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Short Communication

Synthesis and biological evaluation of some novel 4*H*-benzopyran-4-one derivatives as nonsteroidal antiestrogens

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Abstract – The preparation and characterization of some novel 2- and 3-substituted-7-methoxy-4*H*-1-benzopyran-4-one are presented. The synthesized compounds were evaluated for their uterotrophic, antiuterotrophic and antiimplantation activities in mature female albino rats. 3-Benzyl-7-methoxy-4*H*-1-benzopyran-4-one (**14**) showed the highest uterotrophic activity (87%) based on dry uterine weight gain. The antifertility activity, as assessed by the post-coital antiimplantation activity test, was of weak potency for most compounds (14–29%). Among the products, the 2-(4′-methoxyphenyl)-7-methoxy-4*H*-1-benzopyran-4-one (**19**) exhibited the highest antiestrogenic activity of 65%. It also elicited 31% of the uterotrophic activity of estradiol. © 2001 Éditions scientifiques et médicales Elsevier SAS

4*H*-1-benzopyran-4-one / antiestrogens / uterotrophic activity / antiimplantation activity

1. Introduction

The phytoestrogens formononetin, daidzein, biochanin A and genistein as well as the coumestan coumestrol (*figure 1*) are known to be present in various plant species, and particularly in soybean extracts and in vegetable dietary compounds like alfalfa [1–3]. They have been considered as responsible for the depression of fertility observed in sheep grazing clover pasture by acting on progesterone levels [4] or on pituitary luteinising hormone release [5, 6]. Their estrogenic activity has been assessed in biological assays such as the increase in the uterine weight of sheep [7], mouse [8] or rat [9] and by biochemical tests like binding to estrogen receptors [10, 11]. Several studies have shown a possible effect of these compounds on the synthesis of sex hormone-binding globulins (SHBG) by the liver, as well as on sex steroid metabolism [12–14]. Genistin and daidzein possess anticancer effects at relatively early stages of prostate cancer development, providing experimental support for epidemiological findings [15]. High intake of phytoestrogens through soybeans and their products is thought to be associated with low incidences of prostate cancer in Asian countries [15], while the incidence is much higher in black men in the USA [16].

One of the interesting findings about flavonoids is the influence they have on the incidence of cancer by modulating the cytochrome p-450 monoxygenase system [17] and inhibition of the effects of tumor promoters [18]. Flavonoids may also influence the incidence of breast cancer by acting as antiestrogens [10, 19] or as aromatase inhibitors [20].

Moreover, a series of flavones has been prepared which were variously substituted [21], for evaluation of their cytotoxicity to ANN-1 cells which contain a tyrosine kinase. 3-Amino-4-methoxyflavone was the most cytotoxic compound.

In this report, we describe the synthesis of two series of flavones substituted at the 2- or 3-position (*figure 2*) to study the effect of structural modulation around the flavone nucleus on its estrogenic and antifertility activities.

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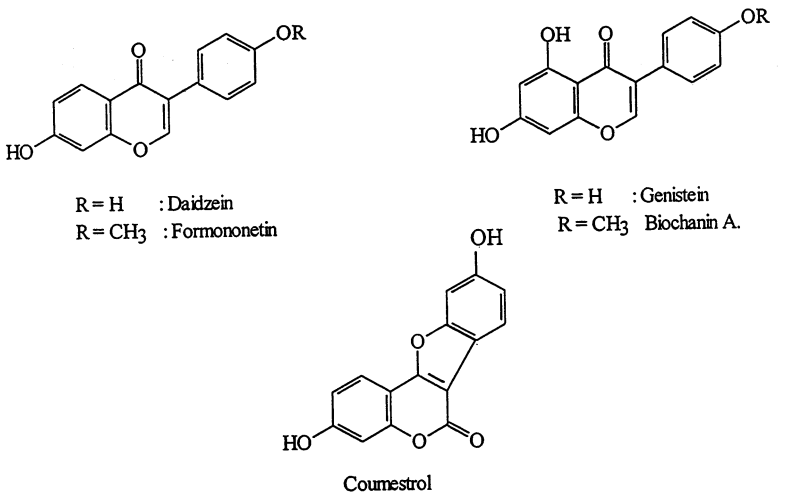


Fig. 1. Structure of several phytoestrogens.

2. Chemistry

A number of synthetic methods for the preparation of the 3-substituted flavones have been developed [22, 23] but these require several sequential reactions involving the application of the Hoesch reaction [24] on the 2-hydroxyacetophenone derivatives using different substituted nitriles.

Herein we report the synthesis of the new 3-substituted-7-methoxy-4*H*-1-benzopyran-4-ones (**11–14**) starting from 2-hydroxy-4-methoxyacetophenone (**1**) according to *figure 3*. The key step in this synthesis involved the alkylation with alkyl halide using potassium tertiary butoxide of 2-(*t*-butyldimethylsilyloxy)-4-methoxyacetophenone (**2**) which was prepared by the protection of the hydroxyl group of **1** using *t*-butyldimethylsilylchloride. The *t*-butyldimethylsilyl protecting group has been utilized due to its easy introduction and subsequent cleavage in high yield [25, 26]. The *O*-silyl protected alkylacetophenone derivatives (**3–6**) were therefore treated with tetra-*n*-butylammonium fluoride [27] to produce the corresponding 2′-alkyl-2-hydroxy-4-methoxyacetophenone (**7–10**) in good yield. Cyclization of the alkyl derivatives (**7–10**) was achieved via methanesulfonylchloride using boron trifluoride diethyl etherate at 0°C [23] to give the desired 3-substituted-7-methoxy-4*H*-1-benzopyran-4-ones (**11–14**) which were purified by crystallisation from ethanol to produce yellow crystals in moderate yields.

On the other hand, acylation of 2-(*t*-butyldimethylsilyloxy)-4-methoxyacetophenone (**2**) with acyl chloride using lithium diisopropylamide (LDA) at −78°C [28] (*figure 4*) gave 1-[2′-(*t*-butyldimethylsilyloxy) - 4′ - methoxyphenyl] - 3 - substituted propane-1,3-dione (**15–18**) as viscous residue which was dried under reduced pressure. The ^{1}H NMR spectra of the crude products showed that they exist as a tautomer mixture [29–31] and they were used as such in subsequent reactions without any further purification. Treatment of the propane-1,3-dione derivatives (**15–18**) with glacial acetic acid containing 0.5% H_2SO_4 at 95–100°C for 3 h resulted in cleavage of the silyl protecting group followed by cyclization to provide 2-substituted-7-methoxy-4*H*-1-benzopyran-4-one (**19–22**) as a yellow precipitate, in moderate yields, which were crystallized from EtOAc–hexane.

