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Synthesis of 9- and 10-membered macrolactones by selective ozonolysis of 1,4-diazaphenanthrene derivatives

Elisa Pérez-Sacau,[a,b] Jorge Soto-Delgado,[a,b] Ana Estévez-Braun[a,b,*] and Ángel G. Ravelo[a,b,*]

[a]*Instituto Universitario de Bio-Orgánica 'Antonio González', Avda. Astrofísico Fco. Sánchez 2, 38206, La Laguna, Tenerife, Spain*
[b]*Instituto Canario de Investigación del Cáncer, Hospital Universitario de La Candelaria, 38010, Tenerife, Spain*

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Abstract—9- and 10-membered macrolactones bearing benzo and diazine rings were obtained by chemoselective ozonolysis of dihydrofuran and pyran 1,4-diazaphenathrene derivatives. This is the first example of preparation of macrolactones by chemoselective ozonolysis of an enol double bond shared by aromatic and heterocyclic rings.

1. Introduction

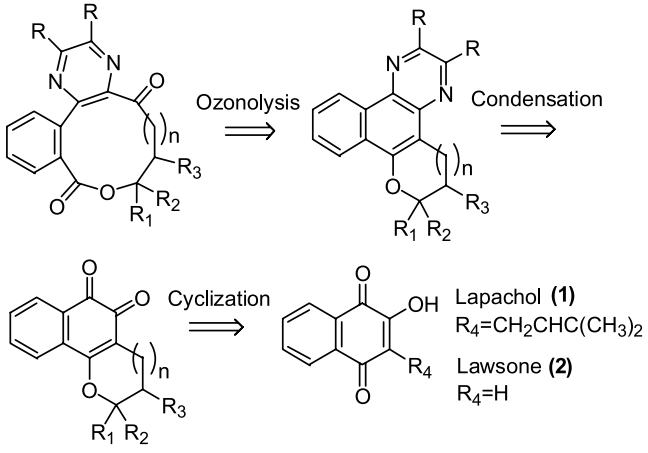
Macrolides are an attractive class of compounds that have shown a wide variety of interesting bioactivities.[1] Some representative examples are leucascandrolide,[2] epothilone,[3] erythromycin,[4] or salicylihalamide.[5] Among the 9- and 10-membered macrolactones, the antibiotic activity of lustromycin,[6] the anti-proliferative properties of apicularen,[7] or the bacterial DNA primase inhibitory activity of Sch 642305,[8] stand out. This variety of activities may be due to the fact that macrolides often show multiple low-energy conformations. Changes in the position and nature of the substituents can alter the free energy penalty for distortion of one of these small molecules upon binding to a protein target.[9] Consequently, the ability of these host molecules to bind guests is often very specific, enabling the host to recognize just one molecule or ion in a mixture.

On the other hand, there are many examples of natural and synthetic phenazines which exhibit diverse activities like antimalarial,[10] trypanocidal,[11] fungicidal,[12] or antiplatelet.[13] These heterocyclic compounds fulfill the fundamental physicochemical requirements for DNA intercalation, exhibiting antitumor activity in leukaemia and solid tumours. Some benzophenazines are dual inhibitors of topoisomerase I and II, two key enzymes that affect the topology of DNA at different points in the cell cycle.[14]

This paper describes the preparation of macrocyclic compounds with fused benzo and diazine moieties. The presence of diaza heterocyclic rings close to the ion-binding macrolactone moiety opens attractive possibilities, offering the potential of coupling DNA-damage with ion-binding properties.

2. Results and discussion

Scheme 1 shows the retrosynthetic pathway toward the macrolactones. It involves ozonolysis, condensation and cyclization processes.



Scheme 1.

The initial precursors, lapachol **1** and lawsone **2**, are bioactive naphthoquinones isolated from plants of the

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* Corresponding authors. Tel.: +34 922 318576; fax: +34 922 318571; e-mail addresses: aestebra@ull.es; agravelo@ull.es

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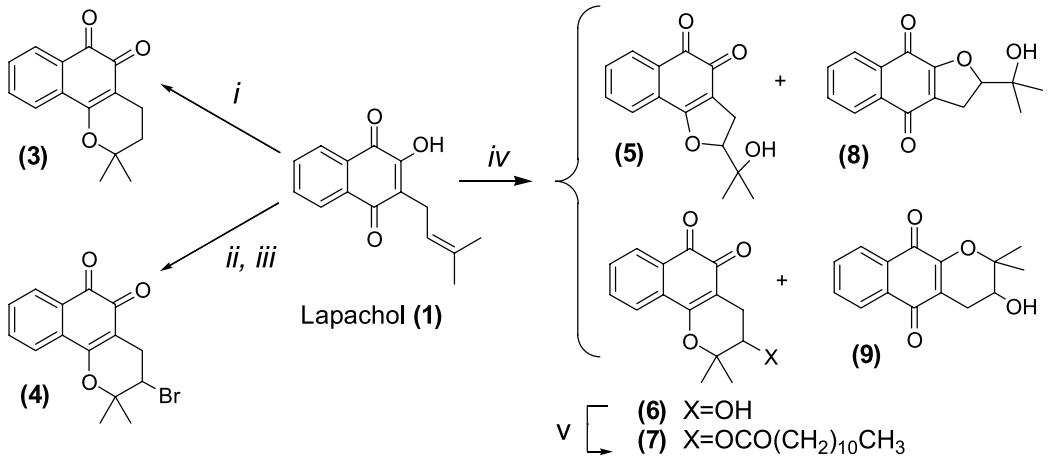
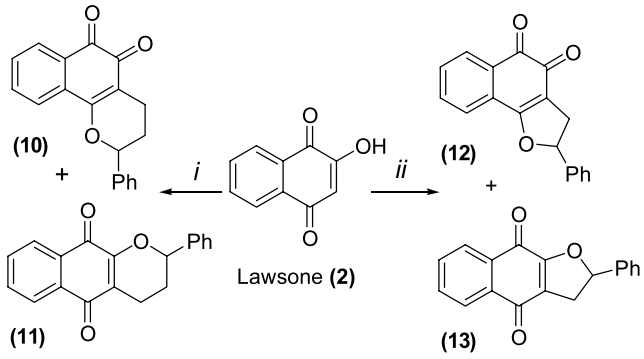


Scheme 2. Reagents and conditions: (i) H_2SO_4, 0 °C; (ii) Lutidine, $ClCOCH_3$, dry CH_2Cl_2, 0 °C; (iii) Br_2, dry CH_2Cl_2; (iv) *m*-CPBA, CH_2Cl_2, 0 °C; (v) Py, $ClCO(CH_2)_{10}CH_3$, dry CH_2Cl_2, 0 °C.

Bignoniaceae family.[15] They are also commercial products easily available. The furan ($n=0$) and pyran ($n=1$) *ortho*-1,2-naphthoquinones were synthesized from **1** and **2**. Lapachol was converted into *ortho*-naphthoquinones by intra-cyclization in different conditions[15,16] (H_2SO_4, Br_2, *m*-CPBA). The treatment of **1** with *m*-CPBA also afforded *para*-1,4-naphthoquinone analogues (α-isomers **8** and **9**) (see Scheme 2).

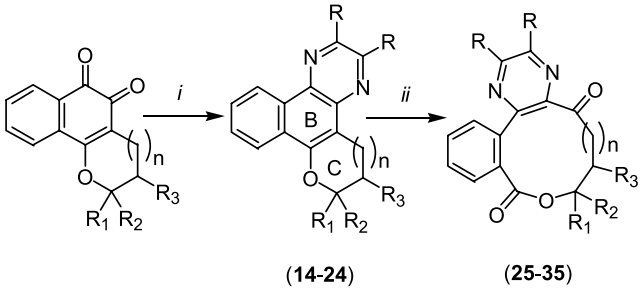
The non-prenyl *ortho*-naphthoquinones **10** and **12** were obtained from lawsone **2** following the reactions shown in Scheme 3. The Knoevenagel condensation of **2** and paraformaldehyde $(CH_2O)_n$ leads to a quinone methide intermediate, which undergoes hetero Diels–Alder reaction with styrene as dienophile[17] yielding, in one-pot reaction, the pyran-naphthoquinone derivatives **10** and **11**. The treatment of **2** with CAN and styrene[18] also yielded in one-pot reaction the dihydrofuran-naphthoquinone derivatives **12** and **13** via [3+2] type cycloaddition.

