ARTICLE

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Synthesis and cytotoxicity evaluation of novel C7–C7, C7–N3 and N3–N3 dimers of 1-chloromethyl-5-hydroxy-1,2-dihydro-3*H*-benzo[*e*]indole (*seco*-CBI) with pyrrole and imidazole polyamide conjugates

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The C7–C7, C7–N3 and N3–N3 dimers of 1-chloromethyl-5-hydroxy-1,2-dihydro-3*H*-benzo[*e*]indole (*seco*-CBI) with pyrrole and imidazole polyamides were synthesized and preliminary anti-cancer evaluation carried out by NCI against three types of cancer cells.

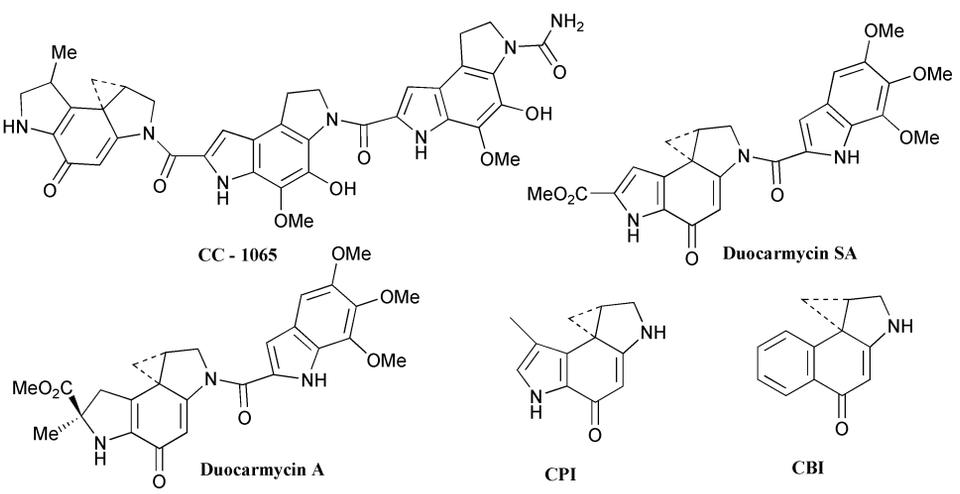
Introduction

DNA has for many years been a traditional target for chemotherapeutic intervention[1] in human cancers, especially for those where high proliferation rates of some tumor cell types have resulted in sensitivity to drugs, which block replication and transcription of their DNA.[2] Substantial progress has been made in understanding the fundamental principles responsible for the sequence-selective recognition of DNA by small organic molecules[3] including a range of naturally occurring antitumor antibiotics. Three fundamental issues that arise in the examination of DNA binding agents are the origin of binding affinity, binding selectivity and reaction selectivity including DNA alkylation or cleavage. Each factor can independently assert levels of control on the sequence-selective recognition of DNA and the relative role and origin of these effects remain a primary objective of many investigations. A powerful complement to such tools in the examination of naturally derived DNA binding agents is the preparation and subsequent examination of key partial structure modifications or variations in the natural product and their corresponding unnatural enantiomers.

In addition, DNA sequence specificity or selectivity has recently become recognized as an important component of many cytotoxic agents,[4,5] CC-1065 and duocarmycins,[6] saramycin,[7] distamycin,[8–10] netropsin,[8–10] pyrrolo[1,4]benzodiazepinone,[11] bleomycin,[12,13] several of which are of clinical interest in the treatment of human malignancies. CC-1065 and the duocarmycins represent members of a class of exceptionally potent antitumor antibiotics that derive their biological effects through the reversible, sequence selective alkylation of duplex DNA.[14–22] CC-1065 and some of its derivatives irreversibly alkylate DNA and some of compounds reversibly alkylate DNA. Subsequent to their disclosure, extensive efforts have been devoted to establish their duplex DNA alkylation selectivity and its structural origin,[14–22] to establish the link between DNA alkylation and the concomitant biological properties,[23] and to define the fundamental principles underlying the relationships between structure, chemical reactivity, and biological properties.[24–33]

Compared with other anticancer agents (+)-CC-1065 has a high bioactivity, and is 400 times more potent than doxorubicin, 80 times more potent than actinomycin D, and about twice as potent as maytansine against L1210 leukemia cells *in vitro*. Despite its high potency CC-1065 cannot be used in humans because it was found to cause delayed death in experimental animals. Because of the unique structure and properties of these natural products, many chemists were interested in synthesizing derivatives and analogues of CC-1065 and duocarmycins with better antitumor selectivity and DNA-sequence specific binding properties,[34] in an attempt to avoid the undesired side effects while retaining their potency against tumor cells.[34] As a successful example of the modification of 1,2,8,8a-tetrahydro-7-methylcyclopropa[*c*]pyrrolo[3,2-*e*]indole-4-one (CPI), the DNA alkylating moiety of CC-1065, Boger first reported the synthesis of 1,2,9,9a-tetrahydrocyclo-propa[*c*]-benzo[*e*]indole-4-one (CBI).[35]

Studies of the CBI-based analogues of CC-1065 have shown that they are chemically more stable, biologically more potent, and considerably more synthetically accessible than the corresponding agents incorporating the natural CPI



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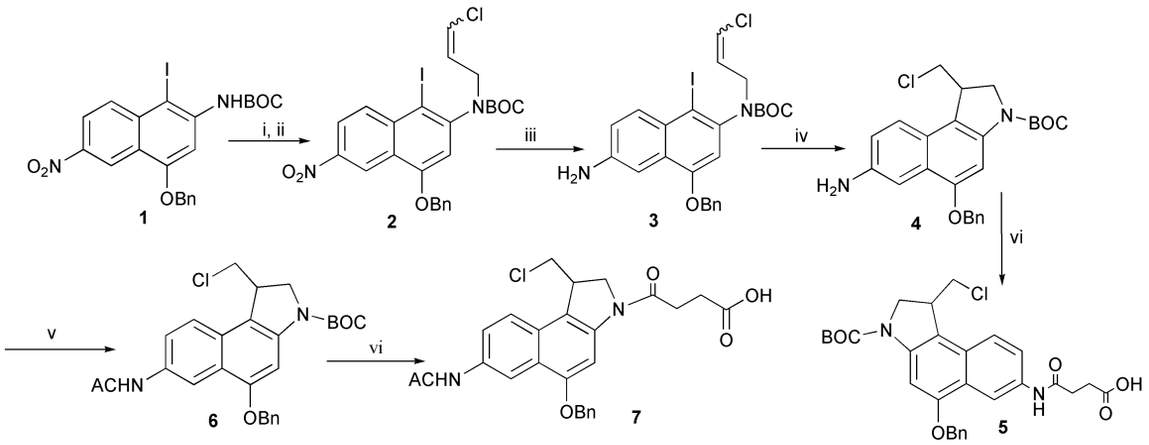


Scheme 1 *Reagents and conditions:* i. NaH; ii. ClCH=CHCH$_2$Cl, Bu$_4$NI; iii. hydrazine hydrate, FeCl$_3$, activated carbon; iv. Bu$_3$SnH, AlBN; v. CH$_3$COCl, DIEA; vi. succinic anhydride, THF, Et$_3$N, RT.

(cyclopropapyrroloindolone) alkylation subunit of CC-1065.[29] Moreover, the natural enantiomers of the CBI based analogs alkylate DNA with an unaltered sequence selectivity at an enhanced rate and with a greater efficiency than the corresponding CPI analogs, indicating that they possess characteristics that make them especially attractive to pursue.[36] These observations have prompted us to study certain CBI-based analogs of CC-1065 in detail.

In addition studies on netropsin, distamycin and related compounds have led to the concept of polyamides as information reading agents.[37] A predominantly 4–5 AT base pair sequence is recognized by netropsin and distamycin in the minor groove of DNA. In our group attempts have been made to link CPI[38] and CBI[39] with polyamides, the well established DNA minor groove binders. It was found that some optimized CPI-polyamide conjugates exhibit up to 10000 times higher potency than CC-1065 against KB human cancer cells.[38] Studies have also shown that some synthetic compounds, which contain two CPI moieties linked from two possible positions by a flexible methylene chain of variable length, are significantly more potent than CC-1065 both *in vitro* and *in vivo*.[40] In fact many antitumor agents act by cross-linking DNA. Recently a C8-linked pyrrolo[1,4]benzodiazepinone dimer was prepared[41] which forms a symmetrical interstrand cross link with duplex DNA involving a four base pairs bonding site but spanning six base pairs overall.[42] To date only a few CPI dimers have been prepared to examine the interstrand cross-linking of DNA.[40] We have also reported the synthesis and biological evaluation of *seco*-CBI dimers against nine types of cancer cells. Certain examples showed significant activity against CCRT-CEM, HL-60 (TB), MOLT-4, leukemia, CNS cancer, melanoma, and prostate cancer cell lines with Gl 50 values < 0.01 μm.[43]

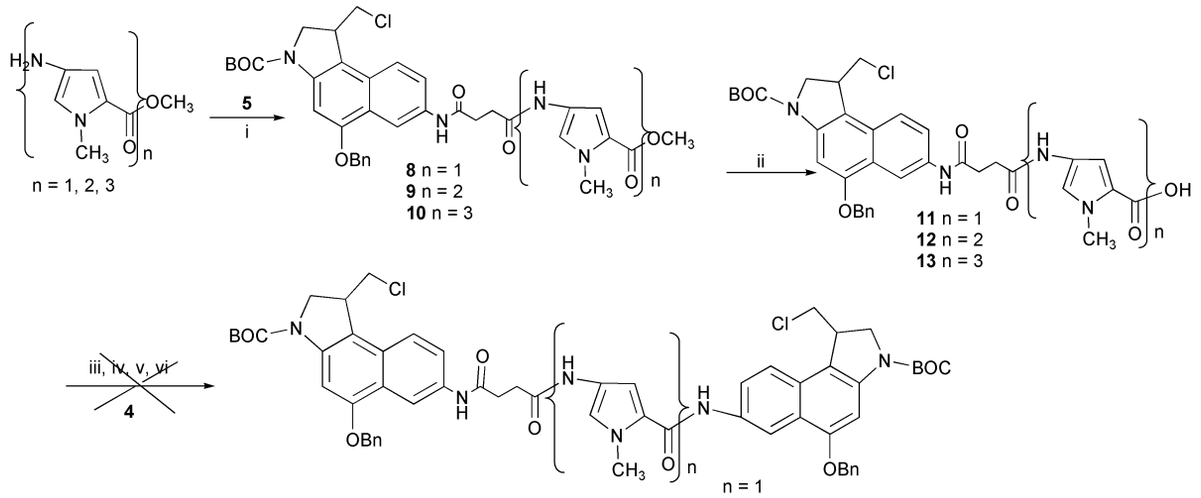
In view of the commonly observed activity of these PBD, CPI and *seco*-CBI dimers and some CPI polyamide conjugates we attempted to conjugate two *seco*-CBI units with pyrrole and imidazole polyamide from both sides by a flexible methylene chain of varible length. In our previous studies, we reported the synthesis of bis 1-chloromethyl-5-hydroxy-1,2-dihydro-3*H*-benzo[*e*]indole (*seco*-CBI)–pyrrole polyamide conjugates[44] which contain two racemic CBI moieties linked from two different positions to a polyamide by a flexible methylene chain of variable length. In order to investigate the structure–activity relationships systematically as well as their cytotoxicity against human cancer cells, we herein describe the synthesis and testing of novel C7–C7, C7–N3 and N3–N3 dimers of 1-chloromethyl-5-hydroxy-1,2-dihydro-3*H*-benzo[*e*]indole (*seco*-CBI) with polyamide conjugates which contain two racemic CBI moieties linked from two different positions with pyrrole and imidazole bearing polyamides by a flexible methylene chain of variable length.

Results and discussion

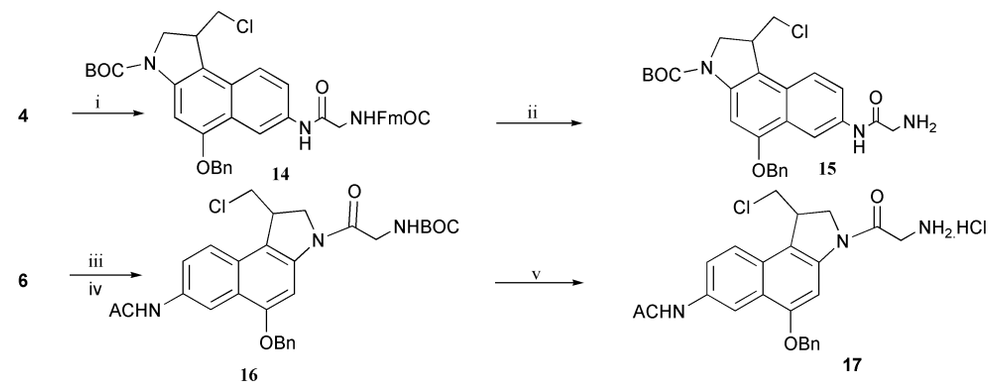
In our previous work the *seco*-CBI moiety was synthesized[43] using the following convenient route in good yield. Deprotonation of carbamate **1**, (Scheme 1)[43] using NaH, followed by alkylation of the resulting anion with 1,3-dichloropropene in the presence of phase transfer catalyst Bu$_4$NI gave a mixture of *Z* and *E* isomers of vinyl chloride **2**. Selective reduction of the nitro group of **2** using hydrazine provided amine **3**, the desired precursor for the intramolecular aryl radical cyclization on to a tethered vinyl chloride. A deoxygenated solution of **3** in dry benzene was heated at reflux for 15 h in the presence of 2 equivalents of Bu$_3$SnH and a catalytic amount of AIBN to give the bifunctionalized *seco*-CBI prodrug **4**. Treatment of the *seco*-CBI **4** with 1.0 equivalent of succinic anhydride in the presence of triethylamine in dry THF at 60 °C afforded acid *seco*-CBI acid **5** in 80% yield. Treatment of the amine group at the C7 position with acetyl chloride almost quantitatively gave its acetyl derivative **6**. Acid mediated deprotection of the Boc group from compound **6** followed by reaction with 1.0 equivalent of succinic anhydride in the presence of triethylamine in dry THF at 60 °C provided acid **7** in 80% yield. (Scheme 1).

The *seco*-CBI acid **5** was then coupled with the amine moiety of pyrrole polyamides, using EDCI and HOBt as the coupling agents, in dry DMF at room temperature for about 12 h to afford the corresponding coupled *seco*-CBI polyamide methyl esters **8**–**10** in 80% yield which upon hydrolysis with 0.5 M NaOH at room temperature produced the corresponding *seco*-CBI polyamide acids **11**–**13** in 70% yield. The corresponding amino compounds were then prepared by hydrogenation of the nitro polyamides. These *seco*-CBI polyamide acids **11**–**13** were treated with the *seco*-CBI prodrug **4** under standard EDCI, HOBt coupling conditions *via* its acid chloride route (Scheme 2). Unfortunately both reactions failed to produce the desired product, owing to the less reactive aromatic amino group of the *seco*-CBI **4**. In this case we needed to increase the reactivity of the amino group at the C7 and N3 positions by introducing a more nucleophilic primary amine moiety in *seco*-CBI **4** through a suitable linker.

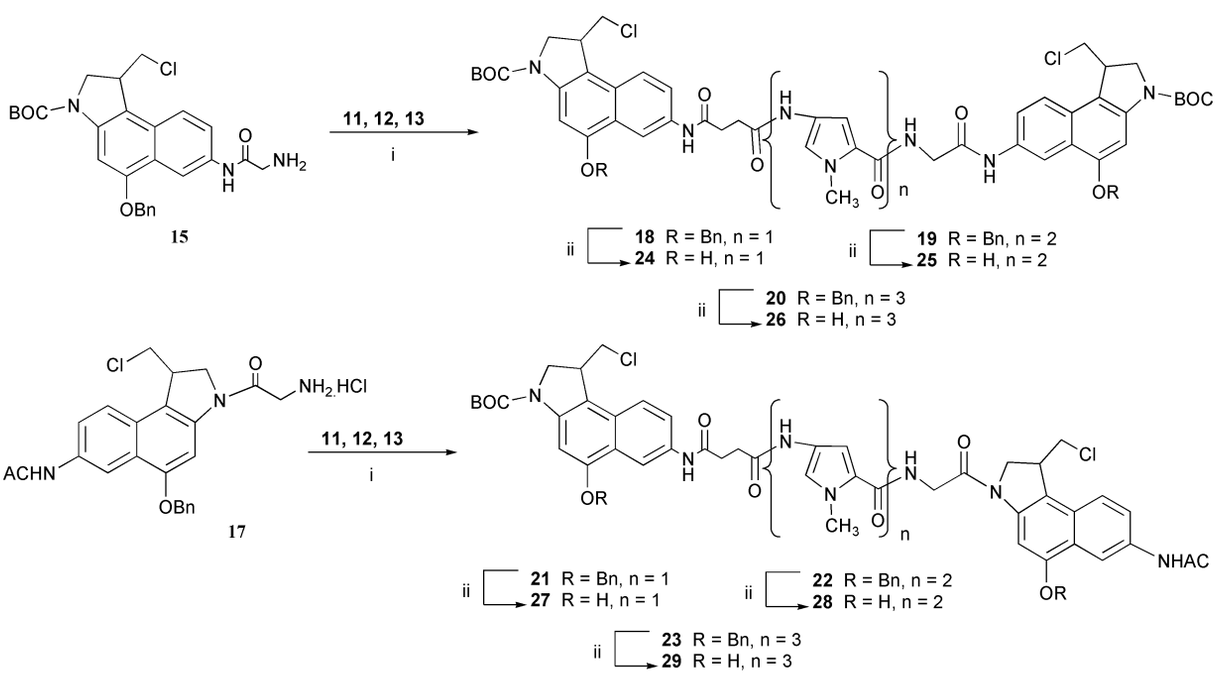
Condensation of the *seco*-CBI **4** in the presence of EDCI and HOBt in dry DMF at room temp with 1.0 equiv *N*-Fmoc glycine gave compound **14** in 70% yield. Detachment of the Fmoc group from **14** with TBAF in dry THF gave the free amine **15** in 70% yield. Acid mediated deprotection of the Boc group from compound **6** followed by coupling with 1.0 equiv. *N*-Boc glycine under standard EDCI, HOBt coupling conditions in dry DMF afforded compound **16** in good yield. Detachment of the Boc group from **16** gave the free amine **17** (Scheme 3).



Scheme 2 *Reagents and conditions:* i. **5**, EDCl, HOBt, DMF, RT; ii. 1 M NaOH, THF–MeOH (1 : 1), RT; 111. EDCI, HOBt, DMF, RT; iv. DCC, HOBt, DMF, RT; v. EDCI, DMF, RT; vi. a) TBDMS, imidazole, RT; b) oxalyl chloride–DCM, 0 °C; c) Et_3N, THF, RT.



Scheme 3 *Reagents and conditions:* i. *N*-FmOC glycine, EDCI, HOBt, DMF, RT; ii. TBAF, THF, RT; iii. 4 M HCl in dioxane, RT, 2 h; iv. *N*-BOC glycine, EDCl, HOBt, $NaHCO_3$, DMF, RT; v. 4 M HCl in dioxane, RT, 2 h.

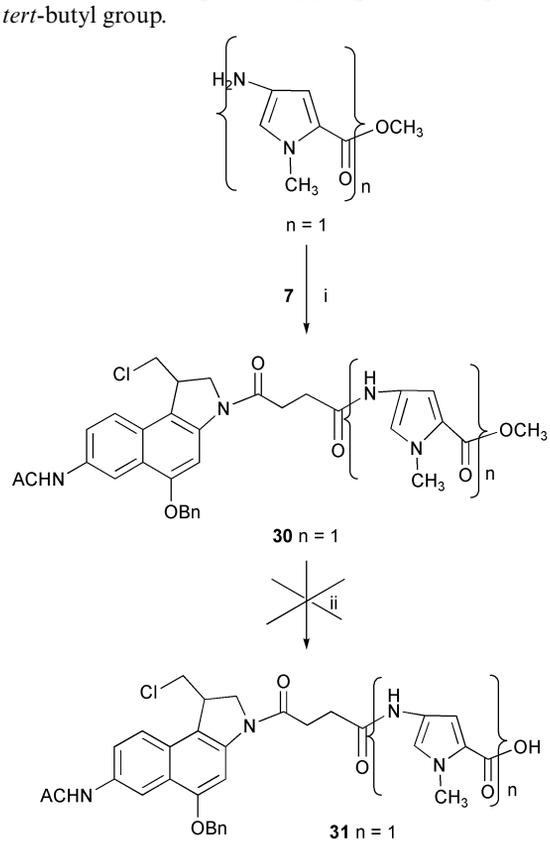


Scheme 4 *Reagents and conditions:* i. EDCl, HOBt, DMF, RT; ii. 10% $HCOONH_4$, Pd/C, THF, RT.

