**HETEROCYCLES, Vol. 60, No. 4, 2003, pp. 865 - 877**
**Received, 18th December, 2002, Accepted, 6th February, 2003, Published online, 10th February, 2003**

# SYNTHESIS OF NEW MELATONIN ANALOGUES FROM DIMERS OF AZAINDOLE AND INDOLE BY USE OF SUZUKI HOMOCOUPLING

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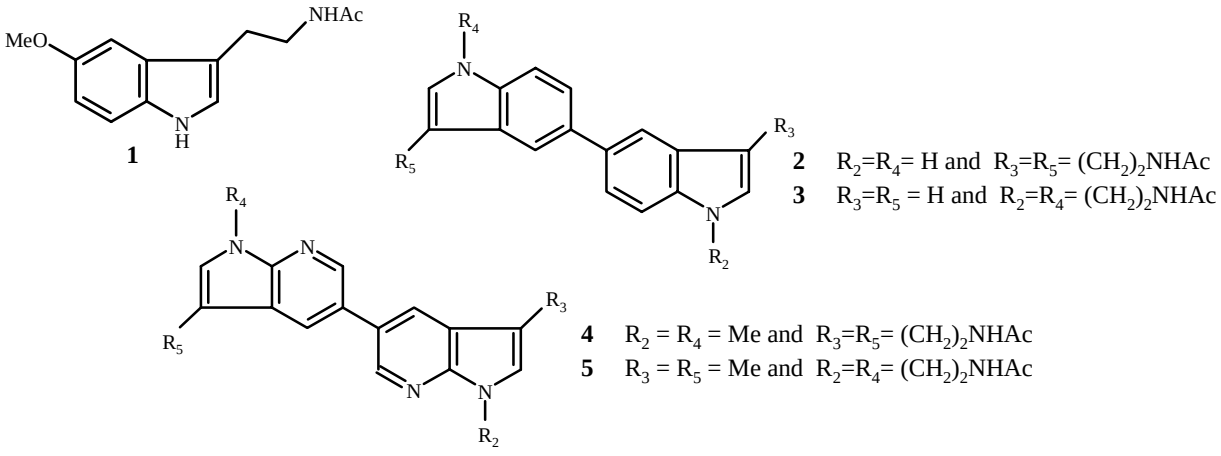
**Abstract**- *N*-{2-[3'-(2-Acetylaminoethyl)-1*H*,1'*H*-[5,5']biindol-3-yl]- and *N*-{2-[1'-(2-acetylaminoethyl)-1'*H*-[5,5']biindol-1-yl]ethyl}acetamide (**2,3**) and their analogues in 7-azaindole series (**4,5**) were synthesized by palladium catalysed reaction starting from indole or 7-azaindole using [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium, as catalyst.

Melatonin (**1**)**,** a pineal hormone, plays a major role in the regulation of seasonal cycles and the control of circadian rhythms[1,2] and has been the focus of considerable clinical interest.[3] Two human melatonin receptors have been cloned[4,5] and defined as MT1 and MT2 receptors.[6] These two receptors belong to the family of seven-transmembrane domain G-protein-coupled receptors. Both receptors have similar binding for melatonin and display similar rank orders for the binding of reference melatonin ligands despite 60% homology between the two receptors. The synthesis of selective melatonin analogues is still a challenge, it is why our attention has been focused on developing a catalytic approach to dimers of indoles (**2,3**) and 7-azaindoles (**4,5**) (Figure 1).

Figure 1




Palladium catalysed cross-coupling between aryl boronic acids and haloarenes or aryl triflates has been shown to be a versatile method for the preparation of biaryls.[7] Suzuki *et al.*[8] recently reported the preparation of *cis*-diborylalkene *via* its transition metal catalysed addition with tetraalkoxydiboron (**6**). Moreover the alkoxydiboron (**6**) which is thermally stable and easily handled in air, has been shown to be

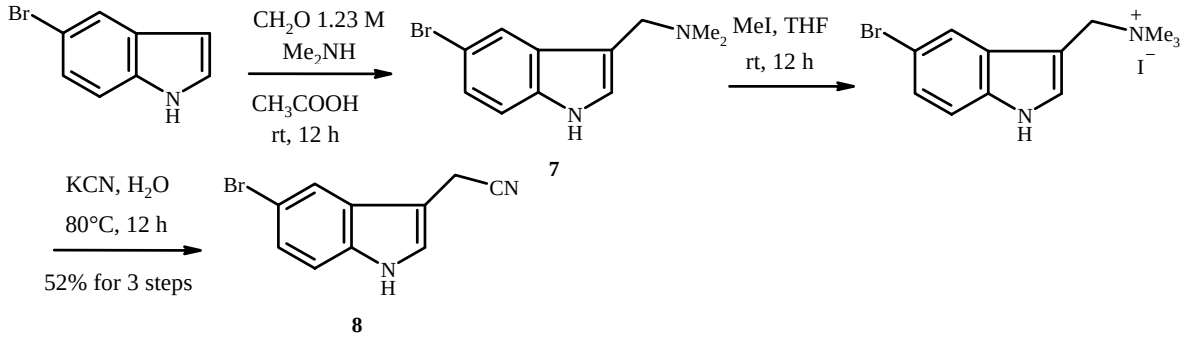
a useful boron nucleophile for the cross or homocoupling reaction with aryl halides.[9,10] Thus we have used this method for a one-pot preparation of symmetrical bi-indoles and bi-azaindoles *via* a modified *in situ* Suzuki homocoupling reaction.

## RESULTS AND DISCUSSION

### Synthesis of *N*-{2-[ 3'-(2-acetylaminoethyl)-1*H*,1'*H*-[5,5']biindol-3-yl]ethyl}acetamide (2)

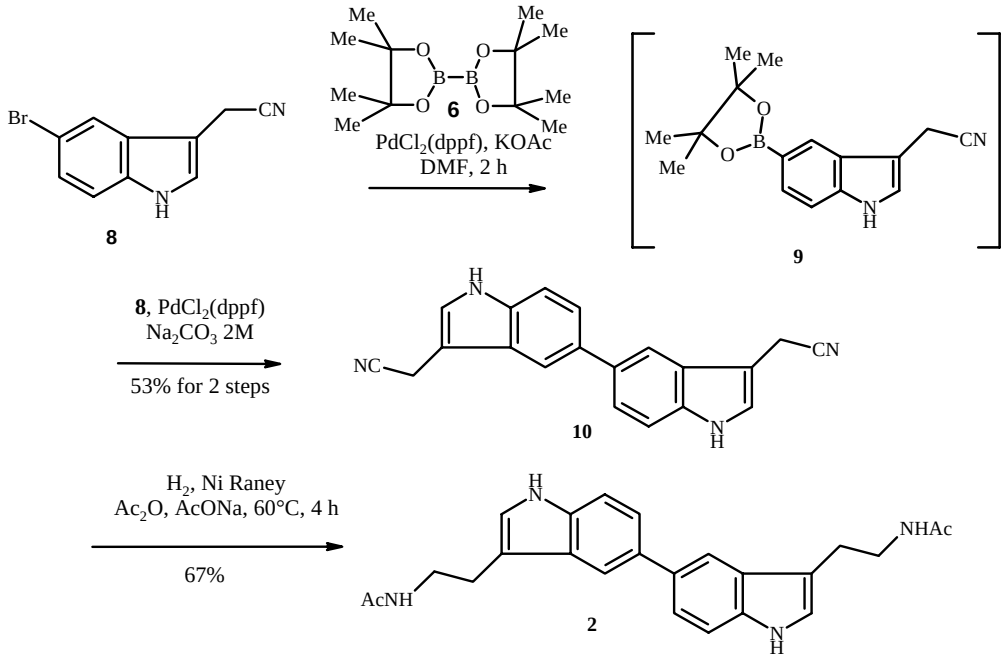
The synthesis of 5-bromo-3-(*N*,*N*-dimethylamino)methylindole (**7**) was accomplished *via* Mannich's reaction[11] with 5-bromoindole in the presence of formaldehyde and dimethylamine in acetic acid. Next, treatment of **7** with methyl iodide in THF followed by a nucleophilic substitution with potassium cyanide afforded the nitrile (**8**)[12] in 52% overall yield from 5-bromoindole (Scheme 1).

