Derivatives of 5-Oxy-pyrido[2,3-*b*]quinoxaline-9-carboxylic Acid: A Tricyclic System Useful for the Synthesis of Potential Intercalators

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The synthesis of a new series of 5-oxy-pyrido[2,3-*b*]quinoxaline-9-carboxamides **4a-i** and N^1,N^2-Bis(5-oxy-pyrido[2,3-*b*]quinoxaline-9-benzoyl)ethylenediamine (**5**) is reported starting from 2-chloro-3-nitropyridine. Fundamental steps of the synthetic pathway are i) preparation of 2-(3-nitro-pyridin-2-ylamino)benzoic acid (**1**) *via* copper-catalyzed condensation of 2-chloro-3-nitropyridine with *o*-anthranilic acid, ii) intramolecular cyclization of the acid **1** to 5-oxy-pyrido[2,3-*b*]quinoxaline-9-carboxylic acid (**2b**) upon treatment with concentrated sulfuric acid and oleum and iii) conversion of the acid **2** to the desired amides **4a-i** and **5**. Compounds **4a-i** and **5** are oxygenated azaanalogs of phenazines, a wellknown series of intercalators with cytotoxic activity.

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Introduction.

Several classes of compounds including the anthracendiones [1], anthrapyrazoles [2], thioxanthenones [3], (aza)acridine-4-carboxamides [4,5], (aza)dibenzodioxin-1-carboxamides [6], phenazine-1-carboxamides [7] and pyrido-, pyrazino-, imidazo-, pyrrolo-, pyrazolophenazinecarboxamides [8] can be distinguished among the currently recognized synthetic antineoplastic compounds designed as "DNA complexing agents".

These compounds are characterized by two common features which seem to determine their antineoplastic activity: a planar polycyclic nucleus, capable of binding to DNA by intercalation [9] and one or two cationic side chains, which have the function of additionally stabilizing the drug-DNA complex [10].

Furthermore, some *N*-oxides of DNA intercalators are bioreductive prodrugs that selectively kill hypoxic cells [11]. Many human tumors differ from normal tissues in that they contain a substantial number of hypoxic cells [12]. It is known that these cells can contribute to radiation resistance of tumors [13] and to neoplastic progression within unirradiated tumors [14].

On the basis of these considerations and in continuation of our research on such polyheterocyclic DNA binding agents with cytotoxic activity [15-18], we report in the present study the synthesis of a new series of potential intercalators, hypoxia selective agents, the pyrido[2,3-*b*]-quinoxaline-9-carboxamides 5-oxides **4a-i** and N^1,N^2-Bis-(5-oxy-pyrido[2,3-*b*]quinoxaline-9-benzoyl)ethylenediamine (**5**) considered as azaanalogs of phenazine-1-carboxamides.

Results and Discussion.

The synthetic pathway followed for the preparation of compounds **4a-i** and **5** is delineated in Scheme 1. Thus, commercially available 2-chloro-3-nitropyridine reacted with *o*-anthranilic acid under Ullmann conditions to afford the hitherto unknown acid **1**. Attempts to cyclize the acid **1** under alkaline conditions failed. When 2-(3-nitro-pyridin-2-ylamino)benzoic acid (**1**) was heated with potassium hydroxide powder at 130-190 °C [19,20], a mixture of the uncyclized compound **1** and *o*-anthranilic acid was isolated, as it was indicated from the ^{1}H nmr and mass spectra.

Moreover, the reactions of the acid **1** with sodium borohydride either in refluxing sodium hydroxide solution [7] or in refluxing ethanol in the presence of sodium ethoxide [21,22] afforded 2-(3-amino-pyridin-2-ylamino)benzoic acid (**2a**) or *o*-anthranilic acid, respectively.

