SYNTHESES IN THE SERIES OF PYRAZOLYL-SUBSTITUTED QUINOXALINES

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Abstract - Starting from 3-(3-chloro-1*H*-pyrazol-5-yl)-1*H*-quinoxalin-2-one (**2**), a dihydroquinoxalinone derivative (**6**) was synthesised as potential HIV-1 reverse transcriptase inhibitor. Moreover, a series of N^4-[3-(3-pyrazolyl)-2-quinoxalinyl]-N^1,N^1-diethyl-1,4-pentanediamines (compounds of type **B**) and *N*-[3-(3-pyrazolyl)-2-quinoxalinyl]-*N*-(3-pyridyl)methylamines (**11-13**) – structurally related to antimalarial agents – could be prepared *via* the 2-chloro-3-[3(5)-chloro-1*H*-pyrazol-5(3)-yl]-quinoxaline (**7**). The position of the alkyl substituent on the pyrazole nitrogen was determined unequivocally from NOE difference experiments or X-Ray structure analysis.

INTRODUCTION

In the course of our efforts directed at the synthesis of bioactive compounds bearing a heterocyclic moiety, we have recently observed an unexpected 1,2-diazine → 1,2-diazole transformation.[1] The product of this ring contraction – the pyrazolyl substituted quinoxalinone (**2**) – now appeared to be an attractive educt for the development of potential bioactive agents.

(1) (2)

Scheme 1. Formation of the pyrazolyl-substituted quinoxalinone (**2**) from **1**

Here we report on the synthesis of heterocyclic compounds of type **A** and **B** which are structurally related to the HIV-1 reverse transcriptase inhibitors **S-2720** and **HBY 097** (characterised by a quinoxaline

This paper is dedicated to 25th Anniversary of HETEROCYCLES.

system)[2] and the antimalarial agents chloroquine and primaquine (characterised by a planar bicyclic hetero-aromatic moiety and the 'antimalarial-side chain').[3]

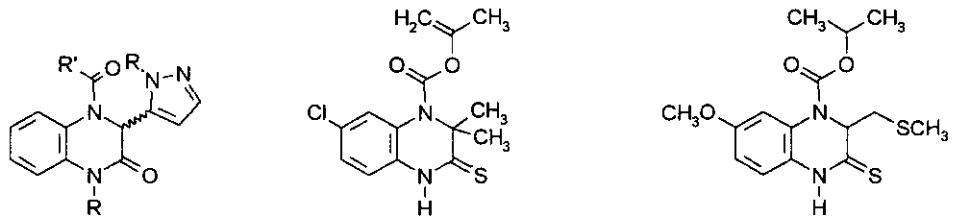


Figure 1. Structures of the target compounds of type **A** and the non-nucleoside HIV-reverse transcriptase inhibitors **S-2720** and **HBY 097**

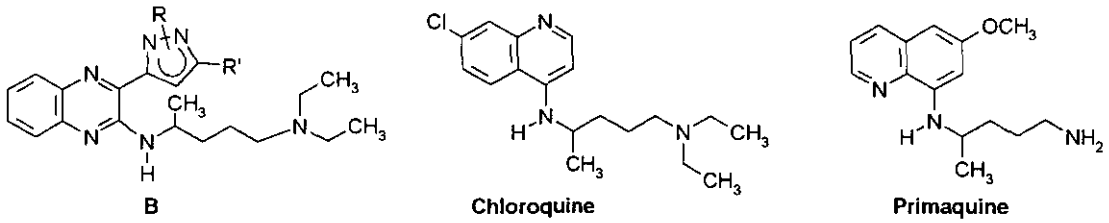
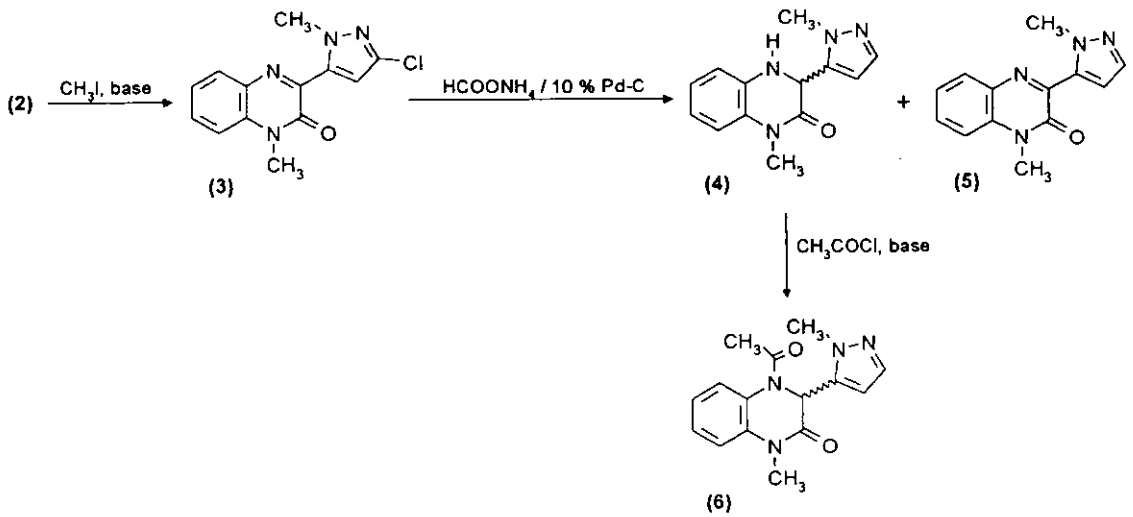


Figure 2. Structures of the target compounds of type **B** and the antimalarial agents **chloroquine** and **primaquine**

