Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron
ELSEVIER
Tetrahedron 60 (2004) 10825–10832

Synthesis of 5-alkyl(or aryl)pyrrolo[1,2-*a*]quinoxalin-4(5*H*)-ones by denitrocyclisation of *N*-alkyl(or aryl)-1-(2-nitrophenyl)-1*H*-pyrrole-2-carboxamides. Evidence of a Smiles rearrangement

Georgios Rotas, Athanasios Kimbaris and George Varvounis*

Department of Chemistry, University of Ioannina, GR-451 10 Ioannina, Greece

Received 16 July 2004; revised 25 August 2004; accepted 16 September 2004

Available online 2 October 2004

Abstract—An efficient method for the synthesis of hitherto unknown alkyl(or aryl)pyrrolo[1,2-*a*]quinoxalin-4(5*H*)-ones **8a**–**g**, **16** and **17** has been established. The method is based on the synthesis of the corresponding *N*-alkyl(or aryl)-1-(2-nitrophenyl)-1*H*-pyrrole-2-carboxamides **3a**–**c** and **7a**–**c**,**e** which undergo denitrocyclisation with NaH in DMF in 4.5 or 2 h. When **3a** was treated with NaH in DMF for 30 min the product of a Smiles rearrangement, **9**, was isolated. Under similar conditions but for 4.5 h **9** was converted into **8a**. This confirms the involvement of a Smiles rearrangement during the denitrocyclisation process. Conversion of **3b** into isomeric pyrroloquinoxalinones **12** and **13** confirms a process involving two pathways, direct denitrocylisation of **3b** and Smiles rearrangement of **3b** followed by denitrocylisation, respectively. Furthermore, denitrocylisation of **7d** into pyrroloquinoxalinones **16** and **17** suggests that similar cyclisation pathways are followed by *N*-arylcarboxamides.
© 2004 Elsevier Ltd. All rights reserved.

1. Introduction

Pyrrolo[1,2-*a*]quinoxalines are best known as high-affinity and selective agonists of the 5-HT_3 receptors.[1–3] More recently, several bispyrrolo[1,2-*a*]quinoxaline derivatives were found to have significant antimalarial activity[4] whereas certain pyrrolo[1,2-*a*]quinoxalin-4(5*H*)-ones have shown promising antiviral[5] and antiallergic[6] properties.

5-Alkylpyrrolo[1,2-*a*]quinoxalin-4(5*H*)-ones may be formed by first synthesising the lactam derivatives[1–3,7] followed by alkylation.[5] Other routes include the use of benzimidazolium *N*-ylides in 1,3-dipolar cycloadditions with alkenes[6,8] and alkynes[9] or reaction with 2,2-dihydropoly(per)fluoroalkanoates,[10] and by reductive ring-opening/ring-closure of pyridazinoquinoxalinones.[11]

2. Results and discussion

Following our previous interest in the synthesis of pyrrolo[1,2-*a*]quinoxalines[12] we now wish to report our findings that lead to the synthesis of 5-alkyl(or aryl)-pyrrolo[1,2-*a*]quinoxalin-4(5*H*)-ones by denitrocyclisation of *N*-alkyl(or aryl)-1-(2-nitrophenyl)-1*H*-pyrrole-2-carboxamides.

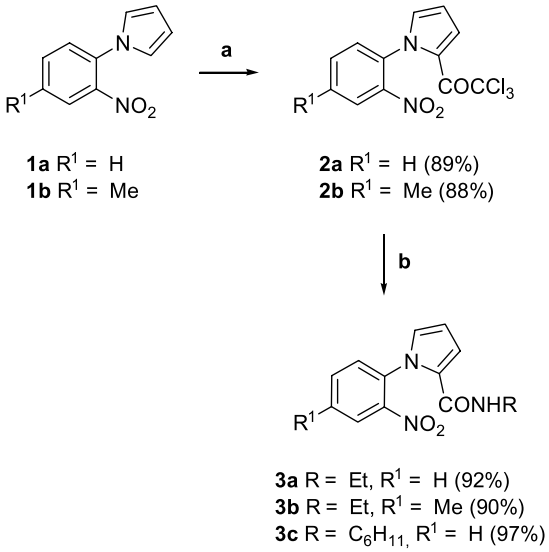
Carboxamides **3a**–**c** were prepared by reacting appropriate 2-trichloroacetylpyrroles **2a**–**b**, derived by treating 1-arylpyrroles **1a**–**b** with trichloroacetyl chloride, with diethylamine or cyclohexylamine in 1,4-dioxane for 1.5 h (Scheme 1).

In contrast, the preparation of aromatic carboxamides **7a**–**e** required first hydrolysis of trichloroacetyl derivative **2a** to the carboxylic acid **4**, conversion of the latter with thionyl chloride into acid chloride **5** and then, without isolation, treatment of **5** with aromatic amines **6a**–**e** for 2 days in a 1:1 pyridine–toluene mixture (Scheme 2). Attempts to react 4-chloro-2-nitroaniline or 2-trifluoromethylaniline with acid chloride failed. This is probably due to a combination of steric and electronic reasons which is reflected in the low yield (45%) of **7b**. Railey and Johnson have previously prepared a large number of *N*-alkyl(or aryl)-4,5-dihalo-1*H*-pyrrole-2-carboxamides, as potential antibacterial agents, in a similar manner.[13]

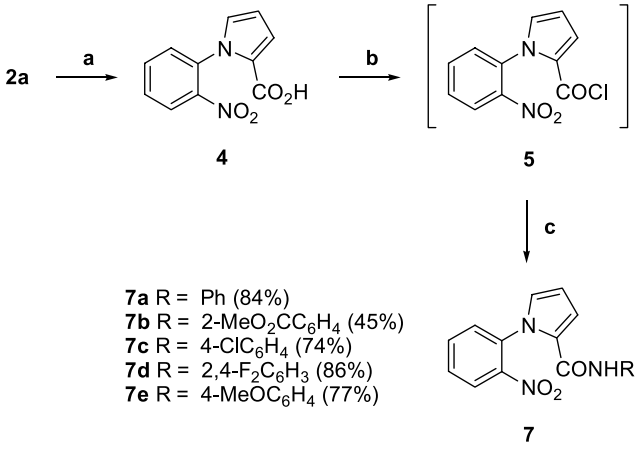
Upon treating carboxamides **3a**,**c** or **7a**–**c**,**e** with NaH in DMF for 4.5 or 2 h, pyrroloquinoxalinones **8a**–**f** were obtained in excellent yields (77–95%). The work-up involved adding to water and neutralising with 2 N HCl. This led to hydrolysis of the initially formed ester **8e** to the carboxylic acid **8d**. The ester **8e** was isolated when the

Keywords: Pyrroles; Pyrroloquinoxalinones; Denitrocyclisation; Defluorocyclisation; Smiles rearrangement.
* Corresponding author. Tel.: +30 26510 98382; fax: +30 26510 98799; e-mail: gvarvoun@cc.uoi.gr

0040–4020/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2004.09.048



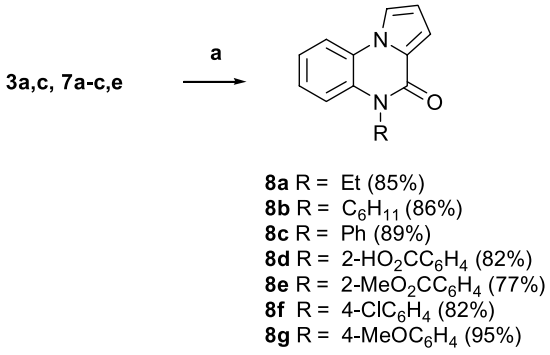
Scheme 1. Reagents (a) Cl_3CCOCl, 1,4-dioxane; (b) 70% $EtNH_2$ in H_2O, CH_2Cl_2 or cyclohexylamine, Et_3N, 1,4-dioxane, 75 °C.



Scheme 2. Reagents (a) 10% aq. NaOH, reflux; (b) $SOCl_2$, reflux; (c) **6a** $PhNH_2$, **6b** 2-$MeO_2CC_6H_4NH_2$, **6c** 4-$ClC_6H_4NH_2$, **6d** 2,4-$F_2C_6H_3NH_2$ or **6e** 4-$MeOC_6H_4NH_2$, pyridine.

reaction mixture was poured into ice-water containing sodium bicarbonate. To the best of our knowledge, this intramolecular displacement of an aromatic nitro group by *N*-substituted carboxamides, under mild conditions, to form 5-substituted pyrroloquinoxalinones, is unprecedented in the literature. The closest analogy was published by Nacci et al.[7c] who cyclised 1-(2-nitrophenyl)-1*H*-pyrrole-2-carboxamide to the parent pyrrolo[1,2-*a*]quinoxalin-4(5*H*)-one, by heating in DMF containing potassium carbonate (Scheme 3).

