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Short communication

Synthesis and biological evaluation of β-chloro vinyl chalcones as inhibitors of TNF-α and IL-6 with antimicrobial activity

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ABSTRACT

A series of β-chloro vinyl chalcones have been synthesized by Claisen–Schmidt condensation. β-chloro vinyl aldehyde has been synthesized by the Vilsmayer–Hack formylation reaction. The structures of the newly synthesized compounds were confirmed by ^{1}H NMR, IR and Mass spectral analysis. All the compounds were evaluated for their anti-inflammatory activity (against TNF-α and IL-6) and antimicrobial (antibacterial and antifungal) activity. Compounds **5a**, **5d**, **5e**, **5g** and **5i** exhibited promising activity against IL-6 with 58–83% inhibition at 10 μM concentration. None of the compound was found to be cytotoxic in CCK-8 cells at 10 μM concentration. Whereas compounds **5b**, **5d**, **5e** and **5i** showed very good antibacterial activity and compounds **5a**, **5b**, **5e** and **5i** showed good antifungal activity.

1. Introduction

Inflammation is the complex process due to which it causes a large number of diseases, amongst this some commonest are rheumatoid arthritis (RA), inflammatory bowel disease, psoriasis and multiple sclerosis [1,2]. Tumour necrosis factor-alpha (TNF-α) and Interleukin-6 (IL-6) are two major multifunctional pro-inflammatory mediators of a variety of autoimmune diseases such as pain and joint destruction characteristics of RA [3]. The inhibition of release of cytokines becomes a major focus of current drug development and an important method for evaluating the bioactivity of drugs [4]. It is a key cytokine in the inflammation cascade, causing the production and/or release of other cytokines and agents.

Over-expression of TNF-α is responsible for a number of pathological conditions like Crohn's disease, ulcerative colitis [5], diabetes [6], multiple sclerosis [7], atherosclerosis [8] and stroke [9]. In spite of enormous efforts, no small molecule has yet been approved to specifically inhibit TNF-α activity. TNF-α inhibitor drugs in clinics are proteins (Etanercept, Infliximab, Adalimumab and Anakinra) that display adverse effects such as aplastic anemia, pancytopenia, vasculitis, demyelination and congestive heart failure [10], while the IL-6 inhibitors can be used in Alzheimer's disease, psychiatric disorders, cancer, diabetes, and depression [11–13].

Amongst pro-inflammatory cytokines the IL-6, is a pleiotropic cytokine that is abundant in both the synovium and serum of RA patients and induces a broad range of cellular and physiological responses during the inflammation reaction. It is a multifunctional cytokine produced by a variety of cells in response to infection, trauma, or immunological challenge. It plays a key role in the regulation of inflammation, immune responses, the acute-phase reaction, and hematopoiesis, exerting its effects at the systemic and local tissue levels and across a range of cell types. It appears to be the central mediator of anemia of chronic disease in a range of inflammatory diseases, including end-stage renal disease and rheumatoid arthritis [14]. Till-date, designing the IL-6 inhibitory agents has remained a significant hope in the mainstream of anti-inflammatory drug development.

Chalcones are the main precursors for the biosynthesis of flavonoids and are present in variety of plant species such as fruits, vegetables, spices, tea and soy based foodstuff. Chalcones

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isolated from natural products are known to possess several important activities including antifungal [15], leishmanicidal [16] and anti-malarial [17]. Synthesis of chalcones from substituted acetophenones and benzaldehydes makes them an attractive drug scaffold, so they have been shown to display interesting biological activities including antimitotic [18], anti-inflammatory [19], cytotoxic [20], anticancer [21–23], anti-tubercular [24], cardiovascular [25] and hyperglycemic agents [26]. It is well known that 2′-hydroxychalcones were shown to possess anti-inflammatory agents involved in inhibition of cell migration and inhibition of TNF-α synthesis in mouse [27]. The literature investigation reveals that no endeavor was proposed the synthesis of β-chloro vinyl chalcones to verify the effects on the biological activity. Thus, we investigated that 2-hydroxy β-chloro vinyl chalcones are the inhibitors of TNF-α and IL-6 with anti-microbial activity.

