

Synthesis of 12,13-dihydro-5-oxoquinolino[2,3-*a*]carbazoles, 3,11-dihydro-2,4-dioxopyrano[2,3-*a*]carbazoles and quinolino[2,3-*b*]carbazolo[6,5-*a*]pyran-7,8-diones

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The reaction of 1-hydroxycarbazoles **1a-d** with anthranilic acid in the presence of fused zinc chloride and phosphorus oxychloride at room temperature affords 1,7-dibenzozocin-6,12-dione **2** in all the cases and the expected 12,13 dihydro-5-oxoquinolino[2,3-*a*]carbazoles **3a-d**. In another reaction, 1-hydroxycarbazoles **1a-d** with malonic acid in the presence of fused zinc chloride and phosphorus oxychloride at room temperature yields 3,11-dihydro-2,4-dioxopyrano[2,3-*a*]carbazoles **4a-d**. Further, the attempted synthesis of c/b fused quinolinodipyrano annelated carbazoles **7a-d** or **8a-d** or both from the reaction of 3,11-dihydro-2,4-dioxopyrano[2,3-*a*]carbazoles **4a-d** with vinyl acetate and 2,4-dihydroxyquinoline **6** results in the formation of new dimerised product, quinolino[2,3-*b*]carbazolo[6,5-*a*]pyran-7,8-diones **9a-d**. A plausible mechanism has been suggested to explain this reaction.

Keywords: 1-Hydroxycarbazoles, 1,7-dibenzozocin-6,12-dione, 12,13-dihydro-5-oxoquinolino[2,3-*a*]carbazoles, 3,11-dihydro-2,4-dioxopyrano[2,3-*a*]carbazoles, quinolino[2,3-*b*]carbazolo[6,5-*a*]pyran-7,8-diones

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Development of new methods for the synthesis of heterocyclo-fused carbazoles is currently attracting the organic chemists due to the discovery of many carbazole alkaloids with varied biological activities^{1,2}. Pyrano[3,2-*a*]carbazoles such as grinimbine, mupamine, mahanimbine, murrayanol and mahanine isolated from plant species of *Rutaceae* family were reported to possess mosquitocidal, antimicrobial, anti-inflammatory and antioxidant activities^{3,4}. Among the carbazole derivatives, ellipticine, 9-hydroxy ellipticine, olivacine representing 3-aza analogs of pyrido[4,3-*b*]carbazoles elicit high antitumour properties⁵. Recently, pyrido carbazole was reported to possess anti-HIV activity⁶. Pyrido[4,3-*a*]carbazoles are well known for their anticancerous properties⁷. In view of the above, a facile and the convenient synthesis of some new 3,11-dihydro-2,4-dioxopyrano[2,3-*a*]carbazoles and 12,13-dihydro-5-oxoquinolino[2,3-*a*]carbazoles (considered as substituted pyridocarbazoles) is reported utilizing the easily accessible 1-hydroxycarbazoles⁸ which can be expected to enhance the pharmacological properties.

Results and Discussion

Treatment of 1-hydroxy-6-methylcarbazole **1a** with anthranilic acid in the presence of fused zinc chloride and phosphorus oxychloride at RT afforded 12,13-dihydro-5-oxo-9-methylquinolino[2,3-*a*]- carbazole **3a**. Appearance of two spots on TLC indicated a mixture, which was separated by performing column chromatography on silica gel using petroleum ether - ethyl acetate mixture as an eluent. The two products obtained from petroleum ether-ethyl acetate fractions, 99:1 and 97:3, were found to be 7-dibenzozocin-6,12-dione **2** and 12,13-dihydro-5-oxo-9-methyl-quinolino[2,3-*a*]-carbazole **3a**, respectively.

