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Original article

Amide isosteres in structure-activity studies of antibacterial minor groove binders

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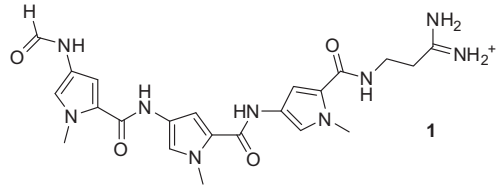
ABSTRACT

Antibacterial minor groove binders related to the natural product, distamycin, are development candidates for novel antibiotics. Alkenes have been found to be effective substitutes for the isosteric amide links in some positions and alkyl groups larger than methyl have been found to increase binding to DNA in both selectivity and affinity. However the impact of other isosteres such as diazenes and the position of an alkyl group with respect to DNA binding and antibacterial activity are not known. The effects of some systematic variations in the structure of polyamide minor groove binders are investigated. Isosteres of the amide link (alkenes and diazenes) are compared: it is shown that all three are competent for binding to DNA but that alkene links give the tightest binding and highest antibacterial activity; no significant antibacterial activity was found for compounds with a diazene link. Within a series of alkene linked compounds, the effect of branched *N*-alkyl substituents on binding to DNA and antibacterial activity is investigated: it was found that C3 and C4 branched chains are acceptable at the central pyrrole residue but that at the pyrrole ring adjacent to the basic tail group, a C4 branched chain was too large both for DNA binding and for antibacterial activity. The active branched alkyl chain compounds were found to be especially active against *Mycobacterium aurum*, a bacterium related to the causative agent of tuberculosis.

1. Introduction

The importance of new antibacterial agents has been widely recognized as resistance develops to existing drugs [1]. In several studies, we have shown that minor groove binders for DNA based loosely upon the structure of the natural product, distamycin **1**, are effective antibacterial agents [2–4]. Key structural features of these compounds are the presence of an alkene isostere replacement for the *N*-terminal amide [3] and branched *N*-alkyl chains on pyrrole components [2]. These features are seen in the *C*-alkyl thiazole, **2**, known as thiazotropsin A, and in the quinolyl alkene, **3a**. Because of the large number of potential structural variations, there is no systematic understanding of the structure–activity relationships associated with antibacterial activity. Moreover other isosteric replacements for amides than alkenes exist, such as diazenes. Within the highly active alkene series, the potential significance of different *N*-substituents in compounds such as **3a** has not been investigated. In this paper we describe the synthesis and properties of a novel class of minor groove binder, diazenyl isosteres of the amides related to the highly active alkenes. We also describe the synthesis and properties of *N*-isopropyl and *N*-2-methylpropyl analogues of the *N*-methylpyrroles in the quinolyl alkene **3a** to shed some light on the positions that are amenable to larger substituents in such antibacterial minor groove binders.



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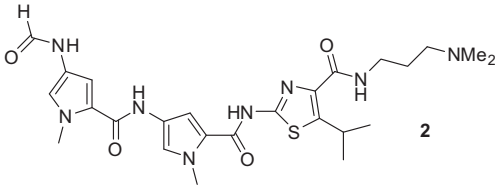

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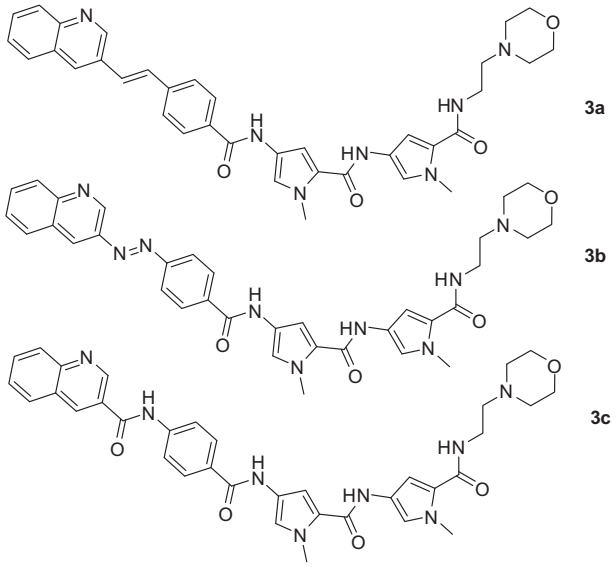
2. Results and discussion

2.1. Design of diazenyl and branched alkyl substituted minor groove binders

To a first approximation it would be expected that a diazenyl analogue of **3a** such as **3b** would have a very similar shape to **3a** but would present different opportunities for binding to DNA. Potential steric clashes with DNA through the alkenyl hydrogens would be removed and the



lone pairs of the nitrogen atoms introduced might be able to take part in hydrogen bonding with DNA and accommodate GC base pairs. Other effects such as the overall lipophilicity of **3a** and related compounds might also play a role in the biological properties of diazenyl linked minor groove binders [4]. However in the first instance, the binding of such compounds to DNA is of interest. The relationship of the three links in compounds with quinolyl head groups **3a**–**c** has been investigated by molecular modelling to examine whether isohelical geometry is affected. Calculations were performed using the cff91 force field [5] docking **3a**–**c** into the minor groove co-ordinates of a 5′-GCGATATATGCG-3′ DNA oligomer duplex using parameters to widen the minor groove [6] so as to accommodate two ligands binding side-by-side. The DNA oligomer was minimized *in vacuo* using 100 steps of the conjugate gradient (CG) algorithm and a distant-dependent dielectric constant of $4r_{ij}$, [7], with the terminal base pairs fixed. The ligands were manually docked to span the central bases of the oligomer and minimized with the DNA co-ordinates fixed until a derivative of 0.1 kcal mol^{-1} $Å^{-2}$ was achieved. All three ligand dimers appeared to adopt the same conformation upon minimisation (Fig. 1), with minimal heavy atom root mean square deviations (RMSDs) between them. The RMSDs of the bound **3a** dimer to the **3b** and **3c** dimers were 0.25 and 0.50 respectively and the RMSD of the **3b** dimer to the **3c** dimer was 0.34.

Minimum energy conformations of **3a**–**c** were calculated followed by superimposition of the ligands as monomers with each other. This showed that they had to adapt their conformations to match the requirements of the DNA dodecamer, with **3c** (amide linked ligand) requiring a slightly greater adaptation energy than **3b**, and again greater than **3a** (Fig. 2 and Table 1). This evaluation suggests that a diazenyl minor groove binder would be expected to

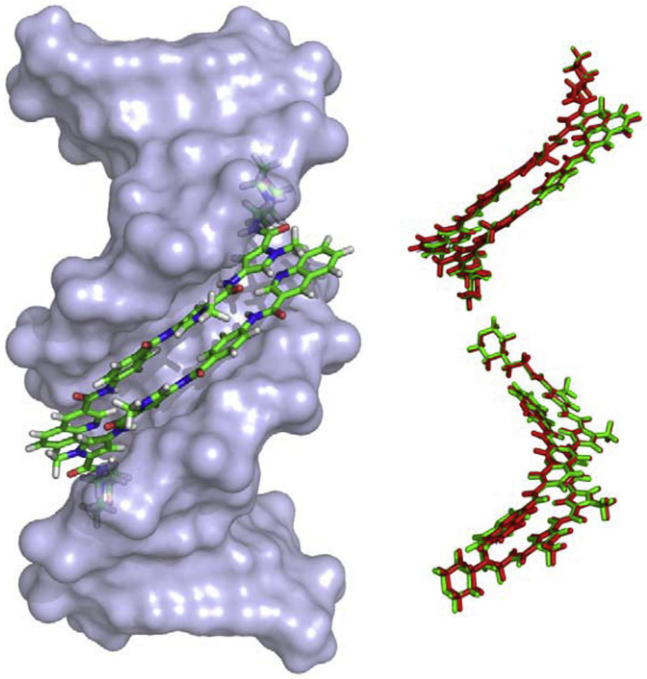


Fig. 1. Left: minimised conformation of **3c** dimer (stick model) in the minor groove of a 5′-GCGATATATCGC-3′ DNA dodecamer (in grey, surfaced rendering). Right: two views (the bottom view is rotated by 90° around the *Z* axis of DNA when compared with the left-hand-side and top pictures) of minimised conformations of **3a** (alkene, red), **3b** (diazene, blue) and **3c** (amide, green) dimers in the minor groove of a 5′-GCGATATATCGC-3′ DNA dodecamer (not shown for clarity). The **3b** dimer does not appear as it overlaps the **3a** dimer almost perfectly. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

bind to DNA in a similar manner to the alkene but that there might be quantitative differences with respect to the strength of binding. Greater differences might be expected between alkene and diazene on the one hand and amide on the other.

The comparison of amide, alkene, and diazene as isosteric links in minor groove binders has been investigated in three series

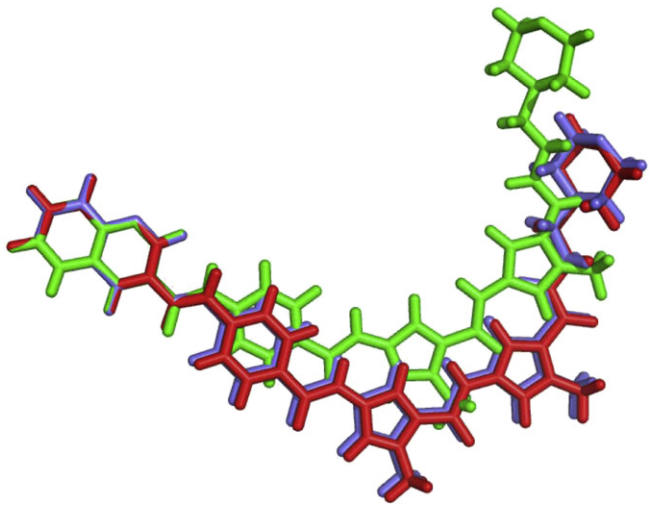


Fig. 2. Superimposition of **3a** (red), **3b** (blue) and **3c** (green) on their quinoline rings (on the left-hand-side) showing that the amide group of **3c** favours a tighter curvature when compared with the alkene (**3a**) and diazene (**3b**) groups. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 1
Calculated energies (values are in kcal.mol^{-1}) of monomers of **3a**–**c**.

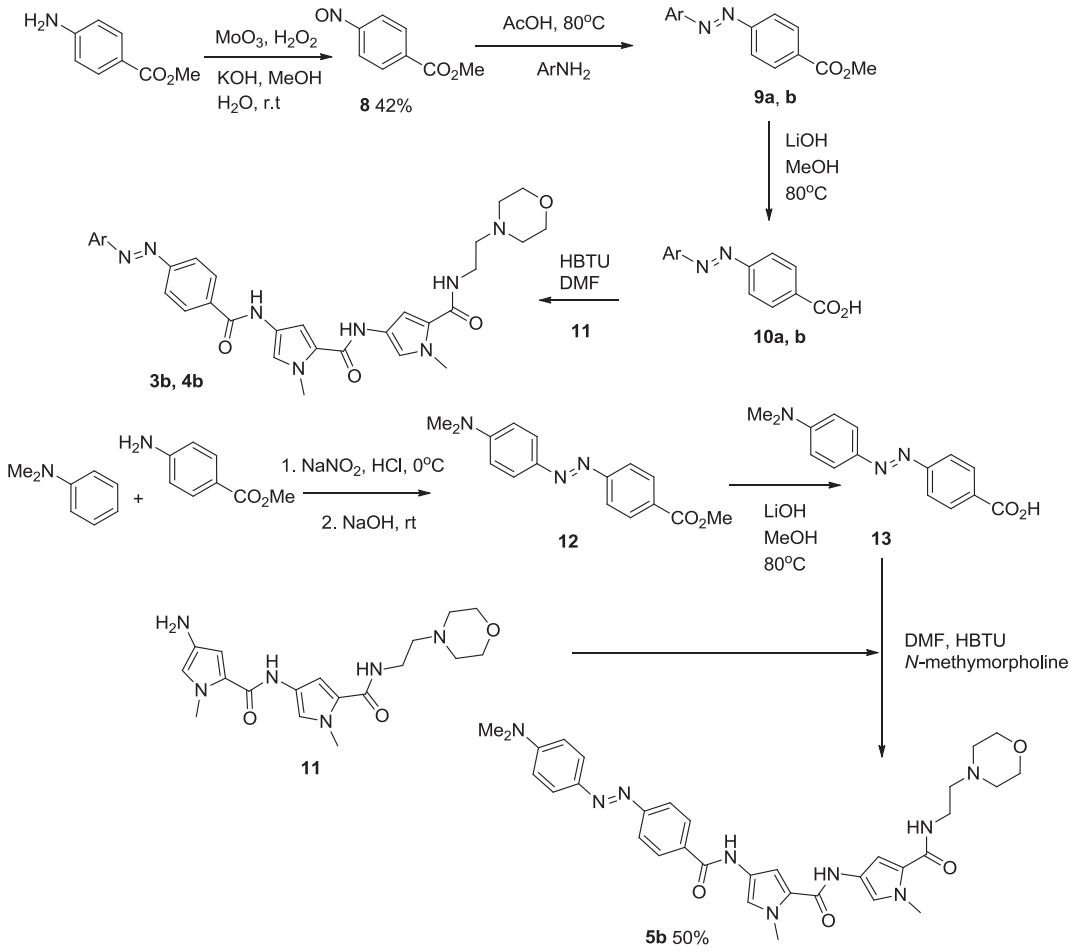
Ligand	Minimised energy *in vacuo* (E1)	Minimised energy in DNA (for a single ligand) (E2)	Adaptation energy (E2-E1)
3a	101.5	104.4	2.9
3b	102.4	105.9	3.5
3c	103.8	107.4	3.7

including the quinolyl series evaluated above. Additionally, the 3-methoxyphenyl compounds (**4a**–**c**) and 4-dimethylaminophenyl compounds (**5a**–**c**) have been prepared and studied.

