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A new synthesis of 3-hydroxy-2,3-dihydro-1,4-benzodioxin-2-carboxamides and 3-aminomethylene-1,4-benzodioxin-2(3*H*)-one derivatives

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Abstract—The 1,4-benzodioxin-2-carboxylic esters or carboxamides react with nucleophilic amines to give access to 3-hydroxy-2,3-dihydro-1,4-benzodioxin-2-carboxamides and 3-aminomethyn-1,4-benzodioxin-2(3*H*)-one precursors of potential therapeutical compounds. The basic environment (K_2CO_3 or amine) facilitates the process.

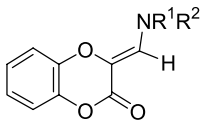
1. Introduction

2,3-Disubstituted-2,3-dihydro-1,4-benzodioxines represent a series of compounds of considerable medicinal importance.[1,2] This has generated increasing interest in the synthetic chemistry and the reactivity of this dioxygenated heterocyclic system.[3,4] However, the unsaturated system is still rare as a substructure of new medicinal compounds, and its reactivity offers interesting possibilities.

As part of a wide synthetic program aimed to study the therapeutical value of substituted 1,4-benzodioxins we required access to structures **A** and **B** which are not readily available (Fig. 1). Our interest in the biological activities of many 1,4-benzodioxines led us to seek a general expeditious route to 1,4-benzodioxine derivatives from a simple starting material.

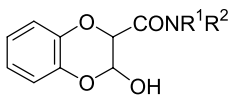
2. Chemistry

During investigations on the reactivity of 1,4-benzodioxine derivatives, we found that the reaction of the 1,4-benzodioxin-2-carboxylic acid **1**[5,6] with $SOCl_2$ and subsequent addition of the corresponding amine promoted the amide formation in good yields[7] (route A). Under tough conditions (route B) the behaviour of the benzodioxine acid was different and yielded a mixture of products: amides (**2**–**3**), lactones (**4**–**5**) and hydroxyamides (**6**–**7**) (see Scheme 1).



A

(*Z*)-3-*N*,*N*-Disubstitutedaminomethylene-1,4-benzodioxin-2(3*H*)-one



B

N,*N*-Disubstituted-3-hydroxy-2,3-dihydro-1,4-benzodioxin-2-carboxamide

Figure 1.

Keywords: 1,4-benzodioxin-2-carboxamides; 1,4-benzodioxin-2-carboxylic esters; 2,3-disubstituted-1,4-benzodioxines; Michael addition.

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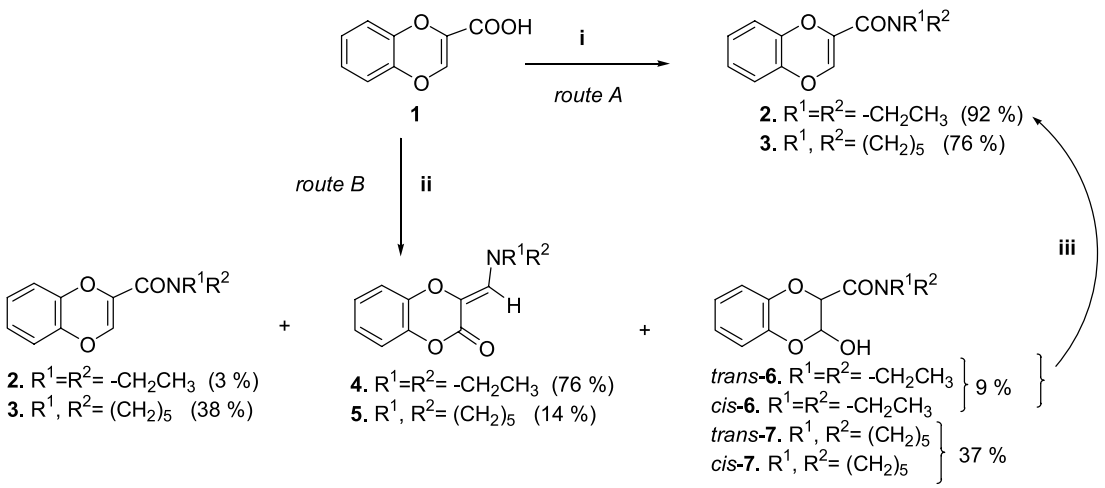


Scheme 1. *Reagents and conditions*: (i): (a) $SOCl_2$/toluene. (b) R^1R^2NH/toluene/reflux 4 h. (ii): (a) $SOCl_2$/toluene. (b) R^1R^2NH/toluene/reflux 24 h. (iii): (a) $SOCl_2$ (92%). (b) DBU, CH_2Cl_2 (94%).

The reported benzodioxines were identified by comparison of the NMR-data[8,9] and by interpretation of the interesting results furnished by the X-ray crystallography[10] of the lactone **5** and the *trans* hydroxyamide **6**. The ORTEP views of the two molecules are shown in Figures 2 and 3. The results indicate that the piperidine group is out of plane and confirm the assignment of the (*Z*)-isomer for the lactone **5** (Fig. 2).

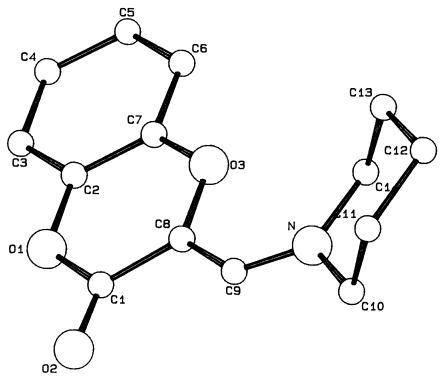


Figure 2. ORTEP drawing of **5**.

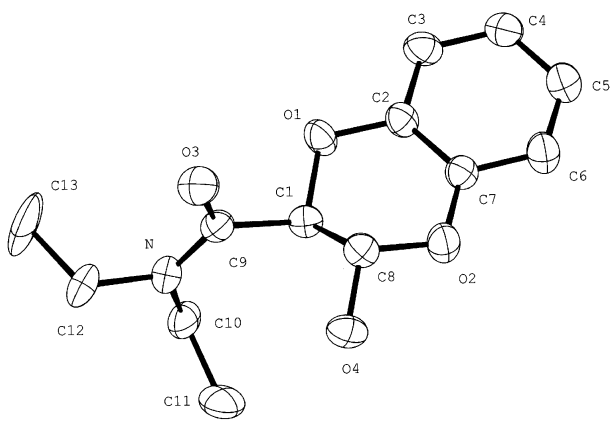
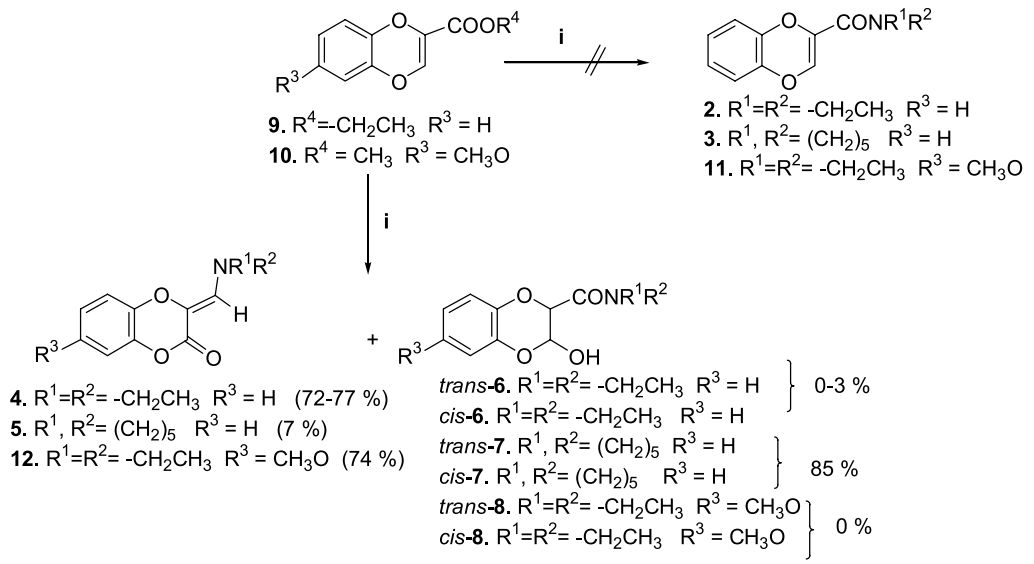


Figure 3. ORTEP drawing of *trans*-**6**.