The reaction of amines **15** and **17** with 1.0 equivalent of the *seco*-CBI polyamide acids **11**–**13** using EDCI, HOBt (and $NaHCO_3$ in the case of amine **17**) as the coupling agents in dry DMF at room temperature for about 12 h, afforded the corresponding coupled bis *seco*-CBI polyamides **18**–**23** in 70% yield. Hydrogenolysis of the bis *seco*-CBI polyamides **18**–**23** in THF with 4.0 equiv. of 10% aqueous ammonium formate in the presence of Pd–C for about 2 h to remove the benzyl ether provided almost quantitatively the final C7–C7 and C7–N3 bis *seco*-CBI pyrrole polyamide dimers **24**–**29** in 80–90% yield (Scheme 4).

The reaction of *seco*-CBI acid **7** with the amine moiety of pyrrole polyamide methyl ester, using standard EDCI and

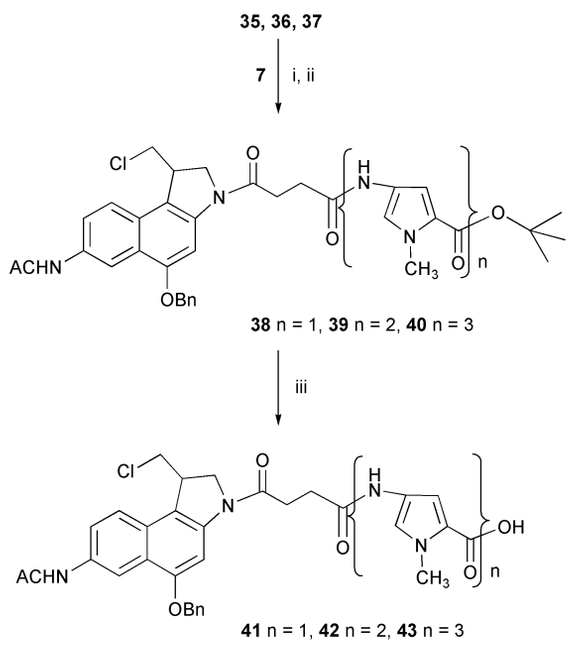
HOBt coupling conditions gave the corresponding coupled N3 *seco*-CBI polyamide methyl ester **30** in 80% yield. This ester **30** was treated with 0.5 M NaOH at room temp. and with aq. LiOH to produce the desired acid (Scheme 5). Unfortunately both reactions failed to produce the desired product, due to the acetate group at the C7 position. In this case we need to employ an acid labile deprotecting group in the nitropolyamides *e.g. tert*-butyl group.



Scheme 5 *Reagents and conditions:* i. 7, EDCl, HOBt, DMF, RT; ii. a) 1 M NaOH, THF–MeOH (1 : 1), RT; b) LiOH, THF–MeOH (1 : 1), RT.

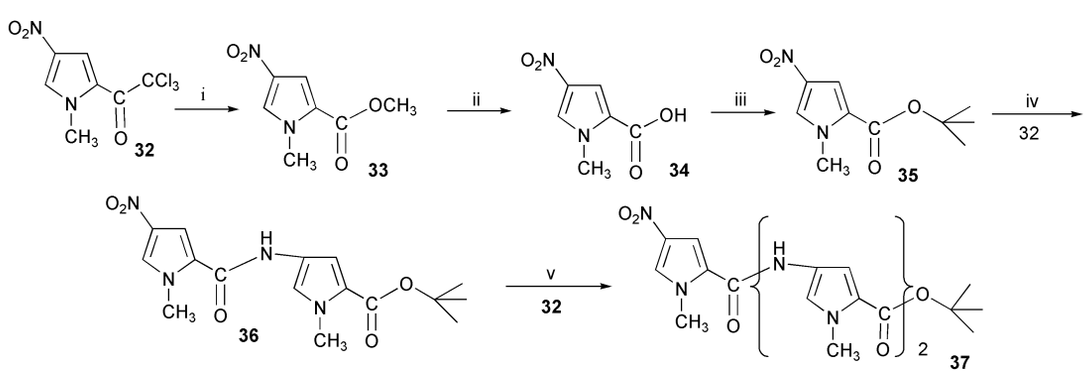
Treatment of the 4-nitro-2-(trichloroacetyl)-1-methyl pyrrole **32** with methanol gave methyl ester **33** in quantitative yield. Basic hydrolysis of compound **33** gave the corresponding acid compound **34**, which was converted into an acidic labile *tert*-butyl ester compound **35** by treating the acid **34** with isobutylene under acidic conditions. The nitro group of compound **35** was reduced with hydrogen in the presence of Pd/C catalyst into the corresponding amino compound which was then treated with the 4-nitro-2-(trichloroacetyl)-1-methyl pyrrole **32** in the presence of triethylamine and gave compound **36**. The nitro group of compound **36** was reduced, using the same procedure, into its corresponding amino compound and then the latter was treated with the 4-nitro-2-(trichloroacetyl)-1-methyl pyrrole **32** in the presence of triethylamine to give compound **37** in good yield (Scheme 6).

Coupling of the *seco*-CBI acid **7** with the amine moiety of *tert*-butyl ester pyrrole polyamides **35**–**37**, using EDCI and HOBt as coupling agents in dry DMF afforded the corresponding coupled N3 *seco*-CBI polyamide *tert*-butyl esters **38**–**40** in 80% yield which were hydrolyzed under acidic conditions by using 1 M solution of $TiCl_4$ in dichloromethane to give the corresponding N3 *seco*-CBI polyamide acid compounds **41**–**43** in fair yield. The corresponding amino compounds were then prepared by hydrogenation of the corresponding nitro polyamides **35**–**37**. Coupling of these N3 *seco*-CBI polyamide acids **41**–**43** with the *seco*-CBI amine **17** using EDCI, HOBt and $NaHCO_3$ as coupling agents in dry DMF afforded the corresponding coupled N3–N3 bis *seco*-CBI pyrrole polyamides **44**–**46** in good yield. Treatment of **44**–**46** with ammonium formate in the presence of Pd–C for about 2 h provided the final N3–N3 bis-*seco*-CBI pyrrole polyamide dimers **47**–**49** in fair yield (Schemes 7 and 8).

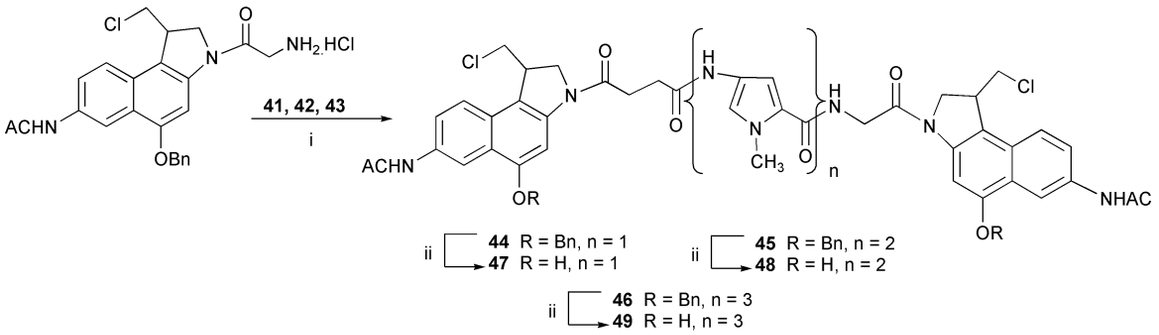


Scheme 7 *Reagents and conditions:* i. H_2, Pd/C, MeOH, RT; ii. **7**, EDCl, HOBt, DMF, RT; iii. 1 M $TiCl_4$, DCM, RT, 12 h.

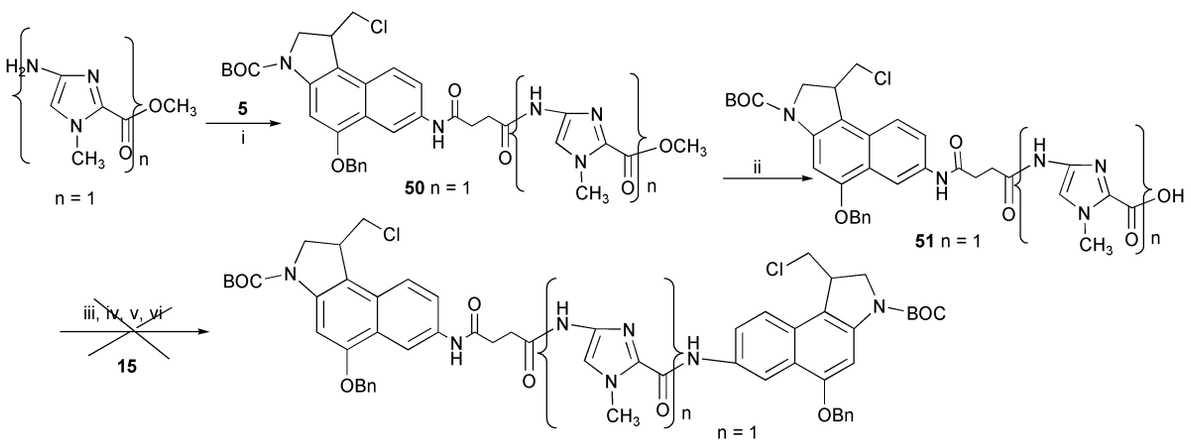
Condensation of the *seco*-CBI acid **5** with the amine moiety of 1-methyl-4-nitro-1*H*-imidazole-2-carboxylic acid methyl ester polyamide, using EDCI and HOBt as the coupling agents, in dry DMF afforded the corresponding coupled *seco*-CBI imidazole polyamide methyl ester 50 in 80% yield which upon hydrolysis with 1 M NaOH produced the corresponding *seco*-CBI polyamide acid compound **51** in 70% yield. The



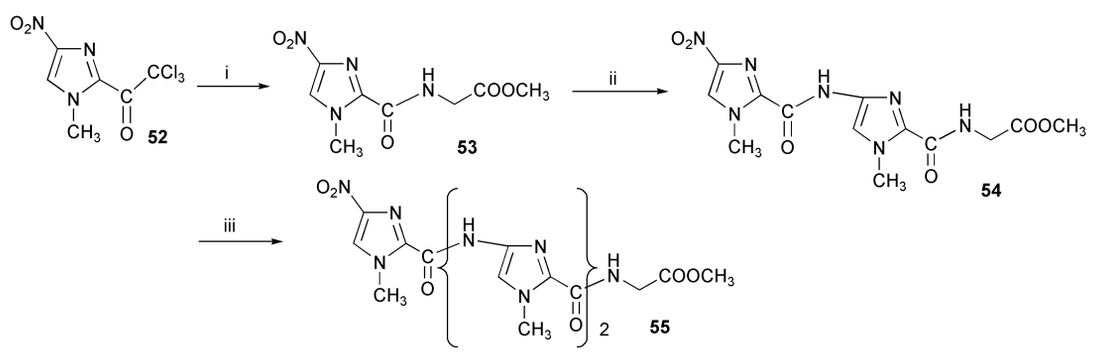
Scheme 6 *Reagents and conditions:* i. MeOH, 80 °C; ii. 1 M NaOH, THF–MeOH (1 : 1), RT; iii. isobutylene, H_2SO_4, RT, 12 h; iv. H_2 Pd/C, **32**, Et_3N, THF, RT; v. H_2 Pd/C, **32**, ET_3N, THF, RT.



Scheme 8 *Reagents and conditions:* i. EDCl, HOBt, DMF, RT; ii. 10% $HCOONH_4$, Pd/C, THF, RT.



Scheme 9 *Reagents and conditions:* i. **5**, EDCl, HOBt, DMF, RT; ii. 1 M NaOH, THF–MeOH (1 : 1), RT; iii. EDCl, HOBt, DMF, RT; iv. DCC, HOBt, DMF, RT; v. EDCl, DMF, RT; vi. a) TBDMS, imidazole, RT; b) oxalyl chloride–DCM 0 °C; c) Et_3N, THF, RT.



Scheme 10 *Reagents and conditions:* i. glycine methyl ester hydrochloride, THF, Et_3N, RT; ii. H_2 Pd/C, MeOH or DMF, **52**, Et_3N, THF, RT; iii. H_2 Pd/C **52**, Et_3N, THF, RT.

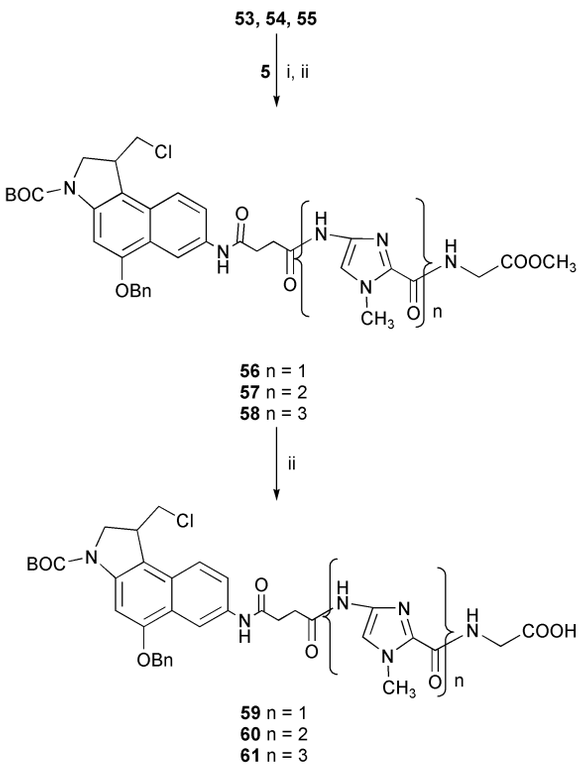
corresponding amino compounds were then prepared by hydrogenation of the nitropolyamides. The *seco*-CBI polyamide acid **51** was then coupled with the *seco*-CBI amines **15** or **17**, containing a more nucleophilic primary amine group, under EDCI, HOBt coupling conditions and *via* its acid chloride derivative (Scheme 9). Unfortunately both reactions failed to produce the desired products, due to the less reactive carboxyl group in the *seco*-CBI imidazole polyamide acid **51** residing between two nitrogen functions. In this case we needed to increase the reactivity of the carboxyl group in the imidazole polyamide esters by introducing a more electrophilic primary carboxylic group through a suitable linker.

Treatment of the 4-nitro-2-(trichloroacetyl)-1-methyl imidazole **52** with glycine methyl ester hydrochloride in the presence of triethylamine afforded compound **53** in good yield. The nitro group of compound **53** was reduced with hydrogen in the presence of Pd/C catalyst into the corresponding amino compound which was then treated with the 4-nitro-2-(trichloroacetyl)-1-methyl imidazole **52** in the presence of triethylamine and to give compound **54**. The nitro group of compound **54** was reduced, using the same procedure, into its corresponding amino compound and then the latter was treated with the 4-nitro-2-(trichloroacetyl)-1-methyl imidazole **52** in the presence of triethylamine to give compound **55** in good yield (Scheme 10).

Coupling of the acid **5** with the amine moiety of imidazole polyamides **53**–**55**, using EDCI and HOBt coupling conditions, in dry DMF afforded the corresponding coupled *seco*-CBI polyamide methyl esters **56**–**58** in 80% yield which upon hydrolysis with 1 M NaOH produced the corresponding *seco*-CBI polyamide acid compounds **59**–**61** in 70% yield. The corresponding amino compounds were then prepared by hydrogenation of the nitropolyamides. Coupling of these C7 *seco*-CBI polyamide acids **59**–**61** with the *seco*-CBI amines **15** and **17** using EDCI and HOBt (and $NaHCO_3$ in the case of amine **17**) as coupling agents in dry DMF afforded the corresponding coupled C7–C7 and C7–N3 bis *seco*-CBI imidazole polyamides **62**–**66** in 60% yield. Treatment of **62**–**67** with ammonium formate in the presence of Pd–C for about 2 h provided the final C7–C7 and C7–N3 bis-*seco*-CBI imidazole polyamide dimers **68**–**73** in fair yield (Schemes 11 and 12).

Basic hydrolysis of compound **53** gave the corresponding acid compound **74**, which was converted into an acid labile

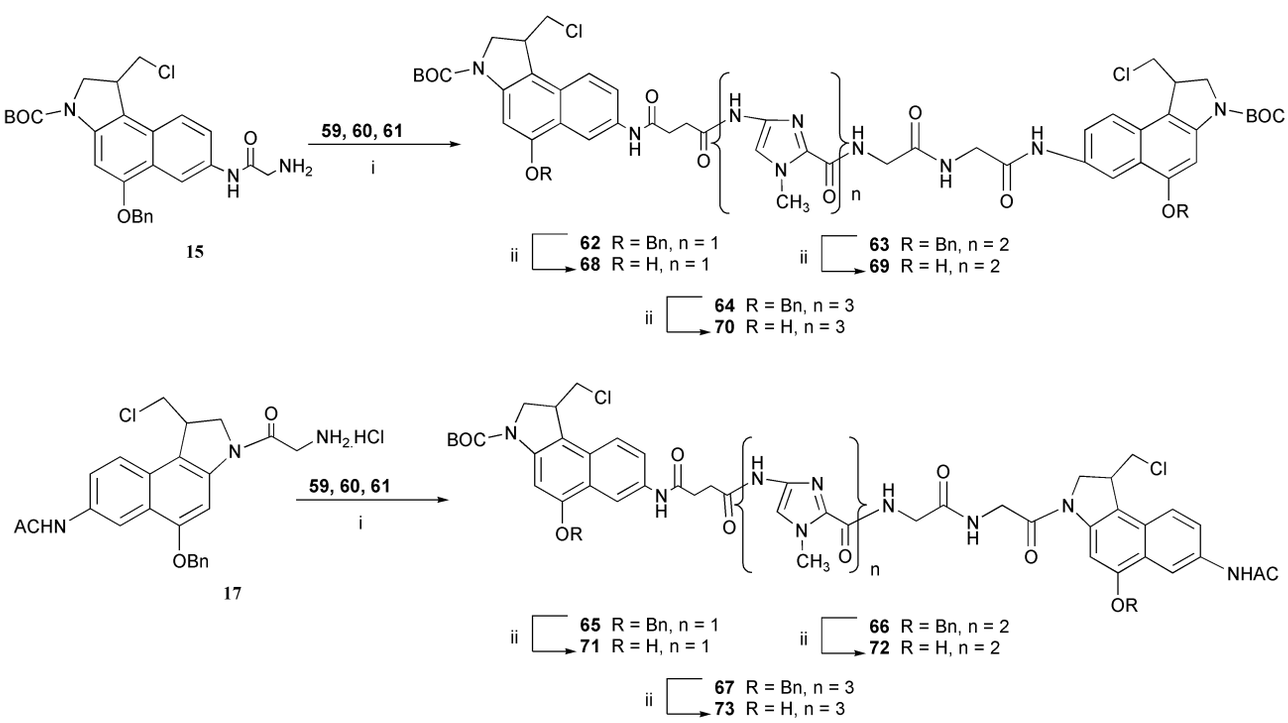
tert-butyl ester compound **75** by treating the acid **74** with isobutylene under acidic conditions. The nitro group of compound **75** was reduced with hydrogen in the presence of Pd/C catalyst into the corresponding amino compound which was then treated with the 4-nitro-2-(trichloroacetyl)-1-methyl imidazole **52** in the presence of triethylamine to give compound **76**. The nitro group of compound **76** was reduced, using the same procedure, into its corresponding amino compound and then the latter was treated with the 4-nitro-2-(trichloroacetyl)-1-methyl imidazole **52** in the presence of triethylamine to give compound **77** in good yield (Scheme 13).



Scheme 11 *Reagents and conditions:* i. H_2 Pd/C, MeOH or DMF, RT; ii. **5**, EDCl, HOBt, DMF, RT; iii. 1 M NaOH, THF–MeOH (1 : 1), RT.

Coupling of the *seco*-CBI acid **7** with the amine moiety of *tert*-butyl ester imidazole polyamides **75**–**77**, using EDCI and HOBt as coupling agents in dry DMF afforded the corresponding coupled N3 *seco*-CBI polyamide *tert*-butyl esters **78**–**80** in 75% yield which was hydrolyzed under acidic conditions by using a 1 M solution of $TiCl_4$ in dichloromethane to give the corresponding N3 *seco*-CBI imidazole polyamide acid compounds **81**–**83** in fair yield. The corresponding amino compounds were then prepared by hydrogenation of the nitro polyamides **75**–**77**. Coupling of these N3 *seco*-CBI polyamide acids **81**–**83** with the *seco*-CBI amine **17** using EDCI, HOBt and $NaHCO_3$ as coupling agents in dry DMF afforded the corresponding coupled N3–N3 bis *seco*-CBI imidazole polyamides **84**–**86** in good yield. Hydrogenolysis of the bis *seco*-CBI polyamides **84**–**86** in THF with 4.0 equiv of 10% aqueous ammonium formate in the presence of Pd–C for about 2 h to remove the benzyl ether provided almost quantitatively the final N3–N3 bis *seco*-CBI imidazole polyamide dimers **87**–**89** in 80% yield (Schemes 14 and 15).

