide use in molecular recognition. They serve as binding sites in the development of chemosensors,[1] study metalloenzyme function in bioinorganic chemistry,[2] or direct supramolecular self-assembly.[3] Metal complexes of cyclen are particular useful because of their high binding affinity to many transition metal ions, the kinetic inertness and high stability of many of their metal complexes, and the variety of methods for functionalization of the ligand. Starting from the commercially available parent cyclen macrocycle, alkylation,[4] acylation,[5] and arylation[6] of the nitrogen atoms in a regioselective

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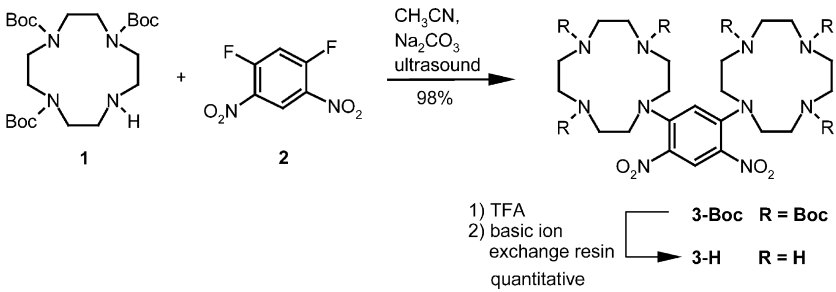
manner using peptide protecting groups has been described. In this article, we describe the extension of cyclen arylation by nucleophilic aromatic substitution to the preparation of selectively functionalized arene substituents.

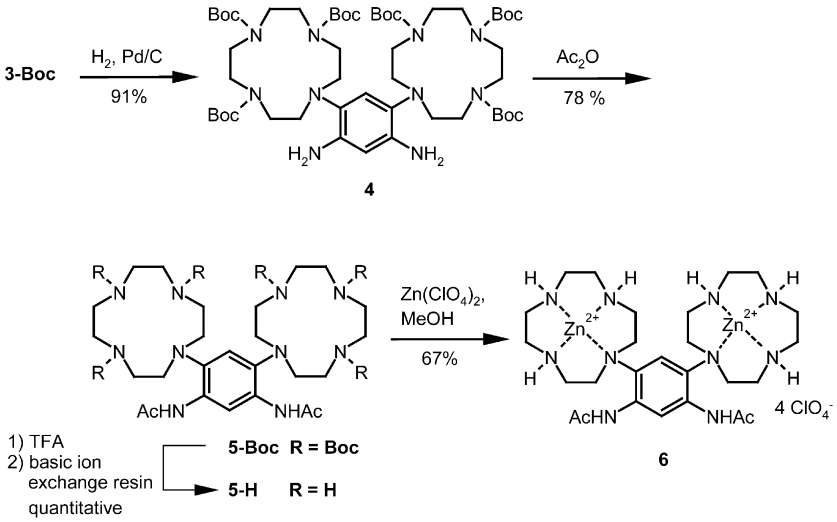
RESULTS AND DISCUSSION

Koike et al.[7] have reported the reaction of a threefold protected cyclen with Sangers reagent, 2,4-dinitrofluorobenzene. This reaction can be extended to difluoro-dinitrobenzene (**2**), giving aryl-bridged bis-cyclen (**3-Boc**) in nearly quantitative yield. The use of ultrasound to promote the reaction is advantageous. Boc protecting groups are removed quantitatively by trifluoroacetic acid (TFA), and elution from a basic ion-exchange resin gives ligand **3-H** (Scheme 1). Alternatively, reduction of the nitro groups in **3-Boc** by hydrogenation on Pd/C yields **4**, which now allows further functionalization, for example by acylation giving **5-Boc**. Deprotection with TFA and elution from basic ion-exchange resin as described for **3-Boc** gives ligand **5-H**, which was transformed into bis-zinc(II) complex **6** to illustrate its metal ion complexing properties (Scheme 2).

The reaction of compound **1** with 2,4-dinitrofluorobenzene (**7**) also benefits from ultrasound agitation, and **8-Boc** is obtained in nearly quantitative yield. Deprotection with TFA affords **8-H**, and reduction of both nitro substituents gives **9-Boc** (Scheme 3). A reduction of one of the nitro groups, leaving the other untouched, is possible using milder reduction conditions. Method A, according to a previously published procedure by Chambers,[8] uses six equivalents of sulphur and sodium sulphide in water/ethanol. After 30 min, the starting material was completely converted and **11-Boc** obtained as the major reaction product. Nearly equal amounts of **10-Boc** and **9-Boc** were isolated as side products. Method B employs Pd/C and triethylammonium formiate as reducing agent in acetonitrile under reflux. These conditions give diamino compound **9-Boc** as the major product and the nitro amino compounds **10-Boc** and **11-Boc** in only 28 and 12% yield, respectively (Scheme 4).



Scheme 1.

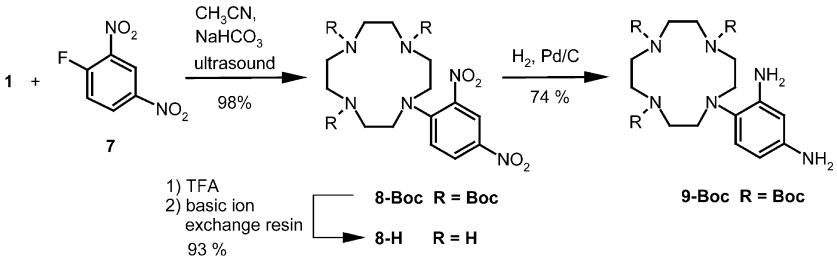


Scheme 2.

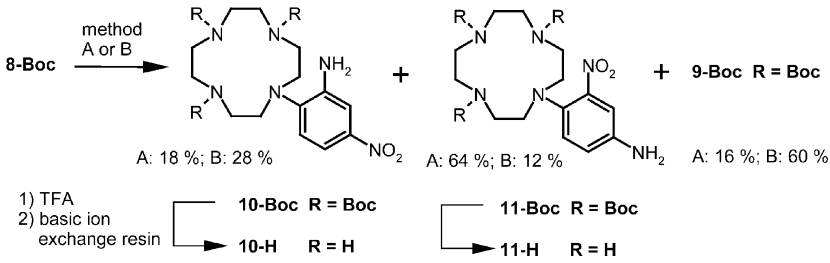
The isomers **10-Boc** and **11-Boc** were assigned from their aromatic proton chemical shifts by comparison with calculated increment values. In particular, the chemical shift of proton H-5 is indicative. Table 1 summarizes the measured and calculated chemical shifts, which are in very good agreement.

The reduction of the nitro groups is reflected in changes of the absorption spectra of the compounds. Figure 1 shows the UV absorption spectra of **8-Boc**, **10-Boc**, and **11-Boc**, in acetonitrile. The longest wavelength absorption of **10-Boc** shifts 26 nm bathochromic compared to **8-Boc**, and the extinction coefficient of **11-Boc** at 391 nm (lg $\varepsilon = 3.44$) is much weaker that that of **10-Boc** (397 nm, lg $\varepsilon = 4.14$).

Deprotection of **10-Boc** and **11-Boc** with TFA gave amines **10-H** and **11-H**. To probe the effect of the isomeric position of nitro and amino groups on the protonation equilibria of the cyclen nitrogen atoms, the pK_a values were determined by potentiometric titration. The data (**10-H**: lg



Scheme 3.



Scheme 4.

$K_1 = 10.74 \pm 0.03$; lg $K_2 = 8.13 \pm 0.05$; **11-H**: lg $K_1 = 10.42 \pm 0.04$; lg $K_2 = 8.20 \pm 0.06$; for comparison, **8-H**: lg $K_1 = 11.04 \pm 0.05$; lg $K_2 = 9.86 \pm 0.03$) (lg K_3 and lg K_4 for all systems <2) showed no or very little effect of the position of the arene substituents on the cyclen p*K*a values.

