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Synthesis of Pyrido[2,3-*b*]indole Derivatives via Diels–Alder Reactions of 2- and 3-Vinylpyrrolo[2,3-*b*]pyridines

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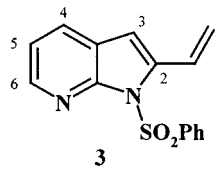
Abstract—Diels–Alder reactions between 2- or 3-vinylpyrrolo[2,3-*b*]pyridine with various dienophiles were investigated. The pyrido[2,3-*b*]indole adducts **9** and **13** obtained led us to the preparation of potential cytotoxic agents **19** and **20**.

The Diels–Alder reactions of 2- or 3-vinylindoles represent an interesting methodology for the syntheses of many indole alkaloids and carbazoles. The general success of this cycloaddition has been documented fairly well.[1] Similarly, studies on biological activity of 1*H*-pyrrolo[2,3-*b*]pyridine (7-azaindole) derivatives have been expanded significantly in recent years: mimics of adenosine base,[2] anticancer agents,[3–5] dopaminergic ligands,[6] melatoninergic ligands.[7]

To the best of our knowledge, the reactivity of 2- or 3-vinyl-7-azaindole as dienes remains unexplored. Nevertheless, the [4+2] cycloadditions of 1-methyl-2-vinyl-4-azindole with *N*-phenylmaleimide or dimethyl acetylenedicarboxylate (DMAD) have been recently reported.[8]

Our research group is involved in the development of potential cytotoxic agents[9] and we became interested in the synthesis of pyrido[2,3-*b*]indole derivatives using Diels–Alder methodology. Thus, we planned to prepare 1-phenylsulfonyl-2-vinylpyrrolo[2,3-*b*]pyridine **3** and 1-methyl-3-vinylpyrrolo[2,3-*b*]pyridine **6** as attractive heterocyclic dienes.



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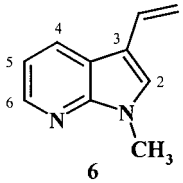
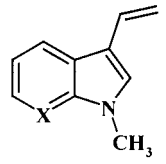
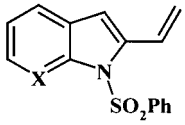


6

The reactivity of 2- or 3-vinyl-7-azaindoles is lower than the same indole derivatives due to a decrease of the energy level of the HOMO of the diene.[10]



X= CH E_{HOMO} (eV) *-8.0380*
X= N E_{HOMO} (eV) *-8.7613*



X= CH E_{HOMO} (eV) *-8.6133*
X= N E_{HOMO} (eV) *-8.8208*

The 2-vinyl derivative **3** was synthesised in two steps from 1-phenylsulfonyl-2-iodopyrrolo[2,3-*b*] pyridine **1**.[11] Regioselective lithiation[4] of **1** in position 2 with LDA in the presence of *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA) in THF at −22°C and quenching with iodine provided 2-iodo derivative **2**[12] in 83% yield. The Stille reaction[13] between **2** and vinyltributyltin in the presence of *tetrakis*(triphenylphosphine)palladium (6 mol%) and lithium chloride in DMF at 90°C was performed to give unstable compound **3** in 80% yield (Scheme 1).

The synthesis of **6** was achieved from pyrrolo[2,3-*b*]pyridine-3-carboxaldehyde **4**[14] by heating with malonic acid in pyridine and piperidine. We directly obtained the 3-vinyl derivative **5** in 77% yield through a double decarboxylation and not the α,β-ethylenic acid as described in the literature.[15] Finally, *N*-methyl alkylation of **5** afforded **6** in 78% yield (Scheme 2).

The vinyl derivative **3** was, first, engaged in [4+2] cycloadditions with symmetrical carbodienophiles naphthoquinone and DMAD (Scheme 3). 1,2-Dichloroethane was found to be the best solvent for these Diels–Alder reactions. In a sealed tube, reaction of **3** with naphthoquinone (1.5 equiv.) was carried out in 1,2-dichloroethane at 90°C

Keywords: Diels–Alder reaction; pyrido[2,3-*b*]indole; heterocyclic dienes.
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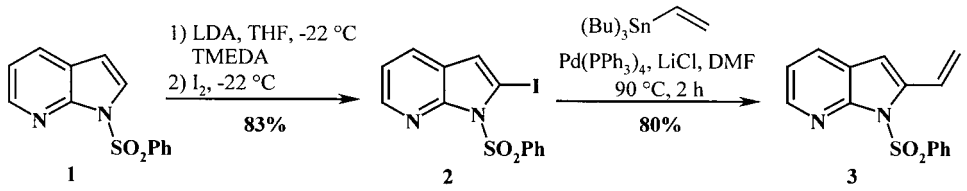
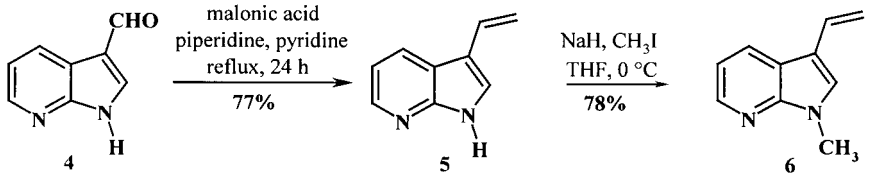
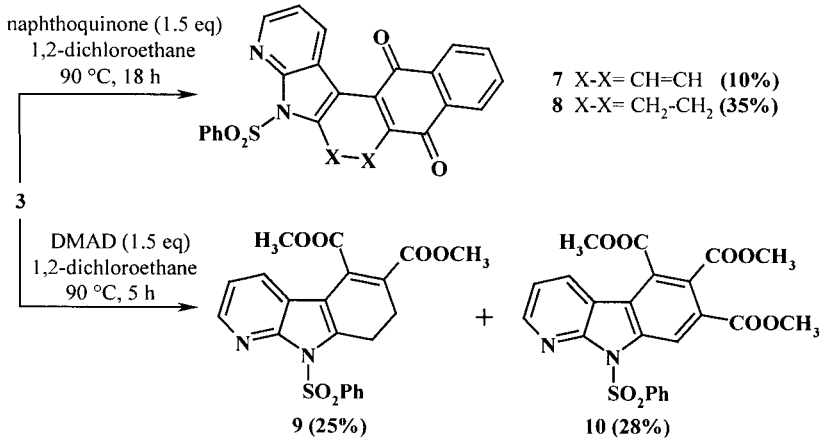


