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New and efficient routes for the synthesis of murrayaquinone A and murrayanine

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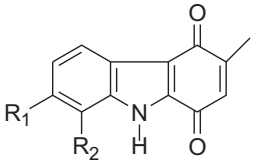
ABSTRACT

Three new routes were established for the synthesis of biologically active murrayaquinone A and a new method was developed for synthesis of murrayanine from the same starting material as 4-hydroxy carbazole. During the synthetic course a few novel observation were recorded, which include two one pot reaction sequences and C–N bond cleavage by sodium cyanoborohydride.

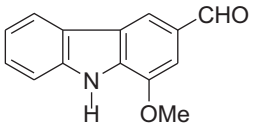
1. Introduction

Plants of genus *Murraya* (Rutaceae family) are the major source of biologically active carbazoles. Extracts of the leaves and bark of these trees have been used as a folk medicine for analgesia and local anesthesia, as well as for the treatment of eczema, rheumatism, and dropsy.[1] The search for the biologically active compounds of *Murraya* led to the discovery of a broad variety of carbazole alkaloids including murrayaquinone family and murrayanine. The carbazole-1,4-quinone, murrayaquinone A (**1**) was first isolated from the root bark of *Murraya eucrestifolia* HAYATA (Rutaceae) collected in Taiwan together with three closely related alkaloids [murrayaquinones B-D (**2**–**4**)] by Furukawa and co-workers.[1,2] Among these alkaloids, murrayaquinone A (**1**) has been found to exhibit the cardiotonic activity on guinea pig papillary muscle.[3] There are fifteen synthetic methods reported[4,5] for murrayaquinone A using various approaches.

Murrayanine was the first biologically active carbazole isolated from the plant Murraya koenigii Spreng. Chakraborty et al. reported[6] the isolation of murrayanine, independently from two different genera of the family Rutaceae, *M. koenigii* and *C. heptaphylla*. More recently; Cuong et al. isolated murrayanine from *G. stenocarpa Guillaumin* from Northern Vietnam.[7] Murrayanine showed antimicrobial properties against human pathogenic fungi.[8] Murrayanine is an attractive synthetic target since it is the intermediate for the synthesis of several other members of the group, which includes murrayafoline A, koenoline, mukoeic acid, mukonine, 1-hydroxy-3-methylcarbazole, *O*-demethylmurrayanine, clausine E (clauszoline-I) and 3-formylcarbazole. There are various reports available for the synthesis of murrayanine.[9] In continuation with our interest in the total synthesis of biologically active carbazoles, herein we report three new routes for the synthesis of murrayaquinone A and an efficient route for murrayanine.



		R_1	R_2
1	A	H	H
2	B	OMe	
3	C	OMe	
4	D	OH	



Murrayanine (**5**)

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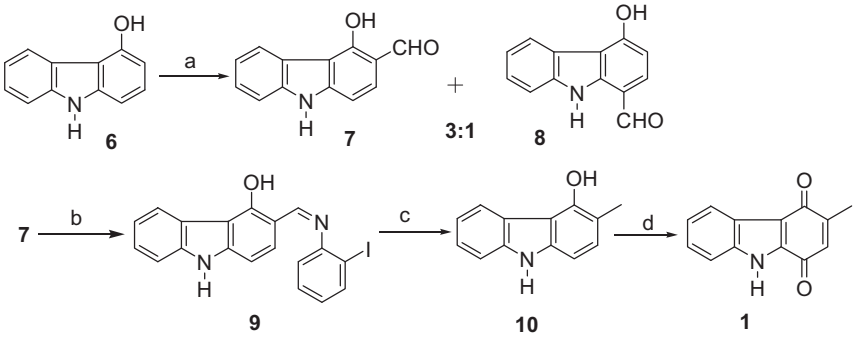
2. Results and discussion

2.1. Synthesis of murrayaquinone A

It was envisaged to use the novel unexpected intermediates obtained during the other synthetic sequences in our laboratory, for the synthesis of biologically active murrayaquinone A. Three different simple routes were planned from *ortho* and *para* formylated derivatives of 4-hydroxyl carbazole.

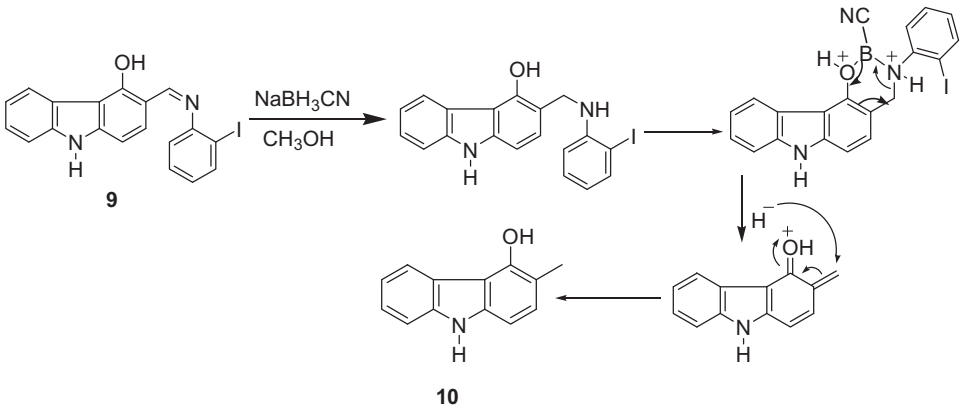
As shown in Scheme 1, synthesis started by the Vilsmeier–Hacck formylation of commercially available 4-hydroxyl carbazole, which furnished the *ortho* and *para* formylated products **7** and **8** in 3:1 ratio, respectively. Compound **7** was converted to imine **9** using *o*-iodo aniline in presence of catalytic amount of *p*TSA in methanol. Further, imine **9** was subjected to reduction using sodium cyanoborohydride furnishing product **10**. It showed a singlet for $-CH_3$ protons at δ 2.37 in ^{1}H NMR and a singlet for methyl group at δ 14.80 in ^{13}C NMR. The spectroscopic data of this compound was in good agreement with that of the reported[10] compound **10**. Interestingly, product **10** was obtained by reduction of imine–amine and further C–N bond breakage. The cleavage of C–N bond in the amine can be explained by the possibility of formation of six membered intermediate of boron,[11] which on further cleavage would furnish product **10** as shown in Scheme 2. Finally quinone formation of compound **10** by using iodobenzene diacetate led to the target molecule murrayaquinone A in 80% yield.