2. Chemistry

Compounds described in this study were prepared using a straight forward chemistry (Scheme 1). Xanthoxyline **2** was synthesized following the method described in the literature with minor modifications [28]. β-Chloro vinyl aldehyde (**4**) was synthesized following the method described in the literature with minor modifications [29]. (2*E*,4*Z*)-5-Chloro-1-(2-hydroxy-4,6-dimethoxyphenyl)-5-phenylpenta-2,4-dien-1-one (**5**) was prepared by the Claisen–Schmidt condensation between 2-hydroxy-4,6-dimethoxy acetophenone (**2**) and various β-chloro vinyl aldehydes (**4**) in alkaline medium furnished the desired derivatives with minor modifications to previously described method [30] Table 1. The desired derivatives were obtained in 55% yield after purification. All synthesized compounds were characterized by using IR, ^{1}H NMR and mass spectra.

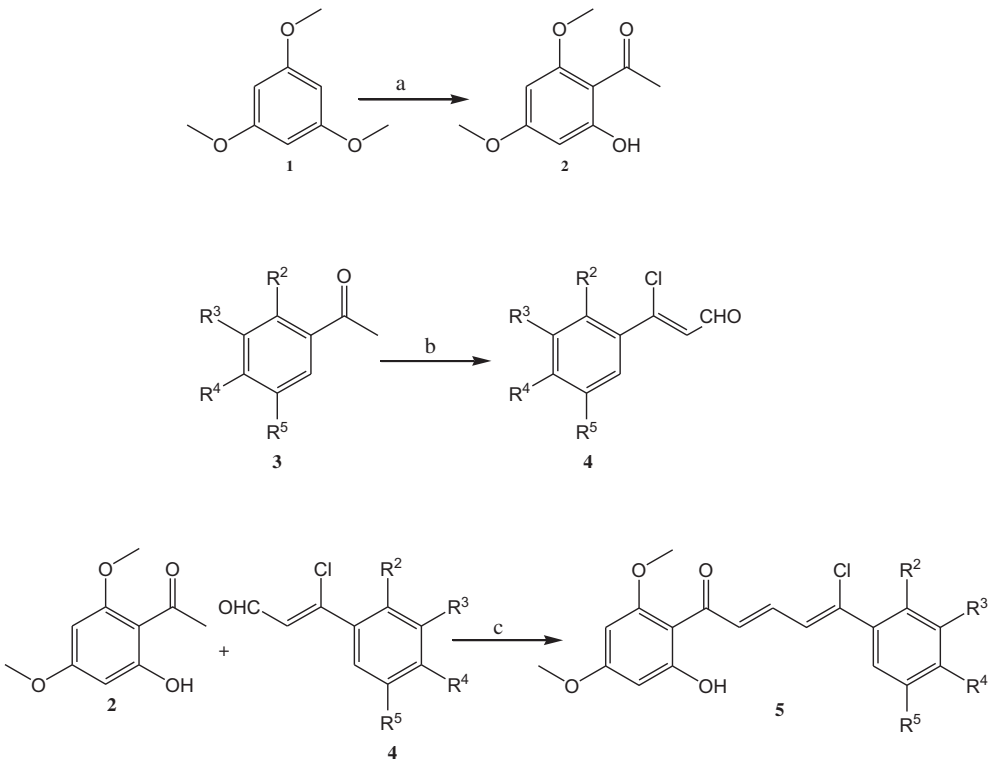
3. Biological evaluation

All the synthesized compounds were evaluated for anti-inflammatory and antimicrobial activity. Anti-inflammatory activity against TNF-α and IL-6 at 10 μM concentration. Inhibitory activity results are summarized in Table 2. Dexamethasone was used as a reference compound. Compounds **5b**, **5d**, **5e**, **5f**, **5h** and **5j** shown 13–18% inhibition at 10 μM, while none of the compounds showed significant TNF-α inhibitory activity.

All the synthesized compounds were shown moderate to good IL-6 inhibitory activity. Compounds **5a**, **5d**, **5e**, **5g** and **5i** showed promising activity against IL-6 with inhibition 58–83% at 10 μM concentration. Compounds **5b**, **5c**, **5g**, **5h**, **5j** and **5k** showed 31–45% inhibition of IL-6 at 10 μM. All compounds did not show significant toxicity at 10 μM.

