Synthesis and Cytotoxicity Evaluation of Metal-Chelator-Bearing Flavone, Carbazole, Dibenzofuran, Xanthone, and Anthraquinone

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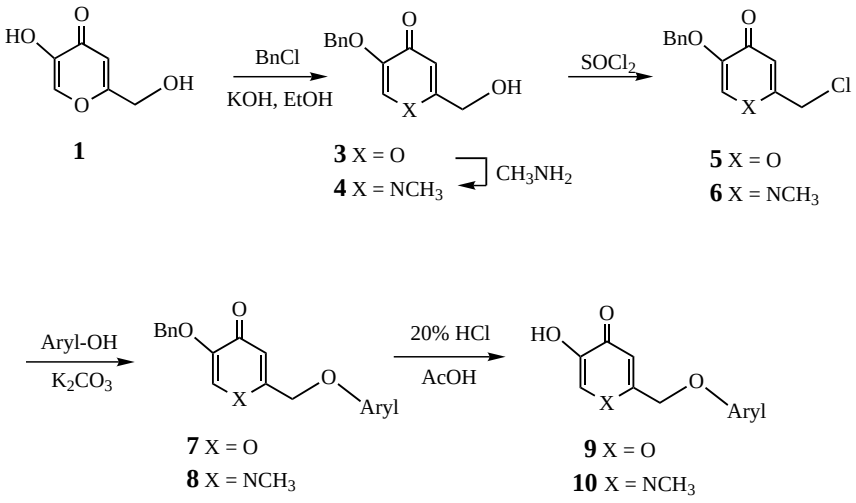
2-(Aryloxymethyl)-5-benzyloxy-1-methyl-1*H*-pyridin-4-ones **8a**–**8g**, 2-(aryloxymethyl)-5-hydroxy-4*H*-pyran-4-ones **9a**–**9g**, and 2-(aryloxymethyl)-5-hydroxy-1-methyl-1*H*-pyridin-4-ones **10a**–**10g** were prepared from the known 5-benzyloxy-2-(hydroxymethyl)pyran-4-one (**3**) in a good overall yield. These compounds were evaluated *in vitro* against a three-cell lines panel consisting of MCF 7 (breast), NCI-H460 (lung), and SF-268 (CNS), and the active compounds passed on for evaluation in the full panel of 60 human tumor cell lines derived from nine cancer cell types. The results indicated that 5-hydroxy derivatives are more favorable than their corresponding 5-benzyloxy precursors (**10a**–**10g** *vs.* **8a**–**8g**), and 1-methyl-1*H*-pyridin-4-ones are more favorable than their corresponding pyran-4(1*H*)-ones (**10a**–**10g** *vs.* **9a**–**9g**). Among these three types of compounds, 2-(aryloxymethyl)-5-hydroxy-1-methyl-1*H*-pyridin-4-ones **10a**–**10g** were the most cytotoxic; they inhibited the growth of almost all the cancer cells tested. On the contrary, compound **8a** (a mean $GI_{50} = 27.8$ μM), **8b** (38.5), **8d** (11.0), and **8e** (30.5) are especially active against the growth of SK-MEL-5 (a melanoma cancer cell) with a GI_{50} of < 0.01, 5.65, 0.55, and 0.03 μM, respectively (cf. *Table 2*).

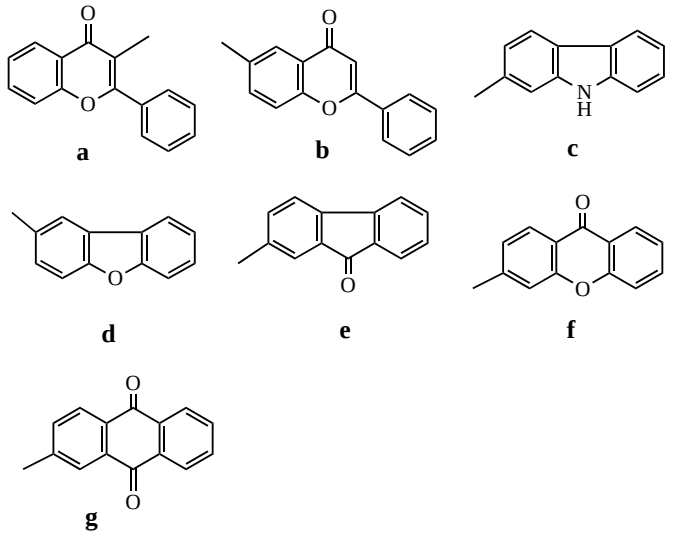
Introduction. – 3-Hydroxy-4*H*-pyran-4-one and 3-hydroxy-1*H*-pyridin-4-one derivatives have received increasing attention due to their biological activities, such as orally active iron chelators, antioxidant, antibacterial, antitumor activities, and in treatment of *Parkinson*'s disease [1–9]. The commercially available plant product, kojic acid (**1**; 5-hydroxy-2-(hydroxymethyl)-4*H*-pyran-4-one), isolated from fermentative products of *Aspergillus* species, has been reported to inhibit tyrosinase *via* chelation of its copper [10][11], which is indispensable for tyrosinase activity [12][13]. Recently, the nonproteinogenic amino acid mimosine (**2**; α-amino-3-hydroxy-4-oxo-4*H*-pyridine-1-propanoic acid), derived from seeds of *Leucaena leucocephala* or *Mimosa pudica*, has been reported to inhibit DNA synthesis in DNA viruses by altering iron and ribonucleotide triphosphate metabolism [14][15]. A recent study showed that mimosine (**2**) might block cell proliferation by multiple mechanisms in human lung cancer cells [16]. Recently, we reported the preparation of alkylating α-methylidene-γ-butyrolactones linked to potential DNA-intercalating carriers such as flavone, xanthone, carbazole, dibenzofuran, and anthraquinone, along with their evaluation against 60 human cancer cell lines derived from nine cancer cell types. The results indicated that these compounds inhibit not only leukemia but also certain solid-cancer cell lines [17–19]. In continuation of our search for more potent anticancer agents, we have linked metal-chelating 3-hydroxy-4*H*-pyran-4-one and 1-methyl-1*H*-pyridin-4-one to these DNA-intercalating moieties for evaluation.

