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A simple and efficient access to new functionalized 4-phenacylideneflavenes*

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Abstract
An innovative and efficient approach toward diversity oriented synthesis of 4-phenacylideneflavenes has been developed from substituted salicylaldehydes and acetophenones using iodine under solvent free conditions. Both symmetrical and unsymmetrical functionalized 4-phenacylideneflavenes were synthesized in good to excellent yields and their mechanism of formation is discussed.

Keywords: Iodine; Salicylaldehyde; Acetophenones; Symmetrical 4-phenacylideneflavenes; Unsymmetrical 4-phenacylideneflavenes;

Introduction
Benzopyran is a well known privileged structural motif that is present in many bioactive natural products [1,2] and they are known to exhibit significant biological activities such as anti-HIV[3] and antihypertensive.[4] Furthermore, Figure 1 shows representative example of this important scaffold found in pharmaceuticals such as Centchroman (Nonsteroidal Contraceptive Agent),[5] CHF 4227 (Selective Estrogen Receptor Modulator),[6] and Acolbifene (Selective Estrogen Receptor Modulator).[7]

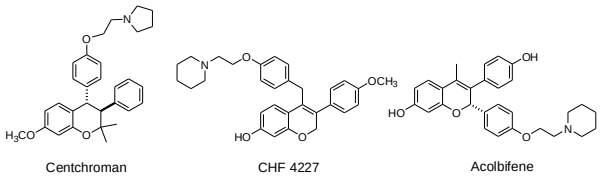


Figure 1. Examples of pharmaceuticals containing benzopyran frameworks.

Consequently, several groups have described synthesis of pyran core by formal [3+3] cyclo-addition between α,β-unsaturated aldehydes and 1,3-diketones using Lewis acid as catalyst,[8] or a reaction between an activated α,β-unsaturated iminium salt and 1,3-diketones,[9] or palladium catalyzed tandem Stille-oxo-electrocyclization reaction between 2-iodenones and 4-*cis*-stannylenones.[10–13] Also, Moreau et al. synthesized 3,4-dihydro-2H-pyran derivatives by the addition of enolizable β-diketones to α,β-unsaturated aldehydes and subsequent selective hydrogenation of resultant dihydro-2H-chromenones.[14] Recently, Narender et al. synthesized pyran core embedded derivatives from bisalkenylated 1,3-diketones and 1,3-diketoesters via tandem C-dealkenylation and cyclization.[15]

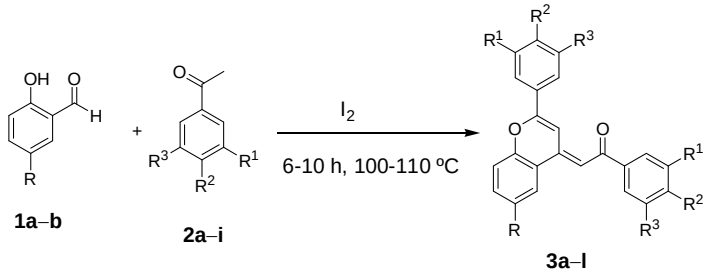
However, 4-phenacylideneflavenes possessing the pyran core, have limited number of synthetic methods in the literature. Hill[16] et al. reported the synthesis of 4-phenacylideneflavenes by reaction of salicylaldehydes with acetophenone in three steps sequence using NaOH, cold AcOH and hot HCl. While, Vanallan[17] et al. repeated the work of Hill by substituting AcOH with hot HCl and postulated that it's the flavylium acetate which is an intermediate and acts as a hydride transfer agent. Recently, Mayr[18] et al. described the synthesis of 4-phenacylideneflavenes by reacting flavylium ions with 1-phenyl-1-(trimethylsiloxy)ethene in presence of $HBF_4.OEt_2$ or HOTf and also investigated the kinetics of the reactions of flavylium ions with various π-nucleophiles. The common drawbacks of these known methods, however, are the use of toxic reagents, poor reaction selectivity, multiple steps, hazardous acid catalysts, complicated by-products, and low yields. Therefore, the development of simple, efficient, inexpensive, nontoxic and readily available reagents providing convenient procedures for the synthesis of 4-phenacylideneflavene with improved yields, are necessary. Moreover, till date the synthesis of unsymmetrical 4-phenacylideneflavenes remains unknown.

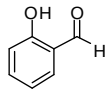
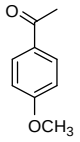
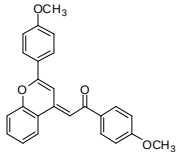
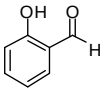
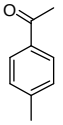
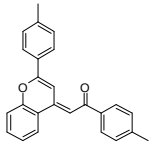
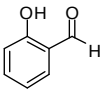
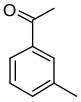
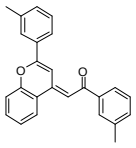
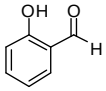
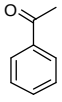
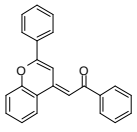
As part of our enduring drug discovery efforts on oxygenated heterocycles,[19] herein, we wish to report a simple and efficient one-pot procedure for the synthesis of functionalized 4-phenacylideneflavenes by the condensation of substituted salicylaldehyde or 2-hydroxychalcones with various acetophenones using molecular iodine as an efficient catalyst under solvent free conditions.

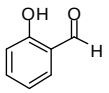
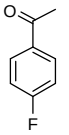
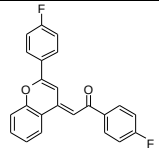
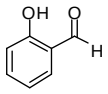
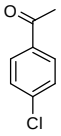
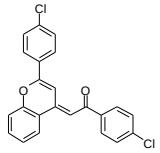
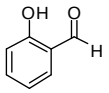
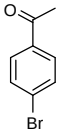
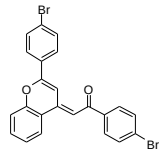
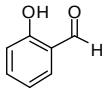
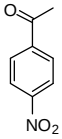
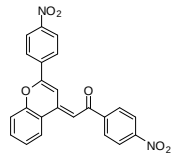
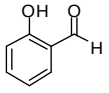
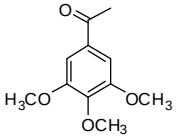
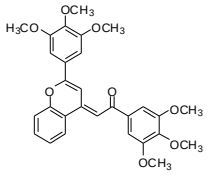
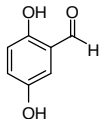
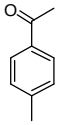
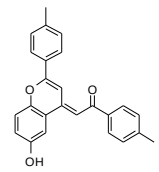
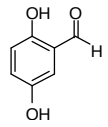
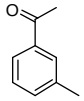
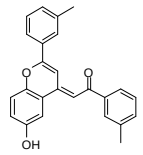
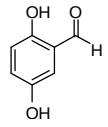
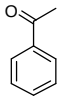
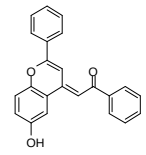
Results and Discussion