1,4-Diazaphenanthrene derivatives were synthesized by condensation of the *ortho*-quinones with 1,2-ethylendiamine or *trans*-1,2-diaminecyclohexane.[19]



Scheme 3. Reagents and conditions: (i) Dioxane, 7 equiv $(CH_2O)_n$, reflux, 3 equiv styrene; (ii) CH_3CN/H_2O (3/1), 2 equiv CAN, 0 °C-rt, 10 equiv styrene.

The dihydrofuran or pyran 1,4-diazaphenanthrene compounds were treated with ozone, which produced a selective oxidative cleavage of the enol double bond shared by rings B and C, leading to the corresponding macrolactones (Scheme 4).



Scheme 4. Reagents and conditions: (i) 1,2-ethylenediamine or *trans*-1,2-diamine cyclohexane, molecular sieves 4 Å toluene, Δ, 24 h–2 days; (ii) (a) O_3, −78 °C, dry CH_2Cl_2, 10–20 min. (b) Me_2S.

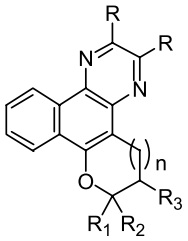
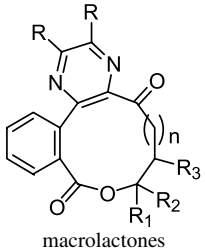
This enol double bond shows a behaviour similar to the 9,10-double bond in polyaromatic phenanthrene systems, which is the most labile in terms of its chemical reactivity, and readily broken under oxidative conditions to yield dialdehydes or acid derivatives.[20]

By far, the most general route to macrolactones is by intramolecular ring closure.[21] Other strategies are ring contraction and ring expansion. Ring contractions leading to macrolactones are relatively rare because of the problem of finding suitable large ring precursors for reactions.[22] The ring expansion can be achieved by cleavage of a C–C bond of suitable starting materials,[23] by C=C double bond cleavage of bicyclic vinyl ethers,[24] and sometimes also by a Baeyer-Villiger oxidation reaction.[25]

To the best of our knowledge, this letter presents the first example of macrolide formation by ozonolysis of an aromatic double bond at the site of fusion of the pyran or dihydrofuran moiety.

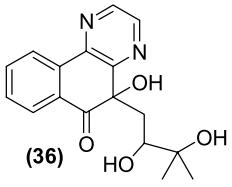
Table 1 summarizes the results obtained in the formation of 1,4-diazaphenanthrene derivatives and macrocyclic compounds. The reactivity seemed quite substrate dependent. The diazines from 1,2-ethylenediamine were obtained in yields higher than those from *trans*-1,2-

Table 1. Yields of 1,4-diazaphenanthrenes (**14**–**24**) and macrolactones (**25**–**35**)

Entry	*n*	R	R_1	R_2	R_3	 1,4-diazaphenanthrenes	 macrolactones
1	0	$-(CH_2)_4-$	$-C(OH)(CH_3)_2$	H	H	**14** 70%	**25** 68%
2	0	$-(CH_2)_4-$	Ph	H	H	**15** 49%	**26** 22%
3	1	$-(CH_2)_4-$	Me	Me	H	**16** 71%	**27** 68%
4	1	$-(CH_2)_4-$	Me	Me	OH	**17** 47%	**28** 47%
5	1	$-(CH_2)_4-$	Me	Me	Br	**18** 51%	**29** 46%
6	1	$-(CH_2)_4-$	Me	Me	$-OCO(CH_2)_{10}CH_3$	**19** 78%	**30** 22%
7	0	H	$-C(OH)(CH_3)_2$	H	H	**20** 70%	**31** 70%
8	1	H	Me	Me	H	**21** 68%	**32** 61%
9	1	H	Me	Me	OH	**22** 89%	**33** 68%
10	1	H	Me	Me	Br	**23** 80%	**34** 37%
11	1	H	Ph	H	H	**24** 51%	**35** 53%

diaminecyclohexane. The best results in the ozonolysis were found for 1,4-diazaphenanthrene derivatives bearing non-voluminous substituents at the pyran or dihydrofuran ring (compounds **25**, **27**, **31** and **32**).

We also tried an oxidative cleavage using *m*-CPBA as oxidative agent, but mixtures of several N-oxide derivatives and polyalcohols were obtained. However, the ozonolysis process provides cleaner and more selective reactions, only in one case (Entry 9), was the polyalcohol **36** (21%) produced together with the desired macrolactone **33**.



(36)

The NMR spectra of the 10-membered macrolactones ($n=1$) with $R_3=$Br, –OH or $-OCO(CH_2)_{10}CH_3$ (compounds **28**, **29**, **30**, **33** and **34**), showed the existence of two thermodynamically interchangeable conformers in a ratio 3:1. When $R_3=$Br (**27** and **32**), the two conformers are easy to distinguish in their ^{1}H and ^{13}C NMR spectra. In order to obtain an approximate idea on the geometry and energy of these molecules, an analysis was made using GMMX calculations.[26] After multiple minimizations of **32**, two main lower-energy conformers I and II were found (see Fig. 1). According to the studies on C_7–C_{10} cycloalkanes conformers recently carried out by Wiberg,[27] the structures of conformers I and II are similar to the geometries defined as S_5 and S_9 respectively, with slight distortions due to the presence of aromatics rings.

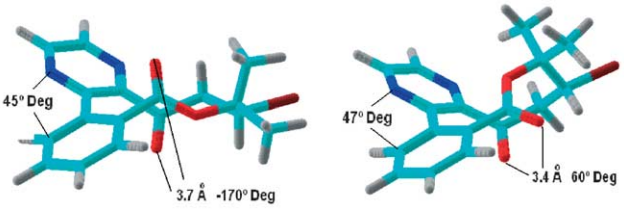


Figure 1. Lower-energy Conformers I and II.

The values of coupling constants between the proton geminal to the bromine group and the contiguous hydrogens were estimated, and the results agree with the experimental data.

Macrolides are very important target molecules in synthetic studies because of their biological and medicinal activities. Our work describes a new pathway to form highly functionalized 9- and 10-membered lactone rings from phenanthrenic aromatic systems linked face-to-face in a heterocyclic system.

Studies concerning the evaluation of biological activities, and the extended application of this methodology to other phenanthrenic systems, are in progress.

3. Experimental

3.1. General methods

All condensation reactions of the *ortho*-quinones with 1,2-diamine were carried out in toluene using activated molecular sieves 4 Å. Ozonolysis reactions were carried out on anhydrous conditions using glassware dried overnight at 100 °C and flamed just before using it. CH_2Cl_2 was dried on CaH_2 and distilled before use. Me_2S was dried on CaH_2 and distilled over molecular sieves. Ozon-Generator OZIV Fisher Labortechnik was used to generate O_3 flow. Reactions were monitored by TLC (on silica gel POLYGRAM® SIL G/UV_{254} foils). Purification by column flash-chromatography used Merck Kiesel 60-H (0.063–0.2 mm) as adsorbent and different mixtures of hexanes–ethylacetate as eluent. Pre-coated TLC plates SIL G-100 UV_{254} (Macherey-Nagel) were used for preparative-TLC purification. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ or C_6D_6 using a Bruker AMX-300 MHz. Chemical

shifts are given in parts per million (ppm) and J values are given in Hertz (Hz). Complete ^{1}H and ^{13}C assignments were achieved by 2D NMR spectroscopy (COSY, HMBC and HSQC). Bidimensional spectra were recorded in $CDCl_3$ or C_6D_6 using a Bruker AMX-400 MHz. MS and HRMS were recorded at VG Micromass ZAB-2F. All compounds were named using ACD40 Name-Pro program, which is based on IUPAC rules.

