Available online at www.sciencedirect.com
SCIENCE DIRECT®
European Journal of Medicinal Chemistry 38 (2003) 189–197
EUROPEAN JOURNAL OF MEDICINAL CHEMISTRY
www.elsevier.com/locate/ejmech

Original article

# New propylamine oligopyrrole carboxamides linked to a heterocyclic or anthraquinone system: synthesis, DNA binding, topoisomerase I inhibition and cytotoxicity

Christian Hotzel, Annalisa Marotto, Ulf Pindur *

*Department of Pharmacy, Johannes Gutenberg-University, Staudingerweg 5, 55099 Mainz, Germany*

Received 10 June 2002; received in revised form 4 November 2002; accepted 20 November 2002

**Abstract**

Continuing our studies on combilexines, compounds consisting of a DNA intercalator linked to a minor groove ligand, new results are presented. The synthesis of a series of new propylamine oligopyrrole carboxamides closely related to netropsin and distamycin A, linked to a heterocyclic or anthraquinone system is reported. The cytotoxic activity in vitro, the DNA binding characteristics and the inhibition of the topoisomerase I of the compounds were studied in order to explain the biological mechanism of action of these new potential combilexines. Some of the synthesised compounds showed cytotoxic activity against human tumour cell lines, as well as DNA binding and topoisomerase I inhibiting properties.


*Keywords:* Combilexines; DNA-binding; Topoisomerase I inhibition; Cytotoxic antitumour agents

## 1. Introduction

Molecular recognition is a fundamental principle in biology and pharmacology. In this context creating DNA-binding compounds which additionally recognise specific sequences is a central goal in the development of DNA-targeted drugs [1,2]. Some highly interesting lead compounds are the naturally occurring antibiotics netropsin and distamycin A (see Fig. 1) [3,4], which bind in the minor groove of the DNA with high AT base selectivity [5]. Meanwhile the oligopyrrole carboxamide chain of these natural antibiotics has been used as sequence selective carriers for other cytotoxic DNA ligands such as intercalators in compounds called combilexines [6]. Among this group of compounds, some promising candidates have been described from several laboratories—for example NetAmsa (see Fig. 1) [6]. Starting from this background, we conducted systematic studies in the pyrrole carboxamide chemistry with different ligands for the C- and N-terminal ends and reported DNA binding and cytotoxicity effects of some new compounds [7]. Encouraged by the results of this basic study and from the perspective of a more systematic structure activity profile, we continued our synthetic efforts. Thus, we now report the preparation of new potential combilexines of the pyrrole carboxamide series with an *N*,*N*-dimethylamino-propylamidic group at the C-terminal end and a heterocyclic, a quinone or a nucleic base moiety linked via an aliphatic chain at the N-terminal end (see Fig. 2). This amino-propylamidic group should represent a structural equivalent of the amidine group presented in distamycin A and netropsin. In addition, the DNA binding, the topoisomerase I inhibition and the antitumour activity were investigated.

## 2. Chemistry

Following the protocols recently described [7], a variety of new *N*,*N*-dimethylamino-propylamide-based

* Corresponding author.
*E-mail address:* pindur@mail.uni-mainz.de (U. Pindur).

0223-5234/02/$ - see front matter 
doi:10.1016/S0223-5234(02)01441-1

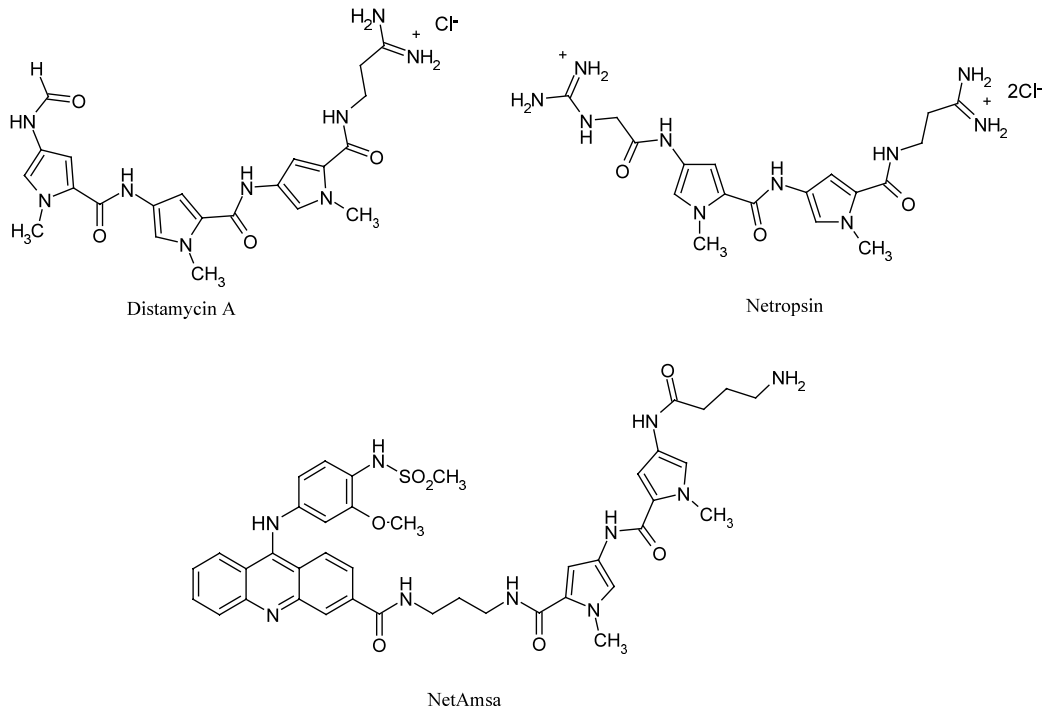



Fig. 1. The minor groove binding ligands distamycin A and netropsin and, as a typical example, the combilexine NetAmsa [6].

compounds with a variable number of pyrrole units and different ligands at the N-terminal side were synthesised by a multi-step procedure closely related to classical peptide synthesis (see Fig. 2). The synthesis started with commercially available *N*-methylpyrrole **1**, which was acylated with trichloroacetylchloride [8] to compound **2** (for detaild see Ref. [7]). After nitration of compound **2** to **3**, *N*,*N*-dimethyl-1,3-diaminopropane was added to produce the C-terminal side chain **4**. The bispyrrole **5** was synthesised by reduction of compound **4** over Pd/charcoal and successive additions of building block **3**. The trispyrrole (**6**) (see Fig. 2) was prepared by the same procedure starting from bispyrrole **5** [9]. The *N*-acetylated compound **16** was synthesised by reduction of compound **5** and successive acetylation. The indole and carbazole acids were synthesised by the same method as described in earlier publications [7,10–12]. The final combilexines were all synthesised by the classic DCC-method starting from the reduced form of compounds **4** or **5** (see Fig. 3) [7]. The anthraquinone derivatives were synthesised starting from sodium-anthraquinone sulphonate (**13a**). This compound was melted with phosphorpentachloride to yield compound **13b** (yield: 91%) and successively coupled with the mono- or the bispyrrole units after their reduction to **4a** and **5a** to get compounds **14** and **15**, respectively (see Fig. 4). The yield was 52 and 19%, respectively. The constitution of the *N*-methyl-pyrrole derivatives **6**–**12** and **14**–**16** were unambigously clarified by the combination of several NMR techniques ($^{1}$H-NOE, proton decoupling experiments, $^{13}$C-spin echo experiments).

