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NOVEL 1,4-BENZOXAZINE DERIVATIVES OF PHARMACOLOGICAL INTEREST. ELECTROCHEMICAL AND CHEMICAL SYNTHESES.

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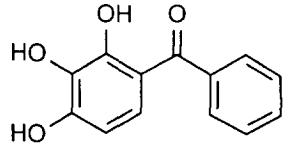
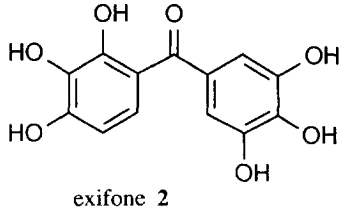
Abstract: *The reaction of electrochemically or chemically generated orthoquinones with aminoalcohols, in methanol, affords a convenient route to novel 1,4-benzoxazine derivatives. Some of these compounds are found to possess interesting pharmacological properties.*

Exifone (*Adlone*^{R})[1] is a molecule of the benzophenone series (see structure **2**) which has been launched in France in 1988. It was indicated for the treatment of cognitive problems in the ederly and was reported to have a number of pharmacological properties including activation of neuronal oxygen and glucose metabolism, antagonism of aminergic neurotransmission impairment induced by temporary ischemia[2,3]. Furthermore, exifone demonstrated remarkable scavenger properties against free radicals which have been suggested to be an etiological factor in pathological aging. Unfortunately, in 1990, because of reports of hepatotoxicity associated with the product, the registration was revoked and exifone was withdrawn in the market where it was launched and in several countries where it was available for compassionate use.



1



exifone **2**

In this context, it would be of interest to obtain information about the mechanism by which exifone expresses its pharmacological properties. Due to the ease of oxidation of the pyrogallol ring at physiological pH, oxidative biological pathways cannot be dismissed. Therefore, we were primarily interested in the role of the oxidation chemistry in the hepatotoxic effects of exifone.

In the toxicological field, a theory has been advanced to explain how the autoxidation of the catecholaminergic 6-hydroxydopamine results in neuronal degeneration. It postulates that autoxidation reaction generates an electrophilic paraquinone which can then react with several groups within the cellular

proteins (especially R-SH and R-NH_2 groups), and which cross-links neuronal membrane proteins[4-6].

In the event that exifone can similarly undergo oxidation at physiological pH, it seems reasonable to suggest that a potential toxic product of exifone would be the transient orthoquinone species. Therefore, we embarked upon a study whose objectives were twofold, chemical and pharmacological:

- to stabilize the transient orthoquinone, unstable and very prone to polymerization, thanks to the formation of an adduct blocking the electrophilic sites generally attacked by nucleophiles;

- to decrease the toxicity of exifone as this could be initiated by cross-linking involving the transient orthoquinone and the membrane protein groups[7-9].

We report hereafter the results of this study concerning the oxidation chemistry of exifone. At a first step, we used 2,3,4-trihydroxybenzophenone **1** as model of exifone **2**, whereas aminoalcohols were intended as models for aminoacids which have been strongly implicated in protein-coupling reactions.

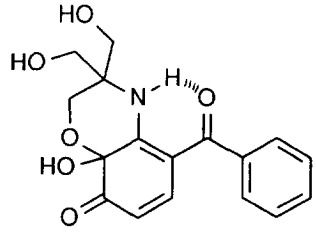
RESULTS AND DISCUSSION

Model Compound 1

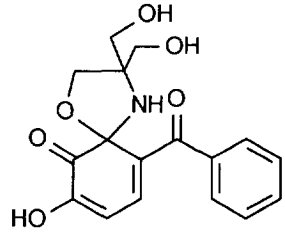
Electrochemical oxidation of 2,3,4-trihydroxybenzophenone 1

The cyclic voltammogram of **1**, in methanol containing tetraethylammonium perchlorate (TEAP) as the supporting electrolyte and an excess of tris(hydroxymethyl)-aminomethane (Tris), at a stationary platinum electrode, showed an oxidation peak Pa at +350 mV s.c.e., the sweep rate being 0.1 $V.s^{-1}$. After sweep reversal, no cathodic peak was recorded in the reverse sweep of the cyclic voltammogram of **1**, showing the irreversibility of the anodic process.

When the controlled potential of the platinum working electrode was fixed at +400 mV s.c.e., i.e. at a potential immediately following the peak Pa, a coulometric value of 2.0 ± 0.1 was found for the number of electrons involved in the oxidation of one molecule of **1**. As the electrolysis proceeded, a decrease in the Pa intensity was observed and no more anodic peak was recorded in the cyclic voltammogram exhibited by the exhaustively oxidized solution of compound **1**. Finally, preparative scale electrolyses allowed the isolation of a major compound in 70% yield (see experimental). On the basis of the coulometric observations, it was reasonable to assume that the proximate oxidation product was the 3,4-quinone. Moreover, study of the ^1H NMR, ^{13}C NMR and mass spectra indicated that the orthoquinone was converted into a quinone-aminoalcohol adduct **3**. Two structures **3a** and **3b** can be considered for the bicyclic form of the yielded adduct **3**:



3a

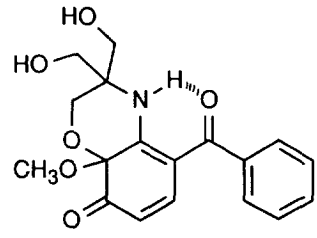


3b

Because this spectral study did not provide unambiguous discrimination between structures **3a** and **3b**,

we decided to perform further spectral experiments to bring additional informations. The absence of any change in UV-absorption spectra when a methanolic solution of compound **3** was made more basic ruled out its formulation as structure **3b**, since the ionization of the phenolic group engaged in the resonance of the chromophoric group would result in a bathochromic shift of the absorption maximum.

To ensure that, we undertook a study of the spectral properties of the methylated adduct **4**. Homo and heteronuclear ^{2}D NMR spectroscopy (see experimental) were necessary to establish the structure of the methylated adduct **4** as (RS)-5-benzoyl-3,3-bis(hydroxymethyl)-8a-methoxy-3,4-dihydro-2H-1,4-benzoxazin-8(8aH)-one, i.e. a derivative of the hemiketal **3a** rather than of the spiro-2,4-dienone **3b**.



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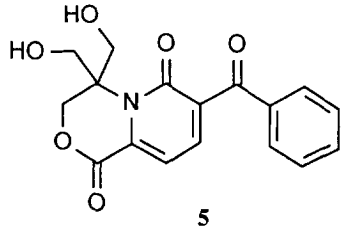
Examination of literature data showed that there was good evidence to support the structure we have assigned. Indeed, the reaction of amines with electrophilic orthoquinones have been the subject of many investigations[10-14]. Whereas unsubstituted 1,2-quinones react with primary aliphatic amines to produce a number of compounds, the most important of which being the substituted hydroquinone[10], substituted 1,2-quinones undergo nucleophilic substitution of the leaving group[10,12]. Furthermore, in a significant number of cases, a subsequent step consisting of an intramolecular ring-closure reaction provides a versatile pathway to a number of heterocyclic ring systems[13,14]. In a similar way, previous workers have focused on the properties of paraquinone-aminoethanol adducts[15,16].

Interesting enough, the by-product **5**, isolated in about 15% yield (see experimental), likewise would derive from an intramolecular rearrangement implying the transient orthoquinone and one molecule of Tris so that a good conversion of 3,4-quinone into stable quinone-aminoalcohol adducts was observed (overall yield 85%).