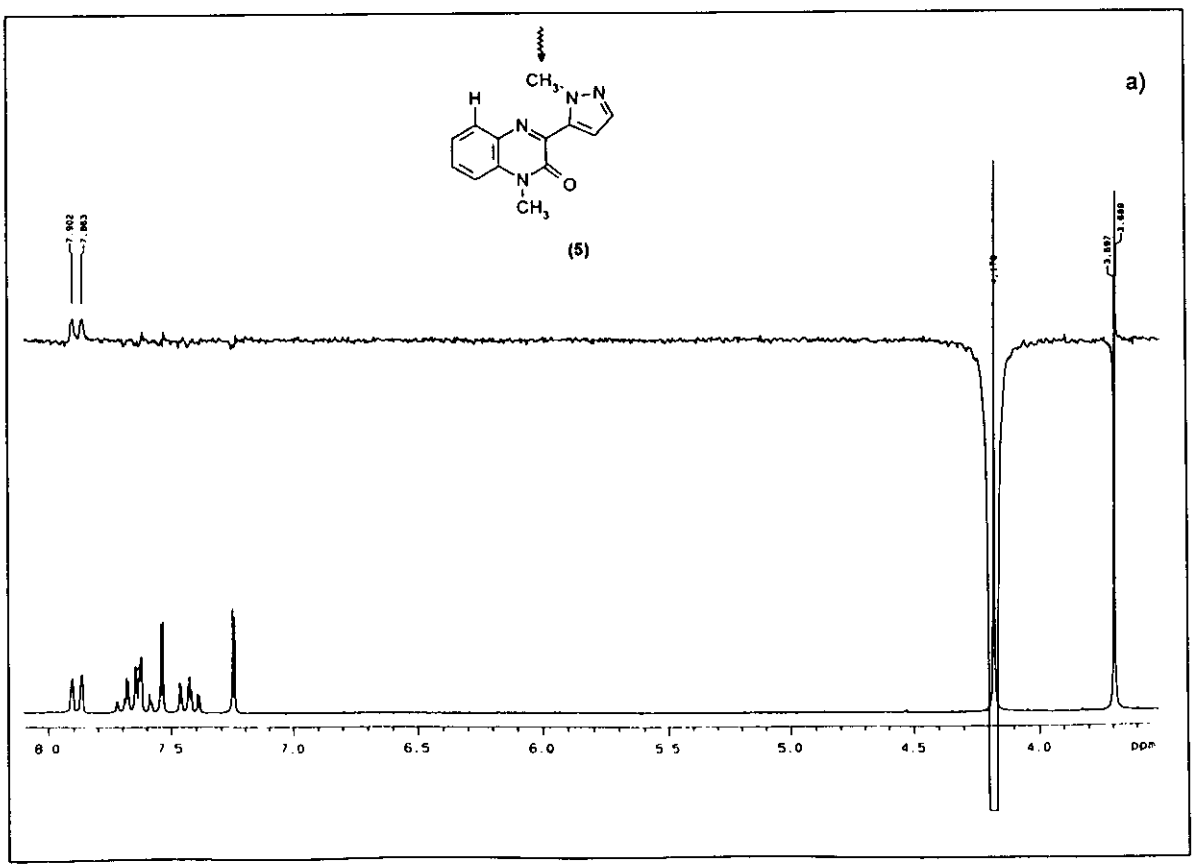
RESULTS AND DISCUSSION

The synthesis of compounds of type **A** is shown in Scheme 2. Alkylation of **2** was performed in dry DMSO using two equivalents of base (potassium hydroxide) and an excess of methyl iodide at room temperature. The assignment of structure **(3)** follows unequivocally from the NOE difference experiments of the dehalogenated product **(5)** (see Figure 3). Catalytic transfer hydrogenation of **3** (using ammonium formate as hydrogen source and 10 % Pd/C as catalyst) leads to a mixture of **4** and **5** which could be separated by column chromatography. Compound (**4**) turned out to be stable only under a nitrogen atmosphere; in the presence of air, this dihydroquinoxalinone is transformed into **5**. Attempts to convert **3** or **4** into the corresponding thiones (treatment with phosphorus pentasulfide in dry tetrahydrofuran or pyridine) so far failed. Synthesis of **6** was accomplished by reacting **4** with acetyl chloride and triethylamine in dry 1,4-dioxane at 100 °C. This procedure was found to afford an 81 % yield of **6**.

Compounds (6) as well as 2 and 5 were tested against the replication of HIV-1 (III_B) and HIV-2 (ROD) in acute infected MT-4 cells. They were found not to show any significant antiviral activity.



Scheme 2. Synthesis of the target compounds of type A



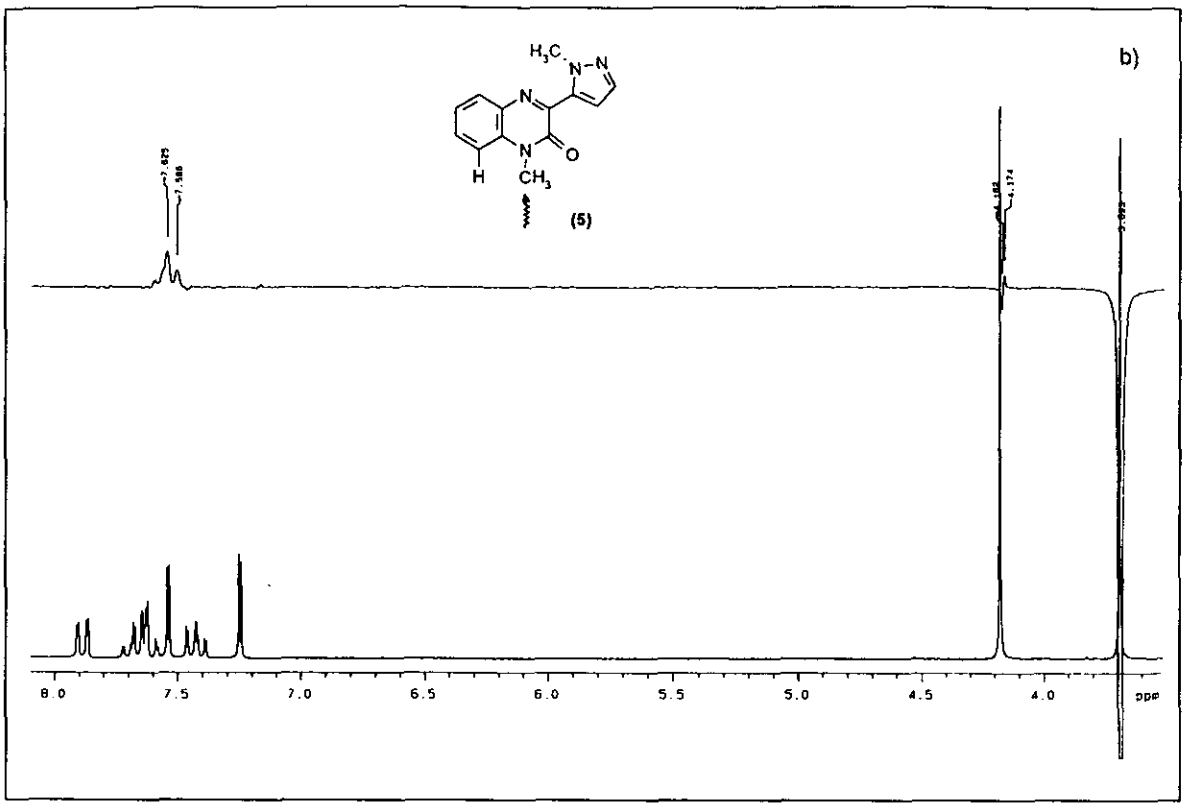
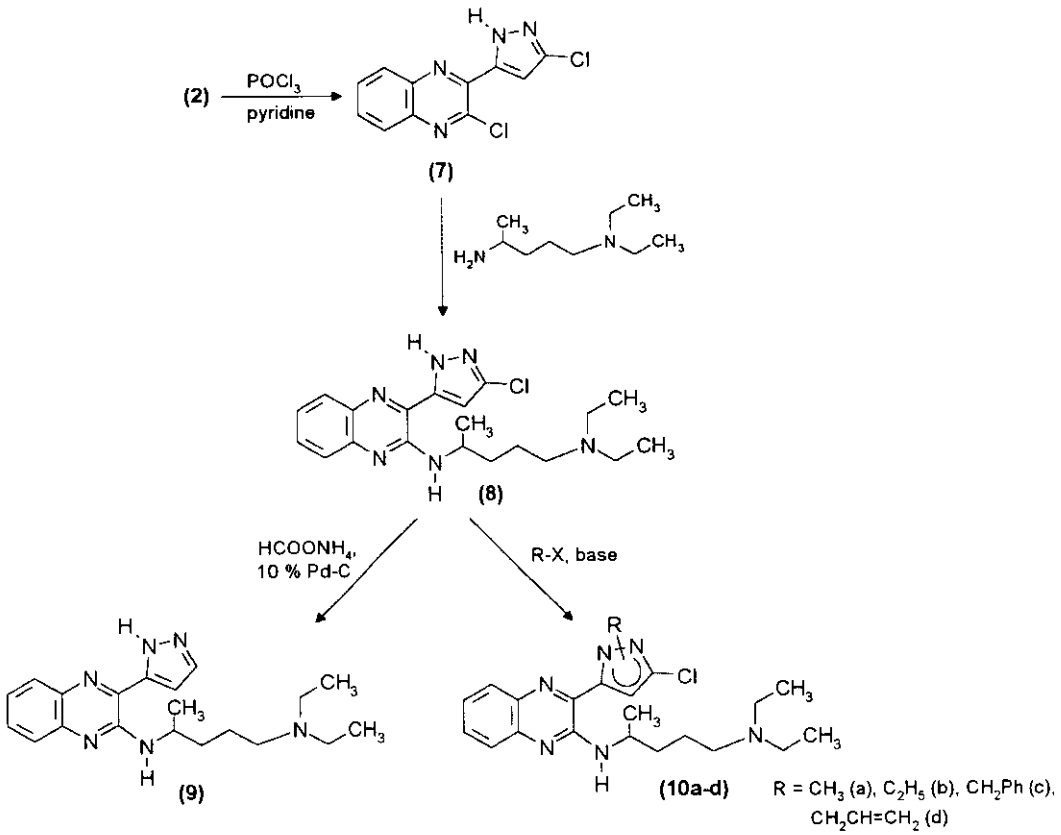


