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Reduction of indolo[2,3-*b*]quinoxalines

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Abstract—Reduction of indolo[2,3-*b*]quinoxalines with zinc in the presence of an anhydride gave *N*,*N*-diacyl trapped 6,11-dihydroindolo[2,3-*b*]quinoxalines in 43–92% yields. When the reduction with zinc was performed in TFA/TFAA, an unexpected ring opened product was isolated in 49% yield. The structure of this product could be identified as 1,2-dihydro-1-trifluoroacetyl-3-[(2-trifluoroacetylamino)phenyl]quinoxaline.

1. Introduction

Ellipticine (**1**) and a large numbers of its derivatives and analogues have potent antitumour activities.[1] Several indolo[2,3-*b*]quinoxalines have been studied in this context, which led us to the development of the lead compound 6-(*N*,*N*-dimethylaminoethyl-)2,3-dimethylindolo[2,3-*b*]-quinoxaline, **2a** (B-220), which contrary to ellipticine B-220 is inactive in most cancer models but does show potent activity against certain types of viruses (HSV-1, VZV, CMV).[2] The molecule B-220 exerts also a stabilizing effect on the formation of triple helixes of nucleic acids.[3]

Merour et al. have published an alternative route to tetracyclic indolic and azaindolic derivatives starting from 1-acetyl-2-bromo-3-indolinone and the appropriate diamine.[4] This reaction gave a mixture of dihydro compounds (e.g., **3a**) and the fully aromatized compounds (e.g., **2b**). Hydrolysis of **3a** gave the highly unstable parent dihydro compound **3b**.[4] At that point we wanted to synthesize dihydro derivatives of **2a**, such as **4a** and **4b**, because the dihydro derivative **4a** might be an active metabolite of **2a** and the diacetyl derivative **4b** might in vivo be hydrolysed to **4a**.

In this paper we report the outcome of the reduction of indolo[2,3-*b*]quinoxalines with Zn in the presence of anhydrides (Fig. 1).

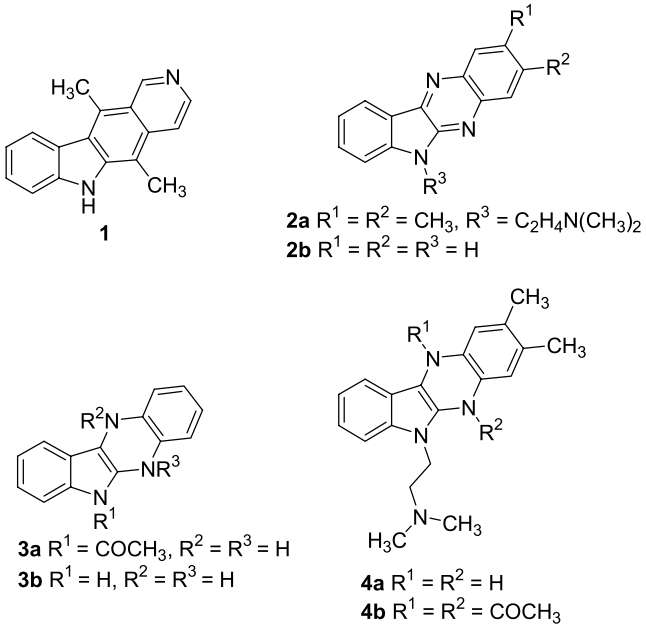

Figure 1.

2. Results and discussion

As a part of our ongoing development of B-220 we aimed to have methodology to synthesize 5,11-dihydroindolo[2,3-*b*]quinoxalines (potential metabolites). Reducing reagents such as Pd(C)/H_2,[5] $Na_2S_2O_4$,[6] $LiAlH_4$,[7] Zn in acetic acid[8] are known to reduce, the structurally related, phenazines to the corresponding 5,10-dihydrophenazines. Reduction of phenazine itself with zinc in acetic anhydride was found, as

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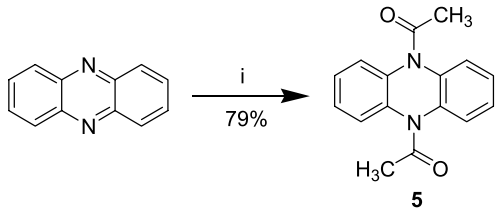


Scheme 1. (i) Ac_2O, Zn, reflux.

