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Synthesis of some *bis*(arylidenes) containing heterocyclic chromones and *α*-pyronochromones

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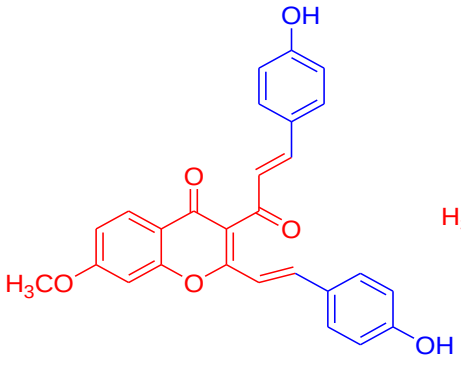
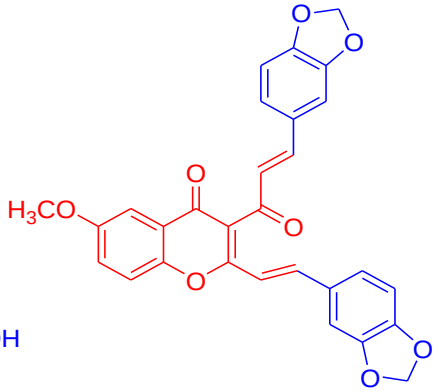
Abstract

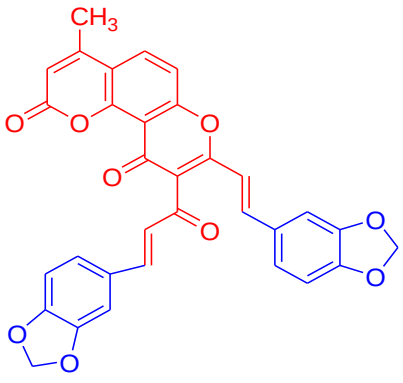
Five chromone and *α*-pyronochromone derivatives have been synthesized by reaction of *o*-hydroxyacetophenones and *o*-acetylhydroxycoumarins with anhydride acetic and sodium acetate as a catalyst. Then, these derivatives reacted with some aromatic aldehydes and received fourteen new *bis*(arylidenes). Furthermore, the intermediate product resulting from the reaction of 3-acetyl-7-methoxy-2-methylchromone and *p*-hydroxybenzaldehyde was successfully isolated and identified as 7-methoxy-2-methyl-3-[(2'*E*)-3'-(*p*-hydroxyphenyl)-prop-2'-enoyl]chromone. The antioxidant activity of all compounds was evaluated. The results show that 2-(4-hydroxystyryl)-3-((*E*)-3-(4-hydroxyphenyl)prop-2-enoyl)-7-methoxychromone has the highest antioxidant activity in tested compounds with inhibition of 88.48% at 50 µg/mL.



%inhibition of DPPH: 88.48±0.21 (at 50µg/mL)
Ascorbic acid: 97.65±0.1 (at 50µg/mL)



%inhibition of DPPH: 87.84±0.22 (at 50µg/mL)
Ascorbic acid: 97.65±0.1 (at 50µg/mL)



%inhibition of DPPH: 86.92±0.22 (at 50µg/mL)
Ascorbic acid: 97.65±0.1 (at 50µg/mL)

Keywords: *bis*(arylidenes); *α*,*β*-unsaturated ketones, chromones, *α*-pyronochromones, antioxidant activity
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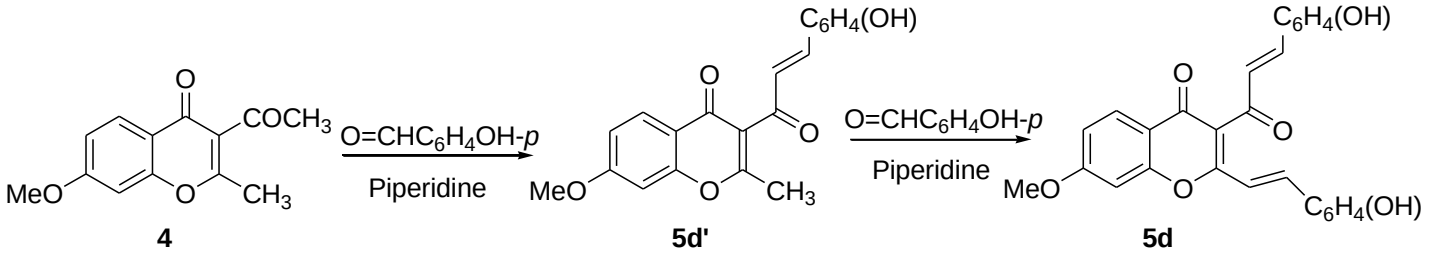
Introduction

Compounds containing chromone heterocyclic are widespread and have many important biological functions in nature.[1,2] These compounds have various biological activities, and their applications are wide-ranging, such as anticancer,[3] HIV-1 inhibition[4] antiplatelet,[5] anti-inflammatory,[6] antibacterial, antifungal,[7]] antioxidant,[8] inhibits the enzyme acetylcholinesterase,[9,10], *etc*. Several chromone-containing derivatives have been used as drugs such as khelin, sodium cromoglycate,[11,12] crodimyl,[13] diosmin,[14,15], and flavoxate.[16] Synthetic studies to create new compounds containing chromone frameworks attract further research interest. There are some ways to synthesize these heterocyclic systems, including i) Synthesis of chromones by bicyclic construction: synthesis of chromones from *o*-hydroxyarylalkylketones, they enclose three synthetic approaches: synthesis via Claisen condensation (classic Claisen condensation, Baker−Venkatamaran, and Kostanecki−Robinson reaction),[17-19] synthesis via benzopyrylium salts,[20-23] and via Vilsmeier−Haack reaction;[24] synthesis of chromones from phenols;[17] synthesis of chromones from salicylic acid and derivatives; [25,26] synthesis of chromones via C-C Cross-coupling reactions,[27,28] ii) Synthesis of chromones from chromanones,[29,30] iii) Synthesis of chromones from chromones,[31,32], *etc*. In this study, we report the successful synthesis of chromones and *α*-pyronochromones through the Kostanecki-Robinson reaction, utilizing *o*-hydroxyacetophenones and *o*-acetylhydroxycoumarins in the presence of acetic anhydride. This method offers a straightforward approach with high yield and efficient reaction conditions. Additionally, we synthesized a series of *bis*(arylidenes) containing heterocyclic chromones and *α*-pyronochromones by the Claisen-Schmidt condensation reaction of 3-acetyl-2-methylchromones with aromatic aldehydes. These compounds were subjected to antioxidant evaluation to assess their potential for practical applications.

