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REGIOSELECTIVE SYNTHESES OF 1-, 2-, 3- AND 4-AMINOINDOLO-[2,3-*b*]QUINOXALINES

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Abstract – In view of the contradictory results published in the literature concerning the structure of the indoloquinoxalines obtained by condensation of isatin with an unsymmetrical benzene-1,2-diamine, regioselective syntheses of the 1-, 2-, 3-, and 4-aminoindolo[2,3-*b*]quinoxalines have been developed. With the four derivatives in hand, isomers obtained by direct cyclocondensations starting from amino or nitro substituted benzene-1,2-diamines could be unambiguously identified. The results of these studies show, on the one hand, that some previous findings need revision and, on the other hand, that the 1-amino isomer could be prepared in one step and in 58% yield.

INTRODUCTION

As part of a program directed at developing new antitumor agents which target DNA, the biological activity of indolo[2,3-*b*]quinoxalines prompted us to design new derivatives bearing aminoalkylamino chains in various positions. A previous work has described the *N,N'*-dialkylation of the indolo[2,3-*b*]-quinoxaline nucleus. The three possible regioisomers have been selectively synthesized and the structures of the *N,N'*-dimethylated salts have been unambiguously determined by NMR correlation sequences (NOESY ^{1}H-^{1}H, HMQC ^{1}H-^{13}C, HMBC ^{1}H-^{13}C).[1] In order to introduce chains on the D-ring, we need to have in hand the corresponding amino heterocycles.

The most classical pathway for the synthesis of indolo[2,3-*b*]quinoxalines consists in the cyclocondensation of an indole-2,3-dione (**1**) (isatin) with a benzene-1,2-diamine. When unsymmetrical diamines are used (3- or 4-substituted diamines **5** or **2**), the condensation may obviously lead to the

production of structural isomers *i.e.* a mixture of the 1- and 4-substituted indoloquinoxalines **6**–**7** in the first case and of the 2- and 3-isomers in the later one **3**–**4** (cf. Table 1). Some authors claimed that the results can be rationalized according to the mechanism of the cyclocondensation: the more nucleophilic amino group of the phenylenediamine reacts with the more electrophilic 3-carbonyl group of isatin and a subsequent dehydratation between the second amino group and the lactamic carbonyl affords the tetracycle.[2-4] However, several contradictory examples have been published in the literature.

Syntheses starting from benzene-1,2-diamines **2** substituted in the 4-position by various substituents, have been claimed to give only the 2-substituted indoloquinoxalines (**3**, R = NO_2[4], Cl[5] , F[6] , CF_3[6], CH_3[7]), only the 3-substituted isomer (**4**, R = Cl[8], COOH[8]), one isomer whose structure was not specified (R = COOH[9], NO_2[2], F[10], CF_3[11]) or a mixture of both derivatives (R = OCH_3[12], CN[13], OEt[9]). Drushlyak *et al.* claimed to have obtained only the 3-nitroindoloquinoxaline (**4a**) in a three step pathway: condensation of the 4-nitrobenzene-1,2-diamine (**2a**) with the *N*-acetylisatin to give the 3-(2-acetylaminophenyl)-7-nitroquinoxalin-2-one, deacetylation and subsequent cyclization in boiling acetic acid.[4]

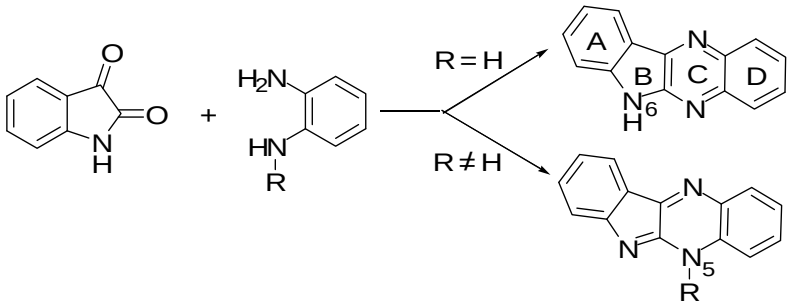
Under the same manner, from the corresponding 3-substituted benzene-1,2-diamines **5**, the preparation of indoloquinoxalines bearing a substituent in the 1-position **6** and in the 4-position **7** has been published (R = halogen[12] , OCH_3[14], COOH[15], $COOCH_3$[13]).

Structural assignments, usually only based on elemental analyses and, in two cases, on melting points[4,9] are not convincing. Furthermore, on most cases, when a mixture of isomers was known to be obtained, they were not separable. As an exception, the 1- and 4-methyl esters have been isolated after flash column chromatography on silica gel but have not been unambiguously identified.[13] Regardless, it was not possible to assign structures from ^{1}H or ^{13}C NMR spectra to the indoloquinoxalines substituted either on the 2- or 3- position or on the 1- or 4-position. More recently, by condensation of 2,3-diaminobenzoic acid (**5**, R = COOH) with isatin (**1**), Deady *et al.*[15] have obtained indolo[2,3-*b*]quinoxaline-1- and 4-carboxylic acids respectively in a 1:4 ratio using indirect chemical proof in the structural elucidation. According to these authors, treatment of the mixture with H_2O_2 in acetic acid afforded only the *N*-oxide of the 4-substituted isomer.

In contrast to the reaction with C-substituted diamines, it is well known that the reaction of isatin with a *N*-alkylated benzene-1,2-diamine led exclusively to the corresponding N^5-alkylated heterocycle, the primary amine reacting initially with the keto function of isatin (Scheme 1).[1] In light of these results, regioselective syntheses of the 1- and 4-hydroxyindolo[2,3-*b*]quinoxalines have been described in 1970 by Kidani *et al*. respectively from the N^1-methyl- and N^2-methyl-3-methoxybenzene-1,2-diamines.[14]

Treatment of the 1- or 4-methoxy-5-methyl intermediates by boiling hydrobromic acid in acetic acid resulted in simultaneous *N*- and *O*-demethylations. According to this pathway, Bergman *et al.* have patented the preparation of several indoloquinoxalines substituted in the 2 or 3-positions by methyl,

methoxy and carboxylic groups.[16] Surprisingly contrary to the previous paper, methoxyindoloquinoxalines have been obtained after hydrobromic acid-acetic acid treatment of the corresponding N^5-methylated analogues. However, such drastic experimental conditions of demethylation are not usable with unstable groups such as amines.



Scheme 1 Classical syntheses of indolo[2,3-*b*]quinoxalines

In this paper, we report regioselective syntheses of the 1-, 2-, 3-, and 4-aminoindolo[2,3-*b*]quinoxalines and we unambiguously determine the isomeric structures obtained by cyclocondensation of isatin with substituted benzene-1,2-diamines.