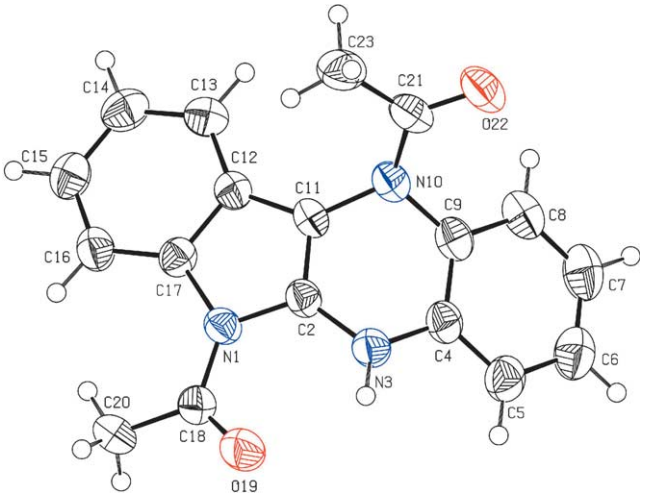
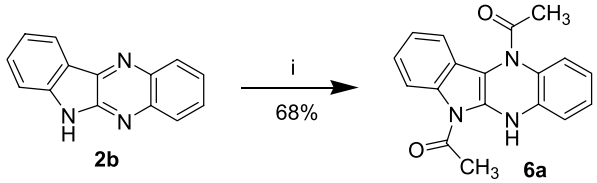


Figure 2. Atom numbering scheme for **6a** used in the crystal structure investigation. The displacements of the non-H atoms are drawn as ellipsoid at 50% probability level. H-atoms are shown as spheres with arbitrary radii.



Scheme 2. (i) Ac_2O, THF, Zn, reflux.

expected, to give *N*,*N*-diacetyl-5,10-dihydrophenazine (**5**) in a good yield (79%) (Scheme 1).

Similar reduction of **2b** gave the desired product **6a** albeit contaminated with the *N*-acetylated product **2c**. Attemps to reduce **2c** failed. The formation of this by-product could be avoided by running the reaction in THF which exclusively gave **6a**. Recrystallisation of **6a** (Scheme 2) from ethyl acetate provided good quality crystals, which were used to confirm the structure of **6a** by X-ray crystallography (Fig. 2). According to this analysis, the dihedral angle between the two planes intersecting along the *N*,*N*-axis in the *N*,*N*-dihydropyrazine is 139°. This value could be compared with the corresponding angle reported for *N*,*N*-dihydrodimethylphenazine (144°).[9]

The corresponding dipropionylated compound, **6b**, could similarly be prepared (43%) using propionic anhydride without any co-formation of **2d**. When **2b** was treated with zinc in boiling propionic anhydride (neat) for 20 h even the tripropionylated compound **6c** could be obtained. Triacetyl or trifluoroacetyl derivatives could not be obtained even under forcing conditions, which most likely can be explained in terms of the relatively high boiling point (167 °C) of propionic anhydride compared to the boiling points of TFAA and acetic anhydride. When the reduction of **2a** and **2b** was performed with TFAA and zinc in THF the mono trifluoroacetylated compounds **6d** and **6f**, respectively, were isolated. To characterize **6d**, NOE experiments were performed at 25 °C in DMSO. Due to the bent structure a very weak NOE interaction between the NH peaks (δ 11.11 and 9.72) could be observed. Because of a very weak NOE interaction between the NH peaks **6d** was acetylated to attach a substituent (CH_3) which will be closer to the NH. This would corroborate the structure of the product to be **6d** and exclude the structure **6i**. The initial attempts were made with acetic anhydride with and without a solvent (THF) at room temperature and under heating failed and the product formed was **2c** (quantitatively). The acetylation was successful under reductive conditions (zinc, THF, acetic anhydride) and the product thus formed was **6e**.

