DESIGN AND SYNTHESIS OF SEQUENCE-SPECIFIC DNA MINOR GROOVE RECOGNIZING LIGANDS OF THE CROSS-LINKED LEXITROPSIN CLASS

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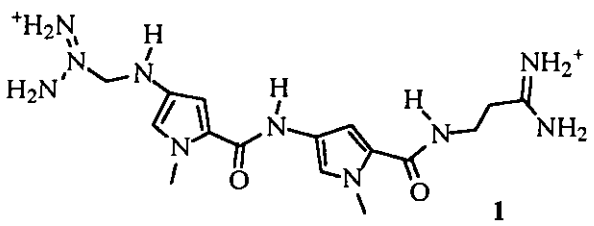
Abstract- On the basis of previous studies on pyrrole-containing cross-linked lexitropsins, symmetric and non-symmetric cross-linked lexitropsins incorporating imidazole rings are designed to bind selectively to GC-containing oligonucleotide sequences and their syntheses are described.

Accurate sequence specific information readout of the genetic material DNA is central to a range of important biological processes such as DNA replication, transcription, repairing and recombination. Judiciously engineered intervention into these processes by molecules capable of sequence specific recognition constitutes a medically relevant[1] and chemically challenging[2] subject of studies. The last decade has witnessed acceleration in activities in the development of DNA minor groove recognizing molecules. In particular, the naturally occurring oligopeptidic antibiotics netropsin (**1**) and distamycin A (**2**) have served as molecular paradigms in such development.[3] The term 'lexitropsin', implying a generalized information-reading ligand, was coined for analogues of these two prototype molecules[4a] and efforts have been made to enable these designed molecules to specifically recognize GC-containing and longer sequences by, for example, substituting imidazole for pyrrole[5]



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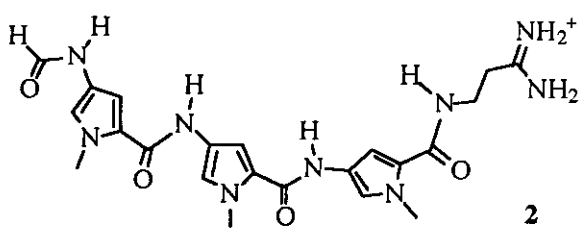

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and increasing the number of the aminoacid residue.[6]

Structural information from X-ray diffraction analysis and nmr spectroscopy is instrumental in guiding the process of molecular design. Recent solution nmr studies[7] elucidated a structural motif different from what was previously observed from X-ray diffraction analysis on crystals of minor groove binders and oligonucleotides[4] and confirmed an earlier speculation from hydrodynamic studies.[8] As shown on the left of Figure 1, this new motif has two oligopeptide molecules, instead of one, packed in the same site of the minor groove in an antiparallel side by side manner with each positively charged end pointing to the 3' direction of the corresponding neighboring strand and covering five base pairs most frequently. Generality of this structural motif was further supported from studies on imidazole-containing lexitropsins.[9,11] A notable phenomenon is that one distamycin molecule and one imidazole-containing lexitropsin can interact with the corresponding matched sequence with greater strength and cooperativity than a pair of identical distamycin A or lexitropsin molecules, which constitutes a unique pattern of strand specific information readout.[9]

To further explore this antiparallel side by side motif, we have recently designed covalently cross-linked dimeric lexitropsins, as illustrated on the right of Figure 1.[11a,b] The underlying concept is to convert a termolecular binding process into a bimolecular one. Because the binding strength of an optimized covalently linked

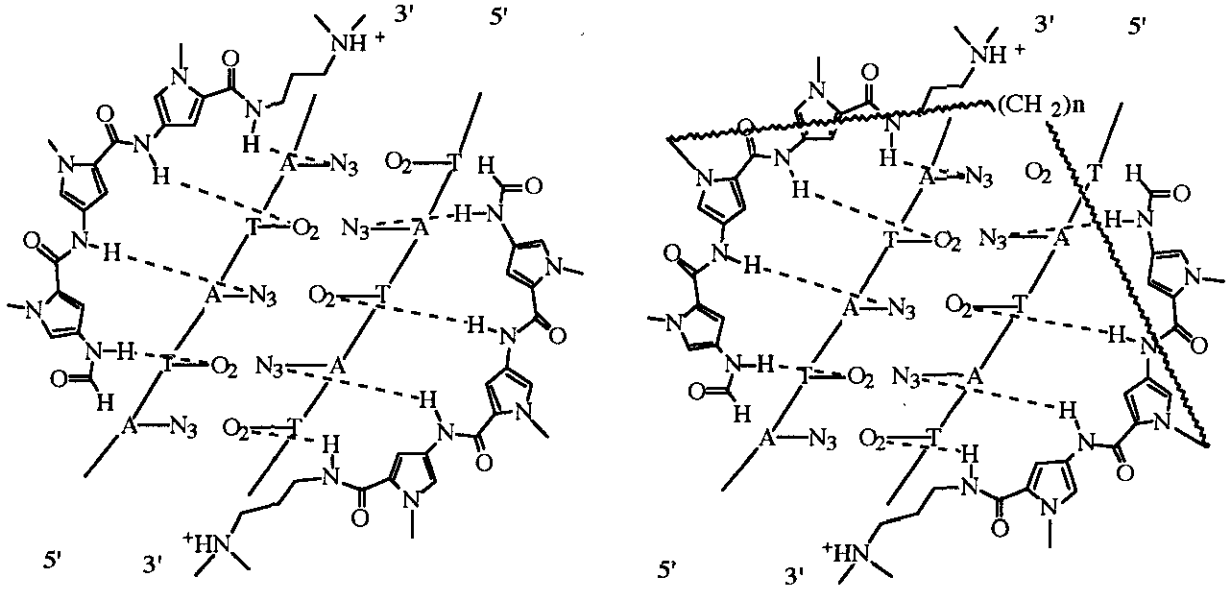
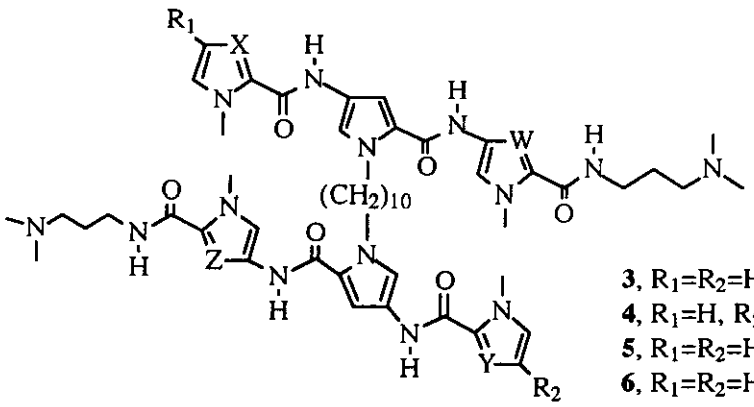


Figure 1 The antiparallel side by side binding motif and the designed bidentate binding of a cross-linked lexitropsin (Only hydrogen bonding interactions are shown).

lexitropsin is more than the product of two stepwise binding constants due to free energy additivity,[10] binding mechanisms except the bidentate binding by the dimeric ligand would be greatly suppressed. The covalent cross linkage may also restrict two tripeptide binding moieties to covering only five base pairs at maximum. The homogeneity of binding mode and thus the binding specificity to the DNA sequence accomodating such a covalently-linked antiparallel side by side binding motif could be improved. Others have explored the same idea as well.[11c] Experimentally, we demonstrated greatly enhanced binding strength and therefore specificity of suitably cross-linked dimeric pyrrole-containing lexitropsins in comparison to the monomer, by circular dichroism and ethidium fluorometry.[11a] Using the same methodology, the decakis(methylene) chain was identified to be the optimal cross-linker among all screened polymethylene chains.[11b,d] Therefore, the stage is set for further expansion into imidazole-containing cross-linked lexitropsins which may specifically recognize defined GC-containing sequences.[11e] In this article, we will present the design and synthesis of selected cross-linked lexitropsins incorporating imidazole rings.