It was interesting to note that TLC examination of reactions **3a** or **c** with NaH in DMF after 0.5 h, revealed a new spot together with spots corresponding to starting material and product. We therefore investigated further the reaction of **3a** with NaH in DMF by allowing it to proceed for 0.5 h. After work-up and column chromatography three compounds were isolated, starting material **3a**, pyrroloquinoxalinone **8a** and carboxamide **9** in 13, 27 and 21% yield, respectively (Scheme 4). This result provides conclusive evidence that a Smiles rearrangement is taking place. Furthermore, reaction



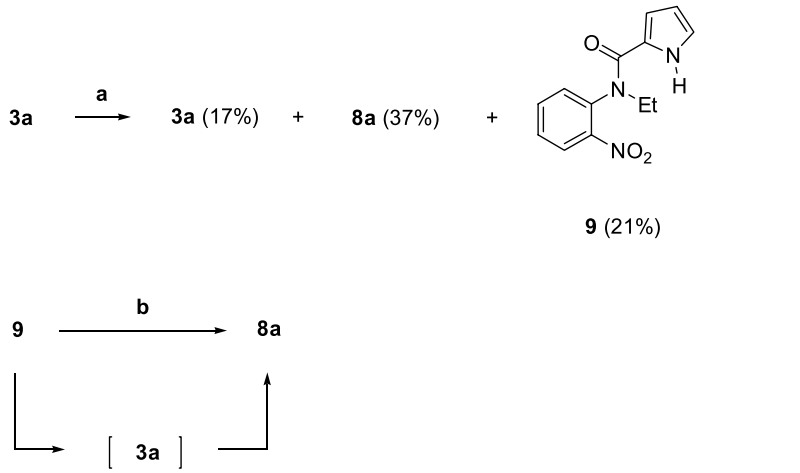
Scheme 3. Reagents (a) NaH (60% in oil), DMF.

of **9** with NaH in DMF for 4.5 h gave **8a** as sole product. TLC examination of this reaction after 0.5 h revealed three spots that corresponded to **3a**, **8a** and starting material **9**.

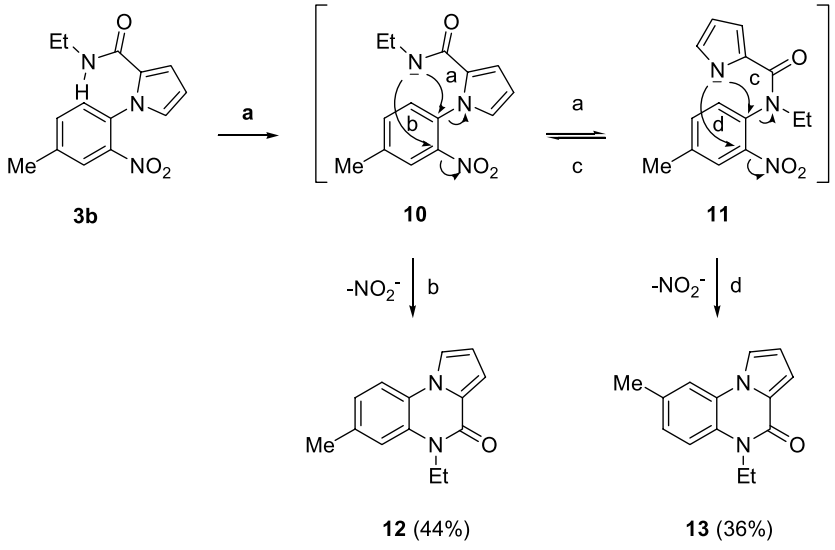
From the above observations we can confidently propose that carboxamide **3a** undergoes a Smiles rearrangement to give carboxamide **9**. However, although there is ample indication that the transformation of **3a** to **9** is reversible, there is no direct evidence as to whether **3a** or **9** or both lead to **8a**.

Further insight into the mechanism of 4-alkylpyrroloquinoxalinone formation was obtained by reacting carboxamide **3b** with NaH in DMF for 1.5 h. This gave a mixture containing pyrroloquinoxalinones **12** and **13** (Scheme 5). Since the separation of these two compounds by column chromatography was not possible, **12** was synthesised unambiguously by *N*-ethylating 7-methylpyrrolo[1,2-*a*]-quinoxalin-4(5*H*)-one[3] with ethyl iodide in DMF containing NaH. The ^1H NMR spectra of compound **12** and that of the mixture **12/13** were then compared and the peaks corresponding to **12** and **13** assigned. It turned out that **12** and **13** are in a ratio of about 44:36. Compounds **12** and **13** could only have been obtained from the corresponding anions of carboxamides **10** and **11** by denitrocyclisation through paths b and d. Compound **11** can only be obtained from **10** by a Smiles rearrangement that follows path a. Furthermore, based on previous observations (vide infra), it is quite reasonable to assume that the transformation of **10** to **11** is reversible through path c.

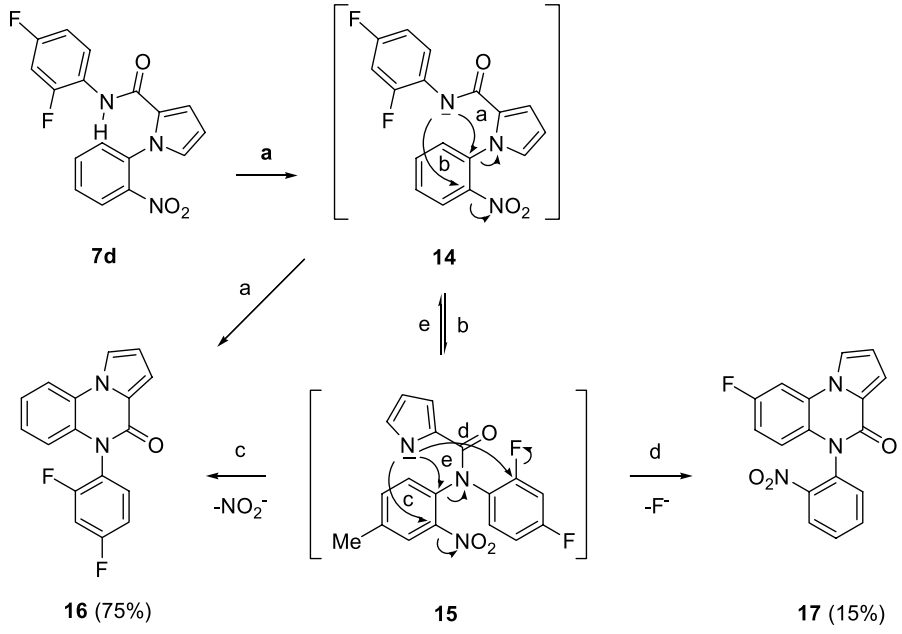
In order to verify whether a Smiles rearrangement occurred during the denitrocyclisation of aromatic carboxamides **7a–c**,**e** to pyrroloquinoxalinones **8c**,**e–g**, *N*-(2,4-difluorophenyl)carboxamide **7d** was employed as a potentially useful precursor. When **7d** was treated with NaH in DMF for 1.5 h, two products **16** and **17** were obtained in 75 and 15% yield, respectively. A proposed mechanism for this reaction is shown in Scheme 6. The initially formed carboxamide anion **14** could follow two paths a or b. Path a would lead to pyrroloquinoxalinone **16** by direct denitrocylisation whereas path b would lead to intermediate carboxamide **15** via a Smiles rearrangement. Taking into account previous observations (vide infra) it is reasonable to assume that **15** can reverse to **14** through path e and denitrocyclise to **16** through path c. On the other hand, pyrroloquinoxalinone **17** can only be formed through path d, that is, intramolecular nucleophilic displacement of fluoride anion by pyrrolyl anion of



Scheme 4. Reagents (a) NaH (60% in oil), DMF, 30 min; (b) NaH (60% in oil), DMF, 4.5 h.



Scheme 5. Reagents (a) NaH (60% in oil), DMF, 1.5 h.



Scheme 6. Reagents (a) NaH (60% in oil), DMF, 4.5 h.

intermediate **15**. The formation of **17** strongly suggests that intermediate **15** is its precursor. However, there is no substantial evidence to support that **16** is obtained directly from **14** or from intermediate **15** or from both.