Results and Discussion. – Preparation of the 2-(aryloxymethyl)-5-hydroxy-4*H*-pyran-4-ones **9a**–**9g** and 2-(aryloxymethyl)-5-hydroxy-1-methyl-1*H*-pyridin-4-ones

10a – **10g** is illustrated in the *Scheme*. The known 5-benzyloxy-2-(hydroxymethyl)-4*H*-pyran-4-one (**3**) [20], obtained by benzylation of kojic acid (**1**), was treated with $SOCl_2$ to afford 5-benzyloxy-2-(chloromethyl)-4*H*-pyran-4-one (**5**) in an overall yield of 70%. Treatment of **3** with 40% aqueous $MeNH_2$ gave 5-benzyloxy-2-(hydroxymethyl)-1-methyl-1*H*-pyridin-4-one (**4**) [21], which was reacted with $SOCl_2$ to give 5-benzyloxy-2-(chloromethyl)-1-methyl-1*H*-pyridin-4-one (**6**). Condensation of **5** and **6** with Aryl–OH in the presence of K_2CO_3 and KI afforded 2-(aryloxymethyl)-5-benzyloxy-4*H*-

Scheme





pyran-4-ones **7a**–**7g** and their 1-methyl-1*H*-pyridin-4-one counterparts **8a**–**8g**, respectively, in a yield of 46–95%. Removal of Bn group was achieved with 20% aqueous HCl, and the final products **9a**–**9g** and **10a**–**10g** respectively, were obtained in 60–96% yield.

The 4*H*-pyran-4-ones **9a**–**9g** and the 1*H*-pyridin-4-ones **8a**–**8g** and **10a**–**10g** were evaluated *in vitro* against a panel of three cell lines consisting of MCF 7 (breast), NCI-H460 (lung), and SF-268 (CNS). In this protocol, each cell line is inoculated and preincubated on a microtiter plate. Test agents are then added at a single concentration (100 μM), and the culture was incubated for 48 h. End-point determinations are made with sulforhodamine B, a protein-binding dye. Results for each test agent are reported as the percent of growth of the treated cells compared to the untreated control cells. Compounds that reduced the growth of any one of the cell lines to 32% or less (negative numbers indicate cell kill) are passed on for evaluation in the full panel of 60 human tumor cell lines derived from nine cancer cell types (leukemia, non-small-cell lung cancer, colon cancer, CNS cancer, melanoma, ovarian cancer, renal cancer, prostate cancer, and breast cancer). For each compound, dose-response curves for each cell line were measured at five different drug concentrations, and the concentration causing 50% cell-growth inhibition (GI_{50}) relative to the control was calculated [22]. Results from *Table 1* indicated that, with the exception of compounds **8c**, **8f**, **8g**, **9b**, and **9e**, all are active. Therefore, 5-OH derivatives are more favorable than their

Table 1. In vitro *Anticancer Assay of 4*H-*Pyran-4-one and 1*H-*Pyridin-4-one Derivatives*

Compound	Growth percentages			Mean GI_{50} (μM)[a])
	NCI-H460 (Lung)	MCF 7 (Breast)	SF-268 (CNS)	
7c	15	37	−31	58.8
7d	88	74	8	46.7
8a	22	36	36	27.8
8b	18	32	−3	38.5
8c	73	54	63	n.d.[b])
8d	19	14	46	11.0
8e	67	55	13	30.5
8f	77	77	85	n.d.
8g	77	71	72	n.d.
9a	−58	11	−70	13.7
9b	86	66	38	n.d.
9c	−88	−70	−59	3.42
9d	−72	−74	−79	7.65
9e	93	44	41	n.d.
9f	−6	0	−66	43.2
9g	118	51	3	82.6
10a	12	17	17	3.81
10b	11	12	31	1.84
10c	−76	−41	−36	0.35
10d	−77	−10	−76	0.68
10e	5	10	18	4.61
10f	0	8	11	0.38
10g	−20	11	17	0.27

[a]) Mean values over all 60 cancer cell lines tested. [b]) Not determined.

corresponding 5-benzyloxy precursors (**10a**–**10g** *vs.* **8a**–**8g**), and 1-methyl-1*H*-pyridin-4-ones are more favorable than the corresponding 4*H*-pyran-4-ones (**10a**–**10g** *vs.* **9a**–**9g**). Among these metal-chelator-bearing intercalating agents, carbazole **10c**, dibenzofuran **10d**, xanthone **10f**, and anthraquinone **10g** exhibited most significant cytotoxicity, with mean GI_{50} values in a range of 0.27–0.68 μM.

Although 2-(aryloxymethyl)-5-hydroxy-1-methyl-1*H*-pyridin-4-ones **10a**–**10g** were the most cytotoxic, they inhibited the growth of almost all the cancer cells tested (*Table 2*). On the contrary, compounds **8a** (a mean $GI_{50} = 27.8$ μM), **8b** (38.5), **8d** (11.0), and **8e** (30.5) are especially active against the growth of SK-MEL-5 (a melanoma cancer cell) with a GI_{50} of < 0.01, 5.65, 0.55, and 0.03 μM, respectively.

Table 2. *Growth Inhibition* (GI_{50} (μM)) *of Melanoma Cancer Subpanels by 4*H*-Pyran-4-one and 1*H*-Pyridin-4-one Derivatives*

Compd.	MALME-3M	M14	SK-MEL-2	SK-MEL-5	UACC-257	UACC-62
7c	> 100	> 100	25.8	n.d.	> 100	37.5
7d	37.0	35.6	44.9	1.68	> 100	25.9
8a	> 100	41.3	28.4	< 0.01	64.0	18.9
8b	41.1	33.2	27.9	5.65	> 100	25.9
8d	12.9	13.1	14.4	0.55	15.7	11.7
8e	32.6	25.8	19.7	0.03	> 100	17.5
9a	22.3	19.5	15.1	12.4	16.5	1.70
9c	2.57	4.27	n.d.	2.57	1.03	1.73
9d	13.7	10.9	5.73	7.21	9.65	4.79
9f	32.7	63.5	27.6	41.9	43.2	26.9
9g	46.1	> 100	> 100	30.5	> 100	28.9
10a	9.71	1.83	4.83	0.89	30.6	4.44
10b	1.88	1.46	1.99	1.24	5.04	1.78
10c	1.32	0.24	0.77	0.17	3.25	0.35
10d	1.53	0.53	1.26	0.28	4.06	1.35
10e	15.9	5.13	8.35	4.71	40.7	3.25
10f	0.30	0.53	0.35	0.31	0.32	0.41
10g	0.29	0.28	0.29	0.21	0.31	0.22

