SYNTHESIS OF NEW MELATONINERGIC LIGANDS INCLUDING AZAINDOLE MOIETY

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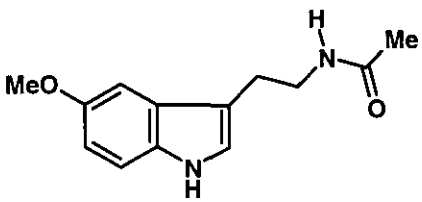
Abstract - A novel series of melatonin analogues, based on the azaindole nucleus is described. These compounds are prepared in several steps directly from the commercial available 7-azaindole or from substituted amino-, iodo- or/and nitropyridines using a catalysed palladium reaction or vicarious nucleophilic substitution of hydrogen (VNS) in order to elaborate the 6-, 5- and 4-azaindole derivatives respectively.

Melatonin (Figure 1) is a pineal hormone which regulates a variety of endocrinological, neurophysiological, and behavioural functions in vertebrates. It is now recognised to be the regulator of circadian rhythm in humans and of seasonal breeding in different animal species.[1]

Figure 1



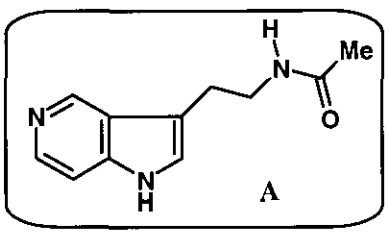
Melatonin

Melatonin also appears to be involved in a number of physiological and pathological conditions, and there is strong evidence for its use in pathologies associated with circadian rhythm disorders. It was shown that administration of melatonin in humans could altercate jet lag,[2] induce sleep,[3] and advance the sleep phase of subjects with delayed sleep phase syndrome.[4] Numerous studies on elderly people or depressed patients have also reported a decrease in overnight melatonin biosynthesis, thus suggesting a

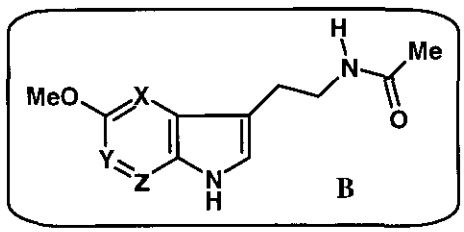
role of this hormone in the ageing process[5] and in seasonal depression.[6] Despite melatonin's potential involvement in the regulation in many possible physiological processes, two drawbacks limit its therapeutic use. The first is its very short biological half-life (15-30 min) due to its rapid catabolism.[7] The second shortcoming is the lack of selectivity of melatonin for its target sites. Moreover, considerable interest has evolved in the search for new molecules capable of mimicking or antagonising responses to melatonin. Such compounds constitute important tools for elucidation of the physiological roles of melatonin. Several indolic analogs of melatonin have been found to act as ligands.[8]

Considering bio-isosteric relationships, which are very important in therapeutic chemistry, we have undertaken the replacement of the indole ring with an azaindole structure while keeping the methoxy group and the ethylamido chain present in melatonin itself. However, recent articles relating the synthesis of substituted 5-,6- and 7-azaindoles[9] have prompted the publication of our results in this domain.[10] We now describe the synthesis of substituted 3-amidoethylpyrrolopyridine derivatives (**A, B**) which are represented in Figure 2.

Figure 2



5-azaindole derivative

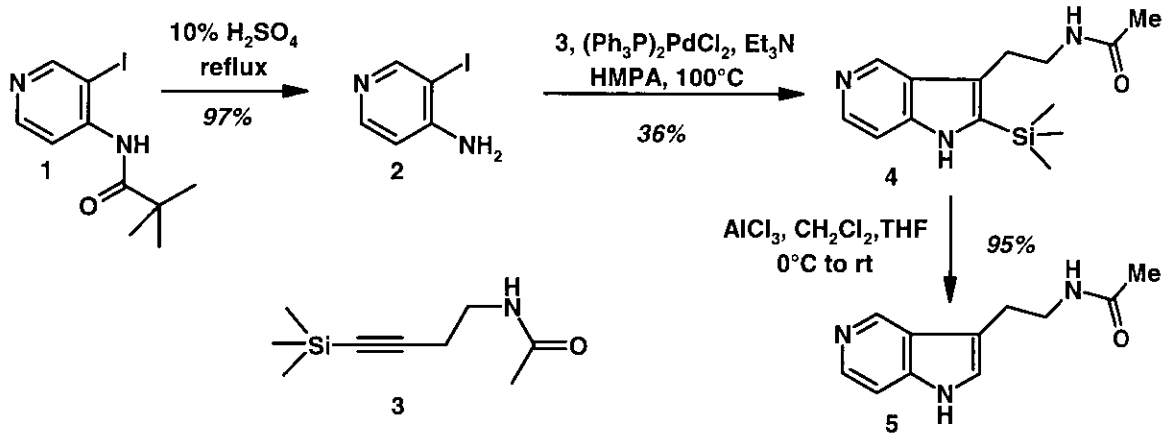


Z = N Y,X = CH *7-azaindole derivative*
Y = N X,Z = CH *6-azaindole derivative*
X = N, Z,Y = CH *4-azaindole derivative*

At first, our work focused on the elaboration of the 5-azaindole ring system whose synthetic pathway is outlined in Scheme 1. Since 5-azaindole was not commercially available, the synthesis of this heterocycle and related melatoninergic analogs (Figure 2, structure **A**) where the nitrogen atom replaces the methoxy group, was realised using Gronowitz's methodology.[11]

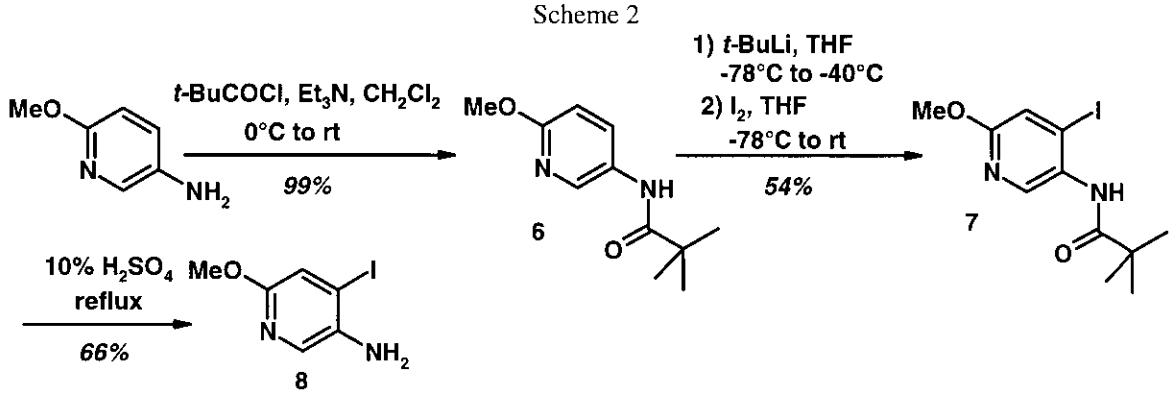
This reaction involved, as the key step, a palladium-catalyzed coupling reaction between the 4-amino-3-iodopyridine (**2**) and an acetylenic derivative (**3**).[12] In order to prevent coupling at the terminal carbon of the acetylenic derivative, silyl protection was employed. Treatment of the derivative (**1**)[13] with a solution of sulfuric acid (10%) provided a very good yield of the expected aminopyridine (**2**). This compound was then subjected to the palladium coupling reaction with acetylene (**3**) in hexamethylphosphoramide in the presence of triethylamine at 100°C. Compound (**4**) was obtained in moderate yield followed by desilylation[14] with aluminium chloride in a mixture of methylene chloride and tetrahydrofuran. This furnished the melatoninergic analog (**5**) in 95% yield (Scheme 1).

