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From phenylacetylphenylacetic acids to indoles: a simple new divergent synthesis of 6,11-dihydro-5*H*-benzo[*a*]carbazol-5,6-diones and 6,11-dihydro-5*H*-benzo[*b*]carbazol-6,11-diones

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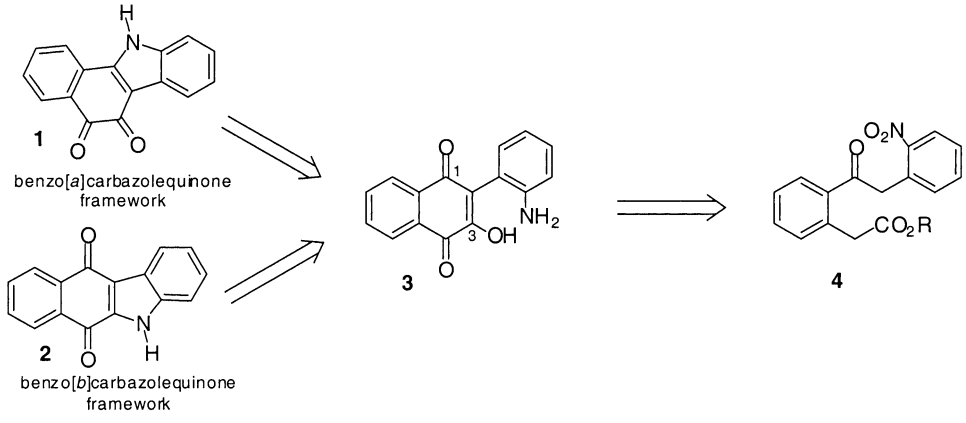
Abstract—The synthesis 6,11-dihydro-5*H*-benzo[*a*]carbazole-5,6-diones and 6,11-dihydro-5*H*-benzo[*b*]carbazole-6,11-diones from common starting materials, 1-(2′-nitrophenylacetyl)phenylacetic acids is described.

Numerous methods have been developed for the synthesis of indoles due to the importance of compounds that incorporate the indole subunit. However, the search for new methods for the simple and efficient construction of the indole ring system continues to be an important synthetic goal.[1] Of particular interest are methods for the synthesis of polycyclic indoles, including benzo- or pyrido-fused carbazoles, because of their potential in the development of antitumor agents.[2] Antineoplastic activity in these compounds has been attributed[3] to their ring systems, which contain an embedded 2-phenylnaphthalene-like structure in a planar conformation. Interesting examples are benzo[*a*]carbazoles which, besides having industrial applications as colorants,[4] are known carcinogens with antiarrhythmic, antimicrobial and antitumoral activity,[5] and are also related to indolo[2,3-*a*]quinolizine alkaloids.[6] Benzo[*b*]carbazoles[7] are closely related to pyrido[*b*]carbazoles,[2b] which have well documented antitumour properties, and examples include elliptinium, a compound used for treatment of thyroid, breast and kidney cancer. Nevertheless, oxidized derivatives like benzo[*a*]carbazolequinones **1** (Scheme 1) have received very little attention to date and, in the course of our studies on these compounds, only one recent synthesis has been described.[8] In contrast, benzo[*b*]-carbazolequinones **2** have been the object of great synthetic interest in the past decade because they were related to the kynamicin family of antibiotics.[9] The antitumour activity of these compounds has also been established.[10]



Scheme 1. Retrosynthetic scheme for the syntheses of benzo[*a*]carbazolequinones and benzo[*b*]carbazolequinones.

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We describe here a single and efficient divergent synthesis of benzo[*a*]carbazolequinones and benzo[*b*]carbazolequinones from readily available phenylacetylphenylacetic acids, a class of compounds previously used by ourselves[11] and others[12] for the efficient syntheses of a variety of compounds, including isoquinolines and related compounds, benzo[*b*]naphtho[2,1-*d*]furans and benzo[*a*]-carbazoles.