Conclusions. – Certain metal-chelator-bearing compounds were synthesized and evaluated for their cytotoxicity. The preliminary results indicated 2-(aryloxymethyl)-5-hydroxy-1-methyl-1*H*-pyridin-4-ones **10a**–**10g** were the most cytotoxic. Among them, carbazole **10c**, dibenzofuran **10d**, xanthone **10f**, and anthraquinone **10g** exhibited mean GI_{50} values in a range of 0.27–0.68 μM. However, certain 2-(aryloxymethyl)-5-benzyloxy-1-methyl-1*H*-pyridin-4 -ones **8** demonstrated selective cytotoxicity. Compounds **8a** (a mean $GI_{50} = 27.8$ μM), **8b** (38.5), **8d** (11.0), and **8e** (30.5) are especially active against the growth of SK-MEL-5 (a melanoma cancer cell) with GI_{50} values of < 0.01, 5.65, 0.55, and 0.03 μM, respectively.

Experimental Part

General. M.p.: *Electrothermal IA9100* digital melting-point apparatus; uncorrected. TLC: silica gel *60 F-254* plates from *EM Laboratories, Inc.*; detection by UV light (254 nm). NMR (^{1}H and ^{13}C) Spectra: *Varian Unity-400* or *Varian Gemini-200* spectrometer, chemical shifts δ in ppm with Me_4Si as an internal standard

(=0 ppm), coupling constants *J* in Hz. Elemental analyses were carried out on a *Heraeus CHN-O-Rapid* elemental analyzer, and results were within ±0.4% of calc. values.

*5-Benzyloxy-2-(chloromethyl)-4*H-*pyran-4-one* (**5**). To a suspension of *5-benzyloxy-2-(hydroxymethyl)-1-methyl-1*H-*pyridin-4-one* (**3**; 2.32 g, 10 mmol) at r.t. in Et_2O (15 ml) was added $SOCl_2$ (2 ml, 12.24 mmol), and the mixture was stirred for 1 h. After treatment with H_2O, more Et_2O was added, and the org. layer was washed with H_2O, dried (Na_2SO_4), and concentrated at r.t. to give **5** (2.24 g, 89%). Pale yellow solid: M.p. 115–117° ([20]: 118–120°). ^{1}H-NMR (DMSO): 4.67 (*s*, PhCH_2); 4.96 (*s*, CH_2Cl); 6.58 (*s*, H–C(3)); 7.41 (*m*, 5 arom. H); 8.29 (*s*, H–C(6)). ^{13}C-NMR (DMSO): 41.21; 70.68; 114.54; 128.23; 128.34 (2 C); 128.54 (2 C); 136.03; 141.77; 146.93; 161.93; 173.15. Anal. calc. for $C_{13}H_{11}O_3Cl$: C 62.29, H 4.42; found: C 62.33, H 4.53.

*5-Benzyloxy-2-(chloromethyl)-1-methyl-1*H-*pyridin-4-one and 5-Benzyloxy-2-(chloromethyl)-1,4-dihydro-1-methyl-4-oxopyridinium Chloride* (**6**). Compound **6** was prepared from **4** [21] by the same procedure as described for **5** in 73% yield. M.p. 179–180°. ^{1}H-NMR (DMSO): 4.13 (*s*, MeN); 5.11 (*s*, CH_2Cl); 5.23 (*s*, PhCH_2); 7.40–7.50 (*m*, 5 arom. H); 7.55 (*s*, H–C(3)); 8.77; 8.90 (*s*, H–C(6)). ^{13}C-NMR (DMSO) 40.33; 42.84; 71.59; 114.44; 128.28 (2 C); 128.58 (2 C); 132.74; 135.32; 145.46; 146.29; 162.50. Anal. calc. for $C_{14}H_{14}ClNO_2$: C 63.76, H 5.35, N 5.31; found: C 63.69, H 5.44, N 5.21.

*General Procedure for Coupling of 5-Benzyloxy-2-(chloromethyl)-4*H-*pyran-2-one* (**5**) *and 5-Benzyloxy-2-(chloromethyl)-1-methyl-1*H-*pyridin-4-one* (**6**) *with Heterocyclic Phenol Derivatives.* A mixture of **5** (5 mmol) or **6** (5 mmol), K_2CO_3 (0.69 g, 5 mmol), KI (50 mg), and corresponding heterocyclic phenol derivative (5 mmol) in acetone (50 ml) was refluxed (monitored until the reactant disappeared by TLC). Evaporation of the solvent gave a residue, which was poured into ice water (50 ml). The resulting solid was collected and crystallized from EtOH.

*3-[(5-Benzyloxy-4-oxo-4*H-*pyran-2-yl)methoxy]-2-phenyl-4*H-*[1]benzopyran-4-one* (**7a**). Yield: 81% (from **5** and 3-hydroxy-2-phenyl-4*H*-[1]benzopyran-4-one). M.p. 161–163°. ^{1}H-NMR ($CDCl_3$): 4.93 (*s*, PhCH_2); 4.97 (*s*, CH_2O); 6.33 (*s*, H–C(3′)); 7.22 (*s*, H–C(6′)); 7.36 (*m*, 5 arom. H); 7.43–7.56 (*m*, 5 arom H); 7.72 (*m*, arom. H); 7.93 (*m*, 2 arom. H); 8.25 (*dd*, *J* = 8.0, 1.2, H–C(5)). ^{13}C-NMR ($CDCl_3$): 69.35; 71.89; 115.44; 118.16; 124.01; 125.11; 125.80; 127.77 (2 C); 128.42 (2 C); 128.63; 128.71 (2 C); 128.87 (2 C); 130.38; 130.97; 133.91; 135.73; 138.69; 141.47; 147.06; 155.38; 157.00; 161.80; 174.35. Anal. calc. for $C_{29}H_{22}O_5$: C 74.33, H 4.46; found: C 74.06, H 4.48.

