

A STRAIGHTFORWARD SYNTHESIS OF PYRIDO-PYRAZINO[2,3-*b*]INDOLES AND INDOL[2,3-*b*]-QUINOXALINE

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Abstract- 1,2-Diamines (ethylenediamine, *o*-phenylenediamine, 2,3-diaminopyridine, 3,4-diaminopyridine) were reacted with 1-acetyl-2-bromo-3-indolinone to afford 5*H*-pyrazino[2,3-*b*]indoles, indolo[2,3-*b*]quinoxaline and pyridopyrazino[2,3-*b*]indole in good yields. Alkylation of the indolic nitrogen atom of these indolic derivatives with 2-chloroethylmorpholine, 2-chloroethyl-dimethylamine and allyl bromide was carried out in order to obtain the corresponding *N*-alkylated derivatives.

Ellipticine and a large number of analogues have been intensely studied for their antitumor properties.^{1,2} 6*H*-Indolo[2,3-*b*]quinoxalines which are structural analogues of ellipticine have also been largely explored by Bergman *et al.*³⁻⁶ These researches led to the development of 2,3-dimethyl-6-(2-dimethylaminoethyl)-6*H*-indolo[2,3-*b*]quinoxaline (**B-220**) (Figure 1) which is a potent antiviral compound against certain types of virus (HIV-1, CMV, VZV).

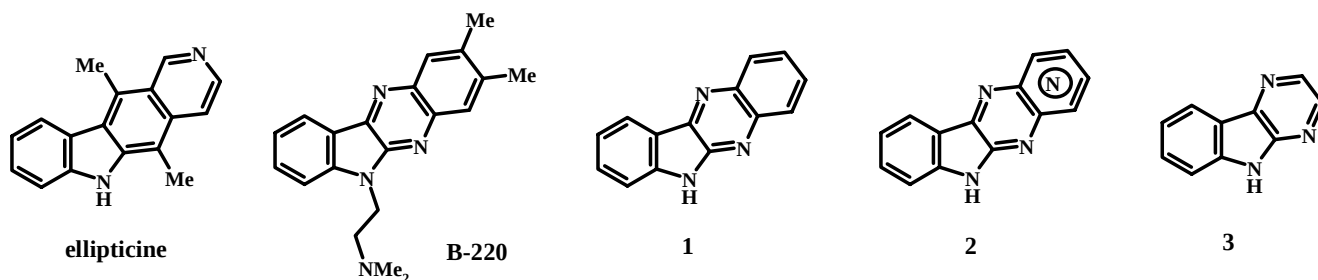
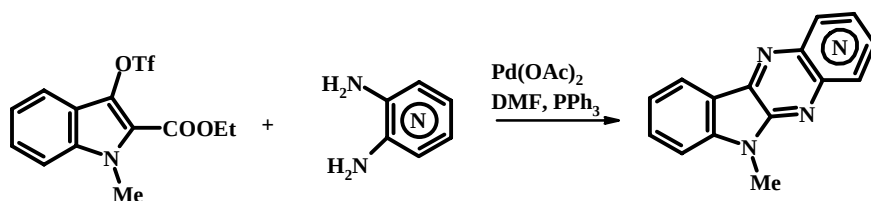


Figure 1.

This compound showed no effect on virus polymerases and it was instead believed to inhibit the virus decapsidation. The susceptibility of **B-220** to be reversibly intercalated in DNA may play a role in this

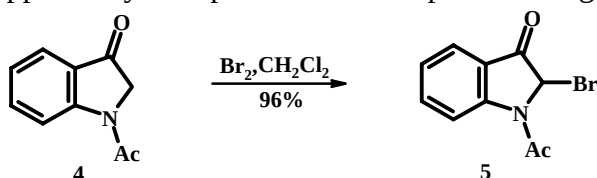
phenomena.³ In the same time, Bergman described⁷ the reaction of isatin with 1,2-diamines to afford derivatives (**1**, **2** and **3**) in three steps. In its approach all compounds of type (**2**) were obtained as mixture of regioisomers.

For some years we became interested in developing new approach to tetracyclic indolic⁸ and 7-azaindolic derivatives⁹ as new potential anticancer drugs. We have recently reported a new access to some indolic *N*-methylated analogs of **1**, **2** and **3** through the reaction of indolic triflates with 1,2-diamines¹⁰ (Scheme 1).



Scheme 1.

The major drawbacks for these reported procedures were the drastic conditions of synthesis and purification for compound (**2**) in the first case and the presence of the methyl group on the indolic nitrogen atom in our approach which impeded further substitution. More appropriate substituent such as an acetyl group would increase the versatility of the approach to **1**, **2** and **3** and might also improve the regioselectivity for **2**, giving opportunity to expand the desired pharmacological properties.



Scheme 2.

In the literature, Russian workers¹¹ have first described the bromination of 1-acetyl-3-indolinone (**4**)¹²⁻¹⁴ (Scheme 2) to obtain compound (**5**). This compound has been also recently condensed with ethyl imidazole-2-carboxylate¹⁵ to afford imidazo[1,2-*a*]pyrazin-4-one derivatives. Reactivity of bromo ketone (**5**) has been examined¹¹ with simple nucleophiles such as benzylamine, alcohols to afford 2-substituted 3-indolinones.

In the same way we have investigated the reaction of *t*Boc-β-alanine methyl ester with **5** in presence of various basic conditions. The 2-substituted derivative was only obtained with poor yield as an unstable oil. A dimeric derivative (**4b**) (Figure 2) was the major component of the reaction and the exclusive product using bromo ketone (**5**) with an appropriate base. To overcome this self condensation, freshly prepared **5** was directly used for condensation. First attempts with 1,2-diamines showed good condensation reactions.

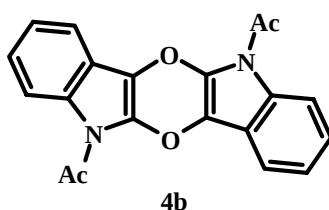
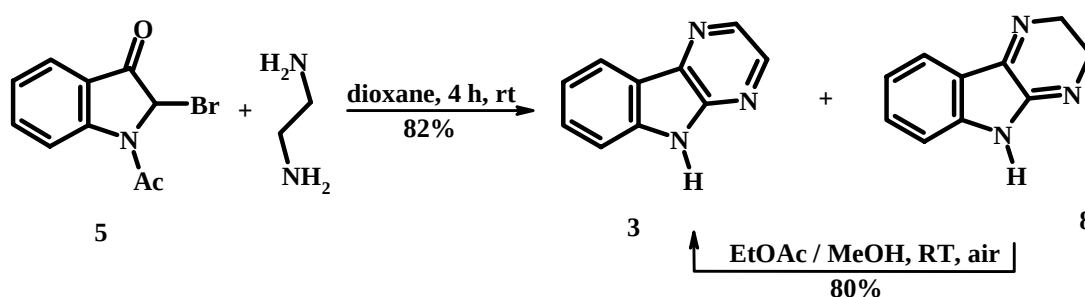


Figure 2.

Reaction with ethylenediamine

Ethylenediamine was first reacted with compound (**5**) in dioxane at rt to afford a mixture of two compounds (**3**) and (**8**) in 10 and 72 % yields respectively. Compound (**8**) was spontaneously aromatized (80 % yield) by air contact with stirring in ethyl acetate / methanol. Thus 5*H*-pyrazino[2,3-*b*]indole (**3**) was obtained in a global yield of 68 % (Scheme 3).

