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Synthesis of 6,7-ethylenedioxyquinoxalines and pyrido[2,3-*b*]-pyrazines as intermediates in the preparation of antineoplastic agents

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Abstract—A convenient procedure for the synthesis of quinoxalines and pyridopyrazines has been developed from aryldiamines. The condensation of aminocarbamates such as **12** with ethyl 2,3-dibromopropionate provide the quinoxaline **14** directly, in a one-step operation. The methodology reported herein represents an alternative to condensation of *o*-phenylenediamines with α-dicarbonyl compounds for the quinoxalines formation. The same procedure was applied to the 2,3-diaminopyridine to obtain the corresponding pyridopyrazines. © 2002 Elsevier Science Ltd. All rights reserved.

1. Introduction

Some time ago, we started a research program to synthesize a new class of compounds related to known antineoplastic agents such as ellipticine[1] or podophyllotoxin.[2] The compounds studied exhibited the 1,4-benzodioxine ring system (**A**) as part of their structure and this, along with the search for further information in SAR studies, led us to synthesize 6,7-ethylenedioxyquinoxalines (**B**) and pyrido[2,3-*b*]pyrazines (**C**) in order to introduce these nuclei into the synthesis of new anticancer agents.

Quinoxaline derivatives have attracted interest as biologically active materials. They also find considerable application as angiotensin II receptor antagonists,[3] NMDA antagonists,[4] anti-inflammatory,[5] antidepressant-tranquilizing agents,[6] and antitumor drugs (Fig. 1).[6,7]

2. Chemistry

Of the routes available for the synthesis of quinoxalines, the condensation of *o*-phenylenediamines with α-dicarbonyl compounds is the most studied to date, but the alkylation of 1,2-diamines with 1,2-dihalogenated (α,β-dibromopropionaldehyde or tribromoacetone) compounds followed by oxidation is also well known.[8–14] Our investigations on the preparation of the title compounds involved an oxidative condensation of *o*-diaminated compounds with ethyl-2,3-dibromopropionate in DMF.

The synthesis of quinoxaline **14** is shown in Scheme 2. The commercial (available from Aldrich Chemical Co.) 6-amino-2,3-dihydro-1,4-benzodioxine (**1**) was converted to *N*-alkylated compounds **2** and **3** using $(CH_3)_2SO_4$ or benzyl bromide, respectively, according to standard procedure[15] (Scheme 1). The acylated compounds **4** and **5** were prepared from **1** by treatment with acetic anhydride or ethyl chloroformate, respectively, in good yields. For the nitration of compounds **2**–**5** we employed a mild, general and efficient procedure using a mixture of HNO_3/AcOH (1:2) and operating at below 5°C.[16] Thus, the *N*-acyl derivatives **8** and **9** were obtained in 88 and 95% yield, respectively, whereas the nitration of *N*-alkyl derivatives

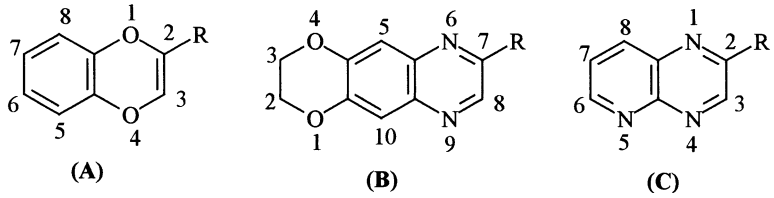

Figure 1. 1,4-Benzodioxines, ethylenedioxyquinoxalines and pyrido[2,3-*b*]pyrazines.

Keywords: quinoxalines; *o*-phenylenediamines; polycyclic systems; pyridopyrazines.
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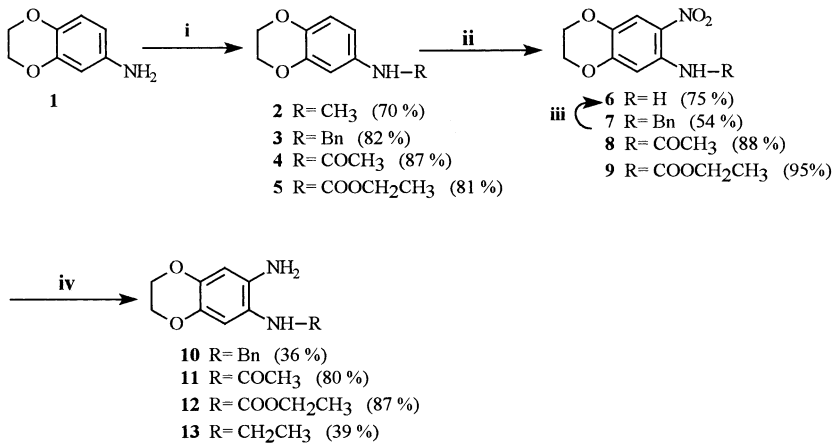
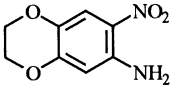
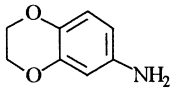
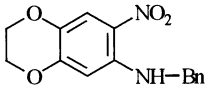
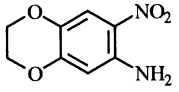
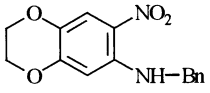
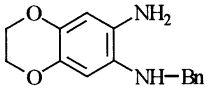
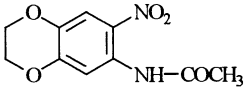
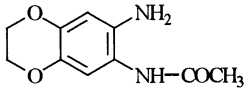
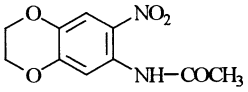
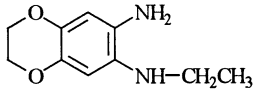
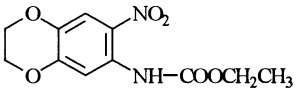
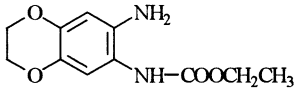
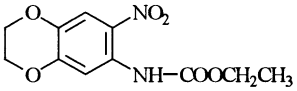
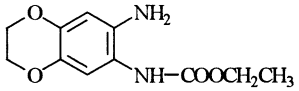


Scheme 1. (i) $(CH_3CO)_2O$ or $ClCOOCH_2CH_3$ (3). (ii) HNO_3–CH_3COOH (1:2) <5°C. (iii) Fe/AcOH; (iv) H_2/Pd–C/CH_3OH or Zn/HCl (see Table 1).

such as **3** proceeded with a lower yield (54%), possibly due to oxidation at the benzylic position. Similarly, 6-amino-7-nitro-2,3-dihydro-1,4-benzodioxine (**6**) was obtained in 54% yield by reacting **1** directly with the oxidative mixture. The reduction of the nitro group was the next key step in the preparation of these quinoxalines. It should be mentioned that reduction of the nitroamine **6** by hydrogenation using Pd–C,[17] with hydrides as $LiAlH_4$, $BH_3{\cdot}(CH_3)_2S$ or $LiB(C_2H_5)_3H$[18] or with metals as Zn/HCl or Sn/HCl,[19] was unsuccessful. All attempts led to aniline **1** by hydride *ipso*-substitution of the nitro group[20] (see Table 1).