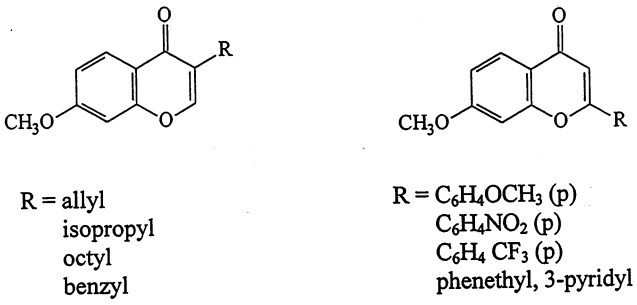
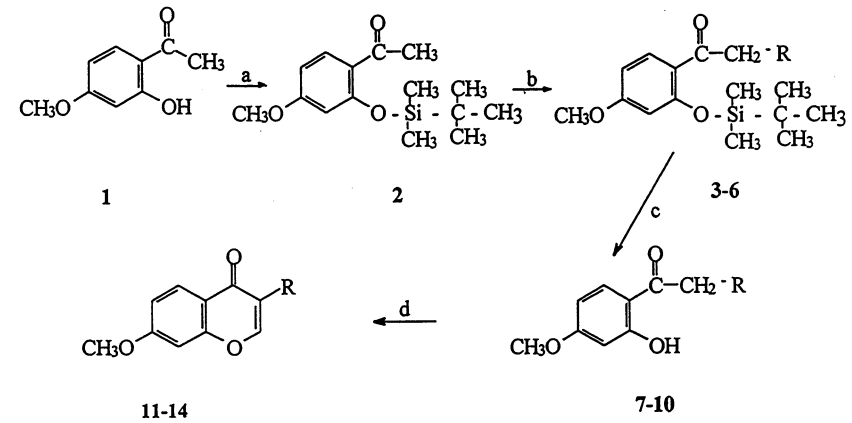
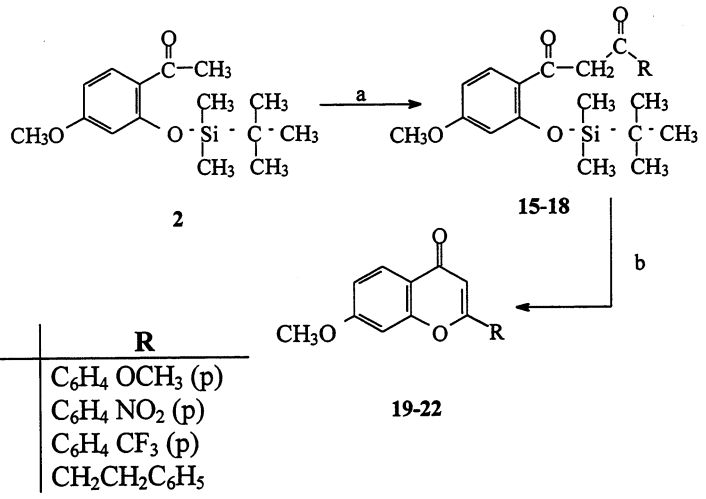


Fig. 2. General structure of designed compounds.



	R
3,7,11	allyl
4,8,12	isopropyl
5,9,13	octyl
6,10,14	benzyl

Fig. 3. Reactions and conditions: (a) TBSCl, Et_3N, DMAP, CH_2Cl_2, room temperature overnight; (b) RBr, *t*-BuOK, DMF, 0°C, 8 h; (c) $(n\text{-}Bu)_4$ NF, THF, 0°C, 45 min; (d) BF_3-Et_2O, $MeSO_2Cl$, DMF, heat on water bath, 2 h.



	R
15,19	C_6H_4 OCH_3 (p)
16,20	C_6H_4 NO_2 (p)
17,21	C_6H_4 CF_3 (p)
18,22	$CH_2CH_2C_6H_5$

Fig. 4. Reactions and conditions: (a) RCOCl, LDA, THF, −78°C; (b) HOAc, H_2SO_4, heat at 95–100°C, 3 h.

In addition, the 2-(3-pyridyl)-7-methoxy-4*H*-1-benzopyran-4-one (**24**) [32] was prepared in 70.5% yield by a modified condensation reaction involving the treatment of 2-(*t*-butyldimethylsilyloxy)-4-methoxyacetophenone (**2**) with methyl nicotinate using lithium hexamethyldisilylamide (LiHMDS) at −78°C to obtain 1-[2′-(*t*-butyldimethylsilyloxy)-4′-methoxyphenyl]-3-(3-pyridyl)-propane-1,3-dione (**23**) as a yellow precipitate which crystallized from methanol and was identified by IR, ^{1}H NMR and ^{13}C NMR. Compound **23** was cyclized into 2-(3-pyridyl)-7-methoxy-4*H*-1-benzo-pyran-4-one (**24**) using glacial acetic acid containing 0.5% H_2SO_4 at 95–100°C for 3 h (*figure 5*).

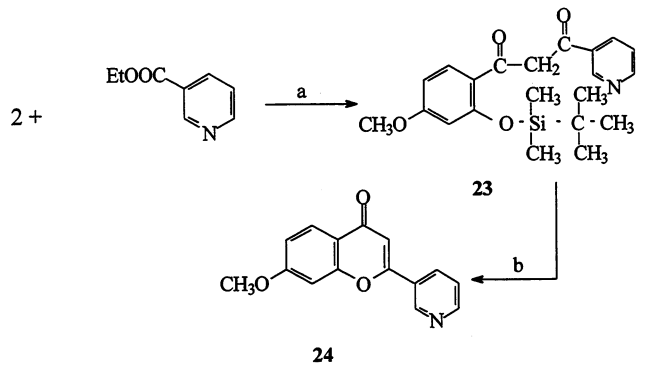


Fig. 5. Reactions and conditions: (a) LiHMDS, THF, −78°C; (b) (i) HOAc, H_2SO_4, heat at 95–100°C, 3 h; (ii) Na_2CO_3.

3. Biological activity

3.1. Uterotrophic activity

The uterotrophic activity [33, 34] of the synthesized compounds was evaluated by determining the uterine weight gain in mature ovariectomized female albino rats (about 150 g) (obtained from the animal house of the Faculty of Pharmacy, Alexandria). The animals were divided into 13 groups, each with six rats. The rats were ovariectomized 2–4 days before starting the injection and then injected subcutaneously for three consecutive days as follows:

- The first group received the vehicle (DMSO) and served as a control.
- The second group received a standard daily dose of estradiol (0.16 mg kg^{-1}) subcutaneously dissolved in the vehicle.
- The remaining groups were injected with the compounds under investigation subcutaneously once daily over the 3-day period in 0.1 mL DMSO (0.09 μmol day^{-1} rat^{-1}).

The rats were weighed 24 h after the last dose and vaginal smears were taken and examined under the microscope. The rats were sacrificed by cervical dislocation. The uteri were removed, freed from extraneous tissues, blotted between a filter paper and weighed (wet weight). The uteri were dried in an oven at 60°C for 48 h and then weighed (dry weight). The gain in uterine weight calculated as mg uterine weight/100 g body weight and the percentage of dry/wet weight are shown in *table I*. The agonistic activity (%) estimated by the following formula [35] (*table I*).

$$\%\ \text{Agonistic activity} = \frac{(W_T - W_V)}{(W_S - W_V)} \times 100$$

where W_T is the relative dry uterine weight of animals treated with test compound, W_S the relative dry uterine weight of animals treated with a standard dose of estradiol (0.16 mg kg^{-1}), and W_V the relative dry uterine weight of control animals.