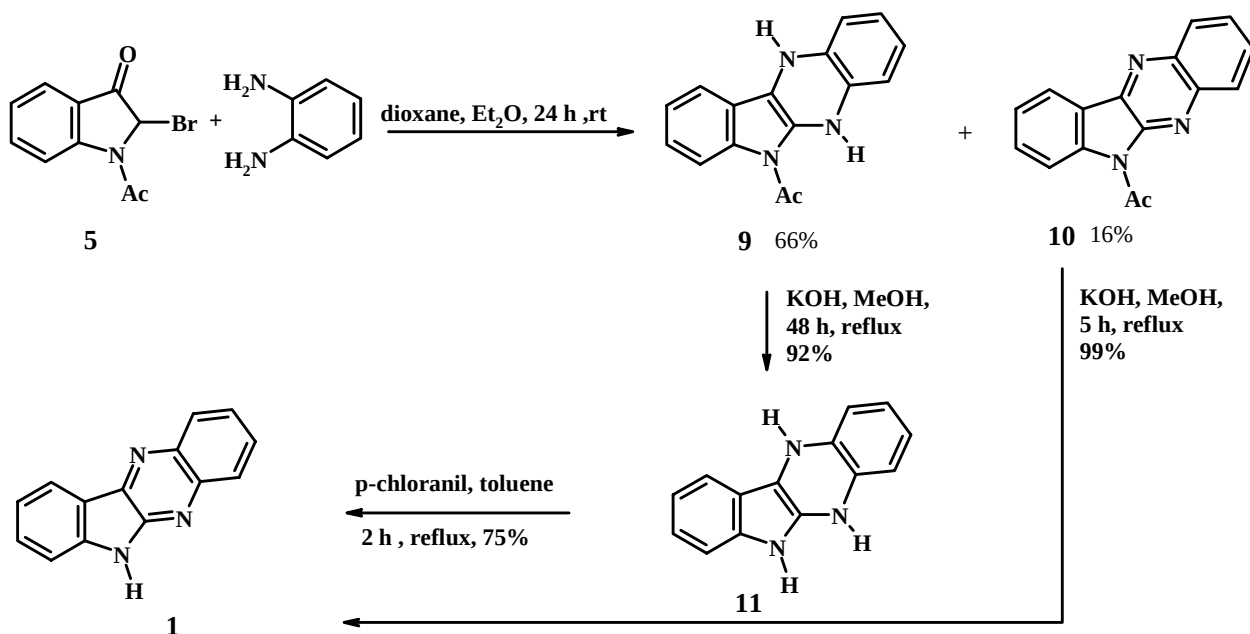


Scheme 3.

Deacetylation of the indolic nitrogen atom observed for cyclized derivatives (**3**)^{10,16} and (**8**) was attributed to the excess of ethylenediamine, leading to a one pot process of two steps (condensation and deacetylation). Bergman *et al.* have obtained **3**¹⁶ from *N*-acetylisatin in 4 steps in 41 % yield.¹⁷ Our results showed an improvement of previous synthesis of **3**.

Reaction with *o*-phenylenediamine

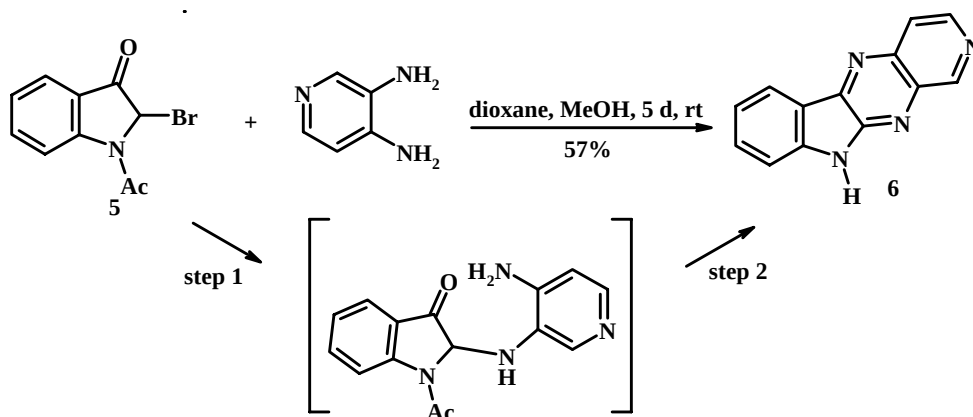
With this encouraging result, other diamines were tested. *o*-Phenylenediamine was reacted with **5** in dioxane / diethyl ether to afford a mixture of acetylated derivatives (**9**) and (**10**) in 66 and 16 % yields, respectively. No direct deacetylation was observed (Scheme 4). This step was achieved by refluxing for 2 days of a methanolic potassium hydroxide solution. Compound (**11**) so obtained in 92 % yield was treated in refluxing toluene in presence of *p*-chloranil to afford the 6*H*-indolo[2,3-*b*]quinoxaline (**1**)^{10,17} in 75 % yield. Basic hydrolysis of the amide bond of **10** was carried out in the same conditions as for **9** to afford also aromatized compound (**1**) in quantitative yield. The rate of hydrolysis of **10** was higher than for **9** (5 h instead of 48 h). Compound (**1**) was prepared with a global yield of 61 % for 3 steps.



Scheme 4.

Reaction with pyridinediamines

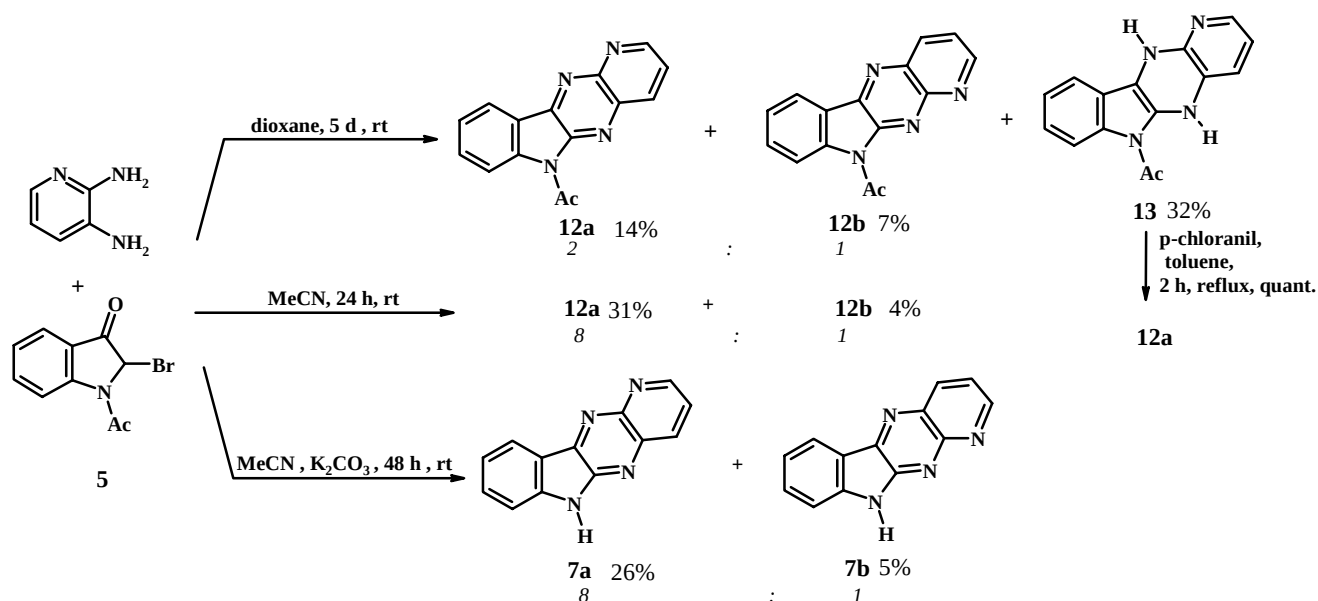
Further attempts with pyridinediamines were explored. Condensation of 3,4-diaminopyridine with **5** in dioxane /methanol at room temperature exclusively afford the fully aromatized derivative (**6**)^{7,10} in 60 % yield. The 3-amino substituent of the starting pyridine possesses the more nucleophilic nitrogen atom which displaced the bromo atom of **5** in the first step of the reaction. The indolic heterocycle was generated in the second step by condensation of the amino group and the carbonyl group followed by aromatization. Large excess of 3,4-diaminopyridine and the reaction time could explain the deacetylation of the final product (**6**). The selective regioselectivity might result from this postulated mechanism (Scheme 5).



Scheme 5.

In contrast, this regioselectivity was less efficient using 2,3-diaminopyridine (Scheme 6). Different conditions were performed to increase this effect. The condensation reaction of 2,3-diaminopyridine with

5 was also achieved according to several protocols in order to isolate only one regioisomer and to increase the selectivity of the reaction.



Scheme 6.