Owing to its unique catalytic properties, molecular iodine has recently received considerable attention[20] as an inexpensive, nontoxic, readily available catalyst for various organic transformations, affording the corresponding products in excellent yields with high selectivity. Initially, we have proceeded to a preliminary study of a catalytic evaluation of iodine using salicylaldehyde **1a** with 4-methoxyacetophenone (**2a**) in the presence of iodine (5 mol%) at room temperature to furnish 4-phenacylideneflavene **3a** in moderate yields (65%). It is important to mention that the catalytic efficiency of various Lewis acids, such as $BF_3.OEt_2$, $SnCl_2.2H_2O$, $Bi(NO_2)_3$, $AlCl_3$, CuI, was tested for this transformation without success. Much to our delight, we observed that only Iodine (10 mol %) can catalyse efficiently the reaction at temperature 100-110 ºC to furnish 4-phenacylideneflavene **3a** in good yield (Scheme 1). However, in the absence of iodine, the reactions did not proceed even after prolonged heating, clearing indicating that molecular iodine is essential to facilitate the reaction. Notably, the reaction was conducted under solvent-free conditions. Initially, the reaction was attempted with different solvents but the yields were found to be better in absence of any solvent.

Scheme 1: One pot synthesis of symmetrical 4-phenacylideneflavenes



Entry	Substrate (1)	Substrate (2)	Product[a]	Time (h)	Yield[b] (%)
1	 **1a**	 **2a**	 **3a**	6.2	70
2	 **1a**	 **2b**	 **3b**	6.5	68
3	 **1a**	 **2c**	 **3c**	6.5	68
4	 **1a**	 **2d**	 **3d**	7.0	67
5				8.0	64

	 **1a**	 **2e**	**3e** 		
6	 **1a**	 **2f**	 **3f**	7.5	66
7	 **1a**	 **2g**	 **3g**	7.2	66
8	 **1a**	 **2h**	 **3h**	10.0	53
9	 **1a**	 **2i**	 **3i**	6.0	72
10	 **1b**	 **2b**	 **3j**	7.5	62
11	 **1b**	 **2c**	 **3k**	7.6	63
12	 **1b**	 **2d**	 **3l**	8.0	62

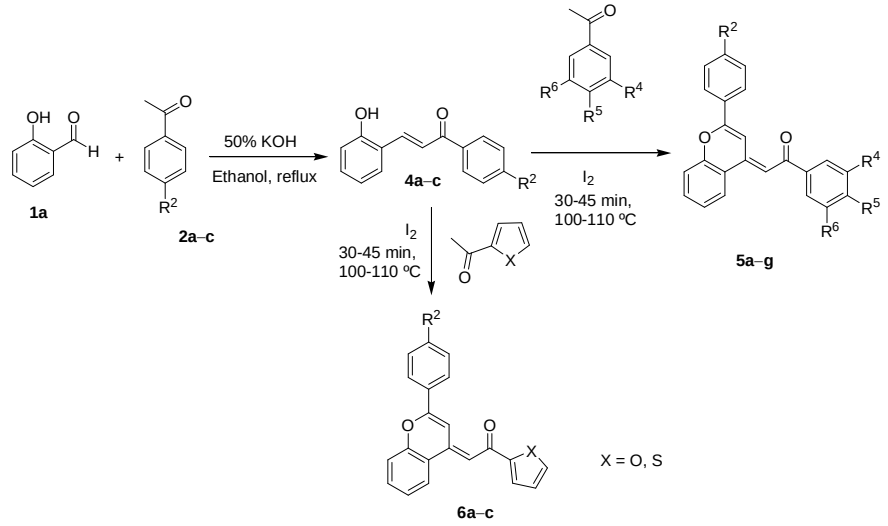
[a]Reaction conditions: Substrate 1 (0.8 mmol), Substrate 2 (1.6 mmol), Iodine (0.08 mmol), [b]Isolated yields after chromatography.

Under the established conditions, we investigated the application scope of this process by using a wide range of different acetophenones, and the corresponding products (**3b** to **3l**) were generally afforded in good to excellent yields (Scheme 1). The substituents present on acetophenones slightly affect the reaction time and yield. In general, electron donating groups accelerate the reaction rate as well as yield (Scheme 1, entry 1–3, 9) while

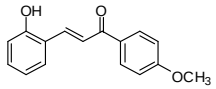
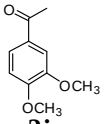
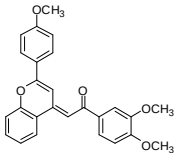
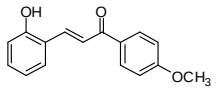
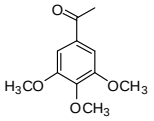
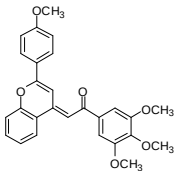
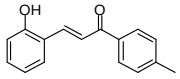
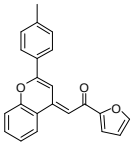
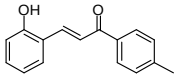
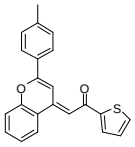
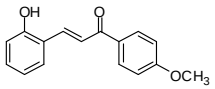
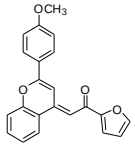
electron withdrawing show the reverse trend (Scheme 1, entry 5–8). The chalcone intermediate formed initially in these reactions has been isolated by terminating the reaction half the way.