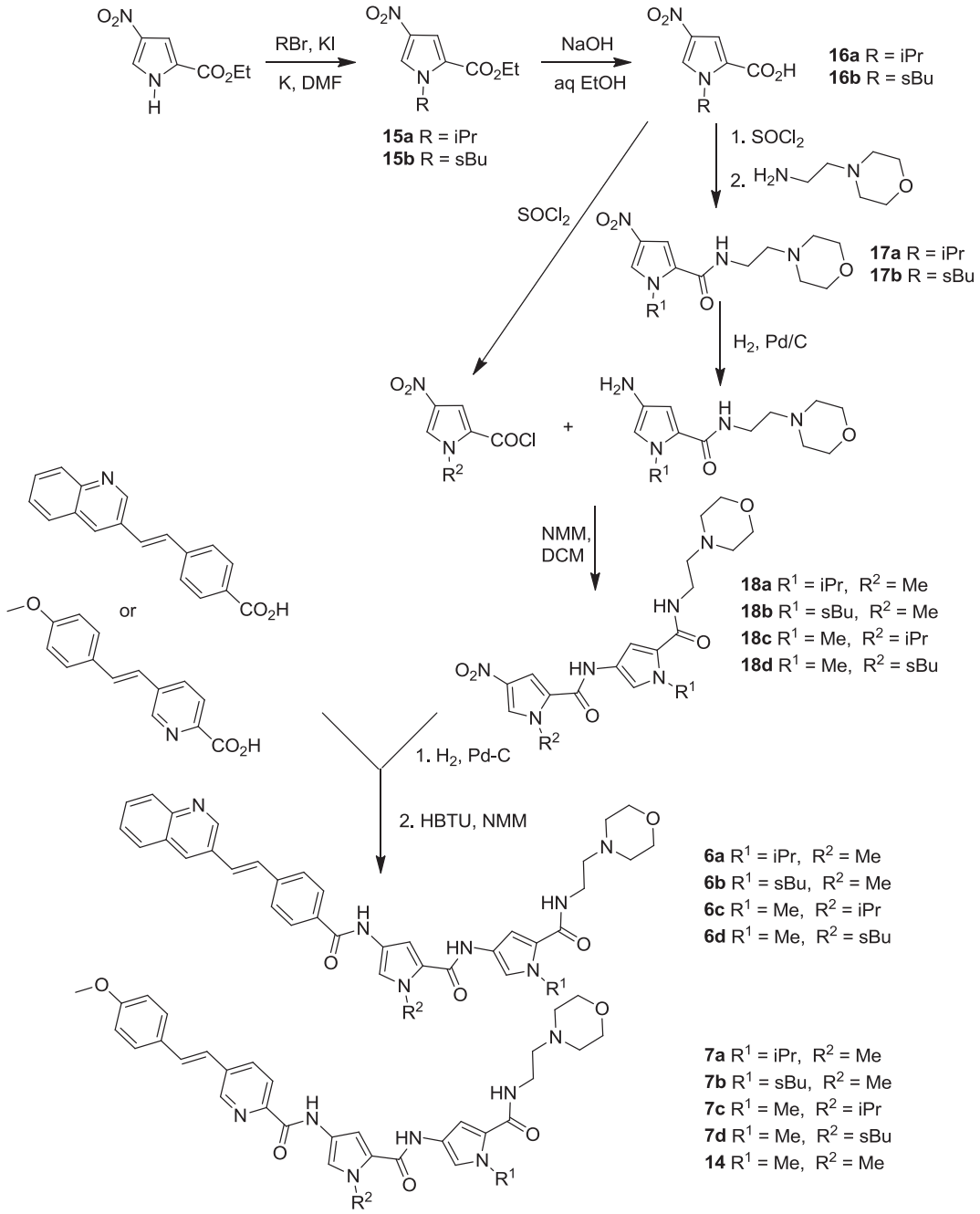
Turning to the effects of alkyl group substitution on the pyrrole nitrogen atoms, structural studies of thiazotropsin A **2** and other compounds containing isopropyl substituents have shown the importance of the isopropyl group in the side-by-side interaction of two molecules of these minor groove binders in the DNA groove [8,9]; the intermolecular contacts between the two molecules of **2** show close interactions between the isopropyl group of **2** and the dimethylamino tail group of its partner in the minor groove of its preferred double stranded oligodeoxynucleotide [8]. It has further been shown that if the branched *N*-alkyl chains in a minor groove binder are too close together, for example on adjacent pyrrole rings, the formation of strong 2:1 ligand/DNA complexes does not occur [2]. In order to understand the extent to which increasing the size of such *N*-alkyl groups might be compatible with binding to DNA and antibacterial activity, we have prepared a series of *N*-alkyl analogues of our most active antibacterial alkene-containing minor groove binders [3]. A panel of eight compounds (**6a**–**d**, and **7a**–**d**, see Scheme 2) was assembled in which isopropyl, 2-methylpropyl, and methyl groups were chosen.

2.2. Synthesis of diazenyl minor groove binders

To our knowledge, diazenyl substituents have been introduced to minor groove binders as pendant chromophores but not as an intrinsic link within the compound [10]; new synthetic routes were therefore required. The strategy employed was to prepare the diazenyl dimers with each of the three head groups and to couple them to the pyrrolyl-pyrrolyl-morpholinoethyl component that has been used previously (Scheme 1) [3]. For the quinolyl and 3-methoxyphenyl compounds, **3b** and **4b**, that contain a head group arene or heteroarene that was unreactive for diazo coupling, condensation with methyl 4-nitrosobenzoate afforded the required precursors **10a**, **b** [11,12]. For the 4-dimethylamino compound, **10c**, diazo coupling was used [13]. Compounds **3a**, **4a**, and **14** were available from previous studies [2,3] and the remaining alkenyl and amide linked minor groove binders to complete the panel of compounds were prepared by methods used routinely using the same coupling strategy. The *N*-alkyl pyrroles required for the synthesis of compounds **6**–**7** were prepared by alkylation of the potassium salt of ethyl 5-nitropyrrole-2-carboxylate as described previously [2]; assembly of the minor groove binders also followed standard methods as illustrated in Schemes 1 and 2.



Scheme 1. Synthesis of diazenyl minor groove binders.



Scheme 2. Synthesis of branched alkyl substituted compounds.

2.3. Assessment of binding to DNA

The accumulated evidence with our alkene and amide containing minor groove binders strongly suggests that they bind most readily to AT rich regions of DNA; this is consistent with the presence of the two pyrroles and the phenyl group, all of which are incompatible with binding to GC base pairs. There are many techniques available to investigate the binding of ligands to DNA and in this study, we have focused on two, melting temperature measurements and capillary electrophoresis. Melting temperature measurements give an indication of the ability of a minor groove binder to stabilize the DNA duplex of an oligonucleotide and have been widely used in studies of this class of compound and the melting temperature can be correlated with specific binding to oligoDNA duplexes [14]. The oligonucleotide chosen as target for the current study was GCGATATATGCG and its complement; this was selected because of the AT run and because its melting temperature in the absence of minor groove binding was expected to be in the range 45–50 °C. If binding occurs, the melting temperature will usually be increased, in cases of strong binding up to and above 20 °C. However, binding may still be occurring if no increase in melting temperature is observed although such a result indicates that the oligonucleotide duplex is not strongly stabilized by the minor groove binder. It is important, therefore, to use further techniques for studying binding to DNA and in our work, capillary electrophoresis has been especially useful [15]. It has been found that DNA complexes with minor groove binders usually show different retention times in capillary electrophoresis from the

uncomplexed oligonucleotide. In principle, this makes it possible both to compare the affinity of a DNA binder to a given sequence and to investigate the stoichiometry of binding [16]. However since a DNA-oligo complex peak may overlap with the parent oligo peak in some cases, the absence of a new peak in a CE experiment does not of itself show that binding is not occurring. In both of these methods, therefore, positive results can be taken as conclusive but negative results are inconclusive. The data we have obtained for the isosteres panel are shown in Table 2 and those for the *N*-alkyl panel in Table 3.

2.3.1. Assessment of amide isosteres

The observed T_m depends upon the detailed experimental conditions and the affinity of the ligand for the particular oligonucleotide target selected. In these experiments, it was necessary in some cases to use four equivalents of ligand to observe a significant change in T_m and in some, two T_ms were observed, one corresponding to the free oligonucleotide and the other to the ligand/DNA complex. Although far from a quantitative measurement equivalent to a dissociation constant, the observations reported here give an indication of the affinity of the three series of ligands and for the DNA target selected and emphasise that the results are obtained under equilibrium conditions.

All the compounds containing a quinolyl head group (**3a**–**c**) bound strongly to the target oligonucleotide according to T_m measurements. In the case of the amide linked minor groove binder **3c**, there was no additional peak observed in the CE experiment which, as noted above, could be due to overlapping peaks. It is probable that the quinoline group itself plays a major role in binding to DNA which would make it difficult to perceive differences in affinity according to the link present. Footprinting studies have shown that the quinolyl alkenyl ligand **3a** binds exceptionally strongly to larger DNA oligonucleotides at sub-micromolar concentrations and at several AT containing sites (Prof. Keith Fox, unpublished observations), in support of the dominant effect of the quinolyl group in these cases. With respect to our modelling study, it is clear that the binding affinity of the dimers compensates for any adaptation energy penalties incurred through geometrical rearrangements to have compatible isohelicity with the groove floors.

The 3-methoxyphenyl head group provided a series of compounds (**4a**–**c**) with apparently ambiguous behaviour. The alkene linked compound **4a** has strong antibacterial properties but apparently did not stabilize this particular DNA duplex according to T_m measurements. Nevertheless, the observation of a new peak in the CE is good evidence for complexation and this has been confirmed by a detailed NMR study of this ligand [17]; the interaction of **4a** with its DNA host was resolved at atomic detail and shows evidence for specific hydrogen bonding of amide and methoxy groups. In terms of binding to this oligonucleotide, the diazenyl isostere **4b** behaves very similarly in that there is little duplex stabilization but evidence for binding from CE. This is the first clear evidence for the similarity in molecular recognition terms between alkene and diazene. In contrast, the amide linked minor groove binder **4c** had a significant but smaller increase in T_m although unlike its alkene isostere **4a**, an additional peak was not observed in the CE trace.

The 4-dimethylamino head group series (**5a**–**c**) showed a different pattern. In this series, the amide **4c** had both a substantial T_m increase and showed a new peak in the CE trace. The diazene isostere **4b** showed similar evidence of binding from both measurements. However the alkene isostere **4a** showed very little evidence of binding to this particular target by either technique; at present, we have no explanation for this observation.

Taken together these results emphasise that multiple interactions govern the association of a given minor groove binder with a particular DNA target and it is probable that some of the compounds investigated here have different oligonucleotide targets. On the basis of the available evidence, however, it appears that the diazenyl compounds are less effective ligands for DNA than their amide or alkene isosteres for this particular representative type of AT rich sequence. Bearing in mind the similarity in geometry observed in the molecular modelling, it appears that both the electronic and hydrogen bonding properties of the diazene link may be relevant in reducing binding to this short oligonucleotide compared with the alkene [24, 26].

Table 2
Evaluation of ligand binding to GCGATATATGCG and its complement.

Sample	Link	Equiv	1st T_m	2nd T_m	ΔT_m	CE results
Oligo target	–	–	48	–	–	–
3a (quinoline)	alkene	4	66	–	18	New peak
		2	46	68	20	–
3b	diazo	4	48	65	17	New peak
3c	amide	4	46	65	17	No new peak
4a (3-MeO)	alkene	4	46	–	–	New peak
4b	diazo	4	49	–	1	New peak
4c	amide	4	60	–	12	No new peak
		2	58	–	10	
5a (4-NMe_2)	alkene	4	50	–	2	No New peak
5b	diazo	4	56	–	8	New peak
5c	amide	4	48	66	18	New peak

Table 3
Evaluation of binding of branched alkyl chain minor groove binders. 2 equivalents of minor groove binder were used.

Compound	R^1	R^2	T_m (°C)	T_m increase
3a	Me	Me	66	19
6a	iPr	Me	58.9	10
6b	sBu	Me	47.1	0
6c	Me	iPr	47.0 66.0	18
6d	Me	sBu	47.1 63.1	15
14	Me	Me	64.0	16
7a	iPr	Me	63.9	16
7b	sBu	Me	61.1	13
7c	Me	iPr	67.1	19
7d	Me	sBu	63.9	16

2.3.2. Branched N-alkyl minor groove binders panel

The introduction of the isopropyl group into thiazatropsin A **2** was an important structural innovation together with the thiazole, both being hydrophobic groups [8]. The extent to which branched alkyl groups can modulate DNA binding and biological activity is therefore of general interest in this field, as explained above. Taking two of our lead antibacterial compounds as prototypes (**3a** and **14**), we therefore prepared a series of eight new compounds to evaluate the effect of isopropyl and 2-methylpropyl (*s*-butyl) groups as pyrrole nitrogen substituents with respect to DNA binding and biological activity. The results for the DNA binding study are shown in Table 3.