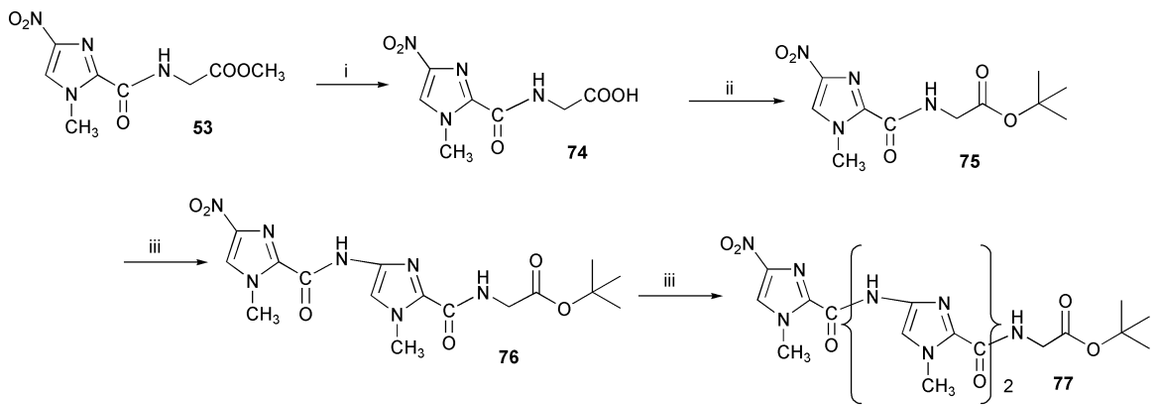
The bis-*seco*-CBI pyrrole and imidazole polyamide conjugates **24**–**29** and **68**–**73** containing one or more pyrrole and imidazole units were selected by the US National Cancer Institute for evaluation in an *in vitro* preclinical antitumor screening program for primary anticancer assays against three human tumor cell lines consisting of MCF7 (Breast), NCI-H460 (Lung), and SF-268 (CNS) cells. In the current protocol, each cell line is inoculated and preincubated on a mirotiter plate. Test agents are then added at a single concentration and the culture incubated for 48 hours. End-point determinations are made with alamar blue. Results of each test agent are reported as the percent of growth of the treated cells when compared to the untreated control cells. The compounds listed in Table 1 have been evaluated in the 3-cell line, one dose primary anticancer assay. It is observed from the initial cytotoxic data (Table 1) that all compounds have varying cytotoxic potency activity against these three cancer cell lines. Very surprising from this preliminary data and our previously reported data[43] is that the monomer compounds and alkyl linked *seco*-CBI dimer give the higher cytotoxicity. It has been suggested by a reviewer that from the initial biological data it can be concluded that if the compound is too long, it might be out of the phase in the minor groove of DNA, which lowers the DNA-binding affinity or due



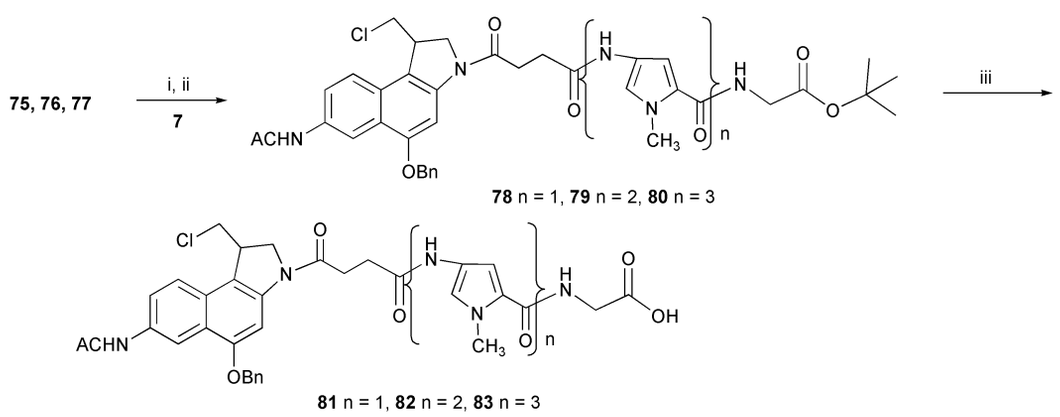
Scheme 12 *Reagents and conditions:* i. EDCl, HOBt, DMF, RT; ii. 10% $HCOONH_4$, Pd/C, THF, RT.

Table 1 *In vitro* preclinical cytotoxic data of bis-*seco*-CBI-polyamides

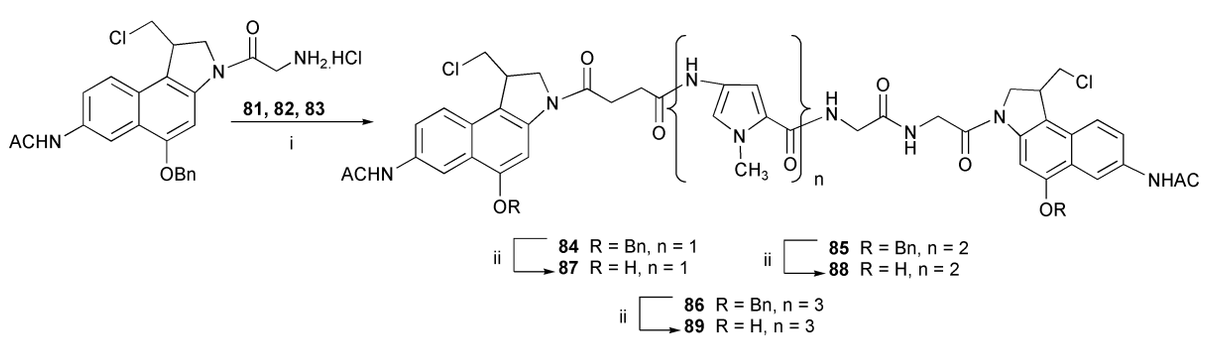
Compound no.	Concentration/M	Growth percentage (Breast) MCF-7	(Non-small cell lung) NCI-H460	(CNS) SF-268
24	1.000E−04	69	91	110
25	1.000E−04	77	80	98
26	1.000E−04	53	75	93
27	1.000E−04	55	82	94
28	1.000E−04	70	78	99
29	1.000E−04	61	88	86
68	1.000E−04	64	87	86
69	1.000E−04	71	89	98
70	1.000E−04	71	75	93
71	1.000E−04	56	97	71
72	1.000E−04	73	78	91
73	1.000E−04	103	78	92



Scheme 13 *Reagents and conditions:*i. 1 M NaOH, THF–MeOH (1 : 1); ii. isobutylene, H_2SO_4, RT; iii. H_2 Pd/C, **52**, Et_3N, THF, RT.



Scheme 14 *Reagents and conditions:*i. H_2 Pd/C, MeOH, RT; ii. 7, EDCl, HOBt, DMF, RT; iii. 1 M $TiCl_4$, DCM, RT, 12 h.



Scheme 15 *Reagents and conditions:*i. EDCl, HOBt, DMF, RT; ii. 10% $HCOONH_4$, Pd/C, THF, RT.

to the large size of the molecule might lead to low binding affinity. We are now in the course of performing cellular uptake studies of these types of compounds, which bear fluorescent tags. Cellular uptake results and more extensive cytotoxicity data will be published in due course.

In summary, we have described the first synthesis of the C7–C7, C7–N3 and N3–N3 dimers of 1-chloromethyl-5-hydroxy-1,2-dihydro-3*H*-benzo[*e*]indole (*seco*-CBI) with pyrrole and imidazole polyamides and also their preliminary anti-cancer evaluation.

Experimental

Kieselgel 60 (230–400 mesh) of E. Merck was used for flash column chromatography, and precoated silica gel 60F-254 sheets of E-Merck were used for TLC, with the solvent system indicated in the procedure. TLC plates were visualized by using uv light. All compounds obtained commercially were used without further purification unless otherwise stated. Methanol was freshly distilled over magnesium turnings; tetrahydrofuran was distilled over sodium benzophenone ketyl under an atmosphere of dry argon, ether was dried over sodium; methylene chloride was freshly distilled from calcium hydride, triethylamine was treated with potassium hydroxide then distilled from barium oxide and stored over 3Å molecular sieves, Dry dimethylformamide and all commercially available chemicals were purchased from Aldrich Chemical Co. The ^{1}H NMR spectra were recorded on a Bruker WH-300 spectrometer. Proton chemical shifts are reported in parts per million (δ) downfield from tetramethylsilane ($SiMe_4$) as an internal standard. Coupling constants (J values) are given in hertz and spin multiplicates are described as follows: s (singlet), d (doublet), dd (doublet of doublets), t (triplet), q (quartet), p (pentet) or m (multiplet). FAB (fast atom bombardment) mass spectra with glycerol as the matrix were determined on Associate Electrical Ind. (AEI) MS – 9 and MS – 50 focusing high-resolution mass spectrometers.

5-Benzyloxy-7-(3-carboxypropionylamino)-1-chloromethyl-1,2-dihydrobenzo[*e*]indole-3-carboxylic acid *tert*-butyl ester (5)

A solution of 7-amino-5-benzyloxy-1-chloromethyl-1,2-dihydro-benzo[*e*]indole-3-carboxylic acid *tert*-butyl ester (**4**) (2.5g, 5.70 mmol) in THF (50.0 ml) was added dropwise to a stirred solution of succinic anhydride (0.63 g, 6.3 mmol) and triethylamine (1 ml) in dry THF at 0 °C. The reaction mixture was stirred for 12 h at room temperature. After the completion of the reaction, as indicated by TLC, the mixture was concentrated under reduced pressure and the residue was purified by column chromatography using MeOH–DCM, 1 : 9 to give **5** as a solid (2.8 g, 91% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.57 (s, 9H, Boc–H), 2.60–2.75 (m, 4H, 2 × –CH_2CO–), 3.56–4.20 (m, 5H, –CH, CH_2Cl, CH_2N), 5.24 (s, 2H, –OC$H_2C_6H_5$), 7.07 (dd, 1H, J = 2.4, 8.8 Hz), 7.37–7.46 (m, 4H, Ar–H), 7.56–7.76 (m, 4H, Ar–H), 9.50 (s, 1H, –NH–). HR–MS m/z calculated for $C_{29}H_{31}N_2O_6Cl$ 538.00, found 539.02 (M + 1).

4-(7-Acetylamino-5-benzyloxy-1-chloromethyl-1,2-dihydro-benzo[*e*]indol-3-yl)-4-oxo-butyric acid (7)

7-Acetylamino-5-benzyloxy-1-chloromethyl-1,2-dihydrobenzo-[*e*]indole-3-carboxylic acid *tert*-butyl ester (**6**) (2.5 g, 5.20 mmol) was added to a solution of 4 M HCl in dioxane (20 ml) at 0 °C under argon. The reaction mixture was stirred at 23 °C for 5 h before the solvent was removed. After being dried *in vacuo*, the residue, triethylamine (1 ml) and succinic anhydride (0.57 g, 5.70 mmol) were dissolved in anhydrous THF (50 ml), and the reaction mixture was stirred at 23 °C for 12 h then the solvent was removed and the residue was purified by column chromatography 10% MeOH–DCM as a eluting solvent in 80% yield (2.0 g) as a white solid. ^{1}H NMR (300 MHz, acetone-d_6) δ 1.80–1.86 (m, 2H, –CH_2CO–), 2.05 (s, 3H, –NHCOCH_3), 2.56–2.66 (m, 2H, –NCOCH_2–), 3.59–4.22 (m, 5H, –CH, CH_2Cl, CH_2N), 5.26 (s, 2H, –OC$H_2C_6H_5$), 7.37–7.57 (m, 5H, Ar–H), 7.76–7.84 (m, 3H, Ar–H), 8.33 (s, 1H, Ar–H), 10.05 (s, 1H, –NH–). HR–MS m/z calculated for $C_{26}H_{25}N_2O_5Cl$ 480.15, found 480.18.

General procedure A

A solution of the nitropolyamides (pyrrole or imidazole) in MeOH or DMF was hydrogenated over 10% Pd/C at 50 psi pressure for two hours and the catalyst was removed by filtration through a Celite pad. The filtrate was concentrated to dryness under reduced pressure (at RT) to afford the corresponding amine. Owing to the sensitivity of the amine to oxidation, it was used for the next reaction immediately. It was dissolved in dry DMF and a mixture of the *seco*-CBI acid **5** (1.0 equivalent), hydroxybenzotriazole (1.0 equivalent), and EDCI (2.5 equivalent), in dry DMF was added. This mixture was stirred at RT for 12 h and after completion of the reaction the solvent was removed under reduced pressure to afford a dark oil which was purified by flash column chromatography on silica gel by using methanol–dichloromethane as eluent to afford the *seco*-CBI pyrrole or imidazole polyamide esters as white solids in good yield.

5-Benzyloxy-1-chloromethyl-7-[3-(5-methoxycarbonyl-1-methyl-1*H*-pyrrol-3-ylcarbamoyl)propionylamino]-1,2-dihydrobenzo[*e*]-indole-3-carboxylic acid *tert*-butyl ester (8)

This compound was prepared starting from 1-methyl-4-nitro-1*H*-pyrrole-2-carboxylic acid methyl ester (0.410 g, 2.22 mmol) and the acid **5** (1.0 g, 1.85 mmol) according to general procedure A (1.0 g, 80% yield) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.52 (s, 9H, Boc-H), 2.56–2.70 (m, 4H, 2 × CH_2CO–), 3.82 (s, 3H, –NCH_3), 3.85 (s, 3H, – OCH_3), 3.90–4.10 (m, 5H, –CH, CH_2Cl, CH_2N), 5.24 (s, 2H, –OC$H_2C_6H_5$), 6.96 (d, 1H, J = 1.8 Hz, Py–H), 7.20 (d, 1H, J = 1.8 Hz, Py–H), 7.52–7.90 (m, 8H, Ar–H), 8.40 (s, 1H, C6–H), 9.80 (s, 1H, –NH–), 10.20 (s, 1H, –NH–). HR–MS m/z calculated for $C_{36}H_{39}N_4O_7Cl$ 674.25, found 697.22 (M + Na).

5-Benzyloxy-1-chloromethyl-7-{3-[5-(5-methoxycarbonyl-1-methyl-1*H*-pyrrol-3-ylcarbamoyl)-1-methyl-1*H*-pyrrol-3-ylcarb-amoyl]propionylamino}-1,2-dihydrobenzo[*e*]indole-3-carboxylic acid *tert*-butyl ester (9)

Prepared according to general procedure A by using 1-methyl-4-[(1-methyl-4-nitro-1*H*-pyrrole-2-carbonyl)amino]-1*H*-pyrrole-2-carboxylic acid methyl ester (0.68 g, 2.22 mmol) and the acid **5** (1.0 g, 1.85 mmol) in 81% yield (1.2 g) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.53 (s, 9H, Boc–H), 2.52–2.71 (m, 4H, 2 × CH_2CO–), 3.82 (s, 3H, –NCH_3), 3.85 (s, 3H, –NCH_3), 3.88 (s, 3H, –OCH_3), 3.91–4.15 (m, 5H, –CH, CH_2Cl, CH_2N), 5.25 (s, 2H, –OC$H_2C_6H_5$), 6.96 (d, 1H, J = 1.8 Hz, Py–H), 7.05 (d, 1H, J = 1.8 Hz, Py–H), 7.18 (d, 1H, J = 1.8 Hz, Py–H), 7.45 (d, 1H, J = 1.8 Hz, Py–H), 7.50–7.90 (m, 8H, Ar–H), 8.45 (s, 1H, C6–H), 10.00 (s, 1H, –NH–), 10.12 (s, 1H, –NH–), 10.20 (s, 1H, –NH–). HR–MS m/z calculated for $C_{42}H_{45}N_6O_8Cl$ 796.30, found 819.28 (M + Na).

5-Benzyloxy-1-chloromethyl-7-(3-{5-[5-(5-methoxycarbonyl-1-methyl-1*H*-pyrrol-3-ylcarbamoyl)-1-methyl-1*H*-pyrrol-3-ylcarb-amoyl]-1-methyl-1*H*-pyrrol-3-ylcarbamoyl}propionylamino)-1,2-dihydrobenzo[*e*]indole-3-carboxylic acid *tert*-butyl ester (10)

This compound was prepared according to the method described for the compounds **8** by employing 1-methyl-4-({1-methyl-4-[(1-methyl-4-nitro-1*H*-pyrrole-2-carbonyl)amino]-1*H*-pyrrole-2-carbonyl}amino)-1*H*-pyrrole-2-carboxylic acid methyl ester (0.95 g, 2.22 mmol) and the acid **5** (1.0 g, 1.85 mmol) in 80% yield (1.40 g) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.52 (s, 9H, Boc–H), 2.56–2.70 (m, 4H, 2 × CH_2CO–), 3.82 (s, 3H, –NCH_3), 3.84 (s, 3H, –NCH_3), 3.86 (s, 3H, –NCH_3), 3.89 (s, 3H, –OCH_3), 3.92–4.20 (m, 5H, –CH, CH_2Cl, CH_2N), 5.25 (s, 2H, –OC$H_2C_6H_5$), 6.81 (d, 1H, J = 1.8 Hz, Py–H), 6.96 (d, 1H, J = 1.8 Hz, Py–H), 7.15 (d, 1H, J = 1.8 Hz, Py–H), 7.25 (d, 1H, J = 1.8 Hz, Py–H), 7.31 (d, 1H, J = 1.8 Hz, Py–H), 7.41 (d, 1H, J = 1.8 Hz, Py–H), 7.46–7.91 (m, 8H, Ar–H), 8.45 (s, 1H, C6–H), 9.95 (s, 1H, –NH–), 10.12 (s, 1H, –NH–), 10.20 (s, 1H, –NH–), 10.30 (s, 1H, –NH–). HR–MS m/z Calculated for $C_{48}H_{51}N_8O_9Cl$ 918.35, found 941.32 (M + Na).

General procedure B

A mixture of *seco*-CBI pyrrole or imidazole polyamide methyl esters in methanol and 10 ml of 0.5 M NaOH was placed in a flask, then the reaction mixture was stirred at room temperature until the ester completely disappeared as shown by TLC. The reaction was cooled in ice with stirring and neutralized with 0.5 M HCl slowly to pH 2. The reaction mixture was extracted with ethyl acetate and THF (1 : 1) three times and dried over sodium sulfate and the solvent was removed under reduced pressure. The residue was purified by column chromatography using MeOH–dichloromethane as eluent to afford the *seco*-CBI pyrrole or imidazole polyamide acids in good yield.

5-Benzyloxy-7-[3-(5-carboxy-1-methyl-1*H*-pyrrol-3-ylcarbamoyl)-propionylamino]-1-chloromethyl-1,2-dihydrobenzo[*e*]indole-3-carboxylic acid *tert*-butyl ester (11)

This compound was prepared according to general procedure B by employing compound **8** (1.0 g, 1.48 mmol) and 0.5 M NaOH in 76% yield (0.75 g) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.52 (s, 9H, Boc–H), 2.56–2.70 (m, 4H, 2 × CH_2CO–), 3.82 (s, 3H, –NCH_3), 3.90–4.10 (m, 5H, –CH, CH_2Cl, CH_2N), 5.24 (s, 2H, –O$CH_2C_6H_5$), 7.18 (d, 1H, J = 1.8 Hz, Py–H), 7.25 (d, 1H, J = 1.8 Hz, Py–H), 7.56–7.90 (m, 8H, Ar–H), 8.40 (s, 1H, C6–H), 10.0 (s, 1H, –NH–), 10.20 (s, 1H, –NH–), 12.52 (br s, 1H, –COOH). HR–MS *m*/*z* calculated for $C_{35}H_{37}N_4O_7Cl$ 660.24, found 683.22 (M + Na).

5-Benzyloxy-7-{3-[5-(5-carboxy-1-methyl-1*H*-pyrrol-3-ylcarbamoyl)-1-methyl-1*H*-pyrrol-3-ylcarbamoyl]propionylamino}-1-chloromethyl-1,2-dihydrobenzo[*e*]indole-3-carboxylic acid *tert*-butyl ester (12)

Prepared according to general procedure B by using compound **9** (1.0 g, 1.25 mmol) and 0.5 M NaOH solution in 77% yield (0.76 g) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.51 (s, 9H, Boc–H), 2.52–2.72 (m, 4H, 2 × CH_2CO–), 3.81 (s, 3H, –NCH_3), 3.84 (s, 3H, –NCH_3), 3.90–4.20 (m, 5H, –CH, CH_2Cl, CH_2N), 5.25 (s, 2H, –O$CH_2C_6H_5$), 6.93 (d, 1H, J = 1.8 Hz, Py–H), 7.15 (d, 1H, J = 1.8 Hz, Py–H), 7.22 (d, 1H, J = 1.8 Hz, Py–H), 7.42 (d, 1H, J = 1.8 Hz, Py–H), 7.51–7.86 (m, 8H, Ar–H), 8.45 (s, 1H, C6–H), 10.00 (s, 1H, –NH–), 10.12 (s, 1H, –NH–), 10.25 (s, 1H, –NH–), 12.60 (br s, 1H, –COOH). HR–MS *m*/*z* calculated for $C_{41}H_{43}N_6O_8Cl$ 782.25, found 805.22 (M + Na).