In the ORTEP of the hydroxyamide **6**, the substituents of the C-2 and C-3 are in *trans* configuration (Fig. 3). The isomer *trans*-**6** in $CDCl_3$ undergoes isomerisation to the *cis*-**6** until obtaining a mixture of *cis* and *trans* diastereoisomers in a ratio about 1:1, whereas in DMSO solution isomerisation was not observed. The major geometrical isomer of **6** was assigned to have the *trans* configuration based on an X-ray crystallographic analysis. Also **7** obtained from the amide **3** was assigned as *trans* by comparison of the chemical shifts in ^1H NMR spectroscopy. Isolation of each isomer (above 99% purity) was achieved by recrystallization with lower yield. Moreover, mixtures of the two isomers of which ratios were determined by the integrated values of ^1H NMR were obtained. In addition, a mixture of both *cis* and *trans* **6** was treated with $SOCl_2$, and the corresponding 2-chloro-carboxamide was obtained in good yield. The chloro derivative, as expected, was more reactive than the corresponding hydroxyamide, and the treatment with DBU resulted in complete transformation to the amide **2**. The results are summarized in Scheme 1.

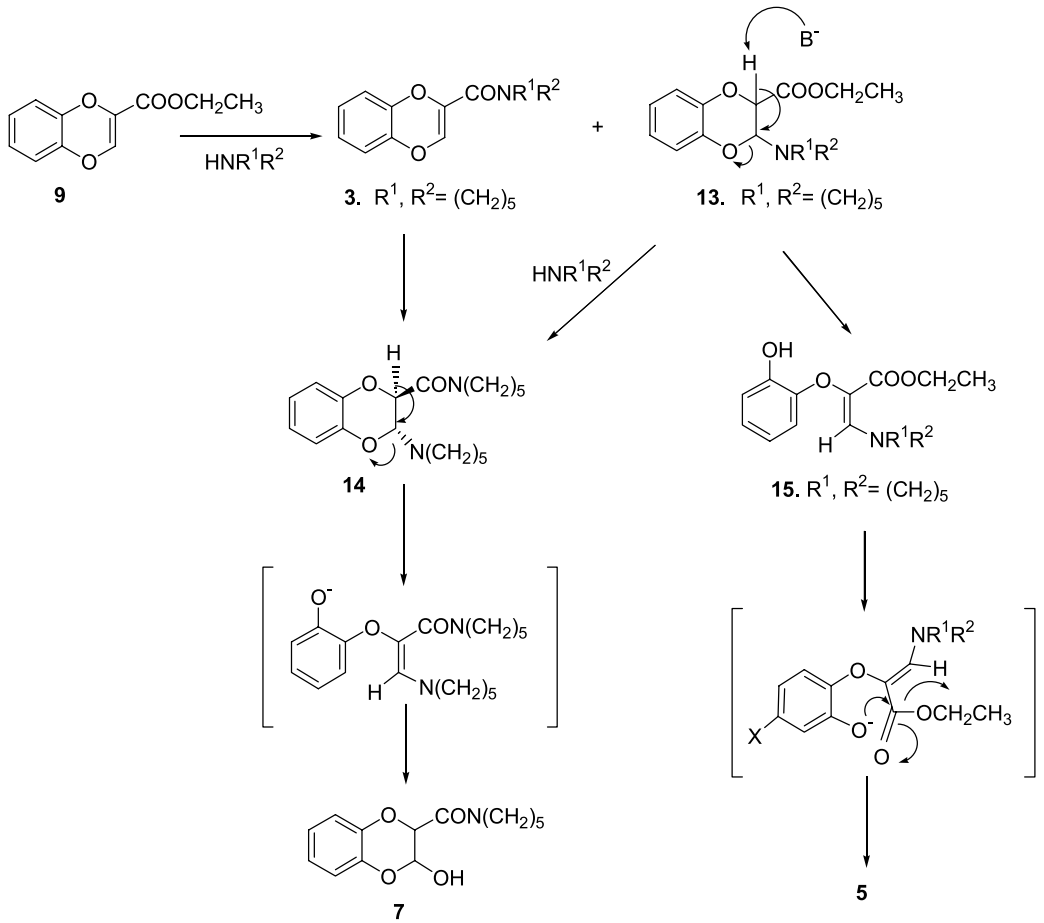
With these results in hand, it was deemed appropriate to investigate the reaction of the ester (**9** and **10**) with the corresponding amine.[11,12] The treatment of **9** and **10** with a secondary amine in toluene at reflux temperature, under the presence of DCC (dicyclohexylcarbodiimide) and K_2CO_3, does not give the expected amides (**2**, **3** or **11**) but provide a mixture of the lactones (**4**, **5** or **12**) and the hydroxyamides (**6** or **7**) in variable ratios, depending of the amine used (Scheme 2). The results are of some interest, and the compounds obtained can be considered as useful precursors for the synthesis of potential medicinal agents.

The lactone **4** was obtained as the major product when the ester **9** was treated with diethylamine, whereas the treatment with piperidine provided only a trace of the corresponding lactone and for the most part a mixture of the *cis* and *trans*-hydroxyamides (**7**). Other attempts on the ester **9** confirmed the formation of the lactone **4** as the major product (72–77% yield), and provided interesting conclusions: (a) these products were obtained in the presence or absence of DCC and K_2CO_3. (b) In absence of the Dean–Stark collector, the lactone **4** was obtained in good yields. Also of interest is the

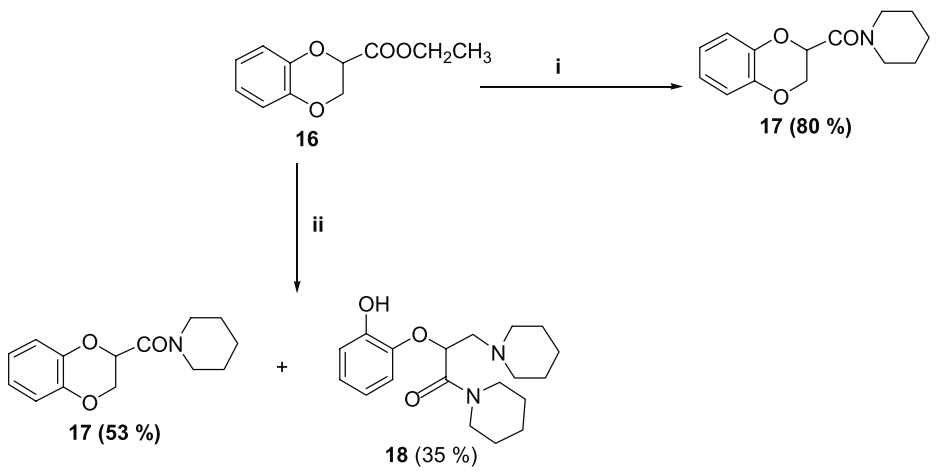


Scheme 2. Reagents and conditions: (i): R^1R^2NH/K_2CO_3/DCC/toluene/reflux 4 h.

stability showed by the hydroxyamides (**6** and **7**). The reactions were also performed from the ester **10**, and the behaviour was the same as that of **9**. We have attempted to explain the formation of the obtained compounds and found that different pathways were involved. The presence of a base in the medium of this reaction and the existence of the proton (H) on α-position of the carbonyl group led us to postulate a previous Michael addition of the amine to the ester (intermediate **13**) or to the amide (intermediate **14**). Additionally, the base attack at the α-position on the aminoamide **14**, the heterocyclic ring is opened and the resulting phenoxide anion drives to the corresponding



Scheme 3.



Scheme 4. Reagents and conditions: (i): $HN(CH_2)_5$/toluene/reflux 15 days. (ii): $HN(CH_2)_5$, DCC, K_2CO_3 /toluene/reflux 40 h.