Scheme 1




The homocoupling of (5-bromo-1*H*-indol-3-yl)acetonitrile (**8**) using borane (**9**) generated *in situ* gave the corresponding dimer (**10**) in 53% yield, which was converted to the final compound (**2**) after hydrogenation over Raney nickel and concomitant *N*-acetylation in 67% overall yield from **10** (Scheme 2).

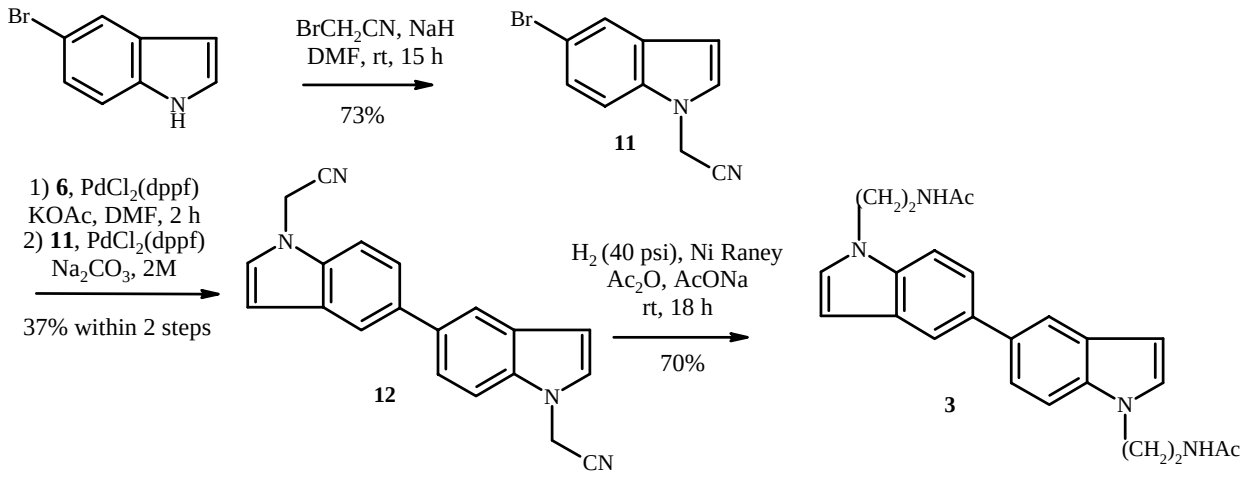
Scheme 2



**Synthesis of *N*-{2-[ 1'-(2-acetylaminoethyl)-1'*H*-[5,5']biindol-1-yl]ethyl}acetamide (3)**

The reaction of 5-bromoindole with sodium hydride followed by an addition of bromoacetonitrile provided **11** in 73% yield. Using the method described above, dimer (**12**) was prepared in 2 steps from **10** in 37 % yield ; the nitrile group was then reduced to acetamide on Raney nickel in acetic anhydride to give dimer (**3**) with a moderate yield (70%) (Scheme 3).

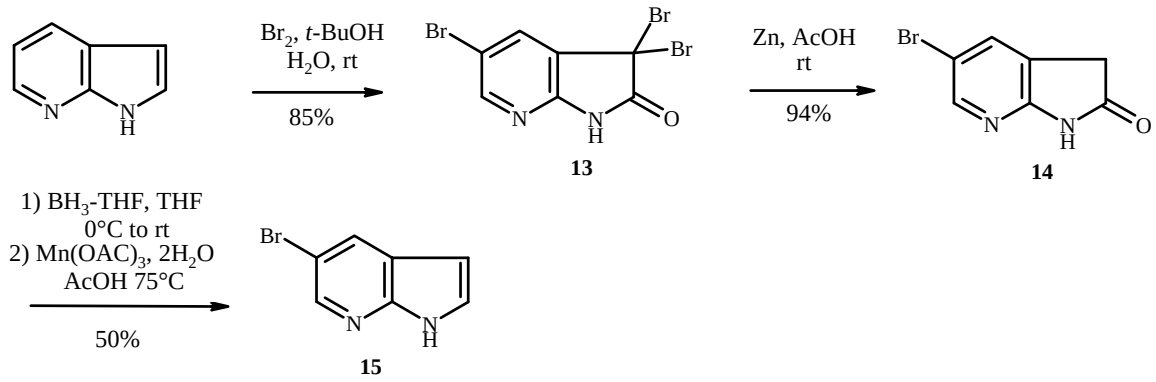
Scheme 3




**Synthesis of *N*-{2-[ 3'-(2-acetylaminoethyl)-1,1'-dimethyl-1*H*,1'*H*-[5,5']bi[pyrrolo[2,3-*b*]pyridin]-3-yl]ethyl}acetamide (4)**

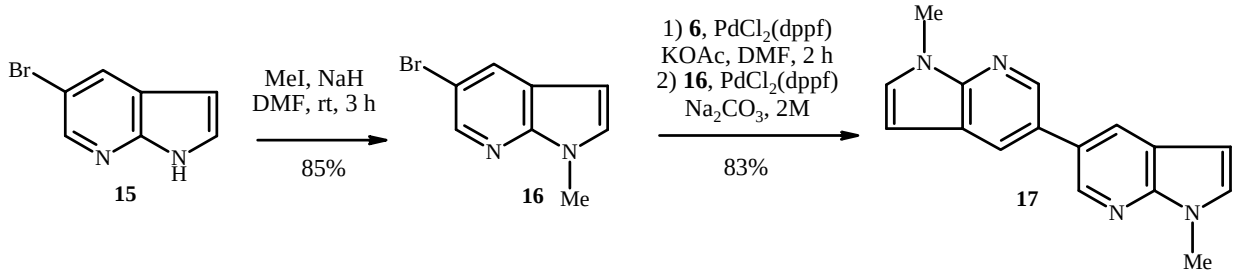
The required 5-bromo-7-azaindole (**15)** was prepared in 4 steps from 7-azaindole. The first step involved bromination with bromine in a mixture of *t*-butanol and water at room temperature to provide the tribromo derivative (**13**) (85%). 3,3,5-Tribromo-2-oxo-1,3-dihydropyrrolo[2,3-*d*]pyridine (**13**) was then treated with zinc in acetic acid to give **14** in 94% yield.[13] Reduction of the amide function was realised with the borane-tetrahydrofuran complex. The resulting indoline was oxidised by heating in acetic acid in the presence of manganese triacetate to provide 7-azaindole (**15**) in a 50% overall yield (Scheme 4).