5

At that point, a first conclusion could be drawn: thanks to the formation of 1,4-benzoxazin-8-one derivative, it was possible to stabilize the transient orthoquinone generated in the course of the electrooxidation of **1**. Furthermore, since the N-H group is a strong electron donating group, the resulting adduct **3** was less susceptible to further 1,4-addition at the 6-position. Therefore, we focused our attention on this type of reaction and we decided to investigate the electrochemical oxidation of **1** in methanol in presence of various aminoalcohols. The results of the preparative scale electrolyses obtained with a series of aminoalcohol derivatives are collected in table.

Table: Products and Yields of Controlled Potential Electrolyses of **1** *in methanol containing an excess of Aminoalcohol* CH_2OH-$C(R^1, R^2)$-NH_2.

R^1	R^2	pKa	product	yield
CH_2OH	CH_2OH	8.20	**3**	70%
CH_2OH	CH_3	8.75	**6**	60%
CH_3	CH_3	9.75	**7**	35%
CH_2OH	H	8.70	–	–
CH_3	H	9.60	–	–
H	H	9.50	–	–

Data reported in table reveal that:

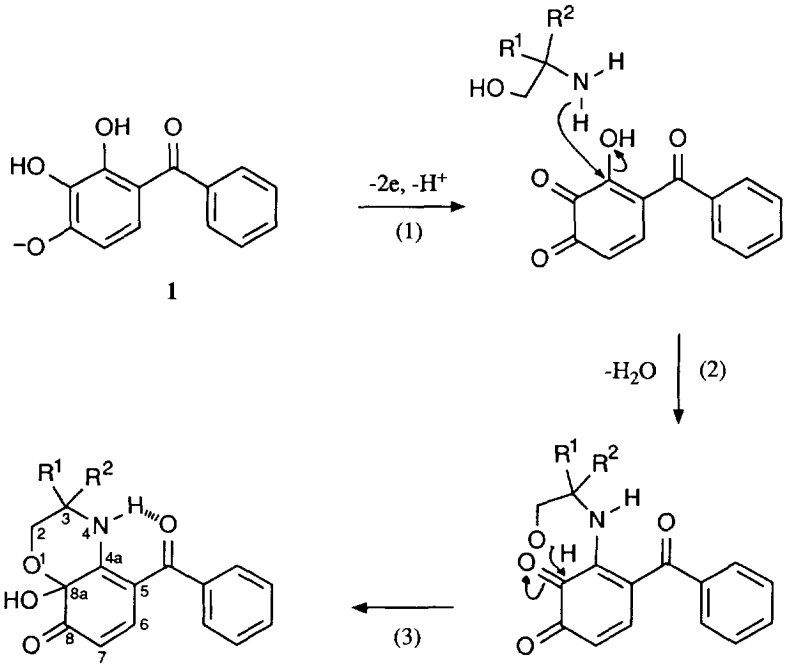
a) in the series studied, neither R^1 nor R^2 may be an hydrogen; this condition appears to constitute a **first prerequisite** to the formation of 1,4-benzoxazin-8-one derivatives.

b) increasing basicity of aminoalcohol led to lower yield of benzoxazine derivatives. When using Tris as nucleophilic species, the monoionized form of compound **1** predominated in the electrolysis solution since only the phenolic group at the 4-position could be ionized (pKa = 7.2).

In contrast, when using 2-amino-2-methylpropanol as nucleophilic species, the bulk solution pH increased markedly so that the phenolic group at the 3-position likewise existed predominantly as the phenolate anion (pKa = 10.0). It resulted that the bianionic species no longer underwent the ring-closure reaction yielding the 1,4-benzoxazin-8-one derivative (scheme 1), but followed the alternative polymerization route. Consistent with these results, the non-ionization of the phenolic group at the 3-position of compound **1** appears to constitute a **second prerequisite** to the 1,4-benzoxazin-8-one derivatives formation.

A tentative mechanism for the electrochemical oxidation of **1** can be proposed. The formation of the transient 3,4-quinone would result from a two electron-oxidation of the monoanionic species of **1** [eqn. (1)]. The subsequent step would consist in a substitution reaction of the hydroxyl group at the 2-position by the aminoalcohol [eqn. (2)], to yield finally, after intramolecular ring-closure, the 1,4-benzoxazin-8-one derivatives **3**, **6** and **7** [eqn. (3), scheme 1].

Note that a strong intramolecular hydrogen bonding between the oxygen of the carbonyl of the 5-benzoyl substituent and the NH group of the 1,4-benzoxazin-8-one appeared to be needed to the stability of the derivatives **3**, **6** and **7**. This feature would constitute a **third prerequisite** to the 1,4-benzoxazin-8-one derivative formation, as evidenced by the cathodic behaviour of compound **3**.



3: $R^1 = R^2 = CH_2OH$

6: $R^1 = CH_2OH$, $R^2 = CH_3$

7: $R^1 = R^2 = CH_3$

Scheme 1

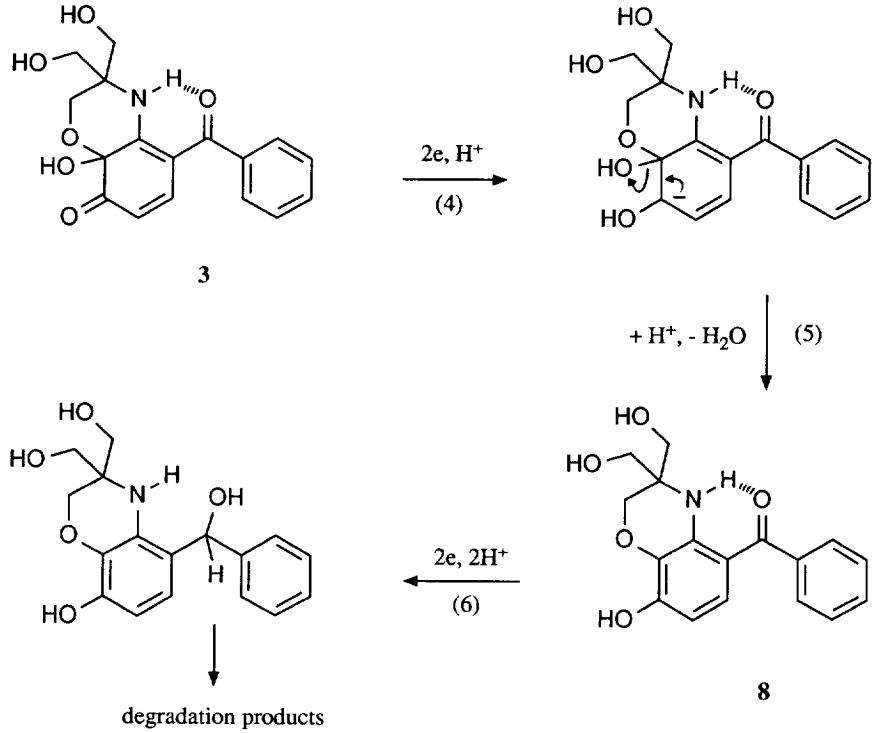
Electrochemical reduction of 1,4-benzoxazin-8-one 3

The cyclic voltammogram of **3** in methanol containing TEAP as the supporting electrolyte, at a stationary mercury electrode, clearly showed two distinct reduction peaks Pc_1 and Pc_2, around -1150 and -1720 mV s.c.e. respectively, the sweep rate being 0.1 $V.s^{-1}$. When the potential scan was reversed after Pc_1 or after Pc_2, no anodic peak was recorded in the reverse sweep of the cyclic voltammogram of **3**, showing the irreversibility of the cathodic process.