3.2. General procedure for the preparation of 1,4-diazaphenantrenes (14–24)

A solution of *ortho*-naphthoquinone and *trans*-1,2-diaminecyclohexane or 1,2-ethylendiamine (1.2–2 equiv) in dry toluene was stirred under reflux for 24 h in the presence of molecular sieves 4 Å. The reaction mixture was cooled to room temperature, filtered and the solvent removed under vacuum. The crude product was chromatographed using mixtures of hexanes/EtOAc as eluent.

3.2.1. 2-(1,2,9,10,11,12-Hexahydrobenzo[*a*]furo[2,3-*c*]phenazin-2-yl)-2-propanol (14). Following the general procedure described above, 30 mg (0.12 mmol) of **5** were treated with 17 μL (0.14 mmol) of *trans*-1,2-diaminecyclohexane. The crude was chromatographed on silica gel with 9:1 to 1:1 Hex/EtOAc, to obtain 27 mg (70%) of **14**. ^{1}H NMR ($CDCl_3$) δ: 9.15 (1H, m, H-7), 8.04 (1H, m, H-4), 7.71 (2H, m, H-5+H-6), 4.99 (1H, m, H-2), 3.66 (1H, dd, J=15.8, 9.9 Hz, H-1a), 3.58 (1H, dd, J=15.8, 8.8 Hz, H-1b), 3.17 (4H, m, H-9+H-12), 2.04 (4H, m, H-10+H-11), 1.46 (3H, s, H-2′), 1.31 (3H, s, H-3′). ^{13}C NMR ($CDCl_3$) δ: 155.8 (s, C-3a), 152.9 (s, C-8a), 148.7 (s, C-12a), 139.2 (s, C-13a), 136.6 (s, C-7b), 131.3 (s, C-7a), 128.0 (d, C-5), 127.2 (d, C-6), 124.8 (d, C-7), 122.5 (s, C-3b), 121.4 (d, C-4), 114.3 (s, C-13b), 91.1 (d, C-2), 72.2 (s, C-1′), 32.9 (t, C-12), 32.8 (t, C-9), 29.9 (t, C-1), 26.0 (q, C-2′), 23.8 (q, C-3′), 23.0×2 (t, C-10, 11). MS *m*/*z* (rel. int): 334 (M^+, 100), 275 (M^+ − C(OH)$(CH_3)_2$, 78), 263 (M^+ −71, 97). HRMS: 334.1674 (calcd for $C_{21}H_{22}N_2O_2$ (M^+) 334.1681).

3.2.2. 2-Phenyl-1,2,9,10,11,12-hexahydrobenzo[*a*]furo[2,3-*c*]phenazines (15). Following the general procedure described above, 108 mg (0.39 mmol) of **12** were treated with 88 μL (0.73 mmol) of *trans*-1,2-diaminecyclohexane. The crude was chromatographed on silica with 19:1 to 4:1 Hex/EtOAc, to yield 67 mg (49%) of **15**. ^{1}H NMR ($CDCl_3$) δ: 9.18 (1H, m, H-7), 8.13 (1H, m, H-4), 7.71 (2H, m, H-5+H-6), 7.50 (2H, m, H-2′+H-6′), 7.34 (3H, m, H-3′+H-4′+H-5′), 6.15 (1H, m, H-2), 4.15 (1H, dd, J=15.6, 10.1 Hz, H-1a), 3.69 (1H, dd, J=15.6, 7.4 Hz, H-1b), 3.19 (2H, bs, H-9), 3.14 (2H, bs, H-12), 2.03 (4H, bs, H-10+H-11). ^{13}C NMR ($CDCl_3$) δ: 156.0 (s, C-3a), 152.9 (s, C-8a), 148.6 (s, C-12a), 142.1 (s, C-1′), 139.3 (s, C-13a), 136.7 (s, C-7b), 131.5 (s, C-7a), 128.7×2 (d, C-3′, 5′), 128.1×2 (d, C-5, 4′), 127.2 (d, C-6), 125.7×2 (d, C-2′, 6′), 124.8 (d, C-7), 122.7 (s, C-3b), 121.8 (d, C-4), 113.3 (s, C-13b), 85.6 (d, C-2), 37.3 (t, C-1), 32.9 (t, C-12), 32.8 (t, C-9), 23.1 (t, C-11), 23.0 (t, C-10). MS *m*/*z* (rel. int): 352 (M^+, 100), 275 (M^+ − Ph, 69). HRMS: 352.1596 (calcd for $C_{24}H_{20}N_2O$ (M^+) 352.1576).

3.2.3. 3,3-Dimethyl-2,3,10,11,12,13-hexahydro-1*H*-benzo[*a*]pyrano[2,3-*c*]phenazines (16). Following the general procedure described above, 219 mg (0.90 mmol) of **3** were treated with 230 μL (1.92 mmol) of *trans*-1,2-diaminecyclohexane. The crude was purified by flash chromatography on silica gel using Hex/EtOAc (9:1) as eluent, to obtain 204 mg (71%) of **16**. ^{1}H NMR (C_6D_6) δ: 9.57 (1H, m, H-8), 8.55 (1H, m, H-5), 7.53 (2H, m, H-6+H-7), 3.32 (2H, t, J=6.7 Hz, H-1), 3.06 (4H, m, H-10+H-13), 1.66 (2H, t, J=6.7 Hz, H-2), 1.61 (4H, m, H-11+H-12), 1.26 (6H, s, H-1′+H-2′). ^{13}C NMR (C_6D_6) δ: 151.9 (s, C-9a), 149.7 (s, C-4a), 148.4 (s, C-13a), 141.3 (s, C-14a), 135.9 (s, C-8b), 131.0 (s, C-8a), 128.1 (s, C-4b), 127.9 (d, C-6), 126.9 (d, C-7), 124.5 (d, C-8), 122.0 (d, C-5), 110.3 (s, C-14b), 74.9 (s, C-3), 33.0 (t, C-2), 32.6 (t, C-10 or 13), 32.3 (t, C-13 or 10), 26.4×2 (q, C-1′+C-2′), 23.0×2 (t, C-11, 12), 18.3 (t, C-1). MS *m*/*z* (rel. int): 318 (M^+, 83), 303 (M^+ − Me, 6), 275 (M^+ − C_3H_7, 100). HRMS: 318.1723 (calcd for $C_{21}H_{22}N_2O$ (M^+) 318.1732).

3.2.4. 3,3-Dimethyl-2,3,10,11,12,13-hexahydro-1*H*-benzo[*a*]pyrano[2,3-*c*]phenazin-2-ol (17). Following the general procedure described above, 180 mg (0.70 mmol) of **6** were treated with 100 μL (0.83 mmol) of *trans*-1,2-diaminecyclohexane. The crude was chromatographed on silica gel with 9:1 to 1:1 Hex/EtOAc, to obtain 108 mg (49%) of **17**. ^{1}H NMR ($CDCl_3$) δ: 9.01 (1H, m, H-8), 8.21 (1H, m, H-5), 7.66 (2H, m, H-6+H-7), 4.02 (1H, bs, H-2), 3.32 (2H, m, H-1), 3.27–3.10 (2H, m, H-13), 3.04 (2H, m, H-10), 2.46 (1H, bs, OH), 2.03 (4H, m, H-11+H-12), 1.58 (3H, s, H-1′), 1.39 (3H, s, H-2′). ^{13}C NMR ($CDCl_3$) δ: 152.2 (s, C-9a), 149.0 (s, C-13a), 148.4 (s, C-4a), 140.7 (s, C-14a), 135.5 (s, C-8b), 130.1 (s, C-8a), 127.7 (d, C-7), 127.1 (d, C-6), 126.9 (s, C-4b), 123.9 (d, C-8), 121.6 (d, C-5), 107.6 (s, C-14b), 78.0 (s, C-3), 69.5 (d, C-2), 32.9 (t, C-13), 32.6 (t, C-10), 27.5 (t, C-1), 24.4 (q, C-1′), 23.0×2 (t, C-11+C-12), 22.6 (q, C-2′). MS *m*/*z* (rel. int): 334 (M^+, 36), 263 (M^+ − $C(CH_3)_2CHOH$, 100). HRMS: 334.1674 (calcd for $C_{21}H_{22}N_2O_2$ (M^+) 334.1681).