3. Conclusion

In conclusion, we have shown that denitrocyclisation of *N*-alkyl(or aryl)-1-(2-nitrophenyl)-1*H*-pyrrole-2-carboxamides is a mild method that gives 5-alkyl(or aryl)pyrrolo[1,2-*a*]quinoxalin-4(5*H*)-ones in high yields. For *N*-alkyl-1-(2-nitrophenyl)-1*H*-pyrrole-2-carboxamides there is direct evidence that reaction occurs through two pathways: (a) intramolecular nitro group displacement by the anion of *N*-alkyl-1-(2-nitrophenyl)-1*H*-pyrrole-2-carboxamides and (b) Smiles rearrangement of *N*-alkyl-1-(2-nitrophenyl)-1*H*-pyrrole-2-carboxamide anions into *N*-(2-nitrophenyl)-*N*-alkyl(or aryl)-1*H*-pyrrole-2-carboxamide anions, followed by intramolecular pyrrolyl anion displacement of the nitro group. It is highly probable that *N*-aryl-1-(2-nitrophenyl)-1*H*-pyrrole-2-carboxamides give 5-arylpyrrolo[1,2-*a*]quinoxalin-4(5*H*)-ones by following similar pathways.

4. Experimental

4.1. General methods

Melting points were taken on a Büchi 510 apparatus and are uncorrected. Infrared spectra were recorded on a Perkin–Elmer 257 spectrometer, as Nujol mulls and liquids between sodium chloride discs. Elemental analyses were performed on a Perkin–Elmer 2400 or a Carlo Erba 1106 elemental analysers. Nuclear magnetic resonance spectra were measured at 360 MHz on a Brüker AM 360 spectrometer or at 400 MHz on a Brüker AMX 400 spectrometer using tetramethylsilane as internal standard. Mass spectra were obtained using a JEOL JMS-AX 505W or a Bruker Apex III high-resolution instruments. Analytical TLC was carried out on Fluka silica gel 60 F_{254}. Preparative flash chromatography was carried out for all separations using Merck 9385 silica gel. Solvents and reagents were used as received from the manufacturers, except for dichloromethane, ethanol, ethyl acetate, hexane and methanol that were purified and dried according to recommended procedures.[14]

4.1.1. Preparation of 2-trichloroacetylpyrroles 2a,b: general procedure A. To a recently distilled solution of trichloroacetyl chloride (41.8 mL, 372 mmol) in dry 1,4-dioxane (140 mL), a solution of pyrrole **1a** or **1b** in (0.124 mol) in dry 1,4-dioxane (140 mL) was added dropwise. The reaction mixture was left to stir at room temperature for 6 days and then a saturated solution of potassium carbonate was slowly added until the pH was 7. Water (120 mL) was added and extracted with dichloromethane (3×80 mL). The combined organic extracts were dried (Na_2SO_4) and the solvent removed under reduced pressure to afford a residue, which on crystallisation from ethanol gave 2,2,2-trichloro-1-(1-(2-nitrophenyl)-1*H*-pyrrol-2-yl)ethanone **2a** or 2,2,2-trichloro-1-(1-(4-methyl-2-nitrophenyl)-1*H*-pyrrol-2-yl)-ethanone **2b**.

4.1.1.1. 2,2,2-Trichloro-1-[1-(2-nitrophenyl)-1*H*-pyrrol-2-yl)]ethanone 2a. 4.20 g, 89%, as pale yellow needles (ethanol), mp 115–117 °C. [Found: C, 43.19; H, 2.15; N, 8.41. $C_{12}H_7Cl_3N_2O_3$ requires, 43.21; H, 2.12; N, 8.40%]; ν_{max} (Nujol) 1660, 1520, 1340 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 6.41 (t, J=3.8 Hz, 1H, H-4), 6.96 (s, 1H, H-3), 7.34 (d, J=7.8 Hz, 1H, H-6′), 7.54–7.60 (2H, m, H-5, H-4′), 7.65 (t, J=7.7 Hz, 1H, H-5′), 8.08 (d, J=8.1 Hz, 1H, H-3′); δ_C (100 MHz; $CDCl_3$) 111.60, 122.60, 124.76, 125.19, 130.13, 130.34, 133.65, 134.75, 135.03, 145.41, 171.73; *m*/*z* (EI) 332 (M^++1, 32), 215 (92), 187 (82), 171 (100%).

4.1.1.2. 2,2,2-Trichloro-1-[1-(4-methyl-2-nitrophenyl)-1*H*-pyrrol-2-yl)]ethanone 2b. 37.9 g, 88%, as pale yellow needles (ethanol), mp 122–124 °C. [Found: C, 45.03; H, 2.67; N, 8.01. $C_{13}H_9Cl_3N_2O_3$ requires C, 44.92; H, 2.61; N, 8.06%]; ν_{max} (Nujol) 3124, 1670, 1528, 1347 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 2.52 (s, 3H, Me), 6.47 (dd, J=4.3, 2.7 Hz, 1H, H-4), 7.02 (dd, J=2.6, 1.6 Hz, 1H, H-5), 7.29 (d, J=7.9 Hz, 1H, H-6′), 7.51 (dd, J=7.9, 1.3 Hz, 1H, H-5′), 7.66 (dd, J=4.4, 1.5 Hz, 1H, H-3), 7.96 (d, J=1.3 Hz, 1H, H-3′); δ_C (100 MHz; $CDCl_3$) 20.88, 95.44, 111.00, 123.64, 124.31, 125.61, 129.34, 131.71, 132.77, 134.44, 140.59, 145.09, 172.28; *m*/*z* (EI) 348 (M^++2, 6), 346 (M^+, 7), 302 (5) 300 (5), 283 (7), 265 (5), 229 (50), 201 (40), 183 (100), 154 (21), 84 (30%).

4.1.2. Preparation of 1*H*-pyrrole-2-carboxamides 3a,b: general procedure B. To a solution of 2,2,2-trichloro-1-(1*H*-pyrrol-2-yl)ethanone **2a** or **2b** (9.04 mmol) in dichloromethane (40 mL) was added a solution of ethylamine 70% in water (3.5 mL, 54.225 mmol). The reaction mixture was stirred at room temperature for 18 h. Water was added (90 mL), the organic phase separated and the aqueous phase extracted with dichloromethane (3×30 mL). The combined organic phases were dried (Na_2SO_4) and the solvent removed under reduced pressure to afford a residue which was triturated with toluene and filtered. The residue was purified by dissolving in ethyl acetate and precipitating by addition of hexane to afford *N*-ethyl-1-(2-nitrophenyl)-1*H*-pyrrole-2-carboxamide **3a** or *N*-ethyl-1-(4-methyl-2-nitrophenyl)-1*H*-pyrrole-2-carboxamide **3b**.

4.1.2.1. *N*-Ethyl-1-(2-nitrophenyl)-1*H*-pyrrole-2-carboxamide 3a. 2.16 g, 92%, as a pale-yellow solid (ethyl acetate/hexane); mp 93–95 °C; ν_{max} (CCl_4) 3450, 2980, 1665, 1350 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 1.05 (t, J=7.4 Hz, 3H, Me), 3.20 (q, J=6.9 Hz, 2H, CH_2), 5.79 (br, s, 1H, NH), 6.26 (t, J=3.3 Hz, 1H, H-4), 6.60 (d, J=3.9 Hz, 1H, H-3), 6.82 (s, 1H, H-5), 7.37 (d, J=7.9 Hz, 1H, H-6′), 7.47 (dd, J=8.0, 7.7 Hz, 1H, H-4′), 7.59 (dd, J=7.9, 7.7 Hz, 1H, H-5′), 7.98 (d, J=8.0 Hz, 1H, H-3′); δ_C (100 MHz; $CDCl_3$) 14.80, 34.03, 109.54, 112.24, 124.67, 127.01, 127.49, 128.67, 129.58, 133.31, 134.95, 145.02, 160.48; *m*/*z* (EI) 259 (M^+, 20), 213 (100), 188 (24), 171 (71) 169 (80), 155 (22), 143 (30), 118 (22%). HRMS (EI): (M^+), found 259.0961. $C_{13}H_{13}N_3O_3$ requires 259.0957.

