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A Simple and Efficient Access to New Functionalized 4-Phenacylideneflavenes[#]

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Abstract: An innovative and efficient approach towards 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: acetophenones; iodine; salicylaldehyde; 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 (non-steroidal contraceptive agent),[5] CHF 4227 (selective estrogen receptor modulator),[6] and Acolbifene (selective estrogen receptor modulator).[7]

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

However, for 4-phenacylideneflavenes possessing the pyran core, only a limited number of synthetic methods can be found in the literature. Hill[16] et al.

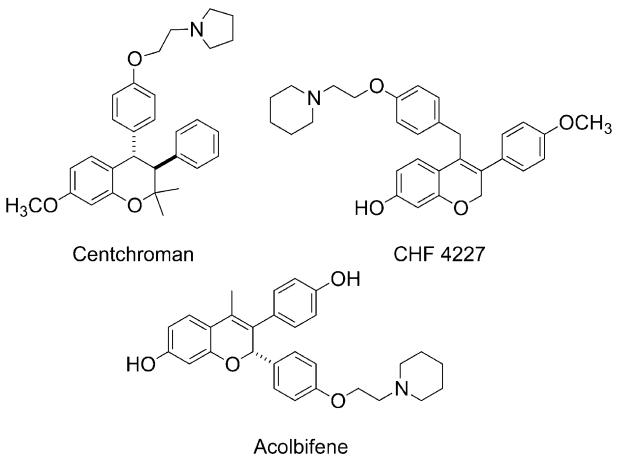


Figure 1. Examples of pharmaceuticals containing benzopyran frameworks.

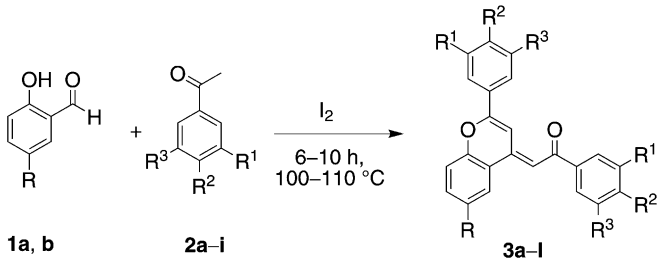
reported the synthesis of 4-phenacylideneflavenes by reaction of salicylaldehydes with acetophenone in three steps sequence using NaOH, cold AcOH and hot HCl. Meanwhile Vanallan[17] et al. have repeated the work of Hill by substituting AcOH with hot HCl and postulated that it is the flavylium acetate 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 the presence of $HBF_4{\cdot}OEt_2$ 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, non-toxic and readily available reagents providing convenient procedures for the synthesis of 4-phenacylideneflavene with improved yields is necessary. Moreover, up to 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, non-toxic, readily available catalyst for various organic transformations, affording the corresponding products in excellent yields with high selectivity. Initially, we carried out a preliminary study for the 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 $BF_3{\cdot}OEt_2$, $SnCl_2{\cdot}2H_2O$, $Bi(NO_2)_3$, $AlCl_3$, CuI, was tested for this transformation without success. Much to our delight, we observed that only iodine (10 mol%) can catalyze efficiently the reaction at a temperature 100–110 °C to furnish 4-phenacylideneflavene **3a** in good yield (Table 1). However, in the absence of iodine, the reactions did not proceed even after prolonged heating, clearly indicating that molecular iodine is essential to facilitate the reaction. Notably, the reaction was conducted under solvent-free conditions. Initially, the re-

Table 1. One-pot synthesis of symmetrical 4-phenacylideneflavenes.



1a, b **2a–i** **3a–l**

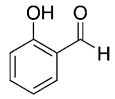
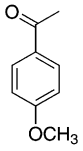
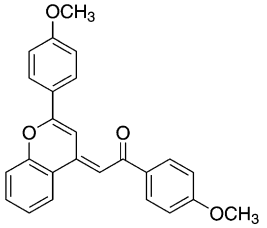
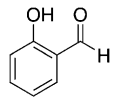
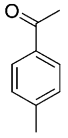
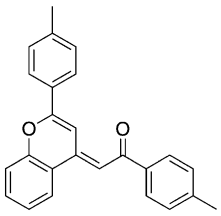
Entry	Substrate **1**	Substrate **2**	Product[a]	Time [h]	Yield[b] [%]
1	**1a** 	**2a** 	**3a** 	6.2	70
2	**1a** 	**2b** 	**3b** 	6.5	68