RESULTS AND DISCUSSION

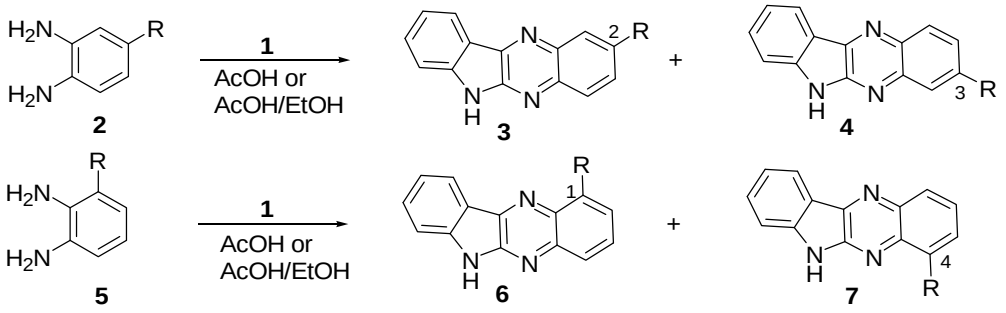
In view of the contradictory results published in the literature, we decided to study first the cyclocondensation of isatin (**1**) with easily available amino- or nitro-benzene-1,2-diamines. By reaction of the 4-nitro-1,2-diaminobenzene (**2a**) with isatin (**1**) in refluxing acetic acid, Drushlyak *et al.*[4] claimed to have isolated 72% of the 2-nitroisomer **3a** (mp 338-340 °C). Previously, in the same conditions, Buu Hoï *et al.*[2] has observed that one of the isomers, which structure assignment was not undertaken, is predominantly produced and seems to be isolated in the pure state after recrystallization from pyridine (mp 340 °C, 80% yield).

In our hands, this reaction afforded, in 70% yield, a mixture of the 2- and 3-nitro isomers **3a**-**4a** in a 1:2 ratio determined by ^{1}H NMR (Table 1). The melting point of the crude mixture (337 °C) coincide with the data published for a pure 2-nitro derivative.[2,4] The two isomers could not be separated by chromatography. Catalytic hydrogenation led also to a 1:2 inseparable mixture of the corresponding amines **3b**–**4b**. Similarly, an isomeric mixture of acetylamino derivatives **3c**–**4c** (1:1 ratio) was obtained starting from the 4-acetylaminobenzene-1,2-diamine[17] (**2c**). Finally, reaction of the unstable benzene-1,2,4-triamine[18] (**2b**) gave a mixture of unidentified products.

In contrast, under similar conditions, the benzene-1,2,3-triamine[19] (**5b**) led to a 97:3 mixture of the 1- and 4- isomers **6b**–**7b** (60%) and the major isomer could be isolated in a pure state by washing the mixture

with acetone. NMR spectra did not allow unambiguous assignment of the isomeric structure.

Table 1 Cyclocondensation of isatin (**1**) with substituted benzene-1,2-diamines **2** and **5**



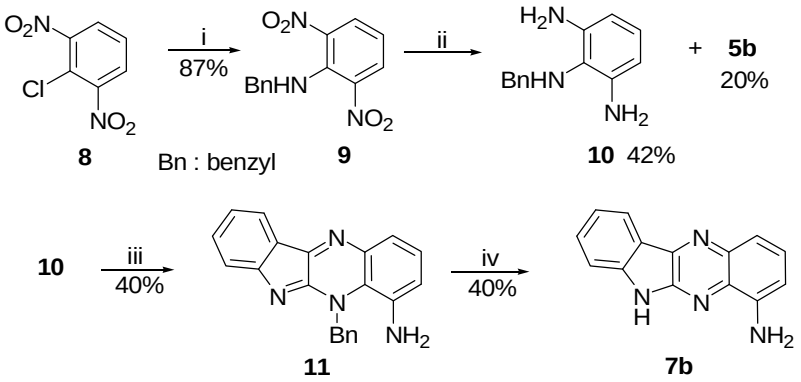
a R = NO_2 **b** R = NH_2 **c** R = NHAc

Amine	Yield (%)	Ratio
2a	70	b **3a** - **4a** 1:2; **3b** - **4b** 1:2[a]
2b	—[c]	
2c	58	**3c** - **4c** 1:1
5b	60	d **6b** - **7b** 97:3[a]
	58	**6b**

a Determined by comparison with the ^{1}H NMR spectra of pure isomers. b Catalytic reduction. c Complex mixture of unidentified products. d Washings with acetone.

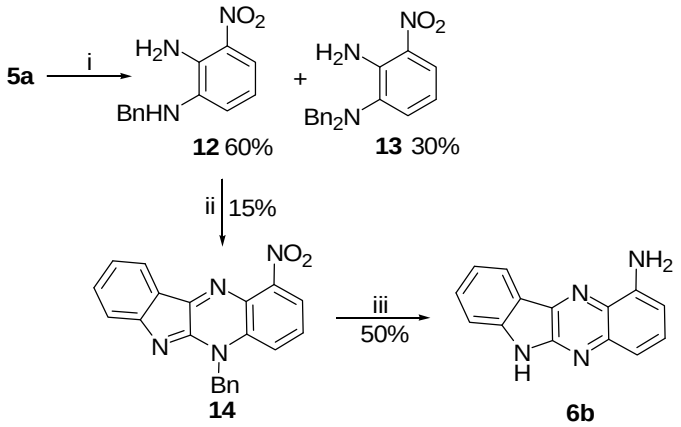
In this light, we found it convenient to envisage regioselective syntheses of the four aminoindolo[2,3-*b*]-quinoxalines **3b**, **4b**, **6b**, **7b** *via* the N^5-benzyl heterocycles which can be deprotected in mild conditions by catalytic hydrogenation.

Synthesis of the 5-benzyl-4-aminoindoloquinoxaline (**11**) could be envisaged by condensation of the symmetrical N^2-benzylbenzene-1,2,3-triamine (**10**) with isatin (**1**) (Scheme 2). Therefore, the dinitrobenzylaniline **9** was prepared by nucleophilic aromatic substitution of the commercially available 2,6-dinitrochlorobenzene (**8**). Unfortunately, it was not possible to reduce the nitro groups of **9** without concomitant *N*-debenzylation into **5b**. On the contrary to the other syntheses (Scheme 4), catalytic hydrogenation over Raney nickel afforded triamine **5b** as a major product with a small amount of the expected compound. Finally, compound **10** was obtained in 42% yield using a mixture of hydrazine hydrate and Raney nickel as a reducing agent. Condensation of **10** with isatin (**1**) and subsequent catalytic debenzylation (H_2/Pd-C) afforded the 4-aminoindolo[2,3-*b*]quinoxaline (**7b**).



Scheme 2 Reagents and conditions: i, $BnNH_2$, AcONa, EtOH, reflux; ii, H_2N-$NH_2.H_2O$, Raney Ni, EtOH-$ClCH_2CH_2Cl$, 50 °C; iii, **1**, EtOH-AcOH, reflux; iv, H_2, Pd-C, EtOH, rt.

