Synthesis of Some Chromanone Derivatives and the Use of DNA in Evaluation of their Biological Activity

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6-Formyl-7-hydroxy-5-methoxy-2-pentamethylenechromanone (**2**) was prepared from the naturally occurring "Visnagin" and condensed with benzil, *o*-phenylenediamine and 3,4-diaminobenzophenone to give the corresponding imidazolylchromanone derivatives **3–5**. Knoevenagel reaction of compound **2** with different active methylene compounds afforded benzodipyranone derivatives **12a–c** which may be considered as analogues to the naturally occurring "Xanthyletin and Graveolone Compounds". The structural formula of the new compounds were established by using different methods for their preparation in addition to the instrumental analyses. Some compounds in this study were biologically evaluated for their ability to bind to DNA.

Introduction

Furochromones and related compounds are useful as protective against atherosclerosis [1–3]. Also, benzopyranones occur abundantly in plants and exhibit different biological and pharmacological activities *e.g.* spasmolytic, cytotoxic, antihepatotoxic and antidiabetic [4–7]. Furocoumarins and pyranocoumarin exhibit antifertility, antifungal, antibacterial and insecticidal activities [8–10]. In continuation of our research program for the synthesis of simple and fused furochromones [11–13]. This work deals with the synthesis and biological evaluation of series from furochromanones compounds.

Chemistry and Discussion

In the present work, the furochroman-4-one **1a** [12] was oxidized to give 6-formyl-7-hydroxy-5-methoxy-2-pentamethylenechroman-4-one (**2**) which was treated with benzil in acetic acid/ammonium acetate to give 6-(4′,5′-diphenyl-2′-imidazolyl)-7-hydroxy-5-methoxy-2-pentamethylene chroman-4-one (**3**). Compound **3** was established by elemental and spectral analyses and by using another method for its preparation *via* spirocyclization of compound **4** [13] with cyclohexanone (*cf.* Scheme 1).

Compound **2** was allowed to react with *o*-phenylenediamine or 3,4-diaminobenzophenone to give the corresponding benzimidazolyl chroman-4-one **5a** and **5b** respectively which were established by another method for their preparation as outlined in Scheme 2. When 6-formyl-7-hydroxy-5-methoxy-2-methylchrom-4-one (**6**) [14] was treated with *o*-phenylenediamine or 3,4-diaminobenzophenone, the corresponding benzimidazolyl chromones **8a,b** were obtained *via* the anils **7a,b**. Thereafter hydrolysis of **8** in alkaline medium to give **9a,b** which were spirocyclized using cyclohexanone to yield the desired products **5a** and **5b**.

Electrophilic substitution of compound **2** using bromine or nitric acid afforded the corresponding 8-bromo (or nitro) chroman-4-one derivatives **10a** and **10b**, respectively. Also, condensation of the above spirochroman-4-one **2** with hydroxylamine hydrochloride and different aromatic amines, (aniline, *p*-anisidine and *p*-nitroaniline) yielded a quantitive yield of the corresponding oxime and anil derivatives **11a–d**.

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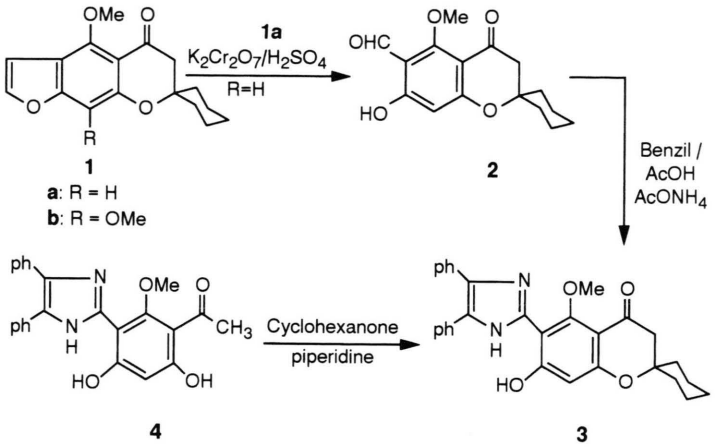


