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Synthesis and Reactions of Some New Substituted Spirofurochromanone Derivatives

El-Sayed I. El-Desoky[*], *Mahmoud A. Hammad*[**], *Nabil Grant*[**], *Emad M. El-Telbany*[**] *and Abdel Rahman H. Abdel-Rahman*[*]

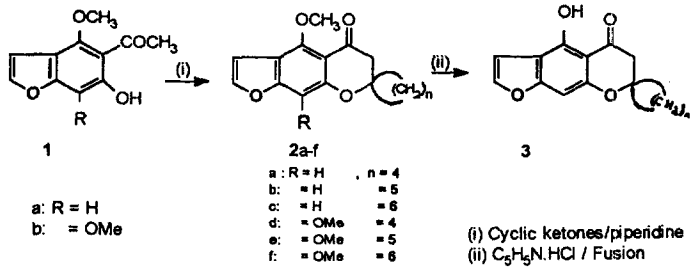
[*] Faculty of Science, Chemistry Department., Mansoura University, EGYPT

[**] National Research Centre, Dokki, Giza, Cairo, EGYPT

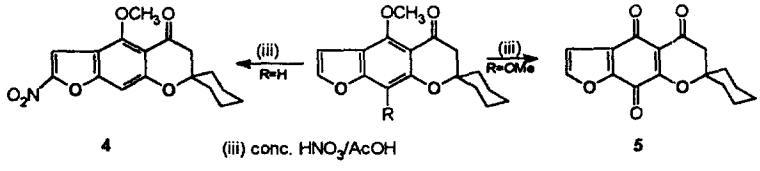
Abstract: Condensation of different cyclic ketones with visnaginone **1a** and khellinone **1b** afforded spirofurochromanone derivatives **2a-f**. Compounds **2a** and **2b** were readily demethylated to give the compounds **3a** and **3b**. Nitration of **2b** and **2e** gave the nitrofurochromonone and quinone derivatives **4** and **5** respectively. The chroman-4-ol derivatives **6a** and **6b** were obtained from reduction of **2b** and **2e** which were directly dehydrated to give compounds **7a** and **7b** respectively. Also, amide **6c** was prepared which failed to provide **6d** on acid hydrolysis. Bromination of the chromene **7a** gave the corresponding 9-bromo derivative **7c** and failed to give compound **8**. Treatment of **2b** with NBS afforded the corresponding 2,9-dibromo derivative **10**. The chromanones **2b** and **2e** were reacted with hydroxylamine, phenyl hydrazine, aniline and paraformaldehyde to give the products **11a-e** and **12a,b**.

As early as 2270 B.C. The ancient Egyptians were using "Mem" (hieroglyphic name of a common annual herbaceous plant Ammi visnaga) as antispasmodics for the relief of spasms of the ureter, bile duct, gall bladder, renal colic and bronchial asthma and also as potent coronary vasodilator.[1,2] Furochromone derivatives (the essential constituent of Ammi visnaga) possess desirable lipid altering activity for example decreasing the atherogenic cholesterol fraction, elevating antiatherogenic HDL cholesterol fraction and antiatherosclerotic activity.[3-5] 2,3-dihydro-2-phenyl-4H-1-benzopyran-4-one occurs abundantly in plants and exhibit various biological activities e.g. spasmolytic, cytotoxic, antihepatotoxic and antidiabetic.[6,7] Thus this high pharmacological importance of furochromanones prompted us to investigate the synthesis of some new derivatives with possible biologically activity.

Spirocyclization of visnaginone (1a) and khellinone (1b) with cyclopentanone, cyclohexanone and cycloheptanone afforded the corresponding 7-tetra(penta and hexa) methylenefuro[3,2 g]-1-chromanones 2a-f in quantitative yields. The spectral data were compatible with the assigned structures. The infra-red spectra showed the chromone keto group at 1670 cm^{-1} and the ^1H NMR spectra showed a characteristic singlet peak in the region δ2.7-2.8 for -$COCH_2$-. Demethylation of the compounds 2b and 2c using pyridinum chloride afforded the corresponding 4-hydroxyfurochromanone derivatives 3a and 3b which gaves a violet colour with ferric chloride solution. The infrared spectra showed a broad absorption band for the OH group at 3300-3500 cm^{-1}, while the absorption band of C=O appeared at a lower value (1660 cm^{-1}) due to intramolecular hydrogen bonding.