To demonstrate the use of compounds **10-Boc** and **11-Boc** in the synthesis of functionalized cyclens, we describe the preparation of cobalt complex **14**, with potential DNA binding ability (Scheme 5). Compound **11-Boc** was coupled with dipyrrole **12** using standard peptide coupling conditions. Dipyrrol **12** is a substructure found in natural DNA binding agents, such as distamycin or netropsin.[9] Compound **13-Boc**, isolated in 82% yield, was deprotected to **13-H** and transformed into the target complex **14**. Preliminary DNA binding studies showed high affinity of **14** to dDNA in an ethidium bromide displacement assay.[10]

EXPERIMENTAL

General

Solvents and chemicals were purified and dried according to standard laboratory procedures. If not otherwise stated, commercially available solvents of the highest purity were used. UV-VIS spectra were measured using a

Table 1. Calculated and observed chemical shifts of compounds **8-Boc**, **10-Boc**, and **11-Boc** (400 MHz, $CDCl_3$, TMS as internal standard)

	8-Boc		**10-Boc**		**11-Boc**	
Proton	$\delta_{calcd.}$	$\delta_{observed}$	$\delta_{calcd.}$	$\delta_{observed}$	$\delta_{calcd.}$	$\delta_{observed}$
H-6	7.12	7.17	6.61	6.98	6.61	7.08
H-5	8.41	8.20	7.38	7.58	6.71	6.77
H-3	8.98	8.56	7.28	7.54	7.28	6.90

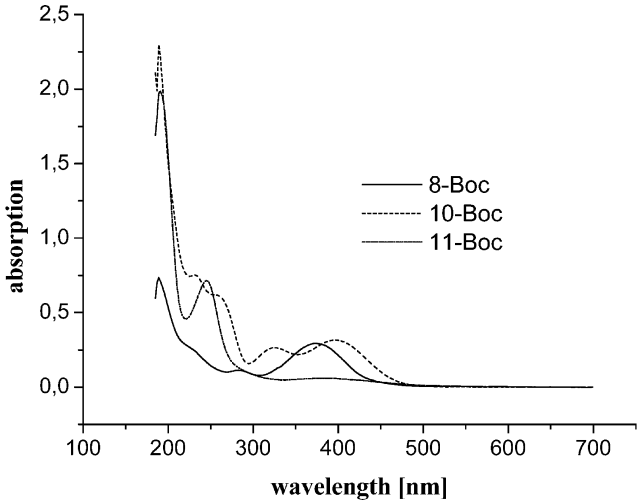
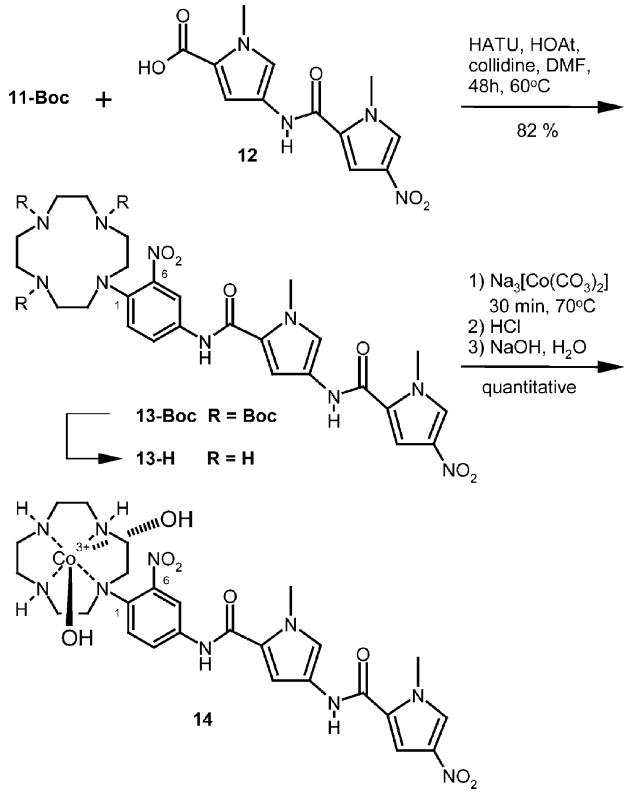


Figure 1. UV/vis spectra of **8-Boc** (3), **10-Boc** (11), and **11-Boc** (12) ($c = 2 \cdot 10^{-5}$ mol/L) in acetonitrile.

Varian Cary BIO 50 UV/VIS/NIR spectrometer, with a 1-cm quartz cell (Hellma) and Uvasol solvents (Merck), reported as λ_{max} in nm (ε). IR spectra were measured using a Bio-Rad FT-IR spectrometer FTS 155. NMR spectra were measured using a Bruker Avance 300 (^{1}H: 300.1 MHz, ^{13}C: 75.5 MHz) and Bruker Avance 600 (^{1}H: 600.1 MHz, ^{13}C: 150.1 MHz). The chemical shifts are in δ values relative to the internal (or external) standard TMS and are reported as chemical shift (multiplicity, coupling constant, number of protons, assignment). Mass spectra were measured using a Varian CH-5 (EI), Finnigan MAT 95 (CI; FAB and FD), and Finnigan MAT TSQ 7000 (ESI). Melting points are uncorrected and were determined according to Tottoli using instrumentation from Büchi. The microanalytical laboratory of the School of Chemistry and Pharmacy, University of Regensburg, determined all elemental analyses. CC means column chromatography; PE means petrol ether with a boiling range from 60 to 70 °C, and EA means ethyl acetate.

Potentiometric Titrations

Potentiometric titrations were performed in aqueous 0.1 M tetraethyl ammonium perchlorate solution to assure a constant ionic strength of $I = 0.1$. Tetraethylammonium hydroxide (0.1 M) was added as base by an automatic burette (Dosimat 665 bzw. 765, Metrohm) at 25°C to a solution hold at the same temperature. The base solution was calibrated with sodium



Scheme 5.

phthalate. A microprocessor pH meter (pH 3000, WTW, Wiss.-tech. Werkstätten Weilheim) recorded the pH values during titration. The self-dissociation of water log K_w was calculated from titration of 0.1 M perchloric acid, and the program Hyperquad 2000 (vers. 2.1) was used to determine pK_a values.[11]

The following solution equilibria were considered for data fitting:

$$[\mathbf{L}] + \mathrm{H}^+ \overset{\log K_1}{\rightleftharpoons} \mathrm{H}[\mathbf{L}]^+ \quad (1)$$

$$\mathrm{H}[\mathbf{L}]^+ + \mathrm{H}^+ \overset{\log K_2}{\rightleftharpoons} \mathrm{H}_2[\mathbf{L}]^{2+} \quad (2)$$

$$\mathrm{H}_2[\mathbf{L}]^{2+} + \mathrm{H}^+ \overset{\log K_3}{\rightleftharpoons} \mathrm{H}_3[\mathbf{L}]^{3+} \quad (3)$$

$$\mathrm{H}_3[\mathbf{L}]^{3+} + \mathrm{H}^+ \overset{\log K_4}{\rightleftharpoons} \mathrm{H}_4[\mathbf{L}]^{4+} \quad (4)$$