For the synthesis of the 1-amino isomer **6b**, it was not possible to use the unsymmetrical N^1-benzylbenzene-1,2,3-triamine. We had envisioned a selective *N*-alkylation of the nitro-diamine **5a** (Scheme 3). Using benzyl bromide, **5a** was regioselectively benzylated on the less hindered amino function to give **12** (structure confirmed by NOESY correlations between CH_2 of the benzyl group and 6-H) but, whatever the conditions, the *N,N*-dibenzyl derivative **13** was also obtained. Total conversion of

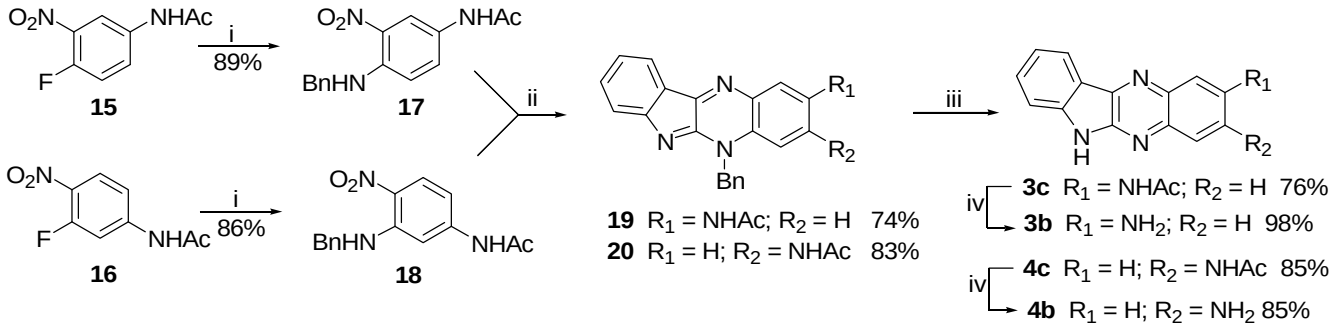


Scheme 3 Reagents and conditions: i, BnBr, K_2CO_3, DMF, rt; ii, **1**, AcOH, AcONa, reflux; iii, H_2, Raney Ni, EtOH then H_2, Pd-C.

5a was accomplished only when using 1.5 equivalent of the alkylating agent; under such conditions, compound **12** could be isolated in 60% yield after flash chromatography. Reaction with isatin (**1**) afforded a mixture of several products. In the best case, the expected benzylindoloquinoxaline **14** was obtained in 15% yield. The first attempt for the transformation of **14** into **6b** by hydrogenation using Pd-C as a catalyst was unsuccessful. Finally, compound **6b** was obtained by two successive catalytic hydrogenations without isolation of the intermediate. This pathway furnished the 1-aminoindoloquinoxaline (**6b**) in three steps and in only 4.5% yield but without any doubt on the position

of the amino group. This unambiguous regioselective synthesis allowed us to identify as the 1-amino isomer **6b**, the major product obtained in 58% yield by reaction of the triamine **5b** with isatin (**1**) (Table 1).

For the syntheses of the 2-amino and 3-aminoindolo[2,3-*b*]quinoxalines (**3b**) and **(4b**) (Scheme 4), the intermediate 2-amino-*N*-benzylanilines substituted either in the 4- or in the 5-position could be obtained from the corresponding fluoronitroanilines. In order to introduce the benzylamino functions *via* a S_{Nar}, the amino groups have to be protected first.



Scheme 4 Reagents and conditions: i, $BnNH_2$, AcONa, EtOH, reflux; ii, H_2, Raney Ni, EtOH then **1**, AcOH, reflux; iii, H_2, Pd-C, EtOH; iv, HCl, EtOH, reflux.

Consequently, compounds **17** and **18** have been prepared by reaction of benzylamine on the fluoro derivatives **15**[20] and **16**[21]. The latter was synthesized by nitration of 3-fluoroacetanilide according to Lynch[21] but obtained only in 40% yield besides 20% of the 6-nitro isomer (lit.,[21] ratio 6/4: 0.04, 52% yield in pure 4-nitro). On the contrary to the previous series, the nitro groups of derivatives **17** and **18** can be reduced by catalytic hydrogenation using Raney nickel as a catalyst without debenzylation. The resulting unstable diamines were immediately condensed with isatin (**1**) to give the 5-benzylindolo[2,3-*b*]quinoxalines **19** and **20** which structures were confirmed by NOESY correlations between CH_2 and 4-H. After hydrogenolysis (Pd-C) to give compounds **3c** and **4c**, the removal of the acetyl protective groups were achieved by acid hydrolysis. According to these pathways, the 2-amino and the 3-aminoisomers **3b** and **4b** were obtained from the fluoronitroacetanilide **15** and **16** in 4 steps with yields of 49% and 52%, respectively.

CONCLUSION

In view of the contradictory results published in the literature concerning the structure of the indoloquinoxalines obtained by condensation of isatin with an unsymmetrical benzene-1,2-diamine, regioselective syntheses of the 1-, 2-, 3-, and 4-aminoindolo[2,3-*b*]quinoxalines have been developed.

With the four isomers in hand, it is now possible to identify the products obtained by direct cyclocondensations of substituted benzene-1,2-diamines with isatin. It is noteworthy that the major derivative obtained starting from benzene-1,2-3-triamine is the 1-aminoisomer which could then be prepared in one step and in 58% yield.

These results show that the structure of the obtained indoloquinoxalines cannot be rationalized in terms of difference in nucleophilicity between the two functions of the benzene-1,2-diamine used as a starting material. The more nucleophilic 2-amino function of 1,2,3-triaminobenzene (**5b**) reacted with the keto function of isatin and furnished mixed yield 60% (ratio **6b**:**7b** = 97:3). In contrast, the 3-nitro isomer **4a** was obtained as a major product using 4-nitrodiamine **2a** by reaction of the amine *para* to the electronwithdrawing nitro group and the reaction of the 4-acetylaminodiamine **2c** afforded a 1:1 mixture of both 2- and 3-isomers **3c**–**4c**, indicating that previously reported structures need revisions.

The new synthetic pathways could be expanded to the preparation of different indolo[2,3-*b*]quinoxalines, either mono or polysubstituted by aminoalkyl chains in various positions.

EXPERIMENTAL

Thin-layer chromatography was carried out on Merck GF 254 silica gel plates. Flash chromatography was performed on Merck silica gel 70 (30-70 μm) or on Merck aluminum oxide 90 active, neutral. Melting points were determined on a Maquenne apparatus and are uncorrected. Element analyses were performed at the C.N.R.S. Analysis Laboratory, Gif-sur-Yvette. ^{1}H and ^{13}C NMR spectra were recorded on Bruker AC 300 and COSY, HSQC, HMBC, NOESY spectra with AC 400 spectrometers. Multiplicities were listed as s (singlet), d (doublet), t (triplet), and m (multiplet). Chemical shift values are given in ppm (δ), using residual protic solvent as internal standard. IR spectra were obtained on Nicolet 510FT-IR.