3.2.5. 2-Bromo-3,3-dimethyl-2, 3,10,11,12,13-hexahydro-1*H*-benzo[*a*]pyrano[2,3-*c*]phenazines (18). Following the general procedure described above, 97 mg (0.30 mmol) of **4** were treated with 43 μL (0.36 mmol) of *trans*-1,2-diaminecyclohexane. The crude was purified by flash chromatography on silica gel using Hex/EtOAc (19:1) as eluent, to obtain 61 mg (51%) of **18**. ^{1}H NMR ($CDCl_3$) δ: 9.11 (1H, m, H-8), 8.25 (1H, m, H-5), 7.68 (2H, m, H-6+H-7), 4.47 (1H, dd, J=8.5, 5.6 Hz, H-2), 3.92 (1H, dd, J=18.0, 5.6 Hz, H-1a), 3.61 (1H, dd, J=18.0, 8.5 Hz, H-1b), 3.16 (4H, m, H-13+H-10), 2.03 (4H, m, H-11+H-12), 1.70 (3H, s, H-1′), 1.58 (3H, s, H-2′). ^{13}C NMR ($CDCl_3$) δ: 152.4 (s, C-9a), 149.2 (s, C-13a), 148.4 (s, C-4a), 140.1 (s, C-14a), 135.8 (s, C-8b), 130.4 (s, C-8a), 128.0 (d, C-6), 127.2 (d, C-7), 127.0 (s, C-4b), 124.0 (d, C-8), 121.7 (d, C-5), 108.9 (s, C-14b), 77.9 (s, C-3), 53.0 (d, C-2), 32.9 (t, C-13), 32.7 (t, C-10), 30.3 (t, C-1), 26.8 (q, C-1′), 23.1 (t, C-11), 23.0 (t, C-12), 22.0 (q, C-2′). MS *m*/*z* (rel. int): 398 (M^++2, 46), 396 (M^+, 46), 317 (M^+ − Br, 100). HRMS: 396.0860 (calcd for $C_{21}H_{21}N_2O\,Br^{79}$ (M^+) 396.0837).

3.2.6. 3,3-Dimethyl-2,3,10,11,12,13-hexahydro-1*H*-benzo[*a*]pyrano[2,3-*c*]phenazin-2-yl laurate (19). Following the general procedure described above, 98 mg (0.22 mmol) of **7** were treated with 52 μL (0.43 mmol) of *trans*-1,2-

diaminecyclohexane. The crude was chromatographed on silica gel with 19:1 to 4:1 Hex/EtOAc, to obtain 88 mg (78%) of **19**. ^{1}H NMR ($CDCl_3$) δ: 9.12 (1H, m, H-8), 8.30 (1H, m, H-5), 7.68 (2H, m, H-6+H-7), 5.28 (1H, t, J= 5.2 Hz, H-2), 3.51 (1H, dd, J=18.1, 5.3 Hz, H-1a), 3.27 (dd, 1H, J=18.1, 5.2 Hz, H-1b), 3.18 (2H, bs, H-13), 3.13 (2H, bs, H-10), 2.30 (2H, m, H-4′), 2.02 (4H, m, H-11+H-12), 1.57 (4H, m, H-5′+H-6′), 1.48 (3H, s, H-2′), 1.46 (3H, s, H-1′), 1.21 (14H, bs, H-7′+H-8′+H-9′+H-10′+H-11′+ H-12′+H-13′), 0.87 (3H, m, H-14′). ^{13}C NMR ($CDCl_3$) δ: 173.3 (s, C-3′), 152.3 (s, C-9a), 149.0 (s, C-13a), 148.5 (s, C-4a), 140.7 (s, C-14a), 135.8 (s, C-8b), 130.4 (s, C-8a), 127.9 (d, C-7), 127.2 (d, C-6), 127.1 (s, C-4b), 124.0 (d, C-8), 121.8 (d, C-5), 107.7 (s, C-14b), 76.2 (s, C-3), 70.7 (d, C-2), 34.5 (t), 32.9 (t), 32.7 (t), 31.9 (t), 29.5×2 (t), 29.4 (t), 29.3 (t), 29.2 (t), 29.1 (t), 25.1 (t), 24.8 (q, C-1′), 24.7 (t), 23.1 (t, C-12), 23.0 (t, C-11), 22.6 (t), 22.6 (q, C-2′), 14.1 (q, C-14′). MS *m/z* (rel. int): 516 (M^+, 8), 316 (M^+ − $OCO(CH_2)_{10}CH_3$, 61), 301 (316-Me, 100). HRMS: 516.3351 (calcd for $C_{33}H_{44}N_2O_3$ (M^+) 516.3352).

3.2.7. 2-(2,3-Dihydrobenzo[*f*]furo[2,3-*h*]quinoxalin-2-yl)-2-propanol (20). Following the general procedure described above, 101 mg (0.39 mmol) of **5** were treated with 52 μL (0.78 mmol) of 1,2-ethylendiamine. The crude was chromatographed on silica gel with 4:1 to 2:3 Hex/EtOAc, to obtain 79 mg (70%) of **20**. ^{1}H NMR ($CDCl_3$) δ: 9.09 (1H, m, H-8), 8.72 (1H, d, J=2.1 Hz, H-5), 8.67 (1H, d, J=2.1 Hz, H-6), 7.98 (1H, m, H-11), 7.67 (2H, m, H-9+ H-10), 4.98 (1H, t, J=9.3 Hz, H-2), 3.60 (2H, d, J=9.3 Hz, H-3), 1.47 (3H, s, H-2′), 1.31 (3H, s, H-3′). ^{13}C NMR ($CDCl_3$) δ: 157.0 (s, C-11b), 143.9 (d, C-5), 141.4 (s, C-3b), 139.7 (d, C-6), 138.9 (s, C-8b), 131.3 (s, C-8a), 128.7 (d, C-10), 127.6 (d, C-9), 125.0 (d, C-8), 122.8 (s, C-11a), 121.5 (d, C-11), 114.5 (s, C-4b), 91.5 (d, C-2), 72.0 (s, C-1′), 29.5 (t, C-3), 26.0 (q, C-2′), 24.0 (q, C-3′). MS *m/z* (%): 280 (M^+, 41), 221 (M^+ −71, 100). HRMS: 280.1210 (calcd for $C_{17}H_{16}N_2O_2$ (M^+) 280.1212).

3.2.8. 7,7-Dimethyl-6,7-dihydro-5*H*-benzo[*f*]pyrano [2,3-*h*]quinoxaline (21). Following the general procedure described above, 110 mg (0.45 mmol) of **3** were treated with 60 μL (0.90 mmol) of 1,2-ethylendiamine. The crude was chromatographed on silica gel with 19:1 to 4:1 Hex/EtOAc, to obtain 81 mg (68%) of **21**. ^{1}H NMR ($CDCl_3$) δ: 9.13 (1H, m, H-12), 8.80 (1H, d, J=2.0 Hz, H-3), 8.71 (1H, d, J=2.0 Hz, H-2), 8.33 (1H, m, H-9), 7.73 (2H, m, H-10+ H-11), 3.23 (2H, t, J=6.7 Hz, H-5), 2.03 (2H, t, J=6.7 Hz, H-6), 1.50 (6H, s, H-1′+H-2′). ^{13}C NMR ($CDCl_3$) δ: 150.8 (s, C-8a), 143.4 (s, C-4a), 143.4 (d, C-3), 139.9 (d, C-2), 138.1 (s, C-12b), 130.3 (s, C-12a), 128.6 (d, C-10), 128.2 (s, C-8b), 127.3 (d, C-11), 124.2 (d, C-12), 121.9 (d, C-9), 110.0 (s, C-4b), 75.7 (s, C-7), 32.4 (t, C-6), 26.7×2 (q, C-1′+C-2′), 18.2 (t, C-5). MS *m/z* (rel. int): 264 (M^+, 65), 249 (M^+ −Me, 16), 221 (M^+ −Me–CO, 100). HRMS: 264.1249 (calcd for $C_{17}H_{16}N_2O$ (M^+) 264.1263).