5-Benzyloxy-7-(3-{5-[5-(5-carboxy-1-methyl-1*H*-pyrrol-3-ylcarbamoyl)-1-methyl-1*H*-pyrrol-3-ylcarbamoyl]-1-methyl-1*H*-pyrrol-3-ylcarbamoyl}propionylamino)-1-chloromethyl-1,2-dihydrobenzo[*e*]indole-3-carboxylic acid *tert*-butyl ester (13)

This compound was prepared according to general method B by using compound **10** (1.0 g, 1.08 mmol) and 0.5 M NaOH solution in 81% yield (0.80 g) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.56 (s, 9H, Boc–H), 2.54–2.68 (m, 4H, 2 × CH_2CO–), 3.82 (s, 3H, –NCH_3), 3.85 (s, 3H, –NCH_3), 3.88 (s, 3H, –NCH_3), 3.92–4.20 (m, 5H, –CH, CH_2Cl, CH_2N), 5.24 (s, 2H, –O$CH_2C_6H_5$), 6.83 (d, 1H, J = 1.8 Hz, Py–H), 6.96 (d, 1H, J = 1.8 Hz, Py–H), 7.15 (d, 1H, J = 1.8 Hz, Py–H), 7.20 (d, 1H, J = 1.8 Hz, Py–H), 7.35 (d, 1H, J = 1.8 Hz, Py–H), 7.42 (d, 1H, J = 1.8 Hz, Py–H), 7.49–7.90 (m, 8H, Ar–H), 8.40 (s, 1H, C6–H), 9.95 (s, 1H, –NH–), 10.12 (s, 1H, –NH–), 10.20 (s, 1H, –NH–), 10.31 (s, 1H, –NH–) 12.59 (br s, 1H, –COOH). HR–MS *m*/*z* calculated for $C_{47}H_{49}N_8O_9Cl$ 904.33, found 927.32 (M + Na).

5-Benzyloxy-1-chloromethyl-7-[2-(9*H*-fluoren-9-ylmethoxycarbonylamino)acetylamino]-1,2-dihydrobenzo[*e*]indole-3-carboxylic acid *tert*-butyl ester (14)

7-Amino-5-benzyloxy-1-chloromethyl-1,2-dihydro-benzo[*e*]-indole-3-carboxylic acid *tert*-butyl ester (**4**) (1.0 g, 2.28 mmol) was dissolved in dry DMF (10 ml) and added to a mixture of the *N*-Fmoc glycine (0.746 g, 2.50 mmol), HOBT (0.308 g, 2.27 mmol), and EDCI (1.09 g, 5.68 mmol) in DMF (15 ml). This mixture was stirred at RT for 12 h and the solvent was removed under reduced pressure to afford a dark oil which was purified by flash chromatography on silica gel (2% methanol–dichloromethane) to afford compound **14** as a white solid in 80% yield (1.31 g). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.58 (s, 9H, Boc–H), 3.71 (dd, J = 8.4, 10.0 Hz, 1H), 3.75 (m, 2H, –CH_2NH–), 4.01 (dd, J = 3.1, 11.1 Hz, 1H), 4.05–4.22 (m, 3H), 4.30 (t, J = 6.9 Hz, 1H), 4.50 (d, J = 6.9 Hz, 2H), 5.29 (s, 2H, –O$CH_2C_6H_5$), 7.30–7.88 (m, 16H, Ar–H), 8.38 (s, 1H, C6–H), 9.10 (s, 1H, –NH–), 10.0 (s, 1H, –NH–). HR–MS *m*/*z* Calculated for $C_{42}H_{40}N_3O_6Cl$ 717.26, found 740.25 (M + Na).

7-(2-Aminoacetylamino)-5-benzyloxy-1-chloromethyl-1,2-dihydrobenzo[*e*]indole-3-carboxylic acid *tert*-butyl ester (15)

To a solution of 5-benzyloxy-1-chloromethyl-7-[2-(9*H*-fluoren-9-ylmethoxycarbonylamino)acetylamino]-1,2-dihydrobenzo[*e*]-indole-3-carboxylic acid *tert*-butyl ester (**14**) (2.5 g, 3.48 mmol) in dry THF (100 ml) was added tetrabutylammonium fluoride (3.12 ml, 1.0 M in THF) and the mixture was stirred at room temperature for 2 h. After the completion of the reaction as indicated by TLC, the mixture was concentrated under reduced pressure and the residue was purified by column chromatography using 10% MeOH–DCM as a eluting solvent to give **15** in 73% yield (1.25 g). ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.57 (s, 9H, Boc–H), 3.60–3.65 (m, 1H), 3.75 (m, 2H, –CH_2NH–), 3.95–4.20 (m, 4H, –CH_2Cl, –CH_2N), 4.82 (m, 2H, –CH_2NH_2–), 5.26 (s, 2H, –O$CH_2C_6H_5$), 7.07 (dd, 1H, J = 2.4, 8.8 Hz, 1-H), 7.37–7.45 (m, 4H, Ar–H), 7.56–7.61 (m, 4H, Ar–H), 9.05 (s, 1H, –NH–). HR–MS *m*/*z* calculated for $C_{27}H_{30}N_3O_4Cl$ 495.19, found 496.00 (M + 1).

[2-(7-Acetylamino-5-benzyloxy-1-chloromethyl-1,2-dihydrobenzo[*e*]indol-3-yl)-2-oxo-ethyl]carbamic acid *tert*-butyl ester (16)

Compound (**6**) (1.2 g, 2.5 mmol) was added to a solution of 4 M HCl in dioxane (20 ml) at 0 °C under argon. The reaction mixture was stirred at 23 °C for 5 h before the solvent was removed. After being dried *in vacuo*, the residue, was dissolved in dry DMF (10 ml) and added to a mixture of the *N*-Boc glycine (0.438 g, 2.50 mmol), HOBT (0.338 g, 2.50 mmol), EDCI (1.2 g, 6.25 mmol) and $NaHCO_3$ (0.525 g, 6.24 mmol) in DMF (15 ml). This mixture was stirred at RT for 12 h and the solvent was removed under reduced pressure to afford a coloured oil which was purified by column chromatography on silica gel (3% methanol–dichoromethane) to afford compound **14** as a white solid in 78% yield (1.05 g). ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.54 (s, 9H, Boc–H), 2.05 (s, 3H, NHCOCH_3), 3.78–4.20 (m, 7H, –CH_2NH–, –CH_2Cl, –CH_2N, –CH–), 5.26 (s, 2H, –O$CH_2C_6H_5$), 7.37–7.57 (m, 5H, Ar–H), 7.76–7.84 (m, 3H, Ar–H), 8.34 (s, 1H, Ar–H), 9.80 (s, 1H, –NH–), 10.09 (s, 1H, –NH–). HR–MS *m*/*z* calculated for $C_{29}H_{32}N_3O_5Cl$ 537.20, found 560.15 (M + Na).

***N*-[3-(2-Aminoacetyl)-5-benzyloxy-1-chloromethyl-2,3-dihydro-1*H*-benzo[*e*]indol-7-yl]acetamide hydrochloride (17)**

[2-(7-Acetylamino-5-benzyloxy-1-chloromethyl-1,2-dihydrobenzo[*e*]indol-3-yl)-2-oxoethyl]carbamic acid *tert*-butyl ester (**16**) was added to a solution of 4 M HCl in dioxane (20 ml) at 0 °C under argon. The reaction mixture was stirred at 23 °C for 5 h before the solvent was removed. After drying the residue at high vaccum it was used imidiately in the next step reaction without purification.

General procedure C

To a solution of *seco*-CBI pyrrole or imidazole polyamide acids in dry DMF (20 ml) were added EDCI (2.5 mol), HOBt (1.0

mol), and *seco*-CBI amine **15** (1.1 mol) or *seco*-CBI amine **17** (1.1 mol) and $NaHCO_3$ (3.0 mol) in the case of amine **17** under a nitrogen atmosphere and the mixture was stirred for 12 h. When TLC indicated the absence of starting material, DMF was removed under reduced pressure. The dark residue was purified by column chromatography on silica gel using MeOH–dichloromethane as eluent to afford the coupled conjugates as white solids in good yields.

Compound 18

Prepared according to general procedure C by using compound **11** (0.25 g, 0.378 mmol) and *seco*-CBI amine **15** (0.2 g, 0.404 mmol) in 70% yield (0.30 g) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.52 (s, 18H, 2 × Boc–H), 2.56–2.70 (m, 4H, 2 × CH_2CO–), 3.82 (s, 3H, –NCH_3), 3.89–4.10 (m, 12H, Cl, 2-H, 2 × CH_2Cl, 2 × CH_2N, NHCH_2), 5.24 (s, 2H, –OCH_2-C_6H_5), 5.25 (s, 2H, –OC$H_2C_6H_5$), 6.86 (d, 1H, J = 1.8 Hz, Py–H), 7.18 (d, 1H, J = 1.8 Hz, Py–H), 7.59–7.75 (m, 16H, Ar–H), 8.30 (m, 1H, NHCH_2), 8.40 (s, 2H, 2 × C6–H), 9.91 (s, 1H, –NH–), 10.09 (s, 1H, –NH–), 10.27 (s, 1H, –NH–). ES–MS m/z calculated for $C_{62}H_{65}N_7O_{10}Cl_2$ 1137.42, found 1160.40 (M + Na).

Compound 19

This compound was prepared according to the method described for the compound **18**, employing *seco*-CBI pyrrole polyamide acid **12** (0.25 g, 0.319 mmol) and the amine **15** (0.175 g, 0.353 mmol) in 70% yield (0.28 g) as a solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.56 (s, 18H, 2 × Boc–H), 2.52–2.70 (m, 4H, 2 × CH_2CO–), 3.81 (s, 3H, –NCH_3), 3.85 (s, 3H, –NCH_3), 3.90–4.20 (m, 12H, Cl, 2-H, 2 × CH_2Cl, 2 × CH_2N, NHCH_2), 5.23 (s, 2H, –OC$H_2C_6H_5$), 5.26 (s, 2H, –OC$H_2C_6H_5$), 6.85 (d, 1H, J = 1.8 Hz, Py–H), 7.15 (d, 1H, J = 1.8 Hz, Py–H), 7.24 (d, 1H, J = 1.8 Hz, Py–H), 7.28 (d, 1H, J = 1.8 Hz, Py–H), 7.60–7.85 (m, 16H, Ar–H), 8.35 (m, 1H, NHCH_2), 8.40 (s, 2H, 2 × C6–H), 9.91 (s, 1H, –NH–), 9.94 (s, 1H, –NH–), 10.09 (s, 1H, –NH–), 10.12 (s, 1H, –NH–). ES–MS m/z calculated for $C_{68}H_{71}N_9O_{11}Cl_2$ 1259.47, found 1282.45 (M + Na).

Compound 20

This compound was prepared starting from *seco*-CBI amine **15** (0.180 g, 0.363 mmol) and the acid **13** (0.30 g, 0.331 mmol) according to general procedure described for compound **19** as a white solid (0.30 g, 65% yield).^{1}H NMR (300 MHz, DMSO-d_6) δ 1.54 (s, 18H, 2 × Boc–H), 2.52–2.72 (m, 4H, 2 × CH_2CO–), 3.81 (s, 3H, –NCH_3), 3.83 (s, 3H, –NCH_3), 3.86 (s, 3H, –NCH_3), 3.91–4.15 (m, 12H, Cl, 2-H, 2 × CH_2Cl, 2 × CH_2N, NHCH_2), 5.25 (s, 2H, –OC$H_2C_6H_5$), 5.26 (s, 2H, –OC$H_2C_6H_5$), 6.88 (d, 1H, J = 1.8 Hz, Py–H), 6.96 (d, 1H, J = 1.8 Hz, Py–H), 7.05 (d, 1H, J = 1.8 Hz, Py–H), 7.15 (d, 1H, J = 1.8 Hz, Py–H), 7.25 (d, 1H, J = 1.8 Hz, Py–H), 7.28 (d, 1H, J = 1.8 Hz, Py–H), 7.60–7.85 (m, 16H, Ar–H), 8.35 (m, 1H, NHCH_2), 8.40 (s, 2H, 2 × C6–H), 9.91 (s, 1H, –NH–), 9.95 (s, 1H, –NH–), 10.09 (s, 1H, –NH–), 10.12 (s, 1H, –NH–), 10.32 (s, 1H, –NH–). ES–MS m/z calculated for $C_{74}H_{77}N_{11}O_{12}Cl_2$ 1381.51, found 1404.50 (M + Na).

Compound 21

This compound was prepared starting from *seco*-CBI amine **17** (0.290 g, 0.663 mmol) and the acid **11** (0.30 g, 0.454 mmol) according to general procedure C (0.30 g, 61% yield) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ_H 1.52 (s, 9H, Boc–H), 2.05 (s, 3H, CH_3CON), 2.56–2.70 (m, 4H, 2 × CH_2CO–), 3.82 (s, 3H, –NCH_3), 3.90–4.40 (m, 12H, Cl, 2-H, 2 × CH_2Cl, 2 × CH_2N, NHCH_2), 5.25 (s, 2H, –OC$H_2C_6H_5$), 5.26 (s, 2H, –OC$H_2C_6H_5$), 6.81 (d, 1H, J = 1.5 Hz, Py–H), 7.16 (d, 1H, J = 1.5 Hz, Py–H), 7.55–7.89 (m, 16H, Ar–H), 8.21–8.30 (m, 1H, NHCH_2), 8.35–8.42 (m, 2H, 2 × C6–H), 9.95 (s, 1H, –NH–), 10.07 (s, 1H, –NH–), 10.14 (s, 1H, –NH–). HR-ESMS m/z calculated for $C_{59}H_{59}N_7O_9Cl_2$ 1079.38, found 1102.40 (M + Na).

Compound 22

This compound was prepared according to the method described for the compound **21**, employing *seco*-CBI polyamide acid **12** (0.3 g, 0.383 mmol) and the amine **17** (0.25 g, 0.572 mmol) in 70% yield (0.321 g) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.54 (s, 9H, Boc–H), 2.04 (s, 3H, CH_3CON), 2.58–2.72 (m, 4H, 2 × CH_2CO–), 3.82 (s, 3H, –NCH_3), 3.85 (s, 3H, –NCH_3), 3.90–4.35 (m, 12H, Cl, 2-H, 2 × CH_2Cl, 2 × CH_2N, NHCH_2), 5.22 (s, 2H, –OC$H_2C_6H_5$), 5.24 (s, 2H, –OC$H_2C_6H_5$), 6.85 (d, 1H, J = 1.5 Hz, Py–H), 7.06 (d, 1H, J = 1.5 Hz, Py–H), 7.19 (d, 1H, J = 1.5 Hz, Py–H), 7.26 (d, 1H, J = 1.5 Hz, Py–H), 7.50–7.85 (m, 16H, Ar–H), 8.25–8.32 (m, 1H, NHCH_2), 8.35–8.42 (m, 2H, 2 × C6–H), 9.91 (s, 1H, –NH–), 10.05 (s, 1H, –NH–), 10.09 (s, 1H, –NH–), 10.20 (s, 1H, –NH–). HR-ESMS m/z calculated for $C_{65}H_{65}N_9O_{10}Cl_2$ 1201.42, found 1224.41 (M + Na).

Compound 23

Prepared according to general procedure C using compound **13** (0.3 g, 0.331 mmol) and *seco*-CBI amine **17** (0.213 g, 0.487 mmol) in 72% yield (0.32 g) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.52 (s, 9H, Boc–H), 2.05 (s, 3H, CH_3CON), 2.58–2.70 (m, 4H, 2 × CH_2CO–), 3.81 (s, 3H, –NCH_3), 3.83 (s, 3H, –NCH_3), 3.85 (s, 3H, –NCH_3), 3.89–4.40 (m, 12H, Cl, 2-H, 2 × CH_2Cl, 2 × CH_2N, NHCH_2), 5.25 (s,2H, –OC$H_2C_6H_5$), 5.26 (s, 2H, –OC$H_2C_6H_5$), 6.88 (d, 1H, J = 1.5 Hz, Py–H), 6.98 (d, 1H, J = 1.5 Hz, Py–H), 7.08 (d, 1H, J = 1.5 Hz, Py–H), 7.18 (d, 1H, J = 1.5 Hz, Py–H), 7.24 (d, 1H, J = 1.5 Hz, Py–H), 7.27 (d, 1H, J = 1.5 Hz, Py–H), 7.59–7.85 (m, 16H, Ar–H), 8.20–8.30 (m, 1H, NHCH_2), 8.35–8.42 (m, 2H, 2 × C6–H), 9.89 (s, 1H, –NH–), 9.92 (s, 1H, –NH–), 10.15 (s, 1H, –NH–), 10.18 (s, 1H, –NH–), 10.22 (s, 1H, –NH–). HR-ESMS m/z calculated for $C_{71}H_{71}N_{11}O_{11}Cl_2$ 1323.47, found 1346.50 (M + Na).

General procedure D

To a solution of bis-*seco*-CBI pyrrole or imidazole dimers with benzyl group in THF or DMF was added 10% Pd/C under argon. The mixture was cooled to 0 °C and 10% aqueous ammonium formate was added. The mixture was stirred at 23 °C until the reaction was complete (TLC). The mixture was then filtered through a pad of Celite, and concentrated *in vacuo*. The crude product was purified by flash column chromatography using MeOH–dichloromethane as eluent to afford the C7–C7, C7–N3 bis-*seco*-CBI-pyrrole or imidazole polyamide conjugates compounds as white solids in good yield.

Compound 24

Prepared according to general procedure D by using compound **18** (0.2 g, 0.175 mmol), 0.2 ml of 10% aqueous ammonium formate and 0.2 g of 10% Pd/C in 15 ml of THF to give compound **24** as a white solid in 89% yield (0.15 g). ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.52 (s, 18H, 2 × Boc–H), 2.50–2.71 (m, 4H, 2 × CH_2CO–), 3.82 (s, 3H, –NCH_3), 3.90–4.10 (m, 12H, Cl, 2-H, 2 × CH_2Cl, 2 × CH_2N, NHCH_2), 6.85 (d, 1H, J = 1.8 Hz, Py–H), 7.18 (d, 1H, J = 1.8 Hz, Py–H), 7.59–7.75 (m, 6H, 2 × C4-H, C7-H, C8-H), 8.32 (m, 1H, NHCH_2), 8.40 (s, 2H, 2 × C6–H), 9.91 (s, 1H), 10.09 (s, 1H), 10.12 (s, 1H), 10.25 (s, 1H), 10.30 (s, 1H). ES–MS m/z calculated for $C_{48}H_{53}N_7O_{10}Cl_2$ 957.32, found 980.30 (M + Na).

Compound 25

This compound was prepared according to the method described for the compound **24**, employing compound **19** (0.2 g, 0.158 mmol) and aq. ammonium formate (0.2 ml) in 90% yield

(0.154 g) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.56 (s, 18H, 2 × Boc–H), 2.54–2.72 (m, 4H, 2 × CH_2CO–), 3.82 (s, 3H, –NCH_3), 3.85 (s, 3H, –NCH_3), 3.89–4.20 (m, 12H, Cl, 2-H, 2 × CH_2Cl, 2 × CH_2N, NHCH_2), 6.85 (d, 1H, J = 1.8 Hz, Py–H), 6.96 (d, 1H, J = 1.8 Hz, Py–H), 7.15 (d, 1H, J = 1.8 Hz, Py–H), 7.25 (d, 1H, J = 1.8 Hz, Py–H), 7.55–7.85 (m, 6H, 2 × C4–H, C7–H, C8–H), 8.32 (m, 1H, NHCH_2), 8.43 (s, 2H, 2 × C6–H), 9.89 (s, 1H), 10.05 (s, 1H), 10.09 (s, 1H), 10.12 (s, 1H), 10.22 (s, 1H), 10.28 (s, 1H). ES–MS m/z calculated for $C_{54}H_{59}N_9O_{11}Cl_2$ 1079.37, found 1102.30 (M + Na^+).