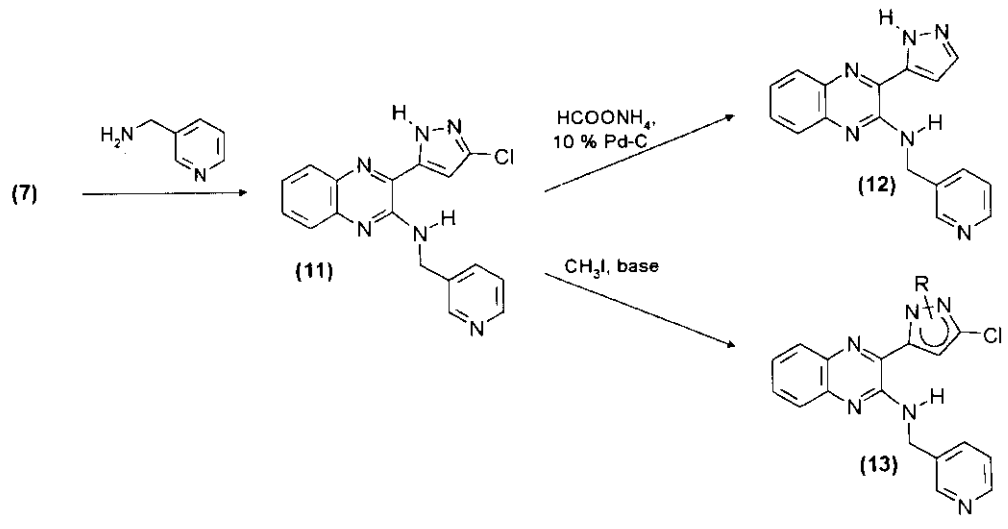
Figure 3. **a)** NOE-difference spectrum of (**5**) (in DMSO-d_6) resulting from irradiation of the pyrazole-*N*-CH_3 resonance. **b)** NOE-difference spectrum of (**5**) (in DMSO-d_6) resulting from irradiation of the quinoxaline-*N*-CH_3 resonance.

The new compounds of type **B** were prepared as outlined in Scheme 3. Treatment of **2** with phosphorus oxychloride in the presence of pyridine[4] yielded the chloroquinoxaline derivative (**7**). The latter reacted with novaldiamine base (= 5-diethylamino-2-pentylamine) in dry 1,4-dioxane at 100°C to afford compound (**8**). Further structural modifications were performed by reductive dehalogenation (synthesis of **9**) and *N*-alkylation (using potassium *tert*-butoxide as a base and the appropriate alkyl halide in dry 1,4-dioxane at room temperature).

The position of *N*-alkylation in compounds (**10a-d**) could not be determined unequivocally by NMR spectroscopy (no NOE could be observed upon irradiation of the *N*-CH_3 resonance of **10a**) and moreover attempts to prepare crystals suitable for single crystal X-Ray analysis failed. Thus, compounds (**11**), (**12**) and especially (**13**), where the 'antimalarial-side chain' is formally replaced by 3-picolylamine were synthesised (see Scheme 4). A crystal suitable for X-Ray analysis could then be obtained for compound (**13**).



Scheme 3. Synthesis of the target compounds of type **B**



Scheme 4. Synthesis of compounds of type **11-13**.

From the X-Ray analysis of compound (**13**), the position of alkylation is the pyrazole-*N* next to the chlorine atom (see Figure 4). A possible explanation for the 'change' in the point of alkylation of compound (**11**) compared to **2** is the formation of an intramolecular hydrogen bond from the amino-NH to the pyrazole-*N* which is further apart from the chlorine atom.

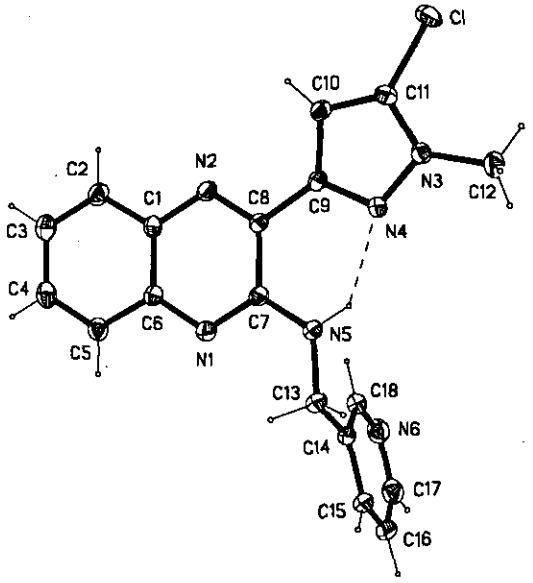


Figure 4. Thermal ellipsoid plot (20% ellipsoids) of $C_{18}H_{15}N_6Cl$ (**13**).

Based on the results of the X-Ray crystal analysis and the explanation given above, we conclude that the alkylation of compound (**8**) also takes place at the nitrogen atom next to the chlorine atom. Thus, a comparison of selected ^{1}H- and ^{13}C-NMR data of compound (**13**) with the corresponding data of compounds (**3**) and (**10a**) (Table 1) also revealed that the methyl group is attached to the nitrogen atom next to the chlorine.