When the controlled potential of the mercury working electrode (E) was fixed at -1300 mV s.c.e., i.e. at a potential following the first peak Pc_1 and preceding the second peak Pc_2, a coulometric value of 2.3 ± 0.1 was found for the number of electrons (n) involved in the reduction of one molecule of **3**. As the electrolysis proceeded, a decrease in the first cathodic peak intensity was observed and the voltammogram of the exhaustively reduced solution exhibited a sole cathodic peak at -1720 mV s.c.e. Finally, preparative scale electrolyses allowed the isolation of the phenolic product **8** in 80% yield (see experimental).

When E was fixed at -1850 mV s.c.e., i.e. at a potential following the second cathodic peak Pc_2, a coulometric value of 4.0 ± 0.1 was found for n. No cathodic peak was observed in the cyclic voltammogram of the exhaustively reduced solution of **3**. Finally, no stable product was isolated after preparative scale electrolyses.

From these results, it can be deduced that the cathodic electrolysis of the 1,4-benzoxazin-8-one derivative **3** proceeds through a two electrons irreversible transfer [eqn. (4)] producing, after elimination of one molecule of water, the phenolic product **8** [eqn. (5)]. The subsequent step would consist in a further two-electron reduction of the carbonyl group of the benzoyl moiety to an unstable alcohol species [eqn. (6)] which subsequently decomposed (scheme 2).



Scheme 2

Consequently, there was little doubt left that hydrogen bonding between the oxygen of the carbonyl of the benzoyl group and the NH group of the benzoxazine moiety accounted for the stability of the 1,4-benzoxazine derivatives. In other words, thanks to this intramolecular hydrogen bonding, the driving force in the reaction-scheme 1 would be the tendency to recover a stable tricyclic ring system. It is noteworthy that very strong intramolecular hydrogen bondings have been previously reported in the case of 2-hydroxy-4-substituted-benzophenones[17,18].

The influence of the hydrogen bonding on the stability of the 1,4-benzoxazine derivatives could be further substantiated when considering the specific behaviour of exifone **2**, studied under the same experimental conditions.

Exifone 2

Electrochemical oxidation of exifone 2

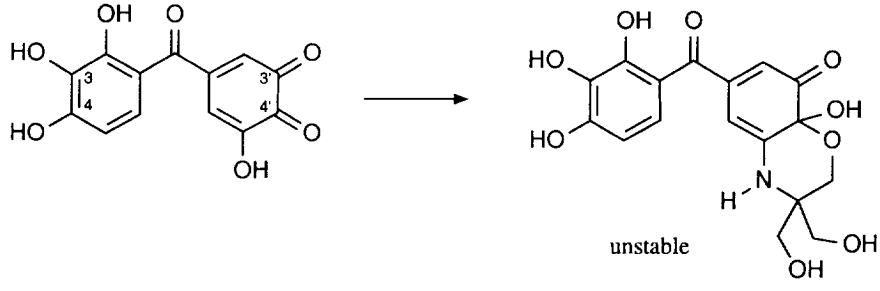
The introduction of a second pyrogallol ring induced noticeable changes in the electrochemical

behaviour of exifone **2**, compared with that of compound **1**.

A first problem encountered in the course of the electrooxidation of exifone was that both the 2,3,4-trihydroxyphenyl ring and the 3',4',5'-trihydroxyphenyl ring could participate to the oxidation into orthoquinone. Under our experimental conditions, the monoionization of the pyrogallol ring would constitute a step antecedent to the oxidation of **2**. Unfortunately, the roughly identical pKa values (pKa ~ 7.5) found for the phenolic groups at the 4- and 4'-positions did not allow us to decide which of the pyrogallol rings was at first ionized, in other words, which of the pyrogallol rings was prone to subsequent oxidation into orthoquinone. Nevertheless, a distinction could be made on the basis of whether, or not, the carbonyl function of the benzophenone skeleton extended the electronic conjugation of the enolate anion. Methylation of the latter allowed the conclusion that the phenol group at the 4'-position was ionized in preference to the phenol group at the 4-position.

The cyclic voltammogram of exifone **2**, in methanol containing TEAP as the supporting electrolyte and an excess of Tris, at a stationary platinum electrode, showed a poorly defined oxidation peak Pa around +350 mV s.c.e., the sweep rate being 0.1 $V.s^{-1}$. In the course of the electrolytic procedure, with E being held more positive than Ep_a, an anomalous decrease in the current intensity was noted. It was very likely due to passivation phenomena of the working platinum electrode. Consequently, because of the inertness of this procedure, we chose to replace the platinum working electrode by a mercury pool electrode, working at E = 0 mV s.c.e., i.e. at a potential immediately following the oxidation peak Pa (Ep_a = -100 mV s.c.e.). Then, a coulometric value of 2.0 ± 0.1 was found for n, consistent with a two-electron oxidation into orthoquinone. Unfortunately, no well-defined products could be isolated.

According to scheme 1, though the first-formed intermediate seemed likely the putative 3',4'-quinone, apt to give subsequently the Tris-adduct, the latter could no longer contract an intramolecular bonding between the NH group of the benzoxazine moiety and the oxygen of the carbonyl group of the 2,3,4-trihydroxybenzoyl substituent:



It resulted that the tendency to recover a tricyclic ring system could no longer exert a driving force. Consequently, various by-products more likely resulting from the polymerization of the transient 3',4'-quinone was produced instead of the benzoxazine derivative.

So, in order to hinder the formation of 3',4'-quinone, and at the same time to promote that of 3,4-quinone, we turned our attention towards the protection of the phenolic group at the 4'-position.

Chemical oxidation of the 4'-protected exifone 9.

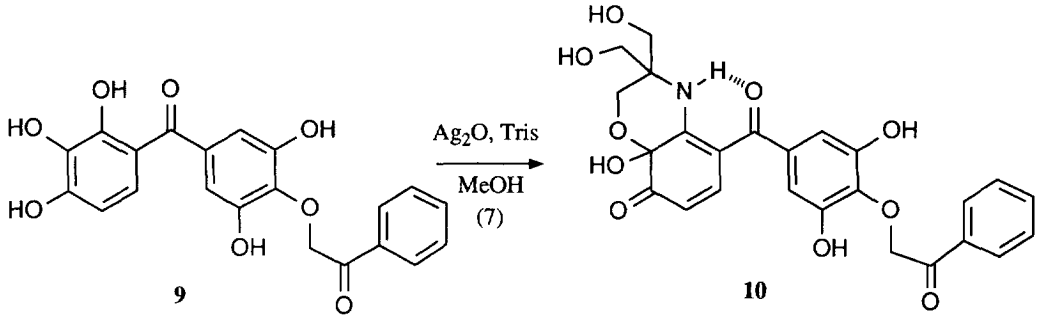
A wide range of methods met with failure, demonstrating that the regioselective protection of exifone was a difficult problem. A particular attention was devoted to the methylation reaction as it was reported in the literature that phenolic groups with pKa ≤ 8.0 could be alkylated selectively with an alkyl halide, in

N,N-dimethylformamide, in the presence of lithium carbonate[19]. Under these experimental conditions, the expected methoxy derivative at the 4'-position was produced in poor yields ranging from 10 to 15%. Then, it was easy to afford the expected 1,4-benzoxazin-8-one derivative after oxidation of the 4'-protected exifone. Unfortunately, the experimental conditions of the removal of the methyl ether[20] were so hard that they led to the simultaneous ring-opening of the benzoxazine moiety.

