Studies in Synthesis of Furoflavones Possessing Anti-cancer Activity

Jagdish M. Patel and Shubhangi S. Soman*

Department of Chemistry, Faculty of Science,
The Maharaja Sayajirao University of Baroda, Vadodara 390 002, India.
E-mail: shubhangiss@rediffmail.com, jakpatel21@yahoo.com

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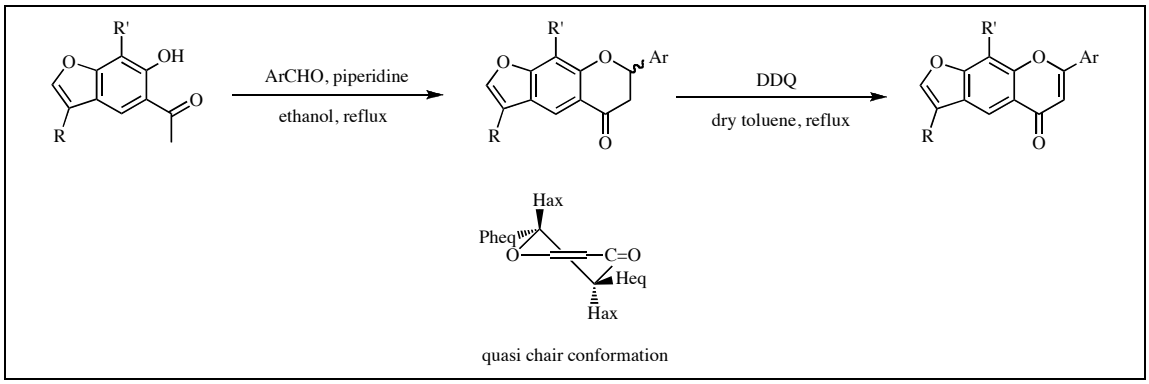

Several new furoflavanones **(3a-3l)** have been synthesized from the *in-situ* generated chalcones by the reaction of *ortho*-hydroxy acetyl benzofuran and aryl aldehyde in presence of piperidine. Ethanolic sodium hydroxide (1%) gave chalcones **(2a-2l)** as the exclusive product. Flavindogenides (3-arylidene flavanones) **(5a-5d)** have been isolated as the co-product along with chalcones and flavanones in cases where excess of aryl aldehyde was used. The stereochemistry of 3-arylidene flavanones has been established by the preparation of both *Z* **(6)** and *E* **(5a-5d)** diastereomers. Single crystal X-ray diffraction data shows the flavanone ring to exist in quasi chair conformation with phenyl ring equatorial. Furoflavanones were finally dehydrogenated to furoflavones **(4a-4l)** using DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone). The compounds have been screened for *in-vitro* cytotoxicity against human cancer cell lines.

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INTRODUCTION

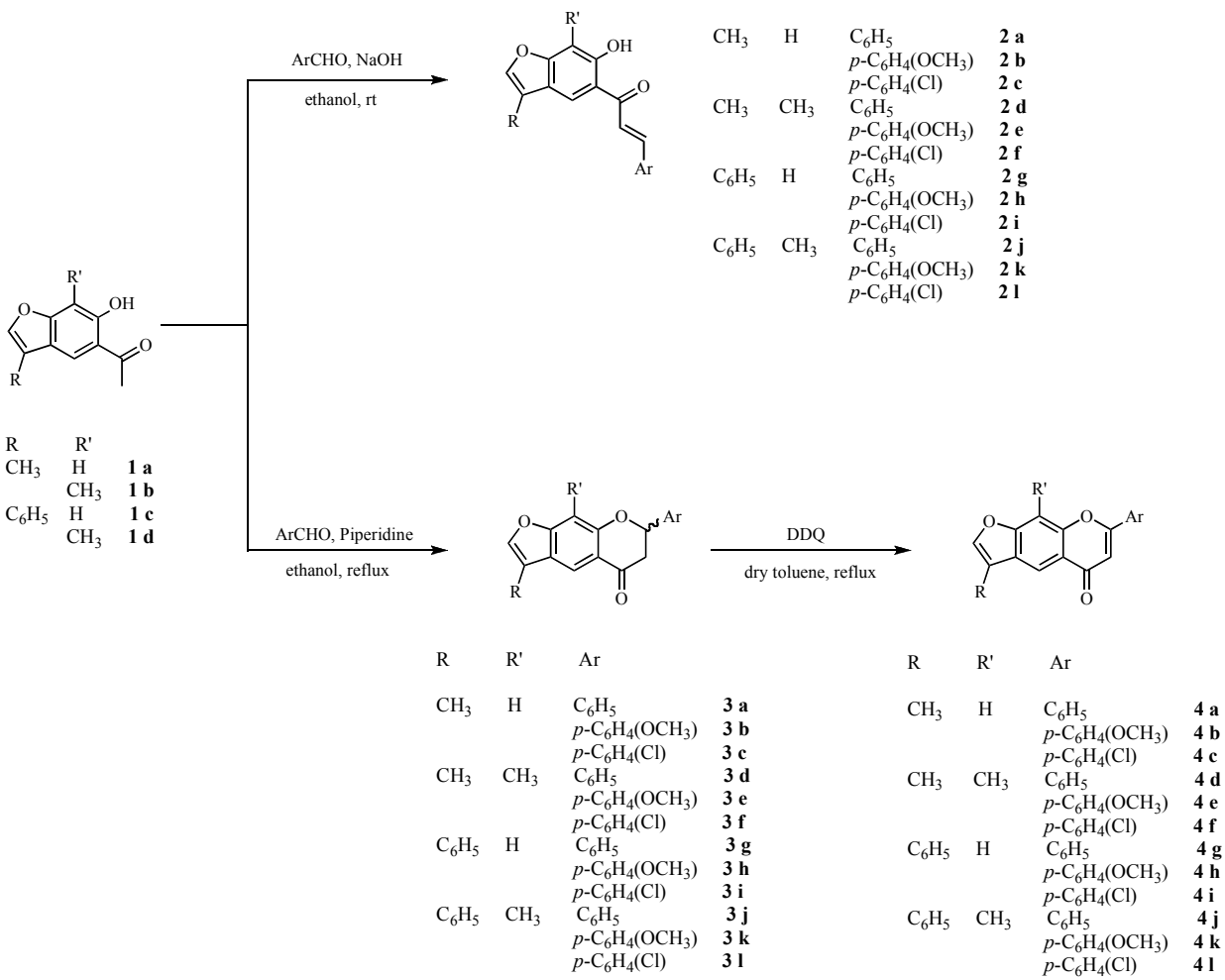
2-Phenyl chromones are a group of flavonoids widely occurring in plants where they play several biological functions [1]. Naturally occurring flavone derivatives like Pongachalcone I, Quercetin, Acacetin, Apigenin, Kaempferol, Kanjone and Pongaglaborrone are known to exhibit variety of pharmacological activities [2-4]. Alkylaminomethyl furoflavones can be used as gastroprotective agents [5]. Quercetin and related flavonoids are known to inhibit the growth of tumor cells. Flavone-8-acetic acid inhibits endothelial cell proliferation *in-vitro* and selectively destroys tumor vasculature, leading to tumor cell death by ischemia. Flavonoids have also been used as modulators of P-glycoprotein in tumor cells [6]. Several methods have been reported for the synthesis of flavonoids in literature [7,8]. Most of the study done hitherto shows the formation of chalcones and flavanones (or flavones) from *ortho*-hydroxy acetophenone in acidic or alkaline conditions [9]. The disadvantage with the basic conditions is the decomposition or retro-Aldol reaction [10], whereas acid catalyzed condensation is known to give mixture of chalcones, flavanones and 3-benzylidene flavanones (flavindogenides) [11]. Several furoflavones, furoflavanones and furochalcones have been reported to possess interesting pharmacological properties [12], which prompted us to synthesize some new furoflavones and study their cytotoxicity behaviour, which has not been reported till date. It was also of considerable interest to study the orientation and conformation of flavanone ring in furoflavanones, since no such data was available in literature.

Herein, a facile one-pot method for the synthesis of some new furoflavanones and its crystal structure has been reported. Two of the furoflavones have been screened for *in-vitro* cytotoxicity against human cancer cell lines. The quasi chair conformation of the flavanone ring has been established on the basis of X-ray crystallography. The reaction sequence for different title compounds is outlined in Scheme 1.

RESULTS AND DISCUSSION

Ortho-hydroxy acetyl benzofurans **(1a-1d)** [13], were condensed with different aryl aldehydes in 1 % ethanolic sodium hydroxide to give corresponding chalcones **(2a-2l)**. Though such a low concentration of alkali was used, there was no evidence of formation of flavanones, which was contradictory to the reports in literature which indicated that low concentration of alkali favoured ring closure

Scheme 1



R	R'		
CH_3	H	**1 a**	
	CH_3	**1 b**	
C_6H_5	H	**1 c**	
	CH_3	**1 d**	

R	R'	Ar	
CH_3	H	C_6H_5	**2 a**
		p-$C_6H_4(OCH_3)$	**2 b**
		p-$C_6H_4(Cl)$	**2 c**
CH_3	CH_3	C_6H_5	**2 d**
		p-$C_6H_4(OCH_3)$	**2 e**
		p-$C_6H_4(Cl)$	**2 f**
C_6H_5	H	C_6H_5	**2 g**
		p-$C_6H_4(OCH_3)$	**2 h**
		p-$C_6H_4(Cl)$	**2 i**
C_6H_5	CH_3	C_6H_5	**2 j**
		p-$C_6H_4(OCH_3)$	**2 k**
		p-$C_6H_4(Cl)$	**2 l**

R	R'	Ar	
CH_3	H	C_6H_5	**3 a**
		p-$C_6H_4(OCH_3)$	**3 b**
		p-$C_6H_4(Cl)$	**3 c**
CH_3	CH_3	C_6H_5	**3 d**
		p-$C_6H_4(OCH_3)$	**3 e**
		p-$C_6H_4(Cl)$	**3 f**
C_6H_5	H	C_6H_5	**3 g**
		p-$C_6H_4(OCH_3)$	**3 h**
		p-$C_6H_4(Cl)$	**3 i**
C_6H_5	CH_3	C_6H_5	**3 j**
		p-$C_6H_4(OCH_3)$	**3 k**
		p-$C_6H_4(Cl)$	**3 l**