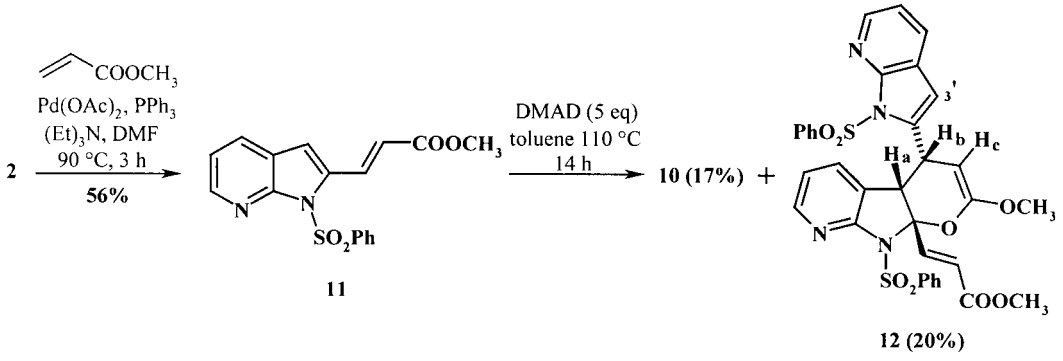
Scheme 1.



Scheme 2.



Scheme 3.



Scheme 4.

for 18 h to provide a mixture of cycloadducts **7** and **8**, respectively, in 10 and 35% yield. The similar reaction conditions applied to **3** with DMAD (1.5 equiv.) afforded compound **9** and the unexpected derivative **10**, in 25 and 28% yield respectively. Until now, we have not been able to present a convincing mechanism for the formation of **10**.[16] Traces of the aromatised derivative from **9** were also detected. Attempts to run the cycloaddition reaction under atmospheric pressure gave solely **9** in 30% yield.

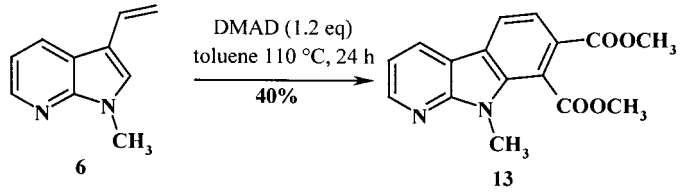
The structural assignment for **10** is based on 1D, 2D NOESY and HETCOR data[17] and through the preparation of this compound by an alternative synthetic route from compound **11**, which was obtained in 56% yield by way of the Heck reaction between **2** and methyl acrylate (Scheme 4). Cycloaddition between **11** and DMAD (5 equiv.) in toluene at 110°C for 14 h led to compound **10** in low yield (17%) due to the decreased reactivity of the diene (22% of starting material was recovered) and the

formation of cyclodimer **12** (20%) resulting from an intermolecular hetero Diels–Alder reaction of **11** with itself. 2D NOESY experiment[17] on **12** clearly demonstrated the *cis* relationship between the protons H_a, H_b and the propenyl chain.

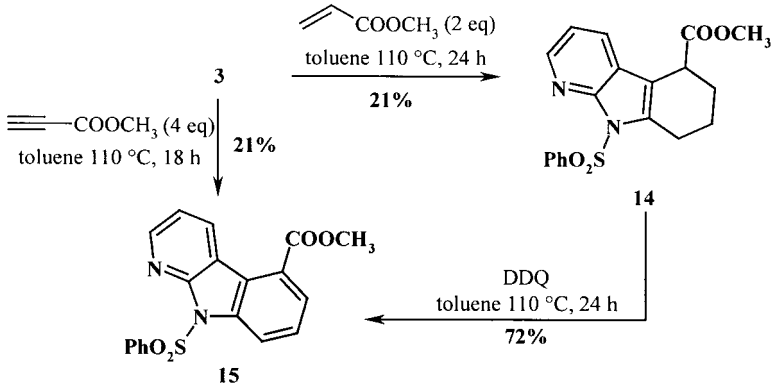
Similarly, vinyl compound **6** was treated with DMAD (1.2 equiv.) in toluene at 110°C to give the dimethyl 9-methyl-9*H*-pyrido[2,3-*b*]indole-7,8-dicarboxylate **13** in 40% yield (Scheme 5).

Once this part was achieved, we investigated the regioselectivity of the Diels–Alder reaction with **3**. In a sealed tube, cycloaddition of **3** with methyl acrylate (2 equiv.) was performed in toluene at 110°C for 24 h to afford exclusively the tetrahydro derivative **14** in 21% yield (Scheme 6). The relative position of the ester on the ring system was unambiguously confirmed by the 2D NOESY experiments and by the synthesis of the aromatised compound **15** according to a standard methodology (DDQ, toluene, 72% yield). Reaction of **3** with methyl propynoate (4 equiv.) in toluene at 110°C for 18 h also gave exclusively **15** in 21% yield.

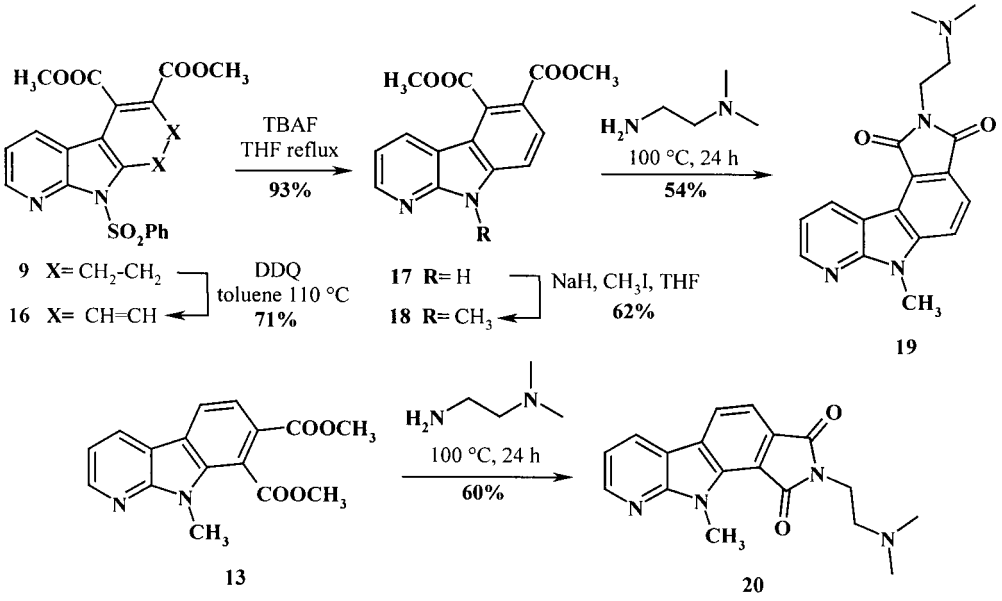
Compounds **9** and **13** having a pyrido[2,3-*b*]indole moiety were used as the starting material for the syntheses of potential cytotoxic agents through introduction of a dialkylamino chain often encountered in anticancer agents (Scheme 7).[18] Thus, the diester **9** was, first, aromatised with DDQ in



Scheme 5.