Scheme 1



Since 6-azaindole is not commercially available, the same synthetic sequence described in Scheme 1 was applied to the elaboration of the melatoninergic analogs in 6-azaindole series. The synthesis of 5-amino-4-iodo-2-methoxypyridine (**8**) is described in Scheme 2. The first step involved protection of the amino group with pivaloyl chloride to furnish **6** in near-quantitative yield. Iodination of **6** was examined using different bases such as *t*-BuLi, PhLi, BuLi and LDA and varying the temperature. It was found that *t*-BuLi in tetrahydrofuran at -78°C to -40°C gave the best results. Using these conditions the expected iodo compound (**7**) was obtained in 54% yield. The cleavage of the pivaloyl group was carried out using a solution of sulfuric acid (10%) under reflux to afford 5-amino-4-iodo-2-methoxypyridine (**8**) in 66% yield.

Scheme 2

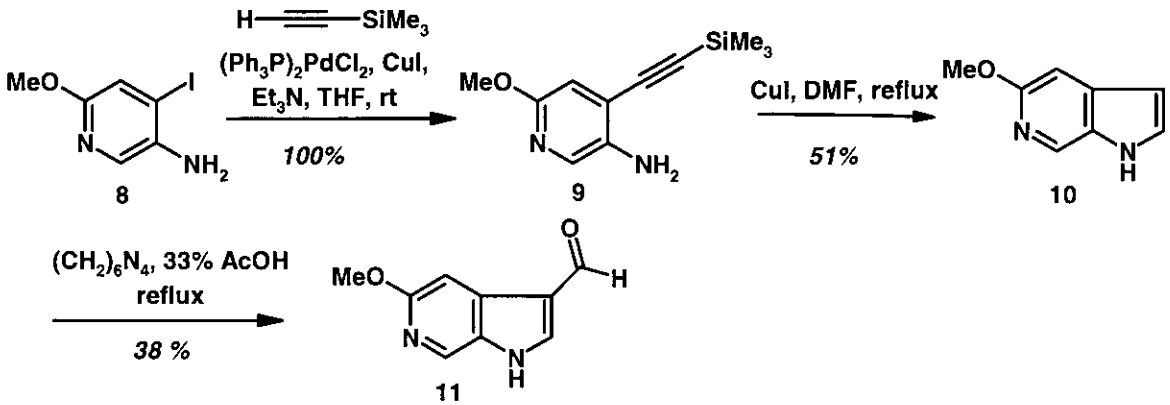


Compound (**8**) was then treated with **3** in the presence of bis(triphenylphosphine)palladium chloride and triethylamine in hexamethylphosphoramide as described in Scheme 1. Unfortunately, this reaction gave rise to a mixture of 5-methoxypyrrolo[2,3-*c*]pyridines substituted at positions C2 and C3 with the amidoethyl chain and in very poor yields. Therefore, we turned our attention to another strategy outlined in Scheme 3. This route led to the desired **11** in overall 19.4% yield.

The initial step in this route used Sonogashira's reaction[15] which involved sp^2-sp palladium coupling of an acetylene and a halogenated pyridine. Compound (**9**) was obtained in quantitative yield, followed by

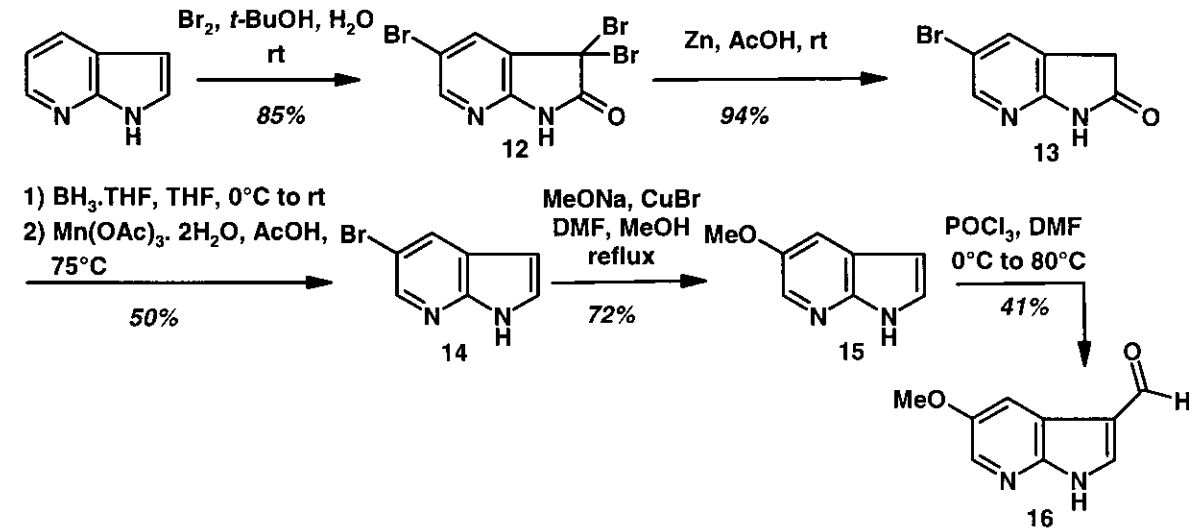
ring closure in refluxing *N,N*-dimethylformamide in the presence of two equivalents of copper(I) iodide under an inert atmosphere to provide the expected 5-methoxy-6-azaindole (**10**) in 51% yield. Formylation of **10** was carried out using the traditional procedure of Vilsmeier-Haack. Even though we varied experimental conditions (temperature, excess of reagent), in all cases degradation of the starting product was observed. Consequently, this reaction was performed in hexamethylenetetramine in refluxing aqueous acetic acid[16] and the 3-formylated 6-azaindole (**11**) was obtained in 38% yield (Scheme 3).

Scheme 3



In the case of pyrrolo[2,3-*b*]pyridine, the starting 7-azaindole was commercially available. The first step involved halogenation with bromine in a mixture of *t*-butanol and water[17] at room temperature (Scheme 4) to provide the tribromo derivative (**12**) (85%).

Scheme 4

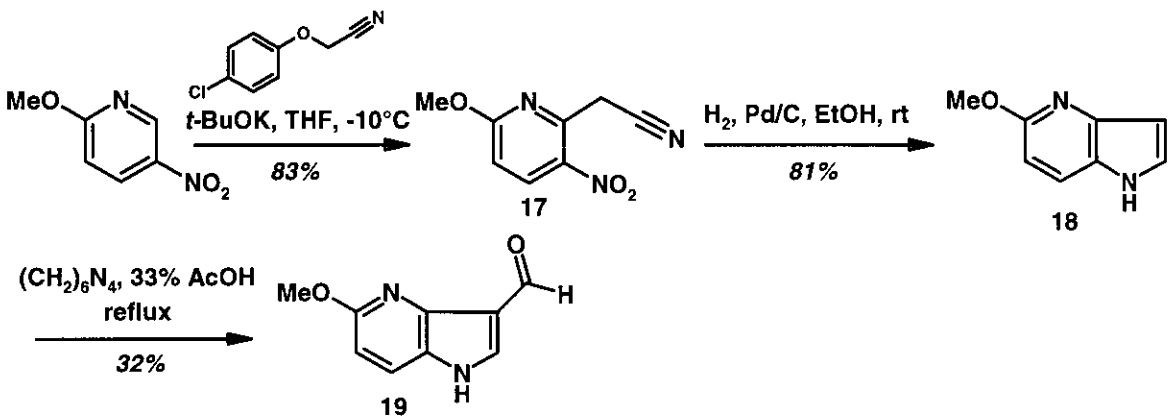


Compound (**12**) was then treated with zinc in acetic acid to furnish **13** in 94% yield. Reduction of the amide function was realised with the borane-tetrahydrofuran complex, and the resulting indoline was oxidised with manganese triacetate in acetic acid at 75°C to give compound (**14**) in an overall 50% yield. 5-Bromo-1*H*-pyrrolo[2,3-*b*]pyridine (**14**) was next treated in a mixture of *N,N*-dimethylformamide and

methanol with sodium methoxide in the presence of copper(I) bromide[18] to provide the intermediate (**15**) in moderate yield. This derivative was subjected to the Vilsmeier's reaction, to afford compound (**16**) in 41% yield (Scheme 4).