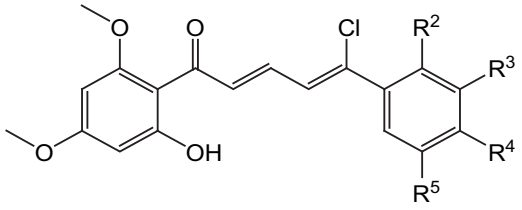
3.1. Assay for TNF-α and IL-6 inhibition

Pro-inflammatory cytokine production by lipopolysaccharide (LPS) in THP-1 cells was measured according to the method described by Hwang et al., 1933 [31]. Briefly, THP-1 cells were cultured in RPMI 1640 culture medium (Gibco BRL, Pasley, UK) containing 100 U/mL penicillin and 100 mg/mL streptomycin (100× solution, Sigma Chemical Co. St. Louis, MO) containing 10% fetal bovine serum (FBS, JRH). Cells were differentiated with phorbol myristate acetate (PMA, Sigma). Following cell plating, the test compounds or vehicle (0.5% DMSO) was added to each well and the plate was incubated for 30 min at 37 °C. Finally, LPS (Escherichia coli0127:B8, Sigma Chemical Co., St. Louis, MO) was added, at a final concentration of 1 μg/mL. Plates were incubated at 37 °C for 24 h, 5% CO_2. Supernatants were harvested and assayed for TNF-α and IL-6 by ELISA as described by the manufacturer (BD Biosciences). The cells were simultaneously evaluated for cytotoxicity



Scheme 1. Synthetic route used for the synthesis of β-chloro vinyl chalcones: (a) $AlCl_3$, CH_3COCl, Dry ether, 0 °C, 48 h rt, (b) DMF, $POCl_3$, 0 °C–80 °C, 1 h, (c) β-chloro vinyl aldehydes, NaOH, EtOH, H_2O, rt, 60–65%.

Table 1
Substitution pattern of chalcones studied for the TNF-α, IL-6 and antimicrobial activity



Entry	R^2	R^3	R^4	R^5
5a	H	H	Br	H
5b	Cl	H	H	H
5c	H	Cl	H	H
5d	H	H	Cl	H
5e	H	H	F	H
5f	H	H	OMe	H
5g	OMe	H	OMe	H
5h	H	OMe	H	OMe
5i	Cl	H	Cl	H
5j	H	H	Me	H
5k	H	OMe	H	H

using CCK-8 from Dojindo Laboratories. Percent inhibition of cytokine release compared to the control was calculated.

3.2. Antibacterial studies

The newly synthesized compounds were screened for their antibacterial activity against *Bacillus subtilis* (NCIM 2546), *Escherichia coli* (NCIM 2065), *Staphylococcus aureus* (NCIM 2120), *Klebsiella pneumoniae* (NCIM 5082), *and Proteus vulgaris* (NCIM 2813) bacterial strains by disc diffusion method [32,33]. Disc measuring 6.25 mm in diameter was punched from Whatmann no.1 filter paper. Batches of 100 discs were dispensed to each screw capped bottles and sterilized by dry heat at 140 °C for an hour. The test compounds were prepared with different concentrations using dimethylsulfoxide. 1 mL containing 100 times the amount of chemical in each disc was added to each bottle, which contains 100 discs. The discs of each concentration were placed in triplicate in nutrient agar medium seeded with fresh bacterial culture separately and incubated at 37 °C for 24 h. Penicillin and Gentamycin were used as standard drugs. Solvent and growth controls were prepared and kept. Zones of inhibition and minimum inhibitory concentrations (MICs) were noted. The results of antibacterial studies are given in Table 3.

Table 2
Antiinflammatory (TNF-alpha, IL-6) inhibitory activity of β-chloro vinyl chalcones.

Compound	% Inhibition at 10 mM		
	TNF-a	IL-6	Cytotoxicity
5a	08	58	26
5b	17	43	24
5c	00	31	00
5d	13	74	23
5e	16	83	26
5f	18	78	15
5g	00	33	00
5h	13	45	17
5i	00	67	00
5j	17	36	19
5k	11	39	21
DMS	69	90	00

The results summarized are the mean values of $n = 2$, DMS = Dexamethasone, ND = Not Determined, NR = Not Reactive.

The antibacterial screening data revealed that compounds **5a**, **5b**, **5d**, **5e**, **5i** and **5j** showed very good activity, almost equal to that of standard drugs, whereas all other tested compounds showed moderate to good antibacterial activity.