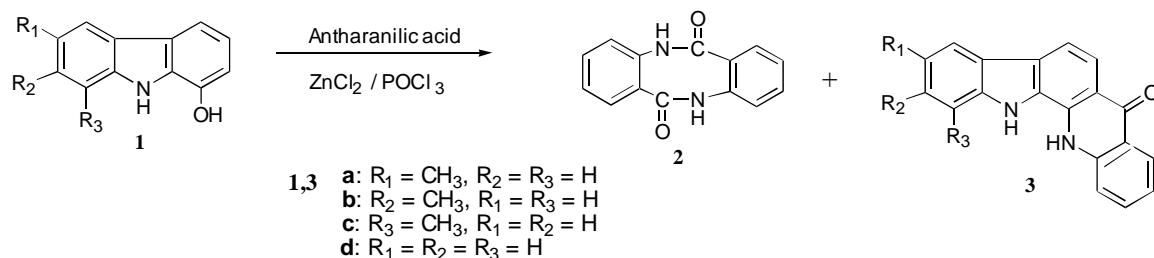
The IR spectrum of the first compound showed two strong absorption bands at 3450 and 1625 cm⁻¹ for -NH and >C=O stretchings respectively. Its ¹H NMR spectrum showed a multiplet at δ 7.25-7.79 for eight aromatic protons and a broad singlet for two protons at δ 8.20 for N₁-H and N₇-H. The elemental analysis agreed well with the molecular formula C₁₄H₁₀N₂O₂. Based on the above mentioned spectral data the structure of **2** was proposed as 1,7-dibenzozocin-6,12-dione **2**.

The IR spectrum of **3a** showed two strong absorptions at 1681 and 3327 cm^{-1} for $>\text{C=O}$ and $-\text{NH}$ stretching vibrations, respectively. The ^1H NMR spectrum of **3a** registered the signals as a singlet at δ 2.53 for $\text{C}_9\text{-CH}_3$ and a broad singlet at δ 5.81 for quinolino $-\text{NH}$. A multiplet appeared at δ 6.74-8.23 corresponding to nine aromatic protons and indole $-\text{NH}$ proton. The elemental analysis data of compound **3a** was also in good agreement with the molecular formula $\text{C}_{20}\text{H}_{14}\text{N}_2\text{O}$. The same outcome leading to **3b-d** was realized when **1b-d** was treated with anthranilic acid under identical conditions along with 1,7-dibenzoazocin-6,12-dione **2** in all the cases. Due to

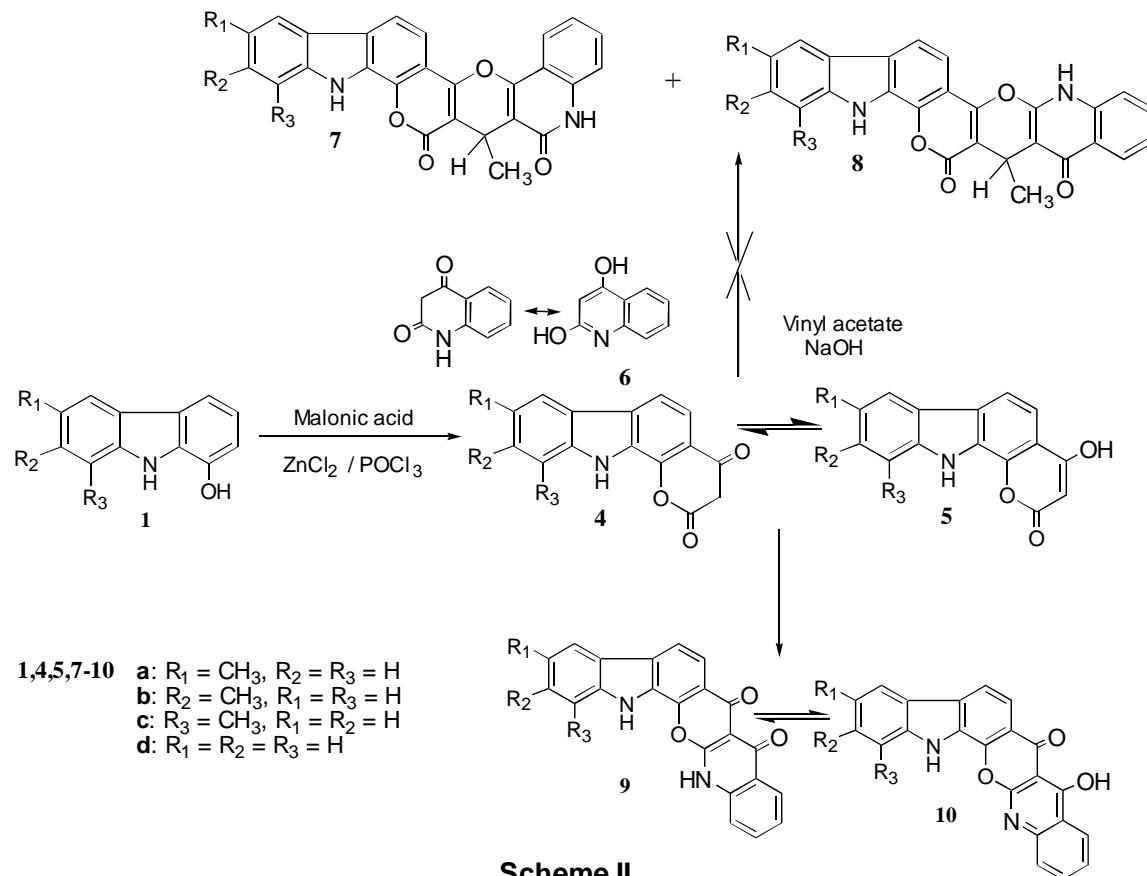
the formation of similar product **2** in all the cases, it was concluded that anthranilic acid gets dimerised to give 1,7-dibenzoazocin-6,12-dione **2** (**Scheme I**).