Synthesis of Compounds

1,3-Bis-(1,4,7-tris[tert-butyloxycarbonyl]-1,4,7,10-tetraaza-cyclododecane)-4,6-dinitro-benzene (**3-Boc**): $NaHCO_3$ (0.45 g, 5.33 mmol) was suspended in dry acetonitrile (30 mL) by sonification using an ultrasound bath under dinitrogen atmosphere at 30°C for 20 min. 1,3-Difluoro-4,6-dinitrobenzene (0.26 g, 1.27 mmol) and tri-*tert*-butyl 1,4,7,10-tetraaza cyclododecan-1,4,7-tricarbonate (1.20 g, 2.54 mmol) were added, and the reaction mixture was sonicated for 18 h at 30°C. Monitoring of the reaction shows quantitative formation of a monosubstituted derivative ($R_f = 0.48$, EA/PE = 1:1) after 90 min. After complete reaction, acetonitrile (30 mL) was added, and the mixture was filtered to remove insoluble salts. The solvent was removed and CC on silica gel (EA/PE = 1:1) gave 1.39 g (98%) **3-Boc** ($R_f = 0.22$, EE/PE = 1:1), mp 105°C. IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 2974, 2932, 1703, 1561, 1366, 1164, 859, 776; UV/Vis (CH_3CN): λ_{max} (nm) (lg ε) = 229 (4.206), 365 (4.239); ^1H NMR (250 MHz, $CDCl_3$): $\delta = 1.41$ (s, 36H, CH_3-Boc), 1.44 (s, 18H, CH_3-Boc), 3.39–3.55 (m, 32H, CH_2-cyclen), 6.59 (bs, 1H, CH 1), 8.44 (s, 1H, CH 4); ^{13}C NMR (63 MHz, $CDCl_3$): $\delta = 28.4$, 28.5 (+, CH_3-Boc), 47.6, 49.5, 50.5, 51.4 (−, CH_2-cyclen), 80.3, 80.4 (C_{quat}, C-Boc), 106.9 (+, C_{aryl}-H 1), 129.0 (+, C_{aryl}-H 4), 130.9 (C_{quat}, C_{aryl}-N 2 and 6), 149.1 (C_{quat}, C_{aryl}-N 3 and 5), 156.4, 156.6 (C_{quat}, C=O Boc); MS (ESI, CH_2Cl_2/MeOH + 1% AcOH): m/z (%) = 1109 (100) $[MH]^+$, 1009 (20) $[MH\text{-Boc}]^+$; elemental analysis ($C_{52}H_{88}N_{10}O_{16}$): calcd. C, 56.30; H, 8.00; N, 12.63; found: C, 55.85; H, 7.94; N, 11.98.

1,3-Di-(1,4,7,10-tetraaza cyclododecane-1-yl)-4,6-dinitrobenzene (**3-H**): Compound **3-Boc** (1.97 g, 1.78 mmol) was dissolved in CH_2Cl_2 (40 mL), trifluoro acetic acid (TFA) (11.5 mL, 17.02 g, 149.3 mmol) was added, and the reaction mixture stirred for 16 h at room temp. Solvent and excess TFA were removed in vacuum to give 2.13 g (quantitative) 1,3-bis-(10-aza-1,4,7-hexaazonium-cyclododec-10-yl)-4,6-dinitrobenzene hexakis-trifluoroacetate as a yellow solid, mp 125–127°C. IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 3431, 2991, 2872, 1572, 1194, 857, 774; UV/Vis (CH_3CN): λ_{max} (nm) (lg ε) = 223 (3.932), 361 (4.161); ^1H NMR (400 MHz, CD_3CN): $\delta = 3.02$–3.05 (m, 8H, CH_2-cyclen), 3.12–3.21 (m, 16H, CH_2-cyclen), 3.46–3.48 (m, 8H, CH_2-cyclen), 7.18 (bs, 12H, NH_2^+), 7.80 (s, 1H, CH 2), 8.56 (s, 1H, CH 5); ^{13}C NMR (100 MHz, CD_3CN): $\delta = 43.5$, 44.9, 46.5, 51.1 (−, CH_2-cyclen), 117.1 (C_{quat}, q, $^1J_{C,F} = 290.0$ Hz, CF_3COO^-), 127.2 (+, C_{aryl}-H 5), 130.8 (+, C_{aryl}-H 2), 143.8, 148.7 (C_{quat}, C_{aryl}-N), 160.9 (C_{quat}, q, $^2J_{C,F} = 36.7$ Hz, CF_3COO^-); MS (ESI, MeOH + 1% AcOH): m/z (%) = 509 (100) $[M^{6+} - 5H]^+$, 255 (90) $[M^{6+} - 4H]^{2+}$.

The obtained salt (1.56 g, 1.31 mmol) was dissolved in water (30 mL) and eluated over 90 mL of a strong basic ion-exchange resin (OH^- capacity: 0.9 mmol/mL) with 200 mL of water and 50 mL of CH_3CN. The organic solvent was removed from the combined eluates and the aqueous phase was

lyophilized yielding 0.67 g (quantitative) of **3-H** as a yellow solid; mp 91°C. IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 3411, 2926, 2848, 1599, 1558, 1348, 1282, 1118, 823, 761; UV/Vis (CH_3CN): λ_{max} (nm) (lg ε) = 230 (4.575), 368 (4.188); ^1H NMR (300 MHz, $CDCl_3$): δ = 2.36 (bs, 6H, NH), 2.57–2.61 (m, 8H, CH_2-cyclen), 2.66–2.74 (m, 16H, CH_2-cyclen), 3.31–3.38 (m, 8H, CH_2-cyclen), 7.58 (s, 1H, CH 2), 8.22 (s, 1H, CH 5); (300 MHz, CD_3CN): δ = 2.58–2.60 (m, 8H, CH_2-cyclen), 2.67–2.72 (m, 8H, CH_2-cyclen), 2.75–2.91 (m, 14H, CH_2-cyclen und NH), 3.36–3.40 (m, 8H, CH_2-cyclen), 7.65 (s, 1H, CH 2), 8.23 (s, 1H, CH 5); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 46.1, 46.3, 47.8, 49.4 (−, CH_2-cyclen), 120.2 (+, C_{aryl}-H 2), 125.4 (+, C_{aryl}-H 5), 136.0, 149.1 (C_{quat}, C_{aryl}-N); (75 MHz, CD_3CN): δ = 46.5, 47.2, 48.8, 53.2 (−, CH_2-cyclen), 121.4 (+, C_{aryl}-H 2), 126.8 (+, C_{aryl}-H 5), 136.0, 149.5 (C_{quat}, C_{aryl}-N); MS (ESI, MeOH/CH_2Cl_2 + 1% AcOH): m/z (%) = 255 (100) $[M + 2\ H]^{2+}$, 509 (70) $[MH]^+$, 1017 (3) $[2M + H]^+$; HRMS ($C_{22}H_{41}N_{10}O_4$): calcd. 509.3312 $[MH]^+$, found: 509.3317 $[MH]^+$ ± 1.02 ppm.

1,3-Bis-(1,4,7-tris[tert-butyloxycarbonyl]-1,4,7,10-tetraazacyclododecane)-4,6-diamino-benzene (**4**): After dissolving **3-H** (2 g, 1.81 mmol) in dry ethanol (25 mL), 0.50 g of Pd/C (10% palladium) were added and the mixture was pressurized with 10 bar dihydrogen for 48 h at room temp. The catalyst was filtered off over Celite® and washed with ethanol. The combined solvents were evaporated in vacuum, and the remaining crude product was purified by CC on silica gel (EA/PE = 1:1) yielding **4** (1.73 g, 91%; (R_f = 0.12, EA/PE = 1:1) as a yellow solid, mp 93°C. IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 3466, 3364, 2975, 2931, 1698, 1463, 1248, 1176, 861, 774; UV/Vis (CH_3CN): λ_{max} (nm) (lg ε) = 212 (4.471), 249 (3.905), 316 (3.763); ^1H NMR (300 MHz, $CDCl_3$): δ = 1.41 (s, 36H, CH_3-Boc), 1.49 (s, 18H, CH_3-Boc), 2.85–3.01 (m, 8H, CH_2-cyclen), 3.24–3.35 (m, 8H, CH_2-cyclen), 3.43–3.72 (m, 16H, CH_2-cyclen), 6.10 (s, 1H, CH 5), 6.69 (s, 1H, CH 2); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 28.4, 28.6 (+, CH_3-Boc), 47.0, 49.4, 53.4 (−, CH_2-cyclen), 79.7, 79.8 (C_{quat}, C-Boc), 103.5 (+, C_{aryl}-H 5), 114.4 (+, C_{aryl}-H 2), 128.0, 140.6 (C_{quat}, C_{Aryl}-N), 155.7, 156.2 (C_{quat}, C=O Boc); MS (ESI, MeOH/CH_2Cl_2 + 1% AcOH): m/z (%) = 1050 (100) $[MH]^+$, 950 (5) $[MH\text{-Boc}]^+$; elemental analysis ($C_{52}H_{92}N_{10}O_{12}$): calcd. C, 59.52; H, 8.84; N, 13.35; found: C, 59.20; H, 8.79; N, 13.28.