R	R'	Ar	
CH_3	H	C_6H_5	**4 a**
		p-$C_6H_4(OCH_3)$	**4 b**
		p-$C_6H_4(Cl)$	**4 c**
CH_3	CH_3	C_6H_5	**4 d**
		p-$C_6H_4(OCH_3)$	**4 e**
		p-$C_6H_4(Cl)$	**4 f**
C_6H_5	H	C_6H_5	**4 g**
		p-$C_6H_4(OCH_3)$	**4 h**
		p-$C_6H_4(Cl)$	**4 i**
C_6H_5	CH_3	C_6H_5	**4 j**
		p-$C_6H_4(OCH_3)$	**4 k**
		p-$C_6H_4(Cl)$	**4 l**

whereas high concentration of alkali favoured ring fission [14]. ^{1}H nmr of chalcone *E*-3-(4-chloro-phenyl)-1-(6-hydroxy-3,7-dimethyl-benzofuran-5-yl)-propenone **2f** exhibited two doublets corresponding to one proton each at δ 7.70-7.74 ppm with J = 15.48 Hz and δ 7.88-7.92 ppm with J = 15.48 Hz for C(α)H and C(β)H respectively, showing the formation of chalcone in *E* configuration. The broad and shallow ir absorption at 3445 cm^{-1} (*s*) for phenolic –OH indicates strong intramolcular hydrogen bonding. The carbonyl absorption at 1633 cm^{-1} (*s*) along with absorption at 1556 cm^{-1} indicated presence of α,β-unsaturated carbonyl system, which further supports the *E* configuration of chalcone **2f**. The furan ring (-C=C-) stretching was observed at 1609 cm^{-1} (*s*). The lcms for chalcone **2f** was obtained as *m/z*: 349 (M+23, 14 %), 329.2 (M+2, 37), 327.1 (M+1, 100), 301.2 (11), 300.3 (26), 295.1 (20), 293.2 (17), 279.2 (9) and 269.2 (6). The UV spectrum in ethanol showed absorption at 323, 247 and 225 nm.

However when o*rtho*-hydroxy acetyl benzofuran **(1a-1d)** were condensed with different aryl aldehydes in presence of catalytic amount of piperidine, it gave a mixture of chalcones and flavanones **(3a-3l)**. Flavanone being the major product, crystallized out from the mixture of ethanol:toluene (3:7). In the ^{1}H nmr of 7-(4-chloro-phenyl)-3,9-dimethyl-6,7-dihydrofuro[3,2-*g*]chromen-5-one **3f**, the flavanone ring proton C(2)H appeared as a doublet of doublet at δ 5.48-5.52 ppm. The double doublet for one proton at δ 3.02-3.10 ppm with J = 16.8 Hz (geminal coupling – diastereotopic protons) and J = 12.4 Hz (vicinal diaxial coupling) indicated C(3)H proton to be axial, and a doublet of doublet at δ 2.89-2.94 ppm with J = 3.2 Hz (vicinal coupling) and J = 16.8 Hz (geminal coupling – diastereotopic protons) indicated another proton at C(3) to be equatorial; forming an ABX system. The coupling constant of C(2)H proton, 12.4 Hz (vicinal diaxial coupling) and 3.2 Hz (vicinal axial-equatorial coupling) indicated it to be axial in the quasi chair conformation of the flavanone ring, with phenyl ring equatorial [15], as shown in Figure 1. The ^{13}C nmr of the same compound with signals at δ 44.61 ppm (C-3

methylene), 77.76 ppm (C-2 oxymethine) and 192.29 ppm (C-4 >C=O) further confirmed the structure of flavanone. The lower ir absorption at 1681 cm^{-1} (*s*) indicated conjugation and hence coplanarity of the carbonyl group with the phenyl ring. The band at 1629 cm^{-1} (*s*) indicated (-C=C-) stretching vibration of the furan ring. The lcms for flavanone 7-(4-methoxy-phenyl)-3,9-dimethyl-6,7-dihydro-furo[3,2-*g*]chromen-5-one **3e** was obtained as *m/z*: 345.2 (M+23, 16 %), 324.3 (M+2, 26) and 323.3 (M+1, 100). The UV spectrum in ethanol showed absorption at 340, 242 and 227 nm. The quasi chair conformation of the flavanone ring is further confirmed by single crystal X-ray diffraction data of **3f**.

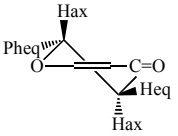
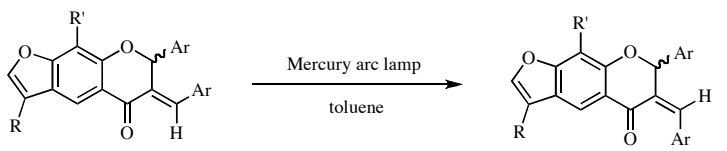


Figure 1. Quasi chair conformation of the flavanone ring.

When excess of aryl aldehyde was used during the reaction, it was observed that along with flavanones, 3-arylidene flavanones **(5a-5d)** were also formed. They were isolated by column chromatography and characterized (whether *E* or *Z*) by carrying out reaction of some of the o*rtho*-hydroxy acetyl benzofuran with excess aryl aldehyde in a specific experiment. When two moles of aryl aldehyde were condensed with one mole of *ortho*-hydroxy acetyl benzofuran in presence of piperidine, 3-arylidene flavanone was the major product obtained. Stereochemistry of 3-arylidene flavanones has been determined by carrying out synthesis of both *Z* and *E* diastereomers. In the ^{1}H nmr of *E*-6-benzylidene-3-methyl-7-phenyl-6,7-dihydro-furo[3,2-*g*]chromen-5-one **5a**, two singlets at δ 6.6 ppm and 8.1 ppm for one proton each indicated C(2)H flavanone proton and vinylic proton respectively. This shows the formation of 3-arylidene flavanones in *E* configuration since the vinylic proton is deshielded due to the diamagnetic anisotropy of the carbonyl group [16]. The *E* configuration of 3-arylidene flavanone was further confirmed by converting compound **5a** into its *Z* isomer **6** photochemically, using mercury arc 450 W lamp and toluene as solvent (Scheme 2). *Z*-6-Benzylidene-3-methyl-7-phenyl-6,7-dihydro-furo[3,2-*g*]-chromen-5-one **6** was purified by column chromatography using neutral alumina, as silica gel showed some conversion back into the *E* isomer. The ^{1}H nmr of compound **6** showed two singlets at δ 6.15 and 6.7 ppm for one proton each indicating C(2)H flavanone proton and vinylic proton respectively. Since the vinylic proton is now shielded, it confirmed compound **6** to be in *Z* configuration. It was further supported by the ir absorption band of carbonyl group at 1670 cm^{-1} (*s*) for the *E* isomer and at 1661 cm^{1}(*s*) for the *Z* isomer. The absorption bands at 1624 cm^{-1} (*s*) and 1604 cm^{-1} (*s*) indicated furan ring (-C=C-) stretching and alkene (-C=C-) stretching respectively in both *E* and *Z* isomers. The UV spectrum in ethanol showed absorption at 309, 257 and 227 nm for the *E* isomer and 306, 248 and 227 nm for the *Z* isomer.

Finally, all the flavanones were dehydrogenated to flavones **(4a-4l)** using DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone) in dry toluene. In the ^{1}H nmr of 7-(4-methoxy-phenyl)-3,9-dimethyl-furo[3,2-*g*]chromen-5-one **4e**, singlet at δ 6.82 ppm for one proton corresponding to C(3)H of the flavone ring confirms that dehydrogenation has taken place (disappearance of all double doublets). The ^{13}C nmr of this compound showed values at δ 104.49 ppm (C-3) and 163.32 ppm (C-2), which supports the dehydrogenated product. In the ir spectrum, the carbonyl absorption was further lowered and observed at 1651 cm^{-1} (*s*), while (-C=C-) stretching vibration of flavone and furan ring was observed at 1610 cm^{-1} (*s*) and 1621 cm^{-1} (*s*) respectively. The UV spectrum in ethanol showed absorption at 307, 278, 245 and 227 nm. The lcms for flavone 3,7-diphenyl-furo[3,2-*g*]chromen-5-one **4g** was obtained as *m/z*: 361.1 (M+23, 11 %), 340.1 (M+2, 22) and 339.1 (M+1, 100).

Scheme 2. Photoisomerization of *E*-3 Arylidene flavanones to *Z*-3 Arylidene flavanones.



E-3 Arylidene flavanones

R	R'	Ar	
CH_3	H	C_6H_5	**5 a**
CH_3	H	*p*-C_6H_4(Cl)	**5 b**
CH_3	CH_3	*p*-$C_6H_4(OCH_3)$	**5 c**
C_6H_5	CH_3	*p*-$C_6H_4(OCH_3)$	**5 d**

Z -3 Arylidene flavanones

R	R'	Ar	
CH_3	H	C_6H_5	**6**

The structures of all compounds have been established on the basis of their elemental analyses and spectral (ir, nmr) data. The long range coupling between C3-CH_3 and C2-H of the furan ring in the compounds synthesized from **1a** and **1b** has been confirmed by ^{1}H-COSY spectra.