Results and Discussion

We have applied Kostanecki-Robinson for the synthesis of required chromones **2**, **4**, **6** and *α*-pyronochromones **9**, **12** from *o*-hydroxyacetophenones and *o*-acetylhydroxycoumarins with anhydride acetic in the presence of AcONa as a base catalyst (see Scheme 2). *Bis*(arylidenes) were prepared by using Claisen-Schmidt condensation reaction of **2**, **4**, **6**, **9**, and **12** with aromatic aldehydes. Catalysts are weak bases such as piperidine, trimethyl amine, and pyridine... used for this reaction in chloroform or ethanol solvents. Meanwhile, strong inorganic catalysts, such as KOH and NaOH, produce smaller yields of main product *bis*(arylidenes) because chromones and *α*-pyronochromones were ring-opened under strong base conditions caused by these catalysts. In this reaction, the first step involves the reaction of 3-acetyl groups with aromatic aldehydes to produce *α,β*-unsaturated ketones, and the next step is the reaction of *α,β*-unsaturated ketones with aromatic aldehydes to yield *bis*(arylidenes). In some cases, *α,β*-unsaturated ketones may be difficult to dissolve under reaction conditions, resulting in their separation as solids and causing the reaction to stop. Some *α,β*-unsaturated ketones dissolved in the reaction mixture can undergo a condensation reaction of the methyl groups at position 2 on the *γ*-pyrone ring with aromatic aldehydes, forming *bis*(arylidenes). To support this hypothesis, 7-methoxy-2-methyl-3-[(2'*E*)-3'-(*p*-hydroxyphenyl)-prop-2'-enoyl]chromone (**5d')** was isolated and its structure was confirmed. Then, it was condensed with *p*-hydroxybenzaldehyde in a 1:1 mol ratio using Claisen-Schmidt condensation reaction conditions, forming **5d** (see Scheme 1).



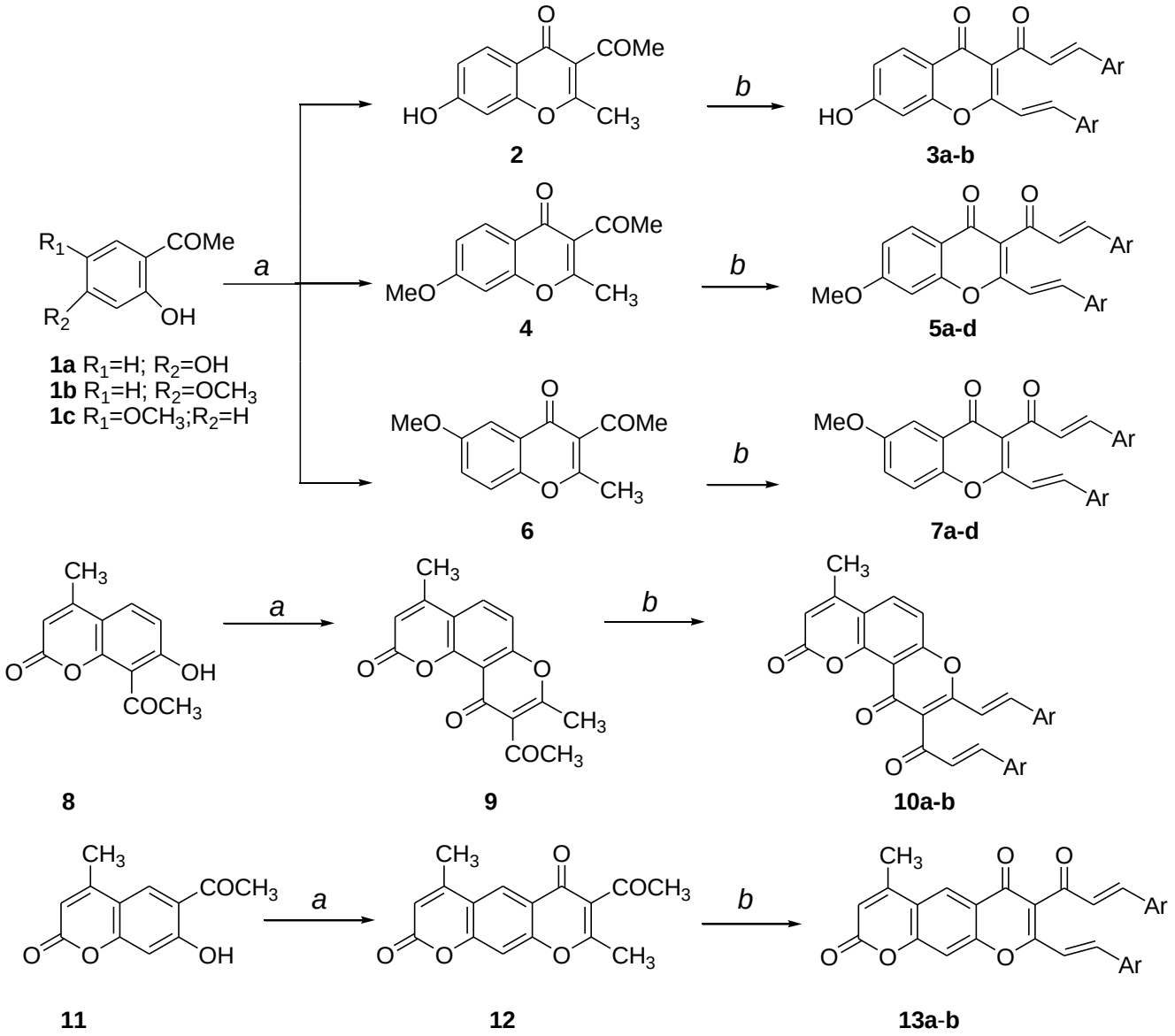
Scheme 1. Synthetic path to α,β-unsaturated ketone intermediate (**5d'**) and bis(arylidene) **5d.**

IR spectra of **5d'** had a characteristic absorption band of *trans*-vinyl at 976 cm^{-1}. Other absorption bands appeared at 1684 cm^{-1} (for pyrone carbonyl group), and 3093 cm^{-1} (*br*, for phenol OH group). ^{1}H NMR spectra of **5d'** indicated the presence of this *trans*-vinyl group through two signals at δ=6.96 ppm and δ=7.77 ppm for two protons vinyl, respectively. These signals had the roof effects that showed the coupling constants *J* 16.0 Hz. These values of the coupling constants indicated that the formed alkene had *trans* configuration.

