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Acid-Free Synthesis of Carbazoles and Carbazolequinones by Intramolecular Pd-Catalyzed, Microwave-Assisted Oxidative Biaryl Coupling Reactions – Efficient Syntheses of Murrayafoline A, 2-Methoxy-3-methylcarbazole, and Glycozolidine

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A mild and efficient methodology for the synthesis of oxygenated carbazoles from diarylamines under non-acidic conditions was developed, based on a palladium-catalyzed, microwave-assisted double C–H bond activation process. This new protocol was successfully applied to the synthesis of three naturally occurring carbazoles, namely murrayafoline A, 2-methoxy-3-methylcarbazole, and glycozolidine. The scope of the reaction was also expanded to include the synthesis of benzo fused carbazolequinones.

Introduction

Heterocycles are the largest class of organic compounds and are of immense importance to the functioning of human societies.[1] Among the different classes of nitrogen heterocycles, carbazoles are widespread in nature and possess several interesting biological activities including antibacterial, antifungal, antiviral, antiinflammatory and antitumor properties.[2–4] Carbazole derivatives have also been extensively applied as organic materials and investigated for the development of optoelectronic applications such as polymeric light-emitting diodes (PLED) and organic light-emitting devices (OLED).[5,6] Due to their intense native fluorescence, carbazoles are also very important as components of fluorescence sensors, including such applications as the design of fluorescent markers of cancer cells[7] or excited state proton transfer fluorescent probes for lipid bilayers.[8]

Owing to the importance of carbazoles, considerable effort has been devoted to the development of methods for their synthesis.[9] One of the simplest and potentially more efficient procedures is the palladium-mediated cyclodehydrogenation of diarylamines to carbazoles, a reaction that is normally performed in refluxing acetic acid and involves the oxidative functionalization of the two C–H bonds adjacent to the amino group in both aromatic rings. While this reaction starts from readily available starting materials[10] and has found widespread use,[11] it has the disadvantage that electron-rich diarylamines are known to be challenging substrates.[11j] In fact, electron-rich carbazoles such as those bearing several alkoxy substituents conjugated with the carbazole nitrogen are difficult or impossible to obtain by this method because of extensive product decomposition in the reaction media. For this reason, literature examples of the preparation of polyoxygenated carbazoles by cyclodehydrogenation of diarylamines are scarce and proceed in moderate yields.[12] This is an important limitation, since the majority of the naturally occurring carbazoles, exemplified by murrayafoline A (**1**), 2-methoxy-3-methylcarbazole (**2**), glycozolidine (**3**), clausenaquinone A and koeniginequinone A, contain hydroxy or alkoxy groups as structural features (Figure 1). It has recently been shown that the use of pivalic acid as solvent results in improved reproducibility, higher yields, and broader scope for the intramolecular aryl–aryl coupling, although harsh reaction conditions (at least 14 h at 110 °C) were needed.[11j]

We felt that the development of non-acidic conditions for transformation of diarylamines into carbazoles would be synthetically very attractive, specially if the conditions developed encompassed the challenging case of the oxygenated carbazoles. We have previously demonstrated[13] the use of a domestic microwave oven for the synthesis of oxygenated carbazoles from diarylamines.[14] Although this methodology gave good yields, it required to use two equivalents of expensive palladium(II) acetate and was subject to the reproducibility and safety issues associated to the use of domestic microwave ovens in synthesis. Herein, we show that focused microwave significantly improves the yields with regard to our original method and, furthermore, we

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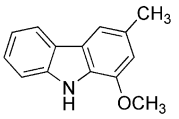
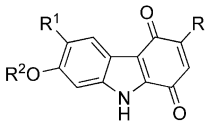


Murrayafoline A, **1**

R	Alkaloid
H	2-Methoxy-3-methyl-carbazole, **2**
OMe	Glycozolinine, **3**



R	R^1	R^2	Alkaloid
OMe	Me	H	Clausenaquinone A
Me	H	Me	Koeniginequinone A

Figure 1. Representative carbazole alkaloids.

also report conditions that allow the use of substoichiometric amounts of the palladium species.[15] Finally, we extend the scope of the reaction to the synthesis of three oxygenated carbazole natural products and also to carbazolequinones.

Results and Discussion

Besides the previously mentioned disadvantages, the main drawback of our previous method was the need for a large excess of palladium(II) acetate, which is due to reduction of Pd^{II} to Pd^0 in the course of the reaction. In order to carry out the process with a catalytic amount of Pd^{II}, it is necessary to use a co-oxidant to regenerate this species during the catalytic cycle. The use of copper(II) acetate for this purpose was first demonstrated by Knölker in cyclodehydrogenation reactions in acetic acid,[16] and has been further explored by other groups recently.[17] With this precedent in mind, we undertook the optimization of the transformation of diphenylamine into carbazole in the presence of a mixture of palladium(II) acetate and copper(II) acetate and a few drops of dimethylformamide as an energy transfer agent.[18]

As shown in Table 1, our first experiments (entries 1–4), for which we used 0.4 equiv. of $Pd(OAc)_2$ and 2.5 equiv. of $Cu(OAc)_2$, were carried out at 100 W power and 100 °C temperature, using progressively longer reaction times and achieved a 76% yield in 60 min. An attempt to decrease reaction time by increasing power to 200 W, together with an increase in temperature (entries 5 and 6), was thwarted by a sudden increase in pressure and concomitant breaking of the reaction tube under these conditions, which led us to restrict the power to 100 W for all subsequent experiments. An increase in the reaction temperature to 130 °C while maintaining the 60 min reaction time led to a 84% yield (entries 7–9), while a further increase in the reaction time did not provide a significantly improved yield (entry 10). A reaction using 0.2 equiv. of the palladium species gave a respectable 70% yield, but a long reaction time was needed (entry 11). For comparison purposes, we also ran this model reaction under our optimal conditions (100 W, 130 °C) but in the absence of copper(II) acetate, finding that 2.5 equiv. of palladium(II) acetate were required to achieve a 82% yield of carbazole, although in this case the reaction time could be reduced to 30 min without a significant loss in yield (entry 12).

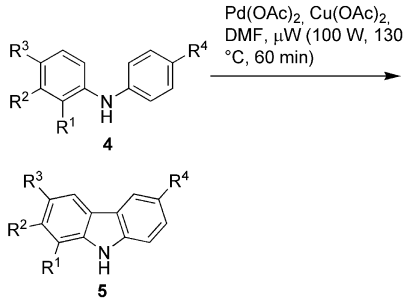
Table 1. Optimization studies of the $Pd(OAc)_2$-promoted cyclodehydrogenation of diphenylamine to carbazole in the presence of $Cu(OAc)_2$ as a co-oxidant. All experiments were carried out in DMF with 0.4 equiv. of $Pd(OAc)_2$ and 2.5 equiv. of $Cu(OAc)_2$, except the ones described in entries 11 and 12.