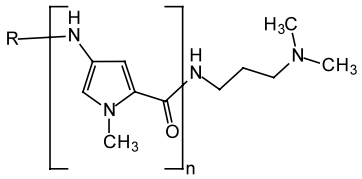
## 3. Biochemical and biological results

### 3.1. Cytotoxicity assay

The newly synthesised potential combilexines reported in Fig. 2 were submitted for cytotoxicity testing to the Developmental Therapeutics Program of the National Cancer Institute (USA) [7,13,14]. In the prescreening assay for the determination of the cytotoxicity in a three cell line panel consisting of the highly sensitive cell lines NCI-H460 (lung carcinoma), MCF-7 (breast carcinoma) and SF 268 (glioma) most of the substances are inactive [15]. The weak effect noticed with the anthraquinone derivative **14** and its analogue **15** has not been confirmed in the NCI 60-cell lines panel screening with the sulphorhodamine B-assay in a dose–response analysis (concentration range from $10^{-4}$ to $10^{-8}$ M) except for the marked selectivity of compound **15** for the ovarian cell line SK-OV-3 ($GI_{50} < 10^{-8}$ M).

### 3.2. DNA-binding studies and topoisomerase I inhibition

To explain the cytotoxicity and the mechanism of action of the new compounds in the given series, we studied their interactions with the DNA and the topoisomerase I as possible molecular targets [16,17]. The DNA-binding was evaluated by the spectrophotometric determination of the melting curve of dsDNA in the presence of the potential ligands [7,18,19] and additionally with the ethidium bromide displacement assay, which comprises a fluorimetric titration [20,21].



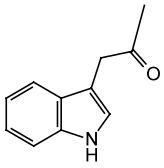
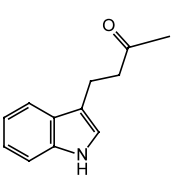
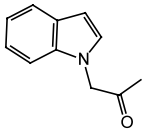
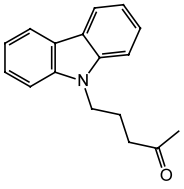
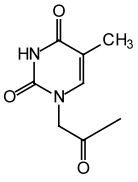
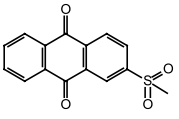
| R | compound | n |
|---|---|---|
| $O_2N$— | **5** | 2 |
| | **6** | 3 |
|  | **7** | 2 |
|  | **12** | 1 |
|  | **8** | 2 |
|  | **11** | 2 |
|  | **10** | 2 |
|  | **9** | 2 |
|  | **14** | 1 |
| | **15** | 2 |
|  | **16** | 2 |

Fig. 2. Synthesised oligopyrrole carboxamides.

The inhibition of the catalytic activity of the topoisomerase I was determined by analysis of the different population distributions of DNA topoisomers after incubation of a DNA-topoisomerase I mixture in the absence of and in the presence of the test drugs in three different concentrations (5, 20 and 50 μM) [22–24]. For details about these three assays, see Refs. [7,25,26]. Results of the melting experiments and of the topoisomerase I inhibition assay are reported in Table 1. Compounds **6**–**9**, **11**, **14** and **16** showed a relevant DNA binding expressed in the $\Delta T_m$-values in the range of 8–13 °C. Interestingly, seven of the compounds revealed probably non-specific inhibition of the catalytic activity of topoisomerase I in different concentrations. However, the good DNA binding compounds **11** and **16** showed no inhibition of the topoisomerase I according to the procedures established in our laboratory [7].

## 4. Discussion of the results and conclusion

Our presumption of the importance of H-bond donor and acceptor groups in the lexine chain for DNA interactions, which were recently described [7], has been confirmed with the compounds of this second series. Almost all *N*,*N*-dimethylamino-propylamide derivatives showed DNA binding according to the melting experiments. The cytotoxic activity of these compounds can be explained by their ability to bind to the DNA and/or to inhibit the catalytic activity of the topoisomerase I. A convincing determination of structure–activity relationships of the new combilexines is not possible at the moment. However, the overall results demonstrate that not only the dimethylamino-propylamide side chain but also the presence of a minimum of three carbonylic acceptor groups are necessary for binding to the DNA. In summarizing all data available, it becomes obvious that the compounds **14** and **15** with the anthraquinone moiety should be very promising candidates for further studies. The lack of cytotoxicity in the NCI antitumour screening assay for a variety of the compounds which showed discrete DNA binding and topoisomerase I inhibiting activity can perhaps be attributed to a diminished absorption of the substances into the cells.

Our synthetic and analytical studies to develop potential combilexines including nucleobase derivatives and to obtain more information about systematic structure–activity relationships will be continued.

## 5. Experimental

### 5.1. Chemistry

Melting points were measured with a Büchi 510 instrument and are uncorrected. IR spectra were recorded on a Perkin–Elmer 1310 IR-spectrometer using KBr pellets ($\nu$ in $cm^{-1}$). $^1H$-, $^{13}C$-NMR spectra including NOE were recorded on a Bruker AC-300 apparatus (300 MHz). The samples were dissolved in DMSO-$d_6$. The chemical shift values are reported in parts per million (ppm, $\delta$ units) and spin–spin coupling $J$ were listed in Hz. Seventy electron volts EI-mass spectra were obtained with a Mascom 311-A apparatus and FD mass

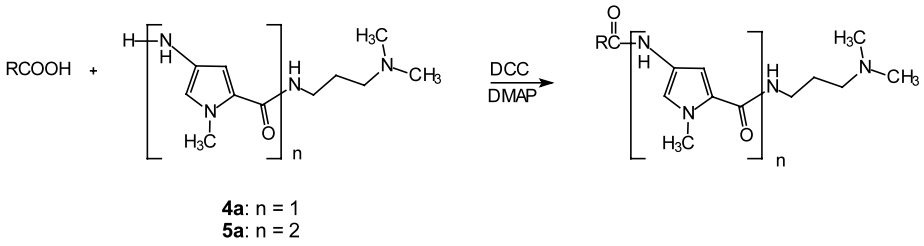



Fig. 3. Final step in the synthesis of the different combilexines (see Fig. 2).

spectra. with a Finnigan MAT 7 instrument. C,H,N-analysis was performed using a Haereus CHN rapid apparatus. Analyses indicated by the symbols of the elements or functions were within ±0.4% of the theoretical values.

### 5.1.1. 2,2,2-Trichloro-1-(1-methyl-1H-2-pyrrolyl)-1-ethanone (2)

To a solution of trichloroacetyl chloride (4.55 g, 28 mmol) in $CH_2Cl_2$ (25 mL), was added a solution of *N*-methylpyrrole (**1**, 2.03 g, 25 mmol) in $CH_2Cl_2$ (15 mL) over a period of 3 h. During this time, the reaction mixture was stirred vigorously and nitrogen was swept through to remove HCl as it was formed. The solution was stirred overnight and then evaporated. The dark red residue was dissolved in $CHCl_3$ and filtered through a short column of silica gel. Evaporation of the solvent gave pale yellow needles (2.3 g) (10.16 mmol) (41%), m.p. 62 °C (lit. m.p.: 62–63 °C [8]); IR: 3350, 3000, 2850, 1600, 1400, 1350, 1300, 1280, 1200, 1160, 1050, 1020, 920, 820, 800, 760, 700, 650; $^1$H-NMR (DMSO-