To further expand the scope of this method, we next examined the ability of this reaction to synthesize unsymmetrical 4-phenacylideneflavenes. The *trans*-2-hydroxychalcones (**4a**–**c**)[21] obtained by the condensation reaction of salicyladehyde **1a** with different acetophenones (**2a**–**c**) (Scheme 2) cleanly underwent reaction with variety of acetophenones in presence of iodine to furnish unsymmetrical 4-phenacylideneflavenes (**5a**–**f**) in good to excellent yields (Scheme 2). Furthermore, heteroaromatic motifs such as 2-acetylfuran or 2-acetylthiophene could also be easily incorporated to form corresponding unsymmetrical 4-phenacylideneflavenes (**6a**–**c**) in impressive yields (Scheme2).

Scheme 2. Synthesis of unsymmetrical 4-phenacylideneflavenes



Entry	Substrate (1)	Substrate (2)	Product[a]	Time (min)	Yield[b] (%)
1	**4b**	**2a**	**5a**	40	74
2	**4b**	**2j**	**5b**	35	76
3	**4b**	**2i**	**5c**	30	78
4	**4b**	**2k**	**5d**	40	74

5	 **4a**	 **2j**	 **5e**	40	75
6	 **4a**	 **2i**	 **5f**	30	77
7	 **4b**	 **2l**	 **6a**	40	73
8	 **4b**	 **2m**	 **6b**	45	72
9	 **4a**	 **2l**	 **6c**	35	74

[a]Reaction conditions: Substrate 1 (0.8 mmol), Substrate 2 (0.8 mmol), Iodine (0.08 mmol), [b]Isolated yields after chromatography.

The structure of the representative unsymmetrical compound **5b** was unambiguously confirmed by single crystal X-ray analysis (Figure 2).

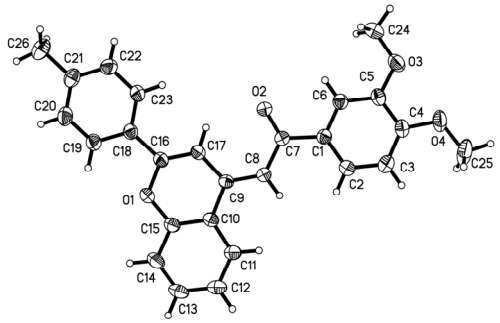
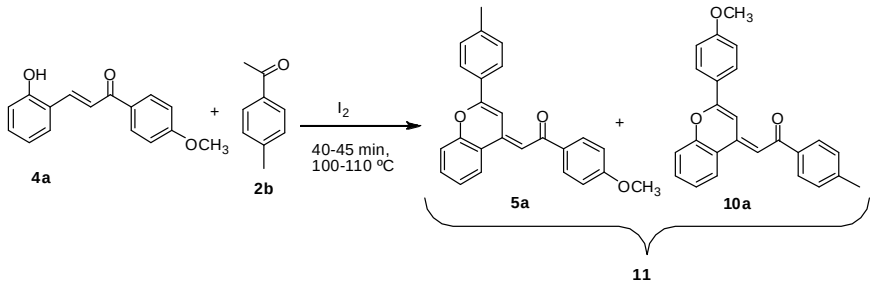


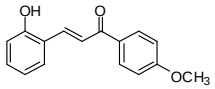
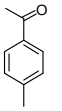
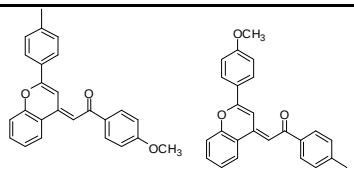
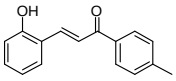
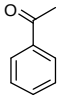
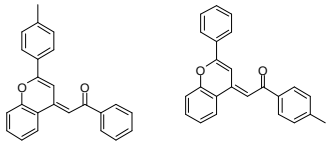
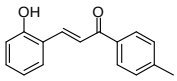
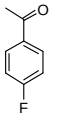
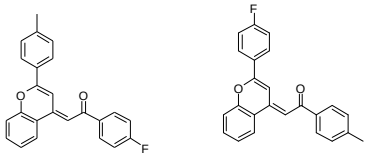
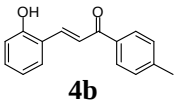
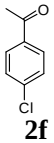
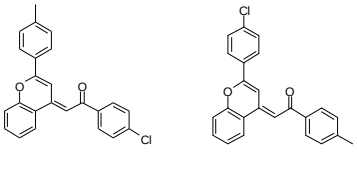
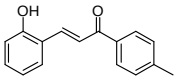
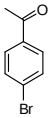
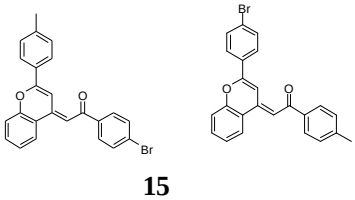
Figure 2. X-ray of Compound **5b**

To further explore the synthesis of unsymmetrical 4-phenacylideneflavenes, we next investigated the electronic effects of substitution in the acetophenone derivatives on the regioselective outcome of their reaction with 2-hydroxychalcone derivatives. Thus, the reaction of 4-methylacetophenone (**2b**) with *trans*-3-(2-hydroxyphenyl)-1-(4-methoxyphenyl)prop-2-en-1-one (**4a**) surprisingly gave mixture of two unsymmetrical 4-phenacylideneflavenes isomers **5a** and **10a** as shown in scheme 3. The ^{1}H NMR of inseparable 1:1 mixture (**5a**+**10a** = **11**) of products was confirmed by duplication of key NMR signals (such as δ at 2.40 & 2.41, 3.86 & 3.87, 7.08 & 7.09 and 8.87 & 8.88 for $-CH_3$, $-OCH_3$, and two allylic protons respectively) and by comparing the spectra of compound **5a** (See Supporting Information). Our further preliminary investigation revealed that there are competitive electronic factors that play a role in the formation of mixture of products. Interestingly,

the formation of a single product or a mixture of unsymmetrical 4-phenacylideneflavenes is strongly influenced by the relative nucleophilicity of the participating acetophenones. It is noteworthy to observe that, when the nucleophilicity of the initial reacting acetophenone that condense with salicylaldehyde to form 2-hydroxychalcone derivatives, (for example **4a**) is comparatively less than the subsequently reacting acetophenone typically yield regioselective 4-phenacylideneflavenes (Scheme 2), while when the opposite is true, the reaction yield a mixture of two unsymmetrical 4-phenacylideneflavenes isomers (Scheme 3).