Entry	Power [W]	Temperature [°C]	Time [min]	% Yield
1	100	100	5	38
2	100	100	20	67
3	100	100	40	73
4	100	100	60	76
5	200	150	15	51
6	200	180	5	–[a]
7	100	130	30	71
8	100	150	30	72
9	100	130	60	84
10	100	130	120	86
11	100	130	150	70[b]
12	100	130	30	82[c]

[a] These conditions led to a sudden increase of pressure and breaking of the reaction tube. [b] Using 0.2 equiv. of $Pd(OAc)_2$ and 2.5 equiv. of $Cu(OAc)_2$. [c] Using 2.5 equiv. of $Pd(OAc)_2$ and no $Cu(OAc)_2$.

The next phase of our investigation began with the synthesis of diarylamines **4** by ligand-coupling reaction of the suitable arylamines with aryllead triacetates in the presence of copper diacetate.[19,20] As shown in Scheme 1 and Table 2, application of our optimized cyclodehydrogenation conditions to these compounds gave in all cases excellent yields of the oxygenated carbazoles **5**, which were consistently 15–20% higher than the ones previously obtained using the domestic oven. Comparison with the conventional method is rendered difficult by the previously mentioned problems found in the preparation of polyoxygenated carbazoles by cyclodehydrogenation of diarylamines under the classical conditions. In those cases where the availability of literature data allowed a comparison, the yields were 10–15% higher for our conditions, besides having the advantage of using sub-stoichiometric palladium. Thus, compounds **5a**[11a] and **5c**[11a] have been prepared in 70% and 75% yields, respectively, by reflux of the corresponding diarylamine in acetic acid in the presence of excess palladium(II) acetate. Compounds **5b**,[21] **5d**,[11d] **5e**,[22a] **5h**[22b] and **5i**[4d] have been previously prepared using alternative methods.

The generality and flexibility of this new methodology were then tested by its application to the total synthesis of three naturally occurring oxygenated carbazoles, namely murrayafoline A (**1**), 2-methoxy-3-methylcarbazole (**2**) and glycozolidine (**3**). Among these alkaloids, **1** is the one that has attracted more attention from synthetic chemists,[23] who have employed its preparation to illustrate a variety of



Scheme 1. Microwave-assisted synthesis of oxygenated carbazoles from diarylamines.

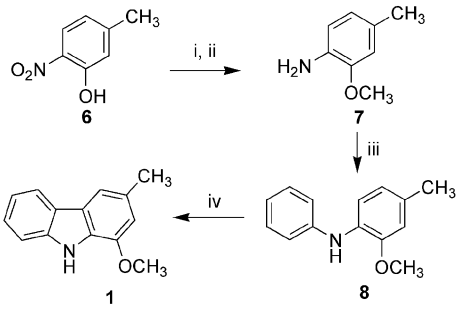
Table 2. Scope and yields of the synthesis of carbazoles.

Entry		R^1	R^2	R^3	R^4	% Yield
1	**5a**	H	H	H	H	84
2	**5b**	H	OMe	H	H	84
3	**5c**	H	H	OMe	H	86
4	**5d**	OMe	H	H	OMe	89
5	**5e**	H	OMe	H	OMe	90
6	**5f**	H	H	F	OMe	85
7	**5g**	H	OEt	H	OMe	91
8	**5h**	H	Me	H	OMe	83
9	**5i**	H	OMe	H	Me	85
10	**5j**	H	OEt	H	Me	80

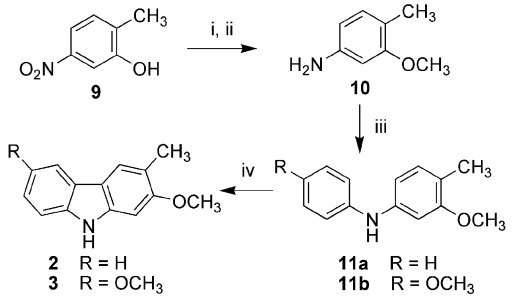
carbazole synthetic protocols. On the other hand, only a few reports are available on the synthesis of **2**[14,24] and **3**.[25] Most of these routes are lengthy, typically involving more than 5 steps from commercially available materials, and suffer from low overall yields.

Our route to murrayafoline A (**1**) began from the commercially available 2-nitro-5-methylphenol **6**, which was transformed into diarylamine **8** in three steps that included a phase transfer-catalyzed methylation and reduction of the nitro group to give **7**, followed by copper(II) acetate catalyzed *N*-arylation with phenylead triacetate under Barton conditions.[19] Microwave irradiation of **8** with palladium(II) acetate in the presence of copper(II) acetate gave murrayafoline A (**1**) in an excellent 88% yield (Scheme 2). The overall yield of the route was 63%, making it the most efficient synthesis of murrayafoline A to date and illustrating the way in which the microwave-assisted construction of an aryl–aryl bond from readily available diarylamines leads to considerable strategic advantages in the synthesis of carbazoles.

We employed a similar strategy for the synthesis of 2-methoxy-3-methylcarbazole (**2**) and glycozolidine (**3**). As depicted in Scheme 3, the suitable diarylamines **11a** and **11b** were synthesized from 2-methyl-5-nitrophenol **9** using a methylation/reduction/*N*-arylation sequence similar to the one employed for the murrayafoline A synthesis, with compound **10** as an intermediate. The final cyclodehydrogenation reactions were carried out under our standard microwave conditions and proceeded in excellent 89% and 80% yields, respectively, affording the target molecules **2** and **3** in 61% and 57% overall yields for the four-step sequences.



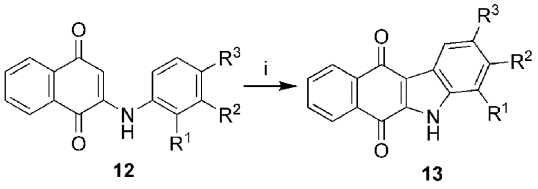
Scheme 2. Total synthesis of murrayafoline A (**1**). Reagents and conditions: i) KOH, ICH_3, $Bu_4N^+HSO_4^-$, toluene, room temp., overnight, 97%. ii) H_2, 10% Pd–C, room temp., 3 h, 96%. iii) $PhPb(OAc)_3$, $Cu(OAc)_2$, DCM, room temp., 2 h, 76%. iv) $Pd(OAc)_2$ (0.4 equiv.), $Cu(OAc)_2$ (2 equiv.), DMF, focused microwave (100 W, 130 °C, 60 min), 88%.