3.2.9. 7,7-Dimethyl-6,7-dihydro-5*H*-benzo[*f*]pyrano [2,3-*h*]quinoxalin-6-ol (22). Following the general procedure described above, 152 mg (0.59 mmol) of **6** were treated with 80 μL (1.20 mmol) of 1,2-ethylendiamine. The crude was purified by flash chromatography on silica gel using Hex/EtOAc (3:2) as eluent, to obtain 147 mg (89%) of **22**. ^{1}H NMR ($CDCl_3$) δ: 9.12 (1H, m, H-12), 8.76 (1H, bs, H-3), 8.72 (1H, bs, H-2), 8.33 (1H, m, H-9), 7.73 (2H, m, H-10+ H-11), 5.11 (1H, m, H-6), 3.46 (1H, dd, J=17.7, 5.0 Hz, H-5a), 3.31 (1H, dd, J=17.7, 4.5 Hz, H-5b), 1.57 (3H, s, H-1′), 1.47 (3H, s, H-2′). ^{13}C NMR ($CDCl_3$) δ: 149.8 (s, C-8a), 143.5 (d, C-3), 140.3 (d, C-2), 138.7 (s, C-4a), 134.7 (s, C-12b), 130.4 (s, C-12a), 128.8 (d, C-10), 127.6 (d, C-11), 127.5 (s, C-8b), 124.2 (d, C-12), 122.0 (d, C-9), 108.0 (s, C-4b), 78.3 (s, C-7), 69,4 (d, C-6), 27.5 (t, C-5), 24.7 (q, C-1′), 22.2 (q, C-2′). MS *m/z* (rel. int): 280 (M^+, 41), 209 (M^+ −71, 100). HRMS: 280.1197 (calcd for $C_{17}H_{16}N_2O$ (M^+) 280.1212).

3.2.10. 6-Bromo-7,7-dimethyl-6,7-dihydro-5*H*-benzo[*f*] pyrano[2,3-*h*]quinoxaline (23). Following the general procedure described above, 108 mg (0.33 mmol) of **4** were treated with 45 μL (0.67 mmol) of 1,2-ethylendiamine. The crude was purified by flash chromatography on silica gel using Hex/EtOAc (9:1) as eluent, to obtain 88 mg (80%) of **23**. ^{1}H RMN ($CDCl_3$) δ: 9.15 (1H, m, H-12), 8.81 (1H, d, J=1.9 Hz, H-3), 8.76 (1H, d, J=1.9 Hz, H-2), 8.32 (1H, m, H-9), 7.76 (2H, m, H-10+H-11), 4.49 (1H, dd, J=8.4, 5.6 Hz, H-6), 3.94 (1H, dd, J=17.9, 5.6 Hz, H-5a), 3.65 (1H, dd, J=17.9, 8.4 Hz, H-5b), 1.71 (3H, s, H-1′), 1.60 (3H, s, H-2′). ^{13}C RMN ($CDCl_3$) δ: 149.7 (s, C-8a), 143.6 (d, C-3), 142.5 (s, C-4a), 140.5 (d, C-2), 138.4 (s, C-12b), 130.5 (s, C-12a), 128.9 (d, C-10), 127.8 (d, C-11), 127.5 (s, C-8a), 124.3 (d, C-12), 121.9 (d, C-9), 109.0 (s, C-4b), 78.3 (s, C-7), 52.4 (d, C-6), 30.3 (t, C-5), 26.7 (q, C-1′), 22.3 (q, C-2′). MS *m/z* (rel. int): 398 (M^+ +2, 46), 396 (M^+, 46), 317 (M^+ −Br, 100). HRMS: 396.0860 (calcd for $C_{21}H_{21}N_2O\,Br^{79}$ (M^+) 396.0837).

3.2.11. 7-(1-Hydroxy-1-methylethyl)-6,7-dihydro[2] benzoxonino[6,7-*b*]pyrazine-5,9-dione (24). Following the general procedure described above, 43 mg (0.15 mmol) of **4** were treated with 20 μL (0.30 mmol) of 1,2-ethylendiamine. The crude was purified by flash chromatography on silica gel using Hex/EtOAc (9:1) as eluent, to obtain 22 mg (51%) of **24**. ^{1}H RMN ($CDCl_3$) δ: 9.16 (1H, m, H-12), 8.81 (1H, d, J=2.0 Hz, H-3), 8.75 (1H, d, J=2.0 Hz, H-2), 8.37 (1H, m, H-9), 7.74 (2H, m, H-10+H-11), 7.55 (2H, m, H-2′+H-6′), 7.44 (3H, m, H-3′+H-4′+H-5′), 5.34 (1H, d, J=10.1 Hz, H-7), 3.43 (1H, m, H-6a), 3.24 (1H, m, H-6b), 2.52 (1H, m, H-5a), 2.25 (1H, m, H-5b). ^{13}C NMR ($CDCl_3$) δ: 151.8 (s, C-8a), 143.5 (d, C-3), 143.2 (d, C-4a), 141.1 (s, C-1′), 140.3 (d, C-2), 138.3 (s, C-12b), 130.3 (s, C-12a), 128.8 (d, C-10), 128.6×2 (d, C-3′+C-5′), 127.9 (d, C-4′), 127.6 (s, C-8b), 127.5 (d, C-11), 125.9×2 (d, C-2′+ C-6′), 124.3 (d, C-12), 121.8 (d, C-9), 111.5 (s, C-4b), 78.3 (s, C-7), 29.5 (t, C-6), 20.5 (t, C-5). MS *m/z* (rel. int): 312 (M^+, 62), 221 (M^+ −N–Ph, 100). HRMS: 312.1282 (calcd for $C_{21}H_{16}N_2O$ (M^+) 312.1263).

3.3. General procedure for the preparation of the macrolactones (25–35)

A solution of diazine in dry CH_2Cl_2 cooled to −78 °C, was ozonized until the colour of the solution changed to dark blue-grey. The reaction mixture was then quenched with dry Me_2S (2 equiv), concentrated under vacuum and chromatographed by preparative-TLC using mixtures of hexanes/

EtOAc as eluent, to afford the corresponding macrolactones **25**–**35**.

3.3.1. 7-(1-Hydroxy-1-methylethyl)-7,8,11,12,13,14-hexahydro[2]benzoxonino[6,7-*b*]quinoxaline-5,9-dione (25). 16 mg (0.05 mmol) of **14** in 8 mL of dry CH_2Cl_2 were ozonized following the general procedure described above. The crude was quenched with 6 μL of dry Me_2S and chromatographed by preparative-TLC using Hex/EtOAc (7:3) as eluent, to obtain 12 mg (68%) of **25**. ^{1}H RMN ($CDCl_3$) δ: 8.03 (1H, m, H-4), 7.92 (1H, m, H-1), 7.72 (1H, m, H-3), 7.52 (1H, m, H-2), 5.49 (1H, bs, H-7), 4.12 (2H, m, H-8), 3.05 (4H, bs, H-11+H-14), 2.00 (4H, bs, H-12+H-13), 1.19 (3H, s, H-2′), 1.16 (3H, s, H-3′). MS *m*/*z* (rel. int): 366 (M^+, 2), 348 (M^+-H_2O, 3), 289 (348-C(OH)$(CH_3)_2$, 100). HRMS: 366.1548 (calcd for $C_{21}H_{22}N_2O_4$ (M^+) 366.1579).

3.3.2. 7-Phenyl-7,8,11,12,13,14-hexahydro[2] benzoxonino[6,7-*b*]quinoxaline-5,9-dione (26). 48 mg (0.13 mmol) of **15** in 10 mL of dry CH_2Cl_2 were ozonized following the general procedure described above. The crude was quenched with 15 μL of dry Me_2S and chromatographed by preparative-TLC using Hex/EtOAc (7:3) as eluent, to obtain 11 mg (22%) of **26**. ^{1}H RMN ($CDCl_3$) δ: 8.02 (1H, bs, H-1), 7.90 (1H, d, J=7.8 Hz, H-4), 7.67 (1H, t, J=7.5 Hz, H-2), 7.49 (1H, t, J=7.5 Hz, H-3), 7.25 (3H, m, H-3′+H-4′+H-5′), 7.06 (2H, bs, H-2′+H-6′), 6.49 (1H, bs, H-7), 3.95 (1H, bs, H-8a), 3.52 (1H, bs, H-8b), 3.01 (4H, m, H-11+H-14), 1.92 (4H, s, H-12+H-13). MS *m*/*z* (rel. int): 384 (M^+, 1), 340 (M^+-CO_2, 9), 252 (M^+-COCH_2CHPh, 100). HRMS: 384.1466 (calcd for $C_{24}H_{20}N_2O_3$ (M^+) 384.1474).