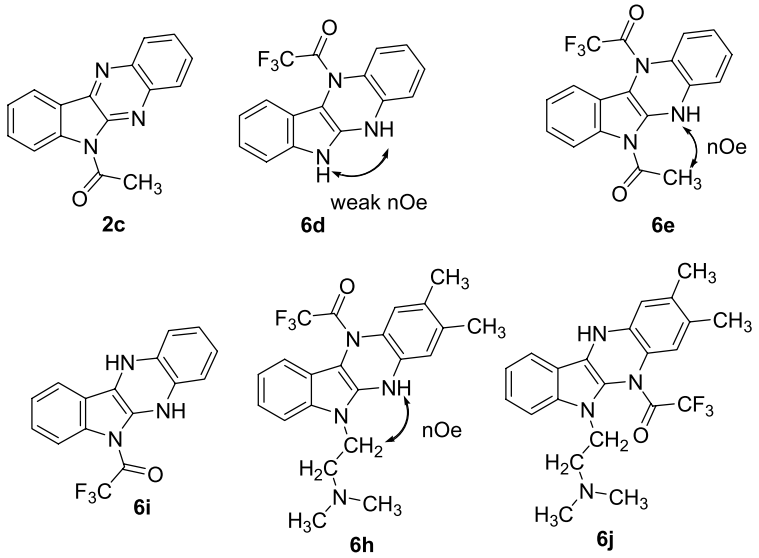
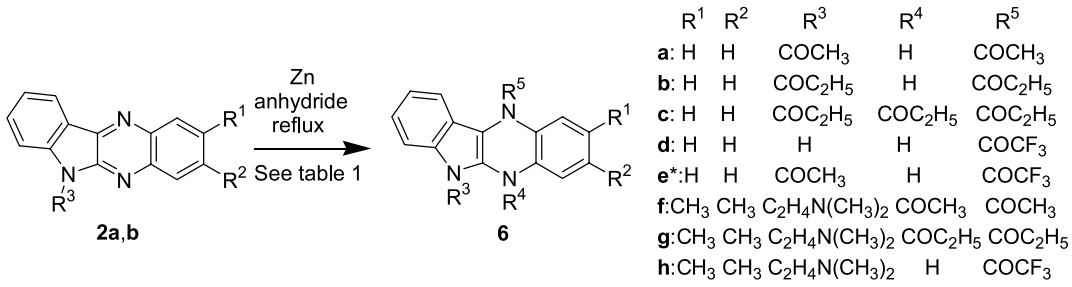
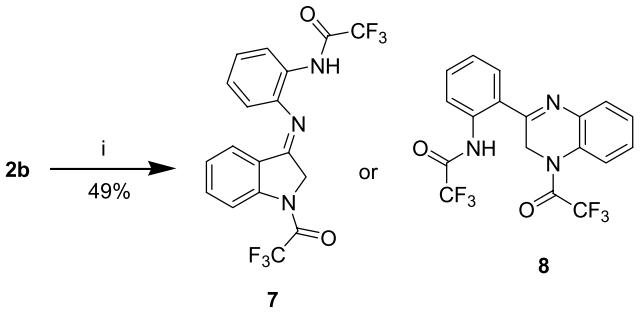


Figure 3.

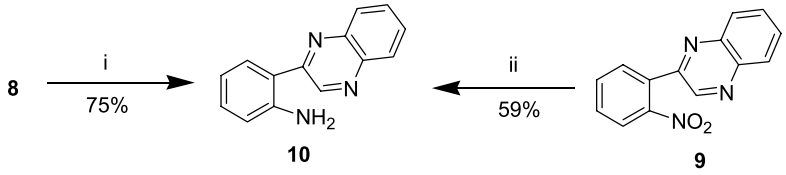


	R^1	R^2	R^3	R^4	R^5
a:	H	H	$COCH_3$	H	$COCH_3$
b:	H	H	COC_2H_5	H	COC_2H_5
c:	H	H	COC_2H_5	COC_2H_5	COC_2H_5
d:	H	H	H	H	$COCF_3$
e*:	H	H	$COCH_3$	H	$COCF_3$
f:	CH_3	CH_3	$C_2H_4N(CH_3)_2$	$COCH_3$	$COCH_3$
g:	CH_3	CH_3	$C_2H_4N(CH_3)_2$	COC_2H_5	COC_2H_5
h:	CH_3	CH_3	$C_2H_4N(CH_3)_2$	H	$COCF_3$

Scheme 3. Reduction of indolo[2,3-*b*]quinoxalines to the corresponding mono-, di- or triacylated dihydro indolo[2,3-*b*]quinoxalines. * From **6d**.



Scheme 4. (i) Zn, TFAA, TFA, rt, 5 min.



Scheme 5. (i) KOH, EtOH, reflux, 48 h. (ii) Pd(C), H_2, rt, 70 h.