During the second route (Scheme 3) *ortho* formylated compound **7** was initially brominated to compound **11** using NBS in quantitative yield. Further, both –NH and –OH groups were protected by benzyl group in 93% yield. Having protected bromo aldehyde **12** in hand, attempt was made to replace bromine by methoxy group. Thus, reaction of aldehyde **12** in dry DMF with sodium methoxide in methanol and CuI for 10 h at 120 °C, furnished[12] alcohol **13** in 77% yield. In this one pot reaction sequence bromine and benzyloxy groups were replaced by methoxy groups and subsequently aldehyde was reduced to alcohol. Compound **13** was converted to quinone **14** by using CAN at 0 °C in 89% yield. Further, compound **14** was treated with triphenyl phosphine and bromine at 0 °C to give the expected product **15** in 95% yield. The next task was to reduce $-CH_2Br$ to methyl group. Thus, bromoquinone **15** was treated with $LiAlH_4$ in dry THF to furnish compound **16** in 79% yield. Finally, the deprotection of *N*-benzyl group of protected murrayaquinone **16**, using $Pd(OH)_2$ led to the target molecule murrayaquinone A (**1**) in 70% yield.

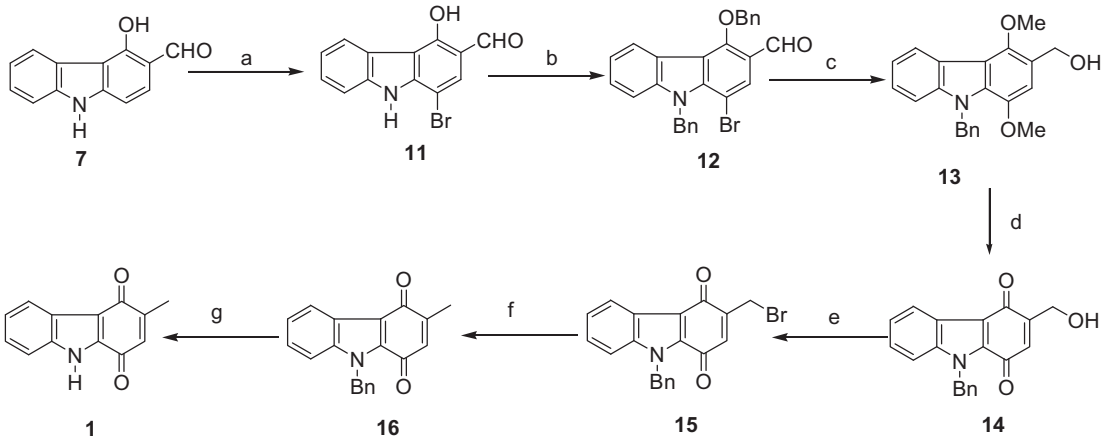


Scheme 1. Reagents and conditions: (a) $POCl_3$, DMF, 0 °C to rt 3 h, 95% (b) *o*-iodoaniline, cat. *p*TSA, MeOH, rt, 5 h, 90% (c) $NaBH_3CN$, CH_3OH, rt, 3 h, 80% (d) $PhI(OAc)_2$, MeOH, AcOH: TFA, 50 °C, 30 min, 80%.

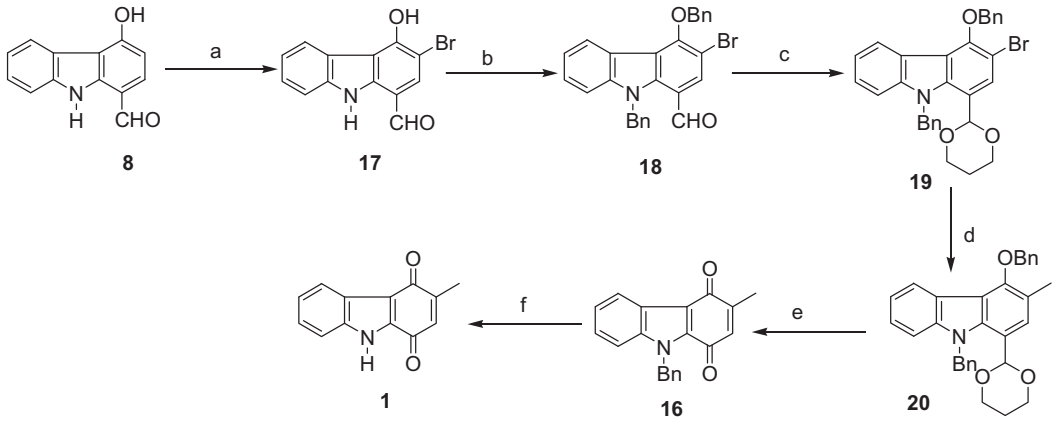
In the third route (Scheme 4) synthesis of murrayaquinone A started from 4-hydroxy-9*H*-carbazole-1-carbaldehyde **8**. Compound **8** was first treated with NBS in DMF at room temperature, which gave brominated compound **17** in quantitative yield. Compound **17** was subjected to bis protection of –NH and –OH groups by benzyl bromide and sodium hydride in DMF, which afforded product **18** in 94% yield. Subsequently, compound **18** was treated with 1,3-propanediol in presence of catalytic amount of *p*TSA in toluene at reflux condition to give product **19** in 80% yield. For



Scheme 2. Proposed mechanism for C–N bond cleavage.



Scheme 3. Reagents and conditions: (a) NBS, DMF, rt, 1 h, 96% (b) NaH, benzyl bromide, DMF, 0 °C to rt, 2 h, 93% (c) CH_3ONa–CH3OH, CuI, DMF, 120 °C, 10 h, 77% (d) CAN, CH_3CN:H_2O (3:1), 0 °C, 15 min, 89% (e) DCM, PPh_3, Br_2, rt, 4 h, 95% (f) LAH, dry THF, 0 °C, 1 h, 79% (g) $Pd(OH)_2$, H_2, CH_3OH, rt, 3 h, 70%.