3.3.3. 7,7-Dimethyl-8,9,12,13,14,15-hexahydro-5*H*-[2]benzoxecino[7,8-*b*]quinoxaline-5,10(7*H*)-dione (27). 97 mg (0.30 mmol) of **16** in 10 mL of dry CH_2Cl_2 were ozonized following the general procedure described above. The crude was quenched with 40 μL of dry Me_2S and chromatographed by preparative-TLC using Hex/EtOAc (4:1) as eluent, to obtain 71 mg (68%) of **27**. ^{1}H NMR (C_6D_6) δ: 8.22 (1H, d, J=7.8 Hz, H-4), 7.68 (1H, d, J=7.8 Hz, H-1), 7.23 (1H, m, H-2), 7.02 (1H, m, H-3), 3.78 (1H, ddd, J=13.8, 6.3, 4.2 Hz, H-9a), 2.74 (4H, m, H-12+H-15), 2.59 (1H, ddd, J=15.1, 11.2, 3.9 Hz, H-9b), 2.16 (1H, ddd, J=14.8, 11.2, 4.2 Hz, H-8b), 1.66 (1H, ddd, J=18.7, 16.5, 5.8 Hz, H-7a), 1.44 (3H, s, H-1′), 1.42 (m, 4H, H-13+H-14), 1.16 (3H, s, H-2′). ^{13}C NMR (C_6D_6) δ: 201.6 (s, C-10), 165.5 (s, C-5), 152.9 (s, C-15a), 150.4 (s, C-16b), 149.1 (s, C-11a), 148.4 (s, C-10a), 139.0 (s, C-16a), 133.4 (d, C-3), 132.0 (d, C-2), 130.6 (d, C-4), 129.2 (s, C-4a), 128.6 (d, C-1), 83.8 (s, C-7), 37.9 (t, C-8), 36.1 (t, C-9), 31.9 (t, C-12 or C-15), 31.4 (t, C-15 or C-12), 26.6 (q, C-1′), 23.8 (q, C-2′), 22.4 (t, C-13 or C-14), 22.3 (t, C-14 or C-13). MS *m*/*z* (rel. int): 350 (M^+, 4), 335 (M^+-Me, 2), 253 ($M^+-CO(CH_2)C(Me)_2$, 100). HRMS: 350.1657 (calcd for $C_{21}H_{22}N_2O_3$ (M^+) 350.1630).

3.3.4. 8-Hydroxy-7,7-dimethyl-8,9,12,13,14,15-hexahydro-5*H*-[2]benzoxecino[7,8-*b*]quinoxaline-5,10 (7*H*)-dione (28). 33 mg (0.10 mmol) of **17** in 10 mL of dry CH_2Cl_2 were ozonized following the general procedure described above. The crude was quenched with 12 μL of dry Me_2S and chromatographed by preparative-TLC using Hex/EtOAc (7:3) as eluent, to obtain 17 mg (47%) of **28**. Major conformer: ^{1}H NMR ($CDCl_3$) δ: 8.00 (1H, m, H-4), 7.64 (1H, m, H-1), 7.47 (2H, m, H-2+H-3), 4.02–3.96 (2H, m, H-8+H-9a), 3.02 (4H, bs, H-12+H-15), 2.73 (1H, m, H-9b), 2.30 (1H, bd, J=5.6 Hz, OH), 2.00 (4H, bs, H-13+H-14), 1.61 (3H, s, H-1′), 1.52 (3H, s, H-2′). ^{13}C NMR ($CDCl_3$) δ: 197.0 (s, C-10), 171.4 (s, C-5), 154.6 (s, C-15a), 153.4 (s, C-16b), 152.5 (s, C-11a), 149.5 (s, C-10a), 135.4 (s, C-16a), 132.8 (d, C-3), 132.0 (d, C-2), 130.9 (s, C-4a), 128.6 (d, C-4), 124.8 (d, C-1), 78.6 (s, C-7), 70.2 (d, C-8), 44.5 (t, C-9), 32.1 (t, C-12 or C-15), 31.4 (t, C-15 or C-12), 27.4 (q, C-1′), 24.4 (q, C-2′), 22.5 (t, C-13 or C-14), 22.4 (t, C-14 or C-13). Minor conformer: ^{1}H NMR ($CDCl_3$) δ: 8.00 (1H, m, H-4), 7.64 (1H, m, H-1), 7.47 (2H, m, H-2+H-3), 4.34 (1H, bs, H-9a), 3.92 (1H, m, H-8), 3.02 (4H, bs, H-12+H-15), 2.88 (1H, m, H-9b), 2.61 (1H, bd, J=4.8 Hz, OH), 2.00 (4H, bs, H-13+H-14), 1.67 (3H, s, H-1′), 1.31 (3H, s, H-2′). MS *m*/*z* (rel. int): 366 (M^+, 4), 350 (M^+-Me, 2), 295 (M^+-71, 100). HRMS: 366.7127 (calcd for $C_{21}H_{22}N_2O_4$ (M^+) 350.7101).

3.3.5. 8-Bromo-7,7-dimethyl-8,9,12,13,14,15-hexahydro-5*H*-[2]benzoxecino[7,8-*b*]quinoxaline-5,10(7*H*)-dione (29). 20 mg (0.05 mmol) of **18** in 8 mL of dry CH_2Cl_2 were ozonized following the general procedure described above. The crude was quenched with 6 μL of dry Me_2S and chromatographed by preparative-TLC using Hex/EtOAc (4:1) as eluent, to obtain 10 mg (46%) of **29**. Major conformer: ^{1}H RMN ($CDCl_3$) δ: 8.07 (1H, d, J=7.5 Hz, H-4), 7.66 (1H, m, H-1), 7.50 (2H, m, H-2+H-3), 4.32 (1H, dd, J=12.5, 4.1 Hz, H-8), 4.10 (1H, dd, J=14.4, 4.2 Hz, H-9a), 3.10 (1H, m, H-9b), 3.03 (4H, m, H-12+H-15), 2.02 (4H, m, H-13+H-14), 1.74 (3H, s, H-1′), 1.69 (3H, s, H-2′). ^{13}C NMR ($CDCl_3$) δ: 197.6 (s, C-10), 164.3 (s, C-5), 153.7 (s, C-15a), 149.9 (s, C-16b), 149.8 (s, C-11a), 148.0 (s, C-10a), 138.1 (s, C-16a), 133.1 (d, C-2 or C-3), 132.9 (d, C-2 or C-3), 131.3 (d, C-4), 130.9 (s, C-4a), 128.7 (d, C-1), 87.1 (s, C-7), 52.6 (d, C-8), 47.2 (t, C-9), 32.1 (t, C-12 or C-15), 31.5 (t, C-12 or C-15), 25.4 (q, C-1′), 22.5×2 (t, C-13+C-14), 18.3 (q, C-2′). Minor conformer. ^{1}H RMN ($CDCl_3$) δ: 7.91 (1H, d, J=7.8 Hz, H-4), 7.70 (1H, m, H-1), 7.53 (2H, m, H-2+H-3), 5.22 (1H, dd, J=12.6, 4.6 Hz, H-8), 4.71 (1H, m, H-9a), 3.03 (5H, m, H-9b+H-12+H-15), 2.00 (4H, m, H-13+H-14), 1.86 (3H, s, H-1′), 1.16 (3H, s, H-2′). MS *m*/*z* (rel. int): 430 (M^++2, 3), 428 (M^+, 3), 349 (M^+-Br, 4), 253 ($M^+-CO(CH_2)CH(Br)C(Me)_2$, 100). HRMS: 428.0722 (calcd for $C_{21}H_{21}N_2O_3Br^{79}$ (M^+) 428.0736).