Scheme 6.



Scheme 7.

Table 1. Growth-inhibitory activity and cellular cycle accumulation of **19** and **20**

Compound	IC_{50}[a] (μM) L1210	Cellular cycle accumulation[b] L1210
Adriamycine	0.025	G_2+M (>70% at 0.1 μM)
19	26.9	Not tested
20	3.4	G_2+M (>70% at 10 μM)

[a] Inhibition of L1210 cell proliferation was measured by the MMT assay.
[b] 24% of untreated control cells were in the G_2+M phase of the cell cycle.

toluene to give **16** in 71% yield. Then, the *N*-phenylsulfonyl group was removed using tetrabutylammonium fluoride (TBAF)[19] in refluxing THF to afford **17** in good yield. Alkylation of **17** was carried out with iodomethane in THF at 0°C in the presence of sodium hydride to give **18** (62% yield). Finally, the latter compound was treated with an excess of *N*,*N*-dimethylaminoethylamine to afford the expected compound **19** in 54% yield. In the same condition, compound **16** gave essentially the desulfonylated derivative **17** due to the basic character of the diamine.

The diester **13** heated at 100°C with a large excess of *N*,*N*-dimethylaminoethylamine gave the imide **20** in 60% yield.

The study of the cytotoxic property of the derivatives **19** and **20** was carried out in vitro on murine L1210 leukemia cells.[20] The results (IC_{50}) were summarised in Table 1. Compound **20** exhibits significant cytotoxic activity and induces a massive accumulation of L1210 cells in G_2+M phase. Pharmacomodulation and modification of the position of the aminoalkyl chain are in progress to improve the potency of this series.

In conclusion, Diels–Alder reactions between 2- or 3-vinylpyrrolo[2,3-*b*]pyridine **3** and **6** with various dienophiles were investigated. Among adducts obtained, the pyrido[2,3-*b*]indole derivative **9** led us to the preparation of novel potent cytotoxic agent **20**.

Experimental

Melting points were determined using a Büchi SMP-20 melting point apparatus and are uncorrected. The infrared spectra of compounds were recorded on a Perkin–Elmer FTIR paragon 1000 spectrometer. NMR spectra were recorded at 300 K in $CDCl_3$ on a Bruker Avance DPX 250. Chemical shifts are expressed in parts per million and referenced to TMS. Mass spectra were recorded on Perkin–Elmer SCIEX API 300 using ionspray methodology. Thin layer chromatography was performed on precoated plates of silica gel $60F_{254}$ (Merck) and the spots visualised using an ultraviolet lamp. Flash chromatography was conducted using silica gel 60 Merck (40–63 μm) as the stationary phase.

1-Phenylsulfonyl-2-iodo-1*H*-pyrrolo[2,3-*b*]pyridine (2).[12] To a solution of **1**[11] (1.0 g, 3.9 mmol) and *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (0.6 ml, 3.9 mmol) in dry THF (50 ml) was added dropwise a solution of 2 M lithium diisopropylamide in heptane (2.32 ml, 4.7 mmol) under argon at −22°C. After 30 min, a solution of iodine (1.96 g, 7.7 mmoles) in dry THF (10 ml) was added dropwise with vigorous stirring at −22°C. The mixture was stirred for 30 min, hydrolysed with water (10 ml), then THF was removed in vacuo. The residue was partitioned between ethyl acetate (10 ml) and water (10 ml), the aqueous phase was separated and extracted with ethyl acetate (2×10 ml). The organic phase was dried over $MgSO_4$ and evaporated in vacuo. The crude oil was purified by column chromatography (eluent petroleum ether–ethyl acetate 7:3) to afford **2** (1.23 g, 83%) as white crystals; mp 115–116°C (ethyl acetate–petroleum ether); ^{1}H NMR (250 MHz, $CDCl_3$) δ 6.99 (s, 1H, H_3), 7.14 (dd, 1H, *J*=4.8, 7.8 Hz, H_5), 7.46–7.61 (m, 3H, H_{Ar}), 7.72 (dd, 1H, *J*=1.5, 7.8 Hz, H_4), 8.22 (d, 2H, *J*=8.0 Hz, H_{Ar}), 8.39 (dd, 1H, *J*=1.5, 4.8 Hz, H_6); ^{13}C NMR (62.90 MHz, $CDCl_3$) δ 76.2 (C), 119.3 (CH), 120.3 (CH), 123.8 (C), 127.7 (CH), 128.1 (2 CH), 129.0 (2 CH), 134.1 (CH), 138.6 (C), 144.7 (CH), 149.5 (C); Anal. Calcd for $C_{13}H_9N_2O_2SI$: C, 40.64; H, 2.36; N, 7.29. Found: C, 40.89; H, 2.18; N, 7.35; MS *m*/*z* 385 $(M+1)^+$.