1,3-Bis-(1,4,7-tris[tert-butyloxycarbonyl]-1,4,7,10-tetraazacyclododecane)-4,6-di-(acetyl-amino)-benzene (**5-Boc**): Compound **4** (1.20 g, 1.14 mmol) was dissolved in CH_2Cl_2 (50 mL) and freshly distilled (from P_2O_5) acetic anhydride (430 µl, 0.47 g, 4.56 mmol) was added. The reaction mixture was stirred for 24 h at room temp. under nitrogen, the solvent and excess acetic anhydride were removed in vacuum, and the crude product was purified by CC on silica gel (EA/PE = 4 : 1) to give **5-Boc** (1.01 g, 78%) as a yellow solid (R_f = 0.21, EA), mp 106–108°C. IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 3508, 3372, 2976, 2932, 1703, 1523, 1247, 1163, 860, 773; UV/Vis (CH_3CN): λ_{max}

(nm) (lg ε) = 253 (3.985), 349 (3.634); ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.32 (s, 36H, CH_3-Boc), 1.44 (s, 18H, CH_3-Boc), 2.04 (s, 6H, CH_3-amide), 2.78–2.93 (m, 8H, CH_2-cyclen), 3.27–3.68 (m, 24H, CH_2-cyclen), 6.93 (s, 1H, CH 2), 8.12 (bs, 2H, NH-amide), 9.05 (s, 1H, CH 5); ^{13}C NMR (63 MHz, $CDCl_3$): δ = 24.7 (+, CH_3-amide), 28.4, 28.5 (+, CH_3-Boc), 45.7, 48.9, 50.9 (−, CH_2-cyclen), 80.2, 80.3 (C_{quat}, C-Boc), 113.6 (+, C_{aryl}-H 2), 115.5 (+, C_{aryl}-H 5), 132.4, 136.5 (C_{quat}, C_{aryl}-N), 155.9, 156.2 (C_{quat}, C=O Boc), 168.0 (C_{quat}, C=O amide); MS (ESI, MeOH/CH_2Cl_2 + 1% AcOH): m/z (%) = 1156 (100) $[M + Na]^+$, 1134 (55) $[MH]^+$; elemental analysis ($C_{56}H_{96}N_{10}O_{14}$): calcd. C, 59.34; H, 8.54; N, 12.36; found: C, 59.52; H, 8.59; N 12.16.

1,3-Di-(1,4,7,10-tetraazacyclododecane-1-yl)-4,6-di-(acetylamino)-benzene (**5-H**): A solution of **5-Boc** (700 mg, 0.62 mmol) in CH_2Cl_2 (25 mL) and TFA (2.8 mL, 4.14 g, 36.35 mmol) was stirred for 18 h at room temp., the solvent and excess TFA was removed in vacuum, and the oily residue was dissolved in a small amount of acetonitrile and again evaporated in vacuum to remove traces of TFA. 1,3-Bis-(10-aza-1,4,7-hexazonium-cyclododec-10-yl)-4,6-di-(acetylamino)-benzene hexakis-trifluoroacetate (763 mg, quantitative) was obtained as a yellow solid, mp 118–120°C. IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 3628, 3372, 2936, 1523, 1252, 1162, 862, 773; UV/Vis (CH_3CN): λ_{max} (nm) (lg ε) = 242 (3.732), 342 (3.544); ^{1}H NMR (300 MHz, CD_3CN): δ = 1.96 (s, 6H, CH_3-amide), 3.11–3.17 (m, 8H, CH_2-cyclen), 3.23–3.31 (m, 16H, CH_2-cyclen), 3.48–3.55 (m, 8H, CH_2-cyclen), 6.87 (s, 1H, CH 2), 7.39 (bs, 14H, NH^{2+} und NH-amide), 8.89 (s, 1H, CH 5); ^{13}C NMR (75 MHz, CD_3CN): δ = 25.1 (+, CH_3 amide), 42.9, 44.2, 45.7, 50.2 (−, CH_2-cyclen), 113.1 (+, C_{aryl}-H 2), 114.9 (+, C_{aryl}-H 5), 117.6 (C_{quat}, q, $^1J_{C,F}$ = 290.3 Hz, CF_3COO^-), 131.3, 135.0 (C_{quat}, C_{aryl}-N), 161.2 (C_{quat}, q, $^2J_{C,F}$ = 36.5 Hz, CF_3COO^-), 169.6 (C_{quat}, C=O amide); MS (ESI, MeOH + 1% AcOH): m/z (%) = 533 (100) $[M^{6+} - 5H]^+$, 267 (65) $[M^{6+} - 4H]^{2+}$.

The TFA salt (600 mg, 0.49 mmol) was dissolved in water (10 mL) and was passed through 30 mL of a strong basic ion-exchange resin (OH^- capacity 0.9 mmol/mL) followed by water (120 mL) and acetonitrile (30 mL). The organic solvent was removed from the eluate and the aqueous phase lyophilized to yield 5-H (262 mg, quantitative) as a yellow solid, mp 96°C. IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 3618, 3381, 2986, 2928 1503, 1222, 1161, 864, 771; UV/Vis (CH_3CN): λ_{max} (nm) (lg ε) = 249 (3.796), 349 (3.618); ^{1}H NMR (250 MHz, CD_3CN): δ = 1.99 (s, 6H, CH_3-amide), 2.61–2.65 (m, 8H, CH_2-cyclen), 2.73–2.81 (m, 8H, CH_2-cyclen), 2.96–3.11 (m, 14H, CH_2-cyclen und NH), 3.38–3.44 (m, 8H, CH_2-cyclen), 6.91 (s, 1H, CH 2), 8.23 (bs, 2H, NH-amide), 8.92 (s, 1H, CH 5); ^{13}C NMR (63 MHz, CD_3CN): δ = 24.8 (+, CH_3-amide), 44.6, 45.5, 47.2, 51.1 (−, CH_2-cyclen), 114.9 (+, C_{aryl}-H 2), 116.7 (+, C_{aryl}-H 5), 131.9, 136.0 (C_{quat}, C_{aryl}-N), 169.2 (C_{quat}, C=O amide); MS (ESI, MeOH/CH_2Cl_2 + 1% AcOH): m/z (%) = 533 (100) $[MH]^+$, 267 (35) $[M + 2H]^{2+}$; HRMS ($C_{26}H_{49}N_{10}O_2$): calcd. 533.4040 $[MH]^+$, found: 533.4037 $[MH]^+$ ± 0.96 ppm.

1,3-Di-(zinc (II)-1,4,7,10-tetraazacyclododecane-1-yl)-4,6-di-(acetylamino)-benzol-tetra-perchlorate (**6**): $Zn(ClO_4)_2 \cdot 6H_2O$ in methanol (10 mL) was added to a solution of ligand **5-H** (195 mg, 0.37 mmol), dissolved in methanol (15 mL), and the mixture was stirred for 24 h at room temp. The product precipitates from solution. The mixture was heated to reflux for 30 min to ensure complete reaction, the solvent was removed in vacuum and the crude product recrystallized from CH_3CN/water (3 : 1) to give **6** (264 mg, 67%) as yellow crystals, mp 219°C (dec). IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 3609, 3372, 2991, 2919 1513, 1170, 865, 777; UV/Vis (CH_3CN): λ_{max} (nm) (lg ε) = 245 (3.709), 346 (3.562); ^{1}H NMR (300 MHz, CD_3CN): δ (ppm) = 2.09 (s, 6H, CH_3-amide), 2.78–2.83 (m, 4H, CH_2-cyclen), 2.97–3.20 (m, 8H, CH_2-cyclen), 3.35–3.45 (m, 8H, CH_2-cyclen), 3.58–3.74 (m, 14H, CH_2-cyclen und NH), 4.24–4.38 (m, 4H, CH_2-cyclen), 7.12 (s, 1H, CH 2), 8.31 (bs, 2H, NH-amide), 9.28 (s, 1H, CH 5); ^{13}C NMR (75 MHz, CD_3CN): δ (ppm) = 24.4 (+, CH_3-amide), 44.0, 45.1, 46.5, 49.8 (−, CH_2-cyclen), 114.9 (+, C_{aryl}-H 2), 116.7 (+, C_{aryl}-H 5), 133.1, 139.3 (C_{quat}, C_{aryl}-N), 170.6 (C_{quat}, C=O amide); MS (ESI, CH_3CN): m/z (%) = 409 (100) $[M^{4+} + CH_3COO^- + ClO_4^-]^{2+}$, 389 (60) $[M^{4+} + 2\ CH_3COO^-]^{2+}$; (ESI, neg., CH_3CN): m/z (%) = 1115 (100) $[M^{4+} + 4\ ClO_4^- + CH_3COO^-]^-$.