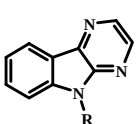
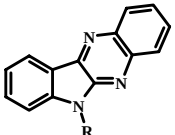
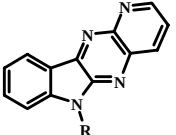
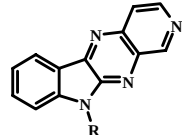
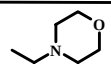
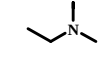
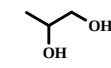
In dioxane, at room temperature for 5 days a mixture of three derivatives (**12a**, **12b** and **13**) was obtained in a global yield of 55%. After purification, compounds (**12a**) and (**13**) were obtained in 14 and 32 % yields, respectively. Major chromatographic fractions of **12b** were contaminated by **12a** (yield for **12b** (7%) was determined by NMR spectral data). The fully aromatized acetylated derivatives (**12a**) and (**12b**) were obtained in a 2 : 1 ratio and the regioselectivity of the reaction was in a 7 : 1 ratio (including **13**). In acetonitrile the reaction is more rapid (24 h) and only compounds (**12a**) and (**12b**) were obtained in a 8 : 1 ratio in a global yield of 36 %. Compound (**12a**) partially crystallized from the reaction mixture allowing an easy separation of the pure regioisomer (31% yield). If the reaction mixture is treated with potassium carbonate for 24 h, deacetylation occurred and compounds (**7a**)^{7,10} and (**7b**)^{7,10} were isolated as a mixture in a 8 : 1 ratio with a global yield of 44 %. After purification, **7a** was obtained in 26 % yield and compound (**7b**), contaminated by **7a** (2 : 5), was isolated in an approximate yield of 5 %. Compound (**13**) was aromatized with *p*-chloranil as for **1** to give exclusively compound (**12a**) in quantitative yield. Deacetylation of **12a** to **7a** was achieved, in quantitative yield, by refluxing for 12 h in a methanolic potassium hydroxide solution.

The regioselectivity could again be explained for the predominant regioisomers (**12a**) and (**7a**) by the result of displacement of the bromo atom by the more nucleophilic 3-amino group of the starting 2,3-diaminopyridine. The global yield of these reactions and the best regioselectivity are in favor of the synthesis using acetonitrile as solvent which simplify the purification of **12a**. The one pot synthesis is consistent with four consecutive reactions: 2 steps for heterocycle building, deacetylation and aromatiza-

tion to afford compound (**7a**) and (**7b**).

Having prepared the different heterocyclic derivatives (**1**, **3**, **6** and **7a**), introduction of aminoalkyl or hydroxyalkyl chains was achieved to increase both the solubility and mostly the potential anti-tumoral activity. To produce a large homogeneous family of compounds, three different chains were introduced using *N*-2-chloroethylmorpholine, 2-chloroethyldimethylamine and allyl bromide. The halides were reacted with **1**, **3**, **6** and **7a** in the presence of potassium carbonate according to the procedure of Zawadowski (Table 1).¹⁹ *N*-Alkylation of the indolic nitrogen atom was checked by NOESY experiments which excluded the alkylation of the pyrazine nitrogen atom.^{7,18} Compounds (**14-25**) prepared were reported in Table 1. Potassium permanganate oxidation of the double bond of compounds (**22-25**) affords diols (**26-29**) which might mimicked an hydrophilic residue and enhanced the water solubility.

Table 1.

Compounds R				
	14	15	16	17
	18	19	20	21
	22	23	24	25
	26	27	28	29

Our goal to develop a new access to pyridopyrazino[2,3-*b*]indoles and indolo[2,3-*b*]quinoxalines which were easily prepared and alkylated, was fully achieved. This straightforward and regioselective approach allowed us to prepare a set of functionalized derivatives which constituted a fully homogeneous family.

EXPERIMENTAL

¹H and ¹³C NMR spectra were recorded on a Bruker 250 instrument using CDCl₃ or DMSO-*d*₆. The chemical shifts are reported in ppm (δ scale) and all *J* values are in Hz. Melting point are uncorrected. IR absorption were recorded on a Perkin Elmer PARAGON 1000 PC and values were reported in cm⁻¹. MS spectra (Ion Spray) were performed on a Perkin Elmer Sciex PI 300. Monitoring of the reactions was performed using silica gel TLC plates (silica Merck 60 F₂₅₄). Spots were visualised by UV light at 254 and 356 nm. Column chromatography were performed using silica gel 60 (0.063-0.200 mm, Merck).

6H-Indolo[2,3-*b*]quinoxaline (1**)**^{10,17}

Method 1: Compound (**11**) (608 mg, 2.8 mmol) was dissolved in dry toluene (30 mL) under argon and *p*-chloranil (676.5 mg, 2.8 mmol) was then added; the reaction mixture was refluxed for 2 h. The solvent was removed under reduced pressure and the crude residue was chromatographed on a silica gel column with petroleum ether/ EtOAc 6:4 and Et₃N (1%) as eluent to give compound (**2**) as a yellow solid (448 mg, 75%).

Method 2: Compound (**10**) (213 mg, 1 mmol) was dissolved in a solution containing MeOH (25 mL), water (15 mL) and KOH (2.1 g, 37.5 mmol). The reaction mixture was refluxed for 48 h, then cooled and a solution of saturated NH₄Cl (25 mL) was added to obtain pH 8. The precipitate was filtered, washed with water (2 x 15 mL) and dried under vacuum to give compound (**1**) (181 mg, 99%): mp > 250°C (lit.,¹⁷ 295-296°C). IR (KBr, cm⁻¹) ν 748, 1209, 1407, 1616, 1704, 3144 (NH). ¹H NMR (DMSO-d₆) δ 7.37 (t, 1H, *J* = 8.2 Hz, Harom), 7.58 (d, 1H, *J* = 8.2 Hz, Harom), 7.68-7.83 (m, 3H, Harom), 8.06 (d, 1H, *J* = 7.7 Hz, Harom), 8.27 (d, 1H, *J* = 7.7 Hz, Harom), 8.33 (d, 1H, *J* = 7.7 Hz, Harom), 12.03 (s, 1H, NH, exchangeable with D₂O). ¹³C NMR (DMSO-d₆) δ 112.8 (CH), 118.8 (C), 121.5 (CH), 123.1 (CH), 126.4 (CH), 128.3 (CH), 129.6 (CH), 130.3 (CH), 135.2 (CH), 138.4 (C), 139.6 (C), 140.0 (C), 143.9 (C), 145.7 (C). MS (IS) 220 (M+H)⁺.

5*H*-Pyrazino[2,3-*b*]indole (**3**)^{10,16}

Compound (**8**) was dissolved in EtOAc (5 mL) and MeOH (5 mL) and the reaction mixture was stirred for 6 days at rt. The solvent was removed under reduced pressure and the crude residue was purified by flash chromatography with EtOAc - MeOH 8:2 as eluent to give compound (**3**) as a white solid (77 mg, 80 %): mp 240°C (lit.,¹⁶ 241-244°C). IR (KBr, cm⁻¹) ν 1182, 1399, 3414 (NH). ¹H NMR (DMSO-d₆) δ 7.35-7.41 (m, 1H, Harom), 7.55-7.67 (m, 2H, 2Harom), 8.22 (d, 1H, *J* = 8.2 Hz, Harom), 8.42 (d, 1H, *J* = 2.8 Hz, Harom), 8.48 (d, 1H, *J* = 2.8 Hz, Harom), 12.14 (s, 1H, NH). ¹³C NMR (DMSO-d₆) δ 112.9 (CH), 120.1 (C), 121.3 (CH), 121.8 (CH), 129.8 (CH), 136.1 (C), 137.2 (CH), 140.7 (CH), 141.1 (C), 146.3 (C). MS (IS) 170 (M+H)⁺.

1-Acetyl-2-bromo-3-indolinone (**5**)¹¹

A solution of 1-acetyl-3-indolinone (500 mg, 2.86 mmol) in dry CH₂Cl₂ (12 mL) was stirred under argon at rt. Bromine (170 μ L, 3.32 mmol) was added dropwise and the mixture was stirred for 20 min. The solvent was removed by distillation under reduced pressure and the residue triturated with petroleum ether 40-60 (20 mL). The brown solid was filtered, washed with petroleum ether (2x10 mL), dried under vacuum to give compound (**5**) (696 mg, 96 %): mp 134°C (lit.,¹¹ 129-130°C). IR (KBr, cm⁻¹) ν 1693, 1733. ¹H NMR (CDCl₃) δ 2.56 (s, 3H, CH₃), 6.14 (s, 1H, CHBr), 7.30 (td, 1H, *J* = 0.9 Hz, *J* = 7.5 Hz, Harom), 7.76 (td, 1H, *J* = 1.3 Hz, *J* = 7.5 Hz, Harom), 7.85 (dd, 1H, *J* = 1.3 Hz, *J* = 7.5 Hz, Harom), 8.35-8.45 (m, 1H, Harom). ¹³C NMR (CDCl₃) δ 21.1 (CH₃), 58.5 (CHBr), 118.7 (CH), 121.4 (C), 125.1

(CH), 125.3 (CH), 137.8 (CH), 150.7 (C), 168.2 (NCO), 190.7 (CO).