Table 1. (Continued)

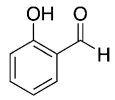
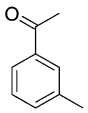
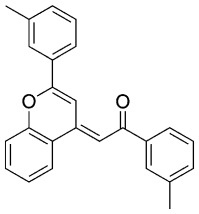
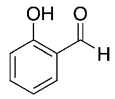
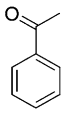
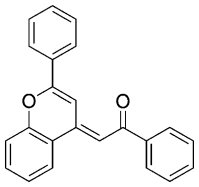
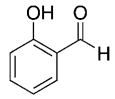
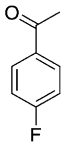
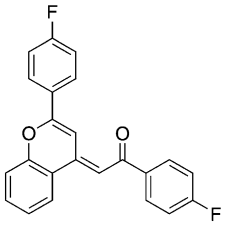
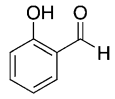
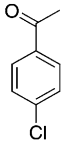
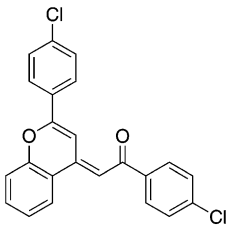
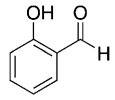
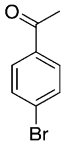
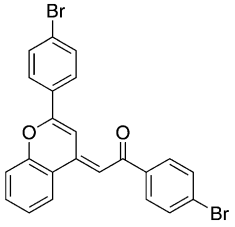
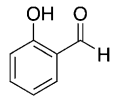
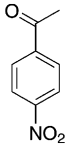
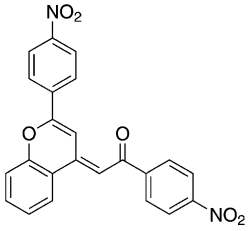
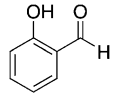
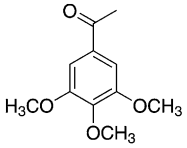
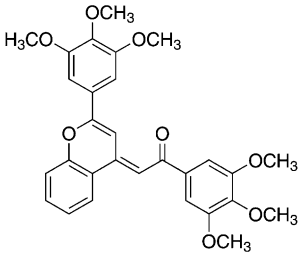
Entry	Substrate **1**	Substrate **2**	Product[a]	Time [h]	Yield[b] [%]
3	**1a** 	**2c** 	**3c** 	6.5	68
4	**1a** 	**2d** 	**3d** 	7.0	67
5	**1a** 	**2e** 	**3e** 	8.0	64
6	**1a** 	**2f** 	**3f** 	7.5	66
7	**1a** 	**2g** 	**3g** 	7.2	66
8	**1a** 	**2h** 	**3h** 	10.0	53
9	**1a** 	**2i** 	**3i** 	6.0	72

Table 1. (Continued)

Entry	Substrate **1**	Substrate **2**	Product[a]	Time [h]	Yield[b] [%]
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.

action was attempted with different solvents but the yields were found to be better in absence of any solvent.