Therefore, we decided to perform the cyclization in acidic media by using the concentrated sulfuric acid-oleum method, developed in the literature for the preparation of phenazines *N*-oxides from *o*-nitrodiphenylamines [20,23]. In our case, the application of this method led to the desired azaphenazine *N*-oxide **2b** in 75% yield, only when the quantity of oleum was 7-fold decreased, otherwise a mixture of decomposition products was obtained.

To the best of our knowledge, compound **2b** has not been reported before and we believe that **2b** is a useful starting material for the synthesis of other 9-substituted azaphenazines.

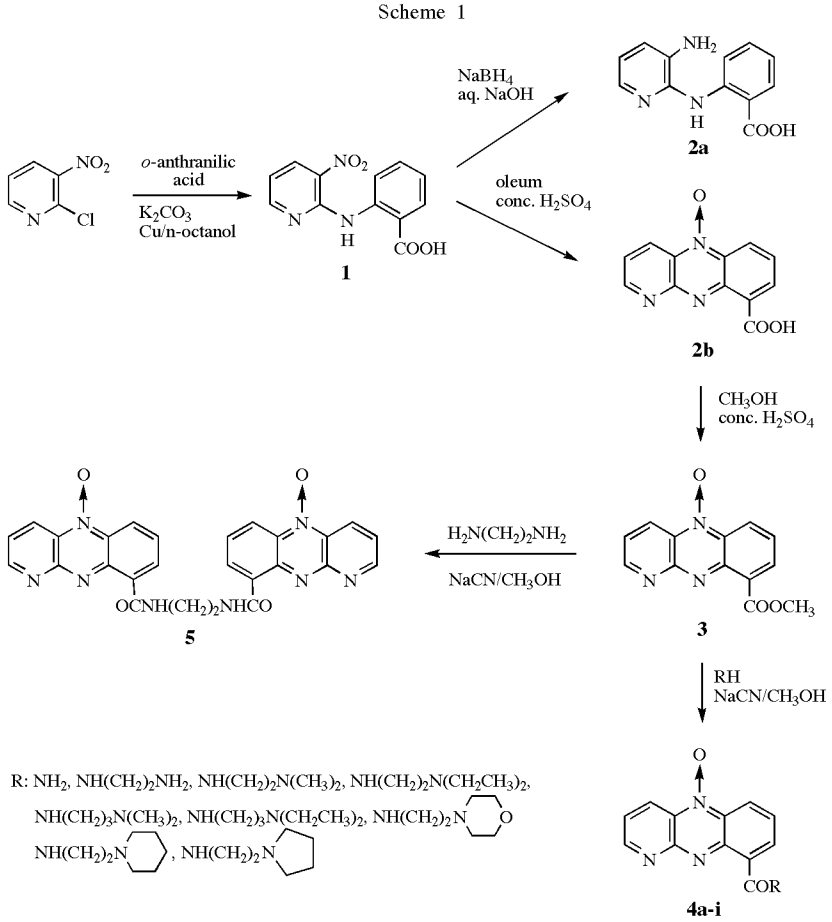
Attempts to couple the acid **2b** with the appropriate amines by using 1,1-carbonyldiimidazole were unsuccessful. Finally, the acid **2b** was transformed to the corresponding methylester **3** upon heating in methanol in the presence of concentrated sulfuric acid.

Reaction of the ester **3** with the appropriate amines in the presence of sodium cyanide in methanol [24] afforded the desired amides **4a-i** and **5**.

In conclusion, we have herein described an efficacious procedure for obtaining derivatives of **2b**, a novel tricyclic ring system useful as lead structure for the design of new potential DNA interactive agents.

The new compounds **4a-i** and **5** and their deoxygenated analogs (unpublished results) are currently being evaluated for their cytotoxicity against a broad spectrum of tumour cell lines.