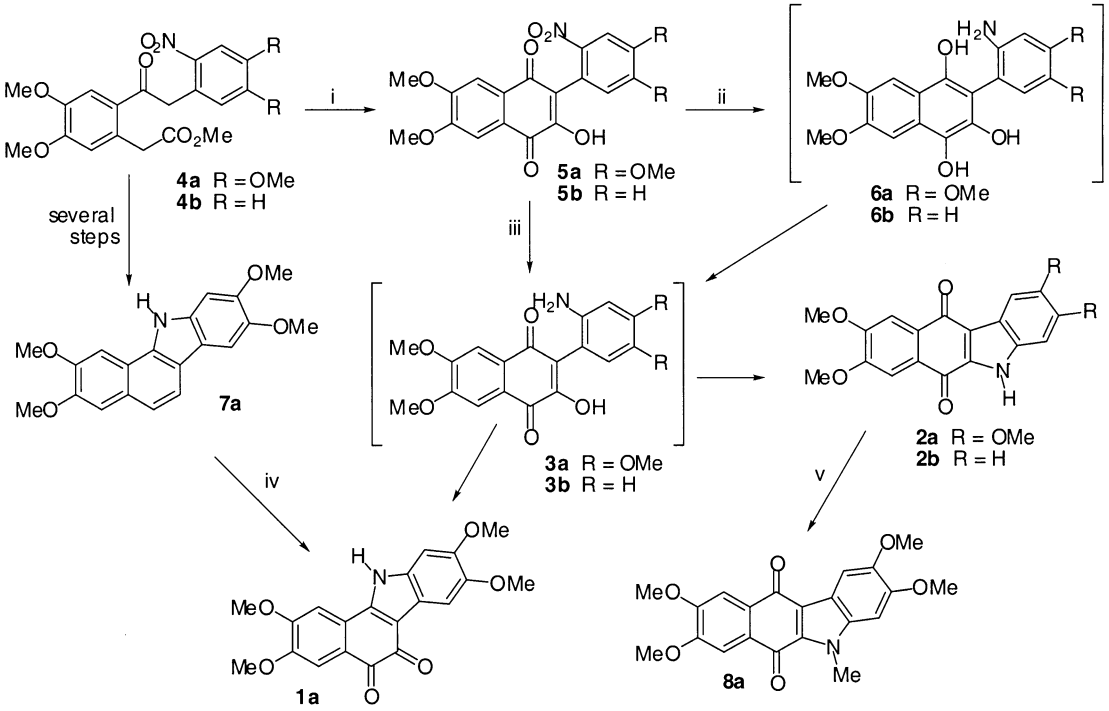
Retrosynthetic considerations suggested that benzo[*a*]- and benzo[*b*]carbazolequinones might be obtained from aminophenylhydroxynaphthoquinones **3** (by linking the amino to positions 1 and 3, respectively), and that aminophenylhydroxynaphthoquinones **3** should be readily available from nitrophenylacetylphenylacetic acids **4**.

Accordingly, we studied the transformation of nitroketoacids **4** into benzo[*a*]carbazolequinone **1a** and benzo[*b*]carbazolequinones **2a** and **2b** (Scheme 2). Nitroketoester **4a** was easily prepared by nitration of the corresponding ketoacid[13] followed by esterification upon treatment with methanol containing a few drops of concentrated sulfuric acid. Treatment of the nitroketoester **4a** with 15% aqueous potassium hydroxide in refluxing ethanol for 30 min afforded nitrophenylhydroxynaphthoquinone **5a** in 98% yield, probably by a mixed intramolecular Claisen condensation followed by oxidation of the dinaphthol intermediate in the reaction medium.