Table 1
Results of the determination of the melting temperature of dsDNA (reported as $\Delta T_m$, the difference between the melting temperature of the dsDNA in the presence and in the absence of the ligands) and of topoisomerase I inhibition assay (reported as the concentration by which an inhibition of the enzyme was detected) the for compounds **6**–**9**, **11**, **12** and **14**–**16**

| Compound | $\Delta T_m$ (°C) | TOPO I-inhibition (μM) |
|---|---|---|
| **6** | 9.0±0.5 | 50 |
| **7** | 8.4±0.5 | 50 |
| **8** | 10.4±0.5 | 5 |
| **9** | 7.6±0.5 | 50 |
| **11** | 14.0±0.5 | no inhibition |
| **12** | 0 | 5 |
| **14** | 15.0±0.5 | 20 |
| **15** | 0 | 50 |
| **16** | 12.7±0.5 | no inhibition |

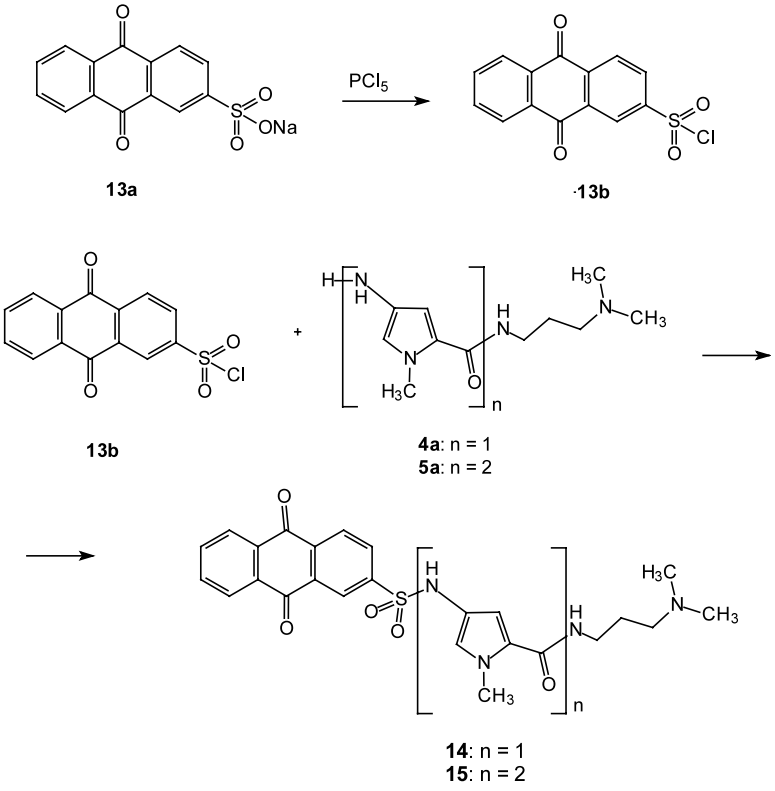



Fig. 4. Synthesis of the anthraquinone combilexines.

$d_6$): $\delta$ 3.89 (s, 3H, $CH_3$), 6.27 (dd, 1H, pyrrole-H), 7.40 (d, 1H, $^4J = 1.56$ Hz, pyrrole-H), 7.42 (d, 1H, $^4J = 1.71$ Hz). MS: *m/z* 226 [$M^+$].

### 5.1.2. 2,2,2-Trichloro-1-(1-methyl-4-nitro-1H-2-pyrrolyl)-1-ethanone

To a suspension of **2** (1 g, 4.43 mmol) in $Ac_2O$ (6 mL) at −40 °C, a mixture of 4 mL $Ac_2O$ and $HNO_3$ (70%, 0.8 mL) was added over a period of 30 min and then warmed up to room temperature (r.t.). After stirring at r.t. for 2 h, the mixture was cooled to −20 °C. Isopropyl alcohol (10 mL) was added and the resultant colourless solid was collected, washed with cold isopropyl alcohol, and dried under reduced pressure (colourless solid) (640 mg) (2.35 mmol) (53.3%), m.p. 134 °C (lit. m.p.: 135–140 °C [8]); IR: 3250, 3020, 2970, 1630, 1480, 1440, 1380, 1350, 1260, 1180, 1060, 1030, 950, 810, 800, 760, 750, 700, 660, 640; $^1$H-NMR (DMSO-$d_6$): $\delta$ 3.98 (s, 3H, $CH_3$), 7.78 (d, 1H, $^4J = 1.84$ Hz, pyrrole-H3), 8.55 (d, 1H, $^4J = 1.7$ Hz). MS: *m/z* 271 [$M^+$].

### 5.1.3. N2-[3-(Dimethylamino)propyl]-1-methyl-4-nitro-1H-2-pyrrole carboxamide (4)

A solution of 3-dimethylaminopropylamine (0.7 g, 6.86 mmol) in $CH_2Cl_2$ (15 mL) was added dropwise to a stirred solution of **3** (1.4 g, 5.16 mmol) in $CH_2Cl_2$ (15 mL) of 0 °C. The reaction mixture was warmed up to r.t. and stirring was continued for 1 h. The solvent was removed under vacuum and the residual solid was recrystallised from EtOH. The residue was chromatographed on neutral $Al_2O_3$ (MeOH–EtOAc (1:4)). Colourless crystals were obtained (688 mg) (2.7 mmol) (66%), m.p. 125 °C (lit. m.p.: 125.5–127 °C [9]); IR (KBr, $cm^{-1}$): 3420, 2720, 2340, 1650, 1540, 1530, 1490, 1470, 1410, 1305, 1265, 1215, 1035, 820, 755; $^1$H-NMR (300 MHz) (DMSO-$d_6$): $\delta$ 1.6 (m, 2H, $^3J = 6.5$ Hz, $CH_2$), 2.05 (s, 6H, 2-$CH_3$), 2.2 (t, 2H, $^3J = 6.7$ Hz, $CH_2N(Me)_2$), 3.18 (q, 2H, $^3J = 6.7$ Hz, $CH_2N$), 3.77 (s, 3H, $CH_3$), 7.38 (d, 1H, $^4J = 1.6$ Hz, pyrrole-H3), 8.09 (1H, d, $^4J = 1.6$ Hz, pyrrole-H5), 8.40 (t, 1H, $^3J = 7.4$ Hz, NH). MS: *m/z* 254 [$M^+$].

### 5.1.4. N2-[5-({[3-(Dimethylamino)propyl]amino}carbonyl)-1-methyl-1-H-3-pyrrolyl]-1-methyl-4-nitro-1H-2-pyrrole carboxamide (5)