1-Phenylsulfonyl-2-vinyl-1*H*-pyrrolo[2,3-*b*]pyridine (3). To a suspension of freshly prepared *tetrakis*(triphenylphosphine)palladium (6 mol%) and LiCl (190 mg, 4.4 mmol) in dry DMF (10 ml) under argon was added a solution of **2** (600 mg, 1.6 mmol) and tributylvinyltin (0.7 ml, 2.4 mmol) in dry DMF (10 ml). The solution was stirred at 90°C for 2 h. After cooling, water (15 ml) and ethyl acetate (15 ml) were added to the mixture. After extraction, the organic layer was washed with potassium fluoride, water, then dried over $MgSO_4$ and concentrated in vacuo. The crude residue was purified by column chromatography (eluent petroleum ether–ethyl acetate 7:3) to give **3** (300 mg, 80%) as an oil which crystallises at low temperature; mp 92–93°C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 5.44 (dd, 1H, *J*=1.5, 11.0 Hz, CH_2=), 5.76 (dd, 1H, *J*=1.5, 17.3 Hz, CH_2=), 6.64 (d, 1H, *J*=0.8 Hz, H_3), 7.12 (dd, 1H, *J*=4.8, 7.8 Hz, H_5), 7.33–7.43 (m, 4H, H_{Ar}+CH=), 7.72 (dd, 1H, *J*=1.6, 7.8 Hz, H_4), 8.03–8.08 (m, 2H, H_{Ar}), 8.39 (dd, 1H, *J*=1.6, 4.8 Hz, H_6); ^{13}C NMR (62.90 MHz, $CDCl_3$) δ 104.8 (CH), 118.6 (CH_2), 119.4 (CH), 121.8 (C), 127.5 (2 CH), 127.6 (CH), 128.6 (CH), 128.8 (2 CH), 133.7 (CH), 138.8 (C), 140.2 (C), 144.6 (CH), 149.2 (Cq); Anal. Calcd for $C_{15}H_{12}N_2O_2S$: C, 63.36; H, 4.25; N, 9.85. Found: C, 63.21; H, 4.32; N, 10.01; MS *m*/*z* 285 $(M+1)^+$.

3-Vinyl-1*H*-pyrrolo[2,3-*b*]pyridine (5).[15] A solution of **4**[14] (1.0 g, 6.9 mmol) and malonic acid (2.1 g, 20.5 mmol) in piperidine (0.3 ml) and pyridine (6 ml) was stirred at reflux under argon for 24 h. After cooling and evaporation, the crude residue was purified by column chromatography (eluent: petroleum ether–ethyl acetate 1:1) to afford **5** (760 mg, 77%) as crystals; mp 128–129°C (ethyl acetate–petroleum ether); IR (KBr) ν 3131 (NH) cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 5.20 (d, 1H, *J*=11.7 Hz, CH_2=), 5.69 (d, 1H, *J*=17.5 Hz, CH_2=), 6.85 (dd, 1H, *J*=11.7, 17.5 Hz, CH=), 7.14 (dd, 1H, *J*=3.5, 8.0 Hz, H_5), 7.40 (s, 1H, H_2), 8.21 (d, 1H, *J*=8.0 Hz, H_4), 8.33 (d, 1H, *J*=3.5 Hz, H_6); ^{13}C NMR (62.90 MHz, $CDCl_3$) δ 111.0 (CH_2), 113.9 (C), 116.1 (CH), 118.5 (C), 124.7 (CH), 128.8 (CH), 129.4 (CH), 142.5 (CH), 149.5 (C); Anal. Calcd for $C_9H_8N_2$: C, 74.98; H, 5.59;

N, 19.43. Found: C, 75.22; H, 5.48; N, 19.37; MS *m/z* 145 $(M+1)^+$.

1-Methyl-3-vinyl-1*H*-pyrrolo[2,3-*b*]pyridine (6). To a solution of **5** (350 mg, 2.4 mmol) in dry THF (10 ml) under argon was slowly added sodium hydride (87 mg, 3.6 mmol) at 0°C for 30 min. After 30 min of stirring, a solution of iodomethane (0.23 ml, 3.6 mmol) in THF (5 ml) was added. The final solution was stirred at 0°C for 1 h, hydrolysed with water (5 ml) and finally THF was removed in vacuo. The residue was partitioned between ethyl acetate (10 ml) and water (10 ml), and the aqueous phase separated and extracted with ethyl acetate (2× 10 ml). The organic phase was dried over $MgSO_4$ and evaporated in vacuo. The crude residue was purified by column chromatography (eluent petroleum ether–ethyl acetate 7:3) to give **6** (300 mg, 78%) as an oil which was used without further characterisation; ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.86 (s, 3H, CH_3), 5.16 (dd, 1H, J=1.2, 11.0 Hz, CH_2=), 5.65 (dd, 1H, J=1.2, 17.8 Hz, CH_2=), 6.80 (dd, 1H, J=11.0, 17.8 Hz, CH=), 7.10 (dd, 1H, J=4.7, 7.7 Hz, H_5), 7.21 (s, 1H, H_2), 8.14 (dd, 1H, J=1.5, 7.7 Hz, H_4), 8.35 (dd, 1H, J=1.5, 4.7 Hz, H_6); ^{13}C NMR (62.90 MHz, $CDCl_3$) δ 31.2 (CH_3), 110.8 (CH_2), 112.7 (C), 116.0 (CH), 118.5 (C), 128.2 (CH), 128.4 (CH), 129.1 (CH), 143.3 (CH), 148.4 (C); Anal. Calcd for $C_{10}H_{10}N_2$: C, 75.92; H, 6.37; N, 17.71. Found: C, 75.68; H, 6.54; N, 17.61; MS *m/z* 159 $(M+1)^+$.

13-Phenylsulfonyl-5,10-dihydro-13*H*-naphtho[2,3-*e*]-pyrido[2,3-*b*]indole-5,10-dione (7) and 13-phenylsulfonyl-5,10,11,12-tetrahydro-13*H*-naphtho[2,3-*e*]pyrido-[2,3-*b*]indole-5,10-dione (8). A solution of compound **3** (300 mg, 1.1 mmol) and naphthoquinone (330 mg, 2.1 mmol) in 1,2-dichloroethane (10 ml) in a sealed tube was heated at 90°C for 18 h. After cooling, the solvent was removed in vacuo. The crude residue was purified by column chromatography (eluent petroleum ether–ethyl acetate 7:3) to afford **7** (48 mg, 10%) as crystals and **8** (168 mg, 35%) as crystals. Compound **7**: mp 274–275°C (methanol); IR (KBr) ν 1672 (CO) cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.40–7.57 (m, 4H, H_{Pyr}+H_{Ar}), 7.79–7.83 (m, 2H, H_{Ar}), 8.20–8.23 (m, 2H, H_{Ar}), 8.30–8.40 (m, 2H, H_{Ar}), 8.62 (d, 1H, J=9.0 Hz, H_{Ar}), 8.66 (dd, 1H, J=1.7, 4.7 Hz, H_{Pyr}), 9.07 (d, 1H, J=9.0 Hz, H_{Ar}), 9.74 (dd, 1H, J=1.7, 8.2 Hz, H_{Pyr}); Anal. Calcd for $C_{25}H_{14}N_2O_4S$: C, 68.48; H, 3.22; N, 6.39. Found: C, 68.17; H, 3.20; N, 6.37; MS *m/z* 439 $(M+1)^+$. The very low solubility of compound **7**, did not allow us to perform ^{13}C NMR. For compound **8**, air oxidation occurred rapidly to lead to **7**. Only the ^{1}H NMR was recorded; ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.10 (t, 2H, J=8.3 Hz, CH_2), 3,56 (t, 2H, J=8.3 Hz, CH_2), 7.27 (dd, 1H, J=4.7, 8.2 Hz, H_{Pyr}), 7.41–7.63 (m, 3H, H_{Ar}), 7.73–7.77 (m, 2H, H_{Ar}), 8.11–8.18 (m, 2H, H_{Ar}), 8.21–8.24 (m, 2H, H_{Ar}), 8.35–8.43 (m, 2H, H_{Pyr}).