Scheme 4



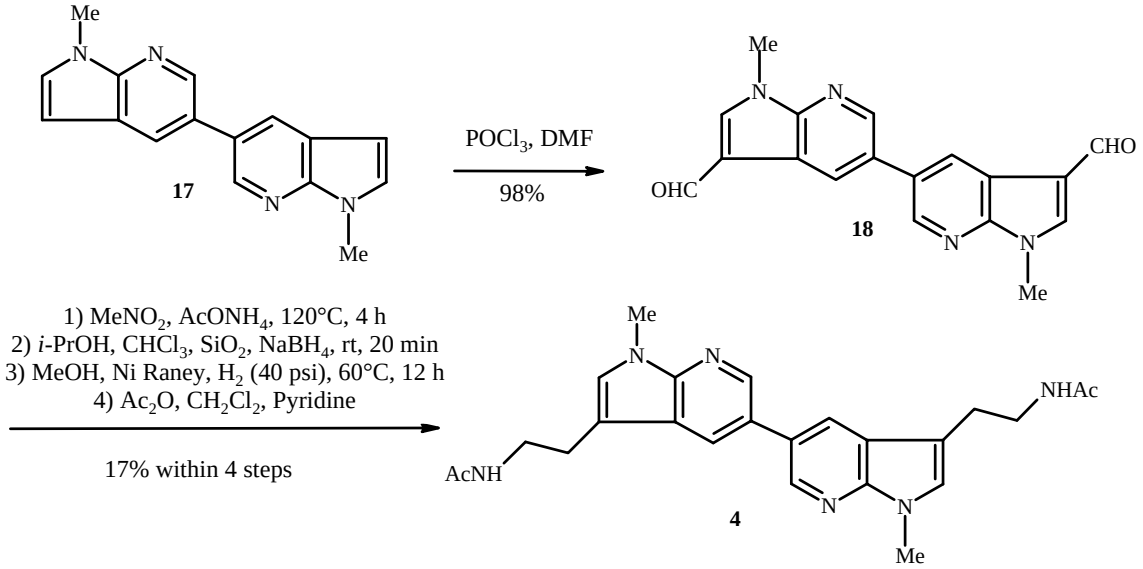

Treatment of **15** with methyl iodide in the presence of sodium hydride in *N*,*N*-dimethylformamide lead to product (**16**) in good yield (85%) which then underwent the modified Suzuki's homocoupling described above to give the corresponding dimer (**17**) in good yield (83%) (Scheme 5).

Scheme 5




According to the C-3 formylation of the indole ring descrided in the literature,[14] we have also introduced a formyl group regioselectively at the C-3 position of compound (**18)** under Vilsmeier-Haack conditions. Subsequent chemical modifications converted the formyl group into *N*-ethylacetamide side chain. Indeed, reaction of aldehyde (**18**) with ammonium acetate in nitromethane led to a nitrovinylic derivative. Treatment of the latter one with sodium borohydride and silica gel in a mixture of chloroform and 2-propanol furnished the corresponding nitro compound. Next the amido group was obtained by catalytic hydrogenation on Raney nickel in methanol followed by acetylation using acetic anhydride and pyridine in dichloromethane. The expected amide (**4**) was prepared in 17% overall yield (Scheme 6).

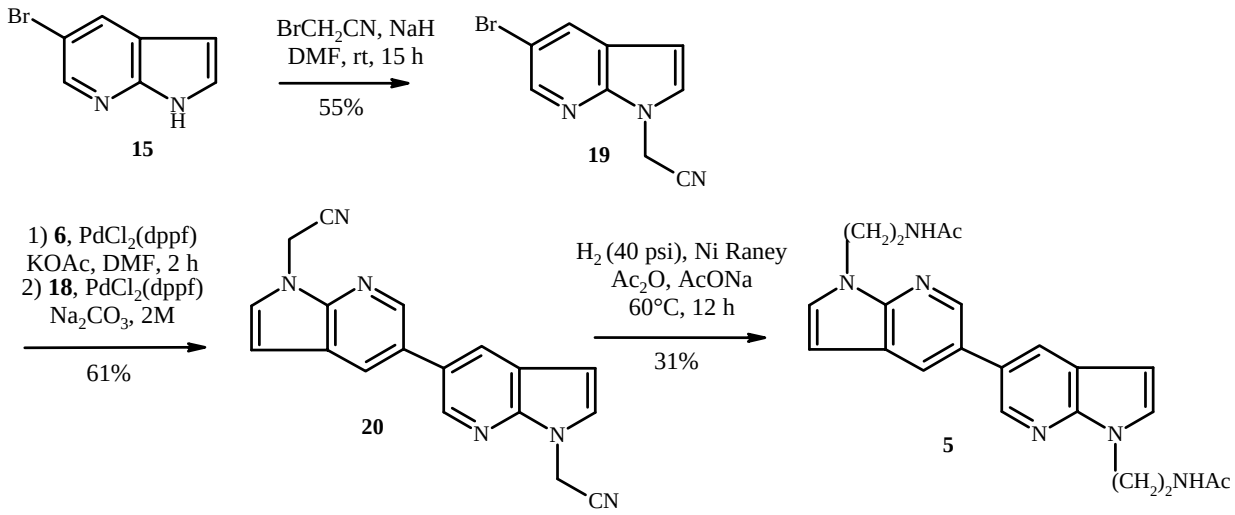
Scheme 6




**Synthesis of *N*-{2-[1'-(2-acetylaminoethyl)-1'*H*-[5,5']bi[pyrrolo[2,3-*b*]pyridin]-1-yl]ethyl}acetamide (5)**

Compound (**5**) was prepared according to the synthetic sequence illustrated in Scheme 7. The first step involved a reaction of **15** with sodium hydride followed by addition of bromoacetonitrile to generate compound (**19)** in 55% yield. Homocoupling using tetra-alkoxydiboron (**6**) provided the corresponding dimer (**20**). The reduction of the nitrile group using hydrogen on Raney nickel in acetic anhydride afforded the desired dimer (**5**) in 31% yield. Low yield of the last step is explained by difficulties encountered during the purification.

Scheme 7




In conclusion, this paper reports the synthesis of an analogue of melatonin which possess an 7-azaindole or an indole skeleton. As a result of these syntheses, we have developed several new procedures allowing access to the dimers using a modified *in situ* Suzuki homocoupling.