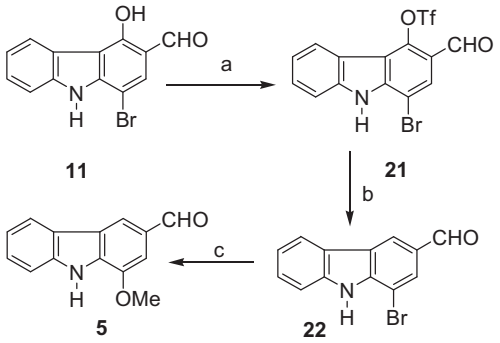


Scheme 4. Reagents and conditions: (a) NBS, DMF, rt, 2 h, 90% (b) NaH, benzyl bromide, DMF, 0 °C to rt, 2 h, 94% (c) 1,3 propanediol, cat *p*TSA, toluene, reflux, 5 h, 80% (d)BuLi, −10 °C, MeI added at−40 °C, dry THF, 90%. (e) boric acid, H_2O_2, H_2SO_4, MeOH, reflux, 30 min, 75% (f) $Pd(OH)_2$, MeOH, H_2, 3 h, 70%.

achieving the conversion of compound **19**–**20** metal halogen exchange reaction was planned. Thus, compound **19** on treatment with *n*-butyl lithium and iodo methane at lower temperature furnished product **20** in 90% yield. Further, Dakin reaction was planned for the conversion of −CHO to −OH group with expected acetal deprotection in acidic medium. Treatment of compound **19** in methanol with catalytic amount of H_2SO_4, H_2O_2, and boric acid furnished quinone **16** in 75%. Along with the expected conversions, the novel observation was the deprotection of *O*-benzyl group and further oxidation. In the last step, compound **16** was subjected to deprotection of *N*-benzyl group using $Pd(OH)_2$ at 60 psi hydrogen pressure in methanol. This resulted in the formation of the target molecule **1** in good yield.

2.2. Synthesis of murrayanine

It was decided to synthesize murrayanine from compound **11**, (Scheme 5) by selective protection, removal of triflate moiety and nucleophilic substitution of bromine. The hydroxyl group of compound **11** was selectively protected as triflate using triflic anhydride and triethyl amine in DCM with 90% yield. In the next step, triflate group of compound **21** was selectively removed using $Pd(PPh_3)_4$ and Bu_3SnH at 80 °C in DMF to give compound **22** in 78% yield. Further, Compound **22** was treated with sodium methoxide and CuI in DMF at 120 °C for 5 h resulting in the formation of murrayanine in 88% yield.



Scheme 5. Reagents and conditions: (a) Triflic anhydride, Et_3N, DCM, rt, 4 h, 90% (b) $Pd(PPh_3)_4$, Bu_3SnH, DMF, 80 °C, 30 min, 78% (c) NaOMe, CuI, DMF, 120 °C, 5 h, 88%.

3. Conclusion

Three new routes were established for murrayaquinone A using intermediates obtained as unexpected products in some other synthetic sequences. Comparing the three new routes, it was observed that the first route (Scheme 1) was shortest with unprecedented C–N bond cleavage by sodium cyanoborohydride. In second and third route (Schemes 3 and 4, respectively), one pot reaction was the key step with very good yield. An efficient method was established for the synthesis of murrayanine, which would be useful for synthesis of various other alkaloids.

4. Experimental

4.1. General information

All reactions were carried out under an inert atmosphere with dry solvents, unless otherwise stated. Reactions were monitored by thin layer chromatography (TLC) on silica gel plates (Kieselgel 60 F_{254}, Merck). Visualization of the spots on TLC plates was achieved either by UV light or by staining the plates in 2, 4-dinitrophenylhydrazine/anisaldehyde and charring on hot plate. All products were characterized by ^{1}H NMR and ^{13}C NMR, IR, mass, and elemental analysis. ^{1}H NMR and ^{13}C NMR were recorded on Varian Mercury 300 MHz spectrometer. Chemical shifts are expressed in parts per million values and ^{1}H NMR spectra are referenced to 0.00 ppm for Me_4Si (TMS) and ^{13}C NMR spectra are referenced to 77.00 ppm for $CDCl_3$. Peak multiplicities are designated by the following abbreviations: s, singlet; br, broad singlet; d, doublet; t, triplet; q, quartet; m, multiplet; J, coupling constant in Hertz. IR spectra were obtained on a Shimadzu FTIR-8400 with samples loaded as thin films on KBr plate, neat or with CH_2Cl_2 as indicated. Mass spectra were recorded at an ionization potential of 70 eV; Elemental analyses were recorded on Flash E. A. 1112 Thermo instrument. Melting points recorded are uncorrected. Column chromatography on silica gel (100–200 mesh) was performed with reagent grade ethyl acetate and hexane as an eluent.

*4.1.1. 4-Hydroxy-9H-carbazole-3-carbaldehyde (7) and 4-hydroxy-9H-carbazole-1-carbaldehyde (**8**).* Freshly distilled phosphorous oxychloride (1 ml, 6.55 mmol) was added drop wise with stirring to DMF (5 ml) in a flask protected from moisture, the temperature being kept at 10–20 °C. 4-Hydroxy carbazole **6** (1 g, 5.46 mmol) in dry DMF (4 ml) was then slowly added at 20–30 °C with constant stirring. Temperature of reaction mixture was kept at 35 °C for 45 min and then poured on crushed ice. The clear solution was treated with sodium hydroxide (1 g) in water (30 ml) at 20–30 °C at such a rate that solution was always acidic until about three quarter of alkali has been added. The last quarter was added all at once and the solution quickly boiled for 1 min. All the reaction mixture was extracted with ethyl acetate (3×100 ml) and the combined organic layer was washed with brine. Evaporation of the solvent, followed by column chromatography (ethyl acetate/hexane 5%) gave *ortho* formylated product **7** (0.807 g 70%) and *para* formylated product **8** (0.287 g, 25%) as yellowish white solids.

*4.1.2. 4-Hydroxy-9H-carbazole-3-carbaldehyde (**7**).* Mp 185 °C; [Found: C, 73.80; H, 4.39; N, 6.35. $C_{13}H_9NO_2$ requires C, 73.92; H, 4.29; N, 6.63]; R_f (20% ethyl acetate/hexane) 0.50; FTIR(KBr cm^{-1}) 3317, 2843, 2740, 1631; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.13–7.15 (1H, d, J=8.54 Hz, Ar*H*), 7.23–7.28 (1H, t, J=7.32 Hz, Ar*H*), 7.39–7.44 (1H, t, J=7.32 Hz, Ar*H*), 7.55–7.58 (1H, d, J=7.93 Hz, Ar*H*), 7.62–7.65 (1H, d, J=8.54 Hz, Ar*H*), 8.18–8.21 (1H, d, J=7.32 Hz, Ar*H*), 9.90 (1H, s, −C*H*O), 11.97 (1H, br, −O*H*), 12.52 (1H, br, N*H*); ^{13}C NMR (75 MHz, $CDCl_3$) δ 104.17, 109.85, 111.41, 112.76, 120.36, 121.87, 122.19, 125.51, 131.12, 139.29, 145.76, 159.11, 195.59; Ms (70 eV) m/z 211(80), 154(30), 105(25), 91(35), 77(45), 57(48), 44(100) 43(80%).