Dimethyl 9-(phenylsulfonyl)-7,8-dihydro-9*H*-pyrido[2,3-*b*]indole-5,6-dicarboxylate (9) and trimethyl 9-(phenylsulfonyl)-9*H*-pyrido [2,3-*b*] indole-5,6,7-tricarboxylate (10). A solution of compound **3** (530 mg, 1.8 mmol) and dimethyl acetylenedicarboxylate (0.34 ml, 2.8 mmol) in 1,2-dichloroethane (10 ml) in a sealed tube was heated at 90°C for 5 h. After cooling, the solvent was removed in vacuo. The crude residue was purified by column chromatography (eluent petroleum ether–ethyl acetate 7:3) to afford **9** (200 mg, 25%) as crystals and **10** (220 mg, 28%) as crystals. Compound **9**: mp 143–144°C (ethyl acetate): IR (KBr) ν 1737, 1708 (CO) cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.91 (t, 2H, J=9.5 Hz, CH_2), 3.51 (t, 2H, J=9.5 Hz, CH_2), 3.81 (s, 3H, CH_3), 3.96 (s, 3H, CH_3), 7.16 (dd, 1H, J=4.7, 8.0 Hz, H_{Pyr}), 7.47–7.64 (m, 4H, H_{Ar}, H_{Pyr}), 8.17 (d, 2H, J=7.8 Hz, H_{Ar}), 8.39 (dd, 1H, J=1.2, 4.6 Hz, H_{Pyr}); ^{13}C NMR (62.90 MHz, $CDCl_3$) δ 21.4 (CH_2), 22.7 (CH_2), 51.9 (CH_3), 52.3 (CH_3), 110.3 (C), 117.4 (C), 119.3 (C), 120.6 (C), 126.4 (C), 127.2 (2 CH), 128.3 (CH), 128.7 (2 CH), 133.9 (CH), 134.6 (CH), 137.9 (C), 139.7 (C), 144.0 (CH), 165.5 (CO), 168.1 (CO); Anal. Calcd for $C_{21}H_{18}N_2O_6S$: C, 59.15; H, 4.25; N, 6.57. Found: C, 59.35; H, 4.09; N, 6.45; MS *m/z* 427 $(M+1)^+$. Compound **10**: mp 217–218°C (ethyl acetate–petroleum ether); IR (KBr) ν 1739, 1725 (CO) cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.96 (s, 3H, CH_3), 4.02 (s, 6H, CH_3), 7.34 (dd, 1H, J=5.0, 8.0 Hz, H_{Pyr}), 7.45–7.57 (m, 3H, H_{Ar}), 8.14–8.18 (m, 2H, H_{Ar}), 8.41 (dd, 1H, J=1.5, 8.0 Hz, H_{Pyr}), 8.65 (dd, 1H, J=1.5, 5.0 Hz, H_{Pyr}), 9.26 (s, 1H, H_{Ar}); ^{13}C NMR (62.90 MHz, $CDCl_3$) δ 53.0 (CH_3), 53.1 (CH_3), 53.2 (CH_3), 115.9 (C), 118.3 (CH), 119.8 (CH), 123.0 (C), 126.4 (C), 127.8 (2 CH), 129.1 (2 CH), 129.3 (C), 129.6 (C), 132.5 (CH), 134.5 (CH), 137.7 (C), 138.0 (C), 149.1 (CH), 151.6 (C), 165.9 (CO), 166.6 (CO), 167.6 (CO); Anal. Calcd for $C_{23}H_{18}N_2O_8S$: C, 57.26; H, 3.76; N, 5.81. Found: C, 57.38; H, 3.83; N, 5.90; MS *m/z* 483 $(M+1)^+$.

Methyl (*E*)-3-[(1-phenylsulfonyl)-1*H*-pyrrolo [2,3-*b*]-pyridin-2-yl]propenoate (11). To a solution of palladium acetate (7.5 mol%) and triphenylphosphine (10 mg) in dry DMF (5 ml) was added successively compound **2** (100 mg, 0.3 mmol), triethylamine (0.07 ml, 0.5 mmol) and methyl acrylate (0.03 ml, 0.3 mmol). The solution was stirred at 90°C for 3 h. After cooling and evaporation of DMF, the crude residue was purified by column chromatography (eluent petroleum ether–ethyl acetate 7:3) to give **11** (57 mg, 56%) as white crystals; mp 184–185°C (methanol); IR (KBr) ν 1729 (CO) cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.86 (s, 3H, CH_3), 6.45 (d, 1H, J=15.7 Hz, CH=), 6.89 (d, 1H, J=0.7 Hz, H_3), 7.20 (dd, 1H, J=4.7, 7.7 Hz, H_5), 7.42–7.59 (m, 3H, H_{Ar}), 7.82 (dd, 1H, J=1.6, 7.7 Hz, H_4), 8.11 (d, 2H, J=8.0 Hz, H_{Ar}), 8.44 (d, 1H, J=15.7 Hz, CH=), 8.47 (dd, 1H, J=1.6, 4.7 Hz, H_6); ^{13}C NMR (62.90 MHz, $CDCl_3$) δ 52.2 (CH_3), 108.1 (CH), 119.9 (CH), 121.5 (C), 121.5 (CH), 127.9 (2 CH), 129.1 (2 CH), 129.6 (CH), 134.2 (CH), 134.4 (CH), 137.9 (C), 138.8 (C), 146.2 (CH), 149.8 (C), 166.5 (CO); Anal. Calcd for $C_{17}H_{14}N_2O_4S$: C, 59.64; H, 4.12; N, 8.18. Found: C, 59.30; H, 4.29; N, 8.34; MS *m/z* 343 $(M+1)^+$.