It is clear from these data that the *N*-alkyl group at the C-terminal pyrrole (R^1) is more strongly sensitive to substitution by the larger alkyl groups than the internal pyrrole (R^2); with the quinolyl head group (**6a** and **6b**) stabilisation of this duplex appears to be very sensitive to the size of the *N*-alkyl group, the isopropyl substituted compound **6a** binding less strongly than the methyl and the 2-methylbutyl **6b**. It is possible that with the quinolyl head group the ligand–ligand association is more intimate close to the quinolyl group than with other smaller head groups and that the larger alkyl groups adjacent to the quinolyl

group in the dimer prevent the association necessary for 2:1 ligand/DNA binding. Our previous work has shown that these minor groove binders preform dimers before binding with DNA, rather than associate sequentially [18].

2.4. Biological activity

The antibacterial activity of all compounds described here has been evaluated against representative strains of Gram positive and Gram negative bacteria as described previously [2,3]. No significant activity with respect to Gram negative bacteria was found but some compounds were strongly antibacterial against *Staphylococcus aureus* (two strains), *Streptococcus faecalis*, and *Mycobacterium aurum* (Table 4, compounds with quantified activity from this study and reference compounds **3a** and **4a** only shown). In addition, measurable but not significant activity was found for the diazenyl compound **3b** against the fungi *Aspergillus niger* and *Candida albicans*. From the point of view of the configuration, structure, and binding to DNA of the quinolyl diazenyl linked compound **3b**, the lack of antibacterial activity is notable, a fact that emphasizes the large number of factors involved in obtaining antibacterial activity, including access to the target as well as intrinsic affinity. The same is true of the diazenyl analogue **4b** with the 3-methoxyphenyl head group, although this compound did not stabilize the DNA duplex studied. None of the 4-dimethylaminophenyl compounds **5** were antibacterial which may in part be due to the lack of a crucial hydrogen bond to the head group that we have described elsewhere [4]. On the other hand, the antibacterial activity of the branched alkyl compounds **6** and **7** is in line with results from previous studies [3] with the quinolyl head group showing especially strong activity against both *S. aureus* and *M. aurum*; the latter activity is the strongest that we have found in this series of compounds.

In our studies of antibacterial minor groove binders there has been an association between antibacterial activity and binding to DNA as measured by several methods [2–4,16]. Thus where no or weak DNA binding was observed, little antibacterial activity was found. It has even been possible to show that specific hydrogen bonding sites in the minor groove binder at the head group or at one of the internal amides is important for both DNA binding and antibacterial activity [17]. However this connection is far from proving that DNA binding is the sole or primary mechanism of antibacterial activity. Recent studies have cautioned against drawing conclusions about the biological mechanism of action and have drawn attention to the importance of the bacterial cell wall and the depolarisation of the membrane by minor groove binders [19]. Consistent with these observations, in preliminary studies with selected compounds from our library, we have found that our compounds do not inhibit DNA biosynthesis but show some inhibition of bacterial DNA gyrase. Other studies have shown conclusively that minor groove binders interfere with DNA processing enzymes (gyrase and helicase) [20,21].

In addition to the potential importance of specific hydrogen bonds, the lipophilicity of our compounds has also been connected with antibacterial activity [4]. There remain two major questions about the biological activity of our minor groove binders namely the origin of the antibacterial activity and the reason for the lack of toxicity to several mammalian cell lines and the answers to these questions require more detailed microbiological studies which we are seeking to address.

Table 4
Antibacterial and antifungal activity of branched *N*-alkyl substituted minor groove binders and diazenyl minor groove binders. Compounds were tested at 500 μM (for *Escherichia coli*) and 200 μM (for *S. aureus*). nd = not determined.

Compound	*E. coli*	*S. aureus*	*S. aureus*	*M. aurum*
	% of control	% of control	MIC (μM)	MIC (μM)
6a	94.7	0.8	<1	2
6b	74.2	0.3	nd	nd
6c	80.9	2.3	<1	2
6d	69.0	2.9	<1	2
7a	103.2	8.5	4	8
7b	115.6	2.8	16	16
7c	98.6	6.7	16	8
7d	100.9	3.2	8	31

Compound	*S. aureus* 1	*S. aureus* 2	*S. faecalis*	*A. niger*	*C. albicans*
	MIC (μM)	MIC (μM)	MIC (μM)	MIC (μM)	MIC (μM)
3a	3.1	12.5	25	50	25
3b	>100	>100	>100	50	25
4a	12.5	25	6.25	50	100
5a	>100	>100	>100	>100	100

3. Experimental

3.1. General

^{1}H and ^{13}C NMR spectra were measured on a Bruker DPX-400 MHz spectrometer with chemical shifts given in ppm (δ values), relative to proton and carbon traces in solvent. Coupling constants are reported in Hz. IR spectra were recorded on a Perkin Elmer, 1 FT-IR spectrometer. Elemental analysis was carried out on a Perkin Elmer 2400, analyser series 2. Mass spectra were obtained on a Jeol JMS AX505. Anhydrous solvents were obtained from a Puresolv purification system, from Innovative Technologies, or purchased as such from Aldrich. Melting points were recorded on a Reichert hot-stage microscope, and are uncorrected. Chromatography was carried out using 200–400 mesh silica gels, or using reverse-phase HPLC on a water system using a C18 Luna column with the gradient given in Table 5.

3.2. Monomers and tail groups

The following were prepared as previously described:

3.2.1. Monomers [22]

1-Methyl-4-nitro-1*H*-pyrrole-2-carboxylic acid 2,2,2-Trichloro-1-(1-methyl-1*H*-pyrrol-2-yl)ethanone
2,2,2-Trichloro-1-(1-methyl-4-nitro-1*H*-pyrrol-2-yl)ethanone
N-[3-(Dimethylamino)propyl]-1-methyl-4-nitro-1*H*-pyrrole-2-carboxamide
Ethyl 1-methyl-4-nitro-1*H*-pyrrole-2-carboxylate

3.2.2. Dimers [2,3,22]

N-[3-(Dimethylamino)propyl]-1-methyl-4-{[(1-methyl-4-nitro-1*H*-pyrrol-2-yl)carbonyl]amino}-1*H*-pyrrole-2-carboxamide

Table 5
Programme for HPLC purification of minor groove binders.

Time/Pump	A	B	Flow rate (ml/min)
0	90	10	4
28	30	70	4
33	10	90	4
38	90	10	4
40	90	10	0

1-Methyl-*N*-[2-(4-morpholinyl)ethyl]-4-nitro-1*H*-pyrrole-2-carboxamide
1-Methyl-4-{[(1-methyl-4-nitro-1*H*-pyrrol-2-yl)carbonyl]amino}-*N*-[2-(4-morpholinyl)ethyl]-1*H*-pyrrole-2-carboxamide

3.2.3. Nitroso compounds [11]

1-Methoxy-3-nitrosobenzene
Ethyl 4-nitrosobenzoate

3.3. New monomers

3.3.1. General alkylation procedure

Ethyl 4-nitro-1*H*-pyrrole-2-carboxylate was dissolved in DMF (40 ml, anhydrous) under nitrogen gas and to this was added potassium metal (2 eq.) whilst maintaining the nitrogen atmosphere within the flask. The reaction mixture was heated to 100 °C and left at that temperature for 1 h, with stirring. The reaction mixture was allowed to cool to 50–60 °C then the required bromoalkane (2 eq.) and potassium iodide (2 eq.) were added, still maintaining the inert atmosphere, and then the reaction mixture was heated, with stirring, to 100 °C and left for 5 h at that temperature. The reaction mixture was left stirring for a further 12 h at room temperature. The DMF was removed at 50 °C under reduced pressure and the crude product was dissolved in DCM (50 mL) and the salt was extracted with water (2 × 20 mL). The organic layer was dried over magnesium sulphate, filtered and the solvent removed at 30 °C under reduced pressure. The crude product was purified by flash column chromatography using an appropriate mobile phase. The material with the required R_f value was collected and the solvent was removed at 30 °C under reduced pressure to furnish the desired product.

3.3.2. Ethyl 1-isopropyl-4-nitro-1H-pyrrole-2-carboxylate **15a**

From ethyl 4-nitro-1*H*-pyrrole-2-carboxylate (2.370 g, 12.87 mmol) and potassium metal (977 mg, 25 mmol) and 2-bromopropane (2.345 mL, 25 mmol) with potassium iodide (4.150 g, 25 mmol). The purification used 1:6 ethyl actetate:hexane as the mobile phase affording an off-white solid (850 mg, 29%), m.p. 60–62 °C. ν_{max} (KBr): 3155, 2984, 1713, 1536, 1502, 1285, 1223, 1175, 1135, 1110, 1084 cm^{-1} δ_H (DMSO-d_6): 7.80 (1H, d, N*H*, $J = 2.0$), 7.45 (1H, d, N*H*, $J = 2.0$), 5.50 (1H, septet, CH_3CHCH_3, $J = 6.6$), 4.33 (2H, q, OCH_2CH_3, $J = 7.1$), 1.50 (6H, d, CH_3CHCH_3, $J = 6.7$), 1.38 (3H, t, CH_2CH_3, $J = 7.6$).

3.3.3. Ethyl 1-sec-butyl-4-nitro-1H-pyrrole-2-carboxylate **15b**

From ethyl 4-nitro-1*H*-pyrrole-2-carboxylate (1.536 g, 8.34 mmol) and potassium metal (585 mg, 14.96 mmol) with 2-bromobutane (1.640 mL, 15.01 mmol) and potassium iodide (2.132 g, 12.84 mmol) as described. The purification used 1:3 ethyl acetate:hexane as the mobile phase affording a pale yellow oil (614 mg 31%). ν_{max} (NaCl): 3143, 2971, 2935, 2879, 1716, 1537, 1505, 1295, 1220, 1176, 1104 cm^{-1} δ_H ($CDCl_3$): 7.75 (1H, d, N*H*, $J = 2.0$), 7.74 (1H, d, N*H*, $J = 2.0$), 5.38 (1H, sextet, CH_2CHCH_3, $J = 6.9$), 4.32 (2H, q, OCH_2CH_3, $J = 7.1$), 1.76–1.85 (2H, m, CH_3CH_2CH), 1.48 (3H, d, $CHCH_3$, $J = 6.8$), 1.38 (3H, t, CH_2CH_3, $J = 7.1$), 0.89 (3H, t, CH_3CH_2, $J = 7.4$) δ_C: ($CDCl_3$) 160.18; 135.89; 123.02; 111.91; 60.80; 51.80; 30.81; 21.38; 14.29; 10.41. HRMS FAB: found 240.1109; $C_{11}H_{17}N_2O_4$ requires 240.110 $[M + 1]^+$.

3.3.4. 1-Isopropyl-4-nitro-1H-pyrrole-2-carboxylic acid **16a**

Ethyl 1-isopropyl-4-nitro-1*H*-pyrrole-2-carboxylate **15a** (650 mg, 2.87 mmol) was dissolved in ethanol (4 mL) and to this was added a solution of sodium hydroxide (420 mg, 10.50 mmol) in water (10 mL) whilst stirring. The reaction mixture was heated at reflux for 2 h, then cooled to 0 °C (ice bath) and acidified with concentrated hydrochloric acid whilst stirring. The precipitate was filtered off, washed with water (2 × 15 mL) and dried at 50 °C under reduced pressure for 8 h to give the product as a white solid (445 mg, 78%), m.p. 194–195 °C. ν_{max} (KBr): 3155, 2983, 1682, 1535, 1507, 1287, 1246, 1180, 1137, 1115. δ_H (DMSO-d_6): 13.16 (1H, bs, CO_2H), 8.35 (1H, d, N*H*, $J = 2.0$), 7.27 (1H, d, N*H*, $J = 2.0$), 5.42 (1H, septet, CH_3CHCH_3, $J = 6.7$), 1.42 (6H, d, CH_3CHCH_3, $J = 6.7$)

3.3.5. 1-sec-Butyl-4-nitro-1H-pyrrole-2-carboxylic acid **16b**

Ethyl 1-*sec*-butyl-4-nitro-1*H*-pyrrole-2-carboxylate **15b** (614 mg, 2.56 mmol) was dissolved in ethanol (4 mL) and to this was added a solution of sodium hydroxide (420 mg, 10.50 mmol) in water (10 mL) whilst stirring. The reaction mixture was heated at reflux for 2 h, cooled to 0 °C (ice bath) and acidified with concentrated hydrochloric acid whilst stirring. The precipitate was filtered off, washed with water (2 × 15 mL) and dried at 50 °C under reduced pressure for 4 h to give the product as white solid at a yield of (565 mg, 96%), m.p. 153–156 °C. ν_{max} (KBr): 2923, 1682, 1511, 1292, 1242, 1183 cm^{-1} δ_H NMR ($CDCl_3$): 7.81 (1H, d, N*H*, $J = 2.0$), 7.58 (1H, d, N*H*, $J = 2.0$), 5.34 (1H, sextet, CH_2CHCH_3, $J = 6.9$), 1.78–1.88 (2H, m, CH_3CH_2CH), 1.50 (3H, d, CH_2CH_3, $J = 7.1$), 0.91 (3H, t, CH_3CH_2, $J = 7.4$) δ_C: ($CDCl_3$) 164.57; 136.16; 124.18; 121.70; 114.91; 55.79; 30.80; 21.38; 10.29. HRMS FAB: found 212.0796; $C_9H_{13}N_2O_4$ requires 212.0797 $[M + 1]^+$.

