Distamycin Analogues with Enhanced Lipophilicity: Synthesis and Antimicrobial Activity

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Forty-eight heterocyclic amino acid trimers, analogues of distamycin, with a number of features that enhance lipophilicity are described. They contain alkyl or cycloalkyl groups larger than methyl; some are N-terminated by acetamide or methoxybenzamide and are C-terminated by dimethylaminopropyl or aliphatic heterocylic aminopropyl substituents. The ability of these compounds to bind principally to AT tracts of DNA has been evaluated using capillary zone electrophoresis. Significant antimicrobial activity against key organisms such as MRSA and *Candida albicans* is shown by several compounds, especially those containing a thiazole. Moreover, these compounds have low toxicity with respect to several mammalian cell lines.

Introduction

Analogues of distamycin and netropsin are widely recognized as candidates for drug development based upon their ability to bind with sequence specificity to the minor groove of DNA.[1] The feasibility of this approach in disease-related assays has been demonstrated for antiviral[2] and cytokine inhibiting activity,[3] while minor-groove binders have been more broadly considered as drugs for the future.[4] When modified at the N-terminus by alkylating functional groups such as α,β-unsaturated amides or chloroethylamines, distamycin analogues also show antitumor activity.[5] In many cases, large oligomers (10mers plus) are required to show substantial biological activity and in several cases, it has been possible to demonstrate that sequence reading by the minor groove binder is related to biological activity.[1−4]

Linear head-to-tail oligomers have featured strongly in drug design.[6] It is also possible to design analogues having a head-to-head link (through the N-terminus) and these are typically dicationic (Figure 1). While there are potential problems in delivering large polyamides to the mammalian nucleus,[2] small analogues of distamycin and netropsin have been shown to have significant antibacterial activity.[7] Typically, such compounds contain *N*-alkyl pyrroles with branched or cycloalkyl substituents in place of the methyl group found in distamycin and netropsin and possess larger head groups than formyl.

We have drawn attention to the influence of structure on the lipophilicity of analogues of distamycin and netropsin.[8] As a major property that influences the ability of a drug to reach targets by transmembrane diffusion, the ability to control lipophilicity would be expected to have a major effect on the biological activity of minor-groove binders. For example, the replacement of an imidazole by a thiazole would be expected to increase log *P* by at least one unit.[9] This argument led us to consider further that distamycin and netropsin, through their methyl groups, do not take full advantage of the available hydrophobic interactions with the methine and methylene group forming the walls of the DNA minor groove. Since the methyl groups point outward from within the minor groove, larger alkyl groups might offer increased contacts with the DNA backbone. This might then lead to an increase in affinity together with a beneficial effect on transport. We have therefore synthesized a number of distamycin analogues that embody these structural features (**1**−**48**) and have investigated their binding to DNA using capillary zone electrophoresis (CE) and their antimicrobial activity against a panel of Gram-positive and -negative bacteria and fungi. In this paper, we outline the synthesis and discuss the emerging structure−activity relationships with these compounds.

Design and Synthesis. The structures of the monomers and head and tail groups are shown in Figure 2, and the structures of the minor-groove binders prepared are shown in Table 1. Table 1 uses the shorthand notation as defined in Figure 2.

***N*-Alkylpyrroles.** To encompass a reasonable range of size and shape, branched *N*-alkyl- and *N*-cycloalkylpyrroles were prepared by alkylation of the potassium salt of ethyl 3-nitropyrrole-5-carboxylate with the appropriate alkyl bromide.[10] Examples with limited conformational flexibility (isopropyl and cyclopentyl) and with substantial conformational flexibility (3-methylbutyl and cyclopropylmethyl) were selected. The various nitro-carboxylate monomers were appropriate for the synthesis of oligomers prepared as previously described typically by alkylation of the potassium salt of ethyl 5-nitropyrrole-2-carboxylate and subsequent functional group modification.[6]

Thiazoles. As noted above, thiazoles can be considered as lipophilic analogues of imidazoles. Since imidazoles have been widely recognized as permitting binding to GC regions,[1] thiazoles can be anticipated to be very

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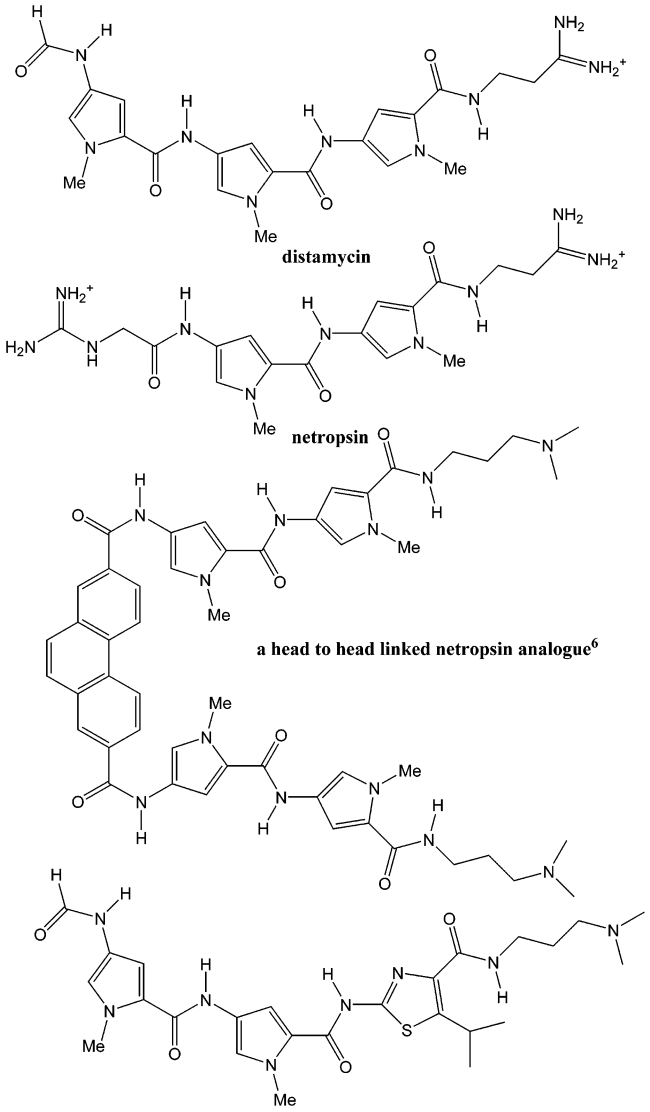
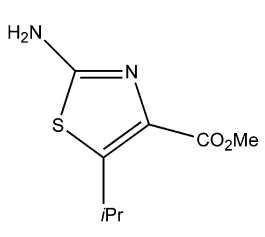
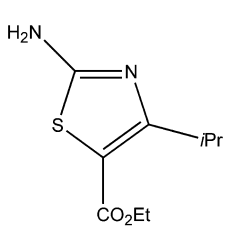


Figure 1. Structures of prototype natural products, distamycin, and netropsin together with synthetic analogues: A head-to-head netropsin analogue[6] and a typical novel compound (**28**) from this work with its abbreviated text code (see Figure 2).

significant in the design of more lipophilic distamycin analogues. *N*-Alkylation of a thiazole is not permitted in this context, since this would introduce an unwanted positive charge and also block access to GC base pairs. There are, however, two isomeric *C*-alkylthiazoles to consider. The use of *C*-alkyl substituents is one novel feature of this research.[11] The synthesis of the thiazoles following the published procedure led to two isomers (Thz*i*Pr and *iso*Thz*i*Pr) with *C*-isopropyl substituents;[12]



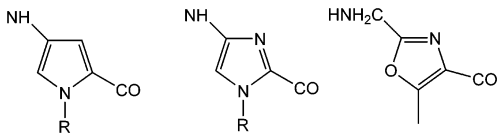
Thz*i*Pr



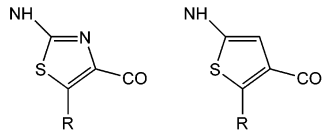
***iso*Thz*i*Pr**

their structures have been unambiguously determined by X-ray crystallography.[13] Unlike the *N*-alkylpyrroles,

Heterocyclic monomers



PyrR **ImiR** **Oxa**



ThzR **ThiR**

R = Me, Et, *i*Pr, *i*Pe (3-methylbutyl), CycPr (cyclopropylmethyl) CycPe (cyclopentyl)

Head groups

Fo = formyl, Ac = acetyl, 3MeOB = 3-methoxybenzoyl, 4MeOPhe = 4-methoxyphenylacetyl, Cin = Cinnamoyl, DmB = Dimethylbutyl, MeP = Methylphenyl

Tail groups

Dmap = 3-dimethylaminopropyl, Pyrrp = 3-*N*-pyrrolidinylpropyl, Morp = 3-*N*-morpholinopropyl, MePipp = 3-(4-methylpiperazinylpropyl)

General compound structure

HEAD - RING 1 - RING 2 - RING 3 - TAIL

N-terminus C-terminus

Example *Fo-PyrMe-PyrMe-Thz-iPr-Dmap*

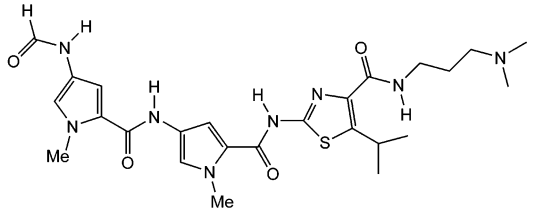


Figure 2. Structures of components of distamycin analogues described in this paper.

for which the nitro group acts as a latent amino group, the thiazoles are prepared by ring synthesis[12] with an unprotected amino group; for elaboration into oligomers, the aminothiazoles were acylated with an *N*-alkylpyrrole, thereby avoiding the need for further protection.

Thiophenes. The replacement of the electronegative nitrogen atom in pyrrole by the much more lipophilic sulfur would also be expected to have a significant influence on the biological activity of minor-groove binders. Accordingly, a *C*-methylthiophene, ThiMe, was prepared as one of the building blocks following published procedures.[14] It was incorporated into the oligomers by standard nitro/amino methodology.

Imidazoles and Oxazoles. A limited range of imidazoles and oxazoles were synthesized to compare for the activity of the more lipophilic *N*-alkylpyrroles and thiazoles. *N*-Ethylimidazole ImiEt was prepared by published methods.[15] Appropriate oxazoles proved very difficult to prepare and we were able only to access one example OxaMe,[16] which differed significantly from the structures of the other heterocyclic building blocks by containing an additional methylene group. This would be expected to increase substantially the conformational flexibility of the minor groove binder and correspondingly alter its ability to bind to DNA.

Head Groups and Tail Groups. It is possible to modify the lipophilicity by a suitable choice of head or tail group. In particular, the successful replacement of the naturally occurring amidine in distamycin by a

Table 1. Abbreviated Structures of Compounds Synthesized and Studied Together with Binding to DNA As Measured by CE

compd	head	P1	P2	P3	tail	CE to AT
			Pyrrole *N*- and *C*-Alkyl Substituents			
1	Fo	PyrMe	PyrMe	PyrMe	Dmap	2 to 1
2	Fo	PyrMe	PyrEt	PyrMe	Dmap	2 to 1
3	Fo	PyrMe	Pyr*i*Pr	PyrMe	Dmap	2 to 1
4	Fo	PyrMe	PyrCycpe	PyrMe	Dmap	2 to 1
5	Fo	PyrMe	PyrCycpr	PyrMe	Dmap	2 to 1
6	Fo	Pyr*i*Pr	PyrMe	Pyr*i*Pr	Dmap	1 to1
7	Fo	PyrMe	Pyr*i*Pe	PyrMe	Dmap	2 to 1
8	Fo	Pyr*i*Pr	Pyr*i*Pr	Pyr*i*Pr	Dmap	weak
9	Fo	Pyr*i*Pe	Pyr*i*Pe	Pyr*i*Pe	Dmap	nb[a]
10	Fo	$PyrMe_2$	$PyrMe_2$	$PyrMe_2$	Dmap	nb
			Pyrrole Head Group Variations			
11	Ac	PyrMe	Pyr*i*Pr	PyrMe	Dmap	1 to1
12	Ac	PyrMe	Pyr*i*Pr	PyrMe	Dmap	1 to1
13	Ac	PyrMe	PyrMe	PyrMe	Dmap	1 to1
14	DmB	PyrMe	PyrMe	PyrMe	Dmap	nb
15	DmB	PyrMe	PyrEt	PyrMe	Dmapc	nb
16	DmB	PyrMe	Pyr*i*Pr	PyrMe	Dmap	nb
17	MPe	PyrMe	Pyr*i*Pr	PyrMe	Dmap	nb
18	3MeOB	PyrMe	PyrMe	PyrMe	Dmap	2 to 1 then complex
19	3MeOB	PyrMe	Pyr*i*Pe	PyrMe	Dmap	2 to 1
20	4MeOPhe	PyrMe	Pyr*i*Pe	PyrMe	Dmap	nb
21	Cin	PyrMe	PyrMe	PyrMe	Dmap	no clear stoichiometry
22	MeThi	PyrMe	PyrMe	PyrMe	Dmap	2 to 1
23	$PyrNO_2$	PyrMe	Pyr*i*Pe	PyrMe	Dmap	nt
			Imidazoles			
24	Fo	PyrMe	PyrMe	ImiEt	Dmap	1 to 1
25	Fo	ImiEt	ImiEt	ImiEt	Dmap	nb
26	Fo	PyrMe	ImiEt	ImiEt	Dmap	nb
			Thiazoles			
27	Fo	PyrMe	PyrMe	isoThz*i*Pr	Dmap	nb
28	Fo	PyrMe	PyrMe	Thz*i*Pr	Dmap	
29	Fo	PyrMe	Thz*i*Pr	PyrMe	Dmap	nb
30	Ac	Thz*i*Pr	PyrMe	PyrMe	Dmap	1 to 1
31	Ac	Thz*i*Pr	PyrMe	Thz*i*Pr	Dmap	nb
32	Ac	PyrMe	PyrMe	Thz*i*Pr	Dmap	nb
33	3MeOB	Thz*i*Pr	PyrMe	PyrMe	Dmap	2 to 1
			Thiophenes			
34	Fo	ThiMe	PyrMe	PyrMe	Dmap	2 to 1
35	Fo	PyrMe	ThiMe	PyrMe	Dmap	2 to 1
36	Fo	ThiMe	Pyr*i*Pe	PyrMe	Dmap	nt
37	Ac	PyrMe	ThiMe	PyrMe	Dmap	1 to 1
38	Ac	ThiMe	PyrMe	PyrMe	Dmap	1 to 1
			Oxazole			
39	Fo	PyrMe	PyrMe	CH_2oxaMe	Dmap	nb
			Pyrrole Tail Group Variations			
40	Fo	PyrMe	Pyr*i*Pe	PyrMe	Morp	1 to 1
41	Fo	PyrMe	Pyr*i*Pr	PyrMe	Morp	1 to 1
42	Ac	PyrMe	Pyr*i*Pe	PyrMe	Morp	nb
43	3MeOB	PyrMe	Pyr*i*Pe	PyrMe	Mepipp	yes
44	Fo	PyrMe	Pyr*i*Pe	PyrMe	Mepipp	1 to 1
45	Ac	PyrMe	Pyr*i*Pe	PyrMe	Mepipp	nb
46	Ac	PyrMe	PyrMe	PyrMe	Pyrrp	1 to 1
47	Fo	PyrMe	PyrMe	PyrMe	Pyrrp	2 to 1
48	Fo	PyrMe	Pyr*i*Pr	PyrMe	Pyrrp	2 to 1

[a] nb = no binding observed.

tertiary alkylamine in many published examples opens the way to use other alkylamines with different physicochemical characteristics. The examples described use 1-pyrrolidyl (Pyrrp), morpholine (Morp), and *N*-methylpiperazine (Mepipp), all linked via a propyl chain, to cover a range of size, conformational flexibility, and lipophilicity in the tail. Variation of head group is synthetically the easiest of all modifications to make; formyl (Fo), acetyl (Ac), substituted benzoyl (3MeOBz), substituted phenylacetyl (4MeOPhe), and cinnamoyl (Cinn) were all used. This selection again includes a wide range of size and conformational flexibility.

Synthesis of Oligomers. As noted above, methods described previously[6] served for the synthesis of the pyrrole-only oligomers. The N-terminal pyrroles substituted by the various tail groups (Figure 2) were prepared from the appropriate amine-substituted with the dimethylamino or heterocyclic amino group using the appropriate nitropyrrole acid chloride (NO_2)PyrRCl or the trichloromethyl ketone $(NO_2)PyrMeCCl_3$ for the first unit. A variety of standard coupling methods was used to prepare the oligomers, including acid chloride, carbodiimide, and HBTU (see the Experimental Section). Similar methods applied for the synthesis of

Table 2. Antibacterial and Antifungal Activity of Compounds Synthesized and Evaluated[a]

						antibacterial activity (MIC, M × 10^6)								antifungal activity (MIC, M × 10^6)		
compd	head	P1	P2	P3	tail	S.aur	S.fae	MRSA	E.clo	M.for	K.aer	P.vul	E.col	A.nig	A.nid	C.alb
					Pyrrole N- and C-Alkyl Substituents											
1	Fo	PyrMe	PyrMe	PyrMe	Dmap	10.0	0.31	na	na	na	164	na	na	na	na	na
3	Fo	PyrMe	Pyr*i*Pr	PyrMe	Dmap	na	157	157	na	na	39.1	157	na	157	na	na
4	Fo	PyrMe	PyrCycpe	PyrMe	Dmap	75.0	75	75.3	na	75.3	na	na	na	37.6	nt	75.3
5	Fo	PyrMe	PyrCycpr	PyrMe	Dmap	153	76.9	76.9	76.9	38.4	38.4	na	na	na	153	76.9
6	Fo	Pyr*i*Pr	PyrMe	Pyr*i*Pr	Dmap	na	na	150	na	na	na	na	na	na	150	75
7	Fo	PyrMe	Pyr*i*Pe	PyrMe	Dmap	150	57.5	150	150	37.5	37.5	150	na	150	na	150
8	Fo	Pyr*i*Pr	Pyr*i*Pr	Pyr*i*Pr	Dmap	144	72	144	36	72	36	144	na	72	72	144
10	Fo	PyrMe2	PyrMe2	PyrMe2	Dmap	na	na	na	na	153	77.7	153	na	153	153	na
					Pyrrole Head Group Variations											
11	Ac	PyrMe	Pyr*i*Pe	PyrMe	Dmap	na	73.5	na	na	147	147	na	na	73.5	na	147
12	Ac	PyrMe	Pyr*i*Pr	PyrMe	Dmap	na	na	na	na	na	153	153	na	153	na	153
13	Ac	PyrMe	PyrMe	PyrMe	Dmap	na	160	40	160	160	80	160	na	160	160	160
14	DmB	PyrMe	PyrMe	PyrMe	Dmap	na	150	150	na	150	150	na	na	na	na	na
17	MPe	PyrMe	PyrMe	PyrMe	Dmap	147	147	na	na	73.5	147	na	na	147	73.5	147
18	3MeOB	PyrMe	PyrMe	PyrMe	Dmap	69.8	140	na	na	140	140	na	na	140	69.8	na
19	3MeOB	PyrMe	Pyr*i*Pe	PyrMe	Dmap	16.2	16.2	2	na	32.4	na	na	na	na	nt	na
20	4MeOPhe	PyrMe	Pyr*i*Pe	PyrMe	Dmap	15.9	15.9	63. 6	na	15.9	15.9	na	na	15.9	15.9	15.9
21	Cin	PyrMe	PyrMe	PyrMe	Dmap	8.8	8.8	140	70.2	140	70.2	70	na	140	70.2	35.1
22	MeThi	PyrMe	PyrMe	PyrMe	Dmap	na	141	141	na	35.4	70.8	na	na	141	70.8	na
23	PyrNO_2	PyrMe	Pyr*i*Pe	PyrMe	Dmap	31.6	15.8	126	na	15.8	15.8	126	na	15.8	25.8	15.8
					Imidazoles											
24	Fo	PyrMe	PyrMe	ImiEt	Dmap	na	na	na	na	160	40	160	na	na	160	na
25	Fo	ImiEt	ImiEt	ImiEt	Dmap	19.0	na	na	na	na	na	na	na	na	na	na
					Thiazoles											
28	Fo	PyrMe	PyrMe	Thz*i*Pr	Dmap	4.7	9.5	38.1	76.2	19	76.2	9.5	na	76.1	76.1	76.1
29	Fo	PyrMe	Thz*i*Pr	PyrMe	Dmap	4.8	9.5	19.1	9.5	19	38.1	na	na	38.1	9.5	38.1
30	Ac	Thz*i*Pr	PyrMe	PyrMe	Dmap	70.0	74.5	149.2	149	74.6	149	149	149	149	nt	74.6
31	Ac	Thz*i*Pr	PyrMe	Thz*i*Pr	Dmap	4.3	4.3	4.3	69.8	17.5	69.8	69.8	70	4.3	nt	34.9
32	Ac	PyrMe	PyrMe	Thz*i*Pr	Dmap	na	74.5	na	na	na	na	na	na	74.5	nt	na
33	3MeOB	Thz*i*Pr	PyrMe	PyrMe	Dmap	32.7	32.7	32.7	131	65.5	32.7	65.5	65.5	131	131	131
					Thiophenes											
34	Fo	ThiMe	PyrMe	PyrMe	Dmap	na	na	na	na	na	na	79.6	na	na	na	159
35	Fo	PyrMe	ThiMe	PyrMe	Dmap	39.8	79.6	159	159	159	159	79.6	159	159	159	159
36	Fo	ThiMe	Pyr*i*Pe	PyrMe	Dmap	146.0	146	73.1	146	146	73.1	146	73.1	146	146	146
37	Ac	PyrMe	ThiMe	PyrMe	Dmap	78.5	na	156	156	38.9	156	156	156	156	38.9	156
38	Ac	ThiMe	PyrMe	PyrMe	Dmap	156.0	na	na	na	na	156	156	na	156	na	na
					Oxazole											
39	Fo	PyrMe	PyrMe	CH_2oxaMe	Dmap	na	na	160	160	na	na	na	na	160	160	na
					Pyrrole Tail Group Variations											
40	Fo	PyrMe	Pyr*i*Pe	PyrMe	Morp	na	na	70.6	na	na	na	na	na	70.6	na	na
41	Fo	PyrMe	Pyr*i*Pr	PyrMe	Morp	na	na	na	na	na	na	na	na	na	na	na
42	Ac	PyrMe	Pyr*i*Pe	PyrMe	Morp	na	na	na	na	140	na	na	na	na	na	na
43	3MeOB	PyrMe	Pyr*i*Pe	PyrMe	Mepipp	60	60.4	121	121	121	121	121	na	121	30.2	121
44	Fo	PyrMe	Pyr*i*Pe	PyrMe	Mepipp	140	69.3	na	140	69.3	140	140	140	140	69.3	na
45	Ac	PyrMe	Pyr*i*Pe	PyrMe	Mepipp	na	na	na	na	136	136	136	na	na	136	na
46	Ac	PyrMe	PyrMe	PyrMe	Pyrrp	na	153	na	153	76.9	153	na	na	153	153	na
47	Fo	PyrMe	PyrMe	PyrMe	Pyrrp	1200	na	na	157	78.5	157	157	157	157	157	157
48	Fo	PyrMe	Pyr*i*Pr	PyrMe	Pyrrp	150	75.2	75.2	75.2	150	37.6	150	na	150	150	na
					Controls											
amoxycilin						0.49	0.49	16.1	4	16.1	8.1	4				
streptomycin						10.8										
fluconazole														>300	90.8	81.6
itraconazole														17.7	35.4	35.4

[a] Abbreviations for microbes: S.aur = *S. aureus* NCTC 6571. S.fae = *S. faecalis* NCTC 775. MRSA = MRSA PHLS M1. E.clo = *E. cloacae* NCTC 10005. M.for = *M. fortuitum* NCTC 10394. K.aer = *K. aerognenes* WRL CN 345. P.vul = *P. vulgaris* NCTC 4175. E.col = *E. coli* NCTC 9001. A.nig = *A. niger* IMI17454. A.nid = *A. nidulans* CABI 0160037. C.alb = *C. albicans* NCPF 3179.

compounds containing thiophenes. Imidazole-containing compounds were prepared similarly by acid chloride or HBTU-mediated coupling. Reaction conditions were not optimized in each case, and yields of coupling were typically in the range 30−80%. Where necessary, intermediates were purified by column chromatography and all final products were stringently purified using preparative-scale HPLC. Full experimental details are given for final products together with general methods for intermediates both with full characterization details.

Binding Evaluation of Lipophilic Distamycin Analogues. The structures of the minor-groove binders and their properties with respect to DNA binding to a target oligonucleotide are shown in Table 1. The antimicrobial activity of these compounds is shown in Table 2.

The primary enquiry concerned the extent to which nonpolar appendages were compatible with binding to DNA. To this end, most of the present compounds contained predominantly *N*-alkylpyrroles which, be-

cause of the steric hindrance between the 2-hydrogen of the pyrrole and the amino group of G in DNA, would be expected to bind predominantly to AT-rich sequences. Footprinting studies on a small number of selected compounds confirmed that expectation, with the exception of **28**, which showed a remarkably strong preference for the sequence ACTAGT.[17−19] The primary evaluation therefore used the AT dodecamer AAATTATATTAT in CE experiments. Almost all compounds synthesized bound to this oligomer to some extent. Notable exceptions included compounds with variations in the head group, alkyl substitution, and tail groups. The stoichiometry of binding to this test DNA oligonucleotide was also structure dependent, as described below. It is important to note that while this assay identifies acceptable features for binding to DNA, a negative result does not mean that there is no sequence of DNA to which that particular minor groove binder might bind.

With respect to the head groups, there was a significant difference between formyl, the benzoates, and cinnamate (in which the head group is essentially coplanar with the amide) and those such as acetyl and phenylacetyl, in which the adjacent atom to the carbonyl group is tetrahedral. For example, the principal mode of binding of the former group of compounds was 2:1 (ligand to DNA duplex, e.g. **1**−**5**). On the other hand, acetamides preferred 1:1 binding (e.g. **11**), and bulky amides such as dimethylbutanamide showed very weak binding, if any, to the probe oligonucleotide (e.g. **14**−**17**).

Modification of the backbone heterocyclic rings also showed significant effects. The introduction of larger alkyl groups than methyl (e.g. **2**−**5**) did not normally perturb the preferred 2:1 binding mode unless more than one large alkyl group was present (e.g. **6**). If the pyrrole contained two methyl substituents (**10**), binding to the test AT oligonucleotide was not observed under CE conditions. Compounds containing two or more imidazoles (**25**, **26**) and some of the thiazoles (**27**, **29**, **31**, **32**) failed to bind. In the case of **28**, CE experiments were performed with the target oligonucleotide suggested by the footprinting results, namely CGACTAGTCG, and in this case, clear evidence for binding was obtained. Moreover, a binding ratio of 4:1 was observed under CE conditions.[20] We have studied this interaction in more detail by NMR, and while it is clear that higher order assemblies are possible, the 2:1 stoichiometry represents a significant energy minimum.[18] This interpretation is also supported by melting-temperature measurements carried out on a selection of the compounds described in this paper.[21] We therefore attach little structural significance at this stage to the observation of higher order associations of our compounds with DNA.

A very clear-cut difference in the behavior of the tail groups was shown between dimethylamino and pyrrolidino on one hand and morpholino and *N*-methylpiperazino on the other. Dimethylamino and pyrrolidino (**47**, **48**) both bound to the test AT oligonucleotide in a 2:1 ratio, but compounds with a six-membered ring tail group (**40**, **41**, **43**, **44**) bound only in a 1:1 ratio, as shown by CE. Interestingly, when two features that promoted 1:1 binding were included in the same molecule (such as in **42** and **45**), binding to the test DNA sequence under CE conditions was not observed at all.

Taken together these results clearly show that it is possible for wide structural variations to be introduced into the basic architecture of distamycin-like minor-groove binders and that there is a structural dependence for binding. The CE results are generally consistent with information from footprinting, a substantial additional study that will be published elsewhere. The structural manipulability is encouraging, since it is highly desirable to have molecules that are both manipulable with respect to affinity for the receptor and with respect to the physicochemical properties that affect transport.

The calculated log *P* values for the neutral form of a selected group of compounds give some insight. The closest analogue of distamycin, **1**, has an estimated clogP of −1.98(±0.47). Replacement of the central *N*-methyl group by isopropyl gives compound **3**, for which clogP is −1.32. The change to a thiazole ring as in **28** causes log *P* to rise to 0.61. Although no real significance can be read into the exact values, a range of nearly 2 orders of magnitude between members of related structure is significant. In terms of Lipinski's rule of five,[22] these minor-groove binders exceed the notional limit of 500, but it is unlikely that such a broad (but useful) generalization will apply strongly to compounds of such distinct structural characteristics. However, it is possible that distamycin analogues may be substrates for biological transporters, as are other antibiotics. We are not aware of any studies on the active transport of distamycin or netropsin, nor of the flexibility of any potential transport mechanism with regard to structural variation. Such mechanisms, if they exist, may be limited to amidine- or guanidine-containing structures, which are closely similar to the natural products.

Recently, the importance of molecular rigidity has been discussed in terms of bioavailability.[23] In general, compounds with limited rotational flexibility show better bioavailability. In the context of minor-groove binders composed of heterocyclic amino acid amides, the principal location of flexibility resides in the tail group and a high overall degree of rigidity exists. On the other hand, a high polar surface area has been argued to be a negative factor in bioavailability. The fact that in vivo these minor-groove binders will be monocations will have a major influence on their real distribution properties, although for aliphatic tertiary amines, a small but significant proportion of the compound would be unprotonated at pH 7. The large number of amide bonds present will also increase the polar surface area. Overall, therefore, the minor-groove binders described herein represent a class of compounds conceptually acceptable as drugs.

Biological Evaluation. Table 2 shows the biological evaluation of the compounds obtained against a set of eight bacteria and three fungi. Toxicity tests have also been run against mammalian cell lines, namely NCTC 2544 (human keratinocytes), E6-1 Jurkat cells (human T-cell lymphoblasts), and CCI 39 (chinese hamster lung). At concentrations of 10 μg mL^{-1} (equivalent to about 16.6 μM for a compound of molecular weight 600) over 4 and 24 h, no cytotoxic effects were observed. However at higher concentrations (up to 100 μg mL^{-1},

~166 μM) some cytotoxicity was observed in the case of the thiazole-containing compounds **29** and **31**, which caused 50% inhibition of the growth of Jurkat cells at 50 and 19 μM, respectively. These concentrations are similar to those at which significant antibacterial and antifungal activity was observed. There is thus some basis for selective toxicity by these minor-groove binders; cytotoxicity was not observed with **28** under the same conditions, for example. However as would be expected, a careful evaluation of the balance between antimicrobial activity and toxic effects must be maintained compound by compound.