4.1.2.2. *N*-Ethyl-1-(4-methyl-2-nitrophenyl)-1*H*-pyrrole-2-carboxamide 3b. 2.22 g, 90%, as a pale-yellow solid (ethyl acetate/hexane); mp 115–117 °C. [Found: C, 61.48; H, 5.47; N, 15.34; $C_{14}H_{15}N_3O_3$ requires C, 61.53; H,

5.53; N, 15.38%]; ν_{max} (Nujol) 3290, 1631, 1530, 1353 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 1.10 (t, $J=7.2$ Hz, 3H, Me), 2.47 (s, 3H, Me), 3.25 (q, $J=7.2$ Hz, 2H, CH_2), 5.92 (br, s, 1H, NH), 6.30 (dd, $J=3.9$, 2.8 Hz, 1H, H-4), 6.65 (dd, $J=3.9$, 1.6 Hz, 1H, H-3), 6.80 (dd, $J=2.8$, 1.6 Hz, 1H, H-5), 7.29 (d, $J=8.1$ Hz, 1H, H-6′), 7.45 (dd, $J=8.1$, 1.3 Hz, 1H, H-5′), 7.86 (d, $J=1.3$ Hz, 1H, H-3′); δ_C (100 MHz; $CDCl_3$) 14.79, 20.80, 34.00, 109.26, 111.91, 125.03, 127.04, 127.49, 128.31, 132.31, 133.83, 139.38, 145.60, 160.49; *m/z* (EI) 273 (M^+, 10), 227 (100), 199 (16), 185 (46), 183 (27), 158 (19%).

4.1.3. *N*-Cyclohexyl-1-(2-nitrophenyl)-1*H*-pyrrole-2-carboxamide 3c. To a solution of 2,2,2-trichloro-1-(1-(2-nitrophenyl)-1*H*-pyrrol-2-yl)ethanone **2a** (3 g, 9.04 mmol) in dry 1,4-dioxane (150 mL) under argon was added dropwise freshly distilled cyclohexylamine (5.17 mL, 45.18 mmol) and triethylamine (1.56 mL, 11.296 mmol) in dry 1,4-dioxane. The reaction mixture was stirred at 75 °C for 2 h and then the solvent removed under reduced pressure. Water was added (60 mL), the solution acidified with 2 N hydrochloric acid until the pH was 5 and then extracted with dichloromethane (3×20 mL). The combined organic extracts were dried (Na_2SO_4) and the solvent removed under reduced pressure to afford a residue which was photosensitive. The residue was suspended in toluene, filtered, and then purified from ethyl acetate/hexane to give the title compound **3c** as a pale-yellow solid (2.75 g, 97%); mp 98–100 °C; ν_{max} (Nujol) 3294, 1627, 1609, 1531, 1357 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 1.09–1.90 [m, 10H, $(CH_2)_5$], 3.67–3.74 (m, 1H, CH), 5.73 (s, 1H, NH), 6.32 (dd, $J=3.8$, 2.8 Hz, 1H, H-4), 6.66 (dd, $J=3.8$, 1.7 Hz, 1H, H-3), 6.82 (dd, $J=2.8$, 1.7 Hz, 1H, H-5), 7.44 (d, $J=7.8$ Hz, 1H, H-6′), 7.53 (dd, $J=8.0$, 7.6 Hz, 1H, H-4′), 7.66 (dd, $J=7.8$, 7.6 Hz, 1H, H-5′), 8.04 (d, $J=8.0$ Hz, 1H, H-3′); δ_C (100 MHz; $CDCl_3$) 24.84, 25.44, 33.07, 47.91, 109.48, 111.93, 124.67, 126.98, 127.80, 128.64, 129.55, 133.26, 134.92, 146.01, 159.69; *m/z* (EI) 313 (M^+, 20), 267 (88), 215 (26), 185 (80), 171 (88) 169 (100), 155 (52), 143 (32), 118 (22%). HRMS (EI): (M^+), found 313.1422, $C_{17}H_{19}N_3O_3$ requires 313.1426.

4.1.4. 1-(2-Nitrophenyl)-1*H*-pyrrole-2-carboxylic acid 4. A suspension of 2,2,2-trichloro-1-[1-(2-nitrophenyl)-1*H*-pyrrol-2-yl)]ethanone **2a** (11.5 g, 35 mmol) in 10% aqueous sodium hydroxide (70 mL) was heated under reflux for 1.5 h. The resulting solution was allowed to cool and then acidified with 2 N hydrochloric acid to pH 4. The precipitate was filtered, washed with water, dried and recrystallised from propan-2-ol to give the title compound **4** as deep yellow microcrystals (6.81 g, 84%); mp 195.5–197 °C. [Found: C, 57.22; H, 3.52; N, 12.08; $C_{11}H_8N_2O_4$ requires C, 56.90; H, 3.47; N, 12.06%]; ν_{max} (Nujol) 3257, 3136, 1690, 1669, 1607, 1528, 1350 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 6.39 (t, $J=3.3$ Hz, 1H, H-4), 6.94 (s, 1H, H-3), 7.20 (d, $J=3.9$ Hz, 1H, H-5), 7.41 (d, $J=7.8$ Hz, 1H, H-6′), 7.59 (t, $J=7.7$ Hz, 1H, H-4′), 7.68 (t, $J=7.7$ Hz, 1H, H-5′), 8.09 (d, $J=8.0$ Hz, 1H, H-3′), 12.32 (s, 1H, COOH); δ_C (100 MHz; $CDCl_3$) 110.05, 118.67, 124.19, 124.18, 129.55, 129.93, 130.22, 134.07, 134.28, 145.93, 161.21; *m/z* (EI) 232 (M^+, 47), 187 (100), 171 (65), 159 (28) 143 (38), 131 (35), 102 (23), 83 (23), 77 (24%).

4.1.5. Preparation of 1*H*-pyrrole-2-carboxamides 7a–e: general procedure C. A suspension of 1-(2-nitrophenyl)-1*H*-pyrrole-2-carboxylic acid **4** (1.5 mmol) in freshly distilled thionyl chloride (8 mL) was heated to reflux under argon for 1 h. Removal of excess thionyl chloride, addition of dry benzene (7 mL) and then evaporation under vacuo gave a brownish oily residue. The residue was dissolved in dry benzene (7 mL) and then added dropwise under argon to a solution of the appropriate amine (1.5 mmol) in dry pyridine (7 mL). The reaction mixture was stirred at room temperature for 2 days. The solvents were evaporated in vacuo, a saturated solution of sodium bicarbonate (50 mL) was added and extracted with dichloromethane (3×20 mL). The combined organic extracts were dried (Na_2SO_4) and the solvent removed under reduced pressure to afford a residue that was purified by flash chromatography (25% ethyl acetate/hexane) to give 1-(2-nitrophenyl)-*N*-phenyl-1*H*-pyrrole-2-carboxamide **7a**, methyl 2-(1-(2-nitrophenyl)-1*H*-pyrrole-5-carboxamido)benzoate **7b**, *N*-(4-chlorophenyl)-1-(2-nitrophenyl)-1*H*-pyrrole-2-carboxamide **7c**, *N*-(2,4-difluorophenyl)-1-(2-nitrophenyl)-1*H*-pyrrole-2-carboxamide **7d**, or *N*-(4-methoxyphenyl)-1-(2-nitrophenyl)-1*H*-pyrrole-2-carboxamide **7e**.

4.1.5.1. 1-(2-Nitrophenyl)-*N*-phenyl-1*H*-pyrrole-2-carboxamide 7a. 387 mg, 84%, as a pale-yellow solid (ethyl acetate/hexane); mp 144–145 °C; ν_{max} (Nujol) 3320, 1637, 1540, 1355 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 6.17–6.20 (m, 1H, H-4), 6.66–6.68 (m, 2H, H-3, H-5), 6.84 (d, $J=7.1$ Hz, 1H, H-4″), 7.02–7.11 (m, 2H, H-3″, H-5″), 7.20–7.53 (m, 6H, H-2″, H-6″, H-6′, H-5′, H-4′, NH), 7.87 (d, $J=7.6$ Hz, 1H, H-3′); δ_C (100 MHz; DMSO-d_6) 109.60, 114.88, 120.36, 123.46, 124.75, 125.98, 128.70, 129.01, 129.19, 129.99, 134.15, 134.72, 139.11, 145.99, 158.79; *m/z* (EI) 307 (M^+, 33), 261 (22), 215 (32), 169 (100), 140 (17), 114 (12%); HRMS (EI): (M^+), found 307.0965, $C_{17}H_{13}N_3O_3$ requires 307.0957.