*6-[(5-Benzyloxy-4-oxo-4*H-*pyran-2-yl)methoxy]-2-phenyl-4*H-*[1]benzopyran-4-one* (**7b**). Yield: 94% (from **5** and 6-hydroxy-2-phenyl-4*H*-[1]benzopyran-4-one). M.p. 222–224°. ^{1}H-NMR ($CDCl_3$): 4.94 (*s*, PhCH_2); 5.09 (*s*, CH_2O); 6.61 (*s*, H–C(3′)); 6.83 (*s*, H–C(3)); 7.38 (*m*, 6 arom. H); 7.55 (*m*, 5 arom. H); 7.60 (*s*, H–C(6′)); 7.94 (*m*, 2 arom. H). ^{13}C-NMR ($CDCl_3$): 65.88; 71.99; 106.02; 106.96; 114.03; 120.16; 124.16; 124.60; 126.32 (2 C); 127.83 (2 C); 128.49; 128.75 (2 C); 129.02; 129.10 (2 C); 131.70; 135.64; 141.59; 147.36; 151.73; 154.81; 161.86; 163.57; 174.40; 178.01. Anal. calc. for $C_{29}H_{22}O_5$: C 74.33, H 4.46; found: C 74.31, H 4.55.

*5-Benzyloxy-2-[[(9*H-*carbazol-2-yl)oxy]methyl]-4*H-*pyran-4-one* (**7c**). Yield: 86% (from **5** and 9*H*-carbazol-2-ol). M.p. 196–198°. ^{1}H-NMR ($CDCl_3$): 4.86 (*s*, PhCH_2); 5.05 (*s*, CH_2O); 6.64 (*s*, H–C(3′)); 6.90 (*m*, 2 arom. H); 7.17–7.37 (*m*, 8 arom. H); 7.55 (*s*, H–C(6)); 7.96 (*m*, 2 arom. H); 8.17 (br. *s*, NH). ^{13}C-NMR ($CDCl_3$): 66.22; 71.99; 96.42; 108.19; 110.49; 114.11; 118.51; 119.71 (2 C); 121.28; 123.20; 125.06; 127.83 (2 C); 128.46; 128.73 (2 C); 135.69; 139.72; 140.55; 141.63; 147.31; 156.79; 162.76; 174.53. Anal. calc. for $C_{25}H_{19}NO_4$: C 75.55, H 4.82, N 3.52; found: C 75.43, H 4.84, N 3.50.

*5-Benzyloxy-2-[[(dibenzo[*a,d*]furan-2-yl)oxy]methyl]-4*H-*pyran-4-one* (**7d**). Yield: 46% (from **5** and 2-hydroxydibenzo[*b,d*]furan). M.p. 144–146°. ^{1}H-NMR ($CDCl_3$): 4.91 (*s*, PhCH_2); 5.10 (*s*, CH_2O); 6.62 (*s*, H–C(3)); 7.07 (*dd*, *J* = 8.8, 2.6, H–C(3)); 7.26–7.53 (*m*, 10 arom. H); 7.59 (*s*, H–C(6)); 7.89 (*m*, 1 arom. H). ^{13}C-NMR ($CDCl_3$): 66.84; 72.00; 105.69; 111.86; 112.46; 114.15; 115.68; 120.66; 122.64; 124.09; 124.98; 127.52; 127.84 (2 C); 128.47; 128.73 (2 C); 135.69; 141.67; 147.31; 151.64; 153.77; 157.03; 162.59; 174.51. Anal. calc. for $C_{25}H_{18}O_5$: C 75.33, H 4.55; found: C 75.19, H 4.62.

*5-Benzyloxy-2-[(9-oxo-9*H-*fluoren-2-yloxy)methyl]-4*H-*pyran-4-one* (**7e**). Yield: 68% (from **5** and 2-hydroxy-9*H*-fluoren-9-one). M.p. 205–207°. ^{1}H-NMR ($CDCl_3$): 4.85 (*s*, PhCH_2); 5.08 (*s*, CH_2O), 6.57 (*s*, H–C(3)); 7.01 (*dd*, *J* = 8.2, 2.6, H–C(3′)); 7.16–7.46 (*m*, 10 arom. H); 7.59 (*m*, H–C(6), 1 arom. H). ^{13}C-NMR ($CDCl_3$): 65.80; 71.95; 109.86; 114.08; 119.86; 121.28; 121.63; 124.46; 127.80 (2 C); 128.31; 128.47; 128.72 (2 C); 134.21; 135.01; 135.60; 135.99; 138.36; 141.52; 144.40; 147.32; 158.56; 161.81; 174.31; 193.30. Anal. calc. for $C_{26}H_{18}O_5 \cdot 0.5\ H_2O$: C 74.46, H 4.56; found: C 74.32, H 4.41.

*3-[(5-Benzyloxy-4-oxo-4*H-*pyran-2-yl)methoxy]-9*H-*xanthen-9-one* (**7f**). Yield: 50% (from **5** and 3-hydroxy-9*H*-xanthen-9-one). M.p. 178–181°. ^{1}H-NMR ($CDCl_3$): 4.93 (*s*, PhCH_2); 5.08 (*s*, CH_2O); 6.60 (*s*, H–C(3′)); 6.93 (*m*, 2 arom. H); 7.31–7.46 (*m*, 7 arom. H); 7.59 (*s*, H–C(6′)); 7.70 (*m*, 1 arom. H); 8.29 (*m*, 2 arom. H). ^{13}C-NMR ($CDCl_3$): 65.73; 71.92; 101.44; 113.01; 114.38; 116.74; 117.68; 121;82; 124.06; 126.63;

127.76 (2 C); 128.44; 128.69 (2 C); 128.77; 134.52; 135.50; 141.53; 147.35; 156.12; 157.71; 161.05; 162.49; 174.17; 176.07. Anal. calc. for $C_{26}H_{18}O_6$: C 73.23, H 4.25; found: C 73.02, H 4.28.