Scheme 3. Total synthesis of 2-methoxy-3-methylcarbazole (**2**) and glycozolidine (**3**). Reagents and conditions: i) KOH, CH_3I, $Bu_4N^+HSO_4^-$, toluene, room temp., 96%; ii) 10% Pd/C, H_2, 97%; iii) $Cu(OAc)_2$, CH_2Cl_2, room temp., $PhPb(OAc)_3$ for **11a**, 73%, *p*-$OCH_3C_6H_4Pb(OAc)_3$ for **11b**, 77%; iv) $Pd(OAc)_2$ (0.4 equiv.), $Cu(OAc)_2$ (2 equiv.), DMF, focused microwave (100 W, 130 °C, 60 min), 89% for **11a**, 80% for **11b**.

Parallel to carbazoles, carbazolequinones have attracted considerable attention from organic chemists due to their potential applications in biology and industry.[2] The most straightforward method to synthesize these compounds involves the palladium-promoted cyclization of 2-arylamino-1,4-quinones, which can be prepared from arylamines and quinones.[26] Nonetheless, all the reported methods required long reaction times, use of acidic solvents, and harsh reaction conditions. Within this context, we exploited the application of our microwave conditions to the cyclodehydrogenation of 2-arylamino-1,4-naphthoquinones (**12**), which were prepared from naphthoquinone and the corresponding arylamines. As shown in Scheme 4 and Table 3, submittal of compounds **12** to our usual microwave irradiation conditions afforded 5*H*-benzo[*b*]carbazole-6,11-diones (**13**) in excellent yields, irrespectively of the nature of the substituents on the arylamine moiety.

The development of a very efficient route 5*H*-benzo[*b*]-carbazole-6,11-diones is significant in that these compounds show a potent cytotoxicity, for which their quinone unit is essential.[27]



Scheme 4. Microwave-assisted synthesis of fused carbazole quinones **13**. Reagents and conditions: i) $Pd(OAc)_2$ (0.4 equiv.), $Cu(OAc)_2$ (2 equiv.), DMF, focused microwave (100 W, 130 °C, 60 min).

Table 3. Scope and yields of the synthesis of 5*H*-benzo[*b*]carbazole-6,11-diones **13**.

Entry		R^1	R^2	R^3	% Yield
1	**13a**	H	H	H	87
2	**13b**	OMe	H	H	91
3	**13c**	H	H	Me	89
4	**13d**	H	H	OMe	84
5	**13e**	H	OEt	H	90
6	**13f**	H	H	F	85

Conclusions

In conclusion, we have developed a mild and very efficient protocol for the double C–H bond activation of diarylamines to give carbazoles bearing oxygenated substituents under non-acidic conditions using focused microwave irradiation, with palladium(II) acetate as a catalyst and copper(II) acetate as a co-oxidant to regenerate the Pd^{II} species. The application of this methodology to the syntheses of oxygenated carbazole natural products and benzo[*b*]-carbazolequinones was demonstrated. These results broaden the scope of intramolecular palladium-catalyzed oxidative biaryl coupling processes.

Experimental Section

General Experimental Information: All reagents (Aldrich, Fluka, SDS, Probus) and solvents (SDS) were of commercial quality and were used as received. Reactions were monitored by thin layer chromatography, on aluminium plates coated with silica gel with fluorescent indicator (SDS CCM221254). Separations by flash chromatography were performed on silica gel (SDS 60 ACC 40–63 μm). Melting points were measured on a Reichert 723 hot-stage microscope, and are uncorrected. Infrared spectra were recorded on a Perkin–Elmer Paragon 1000 FT-IR spectrophotometer, as thin films on NaCl disks or as KBr pellets. NMR spectra were obtained on a Bruker Avance 250 spectrometer operating at 250 MHz for ^1H and 63 MHz for ^{13}C (CAI de Resonancia Magnética Nuclear, Universidad Complutense). Elemental analyses were determined by the CAI de Microanálisis Elemental, Universidad Complutense, using a Leco 932 CHNS combustion microanalyzer.

General Procedure for the Microwave-Assisted Synthesis of Carbazoles: To a mixture of the suitable diarylamine (1 mmol), $Pd(OAc)_2$ (0.4 mmol) and $Cu(OAc)_2$ (2 mmol) was added a few drops of DMF. The mixture was introduced in a 10 mL sealed tube and was irradiated at 100 W and 130 °C for 60 min in a CEM Discover microwave reactor equipped with built-in pressure measurement sensor and a vertically focused IR sensor. After completion of the reaction, the reaction mixture was cooled to 40 °C with an air flow and the reaction mixture was purified by flash silica gel column chromatography eluting with a petroleum ether/ethyl acetate gradient (95:5 to 90:10, v/v). Characterization data for all compounds follow.

Carbazole (5a): White solid, yield 140 mg (84%), m.p. 245–46 °C (243.5–246 °C).[11a] IR (KBr): $\tilde{\nu}$ = 3418.4, 3049.6, 1601.0, 1450.1, 1326.6, 1237.9, 1139.5 cm^{-1}. ^1H NMR ($CDCl_3$, 250 MHz, 25 °C): δ = 7.25–7.32 (m, 2 H, Ar-H), 7.44–7.48 (m, 4 H, Ar-H), 8.08 (br. s, 1 H, NH), 8.13 (d, J = 7.8 Hz, 2 H, Ar-H) ppm. ^{13}C NMR ($CDCl_3$, 63 MHz, 25 °C): δ = 111.0, 119.9, 120.8, 123.7, 126.3, 139.9 ppm. $C_{12}H_9N$ (167.21): calcd. C 86.20, H 5.43, N 8.38; found C 86.06, H 5.48, N 8.48.

2-Methoxycarbazole (5b): White solid, yield 165 mg (84%), m.p. 238–39 °C (235–236 °C).[21] IR (KBr): $\tilde{\nu}$ = 3389.3, 3062.0, 2965.0, 1609.0, 1463.2, 1307.4, 1225.8, 1163.5, 1031.9 cm^{-1}. ^1H NMR ([D_6]DMSO, 250 MHz, 25 °C): δ = 3.85 (s, 3 H, OCH_3), 6.74 (dd, J = 8.6, 2.1 Hz, 1 H, Ar-H), 6.95 (d, J = 2.1 Hz, 1 H, Ar-H), 7.09 (dd, J = 7.6, 7.3 Hz, 1 H, Ar-H), 7.26 (dd, J = 7.9, 7.3 Hz, 1 H, Ar-H), 7.40 (d, J = 7.9 Hz, 1 H, Ar-H), 7.89 (d, J = 8.6 Hz, 1 H, Ar-H), 7.93 (d, J = 7.6 Hz, 1 H, Ar-H), 10.99 (s, 1 H, NH) ppm. ^{13}C NMR ([D_6]DMSO, 63 MHz, 25 °C): δ = 60.7, 99.9, 113.1, 116.1, 121.8, 124.0, 124.6, 126.2, 128.2, 129.5, 145.3, 146.7, 164.0 ppm. $C_{13}H_{11}NO$ (197.23): calcd. C 79.16, H 5.62, N 7.10; found C 79.00, H 5.58, N 7.28.