10H-Pyrido[4',3':5,6]pyrazino[2,3-*b*]indole (6)⁷

To a solution containing compound **(5)** (100 mg, 0.4 mmol) in dry dioxane (2 mL), a solution of 3,4-diaminopyridine (86 mg, 0.8 mmol) in dioxane / MeOH 1:1 (2 mL) was added dropwise at rt under argon. After 5 days, the solvent was removed under reduced pressure and the residue was purified by flash chromatography with EtOAc as eluent to give compound **(6)** as a yellow solid (100 mg, 57%); mp > 250°C (lit.,⁷ 282-284°C). IR (KBr, cm⁻¹) ν 1209, 1409, 1617, 3441 (NH). ¹H NMR (DMSO-*d*₆) δ 7.37 (t, 1H, *J* = 7.4 Hz, Harom), 7.62 (d, 1H, *J* = 7.4 Hz, Harom), 7.78 (td, 1H, *J* = 1.4 Hz, *J* = 7.4 Hz, Harom), 8.12 (d, 1H, *J* = 5.8 Hz, Harom), 8.38 (d, 1H, *J* = 7.4 Hz, Harom), 8.70 (d, 1H, *J* = 5.8 Hz, Harom), 9.45 (s, 1H, Harom), 12.32 (br s, 1H, NH). ¹³C NMR (DMSO-*d*₆) δ 112.0 (CH), 118.1 (C), 120.9 (CH), 121.0 (CH), 122.8 (CH), 132.5 (CH), 134.9 (C), 140.5 (C), 142.9 (CH), 143.2 (C), 144.9 (C), 146.0 (C), 151.8 (CH). MS (IS) 221 (M+H)⁺.

6H-Pyrido[2',3':5,6]pyrazino[2,3-*b*]indole (7a)⁷

Same procedure as for compound **(12a)**. After 24 h, K₂CO₃ (1.1 g, 8 mmol) was added to the reaction mixture which was stirred for 24 h. The precipitate was filtered, washed with MeCN and the solvent was removed under reduced pressure. The residue was purified by flash chromatography on silica gel with petroleum ether / EtOAc 1:9 as eluent to give compound **(7a)** as a yellow solid (54 mg, 26%). Compound **(7a)** was obtained also quantitatively by basic hydrolysis of compound **(12a)** (12 h, MeOH/H₂O/KOH, reflux) as described for compound **(1)**. mp > 250°C (lit.,⁷ > 360°C). IR (KBr, cm⁻¹) ν 1099, 1413, 1647, 3460 (NH). ¹H NMR (DMSO-*d*₆) δ 7.41 (t, 1H, *J* = 8 Hz, Harom), 7.62 (d, 1H, *J* = 8.0 Hz, Harom), 7.75 (t, 1H, *J* = 8.0 Hz, Harom), 7.83 (dd, 1H, *J* = 4.2 Hz, *J* = 8.0 Hz, Harom), 8.41 (d, 1H, *J* = 8.0 Hz, Harom), 8.52 (dd, 1H, *J* = 2.0 Hz, *J* = 8.0 Hz, Harom), 9.05-9.15 (m, 1H, Harom), 12.23 (br s, 1H, NH). ¹³C NMR (DMSO-*d*₆) δ 112.1 (CH), 118.7 (C), 120.9 (CH), 122.7 (CH), 123.9 (CH), 132.0 (CH), 135.1 (C), 136.3 (CH), 142.0 (C), 144.7 (C), 145.7 (C), 147.5 (C), 149.5 (CH). MS (IS) 221 (M+H)⁺.

10H-Pyrido[3',2':5,6]pyrazino[2,3-*b*]indole (7b)⁷

Obtained after column chromatography on silica gel of the mixture **(7a/7b)** with petroleum ether / EtOAc 1:9 as eluent. Yield 5%. ¹H NMR and ¹³C NMR spectral data were in agreement with those reported by Bergman.⁷

5H-Piperazino[2,3-*b*]indole (8)

To a solution of compound **(5)** (200 mg, 0.79 mmol) in dioxane (6 mL), 1,2-ethylenediamine (106 μ L, 1.57 mmol) was added dropwise at rt under argon. The reaction mixture was stirred for 5 h and silica gel was added. The solvent was removed under reduced pressure and the crude residue was purified by flash chromatography using EtOAc / MeOH 2:8 as eluent to give compound **(8)** as an unstable red solid (103

mg, 72%) and compound **(3)** (13 mg, 10 %). ^1H NMR (DMSO- d_6) δ 3.38 (t, 2H, J = 8.2 Hz, CH_2), 3.74 (t, 2H, J = 8.2 Hz, CH_2), 6.86 (t, 2H, J = 7.8 Hz, Harom), 7.31 (d, 1H, J = 7.8 Hz, Harom), 7.44 (d, 1H, J = 7.8 Hz, Harom), 9.17 (br s, 1H, NH). MS (IS) 172 ($\text{M}+\text{H}$) $^+$.

6-Acetyl-6,11-dihydro-5H-indolo[2,3-*b*]quinoxaline (9) and 6-Acetyl-6H-indolo[2,3-*b*]quinoxaline (10)

To a solution of compound **(5)** (500 mg, 2.36 mmol) in dry dioxane (18 mL) and dry diethyl ether (6 mL) at rt under argon, a solution of *o*-phenylenediamine (518 mg, 5.51 mmol) in dry dioxane (18 mL) was added dropwise. The reaction mixture was stirred for 24 h and the solvent was removed under reduced pressure. The crude residue was purified by flash chromatography with petroleum ether / EtOAc 7:3 as eluent to give first, compound **(9)** as a yellow solid (919 mg, 66%) and then compound **(10)** as a white solid (13 mg, 16%). **Compound (9)**: mp 168°C (EtOH). IR (KBr, cm^{-1}) ν 1308, 1544, 1595, 1686 (CO), 3300 (NH). ^1H NMR (DMSO- d_6) δ 2.02 (s, 3H, CH_3), 7.36 (td, 1H, J = 1.3 Hz, 7.8 Hz, Harom), 7.55 (td, 1H, J = 1.6 Hz, J = 8.2 Hz, Harom), 7.89-8.04 (m, 4H, Harom), 8.14-8.20 (m, 2H, Harom), 9.27 (s, 1H, NH), 10.86 (s, 1H, NH). ^{13}C NMR (DMSO- d_6) δ 24.8 (CH_3), 124.5 (CH), 125.4 (CH), 128.0 (C), 129.7 (CH), 130.9 (CH), 131.2 (CH), 131.3 (C), 131.4 (CH), 131.5 (CH), 138.0 (C), 141.2 (C), 141.3 (C), 146.4 (CH), 153.3 (C), 169.2 (C). MS (IS) 264 ($\text{M}+\text{H}$) $^+$. Anal. Calcd for $\text{C}_{16}\text{H}_{13}\text{N}_3\text{O}$: C, 72.99; H, 4.98; N, 15.96. Found: C, 73.38; H, 4.79; N, 16.25. **Compound (10)**: mp 215°C (EtOH). IR (KBr, cm^{-1}) ν 1296, 1383, 1454, 1706 (CO). ^1H NMR (CDCl_3) δ 3.25 (s, 3H, CH_3), 7.52 (td, 1H, J = 1.0 Hz, J = 8.0 Hz, Harom), 7.67-7.81 (m, 3H, Harom), 8.10-8.14 (m, 1H, Harom), 8.23-8.27 (m, 1H, Harom), 8.37-8.41 (m, 1H, Harom), 8.68 (d, 1H, J = 8.0 Hz, Harom). ^{13}C NMR (CDCl_3) δ 30.1 (CH_3), 120.1 (CH), 123.9 (C), 124.6 (CH), 127.1 (CH), 130.6 (CH), 130.9 (CH), 131.3 (CH), 131.6 (CH), 134.3 (CH), 141.7 (C), 142.6 (C), 143.4 (C), 144.5 (C), 147.3 (C), 173.1 (CO). MS (IS) 262 ($\text{M}+\text{H}$) $^+$. Anal. Calcd for $\text{C}_{16}\text{H}_{11}\text{N}_3\text{O}$: C, 73.55; H, 4.24; N, 16.08. Found: C, 73.90; H, 4.12; N, 16.31.