*2-[(5-Benzyloxy-4-oxo-4*H*-pyran-2-yl)methoxy]anthraquinone* (**7g**). Yield: 61% (from **5** and 2-hydroxyanthraquinone). M.p. 183–184°. ^{1}H-NMR (DMSO): 4.93 (*s*, PhCH_2); 5.30 (*s*, CH_2O); 6.64 (*s*, H–C(3′)); 7.41 (*m*, 5 arom. H); 7.55 (*m*, 1 arom. H); 7.73 (*s*, H–C(6′)); 7.93 (*m*, 2 arom. H); 8.21 (*m*, 4 arom. H). ^{13}C-NMR (DMSO): 65.81; 70.59; 106.83; 111.14; 114.15; 121.44; 126.74; 126.79; 128.17 (2 C); 128.26; 128.47 (2 C); 129.65; 133.05; 133.09; 134.32; 134.72; 135.18; 136.01; 141.65; 146.95; 161.60; 162.10; 172.92; 181.38; 182.28. Anal. calc. for $C_{27}H_{18}O_6$: C 73.97, H 4.14; found: C 73.77, H 4.16.

*5-Benzyloxy-1-methyl-2-{[(4-oxo-2-phenyl-4*H*-[1]benzopyran-3-yl)oxy]methyl}-1*H*-pyridin-4-one* (**8a**). Yield: 68% (from **6** and 3-hydroxy-2-phenyl-4*H*-[1]benzopyran-4-one). M.p. 113–115°. ^{1}H-NMR (DMSO): 3.58 (*s*, MeN); 4.96 (*s*, PhCH_2); 4.98 (*s*, CH_2O); 6.10 (*s*, H–C(3)); 7.36 (*m*, 5 arom. H); 7.46 (*s*, H–C(6)); 7.54 (*m*, 4 arom. H); 7.82 (*m*, 4 arom. H); 8.14 (*dd*, *J* = 8.0, 1.6, H–C(5′)). ^{13}C-NMR (DMSO): 39.71; 69.18; 70.51; 118.23; 118.50; 123.45; 125.03; 125.32; 127.86; 127.94 (2 C); 128.30 (2 C); 128.44 (2 C); 128.50 (2 C); 129.14; 130.09; 130.96; 134.31; 137.06; 138.18; 142.81; 147.60; 154.86; 156.81; 171.18; 173.72. Anal. calc. for $C_{29}H_{23}NO_5$: C 74.83, H 4.98, N 3.01; found: C 74.87, H 5.04, N 3.12.

*5-Benzyloxy-1-methyl-2-{[(4-oxo-2-phenyl-4*H*-[1]benzopyran-6-yl)oxy]methyl}-1*H*-pyridin-4-one* (**8b**). Yield: 76% (from **6** and 6-hydroxy-2-phenyl-4*H*-[1]benzopyran-4-one). M.p. 178° (dec). ^{1}H-NMR ($CDCl_3$): 3.63 (*s*, MeN); 4.94 (*s*, PhCH_2); 5.19 (*s*, CH_2O); 6.64 (*s*, H–C(3)); 6.83 (*s*, H–C(3′)); 7.04 (*s*, H–C(6)); 7.31–7.65 (*m*, 11 arom. H); 7.92 (*m*, 2 arom. H). ^{13}C-NMR (DMSO) 40.60; 66.85; 71.85; 106.43; 106.88; 111.99; 119.04; 120.14; 123.82; 124.59; 126.26 (2 C); 127.84 (2 C); 128.06; 128.53 (2 C); 129.06 (2 C); 129.44; 131.59; 131.69; 136.67; 142.22; 148.39; 154.67; 163.53; 173.19; 177.90. Anal. calc. for $C_{29}H_{23}NO_5$: C 74.83, H 4.98, N 3.01; found: C 74.82, H 4.91, N 3.09.

*5-Benzyloxy-2-{[(9*H*-carbazol-2-yl)oxy]methyl}-1-methyl-1*H*-pyridin-4-one* (**8c**). Yield: 59% (from **6** and 9*H*-carbazol-2-ol). M.p. 172° (dec). ^{1}H-NMR (DMSO): 3.72 (*s*, MeN); 5.02 (*s*, PhCH_2); 5.16 (*s*, CH_2O); 6.46 (*s*, H–C(3)); 6.89 (*dd*, *J* = 8.8, 2.4, H–C(3′)); 7.11 (*m*, 2 arom. H); 7.28–7.45 (*m*, 7 arom. H); 7.71 (*s*, H–C(6)); 8.01 (*m*, 2 arom. H); 11.20 (br. *s*, NH). ^{13}C-NMR (DMSO) 39.92; 65.84; 70.56; 96.11; 108.09; 110.70; 117.02; 118.64; 118.87; 119.44; 120.78; 121.02; 112.49; 124.42; 127.91; 128.02 (2 C); 128.35 (2 C); 129.38; 137.07; 139.88; 140.82; 143.98; 156.54; 171.36. Anal. calc. for $C_{26}H_{22}N_2O_3$: C 76.08, H 5.40, N 6.82; found: C 76.02, H 5.44, N 6.74.

*5-Benzyloxy-2-{[(dibenzo[*b*;*d*]furan-2-yl)oxy]methyl}-1-methyl-1*H*-pyridin-4-one* (**8d**). Yield: 73% (from **6** and dibenzo[*b*,*d*]furan-2-ol). M.p. 193–195°. ^{1}H-NMR ($CDCl_3$): 3.64 (*s*, MeN); 4.90 (*s*, PhCH_2); 5.17 (*s*, CH_2O); 6.60 (*s*, H–C(3)); 7.02 (*m*, H–C(6), H–(3′)); 7.29–7.57 (*m*, 10 arom. H); 7.90 (*d*, *J* = 7.2, H–C(4′)). ^{13}C-NMR ($CDCl_3$): 40.70; 67.81; 71.78; 105.53; 111.76; 112.40; 115.55; 119.24; 120.62; 122.61; 123.97; 124.92; 127.48; 127.80 (2 C); 128.02; 128.49 (2 C) ; 129.40; 136.65; 142.80; 148.32; 151.51; 153.55; 156.92; 173.15. Anal. calc. for $C_{26}H_{21}NO_4$: C 75.90, H 5.14, N 3.40; found: C 75.84, H 5.21, N 3.39.