Reduction of the nitro-*N*-benzyl derivative (**7**) by treatment with Zn in acidic media gave the diamine **10** and degradation products (entry c, Table 1), whereas the reduction using

Table 1. Conditions used for the reduction of nitro-compounds **6–9**

Entry	Starting material	Conditions	Compound	Yield (%)
a	 **6**	[a]	 **1**	90
b	 **7**	Fe/AcOH 90–100°C/22 h	 **6**	75
c	 **7**	Zn/HCl reflux/20 h	 **10**	36
d	 **8**	H_2/Pd–C/MeOH rt/12 h	 **11**	80
e	 **8**	$LiAlH_4$/THF reflux/24 h	 **13**	39
f	 **9**	H_2/Pd–C/MeOH rt/12 h	 **12**	87
g	 **9**	Fe/HCl reflux/4 h	 **12**	88

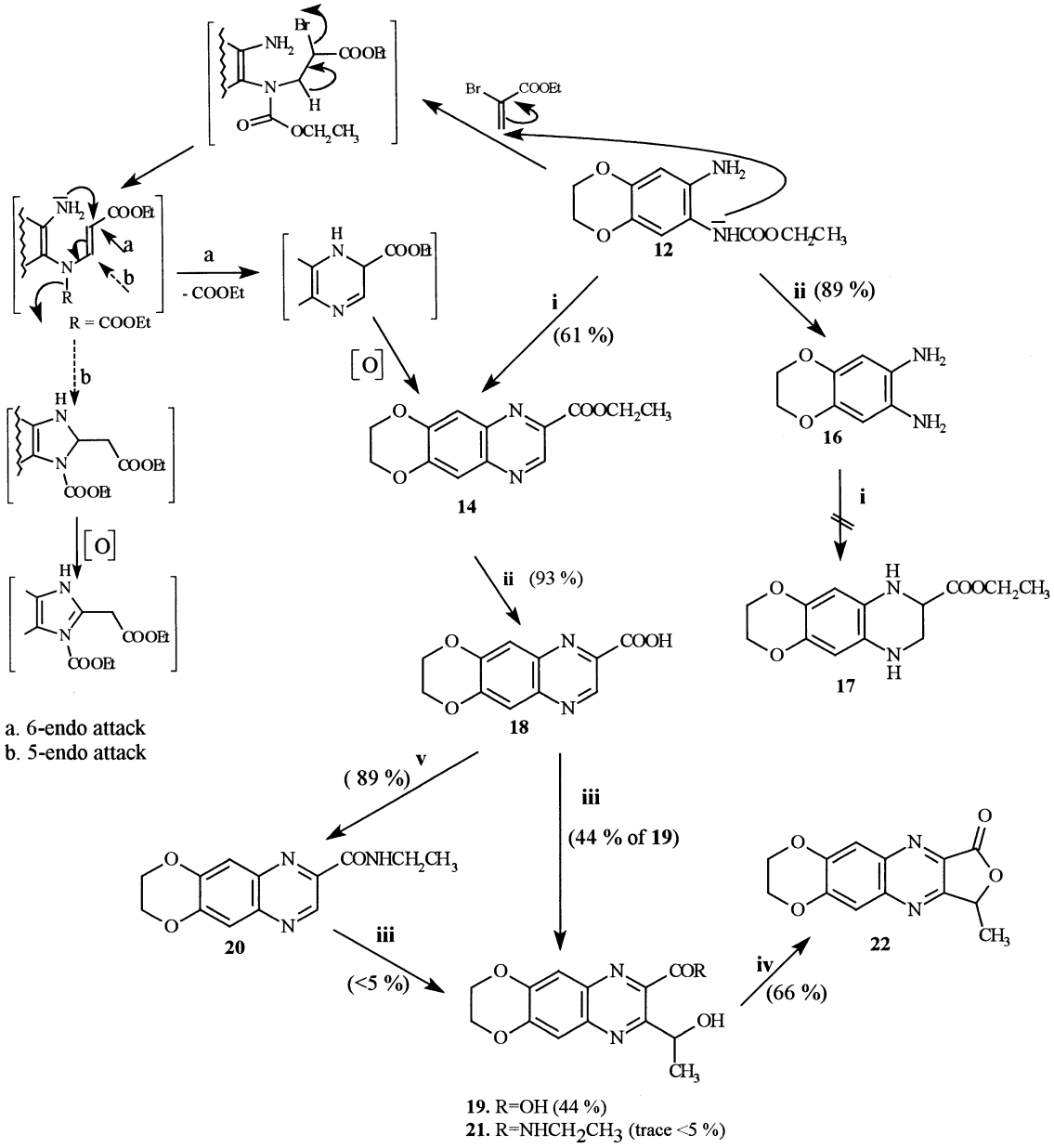
[a] $LiAlH_4$/THF, reflux, 24 h or H_2/Pd–C/MeOH, rt 24 h or Ni–Ra/Zn, AcOH–MeOH, 60°C, 24 h or $SnCl_2$/HCl, CH_2Cl_2, 30°C, 24 h or Zn/NH_4Cl, MeOH, reflux, 1 h.

Fe/AcOH afforded the nitroamine 6 by debenzylation in 75% yield (entry b).

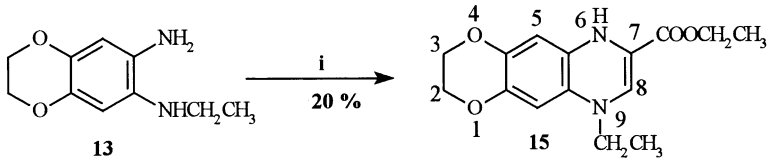
The *N*-acetyl nitro compound (**8**) was converted to the corresponding *N*-acetyl amino **11** in a good yield (entry d, Table 1) by hydrogenation using Pd–C in the methanol. However, when $LiAlH_4$ was used as a reducing agent, the diamine **13** was obtained in low yield (entry e) since reduction of the nitro group and acetyl group was produced simultaneously. The purification of the resulting diamine **13** was laborious because of poor solubility in organic solvents.

Reduction of the nitrocarbamate **9** with Fe in the presence of HCl in methanol afforded the aminocarbamate **12** in 88% yield (entry g). We attempted also the reduction of **9** by catalyzed hydrogenation (entry f). This reduction proceeds with a good yield and we considered the last method as an effective procedure of reduction because the reduced compound obtained was easily purified.

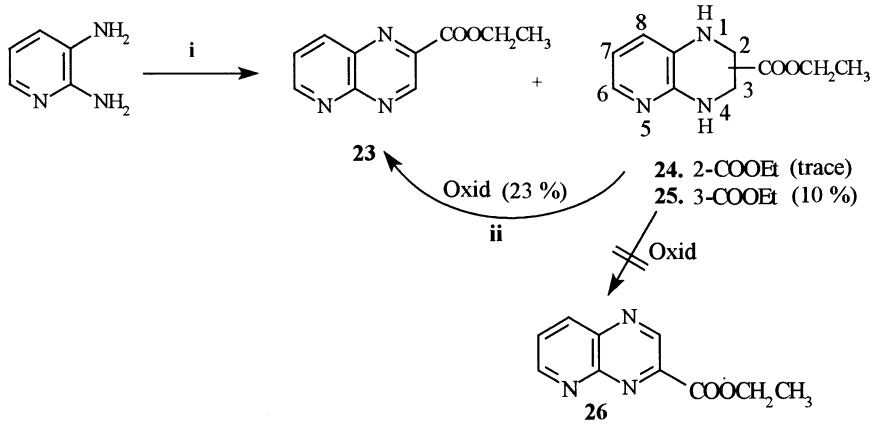
The quinoxaline **14** was prepared by condensation of the amino-carbamate **12** with ethyl 2,3-dibromopropionate in the presence of NaH in DMF in 61% yield (Scheme 2). It seemed likely that under the conditions employed (NaH/DMF/90°C/18 h) elimination of hydrogen bromide from ethyl 2,3-dibromopropionate to give the α-bromoolefinic ester would occur more rapidly than nucleophilic displacement of bromide ion by the formed anion.[21] Under these conditions, elimination of the ethoxy carbonyl group occurred rapidly, and the corresponding tricyclic *N*-protected intermediate was not detected. Since the *o*-carbamate anilines oxidize readily in air, the condensations were carried out under argon atmosphere, but the work-up was carried out with exposure to air. It is thus



Scheme 2. (i) $BrCH_2CHBrCOOCH_2CH_3$/NaH/DMF, 90°C, 18 h; (ii) KOH; (iii) LDA/THF/CH_3CHO/−78°C; (iv) $ZnCl_2$/THF rt; (v) $SOCl_2$/$CH_3CH_2NH_2$ / CH_2Cl_2.