3.3.6. General procedure for coupling the pyrrole carboxylic acid with aminoethylmorpholine

The pyrrole carboxylic acid was dissolved in thionyl chloride (4 mL) then the reaction mixture was heated to reflux and left for 3 h. Excess thionyl chloride was removed at 30 °C under reduced pressure and the acid chloride so formed was used without further purification. *N*-aminoethyl morpholine (1.2 eq.) was dissolved in DCM (20 mL, anhydrous) to which NMM (2 eq.) was added. The acid chloride was dissolved in DCM (5 mL, anhydrous) then added dropwise to the aminoethylmorpholine solution with stirring. The reaction mixture was left stirring for 15 h. The crude product was extracted with a solution of sodium carbonate (540 mg, 5.09 mmol) in water (25 mL) and the organic layer was dried over magnesium sulphate, filtered and the solvent was removed at 30 °C under reduced pressure. The crude product obtained was purified by flash column chromatography using ethyl actetate as the mobile phase. Material with the required R_f value was collected and the solvent removed at 30 °C under reduced pressure to afford the desired product.

3.3.7. 1-Isopropyl-N-[2-(4-morpholinyl)ethyl]-4-nitro-1H-pyrrole-2-carboxamide **17a**

From 1-isopropyl-4-nitro-1*H*-pyrrole-2-carboxylic acid **16a** (350 mg, 1.77 mmol) and aminoethylmorpholine (250 μl, 1.91 mmol) using NMM (250 μl, 2.27 mmol). The product was a pale yellow solid (394 mg, 72%), m.p. 107–110 °C. ν_{max} (KBr): 3312, 3121, 2928, 1638, 1560, 1529, 1503, 1420, 1172, 1110 cm^{-1} δ_H ($CDCl_3$): 7.75 (1H, d, N*H*, $J = 2.2$), 7.06 (1H, d, N*H*, $J = 1.9$), 6.93 (1H, bs, CON*H*), 5.51 (1H, septet, CH_3CHCH_3, $J = 6.7$), 3.79 (4H, t, $CH_2CH_2OCH_2CH_2$, $J = 4.6$), 3.54 (2H, q, $NHCH_2CH_2N$, $J = 5.4$), 2.68 (2H, t, $NHCH_2CH_2N$, $J = 6.0$), 2.61 (4H, bt, $CH_2CH_2NCH_2CH_2$, $J = 4.4$), 1.48 (6H, d, CH_3CHCH_3, $J = 6.6$) δ_C: ($CDCl_3$) 160.66; 135.47; 126.18; 121.75; 107.30; 66.32; 57.01; 53.26; 50.06; 35.92; 23.70. HRMS FAB: found 311.1721; $C_{14}H_{33}N_4O_4$ requires 311.1719 $[M + 1]^+$.

3.3.8. 1-sec-Butyl-N-[2-(4-morpholinyl)ethyl]-4-nitro-1H-pyrrole-2-carboxamide **17b**

From 1-*sec*-butyl-4-nitro-1*H*-pyrrole-2-carboxylic acid **16b** (99 mg, 0.47 mmol) and aminoethylmorpholine (125 μl, 0.95 mmol)

using NMM (125 μl, 1.14 mmol) giving the product as a pale orange oil, (112 mg, 74%). ν_{max} (NaCl): 3335, 2965, 1650, 1292, 1116 cm^{-1} δ_H ($CDCl_3$): 7.72 (1H, d, N*H*, $J = 1.6$), 7.01 (1H, d, N*H*, $J = 1.7$), 6.55 (1H, bs, CON*H*), 5.34 (1H, sextet, CH_2CHCH_3, $J = 6.8$), 3.74 (4H, t, $CH_2CH_2OCH_2CH_2$, $J = 4.4$), 3.48 (2H, q, $NHCH_2CH_2N$, $J = 5.6$), 2.59 (2H, t, $NHCH_2CH_2N$, $J = 5.6$), 2.51 (4H, t, $CH_2CH_2NCH_2CH_2$, $J = 4.4$), 1.75–1.85 (2H, m, CH_3CH_2CH), 1.47 (3H, d, $CHCH_3$, $J = 6.8$), 0.88 (3H, t, CH_3CH_2, $J = 7.6$) δ_C: ($CDCl_3$) 160.56; 135.65; 126.92; 127.9 21.94; 106.65; 66.94; 56.81; 55.30; 53.36; 35.64; 30.93; 21.52; 10.40. HRMS FAB: found 325.1872; $C_{15}H_{25}N_4O_4$ requires 325.1872 $[M + 1]^+$.

3.4. New dimers

3.4.1. General procedure for the coupling reaction to form the dimers

The compound containing the pyrrole ring attached to the tail group was dissolved in ethanol (10 mL), cooled to 0 °C (ice bath) and then to this was added 10% palladium over charcoal (2 weight eq.) under nitrogen. The reaction mixture was hydrogenated at room temperature and atmospheric pressure for 3 h. The catalyst was removed over Kieselguhr and the solvent removed at 50 °C under reduced pressure to give the amine as an amorphous solid which was used in the next step without further purification. The pyrrole carboxylic acid (1 eq.) was dissolved in thionyl chloride (3 mL) and this was heated under reflux for 3 h. Excess thionyl chloride was removed at 50 °C under reduced pressure and the resulting acid chloride was used without further purification. The amine was dissolved in DCM (10 mL, anhydrous) to which NMM (2 eq.) was added at room temperature with stirring. The acid chloride was dissolved in DCM (10 mL, anhydrous) then it was added to the amine solution, dropwise, with stirring. The reaction was left for 14 h. The solvent was removed at 50 °C under reduced pressure then the crude product was dissolved in DCM (30 mL) and extracted with a solution of sodium carbonate (600 mg, 5.66 mmol) in water (20 mL). The organic layer was collected, dried over magnesium sulphate and the solvent removed at 50 °C under reduced pressure. The crude product was purified by flash column chromatography using an appropriate mobile phase. Material with the required R_f value was collected and the solvent removed at 50 °C under reduced pressure to afford the desired product.

3.4.2. 1-Isopropyl-4-{[(1-methyl-4-nitro-1H-pyrrol-2-yl)carbonyl]amino}-N-[2-(4-morpholinyl)ethyl]-1H-pyrrole-2-carboxamide **18a**

From 1-isopropyl-*N*-[2-(4-morpholinyl)ethyl]-4-nitro-1*H*-pyrrole-2-carboxamide (350 mg, 1.13 mmol) and 1-methyl-4-nitro-1*H*-pyrrole-2-carboxylic acid (192 mg, 1.13 mmol) used as the acid chloride in the presence of NMM (300 μl, 2.72 mmol). The purification used 99:1 ethyl actetate:triethylamine as the mobile phase affording product as a pale orange solid, (360 mg, 74%), m.p. 97–100 °C. ν_{max} (KBr): 3394, 3311, 3128, 2959, 2928, 2854, 2813, 1657, 1573, 1535, 1501, 1253, 1202, 1189, 1177, 1141, 1114, 1069 cm^{-1} δ_H ($CDCl_3$): 7.61 (1H, d, N*H*, $J = 1.8$), 7.58 (1H, bs, CON*H*), 7.39 (1H, d, N*H*, $J = 1.7$), 7.18 (1H, d, N*H*, $J = 1.7$), 6.51 (1H, d, N*H*, $J = 1.7$), 6.45 (1H, bs, CON*H*), 5.54 (1H, septet, CH_3CHCH_3, $J = 6.7$), 4.05 (3H, s, NCH_3), 3.76 (4H, t, $CH_2CH_2OCH_2CH_2$, $J = 4.6$), 3.49 (2H, q, $NHCH_2CH_2N$, $J = 5.6$), 2.59 (2H, t, $NHCH_2CH_2N$, $J = 6.1$), 2.52 (4H, t, $CH_2CH_2NCH_2CH_2$, $J = 4.4$), 1.45 (6H, d, CH_3CHCH_3, $J = 6.7$) δ_C: ($CDCl_3$) 161.73; 157.47; 135.02; 127.00; 126.34; 123.43; 121.24; 113.06; 107.12; 103.36; 66.83; 57.12; 53.32; 48.48; 38.02; 35.42; 23.82. HRMS FAB: found 433.2202; $C_{20}H_{29}N_6O_5$ requires 433.2199 $[M + 1]^+$.

3.4.3. 1-sec-Butyl-4-{[(1-methyl-4-nitro-1H-pyrrol-2-yl)carbonyl]amino}-N-[2-(4-morpholinyl)ethyl]-1H-pyrrole-2-carboxamide **18b**

From 1-*sec*-butyl-*N*-[2-(4-morpholinyl)ethyl]-4-nitro-1*H*-pyrrole-2-carboxamide (250 mg, 0.77 mmol) and 1-methyl-4-nitro-1*H*-pyrrole-2-carboxylic acid (150 mg, 0.88 mmol) used as the acid chloride in the presence of NMM (250 μl, 2.27 mmol).The purification used 99:1 ethyl actetate:triethylamine as the mobile phase affording the product as a pale yellow solid (120 mg, 35%), m.p. 161–164 °C. ν_{max} (KBr): 3400, 3312, 3130, 2961, 2932, 2854, 2814, 1658, 1621, 1569, 1535, 1501, 1456, 1254, 1204, 1186, 1170, 1143, 1116 cm^{-1} δ_H ($CDCl_3$): 7.65 (1H, bs, CON*H*), 7.61 (1H, d, N*H*, $J = 2.2$), 7.36 (1H, d, N*H*, $J = 2.2$), 7.19 (1H, d, N*H*, $J = 2.2$), 6.45–6.55 (2H, m, N*H* and CON*H*), 5.34 (1H, sextet, CH_2CHCH_3, $J = 7.0$), 4.05 (3H, s, NCH_3), 3.77 (4H, t, $CH_2CH_2OCH_2CH_2$, $J = 5.2$), 3.49 (2H, q, $NHCH_2CH_2N$, $J = 5.7$), 2.50–2.63 (6H, m, $NHCH_2CH_2N$ and $CH_2CH_2NCH_2CH_2$), 1.70–1.85 (2H, m, CH_3CH_2CH), 1.44 (3H, d, $CHCH_3$, $J = 7.0$), 0.85 (3H, t, CH_3CH_2, $J = 7.4$) δ_C: ($CDCl_3$) 161.75; 157.40; 135.04; 126.97; 126.97; 124.34; 121.21; 113.04; 106.91; 102.80; 67.00; 57.04; 53.88; 53.36; 37.99; 35.52; 31.05; 21.78; 10.71. HRMS FAB: found 447.2361 $C_{21}H_{31}N_6O_6$ requires 447.2356 $[M + 1]^+$.

3.4.4. 4-{[(1-Isopropyl-4-nitro-1H-pyrrol-2-yl)carbonyl]amino}-1-methyl-N-[2-(4-morpholinyl)ethyl]-1H-pyrrole-2-carboxamide **18c**

From 1-methyl-*N*-[2-(4-morpholinyl)ethyl]-4-nitro-1*H*-pyrrole-2- carboxamide (116 mg, 0.41 mmol) and 1-isopropyl-4-nitro-1*H*-pyrrole-2-carboxylic acid (70 mg, 0.35 mmol) used as the acid chloride in the presence of NMM (140 μl, 1.27 mmol). The purification used ethyl actetate as the mobile phase affording the product as a pale brown solid, (72 mg, 40%), m.p. 105–115 °C. ν_{max} (KBr): 3294, 3138, 2933, 1659, 1533, 1402, 1282, 1233, 1202, 1174, 1149, 1114, 1061 cm^{-1} δ_H ($CDCl_3$): 7.81 (1H, d, N*H*, $J = 2.2$), 7.60 (1H, bs, CON*H*), 7.20 (1H, d, N*H*, $J = 2.2$), 7.16 (1H, d, N*H*, $J = 1.8$), 6.54 (1H, d, N*H*, $J = 1.8$), 6.44 (1H, bs, CON*H*), 5.53 (1H, septet, CH_3CHCH_3, $J = 6.7$), 3.94 (3H, s, NCH_3), 3.76 (4H, t, $CH_2CH_2OCH_2CH_2$, $J = 4.5$), 3.49 (2H, q, $NHCH_2CH_2N$, $J = 5.7$), 2.59 (2H, t, $NHCH_2CH_2N$, $J = 5.7$), 2.52 (4H, t, $CH_2CH_2NCH_2CH_2$, $J = 4.5$), 1.52 (6H, d, CH_3CHCH_3, $J = 6.7$) δ_C: ($CDCl_3$) 161.55; 157.66; 135.57; 126.08; 123.83; 122.12; 120.65; 119.01; 107.23; 103.19; 66.89; 57.02; 53.30; 50.27; 36.69; 35.38; 23.74. HRMS FAB: found 433.2201; $C_{20}H_{29}N_6O_5$ requires 433.2199 $[M + 1]^+$.