6,11-Dihydro-5H-indolo[2,3-*b*]quinoxaline (11)

Compound **(9)** (919 mg, 3.5 mmol) was dissolved in a solution containing MeOH (50 mL), water (10 mL) and KOH (4.6 g, 82 mmol). The reaction mixture was refluxed for 48 h. A solution of saturated NH_4Cl (25 mL) was added and pH was adjusted to pH = 8. The precipitate was filtered, washed with water (2 x 15 mL) and dried under vacuum to give compound **(11)** as a yellow solid (702 mg, 92 %); mp 230°C (EtOH). IR (KBr, cm^{-1}) ν 1088, 1539, 1615, 3255 (NH), 3359 (NH). ^1H NMR (DMSO- d_6) δ 6.70 (td, 1H, J = 1.2 Hz, J = 7.0 Hz, Harom), 6.85 (dd, 1H, J = 1.0 Hz, J = 8.2 Hz, Harom), 7.13 (s, 2H, NH), 7.21 (td, 1H, J = 1.2 Hz, J = 7.0 Hz, Harom), 7.79-7.82 (m, 2H, Harom), 7.93 (dd, 1H, J = 1.0 Hz, J = 8.2 Hz, Harom), 8.06 (td, 2H, J = 1.8 Hz, J = 7.2 Hz, Harom), 9.42 (s, 1H, NH). ^{13}C NMR (DMSO- d_6) δ 116.9 (CH), 117.2 (C), 117.7 (CH), 129.2 (CH), 129.4 (CH), 130.2 (CH), 130.3 (CH), 131.4 (CH), 132.1 (C),

140.1 (C), 140.7 (C), 145.6 (CH), 149.7 (C), 154.1 (C). MS (IS) 222 (M+H)⁺. Anal. Calcd for C₁₄H₁₁N₃: C, 76.00; H, 5.01; N, 18.99. Found: C, 76.35; H, 5.17; N, 18.71.

6-Acetyl-6H-pyrido[2',3':5,6]pyrazino[2,3-b]indole (12a)

To a solution containing compound **(5)** (240 mg, 0.95 mmol) in dry MeCN (6 mL), a solution of 2,3-diaminopyridine (129 mg, 1.18 mmol) in MeCN (9 mL) was added dropwise at rt under argon. After 24 h, the solution was filtered to isolate pure **12a** and the solvent was removed under reduced pressure; the residue was purified by flash chromatography with petroleum ether/ EtOAc 1:9 as eluent to afford a small amount of **12a** as a yellow solid. Global yield 31% (76 mg). Compound **(12a)** was also obtained in quantitative yield from compound **(13)** by aromatization, using the procedure described for compound **(1)** (*Method 1*). mp 212°C (EtOH). IR (KBr, cm⁻¹) ν 781, 1177, 1389; 1707 (CO). ¹H NMR (DMSO-d₆) δ 3.14 (s, 3H, CH₃), 7.61 (t, 1H, *J* = 7.7 Hz, Harom), 7.84-7.93 (m, 2H, Harom), 8.42 (d, 1H, *J* = 7.7 Hz, Harom), 8.59 (dd, 1H, *J* = 1.8 Hz, *J* = 8.4 Hz, Harom), 8.66 (dd, 1H, *J* = 0.8 Hz, *J* = 8.4 Hz, Harom), 9.15 (dd, 1H, *J* = 1.8 Hz, *J* = 8.4 Hz, Harom). ¹³C NMR (DMSO-d₆) δ 28.3 (CH₃), 118.2 (CH), 121.9 (C), 125.9 (CH), 126.0 (CH), 132.2 (C), 133.9 (CH), 135.1 (CH), 138.4 (C), 143.6 (CH), 144.3 (CH), 153.1 (C), 153.2 (C), 157.4 (C), 171.3 (CO). MS (IS) 263 (M+H)⁺. Anal. Calcd for C₁₅H₁₀N₄O: C, 68.69; H, 3.84; N, 21.36. Found: C, 68.97; H, 3.96; N, 21.54.

10-Acetyl-10H-pyrido[3',2':5,6]pyrazino[2,3-b]indole (12b)

Compound **(12b)** was eluted after **12a** using the same eluent; yield 4%; solid; mp 204°C (EtOH). ¹H-NMR (DMSO-d₆) δ 3.16 (s, 3H, CH₃), 7.61 (t, 1H, *J* = 7.7 Hz, Harom), 7.82-7.93 (m, 2H, Harom), 8.37 (d, 1H, *J* = 7.7 Hz, Harom), 8.66 (d, 1H, *J* = 8.0 Hz, Harom), 8.71 (d, 1H, *J* = 8.0 Hz, Harom), 9.14-9.17 (m, 1H, Harom).

10-Acetyl-10,11-dihydro-5H-pyrido[2',3':5,6]pyrazino[2,3-b]indole (13)

To a solution containing compound **(5)** (240 mg, 0.95 mmol) in dry dioxane (3 mL), a solution of 2,3-diaminopyridine (129 mg, 1.18 mmol) in dioxane (9 mL) was added dropwise at rt under argon. After 5 days, the solvent was removed under reduced pressure and the residue was purified by flash chromatography with petroleum ether - EtOAc 2:8 as eluent to give compound **(12a)** (15 mg, 14%), **(12b)** (7% obtained by NMR) and unstable compound **(13)** (80 mg, 32%). ¹H NMR (DMSO-d₆) δ 2.01 (s, 3H, CH₃), 7.34 (t, 1H, *J* = 7.7 Hz, Harom), 7.50-7.58 (m, 1H, Harom), 7.89 (dd, 1H, *J* = 4.2 Hz, *J* = 8.4 Hz, Harom), 8.01 (t, 2H, *J* = 7.7 Hz, Harom), 8.56 (dd, 1H, *J* = 1.8 Hz, *J* = 8.4 Hz, Harom), 9.18 (dd, 1H, *J* = 1.8 Hz, *J* = 4.2 Hz, Harom), 9.40 (s, 1H, NH), 11.10 (s, 1H, NH). ¹³C NMR (DMSO-d₆) δ 24.8 (CH₃), 123.7 (C), 125.4 (CH), 126.4 (CH), 127.4 (C), 131.5 (CH), 131.9 (CH), 136.4 (C), 138.2 (C), 138.7 (CH), 147.5 (CH), 150.0 (C), 155.4 (CH), 156.1 (C), 169.2 (CO). MS (IS) 265 (M+H)⁺. Anal. Calcd for C₁₅H₁₂N₄O: C, 68.17; H, 4.58; N, 21.20. Found: C, 68.42; H, 4.75; N, 21.01.

General procedure for alkylation

To a well stirred solution containing the derivative (**1**, **2**, **3** or **6**) dissolved in dry acetone (20 mL / 1 mmol) and K₂CO₃ (40 eq), the halogenated compound was added and the mixture stirred at reflux or rt. The solution was filtered and the precipitate was washed with acetone (10 mL). The solvent was removed under reduced pressure and the residue was purified by flash chromatography.

5-(2-Morpholinoethyl)-5*H*-pyrazino[2,3-*b*]indole (**14**)

Reflux, 30 h; eluent EtOAc; yield 65%; brown hygroscopic solid. IR (KBr, cm⁻¹) ν 1215, 1414, 3018. ¹H NMR (CDCl₃) δ 2.54-2.58 (m, 4H, Hmorph), 2.80 (t, 2H, *J* = 7.1 Hz, CH₂), 3.63 (t, 4H, *J* = 4.8 Hz, Hmorph), 4.59 (t, 2H, *J* = 7.1 Hz, CH₂), 7.38 (td, 1H, *J* = 1.0 Hz, *J* = 7.2 Hz, Harom), 7.53 (d, 1H, *J* = 8.4 Hz, Harom), 7.63 (dd, 1H, *J* = 1.0 Hz, *J* = 7.2 Hz, Harom), 8.34-8.38 (m, 2H, Harom), 8.47 (d, 1H, *J* = 2.8 Hz, Harom). ¹³C NMR (CDCl₃) δ 40.1 (CH₂), 54.9 (2CH₂), 57.7 (CH₂), 68.0 (2CH₂), 110.7 (CH), 120.8 (C), 122 (CH), 122.9 (CH), 130.2 (CH), 137.2 (C), 137.6 (CH), 140.5 (CH), 142 (C), 146.7 (C). MS (IS) 283.5 (M+H)⁺. Anal. Calcd for C₁₆H₁₈N₄O: C, 68.06; H, 6.43; N, 19.84. Found: C, 68.37; H, 6.25; N, 20.09.

