Synthesis of 3,4-diaryl- and 4-acyl-3-arylpyrroles and study of their antimitotic activity

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The Barton—Zard reaction of nitro substituted stilbenes and chalcones with ethyl isocyanoacetate afforded 3,4-diaryl- and 4-acyl-3-arylpyrroles, respectively. 3-Arylpyrrole-2,4-dicarboxylates and 4-arylisoxazoline *N*-oxides were side reaction products. Antimitotic activity of target 3,4-disubstituted pyrroles was studied on a sea urchin embryo model. Pyrroles unsubstituted at positions 2 and 5 were the most active. The activity increased with the number of methoxy groups in the Ar substituent.

Key words: antimitotic activity, combretastatin, nitrostilbenes, nitrochalcones, ethyl isocyanoacetate, Barton—Zard reaction, 3,4-diarylpyrroles, 4-acyl-3-arylpyrroles, sea urchin embryo.

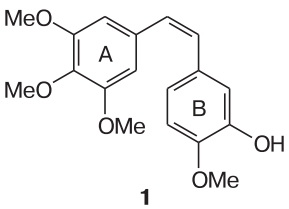
A number of modern studies in medicinal chemistry are devoted to the development of new synthetic analogs of natural antimitotic combretastatin A-4 (CA4, **1**), featuring steric stability, strong antiproliferative activity with minimum side effects and the ability to overcome multidrug resistance.[1,2]

Methods for their synthesis are reported in a number of reviews.[1,3] Combretastatin derivatives CA4P (fosbretabulin), AVE8062, and ZD6186 are at 2/3 stages of clinical trials as anticancer drugs. Their mechanism of action involves inhibition of intracellular protein tubulin resulting in microtubule destabilization and tumor blood vessel destruction.[4]

For optimal binding to tubulin and high antimitotic activity, molecules of combretastatins should have *cis*-configuration.[1,5,6] Five-membered heterocycles are considered as nonisomerizable and metabolically stable bioisosteric replacement of the double bond in combretastatins, fixing rings A and B in *cis*-position.

Earlier, diaryl-substituted pyrazole,[7,8] 1,3,4-oxadiazole,[9,10] isoxazole,[11—13] triazole,[14] tetrazole,[8,13,15,16] imidazole,[8,17] and thiazole[8] derivatives have already been studied. In the present work, we consider 3,4-diarylpyrrole derivatives.

A linker binding two aromatic rings may also include three carbon atoms; in particular, some chalcones (*e.g.*, pedicin (**2**) or derricin (**3**)[18]) exhibit cytostatic activity. Such compounds, in which the C = C bond is replaced by the pyrrole ring, were also studied in this work.



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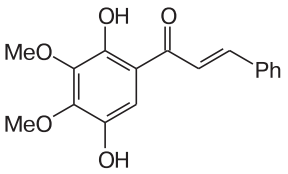

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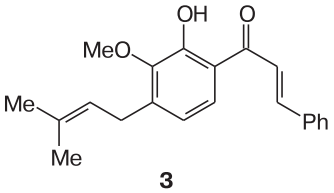

3

Results and Discussion

Ethyl pyrrole-2-carboxylates were obtained by the Barton—Zard reaction[19] from diarylethylenes **4a—d** and 1,3-diaryl-2-nitroprop-2-en-1-ones **5a**,**b** (Scheme 1, Table 1).

In the ^{1}H NMR spectra of target compounds **6** and **7**, the signal for pyrrole NH proton was found at δ_H 11.87—12.21 and 12.33—12.50, respectively.

The yields of target product are quite moderate (which is consistent with the literature data[19—21]) due to the formation of by-products. As far as we know, by-products in the Barton-Zard reaction were not yet objects of study; in

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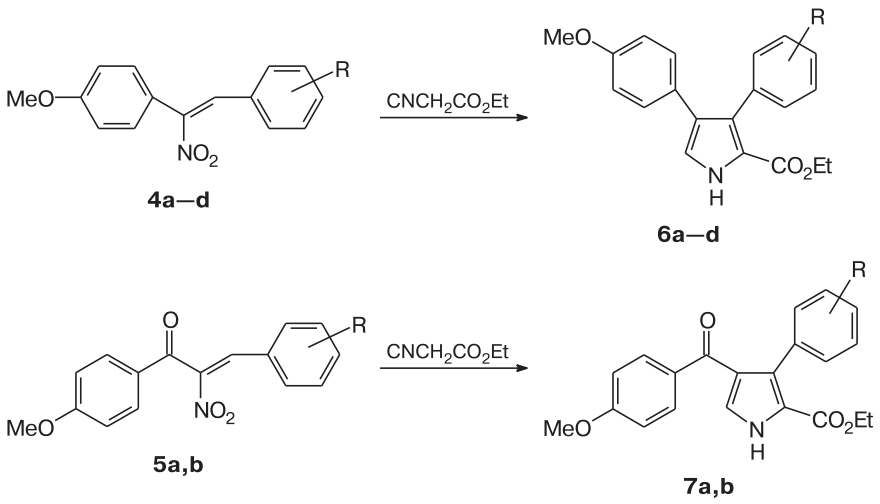
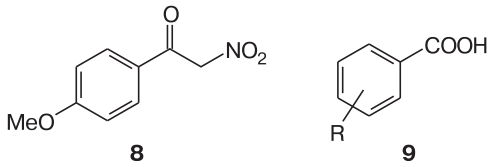
Scheme 1



Reagents and conditions: DBU, THF, 20 °C, 12 h.

the present work we succeeded in establishing the structures of some of them.

For the reactions with nitrochalcones **5**, the ^{1}H NMR spectra showed that α-nitrochalcones decomposed to the starting compounds, *p*-methoxybenzoylnitromethane (**8**) and aldehyde, which under the reaction conditions underwent oxidation to acid **9** (no such products were detected for the reactions with nitrostilbenes **4**).