4.1.5.2. Methyl 2-(1-(2-nitrophenyl)-1*H*-pyrrole-5-carboxamido)benzoate 7b. 247 mg, 45%, as a pale-yellow solid (ethyl acetate/hexane); mp 166–168 °C. [Found: C, 62.31; H, 4.35; N, 11.45; $C_{19}H_{15}N_3O_5$ requires C, 62.46; H, 4.14; N, 11.50%]; ν_{max} (Nujol) 3257, 3136, 1690, 1669, 1607, 1528, 1350 cm^{-1}; δ_H (400 MHz; DMSO-d_6) 6.45–6.48 (m, 1H, H-4), 7.08–7.16 (m, 2H, H-3, H-4″), 7.26–7.27 (m, 1H, H-5), 7.51–7.61 (m, 2H, H-6′, H-5″), 7.71 (t, $J=7.7$ Hz, 1H, H-4′), 7.84 (t, $J=7.6$ Hz, 1H, H-5′), 7.97 (d, $J=7.9$ Hz, 1H, H-6″), 8.16 (d, $J=8.0$ Hz, 1H, H-3″), 8.26 (d, $J=8.4$ Hz, 1H, H-3′), 11.41 (br, s, 1H, NH); δ_C (100 MHz; DMSO-d_6) 52.77, 110.15, 114.24, 116.00, 120.21, 122.85, 124.82, 126.73, 129.55, 129.89, 130.16, 130.86, 134.17, 134.26, 134.52, 140.56, 145.84, 158.21, 168.31; *m/z* (EI) 365 (M^+, 29), 319 (22), 287 (21), 215 (28), 188 (26), 169 (100), 145 (34%).

4.1.5.3. *N*-(4-Chlorophenyl)-1-(2-nitrophenyl)-1*H*-pyrrole-2-carboxamide 7c. 379 mg, 74%, as a pale-yellow solid (ethyl acetate/hexane); mp 136–137 °C; ν_{max} (Nujol) 3320, 1635, 1520, 1350 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 6.39 (dd, $J=3.8$, 2.8 Hz, 1H, H-4), 6.86–6.90 (m, 2H, H-3, H-5), 7.18–7.26 (m, 2H, H-3″, H-5″), 7.35–7.38 (d, m, 2H, H-2″, H-6″), 7.46 (dd, $J=7.7$, 1.5 Hz, 1H, H-6′), 7.57 (t, $J=7.6$ Hz 1H, H-4′), 7.65–7.70 (m, 2H, H-5′, NH), 8.07 (d, $J=$

7.9 Hz, 1H, H-3′); δ_C (100 MHz; DMSO-d_6) 107.51, 109.6, 115.09, 121.73, 124.74, 126.64, 126.98, 128.56, 129.24, 130.01, 134.16, 134.56, 138.07, 145.93, 158.73; *m/z* (EI) 343 ($M^+ + 2$, 8), 341 (M^+, 24), 297 (4), 295 (10), 215 (43), 171 (23), 169 (100), 140 (14), 114 (10%); HRMS (EI): (M^+), found 341.0557, $C_{17}H_{12}ClN_3O_3$ requires 341.0567.

4.1.5.4. *N*-(2,4-Difluorophenyl)-1-(2-nitrophenyl)-1*H*-pyrrole-2-carboxamide 7d. 443 mg, 86%, as a pale-yellow solid (ethyl acetate/hexane); mp 81–83 °C. [Found: C, 59.33; H, 3.29; N, 12.16;. $C_{17}H_{11}F_2N_3O_3$ requires C, 59.48; H, 3.23; N, 12.24%]; ν_{max} (Nujol) 3237, 1639, 1524, 1359 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 6.42 (t, J=3.3 Hz, 1H, H-4), 6.77 (dddd, J=9.2, 8.3, 2.8, 1.7 Hz, 1H, H-5″), 6.84 (ddd, J=11.3, 8.3, 2.8 Hz, 1H, H-3″), 6.91–6.92 (m, 2H, H-3, H-5), 7.47 (dd, J=7.8, 1.3 Hz, 1H, H-6′), 7.58 (td, J=8.1, 1.3 Hz, 1H, H-4′), 7.67–7.71 (m, 2H, H-5′, NH), 8.03 (td, J=9.2, 6.0 Hz, 1H, H-6″), 8.10 (dd, J=8.1, 1.4 Hz, 1H, H-3′); δ_C (100 MHz; $CDCl_3$) 103.47 (dd, J=26.6, 23.7 Hz), 110.13, 111.09 (dd, J=21.5, 3.7 Hz), 113.75, 122.40 (dd, J=10.4, 3.8 Hz), 122.95 (dd, J=9.0, 2.1 Hz), 124.99, 126.84, 128.63, 129.21, 129.81, 133.52, 134.47, 146.00, 153.77 (dd, J=246.2, 11.8 Hz), 158.29, 158.94 (dd, J=246.0, 11.4 Hz); δ_F (376 MHz; $CDCl_3$) −115.37 (tdd, J=8.3, 6.0, 4.6 Hz, 1F, F-4″), −126.27 (ddddd, J=11.0, 9.2, 4.6, 2.9, 1.7 Hz, 1F, F-2″); *m/z* (EI) 343 (M^+, 23), 215 (36), 169 (100), 119 (51), 105 (85%).

4.1.5.5. *N*-(4-Methoxyphenyl)-1-(2-nitrophenyl)-1*H*-pyrrole-2-carboxamide 7e. 390 mg, 77%, as a pale-yellow solid (ethyl acetate/hexane); mp 107–109 °C;. ν_{max} (Nujol) 3315, 1630, 1510, 1345 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 3.75 (s, 3H, OMe), 6.37–6.39 (m, 1H, H-4), 6.79 (d, J=7.3 Hz, 2H, H-3″, H-5″), 6.83–6.87 (m, 2H, H-3, H-5), 7.30 (d, J=7.3 Hz, 2H, H-2″, H-6″), 7.46 (d, J=7.8 Hz, 1H, H-6′), 7.52–7.56 (m, 2H, H-4′, NH), 7.66 (t, J=7.8 Hz, 1H, H-5′), 8.05 (d, J=8.1 Hz, 1H, H-3′); δ_C (100 MHz; $CDCl_3$) 55.35, 109.53, 113.85, 114.42, 122.00, 124.71, 127.07, 128.71, 129.13, 129.95, 132.07, 134.13, 134.77, 145.99, 155.51, 158.51; *m/z* (EI) 337 (M^+, 85), 291 (14), 215 (40), 169 (100), 149 (30), 134 (15); HRMS (EI): (M^+), found 337.1060, $C_{18}H_{15}N_3O_4$ requires 337.1063.

4.1.6. Preparation of pyrrolo[1,2-*a*]quinoxalin-4(5*H*)-ones 8a,b: general procedure D. To a stirred solution of carboxamide **3a** or **c** (0.65 mmol) in dry DMF (10 mL) under argon, was added NaH (60% in oil, 1.10 mmol) and left to stir at room temperature for 1.5 h. The reaction mixture was poured into water (50 mL), neutralised with 2 N HCl and extracted with ethyl acetate (3×10 mL). The combined organic phases were dried (Na_2SO_4) and evaporated in vacuo. The oily residue was triturated with hexane, the solid collected and purified by flash chromatography (25% ethyl acetate/hexane) to afford 5-ethylpyrrolo[1,2-*a*]quinoxalin-4(5*H*)-one **8a** or 5-cyclo-hexylpyrrolo[1,2-*a*]quinoxalin-4(5*H*)-one **8b**.

4.1.6.1. 5-Ethylpyrrolo[1,2-*a*]quinoxalin-4(5*H*)-one 8a. 119 mg, 85%, as a pale-yellow solid (ethyl acetate/hexane); mp 78–80 °C. [Found: C, 73.45; H, 5.63; N, 13.14;. $C_{13}H_{12}N_2O$ requires C, 73.56; H, 5.70; N, 13.20%]; ν_{max} (Nujol) 3118, 1638 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 1.29 (t, J=7.0 Hz, 3H, CH_3), 4.25, (q, J=7.2 Hz, 2H, CH_2), 6.58 (dd, J=3.6, 2.8 Hz, 1H, H-2), 7.12–7.19 (m, 2H, H-3, H-8), 7.24–7.27 (m, 2H, H-6, H-7), 7.57 (dd, J=2.8, 1.6 Hz, 1H, H-1), 7.61 (d, J=7.6 Hz, 1H, H-9); δ_C (100 MHz; $CDCl_3$) 13.19, 36.58, 112.85, 113.61, 115.19, 115.96, 116.21, 123.07, 123.75, 124.63, 125.98, 129.56, 155.59; *m/z* (EI) 212 (M^+, 79), 197 (39), 184 (100) 167 (25), 155 (17%).