6-(2-Morpholinoethyl)-6*H*-indolo[2,3-*b*]quinoxaline (**15**)¹⁹

Reflux, 28 h; eluent EtOAc; yield 75%; yellow solid; mp 135°C (lit.,¹⁹ 135-137°C). IR (KBr, cm⁻¹) ν 1117, 1413, 2816, 2950; ¹H NMR (CDCl₃) δ 2.59-2.62 (m, 4H, Hmorph), 2.80 (t, 2H, *J* = 6.9 Hz, CH₂), 3.60-3.64 (m, 4H, Hmorph), 4.61 (t, 2H, *J* = 6.9 Hz, CH₂), 7.35 (td, 1H, *J* = 0.8 Hz, *J* = 8.0 Hz, Harom), 7.48 (d, 1H, *J* = 8.0 Hz, Harom), 7.64-7.78 (m, 3H, Harom), 8.10 (dd, 1H, *J* = 1.0 Hz, *J* = 8.3 Hz, Harom), 8.30 (dd, 1H, *J* = 1.8 Hz, *J* = 8.3 Hz, Harom), 8.48 (d, 1H, *J* = 8.0 Hz, Harom). ¹³C NMR (CDCl₃) δ 39.3 (CH₂), 54.2 (CH₂), 56.7 (2CH₂), 67.3 (2CH₂), 109.8 (CH), 120.0 (C), 121.3 (CH), 123.2 (CH), 126.4 (CH), 128.2 (CH), 129.1 (CH), 129.7 (CH), 131.3 (CH), 139.7 (C), 140.4 (C), 141.0 (C), 144.7 (C), 146.1 (C). MS (IS) 333.5 (M+H)⁺.

6-(2-Morpholinoethyl)-6*H*-pyrido[2',3':5,6]pyrazino[2,3-*b*]indole (**16**)

Reflux, 19 h; eluent EtOAc / MeOH 9:1; yield 75%; yellow solid; mp 136°C (EtOH/H₂O). IR (KBr, cm⁻¹) ν 1114, 1415, 1605, 2824; ¹H NMR (CDCl₃) δ 2.47-2.51 (m, 4H, Hmorph), 2.79 (t, 2H, *J* = 6.4 Hz, CH₂), 3.4 (t, 4H, *J* = 4.7 Hz, Hmorph), 4.61 (t, 2H, *J* = 6.4 Hz, CH₂), 7.41-7.47 (m, 1H, Harom), 7.81-7.85 (m, 3H, Harom), 8.43 (d, 1H, *J* = 7.5 Hz, Harom), 8.50 (dd, 1H, *J* = 1.9 Hz, *J* = 8.2 Hz, Harom), 9.00 (dd, 1H, *J* = 1.9 Hz, *J* = 4.2 Hz, Harom). ¹³C NMR (CDCl₃) δ 40.7 (CH₂), 54.2 (2CH₂), 56.7 (CH₂), 67.0 (2CH₂), 111.8 (CH), 119.2 (C), 122.1 (CH), 123.6 (CH), 125.0 (CH), 132.9 (CH), 135.9 (C), 137.3 (CH), 142.6 (C), 145.8 (C), 146.0 (C), 148.6 (C), 150.5 (CH). MS (IS) 334.5 (M+H)⁺. Anal. Calcd for C₁₉H₁₉N₅O: C, 68.45; H, 5.74; N, 21.01. Found: C, 68.78; H, 5.90; N, 20.73.

10-(2-Morpholinoethyl)-10*H*-pyrido[4',3':5,6]pyrazino[2,3-*b*]indole (**17**)

Reflux, 28 h; eluent EtOAc; yield 74%; yellow solid; mp 198°C (EtOH/H₂O). IR (KBr, cm⁻¹) ν 1113, 1604, 2958. ¹H NMR (CDCl₃) δ 2.58-2.61 (m, 4H, Hmorph), 2.86 (t, 2H, J = 7.0 Hz, CH₂), 3.60 (t, 4H, J = 5.0 Hz, Hmorph), 4.59 (t, 2H, J = 7.0 Hz, CH₂), 7.37 (t, 1H, J = 8.0 Hz, Harom), 7.48 (d, 1H, J = 8.0 Hz, Harom), 7.74 (td, 1H, J = 1.3 Hz, J = 8.0 Hz, Harom), 8.06 (d, 1H, J = 5.8 Hz, Harom), 8.45 (d, 1H, J = 8.0 Hz, Harom), 8.72 (d, 1H, J = 5.8 Hz, Harom), 9.51 (s, 1H, Harom). ¹³C NMR (CDCl₃) δ 41.3 (CH₂), 563.0 (2CH₂), 58.4 (CH₂), 69.0 (2CH₂), 112.0 (CH), 121.0 (C), 123.7 (CH), 123.7 (CH), 125.3 (CH), 125.8 (C), 134.6 (CH), 137.6 (C), 143.8 (CH), 145.8 (C), 147.6 (C), 148.3 (C), 154.9 (CH). MS (IS) 334.5 (M+H)⁺. Anal. Calcd for C₁₉H₁₉N₅O: C, 68.45; H, 5.74; N, 21.01. Found: C, 68.81; H, 5.88; N, 21.34.

5-(2-Dimethylaminoethyl)-5H-pyrazino[2,3-*b*]indole (18)^{17a}

Reflux, 8 h; eluent EtOAc / MeOH 2:8; yield 65%; brown hygroscopic solid. IR (NaCl) ν 1179, 1413, 1623, 1667, 2822, 2945. ¹H NMR (CDCl₃) δ 2.34 (s, 6H, CH₃), 2.77 (t, 2H, J = 7.3 Hz, CH₂), 4.57 (t, 2H, J = 7.3 Hz, CH₂), 7.36 (td, 1H, J = 1.2 Hz, J = 7.2 Hz, Harom), 7.51 (d, 1H, J = 8.2 Hz, Harom), 7.62 (td, 1H, J = 1.2 Hz, J = 7.2 Hz, Harom), 8.33-8.38 (m, 1H, Harom), 8.29 (d, 1H, J = 2.8 Hz, Harom), 8.47 (d, 1H, J = 2.8 Hz, Harom). ¹³C NMR (CDCl₃) δ 40.2 (CH₂), 46.2 (2CH₃), 57.8 (CH₂), 110.0 (CH), 120.1 (C), 121.2 (CH), 122.1 (CH), 129.5 (CH), 136.5 (C), 136.9 (CH), 139.8 (CH), 141.3 (C), 145.8 (C). MS (IS) 241 (M+H)⁺. Anal. Calcd for C₁₄H₁₆N₄: C, 69.97; H, 6.71; N, 23.31. Found: C, 69.61; H, 6.93; N, 23.55.

6-(2-Dimethylaminoethyl)-6H-indolo[2,3-*b*]quinoxaline (19)^{18,20}

Reflux, 16 h; eluent EtOAc / MeOH 2:8; yield 89%; solid; mp 88°C (lit.,¹⁸ 88-90°C). IR (KBr, cm⁻¹) ν 1116, 1470, 1582, 2767. ¹H NMR (CDCl₃) δ 2.38 (s, 6H, CH₃), 2.83 (t, 2H, J = 7.2 Hz, CH₂), 4.57 (t, 2H, J = 7.2 Hz, CH₂), 7.33 (t, 1H, J = 7.2 Hz, Harom), 7.46 (d, 1H, J = 8.1 Hz, Harom), 7.45-7.77 (m, 3H, Harom), 8.11 (dd, 1H, J = 1.4 Hz, J = 8.1 Hz, Harom), 8.28 (dd, 1H, J = 1.4 Hz, J = 8.1 Hz, Harom), 8.45 (d, 1H, J = 8.1 Hz, Harom). ¹³C NMR (CDCl₃) δ 39.8 (CH₂), 45.8 (2CH₃), 57.0 (CH₂), 109.4 (CH), 119.6 (C), 120.8 (CH), 122.7 (CH), 125.9 (CH), 127.9 (CH), 128.6 (CH), 129.3 (CH), 130.9 (CH), 139.3 (C), 140.0 (C), 140.6 (C), 144.3 (C), 145.6 (C). MS (IS) 291 (MH)⁺.