These results prompted us to use the methyl or phenyl ester groups as an alternative since they were removed with great facility[21]. This approach was to no avail: in the course of the overall oxidation reaction yielding the benzoxazine derivative, the nucleophilicity of the Tris species was high enough to provoke the release of the protecting ester group.

Therefore, we wondered whether the use of the phenacyl group, which was proved to be a convenient protecting group of phenols, removed with great facility by reduction[22], would constitute a convenient strategy. When using the phenacyl group, exifone could be converted efficiently into the corresponding 4'-phenacyl ether **9** (40% yield), whereas the 4,4'-diether was obtained in 20% yield along with a noticeable amount of starting material **2** (30% yield). Conversely, the 4-phenacyl ether was not afforded in appreciable amount (see experimental).

The above electrolytic oxidation procedure described for compound **1** was inadequate because of passivation phenomena of the working electrode. Consequently, a chemical oxidation using silver oxide was elaborated (see experimental). This procedure gave the expected 1,4-benzoxazin-8-one derivative **10** as the predominant product in yields ranging from 35 to 40% [eqn. (7)].



9 **10**

Removal of the phenacyl protecting group

At first, the removal of the phenacyl protecting group was performed electrochemically. As 1,4-benzoxazin-8-one derivative **10** exhibited three carbonyl groups, cyclic voltammetry offered an easy prediction of the reducibility sequence. The cyclic voltammogram of compound **10**, in methanol containing TEAP as the supporting electrolyte, at a stationary mercury cathode, showed three well-defined cathodic peaks Pc_1, Pc_2 and Pc_3 around -1150, -1450 and -1720 mV s.c.e. respectively, the sweep rate being 0.1 $V.s^{-1}$. Whatever the inversion potential, no anodic peak appeared in the reverse sweep of the cyclic voltammogram, demonstrating the irreversibility of the three successive reduction steps. At that point, it could be underlined that the two peaks Pc_1 and Pc_3 were already recorded in the course of the reduction of compound **3**. Therefore, Pc_1 and Pc_3 could be assigned to the reduction of the carbonyl group at the 8-position of the benzoxazine ring and to that of the 5-benzoyl substituent, respectively.

Of particular interest was the electrolysis whose advantages derived from the possibility of smooth

variation in the strength of reducing reagent (cathode) by merely changing its potential.

When the controlled-potential of the mercury pool working electrode (E) was fixed at -1200 mV s.c.e., i.e. at a potential immediately following the first peak Pc_1 and preceding the second peak Pc_2, a coulometric value of 2.3 ± 0.1 was found for the number of electrons (n) involved in the reduction of one molecule of derivative **10**. As the electrolysis proceeded, a decrease in the Pc_1 intensity was observed and the voltammogram of the exhaustively reduced solution showed the two cathodic peaks Pc_2 and Pc_3. Finally, preparative scale electrolyses allowed the isolation of compound **11** in 70% yield (see experimental). So, it was confirmed that the first cathodic peak Pc_1 corresponded to the reduction of the carbonyl group at the 8-position of the benzoxazine moiety according to a route similar to scheme 2.

When E was fixed at -1500 mV s.c.e., i.e. at a potential immediately following the second peak Pc_2 and preceding the third peak Pc_3, a coulometric value of 4.2 ± 0.1 was found for n. As the electrolysis proceeded, a decrease in the two cathodic peaks (Pc_1 and Pc_2) intensity was observed and the voltammogram of the exhaustively reduction solution exhibited a sole cathodic peak Pc_3 at -1720 mV s.c.e. Compound **12** was isolated after preparative scale electrolysis in 80% yield (see experimental). No doubt the peak Pc_2 could be attributed to the reductive removal of the protecting phenacyl group. This reduction reaction generated one molecule of acetophenone which could be subsequently reduced around -1800 mV s.c.e.

At last, when E was fixed at -1800 mV s.c.e., i.e. at a potential immediately following the third cathodic peak Pc_3, a coulometric value of 7.8 ± 0.2 was found for n, arguing in favour of the simultaneous reduction of the carbonyl group at the 8-position of the benzoxazine moiety, the removal of the phenacyl protecting group and the reduction of the oxo of the 5-benzoyl substituent, as well as the reduction of the released acetophenone. Then, as reported already in the case of compound **3**, no well-defined product could be isolated after preparative scale electrolysis, because of the instability of the alcohol species which could no longer give an hydrogen bonding.

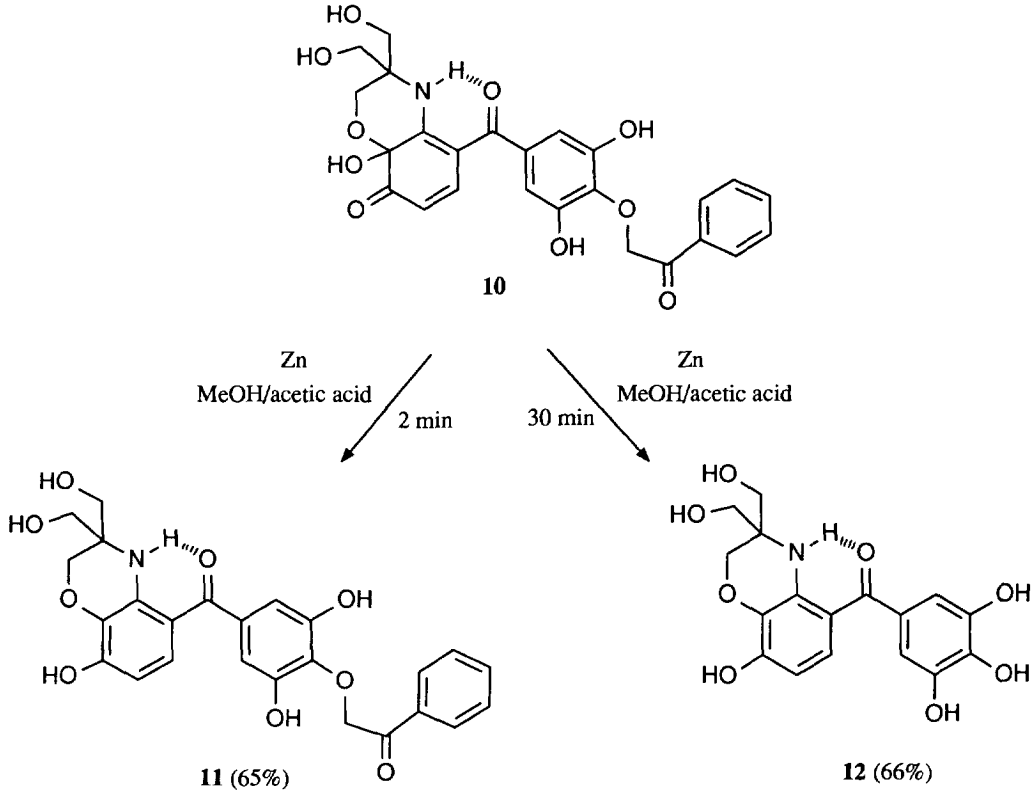
Note that, according to the reducibility sequence ($Ep_{C1} > Ep_{C2}$), removal of the phenacyl protecting group exclusive of the reduction of the carbonyl group at the 8-position of the benzoxazine moiety was impossible in the studied series.

Finally, the reduction of compound **10** was achieved on more large scale using zinc in methanolic acetic acid solution as a surrogate of the electrochemical reduction. Then, formation of derivative **11** or **12** alternatively could be regarded as depending accurately on reaction time, at constant molar excess of zinc (see experimental). Although the chemical procedure induced a loss of selectivity, compound **10** was reduced with a satisfactory efficiency (scheme 3).