3.4.5. 4-{[(1-sec-Butyl-4-nitro-1H-pyrrol-2-yl)carbonyl]amino}-1-methyl-N-[2-(4-morpholinyl)ethyl]-1H-pyrrole-2-carboxamide **18d**

From 1-methyl-*N*-[2-(4-morpholinyl)ethyl]-4-nitro-1*H*-pyrrole-2-carboxamide (164 mg, 0.58 mmol) and 1-*sec*-butyl-4-nitro-1*H*-pyrrole-2-carboxylic acid (90 mg, 0.42 mmol) used the acid chloride in the presence of NMM (200 μl, 1.82 mmol). The purification used ethyl actetate as the mobile phase affording the product as a pale yellow solid, (83 mg, 44%), m.p.168–178 °C. ν_{max} (KBr): 3317, 3136, 2854, 1658, 1566, 1533, 1494, 1292, 1230, 1142, 1112, 1072 cm^{-1} δ_H ($CDCl_3$): 7.88 (1H, bs, CON*H*), 7.75 (1H, d, N*H*, $J = 1.8$), 7.22 (1H, d, N*H*, $J = 1.8$), 7.18 (1H, d, N*H*, $J = 1.8$), 6.55–6.65 (2H, m, N*H* and CON*H*), 5.37 (1H, sextet, CH_2CHCH_3, $J = 6.8$), 3.93 (3H, s, NCH_3), 3.79 (4H, t, $CH_2CH_2OCH_2CH_2$, $J = 4.6$), 3.51 (2H, q, $NHCH_2CH_2N$, $J = 5.6$), 2.55–2.77 (6H, m, $NHCH_2CH_2N$ and $CH_2CH_2NCH_2CH_2$), 1.75–1.88 (2H, m, CH_3CH_2CH), 1.50 (3H, d, $CHCH_3$, $J = 6.8$), 0.89 (3H, t, CH_3CH_2, $J = 7.4$). δ_C: ($CDCl_3$) 161.56; 157.73; 135.71; 126.69; 123.79; 122.34; 120.72; 119.05; 107.04; 103.22; 66.89; 57.05; 55.50; 53.31; 36.69; 35.37; 30.89; 21.59; 10.42. HRMS FAB: found 447.2365; $C_{21}H_{31}N_6O_5$ requires 447.2356 $[M + 1]^+$.

3.5. Head groups

3.5.1. Methyl 4-[(E)-3-quinolinyldiazenyl]benzoate **9a**

To a solution of 3-aminoquinoline (0.05 g; 0.34 mmol) in glacial acetic acid was added a solution of methyl 4-nitrosobenzoate, **8** (0.06 g; 0.34 mmol) in glacial acetic acid (2 mL) with stirring at room temperature. The solution was then stirred at 70 °C under

a nitrogen atmosphere for 24 h during which time a brown precipitate formed and the solution became almost solid. The solid was collected by filtration. The filtrate was neutralised with saturated aqueous sodium bicarbonate solution (50 mL). Ethyl acetate (100 mL) was then added and the resulting organic layer separated, washed with brine and, dried ($MgSO_4$), and concentrated under reduced pressure to give a brown solid which was combined with the solid obtained by filtration. The combined solid products were then purified by flash column chromatography (20% ethyl acetate in hexane as eluant) to give the required diazo compound **9a** as an orange solid (0.06 g, 60%), m.p. 150–152 °C, ν_{max} (KBr): 3420, 1727, 1603, 1573, 1497, 1462 cm^{-1} δ_H ($CDCl_3$): 9.53 (1H, s, CH quinolyl), 8.68 (1H, s, CH quinolyl), 8.25 (2H, d, J = 8.6, CH Ar), 8.22 (1H, d, J = 8.6, CH Ar), 8.02–8.06 (3H, m, CH Ar), 7.85 (1H, t, J = 7.0, CH Ar), 7.65 (1H, t, J = 7.4, CH Ar), 3.98 (3H, s, CH_3). δ_C ($CDCl_3$): 52.3; 123.12; 124.0; 127.9; 129.6; 129.67; 130.9; 131.5; 132.4; 142.3; 144.6; 145.1; 155.2; 166.7; 178.3. HRFABMS: found 292.1082; $C_{17}H_{14}O_2N_3$ $(M + H)^+$ requires 292.1086.

3.5.2. 4-[(E)-3-quinolinyldiazenyl]benzoic acid **10a**

The foregoing methyl ester **9a** (0.08 g; 0.275 mmol) was dissolved in methanol (2 mL) and to this was added a solution of lithium hydroxide (0.014 g; 2 equiv) in water (10 mL) causing the ester to precipitate. The mixture was then heated to 70 °C and stirred for 24 h during which time a strong red colour was produced. TLC analysis of the mixture showed 100% conversion to the lithium salt of the acid. The solution was then acidified to pH 6 using hydrochloric acid (10% solution in water). Ethyl acetate (100 mL) was added to this mixture, the resulting organic layer was removed, washed with brine (50 mL) and saturated aqueous sodium bicarbonate solution (2 × 50 mL) and dried ($MgSO_4$). Evaporation of the solvents under reduced pressure gave the required carboxylic acid as an orange solid (0.075 g, 98%), with no distinct melting point. ν_{max} (KBr): 3445, 1634, 1462, 1425 cm^{-1} δ_H ($CDCl_3$): 9.45 (1H, s, CH quinolyl), 8.93 (1H, s, CH quuinolyl), 8.36 (1H, d, CH Ar, J = 8.4), 8.27 (1H, d, J = 8.0, CH Ar), 8.05–8.19 (4H, m, CH Ar), 7.95 (1H, t, CH Ar, J = 7.6), 7.69 (1H, t, CH Ar, J = 7.4). δ_C (DMSO-d_6): 167.4; 166.8; 154.3; 149.2; 144.8; 131.2; 130.7; 130.5; 130.1; 129.7; 128.3; 125.1; 123.1; 122.9. HRFABMS: found 278.0925; $C_{16}H_{12}O_2N_3$ $(M + H)^+$ requires 278.0924.

Similarly prepared were:

3.5.3. Methyl 4-[(E)-(3-methoxyphenyl)diazenyl]benzoate **9b**

From *m*-Anisidine (0.23 g; 1.8 mmol) and methyl 4-nitrosobenzoate (0.3 g; 1.8 mmol) in acetic acid (glacial, 10 mL) at reflux for 24 h. Purification by flash column chromatography (30% ethyl acetate/hexane). Removal afforded the required diazene **139**, as an orange solid (0.19 g, 40%), m.p. 93–95 °C. ν_{max} (KBr): 2958, 1727, 1600, 1435 $cm^{-1}\delta_H$ ($CDCl_3$): 8.18–8.21 (2H, m, CH Ar), 7.98 (2H, d, J = 8.6, CH Ar), 7.61 (1H, d, J = 7.7 CH Ar), 7.43–7.49 (m, 2H, CH Ar), 7.1 (1H, dd, J = 8.2 and J = 1.8, CH Ar), 3.99 (3H, s, OCH_3), 3.91(3H, s, OCH_3). δ_C ($CDCl_3$): 52.5; 55.7; 106.0; 117.8; 118.7; 122.8; 130.1; 130.8; 132.1; 154.1; 155.3; 160.6; 166.6. HREIMS: found 270.1002; $C_{15}H_{14}N_2O_3$ requires 270.1004. Found: C, 66.4; 5.24; N, 10.01; $C_{15}H_{14}N_2O_3$ requires C, 66.66; H, 5.22; N, 10.36%.

3.5.4. [(E)-(3-Methoxyphenyl)diazenyl]benzoic acid **10b**

From the foregoing ester in 85% yield as an orange solid with no distinct melting point. ν_{max} (KBr): 2934, 2834, 1680, 1600, 1429 cm^{-1} δ_H (DMSO-d_6): 8.13–8.16 (2H, m, CH Ar), 7.97 (2H, dd, J = 6.8 and J = 2.0, CH Ar), 7.54–7.56 (2H, m, CH Ar), 7.45 (1H, t, J = 2.0, CH Ar), 7.18–7.21 (1H, m, CH Ar), 3.99 (3H, s, OCH_3). δ_C (DMSO-d_6): 56.3; 107.1; 117.5; 119.4; 123.4; 131.2; 131.5; 133.8; 154.0; 155.1; 161.0; 167.5. HRFABMS: found 257.0928; $C_{14}H_{13}N_2O_3$ $(M + H)^+$ requires 257.0926.

3.5.5. Methyl 4-{(E)-[4-(dimethylamino)phenyl]diazenyl} benzoate **12** [13]

Methyl 4-aminobenzoate (0.38 g, 2.5 mmol) was disssolved in hydrochloric acid solution (20% of 12 M hydrochloric acid in water; 20 mL) and the solution cooled to 0 °C using an ice/salt bath with vigorous stirring. A solution of sodium nitrite (0.17 g; 2.5 mmol) in water (1 mL) was then added dropwise and the solution stirred at 0 °C for 30 min to allow formation of the diazonium salt to occur. During this time, *N,N*-dimethylaniline (0.3 g; 2.5 mmol) dissolved in methanol (5 mL) and sodium hydroxide (10% soln. in water; 20 mL) was cooled to 0 °C. This solution was then added dropwise to the diazonium salt solution. The solution was then adjusted to pH 6 by the addition of 10% aqueous sodium hydroxide solution. The solution was extracted with ethyl acetate (100 mL), the organic layer was separated, washed with brine (1 × 50 mL) and saturated aqueous sodium bicarbonate solution (2 × 50 mL), dried ($MgSO_4$), then concentrated under reduced pressure to give a brown solid. The brown solid was purified by flash column chromatography (10% EtOAc in hexane as eluant). Evaporation of the solvents gave the required diazene **12** as a red solid (0.42 g, 60%), m.p. 183–184 °C. ν_{max} (KBr): 3358, 2905, 1710, 1606 cm^{-1} δ_H ($CDCl_3$): 8.16 (2H, dd, J = 6.8 and J = 1.7, CH Ar), 7.86–7.92 (4H, m, CH Ar), 6.78 (2H, d, J = 9.2 Hz, CH Ar), 4.14 (3H, s, CH_3), 3.11 (6H, s, $(CH_3)_2$). HREIMS: found 283.1320; $C_{16}H_{17}O_2N_3$ requries 283.1321.

3.5.6. 4-{(E)-[4-(Dimethylamino)phenyl]diazenyl}benzoic acid **13** [23]

From the foregoing ester using the method described above as a red solid 53% yield, m.p. >230 °C (lit. > 230 °C) [22], ν_{max} (KBr): 3374, 3076, 2653, 1681, 1597, 1521 cm^{-1} δ_H (DMSO-d_6): 8.08 (2H, d, J = 8.8, CH Ar), 7.81–7.84 (4H, m, CH Ar), 6.86 (2H, d, J = 9.2, CH Ar), 3.08 (6H, s,$(CH_3)_2$). HREIMS: found 269.1162; $C_{15}H_{15}O_2N_3$ requires 269.1164.

3.6. Amides

3.6.1. Methyl 4-[(3-quinolinylcarbonyl)amino]benzoate **19a** [2]

Quinoline 3-carboxylic acid (0.20 g, 1.15 mmol) was dissolved in methanol (5 mL) and DMF (1 mL); methyl 4-aminobenzoate (0.17 g, 1.15 mmol) was then added followed by DMT-MM (0.30 g, 1.15 mmol). The mixture was then stirred at room temperature for 24 h. During this time the product formed as a white precipitate which was collected by filtration and dried under reduced pressure (0.25 g, 70%), m.p. >230 °C (lit. >230 °C) [2], ν_{max} (KBr): 3249, 2994, 1715, 1676, 1600, 1478 cm^{-1} δ_H (DMSO-d_6): 10.9 (1H, s, NH), 9.36 (1H, d, J = 2.3, CH Ar), 8.9 (1H, d, J = 1.9, CH Ar), 8.12–8.17 (2H, m, CH Ar), 7.99–8.02 (4H, m, CH Ar), 7.89–7.91 (1H, m, C12), 7.74 (1H, t, J = 7.5, C13), 3.85 (3H, s, CH_3). HREIMS: found 306.1007; $C_{18}H_{14}N_2O_3$ requires 306.1004.

3.6.2. 4-[(3-Quinolinylcarbonyl)amino]benzoic acid **20a** [2]

To a solution of methyl 4-[(3-quinolinylcarbonyl)amino] benzoate, **19a**, (0.15 g, 0.51 mmol) in methanol (5 mL) a solution of lithium hydroxide (0.02 g, 0.92 mmol) in water (4 mL) was added. The resulting suspension was heated at 80 °C with stirring for 5 h. The solution was then acidified using dilute hydrochloric acid and the precipitated solid filtered off and dried under reduced pressure to give the required carboxylic acid, **20a**, as a pale brown solid (0.14 g, 95%), m.p. >230 °C (lit. >230 °C) [2], ν_{max} (KBr): 3320, 3052, 2928, 2473, 1930, 1695, 1542 cm^{-1} δ_H (DMSO-d_6): 10.9 (1H, s, NH), 9.38 (1H, s, CH Ar), 9.03 (1H, d, J = 2.0, CH Ar), 8.13–8.19 (2H, m, CH Ar), 7.91–7.99 (5H, m, CH Ar), 7.9 (1H, t, J = 7.1, CH Ar). HRFABMS: found 293.0924; $C_{17}H_{13}O_3N_2$ $(M + H)^+$ requires 293.0921.