A solution of **4** (2 g, 7.86 mmol) in dioxane (20 mL) was hydrogenated under reduced pressure over Pd/C (800 mg) for 12 h. The catalyst was removed by filtration and then the solvent was removed in vacuo. The residual solid was dissolved in DMF (20 mL) and concentrated to half of its original volume under reduced pressure to remove dioxane completely. A solution of **3** (2 g, 7.36 mmol) in DMF (15 mL) was added with stirring at 0 °C. The temperature was allowed to rise to ambient temperature. The solvent was removed in vacuo, and the residue was treated with *i*-PrOH. The resultant crystalline solid was collected and washed with *i*-PrOH. The filtrate was concentrated, and the residue was purified by column chromatography on silica gel with MeOH–$NH_3$ (25%, 97:3); (yellow solid) (655 mg) (1.74 mmol) (22.14%), m.p. 190 °C (lit. m.p.: 190–191 °C [9]); IR (KBr, $cm^{-1}$): 3200, 3000, 2850, 2720, 2700, 1610, 1560, 1520, 1410, 1380, 1250, 1200, 1150, 1100, 1060, 1000, 980, 880, 840, 800, 760, 720, 700, 650; $^1$H-NMR (DMSO-$d_6$): $\delta$ 1.62 (quint, 2H, $^3J = 7.14$ Hz, $CH_2$), 2.10 (s, 6H, 2-$CH_3$), 2.23 (t, 2H, $^3J = 3.0$ Hz, $CH_2$), 3.14 (q, 2H, $^3J = 6.95$ Hz, $CH_2$), 3.79 (s, 3H, $CH_3$), 3.91 (s, 3H, $CH_3$), 6.79 (d, 1H, $^4J = 1.94$ Hz, pyrrole-H3), 7.19 (d, 1H, $^4J = 1.65$, pyrrole-H5), 7.55 (d, 1H, $^4J = 1.92$, pyrrole-H3′), 8.10 (t, 1H, $^4J = 1.63$ Hz, NH), 8.16 (d, 1H, $^4J = 1.71$ Hz, pyrrole-H5′), 10.22 (s, 1H, NH); $^{13}$C-NMR (DMSO-$d_6$): $\delta$ 27.3 (s), 36.3 (p), 37.3 (s), 37.6 (p), 45.5 (p), 45.5 (p), 57.7 (s), 104.1 (t), 107.7 (t), 107.8 (t), 117.5 (t), 121.7 (q), 123.6 (q), 126.6 (q), 134.1 (q), 157.1 (q), 161.4 (q). MS: *m/z* 376 [$M^+$]; Anal. $C_{17}H_{24}N_6O_4$ (C,H,N).

### 5.1.5. N2-[5-({[3-(Dimethylamino)propyl]amino}carbonyl)-1-methyl-1-H-3-pyrrolyl]-1-methyl-4-{[(1-methyl-4-nitro-1H-pyrrolyl)carbonyl]amino}-1H-2-pyrrole carboxamide (6)

This compound was synthesised by the same procedure as for **5**; instead of **4** compound **5** (2 g, 5.3 mmol) was used; (yellow solid) (900 mg) (1.8 mmol) (34.0%), m.p. 127 °C (lit. m.p.: 136–137 °C [9]); IR: 3380, 3250, 3100, 2900, 2820, 2800, 1640, 1620, 1560, 1500, 1450, 1420, 1380, 1290, 1240, 1200, 1150, 1100, 1050, 1020, 1000, 980, 880, 800, 760, 740, 700, 650; $^1$H-NMR (DMSO-$d_6$): $\delta$ 1.60 (quint, 2H, $^3J = 6.9$ Hz, $CH_2$), 2.15 (s, 6H, 2-$CH_3$), 2.26 (t, 2H, $^3J = 6.9$ Hz, $CH_2$), 3.17 (q, 2H, $^3J = 6.0$ Hz, $CH_2$), 3.78 (s, 3H, $CH_3$), 3.84 (s, 3H, $CH_3$), 3.9 (s, 3H, $CH_3$), 6.81 (d, 1H, $^4J = 1.6$ Hz, pyrrole-H), 7.02 (d, 1H, $^4J = 1.6$ Hz, pyrrole-H), 7.18 (d, 1H, $^4J = 1.5$ Hz, pyrrole-H), 7.26 (d, 1H, $^4J = 1.6$ Hz, pyrrole-H), 7.58 (d, 1H$^4$, $J = 1.5$ Hz, pyrrole-H), 8.08 (t, 1H, $^3J = 5.3$ Hz, NH), 8.17 (d, 1H, $^4J = 1.5$ Hz, pyrrole-H), 9.94 (s, 1H, NH), 10.30 (s, 1H, NH); $^{13}$C-NMR (DMSO-$d_6$): $\delta$ 26.6 (s), 36.2 (p), 36.3 (p), 37.7 (s), 38.9 (p), 45.5 (p), 45.5 (p), 57.4 (s), 104.2 (t), 104.2 (t), 104.3 (t), 104.7 (t), 107.8 (t), 107.8 (t), 121.7 (q), 122.3 (q), 123.3 (q), 123.6 (q), 126.6 (q), 134.0 (q), 157.2 (q), 158.6 (q), 161.4 (q). MS: *m/z* 498 [$M^+$]; Anal. $C_{23}H_{30}N_8O_5$ (C,H,N).

### 5.1.6. General procedure for the synthesis of the pyrrole and the oligopyrrole carboxamides

Carboxylic acid (1 mmol) was dissolved in 20 mL dioxane. Then 1 mmol of the pyrrole amine (prepared from the nitropyrrole analogues by hydrogenation in MeOH over Pd on charcoal) and 0.1 mmol (12 mg) of

dimethylaminopyridine (DMAP) were added. The mixture was stirred at r.t.; a solution of dicyclohexylcarbodiimide (DCC) (288 mg) 1.4 mmol) in dioxane (10 mL) was added dropwise. After stirring for 24 h the precipitate, a dicyclohexyl urea, was removed by filtration. The solution was evaporated to dryness, and the residue was chromatographed on silica gel (MeOH–$NH_3$ (25%, 97:3)).

*5.1.6.1. N2-[5-({[3-(Dimethylamino)propyl]amino}carbonyl)-1-methyl-1-H-3-pyrrolyl]-4-{[2-(1H-3-indolyl)acetyl]amino}-1-methyl-1H-2-pyrrole carboxamide (**7**).* Yellow solid (140 mg) (0.28 mmol) (27.8%), m.p. 96 °C; IR (KBr, $cm^{-1}$): 3360, 3250, 3080, 2900, 2830, 2800, 1620, 1560, 1500, 1450, 1420, 1380, 1350, 1290, 1250, 1190, 1130, 1090, 1050, 1000, 800, 760, 730, 650; $^1$H-NMR (DMSO-$d_6$): $\delta$ 1.6 (quint, 2H, $^3J = 7.0$ Hz, $CH_2$), 2.1 (s, 6H, 2-$CH_3$), 2.3 (t, 2H, $^3J = 5.8$ Hz, $CH_2$), 3.7 (s, 3H, $CH_3$), 3.8 (s, 3H, $CH_3$), 5.7 (s, 2H, $CH_2$), 6.8 (d, 1H, $^4J = 1.65$ Hz, pyrrole-H3), 6.9 (d, 1H, $^4J = 1.63$ Hz, pyrrole-H5), 6.95 (pt, 1H, $^3J = 7.1$ Hz, indole-H 5 or 6), 7.04 (pt, 1H, $^3J = 7.0$ Hz, indole-H 5 or 6), 7.13 (d, 1H, $^4J = 1.41$ Hz, pyrrole-H3′), 7.15 (d, 1H, $^3J = 1.51$ Hz, pyrrole-H5′), 7.21 (s, 1H, indole-H2), 7.33 (d, 1H, $^3J = 8.0$ Hz, indole-H7), 7.57 (d, 1H, 7.9 Hz, indole-H4), 8.05 (t, 1H, $^3J = 5.03$ Hz, NH), 9.8 (s, 1H, NH), 9.9 (s, 1H, NH), 10.87 (s, 1H, NH); $^{13}$C-NMR (DMSO-$d_6$); $\delta$ 27.5 (s), 33.4 (s), 36.2 (p), 36.3 (p), 37.3 (s), 45.5 (p), 45.5 (p), 57.4 (s), 104.2 (t), 109.2 (q), 111.6 (t), 111.6 (t), 118.6 (t), 118.6 (t), 119.0 (t), 121.2 (t), 121.2 (t), 122.3 (q), 122.3 (q), 123.0 (q), 123.3 (q), 124.0 (t), 127.5 (q), 136.4 (q), 158.6 (q), 161.4 (q), 168.3 (q). MS: *m/z* 503 [$M^+$]; Anal. $C_{27}H_{33}N_7O_3$ (C,H,N).