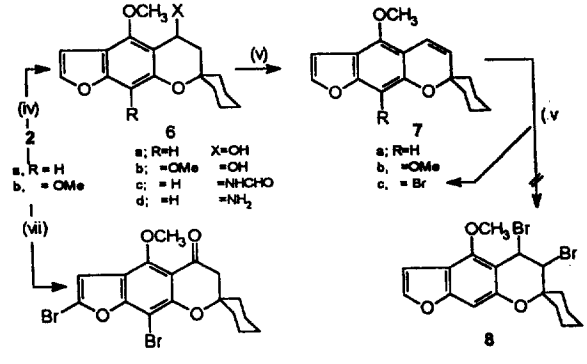


Whereas nitration of 4-methoxy-7-methyl-5H-furo[3,2-g][1]-benzopyran-5-one (visnagin) -5-one (visnagin) with nitric acid reported by C-9 (in the benzene ring), in the present work treatment of 2b with nitric acid, the nitro group entered the 2-position of the furan ring. The resulting 4-methoxy-2-nitro-7-pentamethylene furo [3,2-g]-1-chroman-5-on 4a showed in the ^1H NMR spectrum a singlet proton at δ 6.83 characteristic for H-9, the absence of the two one proton doublets for the furan protons and instead a new singlet at δ 7.88. In contrast, 2e gave the corresponding quinone derivative 5[1], the absence of the two methoxy singlets in the ^1H NMR supports the quinone structure.



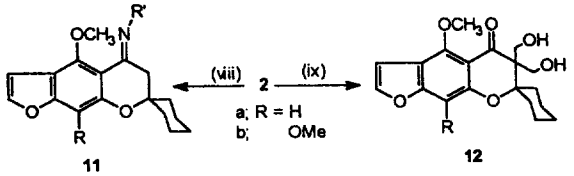
Reduction of 2b or 2e using sodium borohydride afforded the corresponding spirofurochroman-5-ols 6a and 6b which readily dehydrated to give the known antijuvenile hormone[8,9] analogues 4-methoxy (and 4,9-dimethoxy)-7-pentamethylene-7H-furo [3,2-g]- chromen (7a) and (7b). Also, N-chromanylformamide derivative 6c which was prepared from reaction of 2b with formic acid/formamide mixture failed to undergo acid hydrolysis to give spirofurochroman-5-amine 6d. Reaction of the

chromene **7a** with bromine failed to give compound **8** and instead, 9-bromo-4-methoxy-7-pentamethylene furo[3,2-g]chromen (**7c**) was obtained. The infra-red spectra of the compounds **6a-d** and **7a,b** showed the absence of γ-chromanone keto group in the parent derivatives and the ^1H NMR of the chromene **7b** revealed the presence two one proton doublets at δ5.68 and 6.73 (J=12.5 Hz). Another extension work will be carried out on the chromone derivatives **7** with biological activity study in the future.



(iv) $NaBH_4$ or $HCHO/HCONH_2$ (vi) $Br_2/CHCl_3$
(v) *p*-Toluene sulphonic acid (vii) $NBS/CHCl_3$