6-(2-Dimethylaminoethyl)-6H-pyrido[2',3':5,6]pyrazino[2,3-*b*]indole (20)⁷

Reflux, 4 h; eluent EtOAc / MeOH 2:8; yield 48%; yellow solid; mp 95°C (lit.,⁷ 93-94°C). IR (KBr, cm⁻¹) ν 1414, 1471, 1608. ¹H NMR (CDCl₃) δ 2.37 (s, 6H, CH₃), 2.83 (t, 2H, J = 7.0 Hz, CH₂), 4.59 (t, 2H, J = 7.0 Hz, CH₂), 7.36 (t, 1H, J = 8.3 Hz, Harom), 7.50 (d, 1H, J = 8.3 Hz, Harom), 7.65-7.82 (m, 2H, Harom), 8.46 (dd, 1H, J = 2.0 Hz, J = 8.3 Hz, Harom), 8.53 (d, 1H, J = 7.7 Hz, Harom), 9.08 (dd, 1H, J = 2.0 Hz, J = 4.2 Hz, Harom). ¹³C NMR (CDCl₃) δ 39.8 (CH₂), 45.5 (2CH₃), 56.8 (CH₂), 109.4 (CH), 119.2 (C), 121.1 (CH), 123.4 (CH), 123.6 (CH), 131.6 (CH), 135.4 (C), 136.5 (CH), 142.3 (C), 144.9 (C),

145.4 (C), 148.2 (C), 149.4 (CH). MS (IS) 292 (M+H)⁺.

10-(2-Dimethylaminoethyl)-10H-pyrido[4',3':5,6]pyrazino[2,3-b]indole (21)⁷

Reflux, 22 h; eluent EtOAc / MeOH 2:8; yield 96%; yellow solid; mp 150°C; (lit.,⁷ 148-149.5°C). IR (KBr, cm⁻¹) ν 1409, 1605, 2764. ¹H NMR (CDCl₃) δ 2.39 (s, 6H, CH₃), 2.86 (t, 2H, *J* = 7.0 Hz, CH₂), 4.63 (t, 2H, *J* = 7.0 Hz, CH₂), 7.45 (t, 1H, *J* = 8.2 Hz, Harom), 7.54 (d, 1H, *J* = 8.2 Hz, Harom), 7.75 (t, 1H, *J* = 8.2 Hz, Harom), 8.10 (d, 1H, *J* = 5.9 Hz, Harom), 8.50 (d, 1H, *J* = 8.2 Hz, Harom), 8.74 (d, 1H, *J* = 5.9 Hz, Harom), 9.57 (s, 1H, Harom). ¹³C NMR (CDCl₃) δ 40.0 (CH₂), 45.8 (2CH₃), 57.0 (CH₂), 109.8 (CH), 118.9 (C), 121.4 (CH), 121.5 (CH), 123.6 (CH), 132.5 (CH), 135.5 (C), 141.7 (C), 143.6 (CH), 143.7 (C), 145.5 (C), 146.1 (C), 152.9 (CH). MS (IS) 292 (M+H)⁺.

5-Allyl-5H-pyrazino[2,3-b]indole (22)

Reflux, 17 h; eluent petroleum ether/ EtOAc 5:5; yield 65%; yellow oil. IR (KBr, cm⁻¹) ν 1180, 1409, 1462, 3052. ¹H NMR (CDCl₃) δ 5.08-5.22 (m, 4H, =CH₂, CH₂N), 5.95-6.10 (m, 1H, =CH), 7.38 (t, 1H, *J* = 8.1 Hz, Harom), 7.46 (d, 1H, *J* = 8.1 Hz, Harom), 7.61 (td, 1H, *J* = 1.0 Hz, *J* = 8.1 Hz, Harom), 8.35-8.39 (m, 2H, Harom), 8.48 (d, 1H, *J* = 2.6 Hz, Harom). ¹³C NMR (CDCl₃) δ 46.0 (CH₂), 112.5 (CH), 119.7(CH₂), 122.1 (C), 123.4 (CH), 124.1 (CH), 131.6 (CH), 134.5 (CH), 138.6 (C), 139.1 (CH), 141.9 (CH), 143.4 (C), 147.6 (C). MS (IS) 210 (M+H)⁺. Anal. Calcd for C₁₃H₁₁N₃: C, 74.62; H, 5.30; N, 20.08. Found: C, 74.90; H, 5.48; N, 19.87.

6-Allyl-6H-indolo[2,3-b]quinoxaline (23)

Reflux, 2 h; eluent petroleum ether/ EtOAc 8:2; yield 85%; yellow oil. IR (KBr, cm⁻¹) ν 1117, 1466, 1609. ¹H NMR (CDCl₃) δ 5.08-5.24 (m, 4H, =CH₂, CH₂N), 5.79-6.13 (m, 1H, =CH), 7.39 (t, 2H, *J* = 7.0 Hz, Harom), 7.60-7.77 (m, 3H, Harom), 8.11 (dd, 1H, *J* = 1.6 Hz, *J* = 8.2 Hz, Harom), 8.30 (dd, 1H, *J* = 1.9 Hz, *J* = 8.2 Hz, Harom), 8.46 (dd, 1H, *J* = 0.6 Hz, *J* = 7.2 Hz, Harom). ¹³C NMR (CDCl₃) δ 43.0 (CH₂), 109.4 (CH), 118.9 (CH₂), 118.9 (C), 120.4 (CH), 122.0 (CH), 125.4 (CH), 127.1 (CH), 128.1 (CH), 128.7 (CH), 130.3 (CH), 131.3 (CH), 138.7 (C), 139.4 (C), 139.9 (C), 143.7 (C), 144.7 (C). MS (IS) 260 (M+H)⁺. Anal. Calcd for C₁₇H₁₃N₃: C, 78.74; H, 5.05; N, 16.20. Found: C, 79.06; H, 5.21; N, 16.38.

6-Allyl-6H-pyrido[2',3':5,6]pyrazino[2,3-b]indole (24)

rt, 17 h; eluent EtOAc, yield 80%; yellow solid; mp 196°C (EtOAc). IR (KBr, cm⁻¹) ν 1111, 1407, 1603. ¹H NMR (CDCl₃) δ 5.08-5.30 (m, 4H, =CH₂, CH₂N), 5.90-6.12 (m, 1H, =CH), 7.36-7.43 (m, 2H, Harom), 7.60-7.70 (m, 2H, Harom), 8.42 (d, 1H, *J* = 8.0 Hz, Harom), 8.53 (d, 1H, *J* = 7.8 Hz, Harom), 9.07 (d, *J* = 2 Hz, 1H, Harom). ¹³C NMR (CDCl₃) δ 44.2 (CH₂), 110.6 (CH), 117.5 (CH₂), 119.2 (C), 121.9 (CH), 124.2 (CH), 124.2 (CH), 132.0 (CH), 132.3 (CH), 135.5 (C), 137.0 (CH), 142.4 (C), 144.9 (C), 145.2 (C), 148.4 (C), 149.6 (CH). MS (IS) 261 (M+H)⁺. Anal. Calcd for C₁₆H₁₂N₄: C, 73.83; H, 4.65;

N, 21.52. Found: C, 73.54; H, 4.81; N, 21.63.

10-Allyl-10H-pyrido[4',3':5,6]pyrazino[2,3-b]indole (25)

rt, 23 h; eluent EtOAc; yield 85%; yellow solid; mp 193°C (EtOAc / petroleum ether). IR (KBr, cm^{-1}) ν 1201, 1447, 1604. ^1H NMR (CDCl_3) δ 5.10-5.25 (m, 4H, $=\text{CH}_2$, CH_2N), 6.02-6.13 (m, 1H, $=\text{CH}$), 7.43 (t, 2H, $J = 7.8$ Hz, Harom), 7.73 (d, 1H, $J = 7.8$ Hz, Harom), 8.07 (d, 1H, $J = 5.8$ Hz, Harom), 8.46 (d, 1H, $J = 7.8$ Hz, Harom), 8.73 (d, 1H, $J = 5.8$ Hz, Harom), 9.54 (s, 1H, Harom). ^{13}C NMR (CDCl_3) δ 44.2 (CH_2), 110.7 (CH), 118.2 (CH_2), 119.2 (C), 121.9 (CH), 122.3 (C), 123.9 (CH), 131.9 (CH), 132.9 (CH), 135.9 (C), 142.1 (C), 143.9 (CH), 144.1 (CH), 145.8 (C), 146.1 (C), 153.2 (CH). MS (IS) 261 ($\text{M}+\text{H}$) $^+$. Anal. Calcd for $\text{C}_{16}\text{H}_{12}\text{N}_4$: C, 73.83; H, 4.65; N, 21.52. Found: C, 73.54; H, 4.78; N, 21.69.