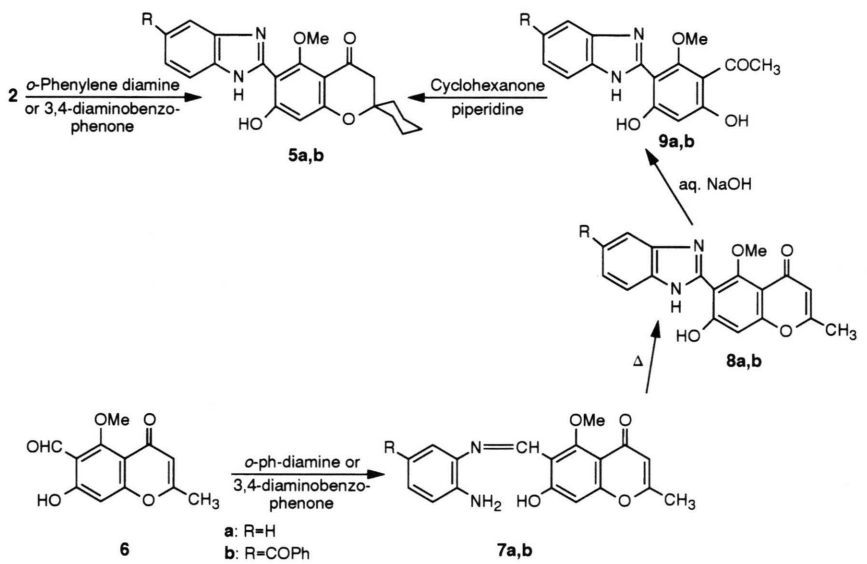
1
a: R = H
b: R = OMe

2

4

3

Scheme 1



5a,b

9a,b

8a,b

6

a: R=H
b: R=COPh

7a,b

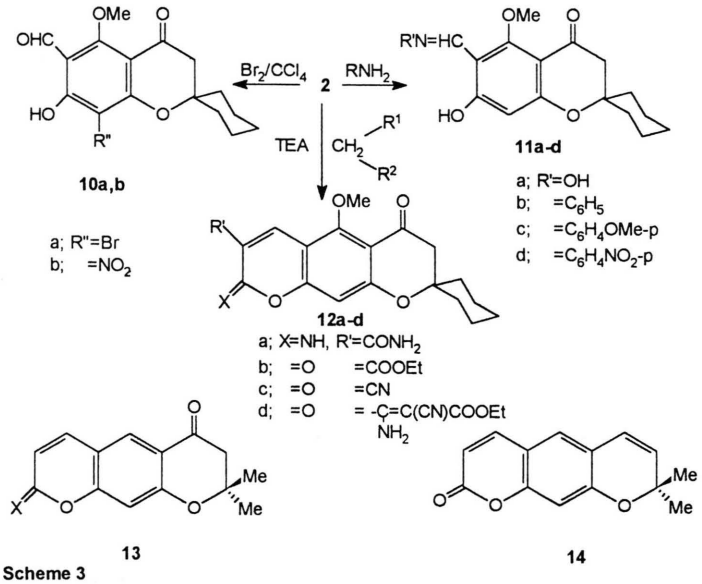
Scheme 2

Application of Knoevenagel reaction on 2-hydroxy aromatic aldehyde substituent **2** with active methylene compounds to give benzodipyran derivatives **12a–c** which may be considered as analogues to the naturally occurring Gravelone and Xathyletin Compounds **13** and **14** [15]. When **2** was condensed with one mole of cyanoacetamide or diethyl malonate, the corresponding Knoevenagel derivatives **12a** and **12b** were obtained. Also, at treatment **2** with two moles of ethyl cyanoacetate afforded 3-cyanocoumarin derivative **12c** which directly reacted with another molecule to give compound **12d**. The elemental and spectral analyses of **12a–d** were in agreement with their structural formula also, the mass spectra of **12a** and **12d** showed M^+ at m/z = 356 and 452 respectively.

Claisen condensation of compound **1a** or **1b** with diethyl carbonate or ethyl acetate allowed the isolation of compounds which possessed elemental analysis and spectral data concordant with the formation of benzofuran derivatives **17a–c** instead of

Table I. Characterization data of the newly prepared compounds.