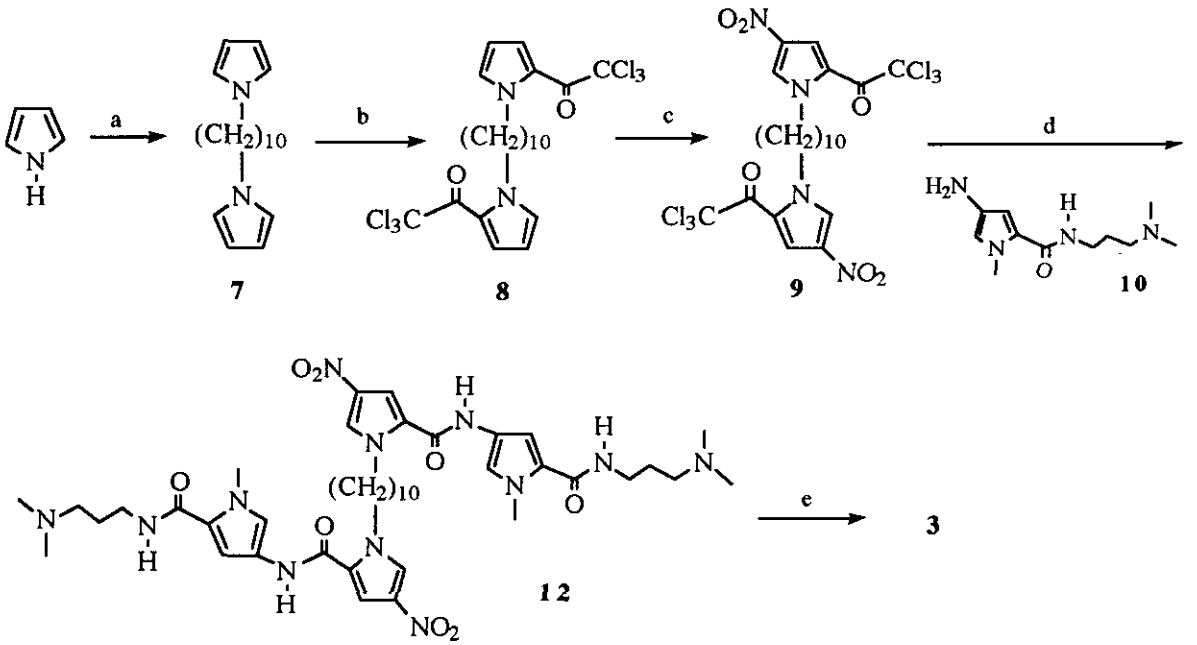
The first two imidazole-containing lexitropsins are selected as **3** and **4** since interactions of their constituent monomeric units with corresponding sequences have been well characterized by footprinting, affinity cleavage and ^{1}H-nmr spectroscopy.[9a,12] They should recognize 5'-(A,T)G(A,T)C(A,T)-3' (sequence a) and 5'-(A,T)G(A,T)(A,T)(A,T)-3' (sequence b) sequences respectively. The next two imidazole-containing lexitropsins are chosen as **5** and **6** which have imidazole substituting for pyrrole in the dimethylamino end. Although interactions of individual monomeric units with DNA are not yet clear, they are expected to specifically recognize 5'-(A,T)C(A,T)G(A,T)-3' (sequence c) and 5'-(A,T)C(A,T)(A,T)(A,T)-3' (sequence d) sequences respectively, according to the antiparallel side by side motif. Sequences (c) and (d) are simply from G and C transversion of (a) and (b) respectively. Whether or not these subtle differences can be differentiated by the selected cross-linked



3, R_1=R_2=H, X=Y=N, W=Z=CH.
4, R_1=H, R_2=HCONH, X=N,Y=CH,W=Z=CH.
5, R_1=R_2=HCONH, X=Y=CH, W=Z=N.
6, R_1=R_2=HCONH, X=Y=CH, W=N, Z=CH.

lexitropsins presents an opportunity to examine the usefulness and limitation of the designed covalently cross-linked antiparallel side by side binding motif.

Synthesis of these target molecules shares a common intermediate (**9**), the preparation of which followed a protocol previously developed for its analogues of shorter polymethylene linkers.[11a] Pyrrole was converted into its potassium salt and reacted with 1,10-dibromodecane to give 1,1'-decanediylbispyrrole (**7**). Regiospecific bis-trichloroacetylation of **7** to **8** and the following bis-nitration of **8** afforded **9** in an overall yield of 34%.[10a,12a] (Scheme 1) Coupling of **9** with the air-sensitive amine (**10**), obtained from catalytic hydrogenation of the known compound[13a] (**11**) provided tetrapyrrole intermediate (**12**). Catalytic hydrogenation of **12** and subsequent reaction with 1-methyl-2-trichloroacetylimidazole[13a] provided the cross-linked lexitropsin (**3**) in 63% yield.

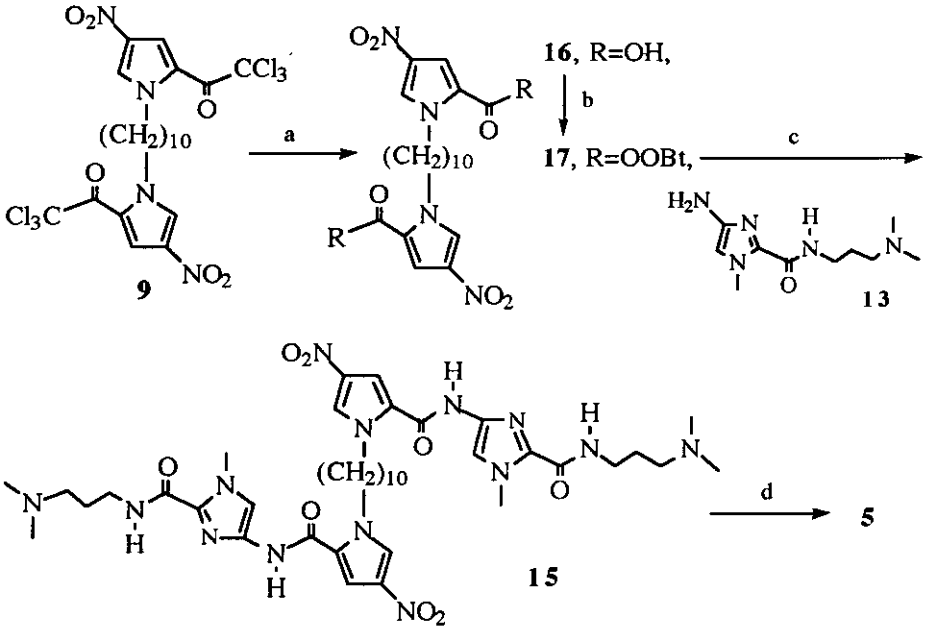


a. K, THF, reflux; $Br(CH_2)_{10}Br$, 89%. b. CCl_3COCl, CH_2Cl_2, 74%. c. Ac_2O, HNO_3, -40°C to room temperature, 51%. d. **10**, H_2, PtO_2, MeOH; DMF, 55°C, 60%. e. H_2, PtO_2, MeOH; DMF, 55°C, 63%.

Scheme 1

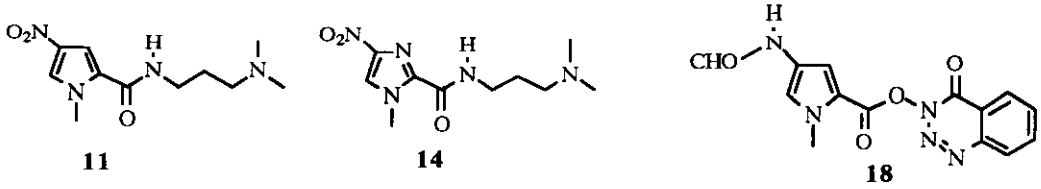
The coupling reaction between **9** and the air-sensitive diamino intermediate (**13**) from reduction of **14**[13b] proved to be capricious, giving inconsistent and low yields of **15**. Therefore, **9** was hydrolyzed to the corresponding diacid (**16**) in water and THF mixture with sodium hydride in a yield of 92% (Scheme2). This diacid was converted to its corresponding activated diester (**17**) by DCC and HOOBt (3-hydroxy-1, 2, 3-benzotriazolin-4-one) in 98% yield. The latter was coupled successfully with the labile amine (**13**), obtained from reduction of

14,[13b] to generate compound (**15**) in 54% yield. Catalytic hydrogenation of **15** and subsequent reaction with activated ester (**18**)[11a] furnished **5** in a yield of 50%.