3.3.6. 7,7-Dimethyl-5,10-dioxo-7,8,9,10,12,13,14,15-octahydro-5*H*-[2]benzoxecino[7,8-*b*]quinoxalin-8-yl laurate (30). 54 mg (0.10 mmol) of **19** in 10 mL of dry CH_2Cl_2 were ozonized following the general procedure described above. The crude was quenched with 13 μL of dry Me_2S and chromatographed by preparative-TLC using Hex/EtOAc (4:1) as eluent, to obtain 18 mg (22%) of **30**. Major conformer: ^{1}H NMR (C_6D_6) δ: 8.44 (1H, d, J=7.9 Hz, H-4), 7.72 (1H, d, J=7.9 Hz, H-1), 7.34 (1H, m, H-2), 7.13 (1H, m, H-3), 5.74 (1H, dd, J=11.4, 4.6 Hz, H-8), 4.29 (1H, dd, J=13.4, 4.6 Hz, H-9a), 2.93 (1H, dd, J=13.4, 11.4 Hz, H-9b), 2.78 (4H, m, H-12+H-15), 2.10 (2H, m, H-13+H-14), 1.77 (3H, s, H-1′), 1.60 (3H, s, H-2′), 1.49 (3H, s,

H-14′), 1.37 (18H, m, H-5′+H-6′+H-7′+H-8′+H-9′+H-10′+H-11′+H-12′+H-13′), 1.01 (s, 3H, H-2′). ^{13}C NMR (C_6D_6) δ: 196.9 (s, C-10), 171.5 (s, C-5), 164.3 (s, C-1′), 153.5 (s, C-15a), 150.2 (s, C-16b), 149.5 (s, C-11a), 148.9 (s, C-10a), 139.4 (s, C-16a), 133.8 (d, C-3), 132.6 (d, C-2), 132.4 (s, C-4a), 131.2 (d, C-4), 128.5 (d, C-1), 84.8 (s, C-7), 72.8 (d, C-8), 42.5 (t, C-4′), 34.0 (t), 32.0×2 (t), 31.9 (t), 31.3 (t), 29.9 (t), 29.7 (t), 29.6 (t), 29.5 (t), 29.3×2 (t), 24.9 (t), 23.8 (q, C-1′), 22.5 (t), 22.2 (t), 18.6 (q, C-2′), 14.1 (q, C-14′). MS *m/z* (rel. int): 549 (M^++1, 41), 349 (M^++1-OCO$(CH_2)_{10}CH_3$, 23), 253 (349-CO$(CH_2)_2C(Me)_2$, 7), 69 (100). HRMS: 549.3341 (calcd for $C_{33}H_{45}N_2O_5$ (M^++1) 549.3328).

3.3.7. 7-(1-Hydroxy-1-methylethyl)-6, 7-dihydro[2] benzoxonino[6,7-*b*]pyrazine-5,9-dione (31). 37 mg (0.13 mmol) of **20** in 10 mL of dry CH_2Cl_2 were ozonized following the general procedure described above. The crude was quenched with 20 μL of dry Me_2S and chromatographed by preparative-TLC using Hex/EtOAc (1:4) as eluent, to obtain 28 mg (70%) of **31**. ^{1}H NMR ($CDCl_3$) δ: 8.74 (1H, d, J=2.4 Hz, H-2), 8.50 (1H, d, J=2.4 Hz, H-3), 8.19 (1H, bs, H-13), 7.92 (1H, d, J=7.8 Hz, H-10), 7.72 (1H, m, H-12), 7.56 (1H, m, H-11), 5.53 (1H, bs, H-7), 2.86 (1H, bs, H-6a), 1.87 (1H, bs, H-6b), 1.15 (3H, s, H-1′), 1.13 (3H, s, H-2′). MS *m/z* (rel. int): 312 (M^+, 1), 297 (M^+−Me, 5), 254 (M^+−Me–CO_2, 54), 183 (254-CHCOH$(CH_3)_2$, 100). HRMS: 297.0863 (calcd for $C_{16}H_{13}N_2O_4$ (M^+−Me) 297.0875).

3.3.8. 8,8-Dimethyl-7,8-dihydro-6*H*-[2]benzoxecino [7,8-*b*]pyrazine-5,10-dione (32). 58 mg (0.21 mmol) of **21** in 10 mL of dry CH_2Cl_2 were ozonized following the general procedure described above. The crude was quenched with 27 μL of dry Me_2S and chromatographed by preparative-TLC using Hex/EtOAc (3:2) as eluent, to obtain 38 mg (61%) of **32**. ^{1}H NMR ($CDCl_3$) δ: 8.70 (1H, m, H-2), 8.49 (1H, m, H-3), 8.04 (1H, m, H-11), 7.65 (1H, m, H-14), 7.51 (2H, m, H-12+H-13), 3.65 (1H, ddd, J=14.5, 5.8, 4.1 Hz, H-6a), 2.67 (1H, ddd, J=16.5, 14.5, 3.9 Hz, H-6b), 2.18 (1H, ddd, J=18.7, 4.1, 3.9 Hz, H-7b), 1.99 (1H, ddd, J=18.7, 16.5, 5.8 Hz, H-7a), 1.63 (3H, s, H-1′), 1.39 (3H, s, H-2′). ^{13}C NMR ($CDCl_3$) δ: 201.9 (s, C-5), 164.9 (s, C-10), 153.4 (s, C-14b), 151.6 (s, C-4a), 144.4 (d, C-2), 140.5 (d, C-3), 137.9 (s, C-14a), 132.7×2 (d, C-12, 13), 130.8 (d, C-11), 129.0 (d, C-14), 128.2 (s, C-10a), 84.4 (s, C-8), 38.3 (t, C-7), 36.3 (t, C-6), 26.9 (q, C-1′), 23.7 (q, C-2′). MS *m/z* (rel. int): 296 (M^+, 17), 268 (M^+−CO, 9), 199 (M^+−CO–Me–NCH=CHN, 100). HRMS: 296.1164 (calcd for $C_{17}H_{16}N_2O_3$ (M^+) 296.1161).

3.3.9. 7-Hydroxy-8,8-dimethyl-7,8-dihydro-6*H*-[2] benzoxecino[7,8-*b*]pyrazine-5, 10-dione (33). 21 mg (0.08 mmol) of **22** in 10 mL of dry CH_2Cl_2 were ozonized following the general procedure described above. The crude was quenched with 10 μL of dry Me_2S and chromatographed by preparative-TLC using Hex/EtOAc (7:3) as eluent, to obtain 16 mg (68%) of **33** and 5 mg (21%) of **36**. Major conformer: ^{1}H NMR ($CDCl_3$) δ: 8.77 (1H, d, J=2.3 Hz, H-2), 8.51 (1H, d, J=2.3 Hz, H-3), 8.05 (1H, d, J=7.8 Hz, H-11), 7.67 (1H, m, H-14), 7.52 (2H, m, H-12+H-13), 4.12 (1H, m, H-7), 3.90 (1H, dd, J=13.9, 4.4 Hz, H-6a), 2.79 (1H, dd, J=13.9, 10.3 Hz, H-6b), 2.26 (1H, bd, J=5.8 Hz, OH), 1.62 (3H, s, H-1′), 1.51 (3H, s, H-2′). ^{13}C NMR ($CDCl_3$) δ: 196.7 (s, C-10), 175.4 (s, C-5), 150.6 (s, C-14a), 150.6 (s, C-4a), 144.7 (d, C-3), 140.9 (d, C-2), 134.6 (s, C-14b), 132.9×2 (d, C-12+C-13), 131.0 (d, C-11), 129.3 (s, C-10a), 129.1 (d, C-14), 86.6 (s, C-8), 74.1 (d, C-7), 44.6 (t, C-6), 24.4 (q, C-1′), 24.1 (q, C-2′). Minor conformer: ^{1}H NMR ($CDCl_3$) δ: 8.77 (d, J=2.3 Hz, 1H, H-2), 8.51 (m, 1H, H-3), 8.03 (m, 1H, H-11), 7.67 (m, 1H, H-14), 7.52 (m, 2H, H-12, 13), 4.50 (m, 1H, H-7), 4.04 (m, 1H, H-6a), 2.89 (dd, J=12.9, 4.6 Hz, 1H, H-6b), 2.36 (bd, J=4.1 Hz, 1H, OH), 1.70 (s, 3H, H-1′), 1.16 (s, 3H, H-2′). MS *m/z* (rel. int): 312 (M^+, 1), 297 (M^+−Me, 2), 199 (M^+−$COCH_2CH(OH)C(CH_3)_2$, 65), 183 (199-16, 100). HRMS: 312.1128 (calcd for $C_{17}H_{16}N_2O_4$ (M^+) 312.1110).