Comp.	M.p. °C	Yield %	M. Formula	M. Weight	Analysis Calcd			Found		
					C	H	N	C	H	N
2	200	90	$C_{16}H_{18}O_5$	290.315	66.20	6.25	–	66.07	6.44	–
3	208–210	81	$C_{30}H_{28}N_2O_4$	480.56	74.98	5.87	5.83	74.71	5.69	5.58
5a	>300	65	$C_{22}H_{22}N_2O_4$	378.43	69.83	5.86	7.40	69.68	5.66	7.59
5b	270–273	70	$C_{29}H_{26}N_2O_5$	483.53	72.19	5.43	5.81	72.34	5.61	5.59
7a	262–263	–	$C_{18}H_{16}N_2O_4$	324.33	66.66	4.97	8.64	66.41	5.22	8.59
7b	280–282	–	$C_{25}H_{20}N_2O_5$	428.44	70.09	4.70	6.54	70.32	4.53	6.80
8a	>300	78	$C_{18}H_{14}N_2O_4$	322.32	67.08	4.38	8.69	66.91	4.51	8.44
8b	249–250	80	$C_{25}H_{18}N_2O_5$	426.43	70.42	4.25	6.57	70.63	4.09	6.33
9b	237–238	78	$C_{23}H_{18}N_2O_5$	402.41	68.65	4.51	6.96	68.48	4.74	7.18
10a	179–180	84	$C_{16}H_{17}O_5Br$	369.21	52.05	4.64	–	52.25	4.40	–
10b	118–120	92	$C_{16}H_{17}NO_7$	335.31	57.31	5.11	4.18	57.09	5.43	4.36
11a	185–186	83	$C_{16}H_{19}NO_5$	305.33	62.94	6.27	4.59	62.69	6.44	5.37
11b	110–112	87	$C_{22}H_{23}NO_4$	365.43	72.31	6.34	3.83	72.49	6.59	3.79
11c	190–192	92	$C_{23}H_{25}NO_5$	395.43	69.86	6.37	3.54	69.61	6.60	3.66
11d	137–138	86	$C_{22}H_{22}N_2O_6$	410.426	64.38	5.40	6.83	64.09	5.17	6.98
12a	220–222	80	$C_{19}H_{20}N_2O_5$	356.38	64.04	5.66	7.86	64.29	5.38	7.79
12b	230–233	83	$C_{21}H_{22}O_7$	386.40	65.28	5.74	–	65.50	5.59	–
12d	245–246	93	$C_{24}H_{24}N_2O_7$	452.46	63.71	5.35	6.19	63.92	5.54	6.41
17a	108–110	89	$C_{17}H_{18}O_4$	286.33	71.31	6.34	–	71.19	6.53	–
17b	172–174	79	$C_{18}H_{20}O_5$	316.35	68.34	6.37	–	68.52	6.07	–
17c	97–99	85	$C_{18}H_{20}O_4$	300.35	71.98	6.71	–	71.73	6.58	–



Scheme 3

compounds **15a–c**. Also, under the effect of ethoxide ion a methyl/ethyl exchange was occurred as reported from ^{1}H NMR of compound **17c** [16] (*cf.* Table II). The same product **17a** was obtained instead of compound **16** when compound **1a** was reacted with anisaldehyde in sodium ethoxide solution as inferred from the complete agreement of the spectral data and the rate of flow

in TLC [petroleum ether/ethyl acetate (4:1) R_f = 0.3]. ^{1}H NMR spectrum of compound **17a** showed a characteristic olefinic CH and exchangeable OH signals at δ = 5.4 and 13.1 ppm respectively in addition to disappearance of methylene protons at δ = 2.8 ppm.

Experimental

All melting points are uncorrected. The IR spectra were recorded (KBr) on a Mattson 5000 FTIR spectrometer. The ^{1}H NMR were recorded on a Varian-Gemini at 200 MHz and chemical shifts are expressed in ppm using TMS as the internal standard. Elemental analyses were carried out in the microanalytical unit, Faculty of Science, Mansoura and Cairo University. Thin layer chromatography (TLC): Merck-plates, silica gel 60 F_{254}, layer thickness 0.2 mm [Tables I and II show the characterization and spectral data of the newly prepared compounds].

The compounds **1a,b, 2, 4, 6** and **9** were prepared following a known procedures [12–14]. The characterization data of the new products of them are reported in Table I and II.