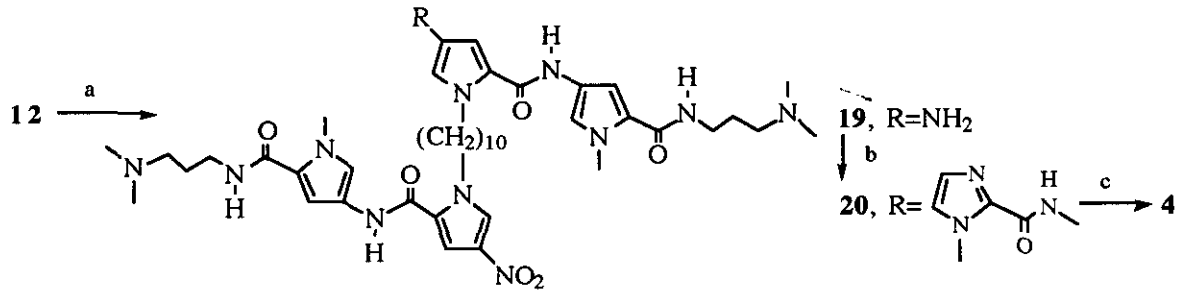


a. THF/H_2O, NaH, 92%. b. HOBt, DCC, DMF, 98%. c. DMF, 55°C, 54%. d. H_2, 10% Pd-C, MeOH; HOOBt, DCC, DMF, 55°C, 50%.

Scheme 2



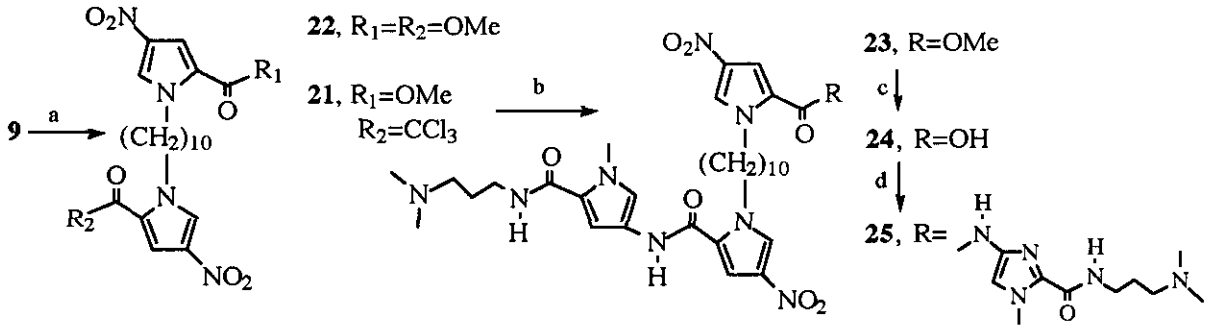
To prepare the non-symmetric molecule (**4**), the yield of the monoamino intermediate (**19**) from partial reduction of **12** was maximized by reducing the amount of catalyst used and monitoring the reaction closely (Scheme 3). Interception of this reduction with 1-methyl-2-trichloroacetylimidazole afforded **20** in 35% yield after repeated column chromatography purification. Reduction of the mono-nitro intermediate (**20**), followed by coupling with the activated ester (**18**) produced **4** in a yield of 65%.



a. H_2, PtO_2, MeOH. b. 1-methyl-2- trichloroacetylimidazole, DMF, 35%. c. H_2, PtO_2, MeOH; **18**, DMF, 55°C, 65%.

Scheme 3

For synthesis of the other non-symmetric molecule (**6**), compound (**9**) was first converted to monoester (**21**) in a yield of 47% by treatment with one equivalent of methanol (Scheme 4). Diester (**22**) was obtained as well, as a result of bisesterification (39% yield). Coupling of **21** with the reduction product (**10**) in DMF provided **23** smoothly, which was further hydrolyzed to acid (**24**) under basic conditions. Reaction of **24** with the labile amine (**13**) in the presence of DCC and HOOBt generated the non-symmetric intermediate (**25**). Finally, catalytic hydrogenation reduced **25** to its diamino product, which was treated with activated ester (**18**) to complete the synthesis of **6** in 43% yield.

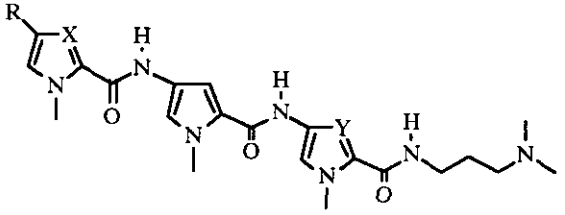


a. MeOH, THF, NaH, 47%. b. **11**, DMF, 67%. c. MeOH, H_2O, NaOH, 90%. d. **14**, HOOBt, DCC, DMF, 55°C, 58%.

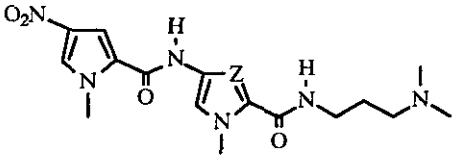
Scheme 4

In order to provide experimental controls for binding studies of these imidazole-containing dimers, we have also prepared their constituent monomers (**26**), (**28**), and (**30**). Compound (**26**) was prepared as previously described.[11a] Compound (**28**) was prepared by reducing the nitro group of the known intermediate (**27**) to the corresponding amino group and, without isolation, coupling the labile intermediate with 1-methyl-2-tricloroacetylimizazole (90% yield). To synthesize compound (**30**), the intermediate (**29**) was prepared by

coupling **13** with 1-methyl-4-nitro-2-trichloroacetylpyrrole in a yeild of 52%. Hydrogenation of **29** went smoothly to afford the corresponding amine which upon treatment with the activated ester (**18**) generated the desired compound (**30**) in 70% yield.



26, R=HCONH, X=Y=CH.
28, R=H, X=N,Y=CH.
30, R=HCONH, X=H, Y=N.



27, Z=CH.
29, Z=N.

In summary, we have designed imidazole-incorporating lexitropsins in order to explore the generality of the covalently linked antiparallel side by side binding motif, in the context of specific recognition of GC-containing double-stranded DNA sequences, and developed general synthetic routes to incorporate imidazole rings into both symmetric and non-symmetric cross-linked lexitropsins illustrated above.

With these selected cross-linked lexitropsins (**3**)-(**6**) and their corresponding monomers (**26**), (**28**) and (**30**) now available, biophysical and biochemical analysis of interactions between these imidazole-containing cross-linked lexitropsins and DNA are ongoing and will be reported in due course.

EXPERIMENTAL

Melting points were determined on a Fisher-Johns apparatus and uncorrected. Uv spectra were taken on a Hewlett-Packard diode array HP8542 spectrophotometer. Ir spectra were recorded on Nicolet magna 750 spectrophotometer with a Nic-plane microscope. In the ir data presentation, bracketed w, m, s, and vs indicate the extent of absorption as weak, medium, strong, and very strong and maximal absorption frequencies (ν_{max}) are reported in cm^{-1}. ^{1}H-Nmr spectra were measured on a Varian 300 instrument with TMS as internal standard on the ppm scale (δ). Multiplicities of resonance peaks are indicated as singlet (s), doublet (d), triplet (t), broad singlet (br s), quartet (q), and multiplet (m) and coupling constants (J) are expressed in Hz. Electron impact (EI) mass measurement was performed on a Kraytos MS 50 high resolution mass spectrometer while fast atom bombardment (FAB) mass measurement was carried out with AEI MS-9 and MS-50 mass spectrometers using 1,4-dithiothreol (Cleland's reagent) as the matrix. Elemental analysis was performed by the departmental service at the University of Alberta on a Carlo Erba Instruments EA 1108 elemental analyzer. Anhydrous THF was

distilled from sodium and dichloromethane from phosphorus pentaoxide. Anhydrous DMF and methanol were purchased from the Aldrich Chemical Company and used without further purification. Both plastic-backed analytical and glass-backed preparative silica gel tlc plates, 0.1 mm and 1.0 mm thick respectively, were purchased from the BDH ltd., while silica gel for column chromatography (230-400 mesh) was from the Merck company.