Scheme 3. (i) $BrCH_2–CHBr–COOCH_2CH_3/K_2CO_3/DMF/110°C/24$ h.



Scheme 4. (i) $BrCH_2–CHBr–COOCH_2CH_3/K_2CO_3/DMF$; (ii) DDQ/CH_2Cl_2.

probable that the oxidation to quinoxaline occurs during this time.[22,23] In the next step, hydrolysis of the ester **14** using KOH 8% gave the corresponding acid **18** in an excellent yield (Scheme 2). The intermediate 6,7-diaminobenzodioxane **16** was prepared by hydrolysis of the carbamate **12** in 89% yield, but condensation of **16** with ethyl 2,3-dibromopropionate in basic media (K_2CO_3 or NaH) was unsuccessful. In the latter case, the poor solubility in organic solvents and facile oxidation of unsubstituted diamines may account for the failure. On the other hand, the same conditions applied to the monoalkylated diamine **13** gave the *N*-ethyl quinoxaline **15** in poor yield (20%) (Scheme 3). In the last reaction, the *N*-ethyl group impedes the aromatization of the heterocyclic system, although the oxidation of C-7 and C-8 was observed.

The carboxylic acid **18** treated with LDA at −78°C followed by the addition of acetaldehyde gave the desired hydroxy-acid **19**.

The analogous conditions applied to the carboxamide **20**, prepared from the carboxylic acid **18** by a conventional procedure,[24] afforded only traces of the corresponding hydroxy-amide **21** and this route was abandoned. The

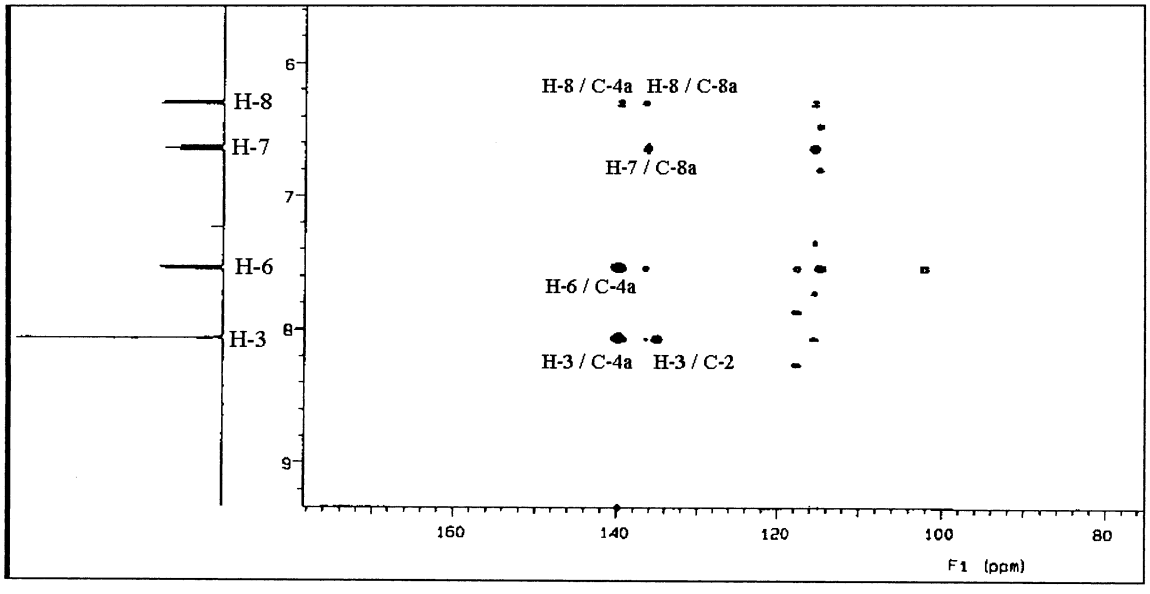


Figure 2. HMBC spectrum of **23** (500 MHz, $CDCl_3$). The horizontal axis of the spectrum corresponds to the ^{13}C spectrum and the vertical axis refers to the ^{1}H spectrum.

hydroxy-acid **19** was readily dehydrated to the corresponding lactone **22** in THF with $ZnCl_2$. The last intramolecular cyclization gave the lactone in low yield. This step proved to be of relatively tedious elaboration, both in basic and acidic (APTS/Toluene or $ZnCl_2/CH_2Cl_2$) protocols.

Scheme 4 depicts the synthesis of related compounds pyridopyrazine **23** and the tetrahydropyrazines **24** and **25**. Treatment of 2,3-diaminopyridine, commercially available, with the ethyl 2,3-dibromopropionate gave the pyrazine **23** as the major compound, and also a mixture of position isomers **24** and **25**. The small quantity of the isomer **24** obtained was converted into the aromatic heterocycle **23** by treatment with DDQ. By contrast, isomer **25** led to none of the corresponding aromatic system **26**. These results can be rationalized in terms of the spontaneous oxidation of the tetrahydro intermediate **24** that led to the direct formation of the 2-substituted isomer **23**. The results are also consistent with the fact that the intermediate **25** was the most difficult to obtain (Scheme 4).

With this condensation, it is possible, in principle, to obtain two regioisomeric pyrido-pyrazine compounds. In order to identify the main isomer formed, we performed 2D NMR-experiments (HMQC and HMBC) and the results confirm the proposed structure for **23** (Fig. 2).

The carbon at 136.7 ppm is assignable as the C-8a and this carbon shows a cross peak with the 7-H. Whereas 3-H gives a cross peak to a carbon signal at 140.0 ppm corresponding to C-4a, and also 6-H shows a correlation peak to C-4a.

3. Experimental

3.1. General

Melting points were determined on an MFB 595010 M Gallenkamp melting point apparatus and are uncorrected. The ^1H and ^{13}C NMR spectra were recorded on a Varian Gemini 200 or Varian Gemini 300 spectrometer or on a Varian VXR-500 spectrometer with tetramethylsilane as internal standard and using $CDCl_3$ as solvent or CD_3OD. Chemical shifts were expressed in ppm downfield from internal TMS or residual signal of deuterated solvent (δ). IR spectra were recorded on a FTIR Perkin Elmer 1600 spectrophotometer. Mass spectra were recorded on a Hewlett-Packard spectrometer 5988-A (70 eV). The chromatography was carried out on SiO_2 (silica gel 60, SDS, 60–200 μm). Microanalyses were determined on a Carlo Erba 1106 Analyzer by Serveis Científico-Tècnics, Universitat de Barcelona, and analytical values obtained were within ±0.4% of the calculated values. All reagents were of commercial quality or were purified before use and the organic solvents were of analytical grade or purified by standard procedures.

3.1.1. *N*-(2,3-Dihydro-1,4-benzodioxin-6-yl) methylamine (2). To a solution of *N*-(2,3-dihydro-1,4-benzodioxin-6-yl)amine **1** (1 g, 6.61 mmol) in anhydrous acetone was added anhydrous K_2CO_3 (2.74 g, 19.8 mmol). After 0.5 h of stirring, $(CH_3)_2SO_4$ (4.2, 33 mmol) was added and the mixture was stirred for 4 h at room temperature. Concentration of the mixture under vacuum afforded an oil, and the residue was purified by a chromatography column on silica gel eluting with hexane/ethyl acetate to afford **2** (70% yield) as an oil. IR (NaCl) ν (cm^{-1}) 3050, 1664, 1260, 1110. ^1H NMR ($CDCl_3$, 200 MHz) δ (ppm) 2.85 (s, 3H, CH_3); 3.42 (bs, 1H, NH); 4.19 (m, 4H, CH_2–O–); 6.20 (s, 1H, Ar); 6.38 (m, 1H, Ar); 6.60 (m, 1H, Ar). ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ (ppm) 29.8 (CH_3, CH_3–N); 64.3 (CH_2, CH_2–O); 102.4 (CH, C5H); 107.1 (CH, C8H); 117.3 (CH, C7H); 137.2 (C, C6); 142.1 (C, C4a); 142.3 (C, C8a).