With respect to the antibacterial activity,[24] it is noticeable that Gram-positive organisms are much more susceptible to these compounds than Gram-negative organisms, consistent with previous studies.[7] For Gram-negative organisms, some compounds containing branched or cycloalkyl substituents (**3**, **5**, **8**, **23**, **29**, and **48**) showed similar activity to the control drug (amoxycillin) in activity against *Klebsiella aerogenes* especially, but this appears to be exceptional. Against *Proteus vulgaris* and *Escherichia coli*, much weaker activity was obtained. The greatest activity against *P. vulgaris* was shown by the thiazole-containing compound **28**. The greatest activity against *E. coli* and *P. vulgaris* together was shown by **31**, also a thiazole-containing compound and the compound with the broadest spectrum of activity overall. It is probable that the lower activity with respect to Gram-negative bacteria is due to the smaller pores in the bacterial cell wall compared with the Gram-positive bacteria. Indeed, it is possible that poor cell penetration may account for the low toxicity of these compounds in the mammalian cell lines tested.

For Gram-positive organisms, several of the tested organisms are examples of infecting agents that currently have a high profile with respect to drug resistance. The activity of **19** (MIC = 2.0 μM), which contains two hydrophobic components (isopentyl side chain and 3-methoxybenzamide), and **31** (MIC = 4.3 μM), which contains two thiazole residues, against MRSA was greater than that of the control, amoxycillin (MIC = 16.1 μM). Several other compounds showed activity on the order of magnitude of amoxycillin. The thiazole-containing compound **29** was also similar in activity to amoxyicillin against *Enterobacter cloacae*. Both **29** and **31** showed significant activity against *Mycobacterium fortuitum*, a fast growing relative of *Mycobacterium tuberculosis*, compared with streptomycin as a control.

With respect to antifungal activity, many compounds were vastly superior to fluconazole and also similar in potency or better than the more potent antifungal drug, itraconazole. Against *Aspergillus niger*, the most active was **31**. In this test, not only thiazole-containing compounds but also the larger alkylpyrrole-containing compounds such as **4** and **40** were active. *Aspergillus nidulans* was also susceptible to **31**. Finally, in the panel tested, the thiazole-containing compounds (**28**−**33**) in general were similarly active to fluconazole and itraconazole against *Candida albicans*.

As has been noted above, the thiazole-containing compounds showed the greatest overall activity. However it is possible to perceive structural effects from the other modifications also. The closest relative of distamycin **1** was active against *Staphylococcus aureus*, *Streptococcus faecalis*, and *K. aerogenes* but against no other organism tested. The introduction of a larger alkyl group such as isopentyl (**7**) or cyclopropylmethyl (**5**) expanded the range of measured activity but without higher activity being observed.

Thiophene-containing compounds (**34**−**38**) showed some activity against bacteria and fungi over a wider range of species than their immediate pyrrole-containing analogues. For example, **35**, which contains one thiophene in the center of the heterocyclic trimer, was measurably active against *P. vulgaris*, whereas the prototype compound **1** was inactive against this organism. Conversely, the activity of **1** was greater than that of **35** against *S. aureus* and *S. faecalis*. Overall, *C*-methylthiophenes show no particular benefit over *N*-methylpyrroles, although branched *C*-alkylthiophenes remain to be tested.

As has been noted already in the case of **19**, the introduction of a planar, hydrophobic head group can enhance activity compared, for example, with **7**. The same effect is evident with the cinnamoyl head group in **21**, which shows much broader activity than the parent compound **1**. In this series, however, a 3-methoxylbenzoyl head group alone, as in **18**, was insufficient to improve the activity compared with the parent compound **1**.

Although we found a significant influence of tail group on the stoichiometry of binding to DNA in CE experiments, no substantial beneficial influence on antimicrobial activity was apparent in these tests. In general, larger tail groups than dimethylamino showed decreased activity. Pyrrolidinyl, however, permitted measurable activity (**48**) greater than that of the respective dimethylamino compound (**3**).

Taking all of the data together, it is interesting to note that some antimicrobial activity is found in representatives of almost all of the structural variations included. The most significant cluster of activity, however, is in those compounds that contain thiazoles (**28**−**33**). *C*-Methylthiazoles have been used before in minor-groove binders[25] but the *C*-isopropyl group seems to be a novel and significant substructure leading to high selectivity and affinity. The detailed structural analysis of these effects is presented elsewhere.[18] The presence of one branched alkyl substituent also promotes activity (**5**, **7**, **19**, **23**), as does a nonpolar, planar head group (**19**, **21**, **33**). These features are consistent with the structures of compounds from other groups that show significant antibacterial activity.[7] Notably, among the distamycin analogues, a lipophilic head group (a chloroisothiazole) gives high activity,[7b] and among the netropsin analogues, the cyclopropylmethyl *N*-substituent is prominent.[7a] Tail groups, which are known to be significant in binding,[26] have so far not been significantly useful in improving activity, although more examples need to be tried. It will be worthwhile to make a systematic effort to optimize the activity of any of these variations with respect to a given organism.

Conclusion

Within the scope of this series of trimers, significant antimicrobial activity is clustered around a small number of structural features, namely branched *N*-alkylpyrroles, hydrophobic *N*-terminal amides, and especially

C-isopropylthiazoles. These clusters of activity are all different embodiments of the design principle of increasing hydrophobicity in the compounds; it could be that this feature gives enhanced membrane permeability for the microbes examined. It is also clear that such structural features have a major influence on the binding of compounds to DNA, as shown by our recent NMR studies[18] and supported by the CE results reported here. While a distinction between access to cells and enhancement of specific binding as sources of the antimicrobial activity observed cannot be made, it is clear, however, that a wide range of structural variation is possible to obtain significant activity and that the concept of preparing lipophilic analogues of distamycin as candidates for anti-infective compounds has a sound basis.

Experimental Section

Abbreviations. br, broad; s, singlet; d, doublet; t, triplet; q, quartet; exch, exchangeable; DMF, *N*,*N*-dimethylformamide; HBTU, *O*-benzotriazol-1-yl-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate; HPLC, high performance liquid chromatography; HREIMS, high-resolution electron impact mass spectroscopy; HRFABMS, high-resolution fast atom bombardment mass spectroscopy; LRESMS, low-resolution electrospray mass spectroscopy; Pd/C, palladium on carbon; TFA, trifluoroacetic acid. HREIMS and HRFABMS were obtained on a Jeol JMS-AX505HA mass spectrometer. LRESMS were obtained on a Fisons VG Platform Benchtop LC-MS. NMR spectra were obtained on a Bruker AMX 400 spectrometer. HPLC purification of the final compounds was carried out using a Vydac protein and peptide C18 column on a gradient eluting system.[6] IR spectra were run as KBr disks and liquids as films, using a Nicolet Impact 400D. Column chromatography was performed with silica gel Prolabo (200−400 mesh).

Intermediates. Pyrroles. Acid Chloride Method. *N*-[3-(Dimethylamino)propyl]-1-isopropyl]-4-nitro-1*H*-pyrrole-2-carboxamide [(NO_2)Pyr*i*Pr-Dmap]. 4-Nitro-*N*-isopropylpyrrole-2-carboxylic acid (312 mg, 1.574 mmol) was dissolved in thionyl chloride (5 mL) and heated at reflux for 4 h. The excess thionyl chloride was removed under reduced pressure at 50 °C to give the acid chloride as a white solid, material that was used without further purification. 3-(Dimethylamino)-propylamine (250 μL) was dissolved in dichloromethane (25 mL, dry) to which *N*-methylmorpholine (250 μL) was added at room temperature with stirring. The acid chloride was dissolved in dichloromethane (5 mL, dry) and added dropwise to the amine solution at room temperature with stirring. The reaction mixture was then left stirring at room temperature overnight. Following this, the solvent was removed under reduced pressure at 50 °C and then the crude product was extracted with aqueous potassium carbonate solution (25 mL, 10% w/v) and dichloromethane (2 × 50 mL). The organic layer was collected, dried (Na_2SO_4), and filtered, and the solvent was removed under reduced pressure. The crude product was purified by chromatography over silica gel using 49.5:49.5:1 methanol/ethyl acetate/triethylamine to give the product as a pale yellow oil, $R_f = 0.25$, (400 mg, 90%). ^{1}H NMR ($CDCl_3$): δ 1.46 (6H, d, $J = 6.7$ Hz), 1.71−1.77 (2H, quintet, $J = 6.0$ Hz), 2.32 (6H, s), 2.51 (2H, t, $J = 5.7$ Hz), 3.49 (2H, quintet, $J = 5.0$ Hz), 5.62 (1H, qt, $J = 6.7$ Hz), 6.92 (1H, d, $J = 1.6$ Hz), 7.73 (1H, d, $J = 1.6$ Hz), 8.58 (1H, s). IR (KBr): 3330, 3136, 2979, 1650, 1535, 1430, 1279, 1258 cm^{-1}. HREIMS found: 282.16908. Calculated for $C_{13}H_{22}N_4O_3$: 282.16919.

Ethyl 1-isopentyl-4-nitro-1*H*-pyrrole-2-carboxylate [(NO_2)Pyr*i*Pe-OEt] was prepared according to a published procedure[10] in 85% yield, mp 46−47 °C (lit.[10] mp 46−47 °C). ^{1}H NMR ($CDCl_3$): δ 0.97 (6H, d, $J = 6.5$ Hz), 1.38 (3H, t, $J = 7.2$ Hz), 1.61−1.73 (3H, m), 4.30−4.39 (4H, m), 7.43 (1H, d, $J = 1.6$ Hz), 7.63 (1H, d, $J = 1.6$ Hz). IR (KBr): 3138, 2970, 1707, 1539, 1510, 1487, 1426, 1389, 1321, 1259, 1204, 1130, 1097 cm^{-1}.

1-Isopentyl-4-nitro-1*H*-pyrrole-2-carboxylic acid [(NO_2)-Pyr*i*Pe-OH] was also prepared according to a published procedure[10] in 95% yield, mp 154−157 °C (lit.[10] mp 154−156 °C). ^{1}H NMR ($CDCl_3$): δ 0.98 (6H, d, $J = 6.5$ Hz), 1.62−1.75 (3H, m), 4.38 (2H, t, $J = 7.5$ Hz), 7.58 (1H, d, $J = 1.9$ Hz), 7.69 (1H, d, $J = 1.9$ Hz). IR (KBr): 3120, 1677, 1540, 1517, 1480, 1315, 1250 cm^{-1}.

Ethyl 5-methylpyrrole-2-carboxylate (Pyr-OEt) was prepared according to a published procedure[27] in 38% yield, mp 94−96 °C (lit.[26] mp 97−99 °C).

Ethyl 5-methyl-1-methylpyrrole-2-carboxylate [PyrMe$_2$-OEt] was prepared according to a published procedure[28] in 91% yield as a pale yellow oil.

Ethyl 4-nitro-5-methyl-1-methylpyrrole-2-carboxylate [NO$_2$PyrMe$_2$-OEt] was prepared according to a published procedure in 84% yield, mp 74−76 °C (lit.[28] mp 79−80 °C).

4-Nitro-5-methyl-1-methylpyrrole-2-carboxylic acid [NO$_2$PyrMe$_2$-OH] was prepared according to the literature procedure in 66% yield, mp 225−228 °C (lit.[28] mp 212−213 °C).

Carbodiimide Method. *N*-[3-(Dimethylamino)propyl]-1,5-dimethyl-4-nitro-1*H*-pyrrole-2-carboxamide (NO$_2$-PyrMe$_2$-Dmap). The carboxylic acid NO_2PyrMe$_2$-OH (100 mg, 0.543 mmol), EDCI (208 mg, 1.085 mmol), and DMAP (166 mg, 1.359 mmol) were dissolved in DMF (2 mL, dry). *N*,*N*-Dimethylaminopropylamine (67 mg, 69 μL, 0.656 mmol) was added to the reaction mixture with stirring at room temperature. The reaction mixture was left stirring at room temperature overnight before being diluted with ethyl acetate (50 mL) and extracted with water (50 mL). The water layer was extracted with ethyl acetate (2 × 50 mL). The organic layers were combined and washed with saturated solution of sodium bicarbonate (50 mL) and then with brine (50 mL). The ethyl acetate layer was dried ($MgSO_4$) and the solvent removed under reduced pressure at 50 °C. The crude product was purified by silica gel column chromatography using methanol/ethyl acetate (1/4, containing 1% triethylamine). The pure product ($R_f = 0.1$) was collected, and the solvent removed was removed under reduced pressure to give pale yellow oil (108 mg, 74%). ^{1}H NMR ($CDCl_3$): δ 1.71−1.76 (2H, quintet, $J = 5.9$ Hz, CH_2), 2.28 (6H, s, NMe_2), 2.49−2.52 (2H, t, $J = 5.9$ Hz, CH_2), 2.64 (3H, s, C-CH_3), 3.45−3.50 (2H, q, $J = 5.9$ Hz, CH_2), 3.92 (3H, s, N-CH_3), 7.00 (1H, s), 8.47 (1H,broad, CONH, exch). IR (KBr): 3131, 2964, 1655, 1546, 1523, 1494, 1300, 1141, 1104 cm^{-1}. HRFABMS found: 269.16200. Calculated for $C_{12}H_{21}N_4O_3$: 269.16137.

2,2,2-Trichloro-1-(1-methyl-4-nitro-1*H*-pyrrol-2-yl)ethanone Method. 1-Methyl-4-nitro-*N*-[3-(1-pyrrolidinyl)-propyl]-1*H*-pyrrole-2-carboxamide (NO$_2$PyrMe-Pyrrp). 3-(1-Pyrrolidinyl)propanamine (236 mg, 1.842 mmol) was dissolved in THF (25 mL, dry) to which a solution of 2,2,2-trichloro-1-(1-methyl-4-nitro-1*H*-pyrrol-2-yl)ethanone (508 mg, 1.842 mmol) in THF (2 mL, dry) was added at room temperature with stirring. The reaction mixture was left stirring at room temperature overnight. The solvent was removed under reduced pressure and the crude product was purified by column chromatography using 49.5:49.5:1 ethyl acetate/methanol/triethylamine. The product was obtained as a glassy yellow solid, $R_f = 0.1$ (503 mg, 98%), mp 113−115 °C. ^{1}H NMR (DMSO-d_6): δ 1.70−1.79 (6H, m), 2.48−2.51 (6H, m), 3.28−3.51 (2H, q, $J = 6.9$ Hz), 3.89 (3H, s), 7.45 (1H, d, $J = 1.6$ Hz), 8.18 (1H, d, $J = 1.6$ Hz), 8.51 (1H, t, $J = 5.4$ Hz). IR (KBr): 3131, 2966, 2794, 1654, 1545, 1525, 1492, 1305 cm^{-1}. HRFABMS found: 281.16249. Calculated for $C_{13}H_{21}N_4O_3$: 281.16137.

***N*-[3-(Dimethylamino)propyl]-1-isopentyl-4-nitro-1*H*-pyrrole-2-carboxamide (NO$_2$Pyr*i*Pe-Dmap)** was prepared using the acid chloride method as a pale yellow solid in 95% yield, mp 72−73 °C. ^{1}H NMR ($CDCl_3$): δ 0.95 (6H, d, $J = 6.5$ Hz), 1.57−1.76 (5H, m), 2.32 (6H, s), 2.51 (2H, t, $J = 10.3$ Hz), 3.47−3.51 (2H, quintet, $J = 4.8$ Hz), 4.40−4.44 (2H, q, $J =$

7.5 Hz), 6.92 (1H,d, J = 1.9 Hz), 7.56 (1H,d, J = 1.9 Hz), 8.61 (1H, s, br, CONH). IR (KBr): 1656, 1637, 1565, 1534, 1498, 1417, 1333 cm^{-1}. HREIMS found: 310.20031. Calculated for $C_{15}H_{26}O_4N_3$: 310.20049.

***N*-Alkylation Method. Ethyl 1-(Cyclopropylmethyl)-4-nitro-1*H*-pyrrole-2-carboxylate [(NO$_2$)PyrCycPr-OEt].** Ethyl 4-nitro-1*H*-pyrrole-2-carboxylate (1.042 g, 5.626 mmol) was dissolved in DMF (20 mL, dry) to which potassium metal (0.435 g, 11.124 mmol) was added. The reaction mixture was heated to 100 °C with stirring and it was left at that temperature for 1 h. The reaction mixture was cooled to 50−60 °C, then (chloromethyl)cyclopropane (1.000 g, 11.04 mmol) (purchased from Aldrich) and potassium iodide (1.349 g, 8.127 mmol) were added, and the reaction mixture was heated again with stirring to 80 °C for 5 h, after which time it was left stirring overnight at room temperature. The reaction mixture was diluted with brine (50 mL) and extracted with ethyl acetate (3 × 100 mL). The combined organic extracts were collected, and the solvent was removed under reduced pressure. The crude product obtained (containing some DMF) was purified by flash chromatography using silica gel eluting with 1/10 ethyl acetate/*n*-hexane. The product was obtained as a white microcrystalline solid, R_f = 0.2 (1.070 g, 80%), mp 65−66 °C. ^{1}H NMR (DMSO-d_6): δ 8.34 (1H, d, J = 1.3 Hz), 7.35 (1H, d, J = 1.3 Hz), 4.30−4.24 (2H, q, J = 7.1 Hz), 4.21 (2H, d, J = 7.2 Hz), 1.34−1.23 (2H, t, J = 7.1 Hz; 1H, m), 0.53−0.45 (2H, m), 0.42−0.38 (2H, m). IR (KBr): 3142, 2996, 2921, 1704, 1502, 1310, 1270, 1225, 1184, 1091 cm^{-1}. HREIMS found: 238.09585. Calculated for $C_{11}H_{14}N_2O_4$: 238.09536.

Ester Hydrolysis Method. 1-(Cyclopropylmethyl)-4-nitro-1*H*-pyrrole-2-carboxylic Acid [(NO$_2$)PyrCycPr-OH]. Ethyl 1-(cyclopropylmethyl)-4-nitro-1*H*-pyrrole-2-carboxylate (482 mg, 2.023 mmol) was dissolved in ethanol (4 mL) to which a solution of sodium hydroxide (393 mg, 9.825 mmol) in water (10 mL) was added. The reaction mixture was heated under reflux for 2 h and then cooled to 0 °C. Concentrated hydrochloric acid was added dropwise with stirring until the solution reached pH 2. The white solid material, which precipitated was filtered off, washed with water, and dried under reduced pressure at 60 °C overnight. The product was obtained as a white solid material (382 mg, 90%), mp 215−217 °C. ^{1}H NMR (DMSO-d_6): 13.14 (1H, br), 8.29 (1H, d, J = 2.4 Hz), 7.29 (1H, d, J = 2.1 Hz), 4.20 (2H, d, J = 2.2 Hz), 1.34−1.27 (1H, m), 0.52−0.38 (4H, m). IR (KBr): 3115, 3005, 2922, 2854, 1680, 1540, 1517, 1481, 1420, 1314 cm^{-1}. HREIMS found: 210.06469. Calculated for $C_9H_{10}N_2O_4$: 210.06406.

Ethyl 1-cyclopentyl-4-nitro-1*H*-pyrrole-2-carboxylate [(NO$_2$)PyrCycPr-OEt] was prepared by the *N*-alkylation method as a pale yellow oil in 32% yield, using bromocyclopropane as the alkylating agent. ^{1}H NMR ($CDCl_3$): δ 7.77 (1H, d, J = 2.0 Hz), 7.45 (1H, d, J = 2.0 Hz), 5.57−5.50 (1H, quintet, J = 6.6 Hz), 4.33 (2H, q, J = 7.1 Hz), 2.30−2.24 (2H, m), 1.98−1.75 (6H, m), 1.37 (3H, t, J = 7.1 Hz). IR (KBr): 2965, 2875, 1717, 1534, 1508, 1426, 1335, 1294, 1222, 1187, 1084 cm^{-1}. HRFABMS found: 253.11824. Calculated for $C_{12}H_{17}N_2O_4$: 253.11883.

1-Cyclopentyl-4-nitro-1*H*-pyrrole-2-carboxylic acid [(NO$_2$)PyrCycpe-OH] was prepared by the ester hydrolysis method as a white solid in 89% yield, mp 195−198 °C. ^{1}H NMR (DMSO-d_6): δ 13.13 (1H, br), 8.27 (1H, d, J = 2.0 Hz), 7.29 (1H, d, J = 2.0 Hz), 5.45 (1H, quintet, J = 7.1 Hz), 2.16−2.07 (2H, m), 1.88−1.78 (4H, m), 1.65−1.61 (2H, m). IR (KBr): 3152, 2964, 2880, 1683, 1508, 1430, 1331, 1292, 1078, 911 cm^{-1}. HREIMS found: 224.07926. Calculated for $C_{10}H_{12}N_2O_4$: 224.07971.

All remaining pyrroles were samples prepared previously or as previously described.[6]

Imidazoles. 1-Ethyl-1*H*-imidazole (ImiEt) was prepared according to a published procedure[16] in 90% yield, bp 110 °C/16 mmHg. ^{1}H NMR ($CDCl_3$): δ 1.43−1.47 (3H, t, J = 7.4 Hz, CH_2CH_3), 3.96−4.02 (2H, q, J = 7.4 Hz, CH_2CH_3), 6.92 (1H, t, J = 1.1 Hz), 7.05 (1H, s), 7.48 (1H, s). IR (liq film): 3105, 2979, 2937, 2885, 1682, 1598, 1511, 1464, 1395, 1356, 1286, 1228, 1286 cm^{-1}.

Ethyl 1-ethyl-1*H*-imidazole-2-carboxylate (ImiEt-OEt) was prepared according to a published procedure[29] in 68% yield, bp 110−115 °C /2 mmHg. ^{1}H NMR ($CDCl_3$): δ 1.41−1.47 (6H, 2xt, J = 7.0 Hz, $2CH_2CH_3$), 4.38−4.43 (2H, q, J = 7.0 Hz, CH_2CH_3), 4.43−4.48 (2H, q, J = 7.0 Hz, CH_2CH_3), 7.08 (1H, d, J = 0.6 Hz), 7.15 (1H, d, J = 0.6 Hz). IR (liq film): 3107, 2990, 2941, 1709, 1509, 1477, 1443, 1419, 1385, 1311, 1260, 1236 cm^{-1}.

Ethyl 1-Ethyl-4-nitro-1*H*-imidazole-2-carboxylate [(NO$_2$)ImiEt-OEt] and Ethyl 1-Ethyl-5-nitro-1*H*-imidazole-2-carboxylate. Ethyl 1-ethyl-1*H*-imidazole-2-carboxylate (12.9 g, 76.8 mmol) was carefully dissolved in sulfuric acid (30 mL, concentrated) and cooled to 0 °C. Fuming nitric acid (30 mL) was slowly added while a temperature of 0 °C was maintained. The reaction mixture was then heated under reflux with an efficient condenser (ethyl acetate/solid carbon dioxide) for 30 min. The reaction mixture was cooled with an ice bath and quenched by adding ice. The resulting blue solution was then extracted with dichloromethane (3 × 100 mL), dried over $MgSO_4$, and concentrated under reduced pressure to give pale yellow, semisolid material, which was chromatographed over silica gel to give the two isomers:

Fraction 1: 3.16 g, 19%, mp 45−47 °C. 1-Ethylimidazole-5-nitro-2-carboxylic acid ethyl ester: ^{1}H NMR ($CDCl_3$): δ 1.43−1.50 (3H, t, J = 7.0 Hz, CH_2CH_3), 1.51−1.58 (3H, t, J = 7.0 Hz, CH_2CH_3), 4.45−4.56 (2H, q, J = 7.0 Hz, CH_2CH_3), 4.90−4.95 (2H, q, J = 7.0 Hz, CH_2CH_3), 8.04 (1H, s). IR (KBr): 3117, 2982, 1724, 1535, 1492, 1478, 1444, 1384, 1353, 1282, 1234, 1147 cm^{-1}. HRFABMS found: 214.08208. Calculated for $C_8H_{12}N_3O_4$: 214.08278.

Fraction 2: 5.70 g, 35%, mp 90−92 °C. 1-Ethylimidazole-4-nitro-2-carboxylic acid ethyl ester [(NO$_2$)ImiEt-OEt]: ^{1}H NMR ($CDCl_3$): δ 1.43−1.46 (3H, t, J = 7.0 Hz, CH_2CH_3), 1.53−1.56 (3H, t, J = 7.0 Hz, CH_2CH_3), 4.44−4.49 (2H, t, J = 7.0 Hz, CH_2CH_3), 4.52−4.58 (2H, t, J = 7.0 Hz, CH_2CH_3), 7.89 (1H, s). IR (KBr): 3140, 2993, 1725, 1535, 1496, 1389, 1346, 1320, 1270, 1231, 1138, 1080, 1015 cm^{-1}. HRFABMS found: 214.08296. Calculated for $C_8H_{12}N_3O_4$: 214.08278.

1-Ethyl-4-nitro-1*H*-imidazole 2-carboxylic Acid Hydrochloride [(NO$_2$)ImiEt-OH]. Ethyl 1-ethyl-4-nitro-1*H*-imidazole-2-carboxylate (253 mg, 1.188 mmol) was suspended in a sodium hydroxide solution [sodium hydroxide 186 mg, 4.65 mmol and water (2 mL)]. The reaction mixture was heated until reflux for (15 min) then cooled to 15 °C and hydrochloric acid (dilute) was added with stirring (pH 1). The solution was freeze-dried to give a light brown solid (175 mg, 80%). ^{1}H NMR (DMSO-d_6): δ 1.31−1.35 (3H, t, J = 7.0 Hz, CH_2CH_3), 4.45−4.51 (2H, q, J = 7.0 Hz, CH_2CH_3), 8.37 (1H, s). IR (KBr): 3430, 3255, 3160, 1730, 1543, 1504, 1393, 1352, 1279, 1218, 1148 cm^{-1}.

Mixed Anhydride Method. *N*-[3-(Dimethylamino)-propyl]-1-ethyl-4-nitro-1*H*-imidazole-2-carboxamide [(NO$_2$)ImiEt-Dmap]. The carboxylic acid NO_2ImiEt-Dmap (230 mg, 1.243 mmol) was dissolved in THF (25 mL, dry) to which triethylamine (500 μL, dry) was added followed by pivaloyl chloride (400 μL, 3.30 mmol) with stirring at room temperature. Stirring was continued for 15 min, then *N*,*N*-dimethylaminopropylamine (400 μL, 3.30 mmol) was added at room temperature with stirring. Stirring was continued overnight at room temperature. The solvent was removed under reduced pressure and the residue was extracted with ether and sodium hydroxide solution (40 mL, 1 N). The organic layer was extracted with brine and dried ($MgSO_4$), and the solvent was then removed under reduced pressure. The crude product was purified by column chromatography using silica gel, following which it was eluted with methanol/ethyl acetate 1/4 (R_f = 0.1). The product was obtained as a colorless oil, which crystallized on standing at room temperature (208 mg, 79%), mp 72−75 °C. ^{1}H NMR ($CDCl_3$): δ 1.51−1.53 (3H, t, J = 7.0 Hz, CH_2CH_3), 1.75−1.80 (2H, quintet, J = 7.0 Hz CH_2), 2.28 (6H, s, NMe_2), 2.40−2.44 (2H, t, J = 7.0 Hz, CH_2), 3.45−3.50 (2H, q, J = 7.0 Hz, CH_2), 4.60−4.65 (2H, q, CH_2CH_3), 7.82 (1H, s), 8.42 (1H,s, CONH, exch). IR (KBr): 3099, 2947, 2821,

1672, 1534, 1453, 1416, 1347, 1314, 1250, 1158, 833,762 cm^{-1}. HRFABMS found: 270.15778. Calculated for $C_{11}H_{20}N_5O_3$: 270.15661.

Thiazoles. Methyl 2-amino-5-isopropyl-1,3-thiazole-4-carboxylate (Thz*i*Pr-OMe) was prepared according to a published procedure[12] in 41% yield, mp 151−152 °C. (lit.[12] mp 150−151 °C).

Ethyl 2-amino-4-isopropyl-1,3-thiazole-5-carboxylate (*iso*Thz*i*Pr-OEt) was prepared according to a literature procedure[12] in 49% yield, mp 176−178 °C (lit.[12] mp 176−178 °C).

Thiophenes. Ethyl 2-Methyl-4,5-dihydro-3-thiophenecarboxylate. A standard procedure[14] was employed to give the product as a colorless oil (96% yield).

Ethyl 2-Methyl-3-thiophenecarboxylate (ThiMe-OEt). A standard procedure[14] was employed to give the product as a colorless oil (82% yield).

2-Methyl-3-thiophenecarboxylic acid (ThiMe-OH) was prepared according to a published method in 77% yield, mp 115−117 °C (lit.[30] mp 116−117 °C).

2-Methyl-5-nitro-3-thiophenecarboxylic Acid [(NO_2)-ThiMe-OH]. A mixture of concentrated nitric acid (10 mL, specific gravity 1.42) and concentrated sulfuric acid (6 mL) was mechanically stirred and cooled to (−10 °C) by a dry ice−methanol bath. The temperature was kept below −5 °C while 2-methyl-3-thiophenecarboxylic acid (996 mg, 7.006 mmol) was added in small portions. The reaction mixture was stirred at the same temperature for 15 min and then was poured on to ice water. The solid material that precipitated was filtered off, washed with water, and dried to give light brown solid (883 mg, 67%), mp 177−180 °C. ^{1}H NMR (DMSO-d_6): δ 13.35 (1H, br), 8.11 (1H, s), 2.76 (3H, s). IR (KBr): 1706, 1543, 1514, 1457, 1335, 1257 cm^{-1}. HREIMS found: 186.99431. Calculated for $C_6H_5NO_4S$: 186.99393.

Oxazoles. Methyl 2-({[(benzyloxy)carbonyl]amino}methyl)-5-methyl-1,3-oxazole-4-carboxylate was prepared according to a literature procedure[15] in 74% yield as a pale yellow crystalline solid, mp 85−86 °C (lit.[15] mp 86−87 °C).

2-({[(Benzyloxy)carbonyl]amino}methyl)-5-methyl-1,3-oxazole-4-carboxylic Acid. The foregoing ester (650 mg, 2.138 mmol) was dissolved in methanol (15 mL) to which sodium hydroxide (428 mg) in water (5 mL) was added at room temperature with stirring. The stirring was continued overnight at room temperature. The solution was concentrated to a minimium amount, cooled to 0 °C, and diluted with water (30 mL). Hydrochloric acid (concentrated) was added dropwise with stirring at 0 °C until pH 1. The pale yellow solid was collected and dried under reduced pressure at 60 °C overnight to give the required product (471 mg, 76%), mp 177−180 °C. ^{1}H NMR (DMSO-d_6): δ 2.50 (3H, s, Me), 4.21 (2H, t, J = 8.6 Hz, CH_2NH), 5.02 (2H, s, CH_2Ph), 7.28−7.32 (5H, m, PhH), 7.90−7.92 (1H, t, J = 5.6 Hz, CONH, exch), 12.80 (1H, s, CO_2H, exch). IR (KBr): 3336, 3068, 2927, 2851, 1696, 1619, 1542, 1447, 1344, 1274 cm^{-1}. HREIMS found: 276.07348. Calculated for $C_{13}H_{12}N_2O_5$: 276.07462.