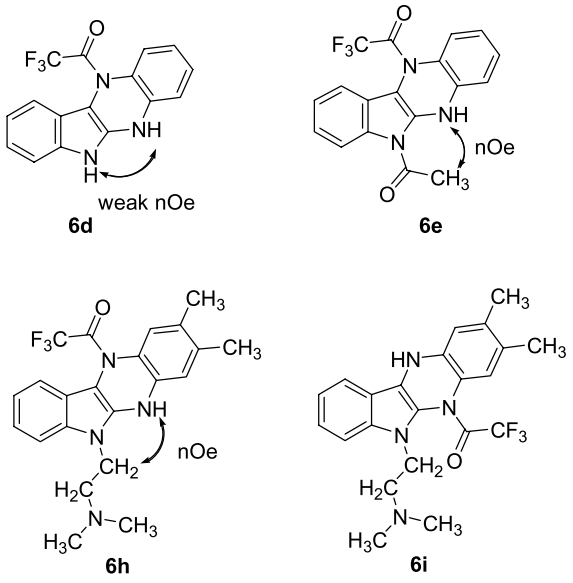


Figure 4.

To corroborate the structure of **6e** NOE experiments were performed, at 25 °C in DMSO, an NOE interaction between the NH peak and the methyl peak, from the acetyl group (δ 9.65 and 2.83) could be observed. Similarly, the product obtained by reduction of **2a** in the presence of zinc was confirmed to be **6h** rather than the isomer **6j** (Fig. 3). Attempted hydrolysis of e.g. **6h** failed because the intended product **4a** is too prone to undergo dehydrogenation back to **2a** (Scheme 3).

When **2b** was reduced with zinc in a mixture of TFA and TFAA at room temperature a compound with the molecular weight of 415 was obtained. With this information the two structures **7** and **8** were contemplated (Scheme 4). Both trifluoroacetyl groups could be removed by KOH in refluxing ethanol. By reduction of the known nitro derivative **9**[10] with Pd(C)/H_2 to **10** we could exclude the imine derivative **7** and confirm the structure as the dihydroquinoxaline derivative **8** (Scheme 5) (Fig. 4).

In summary, we have described the reduction of the biologically interesting indolo[2,3-*b*]quinoxalines with zinc and an appropriate anhydride delivering the corresponding dihydroindolo[2,3-*b*]quinoxalines in 43–92% yields (Scheme 3, Table 1).

3. Experimental

3.1. General

Melting points were recorded on a Büchi Melting Point B-545 apparatus and are uncorrected. NMR spectra were recorded on a Brucker Advance 300 DPX spectrometer operating at 300 MHz (^{1}H)/75 MHz (^{13}C) and a Jeol Eclipse+500 FT NMR spectrometer operating at 500 MHz (^{1}H) (NOE experiments). DMSO-d_6 was used as solvent and internal standard if not otherwise noted. The IR spectra were recorded on an Avatar 330 FT-IR Thermo-Nicolet. Solvents were of analytical grade and used as received. Compound **9** was prepared according to a literature procedure.[10] Crystallographic data (excluding structure factors) for the structure in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 251958.

Table 1. Reduction of indolo[2,3-*b*]quinoxalines with zinc in the presence of an appropriate anhydride

Entry	S.m.	Solvent	Anhydride	Time (h)	Product (**6**)	Yield (%)
1	**2b**	THF	$(CH_3CO)_2O$	20	**a**	68
2	**2b**	THF	$(C_2H_5CO)_2O$	32	**b**	43
3	**2b**	—	$(C_2H_5CO)_2O$	20	**c**	40
4	**2b**	THF	$(CF_3CO)_2O$	2	**d**	92
5	**6d**	THF	$(CH_3CO)_2O$	24	**e**	26
6	**2a**	—	$(CH_3CO)_2O$	2	**f**	71
7	**2a**	—	$(C_2H_5CO)_2O$	2	**G**	66
8	**2a**	THF	$(CF_3CO)_2O$	1	**H**	50

Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].

3.1.1. Synthesis of *N*,*N*-diacetyl-5,10-dihydrophenazine (5). Phenazine (3.60 g, 20 mmol) was heated at reflux with zinc powder (3.0 g, 46 mmol) in acetic anhydride (40 mL) for 3 h. The filtered mixture upon cooling deposited white crystals, 1.60 g. Concentration of the mother liquor gave a second crop 2.60 g, resulting in a total yield of 79%. Mp: 184–185 °C (lit.[11] mp: 180 °C). IR (neat): 3044, 2928, 1669, 1480, 1372, 1326, 1267, 1017, 780 cm^{-1}; ^1H NMR: δ 7.68–7.62 (m, 4H, Ar*H*), 7.33–7.27 (m, 4H, Ar*H*), 2.30 (s, 6H, 2*Me*); ^{13}C NMR: δ 167.8 (s), 136.2 (s), 125.8 (d), 125.2 (d), 23.0 (q).