The reaction of 1-hydroxy-6-methylcarbazole **1a** with malonic acid in the presence of fused zinc chloride and phosphorus oxychloride at RT afforded a single product, which was purified by column chromatography using petroleum ether - ethyl acetate mixture as an eluant. It yielded a single product which was found to be 3,11-dihydro-2,4-dioxo-8-methyl-pyran[2,3-*a*]carbazole **4a**.

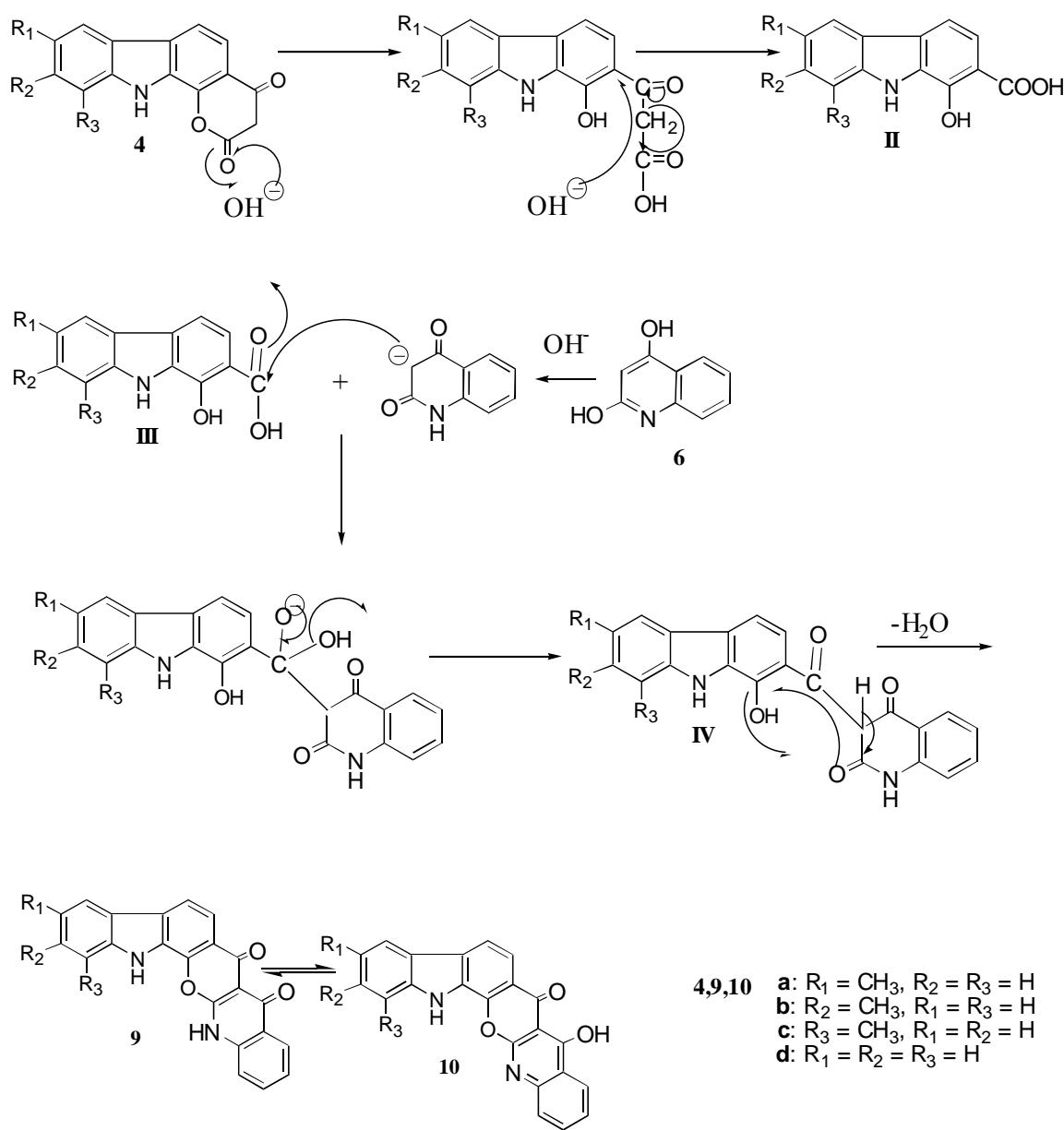
The IR spectrum of newly synthesized **4a** showed two strong $>\text{C=O}$ stretching vibrations at 1722 and



Scheme I



Scheme II



Scheme III

1643 cm^{-1} and ^1H NMR spectrum showed the appearance of two singlets at δ 2.50 and 2.91 for $\text{C}_8\text{-CH}_3$ and $\text{C}_3\text{-H}_2$ protons. A multiplet for six aromatic protons appeared at δ 7.02 - 7.70 for $\text{C}_3\text{-H}$, $\text{C}_5\text{-H}$, $\text{C}_6\text{-H}$, $\text{C}_7\text{-H}$, $\text{C}_9\text{-H}$ and $\text{C}_{10}\text{-H}$ protons and a broad singlet at δ 7.74 for $-\text{NH}$ proton. A sharp singlet appeared at δ 11.04 for $\text{C}_4\text{-OH}$ proton. From the proton integration of $\text{C}_3\text{-H}_2$ of 4-oxo form **4a** and that of $\text{C}_3\text{-H}$ and $\text{C}_4\text{-OH}$ of 4-hydroxy form **5a**, the ratio of keto and enol forms was found to be 3:1. The elemental analysis agreed well with the proposed molecular

formula $\text{C}_{16}\text{H}_{11}\text{NO}_3$. Based on the above spectral assignments and analytical data it was established that the product was 3,11-dihydro-2,4-dioxo-8-methylpyrano[2,3-*a*]carbazole **4a**. A series of similar compounds **4b-d** were obtained from **1b-d** under identical conditions (**Scheme II**).