Benzyl [4-({[3-(Dimethylamino)propyl]amino}carbonyl)-5-methyl-1,3-oxazol-2-yl]methylcarbamate. Triethylamine (101 μL, 0.724 mmol) and trimethylacetyl chloride (89 μL, 0.724 mmol) were added sequentially to a stirred solution of the oxazole carboxylic acid (100 mg, 0.362 mmol) in THF (10 mL, dry) at 0 °C. The mixture was stirred for 30 min at 0 °C, a solution of the amine (91 μL, 0.724 mmol) in THF (2 mL, dry) was added, then the reaction was stirred for 45 min and partitioned between ethyl acetate (30 mL) and water (30 mL). The aqueous layer was further extracted with ethyl acetate (2 × 30 mL). The organic extracts were combined, washed sequentially with saturated aqueous sodium hydrogen carbonate (50 mL) and brine (50 mL), dried ($MgSO_4$), and then evaporated under reduced pressure before purification by flash chromatography on silica followed by eluting with methanol/ethyl acetate (1/3 containing 1% triethylamine, R_f = 0.2). The product was obtained as a colorless oil (90 mg, 67%). ^{1}H NMR ($CDCl_3$): δ 1.71−1.78 (2H, quintet, J = 6.8 Hz, CH_2), 2.24 (6H, s, NMe_2), 2.38−2.41 (2H, t, J = 6.8 Hz, CH_2NMe_2), 2.61 (3H, s, Ar-CH_3), 3.42−3.49 (2H, q, J = 7.4 Hz, CH_2NHCO), 4.45−4.46 (2H, d, J = 5.2 Hz, Ar-CH_2-$NHCO_2$), 5.16 (2H, s, CH_2O), 5.35 (1H, s, CONH, exch), 7.33−7.37 (5H, m, Ar-H), 7.61 (1H, s, CONH, exch). IR (liquid film): 3296, 2947, 2819, 2779, 1720, 1653, 1529, 1455, 1045 cm^{-1}. HREIMS found: 374.195228. Calculated for $C_{19}H_{26}N_4O_4$: 374.19541.

Dimers. Standard Procedure for Reduction of Nitro Groups of Monomers. The appropriate nitromonomer (3 mmol) was dissolved in ethanol (30 mL), and palladium on charcoal (10%, 500 mg) was added. Hydrogenation was carried out at room temperature and atmospheric pressure for 4 h. The catalyst was removed by filtration through Kieselguhr and the filtrate evaporated under reduced pressure to yield the required amine, which was used forthwith for coupling.

Standard Procedure for Preparing Acid Chlorides of Monomers. The appropriate monomer carboxylic acid (2 mmol) was dissolved in thionyl chloride (3 mL) and the solution heated under reflux for 3 h. The solution was evaporated to dryness and the product used directly for coupling.

Standard Procedure for Acid Chloride Coupling. The appropriate acid chloride in THF or dichloromethane solution was added to a solution of the amino monomer, prepared as described for reduction above, in the same solvent. *N*-Methylmorpholine was used as the standard base and the reaction time was typically 2−12 h.

***N*-[5-({[3-(Dimethylamino)propyl]amino}carbonyl)-1-methyl-1*H*-pyrrol-3-yl]1-ethyl-4-nitro-1*H*-pyrrole-2-carboxamide.** (NO_2)PyrEt-PyrMe-Dmap was prepared using the acid chloride method. The crude product was chromatographed over silica gel using ethyl acetate/methanol/ammonia (49/49/2) as eluant. The required product was obtained as a yellow solid (499 mg, 60%), which was further purified by trituration with a small amount of ethyl acetate/*n*-hexane, mp 172−174 °C. ^{1}H NMR (DMSO-d_6): δ 1.33−1.37 (3H, t, J = 7.2 Hz), 1.62−1.66 (2H, m), 2.22 (6H, s), 2.33−2.36 (2H, t, J = 6.8 Hz), 3.17−3.22 (2H, quintet, J = 1.6 Hz), 3.81 (3H, s), 4.41−4.46 (2H, q, 7.2 Hz), 6.84 (1H, d, J = 2.0 Hz), 7.20 (1H, d, J = 2.0 Hz), 7.57 (1H, d, J = 2.0 Hz), 8.09−8.12 (1H, t, 5.6 Hz), 8.23 (1H, d, J = 2.0 Hz), 10.24 (1H, s). IR (KBr): 3428, 3275, 3135, 1658, 1624, 1570, 1539, 1496, 1439, 1307 cm^{-1}. HRFABMS found: 391.20942. Calculated for $C_{18}H_{27}N_6O_4$: 391.20938.

***N*-[5-({[3-(Dimethylamino)propyl]amino}carbonyl)-1-methyl-1*H*-pyrrol-3-yl]-1-isopropyl-4-nitro-1*H*-pyrrole-2-carboxamide.** (NO_2)Pyr*i*Pr-PyrMe-Dmap was prepared using the acid chloride method. The crude product was purified by chromatography on silica gel using ethyl acetate/methanol/ammonia (49/49/2). Fractions with R_f value of 0.3 were collected. The product was obtained as a yellow solid (640 mg, 49%), mp 205−207 °C. Found: C, 56.25, H, 6.78, N, 20.59. Calculated for $C_{19}H_{28}N_6O_4$: C, 56.42, H, 6.98, N, 20.78. ^{1}H NMR (DMSO-d_6): δ 1.42−1.57 (6H, d, J = 6.7 Hz), 1.60−1.65 (2H, quintet, J = 6.7 Hz), 2.12 (6H, s), 2.20−2.25 (2H, t, 7.0 Hz), 3.17−3.22 (2H, q, J = 6.7 Hz), 3.81 (3H, s), 5.40−5.51 (1H, m), 6.83 (1H, s), 7.22 (1H, s), 7.48 (1H, s), 8.11−8.15 (1H, t, J = 5.8 Hz), 8.34 (1H, s), 10.29 (1H, s). IR (KBr): 1640, 1555, 1506, 1480, 1322, 1279, 1240, 1203 cm^{-1}. HRFABMS found: 405.22509. Calculated: 405.22503.

***N*-[5-({[3-(Dimethylamino)propyl]amino}carbonyl)-1-isopropyl-1*H*-pyrrol-3-yl]-1-isopropyl-4-nitro-1*H*-pyrrole-2-carboxamide.** (NO_2)Pyr*i*Pr-Pyr*i*Pr-Dmap was prepared using the acid chloride in THF solution in the presence of *N*-methylmorpholine. The crude product was chromatographed on silica gel using 50:50:0.5 methanol/ethyl acetate/triethylamine. Fractions with R_f value of 0.1 were collected. The solvent was removed at 50 °C under reduced pressure to give the product as a yellow glassy material (471 mg, 77%), mp 86−90 °C (softening). ^{1}H NMR ($CDCl_3$): δ 1.42 (6H, d, 6.7 Hz), 1.75 (6H, d, J = 6.7 Hz), 1.72−1.77 (2H, m), 2.31 (6H, s), 2.46 (2H, t, J = 6.1 Hz), 3.44−3.49 (2H, q, J = 6.0 Hz), 5.51−5.64 (2H, m), 6.45 (1H, d, 1.6 Hz), 7.17 (1H, d, J = 1.6 Hz), 7.40 (1H, d, J = 1.6 Hz), 7.69 (1H, s, br, CONH), 7.79 (1H, d, J = 1.6 Hz). IR (KBr): 2974, 2927, 1636, 1574, 1531, 1507, 1407, 1282, 1237, 1170 cm^{-1}. HREIMS found: 432.24833. Calculated for $C_{21}H_{32}N_6O_4$: 432.24850.

1-Methyl-*N*-[1-methyl-5-({[3-(1-pyrrolidinyl)propyl]amino}carbonyl)-1*H*-pyrrol-3-yl]-4-nitro-1*H*-pyrrole-2-carboxamide. (NO_2)PyrMe-PyrMe-Pyrrp was prepared using 2,2,2-trichloro-1-(1-methyl-4-nitro-1*H*-pyrrol-2-yl)ethanone (PyrMe-CCl_3) in THF solution. The crude product was purified by chromatography on silica gel using 49.5:49.5:1 ethyl acetate/methanol/triethylamine. The product was obtained as a glassy yellow material (192 mg, 56%), $R_f = 0.1$, mp 170−173 °C. ^{1}H NMR (DMSO-d_6) δ 1.61−1.67 (6H, m), 2.39−2.42 (6H, m), 3.18−3.23 (2H, q, $J = 6.8$ Hz), 3.81 (3H, s), 3.95 (3H, s), 6.81 (1H, d, $J = 1.6$ Hz), 7.18 (1H, d, $J = 1.6$ Hz), 7.56 (1H, d, $J = 1.6$ Hz), 8.08 (1H, t, $J = 5.37$ Hz), 8.16 (1H, s), 10.20 (1H,s). IR (KBr): 1661, 1621, 1572, 1537, 1495, 1303 cm^{-1}. HRFABMS found: 403.20555. Calculated for $C_{19}H_{27}N_6O_4$: 403.20938.

***N*-[3-(Dimethylamino)propyl]-1-isopentyl-4-{[(1-isopentyl-4-nitro-1*H*-pyrrol-2-yl)carbonyl]amino}-1*H*-pyrrole-2-carboxamide.** (NO_2)Pyr*i*Pe-Pyr*i*Pe-Dmap was prepared using the acid chloride method in THF solution in the presence of *N*-methylmorpholine. The crude product was purified by column chromatography using ethyl acetate/methanol/triethylamine 100:100:1. Fractions containing the required material were collected, and the solvent was then removed under reduced pressure and coevaporated with *n*-hexane to give the pure product as a glassy yellow material, $R_f = 0.34$, (223 mg, 94%), mp 57−60 °C (transparent). ^{1}H NMR ($CDCl_3$): δ 0.92616 (6H, d, $J = 4.5$ Hz), 0.95 (6H, d, $J = 4.5$ Hz), 1.57−1.83 (4H, m), 2.35 (6H, s), 2.52 (2H,t, $J = 6.1$ Hz), 3.45−3.49 (2H, q, $J = 5.6$ Hz), 4.36 (2H, t, $J = 7.4$ Hz), 4.43 (2H, t, $J = 7.4$ Hz), 6.51 (1H, d, $J = 1.9$ Hz), 7.20 (1H, d, $J = 1.9$ Hz), 7.22 (1H, d, $J = 1.9$ Hz), 7.64 (1H, d, $J = 1.9$ Hz), 7.77 (2H, m). IR (KBr): 2953, 1633, 1592, 1573, 1539, 1525, 1503, 1312 cm^{-1}. HREIMS found: 488.31163. Calculated for $C_{25}H_{40}O_4N_6$: 488.31110.

1-Isopropyl-*N*-[1-methyl-5-({[3-(4-moropholinyl)propyl]amino}carbonyl)-1*H*-pyrrol-3-yl]-4-nitro-1*H*-pyrrole-2-carboxamide. (NO_2)Pyr*i*Pr-PyrMe-Morp was prepared using HBTU in the presence of *N*-methylmorpholine in DMF solution. The crude product was chromatographed over flash silica gel using 1/3 methanol/ethyl acetate. Fractions containing the product ($R_f = 0.30$) were collected and the solvents were removed under reduced pressure at 50 °C. The product was obtained as a hygroscopic glassy yellow material (260 mg, 73%) with no distinct melting point. ^{1}H NMR (DMSO-d_6): δ 10.28 (1H, s), 8.33 (1H, d, $J = 1.8$ Hz), 8.07−8.05 (1H, t, $J = 5.5$ Hz), 7.48 (1H, d, $J = 1.8$ Hz), 7.19 (1H, d, $J = 1.8$ Hz), 6.85 (1H, d, $J = 1.8$ Hz), 5.89−5.42 (1H, heptet, 6.7 Hz), 3.80 (3H, s), 3.58−3.56 (4H, t, $J = 4.5$ Hz), 3.21−3.16 (2H, q, $J = 6.6$ Hz), 2.32−2.28 (6H, m), 1.67−1.61 (2H, quintet, $J = 7.0$ Hz), 1.44−1.43 (6H, d, $J = 6.7$ Hz). IR (KBr): 1661, 1582, 1540, 1441, 1389, 2326, 1284, 1242, 1116, 850, 755 cm^{-1}. HREIMS found: 446.22568. Calculated for $C_{21}H_{30}N_6O_5$:446.22777.

1-Isopropyl-*N*-[1-methyl-5-({[3-(1-pyrrolidinyl)propyl]amino}carbonyl)-1*H*-pyrrol-3-yl]-4-nitro-1*H*-pyrrole-2-carboxamide. (NO_2)Pyr*i*Pr-PyrMe-Pyrrp was prepared using HBTU in the presence of *N*-methylmorpholine in DMF solution. The product was purified by column chromatography using 1/2/0.1 methanol/ethyl acetate/triethylamine. The product was obtained as a yellow material (300 mg, 86%) with no distinct melting point. Some of this material was further purified by HPLC. ^{1}H NMR (DMSO-d_6): δ 10.30 (1H, s), 9.47 (1H, br, TFA), 8.34 (1H, d, $J = 1.8$ Hz), 8.21−8.18 (1H, t, $J = 5.5$ Hz), 7.48 (1H, d, $J = 1.8$ Hz), 7.27 (1H, d, $J = 1.8$ Hz), 6.92 (1H, d, $J = 1.8$ Hz), 5.48−5.41 (1H, heptet, $J = 6.7$ Hz), 3.82 (3H, s), 3.56−3.54 (2H, m), 3.27−3.22 (2H, q, $J = 6.6$ Hz), 3.17−3.11 (2H, m), 2.99−2.96 (2H, m), 2.01 (2H, m), 1.86−1.82 (4H, m), 1.45−1.43 (6H, d, $J = 6.7$ Hz). IR (KBr): 3433, 1672, 1650, 1535, 1462, 1426, 1371, 1321, 1283, 1237, 1200, 1178, 1131 cm^{-1}. HRFABMS found: 430.23179. Calculated for $C_{21}H_{30}N_6O_4$: 430.23285.

***N*-[3-(Dimethylamino)propyl]-4-{[(1,5-dimethyl-4-nitro-1*H*-pyrrol-2-yl)carbonyl]amino}-1,5-dimethyl-1*H*-pyrrole-2-carboxamide [(NO_2)PyrMe$_2$-PyrMe$_2$-Dmap]** was prepared using carbodiimide coupling (EDC) in DMF solution in the presence of DMAP. The crude product was purified by silica gel column chromatography using methanol/ethyl acetate (1/4, containing 1% triethylamine). The pure product ($R_f = 0.1$) was collected and the solvent removed under reduced pressure to give pale yellow oil (90 mg, 57%), mp 90−95 °C (softening). ^{1}H NMR (DMSO-d_6): δ 1.58−1.65 (2H, quintet, $J = 5.9$ Hz, CH_2), 2.10 (3H, s, C-CH_3), 2.19 (6H, s, NMe_2), 2.29−2.31 (2H, t, $J = 5.9$ Hz, CH_2), 2.61 (3H, s, C-CH_3), 3.15−3.20 (2H, q, $J = 5.9$ Hz, CH_2), 3.77 (3H, s, NMe), 3.85 (3H, s, NMe), 6.80 (1H, s), 7.56 (1H, s), 7.94−7.97 (1H, t, $J = 5.6$ Hz, CONH, exch), 9.52 (1H, s, CONH, exch). IR (KBr): 3419, 2940, 1651, 1591, 1523, 1458, 1412, 1316, 1256, 1183 cm^{-1}. HRFABMS found: 405.22659. Calculated for $C_{19}H_{29}N_6O_4$: 405.22503.

***N*-[5-({[3-(Dimethylamino)propyl]amino}carbonyl)-1-methyl-1*H*-pyrrol-3-yl]-1-isopentyl-4-nitro-1*H*-pyrrole-2-carboxamide [(NO_2)Pyr*i*Pe-PyrMe-Dmap]** was prepared by the acid chloride method in dichloromethane solution in the presence of *N*-methylmorpholine. The product was purified by column chromatography using 1/3/0.030 methanol/ethyl acetate/triethylamine. Fractions containing the product ($R_f = 0.20$) were collected and the solvents were removed under reduced pressure at 50 °C to give the product as a yellow powder (347 mg, 81%), mp 148−151 °C. ^{1}H NMR (DMSO-d_6): δ 10.22 (1H, s), 8.23 (1H, d, $J = 1.8$ Hz), 8.13−8.10 (1H, t, $J = 5.5$ Hz), 7.54 (1H, d, $J = 1.8$ Hz), 7.19 (1H, d, $J = 1.8$ Hz), 6.81 (1H, d, $J = 1.8$ Hz), 4.45−4.41 (2H, t, $J = 7.3$ Hz), 3.81 (3H, s), 3.21−3.17 (2H, q, $J = 6.7$ Hz), 2.34−2.31 (2H, t, $J = 7.1$ Hz), 2.20 (6H, s), 1.67−1.57 (4H, m), 1.55−1.45 (1H, m), 0.88−0.86 (6H, d, $J = 7.5$ Hz). IR (KBr): 1665, 1642, 1599, 1528, 1499,1425, 1312 cm^{-1}. HRFABMS found: 433.25630. Calculated for: $C_{21}H_{33}N_6O_4$ 433.25633.

1-(Cyclopropylmethyl)-*H*-[5-({[3-(dimethylamino)propyl]amino}carbonyl)-1-methyl-1*H*-pyrrol-3-yl]-4-nitro-1*H*-pyrrole-2-carboxamide [(NO_2)PyrCycPr-PyrMe-Dmap] was prepared using HBTU in DMF solution in the presence of *N*-methylmorpholine. Purification by flash column chromatography over silica gel using 1/2/0.1 methanol/ethyl acetate/triethylamine gave the required product as a glassy yellow material, $R_f = 0.5$ (130 mg, 80%) with no distinct melting point. ^{1}H NMR (DMSO-d_6): δ 10.26 (1H, s), 8.24 (1H, d, $J = 1.9$ Hz), 8.10 (1H, t, $J = 5.6$ Hz), 7.57 (1H, d, $J = 1.9$ Hz), 7.21 (1H, d, $J = 1.9$ Hz), 6.83 (1H, d, $J = 1.9$ Hz), 4.27 (2H, d, $J = 7.2$ Hz), 3.81 (3H, s), 3.21−3.16 (2H, q, $J = 6.9$ Hz), 2.28 (2H, t, $J = 7.1$ Hz), 2.17 (6H, s), 1.65−1.59 (2H, quintet, $J = 7.1$ Hz), 1.34−1.29 (1H, m), 0.51−0.38 (4H, m). IR (KBr): 3283, 3126, 2944, 1642, 1573, 1532, 1504, 1463, 1427, 1389, 1309, 1233 cm^{-1}. HRFABMS found: 417.22460. Calculated for $C_{20}H_{29}N_6O_4$: 417.22503.

1-Cyclopentyl-*N*-[5-({[3-(dimethylamino)propyl]amino}carbonyl)-1-methyl-1*H*-pyrrol-3-yl]-4-nitro-1*H*-pyrrole-2-carboxamide [(NO_2)PyrCycPe-PyrMe-Dmap] was prepared using HBTU in DMF in the presence of *N*-methylmorpholine. The crude product was purified by column chromatography using silica gel and 1/2/0.1 methanol/ethyl acetate/triethylamine. The product was obtained as a yellow oil, $R_f = 0.45$ (157 mg, 93%). ^{1}H NMR (DMSO-d_6): 10.27 (1H, s), 8.24 (1H, d, $J = 1.7$ Hz), 8.11 (1H, t, $J = 5.2$ Hz), 7.47 (1H, s), 7.20 (1H, d, $J = 1.7$ Hz), 6.83 (1H, d, $J = 1.7$ Hz), 5.48 (1H, quintet, $J = 7.4$ Hz), 3.80 (3H, s), 3.18 (2H, q, $J = 6.6$ Hz), 2.66 (2H, m), 2.30 (2H, t, $J = 7.1$ Hz), 2.14 (6H, s), 2.12 (2H, m), 1.82 (4H, m), 1.62 (2H, quintet, $J = 7.1$ Hz). IR (KBr): 1644, 1575, 1534, 1504, 1437, 1401, 1313, 1287, 748 cm^{-1}. HRFABMS found: 431.24204. Calculated for $C_{21}H_{31}N_6O_4$: 431.24068.

***N*-[3-(Dimethylamino)propyl]-1-ethyl-4-{[(1-methyl-4-nitro-1*H*-pyrrol-2-yl) carbonyl]amino}-1*H*-imidazole-2-carboxamide [(NO_2)PyrMe-ImiEt-Dmap]** was prepared using acid chloride coupling in dichloromethane solution. The crude product was purified by reverse phase column chromatography using acetonitrile/water/hydrochloric acid (25:100:1, $R_f = 0.15$). Fractions containing the product were combined and freeze-dried to give the required product as a pale yellow solid (slightly hygroscopic) (87 mg, 55%) as the hydrochloric acid salt with no distinct melting point. ^{1}H NMR (DMSO-d_6): δ 1.32−1.35 (3H,t, $J = 7.0$ Hz, CH_2CH_3), 1.88−1.92 (2H, quintet, $J = 7.7$ Hz, CH_2), 2.73−2.74 (6H, d, $J = 4.8$ Hz, NMe_2),

3.02−3.07 (2H, m), 3.30−3.35 (2H, q, J = 6.4 Hz, CH_2), 3.95 (3H, s, NMe), 4.39−4.45 (2H, q, J = 6.4 Hz, CH_2), 7.58 (1H, s), 7.75 (1H, d, J = 1.4 Hz), 8.14 (1H, t, J = 6.1 Hz, CONH, exch), 8.20 (1H, d, J = 1.4 Hz), 10.15 (1H, br, hydrochloric acid, exch), 10.761 (1H, s, CONH, exch). IR (KBr): 2950, 2865, 2822, 1659, 1536, 1506, 1467, 1423, 1314 cm^{-1}. HRFABMS found: 392.20579. Calculated for $C_{17}H_{26}O_4N_7$: 392.20463.

***N*-[3-(Dimethylamino)propyl]-1-ethyl-4-{[(1-ethyl-4-nitro-1*H*-imidazol-2-yl)carbonyl]amino}-1*H*-imidazole-2-carboxamide [(NO_2)ImiEt-ImiEt-Dmap]** was prepared using HBTU coupling in DMF solution in the presence of triethylamine. The crude product was purified by reverse phase column chromatography. Water was used first, then a mixture of 1/4 acetonitrile/water (containing 1% hydrochloric acid). Fractions containing the pure product were collected and freeze-dried. The freeze-dried material was dissolved in water (25 mL) and freeze-dried again. The product (60 mg, 46%) was obtained as a pale yellow sticky material (hygroscopic), mp 120−125 °C (transparent). ^{1}H NMR (DMSO-d_6): δ 1.33−1.36 (3H, t, J = 7.0 Hz, CH_2CH_3), 1.40−1.44 (3H, t, J = 7.0 Hz, CH_2CH_3), 1.86−1.91 (2H, quintet, J = 7.7 Hz, CH_2), 2.75−2.77 (6H, d, J = 4.8 Hz, NMe_2), 3.04−3.09 (2H, m, CH_2), 3.28−3.31 (2H, q, J = 6.4 Hz, CH_2), 4.43−4.54 (4H, m, 2xCH_2CH_3), 7.61 (1H, s), 8.48−8.51 (1H, t, J = 6.1 Hz, CONH, exch), 8.61 (1H, s), 9.55 (1H, br, hydrochloric acid, exch), 10.14 (1H, s, CONH, exch). IR (KBr): 3414, 1665, 1542, 1476, 1380, 1349, 1150, 1088, 847 cm^{-1}. HRFABMS found: 407.21498. Calculated for $C_{17}H_{27}N_8O_4$: 407.21553.

Methyl 5-isopropyl-2-{[(1-methyl-4-nitro-1*H*-pyrrol-2-yl)carbonyl]amino}-1,3-thiazole-4-carboxylate [(NO_2)-PyrMe-Thz*i*Pr-OMe] was prepared using acid chloride coupling in dichloromethane solution in the presence of *N*-methylmorpholine. The crude product was purified by flash chromatography over silica gel [1/1 ethyl acetate/pet. ether], which gave the required product as a white crystalline solid (460 mg, 43% yield), mp 118−120 °C (softening). ^{1}H NMR ($CDCl_3$): δ 1.32−1.34 (6H, CH-$(CH_3)_2$, d, J = 6.4 Hz), 3.89 (3H, s, CO_2-Me), 4.08 (3H, s, NMe), 4.11−4.18(1H, m), 7.23 (1H, pyrrole, d, J = 1.4 Hz), 7.67 (1H, pyrrole, d, J = 1.4 Hz), 9.85 (1H, br, CONH, exch). IR (KBr): 3557, 3119, 2975, 1712, 1646, 1574, 1509, 1319, 1208 cm^{-1}. HREIMS found: 352.08579. Calculated for $C_{14}H_{16}N_4O_5S$: 352.08414.

5-Isopropyl-2-{[(1-methyl-4-nitro-1*H*-pyrrol-2-yl)carbonyl]amino}-1,3-thiazole-4-carboxylic Acid [(NO_2)PyrMe-Thz*i*Pr-OH]. The above methyl ester (480 mg, 1.363 mmol) was suspended in ethanolic potassium hydroxide (0.5M, 25 mL). The reaction mixture was heated under reflux for 4 h and then cooled to 0 °C. Hydrochloric acid (concentrated) was added dropwise with stirring until pH 2. The pale yellow solid obtained was filtered off, washed with deionized water, and dried under reduced pressure at 45 °C overnight to give the required material (440 mg, 96%), mp 315−319 °C (dec). ^{1}H NMR (DMSO-d_6): δ 1.23−1.25 (6H, CH-$(CH_3)_2$, d, J = 6.4 Hz), 3.98 (3H, s, NMe), 4.00−4.07 (1H, m), 7.99 (1H, pyrrole, d, J = 1.4 Hz), 8.28 (1H, pyrrole, d, J = 1.4 Hz), 12.5−13.2 (1H, br, CO_2H, exch). IR (KBr): 3189, 3132, 2972, 1668, 1566, 1537, 1512, 1497, 1319, 1231 cm^{-1}. HRFABMS found: 337.06396. Calculated for $C_{13}H_{13}O_5N_4S$: 337.06067.

***N*-[3-(Dimethylamino)propyl]-5-isopropyl-2-{[(1-methyl-4-nitro-1*H*-pyrrol-2-yl)carbonyl]amino}-1,3-thiazole-4-carboxamide [AIK-12/99] [(NO_2)PyrMe-Thz*i*Pr-Dmap]** was prepared using the acid chloride method. The crude product was purified by column chromatography using (1:1 methanol/ethyl acetate containing 1% triethylamine). The product was obtained as a yellow glassy material (159 mg, 29%), mp 85−90 °C (softening). ^{1}H NMR ($CDCl_3$): δ 1.26−1.28 (6H, CH-$(CH_3)_2$, d, J = 6.4 Hz), 1.79−1.86 (2H, CH_2, quintet, J = 6.9 Hz), 2.31 (6H, s, NMe_2), 2.45−2.48 (2H, CH_2, t, J = 6.9 Hz), 3.43−3.50 (2H, CH_2, q, J = 6.9 Hz), 4.09 (3H, s, NMe), 4.37−4.44 (1H, $CH(CH_3)_2$), m), 7.55 (1H, pyrrole, d, J = 1.4 Hz), 7.62 (1H, s, CONH, exch), 7.68 (1H, pyrrole, d, J = 1.4 Hz). IR (KBr): 3131, 2959, 1668, 1551, 1500, 1418, 1310, 1286 cm^{-1}. HREIMS found: 422.17695. Calculated for $C_{18}H_{26}O_4N_6S$: 422.17363.

Ethyl 4-isopropyl-2-{[(1-methyl-4-nitro-1*H*-pyrrol-2-yl)carbonyl]amino}-1,3-thiazole-5-carboxylate [(NO_2)PyrMe-*iso*Thz*i*Pr-OEt] was prepared using acid chloride coupling. The crude product was purified by column chromatography using silica gel and 1/3 ethyl acetate/*n*-hexane as eluant, R_f = 0.33. The product was obtained as a pale yellow fine needles (802 mg, 35%), mp >230 °C. ^{1}H NMR (DMSO-d_6): δ 1.19 (6H, d, J = 6.8 Hz), 1.24−1.31 (3H, t, J = 7.1 Hz), 3.90−3.95 (1H, m), 3.98 (3H, s), 4.22−4.28 (2H, q, J = 7.0 Hz), 8.04 (1H, s), 8.30 (1H, s), 12.8−13.0 (1H, s, br, exch). IR (KBr): 3355, 3144, 2978, 1690, 1674, 1556, 1515, 1501, 1311, 1251, 1061 cm^{-1}. HREIMS found: 367.10959. Calculated for $C_{15}H_{19}N_4O_5S$: 367.10762.

2-(1-Methyl-4-nitropyrrole-2-carboxamido)-4-isopropylthiazole-5-carboxylic Acid [(NO_2)PyrMe-*iso*-ThzOH]. The above ester, (NO_2)PyrMe-*iso*Thz*i*Pr-OEt (491 mg, 1.400 mmol), was suspended in ethanolic potassium hydroxide (1 M, 25 mL). The reaction mixture was heated under reflux for 4 h, and then cooled to 0 °C. Hydrochloric acid concentrated was then added dropwise with stirring until pH 2. The pale yellow solid obtained was filtered off, washed with deionized water, and then dried under reduced pressure at 45 °C overnight to give the required material (379 mg, 84%), mp >230 °C. ^{1}H NMR (DMSO-d_6): δ 1.21 and 1.23 (6H, d, J = 6.8 Hz), 3.92−4.03 (1H, m, 3H, s), 7.98 (1H, s), 8.20 (1H, s), 12.6−13.0 (2H, br, exch). IR (KBr): 3444, 3138, 2972, 1685, 1568, 1543, 1500,1467, 1319, 1112, 1067 cm^{-1}. HREIMS found: 337.06396. Calculated for $C_{13}H_{13}N_4O_5S$: 337.06067.