1,1'-(1,10-Decanediyl)bis[*1H*-pyrrole] (**7**). To a solution of freshly distilled pyrrole (15.3 ml, 0.22 mol) in anhydrous THF (150 ml) was introduced pieces of potassium metal (8.60 g, 0.22 mol) under a nitrogen atmosphere. The solution was refluxed for 5 h during which time the potassium disappeared and a white suspension resulted. 1,10-Dibromodecane (24.7 ml, 0.11 mol) was added dropwise over 30 min and the mixture was heated to reflux overnight. The reaction mixture was cooled to room temperature and filtered. The white solid residue was dissolved in water (100 ml) and the solution extracted with ether (2x100 ml). The combined organic fractions were concentrated in vacuo to give a yellowish oil. Fractional vacuum distillation (0.05 mmHg) furnished **7** as a colorless oil (26.54 g, 89%) at 176-178°C (0.05 mmHg). Ir (film) ν_{max}: 3100 (w), 2927 (vs), 2854 (s), 1500 (s), 1281 (s), 1088 (s), 721 (vs). ^{1}H Nmr ($CDCl_3$) δ: 1.28 (12H, s), 1.76 (4H, m), 3.86 (4H, t, J=7.2), 6.15 (4H, t, J=2.0), 6.65 (4H, t, J=2.0). EIms *m/z* (relative intensity): 272.22519 (57.6, M^+, 272.22525 calcd for $C_{18}H_{28}N_2$), 192 (5.6), 150 (8.0), 136 (26.3), 122 (26.3), 94 (15.1), 81 (100.0). Anal. Calcd for $C_{18}H_{28}N_2$: C, 79.34, H, 10.04, N, 10.28. Found: C, 79.18, H, 10.05, N, 10.29.

1,1'-(1,10-Decanediyl)-bis[2-(trichloroacetyl)-*1H*-pyrrole] (**8**). To the solution of **7** (8.00 g, 29.4 mmol) in anhydrous dichloromethane (50 ml) was added trichloroacetyl chloride (7.00 ml, 61.7 mmol) over one h under nitrogen at room temperature. Rapid evolution of gas was observed. The resulting brown solution was stirred for 24 h. The reaction mixture was filtered rapidly through a small layer of silica gel and dried ($MgSO_4$). Evaporation of the yellowish filtrate *in vacuo* provided **8** as a light yellow oil (12.23 g, 74%). Ir (film) ν_{max}: 3100 (w), 2927 (s), 2855 (m), 1668 (vs), 1407 (s), 741 (vs). ^{1}H Nmr ($CDCl_3$) δ: 1.30 (12H, m), 1.75 (4H, m), 4.30 (4H, t, J=7.2), 6.23 (2H, dd, J=4.5 and 2.5), 7.10 (2H, t, J=2.5), 7.53 (2H, dd, J=4.5 and 2.5). EIms *m/z* (relative intensity): 566.00315 (5.1, M^+, 566.00372 calcd for $C_{22}H_{36}N_2O_2{}^{35}Cl_3{}^{37}Cl_3$), 564.00631 (12.6, M^+, 564.00665 calcd for $C_{22}H_{36}N_2O_2{}^{35}Cl_4{}^{37}Cl_2$), 562.00946 (15.4, M^+, 562.00958 calcd for $C_{22}H_{36}N_2O_2{}^{35}Cl_5{}^{37}Cl$), 560.01236 (7.6, M^+, 560.01257 calcd for $C_{22}H_{36}N_2O_2{}^{35}Cl_6$), 527 (8.0), 499 (8.4), 443 (78.6), 415 (62.9), 163 (100.0).

1,1'-(1,10-Decanediyl)bis[4-nitro-2-(trichloroacetyl)-*1H*-pyrrole] (**9**). A suspension of **8** (8.00 g, 12.9 mmol) in a mixture of acetic anhydride (35 ml) and dichloromethane (35 ml) was cooled to -78°C. To this

mixture was introduced fuming nitric acid (2.10 ml, >90%) dropwise for 15 min. The brown mixture was warmed to room temperature gradually over 35 min and stirred for 1.5 h. The final reaction mixture was diluted with dichloromethane, neutralized with saturated sodium bicarbonate solution, and dried ($MgSO_4$). A brown foam was obtained after evaporation of solvents *in vacuo*. Silica gel chromatography with petroleum ether and dichloromethane (1:1, v/v) provided **9** as a yellowish solid (4.50 g, 49%). mp 118-120°C. Ir (film) ν_{max}: 3140 (m), 2828 (s), 2856 (m), 1693 (vs), 1515 (s), 1315 (vs), 747 (s). ^{1}H Nmr ($CDCl_3$) δ: 1.33 (12H, m), 1.81 (4H, m), 4.37 (4H, t, J=7.6), 7.78 (2H, d, J=1.6), 7.98 (2H, d, J=1.6). EIms *m/z* (relative intensity): 655.97216 (1.8, M^+, 655.97388 calcd for $C_{22}H_{24}N_4O_6{}^{35}Cl_3{}^{37}Cl_3$), 653.97569 (2.7, M^+, 653.97681 calcd for $C_{22}H_{24}N_4O_6{}^{35}Cl_4{}^{37}Cl_2$), 651.98302 (3.7, M^+, 651.97974 calcd for $C_{22}H_{24}N_4O_6{}^{35}Cl_5{}^{37}Cl$), 649.98685 (1.6, M^+, 649.98273 calcd for $C_{22}H_{24}N_4O_6{}^{35}Cl_6$), 535 (58.2), 370 (16.2), 208 (68.4), 120 (45.0), 68 (100). Anal. Calcd for $C_{22}H_{24}N_4O_6Cl_6$: C, 40.46, H, 3.70, N, 8.58. Found: C, 40.80, H, 3.65, N, 8.28.

1,1'-(1,10-Decanediyl)bis[*N*-[5-[[(3,3-dimethylaminopropyl)amino]carbonyl]-1-methyl-*1H*-pyrrol-3-yl]-4-nitro-*1H*-pyrrole-2-carboxamide] (**12**). Platinum oxide (55 mg) was added to (3,3-dimethylamino)propyl-1-methyl-4-nitro-pyrrolecarboxamide (**11**) (535 mg, 2.11 mmol) in anhydrous methanol (10.0 ml). This mixture was degassed by the freeze and thaw procedure and then charged with 1 atm hydrogen. A vigorous stirring was maintained at room temperature for 3 h. The methanol was removed *in vacuo* and DMF (5.0 ml) was introduced. The DMF solution was evaporated to dryness *in vacuo* and anhydrous DMF (5.0 ml) was reintroduced. To this DMF solution was then added compound (**9**) (654 mg, 1.00 mmol) and stirring was continued for 5 h at room temperature under nitrogen. The crude mixture was chromatographed over a silica gel column with conc. ammonia solution and methanol mixture (1/19, v/v) as eluent. The desired product (**12**) (475 mg, 56%) was obtained as a yellow solid after evaporation of solvents. mp 90-92 °C. Ir (solid) ν_{max}: 3600-2300 (s, br), 2929 (s), 1644 (vs), 1535 (s), 1313 (vs), 751 (s). ^{1}H Nmr (DMSO-d_6) δ: 1.20 (12H, br s), 1.67 (8H, m), 2.15 (12H, s), 2.25 (4H, t, J=7.2), 3.18 (4H, q, J=7.2), 3.67 (6H, s), 3.80 (6H, s), 4.38 (4H, t, J=7.0), 6.80 (2H, d, J=1.8), 7.18 (2H, d, J=1.8), 7.54 (2H, d, J=1.8), 8.11 (2H, t, J=7.2), 8.20 (2H, d, J=1.8), 10.27 (2H, s). LRFABms *m/z* (relative intensity): 863 ($M+H^+$, 29.3), 848 (5.8), 775 (0.8), 735 (0.5), 357 (6.6), 155 (40.2), 119 (100.0); HRFABms: 863.4864 ($M+H^+$, 863.4892 calcd for $C_{42}H_{62}N_{12}O_8H$).