Table 1. ^{1}H- and ^{13}C-NMR data of compounds (**3**, **10a**, and **13**)

Compound (solvent)	**^{1}H-NMR**		**^{13}C-NMR**	
	N-CH_3	pyrazole-H-4	*N*-CH_3	pyrazole-H-4
3 (DMSO-d_6)	4.14 ppm	7.17 ppm	40.3 ppm	109.3 ppm
10a ($CDCl_3$)	3.99 ppm	7.20 ppm	37.0 ppm	105.7 ppm
13 ($CDCl_3$)	3.92 ppm	7.22 ppm	36.7 ppm	105.7 ppm
13 (DMSO-d_6)	3.96 ppm	7.21 ppm	–	–

The pyrazolyl-substituted aminoquinoxaline derivatives (**8**, **9**, **10a-d**, **11**, and **12**) were screened as antimalarial agents. Using 150 ng/mL no inhibitoric effect on *Plasmodium falciparum* could be observed (chloroquine: EC_{50} = 5 ng/mL).

EXPERIMENTAL

Melting points were determined on a Kofler hot-stage microscope (Reichert) and are uncorrected. IR spectra were taken on a Mattson Galaxy Series FT-IR 3000 spectrophotometer (KBr pellets). ^{1}H and ^{13}C NMR spectra were recorded on a Varian Gemini 200 spectrometer (^{1}H: 199.98 MHz, ^{13}C: 50.29 MHz). The centre of the solvent multiplet (DMSO-d_6 or $CDCl_3$) was used as internal standard (chemical shifts in δ ppm), which was related to TMS with δ 2.49 ppm for ^{1}H and δ 39.5 ppm for ^{13}C (DMSO-d_6) or with δ 7.26 ppm for ^{1}H and δ 77.0 ppm for ^{13}C ($CDCl_3$). MS spectra were obtained on a Finnigan MAT SSQ 7000. Reactions were monitored by TLC using Polygram® SIL G/UV_{254} (Macherey-Nagel) plastic-backed plates (0.25 mm layer thickness). Column chromatography was performed using Kieselgel 60 (0.040-0.063 mm, Merck). Microanalyses were performed at the Institute of Physical Chemistry (Mag. J. Theiner), University of Vienna, Austria. Light petroleum refers to the fraction of bp 40-60 °C. The yields are not optimised.

Starting materials:

3-(3-Chloro-1*H*-pyrazol-5-yl)-1*H*-quinoxalin-2-one (**2**) became accessible by reaction of *N*-(2-aminophenyl)-3,6-dichloro-4-pyridazinecarboxamide (**1**) with sodium hydride in dry DMF.[1] *N*-(2-Aminophenyl)-3,6-dichloro-4-pyridazinecarboxamide was prepared from 3,6-dichloropyridazine-4-carboxylic acid chloride and *o*-phenylenediamine in dry dichloromethane.[1] The acid chloride was available from 3,6-dichloro-4-methylpyridazine[5] by oxidation with $K_2Cr_2O_7$ in H_2SO_4 [6] and subsequent treatment with $SOCl_2$.[7]

3-(3-Chloro-1-methyl-1*H*-pyrazol-5-yl)-1-methyl-1*H*-quinoxalin-2-one (3)

Powdered potassium hydroxide (0.449 g, 8.0 mmol) was added at rt to a solution of **2** (0.987 g, 4.0 mmol) in dry dimethyl sulfoxide (15 mL) under a nitrogen atmosphere. After stirring for 1 h at rt, methyl iodide (1.277 g, 9 mmol) was added and stirring was continued until the starting material was completely alkylated (60 min). Then the mixture was poured into cold 0.5 N HCl (150 mL), resulting crystals were collected, washed with water and subsequently with light petroleum. The product was purified by recrystallisation from ethyl acetate to yield 0.778 g (71 %) of light yellow crystals, mp 220-223 °C. IR (KBr): 1655 cm^{-1}. ^{1}H-NMR (DMSO-d_6, 60 °C): δ = 7.92-7.87 (m, 1H), 7.75-7.59 (m, 2H), 7.78-7.40 (m, 1H, H-5, H-6, H-7, H-8), 7.17 (s, 1H, pyrazole-H-4), 4.14 (s, 1H, pyrazole-*N*-CH_3), 3.70 (m, 3H, quinoxalinone-*N*-CH_3). ^{13}C-NMR (DMSO-d_6): δ = 152.8, 144.9 (quinoxaline-C-2, C-3), 138.3, 135.8, 133.1 (quinoxaline-C-4a, -C-8a, pyrazole-C-3, -C-5), 131.5, 129.7, 123.8, 114.9 (quinoxaline-C-5, -C-6, -C-7, -C-8), 109.3 (pyrazole-C-4), 40.3 (CH_3), 29.4 (CH_3). EI MS (70

eV): *m/z* = 274 [M^+]. *Anal.* Calcd for $C_{13}H_{11}N_4OCl$: C, 56.84; H, 4.04; N, 20.39. Found: C, 56.79; H, 3.87; N, 20.09.

Procedure for the Synthesis of 3,4-Dihydro-1-methyl-3-(1-methyl-1*H*-pyrazol-5-yl)-1*H*-quinoxalin-2-one (4) and 1-Methyl-3-(1-methyl-1*H*-pyrazol-5-yl)-1*H*-quinoxalin-2-one (5)

A mixture of **3** (0.105 g, 0.38 mmol), ammonium formate (0.240 g, 3.8 mmol) and 0.050 g of Pd/C (10 %) in methanol (15 mL) was stirred under a nitrogen atmosphere at 48 °C for 60 min. The catalyst was filtered off, the solvent was removed in vacuo, and the residue was taken up in dichloromethane. This solution was washed with water and brine, dried over anhydrous sodium sulfate and evaporated. The products thus obtained were purified by column chromatography (ethyl acetate) followed by recrystallisation to yield 0.058 g (63 %) of **4** and 0.026 g (28 %) of **5**.

3,4-Dihydro-1-methyl-3-(1-methyl-1*H*-pyrazol-5-yl)-1*H*-quinoxalin-2-one (4)

Colourless crystals, mp 150-151.5 °C (ethyl acetate). IR (KBr): 3293, 1655 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ = 7.34 (d, *J* = 1.9 Hz, pyrazole-H-3), 7.04-6.92 (m, 3H), 6.79-6.74 (m, 1H, quinoxaline-H-5, -H-6, -H-7, -H-8), 6.08 (d, *J* = 1.9 Hz, 1H, pyrazole-H-4), 5.18 (s, 1H, quinoxaline-H-3), 4.28 (br s, 1H, D_2O-exchangeable, NH), 3.98 (s, 3H, CH_3), 3.39 (s, 3H, CH_3). EI MS (70 eV): *m/z* = 242 [M^+]. *Anal.* Calcd for $C_{13}H_{14}N_4O$: C, 64.45; H, 5.82; N, 23.12. Found: C, 64.22; H, 5.68; N, 22.91.

1-Methyl-3-(1-methyl-1*H*-pyrazol-5-yl)-1*H*-quinoxalin-2-one (5)

Light yellow crystals, mp 185-187 °C (ethanol). IR (KBr): 1655 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ = 7.89 (d, *J* = 7.7 Hz, 1H), 7.63-7.59 (m, 1H), 7.41-7.32 (m, 2H, quinoxaline-H-5, H-6, H-7, H-8), 7.56 (d, *J* = 2.0 Hz, 1H), 7.46 (d, *J* = 2 Hz, 1H, pyrazole-H-3, H-4), 4.32 (s, 3H, CH_3), 3.76 (s, 3H, CH_3). ^{13}C-NMR ($CDCl_3$): δ = 153.5, 146.2 (quinoxaline-C-2, -C-3), 137.7 (pyrazole-C-3), 136.0, 132.9, 132.3 (quinoxaline-C-4a, -C-8a, pyrazole-C-5), 130.7, 130.2, 123.9, 113.7 (quinoxalinone-C-5, -C-6, -C-7, -C-8), 112.1 (pyrazole-C-4), 40.7 (CH_3), 29.3 (CH_3). EI MS (70 eV): *m/z* = 240 [M^+]. *Anal.* Calcd for $C_{13}H_{12}N_4O$: C, 64.99; H, 5.03; N, 23.32. Found: C, 65.25; H, 4.73; N, 23.22.