*5-Benzyloxy-1-methyl-2-{[(9-oxo-9*H*-fluoren-2-yl)oxy]methyl}-1*H*-pyridin-4-one* **(8e).** Yield: 54% (from **6** and 2-hydroxy-9*H*-fluoren-9-one). M.p. 216–217°. ^{1}H-NMR (DMSO): 3.69 (*s*, MeN); 5.01 (*s*, PhCH_2); 5.19 (*s*, CH_2O); 6.41 (*s*, H–C(3)); 7.26–7.45 (*m*, 8 arom. H); 7.57 (*m*, 2 arom. H); 7.69 (*s*, H–C(6)); 7.73 (*m*, 2 arom. H). ^{13}C-NMR (DMSO): 40.59; 65.81; 70.54; 110.48; 116.91; 120.56; 121.57; 122.42; 123.98; 127.87; 127.96 (2 C); 128.31 (2 C); 128.41; 129.41; 133.39; 135.04; 135.51; 137.02; 137.21; 143.35; 144.13; 147.50; 158.71; 171.28; 192.81. Anal. calc. for $C_{27}H_{21}NO_4$: C 76.58, H 5.00, N 3.31; found: C 76.58, H 5.03, N 3.36.

*5-Benzyloxy-1-methyl-2-{[(9-oxo-9*H*-xanthen-3-yl)oxy]methyl}-1*H*-pyridin-4-one* (**8f**). Yield: 94% (from **6** and 3-hydroxy-9*H*-xanthen-9-one). M.p. 204–206°. ^{1}H-NMR (DMSO): 3.71 (*s*, MeN); 5.02 (*s*, PhCH_2); 5.31 (*s*, CH_2O); 6.45 (*s*, H–C(3)); 7.19 (*dd*, *J* = 9.0, 2.0, H–C(2′)); 7.33–7.88 (*m*, arom. H); 8.17 (*m*, 7 arom. H). ^{13}C-NMR (DMSO): Anal. calc. for $C_{27}H_{21}NO_5$: C 73.79, H 4.82, N 3.19; found: C 73.80, H 4.88, N 3.12.

2-[(5-Benzyloxy-1,4-dihydro-1-methyl-4-oxopyridin-2-yl)methoxy]anthraquinone (**8g**). Yield: 87% (from **6** and 2-hydroxyanthraquinone). M.p. 229–231°. ^{1}H-NMR (DMSO): 3.71 (*s*, MeN); 5.02 (*s*, PhCH_2); 5.36 (*s*, CH_2O); 6.45 (*s*, H–C(3′)); 7.33–7.78 (*m*, 8 arom. H); 7.93 (*m*, 2 arom. H); 8.20 (*m*, 3 arom. H). ^{13}C-NMR (DMSO): 40.52; 65.91; 70.48; 106.32; 111.21; 117.14; 121.49; 126.62; 126.69; 127.09; 127.81; 127.89 (2 C); 128.25 (2 C); 129.39; 129.47; 133.00; 134.19; 134.61; 135.06; 136.95; 142.81; 147.52; 162.06; 171.21; 181.27; 182.22. Anal. calc. for $C_{28}H_{21}NO_5$: C 74.49, H 4.69, N 3.10; found: C 74.50, H 4.76, N 3.11.

General Procedure for Removal of the Protecting Group. A suspension of the (5-benzyloxy-4-oxo-4*H*-pyran-2-yl)methoxy derivative **7** (3 mmol) or the corresponding (5-benzyloxy-1-methyl-4-oxo-1,4-dihydropyridin-2-yl)methoxy derivative **8** (3 mmol) in AcOH (15 ml) was treated with 20% HCl (15 ml), and the mixture was heated at reflux for 8–34 h (monitored by TLC). After evaporation of the AcOH, the residue was suspended in H_2O (30 ml). The resulting precipitate was filtered and washed with H_2O. The crude product was crystallized from EtOH.

*3-[(5-Hydroxy-4-oxo-4*H*-pyran-2-yl)methoxy)]-2-phenyl-4*H*-[1]benzopyran-4-one* (**9a**). Yield: 81% (from **7a**). M.p. 149–152°. ^{1}H-NMR (DMSO) 4.96 (*s*, CH_2O); 6.37 (*s*, H–C(3′)); 7.55 (*m*, 4 arom. H); 7.47–7.87 (*m*, H–C(6′), 2 arom. H); 7.98 (*m*, 2 arom. H); 8.13 (*m*, 1 arom. H); 9.10 (br. *s*, OH). ^{13}C-NMR (DMSO): 69.38; 113.33; 118.51; 123.43; 124.99; 125.25; 128.41 (2 C); 128.54 (2 C); 130.06; 130.93; 134.28; 138.75; 139.52; 145.82; 154.82; 156.07; 161.75; 173.50; 173.58. Anal. calc. for $C_{21}H_{14}O_6$: C 69.61, H 3.89; found: C 69.63, H 3.92.

*6-[(5-Hydroxy-4-oxo-4*H*-pyran-2-yl)methoxy]-2-ph enyl-4*H*-[1]benzopyran-4-one* (**9b**). Yield: 94% (from **7b**). M.p. 245–247°. ^{1}H-NMR (DMSO) 5.16 (*s*, CH_2O); 6.61 (*s*, H–C(3′)); 7.04 (*s*, H–C(3)); 7.57 (*m*, 5 arom. H); 7.81 (*m*, 1 arom. H); 8.10 (*m*, 2 arom. H); 8.15 (*s*, H–C(6′)); 9.26 (br. *s*, OH). ^{13}C-NMR (DMSO) 65.86; 106.13; 106.29; 112.62; 120.35; 123.64; 123.93; 126.24 (2 C); 129.04 (2 C); 131.04; 131.72; 139.90; 145.98; 150.77; 154.69; 161.92; 162.41; 173.58; 176.69. Anal. calc. for $C_{21}H_{14}O_6$: C 69.61, H 3.89; found: C 69.64, H 3.95.