3-Methoxycarbazole (5c): White solid, yield 169 mg (86%), m.p. 148–49 °C (149–151 °C).[11a] IR (KBr): $\tilde{\nu}$ = 3406.4, 3053.3, 2994.5, 1625.1, 1494.2, 1331.0, 1209.1, 1034.4 cm^{-1}. ^1H NMR ([D_6]DMSO, 250 MHz, 25 °C): δ = 3.86 (s, 3 H, OCH_3), 7.03 (dd, J = 8.7, 2.3 Hz, 1 H, Ar-H), 7.11 (dd, J = 7.4, 7.3 Hz, 1 H, Ar-H), 7.32–7.47 (m, 3 H, Ar-H), 7.69 (d, J = 2.3 Hz, 1 H, Ar-H), 8.10 (d, J = 7.8 Hz, 1 H, Ar-H), 11.05 (s, 1 H, NH) ppm. ^{13}C NMR ([D_6]DMSO, 63 MHz, 25 °C): δ = 60.7, 108.0, 116.1, 116.7, 119.9, 123.1, 125.4, 127.9, 130.5, 139.6, 145.5, 158.1 (one aromatic carbon signal is merged with others) ppm. $C_{13}H_{11}NO$ (197.23): calcd. C 79.16, H 5.62, N 7.10; found C 78.95, H 5.51, N 7.18.

1,6-Dimethoxycarbazole (5d): White solid, yield 202 mg (89%), m.p. 122–23 °C. (118–120 °C).[11d] IR (KBr): $\tilde{\nu}$ = 3412.0, 3066.0, 2998.1, 1614.7, 1578.7, 1485.1, 1391.7, 1297.1, 1219.0, 1034.4 cm^{-1}. ^1H NMR ([D_6]DMSO, 250 MHz, 25 °C): δ = 3.85 (s, 3 H, OCH_3), 3.98 (s, 3 H, OCH_3), 6.93–7.08 (m, 3 H, Ar-H), 7.41 (d, J = 8.8 Hz, 1 H, Ar-H), 7.63–7.70 (m, 2 H, Ar-H), 11.11 (s, 1 H, NH) ppm. ^{13}C NMR ([D_6]DMSO, 63 MHz, 25 °C): δ = 55.5, 55.9, 94.7, 102.8, 107.7, 111.5, 113.3, 116.7, 121.3, 123.5, 134.8, 142.1, 153.4, 158.8 ppm. $C_{14}H_{13}NO_2$ (227.26): calcd. C 73.99, H 5.77, N 6.16; found C 73.95, H 5.61, N 6.18.

2,6-Dimethoxycarbazole (5e):[22a] White solid, yield 204 mg (90%), m.p. 163–164 °C. IR (KBr): $\tilde{\nu}$ = 3397.1, 3002.7, 2958.7, 1626.7, 1490.7, 1284.7, 1162.0, 1029.4 cm^{-1}. ^1H NMR ([D_6]DMSO, 250 MHz, 25 °C): δ = 3.84 (s, 6 H, OCH_3), 6.74 (dd, J = 8.6, 1.7 Hz, 1 H, Ar-H), 6.91–6.94 (m, 2 H, Ar-H), 7.34 (d, J = 8.7 Hz, 1 H, Ar-H), 7.58 (d, J = 1.7 Hz, 1 H, Ar-H), 7.95 (d, J = 8.6 Hz, 1 H, Ar-H), 10.91 (s, 1 H, NH) ppm. ^{13}C NMR ([D_6]DMSO, 63 MHz, 25 °C): δ = 55.5, 55.9, 94.7, 102.8, 107.7, 111.5, 113.3, 116.7, 121.4, 123.5, 134.8, 142.1, 153.4, 158.8 ppm. $C_{14}H_{13}NO_2$ (227.26): calcd. C 73.99, H 5.77, N 6.16; found C 73.88, H 5.67, N 6.25.

3-Fluoro-6-methoxycarbazole (5f): White solid, yield 183 mg (85%), m.p. 115–116 °C. IR (KBr): $\tilde{\nu}$ = 3416.8, 3065.3, 2940.3, 1613.6, 1496.6, 1297.5, 1148.7, 1026.6 cm^{-1}. ^1H NMR ($CDCl_3$, 250 MHz, 25 °C): δ = 3.95 (s, 3 H, OCH_3), 7.11 (dd, J = 8.7, 2.5 Hz, 1 H, Ar-H), 7.17 (dd, J = 9.0, 2.5 Hz, 1 H, Ar-H), 7.29–7.36 (m, 2 H, Ar-H), 7.50 (d, J = 2.5 Hz, 1 H, Ar-H), 7.70 (dd, J = 9.0, 2.5 Hz, 1 H, Ar-H), 7.91 (br. s, 1 H, NH) ppm. ^{13}C NMR ($CDCl_3$, 63 MHz,

25 °C): δ = 51.2, 98.1, 100.9 (d, J = 23.6 Hz), 106.5 (d, J = 8.9 Hz), 106.8, 108.8 (d, J = 25.5 Hz), 111.1, 118.6 (d, J = 3.9 Hz), 118.9 (d, J = 9.4 Hz), 130.6, 131.7, 148.9, 152.4 (d, J = 235.3 Hz) ppm. $C_{13}H_{10}FNO$ (215.22): calcd. C 72.55, H 4.68, N 6.51; found C 72.38, H 4.61, N 6.35.

