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Regioselective Diels–Alder reactions of 3-indolylquinones

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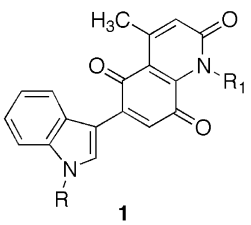
Abstract—6-(3-Indolyl)quinolinequinone derivatives gave regioselective Diels–Alder reactions with a variety of dienophiles, yielding polycyclic carbazole derivatives. One-pot reactions, proceeding through a cascade of reactions including regioselective Michael and Diels–Alder steps, gave heptacyclic derivatives starting from indoles and 2,5,8(1*H*)-quinolinetriones. Double Diels–Alder reactions of 6-(3-indolyl)quinolinequinones and dihalobenzoquinones gave eleven-cycle products in one step.

1. Introduction

2-Vinylindoles and 3-vinylindoles have been widely employed as dienes in Diels–Alder reactions.[1] However, indolylquinones have received very little attention in their role of Diels–Alder dienes and only symmetrical quinones like benzoquinone and naphthoquinone have been studied, thus avoiding regioselectivity issues.[2] These Diels–Alder reactions are also of interest because they would provide easy access to a number of polyheterocyclic quinone systems, heterocyclic quinones[1] being a very important class of compounds from a biological point of view, particularly as antitumour agents.[2]

On the other hand, while many polycyclic aromatic quinones are known, some of them with interesting properties,[3] their heterocyclic counterparts have received very little attention. For these reasons, and due to our interest in the chemistry of heterocyclic quinones,[4] we describe here our results on the Diels–Alder reactivity and regioselectivity of the dienes **1**.



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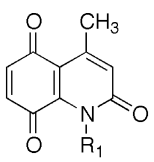

Comp.	R_1
2a	H
2b	CH_3

2. Results and discussion

Compounds **1a**,**b** were prepared by Michael addition of the suitable indole derivative to **2a**[5] in ethanol containing a small amount of HCl. When the reaction between 1-methylindole and **2a** was carried out in an argon atmosphere, it gave hydroquinone **3**, which was easily transformed into **1b** by air oxidation. Alternatively, **1a**,**b** could be prepared directly by carrying out the Michael reaction in air. Under these conditions, the reaction starting from **1b** gave a small amount (8%) of a second product, which was identified as the heptacyclic derivative **4b**, arising from cycloaddition of **1b** onto a second molecule of **2a** followed by oxidation (Scheme 1). The formation of **4b**, which will be discussed in more detail below, was encouraging because it proved the feasibility of our initial assumption that coumpounds **1** would behave as Diels–Alder dienes.

The addition of indole to quinone **2a** took place in a regioselective fashion, and can be assumed to occur at the C-6 position because electron donation of N-1 to the C-5 carbonyl renders its conjugated C-7 position less electrophilic than C-6, in agreement with our previous observations on the regiochemistry of the Diels–Alder reactions of quinones **2**.[4a] Since the unambiguous knowledge of the structure of compounds **1** was crucial for the rest of our work, we needed to confirm this assumption by spectroscopic means. The quaternary carbons C-4a and C-8a are easily assigned in carbostyril derivatives, with typical chemical shift values being around 115 ppm for C-4a and 140–145 ppm for C-8a,[6] and therefore long-range couplings of these signals can be used to distinguish 6- and 7-substituted carbostyril derivatives. In the case of compound **1b**, the signal due to H-7 in its HMBC spectrum shows a correlation with the one assigned to C-8a (at 145.5 ppm), but not with the one due to C-4a (117.7 ppm). This is compatible with a C-6 substituted carbostyril ring

Keywords: Diels–Alder reactions; Michael reactions; indoles; quinones; 2-quinolinones.

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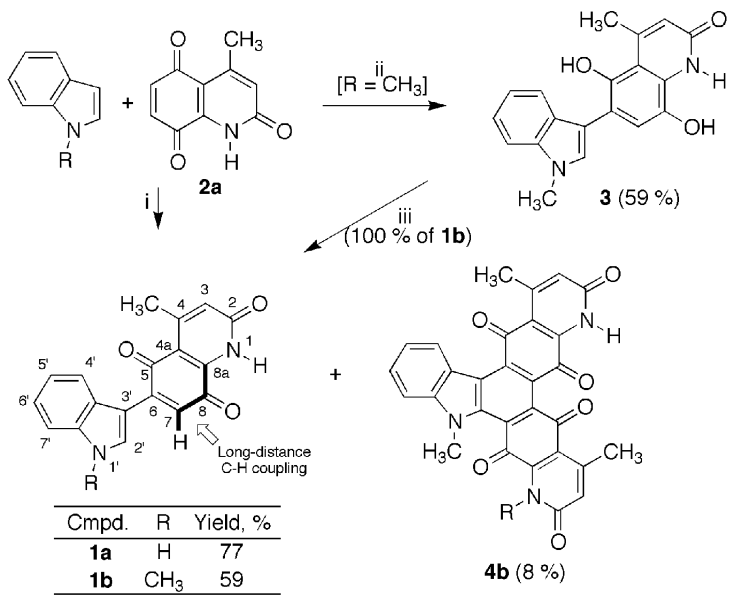
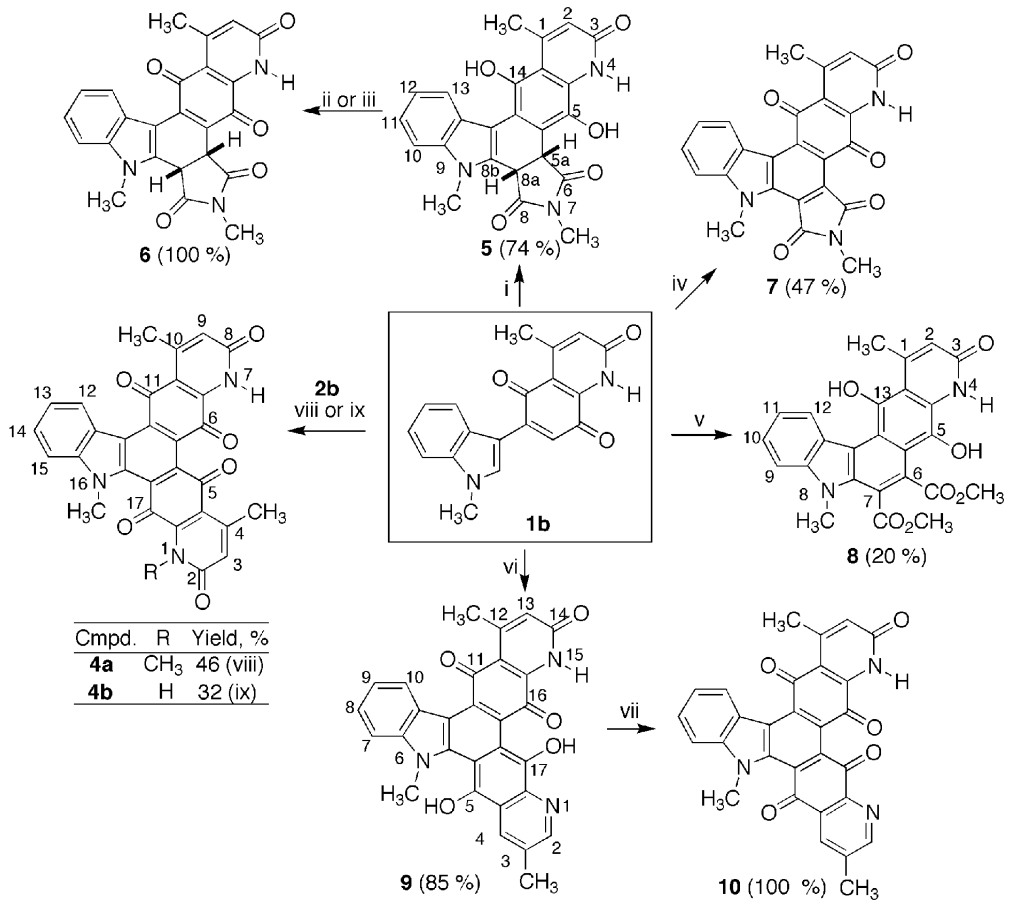


Cmpd.	R	Yield, %
1a	H	77
1b	CH_3	59

Scheme 1. *Reagents and conditions*: (i) EtOH, HCl (air), 1 h; (ii) EtOH, HCl (Ar), 18 h; (iii) $CHCl_3$ (air) reflux, 1 h.