In our opinion, the 2-methyl group is activated by the electron attraction of the 3-acetyl group. On the other hand, it also has a hyperconjugation effect with the vinyl ketone group, so it is very activated. In addition, quantum chemical calculations by HyperChem Release 8.0 software have also shown that the charge density of the carbon atoms in the 2-methyl and 3-acetyl groups in the *γ*-pyrone ring is quite similar: **2**, -0.265, and -0.201 respectively, whereas, with **4**, the values are -0.264 and -0.201, with **6**, -0.265 and -0.203, with **9**, -0.267 and -0.199, and with **12**, -0.265 and -0.204. As a result, the *γ*-pyrone ring's 2-methyl and 3-acetyl groups can react with aromatic aldehydes to form *bis*(arylidene) compounds.

Synthesis of *bis*(arylidenes) took place relatively slowly, and the end of the reaction required intervals of up to 30-40 hrs (the reaction was monitored by TLC) and a molar ratio of **2**, **4**, **6, 9**, **12**, and aromatic aldehydes was 1:2. In this reaction, chloroform and 0.5 mol% of piperidine were used as a solvent and weak base catalyst, respectively. The reaction mixture was heated under reflux conditions. Based on the difference in solubility of the initial reactants and products, the reaction progress was monitored through the precipitate separated during the reaction. *Bis*(arylidene) derivatives containing chromones and *α*-pyronochromones are solids, have high melting points, and are difficult to dissolve in organic solvents such as ethanol, acetone, and DMF. The successful synthesis of *bis*(arylidenes) containing chromones and *α*-pyronochromones from acetylmethylchromone derivatives and aromatic aldehydes was confirmed through analysis of IR, NMR, and MS spectral data.

The IR spectra of *bis*(arylidenes) showed the absorption peaks characterized by the carbonyl ketone and pyrone groups appearing in 1622-1763 cm^{-1} region. The *trans*-configuration of *α,β*-unsaturated ketones, and vinyl was confirmed by IR absorption bands in the 959–998 cm^{-1} range.



Scheme 2. Synthetic path to chromone, α-pyronochromone, and bis(arylidene). Reaction conditions: (a) Ac_2O, CH_3COONa, 130-140°C for 8 hrs; (b) O=CHAr, piperidine (catalyst), chloroform, 30–40 hrs, under reflux conditions.

The ^{1}H-NMR spectra of *bis*(arylidenes) showed four pairs of doublets-doublets with roof effect at 6.68-8.06 ppm with coupling constant in the range of 15.5-16.0 Hz. This showed two vinyl groups have *trans* configuration. In addition, the disappearance of the two resonance signals of the acetyl and methyl groups in the spectrum compared to the starting compound indicates that the condensation reaction has successfully occurred, resulting in the formation of the *bis*(arylidenes) structure. Besides, the ^{1}H-NMR also showed resonance signals of other protons in chromones, *α*-pyronochromones, and substituted benzenes. The identification of aromatic proton signals is based on spin-spin splitting (s, d, t,..), signal intensity (1H, 2H, 3H,..), and the effect of substituted groups attached to the aromatic ring.

The ^{13}C-NMR, HSQC, and HMBC spectra of compounds **3b**, **5b**, and **5c** confirmed the proposed structures. In the ^{13}C NMR spectra, the carbon atoms in the ketone carbonyl functional group of these compounds showed chemical shifts in the region of δ = 191.3-193.5 ppm. Additionally, four carbons in two

types of vinyl had chemical shifts in the ranges of 141.5-145.0 ppm and 118.2-131.8 ppm. The ^{13}C-NMR, HSQC, and HMBC spectra of compounds **3b**, **5b**, and **5c** showed the expected signals. However, compound **13a** poorly dissolves in the DMSO-d_6 solvent, affecting the signal appearance in low-resolution spectra.

The presence of ion-molecule peaks corresponding to the calculated molecular formula confirms the successful synthesis of the *bis*(arylidene) compounds. These peaks represent the mass-to-charge ratio (*m/z*) of ions formed during the ionization process, matching the expected molecular weight of the synthesized compounds. For compound **5b**, the molecular ion has three peaks at 476.0540 amu (100%); 478.0532 amu (69.70%); 480.0513 amu (14.33%). This indicates that compound **5b** contains two chlorine atoms.

The antioxidant activity of synthesis compounds was tested using the DPPH radical scavenging method. The details of the results are given in Table 1. All of the test compounds exhibited good antioxidant properties, with the strongest being observed in compounds **5d**, **7d**, and **10b**. However, all the synthesized compounds were less potent than ascorbic acid as the control. The potencies for the antioxidant activity of the strongest test compounds to the reference drug are in the following order: Ascorbic acid > **5d** > **10b**> **7d**.

Table 1. Inhibition (%) of test compounds

Comp.	Concentration (μg/mL)	% Inhibition	Comp.	Concentration (μg/mL)	% Inhibition
3a	10	27.65±1.27	7b	10	27.81±1.34
	50	60.34±0.24		50	56.82±0.22
3b	10	30.25±1.41	7c	10	29.26±1.28
	50	62.10±0.18		50	56..82±0.19
5a	10	23.52±1.31	7d	10	37.62±1.26
	50	54.13±0.14		50	86.92±0.22
5b	10	28.58±1.27	10a	10	32.52±1.28
	50	59.55±0.22		50	62.56±0.18
5c	10	26.63±1.28	10b	10	38.28±1.30
	50	51.45±0.24		50	87.84±0.22
5d	10	38.56±1.28	13a	10	30.04±1.32
	50	88.48±0.21		50	60.85±0.19
7a	10	25.92±1.28	13b	10	33.46±1.32
	50	50.45±0.20		50	58.88±0.21
Ascorbic acid*	10	40.49±2.27	Ascorbic acid*	10	40.49±2.27
	50	97.65±0.1		50	97.65±0.1

*Ascorbic acid as the control

Conclusions

A series of novel *bis*(arylidene) derivatives containing chromones and *α*-pyronochromones have been successfully synthesized. Their structures have been clarified by IR, NMR, and MS spectra data. The intermediate product of synthesis of **5d'** has been isolated, which is 7-methoxy-2-methyl-3-[(2'*E*)-3'-(*p*-hydroxyphenyl)-prop-2'-enoyl]chrom-one. The structure of this product has been verified through the use of IR, ^{1}H-NMR, and HR-MS spectra data. The antioxidant activity of all compounds was evaluated. 2-(4-

hydroxystyryl)-3-((*E*)-3-(4-hydroxyphenyl)prop-2-enoyl)-7-methoxychromone (**5d**) has the highest antioxidant activity in tested compounds with inhibition of 88.48% at 50 µg/mL.