Synthesis of the 4-aminoindolo[2,3-*b*]quinoxaline (7b)

***N*-Benzyl-2,6-dinitroaniline (9).** A mixture of 2,6-dinitrochlorobenzene (**8**) (0.81 g, 4.00 mmol), benzylamine (0.7 mL, 6.00 mmol), and anhydrous sodium acetate (0.66 g, 8.00 mmol) in EtOH (100 mL) was refluxed for 3 h. After the solvent had been removed by evaporation, the solid residue was dissolved in CH_2Cl_2 and washed with water. The organic layer was dried over Na_2SO_4 and evaporated. The oily residue was triturated with MeOH (10 mL) and the resulting precipitate was filtered off to give a pure yellow powder (0.95 g, 87%), which was used in the next step without further purification. An analytical sample was prepared by flash chromatography (silica gel, CH_2Cl_2-MeOH, 100:0 to 95:5); mp 98 °C. IR (KBr): ν = 3332, 1620, 1572, 1521, 1498, 1449, 1349, 1277, 1105, 916, 906, 747, 716, 698 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.20 (s, 2H, CH_2), 6.83 (t, J = 8 Hz, 1H, 4-H), 7.29 (m, 2H, 2 × ArH), 7.39 (m, 3H, 3 × ArH), 8.23 (d, J = 8 Hz, 2H, 3-H and 5-H), 8.63 (s, 1H, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ =

50.9 (CH_2), 114.6 (C-4), 127.9 (2 × CH), 128.5 (CH), 129.2 (2 × CH), 132.4 (C-3 and C-5), 136.5 (2 × C-q), 138.1 (C-q), 139.7 (C-q). Anal. Calcd for $C_{13}H_{11}N_3O_4.1/4H_2O$: C, 56.22; H, 4.17; N, 15.13. Found: C, 56.18; H, 3.92; N, 15.09.

***N*^{2}-Benzylbenzene-1,2,3-triamine 10 and benzene-1,2,3-triamine (5b).** Hydrazine hydrate (0.73 mL, 15.00 mmol) was added dropwise over a 30 min period to a suspension of *N*-benzyl-2,6-dinitroaniline (**9**) (0.82 g, 3.00 mmol) and Raney nickel (0.40 g) in a 1:1 EtOH/1,2-dichloroethane mixture (40 mL). After heating for 15 min at 50 °C, the catalyst was filtered off, and the solvents were eliminated in vacuo. The resulting brown oil was purified by flash chromatography (silica gel, CH_2Cl_2) to give **10** (0.27 g, 42%) and then **5b** (0.07 g, 20%) as brown oils. The unstable amine **10** was used immediately in the next step. **10**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.32 (br s, 4H, 2 × NH_2), 4.16 (s, 2H, CH_2), 6.20 (d, *J* = 8 Hz, 2H, 4-H and 6-H), 6.80 (t, *J* = 8, 1H, 5-H), 7.35 (m, 6H, 5 × ArH and NH). **5b**[19]: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.24 (br s, 6H, 3 × NH2), 6.34 (d, *J* = 8 Hz, 2H, 4-H and 6-H), 6.63 (t, *J* = 8 Hz, 1H, 5-H).

4-Amino-5-benzyl-5*H*-indolo[2,3-*b*]quinoxaline (11). A solution of isatin (**1**) (0.10 g, 0.68 mmol) in AcOH (10 mL) was added to a solution of triamine **10** (0.19 g, 0.88 mmol) in EtOH (10 mL) and the mixture was refluxed for 30 min. The solvents were eliminated under reduced pressure and MeOH was added to give a precipitate which was filtered off, washed with water and purified by flash chromatography (aluminum oxide, CH_2Cl_2-MeOH, 98:2) to give a red solid (0.09 g, 40%); mp 194 °C. IR (KBr): ν = 3429, 3277, 1627, 1577, 1565, 1531, 1440, 1419, 1365, 1307, 1265, 1217, 1195, 1116, 1012, 952, 870, 832, 758, 738, 723, 690 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 5.16 (s, 2H, NH_2), 6.42 (s, 2H, CH_2), 7.13 (d, *J* = 7 Hz, 2H, 2 × ArH), 7.22 (m, 5H, 1-H or 3-H, 9-H and 3 × ArH), 7.28 (t, *J* = 9 Hz, 1H, 2-H), 7.52 (d, *J* = 8 Hz, 1H, 7-H), 7.61 (t, *J* = 8 Hz, 1H, 8-H), 7.65 (d, *J* = 9 Hz, 1H, 1-H or 3-H), 8.14 (d, *J* = 8 Hz, 1H, 10-H). ^{13}C NMR (75 MHz; DMSO-d_6): δ = 51.2 (CH_2), 118.6 (C-7), 120.1 (C-q), 120.3 (C-1 or C-3), 121.3 (C-9), 121.5 (C-1 or C-3), 122.8 (C-10), 123.4 (C-q), 124.7 (C-2), 126.6 (2 × CH), 127.8 (CH), 129.2 (2 × CH), 133.0 (C-8), 137.3 (C-q), 137.9 (C-q), 138.6 (C-q), 148.8 (C-q), 152.7 (C-q), 159.1 (C-q). Anal. Calcd for $C_{21}H_{16}N_4$: C, 77.76; H, 4.97; N, 17.27. Found: C, 78.02; H, 5.23; N, 17.25.

4-Amino-6*H*-indolo[2,3-*b*]quinoxaline (7b). A suspension of *N*-benzylated derivative **11** (0.10 g, 0.3 mmol) in EtOH (20 mL) was hydrogenated for 1 h at rt under a 5 bar pressure in the presence of 10% palladium on charcoal (0.05 g). After filtration of the catalyst, the solution was concentrated under reduced pressure. The resulting precipitate was filtered off and purified by flash chromatography (aluminum oxide, CH_2Cl_2) to give **7b** as a yellow solid (0.03 g, 40%); mp 312 °C. IR (KBr): ν = 3413, 3284, 1636, 1602, 1515, 1480, 1460, 1397, 1347, 1322, 1285, 1242, 1204, 1173, 1102, 1084, 887, 853,

820, 788, 749, 732 cm^{-1}. ^1H NMR (300 MHz; DMSO-d_6): δ = 5.84 (s, 2H, NH_2), 6.96 (t, J = 6 Hz, 1H, 2-H), 7.34 (t, J = 8 Hz, 1H, 9-H), 7.42 (m, 2H, 1-H and 3-H), 7.56 (d, J = 8 Hz, 1H, 7-H), 7.68 (t, J = 8 Hz, 1H, 8-H), 8.32 (d, J = 8 Hz, 1H, 10-H), 11.93 (s, 1H, NH). ^{13}C NMR (75 MHz; DMSO-d_6): δ = 108.7 (C-2), 112.4 (C-7), 115.9 (C-1 or C-3), 119.5 (C-q), 120.9 (C-9), 122.5 (C-10), 127.1 (C-1 or C-3), 130.0 (C-q), 131.3 (C-8), 139.7 (C-q), 139.9 (C-q), 144.2 (C-q), 144.3 (C-q), 144.7 (C-q). Anal. Calcd for $C_{14}H_{10}N_4.1/2H_2O$: C, 69.12; H, 4.56; N, 23.03. Found: C, 69.15; H, 4.39; N, 23.31.