Preparation of 6-(4',5'-diphenylimidazol-2'-yl)-7-hydroxy-5-methoxy-2-pentamethylene chroman-4-one (**3**)

Method A: A mixture of aldehyde **2** (2.9 g, 10 mmol), benzil (2.1 g, 10 mmol) and ammonium acetate (2.3 g, 30 mmol) in glacial acetic acid (40 ml) was refluxed for 3 h. The formed precipitate was filtered, washed several times with water, dried and cystallized from ethanol to give compound **3**.

Method B: A mixture of compound **4** [13] (4.0 g, 10 mmol), cyclohexanone, (1.0 g, 1.0 ml, 10 mmol) and piperidine (1 ml) in toluene (50 ml) was boiled using Dean and Stark apparatus. The solvent was evaporated *in vacuo* after removing the calculated amount of water and the residue was collected, dried and crystallized from ethanol to give the same compound **3** [melting point and R_f = 0.37 (petroleum ether/ethyl acetate 8:1) are the same].

Preparation of 6-[(benzimidazol-2'-yl) and 5'-benzoylbenzimidazol-2'-yl)]-7-hydroxy-5-methoxy-2-pentamethylene chroman-4-one **5a** *and* **5b**

Method A: A mixture of compound **2** (2.9 g, 10 mmol) and *o*-phenylenediamine or 3,4-diaminobenzophenone (10 mmol) was refluxed in dry butanol (30 ml) for 8 h. After cooling the formed precipitate was filtered, dried and crystallized from ethanol to give compound **5a** and **5b** respectively.

Method B: Compounds **5a** and **5b** were also prepared from the compounds **9a** and **9b** following the procedure described above in preparation of compound **3** "Method B".

Condensation of compound **6** *with o-phenylenediamine or 3,4-diaminobenzophenone; preparation of compound* **7a,b** *and* **8a,b**

A mixture from compound **6** (2.3 g, 10 mmol) and *o*-phenylenediamine or 3,4-diaminobenzophenone (10 mmol) in butanol (30 ml) was boiled under reflux for 5 h. After cooling the formed precipitate was filtered dried and recrystallized from ethanol to give a yellow precipitate from compound **8a** and **8b**, respectively. Concentration of the mother liquor *in vacuo* and the residue was crystallized from ethanol to give yellow crystals from the corresponding anils **7a** and **7b**.

Preparation of 8-bromo (and 8-nitro)-6-formyl-7-hydroxy-5-methoxy-2-pentamethylene chroman-4-one **10a** *and* **10b**

Compound **10a:** To a solution of **2** (2.9 g, 10 mmol) in 20 ml chloroform was added dropwise a solution from [bromine (1.0 g, 0.3 ml, 12 mmol) in chloroform (10 ml)]. The reaction mixture was stirred at room temperature for 5 h and left to stand for 24 h. The formed precipitate was filtered and crystallized from ethanol to give pale yellow crystals of compound **10a**.

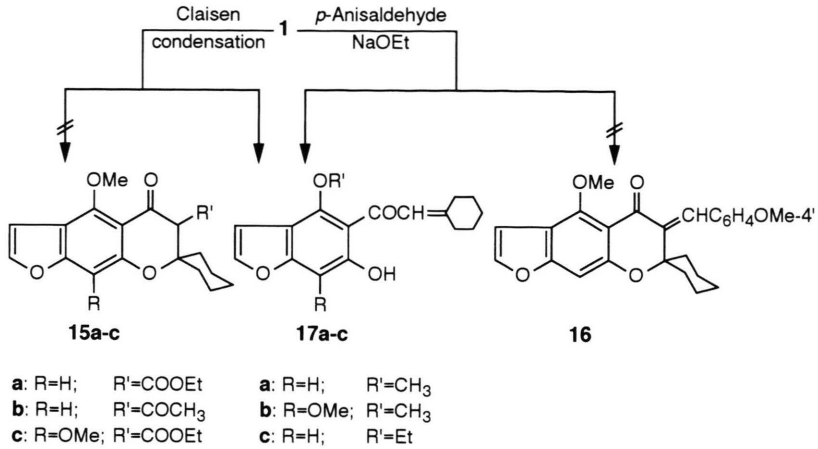
Compound **10b:** To a suspension of **2** (1 g) in glacial acetic acid (5 ml) was added a mixture of concentrated nitric acid (1 ml) and glacial acetic acid (2 ml). The reaction mixture was stirred at room temperature for 3 h then poured onto crushed ice (100 ml). The formed precipitate was filtered, dried and crystallized from ethanol to give yellow crystals of compound **10b**.