To evaluate the potential applications of the synthesized compounds, the antibacterial and anticancer activities of the synthesized compounds will be assessed next.

Experimental Section

Instrumentation: Stuart SMP3 was used to confirm the melting point of the synthetic compounds. IR spectrum was analyzed by an Impact 410-Nicolet Spectrometer using KBr pellets. NMR spectra were obtained at 500 MHz for ^{1}H and 125 MHz for ^{13}C by an Avance AV500 Spectrometer made by Bruker, a company based in Germany., using d_6- DMSO as the solvent and TMS as the internal standard. LC-MS data was recorded by LC-MS-ORBITRAP-XL, MS data was recorded by 5989B Hewlett–Packard Mass spectrometer, and HR-MS data was recorded by Micromass AutoSpec Premier Instrument (WATER, USA). We use Merck Kieselgel 60F254 pre-coated plates for conducting thin-layer chromatography (TLC).

The charge density was calculated by the HyperChem Release 8.0 software using the Semi-Empirical methods. All compounds are built and geometrically optimized by RM1[33] with a convergence limit of 10^{-4} and an iteration limit of 50. The Polak-Ribiere algorithm was used with a termination condition of RMS gradient = 0.1000 kcal/(A mol), and RHF calculation.

Synthesis: Chemical reagents with high purity were bought from Merck Chemical Company. All reagents were of a grade for organic synthesis. Compounds **9** and **12** were synthesized according to literature procedures.[34,35] Chromones, *α*-pyronochromones , and *bis*(arylidenes) have been synthesized according to scheme 2.

***General procedure for preparing* 2, 4, 6, 9, and 12:** 0.01 mol of **1a-c**, **8,** and **11** was dissolved in 0.10 mol (9.5 mL) of anhydride acetic. A catalyst of 3.0 g sodium acetate was added to the solution mentioned above. The reaction was conducted with reflux conditions at a temperature range of 130-140^{o}C for 8 hours. Afterward, the solution's reaction was cooled, and the mixture was poured into a cup with 100 g of ice water. Once the separated product was filtered, washed with distilled water, and then dried. The final products **2, 4, 6, 9,** and **12** were obtained by recrystallizing them in an appropriate solvent. Physical, IR, NMR, and MS spectra data of all compounds are reported as follows:

3-Acetyl-7-hydroxy-2-methylchromone (2): From **1a** (0.01 mol, 1.52 gram): Yield 0.654 g (30%) of **2**, crystallized from EtOH as white crystals. Mp 185-187^{o}C. IR: $\upsilon_{C=O}$ (γ-pyrone) at 1687 cm^{-1}, $\upsilon_{C=O}$ (acetyl) at 1622 cm^{-1}, υ_{OH} at 3493 cm^{-1}, and 3393 cm^{-1}. ^{1}H-NMR: 2.36 (3H, s, CH_3), 2.48 (3H, s, $COCH_3$); 6.82 (1H, d, *J* 2.0 Hz, H_{benzo}); 6.92 (1H, dd, *J* 8.5 and 2.0 Hz, H_{benzo}); 7.89 (1H, d, *J* 8.5 Hz, H_{benzo}). EI-MS (*m/z*): 218 (M^+, 70.0%), Anal. Calcd for $C_{12}H_{10}O_4$.

3-Acetyl-7-methoxy-2-methylchromone (4): From **1b** (0.01 mol, 1.66 gram): Yield 0.696 g (30%) of **4**, crystallized from EtOH as pale-yellow crystals. Mp 164-166^{o}C. IR: $\upsilon_{C=O}$ (γ-pyrone, acetyl) at 1699 cm^{-1} (br). ^{1}H-NMR: 2.40 (3H, s, CH_3); 2.50 (3H, s, $COCH_3$); 3.90 (3H, s, OCH_3); 7.08 (1H, dd, *J* 8.0 and 2.5 Hz, H_{benzo}); 7.14 (1H, d, *J* 3.0 Hz, H_{benzo}); 7.96 (1H, d, *J* 8.5 Hz, H_{benzo}). HR-MS (*m/z*): 231.9436 (M^+, 92.6%), Anal. Calcd for $C_{13}H_{12}O_4$.

3-Acetyl-6-methoxy-2-methylchromone (6): From **1c** (0.01 mol, 1.66 gram): Yield 0.464 g (20%) of **6**, crystallized from EtOH as brown crystals. Mp 130-132^{o}C. IR: $\upsilon_{C=O}$ (γ-pyrone) at 1690 cm^{-1}, $\upsilon_{C=O}$ (acetyl) at 1647 cm^{-1}. ^{1}H-NMR: 2.45 (3H, s, CH_3); 2.53 (3H, s, $COCH_3$); 3.92 (3H, s, OCH_3); 7.36 (1H, dd, *J* 9.0 Hz and 3.0 Hz, H_{benzo}); 7.50 (1H, d, *J* 3.0 Hz, H_{benzo}); 7.52 (1H, d, *J* 9.0 Hz, H_{benzo}). HRMS (*m/z*): 232.0728 (M^+, 90.2%), Anal. Calcd for $C_{13}H_{12}O_4$.

9-Acetyl-4,8-dimethylpyrano[6,5-*f*]chromene -2,10-dione (9): From **8** (0.01 mol, 2.18 gram)**:** Yield: 1.287 gram (45%) of **9**, crystallized from DMF as yellow-brown crystals. Mp 245-246°C. IR: $\upsilon_{C=O}$ (pyrone) at 1726 cm^{-1}, 1698 cm^{-1} and CO-acetyl at 1649 cm^{-1}. ^{1}H-NMR: 2.40 (3H, s, $CH_{3\gamma\text{-pyrone}}$); 2.48 (3H, d, *J* 1.5 Hz, $CH_{3\alpha\text{-pyrone}}$); 2.49 (3H, s, $COCH_3$); 6.49 (1H, d, *J* 1.0 Hz, $H_{\alpha\text{-pyrone}}$); 7.56 (1H, d, *J* 9.0 Hz, H_{benzo}); 8.13 (1H, d, *J* 9.0 Hz, H_{benzo}). HRMS (*m/z*): 284.0687 (M^+, 100%), Anal. Calcd for $C_{16}H_{12}O_5$.