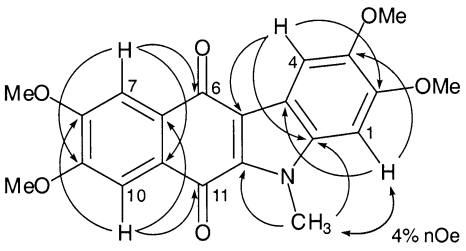
A solution of **5a** in ethyl acetate was subjected to catalytic hydrogenation at room temperature, using PtO_2 as the catalyst, and reduction of the nitro group to the amino was achieved along with reduction of the quinone system to give the aminophenyltrinaphthol **6a**, which was not isolated. The reaction mixture was heated under reflux in an air atmosphere for 24 h in order to oxidize the hydroquinone **6a** to the aminophenylnaphthoquinone **3a**. This reaction gave two new isomeric compounds, **1a** and **2a**, of molecular formula $C_{20}H_{17}NO_6$ (as deduced by microanalysis and mass spectrometry). The two isomers could result from aminophenylnaphthoquinone **3a** by spontaneous attack of the amino group on the naphthoquinone system. The direct amino-carbonyl condensation would led to indolonaphthoquinone **1a**. The alternative conjugate addition of the amino group to the quinone system and subsequent dehydration would furnish indolonaphthoquinone **2a**.

The ^1H NMR spectra of these two compounds are very similar, with the major component showing three singlets at 7.28, 7.63 and 7.82 ppm, corresponding to four aromatic protons, and a singlet at 12.81 ppm, corresponding to the N–H proton; the minor component shows three singlets at 6.93, 7.50 and 7.52 ppm, due to the four aromatic protons, and a singlet at 12.79 ppm, corresponding to the N–H proton. Further evidence for the structural assignment was provided by the IR spectra. The *o*-quinone **1a** presented two carbonyl bands at 1668 and 1618 cm^{-1}, and for the isomeric *p*-quinone **2a**, a typical stretching band for the *p*-quinone system at 1642 cm^{-1} was observed.

The structure proposed for compound **1a** was confirmed by direct comparison with a sample of this compound obtained by oxidation of benzo[*a*]carbazole **7a**, previously prepared by us[11f] from nitroketoester **4a** (Scheme 2). On the other hand, when indolonaphthoquinone **2a** was treated with NaH and MeI in dry DMF, the *N*-methylindolonaphthoquinone **8a** was obtained in 98% yield (Scheme 2). The availability of the *N*-methyl indole **8a**, which proved to be more soluble than the indoles **1a** and **2a**, prompted us to obtain further confirmation of the structural assignment by



Scheme 2. (i) KOH, EtOH, reflux, 30 min. (ii) (a) H_2 (1 atm), PtO_2, AcOEt, room temperature, 1 h; (b) air, reflux, 23 h. (iii) $NaBH_4$, *i*-PrOH. (iv) NaOH, O_2, room temperature, 96 h. (v) NaH, MeI, DMF, room temperature, 1 h.



8a

Figure 1. Important $^{1}H-^{13}C$ couplings observed in the HMBC experiment.

means of nOe, HMQC and HMBC correlation experiments (Fig. 1). Irradiation of the *N*-methyl group of **8a** at δ 4.18 showed an nOe enhancement at 6.73 ppm for only one aromatic proton. In addition, the HMBC experiment showed correlations between δ 7.57 (H7) and 177.52 (C6), and between δ 7.61 (H10) and 181.14 (C11). These results allowed us to confirm the structure proposed for benzo[*b*]-carbazole-6,11-dione **2a**.

The next part of this study involved finding the best conditions for the selective transformation of nitrophenylnaphthoquinones **5** into benzo[*b*]carbazolequinones **2** as the conditions described above allowed the formation of **1a** as the major product. In this respect, we found that treatment of nitrophenylnaphthoquinone **5a** with $NaBH_4$ in isopropanol at room temperature for 4 h led exclusively to the benzo[*b*]carbazolequinone **2a** in 99% yield. It is possible that these new conditions prevent the reduction of the quinone system, thus allowing selective reduction of the nitro group to the amino group and spontaneous regioselective conjugate addition of the amino group to the quinone system.