Treatment of **2b** with N-bromosuccinimide, compound 6-bromo-4-methoxy-7-pentamethylenefuro[3,2-g]chroman-5-one (**9**) was not obtained but instead 2,9-dibromo furochromanone derivative **10** was obtained. Condensation of **2b** and **2e** with hydroxylamine hydrochloride, phenylhydrazine, aniline and paraformaldehyde afforded the corresponding oxime, phenylhydrazone, anil and chroman-6,6-dimethanol derivatives **11a-e** and **12a,b**. The infrared spectra of the above derivatives **11a-e** showed the absorption band of the C=N at 1610-1625 cm^{-}



a; R=H , R'=OH
b; =H =NHPh
c; =OMe =CH
d; =OMe =NHPh
e; =OMe =Ph

a, R = H
b, = OMe

(viii) $R'NH_2$ (ix) HCHO/DMSO

Experimental

All melting points are uncorrected. The IR spectra were recorded (KBr) on a MATTSON 5000 FTIR spectrometer. The ^1H NMR was recorded on a Varian - Gemini at 200 MHz and chemical shifts are expressed in ppm using TMS as the internal standard and $CDCl_3$ as solvent. Elemental analyses were carried out in the Microanalytical Unit, Faculty of Science, Mansoura and Cairo University. Thin Layer Chromatography (TLC): Merck Plates, Silica gel $60F_{254}$, layer thickness 0.2 mm. Tables 1 and 2 show the characterization and spectral data of the newly prepared compounds.

Preparation of Spirodihydrofurochromanones: 2a-f General Procedure A mixture of visnaginone **1a** or khellinone b[10a,b] (10 mmol), the appropriate cyclic ketone (10 mmol) and 1 ml of piperidine in toluene (100 ml) heated at reflux using Dean-Stark apparatus for 3-5 hrs. The solvent was evaporated under vacuum and the residue was collected, dried and crystallized from ethanol to give colourless crystals of the corresponding chromanones **2a-f**.

Preparation of 4-hydroxy-7-penta (and hexa) methylene furo[3,2-g]-chroman-5-ones] 3a and 3b A mixture of compound **2b** or **2c** (1 g) and freshly prepared pyridinium chloride (2 g) were heated at temperature of 160°C for 1 hr. The viscous mixture was left to cool, then decomposed with dilute hydrochloric acid. The solid formed was filtered off, washed with water, dried and crystallized from ethanol to give a colourless crystals of compound **3a** and **b**.

Reaction of compound 2b and 2e with nitric acid. Preparation of compounds 4 and 5 A solution of nitric acid (12 mmol) dissolved in acetic acid (5 ml) was added dropwise to a solution of compound **2b** or **2e** (10 mmol) in acetic acid (20 ml) with stirring at room temperature during 30 min. The reaction mixture was stirred at 40°C for 1h, cooled and poured into crushed ice. The precipitate which formed was filtered off, washed with water, dried and crystallized from ethanol to give compound **4** as yellow crystals and compound **5** as red crystals.

Preparation of 4-methoxy(and 4,9-dimethoxy)7-pentamethylenefuro [3,2-g]chroman-5-ol 6a and 6b. Sodium borohydride (0.5 g, 13 mmol) was added portionwise during 30 min to a solution of compound **2b** or **2e** (10 mmol) in absolute ethanol (50 ml) with stirring at room temperature. Stirring was continued for 3 hrs then the mixture was poured into crushed ice. The organic product was extracted using ether (3x50 ml), dried ($MgSO_4$), evaporated in vacuo and crystallized from diluted ethanol (1:1) to give a colourless crystals from compound **6a** and **6b**.

Reaction of compound 2b with formamide: synthesis of compound 6c. A solution of 2.86 g (10 mmol) of **2b** in 10 ml of 90% formic acid and 25 ml of formamide was heated at the reflux temperature for 10 hrs. Dilution with water gave a crude yellow product. Recrystallization from ethanol gave yellow crystals of compound **6c**.

Synthesis of 4-methoxy(and 4,9-dimethoxy)-7-pentamethylene-7H-furo[3,2-g]chromen 7a and 7b. To a solution of chromen-5-ol **6a** or **6b** (10 mmol) in dry benzene (50 ml), p-toluene sulphonic acid (0.1 g) was added and heated at reflux using Dean-Stark apparatus for 1 hr, cooled to room temperature, washed with $NaHCO_3$ solution. The organic layer was separated, dried ($MgSO_4$), evaporated under vacuum and the residue was crystallized from benzene/petroleum ether (1:1) to give colourless crystals of compound **7a** and **7b**.