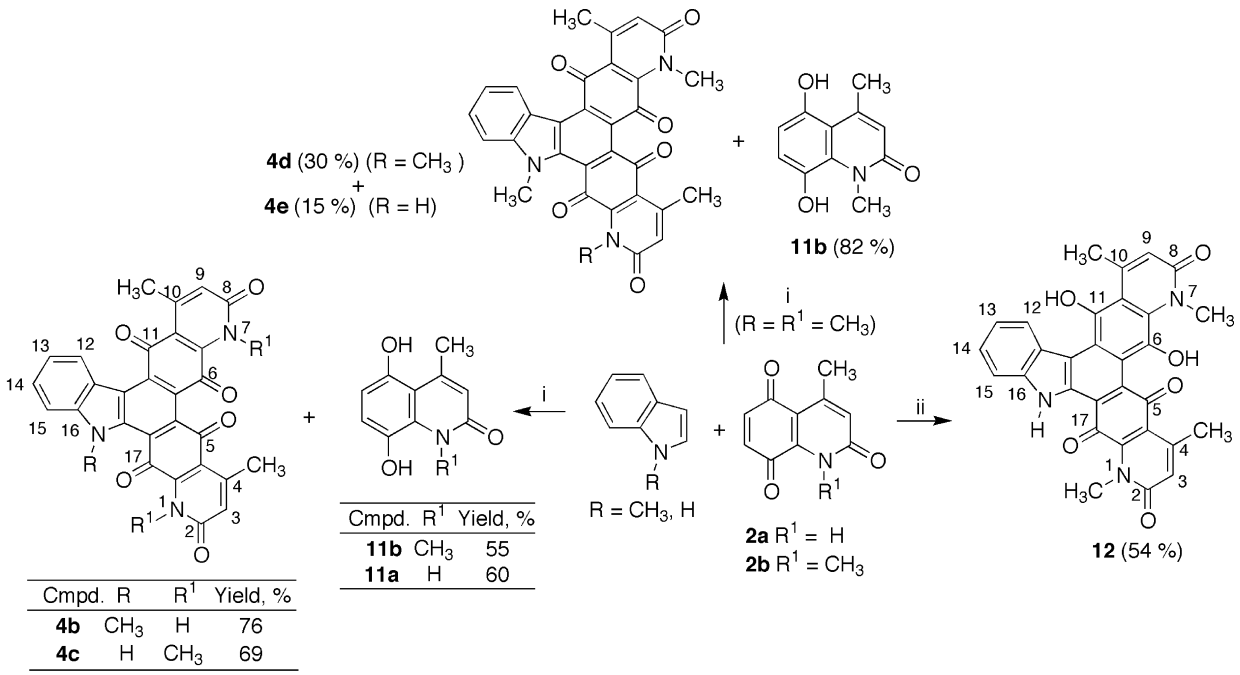
but not with a C-7 substituted one, and therefore supports the structure **1** predicted for the Michael adducts from electronic considerations.

Compound **1a** was inert to all dienophiles assayed, but this was attributed to its poor solubility in all the reaction media that were tested. Indeed, when its more soluble analogue **1b** was employed, the reactions summarized in Scheme 2 were observed. The reaction using *N*-methylmaleimide as the dienophile was employed for studying the effect of the



Cmpd.	R	Yield, %
4a	CH_3	46 (viii)
4b	H	32 (ix)

Scheme 2. *Reagents and conditions*: (i) *N*-Methylmaleimide, $(CH_2Cl)_2$ reflux, 18 h; (ii) DMSO, air, 120°C, 20 min, (iii) Sillica gel chromatography ($CHCl_3$); (iv) *N*-methylmaleimide, ethanol, HCl(trace), reflux, 24 h; (v) Dimethyl acetylenedicarboxylate, *o*-dichlorobenzene, microwave, 400 W, 9 min; (vi) 6-Chloro-3methyl 5,8-quinolinequinone, $(CH_2Cl)_2$ reflux, 6 h; (vii) DMSO, air, 150°C, 3 h. (viii) Ethanol, HCl (trace), reflux 45 min; (ix) Ethanol, HCl (trace), reflux, 2.5 h.

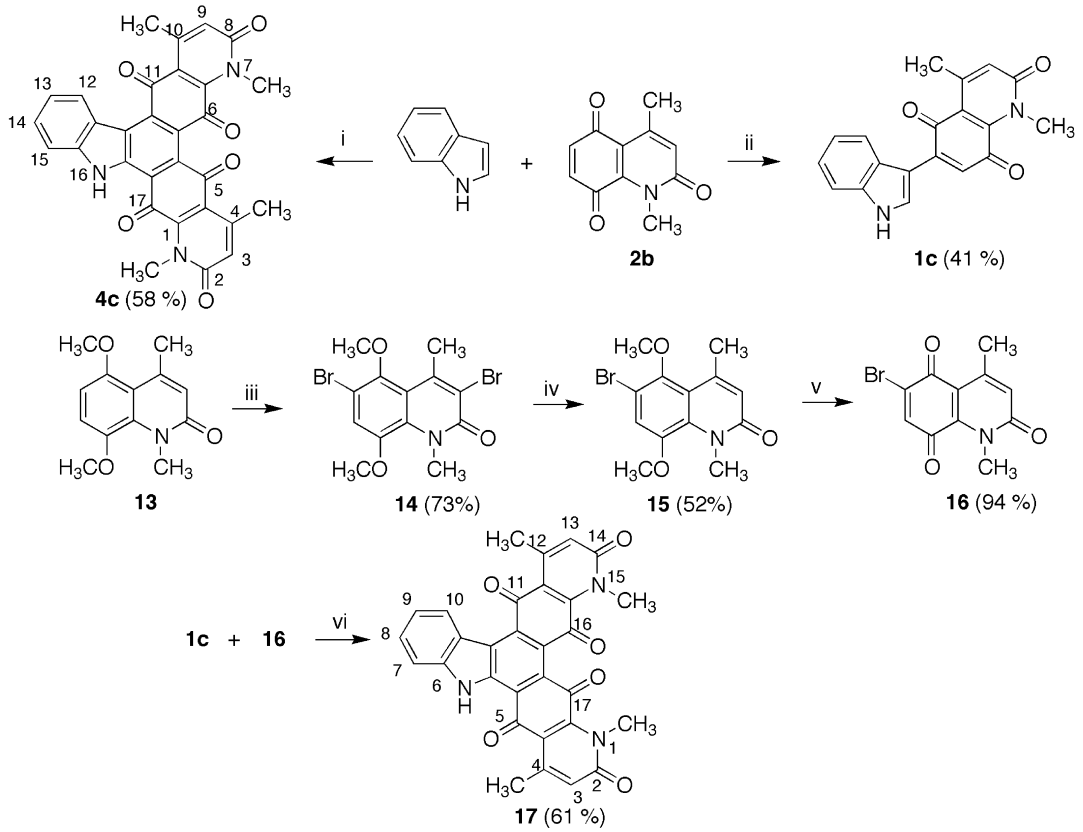


Scheme 3. *Reagents and conditions*: (i) **2a**,**b** (0.16 M in EtOH), HCl (trace), reflux, 1 h; (ii) **2b** (0.33 M in EtOH) HCl (trace), reflux, 6 h.

reaction conditions on the degree of oxidation of the final products. Thus, treatment of **1b** with *N*-methylmaleimide in refluxing 1,2-dichloroethane gave a 76% yield of compound **5**, a tautomer of the primary Diels–Alder adduct that precipitated from the reaction medium, which is assumed to be the *endo* product. Silica gel chromatography of **5**, or its air oxidation in DMSO at 120°C, led to the oxidation of its hydroquinone moiety to a quinone, affording compound **6** in quantitative yield. On the other hand, when the reaction was performed in refluxing ethanol, where both **5** and **6** are slightly soluble, the only product isolated was compound **7** in 47% yield. The reaction with dimethyl acetylenedicarboxylate failed under a variety of reflux conditions, but we succeeded in isolating compound **8** in modest yield following microwave irradiation (9 min) of a solution of the starting materials in *o*-dichlorobenzene, using a domestic microwave oven operating at 400 W; to our knowledge, this is the first report of the use of microwave irradiation for enhancing a Diels–Alder reaction of a vinylindole, although related cycloadditions of vinylpyrazoles under microwave irradiation have been described.[7]

Having thus established several reaction conditions suitable for the use of compound **1b** as the diene partner in Diels–Alder cycloadditions, we next considered the use of unsymmetrical dienophiles. Treatment of **1b** with 6-chloro-3-methylquinolinequinone[8] gave a single reaction product, namely hydroquinone **9**, in 85% yield. The regiocontrol observed can be attributed to the presence of the halogen atom, which is known to orient the attack of the nucleophilic end of the diene to the non-halogenated carbon atom of the dienophile.[9] Compound **9** was subsequently transformed into quinone **10** in quantitative yield by air oxidation in DMSO at 150°C for 3 h. The location of the hydroquinone ring in **9** is proposed on the basis of the absence of an upfield shift for the H-4 proton, which is observed at the expected chemical shift (part of a multiplet at 8.05–8.20 ppm), while in quinone **10** this signal appears at 8.37–8.30 ppm because of the influence of the C(5) carbonyl. A similar shift can be observed in a situation where the position of the hydroquinone system is unambiguous, namely the H-13 signal of compound **6** in comparison with its hydroquinone **5**. We also examined the reaction of **1b** with **2b**,[10] which also proceeded with complete regioselectivity and gave compound **4a** after a 45 min reflux in ethanol–HCl, but the *N*-demethylated derivative **4b** if the reaction time was extended to 2.5 h. In this case, the regioselectivity can be attributed to the above-mentioned electron donation of the carbostyril nitrogen to its conjugated C(5)=O group, which causes C-8 to be the more electrophilic carbonyl and hence C-6 to be the electrophilic end of the dienophile. The partial demethylation of **4a** under the conditions employed is apparently due to the proximity of the N(1)–Me, C(17)=O and N(16)–Me groups (see also the reaction leading to compounds **4d** and **4e** in Scheme 3 below), and can be ascribed to steric congestion of this region of the molecule, which prevents the complete planarity of the lactam bond at N(1)–C(2) and thereby facilitates the protonation of N(1) by the acidic reaction medium prior to demethylation by nucleophilic attack of an ethanol molecule to the methyl group.