As a consequence of this work, the attachment of an aminoalcohol residue was identified as an easy pathway to stabilize the transient unstable 3,4-quinone, electrochemically or chemically generated, by blocking the electrophilic sites. The reaction afforded novel 1,4-benzoxazine derivatives **10**, **11** and **12**.

Furthermore, we wondered whether these compounds were endowed with pharmacological properties. Consequently, we decided to investigate their activity versus that of the parent exifone **2**, a drug unfortunately withdrawn in the market because of its hepatotoxicity. With this object, we used a simple alloxanic diabetes model. Indeed, it is accepted that alloxan toxicity is linked to the production of hydroxylated free radicals and that a substance preventing the development of alloxanic diabetes possesses radical scavenger properties[23-26]. Reflecting these properties, compounds **10**, **11** and **12** were identified as about five fold more active than the parent exifone **2**. Moreover, recent cytotoxicity experiments in rat hepatocytes, performed in the

Rhône-Poulenc Rorer Laboratories[27], indicated that these compounds were significantly less toxic than exifone **2**. So these novel compounds have been protected by a patent[28].



Scheme 3

EXPERIMENTAL

Materials

Exifone (*Adlone*^{R}) was supplied by the Pharmascience Laboratories. 2,3,4-trihydroxybenzophenone, tris (hydroxymethyl)-aminomethane (Tris), 2-amino-2-methyl-1,3-propanediol, serinol, ω-bromoacetophenone, silver oxide (Ag_2O), zinc dust were Aldrich products. Tetraethylammonium perchlorate (TEAP) was obtained from Fluka. 2-amino-2-methylpropanol was obtained from Lancaster. Methanol was obtained from Prolabo. N,N-dimethylformamide, ethanolamine, anhydrous sodium sulphate, lithium carbonate, and sodium acetate were Merck products. The solvents used for extractions and chromatography were obtained from SDS.

Chromatography

Analytical TLC were performed on Merck Silica Gel 60F 254 (lot 5714). Column chromatography was conducted on open glass columns packed with Merck Silica Gel 60 (lot 9385).

Apparatus, cells and electrodes

The apparatus, cells and electrodes were identical with those described previously[29].

Isolation and spectroscopic data of products 3-12

(RS)-5-benzoyl-3,3-bis(hydroxymethyl)-8a-hydroxy-3,4-dihydro-2H-1,4-benzoxazin-8(8aH)-one 3 and 7-benzoyl-4,4-bis(hydroxymethyl)-3,4-dihydropyrido[1,2-a][1,4]oxazin-1,6- dione 5

A solution of 2,3,4-trihydroxybenzophenone **1** (0.12 g, 0.5 mmol), TEAP (1.15 g, 5.0 mmol) and Tris (3.02 g, 25.0 mmol) in methanol (250 mL) was oxidized under nitrogen, at 25°C, at a platinum electrode (E = +400 mV s.c.e.). After exhaustive electrolysis, i.e., when a steady state minimum value of the current was recorded, the resulting solution was evaporated to dryness under reduced pressure at 35°C. The residue was poured into a molar acetic acid-buffered aqueous solution of pH ~ 4 (100 mL) and extracted with ethyl acetate (200 mL). The organic phase was dried over anhydrous sodium sulphate and the solvent removed under reduced pressure, at 35°C. Chromatography [ethyl acetate:methanol (98:2)] afforded compounds **3** (115 mg, 70% yield, decomposes above 170°C), and **5** (25 mg, 15% yield) as amorphous solids.

(RS)-5-benzoyl-3,3-bis(hydroxymethyl)-8a-hydroxy-3,4-dihydro-2H-1,4-benzoxazin-8(8aH)-one 3: ^{1}H NMR (300 MHz, DMSO D_6): δ 3.40 [dd, 1H, $CH_2OH(3)$, J = 12 Hz, J = 5 Hz], 3.50 [d, 2H, $CH_2OH(3)$, J = 5 Hz], 3.60 [dd, 1H, $CH_2OH(3)$, J = 12 Hz, J = 5 Hz], 3.85 [d, 1H, $CH_2(2)$, J = 12 Hz], 4.20 [d, 1H, $CH_2(2)$, J = 12 Hz], 5.20 [d, 1H, H(7), J = 10 Hz], 5.40 [m, 2H, OH(alcohol), D_2O exchanged], 7.20 [d, 1H, H(6), J = 10 Hz], 7.50 [m, 5H, aromatic, benzoyl(5)], 8.30 [s, 1H, OH(8a), D_2O exchanged], 12.30 [s, 1H, NH, D_2O exchanged]; ^{13}C NMR (75 MHz, DMSO D_6): δ 56.5 (C-3), 58.3 [$CH_2(2)$], 60.7 [$CH_2OH(3)$], 61.2 [$CH_2OH(3)$], 86.6 (C-8a), 98.8 (C-5), 107.7 [CH(7)], 127.5, 128.2 and 130.0 [CH, aromatic, benzoyl(5)], 139.4 [Cq, benzoyl(5)], 146.0 [CH(6)], 167.1 (C-4a), 190.0 [CO(8)], 192.6 [CO, benzoyl(5)]; MS (DCI): m/z = 332 (MH^+), (EI): m/z = 331 ($M^{+\cdot}$), m/z = 314 (M-OH), m/z = 226 [M-(C_6H_5-CO)], m/z = 105 (C_6H_5-CO, 100%).

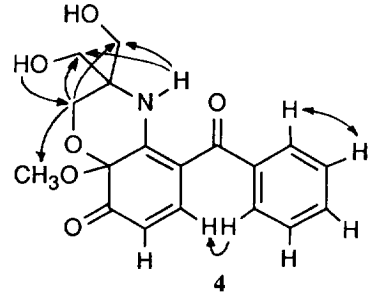
7-benzoyl-4,4-bis(hydroxymethyl)-3,4-dihydropyrido[1,2-a][1,4]oxazin-1,6-dione 5: ^{1}H NMR (300 MHz, DMSO D_6): δ 3.70 [dd, 2H, $CH_2OH(4)$, J = 11 Hz, J = 5 Hz], 4.15 [dd, 2H, $CH_2OH(4)$, J = 11 Hz, J = 5 Hz], 4.70 [s, 2H, $CH_2(3)$], 5.20 [t, 2H, OH(alcohol), J = 5 Hz, D_2O exchanged], 7.20 [d, 1H, H(9), J = 7 Hz], 7.50, 7.65 and 7.90 [5H, aromatic, benzoyl(7)], 7.80 [d, 1H, H(8), J = 7 Hz]; ^{13}C NMR (75 MHz, DMSO D_6): δ 60.6 [$CH_2OH(4)$], 64.6 (C-4), 70.6 [$CH_2(3)$], 112.2 [CH(9)], 129.7, 130.4 and 134.7 [CH, aromatic, benzoyl(7)], 136.1 (C-7), 136.2 [Cq, benzoyl(7)], 137.4 (C-9a), 139.5 [CH(8)], 160.4 [CO(1) and CO(6)], 194.7 [CO, benzoyl(7)]; MS (DCI): m/z = 330 (MH^+), (EI): m/z = 329 ($M^{+\cdot}$), m/z = 312 (M-OH), m/z = 105 (C_6H_5-CO), m/z = 77 (C_6H_5, 100%);

(RS)-5-benzoyl-3,3-bis(hydroxymethyl)-8a-methoxy-3,4-dihydro-2H-1,4-benzoxazin-8(8aH)-one 4

A solution of compound **3** (165 mg, 0.5 mmol) and sodium methoxide (27 mg, 0.5 mmol) in N,N-dimethylformamide (2 mL) was stirred for 2 min, at room temperature, under nitrogen. Methyl iodide (1.1 g, 8 mmol) was added, and stirring was continued for 3h. Then, the resulting solution was poured into water (40 mL) and extracted with ethyl acetate (100 mL). The organic phase was washed vigorously with water and dried over anhydrous sodium sulphate, and the solvent was removed under reduced pressure at 35°C.