3.1.2. *N*-(2,3-Dihydro-1,4-benzodioxin-6-yl) benzylamine (3). To a solution of **1** (1 g, 6.61 mmol) in toluene was added benzaldehyde (0.84 g, 7.9 mmol), and APTS (catalytic, amount). The resulting mixture was stirred at 120°C for 24 h. Then the reaction was cooled to room temperature and the product extracted with ether (60 mL). The organic solution was washed with aqueous sodium bicarbonate, dried over Na_2SO_4, and concentrated under vacuum to obtain the crude of reaction as an oil. After, the residue was dissolved in methanol (20 mL) and the $NaBH_4$ (0.3 g, 7.9 mmol) was added in several portions. The resulting mixture was stirred at room temperature for 2 h. The solvent was removed under vacuum and the residue was poured into ice-water (20 mL). The product was extracted with CH_2Cl_2 (3×20 mL), dried over Na_2SO_4, and concentrated under vacuum. The residue was chromatographed on silica gel eluting with hexane/ethyl acetate to afford **3** (82% yield) as an oil. IR (NaCl) ν (cm^{-1}) 3100, 1590, 1240, 1090. ^1H NMR ($CDCl_3$, 200 MHz) δ (ppm) 3.92 (m, 2H, CH_2–O–); 3.98 (m, 2H, CH_2–O–); 4.24 (s, 2H, CH_2–Ar); 6.38 (m, 2H, Ar); 6.60 (s, 1H, Ar); 7.38 (m, 5H, Ar). ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ (ppm) 48.2 (CH_2, CH_2–N); 70.5 (CH_2, CH_2–O); 104.2 (CH, C5H); 112.0 (CH, C8H); 113.8 (CH, C7H); 125.8 (CH, C4′H); 128.7 (CH, C2′H, C6′H); 129.0 (CH, C3′H, C5′H); 130.2 (C, C1′); 138.2 (C, C6); 140.1 and 141.8 (C, C4a and C8a). Analysis calculated for $C_{15}H_{15}NO_2$: C, 74.67; H, 6.27; N, 5.80%. Found: C, 74.28; H, 5.81; N, 5.42%.

3.1.3. *N*-(2,3-Dihydro-1,4-benzodioxin-6-yl) acetamide (4). A mixture of **1** (2.61 g, 17.26 mmol) and acetic anhydride (50 mL) was stirred at 140°C for 8 h. The resulting reaction mixture was poured onto ice and extracted with CH_2Cl_2 (100 mL). The organic phase was dried, filtered and concentrated under vacuum to gave a brown solid which was purified by silica gel chromatography, using as eluent hexane/ethyl acetate 6:4 to give the white solid **4** in 87% yield (2.9 g). Mp: 129–130°C (hexane/ethyl acetate). IR (KBr) ν (cm^{-1}) 3312, 1664, 1258, 1067. ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm) 2.14 (s, 3H, CH_3); 4.25 (m, 4H, C2H_2 and C3H_2); 6.79 (d, J=8.5 Hz, 1H, C8H); 6.86 (dd, J=8.5 Hz, J'=2.3 Hz, 1H, C7H); 7.08 (ba, 1H, NH); 7.12 (d, J=2.3 Hz, 1H, C5H). ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ (ppm) 22.9 (CH_3, –CH_3); 63.8 (CH_2, CH_2–O); 63.9 (CH_2, CH_2–O); 109.4 (CH, C5H); 113.3 (CH, C7H); 116.5 (CH, C8H); 131.5 (C, C6); 139.8 (C, C8a); 142.8 (C, C4a); 169.5 (C, CO). Analysis calculated for $C_{10}H_{11}NO_3$: C, 62.17; H, 5.74; N, 7.25%. Found: C, 62.52; H, 5.31; N, 6.80%.

3.1.4. 6-Ethoxycarbonylamino-2,3-dihydro-1,4-benzodioxine (5). To a solution of ethyl chloroformate

(0.47 mL, 4.96 mmol) in dry CH_2Cl_2 (5 mL) was cooled to 0°C and then a solution of 6-amino-2,3-dihydro-1,4-benzodioxine (500 mg, 3.30 mmol) and K_2CO_3 (252 mg, 6.61 mmol) in dry CH_2Cl_2 (15 mL) was added dropwise, the reaction mixture was stirred at room temperature for 1 h. Then, water (25 mL) was added and extracted with CH_2Cl_2 (3×15 mL). The extracts were dried (Na_2SO_4), filtered off and evaporated under vacuum giving 603 mg of carbamate as a white solid (81% yield). Mp: 124–125°C (hexane/ethyl acetate). IR (KBr) ν (cm^{-1}) 3329, 2985, 1699, 1543, 1228, 1064. ^1H NMR ($CDCl_3$, 200 MHz) δ (ppm) 1.29 (t, J=7.2 Hz, 3H, OCH_2CH_3); 4.18 (q, J=7.2 Hz, 2H, OCH_2CH_3); 4.22 (m, 4H, $C2H_2$ and $C3H_2$); 6.57 (bs, 1H, NH); 6.78 and 6.78 (s, 2H, C5H and C7H); 6.98 (bs, 1H, C8H). ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ (ppm) 14.5 (CH_3, OCH_2CH_3); 61.1 (CH_2, OCH_2CH_3); 64.1 and 64.3 (CH_2, C2 and C3); 108.5 (CH, C5); 112.4 (CH, C7); 117.0 (CH, C8); 131.6 (C, C6); 139.5 (C, C8a); 143.4 (C, C4a); 153.7 (C, CO). Analysis calculated for $C_{11}H_{12}N_2O_6$: C, 49.26; H, 4.51; N, 10.44%. Found: C, 49.68; H, 4.4.32; N, 10.09%.

3.1.5. 6-Amino-7-nitro-2,3-dihydro-1,4-benzodioxine (6). *Method A*: To aniline **1** (500 mg, 3.3 mmol) was added at 0°C dropwise a solution of HNO_3 (5 mL) in acetic acid (40 mL). The mixture was stirred for 3 h at room temperature. After the mixture was poured into ice-water, and pH value was adjusted to 8–9 by the addition of NaOH 50%, then extracted with CH_2Cl_2. The organic layer was separated, dried over Na_2SO_4, and concentrated to give the nitro **6** as a yellow solid (352 mg, 54% yield). Mp: 150–152°C (ethyl acetate). ^1H NMR ($CDCl_3$, 200 MHz) δ (ppm) 4.34 (m, 4H, $C2H_2$ and $C3H_2$); 6.94 (s, 1H, C5H); 7.79 (s, 1H, C8H). ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ (ppm) 64.0 and 64.6 (CH_2, CH_2–O); 113.2 (CH, C5H); 117.4 (CH, C8H); 136.2 (C, C6); 142.0 (C, C8a); 143.5 (C, C7); 149.3 (C, C4a). Analysis calculated for $C_8H_8N_2O_4$: C, 48.98; H, 4.11; N, 14.28%. Found: C, 48.60; H, 4.28; N, 13.98%.