The results described above for the reaction leading to **4** prompted us to attempt the one-pot synthesis of these compounds from indoles and quinolinetriones. As shown in Scheme 3, a simple 1 h reflux of indole or 1-methylindole with the 2,5,8(1*H*)-quinolinetrione derivatives gave the heptacyclic derivatives **4b**–**e** in a single synthetic operation and in moderate to good yields.[11] Again, a reaction leading to the N(1)-methyl derivative **4d** was accompanied by partial demethylation of N(1), leading to **4e** as a minor product. Hydroquinones **11**, from reduction of the starting quinolinequinones, were also isolated from these reaction mixtures. The proposal of the bis-quinone oxidation state for compounds **4** was based on the absence of signals assignable to hydroquinone hydroxyls in their IR and ^{1}H



Scheme 4. *Reagents and conditions*: (i) Ethanol, HCl (trace), rt, 18 h; (ii) indole (3 equiv.) Et_2O–EtOH, HCl (trace), air, rt, 13 h; (iii) Br_2 (5 equiv.), AcOH, rt, 20 h; (iv) Zn, EtOH, reflux, 15 h; (v) $(NH_4)_2Ce(NO_3)_6$ (3 equiv.), CH_3CN–H_2O, rt, 30 EtOH, reflux, 2.5 h.

NMR spectra, and also on the molecular mass of 517 deduced for compound **4c** from its ESI mass spectrum, but confirmation of this structure by the observation of the suitable carbonyl signals in the ^{13}C NMR spectra of compounds **4** was not possible because of their extremely low solubility in all solvents. In order to provide a reliable reference material for the spectral comparisons and definitely discard the hydroquinone structure, we isolated this intermediate by carrying out the reaction at a higher concentration, which caused its precipitation from the reaction medium in 54% yield for solubility reasons in spite of the higher concentration of an oxidative species. Compound **12** thus isolated showed the expected molecular peak at m/z=519 and clear spectral differences with compound **4c**. In particular, the chemical shift of H-12 is 8.18 ppm for **12** and 8.36 ppm for **4c**, which can be attributed to the influence of the neighbouring C-11 carbonyl group in the bis-quinone **4c**.

The regiochemistry proposed for compounds **4** was based on our previous experience on Diels–Alder reactions of quinones **2**, where the more nucleophilic end of the diene is always attached to the more electron-deficient position of the quinone (i.e. C-6).[4a] Nevertheless, we sought to confirm the structure of compounds **4** by preparing the other possible regioisomer through a route based on the previously mentioned directing effect of the bromine atom in bromoquinones, which is well documented in the literature and therefore can be considered as leading to an unambiguous structure.[9] In our case, preparation of the desired regioisomer required the presence of a bromine atom at C-6 of the quinone, which would direct the attack of the more electron-rich end of the diene to its neighboring C-7 position.

In order to prepare the regioisomer of compound **4c**, we required the indolylquinone **1c**, which was prepared by treatment of indole with **2b**.[10] Under our standard conditions previously described for the preparation of **1a** and **1b** (reflux in ethanol containing a trace of HCl), the desired compound **1c** did not precipitate from the reaction medium and reacted with a second molecule of quinone, giving a 58% yield of compound **4c** as the only observed product. However, after extensive tuning of the experimental conditions, we found that by using a three-fold excess of the quinone and by carrying out the reaction in an ethyl ether–ethanol mixture, compound **1c** precipitated during the course of the reaction and could be isolated in 41% yield (Scheme 4).

Our initial efforts to prepare a suitable bromoquinone as the Diels–Alder partner to compound **1c** were hampered by the fact that we could not achieve regioselective bromination of 1,4-dimethyl-5,8-dimethoxycarbostiryl (**13**)[10] at its C-6 position under a variety of conditions, because we could not avoid the concomitant reaction at C-3. Fortunately, we discovered that the 3,6-dibromo derivative **14**, obtained in 73% yield by treatment of the starting carbostiryl with excess bromine in acetic acid, could be selectively debrominated at C-3 by reflux with zinc in acetic acid,

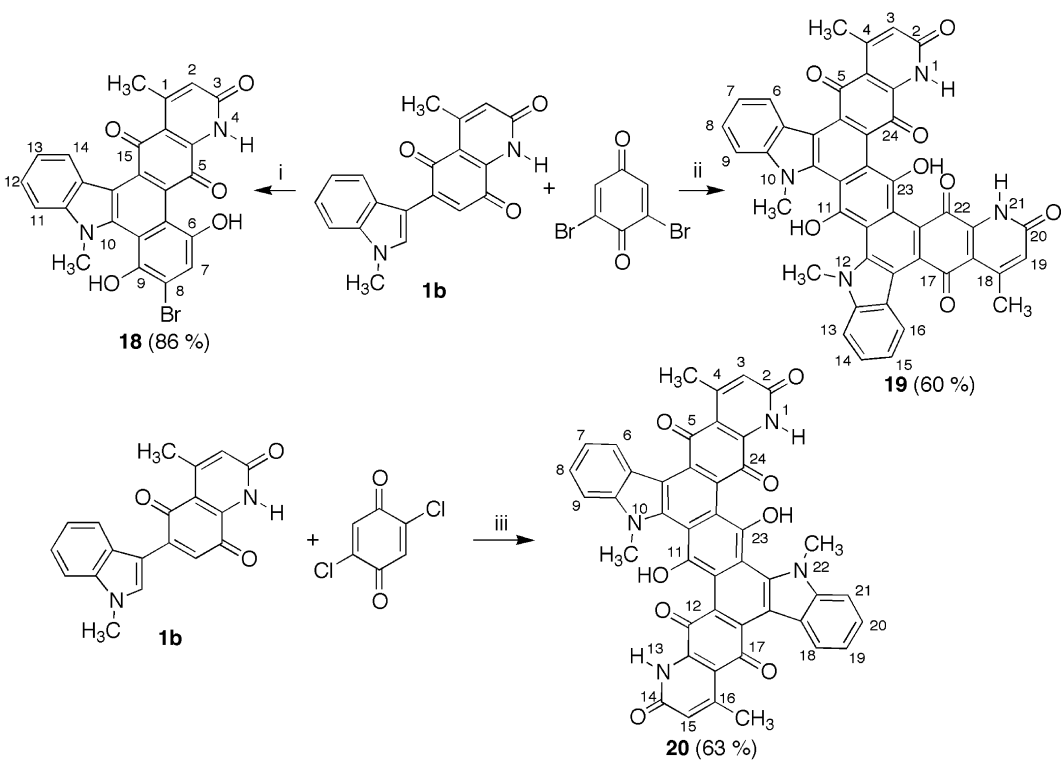
Table 1. Comparison of selected ^{1}H NMR data (500 MHz, d_5-pyridine) for compounds **4c** and **17**

Compound	$H_{\alpha(CO-N)}$	$N-CH_3$	$C-CH_3$
4c	6.87 (s, 1H)	4.48 (s, 3H)	2.80 (s, 3H)
	6.82 (s, 1H)	4.33 (s, 3H)	2.78 (s, 3H)
17	6.88 (s, 2H)	4.37 (s, 6H)	2.83 (s, 6H)