To study the scope of this synthetic strategy, we prepared the benzo[*b*]carbazolequinone **2b** possessing only two aromatic methyl ethers. The starting nitroketoester **4b** was easily obtained by Friedel–Crafts acylation of ethyl homoveratrate with *o*-nitrophenylacetic acid chloride.[11f] The procedure was the same as that for the synthesis of **2a** and, as such, compound **4b** was refluxed with an ethanolic solution of KOH to give the expected dimethoxylated nitrophenylnaphthoquinone **5b**. Finally, nitroquinone **5b** was reacted with $NaBH_4$ in isopropanol at room temperature to give the benzo[*b*]carbazolequinone **2b** in 97% yield, as confirmed by analytical and spectroscopic data. The IR spectrum of this compound showed a single band at 1653 cm^{-1} due to the *p*-quinone system and a band at 3280 cm^{-1} corresponding to the N–H group. The ^{1}H NMR spectrum presented signals at 7.30–7.38, 7.40–7.43 and 8.13 ppm for a total of six aromatic protons and a singlet at 12.92 ppm due to the N–H proton.

In summary, we have developed a new divergent synthesis for benzo[*a*]carbazolequinone **1a** and benzo[*b*]carbazolequinones **2a** and **2b** from key nitrophenylnaphthoquinones **5a** and **5b**, which can be easily obtained from nitrophenylacetylphenylacetates **4a** and **b**. Conditions were developed for the synthesis of benzo[*a*]carbazolequinone **1a** as the major product and for the regiospecific synthesis of benzo[*b*]carbazolequinone **2b**. The convenient new route to benzo[*b*]carbazolequinones is now being applied to the synthesis of antitumoral ellipticines.[6b,14] In addition, we believe that it will not prove difficult to extend this method to other classes of biologically interesting compounds such as indeneindoles, compounds that are inhibitors of pathogenic radical chain reactions resulting in them possessing potent antioxidant properties.[15]

1. Experimental

1.1. General

Melting points were determined on a Kofler Thermogerate apparatus and are uncorrected. Infrared spectra were recorded on a MIDAC FTIR spectrophotometer. Nuclear magnetic resonance spectra were recorded on a Bruker WM-250 apparatus, using deuterochloroform solutions containing tetramethylsilane as an internal standard. Mass spectra were obtained on a Kratos MS 50 TC mass spectrometer. Thin layer chromatography (tlc) was performed using Merck GF-254 type 60 silica gel and CH_2Cl_2/MeOH mixtures as eluents; the tlc spots were visualized with ultraviolet light or iodine vapour. Column chromatography was carried out using Merck type 9385 silica gel. Solvents were purified as per Ref. 16.

1.1.1. Methyl 2-[2-(4,5-dimethoxy-2-nitrophenyl)acetyl]-4,5-dimethoxyphenylacetate (4a). 2-[2-(4,5-Dimethoxy-2-nitrophenyl)acetyl]-4,5-dimethoxyphenylacetic acid[13] (2 g, 4.75 mmol) was dissolved in 110 mL of methanol and 1 mL of concentrated H_2SO_4 was added. The mixture was heated under reflux for 2.5 h and the methanol was then evaporated in vacuo. The residue was suspended in water (100 mL) and extracted with dichloromethane (3×25 mL). The combined organic layers were dried with anhydrous sodium sulfate, filtered and the solvent removed in vacuo to give methyl 2-[2-(4,5-dimethoxy-2-nitrophenyl)acetyl]-4,5-dimethoxyphenylacetate (**4a**) (2.05 g, 99% yield) as a white solid, mp 130–131°C (MeOH). IR (ν, cm^{-1}, KBr): 1741 (C═O), 1678 (C═O), 1516 (NO_2), 1341 (NO_2). ^{1}H NMR (δ, ppm): 3.62 (s, 3H, OCH_3), 3.86 (s, 2H, CH_2), 3.94 (s, 3H, OCH_3), 3.95 (s, 9H, 3×OCH_3), 4.63 (s, 2H, CH_2), 6.73 (s, 1H, Ar-H), 6.74 (s, 1H, Ar-H), 7.48 (s, 1H, Ar-H), 7.75 (s, 1H, Ar-H). ^{13}C NMR (δ, ppm): 40.24 (CH_2), 46.59 (CH_2), 56.26 (OCH_3), 56.42 (OCH_3), 56.60 (OCH_3), 56.75 (OCH_3), 56.80 (OCH_3), 108.81 (CH), 113.04 (CH), 115.31 (CH), 115.68 (CH), 126.43 (C), 129.30 (C), 129.68 (C), 141.36 (C), 147.87 (C), 148.35 (C), 152.24 (C), 153.65 (C), 172.61 (C═O), 197.50 (C═O). MS (*m/z*, %): 433 (M^+, 1), 237 (34), 209 (100). Anal. Calcd for $C_{19}H_{19}NO_7$: C, 61.12; H, 5.13; N, 3.75. Found: C, 60.99; H, 5.18; N, 3.81.