3.3. Antifungal studies

Newly synthesized compounds were screened for their antifungal activity against *Aspergillus fumigatus* (NCIM 902), *Aspergillus niger* (NCIM 545), *Trichoderma viride* (TT), *Candida albicans* (NCIM 3100) and *Penicillium chrysogenum* (NCIM 707). Antifungal activity was assessed by disc diffusion method in a modified condition [34,35]. Fluconazole (200 mg/disc) was used as standard fungicide. Potato dextrose agar (PDA) was used as basal medium for test fungi. Glass petridishes used were sterilized. Sterilized melted PDA medium (~45 °C) was poured at the rate of 15 mL into each petridish (90 mm). After solidification of the medium, small portions of the mycelium of each fungus were spread carefully over the centre of each PDA plate with the help of sterilized needles. Thus, each fungus was transferred to a number of PDA plates, which were then incubated at (25 ± 2) °C and ready for use after five days of incubation.

Prepared discs of samples were placed gently on solidified agar plates, freshly seeded with the test organisms with sterile forceps. A control disc was also placed on the test plates to compare the effect of the test samples and to nullify the effect of solvent respectively. The plates were then kept in a refrigerator at 4 °C for 24 h so that the materials had sufficient time to diffuse over a considerable area of the plates. After this, the plates were incubated at 37 ± 5 °C for 72 h. Dimethyl sulphoxide (DMSO) was used as solvent to prepare desired solutions (10 mg/mL) of the compounds initially and also to maintain proper control. The results of the antifungal studies are given in Table 4.

The antifungal screening data revealed that compounds **5a**, **5b**, **5d**, **5e**, **5i** and **5j** showed very good activity almost equal to that of standard drugs, whereas all other tested compounds showed moderate to good fungal activity.

4. Conclusion

A new series of β-chloro vinyl chalcones exhibiting anti-inflammatory and antimicrobial activity were synthesized. From the results of the tested compounds, **5a**, **5b**, **5d**, **5e**, **5f**, **5h** and **5i** showed promising activity against IL-6. None of the compound was

Table 3
Antibacterial activity of β-chloro vinyl chalcones.

Compound no.	*Bacillius subtilis*	*Esherichia coli*	*Staphylococcus aureus*	*Klebsiella pneumoniae*	*Proteus valgaris*
5a	18 (25)	15 (50)	14 (50)	20 (25)	12 (100)
5b	16 (50)	14 (50)	16 (50)	18 (25)	20 (25)
5c	12 (100)	16 (50)	–	–	18 (25)
5d	20 (25)	15 (50)	18 (25)	18 (25)	15 (50)
5e	22 (25)	16 (50)	14 (50)	14 (50)	18 (25)
5f	–	–	–	–	17 (50)
5g	–	–	14 (50)	13 (100)	–
5h	–	–	–	–	–
5i	17 (50)	14 (50)	19 (25)	15 (50)	19 (25)
5j	15 (50)	12 (100)	16 (50)	18 (25)	19 (25)
5k	–	10 (100)	15 (50)	14 (50)	–
A	22 (25)	18 (25)	20 (25)	21 (25)	22 (25)
B	24 (25)	21 (25)	18 (25)	22 (25)	18 (25)

"—" Indicates bacteria are resistant to the compounds at concentrations >100 mg/mL; MIC values are given in brackets; MIC (mg/mL) = minimum inhibitory concentration, i.e., concentration to completely inhibit bacterial growth; zone of inhibition is expressed in mm. A = Penicillin, B = Gentamycin.

Table 4
Antifungal activity of β-chloro vinyl chalcones.

Compound no.	*Aspergillus fumigatus*	*Aspergillus niger*	*Trichoderma viridie*	*Candida albicans*	*Penicillium chrysogenum*
5a	20 (25)	14 (50)	18 (25)	14 (25)	18 (25)
5b	14 (50)	16 (50)	14 (50)	–	16 (50)
5c	–	–	–	–	–
5d	17 (25)	16 (50)	15 (50)	12 (100)	12 (100)
5e	14 (50)	17 (25)	16 (50)	10 (100)	14 (50)
5f	–	16 (50)	–	–	–
5g	10 (100)	–	10 (100)	–	14 (50)
5h	14 (50)	16 (50)	14 (50)	12 (100)	15 (50)
5i	17 (50)	10 (100)	18 (25)	10 (100)	17 (25)
5j	10 (100)	–	13 (100)	–	–
5k	16 (50)	16 (50)	16 (50)	13 (100)	17 (25)
A	20 (25)	20 (25)	22 (25)	18 (25)	22 (25)