4-Acetyl-3,4-dihydro-1-methyl-3-(1-methyl-1*H*-pyrazol-5-yl)-1*H*-quinoxalin-2-one (6)

A solution of acetyl chloride (0.157 g, 2 mmol) in dry 1,4-dioxane (2 mL) was added dropwise to a stirred solution of **4** (0.242 g, 1 mmol) and triethylamine (0.202 g, 2 mmol) in dry 1,4-dioxane (10 mL). The reaction mixture was stirred under reflux for 12 h. The solvent was removed in vacuo and the residue was taken up in ethyl acetate. This solution was washed with water and brine, dried over anhydrous sodium sulfate and evaporated. The product thus obtained was purified by column chromatography (ethyl acetate) followed by recrystallisation from ethyl acetate/diisopropyl ether to yield 0.230 g (81 %) of colourless crystals, mp 145-151 °C. IR (KBr): 1669, 1647 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ = 7.37-7.29 (m, 1H), 7.20-7.08 (m, 4H, quinoxaline-H5, -H-6, -H-7, -H-8, pyrazole-H3), 6.76 (s, 1H, quinoxaline-H-3), 5.51 (d, *J* = 1.8 Hz, 1H, pyrazole-H4), 4.01

(s, 3H, CH_3), 3.44 (s, 3H, CH_3), 2.28 (s, 3H, CH_3). EI MS (70 eV): *m/z* = 284 [M^+]. *Anal.* Calcd for $C_{15}H_{16}N_4O_2$: C, 63.37; H, 5.67; N, 19.71. Found: C, 63.19; H, 5.55; N, 19.59.

2-Chloro-3-[3(5)-chloro-1*H*-pyrazol-5(3)-yl]quinoxaline (7)

A suspension of **2** (1.233 g, 5 mmol) in phosphorus oxychloride (15 mL) and pyridine (1.5 mL) was refluxed until the starting material was completely consumed (TLC monitoring, diethyl ether, *ca.* 2 h). After cooling, the mixture was slowly poured into ice-water, the precipitate was collected, washed with water and light petroleum and recrystallised from ethyl acetate to afford 1.140 g (86 %) of compound **(7)** as light yellow needles, mp 242-244 °C (sublimation above 160 °C). IR (KBr): 3229 cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ = 14.06 (s, 1H, NH), 8.19-7.89 (m, 4H, H-5, H-6, H-7, H-8), 7.24 (s, 1H, pyrazole-H-4). ^{13}C-NMR (DMSO-d_6): δ = 143.5, 140.4, 139.7 (quinoxaline-C-2, -C-3, -C-4a, -C-8a, pyrazole-C-3, -C-5), 132.0, 131.5, 128.7, 127.9 (quinoxaline-C-5, -C-6, -C-7, -C-8), 107.2 (pyrazole-C-4). EI MS (70 eV): *m/z* = 264 [M^+]. *Anal.* Calcd for $C_{11}H_6N_4Cl_2$: C, 49.84; H, 2.28; N, 21.13. Found: C, 49.92; H, 2.50; N, 20.95.

***N*^{1}-{3-[3(5)-Chloro-1*H*-5(3)-pyrazolyl]-2-quinoxalinyl}-*N*^{1},*N*^{1}-diethyl-1,4-pentanediamine (8)**

A mixture of **7** (0.715 g, 2.7 mmol) and 5-diethylamino-2-pentylamine (2.137 g, 13.5 mmol) in dry 1,4-dioxane (20 mL) was stirred at 100 °C until TLC indicated completion of the reaction (*ca.* 30 h). After cooling, the mixture was poured into ice-water and extracted with ethyl acetate. The organic layer was washed with water and brine, dried over anhydrous sodium sulfate and evaporated. The residue was purified by column chromatography (dichloromethane/ethanol, 9:1) and the eluent was evaporated. In order to remove traces of silica gel, the oily residue was dissolved in ethyl acetate and this solution was washed with 1N NaOH, water, and brine, dried over anhydrous sodium sulfate and evaporated *in vacuo* to yield 0.804 g (77 %) of analytically pure **8** (yellow powder), mp 64-70 °C; IR (KBr): 3319 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ = 8.53 (br s, 2H, 2× NH), 7.87 (dd, *J* = 8.0 Hz, *J* = 1.0 Hz, 1H), 7.65 (dd, *J* = 8.0 Hz, *J* = 1.0 Hz, 1H, H-5, H-8), 7.55-7.47 (m, 1H), 7.37-7.29 (m, 1H, H-6, H-7), 7.00 (s, 1H, pyrazole-H), 4.55-4.46 (m, 1H, CH), 2.75-2.64 (m, 6H, 3× CH_2), 1.80-1.62 (m, 4H, 2× CH_2), 1.30 (d, *J* = 6.4 Hz, 3H, CH_3), 1.09 (t, *J* = 7.2 Hz, 6H, 2× CH_3). ^{13}C-NMR ($CDCl_3$): δ = 151.7, 149.8, 141.7, 136.2, 136.0, 129.5 (quinoxaline-C-2, -C-3, -C-4a, -C-8a, pyrazole-C-3, -C-5), 129.4, 128.7, 125.6, 123.6 (quinoxaline-C-5, -C-6, -C-7, -C-8), 104.4 (pyrazole-C-4), 52.2 (CH_2), 46.2 (CH_2), 45.3 (CH), 34.9 (CH_2), 21.9 (CH_2), 21.0 (CH_3), 10.4 (CH_3). EI MS (70 eV): *m/z* = 386 [M^+]. *Anal.* Calcd for $C_{20}H_{27}N_6Cl$: C, 62.08; H, 7.03; N, 21.72. Found: C, 62.10; H, 6.98; N, 21.54.