## EXPERIMENTAL

Melting points are uncorrected. $^{1}$H-NMR and $^{13}$C-NMR spectra were recorded on a Bruker AM-300 WB (300 MHz). The coupling constants are recorded in Hz and the chemical shifts are reported in ppm (δ, ppm) downfield from TMS which was used a internal standard. IR spectra were obtained with a Perkin-Elmer FT Paragon 1000 PC. MS spectra were registered on a Perkin-Elmer SCIEX API 3000 spectrometer. Reaction products were purified by flash chromatography using silica gel (Merck 230-400 mesh). Analytical TLC was carried out on silica gel $F_{254}$ plates. All anhydrous reactions were performed in oven-dried glassware under an atmosphere of argon. Anhydrous solvents were transferred *via* syringe.

**5-(Bromo-1*H*-indol-3-yl)acetonitrile (8)**

Dimethylamine (2.12 mL, 16.83 mmol) and formaldehyde (13.70 mL 1.23 M solution, 16.83 mmol) were respectively added to a solution of acetic acid at 5°C. The mixture was stirred an additional time (5 min) with continued cooling. After, the 5-bromoindole (3 g, 15.30 mmol) was added and the mixture was stirred for 12 h, allowing the temperature to increase slowly at room rt. After cooling at 0°C, the mixture was basified using 10% sodium hydroxide solution (16 mL). The white precipitate that separated was filtered under vacuum and dried. The product (**7**) without purification, was then taken up in THF (50 mL) under an inert atmosphere and methyl iodide (2.4 g, 16.83 mmol) was added at 0°C. The solution which resulted was stirred at rt for 12 h. The solvent was removed in vacuo and the crude residue was taken up in 5% aqueous sodium hydroxide (30 mL) and potassuim cyanid (9.94 g, 153 mmol) was added. The mixture was heated slowly at 80°C during 12 h, cooled at rt and then extracted with ethyl acetate. The

combined organic extracts were dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (eluent : light petroleum/ethyl acetate, 1/1) to give compound (**8**) (1.86 g, 52% within 3 steps) as a colourless oil : IR (film) ν : 3377, 2915, 2249 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) δ : 3.72 (s, 2H, C**H**$_2$CN), 7.11 (d, 1H, J = 2.2 Hz, **H**$_2$), 7.20 (d, 1H, J =8.7 Hz, **H**$_7$), 7.28 (dd, 1H, J = 8.7 Hz, J = 1.7 Hz, **H**$_6$), 7.67 (d, 1H, J = 1.7 Hz, **H**$_4$), 8.52 (s, 1H, N**H**). $^{13}$C-NMR ($CDCl_3$) δ : 14.6 (**C**$H_2$CN), 104.3 (**C**$_3$), 113.6 (**C**$_2$), 118.6 (**C**$_q$), 121.0 (**C**H), 121.1 (**C**$_q$), 124.7 (**C**H), 126.1 (**C**H), 128.0 (**C**$_{7a}$), 135.3 (**C**$_5$). MS (IS) *m/z* : 235 (M+1 for $^{79}$Br) *m/z* = 237 (M+1 for $^{81}$Br). *Anal.* Calcd for $C_{10}H_7N_2Br$ : C, 51.09 ; H, 3.00 ; N, 11.92 ; Br, 33.99. Found : C,51.06 ; H,2.98 ; N,11.89 ; Br, 33.95.

**(3'-Cyanomethyl-1*H*,1'*H*-[5,5']biindol-3-yl)acetonitrile (10)**

Under an inert atmosphere, bis(pinacolato)diborane (**6**) (0.32 g, 1.27 mmol), potassium acetate (0.25 g, 2.55 mmol), and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (0.07 g, 0.01 mmol) were added to a stirred solution of **7** (0.2 g , 0.85 mmol) in dry DMF (5 mL). The mixture was stirred at 80°C under nitrogen for 2 h. After cooling the solution to rt, **8** (0.4 g, 1.7 mmol), [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (0.07 g, 0.01 mmol) and 2 M $Na_2CO_3$ (2.25 mL, 4.25 mmol) were added and the mixture was stirred at 80°C under nitrogen overnight. The solution was cooled to rt, the product was extracted with dichloromethane (15 mL) and washed with water (15 mL), brine and dried over anhydrous $MgSO_4$. Finally, purification by flash chromatography on silica gel using 40% ethyl acetate in light petroleum as eluent gave 140 mg (53%) of (3'-cyanomethyl-1*H*,1'*H*-[5,5']biindol-3-yl)acetonitrile (**10**) as white needles. mp 206-207°C (pentane). IR (KBr) ν : 3405, 2918, 2250 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) δ : 3.87 (s, 4H, C**H**$_2$CN), 7.23 (s, 2H, **H**$_2$), 7.44 (d, 2H, J = 8.5 Hz, **H**$_7$), 7.54 (dd, 2H, J = 8.5 Hz, J =1.4 Hz, **H**$_6$), 7.77 (d, 2H, J = 1.4 Hz, **H**$_4$), 8.41 (s, 2H, N**H**). $^{13}$C-NMR ($CDCl_3$) δ : 14.4 (2x**C**$H_2$CN), 103.3 (2x**C**$_3$), 111.8 (2x**C**$_2$), 118.3 (2x**C**H), 120.3 (2x**C**N), 123.2 (2x**C**H), 123.7 (2x**C**H), 126.5 (2x**C**$_q$), 134.7 (2x**C**$_q$), 135.4 (2x**C**$_q$). MS (IS) *m/z* = 311 (M+1). *Anal.* Calcd for $C_{20}H_{14}N_4$ : C, 77.40 ; H, 4.55 ; N, 18.05. Found : C,77.61 ; H,4.58 ; N, 18.12.

***N*-{2-[ 3'-(2-Acetylaminoethyl)-1*H*,1'*H*-[5,5']biindol-3-yl]ethyl}acetamide (2)**

A solution of compound (**10**) (0.12 g, 0.39 mmol) in acetic anhydride (30 mL) was hydrogenated over Raney nickel (0.01 g) in the presence of sodium acetate (0.13 g, 1.56 mmol) for 4 h at 60°C. The reaction was cooled to rt and the catalyst was filtered on Celite and the filtrate concentrated in vacuo. The residue was taken up in dichloromethane, washed with water and dried over anhydrous $MgSO_4$. After removal of the solvent, the crude residue was chromatographed over silica gel (eluent : ethyl acetate/methanol : 9/1) to afford **2** (0.105 g, 67%) as a white solid. mp 237-238°C (pentane). IR (KBr) ν : 3406**,** 3260, 2925, 1629 $cm^{-1}$. $^1$H-NMR ($CD_3OD$) δ : 1.91 (s, 6H, COC**H**$_3$), 2.99 (t, 4H, J = 7.2 Hz, **H**$_{1'}$), 3.51 (t, 4H, J = 7.2 Hz, **H**$_{2'}$), 7.09 (s, 2H, **H**$_2$), 7.38 (d, 2H, J = 8.2 Hz, **H**$_7$), 7.44 (dd, 2H, J = 8.2 Hz, J = 1.5 Hz, **H**$_6$),

7.79 (d, 2H, J = 1.5 Hz, **H**$_4$). $^{13}$C-NMR ($CD_3OD$) δ : 21.2 (2xCO**C**$H_3$), 24.9 (2x**C**$_{1'}$), 40.4 (2x**C**$_{2'}$), 110.9 (2x**C**$_2$), 112.2 (2x**C**$_3$), 116.1 (2x**C**$_7$), 121.6 (2x**C**H), 122.5 (2x**C**H), 127.9 (2x**C**$_q$), 133.7 (2x**C**$_q$), 135.9 (2x**C**$_q$), 171.9 (2x**C**O). MS (IS) *m/z* = 403 (M+1). *Anal.* Calcd for $C_{22}H_{24}N_2$ : C, 83.50 ; H, 7.64 ; N, 8.85. Found : C, 83.8 ; H, 7.58 ; N, 8.83.