1,1'-(1,10-Decanediyl)bis[*N*-[5-[[(3,3-dimethylaminopropyl)amino]carbonyl]-1-methyl-*1H*-pyrrol-3-yl]-4-[[[1-methyl-*1H*-imidazol-2-yl]carbonyl]amino]-*1H*-pyrrole-2-carboxamide] (**3**). Compound (**12**) (35 mg, 0.041 mmol) was dissolved in methanol (2.0 ml) and platinum oxide (12 mg) introduced. Removal of air by the freeze-thaw procedure was followed by stirring under 1 atm hydrogen at room

temperature for 4 h. The reaction mixture was concentrated and redissolved in anhydrous DMF (2.0 ml). After evacuation of DMF to eliminate the residual methanol, 1-methyl-2-triacetylimidazole (28 mg, 0.12 mmol) and anhydrous DMF (2.0 ml) were added. The mixture was stirred at room temperature under nitrogen for 3 h. Tlc chromatography with 5% concnetrated ammonia solution in methanol (v/v) provided **3** as a yellowish solid (26 mg, 63%). mp 149-151°C. Ir (solid) ν_{max}: 3600-2600 (s, broad), 3110 (w), 2925 (s), 2854 (m), 1649 (vs), 1533 9s), 1464 (s), 1428 (s), 1124 (s). ^{1}H Nmr (DMSO-d_6) δ: 1.23 (12H, m), 1.61 (8H, m), 2.14 (6H, s), 2.25 (4H, t, J=6.3), 3.18 (4H, t, J=6.3), 3.81 (6H, s), 4.00 (6H, s), 4.28 (4H, m), 6.84 (2H, d, J=2.0), 7.06 (2H, d, J=0.8), 7.11 (2H, d, J=2.0), 7.19 (2H, d, J=2.0), 7.34 (2H, d, J=2.0), 7.39 (2H, d, J=0.8), 8.10 (4H, m), 9.92 (2H, s), 10.43 (2H, s). LRFABms *m/z* (relative intensity): 1020 ($M+H^+$, 3.3), 897 (0.3), 663 90.6), 463 (2.2), 371 (4.5), 242 (66.6), 177 (100.0); HRFABms: 1019.6045 ($M+H^+$, 1019.6055 calcd for $C_{52}H_{74}N_{16}O_6H$).

1,1'-(1,10-Decanediyl)bis[*N*-[5-[[(3,3-dimethylaminopropyl)amino]carbonyl]-1-methyl-*1H*-pyrrol-3-yl]]-4-[[[4-formylamino-1-methyl-*1H*-pyrrol-2-yl]carbonyl]amino]-4'-nitro-bis[*1H*-pyrrole-2-carboxamide] (20). To the solution of **12** (100 mg, 0.12 mmol) in methanol (8.0 ml) was added platinum oxide (8.0 mg). After removal of air by the freeze-thaw procedure, the mixture was stirred vigorously at room temperature under 1 atm hydrogen for 1.3 h. The solvent was removed. Then, anhydrous DMF (3.0 ml) was introduced and reevacuated to eliminate the residual methanol. After addition of 1-methyl-2-trichloroacetylimidazole (60 mg, 0.26 mmol) and DMF (anhydrous, 3.0 ml), the mixture was stirred under nitrogen for 2 h. Repeated chromatography with 5% concentrated ammonia solution in methanol (v/v) provided the recovered starting material (**12**) (25 mg), **20** (29 mg, 35% based on starting material recovery) and **3** (40 mg, 45% based on starting material recovery). mp 117-120°C. Ir (solid) ν_{max}: 3700-2400 (s, br), 2927 (s), 2855 (m), 1656 (vs), 1536 (vs), 1312 (s). ^{1}H Nmr (DMSO-d_6) δ: 1.20 (12H, s), 1.70 (8H, m), 2.61 (12H, br s), 2.85 (4H, m), 3.22 (4H, m), 3.80 (6H, br s), 3.97 (3H, s), 4.25 (2H, t, J=7.8), 4.38 (2H, t, J=7.8), 6.96 (1H, d, J=1.7), 6.98 (1H, d, J=1.7), 7.03 (1H, d, J=0.9), 7.10 (1H, d, J=1.7), 7.17 (1H, d, J=1.7), 7.32 (1H, d, J=1.7), 7.39 (1H, J=0.9), 7.55 (1H, d, J=1.7), 8.10-8.15 (3H, m), 9.92 (1H, s), 10.27 (1H, s), 10.46 (1H, s). LRFABms *m/z* (relative intensity): 941 ($M+H^+$, 9.6), 863 (1.4), 471 90.9), 355 (1.4), 149 (47.2), 135 (59.1), 119 (94.1), 109 (100.0); HRFABms: 941.5459 ($M+H^+$, 941.5474 calcd for $C_{47}H_{68}N_{14}O_7H$).

1,1'-(1,10-Decanediyl)bis[*N*-[5-[[(3,3-dimethylaminopropyl)amino]carbonyl]-1-methyl-*1H*-pyrrol-3-yl]]-4-[[[4-formylamino-1-methyl-*1H*-pyrrol-2-yl]carbonyl]amino]-4'-[[[1-methyl-*1H*-imidazol-2-yl]carbonyl]amino]-bis[*1H*-pyrrole-2-carboxamide] (4). To a solution of compound

(**20**) (21 mg, 0.022 mmol) in methanol (2.0 ml) was added platinum oxide (5.5 mg). After air purging, the mixture was vigorously stirred under 1 atm hydrogen at room temperature for 3 h. Concentration *in vacuo* gave an oil which was treated with anhydrous DMF (2.0 ml). DMF was then evacuated to remove the residual methanol. After addition of activated ester (**18**) (15 mg, 0.048 mmol) and anhydrous DMF (2.0 ml), the mixture was heated at 55°C for 2 h. Purification by silica gel tlc chromatography with 5% ammonia in methanol (v/v) as eluent afforded **4** as yellowish solid (15 mg, 65%). mp 142-143°C. Ir (solid) ν_{max}: 3600-2800 (s, br), 2925 (s), 2854 (m), 1640 (vs), 1529 (vs), 1254 (s). ^{1}H Nmr (DMSO-d_6) δ: 1.20 (12H, br s), 1.60 (8H, m), 2.15 (12H, s), 2.24 (4H, t, J=6.3), 3.19 (4H, m), 3.80 (6H, s), 3.99 (3H, s), 4.26 (4H, br s), 6.83 (2H, br s), 7.05 (2H, br s), 7.11 (2H, br s), 7.18 (2H, br s), 7.33 (2H, br s), 7.40 (2H, br s), 8.09 (3H, m), 9.90 (2H, br s), 10.45 (2H, s). LRFABms *m/z* (relative intensity): 1061 ($M+H^+$, 1.0), 1049 (0.6), 898 (0.3), 309 (12.8), 119 (100.0); HRFABms: 1061.6113 ($M+H^+$, 1061.6161 calcd for $C_{54}H_{76}N_{16}O_7H$).

1,1'-(1,10-Decanediyl)bis[4-nitro-*1H*-pyrrole-2-carboxylic acid] (16). Compound (**9**) (1.00 g, 1.52 mmol) was dissolved in the mixture of THF (4.0 ml) and water (4.0 ml) and cooled to 0°C. To the solution was added 80% sodium hydride in paraffin oil (185 mg, 6.17 mmol) slowly. The resulting solution was stirred at room temperature under nitrogen for 3 h. After removal of THF *in vacuo*, the aqueous solution was neutralized with 2 M hydrochloric acid and a white precipitate appeared. After cooling to 0°C, the white precipitate of **16** was collected by filtration (620 mg, 92%). mp 194-196°C (decomp.). Ir (solid) ν_{max}: 3300-2400 (s, br), 3115 (m), 2934 (s), 2861 (m), 1675 (vs), 1315 (vs). ^{1}H Nmr (DMSO-d_6) δ: 1.21 (12H, br s), 1.72 (4H, m), 4.32 (4H, t, J=7.2), 7.28 (2H, d, J=2.0), 8.27 (2H, d, J=2.0), 12.98 (2H, br s). EIms *m/z* (relative intensity): 450.17612 (3.0, M^+, 450.17508 calcd for $C_{20}H_{26}N_4O_8$), 375 (13.9), 170 (28.2), 126 (94.5), 120 (100.0), 106 (59.6), 80 (77.1). Anal. Calcd for $C_{20}H_{26}N_4O_8$: C, 53.33, H, 5.82, N, 12.44. Found: C, 53.10, H, 5.82, N, 12.14.