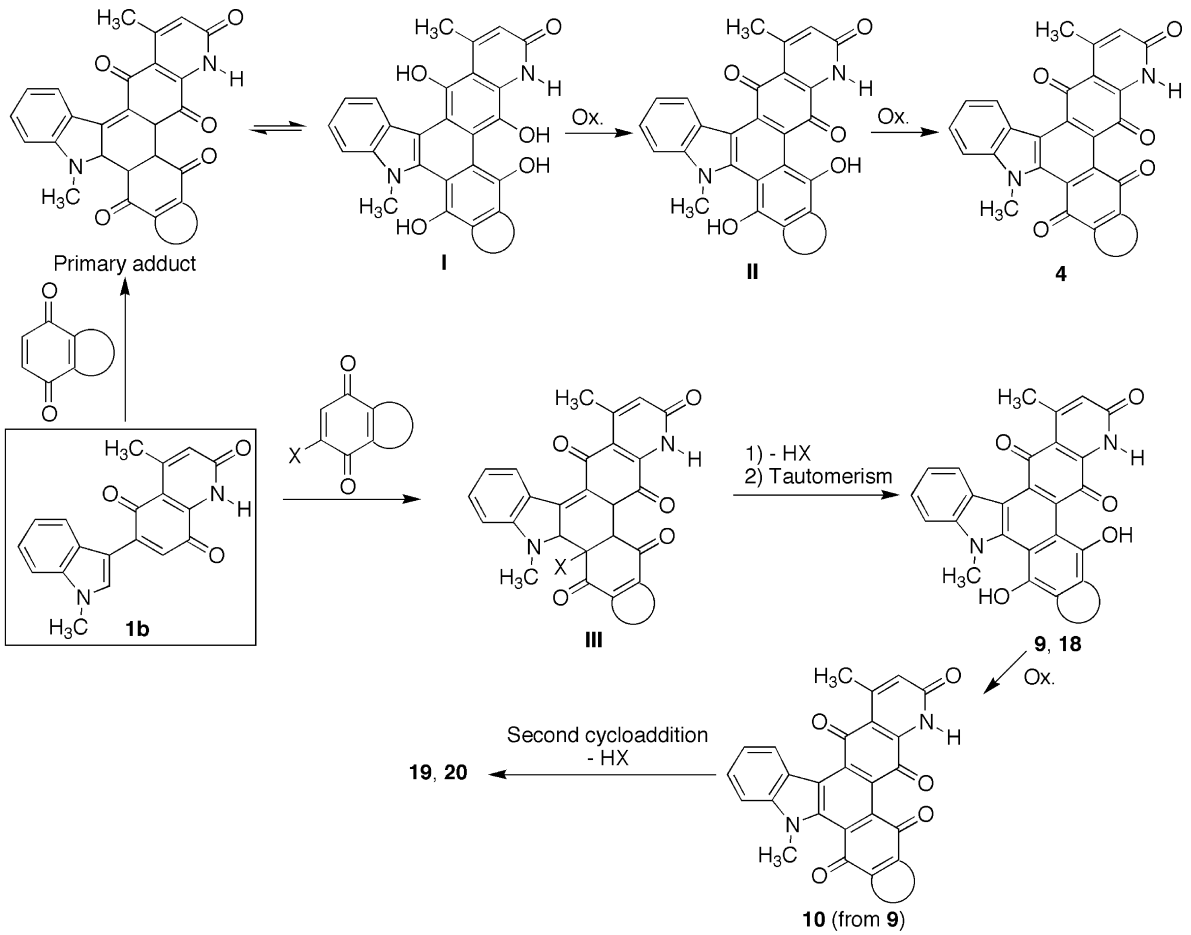
leading to compound **15** in 52% yield. This debromination can be related to known[12] zinc-promoted reductions of carbon–halogen bonds α to carbonyl groups. Finally, oxidative demethylation of compound **15** with cerium ammonium nitrate gave the bromoquinone **16**. When a mixture of compounds **1c** and **16** was refluxed in ethanol, compound **17**, the desired regioisomer of **4c**, precipitated in 61% yield. The regiochemical assignments were supported by the fact that the ^{1}H NMR spectrum of compound **4c** showed two clearly differentiated signals for some of the protons (H-3 and H-9, N_1-CH_3 and N_7-CH_3 and C_4-CH_3 and $C_{10}-CH_3$), which were equivalent in the more symmetrical compound **17** giving rise to a single signal for the corresponding protons (H-3 and H-13, N_1-CH_3 and $N_{15}-CH_3$ and C_4-CH_3 and $C_{12}-CH_3$ taking into account the different numbering of both compounds), as shown in Table 1.

To complete our study of the reactivity of indolylquinones **1**, we examined the possibility of carrying out double Diels–Alder reactions, which would provide a very concise access to complex and unusual polyheterocyclic quinone systems. As shown in Scheme 5, treatment of compound **1b** with 2 equiv. of 2,6-dibromobenzoquinone[13] gave a 86% yield of compound **18**, which precipitated at the hydroquinone stage from the reaction medium, thus preventing its oxidation and a second cycloaddition. However, when 10 equiv. of quinone were employed, compound **19**, arising from a double cycloaddition, was isolated in 60% yield, with no trace of the alternative regioisomer being observed. This regioisomer (compound **20**) was prepared by a similar treatment of **1b** with a large excess of 2,5-dichlorobenzoquinone, again in a completely regioselective fashion. Although the NMR data of compounds **19** and **20** are almost identical, the fact that **19** has an axis of symmetry (causing its OH groups to be non-equivalent) while **20** has a center of symmetry, potentially allows to establish a difference between them. Indeed, the ^{1}H NMR spectrum of **19** shows two broad singlets centered at 10.91 and 9.82 ppm, assigned to the C_{11} and C_{23} hydroxyls, while that of **20** has only one such signal, at 9.87 ppm, in agreement with the proposed regiochemistries. The monohydroquinone structure is in agreement with the molecular peak at 739 (M^++1) in the ESI mass spectrum of both compounds and by the observation of three carbonyl signals at 211.3, 206.1 and 192.1 ppm in the solid-state ^{13}C NMR spectrum of **20**. To our knowledge, these are the first double Diels–Alder reactions of an indolylquinone and, again, their proposed regiochemistry agrees with the one expected for an halogenated quinone as the dienophile (see above the comment on the reaction leading to compound **9**).

The experimental observations described so far can be explained by the mechanism depicted in Scheme 6, which has been written using quinones as the dienophiles. In the case of non-halogenated dienophiles, the primary Diels–Alder adducts evolve by a double tautomerization to



Scheme 5. *Reagents and conditions*: (i) 2 equiv. quinone, $(CH_2Cl)_2$, reflux, 5 h; (ii) 10 equiv. quinone, $(CH_2Cl)_2$ reflux, 5 h; (iii) 10 equiv. quinone, $(CH_2Cl)_2$, reflux, 3 h.



Scheme 6.

bis-hydroquinones **I**. Since these compounds contain a structural fragment identical to that found in compounds **3** (i.e. the hydroquinone structure is attached to the C-3 position of an indole ring), they can be assumed to undergo oxidation, predominantly by air, to the corresponding quinones **II** (not isolated). Further oxidation to give bis-quinones **4** (Scheme 2) must be due again to air oxidation, but when compound **1b** is prepared in situ from 1-methyl-indole and **2a** (Scheme 3), this oxidation step is probably coupled to reduction of a molecule of the starting quinone, which would explain the isolation of hydroquinones **11**. The behaviour of non-quinonoid dienophiles can also be explained by the above mechanism, since compounds **5** and **8** can be considered as examples of intermediates **I** and compound **6** is related to intermediates **II**. When halo-genated quinones are employed as dienophiles, the primary Diels–Alder adducts are intermediates **III**, which give rise to the hydroquinone structures found in compounds **9** and **18** by loss a molecule of hydrogen halide followed by tautomerization. Air oxidation of these hydroquinones would lead to the corresponding quinones, among which only compound **10** has been isolated, although the quinone derived from the oxidation of **18** has been detected by ESI mass spectrometry of a d_6-DMSO solution of **18** kept at room temperature for a few days (M^++1 peaks at m/z=501 and 503). A second cycloaddition of **18**, followed by elimination of HX and tautomerization, would afford compounds **19** and **20**.

3. Experimental

3.1. General

All reagents were of commercial quality (Aldrich, Fluka, SDS, Probus) and were used as received. Solvents (from SDS) were dried and purified using standard techniques. Reactions were monitored by thin layer chromatography, on aluminium plates coated with silica gel with fluorescent indicator (SDS CCM221254 and Macherey-Nagel Alugram Sil G/UV_{254}). Separations by flash chromatography were performed on silica gel (SDS 60 ACC, 230–40 mesh). Melting points were measured with a Reichert 723 hot stage microscope, and are uncorrected. Infrared spectra were recorded on a Perkin Elmer Paragon 1000 FT-IR spectro-photometer, with all compounds examined in KBr pellets. NMR spectra were obtained on Bruker AC-250 (250 MHz for ^{1}H, 63 MHz for ^{13}C) and Bruker AC-500 (500 MHz for ^{1}H) spectrometers (Servicio de RMN, Universidad Complutense), with $CDCl_3$, d_5-pyridine, and d_6-DMSO. Mass spectra were obtained by the unidad de espectrometría de masas (Servicio de Espectroscopia), Universidad Complutense. Combustion elemental analyses were determined by the Servicio de Microanálisis Elemental, Universidad Complutense.