**(5-Bromoindo-1-yl)acetonitrile (11)**

Under an inert atmosphere, sodium hydride (60% in oil, 0.18 g, 7.65 mmol) was added to a stirred solution of 5-bromoindole (1 g, 5.10 mmol) in *N*,*N*-dimethylformamide 99.8% (25 mL) at 0°C during 30 min. The addition was finished, the mixture was stirred an additional time (30 min) under continued cooling. After, the bromoacetonitrile (1.22 mL, 10.20 mmol) was added dropwise and the mixture was stirred for 12 h, allowing the temperature to increase at rt. Then water was added, the product was extracted with dichloromethane, purified by flash chromatography on silica gel (eluent : light petroleum/ethyl acetate : 85/15) to give compound (**11**) (0.78 g, 65%) as yellow solid. mp 94-95°C (pentane). IR (KBr) ν : 2967, 2258 cm$^{-1}$. $^1$H-NMR ($CDCl_3$) δ : 4.97 (s, 2H, C**H**$_2$CN), 6.55 (dd, 1H, J = 3.5 Hz, J = 0.2 Hz, **H**$_3$), 7.09 (d, 1H, J = 3.5 Hz, **H**$_2$), 7.23 (d, 1H, J = 8.5 Hz, **H**$_7$), 7.39 (dd, 1H, J = 8.5 Hz, J = 1.7 Hz, **H**$_6$), 7.78 (d, 1H, J = 1.7 Hz, **H**$_4$). $^{13}$C-NMR ($CDCl_3$) δ : 34.8 (**C**$H_2$CN), 104.1 (**C**$_3$), 110.6 (**C**$_2$), 114.4 (**C**$_q$), 114.6 (**C**$_q$), 124.5 (**C**H), 126.2 (**C**H), 128.7 (**C**H), 131 (**C**$_q$), 134.8 (**C**$_q$). MS (IS) *m/z* = 235 (M+1, for $^{79}$Br), *m/z* = 237 (M+1, for $^{81}$Br). *Anal.* Calcd for $C_{10}H_7N_2Br$ : C, 51.09 ; H, 3.00 ; N, 11.92 ; Br, 33.99. Found : C, 51.20 ; H, 2.98 ; N,11.90 ; Br, 34.01.

**(1'-Cyanomethyl-1'*H*-[5,5']biindol-1-yl)acetonitrile (12)**

Under an inert atmosphere, bis(pinacolato)diborane (**6**) (0.32 g, 1.27 mmol), potassium acetate (0.25 g, 2.55 mmol), and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium (II) (0.07 g, 0.01 mmol) were added to a stirred solution of **11** (0.2 g , 0.85 mmol) in dry DMF (5 mL). The mixture was stirred at 80°C under nitrogen for 2 h. After cooling the solution to rt, **11** (0.4 g, 1.7 mmol), [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (0.07 g, 0.01 mmol) and 2 M $Na_2CO_3$ (2.25 mL, 4.25 mmol) were added and the mixture was stirred at 80°C, under nitrogen overnight. The solution was cooled to rt, the product was extracted with dichloromethane (15 mL) and washed with water (15 mL), brine and dried over anhydrous $MgSO_4$. Finally, purification by flash chromatography on silica gel using 30% ethyl acetate in light petroleum as eluent gave 140 mg (53%) of (1'-cyanomethyl-1'*H*-[5,5']biindol-1-yl)acetonitrile (**12**) as white needles. mp 201-202°C (pentane). IR (KBr) ν : 2913, 2252 cm$^{-1}$. $^1$H-NMR (DMSO-$d_6$) δ : 5.55 (s, 4H, C**H**$_2$CN), 6.59 (d, 2H, J = 3.2 Hz, **H**$_3$),7.44(d,2H, J = 3.2 Hz, **H**$_2$), 7.56 (dd, 2H, J = 8.7 Hz, J = 1.7 Hz, **H**$_6$), 7.65 (d, 2H, J = 8.7 Hz, **H**$_7$), 7.85 (d, 2H, J = 1.7 Hz, **H**$_4$). $^{13}$C (DMSO-$d_6$) δ : 34.4 (2x**C**$H_2$CN), 103.8 (2x**C**$_3$), 110.9 (2x**C**$_2$), 117.5 (2x**C**$_q$), 119.8 (2x**C**$_7$), 122.7

(2x**C**H), 129.9 (2x**C**H), 130.1 (2x$\mathbf{C}_q$), 134.8 (2x$\mathbf{C}_q$), 135.7 (2x$\mathbf{C}_q$). MS (IS) *m/z* = 311 (M+1). *Anal.* Calcd for $C_{20}H_{14}N_4$ : C, 77.40 ; H, 4.55 ; N, 18.05. Found : C, 77.86 ; H, 4.62 ; N, 18.20.