Table I. Estrogenic potencies and post-coital antiimplantation efficacies of the synthesized compounds in ovariectomized mature female rats.

Comp.	Wet uterine weight (mg/100 g)	Dry uterine weight (mg/100 g)	Dry weight/wet weight % (*n*)[a]	% Uterotrophic activity based on dry weight	Antiimplantation activity[c] (no. of implants)	% Antiimplantation activity[c]
Control[b]	11.22 ± 0.64	3.82 ± 0.66	34.18 ± 2.28 (6)		8.00 ± 0.7	0
Estradiol	20.16 ± 2.82**	7.42 ± 1.72**	35.86 ± 1.18	100	0	100
11	19.48 ± 2.56**	6.82 ± 0.96**	34.71 ± 1.72	83	3.50 ± 1.19	29
12	18.35 ± 1.43**	5.96 ± 0.82**	31.52 ± 1.12	59	5.2 ± 0.912	19
13	11.16 ± 0.86	4.22 ± 0.37*	38.98 ± 0.72*	11	7.01 ± 1.50	14
14	19.56 ± 1.82**	6.96 ± 0.88**	35.11 ± 0.96	87	4.20 ± 1.50	24
19	13.25 ± 2.16*	4.94 ± 1.55*	37.48 ± 0.82	31	7.18 ± 1.55	15
20	12.54 ± 0.89	4.82 ± 0.58*	38.68 ± 0.64*	28	7.00 ± 3.50	14
21	12.46 ± 0.81	4.56 ± 1.26*	36.16 ± 0.48	21	4.0 ± 1.65	21
22	13.66 ± 1.87*	4.12 ± 1.26	31.18 ± 0.52	8	7.20 ± 3.50	15
24	16.28 ± 0.92**	5.14 ± 0.73*	30.42 ± 0.71	37	4.5 ± 1.50	23

[a] Number of animals in each group = 5.
[b] Rats received vehicle (DMSO) and served as control.
[c] Minimum effect dose for prevention of pregnancy (0.05 mg kg^{-1} body weight for estradiol). Doses of the tested compounds were calculated on a molar ratio basis. Results are expressed as mean ± SEM. Data were analyzed by one-way variance. Student's *t*-test for unpaired observations was used. Differences between means were considered significant if $*P<0.05$; $**P<0.001$.

Dose	Dry uterine weight mg/100g		% uterotrophic activity based on dry uterine weight
	Estradiol	Comp.14	
0.0225	6	2.6	15%
0.045	7.2	4.7	53%
0.09	9.5	7.8	78%
0.18	11	9.11	79%

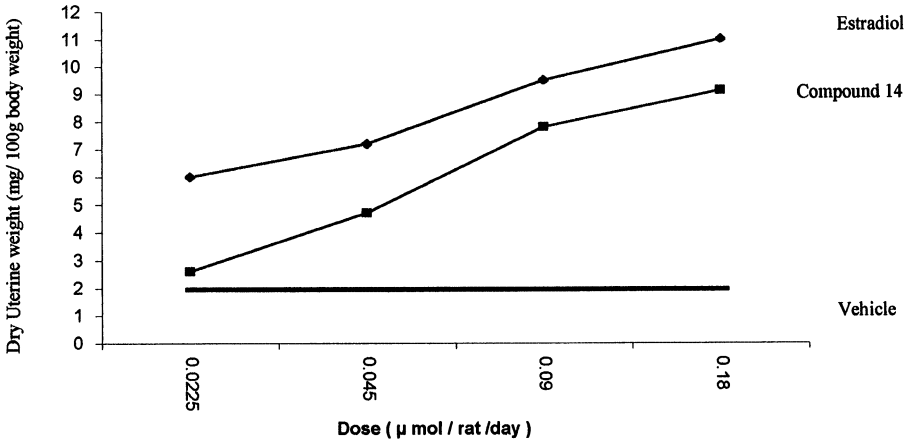


Fig. 6. Uterotrophic activity of estradiol and compound **14** in ovariectomized mature female rats.

The previous procedure was repeated using different doses of compound **14** (0.039, 0.079, 0.159, 0.319 mg kg^{-1}) (*figure 6*).

3.2. Antiuterotrophic activity

The antiuterotrophic activity [36, 37] of the synthesized compounds was assessed in mature ovariectomized albino female rats (about 250 g). The compounds were administered subcutaneously in 0.1 mL DMSO along with of E2-17β (0.098 mg kg^{-1} in 0.1 mL DMSO) at two different sites for three consecutive days. Inhibition was expressed as percent inhibition from the formula of Hatmann et al. [37] (*table II*).

$$\% \text{ Inhibition } = 100 - \left[\frac{(W_{S,T} - W_V)}{(W_S - W_V)} \times 100 \right]$$

where $W_{S,T}$ is the relative dry uterine weight of animals treated with estradiol+test compounds, W_S the relative dry uterine weight of animals treated with a standard dose of estradiol, and W_V the relative dry uterine weight of control animals.

The previous procedure was repeated using different doses of compound **19** (0.029, 0.053, 0.106, 0.213 mg kg^{-1}) (*figure 7*).

3.3. Antiimplantation activity

Mature female cycling albino rats (150–200 g) were mated with active males during the night after the day of proestrus. Animals with evidence of positive mating (presence of sperm in the vaginal smears) received the test compound dissolved in 0.1 mL DMSO subcutaneously on days 1–7 post-coitum [34, 36–38]. The animals were examined by laparatomy on day 10 of pregnancy for the number of implantation sites. Results were compared with those obtained on administration of the standard estradiol (*table I*).

4. Results and discussion

The results of biological screening (*tables I and II*) showed that the 3-allyl flavone derivative **11**, at a dose of 0.09 μmol rat^{-1} day^{-1}, produced an 83% increase in uterine weight and reduced the postcoital antiimplantation activity to 29% relative to estradiol (*table I*). It also produced weak (38%) antiuterotrophic activity (*table II*). Replacement of the allyl group by the isopropyl group (compound **12**) decreased the uterotrophic activity to 59% and replacement by octyl group notably decreased the uterotrophic activity to 11%. In contrast, the 3-benzylflavone derivative **14**, increased the uterotrophic activity to 87% and exhibited a postcoital antifertility activity of 24% relative to estradiol and was almost (15%) devoid of antiuterotrophic activity.

Table II. Antiuterotrophic activity of the synthesized compounds in ovariectomized mature female rats (number of animals in each group = 6; doses of the tested compounds were calculated on a molar ratio basis; results were expressed as mean ± S.E.M.; data are analyzed by one-way variance. Student's *t*-test for unpaired observations was used; Differences between means were considered significant if $*P<0.005$; $**P<0.001$).

Compound	Dry uterine weight mg rat^{-1}	% Antiuterotrophic activity
Control[a]	4.68 ± 0.54	
Estradiol	49.26 ± 3.62**	
11	32.41 ± 2.12**	38
12	29.68 ± 1.43**	44
13	26.52 ± 0.92**	51
14	42.53 ± 0.86*	15
19	20.16 ± 0.76	65
20	43.21 ± 1.28*	14
21	38.65 ± 0.88**	24
22	40.11 ± 1.16*	21
24	33.68 ± 1.15**	35

[a] Rats received vehicle (DMSO) and served as control.