3-Acetyl-2,6-dimethyl-4*H*-pyrano[3,2-*g*]chromone-8-one (12): From **11** (0.01 mol, 2.18 gram)**:** Yield: 1.221 gram (43%) of **12**, crystallized from acetonitrile as pale-yellow crystals. Mp 246-247°C. IR: CO-lactone, γ-pyrone, acetyl at 1735 cm^{-1} and 1696 cm^{-1}. ^{1}H-NMR: 2.44 (3H, s, $CH_{3\gamma\text{-pyrone}}$); 2.50 (3H, s, $CH_{3\alpha\text{-pyrone}}$); 2.51 (3H, s, $COCH_3$); 6.48 (1H, s, $H_{\alpha\text{-pyrone}}$); 7.61 (1H, s, H_{benzo}), and 8.30 (1H, s, H_{benzo}). EI-MS (*m/z*): 284 (M^+, 75.3%), Anal. Calcd for $C_{16}H_{12}O_5$.

Synthesis of intermediates **7-methoxy-2-methyl-3-[(2'*E*)-3'-(*p*-hydroxyphenyl)-prop-2'-enoyl]chromone** (**5d'**): A mixture of 3-acetyl-7-methoxy-2-methylchromone **4** (5 mmol, 1.16 g) and *p*-hydroxybenzaldehyde (5 mmol, 0.61 g) in 30 mL ethanol, piperidine (0.5 mL; 0.5 mol %) was heated under reflux conditions for 20 hrs. After the reaction is complete, the mixture is cooled using ice. Next, the resulting precipitate is filtered and washed with distilled water followed by cold ethanol. The obtained product was air-dried at room temperature and recrystallized from ethanol to get the compound **5d'**. Physical, IR, ^{1}H-NMR, and HR-MS spectra data of compound **5d'** are reported as follows: Yield 0.588 g (35%) of **5d'** as pale-yellow crystals. Mp 287-289°C. IR: ν_{CO} (γ-pyrone, ketone) at 1684 cm^{-1}; $\gamma_{CH=trans}$ at 976 cm^{-1}. ^{1}H-NMR: 2.57 (3H, s, CH_3), 3.82 (3H, s, OCH_3), 6.94 (1H, d, *J* 8.5 and 2.5 Hz, H_{benzo}), 6.96 (1H, d, *J* 16.0 Hz, $H_{vinylketone}$), 6.98 (1H, d, *J* 2.5 Hz, H_{benzo}), 7.01 (2H, d, *J* 9.0 Hz, H_{phenyl}), 7.64 (2H, d, *J* 8.5 Hz, H_{phenyl}), 7.77 (1H, d, *J* 16.0 Hz, $H_{vinylketone}$), 7.89 (1H, d, *J* 8.5 Hz, H_{benzo}). HR-MS: *m/z* 336.1212 (M^+, 82.5%), Anal. Calcd for $C_{20}H_{16}O_5$.

General procedure for preparing bis(arylidene): A mixture of **2, 4, 6, 9, and 12** (5 mmol) and aromatic aldehydes (10 mmol) in chloroform (30 mL), piperidine (0.5 mL; 0.5 mol %) were heated under reflux conditions for 30-40 hrs. At first, when heating the reaction mixture the substances dissolve, then products are formed and separated in the form of a precipitate while heating. Filter the precipitate, and wash it several times with hot chloroform. The obtained products were air-dried at room temperature, and recrystallized from DMF to get the compounds **3a-b**; **5a-d**; **7a-d**; **10a-b**; and **13a-b**. Physical and IR, MS, and NMR spectra data of *bis*(arylidene) derivatives are reported as follows:

2-(4-Chlorostyryl)-3-((*E*)-3-(4-chlorophenyl) prop-2-enoyl)-7-hydroxychromone (Ar=4-ClC_6H_4, **3a):** Yield 0.962 g (40%) of **3a** as yellow crystals. Mp 295-297°C. IR: ν_{CO} (γ-pyrone, ketone) 1668 cm^{-1}, $\gamma_{CH=trans}$ at 961 cm^{-1}. ^{1}H-NMR: 6.94 (1H, d, *J* 16.0 Hz, $H_{vinylketone}$); 6.95 (1H, dd, *J* 8.0 and 3.0 Hz, H_{benzo}); 7.03 (1H, d, *J* 2.0 Hz, H_{benzo}); 7.20 (1H, d, *J* 16.5 Hz, H_{vinyl}); 7.48 (2H, d, *J* 8.0 Hz, H_{phenyl}); 7.49 (2H, d, *J* 8.0 Hz, H_{phenyl}); 7.62 (1H, d, *J* 16.0 Hz, H_{vinyl}); 7.71 (2H, d, *J* 8.0 Hz, H_{phenyl}); 7.76 (2H, d, *J* 8.5 Hz, H_{phenyl}); 7.84 (1H, d, *J* 16.0 Hz, $H_{vinylketone}$); 7.89 (1H, d, *J* 8.0 Hz, H_{benzo}). EI-MS (*m/z*): M^+ 462 (4.8%); 464 (3.1%); 463 (1.3%),.. Anal. Calcd for $C_{26}H_{16}Cl_2O_4$.