"—" Indicates bacteria are resistent to the compounds at concentrations >100 mg/mL; MIC values are given in brackets; MIC (mg/mL) = minimum inhibitory concentration, i.e., concentration to completely inhibit fungal growth; zone of inhibition is expressed in mm. A = Fluconazole.

found to be active against TNF-α. The screening result of antimicrobial study of the **11** compounds reveals that only six compounds showed good antibacterial and antifungal activity. Compounds having bromo, chloro, fluoro substitution at *ortho* and *para* position found to be favorable for both antibacterial and antifungal screening. However the β-chloro vinyl chalcones are considered as one of the scaffolds for design and development of anti-inflammatory (TNF-α and IL-6) and antimicrobial agents.

5. Experimental

IR spectra were recorded on FT-IR Shimadzu 8300 spectrophotometer in KBr pellet and ^{1}H NMR spectra were recorded on a Bruker 300 MHz spectrometer in $CDCl_3$ using tetramethylsilane as internal standard and chemical shifts are reported in δ units and the coupling constants (J) are reported in hertz. Mass spectra were obtained with a Shimadzu LCMS-2010EV. TLC was performed on aluminium-backed silica plate with visualization by UV-light and column chromatography using silica gel (mesh size 100–200).

*5.1. Procedure for the preparation of (2E,4Z)-5-chloro-1-(2-hydroxy-4,6-dimethoxyphenyl)-5-phenylpenta-2,4-dien-1-one (**5**)*

To a mixture of 1-(2-hydroxy-4,6-dimethoxyphenyl)ethanone (**2**) (1 mmol) in ethanol (15 mL) was added NaOH (0.1 g, 2–3 drops of water) and stirred for 5 min. Then, added the purified β-chloro vinyl aldehydes and stirred the reaction mixture at room temperature. After completion of reaction (TLC), reaction mixture was poured over crushed ice and acidified with acetic acid. The precipitated solid was filtered, washed with water and oven dried. It was column purified by column chromatography using silica gel mesh size, 100–200 and elution with petroleum ether.

*5.1.1. (2E,4Z)-5-(4-Bromophenyl)-5-chloro-1-(2-hydroxy-4,6-dimethoxyphenyl)penta-2,4-dien-1-one (**5a**)*

Yield (39%), IR (KBr, cm^{-1}) 3559 (OH), 3017 (Ar-H), 1615 (C═O), 1597 (C═C). ^{1}H NMR ($CDCl_3$, δ) 14.18 (s, 1H, OH), 7.86 (d, 1H, Ar-H, J = 14 Hz), 7.79 (d, 1H, Ar-H, J = 14 Hz), 7.34 (d, 1H, Ar-H, J = 8 Hz), 7.29–7.23 (m, 4H, Ar-H), 6.09 (s, 1H, Ar-H), 5.94 (s, 1H, Ar-H), 3.93 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3). MS: m/z 424 (M + 1).

*5.1.2. (2E,4Z)-5-Chloro-5-(2-chlorophenyl)-1-(2-hydroxy-4,6-dimethoxyphenyl)penta-2,4-dien-1-one (**5b**)*

Yield (39%), IR (KBr, cm^{-1}) 3618 (OH), 3018 (Ar-H), 1626 (C═O), 1589 (C═C). ^{1}H NMR ($CDCl_3$, δ) 14.83 (s, 1H, OH), 7.91 (d, 1H, Ar-H, J = 12 Hz), 7.78 (d, 1H, Ar-H, J = 12 Hz and 10 Hz), 7.69 (d, 1H, Ar-H, J = 10 Hz), 7.11 (m, 2H, Ar-H), 6.93 (m, 2H, Ar-H), 6.09 (s, 1H, Ar-H), 5.93 (s, 1H, Ar-H), 3.88 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3). MS: m/z 379 (M + 1).