Scheme 1



EXPERIMENTAL

Melting points were determined on a Büchi 530 apparatus and are uncorrected. IR spectra were run on a Perkin Elmer 883 spectrophotometer. NMR spectra were taken in deuterochloroformor dimethylsulfoxide-d_6, or acetone-d_6. ^{1}H nmr spectra were recorded either on a Brucker AC200 or a Brucker DRX400 MHz spectrometer, and the spectra are reported in δ. ^{13}C nmr spectra were taken at 50 MHz on a Brucker AC200 spectrometer and are reported in δ. Tetramethylsilane was used as internal standard. Molecular weights were determined by ESI mass spectrometry on a Finnigan AQA mass spectrometer. All the experiments were carried out under atmosphere of Argon unless stated otherwise. The solvents used were dried as follows: Methanol and octanol over calcium oxide. DC-Alufolien plates (Kieselgel 60 F_{254}, Schichtdicke 0.2 mm, Merck) were used for analytical TLC and were visualized with ultraviolet light or developed with iodine or phosphomolybdic acid. Microanalyses were carried out by the Microanalytical Section of the Institute of Organic and Pharmaceutical Chemistry, NHRF-Greece.

2-(3-Nitro-pyridin-2-ylamino)benzoic Acid (**1**).

A mixture of 2-chloro-3-nitropyridine (2 g, 0.013 mole), anthranilic acid (1.48 g, 0.011 mole), potassium carbonate (9.28 g, 0.067 mole), a catalytic amount of potassium iodide and copper powder (0.132 g, 0.002 mole) in octanol (20 ml) was heated at 180-190 °C, under stirring for 5 hours. The reaction mixture was cooled to room temperature, water and ethyl acetate were added and the precipitate formed was removed by filtration. The organic layer was discarded from the filtrate and the aqueous layer was extracted with ethyl acetate (2x50 ml). The aqueous phase was carefully acidified with acetic acid (60 ml). The deposited material was filtered, washed with hot water, dried and recrystallized from benzene to give 1.25 g (44%) of **1**, mp 185-187 °C; R_f 0.37 (eluent ethyl acetate); ir (Nujol): 3265 (NH), 1705 (CO), 1490, 1310; ^{1}H nmr (dimethylsulfoxide-d_6, 400 MHz): δ 8.56 (m, 4H), 7.96 (m, 1H), 7.57 (m, 1H), 7.15 (m, 2H).

Anal. Calcd for $C_{12}H_9N_3O_4$: C, 55.60; H, 3.50; N, 16.21. Found: C, 55.93; H, 3.17; N, 16.56.

2-(3-Amino-pyridin-2-ylamino)benzoic Acid (**2a**).

To a mixture of **1** (0.05 g, 0.00019 mole) and sodium borohydride (0.05 g, 0.0013 mole) an aqueous solution of sodium hydroxide (4.6 ml, 2 *N*) was added. The resulting mixture was refluxed for 1 hour, allowed to reach room temperature, cooled at 0 °C and acidified with acetic acid (10 ml). The mixture was extracted with ethyl acetate, the organic layer dried (sodium sulfate) and concentrated *in vacuo*. After addition of benzene, the mixture was stirred and filtered. The filtrate was evaporated to dryness. Crystallization of the residue from cyclohexane afforded 0.026 g (59%) of 2-(3-amino-pyridin-2-ylamino)-benzoic acid (**2a**), mp 142-144 °C; ^{1}H nmr (deuterochloroform, 200 MHz): δ

8.40 (d, J=8.4 Hz, 1H), 8.34 (dd, J=6.9 Hz, J=1.5 Hz, 1H), 7.77 (m, 2H), 7.45 (m, 1H), 6.70 (d, J=6.9 Hz, 1H), 6.64 (dd, J=7.5 Hz, J=1.5 Hz, 1H), 5.30 (br s, 3H, D_2O exch., NH+NH_2); (dimethylsulfoxide-d_6, 400 MHz): δ 8.25 (d, J=8.8 Hz, 1H), 8.13 (dd, J= 7.1 Hz, J=1.1 Hz, 1H), 7.84 (m, 1H), 7.74 (d, J=7.7, 1H), 7.46 (m, 1H), 6.88 (m, 1H), 6.70 (dd, J=7.7 Hz, J=1.1 Hz, 1H), 6.15 (br s, 3H, D_2O exch., NH+NH_2); ^{13}C nmr (dimethylsulfoxide-d_6, 50 MHz): δ 159.0, 147.3, 140.4, 134.2, 133.7, 126.9, 124.6, 116.4, 115.8, 114.5, 113.4, 107.6.