Scheme 3. Formation of mixture of two unsymmetrical 4-phenacylideneflavenes



Entry	Substrate (1)	Substrate (2)	Mixture[a,b]	Time (min)	Yield[c] (%)
1	 **4a**	 **2b**	 **11**	40	73
2	 **4b**	 **2d**	 **12**	40	72
3	 **4b**	 **2e**	 **13**	45	70
4	 **4b**	 **2f**	 **14**	45	71
5	 **4b**	 **2g**	 **15**	40	71

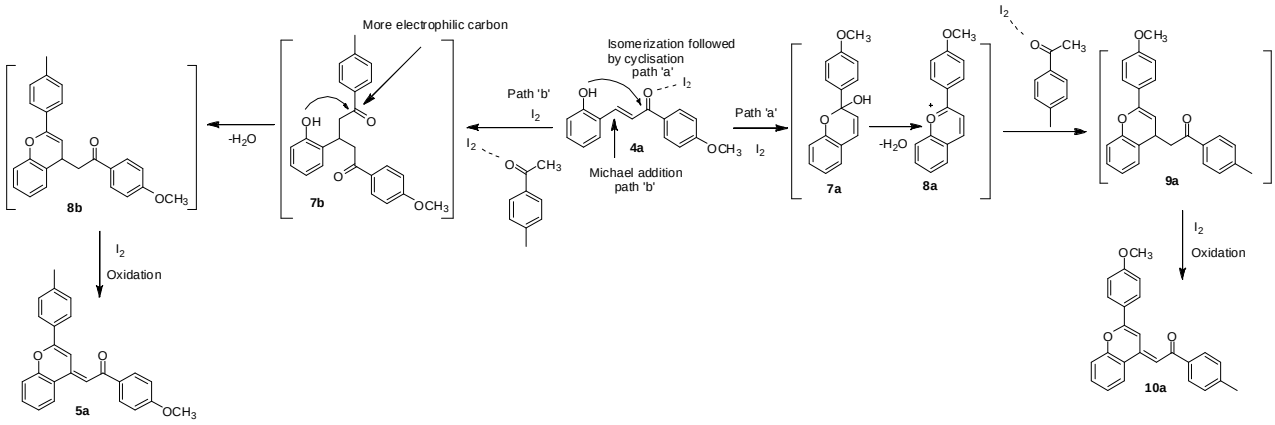
[a]Reaction conditions: Substrate 1 (0.8 mmol), Substrate 2 (0.8 mmol), Iodine (0.08 mmol), [b]The ratio of isomers (1:1) in mixture was based on ^{1}H NMR, [c]Isolated yields after chromatography.

.

On the basis of the experimental results, a plausible mechanism for the formation of 4-phenacylideneflavenes is proposed in Scheme 4. The mild Lewis acidity associated with iodine and its role as a oxidising agent to

promote cyclisation is well known.[22] The mechanism in path 'a' involves the following steps: Isomerization (the possibility of thermally induced *trans- cis* chalcone isomerization cannot be ruled out) of the initial adduct, *trans*-3-(2-hydroxyphenyl)-1-(4-methoxyphenyl)prop-2-en-1-one (Scheme 4, **4a**) to *cis* isomer[23] followed by intramolecular cyclization results in it's hemiacetal species **7a**, which gets converted to more reactive flavylium ion (**8a**).[18] This electrophile further reacts with 4-methylacetophenone (*C*-nucleophiles) to form adduct **9a**, that on oxidation in presence of iodine yields unsymmetrical 4-phenacylideneflavenes (**10a**). In the path 'b', the *trans*-3-(2-hydroxyphenyl)-1-(4-methoxyphenyl)prop-2-en-1-one (**4a**) underwent Michael addition[24] with 4-methylacetophenone in presence of iodine catalyst to form adduct **7b**, which then undergoes intramolecular cyclization, followed by dehydration to furnish adduct **8b**, which then oxidises to yield the product **5a**. It is proposed that for the formation of unsymmetrical 4-phenacylideneflavenes single regioisomer (Scheme 2), pathway 'a' is mainly operative, as the O-cyclization is fast onto the keto-carbonyl of aceto-*para*-tolyl-phenone, a real aryl ketone, than a 1,4 addition as shown in path 'b'. On the other hand, the mechanism of formation of mixture of unsymmetrical 4-phenacylideneflavenes (Scheme 3) might involve both pathways (Scheme 4) since the O-cyclization in 'a' is slower (than 1, 4-addition) onto the keto-carbonyl given that is from an aceto-*para*-methoxy-phenone, which is NOT a real aryl ketone, but more of a vinylogous ester (delocalization of oxygen lone pair of the -OCH_3 group into the carbonyl). Though the intimate mechanistic details of this reaction are not yet fully understood, further studies are in progress to understand the mechanism of this quite interesting reaction.

Scheme 4. Proposed mechanism for the formation of mixture of 4-phenacylideneflavenes



Conclusions

To the best of our knowledge, there is no simple, general, and efficient catalytic method for the diversity oriented synthesis of 4-phenacylideneflavenes. We have successfully demonstrated an easy and efficient method for the synthesis of new functionalized 4-phenacylideneflavenes utilizing iodine as a catalyst under solvent free condition. This environmentally benign process will contribute to the development of a strategy for synthesizing various biologically relevant flavenes and natural products.

Experimental Section

General Information

Unless otherwise specified all the reagents and catalysts were purchased from Sigma–Aldrich and were used without further any purification. Infrared spectra were recorded with FT-IR as a thin film and are expressed in cm^{-1}. ^1H NMR (at 200 or 300 or 400 MHz) and ^{13}C NMR (50 or 75 or 100 MHz) spectra were recorded using DMSO-d_6, TFA-d_1 and $CDCl_3$ as solvents and TMS as internal standard. Chemical shifts are reported in parts per million. Splitting patterns are described as singlet (s), broad singlet (bs), doublet (d), broad doublet (bd), double doublet (dd), triplet (t), quartet (q), and multiplet (m). Mass spectra were obtained on ESI mass spectrometer and HR/ESI mass spectra were obtained on high resolution ESI mass spectrometer. Elemental analyses were carried out with C, H-analyzer.