Synthesis of the 1-aminoindolo[2,3-*b*]quinoxaline (6b)

***N*^{1}-Benzyl-3-nitrobenzene-1,2-diamine (12) and *N*^{1},*N*^{1}-dibenzyl-3-nitrobenzene-1,2-diamine (13).** To a suspension of diamine **5a** (0.61 g, 4.00 mmol) and dried potassium carbonate (0.61 g, 4.40 mmol) in DMF (20 mL) was added benzyl bromide (0.52 mL, 4.40 mmol). The mixture was stirred at rt for 72 h and then a second amount of benzyl bromide (0.19 mL, 1.60 mmol) was added. Two days later, after elimination of the solvent, the residue was extracted with CH_2Cl_2. The organic layers were washed with water, dried over Na_2SO_4 and evaporated. The oily residue was purified by flash chromatography (silica gel, CH_2Cl_2-cyclohexane, 50:50 to 80:20) to give compound **13** as a yellow oil (0.40 g, 30%) and then the expected derivative **12** as a purple solid (0.58 g, 60%). **13:** IR: ν = 3490, 3367, 1617, 1575, 1517, 1497, 1453, 1358, 1322, 1265, 1182, 1078, 1028, 876, 738, 699 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 4.06 (s, 4H, 2 × CH_2), 6.55 (dd, J = 7 and 8 Hz, 1H, 5-H), 6.84 (br s, 1H, NH_2), 7.04 (dd, J = 1 and 7 Hz, 1H, 6-H), 7.22 (m, 4H, 4 × ArH), 7.29 (m, 6H, 6 × ArH), 7.91 (dd, J = 1 and 8 Hz, 1H, 4-H). ^{13}C NMR (75 MHz; $CDCl_3$): δ = 56.8 (2 × CH_2), 114.8 (C-5), 122.2 (C-4), 127.6 (2 × CH), 128.2 (4 × CH), 128.8 (4 × CH), 129.7 (C-6), 132.4 (C-q), 136.9 (2 × C-q), 139.0 (C-q), 142.1 (C-q). Anal. Calcd for $C_{20}H_{19}N_3O_2$: C, 72.05; H, 5.74; N, 12.60. Found: C, 72.16; H, 5.91; N, 12.28. **12:** mp 95 °C. IR (KBr): ν = 3459, 3377, 3353, 1624, 1593, 1523, 1465, 1426, 1381, 1353, 1331, 1269, 1254, 1223, 754, 733, 721, 701 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 4.37 (s, 2H, CH_2), 6.00 (s, 2H, NH_2), 6.70 (dd, J = 7 and 9 Hz, 1H, 5-H), 6.92 (dd, J = 1 and 7 Hz, 1H, 6-H), 7.37 (m, 5H, 5 × ArH), 7.74 (dd, J =1 and 9 Hz, 1H, 4-H), 8.63 (s, 1H, NH). ^{13}C NMR (75 MHz; $CDCl_3$): δ = 49.8 (CH_2), 116.9 (C-5), 118.1 (C-4), 119.6 (C-6), 128.1 (CH), 128.3 (2 × CH), 128.8 (2 × CH and C-q), 133.5 (C-q), 136.8 (2 × C-q). Anal. Calcd for $C_{13}H_{13}N_3O_2$: C, 64.19; H, 5.39; N, 17.27. Found: C, 64.29; H, 5.11; N, 17.19.

5-Benzyl-1-nitro-5*H*-indolo[2,3-*b*]quinoxaline (14). A mixture of isatin (**1**) (0.27 g, 1.85 mmol), diamine **12** (0.58 g, 2.40 mmol), and anhydrous sodium acetate (0.39 g, 4.81 mmol) in AcOH (50 mL) was refluxed for 24 h. After evaporation of the solvent under reduced pressure, addition of CH_2Cl_2, the organic layer was washed with water, dried over Na_2SO_4 and evaporated. The oily residue was purified by flash chromatography (silica gel, CH_2Cl_2-MeOH, 100:0 to 95:5) to give indoloquinoxaline **14** as a red

solid (0.10 g, 15%); mp 241 °C. IR (KBr): ν = 1580, 1568, 1528, 1482, 1438, 1375, 1283, 1199, 1184, 1104, 869, 800, 746, 701 cm^{-1}. ^1H NMR (300 MHz; DMSO-d_6): δ = 6.15 (s, 2H, CH_2), 7.32 (m, 6H, 5 × ArH and 9-H), 7.64 (d, J = 8 Hz, 1H, 7-H), 7.74 (t, J = 8 Hz, 1H, 8-H), 7.89 (t, J = 9 Hz, 1H, 3-H), 8.03 (dd, J = 2 and 9 Hz, 1H, 2-H), 8.13 (dd, J = 2 and 9 Hz, 1H, 4-H), 8.20 (d, J = 8 Hz, 1H, 10-H). ^{13}C NMR (75 MHz; DMSO-d_6): δ = 49.2 (CH_2), 117.2 (C-4), 119.1 (C-2), 119.3 (C-7), 122.2 (C-9), 122.9 (C-q), 123.8 (C-10), 126.1 (C-q), 127.4 (2 × CH), 128.2 (CH), 129.3 (2 × CH), 130.0 (C-3), 130.2 (C-q), 134.5 (C-8), 135.5 (C-q), 147.0 (C-q), 149.3 (C-q), 155.4 (C-q), 159.8 (C-q). Anal. Calcd for $C_{21}H_{14}N_4O_2.1/2H_2O$: C, 69.41; H, 4.16; N, 15.42. Found: C, 69.41; H, 4.17; N, 15.11.

1-Amino-6*H*-indolo[2,3-*b*]quinoxaline (6b). A suspension of **14** (0.06 g, 0.17 mmol) in EtOH (10 mL) was first hydrogenated for 3 h at rt under a 5 bar pressure in the presence of Raney nickel (0.05 g). After filtration of the catalyst, 10% palladium on charcoal (0.05 g) was added and a second hydrogenation was performed for 16 h at rt under a 5 bar pressure. The crude product, obtained after filtration of the catalyst and elimination of the solvent, was purified by flash chromatography (aluminum oxide, CH_2Cl_2) to give **6b** as a yellow solid (0.02 g, 50%); mp 330 °C. IR (KBr): ν = 3415, 3320, 1612, 1524, 1491, 1480, 1459, 1407, 1339, 1328, 1245, 1211, 1196, 1101, 1077, 1028, 1005, 877, 814, 750, 727 cm^{-1}. ^1H NMR (300 MHz; DMSO-d_6): δ = 6.16 (s, 2H, NH_2), 6.82 (d, J = 9 Hz, 1H, 2-H or 4-H), 7.17 (d, J = 9 Hz, 1H, 2-H or 4-H), 7.35 (t, J = 8 Hz, 1H, 9-H), 7.47 (t, J = 9 Hz, 1H, 3-H), 7.55 (d, J = 8 Hz, 1H, 7-H), 7.66 (t, J = 8 Hz, 1H, 8-H), 8.31 (d, J = 8 Hz, 1H, 10-H), 11.87 (s, 1H, NH). ^{13}C NMR (75 MHz; [D_6]DMSO): δ = 106.1 (C-2 or C-4), 112.3 (C-7), 113.8 (C-2 or C-4), 119.8 (C-q), 120.9 (C-9), 122.1 (C-10), 128.9 (C-q), 130.4 (C-3), 130.9 (C-8), 136.7 (C-q), 141.5 (C-q), 143.9 (C-q), 146.4 (C-q), 146.6 (C-q). Anal. Calcd for $C_{14}H_{10}N_4.H_2O$: C, 66.65; H, 4.79; N, 22.21. Found: C, 66.34; H, 4.49; N, 21.91.