Since 4-azaindole is not commercially available, the synthesis of this ring system is depicted in Scheme 5. Compound (**17**) was obtained *via* a vicarious nucleophilic substitution of hydrogen (VNS) described by Makosza *et al.*[19] 2-Methoxy-5-nitropyridine was treated with 4-chlorophenoxyacetonitrile and potassium *t*-butoxide in tetrahydrofuran at -10°C to give 2-cyanomethyl-6-methoxy-3-nitropyridine (**17**) in 83 % yield. Elaboration to 5-methoxy-1*H*-pyrrolo[3,2-*b*]pyridine (**18**) was accomplished by catalytic hydrogenation using palladium on charcoal (81% yield). Again, several attempts of formylation using Vilsmeier's conditions were tried without success, therefore the introduction of the formyl group in the 3-position was accomplished using hexamethylenetetramine in refluxing aqueous acetic acid solution to provide **19** in 32% yield. (Scheme 5).

Scheme 5

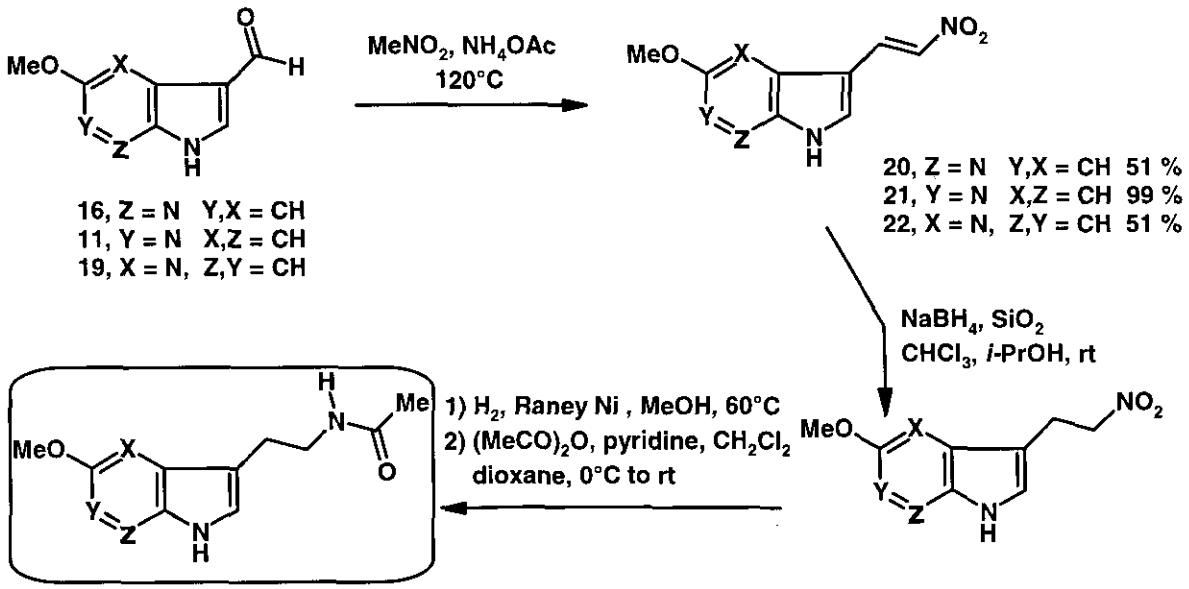


The target derivatives (**26**, **27**, **28**) were prepared according to the synthetic sequence[20] illustrated in Scheme 6. The first step involved a reaction of either **11**, **16**, **19** with nitromethane in the presence of sodium acetate to furnish the expected nitrovinyl products (**20**, **21**, **22**) in moderate to good yields. The reduction of the double bond was performed with sodium borohydride in a mixture of chloroform and isopropanol in the presence of silica gel followed by the reduction of the nitro group using hydrogen in the presence of Raney nickel. Acetylation of the ethylamino function was achieved on the crude amino products with acetic anhydride in a mixture of methylene chloride and pyridine and provided the desired 7-, 6-, 4-azaindole analogs of melatonin (**26**), (**27**), (**28**) in 37%, 45% and 64% yields, respectively.

In conclusion, this paper reports the elaboration of a new class of analogs of melatonin which possess an azaindole skeleton. In the course of these syntheses, we developed several new procedures leading to the

access of the pyrrolopyridines moieties using palladium catalysed chemistry and vicarious nucleophilic substitution of hydrogen.

Scheme 6



EXPERIMENTAL

Melting points were determined on a Köfler hot-stage apparatus and are uncorrected. Proton NMR were recorded on a Bruker Avance DPX250 (250.131 MHz). The coupling constants are recorded in Hertz (Hz) and the chemical shifts are reported in parts per million (δ, ppm) downfield from tetramethylsilane (TMS), which was used as an internal standard. IR spectra were obtained with a Perkin-Elmer FT Paragon 1000 PC. MS spectra were recorded on a Perkin-Elmer SCIEX API 3000 spectrometer. Organic solvents were purified when necessary by the methods described by D. D. Perrin W. L. F. Armarego and D. R. Perrin (*Purification of Laboratory Chemicals*; Pergamon : Oxford, 1986) or purchased from Aldrich Chimie. All solutions were dried over anhydrous magnesium sulfate and evaporated on a Büchi rotatory evaporator. Analytical thin-layer chromatography (TLC) was carried out on precoated plates (silica gel, 60 F-254), and spots were visualised with UV light or an alcohol solution of ammonium cerium (IV) nitrate. Column chromatography was performed on Kieselgel 60 (230-400 mesh) silica gel (Merck) for flash columns. All anhydrous reactions were performed in oven-dried glassware under an atmosphere of argon. The column chromatography solvents employed were distilled and solvent mixtures were reported as volume to volume ratios.

4-Amino-3-iodopyridine (2)

Compound (**1**)[13] (2.21 g, 7.3 mmol) was treated with a solution of 10% sulfuric acid (73 mL) at reflux during 15 h. After cooling, the mixture was basified with a 50% NaOH solution and then extracted with ethyl acetate. The organic layers were dried and evaporated *in vacuo*. The residue was purified by flash chromatography (eluent: methylene chloride/ methanol, 95/5) to provide compound (**2**) (1.54 g, 97%) as a white solid: mp 80-81°C (Et_2O); IR (KBr) ν: 3425 (NH_2), 3297 (NH_2) cm^{-1} ; ^{1}H-NMR ($CDCl_3$) δ : 4.69 (br s, 2H, N**H**$_2$), 6.59 (d, J=5.1 Hz, 1H, **H**$_5$), 8.11 (d, J=5.1 Hz, 1H, **H**$_6$), 8.57 (s, 1H, **H**$_2$). *Anal.* Calcd for $C_5H_5N_2I$: C, 27.30; H, 2.29; N, 12.73. Found: C, 27.17; H, 2.20; N, 12.70.