3,11-Dihydro-2,4-dioxo-8-methylpyrano[2,3-*a*]carbazole **4a** was treated with vinyl acetate and 2,4-dihydroxyquinoline **6** in presence of 4% alc. KOH with the expected formation of either **7** or **8** or both as indicated in **Scheme II**. The reaction mixture after

Table I – Characterization data of compounds **2**, **3a-d**, **4a-d** and **9a-d**

Compd	m.p.(°C)	Yield (%)	Mol.formula Mol. wt	(Calcd) Found %			¹ H NMR (δ ppm)
				C	H	N	
2	195	90	C ₁₄ H ₁₀ N ₂ O ₂ 238.245	(70.58 70.41)	04.30 04.41	11.76 11.81	7.25-7.79 (m, 8H, C ₂ , C ₃ , C ₄ , C ₅ , C ₈ , C ₉ and C ₁₁ -H), 8.20 (b s, 2H, N ₁ and N ₇ -H)
3a	185	30	C ₂₀ H ₁₄ N ₂ O 298.550	(80.46 80.52)	04.76 04.65	09.45 09.33	2.53 (s, 3H, C ₉ -CH ₃), 5.81 (b s, 1H, N ₁₃ -H), 6.74 – 8.23 (m, 10H, aromatic 9H and N ₁₂ -H)
3b	178	35	C ₂₀ H ₁₄ N ₂ O 298.550	(80.46 80.37)	04.76 04.64	09.45 09.51	2.51 (s, 3H, C ₁₀ -CH ₃), 5.82 (b s, 1H, N ₁₃ -H), 6.75 – 8.24 (m, 10H, aromatic 9H and N ₁₂ -H)
3c	175	30	C ₂₀ H ₁₄ N ₂ O 298.550	(80.46 80.59)	04.76 04.70	09.45 09.21	2.53 (s, 3H, C ₁₁ -CH ₃), 5.84 (b s, 1H, N ₁₃ -H), 6.62 – 8.40 (m, 10H, aromatic 9H and N ₁₃ -H)
3d	180	39	C ₁₉ H ₁₂ N ₂ O 284.316	(80.26 80.39)	04.25 04.35	09.85 09.73	5.82 (b s, 1H, N ₁₃ -H), 6.75 – 8.24 (m, 11H, aromatic 10H and N ₁₂ -H)
4a	102	40	C ₁₆ H ₁₁ NO ₃ 265.266	(72.44 72.31)	04.17 04.25	05.28 05.13	2.50 (s, 3H, C ₈ -CH ₃) 2.91 (s, 2H, C ₃ -H ₂), 7.02-7.70 (m, 6H, C ₃ -H, C ₅ -H, C ₆ -H, C ₇ -H, C ₉ -H and C ₁₀ -H), 7.74 (b s, 1H, NH), 11.04 (s, 1H, OH), (The ratio of 4-oxo- and 4-hydroxy forms, 3:1)