3.6.3. Methyl 4-[(3-methoxybenzoyl)amino]benzoate ***19b*** *[17]*

3-Methoxybenzoyl chloride (0.20 g, 1.17 mmol) was dissolved in dichloromethane (5 mL, dry) to which a solution of methyl 4-aminobenzoate (0.18 g, 1.17 mmol) in dichloromethane (5 mL, dry) was added followed by *N*-methylmorpholine (0.25 mL, 2.34 mmol). The solution was then stirred at room temperature for 3 h. Sodium hydroxide solution (aq. 10% w/v, 20 mL) was then added to the solution, the dichloromethane layer removed, dried ($MgSO_4$), and the solvent evaporated under reduced pressure to give a pale brown solid which was purified using silica gel column chromatography (eluant: 30% ethyl acetate/n-hexane). Removal of the solvent gave the required amide, as a brown solid (0.20 g, 60%), m.p. 88–90 °C (lit. 79–81 °C) [17], ν_{max} (KBr): 3356, 2942, 1709, 1666, 1522 cm^{-1} δ_H ($CDCl_3$): 8.07 (2H, dd, $J = 6.8$ and 1.9, CH Ar), 7.75 (2H, dd, $J = 6.9$ and $J = 1.9$, CH Ar), 7.45 (1H, s, CH Ar), 7.40–7.41 (2H, m, CH Ar), 7.10–7.12 (1H, m, CH Ar), 3.92 (3H, s, OCH_3), 3.85(3H, s, OCH_3). HRFABMS: found 286.1075; $C_{16}H_{16}NO_4$ $(M + H)^+$ requires 286.1079.

3.6.4. 4-[(3-Methoxybenzoyl)amino]benzoic acid ***20b*** *[2]*

From the foregoing methyl ester using the method described above in 90% yield as a white solid. m.p. >230 °C (lit. >230 °C) [2], ν_{max} (KBr): 3401, 2924, 2854, 1681, 1632, 1598, 1513, 1462, 1424 cm^{-1} δ_H (DMSO-d_6): 10.48 (1H, s, NH), 7.90–7.95 (4H, m, CH Ar), 7.40–7.62 (3H, m, CH Ar), 7.16–7.18 (1H, m, CH Ar), 3.85 (3H, s, CH_3). HRFABMS: found 272.0922; $C_{15}H_{14}O_4N$ $(M + H)^+$ requires 272.0923.

Similarly prepared were:

3.6.5. Methyl 4-{[4-(dimethylamino)benzoyl]amino}benzoate ***19c*** *[23]*

From 4-dimethylaminobenzoyl chloride and methyl 4-aminobenzoate as a white solid (0.10 g, 30%), m.p. 208–210 °C, purity by HPLC 94%. ν_{max} (KBr): 3336, 1711, 1655, 1609, 1517 cm^{-1} δ_H (DMSO-d_6): 10.26 (1H, s, NH), 7.90–7.97 (6H, m, CH Ar), 6.83–6.86 (2H, m, CH Ar), 3.8 (3H, s, CH_3), 3.05 (6H, s, $(CH_3)_2$). HRCIMS: found 299.1390; $C_{17}H_{19}NO_4$ $(M + H)^+$ requires 299.1396.

3.6.6. 4-{[4-(Dimethylamino)benzoyl]amino}benzoic acid ***20c***

From the foregoing ester in 85% yield as a white solid, m.p. >230 °C, ν_{max} (KBr): 3341, 2561, 1675, 1606, 1502 cm^{-1} δ_H (DMSO-d_6): 10.12 (1H, s, NH), 7.86–7.89 (6H, m, CH Ar), 6.86 (2H, d, $J = 8.8$, CH Ar), 3.0 (6H, s, $(CH_3)_2$). δ_C (DMSO-d_6): 38.8; 111.3; 119.2; 124.7; 129.4; 130.1; 143.8; 152.1; 165.4; 166.9. HRFABMS: found 285.1242 $C_{16}H_{17}N_2O_3$ $(M + H)^+$ requires 285.1239.

3.7. Alkenes

3.7.1. Methyl 4-{(E)-2-[4-(dimethylamino)phenyl]ethenyl} benzoate ***21*** *[25]*

Diethyl (4-(methoxycarbonyl)phenyl)methylphosphonate (0.10 g; 0.35 mmol) was dissolved in THF (dry, 5 mL) and the solution was cooled to 0 °C. Sodium hydride (0.13 g; 8 equiv) was then added slowly in small portions to this solution which was then stirred for 20 min. 4-(Dimethylamino)benzaldehyde (0.052 g; 0.35 mmol) was dissolved in THF (dry, 3 mL) and added dropwise to this solution. The resulting mixture was stirred at room temperature for 4 h. The reaction was then quenched with water (10 mL) causing a white solid to precipitate. The precipitate was collected by filtration and dried under reduced pressure. The product obtained was shown to be a mixture of the ester and the corresponding carboxylic acid by LRMS the mixture was therefore hydrolysed directly to the carboxylic acid.

3.7.2. 4-{(E)-2-[4-(Dimethylamino)phenyl]ethenyl}benzoic acid ***22*** *[25]*

From the above mixture in 85% yield, m.p. >230 °C (lit. >230 °C) [25], ν_{max} (KBr): 3429, 2925, 1681, 1595 cm^{-1} δ_H (DMSO-d_6): 7.9 (2H, d, $J = 7.8$, CH Ar), 7.64 (2H, d, $J = 7.4$, CH Ar), 7.49 (2H, d, $J = 7.8$, CH Ar), 7.32 (1H, d, $J = 16.8$, CH═CH), 7.09 (1H, d, $J = 16.8$, CH═CH), 6.83 (2H, s (broad), CH Ar), 2.96 (6H, s, $(CH_3)_2$). HRFABMS: found 268.1341; $C_{17}H_{18}NO_2$ $(M + H)^+$ requires 268.1338.

3.8. Minor groove binders

3.8.1. 1-Methyl-N-[1-methyl-5-({[2-(4-morpholinyl)ethyl]amino} carbonyl)-1H-pyrrol-3-yl]-4-({4-[(E)-3-quinolinyldiazenyl] benzoyl}amino)-1H-pyrrole-2-carboxamide ***3b***

A solution of the dipyrrole dimer, 1-methyl-4-{[(1-methyl-4-nitro-1*H*-pyrrol-2-yl)carbonyl]amino}-*N*-[2-(4-morpholinyl) ethyl]-1*H*-pyrrole-2-carboxamide **11** (0.06 g; 0.15 mmol) in methanol (25 mL) was cooled in an ice/salt bath to 0 °C with stirring under a nitrogen atmosphere. To this was added palladium on carbon (10% w/w, 25 mg) slowly in small portions. The reaction vessel was evacuated and then filled with hydrogen. The reaction mixture was then sealed and left to stir vigorously for 3 h. The solution was then filtered under suction through Kieselguhr and the filtrate evaporated under reduced pressure taking care that the resulting solid was completely free of solvent. The aminopyrrole dimer so obtained was used directly without purification or analysis.

The aminopyrrole dimer was dissolved in dry DMF (1 mL) to which was added HBTU (0.11 g; 0.3 mmol; 2 equiv), 4-methylmorpholine (0.025 mL; 0.45 mmol; 3 equiv) and the dimer 4-[(*E*)-3-quinolinyldiazenyl]benzoic acid (**10a**) (0.04 g; 0.15 mmol). The solution was stirred until all the solid material had dissolved and allowed to stand overnight. The crude product was purified by HPLC giving the required minor groove binder **3b,** as an orange solid with no definite melting point (0.33 g, 35%), purity by HPLC: >95%. ν_{max} (KBr): 3394, 1678, 1554, 1464 cm^{-1} δ_H (DMSO-d_6): 10.57 (1H, s, NH); 10.0 (1H, s, NH), 9.80 (1H, bs, TFA), 9.46 (1H, d, $J = 2.0$, CH quinolyl), 8.94 (1H, d, $J = 2.4$, quinolyl), 8.28–8.29 (1H, m, NH), 8.22–8.27 (2H, m, CH quinolyl), 8.10–8.16 (4H, m, CH Ar), 7.92 (1H, t, $J = 7.0$, CH Ar), 7.76 (1H, t, $J = 7.6$, CH Ar), 7.37 (1H, d, $J = 2.0$, CH pyrrole), 7.23 (1H, d, $J = 2.0$, CH pyrrole), 7.16 (1H, d, $J = 1.6$, CH pyrrole), 7.01 (1H, d, $J = 1.6$, CH pyrrole), 3.99–4.02 (2H, m, CH_2), 3.92 (3H, s, CH_3), 3.89 (3H, s, CH_3), 3.55–3.70 (6H, m, 3 × CH_2), 3.26–3.29 (2H, m, CH_2), 3.12–3.16 (2H, m, CH_2).HRFABMS: found 634.2889; $C_{34}H_{36}O_4N_9^+$ requires 634.2890.

Similarly prepared were:

3.8.2. N-[4-({[1-Methyl-5-({[1-methyl-5-({[2-(4-morpholinyl) ethyl]amino}carbonyl)-1H-pyrrol-3-yl]amino}carbonyl)-1H-pyrrol-3-yl]amino}carbonyl)phenyl]-3-quinoline carboxamide ***3c***

From 1-methyl-4-{[(1-methyl-4-nitro-1*H*-pyrrol-2-yl) carbonyl]amino}-*N*-[2-(4-morpholinyl)ethyl]-1*H*-pyrrole-2-carboxamide (**11**) and 4-[(3-quinolinylcarbonyl)amino] benzoic acid **20a** in 15% yield, purity by HPLC >95%. ν_{max} (KBr): 3424, 1676, 1530, 1436, 1406 cm^{-1} δ_H (DMSO-d6): 10.87 (1H, s, NH), 10.28 (1H, s, NH), 9.98 (1H, s, NH), 9.68 (1H, bs, TFA), 9.39 (1H, d, $J = 2.0$, CH quinlolyl), 9.01 (1H, d, $J = 1.6$, CH quinloly), 8.20–8.22 (1H, m, NH), 8.12–8.19 (2H, m, CH quinloyl), 7.80–7.90 (5H, m, CH Ar), 7.75–7.76 (1H, m, CH Ar), 7.33 (1H, d, $J = 1.6$, CH pyrrole), 7.22 (1H, d, $J = 1.6$, CH pyrrole), 7.12 (1H, d, $J = 1.6$, CH pyrrole), 7.0 (1H, d, $J = 2.0$, CH pyrrole), 3.99–4.0 (2H, m, CH_2), 3.88 (3H, s, CH_3), 3.83 (3H, s, CH_3), 3.69–3.73 (2H, m, CH_2), 3.54–3.55 (4H, m, 2 × CH_2), 3.26–3.29 (2H, m, CH_2); 3.11–3.15 (2H, m, CH_2). HRFABMS: found 649.2887; $C_{35}H_{37}N_7O_5^+$ requires 649.2902.

3.8.3. ({4-[(E)-(3-Methoxyphenyl)diazenyl]benzoyl}amino)-1-methyl-N-[1-methyl-5-({[2-(4-morpholinyl)ethyl]amino} carbonyl)-1H-pyrrol-3-yl]-1H-pyrrole-2-carboxamide ***4b***

From 1-methyl-4-{[(1-methyl-4-nitro-1*H*-pyrrol-2-yl) carbonyl]amino}-*N*-[2-(4-morpholinyl)ethyl]-1*H*-pyrrole-2-

carboxamide **11** and [(*E*)-(3-methoxyphenyl)diazenyl] benzoic acid **10b** (0.026 g; 0.1 mmol) to give the product as an orange solid with no distinct melting point (0.021 g, 35%), purity by HPLC >95%. ν_{max} (KBr): 3414, 1678, 1600, 1526, 1436 cm^{-1} δ_H (DMSO-d_6): 10.56 (1H, s, NH), 10.03 (1H, s, NH), 9.65 (1H, bs, TFA), 8.20–8.26 (1H, m, NH) 8.2 (2H, d, $J = 8.4$, CH Ar), 8.03 (2H, d, $J = 8.4$, CH Ar), 7.53–7.57 (2H, m, CH Ar), 7.46 (1H, s, CH pyrrole), 7.37 (1H, s, CH pyrrole), 7.21–7.24 (2H, m, CH Ar), 7.15 (1H, s, CH pyrrole), 7.01 (1H, s, CH pyrrole), 4.00–4.01 (2H, m, CH_2), 3.89 (3H, s, CH_3), 3.88 (3H, s, CH_3), 3.84 (3H, s, CH_3), 3.67–3.70 (2H, m, CH_2), 3.53–3.57 (4H, m, 2 × CH_2), 3.26–3.28 (2H, m, CH_2); 3.13–3.17 (2H, m, CH_2). HRFABMS: found 613.2899; $C_{32}H_{37}N_8O_5^+$ requires 613.2887 $[M + 1]^+$.