*5.1.6.2. N2-[5-({[3-(Dimethylamino)propyl]amino}carbonyl)-1-methyl-1-H-3-pyrrolyl]-4-{[2-(1H-3-indolyl)propanoyl]amino}-1-methyl-1H-2-pyrrole carboxamide (**8**).* Yellow solid (120 mg) (0.23 mmol) (23.1%), m.p. 75 °C; IR (KBr, $cm^{-1}$): 3400, 3250, 3100, 2920, 2840, 2800, 2750, 1620, 1560, 1520, 1450, 1420, 1380, 1300, 1240, 1200, 1150, 1130, 1100, 1080, 1050, 1030, 980, 880, 800, 760, 740, 650; $^1$H-NMR (DMSO-$d_6$): $\delta$ 1.57 (quint, 2H, $^3J = 6.96$ Hz, $CH_2$), 2.12 (s, 6H, 2-$CH_3$), 2.22 (t, 2H, $^3J = 7.11$ Hz, $CH_2$), 2.59 (t, 2H, $^3J = 7.4$ Hz, $CH_2$), 2.98 (t, 2H, $^3J = 7.5$ Hz, $CH_2$), 3.15 (t, 2H, $^3J = 6.15$ Hz, $CH_2$), 3.77 (s, 3H, $CH_3$), 3.80 (s, 3H, $CH_3$), 6.79 (d, 1H, $^4J = 1.66$ Hz, pyrrole-H3), 6.83 (d, 1H, $^4J = 1.4$ Hz, pyrrole-H5), 6.97 (pt, 1H, $^3J = 7.65$ Hz, indole-H5 or 6), 7.04 (pt, 1H, $^3J = 7.8$ Hz, indole-H5 or 6), 7.13 (d, 1H, $^4J = 1.62$ Hz, pyrrole-H3′), 7.16 (d, 1H, $^4J = 1.66$ Hz, pyrrole-H5′), 7.19 (s, 1H, indole-H2), 7.30 (d, 1H, $^3J = 7.8$ Hz, indole-H7), 7.54 (d, 1H, $^3J = 8.4$ Hz, indole-H4), 8.05 (t, 1H, $^3J = 5.05$ Hz, NH), 9.82 (s, 1H, NH), 10.22 (s, 1H, NH), 10.82 (s, 1H, NH); $^{13}$C-NMR (DMSO-$d_6$): $\delta$ 21.3 (s), 27.5 (s), 33.4 (s), 36.2 (p), 36.3 (p), 37.3 (s), 45.5 (p), 45.5 (p), 57.4 (s), 104.2 (t), 109.2 (q), 116.6 (t), 111.6 (t), 118.6 (t), 118.6 (t), 119.0 (t), 121.2 (t), 121.2 (t), 122.3 (q), 122.3 (q), 123.0 (q), 123.3 (q), 124.0 (t), 127.5 (q), 136.4 (q), 158.6 (q), 161.4 (q), 168.3 (q). MS: *m/z* 517 [$M^+$]; Anal. $C_{28}H_{35}N_7O_3$ (C,H,N).

*5.1.6.3. N2-[5-({[3-(Dimethylamino)propyl]amino}carbonyl)-1-methyl-1-H-3-pyrrolyl]-4-{[2-(5-methyl-2,4-dioxo-1,2,3,4-tetrahydro-1-pyrimidinyl)acetyl]amino}-1H-2-pyrrole carboxamide (**9**).* Yellow solid (180 mg) (0.35 mmol) (35.1%), m.p. 206 °C; IR (KBr, $cm^{-1}$): 3400, 3250, 3100, 2900, 2800, 1650, 1600, 1560, 1500, 1410, 1380, 1340, 1210, 1190, 1150, 1000, 950, 880, 790, 750, 650; $^1$H-NMR (DMSO-$d_6$): $\delta$ 1.60 (quint, 2H, $^3J = 6.99$ Hz, $CH_2$), 1.76 (s, 3H, $CH_3$), 2.10 (s, 6H, 2-$CH_3$), 2.24 (t, 2H, $^3J = 6.97$ Hz, $CH_2$), 3.17 (q, 2H, $^3J = 7.2$ Hz, $CH_2$), 3.77 (s, 3H, $CH_3$), 3.81 (s, 3H, $CH_3$), 4.43 (s, 2H, $CH_2$), 5.7 (s, 1H, thymine-H), 6.79 (d, 1H, $^4J = 4.67$ Hz, pyrrole-H3), 6.89 (d, 1H, $^4J = 1.68$ Hz, pyrrole-H5), 7.13 (d, 1H, $^4J = 1.4$ Hz, pyrrole-H3′), 7.16 (d, 1H, $^4J = 1.5$ Hz, pyrrole-H5′), 8.05 (t, 1H, $^3J = 5.1$ Hz, NH), 9.83 (s, 1H, NH), 10.16 (s, 1H, NH), 10.28 (s, 1H, NH); $^{13}$C-NMR (DMSO-$d_6$): $\delta$ 12.2 (p), 27.4 (s), 36.2 (p), 36.4 (p), 37.3 (s), 45.4 (p), 45.4 (p), 49.8 (s), 57.3 (s), 104.2 (t), 104.2 (t), 104.3 (t), 104.7 (t), 108.2 (q), 121.5 (q), 122.2 (q), 123.2 (q), 131.9 (q), 142.7 (t), 151.4 (q), 158.5 (q), 161.4 (q), 164.3. MS: *m/z* 512 [$M^+$]; Anal. $C_{24}H_{32}N_8O_5$ (C,H,N).

*5.1.6.4. N2-[5-({[3-(Dimethylamino)propyl]amino}carbonyl)-1-methyl-1-H-3-pyrrolyl]-4-{[9H-9-carbazolyl)butanoyl]amino}-1-methyl-1H-2-pyrrole carboxamide (**10**).* Yellow solid (180 mg) (0.3 mmol) (48.9%), m.p. 99 °C; IR (KBr, $cm^{-1}$): 3250, 3100, 3000, 2900, 2820, 2790, 1640, 1600, 1560, 1500, 1450, 1380, 1290, 1240, 1190, 1090, 1050, 880, 800, 740, 700, 650; $^1$H-NMR (DMSO-$d_6$): $\delta$ 1.6 (quint, 2H, $^3J = 6.8$ Hz, $CH_2$), 2.18 (s, 6H, 2-$CH_3$), 2.0 (quint, 2H, $^3J = 6.5$ Hz), 2.23 (t, 2H, $^3J = 7.0$ Hz, $CH_2$), 2.27 (t, 2H, $^3J = 6.6$ Hz, $CH_2$), 3.11 (q, 2H, $^3J = 6.4$ Hz, $CH_2$), 3.75 (s, 3H, $CH_3$), 3.79 (s, 3H, $CH_3$), 4.4 (t, 2H, $^3J = 6.7$ Hz, $CH_2$), 6.80 (d, 1H, $^4J = 1.55$ Hz, pyrrole-H3), 6.84 (d, 1H, $^4J = 1.6$ Hz, pyrrole-H5), 7.13 (d, 1H, $^4J = 1.62$ Hz, pyrrole-H3′), 7.16 (d, 1H, $^4J = 1.66$ Hz, pyrrole-H5′), 7.19 (d, 2H, $^3J = 7.3$ Hz, carbazole-H2,8), 7.4 (pt, 2H, $^3J = 7.5$ Hz, carbazole-H2,7), 7.6 (pt, 2H, $^3J = 8.1$ Hz, carbazole-H3,8), 8.05 (t, 1H, $^3J = 5.2$ Hz, NH), 8.1 (d, 2H, $^3J = 7.6$ Hz, carbazole-H4,5), 9.8 (s, 1H, NH), 9.85 (s, 1H, NH), 10.25 (s, 1H, NH); $^{13}$C-NMR (DMSO-$d_6$): $\delta$ 24.7 (s), 27.4 (s), 30.6 (s), 31.7 (s), 36.2 (p), 36.3 (p), 37.2 (s), 45.3 (p), 45.3 (p), 57.2 (s), 104.2 (t), 104.3 (t), 109.5 (t), 109.5 (t), 119.0 (t), 119.0 (t), 120.5 (t), 120.5 (t), 120.6 (t), 121.7 (t), 122.3 (q), 122.4 (q), 122.4 (q), 123.0 (q), 124.0 (q), 125.9 (t), 125.9 (t),