*4.1.3. 4-Hydroxy-9H-carbazole-1-carbaldehyde(**8**).* Mp 259 °C; [Found: C, 74.10; H, 4.17; N, 6.25. $C_{13}H_9NO_2$ requires C, 73.92; H, 4.29; N, 6.63]; R_f (20% ethyl acetate/hexane) 0.45; FTIR (KBr cm^{-1}) 3327, 2833, 2740, 1664; ^{1}H NMR (300 MHz, DMSO-d_6) δ 6.78 (1H, d, J=8.1 Hz, Ar*H*), 7.20–7.25 (1H, t, J=7.6 Hz, Ar*H*), 7.36–7.42 (1H, t, J=8.1 Hz, Ar*H*), 7.72–7.82 (2H, dd, J=8.1&8.6 Hz, Ar*H*), 8.19 (1H, d, J=7.6 Hz, Ar*H*), 9.98 (1H, s, Ar*H*), 11.40 (1H, br, −O*H*), 11.77(1H, br, N*H*); ^{13}C NMR (75 MHz, DMSO-d_6) δ 110.68, 116.20, 117.20, 118.54, 125.11, 126.18, 127.14, 130.13, 139.70, 144.72, 144.85, 165.03, 195.39; Ms (70 eV) m/z 211; 211(100), 183(35), 157(30), 133(32), 117(35%).

*4.1.4. 3-[(2-Iodophenylimino)methyl]-9H-carbazol-4-ol(**9**).* To a stirred solution of compound **7** (0.800 g, 3.79 mmol) in methanol (15 ml) was added *ortho* iodoaniline (0.996 g, 4.54 mmol) with catalytic amount of *p*TSA. Reaction was stirred for 5 h at rt. The yellow colored compound **9** was filtered off (1.50 g, 90%). Mp 210 °C; [Found: C, 53.16; H, 3.32; N, 6.25. $C_{19}H_{13}IN_2O$ requires C, 53.36; H, 3.18; N, 6.80]; R_f (20% ethyl acetate/hexane) 0.45; FTIR (KBr cm^{-1}) 3315, 1614, 1560; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.01–7.10 (2H, m, Ar*H*), 7.22–7.27 (1H, dd, J=6.88, 1.10 Hz, Ar*H*), 7.36–7.42 (1H, dd, J=7.15, 0.833 Hz, Ar*H*), 7.47–7.59 (4H, m, Ar*H*), 7.98–8.22 (1H, d, J=7.98 Hz, Ar*H*), 8.95–8.25 (1H, d, J=7.7 Hz, Ar*H*), 8.95 (1H, s, C*H*=N−), 11.74 (1H, br, N*H*), (−O*H* not detected); ^{13}C NMR (75 MHz, $CDCl_3$) δ 96.54, 104.25, 110.78, 111.13, 111.81, 119.30, 120.87, 122.76, 125.84, 128.58, 130.59, 131.94, 139.43, 139.58, 144.62, 144.78, 148.82, 160.71, 163.75; Ms (70 eV) m/z 412(100), 287(40), 226(38), 202(20), 175(23%).

*4.1.5. 3-Methyl-9H-carbazol-4-ol (**10**).*[10] To a stirred solution of compound **9** (1.50 g, 3.64 mmol) in methanol (50 ml) was added sodium cyanoborohydride (0.229 g, 3.64 mmol) at room temperature. After 2 h TLC showed complete consumption of starting material. The product was extracted with ethyl acetate (3×50 ml) and the combined organic layer was washed with brine. Evaporation of the solvent under reduced pressure, followed by column chromatography (ethyl acetate/hexane 5%) gave compound **10** (0.575 g, 80%); R_f (20% ethyl acetate/hexane) 0.50; FTIR (KBr cm^{-1}) 3317, 1660; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.37 (3H, s, −C*H*$_3$), 5.20 (1H, s, −O*H*), 6.88–6.91 (1H, d, J=8.1 Hz, Ar*H*), 7.13–7.15 (1H, d, J=7.6 Hz, Ar*H*), 7.21–7.25 (1H, m, Ar*H*), 7.35–7.40 (2H, m, Ar*H*), 7.88 (1H, br, N*H*), 8.25–8.27 (1H, d, J=7.6 Hz, Ar*H*); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.80, 102.75, 110.01, 111.98, 119.46, 122.26, 122.54, 124.98, 128.50, 139.15, 139.97, 149.63; Ms (70 eV) m/z 197(80), 169(70), 105(60), 91(50), 77(65), 44(100%).

*4.1.6. 3-Methyl-9H-carbazole-1,4-dione (**1**).*[4] To a stirred solution of compound **10** (0.500 g, 2.53 mmol) in 2:3 mixture of AcOH and TFA (10 ml) containing a few drops of water, was added iodobenzene diacetate (1.62 g, 5.07 mmol). The solution was stirred for 30 min at 50 °C, then MeOH (5 ml) was added and stirring was continued for an additional 30 min. The solution was extracted several times with ethyl acetate and the combined organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Purification of the residue by column chromatography on silica gel using 10% ethyl acetate/hexane afforded **1** as red product (0.428 g, 80%); mp 195 °C; [Found: C, 73.80; H, 4.39; N, 6.15. $C_{13}H_9NO_2$ requires C, 73.92; H, 4.29; N, 6.63; R_f (30% ethyl acetate/hexane) 0.40; FTIR (KBr cm^{-1}) 3398, 1680; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.05 (3H, s, −C*H*$_3$), 6.58 (1H, s, −C*H*=C−), 7.28–7.40 (2H, m, Ar*H*), 7.53 (1H, d, J=8.6 Hz, Ar*H*), 8.04 (1H, d, J=8.1 Hz, Ar*H*), 12.8 (1H, br, N*H*); ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.54, 113.74, 115.33, 121.54, 123.49, 123.72, 126.13, 131.51, 135.83, 137.35, 147.85, 179.98, 182.96; Ms (70 eV) m/z 211(40), 183(35), 154(28), 143(35), 115(30), 44(100%).