Crystal structure of flavanone (7-(4-chloro-phenyl)-3,9-dimethyl-6,7-dihydro-furo[3,2-*g*]chromen-5-one 3f). Crystallization of flavanones **(3a-3l)** was studied in ethanol: toluene mixture (3:7). Compound **3f** gave good quality needle like crystals, which were submitted for single crystal X-ray analysis. Compound **3f** crystallizes in a centro symmetric monoclinic space group $P2_1/c$. The asymmetric unit consists of a single flavanone molecule at a normal position. As can be seen from Figure 2 (ORTEP diagram) flavanone ring exists in quasi-chair conformation, with phenyl ring at equatorial position. The crystal structure shows the (*S*)-configuration of furoflavanone. All the atoms

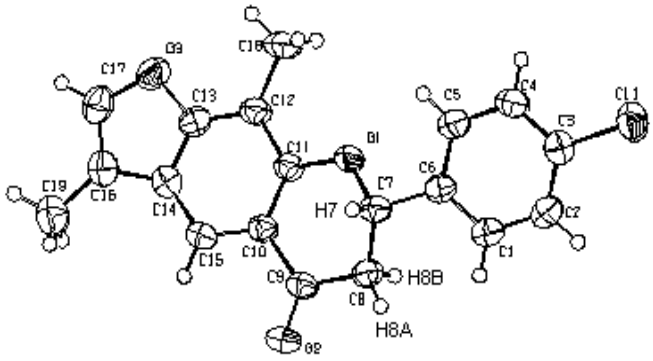


Figure 2. ORTEP diagram of 7-(4-chloro-phenyl)-3,9-dimethyl-6,7-dihydro-furo[3,2-*g*]chromen-5-one **3f** (50% probability factor for thermal ellipsoid with atom numbering scheme).

apart from C-7 are coplanar. Atom C-7 deviates from the plane defined by atoms C8/C9/C10/C11/O1 by 0.610 Å. The dihedral angle between the planes formed by O1/C7/C8 and C8/C9/C10/C11/O1 is 47.20° whereas the dihedral angle between C1/C2/C3/C4/C5/C6 and C8/C9/C10/C11/O1 planes is 4.56°. The torsion angle –54.31 for H7-C7-C8-$H8_A$ indicates that H-7 and $H8_A$ are not in one plane *i.e.* H-7 is axial and H-8_A is equatorial, while the torsion angle –171.97 for H7-C7-C8-$H8_B$ indicates that H-7 and H-8_B are almost in one plane *i.e*. H-7 is axial and H-8_B is also axial. The torsion angle –51.16 for C6-C7-C8-$H8_B$ indicates that phenyl ring and H-8_B are not in one plane (*i.e*. phenyl ring is equatorial and H-8_B is axial). Further, the torsion angle –81.77 for H7-C7-C6-C5 and 95.76 for H7-C7-C6-C1 clearly indicates that phenyl ring and H-7 are almost perpendicular to each other *i.e*. H-7 is axial and phenyl ring is equatorial and parallel to the plane formed be C8/C9/C10/C11/O1. The torsion angle values for selected atoms as observed for the molecule is shown below which proves the existence of flavanone ring in quasi chair conformation with phenyl ring at equatorial position and H-7 hydrogen at axial position. The values of final R indices R_1= 0.0691 and WR_2= 0.1634 indicates the crystal structure is well resolved. Selected torsion angles are shown below.

Selected Atoms	Torsion Angle
H7-C7-C8-$H8_A$	-54.31
H7-C7-C8-$H8_B$	-171.97
C6-C7-C8-$H8_A$	66.51
C6-C7-C8-$H8_B$	-51.16
H7-C7-C6-C5	-81.77
H7-C7-C6-C1	95.76

Crystal structure data & structure refinement for the molecule is shown below:

Empirical formula	$C_{19}H_{15}ClO_3$
Formula weight	326.76
Temperature	273(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	$P2_1/c$
Unit cell dimensions	a = 14.401(3) Å α = 90° b = 5.4980(11) Å β = 109.841(3)° c = 21.006(4)Å γ = 90°
Volume	1564.4(6) $Å^3$
Z	4
Density (calculated)	1.387 mg/m^3
Absorption coefficient ($\mu M_o K_\alpha$)	0.257 mm^{-1}
F(000)	680
Crystal size	0.24 x 0.15 x 0.10 mm
Theta range for data collection	1.50° to 28.26°
Index ranges	-18<=h<=19, -5<=k<=7, -26<=l<=26
Reflections collected	8544
Independent reflections	3574 [R(int) = 0.0311]
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3574 / 0 / 210
Goodness-of-fit on F^2	1.085
Final R indices [$I>2\sigma(I)$]	R1 = 0.0691, wR2 = 0.1634
R indices (all data)	R1 = 0.0935, wR2 = 0.1765
Largest diff. peak and hole	0.421 and -0.234 $e.A^{-3}$

Crystallographic data (excluding structure factors) for the structure in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 621173.

Physiological activity.

Anticancer activity. Compounds 7-(4-chlorophenyl)-3-methyl-furo[3,2-*g*]chromen-5-one **4c** and 3,7-diphenyl-furo[3,2-*g*]chromen-5-one **4g** were randomly selected from the group of furoflavones **(4a-4l)** synthesized and were evaluated for *in-vitro* cytotoxicity against human cancer cell lines. The human cancer cell lines produced from National Cancer Institute, Frederick, U.S.A. were used in present study. Cells were grown in tissue culture flasks in complete growth medium (RPMI-1640 medium with 2 m*M* glutamine, 100 μg/mL streptomycin, pH 7.4, sterilized by filtration and supplemented with 10 % fetal

Table 1

Cell Line Type		Colon	Colon	Colon	Prostate	Liver	Breast
Cell line		502713	HT-29	SW-620	DU-145	HEP-2	MCF-7
Compound	Conc. (M)	Growth Inhibition (%)					
4c	1 X 10^{-6}	0	10	0	3	-	-
	1 X 10^{-5}	0	12	0	8	0	6
	1 X 10^{-4}	-	-	0	11	3	30
4g	1 X 10^{-6}	0	5	0	0	-	-
	1 X 10-5	0	6	29	5	15	35
	1 X 10-4	-	-	32	40	30	74
5FU	5 X 10-5	25	36	41	31	-	-
Mito-C	1 X 10-5	84	63	67	79	-	65
Paclitaxel	1 X 10-5	26	76	41	-	-	-
Adriamycin	1 X 10-6	-	-	-	67	47	78

calf serum and 100 units/mL penicillin before use) at 37 °C in an atmosphere of 5 % CO_2 and 90 % relative humidity in a carbon dioxide incubator. The cells at subconfluent stage were harvested from the flask by treatment with trypsin (0.05 % in PBS containing 0.02 % EDTA) for determination of cytotoxicity. Cells with viability of more than 98 %, as determined by trypan blue exclusion, were used for assay. The cell suspension of 1 x 10^5 cells/mL was prepared in complete growth medium for determination of cytotoxicity.

Stock solutions of 2 x 10^{-2} *M* of **4c** and **4g** were prepared in DMSO. The stock solutions were serially diluted with complete growth medium containing 50 μg/mL of gentamycin to obtain working test solutions of required concentrations.

In-vitro cytotoxicity against six human cancer cell lines was determined by two different experiments, using 96-well tissue culture plates. The 100 μL of cell suspension was added to each well of the 96-well tissue culture plate. The cells were incubated for 24 hours. Test materials in complete growth medium (100 μL) were added after 24 hours incubation to the wells containing cell suspension. The plates were further incubated for 48 hours (at 37 °C in an atmosphere of 5 % CO_2 and 90 % relative humidity in a carbon dioxide incubator) after addition of test material and then the cell growth was stopped by gently layering trichloroacetic acid (50 % TCA, 50 μL) on top of the medium in all the wells. The plates were incubated at 4 °C for one hour to fix the cells attached to the bottom of the wells. The liquid of all the wells was gently pipetted out and discarded. The plates were washed five times with distilled water to remove TCA, growth medium low molecular weight metabolites, serum proteins *etc*. and air-dried. Cell growth was measured by staining with Sulforhodamine B dye. The adsorbed dye was dissolved in Tris-Buffer (100 μL, 0.01 *M*, pH 10.4) and plates were gently shaken for 10 minutes on a mechanical shaker. The optical density (OD) was recorded on ELISA reader at 540 nm. The cell growth was calculated by subtracting mean OD value of respective blank from the mean OD value of experiment set. Percent growth in presence of test material was calculated considering the growth in absence of any test material as 100 % and in turn percent growth inhibition in presence of test material was calculated.

Compound **4g** showed 74 % growth inhibition against Breast MCF-7 cell line and 40 % growth inhibition against Prostate DU-145 cell line at 1 x 10^{-4} concentrations. 5FU, Mito-C, Paclitaxel and Adriamycin are the standard drugs used. The results are shown in Table 1.

CONCLUSIONS

Present investigation provides a one-pot process for the synthesis of furoflavanones. The reaction when carried out in ethanolic sodium hydroxide gave chalcone as the exclusive product, while reaction in piperidine gave flavanone as the major product. Molar excess of aryl aldehyde in the preparation of flavanones using piperidine, leads to the formation of 3-arylidene flavanones as a co-product. The quasi chair conformation of the flavanone ring has been confirmed by its X-ray crystal structure. One of the furoflavone **4g**, shows growth inhibition up to 74 % against Breast MCF–7 cancer cell line and 40 % against Prostate DU-145 cell line, so other compounds can also be explored for anti-cancer activity.

EXPERIMENTAL

^{1}H and ^{13}C nmr spectra were recorded on Bruker NMR spectrometer. Chemical shifts are given in δ ppm downfield from tetramethylsilane as internal standard and coupling constants are in Hertz. Infrared spectra were recorded on Perkin-Elmer FT-IR spectrometer (spectrum RX1) using potassium bromide optics. UV spectra were recorded on

Perkin Elmer Lambda 35 UV/Vis spectrophotometer. Elemental analyses were carried out on Perkin-Elmer C, H, N, S analyzer (Model-2400) and are given in percentage. The mass spectrum was obtained on Perkin-Elmer Sciex Triple Quadrupole LC/MS/MS Mass Spectrometer (Model-016932) with Ion Spray source using mobile phase Acetonitrile: Ammonium acetate 1mM (90:10 % v/v). X-ray diffraction data were collected using Mo Kα (λ=0.71073 Å) radiation on a SMART APEX diffractometer equipped with a CCD area detector. Data collection, data reduction, structure solution/refinement were carried out using the software package of SMART APEX. Graphics were generated using MERCURY 1.4.1 [17]. Melting points are uncorrected and were determined using a scientific capillary melting point apparatus. Purity of the compounds was checked by tlc on Acme's silica gel G plates using UV/I_2 vapor as visualizing agent. Acme's silica gel (60-120 mesh) and neutral alumina powder was used for column chromatographic purification.