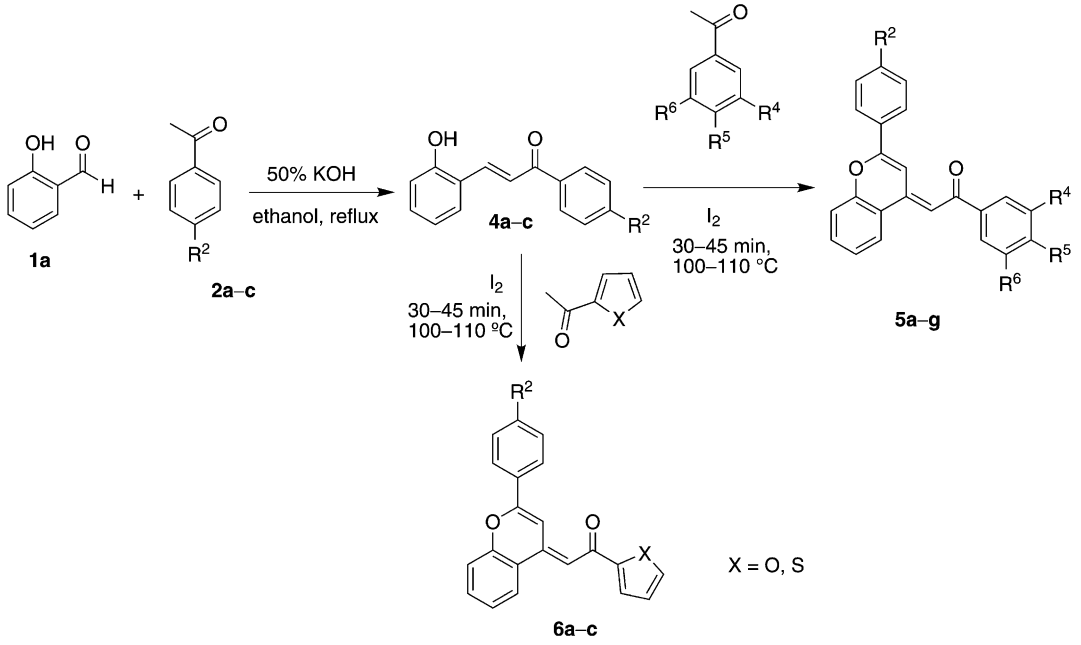
Under the established conditions, we investigated the application scope of this process by using a wide range of different acetophenones, and the corresponding products (**3b** to **3l**) were generally afforded in good to excellent yields (Table 1). The substituents present on the acetophenones slightly affect the reaction time and yield. In general, electron-donating groups accelerate the reaction rate as well as improve the yield (Table 1, entry 1–3, 9) while electron-withdrawing show the reverse trends (Table 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**) (Table 2) cleanly underwent reaction with variety of acetophenones in thte presence of iodine to furnish unsymmetrical 4-phenacylideneflavenes (**5a–f**) in good to excellent yields (Table 2). Furthermore, heteroaromatic motifs such as 2-acetylfuran or 2-acetylthiophene could also be easily incorporated to form the corresponding unsymmetrical 4-phenacylideneflavenes (**6a–c**) in impressive yields (Table 2).

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

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 Table 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 $\delta = 2.40$ & 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 the Supporting Information). Our further preliminary investigation revealed that there are competitive electronic factors that play a role in the formation of the mixture of products. Interestingly, the formation of a single product or a mixture of unsymmetrical 4-

Table 2. Synthesis of unsymmetrical 4-phenacylideneflavenes.



Entry	Substrate **4**	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

Table 2. (Continued)

Entry	Substrate **4**	Substrate **2**	Product[a]	Time [min]	Yield[b] [%]
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 **4** (0.8 mmol), substrate **2** (0.8 mmol), iodine (0.08 mmol).
[b] Isolated yields after chromatography.

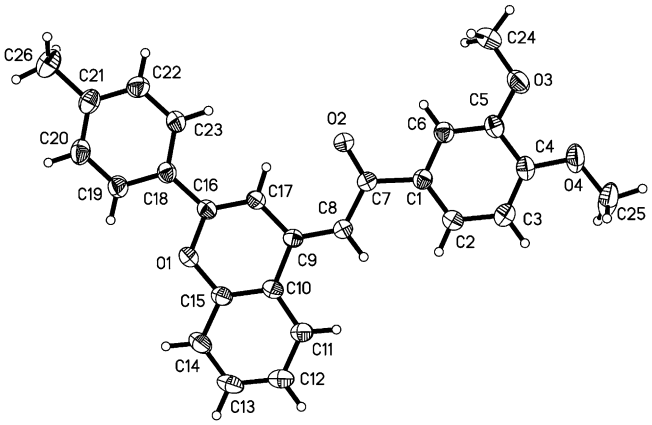
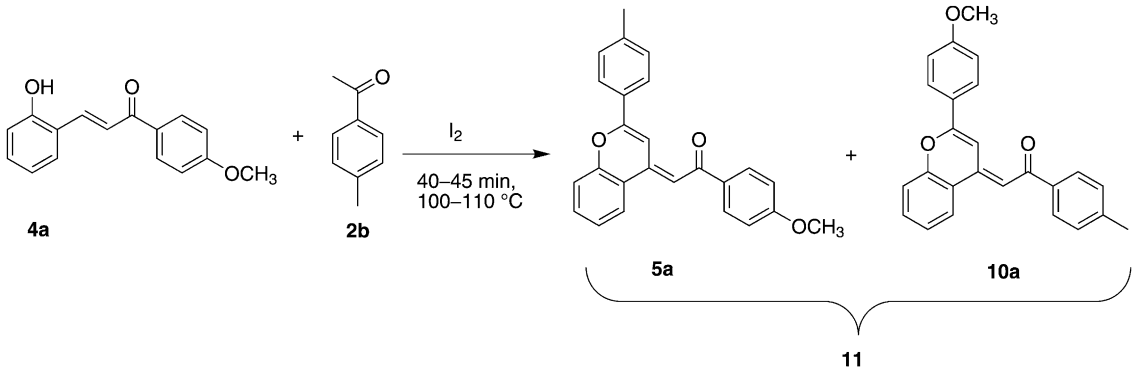