*4.1.7. 1-Bromo-4-hydroxy-9H-carbazole-3-carbaldehyde (**11**).* To a stirred solution of **7** (1.0 gm, 4.73 mmol) in dry DMF (15 ml) at room temperature, was added freshly recrystallized NBS (0.837 gm, 4.73 mmol). After 30 min reaction mixture was poured on crushed ice and the white solid precipitated out, was filtered and recrystallized in ethanol, to furnish product **11** (1.31 g, 96%); mp 230 °C; [Found: C, 54.05; H, 2.59; N, 4.61. $C_{13}H_8BrNO_2$ requires C, 53.82; H, 2.78; N, 4.83]; R_f (20% ethyl acetate/hexane) 0.60; FTIR(KBr cm^{-1}) 3320, 2850, 2735; ^{1}H NMR (300 MHz, $CDCl_3$+DMSO-d_6) δ 7.25–7.30 (1H, t, J=7.32 Hz, Ar*H*), 7.38–7.50 (1H, m, Ar*H*), 7.62–7.68 (2H, m,

Ar*H*), 8.19–8.22 (1H, d, *J*=7.93 Hz, Ar*H*), 9.81(1H, s, −C*H*O), 11.69 (1H, br, −O*H*), 12.31 (1H, br, N*H*); ^{13}C NMR (75 MHz, $CDCl_3$+DMSO-d_6) δ 93.53, 110.88, 112.79, 119.83, 121.51, 124.77, 130.80, 138.16, 142.58, 157.60, 193.21; Ms (70 eV) *m*/*z* 291(85). 289(100), 230(30), 232(32), 154(40), 151(38), 124(25), 126(27), 91(30), 77(60), 63(50).

*4.1.8. 9-Benzyl-(4-benzyloxy)-1-bromo-9H-carbazole-3-carbaldehyde (**12**).* To a stirred solution of compound **11** (0.800 g, 2.75 mmol) in dry DMF (15 ml) at 0 °C was added NaH (8.27 mmol, 0.317 g, 60% dispersion in mineral oil). The mixture was stirred for 30 min at 0 °C and allowed to warm to room temperature. Benzyl bromide (1.25 ml, 6.05 mmol) was then added and the mixture was stirred for an additional 1 h. After it was quenched with water (100 ml), the mixture was extracted several times with CH_2Cl_2 and the combined organic layer was dried over anhydrous Na_2SO_4. Filtrate was concentrated on rota evaporator and the residue was purified by column chromatography (ethyl acetate/hexane 4%), which gave white compound **12** (1.20 g, 93%); mp 146–148 °C; [Found: C, 69.13; H, 4.11; N, 3.13. $C_{27}H_{20}BrNO_2$ requires C, 68.95; H, 4.29; N, 2.98]; R_f (20% ethyl acetate/hexane) 0.65; FTIR(KBr cm^{-1}) 2845, 2740; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.27 (2H, s, NCH_2), 6.02 (2H, s, −OCH_2), 7.07 (2H, d, *J*=7.5 Hz, Ar*H*), 7.21–7.46 (11H, m, Ar*H*), 8.05 (1H, s, Ar*H*), 8.25–8.27 (1H, d, *J*=7.9 Hz, Ar*H*), 10.14 (1H, s, −C*H*O); ^{13}C NMR (75 MHz, $CDCl_3$) δ 47.43, 78.01, 99.07, 110.14, 119.14, 120.93, 121.82, 122.72, 122.81, 125.86, 127.05, 127.39, 128.34, 128.72, 128.76, 130.95, 135.64, 137.28, 141.59, 141.61, 157.47, 187.26; Ms (70 eV) *m*/*z* 471; 471(100), 243(25), 391(55), 363(60), 301(20), 226(15%).

*4.1.9. (9-Benzyl-1,4-dimethoxy-9H-carbazol-3-yl)methanol (**13**).* To a solution of compound **12** (2 g, 4.25 mmol) in dry DMF were added CuI (0.807 g, 4.25 mmol) and sodium methoxide (4.51 g, 85.10 mmol) in methanol (5 ml). Reaction was degassed by nitrogen and kept at 120 °C for 10 h. It was neutralized by addition of water (100 ml). Reaction mixture was extracted with ethyl acetate (3×75 ml) and combined organic layer was dried on Na_2SO_4. Filtrate was concentrated on rota evaporator and the residue was purified by column chromatography in 10% ethyl acetate/hexane, which gave white colored product **13** (1.13 g, 77%); mp 138–140 °C; [Found: C, 76.21; H, 5.92; N, 4.14. $C_{22}H_{21}NO_3$ requires C, 76.06; H, 6.09; N, 4.03]; R_f (30% ethyl acetate/hexane) 0.41; FTIR (KBr cm^{-1}) 3429, 3381, 1668, 1600; ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.84 (3H, s, −OCH_3), 3.87 (3H, s, −OCH_3), 4.69 (2H, s, −CH_2OH), 5.24 (1H, br, −CH$_2$O*H*), 5.82 (2H, s, NCH_2), 7.04–7.22 (7H, m, Ar*H*), 7.34–7.39 (1H, t, *J*=7.6 Hz, Ar*H*), 7.50–7.53 (1H, d, *J*=8.2 Hz, Ar*H*), 8.12–8.14 (1H, d, *J*=7.6 Hz, Ar*H*); ^{13}C NMR (75 MHz, DMSO-d_6) δ 47.90, 56.24, 57.78, 61.29, 109.04, 110.00, 116.86, 119.82, 121.08, 122.29, 125.12, 125.71, 126.65, 127.20, 128.63, 129.72, 139.20, 140.48, 143.02, 146.49; Ms (70 eV) *m*/*z* 347(55), 307(30), 295(25), 217(23), 127(20), 91(100%).