***N*-{2-[2-Trimethylsilyl-1*H*-pyrrolo[3,2-*c*]pyridin-3-yl]ethyl}acetamide (4)**

To a stirred solution of compound (**2**) (0.2 g, 0.91 mmol) and the acetylenic derivative (**3**)[12] (0.334 mg, 1.82 mmol) in hexamethylphosphoramide (4 mL), under inert atmosphere, were added triethylamine (0.38 mL, 2.7 mmol) and bis(triphenylphosphine)palladium (II) chloride (0.064 g, 0.091 mmol). The reaction mixture was stirred at 100°C during 15 h. After cooling the residue was diluted with water and extracted with ethyl acetate. The organic layers were dried and evaporated to dryness. The crude mixture was purified by flash chromatography (eluent: methylene chloride/ methanol, 85/15) to provide compound (**4**) (0.90 g, 36%) as a white solid: mp 234-235°C (Et_2O); IR (KBr) ν: 3253 (NH), 1653 (C=O) cm^{-1} ; ^{1}H-NMR (DMSO-d_6) δ : 0.37 (s, 9H, Si(C**H**$_3$)$_3$), 1.79 (s, 3H, COC**H**$_3$), 2.94 (t, J=6.5 Hz, 2H, C**H**$_2$), 3.23 (td, J=6.5 Hz, J=6.6 Hz, 2H, C**H**$_2$), 7.40 (d, J=5.8 Hz, 1H, **H**$_7$), 8.03 (t, J=6.6 Hz, 1H, N**H**Ac), 8.15 (d, J=5.8 Hz, 1H, **H**$_6$), 8.90 (s, 1H, **H**$_4$), 11.20 (br s, 1H, **H**$_1$). MS (IC/NH_3) *m/z*: 276 (M+1). *Anal.* Calcd for $C_{14}H_{21}N_3OSi$: C, 61.05; H, 7.68; N, 15.26. Found: C, 60.67; H, 7.64; N, 14.97.

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

To a stirred solution of compound (**4**) (0.347 g, 1.26 mmol) in a mixture of methylene chloride (36 mL) and tetrahydrofuran (0.15 mL) was added at 0°C under inert atmosphere aluminum chloride (1.68 g, 12.6 mmol) and then, the mixture was stirred at rt during 3 h. To this reaction mixture was added a saturated solution of sodium hydrogencarbonate until pH basic followed by a filtration under celite pad which was rinsed out with water and methylene chloride. After extraction, the aqueous layer was concentrated *in vacuo* and the crude mixture was purified by flash chromatography (eluent: methylene chloride/ methanol, 4/1) to provide compound (**5**) (0.242 g, 95%) as a white solid: mp 184-185°C (pentane); IR (KBr) ν: 3159 (NH), 1651 (C=O) cm^{-1} ; ^{1}H-NMR (DMSO-d_6) δ : 1.79 (s, 3H, COC**H**$_3$), 2.88 (t, J=7.2 Hz, 2H, C**H**$_2$), 3.35 (td, J=7.2 Hz, J=6.0 Hz, 2H, C**H**$_2$), 7.34 (s, 1H, **H**$_2$), 7.46 (d, J=5.4 Hz, 1H, **H**$_7$), 8.10 (t, J=6.0 Hz, 1H, N**H**Ac), 8.07-8.25 (m, 1H, **H**$_6$), 8.82-9.00 (m, 1H, **H**$_4$), 11.77 (br s, 1H, **H**$_1$). MS (IC/NH_3) *m/z*: 204 (M+1). *Anal.* Calcd for $C_{11}H_{13}N_3O$: C, 65.01; H, 6.45; N, 20.67. Found: C, 64.88 H, 6.40; N, 20.64.

2,2-Dimethyl-*N*-(5-(2-methoxypyridinyl)]propanamide (6)

Under inert atmosphere, a solution of pivaloyl chloride (10.7 mL, 89.1 mmol) in 20 mL of CH_2Cl_2 was added, slowly at 0°C, to 5-amino-2-methoxypyridine (10 g, 81 mmol) and triethylamine (14.5 mL, 101.25 mmol) in CH_2Cl_2 (100 mL) and then the mixture was stirred during 10 min at 0°C and 2 h at rt. The mixture was hydrolysed, extracted with methylene chloride and dried. After evaporation of solvent, the resulting product was purified by flash chromatography (eluent: petroleum ether/ethyl acetate, 3/1) to provide compound (**6**) (16.6 g, 99%) as a yellow solid: mp 79-80°C (pentane); IR (KBr) ν: 3287 (NH), 1645 (CO) cm^{-1} ; ^{1}H-NMR($CDCl_3$) δ : 1.33 (s, 9H, C(**CH**$_3$)$_3$), 3.90 (s, 3H, O**CH**$_3$), 6.69 (d, J=8.8 Hz, 1H, **H**$_3$), 7.42 (br s, 1H, N**H**), 7.87 (dd, J=8.8 Hz, J=2.8 Hz, 1H, **H**$_4$), 8.13 (d, J=2.8 Hz, 1H, **H**$_6$). ^{13}C-NMR ($CDCl_3$) δ : 27.6 (C(**CH**$_3$)$_3$), 39.4 (**C**(CH$_3$)$_3$), 53.5 (OCH$_3$), 110.4 (**C**$_3$), 128.7, 132.8 (**C**$_4$), 139.0 (**C**$_6$), 161.0, 177.1 (**C**O). *Anal.* Calcd for $C_{11}H_{16}N_2O_2$: C, 64.21; H, 7.10; N, 17.02. Found: C, 64.08 H, 7.05; N, 17.00.

2,2-Dimethyl-*N*-(4-iodo-6-methoxy-3-pyridinyl)]propanamide (7)

Under inert atmosphere at -78°C, *t*-butyllithium (15 mL, 25 mmol, 1.7 M solution in pentane) was added dropwise to a stirred solution of the compound (**6**) (2.08 g, 10 mmol) in anhydrous tetrahydrofuran (50 mL). After 1 h at -78°C, iodine (6.35 g, 25 mmol) in anhydrous tetrahydrofuran (30 mL) was added to this solution at the same temperature. The mixture was stirred during 15 min at -78°C then 30 min to rt. After dilution with water, the crude product was extracted with methylene chloride. The organic layers were dried and evaporated to dryness. The residue was purified by flash chromatography (eluent: petroleum ether/ethyl acetate, 5/1) to provide compound (**7**) (1.79 g, 54%) as a white solid: mp 119-120°C (Et_2O); IR (KBr) ν: 3279 (NH), 1647 (C=O) cm^{-1} ; ^{1}H-NMR ($CDCl_3$) δ : 1.36 (s, 9H, C(**CH**$_3$)$_3$), 3.91 (s, 3H, O**CH**$_3$), 7.23 (s, 1H, **H**$_3$), 7.38 (br s, 1H, N**H**), 8.69 (s, 1H, **H**$_6$). ^{13}C-NMR ($CDCl_3$) δ : 27.7 (C(**CH**$_3$)$_3$), 39.7 (**C**(CH$_3$)$_3$), 54.0 (OCH$_3$), 105.6, 120.3 (**C**$_3$), 129.4, 140.8 (**C**$_6$), 160.9, 176.6 (**C**O). *Anal.* Calcd for $C_{11}H_{15}N_2O_2I$: C, 53.16; H, 5.95; N, 13.15. Found: C, 53.01; H, 5.90; N, 13.10.