After chromatography [ethyl acetate:methanol (97:3)], **4** was recovered as an amorphous orange solid (157 mg, 91% yield, decomposes above 168°C): ^{1}H NMR (300 MHz, DMSO D_6): δ 3.20 (s, 3H, OCH_3), 3.40 [dd, 1H, $CH_2OH(3)$, J = 12 Hz, J = 5 Hz], 3.50 [d, 2H, $CH_2OH(3)$, J = 5 Hz], 3.65 [dd, 1H, $CH_2OH(3)$, J = 12

Hz, J = 5 Hz], 3.95 [s, 2H, CH_2(2)], 5.20 [d, 1H, H(7), J = 10 Hz], 7.40 to 7.50 [m, 5H, aromatic, benzoyl(5)], 12.30 (s, 1H, NH, D_2O exchanged); ^{13}C NMR (75 MHz, DMSO D_6): δ 51.0 (OCH_3), 57.0 (C-3), 59.5 [CH_2(2)], 61.5 [CH_2OH(3)], 62.0 [CH_2OH(3)], 90.0 (C-8a), 100.0 (C-5), 108.0 [CH(7)], 128.0, 129.0 and 130.8 [CH, aromatic, benzoyl(5)], 139.7 [Cq, benzoyl(5)], 147.0 [CH(6)], 166.0 (C-4a), 189.0 [CO(8)], 193.0 [CO, benzoyl(5)]; MS (DCI): m/z = 346 (MH^+), (E.I.): m/z = 345 ($M^{+\cdot}$), m/z = 330 ($M-CH_3$), m/z = 105 (C_6H_5-CO).



4

Figure 1: NOESY experiment[30] (DMSO D_6, mixing time: 300 msec). Heteronuclear relays are indicated by arrows.

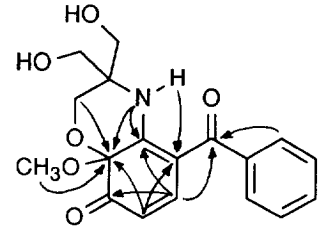


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Figure 2: Long range ^1H-^{13}C connectivities detected in the reverse mode[31] - HMBC experiment (DMSO D_6, mixing delay: 50 msec). Correlations are indicated by arrows.

(RS)-5-benzoyl-3,3-(hydroxymethyl, methyl)-8a-hydroxy-3,4-dihydro-2H-1,4-benzoxazin-8(8aH)-one 6

When the controlled potential was fixed at +400 mV s.c.e., the above described procedure replacing Tris by 2-amino-2-methyl-1,3-propanediol (2.63 g, 25 mmol) afforded compound **6** (95 mg, 60% yield, decomposes above 155°C) as a mixture (65:35) of two diastereoisomers A and B that could not be separated.

Diastereoisomer A: ^1H NMR (300 MHz, DMSO D_6): δ 1.25 [s, 3H, CH_3(3)], 3.45 [s, 2H, CH_2OH(3)], 3.85 [d, 1H, CH_2(2),J = 12 Hz], 4.15 [d, 1H, CH_2(2), J = 12 Hz], 5.20 [d, 1H, H(7), J = 10 Hz], 5.45 [broad s, 1H, OH(alcohol), D_2O exchanged], 7.20 [d, 1H, H(6), J = 10 Hz], 7.45 [m, 5H, aromatic, benzoyl(5)], 8.40 [broad s, 1H, OH(8a), D_2O exchanged], 12.20 [s, 1H, NH, D_2O exchanged]; ^{13}C NMR (75 MHz, DMSO D_6): δ 21.6 [CH_3(3)], 54.7 (C-3), 62.2 [CH_2(2)], 67.2 [CH_2OH(3)], 87.7 (C-8a), 99.8 (C-5), 108.9 [CH(7)], 128.7, 129.4 and 131.2 [CH, aromatic, benzoyl(5)], 140.5 [Cq, benzoyl(5)], 147.2 [CH(6)], 168.1 (C-4a), 191.2 [CO(8)], 194.0 [CO, benzoyl(5)];

Diastereoisomer B: ^1H NMR (300 MHz, DMSO D_6): δ 1.35 [s, 3H, CH_3(3)], 3.47 [s, 2H, CH_2OH(3)], 3.75 [d, 1H, CH_2(2), J = 12 Hz], 4.25 [d, 1H, CH_2(2), J = 12 Hz], 5.15 [d, 1H, H(7), J = 10 Hz], 5.45 [broad s, 1H, OH(alcohol), D_2O exchanged], 7.15 [d, 1H, H(6), J = 10 Hz], 7.45 [m, 5H, aromatic, benzoyl(5)], 8.30 [broad s, 1H, OH(8a), D_2O exchanged], 12.30 [s, 1H, NH, D_2O exchanged]; ^{13}C NMR (75 MHz, DMSO D_6): δ 24.7

[CH_3(3)], 55.5 (C-3), 63.6 [CH_2(2)], 66.0 [CH_2OH(3)], 87.9 (C-8a), 98.8 (C-5), 108.7 [CH(7)], 128.7, 129.4 and 131.2 [CH, aromatic, benzoyl(5)], 140.5 [Cq, benzoyl(5)], 147.2 [CH(6)], 166.0 (C-4a), 191.2 [CO(8)], 194.0 [CO, benzoyl(5)]; MS (mixture of A and B)(DCI): m/z = 316 (MH^+), (EI): m/z = 315 ($M^{+\cdot}$), m/z = 105 (C_6H_5-CO), m/z = 74 (100%); Elemental analysis (mixture of A and B): found (C, 58.08; H, 5.90; N, 4.01%), $C_{17}H_{17}NO_5$, $2H_2O$ requires (C, 58.12; H, 5.98; N, 3.99%).

(RS)-5-benzoyl-3,3-bis(methyl)-8a-hydroxy-3,4-dihydro-2H-1,4-benzoxazin-8(8aH)-one 7

When the controlled potential was fixed at +400 mV s.c.e., the above described procedure replacing Tris by 2-amino-2-methylpropanol (2.23 g, 25 mmol) afforded after chromatography [dichloromethane methanol (98:2)] compound **7** as an amorphous orange solid (52 mg, 35% yield, decomposes above 140°C). ^{1}H NMR (300 MHz, DMSO D_6): δ 1.35 [s, 3H, CH_3(3)], 1.40 [s, 3H, CH_3(3)], 3.75 [d, 1H, CH_2(2), J = 12 Hz], 4.20 [d, 1H, CH_2(2), J = 12 Hz], 5.20 [d, 1H, H(7), J = 10 Hz], 7.20 [d, 1H, H(6), J = 10 Hz], 7.50 [m, 5H, aromatic, benzoyl(5)], 8.35 [s, 1H, OH(8a), D_2O exchanged], 12.30 [broad s, 1H, NH, D_2O exchanged]; ^{13}C NMR (75 MHz, DMSO D_6): δ 25.8 [CH_3(3)], 28.8 [CH_3(3)], 52.1 (C-3), 66.7 [CH_2(2)], 87.8 (C-8a), 99.7 (C-5), 108.7 [CH(7)], 128.7, 129.5 and 131.3 [CH, aromatic, benzoyl(5)], 140.5 [Cq, benzoyl(5)], 147.2 [CH(6)], 167.9 (C-4a), 191.2 [CO(8)], 193.7 [CO, benzoyl(5)]; MS(DCI): m/z = 300 (MH^+), (EI): m/z = 299 ($M^{+\cdot}$), m/z = 105 (C_6H_5-CO), m/z = 84 (100%); Elemental analysis: found (C, 64.50; H, 5.70; N, 4.48%), $C_{17}H_{17}NO_4$, H_2O requires (C, 64.35; H, 5.99; N, 4.44%).