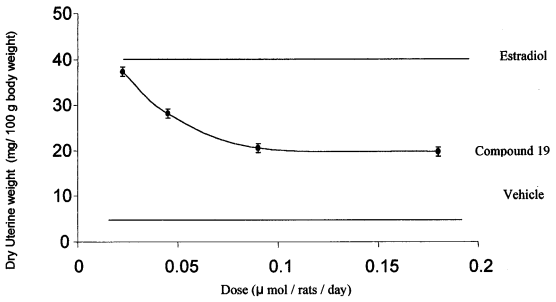


Fig. 7. Dose–response curve of the antiuterotrophic activity of compound **19** in ovariectomized mature female rats. Results are expressed as mean ± S.E.M.

On the other hand, introduction of various *p*-substituted phenyl groups (compounds **19** and **20**), phenethyl group (compound **22**) and pyridyl group (compound **24**) at the 2-position of flavone induced a weak uterotrophic activity. Compound **19**, having a *p*-methoxyphenyl moiety, elicited the highest (65%) antiuterotrophic activity (*table II*).

Summing up the results, compounds **14** and **19** are the most active among the series. The former produced the highest uterotrophic (87%) and the latter produced the highest (65%) antiuterotrophic response.

A more precise assessment of the uterotrophic activity of **14** and antiuterotrophic activity of **19** is illustrated in *figures 6 and 7*, respectively. The uterotrophic effect in response to different doses (0.0225–0.18 μmol rat^{-1} day^{-1}) of 3-benzyl-7-methoxy-4*H*-1-benzopyran-4-one (**14**) was compared to that of similar doses of estradiol. Compound **14** at a dose of 0.0225, 0.045 and 0.09 μmol rat^{-1} day^{-1} caused a 15, 53 and 78% uterotrophic effect, respectively (*figure 6*). At a higher dose (0.18 μmol rat^{-1} day^{-1}), compound **14** did not produce a greater uterotrophic response.

On the other hand, the antiuterotrophic activity of 2-(4′-methoxyphenyl)-7-methoxy-4*H*-1-benzopyran-4-one **19** was studied by simultaneous administration of various doses (0.0225–0.18 μmol rat^{-1} day^{-1}) of this compound and a standard dose of estradiol (0.09 μmol rat^{-1} day^{-1}). Compound **19** at 0.0225–0.045 μmol rat^{-1} day^{-1} caused a dose-related inhibition of estradiol-induced increase in uterine weight (*figure 7*). A maximal inhibition (65%) was attained at a dose of 0.18 μmol rat^{-1} day^{-1}, indicating its partial but significant antiestrogenic effect.

The results obtained in this study have indicated that these newly synthesized compounds should be useful for seeking novel chemical approach to the discovery of potent nonsteroidal antiestrogens.

5. Experimental protocols

5.1. Chemistry

Materials: Chemical reagents were bought from Aldrich. Thin layer chromatography (TLC) was performed on Whatman precoated silica gel F_{254} aluminum

foils. Visualization was accomplished with UV light/or phosphomolybdic acid solution followed by heating. Purification of the reaction products was carried out by flash column chromatography using glass column dry packed with neutral alumina a grade I or silica gel (230–400 mesh). Organic solutions were dried over anhydrous $MgSO_4$; evaporation refers to removal of solvent on a rotary evaporator under reduced pressure. Melting point were determined using a Thomas Hoover capillary melting point apparatus and are uncorrected. IR spectra were obtained on salt plates in KBr, pellet or in CCl_4, using a Nicolet Protege 460 model spectrometer. Peaks were reported in cm^{-1}. ^1H NMR spectra were recorded on a Bruker 250 MHz spectrometer with TMS as internal standard in $CDCl_3$ unless otherwise noted. Mass spectral data were determined at the Ohio State University Chemical Instrument center with a Kratos MS-30 mass spectrometer. Elemental analyses were performed by the Microanalytical Unit, Faculty of Science, Cairo University, Egypt. Analyses indicated by the symbols of elements were within ±0.4% of the theoretical values. All reactions were carried out under an argon atmosphere, unless otherwise noted.

*5.1.1. 2-(t-Butyldimethylsilyloxy)-4-methoxyacetophenone (**2**)*

Et_3N (6.29 mL, 45.13 mmol) was added to a cooled (0°C) solution of 2-hydroxy-4-methoxyacetophenone (**1**) (5 g, 30.08 mmol) and DMAP (0.36 g, 3 mmol) in CH_2Cl_2 (40 mL). A solution of *t*-butyldimethylsilylchloride (TBSCl) (5 g, 33.09 mmol) in CH_2Cl_2 (10 mL) was added to the reaction mixture dropwise over 10 min and the mixture was stirred at r.t. overnight. The reaction mixture was poured into ice water (500 mL) and extracted with CH_2Cl_2 (3×50 mL). The combined extracts were washed with brine (3×50 mL) and dried over $MgSO_4$, filtered and evaporated under reduced pressure to produce a yellow oil which was purified by flash chromatography on neutral alumina (eluent: 10% EtOAc in hexanes) to give a colorless oil (yield: 7 g, 83%). ^1H NMR ($CHCl_3$-*d*) δ 7.69 (d, $J = 10.6$ Hz, 1H, H_5), 6.5 (dd, $J = 10.6$ and 2 Hz, 1H, H_6), 6.35 (d, $J = 2$ Hz, 1H, H_3), 3.79 (s, 3H, OCH_3), 2.51 (s, 3H, $COCH_3$), 1 (s, 9H, $(CH_3)_3$), 0.24 (s, 6H, $(CH_3)_2$). ^{13}C NMR ($CHCl_3$-*d*) δ 198.7 (C=O), 164, 157.3, 132.5, 124.2, 107.1 and 106.1 (aromatic C), 55.7 (OCH_3), 31.65 (C–$(CH_3)_3$), 26.3, 25.1 and 18.3 (CH_3 groups). MS *m*/*z* (relative intensity, %): 281 ($[MH]^+$, 65), 165 ($[M-C_6H_{15}Si]^+$, 100). Anal. Found: C, 64.22; H, 8.66. Calc. for $C_{15}H_{24}O_3Si$: C, 64.25; H, 8.62%.

*5.1.2. General procedure for the alkylation of 2-(t-butyldimethylsilyloxy)-4-methoxyacetophenone (**2**) (synthesis of compounds **3**–**6**)*

Potassium *t*-butoxide (0.5 g, 4.5 mmol) was added to a solution of 2-(*t*-butyldimethylsilyloxy)-4-methoxyacetophenone (**2**, 0.84 g, 3 mmol) in anhydrous DMF (10 mL) under argon atmosphere at 0°C. The mixture was stirred at 0°C for 1 h. A solution of freshly distilled alkyl bromide (6 mmol) in anhydrous DMF (3 mL) was added via a cannula to the reaction mixture with stirring at 0°C. The stirring was continued at 0°C for 8 h. The solution was quenched with saturated solution of NH_4Cl, extracted with EtOAc (3×30 mL), dried over $MgSO_4$, filtered and evaporated under reduced pressure to produce sticky mass, which was purified by flash chromatography on neutral alumina (eluent: 25% EtOAc in hexanes).