1,1'-(1,10-Decanediyl)bis[2-[[(1,2,3)-benzotriazin-4(*3H*)-one-3-yl]oxy]carbonyl-4-nitro-*1H*-pyrrole] (17). To the solution of diacid (**16**) (450 mg, 1.00 mmol) in anhydrous DMF (5.0 ml) was added HOOBt (340 mg, 2.09 mmol) and DCC (439 mg, 2.09 mmol). The mixture was stirred at room temperature under nitrogen for 1 h, filtered and concentrated *in vacuo*. Chromatography with dichloromethane provided activated diester (**17**) as a yellowish solid (712 mg, 98%). mp 151-153°C. Ir (solid) ν_{max}: 3130 (s), 3110 (s), 2931 (vs), 2857 (s), 1764 (vs), 1708 (vs). ^{1}H Nmr ($CDCl_3$) δ: 1.30 (12H, br s), 1.82 (4H, br s), 4.34 (4H, t, J=7.3), 7.82 (2H, d, J=1.9), 7.86-7.92 (4H, m), 8.05 (2H, td, J=8.5 and 1.5), 8.27 (2H, dd, J=8.5 and 1.5), 8.41 (2H, dd, J=8.5 and 1.5). LRFABms *m/z* (relative intensity): 741 ($M+H^+$, 0.5), 582 (0.4), 471 (0.5), 326

(11.7), 216 (0.6), 118 (100.0); HRFABms: 741.2352 ($M+H^+$, 741.2382 calcd for $C_{34}H_{32}N_{10}O_{10}H$). Anal. Calcd for $C_{34}H_{32}N_{10}O_{10}$: C, 55.13, H, 4.35, N, 18.91. Found: C, 55.24, H, 4.39, N, 18.57.

1,1'-(1,10-Decanediyl)bis[*N*-[2-[[(3,3-dimethylaminopropyl)amino]carbonyl]-1-methyl-*1H*-imidazol-4-yl]-4-nitro-*1H*-pyrrole-2-carboxamide] (15). To the solution of **14** (300 mg, 1.18 mmol) in methanol (5.0 ml) was added 10% palladium on charcoal (75 mg). After removal of air by the freeze and thaw procedure, the mixture was stirred vigorously under 1 atm hydrogen at room temperature for 2 h. Concentration in vacuo gave an oil which was treated DMF (5 ml). The mixture was re-evacuated to remove the residual methanol. After introduction of compound (**17**) (430 mg, 0.59 mmol) and anhydrous DMF (5.0 ml), the resulting mixture was heated at 55°C for 3 h. Silica gel chromatography with 3% ammonia in methanol (v/v) furnished **15** as a pale yellowish solid (275 mg, 54%). mp 91-93°C. Ir (solid) ν_{max}: 3600-1500 (s), 2932 (s), 2857 (m), 1659 (vs), 1529 (vs), 750 (m). ^{1}H Nmr (DMSO-d_6) δ: 1.20 (12H, br s), 1.65 (8H, m), 2.12 (12H, s), 2.22 (4H, t, J=7.2), 3.25 (4H, q, J=7.5), 3.91 (6H, s), 4.37 (4H, t, J=6.5), 7.50 (2H, br s), 7.75 (2H, br s), 8.00 (2H, t, J=7.2), 8.22 (2H, br s), 10.79 (2H, s). LRFABms *m/z* (relative intensity): 865 ($M+H^+$, 21.2), 835 (4.0), 584 (1.8), 555 (2.2), 432 (100.0), 306 (19.1), 129 (96.4); HRFABms: 865.4802 ($M+H^+$, 865.4808 calcd for $C_{40}H_{60}N_{14}O_8H$).

1,1'-(1,10-Decanediyl)bis[*N*-[2-[[(3,3-dimethylaminopropyl)amino]carbonyl]-1-methyl-*1H*-imidazol-4-yl]-4-[[[4-formylamino-1-methyl-*1H*-pyrrol-2-yl]carbonyl]amino]-*1H*-pyrrole-2-carboxamide] (5). Compound (**15**) (32 mg, 0.037 mmol) was dissolved in anhydrous methanol (2.0 ml) and platinum oxide (8.0 mg) was introduced. After removal of air, the mixture was stirred under 1 atm hydrogen for 2.5 h at room temperature. Concentration in vacuo afforded a viscous oil to which DMF (2.0 ml) was introduced and reevacuated to remove the residue methanol. After addition of activated ester (**18**) (14 mg, 0.045 mmol) and DMF (2.0 ml), the mixture was stirred at 55°C under nitrogen for 1.5 h. Silica gel tlc chromatography with 5% ammonia in methanol (v/v) provided **5** as a yellowish solid (20 mg, 50%). mp 154-156°C. Ir (solid) ν_{max}: 3127 (m), 2932 (s), 2857 (m), 1659 (vs), 1529 (vs), 1383 (s), 1361 (s), 750 (m). ^{1}H Nmr (DMSO-d_6) δ: 1.20 (12H, br s), 1.60 (8H, m), 2.10 (12H, s), 2.21 (4H, t, J=7.2), 3.23 (4H, t, J=7.2), 3.81 (6H, s), 3.91 (6H, s), 4.25 (4H, t, J=7.0), 6.90 (2H, d, J=2.0), 7.03 (2H, d, J=2.0), 7.19 (2H, d, J=2.0), 7.33 (2H, d, J=2.0), 7.47 (2H, s), 8.08 (2H, t, J=7.2), 8.11 (2H, s), 9.95 (2H, s), 10.08 (2H, s), 10.25 (2H, s). LRFABms *m/z* (relative intensity): 1106 ($M+H^+$, 4.1), 890 (5.4), 590 (1.5), 444 (6.2), 177 (79.0), 151 (100.0); HRFABms: 1105.6160 ($M+H^+$, 1105.6172 calcd for $C_{54}H_{76}N_{18}O_8H$).

1,1'-(1,10-Decanediyl)-2-methoxycarbonyl-2'-trichloroacetyl-bis[4-nitro-*1H*-pyrrole] (**21**) and **1,1'-(1,10-Decanediyl)-bis[2-methoxycarbonyl-4-nitro-*1H*-pyrrole]** (**22**). To the solution of compound (**9**) (1.00 g, 1.54 mmol) in anhydrous THF (5.0 ml) under nitrogen was introduced anhydrous methanol (62.3 µl, 1.54 mmol) and sodium hydride (15 mg, 0.50 mmol, 80% in paraffin oil). The mixture was stirred at room temperature for 1 h. Concentration furnished the crude product which was chromatographed over silica gel with methylene chloride. Starting material (**9**) (143 mg, 14%), semiester (**21**) (351 mg, 47% yield based on starting material recovery), and diester (**22**) (228 mg, 39% based on starting material recovery) were obtained. **21**: mp 83-86°C. Ir (solid) ν_{max}: 3142 (s), 2925 (s), 2855 (s), 1725 (vs), 1710 (vs), 1459 (s), 1092 (vs). ^{1}H Nmr ($CDCl_3$) δ: 1.30 (12H, br s), 1.80 (4H, t, J=6.3), 4.37 (4H, m), 3.87 (3H, s), 7.43 (1H, d, J=1.9), 7.63 (1H, d, J=1.9), 7.77 (1H, d, J=1.9), 7.98 (1H, d, J=1.9). EIms *m/z* (relative intensity): 566.09272 (6.5, M^+, 566.09155 calcd for $^{35}Cl_2{}^{37}Cl$), 564.09472 (6.7, M, 564.09454 calcd for $C_{22}H_{27}N_4O_7{}^{35}Cl_3$), 447 (47.4), 342 (9.1), 279 (5.4), 184 (100.0), 120 (71.1). Anal. Calcd for $C_{22}H_{27}N_4O_7Cl_3$: C, 46.70, H, 4.81, N, 9.90. Found: C, 47.05, H, 4.91, N, 10.01. **22**: mp 120-121°C. Ir (solid) ν_{max}: 3139 (w), 2929 (w), 2855 (w), 1711 (vs), 1507 (s), 1320 (vs), 1094 (m), 750 (m). ^{1}H Nmr ($CDCl_3$) δ: 1.29 (12H, br s), 1.79 (4H, m), 3.85 (6H, s), 4.32 (4H, t, J=7.5), 7.41 (2H, d, J=2.0), 7.60 (2H, d, J=2.0). EIms *m/z* (relative intensity): 478.20515 (16.9, M^+, 478.20636 calcd for $C_{22}H_{30}N_4O_8$), 432 (21.4), 373 (52.7), 356 (22.1), 184 (100.0), 168 (14.6), 120 (52.6), 55 (53.7). Anal. Calcd for $C_{22}H_{30}N_4O_8$: C, 55.22, H, 6.32, N, 11.71. Found: C, 54.89, H, 6.25, N, 11.44.