3.2. General procedure for the reduction of indolo-[2,3-*b*]quinoxalines

Method A. Zinc powder (1.30 g; 20 mmol) was added to a solution of the appropriate indoloquinoxaline (**2a** or **2b**, 5 mmol) in THF (50 mL) containing the appropriate anhydride (5 mL). The reaction mixture was heated under reflux until no starting material was left (determined by TLC). Thereafter the solution was poured into cold water and after a while a solid was formed. The crude product was isolated by filtration and washed with water and purified by recrystallisation.

Method B. Zinc powder (1.30 g; 20 mmol) was added to a solution of the appropriate indoloquinoxaline (**2a** or **2b**, 5 mmol) containing the appropriate anhydride (10 mL). The reaction mixture was heated under reflux until no starting material was left (determined by TLC). Thereafter, the solution was poured into cold water and extracted with ethyl acetate. The organic phase was washed with aq. $NaHCO_3$, brine, dried with $MgSO_4$ and purified by chromathography (ethyl acetate–hexane).

Method C. Zinc powder (1.30 g; 20 mmol) was carefully added to mixture of **2b** (1.09 g; 5 mmol), TFA (2 mL) and TFAA (15 mL) at room temperature and the reaction mixture was stirred for 5 min and thereafter poured into ice-water. The solid thus formed was collected by filtration and washed with water. The solid was dissolved in EtOAc and washed with aq. $NaHCO_3$ (sat.), brine, dried with $MgSO_4$ and purified by chromatography (ethyl acetate–hexane, 3:7).

3.2.1. Synthesis of 6,11-diacetyl-5,11-dihydro-6*H*-indolo[2,3-*b*]quinoxaline (6a) via method A. Yield: 2.07 g (white crystals, double scale, 68%); mp: 201–204 °C; IR (neat): 3343, 1696, 1656, 1480, 1371, 1307, 1282, 752, and 746 cm^{-1}; ^1H NMR: δ 9.18 (s, 1H, N*H*), 7.77 (d, $J=8.2$ Hz, 1H, Ar*H*), 7.42 (d, $J=7.9$ Hz, 1H, Ar*H*), 7.36–7.32 (m, 2H, Ar*H*), 7.24 (t, $J=7.3$ Hz, 1H, Ar*H*), 7.17–7.11 (m, 2H, Ar*H*), 6.98 (dt, $J=7.6$, 1.2 Hz, 1H, Ar*H*), 2.82 (s, 3H, *Me*), 2.14 (s, 3H, *Me*); ^{13}C NMR: δ 170.9 (s), 170.8 (s), 138.9 (s), 136.9 (s), 131.3 (s), 128.3 (d), 126.9 (s), 126.1 (d), 125.5 (d), 124.5 (s), 123.4 (d), 121.2 (d), 117.1 (s), 116.7 (d), 114.5 (d), 103.2 (s), 26.8 (q), 21.9 (q). HR-MS (FAB): [M^+], found 305.1156. $C_{18}H_{15}N_3O_2$ requires 305.1164.

3.2.2. Synthesis of 6,11-dipropionyl-5,11-dihydro-6*H*-indolo[2,3-*b*]quinoxaline (6b) via method A. 2.5 equiv of propionic anhydride was used. 1.6 mL. Yield: 0.71 g (white crystals, 43%); mp: 120–123 °C; IR (neat): 3393, 2983, 2939, 1700, 1674, 1480, 1458, 1365, 1272, 1202 and 741 cm^{-1}; ^1H NMR: δ 9.25 (s, 1H, N*H*), 7.76 (d, $J=8.3$ Hz, 1H, Ar*H*), 7.41 (d, $J=7.8$ Hz, 1H, Ar*H*), 7.35–7.29 (m, 2H, Ar*H*), 7.23 (t, $J=7.4$ Hz, 1H, Ar*H*), 7.16–7.08 (m, 2H, Ar*H*), 7.00 (t, $J=7.8$ Hz, 1H, Ar*H*), 3.20 (q, $J=7.0$ Hz, 2H, CH_2), 2.47 (q, $J=7.2$ Hz, 2H, CH_2), 1.23 (t, $J=7.0$ Hz, 3H, *Me*), 0.98 (t, $J=7.2$ Hz, 3H, *Me*); ^{13}C NMR (50 °C): δ 174.3 (s), 174.0 (s), 138.8 (s), 137.0 (s), 131.0 (s), 126.8 (s), 125.8 (d), 125.5 (d), 124.5 (s), 123.1 (d), 121.0 (d), 120.9 (d), 116.6 (d), 116.4 (d), 114.4 (d), 103.0 (s), 31.1 (t), 26.0 (t), 8.8 (q), 8.1 (q). HR-MS (FAB): [M^+], found 333.1491. $C_{20}H_{19}N_3O_2$ requires 333.1477.