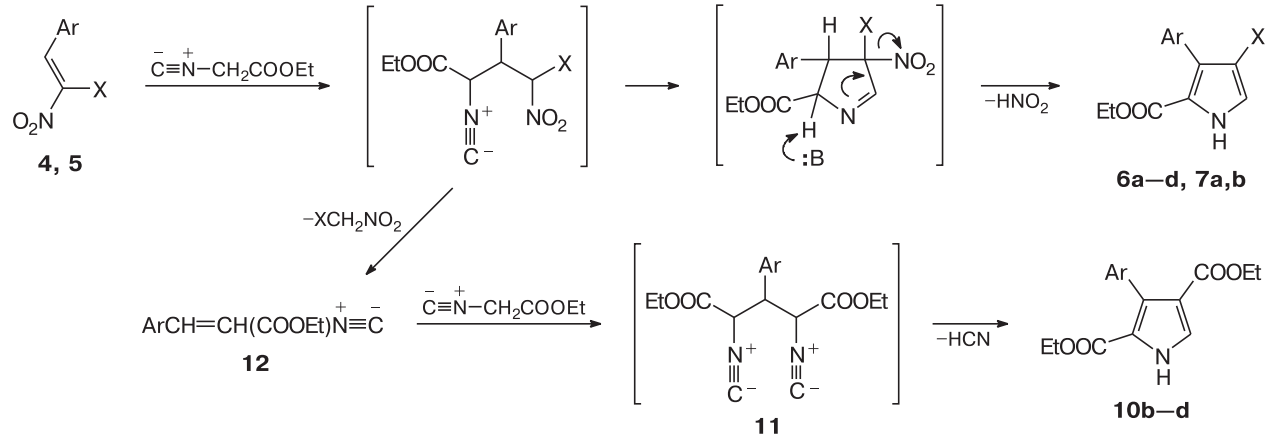


In the reactions of both nitrostilbenes **4** and nitrochalcones **5**, we observed the formation of diethyl pyrrole-2,4-dicarboxylates **10** (Scheme 2) resulting from elimination of hydrogen cyanide from the intermediate compound **11**, which, in turn, was formed from isocyanide **12** in the reaction with ethyl isocyanoacetate. In the ^{1}H NMR spectra, the admixture of **10** can be distinguished from compounds **6**

Table 1. The yields of compounds **6** and **7**

Compound	R	Yield (%)
6a	4-MeO	39
6b	4-Cl	43
6c	3,5-$(MeO)_2$	37
6d	4-NO_2	34
7a	4-MeO	37
7b	4-Cl	41

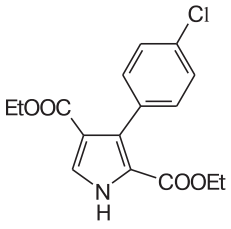
Scheme 2



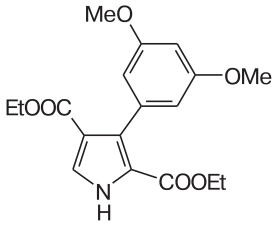
X = 4-$MeOC_6H_4$, 4-$MeOC_6H_4CO$

and **7** by the shift of the NH proton, which was found in lower field at δ_H 12.35—12.60.

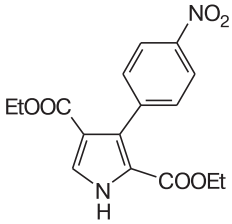
Pure compounds **10b**, **10c**, and **10d** were isolated by chromatographic separation.



10b

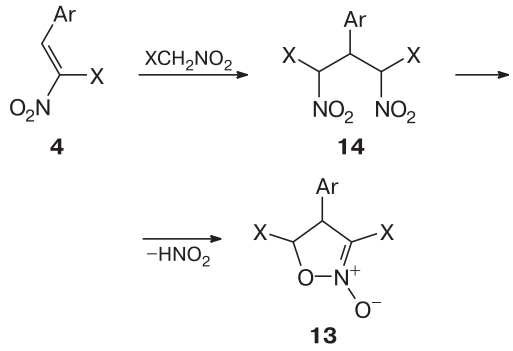


10c



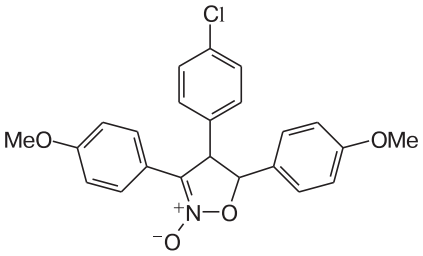
10d

Scheme 3



4 **14** **13**

X = 4-$MeOC_6H_4$



13b

In the reactions with nitrostilbenes **4**, isoxazoline *N*-oxides **13** were detected as side products (Scheme 3), which in the ^{1}H NMR spectra have indicative doublets with J = 4.3—4.6 Hz and chemical shifts at δ_H 5.11—5.30 (H(4)) and δ_H 5.41—5.52 (H(5)). Apparently, they are formed by the addition of *p*-methoxyphenylnitromethane to nitrostilbenes **4** and subsequent cyclization of the intermediate adducts **14**.

Pure isoxazoline oxide **13b** was isolated in the course of synthesis.

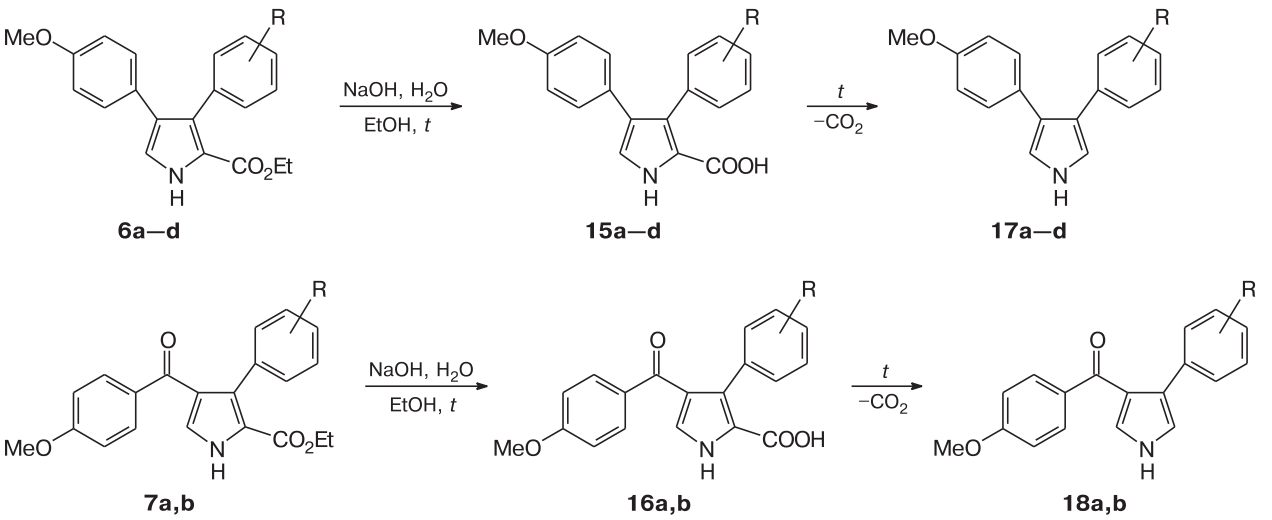
Formation of similar isoxazoline *N*-oxides was not detected in the reactions involving nitrochalcones **5**.

Alkaline hydrolysis of esters **6** and **7** gave the corresponding acids **15** and **16**, while their subsequent decarboxylation resulted in pyrroles **17** and **18** (Scheme 4, Table 2).

There is an example[19] of *one-pot* synthesis of 3,4-diarylpyrroles by reflux of pyrrole-2-carboxylates **6** and **7** with alkali in ethylene glycol. However, in our experiments the higher yields were obtained in the two-step procedure including heating with NaOH in aqueous ethanol (with subsequent acidification) and decarboxylation of thus isolated acid.