4b	110	37	C ₁₆ H ₁₁ NO ₃ 265.266	(72.44 72.52)	04.17 04.09	05.28 05.31	2.55 (s, 3H, C ₉ -CH ₃), 2.83 (s, 2H, C ₃ -H ₂), 7.02-7.74 (m, 6H, C ₃ -H, C ₅ -H, C ₆ -H, C ₇ -H, C ₈ -H and C ₁₀ -H), 8.39 (b s, 1H, NH), 10.10 (s, 1H, OH), (The ratio of 4-oxo- and 4-hydroxy forms, 3:1)
4c	115	41	C ₁₆ H ₁₁ NO ₃ 265.266	(72.44 72.37)	04.17 04.10	05.28 05.35	2.93 (s, 3H, C ₁₀ -CH ₃), 2.75 (s, 2H, C ₃ -H ₂), 7.04-7.95 (m, 6H, C ₃ -H, C ₅ -H, C ₆ -H, C ₇ -H, C ₈ -H and C ₉ -H), 7.97 (s, 1H, NH), 10.95 (s, 1H, OH), (The ratio of 4-oxo- and 4-hydroxy forms, 3:1)
4d	120	45	C ₁₅ H ₉ NO ₃ 251.240	(71.71 71.84)	03.61 03.57	05.57 05.48	2.94 (s, 2H, C ₃ -H ₂), 7.00-7.90 (m, 7H, C ₃ -H, C ₅ -H, C ₆ -H, C ₇ -H, C ₈ -H, C ₉ -H and C ₁₀ -H), 7.95 (b s, 1H, NH), 11.04 (s, 1H, OH), (The ratio of 4-oxo- and 4-hydroxy forms, 3:1)
9a	>300	65	C ₂₃ H ₁₄ N ₂ O ₃ 366.374	(75.40 75.31)	03.85 03.75	07.64 07.59	2.58 (s, 3H, C ₁₂ -CH ₃) 5.70 (b s, 1H, N ₂ -H), 7.56-7.62 (m, 8H, aromatic-H), 8.12 (s, 1H, C ₁₁ -H), 8.61 (b s, 1H, carbazole-NH), 11.01 (s, 1H, OH), (The ratio of quinone and quinolforms, 1:1)
9b	>300	72	C ₂₃ H ₁₄ N ₂ O ₃ 366.374	(75.40 75.51)	03.85 03.76	07.64 07.57	2.55 (s, 3H, C ₁₃ -CH ₃) 5.68 (b s, 1H, N ₂ -H), 7.05-7.98 (m, 9H, aromatic-H), 8.62 (b s, 1H, carbazole-NH), 11.03 (s, 1H, OH), (The ratio of quinone and quinol forms, 1:1)
9c	>300	69	C ₂₃ H ₁₄ N ₂ O ₃ 366.374	(75.40 75.52)	03.85 03.91	07.64 07.72	2.68 (s, 3H, C ₁₄ -CH ₃) 5.68 (b s, 1H, N ₂ -H), 7.16-8.11 (m, 9H, aromatic-H), 8.62 (b s, 1H, carbazole-NH), 11.05 (s, 1H, OH), (The ratio of quinone and quinol forms, 1:1)
9d	>300	77	C ₂₂ H ₁₂ N ₂ O ₃ 354.374	(74.99 74.81)	03.43 03.57	07.99 07.83	5.67 (b s, 1H, N ₂ -H), 7.17-8.05 (m, 10H, aromatic-H), 8.61 (b s, 1H, Carbazole-NH), 11.09 (s, 1H, OH), (The ratio of quinone and quinol forms, 1:1)