Table 1. Characterization data of the newly prepared compounds.

Comp No.	M.P. °C	Yield %	Analysis			
			Calcd.		Found	
			C	H	C	H
2a	86-88	90	70.57	5.92	70.41	5.81
2b	133-135	95	71.31	6.31	71.44	6.18
2c	112-113	80	71.98	6.71	71.87	6.54
2d	98-100	91	67.54	6.00	67.32	6.19
2e	100-101	96	68.34	6.37	68.51	6.09
2f	83.84	85	69.07	6.71	69.33	6.52
3a	108-109	84	70.58	5.92	70.40	5.65
3b	210-212	89	71.31	6.34	71.53	6.13
4	184-186	87	61.63	5.17	61.49	5.01
5	198-200	95	67.13	4.93	67.31	4.76
6a	70-72	88	70.81	6.99	70.62	6.73
6b	116-117	85	67.91	6.96	67.70	6.63
6c	148-150	79	68.55	6.71	68.22	6.53
7a	98-100	96	75-53	6.71	75.66	6.96
7b	58-60	93	71.98	6.71	71.79	6.93
7c	260-262	80	58.46	4.91	58.63	4.67
10	109-110	88	45.98	3.63	45.73	3.89
11a	220-222	83	67.76	6.35	67.41	6.12
11b	118-120	93	73.38	6.43	73.55	6.51
11c	188-190	78	65.24	6.39	65.41	6.17
11d	94-95	90	70.92	6.45	70.75	6.30
11e	160-161	85	76.43	6.41	76.70	6.28
12a	216-218	75	65.88	6.40	65.71	6.58
12b	230-231	80	63.82	6.43	63.69	6.58

Table 2. Spectral data of the newly prepared compounds.