3.8.4. 4-({4-[(3-Methoxybenzoyl)amino]benzoyl}amino)-1-methyl-N-[1-methyl-5-({[2-(4-morpholinyl)ethyl]amino} carbonyl)-1H-pyrrol-3-yl]-1H-pyrrole-2-carboxamide **4c**

From 1-methyl-4-{[(1-methyl-4-nitro-1*H*-pyrrol-2-yl) carbonyl]amino}-*N*-[2-(4-morpholinyl)ethyl]-1*H*-pyrrole-2-carboxamide **11** and 4-[(3-Methoxybenzoyl)amino]benzoic acid **20b** to give the product as a white solid with no distinct melting point (12 mg, 20%), purity by HPLC >95%. ν_{max} (KBr): 3421, 1673, 1592, 1525 cm^{-1} δ_H (DMSO-d_6): 10.45 (1H, s, NH), 10.24 (1H, s, NH), 9.97 (1H, s, NH), 9.59 (1H, bs, TFA), 8.25 (1H, s, NH), 7.91–7.98 (4H, m, CH Ar), 7.47–7.56 (3H, m, CH Ar), 7.32 (1H, d, $J = 1.6$, CH pyrrole), 7.20–7.22 (2H, m, CH Ar), 7.11 (1H, d, $J = 1.6$, CH pyrrole), 7.00 (1H, d, $J = 1.6$, CH pyrrole), 4.00–4.03 (2H, m, CH_2), 3.88 (3H, s, CH_3), 3.86 (3H, s, CH_3), 3.84 (3H, s, CH_3), 3.64–3.72 (2H, m, CH_2), 3.54–3.56 (4H, m, 2 × CH_2), 3.25–3.29 (2H, m, CH_2), 3.12–3.16 (2H, m, CH_2) HRFABMS: found 628.2879 calculated for $C_{34}H_{38}N_7O_6^+$ requires 628.2884 $[M + 1]^+$.

3.8.5. 4-[(4-{(E)-[4-(Dimethylamino)phenyl]diazenyl}benzoyl) amino]-1-methyl-N-[1-methyl-5-({[2-(4-morpholinyl)ethyl]amino} carbonyl)-1H-pyrrol-3-yl]-1H-pyrrole-2-carboxamide **5b**

From 1-methyl-4-{[(1-methyl-4-nitro-1*H*-pyrrol-2-yl)carbonyl] amino}-*N*-[2-(4-morpholinyl)ethyl]-1*H*-pyrrole-2-carboxamide **11** and 4-{(*E*)-[4-(dimethylamino)phenyl] diazenyl}benzoic acid **13** as a white solid (35 mg, 40%) with no distinct melting point, purity by HPLC >95%. ν_{max} (KBr): 3422, 2927, 1681, 1647, 1596 cm^{-1} δ_H: (DMSO-d_6) 10.43 (1H, s, NH); 9.98 (1H, s, NH), 9.65 (1H, bs, TFA), 8.23 (1H, m, NH), 8.1 (2H, d, $J = 8.4$, CH Ar), 7. 22–7.88 (4H, m, CH Ar), 7.34 (1H, s, CH pyrrole), 7.21 (1H, s, CH pyrrole), 7.13 (1H, s, CH pyrrole), 7.0 (1H, s, CH pyrrole), 6.8 (2H, d, $J = 9.6$, CH Ar), 3.99–4.02 (2H, m, CH_2), 3.88 (3H, s, CH_3), 3.83 (3H, s, CH_3), 3.54–3.71 (6H, m, 3 × CH_2), 3.27–3.29 (2H, m, CH2), 3.12–3.15 (2H, m, CH_2), 3.09 (6H, s, $(CH3)_2$). HRFABMS: found 626.3204; $C_{33}H_{40}O_4N_9^+$ requires 626.3203 $[M + 1]^+$.

3.8.6. 4-[(4-{(E)-2-[4-(Dimethylamino)phenyl]ethenyl}benzoyl) amino]-1-methyl-N-[1-methyl-5-({[2-(4-morpholinyl)ethyl] amino} carbonyl)-1H-pyrrol-3-yl]-1H-pyrrole-2-carboxamide **5a**

From 1-methyl-4-{[(1-methyl-4-nitro-1*H*-pyrrol-2-yl) carbonyl] amino}-*N*-[2-(4-morpholinyl)ethyl]-1*H*-pyrrole-2-carboxamide **11** and 4-{(*E*)-2-[4-(dimethylamino) phenyl]ethenyl}benzoic acid **22** as a brown solid with no distinct melting point (29 mg, 40%), purity by HPLC >95%. ν_{max} (KBr): 3421, 1678, 1594, 1524, 1434, 1400 cm^{-1} δ_H (DMSO-d6): 10.35 (1H, s, NH), 10.03 (1H, s, NH), 9.80 (1H, bs, TFA), 8.24–8.27 (1H, m, NH), 7.94 (2H, d, $J = 8.0$, CH Ar), 7.92 (2H, d, $J = 8.4$, CH Ar), 7.47–7.49 (2H, d, $J = 8.8$, CH Ar), 7.00–7.42 (5H, mAr and pyrrole), 6.77 (2H, d, $J = 8.8$, CH Ar), 6.57 (1H, s, CH Ar), 4.02–4.04 (2H, m, CH2), 3.9 (3H, s, CH_3), 3.88 (3H, s, CH_3), 3.67–3.73 (2H, m, CH_2), 3.53–3.57 (4H, m, 2 × CH_2), 3.26–3.30 (2H, m, CH_2), 3.11–3.15 (2H, m, CH_2), 2.96 (6H, s, $(CH_3)_2$). HRFABMS: found 624.0345; $C_{36}H_{42}N_7O_4^+$ requires 624.0320 $[M + 1]^+$.

3.8.7. 4-[(4-{[4-(Dimethylamino)benzoyl]amino}benzoyl)amino]-1-methyl-N-[1-methyl-5-({[2-(4-morpholinyl)ethyl]amino} carbonyl)-1H-pyrrol-3-yl]-1H-pyrrole-2-carboxamide **5c**

From 1-methyl-4-{[(1-methyl-4-nitro-1*H*-pyrrol-2-yl)carbonyl] amino}-*N*-[2-(4-morpholinyl)ethyl]-1*H*-pyrrole-2-carboxamide **11** and 4-{[4-(dimethylamino)benzoyl] amino}benzoic acid **20c** as a brown solid with no distinct melting point (12 mg, 20%), purity by HPLC >95%. ν_{max} (KBr): 3414, 2963, 1650, 1604, 1536, 1437 cm^{-1} δ_H (DMSO-d_6): 10.19 (1H, s, NH), 10.06 (1H, s, NH), 9.96 (1H, s, NH), 9.72 (1H, bs, TFA), 8.23 (1H, s, NH), 7.88–7.91 (6H, m, CH Ar), 7.31 (1H, s, CH pyrrole), 7.21 (1H, s, CH pyrrole), 7.10 (1H, s, CH pyrrole), 7.00 (1H, s, CH pyrrole), 6.7 (2H, d, $J = 9.2$, CH Ar), 3.99–4.0 (2H, m, CH_2), 3.87 (3H, s, CH_3), 3.83 (3H, s, CH_3), 3.64–3.72 (2H, m, CH_2), 3.54–3.58 (4H, m, 2 × CH_2), 3.26–3.29 (2H, m, CH_2), 3.11–3.15 (2H, m, CH_2), 3.01 (6H, s, $(CH_3)_2$). HRFABMS: Found 641.3197; $C_{34}H_{41}N_8O_5^+$ requires 641.3200 $[M + 1]^+$.

3.8.8. 1-Isopropyl-4-({[1-methyl-4-({4-[(E)-2-(3-quinolinyl) ethenyl]benzoyl}amino)-1H-pyrrol-2-yl]carbonyl}amino)-N-[2-(4-morpholinyl)ethyl]-1H-pyrrole-2-carboxamide **6a**

From 1-isopropyl-4-{[(1-methyl-4-nitro-1*H*-pyrrol-2-yl) carbonyl]amino}-*N*-[2-(4-morpholinyl)ethyl]-1*H*-pyrrole-2-carboxamide **18a** (35 mg, 0.08 mmol) and 4-[(*E*)-2-(3-quinolinyl) ethenyl]benzoic acid (22 mg, 0.08 mmol) using HBTU (60 mg, 0.16 mmol). Purification by HPLC furnished the desired product as a pale yellow solid, giving a yield of (14 mg, 25%), purity by HPLC >95% with no distinct melting point. ν_{max} (KBr): 3414, 1674, 1580, 1529, 1406, 1259, 1201, 1133, 838 cm^{-1} δ_H NMR (DMSO-d_6): 10.38 (1H, s, Ar*H*), 10.00 (1H, s, Ar*H*), 9.61 (1H, bs, TFA), 9.27 (1H, s, Ar*H*, $J = 2.1$), 8.57, (1H, s, Ar*H*, $J = 2.1$), 8.23 (1H, t, CON*H*, $J = 8.0$), 7.99–8.04 (5H, m), 7.74–7.83 (4H, m), 7.60–7.72 (4H, m), 7.38 (1H, d, $J = 1.7$), 7.34 (1H, d, $J = 1.7$), 7.13 (1H, d, $J = 1.7$), 6.98 (1H, d, $J = 1.7$), 5.49 (1H, septet, CH_3CHCH_3, $J = 6.7$), 3.83 (3H, s, NCH_3), 3.99–4.02 (2H, m), 3.61–3.68 (2H, m), 3.53–3.58 (4H, m), 3.25–3.29 (2H, m), 3.05–3.18 (2H, m), 1.34 (6H, d, CH_3CHCH_3, $J = 6.7$). HRMS FAB: found 660.3270; $C_{38}H_{41}N_7O_4$ requires 660.3293 obtained for $[M + 1]^+$.

3.8.9. 1-sec-Butyl-4-({[1-methyl-4-({4-[(E)-2-(3-quinolinyl) ethenyl]benzoyl}amino)-1H-pyrrol-2-yl]carbonyl}amino)-N-[2-(4-morpholinyl)ethyl]-1H-pyrrole-2-carboxamide **6b**

From 1-*sec*-butyl-4-{[(1-methyl-4-nitro-1*H*-pyrrol-2-yl) carbonyl]amino}-*N*-[2-(4-morpholinyl)ethyl]-1*H*-pyrrole-2-carboxamide **18b** (20 mg, 0.045 mmol) and 4-[(*E*)-2-(3-quinolinyl) ethenyl]benzoic acid (12 mg, 0.045 mmol) using HBTU (30 mg, 0.08 mmol) as described. Purification by HPLC furnished the desired product as a bright orange solid, (6 mg, 11%), purity by HPLC >95%. ν_{max} (KBr): 3420, 2925, 1683, 1639, 1406, 1206, 1136, 803, 723, 609 cm^{-1} δ_H (DMSO-d_6): 10.36 (1H, s, Ar*H*), 9.98 (1H, s, Ar*H*), 9.66 (1H, bs, TFA), 9.26 (1H, d, Ar*H*, $J = 2.1$), 8.55, (1H, d, Ar*H*, $J = 2.1$), 8.22 (1H, m, CON*H*), 7.99–8.04 (5H, m), 7.74–7.83 (4H, m), 7.60–7.71 (4H, m), 7.33 (2H, m), 7.13 (1H, d, $J = 1.7$), 6.96 (1H, s), 5.33 (1H, sextet, CH_2CHCH_3, $J = 6.8$), 3.99–4.02 (2H, m), 3.88 (3H, s, NCH_3), 3.62–3.68 (2H, m), 3.53–3.58 (4H, m), 3.25–3.29 (2H, m), 3.05–3.18 (2H, m), 1.70–1.74 (2H, m, CH_3CH_2CH), 1.34 (3H, d, $CHCH_3$, $J = 6.7$), 0.75 (3H, t, CH_3CH_2, $J = 7.3$). HRMS FAB: found 674.3452; $C_{39}H_{44}N_7O_4$ requires 674.3455 $[M + 1]^+$.

3.8.10. 4-({[1-isopropyl-4-({4-[(E)-2-(3-quinolinyl)ethenyl] benzoyl}amino)-1H-pyrrol-2-yl]carbonyl}amino)-1-methyl-N-[2-(4-morpholinyl)ethyl]-1H-pyrrole-2-carboxamide **6c**

From 4-{[(1-isopropyl-4-nitro-1*H*-pyrrol-2-yl)carbonyl] amino}-1-methyl-*N*-[2-(4-morpholinyl)ethyl]-1*H*-pyrrole-2-carboxamide **6c** (30 mg, 0.07 mmol) and 4-[(*E*)-2-(3-quinolinyl) ethenyl]benzoic acid (19 mg, 0.07 mmol) using HBTU (50 mg,

0.14 mmol). Purification by HPLC furnished the desired product as a bright orange solid, (15 mg, 33%), purity by HPLC >95% with no distinct melting point. ν_{max} (KBr): 3421, 1676, 1582, 1532, 1410, 1251, 1201, 1132, 971 cm^{-1} δ_H (DMSO-d_6): 10.38 (1H, s, Ar*H*), 10.04 (1H, s, Ar*H*), 9.54 (1H, bs, TFA), 9.27 (1H, s, Ar*H*, *J* = 2.1), 8.56, (1H, s, Ar*H*), 8.24 (1H, t, CON*H*, *J* = 8.0), 7.99–8.04 (5H, m), 7.74–7.83 (4H, m), 7.60–7.71 (4H, m), 7.51 (1H, d, *J* = 1.7), 7.21 (1H, d, *J* = 1.7), 7.04 (1H, d, *J* = 1.7), 7.01 (1H, d, *J* = 1.7), 5.46 (1H, septet, CH_3CHCH_3, *J* = 6.7), 3.83 (3H, s, NCH_3), 3.99–4.02 (2H, m), 3.62–3.68 (2H, m), 3.53–3.58 (4H, m), 3.25–3.29 (2H, m), 3.05–3.18 (2H, m), 1.39 (6H, d, CH_3CHCH_3, *J* = 6.8). HRMS FAB: found 660.3298; $C_{38}H_{41}N_7O_4$ requires 660.3274 $[M + 1]^+$.