***N*-{2-[ 1'-(2-Acetylaminoethyl)-1'*H*-[5,5']biindol-1-yl]ethyl}acetamide (3)**

A solution of compound (**12**) (0.12 g, 0.39 mmol) in acetic anhydride (30 mL) was hydrogenated (40 psi) over Raney nickel (0.01 g) in the presence of sodium acetate (0.13 g, 1.56 mmol) for 4 h at 60°C. The reaction was cooled to rt and the catalyst was filtered on Celite and the filtrate concentrated in vacuo. The residue was taken up in dichloromethane, washed with water and dried over anhydrous $MgSO_4$. After removal of the solvent, the crude residue was chromatographed over silica gel (eluent : ethyl acetate/methanol : 9/1) to afford **3** (0.11 g, 70%) as a white solid. mp 236-237°C (pentane). IR (KBr) ν : 3273, 2929, 1637 $cm^{-1}$. $^1$H-NMR (DMSO-$d_6$) δ : 1.77 (s, 6H, COC$\mathbf{H}_3$), 3.40 (t, 4H, J = 6.2 Hz, $\mathbf{H}_{2'}$), 4.24 (t, 4H, J = 6.2 Hz, $\mathbf{H}_{1'}$), 6.47 (d, 2H, J = 3.4 Hz, $\mathbf{H}_3$), 7.33 (d, 2H, J = 3.4 Hz, $\mathbf{H}_2$), 7.45 (dd, 2H, J = 8.5 Hz, J = 1.5 Hz, $\mathbf{H}_6$), 7.51 (d, 2H, J = 8.5 Hz**,** $\mathbf{H}_7$), 7.78 (d, 2H, J = 1.5 Hz, $\mathbf{H}_4$), 7.99 (t, 2H, J = 5.3 Hz, N**H**Ac). $^{13}$C (DMSO-$d_6$) δ : 23.4 (2xCO**C**$H_3$), 40 (2x$\mathbf{C}_{1'}$), 45.8 (2x$\mathbf{C}_{2'}$), 100.8 (2x$\mathbf{C}_3$), 110.7 (2x$\mathbf{C}_2$), 119.2 (2$\mathbf{C}_4$), 121.7 (2x$\mathbf{C}_6$) 129.8 (2x**C**H), 130.1 (2x$\mathbf{C}_{7a}$), 134.7 (2x$\mathbf{C}_q$), 135.8 (2x$\mathbf{C}_q$), 170.3 (2x**C**O). MS (IS) *m/z* = 403 (M+1). ). *Anal.* Calcd for $C_{24}H_{26}N_4O_2$ : C, 71.62 ; H, 6.51 ; N, 13.92. Found : C, 71.34 ; H, 6.66 ; N, 13.68.

**5-Bromo-1*H*-pyrrolo[2,3-*b*]pyridine (15)**

Under an inert atmosphere, a solution of borane-tetrahydrofuran complex (37.6 mL, 1 M solution in THF, 37.6 mmol) was added dropwise to a suspension of 5-bromo-1,3-dihydro-2-oxopyrrolo[2,3-*b*]pyridine (**14**)[11] (2.00 g, 9.4 mmol) in dry THF (30 mL) at 0°C. After all complex was added, the mixture was stirred an additional time (35 min) at rt. The solvent was then removed under reduced pressure. The residue was dilued with a solution of hydrochloric acid (20 mL, 6 M) and heated until the complete dissolution of the solid. After cooling at 10°C, the mixture was basified using 10% sodium hydroxide solution until pH = 9 and extracted with ethyl acetate. The combined extracts were dried over anhydrous $MgSO_4$. Removal of the solvent in vacuo, the product was dissolved in acetic acid (20 mL) and the resulting solution was added to a suspension of manganese triacetate (4.1 g, 15.28 mmol) in acetic acid (20 mL). After, the mixture was heated at 75°C for 45 min and the solvent was removed under reduced pressure. The crude was taken up in water, basified with saturated hydrogenocarbonate solution and extracted with ethyl acetate. The combined extracts were dried over anhydrous $MgSO_4$. Removal of the solvent in vacuo, the product was purified by flash chromatography on silica gel (eluent : light petroleum/ethyl acetate : 8/2) to afford compound (**15**) (0.92 g, 50% within 2 steps) as a yellow solid. mp 176-177°C (pentane). IR (KBr) ν : 3300-3000 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) δ : 6.39 (d, 1H, J = 2.9 Hz, $\mathbf{H}_3$), 7.30 (d, 1H, J = 2.9 Hz, $\mathbf{H}_2$), 8.01 (d, 1H, J = 2.2 Hz, $\mathbf{H}_4$), 8.29 (d, 1H, J = 2.2 Hz, $\mathbf{H}_6$), 10.9 (s, 1H, N**H**).

$^{13}$C-NMR ($CDCl_3$) δ : 100 (**C**$_3$), 111. 1 (**C**$_q$), 121.9 (**C**$_q$), 126.5 (**C**H), 130.9 (**C**H), 142.4 (**C**H), 146.6 (**C**$_q$). MS (IS) *m/z* = 198 (M+1). *Anal.* Calcd for $C_7H_5N_2Br$ : C, 42.67 ; H, 2.56 ; N, 14.22 ; Br, 40.55. Found : C, 42.81 ; H, 2.55 ; N, 14.48 ; Br, 40.49.

**5-Bromo-1-methyl-1*H*-pyrrolo[2,3-*b*]pyridine (16)**

Under an inert atmosphere, sodium hydride (60% in oil, 0.36 g, 15.23 mmol) was added to a stirred solution of 5-bromo-1*H*-pyrrolo[2,3-*b*]pyridine (**15**) (2.00 g, 10.15 mmol) in *N*,*N*-dimethylformamide (75 mL) at 0°C for 30 min. Then the mixture was stirred an additional time (30 min) under continued cooling. Then methyl iodide (2.16 g, 15.23 mmol) was added dropwise and the mixture was stirred for 12 h, allowing the temperature to increase at rt. Then, water was added and the product was extracted with dichloromethane, purified by flash chromatography on silica gel (eluent : light petroleum/ethyl acetate : 9/1) to give 5-bromo-1-methyl-1*H*-pyrrolo[2,3-*b*]pyridine (**16**) (1.37 g, 63%) as yellow oil. IR (film) ν : 1590 cm$^{-1}$. $^1$H-NMR ($CDCl_3$) δ : 3.73 (s, 3H, NC**H**$_3$), 6.25 (d, 1H, J = 3.4 Hz, **H**$_3$), 7.05 (d, 1H, J = 3.4 Hz, **H**$_2$), 7.86 (d, 1H, J = 2.0 Hz, **H**$_4$), 8.26 (d, 1H, J = 2.0 Hz, **H**$_6$). $^{13}$C-NMR ($CDCl_3$) δ : 31.7 (N**C**H$_3$), 99.2 (**C**$_3$), 111.9 (**C**$_q$), 122.3 (**C**$_q$), 130.8 (**C**H), 130.9 (**C**H), 143.5 (**C**H), 146.4 (**C**$_q$). MS (IS) *m/z* = 211 (M+1 for $^{79}$Br), *m/z* = 213 (M+1 for $^{81}$Br). *Anal.* Calcd for $C_8H_7N_2Br$ : C, 45.53 ; H, 3.34 ; N, 13.27; Br, 37.86. Found : C, 45.89 ; H, 3.20 ; N, 13.39; Br, 37.78.