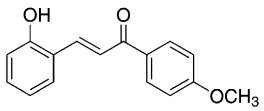
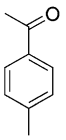
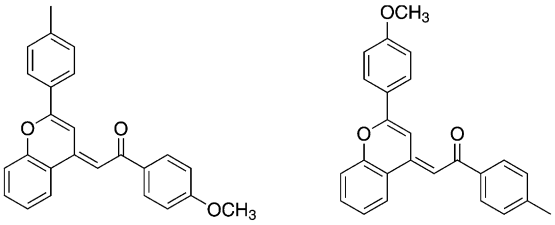
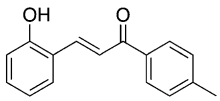
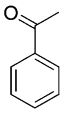
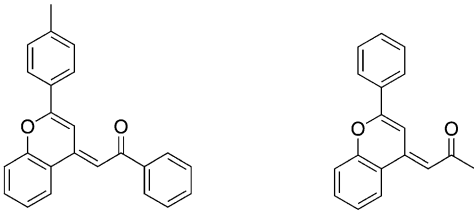
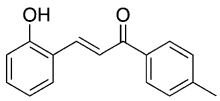
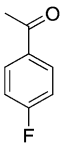
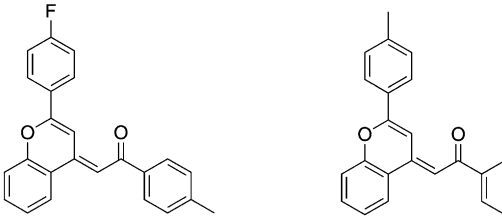
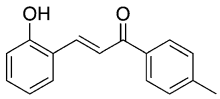
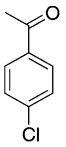
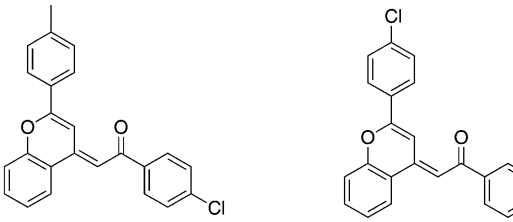
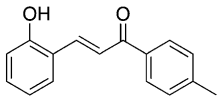
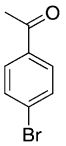
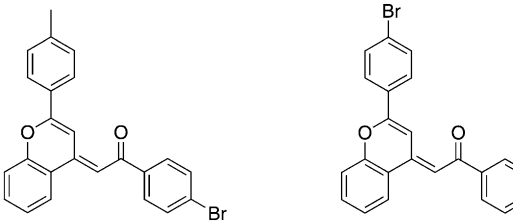
Figure 2. X-ray structure of compound **5b**.

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 condenses with salicylaldehyde to form 2-hydroxychalcone derivatives, (for example **4a**) is comparatively less than that of the subsequently reacting acetophenone, the reactions typically yield regioselective 4-phenacylideneflavenes (Table 2), while when the opposite is true, the reactions yield a mixture of two unsymmetrical 4-phenacylideneflavenes isomers (Table 3).