*4.1.10. 9-Benzyl-3-(hydroxymethyl)-9H-carbazole-1,4-dione (**14**).* To a stirred solution of compound **13** (1 g, 2.88 mmol) in 3:1 CH_3CN:H_2O was added CAN (4.73 g, 8.64 mmol) at 0 °C. After 15 min water was added to the reaction mixture. Reaction mixture was extracted with ethyl acetate (3×50 ml). Combined organic layer was dried on anhydrous Na_2SO_4 and removed under reduced pressure. Column chromatography using 10% ethyl acetate/hexane gave the expected red colored product **14** (0.812 g, 89%); mp 200–202 °C; [Found C, 75.79; H, 4.60; N, 4.65. $C_{20}H_{15}NO_3$ requires C, 75.70; H, 4.76; N, 4.41]; R_f (30% ethyl acetate/hexane) 0.41; FTIR (KBr cm^{-1}) 3433, 1639, 1612; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.5 (2H, s, −CH_2OH), 5.76.(2H, s, NCH_2), 6.58 (1H, s, −C*H*=C−), 7.05–7.55 (8H, m, Ar*H*), 8.11–8.14 (1H, d, *J*=7.1 Hz, Ar*H*), (−O*H* not detected); ^{13}C NMR (75 MHz, $CDCl_3$) δ 47.30, 57.62, 111.12, 122.15, 122.82, 123.90, 126.09, 126.25, 127.10, 128.11, 129.58, 132.82, 135.77, 138.22, 149.75, 180.50, 182.70; Ms (70 eV) *m*/*z* 317(100), 301(33), 199(24), 157.72(20), 125(18%).

*4.1.11. 9-Benzyl-3-(bromomethyl)-9H-carbazole-1,4-dione (**15**).* To a stirred solution of compound **14** (0.7 g, 2.20 mmol) in DCM at 0 °C was added triphenylphosphine (0.578 g, 2.20 mmol). Reaction was continued at the same temperature for 30 min and then bromine (0.134 ml, 2.6 mmol**)** in DCM (1 ml) was added to it. After confirming the absence of starting material, water was added to the reaction mixture and extracted with DCM (3×30 ml). Combined organic layer was washed with brine and dried over anhydrous Na_2SO_4. The organic layer was evaporated. The residue was chromatographed using 2% ethyl acetate/hexane as an eluent system, which gave red colored product **15** (0.797 g, 95%); mp 150 °C (decomposed); [Found C, 63.29; H, 3.40; N, 3.81. $C_{20}H_{14}BrNO_2$ requires C, 63.18; H, 3.71; N, 3.68]; R_f (20% ethyl acetate/hexane) 0.70; FTIR (KBr cm^{-1}) 1647, 1608; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.36 (2H, s, −CH_2Br), 5.82 (2H, s, NCH_2), 6.70 (1H, s, −C*H*=C−), 7.14–7.44 (8H, m, Ar*H*), 8.30–8.32 (1H, dd, *J*=5.8 and 1.7 Hz, Ar*H*); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.08, 48.08, 111.51, 117.17, 123.18, 123.61, 124.83, 126.68, 127.31, 127.82, 128.74, 133.29, 134.36, 135.95, 139.13, 145.11, 180.41, 180.73.

*4.1.12. 9-Benzyl-3-methyl-9H-carbazole-1,4-dione (**16**).* Solution of compound **15** (0.5 g, 1.31 mmol) in dry THF was added slowly to the solution of LAH (0.014 g, 0.394 mmol), in dry THF. Reaction was continued for 1 h and quenched by addition of 5 ml ethyl acetate and then water. THF was removed on rota evaporator. Reaction mixture was extracted with ethyl acetate. Combined organic layer was dried on anhydrous Na_2SO_4 and after column chromatography using 6% ethyl acetate/hexane gave the expected red colored product **16** (0.312 g, 79%); mp 157 °C; [Found C, 80.00; H, 5.52; N, 4.30. $C_{20}H_{15}NO_2$ requires C, 79.72; H, 5.02; N, 4.65]; R_f (30% ethyl acetate/hexane) 0.50; FTIR (KBr cm^{-1}) 1637, 1600; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.13 (3H, s, −CH_3), 5.81 (2H, s, NCH_2), 6.42 (1H, s, −C*H*=C−), 7.13–7.39 (8H, m, Ar*H*), 8.29–8.32 (1H, dd, *J*=8.8 &2.3 Hz, Ar*H*); ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.76, 111.51, 123.17, 123.85, 124.53, 126.77, 126.88, 127.78, 128.78, 132.81, 133.52, 136.35, 138.95, 147.45, 181.17, 183.70; Ms (70 eV) *m*/*z* 301(100), 273(52), 261(35), 210(45), 143(30), 115(25).

*4.1.13. 3-Methyl-9H-carbazole-1,4-dione (**1**).* To a solution of compound **16** (0.2 g, 0.3 mmol) in methanol was added catalytic 20% Pd/C and reaction was subjected for hydrogenation at 60 psi pressure for 3 h. Reaction mixture was filtered through sintered funnel and Celite was washed with 50 ml acetone. Reaction mixture was concentrated on rota evaporator and then extracted with ethyl acetate (3×50 ml). The combined organic layer was dried on Na_2SO_4, concentrated on rota evaporator and purified by column chromatography using 10% ethyl acetate/hexane as an eluent system, which gave red colored solid product **1** (0.098 g, 70%).

*4.1.14. 3-Bromo-4-hydroxy-9H-carbazole-1-carbaldehyde (**17**).* To a stirred solution of compound **8** (1 g, 4.73 mmol) in DMF was added *N*-bromosuccinimide (0.922 g, 5.21 mmol) in DMF at room temperature and reaction was continued for 30 min. After addition of water, product **17** was precipitated. It was filtered and used for further reaction.

Yield (1.23 g, 90%); mp: 220 °C; [Found C, 53.50; H, 3.00; N, 4.48. $C_{13}H_8$ $BrNO_2$ requires C, 53.82; H, 2.78; N, 4.83]; R_f (20% ethyl acetate/hexane) 0.55; FTIR (KBr cm^{-1}) 3398, 2850, 2745, 1660; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.24–7.29 (1H, m, Ar*H*), 7.40–7.46 (1H, m, Ar*H*), 7.53 (1H, s, Ar*H*), 7.6–7.64 (1H, d, *J*=7.9 Hz, Ar*H*), 7.90 (s, 1H, O*H*), 8.31–8.33 (1H, d, *J*=7.5 Hz, Ar*H*), 9.95 (1H, s, −C*H*O), 10.94 (1H, br, N*H*); ^{13}C NMR (75 MHz, $CDCl_3$) δ 98.57, 110.91, 114.06, 119.88,

120.26, 122.13, 125.30, 135.04, 138.58, 138.95, 154.67, 189.21; Ms (70 eV) *m*/*z* 291(85), 289(24), 230(30), 232(32), 154(40), 151(38), 124(25), 126(27), 91(100%).