[3,3-bis(hydroxymethyl)-8-hydroxy-3,4-dihydro-2H-1,4-benzoxazin-5-yl][phenyl]methanone 8

A solution of compound **3** (165 mg, 0.5 mmol) and TEAP (2.3 g, 10 mmol) in methanol (250 mL) was reduced under nitrogen, at 25°C, at a mercury pool working electrode (E = -1300 mV s.c.e.). After exhaustive electrolysis, the resulting solution was evaporated to dryness under reduced pressure, at 35°C. The residue was poured into a molar acetic acid-buffered solution (pH ~ 4.5) (40 mL) and extracted with ethyl acetate (100 mL). The organic phase was dried over anhydrous sodium sulphate, and the solvent was removed under reduced pressure at 35°C.

Chromatography (ethyl acetate) afforded **8** as an amorphous yellow solid (126 mg, 80% yield, decomposes above 90°C). ^{1}H NMR (300 MHz, DMSO D_6): δ 3.30 [dd, 1H, CH_2OH(3), J = 10 Hz, J = 4 Hz], 3.45 [dd, 2H, CH_2OH(3), J = 10 Hz, J = 4 Hz], 3.90 [s, 2H, CH_2(2), J = 12 Hz], 5.00 [t, 2H, OH(alcohol), J = 4 Hz, D_2O exchanged], 6.05 [d, 1H, H(7), J = 9 Hz], 6.80 [d, 1H, H(6), J = 9 Hz], 7.50 (m, 5H, aromatic, phenyl), 8.80 [s, 1H, NH, D_2O exchanged], 9.90 [s, 1H, OH(8), D_2O exchanged]; ^{13}C NMR (75 MHz, DMSO D_6): δ 56.5 (C-3), 61.2 [CH_2OH(3)], 65.7 [CH_2(2)], 105.2 [CH(7)], 111.2 (C-5), 129.2 and 131.3 (CH, aromatic, phenyl), 129.7 [CH(6)], 130.3 (C-8a), 141.0 (Cq, phenyl) 141.7 (C-4a), 150.8 (C-8), 197.0 (CO, methanone); MS (DCI): m/z = 316 (MH^+); Elemental analysis: found (C, 61.40; H, 5.55; N, 4.17%), $C_{17}H_{17}NO_6$,H_2O requires (C, 61.26; H, 5.71; N, 4.20%).

[2,3,4-trihydroxyphenyl][3',5'-dihydroxy-4'-(2-oxo-2-phenylethoxy)phenyl]methanone 9

To a reaction mixture of exifone **2** (10.0 g, 36 mmol) and lithium carbonate (6.0 g, 90 mmol) in N,N-dimethylformamide (20 mL) was added at room temperature, 7.0 g of ω-bromoacetophenone (36 mmol). The reaction mixture was stirred for 15h at room temperature, under nitrogen. Then, the resulting mixture was poured into a molar acetic acid-buffered solution (pH ~ 4.5) (400 mL) and extracted with ethyl acetate (200 mL). The organic phase was washed vigorously with water and dried over anhydrous sodium sulphate, and

the solvent was removed under reduced pressure at 35°C.

Flash-chromatography [dichloromethane:acetone (90:10)] afforded a pale yellow solid. Recrystallization of this material from dichlomethane:acetone (98:2) led to compound **9** (5.7 g, 40% yield, decomposes above 180°C). ^{1}H NMR (300 MHz, DMSO D_6): δ 4.00 (d, 1H, CH_2, J = 12 Hz), 4.10 (d, 1H, CH_2, J = 12 Hz), 6.40 [d, 1H, H(5), J = 9 Hz], 6.75 and 6.80 [d, 2H, H(2') and H(6'), J = 1.7 Hz], 7.02 [d, 1H, H(6), J = 9 Hz], 7.40 to 7.60 (m, 5H, aromatic, phenylethoxy), 8.70 [s, 1H, OH(3), D_2O exchanged], 9.70 [s, 2H, OH(3') and OH(5'), D_2O exchanged], 10.20 [s, 1H, OH(4), D_2O exchanged], 12.60 [s, 1H, OH(2), D_2O exchanged]; ^{13}C NMR (75 MHz, DMSO D_6): δ 71.3 (CH_2), 95.2 (Cq, phenylethoxy), 108.6 [CH(5)], 110.9 [CH(2') and CH(6')], 114.1 (C-1), 125.7 [CH(6)], 127.5, 129.4 and 130.0 [CH, aromatic, phenylethoxy], 131.4 (C-4'), 133.8 (C-3), 135.9 (C-1'), 141.0 and 143.5 (C-3' and C-5'), 147.0 (CO, phenylethoxy), 153.0 (C-2 and C-4), 199.0 (CO, methanone); MS (DCI): m/z = 397 (MH^+); Elemental analysis: found (C, 63.50, H, 3.95%), $C_{21}H_{16}O_8$ requires: (C, 63.63, H, 4.00%).

(RS)-5-[3,5-dihydroxy-4-(2-oxo-2-phenylethoxy)]-benzoyl-3,3-bis(hydroxymethyl)-8a-hydroxy-3,4-dihydro-2H-1,4-benzoxazin-8(8aH)-one 10

To a solution of compound **9** (0.79 g, 2 mmol) and Tris (12.10 g, 100 mmol) in methanol (1 L) was added 2.30 g of silver oxide (10 mmol). The mixture was stirred at room temperature for 2h, under nitrogen. Then, the solid residue was removed by filtration and the filtrate was evaporated to dryness under pressure. The residue was poured into a molar acetic acid-buffered solution (pH ~ 4.0) (200 mL) and extracted with ethyl acetate (400 mL). The organic phase was dried over anhydrous sodium sulphate, and the solvent was removed under reduced pressure at 35°C.