4.1.6.2. 5-Cyclohexylpyrrolo[1,2-*a*]quinoxalin-4(5*H*)-one 8b. 149 mg, 86%, as a pale-yellow solid (ethyl acetate/hexane); mp 109–111 °C. [Found: C, 76.38; H, 6.88; N, 10.46;. $C_{17}H_{18}N_2O$ requires C, 76.66; H, 6.81; N, 10.52%]; ν_{max} (Nujol) 3115, 1640, 1609 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 1.25–2.63 [m, 10H, $(CH_2)_5$], 4.75 (br, s, 1H, CH), 6.63–6.64 (m, 1H, H-2), 7.22–7.16 (m, 2H, H-3, H-8), 7.28 (t, J=7.3 Hz, 1H, H-7), 7.60–7.56 (m, 2H, H-1, H-6), 7.66 (d, J=7.8 Hz, 1H, H-9); δ_C (100 MHz; $CDCl_3$) 25.32, 26.51, 29.15, 55.98, 112.08, 113.03, 114.84, 115.30, 116.43, 122.43, 123.79, 124.31, 124.82, 129.76, 155.97; *m/z* (EI) 266 (M^+, 18), 184 (100), 155 (12), 129 (8%).

4.1.7. Preparation of pyrrolo[1,2-*a*]quinoxalin-4(5*H*)-ones 8c,d,f,g: general procedure E. To a stirred solution of the corresponding carboxamide **7a–c**,**e** (0.65 mmol) in dry DMF (10 mL) under argon, was added NaH (60% in oil, 1.10 mmol) and left to stir at room temperature for 4.5 h. The reaction mixture was poured into water (50 mL), neutralised with 2 N HCl and the precipitate filtered, washed with water and dried to afford 5-phenylpyrrolo[1,2-*a*]quinoxalin-4(5*H*)-one **8c**, 2-(4-oxo-pyrrolo[1,2-*a*]quinoxalin-5(4*H*)-yl)benzoic acid **8d**.

4.1.7.1. 5-Phenylpyrrolo[1,2-*a*]quinoxalin-4(5*H*)-one 8c. 178 mg, 89%, as a pale-yellow solid (ethyl acetate/hexane); mp 168–170 °C. [Found: C, 78.10; H, 4.68; N, 10.74;. $C_{17}H_{12}N_2O$ requires C, 78.44; H, 4.65; N, 10.76%]; ν_{max} (Nujol) 3110, 1652 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 6.50 (dd, J=8.4, 1.1 Hz, 1H, H-6), 6.75 (dd, J=3.9, 2.6 Hz, 1H, H-2), 7.11 (dd, J=3.9, 1.4 Hz, 1H, H-3), 7.18 (td, J=7.8, 1.1 Hz, 1H, H-8), 7.26 (td, J=7.7, 1.2 Hz, 1H, H-7), 7.40 (d, J=7.2 Hz, 2H, H-2′, H-6′), 7.56 (t, J=7.3 Hz, 1H, H-4′), 7.63 (t, J=7.4 Hz, 2H, H-3′, H-5′), 8.16 (dd, J=8.1, 1.2 Hz, 1H, H-9), 8.29 (dd, J=2.6, 1.4 Hz, 1H, H-1); δ_C (100 MHz; $CDCl_3$) 112.40, 113.16, 115.26, 116.73, 118.22, 122.68, 122.99, 123.03, 125.46, 128.76, 129.57, 129.93, 130.98, 136.70, 154.32; *m/z* (EI) 260 (M^+, 100), 259 (100), 231 (6) 205 (7), 178 (6), 166 (7), 115 (8), 102 (8%).

4.1.7.2. 2-(4-Oxopyrrolo[1,2-*a*]quinoxalin-5(4*H*)-yl)benzoic acid 8d. 162 mg, 82%, as a pale-yellow solid (2 N NaOH/2 N HCl); mp 260–262 °C. [Found: C, 70.73; H, 4.03; N, 9.17; $C_{18}H_{12}N_2O_3$ requires C, 71.05; H, 3.97; N, 9.21%]; ν_{max} (Nujol) 2900, 3135, 1709, 1651 cm^{-1}; δ_H (250 MHz; DMSO-d_6) 6.43 (d, J=8.1 Hz, 1H, H-6), 6.73–6.76 (m, 1H, H-2), 7.11 (m, 1H, H-3), 7.17 (t, J=7.5 Hz, 1H, H-8), 7.25 (t, J=7.5 Hz, 1H, H-7), 7.49 (d, J=7.7 Hz, 1H, H-6′), 7.69 (t, J=7.6 Hz, 1H, H-4′), 7.86 (t, J=7.6 Hz, 1H, H-5′), 8.17 (d, J=7.7 Hz, 2H, H-9, H-3′), 8.29 (m, 1H, H-1), 12.80 (bs, 1H, CO_2H); δ_C (63 MHz; DMSO-d_6) 112.63, 113.32, 115.45, 116.63, 118.42, 123.07 (2C), 123.34, 125.76, 129.57, 130.56, 131.37, 131.68, 132.13, 134.13, 136.74, 154.70, 165.79; *m/z* (EI) 304 (M^+, 60), 259 (100%).

4.1.7.3. Methyl 2-(4-oxopyrrolo[1,2-*a*]quinoxalin-5(4*H*)-yl)benzoate 8e. 159 mg, 77%, as a pale-yellow solid (ethyl acetate /hexane); mp 159–161 °C. [Found: C, 71.40; H, 4.48; N, 8.77; $C_{19}H_{14}N_2O_3$ requires C, 71.69; H, 4.43; N, 8.80%]; ν_{max} (Nujol) 3148, 1724, 1660 cm^{-1}; δ_H (250 MHz; DMSO-d_6) 3.55 (s, 1H, Me), 6.41 (d, J=8.1 Hz, 1H, H-6), 6.74–6.77 (m, 1H, H-2), 7.09–7.11 (m, 1H, H-3), 7.16 (t, J=7.8 Hz, 1H, H-8), 7.26 (t, J=7.7 Hz, 1H, H-7), 7.54 (d, J=7.7 Hz, 1H, H-6′), 7.72 (t, J=7.6 Hz, 1H, H-4′), 7.88 (t, J=7.6 Hz, 1H, H-5′), 8.18 (d, J=7.7 Hz, 2H, H-9, H-3′), 8.30–8.31 (m, 1H, H-1); δ_C (63 MHz; DMSO-d_6) 52.26, 112.68, 113.12, 113.27, 115.45, 116.45, 118.52, 122.92, 123.13, 123.31, 125.73, 128.94, 129.68, 131.16, 131.84, 134.59, 136.92, 154.61, 164.37; *m/z* (EI) 318 (M^+, 56), 259 (100%).

4.1.7.4. 5-(4-Chlorophenyl)pyrrolo[1,2-*a*]quinoxalin-4-(5*H*)-one 8f. 182 mg, 82%, as a pale-yellow solid (ethyl acetate/hexane); mp 236–238 °C. [Found: C, 68.93; H, 3.82; N, 9.47; $C_{17}H_{11}ClN_2O$ requires C, 69.28; H, 3.76; N, 9.50%]; ν_{max} (Nujol) 3088, 1660 cm^{-1}; δ_H (400 MHz; DMSO-d_6) 6.55 (dd, J=8.3, 1.1 Hz, 1H, H-6), 6.77 (dd, J=3.8, 2.8 Hz, 1H, H-2), 7.13 (dd, J=3.8, 1.4 Hz, 1H, H-3), 7.21 (td, J=7.8, 1.1 Hz, 1H, H-8), 7.29 (td, J=7.7, 1.2 Hz, 1H, H-7), 7.48 (d, J=8.6 Hz, 2H, H-2′, H-6′), 7.70 (d, J=8.6 Hz, 2H, H-3′, H-5′), 8.19 (dd, J=8.1, 1.2 Hz, 1H, H-9), 8.32 (dd, J=2.8, 1.4 Hz, 1H, H-1); δ_C (100 MHz; DMSO-d_6) 113.46, 114.11, 116.21, 117.62, 119.27, 123.45, 124.03, 126.47, 130.92, 131.66, 132.54, 134.32, 136.51, 155.20; *m/z* (EI) 294 (M^+, 100), 258 (18), 230 (11) 204 (6), 167 (7), 130 (12), 115 (9).