Method B: A solution of **7** (100 mg, 0.35 mmol) in acetic acid (10 mL) was added Fe (39 mg, 0.70 mmol) and the resulting mixture was stirred at 90–100°C for 22 h. The mixture was then filtered and extracted with ether (3×20 mL). The organic phase was separated and dried over Na_2SO_4, and the solvent was removed by rotary evaporation. The resulting residue was purified by column chromatography (hexane/ethyl acetate 70:30) giving the debenzylated coumpond **6** in 75% yield.

3.1.6. 6-Benzylamino-7-nitro-2,3-dihydro-1,4-benzodioxine (7). A mixture of 7-bromo-6-nitro-2,3-dihydro-1,4-benzodioxin (500 mg, 1.92 mmol) and benzylamine (4 mL, 38.1 mmol) was stirred at 170°C for 2 h. A solution of HCl 5N was added until acidic pH and extracted with ether (3×15 mL).

The combined organic phase was dried (Na_2SO_4), filtered off and the solvent removed under vacuum. The residue was purified by column chromatography (on silica gel hexane/ethyl acetate in a ratio 9:1) giving 184 mg of starting product, (hexane/ethyl acetate in a ratio 7:3) give the 6-benzylamino-7-nitro-2,3-dihydro-1,4-benzodioxine as a red oil (300 mg, 54% yield). IR (NaCl) ν (cm^{-1}) 3383, 2923, 1513, 1230, 1066. ^1H NMR ($CDCl_3$, 200 MHz) δ (ppm) 4.27 (m, 4H, $C2H_2$ and $C3H_2$); 4.45 (d, J=4.4 Hz, 2H, CH_2–N); 6.20 (CH, 1H, C5H); 7.33 (CH, 5H, Ar); 7.76 (CH, 1H, C8H); 8.40 (s, 1H, NH). ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ (ppm) 47.3 (CH_2, CH_2–N); 63.8 and 65.3 (CH_2, $C2H_2$ and $C3H_2$); 100.1 (CH, C5H); 114.1 (CH, C8H); 127.0 (CH, C2′H and C6′H); 127.6 (CH, C4′H); 128.8 (CH, C3′H and C5′H); 131.8 (C, C8a); 134.6 (C, C6); 137.4 (C, C7); 142.6 (C, C4a); 152.0 (C, C1′). Analysis calculated for $C_{15}H_{14}N_2O_4$: C, 62.93; H, 4.93; N, 9.78%. Found: C, 63.02; H, 4.51; N, 9.39%.

3.1.7. 6-Acetamido-7-nitro-2,3-dihydro-1,4-benzodioxine (8). Using the same procedure as **6**, the nitro-derivative **8** as a yellow solid (2.17 g, 88% yield) was obtained from the *N*-acetyl-2,3-dihydro-1,4-benzodioxin-6-amina (**4**) (2 g, 10.4 mmol). Mp: 165–167°C (hexane/ethyl acetate). IR (KBr) ν (cm^{-1}) 3312, 1664, 1520, 1230, 1110. MS (EI) *m*/*z* (%): 238 (59); 196 (100); 94 (49). ^1H NMR ($CDCl_3$, 200 MHz) δ (ppm) 2.30 (s, 3H, CH_3); 4.35 (m, 4H, CH_2–O); 6.76 (s, 1H, C5H); 7.78 (s, 1H, C8H); 8.31 (s, 1H, NH). ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ (ppm) 26.6 (CH_3, –CH_3); 64.2 (CH_2, CH_2–O); 115.8 (CH, C5H); 119.8 (CH, C8H); 139.1 (C, C6); 144.2 (C, C8a); 148.6 (C, C7); 150.2 (C, C4a); 172.3 (C, CO). Analysis calculated for $C_{10}H_{10}N_2O_5$: C, 50.43; H, 4.23; N, 11.76%. Found: C, 50.08; H, 4.74; N, 12.09%.

3.1.8. 6-Ethoxycarbonylamino-7-nitro-2,3-dihydro-1,4-benzodioxine (9). A solution of the carbamate **6** (460 mg, 2.06 mmol) in acetic acid (3 mL) was cooled to −10°C. Then nitric acid 60% (1.5 mL) was added dropwise and the mixture was stirred for 20 min at the same temperature. Then a solution of NaOH 30% was added until basic pH and extracted with ether (3×15 mL). The combined organic layer was dried (Na_2SO_4), filtered off and the solvent evaporated under vacuum giving 538 mg of nitro **9** as a yellow solid (95% yield). Mp: 145–146°C (hexane/ethyl acetate). IR (KBr) ν (cm^{-1}) 3333, 2978, 1747, 1519, 1257. ^1H NMR ($CDCl_3$, 200 MHz) δ (ppm) 1.33 (t, J=7.2 Hz, 3H, OCH_2CH_3); 4.23 (q, J=7.2 Hz, 2H, OCH_2CH_3); 4.34 (m, 4H, $C2H_2$ and $C3H_2$); 7.79 (s, 1H, C5H); 8.08 (s, 1H, C8H); 9.90 (s, 1H, NH). ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ(ppm) 14.4 (CH_3, OCH_2CH_3); 61.7 (CH_2, OCH_2CH_3); 63.9 and 65.0 (CH_2, C2 and C3); 107.9 (CH, C5); 114.1 (CH, C8); 129.3 (C, C6); 131.1 (C, C7); 139.5 (C, C8a); 150.5 (C, C4a); 153.0 (C, CO). Analysis calculated for $C_{11}H_{12}N_2O_6$: C, 49.26; H, 4.51; N, 10.44%. Found: C, 48.87; H, 4.30; N, 10.78%.

3.1.9. 6-Amino-7-benzylamino-2,3-dihydro-1,4-benzodioxine (10). To a solution of 6-benzylamino-7-nitro-2,3-dihydro-1,4-benzodioxine (100 mg, 0.34 mmol) in a mixture of ethanol/water (4:1) was added Zn (113 mg, 1.74 mmol) and HCl concentrated (0.5 mL). The mixture reaction was refluxed for 20 h. The Zn was filtered off and the solvent was removed under vacuum. A solution of NaOH 2N was added until basic pH and the mixture was extracted with ethyl acetate (3×15 mL). The combined organic solution was dried (Na_2SO_4) and filtered off and the solvent evaporated under vacuum. The residue was purified by column chromatography (on silica gel hexane/ethyl acetate/metanol in a ratio 6:3:1) to give the 6-amino-7-

benzylamino-2,3-dihydro-1,4-benzodioxine as an oil (32 mg, 36% yield). IR (NaCl) ν (cm^{-1}) 3383, 2874, 1470, 1183. ^1H NMR ($CDCl_3$, 200 MHz) δ (ppm) 4.25 (s, 4H, $C2H_2$ and $C3H_2$); 5.20 (s, 2H, CH_2–N); 6.67 (s, 1H, C5H); 7.20 (s, 1H, C8H); 7.29 (m, 5H, Ar). ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ (ppm) 47.2 (CH_2, CH_2–N); 64.1 and 64.4 (CH_2, $C2H_2$ and $C3H_2$); 96.9 (CH, C5H); 106.1 (CH, C8H); 126.2 (CH, C2′H and C6′H); 127.8 (CH, C4′H); 128.9 (CH, C3′H and C5′H); 135.8 (C, C6); 136.8 (C, C7); 140.3 and 140.7 (C, C4a and C8a); 151.4 (C, C1′). Analysis calculated for $C_{15}H_{16}N_2O_2$: C, 70.29; H, 6.29; N, 10.93%. Found: C, 70.73; H, 6.01; N, 10.57%.