*5.1.2.1. 2′-Allyl-2-(t-butyldimethylsilyloxy)-4-methoxyacetophenone (**3**)*

White solid (0.65 g, 68%): m.p. 95–92°C. IR (cm^{-1}, KBr) 3100 (CH=CH_2). 1637 (C=O), 1302 (Si–CH_3). ^1H NMR ($CHCl_3$-*d*) δ 7.65 (d, $J = 10$ Hz, 1H, H_5), 6.55 (dd, $J = 10$ and 2 Hz, 1H, H_6), 6.4 (d, $J = 2$ Hz, 1H, H_3), 5.6–5.95 (m, 1H, CH=), 4.9–5.15 (m, 2H, CH_2=), 3.8 (s, 3H, OCH_3), 3–3.15 (m, 2H, CH_2), 2.4–2.6 (t, 2H, CH_2), 1.02 (s, 9H, $(CH_3)_3$), 0.3 (s, 6H, $(CH_3)_2$). ^{13}C NMR ($CHCl_3$-*d*) δ 199 (C=O), 164.2, 158, 132.4, 124.5, 107.5 and 106.2 (aromatic C), 105.7 (CH=), 91.2 (CH_2=), 55.6 (OCH_3), 44.5 ($COCH_2$), 33.5 (C–$(CH_3)_3$), 33.1 (CH_2), 26.1, 25.4 and 18.4 (CH_3 groups). MS *m*/*z* (relative intensity, %): 320 ($[M]^{\bullet+}$, 15), 205 ($[M-C_6H_{15}Si]^{\bullet+}$, 100). Anal. Found: C, 67.45; H, 8.85. Calc. for $C_{18}H_{28}O_3Si$: C, 67.46; H, 8.80%.

*5.1.2.2. 2-(t-Butyldimethylsilyloxy)-2′-isopropyl-4-methoxyacetophenone (**4**)*

White solid (0.67 g, 69%): m.p. 110–112°C. IR (cm^{-1}, KBr) 1639 (C=O), 1300 (Si–CH_3). ^1H NMR ($CHCl_3$-*d*) δ 7.71 (d, $J = 10$ Hz, 1H, H_5), 6.59–6.5 (m, 2H, H_6+H_3), 3.8 (s, 3H, OCH_3), 2.75 (d, $J = 8$ Hz, 2H, $COCH_2$), 2.44–2.3 (m, 1H, CH), 1.4 (d, $J = 9.75$ Hz, 6H, $(CH_3)_2$), 1.05 (s, 9H, $(CH_3)_3$), 0.32 (s, 6H, $Si(CH_3)_2$). ^{13}C NMR ($CHCl_3$-*d*) δ 198.2 (C=O), 166.4, 165.5, 164.7, 159.6, 132.9 and 122.3 (aromatic C), 55.7 (OCH_3), 42.2 ($CO\boldsymbol{C}H_2$), 32.5 (C–$(CH_3)_3$), 26.4 (CH), 25.6, 22.3 and 18.2 (CH_3 groups). MS *m*/*z* (relative intensity, %): 322 ($[M]^{\bullet+}$, 30), 208 ($[MH-C_6H_{15}Si]^{\bullet+}$, 100), 165($[MH-C_9H_{22}Si]^{\bullet+}$, 97). Anal. Found: C, 67.08; H, 9.39. Calc. for $C_{18}H_{30}O_3Si$: C, 67.04; H, 9.37%.

5.1.2.3. 2-(t-Butyldimethylsilyloxy)-4-methoxy-2′-octylacetophenone ***(5)***

White solid (0.75 g, 64%): m.p. 129–131°C. IR (cm^{-1}, KBr) 1636 (*C*=O), 1305 (Si–CH_3). ^1H NMR ($CHCl_3$-*d*) δ 7.79 (d, $J = 10$ Hz, 1H, H_5), 6.45 (dd, $J = 10$ and 2 Hz, 1H, H_6), 6.36 (s, 1H, H_3), 3.1–2.9 (m, 2H, $COCH_2$), 1.95–1.75 (m, 2H, CH_2), 1.45–1.2 (m, 12H, $(CH_2)_6$), 1–0.85 (m, 12H, CH_3 of octyl+$(CH_3)_3$), 0.3 (s, 6H, $Si(CH_3)_2$. ^{13}C NMR ($CHCl_3$-*d*) δ 198.0 (*C*=O), 164.8, 161.0, 152.2, 132.9, 121.4, 105.3 (aromatic C), 55.8 (OCH_3), 43.1 ($COCH_2$), 32.5 (*C*–$(CH_3)_3$, 30.2, 29.6 and 29.5 (CH_2) 26.6, 23.0 and 14.4 (CH_3 groups). Anal. Found: C, 70.38; H, 10.25. Calc. for $C_{23}H_{40}O_3Si$: C, 70.36; H, 10.26%.

5.1.2.4. 2′-Benzyl-2-(t-butyldimethylsilyloxy)-4-methoxyacetophenone ***(6)***

White solid (0.6 g, 54.5%): m.p. 97–99°C. IR (cm^{-1}, KBr) 1639 (C=O), 1301 (Si–CH_3). ^1H NMR ($CHCl_3$-*d*) δ 7.8 (d, $J = 10$ Hz, 1H, H_5), 7.5–7.3 (m, 5H, phenyl-H), 6.55–6.49 (m, 2H, H_3+H_6), 3.86 (s, 3H, OCH_3), 2.95 (t, 2H, $COCH_2$), 2.6–2.45 (m, 2H, CH_2), 1.03 (s, 9H C–$(CH_3)_3$), 0.3 (s, 6H, $Si(CH_3)_2$). ^{13}C NMR ($CHCl_3$-*d*) δ 198.1 (C=O), 166.5, 165.6, 136.4, 133.1, 129.1, 128.6, 128.0, 121.8, 108.0, 105.7 and 101.2 (aromatic C) 55.9 (OCH_3), 40.28 ($COCH_2$), 32.5 (*C*–$(CH_3)_3$), 29.44 (CH_2), 26.5, 19.4 and 18.9 (CH_3 groups). MS *m*/*z* (relative intensity, %): 370 ($[M^{\bullet+}]$, 11), 165 ($[MH-C_{13}H_{22}Si]^{\bullet+}$, 100). Anal. Found: C, 71.35; H, 8.15. Calc. for $C_{22}H_{30}O_3Si$: C, 71.31; H, 8.16%.

5.1.3. 2′-Alkyl-2-hydroxy-4-methoxyacetophenone ***(7–10)***

A solution of *t*-*n*-butylammonium fluoride in THF (1 M, 15 mL, 15 mmol) was added to a solution of 2′-alkyl-2-(*t*-butyldimethylsilyloxy)-4-methoxyacetophenone (**3**–**6**, 5 mmol) in THF (30 mL) at 0°C and stirring was continued for 45 min. THF was distilled off at reduced pressure and the residue was treated with water (100 mL). The precipitate was filtered, washed with water, dried and crystallized from ethanol.