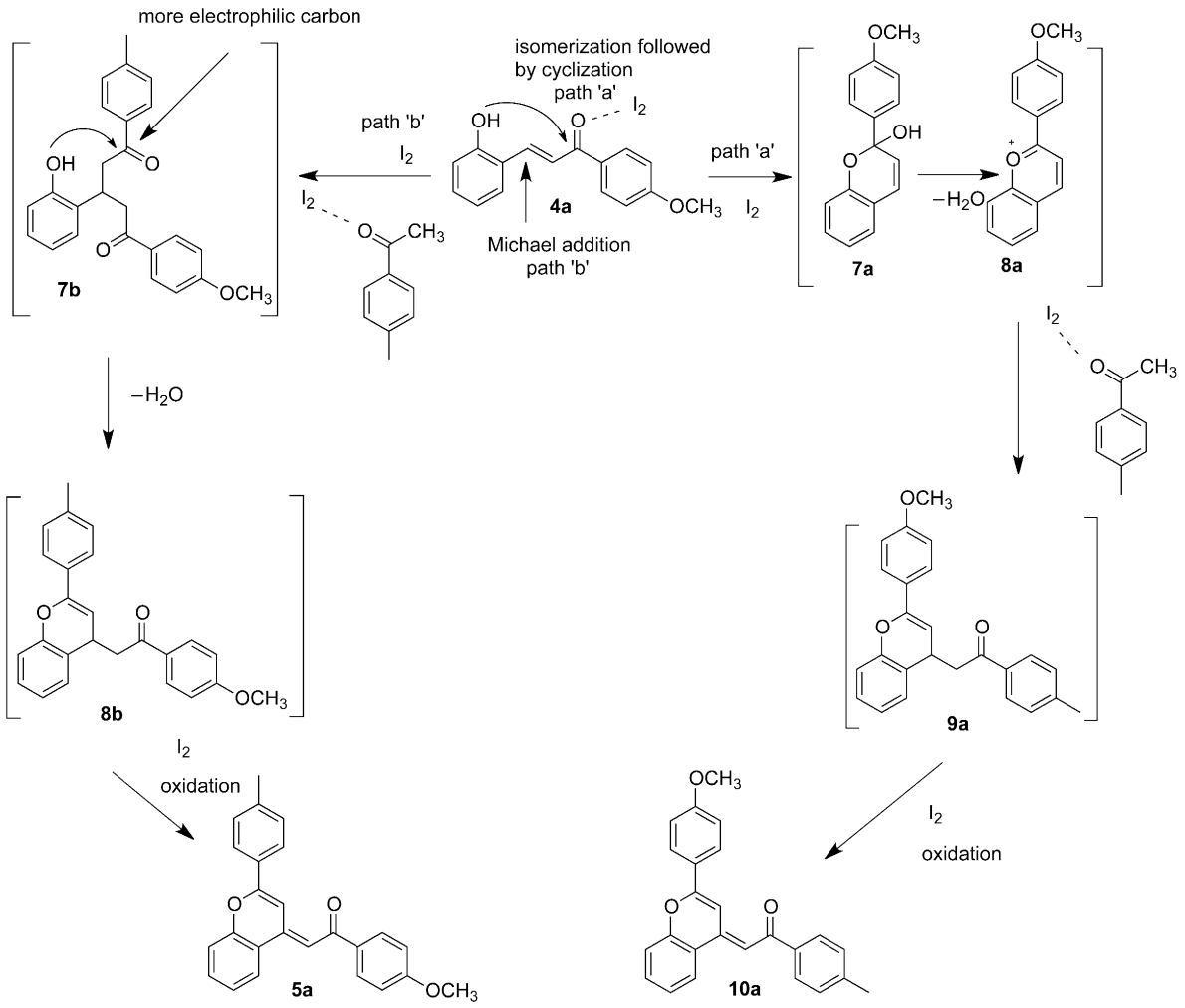
On the basis of the experimental results, a plausible mechanism for the formation of 4-phenacylideneflav-

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



Entry	Substrate **4**	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 **4** (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.



Scheme 1. Proposed mechanism for the formation of the mixture of 4-phenacylideneflavenes.

enes is proposed in Scheme 1. The mild Lewis acidity associated with iodine and its role as a oxidizing agent to promote cyclization 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 1, **4a**) to the *cis* isomer[23] followed by intramolecular cyclization which results in its hemiacetal species **7a**, which gets converted to the more reactive flavylium ion (**8a**).[18] This electrophile further reacts with 4-methylacetophenone (*C*-nucleophiles) to form adduct **9a**, that on oxidation in the 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 the presence of iodine catalyst to form adduct **7b**, which then undergoes intramolecular cyclization, followed by dehydration to furnish adduct **8b**, which then oxidizes to yield the product **5a**. It is proposed that for the formation of unsymmetrical 4-phenacylideneflavenes as a single regioisomer (Table 2), pathway 'a' is mainly operative, as the O-cyclization is faster onto the keto-carbonyl of aceto-*para*-tolylphenone, a real aryl ketone, than a 1,4 addition as shown in path 'b'. On the other hand, the mechanism of formation of the mixture of unsymmetrical 4-phenacylideneflavenes (Table 3) might involve both pathways (Scheme 1) since the O-cyclization in 'a' is slower (than 1, 4-addition) onto the keto-carbonyl given that it is from an aceto-*para*-methoxyphenone, 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). Although the intimate mechanistic details of this reaction are not yet fully understood, further studies are in progress to elucidate the mechanism of this quite interesting reaction.