3.2.3. Synthesis of 5,11-dihydro-5,6,11-tripropionyl-6*H*-indolo[2,3-*b*]quinoxaline (6c) via method B. Yield: 0.77 g (yellowish solid, 40%); mp: 165–166 °C; IR (neat): 2997, 2977, 2938, 2877, 1712, 1685, 1671, 1357, 1266, 1199, 1136, 767, 760, and 751 cm^{-1}; ^1H NMR: δ 8.24 (d, $J=$ 7.5 Hz, 1H, Ar*H*), 7.81–7.77 (m, 2H, Ar*H*), 7.61 (d, $J=$ 6.8 Hz, 1H, Ar*H*), 7.41–7.29 (m, 4H, Ar*H*), 2.98–2.40 (m, 6H, 3CH_2), 1.17–0.97 (m, 9H, 3*Me*); ^{13}C NMR (75 °C): δ 174.4 (s), 172.8 (s), 171.8 (s), 138.2 (s), 136.4 (s), 133.1 (s), 130.6 (s), 126.5 (d), 126.1 (s), 125.8 (d), 125.4 (d), 124.8 (s), 124.5 (d), 123.0 (d), 121.6 (s), 119.1 (d), 118.8 (s), 115.3 (d), 29.2 (t), 27.1 (t), 26.8 (t), 8.7 (q), 8.4 (q) and 8.2 (q). HR-MS (FAB): [M^+], found 389.1743. $C_{23}H_{23}N_3O_3$ requires 389.1739.

3.2.4. Synthesis of 5,11-dihydro-11-trifluoroacetyl-6*H*-indolo[2,3-*b*]quinoxaline (6d) via method A. Yield: 2.93 g (yellowish solid, double scale, 92%); mp: 231–232 °C; IR (neat): 3359, 3287, 1665, 1608, 1578, 1494, 1147, 1131, 758, 735, and 722 cm^{-1}; ^1H NMR: δ 11.11 (s, 1H, N*H*), 9.72 (s, 1H, N*H*), 7.44 (d, $J=8.0$ Hz, 1H, Ar*H*), 7.35–7.15 (m, 4H, Ar*H*), 7.02–6.94 (m, 3H, Ar*H*); ^{13}C NMR (75 °C): δ

154.7 (s, q, J_{CF}=35.6 Hz), 139.4 (s), 137.2 (s), 132.1 (s), 127.1 (d), 124.2 (d), 123.9 (d), 123.8 (d), 121.5 (s), 120.4 (d), 119.3 (d), 118.5 (d), 117.0 (d), 116.7 (s, q, J_{CF}= 288.5 Hz), 110.6 (d) and 97.0 (s). HR-MS (FAB): [M^+], found 317.0773. $C_{18}H_{15}N_3O_2$ requires 317.0776.