Notably, the impurity of isoxazoline *N*-oxides **13** in esters **6** (of which it is not always easy to get rid by recrystallization or chromatography) does not prevent the

Scheme 4



6a—d **15a—d** **17a—d**

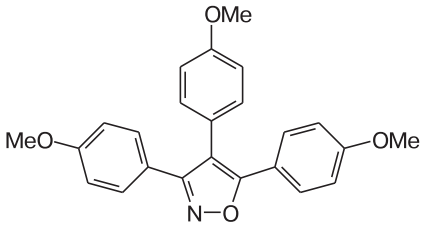
7a,b **16a,b** **18a,b**

Table 2. The yields of compounds **15**—**18**

Compound	R	Yield (%)
15a	4-MeO	80
15b	4-Cl	57
15c	3,5-$(MeO)_2$	80
15d	4-NO_2	85
16a	4-MeO	83
16b	4-Cl	83
17a	4-MeO	68
17b	4-Cl	46
17c	3,5-$(MeO)_2$	46
17d	4-NO_2	67
18a	4-MeO	66
18b	4-Cl	67

isolation of pure hydrolysis products, pyrrole-2-carboxylic acids **15**. The alkaline hydrolysis gives water-soluble sodium salts of the acids, while isoxazoline *N*-oxides **13** through recyclization and elimination of water are converted to water-insoluble isoxazoles **19** (Scheme 5).[22] Thus, the impurity can be removed by simple filtration of the reaction mixture.

This procedure was used to isolate pure isoxazole **19a**.



19a

Acid **15** and **16** were decarboxylated by heating to melting points (in the absence of solvent). Acid **15** was completely decarboxylated for a shorter time (~30 s) than acid **16** (~2 min).

Table 3. Effects of 3,4-diaryl- and 3-aryl-4-benzoylpyrroles on sea urchin embryos *Paracentrotus lividus*

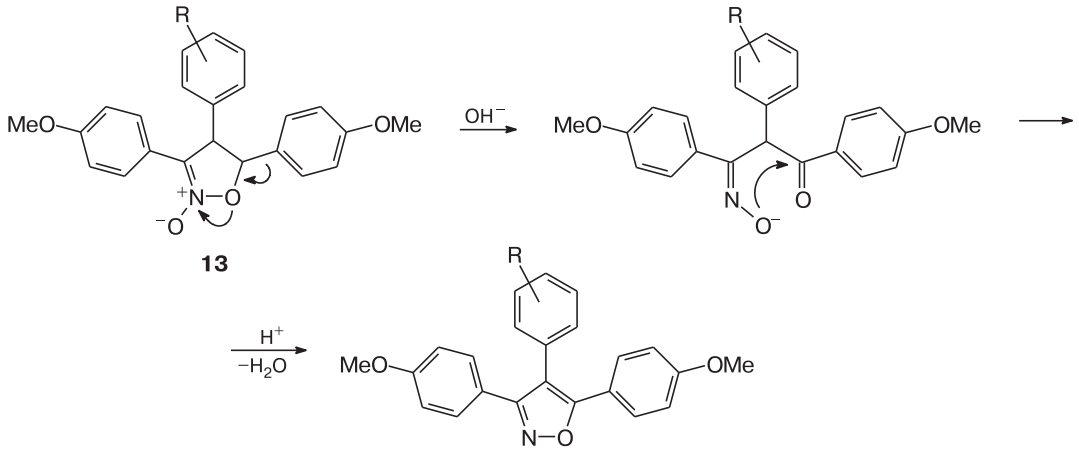
Compound	EC[a]/μmol L^{-1}		
	Cleavage alteration	Cleavage arrest	Embryo spinning
6a	>4	>4	>4
6b	>4	>4	>4
6c	1	4[b]	>4
7a	>4	>4	>4
7b	>4	>4	>4
15c	>4	>4	>4
16a	>4	>4	>4
17b	4	>4	>4
17c	0.5	1	5
17d	4[c]	>4	>4
18a	>4	>4	>4
CA4[d]	0.002	0.01	0.05

[a] EC is the threshold concentration causing the effect.
[b] Arrested eggs acquired tuberculate shape typical of microtubule destabilizers.
[c] Developmental delay without visible morphological abnormalities.
[d] Combretastatin A-4 (CA4) was used as a positive control.

Biological activity of 3,4-diaryl- and 3-aryl-4-benzoylpyrroles was studied in sea urchin *Paracentrotus lividus* embryos according to the published procedure.[23] This phenotypic assay does not require complicated and expensive equipment and provides quick identification of antimitotic compounds that alter fertilized egg division (cleavage). After treatment at the hatched blastula stage, embryo settlement on the bottom of the vessel together with rapid spinning around the animal-vegetal axis suggest tubulin-targeting microtubule destabilizing effect of a compound.

Compounds **6a**, **6b**, **7a**, **7b**, **15c**, **16a**, and **18a** at a concentration of up to 4 μmol L^{-1} did not affect cell division (Table 3). Nitro-substituted compound **17d** caused cleav-

Scheme 5



13 **19**

age delay without visible alteration of early sea urchin embryos morphology. Pyrrole **17b** inhibited cleavage only at the maximal tested concentration (4 μmol L^{-1}). Pyrrole **17c** unsubstituted at position 2 exhibited antimitotic effect due to the microtubule destabilization. Its 2-carbethoxy-substituted analog **6c** showed markedly lower antitubulin activity. Compound **6c** did not cause embryo spinning, however, the arrested eggs acquired a specific tuberculate shape typical of antitubulin agents. Interestingly, hydrolysis of the ester group resulted in a complete loss of activity in 2-carboxy analog **15c**. Analysis of the structure—activity relationship for the tested pyrroles identified 3-(3,5-dimethoxyphenyl)-4-(4-methoxyphenyl)pyrrole (**17c**) as the most potent antimitotic antitubulin molecule.

Experiment

NMR spectra were recorded on Bruker-DRX 500 (500.13 MHz for ^{1}H, 125.76 MHz for ^{13}C) and Bruker-AM 300 (300.13 MHz for ^{1}H, 75.47 MHz for ^{13}C) spectrometers. Mass spectra were recorded on a Finningan MAT/INCOS50 spectrometer with ionization energy of 70 eV. The eluent for TLC was a mixture of ethyl acetate—heptane (1 : 5). The starting 4-methoxyphenyl nitromethane and 1-(4-methoxyphenyl)-2-nitroethanone were obtained according to the known procedures.[24,25] THF was purified by keeping over NaOH with subsequent distillation over sodium metal under Ar atmosphere. Compounds **4c,d** were obtained according to the procedure described in the literature.[26]

Synthesis of 1,2-diarylnitroethylenes 4a,b (general procedure). A mixture of aromatic aldehyde (2 mmol) and 4-methoxyphenylnitromethane (334 mg, 2 mmol) was dissolved in methanol (0.25 mL) and after addition of *n*-butylamine (1 drop) was allowed to stand for several days. Once layers were formed, methanol (0.25 mL) was added and a precipitate formed was collected by filtration. Yellow crystals of **4a,b** were obtained by recrystallization from ethanol (7 mL).[27]

1,2-Bis(4-methoxyphenyl)-1-nitroethylene (4a). The yield was 44%. M.p. 137—138 °C (from ethanol); *cf.* Ref. 28: m.p. 142—144 °C. ^{1}H NMR ($CDCl_3$, 500 MHz), δ: 3.78 (s, 3 H, OCH_3); 3.88 (s, 3 H, OCH_3); 6.76 (d, 2 H, Ar, J = 8.9 Hz); 7.01 (d, 2 H, Ar, J = 8.7 Hz); 7.08 (d, 2 H, Ar, J = 8.9 Hz); 7.25 (d, 2 H, Ar, J = 8.7 Hz); 8.20 (s, 1 H, HC).