Compound 26

This compound was prepared starting from compound **20** (0.20 g, 0.144 mmol) and aq. ammonium formate (0.2 ml) according to general procedure D (0.155 g, 90% yield) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.52 (s, 18H, 2 × Boc–H), 2.56–2.70 (m, 4H, 2 × CH_2CO–), 3.81 (s, 3H, –NCH_3), 3.82 (s, 3H, –NCH_3), 3.85 (s, 3H, –NCH_3), 3.90–4.10 (m, 12H, Cl, 2-H, 2 × CH_2Cl, 2 × CH_2N, NHCH_2), 6.88 (d, 1H, J = 1.8 Hz, Py–H), 6.96 (d, 1H, J = 1.8 Hz, Py–H), 7.05 (d, 1H, J = 1.8 Hz, Py–H), 7.18 (d, 1H, J = 1.8 Hz, Py–H), 7.24 (d, 1H, J = 1.8 Hz, Py–H), 7.26 (d, 1H, J = 1.8 Hz, Py–H), 7.59–7.75 (m, 6H, 2 × C4–H, C7–H, C8–H), 8.32 (m, 1H, NHCH_2), 8.40 (s, 2H, 2 × C6–H), 9.89 (s, 1H), 9.93 (s, 1H), 9.95 (s, 1H), 10.09 (s, 1H), 10.12 (s, 1H), 10.30 (s, 1H), 10.32 (s, 1H). ES–MS m/z calculated for $C_{60}H_{65}N_{11}O_{12}Cl_2$ 1201.42, found 1224.40 (M + Na).

Compound 27

This compound was prepared starting from compound **21** (0.20 g, 0.185 mmol) and aq. ammonium formate (0.2 ml) according to general procedure D (0.15 g, 90% yield) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.53 (s, 9H, Boc–H), 2.04 (s, 3H, CH_3CON), 2.56–2.72 (m, 4H, 2 × CH_2CO–), 3.82 (s, 3H, –NCH_3), 3.90–4.40 (m, 12H, Cl, 2-H, 2 × CH_2Cl, 2 × CH_2N, NHCH_2), 6.80 (d, 1H, J = 1.7 Hz, Py–H), 7.16 (d, 1H, J = 1.7 Hz, Py–H), 7.60–7.79 (m, 5H, 2 × C8, C9–H, C4–H), 7.90 (d, 1H, C4–H), 8.15–8.25 (m, 1H, NHCH_2), 8.35–8.42 (m, 2H, 2 × C6–H), 9.91 (s, 1H), 10.05 (s, 1H), 10.07 (s, 1H), 10.14 (s, 1H), 10.32 (s, 1H). HR-ESMS m/z calculated for $C_{45}H_{47}N_7O_9Cl_2$ 899.28, found 922.31 (M + Na).

Compound 28

Prepared according to general procedure for compounds B by using compound **22** (0.20 g, 0.166 mmol) and aq. ammonium formate (0.25 ml) in 88% yield (0.15 g) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.54 (s, 9H, Boc–H), 2.05 (s, 3H, CH_3CON), 2.60–2.72 (m, 4H, 2 × CH_2CO–), 3.82 (s, 3H, –NCH_3), 3.84 (s, 3H, –NCH_3), 3.91–4.40 (m, 12H, Cl, 2-H, 2 × CH_2Cl, 2 × CH_2N, NHCH_2), 6.89 (d, 1H, J = 1.7 Hz, Py–H), 6.96 (d, 1H, J = 1.7 Hz, Py–H), 7.18 (d, 1H, J = 1.7 Hz, Py–H), 7.23 (d, 1H, J = 1.7 Hz, Py–H), 7.60–7.79 (m, 5H, 2 × C8, C9–H, C4–H), 7.91 (d, 1H, C4–H), 8.20–8.30 (m, 1H, NHCH_2), 8.35–8.42 (m, 2H, 2 × C6–H), 9.90 (s, 1H), 10.03 (s, 1H), 10.05 (s, 1H), 10.07 (s, 1H), 10.14 (s, 1H), 10.30 (s, 1H). HR-ESMS m/z calculated for $C_{51}H_{53}N_9O_{10}Cl_2$ 1021.33, found 1044.31 (M + Na).

Compound 29

This compound was prepared according to the method described for the compound **27**, employing compound **23** (0.20 g, 0.151 mmol) and the aq. ammonium formate (0.2 ml) in 90% yield (0.156 g) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.52 (s, 9H, Boc–H), 2.04 (s, 3H, CH_3CON), 2.58–2.70 (m, 4H, 2 × CH_2CO–), 3.81 (s, 3H, –NCH_3), 3.82 (s, 3H, –NCH_3), 3.85 (s, 3H, –NCH_3), 3.90–4.40 (m, 12H, Cl, 2-H, 2 × CH_2Cl, 2 × CH_2N, NHCH_2), 6.88 (d, 1H, J = 1.7 Hz, Py–H), 6.96 (d, 1H, J = 1.7 Hz, Py–H), 7.05 (d, 1H, J = 1.7 Hz, Py–H), 7.16 (d, 1H, J = 1.5 Hz, Py–H), 7.23 (d, 1H, J = 1.5 Hz, Py–H), 7.26 (d, 1H, J = 1.5 Hz, Py–H), 7.60–7.79 (m, 5H, 2 × C8, C9–H, C4–H), 7.90 (d, 1H, C4–H), 8.20–8.30 (m, 1H, NHCH_2), 8.35–8.42 (m, 2H, 2 × C6–H), 9.91 (s, 1H), 9.94 (s, 1H), 10.03 (s, 1H), 10.05 (s, 1H), 10.07 (s, 1H), 10.14 (s, 1H), 10.32 (s, 1H). HR-ESMS m/z calculated for $C_{57}H_{59}N_{11}O_{11}Cl_2$ 1143.38 found 1166.36 (M + Na).

4-[4-(7-Acetylamino-5-benzyloxy-1-chloromethyl-1,2-dihydro-benzo[*e*]indol-3-yl)-4-oxo-butyrylamino]-1-methyl-1*H*-pyrrole-2-carboxylic acid methyl ester (30)

This compound was prepared starting from 1-methyl-4-nitro-1*H*-pyrrole-2-carboxylic acid methyl ester (0.421 g, 2.28 mmol) and the *seco*-CBI acid **7** (1.0 g, 2.08 mmol) according to general procedure A (0.90 g, 70% yield) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.04 (s, 3H, CH_3CON), 2.56–2.70 (m, 4H, 2 × CH_2CO–), 3.82 (s, 3H, –NCH_3), 3.89 (s, 3H, –OCH_3), 3.90–4.10 (m, 5H, –CH, CH_2Cl, CH_2N), 5.24 (s, 2H, –OC$H_2C_6H_5$), 6.96 (d, 1H, J = 1.8 Hz, Py–H), 7.18 (d, 1H, J = 1.8 Hz, Py–H), 7.52–7.90 (m, 7H, Ar–H), 8.14 (s, 1H, Ar–H), 8.37 (s, 1H, Ar–H), 9.99 (s, 1H, –NH–),10.0 (s, 1H, –NH–). ES–MS m/z calculated for $C_{33}H_{33}N_4O_6Cl$ 616.21, found 639.22 (M + Na).

1-Methyl-4-nitro-1*H*-pyrrole-2-carboxylic acid *tert*-butyl ester (35)

1-Methyl-4-nitro-1*H*-pyrrole-2-carboxylic acid (**34**) was obtained from the basic hydrolysis of the corresponding 1-methyl-4-nitro-1*H*-pyrrole-2-carboxylic acid methyl ester (**33**) from the above described reported procedure. Compound **34** (5.0 g, 29.41 mmol) was added to 200 ml of diethyl ether and 6 ml of concentrated sulfuric acid in a round bottom pressure bottle. The colloidal solution was cooled to −60 °C and a slow stream of isobutylene was bubbled through this solution for several minutes. The solution was capped tightly with a teflon cork and allowed to warm to room temperature and stirred for 36 h. The crude reaction mixture was washed with saturated $NaHCO_3$ repeatedly. The crude product was further purified by column chromatography using using pure DCM as eluent to give compound **35** in 82% yield (5.5 g) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.59 (s, 9H, –$C(CH_3)_3$), 3.85 (s, 3H, –NCH_3), 7.36 (d, 1H, J = 1.8 Hz, Py–H), 7.76 (d, 1H, J = 1.8 Hz, Py–H). HR–MS m/z calculated for $C_{10}H_{14}N_2O_4$ 226.10, found 226.20.

1-Methyl-4-[(1-methyl-4-nitro-1*H*-pyrrole-2-carbonyl)amino]-1*H*-pyrrole-2-carboxylic acid *tert*-butyl ester (36)

To a solution of compound **35** (1.0 g, 4.42 mmol) in 25.0 ml of methanol was added 0.200 g of 10% Pd/C. The reaction mixture was hydrogenated in a Parr shaker at 50 psi for 2 h. The catalyst was removed by filtration and the solvent was evaporated *in vacuo*. The residue was dissolved in dry THF (10.0 ml), Et_3N (1.0 ml) and a solution of compound **32** (1.32 g, 4.86 mmol) in THF (5.0 ml), was added slowly with stirring at 0 °C under a nitrogen atmosphere. The reaction mixture was brought to room temperature and stirred for 2 h. After completion of the reaction the residue was concentrated to dryness under reduced pressure and was purified by column chromatography eluting with 5% MeOH–DCM to give **36**, 1.3 g in 85% yield as a white solid. ^{1}H NMR : (300 MHz, DMSO-d_6) δ 1.60 (s, 9H, –$C(CH_3)_3$), 3.82 (s, 3H, –NCH_3), 3.86 (s, 3H, –NCH_3), 6.81 (d, 1H, J = 1.8 Hz, Py–H), 6.96 (d, 1H, J = 1.8 Hz, Py–H), 7.10 (d, 1H, J = 1.8 Hz, Py–H), 7.25 (d, 1H, J = 1.8 Hz, Py–H), 9.99 (s, 1H, –NH–) HR–MS m/z calculated for $C_{16}H_{20}N_4O_5$ 348.14, found 348.28.

1-Methyl-4-({1-methyl-4-[(1-methyl-4-nitro-1*H*-pyrrole-2-carbonyl)amino]-1*H*-pyrrole-2-carbonyl}amino)-1*H*-pyrrole-2-carboxylic acid *tert*-butyl ester (37)

This compound was prepared according to the method described for the compound **36**, employing compound **36** (1.0 g,

2.87 mmol) and **32** (0.85 g, 3.13 mmol) and the crude product was purified by column chromatography by using 7% MeOH–DCM as eluting solvent in 75% yield (1.0 g) as a white solid. ^{1}H NMR : (300 MHz, DMSO-d_6) δ 1.61 (s, 9H, –C(CH_3)$_3$), 3.81 (s, 3H, –NCH_3), 3.83 (s, 3H, –NCH_3), 3.85 (s, 3H, –NCH_3), 6.86 (d, 1H, J = 1.8 Hz, Py–H), 7.05 (d, 1H, J = 1.8 Hz, Py–H), 7.14 (d, 1H, J = 1.8 Hz, Py–H), 7.23 (d, 1H, J = 1.8 Hz, Py–H), 7.31 (d, 1H, J = 1.8 Hz, Py–H), 7.39 (d, 1H, J = 1.8 Hz, Py–H), 9.98 (s, 1H, –NH–), 10.15 (s, 1H, –NH–) HR–MS *m*/*z* calculated for $C_{22}H_{26}N_6O_6$ 470.19, found 470.28.

4-[4-(7-Acetylamino-5-benzyloxy-1-chloromethyl-1,2-dihydrobenzo[*e*]indol-3-yl)-4-oxo-butyrylamino]-1-methyl-1*H*-pyrrole-2-carboxylic acid *tert*-butyl ester (38)

This compound was prepared starting from 1-methyl-4-nitro-1*H*-pyrrole-2-carboxylic acid *tert*-butyl ester (**35**) (0.517 g, 2.28 mmol) and the *seco*-CBI acid **7** (1.0 g, 2.08 mmol) according to general procedure A (1.0 g, 73% yield) as a solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.59 (s, 9H, –C(CH_3)$_3$), 2.04 (s, 3H, CH_3CON), 2.54–2.70 (m, 4H, 2 × CH_2CO–), 3.82 (s, 3H, –NCH_3), 3.90–4.20 (m, 5H, –CH, CH_2Cl, CH_2N), 5.26 (s, 2H, –OC$H_2C_6H_5$), 6.96 (d, 1H, J = 1.8 Hz, Py–H), 7.15 (d, 1H, J = 1.8 Hz, Py–H), 7.56–7.89 (m, 7H, Ar–H), 8.14 (s, 1H, Ar–H), 8.35 (s, 1H, Ar–H), 9.98 (s, 1H, –NH–), 10.10 (s, 1H, –NH–). HR–MS *m*/*z* calculated for $C_{36}H_{39}N_4O_6Cl$ 658.26, found 681.30 (M + Na).

4-({4-[4-(7-Acetylamino-5-benzyloxy-1-chloromethyl-1,2-dihydrobenzo[*e*]indol-3-yl)-4-oxo-butyrylamino]-1-methyl-1*H*-pyrrole-2-carbonyl}amino)-1-methyl-1*H*-pyrrole-2-carboxylic acid *tert*-butyl ester (39)

Prepared according to general procedure A by using 1-methyl-4-[(1-methyl-4-nitro-1*H*-pyrrole-2-carbonyl)amino]-1*H*-pyrrole-2-carboxylic acid *tert*-butyl ester (**36**) (0.797 g, 2.28 mmol) and the acid **7** (1.0 g, 2.08 mmol) in 80% yield (1.30g) as a white solid. ^{1}H NMR (300 M Hz, DMSO-d_6) δ 1.59 (s, 9H, –C(CH_3)$_3$), 2.04 (s, 3H, CH_3CON), 2.54–2.70 (m, 4H, 2 × CH_2CO–), 3.82 (s, 3H, –NCH_3), 3.85 (s, 3H, –NCH_3), 3.91–4.20 (m, 5H, –CH, CH_2Cl, CH_2N), 5.25 (s, 2H, –OC$H_2C_6H_5$), 6.96 (d, 1H, J = 1.8 Hz, Py–H), 7.05 (d, 1H, J = 1.8 Hz, Py–H), 7.26 (d, 1H, J = 1.8 Hz, Py–H), 7.31 (d, 1H, J = 1.8 Hz, Py–H), 7.55–7.92 (m, 7H, Ar–H), 8.18 (s, 1H, Ar–H), 8.38 (s, 1H, Ar–H), 9.98 (s, 1H, –NH–), 10.12 (s, 1H, –NH–), 10.20 (s, 1H, –NH–). HR–MS *m*/*z* calculated for $C_{42}H_{45}N_6O_7Cl$ 780.30, found 803.31 (M + Na).

4-{[4-({4-[4-(7-Acetylamino-5-benzyloxy-1-chloromethyl-1,2-dihydrobenzo[*e*]indol-3-yl)-4-oxo-butyrylamino]-1-methyl-1*H*-pyrrole-2-carbonyl}amino)-1-methyl-1*H*-pyrrole-2-carbonyl]-amino}-1-methyl-1*H*-pyrrole-2-carboxylic acid *tert*-butyl ester (40)

This compound was prepared according to the method described for the compounds **38**–**40**, employing 1-methyl-4-({1-methyl-4-[(1-methyl-4-nitro-1*H*-pyrrole-2-carbonyl)amino]-1*H*-pyrrole-2-carbonyl}amino)-1*H*-pyrrole-2-carboxylic acid *tert*-butyl ester (**37**) (1.07 g, 2.27 mmol) and the *seco*-CBI acid **7** (1.0 g, 2.08 mmol) in 72% yield (1.35 g) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.60 (s, 9H, –C(CH_3)$_3$), 2.05 (s, 3H, CH_3CON), 2.56–2.70 (m, 4H, 2 × CH_2CO–), 3.81 (s, 3H, –NCH_3), 3.84 (s, 3H, –NCH_3), 3.87 (s, 3H, –NCH_3), 3.92–4.20 (m, 5H, –CH, CH_2Cl, CH_2N), 5.26 (s, 2H, –OC$H_2C_6H_5$), 6.89 (d, 1H, J = 1.8 Hz, Py–H), 6.98 (d, 1H, J = 1.8 Hz, Py–H), 7.05 (d, 1H, J = 1.8 Hz, Py–H), 7.15 (d, 1H, J = 1.8 Hz, Py–H), 7.25 (d, 1H, J = 1.8 Hz, Py–H), 7.31 (d, 1H, J = 1.8 Hz, Py–H), 7.45–7.90 (m, 7H, Ar–H), 8.20 (s, 1H, Ar–H), 8.35 (s, 1H, Ar–H), 9.98 (s, 1H, –NH–), 10.15 (s, 1H, –NH–), 10.22 (s, 1H, –NH–), 10.35 (s, 1H, –NH–). HR–MS *m*/*z* calculated for $C_{48}H_{51}N_8O_8Cl$ 902.35, found 925.40 (M + Na).

General procedure E

A solution of the compounds **38**, **39**, or **40** was prepared in dry dichloromethane or dry THF and to it 1.0 molar $TiCl_4$ solution in dichloromethane was added slowly dropwise with constant stirring at room temperature. After complete addition the stirring was continued for 24 h. The TLC observation at this time indicated completion of the reaction. The reaction mixture was concentrated *in vacuo* and purified by column chromatography. Elution with 7% MeOH–DCM gave pure compounds **41**–**43** in 50% yield.

4-[4-(7-Acetylamino-5-benzyloxy-1-chloromethyl-1,2-dihydrobenzo[*e*]indol-3-yl)-4-oxo-butyrylamino]-1-methyl-1*H*-pyrrole-2-carboxylic acid (41)

Prepared according to general method E by using compound **38** (1.0g, 1.51 mmol) and 1.0 M solution of $TiCl_4$ (3.0 ml) in dichloromethane to give compound **41** as a solid in 65% yield (0.60g). ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.05 (s, 3H, CH_3CON), 2.58–2.72 (m, 4H, 2 × CH_2CO–), 3.82 (s, 3H, –NCH_3), 3.92–4.20 (m, 5H, –CH, CH_2Cl, CH_2N), 5.24 (s, 2H, –OC$H_2C_6H_5$), 6.98 (d, 1H, J = 1.8 Hz, Py–H), 7.20 (d, 1H, J = 1.8 Hz, Py–H), 7.52–7.90 (m, 7H, Ar–H), 8.18 (s, 1H, Ar–H), 8.39 (s, 1H, Ar–H), 10.00 (s, 1H, –NH–), 10.20 (s, 1H, –NH–), 12.52 (br s, 1H, –COOH). HR–MS *m*/*z* calculated for $C_{32}H_{31}N_4O_6Cl$ 602.19, found 625.22 (M + Na).

4-({4-[4-(7-Acetylamino-5-benzyloxy-1-chloromethyl-1,2-dihydrobenzo[*e*]indol-3-yl)-4-oxo-butyrylamino]-1-methyl-1*H*-pyrrole-2-carbonyl}amino)-1-methyl-1*H*-pyrrole-2-carboxylic acid (42)

Prepared, according to general procedure E using compound **39** (1.0g, 1.28 mmol) and 1.0 M solution of $TiCl_4$ (3.0 ml) solution, in 65% yield (0.60 g) as solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.04 (s, 3H, CH_3CON), 2.54–2.75 (m, 4H, 2 × CH_2CO–), 3.82 (s, 3H, –NCH_3), 3.85 (s, 3H, –NCH_3), 3.91–4.20 (m, 5H, –CH, CH_2Cl, CH_2N), 5.25 (s, 2H, –OC$H_2C_6H_5$), 6.96 (d, 1H, J = 1.8 Hz, Py–H), 7.15 (d, 1H, J = 1.8 Hz, Py–H), 7.23 (d, 1H, J = 1.8 Hz, Py–H), 7.33 (d, 1H, J = 1.8 Hz, Py–H), 7.52–7.96 (m, 7H, Ar–H), 8.15 (s, 1H, Ar–H), 8.35 (s, 1H, Ar–H), 10.05 (s, 1H, –NH–), 10.12 (s, 1H, –NH–), 10.20 (s, 1H, –NH–), 12.52 (br s, 1H, –COOH). HR–MS *m*/*z* calculated for $C_{38}H_{37}N_6O_7Cl$ 724.24, found 747.25 (M + Na).

4-{[4-({4-[4-(7-Acetylamino-5-benzyloxy-1-chloromethyl-1,2-dihydrobenzo[*e*]indol-3-yl)-4-oxo-butyrylamino]-1-methyl-1*H*-pyrrole-2-carbonyl}amino)-1-methyl-1*H*-pyrrole-2-carbonyl]-amino}-1-methyl-1*H*-pyrrole-2-carboxylic acid (43)

Prepared according to general method E by using compound **40** (1.0g, 1.10 mmol) and 1.0 M solution of $TiCl_4$ (3.0 ml) to give compound **43** as a light yellow solid in 58% yield (0.55g). ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.04 (s, 3H, CH_3CON), 2.58–2.73 (m, 4H, 2 × CH_2CO–), 3.81 (s, 3H, –NCH_3), 3.84 (s, 3H, –NCH_3), 3.86 (s, 3H, –NCH_3), 3.91–4.20 (m, 5H, –CH, CH_2Cl, CH_2N), 5.24 (s, 2H, –OC$H_2C_6H_5$), 6.81 (d, 1H, J = 1.8 Hz, Py–H), 6.96 (d, 1H, J = 1.8 Hz, Py–H), 7.05 (d, 1H, J = 1.8 Hz, Py–H), 7.15 (d, 1H, J = 1.8 Hz, Py–H), 7.24 (d, 1H, J = 1.8 Hz, Py–H), 7.32 (d, 1H, J = 1.8 Hz, Py–H), 7.49–7.90 (m, 7H, Ar–H), 8.18 (s, 1H, Ar–H), 8.35 (s, 1H, Ar–H), 9.95 (s, 1H, –NH–), 10.12 (s, 1H, –NH–), 10.22 (s, 1H, –NH–), 10.30 (s, 1H, –NH–), 12.56 (br s, 1H, –COOH). HR–MS *m*/*z* calculated for $C_{44}H_{43}N_8O_8Cl$ 846.29, found 869.31 (M + Na).