2-(4-Nitrostyryl)-3-((*E*)-3-(4-nitrophenyl) prop-2-enoyl)-7-hydroxychromone (Ar=4-$O_2NC_6H_4$, **3b):** Yield 0.962 g (35%) of **3b** as yellow crystals. Mp 297-299°C. IR: ν_{CO} (γ-pyrone, ketone) 1663 cm^{-1}; $\gamma_{CH=trans}$ at 979 cm^{-1}. ^{1}H-NMR: 6.97 (1H, d, *J* 8.5 Hz, H_{benzo}); 7.05 (1H, s, H_{benzo}); 7.17 (1H, *J* 16.0 Hz, $H_{vinylketone}$); 7.40 (1H, d, *J* 16.0 Hz, H_{vinyl}); 7.75 (1H, d, *J* 16.0 Hz, H_{vinyl}); 7.91 (1H, d, *J* 8.5 Hz, H_{benzo}); 7.96 (1H, *J* 16.0 Hz, $H_{vinylketone}$); 7.97 (2H, d, *J* 8.0 Hz, H_{phenyl}); 8.01 (2H, d, *J* 9.0 Hz, H_{phenyl}); 8.24 (2H, d, *J* 8.0 Hz, H_{phenyl}); 8.25 (2H, d, *J* 8.0 Hz, H_{phenyl}). ^{13}C-NMR: 102.9; 116.0; 116.3; 122.3; 123.0; 124.4; 124.6; 127.4; 129.6; 130.2; 131.8; 136.7; 141.4; 141.5; 141.8; 148.2; 148.6; 157.3; 159.2; 164.1; 175.4; and 192.5.

2-(4-Bromostyryl)-3-((*E*)-3-(4-bromophenyl)prop-2-enoyl)-7-methoxychromone (Ar=4-BrC_6H_4, **5a):** Yield 0.991 g (35%) of **5a** as yellow crystals. Mp 196-198°C. IR: ν_{CO} (γ-pyrone, ketone) 1622 (br) cm^{-1}; $\gamma_{CH=trans}$ at 979 cm^{-1}. ^{1}H-NMR: 3.95 (3H, s, OCH_3); 6.98 (1H, d, *J* 16.0 Hz, $H_{vinylketone}$); 7.10 (1H, d, *J* 9.0 Hz, H_{benzo}); 7.23 (1H, d, *J* 16.0

Hz, H_{vinyl}); 7.33 (s, 1H, H_{benzo}); 7.70-7.61 (8H, m, H_{phenyl}); 7.68 (1H, d, *J* 15.5 Hz, H_{vinyl}); 7.86 (1H, d, *J* 16.0 Hz, $H_{vinylketone}$); 7.95 (1H, d, *J* 9.0 Hz, H_{benzo}).

2-(4-Chlorostyryl)-3-((*E*)-3-(4-chlorophenyl) prop-2-enoyl)-7-methoxychromone (Ar=4-ClC_6H_4, **5b):** Yield 0.904 g (38%) of **5b** as yellow crystals. M.p: 200-202°C. IR: ν_{CO} (γ-pyrone, ketone) 1669 cm^{-1}; $\gamma_{CH=trans}$ at 978 cm^{-1}. ^{1}H-NMR: 3.96 (3H, s, OCH_3); 6.99 (1H, d, *J* 15.5 Hz, $H_{vinylketone}$); 7.09 (1H, dd, *J* 9.0 and 2.0 Hz, H_{benzo}); 7.19 (1H, d, *J* 16.0 Hz, H_{vinyl}); 7.28 (1H, d, *J* 2.0 Hz, H_{benzo}); 7.46 (4H, t, *J* 8.0 and 8.0 Hz, H_{phenyl}); 7.60 (1H, d, *J* 16.0 Hz, H_{vinyl}); 7.72 (2H, d, *J* 8.5 Hz, H_{phenyl}); 7.66 (2H, d, *J* 8.5 Hz, H_{phenyl}); 7.84 (1H, d, *J* 16.0 Hz, $H_{vinylketone}$); and 7.97 (1H, d, *J* 9.0 Hz, H_{benzo}). ^{13}C-NMR: 55.8; 100.6; 114.3; 116.7; 118.2; 121.7; 126.1; 128.3; 128.5; 128.7; 129.1; 129.8; 133.0; 133.3; 134.3; 134.9; 137.0; 142.3; 156.4; 159.0; 164.1; 174.4; 191.3. HR-MS (*m/z*): M^+ 476.0540 (100%); 478.0523 (69.7%); 480.0513 (14.33%), Anal. Calcd for $C_{27}H_{18}Cl_2O_4$.

2-(4-Methylstyryl)-3-((*E*)-3-(4-methylphenyl) prop-2-enoyl)-7-methoxychromone (Ar=4-MeC_6H_4, **5c):** Yield 0.915 g (43%) of **5c** as pale yellow crystals. Mp 150-152°C. IR: ν_{CO} (γ-pyrone, ketone) 1665 cm^{-1}; $\gamma_{CH=trans}$ at 959 cm^{-1}. ^{1}H-NMR: 2.32 (3H, s, CH_3); 2.35 (3H, s, CH_3); 3.95 (3H, s, OCH_3); 6.88 (1H, d, *J* 15.5 Hz, $H_{vinylketone}$); 7.09 (1H, dd, *J* 8.5 and 1.5 Hz, H_{benzo}); 7.14 (1H, d, *J* 16.0 Hz, H_{vinyl}); 7.24 (4H, t, *J* 7.5 and 7.0 Hz, H_{phenyl}); 7.34 (1H, d, *J* 1.5 Hz, H_{benzo}); 7.57 (1H, d, *J* 16.0 Hz, H_{vinyl}); 7.63-7.54 (4H, m, H_{phenyl}); 7.84 (1H, d, *J* 16.0 Hz, $H_{vinylketone}$); and 7.95 (1H, d, *J* 8.5 Hz, H_{benzo}). ^{13}C-NMR: 20.9; 21.0; 56.1; 100.7; 114.8; 116.4; 116.8; 121.6; 126.4; 127.0; 127.9; 128.7; 129.5; 129.7; 131.5; 131.9; 138.6; 140.3; 141.0; 145.0; 156.8; 159.3; 164.3; 174.8; 192.3. HR-MS (*m/z*): M^+ 436.1267 (100%), Anal. Calcd for $C_{29}H_{24}O_4$.