Comp No.	Spectral data
2a	**IR:** ν=1677(C=O) and 1618 cm^{-1} (Ar.). **^{1}H NMR:** δ = 1.2-2.1(m, 8H, 4xCH_2), 2.8(s,2H,6-H), 4.1(s,3H,OMe), 6.7(s,1H,9-H), 6.9(d,1H,3-H, J=2.7 Hz) and 7.4 ppm(d, 1H,2-H, J=2.7 Hz
2b	**IR:** ν=1673(C=O) and 1610 cm^{-1} (Ar.). **^{1}H NMR:** δ = 1.2-2.0(m,10H, 5xCH_2), 2.65(s,2H,6-H), 4.1(s,3H,OMe), 6.75(s,1H,H,9-H), 6.85(d,1H,H-3, J=2.7 Hz) and 7.4 ppm(d,1H,H-2,J=2.7 Hz) **MS:** m/e = 286[M^+], 244[M-oxirene]
2c	**IR:** ν= 1675(C=O) and 1612 cm^{-1} (Ar.). **^{1}HNMR:** δ=1.35-2.11(m,12H, 6x CH_2), 2.71(s, 2H, 6-H), 4.1(s, 3H, OMe), 6.75(s, 1H, H-9), 6.9(d, 1H, H-3, J=2.7 Hz) and 7.42 ppm (d, 1H, H-2, J=2.7 Hz)
2d	**IR:** ν=1683(C=O) and 1612 cm^{-1} (Ar.). **^{1}HNMR:** δ = 1.0-2.0(m, 8H, 4x CH_2), 2.18(s, 2H,6-H), 3.85(s, 3H, OMe), 3.95(s, 3H, OMe), 7.1(d, 1H, H-3, J=2.7 Hz) and 7.9 ppm (d, 1H, H-2, J=2.7Hz).
2e	**IR:** ν = 1685(C=O) and 1619 cm^{-1} (Ar.) **^{1}HNMR:** δ = 1.3-2.1(m, 10H, 5x CH_2), 2.7(s, 2H, H-6), 4.04(s, 3H, MeO), 4.05(s,3H, MeO), 6.81(d, 1H, H-3, J=2.7 Hz) and 7.43 ppm (d, 1H, H-2, J=2.7 Hz).
2f	**IR:** ν = 1685(C=O) and 1619 cm^{-1} (Ar.) **^{1}H NMR**: δ=1.35-2.15(m,12H,6xCH_2), 2.65(s,2H,6-H), 3.95(s,3H,OMe), 4.01(s, 3H, OMe), 6.85(d,1H,H-z,J=2.7 Hz) and 7.45 ppm(d, 1H,H=--2, J=2.7 Hz).
3a	**IR:** ν = 2060-3170(CH), 3320-3170(br.OH) and 1660-1580 cm^{-1} (br.C=O, Ar.) **^{1}HNMR:** δ = 1.2-2.8(m, 10H, 5x CH_2), 2.7(s, 2H, $COCH_2$), 6.55(s, 1H, Ar.-H), 6.8(d, 1H, H-3, J=2.7 Hz), 7.4(d, 1H, H-2, J=2.7 Hz) and 12.7 ppm (s, br.OH which disappeared after addition D_2O).
3b	**IR:** ν = 3550-3300(br. OH), 3000-2800(CH), 1610(C=O) and 1600 cm^{-1} (Ar.) **^{1}H NMR:** δ=1.3-2.1(m,12H,6xCH_2), 2.7(s,2H,$COCH_2$), 4.1(s, 3H, OMe), 4.15(s, 3H, OMe), 6.84(d, 1H, H-3, J = 2.7 Hz), 7.4(d, 1H, H-2, J = 2.7 Hz) and 12.4 (s, br. OH)
4	**IR:** ν = 3100, 2935(CH), 1683(C=O) 1616, 1574 (Ar.) and 1514 cm^{-1} (NO_2). **^{1}HNMR:** δ = 1.49-1.99(m, 10H, 5x CH_2), 2.73(s, 2H,$COCH_2$), 4.26(s, 3H,OCH_3), 6.83(s, 1H,H-9) and 7.88 ppm (s, 1H, H-3).
5	**IR:** ν = 3160, 3140, 2940(CH), 1705, 1695(quinone), C=O) and 1590 cm^{-1} (Ar.) **^{1}HNMR:** δ = 1.27-2.10(m, 10H, 5x CH_2), 2.69(s, 2H, $COCH_2$), 6.89(d, 1H, H-3, J=2.7 Hz) and 7.76 ppm(d, 1H, H-2, J=2.7 Hz).
6a	**IR:** ν = 3600-3200(br., OH), 1624(Ar.) **^{1}HNMR:** δ = 1.32-1.81(m, 10H, 5xCH_2), 2.04(dd, 2H, 6-H), 3.4(s, 1H, OH), 4.05(s, 3H, OMe), 5.15(t, 1H, 5-H), 6.72(s, 1H, 9-H), 6.81(d, 1H, H-3, J = 2.7Hz) and 7.4 ppm (d, 1H, H-2, J = 2.7 Hz.
6b	**IR:** ν = 3576(free OH), 3600-3250(br.OH), 3159(CH) and 1626 cm^{-1} (Ar.) **^{1}H NMR:** δ=1.3-1.9(m,10H, 5xCH_2), 2.05(dd,2H,6-H), 3.4(s,1H,OH), 4.0(s,3H,OMe), 4.1(s,3H,OMe), 5.1(t,1H,5-H), 6.7(d,1H,3-H,J=2.7 Hz) and 7.4 ppm(d,1H,2-H - J = 2.7 Hz) **MS:** m/e = 318[M^+]
6c	**IR:** ν = 3600-3300(br. amide NH), 2931, 2857(CH), 1732(C=O) and 1625 cm^{-1} (Ar.) **^{1}HNMR:** δ = 1.38-1.89(m, 10H, 5xCH_2), 2.1(dd, 2H, 6-H), 4.1(s, 3H, OMe), 5.22(t, 1H, 5-H), 6.7(s, 1H, 9-H), 6.8(d, 1H, H-3, J = 27 Hz), 7.42(d, 1H, H-2, J = 2.7 Hz and 11.2 ppm(s, br. 2H, NH and CHO).
7a	**IR:** ν = 1626(C=C) and 1594 cm^{-1} (Ar.) **^{1}HNMR:** δ = 1.3-1.9(m, 10H, 5xCH_2), 4.1(s, 3H, OMe), 5.7(d, 1H, H-5, J = 12.2 Hz), 6.6(d, 1H, H-6, J = 12.2 Hz), 6.73(s, 1H, H-9), 6.82(d, 1H, H-3, J = 2.7 Hz) and 7.45 ppm (d, 1H, H-2, J = 2.7 Hz).