***N*-[3-(Dimethylamino)propyl]-4-isopropyl-2-{[(1-methyl-4-nitro-1*H*-pyrrol-2-yl)carbonyl]amino}-1,3-thiazole-5-carboxylate [(NO_2)PyrMe-*iso*Thz*i*Pr-Dmap]** was prepared by the acid chloride method. The crude product was purified by silica gel column chromatography. The product was eluted by methanol/ethyl acetate/triethylamine (49/49/2) and was obtained as a yellow solid. This material was extracted using ethyl acetate/water. The organic layer was dried (Na_2SO_4) and filtered, and then the solvent was removed under reduced pressure to give the required product as a glassy solid material (358 mg, 76%), R_f = 0.1, mp 95−100 °C (softening). ^{1}H NMR ($CDCl_3$): δ 1.26 (6H, d, J = 6.8 Hz), 1.83 (2H, m), 2.41 (6H, s), 2.61 (2H, t, unresolved), 3.48−3.57 (2H, q, 5.6 Hz), 3.82−3.91 (1H, m), 4.09 (3H, s), 7.41 (1H, d, J = 1.8 Hz), 7.68 (1H, d, J = 1.8 Hz), 8.01 (1H, br, CONH, exch). IR (KBr): 3438, 2985, 1668, 1634, 1543, 1526, 1421, 1319, 1279 cm^{-1}. HREIMS found: 422.17189. Calculated for $C_{18}H_{26}N_6O_4S$: 422.17363.

Methyl 5-isopropyl-2-[(3-methoxybenzoyl)amino]-1,3-thiazole-4-carboxylate (3MeOB-Thz*i*Pr-OMe). Methyl 2-amino-5-isopropyl-1,3-thiazole-4-carboxylate (383 mg, 1.913 mmol) was dissolved in dichloromethane (10 mL) at room temperature with stirring. *N*-methylmorpholine (0.3 mL) was added followed by 3-methoxybenzoyl chloride (326 mg, 1.913 mmol) at room temperature with stirring. The reaction mixture was heated until reflux for 10 min and then was left stirring at room temperature overnight. The solvent was removed under reduced pressure and the crude product was purified by column chromatography using silica gel and 1/2 ethyl acetate/petroleum ether. Fractions containing the required material (R_f = 0.4) were collected and the solvents were removed under reduced pressure to give the product as a white solid (530 mg, 83%), mp 60−63 °C. ^{1}H NMR ($CDCl_3$): δ 9.89 (1H, s), 7.45−7.38 (3H, m), 7.16−7.13 (1H, m), 4.16 (1H, heptet, J = 6.8 Hz), 3.86 (3H, s), 3.85 (3H, s), 1.40 (6H, d, J = 6.8 Hz). IR (KBr): 2958, 1720, 1669, 1547, 1463, 1298, 1208, 1045, 822, 743 cm^{-1}. HRFABMS found: 335.10620. Calculated for $C_{16}H_{19}N_2O_4S$: 35.10655.

5-Isopropyl-2-[(3-methoxybenzoyl)amino]-1,3-thiazole-4-carboxylic Acid (3MeOB-Thz*i*Pr-OH). The above ester, 3MeOB-Thz*i*Pr-OMe (330 mg, 0.998 mmol), was dissolved in ethanolic potassium hydroxide (561 mg, in 10 mL ethanol, 10 mmol). The reaction mixture was heated under reflux for 3 h, and then it was cooled to 0 °C. Hydrochloric acid (concentrated) was added dropwise with stirring at 0 °C, and the resulting solid was filtered off, washed with water, and dried under

reduced pressure at 45 °C overnight. The product was obtained as a white solid (290 mg, 91%), mp >230 °C (sublimation). ^{1}H NMR (DMSO-d_6): δ 7.69 (2H, m), 7.44 (1H, t, J = 3.9 Hz), 7.19 (1H, m), 4.06 (1H, heptet, J = 6.8 Hz), 3.84 (3H, s), 1.31 (6H, d, J = 6.8 Hz). IR (KBr): 2963, 1672, 1555, 1463, 1306, 1221, 1043, 936, 820, 736 cm^{-1}. HRFABMS found: 321.09056. Calculated for $C_{15}H_{17}N_2O_4S$: 321.09090.

***N*-[3-(Dimethylamino)propyl]-5-methyl-2-({[(1-methyl-4-nitro-1*H*-pyrrol-2-yl)carbonyl]amino}methyl)-1,3-oxazole-4-carboxamide [(NO$_2$)PyrMe-OxaMe-Dmap]** was prepared in dichloromethane solution using (NO$_2$)PyrMe-CCl$_3$ as acylating agent. The crude product was purified by flash chromatography using methanol/ethyl acetate (1/1 containing 1% triethylamine, R_f = 0.2). The product was obtained as a light brown solid (61 mg, 69%), mp 60−63 °C. ^{1}H NMR (CDCl$_3$): 1.74−1.81 (2H, quintet, J = 6.8 Hz, CH_2), 2.28 (6H, s, NMe$_2$), 2.43−2.46 (2H, t, J = 7.0 Hz, CH_2NMe$_2$), 2.63 (3H, s, oxazole-CH_3), 3.43−3.49 (2H, q, J = 7.4 Hz, CONHCH_2), 4.01 (3H, s, N-Me), 4.63−4.64 (2H, d, J = 5.2 Hz, CONH-CH_2-oxazole), 6.73 (1H, s, CONH, exch), 7.25 (1H, d, J = 1.4 Hz), 7.59 (1H, d, J = 1.4 Hz), 7.63 (1H, s, CONH, exch). IR (KBr): 3410, 2946, 1654, 1528, 1419, 1311, 1262, 1128 cm^{-1}. HREIMS found: 392.18101. Calculated for $C_{17}H_{24}N_6O_5$: 392.18082.

***N*-[3-(Dimethylamino)propyl]-1-methyl-4-{[(2-methyl-5-nitro-3-thienyl)carbonyl]amino}-1*H*-pyrrole-2-carboxamide [(NO$_2$)ThiMe-PyrMe-Dmap]** was prepared using the acid chloride method in dichloromethane solution in the presence of *N*-methylmorpholine. The crude product was applied to a silica gel column chromatography using methanol/ethyl acetate/triethylamine 1/1/0.05. The product was obtained as a yellow solid (440 mg, 69%), mp 180−183 °C, R_f = 0.4. ^{1}H NMR (DMSO-d_6): δ 10.27 (1H, s), 8.52 (1H, s), 8.11 (1H, t, J = 5.6 Hz), 7.23 (1H, d, J = 1.8 Hz), 6.84 (1H, d, J = 1.8 Hz), 3.81 (3H, s), 3.20 (2H, q, J = 6.7 Hz), 2.76(3H, s), 2.39 (2H, t, J = 4.5 Hz), 2.25 (6H, s), 1.65 (2H, quintet, J = 7.1 Hz). IR (KBr): 1655, 1621, 1573, 1530, 1437, 1326, 1267 cm^{-1}. HRFABMS found: 394.15481. Calculated for $C_{17}H_{24}N_5O_4S$: 394.15490.

1-Isopentyl-*N*-[1-methyl-5-({[3-(4-methyl-1-piperazinyl)-amino}carbonyl)-1*H*-pyrrol-3-yl]-4-nitro-1*H*-pyrrole-2-carboxamide [(NO$_2$)Pyr*i*Pe-PyrMe-MepipP] was prepared by the acid chloride method in dichloromethane in the presence of *N*-methylmorpholine. The crude product was purified by column chromatography using silica gel and 1/2/0.1 methanol/ethyl acetate/triethylamine. The product was obtained as a glassy yellow material (R_f = 0.45) (278 mg, 84%) with no distinct melting point. ^{1}H NMR (DMSO-d_6): δ 10.21 (1H, s), 8.23 (1H, d, J = 1.8 Hz), 8.05 (1H, t, J = 5.4 Hz), 7.54 (1H, d, J = 1.8 Hz), 7.18 (1H, d, J = 1.8 Hz), 6.82 (1H, d, J = 1.8 Hz), 4.43 (2H, t, J = 7.4 Hz), 3.81 (3H, s), 3.21−3.16 (2H, q, J = 6.6 Hz), 2.32−2.28 (10H, m), 2.15 (3H, s), 1.66−1.59 (4H, quintet, J = 6.7 Hz), 1.55−1.47 (1H, m), 0.90 (6H, d, J = 6.5 Hz). IR (KBr): 2951, 2805, 1642, 1575, 1532, 1506, 1437, 1312 cm^{-1}. HRFABMS found: 488.29707. Calculated for $C_{24}H_{38}N_7O_4$: 488.29853.

1-Isopentyl-*N*-[1-methyl-5-({[3-(4-morpholinyl)propyl]-amino}carbonyl)-1*H*-pyrrol-3-yl]-4-nitro-1*H*-pyrrole-2-carboxamide [(NO$_2$)Pyr*i*Pe-PyrMe-Morp] was prepared by the acid chloride method in dichloromethane in the presence of *N*-methylmorpholine. The crude product was purified by column chromatography using silica gel and 1/2/0.1 methanol/ethyl acetate/triethylamine. Fractions containing the pure material (R_f = 0.45) were collected and the solvents removed under reduced pressure to give yellow glassy material, which was dissolved in small amount of ethyl acetate and precipitated with *n*-hexane to give the required product as a yellow powder (670 mg, 79%), mp 155−158 °C. ^{1}H NMR (CDCl$_3$): δ 7.64 (1H, d, J = 1.7 Hz), 7.60 (1H, s), 7.22 (1H, unresolved triplet), 7.18 (1H, d, J = 1.7 Hz), 7.07 (1H, d, J = 1.7 Hz), 6.66 (1H, d, J = 1.6 Hz), 4.43 (2H, t, J = 7.5 Hz), 3.93 (3H, s), 3.77 (2H, t, J = 4.6 Hz), 3.49 (2H, q, J = 5.6 Hz), 2.52 (6H, m), 1.80−1.58 (5H, m), 0.97 (6H, d, J = 6.5 Hz). IR (KBr): 1647, 1589, 1513, 1399, 1309, 1252, 1114 cm^{-1}. HRFABMS found: 475.26789. Calculated for $C_{23}H_{35}N_6O_5$: 475.26689.

Trimers. Amino precursors were prepared as for the dimers by hydrogenation over Pd on C (10%).

***N*-[5-({[5-({[3-(Dimethylamino)propyl]amino}carbonyl)-1-methyl-1*H*-pyrrol-3-yl]amino}carbonyl)-1-ethyl-1*H*-pyrrol-3-yl]-1-methyl-4-nitro-1*H*-pyrrole-2-carboxamide [(NO$_2$)PyrMe-PyrEt-PyrMeDmap]** was prepared using (NO$_2$)PyrMeCCl$_3$ in THF solution. The crude product was purified by column chromatography (silica gel, 49:49:2 ethyl acetate/methanol/ammonia). Fractions containing the required material (R_f = 0.1) were collected. The product was obtained as a yellow solid (261 mg, 71%) with no distinct melting point. ^{1}H NMR (DMSO-d_6): δ 1.23−1.30 (3H, t, J = 7.2 Hz), 1.68−1.76 (2H, m), 2.39 (6H, s), 2.56−2.58 (2H, t, J = 6.8 Hz), 3.18−3.24 (2H, quintet, J = 6.1 Hz), 3.79 (3H, s), 3.97 (3H, s), 4.31−4.36 (2H, q, J = 7.2 Hz), 6.89 (1H, d, J = 2.0 Hz), 7.02 (1H, d, J = 2.0 Hz), 7.22 (1H, d, J = 2.0 Hz), 7.33 (1H, d, J = 2.0 Hz), 7.59 (1H, d, J = 2.0 Hz), 8.09−8.12 (1H, t, J = 5.8 Hz), 8.18 (1H, d, J = 2.0 Hz), 9.93 (1H, s), 10.29 (1H, s). IR (KBr): 3419, 3122, 2929, 1647, 1579, 1533, 1502, 1398, 1307 cm^{-1}. HRFABMS found: 513.25735. Calculated for $C_{24}H_{33}N_8O_5$: 513.25739.

***N*-[5-({[3-(Dimethylamino)propyl]amino}carbonyl)-1-isopropyl-1*H*-pyrrol-3-yl]-1-isopropyl-4-{[(1-isopropyl-4-nitro-1*H*-pyrrol-2-yl)carbonyl]amino}-1*H*-pyrrole-2-carboxamide [(NO$_2$)Pyr*i*Pr-Pyr*i*Pr-Pyr*i*Pr-Dmap].** The nitro dimer (NO$_2$)Pyr*i*Pr-Pyr*i*Pr-Dmap (209 mg, 0.483 mmol) was dissolved in ethanol (20 mL) at 0 °C with stirring. Pd/C (10%, 180 mg) was added to the solution at 0 °C and under N_2 with stirring. The reaction mixture was hydrogenated for 4 h and then the catalyst was removed by filtration over Kieselguhr and the solvent removed under reduced pressure at 50 °C. The carboxylic acid (92 mg, 0.462 mmol) was dissolved in thionyl chloride (3 mL) and heated under reflux for 3 h. Excess thionyl chloride was removed under reduced pressure at 50 °C. The amine was dissolved in THF (20 mL, dry) to which the acid chloride [dissolved in THF (20 mL, dry)] was added dropwise with stirring at room temperature. The reaction mixture was left stirring at room temperature overnight. The solvent was removed under reduced pressure and the crude product dissolved in dichloromethane (2 × 50 mL), after which it was extracted with Na_2CO_3 (50 mL, 5%). The organic layer was dried and then the solvent removed. The crude product was chromatographed over silica gel using 49.5:49.5:1 ethyl acetate/methanol/triethylamine as eluant. The product was obtained as a yellow glassy material, R_f = 0.15 (230 mg, 82% yield), mp 130−133 °C (softening). ^{1}H NMR (CDCl$_3$): δ 1.43 (6H, d, J = 6.7 Hz), 1.47 (6H, d, J = 6.7 Hz), 1.52 (6H, d, J = 6.7 Hz), 1.73−1.79 (2H, m), 2.32 (6H, s), 2.47−2.50 (2H, t, 6.1 Hz), 3.46−3.50 (2H, q, 6.0 Hz), 5.53−5.61 (3H, m), 6.42 (1H, d, J = 1.6 Hz), 6.60 (1H, d, J = 1.6 Hz), 7.28 (1H, d, J = 1.6 Hz), 7.40 (1H, d, J = 1.6 Hz), 7.41 (1H,s), 7.44 (1H, s), 7.63 (1H, s, br, CONH), 7.81 (1H, d, J = 1.6 Hz), 8.02 (1H, s). IR (KBr): 2979, 2937, 1645, 1593, 1525, 1504, 1410, 1279, 1237, 1190 cm^{-1}. HRFABMS found: 583.33440. Calculated for $C_{29}H_{43}N_8O_5$: 583.33564.

***N*-[5-({[3-(Dimethylamino)propyl]amino}-1-methyl-1*H*-pyrrol-3-yl]-1-isopropyl-4-{[(1-methyl-4-{[(1-methyl-4-nitro-1*H*-pyrrol-2-yl)carbonyl]amino}-1*H*-pyrrole-2-carboxamide [(NO$_2$)PyrMe-Pyr*i*Pr-PyrMe-Dmap]** was prepared using (NO$_2$)PyrMeCCl$_3$ in THF solution. The crude product was purified by silica gel column chromatography ethyl acetate/methanol/ammonia (49/49/2). Fractions containing the product (R_f = 0.3) were collected. The product was obtained as a yellow solid (221 mg, 63%) with no distinct melting point. ^{1}H NMR (DMSO-d_6): δ 1.36−1.38 (6H, d, J = 6.7 Hz), 1.64−1.71 (2H, m), 2.31 (6H, s), 3.16−3.22 (2H, q, J = 6.7 Hz), 3.81 (3H, s), 3.96 (3H, s), 5.40−5.50 (1H, m), 6.85 (1H, d, J = 1.6 Hz), 6.93 (1H, d, J = 1.6 Hz), 7.18 (1H, d, J = 1.6 Hz), 7.43 (1H, d, J = 1.6 Hz), 7.58 (1H, d, J = 1.6 Hz), 8.07−8.10 (1H, t, J = 5.8 Hz), 8.18 (1H, d, J = 1.6 Hz), 9.96 (1H, s), 10.29 (1H, s). IR (KBr): 1643, 1579, 1534, 1507, 1464, 1407, 1310, 1247 cm^{-1}. HRFABMS found: 527.27341. Calculated for $C_{25}H_{35}N_8O_5$: 527.27304.

***N*-[5-({[5-({[3-(Dimethylamino)propyl)-1-methyl-1*H*-**

pyrrol-3-yl]amino}carbonyl)-1-methyl-1*H*-pyrrol-3-yl]-1-methyl-4-nitro-1*H*-pyrrole-2-carboxamide [(NO_2)PyrMe-PyrMe-PyrMe-Dmap] was prepared using (NO_2)PyrMeCCl_3 in THF solution. The crude product was chromatographed over flash silica gel using methanol/ethyl acetate/ammonia (49/49/2). The product was obtained as a yellow solid (1.050 g, 70%), $R_f = 0.1$, mp 198−200 °C. (lit.[32] mp 203−205 °C).

^{1}H NMR (DMSO-d_6) δ 1.57−1.63(2H, t, $J = 7.2$ Hz), 2.13 (6H, s), 2.20−2.26 (2H, t, $J = 6.8$ Hz), 3.15−3.19 (2H, m), 3.79 (3H, s), 3.85 (3H, s), 3.96 (3H, s), 6.81 (1H, d, $J = 1.9$ Hz), 7.02 (1H, d, $J = 1.9$ Hz), 7.19 (1H, d, $J = 1.9$ Hz), 7.27 (1H, d, $J = 1.9$ Hz), 7.59 (1H, d, $J = 1.9$ Hz), 8.09 (1H, t, $J = 5.8$ Hz), 8.19 (1H, d, $J = 1.9$ Hz), 9.95 (1H, s), 10.30 (1H, s). IR (KBr): 1647, 1580, 1533, 1502, 1398, 1307 cm^{-1}.

***N*-[5-({[3-(Dimethylamino)propyl]amino}carbonyl)-1-isopropyl-1*H*-pyrrol-3-yl]-1-isopropyl-4-{[(1-isopropyl-4-nitro-1*H*-pyrrol-2-yl)carbonyl]amino}-1*H*-pyrrole-2-carboxamide [(NO_2)Pyr*i*Pr-Pyr*i*Pr-Pyr*i*Pr-Dmap]** was prepared using the acid chloride method. The crude product was chromatographed on silica gel using 49.5:49.5:1 ethyl acetate/methanol/triethylamine as eluant. The product was obtained as a yellow glassy material $R_f = 0.15$, (230 mg, 82%), mp 130−133 °C (softening). ^{1}H NMR ($CDCl_3$): δ 1.43 (6H, d, $J = 6.7$ Hz), 1.47 (6H, d, $J = 6.7$ Hz), 1.52 (6H, d, $J = 6.7$ Hz), 1.73−1.79 (2H, m), 2.32 (6H, s), 2.47−2.50 (2H, t, 6.1 Hz), 3.46−3.50 (2H, q, 6.0 Hz), 5.53−5.61 (3H, m), 6.42 (1H, d, $J = 1.6$ Hz), 6.60 (1H, d, $J = 1.6$ Hz), 7.28 (1H, d, $J = 1.6$ Hz), 7.40 (1H, d, $J = 1.6$ Hz), 7.41 (1H,s), 7.44 (1H, s), 7.63 (1H, s, br, CONH), 7.81 (1H, d, $J = 1.6$ Hz), 8.02 (1H, s). IR (KBr): 2979, 2937, 1645, 1593, 1525, 1504, 1410, 1279, 1237, 1190 cm^{-1}. HRFABMS found: 583.33440. Calculated for $C_{29}H_{43}N_8O_5$: 583.33564.

***N*-[5-({[5-({[3-(Dimethylamino)propyl]amino}carbonyl)-1-isopentyl-1*H*-pyrrol-3-yl]amino}carbonyl)-1-isopentyl-1*H*-pyrrol-3-yl]-1-isopentyl-4-nitro-1*H*-pyrrole-2-carboxamide [(NO_2)Pyr*i*Pe-Pyr*i*Pe-Pyr*i*Pe-Dmap]** was prepared using the acid chloride method in THF containing *N*-methylmorpholine. The crude product was purified by column chromatography using methanol/ethyl acetate/triethylamine (100:100:1) to give the product as a yellow glassy material, $R_f = 0.20$, (223 mg, 82%). mp 110−115 °C (transparent). ^{1}H NMR ($CDCl_3$): δ 0.93 (6H, d, $J = 1.6$ Hz), 0.95 (6H, d, $J = 5.6$ Hz), 0.98 (6H, d, $J = 3.7$ Hz), 1.57−1.78 (5H, m), 2.47 (6H, s), 2.70 (2H, m), 3.49 (2H, m), 4.31−4.49 (6H, m), 6.57 (1H, s), 7.28 (1H, s), 7.33 (1H, s), 7.41 (1H, s), 7.44 (1H. s), 7.61 (1H, s), 7.64 (1H, d, $J = 1.8$ Hz), 7.75 (1H, s), 8.22 (1H, s). IR (KBr): 2953, 1646, 1583, 1534, 1505, 1464, 1422, 1311 cm^{-1}. HRFABMS found: 667.42932. Calculated for $C_{35}H_{55}O_5N_8$: 667.42954.

***N*-[1-(Cyclopropylmethyl)-5-({[5-({[3-(dimethylamino)-propyl]amino}carbonyl)-1-methyl-1*H*-pyrrol-3-yl]amino}-carbonyl)-1*H*-pyrrol-3-yl]-1-methyl-4-nitro-1*H*-pyrrole-2-carboxamide [(NO_2)PyrMe-PyrCycpr-PyrMe-Dmap]** was prepared using HBTU in DMF in the presence of *N*-methylmorpholine. The crude product obtained was purified by column chromatography using silica gel and 1/2/0.1 methanol/ethyl acetate/triethylamine. Fractions containing the pure product (R_f = 0.4) were collected and the solvents were removed under reduced pressure at 50 °C to give the required product as a glassy yellow solid (110 mg, 71%) with no distinct melting point. ^{1}H NMR (DMSO-d_6): δ 10.27 (1H, s), 9.94 (1H, s), 8.18 (1H, d, $J = 1.7$ Hz), 8.06 (1H, t, $J = 5.2$ Hz), 7.59 (1H, d, $J = 1.9$ Hz), 7.36 (1H, d, 1.9 Hz), 7.18 (1H, d, $J = 1.9$ Hz), 7.02 (1H, d, $J = 1.9$ Hz), 6.83 (1H, d, $J = 1.9$ Hz), 4.19 (2H, d, $J = 7.0$ Hz), 3.97 (3H, s), 3.80 (3H, s), 3.21−3.16 (2H, q, $J = 6.9$ Hz), 2.26 (2H, t, $J = 7.1$ Hz), 2.15 (6H, s), 1.65−1.58 (2H, quintet, $J = 7.1$ Hz), 1.26−1.13 (1H, m), 0.47−0.42 (2H, m), 0.33−0.31 (2H, m). IR (KBr): 3286, 3126, 2938, 1646, 1580, 1531, 1462, 1439, 1400, 1309, 1248 cm^{-1}. HRFABMS found: 539.27295. Calculated for $C_{26}H_{35}N_8O_5$: 539.27304.

1-Cyclopentyl-*N*-[5-({[3-(dimethylamino)propyl]amino}-carbonyl)-1-methyl-1*H*-pyrrol-3-yl]-4-{[(1-methyl-4-nitro-1*H*-pyrrol-2-yl)carbonyl]amino}-1*H*-pyrrole-2-carboxamide [(NO_2)PyrMe-PyrCycpr-PyrMe-Dmap] was prepared using HBTU in DMF in the presence of *N*-methylmorpholine. The crude product was purified by column chromatography using silica gel and 1/2/0.1 methanol/ethyl acetate/triethylamine, $R_f = 0.40$. The product was obtained as a glassy solid material with no distinct melting point (110 mg, 55%). ^{1}H NMR (DMSO-d_6): δ 10.28 (1H, s), 9.96 (1H, s), 8.18 (1H, d, $J = 1.8$ Hz), 8.07 (1H, t, $J = 5.2$ Hz), 7.58 (1H, d, $J = 1.8$ Hz), 7.41 (1H, d, $J = 1.8$ Hz), 7.18 (1H, d, $J = 1.8$ Hz), 6.93 (1H, d, $J = 1.8$ Hz), 6.85 (1H, d, $J = 1.8$ Hz), 5.53 (1H, quintet, $J = 7.3$ Hz), 3.97 (3H, s), 3.80 (3H, s), 3.20 (2H, m), 2.83 (2H, m), 2.42 (2H, t, $J = 7.2$ Hz), 2.27 (6H, s), 2.09 (2H, m), 1.79−1.64 (6H, m). IR (KBr): 1642, 1584, 1529, 1505, 1403, 1309 cm^{-1}. HRFABMS found: 553.28890. Calculated for $C_{27}H_{37}N_8O_5$: 553.28869.

***N*-[5-({[5-({[3-(Dimethylamino)propyl]amino}carbonyl)-1,2-dimethyl-1*H*-pyrrol-3-yl]amino}carbonyl)-1,2-dimethyl-1*H*-pyrrol-3-yl]-1,5-dimethyl-4-nitro-1*H*-pyrrole-2-carboxamide [(NO_2)PyrMe$_2$-PyrMe$_2$-PyrMe$_2$-Dmap]** was prepared using EDC in DMF solution in the presence of 4-(dimethylamino)pyridine. The crude product was purified by silica gel column chromatography using methanol/ethyl acetate (1/4, containing 1% triethylamine). The pure product ($R_f = 0.1$) was collected and the solvent removed under reduced pressure to give a pale yellow oil (80 mg, 64%), with no distinct melting point. ^{1}H NMR(DMSO-d_6): δ 1.55−1.62 (2H, quintet, $J = 5.9$ Hz, CH_2), 2.07 (3H, s, C-CH_3), 2.11 (6H, s, NMe_2), 2.12 (3H, s, C-CH_3), 2.20−2.23 (2H, t, $J = 5.9$ Hz, CH_2), 2.62 (3H, s, C-CH_3), 3.14−3.19 (2H, q, $J = 5.9$ Hz, CH_2), 3.76 (3H, s, NMe), 3.79 (3H, s, NMe), 3.86 (3H, s, NMe), 6.76 (1H, s), 7.00 (1H, s), 7.58 (1H, s), 7.89−7.90 (1H, t, $J = 5.6$ Hz, CONH, exch), 9.02 (1H, s, CONH, exch), 9.56 (1H, s, CONH, exch). IR (KBr): 2940, 2863, 1638, 1589, 1521, 1458, 1404, 1314, 1249, 1189, 1168 cm^{-1}. HRFABMS found: 541.28620. Calculated for $C_{26}H_{37}N_8O_5$: 541.28869.

***N*-[5-({[5-({[3-(Dimethylamino)propyl]amino}carbonyl)-1-methyl-1*H*-pyrrol-3-yl]amino}carbonyl)-1-isopentyl-1*H*-pyrrol-3-yl]-1-methyl-4-nitro-1*H*-pyrrole-2-carboxamide [(NO_2)PyrMe-Pyr*i*Pe-PyrMe-Dmap]** was prepared by the acid chloride method in dichloromethane solution in the presence of *N*-methylmorpholine. The product was purified by column chromatography using 1/3/0.03 methanol/ethyl acetate/triethylamine. Fractions containing the product ($R_f = 0.2$) were collected and the solvents were removed under reduced pressure at 50 °C to give the product as a yellow solid (335 mg, 78%), mp 110−115 °C (transparent). ^{1}H NMR (DMSO-d_6): δ 10.27 (1H, s), 9.91 (1H, s), 8.18 (1H, d, $J = 1.8$ Hz), 8.10−8.07 (1H, t, $J = 5.5$ Hz), 7.59 (1H, d, $J = 1.8$ Hz), 7.31 (1H, d, $J = 1.8$ Hz), 7.17 (1H, d, $J = 1.8$ Hz), 6.98 (1H, d, $J = 1.8$ Hz), 6.90 (1H, d, $J = 1.8$ Hz), 6.82 (1H, d, $J = 1.8$ Hz), 4.35−4.31 (2H, t, $J = 7.0$ Hz), 3.96 (3H, s), 3.80 (3H, s), 3.22−3.17 (2H, q, $J = 6.7$ Hz), 2.36−2.32 (2H, t, $J = 7.1$ Hz), 2.21 (6H, s), 1.67−1.62 (2H, q, $J = 7.0$ Hz), 1.60−1.44 (3H, m), 1.04−0.99 (2H, m), 0.89−0.88 (6H, d, $J = 6.7$ Hz). IR (KBr): 3401, 3289, 1643, 1582, 1533, 1594, 1463, 1400, 1309, 1253 cm^{-1}. HRFABMS found: 555.30169. Calculated for $C_{27}H_{39}N_8O_5$: 555.30434.

***N*-[3-(Dimethylamino)propyl]-5-methyl-2-({[(1-methyl-4-{[(1-methyl-4-nitr o-1*H*-pyrrol-2-yl)carbonyl]amino}-1*H*-pyrrol-2-yl)carbonyl]amino}methyl)-1,3-oxazole-4-carboxamide [(NO_2)PyrMe-PyrMe-OxaMe-Dmap]** was prepared by the acid chloride method in dichloromethane. The crude product was purified by flash chromatography using methanol/ethyl acetate 1/1 containing 1% triethylamine. The product was obtained as a pale yellow solid, $R_f = 0.2$ (54 mg, 71%) with no distinct melting point. ^{1}H NMR ($CDCl_3$): δ 1.74−1.83 (2H, quintet, $J = 6.8$ Hz, CH_2), 2.30 (6H, s, NMe_2), 2.45−2.48 (2H, t, $J = 7.0$ Hz, CH_2NMe_2), 2.65 (3H, s, oxazole-CH_3), 3.44−3.49 (2H, q, $J = 7.4$ Hz, CONHCH_2), 3.90 (3H, s, NMe), 3.99 (3H, s, NMe), 4.61−4.63 (2H, d, $J = 5.2$ Hz, CONH-CH_2-oxazole), 6.48−6.50 (1H, t, 5.0 Hz, CONH, exch), 6.73 (1H, d, $J = 1.4$ Hz), 7.27 (1H, d, $J = 1.4$ Hz), 7.32 (1H, d, $J = 1.4$ Hz), 7.60−7.60 (1H, pyrrole and 1H, CONH, exch), 8.35(1H, s, CONH, exch). IR (KBr): 3412, 3138, 2934, 1657, 1529, 1446,

1312, 1261 cm^{-1}. HRFABMS found: 515.23487. Calculated for $C_{23}H_{31}N_8O_6$: 515.23666.