3.2.5. Synthesis of 6-acetyl-5,11-dihydro-11-trifluoroacetyl-6*H*-indolo[2,3-*b*]quinoxaline (6e) via method A. Yield: 0.23 g (yellowish crystals, 1/2 scale, 26%); mp: 193–194 °C; IR (neat): 3336, 3061, 2995, 2940, 1704, 1686, 1479, 1203, 1138, 1109, 995, 760, 744, and 720 cm^{-1}:. ^1H NMR: δ 9.65 (s, 1H, N*H*), 7.79 (d, J=8.2 Hz, 1H, Ar*H*), 7.51 (d, J=8.1 Hz, 1H, Ar*H*), 7.46 (d, J=8.1 Hz, 1H, Ar*H*), 7.36 (d, J=7.6 Hz, 1H, Ar*H*), 7.29–7.23 (m, 2H, Ar*H*), 7.18 (t, J=8.2 Hz, 1H, Ar*H*), 7.08 (t, J=7.6 Hz, 1H, Ar*H*), 2.83 (s, 3H, *Me*); ^{13}C NMR (55 °C): δ 170.7 (s), 155.4 (s, q, J_{CF}=36.5 Hz), 138.7 (s), 137.5 (s), 131.1 (s), 127.5 (d), 123.8 (d), 123.4 (s), 123.2 (d), 121.7 (d), 121.5 (d), 117.5 (d), 171.1 (d), 115.9 (s, q, J_{CF}=287.9 Hz), 114.2 (d), 101.2 (s), and 26.5 (q). HR-MS (FAB): [M^+], found 359.0876. $C_{18}H_{12}F_3N_3O_2$ requires 359.0882.

3.2.6. Synthesis of 5,11-diacetyl-5,11-dihydro-2,3-dimethyl-6-(2-dimethylaminoethyl)-6*H*-indolo[2,3-*b*]-quinoxaline (6f) via method B. Yield: 1.43 g (white crystals, 71%); mp 86–88 °C; IR (neat): 3051, 2940, 2820, 2768, 1682, 1493, 1454, 1366, 1314, 1266, 1017, 743 cm^{-1}; ^1H NMR: δ 7.64–7.54 (m, 3H, Ar*H*), 7.45 (s, 1H, Ar*H*), 7.22–7.10 (m, 2H, Ar*H*), 4.39–4.15 (m, 2H, –CH_2–), 2.52–2.48 (m, 2H, –CH_2–), 2.35 (s, 3H, *Me*), 2.32 (s, 3H, *Me*), 2.25 (s, 3H, *Me*), 2.23 (s, 3H, *Me*), 2.06 (s, 6H, 2*Me*); ^{13}C NMR (110 °C): δ 169.5 (s), 167.6 (s), 136.0 (s), 134.2 (s), 133.5 (s), 133.4 (s), 133.2 (s), 133.0 (s), 125.6 (d), 125.3 (d), 121.0 (d), 119.7 (s), 119.3 (d), 118.0 (d), 112.6 (s), 110.0 (d), 56.9 (t), 44.3 (q), 41.7 (t), 21.8 (q), 21.4 (q), 18.0 (q) and 17.9 (q). HR-MS (FAB): [M^++H], found 405.2299. $C_{24}H_{29}N_4O_2$ requires 405.2291.

3.2.7. Synthesis of 5,11-dipropionyl-5,11-dihydro-2,3-dimethyl-6-(2-dimethylaminoethyl)-6*H*-indolo[2,3-*b*]-quinoxaline (6g) via method B. Yield: 1.43 g (white crystals, 66%); At larger scales a convenient work-up consist of: removing the remaining zinc by filtration and thereafter treating the reaction mixture with water and separating the two phases thus formed. The water phase was cooled and basified with ammonia (aq., conc.). The solid thus formed was collected by filtration and washed with water and dried. Yield: 6.90 g (80%, from 20 mmol B-220). mp: 66–68 °C; IR (neat): 2973, 2939, 2821, 2769, 1678, 1490, 1452, 1358, 1244, 1173, and 742 cm^{-1}; ^1H NMR: δ 7.55–7.48 (m, 3H, Ar*H*), 7.45 (s, 1H, Ar*H*), 7.19 (t, J= 7.3 Hz, 1H, Ar*H*), 7.11 (t, J=7.3 Hz, 1H, Ar*H*), 4.37–4.17 (m, 2H, –CH_2–), 2.94–2.65 (m, 3H), 2.55–2.39 (m, 3H), 2.24 (s, 3H, *Me*), 2.22 (s, 3H, *Me*), 2.06 (s, 6H, 2*Me*), 1.02 (q, J=7.4 Hz, 6H, 2*Me*); ^{13}C NMR (110 °C): δ 173.3 (s), 171.4 (s), 136.3 (s), 134.1 (s), 133.7 (s), 133.6 (s), 133.4 (s), 133.0 (s), 125.8 (d), 125.4 (d), 121.0 (d), 119.8 (s), 119.4 (d), 117.7 (d), 112.5 (s), 110.1 (d), 57.0 (t), 44.4 (q), 41.6 (t), 26.6 (t), 26.4 (t), 18.1 (q), 18.0 (q), 8.5 (q) and 8.1 (q). HR-MS (FAB): [M^++H], found 433.2601. $C_{26}H_{33}N_4O_2$ requires 433.2604.