*2-[[(9*H*-Carbazol-2-yl)oxy]methyl]-5-hydroxy-4*H*-pyran-4-one* (**9c**). Yield: 76% (from **7c**). M.p. 185–187°. ^{1}H-NMR ((D_6)DMSO): 5.10 (*s*, CH_2O); 6.59 (*s*, H–C(3)); 6.86 (*dd*, *J* = 8.6, 2.2, H–C(3′)); 7.06 (*d*, *J* = 2.4, H–C(1′)); 7.13 (*m*, 1 arom. H); 7.27 (*m*, 2 arom. H); 7.42 (*d*, *J* = 8.0, H–C(4)); 8.00 (*m*, 2 arom. H); 8.14 (*s*, H–C(6′)); 9.23 (br. *s*, OH); 11.17 (br. *s*, NH). ^{13}C-NMR ((D_6)DMSO): 65.66; 95.85; 107.88; 110.58; 112.35; 116.92; 118.52; 119.32; 120.94; 122.35; 124.32; 128.36; 139.76; 140.69; 145.94; 156.42; 162.68; 173.57. Anal. calc. for $C_{18}H_{13}NO_4$: C 70.35, H 4.26, N 4.56; found: C 70.38, H 4.21, N 4.54.

*2-[[(Dibenzo[*b,d*]furan-2-yl)oxy]methyl]-5-hydroxy-4*H*-pyran-4-one* (**9d**). Yield: 88% (from **7d**). M.p. 184–186°. ^{1}H-NMR ((D_6)DMSO): 5.12 (*s*, CH_2O); 6.62 (*s*, H–C(3)); 7.22 (*dd*, *J* = 9.0, 2.8, H–C(3′)); 7.40 (*m*, 1 arom. H); 7.53 (*m*, 1 arom. H); 7.67 (*m*, 2 arom. H); 7.86 (*d*, *J* = 2.8, H–C(1′)); 8.16 (*m*, H–C(6), 1 arom. H); 9.25 (br. *s*, OH). ^{13}C-NMR ($CDCl_3$): 66.26; 106.02; 111;72; 112.32; 112.50; 116.02; 121.24; 122.89; 123.71; 124.24; 127.70; 139.93; 146.04; 150.52; 153.80; 156.20; 162.53; 173.71. Anal. calc. for $C_{18}H_{12}O_5$: C 70.13, H 3.92; found: C 70.08, H 3.98.

*5-Hydroxy-2-[[(9-oxo-9*H*-fluoren-2-yl)oxy]methyl]-4*H*-pyran-4-one* (**9e**). Yield 65% (from **7e**). M.p. 216–218°. ^{1}H-NMR (DMSO): 5.12 (*s*, CH_2O); 6.59 (*s*, H–C(3)); 7.27 (*m*, 3 arom. H); 7.57 (*m*, 2 arom. H); 7.71 (*m*, 2 arom. H); 8.14 (*s*, H–C(6)); 9.30 (br. *s*, OH). ^{13}C-NMR ((D_6)DMSO): 65.71; 110.24; 112.54; 120.47; 121.23; 122.37; 123.90; 128.35; 133.31; 134.99; 135.43; 137.13; 139.88; 144.00; 145.96; 158.63; 161.96; 173.58; 192.68. Anal. calc. for $C_{19}H_{12}O_5$: C 71.25, H 3.78; found: C 71.26, H 3.82.

*3-[(5-Hydroxy-4-oxo-4*H*-pyran-2-yl)methoxy]-9*H*-xanthen-9-one* (**9f**). Yield 95% (from **7f**). M.p. 251–253°. ^{1}H-NMR (DMSO): 5.23 (*s*, CH_2O); 6.65 (*s*, H–C(3′)); 7.16 (*dd*, *J* = 8.6, 2.4, H–C(2)); 7.31 (*d*, *J* = 2.4, H–C(4)); 7.48 (*m*, 1 arom. H); 7.63 (*d*, *J* = 8.6, H–C(1)); 7.86 (*m*, 1 arom. H); 8.16 (*m*, H–C(6′), 2 arom. H); 9.30 (br. *s*, OH). ^{13}C-NMR (DMSO) 65.89; 101.67; 112.82; 113.78; 115.53; 117.84; 121.09; 124.32; 125.82; 127.76; 135.07; 139.97; 146.03; 155.53; 157.24; 161.34; 162.83; 173.56; 174.84. Anal. calc. for $C_{19}H_{12}O_6$: C 67.86, H 3.60; found: C 67.76, H 3.68.

*2-[(5-Hydroxy-4-oxo-4*H*-pyran-2-yl)methoxy]anthraquinone* (**9g**). Yield 91% (from **7g**). M.p. 237–238°. ^{1}H-NMR (DMSO): 5.28 (*s*, CH_2O); 6.64 (*s*, H–C(3′)); 7.55 (*dd*, *J* = 8.4, 2.6, H–C(3)); 7.70 (*d*, *J* = 2.6, H–C(1)); 7.92 (*m*, 2 arom. H); 8.15 (*s*, H–C(6′)); 8.18 (*m*, 3 arom. H); 9.30 (br. *s*, OH). ^{13}C-NMR (DMSO) 65.92; 111.08; 112.89; 121.36; 126.65; 126.73; 127.15; 129.56; 132.99; 133.02; 134.22; 134.63; 135.12; 140.03; 146.10; 161.46; 162.08; 173.62; 181.29; 182.20. Anal. calc. for $C_{20}H_{12}O_6$: C 68.97, H 3.47; found: C 68.95, H 3.49.

*5-Hydroxy-1-methyl-2-[[(4-oxo-2-phenyl-4*H*-[1]-benzopyran-3yl)oxy]methyl]-1*H*-pyridin-4-one* (**10a**). Yield: 73% (from **8e**). M.p. 185–186°. ^{1}H-NMR (DMSO): 3.88 (br. *s*, OH); 4.02 (*s*, MeN); 5.24 (*s*, CH_2O); 7.38 (*s*, H–C(3)); 7.58 (*m*, 4 arom. H); 7.88 (*m*, 4 arom. H); 8.15 (*dd*, *J* = 8.0, 1.4, H–C(5′)); 8.23 (*s*, H–C(6)). ^{13}C-NMR (DMSO) 42.84; 68.27; 113.75; 118.59; 123.42; 125.02; 125.43; 128.49 (2 C); 128.66 (2 C); 129.92; 131.14; 133.02; 134.47; 138.50; 144.04; 144.64; 154.91; 156.67; 160.12; 173.69. Anal. calc. for $C_{22}H_{17}NO_5 \cdot 0.2\ H_2O$: C 69.73, H 4.62, N 3.70; found: C 69.62, H 4.64, N 3.66.