4.1.7.5. 5-(4-Methoxyphenyl)pyrrolo[1,2-*a*]quinoxalin-4-(5*H*)-one 8g. 208 mg, 95%, as a pale-yellow solid (ethyl acetate/hexane); mp 207–209 °C. [Found: C, 74.16; H, 4.90; N, 9.58; $C_{18}H_{14}N_2O_2$ requires C, 74.47; H, 4.86; N, 9.65%]; ν_{max} (Nujol) 3148, 1724, 1660 cm^{-1}; δ_H (400 MHz; DMSO-d_6) 3.85 (s, 3H, Me), 6.55 (d, J=8.1 Hz, 1H, H-6), 6.74 (dd, J=3.8 Hz, 2.7 Hz, 1H, H-2), 7.09 (dd, J=3.8, 1.5 Hz, 1H, H-3), 7.20–7.14 (m, 3H, H-8, H-2′, H-6′), 7.25 (td, J=7.5, 1.1 Hz, 1H, H-7), 7.29 (d, J=8.8 Hz, 2H, H-3′, H-5′), 8.12 (d, J=8.1 Hz, 1H, H-9), 8.27 (dd, J=2.7, 1.5 Hz, 1H, H-1); δ_C (100 MHz; DMSO-d_6) 55.60, 112.55, 113.35, 115.33, 115.42, 117.09, 118.36, 123.01, 123.15, 123.27, 125.67, 128.25, 130.80, 131.52, 154.78, 159.39; *m/z* (EI) 290 (M^+, 100), 275 (11), 167 (18), 145 (8%).

4.1.8. Reaction of *N*-ethyl-1-(2-nitrophenyl)-1*H*-pyrrole-2-carboxamide 3a with NaH in DMF. To a stirred solution of carboxamide **3a** (170 mg, 0.65 mmol) in dry DMF (10 mL) under argon, was added NaH (60% in oil, 44 mg, 1.10 mmol) and left to stir at room temperature for 30 min. The reaction mixture was added to a cold saturated aqueous sodium bicarbonate solution (50 mL), neutralised with 2 N HCl and extracted with ethyl acetate (3×10 mL). The combined organic phases were dried (Na_2SO_4) and evaporated in vacuo. The oily residue was triturated with hexane, the solid collected and purified by flash chromatography (25, 50% ethyl acetate/hexane) to afford *N*-ethyl-1-(2-nitrophenyl)-1*H*-pyrrole-2-carboxamide **3a**, 5-ethylpyrrolo[1,2-*a*]quinoxalin-4(5*H*)-one **8a** and *N*-ethyl-*N*-(2-nitrophenyl)-1*H*-pyrrole-2-carboxamide **9**.

4.1.8.1. *N*-Ethyl-*N*-(2-nitrophenyl)-1*H*-pyrrole-2-carboxamide 3a. 29 mg, 17%, as a pale-yellow solid (ethyl acetate/hexane), mp 93–95 °C, identical in all respects to an authentic sample (vide infra).

4.1.8.2. 5-Ethylpyrrolo[1,2-*a*]quinoxalin-4(5*H*)-one 8a. 51 mg, 37%, as a pale-yellow solid (ethyl acetate/hexane), mp 78–80 °C, identical in all respects to an authentic sample (vide infra).

4.1.8.3. *N*-Ethyl-*N*-(2-nitrophenyl)-1*H*-pyrrole-2-carboxamide 9. 36 mg, 21%, as a pale-yellow solid (ethyl acetate/hexane); mp 165.5–167.5 °C. [Found: C, 60.30; H, 5.26; N, 16.25; $C_{13}H_{13}N_3O_3$ requires C, 60.22; H, 5.05; N, 16.21%]; ν_{max} (Nujol) 3268, 1615 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 1.29 (t, J=7.2 Hz, 3H, Me), 3.60 (br, s, 1H, CH_2), 4.27–4.32 (m, 1H, CH_2) 4.94 (br, s, 1H, H-4), 5.96 (s, 1H, H-3), 6.87 (s, 1H, H-5), 7.50 (dd, J=7.8, 1.4 Hz, 1H, H-6′), 7.66 (td, J=7.6, 1.3 Hz, 1H, H-4′), 7.77 (td, J=7.7, 1.5 Hz, 1H, H-5′), 8.12 (dd, J=8.1, 1.5 Hz, 1H, H-3′), 9.69 (br, s, 1H, NH); δ_C (100 MHz; $CDCl_3$) 13.47, 46.00, 110.35, 112.99, 121.87, 125.05, 126.35, 129.83, 132.93, 134.55, 136.78, 147.67, 161.18; *m/z* (EI) 259 (M^+, 27), 213 (65), 184 (6) 166 (54), 151 (25), 131 (7), 106 (42), 94 (100), 66 (26%).

4.1.9. Preparation of 5-ethyl-7-methylpyrrolo[1,2-*a*]-quinoxalin-4(5*H*)-one 12. To a stirred solution of 7-methylpyrrolo[1,2-*a*]quinoxalin-4(5*H*)-one[1] (300 mg, 1.51 mmol) in dry DMF (10 mL) under argon, was added NaH (60% in oil, 65 mg, 1.61 mmol) and left to stir at room temperature for 1 h. Ethyl iodide (242 mg, 1.55 mmol) was added and the reaction mixture stirred for 15 min. Water (50 mL) was added and extracted with ethyl acetate (3×20 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated in vacuo. The oily residue was purified by flash chromatography (25% ethyl acetate/hexane) to afford 5-ethyl-7-methylpyrrolo[1,2-*a*]quinoxalin-4(5*H*)-one **12** (270 mg, 79%) as a colourless solid (propan-2-ol/hexane); mp 104–105 °C. [Found: C, 73.98; H, 6.29; N, 12.36; $C_{14}H_{14}N_2O$ requires C, 74.31; H, 6.24; N, 12.38%]; ν_{max} (Nujol) 3130, 1651 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 1.34 (t, J=7.2 Hz, 3H, CH_2CH_3), 2.42 (s, 3H, Me), 4.27 (q, J=7.2 Hz, 2H, CH_2CH_3), 6.60 (dd, J=3.9, 2.8 Hz, 1H, H-2), 6.97 (dd, J=8.2, 0.8 Hz, 1H, H-8), 7.06 (s, 1H, H-6), 7.17 (dd, J=3.9, 1.6 Hz, 1H, H-3), 7.50 (d, J=8.2 Hz, 1H, H-9), 7.55 (dd, J=2.8, 1.6 Hz, 1H, H-1); δ_C (100 MHz; $CDCl_3$) 12.65, 35.94, 68.54, 111.94, 112.75, 114.39, 115.50, 115.66, 121.85, 122.94, 123.27, 128.76, 135.38, 155.15; *m/z* (EI) 226 (M^+, 100), 211 (43), 198 (96), 181 (25), 169 (14%).

4.1.10. Reaction of *N*-ethyl-1-(4-methyl-2-nitrophenyl)-1*H*-pyrrole-2-carboxamide 3b with NaH in DMF. Following general procedure D carboxamide **3b** (0.65 mmol) in dry DMF (10 mL) and NaH (60% in oil, 1.10 mmol) at room temperature for 1.5 h gave a mixture (118 mg, 80%) of 5-ethyl-7-methylpyrrolo[1,2-*a*]quinoxalin-4(5*H*)-one **12** (44% in mixture from ^{1}H NMR) and 5-ethyl-8-methylpyrrolo[1,2-*a*]quinoxalin-4(5*H*)-one **13** (44% in mixture from ^{1}H NMR); δ_H (400 MHz; $CDCl_3$) 1.29–1.34 (m, 4H, 2×CH_2CH_3 of **12** and **13**), 2.41 (s, 3H, Me of **12**), 2.42 (s, 3H, Me of **13**), 4.24–4.30 (m, 4H, 2×CH_2CH_3 of **12** and **13**), 6.59–6.62 (m, 2H, 2×H-2 of **12** and **13**), 6.97

(d, $J=8.2$ Hz, 1H, H-8 of **12**), 7.06 (s, 1H, H-6 of **12**), 7.07 (d, $J=7.8$ Hz, H-7 of **13**), 7.14–7.18 (m, 3H, H-3 of **12** and **13**, H-6 of **13**), 7.45 (s, 1H, H-9 of **13**), 7.50 (d, $J=8.2$ Hz, 1H, H-9 of **12**), 7.55 (dd, $J=2.8$, 1.6 Hz, 1H, H-1 of **12**).

4.1.11. Reaction of *N*-(2,4-difluorophenyl)-1-(2-nitrophenyl)-1*H*-pyrrole-2-carboxamide 7d with NaH in DMF. Following general procedure E carboxamide **7d** (0.65 mmol) in dry DMF (10 mL) and NaH (60% in oil, 1.10 mmol) at room temperature for 4.5 h gave, after purification by flash chromatography (33% ethyl acetate/hexane), 5-(2,4-difluorophenyl)pyrrolo[1,2-*a*]quinoxalin-4(5*H*)-one **16** and 8-fluoro-5-(2-nitrophenyl)pyrrolo[1,2-*a*]quinoxalin-4(5*H*)-one **17**.