140.3 (q), 140.4 (q), 153.5 (q), 158.7 (q), 161.5 (q), 169.1 (q), 169.2 (q). MS: *m/z* 582 [$M^+$]; Anal. $C_{33}H_{39}N_7O_3$ (C,H,N).

*5.1.6.5. N2-[5-({[3-(Dimethylamino)propyl]amino}carbonyl)-1-methyl-1-H-3-pyrrolyl]-4-{[2-(1H-1-indolyl)acetyl]amino}-1-methyl-1H-2-pyrrole carboxamide (**11**).* Yellow solid (340 mg) (0.73 mmol) (80.6%), m.p. 98 °C; IR (KBr, $cm^{-1}$): 3400, 3250, 3080, 2900, 2850, 2800, 1620, 1560, 1510, 1450, 1420, 1380, 1340, 1250, 1190, 1140, 1090, 1050, 1000, 950, 800, 750, 730, 650; $^1$H-NMR (DMSO-$d_6$): $\delta$ 1.56 (quint, 2H, $^3J = 7.0$ Hz, $CH_2$), 2.1 (s, 6H, 2-$CH_3$), 2.22 (t, 2H, $^3J = 7.0$ Hz, $CH_2$), 3.16 (q, 2H, $^3J = 6.3$ Hz, $CH_2$), 3.77 (s, 3H, $CH_3$), 3.79 (s, 3H, $CH_3$), 4.96 (s, 2H, $CH_2$), 6.44 (d, 1H, $^3J = 3.1$ Hz, indole-H3), 6.78 (d, 1H, $^4J = 1.7$ Hz, pyrrole-H3), 6.89 (d, 1H, $^4J = 2.0$ Hz, pyrrole-H5), 7.02 (pt, 1H, $^3J = 6.9$ Hz, indole-H 5 or 6), 7.11 (pt, 1H, $^3J = 6.9$ Hz, indole-H 5 or 6), 7.13 (d, 1H, $^4J = 1.4$ Hz, pyrrole-H3′), 7.16 (d, 1H, $^4J = 1.7$ Hz, pyrrole-H5′), 7.36 (d, 1H, $^3J = 3.0$ Hz, indole-H2), 7.38 (d, 1H, $^3J = 8.1$ Hz, indole-H7), 7.54 (d, 1H, $^3J = 7.9$ Hz, indole-H4), 8.06 (t, 1H, $^3J = 5.3$ Hz, NH), 9.85 (s, 1H, NH), 10.29 (s, 1H, NH); $^{13}$C-NMR (DMSO-$d_6$): $\delta$ 27.4 (s), 36.2 (p), 36.4 (p), 37.3 (s), 45.4 (p), 45.4 (p), 49.2 (s), 57.3 (s), 101.0 (t), 104.2 (t), 104.3 (t), 110.0 (t), 119.4 (t), 119.4 (t), 120.6 (t), 120.6 (t), 121.3 (t), 121.3 (t), 122.3 (q), 123.3 (q), 128.4 (q), 128.4 (q), 130.2 (q), 136.6 (q), 158.6 (q), 161.5 (q), 164.9 (q). MS: *m/z* 517 [$M^+$]; Anal. $C_{28}H_{35}N_7O_3$ (C,H,N).

*5.1.6.6. N2-[3-(Dimethylamino)propyl]-4-{[2-(1H-3-indolyl)acetyl]amino}-1-methyl-1H-2-pyrrole carboxamide (**12**).* Yellow solid (170 mg) (0.45 mmol) (44.6%), m.p. 65 °C; IR (KBr, $cm^{-1}$): 3350, 3250, 3080, 2900, 2820, 2800, 1640, 1620, 1560, 1500, 1440, 1420, 1380, 1270, 1240, 1210, 1140, 1090, 1000, 980, 950, 800, 770, 730, 600; $^1$H-NMR (DMSO-$d_6$): $\delta$ 1.57 (quint, 2H, $^3J = 6.8$ Hz, $CH_2$), 2.11 (s, 6H, 2-$CH_3$), 2.21 (t, 2H, $^3J = 7.13$ Hz, $CH_2$), 3.14 (q, 2H, $^3J = 6.0$ Hz, $CH_2$), 3.73 (s, 3H, $CH_3$), 5.71 (s, 2H, $CH_2$), 6.63 (d, 1H, $^4J = 1.7$ Hz, pyrrole-H3), 6.95 (pt, 1H, $^3J = 7.2$ Hz, indole-H5 or 6), 7.05 (pt, 1H, $^3J = 6.2$ Hz, indole-H5 or 6), 7.07 (d, 1H, $^4J = 1.4$ Hz, pyrrole-H5), 7.20 (s, 1H, indole-H2), 7.32 (d, 1H, $^3J = 8.0$ Hz, indole-H7), 7.56 (d, 1H, $^3J = 7.8$ Hz, indole-H4), 8.03 (t, 1H, $^3J = 5.3$ Hz, NH), 9.89 (s, 1H, NH), 10.87 (s, 1H, NH); $^{13}$C-NMR (DMSO-$d_6$): $\delta$ 27.4 (s), 33.4 (s), 36.2 (p), 37.3 (s), 45.4 (p), 45.4 (p), 57.3 (s), 103.6 (t), 109.2 (q), 111.6 (t), 117.7 (t), 118.6 (t), 119.0 (t), 121.2 (t), 122.3 (q), 124.0 (q), 127.4 (q), 136.4 (q), 161.4 (q), 168.3 (q). MS: *m/z* 381 [$M^+$]; Anal. $C_{21}H_{27}N_5O_2$ (C,H,N).

*5.1.7. 9,10-Dioxo-9,10-dihydro-2-anthracensulphonyl chloride (**13b**)*

Dry sodium anthraquinonesulphonate (**13a**) (1 g, 3.95 mmol) was mixed with $PCl_5$ (2 g, 9.6 mmol). The mixture was heated under reflux for 30 min (120 °C). After cooling to ambient temperature, $C_6H_3CH_3$ (20 mL) was added, heated to boiling point and filtered after cooling to ambient temperature. The $C_6H_3CH_3$ was removed under vacuum; (yellow solid) (930 mg) (3.66 mmol) (91.7%), m.p. 197 °C; IR (KBr, $cm^{-1}$): 3400, 3050, 2950, 1710, 1560, 1360, 1310, 1270, 1170, 1140, 1050, 950, 910, 840, 800, 780, 690, 650; $^1$H-NMR (DMSO-$d_6$): $\delta$ 7.89 (m, 2H, aromatic-H), 8.09 (pd, 1H, aromatic-H), 8.19 (m, 3H, aromatic-H), 8.38 (ps, 1H, aromatic-H). MS: *m/z* 306 [$M^+$].