2-(4-Chlorophenyl)-1-(4-methoxyphenyl)-1-nitroethylene (4b). The yield was 49%. M.p. 118—119 °C (from ethanol). ^{1}H NMR ($CDCl_3$, 500 MHz), δ: 3.87 (s, 3 H, OCH_3); 7.00 (d, 2 H, Ar, J = 8.5 Hz); 7.06 (d, 2 H, Ar, J = 8.4 Hz); 7.21—7.26 (m, 4 H, Ar); 8.12 (s, 1 H, HC). Found (%): C, 62.28; H, 4.22; N, 4.63. $C_{15}H_{12}ClNO_3$. Calculated (%): C, 62.19; H, 4.17; N, 4.83.

Synthesis of 1,3-diaryl-2-nitroprop-2-en-1-ones 5a,b (general procedure). A mixture of 1-(4-methoxyphenyl)-2-nitroethanone (780 mg, 4 mmol), arylaldehyde (4.2 mmol), β-alanine (30 mg, 0.33 mmol), and acetic acid (0.64 mL) in benzene (6.4 mL) was refluxed in a flask equipped with a Dean—Stark trap for 4 h. Then, the reaction mixture was washed with water (3×6 mL), benzene was removed *in vacuo* of a water-jet pump. The residue was recrystallized from ethanol (14 mL).[29]

1,3-Bis(4-methoxyphenyl)-2-nitroprop-2-en-1-one (5a). The yield was 40%. An oil. ^{1}H NMR (DMSO-d_6, 500 MHz), δ: 3.77 (s, 3 H, OCH_3); 3.86 (s, 3 H, OCH_3); 6.99 (d, 2 H, Ar, J = 8.9 Hz); 7.09 (d, 2 H, Ar, J = 8.9 Hz); 7.47 (d, 2 H, Ar, J = 8.9 Hz); 7.96 (d, 2 H, Ar, J = 8.9 Hz); 8.48 (s, 1 H, HC). Found (%): C, 65.13; H, 5.09; N, 4.38. $C_{17}H_{15}NO_5$. Calculated (%): C, 65.17; H, 4.83; N, 4.47.

3-(4-Chlorophenyl)-1-(4-methoxyphenyl)-2-nitroprop-2-en-1-one (5b). The yield was 50%. M.p. 117—118 °C (from ethanol). ^{1}H NMR (DMSO-d_6, 500 MHz), δ: 3.86 (s, 3 H, OCH_3); 7.09 (d, 2 H, Ar, J = 8.9 Hz); 7.50 (m, 4 H, Ar); 7.97 (d, 2 H, Ar, J = 8.9 Hz); 8.54 (s, 1 H, HC). MS (EI, 70 eV), m/z (I_{rel} (%)): 317 $[M]^+$ (9), 166 (40), 135(41), 123 (100). Found (%): C, 60.16; H, 3.75; N, 4.29. $C_{16}H_{12}ClNO_4$. Calculated (%): C, 60.48; H, 3.81; N, 4.41.

Synthesis of ethyl pyrrole-2-carboxylates 6a—d and 7a,b (general procedure). The reagent DBU (0.75 mmol) was added slowly to a solution of 1,2-diarylnitroethylene or 1,3-diaryl-2-nitroprop-2-en-1-one (0.5 mmol) and ethyl isocyanoacetate (85 mg, 0.75 mmol) in THF (2 mL). The mixture was stirred at room temperature for 12 h, poured into water containing dilute aqueous hydrochloric acid, and extracted with ethyl acetate. The extract was washed with water and concentrated, the residue was purified by flash-chromatography (ethyl acetate—heptane, 1 : 5).[19]

Ethyl 3,4-bis(4-methoxyphenyl)pyrrole-2-carboxylate (6a). The yield was 39%. M.p. 133—135 °C (*cf.* Ref. 30: m.p. 136 °C). ^{1}H NMR (DMSO-d_6, 500 MHz), δ: 1.10 (t, 3 H, CH_3, J = 7.1 Hz); 3.68 (s, 3 H, OCH_3); 3.75 (s, 3 H, OCH_3); 4.07 (q, 2 H, CH_2, J = 7.1 Hz); 6.75 (d, 2 H, Ar, J = 8.7 Hz); 6.84 (d, 2 H, Ar, J = 8.6 Hz); 6.99 (d, 2 H, Ar, J = 8.6 Hz); 7.07 (d, 2 H, Ar, J = 8.7 Hz); 7.15 (d, 1 H, CH_{pyrr}, J = 3.1 Hz); 11.87 (s, 1 H, NH).

Ethyl 3-(4-chlorophenyl)-4-(4-methoxyphenyl)pyrrole-2-carboxylate (6b). The yield was 43%. M.p. 131—133 °C. ^{1}H NMR (DMSO-d_6, 500 MHz), δ: 1.08 (t, 3 H, CH_3, J = 7.1 Hz); 3.69 (s, 3 H, OCH_3); 4.08 (q, 2 H, CH_2, J = 7.1 Hz); 6.77 (d, 2 H, Ar, J = 8.7 Hz); 6.97 (d, 2 H, Ar, J = 8.6 Hz); 7.17 (d, 2 H, Ar, J = 8.6 Hz); 7.19 (d, 1 H, CH_{pyrr}, J = 3.1 Hz); 7.33 (d, 2 H, Ar, J = 8.7 Hz); 12.01 (s, 1 H, NH). Found (%): C, 67.60; H, 4.99; N, 3.78. $C_{20}H_{18}ClNO_3$. Calculated (%): C, 67.51; H, 5.10; N, 3.94.