2-(4-Hydroxystyryl)-3-((*E*)-3-(4-hydroxyphenyl)prop-2-enoyl)-7-methoxychromone (Ar=4-HOC_6H_4, **5d):** Yield 0.858 g (39%) of **5d** as yellow crystals. Mp 239-241°C. IR: ν_{CO} (γ-pyrone, ketone) 1697 cm^{-1}; $\gamma_{CH=trans}$ at 968 cm^{-1}, ν_{OH} at 3170 (*br*) cm^{-1}. ^{1}HNMR: 3.95 (3H, s, OCH_3); 6.68 (1H, d, *J* 15.5 Hz, $H_{vinylketone}$); 6.79 (2H, d, *J* 8.5 Hz, H_{phenyl}); 6.86 (2H, d, *J* 8.5 Hz, H_{phenyl}); 6.96 (1H, d, *J* 16.0 Hz, H_{vinyl}); 7.07 (1H, dd, *J* 8.5 and 2.5 Hz, H_{benzo}); 7.32 (1H, d, *J* 2.5 Hz, H_{benzo}); 7.49 (2H, *J* 8.5 Hz, H_{phenyl}); 7.52 (1H, d, *J* 16.0 Hz, H_{vinyl}); 7.58 (2H, d, *J* 9.0 Hz, H_{phenyl}); 7.77 (1H, d, *J* 16.0 Hz, $H_{vinylketone}$); 7.93 (1H, d, *J* 8.5 Hz, H_{benzo}); 10.07 (2H, s, br, OH).

6-Methoxy-3-((*E*)-3-phenylprop-2-enoyl)-2-styrylchromone (Ar=C_6H_5, **7a):** Yield 0.714 g (35%) of **7a** as pale yellow crystals. Mp 185-187°C. IR: ν_{CO} (γ-pyrone, ketone) 1665 cm^{-1}; $\gamma_{CH=trans}$ at 975 cm^{-1}. ^{1}H-NMR: 3.88 (3H, s, OCH_3); 6.97 (1H, d, *J* 16.0 Hz, $H_{vinylketone}$); 7.22 (1H, d, *J* 16.0 Hz, H_{vinyl}); 7.46-7.41 (7H, m, H_{phenyl}); 7.49 (1H, dd, *J* 9.0 and 3.0 Hz, H_{benzo}); 7.66 (1H, d, *J* 16.0 Hz, H_{vinyl}); 7.67 (2H, d, *J* 7.0 Hz, H_{phenyl}); 7.75-7.73 (2H, m, $H_{phenyl,\ benzo}$); 7.79 (1H, d, *J* 9.0 Hz, H_{benzo}); 7.89 (1H, d, *J* 16.0 Hz, $H_{vinylketone}$).

2-(4-Chlorostyryl)-3-((*E*)-3-(4-chlorophenyl) prop-2-enoyl)-6-methoxychromone (Ar=4-ClC_6H_4, **7b):** Yield 0.954 g (40%) of **7b** as pale yellow crystals. Mp 210-212°C. IR: ν_{CO} (γ-pyrone, ketone) 1671 cm^{-1}; $\gamma_{CH=trans}$ at 978 cm^{-1}. ^{1}H-NMR: 3.88 (3H, s, OCH_3); 6.99 (1H, d, *J* 16.0 Hz, $H_{vinylketone}$); 7.22 (1H, d, *J* 16.0 Hz, H_{vinyl}); 7.44 (1H, d, *J* 3.0 Hz, H_{benzo}); 7.49 (5H, dd, *J* 8.5 and 8.5 Hz, H_{phenyl}); 7.65 (1H, d, *J* 16.0 Hz, H_{vinyl}); 7.72 (2H, d, *J* 8.5 Hz, H_{phenyl}); 7.77 (3H, d, *J* 9.0 Hz; $H_{benzo,\ phenyl}$); 7.88 (1H, d, *J* 16.0 Hz, $H_{vinylketone}$).

2-(3-Nitrostyryl)-6-methoxy-3-((*E*)-3-(3-nitrophenyl)prop-2-enoyl)chromone (Ar=3-$O_2NC_6H_4$, **7c):** Yield 1.120 g (45%) of **7c** as pale yellow crystals. Mp 266-267°C. IR: ν_{CO} (γ-pyrone, ketone) 1666 cm^{-1}; $\gamma_{CH=trans}$ at 968 cm^{-1}; $\nu_{s,\ as}$ (NO_2) 1532, 1355 cm^{-1}. ^{1}H-NMR: 3.89 (3H, s, OCH_3); 7.18 (1H, d, *J* 16.0 Hz, $H_{vinylketone}$); 7.40 (1H, d, *J* 16.5 Hz, H_{vinyl}); 7.46 (1H, s, H_{benzo}); 7.53 (1H, dd, *J* 9.0 and 2.5 Hz, H_{benzo}); 7.72 (2H, t, *J* 8.0 and 7.5 Hz, H_{phenyl}); 7.78 (1H, d, *J* 9.0 Hz, H_{benzo}); 7.84 (1H, d, *J* 16.0 Hz, H_{vinyl}); 8.06 (1H, d, *J* 16.0 Hz, $H_{vinylketone}$); 8.25-8.16 (4H, m, H_{phenyl}); 8.52 (1H, s, H_{phenyl}); 8.55 (1H, s, H_{phenyl}).

3-((*E*)-3-(3,4-Methylenedioxyphenyl)prop-2-enoyl)-2-((*E*)-3,4-methylenedioxystyryl)-6-methoxychromone (Ar=3,4-$O_2CH_2C_6H_3$, **7d):** Yield 0.620 (25%) of **7d** as yellow crystals. Mp: 180-182°C. IR: ν_{CO} (γ-pyrone, ketone) 1662 cm^{-1}; $\gamma_{CH=trans}$ at 989 cm^{-1}. ^{1}H-NMR: 3.88 (3H, s, OCH_3); 6.08 (2H, s, O_2CH_2); 6.08 (2H, s, O_2CH_2); 6.77 (1H, d, *J* 16.5 Hz, $H_{vinylketone}$); 6.95 (1H, d, *J* 8.0 Hz, H_{phenyl}); 6.98 (1H, d, *J* 8.0 Hz, H_{phenyl}); 7.04 (1H, d, *J* 16.0 Hz, H_{vinyl});

7.19 (1H, d, *J* 8.0 Hz, H_{phenyl}); 7.22 (1H, d, *J* 8.0 Hz, H_{phenyl}); 7.29 (1H, s, H_{phenyl}); 7.40 (1H, s, H_{phenyl}); 7.43 (1H, d, *J* 3.0 Hz, H_{benzo}); 7.48 (1H, dd, *J* 9.0 and 3.0 Hz, H_{benzo}); 7.53 (d, 1H, *J* 16.0 Hz, H_{vinyl}); 7.74 (1H, d, *J* 9.0 Hz, H_{benzo}); 7.78 (1H, *J* 16.0 Hz, $H_{vinylketone}$). ESI-LC-MS: $[M+H]^+$ 497.15 (100%); $[M+Na]^+$ 519.06 (36.2%), Anal. Calcd for $C_{29}H_{20}O_8$.