5-Amino-4-iodo-2-methoxypyridine (8)

This compound was prepared from **7** (2.57 g, 7.7 mmol) according to the method used for the product (**2**). The expected derivative (**8**) was obtained after purification by flash chromatography (eluent: petroleum ether/ethyl acetate, 5/1) in 66% yield as a yellow solid: mp 64-65°C (Et_2O); IR (KBr) ν: 3398 (NH), 3301 (NH) cm^{-1} ; ^{1}H-NMR ($CDCl_3$) δ : 3.72 (br s, 2H, N**H**$_2$), 3.84 (s, 3H, O**CH**$_3$), 7.14 (s, 1H, **H**$_3$), 7.64 (s, 1H, **H**$_6$). ^{13}C-NMR ($CDCl_3$) δ : 53.7 (OCH$_3$), 98.8, 119.8 (**C**$_3$), 131.2 (**C**$_6$), 138.1, 157.6. *Anal.* Calcd for $C_6H_7N_2OI$: C, 47.05; H, 5.16; N, 12.66. Found: C, 46.98; H, 5.10; N, 12.60.

5-Amino-2-methoxy-4-[2-(1,1,1-trimethylsilyl)-1-ethynyl]pyridine (9)

Under inert atmosphere, to a solution of compound (**8**) (0.2 g, 0.80 mmol) in triethylamine (5 mL) and

tetrahydrofuran (1 mL) were added successively at rt bis(triphenylphosphine)palladium (II) chloride (0.006 g, 0.008 mmol), cuprous iodide (0.0015 g, 0.008 mmol) and (trimethylsilyl)acetylene (170 µL, 1.2 mmol). The reaction was stirred during 5 h at the same temperature. The mixture was concentrated *in vacuo*. The crude product was purified by flash chromatography (eluent: petroleum ether/ethyl acetate, 4/1) to provide compound (**9**) (0.180 g, 99%) as a white solid: mp 87-88°C (pentane); IR (KBr) ν: 3350 (NH_2), 2153 (C≡C) cm^{-1} ; ^{1}H-NMR ($CDCl_3$) δ : 0.27 (s, 9H, Si(CH_3)$_3$), 3.84 (br s, 5H, NH_2, OCH_3), 6.67 (s, 1H, **H$_3$**), 7.70 (s, 1H, **H$_6$**). ^{13}C-NMR ($CDCl_3$) δ : 0.0 (Si(CH_3)$_3$), 53.7 (OCH_3), 99.0, 104.2, 111.8 (**C$_3$**), 120.2, 132.7 (**C$_6$**), 138.1, 157.4. *Anal.* Calcd for $C_{11}H_{16}N_2OSi$: C, 59.96; H, 7.32; N, 12.71. Found: C, 59.82; H, 7.20; N, 12.65.

5-Methoxy-1*H*-pyrrolo[2,3-*c*]pyridine (10)

The compound (**9**) (0.110 g, 0.5 mmol) was dissolved in *N,N*-dimethylformamide (3 mL). To this solution was added cuprous iodide (0.190 g, 1.0 mmol) and the mixture was stirred at reflux for 2 h. After cooling, dilution with ethyl acetate, filtration under celite and evaporation of solvent, the residue was purified by flash chromatography (eluent: petroleum ether/ethyl acetate, 2/1) to provide compound (**10**) (0.040 g, 51%) as a brown solid: mp 120-121°C (Et_2O); (lit.,[21] 122-124 °C) ; IR (KBr) ν: 3131 (NH) cm^{-1} ; ^{1}H-NMR ($CDCl_3$) δ : 3.97 (s, 3H, OCH_3), 6.41-6.43 (m, 1H, **H$_3$**), 6.94 (s, 1H, **H$_4$**), 7.37 (d, J=2.8 Hz, 1H, **H$_2$**), 8.40 (s, 1H, **H$_7$**), 9.76 (br s, 1H, **H$_1$**). ^{13}C-NMR ($CDCl_3$) δ : 54.9 (OCH_3), 97.5 (**C$_4$**), 101.4 (**C$_3$**), 130.4 (**C$_7$**), 131.1 (**C$_2$**+1C), 137.6, 158.7. *Anal.* Calcd for $C_8H_8N_2O$: C, 64.85; H, 5.44; N, 18.91. Found: C, 64.70; H, 5.32; N, 18.99.

3-Formyl-5-methoxy-1*H*-pyrrolo[2,3-*c*]pyridine (11)

A stirred solution of derivative (**10**) (0.380 g, 2.56 mmol) in 33% acetic acid (4 mL) was treated with hexamethylenetetramine (0.545 g, 3.85 mmol). The reaction mixture was heated at reflux during 4 h. After cooling, the reaction was extracted with ethyl acetate. The organic layers were dried and concentrated *in vacuo*. The residue was purified by flash chromatography (eluent: methylene chloride/methanol, 95/5) to provide compound (**11**) (0.170 g, 38%) as a white solid: mp 183-184°C (pentane); IR (KBr) ν: 3431 (NH), 1655 (C=O) cm^{-1} ; ^{1}H-NMR (DMSO-d_6) δ : 3.86 (s, 3H, OCH_3), 7.31 (s, 1H, **H$_4$**), 8.43 (s, 1H, **H$_2$**), 8.47 (s, 1H, **H$_7$**), 9.92 (s, 1H, CHO), 12.32 (br s, 1H, **H$_1$**). ^{13}C-NMR (DMSO-d_6) δ : 53.8 (OCH_3), 98.4 (**C$_4$**), 117.0, 131.5 (**C$_7$**+1C), 133.7, 142.7 (**C$_2$**), 159.6, 185.1 (CHO). *Anal.* Calcd for $C_{10}H_9NO_2$: C, 58.53; H, 4.75; N, 15.93. Found: C, 58.36; H, 4.89; N, 15.85.

3,3,5-Tribromo-2-oxo-1,3-dihydrophyrrolo[2,3-*b*]pyridine (12)

7-Azaindole (10 g, 0.084 mol) was dissolved in a mixture of *t*-butanol (660 mL) and water (660 mL) at rt. After addition dropwise of bromine (54 mL, 1;05 mol) to this solution then stirring for 19 h at rt, the alcohol was evaporated under reduced pressure and the residual aqueous phase was treated with a

saturated solution of sodium hydrogenocarbonate until pH 9. The product was obtained after filtration, and dried over P_2O_5 *under vacuum* overnight. The desired tribrominated oxindole (**12**) (26.7 g, 85%) was isolated as a brown solid, mp 157-158°C (ethyl acetate); IR (KBr) ν : 3300-3000 (NH), 1746 (C=O) cm^{-1} ; ^{1}H-NMR ($CDCl_3$) δ :7.98 (d, J=2.7 Hz, 1H, $\mathbf{H_4}$), 8.33 (d, J=2.7 Hz, 1H, $\mathbf{H_6}$), 10.39 (s, 1H, $\mathbf{H_1}$). *Anal.* Calcd for $C_7H_3N_2OBr_3$: C, 22.67; H, 0.82; N, 7.55. Found: C, 22.90; H, 0.90; N, 7.59.