2-Ethoxy-6-methoxycarbazole (5g): White solid, yield 219 mg (91%), m.p. 158–159 °C. IR (KBr): $\tilde{\nu}$ = 3390.3, 2977.0, 2935.2, 1633.8, 1491.7, 1397.1, 1287.3, 1170.3, 1033.9 cm^{-1}. ^1H NMR ($CDCl_3$, 250 MHz, 25 °C): δ = 1.47 (t, J = 7.0 Hz, 3 H, CH_3), 3.95 (s, 3 H, OCH_3), 4.02 (q, J = 7.0 Hz, 2 H, OCH_2), 6.67 (d, J = 2.2 Hz, 1 H, Ar-H), 6.86 (dd, J = 8.6, 2.2 Hz, 1 H, Ar-H), 7.01 (dd, J = 8.7, 2.4 Hz, 1 H, Ar-H), 7.19 (d, J = 8.7 Hz, 1 H, Ar-H), 7.50 (d, J = 2.4 Hz, 1 H, Ar-H), 7.65 (br. s, 1 H, NH), 7.90 (d, J = 8.6 Hz, 1 H, Ar-H) ppm. ^{13}C NMR ($CDCl_3$, 63 MHz, 25 °C): δ = 15.3, 56.5, 64.2, 95.6, 103.1, 109.0, 111.4, 113.7, 117.5, 121.4, 124.4, 134.7, 142.0, 154.4, 158.8 ppm. $C_{15}H_{15}NO_2$ (241.29): calcd. C 74.67, H 6.27, N 5.81; found C 74.60, H 6.32, N 5.75.

6-Methoxy-2-methylcarbazole (5h):[22b] White solid, yield 175 mg (83%), m.p. 125–126 °C. IR (KBr): $\tilde{\nu}$ = 3392.7, 3001.4, 2913.8, 1631.9, 1582.5, 1490.2, 1284.5, 1206.3, 1034.3 cm^{-1}. ^1H NMR ($CDCl_3$, 250 MHz, 25 °C): δ = 2.54 (s, 3 H, CH_3), 3.95 (s, 3 H, OCH_3), 7.02–7.07 (m, 2 H, Ar-H), 7.19 (s, 1 H, Ar-H), 7.30 (d, J = 8.4 Hz, 1 H, Ar-H), 7.55 (d, J = 2.4 Hz, 1 H, Ar-H), 7.80 (br. s, 1 H, NH), 7.93 (d, J = 8.0 Hz, 1 H, Ar-H) ppm. ^{13}C NMR ($CDCl_3$, 63 MHz, 25 °C): δ = 22.5, 56.5, 103.4, 111.3, 111.6, 114.7, 120.3, 121.0, 121.5, 124.3, 134.8, 136.4, 141.2, 154.2 ppm. $C_{14}H_{13}NO$ (211.26): calcd. C 79.59, H 6.20, N 6.63; found C 79.39, H 6.28, N 6.58.

2-Methoxy-6-methylcarbazole (5i): White solid, yield 179 mg (85%), m.p. 228–229 °C. (227–28 °C).[4d] IR (KBr): $\tilde{\nu}$ = 3400.7, 3007.3, 2911.9, 1616.4, 1464.7, 1311.9, 1227.8, 1165.1, 1036.0 cm^{-1}. ^1H NMR ([D_6]DMSO, 250 MHz, 25 °C): δ = 2.45 (s, 3 H. CH_3), 3.84 (s, 3 H, OCH_3), 6.75 (dd, J = 8.5, 2.0 Hz, 1 H, Ar-H), 6.94 (d, J = 2.0 Hz, 1 H, Ar-H), 7.11 (d, J = 8.1 Hz, 1 H, Ar-H), 7.32 (d, J = 8.1 Hz, 1 H, Ar-H), 7.78 (s, 1 H, Ar-H), 7.91 (d, J = 8.5 Hz, 1 H, Ar-H), 10.99 (s, 1 H, NH) ppm. ^{13}C NMR ([D_6]DMSO, 63 MHz, 25 °C): δ = 21.5, 55.6, 94.7, 107.8, 110.7, 116.4, 119.5, 121.1, 123.2, 125.7, 127.5, 138.3, 141.7, 158.7 ppm. $C_{14}H_{13}NO$ (211.26): calcd. C 79.59, H 6.20, N 6.63; found C 79.48, H 6.22, N 6.60.

2-Ethoxy-6-methylcarbazole (5j): White solid, yield 180 mg (80%), m.p. 232–233 °C. IR (KBr): $\tilde{\nu}$ = 3388.4, 2978.2, 2933.7, 1613.6, 1500.5, 1460.1, 1314.9, 1228.3, 1181.0, 1045.0 cm^{-1}. ^1H NMR ([D_6]DMSO, 250 MHz, 25 °C): δ = 1.38 (t, J = 6.9 Hz, 3 H, CH_3), 2.45 (s, 3 H, CH_3), 4.09 (q, J = 6.9 Hz, 2 H, OCH_2), 6.73 (dd, J = 8.5, 2.2 Hz, 1 H, Ar-H), 6.93 (s, 1 H, Ar-H), 7.11 (d, J = 8.1 Hz, 1 H, Ar-H), 7.32 (d, J = 8.1 Hz, 1 H, Ar-H), 7.77 (s, 1 H, Ar-H), 7.90 (d, J = 8.5 Hz, 1 H, Ar-H), 10.96 (s, 1 H, NH) ppm. ^{13}C NMR ([D_6]DMSO, 63 MHz, 25 °C): δ = 15.2, 21.5, 63.5, 95.3, 108.2, 110.6, 116.3, 119.5, 121.1, 123.2, 125.7, 127.4, 138.3, 141.7, 157.9 ppm. $C_{15}H_{15}NO$ (225.29): calcd. C 79.97, H 6.71, N 6.22; found C 79.80, H 6.52, N 6.21.

Synthesis of 1-Methoxy-3-methylcarbazole (Murrayafoline A, Compound 1)

2-Methoxy-4-methylaniline (7): To a stirred solution of 2-nitro-5-methylphenol **6** (1.00 g) in toluene (20 mL) were added tetrabutylammonium hydrogen sulfate (0.5 g), 50% aqueous KOH solution (4 mL), and methyl iodide (2 mL). The mixture was stirred at room temperature overnight. After completion of the reaction, as monitored by TLC, the mixture was extracted with diethyl ether, washed with KOH solution, water, dried (Na_2SO_4) and solvent was evaporated under reduced pressure. The product obtained was checked by ^1H NMR [($CDCl_3$, 250 MHz, 25 °C): δ = 2.44 (s, 3 H, CH_3), 3.97 (s, 3 H, OCH_3), 6.84 (d, J = 8.3 Hz, 1 H, Ar-H), 6.90 (s, 1 H, Ar-H), 7.82 (d, J = 8.3 Hz, 1 H, Ar-H)] ppm, and considered to be pure enough for the next step without further purification.