***N*-{3-[3(5)-Chloro-1*H*-5(3)-pyrazolyl]-2-quinoxalinyl}-*N*-(3-pyridyl)methylamine (11)**

A mixture of **7** (0.742 g, 2.8 mmol) and 3-picolylamine (1.514 g, 14.0 mmol) in dry 1,4-dioxane (20 mL) was stirred at 100 °C until TLC indicated completion of the reaction (*ca.* 15 h). After cooling, the mixture was poured into ice-water (50 mL). The crystals thus obtained were collected by filtration, washed with water and light petroleum and were recrystallised from tetrahydrofuran to yield 0.900 g (95 %) of light yellow crystals, mp

338-342 °C; IR (KBr): 3302 cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ = 14.00 (br s, 1H, NH), 8.68 (d, *J* = 1.8 Hz, 1H, pyridine-H-2), 8.65-8.15 (br, 1H, NH), 8.44 (dd, *J* = 4.9 Hz, *J* = 1.5 Hz, 1H, pyridine-H-6), 7.88-7.81 (m, 2H), 7.63-7.57 (m, 2H), 7.44-7.30 (m, 2H, H-5, H-6, H-7, H-8, pyridine-H-4, pyridine-H-5), 7.12 (s, 1H, pyrazole-H-4), 4.79 (d, *J* = 5.6 Hz, 2H, CH_2). ^{13}C-NMR (DMSO-d_6): δ = 149.3, 148.1 (pyridine-C-2, -C-6), 149.2, 140.8, 135.8, 135.5, 135.1 (quinoxaline-C-2, -C-3, -C-4a, -C-8a, pyrazole-C-3, -C-5, pyridine-C-3), 135.5, 130.2, 128.4, 125.6, 124.6, 123.5 (quinoxaline-C-5, -C-6, -C-7, -C-8, pyridine-C-4, -C-5), 104.6 (pyrazole-C-4). EI MS (70 eV): *m/z* = 336 [M^+]. *Anal.* Calcd for $C_{17}H_{13}N_6Cl$: C, 60.63; H, 3.89; N, 24.95. Found: C, 60.35; H, 3.96; N, 24.65.

General Procedure for Preparation of 9 and 12:

A mixture of **8** (0.170 g, 0.44 mmol) or **11** (0.519 g, 1.54 mmol), ammonium formate (2.2 mmol or 7.7 mmol) and Pd/C (10 %) (0.100 g/mmol educt) in methanol (20-50 mL) was stirred under a nitrogen atmosphere at 48 °C for 30 min. The catalyst was filtered off, the solvent was removed *in vacuo*, and the residue was taken up in dichloromethane. This solution was washed with water and brine, dried over anhydrous sodium sulfate and evaporated.

N^1,N^1-Diethyl-N^4-{3-[1*H*-5(3)-pyrazolyl]-2-quinoxalinyl}-1,4-pentanediamine (9)

The crude product was purified by column chromatography (dichloromethane/ethanol, 9:1) and the eluent was evaporated. In order to remove traces of silica gel, the oily residue was dissolved in ethyl acetate and this solution was washed with 1N NaOH, water, and brine, dried over anhydrous sodium sulfate and evaporated *in vacuo* to yield 0.100 g (65 %) of an amorphous yellow product; IR (KBr): 3290 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ = 8.80 (d, *J* = 7.6 Hz, 1H, D_2O-exchangeable, NH), 7.88 (dd, *J* = 8.0 Hz, *J* = 1.2 Hz, 1H), 7.66 (dd, *J* = 8.0 Hz, *J* = 1.0 Hz, 1H, H-5, H-8), 7.58 (d, 1H, pyrazole-H-3), 7.55-7.47 (m, 1H), 7.36-7.28 (m, 1H, H-6, H-7), 7.26 (d, *J* = 2.4 Hz, 1H, pyrazole-H-4), 4.60-4.44 (m, 1H, CH), 2.69-2.58 (m, 6H, 3× CH_2), 1.80-1.60 (m, 4H, 2× CH_2), 1.32 (d, *J* = 6.4 Hz, 3H, CH_3), 1.06 (t, *J* = 7.2 Hz, 6H, 2× CH_3). ^{13}C-NMR ($CDCl_3$): δ = 151.3, 149.9, 141.6, 137.1, 136.1 (quinoxaline-C-2, -C-3, -C-4a, -C-8a, pyrazole-C-5), 129.1, 128.7, 128.6, 125.5, 123.4 (quinoxaline-C-5, -C-6, -C-7, -C-8, pyrazole-C-3), 106.1 (pyrazole-C-4), 52.5 (CH_2), 46.5 (CH_2), 45.5 (CH), 34.8 (CH_2), 22.4 (CH_2), 20.8 (CH_3), 10.8 (CH_3). EI MS (70 eV): *m/z* = 352 [M^+]. *Anal.* Calcd for $C_{20}H_{28}N_6 \cdot 0.3\ H_2O \cdot 0.1$ ethyl acetate: C, 66.82; H, 8.08; N, 22.92. Found: C, 67.01; H, 8.29; N, 22.77.

N-{3-[1*H*-5(3)-Pyrazolyl]-2-quinoxalinyl}-N-(3-pyridyl)methylamine (12)

Recrystallisation from ethyl acetate yielded 0.400 g (86 %) of a light yellow solid, mp 233-238 °C; IR (KBr): 3320 cm^{-1}. ^{1}H-NMR (DMSO-d_6): δ = 13.46 (s, 1H, NH), 9.31 (t, *J* = 5.4 Hz, 1H, NH), 8.70 (d, *J* = 1.7 Hz, 1H, pyridine-H-2), 8.47 (dd, *J* = 4.8 Hz, *J* = 1.8 Hz, 1H, pyridine-H-6), 7.99 (d, *J* = 2.5 Hz, 1H, pyrazole-H-3), 7.89-7.82 (m, 2H), 7.64-7.52 (m, 2H), 7.43-7.32 (m, 2H, H-5, H-6, H-7, H-8, pyridine-H-4, -H-5), 7.16 (d, *J* = 2.5 Hz, 1H, pyrazole-H-4), 4.87 (d, *J* = 5.4 Hz, 2H, CH_2). EI MS (70 eV): *m/z* = 302 [M^+]. *Anal.* Calcd for $C_{17}H_{14}N_6$: C, 67.54; H, 4.67; N, 27.80. Found: C, 67.41; H, 4.87; N, 27.57.

General Procedure for N-Alkylation:

Potassium *tert*-butoxide (0.045-0.136 g, 0.39-1.18 mmol) was added at rt to a solution of **8** (0.287-0.414 g, 0.74-1.07 mmol) or **11** (0.118 g, 0.35 mmol) in dry 1,4-dioxane (10 mL) under a nitrogen atmosphere. After stirring for 1 h at rt, the appropriate alkyl halide (methyl iodide, ethyl iodide, allyl iodide, or benzyl bromide) (0.39-1.18 mmol) was added and the stirring was continued until the starting material was completely alkylated (TLC monitoring, *ca.* 9-21 h). Then the solvent was removed *in vacuo* and the residue thus obtained was partitioned between ethyl acetate and water. The organic layer was dried over anhydrous sodium sulfate and evaporated. The products (**10a-d**) were purified by column chromatography (dichloromethane/ethanol, 9:1) and the eluent was evaporated. In order to remove traces of silica gel, the oily residue was dissolved in ethyl acetate and this solution was washed with 1N NaOH, water, and brine, dried over anhydrous sodium sulfate and evaporated *in vacuo* to yield the analytically pure compounds.