2-Methoxy-9-phenylsulfonyl-4-[1-phenylsulfonyl-1*H*-pyrrolo[2,3-*b*]pyridin-2-yl]-9a-[2-methoxycarbonyl-ethenyl]-4,4a,9,9a-tetrahydropyrano[3′,2′:4,5]pyrrolo[2,3-*b*]pyridine (12). Following the procedure used for the preparation of **9** using toluene as solvent instead of 1,2-dichloroethane, compounds **10** and **12** were obtained from **11** (column chromatography: eluent petroleum ether–ethyl acetate 7:3), respectively, in 17 and 20% yield. Compound **12**: mp 143–144°C (methanol); IR (KBr) ν 1730 (CO) cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.80 (s, 3H, CH_3), 3.86 (s, 3H, CH_3), 4.35 (dd, 1H, J_{ca}=1.3 Hz, J_{bc}=8.8 Hz,

H_c), 4.59 (broad d, 1H, J_{ba}=10.1 Hz, H_a), 4.99 (ddd, 1H, J_{ba}=10.1 Hz, J_{bc}=8.8 Hz, $J_{b3'}$=1.4 Hz, H_b), 6.08 (d, 1H, J=16.0 Hz, CH=), 6.16 (d, 1H, $J_{b3'}$=1.4 Hz, $H_{3'}$), 6.67 (dd, 1H, J=5.1, 7.3 Hz, H_{Pyr}), 7.09 (dd, 1H, J=5.3, 7.7 Hz, H_{Pyr}), 7.43–7.62 (m, 8H, 6 H_{Ar}+2 H_{Pyr}), 7.77 (d, 1H, J=16.0 Hz, CH=), 8.04 (dd, 1H, J=1.3, 5.1 Hz, H_{Pyr}), 8.19–8.23 (m, 2H, H_{Ar}), 8.28–8.32 (m, 2H, H_{Ar}), 8.34 (dd, 1H, J=1.9, 5.3 Hz, H_{Pyr}); ^{13}C NMR (62.90 MHz, $CDCl_3$) δ 38.7 (CH), 50.5 (CH), 52.1 (CH_3), 52.7 (CH), 52,9 (CH_3), 69.3 (C), 106.6 (CH), 119.0 (CH), 119.5 (CH), 120.9 (C), 121.0 (C), 123.2 (CH), 128,0 (2 CH), 128.7 (2 CH), 128.8 (2 CH), 129.1 (CH), 129.3 (2 CH), 133.6 (CH), 134.4 (CH), 135.1 (CH), 137.7 (C), 138.7 (C), 140.4 (C), 143.1 (CH), 144.8 (CH), 148.1 (CH), 149.1 (C), 157.2 (C), 166.2 (C), 170.3 (CO); Anal. Calcd for $C_{34}H_{28}N_4O_8S_2$: C, 59.64; H, 4.12; N, 8.18. Found: C, 59.99; H, 4.00; N, 8.31; MS *m/z* 685 $(M+1)^+$.

Dimethyl 9-methyl-9*H*-pyrido[2,3-*b*]indole-7,8-dicarboxylate (13). A solution of compound **6** (190 mg, 0.97 mmol) and dimethyl acetylenedicarboxylate (0.18 ml, 1.46 mmol) in toluene (10 ml) in a sealed tube was heated at 110°C for 24 h. After cooling, the solvent was removed in vacuo. The crude residue was purified by column chromatography (eluent petroleum ether–ethyl acetate 7:3) to afford **13** (143 mg, 40%) as crystals; mp 151–152°C (methanol); IR (KBr) ν 1736, 1710 (CO) cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.96 (s, 3H, CH_3), 3.99 (s, 3H, CH_3), 4.10 (s, 3H, CH_3), 7.21 (dd, 1H, J=4.8, 7.5 Hz, H_{Pyr}), 7.92 (d, 1H, J=7.2 Hz, H_{Ar}), 8.11 (d, 1H, J=7.2 Hz, H_{Ar}), 8.33 (dd, 1H, J=1.5, 7.5 Hz, H_{Pyr}), 8.58 (dd, 1H, J=1.5, 4.8 Hz, H_{Pyr}); ^{13}C NMR (62.90 MHz, $CDCl_3$) δ 28.4 (CH_3), 52.6 (CH_3), 52.9 (CH_3), 114.2 (C), 115.9 (CH), 119.3 (C), 121.0 (CH+C), 121.3 (CH), 125.3 (C), 129.0 (CH), 135.5 (C), 148.0 (CH), 152.8 (C), 166.5 (CO), 169.1 (CO); Anal. Calcd for $C_{16}H_{14}N_2O_4$: C, 64.42; H, 4.73; N, 9.39. Found: C, 64.07; H, 4.81; N, 9.50; MS *m/z* 299 $(M+1)^+$.

Methyl 9-phenylsulfonyl-5,6,7,8-tetrahydro-9*H*-pyrido[2,3-*b*]indole-5-carboxylate (14). Following the procedure used for the preparation of **13**, compound **3** in the presence of methyl acrylate in toluene gave **14** in 21% yield as an oil; IR (film) ν 1735 (CO) cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.88–2.26 (m, 4H, CH_2), 3.02–3.32 (m, 2H, CH_2), 3.67 (s, 3H, CH_3), 3.66–3.80 (m, 1H, CH), 7.12 (dd, 1H, J=4.9, 7.8 Hz, H_{Pyr}), 7.43–7.58 (m, 3H, H_{Ar}), 7.69 (dd, 1H, J=1.2, 7.8 Hz, H_{Pyr}), 8.15 (broad d, 2H, J=8.2 Hz, H_{Ar}), 8.35 (dd, 1H, J=1.2, 4.9 Hz, H_{Pyr}); ^{13}C NMR (62.90 MHz, $CDCl_3$) δ 20.6 (CH_2), 24.5 (CH_2), 25.4 (CH_2), 38.3 (CH), 52.2 (CH_3), 111.9 (C), 118.9 (CH), 121.7 (C), 127.1 (CH), 127.8 (2 CH), 129.0 (2 CH), 133.8 (CH), 137.9 (C), 139.4 (C), 143.9 (CH), 148.5 (C), 173.9 (CO); Anal. Calcd for $C_{19}H_{18}N_2O_4S$: C, 61.61; H, 4.90; N, 7.56. Found: C, 61.35; H, 4.75; N, 7.67; MS *m/z* 371 $(M+1)^+$.