3.2.8. Synthesis of 5,11-dihydro-11-trifluoroacetyl-2,3-dimethyl-6-(2-dimethylaminoethyl)-6*H*-indolo[2,3-*b*]-quinoxaline (6h) via method B. Yield: 1.03 g (yellowish solid, 50%); mp: 170–173 °C; IR (neat): 3053, 2955, 2796, 1676, 1494, 1463, 1141, 855, and 723 cm^{-1}; ^1H NMR: δ 9.88 (s, 1H, N*H*), 7.34 (d, J=6.6 Hz, 1H, Ar*H*), 7.29 (d, J= 7.2 Hz, 1H, Ar*H*), 7.22 (s, 1H, Ar*H*), 7.00–6.95 (m, 3H, Ar*H*), 4.29 (t, J=6.0 Hz, 2H, –CH_2–), 2.60 (t, J=6.0 Hz, 2H, –CH_2–), 2.27 (s, 6H, 2*Me*), 2.22 (s, 3H, *Me*), 2.18 (s, 3H, *Me*). No ^{13}C NMR could be recorded due to low solubility and instability in warm DMSO. HR-MS (FAB): [M^+], found 416.1823. $C_{22}H_{23}F_3N_4O$ requires 416.1824.

3.2.9. Synthesis of 1,2-dihydro-1-trifluoroacetyl-3-[(2-trifluoroacetylamino)phenyl]-quinoxaline (8) via method C. Yield: 1.02 g (yellowish solid, 49%). mp: 150–151 °C; IR (neat): 2858, 1706, 1542, 1266, 1190, 1155, 1138, 1091, 749, 727, and 703 cm^{-1}; ^1H NMR ($CDCl_3$): δ 14.49 (s, 1H, N*H*), 8.80 (d, J=8.4 Hz, 1H, Ar*H*), 7.85–7.75 (m, 2H, Ar*H*), 7.61 (dt, J=7.9 Hz, 1.2, 1H, Ar*H*), 7.54–7.30 (m, 4H, Ar*H*), 4.90 (s, 2H, –CH_2–). Due to instability in most solvents no ^{13}C NMR could be recorded. HR-MS (FAB): [M^++H], found 416.0840. $C_{18}H_{12}F_6N_3O_2$ requires 416.0834.

3.2.10. Syntheses of 2-(2-aminophenyl)-quinoxaline (10). *From compound* **8**. A solution of KOH (0.41 g; 7.3 mmol), **8** (0.75 g; 1.8 mmol) and ethanol (10 mL) was refluxed for 48 h. The reaction mixture was poured into water (100 mL) and the solid thus formed was collected by filtration, washed with water, dried and purified by chromatography (EtOAc–Hexane, 1:4). Yield: 0.30 g (yellow solid, 75%).

From compound **9**. A solution of **9**10 (0.50 g; 2 mmol), Pd(C) (5%, 0.05 g) and ethanol (100 mL) was treated under H_2 at for 70 h. The reaction mixture was filtered through Celite, the solvent was removed under reduced pressure and the solid thus formed was purified by chromatography (EtOAc–Hexane, 1:4). Yield: 0.26 g (yellow solid, 59%).

Mp: 127 °C (dec.); IR (neat): 3340, 3148, 1613, 1538, 1472, 1249, 760, and 735 cm^{-1}.; ^1H NMR ($CDCl_3$): δ 9.34 (s, 1H, Ar*H*), 8.10 (dd, J=8.0 Hz, 1.9, Ar*H*), 8.05 (dd, J=7.5 Hz, 2.0, Ar*H*), 7.78–7.73 (m, 2H, Ar*H*), 7.28 (dt, J=7.7 Hz, 1.3, Ar*H*), 6.90–6.83 (m, 2H, Ar*H*), 6.21 (s, 2H, –NH_2); ^{13}C NMR ($CDCl_3$): δ 153.8 (s), 148.4 (s), 145.0 (d), 140.8 (s), 140.5 (s), 131.6 (d), 130.5 (d), 129.7 (2C, d), 128.9 (d), 118.5 (s), 117.9 (d), 117.8 (d). HR-MS (FAB): [M^++H], found 222.1039. $C_{14}H_{12}N_3$ requires 222.1031.

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