Anal. Calcd for $C_{12}H_{11}N_3O_2$: C, 62.87; H, 4.84; N, 18.33. Found: C, 62.61; H, 5.13; N, 17.91.

5-Oxy-pyrido[2,3-*b*]quinoxaline-9-carboxylic Acid (**2b**).

Concentrated sulfuric acid (8.4 ml) was added at 0 °C to (3 g, 0.012 mole) of **1**. To the stirred and cooled (0 °C) solution, oleum 30% (1.5 ml) was added dropwise for five minutes. After being warmed to room temperature, the mixture was stirred for 1 hour. The reaction mixture was then basified by ammonium hydroxide 25% (31 ml) at 0 °C. The resulted solid was collected, treated with hot benzene and filtered. The filtrate was evaporated *in vacuo*. Crystallization of the residue from cyclohexane afforded 2.1 g (75%) of 5-oxy-pyrido[2,3-*b*]quinoxaline-9-carboxylic acid (**2b**), mp 202-205 °C; R_f 0.93 (eluent ethyl acetate); ir (Nujol): 1705 (CO), 1510, 1414; ^1H nmr (deuterochloroform, 200 MHz): δ 8.97 (dd, J=7.3 Hz, J=1.5 Hz, 1H), 8.44 (dd, J=8.4 Hz, J=1.1 Hz, 1H), 7.90 (m, 2H), 7.56 (m, 1H), 6.82 (t, J=7.1 Hz, 1H); ^1H nmr (dimethylsulfoxide-d_6, 200 MHz): δ 8.93 (dd, J=7.7 Hz, J=1.5 Hz, 1H), 8. 36 (m, 1H), 7.97 (m, 1H), 7.74 (dd, J=8.4 Hz, J=0.7 Hz, 1H), 7.61 (m, 1H), 7.11 (t, J=7.3 Hz, 1H); ^{13}C nmr (dimethylsulfoxide-d_6, 50 MHz): δ 158.6, 147.8, 145.5, 141.1, 136.7, 131.2, 131.1, 129.3, 128.0, 127.3, 117.5, 111.2; ms: m/z 241 (M^+)

Anal. Calcd for $C_{12}H_7N_3O_3$: C, 59.75; H, 2.93; N, 17.42. Found: C, 59.60; H, 3.10; N, 17.71.

5-Oxy-pyrido[2,3-*b*]quinoxaline-9-carboxylic Acid Methyl Ester (**3**).

To a solution of 5-oxy-pyrido[2,3-*b*]quinoxaline-9-carboxylic acid (**2**) (2 g, 0.008 mole) in dry methanol (140 ml) concentrated sulfuric acid (1 ml) was added and the mixture was heated at 55 °C for 3 hours. The solvent was evaporated *in vacuo* and then the residue was made alkaline with a solution of sodium hydrogen carbonate (280 ml, 0.08 *M*). The mixture was extracted with ethyl acetate, the organic layer dried (sodium sulfate) and concentrated *in vacuo*. Crystallization from cyclohexane afforded 2 g (95%) of **3**, mp 177-180 °C; R_f 0.61 (eluent chloroform); ^1H nmr (deuterochloroform, 400 MHz): δ 8.52 (m, 2H), 8.05 (m, 1H), 7.52 (m, 1H), 7.11 (m, 1H), 6.88 (m, 1H), 3.96 (s, 3H, CH_3).