1.1.2. 6,7-Dimethoxy-2-(3,4-dimethoxy-2-nitrophenyl)-3-hydroxy-1,4-naphthoquinone (5a). A mixture of nitroketoester **4a** (2.4 g, 5.54 mmol), EtOH (180 mL) and 15% aqueous KOH solution (36 mL) was heated under reflux for 30 min. The EtOH was then evaporated in vacuo and the residue suspended in water (250 mL). The mixture was acidified with 10% aqueous HCl solution (20 mL) and extracted with CH_2Cl_2 (3×50 mL). The combined organic layers were dried with anhydrous sodium sulfate, filtered and evaporated in vacuo to give quinone **5a** (2.26 g, 98%) as a red solid, mp 258–260°C (MeOH). IR (ν, cm^{-1}, KBr):

3382 (OH), 1653 (C═O), 1520 (NO_2), 1335 (NO_2). ^{1}H NMR (δ, ppm): 3.96 (s, 3H, OCH_3), 4.01 (s, 3H, OCH_3), 4.03 (s, 3H, OCH_3), 4.04 (s, 3H, OCH_3), 6.87 (s, 1H, Ar-H), 7.55 (s, 1H, Ar-H), 7.56 (s, 1H, Ar-H), 7.61 (s, 1H, OH), 7.77 (s, 1H, Ar-H). ^{13}C NMR (δ, ppm): 56.87 (OCH_3), 56.94 (OCH_3), 57.01 (OCH_3), 57.12 (OCH_3), 108.21 (CH), 108.39 (CH), 109.51 (CH), 113.96 (CH), 120.43 (2×C), 123.95 (C), 128.43 (C), 142.16 (C), 149.45 (C), 151.68 (C), 153.37 (C), 153.65 (C), 155.24 (C), 180.91 (C═O), 182.77 (C═O). MS (*m/z*, %): 369 (M^+, 100), 164 (21), 136 (26), 58 (37). Anal. Calcd for $C_{20}H_{17}NO_9$: C, 57.83; H, 4.13; N, 3.37. Found: C, 58.01; H, 4.27; N, 3.21.