Methyl 9-(phenylsulfonyl)-9*H*-pyrido[2,3-*b*]indole-5-carboxylate (15). *Method A:* Following the procedure used for the preparation of **14**, compound **3** in the presence of methyl propynoate in toluene gave **15** in 21% yield as crystals.

Method B: A solution of **14** (160 mg, 0.27 mmol) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (150 mg, 0.65 mmol) in toluene (10 ml) was heated at reflux for 24 h. After cooling, the solvent was removed in vacuo. The crude residue was partitioned between dichloromethane (10 ml) and 10% sodium hydroxide, then the aqueous phase was separated and extracted with dichloromethane (2×10 ml). The organic phase was dried over $MgSO_4$ and evaporated in vacuo. The crude residue was purified by column chromatography (eluent petroleum ether–ethyl acetate 7:3) to afford **15** (70 mg, 72%) as crystals; mp 176–177°C (ethyl acetate); IR (KBr) ν 1723 (CO) cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.99 (s, 3H, CH_3), 7.30 (dd, 1H, J=4.8, 8.2 Hz, H_{Pyr}), 7.34–7.52 (m, 3H, H_{Ar}), 7.59 (t, 1H, J=8.0 Hz, H_{Ar}), 8.00 (dd, 1H, J=1.0, 8.0 Hz, H_{Ar}), 8.08 (broad d, 2H, J=7.5 Hz, H_{Ar}), 8.58 (dd, 1H, J=1.5, 4.8 Hz, H_{Pyr}), 8.80 (dd, 1H, J=1.0, 8.0 Hz, H_{Ar}), 9.09 (dd, 1H, J=1.5, 8.2 Hz, H_{Pyr}); ^{13}C NMR (62.90 MHz, $CDCl_3$) δ 52.5 (CH_3), 117.4 (C), 119.1 (CH), 119.4 (CH), 122.5 (C), 125.9 (C), 126.8 (CH), 127.4 (CH), 127.7 (2 CH), 128.9 (2 CH), 134.1 (CH), 134.6 (CH), 138.4 (C), 138.6 (C), 147.7 (CH), 151.0 (C), 167.2 (CO); Anal. Calcd for $C_{19}H_{14}N_2O_4S$: C, 62.29; H, 3.85; N, 7.65. Found: C, 62.07; H, 3.81; N, 7.50; MS *m/z* 367 $(M+1)^+$.

Dimethyl 9-(phenylsulfonyl)-9*H*-pyrido[2,3-*b*]indole-5,6-dicarboxylate (16). A solution of **9** (100 mg, 0.2 mmol) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (160 mg, 0.7 mmol) in dry toluene was stirred at reflux under argon for 24 h. After cooling, the solution was diluted with dichloromethane, then washed successively with 10% sodium hydroxide twice and water once. The organic layer was dried over $MgSO_4$ and evaporated in vacuo. The crude residue was purified by column chromatography (eluent petroleum ether–ethyl acetate 7:3) to afford **16** (70 mg, 71%) as white crystals; mp 169–170°C (methanol); IR (KBr) ν 1737, 1719 (CO) cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.96 (s, 3H, CH_3), 4.07 (s, 3H, CH_3), 7.30 (dd, 1H, J=4.8, 7.9 Hz, H_{Pyr}), 7.40–7.59 (m, 3H, H_{Ar}), 8.10 (dd, 1H, J=1.6, 7.9 Hz, H_{Pyr}), 8.16 (d large, 2H, J=8.2 Hz, H_{Ar}), 8.24 (d, 1H, J=9.0 Hz, H_{Ar}), 8.61 (dd, 1H, J=1.6, 4.8 Hz, H_{Pyr}), 8.65 (d, 1H, J=9.0 Hz, H_{Ar}); ^{13}C NMR (62.90 MHz, $CDCl_3$) δ 52.7 (CH_3), 53.2 (CH_3), 115.4 (CH), 116.3 (C), 119.6 (CH), 119.7 (C), 123.0 (C), 127.7 (2 CH), 129.0 (2 CH), 129.7 (CH), 129.8 (C), 130.1 (CH), 134.4 (CH), 138.2 (C), 140.1 (C), 148.1 (CH), 151.0 (C), 165.7 (CO), 168.7 (CO); Anal. Calcd for $C_{21}H_{16}N_2O_6S$: C, 59.43; H, 3.80; N, 6.60. Found: C, 59.76; H, 3.97; N, 6.75; MS *m/z* 425 $(M+1)^+$.

Dimethyl 9*H*-pyrido[2,3-*b*]indole-5,6-dicarboxylate (17). A solution of **16** (80 mg, 0.19 mmol) and freshly prepared tetrabutylammonium fluoride (60 mg, 0.19 mmol) in dry THF was stirred at reflux under argon for 2 h. After cooling, THF was removed in vacuo. The residue was partitioned between ethyl acetate (10 ml) and water (10 ml), then the aqueous phase was separated and extracted with ethyl acetate (2×5 ml). The organic layer was dried over $MgSO_4$ and concentrated in vacuo. The crude oil was purified by column chromatography (eluent petroleum ether–ethyl acetate 6:4) to afford **17** (50 mg, 93%) as white crystals; mp 210–211°C (ethyl acetate); IR (KBr) ν 1728, 1715 (CO) cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.96 (s, 3H, CH_3), 4.15 (s, 3H, CH_3), 7.26 (dd, 1H, J=5.0, 7.8 Hz, H_{Pyr}), 7.60 (d, 1H, J=8.5 Hz, H_{Ar}), 8.17 (d, 1H, J=8.5 Hz, H_{Ar}), 8.27 (dd, 1H, J=1.5, 7.8 Hz, H_{Pyr}), 8.57 (dd, 1H, J=1.5, 5.0 Hz, H_{Pyr}), 11.23 (s, 1H, NH); ^{13}C NMR (62.90 MHz, $CDCl_3$) δ

52.5 (CH_3), 53.1 (CH_3), 111.9 (CH), 114.9 (CH), 116.5 (C), 117.2 (C), 119.3 (C), 128.5 (CH), 130.3 (C), 130.6 (CH), 141.4 (C), 146.3 (CH), 152.6 (C), 166.5 (CO), 169.6 (CO); Anal. Calcd for $C_{15}H_{12}N_2O_4$: C, 63.38; H, 4.25; N, 9.85. Found: C, 63.06; H, 4.38; N, 10.02; MS *m/z* 285 $(M+1)^+$.