Tri-tert-butyl 10-(2,4-dinitrobenzene-1-yl)-1,4,7,10-tetraaza cyclododecane-1,4,7-tricarbamate (**8-Boc**):[7] A suspension of $NaHCO_3$ (1.07 g, 12.72 mmol) in dry CH_3CN (80 mL) was sonicated at 40°C under nitrogen for 15 min, 1-fluoro-2,4-dinitrobenzene (**7**, 1.18 g, 6.36 mmol) and **1** (3.00 g, 6.36 mmol) were added, and the reaction mixture was heated for 8 h in the sonicator bath to 40°C. The mixture was filtered through Celite®, the filter was washed with CH_3CN (30 mL) and the combined eluates were evaporated in vacuum. The crude product was chromatographed on silica gel (EA/PE = 1 : 1, R_f = 0.37) giving **8-Boc** (3.98 g, 98%) as a yellow solid, mp 70°C, ^{1}H NMR (250 MHz, $CDCl_3$): δ (ppm) = 1.47 (s, 9H, CH_3-Boc), 1.48 (s, 18H, CH_3-Boc), 3.39–3.62 (m, 16H, CH_2-cyclen), 7.17 (d, 1H, ^3J = 9.5 Hz, CH 6), 8.20 (dd, 1H, ^3J = 9.5 Hz, ^4J = 2.7 Hz, CH 5), 8.56 (d, 1H, ^4J = 2.7 Hz, CH 3); ^{13}C NMR (63 MHz, $CDCl_3$): δ (ppm) = 28.4, 28.5 (+, CH_3-Boc), 47.8, 49.6, 50.5, 52.2 (−, CH_2-cyclen), 80.6, 80.8 (C_{quat}, C-Boc), 118.2 (+, C_{aryl}-H 6), 123.7, 127.8 (+, C_{aryl}-H 3 und 5), 137.5 (C_{quat}, C_{aryl}-N 2 und 4), 147.7 (C_{quat}, C_{aryl}-N 1), 156.3, 156.9 (C_{quat}, C=O Boc).

1-(2,4-Dinitrobenzene-1-yl)-1,4,7,10-tetraaza cyclododecane (**8-H**): TFA (4.3 mL, 6.36 g, 55.79 mmol) was added to a solution of compound **8-Boc** (1.20 g, 1.88 mmol) in 50 mL of CH_2Cl_2. The reaction mixture was stirred for 4 h at room temp., and all volatile components were removed in vacuum to give 10-(2,4-dinitrobenenel-1-yl)-10-aza-1,4,7-triazonium-cyclododecane tris-trifluoroacetate (1.29 g, 1.88 mmol, quantitative) after drying in high

vacuum as a yellow solid, mp 137°C. IR (KBr):$\tilde{\nu}$ (cm^{-1}) = 3588, 3420, 2950, 1531, 1467, 1346, 1288, 1070, 954, 741; UV/Vis (CH_3CN): λ_{max} (nm) (lg ε) = 210 (3.858), 371 (3.903); ^1H NMR (250 MHz, CD_3CN): δ (ppm) = 3.06–3.27 (m, 12H, CH_2-cyclen), 3.46–3.54 (m, 4H, CH_2-cyclen), 7.25 (bs, 6H, NH_2^+), 7.77 (d, 1H, ^3J = 9.1 Hz, CH 6), 8.43 (d, 1H, ^3J = 9.1 Hz, ^4J = 2.7 Hz, CH 5), 8.67 (d, 1H, ^4J = 2.7 Hz, CH 3); ^{13}C NMR (63 MHz, CD_3CN): δ (ppm) = 43.7, 44.9, 45.6, 51.6 (−, CH_2-cyclen), 117.3 (C_{quat}, q, $^1J_{C,F}$ = 290.9 Hz, CF_3COO^-), 123.1, 127.5, 129.5 (+, C_{aryl}-H), 144.7, 145.6, 148.8 (C_{quat}, C_{aryl}-N), 161.2 (C_{quat}, q, $^2J_{C,F}$ = 36.1 Hz, CF_3COO^-); MS (ESI, CH_3CN): m/z (%) = 339 (100) $[M^{3+} - 2H]^+$.

The ammonium salt (1.00 g, 1.46 mmol) was dissolved in water (25 mL) and eluated over a strong basic ion-exchange resin (30 mL, capacity: 0.9 mmol OH^-/mL) with water. The eluate was lyophilized yielding **8-H** (0.46 g, 93%), as a yellow solid, mp 94°C. IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 3426, 3097, 2925, 1604, 1326, 1170, 742, 714; UV/Vis (CH_3CN): λ_{max} [nm] (lg ε) = 218 (4.033), 378 (3.962); ^1H NMR (250 MHz, $CDCl_3$): δ (ppm) = 2.04 (bs, 3H, NH), 2.61–2.70 (m, 4H, CH_2-cyclen), 2.74–2.84 (m, 8H, CH_2-cyclen), 3.50–3.58 (m, 4H, CH_2-cyclen), 7.66 (s, 1H, ^3J = 9.4 Hz, CH 6), 8.23 (d, 1H, ^3J = 9.4 Hz, ^4J = 2.7 Hz, CH 5), 8.56 (d, 1H, ^4J = 2.7 Hz, CH 3); ^{13}C NMR (63 MHz, $CDCl_3$): δ (ppm) = 46.1, 46.2, 48.1, 52.7 (−, CH_2-cyclen), 122.5, 123.7, 127.4 (+, C_{aryl}-H), 139.0, 140.7, 148.9 (C_{quat}, C_{aryl}-N); MS (ESI, MeOH + 1% AcOH): m/z (%) = 339 (100) $[MH]^+$, 361 (15) $[M + Na]^+$; HRMS ($C_{14}H_{23}N_6O_4$): calcd. 339.1781 $[MH]^+$, found: 339.1877 $[MH]^+$ ± 1.19 ppm.

Tri-tert-butyl 10-(2,4-diamionbenzene-1-yl)-1,4,7,10-tetraaza cyclododecane-1,4,7-tricarbamate (**9-Boc**): To a solution of **8-Boc** (1 g, 1.57 mmol) in EtOH (10 mL), 250 mg of Pd/C (10% palladium) was added and the mixture was pressurized by H_2 (10 bar) for 48 h at room temp. The catalyst was removed by filtration through Celite®, the solvent was removed in vacuum, and the crude product was chromatographed (EA/PE = 4 : 1; R_f = 0.25, EA/PE = 1 : 1). Yield: 668 mg (74%) of **9-Boc**, as a solid, mp 110°C (dec.). IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 3363, 3458, 2976, 2930, 1685, 1529, 1417, 1366, 1249, 1168, 861, 774; UV/Vis (CH_3CN): λ_{max} (nm) (lg ε) = 217 (4.395), 307 (3.491); ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.41 (s, 18H, CH_3-Boc), 1.49 (s, 9H, CH_3-Boc), 2.81–3.16 (m, 4H, CH_2-cyclen), 3.18–3.41 (m, 4H, CH_2-cyclen), 3.47–3.82 (m, 8H, CH_2-cyclen), 6.02–6.07 (m, 2H, CH-arene), 6.78 (d, 1H, ^3J = 7.9 Hz, CH-arene); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 28.4, 28.5 (+, CH_3-Boc), 47.3, 49.5, 51.0, 52.9 (−, CH_2-cyclen), 79.4, 79.7 (C_{quat}, C-Boc), 102.8, 105.0, 122.2 (+, C_{aryl}-H), 128.9 (C_{quat}, C_{aryl}-N 2 und 4) 143.9 (C_{quat}, C_{aryl}-N 1), 155.8, 156.3 (C_{quat}, C=O Boc); MS (ESI, MeOH + 1% AcOH): m/z (%) = 579 (100) $[MH]^+$.