3.1.1. 6-(3-Indolyl)-4-methyl-2,5,8(1*H*)-quinolinetrione (1a). To a stirred solution of 4-methyl-2,5,8(1*H*)-quinolinetrione

(**2a**)[5] (203 mg, 1.07 mmol) in ethanol (3 mL) was added indole (62.5 mg, 0.53 mmol) and 35% aqueous HCl (0.5 mL). The solution was refluxed for 1 h, and the deep blue precipitate was filtered and washed with ethanol, being identified as compound **1a** (125 mg, 77%). [Found: C, 70.73; H, 4.09; N, 9.10. $C_{18}H_{12}N_2O_3$ requires C, 71.05; H, 3.94; N, 9.21]; mp >300°C. ν_{max} (KBr) 3151, 1640 cm^{-1}; δ_H (250 MHz, d_6-DMSO): 12.16 (br. s, 1H, H-1′); 11.65 (s, 1H, H-1); 8.13 (d, 1H, *J*=3 Hz, H-2′); 7.86 (dd, 1H, *J*=6.7 and 2.5 Hz, H-4′); 7.53 (dd, 1H, *J*=6.7 and 2.5 Hz, H-7′); 7.25–7.20 (m, 2H, H-5′,6′); 7.12 (s, 1H, H-7); 6.52 (s, 1H, H-3); 2.53 (s, 3H, C_4–CH_3).

3.1.2. 6-(3-Indolyl)-1′,4-dimethyl-2,5,8(1*H*)-quinolinetrione (1b). To a magnetically stirred solution of 1-methylindole (69 mg, 0.53 mmol) in ethanol (4 mL) and 35% aqueous HCl (0.05 mL), kept under an argon atmosphere, was added a suspension of quinone **2a**[5] (200 mg, 1.06 mmol) in ethanol (2 mL). The reaction mixture was stirred at room temperature for 18 h, and a brown precipitate[14] was filtered and washed with ethanol. The solid was dissolved in $CHCl_3$ (400 mL), which was washed with water and evaporated. The residue was taken up with ethyl ether and filtered, yielding 120 mg (59%) of compound **1b**, as a blue solid. [Found: C, 71.38; H, 5.11; N, 8.24. $C_{19}H_{14}N_2O_3$ requires C, 71.69; H, 4.43; N, 8.80]; mp 299–301°C. ν_{max} (KBr) 3437 (NH), 1631 (CO) cm^{-1}; δ_H (250 MHz, d_5-pyridine) 8.25 (s, 1H, H-2′); 7.92 (d, 1H, *J*=7.6 Hz, H-4′); 7.50–7.20 (m, 4H, H-5′,6′,7′,7); 6.51 (s, 1H, H-3); 3.62 (s, 3H, N–CH_3); 2.55 (s, 3H, C_4–CH_3); δ_C (d_5-pyridine, 63 MHz) 187.2 (C-8); 182.4 (C-5); 164.5 (C-2); 153.2 (C-4); 145.5 (C-8a); 143.7 (C-6); 140.3 (C-7a′); 140.2 (C-2′); 129.1 (C-3a′); 128.5 (C-3); 125.3, 125.0 and 124.7 (C-7, C-6′, C-5′); 123.3 (C-4′); 117.2 (C-4a); 113.4 (C-7′); 110.4 (C-3′); 35.4 (N–CH_3); 24.8 (C_4–CH_3).

3.1.3. 6-(3-Indolyl)-1,4-dimethyl-2,5,8(1*H*)-quinolinetrione (1c). To a stirred solution of indole (43 mg, 0.367 mmol) in diethyl ether (1 mL), was slowly added a solution of quinone **2b**[10] (25 mg, 0.122 mmol) in diethyl ether (2 mL), and 0.2 mL of a mixture of ethanol (1 mL) and 35% aqueous HCl (1 drop). The solution was stirred for 13 h in an open flask, whereby the solvent evaporated to dryness. The black residue was treated with $CHCl_3$ and filtered and the filtrate was chromatographed on silica gel, eluting with pure CH_2Cl_2 to 1:9 ethyl ether–CH_2Cl_2, to yield 8 mg (41%) of compound **1c**, as a black–purple solid, and hydroquinone **11b** (10 mg, 40%). The red precipitate was identified as compound **4c** (2 mg, 6%; see data below).

Data for **1c**: [Found: C, 71.43; H, 4.18; N, 8.61. $C_{19}H_{14}N_2O_3$ requires C, 71.69; H, 4.43; N, 8.80]; mp 263–265°C. ν_{max} (KBr) 3254 (NH), 1662, 1641 (CO) cm^{-1}; δ_H (500 MHz, d_6-DMSO): 12.09 (br. s, 1H, H-1′); 8.17 (d, 1H, *J*=2.5 Hz, H-2′); 7.88 (d, *J*=7.2 Hz, 1H, H-4′); 7.54 (d, *J*=7.5 Hz, 1H, H-7′); 7.26–7.21 (m, 2H, H-5′,6′); 7.11 (s, 1H, H-7); 6.65 (d, 1H, *J*=1 Hz, H-3); 3.76 (s, 3H, N_1–CH_3); 2.55 (d, 3H, *J*=0.8 Hz, C_4–CH_3); δ_C (126 MHz, d_6-DMSO) 185.9 (C-8); 182.2 (C-5); 161.9 (C-2); 149.7 (C-4); 143.2 (C-8a); 142.2 (C-6); 137.7 (C-7a′); 134.0 (C-2′); 126.0 (C-3a′); 125.19 (C-3); 124.2, 123.5 and 122.3 (C-7, C-6′, C-5′); 120.9 (C-4′); 118.1 (C-4a); 113.5 (C-7′); 107.8 (C-3′); 55.7 (*N*–CH_3); 31.5 (C_4–CH_3).

3.1.4. 1,4,10,16-Tetramethyl-1,2,5,6,7,8,11,17-octahydroquino[7,6-*a*]quino[7,6-*c*]carbazole-2,5,6,8,11,17-hexaone (4a). To a solution of indolylquinone **1b** (20 mg, 0.06 mmol) in ethanol (1 mL) was added quinone **2b** (25.6 mg, 0.12 mmol) and 35% aqueous HCl (0.05 mL). The reaction mixture was refluxed for 45 min and the red precipitate of compound **4a** (15 mg, 46%) was filtered and washed with ethanol. [Found: C, 69.33; H, 3.43; N, 7.92. $C_{30}H_{19}N_3O_6$ requires C, 69.63; H, 3.70; N, 8.12%]; mp >320°C. ν_{max} (KBr) 1649 cm^{-1}; δ_H (250 MHz, d_6-DMSO) 9.10 (d, 1H, *J*=7.2 Hz, H-12); 9.50 (br. s, 1H, NH); 7.80–7.60 (m, 2H, H-13,15); 7.55 (d, 1H, *J*=7.2 Hz, H-14); 6.78 and 6.70 (2 s, 2H, H-3,9); 4.00 (s, 3H, N_{16}–CH_3); 3.90 (s, 3H, N_1–CH_3); 2.07 and 2.02 (2 s, 6H, C_4–CH_3 and C_{10}–CH_3).

3.1.5. 4,10,16-Trimethyl-1,2,5,6,7,8,11,17-octahydroquino[7,6-*a*]quino[7,6-*c*]carbazole-2,5,6,8,11,17-hexaone (4b). *Method A*. To a solution of indolylquinone **1b** (20 mg, 0.06 mmol) in ethanol (1 mL) was added quinone **2b** (13 mg, 0.06 mmol) and 35% aqueous HCl (0.05 mL). The mixture was refluxed for 2.5 h and the red precipitate of compound **4b** (10 mg, 32%) was filtered and washed with ethanol.

Method B. To a solution of quinone **2a** (206 mg, 1.09 mmol) in ethanol (3 mL) was added 1-methylindole (70 mg, 0.54 mmol) and 35% aqueous HCl (0.05 mL). The mixture was refluxed for 1.5 h and filtered, the red precipitate being identified as compound **4b** (100 mg, 76%). Evaporation of the filtrate gave hydroquinone **11a**[5] (114 mg, 55%).

Data for **4b**: [Found: C, 68.95; H, 3.03; N, 7.99. $C_{29}H_{17}N_3O_6$ requires C, 69.18; H, 3.40; N, 8.35]; mp >300°C. ν_{max} (KBr) 3423 (NH), 1648 (CO) cm^{-1}; δ_H (250 MHz, d_6-DMSO) 9.50 (s, 2H, 2 NH); 9.07 (d, 1H, *J*=7.5 Hz, H-12); 7.80–7.45 (m, 3H, H-13,14,15); 6.72 and 6.70 (2 s, 2H, H-3,9); 4.00 (s, 3H, N_{16}–CH_3); 2.79 and 2.68 (2 s, 6H, C_4–CH_3 and C_{10}–CH_3).