*5.1.8. N2-[5-({[3-(Dimethylamino)propyl]amino}carbonyl)-1-methyl-1-H-3-pyrrolyl]-4-{8,9,10-dioxo-9,10-dihydro-2-anthracenyl)sulphonyl]amino}-1-methyl-1H-2-pyrrole carboxamide (**15**)*

Compound **5** (376 mg, 1 mmol) was dissolved in dioxane–DMF (1:1) and reduced with Pd/C under hydrogen atmosphere (18 h). After removing the catalyst anthraquinonesulphonylchloride **13b** (50.1 mg, 0.2 mmol) was dissolved in dioxane–DMF and added dropwise at r.t. The precipitate was chromatographed over silica gel (MeOH–$NH_3$ (25%); (brown solid) (120 mg) (0.2 mmol) (19.4%), m.p. 110 °C; IR (KBr, $cm^{-1}$): 3890, 2900, 1620, 1560, 1520, 1450, 1420, 1380, 1270, 1240, 1140, 950, 800, 760, 650; $^1$H-NMR (DMSO-$d_6$): $\delta$ 1.6 (quint, 2H, $^3J = 7.0$ Hz, $CH_2$), 2.11 (s, 6H, 2-$CH_3$), 2.27 (t, 2H, $^3J = 7.19$ Hz, $CH_2$), 3.16 (q, 2H, $^3J = 5.75$ Hz, $CH_2$), 3.72 (s, 3H, $CH_3$), 3.74 (s, 3H, $CH_3$), 6.68 (d, 1H, $^4J = 1.60$ Hz, pyrrole-H3), 6.70 (d, 1H, $^4J = 1.56$ Hz, pyrrole-H5), 6.74 (d, 1H, $^4J = 1.66$ Hz, pyrrole-H3′), 7.09 (d, 1H, $^4J = 1.65$ Hz, pyrrole-H5′), 7.93 (m, 2H, anthraquinone-H), 8.05 (t, 1H, $^3J = 5.1$ Hz, NH), 8.10 (pd, 1H, anthraquinone-H), 8.20 (m, 3H, anthraquinone-H), 8.32 (ps, 1H, $^3J = 8.1$ Hz, anthraquinone-H), 9.78 (s, 1H, NH), 10.08 (s, 1H, NH); $^{13}$C-NMR (DMSO-$d_6$): $\delta$ 27.05 (s), 36.2 (p), 36.3 (p), 37.3 (s), 45.5 (p), 45.5 (p), 57.1 (s), 104.2 (t), 107.4 (t), 118.7 (q), 118.7 (q), 121.2 (t), 123.0 (q), 124.0 (t), 124.6 (q), 125.1 (t), 127.2 (t), 127.2 (t), 128.3 (t), 132.0 (t), 133.3 (q), 133.9 (q), 135.0 (t), 135.0 (t), 136.6 (q), 145.1 (q), 159.2 (q), 161.0 (q), 181.8 (q), 182.0 (q). MS: *m/z* 616 [$M^+$]; Anal. $C_{31}H_{32}N_6O_6S$ (C,H,N,S).

*5.1.9. N2-[3-(Dimethylamino)propyl]-4-{[(9,10-dioxo-9,10-dihydro-2-anthracenyl)sulphonyl]amino}-1-methyl-1H-2-pyrrole carboxamide (**14**)*

This compound was synthesised by the same procedure as **15**; instead of **5** compound **4** (254 mg, 1 mmol) was used (yellow amorphous solid) (510 mg) (1.03 mmol) (52.4%), m.p. 195 °C; IR (KBr, $cm^{-1}$): 3360,

3050, 2900, 2850, 2800, 2750, 1650, 1600, 1570, 1500, 1450, 1420, 1380, 1360, 1310, 1270, 1170, 1140, 1060, 1000, 950, 900, 850, 750, 650; $^1$H-NMR (DMSO-$d_6$): $\delta$ 1.55 (quint, 2H, $^3J = 6.9$ Hz, $CH_2$), 2.17 (s, 6H, 2-$CH_3$), 2.24 (t, 2H, $^3J = 7.0$ Hz, $CH_2$), 3.07 (q, 2H, $^3J = 6.2$ Hz, $CH_2$), 3.67 (s, 3H, $CH_3$), 6.43 (d, 1H, $^4J = 1.6$ Hz, pyrrole-H3), 6.62 (d, 1H, $^4J = 1.6$ Hz, pyrrole-H5), 7.9 (m, 2H, anthraquinone-H), 8.05 (t, 1H, $^3J = 5.4$ Hz, NH), 8.10 (pd, 1H, anthraquinone-H), 8.19 (m, 3H, anthraquinone-H), 8.32 (ps, 1H, anthraquinone-H), 9.3 (s, 1H, NH); $^{13}$C-NMR (DMSO-$d_6$): $\delta$ 27.0 (s), 36.5 (p), 37.1 (p), 45.1 (p), 45.1 (p) 57.0 (s), 107.4 (t), 118.7 (q), 118.7 (q), 121.2 (t), 124.6 (q), 125.1 (t), 127.2 (t), 127.2 (t), 128.3 (t), 132.0 (t), 133.3 (q), 133.8 (q), 135.0 (q), 135.0 (q), 136.6 (q), 145.1 (q), 160.9 (q), 181.8 (q), 181.9 (q). MS: *m/z* 494 [$M^+$]; Anal. $C_{25}H_{36}N_4O_5$ (C,H,N,S).

#### 5.1.10. *N2-[5-({[3-(Dimethylamino)propyl]amino}carbonyl)-1-methyl-1-H-3-pyrrolyl]-4-(acetylamino)-1-methyl-1H-2-pyrrole carboxamide (**16**)*

Compound **5** (376 mg, 1 mmol) was dissolved in dry dioxane. Palladium-on-carbon (500 mg) was added and the reduction ran under a hydrogen atmosphere. After removing the catalyst by filtration, the yellow solution was cooled on ice. Hünig's Base was added (1 mL). Distilled acetylchloride (157 mg, 2 mmol) was added dropwise and stirred for 12 h. After removing dioxane under vacuum, the brown solid was chromatographed over silica gel (MeOH–$NH_3$ (25%, 97:3); (yellow, solid) (180 mg) (0.46 mmol) (46.34%), m.p. 77 °C; IR (KBr, $cm^{-1}$): 3400, 3250, 3080, 2900, 2830, 2800, 1620, 1560, 1510, 1450, 1420, 1380, 1250, 1200, 1150, 1090, 1050, 1020, 980, 800, 760, 650; $^1$H-NMR (DMSO-$d_6$): $\delta$ 1.6 (quint, 2H, $^3J = 7.1$ Hz, $CH_2$), 1.9 (s, 3H, $CH_3$), 2.10 (s, 6H, 2-$CH_3$), 2.26 (t, 2H, $^3J = 7.2$ Hz, $CH_2$), 3.17 (q, 2H, $^3J = 5.8$ Hz, $CH_2$), 3.77 (s, 3H, $CH_3$), 3.79 (s, 3H, $CH_3$), 6.79 (d, 1H, $^4J = 1.85$ Hz, pyrrole-H3), 6.82 (d, 1H, $^4J =$ 1.87 Hz, pyrrole-H5), 7.12 (d, 1H, $^4J = 1.6$ Hz, pyrrole-H3′), 7.16 (d, 1H, $^4J = 1.71$ Hz, pyrrole-H5′), 8.05 (t, 1H, $^3J = 5.0$ Hz, NH), 9.8 (s, 1H, NH), 9.9 (s, 1H, NH); $^{13}$C-NMR (DMSO-$d_6$): $\delta$ 23.3 (s), 27.4 (s), 36.2 (p), 36.3 (p), 37.3 (s), 45.4 (p), 45.4 (p), 57.3 (s), 104.0 (t), 104.0 (t), 104.3 (t), 104.3 (t), 122.3 (q), 122.4 (q), 123.0 (q), 123.3 (q), 158.6 (q), 161.5 (q), 166.8 (q). MS: *m/z* 388 [$M^+$]; Anal. $C_{19}H_{28}N_6O_3$ (C,H,N).