1.1.1. Representative synthesis of 1-(4-methoxy-phenyl)-2-[2-(4-methoxyphenyl)-chromen-4-ylidene]-ethanone (3a):

A mixture salicylaldehyde **1a** (0.8 mmol), 4-methoxyacetophenone **2a** (1.6 mmol) and I_2 (0.08 mmol) heated at 100-110 ºC temperature for 6 h. After completion of the reaction, the mixture treated with aq. $Na_2S_2O_3$ solution (5%, 10 mL) and the product was extracted with chloroform (3×20 mL). The combined organic layers were dried with anhydrous sodium sulphate, concentrated in vacuo and purified by column chromatography (100-200 mesh) (2: 98 ethyl acetate: hexane) to afford the pure compound **3a**.

Light yellow solid; yield: 70%; mp 168-170 ºC; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.83 (s, 1H), 8.02 (d, 2H, J = 8.8 Hz), 7.96-7.90 (m, 3H), 7.51-7.45 (m, 1H), 7.33 (bd, 1H, J = 7.4 Hz), 7.30-7.25 (m, 1H), 7.06 (s, 1H), 6.95 (d, 4H, J = 8.8 Hz), 3.88 (s, 3H), 3.87 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 189.0, 162.5, 161.6, 155.8, 153.0, 142.2, 134.4, 131.5, 129.9, 127.7, 125.2, 124.9, 123.2, 120.7, 118.5, 114.2, 113.7, 102.3, 101.6, 55.5; IR (KBr): 3049, 1708, 1603, 1002 cm^{-1}; ESI-MS (*m*/*z*): 385 (M+H)$^+$. Anal. calcd for $C_{25}H_{20}O_4$: C, 78.11; H, 5.24; Found: C, 78.22; H, 5.13.

The compounds (**3b**–**l**) have been synthesized by similar procedure as described above for **3a**.

1.1.2. 1-*p*-Tolyl-2-(2-*p*-tolylchromen-4-ylidene)-ethanone (3b):
Light yellow solid; yield: 68%; mp 148-150 ºC; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.91 (s, 1H), 8.01-7.89 (m, 5H), 7.53 (t, 1H, J = 7.1 Hz), 7.40 (d, 1H, J = 7.7 Hz), 7.34-7.26 (m, 5H), 7.12 (s, 1H), 2.43 (s, 3H), 2.42 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 190.0, 156.1, 153.0, 142.4, 142.1, 140.9, 138.8, 131.5, 129.8, 129.5, 129.1, 127.8, 125.9, 124.9, 123.2, 120.6, 118.5, 102.8, 102.3, 21.6, 21.5; IR (KBr): 3015, 1712, 1592, 1008 cm^{-1}; ESI-MS (*m*/*z*): 353 (M+H)$^+$. Anal. calcd for $C_{25}H_{20}O_2$: C, 85.20; H, 5.72; Found: C, 85.28; H, 5.64.

1.1.3 1-*m*-Tolyl-2-(2-*m*-tolylchromen-4-ylidene)-ethanone (3c):
Light yellow solid; yield: 68%; mp 152-153 ºC; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.90 (s, 1H), 7.95 (bd, 1H, J = 7.0 Hz), 7.83-7.77 (m, 4H), 7.52-7.47 (m, 1H), 7.38-7.24 (m, 6H), 7.09 (s, 1H), 2.44 (s, 3H), 2.42 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 190.6, 156.2, 153.1, 142.5, 141.5, 138.5, 138.2, 132.6, 132.4, 131.7, 131.4, 128.7, 128.4, 128.3, 126.6, 125.0, 124.9, 123.3, 123.2, 120.6, 118.6, 103.3, 103.0, 21.6, 21.5; IR (KBr): 3019, 1715, 1592, 1028 cm^{-1}; ESI-MS (*m*/*z*): 353 (M+H)$^+$. Anal. calcd for $C_{25}H_{20}O_2$: C, 85.20; H, 5.72; Found: C, 85.13; H, 5.72.

1.1.4. 1-Phenyl-2-(2-phenylchromen-4-ylidene)-ethanone (3d):
Light yellow solid; yield: 67%; mp 128-130 ºC; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.94 (s, 1H), 8.04-7.98 (m, 5H), 7.56-7.39 (m, 8H), 7.32 (t, 1H, J = 7.1 Hz), 7.14 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 190.4, 156.0, 153.1, 142.5, 141.4, 132.6, 131.8, 131.7, 130.6, 128.8, 128.5, 127.8, 126.1, 125.1, 123.3, 120.6, 118.6, 103.2, 103.0; IR (KBr): 3040, 1704, 1597, 997 cm^{-1}; ESI-MS (*m*/*z*): 325 (M+H)$^+$. Anal. calcd for $C_{23}H_{16}O_2$: C, 85.16; H, 4.97; Found: C, 85.07; H, 5.06.

1.1.5. 1-(4-Fluorophenyl)-2-[2-(4-fluorophenyl)-chromen-4-ylidene]-ethanone (3e):
Light yellow solid; yield: 64%; mp 170-171 ºC; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.85 (s, 1H), 8.07-7.96 (m, 5H), 7.55 (t, 1H, J = 7.1 Hz), 7.35 (d, 1H, J = 8.2 Hz), 7.33 (t, 1H, J = 7.2 Hz), 7.19-7.12 (m, 4H), 7.08 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 188.9, 162.5, 161.8, 155.3, 154.0, 153.0, 145.2, 144.8, 142.7, 137.7, 132.0, 130.3, 130.2, 128.8, 128.1, 125.2, 123.3, 120.4, 118.7, 116.3, 115.8, 115.3, 102.8, 102.7; IR (KBr): 3017, 1723, 1599, 1007 cm^{-1}; ESI-MS (*m*/*z*): 361 (M+H)$^+$. HRMS calcd for $C_{23}H_{15}F_2O_2$ (M+H)$^+$ 361.1040, Found: 361.1061.

1.1.6. 1-(4-Chlorophenyl)-2-[2-(4-chlorophenyl)-chromen-4-ylidene]-ethanone (3f):
Light yellow solid; yield: 66%; mp 167-168 ºC; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.88 (s, 1H), 7.97-7.89 (m, 5H), 7.55 (t, 1H, J = 7.2 Hz), 7.46-7.30 (m, 6H), 7.06 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 188.9, 155.2, 153.0, 142.8, 139.7, 138.1, 136.9, 132.1, 131.1, 129.3, 129.2, 128.8, 127.4, 125.3, 123.3, 120.4, 118.7, 103.2, 103.0; IR (KBr): 3041, 1719, 1592, 1008 cm^{-1}; ESI-MS (*m*/*z*): 393 (M+H)$^+$. HRMS calcd for $C_{23}H_{15}Cl_2O_2$ (M+H)$^+$ 393.0449, Found: 393.0486.