Ethyl 3-(3,5-dimethoxyphenyl)-4-(4-methoxyphenyl)pyrrole-2-carboxylate (6c). The yield was 37%. M.p. 168—169 °C. ^{1}H NMR (DMSO-d_6, 500 MHz), δ: 1.08 (t, 3 H, CH_3, J = 7.1 Hz); 3.65 (s, 6 H, OCH_3); 3.69 (s, 3 H, OCH_3); 4.08 (q, 2 H, CH_2, J = 7.1 Hz); 6.31 (d, 2 H, Ar, J = 2.1 Hz); 6.40 (s, 1 H, Ar); 6.76 (d, 2 H, Ar, J = 8.5 Hz); 7.03 (d, 2 H, Ar, J = 8.6 Hz); 7.17 (d, 1 H, CH_{pyrr}, J = 3.1 Hz); 11.94 (s, 1 H, NH). ^{13}C NMR (DMSO-d_6, 125.76 MHz), δ: 14.1 (CH_3), 54.9 (OCH_3), 55.0 (2 C, OCH_3), 59.3 (CH_2), 98.5 (CH_{arom}), 108.9 (2 C, CH_{arom}), 113.6 (2 C, CH_{arom}), 119.3 (C_{arom}), 121.0 (CH_{pyrr}), 124.6 (C_{arom}), 127.1 (C_{arom}), 128.0 (C_{arom}), 128.8 (2 C, CH_{arom}), 137.1 (C_{arom}), 157.5 (C_{arom}), 159.6 (2 C, C_{arom}), 160.4 (COOH). MS (EI, 70 eV), m/z (I_{rel} (%)): 381 $[M]^+$ (85), 366 (36), 335 (100), 320 (48). Found (%): C, 69.07; H, 6.15; N, 3.72. $C_{22}H_{23}NO_5$. Calculated (%): C, 69.28; H, 6.08; N, 3.67.

Ethyl 4-(4-methoxyphenyl)-3-(4-nitrophenyl)pyrrole-2-carboxylate (6d). The yield was 34%. M.p. 158—161 °C. ^{1}H NMR (DMSO-d_6, 500 MHz), δ: 1.08 (t, 3 H, CH_3, J = 7.1 Hz); 3.69 (s, 3 H, OCH_3); 4.10 (q, 2 H, CH_2, J = 7.1 Hz); 6.78 (d, 2 H, Ar, J = 8.8 Hz); 6.96 (d, 2 H, Ar, J = 8.7 Hz); 7.25 (d, 1 H, CH_{pyrr}, J = 3.2 Hz); 7.45 (d, 2 H, Ar, J = 8.8 Hz); 8.15 (d, 2 H, Ar, J = 8.8 Hz); 12.21 (s, 1 H, NH). MS (EI, 70 eV), m/z (I_{rel} (%)): 366 $[M]^+$ (85), 320 (100), 203 (18), 135 (15), 29 (27). Found (%):

C, 65.73; H, 4.84; N, 7.59. $C_{20}H_{18}N_2O_5$. Calculated (%): C, 65.57; H, 4.95; N, 7.65.

Ethyl 4-(4-methoxybenzoyl)-3-(4-methoxyphenyl)pyrrole-2-carboxylate (7a). The yield was 37%. M.p. 109—111 °C. ^{1}H NMR (DMSO-d_6, 500 MHz), δ: 1.12 (t, 3 H, CH_3, J = 7.1 Hz); 3.73 (s, 3 H, OCH_3); 3.81 (s, 3 H, OCH_3); 4.12 (q, 2 H, CH_2, J = 7.1 Hz); 6.79 (d, 2 H, Ar, J = 8.7 Hz); 6.95 (d, 2 H, Ar, J = 8.7 Hz); 7.14 (d, 2 H, Ar, J = 8.7 Hz); 7.31 (d, 1 H, CH_{pyrr}, J =3.5 Hz); 7.67 (d, 2 H, Ar, J = 8.7 Hz); 12.33 (s, 1 H, NH). ^{13}C NMR (DMSO-d_6, 125.76 MHz), δ: 13.9 (CH_3), 54.9 (OCH_3), 55.3 (OCH_3), 59.6 (CH_2), 112.3 (2 C, CH_{arom}), 113.4 (2 C, CH_{arom}), 119.8 (C_{arom}), 123.8 (C_{arom}), 125.9 (C_{arom}), 127.5 (CH_{pyrr}), 131.1 (C_{arom}), 131.3 (2 C, CH_{arom}), 131.5 (2 C, CH_{arom}), 158.0 (C_{arom}), 160.2 (COOH), 162.3 (C_{arom}), 188.9 (CO). MS (EI, 70 eV), m/z (I_{rel} (%)): 379 $[M]^+$ (100), 333 (20), 226 (8), 135 (12). Found (%): C, 69.81; H, 5.63; N, 3.34. $C_{22}H_{21}NO_5$. Calculated (%): C, 69.64; H, 5.58; N, 3.69.

Ethyl 3-(4-chlorophenyl)-4-(4-methoxybenzoyl)pyrrole-2-carboxylate (7b). The yield was 41%. M.p. 136—137 °C. ^{1}H NMR (DMSO-d_6, 500 MHz), δ: 1.10 (t, 3 H, CH_3, J = 7.1 Hz); 3.81 (s, 3 H, OCH_3); 4.12 (q, 2 H, CH_2, J = 7.1 Hz); 6.98 (d, 2 H, Ar, J = 8.8 Hz); 7.24 (d, 2 H, Ar, J = 8.5 Hz); 7.29 (d, 2 H, Ar, J = 8.5 Hz); 7.37 (s, 1 H, CH_{pyrr}); 7.69 (d, 2 H, Ar, J = 8.8 Hz); 12.50 (s, 1 H, NH). ^{13}C NMR (DMSO-d_6, 125.76 MHz), δ: 13.9 (CH_3), 55.5 (OCH_3), 60.0 (CH_2), 113.6 (2 C, CH_{arom}), 120.4 (C_{arom}), 123.8 (C_{arom}), 126.9 (2 C, CH_{arom}), 128.1 (CH_{pyrr}), 130.1 (C_{arom}), 131.3 (C_{arom}), 131.4 (2 C, CH_{arom}), 131.5 (C_{arom}), 132.2 (2 C, CH_{arom}), 133.1 (C_{arom}), 160.1 (COOH), 162.5 (C_{arom}), 188.6 (CO). MS (EI, 70 eV), m/z (I_{rel} (%)): 383 $[M]^+$ (100), 336 (35), 310 (18), 230 (23), 135 (15). Found (%): C, 66.01; H, 4.57; N, 3.38. $C_{21}H_{18}ClNO_4$. Calculated (%): C, 65.71; H, 4.73; N, 3.65.

Diethyl 3-(4-chlorophenyl)pyrrole-2,4-dicarboxylate (10b). The yield was 5%. M.p. 116—118 °C (*cf.* Ref. 31: m.p. 117—120 °C). ^{1}H NMR (DMSO-d_6, 500 MHz), δ: 1.05 (t, 3 H, CH_3, J = 7.1 Hz); 1.07 (t, 3 H, CH_3, J = 7.1 Hz); 4.02 (q, 2 H, CH_2, J = 7.1 Hz); 4.06 (q, 2 H, CH_2, J = 7.1 Hz); 7.25 (d, 2 H, Ar, J = 8.7 Hz); 7.35 (d, 2 H, Ar, J = 8.7 Hz); 7.58 (d, 1 H, CH_{pyrr}, J =3.5 Hz); 12.49 (s, 1 H, NH). Found (%): C, 59.99; H, 5.10; N, 4.07. $C_{16}H_{16}ClNO_4$. Calculated (%): C, 59.73; H, 5.01; N, 4.35.