Preparation of compounds **11a–d**

General procedure: A mixture of compound **2** (5 mmol) and equimolar ratio of hydroxylamine hydrochloride or aniline or *p*-anisidine or *p*-nitro aniline in absolute ethanol (25 ml) was boiled for a time 3–5 h. After cooling the formed precipitate was filtered washed with water, dried and crystallized from ethanol to give colourless crystals of compound **11a** and yellow crystals of the corresponding anils **11b–d**.

Table II. Spectral data of the newly prepared compounds.

Comp.	Spectral data
2	IR: ν = 3518 (Free OH), 3480–3150 (bonded OH), 2931, 2850 (CH), 1675 (chromone C=O), 1660 (aldehyde C=O) and 1600 cm^{-1} (Ar).
3	IR: ν = 3427 (OH), 3325 (NH), 2932, 2856 (CH), 1675 (C=O), 1610 (C=N) and 1598 cm^{-1} (Ar). ^1H NMR ($CDCl_3$): δ = 1.2–2.1 (m, 10H 5×CH_2), 2.7 (s, 2H, CH_2) 4.0 (s, 3H, OMe), 6.5 (s, 1H, H-8), 7.3–7.6 (m, 10H, Ar-H) 10.5 (s, 1H, NH) and 13.6 ppm (s, 1H, OH).
5a	IR: ν = 3600–3100 (br. OH), 3365 (NH), 2928, 2850 (CH) 1660–1590 (br., C=N, C=O)
5b	IR: ν = 3600–3200 (br. OH), 3365 (NH), 2928, 2856 (CH), 1680–1600. (br., C=O and C=N). ^1H NMR ($CDCl_3$): δ = 1.5–2.1 (m, 10H, 5×CH_2), 2.7 (s, 2H, $COCH_2$), 4.0 (s, 3H, OMe), 6.5 (s, 1H, H-8) and 7.4–8.1 ppm (m, 9H, Ar-H).
7a	IR: υ = 3344, 3281 (NH_2), 3069 (OH), 3600–3180 (br. bonded OH), 1640 (C=O), 1605 (C=N) and 1590 cm^{-1} (Ar). ^1H NMR ($CDCl_3$): δ = 1.8 (s, 2H, NH_2), 2.3 (s, 3H, CH_3), 4.0 (s, 3H, OMe) 6.0 (s, 1H, H-3), 6.7 (s, 1H, H-8), 7.2–7.5 (m, 4H, Ar-H), 9.1 (s, 1H, C*H*=N) and 14.5 ppm (s, 1H, OH).
7b	IR: υ = 3346, 3285 (NH_2), 3063 (free OH), 3600–3100 (br. bonded OH), 1638 (br., two –(C=O), 1607 (C=N) and 1590 cm^{-1} (Ar). ^1H NMR (DMSO): δ = 2.25 (s, 3H, OMe), 3.55 (s, 2H, NH_2), 3.93 (s, 3H, OMe) 5.8 (s, 1H, H-3, 6.4 (s, 1H, H-8), 7.2–7.6 (m, 8H, Ar-H) and 10.5 ppm (br. s, 1H, OH).
8a	IR: υ = 3600–3100 (br. OH), 3360 (NH), 1651 (C=O) and 1600–1550 cm^{-1} (br. C=N and Ar). ^1H NMR ($CDCl_3$): δ = 2.3 (s, 3H, CH_3), 4.1 (3H, OMe), 6.1 (s, 1H, H-3) 6.8 (s, 1H, H-8), 7.3–7.8 (m, 5H, ArH and OH) and 10.8 ppm (s, 1H, NH).
8b	IR: υ = 3600–3150 (OH), 3343 (NH), 2924 (CH), 1655 (C=O, chromone), 1629 (ph C=O) and 1595 cm^{-1} (Ar). ^1H NMR ($CDCl_3$): δ = 2.3 (s, 3H, CH_3), 4.1 (s, 3H, OMe), 6.0 (s, 1H, H-3), 6.8 (s, 1H, H-8), 7.4–7.9 (m, 8H, Ar-H), 8.2 (s, 1H, NH) and 11.1 ppm (d, 1H, OH).
9b	IR: υ = 3370 (NH), 2918 (CH) and 1670–1560 cm^{-1} (br., C=O and C=N). ^1H NMR (DMSO): δ = 2.51 (s, 3H, $COCH_3$), 3.84 (s, 3H, OMe) 6.36 (s, 1H, Ar-H), 7.57–7.86 (m, 7H, Ar-H), 8.09 (s, 1H, Ar-H), 12.04 (s, 1H, NH) and 13.6 (s, br. 2H two OH).
10a	IR: υ = 3650–3100 (br. bonded OH), 2933, 2862 (CH), 1707 (C=O, chromone), 1645 (C=O, aldehyde) and 1569 cm^{-1} (Ar).