Single crystal X-ray diffraction. X-ray quality single crystals of **3f** were grown in a slow evaporation condition at room temperature. Crystals were obtained from a mixture of ethanol and toluene (3:7). The structure was solved by direct methods and refined in a routine manner. All hydrogen atoms were geometrically fixed and refined.

General procedure for (2a-2l).

***E*-1-(6-Hydroxy-3-methyl-benzofuran-5-yl)-3-phenyl-propenone 2a.** A mixture of 1-(6-hydroxy-3-methyl-benzofuran-5-yl)-ethanone **1a** (0.0043 moles) and benzaldehyde (0.0043 moles) in ethanolic sodium hydroxide (50 mL, 1%) was stirred for 8 hours at room temperature. The excess of ethanol was distilled off *in vacuo* and the reaction mixture was poured into ice hydrochloric acid and the solid collected by filtration. The product was purified by column chromatography using petroleum ether (60-80 ℃): ethyl acetate (9:1) mixture as eluent to give *E*-1-(6-hydroxy-3-methyl-benzofuran-5-yl)-3-phenyl-propenone **2a** (81 %) as orange crystals, mp 127-128 °C; ν_{max}/cm^{-1}: 3437, 3110, 2986, 1632, 1556, 1521, 1217 and 1164; ^{1}H nmr (300 MHz; $CDCl_3$; Me_4Si): δ 2.27 (3H, d, J = 1.1, C(3)CH_3), 7.02 (1H, s, C(7)H), 7.34 (1H, d, J = 1.1, C(2)H), 7.45-7.47 (3H, m, C(3')H, C(4')H, C(5')H), 7.70-7.75 (1H, d, J = 15.5, C(α)H), 7.71-7.72 (2H, m, C(2')H and C(6')H), 7.92-7.97 (1H, d, J = 15.5, C(β)H), 8.01 (1H, s, C(4)H) and 13.05 (1H, s, C(6)OH). *Anal*. Calcd. for $C_{18}H_{14}O_3$ (278.30): C, 77.68; H, 5.07. Found: C, 77.59; H, 5.01.

***E*-1-(6-Hydroxy-3-methyl-benzofuran-5-yl)-3-(4-methoxy-phenyl)-propenone 2b.** 55 %; orange crystals; mp 127-129 °C; ν_{max}/cm^{-1}: 3452, 3124, 2926, 1637, 1601, 1561, 1508, 1188, 1167 and 1144; ^{1}H nmr (400 MHz; $CDCl_3$; Me_4Si): δ 2.26 (3H, d, J = 1.1, C(3)CH_3), 3.89 (3H, s, C(4')OCH_3), 6.95-6.97 (2H, d, J = 8.44, C(3')H and C(5')H), 7.01 (1H, s, C(7)H), 7.33 (1H, d, J = 1.1, C(2)H), 7.58-7.62 (1H, d, J = 15.32, C(α)H), 7.65-7.67 (2H, d, J = 8.44, C(2')H and C(6')H), 7.90-7.94 (1H, d, J = 15.32, C(β)H), 8.01 (1H, s, C(4)H) and 13.14 (1H, s, C(6)OH). *Anal*. Calcd. for $C_{19}H_{16}O_4$ (308.33): C, 74.01; H, 5.23. Found: C, 73.71; H, 4.93.

***E*-3-(4-Chloro-phenyl)-1-(6-hydroxy-3-methyl-benzofuran-5-yl)-propenone 2c.** 68 %; orange crystals; mp 159-160 °C; ν_{max}/cm^{-1}: 3444, 3122, 2916, 1629, 1611, 1569, 1511, 1178, 1156 and 1139; ^{1}H nmr (400 MHz; $CDCl_3$; Me_4Si): δ 2.27 (3H, d, J = 1.1, C(3)CH_3), 7.03 (1H, s, C(7)H), 7.35 (1H, d, J = 1.1, C(2)H), 7.42-7.44 (2H, d, J = 8.36, C(3')H and C(5')H), 7.63-7.65 (2H, d, J = 8.36, C(2')H and C(6')H), 7.68-7.72 (1H, d, J = 15.44, C(α)H), 7.88-7.91 (1H, d, J = 15.44, C(β)H), 8.00 (1H, s, C(4)H), 12.97 (1H, s, C(6)OH). *Anal*. Calcd. for $C_{18}H_{13}O_3Cl$ (312.75): C, 69.12; H, 4.18. Found: C, 68.78; H, 3.98.

***E*-1-(6-Hydroxy-3,7-dimethyl-benzofuran-5-yl)-3-phenyl-propenone 2d.** 77 %; orange crystals; mp 113-114 °C; ν_{max}/cm^{-1}: 3445, 3115, 2956, 1644, 1566, 1528, 1209 and 1163; ^{1}H nmr (300 MHz; $CDCl_3$; Me_4Si): δ 2.29 (3H, d, J = 1.2, C(3)CH_3), 2.48 (3H, s, C(7)CH_3), 7.34 (1H, d, J = 1.2, C(2)H), 7.46-7.49 (3H, m, C(3')H, C(4')H, C(5')H), 7.70-7.75 (1H, d , J = 15.6, C(α)H), 7.73-7.74 (2H, m, C(2')H and C(6')H), 7.94-7.99 (1H, d, J = 15.6, C(β)H), 8.1 (1H, s, C(4)H) and 13.1 (1H, s, C(6)OH). *Anal*. Calcd. for $C_{19}H_{16}O_3$ (292.33): C, 78.06; H, 5.51. Found: C, 78.12; H, 5.55.

***E*-1-(6-Hydroxy-3,7-dimethyl-benzofuran-5-yl)-3-(4-methoxy-phenyl)-propenone 2e.** 51 %; orange crystals; mp 144-145 °C; ν_{max}/cm^{-1}: 3441, 3121, 2923, 1631, 1590, 1560, 1518, 1181, 1163 and 1149; ^{1}H nmr (400 MHz; $CDCl_3$; Me_4Si): δ 2.28 (3H, d, J = 1.2, C(3)CH_3), 2.41 (3H, s, C(7)CH_3), 3.89 (3H, s, C(4')OCH_3), 6.976-6.998 (2H, d, J = 8.8, C(3')H and C(5')H), 7.38 (1H, d, J = 1.2, C(2)H), 7.63-7.67 (1H, d, J = 15.6, C(α)H), 7.673-7.695 (2H, d, J = 8.8, C(2')H and C(6')H), 7.904 (1H, s, C(4)H), 7.921-7.960 (1H, d, J = 15.6, C(β)H) and 13.418 (1H, s, C(6)OH). *Anal*. Calcd. for $C_{20}H_{18}O_4$ (322.35): C, 74.51; H, 5.62. Found: C, 74.21; H, 5.34.

***E*-3-(4-Chloro-phenyl)-1-(6-hydroxy-3,7-dimethyl-benzofuran-5-yl)-propenone 2f.** 74.5 %; orange crystals; mp 206-207 °C; ν_{max}/cm^{-1}: 3445, 3114, 2916, 1633, 1609, 1556, 1500, 1178, 1163 and 1141; ^{1}H nmr (400 MHz; $CDCl_3$; Me_4Si): δ 2.3 (3H, d, J = 1.4, C(3)CH_3), 2.4 (3H, s, C(7)CH_3), 7.37 (1H, d, J = 1.4, C(2)H), 7.42-7.44 (2H, d, J = 8.4, C(3')H and C(5')H), 7.64-7.66 (2H, d, J = 8.4, C(2')H and C(6')H), 7.70-7.74 (1H, d, J = 15.48, C(α)H), 7.88-7.92 (1H, d, J = 15.48, C(β)H), 8.05 (1H, s, C(4)H), 12.99 (1H, s, C(6)OH); lcms: *m/z* 349 (M+23, 14 %), 329.2 (M+2, 37), 327.1 (M+1, 100), 301.2 (11), 300.3 (26), 295.1 (20), 293.2 (17), 279.2 (9), 269.2 (6). *Anal*. Calcd. for $C_{19}H_{15}O_3Cl$ (326.77): C, 69.83; H, 4.62. Found: C, 69.57; H, 4.60.

***E*-1-(6-Hydroxy-3-phenyl-benzofuran-5-yl)-3-phenyl-propenone 2g.** 89 %; orange crystals; mp 159-160 °C; ν_{max}/cm^{-1}: 3433, 2933, 1639, 1611, 1555, 1511, 1467, 1376, 1247 and 1135; ^{1}H nmr (300 MHz; $CDCl_3$; Me_4Si): δ 7.12 (1H, s, C(7)H), 7.43-7.69 (12H, m, C(α)H, C(2)H, C(2')H to C(6')H, C(2")H to C(6")H), 7.93-7.99 (1H, d, J = 15.38, C(β)H), 8.30 (1H, s, C(4)H), and 13.03 (1H, s, C(6)OH). *Anal*. Calcd. for $C_{23}H_{16}O_3$ (340.37): C, 81.16; H, 4.73. Found: C, 80.52; H, 4.40.

***E*-1-(6-Hydroxy-3-phenyl-benzofuran-5-yl)-3-(4-methoxy-phenyl)-propenone 2h.** 59.5 %; orange crystals; mp 175-177 °C; ν_{max}/cm^{-1}: 3449, 3113, 2926, 1639, 1605, 1567, 1512, 1207 and 1172; ^{1}H nmr (400 MHz; $CDCl_3$; Me_4Si): δ 3.87 (3H, s, C(4")OCH_3), 6.94-6.96 (2H, d, J = 8.48, C(3")H and C(5")H), 7.12 (1H, s, C(7)H), 7.42-7.46 (1H, m, C(4')H), 7.53-7.57 (1H, d, J = 15.28, C(α)H), 7.54-7.57 (2H, d, J = 8.48, C(2")H and C(6")H), 7.61-7.63 (4H, m, C(2')H, C(3')H, C(5')H, C(6')H), 7.70 (1H, s, C(2)H), 7.92-7.96 (1H, d, J = 15.28, C(β)H), 8.31 (1H, s, C(4)H) and 13.16 (1H, s, C(6)OH). *Anal*. Calcd. for $C_{24}H_{18}O_4$ (370.40): C, 77.82; H, 4.89. Found: C, 77.98; H, 4.91.