*5.1.3. (2E,4Z)-5-Chloro-5-(3-chlorophenyl)-1-(2-hydroxy-4,6-dimethoxyphenyl)penta-2,4-dien-1-one (**5c**)*

Yield (35%), IR (KBr, cm^{-1}) 3618 (OH), 3031 (Ar-H), 1619 (C═O), 1595 (C═C). ^{1}H NMR ($CDCl_3$, δ): 14. 83 (s, 1H, OH), 8.01 (dd, 1H, Ar-H, J = 10.4 Hz and 10.4 Hz), 7.62 (m, 2H, Ar-H), 7.58 (d, 1H, Ar-H, J = 10.4 Hz), 7.52 (m, 1H, Ar-H), 7.55 (m, 1H, Ar-H), 7.01 (d, 1H, Ar-H, J = 10.8 Hz), 6.09 (s, 1H, Ar-H), 5.98 (s, 1H, Ar-H), 3.95 (s, 3H, OCH_3), 3.96 (s, 3H, OCH_3). MS: m/z 379 (M + 1).

*5.1.4. (2E,4Z)-5-Chloro-5-(4-chlorophenyl)-1-(2-hydroxy-4,6-dimethoxyphenyl)penta-2,4-dien-1-one (**5d**)*

Yield (30%), IR (KBr, cm^{-1}) 3648 (OH), 3012 (Ar-H), 1617 (C═O), 1592 (C═C). ^{1}H NMR ($CDCl_3$, δ): 14.19 (s, 1H, OH), 7.95 (dd, 1H, Ar-H, J = 12.8 Hz and 10.8 Hz), 7.61 (m, 2H, Ar-H), 7.57 (d, 1H, Ar-H, J = 12.8 Hz), 7.53 (d, 2H, Ar-H), 7.01 (d, 1H, Ar-H, J = 10.8 Hz), 6.09 (s, 1H, Ar-H), 5.98 (s, 1H, Ar-H), 3.96 (s, 3H, OCH_3), 3.95 (s, 3H, OCH_3). MS: m/z 379 (M + 1).

*5.1.5. (2E,4Z)-5-Chloro-5-(4-fluorophenyl)-1-(2-hydroxy-4,6-dimethoxyphenyl)penta-2,4-dien-1-one (**5e**)*

Yield (30%), IR (KBr, cm^{-1}) 3648 (OH), 3012 (Ar-H), 1617 (C═O), 1592 (C═C). ^{1}H NMR ($CDCl_3$, δ): 14.21 (s, 1H, OH), 7.93 (dd, 1H, Ar-H, J = 10.8 Hz and 12.8 Hz), 7.70 (d, 2H, Ar-H, J = 8 Hz), 7.50 (d, 1H, Ar-H, J = 12.8 Hz), 7.11 (d, 2H, Ar-H, J = 8 Hz), 7.07 (d, 1H, Ar-H, J = 10.8 Hz), 6.01 (s, 1H, Ar-H), 5.99 (s, 1H, Ar-H), 3.90 (s, 3H, OCH_3), 3.98 (s, 3H, OCH_3). MS: m/z 363 (M + 1).

*5.1.6. (2E,4Z)-5-Chloro-1-(2-hydroxy-4,6-dimethoxyphenyl)-5-(4-methoxyphenyl)penta-2,4-dien-1-one (**5f**)*

Yield (30%), IR (KBr, cm^{-1}) 3648 (OH), 3012 (Ar-H), 1617 (C═O), 1592 (C═C). ^{1}H NMR ($CDCl_3$, δ): 14.21 (s, 1H, OH), 7.98 (dd, 1H, Ar-H, J = 10.8 Hz and 12.8 Hz), 7.69 (d, 2H, Ar-H, J = 8 Hz), 7.47 (d, 1H, Ar-H, J = 12.8 Hz), 6.93 (d, 2H, Ar-H, J = 8 Hz), 6.92 (d, 1H, Ar-H, J = 10.8 Hz), 6.01 (s, 1H, Ar-H), 5.99 (s, 1H, Ar-H), 3.92 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3). MS: m/z 375 (M + 1).

*5.1.7. (2E,4Z)-5-Chloro-1-(2-hydroxy-4,6-dimethoxyphenyl)-5-(2,4-dimethoxyphenyl)penta-2,4-dien-1-one (**5g**)*

Yield (30%), IR (KBr, cm^{-1}) 3648 (OH), 3012 (Ar-H), 1617 (C═O), 1592 (C═C). ^{1}H NMR ($CDCl_3$, δ): 14.19 (s, 1H, OH), 7.95 (dd, 1H, Ar-H, J = 10.8 Hz and 12.8 Hz), 7.44 (m, 2H, Ar-H), 7.37 (d, 1H, Ar-H, J = 12.8 Hz), 7.19 (m, 1H, Ar-H), 6.83 (d, 1H, Ar-H, J = 10.8 Hz), 6.00 (s, 1H, Ar-H), 5.92 (s, 1H, Ar-H), 3.99 (s, 3H, OCH_3), 3.92 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3). MS: m/z 405 (M + 1).