work up showed a single product on TLC which was purified by column chromatography. Its IR spectrum showed two strong bands at 3413 and 3274 cm⁻¹ for –OH and –NH stretching vibrations, respectively and a band at 1643 cm⁻¹ which was due to >C=O stretching vibrations. Its ¹H NMR spectrum showed the following signals, a singlet for three protons at δ 2.58, a broad singlet at δ 5.70 for one proton, a multiplet at δ 7.56-7.62 for nine aromatic protons, a broad singlet at δ 8.61 and a singlet at δ 11.01 for two protons respectively. A singlet for three protons at δ 2.58 was assigned to C₁₂-CH₃ and a broad singlet δ 5.70 was assigned to N₂-H proton (of quin-7-one form). A multiplet at δ 7.56-7.62 was due to the eight aromatic

protons. A broad singlet and a singlet at δ 8.61 and 11.01 were assigned to carbazole-NH and C₇-OH (of quinol-OH) respectively. A ratio of quinol and quinone forms from the proton integration of its ¹H NMR spectrum was found to be 1:1. The mass spectrum showed the molecular ion peak at m/z 366 whereas the expected product requires the molecular ion peak at m/z 434. Elemental analysis agreed well with the proposed molecular formula C₂₃H₁₄N₂O₃ with mass 366 from which the structure of the compound was confirmed to be quinolino[2,3-*b*]carbazolo[6,5-*a*]pyran-7,8-diones **9a**. A series of similar compounds **9b-d** were obtained from **4b-d** under identical conditions (**Scheme II**).