3.3.10. 5-(2, 3-Dihydroxy-3-methylbutyl)-5-hydroxy benzo[*f*]quinoxalin-6(5*H*)-one (36). ^{1}H NMR ($CDCl_3$) δ: 8.57 (1H, d, J=2.3 Hz, H-3), 8.52 (1H, d, J=2.3 Hz, H-2), 8.46 (1H, d, J=7.5 Hz, H-10), 8.00 (1H, m, H-7), 7.60 (2H, m, H-8+H-9), 4.44 (1H, d, J=5.5 Hz, H-2′), 3.35 (1H, dd, J=14.2, 5.5 Hz, H-1a′), 2.94 (1H, d, J=14.2 Hz, H-1b′), 1.51 (6H, s, H-1″+H-4′). ^{13}C NMR ($CDCl_3$) δ: 199.8 (s, C-6), 152.7 (s, C-10b), 151.0 (s, C-4a), 144.0 (d, C-3), 143.5 (d, C-2), 132.1 (s, C-10a), 131.1 (d, C-8 or 9), 130.9 (d, C-8 or 9), 129.0 (s, C-6a), 127.5 (d, C-10), 125.6 (d, C-7), 84.0 (d, C-2′), 82.2 (s, C-5), 69.9 (s, C-3′), 38.8 (t, C-1′), 27.3 (q, C-4′), 22.7 (q, C-1″). MS *m/z* (rel. int): 314 (M^+, 15), 299 (M^+−Me, 21), 221 (M^+−93, 100). HRMS: 314.1285 (calcd for $C_{17}H_{18}N_2O_4$ (M^+) 314.1267).

3.3.11. 7-Bromo-8,8-dimethyl-7,8-dihydro-6*H*-[2] benzoxecino[7,8-*b*]pyrazine-5,10-dione (34). 57 mg (0.17 mmol) of **23** in 10 mL of dry CH_2Cl_2 were ozonized following the general procedure described above. The crude was quenched with 20 μL of dry Me_2S and chromatographed by preparative-TLC using Hex/EtOAc (7:3) as eluent, to obtain 23 mg (37%) of **34**. Major conformer: ^{1}H NMR ($CDCl_3$) δ: 8.74 (1H, m, H-2), 8.55 (1H, m, H-3), 8.10 (1H, d, J=7.9 Hz, H-11), 7.73 (1H, m, H-14), 7.51 (2H, m, H-12+H-13), 4.30 (1H, dd, J=12.5, 4.0 Hz, H-7), 4.08 (1H, dd, J=14.3, 4.0 Hz, H-6b), 3.13 (1H, dd, J=14.3, 12.5 Hz, H-6b), 1.76 (3H, s, H-1′), 1.66 (3H, s, H-2′). ^{13}C NMR ($CDCl_3$) δ: 196.8 (s, C-5), 163.9 (s, C-10), 153.5 (s, C-14b), 151.1 (s, C-4a), 144.8 (d, C-2), 141.0 (d, C-3), 137.7 (s, C-14a), 133.1 (d, C-12), 132.9 (d, C-13), 131.4 (d, C-11), 129.1 (d, C-14), 127.6 (s, C-10a), 87.3 (d, C-8), 52.3 (d, C-7), 47.1 (t, C-6), 25.3 (q, C-1′), 18.3 (q, C-2′). Minor conformer: ^{1}H NMR ($CDCl_3$) δ: 8.79 (m, 1H, H-2), 8.56 (m, 1H, H-3), 7.97 (d, J=7.8 Hz, 1H, H-11), 7.73 (m, 1H, H-14), 7.51 (m, 2H, H-12+H-13), 5.25 (dd, J=12.6, 4.6 Hz, 1H, H-7), 4.47 (dd, J=12.6, 12.1 Hz, 1H, H-6a), 3.06 (dd, J=12.1, 4.6 Hz, 1H, H-6b), 1.87 (s, 3H, H-1′), 1.13 (s, 3H, H-1′). ^{13}C NMR ($CDCl_3$) δ: 197.7 (s, C-5), 163.8 (s, C-10), 153.5 (s, C-14b), 151.1 (s, C-4a), 145.5 (d, C-2), 140.7 (d, C-3), 137.7 (s, C-14a), 133.0 (d, C-12), 132.9 (d, C-13), 131.1 (d, C-11), 129.5 (d, C-14), 119.9 (s, C-10a), 86.4 (d, C-8), 51.4 (d, C-7), 44.5 (t, C-6), 26.8 (q, C-1′), 21.6 (q, C-2′). MS *m/z* (rel. int): 376 (M^++2, 0.4), 374 (M^+, 0.4), 295 (M^+−Br, 7), 199 (M^+−CO(CH_2)-CH(Br)C$(Me)_2$, 100). HRMS: 374.0350 (calcd for $C_{17}H_{15}N_2O_3Br^{79}$ (M^+) 374.0266).

3.3.12. 8-Phenyl-7,8-dihydro-6*H*-[2]benzoxecino[7,8-*b*] pyrazine-5,10-dione (35). 19 mg (0.06 mmol) of **24** in 8 mL of dry CH_2Cl_2 were ozonized following the general procedure described above. The crude was quenched with 10 μL of dry Me_2S and chromatographed by preparative-TLC using Hex/EtOAc (7:3) as eluent, to obtain 11 mg (53%) of **35**. ^{1}H NMR ($CDCl_3$) δ: 8.82 (1H, d, $J=2.5$ Hz, H-2), 8.54 (1H, d, $J=2.5$ Hz, H-3), 8.20 (1H, d, $J=7.8$ Hz, H-11), 7.74 (2H, m, H-12+H-13), 7.56 (1H, m, H-14), 7.25 (3H, m, H-3′+H-4′+H-5′), 7.03 (2H, m, H-2′+H-6′), 6.15 (1H, dd, $J=11.3$, 2.8 Hz, H-8), 3.67 (1H, ddd, $J=15.0$, 5.0, 3.6 Hz, H-6a), 2.72 (1H, ddd, $J=15.0$, 12.4, 3.5 Hz, H-6b), 2.50 (1H, ddd, $J=12.3$, 6.1, 3.5 Hz, H-7a), 2.22 (1H, m, H-7b). ^{13}C NMR ($CDCl_3$) δ: 202.2 (s, C-5), 165.3 (s, C-10), 153.1 (s, C-14b), 151.1 (s, C-4a), 144.8 (d, C-2), 140.4 (d, C-3), 138.7 (s, C-15), 137.8 (s, C-14a), 133.6 (d, C-13), 133.4 (d, C-12), 132.2 (d, C-11), 129.4 (d, C-14), 128.5×2 (d, C-3′+C-5′), 128.3 (d, C-18), 126.3 (s, C-10a), 125.8×2 (s, C-2′+C-6′), 77.2 (d, C-8), 39.2 (t, C-6), 32.9 (t, C-7). MS *m/z* (rel. int): 344 (M^+, 93), 316 (M^+-CO, 43), 238 (M^+-CO–Ph, 18), 183 ($M^+-OCH(Ph)(CH_2)_2CO$, 95), 104 (PhCO, 100). HRMS: 344.1158 (calcd for $C_{21}H_{16}N_2O_3$ (M^+) 344.1161).

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