Dimethyl 9-methyl-9*H*-pyrido[2,3-*b*]indole-5,6-dicarboxylate (18). Following the procedure used for the preparation of **6**, compound **18** was obtained from **17** (column chromatography: eluent petroleum ether–ethyl acetate 4:6) in 62% yield as white crystals; mp 200–202°C (ethyl acetate); IR (KBr) ν 1704, 1719 (CO) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 3.95 (s, 3H, CH_3), 3.98 (s, 3H, CH_3), 4.13 (s, 3H, CH_3), 7.21 (dd, 1H, J=4.7, 7.8 Hz, H_{Pyr}), 7.50 (d, 1H, J=8.5 Hz, H_{Ar}), 8.18 (d, 1H, J=8.5 Hz, H_{Ar}), 8.21 (dd, 1H, J=1.5, 7.8 Hz, H_{Pyr}), 8.55 (dd, 1H, J=1.5, 4.7 Hz, H_{Pyr}); ^{13}C NMR (62.90 MHz, $CDCl_3$) δ 28.1 (CH_3), 52.5 (CH_3), 53.2 (CH_3), 109.6 (CH), 114.3 (C), 116.4 (CH), 117.2 (C), 119.0 (C), 128.4 (CH), 129.9 (CH), 130.4 (C), 142.7 (C), 147.4 (CH), 152.4 (C), 166.6 (CO), 169.7 (CO); Anal. Calcd for $C_{16}H_{14}N_2O_4$: C, 64.42; H, 4.73; N, 9.39. Found: C, 64.67; H, 4.60; N, 9.23; MS *m/z* 299 $(M+1)^+$.

2-[2-(Dimethylamino)ethyl]-6-methyl-1,2,3,6-tetrahydropyrido[2,3-*b*]pyrrolo[3,4-*e*]indole-1,3-dione (19). A solution of **18** (100 mg, 0.3 mmol) in *N,N*-dimethylethylenediamine (10 ml) was stirred at 100°C for 24 h. After evaporation, the crude residue was purified by column chromatography (eluent ethyl acetate–methanol 9:1) to give **19** (58 mg, 54%) as yellow crystals; mp 158–159°C (methanol); IR (KBr) ν 1697, 1759 (CO) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 2.33 (s, 6H, CH_3), 2.66 (t, 2H, J=6.6 Hz, CH_2), 3.88 (t, 2H, J=6.6 Hz, CH_2), 4.04 (s, 3H, NCH_3), 7.32 (dd, 1H, J=4.9, 7.8 Hz, H_{Pyr}), 7.68 (d, 1H, J=8.2 Hz, H_{Ar}), 7.96 (d, 1H, J=8.2 Hz, H_{Ar}), 8.12 (dd, 1H, J=1.6, 4.9 Hz, H_{Pyr}), 9.18 (dd, 1H, J=1.6, 7.8 Hz, H_{Pyr}); ^{13}C NMR (62.90 MHz, $CDCl_3$) δ 28.2 (CH_3), 35.9 (CH_2), 45.6 (2 CH_3), 57.4 (CH_2), 112.9 (CH), 113.7 (C), 116.8 (C), 116.9 (CH), 120.7 (CH), 124.1 (C), 125.9 (C), 133.9 (CH), 144.0 (C), 148.5 (CH), 153.0 (C), 169.0 (CO), 169,3 (CO); Anal. Calcd for $C_{18}H_{18}N_4O_2$: C, 67.07; H, 5.63; N, 17.38. Found: C, 67.29; H, 5.74; N, 17.26; MS *m/z* 323 $(M+1)^+$.

2-[2-(Dimethylamino)ethyl]-10-methyl-1,2,3,10-tetrahydropyrido[2,3-*b*]pyrrolo[3,4-*g*]indole-1,3-dione (20). Following the procedure used for the preparation of **19**, compound **20** was obtained from **13** (column chromatography: eluent ethyl acetate–methanol 93:7) in 60% yield as yellow crystals; mp 189–190°C (methanol); IR (KBr) ν 1762, 1698 (CO) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 2.33 (s, 6H, CH_3), 2.65 (t, 2H, J=6.7 Hz, CH_2), 3.87 (t, 2H, J=6.7 Hz, CH_2), 4.51 (s, 3H, CH_3), 7.28 (dd, 1H, J=5.0, 8.2 Hz, H_{Pyr}), 7.73 (d, 1H, J=7.7 Hz, H_{Ar}), 8.34 (d, 1H, J=7.7 Hz, H_{Ar}), 8.37 (dd, 1H, J=1.5, 8.2 Hz, H_{Pyr}), 8.64 (dd, 1H, J=1.5, 5.0 Hz, H_{Pyr}); ^{13}C NMR (62.90 MHz, $CDCl_3$) δ 32.1 (CH_3), 36.0 (CH_2), 45.6 (2 CH_3), 57.2 (CH_2), 114.1 (CH+C), 114.8 (C), 116.5 (CH), 125.9 (CH), 127.2 (C), 128.8 (CH), 131.5 (C), 135.8 (C), 148.3 (CH), 153.2 (C), 167.9 (CO), 168.8 (CO); Anal. Calcd for $C_{18}H_{18}N_4O_2$: C, 67.07; H, 5.63; N, 17.38. Found: C, 66.81; H, 5.70; N, 17.25; MS *m/z* 323 $(M+1)^+$.

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10. For each compound, a conformational search using the random search process as implemented in SYBYL was performed to identify its lowest energy conformations. Only the conformer with the lowest energy has been kept for reoptimisation with the semiempirical MOPAC package version 6.0 using Hamiltonian AM1. This work was conducted by E. Vangrevelinghe.
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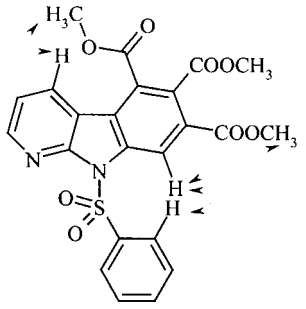
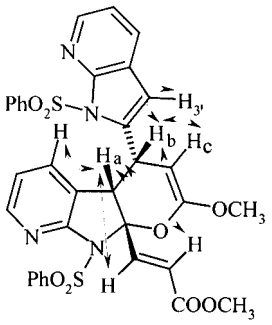
17. Correlations in the NOESY spectra of **10** and **12**



10



12

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