Chromatography [ethyl acetate:methanol (97:3)] afforded **10** as an amorphous orange solid (0.35 g, 35% yield, decomposes above 180°C). ^{1}H NMR (300 MHz, DMSO D_6): δ 3.40 [dd, 1H, $CH_2OH(3)$, J = 12 Hz, J = 5 Hz], 3.50 [d, 2H, $CH_2OH(3)$, J = 5 Hz], 3.60 [dd, 1H, $CH_2OH(3)$, J = 12 Hz, J = 5 Hz], 3.85 [d, 1H, $CH_2(2)$, J = 12 Hz], 3.90 [dd, 1H, CH_2(phenylethoxy), J = 12 Hz, J = 5 Hz], 4.20 [d, 2H, $CH_2(2)$ and CH_2(phenylethoxy), J = 12 Hz], 5.20 [dd, 1H, H(7), J = 10 Hz, J = 2 Hz], 5.35 [m, 2H, OH(alcohol), D_2O exchanged], 6.55 [m, 2H, H(2) and H(6), benzoyl(5)], 7.30 [dd, 1H, H(6), J = 10 Hz, J = 2 Hz], 7.40 to 7.60 [m, 5H, aromatic, phenylethoxy], 8.30 [s, 1H, OH(8a), D_2O exchanged], 9.60 [s, 2H, OH(3) and OH(5), benzoyl(5), D_2O exchanged], 12.10 [s, 1H, NH, D_2O exchanged]; ^{13}C NMR (75 MHz, DMSO D_6): δ 57.7 (C-3), 59.5 [$CH_2(2)$], 61.9 [$CH_2OH(3)$], 62.4 [$CH_2OH(3)$], 71.3 [CH_2, phenylethoxy], 88.0 (C-8a), 95.2 (Cq, phenylethoxy), 99.9 (C-5), 108.3 [CH(7)], 109.3 and 109.8 [CH(2) and CH(6), benzoyl(5)], 127.4, 129.3 and 130.2 [CH, aromatic, phenylethoxy], 134.5 [C-4, benzoyl(5)], 135.7 [C-1, benzoyl(5)], 141.1 and 143.6 [C-3 and C-5, benzoyl(5)], 146.9 (CO, phenylethoxy), 147.7 [CH(6)], 168.2 (C-4a), 191.4 [CO(8)], 192.4 [CO, benzoyl(5)]; MS (DCI): m/z = 498 (MH^+).

[3,3-bis(hydroxymethyl)-8-hydroxy-3,4-dihydro-2H-1,4-benzoxazin-5-yl][3',5'-dihydroxy-4'-(2-oxo-2-phenylethoxy)phenyl]methanone 11

Method A: A solution of compound **10** (241 mg, 0.5 mmol) and TEAP (2.3 g, 10 mmol) in methanol (250 mL) was reduced under nitrogen, at 25°C, at a mercury pool working electrode (E = -1200 mV s.c.e.). After exhaustive electrolysis, the resulting solution was evaporated to dryness under reduced pressure, at 35°C. The residue was poured into a molar acetic acid-buffered solution (pH ~ 4.5) (40 mL) and extracted with ethyl acetate (100 mL). The organic phase was dried over anhydrous sodium sulphate, and the solvent

was removed under reduced pressure at 35°C.

Chromatography (ethyl acetate) afforded **11** as an amorphous yellow solid (169 mg, 70% yield, decomposes above 270°C). ^{1}H NMR (300 MHz, DMSO D_6): δ 3.35 [dd, 1H, $CH_2OH(3)$, J = 11 Hz, J = 5 Hz], 3.50 [dd, 2H, $CH_2OH(3)$, J = 11 Hz, J = 5 Hz], 3.90 [s, 2H, $CH_2(2)$], 3.95 [d, 1H, CH_2(phenylethoxy), J = 11 Hz], 4.20 [d, 1H, CH_2(phenylethoxy), J = 11 Hz], 5.05 [t, 2H, OH(alcohol), J = 5 Hz, D_2O exchanged], 6.10 [d, 1H, H(7), J = 9 Hz], 6.60 [m, 2H, H(2') and H(6')], 7.00 [d, 1H, H(6), J = 9 Hz], 7.40 to 7.60 (m, 5H, aromatic, phenylethoxy), 8.55 [s, 1H, NH, D_2O exchanged], 9.60 [s, 2H, OH(3') and OH(5'), D_2O exchanged], 9.85 [s, 1H, OH(8), D_2O exchanged]; ^{13}C NMR (75 MHz, DMSO D_6): δ 56.5 (C-3), 61.3 [$CH_2OH(3)$], 65.8 [$CH_2(2)$], 71.3 [CH_2, phenylethoxy], 95.2 (Cq, phenylethoxy), 104.9 [CH(7)], 110.2 and 110.6 [CH(2') and CH(6')], 111.4 (C-5), 127.5 and 129.4 (CH, aromatic, phenylethoxy), 130.0 [CH(6)], 130.4 (C-8a), 133.9 (C-4'), 134.6 (C-1'), 140.7 (C-4a), 141.1 and 143.3 (C-3' and C-5'), 146.6 (CO, phenylethoxy), 150.6 (C-8), 196.1 (CO, methanone); MS (DCI): m/z = 482 (MH^+); Elemental analysis: found (C, 60.08, H, 5.00, N, 2.85%), $C_{25}H_{23}NO_9$,H_2O requires (C, 60.12, H,5.01, N, 2.80%).

Method B: To a solution of compound **10** (0.58 g, 1.2 mmol) in 20 mL of methanol, was added at room temperature, 5 mL of concentrated acetic acid. Then, zinc dust (0.38 g, 6 mmol) was added and the resulting mixture was stirred for 2 min at room temperature. The reaction mixture was filtered and water (20 mL) was then added. The resulting solution was concentrated to 10 mL under reduced pressure at 35°C. Then, a solid residue appeared in the bulk solution which was removed by filtration, washed with water and triturated with a dichloromethane:acetone (98:2) mixture to yield compound **11** (0.38 g, 65% yield).

[3,3-bis(hydroxymethyl)-8-hydroxy-3,4-dihydro-2H-1,4-benzoxazin-5-yl][3',4',5'-trihydroxyphenyl]methanone 12

Using method A, but working at -1500 mV s.c.e., preparative scale electrolysis of **10** afforded compound **12** (145 mg, 80% yield, decomposes above 150°C). ^{1}H NMR (300 MHz, DMSO D_6): δ 3.30 [dd, 1H, $CH_2OH(3)$, J = 11 Hz, J = 5 Hz], 3.50 [dd, 2H, $CH_2OH(3)$, J = 11 Hz, J = 5 Hz], 3.90 [s, 2H, $CH_2(2)$], 3.95 [d, 1H, CH_2(phenylethoxy), J = 11 Hz], 5.00 [t, 2H, OH(alcohol), J = 5 Hz, D_2O exchanged], 6.10 [d, 1H, H(7), J = 9 Hz], 6.50 [m, 2H, H(2') and H(6')], 7.00 [d, 1H, H(6), J = 9 Hz], 8.30 [s, 1H, NH, D_2O exchanged], 8.70 [s, 1H, OH(4'), D_2O exchanged], 9.15 [s, 2H, OH(3') and OH(5'), D_2O exchanged], 9.70 [s, 1H, OH(8), D_2O exchanged]; ^{13}C NMR (75 MHz, DMSO D_6): δ 56.3 (C-3), 61.3 [$CH_2OH(3)$], 65.9 [$CH_2(2)$], 104.5 [CH(7)], 109.7 [CH(2') and CH(6')], 111.9 (C-5), 129.2 [CH(6)], 130.4 (C-8a), 131.5 (C-1'), 137.4 (C-4a), 140.2 (C-4'), 146.3 (C-3' and C-5'), 150.2 (C-8), 196.5 (CO, methanone); MS (DCI): m/z = 364 (MH^+)

Using method B, and after allowing the reaction to react for 30 min, the reaction mixture of **10** was filtered and water (20 mL) was then added. The resulting solution was concentrated to 20 mL under reduced pressure at 35°C, and extracted with ethyl acetate (100 mL). The organic phase was dried over anhydrous soudium sulphate, and the solvent was removed under reduced pressure at 35°C. The residue was triturated with a dichloromethane:acetone (97:3) mixture to produce compound **12** (0.28 g, 66% yield).

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