Compound 44

This compound was prepared starting from *seco*-CBI amine **17** (0.239 g, 0.546 mmol) and the acid **41** (0.30g, 0.498 mmol) according to general procedure C (0.310 g, 61% yield) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.04 (s, 6H,

2 × –CH_3CON), 2.58–2.70 (m, 4H, 2 × CH_2CO–), 3.83 (s, 3H, –NCH_3), 3.92–4.40 (m, 12H, Cl, 2-H, 2 × CH_2Cl, 2 × CH_2N, NHCH_2), 5.24 (s, 2H, –OC$H_2C_6H_5$), 5.25 (s, 2H, –OC$H_2C_6H_5$), 6.94 (d, 1H, J = 1.7 Hz, Py–H), 7.16 (d, 1H, J = 1.7 Hz, Py–H), 7.60–7.90 (m, 14H, Ar–H), 8.13 (s, 2H, Ar–H), 8.21–8.30 (m, 1H, NHCH_2), 8.35 (s, 2H, Ar–H), 10.03 (s, 1H, –NH–), 10.07 (s, 1H, –NH–), 10.14 (s, 1H, –NH–). HR-ESMS m/z calculated for $C_{56}H_{53}N_7O_8Cl_2$ 1021.33, found 1044.45 (M + Na).

Compound 45

This compound was prepared according to the method described for the compound **44**, employing *seco*-CBI N-3 polyamide acid **42** (0.3 g, 0.414 mmol) and the amine **17** (0.20 g, 0.457 mmol) in 63% yield (0.30g). ^{1}H NMR (300 M Hz, DMSOd$_6$) δ 2.04 (s, 6H, 2 × –CH_3CON), 2.58–2.74 (m, 4H, 2 × CH_2CO–), 3.82 (s, 3H, –NCH_3), 3.85 (s, 3H, –NCH_3), 3.90–4.35 (m, 12H, Cl, 2-H, 2 × CH_2Cl, 2 × CH_2N, NHCH_2), 5.22 (s, 2H, –OC$H_2C_6H_5$), 5.24 (s, 2H, –OC$H_2C_6H_5$), 6.89 (d, 1H, J = 1.7 Hz, Py–H), 7.05 (d, 1H, J = 1.7 Hz, Py–H), 7.19 (d, 1H, J = 1.7 Hz, Py–H), 7.26 (d, 1H, J = 1.7 Hz, Py–H), 7.61–7.95 (m, 14H, Ar–H), 8.15 (s, 2H, Ar–H), 8.25–8.30 (m, 1H, NHCH_2), 8.38 (s, 2H, Ar–H), 10.02 (s, 1H, –NH–), 10.10 (s, 1H, –NH–), 10.15 (s, 1H, –NH–), 10.18 (s, 1H, –NH–). HR-ESMS m/z calculated for $C_{62}H_{59}N_9O_9Cl_2$ 1143.38 found 1166.40 (M + Na).

Compound 46

Prepared according to general procedure C by using compound **43** (0.30 g, 0.354 mmol) and *seco*-CBI amine **17** (0.17 g, 0.388 mmol) in 69% yield (0.31 g). ^{1}H NMR (300 M Hz, DMSO-d$_6$) δ 2.04 (s, 6H, 2 ×-CH_3CON), 2.55–2.72 (m, 4H, 2 × CH_2CO–), 3.81 (s, 3H, –NCH_3), 3.82 (s, 3H, –NCH_3), 3.82 (s, 3H, –NCH_3), 3.89–4.40 (m, 12H, Cl, 2-H, 2 × CH_2Cl, 2 × CH_2N, NHCH_2), 5.25 (s,2H, –OC$H_2C_6H_5$), 5.26 (s, 2H, –OC$H_2C_6H_5$), 6.81 (d, 1H, J = 1.7 Hz, Py–H), 6.98 (d, 1H, J = 1.7 Hz, Py–H), 7.08 (d, 1H, J = 1.7 Hz, Py–H), 7.18 (d, 1H, J = 1.7 Hz, Py–H), 7.24 (d, 1H, J = 1.7 Hz, Py–H), 7.27 (d, 1H, J = 1.7 Hz, Py–H), 7.59–7.85 (m, 14H, Ar–H), 8.10 (s, 2H, Ar–H), 8.20–8.30 (m, 1H, NHCH_2), 8.37 (s, 2H, Ar–H), 10.00 (s, 1H, –NH–), 10.07 (s, 1H, –NH–), 10.10 (s, 1H, –NH–), 10.18 (s, 1H, –NH–), 10.25 (s, 1H, –NH–). HR-ESMS m/z calculated for $C_{68}H_{65}N_{11}O_{10}Cl_2$ 1265.43 found 1288.40 (M + Na).

Compound 47

This compound was prepared starting from compound **44** (0.25 g, 0.244 mmol) and 10% aq. ammonium formate (0.2 ml) according to general procedure D in (0.17 g, 82% yield) as a white solid.^{1}H NMR (300 MHz, DMSO-d$_6$) δ 2.04 (s, 6H, 2 × –CH_3CON), 2.56–2.72 (m, 4H, 2 × CH_2CO–), 3.81 (s, 3H, –NCH_3), 3.90–4.35 (m, 12H, Cl, 2-H, 2 × CH_2Cl, 2 × CH_2N, NHCH_2), 6.94 (d, 1H, J = 1.7 Hz, Py–H), 7.19 (d, 1H, J = 1.7 Hz, Py–H), 7.65 (d, J = 8.9 Hz, 2H, Ar–H), 7.73 (d, J = 8.9 Hz, 2H, Ar–H), 7.96 (s, 2H, Ar–H), 8.20–8.30 (m, 1H, NHCH_2), 8.35 (s, 2H, Ar–H), 9.94 (s, 1H), 10.05 (s, 1H), 10.07 (s, 1H), 10.14 (s, 1H). HR-ESMS m/z calculated for $C_{42}H_{41}N_7O_8Cl_2$ 841.24, found 864.19 (M + Na).

Compound 48

Prepared according to general procedure D by using compound **45** (0.25 g, 0.218 mmol) and 10% aq. ammonium formate (0.3 ml) in 82% yield (0.172 g) as a white solid. ^{1}H NMR (300 MHz, DMSO-d$_6$) δ 2.04 (s, 6H, 2 × –CH_3CON), 2.60–2.72 (m, 4H, 2 × CH_2CO–), 3.82 (s, 3H, –NCH_3), 3.84 (s, 3H, –NCH_3), 3.91–4.42 (m, 12H, Cl, 2-H, 2 × CH_2Cl, 2 × CH_2N, NHCH_2), 6.94 (d, 1H, J = 1.7 Hz, Py–H), 7.16 (d, 1H, J = 1.7 Hz, Py–H), 7.23 (d, 1H, J = 1.7 Hz, Py–H), 7.26 (d, 1H, J = 1.7 Hz, Py–H), 7.64 (d, J = 8.9 Hz, 2H, Ar–H), 7.75 (d, J = 9.0 Hz, 2H, Ar–H), 7.96 (s, 2H, Ar–H), 8.20–8.30 (m, 1H, NHCH_2), 8.35 (s, 2H, Ar–H), 9.98 (s, 1H), 10.05 (s, 1H), 10.07 (s, 1H), 10.08 (s, 1H), 10.14 (s, 1H), 10.35 (s, 1H). HR-ESMS m/z calculated for $C_{48}H_{47}N_9O_9Cl_2$ 963.29, found 986.31 (M + Na).

Compound 49

This compound was prepared according to the method described for compound **47**, employing compound **46** (0.3 g, 0.237 mmol) and 10% aq. ammonium formate (0.35 ml) in 81% yield (0.21 g) as a white solid. ^{1}H NMR (300 MHz, DMSO-d$_6$) δ 2.04 (s, 6H, 2 × –CH_3CON), 2.61–2.72 (m, 4H, 2 × CH_2CO–), 3.81 (s, 3H, –NCH_3), 3.82 (s, 3H, –NCH_3), 3.84 (s, 3H, –NCH_3), 3.91–4.40 (m, 12H, Cl, 2-H, 2 × CH_2Cl, 2 × CH_2N, NHCH_2), 6.81 (d, 1H, J = 1.7 Hz, Py–H), 6.96 (d, 1H, J = 1.7 Hz, Py–H), 7.06 (d, 1H, J = 1.7 Hz, Py–H), 7.16 (d, 1H, J = 1.7 Hz, Py–H), 7.24 (d, 1H, J = 1.7 Hz, Py–H), 7.27 (d, 1H, J = 1.7 Hz, Py–H), 7.65 (d, J = 8.8 Hz, 2H, Ar–H), 7.75 (d, J = 8.8 Hz, 2H, Ar–H), 7.95 (s, 2H, Ar–H), 8.20–8.30 (m, 1H, NHCH_2), 8.35 (s, 2H, Ar–H), 9.95 (s, 1H), 10.02 (s, 1H), 10.06 (s, 1H), 10.09 (s, 1H), 10.14 (s, 1H), 10.28 (s, 1H), 10.35 (s, 1H). HR-ESMS m/z calculated for $C_{54}H_{53}N_{11}O_{10}Cl_2$ 1085.34 found 1108.40 (M + Na).

5-Benzyloxy-1-chloromethyl-7-[3-(2-methoxycarbonyl-1-methyl-1*H*-imidazol-4-ylcarbamoyl)propionylamino]-1,2-dihydrobenzo[*e*]indole-3-carboxylic acid *tert*-butyl ester (50)

This compound was prepared starting from 1-methyl-4-nitro-1*H*-imidazole-2-carboxylic acid methyl ester (0.190 g, 1.02 mmol) and the acid **5** (0.5g, 0.929 mmol) according to general procedure A (0.9 g, 79% yield) as a white solid. ^{1}H NMR (300 MHz, DMSO-d$_6$) δ 1.53 (s, 9H, Boc–H), 2.56–2.70 (m, 4H, 2 × CH_2CO–), 3.84 (s, 3H, –NCH_3), 3.85 (s, 3H, –OCH_3), 3.90–4.15 (m, 5H, –CH, CH_2Cl, CH_2N), 5.25 (s, 2H, –OC$H_2C_6H_5$), 7.55 (s, 1H, Im–H), 7.61–7.90 (m, 8H, Ar–H), 8.40 (s, 1H, C6–H), 10.15 (s, 1H, –NH–), 10.55 (s, 1H, –NH–). HR–MS m/z calculated for $C_{35}H_{38}N_5O_7Cl$ 675.25, found 698.23 (M + Na).

5-Benzyloxy-7-[3-(2-carboxy-1-methyl-1*H*-imidazol-4-ylcarbamoyl)propionylamino]-1-chloromethyl-1,2-dihydrobenzo[*e*]-indole-3-carboxylic acid *tert*-butyl ester (51)

This compound was prepared according to general procedure B by employing compound **50** (0.4g, 0.592 mmol) and 0.5 M NaOH in 76% yield (0.30 g) as a white solid. ^{1}H NMR (300 MHz, DMSO-d$_6$) δ 1.52 (s, 9H, Boc–H), 2.56–2.70 (m, 4H, 2 × CH_2CO–), 3.82 (s, 3H, –NCH_3), 3.90–4.20 (m, 5H, –CH, CH_2Cl, CH_2N), 5.24 (s, 2H, –OC$H_2C_6H_5$), 7.45 (s, 1H, Im–H), 7.58–7.90 (m, 8H, Ar–H), 8.40 (s, 1H, C6–H), 10.12 (s, 1H, –NH–), 10.40 (s, 1H, –NH–), 12.52 (br s, 1H, –COOH). HR–MS m/z calculated for $C_{34}H_{36}N_5O_7Cl$ 661.23, found 662.13 (M + 1).

[(1-Methyl-4-nitro-1*H*-imidazole-2-carbonyl)amino]acetic acid methyl ester (53)

To a solution of glycine methyl ester hydrochloride (1.0 g, 7.96 mmol) in dry THF (50.0 ml), Et_3N (1.0 ml) and a solution of compound **52** (2.38 g, 8.73 mmol) in THF (5.0 ml), was added slowly with stirring at 0 °C under nitrogen atmosphere. The reaction mixture was brought to room temperature and stirred for 4 h. After completion of the reaction the residue was concentrated to dryness under reduced pressure and the residue was purified by column chromatography in 87% yield (1.85 g) as a solid. ^{1}H NMR (300 MHz, DMSO-d$_6$) δ 3.55–3.82 (m, 2H, –NHCH_2), 3.85 (s, 3H, –OCH_3), 3.87 (s, 3H, –NCH_3), 7.45 (s, 1H, Im–H), 8.20 (m, 1H, –NHCH_2). HR–MS m/z calculated for $C_8H_{10}N_4O_5$ 242.07, found 242.20.

({1-Methyl-4-[(1-methyl-4-nitro-1*H*-imidazole-2-carbonyl)-amino]-1*H*-imidazole-2-carbonyl}amino)acetic acid methyl ester (54)

To a solution of compound **53** (1.0 g, 4.13 mmol) in 25.0 ml of methanol was added 0.200 g of 10% Pd–C. The reaction

mixture was hydrogenated in a Parr shaker at 50 psi for 2 h. The catalyst was removed by filtration and the solvent was evaporated *in vacuo*. The residue was dissolved in dry THF (20.0 ml), Et_3N (1.0 ml) and a solution of compound **52** (1.12 g, 4.11 mmol) in THF (5.0 ml), was added slowly with stirring at 0 °C under nitrogen atmosphere. The reaction mixture was brought to room temperature and stirred for 2 h. After completion of the reaction the residue was concentrated to dryness under reduced pressure and the residue was purified by column chromatography eluting with 3% MeOH–DCM to give **54**, as a yellow solid 1.3 g in 86% yield. ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.56–3.80 (m, 2H, –NHCH_2), 3.85 (s, 3H, –OCH_3), 3.87 (s, 3H, –NCH_3), 3.89 (s, 3H, –NCH_3), 7.75 (s, 1H, Im–H), 8.15–8.20 (m, 1H, –NHCH_2), 8.60 (s, 1H, Im–H), 10.90 (s, 1H, –NH–). HR–MS *m*/*z* calculated for $C_{13}H_{15}N_7O_6$ 365.11, found 365.32.

{[1-Methyl-4-({1-methyl-4-[(1-methyl-4-nitro-1*H*-imidazole-2-carbonyl)amino]-1*H*-imidazole-2-carbonyl}amino)-1*H*-imidazole-2-carbonyl]amino}acetic acid methyl ester (55)

This compound was prepared according to the method described for compound **54**, employing compounds **54** (1.0 g, 2.73 mmol) and **52** (0.746 g, 2.73 mmol) and the crude product was purified by column chromatography using 7% MeOH–DCM as eluting solvent. Compound **55** was obtained in 75% yield (1.0 g) as a solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.58–3.80 (m, 2H, –NHCH_2), 3.86 (s, 3H, –OCH_3), 3.87 (s, 3H, –NCH_3), 3.89 (s, 3H, –NCH_3), 3.91 (s, 3H, –NCH_3), 7.58 (s, 1H, Im–H), 7.76 (s, 1H, Im–H), 8.15–8.26 (m, 1H, –NHCH_2), 8.58 (s, 1H, Im–H), 10.10 (s, 1H, –NH–), 10.60 (s, 1H, –NH–). HR–MS *m*/*z* calculated for $C_{18}H_{20}N_{10}O_7$ 488.15, found 488.40.

5-Benzyloxy-1-chloromethyl-7-{3-[2-(methoxycarbonylmethylcarbamoyl)-1-methyl-1*H*-imidazol-4-ylcarbamoyl]propionylamino}-1,2-dihydrobenzo[*e*]indole-3-carboxylic acid *tert*-butyl ester (56)

This compound was prepared starting from [(1-methyl-4-nitro-1*H*-imidazole-2-carbonyl)amino]acetic acid methyl ester (**53**) (0.494 g, 2.04 mmol) and the acid **5** (1.0 g, 1.85 mmol) according to general procedure A (1.0 g, 73% yield) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.56 (s, 9H, Boc–H), 2.56–2.70 (m, 4H, 2 × CH_2CO–), 3.58–3.78 (m, 2H, –NHCH_2), 3.84 (s, 3H, –OCH_3), 3.87 (s, 3H, –NCH_3), 3.92–4.15 (m, 5H, –CH, CH_2Cl, CH_2N), 5.24 (s, 2H, –OC$H_2C_6H_5$), 7.47 (s, 1H, Im–H), 7.52–7.90 (m, 8H, Ar–H), 8.18–8.30 (m, 1H, –NHCH_2), 8.40 (s, 1H, C6–H), 10.15 (s, 1H, –NH–), 10.25 (s, 1H, –NH–). HR–MS *m*/*z* calculated for $C_{37}H_{41}N_6O_8Cl$ 732.27, found 733.30 (M + 1).

5-Benzyloxy-1-chloromethyl-7-(3-{2-[2-(methoxycarbonylmethylcarbamoyl)-1-methyl-1*H*-imidazol-4-ylcarbamoyl]-1-methyl-1*H*-imidazol-4-ylcarbamoyl}propionylamino)-1,2-dihydrobenzo[*e*]indole-3-carboxylic acid *tert*-butyl ester (57)

Prepared according to general procedure A by using ({1-methyl-4-[(1-methyl-4-nitro-1*H*-imidazole-2-carbonyl)amino]-1*H*-imidazole-2-carbonyl}amino)acetic acid methyl ester (**54**) (0.746 g, 2.04 mmol) and the acid **5** (1.0 g, 1.85 mmol) in 80% yield (1.2 g) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.53 (s, 9H, Boc–H), 2.52–2.71 (m, 4H, 2 × CH_2CO–), 3.56–3.79 (m, 2H, –NHCH_2), 3.82 (s, 3H, –OCH_3), 3.86 (s, 3H, –NCH_3), 3.88 (s, 3H, – NCH_3), 3.91–4.15 (m, 5H, –CH, CH_2Cl, CH_2N), 5.26 (s, 2H, –OC$H_2C_6H_5$), 7.47 (s, 1H, Im–H), 7.50–7.95 (m, 9H, Ar–H, Im–H), 8.20–8.30 (m, 1H, –NHCH_2), 8.42 (s, 1H, C6–H), 9.55 (s, 1H, –NH–), 10.15 (s, 1H, –NH–), 10.48 (s, 1H, –NH–). HR–MS *m*/*z* calculated for $C_{42}H_{46}N_9O_9Cl$ 855.31, found 856.31 (M + 1).

5-Benzyloxy-1-chloromethyl-7-(3-{2-[2-(2-methoxycarbonylmethylcarbamoyl)-1-methyl-1*H*-imidazol-4-ylcarbamoyl)-1-methyl-1*H*-imidazol-4-ylcarbamoyl]-1-methyl-1*H*-imidazol-4-ylcarbamoyl}propionylamino)-1,2-dihydrobenzo[*e*]indole-3-carboxylic acid *tert*-butyl ester (58)

This compound was prepared according to the method described for compounds **56**, **57** by employing {[1-methyl-4-({1-methyl-4-[(1-methyl-4-nitro-1*H*-imidazole-2-carbonyl)-amino]-1*H*-imidazole-2-carbonyl}-amino)-1*H*-imidazole-2-carbonyl]-amino}acetic acid methyl ester (**55**) (0.998 g, 2.04 mmol) and the acid **5** (1.0 g, 1.85 mmol) in 80% yield (1.45 g) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.55 (s, 9H, Boc–H), 2.56–2.70 (m, 4H, 2 × CH_2CO–), 3.57–3.80 (m, 2H, –$NHCH_2$), 3.83 (s, 3H, –OCH_3), 3.86 (s, 3H, –NCH_3), 3.87 (s, 3H, –NCH_3), 3.89 (s, 3H, –NCH_3), 3.92–4.20 (m, 5H, –CH, CH_2Cl, CH_2N), 5.25 (s, 2H, –O$CH_2C_6H_5$), 7.45 (s, 1H, Im–H), 7.65 (s, 1H, Im–H), 7.69–7.98 (m, 9H, Ar–H, Im–H), 8.20–8.35 (m, 1H, –$NHCH_2$), 8.48 (s, 1H, C6–H), 9.70 (s, 1H, –NH–), 9.80 (s, 1H, –NH–), 10.15 (s, 1H, –NH–), 10.50 (s, 1H, –NH–). HR–MS *m*/*z* calculated for $C_{47}H_{51}N_{12}O_{10}Cl$ 978.35, found 979.36 (M + 1).