1,1'-(1,10-Decanediyl)-2-[[5-[[(3,3-dimethylaminopropyl)amino]carbonyl]-1-methyl-*1H*-pyrrol-3-yl]amino]carbonyl-2'-methoxycarbonyl-bis[4-nitro-*1H*-pyrrole] (**23**). Compound (**12**) (50 mg, 0.20 mmol) was dissolved in anhydrous methanol (2.0 ml) and platinum oxide (5.0 mg) was introduced. After removal of air by the freeze and thaw procedure, the mixture was stirred under 1 atm hydrogen at room temperature for 2.5 h. Concentration *in vacuo* provided a viscous oil which was redissolved in DMF (2.0 ml). The mixture was concentrated again and redissolved in DMF (2.0 ml) to which semiester (**21**) (104 mg, 0.18 mmol) was introduced. The resulting mixture was stirred under nitrogen for 3 h. The crude product was purified by silica gel chromatography with 2% concentrated ammonia solution in methanol (v/v) to afford ester (**23**) in a yield of 83 mg (67%). mp 110-112°C. Ir (solid) ν_{max}: 3600-2600 (s, br), 3132 (m), 2925 (s), 1716 (s), 1673 (s), 1506 (s), 1044 (s), 1320 (s), 752 (m). ^{1}H Nmr (DMSO-d_6) δ: 1.20 (12H, br s), 1.70 (6H, m), 3.20 (2H, m), 4.31 (2H, t, J=7.2), 4.38 (2H, t, J=7.2), 6.85 (1H, d, J=1.8), 7.19 (1H, d, J=1.8), 7.33 (1H, d, J=2.0), 7.54 (1H, d, J=2.0), 8.17 (1H, t, J=6.3), 8.22 (1H, d, J=2.0), 8.31 (1H, d, J=2.0), 10.26 (1H, s). LRFABms

m/z (relative intensity): 671 ($M+H^+$, 57.1), 655 (7.8), 585 (1.4), 549 (2.6), 177 (34.2), 149 (37.4), 129 (100.0); HRFABms: 671.3496 ($M+H^+$, 671.3517 calcd for $C_{32}H_{46}N_8O_8H$).

1,1'-(1,10-Decanediyl)-2'-[[5-[[(3,3-dimethylaminopropyl)amino]carbonyl]-1-methyl-*1H*-pyrrol-3-yl]amino]carbonyl-bis[4-nitro-*1H*-pyrrole]-2-carboxylic acid (24). Compound (**23**) (78 mg, 0.12 mmol) was treated with dissolved in a mixture of 1.0 M sodium hydroxide solution (1.5 ml, 1.5 mmol) and methanol (1.5 ml). The mixture was stirred at room temperature for 6 h. After neutralization with 2.0 M hydrochloric acid, the solution was concentrated *in vacuo* to give a solid material which was extracted with methanol. The methanol solution was concentrated to give crude **23** which was chromatographed with methanol to provide **23** (73 mg, 90%). mp 117-119°C. Ir (solid) ν_{max}: 3500-2500 (s, br), 3127 (m), 2927 (s), 1666 (s), 1625 (s), 1504 (s), 1312 (s). ^1H Nmr (DMSO-d_6) δ: 1.20 (12H, m), 1.62 (6H, m), 2.10 (6H, s), 2.23 (2H, t, J=6.0), 3.15 (2H, m), 3.80 (3H, s), 4.40 (2H, t, J=6.4), 6.71 (1H, d, J=1.9), 6.88 (1H, d, J=1.9), 7.23 (1H, d, J=1.9), 7.58 (1H, d, J=1.9), 7.76 (1H, d, J=1.9), 8.16 (1H, t, J=5.6), 8.22 (1H, d, J=1.9), 10.48 (1H, s). LRFABms *m/z* (relative intensity): 657 ($M+H^+$, 0.6), 612 (0.4), 305 (0.6), 279 (6.2), 119 (100.0); HRFABms: 657.3357 ($M+H^+$, 657.3354 calcd for $C_{31}H_{44}N_8O_8H$).

1,1'-(1,10-Decanediyl)-*N*-[5-[[(3,3-dimethylaminopropyl)amino]carbonyl]-1-methyl-*1H*-pyrrol-3-yl]]-*N*'-[2-[[(3,3-dimethylaminopropyl)amino]carbonyl]-1-methyl-*1H*-imidazol-4-yl]]-bis[*1H*-pyrrole-2-carboxamide] (25). To a solution of **14** (29 mg, 0.11 mmol) in methanol (2.0 ml) was added 10% paladium in charcoal (7.5 mg). Removal of air by the freeze-thaw procedure was followed by stirring under 1 atm hydrogen at room temperature for 2 h. The reaction mixture was concentrated in vacuo, to which DMF (2.0 ml) was introduced. The resulting mixture was reevacuated to give a viscous oil. After addition of acid (**24**) (71 mg, 0.103 mmol), HOOBt (27 mg, 0.17 mmol), DCC (35 mg, 0.17 mmol) and DMF (2.0 ml), the mixture was heated under nitrogen at 55°C for 1.5 h and concentrated *in vacuo*. Silica gel chromatography with 2% concnetrated ammonia solution in methanol (v/v) furnished **25** (51 mg, 58%). mp 92-94°C. Ir (solid) ν_{max}: 3600-2500 (s, br), 3128 (s), 2929 (s), 1652 (s), 1404 (s), 1309 (s), 1101 (m). ^1H Nmr (DMSO-d_6) δ: 1.19 (12H, s), 1.66 (8H, m), 2.15 (12H, m), 2.23 (4H, t, J=7.5), 3.18 (4H, m), 3.80 (3H, s), 3.92 (3H, s), 4.39 (4H, t, J=6.2), 6.80 (1H, d, J=1.9), 7.19 (1H, d, J=1.9), 7.52 (1H, s), 7.55 (1H, d, J=1.9), 7.73 (1H, s), 8.01 (1H, t, J=6.0), 8.10 (1H, t, J=6.0), 8.22 (2H, m), 10.25 (1H, s), 10.80 (1H, s). LRFABms *m/z* (relative intensity): 864 ($M+H^+$) 10.2), 848 (2.1), 742 (1.3), 444 (3.6), 432 (14.1), 225 (16.8), 177 (37.0), 129 (100.0); HRFABms: 864.4833 ($M+H^+$, 864.4844 calcd for $C_{41}H_{61}N_{13}O_8H$).