3.1.10. 6-Acetamido-7-amino-2,3-dihydro-1,4-benzodioxine (11). The nitro **8** (100 mg, 0.42 mmol) in absolute methanol (25 mL) was shaken with 10% palladium on charcoal (10 mg) in the presence of hydrogen at atmospheric pressure for 18 h. After the resultant mixture was filtered off and the solution was evaporated to reduced pressure. The residue was diluted with ethyl acetate and washed with water, dried over Na_2SO_4. The resulting oil obtained was purified by silica gel column chromatography (ethyl acetate/hexane 10:90) to give **11** as an oil (70 mg, 80% yield). IR (NaCl) ν (cm^{-1}) 3307, 1682, 1558, 1260, 1108. ^1H NMR ($CDCl_3$, 200 MHz) δ (ppm) 2.22 (s, 3H, CH_3); 4.38 (m, 4H, CH_2–O); 6.24 (s, 1H, H-8); 6.42 (s, 1H, H-5). ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ (ppm) 26.8 (CH_3, CH_3–); 64.2 and 64.4 (CH_2, CH_2–O–); 95.9 (CH, C5H); 107.2 (CH, C8H); 132.1 (C, C6); 136.1 (C, C7); 140.8 and 141.0 (C, C4a and C8a); 170.1 (C, CO). Analysis calculated for $C_{10}H_{12}N_2O_3$: C, 57.69; H, 5.81; N, 13.45%. Found: C, 57.91; H, 5.39; N, 13.73%.

3.1.11. 7-Amino-6-ethoxycarbonylamino-2,3-dihydro-1,4-benzodioxine (12). *Method A*: Pd–C (5 mg, 10%) was added to a solution of the nitro-carbamate **9** (50 mg, 0.18 mmol) in ethyl acetate (20 mL). The reaction mixture was strongly stirred at room temperature under atmosphere of hydrogen for 12 h. The catalyst was filtered and the filtrate was evaporated to dryness at reduced pressure. The resulting residue was purified by column chromatography (on silica gel hexane/ethyl acetate in a ratio 6:4) to afforded 47 mg of product **12** as a brown solid (37 mg, 87% yield). Mp: 103–104°C (hexane/ethyl acetate). IR (KBr) ν (cm^{-1}) 3367, 3200, 2976, 1719, 1697, 1498, 1191, 1066. ^1H NMR ($CDCl_3$, 200 MHz) δ (ppm) 1.29 (t, J=7.2 Hz, 3H, OCH_2CH_3); 3.43 (bs, 2H, NH_2); 4.14 (q, J=7.2 Hz, 2H, OCH_2CH_3); 4.18 (m, 4H, $C2H_2$ and $C3H_2$); 6.30 (s, 1H, C_5H); 6.40 (bs, 1H, NH); 7.81 (s, 1H, C8H). ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ (ppm) 14.5 (CH_3, OCH_2CH_3); 61.3 (CH_2, OCH_2CH_3); 64.0 and 64.5 (CH_2, C2 and C3); 105.7 (CH, C8H); 114.0 (CH, C5H); 117.9 (C, C6); 134.7 (C, C4a); 136.3 (C, C7); 142.8 (C, C8a); 154.8 (C, CO). Analysis calculated for $C_{11}H_{14}N_2O_4$: C, 55.27; H, 5.95; N, 11.81%. Found: C, 54.90; H, 5.53; N, 11.98%.

Method B: To a solution of the nitro-carbamate derivative **9** (50 mg, 0.18 mmol) in ethanol (15 mL), Fe (50 mg, 0.90 mmol) and concentrated HCl (1 mL) were added, and the resulting suspension was refluxed for 4 h. The solvent was removed under vacuum and a solution of NaOH 2N was added dropwise until pH basic, followed by extraction with ethyl acetate (3×15 mL). The combined organic layers were dried (Na_2SO_4), filtered off and the solvent removed, the resulting residue was purified by column chromatography (on silica gel hexane/ethyl acetate in a ratio 6:4) giving 38 mg of **12** as a brown solid (88% yield).

3.1.12. 6-Amino-7-ethylamino-2,3-dihydro-1,4-benzodioxine (13). A solution of **8** (1.39 g, 5.8 mmol) in THF (30 mL) was cooled to 0°C and treated with $LiAlH_4$ (1.09 g, 28.72 mmol) dropwise over 10 min. The cooling bath was removed and the reaction mixture heated at reflux for 24 h. The reaction mixture was cooled to 0°C and quenched with water. After, the reaction was allowed to reach room temperature and was diluted with ethyl acetate. Anhydrous sodium sulfate was added directly to the mixture with constant stirring for 10 min. The reaction was then filtered and the solvent evaporated. The obtained residue was purified by column chromatography (silicagel-Et_3N, 100% ethyl acetate) and the ethylamine **13** was obtained as a colorless oil (436 mg, 39% yield). IR (KBr) ν (cm^{-1}) 3332, 2964, 1520, 1190, 1067. ^1H NMR ($CDCl_3$, 200 MHz) δ (ppm) 1.27 (t, J=7 Hz, 3H, CH_3); 3.05 (q, J=7 Hz, 2H, CH_2–N); 3.10 (m, 1H, NH); 4.18 (q, 4H, $C2H_2$ and C_3H2); 6.22 (s, 1H, C5H); 6.30 (s, 1H, C8H). ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ (ppm) 15.0 (CH_3, –CH_3); 39.3 (CH_2, CH_2–N); 64.6 (CH_2, C2 and C3); 101.6 (CH, C8); 105.9 (CH, C5); 128.3 (C, C7); 132.8 (C, C6); 135.2 (C, C8a); 137.0 (C, C4a). Analysis calculated for $C_{10}H_{14}N_2O_2$: C, 61.84; H, 7.27; N, 14.42%. Found: C, 62.29; H, 6.93; N, 14.30%.

3.1.13. Ethyl-(2,3-dihydro-1,4-dioxino[2,3-*g*]quinoxalin-7-yl)carboxylate (14). To a suspension of NaH 60% (92 mg, 2.3 mmol) in dry DMF (1 mL) a solution of carbamate **12** (250 mg, 1.05 mmol) in dry DMF (2 mL) was added, the reaction mixture was stirred at room temperature for 30 min. Then a solution of ethyl dibromopropionate (0.3 mL, 2.09 mmol) in dry DMF was added dropwise. After the addition was completed, the mixture was stirred under argon at 90°C for 18 h. Then the residue was hydrolyzed with water (15 mL), and the product extracted with ether (3×15 mL). The organic extracts were dried over Na_2SO_4, filtered, and after removal of the solvent, the residue was purified by column chromatography (on silica gel hexane/ethyl acetate in a ratio 5:5) to give 66 mg of **14** as a brown solid (61% yield). Mp: 129–139°C (hexane/ethyl acetate). IR (KBr) ν (cm^{-1}) 2981, 1715, 1495, 1225, 1061. MS (EI): *m/z* (intensity) 260 (M, 20); 239 (65). ^1H NMR ($CDCl_3$, 200 MHz) δ (ppm) 1.50 (t, J=7 Hz, 3H, OCH_2CH_3); 4.51 (s, 4H, $C2H_2$ and $C3H_2$); 4.55 (q, J=7 Hz, 2H, OCH_2CH_3), 7.56 (s, 1H, C10H); 7.70 (s, 1H, C5H); 9.35 (s, 1H, C8H). ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ (ppm) 14.3 (CH_3, OCH_2CH_3); 62.2 (CH_2, OCH_2CH_3); 64.1 and 64.3 (CH_2, C2 and C3); 113.0 (CH, C10); 114.2 (CH, C5); 138.1 (C, C7); 140.5 and 140.6 (C, C4a and C10a); 143.2 (CH, C8); 147.8 (C, C9a); 149.1 (C, C5a); 164.0 (C, CO). Analysis calculated for $C_{13}H_{12}N_2O_4$: C, 59.99; H, 4.65; N, 10.76%. Found: C, 60.32; H, 4.30; N, 10.32%.