5.1.3.1. 2′-Allyl-2-hydroxy-4-methoxyacetophenone (7)

Yield: 85%. m.p. 115–117°C. IR (cm^{-1}, KBr) 3439 (OH), 1640 (*C*=O). ^1H NMR ($CHCl_3$-*d*) δ 12.8 (s, 1H, phenolic OH), 7.85 (d, $J = 10$ Hz, 1H, H_5), 6.65–6.41 (m, 2H, H_3+H_6), 6.2–6 (m, 1H, CH=), 5.61–5.32 (m, 2H, CH_2=), 3.9 (s, 3H, OCH_3) 3.63–3.52 (m, 2H, $COCH_2$), 2.5–2.36 (m, 2H, CH_2). ^{13}C NMR ($CHCl_3$-*d*) δ 200.0 (*C*=O), 164.7, 160.6, 133.9, 133.3, 121.7, 119.6 (aromatic C), 107.9 (CH=), 99.7 (CH_2), 55.8 (OCH_3), 43.2 $COCH_2$), 32.4 (CH_2). Anal. Found: C, 69.90; H, 6.88. Calc. for $C_{12}H_{14}O_3$: C, 69.89; H, 6.84%.

5.1.3.2. 2-Hydroxy-2′-isopropyl-4-methoxyacetophenone ***(8)***

Yield: 82%. m.p. 125–127°C. IR (cm^{-1}, KBr) 3435 (OH), 1640 (*C*=O). ^1H NMR ($CHCl_3$-*d*) δ 12.6 (s, 1H, phenolic OH), 7.83 (d, $J = 10$ Hz, 1H, H_5), 6.56–6.3 (m, 2H, H_3+H_6), 3.88 (s, 3H, OCH_3), 3.55–3.48 (m, 2H, $COCH_2$), 2.4–2.25 (m, 1H, C*H*$(CH_3)_2$), 1.23 (d, $J = 10$ Hz, 6H, $(CH_3)_2$). ^{13}C NMR ($CHCl_3$-*d*) δ 198.9 (*C* = O), 166.4, 164.7, 159.6, 132.9, 122.3 and 105.3 (aromatic C), 55.8 (OCH_3), 40.2 ($COCH_2$), 26.4 (CH), 22.9 (CH_3). MS *m*/*z* (relative intensity, %): 208 ($[M]^{\bullet+}$, 100). Anal. Found: C, 69.22; H, 7.76. Calc. for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74%.

5.1.3.3. 2-Hydroxy-4-methoxy-2′-octylacetophenone ***(9)***

Yield: 79%. m.p. 151–153°C. IR (cm^{-1}, KBr) 3440 (OH), 1638 (*C*=O). ^1H NMR ($CHCl_3$-*d*) δ 12.6 (s, 1H, phenolic OH), 7.88 (d, $J = 10$ Hz, 1H, H_5), 6.64–6.43 (m, 2H, H_3+H_6), 3.89 (s, 3H, OCH_3), 3.5 (t, 2H, $COCH_2$), 1.95–1.75 (m, 2H, CH_2), 1.59–1.28 (m, 12H,$(CH_2)_6$, 0.9 (t, 3H, CH_3). ^{13}C NMR ($CHCl_3$-*d*) δ 199.3 (*C*=O), 164.5, 161.2, 132.6, 129.3, 128.9, 105.2 (aromatic C), 55.5 (OCH_3), 43.3 ($COCH_2$) 32.2, 29.5, 23.0 and 22.6 (CH_2), 14.4 (CH_3). Anal. Found: C, 73.36; H, 9.42. Calc. for $C_{17}H_{26}O_3$: C, 73.35; H, 9.41%.

5.1.3.4. 2′-Benzyl-2-hydroxy-4-methoxyacetophenone ***(10)***

Yield: 79%. m.p. 119–121°C. IR (cm^{-1}, KBr) 3436 (OH), 1637 (*C*=O). ^1H NMR ($CHCl_3$-*d*) δ 12.5 (s, 1H, phenolic OH), 7.9 (d, $J = 10$ Hz, 1H, H_5), 7.55–7.3 (m, 5H, phenyl H), 6.6–6.45 (m, 2H, H_3+H_6), 3.85 (s, 3H, (OCH_3), 3.3 (t, 2H, $COCH_2$), 2.82 (t, 2H, CH_2). ^{13}C NMR ($CHCl_3$-*d*) δ 201.7 (*C*=O), 156.5, 147.6, 140.5, 136.4, 133.1, 132.7, 129.1, 128.8, 128.3, 124.8, 119.7, 114.2 (aromatic C), 55.9 (OCH_3), 40.0 ($COCH_2$), 29.2 (CH_2). MS *m*/*z* (relative intensity, %): 256 ($[M]^{\bullet+}$, 100). Anal. Found: C, 75.01; H, 6.30. Calc. for $C_{16}H_{16}O_3$: C, 74.98; H, 6.29%.

5.1.4. 3-Substituted-7-methoxy-4H-1-benzopyran-4-ones ***(11–14)***

A solution of 2′-alkyl-2-hydroxy-4-methoxyacetophenone (**7**–**10**, 0.9 mmol) in anhydrous DMF (6 mL) was treated cautiously with freshly distilled $BF_3{\cdot}Et_2O$ (4 equiv.) at 0°C. A solution of $MeSO_2Cl$ (3 equiv.) in

DMF (4 mL) was added to the mixture. The mixture was heated on a steam bath for 2 h. The cooled product was poured with stirring into water. The initial oil quickly solidified to give the chromone (**11**–**14**) as yellow solid which was purified by crystallization from ethanol.

*5.1.4.1. 3-Allyl-7-methoxy-4H-1-benzopyran-4-one (**11**)*

Yield: 75%. m.p. 150–152°C. IR (cm^{-1}, KBr) 1639 (*C*=O). ^{1}H NMR ($CHCl_3$-*d*) δ 8.1 (s, 1H, H_2), 8.0–7.85 (m, 1H, H_6), 7.51–7.3 (m, 2H, H_5+H_8), 6.3–6.13 (m, 1H, CH=), 5.7–5.52 (m, 2H, CH_2=), 3.91 (s, 3H, OCH_3), 2.63–2.5 (m, 2H, CH_2). ^{13}C NMR ($CHCl_3$-*d*) δ 179.7 (*C*=O), 165.0 (C_9), 160.5 (C_7), 156.0 (C_2), 144.9 (C_3), 127.8, 126.9, 125.5, 124.5, 118.3, 99.3 (C_5, C_6, C_8, C_{10}, CH= and CH_2=), 54.0 (OCH_3), 32.5 (CH_2). MS *m*/*z* (relative intensity, %): 216 ($[M]^{\cdot+}$, 100). Anal. Found: C, 72.23; H, 5.61. Calc. for $C_{13}H_{12}O_3$: C, 72.21; H, 5.59%.