Diethyl 3-(3,5-dimethoxyphenyl)pyrrole-2,4-dicarboxylate (10c). The yield was 7%. An oil. ^{1}H NMR (DMSO-d_6, 500 MHz), δ: 1.05 (t, 3 H, CH_3, J = 7.1 Hz); 1.07 (t, 3 H, CH_3, J = 7.1 Hz); 3.72 (s, 6 H, OCH_3); 4.02 (q, 2 H, CH_2, J = 7.1 Hz); 4.06 (q, 2 H, CH_2, J = 7.1 Hz); 6.37 (d, 2 H, Ar, J = 2.3 Hz); 6.43 (t, 1 H, Ar, J = 2.3 Hz); 7.54 (d, 1 H, CH_{pyrr}, J = 3.5 Hz); 12.41 (s, 1 H, NH). Found (%): C, 61.98; H, 6.13; N, 4.25. $C_{18}H_{21}NO_6$. Calculated (%): C, 62.24; H, 6.09; N, 4.03.

Diethyl 3-(4-nitrophenyl)pyrrole-2,4-dicarboxylate (10d). The yield was 5%. An oil. ^{1}H NMR (DMSO-d_6, 500 MHz), δ: 1.03 (t, 3 H, CH_3, J = 7.1 Hz); 1.06 (t, 3 H, CH_3, J = 7.1 Hz); 4.02 (q, 2 H, CH_2, J = 7.1 Hz); 4.06 (q, 2 H, CH_2, J = 7.1 Hz); 7.54 (d, 2 H, Ar, J = 8.8 Hz); 7.65 (d, 1 H, CH_{pyrr}, J = 3.5 Hz); 8.18 (d, 2 H, Ar, J = 8.8 Hz); 12.49 (s, 1 H, NH). Found (%): C, 57.74; H, 4.71; N, 8.69. $C_{16}H_{16}N_2O_6$. Calculated (%): C, 57.83; H, 4.85; N, 8.43.

4-(4-Chlorophenyl)-3,5-bis(4-methoxyphenyl)isoxazoline *N*-oxide (13b). The yield was 11%. M.p. 149—151 °C. ^{1}H NMR (DMSO-d_6, 500 MHz), δ: 3.74 (s, 3 H, OCH_3); 3.76 (s, 3 H, OCH_3); 5.30 (d, 1 H, CH_{izox}, J = 4.5 Hz); 5.47 (d, 1 H, CH_{izox}, J = 4.5 Hz); 6.96 (d, 2 H, Ar, J = 8.9 Hz); 7.01 (d, 2 H, Ar, J = 8.6 Hz); 7.39—7.46 (m, 6 H, Ar); 7.82 (d, 2 H, Ar, J = 8.8 Hz). ^{13}C NMR (DMSO-d_6, 125.76 MHz), δ: 55.1 (CH_{izox}), 55.2 (OCH_3), 55.9 (OCH_3), 82.5 (CH_{izox}), 114.1 (2 C, CH_{arom}), 114.2 (2 C, CH_{arom}), 116.0 (C_{arom}), 118.0 (C_{arom}), 127.5 (2 C, CH_{arom}), 128.2 (2 C, CH_{arom}), 129.0 (2 C, CH_{arom}), 129.4 (2 C, CH_{arom}), 130.0 (C_{arom}), 132.5 (C_{arom}), 138.2 (C_{arom}), 159.6 (C_{arom}), 159.7 (C_{arom}). Found (%): C, 67.44; H, 4.78; N, 3.65. $C_{23}H_{20}ClNO_4$. Calculated (%): C, 67.40; H, 4.92; N, 3.42.

Synthesis of pyrrole-2-carboxylic acids 15a—d and 16a,b (general procedure). A solution of ethyl ester **6** or **7** (0.15 mmol) and sodium hydroxide (12 mg, 0.3 mmol) in a mixture of ethanol (3 mL) with water (0.3 mL) was refluxed until disappearance of the starting compound, monitoring by TLC (ethyl acetate—heptane, 1 : 2). Once the reaction reached completion, a solution of aqueous alkali (1 *M*, 9 mL) was added and the reaction mixture was heated to boiling. The hot suspension was filtered. The filtrate was acidified (pH 1—2), a precipitate formed was collected by filtration.

3,4-Bis(4-methoxyphenyl)pyrrole-2-carboxylic acid (15a). The yield was 80%. M.p. 192—193 °C (*cf.* Ref. 30: m.p. 184 °C). ^{1}H NMR (DMSO-d_6, 500 MHz), δ: 3.68 (s, 3 H, OCH_3); 3.75 (s, 3 H, OCH_3); 6.73 (d, 2 H, Ar, J = 8.8 Hz); 6.82 (d, 2 H, Ar, J = 8.7 Hz); 6.96 (d, 2 H, Ar, J = 8.7 Hz); 7.07 (d, 2 H, Ar, J = 8.8 Hz); 7.09 (s, 1 H, CH_{pyrr}); 11.70 (s, 1 H, NH); 11.97 (br.s, 1 H, COOH). MS (EI, 70 eV), m/z (I_{rel} (%)): 323 $[M]^+$ (93), 305 (100), 279 (55), 191 (23).

3-(4-Chlorophenyl)-4-(4-methoxyphenyl)pyrrole-2-carboxylic acid (15b). The yield was 57%. M.p. 222—224 °C. ^{1}H NMR (DMSO-d_6, 500 MHz), δ: 3.69 (s, 3 H, OCH_3); 6.76 (d, 2 H, Ar, J = 8.6 Hz); 6.95 (d, 2 H, Ar, J = 8.6 Hz); 7.13 (d, 1 H, CH_{pyrr}, J = 3.1 Hz); 7.17 (d, 2 H, Ar, J = 8.3 Hz); 7.32 (d, 2 H, Ar, J = 8.3 Hz); 11.89 (s, 1 H, NH); 12.19 (br.s, 1 H, COOH). ^{13}C NMR (DMSO-d_6, 125.76 MHz), δ: 55.0 (OCH_3), 113.7 (2 C, CH_{arom}), 119.9 (C_{arom}), 120.8 (CH_{pyrr}), 124.7 (C_{arom}), 126.4 (C_{arom}), 127.0 (C_{arom}), 127.5 (2 C, CH_{arom}), 129.0 (2 C, CH_{arom}), 131.1 (C_{arom}), 132.5 (2 C, CH_{arom}), 134.3 (C_{arom}), 157.5 (COOH), 161.8 (C_{arom}). MS (EI, 70 eV), m/z (I_{rel} (%)): 327 $[M]^+$ (96), 309 (100), 294 (18), 45 (19), 28 (27). Found (%): C, 65.78; H, 4.34; N, 4.39. $C_{18}H_{14}ClNO_3$. Calculated (%): C, 65.96; H, 4.31; N, 4.27.