Table 2. Spectral data of the newly prepared compounds (Continued).

Comp No.	Spectral data
7b	**IR:** ν = 1625(C=C) and 1594 cm^{-1} (Ar.) **^{1}HNMR:** δ = 1.25-1.92(m, 10H, 5x CH_2), 3.99, (s, 3H, OMe), 4.06(s, 3H, OCH_3), 5.68(d, 1H, H-5, J=12.5Hz), 6.73(d, 1H, H-6, J=12.5Hz), 6.8(d, 1H, H-3, J=2.7 Hz) and 7.46 ppm (d, 1H, H-2, J=2.7 Hz).
7c	**IR:** ν = 1620(C=C) and 1590 cm^{-1} (Ar.) **^{1}HNMR:** δ = 1.31-1.84(m, 10H, 5xCH_2), 4.0(s, 3H, OMe), 5.7(d, 1H, H-5, J = 12.2 Hz), 6.79(d, 1H, H=3, j = 2.7 Hz) and 7.4 ppm(d, 1H, H-2, J = 2.7 Hz.)
10	**IR:** ν = 3030, 2931(CH), 1678(C=O) and 1616, 1578 cm^{-1} (Ar.) **^{1}HNMR:** δ = 1.2-2.0(m,10H, 5x, CH_2), 2.7(s, 2H, $COCH_2$), 4.08(s, 3H, OCH_3 and 6.94 ppm (s, 1H, H-9)
11a	**IR:** ν = 3600-3400(br.OH), 1612(C=N), and 1581 cm^{-1} (Ar.) **^{1}HNMR:** δ = 1.41-1.80(m, 10H, 5x CH_2), 2.83(s, 2H, $COCH_2$), 3.93(s, 3H, OCH_3), 6.86(s, 1H, H-9), 7.57(d, 1H, H-3, J=2.7 Hz), 7.82(d, 1H, H-2, J=2.7 Hz) and 11.22 ppm (s, 1H,OH)
11b	**IR:** ν = 3450(NH), 1620(C=N) and 1588 cm^{-1} (Ar.) **^{1}H NMR:** δ=1.2-2.1(m,10H,5xCH_2), 2.7(s,2H,6-H), 3.7(s,1H,NH)_, 4.1(s,3H,OMe) and 6.75-7.5 ppm(m,8H,Ar-H).
11c	**IR:** ν = 3500-3100(br.OH) and 1621 cm^{-1} (C=N) **^{1}H NMR:** δ=1.3-2.0(m,10H, 5xCH_2), 3.0(s,2H,6-H, 3.98(s,3H,OMe), 4.02(s,3H,OMe), 6.85(d,1H,H-3, J=2.7 Hz,J=27 Hz) and 7.45 ppm(d,1H,H-z, J=2.7 Hz)
11d	**IR:** ν = 3457(NH) and 1625 cm^{-1} (C=N) **^{1}H NMR:** δ=1.3-2.1(m,10H,5xCH_2), 2.7(s,2H,6-H), 3.9(s,1H,NH), 4.1(s,3H,OMe), 4.2(s,3H,OMe) and 6.9-7.6 ppm (m,7H,Ar-H)
11e	**IR:** ν = 1609(C=N) and 1588 (Ar.) **^{1}HNMR:** δ = 1.3-2.2(m, 10H, 5xCH_2), 2.7(s, 2H, 6-H), 4.1(s, 3H, OMe), 4.2(s, 3H, OMe) and 6.7-7.4 ppm(7H, Ar-H).
12a	**IR:** ν = 3600-3300(br.OH), 3300-2855(CH_2), 1682(C=O) and 1615 cm^{-1} (Ar.) **^{1}HNMR:** δ = 1.2-2.8(m, 10H, 5xCH_2), 2.83(bs, 2H, 2xOH), 3.42(m, 4H, 2xCH_2OH), 4.0(s, 3H, OMe), 6.71(s, 1H, H-9), 6.8(d, 1H, H-3, J = 2.7 Hz) and 7.48 ppm(d, 1H, H-2, J = 2.7 Hz)
12b	**IR:** ν = 3700, 3600 (Free OH), 3580-3300(br, OH), 3120, 2933, 2859(CH), 1679(C=O), 1614, 1547 (Ar.) **^{1}HNMR:** δ = 1.18-2.70(m, 10H, 5x CH_2), 2.8(bs, 2H, 2x OH), 3.47(m, 4H, 2x CH_2), 3.98(s, 3H, OCH_3), 4.06(s, 3H, OCH_3), 6.76(d, 1H, H-3, J=2.7 Hz) and 7.44(d, 1H, 2.7 Hz)