3.1.14. Ethyl 6-ethyl-2,3,6,9-tetrahydro-1,4-dioxino[2,3-*g*]quinoxalin-8-carboxylate (15). To a mixture of the diamine **13** (100 mg, 0.52 mmol) dry K_2CO_3 (176 mg, 1.27 mmol), KI (catalyst amount) in DMF (25 mL) was added ethyl 2,3-dibromopropionate (0.09 mL) in twice separated by 1 h. The resulting solution was heated at

110±10°C for 24 h. The crude of reaction was extracted several times with ether and a crude product obtained was purified by column chromatography (hexane/ethyl acetate) giving compound **15** as an oil (30 mg, 20% yield). IR (KBr) ν (cm^{-1}) 3310, 1731, 1255, 1102. MS (EI) *m/z* (%): 290 (22); 261 (52); 94 (100). ^1H NMR ($CDCl_3$, 200 MHz) δ (ppm) 1.29 (m, 6H, CH_3); 3.65 (m, 2H, CH_2–N); 4.00 (m, 2H, CH_2–O); 4.25 (m, 4H, CH_2–O); 6.40 (d, J=1 Hz, 1H, Ar); 7.12 (d, $J\approx$1 Hz, 1H, Ar); 7.34 (s, 1H, H-7); 8.12 (s, 1H, NH). ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ (ppm) 13.6 (CH_3, CH_3); 13.8 (CH_3, CH_3); 36.2 (CH_2, CH_2–N); 62.3 (CH_2, CH_2–O); 64.8 (CH_2, CH_2–O); 108.2 and 108.6 (CH, C5H and C10H); 130.8 (CH, C8H); 134.2 (C, C7); 140.3 and 141.3 (C, C5a and C9a); 146.8 and 147.5 (C, C4a and C10a), 169.5 (C, CO). Analysis calculated for $C_{15}H_{18}N_2O_4$: C, 62.06; H, 6.25; N, 9.65%. Found: C, 61.88; H, 6.49; N, 9.60%.

3.1.15. 6,7-Diamino-2,3-dihydro-1,4-benzodioxine (16). A solution of the amino-carbamate **12** (40 mg, 0.17 mmol) in ethanol (2 mL) a solution of KOH 2N (5 mL) was added. The mixture was heated at reflux for 4 h. The solvent was removed under vacuum, then resulting mixture was extracted with ethyl acetate (3×10 mL), the combined organic solution was dried (Na_2SO_4), filtered off and evaporated to dryness giving 20 mg as a brown solid of 6,7-diamino-2,3-dihydro-1,4-benzodioxine (89% yield). Mp: 75–76°C (hexane/ethyl acetate). IR (KBr) ν (cm^{-1}) 3336, 2870, 1517, 1192, 1063. ^1H NMR ($CDCl_3$, 200 MHz) δ (ppm) 3.19 (bs, 4H, NH_2); 4.19 (s, 4H, C2H_2 and C3H_2); 6.27 (s, 2H, C5H and C8H). ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ (ppm) 64.5 (CH_2, C2 and C3); 105.8 (CH, C5 and C8); 128.9 (C, C6 and C7); 136.7 (C, C4a and C8a). Analysis calculated for $C_8H_{10}N_2O_2$: C, 57.82; H, 6.07; N, 16.86%. Found: C, 57.49; H, 6.33; N, 16.42%.

3.1.16. (2,3-Dihydro-1,4-dioxino[2,3-*g*]quinoxalin-7-yl)-carboxylic acid (18). A solution of the ester **14** (80 mg, 0.30 mmol) and potassium hydroxide (112 mg, 2 mmol) in methanol (5 mL) and water (5 mL) was stirred at room temperature for 4 h. The solvent was removed under vacuum and the residue was poured onto crushed ice, acidified with HCl 2N until pH 6, and extracted with CH_2Cl_2. The combined extracts were dried (Na_2SO_4) and concentrated to give the acid as a solid product. Chromatography (silica gel, ethyl acetate/methanol 9:1) gave the carboxylic acid **18** as a white solid (65 mg, 93% yield). Mp: 241–242°C (ethyl acetate/hexane). IR (KBr) ν (cm^{-1}) 3428, 1734, 1500, 1234. MS (EI): *m/z* (intensity) 232 (M, 38), 231 (80), 187 (76). ^1H NMR (CD_3OD, 200 MHz) δ (ppm) 4.81 (s, 4H, C2H_2 and C3H_3); 7.28 (s, 1H, C5H); 7.48 (s, 1H, C10H); 9.12 (s, 1H, C8H). ^{13}C NMR (DMSO, 50.3 MHz) δ (ppm) 64.2 (CH_2, CH_2–O); 64.4 (CH2, CH_2–O); 112.3 (CH); 113.2 (CH); 138.1 (C, C-7); 140.0 and 141.2 (C, C-5a, C-9a); 143.1 (CH, C-8); 147.8 and 149.1 (C, C-4a, C-10a); 165.9 (C, C=O). Analysis calculated for $C_{11}H_8N_2O_4$: C, 56.89%; H, 3.47%; N, 12.06%. Found: C, 56.42%; H, 3.32%; N, 12.28%.

3.1.17. 8-(1-(1-Hydroxyethyl))-(2,3-dihydro-1,4-benzodioxino[2,3-*g*]quinoxalin-7-yl)carboxylic acid (19). A solution of compound **18** (60 mg, 0.25 mmol) in dry THF (2 mL) was cooled to −78°C and treated with LDA (2 M in THF/*n*-heptane) (0.28 mL, 0.56 mmol) dropwise over 10 min. The reaction mixture was stirred at this temperature for 3 h. Then acetaldehyde (32 mg, 0.51 mmol) in dry THF was added and the mixture was allowed to reach room temperature over 8 h. The reaction was quenched by the addition of NH_4Cl (2 mL) and then diluted with ether acidified with HCl 2N and extracted. The organic layer was separated and dried (Na_2SO_4), and the solvent was evaporated to dryness. The crude was purified by column chromatography (silica gel, hexane/ethyl acetate 3:7) to afford 27 mg of starting material, (ethyl acetate/methanol 9:1) give the alkylated compound **19** as an oil (32 mg, 44% yield). MS (EI) *m/z* (%): 276 (14); 258 (41); 187 (100). IR (KBr) ν (cm^{-1}) 3490, 1732, 1490, 1260, 1110. ^1H NMR (CD_3OD, 200 MHz) δ (ppm) 1.67 (d, J=6.6 Hz, 3H, –CH_3); 4.43 (s, 4H, C2H_2 and C3H_2); 5.62 (q, J=6.6 Hz, 1H, CH–OH); 7.43 (s, 1H, C5H); 7.47 (s, 1H, C10H); 9.28 (s, 1H, OH). ^{13}C NMR ($CDCl_3$+CD_3OD, 50.3 MHz) δ (ppm) 19.7 (CH_3); 64.8 and 64.9 (CH2, CH_2–O); 74.6 (CH, CH–O); 113.1 (CH); 113.8 (CH); 136.2 (C, C-7); 140.2 and 141.4 (C, C-5a, C-9a); 143.5 (CH, C-8); 147.2 and 148.3 (C, C-4a, C-10a); 168.2 (C, CO). Analysis calculated for $C_{13}H_{12}N_2O_5$: C, 56.52%; H, 4.38%; N, 10.14%. Found: C, 56.91%; H, 4.63%; N, 10.45%.

3.1.18. *N*-Ethyl-2,3-dihydro-1,4-dioxino[2,3-*g*]quinoxalin-2-carboxamide (20). A solution of the carboxylic acid **18** (100 mg, 0.43 mmol) in toluene was cooled at 0°C and $SOCl_2$ (0.1 mL, 1.37 mmol) was slowly added. The resulting mixture was heated at 120°C for 4 h. After, the mixture was cooling to room temperature and the toluene was removed under vacuum.