3.1.6. 1,4,7,10-Tetramethyl-2,5,6,7,8,11,16,17-octahydro-1*H*-quino[7,6-*a*]quino[7,6-*c*]carbazole-2,5,6,8,11,17-hexaone (4c). To a solution of quinone **2b** (200 mg, 0.98 mmol) in ethanol (3 mL) was added indole (58 mg, 0.49 mmol) and 35% aqueous HCl (0.05 mL). The solution was refluxed for 2 h and the red precipitate of compound **4c** (86 mg, 69%) was filtered and washed with ethanol. Evaporation of the filtrate gave 120 mg (60%) of hydroquinone **11b**.[10]

Data for **4c**: [Found: C, 69.38; H, 3.38; N, 7.70. $C_{30}H_{19}N_3O_6$ requires C, 69.63; H, 3.67; N, 8.12]; mp >300°C. ν_{max} (KBr) 3270 (NH); 1657 (CO) cm^{-1}; δ_H (250 MHz, d_6-DMSO) 11.28 (br. s, 1H, NH); 8.36 (s, 1H, H-12); 7.30 and 6.98 (2 s, 3H, H-13,14,15); 6.80 (2 s, 2H, H-3,9); 3.87 (s, 6H, 2 *N*–CH_3); 2.34 (s, 6H, 2 CH_3). Some signals were resolved in d_5-pyridine (500 MHz): 12.64 (br. s, 1H, NH); 8.36 (s, 1H, H-12); 6.87 and 6.82 (2 s, 2H, H-3 and H-9); 4.38 and 4.33 (2 s, 6H, 2 *N*–CH_3); 2.80 and 2.78 (2 s, 6H, 2 CH_3). MS (ESI), *m/z*: 516 (M^+-1).

3.2. Reaction between 1-methylindole and 2 equiv. of quinone 2b

To a solution of quinone **2b** (200 mg, 0.98 mmol) in ethanol (3 mL) was added 1-methylindole (63.5 mg, 0.49 mmol)

and 0.05 mL of 35% aqueous HCl. The mixture was refluxed, and the red precipitate (55 mg, 45%) was filtered and identified as a 2:1 mixture of compounds **4d**[15] and **4e**.[16] Evaporation of the filtrate gave 165 mg (82%) of hydroquinone **11a**.

3.2.1. 5,14-Dihydroxy-1,7,9-trimethyl-3,4,5b,6,8,8a-hexahydropyrrolo[3,4-*a*]quino[7,6-*c*]carbazole-3,6,8-trione (5). A solution of indolylquinone **1b** (20 mg, 0.06 mmol) and *N*-methylmaleimide (47 mg, 0.42 mmol, 7 equiv.) in $(CH_2Cl)_2$ (1 mL) was heated for 18 h at 110°C. The solution was evaporated under reduced pressure and washed with diethyl ether (5 mL), acetone (20 mL), and methanol (20 mL), affording 20 mg (74%) of compound **5**, as a dark red–brown solid. [Found: C, 66.80; H, 4.24; N, 9.55. $C_{24}H_{19}N_3O_5$ requires C, 67.13; H, 4.46; N, 9.79%]; mp >250°C. ν_{max} (KBr) 3301 (NH, OH), 1690 (CO) cm^{-1}; δ_H(250 MHz, d_6-DMSO) 9.91 (br. s, 1H, NH); 9.71 (s, 1H, OH); 8.00 (s, 1H, OH); 7.56–7.47 (m, 2H, H-11,12); 7.20 (t, 1H, *J*=7.9 Hz, H-11); 7.10 (d, 1H, *J*=7.8 Hz, H-13); 6.23 (br. s, 1H, H-2); 4.03 (d, 1H, *J*=8.6 Hz, H-8a); 3.83 (s, 3H, N_9–CH_3); 3.76 (d, 1H, *J*=8.6 Hz, H-5b); 2.50 and 2.49 (2 s, 6H, N_7–CH_3 and C_1–CH_3). MS (ESI), *m*/*z*: 429 (M^+).

3.2.2. 1,7,9-Trimethyl-3,4,5,5b,6,8,8a,14-octahydropyrrolo[3,4-*a*]quino[7,6-*c*]carbazole-3,5,6,8,14-pentaone (6). A solution of compound **5** (10 mg) in DMSO (1 mL) was heated in an open flask for 18 h at 120°C to yield, after cooling, 10 mg (100%) of a precipitate of compound **6**, as a dark red solid. [Found: C, 67.25; H, 3.81; N, 9.69. $C_{24}H_{17}N_3O_5$ requires C, 67.44; H, 4.01; N, 9.83%]; mp >300°C. ν_{max} (KBr) 3376, 3244 (NH, OH), 1702, 1681 (CO) cm^{-1}; δ_H (250 MHz, d_6-DMSO) 12.11 (br. s, 1H, NH); 8.81 (d, 1H, *J*=8.3 Hz, H-13); 7.41 (t, 1H, *J*=7.3 Hz, H-11); 6.83 (d, 1H, *J*=8.2 Hz, H-10); 6.67–6.61 (m, 2H, H-2,12); 4.01 (d, 1H, *J*=8.6 Hz, H-8a); 3.75 (d, 1H, *J*=8.6 Hz, H-5a); 3.34 (s, 3H, N_9–CH_3); 2.49 and 2.43 (2 s, 6H, N_7–CH_3 and C_1–CH_3). MS (ESI): 428 (M^++1).

3.2.3. 1,7,9-Trimethyl-3,4,5,6,8,14-hexahydropyrrolo-[3,4-*a*]quino[7,6-*c*]carbazole-3,5,6,8,14-pentaone (7). To a solution of indolylquinone **1b** (20 mg, 0.06 mmol) in ethanol (1 mL) was added *N*-methylmaleimide (20 mg, 0.18 mmol) and 0.05 mL of 35% aqueous HCl. The mixture was refluxed for 24 h and evaporated. The residue was washed with ethyl ether and methanol, giving 12 mg (47%) of compound **7**, as a dark red solid. [Found: C, 67.39; H, 3.17; N, 9.54. $C_{24}H_{15}N_3O_5$ requires C. 67,76; H. 3,55; N. 9,88%]; mp >300°C. ν_{max} (KBr) 3426 (NH), 1652 (CO) cm^{-1}; δ_H (250 MHz, d_6-DMSO) 8.90 (d, *J*=7.3 Hz, 1H, H-13); 7.50–7.26 (m, 3H, H-10,11,12); 6.44 (s, 1H, H-2); 3.90 (s, 3H, N_9–CH_3); 3.66 (s, 3H, N_7–CH_3); 2.64 (C_1–CH_3). MS (ESI): 448 (M^++Na).

3.2.4. Dimethyl 5,13-dihydroxy-1,8-dimethyl-2-oxo-3,4-dihydroquino[7,6-*c*]carbazole-6,7-dicarboxylate (8). A solution of indolylquinone **1b** (50 mg, 0.157 mmol) and dimethyl acetylenedicarboxylate (300 mg, 2.04 mmol, 13 equiv.) in *o*-dichlorobenzene (12 mL) was irradiated with microwaves for 9 periods of 1 min, with pauses of 3 min after each irradiation, using a domestic microwave oven operating at 400 W. A precipitate was filtered and washed with $CHCl_3$ (5 mL), and CH_2Cl_2 (20 mL), affording 15 mg (20%) of compound **8**, as a black solid. [Found: C, 64.92; H, 4.65; N, 6.01. $C_{25}H_{20}N_2O_7$ requires C, 65.21; H, 4.38; N, 6.08%]; mp >300°C. ν_{max} (KBr) 3425, 3375, 3282, 1647.7 cm^{-1}; δ_H (250 MHz, d_6-DMSO) 12.21 (br. s, 1H, NH); 11.15 (br. s, 1H, OH); 10.20 (br. s, 1H, OH); 8.92 (d, 1H, *J*=8.3 Hz, H-12); 7.80–7.75 (m, 2H, H-9,11); 7.43 (t, 1H, *J*=7.3 Hz, H-10); 6.63 (br. s, 1H, H-2); 3.93 (s, 3H, N_8–CH_3); 3.41 and 3.39 (2 s, 6H, 2 CO_2CH_3), 2.64 (s, 3H, C_1–CH_3).