Synthesis of the 2 and 3-aminoindolo[2,3-*b*]quinoxalines (3b) and (4b)

***N*-(4-Benzylamino-3-nitrophenyl)acetamide (17).** Compound **17** was prepared by using the same procedure as described above for **9** starting from the fluorobenzene **15**[20] (11.26 g, 56.87 mmol) in EtOH (100 mL); reflux: 22 h. Crude **17** was isolated as a pure red solid (14.44 g, 89%) that was used without further purification for the next step. An analytical sample was prepared by flash chromatography (silica gel, CH_2Cl_2-MeOH, 100:0 to 95:5); mp 178 °C. IR (KBr): ν = 3353, 1666, 1639, 1594, 1520, 1491, 1455, 1402, 1354, 1312, 1263, 1222, 1148, 1060, 985, 910, 877, 808, 763, 750, 701 cm^{-1}. ^1H NMR (300 MHz; DMSO-d_6): δ = 2.49 (s, 3H, Me), 4.60 (d, J = 6 Hz, 2H, CH_2), 6.90 (d, J = 9 Hz, 1H, 5-H), 7.24 (m, 1H, 1 × ArH), 7.36 (m, 4H, 4 × ArH), 7.53 (dd, J = 2 and 9 Hz, 1H, 6-H), 8.47 (d, J = 2 Hz, 1H, 2-H), 8,56 (t, J = 6 Hz, 1H, N*H*CH_2), 9.92 (s, 1H, NHCO). ^{13}C NMR (75 MHz; DMSO-d_6): δ = 24.2 (Me), 46.2 (CH_2), 115.6 (C-5), 115.7 (C-6), 127.4 (2 × CH), 127.5 (CH), 128.5 (C-q), 129.0 (2 × CH), 129.7 (C-2), 130.7

(C-q), 139.1 (C-q), 142.1 (C-q), 168.6 (CO). Anal. Calcd for $C_{15}H_{15}N_3O_3$: C, 63.15; H, 5.30; N, 14.73. Found: C, 63.48; H, 5.50; N, 14.82.

***N*-(3-Benzylamino-4-nitrophenyl)acetamide (18).** Compound **18** was prepared by using the same procedure as described above for **9** starting from the fluorobenzene **16**[21] (3.76 g, 19 mmol) in EtOH (50 mL), reflux: 72 h. Crude **18** was obtained as a pure red solid (4.62 g, 86%) that was used without further purification for the next step. An analytical sample was prepared by flash chromatography (silica gel, CH_2Cl_2-MeOH, 100:0 to 95:5); mp 112 °C. IR (KBr): ν = 3392, 1680, 1634, 1555, 1482, 1455, 1418, 1328, 1289, 1245, 1209, 1159, 1054, 859, 843, 818, 758, 736, 696 cm^{-1}. ^1H NMR (300 MHz; $CDCl_3$): δ = 2.19 (s, 3H, Me), 4.55 (d, J = 6 Hz, 2H, CH_2), 6.53 (dd, J = 2 and 9 Hz, 1H, 6-H), 7.34 (m, 5H, 5 × ArH), 7.50 (d, J = 2 Hz, 1H, 2-H), 8.17 (d, J = 9 Hz, 1H, 5-H), 8.65 (t, J = 6 Hz, 1H, N*H*CH_2). ^{13}C NMR (75 MHz; $CDCl_3$): δ = 25.0 (Me), 47.2 (CH_2), 102.2 (C-2), 107.4 (C-6), 127.4 (2 × CH), 127.7 (CH), 128.1 (C-q), 128.4 (C-5), 128.9 (2 × CH), 137.1 (C-q), 144.8 (C-q), 146.8 (C-q), 168.7 (CO). Anal. Calcd for $C_{15}H_{15}N_3O_3.1/2H_2O$: C, 61.22; H, 5.48; N, 14.28. Found: C, 61.15; H, 5.15; N, 14.04.

2-Acetylamino-5-benzyl-5*H*-indolo[2,3-*b*]quinoxaline (19). A suspension of nitro derivative **17** (4.79 g, 16.80 mmol) in EtOH (150 mL) was hydrogenated for 12 h at rt under a 3 bar pressure in the presence of Raney nickel (1.00 g). After filtration of the catalyst, isatin (**1**) (1.90 g, 12.90 mmol) in AcOH (80 mL) was added to the resulting solution and the mixture was refluxed for 1.5 h. The solvents were eliminated under reduced pressure, the residue was triturated with MeOH. The resulting precipitate was filtered off, washed with water and purified by flash chromatography (silica gel, CH_2Cl_2-MeOH, 99:1 to 90:10) to give a red solid (3.49 g, 74%); mp 278 °C. IR (KBr): ν = 3294, 1681, 1578, 1556, 1493, 1470, 1428, 1371, 1341, 1293, 1191, 1139, 1101, 1063, 1027, 882, 811, 763, 748, 702 cm^{-1}. ^1H NMR (400 MHz; DMSO-d_6): δ = 2.09 (s, 3H, Me), 6.07 (s, 2H, CH_2), 7.27 (m, 6H, 9-H and 5 × ArH), 7.55 (d, J = 8 Hz, 1H, 7-H), 7.63 (t, J = 8 Hz, 1H, 8-H), 7.81 (dd, J = 2 and 9 Hz, 1H, 3-H), 7.86 (d, J = 9 Hz, 1H, 4-H), 8.20 (d, J = 8 Hz, 1H, 10-H), 8.62 (d, J = 2 Hz, 1H, 1-H), 10.28 (s, 1H, NH). ^{13}C NMR (75 MHz; DMSO-d_6): δ = 25.1 (Me), 49.2 (CH_2), 116.6 (C-3 or C-4), 119.3 (C-7), 119.8 (C-1), 121.8 (C-9), 123.4 (C-3 or C-4), 123.6 (C-10), 125.8 (C-q), 128.1 (2 × CH), 128.7 (CH), 129.8 (2 × CH), 133.8 (C-8), 135.7 (C-q), 136.4 (C-q), 136.5 (2 x C-q), 147.3 (C-q), 154.3 (C-q), 160.0 (C-q), 169.6 (CO). Anal. Calcd for $C_{23}H_{18}N_4O{\cdot}2H_2O$: C, 68.64; H, 5.51; N, 13.92. Found: C, 68.31; H, 5.16; N, 13.90.

3-Acetylamino-5-benzyl-5*H*-indolo[2,3-*b*]quinoxaline (20). A suspension of nitro derivative **18** (4.56 g, 16.00 mmol) in EtOH (400 mL) was hydrogenated for 18 h at rt under a 3 bar pressure in the presence of Raney nickel (1.00 g). After filtration of the catalyst, isatin (**1**) (1.81 g, 12.3 mmol) in AcOH (150 mL) was added to the resulting solution and the mixture was refluxed for 1 h. The solvents were eliminated