1.1.7. 1-(4-Bromophenyl)-2-[2-(4-bromophenyl)-chromen-4-ylidene]-ethanone (3g):
Light yellow solid; yield: 66%; mp 178-180 ºC; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.91 (s, 1H), 7.99 (bd, 1H, J = 7.2 Hz), 7.90-7.85 (m, 4H), 7.63-7.55 (m, 5H), 7.41 (d, 1H, J = 8.4 Hz), 7.35 (t, 1H, J = 8.3 Hz), 7.08 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 188.4, 155.2, 153.0, 142.7, 137.7, 131.9, 130.3, 130.2, 128.9, 128.8, 128.2, 125.3, 123.3, 120.4, 118.7, 116.2, 115.9, 115.7, 115.4, 102.8, 102.7; IR (KBr): 3053, 1719, 1602, 1008 cm^{-1}; ESI-MS (*m*/*z*): 481 (M+H)$^+$. HRMS calcd for $C_{23}H_{15}Br_2O_2$ (M+H)$^+$ 480.9439, Found: 480.9425.

1.1.8. (E)-1-(4-Nitrophenyl)-2-(2-(4-nitrophenyl)-4H-chromen-4-ylidene)ethanone (3h):
Light yellow solid; yield: 53%; mp 202-204 ºC; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.07(s, 1H), 8.37-8.34 (m, 4H), 8.20-8.15 (m, 4H), 8.03 (d, J = 7.8 Hz, 1H), 7.65 (t, J = 7.4 Hz, 1H), 7.49 (d, J = 8.0 Hz, 1H), 7.44-7.38 (m, 1H), 7.16 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 189.3, 155.2, 153.1, 142.8, 139.7, 138.1, 136.9, 132.1, 131.8, 129.3, 129.2, 128.9, 127.4, 125.4, 123.3, 120.4, 118.7, 103.2, 103.0, 103.0, 102.8, 61.1, 61.0, 56.5; IR (KBr): 3027, 1705, 1599, 1007 cm^{-1}; ESI-MS (*m*/*z*): 415 (M+H)$^+$. Anal. calcd for $C_{23}H_{14}N_2O_6$: C, 66.67; H, 3.41; N, 6.76; Found: C, 66.89; H, 3.20; N, 6.91.

1.1.9. 1-(3,4,5-Trimethoxyphenyl)-2-[2-(3,4,5-trimethoxy-phenyl)-chromen-4-ylidene]-ethanone (3i):
Light yellow solid; yield: 72%; mp 125-127 ºC; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.82 (s, 1H), 7.98 (d, 1H, J = 7.4 Hz), 7.59-7.54 (m, 1H), 7.45 (d, 1H, J = 7.4 Hz), 7.37-7.33 (m, 1H), 7.27 (s, 2H), 7.20 (s, 2H), 7.05 (s, 1H,), 3.99 (s, 6H), 3.97 (s, 6H), 3.93 (s, 3H), 3.92 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 189.6, 156.0, 153.5, 153.1, 153.0, 142.6, 141.5, 140.6, 137.1, 131.8, 128.1, 125.2, 123.2, 120.5, 118.6, 105.3, 103.6, 103.0, 102.8, 61.1, 61.0, 56.5; IR (KBr): 3049, 1712, 1592, 1008 cm^{-1}; ESI-MS (*m*/*z*): 505 (M+H)$^+$. Anal. Calcd for $C_{29}H_{28}O_8$: C, 69.04; H, 5.59; Found: C, 69.15; H, 5.47.

1.1.9 2-(6-Hydroxy-2-*p*-tolylchromen-4-ylidene)-1-*p*-tolyl-ethanone (3j):
Greenish solid; yield: 62%; mp 142-143 ºC; ^{1}H NMR ($CDCl_3$+TFA-d_1, 300 MHz): δ 8.35 (s,1H), 8.25 (d, 2H, J = 6.2 Hz), 8.17 (d, 1H, J = 7.0 Hz), 7.99 (d, 2H, J = 6.0 Hz), 7.87 (dd, 1H, J = 7.0 and 1.9 Hz), 7.56 (d, 2H, J = 6.1 Hz), 7.50 (s, 1H), 7.41 (d, 2H, J = 6.0 Hz), 7.26 (s, 1H), 2.56 (s, 3H), 2.49 (s, 3H); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 188.1, 156.0, 155.0, 152.5, 141.2, 140.7, 132.4, 132.2, 130.7, 130.1, 129.7, 125.7, 124.4, 120.4, 118.7, 116.5, 115.6, 103.5, 101.7; 21.5, 21.4; IR (KBr): 3428, 3021, 1723, 1619, 1020 cm^{-1}; ESI-MS (*m*/*z*): 369 (M+H)$^+$. Anal. Calcd for $C_{25}H_{20}O_3$: C, 81.62; H, 5.47, Found: C, 81.50; H, 5.35.

1.1.10. 2-(6-Hydroxy-2-*m*-tolylchromen-4-ylidene)-1-*m*-tolyl-ethanone (3k):
Greenish solid; yield: 63%; mp 132-134 ºC; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 9.85 (s, 1H), 8.82 (s, 1H), 7.90-7.86 (m, 2H), 7.75 (s, 2H), 7.57 (d, 1H, J = 2.5 Hz), 7.49-7.44 (m, 2H), 7.42-7.36 (m, 3H), 7.14 (dd, 1H, J = 9.0 and 2.6 Hz), 7.09 (s, 1H), 2.43 (s, 3H), 2.42 (s, 3H); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 188.1, 156.1, 154.9, 152.6, 141.2, 140.7, 132.5, 132.3, 130.7, 130.1, 129.7, 125.7, 124.4, 120.4, 118.7, 116.5, 115.6, 103.6, 101.7, 21.5, 21.4; IR (KBr): 3394, 3028, 1716, 1587, 1003 cm^{-1}; ESI-MS (*m*/*z*): 369 (M+H)$^+$. Anal. Calcd for $C_{25}H_{20}O_3$: C, 81.62; H, 5.47, Found: C, 81.73; H, 5.23.