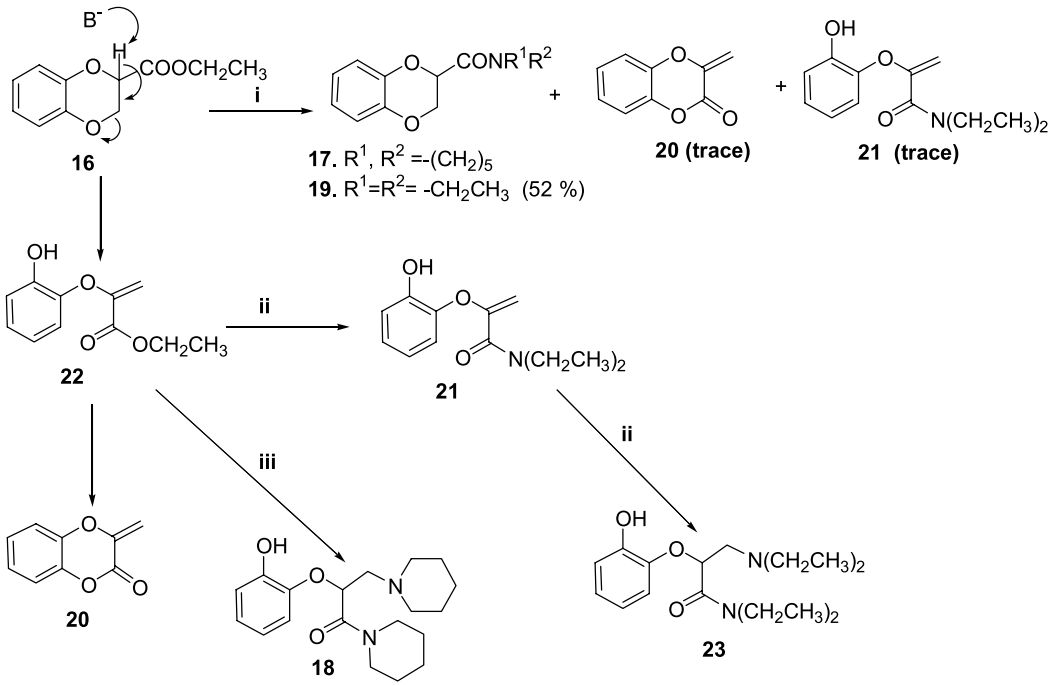
hydroxyamide **7** by a favourable cyclization process. The hydroxyamides **6** and **8** were obtained in the same way from the appropriate aminoamide.

The basic medium involved the formation of the phenoxide anion generated in situ followed by an intramolecular transesterification giving the corresponding lactone (**4** or **5**).

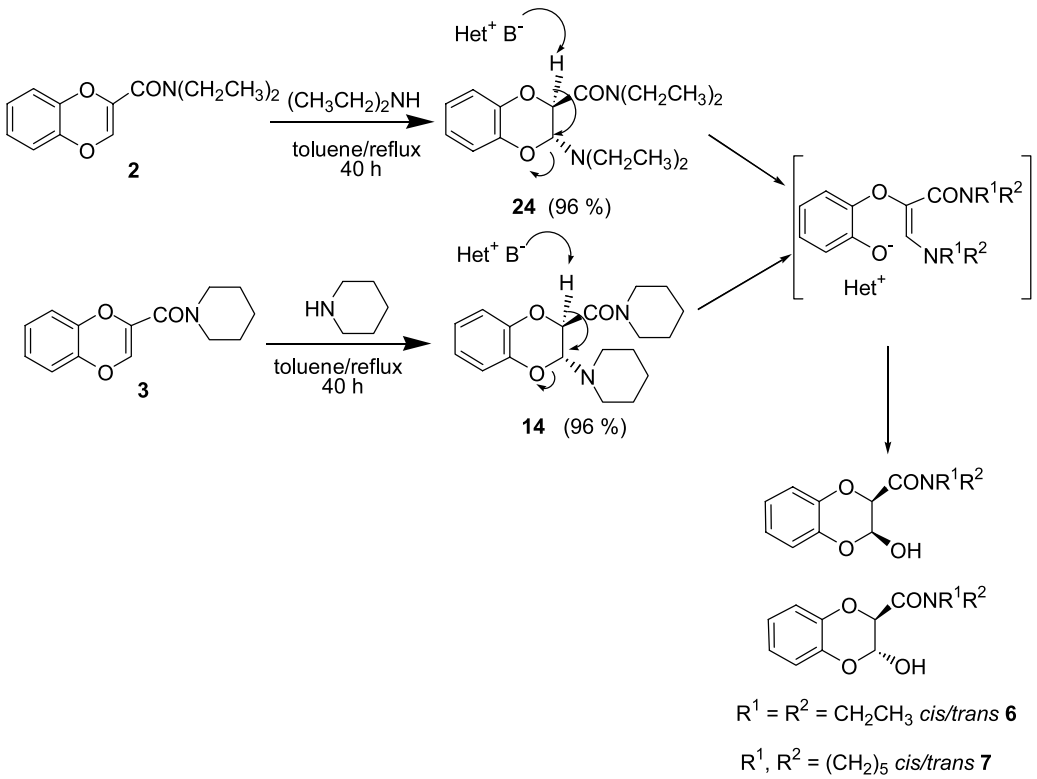
The preparation of the compounds reported here appears to be the first direct conversion of the carboxylic acid, amides or esters containing the 1,4-benzodioxine subunit into the lactones or hydroxyamides. The structures assigned to these compounds are consistent with their analytical data. Several conclusions may be drawn from the results. First, the formation of the aminoester **13** is fully consistent with a Michael addition of the amine to the α,β-unsaturated ester.

The geometry of the lactones (**4**, **5**, and **12**) has been established on the basis of the NMR data and the X-ray crystallographic analysis.

The treatment of **9** with piperidine allows the isolation of the hydroxyamide **7** as the main product and only a trace of the lactone **5** was observed (Scheme 3). At the same time, the reactivity of **9** with dimethylamine afforded the lactone **4**, preponderantly (Scheme 2). The formation of one or another product can be attributed to the structure of the amine used. In the case of diethylamine, the principal compound found was the lactone **4** attributed to the more hindered dimethylamino group, which hinders the attack on the intermediate enamine that should give the corresponding hydroxyamide. When the reaction was performed under the same conditions but during shorten time (<15 h) the



Scheme 5. Reagents and conditions: (i): for **17** $HN(CH_2)_5$/toluene/reflux 15 days. For **19** $(CH_3CH_2)_2NH$, DCC, K_2CO_3/toluene/reflux 6 days. (ii): $(CH_3CH_2)_2$-NH, DCC, K_2CO_3/toluene/reflux. (iii): $HN(CH_2)_5$, DCC, K_2CO_3/toluene/reflux.



Scheme 6.

aminoester **13** and the aminophenol **15** have been isolated and analyzed by NMR. The finding of these intermediates confirms the proposed mechanism.

In order to understand this reactivity with 1,4-benzodioxine derivatives, some experiments were carried out on the saturated ester **16** (Scheme 4). In fact, reactivity of the ester **16**, in basic media, has been studied but the conditions are different to our work.[13–15]

The treatment of **16** with piperidine led to the amide **17** in a good yield in absence of DCC/K_2CO_3. Usage of DCC and K_2CO_3 decreased the formation of the amide **17** and the aminoamide **18** was obtained with a 35% yield. Usage of *N*,*N*-diethylamine as a nucleophile, gave a mixture of compounds that contained the amide **19** as the main product. Under the same conditions but without DCC and K_2CO_3 the reaction was unsuccessful after 7 days. The formation of the hydroxyamide **18** and **23** suggests a reasonable mechanism for this synthetic path (Scheme 5).

This reaction proceeds via an initial attack on the proton at the α-ester or α-amide position followed by the cleavage of the 1,4-benzodioxin ring. This proposed mechanism was supported by obtaining the intermediates **18**, **20**, and **23**. Furthermore, we observed that the phenol **22** by trans-esterification may give the lactone **20**. The aminoamide **23** can be formed by Michael addition of diethylamine to the intermediate amide (**21**) or Michael addition and amidification of the ester (**22**).