***N*-[3-(Dimethylamino)propyl]-4-isopropyl-2-{[(1-methyl-4-{[(1-methyl-4-nitro-1*H*-pyrrol-2-yl)carbonyl]amino}-1*H*-pyrrol-2-yl)carbonyl]amino}-1,3-thiazole-5-carboxamide [(NO_2)PyrMe-PyrMe-*iso*Thz*i*Pr-Dmap]** was prepared using (NO_2)PyrMe-CCl_3 in THF solution. The crude product was chromatographed using 49/49/2 methanol/ethyl acetate/triethylamine. The product obtained was dissolved in dichloromethane, extracted with a solution of sodium carbonate (10 mL, 5%), and then dried, and the solvent was removed under reduced pressure. The product was obtained as a yellow solid (140 mg, 54%) mp 240−244 °C. ^{1}H NMR ($CDCl_3$) δ 1.27 (6H, d, J = 6.8 Hz, 2Me), 1.76 (2H, m, CH_2), 2.32 (6H, s, NMe_2), 2.49 (2H, t, J = 7.0 Hz, CH_2), 3.52 (2H, q, J = 5.4 Hz, CH_2), 3.88 (1H, m, CH), 4.01 (3H, s, NMe), 4.05 (3H, s, NMe), 6.84 (1H, s, PyrH), 7.25 (1H, s, PyrH), 7.36 (1H, s, PyrH), 7.62 (1H, s, PyrH), 7.84 (1H, s, CONH, exch), 7.95 (1H, t, unresolved, CONH, exch), 9.50 (1H, br, CONH, exch). IR (KBr): 1654, 1625, 1585, 1549, 1526, 1503, 1464, 1418, 1398, 1310, 1277 cm^{-1}. HRFABMS found: 545.23168. Calculated for $C_{24}H_{33}N_8O_5S$: 545.22946.

***N*-[3-(Dimethylamino)propyl]-5-isopropyl-2-{[(1-methyl-4-{[(1-methyl-4-nitro-1*H*-pyrrol-2-yl)carbonyl]amino}-1*H*-pyrrol-2-yl)carbonyl]amino}-1,3-thiazole-4-carboxamide [(NO_2)PyrMe-PyrMe-Thz*i*Pr-Dmap]** was prepared using (NO_2)PyrMe-CCl_3 in THF solution. The crude product was chromatographed using 49/49/2 methanol/ethyl acetate/triethylamine. The product obtained was dissolved in dichloromethane, extracted with a solution of sodium carbonate (10 mL, 5%), and then dried, and the solvent was removed under reduced pressure. The product was obtained as a yellow solid (90 mg, 44%), mp 138−141 °C. ^{1}H NMR (DMSO-d_6) δ 1.26 (6H, d, J = 6.8 Hz, 2Me), 1.65 (2H, m, CH_2), 2.19 (6H, s, NMe_2), 2.32 (2H, t, J = 5.2 Hz, CH_2), 3.26 (2H, q, J = 5.4 Hz, CH_2), 3.90 (3H, s, NMe), 3.97 (3H, s, NMe), 4.19 (1H, m, CH), 7.36 (1H, d, J = 1.8 Hz, PyrH), 7.47 (1H, d, J = 1.8 Hz, pyrH), 7.62 (1H, d, J = 1.8 Hz, PyrH), 7.81 (1H, t, 5.9 Hz, CONH exch), 8.19 (1H, d, J = 1.8 Hz, PyrH), 10.35 (1H, s, CONH exch), 12.10 (1H, br, exch). IR (KBr): 1651, 1552, 1506, 1464, 1421, 1398, 1311, 1288, 1202 cm^{-1}. HRFABMS found: 545.22931. Calculated for $C_{24}H_{33}N_8O_5S$: 545.22946.

***N*-[5-({[3-(Dimethylamino)propyl]amino}carbonyl)-1-methyl-1*H*-pyrrol-3-yl]-5-isopropyl-2-{[(1-methyl-4-nitro-1*H*-pyrrol-2-yl)carbonyl]amino}-1,3-thiazole-4-carboxamide [(NO_2)PyrMe-Thz*i*Pr-PyrMe-Dmap]** was prepared using HBTU in DMF solution in the presence of *N*-methylmorpholine. The crude product obtained was chromatographed over silica gel using 1:1:0.2 methanol/ethyl acetate/triethylamine. The product was obtained as a yellow glassy material (415 mg, 72%) with no distinct melting point. ^{1}H NMR (DMSO-d_6): δ 9.59 (1H, s), 8.23 (1H, s), 8.09−8.03 (1H, t, J = 5.5 Hz), 7.82 (1H, s), 7.24 (1H, d, J = 1.8 Hz), 6.90 (1H, d, J = 1.8 Hz), 4.22−4.15 (1H, heptet, J = 6.7 Hz), 4.00 (3H, s), 3.81 (3H, s), 3.24−3.17 (2H, q, J = 6.7 Hz), 2.37−2.34 (2H, t, J = 3.2 Hz), 2.22 (6H, s), 1.68−1.61 (2H, quintet, J = 7.0 Hz), 1.29 (6H, d, J = 6.9 Hz). IR (KBr): 1644, 1551, 1500, 1465, 1402, 1309, 1283, 1194, 1100 cm^{-1}. HRFABMS found: 545.22962. Calculated for $C_{24}H_{33}N_8O_5S$: 545.22946.

***N*-[3-(Dimethylamino)propyl]-1-methyl-4-{[(2-methyl-5-{[(1-methyl-4-nitro-1*H*-pyrrol-2-yl)carbonyl]amino}-3-thienyl)carbonyl]amino}-1*H*-pyrrole-2-carboxamide [(NO_2)PyrMe-ThiMe-PyrMe-Dmap]** was prepared by the acid chloride method in dichloromethane in the presence of *N*-methylmorpholine. The crude product was applied to a silica gel column chromatography using methanol/ethyl acetate/triethylamine (1/1/0.05). The product was obtained as a yellow solid (170 mg, 56%), mp 150−154 °C (softening), R_f = 0.33. ^{1}H NMR (DMSO-d_6): δ 11.39 (1H, s), 9.91 (1H, s), 8.21 (1H, d, J = 1.8 Hz), 8.05 (1H, t, J = 5.6 Hz), 7.67 (1H, d, J = 1.8 Hz), 7.00 (1H, s), 6.77 (1H, d, J = 1.8 Hz), 3.93 (3H, s), 3.77 (3H, s), 3.16 (2H, q, J = 6.4 Hz), 2.50 (3H, s), 2.29 (2H, t, J = 6.9 Hz), 2.17 (6H, s), 1.59 (2H, quintet, J = 6.9 Hz). IR (KBr): 1640, 1535, 1466, 1433, 1412, 1311, 1261 cm^{-1}. HRFABMS found: 516.20321. Calculated for $C_{23}H_{30}N_7O_5S$: 516.20291.

***N*-[5-({[3-(Dimethylamino)propyl]amino}carbonyl)-1-methyl-1*H*-pyrrol-3-yl]-1-methyl-4-{[(2-methyl-5-nitro-3-thienyl)carbonyl]amino}-1*H*-pyrrole-2-carboxamide [(NO_2)ThiMe-PyrMe-PyrMe-Dmap]** was prepared using the acid chloride method in dichloromethane solution in the presence of *N*-methylmorpholine. The crude product was applied to a silica gel column and eluted using methanol/ethyl acetate/triethylamine (1/1/0.05). The product was obtained as an orange solid material (R_f = 0.2) after reprecipitation from methanol/ethyl acetate/*n*-hexane (468 mg, 67% yield), mp 195−198 °C. ^{1}H NMR (DMSO-d_6): 10.33 (1H, s), 9.93 (1H, s), 8.54 (1H, s), 8.06 (1H, t, J = 5.5 Hz), 7.30 (1H, d, J = 1.8 Hz), 7.19 (1H, d, J = 1.8 Hz), 7.04 (1H, d, J = 1.8 Hz), 6.83 (1H, d, J = 1.8 Hz), 3.86 (3H, s), 3.80 (3H, s), 3.21 (2H, q, J = 6.7 Hz), 2.77 (3H, s), 2.31 (2H, t, J = 6.9 Hz), 2.19 (6H, s), 1.62 (2H, quintet, J = 6.9 Hz). IR (KBr): 1638, 1541, 1465, 1434, 1405, 1330, 1263 cm^{-1}. HRFABMS found: 516.20501. Calculated for $C_{23}H_{30}N_7O_5S$: 516.20291.

***N*-[5-({[3-(Dimethylamino)propyl]amino}carbonyl)-1-methyl-1*H*-pyrrol-3-yl]-1-isopentyl-4-{[(2-methyl-5-nitro-3-thienyl)carbonyl]amino}-1*H*-pyrrole-2-carboxamide [(NO_2)ThiMe-Pyr*i*Pe-PyrMe-Dmap]** was prepared by the acid chloride method in dichloromethane in the presence of *N*-methylmorpholine. The crude product was purified by column chromatography using ethyl acetate/methanol/triethylamine (2.5/2.5/0.6), R_f = 0.5. The product was obtained as an amorphous yellow material (237 mg, 90%) with no distinct melting point. ^{1}H NMR (DMSO-d_6): δ 10.37 (1H, s), 9.94 (1H, s), 8.58 (1H, s), 8.12 (1H, t, J = 5.6 Hz), 7.35 (1H, d, J = 1.7 Hz), 7.18 (1H, d, J = 1.7 Hz), 7.14 (1H, d, J = 1.7 Hz), 7.01 (1H, d, J = 1.7 Hz), 6.86 (1H, d, J = 1.7 Hz), 4.34 (1H, t, J = 6.9 Hz), 3.80 (3H, s), 3.22 (2H, q, J = 6.5 Hz), 2.77 (3H, s), 2.64 (2H, m), 2.44 (6H, s), 1.73 (2H, quintet, J = 6.7 Hz), 1.59−1.45 (3H, m), 0.90 (6H, d, J = 6.4 Hz). IR (KBr): 1675, 1650, 1583, 1537, 1465, 1437, 1403, 1263, 1202, 1133 cm^{-1}. HRFABMS found: 572.26551. Calculated for $C_{27}H_{37}N_7O_5S$: 572.26580.

1-Isopropyl-*N*-[1-methyl-5-({[3-(4-morpholinyl)propyl]-amino}carbonyl)-1*H*-pyrrol-3-yl]-4-{[(1-methyl-4-nitro-1*H*-pyrrol-2-yl)carbonyl]amino}-1*H*-pyrrole-2-carboxamide [(NO_2)PyrMe-Pyr*i*Pr-PyrMe-Morp] was prepared using HBTU in DMF solution in the presence of *N*-methylmorpholine. The crude product was chromatographed using flash silica gel and methanol/ethyl acetate/triethylamine (1:3:0.1), R_f = 0.30. Fractions containing the pure material were collected and solvents were removed under reduced pressure at 40 °C to give a semisolid glassy yellow material (170 mg, 53%) with no distinct melting point. ^{1}H NMR (DMSO-d_6): δ 10.30 (1H, s), 9.98 (1H, s), 8.19 (1H, s), 8.03−8.01 (1H, t, J = 5.5 Hz), 7.59 (1H, s), 7.44 (1H, s), 7.18 (1H, s), 6.92 (1H, s), 6.85 (1H, s), 5.48−5.42 (1H, heptet, J = 6.4 Hz), 3.96 (3H, s), 3.79 (3H, s), 3.57−3.56 (4H, t, unresolved), 3.22−3.17 (2H, q, J = 6.8 Hz), 2.32 (2H, q, J = 6.8 Hz), 1.67−1.60 (2H, quintet, J = 6.8 Hz), 1.37−1.36 (6H, d, J = 6.8 Hz), 1.04−1.01 (2H, m). IR (KBr): 3425, 2927, 1662, 1653, 1582, 1543, 1502, 1410, 1307, 1251, 1203, 1115, 848 cm^{-1}. HRFABMS found: 569.28147. Calculated for $C_{27}H_{37}N_8O_6$: 569.28361.

***N*-[1-Isopropyl-5-({[1-methyl-5-({[3-(1-pyrrolidinyl)-propyl]amino}carbonyl)-1*H*-pyrrol-3-yl]amino}carbonyl)-1*H*-pyrrol-3-yl]-1-methyl-4-nitro-1*H*-pyrrole-2-carboxamide [(NO_2)PyrMe-Pyr*i*Pr-PyrMe-Morp]** was prepared using HBTU in DMF solution in the presence of *N*-methylmorpholine. The product was purified by column chromatography using methanol/ethyl acetate/triethylamine (1/2/0.1). The product was obtained as a yellow solid (239 mg, 62%) with no distinct melting point. Some of this material was further purified by HPLC. ^{1}H NMR (DMSO-d_6): δ 10.28 (1H, s), 9.97 (1H, s), 9.46 (1H, br, TFA), 8.19 (1H, s), 8.14 (1H, t, J = 5.5 Hz), 7.58 (1H, s), 7.43 (1H, s), 7.18 (1H, s), 6.94 (2H, s), 5.45−5.43 (1H, m), 3.97 (3H, s), 3.81 (3H, s), 3.55 (2H, m), 3.26 (2H, m), 3.14 (2H, m), 2.99 (2H, m), 2.01 (2H, m), 1.86 (4H, m), 1.38−1.36 (6H, d, J = 6.8 Hz). IR (KBr): 3419, 3136, 1673,

1645, 1586, 1531, 1463, 1409, 1311, 1247, 1199, 1130 cm^{-1}. HRFABMS found: 553.29109. Calculated for $C_{27}H_{37}N_8O_5$: 553.28869.

***N*-[1-Isopentyl-5-({[1-methyl-5-({[3-(4-methyl-1-piperazinyl)propyl]amino}carbonyl)-1*H*-pyrrol-3-yl]amino}carbonyl)-1*H*-pyrrol-3-yl]-1-methyl-4-nitro-1*H*-pyrrole-2-carboxamide [(NO_2)PyrMe-Pyr*i*Pe-PyrMe-Mepipp]** was prepared by the acid chloride method in dichloromethane solution in the presence of *N*-methylmorpholine. Column chromatography (silica gel, 1/2/0.1 methanol/ethyl acetate/triethylamine) was used to purify the required material, which was obtained as a yellow glassy material (131 mg, 75%), R_f = 0.15 with no distinct melting point. ^{1}H NMR (DMSO-d_6): δ 10.27 (1H, s), 9.90 (1H, s), 8.18 (1H, d, J = 1.8 Hz), 8.01 (1H, t, J = 5.6 Hz), 7.59 (1H, d, J = 1.8 Hz), 7.31 (1H, d, J = 1.8 Hz), 7.16 (1H, d, J = 1.8 Hz), 6.98 (1H, J = 1.8 Hz), 6.84 (1H, d, J = 1.8 Hz), 4.33 (1H, t, J = 6.9 Hz), 3.96 (3H, s), 3.79 (3H, s), 3.17 (2H, q, J = 6.5 Hz), 2.32−2.29 (10mH, m), 2.16 (3H, s), 1.66−1.46 (5H, m), 0.89 (6H, d, J = 6.4 Hz). IR (KBr): 2949, 2803, 1650, 1588, 1531, 1506, 1399, 1309 cm^{-1}. HRFABMS found: 610.34797. Calculated for $C_{30}H_{44}N_9O_5$: 610.34654.

***N*-[1-Isopentyl-5-({[1-methyl-5-({[3-(4-morpholinyl)-propyl]amino}carbonyl)-1*H*-pyrrol-3-yl]amino}carbonyl)-1*H*-pyrrol-3-yl]-1-methyl-4-nitro-1*H*-pyrrole-2-carboxamide [(NO_2)PyrMe-Pyr*i*Pe-PyrMe-Morp]** was prepared by the acid chloride method in dichloromethane solution in the presence of *N*-methylmorpholine. The crude product was purified by column chromatography (1/2/0.1 methanol/ethyl acetate/triethylamine, R_f = 0.7). Fractions containing the required material were collected and the solvents were removed under reduced pressure. The yellow glassy residue was dissolved in dichloromethane and extracted with aqueous potassium hydroxide solution (10%, 5 mL). The organic layer was collected and dried ($MgSO_4$), and the solvent was removed under reduced pressure to give a yellow glassy material (115 mg, 67%) with no distinct melting point. ^{1}H NMR (acetone-d_6): δ 9.52 (1H, s), 9.26 (1H, s), 7.95 (1H, d, J = 1.7 Hz), 7.55 (1H, t, unresolved), 7.38 (1H, d, J = 1.9 Hz), 7.33 (1H, d, J = 1.9 Hz), 7.20 (1H, d, J = 1.9 Hz), 6.91 (1H, d, J = 1.9 Hz), 6.84 (1H, d, J = 1.9 Hz), 4.44 (2H, t, J = 7.2 Hz), 4.08 (3H, s), 3.89 (3H, s), 3.64 (4H, m), 3.37 (2H, t, J = 6.7 Hz), 2.42 (6H, m), 1.77−1.56 (5H, m), 0.95 (6H, d, J = 6.5 Hz). IR (KBr): 1640, 1588, 1524, 1464, 1399, 1310, 1252, 1114 cm^{-1}. HRFABMS 597.31332. Calculated for $C_{29}H_{41}N_8O_6$: 597.31491.

Distamycin Analogues. *N*-[5-({[5-({[3-(Dimethylamino)-propyl]amino}carbonyl)-1-methyl-1*H*-pyrrol-3-yl]amino}carbonyl)-1-methyl-1*H*-pyrrol-3-yl]-4-formylamino)-1-methyl-1*H*-pyrrole-2-carboxamide (Fo-PyrMe-PyrMe-pyrMe-Dmap, 1). *N*-[5-({[5-({[3-(Dimethylamino)propyl)-1-methyl-1*H*-pyrrol-3-yl]amino}carbonyl)-1-methyl-1*H*-pyrrol-3-yl]-1-methyl-4-nitro-1*H*-pyrrole-2-carboxamide (104 mg, 0.208 mmol) was dissolved in methanol to which was added Pd/C (106 mg, 10%). The reaction mixture was hydrogenated at room temperature and atmospheric pressure for 5 h. The catalyst was removed by filtration through Kieselguhr and the solvent removed under reduced pressure to give the amine, which was used without further purification. This amine was dissolved in ethanol (5 mL), to which was added ethyl formate (20 mL), and the reaction mixture was heated under reflux for 48 h. The solvent was removed under reduced pressure and the crude product purified by HPLC. The product was obtained as a white solid after freeze-drying (73 mg, 57%, as TFA salt). ^{1}H NMR (DMSO-d_6): δ 1.81−1.85 (2H, m), 2.79 (6H, s), 3.05−3.09 (2H, q, J = 6.7 Hz), 3.23−3.24 (2H, t, J = 3.6 Hz), 3.81 (3H, s), 3.84 (6H, s), 6.92 (1H, s), 6.94 (1H, s), 7.06 (1H, s), 7.17 (1H, s), 7.19 (1H, s), 7.22 (1H, s), 8.12 (1H, s), 8.16 (1H, t), 9.30 (1H, br, TFA), 9.85 (1H, s), 9.91 (1H, s), 10.05 (1H, s). IR (KBr): 1673, 1644, 1582, 1540, 1470, 1441, 1402, 1204, 1139 cm^{-1}. HRFABMS found: 497.26255. Calculated: 497.26248.

***N*-[5-({[5-({[3-(Dimethylamino)propyl]amino}carbonyl)-1-methyl-1*H*-pyrrol-3-yl]amino}carbonyl)-1-ethyl-1*H*-pyrrol-3-yl]-4-(formylamino)-1-methyl-1*H*-pyrrole-2-carboxamide (Fo-PyrMe-PyrEt-PyrMe-Dmap, 2).** *N*-[5-({[5-({[3-(Dimethylamino)propyl]amino}carbonyl)-1-methyl-1*H*-pyrrol-3-yl]amino}carbonyl)-1-ethyl-1*H*-pyrrol-3-yl]-1-methyl-4-nitro-1*H*-pyrrole-2-carboxamide (93 mg, 0.181 mmol) was dissolved in methanol (20 mL) to which Pd/C (108 mg, 10%) was added. The reaction mixture was hydrogenated at room temperature and atmospheric pressure for 5 h. The catalyst was removed by filtration through Kieselguhr and the solvent was then removed under reduced pressure to give the amine, which was used without further purification. The amine was dissolved in ethanol (5 mL), to which ethyl formate (20 mL) was added. The reaction mixture was heated under reflux for 48 h. The solvent was removed under reduced pressure to give the crude product, which was purified by HPLC. The product was obtained as a white solid after freeze-drying (43 mg, 30%, as TFA salt). ^{1}H NMR (DMSO-d_6) δ 1.26−1.91 (2H, t, J = 7.2 Hz), 1.81−1.29 (2H, m), 2.78−2.79 (6H, d, J = 3.6 Hz), 3.05−3.07 (2H, m), 3.23−3.24 (2H, q, J = 5.9 Hz), 3.81 (3H, s), 3.84 (3H, s), 4.28−4.34 (2H, q, J = 6.7 Hz), 6.91 (1H, s), 6.95 (1H, s), 7.03 (1H, s), 7.17 (1H, s), 7.19 (1H, s), 7.27 (1H, s), 8.12 (1H, s), 8.15 (1H, t, J = 5.7 Hz), 9.3 (1H, br TFA), 9.85 (1H, s), 9.91 (1H, s), 10.05 (1H, s). IR (KBr): 1673, 1644, 1582, 1540, 1470, 1441, 1402, 1204, 1139 cm^{-1}. HRFABMS found: 511.27820. Calculated: 511.27813.

***N*-[5-({[5-({[3-(Dimethylamino)propyl]amino}carbonyl)-1-methyl-1*H*-pyrrol-3-yl]amino}carbonyl)-1-isopropyl-1*H*-pyrrol-3-yl]-4-(formylamino)-1-methyl-1*H*-pyrrole-2-carboxamide (Fo-PyrMe-Pyr*i*Pr-PyrMe-Dmap, 3).** *N*-[5-({[3-(Dimethylamino)propyl]amino}-1-methyl-1*H*-pyrrol-3-yl]-1-isoprop yl-4-{[(1-methyl-4-{[(1-methyl-4-nitro-1*H*-pyrrol-2-yl)carbonyl]amino}-1*H*-pyrrole-2-carboxamide (102 mg, 0.194 mmol) was dissolved in methanol (20 mL), to which was added Pd/C (106 mg, 10%). The reaction mixture was hydrogenated for 5 h at room temperature and atmospheric pressure. The catalyst was removed by filtration through Kieselguhr and then ethyl formate (10 mL) was added to the filtrate. The reaction mixture was then heated under reflux for 72 h. The solvent was removed under reduced pressure and the crude product obtained was purified by HPLC. The product was obtained as a white solid after freeze-drying (64 mg, 51%, as TFA salt). ^{1}H NMR (DMSO-d_6): δ 1.35−1.37 (6H, d, J = 6.7 Hz), 1.81−1.85 (2H, m), 2.78−2.79 (6H, d, J = 3.6 Hz), 3.05 (2H, m), 3.23−3.25 (2H, q, J = 5.9 Hz), 3.81 (3H, s), 3.84 (3H, s), 5.40−5.46 (1H, m), 6.92 (1H, s), 6.94 (1H, s), 6.96 (1H, s), 7.17 (1H, s), 7.19 (1H, s), 7.38 (1H, s), 8.12 (1H, s), 8.15 (1H, t, J = 5.7 Hz), 9.3 (1H, br, TFA), 9.85 (1H, s), 9.91 (1H, s), 10.05 (1H, s). IR (KBr): 1673, 1644, 1582, 1540, 1470, 1441, 1402, 1204, 1139 cm^{-1}. HRFABMS found: 525.29372. Calculated: 525.29378.

1-Cyclopentyl-*N*-[5-({[3-(dimethylamino)propyl]amino}-carbonyl)1-methyl-1*H*-pyrrol-3-yl]-4-({[4-(formylamino)-1-methyl-1*H*-pyrrol-2-yl]carbonyl}amino)-1*H*-pyrrole-2-carboxamide (Fo-PyrMe-PyrCycpe-PyrMe-Dmap, 4). 1-Cyclopentyl-*N*-[5-({[3-(dimethylamino)propyl]amino}carbonyl)-1-methyl-1*H*-pyrrol-3-yl]-4-{[(1-methyl-4-nitro-1*H*-pyrrol-2-yl)-carbonyl]amino}-1*H*-pyrrole-2-carboxamide (100 mg, 0.181 mmol) was dissolved in ethanol (20 mL) at 0 °C under N_2 with stirring, to which Pd/C (10%, 92 mg) was added. The reaction mixture was hydrogenated at room temperature and atmospheric pressure for 3 h. The catalyst was removed by filtration through Kieselguhr and ethyl formate (25 mL) was added to the ethanolic solution. The reaction mixture was heated under reflux for 24 h. The solvent was removed under reduced pressure to give the crude product, which was purified by HPLC. Fractions containing the required material were collected and freeze-dried to give the product as a pale yellow solid (21 mg, 18%) with no distinct melting point. ^{1}H NMR (DMSO-d_6): δ 10.06 (1H, s), 9.95 (1H, s), 9.91 (1H, s), 9.21 (1H, br, TFA), 8.14 (1H, t, J = 6.0 Hz), 8.13 (1H, d, J = 1.7 Hz), 7.36 (1H, d, J = 1.7 Hz), 7.19 (1H, d, J = 1.7 Hz), 7.17 (1H, d, J = 1.7 Hz), 6.97 (1H, d, J = 1.7 Hz), 6.95 (1H, d, J = 1.7 Hz), 6.92 (1H, d, J = 1.7 Hz), 5.52 (1H, quintet, J = 7.5 Hz), 3.84 (3H, s), 3.81 (3H, s), 3.24 (2H, m), 3.06 (2H, m), 2.79 (6H, d, J = 3.3 Hz), 2.08 (2H, m), 1.83 (4H, m), 1.64 (4H, m). IR (KBr): 1674, 1647, 1582, 1536, 1463, 1440, 1406, 1201, 1131

cm^{-1}. HRFABMS found: 551.30950. Calculated for $C_{28}H_{39}N_8O_4$: 551.30943.

***N*-[1-(Cyclopropylmethyl)-5-({[5-({[3-(dimethylamino)propyl]amino}carbonyl)-1-methyl-1*H*-pyrrol-3-yl]amino}carbonyl)-1*H*-pyrrol-3-yl]-4-(formylamino)-1-methyl-1*H*-pyrrole-2-carboxamide (Fo-PyrMe-PyrCycpr-PyrMe-Dmap, 5).** *N*-[1-(Cyclopropylmethyl)-5-({[5-({[3-(dimethylamino)propyl]amino}carbonyl)-1-methyl-1*H*-pyrrol-3-yl]amino}carbonyl)-1*H*-pyrrol-3-yl]-1-methyl-4-nitro-1*H*-pyrrole-2-carboxamide (100 mg, 0.186 mmol) was dissolved in ethanol (25 mL) to which Pd/C (10%, 78 mg) was added at 0 °C under N_2 with stirring. The reaction mixture was hydrogenated for 3 h at room temperature and atmospheric pressure. The catalyst was removed by filtration through Kieselguhr. Ethyl formate was added to the ethanolic solution of the amine and the reaction mixture was heated under reflux for 48 h. Ethanol and excess ethyl formate were removed under reduced pressure, and the crude product was purified by HPLC. The product was obtained as a pale yellow solid (52 mg, 42%) after freeze-drying with no distinct melting point. ^{1}H NMR (DMSO-d_6): δ 10.04 (1H, s), 9.91 (1H, s), 9.90 (1H, s), 9.28 (1H, br, TFA), 8.16−8.13 (2H, m), 7.31 (1H, d, J = 1.7 Hz), 7.19 (1H, d, J = 1.7 Hz), 7.16 (1H, d, J = 1.7 Hz), 7.05 (1H, d, J = 1.7 Hz), 6.95 (1H, d, 1.7 Hz), 6.93 (1H, d, J = 1.7 Hz), 4.18 (2H, d, J = 7.0 Hz), 3.85 (3H, s), 3.81 (3H, s), 3.26−3.22 (2H, q, J = 6.3 Hz), 3.07 (2H, m), 2.79 (2H, d, J = 4.3 Hz), 1.87−1.82 (2H, quintet, J = 6.6 Hz), 1.23 (1H, m), 0.47−0.42 (2H, m), 0.33−0.29 (2H, m). IR (KBr): 3410, 3294, 1674, 1649, 1582, 1533, 1464, 1438, 1403, 1201, 1132 cm^{-1}. HRFABMS found: 537.29360. Calculated for $C_{27}H_{37}N_8O_4$: 537.29378.

***N*-[5-({[5-({[3-(Dimethylamino)propyl]amino}carbonyl)-1-isopropyl-1*H*-pyrrol-3yl]amino}carbonyl)-1-methyl-1*H*-pyrrol-3-yl]-4-(formylamino)-1-isopropyl-1*H*-pyrrole-2-carboxamide (Fo-Pyr*i*Pr-PyrMe-Pyr*i*Pr-Dmap, 6).** *N*-[5-({[5-({[3-(Dimethylamino)propyl]amino}carbonyl)-1-isopropyl-1*H*-pyrrol-3-yl]amino}carbonyl)-1-methyl-1*H*-pyrrol-3-yl]-1-isopropyl-4-nitro-1*H*-pyrrole-2-carboxamide (150 mg, 0.291 mmol) was dissolved in ethanol (15 mL). The solution was cooled to 0 °C under N_2 and then Pd/C (10%, 120 mg) was added. The reaction mixture was hydrogenated at room temperature and atmospheric pressure for 4 h. The catalyst was removed by filtration through Kieselguhr and then ethyl formate (20 mL) was added to the ethanolic solution. The reaction mixture was heated under reflux overnight and then the solvent was removed under reduced pressure at 40 °C. The product was purified by HPLC to give the product as a white solid (71 mg, 40%) with no distinct melting point. ^{1}H NMR (DMSO-d_6): δ 10.05 (1H, s), 9.95 (1H, s), 9.89 (1H, s), 9.24 (1H, s, br, TFA), 8.15−8.13 (2H, m), 7.34 (2H, s), 7.21 (1H, s), 7.06 (1H, s), 6.89 (1H, s), 6.67 (1H, s), 5.48−5.42 (1H, m), 3.84 (3H, s), 3.24 (2H, m), 3.05 (2H, m), 2.79 (6H, d, J = 4.7 Hz), 1.83 (2H, m), 1.36−1.33 (12H, m). IR (KBr): 3425, 3285, 2972, 1676, 1639, 1579, 1533, 1465, 1439, 1404, 1257, 1200, 1180, cm^{-1}. HRFABMS found: 554.33484. Calculated for $C_{28}H_{42}N_8O_4$: 554.33290.