*4.1.15. 9-Benzyl-4-(benzyloxy)-3-bromo-9H-carbazole-1-carbaldehyde (**18**).* To a stirred solution of compound **17** (1 g, 3.44 mmol) in dry DMF (15 ml) at 0 °C was added NaH (60% dispersion in mineral oil, 0.330 g, 8.6 mmol). The mixture was stirred for 30 min at 0 °C and allowed to warm to room temperature. Benzyl bromide (0.409 ml, 3.44 mmol) was then added and the mixture was stirred for an additional 1 h. After quenching with water (100 ml) it was extracted several times with CH_2Cl_2 and the combined organic layer was dried over anhydrous Na_2SO_4. Filtrate was concentrated under reduced pressure and the residue was purified by column chromatography (3% ethyl acetate/hexane as an eluent), which gave white product **18** (1.52 g, 94%); mp 190 °C; [Found C, 69.20; H, 4.67; N, 2.59. $C_{27}H_{20}BrNO_2$ requires C, 68.95; H, 4.29; N, 2.98]; R_f (20% ethyl acetate/hexane) 0.65; FTIR (KBr cm^{-1}) 2870, 2765, 1670; ^1H NMR (300 MHz, $CDCl_3$) δ 5.26 (2H, s, NCH_2), 5.88 (2H, s, −OCH_2), 6.94–6.96(2H, m, Ar*H*), 7.18–7.31 (4H, m, Ar*H*), 7.33–7.47 (5H, m, Ar*H*), 7.63–7.66 (d, 2H, *J*=6.7 Hz, Ar*H*), 8.05 (1H, s, Ar*H*), 8.21–8.24 (1H, d, *J*=7.9 Hz, Ar*H*), 9.98(1H, s, −C*H*O); ^{13}C NMR (75 MHz, $CDCl_3$) δ 50.36, 74.85, 106.53, 109.83, 119.53, 120.42, 120.69, 121.40, 122.87, 125.83, 127.20, 127.46, 128.25, 128.50, 128.65, 128.83, 136.05, 136.24, 136.68, 140.19, 141.72, 156.06, 188.14; Ms (70 eV) *m*/*z* 471(75), 469(720), 378(55), 350(45), 91(65), 77(100), 44(80%).

*4.1.16. 9-Benzyl-4-(benzoloxy)-3-bromo-1-(1,3-dioxan-2-yl)-9H-carbazole (**19**).* To a solution of compound **18** (1 g, 2.10 mmol) in toluene was added catalytic amount of *p*TSA and reaction was subjected for reflux with Dean Stark apparatus for 5 h. Reaction was cooled and neutralized by addition of saturated aq Na_2CO_3 (10 ml). Then reaction mixture was extracted by ethyl acetate (3×50 ml). Combined organic layer was dried over Na_2SO_4, concentrated on rota evaporator and purified by column chromatography using 5% ethyl acetate/hexane as an eluent system, which gave compound **19** (0.896 g, 80%). mp 185 °C; [Found C, 67.90; H, 4.50; N, 3.00. $C_{30}H_{26}BrNO_3$ requires C, 68.19; H, 4.96; N, 2.65]; R_f (30% ethyl acetate/hexane) 0.61; FTIR (KBr cm^{-1}) 1670, 1210; ^1H NMR (300 MHz, $CDCl_3$) δ 1.25–1.52 (2H, m, OCH_2–CH_2–CH_2O), 3.72–3.80 (2H, m, OCH_2), 4.08–4.13 (2H, m, OCH_2), 5.20 (2H, s, NCH_2), 5.71 (1H, s, O–CH–O), 5.78 (2H, s, OCH_2Ph), 7.03–7.19 (2H, m, Ar*H*), 7.20–7.30 (5H, m, Ar*H*), 7.35–7.49 (4H, m, Ar*H*), 7.69–7.96 (2H, m, Ar*H*), 7.96 (1H, s, Ar*H*), 8.26–8.29 (1H, m, Ar*H*); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.32, 48.74, 67.15, 74.45, 98.52, 106.14, 109.20, 106.14, 109.20, 119.2, 119.30, 120.37, 120.99, 122.69, 125.35, 126.37, 127.10, 128.21, 128.24, 128.56, 128.84, 129.10, 136.93, 138.04, 138.69, 141.48, 151.59.

*4.1.17. 9-Benzyl-4-(benzyloxy)-1-(1,3-dioxan-2-yl)-3-methyl-9H-carbazole (**20**).* To a stirred solution of compound **19** (0.5 g, 0.946 mmol) in dry THF at −10 °C was added slowly *n*-butyl lithium (1.42 mmol). Stirring was continued for 30 min at the same temperature and then, reaction temperature was decreased to −40 °C and iodomethane (0.07 ml, 1.13 mmol) was added. Reaction was continued for 1 h at the same temperature and then slowly brought to room temperature. Reaction mixture was neutralized by 15 ml saturated aq NH_4Cl and extracted with ethyl acetate (3×30 ml). Combined organic layer was dried on Na_2SO_4, concentrated on rota evaporator and purified by column chromatography using 6% ethyl acetate in hexane as an eluent system, which gave product **20** (0.395 g, 90%). mp 160 °C; [Found C, 80.00; H, 6.52; N, 3.30. $C_{31}H_{29}NO_3$ requires C, 80.32; H, 6.31; N, 3.02]; R_f (30% ethyl acetate/hexane) 0.48; FTIR (KBr cm^{-1}) 1650, 1630, 1180; ^1H NMR (300 MHz, $CDCl_3$) δ 1.25–1.42 (5H, m, OCH_2–CH_2–CH_2O & CH_3), 3.74–3.81 (2H, m, OCH_2), 4.07–4.12 (2H, m, OCH_2), 5.36 (2H, s, NCH_2), 5.71 (1H, s, O–CH–O), 5.85 (2H, s, OCH_2Ph), 6.75 (1H, d, *J*=8.6 Hz, Ar*H*), 7.07 (1H, d, *J*=7.2 Hz, Ar*H*), 7.18–7.45 (9H, m, Ar*H*), 7.56 (2H, d, *J*=7.1 Hz, Ar*H*), 7.63 (1H, d, *J*=8.6 Hz, Ar*H*), 8.40 (1H, d, *J*=7.2 Hz, Ar*H*); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.42, 29.66, 48.80, 67.17, 70.05, 100.00, 101.29, 108.71, 113.61, 114.83, 119.81, 122.37, 123.06, 125.04, 125.52, 125.96, 126.83, 127.44, 127.84, 128.31, 128.55, 128.65, 128.71, 128.77, 135.68, 137.21, 138.66, 139.36, 140.89, 155.77; Ms (70 eV) *m*/*z* 463(60), 437(48), 405(10), 379(57), 314(70%) 409(20), 91(100%).