A solution of the crude 2-methoxy-4-methyl-1-nitrobenzene (1.0 g) in methanol (20 mL) was hydrogenated for 3 h in the presence of 10% Pd/C (0.02 g). After completion of the reaction, the mixture was filtered through celite and the solvent was evaporated to obtain 2-methoxy-4-methylaniline (**7**) as a pale brown liquid. Overall yield in two steps from **6** to **7** is 93%. IR (neat): $\tilde{\nu}$ = 3453.0, 3365.4, 2937.1, 1623.1, 1519.8, 1279.5, 1158.2 cm^{-1}. ^1H NMR ($CDCl_3$, 250 MHz, 25 °C): δ = 2.36 (s, 3 H, CH_3), 3.73 (br. s, 2 H, NH_2), 3.90 (s, 3 H, OCH_3), 6.68–6.69 (m, 3 H, Ar-H) ppm. ^{13}C NMR ($CDCl_3$, 63 MHz, 25 °C): δ = 21.5, 55.8, 111.9, 115.5, 121.7, 128.4, 134.0, 147.8 ppm.

***N*-(2-Methoxy-4-methylphenyl)aniline (8):**[11j] A mixture of phenyllead triacetate (4.4 mmol, 2.03 g), aniline **7** (4 mmol, 0.548 g) and copper(II) acetate (0.4 mmol, 0.072 g) in dry CH_2Cl_2 (50 mL) was stirred for 2 h. After completion of the reaction, as indicated by TLC, the mixture was filtered through celite and solvent was evaporated. The crude mixture was purified through silica column using petroleum ether/ethyl acetate as eluent (9:1, v/v). Pale brown liquid, yield 648 mg (76%). IR (neat): $\tilde{\nu}$ = 3412.1, 3050.7, 2937.8, 1600.0, 1520.0, 1314.1, 1130.6 cm^{-1}. ^1H NMR ($CDCl_3$, 250 MHz, 25 °C): δ = 2.39 (s, 3 H, CH_3), 3.92 (s, 3 H, OCH_3), 6.06 (br. s, 1 H, NH), 6.75–6.78 (m, 2 H, Ar-H), 6.96 (t, J = 7.3 Hz, 1 H, Ar-H), 7.15 (d, J = 7.5 Hz, 2 H, Ar-H), 7.25–7.35 (m, 3 H, Ar-H) ppm. ^{13}C NMR ($CDCl_3$, 63 MHz, 25 °C): δ = 21.6, 56.0, 112.1, 116.3, 118.0, 120.9, 121.3, 129.7, 130.5, 130.6, 143.9, 149.2 ppm.

1-Methoxy-3-methylcarbazole (Murrayafoline A, 1): The general procedure for the synthesis of compounds **5** was employed for the synthesis of murrayafoline A from compound **8**. White solid, yield 185 mg (88%), m.p. 52–53 °C (51–53 °C).[23c] IR (neat): $\tilde{\nu}$ = 3419.2, 3051.2, 2936.6, 1589.3, 1505.3, 1453.1, 1306.0, 1231.0, 1135.1, 1038.7 cm^{-1}. ^1H NMR ($CDCl_3$, 250 MHz, 25 °C): δ = 2.65 (s, 3 H, CH_3), 4.06 (s, 3 H, OCH_3), 6.83 (s, 1 H, Ar-H), 7.28–7.35 (m, 1 H, Ar-H), 7.48–7.50 (m, 2 H, Ar-H), 7.60 (s, 1 H, Ar-H), 8.14 (d, J = 7.8 Hz, 1 H, Ar-H), 8.27 (br. s, 1 H, NH) ppm. ^{13}C NMR ($CDCl_3$, 63 MHz, 25 °C): δ = 22.4, 55.9, 108.2, 111.4, 113.0, 119.6, 120.9, 124.0, 124.8, 125.9, 128.5, 129.9, 139.9, 145.8 ppm. $C_{14}H_{13}NO$ (211.26): calcd. C 79.59, H 6.20, N 6.63; found C 79.50, H 6.24, N 6.62.

Synthesis of 2-Methoxy-3-methylcarbazole (2) and 2,6-Dimethoxy-3-methylcarbazole (Glycozolidine, 3)

3-Methoxy-4-methylaniline (10): Was synthesized from 2-methyl-5-nitrophenol (**9**) in 93% overall yield following the same methylation-reduction procedure previously mentioned for the preparation of **7**. M.p. 62–63 °C. IR (neat): $\tilde{\nu}$ = 3439.7, 3356.5, 2938.0, 1622.6, 1513.7, 1213.8, 1130.2 cm^{-1}. ^1H NMR ($CDCl_3$, 250 MHz, 25 °C): δ = 2.14 (s, 3 H, CH_3), 3.61 (br. s, 2 H, NH_2), 3.82 (s, 3 H, OCH_3), 6.23–6.27 (m, 2 H, Ar-H), 6.93 (d, J = 8.5 Hz, 1 H, Ar-H) ppm. ^{13}C NMR ($CDCl_3$, 63 MHz, 25 °C): δ = 15.9, 55.6, 98.9, 107.2, 116.8, 131.5, 146.2, 158.9 ppm.

3-Methoxy-4-methyl-*N*-phenylaniline (11a) and 3-Methoxy-*N*-(4-methoxyphenyl)-4-methylaniline (11b): Were synthesized from 3-methoxy-4-methylaniline (**10**) and phenyllead triacetate, 4-methoxyphenyllead triacetate respectively in 73% and 77% yields using the procedure described for the synthesis of compound **8**.

11a:[14] Pale brown solid, yield 622 mg (73%), m.p. 81–82 °C. IR (neat): $\tilde{\nu}$ = 3392.7, 2963.8, 1595.9, 1514.0, 1319.3, 1129.8 cm^{-1}. ^1H

NMR ($CDCl_3$, 250 MHz, 25 °C): δ = 2.23 (s, 3 H, CH_3), 3.83 (s, 3 H, OCH_3), 5.69 (br. s, 1 H, NH), 6.64–6.67 (m, 2 H, Ar-H), 6.95 (t, J = 7.3 Hz, 1 H, Ar-H), 7.06–7.11 (m, 3 H, Ar-H), 7.28–7.34 (m, 2 H, Ar-H) ppm. ^{13}C NMR ($CDCl_3$, 63 MHz, 25 °C): δ = 16.1, 55.7, 102.2, 110.9, 117.5, 120.2, 120.8, 129.8, 131.4, 142.3, 144.3, 158.8 ppm.