Anal. Calcd for $C_{13}H_9N_3O_3$: C, 61.18; H, 3.55; N, 16.46. Found: C, 61. 40; H, 3.23; N, 16.67.

5-Oxy-pyrido[2,3-*b*]quinoxaline-9-carboxylic Acid Amide (**4a**).

Ammonium hydroxide 25 % (26 ml) was added to a mixture of ester **3** (0.18 g, 0.0007 mole) and sodium cyanide (0.05 g, 0.001 mole) in methanol (25 ml) and the mixture was stirred at room temperature for 3 hours. The solvent was removed under reduced pressure, the residue suspended in water and extracted with ethyl acetate. The organic phase was dried (sodium sulfate) and evaporated *in vacuo*. Crystallization from cyclohexane gave 0.09 g (53 %) of **4a**, mp 142-143 °C; ^1H nmr (acetone-d_6, 400 MHz): δ 8.20 (d, J= 8.2 Hz, 1H), 7.85 (m, 2H), 7.77 (brs, 1H, D_2O exch., NH), 7.72 (brs, 1H, D_2O exch., NH), 7.58 (m, 1H), 7.35 (m, 1H); ^1H nmr (deuterochloroform, 400 MHz): δ 8.30 (d, J=7.7 Hz, 1H), 7.81 (m, 3H), 7.6 (t, J=6.9 Hz, 1H), 7.30 (br s, 1H), 7.25 (br s, 1H).

Anal. Calcd for $C_{12}H_8N_4O_2$: C, 60.00; H, 3.36; N, 23.32. Found: C, 59.81; H, 3.68; N, 22.90

General Procedure for the Preparation of Amides **4b-i**.

The appropriate amine (0.018 mole) was added to a mixture of ester **3** (0.18 g, 0.0007 mole) and sodium cyanide (0.05 g, 0.001 mole for compound **4b** and 0.01 g, 0.0002 mole for compounds **4c-i**) in methanol (6 ml). The reaction mixture was heated at 45 °C, under continuous stirring, for 30 minutes. The solvent was removed under reduced pressure, the oily residue was diluted with water and extracted with ethyl acetate. The organic phase was dried (sodium sulfate) and evaporated to dryness. Crystallization from cyclohexane gave the desired products in 14-53 % yield.

5-Oxy-pyrido[2,3-*b*]quinoxaline-9-carboxylic Acid (2-Aminoethyl)amide (**4b**).

This compound was obtained in 14% yield (0.028 g), mp 147-150 °C; ^1H nmr (deuterochloroform, 400 MHz): δ 8.32 (d, J=7.2 Hz, 1H), 7.79 (m, 4H), 7.55 (m, 1H), 3.67 (m, 2H, CONHCH_2), 2.79 (m, 2H, C$H_2$$NH_2$).

Anal. Calcd for $C_{14}H_{13}N_5O_2$: C, 59.36; H, 4.63; N, 24.72. Found: C, 59.75; H, 4.26; N, 24.86.

5-Oxy-pyrido[2,3-*b*]quinoxaline-9-carboxylic Acid (2-Dimethylaminoethyl)amide (**4c**).

This compound was obtained in 29% yield (0.063 g), mp 151-153 °C; ir (Nujol): 1645 (CO), 1518, 1420; ^1H nmr (deuterochloroform, 200 MHz): δ 8.23 (m, 2H), 7.73 (m, 3H), 7.47 (m, 1H), 3.26 (m, 2H, NHCH_2), 2.72 (m, 2H, $NHCH_2CH_2$), 2.21 (s, 6H, $N(CH_3)_2$); ms: m/z 311 (M^+), 280 [M^+-(CH_3+O)], 207 [M^+-(O+$NH(CH_2)_2N(CH_3)_2$)], 129, 75.

Anal. Calcd for $C_{16}H_{17}N_5O_2$: C, 61.72; H, 5.50; N, 22.49. Found: C, 61.65; H, 5.26; N, 22.86.