*4.1.18. 9-Benzyl-3-methyl-9H-carbazole-1,4-dione (**16**).* To a stirred solution of compound **20** (0.5 g, 1.07 mmol) in methanol were added catalytic amount of H_2SO_4 and H_2O_2 (1.51 ml 40% in water, 1.61 mmol). Reaction was refluxed for 30 min, brought to room temperature and neutralized by addition of Na_2CO_3. Reaction mixture was extracted with ethyl acetate (3×50 ml). Combined organic layer was dried on Na_2SO_4, concentrated on rota evaporator and purified by column chromatography using 6% ethyl acetate in hexane as an eluent system, which gave red colored solid product **16** (0.243 g, 75%).

*4.1.19. 1-Bromo-3-formyl-9H-carbazol-4-yl trifluoromethanesulfonate (**21**).* To a stirring solution of compound **11** (0.5 g, 1.73 mmol) in DCM at 0 °C was added triethyl amine (0.175 ml, 1.73 mmol). Reaction was continued for 15 min at same temperature and then triflic anhydride (0.583 g, 2.07 mmol) was added slowly. After 2 h reaction was neutralized by addition of water and extracted with ethyl acetate (3×50 ml). Combined organic layer was washed with brine and dried on anhydrous Na_2SO_4. After evaporation of organic layer the residue was chromatographed using 4% ethyl acetate/hexane as an eluent system, which gave white colored product **21** (0.657 g, 90%). mp 220 °C (decomposed); Found [C, 39.50; H, 1.95; N, 3.63. $C_{14}H_7BrF_3NO_4S$ requires C, 39.83; H, 1.67; N, 3.32]; R_f (20% ethyl acetate/hexane) 0.61; FTIR (KBr cm^{-1}) 3431, 1668; ^1H NMR (300 MHz, $CDCl_3$) δ 7.39–7.44 (1H, t, *J*=7.1 Hz, Ar*H*), 7.61–7.75 (2H, m, Ar*H*), 8.15 (1H, d, *J*=8.3 Hz, Ar*H*), 8.24 (1H, s, Ar*H*), 10.09 (1H, s, −C*H*O), 12.60 (1H, br, N*H*); ^{13}C NMR (75 MHz, $CDCl_3$) δ 77.19, 104.59, 111.74, 116.53, 117.55, 120.88, 122.20, 122.49, 123.62, 128.34, 128.60, 139.43, 143.15, 143.58, 184.95; Ms (70 eV) *m*/*z* 423(12), 421(15), 290(32), 288(30), 153(22), 151(17), 69(100%).

*4.1.20. 1-Bromo-9H-carbazole-3-carbaldehyde (**22**).* To a solution of compound **21** (0.5 g, 1.18 mmol) in dry DMF kept under N_2 atmosphere were added tetrakis(triphenylphosphine)palladium (0.134 g, 10 mol %) and tributyl tin hydride (0.344 g, 1.18 mmol). Reaction mixture was heated at 100 °C for 45 min. After consumption of starting material water was added to the reaction mixture and extracted with ethyl acetate (3×25 ml). Combined organic layer was washed with brine and dried on anhydrous Na_2SO_4. The residue obtained after evaporation of organic layer was chromatographed using 5% ethyl acetate/hexane as an eluent system, which gave white colored product **22** (0.252 g, 78%); mp 210 °C; [Found C, 57.21; H, 3.19; N, 5.48. $C_{13}H_8BrNO$ requires C, 56.96; H, 2.94; N, 5.11]; R_f (30% ethyl acetate/hexane) 0.65; FTIR (KBr cm^{-1}) 3204, 1673; ^1H NMR (300 MHz, $CDCl_3$) δ 7.33–7.39 (1H, m, Ar*H*), 7.51–7.56 (2H, m, Ar*H*), 8.11–8.13 (2H, m, Ar*H*), 8.53 (1H, s, Ar*H*), 8.59 (1H, br, N*H*), 10.04 (1H, s, C*H*O); ^{13}C NMR (75 MHz, $CDCl_3$) δ 104.80, 111.58, 121.17, 121.40, 122.88, 123.72, 124.39, 127.59, 128.86, 130.36, 139.50, 141.65, 190.55; Ms (70 eV) *m*/*z* 275(80), 273(90), 246(50), 244(50), 166(20), 165(15), 164(55), 139(34), 137(30), 91(100), 82(60), 69(35%).

*4.1.21. 1-Methoxy-9H-carbazole-3-carbaldehyde (**5**).* To a solution of compound **22** (0.2 g, 1.00 mmol) in dry DMF were added CuI (0.133 g, 1.00 mmol) and sodium methoxide (1.08 g, 20.40 mmol) in methanol (5 ml). Reaction was degassed by nitrogen and kept at 120 °C for 5 h. It was then quenched by addition of water (50 ml). Reaction mixture

was extracted with ethyl acetate (3×20 ml) and combined organic layer was dried on Na_2SO_4. Filtrate was concentrated under reduced pressure and the residue was purified by column chromatography (ethyl acetate/hexane 7%), which gave white colored compound **5** (0.144 g, 88%); mp 165–67 °C; [Found C, 75.00; H, 3.73; N, 6.10. $C_{14}H_{11}NO_2$ requires C, 74.65; H, 4.95; N, 6.22]; R_f (30% ethyl acetate/hexane) 0.42; FTIR (KBr cm^{-1}) 3455, 1662; ^1H NMR (300 MHz, $CDCl_3$) δ 4.08 (3H, s, $-OCH_3$), 7.33 (2H, t, J=6.5 Hz, Ar*H*), 7.47–7.54 (2H, m, Ar*H*), 8.12 (1H, d, J=7.9 Hz, Ar*H*), 8.21(1H, s, Ar*H*), 8.59 (1H, br, $-OH$), 10.06 (1H, s, $-CHO$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55, 103.4, 111.5, 120.5, 120.6, 123.5, 123.6, 126.6, 130.0, 134.0, 139.4, 146.0, 192.0.; Ms (70 eV) m/z 225(100), 210(55), 207(52), 154(60), 73(40), 41(20%).

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