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 conditions. This environmentally benign process will most likely 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 an 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 an ESI mass spectrometer and HR/ESI mass spectra were obtained on a high-resolution ESI mass spectrometer. Elemental analyses were carried out with a C,H-analyzer.

Representative Synthesis of 1-(4-Methoxyphenyl)-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) was heated at 100–110° for 6 h. After completion of the reaction, the mixture was treated with aqueous $Na_2S_2O_3$ solution (5%, 10 mL) and the product was extracted with chloroform (3× 20 mL). The combined organic layers were dried with anhydrous sodium sulfate, concentrated under vacuum and purified by column chromatography (100–200 mesh) (2:98 ethyl acetate: hexane) to afford the pure compound **3a** as a light yellow solid; yield: 70%; mp 168–170 °C. ^1H NMR ($CDCl_3$, 300 MHz): $\delta = 8.83$ (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): $\delta =$ 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): $\nu = 3049$, 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 procedures as described above for **3a**.

1-*p*-Tolyl-2-(2-*p*-tolylchromen-4-ylidene)ethanone (3b): Light yellow solid; yield: 68%; mp 148–150 °C. ^1H NMR ($CDCl_3$, 300 MHz): $\delta = 8.91$ (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): $\delta = 190.0$, 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): $\nu = 3015$, 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-*m*-Tolyl-2-(2-*m*-tolylchromen-4-ylidene)ethanone (3c): Light yellow solid; yield: 68%; mp 152–153 °C. ^1H NMR ($CDCl_3$, 300 MHz): $\delta = 8.90$ (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): $\delta = 190.6$, 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): $\nu = 3019$, 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-Phenyl-2-(2-phenylchromen-4-ylidene)ethanone (3d): Light yellow solid; yield: 67%; mp 128–130 °C. ^1H NMR ($CDCl_3$, 300 MHz): $\delta = 8.94$ (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): $\delta = 190.4$, 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-(4-Fluorophenyl)-2-[2-(4-fluorophenyl)-chromen-4-ylidene]ethanone (3e): Light yellow solid; yield: 64%; mp 170–171 °C. ^1H NMR ($CDCl_3$, 300 MHz): $\delta = 8.85$ (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): $\delta = 188.9$, 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): $\nu = 3017$, 1723, 1599, 1007 cm^{-1}; ESI-MS: $m/z = 361$ $(M+H)^+$; HR-MS: $m/z =$ 361.1061, calcd. for $C_{23}H_{15}F_2O_2$ $(M+H)^+$: 361.1040.

1-(4-Chlorophenyl)-2-[2-(4-chlorophenyl)-chromen-4-ylidene]ethanone (3f): Light yellow solid; yield: 66%; mp 167–168 °C. ^1H NMR ($CDCl_3$, 300 MHz): $\delta = 8.88$ (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): $\delta = 188.9$, 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): $\nu = 3041$, 1719, 1592, 1008 cm^{-1}; ESI-MS: $m/z = 393$ $(M+H)^+$; HR-MS: $m/z = 393.0486$, calcd. for $C_{23}H_{15}Cl_2O_2$ $(M+H)^+$: 393.0449.

1-(4-Bromophenyl)-2-[2-(4-bromophenyl)-chromen-4-ylidene]ethanone (3g): Light yellow solid; yield: 66%; mp 178–180 °C. ^1H NMR ($CDCl_3$, 300 MHz): $\delta = 8.91$ (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): $\delta = 188.4$, 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): $\nu = 3053$, 1719, 1602, 1008 cm^{-1}; ESI-MS: $m/z = 481$ $(M+H)^+$; HR-MS: $m/z = 480.9425$, calcd. for $C_{23}H_{15}Br_2O_2$ $(M+H)^+$: 480.9439.