*5.1.4.2. 3-Isopropyl-7-methoxy-4H-1-benzopyran-4-one (**12**)*

Yield: 79%. m.p. 133–135°C. IR (cm^{-1}, KBr) 1637 (*C*=O). ^{1}H NMR ($CHCl_3$-*d*) δ 8.15 (s, 1H, H_2), 7.91–7.85 (m, 1H, H_6), 7.58–7.35 (m, 2H, H_5+H_8), 3.85 (s, 3H, OCH_3), 2.55 (m, 1H, C*H*(CH_3)$_2$), 1.4 (d, $J=8$ Hz, 6H, $(CH_3)_2$). ^{13}C NMR ($CHCl_3$-*d*) δ 179.8 (*C*=O), 165.5 (C_9), 159.6 (C_7), 149.6 (C_2), 140.2 (C_3), 138.2, 132.9, 124.6, 120.8 (C_5, C_6, C_8 and C_{10}), 56.3 (OCH_3), 29.3 (CH), 22.7, 22.3 (CH_3)$_2$. MS *m*/*z* (relative intensity, %): 218 ($[M]^{\cdot+}$, 100). Anal. Found: C, 71.57; H, 6.50. Calc. for $C_{13}H_{14}O_3$: C, 71.55; H, 6.46%.

*5.1.4.3. 7-Methoxy-3-octyl-4H-1-benzopyran-4-one (**13**)*

Yield: 70.5%. m.p. 175–177°C. IR (cm^{-1}, KBr) 1638 (*C*=O). ^{1}H NMR ($CHCl_3$-*d*) δ 8.17 (s, 1H, H_2), 7.88–7.84 (m, 1H, H_6), 7.56–7.4 (m, 2H, H_5+H_8), 3.87 (s, 3H, OCH_3), 1.95–1.77 (t, 2H, CH_2), 1.7–1.2 (m, 12H, $(CH_2)_6$), 0.9 (br t, 3H, CH_3). ^{13}C NMR ($CHCl_3$-*d*) δ 179.5 (*C*=O), 166.3 (C_9), 161.05 (C_7), 158.3 (C_2), 149.6 (C_3), 138.1, 127.6, 124.6, 118.3 (C_5, C_6, C_8, C_{10}), 55.8 (OCH_3), 32.5, 32.1, 29.6, 29.5, 26.3, 23.0 (CH_2 groups), 14.5 (CH_3). MS *m*/*z* (relative intensity, %): 288 ($[M]^{\cdot+}$, 100), Anal. Found: C, 75.01; H, 8.09. Calc. for $C_{18}H_{24}O_3$: C, 74.97; H, 8.38%.

*5.1.4.4. 3-Benzyl-7-methoxy-4H-1-benzopyran-4-one (**14**) [39]*

Yield: 77% m.p. 129–131°C (reported m.p. 131°C) [39] IR (cm^{-1}, KBr) 1639 (*C*=O). ^{1}H NMR ($CHCl_3$-*d*) δ 8.2 (s, 1H, H_2), 7.87–7.83 (d, $J=8$ Hz, 1H, H_6), 7.5–7.31 (m, 5H, phenyl H), 7.12–7 (m, 2H, H_5+H_8), 3.95 (s, 3H, OCH_3), 3.91 (s, 2H, CH_2-Ar). ^{13}C NMR ($CHCl_3$-*d*) δ 179.6 (*C*=O), 166.5 (C_9), 164.7 (C_7), 146.4 (C_2), 133.1 (C_3), 132.7, 129.1, 128.6, 125.8, 124.9, 124.7, 121.2, 119.8 (aromatic C), 55.9 (OCH_3), 30.1 (CH_2). MS *m*/*z* (relative intensity, %): 266 ($[M]^{\cdot+}$, 100). Anal. Found: C, 76.70; H, 8.09. Calc. for $C_{17}H_{14}O_3$: C, 76.68; H, 8.38%.

*5.1.5. 2-Substituted-7-methoxy-4H-1-benzopyran-4-one (**19**–**22**)*

n-BuLi (4.34 mL, 10 mmol, from 2.3 M in hexanes) was added dropwise to a solution of diisopropylamine (1.41 mL, 10 mmol) in anhydrous THF (50 mL) with stirring at −78°C under argon atmosphere. The mixture was stirred at −78°C for 30 min. A solution of 2-(*t*-butyl-dimethylsilyloxy)-4-methoxyacetophenone (**2**, 4.75 mmol) in THF (10 mL) was added via a cannula to the stirred LDA solution at −78°C. The mixture was warmed to −25°C and stirred for 1 h at this temperature, then cooled to −78°C and a solution of freshly distilled acid chloride (5 mmol) in THF (10 mL) was added via a cannula. Stirring was continued at −78°C for 3 h then at r.t. overnight. The reaction mixture was diluted with EtOAc (50 mL) and acidified to pH 3 with 1 N HCl. The organic layer was separated, dried over $MgSO_4$, filtered and evaporated to give a viscous residue of 1-[2′-(*t*-butyldimethyl-silyloxy)-4′-methoxyphenyl]-3-substituted propane-1,3-dione (**15**–**18**) which was dried under reduced pressure for 24 h (identified by crude ^{1}H NMR). It was mixed with glacial acetic acid (20 mL) and H_2SO_4 (0.1 mL) and heated at 95–100°C under argon atmosphere for 3 h. Acetic acid was distilled off at reduced pressure and the residue was quenched with water (50 mL). It was extracted with $CHCl_3$ (3×20 mL) and the combined extracts were dried over $MgSO_4$, filtered and evaporated to give yellow solid of 2-substituted-7-methoxy-4*H*-1-benzopyran-4-one (**19**–**22**) which was crystallized from EtOAc–hexanes.

*5.1.5.1. 2-(4′-Methoxyphenyl)-7-methoxy-4H-1-benzopyran-4-one (**19**)*

Yield 88%, m.p. 146–148°C (reported m.p. 144°C) [28].

*5.1.5.2. 7-Methoxy-2-(4′-nitrophenyl)-4H-1-benzopyran-4-one (**20**)*

Yield: 89% m.p. 169–171°C. IR (cm^{-1}, KBr) 1647 (*C*=O). ^{1}H NMR ($CHCl_3$-*d*) δ 8.35 (d, $J=12$ Hz, 2H, $H_{3'}+H_{5'}$), 8.17–8 (m, 3H, $H_{2'}+H_{6'}+H_6$), 7.07–6.97 (m,

2H, H_5+H_8), 6.81 (s, 1H, H_3), 3.95 (s, 3H, OCH_3). ^{13}C NMR ($CHCl_3$-*d*) δ 177.7 (*C*=O), 165.0 (C_9), 160.5 (C_7), 158.3 (C_2), 149.6 ($C_{4'}$), 138.5, 133.1, 127.6, 127.4, 124.6, 118.1, 115.3, 112.2, 110.0, 100.8 (aromatic C), 56.3 (OCH_3). MS *m*/*z* (relative intensity, %): 297 ($[M]^{\cdot+}$, 100). Anal. Found: C, 64.66; H, 3.75; N, 4.78. Calc. for $C_{16}H_{11}NO_5$: C, 64.65; H, 3.73; N, 4.71%.