5-Bromo-2-oxo-1,3-dihydropyrrolo[2,3-*b*]pyridine (13)

Under inert atmosphere at rt, zinc (8.80 g, 135 mmol) was added portionwise to a solution of compound (**12**) (5.0 g, 13.5 mmol) in acetic acid (100 mL). The same amount of zinc was added after 3 h of stirring until the complete disappearance of starting compound monitored by TLC. Then the crude mixture was diluted with water and extracted with ethyl acetate. After drying, the organic layers were evaporated and coevaporated with toluene. The crude mixture was purified by flash chromatography (eluent: methylene chloride/methanol, 95/5) to provide compound (**13**) (2.7 g, 94%) as an orange solid: mp 249-250°C (cyclohexane); IR (KBr) ν : 3300-3000 (NH), 1728 (C=O) cm^{-1} ; ^{1}H-NMR (DMSO-d_6) δ : 4.10 (s, 2H, $\mathbf{H_3}$), 7.67 (d, J=2.3 Hz,1H, $\mathbf{H_4}$), 8.07 (d, J=2.3 Hz, 1H, $\mathbf{H_6}$), 11.06 (s, 1H, $\mathbf{H_1}$). *Anal.* Calcd for $C_7H_5N_2OBr$: C, 28.80; H, 1.38; N, 9.60. Found: C, 28.63; H, 1.30; N, 9.78.

5-Bromo-1*H*-pyrrolo[2,3-*b*]pyridine (14)

Under inert atmosphere, a solution of borane-tetahydrofuran complex, 1.0 M solution in anhydrous tetrahydrofuran, (37.6 mL, 37.6 mmol) was added dropwise at 0°C to a solution of compound (**13**) (2.0 g, 9.4 mmol) in anhydrous tetrahydrofuran (50 mL). The mixture was stirred at rt during 35 min, then the solvent was removed under reduced pressure. The residue was diluted with a solution of hydrochloric acid (6N) and heated until the complete dissolution of the solid. After cooling, the mixture was treated with an aqueous solution of sodium hydroxide (6M) until pH 9 and extracted with ethyl acetate. The organic layers were dried and the solvent was removed under reduced pressure. The crude mixture was engaged in the next step without purification. This derivative was dissolved in acetic acid (20 mL) at rt and the resulting solution was added to a suspension of manganese(III) acetate (4.1 g, 15.28 mmol) in acetic acid (20 mL). After 45 min of stirring at 75°C, the solvent was evaporated to dryness and coevaporated with toluene. The crude mixture was diluted with water, extracted with ethyl acetate, and the resulting organic layers were dried. After evaporation of the solvent under reduced pressure, the crude mixture was purified by flash chromatography (eluent: petroleum ether/ethyl acetate, 6/1) to provide compound (**14**) (900 mg, 50%) as a yellowish solid: mp 176-177°C (pentane); IR (KBr) ν : 3300-3000 (NH) cm^{-1} ; ^{1}H-NMR ($CDCl_3$) δ : 6.39 (d, J= 2.9 Hz, 1H, $\mathbf{H_3}$) 7.30 (d, J=2.9 Hz, 1H, $\mathbf{H_2}$), 8.01 (d, J = 2.2 Hz, 1H, $\mathbf{H_4}$), 8.29 (d, J= 2.2 Hz, 1H, $\mathbf{H_6}$), 10.9 (s, 1H, $\mathbf{H_1}$). *Anal.* Calcd for $C_7H_5N_2Br$: C, 32.30; H, 1.68; N, 10.76. Found: C, 32.48; H, 1.44; N, 10.53.

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

Under inert atmosphere, compound (**14**) (986 mg, 5.0 mmol) was dissolved in a mixture of *N,N*-dimethylformamide (32 mL) and methanol (20 mL). To this solution were added successively sodium methoxide (14.3 g, 265 mmol) and copper(I) bromide (1.43 g, 10.0 mmol) at rt. The mixture was heated at reflux during 2.5 h. After cooling, the solvents were removed under reduced pressure then the residue was hydrolysed and extracted with ethyl acetate. The organic layers were dried following by removal of the solvent under reduced pressure. The crude mixture was purified by flash chromatography (eluent: methylene chloride/methanol, 99/1) to provide compound (**15**) (530 mg, 72%) as a yellow solid: mp 162-163°C (Et_2O); IR (KBr) ν : 3300-3000 (NH) cm^{-1} ; ^{1}H-NMR ($CDCl_3$) δ : 3.83 (s,3H, OCH_3), 6.38 (d, J=2.9 Hz, 1H, H_3), 7.28 (d, J= 2.9 Hz, 1H, H_2), 7.41 (d, J=2.6 Hz, 1H, H_4), 8.06 (d, J=2.6 Hz, 1H, H_6), 10.26 (s, 1H, H_1). *Anal.* Calcd for $C_8H_8N_2O$: C, 64.85; H, 5.44; N, 18.91. Found: C, 64.69; H, 5.39; N, 18.79.

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

Under inert atmosphere, phosphorus oxychloride (1.5 mL, 15.5 mmol) was added to a solution of *N,N*-dimethylformamide (20 mL) at 0°C. After 10 min of stirring, a solution of compound (**15**) (230 mg, 1.55 mmol) in *N,N*-dimethylformamide (5 mL) was added. The reaction was stirred for 30 min at 0°C then heated at 80°C during 2 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 and evaporated *in vacuo*. The crude mixture was purified by flash chromatography (eluent: petroleum ether/ethyl acetate, 2/1) to provide compound (**16**) (113 mg, 41%) as a yellowish solid: amorphous solid; IR (KBr) ν : 3300-3000 (NH), 1657 (C=O) cm^{-1} ; ^{1}H-NMR (DMSO-d_6) δ : 3.79 (s, 3H, OCH_3), 7.85 (d, J=3.0 Hz, 1H, H_4), 8.04 (d, J=3.0 Hz, 1H,H_6), 8.32 (s, 1H, H_2), 9.83 (s, 1H, CHO), 12.50 (s, 1H, H_1). *Anal.* Calcd for $C_{10}H_9NO_2$: C, 58.53; H, 4.75; N, 15.93. Found: C, 58.75; H, 4.58; N, 15.74.

2-Cyanomethyl-6-methoxy-3-nitropyridine (17)

Under inert atmosphere, 2-methoxy-5-nitropyridine (15 g, 97.3 mmol) and 4-chlorophenoxyacetonitrile (17.9 g, 107 mmol) were dissolved in anhydrous tetrahydrofuran (292 mL). This solution was added slowly to a solution of potassium *t*-butoxide (24 g, 214 mmol) in anhydrous tetrahydrofuran (220 mL) at -10 °C. The reaction mixture was stirred during 3 h at -15 °C, following by the addition of 5% hydrochloric acid (167 mL). After extraction with ethyl acetate and drying of organic layers, the solvents were removed under reduced pressure. The crude mixture was purified by flash chromatography (eluent : petroleum ether/ethyl acetate, 2:1) to provide compound (**17**) (17.7 g, 83%) as a brown solid: mp 116-117°C (Et_2O); IR (KBr) ν: 2259 (C≡N), 1506 (NO_2), 1337 (NO_2) cm^{-1} ; ^{1}H-NMR ($CDCl_3$) δ: 4.13 (s, 3H, OCH_3), 4.43 (s, 2H, CH_2), 6.87 (d, J=9.0 Hz, 1H, H_5), 8.42 (d, J=9.0 Hz, 1H, H_4). ^{13}C-NMR ($CDCl_3$)

δ: 28.5 (CH_2), 56.4 (OCH_3), 112.8 (C_5), 116.4, 137.7 (C_4), 139.5, 147.2, 166.7 (CN). *Anal.* Calcd for $C_8H_7N_3O_3$: C, 56.30; H, 4.43; N, 20.52. Found: C, 56.15; H, 4.30; N, 20.70.