### 5.2. DNA-binding methods

#### 5.2.1. Melting experiments

Melting curves were measured using an Hitachi U-3200-spectrophotometer coupled to a Julabo thermostat. The measurements were performed in BPE buffer, pH 7 (6 mM $Na_2HPO_4$, 2 mM $NaH_2PO_4$, 1 mM EDTA) with a drug–DNA ratio of 1:1, using [Poly(dAdT)·Poly(dAdT)] as DNA (Amersham Pharmacia). The temperature inside the cuvette was increased over the range 25–90 °C with a heating rate of 1.5 °C $min^{-1}$. The absorption data were registered and plotted against the temperature. The melting curve was analysed using the program ORIGIN for data analysis and technical graphics. The melting temperature ($T_m$) was taken as the midpoint of the hyperchromic transition [19].

#### 5.2.2. Ethidium bromide displacement assay

All fluorescence measurements were conducted on an Hitachi F-2000 spectrofluorometer. Calf thymus DNA (Sigma, Type I; $1.0 \times 10^{-5}$ M in base pairs) was added in small aliquots to ethidium bromide (Invitrogen; $5.0 \times 10^{-6}$ M) resulting in a 2:1 ratio of basepair–ethidium in 2 mL of a 10 mM Tris–HCl (pH 7.4), 75 mM NaCl buffer solution. The fluorescence of the DNA–ethidium buffer solution was calibrated at r.t. to 100% fluorescence and that of the ethidium buffer solution to 0% fluorescence. The premixed DNA–ethidium solution was titrated with 3 μL aliquots of the stock solution of the test substances (3 mM drug in DMSO) and stirred at r.t. for 30 min prior to each fluorescence measurement. The fluorescence was measured with $\lambda = 545$ nm excitation and 595 nm emission with a slit width of 10 nm. The binding affinity was determined at 50% ethidium bromide displacement and measured as a drop in fluorescence to 50%. Results were calculated with the Data Analysis and Graphics Program GRAFIT and with the graphical program ORIGIN. Distamycin A as reference was tested in the same way [25].

### 5.3. Topoisomerase I inhibition

Plasmid DNA (pUC 19, Invitrogen; 0.033 μg $\mu L^{-1}$) was incubated for 15 min at 35 °C with different concentrations of the tested drugs (5, 20 and 50 μM) in 1 × topoisomerase I reaction buffer (50 mM Tris–HCl pH 7.5, 50 mM KCl, 10 mM MgCl, 0.5 mM DTT, 0.1 mM EDTA, 30 μg $mL^{-1}$ BSA) to ensure equilibration. The reaction was initiated by adding topoisomerase I (Topogen; 0.25 U $\mu L^{-1}$) and the samples were reincubated for 15 min at 35 °C. Reactions were stopped by addition of SDS to a final concentration of 0.25% and proteinase K to 250 μg $mL^{-1}$, followed by incubation for 30 min at 50 °C. After addition of 2 μL denaturing loading buffer (Invitrogen), samples were loaded onto a 1% agarose gel in TBE buffer. Electrophoresis was conducted at 120 V for 2 h.

## Acknowledgements

We thank Professor Dr C.B. and his group at the Centre Oscar Lambret pour la Reserche sur le Cancer, Lille, France, for their cooperation in developing the biological assays and the Developmental Therapeutic

Program of the National Cancer Institute, Bethesda, USA, for testing the cytotoxic activity of the compounds.

## References

[1] U. Pindur (Ed.), Curr. Med. Chem., special issue 8 (2001) 475–581.
[2] G. Bischoff, S. Hoffmann, Curr. Med. Chem. 9 (2002) 321–348.
[3] F. Arcamone, S. Penco, P. Orezzi, V. Nicolella, A. Pirelli, Nature 203 (1964) 1064.
[4] A.C. Finlay, F.A. Hochstein, B.A. Sobin, F.X. Murphy, J. Am. Chem. Soc. 73 (1951) 341–344.
[5] U. Pindur, G. Fischer, Curr. Med. Chem. 3 (1996) 379.
[6] C. Bailly, in: Advances in DNA Sequence-Specific Agents 3 (1998) 97–115.
[7] C. Hotzel, A. Marotto, U. Pindur, Eur. J. Med. Chem. 37 (2002) 367–378.
[8] E.E. Baird, P.B. Dervan, JACSAT, J. Am. Chem. Soc. EN 118, 26, (1996) 6141–6146.
[9] E. Nishikawi, S. Tanaka, H. Lee, M. Shibuya, HTCYAM, Heterocycles, EN 27, 8 (1998) 1945–1952.
[10] H. Erdtman, A. Jönsson, Acta Chem. Scand. 8 (1954) 119–126.
[11] V.D. Filimonov, M.M. Sukhoroslova, V.T. Novikov, Chem. Heterocycl. Compd. (Engl. Transl.) 17, 12 (1981) 1213–1216.
[12] W. Reppe, Justus Liebigs Ann. Chem. 596 (1955) 1–218.
[13] NCI home page: http://dtp.nci.nih.gov.
[14] M.R. Boyd, PPO Updates 3 (1989) 1–15.
[15] A. Monks, D. Scudiero, P. Skehan, R. Shoemaker, K. Paull, D. Vistica, C. Hose, J. Langley, P. Cronise, A. Vaigro-Wolff, J. Natl. Cancer Inst. 83 (1991) 757–766.
[16] D. Suh, J.B. Chaires, Bioorg. Med. Chem. 3 (1995) 723–728.
[17] E.C. Long, Acc. Chem. Res. 23 (1990) 271–273.
[18] W.D. Wilson, F.A. Tanios, M. Fernandez-Saiz, C.T. Rigl, in: K.R. Fox (Ed.), Drug–DNA Interaction Protocols, Humana Press, Totowa, 1997, pp. 219–240.
[19] C. Bailly, X. Qu, F. Anizon, M. Prudhomme, J.F. Riou, J.B. Chaires, Mol. Pharm. 55 (1999) 377–385.
[20] H.P. Hsieh, J.G. Muller, C.J. Burrows, Bioorg. Med. Chem. 3 (1995) 823–838.
[21] S.E. Wellmann, Biopolymers 39 (1996) 491–501.
[22] U. Pindur, T. Lemster, Pharmazie 53 (1998) 79–86.
[23] Y. Pommier, Biochimie 80 (1998) 225–270.
[24] N. Osheroff, M.A. Bjornsti (Eds.), DNA-Topoisomerase Protocols, vol. 2, Humana Press, Totowa, 2001, pp. 149–160.
[25] U. Pindur, A. Marotto, E. Schulze, G. Fischer, Pharmazie 55 (2000) 727–732.
[26] A. Marotto, Y.S. Kim, U. Pindur, Pharmazie 57 (2002) 124–127.