**1,1'-Dimethyl-1*H*,1'*H*-[5,5']bi[pyrrolo[2,3-*b*]pyridinyl] (17)**

Under an inert atmosphere, bis(pinacolato)diborane (**6**) (0.58 g, 2.27 mmol), potassium acetate (0.56 g, 5.68 mmol), [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (0.15 g, 0.19 mmol) were added to a stirred solution of **16** (0.4 g , 1.89 mmol) in dry DMF (5 mL). The mixture was stirred at 80°C under nitrogen for 2 h. After cooling the solution to rt, **16** (0.8 g, 3.78 mmol), [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (0.15 g, 0.19 mmol) and 2 M $Na_2CO_3$ (4.72 mL, 9.45 mmol) were added and the mixture was stirred at 80°C, under nitrogen for 12 h. The solution was cooled to rt, the product was extracted with dichloromethane (15 mL) and washed with water (15 mL), brine and dried over anhydrous $MgSO_4$. Finally, purification by flash chromatography on silica gel using ethyl acetate as eluent gave 0.41 g (83%) of 1,1'-dimethyl-1*H*,1'*H*-[5,5']bi[pyrrolo[2,3-*b*]pyridinyl] (**17**) as colourless oil. IR (film) ν : 1596 cm$^{-1}$. $^1$H-NMR ($CDCl_3$) δ : 3.94 (s, 6H, NC**H**$_3$), 6.51 (d, 2H, J = 3.4 Hz, **H**$_3$), 7.21 (d, 2H, J = 3.4 Hz, **H**$_2$), 8.10 (d, 2H, J = 2 Hz, **H**$_4$), 8.59 (d, 2H, J = 2 Hz, **H**$_6$). $^{13}$C-NMR ($CDCl_3$) δ : 31.7 (2xN**C**H$_3$), 99.9 (2x**C**$_3$), 121.4 (2x**C**$_q$), 127.9 (2x**C**H), 128.2 (2x**C**$_q$), 130.2 (2x**C**H), 142.9 (2x**C**H), 147.6 (2x**C**$_q$). MS (IS) *m/z* = 263 (M+1). *Anal.* Calcd for $C_{16}H_{14}N_4$ : C, 73.26 ; H, 5.38 ; N, 21.36. Found : C, 73.48 ; H, 5.40 ; N, 21.51.

**1,1'-Dimethyl-1*H*,1'*H*-[5,5']bi[pyrrolo[2,3-*b*]pyridinyl]-3,3'-dicarbaldehyde (18)**

Under an inert atmosphere, phosphorus oxychloride (2.99 mL, 32.1 mmol) was added to *N*,*N*-dimethylformamide (40 mL) at 0°C. After 10 min of stirring, a solution of compound (**17**) (0.42 g, 1.6 mmol) in *N*,*N*-dimethylformamide (5 mL) was added. The reaction was stirred for 30 min at 0°C, then heated at rt during 3 h. Then the solvent was removed under reduced pressure and the residue diluted with water. After extraction with ethyl acetate, the organic layers were dried over anhydrous $MgSO_4$ and evaporated in vacuo. The crude mixture was purified by flash chromatography (eluent: ethyl acetate) to provide **18** (0.5 g, 98%) as a white solid. mp > 245 °C (pentane). IR (KBr) ν : 1655 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) δ : 4.02 (s, 6H, NC**H**$_3$), 7.91 (s, 2H, **H**$_2$), 8.69 (d, 2H, J = 2.0 Hz, **H**$_4$), 8.80 (d, 2H, J = 2.0 Hz, **H**$_6$), 10.12 (s, 1H, C**H**O). $^{13}$C-NMR ($CDCl_3$) δ : 32.6 (2xN**C**H$_3$), 116.7 (2x**C**$_q$), 118.1 (2x**C**$_q$), 129.7 (2x**C**H), 130.7 (2x**C**$_q$), 139.9 (2x**C**H), 145.1 (2x**C**H), 147.8 (2x**C**$_q$), 184.8 (2x**C**O). MS (IS) *m/z* = 319 (M+1). *Anal.* Calcd for $C_{18}H_{14}N_4O_2$ : C, 67.92 ; H, 4.43 ; N, 17.60. Found : C, 68.02 ; H, 4.38 ; N, 17.62.

***N*-{2-[3'-(2-Acetylaminoethyl)-1,1'dimethyl-1*H*,1'*H*-[5,5']bi[pyrrolo[2,3-*b*]pyridin]-3-yl]ethyl}-acetamide (4)**

To a solution of aldehyde (**18**) (0.48 g, 1.60 mmol) in nitromethane (20 mL) was added to ammonium acetate (0.61 g, 8 mmol) and then the mixture was stirred at 120°C during 4 h. After cooling and dilution with dichloromethane, the mixture was hydrolysed and extracted. The organic layers were dried over anhydrous $MgSO_4$ and concentrated in vacuo. The crude nitrovinyl compound obtained which was used without further purification in the next step. Thus, to a stirred solution of nitro compound in a mixture of isopropanol (35 mL) and chloroform (100 mL) was added at rt under inert atmosphere silica gel 230-400 mesh (0.81 g). To this suspension was added portionwise sodium borohydride (0.3 g, 8 mmol) and then, the mixture was stirred at rt during 12 h. After this time, this mixture was filtered on Celite and filtrate was concentrated in vacuo. The crude compound obtained was used without further purification in the next step. Thus the satured nitro compound (0.85g, 2.43 mmol) was dissolved in methanol (4 mL). To this solution was added Raney nickel (0.015 g) and the mixture was hydrogenated (40 psi) in a Parr shaker at 60°C during 6 h. The catalyst was filtered off and the solvent was removed under reduced pressure. The crude amino derivative was obtained as a yellow oil which was used without purification in the next step. Under an inert atmosphere, the crude aminoderivative was dissolved in dichloromethane (20 mL), pyridine (20 ml) and acetic anhydride (0.45 mL, 4.8 mmol) at 0°C. The mixture was stirred during 12 h at rt before hydrolysis. The aqueous phase was neutralised with saturated hydrogenocarbonate and extracted with dichloromethane. The organics layers were dried over anhydrous $MgSO_4$, the solvent was removed under reduced pressure. The crude mixture was purified by flash chromatography (eluent : ethyl acetate/methanol 95/5) to provide compound (**4**) (0.12 g, 5% within 4 steps) as a brown oil. IR (film) ν 3406**,** 3260, 2925, 1629 $cm^{-1}$. $^1$H-NMR ($CD_3OD$) δ : 1.95 (s, 6H,

COC**H**$_3$), 3.01 (t, 4H, J = 6.8 Hz, **H**$_{1'}$), 3.60 (t, 4H, J = 6.8 Hz, **H**$_{2'}$), 3.89 (s, 6H, NC**H**$_3$), 5.71 (s, 2H, N**H**CH$_3$), 7.07 (s, 2H, **H**$_2$), 8.05 (d, 2H, J = 2 Hz, **H**$_4$), 8.57 (d, 2H, J = 2 Hz, **H**$_6$). $^{13}$C-NMR (CD$_3$OD) δ : 24 (2xCO**C**H$_3$), 26.1 (2x**C**$_{1'}$), 31.8 (2xN**C**H$_3$), 40.6 (2x**C**$_{2'}$), 110.7 (2x**C**$_q$), 120.6 (2x**C**$_q$), 126.1 (2x**C**H), 127.7 (2x**C**$_q$), 128.0 (2x**C**H), 134.8 (2x**C**$_q$), 142.9 (2x**C**H), 170.5 (2x**C**O). MS (IS) *m/z* = 433 (M+1). *Anal.* Calcd for $C_{24}H_{28}N_6O_2$ : C, 66.65 ; H, 6.52 ; N, 19.43. Found : C, 66.80 ; H, 6.69 ; N, 19.40.