***N*-[5-({[5-({[3-(Dimethylamino)propyl]amino}carbonyl)-1-methyl-1*H*-pyrrol-3-yl]amino}carbonyl)-1-isopentyl-1*H*-pyrrol-3-yl]-4-(formylamino)-1-methyl-1*H*-pyrrole-2-carboxamide (Fo-PyrMe-Pyr*i*Pe-PyrMe-Dmap, 7).** *N*-[5-({[5-({[3-(Dimethylamino)propyl]amino}carbonyl)-1-methyl-1*H*-pyrrol-3-yl]amino}carbonyl)-1-isopentyl-1*H*-pyrrol-3-yl]-1-methyl-4-nitro-1*H*-pyrrole-2-carboxamide (89 mg, 0.160 mmol) was dissolved in ethanol (25 mL) to which Pd/C (10%, 95 mg) was added at 0 °C under nitrogen with stirring. The reaction mixture was hydrogenated for 2 h at room temperature and atmospheric pressure. The catalyst was removed by filtration through Kieselguhr. Ethyl formate (25 mL) was added to the ethanolic solution, and then the reaction mixture was heated under reflux overnight. Ethanol and excess ethyl formate were removed under reduced pressure, and the crude product was purified by HPLC to give the required material as a pale yellow solid (37.4 mg, 35%) with no distinct melting point. ^{1}H NMR (DMSO-d_6): δ 10.03 (1H, s), 9.89 (1H, s), 9.87 (1H, s), 9.63 (1H, br, TFA), 8.14−8.12 (2H, m), 7.26 (1H, s), 7.18 (1H, s), 7.15 (1H, s), 7.01 (1H, s), 6.92 (1H, s), 6.91 (1H, s), 4.31−4.29 (2H, t, J = 6.8 Hz), 3.84 (3H, s), 3.81 (3H, s), 3.25−3.23 (2H, m), 3.06 (2H, m), 2.79 (6H, d, J = 3.7 Hz), 1.83−1.81 (2H, m), 1.57−1.48 (3H, m), 0.89 (6H, d, J = 6.2 Hz). IR (KBr): 3428, 3315, 1676, 1644, 1582, 1538, 1464, 1438, 1403, 1262, 1201, 1132 cm^{-1}. HRFABMS found: 553.32520. Calculated for $C_{28}H_{41}N_8O_4$: 553.32508.

***N*-[5-({[3-(Dimethylamino)propyl]amino}carbonyl)-1-isopropyl-1*H*-pyrrol-3-yl]-4-({[4-(formylamino)-1-isopropyl-1*H*-pyrrol-2-yl]carbonyl}amino)-1-isopropyl-1*H*-pyrrole-2-carboxamide (Fo-Pyr*i*Pr-Pyr*i*Pr-Pyr*i*Pr-Dmap, 8).** (NO_2)Pyr*i*Pr-Pyr*i*Pr-Pyr*i*Pr-Dmap (105 mg, 0.180 mmol) was suspended in ethanol (20 mL) to which Pd/C (10%, 80 mg) was added under nitrogen at 0 °C. The reaction mixture was hydrogenated at room temperature and atmospheric pressure for 4 h. The catalyst was removed by filtration through Kieselguhr and the ethanolic solution was then used in the second part of the experiment. Ethyl formate (20 mL) was added to the ethanolic solution of the amine. The reaction mixture was heated under reflux for 4 days. The solvents were removed under reduced pressure at 40 °C, and then the crude product was purified by reverse phase HPLC. The fractions obtained were freeze-dried to give the required material as a white solid (71 mg, 57%, as TFA salt) with no distinct melting point. ^{1}H NMR (DMSO-d_6): δ 1.14−1.36 (18H, m), 1.82−1.91 (2H, m), 2.78 (6H, d, J = 4.62 Hz), 3.04−3.09 (2H, m), 3.22−3.26 (2H, m), 5.42−5.51 (3H, m), 6.82 (1H, d, J = 1.6 Hz), 5.89 (1H, d, J = 1.6 Hz), 6.97 (1H, d, J = 1.6 Hz), 7.35 (1H, d, J = 1.6 Hz), 7.34 (1H, s), 8.12−8.14 (2H, s & t), 9.25 (1H, s, br, TFA), 9.91 (1H, s), 9.93 (1H, s), 10.03 (1H, s). IR (KBr): 3285, 2953, 1650, 1580, 1525, 1460, 1402, 1260 cm^{-1}. HREIMS found: 580.35047. Calculated for $C_{30}H_{44}O_4N_8$: 580.34855.

***N*-[5-({[5-({[3-(Dimethylamino)propyl]amino}carbonyl)-1-isopentyl-1*H*-pyrrol-3-yl]amino}carbonyl)-1-isopentyl-1*H*-pyrrol-3-yl]-4-(formylamino)-1-isopentyl-1*H*-pyrrole-2-carboxamide [(NO_2)Pyr*i*Pe-Pyr*i*Pe-Pyr*i*Pe-Dmap, 9].** (NO_2)Pyr*i*Pe-Pyr*i*Pe-Pyr*i*Pe-Dmap (119 mg, 0.178 mmol) was dissolved in ethanol (20 mL) and Pd/C (10%, 104 mg) was added at 0 °C under N_2 with stirring. The reaction mixture was hydrogenated at room temperature and atmospheric pressure for 3 h. The catalyst was removed by filtration through Kieselguhr, and then ethyl formate (15 mL) was added to the ethanolic solution of the amine. The reaction mixture was heated under reflux for 4 days. The solvent was removed under reduced pressure and the crude product was chromatographed over silica gel using ethyl acetate/methanol/triethylamine (100:100:1). The product was obtained as a light brown solid with no distinct melting point, R_f = 0.15, (84 mg, 71%). Some of this material was purified further by HPLC for analysis. ^{1}H NMR (DMSO-d_6): δ 0.87−0.90 (18H, m), 1.47−1.53 (9H, m), 1.75 (2H, m), 2.78 (6H, d, J = 4.8 Hz), 3.06 (2H, m), 3.25 (2H, m), 4.31 (6H, quintet, J = 7.2 Hz), 6.88 (1H, d, J = 1.8 Hz), 6.92 (1H, d, J = 1.8 Hz), 7.02 (1H, d, J = 1.8 Hz), 7.19 (1H, d, J = 1.8 Hz), 7.23 (2H, m), 8.13 (2H, m), 9.21 (1H, s, br, TFA), 9.88 (1H, s), 9.89 (1H, s), 10.05 (1H, s). IR (KBr): 2953, 1650, 1580, 1525, 1461, 1402, 1260, 1221 cm^{-1}. HRFABMS found: 665.44877. Calculated for $C_{36}H_{57}O_4N_8$: 665.45028.

***N*-[5-({[5-({[3-(Dimethylamino)propyl]amino}carbonyl)-1,2-dimethyl-1*H*-pyrrol-3-yl]amino}carbonyl)-1,2-dimethyl-1*H*-pyrrol-3-yl]-4-(formylamino)-1,5-dimethyl-1*H*-pyrrole-2-carboxamide (Fo-PyrMe$_2$-PyrMe$_2$-PyrMe$_2$-Dmap, 10).** (NO_2)PyrMe$_2$-PyrMe$_2$-PyrMe$_2$-Dmap (70 mg, 0.126 mmol) was dissolved in ethanol (15 mL). The solution was cooled to 0 °C and Pd/C (10%, 67 mg) was added portionwise with stirring. The reaction mixture was hydrogenated at room temperature and atmospheric pressure for 4 h. The catalyst was removed by filtration through Kieselguhr. Ethyl formate (20 mL) was added to the solution and the reaction mixture was then heated until reflux for 24 h. The solvent was removed under reduced pressure and the crude product purified using silica gel and methanol (containing 1% triethylamine). The product was obtained as a pale yellow solid. This material was dissolved in water (20 mL) containing TFA (30 μL) and then

freeze-dried to give the required product (49 mg, 60%) with no distinct melting point. ^{1}H NMR (DMSO-d_6): δ 1.57−1.61 (2H, quintet, J = 5.9 Hz, CH_2), 2.07 (3H, s, C-CH_3), 2.11 (6H, s, NMe_2), 2.12 (3H, s, C-CH_3), 3.16−3.17 (2H, q, J = 5.9 Hz, CH_2), 3.76 (3H, s, NMe), 3.77 (3H, s, NMe), 3.78 (3H, s, NMe), 6.76 (1H, s), 6.95 (1H, s), 7.15 (1H, s), 7.88 (1H, J = 5.6 Hz, CONH, exch), 8.13 (1H, s), 8.96 (1H, s, CONH, exch), 9.09 (1H, s, CONH, exch), 9.47 (1H, s, CONH, exch). IR (KBr): 1676, 1642, 1586, 1540, 1475, 1444, 1401, 1206, 1141 cm^{-1}. HRFABMS found: 539.30776. Calculated for $C_{27}H_{39}N_8O_4$: 539.30943.

4-(Acetylamino)-*N*-[5-({[5-({[3-(Dimethylamino)propyl]amino}carbonyl)-1-methyl-1*H*-pyrrol-3-yl]amino}carbonyl)-1-isopentyl-1*H*-pyrrol-3-yl]-1-methyl-1*H*-pyrrole-2-carboxamide (Ac-PyrMe-Pyr*i*Pe-PyrMe-Dmap, 11). (NO_2)PyrMe-Pyr*i*Pe-PyrMe-Dmap (150 mg, 0.271 mmol) was dissolved in methanol (25 mL) to which was added Pd/C (10%, 100 mg) at 0 °C under N_2 with stirring. The reaction mixture was hydrogenated for 2 h at room temperature and atmospheric pressure. The catalyst was removed by filtration through Kieselguhr and the solvent was then removed under reduced pressure. The amine so formed was dissolved in dichloromethane (10 mL, dry) to which *N*-methylmorpholine (137 μL, dry) and acetyl chloride (64 μL) were added respectively at room temperature with stirring. The stirring was continued at room temperature overnight. Volatile materials were removed under reduced pressure and the crude product was purified by HPLC to give the required product as a white solid (111 mg, 62%) with no distinct melting point. ^{1}H NMR (DMSO-d_6): δ 9.87 (2H, s), 9.80 (1H, s), 9.35 (1H, br), 8.14 (1H, t, J = 5.5 Hz), 7.26 (1H, s), 7.15 (1H, s), 7.13 (1H, s), 7.01 (1H, s), 6.92 (1H, s), 6.86 (1H, s), 4.31 (2H, t, J = 6.7 Hz), 3.83 (3H, s), 3.81 (3H, s), 3.25 (2H, m), 3.06 (2H, m), 2.79 (6H, d, J = 4.0 Hz), 1.97 (3H, s), 1.83 (2H, m), 1.58−1.48 (3H, m), 0.89 (6H, d, J = 6.2 Hz). IR (KBr): 1674, 1643, 1581, 1538, 1464, 1438, 1404, 1259, 1201, 1134 cm^{-1}. HRFABMS found: 567.33800. Calculated for $C_{29}H_{43}N_8O_4$: 567.34073.

4-(Acetylamino)-*N*-[5-({[5-({[3-(Dimethylamino)propyl]amino}carbonyl)-1-methyl-1*H*-pyrrol-3-yl]amino}carbonyl)-1-isopropyl-1*H*-pyrrol-3-yl]-1-methyl-1*H*-pyrrole-2-carboxamide (Ac-PyrMe-Pyr*i*Pr-PyrMe-Dmap, 12). (NO_2)PyrMe-Pyr*i*Pr-PyrMe-Dmap (45 mg, 0.103 mmol) was dissolved in methanol (25 mL) to which was added Pd/C (10%, 48 mg) at 0 °C under N_2 with stirring. The reaction mixture was hydrogenated for 2 h at room temperature and atmospheric pressure. The catalyst was removed by filtration through Kieselguhr and the solvent was removed under reduced pressure. The amine so formed was dissolved in dichloromethane (10 mL, dry) to which *N*-methylmorpholine (100 μL, dry) and acetyl chloride (50 μL) were added sequentially at room temperature with stirring. Stirring was continued at room temperature overnight. Volatile materials were removed under reduced pressure, and the crude product was purified by HPLC to give the required product as a white solid (21 mg, 32%) with no distinct melting point. ^{1}H NMR (DMSO-d_6): δ 9.91 (1H, s), 9.87(1H, s), 9.80 (1H, s), 9.25 (1H, br, TFA), 8.14 (1H, t, J = 5.8 Hz), 7.38 (1H, d, J = 1.8 Hz), 7.17 (1H, d, J = 1.8 Hz), 7.13 (1H, d, J = 1.8 Hz), 6.97 (1H, d, J = 1.8 Hz), 6.95 (1H, d, J = 1.8 Hz), 6.86 (1H, d, J = 1.8 Hz), 5.47−5.40 (1H, m), 3.83 (3H, s), 3.81 (3H, s), 3.25 (2H, q, J = 6.4 Hz), 3.06 (2H, m), 2.79 (6H, d, J = 4.8 Hz), 1.97 (3H, s), 1.90−1.81 (2H, m), 1.37−1.35 (6H, d, J = 6.7 Hz). IR (KBr): 1678, 1642, 1582, 1530, 1463, 1439, 1407, 1254, 1201, 1135 cm^{-1}. HRFABMS found: 539.30790. Calculated for $C_{27}H_{39}N_8O_4$: 539.30943.

4-(Acetamino)-*N*-[5-({[5-({[3-(dimethylamino)propyl]amino}carbonyl)-1-methyl-1*H*-pyrrol-3-yl]amino}carbonyl)-1-methyl-1*H*-pyrrol-3-yl]-1-methyl-1*H*-pyrrole-2-carboxamide (Ac-PyrMe-PyrMe-PyrMe-Dmap, 13). This material was prepared according to a published procedure[31] in 56% yield.

***N*-[5-({[5-({[3-(Dimethylamino)propyl]amino}carbonyl)-1-methyl-1*H*-pyrrol-3-yl]amino}carbonyl)-1-methyl-1-*H*-pyrrol-3-yl]-4-[(3,3-dimethylbutanoyl)amino]-1-methyl-1*H*-pyrrole-2-carboxamide (DmB-PyrMe-PyrMe-PyrMe-Dmap, 14).** *N*-[5-({[5-({[3-(Dimethylamino)propyl)-1-methyl-1*H*-pyrrol-3-yl]amino}carbonyl)-1-methyl-1*H*-pyrrol-3-yl]-1-methyl-4-nitro-1*H*-pyrrole-2-carboxamide (102 mg, 0.205 mmol) was suspended in 2-propanol (30 mL) to which was added Pd/C (102 mg, 10%). The reaction mixture was hydrogenated at room temperature and atmospheric pressure for 3 h. The catalyst was removed by filtration through Kieselguhr and the solvent was then removed under reduced pressure to give the amine, which was used without purification. The amine so formed was dissolved in dichloromethane (10 mL, dry) to which was added 3,3-dimethylbutanoyl chloride (35 mg, 0.260 mmol) [35 μL was dissolved in dichloromethane (5 mL, dry)]. DMAP (5 mg) was added to the reaction mixture at room temperature with stirring. The reaction mixture was left stirring for 48 h at room temperature. The solvent was removed and the crude product chromatographed over silica gel using ethyl acetate/methanol/ammonia (49/49/2). Fractions with an R_f value of 0.1 were collected, and the solvent was then removed under reduced pressure to give the product as a pale yellow glassy material (67 mg, 58% yield), mp 135−140 °C (softening). ^{1}H NMR ($CDCl_3$): δ 1.03 (9H, s), 1.64−1.69 (2H, m), 2.15 (2H, s), 2.19 (6H, s), 2.32−2.37 (2H, t, J = 6.8 Hz), 3.34−3.36 (2H, quintet, J = 6.1 Hz), 3.75 (3H, s), 3.78 (3H, s), 3.79 (3H, s), 6.51 (1H, s), 6.58 (2H, s), 7.07 (1H, s), 7.09 (1H, s), 7.16 (1H, s), 7.68 (1H, t, J = 5.8 Hz), 7.97 (1H, s), 8.49 (1H, s), 8.55 (1H, s). IR (KBr): 3298, 2960, 1644, 1582, 1538, 1405, 1250 cm^{-1}. HRFABMS found: 567.34079. Calculated for $C_{29}H_{43}N_8O_4$: 567.34073.

***N*-[5-({[5-({[3-(Dimethylamino)propyl]amino}carbonyl)-1-methyl-1*H*-pyrrol-3-yl]amino}carbonyl)-1-ethyl-1-*H*-pyrrol-3-yl]-4-[(3,3-dimethylbutanoyl)amino]-1-methyl-1*H*-pyrrole-2-carboxamide (DmB-PyrMe-PyrEt-PyrMe-Dmap, 15).** *N*-[5-({[5-({[3-(Dimethylamino)propyl]amino}-carbonyl)-1-methyl-1*H*-pyrrol-3-yl]amino}carbonyl)-1-ethyl-1*H*-pyrrol-3-yl]-1-methyl-4-nitro-1*H*-pyrrole-2-carboxamide (100 mg, 0.195 mmol) was suspended in methanol (20 mL) to which was added Pd/C (137 mg, 10%). The reaction mixture was hydrogenated overnight at room temperature and atmospheric pressure. The catalyst was removed over Kieselguhr and the solvent then removed under reduced pressure at 40 °C. The amine was dissolved in dichloromethane (10 mL, dry). 3,3-Dimethylbutanoyl chloride (55 μL, 0.409 mmol) was dissolved in dichloromethane (5 mL, dry) and was then added dropwise to the reaction mixture with stirring at room temperature. Diisopropylethylamine (35 μL) was added to the reaction mixture, and then it was left stirring at room temperature overnight. The solvent was removed under reduced pressure and the crude product obtained purified by column chromatography (silica gel, methanol/ethyl acetate/ammonia 49/49/2). The fractions that contained the required material (R_f = 0.1) were collected. The product obtained was dissolved in chloroform (100 mL) and extracted with sodium hydrogen carbonate (200 mg, dissolved in water 50 mL). The organic layer was collected and dried ($MgSO_4$) and the solvent removed under reduced pressure to give the product as a yellow glassy solid (50 mg, 44%) with no distinct melting point. ^{1}H NMR ($CDCl_3$): δ 1.04(9H, s), 1.25−1.32 (3H, t, J = 7.2 Hz), 1.66−1.71 (2H, m), 2.16 (2H, s), 2.23 (6H, s), 2.37−2.42 (2H, t, J = 6.8 Hz), 3.39−3.45 (2H, quintet, J = 6.1 Hz), 3.83 (6H, s), 4.21−4.27 (2H, q, J = 7.2 Hz), 6.49 (1H, s), 6.58 (1H, s), 6.67 (1H, s), 7.06 (1H, s), 7.19 (2H, s), 7.76 (1H, t, J = 5.8 Hz), 7.84 (1H, s), 8.25 (1H, s), 8.29 (1H, s). IR (KBr): 3298, 2960, 1644, 1582, 1538, 1405, 1250 cm^{-1}. HRFABMS found: 581.35631. Calculated for $C_{30}H_{45}N_8O_4$: 581.35638.

***N*-[5-({[5-({[3-(Dimethylamino)propyl]amino}carbonyl)-1-methyl-1*H*-pyrrol-3-yl]amino}carbonyl)-1-isopropyl-1*H*-pyrrol-3-yl]-4-[(3,3-dimethylbutanoyl)amino]-1-methyl-1*H*-pyrrole-2-carboxamide (DmB-PyrMe-PyrMe-Pyr*i*Pr-Dmap, 16).** *N*-[5-({[3-(Dimethylamino)propyl]amino}carbonyl)-1-methyl-1*H*-pyrrol-3-yl]-1-isopropyl-4-nitro-1*H*-pyrrole-2-carboxamide (100 mg, 0.189 mmol) was dissolved in methanol (20 mL) to which was added Pd/C (114 mg, 10%). The reaction mixture was hydrogenated at room temperature and atmospheric pressure for 6.5 h. The catalyst was removed by

filtration through Kieselguhr and the solvent removed under reduced pressure. The amine so formed was dissolved in dichloromethane (10 mL, dry) to which was added a solution of 3,3-dimethylbutanoyl chloride (35 μL, 0.260 mmol), which was dissolved in dichloromethane (5 mL, dry). The addition was dropwise with stirring at room temperature. Di-sopropylamine (35 μL) was then added in one portion to the reaction mixture. Stirring was continued at room temperature overnight. The solvent was removed under reduced pressure and the crude product obtained was purified by column chromatography using silica gel and ethyl acetate/methanol/ammonia (49/49/2). The solvent was removed under reduced pressure and the solid material was dissolved in chloroform (100 mL) and extracted with (5%, 50 mL) sodium bicarbonate. The organic layer was dried (Na_2SO_4) and the solvent removed to give the required product (84 mg, 75%) as a yellow glassy material with no distinct melting point. ^{1}H NMR ($CDCl_3$): δ 1.03 (9H, s), 1.29−1.32 (6H, d, J = 6.7 Hz), 1.68−1.83 (2H, m), 2.15 (2H, s), 2.19 (6H, s), 2.26−2.39 (2H, t, J = 6.2 Hz), 3.39−3.46 (2H, q, J = 6.7 Hz), 3.83 (3H, s), 3.84 (3H, s), 5.42−5.51 (1H, m), 6.47 (1H, d, J = 1.4 Hz), 6.58 (1H, d, J = 1.4 Hz), 6.67 (1H, d, J = 1.4 Hz), 7.05 (1H, d, J = 1.4 Hz), 7.22 (1H, d, J = 1.4 Hz), 7.37 (1H, d, J = 1.4 Hz), 7.78 (1H, t, J = 5.8 Hz), 7.82 (1H, s), 8.18 (1H, s), 8.32 (1H, s). IR (KBr): 3298, 2960, 1644, 1582, 1538, 1405, 1250 cm^{-1}. HRFABMS found: 595.37208. Calculated for $C_{31}H_{46}N_8O_4$: 595.37203.

***N*-[5-({[5-({[3-(Dimethylamino)propyl]amino}carbonyl)-1-methyl-1*H*-pyrrol-3-yl]amino}carbonyl)-1-methyl-1*H*-pyrrol-3-yl]-1-methyl-4-[(4-methylpentanoyl)amino]-1*H*-pyrrole-2-carboxamide (MPe-PyrMe-PyrMe-PyrMe-Dmap, 17).** (NO_2)PyrMe-PyrMe-PyrMe-Dmap (131 mg, 0.263 mmol) was dissolved in ethanol (20 mL) to which Pd/C (10%, 105 mg) was added at 0 °C under N_2 with stirring. The reaction mixture was hydrogenated for 4 h at room temperature and atmospheric pressure. The catalyst was removed by filtration through Kieselguhr and the solvent removed under reduced pressure. The crude amine was dissolved in THF (5 mL, dry) and added to a solution of 4-methylpentanoic acid (31 mg, 0.267 mmol) in DMF (2 mL, dry) containing HBTU (100 mg). The reaction mixture was stirred at room temperature overnight under N_2. Ethyl acetate (100 mL) was added and the reaction mixture was extracted with brine. The organic layer was dried ($MgSO_4$) and solvent removed under reduced pressure. The crude product was purified over silica gel using ethyl acetate/methanol/triethylamine (100:100:1). The product was obtained as a pale yellow solid (91 mg, 61%), R_f = 0.1, mp 125−127 °C (transparent). ^{1}H NMR ($CDCl_3$): δ 0.93 (6H, d, J = 6.3 Hz), 1.59−1.66 (2H, m), 1.73−1.77 (2H, m), 2.29−2.35 (8H NMe_2 & CH_2, m), 2.48 (2H, t, J = 6.3 Hz), 3.43−3.66 (2H, m), 3.90 (9H, s), 6.55 (1H, d, J = 1.8 Hz), 6.59 (1H, d, J = 1.7 Hz), 6.67 (1H, d, J = 1.7 Hz), 7.06 (1H, d, J = 1.7 Hz), 7.13 (1H, d, J = 1.7 Hz), 7.22 (1H, d, J = 1.7 Hz), 7.71 (1H, s), 7.66 (1H, s), 7.70 (1H, s), 7.96 (1H, s). IR (KBr): 2953, 1643, 1582, 1538, 1463, 1433, 1402, 1259, 1207, 1105 cm^{-1}. HRFABMS found: 567.34085. Calculated for $C_{29}H_{43}O_4N_8$: 567.34073.

***N*-[5-({[5-({[3-(Dimethylamino)propyl]amino}carbonyl)-1-methyl-1*H*-pyrrol-3-yl]amino}carbonyl)-1-methyl-1*H*-pyrrol-3-yl]-4-[(3-methoxybenzoyl)amino]-1-methyl-1*H*-pyrrole-2-carboxamide (3MeOB-PyrMe-PyrMe-PyrMe-Dmap, 18).** (NO_2)PyrMe-PyrMe-PyrMe-Dmap (52 mg, 0.105 mmol) was dissolved in methanol (25 mL) to which was added Pd/C (10%, 46 mg) at 0 °C under N_2 with stirring. The reaction mixture was hydrogenated for 2 h at room temperature and atmospheric pressure. The catalyst was removed by filtration through Kieselguhr and the solvent was removed under reduced pressure. The amine so formed was dissolved in dichloromethane (10 mL, dry) to which *N*-methylmorpholine (200 μL, dry) and *m*-anisoyl chloride (36 mg, 210 μL) were added sequencially at room temperature with stirring. The stirring was continued at room temperature overnight. Volatile materials were removed under reduced pressure, and the crude product was purified by HPLC to give the required product as a white solid material (19 mg, 26%) with no distinct melting point. ^{1}H NMR (DMSO-d_6): δ 10.29 (1H, s), 9.96 (1H, s), 9.79 (1H, s), 9.33 (1H, br), 7.53−7.41 (3H, m), 7.32−7.24 (3H, m), 7.19−7.08 (4H, m), 6.97−6.93 (3H, m), 6.61 (1H, d, J = 1.8 Hz), 3.92 (2H, t, J = 6.7 Hz), 3.88 (3H, s), 3.83 (3H, s), 3.82 (3H, s), 3.71 (3H, s), 3.59 (3H, s), 3.21 (2H, m), 2.83 (6H, d, J = 4.0 Hz), 2.85 (2H, m). IR (KBr): 1677, 1642, 1582, 1547, 1465, 1434, 1403, 1262, 1202, 1132 cm^{-1}. HRFABMS found: 603.30331. Calculated for $C_{31}H_{39}N_8O_5$: 603.30434.

***N*-[5-({[5-({[3-(Dimethylamino)propyl]amino}carbonyl)-1-methyl-1*H*-pyrrol-3-yl]amino}carbonyl)-1-isopentyl-1*H*-pyrrol-3-yl]-4-[(3-methoxybenzoyl)amino]-1-methyl-1*H*-pyrrole-2-carboxamide (3MeOB-PyrMe-Pyr*i*Pe-PyrMe-Dmap, 19).** *N*-[5-({[5-({[3-(Dimethylamino)propyl]amino}carbonyl)-1-methyl-1*H*-pyrrol-3-yl]amino}carbonyl)-1-isopentyl-1*H*-pyrrol-3-yl]-1-methyl-4-nitro-1*H*-pyrrole-2-carboxamide (260 mg, 0.469 mmol) was dissolved in methanol (25 mL) to which Pd/C (10%, 132 mg) was added at 0 °C under N_2 with stirring. The reaction mixture was hydrogenated for 3 h. The catalyst was removed by filtration through Kieselguhr and the solvent was removed under reduced pressure to give the amine, which was dissolved in dichloromethane (5 mL). This solution was divided in to two 2.5-mL portions. To one portion, *m*-anisoyl chloride (50 mg, 0.293 mmol) was added dropwise at room temperature with stirring. Stirring was continued overnight. The solvent was removed under reduced pressure and the residue was dissolved in acetonitrile containing 0.1% TFA and purified by HPLC. Fractions containing the required material were collected and freeze-dried to give the product as a light pink solid with no distinct melting point (72.3 mg, 40%). ^{1}H NMR (DMSO-d_6): δ 10.29 (1H, s), 9.96 (1H, s), 9.89 (1H, s), 9.270 (1H, br, TFA), 8.15 (1H, t, J = 5.6 Hz), 7.53−7.37 (3H, m), 7.32 (1H, d, J = 1.6 Hz), 7.29 (1H, d, J = 1.6 Hz), 7.16 (1H, d, J = 1.6 Hz), 7.14−7.10 (2H, m), 7.02 (1H, d, J = 1.6 Hz), 6.93 (1H, d, J = 1.6 Hz), 4.32 (1H, t, J = 6.9 Hz), 3.88 (3H, s), 3.83 (3H, s), 3.82 (3H, s), 3.25 (2H, q, J = 6.2 Hz), 3.07 (2H, m), 2.79 (6H, d, J = 4.5 Hz), 1.84 (2H, quintet, J = 7.3 Hz), 1.59−1.47 (3H, m), 0.90 (6H, d, J = 6.3 Hz). IR (KBr): 1644, 1583, 1533, 1464, 1436, 1402, 1260, 1200, 801, 778 cm^{-1}. HRFABMS found: 659.36784. Calculated for $C_{35}H_{47}N_8O_5$: 659.36694.

***N*-[5-({[5-({[3-(Dimethylamino)propyl]amino}carbonyl)-1-methyl-1*H*-pyrrol-3-yl]amino}carbonyl)-1-isopentyl-1*H*-pyrrol-3-yl]-4-{[(4-methoxyphenyl)acetyl]amino}-1-methyl-1*H*-pyrrole-2-carboxamide (4MeOPhe-PyrMe-Pyr*i*Pe-PyrMeDmap, 20).** The second portion of the amine (prepared in the previous experiment) was used in this experiment. To the amine (2.5 mL) in dichloromethane was added (4-methoxyphenyl)acetyl chloride (50 mg, 0.270 mmol) at room temperature, dropwise with stirring. Stirring was continued overnight. The solvent was removed under reduced pressure and the crude product so formed was purified by HPLC. Fractions containing the required material were collected and freeze-dried to give a white solid (51 mg, 28%) with no distinct melting point. ^{1}H NMR (acetone-d_6): δ 12.15 (1H, br), 9.18 (1H, s), 9.11 (1H, s), 9.05 (1H, s), 7.67 (1H, t, unresolved), 7.29−7.24 (4H, m), 7.13 (1H, d, J = 1.7 Hz), 6.89−6.85 (4H, m), 6.78 (1H, d, J = 1.7 Hz), 4.41 (2H, t, J = 6.5 Hz), 3.90 (6H, s), 3.77 (3H, s), 3.58 (2H, s), 3.45 (2H, q, J = 6.1 Hz), 3.26 (2H, t, J = 6.1 Hz), 2.93 (6H, s), 1.69−1.56 (3H, m), 0.95 (6H, d, J = 6.6 Hz). IR (KBr): 1650, 1588, 1515, 1465, 1402, 1251, 1203, 1133, 826, 779 cm^{-1}. HRFABMS found: 673.38492. Calculated for $C_{36}H_{49}N_8O_5$: 673.38259.