under reduced pressure, the residue was triturated with MeOH. The resulting precipitate was filtered off, washed with water and purified by flash chromatography (silica gel, CH_2Cl_2-MeOH, 99:1 to 90:10) to give a red solid (3.76 g, 83%); mp 289 °C. IR (KBr): ν = 3254, 1691, 1584, 1497, 1432, 1370, 1259, 1201, 1149, 1101, 1073, 821, 786, 765, 746, 697 cm^{-1}. ^1H NMR (400 MHz; DMSO-d_6): δ = 2.11 (s, 3H, Me), 5.98 (s, 2H, CH_2), 7.27 (m, 4H, 9-H and 3 × ArH), 7.37 (m, 2H, 2 × ArH), 7.60 (m, 2H, 7-H and 8-H), 7.65 (dd, J = 2 and 8 Hz, 1H, 2-H), 8.19 (m, 2H, 10-H and 1-H), 8.44 (d, J = 2 Hz, 1H, 4-H), 10.50 (s, 1H, NH). ^{13}C NMR (75 MHz; DMSO-d_6): δ = 24.7 (Me), 49.0 (CH_2), 103.7 (C-4), 116.0 (C-2), 118.8 (C-7 or C-8), 121.4 (C-9), 122.5 (C-1 or C-10), 123.6 (C-q), 127.7 (2 × CH), 128.2 (CH), 129.2 (2 × CH), 130.3 (C-q), 131.2 (C-q), 131.5 (C-1 or C-10), 132.5 (C-7 or C-8), 135.5 (C-q), 141.7 (C-q), 147.1 (C-q), 151.1 (C-q), 158.4 (C-q), 169.7 (CO). Anal. Calcd for $C_{23}H_{18}N_4O.5/4H_2O$: C, 71.03; H, 5.31; N, 14.40. Found: C, 71.26; H, 5.06; N, 14.51.

2-Acetylamino-6*H*-indolo[2,3-*b*]quinoxaline (3c). Compound **19** (12.40 g, 33.88 mmol) in EtOH (500 mL) was debenzylated according to the same procedure as described for **7b** using 10% palladium on charcoal (1.00g), time reaction: 12 h. After work up, **3c** was purified by flash chromatography (silica gel, CH_2Cl_2-MeOH, 99:1 to 70:30 and then CH_2Cl_2-MeOH -Et_3N 69:30:1) to give a yellow solid (7.09 g, 76%); mp 389 °C. IR (KBr): ν = 3271, 1663, 1621, 1543, 1492, 1464, 1406, 1339, 1266, 1196, 1128, 1108, 1031, 1005, 884, 857, 828, 754 cm^{-1}. ^1H NMR (300 MHz; DMSO-d_6): δ = 2.14 (s, 3H, Me), 7.33 (t, J = 8 Hz, 1H, 9-H), 7.54 (d, J = 8 Hz, 1H, 7-H), 7.67 (t, J = 8 Hz, 1H, 8-H), 7.85 (dd, J = 2 and 9 Hz, 1H, 3-H), 7.98 (d, J = 9 Hz, 1H, 4-H), 8.32 (d, J = 8 Hz, 1H, 10-H), 8.64 (d, J = 2 Hz, 1H, 1-H), 10.33 (s, 1H, NHCO), 11.92 (s, 1H, NH). ^{13}C NMR (75 MHz; DMSO-d_6): δ = 24.6 (CH_3), 112.4 (C-7), 116.4 (C-1), 119.3 (C-q), 121.0 (C-9), 122.7 (C-10), 122.9 (C-3), 128.0 (C-4), 131.6 (C-8), 137.2 (C-q), 137.6 (C-q), 139.5 (C-q), 140.2 (C-q), 144.3 (C-q), 145.7 (C-q), 169.2 (CO). Anal. Calcd for $C_{16}H_{12}N_4O$: C, 69.55; H, 4.38; N, 20.28. Found: C, 69.64; H, 4.39; N, 19.93.

3-Acetylamino-6*H*-indolo[2,3-*b*]quinoxaline (4c). Compound **20** (3.77 g, 10.30 mmol) in EtOH (150 mL) was debenzylated using to the same procedure as described for **7b** using 10% palladium on charcoal (1.00g), time reaction: 18 h. After work up, **4c** was purified by flash chromatography (silica gel, CH_2Cl_2-MeOH, 99:1 to 70:30 and then CH_2Cl_2-MeOH -Et_3N 69:30:1) to give a yellow solid (2.42 g, 85%); mp 362 °C. IR (KBr): ν = 3491, 3146, 1679, 1621, 1607, 1588, 1548, 1496, 1461, 1401, 1369, 1342, 1274, 1205, 1146, 1111, 1035, 1015, 873, 848, 833, 799, 757 cm^{-1}. ^1H NMR (300 MHz; DMSO-d_6): δ = 2.16 (s, 3H, Me), 7.34 (t, J = 8 Hz, 1H, 9-H), 7.55 (d, J = 8 Hz, 1H, 7-H), 7.67 (t, J = 8 Hz, 1H, 8-H), 7.78 (dd, J = 2 and 9 Hz, 1H, 2-H), 8.15 (d, J = 9 Hz, 1H, 1-H), 8.29 (d, J = 8 Hz, 1H, 10-H), 8.48 (s, 1H, 4-H), 10.39 (s, 1H, NHCO), 11,96 (s, 1H, NH). ^{13}C NMR (75 MHz; DMSO-d_6): δ = 24.7 (Me), 112.3 (C-7), 114.6 (C-4), 119.7 (C-q), 120.0 (C-2), 121.1 (C-9), 122.3 (C-10), 129.7 (C-1), 131.2 (C-8), 135.8 (C-q),

138.7 (C-q), 140.0 (C-q), 141.4 (C-q), 143.8 (C-q), 146.6 (C-q), 169.4 (CO). Anal. Calcd for $C_{16}H_{12}N_4O.5/4H_2O$: C, 64.31; H, 4.89; N, 18.75. Found: C, 64.37; H, 4.54; N, 18.43.

General procedure for the preparation of the 2- and 3-amino-6*H*-indolo[2,3-*b*]quinoxalines **(3b) and (4b)**

A suspension of acetamide derivative **3c or 4c** (0.28 g, 1.00 mmol) in EtOH (30 mL) and a 0.5 M aqueous solution of HCl (20 mL) was refluxed for 3 h. After the solvents had been removed by evaporation, a saturated aqueous solution of Na_2CO_3 was added until a pH 8-9 was reached to give a precipitate that was filtered off, washed with water and purified by flash chromatography (silica gel, CH_2Cl_2-MeOH, 99:1 to 70:30 and then CH_2Cl_2-MeOH -Et_3N 69:30:1) to give a yellow solid.

2-amino-6*H*-indolo[2,3-*b*]quinoxalines **(3b):** Yield: 0.23 g (98%); mp 386 °C. IR (KBr): ν = 3439, 3302, 1644, 1625, 1579, 1519, 1494, 1473, 1460, 1407, 1341, 1323, 1270, 1248, 1194, 1135, 1104, 1030, 1004, 859, 823, 752 cm^{-1}. ^1H NMR (300 MHz; DMSO-d_6): δ = 5.65 (s, 2H, NH_2), 7.17 (d, J = 2 Hz, 1H, 1-H), 7.25 (dd, J = 2 and 9 Hz, 1H, 3-H), 7.28 (t, J = 8 Hz, 1H, 9-H), 7.51 (d, J = 8 Hz, 1H, 7-H), 7.61 (t, J = 8 Hz, 1H, 8-H), 7.76 (d, J = 9 Hz, 1H, 4-H), 8.26 (d, J = 8 Hz, 1H, 10-H), 11.65 (s, 1H, NH). ^{13}C NMR (75 MHz; DMSO-d_6): δ = 106.7 (C-1), 112.1 (C-7), 119.5 (C-q), 120.3 (C-9), 121.9 (C-3), 122.3 (C-10), 128.2 (C-4), 130.7 (C-8), 134.3 (C-q), 139.0 (C-q), 141.4 (C-q), 143.7 (C-q), 144,1 (C-q), 147.8 (C-q). Anal. Calcd for $C_{14}H_{10}N_4.1/2H_2O$: C, 69.12; H, 4.56; N, 23.03. Found: C, 69.15; H, 4.18; N, 22.88.