4.1.11.1. 5-(2,4-Difluorophenyl)pyrrolo[1,2-*a*]quinoxalin-4(5*H*)-one 16. 144 mg, 75%, as a pale-yellow solid (ethyl acetate/hexane); mp 200–202 °C. [Found: C, 69.07; H, 3.65; N, 9.35; $C_{17}H_{10}F_2N_2O$ requires C, 68.92; H, 3.40; N, 9.46%]; ν_{max} (Nujol) 3122, 1659 cm^{-1}; δ_H (400 MHz; DMSO-d_6) 6.63 (d, $J=8.2$ Hz, 1H, H-6), 6.77 (dd, $J=3.9$, 2.8 Hz, 1H, H-2), 7.17 (dd, $J=3.9$, 1.5 Hz, 1H, H-3), 7.23 (td, $J=7.8$, 1.3 Hz, 1H, H-7), 7.31 (td, $J=7.8$, 1.3 Hz, 1H, H-8), 7.36 (ddd, $J=8.8$, 8.7, 2.8, Hz, 1H, H-5′), 7.61 (ddd, $J=10.1$, 9.2, 2.8 Hz, 1H, H-3′), 7.67 (td, $J=8.8$, 6.2 Hz, 1H, H-6′) 8.19 (dd, $J=8.1$, 1.3 Hz, 1H, H-9), 8.32 (dd, $J=2.8$, 1.5 Hz, 1H, H-1); δ_C (100 MHz; DMSO-d_6) 105.94 (dd, $J=27.1$, 24.2 Hz), 113.37 (dd, $J=22.5$, 3.5 Hz), 113.56, 113.78, 115.93, 116.52, 119.27, 120.62 (dd, $J=13.5$, 3.9 Hz), 122.49, 123.55, 124.01, 126.32, 130.34, 133.51 (d, $J=10.4$ Hz), 154.38, 158.90 (dd, $J=251.1$, 13.3 Hz), 162.80 (dd, $J=248.6$, 11.8 Hz); δ_F (376 MHz; DMSO-d_6) −107.70 (dddd, $J=9.2$, 8.7, 8.6, 6.2 Hz, 1F, F-4′), −117.05 (ddd, $J=10.1$, 8.8, 8.6 Hz, 1F, F-2′); *m/z* (EI) 296 (M^+, 100), 277 (57), 247 (6%).

4.1.11.2. 8-Fluoro-5-(2-nitrophenyl)pyrrolo[1,2-*a*]quinoxalin-4(5*H*)-one 17. 32 mg, 15%, as a pale-yellow solid (ethyl acetate/hexane); mp 264–265 °C. [Found: C, 63.32; H, 3.33; N, 12.86; $C_{17}H_{10}FN_3O_3$ requires C, 63.16; H, 3.12; N, 13.00%]; ν_{max} (Nujol) 1661, 1514, 1346 cm^{-1}; δ_H (400 MHz; DMSO-d_6) 6.64 (dd, $J=9.0$, 5.1 Hz, 1H, H-6), 6.81 (t, $J=3.6$ Hz, 1H, H-2), 7.10 (td, $J=9.0$, 2.7 Hz, 1H, H-7), 7.16 (dd, $J=3.8$, 1.2 Hz, 1H, H-3), 7.77 (d, $J=7.8$ Hz, 1H, H-3′), 7.87 (td, $J=7.8$, 1.3 Hz, 1H, H-5′), 8.01 (td, $J=7.7$, 1.3 Hz, 1H, H-4′), 8.26 (dd, $J=9.8$, 2.7 Hz, 1H, H-9), 8.32–8.36 (m, 2H, H-1, H-6′); δ_C (100 MHz; DMSO-d_6) 103.31 (d, $J=28.4$ Hz), 112.84 (d, $J=22.8$ Hz), 113.91, 114.02, 118.35 (d, $J=9.6$ Hz), 119.88, 122.25, 124.25 (d, $J=11.4$ Hz), 126.16, 126.95, 129.86, 131.13, 132.65, 135.80, 147.26, 153.85, 158.36 (d, $J=240.3$ Hz); δ_F (376 MHz; DMSO-d_6) −118.25 (ddd, $J=9.8$, 9.0, 5.1 Hz, 1F, F-8); *m/z* (EI) 323 (M^+, 39), 277 (100), 247 (15), 222 (8%).

Acknowledgements

This research was funded by the programme "Heraklitos" of the Operational Programme for Education and Initial Vocational Training of the Hellenic Ministry of Education under the 3rd Community Support Framework and the European Social Fund (to G. R.) and partly by a PENED grant (91ED102) (to A. K.) from the General Secretariat of Research and Technology, Athens. We thank Professor Dr. B. Stanovnik of the University of Ljubljana and Professor N. Hadjiliadis of the University of Ioannina for elemental analyses. We are particularly grateful to A. Cakebread and R. Tye for mass spectra, and, J. Cobb for NMR spectra of fluorine containing compounds, obtained on machines funded by the University of London Intercollegiate Research Services Scheme.

References and notes

1. Campiani, G.; Morelli, E.; Gemma, S.; Nacci, V.; Butini, S.; Hamon, M.; Novellino, E.; Greco, G.; Cagnotto, A.; Goegan, M.; Cervo, L.; Dalla Valle, F.; Fracasso, C.; Caccia, S.; Mennini, T. *J. Med. Chem.* **1999**, *42*, 4362.
2. Campiani, G.; Cappelli, A.; Nacci, V.; Anzini, M.; Vomero, S.; Hamon, M.; Cagnotto, A.; Cagnotto, A.; Fracasso, C.; Uboldi, C.; Caccia, S.; Consolo, S.; Mennini, T. *J. Med. Chem.* **1997**, *40*, 3670.
3. Prunier, H.; Rault, S.; Lancelot, J.-C.; Robba, M.; Renard, P.; Delagrange, P.; Pfeiffer, B.; Caignard, D.-H.; Misslin, R.; Guardiola-Lemaitre, B.; Hamon, M. *J. Med. Chem.* **1997**, *40*, 1808.
4. Guillon, J.; Grellier, P.; Labaied, M.; Sonnet, P.; Léger, J.-M.; Déprez-Poulain, R.; Forfar-Bares, I.; Dallemagne, P.; Lemaître, N.; Péhourcq, F.; Rochette, J.; Sergheraert, C.; Jarry, C. *J. Med. Chem.* **2004**, *47*, 1997.
5. Campiani, G.; Aiello, F.; Fabbrini, M.; Morelli, E.; Ramunno, A.; Armaroli, S.; Nacci, V.; Garofalo, A.; Greco, G.; Novellino, E.; Maga, G.; Spadari, S.; Bergamini, A.; Ventura, L.; Bongiovanni, B.; Capozzi, M.; Bolacchi, F.; Marini, S.; Coletta, M.; Guiso, G.; Caccia, S. *J. Med. Chem.* **2001**, *44*, 305.
6. Ager, I. R.; Barnes, A. C.; Danswan, G. W.; Hairsine, P. W.; Kay, D. P.; Kennewell, P. D.; Matharu, S. S.; Miller, P.; Robson, P.; Rowlands, D. A.; Tully, W. R.; Westwood, R. *J. Med. Chem.* **1998**, *31*, 1098.
7. (a) Kumashiro, I. *Nippon Kagaku Zasshi* **1961**, *82*, 1072. *Chem. Abstr.* **1963**, *59*, 607. (b) Nagarajan, K.; Ranga Rao, V.; Venkateswarlu, A. *Indian J. Chem.* **1972**, *10*, 344. (c) Campiani, G.; Nacci, V.; Corelli, F.; Anzini, M. *Synth. Commun.* **1991**, *21*, 1567.
8. Matsuda, Y.; Yamashita, M.; Takahashi, K.; Ide, S.; Torisu, K.; Furuno, K. *Heterocycles* **1992**, *33*, 295.
9. (a) Meth-Cohn, O. *Tetrahedron Lett.* **1975**, *6*, 413. (b) Zhang, X.-C.; Huang, W.-Y. *Tetrahedron* **1998**, *54*, 12465.
10. Zhang, X.-C.; Huang, W.-Y. *Tetrahedron Lett.* **1997**, *38*, 4827.
11. Abbott, P. J.; Acheson, R. M.; Foxton, M. W.; Raulins, N. R.; Robinson, G. E. *J. Chem. Soc., Perkin Trans. 1* **1972**, 2182.
12. Korakas, D.; Kimbaris, A.; Varvounis, G. *Tetrahedron* **1996**, *52*, 10751.
13. Railey, D. M.; Johnson, R. E. *J. Med. Chem.* **1973**, *16*, 1300.
14. Armarego, W. L. F.; Perrin, D. D. *Purification of Laboratory Chemicals*; Butterworth-Heinemann: Oxford, 1996.