N^1-[3-(5-Chloro-1-methyl-1*H*-3-pyrazolyl)-2-quinoxalinyl]-N^1,N^1-diethyl-1,4-pentanediamine (10a)

Yield: 69 % of a yellow solid, mp 142-150 °C; IR (KBr): 3324 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ = 8.22 (d, *J* = 8.0 Hz, 1H, D_2O-exchangeable, NH), 7.87-7.82 (m, 1H), 7.64-7.48 (m, 2H), 7.38-7.30 (m, 1H, H-5, H-6, H-7, H-8), 7.20 (s, 1H, pyrazole-H), 4.61-4.48 (m, 1H, CH), 3.99 (s, 3H, CH_3), 3.16-2.95 (m, 6H, 3× CH_2), 2.11-1.74 (m, 4H, 2× CH_2), 1.38 (d, *J* = 6.4 Hz, 3H, CH_3), 1.28 (t, *J* = 7.3 Hz, 6H, 2× CH_3). ^{13}C-NMR ($CDCl_3$): δ = 150.6, 149.6, 141.4, 136.2, 135.5, 129.3 (quinoxaline-C-2, -C-3, -C-4a, -C-8a, pyrazole-C-3, -C-5), 129.7, 128.8, 125.4, 123.9 (quinoxaline-C-5, -C-6, -C-7, -C-8), 105.7 (pyrazole-C-4), 51.8 (CH_2), 46.7 (CH_2), 45.0 (CH), 37.0 (CH_3), 34.1 (CH_2), 21.2 (CH_3), 20.4 (CH_2), 8.8 (CH_3). EI MS (70 eV): *m/z* = 400 [M^+]. *Anal.* Calcd for $C_{21}H_{29}N_6Cl \cdot 0.2\ H_2O$: C, 62.35; H, 7.33; N, 20.77. Found: C, 62.55; H, 7.59; N, 20.47.

N^1-[3-(5-Chloro-1-ethyl-1*H*-3-pyrazolyl)-2-quinoxalinyl]-N^1,N^1-diethyl-1,4-pentanediamine (10b)

Yield: 70 % of a yellow solid, mp 44-50 °C (ethyl acetate/light petroleum); IR (KBr): 3318 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ = 8.30 (d, *J* = 7.6 Hz, 1H, D_2O-exchangeable, NH), 7.86-7.81 (m, 1H), 7.68-7.43 (m, 1H), 7.55-7.46 (m, 1H), 7.35-7.26 (m, 1H, H-5, H-6, H-7, H-8), 7.18 (s, 1H, pyrazole-H), 4.53-4.42 (m, 1H, CH), 4.26 (q, *J* = 7.2 Hz, 2H, CH_2), 2.57-2.46 (m, 6H, 3× CH_2), 1.72-1.59 (m, 4H, 2× CH_2), 1.53 (t, *J* = 7.2 Hz, 3H, CH_3), 1.35 (d, *J* = 6.4 Hz, 3H, CH_3), 1.00 (t, *J* = 7.2 Hz, 6H, 2× CH_3). ^{13}C-NMR ($CDCl_3$): δ = 150.9, 149.7, 141.9, 136.1, 135.7, 128.2 (quinoxaline-C-2, -C-3, -C-4a, -C-8a, pyrazole-C-3, -C-5), 129.4, 128.7, 125.7, 123.5 (quinoxaline-C-5, -C-6, -C-7, -C-8), 105.7 (pyrazole-C-4), 53.0 (CH_2), 46.8 (CH_2), 45.9 (CH), 44.5 (CH_2), 34.9 (CH_2), 23.5 (CH_2), 20.7 (CH_3), 14.5 (CH_3), 11.6 (CH_3). EI MS (70 eV): *m/z* = 414 [M^+]. *Anal.* Calcd for $C_{22}H_{31}N_6Cl \cdot 0.1$ ethyl acetate: C, 63.49; H, 7.56; N, 19.83. Found: C, 63.38; H, 7.31; N, 19.75.

N^1-[3-(1-Benzyl-5-chloro-1*H*-3-pyrazolyl)-2-quinoxalinyl]-N^1,N^1-diethyl-1,4-pentanediamine (10c)

Yield: 70 % of yellow brown oil; IR (KBr): 3330 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ = 8.16 (d, *J* = 7.4 Hz, 1H, D_2O-exchangeable, NH), 7.82 (dd, *J* = 8.2 Hz, *J* = 1.1 Hz, 1H), 7.64 (dd, *J* = 8.2 Hz, *J* = 1.1 Hz, 1H, H-5, H-8), 7.53-7.45 (m, 1H), 7.41-7.25 (m, 6H, H-6, H-7, phenyl-H), 7.21 (s, 1H, pyrazole-H), 5.36 (s, 2H, CH_2), 4.51-

4.37 (m, 1H, CH), 2.56-2.45 (m, 6H, 3× CH_2), 1.62-1.59 (m, 4H, 2× CH_2), 1.28 (d, J = 6.8 Hz, 3H, CH_3), 0.98 (t, J = 7.3 Hz, 6H, 2× CH_3). ^{13}C-NMR ($CDCl_3$): δ = 151.2, 149.6, 141.8, 136.0, 135.4, 135.2, 128.8 (quinoxaline-C-2, -C-3, -C-4a, -C-8a, pyrazole-C-3, -C-5, phenyl-C-1), 129.5, 128.6, 128.2, 125.7, 123.5 (quinoxaline-C-5, -C-6, -C-7, -C-8, phenyl-C-4,), 128.8, 127.7 (phenyl-C-2, -C-3, -C-5, -C-6), 105.9 (pyrazole-C-4), 53.1 (CH_2), 52.7 (CH_2), 46.6 (CH_2), 45.7 (CH), 34.7 (CH_2), 23.1 (CH_2), 20.7 (CH_3), 11.3 (CH_3). EI MS (70 eV): m/z = 476 [M^+]. *Anal.* Calcd for $C_{27}H_{33}N_6Cl \cdot 0.2\ H_2O \cdot 0.2$ ethyl acetate: C, 67.01; H, 7.08; N, 16.87. Found: C, 67.07; H, 7.04; N, 16.90.

N^1-[3-(1-Allyl-5-chloro-1*H*-3-pyrazolyl)-2-quinoxalinyl]-N^1,N^1-diethyl-1,4-pentanediamine (10d)

Yield: 62 % of a yellow brown oil; IR (KBr): 3324 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ = 8.25 (d, J = 7.2 Hz, 1H, D_2O-exchangeable, NH), 7.87 (dd, J = 8.1 Hz, J = 0.9 Hz, 1H), 7.67-7.62 (m, 1H), 7.55-7.47 (m, 1H), 7.35-7.27 (m, 1H, H-5, H-6, H-7, H-8), 7.21 (s, 1H, pyrazole-H), 6.13-5.93 (m, 1H, CH), 5.35-5.18 (m, 2H, CH_2), 4.86-4.82 (m, 2H, CH_2), 4.52-4.39 (m, 2H, CH_2), 2.64-2.53 (m, 6H, 3× CH_2), 1.73-1.63 (m, 4H, 2× CH_2), 1.37-1.26 (m, 4H, 2× CH_2), 1.03 (t, J = 7.1 Hz, 6H, 2× CH_3). ^{13}C-NMR ($CDCl_3$): δ = 151.1, 149.6, 141.8, 136.0, 135.5, 128.8 (quinoxaline-C-2, -C-3, -C-4a, -C-8a, pyrazole-C-3, -C-5), 131.3, 129.5, 128.6, 125.7, 123.5 (quinoxaline-C-5, -C-6, -C-7, -C-8, CH), 118.8 (CH_2), 105.8 (pyrazole-C-4), 52.7 (CH_2), 51.9 (CH_2), 46.7 (CH_2), 45.8 (CH), 34.7 (CH_2), 23.0 (CH_2), 20.7 (CH_3), 11.2 (CH_3). EI MS (70 eV): m/z = 426 [M^+]. *Anal.* Calcd for $C_{23}H_{31}N_6Cl$: C, 64.70; H, 7.32; N, 19.68. Found: C, 64.54; H, 7.54; N, 19.46.