In this work only traces of the lactone **20** were obtained by transesterification of the hydroxyester **22**, obtained from the ester **16**. The lactone **20** was unstable but this structure is consistent with NMR signals obtained. The lactone **20** was previously reported by Chapleo and co.[13] and later by Rosnati.[15] Both of them described **20** as a by-product in the synthesis of 2,3-dihydro-1,4-benzodioxine derivatives. The ethylene lactone (3-ethylidino-2-oxo-1,4-benzodioxane) analogue of **20** has been reported only once[10] and its preparation involved the reaction of α-halo Michael acceptors with catechol. The yield was rather low about 18%.

Specific experiments carried out with the amide **2** and **3** showed that the unsaturated amides are Michael acceptors[16] and the addition of the amine over the enol ether goes before the ring cleavage and the formation of the lactones. The amine in toluene (aprotic solvent) enters at the 3rd position of the 1,4-benzodioxine ring by a *trans* antiparallel attack and only then the corresponding *trans*-aminoamide was isolated in quantitative yield (Scheme 6).

The pure product is quite stable and can be stored in a cold place for several weeks without decomposition. The aminoamides **14** and **24** were transformed into a mixture of *cis*/*trans* hydroxyamides (**6**–**7**) (Scheme 6). In this attempt, the corresponding lactone was not detected because the amide is less reactive than the ester group (postulated as intermediate in the explained reactivity of the ester **16**, Scheme 5).

Our preparation of the lactones and hydroxyamides represents the first synthesis of these compounds from the corresponding unsaturated carboxylic acid or ester. Further studies of the reactivity of the 1,4-benzodioxin derivatives are currently underway and will be reported in due course.

3. Experimental

3.1. General

Melting points were obtained on an MFB-595010M Gallenkamp apparatus in open capillary tubes and are uncorrected. IR spectra were obtained using a FTIR Perkin–Elmer 1600 Infrared Spectrophotometer. Only noteworthy IR absorptions are listed (cm^{-1}). ^1H and ^{13}C NMR spectra were recorded on a Varian Gemini-200 (200 and 50.3 MHz, respectively) or Varian Gemini-300 (300 and 75.5 MHz) instrument using $CDCl_3$ as solvent with tetramethylsilane as internal standard or $(CD_3)_2CO$. Other ^1H NMR spectra and heterocorrelation $^1H-^{13}C$ (HMQC and HMBC) experiments were recorded on a Varian VXR-500 (500 MHz). Mass spectra were recorded on a Helwett-Packard 5988-A. Microanalysis were determined on a Carlo Erba-1106 analyser. All reagents were of commercially quality or were purified before use. Organic solvents were of analytical grade or were purified by standard procedures.

3.1.1. *N,N*-Diethyl-1,4-benzodioxin-2-carboxamide (2) from 1. In a 250 mL flask, provided with a condenser and a magnetic spin bar was placed the carboxylic acid **1** (3.00 g, 16.8 mmol) dissolved in dry toluene (100 mL). $SOCl_2$ (3.70 mL, 51.0 mmol) was added at 0°C, and the mixture was heated at reflux during 4 h. The mixture was then cooled and the solvent and $SOCl_2$ excess were evaporated to. Without further purification the obtained residue dissolved in toluene (70 mL) was treated with diethylamine (4.36 mL, 42.0 mmol) and heated at reflux overnight. The mixture was then cooled, the solvent evaporated and the residue extracted with ethyl acetate (150 mL). The organic layer was washed with saturated Na_2CO_3 (15 mL), then with water (15 mL), and finally dried with sodium sulfate. Evaporation of the solvent followed by silica gel column chromatography of the crude product with hexane/ethyl acetate (88/12) gave the amide **2** (3.62 g, 15.5 mmol, 92% yield) as a yellow oil. IR (KBr) υ (cm^{-1}), 1628, 1621, 1245. ^1H NMR (500 MHz, $CDCl_3$), δ (ppm), 1.20 (t, J=7 Hz, 6H, CH_3); 3.41 (q, J=7 Hz, 4H, $-CH_2$); 6.59 (s, 1H, CH); 6.66 (m, 2H, H-arom), 6.84 (m, 2H, H-arom). ^{13}C NMR (50.3 MHz, $CDCl_3$), δ (ppm), 13.5 (CH_3); 41.7 (CH_2); 116.1 and 116.3 (C-5 and C-8); 124.5 and 124.6 (C-6 and C-7); 131.9 (C-3); 133.5 (C-2); 141.6 (C-4a); 141.9 (C-8a); 161.9 (CO). Anal. Calcd for $C_{13}H_{15}NO_3$: C, 66.94%; H, 6.48%; N, 6.00%. Found: C, 66.64%; H, 6.25%; N, 5.59%.

3.1.2. *N,N*-Diethyl-1,4-benzodioxin-2-carboxamide (2). A 50 mL, two necked flask, provided with a rubber septum, argon gas inlet and outlet, and magnetic spin bar, was charged with 278 mg (1.1 mmol) of a diastereoisomeric mixture of alcohol *trans*-**6** and *cis*-**6** in a ratio 3:2 (^1H NMR) in dry CH_2Cl_2 (10 mL) and cooled to −78°C by mean of a dry ice bath. Into this solution was first syringed triethylamine (0.61 mL, 4.42 mmol) and then mesyl chloride (0.12 mL, 1.55 mmol) in CH_2Cl_2 (2 mL). The mixture was stirred at −78°C for 3 h and was then brought to room temperature, and quenched with 1N HCl solution (5 mL). The organic layer was separated and the aqueous phase was extracted with CH_2Cl_2 (3×10 mL). The organic extracts were washed with 2N NaOH solution, then with water and dried. Rotoevaporation of the solvent afforded this crude product (309 mg). Silica gel chromatography of the crude product, eluting with hexane/ethyl acetate (90/10), gave the pure *cis*-2-chloro-*N,N*-diethyl-2,3-dihydro-1,4-benzodioxin-2-carboxamide (276 mg, 92% yield). This compound was unstable in solution, confirmed by ^1H NMR spectra and reverts to the hydroxyamide **6**.

3.1.3. *cis*-3-Chloro-*N,N*-diethyl-2,3-dihydro-1,4-benzodioxin-2-carboxamide. IR (KBr) υ (cm^{-1}), 3256, 1616, 1230. ^1H NMR (500 MHz, $CDCl_3$), δ (ppm), 1.11 (t, J=7 Hz, 6H, CH_3); 1.26 (t, J=7 Hz, 3H, CH_3); 3.25 (m, 1H, CH_2-); 3.43 (m, 2H, CH_2-); 3.55 (m, 1H, CH_2-); 4.97 (d, J=2.5 Hz, 1H, H-2); 6.63 (d, J=2.5 Hz, 1H, H-3); 6.97 (m, 4H, H-arom). ^{13}C NMR (50.3 MHz, $CDCl_3$), δ (ppm), 12.3 (CH_3); 14.3 (CH_3); 40.3 (CH_2); 41.8 (CH_2); 74.0 (C-2); 83.9 (C-3); 116.8 and 117.9 (C-5 and C-8); 122.5 and 123.3 (C-6 and C-7); 138.8 and 140.6 (C-4a and C-8a); 164.6 (CO). MS (EI), *m/z* (%): 271 (4); 269 (12); 234 (32); 161 (29); 100 (100); 72 (88).

In a 50 mL flask, provided with a rubber septum, argon inlet and outlet, and magnetic stirring, were added the chloro derivative (309 mg, 26.6 mmol) in dry CH_2Cl_2 (10 mL) and DBU (0.66 mL, 4.42 mmol) and this mixture was stirred at room temperature for 5 days. CH_2Cl_2 (15 mL) was added and the organic layer was washed first with 1N HCl solution and then with water. The organic phase was dried and con-centrated to give a residue, which was purified by column chromatography on silica gel. Eluting with hexane/ethyl acetate (88/12) yielded the amide **2** as a yellow oil (242 mg, 1.04 mmol, 94% yield). This compound was identified by ^1H NMR and ^{13}C NMR as described above.