3-(3,5-Dimethoxyphenyl)-4-(4-methoxyphenyl)pyrrole-2-carboxylic acid (15c). The yield was 80%. M.p. 205—208 °C. ^{1}H NMR (DMSO-d_6, 500 MHz), δ: 3.64 (s, 6 H, OCH_3); 3.69 (s, 3 H, OCH_3); 6.31 (d, 2 H, Ar, J = 2.1 Hz); 6.38 (s, 1 H, Ar); 6.75 (d, 2 H, Ar, J = 8.6 Hz); 7.01 (d, 2 H, Ar, J = 8.6 Hz); 7.11 (d, 1 H, CH_{pyrr}, J = 3.1 Hz); 11.80 (s, 1 H, NH); 12.09 (br.s, 1 H, COOH). MS (EI, 70 eV), m/z (I_{rel} (%)): 353 $[M]^+$ (84), 335 (100), 309 (21). Found (%): C, 67.82; H, 5.34; N, 4.20. $C_{20}H_{19}NO_5$. Calculated (%): C, 67.98; H, 5.42; N, 3.96.

4-(4-Methoxyphenyl)-3-(4-nitrophenyl)pyrrole-2-carboxylic acid (15d). The yield was 85%. M.p. 236—237 °C. ^{1}H NMR (DMSO-d_6, 500 MHz), δ: 3.68 (s, 3 H, OCH_3); 6.77 (d, 2 H, Ar, J = 8.7 Hz); 6.94 (d, 2 H, Ar, J = 8.6 Hz); 7.18 (d, 1 H, CH_{pyrr}, J = 3.1 Hz); 7.44 (d, 2 H, Ar, J = 8.6 Hz); 8.14 (d, 2 H, Ar, J = 8.6 Hz); 12.09 (s, 1 H, NH); 12.39 (br.s, 1 H, COOH). MS (EI, 70 eV), m/z (I_{rel} (%)): 338 $[M]^+$ (87), 320 (100), 305 (15), 294 (9). Found (%): C, 63.98; H, 4.28; N, 8.15. $C_{18}H_{14}N_2O_5$. Calculated (%): C, 63.90; H, 4.17; N, 8.28.

4-(4-Methoxybenzoyl)-3-(4-methoxyphenyl)pyrrole-2-carboxylic acid (16a). The yield was 83%. M.p. 210—211 °C. ^{1}H NMR (DMSO-d_6, 500 MHz), δ: 3.73 (s, 3 H, OCH_3); 3.81 (s, 3 H, OCH_3); 6.77 (d, 2 H, Ar, J = 8.7 Hz); 6.95 (d, 2 H, Ar, J = 8.8 Hz); 7.14 (d, 2 H, Ar, J = 8.7 Hz); 7.23 (s, 1 H, CH_{pyrr}); 7.66 (d, 2 H, Ar, J = 8.8 Hz); 12.20 (s, 1 H, NH); 12.60 (br.s,

1 H, COOH). MS (EI, 70 eV), *m/z* (I_{rel} (%)): 351 $[M]^+$ (100), 307 (20), 226 (13), 135 (31). Found (%): C, 68.40; H, 4.74; N, 4.19. $C_{20}H_{17}NO_5$. Calculated (%): C, 68.37; H, 4.88; N, 3.99.

3-(4-Chlorophenyl)-4-(4-methoxybenzoyl)pyrrole-2-carboxylic acid (16b). The yield was 83%. M.p. 212—213 °C. ^{1}H NMR (DMSO-d_6, 500 MHz), δ: 3.82 (s, 3 H, OCH_3); 6.97 (d, 2 H, Ar, *J* = 8.8 Hz); 7.24 (d, 2 H, Ar, *J* = 8.5 Hz); 7.28 (d, 2 H, Ar, *J* = 8.5 Hz); 7.31 (d, 1 H, CH_{pyrr}, *J* = 3.4 Hz); 7.68 (d, 2 H, Ar, *J* = 8.7 Hz); 12.39 (s, 1 H, NH); 12.62 (br.s, 1 H, COOH). ^{13}C NMR (DMSO-d_6, 125.76 MHz), δ: 55.5 (OCH_3), 113.6 (2 C, CH_{arom}), 121.1 (C_{arom}), 123.8 (C_{arom}), 127.0 (2 C, CH_{arom}), 127.7 (CH_{pyrr}), 129.7 (C_{arom}), 131.2 (C_{arom}), 131.4 (2 C, CH_{arom}), 131.6 (C_{arom}), 132.3 (2 C, CH_{arom}), 133.3 (C_{arom}), 161.6 (COOH), 162.4 (C_{arom}), 188.7 (CO). MS (EI, 70 eV), *m/z* (I_{rel} (%)): 355 $[M]^+$ (100), 230 (89), 135 (81), 92 (91), 77 (73), 64 (46). Found (%): C, 64.25; H, 3.82; N, 3.85. $C_{19}H_{14}ClNO_4$. Calculated (%): C, 64.14; H, 3.97; N, 3.94.

3,4,5-Tris(4-methoxyphenyl)isoxazole (19a). The yield was 11%. M.p. 148—149 °C (*cf.* Ref. 27: m.p. 146—147 °C). ^{1}H NMR (DMSO-d_6, 300 MHz), δ: 3.79 (m, 9 H, OCH_3); 6.90—7.07 (m, 6 H, Ar); 7.21 (d, 2 H, Ar, *J* = 8.7 Hz); 7.33 (d, 2 H, Ar, *J* = 8.7 Hz); 7.45 (d, 2 H, Ar, *J* = 8.7 Hz).

Synthesis of pyrroles 17a—d and 18a,b (general procedure). A corresponding pyrrole-2-carboxylic acid (0.08 mmol) was heated to melting point, the heating was continued until evolution of gas ceased (30 s and 2 min for **17a—d** and **18a**,**b**, respectively), and the heating was removed. A dilute aqueous alkali (3 mL) was added, heated to boiling, cooled, and filtered.

3,4-Bis(4-methoxyphenyl)pyrrole (17a). The yield was 68%. M.p. 117—118 °C (*cf.* Ref. 19: m.p. 116 °C). ^{1}H NMR ($CDCl_3$, 500 MHz), δ: 3.79 (s, 6 H, OCH_3); 6.81 (d, 4 H, Ar, *J* = 8.5 Hz); 6.84 (s, 2 H, CH_{pyrr}); 7.19 (d, 4 H, Ar, *J* = 8.5 Hz); 8.21 (s, 1 H, NH).