11b: Pale brown solid, yield 748 mg (77%), m.p. 64–65 °C. IR (neat): $\tilde{\nu}$ = 3388.0, 2935.2, 1614.3, 1504.6, 1242.8, 1129.5 cm^{-1}. ^{1}H NMR ($CDCl_3$, 250 MHz, 25 °C): δ = 2.20 (s, 3 H, CH_3), 3.80 (s, 3 H, OCH_3), 3.84 (s, 3 H, OCH_3), 5.49 (br. s, 1 H, NH), 6.48–6.51 (m, 2 H, Ar-H), 6.90 (t, J = 8.9 Hz, 2 H, Ar-H), 7.02 (dd, J = 8.1, 0.7 Hz, 1 H, Ar-H), 7.08 (d, J = 8.9 Hz, 2 H, Ar-H) ppm. ^{13}C NMR ($CDCl_3$, 63 MHz, 25 °C): δ = 15.9, 55.7, 56.0, 100.0, 108.5, 115.1, 118.5, 121.8, 131.4, 136.9, 144.5, 155.3, 158.8 ppm.

The general procedure for the synthesis of **5** was employed for the synthesis of 2-methoxy-3-methylcarbazole (**2**) and glycozolidine (**3**) from the corresponding diarylamines; yields: 89% for **2**; 80% for **3**.

2-Methoxy-3-methyl-9*H*-carbazole (2): White solid, yield 188 mg (89%), m.p. 225–226 °C. (225 °C).[24c] IR (KBr): $\tilde{\nu}$ = 3406.6, 2940.2, 2909.1, 1610.5, 1457.2, 1307.6, 1232.2, 1141.1, 1039.9 cm^{-1}. ^{1}H NMR ([D$_6$]DMSO, 250 MHz, 25 °C): δ = 2.32 (s, 3 H, CH_3), 3.88 (s, 3 H, OCH_3), 6.95 (s, 1 H, Ar-H), 7.08 (dd, J = 7.5, 7.4 Hz, 1 H, Ar-H), 7.25 (dd, J = 7.6, 7.2 Hz, 1 H, Ar-H), 7.41 (d, J = 8.0 Hz, 1 H, Ar-H), 7.75 (s, 1 H, Ar-H), 7.89 (d, J = 7.7 Hz, 1 H, Ar-H), 10.84 (s, 1 H, NH) ppm. ^{13}C NMR ([D$_6$]DMSO, 63 MHz, 25 °C): δ = 16.9, 55.5, 92.8, 110.8, 115.6, 117.8, 118.5, 119.1, 121.3, 122.9, 123.9, 139.8, 139.9, 157.1 ppm. $C_{14}H_{13}NO$ (211.26): calcd. C 79.59, H 6.20, N 6.63; found C 79.39, H 6.14, N 6.50.

2,6-Dimethoxy-3-methyl-9*H*-carbazole (Glycozolidine, 3): White solid, yield 193 mg (80%), m.p. 167–168 °C. (166–167 °C).[25c] IR (KBr): $\tilde{\nu}$ = 3404.1, 2996.7, 2938.4, 1634.1, 1487.0, 1429.3, 1322.9, 1277.5, 1206.0, 1134.8, 1028.0 cm^{-1}. ^{1}H NMR ([D$_6$]DMSO, 250 MHz, 25 °C): δ = 2.34 (s, 3 H, CH_3), 3.84 (s, 3 H, OCH_3), 3.88 (s, 3 H, OCH_3), 6.77 (s, 1 H, Ar-H), 6.92 (dd, J = 8.7, 2.4 Hz, 1 H, Ar-H), 7.25 (d, J = 8.7 Hz, 1 H, Ar-H), 7.42 (d, J = 2.4 Hz, 1 H, Ar-H), 7.71 (s, 1 H, Ar-H) 9.56 (br. s, 1 H, NH) ppm. ^{13}C NMR ([D$_6$]DMSO, 63 MHz, 25 °C): δ = 11.8, 50.4, 50.9, 87.6, 97.3, 106.1, 107.8, 110.9, 113.2, 116.2, 118.6, 129.6, 135.4, 148.4, 152.3 ppm. $C_{15}H_{15}NO_2$ (241.29): calcd. C 74.67, H 6.27, N 5.81; found C 74.47, H 6.16, N 5.85.

Synthesis of 5*H*-Benzo[*b*]carbazole-6,11-diones (13): Compounds **12** were prepared from naphthoquinone and anilines using the literature procedure. To a mixture of the suitable 2-(arylamino)naphthalene-1,4-dione **12** (1 mmol), $Pd(OAc)_2$ (0.4 mmol), and $Cu(OAc)_2$ (2 mmol) was added a few drops of DMF and the mixture was irradiated in at 100 W and 130 °C in a CEM Discover microwave reactor for 60 min. After completion of the reaction, the crude 5*H*-benzo[*b*]carbazole-6,11-diones (**13**) were purified by silica gel column chromatography using petroleum ether/ethyl acetate as eluent (8:2, v/v).

5*H*-Benzo[*b*]carbazole-6,11-dione (13a): Orange solid, yield 215 mg (87%), m.p. 301–303 °C. (300–303 °C).[26e] IR (KBr): $\tilde{\nu}$ = 3232.5, 3005.7, 2934.5, 1652.3, 1594.6, 1380.0, 1262.1, 1203.4 cm^{-1}. ^{1}H NMR ([D$_6$]DMSO, 250 MHz, 25 °C): δ = 7.33–7.48 (m, 2 H, Ar-H), 7.59 (d, J = 8.1 Hz, 1 H, Ar-H), 7.77–7.88 (m, 2 H, Ar-H), 8.07–8.10 (m, 2 H, Ar-H), 8.20 (d, J = 7.8 Hz, 1 H, Ar-H), 13.1 (s, 1 H, NH) ppm. ^{13}C NMR ([D$_6$]DMSO, 63 MHz, 25 °C): δ = 114.2, 117.7, 122.7, 124.2, 124.3, 126.3, 126.4, 127.3, 132.9, 133.6, 134.4, 134.6, 137.5, 138.6, 177.9, 180.7 ppm. $C_{16}H_9NO_2$ (247.25): calcd. C 77.72, H 3.67, N 5.67; found C 77.57, H 3.60, N 5.75.