3.1.4. *N,N*-Pentamethylen-1,4-benzodioxin-2-carboxamide (3). Into a flask provided with a magnetic stirrer and a dropping funnel was placed the carboxylic acid (**1**) (3.00 g, 16.8 mmol) dissolved in 100 mL of dry toluene. $SOCl_2$ (3.70 mL, 51.0 mmol) was added at 0°C and the mixture was heated at reflux for 4 h. The mixture was then cooled and the solvent and excess of $SOCl_2$ was evaporated. Without further purification the residue was dissolved in toluene (70 mL), treated with piperidine (4.16 mL, 42.0 mmol), and heated at reflux overnight. The mixture was then cooled, the solvent evaporated and the residue extracted with ethyl acetate (150 mL). The organic layer was washed with saturated Na_2CO_3 solution (15 mL) and with water (15 mL), and dried with sodium sulfate. Rotoevaporation of the solvent, followed by silica gel chromatography of the crude product with hexane/ethyl acetate (88/12) gave the amide **3** (3.62 g, 15.5 mmol, 92% yield) as a yellow oil. IR (KBr) υ (cm^{-1}), 1682, 1633, 1244, 1102. ^1H NMR (200 MHz, $CDCl_3$), δ (ppm), 1.64 (m, 6H, CH_2-); 3.58 (m, 4H, CH_2-); 6.56 (s, 1H, H-3); 6.71 (m, 2H, H-5, H-8), 6.88 (m, 2H, H-6, H-7). ^{13}C NMR (50.3 MHz, $CDCl_3$), δ (ppm), 24.4 (CH_2); 25.9 (CH_2); 45.8 (CH_2); 116.2 (C-5 and C-8); 124.6 (C-6 and C-7); 131.7 (C-3); 132.9 (C-2); 141.5 (C-4a); 141.9 (C-8a); 161.3 (CO). MS (EI), *m/z* (%): 245 (62); 218 (6); 161 (52); 136 (100). Anal. Calcd for $C_{14}H_{15}NO_3$: C, 68.56%; H, 6.16%; N, 5.71%. Found: C, 68.24%; H, 6.36%; N, 5.37%.

3.1.5. *N,N*-Pentamethylen-1,4-benzodioxin-2-carboxamide (3). (*Z*)-3-(Piperidinomethyl)-1,4-benzodioxin-2(3*H*)-one (5). *cis* and *trans*-*N,N*-pentamethylen-3-hydroxy-2,3-dihydro-1,4-benzodioxin-2-carboxamide (7). These compounds were prepared according the above procedure starting with 3 g (16.8 mmol) of the carboxylic acid **1** and refluxing (after the addition of the piperidine) during 120 h, affording a mixture of compounds (4.5 g). The residue was purified by column chromatography (silica gel, hexane/ethyl acetate). Eluting with hexane/ethyl acetate (84/16) gave the pure lactone **5** as a white solid (570 mg, 2.32 mmol, 14% yield). Mp=94–96°C (CH_2Cl_2). Eluting with hexane/ethyl acetate (80/20) the amide **3** was obtained as a yellow oil that solidified (1.59 g, 6.48 mmol, 38% yield). Mp=82–84°C (reported[17] 88–89°C (ether)). Finally, eluting with ethyl acetate 100% gave a mixture of the *trans*, *cis*-hydroxyamides **7** as a yellow oil (1.66 g, 6.30 mmol, 37% yield) in a 1.2:1 ratio (*trans*, *cis*) (analyzed by ^{1}H NMR). The stereochemistry of the lactone **5** was assigned from the results of X-ray diffraction of a crystal formed by recrystallisation process.

*(Z)-3-(Piperidinomethyl)-1,4-benzodioxin-2(3H)-one (**5**).* IR (KBr) υ (cm^{-1}), 1720, 1626, 1601, 1270, 1179. ^{1}H NMR (500 MHz, $CDCl_3$), δ (ppm), 1.64 (bs, 6H, CH_2–); 3.56 (bs, 4H, CH_2–); 6.85 (s, 1H, CH=); 6.86–6.95 (m, 4H, H-arom). ^{13}C NMR (50.3 MHz, $CDCl_3$), δ (ppm), 23.9 (C-4′); 26.1 (C-3′ and C-5′); 52.0 (C-2′ and C-6′); 113.8 (C-3); 115.2 and 116.9 (C-5 and C-8); 122.4 and 124.1 (C-6 and C-7); 133.0 (=CH); 140.3 (C-4a); 141.1 (C-8a); 159.9 (CO). MS (EI), *m/z* (%): 245 (19); 218 (7); 163 (9); 123 (24); 95 (100). Anal. Calcd for $C_{14}H_{15}NO_3$: C, 68.56%; H, 6.16%; N, 5.71%. Found: C, 68.64%; H, 6.25%; N, 5.57%.

trans-N,N-Pentamethylen-3-hydroxy-2,3-dihydro-1,4-benzodioxin-2-carboxamide (7). IR (KBr) υ (cm^{-1}), 3258, 1633, 1265, 1132. ^{1}H NMR (300 MHz, $CDCl_3$), δ (ppm), 1.57 (bs, 6H, CH_2–); 1.65 (bs, 4H, CH_2–); 3.49 (m, 2H, H_{ax}); 3, 69 (m, 2H, H_{eq}); 4.57 (d, J=5.6 Hz, 1H, H-2); 5.61 (d, J=5.6 Hz, 1H, H-3); 6.04 (s, 1H, OH); 6.91 (m, 4H, H-arom). ^{13}C NMR (75.5 MHz, $CDCl_3$), δ (ppm), 24.3 (C-3′); 25.4 (C-4′); 26.4 (C-5′); 43.4 (C-2′); 46.9 (C-6′); 72.2 (C-2); 90.4 (C-3); 116.6 and 117.4 (C-5 and C-8); 121.5 and 122.3 (C-6 and C-7); 141.5 (C-8a); 141.6 (C-4a); 165.0 (CO). MS (EI), *m/z* (%): 263 (10); 245 (15); 154 (17); 138 (100). Anal. Calcd for $C_{14}H_{17}NO_4$: C, 63.87%; H, 6.51%; N, 5.32%. Found: C, 63.92%; H, 6.88%; N, 5.78%.

cis-N,N-Pentamethylen-3-hydroxy-2,3-dihydro-1,4-benzodioxin-2-carboxamide (7). IR (KBr) υ (cm^{-1}), 3264, 1628, 1259, 1131. ^{1}H NMR (300 MHz, $CDCl_3$), δ (ppm), 1.58 (bs, 2H, CH_2–); 1.67 (bs, 4H, CH_2–); 3.43 (m, 1H, H_{ax}); 3, 51 (m, 1H, H_{ax}); 3.71 (m, 2H, H_{eq}); 4.76 (d, J=1.6 Hz, 1H, H-2); 5.64 (bs, 2H, H-3 and OH); 6.92 (m, 4H, H-arom). ^{13}C NMR (75.5 MHz, $CDCl_3$), δ (ppm), 24.3 (C-3′); 25.4 (C-4′); 26.4 (C-5′); 43.4 (C-2′); 46.8 (C-6′); 71.1 (C-2); 89.5 (C-3); 116.8 and 117.8 (C-5 and C-8); 121.8 and 122.7 (C-6 and C-7); 140.9 (C-8a and C-4a); 165.5 (CO). MS (EI), *m/z* (%): 263 (18); 245 (23); 151 (9); 138 (100). Anal. Calcd for $C_{14}H_{17}NO_4$: C, 63.87%; H, 6.51%; N, 5.32%. Found: C, 63.41%; H, 6.80%; N, 5.37%.

3.1.6. (*Z*)-3-(Diethylaminomethyn)-1,4-benzodioxin-2(3*H*)-one (4). *trans* and *cis*-*N,N*-diethyl-3-hydroxy-2,3-dihydro-1,4-benzodioxin-2-carboxamide (6). These compounds were prepared according to the above procedure starting from 2.50 g (14.0 mmol) of the acid, except the reaction times that was prolonged to 60 h, isolating 3.1 g of a mixture of compounds. The residue chromatographed on silica gel, eluting with hexane/ethyl acetate (88/12) gave the amide **2** (3%). Eluting with hexane/ethyl acetate (80/20) gave the lactone **4** (2.49 g, 10.7 mmol, 76% yield), and eluting with ethyl acetate 100% the yellow oil corresponding to a mixture of diastereoisomers *trans* and *cis*-**6** (320 mg, 1.27 mmol, 9% yield) in a ratio 3:2 (analyzed by ^{1}H NMR). The mixture of diastereoisomers was purified by recrystallisation (ether/ethyl acetate) and the crystals obtained were analysed by RX-crystallography. Mp=97–98°C. The crystallised compound was the *trans*-**6** whereas the major compound of the evaporated mother water was the *cis*-**6** isomer.