3.2.5. 5,7-Dihydroxy-3,6,12-trimethyl-11,14,15,16-tetrahydroquino[6,7-*a*]quino[7,6-*c*]carbazole-11,14,15-trione (9). A solution of **1b** (13 mg, 0.04 mmol) and 6-chloro-3-methyl-5,8-quinolinequinone[8] (85 mg, 0.42 mmol, 10 equiv.) in $(CH_2Cl)_2$ (2 mL) was heated for 6 h at 110°C. The solution was evaporated under reduced pressure and washed with $CHCl_3$ (5 mL), acetone (20 mL), and CH_2Cl_2 (20 mL). Then $CHCl_3$ (5 mL) and ethanol (5 mL) was added to dissolve most of the precipitate; this solution was evaporated, affording 17 mg (85%) of compound **9**, as a dark brown solid. [Found: C, 70.93; H, 3.62; N, 8.58. $C_{29}H_{19}N_3O_5$ requires C, 71.16; H, 3.91; N, 8.52%]; mp >340°C. ν_{max} (KBr) 3254, (NH, OH), 1651 (CO) cm^{-1}; δ_H (250 MHz, d_6-DMSO) 12.26 (br. s, 1H, NH); 8.92 (m, 2H, H-2,10); 8.20–8.05 (m, 1H, H-4); 7.90–7.60 (m, 2H, H-7,9); 7.55–7.35 (m, 1H, H-8); 7.30 (br. s, 1H, OH); 7.10 (br. s, 1H, OH); 6.68 (br. s, 1H, H-13); 3.90 (s, 3H, N_6–CH_3); 2.65 (br. s, 6H, C_3–CH_3 and C_{12}–CH_3). MS (ESI): 489 (M^+); 488 (M^+-1).

3.2.6. 3,6,12-Trimethyl-5,11,14,15,16,17-hexahydroquino[6,7-*a*]quino[7,6-*c*]carbazole-5,11,14,16,17-pentaone (10). A solution of compound **9** (10 mg, 0.02 mmol) in DMSO (1 mL) was heated in an open tube for 3 h at 150°C to yield a precipitate of compound **10** (10 mg, 100%), as a red solid. [Found: C, 71.13; H, 3.33; N, 8.31. $C_{29}H_{17}N_3O_5$ requires C, 71.45; H, 3.52; N, 8.62%]; mp >320°C. ν_{max} (KBr) 3410, 1652 cm^{-1}; δ_H (250 MHz, d_6-DMSO) 12.10 (br. s, 1H, NH); 9.05–8.80 (m, 2H, H-2,10); 8.50–8.37 (m, 1H, H-4); 7.95–7.78 (m, 2H, H-7,9); 7.42 (t, 1H, *J*=7.1 Hz, H-8); 6.68 (br. s, 1H, H-13); 3.90 (s, 3H, N_6–CH_3); 2.51 and 2.48 (2 s, 6H, C_3–CH_3 and C_{12}–CH_3). MS (ESI): 510 (M^++Na).

3.2.7. 6,11-Dihydroxy-1,4,7,10-tetramethyl-1,2,5,7,8,17-hexahydroquino[7,6-*a*]quino[7,6-*c*]carbazole-2,5,8,17-tetraone (12). To a solution of 1,4-dimethyl-2,5,8(1*H*)-quinolinetrione **2b** (100 mg, 0.49 mmol) in ethanol (3 mL) was added indole (20 mg, 0.17 mmol) and 35% aqueous HCl (0.05 mL). The solution was refluxed for 6 h and the brownish precipitate of compound **12** (48 mg, 54%) was filtered and washed with ethanol. [Found: C, 69.15; H, 4.01; N, 7.74. $C_{30}H_{21}N_3O_6$ requires C, 69.36; H, 4.07; N, 8.08]; mp >300°C. ν_{max} (KBr) 3405, 3283, 3196 (NH, OH); 2926, 1646 (CO) cm^{-1}; δ_H (250 MHz, d_6-DMSO) 12.49 (br. s, 1H, OH); 10.94 and 10.62 (2 br. s, 1H, NH, OH); 8.18 (s, 1H, H-12); 8.02–7.06 (m, 3H, H-13,14,15); 6.62 and 6.46 (2 s, 2H, H-3,9); 3.45 and 3.22 (2 s, 6H, N_1–CH_3 and N_7–CH_3); 2.75 and 2.64 (2 s, 6H, C_4–CH_3 and C_{10}–CH_3). MS (ESI), *m*/*z*: 519 (M^+).

3.2.8. 3,6-Dibromo-1,4-dimethyl-5,8-dimethoxy-2(1*H*)-quinolinone (14). To a solution of 1,4-dimethyl-5,8-dimethoxy-2(1*H*)-quinolinone **13**[10] (0.150 g, 0.646 mmol)

in acetic acid (2 mL) was added a solution of bromine (0.501 g, 3.23 mmol, 5 equiv.) in acetic acid (11 mL) and the resulting solution was stirred at room temperature for 20 h. A white precipitate was filtered off, the filtrate was evaporated and the residue was chromatographed on silica gel, eluting with $CHCl_3$, to yield 183 mg (73%) of compound **14**, as a pale orange solid. [Found: C, 40.01; H, 3.35; N, 3.65. $C_{13}H_{13}Br_2NO_3$ requires C, 39.90; H, 3.32; N, 3.58.]; mp 144–146°C. ν_{max} (KBr) 1643 (CO) cm^{-1}; δ_H (250 MHz, $CDCl_3$) 7.20 (s, 1H, H-7); 3.87 (s, 3H, C_8-OCH_3), 3.86 (s, 3H, $N-CH_3$), 3.73 (s, 3H, C_5-OCH_3), 2.86 (s, 3H, C_4-CH_3); δ_C (63 MHz, $CDCl_3$) 159.3 (C-2); 148.7 (C-5); 145.9 (C-4); 145.0 (C-8); 131.5 (C-8a); 124.1 (C-4a); 118.8 (C-3); 117.8 (C-7); 111.4 (C-6); 62.4 (C_5-OCH_3); 57.4 (C_8-OCH_3); 38.6 ($N-CH_3$); 23.8 (C_4-CH_3).

3.2.9. 6-Bromo-1,4-dimethyl-5,8-dimethoxy-2(1*H*)-quinolinone (15). A suspension of compound **14** (80 mg, 0.204 mmol) and freshly activated[17] powdered zinc (300 mg) in 95% ethanol (50 mL), was refluxed for 15 h. Then, the reaction mixture was warmed to room temperature and filtered. The solid residue was washed with ethanol (2×20 mL) and the combined filtrates were evaporated and chromatographed on silica gel, eluting with $CHCl_3$-ethyl ether (8:2), to yield 33 mg (52%) of compound **15**, as a pale yellow solid. [Found: C, 50.23; H, 4.75; N, 4.13. $C_{13}H_{14}BrNO_3$ requires C, 50.00; H, 4.48; N, 4.48; mp 131–133°C. ν_{max} (KBr) 1653 (CO) cm^{-1}; δ_H (250 MHz, $CDCl_3$) 7.19 (s, 1H, H-7); 6.55 (s, 1H, H-3); 3.87 (s, 3H, C_8-OCH_3), 3.81 (s, 3H, $N-CH_3$), 3.80 (s, 3H, C_5-OCH_3), 2.62 (s, 3H, C_4-CH_3); δ_C (63 MHz, $CDCl_3$) 163.3 (C-2); 149.5 (C-5); 146.1 and 146.0 (C-4,8); 133.3 (C-8a); 124.3 (C-3); 119.3 (C-4a); 118.0 (C-7); 110.6 (C-6); 62.5 (C_5-OCH_3); 57.4 (C_8-OCH_3); 36.6 ($N-CH_3$); 23.8 (C_4-CH_3).

3.2.10. 6-Bromo-1,4-dimethyl-2,5,8(1*H*)-quinolinetrione (16). To a solution of bromo derivative **15** (20 mg, 0.064 mmol) in acetonitrile (0.7 mL) was added at 0°C a solution of cerium ammonium nitrate (105 mg, 0.192 mmol, 3 equiv.) in water (0.3 mL). After 30 min at room temperature, 2 mL of water was added and the reaction mixture was extracted with $CHCl_3$ (20 mL×2). The combined organic layers were dried (Na_2SO_4) and evaporated under reduced pressure to yield 17 mg (94%) of pure **16** as a yellow–orange solid. [Found: C, 46.48; H, 2.79; N, 4.75. $C_{11}H_8BrNO_3$ requires C, 46.84; H, 2.86; N, 4.97; mp 138–140°C. ν_{max} (KBr) 1654 (CO) cm^{-1}; δ_H (250 MHz, $CDCl_3$) 7.35 (s, 1H, H-7); 6.68 (m, 1H, H-3); 3.84 (s, 3H, $N-CH_3$), 2.58 (d, 3H, J=1 Hz, C_4-CH_3); δ_C (63 MHz, $CDCl_3$) 180.0 (C-5); 177.2 (C-8); 161.9 (C-2); 149.9 (C-8a); 142.2 (C-4); 139.4 (C-6); 137.3 (C-7); 126.1 (C-3); 117.1 (C-4a); 34.6 ($N-CH_3$); 23.4 (C_4-CH_3).