Preparation of 9-bromo-4-methoxy-7-pentamethylene furo[3,2-g] chromen (7c). A solution of bromine (2 g, 12 mmol) in chloroform (10 ml) was added dropwisely to a solution of the chromene 7a (2.7 gm, 10 mmol) in chloroform (30 ml) through 30 min at room temperature. The mixture was stirred for 3 hrs at room temperature thereafter the solvent was evaporated under vacuum. The residue which formed was dried and crystallized from ethanol to give compound 7c as pale yellow crystals.

Preparation of 2,9-dibromo-4-methoxy-7-pentamethylene furo[3,2-g] chroman-5-one (10). A mixture of compound 2b (2.86 g, 10 mmol), N-bromosuccinimide (4.4 g, 25 mmol) in chloroform (100 ml) was heated at reflux for 5 hrs. The reaction mixture was filtered off, evaporated under reduced pressure and the residue which was collected, crystallized from ethanol to give compound 10 as pale yellow crystals.

Condensation of compound 2b and 2e with hydroxylamine hydrochloride and phenyl hydrazine general procedure for the preparation of compounds 11a-d. A mixture of compound 2b or 2e (10 mmol), hydroxylamine hydrochloride (or phenyl hydrazine) (12 mmol) and triethylamine (0.5 ml) was refluxed in absolute ethanol (50 ml) for 5 hrs. The precipitate which formed after cooling was filtered off, dried and crystallized from ethanol to give a colourless crystals of compound **11a**, pale yellow crystals of **11b**, colourless crystals of **11c** and yellow crystals of **11d**.

Condensation compound 2b with aniline preapration of compound 11e. An equal molar ratio of aniline and compound 2b was fused in oil bath at 150°C for 30 min. Diluted hydrochloric acid was added after cooling. The solid product which formed was filtered off, washed with water and crystallized from ethanol to give compound **11e** as yellow crystals.

Synthesis of 4-methoxy(and 4,9-dimethoxy)-6,6-Bis(dihydroxymethyl)-7-pentamethylene furo[3,2-g]chroman-5-one 12a and 12b. A solution of the chromanone: 2b or 2e (10 mmol) in dimethyl sulfoxide (10 ml) was added during 10 minutes to a stirred suspension of paraformaldehyde (20 mmol) in diemethyl sulfoxide (25 ml) containing potassium hydroxide (0.5 g) dissolved in ethanol (2 ml). After 1 h. from stirring at room temperature, the solution was neutralized by dilute hydrochloric acid and then diluted with cold water (200 ml). The organic layer was extracted using ethyl acetate and saturated sodium chloride solution then dried ($Mg.SO_4$) and evaporated in vacuo. The yellow oily product was digested with carbon tetrachloride and triturated with a mixture from acetone/ethanol (1:1) to give a colourless crystals of compound **12a** and **12b.**

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