10b	IR: υ = 3650–3150 (br. bonded OH), 2936, 2861 (CH), 1686 (C=O chromone), 1638 (C=O aldehyde), and 1581 cm^{-1} (Ar). ^1H NMR (DMSO): δ = 1.4–2.1 (m, 10H, five CH_2), 2.7 (s, 2H, CH_2) 4.0 (s, 3H, OMe), 10.1 (s, 1H, CHO) and 12.3 (s, 1H, OH).
11a	IR: υ = 3550–3250 (br. OH), 2926 (CH), 1661 (C=O) 1609 (C=N) and 1590 cm^{-1} Ar.
11b	IR: υ = 3600–3300 (br. bonded OH), 2936, 2856 (CH), 1674 (C=O, chromone), 1612 (C=N) and 1583 cm^{-1} (Ar). ^1H NMR ($CDCl_3$): δ = 1.4–2.1 (m, 10H five CH_2), 2.7 (s, 2H, CH_2) 3.95 (s, 3H, OMe), 6.31 (s, 1H, H-8), 7.3–7.5 (m, 5H, Ar-H) 8.96 (s, 1H, C*H*=N), 15.3 (s, 1H, OH).
11c	IR: υ = 2936, 2858 (CH), 1676 (C=O), 1613 (C=N) and 1591 cm^{-1} (Ar). ^1HNMR ($CDCl_3$): δ = 1.2–2.2 (m, 10H, five CH_2), 2.6 (s, 2H, $COCH_2$) 3.8 (s, 3H, OMe), 3.9 (s, 3H, OMe), 6.3 (s, 1H, H-8), 6.9 (d, 2H, Ar-H), 7.2 (d, 2H, Ar-H), 8.8 (s, 1H, CH=N) and 15.5 ppm (s, br., OH).
11d	IR: υ = 3600–3350 (br. OH), 2932, 2856 (CH), 1676 (C=O) and 1620–1591 cm^{-1} (br., C=N) and Ar).
12a	IR: υ = 3422, 3300, 3155 (NH_2), 2939, 2860 (CH), 1682 (C=O) and 1600–1590 cm^{-1} (br., C=N and Ar). ^1H NMR ($CDCl_3$): δ = 1.5–2.1 (m, 10H, five CH_2), 2.7 (s, 2H, H-3), 3.7 (s, 3H, OMe), 5.7 (s, 1H, HN=), 6.4 (s, 1H, H-10), 7.6 (s, 1H, H-6), 8.7, 8.9 ppm (2H, $CONH_2$). MS: M^+ at *m/z* = 357; M_1 at *m/z* = 313 from [M–$HCONH_2$].
12b	IR: υ = 3580–3200 (br., OH), 2934, 2860 (CH), 1726 (COOEt) 1700, 1678 (C=O, lactone) and 1603 cm^{-1} (Ar).
12d	IR: υ = 3373, 3267, 3203 (NH_2), 2928, 2850 (CH), 2211 (C≡N), 1738 (COOEt), 1700, 1680 (C=O, lactone) and 1574 cm^{-1} (Ar). ^1H NMR ($CDCl_3$): δ = 1.3 (t, 3H, C*H*$_3$$CH_2$), 1.5–2.1 (m, 10H, five CH_2) 2.75 (s, 2H, H-3), 4.0 (s, 3H, OMe), 4.3 (q, 2H, CH_3C*H*$_2$) 6.6 (s, 1H, H-10), 6.9 (s, 1H, H-6) and 8.6, 9.6 ppm (2H, NH_2). MS: M^+ at *m/z* = 453; M^1 at *m/z* = 410 [M–CO_2].
17a	IR: υ = 3600–3300 (br. OH), 1670 (C=O), 1626 (C=C) and 1586 cm^{-1} (Ar). ^1H NMR ($CDCl_3$): δ = 1.5–2.1 (m, 10H, five CH_2), 4.2 (s, 3H, OMe), 5.4 (s, 1H, COC*H*=C_6H_{10}), 6.7 (s, 1H, H-7), 6.8 (d, 1H, H-3, *J* = 2.7 Hz), 7.4 (d, 1H, H-2, *J* = 2.7 Hz) and 13.1 ppm (s, 1H, OH which disappeared when D_2O was added). MS: M^+ at *m/z* = 286.2, M^1 (base peak) at *m/z* = 191 [M^+–C_7H_{10}] and M^2 at *m/z* = 176 [M^1–O·].
17c	IR: υ = 2925, 2844 (CH), 1670 (C=O), 1622 (C=C) and 1582 (Ar). ^1H NMR ($CDCl_3$): δ = 1.5 (t, 3H, C*H*$_3$$CH_2$), 1.55–2.1 (m, 10H five CH_2), 4.5 (q, 2H, CH_3C*H*$_2$), 5.45 (s, 1H, COC*H*=C_6H_{10}) 6.7 (s, 1H, H-7), 6.8 (d, 1H, H-3, *J* = 2.7 Hz), 7.4 (d, 1H, H-2, *J* = 2.7 Hz) and 13.0 ppm (s, 1H, OH). MS: M^+ at *m/z* = 300.3; M^1 at *m/z* = 205 [M^+–C_7H_{10}] and M^2 at *m/z* = 177 (base peak) [M^1–CO].
17b	^1H NMR ($CDCl_3$): δ = 1.6–2.3 (m, 10H, five CH_2), 4.17 (s, 3H, OMe), 4.23 (s, 3H, OMe), 5.84 (1H, COCH=C_6H_{10}), 6.93 (d, 1H, H-3, *J* = 2.7 Hz), 7.66 (d, 1H, H-2, *J* = 2.7 Hz) and 10.8 ppm (1H, OH).