***N*-[5-({[5-({[3-(Dimethylamino)propyl]amino}carbonyl)-1-methyl-1*H*-pyrrol-3-yl]amino}carbonyl)-1-methyl-1*H*-pyrrol-3-yl]-1-methyl-4-{[(2*E*)-3-phenyl-2-propenoyl]amino}-1*H*-pyrrole-2-carboxamide (Cin-PyrMe-PyrMe-PyrMe-Dmap, 21).** (NO_2)PyrMe-PyrMe-PyrMe-Dmap (190 mg, 0.241 mmol) was dissolved in ethanol (20 mL) at 0 °C. Pd/C (10%, 103 mg) was added to the reaction mixture under N_2. The reaction mixture was hydrogenated for 4 h at room temperature and atmospheric pressure. The catalyst was removed by filtration through Kieselguhr and then the solvent was removed under reduced pressure to give the amine, which was used in the coupling reaction without further purification. Cinnamic acid (54 mg, 0.365 mmol) was dissolved in DMF (2

mL, dry) to which were added HBTU (203 mg, 0.535 mmol), *N*-methylmorpholine (0.200 mL, dry), and the amine, which was dissolved in DMF (2 mL, dry) at room temperature with stirring. The stirring was continued at room temperature overnight. The solvent was removed under reduced pressure, then the crude mixture was dissolved in ethyl acetate (100 mL) and extracted with brine (50 mL). The organic layer was dried ($MgSO_4$), and the solvent removed under reduced pressure at 60 °C. The crude product was chromatographed over silica gel using methanol/ethyl acetate/triethylamine (100:100:1) to give the product as a yellow glassy material (36 mg, 25%) with no distinct melting point. This material was further purified by HPLC to give the pure product (19 mg), as the TFA salt. ^{1}H NMR (DMSO-d_6): δ 1.83 (2H, qt), 2.79 (6H, d, J = 4.7 Hz), 3.07 (2H, m), 3.25 (2H, m), 3.81 (3H, s), 3.85 (3H, s), 3.87 (3H, s), 6.76−6.80 (1H, d, J = 15.7 Hz), 6.95 (1H, s), 6.97 (1H, s), 7.07 (1H, s), 7.17 (1H, s), 7.23 (1H, s), 7.31 (1H, s), 7.39−7.46 (3H, m), 7.49−7.53 (1H, d, J = 15.7 Hz), 7.59 (1H, s), 7.61 (1H, s), 8.15 (1H, t, J = 5.5 Hz), 9.19 (1H, br, TFA), 9.19 (1H, s), 9.95 (1H, s), 10.18 (1H, s). IR (KBr): 1648, 1581, 1540, 1465, 1434, 1404, 1262, 1203 cm^{-1}. HRFABMS found: 599.30906. Calculated for $C_{32}H_{39}N_8O_4$: 599.30943.

***N*-[5-({[3-(Dimethylamino)propyl]amino}carbonyl)-1-methyl-1*H*-pyrrol-3-yl]-1-methyl-4-{[(1-methyl-4-{[(2-methyl-3-thienyl)carbonyl]amino}-1*H*-pyrrol-2-yl)carbonyl]amino}-1*H*-pyrrole-2-carboxamide (MeThi-PyrMe-PyrMe-PyrMe-Dmap, 22).** 2-Methyl-3-thiophenecarboxylic acid (50 mg, 0.352 mmol) was dissolved in thionyl chloride (1 mL) and heated until reflux for 2 h. Excess thionyl chloride was removed under reduced pressure to give the acid chloride, which was used without further purification. (NO_2)PyrMe-PyrMe-PyrMe-Dmap (175 mg, 0.352 mmol) was dissolved in methanol (25 mL) to which Pd/C (10%, 95 mg) was added at 0 °C with stirring under N_2. The reaction mixture was hydrogenated for 2 h at room temperature and atmospheric pressure. The catalyst was removed over Kieselguhr and the solvent was removed under reduced pressure. The amine was dissolved in dichloromethane (5 mL) to which *N*-methylmorpholine (0.2 mL) was added at room temperature with stirring. The acid chloride was dissolved in dichloromethane (5 mL) and then it was added to the amine solution dropwise with stirring. The reaction mixture was left standing at room temperature for 48 h. The volatile material was removed under reduced pressure and the crude product was purified by column chromatography using silica gel and methanol/ethyl acetate/triethylamine (1/1/0.05) to give the product as a yellow solid, R_f = 0.5 (110 mg, 53%), mp 140−143 °C (transparent). ^{1}H NMR (DMSO-d_6): δ 9.97 (1H, s), 9.94 (1H, s), 9.87 (1H, s), 8.05 (1H, t, J = 5.5 Hz), 7.42 (1H, d, J = 5.4 Hz), 7.35 (1H, d, J = 5.4 Hz), 7.29 (1H, d, J = 1.7 Hz), 7.24 (1H, d, J = 1.7 Hz), 7.18 (1H, d, J = 1.7 Hz), 7.06 (1H, d, J = 1.7 Hz), 7.04 (1H, d, J = 1.7 Hz), 6.82 (1H, d, J = 1.7 Hz), 3.87 (3H, s), 3.85 (3H, s), 3.79 (3H, s), 3.19 (2H, q, J = 6.7 Hz), 2.66 (3H, s), 2.24 (2H, t, J = 7.0 Hz), 2.14 (6H, s), 1.61 (2H, quintet, J = 7.0 Hz). IR (KBr): 1640, 1580, 1544, 1463, 1434, 1400, 1260 cm^{-1}. HRFABMS found: 593.26448. Calculated for $C_{29}H_{37}N_8O_4S$: 593.26585.

***N*-[5-({[5-({[3-(Dimethylamino)propyl]amino}carbonyl)-1-methyl-1*H*-pyrrol-3-yl]amino}carbonyl)-1-isopentyl-1*H*-pyrrol-3-yl]-1-methyl-4-{[(1-methyl-4-nitro-1*H*-pyrrol-2-yl)carbonyl]amino}-1*H*-pyrrole-2-carboxamide ($PyrNO_2$-PyrMe-Pyr*i*Pe-PyrMe-Dmap, 23).** (NO_2)PyrMe-Pyr*i*Pe-PyrMe-Dmap (320 mg, 0.577 mmol) was dissolved in methanol (25 mL) to which Pd/C (10%, 226 mg) was added at 0 °C under N_2 with stirring. The reaction mixture was hydrogenated for 4 h at room temperature and atmospheric pressure. The catalyst was removed over Kieselguhr and the solvent was removed under reduced pressure at 50 °C. 1-Methyl-4-nitro-1*H*-pyrrole-2-carboxylic acid (98 mg, 0.577 mmol) was suspended in thionyl chloride (2 mL) and heated under reflux for 4 h. Excess thionyl chloride was removed under reduced pressure and the acid chloride so formed was dissolved in dichloromethane (5 mL). The amine was dissolved in dichloromethane (5 mL) to which *N*-methylmorpholine (0.2 mL) was added at room temperature with stirring. The acid chloride solution was added dropwise to the amine solution with stirring. The stirring was continued at room temperature overnight. A solution of sodium hydroxide [sodium hydroxide (186 mg) in water (10 mL)] was added to the reaction mixture. The organic layer was collected and dried ($MgSO_4$), and the solvent was removed under reduced pressure to give the crude product, which was applied to a column chromatography using silica gel and methanol/ethyl acetate/triethylamine (1/4/0.02), R_f = 0.15. The product was obtained as a yellow glassy material (180 mg, 46%) with no distinct melting point. Some of this material was further purified by HPLC for analysis. ^{1}H NMR (DMSO-d_6): δ 10.27 (1H, s), 9.96 (1H, s), 9.88 (1H, s), 9.31 (1H, br, TFA), 8.19 (1H, d, J = 1.8 Hz), 8.14 (1H, t, J = 5.7 Hz), 7.59 (1H, d, J = 1.8 Hz), 7.29 (1H, d, J = 1.8 Hz), 7.27 (1H, d, J = 1.8 Hz), 7.16 (1H, d, J = 1.8 Hz), 7.06 (1H, d, J = 1.8 Hz), 7.02 (1H, d, J = 1.8 Hz), 6.93 (1H, d, J = 1.8 Hz), 4.32 (2H, t, J = 7.1 Hz), 3.97 (3H, s), 3.87 (3H, s), 3.82 (3H, s), 3.25 (2H, quintet, J = 8.1 Hz), 1.59−1.47 (3H, m), 0.90 (6H, d, J = 6.4 Hz). IR (KBr): 1649, 1587, 1528, 1464, 1397, 1308, 1252, 1203 cm^{-1}. HRFABMS found: 677.35253. Calculated for $C_{33}H_{45}N_{10}O_6$: 677.35235.

***N*-[3-(Dimethylamino)propyl]-1-ethyl-4-({[4-({[4-(formylamino)-1-methyl-1*H*-pyrrol-2-yl]carbonyl}amino)-1-methyl-1*H*-pyrrol-2-yl]carbonyl}amino)-1*H*-imidazole-2-carboxamide (Fo-PyrMe-PyrMe-ImiEt-Dmap, 24).** (NO_2)-PyrMe-PyrMe-ImiEt-Dmap (50 mg, 0.091 mmol) was suspended in a mixture of ethanol (20 mL) and water (250 μL), to which Pd/C (10%, 50 mg) was added at 0 °C with stirring. The reaction mixture was hydrogenated at room temperature and atmospheric pressure for 20 h. The catalyst was removed by filtration through Kieselguhr and ethyl formate (20 mL) was added to the ethanolic solution of the amine. The reaction mixture was heated under reflux for 5d. The solvent was removed under reduced pressure and the crude product was purified by reverse phase HPLC. Fractions containing the required material were collected and freeze-dried. The product was obtained as a pale yellow solid (13 mg, 23%) with no distinct melting point. ^{1}H NMR (DMSO-d_6): δ 1.33−1.36 (3H, t, J = 7.0 Hz, CH_2CH_3), 1.85−1.90 (2H, quintet, J = 7.7 Hz, CH_2), 2.77−2.79 (6H, d, J = 4.8 Hz, NMe_2), 3.05−3.10 (2H, m, CH_2), 3.30−3.32 (2H, m, CH_2), 3.84 (3H, s, NMe), 3.84 (3H, s, NMe), 4.40−4.45 (2H, q, J = 4.4 Hz, CH_2), 6.92 (1H, d, J = 1.4 Hz), 7.07 (1H, d, J = 1.4 Hz), 7.18 (1H, d, J = 1.4 Hz), 7.29 (1H, d, J = 1.4 Hz), 7.55 (1H, s), 8.12 (1H, d, J = 1.4 Hz), 8.21 (1H, t, J = 6.1 Hz, CONH, exch), 9.22 (1H, br, hydrochloric acid, exch), 9.91 (1H, s, CONH, exch), 10.03 (1H, s, CONH, exch), 10.12 (1H, s, CONH, exch). IR (KBr): 3438, 3288, 1675, 1559, 1438, 1406, 1203, 1134 cm^{-1}. HRFABMS found: 521.27324. Calculated for $C_{24}H_{34}N_9O_4$: 512.27338.

***N*-[2-({[2-({[3-(Dimethylamino)propyl]amino}carbonyl)-1-ethyl-1*H*-imidazol-4-yl]amino}carbonyl)-1-ethyl-1*H*-imidazol-4-yl]-1-ethyl-4-(formylamino)-1*H*-imidazole-2-carboxamide (Fo-ImiEt-ImiEt-ImiEt-Dmap, 25).** (NO_2)-ImiEt-ImiEt-ImiEt-Dmap (150 mg, 0.193 mmol) was dissolved in ethanol (15 mL), and then Pd/C (10%, 99 mg) was added with stirring at 0 °C under nitrogen. The reaction mixture was hydrogenated at room temperature and atmospheric pressure for 4 h. The catalyst was removed by filtration through Kieselguhr and then ethyl formate (25 mL) was added to the ethanolic solution. The reaction mixture was heated under reflux for 5 d. The solvents were removed under reduced pressure, and the crude product was purified using HPLC. Fractions were collected and freeze-dried to give the required product as a white solid (12 mg, 10%) with no distinct melting point. ^{1}H NMR (DMSO-d_6): δ 1.33−1.40 (9H, m, $3CH_2CH_3$), 1.87−1.94 (2H, quintet, J = 6.7 Hz, CH_2), 2.72−2.73 (6H, d, J = 4.9 Hz, NMe_2), 3.02−3.07 (2H, quintet, J = 5.4 Hz, CH_2), 3.28−3.33 (2H, q, J = 6.4 Hz, CH_2), 4.42−4.52 (6H, m, $3CH_2$), 7.60 (1H, s), 7.61 (1H, s), 7.72 (1H, s), 8.23 (1H, s), 8.49 (1H, t, J = 6.1 Hz, CONH, exch), 9.20 (1H, br, TFA, exch), 9.60 (1H, s, CONH, exch), 9.75 (1H, s, CONH, exch), 10.51 (1H, s, CONH, exch). IR (KBr): 3422, 16, 76, 1568, 1537, 1474, 1431,

1385, 1200, 1132, 899 cm^{-1}. HRFABMS found: 542.29384. Calculated for $C_{24}H_{36}N_{11}O_4$: 542.29517.

***N*-[2-({[3-(Dimethylamino)propyl]amino}carbonyl)-1-ethyl-1*H*-imidazol-4-yl]-1-ethyl-4-({[4-(formylamino)-1-methyl-1*H*-pyrrol-2-yl]carbonyl}amino)-1*H*-imidazole-2-carboxamide (Fo-PyrMe-ImiEt-ImiEt-Dmap, 26).** (NO_2)-PyrMe-ImiEt-ImiEt-Dmap (20 mg, 0.038 mmol) was dissolved in ethanol (25 mL) to which Pd/C (10%, 70 mg) was added at 0 °C under N_2. The reaction mixture was hydrogenated for 5 h at room temperature and atmospheric pressure. The catalyst was removed by filtration through Kieselguhr and to the ethanolic solution ethyl formate (20 mL) was added. The mixture was heated at reflux overnight. The volatile material was removed under reduced pressure and the residue was purified by HPLC. Fractions containing the required material were collected and freeze-dried to give a white solid (5 mg, 21%) which was very hygroscopic and turned to a colorless oil. ^{1}H NMR (DMSO-d_6): δ 10.55 (1H, s), 10.45 (1H, s), 9.36 (1H, s), 9.20 (1H, br, TFA), 8.42 (1H, t, J = 5.4 Hz), 7.69 (1H, s), 7.62 (1H, s), 7.20 (1H, s), 7.10 (1H, s), 4.47 (4H, m), 3.90 (3H, s), 3.29 (2H, m), 3.08 (2H, m), 2.78 (6H, d, J = 4.6 Hz), 1.91 (2H, m), 1.38 (4H, m). IR (KBr): 2950, 2833, 1653, 1590, 1535, 1510, 1400, 1310 cm^{-1}. HRFABMS found: 527.28372. Calculated for $C_{24}H_{35}N_{10}O_4$: 527.28427.

***N*-[3-(Dimethylamino)propyl]-2-({[4-({[4-(formylamino)-1-methyl-1*H*-pyrrol-2-yl]carbonyl}amino)-1-methyl-1*H*-pyrrol-2-yl]carbonyl}amino)-4-isopropyl-1,3-thiazole-5-carboxamide (Fo-PyrMe-PyrMe-*iso*Thz*i*Pr-Dmap, 27).** (NO_2)PyrMe-PyrMe-*iso*Thz*i*Pr-Dmap (91 mg, 0.167 mmol) was suspended in ethanol (20 mL) and then Pd/C (100 mg, 10%) was added at 0 °C and under nitrogen. The reaction mixture was hydrogenated for 4 h at room temperature and atmospheric pressure. The catalyst was removed under reduced pressure and then ethyl formate (10 mL) was added. The reaction mixture was heated under reflux for 48 h, after which the solvent was removed under reduced pressure. The crude product was purified by HPLC. Fractions containing the required material were freeze-dried to give the product as a pale yellow solid (16 mg, 16%) with no distinct melting point. ^{1}H NMR (DMSO-d_6): δ 12.50 (1H, s), 10.05 (1H, s), 9.95 (1H, s), 9.27 (1H, br, TFA), 8.13 (2H, m), 7.45 (1H, s), 7.42 (1H, d, J = 1.6 Hz), 7.20 (1H, d, J = 1.6 Hz), 6.94 (1H, d, J = 1.6 Hz), 3.88 (3H, s), 3.84 (3H, s), 3.26 (2H, q, J = 5.6 Hz), 3.06 (2H, m), 2.79 (6H, d, J = 4.8 Hz), 1.90 (2H, m), 1.22 (6H, d, J = 6.8 Hz). IR (KBr): 1683, 1587, 1549, 1447, 1210, 1134 cm^{-1}. HRFABMS found: 544.25112. Calculated for $C_{25}H_{36}N_8O_4S$: 544.25081.

***N*-[3-(Dimethylamino)propyl]-2-({[4-({[4-(formylamino)-1-methyl-1*H*-pyrrol-2-yl]carbonyl}amino)-1-methyl-1*H*-pyrrol-2-yl]carbonyl}amino)-5-isopropyl-1,3-thiazole-4-carboxamide [(NO_2)PyrMe-PyrMe-Thz*i*Pr-Dmap, 28].** (NO_2)PyrMe-PyrMe-Thz*i*Pr-Dmap (90 mg, 0.165 mmol) was suspended in ethanol (20 mL) and then Pd/C (97 mg, 10%) was added at 0 °C under nitrogen. The reaction mixture was hydrogenated at room temperature and atmospheric pressure for 5 h. The catalyst was removed under reduced pressure, then ethyl formate (20 mL) was added to the ethanolic solution of the amine. The reaction mixture was heated under reflux for 3 d, and then the solvent was removed under reduced pressure. The crude product was dissolved in water (2 mL) containing 0.1% TFA and then purified by HPLC. The fractions collected were freeze-dried to give the desired product as a pale yellow solid (55 mg, 51%) with no distinct melting point. ^{1}H NMR (DMSO-d_6): δ 1.270−1.287 (6H, d, J = 6.9 Hz), 1.86 (2H, m), 2.78−2.79 (6H, d, J = 4.0 Hz), 3.07 (2H, m), 3.37 (2H, m), 3.84 (3H, s), 3.88 (3H, s), 4.19 (1H, m), 6.94 (1H, d, J = 1.6 Hz), 7.19 (1H, s), 7.38 (1H, s), 7.40 (1H, s), 7.96 (1H, t, J = 5.6 Hz), 8.13 (1H, d, J = 1.6 Hz), 9.30 (1H, br, TFA), 9.99 (1H, s), 10.04 (1H, s), 12.02 (1H, s). IR (KBr): 1664, 1555, 1465, 1399, 1294, 1209, 1130 cm^{-1}. HRFABMS found: 544.25962. Calculated for $C_{25}H_{36}N_8O_4S$: 544.25802.

***N*-[5-({[3-(Dimethylamino)propyl]amino}carbonyl)-1-methyl-1*H*-pyrrol-3-yl]-2-({[4-(formylamino)-1-methyl-1*H*-pyrrol-2-yl]carbonyl}amino)-5-isopropyl-1,3-thiazole-4-carboxamide (Fo-PyrMe-Thz*i*Pr-PyrMe-Dmap, 29).** (NO_2)PyrMe-Thz*i*Pr-PyrMe-Dmap (137 mg, 0.252 mmol) was dissolved in ethanol (15 mL), to which Pd/C (10%, 121 mg) was added under N_2 at 0 °C. The reaction mixture was hydrogenated at room temperature and atmospheric pressure for 2.5 h. The catalyst was removed by filtration through Kieselguhr and then ethyl formate (25 mL) was added to the ethanolic solution. The reaction mixture was heated under reflux overnight, following which the solvent was removed under reduced pressure and the product was then purified by HPLC. The product was obtained after freeze-drying as a white solid (41 mg, 25%), with no distinct melting point. ^{1}H NMR (DMSO-d_6): δ 12.09 (1H, s), 10.14 (1H, s), 9.59 (1H, s), 9.23 (1H, br, TFA), 8.35−8.32 (1H, d, J = 1.8 Hz and 1H, t, J = 5.6 Hz), 7.39 (1H, s), 7.28 (1H, d, J = 1.8 Hz), 7.20 (1H, d, J = 1.8 Hz), 7.01 (1H, d, J = 1.8 Hz), 4.17−4.12 (1H, m), 3.88 (3H, s), 3.82 (3H, s), 3.25 (2H, m), 3.06 (2H, m), 2.79 (6H, d, J = 3.7 Hz, NMe_2), 1.86−1.82 (2H, m), 1.31 (6H, d, J = 6.8 Hz). IR (KBr): 3428, 1662, 1545, 1467, 1401, 1284, 1201, 1134 cm^{-1}. HRFABMS found: 543.24988. Calculated for $C_{25}H_{35}N_8O_4S$: 543.25020.

2-(Acetylamino)-*N*-[5-({[5-({[3-(dimethylamino)propyl]amino}carbonyl)-1-methyl-1*H*-pyrrol-3-yl]amino}carbonyl)-1-methyl-1*H*-pyrrol-3-yl]-5-isopropyl-1,3-thiazole-4-carboxamide (Ac-Thz*i*Pr-PyrMe-PyrMe-Dmap, 30). (NO_2)PyrMe-PyrMe-Dmap (105 mg, 0.279 mmol) was dissolved in methanol (25 mL). The solution was cooled to 0 °C under N_2 then Pd/C (10%, 82 mg) was added. The reaction mixture was hydrogenated at room temperature and atmospheric pressure for 3 h. The catalyst was removed by filtration through Kieselguhr and then the solvent was removed under reduced pressure at 50 °C. The amine thus formed was dissolved in DMF (2 mL, dry), to which 2-(acetylamino)-5-isopropyl-1,3-thiazole-4-carboxylic acid (96 mg, 0.418 mmol) was added followed by HBTU (211 mg, 0.556 mmol) and *N*-methylmorpholine (300 μL, dry). The reaction mixture was left stirring at room temperature overnight, after which it was diluted with ethyl acetate and sodium bicarbonate solution with stirring. The organic layer was separated and dried ($MgSO_4$) and the solvent removed under reduced pressure. The product was purified by HPLC to give the pure material as a white solid (71.3 mg, 38%) with no distinct melting point. ^{1}H NMR (DMSO-d_6): δ 12.31 (1H, s), 8.87 (1H, s), 9.57 (1H, s), 9.24 (1H, br), 8.14 (1H, t, J = 5.6 Hz), 7.26 (1H, d, J = 1.8 Hz), 7.17 (1H, d, J = 1.8 Hz), 7.12 (1H, d, J = 1.8 Hz), 6.94 (1H, d, J = 1.8 Hz), 4.19−4.12 (1H, m), 3.85 (3H, s), 3.81 (3H, s), 3.25 (2H, m), 3.07 (2H, m), 2.79 (6H, d, J = 3.7 Hz), 2.16 (3H, s), 1.83 (2H, quintet, J = 7.5 Hz), 1.29 (6H, d, J = 6.8 Hz). IR (KBr): 1676, 1644, 1550, 1465, 1435, 1404, 1202, 1136 cm^{-1}. HRFABMS found: 557.26442. Calculated for $C_{26}H_{37}N_8O_4S$: 557.26585.

2-(Acetylamino)-*N*-[5-({[4-({[3-(dimethylamino)propyl]amino}carbonyl)-5-isopropyl-1,3-thiazol-2-yl]amino}carbonyl)-1-methyl-1*H*-pyrrol-3-yl]-5-isopropyl-1,3-thiazole-4-carboxamide (Ac-Thz*i*Pr-PyrMe-Thz*i*Pr-Dmap, 31). (NO_2)PyrMe-Thz*i*Pr-Dmap (100 mg, 0.236 mmol) was dissolved in methanol (25 mL). The solution was cooled to 0 °C under N_2 and then Pd/C (10%, 82 mg) was added. The reaction mixture was hydrogenated at room temperature and atmospheric pressure for 3 h. The catalyst was removed by filtration through Kieselguhr and the solvent was then removed under reduced pressure at 50 °C. The amine so formed was dissolved in DMF (2 mL, dry), to which 2-(acetylamino)-5-isopropyl-1,3-thiazole-4-carboxylic acid (64 mg, 0.356 mmol) was added followed by HBTU (135 mg, 0.356 mmol) and *N*-methylmorpholine (200 μL, dry). The reaction mixture was left stirring at room temperature overnight, after which it was diluted with ethyl acetate and sodium bicarbonate solution with stirring. The organic layer was separated and dried ($MgSO_4$) and the solvent removed under reduced pressure. The product was purified by HPLC to give the pure material as a white solid (78.8 mg, 47% yield) with no distinct melting point. ^{1}H NMR (DMSO-d_6): δ 12.11 (1H, s), 12.01 (1H, s), 9.64 (1H, s), 9.27 (1H, br), 7.96 (1H, t, J = 5.6 Hz), 7.51 (1H, d, J = 1.8 Hz),

7.42 (1H, d, $J = 1.8$ Hz), 4.22−4.11 (2H, m), 3.90 (3H, s), 3.34 (2H, m), 3.08 (2H, m), 2.79 (6H, d, $J = 3.7$ Hz), 2.16 (3H, s), 1.91−1.85 (2H, qintet, $J = 7.5$ Hz), 1.30−1.27 (12H, m). IR (KBr): 1666, 1549, 1508, 1466, 1398, 1286, 1201, 1134 cm^{-1}. HRFABMS found: 603.25163. Calculated for $C_{27}H_{39}N_8O_4S_2$: 603.25357.

2-({[4-({[4-(Acetylamino)-1-methyl-1*H*-imidazol-2-yl]carbonyl}amino)-1-methyl-1*H*-pyrrol-2-yl]carbonyl}amino)-*N*-[3-(dimethylamino)propyl]-5-isopropyl-1,3-thiazole-4-carboxamide [Ac-PyrMe-PyrMe-Thz*i*Pr-Dmap, 32). (NO_2)PyrMe-Thz*i*Pr-Dmap (105 mg, 0.25 mmol) and Pd/C (10%, 100 mg) were suspended in methanol (20 mL) and hydrogenated for 2.5 h at room temperature. Filtration of catalyst on to Kieselguhr under N_2, followed by removal of the solvent under reduced pressure gave the amine as an off-white solid, which was used without further purification. 4-(Acetylamino)-1-methyl-1*H*-imidazole-2-carboxylic acid sodium salt[33] (120 mg, 0.7 mmol) was dissolved in DMF (0.5 mL, dry), to which was added a solution of HBTU (137 mg, 0.36 mmol) and *N*-methylmorpholine (0.2 mL, dry) in DMF (1 mL, dry) at room temperature with stirring. The stirring was continued for 30 min at room temperature. This mixture was added to the amine with stirring at room temperature and stirring was continued at room temperature overnight, followed by purification by HPLC to give the desired material as the bis-TFA salt (30 mg, 22% yield) with no distinct melting point. ^{1}H NMR (DMSO-d_6): δ 1.27 (6H, d, $J = 6.8$ Hz, isopropyl), 1.87 (2H, m), 2.02 (3H, s), 2.78 (6H, s, NMe_2), 3.07 (2H,m), 3.32 (2H,m), 3.89 (3H, s, NMe), 3.95 (3H, s, COMe), 4.19 (1H, m, isopropyl), 7.44 (2H, m), 7.48 (1H, m), 7.97 (1H, m), 9.3 (1H, br), 10.00 (1H, s), 10.23 (1H, s), 12.03 (1H, s). IR (KBr): 1667, 1550, 1470, 1288, 1198, 1133 cm^{-1}. HRFABMS found: 558.26332. Calculated for $C_{25}H_{36}N_9O_4S$: 558.26110.

***N*-[5-({[5-({[3-(Dimethylamino)propyl]amino}carbonyl)-1-methyl-1*H*-pyrrol-3-yl]amino}carbonyl)-1-methyl-1*H*-pyrrol-3-yl]-5-isopropyl-2-[(3-methoxybenzoyl)amino]-1,3-thiazole-4-carboxamide (3MeOB-Thz*i*Pr-PyrMe-PyrMe-Dmap, 33).** (NO_2)PyrMe-PyrMe-Dmap (113 mg, 0.300 mmol) was suspended in methanol (25 mL) at 0 °C with stirring under N_2. Pd/C (10%, 61 mg) was added with stirring under N_2 and then the reaction mixture was hydrogenated at room temperature and atmospheric pressure for 3 h. Filtration of the catalyst on to Kieselguhr under N_2 and removal of the solvent under reduced pressure gave the amine, which was used in the coupling reaction without further purification. 5-Isopropyl-2-[(3-methoxybenzoyl)amino]-1,3-thiazole-4-carboxylic acid (96 mg, 3.00 mmol) was dissolved in thionyl chloride (2 mL) then heated under reflux for 3 h. The excess thionyl chloride was removed under reduced pressure and the acid chloride so formed was dissolved in dichloromethane (5 mL). The above amine was dissolved in dichloromethane (5 mL), to which *N*-methylmorpholine (0.2 mL) was added. The acid chloride solution was added dropwise at room temperature with stirring and then the stirring was continued overnight at room temperature. The volatile material was removed under reduced pressure and the crude product was purified by HPLC. Fractions containing the required material were collected and freeze-dried to give the product as a pale yellow solid (73 mg, 32%) with no distinct melting point. ^{1}H NMR (DMSO-d_6): δ 12.63 (1H, s), 9.88 (1H, s), 9.55 (1H, s), 9.29 (1H, br), 8.14 (1H, t, 5.8 Hz), 7.69 (1H, s), 7.67 (1H, s), 7.48 (1H, t, $J = 5.9$ Hz), 7.26 (1H, d, 1.7 Hz), 7.23 (1H, m), 7.18 (1H, d, $J = 1.7$ Hz), 7.13 (1H, d, $J = 1.7$ Hz), 6.94 (1H, d, 1.7 Hz), 4.19 (1H, heptet, $J = 6.8$ Hz), 3.86 (6H, s), 3.82 (3H, s), 3.24 (2H, q, $J = 6.7$ Hz), 3.07 (2H, m), 2.79 (6H, d, $J = 3.8$ Hz), 1.86 (2H, quintet, $J = 6.7$ Hz), 1.33 (6H, d, $J = 6.8$ Hz). IR (KBr): 1660, 1547, 1466, 1436, 1403, 1286, 1199, 1137, 1043 cm^{-1}. HRFABMS found: 649.29379. Calculated for $C_{32}H_{41}N_8O_5S$: 649.29206.