N-[3-(5-Chloro-1-methyl-1*H*-3-pyrazolyl)-2-quinoxalinyl]-*N*-(3-pyridyl)methylamine (13)

The product was purified by column chromatography (dichloromethane/ethyl acetate: 19:1 +1 % triethylamine) then the eluent was evaporated. In order to remove traces of silica gel, the oily residue was dissolved in ethyl acetate and this solution was washed with 1N NaOH, water, and brine, dried over anhydrous sodium sulfate and evaporated *in vacuo*. The product thus obtained was recrystallised from ethanol to yield 0.060 g (49 %) of a yellow solid, mp 150-155 °C; IR (KBr): 3302 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ = 8.76-8.68 (m, 2H, pyridine-H-2, NH), 8.52 (dd, J = 4.9 Hz, J = 1.5 Hz, pyridine-H-6), 7.90-7.78 (m, 2H), 7.71-7.66 (m, 1H), 7.59-7.50 (m, 1H), 7.41-7.33 (m, 1H), 7.29-7.25 (m, 1H, H-5, H-6, H-7, H-8, pyridine-H-4, pyridine-H-5), 7.22 (s, 1H, pyrazole-H-4), 4.95 (d, J = 5.6 Hz, 2H, CH_2), 3.92 (s, 3H, CH_3). ^{1}H-NMR (DMSO-d_6): δ = 8.92 (d, J = 6.0 Hz, 1H, NH), 8.69-8.67 (m, 1H, pyridine-H-2), 8.44 (dd, J = 4.7 Hz, J = 1.7 Hz, pyridine-H-6), 7.87-7.80 (m, 2H), 7.60-7.57 (m, 2H), 7.43-7.31 (m, 2H, H-5, H-6, H-7, H-8, pyridine-H-4, pyridine-H-5), 7.21 (s, 1H, pyrazole-H-4), 4.87 (d, J = 6.0 Hz, 2H, CH_2), 3.96 (s, 3H, CH_3). ^{13}C-NMR ($CDCl_3$): δ = 150.6, 149.6, 141.4, 136.6, 135.5, 129.4 (quinoxaline-C-2, -C-3, -C-4a, -C-8a, pyrazole-C-3, -C-5, pyridine-C-3), 149.5, 148.5 (pyridine-C-2, -C-6), 135.5, 129.8, 128.8, 125.9, 124.4 (quinoxaline-C-5, -C-6, -C-7, -C-8, pyridine-C-4, -C-5), 105.7 (pyrazole-C-4), 42.4 (CH_2), 36.7 (CH_3). EI MS (70 eV): m/z = 350 [M^+]. *Anal.* Calcd for $C_{18}H_{15}N_6Cl \cdot 0.2\ H_2O$: C, 61.00; H, 4.38; N, 23.71. Found: C, 61.08; H, 4.32; N, 23.58.

Crystal structure determination of $C_{18}H_{15}N_6Cl$ (13)

Crystal data: $C_{18}H_{15}N_6Cl$, M_r = 350.81, triclinic, space group P $\bar{1}$ (No. 2), a = 7.129 (4) Å, b = 10.547 (6) Å, c = 12.182 (7) Å, α = 69.42 (2)°, β = 85.69 (2)°, γ = 72.79(2)°, V = 818.7 (8) Å^3, Z = 2, D_x = 1.423 g cm^{-3}, λ =

0.71073 Å, $\mu = 0.247$ mm^{-1}, $T = 303$K. A yellow prism was used for data collection with a Siemens Smart area detector platform type diffractometer and Mo Kα radiation. Intensity data were harvested over more than one hemisphere of the reciprocal space using 0.3° ω-scan frames. Data were corrected for Lp, decay, absorption and related effects with the empirical method using program SADABS. The structure was solved with the SHELXTL package of programs and was refined with SHELXL93 [10]. Hydrogen atoms were refined riding with the atoms to which they were bonded. The final refinement varied 229 parameters and used 2860 independent reflections weighted by $w=1/[\sigma^2(F_o^2)+(0.0527P)^2+0.08P]$ where $P=(F_o^2+2F_c^2)/3$. Final $R1 = \Sigma||F_o|-|F_c||/\Sigma|F_o| = 0.066$, $wR2 = [\Sigma(w(F_o^2-F_c^2)^2)/\Sigma(w(F_o^2)^2)]^{1/2} = 0.107$ and $S = 1.005$ for all data; $R1 = 0.038$ for the 1961 reflections with $F_o^2>2\sigma(F_o^2)$. Atomic coordinates are presented in Table 2. [11]

Table 2. Atomic coordinates and equivalent isotropic displacement parameters (Å^2 x 10^3) for $C_{18}H_{15}N_6Cl$ (**13**). U_{eq} is defined as one third of the trace of the orthogonalized U_{ij} tensor.

	x	y	z	U_{eq}
Cl *	0.26579(11)	0.13652(7)	0.90968(5)	67(1)
N(1)	0.2352(3)	0.6515(2)	0.2814(1)	42(1)
N(2)	0.2408(2)	0.6308(2)	0.5184(1)	40(1)
N(3)	0.2735(3)	0.1717(2)	0.6826(1)	42(1)
N(4)	0.2680(3)	0.2676(2)	0.5739(1)	40(1)
N(5)	0.2340(3)	0.4193(2)	0.3413(1)	47(1)
N(6)	0.7600(3)	0.3131(2)	0.1675(2)	65(1)
C(1)	0.2300(3)	0.7565(2)	0.4296(2)	40(1)
C(2)	0.2181(3)	0.8773(2)	0.4571(2)	51(1)
C(3)	0.2075(4)	#10035(2)	0.3699(2)	57(1)
C(4)	0.2094(3)	#10130(2)	0.2522(2)	56(1)
C(5)	0.2198(3)	0.8978(2)	0.2232(2)	50(1)
C(6)	0.2291(3)	0.7659(2)	0.3114(2)	38(1)
C(7)	0.2389(3)	0.5322(2)	0.3677(2)	37(1)
C(8)	0.2452(3)	0.5215(2)	0.4900(2)	34(1)
C(9)	0.2558(3)	0.3896(2)	0.5899(2)	35(1)
C(10)	0.2535(3)	0.3717(2)	0.7090(2)	42(1)
C(11)	0.2640(3)	0.2337(2)	0.7634(2)	43(1)
C(12)	0.2880(4)	0.0269(2)	0.6973(2)	55(1)
C(13)	0.2160(3)	0.4217(2)	0.2233(2)	48(1)
C(14)	0.4069(3)	0.3707(2)	0.1689(2)	41(1)
C(15)	0.4075(4)	0.3448(2)	0.0646(2)	51(1)
C(16)	0.5820(5)	0.3038(2)	0.0135(2)	62(1)
C(17)	0.7532(4)	0.2895(3)	0.0673(2)	66(1)
C(18)	0.5877(4)	0.3526(2)	0.2157(2)	50(1)

* site occupancy factors of Cl refined to 0.957(3).

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