1.1.11. 2-(6-Hydroxy-2-phenylchromen-4-ylidene)-1-phenyl-ethanone (3l):
Greenish solid; yield: 62%; mp 136-137 ºC; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 9.86 (s, 1H), 8.86 (s, 1H), 8.10 (d, 2H, J = 6.8 Hz), 7.96 (bd, 2H, J = 7.6 Hz), 7.60-7.47 (m, 8H), 7.17-7.13 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 189.4, 155.7, 155.4, 146.4, 142.3, 141.1, 132.6, 132.2, 131.3, 129.6, 129.0, 128.1, 126.0, 121.5, 120.9, 120.1, 108.0, 102.7, 101.6; IR (KBr): 3398, 3025, 1729, 1570, 1023 cm^{-1}; ESI-MS (*m*/*z*): 341 (M+H)$^+$. Anal. Calcd for $C_{23}H_{16}O_3$: C, 81.16; H, 4.74; Found: C, 81.08; H, 4.82.

1.2.1. Representative synthesis of 1-(4-methoxyphenyl)-2-(2-*p*-tolyl-chromen-4-ylidene)-ethanone (5a):
A mixture 2-hydroxychalcone **4b** (0.8 mmol), 4-methoxyacetophenone **2a** (0.8 mmol) and I_2 (0.08 mmol) heated at 100-110 ºC temperature for 40 min. After completion of the reaction, the mixture treated with aq. $Na_2S_2O_3$ solution (5%, 10 mL) and the product was extracted with chloroform (3×20 mL). The combined organic layers were dried with anhydrous sodium sulphate, concentrated in vacuo and purified by column chromatography (100-200 mesh) (3: 97 ethyl acetate: hexane) to afford the pure compound **5a**.

1-(4-Methoxyphenyl)-2-(2-*p*-tolylchromen-4-ylidene)-ethanone (5a):
Light yellow solid; yield: 76%; mp 155-138 ºC; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.88 (s, 1H), 8.03 (d, 2H, J = 8.7 Hz), 7.94 (bd, 1H, J = 7.9 Hz), 7.87 (d, 2H, J = 8.2 Hz), 7.48 (t, 1H, J = 8.2 Hz), 7.35 (d, 1H, J = 8.1 Hz), 7.30-7.24 (m, 3H), 7.09 (s, 1H), 6.96 (d, 2H, J = 8.7 Hz), 3.86 (s, 3H), 2.40 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 189.1, 162.6, 155.9, 153.1, 142.0, 140.9, 134.4, 131.5, 129.9, 129.6, 126.0, 124.9, 123.2, 120.8, 118.6, 113.7, 102.9, 102.4, 55.5, 21.6; IR (KBr): 3041, 1732, 1599, 1018 cm^{-1}; ESI-MS (*m*/*z*): 369 (M+H)$^+$. HRMS calcd for $C_{25}H_{20}O_3$ (M+H)$^+$ 369.1491, Found: 369.1447.

The compounds (**5b**–**f** & **6a**–**c**) have been synthesized by similar procedure as described above for **5a**.

1.2.2. 1-(3,4-Dimethoxyphenyl)-2-(2-*p*-tolylchromen-4-ylidene)-ethanone (5b):
Light yellow solid; yield: 78%; mp 157-159 ºC; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.89 (s, 1H), 7.96 (bd, 1H, J = 7.7 Hz), 7.87 (d, 2H, J = 8.2 Hz), 7.68-7.65 (m, 2H), 7.53-7.47 (m, 1H), 7.38-7.35 (m, 1H), 7.31-7.24 (m, 3H), 7.11 (s, 1H), 6.9 (d, 1H, J = 8.1Hz), 3.98 (s, 3H), 3.95 (s, 3H,), 2.40 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 188.9, 156.0, 153.1, 152.3, 149.2, 142.2, 141.0, 134.6, 131.6, 129.9, 129.6, 126.0, 124.9, 123.2, 121.6, 120.7, 118.6, 110.6, 110.1, 102.6, 102.4, 56.1, 21.6; IR (KBr): 3020, 1726, 1592, 1013 cm^{-1}; ESI-MS (*m*/*z*): 399 (M+H)$^+$. Anal. Calcd for $C_{26}H_{22}O_4$: C, 78.37; H, 5.57; Found: C, 78.25; H, 5.67.

1.2.3. 2-(2-*p*-Tolylchromen-4-ylidene)-1-(3,4,5-trimethoxy-phenyl)-ethanone (5c):
Light yellow solid; yield: 80%; mp 120-121 ºC; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.91 (s, 1H), 7.98 (d, 1H, J = 8.0 Hz), 7.91 (d, 2H, J = 8.1 Hz), 7.6-7.5 (m, 1H), 7.43 (d, 1H, J = 8.0 Hz), 7.36-7.26 (m, 5H), 7.05 (s, 1H), 3.97 (s, 6H), 3.93 (s, 3H,), 2.43 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 189.3, 156.5, 155.8, 153.2, 142.9, 141.2, 137.1, 133.9, 131.8, 129.8, 129.6, 126.1, 125.1, 123.2, 120.6, 118.8, 105.4, 102.5, 102.4, 61.1, 56.5, 21.6; IR (KBr): 3009, 1741, 1533, 1010 cm^{-1}; ESI-MS: (*m*/*z*): 429 (M+H)$^+$. Anal. Calcd for $C_{27}H_{24}O_5$: C, 75.68; H, 5.65; Found: C, 75.80; H, 5.52.

1.2.4. 1-(4-Hydroxyphenyl)-2-(2-*p*-tolylchromen-4-ylidene)-ethanone (5d):
Light yellow solid; yield: 76%; mp 167-168 ºC; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 10.19 (s, 1H), 8.8 (s, 1H), 8.36 (d, 1H, J = 7.7 Hz), 8.01 (d, 2H, J = 8.6 Hz), 7.83 (d, 2H, J = 8.1 Hz), 7.67-7.62 (m, 1H), 7.53 (s, 1H, J = 7.5), 7.43-7.38 (m, 3H), 7.31 (s, 1H,), 6.88 (d, 2H), 2.39 (s, 3H) ^{13}C NMR (DMSO-d_6, 75 MHz): δ 188.2, 161.6, 154.9, 152.6, 141.2, 140.7, 132.5, 132.3, 130.7, 130.1, 129.7, 127.9, 125.8, 124.5, 120.4, 118.7, 116.5, 115.5, 103.5, 101.8, 21.5; IR (KBr): 3452, 3043, 1742, 1518, 1031 cm^{-1}; ESI-MS (*m*/*z*): 355 (M+H)$^+$. Anal. Calcd for $C_{24}H_{18}O_3$: C, 81.34; H, 5.12; Found: C, 81.45; H, 5.0.