***N*-[5-({[3-(Dimethylamino)propyl]amino}carbonyl)-1-methyl-1*H*-pyrrol-3-yl]-4-({[5-(formylamino)-2-methyl-3-thienyl]carbonyl}amino)-1-methyl-1*H*-pyrrole-2-carboxamide (Fo-ThiMe-PyrMe-PyrMe-Dmap, 34).** The second portion of the amine solution from the preparation of **38** was used. Ethyl formate (25 mL) was added and the reaction mixture was heated under reflux for 3 days. The volatile material was removed under reduced pressure and the crude product was purified by HPLC. Fractions containing the required material were collected and freeze-dried to give the desired product as a pale yellow solid (25 mg, 18%) with no distinct melting point. ^{1}H NMR (DMSO-d_6): δ 11.32 (1H, s), 9.94 (1H, s), 9.89 (1H, s), 9.23 (1H, br, TFA), 7.16 (1H, d, $J = 1.7$ Hz), 7.05 (1H, d, $J = 1.7$ Hz), 6.95 (1H, d, $J = 1.7$ Hz), 6.94 (1H, s), 3.85 (3H, s), 3.81 (3H, s), 3.25 (2H, q, $J = 6.7$ Hz), 3.07 (2H, m), 2.79 (6H, d, $J = 3.8$ Hz), 2.54 (3H, s), 1.83 (2H, quintet, $J = 6.7$ Hz). IR (KBr): 1677, 1645, 1579, 1541, 1466, 1436, 1403 cm^{-1}. HRFABMS found: 514.22420. Calculated for $C_{24}H_{32}N_7O_4S$: 514.22365.

***N*-[4-({[5-({[3-(Dimethylamino)propyl]amino}carbonyl)-1-methyl-1*H*-pyrrol-3-yl]amino}carbonyl)-5-methyl-2-thienyl]-4-(formylamino)-1-methyl-1*H*-pyrrole-2-carboxamide (Fo-PyrMe-ThiMe-PyrMe-Dmap, 35).** A portion of the amine solution (10 mL) from the preparation of compound **37** was used. Ethyl formate (25 mL) was added and the reaction mixture was heated under reflux for 3 days. The volatile material was removed under reduced pressure and the crude product was purified by HPLC. Fractions containing the required material were collected and freeze-dried to give the desired product as a white solid (30 mg, 29%) with no distinct melting point. ^{1}H NMR (DMSO-d_6): δ 11.05 (1H, s), 10.08 (1H, s), 9.89 (1H, s), 9.26 (1H, br), 8.15 (2H, s & t, $J = 5.8$ Hz), 7.23 (1H, d, $J = 1.7$ Hz), 7.17 (1H, d, $J = 1.7$ Hz), 7.08 (1H, d, $J = 1.7$ Hz), 6.96 (1H, s), 6.90 (1H, d, $J = 1.7$ Hz), 3.84 (3H, s), 3.80 (3H, s), 3.24 (2H, q, $J = 6.7$ Hz), 3.08 (2H, m), 2.77 (6H, d, $J = 3.8$ Hz), 2.50 (3H, s), 1.85 (2H, quintet, $J = 6.7$ Hz). IR (KBr): 1677, 1639, 1577, 1535, 1465, 1436, 1400, 1292, 1200, 1131 cm^{-1}. HRFABMS found: 514.22583. Calculated for $C_{24}H_{32}N_7O_4S$: 514.22365.

***N*-[5-({[3-(Dimethylamino)propyl]amino}carbonyl)-1-methyl-1*H*-pyrrol-3-yl]-4-({[5-(formylamino)-2-methyl-3-thienyl]carbonyl}amino)-1-isopentyl-1*H*-pyrrole-2-carboxamide (Fo-ThiMe-Pyr*i*Pe-PyrMe-Dmap, 36).** (NO_2)-ThiMe-Pyr*i*Pe-PyrMe-Dmap (110 mg, 0.193 mmol) was dissolved in ethanol (20 mL) and cooled to 0 °C. Pd/C (10%, 120 mg) was added under N_2 with stirring and the reaction was hydrogenated at room temperature and atmospheric pressure for 3 h. The catalyst was removed by filtration through Kieselguhr, then ethyl formate (20 mL) was added to the ethanolic solution. The reaction mixture was heated under reflux for 3 d. The volatile material was then removed under reduced pressure and the crude product was purified by HPLC. The product was obtained as a white solid with no distinct melting point (23 mg, 17.4%). ^{1}H NMR (DMSO-d_6): δ 11.32 (1H, s), 9.94 (1H, s), 9.88 (1H, s), 9.24 (1H, br, TFA), 8.29 (1H, s), 8.14 (1H, t, $J = 5.9$ Hz), 7.29 (1H, d, $J = 1.7$ Hz), 6.95 (1H, s), 6.93 (1H, d, $J = 1.7$ Hz), 4.32 (1H, t, $J = 7.0$ Hz), 3.81 (3H, s), 3.25 (2H, q, $J = 5.1$ Hz), 3.06 (2H, m), 2.79 (6H, d, $J = 3.5$ Hz), 2.5 (3H, s), 1.83 (2H, quintet, $J = 6.7$ Hz), 1.57−1.49 (3H, m), 0.90 (6H, d, $J = 6.4$ Hz). IR (KBr): 1671, 1651, 1582, 1537, 1464, 1403, 1200, 1179, 1132 cm^{-1}. HRFABMS found: 570.28565. Calculated for $C_{28}H_{40}N_7O_4S$: 570.28625.

4-(Acetylamino)-*N*-[4-({[5-({[3-(dimethylamino)propyl]amino}carbonyl)-1-methyl-1*H*-pyrrol-3-yl]amino}carbonyl)-5-methyl-2-thienyl]-1-methyl-1*H*-pyrrole-2-carboxamide (Ac-PyrMe-ThiMe-PyrMe-Dmap, 37). (NO_2)PyrMe-ThiMe-PyrMe-Dmap (160 mg, 0.310 mmol) was dissolved in ethanol (20 mL) at 0 °C with stirring under N_2. Pd/C (10%, 129 mg) was added and the reaction mixture was hydrogenated for 2 h at room temperature and atmospheric pressure. The catalyst was removed over Kieselguhr and the amine solution was divided into two equal volumes. The solvent was removed from the first (10 mL) under reduced pressure and the amine so formed was dissolved in dichloromethane (5 mL) to which *N*-methylmorpholine (0.1 mL) was added with stirring at room temperature followed by acetyl chloride (12 μL). The reaction mixture was stirred at room temperature overnight. The volatile material was removed under reduced pressure and the crude product was purified by HPLC. Fractions containing the required material were collected and freeze-dried. The

product was obtained as a white solid (41 mg, 39%) with no distinct melting point. ^{1}H NMR (DMSO-d_6): δ 11.05 (1H, s), 9.91 (1H, s), 9.85 (1H, s), 9.26 (1H, br), 8.15 (1H, t, 5.8 Hz), 7.20 (1H, d, J = 1.7 Hz), 7.19 (1H, d, J = 1.7 Hz), 7.06 (1H, d, J = 1.7 Hz), 6.98 (1H, s), 6.92 (1H, d, J = 1.7 Hz), 3.85 (3H, s), 3.82 (3H, s), 3.32 (2H, q, J = 6.7 Hz), 3.07 (2H, m), 2.79 (6H, d, J = 3.8 Hz), 2.52 (3H, s), 1.98 (3H, s), 1.84 (2H, quintet, J = 6.7 Hz). IR (KBr): 1645, 1577, 1535, 1466, 1436, 1289, 1199, 1134 cm^{-1}. HRFABMS found: 514.22529. Calculated for $C_{24}H_{32}N_7O_4S$: 514.22365.

4-({[5-(Acetylamino)-2-methyl-3-thienyl]carbonyl}amino)-*N*-[5-({[3-(dimethylamino)propyl]amino}carbonyl)-1-methyl-1*H*-pyrrol-3-yl]-1-methyl-1*H*-pyrrole-2-carboxamide (Ac-ThiMe-PyrMe-PyrMe-Dmap, 38). (NO_2)ThiMe-PyrMe-PyrMe-Dmap (213 mg, 0.439 mmol) was dissolved in ethanol (20 mL) at 0 °C with stirring under N_2. Pd/C (10%, 113 mg) was added and the reaction mixture was hydrogenated for 6 h at room temperature and atmospheric pressure. The catalyst was removed over Kieselguhr and the solution was divided into two equal volumes. For the first half, the solvent was removed under reduced pressure and the residue was dissolved in dichloromethane (5 mL) to which *N*-methylmorpholine (0.1 mL) was added with stirring at room temperature followed by acetyl chloride (17 μL, 0.219 mmol). The reaction mixture was stirred overnight at room temperature. The volatile material was removed under reduced pressure and the crude product was purified by HPLC. Fractions containing the required material were combined and freeze-dried to give a white solid (52 mg, 37%) with no distinct melting point. ^{1}H NMR (DMSO-d_6): δ 11.08 (1H, s), 9.89 (1H, s), 9.87 (1H, s), 9.25 (1H, br, TFA), 8.11 (1H, t, J = 5.8 Hz), 7.22 (1H, d, J = 1.7 Hz), 7.14 (1H, d, J = 1.7 Hz), 7.02 (1H, d, J = 1.7 Hz), 6.92 (1H, d, J = 1.7 Hz), 6.81 (1H, s), 3.83 (3H, s), 3.79 (3H, s), 3.22 (2H, q, J = 6.7 Hz), 3.05 (2H, m), 2.77 (6H, d, J = 3.8 Hz), 2.50 (3H, s), 2.05 (3H, s), 1.82 (2H, quintet, J = 6.7 Hz). IR (KBr): 1638, 1578, 1542, 1465, 1435, 1403, 1201, 1133 cm^{-1}. HRFABMS found: 528.24004. Calculated for $C_{25}H_{34}N_7O_4S$: 528.239.

***N*-[3-(Dimethylamino)propyl]-2-[({[4-({[4-(formylamino)-1-methyl-1*H*-pyrrol-2-yl]carbonyl}amino)-1-methyl-1-*H*-pyrrol-2-yl]carbonyl}amino)methyl]-5-methyl-1,3-oxazole-4-carboxamide (Fo-PyrMe-PyrMe-CH$_2$OxaMe-Dmap, 39).** *N*-[3-(Dimethylamino)propyl]-5-methyl-2-({[(1-methyl-4-{[(1-methyl-4-nitro-1 *H*-pyrrol-2-yl)carbonyl]amino}-1*H*-pyrrol-2-yl)carbonyl]amino}methyl)-1,3-oxazole-4-carboxamide (49 mg, 0.095 mmol) was dissolved in ethanol (15 mL), to which Pd/C (10%, 51 mg) was added at 0 °C under N_2. The reaction mixture was hydrogenated for 4 h at room temperature and atmospheric pressure. The catalyst was removed by filtration through Kieselguhr and then ethyl formate (25 mL) was added to the ethanolic solution. The reaction mixture was heated under reflux for 24 h, and then the solvent and excess reagent were removed under reduced pressure at 40 °C. The product was purified by HPLC and was obtained as a white hygroscopic solid as TFA salt after freeze-drying (25 mg, 42%) with no distinct melting point. ^{1}H NMR (DMSO-d_6): δ 10.03 (1H, s), 9.89 (1H, s), 9.21 (1H, br, TFA), 8.65 (1H, t, J = 5.5 Hz), 8.29 (1H, t, J = 5.6 Hz), 8.12 (1H, s), 7.19 (1H, s), 7.17 (1H, s), 4.45 (2H, d, J = 5.4 Hz), 3.26 (2H, m), 3.02 (2H, m), 2.77 (6H, d, J = 4.5 Hz), 2.54 (3H, s), 1.83 (2H, m). IR (KBr): 1675, 1664, 1589, 1533, 1467, 1437, 1404, 1346 cm^{-1}. HRFABMS found: 513.25498. Calculated for $C_{24}H_{33}N_8O_5$: 513.25739.

4-(Formylamino)-*N*-[1-isopentyl-5-({[1-methyl-5-({[3-(4-morpholinyl)propyl]amino}carbonyl)-1*H*-pyrrol-3-yl]-amino}carbonyl)-1*H*-pyrrol-3-yl]-1-methyl-1*H*-pyrrole-2-carboxamide (Fo-PyrMe-Pyr*i*Pe-PyrMe-Morp, 40). To the second half of the amine solution (10 mL) from the preparation of compound **42**, ethyl formate was added (10 mL) and the reaction mixture was heated under reflux for 48 h. Volatile solvents were removed under reduced pressure, and the crude product was purified by HPLC. Fractions containing the required material were collected and freeze-dried to give a white solid material (22.7 mg, 32%, as TFA salt) with no distinct melting point. ^{1}H NMR (DMSO-d_6): δ 10.03 (1H, s), 9.89 (1H, s), 9.87 (1H, s), 9.56 (1H, br, TFA), 8.16 (1H, t, unresolved), 8.12 (1H, d, J = 1.7 Hz), 7.26 (1H, d, J = 1.7 Hz), 7.18 (1H, d, J = 1.7 Hz), 7.15 (1H, d, J = 1.7 Hz), 7.02 (1H, d, J = 1.7 Hz), 6.93 (1H, d, J = 1.7 Hz), 6.92 (1H, d, J = 1.7 Hz), 4.31 (2H, t, J = 7.1 Hz), 4.00 (2H, d, J = 11.8 Hz), 3.84 (3H, s), 3.81 (3H, s), 3.64 (2H, t, J = 11.9 Hz), 3.46 (2H, d, J = 12.8 Hz), 3.26 (2H, q, J = 6.1 Hz), 3.12−3.06 (4H, m), 1.87 (2H, m), 1.58−1.46 (3H, m), 0.90 (6H, d, J = 6.3 Hz). IR (KBr): 1682, 1640, 1584, 1529, 1403, 1263, 1202, 1132, 803 cm^{-1}. HRFABMS found: 595.33717. Calculated for $C_{30}H_{43}N_8O_5$: 595.33564.

4-({[4-(Formylamino)-1-methyl-1*H*-pyrrol-2-yl]carbonyl}amino)-1-isopropyl-*N*-[1-methyl-5-({[3-(4-morpholinyl)propyl]amino}carbonyl)-1*H*-pyrrol-3-yl]-1*H*-pyrrole-2-carboxamide (Fo-PyrMe-Pyr*i*Pr-PyrMe-Morp, 41). (NO_2)PyrMe-Pyr*i*Pr-PyrMe-Morp (160 mg, 0.282 mmol) was dissolved in ethanol (25 mL) to which Pd/C (10%, 150 mg) was added at 0 °C under nitrogen with stirring. The reaction mixture was hydrogenated for 2 h at room temperature and atmospheric pressure. The catalyst was removed by filtration through Kieselguhr. Ethyl formate (25 mL) was added to the ethanolic solution, then the reaction mixture was heated under reflux overnight. Ethanol and excess ethyl formate were removed under reduced pressure, and the crude product was purified by HPLC to give the required material as a white solid (40.1 mg, 21%) with no distinct melting point. ^{1}H NMR (DMSO-d_6): δ 10.05 (1H, s), 9.93 (1H, s), 9.91 (1H, s), 9.58 (1H, br, TFA), 8.17 (1H, t, J = 5.5 Hz), 8.12 (1H, s), 7.38 (1H, s), 7.18 (1H, s), 7.16 (1H, s), 6.96 (1H, s), 6.94 (1H, s), 6.92 (1H, s), 3.84 (3H, s), 3.81 (3H, s), 3.65−3.42 (8H, m), 3.25−3.24 (2H, q, J = 5.9 Hz), 3.12−3.05 (4H, m), 1.87 (2H, m), 1.37 (6H, d, J = 6.6 Hz). IR (KBr): 3423, 1672, 1644, 1581, 1536, 1462, 1440, 1407, 1254, 1200, 1134 cm^{-1}. HRFABMS found: 567.30312. Calculated for $C_{28}H_{39}N_8O_5$: 567.30434.

4-(Acetylamino)-*N*-[1-isopentyl-5-({[1-methyl-5-({[3-(4-morpholinyl)propyl]amino}carbonyl)-1*H*-pyrrol-3-yl]-amino}carbonyl)-1*H*-pyrrol-3-yl]-1-methyl-1*H*-pyrrole-2-carboxamide (Ac-PyrMe-Pyr*i*Pe-PyrMe-Morp, 42). (NO_2)PyrMe-Pyr*i*Pe-PyrMe-Morp (115 mg, 0.193 mmol) was dissolved in ethanol (20 mL) to which was added Pd/C (10%, 104 mg) at 0 °C under N_2 with stirring. The reaction mixture was hydrogenated for 3 h at room temperature and atmospheric pressure. The catalyst was removed by filtration through Kieselguhr and the ethanolic solution was divided into two equal volumes (10 mL). Ethanol was removed from one of the fractions under reduced pressure and dichloromethane (2 mL) was added to the residue with stirring. *N*-Methylmorpholine (0.1 mL) was added followed by acetyl chloride (10 μL) at room temperature with stirring. The stirring was continued overnight. All volatile materials were removed under reduced pressure, and the crude product was purified by HPLC. Fractions containing the required material were collected and freeze-dried to give a white solid material (25.7 mg, 35%, as TFA salt) with no distinct melting point. ^{1}H NMR (DMSO-d_6): δ 9.87 (2H, s), 9.79 (1H, s), 9.55 (1H, br, TFA), 8.16 (1H, t, unresolved), 7.26 (1H, d, J = 1.8 Hz), 7.15 (1H, d, J = 1.8 Hz), 7.13 (1H, d, J = 1.8 Hz), 7.01 (1H, d, J = 1.8 Hz), 6.94 (1H, d, J = 1.8 Hz), 6.87 (1H, d, J = 1.8 Hz), 4.31 (2H, t, J = 6.9 Hz, isopentyl), 4.00 (2H, d, J = 12.4 Hz, morpho), 3.83 (3H, s), 3.81 (3H, s), 3.64 (2H, t, J = 12.0 Hz, morpho), 3.45 (2H, d, J = 12.0 Hz, morpho), 3.24 (2H, q, J = 6.2 Hz), 3.12−3.06 (2H, m, side chain, 2H morpho), 1.97 (3H, s), 1.87 (2H, m, isopentyl), 1.58−1.48 (2H, m, side chain, 1H isopentyl), 0.90 (6H, d, J = 6.4 Hz, isopentyl). IR (KBr): 2925, 2858, 1655, 1583, 1526, 1465, 1400, 1260, 1200, 1131 cm^{-1}. HRFABMS found: 609.34957. Calculated for $C_{31}H_{45}N_8O_5$: 609.35129.

***N*-[1-Isopentyl-5-({[1-methyl-5-({[3-(4-methyl-1-piperazinyl)propyl]amino}carbonyl)-1*H*-pyrrol-3-yl]-amino}carbonyl)-1*H*-pyrrol-3-yl]-4-[(3-methoxybenzoyl)-amino]-1-methyl-1*H*-pyrrole-2-carboxamide (3MeOB-PyrMe-Pyr*i*Pe-PyrMe-MePipp, 43).** The second portion of the solution of amine used for the preparation of compound **45** was used. To this solution, 3-methoxybenzoyl chloride (26 mg, 26 μL, 0.153 mmol) was added dropwise at room temper-

ature with stirring. The stirring was continued overnight at room temperature. The solvent was removed under reduced pressure and the crude product was purified by HPLC. The product was obtained as a light brown solid (60.8 mg, 48%) with no distinct melting point. ^{1}H NMR (DMSO-d_6): δ 10.28 (1H, s), 9.95 (1H, s), 9.88 (1H, s), 8.09 (1H, t, unresolved), 7.53−7.47 (2H, m), 7.43 (1H, t, J = 7.8 Hz), 7.32 (1H, d, J = 1.7 Hz), 7.29 (1H, d, J = 1.7 Hz), 7.15−7.11 (3H, m), 7.02 (1H, d, J = 1.7 Hz), 6.92 (1H, d, J = 1.7 Hz), 4.32 (2H, t, J = 6.6 Hz), 3.88 (3H, s), 3.83 (3H, s), 3.81 (3H, s), 3.24 (2H, q, J = 6.0 Hz), 3.10−2.40 (8H, br; 3H, s), 1.77 (2H, br), 1.59−1.47 (3H, m), 0.91 (6H, d, J = 6.4 Hz). IR (KBr): 1677, 1645, 1583, 1535, 1462, 1435, 1402, 1263, 1197, 1132 cm^{-1}. HRFABMS found: 714.40764. Calculated for $C_{38}H_{52}N_9O_5$: 714.40914.

4-(Formylamino)-*N*-[1-isopentyl-5-({[1-methyl-5-({[3-(4-methyl-1-piperazinyl)propyl]amino}carbonyl)-1*H*-pyrrol-3-yl]amino}carbonyl)-1*H*-pyrrol-3-yl]-1-methyl-1*H*-pyrrole-2-carboxamide (Fo-PyrMe-Pyr*i*Pe-PyrMe-MePipp, 44). (NO_2)PyrMe-Pyr*i*Pe-PyrMe-Mepipp (120 mg, 0.197 mmol) was dissolved in ethanol (20 mL) to which Pd/C (10%, 77 mg) was added at 0 °C under N_2 with stirring. The reaction mixture was hydrogenated for 3 h at room temperature and atmospheric pressure. The catalyst was removed by filtration through Kieselguhr and ethyl formate (20 mL) was added to the ethanolic solution. The reaction mixture was heated under reflux for 48 h. Ethanol and excess ethyl formate were removed under reduced pressure, and the crude product was purified by HPLC. The product was obtained as a yellow solid with no distinct melting point (75 mg, 53%) after freeze-drying. ^{1}H NMR (DMSO-d_6): δ 10.03 (1H, s), 9.89 (1H, s), 9.87 (1H, s), 8.13 (1H, d, J = 1.6 Hz), 8.09 (1H, t, J = 5.6 Hz), 7.26 (1H, d, J = 1.6 Hz), 7.18 (1H, d, J = 1.6 Hz), 7.14 (1H, d, J = 1.6 Hz), 7.01 (1H, d, J = 1.6 Hz), 6.92 (1H, d, J = 1.6 Hz), 6.91 (1H, d, J = 1.6 Hz), 4.31 (2H, t, J = 6.9 Hz), 3.83 (3H, s), 3.81 (3H, s), 3.23 (2H, q, J = 6.5 Hz), 3.10−2.72 (8H, br; 3H, s), 1.77 (2H, s, br), 1.58−1.46 (3H, m), 0.90 (6H, d, J = 6.4 Hz). IR (KBr): 1675, 1584, 1535, 1403, 1199, 1132 cm^{-1}. HRFABMS found: 608.36634. Calculated for $C_{31}H_{46}N_9O_4$: 608.36728.

4-(Acetylamino)-*N*-[1-isopentyl-5-({[1-methyl-5-({[3-(4-methyl-1-piperazinyl)propyl]amino}carbonyl)-1*H*-pyrrol-3-yl]amino}carbonyl)-1*H*-pyrrol-3-yl]-1-methyl-1*H*-pyrrole-2-carboxamide (Ac-PyrMe-Pyr*i*Pe-PyrMe-MePipp, 45). (NO_2)PyrMe-Pyr*i*Pe-PyrMe-Mepipp (186 mg, 0.305 mmol) was dissolved in methanol at 0 °C under N_2 with stirring to which Pd/C (10%, 136 mg) was added. The reaction mixture was hydrogenated for 3 h at room temperature and atmospheric pressure with stirring. The catalyst was removed by filtration through Kieselguhr and the solvent was then removed under reduced pressure. The amine so formed was dissolved in dichloromethane (10 mL) and this solution was subsequently divided in half. Acetyl chloride (12 mg, 12 μL, 0.153 mmol) was added dropwise with stirring at room temperature to the first half. Stirring was continued at room temperature overnight. The solvent was removed under reduced pressure and the crude product formed was dissolved in small amount of acetonitrile/water containing 0.1% TFA and purified by HPLC. Fractions containing the pure material were combined and freeze-dried to give an off-white solid (45 mg, 40%) with no distinct melting point. ^{1}H NMR (DMSO-d_6): δ 9.87 (1H, s), 9.86 (1H, s), 9.79 (1H, s), 8.09 (1H, t, unresolved), 7.26 (1H, d, J = 1.7 Hz), 7.14 (1H, d, J = 1.7 Hz), 7.13 (1H, d, J = 1.7 Hz), 7.01 (1H, d, J = 1.7 Hz), 6.91 (1H, d, J = 1.7 Hz), 6.86 (1H, d, J = 1.7 Hz), 4.31 (2H, t, J = 6.9 Hz), 3.83 (3H, s), 3.81 (3H, s), 3.24 (2H, q, J = 6.4 Hz), 3.10−2.60 (8H, br; 3H, s), 1.97 (3H, s), 1.77 (2H, m), 1.58−1.46 (3H, m), 0.90 (6H, d, J = 6.4 Hz). IR (KBr): 1675, 1647, 1584, 1535, 1459, 1436, 1402, 1197, 1132 cm^{-1}. HRFABMS found: 622.38301. Calculated for $C_{32}H_{48}N_9O_4$: 622.38293.

4-(Acetylamino)-1-methyl-*N*-[1-methyl-5-({[1-methyl-5-({[3-(1-pyrrolidinyl)propyl]amino}carbonyl)-1*H*-pyrrol-3-yl]amino}carbonyl)-1*H*-pyrrol-3-yl]-1*H*-pyrrole-2-carboxamide (Ac-PyrMe-PyrMe-PyrMe-Pyrrp, 46). The solvent was removed from the second half of the solution obtained after hydrogenation in the preparation of the following compound, **47**, and the amine obtained was dissolved in dichloromethane (10 mL) to which *N*-methylmorpholine (100 μL) was added at room temperature with stirring followed by acetyl chloride (14 μL), which was added dropwise. The stirring was continued at room temperature overnight. Volatile material was removed under reduced pressure and the crude product was purified by HPLC. The product was obtained as a pale yellow solid (42 mg, 33%) with no distinct melting point. ^{1}H NMR (DMSO-d_6): δ 9.89 (2H, s), 9.79 (1H, s), 9.37 (1H, br), 8.13 (1H, t, J = 5.9 Hz), 7.21 (1H, d, J = 1.7 Hz), 7.16 (1H, d, J = 1.7 Hz), 7.13 (1H, d, J = 1.7 Hz), 7.05 (1H, d, J = 1.7 Hz), 5.95 (1H, d, J = 1.7 Hz), 5.87 (1H, d, J = 1.7 Hz), 3.85 (3H, s), 3.84 (3H, s), 3.83 (3H, s), 3.26 (2H, q, J = 6.1 Hz), 3.15 (2H, m), 3.00 (2H, m), 2.01 (2H, m), 1.97 (3H, s), 1.86 (4H, m). IR (KBr): 1644, 1583, 1530, 1464, 1435, 1402, 1259, 1201, 1133 cm^{-1}. HRFABMS found: 537.29348. Calculated for $C_{27}H_{37}N_8O_4$: 537.29378.

4-(Formylamino)-1-methyl-*N*-[1-methyl-5-({[1-methyl-5-({[3-(1-pyrrolidinyl)propyl]amino}carbonyl)-1*H*-pyrrol-3-yl]amino}carbonyl)-1*H*-pyrrol-3-yl]-1*H*-pyrrole-2-carboxamide (Fo-PyrMe-PyrMe-PyrMe-Pyrrp, 47). (NO_2)PyrMe-PyrMe-PyrMe-Pyrrp (210 mg, 0.400 mmol) was dissolved in ethanol (24 mL) at 0 °C under N_2. Pd/C (10%, 105 mg) was added and the reaction mixture was hydrogenated for 3 h. The catalyst was removed over Kieselguhr and the amine solution so formed was divided in half. To the first half ethyl formate was added and the mixture was heated under reflux for 48 h. Volatile material was removed under reduced pressure and the crude product was purified by HPLC. The product was obtained as a pale yellow solid (20 mg, 16%) with no distinct melting point. ^{1}H NMR (DMSO-d_6): δ 10.03 (1H, s), 9.89 (1H, s), 9.88 (1H, s), 9.38 (1H, br), 8.13 (2H, d & t), 7.21 (1H, d, J = 1.7 Hz), 7.18 (1H, d, J = 1.7 Hz), 7.15 (1H, d, J = 1.7 Hz), 7.06 (1H, d, J = 1.7 Hz), 5.95 (1H, d, J = 1.7 Hz), 5.92 (1H, d, J = 1.7 Hz), 3.84 (6H, s), 3.81 (3H, s), 3.54 (2H, m), 3.26 (2H, q, J = 6.1 Hz), 3.13 (2H, m), 3.00 (2H, m), 2.01 (2H, m), 1.85 (4H, m). IR (KBr): 1674, 1649, 1583, 1537, 1465, 1436, 1264, 1202, 1133 cm^{-1}. HRFABMS found: 523.27829. Calculated for $C_{26}H_{35}N_8O_4$: 523.27813.

4-(Formylamino)-*N*-[1-isopropyl-5-({[1-methyl-5-({[3-(1-pyrrolidinyl)propyl]amino}carbonyl)-1*H*-pyrrol-3-yl]amino}carbonyl)-1*H*-pyrrol-3-yl]-1-methyl-1*H*-pyrrole-2-carboxamide (Fo-PyrMe-Pyr*i*Pr-PyrMe-Pyrrp, 48). (NO_2)PyrMe-Pyr*i*Pr-PyrMe-Pyrrp (224 mg, 0.406 mmol) was dissolved in ethanol (25 mL) to which Pd/C (10%, 224 mg) was added at 0 °C under nitrogen with stirring. The reaction mixture was hydrogenated for 2.5 h at room temperature and atmospheric pressure. The catalyst was removed by filtration through Kieselguhr. Ethyl formate (15 mL) was added to the ethanolic solution, and then the reaction mixture was heated under reflux overnight. Ethanol and excess ethyl formate were removed under reduced pressure, and the crude product was purified by HPLC to give the required material as a white solid (42.7 mg, 16%) with no distinct melting point. ^{1}H NMR (DMSO-d_6): δ 10.07 (1H, s), 9.94 (1H, s), 9.92 (1H, s), 9.41 (1H, br, TFA), 8.16−8.12 (2H, m), 7.39 (1H, d, J = 1.8 Hz), 7.19 (1H, d, J = 1.8 Hz), 7.17 (1H, d, J = 1.8 Hz), 6.97 (1H, d, J = 1.8 Hz), 6.94 (1H, d, J = 1.8 Hz), 6.92 (1H, d, J = 1.8 Hz), 3.84 (3H, s), 3.61 (3H, s), 3.55 (2H, m), 3.26−3.24 (2H, m), 3.17−3.12 (2H, m), 2.99 (2H, m), 2.01 (2H, m), 1.86 (4H, m), 1.37−1.35 (6H, d, J = 6.7 Hz). IR (KBr): 3429, 1675, 1645, 1582, 1534, 1462, 1440, 1407, 1252, 1200, 1132 cm^{-1}. HRFABMS found: 551.31199. Calculated for $C_{28}H_{39}N_8O_4$: 551.30943.

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