4-Methoxy-5*H*-benzo[*b*]carbazole-6,11-dione (13b):[26b] Orange solid, yield 252 mg (91%), m.p. > 250 °C. IR (KBr): $\tilde{\nu}$ = 3276.2, 3002.7, 2939.5, 1654.8, 1595.6, 1534.4, 1383.0, 1262.1, 1203.4 cm^{-1}. ^{1}H NMR ([D$_6$]DMSO, 250 MHz, 25 °C): δ = 3.96 (s, 3 H, OCH_3), 6.96 (d, J = 7.9 Hz, 1 H, Ar-H), 7.27 (t, J = 7.9 Hz, 1 H, Ar-H), 7.75–7.84 (m, 3 H, Ar-H), 8.07–8.09 (m, 2 H, Ar-H), 13.2 (s, 1 H, NH) ppm. ^{13}C NMR ([D$_6$]DMSO, 63 MHz, 25 °C): δ = 55.9, 107.1, 114.6, 118.2, 125.4, 125.8, 126.3, 126.4, 129.4, 133.1, 133.6, 134.3, 134.5, 137.3, 147.9, 177.5, 180.9 ppm. $C_{17}H_{11}NO_3$ (277.27): calcd. C 73.64, H 4.00, N 5.05; found C 73.40, H 4.12, N 5.11.

2-Methyl-5*H*-benzo[*b*]carbazole-6,11-dione (13c): Orange solid, yield 232 mg (89%), m.p. 254–156 °C. (257–60 °C).[26f] IR (KBr): $\tilde{\nu}$ = 3222.0, 2956.5, 2917.0, 1666.0, 1594.1, 1533.2, 1386.5, 1244.0, 1175.8, 1018.6 cm^{-1}. ^{1}H NMR ([D$_6$]DMSO, 250 MHz, 25 °C): δ = 2.43 (s, 3 H, CH_3), 7.23 (dd, J = 8.6, 1.3 Hz, 1 H, Ar-H), 7.44 (d, J = 8.6 Hz, 1 H, Ar-H), 7.77–7.83 (m, 2 H, Ar-H), 7.95 (s, 1 H, Ar-H), 8.03–8.09 (m, 2 H, Ar-H), 12.9 (s, 1 H, NH) ppm. ^{13}C NMR ([D$_6$]DMSO, 63 MHz, 25 °C): δ = 21.6, 113.8, 117.2, 121.9, 124.6, 126.2, 126.3, 129.1, 132.9, 133.4, 133.6, 134.4, 136.9, 137.3, 177.8, 180.6 (one aromatic carbon is merged with others) ppm. $C_{17}H_{11}NO_2$ (261.27): calcd. C 78.15, H 4.24, N 5.36; found C 78.00, H 4.22, N 5.25.

2-Methoxy-5*H*-benzo[*b*]carbazole-6,11-dione (13d): Orange solid, yield 233 mg (84%), m.p. 297–98 °C (299–300 °C).[26g] IR (KBr): $\tilde{\nu}$ = 3232.5, 3003.9, 1656.4, 1593.6, 1527.4, 1389.2, 1257.7, 1103.9 cm^{-1}. ^{1}H NMR ([D$_6$]DMSO, 250 MHz, 25 °C): δ = 3.84 (s, 3 H, OCH_3), 7.05 (dd, J = 9.0, 2.4 Hz, 1 H, Ar-H), 7.46 (d, J = 9.0 Hz, 1 H, Ar-H), 7.56 (d, J = 2.4 Hz, 1 H, Ar-H), 7.77–7.83 (m, 2 H, Ar-H), 8.03–8.08 (m, 2 H, Ar-H), 12.98 (s, 1 H, NH) ppm. ^{13}C NMR ([D$_6$]DMSO, 63 MHz, 25 °C): δ = 55.7, 102.4, 115.3, 117.3, 118.7, 125.2, 126.3, 133.1, 133.4, 133.8, 134.4, 134.5, 137.3, 157.2, 177.5, 180.5 (one aromatic carbon is merged with others) ppm. $C_{17}H_{11}NO_3$ (277.27): calcd. C 73.64, H 4.00, N 5.05; found C 73.52, H 3.95, N 5.01.

3-Ethoxy-5*H*-benzo[*b*]carbazole-6,11-dione (13e): Orange solid, yield 262 mg (90%), m.p. > 250 °C. IR (KBr): $\tilde{\nu}$ = 3253.6, 2976.2, 2929.4, 1664.7, 1634.8, 1528.5, 1436.2, 1262.3, 1171.6, 1048.5 cm^{-1}. ^{1}H NMR ([D$_6$]DMSO, 250 MHz, 25 °C): δ = 1.38 (t, J = 6.9 Hz, 3 H, CH_3), 4.07 (q, J = 6.9 Hz, 2 H, OCH_2), 6.93–7.00 (m, 2 H, Ar-H), 7.78–7.85 (m, 2 H, Ar-H), 8.01–8.09 (m, 3 H, Ar-H), 12.86 (s, 1 H, NH) ppm. ^{13}C NMR ([D$_6$]DMSO, 63 MHz, 25 °C): δ = 14.9, 63.7, 95.9, 116.1, 118.3, 123.6, 126.2, 126.3, 133.1, 133.6, 134.2, 134.3, 136.7, 140.1, 158.9, 177.1, 180.9 (one aromatic carbon is merged with others) ppm. $C_{18}H_{13}NO_3$ (291.30): calcd. C 74.22, H 4.50, N 4.81; found C 74.10, H 4.44, N 5.00.

2-Fluoro-5*H*-benzo[*b*]carbazole-6,11-dione (13f): Orange solid, yield 225 mg (85%), m.p. > 250 °C. IR (KBr): $\tilde{\nu}$ = 3236.6, 1649.8, 1594.9, 1532.1, 1483.4, 1393.8, 1255.6, 1215.5, 1097.0 cm^{-1}. ^{1}H NMR ([D$_6$]DMSO, 250 MHz, 25 °C): δ = 7.28 (td, J = 9.2, 2.6 Hz, 1 H, Ar-H), 7.56 (dd, J = 9.0, 4.5 Hz, 1 H, Ar-H), 7.73–7.86 (m, 3 H, Ar-H), 8.03–8.06 (m, 2 H, Ar-H), 13.10 (s, 1 H, NH) ppm. ^{13}C NMR ([D$_6$]DMSO, 63 MHz, 25 °C): δ = 106.9 (d, J = 24.1 Hz), 115.9 (d, J = 7.8 Hz), 116.1 (d, J = 26.7 Hz), 117.6 (d, J = 5.3 Hz), 124.6 (d, J = 11.1 Hz), 126.4, 132.9, 133.6, 134.3, 134.6, 135.2, 138.7, 159.8 (d, J = 238.7 Hz), 177.7, 180.4 (one aromatic carbon is merged with others) ppm. $C_{16}H_8FNO_2$ (265.24): calcd. C 72.45, H 3.04, N 5.28; found C 72.40, H 3.11, N 5.09.

Supporting Information (see also the footnote on the first page of this article): Copies of ^{1}H and ^{13}C NMR spectra for all new compounds.

Acknowledgments

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