3.8.11. 4-({[1-sec-butyl-4-({4-[(E)-2-(3-quinolinyl)ethenyl] benzoyl}amino)-1H-pyrrol-2-yl]carbonyl}amino)-1-methyl-N-[2-(4-morpholinyl)ethyl]-1H-pyrrole-2-carboxamide **6d**

From 4-{[(1-*sec*-butyl-4-nitro-1*H*-pyrrol-2-yl)carbonyl] amino}-1-methyl-*N*-[2-(4-morpholinyl)ethyl]-1*H*-pyrrole-2-carboxamide **6d** (35 mg, 0.08 mmol) and 4-[(*E*)-2-(3-quinolinyl)ethenyl]benzoic acid **15** (22 mg, 0.08 mmol) using HBTU (50 mg, 0.14 mmol) as described. Purification by HPLC furnished the desired product as a bright yellow solid (15 mg, 29%), purity by HPLC >95% with no distinct melting point. ν_{max} (KBr): 3404, 1675, 1583, 1530, 1408, 1242, 1201, 1134, 721 cm^{-1} δ_H (DMSO-d_6): 10.37 (1H, s, Ar*H*), 10.03 (1H, s, Ar*H*), 9.55 (1H, bs, TFA), 9.26 (1H, d, Ar*H*, *J* = 2.1), 8.56, (1H, d, Ar*H*, *J* = 2.1), 8.22 (1H, m, CON*H*), 7.99–8.04 (5H, m), 7.74–7.83 (4H, m), 7.60–7.71 (4H, m), 7.47 (1H, d, *J* = 1.7), 7.21 (1H, d, *J* = 1.7), 7.00–7.02 (2H, m), 5.29 (1H, sextet, CH_2CHCH_3, *J* = 6.8), 3.99–4.02 (2H, m), 3.83 (3H, s, NCH_3), 3.62–3.68 (2H, m), 3.53–3.58 (4H, m), 3.25–3.29 (2H, m), 3.05–3.18 (2H, m), 1.70–1.74 (2H, m, CH_3CH_2CH), 1.38 (3H, d, $CHCH_3$, *J* = 6.7), 0.76 (3H, t, CH_3CH_2, *J* = 7.3) HRMS FAB: found 674.3425; $C_{39}H_{42}N_7O_4$ requires 674.3460 $[M + 1]^+$.

3.8.12. N-[5-({[1-Isopropyl-5-({[2-(4-morpholinyl)ethyl]amino} carbonyl)-1H-pyrrol-3-yl]amino}carbonyl)-1-methyl-1H-pyrrol-3-yl]-6-[(E)-2-(4-methoxyphenyl)ethenyl] nicotinamide **7a**

From 1-isopropyl-4-{[(1-methyl-4-nitro-1*H*-pyrrol-2-yl) carbonyl]amino}-*N*-[2-(4-morpholinyl)ethyl]-1*H*-pyrrole-2-carboxamide **18a** (35 mg, 0.08 mmol) and 6-[(*E*)-2-(4-methoxyphenyl)ethenyl]nicotinic acid (21 mg, 0.08 mmol) coupled with with HBTU (60 mg, 0.16 mmol). Purification by HPLC furnished the desired product as a pale orange solid (14 mg, 27%) with no distinct m.p. Purity by HPLC >95%. ν_{max} (KBr): 3413, 1671, 1594, 1513, 1407, 1259, 1174, 1132, 720 cm^{-1} δ_H (DMSO-d_6): 10.47 (1H, s, Ar*H*), 9.97 (1H, s, Ar*H*), 9.60 (1H, bs, TFA), 9.06 (1H, d, Ar*H*, *J* = 2.1), 8.26 (1H, d, *J* = 2.0), 8.24 (1H, d, *J* = 2.1), 8.21 (1H, t, *J* = 4.1), 7.75 (1H, d, C=C*H*, *J* = 16.1), 7.63–7.66 (3H, dd, *J* = 8.8, 3.3), 7.37 (1H, d, *J* = 1.9), 7.33 (1H, d, *J* = 1.8), 7.24 (1H, d, C=C*H*, *J* = 16.1), 7.11 (1H, d, *J* = 1.8), 6.96–7.00 (3H, m), 5.49 (1H, septet, CH_3CHCH_3, *J* = 6.7), 3.83 (3H, s, NCH_3), 3.99–4.03 (2H, m), 3.61–3.68 (2H, m), 3.53–3.58 (4H, m), 3.25–3.29 (2H, m), 3.05–3.18 (2H, m), 1.34 (6H, d, CH_3CHCH_3, *J* = 6.7) HRMS FAB: Found 640.3261; 640.3247 $C_{35}H_{42}N_7O_5$ requires 640.3247 $[M + 1]^+$.

3.8.13. N-[5-({[1-sec-Butyl-5-({[2-(4-morpholinyl)ethyl]amino} carbonyl)-1H-pyrrol-3-yl]amino}carbonyl)-1-methyl-1H-pyrrol-3-yl]-6-[(E)-2-(4-methoxyphenyl)ethenyl]nicotinamide **7b**

From 1-*sec*-butyl-4-{[(1-methyl-4-nitro-1*H*-pyrrol-2-yl) carbonyl]amino}-*N*-[2-(4-morpholinyl)ethyl]-1*H*-pyrrole-2-carboxamide **18b** (30 mg, 0.07 mmol) and 6-[(*E*)-2-(4-methoxyphenyl)ethenyl]nicotinic acid (17 mg, 0.07 mmol) using HBTU (50 mg, 0.13 mmol). Purification by HPLC furnished the desired product as a pale orange solid, (12 mg, 28%) with no distinct m.p. Purity by HPLC >95%. ν_{max} (KBr): 3429, 2925, 1667, 1593, 1513, 1406, 1174, 1132, 799 cm^{-1} δ_H (DMSO-d_6): 10.47 (1H, s, Ar*H*), 9.97 (1H, s, Ar*H*), 9.65 (1H, bs, TFA), 9.06 (1H, d, Ar*H*, *J* = 2.1), 8.26 (1H, d, *J* = 2.0), 8.24 (1H, d, *J* = 2.2), 8.22 (1H, t, *J* = 4.1), 7.75 (1H, d, C=C*H*, *J* = 16.0), 7.63–7.66 (3H, dd, *J* = 8.8, 3.3), 7.34 (1H, s), 7.33 (1H, d, *J* = 1.8), 7.25 (1H, d, C=C*H*, *J* = 16.1), 7.11 (1H, d, *J* = 1.8), 6.96–7.00 (3H, m), 5.33 (1H, sextet, CH_2CHCH_3, *J* = 6.8), 3.99–4.02 (2H, m), 3.88 (3H, s, NCH_3), 3.80 (3H, s, OCH_3), 3.62-3.69 (2H, m), 3.51–3.58 (4H, m), 3.25–3.31 (2H, m), 3.05–3.18 (2H, m), 1.70–1.74 (2H, quintet, CH_3CH_2CH, *J* = 7.7), 1.34 (3H, d, $CHCH_3$, *J* = 6.8), 0.75 (3H, t, CH_3CH_2, *J* = 7.3) HRMS FAB: found 654.3377; $C_{36}H_{44}N_7O_5$ requires 654.3398 $[M + 1]^+$.

3.8.14. N-[1-Isopropyl-5-({[1-methyl-5-({[2-(4-morpholinyl) ethyl] amino}carbonyl)-1H-pyrrol-3-yl]amino}carbonyl)-1H-pyrrol-3-yl]-6-[(E)-2-(4-methoxyphenyl)ethenyl] nicotinamide **7c**

From 4-{[(1-isopropyl-4-nitro-1*H*-pyrrol-2-yl)carbonyl] amino}-1-methyl-*N*-[2-(4-morpholinyl)ethyl] -1*H*-pyrrole-2-carboxamide **18c** (30 mg, 0.07 mmol) and 6-[(*E*)-2-(4-methoxyphenyl)ethenyl]nicotinic acid **32** (18 mg, 0.07 mmol) using HBTU (52 mg, 0.14 mmol). Purification by HPLC furnished the desired product as a bright orange solid (4 mg, 9%), purity by HPLC > 95% with no distinct melting point. ν_{max} (KBr): 3445, 2923, 1670, 1650, 1513, 1412, 1201, 1175, 1133 cm^{-1} δ_H (DMSO-d_6): 10.47 (1H, s, Ar*H*), 10.01 (1H, s, Ar*H*), 9.51 (1H, bs, TFA), 9.06 (1H, d, Ar*H*, *J* = 2.1), 8.26 (1H, d, *J* = 2.0), 8.24 (1H, d, *J* = 2.1), 8.22 (1H, t, *J* = 4.1), 7.75 (1H, d, C=C*H*, *J* = 16.1), 7.63–7.66 (3H, dd, *J* = 8.8, 3.3), 7.50 (1H, d, *J* = 1.9), 7.25 (1H, m, C=C*H*,), 7.21 (1H, d, *J* = 1.8), 7.03 (1H, d, *J* = 1.8), 6.96–7.02 (3H, m), 5.46 (1H, septet, CH_3CHCH_3, *J* = 6.7), 3.83 (3H, s, NCH_3), 3.99–4.03 (2H, m), 3.61–3.68 (2H, m), 3.53–3.58 (4H, m), 3.25–3.29 (2H, m), 3.05–3.18 (2H, m), 1.38 (6H, d, CH_3CHCH_3, *J* = 6.6). HRMS FAB: Found 662.3074; $C_{35}H_{42}N_7O_5Na$ requires 662.3067 $[M + Na]^+$.

3.8.15. N-[1-sec-butyl-5-({[1-methyl-5-({[2-(4-morpholinyl)ethyl] amino}carbonyl)-1H-pyrrol-3-yl]amino}carbonyl)-1H-pyrrol-3-yl]-6-[(E)-2-(4-methoxyphenyl)ethenyl] nicotinamide **7d**

From 4-{[(1-*sec*-butyl-4-nitro-1*H*-pyrrol-2-yl)carbonyl]amino}-1-methyl-*N*-[2-(4-morpholinyl)ethyl]- 1*H*-pyrrole-2-carboxamide **14** (30 mg, 0.07 mmol) and 6-[(*E*)-2-(4-methoxyphenyl)ethenyl] nicotinic acid **32** (17 mg, 0.07 mmol) using HBTU (50 mg, 0.13 mmol). Purification by HPLC furnished the desired product as a bright orange solid (7 mg, 16%), purity by HPLC >95% with no distinct melting point. ν_{max} (KBr): 3435, 1674, 1594, 1513, 1412, 1260, 1204, 1175, 1135 cm^{-1} δ_H (DMSO-d_6): 10.47 (1H, s, Ar*H*), 10.02 (1H, s, Ar*H*), 9.55 (1H, bs, TFA), 9.06 (1H, d, Ar*H*, *J* = 2.1), 8.22–8.26 (3H, m), 7.75 (1H, d, C=C*H*, *J* = 16.0), 7.63–7.66 (3H, dd, *J* = 8.8, 3.3), 7.47 (1H, s), 7.25 (1H, d, C=C*H*, *J* = 16.1), 7.21 (1H, d, *J* = 1.7), 6.96–7.09 (4H, m), 5.33 (1H, sextet, CH_2CHCH_3, *J* = 6.8), 3.99–4.02 (2H, m), 3.83 (3H, s, NCH_3), 3.81 (3H, s, OCH_3), 3.62–3.69 (2H, m), 3.51–3.58 (4H, m), 3.25–3.31 (2H, m), 3.05–3.18 (2H, m), 1.70–1.74 (2H, m, CH_3CH_2CH), 1.34 (3H, d, $CHCH_3$, *J* = 6.7), 0.75 (3H, t, CH_3CH_2, *J* = 7.2) HRMS FAB: found 654.3378; $C_{36}H_{44}N_7O_5$ requires 654.3404 $[M + 1]^+$.

3.9. Melting temperature measurement

DNA oligomers and their complements were melted at a rate of 0.5 °C min^{-1} in 10 mM PBS buffer solution (pH 7.4) with 50 mM NaCl on a Cary 300 BIO UV–visible spectrophotometer. Each oligomer (made to a concentration of 6×10^{-6} M) was mixed with-sufficient MGB to give the appropriate ratio. Samples were heated to 80 °C and cooled to 10 °C. The melting temperatures (T_m) of the hybrids were determined from the derivative maxima.

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