*(Z)-3-(Diethylaminomethyn)-1,4-benzodioxin-2(3H)-one (**4**).* IR (KBr) υ (cm^{-1}), 1719, 1625, 1601, 1252, 1170. ^{1}H NMR (300 MHz, $CDCl_3$), δ (ppm), 1.26 (t, J=7.1 Hz, 6H, CH_3); 3.44 (q, J=7.7 Hz, 4H, H-2); 6.84–7.00 (m, 4H, H-arom); 6.91 (s, 1H, CH=). ^{13}C NMR (75.5 MHz, $CDCl_3$), δ (ppm), 14.4 (CH_3); 47.7 (CH_2); 113, 7 (C-3); 115.0 and 116.6 (C-5 and C-8); 122.1 and 124.0 (C-6 and C-7); 132.6 (CH=); 140.4 and 141.3 (C-4a) C-8a); 159.8 (CO). MS (EI), *m/z* (%): 223 (100); 118 (58); 204 (16); 190 (31). Anal. Calcd for $C_{13}H_{15}NO_3$: C, 66.94%; H, 6.48%; N, 6.00%. Found: C, 66.91%; H, 6.55%; N, 6.02%.

*trans-N,N-Diethyl-3-hydroxy-2,3-dihydro-1,4-benzodioxin-2-carboxamide (**6**).* IR (KBr) υ (cm^{-1}), 3272, 1634, 1260, 1156, 1145. ^{1}H NMR (300 MHz, $CDCl_3$), δ (ppm), 1.17 (t, J=7.1 Hz, 3H, CH_3); 1.26 (t, J=7.1 Hz, 3H, CH_3); 3.46 (m, 4H, CH_2); 4.48 (d, J=6.2 Hz, 1H, H-2); 5.59 (d, J=6.2 Hz, 1H, H-3); 5.97 (bs, 1H, OH); 6.90 (m, 4H, H-arom). ^{13}C NMR (75.5 MHz, $CDCl_3$), δ (ppm), 12.6 (CH_3); 14.5 (CH_3); 41.0 (CH_2); 42.2 (CH_2); 72.2 (C-2); 90.7 (C-3); 116.6 and 117.4 (C-5 and C-8); 121.4 and 122.2 (C-6 and C-7); 141.6 and 141.8 (C-4a) and C-8a); 166.4 (CO). MS (EI), *m/z* (%): 251 (26); 233 (49); 222 (9); 100 (74); 72 (100). Anal. Calcd for $C_{13}H_{17}NO_4$: C, 62.14%; H, 6.82%; N, 5.57%. Found: C, 62.12%; H, 7.08%; N, 5.59%.

*cis-N,N-Diethyl-3-hydroxy-2,3-dihydro-1,4-benzodioxin-2-carboxamide (**6**).* IR (KBr) υ (cm^{-1}), 3273, 1634, 1260, 1156. ^{1}H NMR (300 MHz, $CDCl_3$), δ (ppm), 1.17 (t, J=7.1 Hz, 3H, CH_3); 1.28 (t, J=7.1 Hz, 3H, CH_3); 3.46. (m, 4H, CH_2); 4.72 (d, J=1.5 Hz, 1H, H-2); 5.67 (d, J=1.5 Hz, 1H, H-3); 5.82 (bs, 1H, OH); 6.90 (m, 4H, H-arom). ^{13}C NMR (75.5 MHz, $CDCl_3$), δ (ppm), 12.4 (CH_3); 14.3 (CH_3); 40.7 (CH_2); 42.0 (CH_2); 71.2 (C-2); 89.2 (C-3); 116.7 and 117.8 (C-5 and C-8); 121.7 and 122.5 (C-6 and C-7); 140.6 and 141.4 (C-4a) and C-8a); 166.5 (CO). MS (EI), *m/z* (%): 251 (26); 233 (53); 222 (9); 100 (72); 72 (100). Anal. Calcd for $C_{13}H_{17}NO_4$: C, 62.14%; H, 6.82%; N, 5.57%. Found: C, 62.16%; H, 7.20%; N, 5.82%.

3.2. Preparation of the lactone 4 and the hydroxyamide 6 from the ester 9

To a solution of the ester **9** (900 mg, 4.36 mmol) in dry

toluene (40 mL) was added dropwise over 10 min at room temperature diethylamine (4.50 mL, 43.4 mmol), K_2CO_3 (610 mg, 4.41 mmol) and DCC (catalytic amount). Upon addition the mixture was heated at reflux. After 62 h, the mixture was cooled and additional diethylamine (5 mL, 48.2 mmol) and DCC (catalytic amount) were added and the reaction mixture was heated 24 h. Then, the mixture was extracted with ether, the organic phase was evaporated and the obtained residue was purified by column chromatography on silica gel. Elution with hexane/ethyl acetate (85/15) gave the lactone **4** (764 mg, 3.28 mmol, 75% yield) as a yellow oil which solidified (mp 39–41°C. Elution with ethyl acetate (100%) gave the hydroxyamide **6** (32 mg, 0.13 mmol, 3% yield) as a colourless oil, as a mixture of *trans*-**6** and *cis*-**6** diastereoisomers in a 3.5:2 ratio (analysed by ^{1}H NMR spectrum).

3.2.1. (*Z*)-3-Piperidinomethyn-1,4-benzodioxin-2(3*H*)-one (5). *cis* and *trans*-*N*,*N*-Pentamethylen-3-hydroxy-2,3-dihydro-1,4-benzodioxin-2-carboxamide (7). To a solution of the ester **9** (540 mg, 2.62 mmol) in dry toluene (30 mL), piperidine (2.60 mL, 26.3 mmol), K_2CO_3 (362 mg, 2.62 mmol) and DCC (catalytic amount) were added and the mixture was heated at reflux for 24 h. Then the solution was cooled and while stirring the diethylamine (2.60 mL, 26.3 mmol) and DCC (catalytic amount) were added and the reflux was continued during 72 h. To the residue 15 mL of water were added, extraction with ether (3×20 mL), washing the combined organic extracts with water, drying, and rotoevaporation of the solvents afforded the crude products. Silica gel chromatography of the residue, eluting with hexane/ethyl acetate (85/15) gave the pure lactone **5** (46 mg, 7%), and eluting with a hexane/ethyl acetate (70/30) gave a mixture of *cis*/*trans* diastereoisomers **7** (586 mg, 85% yield) in a 1:1 ratio (analyzed by ^{1}H NMR). When the reaction was repeated under the same conditions but only for 15 h a pure sample of the aminoester **13** and the aminophenol **15** was obtained.

*Ethyl 3-piperidino-2,3-dihydro-1,4-benzodioxin-2-carboxylate (**13**).* IR (KBr) υ (cm^{-1}), 1658, 1230, 1100. ^{1}H NMR (300 MHz, $CDCl_3$), δ (ppm), 1.34 (t, J=7.1 Hz, 3H, CH_3); 1.45–1.65 (m, 6H, H-3′, H-4′, and H-5′); 2.76 (m, 2H, H_{ax}); 2.96 (m, 2H, H_{eq}); 4.31 (q, J=7.1 Hz, 2H, OCH_2); 4.60 (d, J=7 Hz, 1H, H-2); 4.70 (d, J=7 Hz, 1H, H-3); 6.85 (m, 4H, H-arom). ^{13}H NMR (75.5 MHz, $CDCl_3$), δ (ppm), 14.1 (CH_3); 24.0 (CH_3); 25.8 (CH_2); 48.9 (CH_2); 61.2 (O–CH_2); 73.3 (C-2); 90.2 (C-3); 115.4 and 115.8 (C-5 and C-8); 120.8 and 121.8 (C-6 and C-7); 143.1 (C-1′); 141.5 (C-4a); 143.0 (C-8a); 167.4 (CO). MS (EI), *m*/*z* (%): 291 (15); 245 (13); 183 (33); 154 (100). Anal. Calcd for $C_{16}H_{21}NO_4$: C, 65.96%; H, 7.27%; N, 4.81%. Found: C, 66.14%; H, 7.65%; N, 5.27%.