(*E*)-1-(4-Nitrophenyl)-2-[2-(4-nitrophenyl)-4*H*-chromen-4-ylidene]ethanone (3h): Light yellow solid; yield: 53%; mp

202–204 °C. ^{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): ν = 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-(3,4,5-Trimethoxyphenyl)-2-[2-(3,4,5-trimethoxyphenyl)-chromen-4-ylidene]ethanone (3i): Light yellow solid; yield: 72%; mp 125–127 °C. ^{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): ν = 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.

2-(6-Hydroxy-2-*p*-tolylchromen-4-ylidene)-1-*p*-tolylethanone (3j): Greenish solid; yield: 62%; mp 142–143 °C. ^{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): ν = 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.

2-(6-Hydroxy-2-*m*-tolylchromen-4-ylidene)-1-*m*-tolylethanone (3k): Greenish solid; yield: 63%; mp 132–134 °C. ^{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): ν = 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.

2-(6-Hydroxy-2-phenylchromen-4-ylidene)-1-phenylethanone (3l): Greenish solid; yield: 62%; mp 136–137 °C. ^{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.

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) was heated at 100–110 °C for 40 min. After completion of the reaction, the mixture was treated with aqueous $Na_2S_2O_3$ solution (5%, 10 mL) and the product was extracted with chloroform (3 × 20 mL). The combined organic layers were dried with anhydrous sodium sulfate, concentrated under vacuum and purified by column chromatography (100–200 mesh) (3:97 ethyl acetate: hexane) to afford the pure *1-(4-Methoxyphenyl)-2-(2-p-tolylchromen-4-ylidene)-ethanone* (**5a**) as a light yellow solid; yield: 74%; mp 155–138 °C. ^{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): ν = 3041, 1732, 1599, 1018 cm^{-1}; ESI-MS: m/z = 369 $(M+H)^+$; HR-MS: m/z = 369.1447, calcd. for $C_{25}H_{20}O_3$ $(M+H)^+$: 369.1491.

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

1-(3,4-Dimethoxyphenyl)-2-(2-*p*-tolylchromen-4-ylidene)-ethanone (5b): Light yellow solid; yield: 76%; mp 157–159 °C. ^{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 = 8.1 Hz), 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): ν = 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.

2-(2-*p*-Tolylchromen-4-ylidene)-1-(3,4,5-trimethoxyphenyl)ethanone (5c): Light yellow solid; yield: 78%; mp 120–121 °C. ^{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): ν = 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-(4-Hydroxyphenyl)-2-(2-*p*-tolylchromen-4-ylidene)ethanone (5d): Light yellow solid; yield: 74%; mp 167–168 °C. ^{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): ν = 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-(3,4-Dimethoxyphenyl)-2-[2-(4-methoxyphenyl)chromen-4-ylidene]ethanone (5e): Light yellow solid; yield: 75%; mp 167–168 °C. ^{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): $\delta = 188.9$, 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): $\nu = 3041$, 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.

2-[2-(4-Methoxyphenyl)-4*H*-chromen-4-ylidene]-1-(3,4,5-trimethoxyphenyl)ethanone (5f): Light yellow solid; yield: 77%; mp 127–128 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 8.87$ (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): $\delta = 189.3$, 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): $\nu = 3048$, 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-Furan-2-yl-2-(2-*p*-tolylchromen-4-ylidene)ethanone (6a): Light yellow solid; yield: 73%; mp 123–124 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 8.94$ (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): $\delta = 178.8$, 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): $\nu = 3016$, 1719, 1534, 1015 cm^{-1}; ESI-MS: $m/z = 369$ $(M+H)^+$; anal. calcd. for $C_{22}H_{16}O_3$: C 80.47, H 4.91; found: C 80.36, H 5.02.

1-(Thiophen-2-yl)-2-(2-*p*-tolyl-4*H*-chromen-4-ylidene)ethanone (6b): Light yellow solid, yield: 72%; mp 123–125 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 8.92$ (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): $\delta = 182.4$, 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. for $C_{22}H_{16}O_2S$: C 76.72, H 4.68; found: C 76.63, H 4.79.

1-Furan-2-yl-2-[2-(4-methoxyphenyl)chromen-4-ylidene]-ethanone (6c): Light yellow solid; yield: 74%; mp 149–150 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 8.89$ (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): $\delta = 178.6$, 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): $\nu = 3034$, 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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