The crude of reaction was directly treated with ethylamine (58.16 mg, 1.29 mmol) in CH_2Cl_2 (15 mL), stirring at room temperature for 4 h.

Finally, water (15 mL) was added to the crude of reaction and the obtained mixture and was extracted with CH_2Cl_2. The combined organic layers were dried, filtered off, and the solvent removed giving the amide **20**. Purification by column chromatography (SiO_2, hexane/ethyl acetate) gave the desired amide as an oil (99 mg, 0.38 mmol, 89% yield). IR (KBr) ν (cm^{-1}) 3387, 1674, 1494, 1223, 1060. ^1H NMR ($CDCl_3$, 200 MHz) δ (ppm) 1.33 (t, J=7.2 Hz, 3H, CH_3); 3.58 (q, J=7.2 Hz, 2H, CH_2–N); 4.45 (s, 4H, CH_2–O); 7.49 (s, 1H, Ar); 7.56 (s, 1H, Ar); 7.95 (bs, 1H, NH); 9.47 (1s, 1H, H-8). ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ (ppm) 14.9 (CH_3); 34.3 (CH_2, CH_2–N); 64.2 and 64.3 (CH_2, C-2, C-3); 113.3 and 113.8 (CH, C-5, C-10); 136.8 (C, C-7); 140,6 and 141.8 (C, C-5a, C-9a); 141.9 (C, C-8); 147.7 and 148.4 (C, C-10a, C-4a); 163.4 (C, CO). Analysis calculated for $C_{12}H_{13}N_3O_3$: C, 58.29%; H, 5.30%; N, 16.99%. Found: C, 58.72%; H, 5.08%; N, 16.59%.

3.1.19. *N*-Ethyl-8-(1-(1-hydroxyethyl))-(2,3-dihydro-1,4-benzodioxino[2,3-*g*]quinoxalin-7-yl) carboxamide (21). The compound **21** was prepared from the carboxamide **20** following the same procedure described above for **19** from **18**. Under these conditions only was detected trace of **21**.

3.1.20. 3-Methyl-6,7-ethylenedioxi-1-oxofuro [3,4-*b*] quinoxaline (22). A solution of the hydroxyacid **19**

(100 mg, 0.36 mmol) in dry THF (6 mL) was added $ZnCl_2$, anhydrous, powder (99.999%) (58.9 mg, 0.43 mmol). The reaction mixture was stirred at room temperature for 24 h. Then the mixture was filtered and the corresponding residue was washed with a solution of NaOH 1N. The residue was purified by column chromatography (silica gel, hexane/ethyl acetate 8:2) and the desired lactone was obtained as a colourless oil (62 mg, 66%). IR (NaCl) ν (cm^{-1}) 1762, 1204. MS (EI): *m/z* (intensity) 258 (M, 20). ^1H NMR ($CDCl_3$+CD_3OD, 200 MHz) δ (ppm) 1.60 (d, J=6.2 Hz, 3H, CH_3); 4.42 (s, 4H, CH_2–O); 5.42 (q, J=6.2 Hz, 1H, CH–O); 7.45 (s, 1H, Ar); 7.47 (s, 1H, Ar). Analysis calculated for $C_{13}H_{10}N_2O_4$: C, 60.47%; H, 3.90%; N, 10.85%. Found: C, 60.05%; H, 3.68%; N, 10.56%.

3.1.21. Ethyl pyrido[2,3-*b*]pyrazin-2-carboxylate (23) and ethyl 1,2,3,4-tetrahydropyrido[2,3-*b*]pyrazin-3-carboxylate (25). 2,3-Diaminopyridine (500 mg, 4.58 mmol), anhydrous potassium carbonate (3.17 g, 22.94 mmol), and DMF (10 mL) were combined at room temperature. After, ethyl 2,3-dibromopropionate (2.4 g, 9.2 mmol) was added in twice for an hour. The reaction mixture was placed in an oil bath and heated to 60°C for 24 h. Upon cooling to room temperature the solvent was removed under vacuum and the resulting residue was poured into water an extracted with ether. The organic phase was dried over Na_2SO_4 and the solvent was evaporated to dryness. The crude of reaction was purified by column chromatography (ethyl acetate/hexane 30:70). The compounds **24** (36 mg, 2.5%) and **25** (170 mg, 10% yield) were obtained. The compound **24** (30 mg, 0.15 mmol) dissolved in CH_2Cl_2 (10 mL), was treated with DDQ (40 mg, 0.18 mmol). The reaction mixture was stirred at reflux temperature for 4 h. Then, the organic phase was treated with HCl 2N until acid pH, and extracted with CH_2Cl_2. After NaOH 2N was added and extracted with CH_2Cl_2 (3×10 mL) the last organic phase was dried and concentrated to give the crude product. The ^1H NMR of the crude of reaction is the same obtained by the compound **23**. Eluting with ethyl acetate 50:50 the pyrazine **23** was obtained as a yellow oil (367 mg, 20% yield). Compound **23**: IR (KBr) ν (cm^{-1}) 3356, 1727, 1558, 1198, 1024. MS (EI): *m/z* (intensity) 205 (M^{+2}, 100); 159 (82); 78 (35). ^1H NMR ($CDCl_3$, 500 MHz) δ (ppm) 1.39 (t, J=7 Hz, 3H, –CH_3); 4.43 (q, J=7 Hz, 2H, CH_2–O); 6.30 (dd, J_1=8 Hz, J_2=1 Hz, 1H, C8H); 6.64 (t, J=8 Hz, 1H, C7H); 7.54 (dd, J_1=8 Hz, J_2=1 Hz, 1H, C6H); 8.10 (s, 1H, C3H). ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ (ppm) 14.5 (CH_3, CH_3); 61.0 (CH_2, CH_2–O); 102.5 (CH, C8H); 115.1 (CH, C7H); 115.6 (CH, C6H); 118.0 (CH, C3H); 135.2 (C, C2); 136.7 (C, C8a); 140.0 (C, C4a); 163.3 (C, CO). Analysis calculated for $C_{10}H_9N_3O_2$: C, 59.11%; H, 4.46%; N, 20.68%. Found: C, 58.80%; H, 4.82%; N, 20.79%. Compound **25**: IR (KBr) ν (cm^{-1}) 3356, 1721, 1557, 1100. MS (EI): *m/z* (intensity) 207 (M^+, 10); 205 (78) 159 (95); 133 (100); 104 (42); 78 (65). ^1H NMR ($CDCl_3$, 200 MHz) δ (ppm) 1.86 (t, J=7 Hz, 3H, -CH_3); 3.84 (d, J=6.2 Hz, 1H, C2H); 3.94 (d, J=3.4 Hz, 1H, C2H); 4.15 (q, J=7.2 Hz, 2H, CH_2–O); 4.23 (d, J=6.2 Hz, 1H, C3H); 4.39 (bs, 1H, NH); 6.62 (dd, J_1=4.8 Hz, J_2=7.6 Hz, 1H, C7H); 6.83 (dd, J_1=7.6 Hz, J_2=1.4 Hz, 1H, C8H); 7.57 (dd, J_1=4.8 Hz, J_2=1.4 Hz, 1H, C6H). ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ (ppm) 13.1 (CH_3, CH_3); 46.8 (CH_2, CH_2–N); 51.6 (CH, CH–N); 59.9 (CH_2, CH_2–O); 115.1 (CH, C8H); 118.9 (CH, C7H); 127.0 (C, C8a); 136.2 (CH, C6); 140.9 (C, C4a); 169.8 (C, CO). Analysis calculated for $C_{10}H_{13}N_3O_2$ 1/2H_2O: C, 55.55%; H, 6.53%; N, 19.43%. Found: C, 55.89%; H, 6.32%; N, 19.07%.

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