3-(4-Chlorophenyl)-4-(4-methoxyphenyl)pyrrole (17b). The yield was 46%. An oil. ^{1}H NMR (DMSO-d_6, 500 MHz), δ: 3.73 (s, 3 H, OCH_3); 6.84 (d, 2 H, Ar, *J* = 8.7 Hz); 6.87 (t, 1 H, CH_{pyrr}, *J* = 2.4 Hz); 6.98 (t, 1 H, CH_{pyrr}, *J* = 2.4 Hz); 7.08 (d, 2 H, Ar, *J* = 8.7 Hz); 7.18 (d, 2 H, Ar, *J* = 8.5 Hz); 7.28 (d, 2 H, Ar, *J* = 8.5 Hz); 11.09 (s, 1 H, NH). Found (%): C, 71.77; H, 4.83; N, 5.01. $C_{17}H_{14}ClNO$. Calculated (%): C, 71.96; H, 4.97; N, 4.94.

3-(3,5-Dimethoxyphenyl)-4-(4-methoxyphenyl)pyrrole (17c). The yield was 46%. M.p. 127—128 °C. ^{1}H NMR (DMSO-d_6, 500 MHz), δ: 3.61 (s, 6 H, OCH_3); 3.73 (s, 3 H, OCH_3); 6.26 (s, 1 H, Ar); 6.33 (d, 2 H, Ar, *J* = 2.2 Hz); 6.84 (m, 3 H, $CH_{pyrr,Ar}$); 6.98 (s, 1 H, CH_{pyrr}); 7.12 (d, 2 H, Ar, *J* = 8.6 Hz); 11.09 (s, 1 H, NH). Found (%): C, 73.92; H, 6.07; N, 4.76. $C_{19}H_{19}NO_3$. Calculated (%): C, 73.77; H, 6.19; N, 4.53.

4-(4-Methoxyphenyl)-3-(4-nitrophenyl)pyrrole (17d). The yield was 67%. M.p. 189—190 °C. ^{1}H NMR (DMSO-d_6, 500 MHz), δ: 3.75 (s, 3 H, OCH_3); 6.88 (d, 2 H, Ar, *J* = 8.6 Hz); 6.92 (s, 1 H, CH_{pyrr}); 7.12 (d, 2 H, Ar, *J* = 8.6 Hz); 7.23 (s, 1 H, CH_{pyrr}); 7.43 (d, 2 H, Ar, *J* = 8.7 Hz); 8.09 (d, 2 H, Ar, *J* = 8.8 Hz); 11.39 (s, 1 H, NH). Found (%): C, 69.47; H, 4.97; N, 9.25. $C_{17}H_{14}N_2O_3$. Calculated (%): C, 69.38; H, 4.79; N, 9.52.

4-(4-Methoxybenzoyl)-3-(4-methoxyphenyl)pyrrole (18a). The yield was 66%. M.p. 207—208 °C (*cf.* Ref. 32: m.p. 203—205 °C). ^{1}H NMR (DMSO-d_6, 500 MHz), δ: 3.72 (s, 3 H, OCH_3); 3.82 (s, 3 H, OCH_3); 6.82 (d, 2 H, Ar, *J* = 8.3 Hz); 6.99 (m, 3 H, $CH_{pyrr,Ar}$); 7.18 (s, 1 H, CH_{pyrr}); 7.27 (d, 2 H, Ar, *J* = 8.3 Hz); 7.74 (d, 2 H, Ar, *J* = 8.4 Hz); 11.49 (s, 1 H, NH).

3-(4-Chlorophenyl)-4-(4-methoxybenzoyl)pyrrole (18b). The yield was 67%. M.p. 247—248 °C (*cf.* Ref. 33: m.p. 248—250 °C). ^{1}H NMR (DMSO-d_6, 500 MHz), δ: 3.81 (s, 3 H, OCH_3); 7.00 (d, 2 H, Ar, *J* = 8.6 Hz); 7.12 (s, 1 H, CH_{pyrr}); 7.22 (s, 1 H, CH_{pyrr}); 7.30 (d, 2 H, Ar, *J* = 8.4 Hz); 7.36 (d, 2 H, Ar, *J* = 8.4 Hz); 7.76 (d, 2 H, Ar, *J* = 8.6 Hz); 11.61 (s, 1 H, NH). ^{13}C NMR (DMSO-d_6, 125.76 MHz), δ: 55.3 (OCH_3), 113.4 (2 C, CH_{arom}), 119.5 (C_{pyrr}), 120.5 (C_{arom}), 123.9 ($CH_{arom.}$), 127.2 (C_{pyrr}), 127.6 (2 C, CH_{arom}), 129.7 (2 C, CH_{arom}), 131.2 (2 C, CH_{arom}), 132.1 (C_{arom}), 134.2 (C_{arom}), 162.1 (1 C, C_{arom}), 189.1 (CO). MS (EI, 70 eV), *m/z* (I_{rel} (%)): 311 $[M]^+$ (100), 294 (19), 280 (28), 204 (49), 141 (15), 135 (17).

Biological tests (general procedure). Study of the antiproliferative activity of compounds on a model of sea urchin embryos.[23] Experiments were carried out at the biological laboratory of the N. K. Kol´tsov Institute of Developmental Biology of RAS in Cyprus. Adult sea urchins, *Paracentrotus lividus* L. (Echinidae) were collected in the coastal area and kept in an aerated seawater tank. Spawning was triggered by intracoelomic injection of 0.5 *M* KCl (1—2 mL) into the body cavity of animals. The resulting eggs were washed with sea water, filtered through a nylon filter, and then fertilized by adding drops of diluted sperm. The embryos (600—2000 mL^{-1}) were incubated in filtered seawater at room temperature (18—23 °C) in six-well culture plates.

The stock solutions of chemical compounds were prepared in DMSO, followed by a 10-fold dilution with 96% ethanol. This procedure increases the solubility of compounds in the salt-containing media (sea water). The solubility of the test compounds was monitored using an MBS-10 stereomicroscope. Combretastatin A-4 (CA4), synthesized according to the described procedure,[34] was used as a positive control.

The treatment with compounds was carried out in six-well culture plates. 5 mL of a suspension of fertilized eggs or embryos was placed to each well, and a corresponding volume of the test compound solution was added to achieve the desired final concentration. The maximum concentration of the solvent did not exceed the maximum tolerated one (1% for ethanol and 0.05% for DMSO). To evaluate the antimitotic activity, the eggs were treated with test compounds at 8—15 min post fertilization, and cleavage alteration and/or cleavage arrest was detected after 2.5—6 h. The ability of test compounds to affect tubulin and destabilize microtubules was established by the characteristic change in the swimming behavior of embryos exposed to the compounds immediately after hatching of blastulae at 8.5—10 h post fertilization. The lack of forward swimming of the embryos at the surface of the seawater, settling to the bottom of the vessel, and rapid spinning around the animal-vegetal axis suggest the antitubulin mode of action of the test chemical compounds. In the tests 2-fold decreasing concentrations of compounds were used until the effect disappeared. The activity was assessed by the lowest (threshold) concentration EC causing cleavage alteration, cleavage arrest, or embryo spinning. Monitoring of embryonic development was carried out until the beginning of active feeding (mid-pluteus 2) using a Biolam LOMO optical microscope (St. Petersburg, Russia).

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