5-Benzyloxy-7-{3-[2-(carboxymethylcarbamoyl)-1-methyl-1*H*-imidazol-4-ylcarbamoyl]propionylamino}-1-chloromethyl-1,2-dihydrobenzo[*e*]indole-3-carboxylic acid *tert*-butyl ester (59)

This compound was prepared in 81% yield as a solid according to general procedure B by employing compound **56** (1.0 g, 1.36 mmol) and 0.5 M NaOH (0.80 g). ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.54 (s, 9H, Boc–H), 2.55–2.72 (m, 4H, 2 × CH_2CO–), 3.57–3.80 (m, 2H, –$NHCH_2$), 3.87 (s, 3H, –NCH_3), 3.92–4.15 (m, 5H, –CH, CH_2Cl, CH_2N), 5.24 (s, 2H, –O$CH_2C_6H_5$), 7.45 (s, 1H, Im–H), 7.58–7.90 (m, 8H, Ar–H), 8.18–8.35 (m, 1H, –NHCH_2), 8.40 (s, 1H, C6–H), 10.15 (s, 1H, –NH–), 10.38 (s, 1H, –NH–), 12.56 (br s, 1H, –COOH). HR–MS *m*/*z* calculated for $C_{36}H_{39}N_6O_8Cl$ 718.25, found 741.24 (M + Na).

5-Benzyloxy-7-(3-{2-[2-(carboxymethylcarbamoyl)-1-methyl-1*H*-imidazol-4-ylcarbamoyl]-1-methyl-1*H*-imidazol-4-ylcarbamoyl}propionylamino)-1-chloromethyl-1,2-dihydrobenzo[*e*]-indole-3-carboxylic acid *tert*-butyl ester (60)

Prepared according to general procedure B by using compound **57** (1.0 g, 1.16 mmol) and 0.5 M NaOH solution in 81% yield (0.80 g) as a solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.54 (s, 9H, Boc–H), 2.56–2.72 (m, 4H, 2 × CH_2CO–), 3.55–3.80 (m, 2H, –NHCH_2), 3.86 (s, 3H, –NCH_3), 3.88 (s, 3H, –NCH_3), 3.91–4.20 (m, 5H, –CH, CH_2Cl, CH_2N), 5.25 (s, 2H, –OC$H_2C_6H_5$), 7.42 (s, 1H, Im–H), 7.55 (s, Im–H), 7.58–7.89 (m, 8H, Ar–H), 8.20–8.35 (m, 1H, –NHCH_2), 8.47 (s, 1H, C6–H), 9.80 (s, 1H, –NH–), 10.15 (s, 1H, –NH–), 10.50 (s, 1H, –NH–), 12.60 (br s, 1H, –COOH). HR–MS *m*/*z* calculated for $C_{41}H_{44}N_9O_9Cl$ 841.30, found 842.31 (M + 1).

5-Benzyloxy-7-(3-{2-[2-(2-(carboxymethylcarbamoyl)-1-methyl-1*H*-imidazol-4-ylcarbamoyl)-1-methyl-1*H*-imidazol-4-ylcarbamoyl]-1-methyl-1*H*-imidazol-4-ylcarbamoyl}propionylamino)-1-chloromethyl-1,2-dihydrobenzo[*e*]indole-3-carboxylic acid *tert*-butyl ester (61)

This compound was prepared according to general method B by using compound **58** (1.0 g, 1.02 mmol) and 0.5 M NaOH solution in 81% yield (0.80 g) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.52 (s, 9H, Boc–H), 2.56–2.70 (m, 4H, 2 × CH_2CO–), 3.56–3.80 (m, 2H, –NHCH_2), 3.86 (s, 3H, –NCH_3), 3.87 (s, 3H, –NCH_3), 3.89 (s, 3H, –NCH_3), 3.92–4.20 (m, 5H, –CH, CH_2Cl, CH_2N), 5.24 (s, 2H, –OC$H_2C_6H_5$), 7.47 (s, 1H, Im–H), 7.55 (s, 1H, Im–H), 7.58–7.98 (m, 9H, Ar–H, Im–H), 8.15–8.35 (m, 1H, –NHCH_2), 8.40 (s, 1H, C6–H), 9.56 (s, 1H, –NH–), 9.89 (s, 1H, –NH–), 10.20 (s, 1H, –NH–), 10.51 (s, 1H, –NH–), 12.59 (br s, 1H, –COOH). HR–MS *m*/*z* calculated for $C_{46}H_{49}N_{12}O_{10}Cl$ 964.34, found 965.34 (M + 1).

Compound 62

Prepared according to general procedure C by using compound **59** (0.25 g, 0.348 mmol) and *seco*-CBI amine **15** (0.189 g, 0.381 mmol) in 72% yield (0.30 g) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.52 (s, 18H, 2 × Boc–H), 2.56–2.70 (m, 4H, 2 × CH_2CO–), 3.55–3.79 (m, 4H, 2 × –NHCH_2), 3.85 (s, 3H, –NCH_3), 3.91–4.20 (m, 10H, Cl, 2-H, 2 × CH_2Cl, 2 × CH_2N), 5.24 (s, 2H, –OC$H_2C_6H_5$), 5.25 (s, 2H, –OC$H_2C_6H_5$), 7.48 (s, 1H, Im–H), 7.59–7.75 (m, 16H, Ar–H), 8.30 (m, 2H, 2 × –NHCH_2), 8.40 (s, 2H, 2 × C6–H), 10.10 (s, 1H, –NH–), 10.20 (s, 1H, –NH–), 10.40 (s, 1H, –NH–). ES–MS *m*/*z* calculated for $C_{63}H_{67}N_9O_{11}Cl_2$ 1195.43, found 1218.40 (M + Na).

Compound 63

This compound was prepared according to the method described for compound **62**, by employing *seco*-CBI imidazole polyamide acid **60** (0.25 g, 0.297 mmol) and the amine **15** (0.161 g, 0.325 mmol) in 76% yield (0.30 g) as a solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.56 (s, 18H, 2 × Boc–H), 2.52–2.70 (m, 4H, 2 × CH_2CO–), 3.56–3.79 (m, 4H, 2 × –NHCH_2), 3.85 (s, 3H, –NCH_3), 3.87 (s, 3H, –NCH_3), 3.90–4.20 (m, 10H, Cl, 2-H, 2 × CH_2Cl, 2 × CH_2N), 5.24 (s, 2H, –OC$H_2C_6H_5$), 5.26 (s, 2H, –OC$H_2C_6H_5$), 7.48 (s, 1H, Im–H), 7.60–7.95 (m, 17H, Ar–H, Im–H), 8.20–8.35 (m, 2H, 2 × –NHCH_2), 8.40 (s, 2H, 2 × C6–H), 9.51 (s, 1H, –NH–), 10.10 (s, 1H, –NH–), 10.18 (s, 1H, –NH–), 10.25 (s, 1H, –NH–) ES–MS *m*/*z* calculated for $C_{68}H_{72}N_{12}O_{12}Cl_2$ 1318.48, found 1319.50 (M + 1).

Compound 64

This compound was prepared starting from *seco*-CBI amine **15** (0.169 g, 0.341 mmol) and the acid **61** (0.30 g, 0.311 mmol) according to general procedure described for compound **63** (0.30 g, 66% yield) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.54 (s, 18H, 2 × Boc–H), 2.56–2.72 (m, 4H, 2 × CH_2CO–), 3.52–3.76 (m, 4H, 2 × –NHCH_2), 3.86 (s, 3H, –NCH_3), 3.87 (s, 3H, –NCH_3), 3.88 (s, 3H, –NCH_3), 3.91–4.15 (m, 10H, Cl, 2-H, 2 × CH_2Cl, 2 × CH_2N), 5.25 (s, 2H, –OC$H_2C_6H_5$), 5.26 (s, 2H, –OC$H_2C_6H_5$), 7.45 (s, 1H, Im–H), 7.52 (s, 1H, Im–H), 7.60–7.85 (m, 17H, Ar–H, Im–H), 8.15–8.31 (m, 2H, 2 × –NHCH_2), 8.40 (s, 2H, 2 × C6–H), 9.68 (s, 1H, –NH–), 9.80 (s, 1H, –NH–), 10.05 (s, 1H, –NH–), 10.19 (s, 1H, –NH–), 10.49 (s, 1H, –NH–). ES–MS *m*/*z* calculated for $C_{73}H_{77}N_{15}O_{13}Cl_2$ 1441.52, found 1442.50 (M + 1).

Compound 65

This compound was prepared starting from *seco*-CBI amine **17** (0.246 g, 0.562 mmol) and the acid **59** (0.30 g, 0.417 mmol) according to general procedure C (0.30 g, 63% yield) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.52 (s, 9H, Boc–H), 2.05 (s, 3H, CH_3CON), 2.56–2.70 (m, 4H, 2 × CH_2CO–), 3.55–3.79 (m, 4H, 2 × –NHCH_2), 3.87 (s, 3H, –NCH_3), 3.90–4.40 (m, 10H, Cl, 2-H, 2 × CH_2Cl, 2 × CH_2N), 5.25 (s, 2H, –OC$H_2C_6H_5$), 5.26 (s, 2H, –OC$H_2C_6H_5$), 7.46 (s, 1H, Im–H), 7.56–7.89 (m, 16H, Ar–H), 8.18–8.30 (m, 2H, 2 × –NHCH_2), 8.35–8.42 (m, 2H, 2 × C6–H), 10.15 (s, 1H, –NH–), 10.18 (s, 1H, –NH–), 10.40 (s, 1H, –NH–). HR-ESMS *m*/*z* calculated for $C_{60}H_{61}N_9O_{10}Cl_2$ 1137.39, found 1138.40 (M + 1).

Compound 66

This compound was prepared according to the method described for compound **65**, employing *seco*-CBI polyamide acid **60** (0.3 g, 0.356 mmol) and the amine **17** (0.210 g, 0.424 mmol) in 71% yield (0.320 g) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.54 (s, 9H, Boc–H), 2.04 (s, 3H, CH_3CON), 2.56–2.72 (m, 4H, 2 × CH_2CO–), 3.56–3.79 (m, 4H, 2 × –NHCH_2), 3.84 (s, 3H, –NCH_3), 3.89 (s, 3H, –NCH_3), 3.90–4.30 (m, 10H, Cl, 2-H, 2 × CH_2Cl, 2 × CH_2N), 5.24 (s, 2H, –OC$H_2C_6H_5$), 5.25 (s, 2H, –OC$H_2C_6H_5$), 7.47 (s, 1H, Im–H), 7.50–7.95 (m, 17H, Ar–H, Im–H), 8.25–8.32 (m, 2H, 2 × –NHCH_2), 8.30–8.40 (m, 2H, 2 × C6–H), 9.45 (s, 1H, –NH–), 10.12 (s, 1H, –NH–), 10.18 (s, 1H, –NH–), 10.45 (s, 1H, –NH–). HR-ESMS *m*/*z* calculated for $C_{65}H_{66}N_{12}O_{11}Cl_2$ 1260.44 found 1261.40 (M + 1).

Compound 67

Prepared according to general procedure C using compound **61** (0.3 g, 0.311 mmol) and *seco*-CBI amine **17** (0.183 g, 0.369 mmol) in 69% yield (0.30 g) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.56 (s, 9H, Boc–H), 2.05 (s, 3H, CH_3CON), 2.56–2.70 (m, 4H, 2 × CH_2CO–), 3.56–3.80 (m, 4H, 2 × –NHCH_2), 3.86 (s, 3H, –NCH_3), 3.87 (s, 3H, –NCH_3), 3.89 (s, 3H, –NCH_3), 3.91–4.40 (m, 10H, Cl, 2-H, 2 × CH_2Cl, 2 × CH_2N), 5.25 (s,2H, –OC$H_2C_6H_5$), 5.26 (s, 2H, –OCH_2-C_6H_5), 7.48 (s, 1H, Im–H), 7.57 (s, 1H, Im–H), 7.60–7.95 (m, 17H, Ar–H, Im–H), 8.20–8.30 (m, 2H, 2 × –NHCH_2), 8.32–8.42 (m, 2H, 2 × C6–H), 9.62 (s, 1H, –NH–), 9.85 (s, 1H, –NH–), 10.15 (s, 1H, –NH–), 10.18 (s, 1H, –NH–), 10.48 (s, 1H, –NH–). HR-ESMS *m*/*z* calculated for $C_{70}H_{71}N_{15}O_{12}Cl_2$ 1383.48 found 1384.50 (M + 1).

Compound 68

Prepared according to general procedure D by using compound **62** (0.2 g, 0.167 mmol), 0.2 ml of 10% aqueous ammonium formate and 0.2 g of 10% Pd/C in 15 ml of THF to give compound **68** as a white solid in 88% yield (0.15 g). ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.52 (s, 18H, 2 × Boc–H), 2.50–2.71 (m, 4H, 2 × CH_2CO–), 3.52–3.70 (m, 4H, 2 × –NHCH_2), 3.86 (s, 3H, –NCH_3), 3.92–4.20 (m, 10H, Cl, 2-H, 2 × CH_2Cl, 2 × CH_2N), 7.59–7.85 (m, 7H, 2 × C4–H, C7–H, C8–H, Im–H), 8.20–8.32 (m, 2H, 2 × –NHCH_2), 8.40 (s, 2H, 2 × C6–H), 9.95 (s, 1H), 10.05 (s, 1H), 10.12 (s, 1H), 10.25 (s, 1H), 10.30 (s, 1H). ES–MS *m*/*z* calculated for $C_{49}H_{55}N_9O_{11}Cl_2$ 1015.34, found 1038.30 (M + Na).

Compound 69

This compound was prepared according to the method described for the compound **68**, employing compound **63** (0.2 g, 0.151 mmol) and the aq. ammonium formate (0.2 ml) in 87% yield (0.15 g) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.56 (s, 18H, 2 × Boc–H), 2.54–2.72 (m, 4H, 2 × CH_2CO–), 3.55–3.76 (m, 4H, 2 × –NHCH_2), 3.86 (s, 3H, –NCH_3), 3.88 (s, 3H, –NCH_3), 3.91–4.20 (m, 10H, Cl, 2-H, 2 × CH_2Cl, 2 × CH_2N), 7.45 (s, 1H, Im–H), 7.55–7.95 (m, 7H, 2 × C4–H, C7–H, C8–H, Im–H), 8.20–8.32 (m, 2H, 2 × –NHCH_2), 8.43 (s, 2H, 2 × C6–H), 9.50 (s, 1H), 9.98 (s, 1H), 10.05 (s, 1H), 10.12 (s, 1H), 10.32 (s, 1H), 10.48 (s, 1H). ES–MS *m*/*z* calculated for $C_{54}H_{59}N_{12}O_{12}Cl_2$ 1138.38, found 1139.40 (M + 1).

Compound 70

This compound was prepared starting from compound **64** (0.20 g, 0.138 mmol) and aq. ammonium formate (0.2 ml) according to general procedure D (0.155 g, 88% yield) as a solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.50 (s, 18H, 2 × Boc–H), 2.50–2.70 (m, 4H, 2 × CH_2CO–), 3.55–3.80 (m, 4H, 2 × NHCH_2), 3.91 (s, 3H, –NCH_3), 3.94 (s, 3H, –NCH_3), 3.99 (s, 3H, –NCH_3), 4.00–4.10 (m, 10H, Cl, 2-H, 2 × CH_2Cl, 2 × CH_2N), 7.47 (s, 1H, Im–H), 7.53 (s, 1H, Im–H), 7.55–7.80 (m, 7H, 2 × C4–H, C7–H, C8–H, Im–H), 8.32 (m, 2H, 2 × NHCH_2), 8.40 (s, 2H, 2 × C6–H), 9.69 (s, 1H), 9.81 (s, 1H), 9.90 (s, 1H), 10.09 (s, 1H), 10.12 (s, 1H), 10.30 (s, 1H), 10.42 (s, 1H). HR-ESMS *m*/*z* calculated for $C_{59}H_{66}N_{15}O_{13}Cl_2$ 1262.40, found 1262.40 (M + H).

Compound 71

This compound was prepared starting from compound **65** (0.20 g, 0.175 mmol) and aq. ammonium formate (0.2 ml) according to general procedure D (0.15 g, 89% yield) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.53 (s, 9H, Boc–H),

2.05 (s, 3H, CH_3CON), 2.56–2.72 (m, 4H, 2 × CH_2CO–), 3.55–3.78 (m, 4H, 2 × NHCH_2), 3.86 (s, 3H, –NCH_3), 3.95–4.25 (m, 10H, Cl, 2-H, 2 × CH_2Cl, 2 × CH_2N), 7.55–7.79 (m, 6H, 2 × C8, C9–H, C4–H, Im–H), 7.90 (d, 1H, C4–H), 8.15–8.25 (m, 1H, –N*H*CH_2), 8.35–8.42 (m, 3H, 2 × C6–H, –N*H*CH_2), 9.98 (s, 1H), 10.05 (s, 1H), 10.07 (s, 1H), 10.14 (??s, 1H), 10.40 (s, 1H). HR-ESMS *m*/*z* calculated for $C_{46}H_{49}N_9O_{10}Cl_2$ 957.30, found 980.30 (M + Na).

Compound 72

Prepared according to general procedure D by using compound **66** (0.20 g, 0.158 mmol) and aq. ammonium formate (0.25 ml) in 87% yield (0.15 g) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.54 (s, 9H, Boc–H), 2.05 (s, 3H, CH_3CON), 2.56–2.72 (m, 4H, 2 × CH_2CO–), 3.52–3.78 (m, 4H, 2 × NHCH_2), 3.86 (s, 3H, –NCH_3), 3.87 (s, 3H, –NCH_3), 3.95–4.25 (m, 10H, Cl, 2-H, 2 × CH_2Cl, 2 × CH_2N), 7.48 (s, 1H, Im–H), 7.60–7.79 (m, 6H, 2 × C8, C9–H, C4–H, Im–H), 7.91 (d, 1H, C4–H), 8.20–8.30 (m, 1H, N*H*CH_2), 8.35–8.42 (m, 3H, 2 × C6–H, Im–H), 9.50 (s, 1H), 10.03 (s, 1H), 10.05 (s, 1H), 10.35 (s, 1H), 10.37 (s, 1H), 10.48 (s, 1H). HR-ESMS *m*/*z* calculated for $C_{51}H_{54}N_{12}O_{11}Cl_2$ 1080.34, found 1081.30 (M + 1).

Compound 73

This compound was prepared according to the method described for the compound **71**, by employing compound **67** (0.20 g, 0.144 mmol) and aq. ammonium formate (0.2 ml) in 86% yield (0.15 g) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6). δ 1.52 (s, 9H, Boc–H), 2.03 (s, 3H, CH_3CON), 2.58–2.70 (m, 4H, 2 × CH_2CO–), 3.57–3.80 (m, 4H, 2 × NHCH_2), 3.84 (s, 3H, –NCH_3), 3.87 (s, 3H, –NCH_3), 3.89 (s, 3H, –NCH_3), 4.04–4.40 (m, 10H, Cl, 2-H, 2 × CH_2Cl, 2 × CH_2N), 7.45 (s, 1H, Im–H), 7.57 (s, 1H, Im–H), 7.60–7.75 (m, 6H, 2 × C8, C9–H, C4–H, Im–H), 7.90 (d, 1H, C4–H), 8.16–8.25 (m, 1H, N*H*CH_2), 8.35–8.42 (m, 3H, 2 × C6–H, N*H*CH_2), 9.64 (s, 1H), 9.81 (s, 1H), 10.02 (s, 1H), 10.05 (s, 1H), 10.10 (s, 1H), 10.29 (s, 1H), 10.45 (s, 1H). HR-ESMS *m*/*z* calculated for $C_{56}H_{59}N_{15}O_{12}Cl_2Na$ 1226.40 found 1226.40(M + Na).

[(1-Methyl-4-nitro-1*H*-imidazole-2-carbonyl)amino]acetic acid *tert*-butyl ester (75)

[(1-Methyl-4-nitro-1*H*-imidazole-2-carbonyl)amino]acetic acid (**74**) was obtained from the basic hydrolysis of the corresponding [(1-Methyl-4-nitro-1*H*-imidazole-2-carbonyl)amino]-acetic acid methyl ester (**53**) from the reported procedure. Compound **74** (3.0 g, 13.15 mmol) was added to 300 ml of THF and 3 ml of concentrated sulfuric acid in a round bottom pressure bottle. The colloidal solution was cooled to −40 °C and a slow stream of isobutylene was bubbled through this solution for several minutes. The solution was capped tightly with a Teflon cork and was allowed to warm to room temperature and was stirred for 36 h. The crude reaction mixture was dissolved in ethyl acetate and was washed with saturated $NaHCO_3$ repeatedly. The crude product was further purified by column chromatography using pure 2% EtOAc–DCM as eluent to give compound **75** in 72% yield (2.7 g) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.53 (s, 9H, –$C(CH_3)_3$), 3.55–3.75 (m, 2H, NHCH_2), 3.86 (s, 3H, –NCH_3), 7.76 (s, 1H, Im–H), 8.15–8.28 (m, 1H, N*H*CH_2). HR–MS *m*/*z* calculated for $C_{11}H_{16}N_4O_5$ 284.11, found 284.20.