5-Oxy-pyrido[2,3-*b*]quinoxaline-9-carboxylic Acid (2-Diethylaminoethyl)amide (**4d**).

This compound was obtained in 30% yield (0.072 g), mp 152-156 °C; ^1H nmr (acetone-d_6, 400 MHz): δ 9.06 (br s, 1H), 8.15 (d, 1H, J=7.5 Hz), 7.79 (t, 1H, J=7.2 Hz), 7.74 (br s, 1H), 7.44 (t, 1H, J=7.5), 3.87 (t, 2H, $NHCH_2CH_2$, J= 5.4 Hz), 2.81 (t, 2H, $NHCH_2CH_2$, J= 5.4 Hz), 2.66 (q, 4H, $N(CH_2CH_3)_2$, J= 7.1 Hz), 1.05 (t, 6H, $N(CH_2CH_3)_2$, J= 7.1 Hz); ^1H nmr (deuterochloroform, 400 MHz): δ 8.95 (m, 1H), 8.26 (d, J=7.84, 1H), 7.71 (m, 1H), 7.56 (d, J=8.16 Hz, 1H), 7.41 (m, 1H); ms: m/z 339 (M^+).

Anal. Calcd for $C_{18}H_{21}N_5O_2$: C, 63.70; H, 6.24; N, 20.64. Found: C, 63.62; H, 6.26; N, 20.86.

5-Oxy-pyrido[2,3-*b*]quinoxaline-9-carboxylic Acid (3-Dimethylaminopropyl)amide (**4e**).

This compound was obtained in 16% yield (0.036 g), mp 145-148 °C; R_f 0.15 (eluent methanol); ^1H nmr (deuterochloroform, 400 MHz): δ 8.89 (m, 1H), 8.22 (d, J=7.7 Hz, 1H), 7.69 (m, 1H), 7.51 (d, J=8.1 Hz, 1H), 7.39 (m, 1H), 3.71 (br s, 2H, $NHCH_2CH_2CH_2$), 2.43 (br s, 2H, $NHCH_2CH_2CH_2$), 2.23 (s, 6H, $N(CH_3)_2$), 1.91 (m, 2H, $NHCH_2CH_2CH_2$).

Anal. Calcd for $C_{17}H_{19}N_5O_2$: C, 62.75; H, 5.89; N, 21.52. Found: C, 63.10; H, 6.16; N, 21.81.

5-Oxy-pyrido[2,3-*b*]quinoxaline-9-carboxylic Acid (3-Diethyl-aminopropyl)amide (**4f**).

This compound was obtained in 19% yield (0.048 g), mp 153-155 °C; ^{1}H nmr (deuterochloroform, 400 MHz): δ 8.91 (m, 1H), 8.26 (d, J=7.2 Hz, 1H), 7.71 (m, 1H), 7.50 (m, 1H), 7.41 (m, 1H), 3.73 (br s, 2H, NHCH_2CH$_2$CH$_2$), 2.56 (br s, 6H, CH_2N(CH_2CH$_3$)$_2$), 1.91 (m, 2H, NHCH$_2$CH_2CH$_2$), 1.03 (br s, 6H, N(CH$_2$CH_3)$_2$)

Anal. Calcd for $C_{19}H_{23}N_5O_2$: C, 64.57; H, 6.56; N, 19.82. Found: C, 64.18; H, 6.19; N, 20.01.

5-Oxy-pyrido[2,3-*b*]quinoxaline-9-carboxylic Acid (2-Morpholin-4-yl-ethyl)amide (**4g).**

This compound was obtained in 27% yield (0.068 g), mp 164-165 °C; ^{1}H nmr (deuterochloroform, 400 MHz): δ 8.94 (m, 1H), 8.27 (dd, J=7.8 Hz, J=1.0 Hz, 1H), 7.72 (m, 1H), 7.60 (d, J=8.2 Hz, 1H), 7.40 (m, 1H), 3.84 (t, 4H, 2,6-morpholinyl, J= 5.1 Hz), 3.75 (q, 2H, NHCH_2, J= 6.2 Hz), 2.73 (t, 2H, NHCH$_2$CH_2, J= 6.2 Hz), 2.65 (t, 4H, 3,5- morpholinyl, J= 5.3 Hz).