*5.1.8. (2E,4Z)-5-Chloro-1-(2-hydroxy-4,6-dimethoxyphenyl)-5-(3,5-dimethoxyphenyl)penta-2,4-dien-1-one (**5h**)*

Yield (30%), IR (KBr, cm^{-1}) 3648 (OH), 3012 (Ar-H), 1617 (C═O), 1592 (C═C). ^{1}H NMR ($CDCl_3$, δ): 14.19 (s, 1H, OH), 7.95 (dd, 1H, Ar-H, J = 10.8 Hz and 12.8 Hz), 7.44 (m, 2H), 7.37 (d, 1H, Ar-H, J = 12.8 Hz), 7.19 (m, 1H, Ar-H), 6.83 (d, 1H, Ar-H, J = 10.8 Hz), 5.99 (s, 1H, Ar-H), 5.92 (s, 1H, Ar-H), 3.99 (s, 3H, OCH_3), 3.92 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3). MS: m/z 405 (M + 1).

*5.1.9. (2E,4Z)-5-Chloro-5-(2,4-dichlorophenyl)-1-(2-hydroxy-4,6-dimethoxyphenyl)penta-2,4-dien-1-one (**5i**)*

Yield (30%), IR (KBr, cm^{-1}) 3648 (OH), 3012 (Ar-H), 1617 (C═O), 1592 (C═C). ^{1}H NMR ($CDCl_3$, δ): 14. 20 (s, 1H, OH), 7.96 (dd, 1H, Ar-H, J = 10.8 Hz and 12.8 Hz), 7.61 (m, 1H, Ar-H), 7.64 (d, 1H, Ar-H, J = 12.8 Hz), 7.38 (m, 2H, Ar-H), 7.01 (d, 1H, Ar-H, J = 10.8 Hz), 6.09 (s, 1H, Ar-H), 5.99 (s, 1H, Ar-H), 3.90 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3). MS: m/z 414 (M + 1).

*5.1.10. (2E,4Z)-5-Chloro-1-(2-hydroxy-4,6-dimethoxyphenyl)-5-p-tolylpenta-2,4-dien-1-one (**5j**)*

Yield (30%), IR (KBr, cm^{-1}) 3648 (OH), 3012 (Ar-H), 1617 (C═O), 1592 (C═C). ^1H NMR ($CDCl_3$, δ): 14.23 (s, 1H, OH), 7.97 (dd, 1H, Ar-H, $J = 10.8$ Hz and 12.8 Hz), 7.67 (d, 2H, Ar-H, $J = 8$ Hz), 7.41 (d, 1H, Ar-H, $J = 12.8$ Hz), 7.40 (d, 2H, Ar-H, $J = 8$ Hz), 6.98 (d, 1H, Ar-H, $J = 10.8$ Hz), 6.00 (s, 1H, Ar-H), 5.99 (s, 1H, Ar-H), 3.94 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3). MS: m/z 359 (M + 1).

*5.1.11. (2E,4Z)-5-Chloro-1-(2-hydroxy-4,6-dimethoxyphenyl)-5-(3-methoxyphenyl)penta-2,4-dien-1-one (**5k**)*

Yield (30%), IR (KBr, cm^{-1}) 3648 (OH), 3012 (Ar-H), 1617 (C═O), 1592 (C═C). ^1H NMR ($CDCl_3$, δ): 14. 21 (s, 1H, OH), 7.98 (dd, 1H, Ar-H, $J = 10.8$ Hz and 12.8 Hz), 7.68 (d, 2H, Ar-H, $J = 8$ Hz), 7.47 (d, 1H, Ar-H, $J = 12.8$ Hz), 6.93 (d, 2H, Ar-H, $J = 8$ Hz), 6.92 (d, 1H, Ar-H, $J = 10.8$ Hz), 6.01 (s, 1H, Ar-H), 5.99 (s, 1H, Ar-H), 3.92 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 3.85 (S, 3H, OCH_3). MS: m/z 375 (M + 1).

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