3-amino-6*H*-indolo[2,3-*b*]quinoxalines **(4b):** Yield: 0.20 g (85%); mp 365 °C. IR (KBr): ν = 3446, 3311, 1645, 1600, 1581, 1559, 1515, 1495, 1459, 1404, 1341, 1287, 1256, 1223, 1141, 1106, 1033, 1009, 833, 820, 749, 720 cm^{-1}. ^1H NMR (300 MHz; DMSO-d_6): δ = 5.95 (s, 2H, NH_2), 6.94 (d, J = 2 Hz, 1H, 4-H), 7.12 (dd, J = 2 and 9 Hz, 1H, 2-H), 7.27 (t, J = 8 Hz, 1H, 9-H), 7.47 (d, J = 8 Hz, 1H, 7-H), 7.56 (t, J = 8 Hz, 1H, 8-H), 7.86 (d, J = 9 Hz, 1H, 1-H), 8.17 (d, J = 8 Hz, 1H, 10-H), 11.63 (s, 1H, NH). ^{13}C NMR (75 MHz; DMSO-d_6): δ = 104.9 (C-4), 112.0 (C-7), 119.0 (C-q), 120.4 (C-2), 120.6 (C-9), 121.3 (C-10), 129.6 (C-8), 130.1 (C-1), 133.4 (C-q), 135.1 (C-q), 142.6 (C-q), 143.4 (C-q), 146.8 (C-q), 150.4 (C-q). Anal. Calcd for $C_{14}H_{10}N_4.1/4H_2O$: C, 70.43; H, 4.43; N, 23.47. Found: C, 70.79; H, 4.32; N, 23.73.

Reaction of isatin (1) with 4-nitrobenzene-1,2-diamine (2a)

A mixture of isatin (**1**) (1.47 g, 10 mmol), **2a** (1.99 g, 13 mmol) in AcOH (80 mL) was refluxed for 2 h. After elimination of the solvent under reduced pressure and trituration of the residue with MeOH, the resulting precipitate was washed with water, dried and identified by ^1H NMR as a 1:2 mixture of 2- and 3-nitro-6*H*-indolo[2,3-*b*]quinoxalines (**3a**) and (**4a**) (1.86 g, 70%; mp 337 °C). After catalytic reduction, a crude 1:2 mixture of amines **3b** and **4b** was obtained (90%). Comparison with the ^1H NMR spectra of

pure **3b** and **4b** identified **4b** as the major product.

Reaction of isatin (1) with 4-acetylaminobenzene-1,2-diamine[17] (2c)

A solution of isatin (**1**) (0.15 g, 1.0 mmol) in AcOH (10 mL) was added to a solution of **2c** (obtained by reduction of the *N*-(4-amino-3-nitrophenyl)acetamide)[17] (0.21 g, 1.3 mmol) in AcOH (10 mL) was refluxed for 1.5 h. After work up, the crude solid was washed with water, dried and identified by ^{1}H NMR as a 1:1 mixture (0.16 g, 58%) of 2- and 3-acetylaminoquinoxalines (**3c**) and (**4c**).

Reaction of isatin (1) with benzene-1,2,3-triamine[19] (5b)

The same procedure as described above was used starting from 3-nitrobenzene-1,2-diamine (0.46 g, 3.00 mmol), time reaction: 3 h. After elimination of the solvents, the residue was washed with water, dried and identified by ^{1}H NMR as a mixture of **6b**:**7b** (97:3). The 1-amino-6*H*-indolo[2,3-*b*]quinoxaline (**6b)** (0.31 g, 58%; mp 330 °C) was isolated in a pure state by washing the crude precipitate with acetone (5 x 5 mL).

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REFERENCES

1. P. Helissey, S. Desbène-Finck, and S. Giorgi-Renault, *Eur. J. Org. Chem*., 2005, 410.
2. N. P. Buu-Hoï and G. Saint-Ruf, *Bull. Soc. Chim. Fr*., 1960, **11**, 1920.
3. F. Knotz and W. Wendelin, *Sci. Pharm*., 1975, **43**, 249.
4. A. G. Drushlyak, A. V. Ivashchenko, and V. V. Titov, *Khim. Geterotsikl. Soedin.,* 1984, **11**, 1544 [*Chem. Heterocycl. Comp.*, 1984, **20**, 1276].
5. R. R. Mohan, R. Agarwal, and V. S. Misra, *Indian J. Chem*., 1986, **23B**, 1234.
6. K. C. Joshi, P. Chand, and A. Dandia, *Ind. J. Chem.,* 1984, **23B**, 743.
7. O. Hinsberg, *Chem. Ber*., 1886, **19**, 483.
8. R. S. Varma and I. A. Khan, *J. Indian Chem. Soc*., 1978, **55**, 1043.
9. J. Buraczewski and L. Marchlewski, *Chem. Ber*., 1901, **34**, 4008.
10. K. D. Banerji, A. K. D. Mazumdar, K. Kumar, and S. K. Guha, *J. Indian Chem. Soc.,* 1979, **56**, 396.
11. K. D. Banerji, A. K. D. Mazumdar, K. Kumar, and S. K. Guha, *J. Indian Chem. Soc.,* 1980, **57**, 86.
12. S. K. Guha, K. D. Banerji, and K. K. Sen, *J. Indian Chem. Soc.,* 1973, **50**, 263.
13. T. Matsumoto, H. Wada, Y. Migita, K. Hatayama, and Y. Sekiguchi, *EP Pat. 0 695 754 A1*, 1994 (*Chem. Abstr.*, 1995, **122**, P 160684s).

14. Y. Kidani, M. Matsuo, and H. Koike, *Yakugaku Zasshi,* 1970, **90**, 54 (*Chem. Abstr.,* 1970, **72**, 90408c).
15. W. Deady and A. J. Kaye, *Aust. J. Chem.,* 1997, **50**, 473.
16. J. Bergman and S. Akerfeldt, *WO Pat. 87/04436*, 1987 (*Chem. Abstr.*, 1988, **108**, 37866m).
17. F. Kehrmann and C. Mermod, *Helv. Chim. Acta,* 1927, **10**, 62.
18. J. M. Mellor, R. N. Pathirana, M. F. Rawlins, and J. H. A. Stibbard, *J. Chem. Res. Miniprint.,* 1982, **3**, 834.
19. A Marcos, C. Pedregal, and C. Avendano, *Tetrahedron,* 1991, **47**, 7459.
20. M. D. McFarlane, D. J. Moody, and D. M. Smith, *J. Chem. Soc., Perkin Trans. 1,* 1988, 691.
21. B. M. Lynch, C. M. Chen, and Y.-Y Wigfield, *Can. J. Chem.,* 1968, **46**, 1141.