1,1'-(1,10-Decanediyl)-*N*-[5-[[(3,3-dimethylaminopropyl)amino]carbonyl]-1-methyl-*1H*-pyrrol-3-yl]]-*N'*-[2-[[(3,3-dimethylaminopropyl)amino]carbonyl]-1-methyl-*1H*-imidazol-4-yl]]-bis[4-[[[4-formylamino-1-methyl-*1H*-pyrrol-2-yl]carbonyl]amino]-*1H*-pyrrole-2-carboxamide] (6). Compound (**25**) (25 mg, 0.029 mmol) was dissolved in anhydrous methanol (2.0 ml) and platinum oxide (5.0 mg) was introduced. The freeze and thaw procedure was applied to remove dissolved air. The mixture was stirred vigorously under 1 atm hydrogen at room temperature for 2 h. Concentration *in vacuo* afforded a viscous oil to which was added DMF (2.0 ml). The resulting mixture was reevacuated and DMF (2.0 ml) reintroduced. After addition of activated ester (**18**) (11 mg, 0.035 mmol), the reaction mixture was stirred and heated at 55°C under nitrogen for 2 h and concentrated *in vacuo*. Silica gel tlc chromatography (1.0 mm thick) with 5% concnetrated ammonia solution in methanol (v/v) provided compound (**6**) in a yield of 43% (14 mg). mp 158-160°C. Ir (solid) ν_{max}: 3600-2500 (s, br), 2928 (s), 1653 (s), 1540 (s), 1436 (s), 838 (m). ^{1}H Nmr (DMSO-d_6) δ: 1.19 (12H, br s), 1.60 (8H, m), 2.09 (12H, s), 2.21 (4H, t, J=7.0), 3.16 (4H, t, J=7.0), 3.78 (3H, s), 3.83 (6H, br s), 3.92 (3H, s), 4.25 (4H, t, J=6.5), 6.80 (1H, s), 6.88 (1H, s), 6.90 (1H, s), 6.98 (1H, s), 7.02 (1H, s), 7.15 (1H, s), 7.18 (2H, s), 7.25 (1H, s), 7.33 (1H, s), 7.47 (1H, s), 8.09 (4H, m), 9.87 (1H, s), 9.92 (1H, s), 9.94 (1H, s), 10.10 (2H, s), 10.24 (1H, s). LRFABms *m/z* (relative intensity): 1105 ($M+H^+$) (1.7), 983 (0.2), 853 (0.1), 444 (0.8), 401 (0.9), 225 (43.1), 177 (60.1), 151 (100.0), 119 (66.2); HRFABms: 1104.6211 ($M+H^+$, 1104.6219 calcd for $C_{55}H_{77}N_{17}O_8H$).

***N*-[5-[[(3,3-Dimethylaminopropyl)amino]carbonyl]-1-methyl-*1H*-pyrrol-3-yl]-4-[[[1-methyl-*1H*-imidazol-2-yl]carbonyl]amino]-1-methyl-*1H*-pyrrole-2-carboxamide (28).** Compound (**27**) (41 mg, 0.11 mmol) was dissolved in anhydrous methanol (2.5 ml). To this solution was added platinum oxide (15 mg). Air was removed from the resulting mixture by the freeze and thaw procedure. The mixture was then vigorously stirred under 1 atm hydrogen for 4 h and concentrated. The viscous crude product was treated with DMF (2.0 ml) and reevacuated. DMF (2.0 ml) was reintroduced and 1-methyl-2-trichloroacetylimidazole (31 mg, 1.4 mmol) added. The mixture was stirred at room temperature for 2 h under nitrogen. Silica gel chromatography with 3% concentrated ammonia solution in methanol (v/v) gave the desired product (**28**) (45 mg, 90%). mp 103-105°C. Ir (solid) ν_{max}: 3650-2500 (s, br), 2946 (s), 1656 (vs), 1532 (s), 1432 (s), 1258 (s), 776 (m). ^{1}H Nmr (DMSO-d_6) δ: 1.60 (2H, quintet, J=7.2), 2.15 (6H, s), 2.24 (2H, t, J=7.2), 3.19 (2H, q, J=7.2), 3.80 (3H, s), 3.86 (3H, s), 4.00 (3H, s), 7.04 (1H, d, J=0.8), 7.13 (1H, d, J=1.9), 7.18 (1H, d, J=1.9), 7.29 (1H, d, J=1.9), 7.39 (1H, d, J=0.8), 8.07 (1H, t, J=7.2), 9.93 (1H, s), 10.46 (1H, s). EIms *m/z*

(relative intensity): 454.24493 (7.3, M^+, 454.24408 calcd for $C_{22}H_{30}N_8O_3$), 353 (3.2), 332 (2.2), 231 (9.0), 149 (133), 109 (12.8), 58 (100.0).

***N*-[2-[[(3,3-Dimethylaminopropyl)amino]carbonyl]-1-methyl-*1H*-imidazol-4-yl]-1-methyl-4-nitro-*1H*-pyrrole-2-carboxamide (29).** To a solution of **14** (402 mg, 1.58 mmol) in anhydrous methanol (4.5 ml) was introduced platinum oxide (120 mg). After purging of air by the freeze-thaw procedure, the suspension was stirred vigorously at room temperature under an atmosphere of 1 atm hydrogen for 1.5 h. The crude reaction mixture was concentrated *in vacuo* and DMF (5.0 ml) was introduced. The mixture obtained as such was reevacuated and redissolved in DMF (5.0 ml). 1-Methyl-4-nitro-2-trichloroacetylpyrrole (424 mg, 1.56 mmol) was then added. The mixture was stirred under nitrogen overnight at room temperature. Purification by silica gel chromatography with 2% concentrated aqueous ammonia in methanol (v/v) as eluent provided **29** (305 mg) in a yield of 52%. mp 78-79°C. Ir (solid) ν_{max}: 3600-2500 (s, br), 3130 (s), 2949 (s), 1650 (vs), 1309 (s). ^{1}H Nmr (DMSO-d_6) δ: 1.65 (2H, m), 2.19 (6H, s), 2.31 (2H, t, J=7.1), 3.27 (2H, q, J=7.2), 3.93 (3H, s), 3.93 (3H, s), 7.52 (1H, s), 7.77 (1H, d, J=2.1), 8.02 (1H, t, J=7.2), 8.20 (1H, d, J=2.1), 10.77 (1H, s). Elms *m/z* (relative intensity): 377.18077 (0.4, M^+, 377.18115 calcd for $C_{16}H_{23}N_7O_4$), 319 (0.8), 254 (9.0), 153 (7.1), 107 (5.2), 84 (4.5), 58 (100.0).

***N*-[2-[[(3,3-Dimethylaminopropyl)amino]carbonyl]-1-methyl-*1H*-imidazol-4-yl]-4-[[[4-formylamino-1-methyl-*1H*-pyrrol-2-yl]carbonyl]amino]-1-methyl-*1H*-pyrrole-2-carboxamide (30).** Compound (**29**) (42 mg, 0.11 mmol) was dissolved in anhydrous methanol (2.5 ml). To this solution was added platinum oxide (5.0 mg). Air was removed from the resulting mixture by the freeze and thaw procedure. The mixture was then vigorously stirred under 1 atm hydrogen for 1.5 h and concentrated. The viscous crude product was treated with DMF (2.0 ml) and reevacuated. DMF (2.0 ml) was reintroduced and the activated ester (**18**) (44 mg, 1.4 mmol) added. The mixture was heated under nitrogen at 55°C for 2 h. Silica gel chromatography with 2% concentrated ammonia solution/methanol (v/v) gave the desired product (**30**) (38 mg, 70%). mp 177-179°C. Ir (solid) ν_{max}: 3600-2400 (s, br), 2831 (s), 2857 (m), 1660 (vs), 1532 (vs), 834 (m). ^{1}H Nmr (DMSO-d_6) δ: 1.62 (2H, m), 2.12 (6H, s), 2.22 (2H, t, J=7.0), 3.27 (2H, t, J=7.0), 3.84 (6H, s), 3.93 (3H, s), 6.91 (1H, d, J=1.8), 7.06 (1H, d, J=1.8), 7.19 (1H, d, J=1.8), 7.32 (1H, d, J=1.8), 7.49 (1H, s), 8.06 (1H, d, J=7.0), 8.12 (1H, s), 9.95 (1H, s), 10.08 (1H, s), 10.28 (1H, s). Elms *m/z* (relative intensity): 497.25089 (0.6, M^+, 497.24991 calcd for $C_{23}H_{31}N_9O_4$), 375 (2.6), 274 (1.5), 123 (6.5) and 58 (100.0).

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