General procedure for hydroxylation. To a well stirred solution containing the *N*-allyl derivative (**22**, **23**, **24** or **25**, 0.5 mmol) dissolved in acetone / water 3:1 (20 mL / 1 mmol) at 0°C, KMnO_4 (79 mg, 0.5 mmol) dissolved in acetone / water 3:1 (0.06 mmol / mL) was added portionwise and the solution stirred at rt for an appropriate time. After decoloration, the reaction mixture was filtered and the precipitate was washed with MeOH (10 mL). The solvent was removed under reduced pressure and the residue was purified by flash chromatography.

5-(2,3-Dihydroxypropyl)-5H-pyrazino[2,3-b]indole (26)

Reaction time, 6 h, eluent petroleum ether / EtOAc 5:5, yield 85%, yellow solid: mp 164°C (EtOAc). IR (KBr, cm^{-1}) ν 1062, 1133, 1478, 3290 (OH). ^1H NMR ($\text{DMSO}-d_6$) δ 3.47-3.52 (m, 2H, CH_2O), 4.40-4.49 (m, 1H, CH), 4.44 (dd, 1H, $J = 4.4$ Hz, 14.2 Hz, CHN), 4.60 (dd, 1H, $J = 4.4$ Hz, $J = 14.2$ Hz, CHN), 4.86 (t, 1H, $J = 5.6$ Hz, OH, exchangeable with D_2O), 4.99 (d, 1H, $J = 5.4$ Hz, OH exchangeable with D_2O), 7.40 (td, 1H, $J = 1.4$ Hz, $J = 8.2$ Hz, Harom), 7.71 (td, 1H, $J = 1.4$ Hz, $J = 8.2$ Hz, Harom), 7.86 (d, 1H, $J = 8.2$ Hz, Harom), 8.31 (d, 1H, $J = 8.2$ Hz, Harom), 8.55 (dd, 2H, $J = 1.4$ Hz, $J = 8.2$ Hz, Harom). ^{13}C NMR ($\text{DMSO}-d_6$) δ 45.7 (NCH_2), 64.8 (OCH_2), 70.8 (CH), 112.1 (CH), 119.6 (C), 121.4 (CH), 121.6 (CH), 129.8 (CH), 136.0 (C), 137.2 (CH), 140.5 (CH), 142.2 (C), 145.9 (C). MS (IS) 244 ($\text{M}+\text{H}$) $^+$. Anal. Calcd for $\text{C}_{13}\text{H}_{13}\text{N}_3\text{O}_2$: C, 64.19; H, 5.39; N, 17.27. Found: C, 64.57; H, 5.54; N, 17.53.

6-(2,3-Dihydroxypropyl)-6H-indolo[2,3-b]quinoxaline (27)

Reaction time, 3 h, eluent petroleum ether / EtOAc 5:5, yield 74%, yellow solid: mp 216°C (EtOAc / petroleum ether). IR (KBr, cm^{-1}) ν 1121, 1470, 3298 (OH). ^1H NMR ($\text{DMSO}-d_6$) δ 3.51 (s, 2H, CH_2O), 4.12 (m, 1H, CH), 4.44 (dd, 1H, $J = 7.8$ Hz, $J = 14.2$ Hz, CHN), 4.54 (dd, 1H, $J = 4.2$ Hz, $J = 14.2$ Hz, CHN), 4.84 (s, 1H, OH, exchangeable with D_2O), 4.99 (d, 1H, $J = 5.0$ Hz, OH, exchangeable with D_2O), 7.40 (td, 1H, $J = 1.5$ Hz, $J = 7.8$ Hz, Harom), 7.70-7.85 (m, 4H, Harom), 8.11 (d, 1H, $J = 7.8$ Hz, Harom), 8.28 (dd, 1H, $J = 1.3$ Hz, $J = 8.3$ Hz, Harom), 8.38 (d, 1H, $J = 7.8$ Hz, Harom). ^{13}C NMR ($\text{DMSO}-d_6$) δ 45.8 (NCH_2), 64.8 (OCH_2), 70.4 (CH), 112.0 (CH), 119.4 (C), 121.7 (CH), 122.8 (CH),

126.8 (CH), 128.3 (CH), 129.8 (CH), 129.9 (CH), 132.0 (CH), 139.4 (C), 140.5 (C), 140.8 (C), 146.0 (C), 146.3 (C). MS (IS) 294 (M+H)⁺. Anal. Calcd for C₁₇H₁₅N₃O₂: C, 69.61; H, 5.15; N, 14.33. Found: C, 69.97; H, 5.03; N, 14.51.

6-(2,3-Dihydroxypropyl)-6H-pyrido[2',3':5,6]pyrazino[2,3-b]indole (28)

Reaction time, 2 h; eluent EtOAc / MeOH 9:1; yield 59%; yellow solid; mp 240°C (EtOAc). IR (KBr, cm⁻¹) ν 1418, 1471, 1605, 3394 (OH). ¹H NMR (DMSO-d₆) δ 3.51 (t, 2H, *J* = 5.3 Hz, CH₂O), 4.08-4.15 (m, 1H, CH), 4.44 (dd, 1H, *J* = 8.2 Hz, *J* = 14.2 Hz, CHN), 4.54 (dd, 1H, *J* = 8.2 Hz, *J* = 14.2 Hz, CHN), 4.85 (t, 1H, *J* = 5.6 Hz, OH, exchangeable with D₂O), 4.99 (d, 1H, *J* = 5.3 Hz, OH, exchangeable with D₂O), 7.40-7.47 (m, 1H, Harom), 7.80-7.85 (m, 3H, Harom), 8.41 (d, 1H, *J* = 7.5 Hz, Harom), 8.53 (dd, 1H, *J* = 1.9 Hz, *J* = 8.5 Hz, Harom), 9.05 (dd, 1H, *J* = 1.9 Hz, *J* = 4.0 Hz, Harom). ¹³C NMR (DMSO-d₆) δ 46.1 (CH₂), 64.8 (CH₂), 70.4 (CH), 112.3(CH), 119.2 (C), 121.9 (CH), 123.4 (CH), 124.9 (CH), 126.3 (C), 132.8 (CH), 137.3 (CH), 142.8 (C), 146.3 (C), 146.7 (C), 148.6 (C), 150.4 (CH). MS (IS) 295 (M+H)⁺. Anal. Calcd for C₁₆H₁₄N₄O₂: C, 65.30; H, 4.79; N, 19.04. Found: C, 65.74; H, 4.98; N, 19.23.

10-(2,3-Dihydroxypropyl)-10H-pyrido[4',3':5,6]pyrazino[2,3-b]indole (29)

Reaction time, 5 h; eluent EtOAc / MeOH 9:1; yield 36%; yellow solid; mp 244°C (EtOAc / petroleum ether). IR (KBr, cm⁻¹) ν 1125, 1395, 1608, 3321 (OH). ¹H NMR (DMSO-d₆) δ 3.53 (t, 2H, *J* = 5.7 Hz, CH₂O), 4.10-4.17 (m, 1H, CH), 4.44 (dd, 1H, *J* = 7.9 Hz, *J* = 14.3 Hz, CHN), 4.56 (dd, 1H, *J* = 4.4 Hz, *J* = 14.3 Hz, CHN), 4.87 (t, 1H, *J* = 5.7 Hz, OH), 4.99 (d, 1H, *J* = 5.0 Hz, OH), 7.42-7.48 (m, 1H, Harom), 7.84 (d, 2H, *J* = 3.5 Hz, Harom), 8.16 (d, 1H, *J* = 5.5 Hz, Harom), 8.40-8.44 (m, 1H, Harom), 8.73 (d, 1H, *J* = 5.5 Hz, Harom), 9.50 (s, 1H, Harom). ¹³C NMR (DMSO-d₆) δ 48.4 (CH₂), 67.1 (CH₂), 72.6 (CH), 114.7(CH), 121.2 (C), 124.3 (CH), 124.5 (CH), 132.2 (CH), 135.8 (CH), 138.2 (C), 144.1 (CH), 146.5 (C), 149.2 (C), 149.5 (C), 152.2 (CH), 155.2 (C). MS (IS) 295 (M+H)⁺. Anal. Calcd for C₁₆H₁₄N₄O₂: C, 65.30; H, 4.79; N, 19.04. Found: C, 65.03; H, 4.90; N, 18.78.

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