5.1.5.3. 7-Methoxy-2-(4′-trifluoromethylphenyl)-4H-1-benzopyran-4-one ***(21)***

Yield: 76% m.p. 156–158°C. IR (cm^{-1}, KBr) 1645 (*C*=O). ^1H NMR ($CHCl_3$-*d*) δ 8.12–8.04 (d, $J=10$ Hz, 2H, $H_{3'}+H_{5'}$), 7.91–7.8 (m, 3H, $H_2+H_{6'}+H_6$), 6.8 (s, 1H, H_3), 6.72–6.65 (m, 2H, H_5+H_8), 3.85 (s, 3H, OCH_3). ^{13}C NMR ($CHCl_3$-*d*) δ 178.1 (*C*=O), 164.1 (C_9), 160.2 (C_7), 151.5 (C_2) 140.2 ($C_{4'}$), 138.5 (C_6), 135 (C_3), 132.9 (CF_3), 131.8, 131.1, 127.4, 125.8, 121.8, 112.9, 109.8 (aromatic C), 56.2 (OCH_3). MS *m*/*z* (relative intensity, %): 320 ($[M]^{\cdot+}$, 100). Anal. Found: C, 63.75; H, 3.50; F, 17.81. Calc. for $C_{17}H_{11}O_3F_3$: C, 63.75; H, 3.46; F, 17.79%.

5.1.5.4. 2-(β-Phenethyl)-7-methoxy-4H-1-benzopyran-4-one ***(22)***

Yield: 61%. m.p. 166–167°C. IR (cm^{-1}, KBr) 1640 (*C*=O). ^1H NMR ($CHCl_3$-*d*) δ 8.1 (d, $J=12$ Hz, 1H, H_6), 7.2-7.03 (m, 5H, phenyl H), 6.95–6.80 (m, 2H, H_5+H_8), 6.78 (s, 1H, H_3), 3.8 (s, 3H, OCH_3), 2.98 (t, 2H, CH_2), 2.75 (t, 2H, CH_2). ^{13}C NMR ($CHCl_3$-*d*) δ 177.7 (*C*=O), 163.6 (C_9), 157.6 (C_7), 147.3 (C_2), 134.2 (C_3), 129.9, 128.7, 127.9, 127.7, 126.9, 126.6, 126.3, 124.5, 118.7, 115.1 (aromatic C), 56.2 (OCH_3), 42.5 and 29.8 $(CH_2)_2$. MS *m*/*z* (relative intensity, %): 280 ($[M]^{\cdot+}$, 100). Anal. Found: C, 77.12; H, 5.75. Calc. for $C_{18}H_{16}O_3$: C, 77.13; H, 5.75%.

5.1.6. 1-[2′-(t-Butyldimethylsilyloxy)-4′-methoxyphenyl]-3-(3-pyridyl)-propane-1,3-dione ***(23)***

A solution of Li HMDS in THF (7.14 mL, 7.14 mmol, 1 M solution in THF) was added to a well stirred solution of 2-[(*t*-butyldimethylsilyl)-oxy]-4-methoxyacetophenone (**2**, 1 g, 3.5 mmol) in THF (10 mL) under argon at −78°C in 15 min. After 30 min, a solution of methyl nicotinate (0.5 g, 3.5 mmol) in THF (2 mL) was added dropwise. The reaction mixture was stirred at −78°C for 1 h then at r.t. for 18 h. The solution was quenched with water (15 mL), the THF was evaporated, EtOAc (10 mL) was added, the organic layer was washed with saturated solution of NH_4Cl, dried over $MgSO_4$, filtered and evaporated to give a yellow precipitate which was crystallized from MeOH (0.97 g, 70.5%): m.p. 172–174°C. IR (cm^{-1}, KBr,) 1680 and 1640 (free and associated *C*=O). ^1H NMR ($CHCl_3$-*d*) δ 12.3 (s, 0.88H, enol OH), 9.18 (s, 1H), 8.75 (br s, 1H), 8.15 (m, 1H), 7.65 (d, $J=10.6$ Hz, 1H), for pyridine H_2, H_6, H_5 and H_4, respectively, 7.5–7.4 (m, 1H, $H_{5'}$), 6.7 (s, 0.88 H, vinylic proton of the enol form), 6.55–6.4 (m, 2H, $H_{3'}+H_{6'}$), 4.57 (s, 0.2H, the methylene protons of the keto form), 3.91 (s, 3H, OCH_3), 1.08 (s, 9H, $(CH_3)_3$); 0.25 (s, 6H, $Si(CH_3)_2$). ^{13}C NMR ($CHCl_3$-*d*) δ 195.0 (*C*=O), 166.6 (=C–OH), 165.9 ($C_{4'}$), 152.7 ($C_{2'}$), 148.2 (pyridine C_2), 146.9 (pyridine C_6), 138.9, 134.4, 130.6, 123.9, 119.6, 118.7, 113.1 (pyridine C_3, C_4, C_5 and $C_{1'}$, $C_{3'}$, $C_{5'}$, $C_{6'}$), 93.1 (CH=), 56.1 (OCH_3), 26.5, 26.3, 18.9, 18.3 (CH_3 groups).

5.1.7. 2-(3-Pyridyl)-7-methoxy-4H-1-benzopyran-4-one ***(24)*** *[32]*

1-[2′-(*t*-Butyldimethylsilyloxy)-4′-methoxyphenyl]-3-(3-pyridyl) propane-1,3-dione (**23**, 1 g, 2.6 mmol) was mixed with glacial HOAc (15 mL) and H_2SO_4 (0.1 mL) and heated at 95–100°C under anhydrous condition for 3 h. Acetic acid was distilled off at reduced pressure and the residue was quenched with saturated Na_2CO_3 solution (20 mL) to give gray precipitate which was crystallized from MeOH to give a shiny buff precipitate (0.45 g, 69%), m.p. 182–184°C. IR (cm^{-1}, KBr) 1658 (*C*=O), 1610 (*C*=N), 1595, 1565 (γ-pyrone ring). ^1H NMR ($CHCl_3$-*d*) δ 9.14 (s, 1H,), 8.75 (br s, 1H) and 8.13 (m, 2H) for pyridine H_2, H_6, H_4 and H_5, respectively, 7.45 (br s, 1H, H_6), 7.1-6.95 (m, 2H, H_5+H_8), 6.72 (s, 1H, H_3), 3.89 (s, 3H, OCH_3). ^{13}C NMR ($CDCl_3$) δ 177.6 (*C*=O),166.1 (C_9) 164.7 (C_7), 161.3, 160.9, 158.3, 152.4, 147.8, 135.8, 133.7, 128.2, 127.5, 124.0, 118.1 (pyridine C and C_1, C_2, C_5, C_6, C_8, C_{10}), 56.3 (OCH_3). Anal. Found: C, 71.16; H, 4.40; N, 5.55. Calc. for $C_{15}H_{11}NO_3$: C, 71.14; H, 4.37; N, 5.53%.

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