Scheme 4

Reaction of compound **2** *with active methylene compounds: preparation of compounds* **12a,b,d**

To a solution of compound **2** (1.7 g, 6 mmol) and cyanoacetamide or diethyl malonate (8 mmol) or ethyl cyanoacetate (15 mmol) in absolute ethanol (30 ml) a few drops of triethyl amine was added. The reaction mixture was heated for a time from 4–6 h. The colourless crystals that formed after cooling was filtered and crystallized from ethanol to give the corresponding benzodipyran derivatives **12a,b,d.**

Preparation of benzofuran derivatives **17a–c**. *General procedure*

Method A: A solution of **1a** or **1b** (1 g) in diethylcarbonate (10 ml) was slowly added to powdered sodium metal (1 g). When the initial vigorous reaction subsided, the reaction mixture was refluxed for 5 h then left to cool. Ethanol (10 ml) was added to destroy any excess of sodium metal. The reaction mixture was poured on water then acidified with dilute hydrochloric acid and the solid that separated was crystallized from ethanol to give compound **17a** and **17b**, respectively.

N.B.: Compound **17c** was prepared from **1a** and ethylacetate following the same procedure.

Method B: To a mixture of compound **1a** (2 g, 7 mmol) and *p*-anisaldehyde (1.36 g, 10 mmol) in ethanol (30 ml) was dropwise added sodium ethoxide solution (1 g sodium/absolute ethanol 10 ml) at room temperature with stirring. Stirring was continued for 5 h then left at the same temperature overnight. The reaction mixture was poured in crushed ice (100 g) then neutralized with dilute hydrochloric acid. The precipitate that formed was filtered, washed with water, dried and crystallized from ethanol to give the same product **17a** [m.p. and R_f (petroleum ether/ethyl acetate 7:3) are the same].

DNA-binding assay

The mechanism of several known antitumor agents involves interaction with DNA. Examples include agents (*e.g.* chlorabucil, cyclophosphamide, melphalan, streptozocin), antitumor antibiotics (*e.g.* bleomycin, doxorubicin, mithramycin) [17–20]. Some of the new compounds were screened towards the affinity to DNA-binding using a colorimetric assay [21]. Compound **12a** showed the highest affinity, compound **2** followed by compound **10b** are the most inactive while the compounds **7a, 8a, 9b, 10a, 11b,c** and **12d** are equally active but less than **12a**.

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