***E*-3-(4-Chloro-phenyl)-1-(6-hydroxy-3-phenyl-benzofuran-5-yl)-propenone 2i.** 81 %; orange crystals; mp 152-153 °C; ν_{max}/cm^{-1}: 3439, 3122, 2928, 1633, 1611, 1566, 1528, 1222 and 1151; ^{1}H nmr (300 MHz; $CDCl_3$; Me_4Si): δ 7.14 (1H, s, C(7)H), 7.41-7.69 (10H, m, C(2')H, C(3')H, C(4')H, C(5')H, C(6')H,

C(2'')H, C(3'')H, C(5'')H, C(6'')H, C(α)H), 7.71 (1H, s, C(2)H), 7.89-7.94 (1H, d, J = 15.4, C(β)H), 8.29 (1H, s, C(4)H) and 12.98 (1H, s, C(6)OH). *Anal*. Calcd. for $C_{23}H_{15}O_3Cl$ (374.82): C, 73.70; H, 4.03. Found: C, 73.34; H, 4.01.

***E*-1-(6-Hydroxy-7-methyl-3-phenyl-benzofuran-5-yl)-3-phenyl-propenone 2j.** 85.5 %; orange crystals; mp 188-189 °C; ν_{max}/cm^{-1}: 3437, 2932, 1638, 1588, 1556, 1500, 1451, 1386, 1255 and 1175; ^{1}H nmr (400 MHz; $CDCl_3$; Me_4Si): δ 2.48 (3H, s, C(7)CH_3), 7.44-7.74 (12H, m, C(2)H, C(α)H, C(2')H to C(6')H, C(2'')H to C(6'')H), 7.96-8.00 (1H, d, J = 15.6, C(β)H), 8.19 (1H, s, C(4)H) and 13.31 (1H, s, C(6)OH). *Anal*. Calcd. for $C_{24}H_{18}O_3$ (354.40): C, 81.33; H, 5.11. Found: C, 81.16; H, 4.81.

***E*-1-(6-Hydroxy-7-methyl-3-phenyl-benzofuran-5-yl)-3-(4-methoxy-phenyl)-propenone 2k.** 61 %; orange crystals; mp 210-212 °C; ν_{max}/cm^{-1}: 3441, 3110, 2946, 1644, 1615, 1560, 1522, 1201 and 1177; ^{1}H nmr (400 MHz; $CDCl_3$; Me_4Si): δ 2.49 (3H, s, C(7)CH_3), 3.89 (3H, s, C(4'')OCH_3), 6.95-6.97 (2H, d, J = 8.5, C(3'')H and C(5'')H), 7.43-7.47 (1H, m, C(4')H), 7.53-7.57 (1H, d, J = 15.3, C(α)H), 7.56-7.59 (2H, d, J = 8.48, C(2'')H and C(6'')H), 7.62-7.64 (4H, m, C(2')H, C(3')H, C(5')H, C(6')H), 7.70 (1H, s, C(2)H), 7.93-7.97 (1H, d, J = 15.3, C(β)H), 8.33 (1H, s, C(4)H) and 13.19 (1H, s, C(6)OH). *Anal*. Calcd. for $C_{25}H_{20}O_4$ (384.42): C, 78.10; H, 5.24. Found: C, 77.82; H, 5.03.

***E*-3-(4-Chloro-phenyl)-1-(6-hydroxy-7-methyl-3-phenyl-benzofuran-5-yl)-propenone 2l.** 84 %; orange crystals; mp 198-199 °C; ν_{max}/cm^{-1}: 3455, 3105, 2966, 1634, 1560, 1522, 1207 and 1167; ^{1}H nmr (300 MHz; $CDCl_3$; Me_4Si): δ 2.50 (3H, s, C(7)CH_3), 7.44-7.71 (10H, m, C(2')H, C(3')H, C(4')H, C(5')H, C(6')H, C(2'')H, C(3'')H, C(5'')H, C(6'')H, C(α)H), 7.71 (1H, s, C(2)H), 7.90-7.95 (1H, d, J = 15.52, C(β)H), 8.32 (1H, s, C(4)H) and 12.99(1H, s, C(6)OH). *Anal*. Calcd. for $C_{24}H_{17}O_3Cl$ (388.84): C, 74.13; H, 4.40. Found: C, 73.88; H, 4.43.

General procedure for (3a-3l).

3-Methyl-7-phenyl-6,7-dihydro-furo[3,2-*g*]chromen-5-one 3a. A mixture of 1-(6-hydroxy-3-methyl-benzofuran-5-yl)-ethanone **1a** (0.0043 moles) and benzaldehyde (0.0043 moles) was refluxed in absolute ethanol (15 mL) with catalytic amount (3-4 drops) of piperidine for 36 hours. Reaction was monitored on tlc. The excess of ethanol was distilled off *in vacuo* and the reaction mixture was then poured into ice hydrochloric acid and solid collected by filtration. The product was crystallized from ethanol:toluene mixture to give 3-methyl-7-phenyl-6,7-dihydro-furo[3,2-*g*]chromen-5-one **3a** (49.5 %) as light yellow crystals, mp 128-129 °C; ν_{max}/cm^{-1}: 3438, 2928, 1677, 1617, 1469, 1233 and 1129; ^{1}H nmr (300 MHz; $CDCl_3$; Me_4Si): δ 2.24 (3H, d, J = 0.96, C(3)CH_3), 2.91-2.98 (1H, dd, $J_{vicinal}$ = 3.04 and $J_{geminal}$ = 16.9, C(6)equatorial H), 3.09-3.19 (1H, dd, $J_{vicinal}$ = 12.85 and $J_{geminal}$ = 16.9, C(6)axial H), 5.49-5.54 (1H, dd, $J_{vicinal}$ = 2.88 and $J_{vicinal}$ = 12.85, C(7)axial H), 7.08 (1H, s, C(9)H), 7.36 (1H, d, J = 0.96, C(2)H), 7.38-7.57 (5H, m, C(7)phenyl protons) and 8.15 (1H, s, C(4)H). *Anal*. Calcd. for $C_{18}H_{14}O_3$ (278.30): C, 77.68; H, 5.07. Found: C, 77.59; H, 5.01.

7-(4-Methoxy-phenyl)-3-methyl-6,7-dihydro-furo[3,2-*g*]-chromen-5-one 3b. 38 %; light yellow crystals; mp 125-126 °C; ν_{max}/cm^{-1}: 3440, 2931, 1688, 1621, 1467, 1230 and 1130; ^{1}H nmr (300 MHz; $CDCl_3$; Me_4Si): δ 2.24 (3H, d, J = 1.1, C(3)CH_3), 2.87-2.94 (1H, dd, $J_{vicinal}$ = 2.86 and $J_{geminal}$ = 16.88, C(6)equatorial H), 3.10-3.20 (1H, dd, $J_{vicinal}$ = 12.96 and $J_{geminal}$ = 16.88, C(6)axial H), 3.84 (3H, s, C(4')OCH_3), 5.43-5.48 (1H, dd, $J_{vicinal}$ = 2.7 and $J_{vicinal}$ = 12.9, C(7)axial H), 6.95-6.98 (2H, d, J = 8.68, C(3')H and C(5')H), 7.05 (1H, s, C(9)H), 7.36 (1H, d, J = 1.1, C(2)H), 7.42-7.45 (2H, d, J = 8.63, C(2')H and C(6')H) and 8.14(1H, s, C(4)H). *Anal*. Calcd. for $C_{19}H_{16}O_4$ (308.33): C, 74.01; H, 5.23. Found: C, 73.71; H, 4.93.

7-(4-Chloro-phenyl)-3-methyl-6,7-dihydro-furo[3,2-*g*]-chromen-5-one 3c. 50.5 %; light yellow crystals; mp 136-138 °C; ν_{max}/cm^{-1}: 3126, 2922, 1689, 1619, 1611, 1520, 1470, 1355, 1271, 1241 and 1144; ^{1}H nmr (300 MHz; $CDCl_3$; Me_4Si): δ 2.24 (3H, d, J = 1.11, C(3)CH_3), 2.89-2.96 (1H, dd, $J_{vicinal}$ = 3.18 and $J_{geminal}$ = 16.88, C(6)equatorial H), 3.03-3.13 (1H, dd, $J_{vicinal}$ = 12.58 and $J_{geminal}$ = 16.89, C(6)axial H), 5.46-5.51 (1H, dd, $J_{vicinal}$ = 3.12 and $J_{vicinal}$ = 12.58, C(7)axial H), 7.07 (1H, s, C(9)H), 7.36 (1H, d, J = 1.11, C(2)H), 7.40-7.43 (2H, d, J = 8.77, C(3')H and C(5')H), 7.44-7.47 (2H, d, J = 8.74, C(2')H and C(6')H) and 8.14 (1H, s, C(4)H). *Anal*. Calcd. for $C_{18}H_{13}O_3Cl$ (312.75): C, 69.12; H, 4.18. Found: C, 68.78; H, 3.98.

3,9-Dimethyl-7-phenyl-6,7-dihydro-furo[3,2-*g*]chromen-5-one 3d. 54 %; light yellow crystals; mp 153-154 °C; ν_{max}/cm^{-1}: 3440, 2936, 1689, 1621, 1474, 1229 and 1130; ^{1}H nmr (300 MHz; $CDCl_3$; Me_4Si): δ 2.26 (3H, d, J = 1.1, C(3)CH_3), 2.39 (3H, s, C(9)CH_3), 2.92-2.99 (1H, dd, $J_{vicinal}$ = 3.1 and $J_{geminal}$ = 16.6, C(6)equatorial H), 3.08-3.19 (1H, dd, $J_{vicinal}$ = 12.83 and $J_{geminal}$ = 16.4, C(6)axial H), 5.5-5.55 (1H, dd, $J_{vicinal}$ = 2.98 and $J_{vicinal}$ = 12.8, C(7)axial H), 7.39 (1H, d, J = 1.1, C(2)H), 7.4-7.59 (5H, m, C(7)phenyl protons) and 8.19 (1H, s, C(4)H). *Anal*. Calcd. for $C_{19}H_{16}O_3$ (292.33): C, 78.06; H, 5.51. Found: C, 78.12; H, 5.55.