5-Methoxy-1*H*-pyrrolo[3,2-*b*]pyridine (18)

The nitrile (**17**) (17.7 g, 91.7 mmol) was dissolved in ethanol (300 mL). To this solution was added 10% palladium on charcoal (2.49 g) and the mixture was hydrogenated (45 psi) in a Parr shaker at rt during 5 h. The catalyst was filtered off and the solvent was removed under reduced pressure. The crude azaindole was purified by flash chromatography (eluent : petroleum ether/ethyl acetate, 3:1) to provide compound (**18**) (9.7 g, 81%) as a white solid: mp 111-112°C (pentane) (lit.,[21] 114-117 °C) ; IR (KBr) ν: 3412-3058 (NH) cm^{-1} ; ^{1}H-NMR (DMSO-d_6) δ : 3.88 (s, 3H, OCH_3), 6.44 (d, J=3.0 Hz, 1H, H_3), 6.57 (d, J=8.8 Hz, 1H, H_6), 7.48 (d, J=3.0 Hz, 1H, H_2), 7.72 (d, J=8.8 Hz, 1H, H_7), 11.17 (br s, 1H, H_1). ^{13}C-NMR (DMSO-d_6) δ : 51.9 (OCH_3), 100.2 (C_3), 103.7 (C_6), 121.6 (C_7), 123.6, 126.8 (C_2), 141.6, 158.2. *Anal.* Calcd for $C_8H_8N_2O$: C, 64.85; H, 5.44; N, 18.91. Found: C, 64.63; H, 5.60; N, 18.78.

3-Formyl-5-methoxy-1*H*-pyrrolo[3,2-*b*]pyridine (19)

The title compound was prepared from **18** according to the method used for the product (**11**). The crude product was purified by flash chromatography (eluent : petroleum ether/ethyl acetate, 1:1) to provide compound (**19**) in 32 % yield as a white solid: mp 188-189°C (ethyl acetate); IR (KBr) ν: 3114 (NH), 1647 (C=O) cm^{-1} ;^{1}H-NMR (DMSO-d_6) δ : 3.91 (s, 3H, OCH_3), 6.69 (d, J=8.8 Hz, 1H, H_6), 7.82 (d, J=8.8 Hz, 1H, H_7), 8.23 (s, 1H, H_2), 10.12 (s, 1H, CHO), 12.21 (br s, 1H, H_1). ^{13}C-NMR (DMSO-d_6) δ : 54.2 (OCH_3), 107.9 (C_6), 117.9, 125.1 (C_7), 126.6, 135.8 (C_2), 141.8, 162.1, 185.2 (CHO). *Anal.* Calcd for $C_{10}H_9NO_2$: C, 58.53; H, 4.75; N, 15.93. Found: C, 58.76; H, 4.62; N, 15.80.

5-Methoxy-3-[(*E*)-2-nitroethenyl]-1*H*-pyrrolo[2,3-*b*]pyridine (20)

To a solution of aldehyde (**16**) (0.260 g, 1.48 mmol) in nitromethane (6 mL) was added ammonium acetate (0.180 g, 2.3 mmol) and then, the mixture was stirred at 120°C during 4 h. After cooling and dilution with methylene chloride the mixture was hydrolysed and extracted. The organic layers were dried and concentrated *in vacuo*. The crude nitrovinyl compound (**20**) (0.164 g, 51%) was obtained as a yellow solid which was used without further purification in the next step: mp 230- 231°C; IR (KBr) ν : 3300-3000 (NH), 1500 (NO_2), cm^{-1} ; ^{1}H-NMR (DMSO-d_6) δ : 3.91 (s, 3H, OCH_3), 7.97 (d, J =2.7 Hz, 1H, H_4), 8.08 (d, J=2.7 Hz, 1H, H_6), 8.14 (d, J =13.4 Hz, 1H, CH), 8.30 (s, 1H, H_2), 8.37 (d, J =13.4 Hz, 1H, CH), 12.57 (s, 1H, H_1).

5-Methoxy-3-[(*E*)-2-nitroethenyl]-1*H*-pyrrolo[2,3-*c*]pyridine (21)

This compound was prepared according the same methodology described for derivative (**20**) and was obtained in 99% yield as a yellow solid which was used without further purification in the next step: mp 260-261°C; IR (KBr) ν: 3105 (NH), 1485 (NO_2), 1329 (NO_2) cm^{-1} ; ^{1}H-NMR (DMSO-d_6) δ : 3.88 (s,

3H, OCH_3), 7.28 (s, 1H, H_4), 7.99 (d, J=13.4 Hz, 1H, CH), 8.36 (s, 1H, H_7), 8.37 (d, J=13.4 Hz, 1H, CH), 8.46 (s, 1H, H_2), 11.43 (br s, 1H, H_1). ^{13}C-NMR (DMSO-d_6) δ : 53.9 (OCH_3), 98.5 (C_4), 107.0, 131.7, 131.8 (C_7), 132.0 (C), 134.1, 134.2 (C), 140.6 (C_2), 159.4.

5-Methoxy-3-[(*E*)-2-nitroethenyl]-1*H*-pyrrolo[3,2-*b*]pyridine (22)

This compound was prepared according the same methodology described for derivative (**20**) and was obtained in 76% yield as a yellow solid which was used without purification in the next step: mp 208-209°C. IR (KBr) ν: 3227 (NH), cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ : 3.94 (s, 3H, OCH_3), 6.71 (d, J=8.8 Hz, 1H, H_6), 7.83 (d, J=8.8 Hz, 1H, H_7), 8.17 (s, 1H, H_2), 8.29 (d, J=13.0 Hz, 1H, CH), 8.45 (d, J=13.0 Hz, 1H, CH), 11.98 (br s, 1H, H_1). ^{13}C-NMR (DMSO-d_6) δ 53.1 (OCH_3), 106.7 (C_6), 107.6, 124.2 (C_7), 126.3, 133.2 (C), 133.7 (C), 136.1 (C_2), 140.3, 160.7.

5-Methoxy-3-(2-nitroethyl)-1*H*-pyrrolo[2,3-*b*]pyridine (23)

To a stirred solution of nitro compound (**20**) (0.155 g, 0.71 mmol) in a mixture of isopropanol (5 mL) and chloroform (15 mL) was added at rt under inert atmosphere silica gel 230-400 mesh (0.450 g). To this suspension was added portionwise sodium borohydride (0.068 g; 1.78 mmol) and then, the mixture was stirred at rt during 2 h. After this time, to this reaction was added acetic acid (5 mL) and then the mixture was filtered off and the solvents were removed under reduced pressure. The crude mixture was purified by flash chromatography (eluent: methylene chloride/methanol, 99/1) to provide compound (**23**) (0.091 g, 58%) as a white solid: amorphous solid; IR (KBr) ν: 3300-3000 (NH), 1540 (NO_2), cm^{-1} ; ^{1}H-NMR (DMSO-d_6) δ : 3.31 (t, J=7.1 Hz, 2H, CH_2), 3.81 (s, 3H, OCH_3), 4.82 (t, J=7.1 Hz, 2H, CH_2), 7.67 (s, 1H, H_2), 8.05 (d, J=2.8 Hz, 1H, H_4), 8.40 (d, J=2.8 Hz, 1H, H_6), 12.01 (s, 1H, H_1). *Anal.* Calcd for $C_{10}H_{11}N_3O_3$: C, 54.54; H, 4.58; N, 19.08. Found: C, 54.37; H, 4.72; N, 19.22.