**(5-Bromopyrrolo[2,3-*b*]pyridin-1-yl)acetonitrile (19)**

Under an inert atmosphere, sodium hydride (60% in oil, 0.18 g, 7.58 mmol) was added to a stirred solution of 5-bromoindole (1 g, 5.07 mmol) in *N*,*N*-dimethylformamide (25 mL) at 0°C during 30 min. Then the mixture was stirred an additional time (30 min) with continued cooling. After, the bromoacetonitrile (0.71 mL, 10.14 mmol) was added dropwise and the mixture was stirred for 12 h, allowing the temperature to increase at rt. Then water was added, the product was extracted with dichloromethane, purified by flash chromatography on silica gel (eluent : light petroleum/ethyl acetate : 8/2) to give compound (**19**) (0.66 g, 54%) as yellow solid. mp 84-85°C (pentane). IR (KBr) ν : 2252 cm$^{-1}$. $^1$H-NMR (CDCl$_3$) δ : 5.18 (s, 2H, C**H**$_2$CN), 6.50 (d, 1H, J = 3.7 Hz, **H$_3$**), 7.29 (d, 1H, J = 3.7 Hz, **H$_2$**), 8.02 (d, 1H, J = 1.9 Hz, **H$_4$**), 8.35 (d, 1H, J = 1.9 Hz, **H$_6$**). $^{13}$C-NMR (CDCl$_3$) δ : 32.4 (**C**H$_2$CN), 102.3 (**C**$_3$), 113.3 (**C**$_q$), 114.9 (**C**$_q$), 122.4 (**C**$_q$), 128.4 (**C**$_2$), 131.9 (**C**$_4$), 144.7 (**C**$_6$), 145.9 (**C**$_{7a}$). MS (IS) *m/z* = 236 (M+1 for $^{79}$Br), *m/z* = 238 (M+1 for $^{81}$Br). *Anal.* Calcd for $C_9H_6N_3Br$ : C, 45.79 ; H, 2.56 ; N, 17.80 ; Br, 33.85. Found : C, 45.74 ; H, 2.55 ; N, 17.78 ; Br, 33.81.

**1'-Cyanomethyl-1'*H*-[5,5']bi[pyrrolo[2,3-*b*]pyridin]-1-yl)acetonitrile (20)**

Under an inert atmosphere, bis(pinacolato)diborane (**6**) (0.23 g, 0.91 mmol), potassium acetate (0.22 g, 2.28 mmol), and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (0.06 g, 0.01 mmol) were added to a stirred solution of **19** (0.18 g , 0.76 mmol) in dry DMF (5 mL). The mixture was stirred at 80°C under nitrogen for 2 h. After cooling the solution to rt, **19** (0.36 g, 1.52 mmol), [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (0.06 g, 0.01 mmol) and 2 M $Na_2CO_3$ (1.9 mL, 3.81 mmol) were added and the mixture was stirred at 80°C under nitrogen for 12 h. The solution was cooled to rt, the product was extracted with dichloromethane (15 mL) and washed with water (15 mL), brine and dried over anhydrous $MgSO_4$. Finally, purification by flash chromatography on silica gel using 30% ethyl acetate in light petroleum as eluent gave 0.16 g (67%) of 1'-cyanomethyl-1'*H*-[5,5']bi[pyrrolo[2,3-*b*]pyridin]-1-yl)acetonitrile (**20**) as a white solid. mp > 240°C (pentane). IR (KBr) ν : 2923, 2248 cm$^{-1}$. $^1$H-NMR (DMSO-$d_6$) δ : 5.52 (s, 4H, C**H**$_2$CN), 6.65 (d, 2H, J = 3.6 Hz, **H**$_3$), 7.68 (d, 2H, J = 3.6 Hz, **H**$_2$), 8.34 (d, 2H, J = 2.2 Hz, **H**$_4$), 8.67 (d, 2H, J = 2.2 Hz, **H**$_6$). $^{13}$C-NMR (DMSO-$d_6$) δ : 33 (2x**C**H$_2$CN), 102.3 (2x**C**$_3$), 117.4 (2x**C**$_q$), 121.2 (2x**C**$_q$), 128.5 (2x**C**$_q$), 128.7 (2x**C**$_2$), 130.5 (2x**C**$_4$), 143.3

(2x**C**$_6$), 147.1 (2x**C**$_{7a}$). MS (IS) *m/z* = 313 (M+1). *Anal.* Calcd for $C_{18}H_{12}N_6$ : C, 69.22 ; H, 3.87 ; N, 26.91. Found : C, 69.31 ; H, 3.84 ; N, 27.01.

***N*-{2-[1'-(2-acetylaminoethyl)-1'*H*-[5,5']bi[pyrrolo[2,3-*b*]pyridin]-1-yl]ethyl}acetamide (5)**

A solution of compound (**20**) (0.15 g, 0.48 mmol) in acetic anhydride (5 mL) was hydrogenated over Raney nickel (0.01 g) in the presence of sodium acetate (0.16 g, 1.92 mmol) for 18 h at 60°C. The reaction was cooled to rt and the catalyst was filtered on Celite and the filtrate concentrated in vacuo. The residue was taken up in dichloromethane, washed with water and dried over anhydrous $MgSO_4$. After removal of the solvent, the crude residue was chromatographed over silica gel (eluent : ethyl acetate/methanol : 9/1) to afford **5** (0.06 g, 31%) as a white solid. mp 230-231°C (pentane). IR (KBr) ν : 3296, 2920, 1639 cm$^{-1}$. $^1$H-NMR (DMSO-*d*$_6$) δ : 1.77 (s, 6H, COC**H**$_3$), 3.48 (q, 4H, J = 6.1 Hz, **H**$_{2'}$), 4.35 (t, 4H, J = 6.1 Hz, **H**$_{1'}$), 6.52 (d, 2H, J = 3.4 Hz, **H**$_3$), 7.55 (d, 2H, J = 3.4 Hz, **H**$_2$), 8.01 (t, 2H, J = 6.1 Hz, N**H**Ac), 8.25 (d, 2H, J = 1.8 Hz, **H**$_4$), 8.58 (d, 2H, J = 1.8 Hz, **H**$_6$). $^{13}$C-NMR (DMSO-*d*$_6$) δ : 23.4 (2xCO**C**H$_3$), 39.7 (2x**C**$_{1'}$), 44.5 (2x**C**$_{2'}$), 100.1 (2x**C**$_3$), 121.1 (2x**C**$_q$), 127.6 (2x**C**$_2$), 128.0 (2x**C**$_q$), 131.1 (2x**C**$_4$), 142.3 (2x**C**$_6$), 147.3 (2x**C**$_{7a}$), 170.3 (2x**C**O). MS (IS) *m/z* = 405 (M+1). ). *Anal.* Calcd for $C_{22}H_{24}N_6O_2$ : C, 65.33 ; H, 5.98 ; N, 20.77. Found : C, 65.2 ; H, 5.93 ; N, 20.61.

**ACKNOWLEDGEMENTS**

*We are grateful to A.D.I.R. Company (Courbevoie, France) for its multiform support.*

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