Tri-tert-butyl 10-(2-amino-4-nitrophenyl)-1,4,7,10-tetraaza cyclododecane-1,4,7-tricarbamate (**10-Boc**) and *Tri-tert-butyl 10-(4-amino-2-nitrophenyl)-1,4,7,10-tetraaza cyclododecane-1,4,7-tricarbamate* (**11-Boc**) and *Tri-tert-butyl*

10-(2,4-diamionbenzene-1-yl)-1,4,7,10-tetraaza cyclododecane-1,4,7-tricarbamate (**9-Boc**): Method A (reduction with sulphur and sodium sulphide). A solution of **8-Boc** (2.44 g, 3.82 mmol, 1.0 equiv.) was heated to reflux in EtOH (50 mL); sodium sulphide (5.50 g, 22.92 mmol, 6 equiv.) and sulphur (0.73 g, 22.92 mmol, 6 equiv.) were added in water (10 mL) in one portion causing a color change from yellow to dark brown. The reaction mixture was heated for 20 min to reflux, the solvent was removed in vacuum, and the red-brown solid dissolved in water (40 mL) and EA (40 mL). The aqueous phase was extracted with EA (3×), the combined organic phases were dried over sodium sulphate, the solvent was removed in vacuum, and the crude product was chromatographed on silica gel (PE:EA 50 : 50) giving **11-Boc** (1.48 g, 64%, $R_f = 0.20$), **10-Boc** (425 mg, 18%, $R_f = 0.25$ in PE:EA 30 : 70), and **9-Boc** (350 mg, 16%, $R_f = 0.23$ in PE:EA 10 : 90).

Method B (reduction by transfer hydrogenation using triethylammonium formiate). A mixture of **8-Boc** (200 mg, 0.31 mmol, 1.0 equiv.), triethyl amine (0.2 mL, 1.35 mmol, 4.3 equiv.), and 15 mg of Pd/C in 20 mL of acetonitrile was heated to reflux. Formic acid (0.05 mL, 1.35 mmol, 4.3 equiv.) was added; the mixture was heated to reflux for 2 h and, after cooling to room temp., filtered through Celite. The solvent was removed in vacuum and the crude product was purified by column chromatography on silica gel to yield 53 mg (28%) of **10-Boc** ($R_f = 0.20$), 23 mg (12%) of **11-Boc** ($R_f = 0.25$ in PE:EE 30 : 70), and 108 mg (60%) of **9-Boc** ($R_f = 0.23$ in PE:EE 10 : 90).

Tris-tert-Butyl-10-(2-amino-4-nitrophenyl)-1,4,7,10-tetraaza cyclododecane-1,4,7-tricarbamate (**10-Boc**): mp105°C. IR (KBr): $\tilde{\nu} = 2975\,cm^{-1}$, 2924, 1698, 1685, 1508, 1458, 1365, 1250, 1166. UV/Vis (acetonitrile): λ_{max} (lg ε) = 189 nm (5.00), 231 (4.51), 261 (4.42), 325 (4.06), 397 (4.14). ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 1.38–1.50$ (m, 27H, BOC-CH_3), 3.11 (bs, 4H, cyclen-CH_2), 3.43 (bs, 4H, cyclen-CH_2), 3.56 (bs, 8H, cyclen-CH_2), 4.22 (bs, 2H, –NH_2), 6.98 (d, 1H, *H*-6, $^3J = 8.60$ Hz), 7.54 (d, 1H, *H*-3, $^4J = 2.60$ Hz), 7.58 (dd, 1H, *H*-5, $^3J = 8.60$ Hz, $^4J = 2.60$ Hz). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 28.3$ (+, BOC-*C*H_3), 28.5 (+, BOC-*C*H_3), 46.1 (−, cyclen-*C*H_2, 2C), 49.3 (−, cyclen-*C*H_2, 2C), 50.1 (−, cyclen-*C*H_2, 2C), 51.3 (−, cyclen-*C*H_2, 2C), 80.1 (C_{quat}, BOC-*C*$[CH_3]_3$), 80.2 (C_{quat}, BOC-*C*$[CH_3]_3$), 110.0 (+, arene-*C*H), 113.4 (+, arene-*C*H), 119.4 (+, arene-*C*H), 142.7 (C_{quat}), 142.8 (C_{quat}), 144.4 (C_{quat}), 155.9 (C_{quat}), 156.2 (C_{quat}). MS (ESI, CH_2Cl_2), m/z (%): 609.3 (100) [MH^+], 1239.6 (2.4) [2 M + Na^+]. $C_{29}H_{46}N_6O_{10}$ (608.8): calcd. C, 57.22; H, 7.95; N, 13.81; found: C, 57.27; H, 8.19; N, 12.89.

Tris-tert-butyl-10-(4-amino-2-nitrophenyl)-1,4,7,10-tetraaza cyclododecane-1,4,7-tricarbamate (**11-Boc**), mp101°C. IR (KBr): $\tilde{\nu} = 2976\,cm^{-1}$, 2930, 1685, 1529, 1478, 1417, 1366, 1249, 1168, 858, 774, 620. UV/Vis (acetonitrile): λ_{max} (lg ε) = 191 nm (4.97), 245 (4.52), 391 (3.44). ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 1.42$ (s, 18H, BOC-CH_3), 1.46 (s, 9H, BOC-CH_3),

3.16 (m, 4H, cyclen-CH_2), 3.30 (m, 4H, cyclen-CH_2), 3.41 (m, 4H, cyclen-CH_2), 3.53 (m, 4H, cyclen-CH_2), 3.92 (bs, 2H, $-$NH_2), 6.77 (dd, 1H, *H*-5, $^3J = 8.69$ Hz, $^4J = 2.75$ Hz), 6.90 (d, 1H, *H*-3, $^4J = 2.75$ Hz), 7.08 (d, 1H, *H*-6, $^3J = 8.69$ Hz). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 28.4$ (+, BOC-*C*H_3), 28.5 (+, BOC-*C*H_3), 47.8–49.3 (−, cyclen-*C*H_2), 79.6 (C_{quat}, BOC-*C*[CH_3]$_3$), 79.7 (C_{quat}, BOC-*C*[CH_3]$_3$), 109.9 (+, arene-*C*H), 118.9 (+, arene-*C*H), 127.8 (+, arene-*C*H), 134.5 (C_{quat}), 144.1 (C_{quat}), 148.7 (C_{quat}), 155.7 (C_{quat}), 156.0 (C_{quat}). MS (ESI, CH_2Cl_2), m/z (%): 609.3 (100) [MH^+], 1239.6 (2.4) [2 M + Na^+]. $C_{29}H_{46}N_6O_{10}$ (608.8): calcd. C, 57.22; H, 7.95; N, 13.81; found: C, 57.11; H, 8.17; N, 13.26.

5-Nitro-2-(1,4,7,10-tetraazacyclododec-1-yl)-phenylamine (**10-H**): TFA (2.3 mL, 30.0 mmol, 42 equiv.) was added to a solution of **10-Boc** (425 mg, 0.7 mmol, 1 equiv.) in dichloromethane (10 mL), and the mixture was stirred at room temp. overnight. The solvent and excess of TFA was removed in vacuum to give the yellowish TFA salt of the compound. IR (KBr): $\tilde{\nu} = 3007\ cm^{-1}$, 2863, 1677, 1524, 1352, 1203, 1140, 836, 799, 722. ^{1}H NMR (250 MHz, CD_3CN): $\delta = 2.95–3.00$ (m, 4H, cyclen-CH_2), 3.08–3.25 (m, 12H, cyclen-CH_2), 7.40 (d, 1H, *H*-3, $^3J = 8.78$ Hz), 7.69 (dd, 1H, *H*-4, $^3J = 8.77$ Hz, $^4J = 2.67$ Hz), 7.77 (d, 1H, *H*-6, $^4J = 2.66$ Hz). ^{13}C NMR (62 MHz, CD_3CN): $\delta = 43.2$ (−, cyclen-*C*H_2), 43.4 (−, cyclen-*C*H_2), 46.7 (−, cyclen-*C*H_2), 50.3 (−, cyclen-*C*H_2), 114.2 (+, arene-*C*H), 116.4 (+, arene-*C*H), 116.8 (q, $F_3C–CHOO^-$, $J = 288{,}69$ Hz), 125.8 (+, arene-*C*H), 144.2 (C_{quat}), 145.4 (C_{quat}), 147.5 (C_{quat}), 160.5 (q, $F_3C–CHOO^-$, $J = 37.77$ Hz).