1.1.3. 2,3,8,9-Tetramethoxy-6,11-dihydro-5*H*-benzo[*a*]-carbazol-5,6-dione (1a). *Procedure a*. PtO_2 (440 mg, 0.19 mmol) was added to a deoxygenated solution of 6,7-dimethoxy-2-(3,4-dimethoxy-2-nitrophenyl)-3-hydroxy-1,4-naphthoquinone (**5a**) (0.4 g, 1.05 mmol) in ethyl acetate (300 mL) and the resulting mixture was stirred under a hydrogen atmosphere (p=1 atm) for 1 h. The catalyst was filtered off and the solution was heated under reflux in an air atmosphere for 23 h. The brown precipitate formed was then filtered off and identified as 2,3,8,9-tetramethoxy-6,11-dihydro-5*H*-benzo[*a*]carbazol-5,6-dione (**1a**) (254 mg, 71% yield), mp 268–270°C (MeOH). IR (ν, cm^{-1}, KBr): 3433 (NH), 1668 (C═O), 1618 (C═O). ^{1}H NMR (δ, ppm, CF_3CO_2D): 4.21 (s, 3H, OCH_3), 4.24 (s, 3H, OCH_3), 4.29 (s, 6H, 2×OCH_3), 7.28 (s, 1H, Ar-H), 7.63 (s, 2H, 2×Ar-H), 7.82 (s, 1H, Ar-H), 12.81 (s, 1H, NH). MS (*m/z*, %): 367 (M^+, 100), 324 (46), 280 (19), 169 (23). Anal. Calcd for $C_{20}H_{17}NO_6$: C, 65.39; H, 4.66; N, 3.81. Found: C, 65.25; H, 4.49; N, 3.89.

Procedure b. Oxygen was bubbled through a solution of benzo[*a*]carbazole **7** (50 mg, 0.15 mmol) in 5 mL of 1,4-dioxane for 15 min; excess of sodium hydroxide (50 mg) was added and the mixture was stirred for 96 h. The solvent was removed in vacuo and the residue dissolved in 30 mL of dichloromethane and washed with 15 mL portions of water. The organic layer was dried with anhydrous sodium sulfate and concentrated in vacuo and, after preparative tlc of the residue (eluant: 9:1 dichloromethane/methanol), 30 mg of benzo[*a*]carbazol-5,6-dione **1a** were isolated (55.1% yield).

1.1.4. 2,3,8,9-Tetramethoxy-6,11-dihydro-5*H*-benzo[*b*]-carbazol-6,11-dione (2a). $NaBH_4$ (4 g, 106 mmol) was added during 2 h to a solution of 6,7-dimethoxy-2-(3,4-dimethoxy-2-nitrophenyl)-3-hydroxy-1,4-naphthoquinone (**5a**) (1 g, 2.40 mmol) in isopropanol (150 mL). The mixture was stirred at room temperature for 4 h and then added to water (200 mL). The resulting mixture was acidified with 10% aqueous HCl solution (25 mL) and extracted into chloroform (3×50 mL). The combined organic layers were then dried with anhydrous sodium sulfate, filtered and evaporated in vacuo to give 2,3,8,9-tetramethoxy-6,11-dihydro-5*H*-benzo[*b*]carbazol-6,11-dione (**2a**) (0.88 g, 99% yield) as a red solid, mp 296–298°C (MeOH). IR (ν, cm^{-1}, KBr): 3215 (NH), 1642 (C═O). ^{1}H NMR (δ, ppm, DMSO-d_6): 3.84 (s, 6H, 2×OCH_3), 3.94 (s, 6H, 2×OCH_3), 6.93 (s, 1H, Ar-H), 7.50 (s, 2H, 2×Ar-H), 7.52 (s, 1H, Ar-H), 12.79 (s, 1H, NH). MS (*m/z*, %): 367 (M^+, 100), 353 (46), 338 (24). Anal. Calcd for $C_{20}H_{17}NO_6$: C, 65.39; H, 4.66; N, 3.81. Found: C, 65.46; H, 4.53; N, 3.72.