3.2.11. 1,4,12,15-Tetramethyl-2,5,6,11,14,15,16,17-1*H*-octahydroquino[6,7-*a*]quino[7,6-*c*]carbazole-3,5,6,9,11,17-hexaone (17). To a solution of indolylquinone **1c** (10 mg, 0.03 mmol) in ethanol (2 mL) was added quinone **16** (12 mg, 0.042 mmol). The mixture was refluxed for 2.5 h and the red precipitate of compound **17** (10 mg, 61%) was filtered and washed with ethanol, CH_2Cl_2 and acetone. [Found: C, 69.45; H, 3.52; N, 8.00. $C_{30}H_{19}N_3O_6$ requires C, 69.63; H, 3.67; N, 8.12]; mp >300°C. ν_{max} (KBr) 3236 (NH); 1652 (CO) cm^{-1}; δ_H (500 MHz, d_5-pyridine) 12.15 (br. s, 1H, NH); 8.57 (s, 1H, H-10); 7.86 and 7.53 (2 s, 3H, H-8,9,17); 6.88 (s, 2H, H-3 and H-13); 4.37 (s, 6H, N_1-CH_3 and $N_{15}-CH_3$); 2.83 (s, 6H, C_4-CH_3 and $C_{12}-CH_3$). MS(ESI), *m/z*: 517 (M^+).

3.2.12. 8-Bromo-6,9-dihydroxy-1,10-dimethyl-3,5,10,15-tetrahydro-4*H*-benzo[*a*]quino[7,6-*c*]carbazole-3,5,15-trione (18). To a refluxing solution of 2,6-dibromobenzoquinone[13] (50 mg, 0.19 mmol) in $(CH_2Cl)_2$ (10 mL) was added solid compound **1b** (30 mg, 0.09 mmol). The suspension was refluxed for 4 h in an oil bath at 120°C and the brown precipitate was filtered and washed with $(CH_2Cl)_2$ (4×25 mL) and $CHCl_3$ (4×25 mL), affording 41 mg (86%) of compound **18**. [Found: C, 59.48; H, 2.95; N, 5.62. $C_{25}H_{15}BrN_2O_5$ requires C, 59.66; H, 3.00; N, 5.57]; mp >320°C. ν_{max} (KBr) 1652 (C=O) cm^{-1}; δ_H (250 MHz, d_6-DMSO) 9.95 (br. s, 1H, NH); 9.60 (s, 1H, OH); 9.11 (s, 1H, OH); 8.93 (d, 1H, J=7.5 Hz, H-14); 7.82–7.70 (m, 2H, H-11,13); 7.45 (t, 1H, J=7.0 Hz, H-12); 6.93 (s, 1H, H-7); 6.63 (m, 1H, H-2); 3.89 (m, 3H, $N-CH_3$); 2.66 (s, 3H, C_1-CH_3). MS (ESI): 527 and 525 (M^++Na); 503 and 505 (M^++1); 424 (M^++1-Br); 408 (M^+-Br$-CH_3$).

3.2.13. 4,10,12,18-Tetramethyl-11,23-dihydroxy-1,2,5,17,20,21,22,24-octahydroindolo[2,3-*a*]indolo[3,2-*j*]quino[6,7-*c*]quino[7,6-*h*]anthracene-2,5,17,20,22,24-hexaone (19). To a refluxing solution of 2,6-dibromobenzoquinone[13] (209 mg, 0.79 mmol) in $(CH_2Cl)_2$ (10 mL) was added solid compound **1b** (25 mg, 0.08 mmol). The suspension was refluxed for 5 h in an oil bath at 120°C and was left to cool to room temperature overnight. The brown precipitate was filtered and washed with $(CH_2Cl)_2$ (4×25 mL) and $CHCl_3$ (4×25 mL), affording 35 mg (60%) of compound **19**. [Found: C, 71.40; H, 3.00; N, 7.31. $C_{44}H_{26}N_4O_8$ requires C, 71.54; H, 3.55; N, 7.58]; mp >320°C. ν_{max} (KBr) 1653 cm^{-1}; δ_H (250 MHz, d_6-DMSO) 12.30 (br. s, 2H, $N_{1,21}-H$); 8.92 (d, 2H, J=7.5 Hz, H-6,16), 7.80–7.68 (m, 4H, H-7,9,13,15), 7.44 (t, 2H, J=7.5 Hz, H-8,14), 6.63 (s, 2H, H-3,19), 3.88 (s, 6H, $2N-CH_3$), 2.65 (s, 6H, $C_{4,18}-CH_3$). MS (ESI), *m/z*: 739 (M^++1).

3.2.14. 4,10,12,21-Tetramethyl-11,23-dihydroxy-1,2,5,17,18,19,22,24-octahydroindolo[2,3-*a*]indolo[2,3-*h*]-quino[6,7-*c*]quino[6,7-*h*]anthracene-2,5,17,19,22,24-hexaone (20). To a refluxing solution of 2,5-dichlorobenzoquinone (278 mg, 0.79 mmol) in $(CH_2Cl)_2$ (20 mL) was added solid compound **1b** (50 mg, 0.08 mmol). The suspension was refluxed for 3 h in an oil bath at 120°C and was left to cool to room temperature. The brown precipitate was filtered and washed with a 1:1 mixture of methanol, acetone and $CHCl_3$ (15×25 mL), affording 73 mg (63%) of compound **20**. The same reaction conditions could be applied at a larger scale (1 g of compound **1b**), without any noticeable loss of yield. [Found: C, 71.25; H, 3.05; N, 7.28. $C_{44}H_{26}N_4O_8$ requires C, 71.54; H, 3.55; N, 7.58]; mp >320°C. ν_{max} (KBr) 1653 cm^{-1}; δ_H (250 MHz, d_6-DMSO) 12.25 (br. s, 2H, $N_{1,18}-H$); 9.87 (br. s, 2H, OH); 8.93 (d, 2H, J=7.5 Hz, H-6,16), 7.80–7.68 (m, 4H, H-7,9,13,15), 7.44 (t, 2H, J=7.5 Hz, H-8,14), 6.63 (d, 2H, J=1.2 Hz, H-3,20), 3.89 (s, 6H, $N_{10,12}-CH_3$), 2.65 (s, 6H, $C_{4,21}-CH_3$). A solid-state ^{13}C NMR experiment showed three carbonyl signals, at 211.3, 206.1 and 192.1 ppm. MS (ESI), *m/z*: 739 (M^++1).

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14. At this stage of the procedure, this precipitate was identified as compound **3** (120 mg, 59%), which could be quantitatively transformed into **1b** by reflux in $CHCl_3$ for 1 h. However, in some of the experiments the brown solid was contaminated with unreacted quinone **2a** and small amounts of its hydroquinone **11a** and compound **4a** (8%), which are removed by the described procedure with concomitant oxidation of **3** to **1b**. Data for **3**: ν_{max} (KBr) 3437 (OH, NH), 1655 (CO) cm^{-1}. δ_H (250 MHz, d_6-DMSO) 11.85 (br. s, 2H, 2 OH), 8.17 (s, 1H, H-2′), 7.88 (d, 1H, J=7.2 Hz, H-4′), 7.59 (d, 1H, J=7.2 Hz, H-7′), 7.29 (m, 2H, H-5′ and H-6′), 6.50 (s, 1H, H-3), 3.91 (s, 3H, N–CH_3), 2.53 (s, 3H, C_4–CH_3).
15. **4d**: δ_H (250 MHz, d_6-DMSO) 9.05 (d, 1H, J=8.2 Hz, H-12), 7.65 (m, 2H, H-13,14), 7.52 (d, 1H, J=8.2 Hz, H-15), 6.65 and 6.58 (2 s, 1H, H-3,9), 3.84 (s, 9H, 3 N–CH_3), 2.66 and 2.47 (2 s, 6H, CH_3).
16. **4e**: δ_H (250 MHz, d_6-DMSO) 8.69 (d, 1H, J=8.3 Hz, H-12), 7.52 (d, 1H, J=8.2 Hz, H-15), 7.50–7.30 (m, 2H, H-13,14), 6.63 and 6.62 (2s, 1H, H-3,9), 3.95, 3.85 and 3.76 (3s, 3H, N–CH_3), 2.47 (s, 6H, C_4–CH_3 and C_9–CH_3).
17. Zinc can be activated by washing in a Büchner flask with 1 M hydrochloric acid (3×50 mL) then ethanol (50 mL), then ethyl ether (50 mL). The activated zinc is then dried in vacuo and used soon afterwards.