The TFA salt was dissolved in methanol and eluated over a strong basic ion exchange resin. The solvent was removed in vacuum and the product dried in high vacuum to yield **10-H** (400 mg, quantitative) as a yellow solid, mp93°C. IR (KBr): $\tilde{\nu} = 2920\ cm^{-1}$, 2883, 2840, 1628, 1580, 1513, 1450, 1334, 1285, 1195, 1111, 954, 813, 731. UV/Vis (acetonitrile): λ_{max} (lg ε) = 189 nm (7.05), 207 (4.67), 237 (4.42), 269 (4.34), 339 (4.04), 413 (4.17). ^{1}H NMR (250 MHz, CD_3CN): $\delta = 2.53–2.69$ (m, 12H, cyclen-CH_2), 3.02–3.06 (m, 4H, cyclen-CH_2), 7.07 (d, 1H, *H*-3, $^3J = 8.60$ Hz), 7.41 (dd, 1H, *H*-4, $^3J = 8.60$ Hz, $^4J = 2.71$ Hz), 7.46 (d, 1H, *H*-6, $^4J = 2.71$ Hz). ^{13}C NMR (62 MHz, CD_3CN): $\delta = 45.7$ (−, cyclen-*C*H_2), 47.1 (−, cyclen-*C*H_2), 47.5 (−, cyclen-*C*H_2), 50.4 (−, cyclen-*C*H_2), 109.7 (+, arene-*C*H), 112.8 (+, arene-*C*H), 121.7 (+, arene-*C*H), 143.3 (C_{quat}), 145.0 (C_{quat}), 145.1 (C_{quat}). MS (ESI, CH_2Cl_2), m/z (%): 309.1 (100) [MH^+], 331.1 (6) [MNa^+].

3-Nitro-4-(1,4,7,10-tetraazacyclododec-1-yl)-phenylamine (**11-H**): TFA (7.9 mL, 103.0 mmol, 42 equiv.) was added to **11-Boc** (1.48 g, 2.44 mmol, 1 equiv.) in dichloromethane (25 mL), the mixture was stirred overnight at room temp., and the solvent and excess TFA was removed in vacuum to yield the TFA salt. IR (KBr): $\tilde{\nu} = 3131\ cm^{-1}$, 2984, 2875, 2791, 1779,

1678, 1531, 1204, 1171, 835, 797, 722. ^{1}H NMR (250 MHz, CD_3CN): $\delta = 2.93-2.97$ (m, 4H, cyclen-CH_2), 3.05–3.11 (m, 4H, cyclen-CH_2), 3.14–3.24 (m, 8H, cyclen-CH_2), 7.00 (dd, 1H, *H*-6, $^3J = 8.75$ Hz, $^4J = 2.76$ Hz), 7.17 (d, 1H, *H*-2, $^4J = 2.74$ Hz), 7.42 (d, 1H, *H*-5, $^3J = 8.78$ Hz). ^{13}C NMR (62 MHz, CD_3CN): $\delta = 42.7$ (−, cyclen-*C*H_2), 44.0 (−, cyclen-*C*H_2), 45.8 (−, cyclen-*C*H_2), 51.3 (−, cyclen-*C*H_2), 110.6 (+, arene-*C*H), 116.8 (q, $F_3C-CHOO^-$, $J = 288.54$ Hz), 121.6 (+, arene-*C*H), 128.6 (+, arene-*C*H), 131.7 (C_{quat}), 148.7 (C_{quat}), 148.8 (C_{quat}), 160.4 (q, $F_3C-CHOO^-$, $J = 37.86$ Hz).

The TFA salt was dissolved in methanol and eluated over a strong basic ion-exchange resin, the solvent was removed in vacuum, and the product dried in high vacuum to yield **11-H** (610 mg, 82%), as a dark yellow solid, mp 90°C. IR (KBr): $\tilde{\nu} = 3432\ cm^{-1}$, 2925, 2846, 1653, 1523, 1457, 1363. UV/Vis (acetonitrile): λ_{max} (lg ε) = 195 nm (4.90), 243 (4.59), 375 (3.44). ^{1}H NMR (250 MHz, CD_3CN): $\delta = 2.46-2.50$ (m, 8H, cyclen-CH_2), 2.66–2.69 (m, 4H, cyclen-CH_2), 2.89–2.93 (m, 4H, cyclen-CH_2), 4.45 (bs, 2H, –NH_2), 6.77 (d, 1H, *H*-2, $^4J = 2.65$ Hz), 6.83 (dd, 1H, *H*-6, $^3J = 8.69$ Hz, $^4J = 2.73$ Hz), 7.27 (d, 1H, *H*-5, $^4J = 8.60$ Hz). ^{13}C NMR (62 MHz, CD_3CN): $\delta = 45.5$ (−, cyclen-*C*H_2), 46.2 (−, cyclen-*C*H_2), 47.0 (−, cyclen-*C*H_2), 54.0 (−, cyclen-*C*H_2), 108.8 (+, arene-*C*H), 119.8 (+, arene-*C*H), 128.8 (+, arene-*C*H), 134.2 (C_{quat}), 148.6 (C_{quat}), 152.1 (C_{quat}). MS (ESI, CH_2Cl_2), m/z (%): 309.1 (100) [MH^+], 331.1 (8) [MNa^+].

Tris-tert-butyl-10-[4-({1-methyl-4[(1-methyl-4-nitro-1H-pyrrole-2-carbonyl)-amino]-1H-pyrrole-2-carbonyl}-amino)-2-nitro-phenyl]-1,4,7,10-tetraaza cyclododecane-1,4,7-tricarbamate (**13-Boc**): A mixture of **11-Boc** (242 mg, 0.40 mmol), **12**[12] (128 mg (0.44 mmol), HATU (181 mg, 0.48 mmol), HOAt (65 mg, 0.48 mmol), and collidine (481 mg, 3.98 mmol) in DMF (6 mL) was stirred 48 h at 60°C. Water (3 mL) was added, and the mixture was extracted three times with dichloromethane. The combined organic phases were dried over Na_2SO_4, the solvents were removed in vacuum, and the crude product was chromatographed on silica gel (EA/PE = 1 : 1) to give **13-Boc** (198 mg, 82%, $R_f = 0.22$, EE/PE = 7 : 3) as a yellow solid, mp 186°C (dec.). IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 3460, 2927, 1668, 1504, 1419, 1367, 1167, 850; UV/Vis (CH_3CN): λ_{max} (nm) (lg ε) = 201 (4.672), 238 (4.369), 272 (4.421), 307 (4.527); ^{1}H NMR (400 MHz, DMSO-d6): $\delta = 1.43$ (s, 18H, CH_3-Boc), 1.46 (s, 9H, CH_3-Boc), 3.19–3.27 (m, 4H, CH_2-cyclen), 3.34–3.41 (m, 4H, CH_2-cyclen), 3.42–3.49 (m, 4H, CH_2-cyclen), 3.50–3.58 (m, 4H, CH_2-cyclen), 3.95 (s, 3H, CH_3-pyrrole), 4.05 (s, 3H, CH_3-pyrrole), 7.22 (d, 1H, $^4J = 1.9$ Hz, CH-pyrrole), 7.33 (d, 1H, $^4J = 1.7$ Hz, CH-pyrrole), 7.40 (d, 1H, $^3J = 8.9$ Hz, CH 2), 7.60 (d, 1H, $^4J = 1.9$ Hz, CH-pyrrole), 7.90 (dd, 1H, $^3J = 8.9$ Hz, $^4J = 2.5$ Hz, CH 3), 8.19 (d, 1H, $^4J = 1.7$ Hz, CH-pyrrole), 8.30 (d, 1H, $^4J = 2.5$ Hz, CH 5), 10.17 (bs, 1H, NH), 10.32 (bs, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d6): $\delta = 27.9$, 28.0 (+, CH_3-Boc), 36.2, 37.4 (+, CH_3-pyrrole), 46.3, 47.2, 48.0

(−, CH_2-cyclen), 78.5 (C_{quat}, C-Boc), 105.7 (+, CH-pyrrole), 107.5 (+, CH-pyrrole), 115.4 (+, C_{aryl}-H 5), 119.7 (+, CH-pyrrole), 123.9 (+, C_{aryl}-H 3), 126.1 (+, C_{aryl}-H 2), 128.2 (+, CH-pyrrole), 121.4, 122.2, 125.6, 133.7. 135.5, 138.9 (C_{quat}), 154.7, 154.9 (C_{quat}, C=O Boc), 156.8, 159.6 (C_{quat}, C=O amide); MS (ESI, MeOH + 10 mmol NH_4Ac): m/z (%) = 883 (100) $[MH]^+$, 392 (80) $[M\text{-}Boc + 2H]^{2+}$, 783 (30) $[MH\text{-}Boc]^+$; HRMS ($C_{41}H_{59}N_{10}O_{12}$): calcd. 883.4314 $[MH]^+$, found: 883.4322 $[MH]^+ \pm 1.19$ ppm.