1.1.5. *N*-Methyl-2,3,8,9-tetramethoxy-6,11-dihydro-5*H*-benzo[*b*]carbazol-6,11-dione (8a). A solution of 2,3,8,9-tetramethoxy-6,11-dihydro-5*H*-benzo[*b*]carbazol-6,11-dione (**2a**) (25 mg, 0.07 mmol) in dry DMF (11 mL) was added dropwise to a stirred mixture of sodium hydride (25 mg) in dry THF (6 mL). This suspension was stirred at room temperature for 1 h. Excess methyl iodide (1 mL) was added and the mixture stirred at room temperature for a further 3 h. Water (25 mL) was added and the resulting mixture extracted with ethyl acetate (3×15 mL). The combined organic layers were washed with water (2×15 mL), dried with anhydrous sodium sulfate and concentrated in vacuo to give *N*-methyl-2,3,8,9-tetramethoxy-6,11-dihydro-5*H*-benzo[*b*]carbazol-6,11-dione (**8a**) (25 mg, 98% yield), mp 210–212°C (MeOH). IR (ν, cm^{-1}, KBr): 1660 (C═O). ^{1}H NMR (δ, ppm): 4.00 (s, 3H, OCH_3), 4.02 (s, 3H, OCH_3), 4.03 (s, 3H, OCH_3), 4.04 (s, 3H, OCH_3), 4.18 (s, 3H, NCH_3), 6.73 (s, 1H, Ar-H), 7.57 (s, 1H, Ar-H), 7.61 (s, 1H, Ar-H), 7.74 (s, 1H, Ar-H). MS (*m/z*, %): 381 (M^+, 100), 366 (30), 338 (23). Anal. Calcd for $C_{21}H_{19}NO_6$: C, 66.13; H, 5.02; N, 3.67. Found: C, 66.30; H, 4.91; N, 3.59.

1.1.6. 6,7-Dimethoxy-2-(2-nitrophenyl)-3-hydroxy-1,4-naphthoquinone (5b). Compound **5b** was prepared in 99% yield from compound **4b** (1 g, 2.68 mmol) by the same procedure as for compound **5a**. Mp 242–243°C (MeOH). IR (ν, cm^{-1}, KBr): 3349 (OH), 1642 (C═O), 1521 (NO_2), 1340 (NO_2). ^{1}H NMR (δ, ppm): 4.03 (s, 3H, OCH_3), 4.05 (s, 3H, OCH_3), 7.52–7.58 (m, 5H, 4×Ar-H and OH), 7.61–7.71 (m, 1H, Ar-H), 8.17 (dd, J=8.2, 0.9 Hz, 1H, Ar-H). ^{13}C NMR (δ, ppm): 57.00 (OCH_3), 57.10 (OCH_3), 108.21 (CH), 109.60 (CH), 119.60 (C), 123.90 (C), 125.00 (CH), 126.20 (C), 128.30 8C), 129.90 (CH), 133.00 (CH), 133.40 (CH), 149.50 (C), 152.00 (C), 153.40 (C), 155.20 (C), 180.80 (C═O), 180.80 (C═O). MS (*m/z*, %): 355 (M^+, 29), 309 (100), 209 (67) 164 (70). Anal. Calcd for $C_{18}H_{13}NO_7$: C, 60.85; H, 3.69; N, 3.94. Found: C, 60.69; H, 3.76; N, 4.06.

1.1.7. 8,9-Dimethoxy-6,11-dihydro-5*H*-benzo[*b*]carbazol-6,11-dione (2b). A solution of compound **5b** (130 mg, 0.36 mmol) in isopropanol (50 mL) was transformed into compound **2b** (97% yield) following the same procedure as for compound **3a**. Mp 279–281°C (MeOH). IR (ν, cm^{-1}, KBr): 3280 (NH), 1653 (C═O). ^{1}H NMR (δ, ppm, DMSO-d_6): 3.93 (s, 3H, OCH_3), 3.94 (s, 3H, OCH_3), 7.30–7.38 (m, 2H, 2×Ar-H), 7.40–7.43 (m, 3H, 3×Ar-H), 8.13 (d, J=8 Hz, 1H, Ar-H), 12.92 (s, 1H, NH). MS (*m/z*, %): 307 (M^+, 100), 264 (8), 236 (10), 193 (10). Anal. Calcd for $C_{18}H_{13}NO_4$: C, 70.35; H, 4.26; N, 4.56. Found: C, 70.22; H, 4.32; N, 4.71.

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