7-(4-Methoxy-phenyl)-3,9-dimethyl-6,7-dihydro-furo[3,2-*g*]-chromen-5-one 3e. 42.6 %; light yellow crystals; mp 138-139 °C; ν_{max}/cm^{-1}: 3116, 2924, 1680, 1624, 1600, 1518, 1477, 1352, 1272, 1251 and 1142; ^{1}H nmr (400 MHz; $CDCl_3$; Me_4Si): δ 2.24 (3H, d, J = 1.2, C(3)CH_3), 2.39 (3H, s, C(9)CH_3), 2.92-2.97 (1H, dd, $J_{vicinal}$ = 2.8 and $J_{geminal}$ = 16.8, C(6)equatorial H), 3.08-3.15 (1H, dd, $J_{vicinal}$ = 12.8 and $J_{geminal}$ = 16.8, C(6)axial H), 3.86 (3H, s, C(4')OCH_3), 5.44-5.48 (1H, dd, $J_{vicinal}$ = 3.2 and $J_{vicinal}$ = 12.8, C(7)axial H), 6.97-7.00 (2H, d, J = 8.8, C(3')H and C(5')H), 7.38 (1H, d, J = 1.2, C(2)H), 7.45-7.47 (2H, d, J = 8.8, C(2')H and C(6')H) and 8.01 (1H, s, C(4)H); lcms: *m/z* 345.2 (M+23, 16 %), 324.3 (M+2, 26) and 323.3 (M+1, 100). *Anal*. Calcd. for $C_{20}H_{18}O_4$ (322.35): C, 74.51; H, 5.62. Found: C, 74.21; H, 5.34.

7-(4-Chloro-phenyl)-3,9-dimethyl-6,7-dihydro-furo[3,2-*g*]-chromen-5-one 3f. 59 %; light yellow crystals; mp 169-170 °C; ν_{max}/cm^{-1}: 3126, 2929, 1681, 1629, 1597, 1515, 1471, 1357, 1277, 1255 and 1149; ^{1}H nmr (300 MHz; $CDCl_3$; Me_4Si): δ 2.2 (3H, d, J = 1.12, C(3)CH_3), 2.4 (3H, s, C(9)CH_3), 2.93-2.98 (1H, dd, $J_{vicinal}$ = 3.2 and $J_{geminal}$ = 16.8, C(6)equatorial H), 3.02-3.10 (1H, dd, $J_{vicinal}$ = 12.4 and $J_{geminal}$ = 16.8, C(6)axial H), 5.48-5.52 (1H, dd, $J_{vicinal}$ = 3.2 and $J_{vicinal}$ = 12.4, C(7)axial H), 7.40-7.40 (1H, d, J = 1.2, C(2)H), 7.42-7.44 (2H, d, J = 8.4, C(3')H and C(5')H), 7.47-7.49 (2H, d, J = 8.4, C(2')H and C(6')H) and 8.02(1H, s, C(4)H); ^{13}C nmr (100MHz; $CDCl_3$; Me_4Si): δ 7.87 (C3-***C***H_3), 8.45 (C9-***C***H_3), 44.61 (C-6), 78.76 (C-7), 109.75 (C-9), 115.60 (C-3), 116.58 (C-4a), 117.45 (C-4), 123.79 (C-3a), 127.33 (C-3' and C-5'), 129.00 (C-2' and C-6'), 134.33 (C-4'), 137.81 (C-1'), 142.28 (C-2), 156.92 (C-8a), 158.96 (C-9a) and 192.29 (C5->***C***=O). *Anal.* Calcd. for $C_{19}H_{15}O_3Cl$ (326.77): C, 69.83; H, 4.62. Found: C, 69.57; H, 4.60.

3,7-Diphenyl-6,7-dihydro-furo[3,2-*g*]chromen-5-one 3g. 48 %; light yellow crystals; mp 230-231 °C; ν_{max}/cm^{-1}: 3439, 2925, 1689, 1620, 1470, 1231 and 1139; ^{1}H nmr (300 MHz; $(CD_3)_2SO$; Me_4Si): δ 2.90-2.97 (1H, dd, $J_{vicinal}$ = 3.15 and = 16.88, C(6)equatorial H), 3.07-3.16 (1H, dd, $J_{vicinal}$ = 12.56 and $J_{geminal}$ = 16.88, C(6)axial H), 5.50-5.54 (1H, dd, $J_{vicinal}$ = 3.07 and

$J_{vicinal}$ = 12.55, C(7)axial H), 7.18 (1H, s, C(9)H), 7.38-7.82 (11H, m, C(2)H, C(3)phenyl protons, C(7)phenyl protons) and 8.43(1H, s, C4-H). *Anal*. Calcd. for $C_{23}H_{16}O_3$ (340.37): C, 81.16; H, 4.73. Found: C, 80.52; H, 4.40.

7-(4-Methoxy-phenyl)-3-phenyl-6,7-dihydro-furo[3,2-*g*]-chromen-5-one 3h. 39.8 %; light yellow crystals; mp 162-163 °C; ν_{max}/cm^{-1}: 3440, 2930, 1682, 1623, 1469, 1232 and 1131; ^{1}H nmr (300 MHz; $CDCl_3$; Me_4Si): δ 2.90-2.97 (1H, dd, $J_{vicinal}$ = 2.9 and $J_{geminal}$ = 16.88, C(6)equatorial H), 3.12-3.22 (1H, dd, $J_{vicinal}$ = 12.87 and $J_{geminal}$ = 16.88, C(6)axial H), 5.46-5.51 (1H, dd, $J_{vicinal}$ = 2.7 and $J_{vicinal}$ = 12.83, C(7)axial H), 6.96-6.99 (2H, d, J = 8.66, C(3')H and C(5')H), 7.16 (1H, s, C(9)H), 7.37-7.75 (8H, m, C(2)H, C(3)phenyl protons, C(2')H, C(6')H) and 8.45(1H, s, C(4)H). *Anal.* Calcd. for $C_{24}H_{18}O_4$ (370.40): C, 77.82; H, 4.89. Found: C, 77.98; H, 4.91.

7-(4-Chloro-phenyl)-3-phenyl-6,7-dihydro-furo[3,2-*g*]-chromen-5-one 3i. 61 %; light yellow crystals; mp 186-187 °C; ν_{max}/cm^{-1}: 3448, 2931, 1682, 1629, 1471, 1229 and 1130; ^{1}H nmr (300 MHz; $CDCl_3$; Me_4Si): δ 2.92-2.98 (1H, dd, $J_{vicinal}$ = 3.15 and $J_{geminal}$ = 16.88, C(6)equatorial H), 3.06-3.16 (1H, dd, $J_{vicinal}$ = 12.56 and $J_{geminal}$ = 16.88, C(6)axial H), 5.50-5.55 (1H, dd, $J_{vicinal}$ = 3.07 and $J_{vicinal}$ = 12.55, C(7)axial H), 7.18 (1H, s, C(9)H), 7.38-7.76 (10H, m, C(2)H, C(3)phenyl protons, C(7)phenyl protons) and 8.45(1H, s, C(4)H). *Anal.* Calcd. for $C_{23}H_{15}O_3Cl$ (374.82): C, 73.70; H, 4.03. Found: C, 73.34; H, 4.01.

9-Methyl-3,7-diphenyl-6,7-dihydro-furo[3,2-*g*]chromen-5-one 3j. 52.2 %; light yellow crystals; mp 189-190 °C; ν_{max}/cm^{-1}: 3441, 2937, 1688, 1623, 1471, 1238 and 1132; ^{1}H nmr (300 MHz; $(CD_3)_2SO$; Me_4Si): δ 2.43 (3H, s, C(9)CH_3), 2.92-2.98 (1H, dd, $J_{vicinal}$ = 3.1 and $J_{geminal}$ = 16.84, C(6)equatorial H), 3.09-3.17 (1H, dd, $J_{vicinal}$ = 12.6 and $J_{geminal}$ = 16.85, C(6)axial H), 5.51-5.54 (1H, dd, $J_{vicinal}$ = 3.1 and $J_{vicinal}$ = 12.66, C(7)axial H), 7.4-7.84 (11H, m, C(2)H, C(3)phenyl protons, C(7)phenyl protons) and 8.44(1H, s, C(4)H). *Anal.* Calcd. for $C_{24}H_{18}O_3$ (354.40) requires C, 81.33; H, 5.11. Found: C, 81.16; H, 4.81.

7-(4-Methoxy-phenyl)-9-methyl-3-phenyl-6,7-dihydrofuro-[3,2-*g*]chromen-5-one 3k. 41 %; light yellow crystals; mp 211-213 °C; ν_{max}/cm^{-1}: 3439, 2928, 1679, 1617, 1465, 1233 and 1131; ^{1}H nmr (300 MHz; $CDCl_3$; Me_4Si): δ 2.92-2.99 (1H, dd, $J_{vicinal}$ = 2.8 and $J_{geminal}$ = 16.8, C(6)equatorial H), 3.13-3.23 (1H, dd, $J_{vicinal}$ = 12.85 and $J_{geminal}$ = 16.82, C(6)axial H), 5.48-5.53 (1H, dd, $J_{vicinal}$ = 2.8 and $J_{vicinal}$ = 12.8, C(7)axial H), 6.96-6.99 (2H, d, J = 8.62, C(3')H and C(5')H), 7.40-7.75 (8H, m, C(2)H, C(3)phenyl protons, C(2')H, C(6')H) and 8.49(1H, s, C(4)H). *Anal.* Calcd. for $C_{25}H_{20}O_4$ (384.42): C, 78.10; H, 5.24. Found: C, 77.82; H, 5.03.