1-[4-({1-Methyl-4[(1-methyl-4-nitro-1H-pyrrole-2-carbonyl)-amino]-1H-pyrrole-2-carbonyl}-amino)-2-nitro-phenyl]-1,4,7,10-tetraaza cyclododecane (**13-H**): A solution of compound **13-Boc** (150 mg, 0.18 mmol) in 20 mL of TFA/CH_2Cl_2 (60:40, v/v) with a small amount methanol was stirred for 36 h at room temp. All solvents were removed in vacuum, and the remaining solid was dried in high vacuum to yield the TFA salt (156 mg, quantitative) as a yellow solid, mp 147–149°C; IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 3430, 2951, 1667, 1515, 1423, 1161, 853; UV/Vis (CH_3CN): λ_{max} (nm) (lg ε) = 202 (4.551), 239 (4.457), 273 (4.583), 305 (4.605); ^{1}H NMR (400 MHz, D_2O): δ = 2.92–3.03 (m, 4H, CH_2-cyclen), 3.10–3.25 (m, 8H, CH_2-cyclen), 3.25–3.36 (m, 4H, CH_2-cyclen), 3.58 (s, 3H, CH_3-pyrrole), 3.68 (s, 3H, CH_3-pyrrole), 6.64 (s, 1H, CH-pyrrole), 6.89 (s, 1H, CH-pyrrole), 6.97 (d, 1H, ^4J = 1.9 Hz, CH-pyrrole), 7.44 (d, 1H, ^4J = 1.6 Hz, CH-pyrrole), 7.53 (dd, 1H, ^3J = 8.9 Hz, ^4J = 1.9 Hz, CH 3), 7.58 (d, 1H, ^3J = 8.9 HZ, CH 2), 8.01 (d, 1H, ^4J = 2.1 Hz, CH 5); ^{13}C NMR (100 MHz, D_2O): δ = 36.4, 37.6 (+, CH_3-pyrrole), 41.5, 42.6, 44.6, 49.9 (−, CH_2-cyclen), 105.9, 108.1, 115.6 (+, CH-pyrrole), 116.1 (+, C_{aryl}-H 5), 116.4 (C_{quat}, q, $^1J_{C,F}$ = 291.5 Hz, CF_3COO^-), 126.1 (+, C_{aryl}-H 3), 127.0 (+, C_{aryl}-H 2), 128.7 (+, CH-pyrrole), 120.8, 125.2, 125.7, 133.7, 136.9, 137.6, 146.9 (C_{quat}), 157.8, 160.5 (C_{quat}, C=O amide), 162.9 (C_{quat}, q, $^2J_{C,F}$ = 36.6 Hz, CF_3COO^-); MS (ESI, CH_3CN): m/z (%) = 583 (100) $[M^{3+} - 2H]^+$.

The TFA salt (118 mg, 0.13 mmol) was dissolved in 12 mL of H_2O and 1 mL of CH_3CN, and eluated over a strong basic ion exchange resin. The organic solvent was removed from the eluate in vacuum and the remaining aqueous phase was lyophylized to give **13-H** (76 mg, quantitative) as a yellow solid, mp 156°C (dec.). IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 3441, 2913, 1661, 1506, 1417, 1159, 854; UV/Vis (CH_3CN): λ_{max} (nm) (lg ε) = 203 (4.724), 236 (4.546), 279 (4.634), 306 (4.716); ^{1}H NMR (400 MHz, DMSO-d6): δ = 2.42–2.48 (m, 8H, CH_2-cyclen), 2.60–2.66 (m, 4 H, CH_2-cyclen), 2.96–3.03 (m, 4H, CH_2-cyclen), 3.87 (s, 3H, CH_3-pyrrole), 3.97 (s, 3H, CH_3-pyrrole), 7.21 (d, 1H, ^4J = 1.9 Hz, CH-pyrrole), 7.33 (d, 1H, ^4J = 1.7 Hz, CH-pyrrole), 7.60 (d, 1H, ^4J = 1.9 Hz, CH-pyrrole), 7.61 (d, 1H, ^3J = 8.9 HZ, CH 2), 7.88 (dd, 1H, ^3J = 8.9 Hz, ^4J = 2.4 Hz, CH 3), 8.17 (d, 1H, ^4J = 2.4 Hz, CH 5), 8.18 (d, 1H, ^4J = 1.7 Hz, CH-pyrrole), 10.19 (bs, 1H, NH), 10.34 (bs, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d6): δ = 36.2, 37.4 (+, CH_3-pyrrole), 44.9, 45.4, 46.5, 52.0 (−, CH_2-cyclen), 105.8, 107.5 (+, CH-pyrrole), 114.3 (+, C_{aryl}-H 5), 119.7 (+, CH-pyrrol),

123.9 (+, C_{aryl}-H 3), 127.0 (+, C_{aryl}-H 2), 128.1 (+, CH-pyrrole), 121.6, 122.2, 126.1, 133.7, 136.2, 139.0, 147.8 (C_{quat}), 156.9, 159.7 (C_{quat}, C=O amide), MS (ESI, CH_3CN): m/z (%) = 583 (100) $[MH]^+$.

1-[4-({1-Methyl-4[(1-methyl-4-nitro-1H-pyrrole-2-carbonyl)-amino]-1H-pyrrole-2-carbonyl}-amino)-2-nitro-phenyl]-1,4,7,10-tetraaza cyclododecane cobalt (III)-tri-chloride (**14**): $Na_3[(Co)CO_3)_2] \cdot 3H_2O$ (12 mg, 0.03 mmol was added to a solution of **13-H** (20 mg, 0.03 mmol) in 6 mL of H_2O/MeOH (1:1). The mixture was heated to 70°C for 30 min. After cooling to room temp., five to seven drops of conc. HCl were added, causing a color change of the solution to green-yellow. Organic solvents were removed in vacuum and the aqueous phase was lyophylized, yielding **14** (25 mg, quantitative) as a yellow-green solid, mp 177–179°C, IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 3437, 2934, 1668, 1549, 1093, 740; UV/Vis (CH_3CN): λ_{max} (nm) (lg ε) = 298 (3.902); ^{1}H NMR (400 MHz, D_2O): δ = 297–306 (m, 4H, CH_2-cyclen), 3.13–3.28 (m, 8H, CH_2-cyclen), 3.29-3.41 (m, 4H, CH_2-cyclen), 3.56 (s, 3H, CH_3-pyrrole), 3.65 (s, 3H, CH_3-pyrrole), 6.77 (bs, 1H, CH), 6.87 (bs, 1H, CH), 7.09 (bs, 1H, CH), 7.48 (bs, 1H, CH), 7.60 (bs, 2H, CH), 8.03 (bs, 1H, CH); MS (ESI, MeOH/H_2O + 10 mmol NH_4Ac): m/z (%) = 701 (100) $[L + Co^{3+} + CO_3^{2-}]^+$, 350 (25) $[L + Co^{3+} + CH_3COO^-]^{2+}$.

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