*Ethyl 2-(2-hydroxyphenoxy)-3-piperidinoacrylate (**15**).* IR (KBr) υ (cm^{-1}), 3490, 1645, 1210, 1108. ^{1}H NMR (300 MHz, $CDCl_3$), δ (ppm), 1.17 (t, J=7.1 Hz, 3H, CH_3); 1.45–1.65 (m, 6H, CH_2–); 3.45 (m, 4H, CH_2–); 4.12 (q, J=7.1 Hz, 2H, OCH_2); 6.40 (bs, 1H, OH); 6.75–6.95 (m, 4H, H-arom); 7.11 (s, 1H, H-3). ^{13}H NMR (75.5 MHz, $CDCl_3$), δ (ppm), 14.1 (CH_3); 23.7 (CH_2); 25.9 (CH_2); 51.1 (CH_2); 59.6 (O–CH_2); 116.8 (C-3′); 119.7 (C-5′); 121.6 (C-6′); 122.2 (C-2); 122.8 (C-4′); 137.8 (C-3); 146.4 (C-1′); 146.7 (C-2′); 166.0 (CO). MS (EI), *m*/*z* (%): 291 (23); 154 (100). Anal. Calcd for $C_{16}H_{21}NO_4$: C, 65.96%; H, 7.27%; N, 4.81%. Found: C, 66.30%; H, 6, 88%; N, 4.45%.

3.2.2. *trans N*,*N*-Pentamethylen-3-piperidino-2,3-dihydro-1,4-benzodioxin-2-carboxamide (14). To a stirred solution of the amide **3** (185 mg, 0.75 mmol) in acetonitrile (10 mL) was added piperidine (1.50 mL, 15.2 mmol) under argon atmosphere. The reaction mixture was stirred for 40 h at reflux, and then was cooled to room temperature. Evaporation of the solvent and piperidine followed by column chromatography (hexane/ethyl acetate (5/5)) afforded 238 mg of the aminoamide **14** (96% yield). IR (KBr) υ (cm^{-1}), 1620, 1494, 1260, 1105. ^{1}H NMR (300 MHz, $CDCl_3$), δ (ppm), 1.47–1.68 (m, 12H, CH_2–); 2.77 (m, 2H, H_{ax}); 2.95 (m, 2H, H_{eq}); 3.45–3.75 (m, 4H, CH_2–); 4.87 (d, J=6.9 Hz, 1H, H-2); 4.94 (d, J=6.9 Hz, 1H, H-3); 6.87 (m, 4H, H-arom). ^{13}C NMR (75.5 MHz, $CDCl_3$), δ (ppm), 24.2 and 24.3 (C-4′ and C-4″); 25.6 (C-3′); 26.0 (C-3″ C-5″); 26.5 (C-5′); 43.4 (C-2′); 46.6 (C-6′); 49.3 (C-2″ and C-6″); 70.8 (C-2); 90.2 (C-3); 116.7 and, 116.8 (C-5 and C-8); 120.6 and 121.9 (C-6 and C-7); 141.8 and 143.6 (C-4a and C-8a); 165.0 (CO). MS (EI), *m*/*z* (%): 330 (49); 245 (20); 138 (100). Anal. Calcd for $C_{19}H_{26}N_2O_3$: C, 69.07%; H, 7.93%; N, 8.48%. Found: C, 68.79%; H, 8.09%; N, 8.26%.

3.3. General procedure for the preparation of amides 17 and 19

A 100 mL flask, provided with a Dean Stark collector and a magnetic spin bar, was charged with the ester **16** (2.64 mmol) in dry toluene (30 mL) and the corresponding amine (27 mmol); K_2CO_3 (370 mg, 2.68 mmol), and DCC (catalytic amount) were added. The mixture was heated for 40 h. After, the same amount of amine and DCC were added and the reaction prolonged for other 72 h. Then the mixture was cooled to room temperature, 70 mL of ether was added and the reaction mixture washed with water. The organic layer was dried, rotoevaporated, and the residue chromatographed on silica gel.

3.3.1. *N*,*N*-Pentamethylen-2,3-dihydro-1,4-benzodioxin-2-carboxamide (17). 2-(2-Hydroxyphenoxy)-*N*,*N*-pentamethylen-3-piperidinopropanamide (18). These compounds were prepared according the above procedure starting with 920 mg (4.42 mmol) of the ester **16**. Eluting with hexane/ethyl acetate (83/17) a yellow oil was obtained identified as the amide **17** (576 mg, 2.33 mmol, 53% yield), and eluting with hexane/ethyl acetate (25/75) a colourless solid was obtained that was identified as the phenol **18** (50.7 mg, 1.53 mmol, 35% yield), mp=95–96°C.

*N,N-Pentamethylen-2,3-dihydro-1,4-benzodioxin-2-carboxamide (**17**).* IR (KBr) υ (cm^{-1}), 1649, 1269, 1115. ^{1}H NMR (500 MHz, $CDCl_3$), δ (ppm), 1.60 (m, 2H, C5′H_{ax} and C4′H_{ax});1.64 (m, 1H, C3′H_{ax}); 1.68 (m, 2H, C3′H_{eq} and C5′H_{eq}); 3.46 (m, 2H, C2′H_{ax} and C6′H_{ax}); 3.68 (m, 2H, C2′H_{eq} and C6′H_{eq}); 4.29 (dd, J=12 Hz, 8.2 Hz, 1H, C3H_{ax}); 4.46 (dd, J=12.0, 2.5 Hz, 1H, H_{eq}); 4.80 (dd, J=8.2, 2.5 Hz, 1H, H-2); 6.81–6.90 (m, 4H, H-arom). ^{13}C NMR (50.3 MHz, $CDCl_3$), δ (ppm), 24.3 (C-3′); 25.4 (C-4′); 26.4 (C-5′); 43.0 (C-2′); 46.6 (C-6′); 65.2 (C-3′); 70.4 (C-2); 116.9 and 117.2 (C-5 and C-8); 121.3 and 121.9 (C-6 and

C-7); 142.6 (C-8a); 143.1 (C-4a); 164.4 (CO). MS (EI), *m/z* (%): 247 (26); 219 (6); 163 (10); 138 (30); 112 (75); 84 (50); 69 (100). Anal. Calcd for $C_{14}H_{17}NO_3$: C, 67.99%; H, 6.93%; N, 5.66%. Found: C, 68.34%; H, 6.65%; N, 5.48%.

*2-(2-Hydroxyphenoxy)-N,N-pentamethylen-3-piperidino-propanamide (**18**).* IR (NaCl) υ (cm^{-1}), 3460, 1635, 1266, 1196. ^1H NMR (500 MHz, $CDCl_3$), δ (ppm), 1.50 (m, 4H, C3′H_2 and C4′H_2);1.63 (m, 2H, C4″H_2); 1.70 (m, 4H, C3″(C5″)H_2; 2.50 (dd, *J*=14, 1.5 Hz, 1H, CH–N); 2.61 (bs, 2H, C2″and C6″H_{ax}); 2.69 (bs, 2H, C2″ and C6″H_{eq}); 3.00 (dd, *J*=14, 11 Hz, 1H, CH-N); 3.39 (m, 1H, C6′H_{ax}); 3.52 (m, 2H, C2′H_{ax}, C6′H_{eq}); 3.62 (m, 1H, C2′H_{eq}); 4.58 (d, *J*=11 Hz, 1H, CH_2-O); 6.68 (ddd, *J*=8.0, 7.2, 1.5 Hz, 1H, H-5); 6.90 (dd, *J*=8.5, 2.0 Hz, 1H, H-3); 6.97 (m, 2H, H-4 and H-6). ^{13}C NMR (50.3 MHz, $CDCl_3$), δ (ppm), 23.3 (C-2′); 24.1 (C-4″); 24.9 (C-3″ and C-5″); 25.4 (C-3′); 26.2 (C-5′); 43.2 (C-6′); 55.1 (C-2″ and C-6″); 60.9 (CH_2); 80.6 (CH); 117.2 (C-3) and 118.5 (C-5); 122.1 (C-6); 125.5 (C-4); 145.9 (C-1); 150.5 (C-2); 167.5 (CO). MS (EI), *m/z* (%): 332 (5); 223 (43); 138 (19); 98 (100). Anal. Calcd for $C_{19}H_{28}N_2O_3$: C, 68.65%; H, 8.49%; N, 8.43%. Found: C, 68.30%; H, 8.57%; N, 8.47%.