Anal. Calcd for $C_{18}H_{19}N_5O_3$: C, 61.18; H, 5.42; N, 19.82. Found: C, 61.27; H, 5.19; N, 20.07.

5-Oxy-pyrido[2,3-*b*]quinoxaline-9-carboxylic Acid (2-Piperidin-1-yl-ethyl)amide (**4h**).

This compound was obtained in 44% yield (0. 108 g), mp 157-160 °C; ^{1}H nmr (deuterochloroform, 400 MHz): δ 12.26 (s, 1H), 8.94 (m, 1H), 8.23 (d, J=7.84 Hz, 1H), 7.70 (m, 1H), 7.64 (d, J=8.2 Hz, 1H), 7.41 (m, 1H), 3.69 (brs, 2H, NHCH_2), 2.65 (t, 2H, NHCH$_2$CH_2, J= 6.2 Hz), 2.51 (brs, 4H, 2,6-piperidyl), 1.67 (brs, 4H, 3,5- piperidyl), 1.52 (brs, 2H, 4- piperidyl)

Anal. Calcd for $C_{19}H_{21}N_5O_2$: C, 64.94; H, 6.02; N, 19.93. Found: C, 64.77; H, 6.18; N, 20.27.

5-Oxy-pyrido[2,3-*b*]quinoxaline-9-carboxylic Acid (2-Pyrrolidin-1-yl-ethyl)amide (**4i**).

This compound was obtained in 29% yield (0.070 g), mp 150-152 °C; ^{1}H nmr (deuterochloroform, 400 MHz): δ 8.94 (m, 1H), 8.26 (dd, J=8.2 Hz, J= 1.36 Hz, 1H), 7.70 (m, 1H), 7.53 (d, J=8.2 Hz, 1H), 7.41 (m, 1H), 3.73 (q, 2H, NHCH_2, J= 6.2 Hz), 2.86 (t, 2H, NHCH$_2$CH_2, J= 6.2 Hz), 2.68 (brs, 4H, 2,5-pyrolidyl), 1.92 (brs, 4H, 3,4-pyrolidyl); ms: m/z 337 (M^+).

Anal. Calcd for $C_{18}H_{19}N_5O_2$: C, 64.08; H, 5.68; N, 20.76. Found: C, 64.36; H, 5.51; N, 20.39.

N^1,N^2- Bis(5-oxy-pyrido[2,3-*b*]quinoxaline-9-benzoyl)ethylene-diamine (**5**).

Ethylenediamine (0.21 g, 0.0035 mole) was added to a mixture of ester **3** (1.8 g, 0.007 mole) and sodium cyanide (0.5 g, 0.01 mole) in methanol (60 ml). The reaction mixture was refluxed for 1 hour and then cooled at room temperature. Water was added and the resulting precipitate **5** was collected by filtration. Crystallization from benzene gave 0.45 g (13 %) of **5**, mp 160-163 °C; ^{1}H nmr (acetone-d$_6$, 400 MHz): δ 8.40 (d, 2H, J=8.4 Hz), 8.02 (d, 2H, J=7.7 Hz), 7.97 (m, 2H), 7.88 (d, 2H, J=8.4 Hz), 7.67 (m, 2H), 7.40 (s, 2H, NH), 6.94 (d, 2H, J=7.7 Hz), 3.34 (br s, 4H, NH(CH_2)$_2$NH).

Anal. Calcd for $C_{26}H_{18}N_8O_4$: C, 61.66; H, 3.58; N, 22.12. Found: C, 61.94; H, 3.40; N, 22.37.

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