4-Methyl-9-((*E*)-3-phenylprop-2-enoyl)-8-styrylpyrano[6,5-*f*]chromene-2,10-dione (Ar=C_6H_5, **10a):** Yield 1.037 g (45%) of **10a** as pale yellow crystals. Mp 310-312°C. IR: ν_{CO} 1716, 1642 cm^{-1}; $\gamma_{CH=trans}$ at 998 cm^{-1}. ^{1}H-NMR: 2.50 (3H, s, CH_3); 6.50 (1H, d, *J* 1.0 Hz, $H_{\alpha\text{-pyrone}}$); 6.91 (1H, d, *J* 16.0 Hz, $H_{vinylketone}$); 7.19 (1H, d, *J* 16.5 Hz, H_{vinyl}); 7.45 (6H, m, H_{phenyl}); 7.75-7.68 (4H, m, H_{phenyl}); 7.72 (1H, d, *J* 16.0 Hz, H_{vinyl}); 7.79 (1H, d, *J* 9.0 Hz, H_{benzo}); 7.94 (1H, d, *J* 16.0 Hz, $H_{vinylketone}$); 8.24 (1H, d, *J* 9.0 Hz, H_{benzo}). HR-MS (*m/z*): M^+ 460.1456 (24.6%), Anal. Calcd for $C_{30}H_{20}O_5$.

9-((*E*)-3-(3,4-Methylenedioxyphenyl)prop-2-enoyl)-8-((*E*)-3,4-methylenedioxystyryl)-4-methylpyrano[6,5-*f*]chromene -2,10-dione (Ar=3,4-$O_2CH_2C_6H_3$, **10b):** Yield 1.072 g (39%) of **10b** as yellow crystals. Mp 309-311°C. IR: ν_{CO} 1724, 1640 cm^{-1}, $\gamma_{CH=trans}$ at 970 cm^{-1}. ^{1}H-NMR: 2.50 (3H, s, CH_3); 6.08 (4H, s, $2O_2CH_2$); 6.49 (1H, d, *J* 1.0 Hz, $H_{\alpha\text{-pyrone}}$); 6.71 (1H, d, *J* 15.5 Hz, $H_{vinylketone}$); 6.95 (1H, d, *J* 8.0 Hz, H_{phenyl}); 6.98 (1H, *J* 8.0 Hz, H_{phenyl}); 7.02 (1H, d, *J* 16.5 Hz, H_{vinyl}); 7.21 (2H, td, *J* 7.5 and 1.5 Hz, H_{phenyl}); 7.32 (1H, d, *J* 1,5 Hz, H_{phenyl}); 7.41 (1H, d, *J* 1.5 Hz, H_{phenyl}); 7.59 (1H, d, *J* 16.0 Hz, H_{vinyl}); 7.74 (d, 1H, *J* 9.0 Hz, H_{benzo}); 7.82 (1H, d, *J* 16.0 Hz, $H_{vinylketone}$); 8.22 (1H, d, *J* 9.0 Hz, H_{benzo}).

6-Methyl-3-((*E*)-3-phenylprop-2-enoyl)-2-styryl-4*H*-pyrano[3,2-*g*]chromone-8-one (Ar=C_6H_5, **13a):** Yield 0.874 g (38%) of **13a** as pale yellow crystals. Mp 286-287°C. IR: ν_{CO} 1745, 1627 (br) cm^{-1}, $\gamma_{CH=trans}$ at 987 cm^{-1}. ^{1}H-NMR: 2.54 (3H, s, CH_3); 6.53 (1H, d, *J* 1.5 Hz, $H_{\alpha\text{-pyrone}}$); 6.98 (1H, d, *J* 16.0 Hz, $H_{vinylketone}$); 7.21 (1H, d, *J* 16.0 Hz, H_{vinyl}); 7.46-7.43 (7H, m, H_{phenyl}); 7.71 (1H, *J* 16.0 Hz, H_{vinyl}); 7.74-7.67 (3H, m, H_{phenyl}); 7.84 (1H, s, H_{benzo}); 7.95 (1H, d, *J* 16.0 Hz, $H_{vinylketone}$); 8.35 (1H, s, H_{benzo}). EI-MS (*m/z*) M^+ 460 (32.4%), Anal. Calcd for $C_{30}H_{20}O_5$.

3-((*E*)-3-(4chlorophenyl)prop-2-enoyl)-2-(4-chlorostyryl)-6-methyl-4*H*-pyrano[3,2-*g*]chromone-8-one (Ar=4-ClC_6H_4, **13b):** Yield 1.190 g (45%) of **13b** as yellow crystals. Mp 303-304°C. IR: ν_{CO} 1763, 1627 (br) cm^{-1}, $\gamma_{CH=trans}$ at 978 cm^{-1}. ^{1}H-NMR: 2.54 (3H, s, CH_3); 6.51 (1H, s, $H_{\alpha\text{-pyrone}}$); 7.00 (1H, d, *J* 16.0 Hz, $H_{vinylketone}$); 7.20 (1H, d, *J* 16.0 Hz, H_{vinyl}); 7.49 (4H, t, *J* 9.0 Hz, H_{phenyl}); 7.81-7.66 (6H, m, H_{vinyl}, $H_{vinylketone}$, H_{phenyl}); 7.95 (1H, s, H_{benzo}); 8.36 (1H, s, H_{benzo}).

Antioxidant testing: The free radical scavenging activity was determined by the DPPH assay[36,37]. Test compounds are dissolved in DMSO solution to specific concentrations. DPPH was diluted in MeOH to the appropriate concentration. 10 µL of test compounds were incubated with 190 µL of DPPH solution, incubated at 37°C for 20 minutes then the absorbance was measured at 517 nm using the UV-vis spectrophotometer (ELISA). Ascorbic reference was used to control stability and evaluate equivalent inhibitory activity. Tests were repeated 3 times. The optical density was recorded and % inhibition was calculated using the formula given below: Inhibition of DPPH activity (%)= 100 – [(OD_s) / (OD_c) x 100].

Where OD_s is the average optical density of the test sample and OD_c is the average optical density of the control sample.

Supplementary Material

Copies of NMR spectra are provided in supplementary information.

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