*5-Hydroxy-1-methyl-2-[[(4-oxo-2-phenyl-4*H*-6-yl)oxy]methyl]-1*H*-pyridin-4-one* (**10b**). Yield: 75% (from **8f**). M.p. 263–266°. ^{1}H-NMR (DMSO): 3.86 (br. *s*, OH); 4.10 (*s*, MeN); 5.52 (*s*, CH_2O); 7.07 (*s*, H–C(3)); 7.56 (*s*, H–C(3′)); 7.63 (*m*, 5 arom. H); 7.86 (*d*, *J* = 9.0, H–C(8′)); 8.12 (*m*, 2 arom. H); 8.39 (*s*, H–C(6)). ^{13}C-NMR (DMSO): 42.86; 65.08; 106.28; 106.98; 112.39; 120.55; 123.75; 124.11; 126.36 (2 C); 129.16 (2 C); 131.11; 131.88; 133.16; 144.56 (2 C); 151.08; 154.49; 160.64; 162.55; 176.80. Anal. calc. for $C_{22}H_{17}NO_5$: C 70.39, H 4.56, N 3.73; found: C 70.36, H 4.68, N 3.77.

*2-[[(9*H*-Carbazol-2-yl)oxy]methyl]-5-hydroxy-1-methyl-1*H*-pyridin-4-one* (**10c**). Yield: 68% (from **8h**). M.p. 198–199°. ^{1}H-NMR (DMSO): 3.85 (br. *s*, OH); 4.04 (*s*, MeN); 5.41 (*s*, CH_2O); 7.13–7.48 (*m*, 6 arom. H); 8.03 (*m*, 2 arom. H); 8.25 (*s*, H–C(6)); 11.27 (br. *s*, NH). ^{13}C-NMR (DMSO): 42.30; 65.01; 96.33; 107.83; 110.68; 112.46; 118.59; 119.41; 121.00; 122.32; 124.44; 128.43; 131.86; 139.87; 140.71; 144.76; 144.90; 156.12; 161.86. Anal. calc. for $C_{19}H_{16}N_2O_3 \cdot 0.5H_2O$: C 69.29, H 5.20, N 8.50; found: C 69.21, H 5.28, N 8.47.

*2-[[(Dibenzo[*b,d*]furan-2-yl)oxy]methyl]-5-hydroxy-1-methyl-1*H*-pyridin-4-one* (**10d**). Yield: 86% (from **8i**). M.p. 107–109°. ^{1}H-NMR (DMSO): 4.07 (*s*, MeN); 4.15 (br. *s*, OH); 5.44 (*s*, CH_2O); 7.19–7.17 (*m*, 7 arom. H); 8.15 (*m*, 1 arom. H); 8.29 (*s*, H–C(6)). ^{13}C-NMR (DMSO): 42.46; 65.65; 106.39; 111.78; 112.43; 116.26; 121.27; 122.97; 123.68; 124.30; 127.81; 128.50; 128.65; 132.05; 144.83; 150.70; 153.52; 156.24; 161.91. Anal. calc. for $C_{19}H_{15}NO_4$: C 71.02, H 4.71, N 4.36; found: C 69.98, H 4.80, N 4.26.

*5-Hydroxy-1-methyl-2-[[(9-oxo-9*H*-fluoren-2-yl)oxy]methyl]-1*H*-pyridin-4-one* (**10e**). Yield: 72% (from **8j**). M.p. 248–251°. ^{1}H-NMR (DMSO): 3.75 (br. *s*, OH); 4.05 (*s*, MeN); 5.45 (*s*, CH_2O); 7.34 (*m*, 3 arom. H); 7.47 (*s*, H–C(3)); 7.57 (*m*, 2 arom. H); 7.75 (*m*, 2 arom. H); 8.34 (*s*, H–C(6)). ^{13}C-NMR (DMSO): 42.80; 65.01; 110.64; 112.18; 120.69; 121.66; 122.55; 124.05; 128.58; 133.07; 133.40; 135.14; 135.60; 137.60; 144.04; 144.50; 144.65; 158.40; 160.69; 192.79. Anal. calc. for $C_{20}H_{15}NO_4 \cdot 0.8H_2O$: C 69.07, H 4.81, N 4.03; found: C 69.11, H 4.86, N 4.08.

*5-Hydroxy-1-methyl-2-[[(9-oxo-9*H*-xanthen-3-yl)oxy]methyl]-1*H*-pyridin-4-one* (**10f**). Yield: 95% (from **8k**). M.p. 257–259°. ^{1}H-NMR (DMSO): 3.85 (br. *s*, OH); 4.08 (*s*, MeN); 5.57 (*s*, CH_2O); 7.24 (*dd*, *J* = 8.8, 2.2, H–C(2′)); 7.45–8.21 (*m*, 7 arom. H); 8.37 (*s*, H–C(6)). ^{13}C-NMR (DMSO): 43.18; 65.42; 102.45; 107.09; 112.33; 114.31; 116.15; 118.21; 121.47; 124.79; 126.23; 128.22; 133.57; 135.56; 144.42; 144.80; 155.91; 157.64; 162.79; 175.22. Anal. calc. for $C_{20}H_{15}NO_5$: C 68.76, H 4.33, N 4.01; found: C 68.71, H 4.33, N 4.06.

2-[(1,2-Dihydro-5-hydroxy-1-methyl-4-oxopyridin-2-yl)methoxy]anthraquinone (**10g**). Yield: 83% (from **8l**). M.p. 212° (dec). ^{1}H-NMR (DMSO): 3.75 (br. *s*, OH); 4.08 (*s*, MeN); 5.61 (*s*, CH_2O); 7.47 (*s*, H–C(3′)); 7.63 (*dd*, *J* = 8.8, 2.6, H–C(3)); 7.83 (*d*, *J* = 2.6, H–C(1)); 7.94 (*m*, 2 arom. H); 8.22 (*m*, 3 arom. H); 8.32 (*s*, H–C(6′)). ^{13}C-NMR (DMSO): 43.05; 65.40; 107.09; 111.78; 112.99; 121.78; 127.02; 127.07; 127.71; 129.94; 133.07; 133.32; 134.62; 135.03; 135.46; 144.17; 145.07; 161.47; 162.05; 181.63; 182.55. Anal. calc. for $C_{21}H_{15}NO_5$: C 69.80, H 4.18, N 3.88; found: C 69.72, H 4.22, N 3.91.

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