({1-Methyl-4-[(1-methyl-4-nitro-1*H*-imidazole-2-carbonyl)-amino]-1*H*-imidazole-2-carbonyl}amino)acetic acid *tert*-butyl ester (76)

To a solution of compound **75** (1.0 g, 3.51 mmol) in 25.0 ml of methanol was added 0.200 g of 10% Pd–C. The reaction mixture was hydrogenated in a Parr shaker at 50 psi for 2 h. The catalyst was removed by filtration and the solvent was evaporated *in vacuo*. The residue was dissolved in dry THF (20.0 ml), Et_3N (1.0 ml) and a solution of compound **52** (1.05 g, 3.85 mmol) in THF (5.0 ml), was added slowly with stirring at 0 °C under a nitrogen atmosphere. The reaction mixture was brought to room temperature and was stirred for 2 h. After completion of the reaction the residue was concentrated to dryness under reduced pressure and was purified by column chromatography eluting with 5% MeOH–DCM to give **76**, as a solid 1.25 g in 87% yield. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.56 (s, 9H, –$C(CH_3)_3$), 3.56–3.72 (m, 2H, NHCH_2), 3.85 (s, 3H, –NCH_3), 3.87 (s, 3H, –NCH_3), 7.45 (s, 1H, Im–H), 7.75 (s, 1H, Im–H), 8.25 (m, 1H, N*H*CH_2), 10.10 (s, 1H, –NH–). HR–MS *m*/*z* calculated for $C_{16}H_{21}N_7O_6$ 407.16, found 407.30.

{[1-Methyl-4-({1-methyl-4-[(1-methyl-4-nitro-1*H*-imidazole-2-carbonyl)amino]-1*H*-imidazole-2-carbonyl}amino)-1*H*-imidazole-2-carbonyl]amino}acetic acid *tert*-butyl ester (77)

This compound was prepared according to the method described for compound **76**, by employing compounds **76** (1.0 g, 2.45 mmol) and **52** (0.736 g, 2.70 mmol) and the crude product was purified by column chromatography using 7% MeOH–DCM as eluting solvent in 77% yield (1.0 g). ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.56 (s, 9H, –$C(CH_3)_3$), 3.58 (m, 2H, NHCH_2), 3.86 (s, 3H, –NCH_3), 3.88 (s, 3H, –NCH_3), 3.89 (s, 3H, –NCH_3), 7.43 (s, 1H, Im–H), 7.61 (s, 1H, Im–H), 7.79 (s, 1H, Im–H), 8.19–8.30 (m, 1H, N*H*CH_2), 10.05 (s, 1H, –NH–), 10.25 (s, 1H, –NH–). HR–MS *m*/*z* calculated for $C_{21}H_{26}N_{10}O_7$ 530.20, found 530.40.

({4-[4-(7-Acetylamino-5-benzyloxy-1-chloromethyl-1,2-dihydrobenzo[*e*]indol-3-yl)-4-oxo-butyrylamino]-1-methyl-1*H*-imidazole-2-carbonyl}amino)acetic acid *tert*-butyl ester (78)

This compound was prepared starting from [(1-methyl-4-nitro-1*H*-imidazole-2-carbonyl)amino]acetic acid *tert*-butyl ester (**75**) (0.650 g, 2.28 mmol) and the *seco*-CBI acid **7** (1.0 g, 2.08 mmol) according to general procedure A (1.2 g, 80% yield) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.59 (s, 9H, –$C(CH_3)_3$), 2.05 (s, 3H, CH_3CON), 2.56–2.72 (m, 4H, 2 × CH_2CO–), 3.57 (m, 2H, NHCH_2), 3.86 (s, 3H, –NCH_3), 3.90–4.20 (m, 5H, –CH, CH_2Cl, CH_2N), 5.26 (s, 2H, –OC$H_2C_6H_5$), 7.47 (s, 1H, Im–H), 7.56–7.89 (m, 7H, Ar–H), 8.14 (s, 1H, Ar–H), 8.25–8.35 (m, 2H, Ar–H, N*H*CH_2), 10.00 (s, 1H, –NH–), 10.30 (s, 1H, –NH–). HR–MS *m*/*z* calculated for $C_{37}H_{41}N_6O_7Cl$ 716.27, found 717.20 (M + 1).

{[4-({4-[4-(7-Acetylamino-5-benzyloxy-1-chloromethyl-1,2-dihydrobenzo[*e*]indol-3-yl)-4-oxo-butyrylamino]-1-methyl-1*H*-imidazole-2-carbonyl}amino)-1-methyl-1*H*-imidazole-2-carbonyl]amino}acetic acid *tert*-butyl ester (79)

Prepared according to general procedure A by using ({1-methyl-4-[(1-methyl-4-nitro-1*H*-imidazole-2-carbonyl)amino]-1*H*-imidazole-2-carbonyl}amino)acetic acid *tert*-butyl ester (**76**) (0.932 g, 2.28 mmol) and the acid **7** (1.0 g, 2.08 mmol) in 74% yield (1.30 g) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.59 (s, 9H, –$C(CH_3)_3$), 2.04 (s, 3H, CH_3CON), 2.54–2.70 (m, 4H, 2 × CH_2CO–), 3.55–3.75 (m, 2H, NHCH_2), 3.86 (s, 3H, –NCH_3), 3.88 (s, 3H, –NCH_3), 3.91–4.20 (m, 5H, –CH, CH_2Cl, CH_2N), 5.26 (s, 2H, –OC$H_2C_6H_5$), 7.46 (s, 1H, Im–H), 7.55–7.92 (m, 8H, Ar–H, Im–H), 8.18 (s, 1H, Ar–H), 8.23–8.38 (m, 2H, Ar–H, N*H*CH_2), 10.05 (s, 1H, –NH–), 10.20 (s, 1H, –NH–), 10.37 (s, 1H, –NH–). HR–MS *m*/*z* calculated for $C_{42}H_{46}N_9O_8Cl$ 839.32, found 840.30 (M + 1).

4-{[4-({4-[4-(7-Acetylamino-5-benzyloxy-1-chloromethyl-1,2-dihydrobenzo[*e*]indol-3-yl)-4-oxo-butyrylamino]-1-methyl-1*H*-imidazole-2-carbonyl}amino)-1-methyl-1*H*-imidazole-2-carbonyl]amino}-1-methyl-1*H*-imidazole-2-carbonyl]amino}-acetic acid *tert*-butyl ester (80)

This compound was prepared according to the method described for compounds **79**, by employing {[1-methyl-4-({1-methyl-4-[(1-methyl-4-nitro-1*H*-imidazole-2-carbonyl)-amino]-

1*H*-imidazole-2-carbonyl}amino)-1*H*-imidazole-2-carbonyl]-amino}acetic acid *tert*-butyl ester (**77**) (1.21 g, 2.28 mmol) and the *seco*-CBI acid **7** (1.0 g, 2.08 mmol) in 75% yield (1.2 g) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.58 (s, 9H, –C(CH_3)$_3$), 2.05 (s, 3H, CH_3CON), 2.56–2.72 (m, 4H, 2 × CH_2CO–), 3.56–3.72 (m, 2H, NHCH_2), 3.85 (s, 3H, –NCH_3), 3.87 (s, 3H, –NCH_3), 3.89 (s, 3H, –NCH_3), 3.90–4.20 (m, 5H, –CH, CH_2Cl, CH_2N), 5.25 (s, 2H, –OC$H_2C_6H_5$), 7.45 (s, 1H, Im–H), 7.61 (s, 1H, Im–H), 7.75–7.95 (m, 8H, Ar–H, Im–H), 8.17 (s, 1H, Ar–H), 8.25–8.35 (m, 2H, Ar–H, N*H*CH_2), 9.98 (s, 1H, –NH–), 10.15 (s, 1H, –NH–), 10.25 (s, 1H, –NH–), 10.40 (s, 1H, –NH–). HR–MS *m*/*z* calculated for $C_{47}H_{51}N_{12}O_9Cl$ 962.36, found 963.40 (M + 1).

({4-[4-(7-Acetylamino-5-benzyloxy-1-chloromethyl-1,2-dihydrobenzo[*e*]indol-3-yl)-4-oxo-butyrylamino]-1-methyl-1*H*-imidazole-2-carbonyl}amino)acetic acid (81)

This compound was prepared according to general method E by using compound **78** (1.0 g, 1.39 mmol) and 1.0 M solution of $TiCl_4$ (3.0 ml) in dichloromethane to give compound **81** as a white solid in 70% yield (0.65 g). ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.05 (s, 3H, CH_3CON), 2.56–2.72 (m, 4H, 2 × CH_2CO–), 3.55–3.70 (m, 2H, NHCH_2), 3.86 (s, 3H, –NCH_3), 3.92–4.20 (m, 5H, –CH, CH_2Cl, CH_2N), 5.25 (s, 2H, –OC$H_2C_6H_5$), 7.50 (s, 1H, Im–H), 7.60–7.90 (m, 7H, Ar–H), 8.18 (s, 1H, Ar–H), 8.20–8.39 (m, 2H, Ar–H, N*H*CH_2), 10.10 (s, 1H, –NH–), 10.27 (s, 1H, –NH–), 12.56 (br s, 1H, –COOH). HR–MS *m*/*z* calculated for $C_{33}H_{33}N_6O_7Cl$ 660.21, found 683.25 (M + Na).

{[4-({4-[4-(7-Acetylamino-5-benzyloxy-1-chloromethyl-1,2-dihydrobenzo[*e*]indol-3-yl)-4-oxo-butyrylamino]-1-methyl-1*H*-imidazole-2-carbonyl}amino)-1-methyl-1*H*-imidazole-2-carbonyl]amino}acetic acid (82)

Prepared according to general procedure E by using compound **79** (1.0 g, 1.19 mmol) and 1.0 M solution of $TiCl_4$ (3.0 ml) solution in 76% yield (0.71 g) as a solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.04 (s, 3H, CH_3CON), 2.54–2.75 (m, 4H, 2 × CH_2CO–), 3.56–3.75 (m, 2H, NHCH_2), 3.86 (s, 3H, –NCH_3), 3.88 (s, 3H, –NCH_3), 3.95–4.20 (m, 5H, –CH, CH_2Cl, CH_2N), 5.25 (s, 2H, –OC$H_2C_6H_5$), 7.46 (s, 1H, Im–H), 7.53 (s, 1H, Im–H), 7.59–7.96 (m, 8H, Ar–H, Im–H), 8.15 (s, 1H, Ar–H), 8.19–8.36 (m, 2H, Ar–H, *N*H*CH*$_2$), 10.05 (s, 1H, –NH–), 10.22 (s, 1H, –NH–), 10.35 (s, 1H, –NH–), 12.56 (br s, 1H, –COOH). HR–MS *m*/*z* calculated for $C_{38}H_{38}N_9O_8Cl$ 783.25, found 806.30 (M + Na).

4-{[4-({4-[4-(7-Acetylamino-5-benzyloxy-1-chloromethyl-1,2-dihydrobenzo[*e*]indol-3-yl)-4-oxo-butyrylamino]-1-methyl-1*H*-imidazole-2-carbonyl}amino)-1-methyl-1*H*-imidazole-2-carbonyl]amino}-1-methyl-1*H*-imidazole-2-carbonyl]amino}-acetic acid (83)

This compound was prepared according to general method E by using compound **80** (1.0 g, 1.03 mmol) and 1.0 M solution of $TiCl_4$ (3.0 ml) to give compound **83** as a white solid in 63% yield (0.60 g). ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.04 (s, 3H, CH_3CON), 2.56–2.75 (m, 4H, 2 × CH_2CO–), 3.52–3.75 (m, 2H, NHCH_2), 3.85 (s, 3H, –NCH_3), 3.87 (s, 3H, –NCH_3), 3.89 (s, 3H, –NCH_3), 3.91–4.20 (m, 5H, –CH, CH_2Cl, CH_2N), 5.24 (s, 2H, –OC$H_2C_6H_5$), 7.44 (s, 1H, Im–H), 7.56 (s, 1H, Im–H), 7.62–7.90 (m, 8H, Ar–H, Im–H), 8.18 (s, 1H, Ar–H), 8.21–8.35 (m, 2H, Ar–H, N*H*CH_2), 9.98 (s, 1H, –NH–), 10.08 (s, 1H, –NH–), 10.25 (s, 1H, –NH–), 10.40 (s, 1H, –NH–), 12.56 (br s, 1H, –COOH). HR–MS *m*/*z* calculated for $C_{43}H_{43}N_{12}O_9Cl$ 906.30, found 929.32 (M + Na).

Compound 84

This compound was prepared starting from *seco*-CBI amine **17** (0.268 g, 0.50 mmol) and the acid **81** (0.30 g, 0.454 mmol) according to general procedure C (0.320 g, 65% yield) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.05 (s, 6H, 2 × –CH_3CON), 2.58–2.70 (m, 4H, 2 × CH_2CO–), 3.55–3.80 (m, 4H, 2 × –NHCH_2), 3.86 (s, 3H, –NCH_3), 3.95–4.40 (m, 10H, Cl, 2-H, 2 × CH_2Cl, 2 × CH_2N), 5.24 (s, 2H, –OC$H_2C_6H_5$), 5.25 (s, 2H, –OC$H_2C_6H_5$), 7.46 (s, 1H, Im–H), 7.60–7.90 (m, 14H, Ar–H), 8.13 (s, 2H, Ar–H), 8.21–8.30 (m, 2H, 2 × –N*H*CH_2), 8.35 (s, 2H, Ar–H), 10.03 (s, 1H, –NH–), 10.10 (s, 1H, –NH–), 10.35 (s, 1H, –NH–). HR-ESMS *m*/*z* calculated for $C_{57}H_{55}N_9O_9Cl_2$ 1079.35, found 1102.30 (M + Na).

Compound 85

This compound was prepared according to the method described for compound **84**, by employing *seco*-CBI N-3 polyamide acid **82** (0.3 g, 0.383 mmol) and the amine **17** (0.226 g, 0.420 mmol) in 65% yield (0.30 g) as a solid. ^{1}H NMR (300 MHz, $DMSOd_6$) δ 2.05 (s, 6H, 2 × –CH_3CON), 2.52–2.74 (m, 4H, 2 × CH_2CO–), 3.52–3.78 (m, 4H, 2 × –NHCH_2), 3.86 (s, 3H, –NCH_3), 3.88 (s, 3H, –NCH_3), 3.95–4.35 (m, 10H, Cl, 2-H, 2 × CH_2Cl, 2 × CH_2N), 5.23 (s, 2H, –OC$H_2C_6H_5$), 5.24 (s, 2H, –OC$H_2C_6H_5$), 7.49 (s, 1H, Im–H), 7.56 (s, 1H, Im–H), 7.65–7.95 (m, 14H, Ar–H), 8.15 (s, 2H, Ar–H), 8.25–8.30 (m, 2H, 2 × –N*H*CH_2), 8.38 (s, 2H, Ar–H), 10.02 (s, 1H, –NH–), 10.16 (s, 1H, –NH–), 10.25 (s, 1H, –NH–), 10.38 (s, 1H, –NH–). HR-ESMS *m*/*z* calculated for $C_{62}H_{60}N_{12}O_{10}Cl_2$ 1202.39 found 1225.40 (M + Na).

Compound 86

Prepared according to general procedure C by using compound **83** (0.30 g, 0.331 mmol) and *seco*-CBI amine **17** (0.195 g, 0.215 mmol) in 66% yield (0.29 g) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.05 (s, 6H, 2 × –CH_3CON), 2.56–2.72 (m, 4H, 2 × CH_2CO–), 3.54–3.77 (m, 4H, 2 × –NHCH_2), 3.87 (s, 3H, –NCH_3), 3.88 (s, 3H, –NCH_3), 3.89 (s, 3H, –NCH_3), 3.92–4.40 (m, 10H, Cl, 2-H, 2 × CH_2Cl, 2 × CH_2N), 5.25 (s,2H, –OC$H_2C_6H_5$), 5.26 (s, 2H, –OC$H_2C_6H_5$), 7.44 (s, 1H, Im–H), 7.57 (s, 1H, Im–H), 7.62–7.90 (m, 15H, Ar–H, Im–H), 8.15 (s, 2H, Ar–H), 8.20–8.30 (m, 2H, 2 × –N*H*CH_2), 8.38 (s, 2H, Ar–H), 10.00 (s, 1H, –NH–), 10.10 (s, 1H, –NH–), 10.15 (s, 1H, –NH–), 10.25 (s, 1H, –NH–), 10.35 (s, 1H, –NH–). HR-ESMS *m*/*z* calculated for $C_{67}H_{65}N_{15}O_{11}Cl_2$ 1325.44 found 1348.40 (M + Na).

Compound 87

This compound was prepared starting from compound **84** (0.25 g, 0.231 mmol) and 10% aq. ammonium formate (0.2 ml) according to general procedure D in (0.15 g, 72% yield) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.04 (s, 6H, 2 × –CH_3CON), 2.54–2.72 (m, 4H, 2 × CH_2CO–), 3.52–3.71 (m, 4H, 2 × –NHCH_2), 3.87 (s, 3H, –NCH_3), 3.95–4.35 (m, 10H, Cl, 2-H, 2 × CH_2Cl, 2 × CH_2N), 7.49 (s, 1H, Im–H), 7.66 (d, J = 8.9 Hz, 2H, Ar–H), 7.75 (d, J = 8.9 Hz, 2H, Ar–H), 7.96 (s, 2H, Ar–H), 8.18–8.30 (m, 2H, 2 × –N*H*CH_2), 8.35 (s, 2H, Ar–H), 9.94 (s, 1H), 10.06 (s, 1H), 10.07 (s, 1H), 10.24 (s, 1H). HR-ESMS *m*/*z* calculated for $C_{43}H_{43}N_9O_9Cl_2$ 899.26, found 922.30 (M + Na).

Compound 88

Prepared according to general procedure D by using compound **85** (0.25 g, 0.207 mmol) and 10% aq. ammonium formate (0.3 ml) in 81% yield (0.172 g) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.04 (s, 6H, 2 × –CH_3CON), 2.56–2.72 (m, 4H, 2 × CH_2CO–), 3.51–3.75 (m, 4H, 2 × –NHCH_2), 3.86 (s, 3H, –NCH_3), 3.88 (s, 3H, –NCH_3), 3.95–4.42 (m, 10H, Cl, 2-H, 2 × CH_2Cl, 2 × CH_2N), 7.43 (s, 1H, Im–H), 7.56 (s, 1H, Im–H), 7.65 (d, J = 8.9 Hz, 2H, Ar–H), 7.75 (d, J = 9.0 Hz, 2H, Ar–H), 7.96 (s, 2H, Ar–H), 8.20–8.30 (m, 2H, 2 × –N*H*CH_2), 8.35 (s, 2H, Ar–H), 9.98 (s, 1H), 10.06 (s, 1H), 10.08 (s, 1H), 10.09 (s,

1H), 10.24 (s, 1H), 10.35 (s, 1H). HR-ESMS *m/z* calculated for $C_{48}H_{48}N_{12}O_{10}Cl_2$ 1022.30, found 1045.50 (M + Na).

Compound 89

This compound was prepared according to the method described for compound **87**, by employing compound **86** (0.3 g, 0.226 mmol) and 10% aq. ammonium formate (0.35 ml) in 77% yield (0.20 g) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.05 (s, 6H, 2 × –CH_3CON), 2.61–2.72 (m, 4H, 2 × CH_2CO–), 3.55–3.75 (m, 4H, 2 × –NHCH_2), 3.86 (s, 3H, –NCH_3), 3.88 (s, 3H, –NCH_3), 3.91 (s, 3H, –NCH_3), 3.95–4.40 (m, 10H, Cl, 2-H, 2 × CH_2Cl, 2 × CH_2N), 7.44 (s, 1H, Im–H), 7.57 (s, 1H, Im–H), 7.68 (d, J = 8.8 Hz, 2H, Ar–H), 7.75 (d, J = 8.8 Hz, 2H, Ar–H), 7.95 (s, 2H, Ar–H), 8.20–8.30 (m, 2H, 2 × –NHCH_2), 8.36 (s, 2H, Ar–H), 9.95 (s, 1H), 10.04 (s, 1H), 10.05 (s, 1H), 10.08 (s, 1H), 10.24 (s, 1H), 10.31 (s, 1H), 10.40 (s, 1H). HR-ESMS *m/z* calculated for $C_{53}H_{53}N_{15}O_{11}Cl_2$ 1145.34 found 1168.40 (M + Na).

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