3.3.2. *N,N*-Diethyl-2,3-dihydro-1,4-benzodioxin-2-carboxamide (19). This compound was prepared according to the above procedure starting from the ester **16** (550 mg, 2.64 mmol). The reaction mixture was purified by column chromatography (hexane/ethyl acetate (80/20)) to give the amide **19** (326 mg, 1.39 mmol, 52% yield) as a pale yellow oil. Eluting with hexane/ethyl acetate (70/30) gave the phenol **21** (27 mg, 4% yield) as a white solid with mp=93–95°C. Eluting with hexane/ethyl acetate (50/50) give only trace of the lactone **20**. Finally, with ethyl acetate 100% only trace of the aminophenol **23** was obtained. Amide **19**. IR (NaCl) υ (cm^{-1}), 1650, 1250, 1095. ^1H NMR (500 MHz, $CDCl_3$), δ (ppm), 1.16 (t, *J*=7.1 Hz, 3H, CH_3); 1.27 (t, *J*=7.1 Hz, 3H, CH_3); 3.40 (m, 2H, CH_2–); 3.48 (m, 2H, CH_2–); 4.29 (dd, *J*=12, 8.5 Hz, 1H, C3H_{ax}); 4.45 (dd, *J*=12.0, 2.5 Hz, 1H, C3H_{eq}); 4.47 (dd, *J*=8.5, 2.5 Hz, 1H, H-2); 6.86 (m, 4H, H-arom). ^{13}C NMR (75.5 MHz, $CDCl_3$), δ (ppm), 12.6 (CH_3); 14.5 (CH_3); 40.2 (CH_2); 41.8 (CH_2); 65.5 (C-3); 70.7 (C-2); 117.18 and 117.24 (C-5 and C-8); 121.3 and 121.9 (C-6 and C-7); 142.8 and 143.2 (C-4a and C-8a); 165.5 (CO). MS (CI, CH_4), *m/z* (%): 276 (10); 264 (29); 236 (100). Anal. Calcd for $C_{13}H_{17}NO_3$: C, 66.364%; H, 7.28%; N, 5.96%. Found: C, 66.26%; H, 7.56%; N, 5.87%.

*3-Methylene-2,3-dihydro-1,4-benzodioxin-2(3H)-one (**20**).* The compound **20** was obtained as a by-product in the preparation of the amide **19**. IR (KBr) υ (cm^{-1}), 3112, 1643, 1242, 1100. ^1H NMR (300 MHz, $CDCl_3$), δ (ppm), 4.46 (d, *J*=3.2 Hz, 1H, CH); 5.52 (d, *J*=3.1 Hz, 1H, CH); 6.81 (ddd, *J*=8, 7.1, 1.8 Hz, 1H, H-5′); 7.01 (dd, *J*=8.5, 1.8 Hz, 1H, H-3′); 7.07 (m, 2H, H-4′ and H-6′).

*N,N-Diethyl-2-(2-hydroxyphenoxy)acrylamide (**21**).* IR (KBr) υ (cm^{-1}), 3112, 1643, 1611, 1242; 1100. ^1H NMR (300 MHz, $CDCl_3$), δ (ppm), 1.20 (t, *J*=7 Hz, 3H, CH_3); 1.25 (t, *J*=7.1 Hz, 3H, CH_3); 3.47. (q, *J*=7.1 Hz, 2H, CH_2); 3.61 (q, *J*=7.1 Hz, 2H, CH_2); 4.68 (d, *J*=3.2 Hz, 1H, CH); 4.75 (d, *J*=3.1 Hz, 1H, CH); 6.81 (ddd, *J*=8, 7.1, 1.8 Hz, 1H, H-5′); 7.01 (dd, *J*=8.5, 1.8 Hz, 1H, H-3′); 7.07 (m, 2H, H-4′ and H-6′); 8.86 (bs, OH). ^{13}H NMR (75.5 MHz, $CDCl_3$), δ (ppm), 12.4 (CH_3); 14.3 (CH_3); 39.8 (CH_2); 43.5 (CH_2); 96.1 (C-3); 117.9 (C-3′); 119.3 (C-5′); 122.2 (C-6′); 126.4 (C-4′); 143.1 (C-1′); 148.9 (C-2′); 154.5 (C-2); 165.5 (CO). MS (CI, CH_4), *m/z* (%): 292 (10); 264 (14); 236 (100). Anal. Calcd for $C_{13}H_{17}NO_3$: C, 66.36%; H, 7.28%; N, 5.96%. Found: C, 66.64%; H, 7.15%; N, 5.58%.

2-(2-Hydroxyphenoxy)-N,N-diethyl-3-(N′,N′-diethylamino)-propanamide (23). IR (NaCl) υ (cm^{-1}), 3465, 1646, 1258, 1108. ^1H NMR (200 MHz, $CDCl_3$), δ (ppm), 1.22 (m, 12H, CH_3); 3.10 (dd, *J*=14.0, 11.0 Hz, 1H, CH-N); 3.47. (q, *J*=7.0 Hz, 4H, CH_2); 3.65 (m, 4H, CH_2); 4.65 (d, *J*=3.0 Hz, 1H, CH); 4.69 (d, *J*=3.0 Hz, 1H, CH); 6.84 (dd, *J*=8.0, 7.0 Hz 1H, H-5′); 7.10 (d, *J*=9.0 Hz, 1H, H-3′); 7.12 (m, 2H, H-4′ and H-6′); 8.90 (bs, OH). ^{13}C NMR (50.3 MHz, $CDCl_3$), δ (ppm), 12.2 (CH_3); 14.5 (CH_3); 40.2 (CH_2); 43.5 (CH_2); 59.8 (CH_2); 82.3 (CH); 116.9 and 117.8 (C-3 and C-5); 122.8 (C-6); 126.5 (C-4); 145.6 (C-1); 151.2 (C-2); 166.3 (CO). Anal. Calcd for $C_{17}H_{27}N_2O_3$: C, 66.42%; H, 8.85%; N, 9.11%. Found: C, 66.23%; H, 8.50%; N, 9.49%.

3.3.3. *trans N,N*-Diethylamine-3-diethylamino-2,3-dihydro-1,4-benzodioxin-2-carboxa-mide (24). To a stirred solution of the amide **2** (215 mg, 0.92 mmol) in dry toluene (15 mL), was added diethylamine (1.90 mL, 18.30 mmol). The reaction mixture was heated at reflux for 24 h. Then was cooled and diethylamine (1.90 mL, 18.30 mmol) was added. The resulting mixture was stirred at reflux for 24 h. Then the crude of reaction was cooled to room temperature, the solvent was removed and directly passed through a chromatography column on silica gel (hexane/ethyl acetate (6/4)) to give the *trans* aminoamide **24** (272 mg, 96% yield). IR (KBr) υ (cm^{-1}), 1622, 1498, 1258, 1100. ^1H NMR (300 MHz, $CDCl_3$), δ (ppm), 1.08 (t, *J*=7.1 Hz, 6H, CH_3); 1.18 (t, *J*=7.1 Hz, 3H, CH_3); 1.26 (t, *J*=7.1 Hz, 3H, CH_3); 2.75–2.94 (m, 4H, CH_2N); 4.65 (d, *J*=7.7 Hz, 1H, H-2); 5.12 (d, *J*=7.7 Hz, 1H, H-3); 6.75–6.97 (m, 4H, H-arom). ^{13}H NMR (75.5 MHz, $CDCl_3$), δ (ppm), 12.6 (CH_3); 13.8 (CH_3); 14.8 (CH_3); 40.7 (CH_2); 41.9 (CH_2); 43.2 (CH_2); 70.3 (C-2); 88.4 (C-3); 116.7 and 117.0 (C-5 and C-8); 120.5 and 121.8 (C-6 and C-7); 142.1 and 143.8 (C-4a and C-8a); 166.0 (CO). MS (EI), *m/z* (%): 306 (6); 233 (45); 218 (21); 190 (12). Anal. Calcd for $C_{17}H_{26}N_2O_3$: C, 66.64%; H, 8.55%; N, 9.14%. Found: C, 66.87%; H, 8.78%; N, 9.46%.

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