7-(4-Chloro-phenyl)-9-methyl-3-phenyl-6,7-dihydrofuro-[3,2-*g*]chromen-5-one 3l. 59.7 %; light yellow crystals; mp 202-203 °C; ν_{max}/cm^{-1}: 3441, 2930, 1688, 1622, 1471, 1233 and 1129; ^{1}H nmr (400 MHz; $CDCl_3$; Me_4Si): δ 2.46 (3H, s, C(9)CH_3), 2.95-3.00 (1H, dd, $J_{vicinal}$ = 3.6 and $J_{geminal}$ =16.8, C(6)equatorial H), 3.04-3.11 (1H, dd, $J_{vicinal}$ = 12.4 and $J_{geminal}$ = 16.8, C(6)axial H), 5.50-5.54 (1H, dd, $J_{vicinal}$ = 3.2 and $J_{vicinal}$ = 12.4, C(7)axial H), 7.39-7.52 (7H, m, C(3)phenyl protons, C(3')H, C(5')H), 7.65-7.67 (2H, d, J = 8.4, C(2')H and C(6')H), 7.79 (1H, s, C(2)H) and 8.32 (1H, s, C(4)H). *Anal.* Calcd. for $C_{24}H_{17}O_3Cl$ (388.84): C, 74.13; H, 4.40. Found: C, 73.88; H, 4.43.

General procedure for (4a-4l).

3-Methyl-7-phenyl-furo[3,2-*g*]chromen-5-one 4a. A mixture of 3-methyl-7-phenyl-6,7-dihydro-furo[3,2-*g*]chromen-5-one **3a** (0.005 moles) and DDQ (2,3-dichloro-5,6-dicyano-1,4-benzo-quinone) (0.0055 moles) was refluxed in dry toluene (15 mL) for 12 hours. The reaction mixture was washed with water followed by washing with 10 % potassium carbonate solution and then again with water. The toluene layer was dried over sodium sulfate and solvent was distilled off *in vacuo*. The product was purified by column chromatography using petroleum ether (60-80 °C): ethyl acetate (7:3) mixture as eluent to give 3-methyl-7-phenyl-furo[3,2-*g*]chromen-5-one **4a** (86.6 %) as light brown crystals, mp 194 °C dec; ν_{max}/cm^{-1}: 2918, 1648, 1636, 1619, 1525, 1479, 1358, 1260 and 1133; ^{1}H nmr (300 MHz; $CDCl_3$; Me_4Si): δ 2.30 (3H, d, J = 0.58, C(3)CH_3), 6.8 (1H, s, C(6)H), 7.44-8.00 (7H, m, C(2)H, C(9)H, C(7)phenyl protons) and 8.43 (1H, s, C(4)H). *Anal.* Calcd. for $C_{18}H_{12}O_3$ (276.28): C, 78.25; H, 4.37. Found: C, 78.58; H, 4.61.

7-(4-Methoxy-phenyl)-3-methyl-furo[3,2-*g*]chromen-5-one 4b. 69.8 %; light brown crystals; mp 238-240 °C dec; ν_{max}/cm^{-1}: 2935, 1647, 1636, 1612, 1518, 1477, 1361, 1259, 1127 and 831; ^{1}H nmr (300 MHz; $CDCl_3$; Me_4Si): δ 2.32 (3H, d, J = 0.58, C(3)CH_3), 3.91 (3H, s, C(4')OCH_3), 6.76 (1H, s, C(6)H), 7.03-7.06 (2H, d, J = 8.88, C(3')H and C(5')H), 7.51 (1H, d, J = 0.58, C(2)H), 7.60 (1H, s, C(9)H), 7.90-7.93 (2H, d, J = 8.88, C(2')H and C(6')H) and 8.41 (1H, s, C(4)H). *Anal.* Calcd. for $C_{19}H_{14}O_4$ (306.31): C, 74.50; H, 4.60. Found: C, 74.62; H, 4.69.

7-(4-Chloro-phenyl)-3-methyl-furo[3,2-*g*]chromen-5-one 4c. 86 %; light brown crystals; mp 250-252 °C dec; ν_{max}/cm^{-1}: 2920, 1661, 1623, 1601, 1519, 1478, 1359, 1262, 1133 and 838; ^{1}H nmr (300 MHz; $CDCl_3$; Me_4Si): δ 2.30 (3H, d, J = 0.58, C(3)CH_3), 6.85 (1H, s, C(6)H), 7.42-7.44 (2H, d, J = 8.8, C(3')H and C(5')H), 7.45-7.95 (4H, m, C(2)H, C(9)H, C(2')H, C(6')H) and 8.48 (1H, s, C(4)H). *Anal.* Calcd. for $C_{18}H_{11}O_3Cl$ (310.73): C, 69.57; H, 3.56. Found: C, 69.33; H, 3.40.

3,9-Dimethyl-7-phenyl-furo[3,2-*g*]chromen-5-one 4d. 91 %; light brown crystals; mp 180 °C dec; ν_{max}/cm^{-1}: 2933, 1655, 1622, 1617, 1519, 1479, 1361, 1263, 1128 and 821; ^{1}H nmr (300 MHz; $CDCl_3$; Me_4Si): δ 2.33 (3H, d, J = 0.6, C(3)CH_3), 2.74 (3H, s, C(9)CH_3), 6.83 (1H, s, C(6)H), 7.50 (1H, d, J = 0.6, C(2)H), 7.52-8.01 (5H, m, C(7)phenyl protons) and 8.44 (1H, s, C(4)H). *Anal.* Calcd. for $C_{19}H_{14}O_3$ (290.31): C, 78.60; H, 4.86. Found: C, 78.44; H, 4.69.

7-(4-Methoxy-phenyl)-3,9-dimethyl-furo[3,2-*g*]chromen-5-one 4e. 67.6 %; light brown crystals; mp 248 °C dec; ν_{max}/cm^{-1}: 2921, 1651, 1621, 1610, 1507, 1477, 1361, 1254 and 1133; ^{1}H nmr (400 MHz; $CDCl_3$; Me_4Si): δ 2.29 (3H, d, J = 1.2, C(3)CH_3), 2.72 (3H, s, C(9)CH_3), 3.91 (3H, s, C(4')OCH_3), 6.82 (1H, s, C(6)H), 7.04-7.06 (2H, d, J = 8.8, C(3')H and C(5')H), 7.51 (1H, d, J = 1.2, C(2)H), 7.92-7.94 (2H, d, J = 8.8, C(2')H and C(6')H) and 8.25(1H, s, C(4)H); ^{13}C nmr (100MHz; $CDCl_3$; Me_4Si): δ 7.92 (C3-***C***H_3), 8.75 (C9-***C***H_3), 55.53 (C4'-O***C***H_3), 104.49 (C-6), 109.79 (C-9), 113.32 (C-3' and C-5'), 114.52 (C-3), 116.58 (C-4a), 119.71 (C-4), 124.35 (C-3a), 126.88 (C-2' and C-6'), 127.95 (C-1'), 143.41 (C-2), 152.10 (C-8a), 156.80 (C-4'), 162.39 (C-9a), 163.32 (C-7) and 179.33 (C5->***C***=O). *Anal.* Calcd. for $C_{20}H_{16}O_4$ (320.34): C, 74.98; H, 5.03. Found: C, 75.24; H, 5.37.

7-(4-Chloro-phenyl)-3,9-dimethyl-furo[3,2-*g*]chromen-5-one 4f. 88 %; light brown crystals; mp 210 °C dec; ν_{max}/cm^{-1}: 2933, 1656, 1621, 1615, 1515, 1472, 1360, 1263, 1129 and 821; ^{1}H nmr (300 MHz; $CDCl_3$; Me_4Si): δ 2.30 (3H, d, J = 0.58, C(3)CH_3), 2.73 (3H, s, C(9)CH_3), 6.87 (1H, s, C(6)H), 7.42-7.44 (2H, d, J = 8.8, C(3')H and C(5')H), 7.50 (1H, d, J = 0.58, C(2)H), 7.56-7.58 (2H, d, J = 8.8, C(2')H and C(6')H) and 8.50 (1H, s, C(4)H). *Anal.* Calcd. for $C_{19}H_{13}O_3Cl$ (324.76): C, 70.26; H, 4.03. Found: C, 70.21; H, 4.01.

3,7-Diphenyl-furo[3,2-*g*]chromen-5-one 4g. 71 %; light brown crystals; mp 200 °C dec; ν_{max}/cm^{-1}: 2933, 1658, 1622, 1599, 1511, 1471, 1359, 1260, 1131 and 833; ^{1}H nmr (400 MHz; $CDCl_3$; Me_4Si): δ 6.92 (1H, s, C(6)H), 7.43-8.01 (12H, m, C(2)H, C(9)H, C(7)phenyl protons, C(3)phenyl protons) and 8.75 (1H, s, C(4)H); lcms: *m/z* 361.1 (M+23, 11 %), 340.1 (M+2, 22) and 339.1 (M+1, 100). *Anal.* Calcd. for $C_{23}H_{14}O_3$ (338.36): C, 81.64; H, 4.17. Found: C, 81.49; H, 4.05.

7-(4-Methoxy-phenyl)-3-phenyl-furo[3,2-*g*]chromen-5-one 4h. 80 %; light brown crystals; mp 258 °C dec; ν_{max}/cm^{-1}: 2919, 1642, 1616, 1612, 1525, 1477, 1361, 1262, 1133 and 836; ^{1}H nmr (400 MHz; $(CD_3)_2SO$; Me_4Si): δ 3.92 (3H, s, C(4')OCH_3), 6.91 (1H, s, C(6)H), 7.04-7.06 (2H, d, J = 8.8, C(3')H and C(5')H), 7.43-8.01 (9H, m, C(2)H, C(9)H, C(2')H, C(6')H, C(3)phenyl protons) and 8.73 (1H, s, C(4)H). *Anal.* Calcd. for $C_{24}H_{16}O_4$ (368.38) requires C, 78.25; H, 4.37. Found: C, 78.49; H, 4.65.