1.2.5. 1-(3,4-Dimethoxyphenyl)-2-[2-(4-methoxy-phenyl)-chromen-4-ylidene]-ethanone (5e):
Light yellow solid; yield: 77%; mp 167-168 ºC; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.87 (s, 1H), 7.98-7.93 (m, 3H), 7.69-7.66 (m, 2H), 7.51 (t, 1H, J = 10.8 Hz), 7.36 (d, 1H, J = 7.4 Hz), 7.29 (t, 1H, J = 7.8 Hz), 7.10 (s, 1H), 6.98-6.89 (m, 3H), 3.99 (s, 3H), 3.96 (s, 3H), 3.86 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 188.9, 161.7, 155.9, 153.0, 152.2, 149.1, 142.4, 134.5, 131.5, 127.7, 125.1, 124.9, 123.2, 121.6, 120.7, 118.6, 114.2, 110.6, 110.0, 102.1, 101.6, 56.1, 56.1, 55.5; IR (KBr): 3041, 1726, 1601, 1028 cm^{-1}; ESI-MS (*m*/*z*): 415 (M+H)$^+$. Anal. Calcd for $C_{26}H_{22}O_5$: C, 75.35; H, 5.35; Found: C, 75.47; H, 5.24.

1.2.6. 2-(2-(4-Methoxyphenyl)-4H-chromen-4-ylidene)-1-(3,4,5-trimethoxyphenyl)ethanone (5f)
Light yellow solid; yield: 80%; mp 127-128 ºC; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.87 (s, 1H), 7.98-7.94 (m, 3H), 7.57-7.51 (m, 1H), 7.40 (d, 1H, J = 8.0 Hz), 7.34 (d, 1H, J =7.7 Hz), 7.29 (s, 2H), 7.02 (s, 1H), 6.98 (d, 2H, J = 9.0 Hz), 3.97 (s, 6H), 3.93 (s, 3H), 3.88 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 189.3, 161.8, 156.4, 153.1, 143.1, 141.3, 137.1, 131.8, 127.8, 125.0, 124.9, 123.2, 120.5, 118.7, 114.3, 105.2, 101.9, 101.6, 61.1, 56.5, 55.7; IR (KBr): 3048, 1721, 1599, 1023 cm^{-1}; ESI-MS (*m*/*z*): 445 (M+H)$^+$. Anal. Calcd for $C_{27}H_{24}O_6$: C, 72.96; H, 5.44; Found: C, 72.85; H, 5.56.

1.2.8. 1-Furan-2-yl-2-(2-*p*-tolylchromen-4-ylidene)-ethanone (6a):
Light yellow solid; yield: 76%; mp 123-124 ºC; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.94 (s, 1H), 8.01 (d, 1H, J = 7.5 Hz), 7.88 (d, 2H, J = 6.4 Hz), 7.6-7.5 (m, 2H), 7.74 (d, 2H, J = 7.7 Hz), 7.34-7.3 (m, 3H), 7.06 (s, 1H), 6.6-6.5 (m, 1H), 2.41 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 178.8, 156.3, 155.9, 153.1, 144.9, 143.0, 141.1, 131.8,

129.8, 129.6, 126.1, 125.0, 123.5, 120.5, 118.6, 114.6, 112.4, 102.6, 101.9, 21.61; IR (KBr): 3016, 1719, 1534, 1015 cm^{-1}; ESI-MS (*m*/*z*): 369 $(M+H)^+$. Anal. Calcd $C_{22}H_{16}O_3$: for C, 80.47; H, 4.91; Found: C, 80.36; H, 5.02.

1.2.9. 1-(Thiophen-2-yl)-2-(2-*p*-tolyl-4H-chromen-4-ylidene)ethanone (6b):
Light yellow solid, yield: 74%; mp 123-125 ºC; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.92 (s, 1H), 7.97 (d, 1H, J = 7.4 Hz), 7.88 (d, 2H, J = 8.2 Hz), 7.79 (d, 1H, J = 3.0 Hz), 7.56 (d, 1H, J = 4.6 Hz), 7.51 (d, 1H, J = 1.0 Hz), 7.40 (d, 1H, J = 7.4 Hz), 7.35-7.30 (m, 1H), 7.28-7.25 (m, 2H), 7.15 (t, 1H, J = 3.9 Hz), 6.99 (s, 1H), 2.42 (s, 3H,); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 182.4, 156.2, 153.1, 149.0, 142.8, 141.1, 131.9, 129.8, 129.6, 129.3, 128.1, 126.1, 125.0, 123.2, 120.4, 118.6, , 102.5, 102.2, 21.60; IR (KBr): 3028, 1724, 1554, 1020 cm^{-1}; ESI-MS (*m*/*z*): 345 $(M+H)^+$. Anal. Calcd $C_{22}H_{16}O_2S$: for C, 76.72; H, 4.68; Found: C, 76.63; H, 4.79.

1.2.10. 1-Furan-2-yl-2-[2-(4-methoxyphenyl)-chromen-4-ylidene]-ethanone (6c):
Light yellow solid; yield: 77%; mp 149-150 ºC; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.89 (s, 1H), 7.99-7.90 (m, 3H), 7.56 (d, 1H, J = 0.9 Hz), 7.52-7.46 (m, 1H), 7.36-7.26 (m, 1H), 7.20 (d, 1H, J = 3.0 Hz), 7.01 (s, 1H), 6.95 (d, 2H, J = 8.9 Hz), 6.55-6.53 (m, 1H), 3.85 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 178.6, 161.8, 156.3, 153.2, 143.0, 142.3, 131.8, 131.7, 129.9, 129.2, 128.1, 127.8, 127.7, 125.0, 123.3, 120.8, 118.6, 114.3, 113.7, 101.8, 101.7, 55.6; IR (KBr): 3034, 1727, 1598, 1045 cm^{-1}; ESI-MS (*m*/*z*): 345 $(M+H)^+$. Anal. Calcd for $C_{22}H_{16}O_4$: C, 76.73; H, 4.68; Found: C, 76.62; H, 4.80.

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