The reaction was also carried out under similar conditions in the absence of vinyl acetate to give a similar product in all the cases. On the basis of the results obtained, a mechanism has been proposed. In the plausible mechanism (**Scheme III**) it appears that the reaction gets initiated by the degradation of 3,11-dihydro-2,4-dioxopyrano[2,3-*a*]carbazole **1** under basic condition to 1-hydroxycarbazole-2-carboxylic acid **II**. Then the carboxylic carbon of **II** gets attacked by the carbanion generated from 2,4-dihydroxy-quinoline under basic conditions to give the intermediate **III**, which subsequently looses water molecule during cyclisation to yield the final product **9** through the intermediate **IV**. Thus, a facile and convenient synthesis of some new quinolino[2,3-*b*]-carbazolo[6,5-*a*]pyran-7,8-diones (considered as substituted pyridocarbazoles) utilizing 3,11-dihydro-2,4-dioxopyranocarbazoles was achieved, which can be expected to have enhanced pharmacological properties.

Experimental Section

Melting points were determined on Mettler FP-5 apparatus and are uncorrected. The reactions were monitored by thin layer chromatography. Column chromatographic separations were carried out using silica gel. IR spectra were recorded in KBr pellets on Perkin-Elmer model 1600 FT IR instrument. ¹H NMR spectra (400 MHz) were recorded on Varian AMX 400 spectrometer using TMS as an internal standard. Elemental analyses were carried out on Carlo Erba 1108 elemental analyzer. Electron impact (EI) mass spectra were recorded in Jeol (D)-300 EI mass spectrometer.

Preparation of 12,13-dihydro-5-oxoquinolino[2,3-*a*]carbazoles, 3a-d. A mixture of the respective 1-hydroxycarbazole (**1**, 0.005 mole), anthranilic acid (0.005 mole), freshly fused powdered zinc chloride (3 g) and phosphorus oxychloride (7 mL) was kept at RT for 24 hr, with occasional shaking. The reaction mixture was then poured into crushed ice and the precipitate obtained was filtered, washed with water, dried and this crude mixture showed two spots on TLC which were separated by silica gel column chromatography. The product, 1,7-dibenzazocin-6,12-dione **2** obtained from removal of the solvent mixture eluting with pet. ether-ethyl acetate mixture (99:1) fraction, was found to have around 25% yield in all

the cases. The removal of the solvent from second fraction (pet. ether-ethyl acetate mixture, 97:3) afforded the respective 12,13-dihydro-5-oxoquinolino[2,3-*a*]carbazole **3** as white crystals. The physical and spectral data of compounds **2** and **3a-d** are summarized in **Table I**.

Preparation of 3,11-dihydro-2,4-dioxopyrano[2,3-*a*]carbazoles, 4a-d. A mixture of the respective 1-hydroxycarbazole (**1**, 0.005 mole), malonic acid (0.005 mole, fused zinc chloride (1 g) and phosphorus oxychloride (7 mL) was kept at RT for 24 hr, with occasional shaking. The reaction mixture was then poured into crushed ice and the precipitate obtained was filtered, washed with water, dried and purified by column chromatography over silica gel eluting with pet. ether - ethyl acetate mixture (98:2) to get yellow crystals of the respective 3,11-dihydro-2,4-dioxopyrano[2,3-*a*]carbazole **4**. The physical and spectral data of compounds **4a-d** are summarized in **Table I**.

Preparation of quinolino[2,3-*b*]carbazolo[6,5-*a*]pyran-7,8-diones, 9a-d. A mixture of the appropriate 3,11-dihydro-2,4-dioxopyrano[2,3-*a*]carbazole **4** (0.001 mole), vinylacetate (0.001 mole) and 2,4-dihydroxyquinoline **6** (0.001 mole) was stirred with 4% sodium hydroxide (10 mL) for 1 h. The reaction mixture was poured into crushed ice, and neutralized with cold dil. HCl. The solid separated was filtered, dried and purified by column chromatography over silica gel using pet. ether-ethyl acetate mixture (90:10) as an eluant to yield the corresponding quinolino[2,3-*b*]carbazolo[6,5-*a*]pyran-7,8-dione **9**. The physical and spectral data of compounds **9a-d** are summarized in **Table I**.

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