7-(4-Chloro-phenyl)-3-phenyl-furo[3,2-*g*]chromen-5-one 4i. 89 %; light brown crystals; mp 210 °C dec; ν_{max}/cm^{-1}: 2929, 1646, 1622, 1588, 1525, 1476, 1361, 1260, 1131 and 834; ^{1}H nmr (400 MHz; $CDCl_3$; Me_4Si): δ 6.88 (1H, s, C(6)H), 7.4-8.00 (11H, m, C(2)H, C(9)H, C(7)phenyl protons, C(3)phenyl protons) and 8.56 (1H, s, C(4)H). *Anal.* Calcd. for $C_{23}H_{13}O_3Cl$ (372.80): C, 74.10; H, 3.51. Found: C, 73.87; H, 3.39.

9-Methyl-3,7-diphenyl-furo[3,2-*g*]chromen-5-one 4j. 76 %; light brown crystals; mp 220-222 °C dec; ν_{max}/cm^{-1}: 2919, 1648, 1621, 1611, 1525, 1479, 1359, 1262 and 1133; ^{1}H nmr (400 MHz; $CDCl_3$; Me_4Si): δ 2.80 (3H, s, C(9)CH_3), 6.94 (1H, s, C(6)H), 7.41-8.1 (11H, m, C(2)H, C(7)phenyl protons, C(3)phenyl protons) and 8.77 (1H, s, C(4)H). *Anal.* Calcd. for $C_{24}H_{16}O_3$ (352.38): C, 81.80; H, 4.57. Found: C, 81.84; H, 4.61.

7-(4-Methoxy-phenyl)-9-methyl-3-phenyl-furo[3,2-*g*]-chromen-5-one 4k. 79 %; light brown crystals; mp 200 °C dec; ν_{max}/cm^{-1}: 2933, 1651, 1626, 1602, 1515, 1480, 1359, 1261, 1133 and 819; ^{1}H nmr (400 MHz; $(CD_3)_2SO$; Me_4Si): δ 2.70 (3H, s, C(9)CH_3), 3.93 (3H, s, C(4')OCH_3), 6.90 (1H, s, C(6)H), 7.05-7.07 (2H, d, J = 8.8, C(3')H and C(5')H), 7.40-8.05 (8H, m, C(2)H, C(2')H, C(6')H, C(3)phenyl protons) and 8.75 (1H, s, C(4)-H). *Anal.* Calcd. for $C_{25}H_{18}O_4$ (382.41): C, 78.52; H, 4.74. Found: C, 78.51; H, 4.70.

7-(4-Chloro-phenyl)-9-methyl-3-phenyl-furo[3,2-*g*]chromen-5-one 4l. 83.2 %; light brown crystals; mp 230 °C dec; ν_{max}/cm^{-1}: 2936, 1656, 1622, 1611, 1519, 1477, 1361, 1260, 1135 and 836; ^{1}H nmr (400 MHz; $CDCl_3$; Me_4Si): δ 2.80 (3H, s, C(9)CH_3), 6.90 (1H, s, C(6)H), 7.42-7.95 (10H, m, C(2)H, C(7)phenyl protons, C(3)phenyl protons) and 8.59 (1H, s, C(4)H). *Anal.* Calcd. for $C_{24}H_{15}O_3Cl$ (386.83): C, 74.51; H, 3.90. Found: C, 74.31; H, 3.81.

General procedure for (5a-5d).

***E*-6-Benzylidene-3-methyl-7-phenyl-6,7-dihydro-furo[3,2-*g*]chromen-5-one 5a.** A solution of 1-(6-hydroxy-3-methyl-benzofuran-5-yl)-ethanone **1a** (0.026 moles) and freshly distilled benzaldehyde (0.065 moles) and 2-3 drops of piperidine in ethanol (15 mL) was refluxed for 18 hours. Reaction mixture was poured into ice hydrochloric acid mixture and the solid collected by filtration. The crude product was purified by column chromatography using petroleum ether (60-80 ℃): ethyl acetate (8:2) mixture as eluent to give *E*-6-benzylidene-3-methyl-7-phenyl-6,7-dihydro-furo[3,2-*g*]chromen-5-one **5a** (71 %) as yellow crystals; mp 212-214 °C; ν_{max}/cm^{-1}: 3099, 1670, 1621, 1481, 1477 and 1129; ^{1}H nmr (300 MHz; $CDCl_3$; Me_4Si): δ 2.17-2.17 (3H, d, J = 1.5, C(3)CH_3), 6.66 (1H, s, C(7)H), 6.96 (1H, s, C(9)H), 7.25-7.51 (11H, m, C(2)H, C(7)phenyl protons, C(2')H, C(3')H, C(4')H, C(5')H, C(6')H), 8.12 (1H, s, vinylic proton) and 8.15 (1H, s, C(4)H). *Anal.* Calcd. for $C_{25}H_{18}O_3$ (366.41): C, 81.94; H, 4.95. Found: C, 81.76; H, 4.83.

***E*-6-(4-Chloro-benzylidene)-7-(4-chloro-phenyl)-3-methyl-6,7-dihydro-furo[3,2-*g*]chromen-5-one 5b.** 76.5 %; yellow crystals; mp 189-190 °C; ν_{max}/cm^{-1}: 3095, 1672, 1624, 1488, 1471 and 1132; ^{1}H nmr (300 MHz; $CDCl_3$; Me_4Si): δ 2.18-2.18 (3H, d, J = 0.9, C(3)CH_3), 6.53 (1H, s, C(7)H), 6.95 (1H, s, C(9)H), 7.19-7.42 (9H, m, C(2)H, C(7)phenyl protons, C(2')H, C(3')H, C(5')H, C(6')H), 8.09 (1H, s, vinylic proton) and 8.12 (1H, s, C(4)H). *Anal.* Calcd. for $C_{25}H_{16}O_3Cl_2$ (435.30): C, 68.98; H, 3.70. Found: C, 69.01; H, 3.84.

***E*-6-(4-Methoxy-benzylidene)-7-(4-methoxy-phenyl)-3,9-dimethyl-6,7-dihydro-furo[3,2-*g*]chromen-5-one 5c.** 61.8 %; yellow crystals; mp 150-152 °C; ν_{max}/cm^{-1}: 3119, 2999, 1669, 1628, 1600, 1519, 1472, 1249, 1188 and 1120; ^{1}H nmr (300 MHz; $CDCl_3$; Me_4Si): δ 2.18 (3H, d, J = 0.9, C(3)CH_3), 2.36 (3H, s, C(9)CH_3), 3.74 (3H, s, C(4")OCH_3), 3.83 (3H, s, C(4')OCH_3), 6.69 (1H, s, C(7)H), 6.81-6.84 (2H, d, J = 8.64, C(3")H and C(5")H), 6.88-6.91 (2H, d, J = 8.64, C(3')H and C(5')H), 7.25-7.29 (3H, m, C(2)H, C(2")H, C(6")H), 7.41-7.44 (2H, d, J = 8.57, C(2')H and C(6')H), 8.00 (1H, s, vinylic proton) and 8.10 (1H, s, C(4)H). *Anal.* Calcd. for $C_{28}H_{24}O_5$ (440.49): C, 76.34; H, 5.49. Found: C, 76.21; H, 5.37.

***E*-6-(4-Methoxy-benzylidene)-7-(4-methoxy-phenyl)-9-methyl-3-phenyl-6,7-dihydro-furo[3,2-*g*]chromen-5-one 5d.** 59 %; yellow crystals; mp 164-166 °C; ν_{max}/cm^{-1}: 3123, 2993, 1671, 1621, 1602, 1509, 1477, 1251, 1181 and 1115; ^{1}H nmr (300 MHz; $CDCl_3$; Me_4Si): δ 2.38 (3H, s, C(9)CH_3), 3.75 (3H, s, C(4")OCH_3), 3.83 (3H, s, C(4')OCH_3), 6.70 (1H, s, C(7)H), 6.82-6.84 (2H, d, J = 8.6, C(3")H and C(5")H), 6.88-6.90 (2H, d, J = 8.64, C(3')H and C(5')H), 7.26-7.29 (2H, d, J = 8.6Hz, C(2")H and C(6")H), 7.40-7.92 (8H, m, C(2)H, C(2')H, C(6')H, C(3)phenyl protons), 8.01 (1H, s, vinylic proton) and 8.13 (1H, s, C(4)H). *Anal.* Calcd. for $C_{33}H_{26}O_5$ (502.56): C, 78.86; H, 5.21. Found: C, 78.97; H, 5.52.

Photo chemical isomerization of *E*-6-Benzylidene-3-methyl-7-phenyl-6,7-dihydro-furo[3,2-*g*]chromen-5-one 5a to *Z*-6-Benzylidene-3-methyl-7-phenyl-6,7-dihydro-furo[3,2-*g*]-chromen-5-one 6. *E*-6-Benzylidene-3-methyl-7-phenyl-6,7-dihydro-furo[3,2-*g*]chromen-5-one **5a** (0.005 moles) was dissolved in toluene (15 mL) and kept in a chamber containing 450 W mercury arc lamp for 12 hours. Excess of toluene was distilled off *in vacuo* and the product was purified by column chromatography on neutral alumina using petroleum ether (60-80 ℃): ethyl acetate (9:1) mixture as eluent. Use of silica gel was showing some conversion of *Z* isomer back into the *E* isomer. *Z*-6-Benzylidene-3-methyl-7-phenyl-6,7-dihydro-furo-[3,2-*g*]chromen-5-one **6** (81.2 %) was obtained as yellow crystals, mp 101-103 °C; υ_{max}/cm^{-1}: 3069, 2942, 1661, 1624, 1583, 1468, 1453, 1224, 1182, 1128 and 737; ^{1}H nmr (300 MHz; $CDCl_3$; Me_4Si): δ 2.25 (3H, d, J = 1.5, C(3)CH_3), 6.15 (1H, s, C(7)H), 6.77 (1H, s, vinylic proton), 7.09 (1H, s, C(9)H), 7.26-7.70 (11H, m, C(2)H, C(7)phenyl protons, C(2')H, C(3')H, C(4')H, C(5')H, C(6')H) and 8.12 (1H, s, C(4)H). *Anal.* Calcd. for $C_{25}H_{18}O_3$ (366.41): C, 81.94; H, 4.95. Found: C, 81.76; H, 4.83.

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