5-Methoxy-3-(2-nitroethyl)-1*H*-pyrrolo[2,3-*c*]pyridine (24)

This compound was prepared according the same methodology described for derivative (**23**). The crude mixture was purified by flash chromatography (eluent: petroleum ether/ethyl acetate, 2/1) to provide compound (**24**) in 45% yield as a white solid: mp 156-157°C (pentane); IR (KBr) ν: 3183 (NH), 1549 (NO_2) cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ : 3.30 (t, J=6.9 Hz, 2H, CH_2), 3.84 (s, 3H, OCH_3), 4.81 (t, J=6.9 Hz, 2H, CH_2), 6.93 (s, 1H, H_4), 7.42 (s, 1H, H_2), 8.33 (s, 1H, H_7), 11.14 (br s, 1H, H_1). ^{13}C-NMR (DMSO-d_6) δ : 22.8 (C), 53.7 (OCH_3), 75.8 (C), 95.6 (C_4), 107.9, 130.1 (C_2), 130.3 (C_7), 131.0, 135.6, 157.3. *Anal. Calcd for* $C_{10}H_{11}N_3O_3$: C, 54.54; H, 4.58; N, 19.08. *Found:* C, 54.82; H, 4.63; N, 18.95.

5-Methoxy-3-(2-nitroethyl)-1*H*-pyrrolo[3,2-*b*]pyridine (25)

This compound was prepared according the same methodology described for derivative (**23**). The crude mixture was purified by flash chromatography (eluent: petroleum ether/ethyl acetate, 2/1) to provide compound (**25**) in 52 % yield as a white solid: mp 66-67°C (pentane). IR (KBr) ν: 3193 (NH), 1551

(NO_2) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ : 3.48 (t, J=7.0 Hz, 2H, CH_2), 3.98 (s, 3H, OCH_3), 3.48 (t, J=7.0 Hz, 2H, CH_2), 6.60 (d, J=8.8 Hz, 1H, **H$_6$**), 7.12 (d, J=2.7 Hz, 1H, **H$_2$**), 7.51 (d, J=8.8 Hz, 1H, **H$_7$**), 8.13 (br s, 1H, **H$_1$**). ^{13}C-NMR ($CDCl_3$) δ : 23.0 (**C**), 53.3 (OCH_3), 75.1 (**C**), 105.7 (**C$_6$**), 109.8, 121.9 (**C$_7$**), 124.6, 124.8 (**C$_2$**), 141.2, 159.8. *Anal.* Calcd for $C_{10}H_{11}N_3O_3$: C, 54.54; H, 4.58; N, 19.08. Found: C, 54.80; H, 4.70; N, 19.29.

***N*-[2-(5-Methoxy-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)ethyl]acetamide (26)**

The saturated nitro compound (**23**) (0.085 g, 0.38 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 15 h. The catalyst was filtered off and the solvent was removed under reduced pressure. The crude amino derivative was obtained as a colourless oil which was used without purification in the next step. Under inert atmosphere, the crude amino derivative was dissolved in methylene chloride (1 mL), pyridine (86 µL) and acetic anhydride (43 µL, 0.46 mmol) at 0 °C. The mixture was stirred during 30 min at 0 °C then 1 h at rt before hydrolysis. The aqueous phase was neutralised with a saturated solution of sodium hydrogenocarbonate and extracted with methylene chloride. The organic layers were dried, the solvent was removed under reduced pressure. The crude mixture was purified by flash chromatography (eluent: methylene chloride/methanol, 95:5) to provide compound (**26**) (0.033 g, 37%) as a white solid: mp 163-164°C (Et_2O); IR (KBr) ν: 3300-3000 (NH), 1630 (C=O), cm^{-1} ; ^{1}H-NMR (DMSO-d_6) δ : 1.73 (s, 3H, $COCH_3$) ; 2.81 (t, J=7.6 Hz, 2H, CH_2), 3.38 (q, J=7.6 Hz, 2H, CH_2), 3.93 (s, 3H, OCH_3), 7.63 (d, J=2.4 Hz, 1H, **H$_2$**), 7.95 (d, J=2.7 Hz, 1H, **H$_4$**), 8.37 (t, J=7.6Hz, 1H, NHAc), 8.40 (d, J=2.7 Hz, 1H, **H$_6$**), 11.9 (br s, 1H, **H$_1$**). MS (CI/NH_3) *m/z*: 234 (M+1). *Anal.* Calcd for $C_{12}H_{15}N_3O_2$: C, 61.79; H, 6.48; N, 18.01. Found: C, 61.63; H, 6.42; N, 17.73.

***N*-[2-(5-Methoxy-1*H*-pyrrolo[2,3-*c*]pyridin-3-yl)ethyl]acetamide (27)**

This compound was prepared according the same methodology described for derivative (**26**). The crude mixture was purified by flash chromatography (eluent: methylene chloride/methanol, 95:5) to provide compound (**27**) in 45% yield as a white solid: mp 157-158°C (pentane). IR (KBr) ν: 3285 (NH), 1652 (C=O) cm^{-1} ; ^{1}H-NMR (DMSO-d_6) δ : 1.80 (s, 3H, $COCH_3$), 2.75 (t, J=7.2 Hz, 2H, CH_2), 4.81 (td, J=6.9 Hz, J=6.3 Hz, 2H, CH_2), 3.84 (s, 3H, OCH_3), 6.84 (s, 1H, **H$_4$**), 7.37 (s, 1H, **H$_2$**), 8.26-8.32 (m, 1H, NHAc), 8.31 (s, 1H, **H$_7$**), 11.01 (br s, 1H, **H$_1$**). ^{13}C-NMR (DMSO-d_6) δ 22.9 ($COCH_3$), 25.1 (**C**), 39.4 (**C**), 53.6 (OCH_3), 95.6 (**C$_4$**), 111.0, 129.3, 130.1, 131.2 (**C$_2$**), 136.2 (**C$_7$**), 157.1, 169.3 (**C**O). MS (IS) *m/z*: 234 (M+1). *Anal.* Calcd for $C_{12}H_{15}N_3O_2$: C, 61.79; H, 6.48; N, 18.01. Found: C, 61.61; H, 6.37; N, 17.83.

***N*-[2-(5-Methoxy-1*H*-pyrrolo[3,2-*b*]pyridin-3-yl)ethyl]acetamide (28)**

This compound was prepared according the same methodology described for derivative (**26**). The crude

mixture was purified by flash chromatography (eluent: petroleum ether/ethyl acetate, 2/1) to provide compound (**28**) in 64 % yield as a white solid: mp 155-156°C (pentane). IR (film) ν: 3286 (NH), 1659 (C=O) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ : 1.96 (s, 3H, COC**H**$_3$), 2.97 (t, J=6.2 Hz, 2H, C**H**$_2$), 3.57 (td, J=6.2 Hz, J=5.2 Hz, 2H, C**H**$_2$), 4.00 (s, 3H, OC**H**$_3$), 6.57 (d, J=8.8 Hz, 1H, **H**$_6$), 7.10 (d, J=2.5 Hz, 1H, **H**$_2$), 7.54 (d, J=8.8 Hz, 1H, **H**$_7$), 7.63-7.71 (m, 1H, N**H**Ac), 9.79 (br s, 1H, **H**$_1$). ^{13}C-NMR ($CDCl_3$) δ : 23.1 (CO**C**H$_3$), 23.8 (**C**), 41.8 (**C**), 53.2 (O**C**H$_3$), 104.9 (**C**$_6$), 112.9, 122.4 (**C**$_7$), 125.0, 125.2 (**C**$_2$), 141.3, 159.5, 170.5 (**C**O). MS (IS) *m/z*: 234 (M+1). *Anal.* Calcd for $C_{12}H_{15}N_3O_2$: C, 61.79; H, 6.48; N, 18.01. Found: C, 61.64; H, 6.40; N, 17.80.

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