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# MICROWAVE ASSISTED SYNTHESIS AND BIOLOGICAL EVALUATION OF 2-ARYL/HETERYL-3-ARYLOXY/HETERYLOXY-4*H*-CHROMONES (4-OXO-2-ARYL/HETERYL-4*H*-CHROMEN-3-Yl-CARBOXYLATE)

Mangesh P. Gharpure*, Viswas N. Ingle, Harjeet D. Juneja, Ratiram G. Choudhary

Department of Chemistry, Rashtrasant Tukadoji Maharaj Nagpur University, Nagpur-440033, India

*Email Address:* mangesh.gharpure@gmail.com, hd_juneja@yahoo.com

**ABSTRACT**: 2-Aryl/heteryl-3-aryloxy/heteryloxy-4*H*-chromones **5** have been synthesized through a series of reactions starting from phenols under microwave irradiation. This process is an effective alternative to the traditional thermal heating method. The yields are excellent and the reaction time is in a few minutes. These compounds have been characterized on the basis of IR, $^{1}$H NMR, $^{13}$C NMR and Mass spectrometry and evaluated for antibacterial activity.

**Keywords:** Chalcones, flavones, microwave irradiation, antibacterial, antitubercular activity and molinspiration

## INTRODUCTION

Flavonoids are a large family of natural polyphenolic compounds known for their wide range of biological and pharmacological activities including antioxidant, cytotoxic, anticancer, cardioprotective, hepatoprotective, neuroprotective and antimicrobial activities. These compounds show varied biological activities including activity against HIV,[1,2] dengue,[3] influenza virus[4] as well as antitumor[5,6] and antioxidant[7] effects. Beneficial effects of flavonoids on human health have gained increasing interest among researchers over the last few years. Flavonoids and iso-flavonoids, which are natural components of plants with antifungal properties, have been investigated. Consideration has been given to increase the understanding of the mode of action of these natural fungicides and of improving their effectiveness through substitutions. There is evidence that their action is linked with lipophilicity suggesting it may be possible to increase fungitoxicity by replacing a hydroxyl group on a flavones molecule with an acetoxy group. The substituted acetic acid esters were more active in reducing mycelium growth of *C. herbarum* and *P. glabrum* than were the hydroxylated flavones.[8-10] Hence, with the knowledge of designing, flavonoids could be synthesized in the laboratory by convenient methods. Flavonols were synthesised from the corresponding o-hydroxy acetophenones. Aldol condensation of acetophenones with benzaldehydes formed chalcones, which upon Algar-Flynn-Oyamada (AFO) oxidation[11] gave flavonols. These vast literatures prompted us to modify the benzopyrone ring to explore the biological activities associated with this nucleus.[12-19]

Microwave assisted reactions in solvent or solvent free conditions have gained popularity because of rapid reaction rate, cleaner reactions, ease of manipulation, higher yields, and improved selectivity with respect to the conventional reaction conditions.[20] A major advantage is given by the usual reaction time which is in a few minutes even on a few hundred grams scale. The reduction in the amount of solvents and formation of lowered amounts of by-products decrease the pollution at the source and ensure high levels of "atom economy". Another advantage of MW induced organic reaction enhancement chemistry techniques is the lowered energy consumption compared to conventional reactions performed under reflux. The best solvent is no solvent and if a solvent is needed, green or potentially green alternatives should be considered. In the present work, 3-aroyloxychromones have been synthesized and explored for antibacterial and antitubercular activities.

## RESULTS AND DISCUSSION

Aroylation (esterification) of phenols followed by Fries migration gave 2-hydroxy acetophenones, reaction of 2-hydroxy acetophenones with different aromatic aldehydes produced 1-(2-hydroxyphenyl)-3-phenylprop-2-en-1-one (chalcones) (**3a-l**), which on cyclization in alkaline $H_2O_2$ yielded 2-aryl/heteryl-3-hydroxychromones (**4a-l**). 2-Aryl/heteryl-3-hydroxy chromones on o-aroylation under MW irradiation afforded 2-aryl/heteryl-3-aryloxy/heteryloxy-4*H*-chromones (**5a-w**) in excellent yield (**Scheme 1 and Table 1**). These esters have also been prepared by conventional method from appropriate 3-hydroxy chromones (**Figure 1**). The structures of compounds (**5a-w**) were deduced from their IR, $^1$H NMR, $^{13}$C NMR, and Mass spectral data.

**Scheme 1.** Synthesis of 3-aroyloxychromones (**5a-w**)

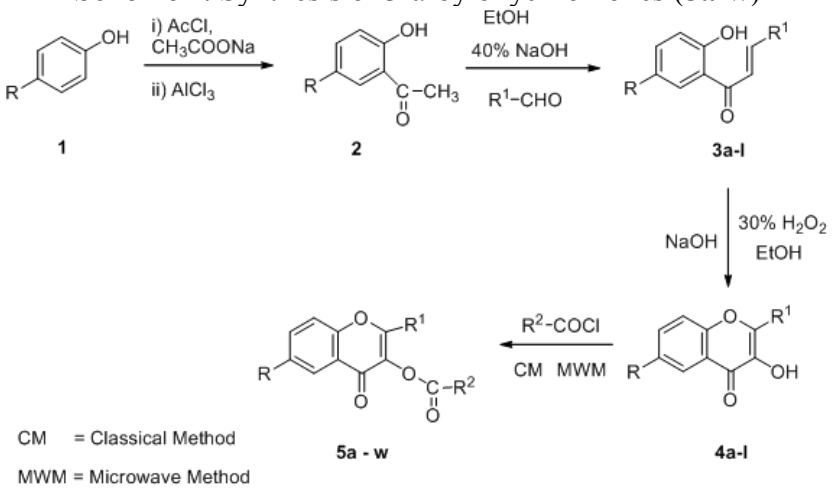


**Table 1**. Characterization of 3-aroyloxychromones (**5a-w**)

| Compound | R | $R^1$ | $R^2$ | M.P. ($^0$C) |
|---|---|---|---|---|
| **5a** | H | $C_6H_5$ | 4-$MeOC_6H_4$ | 168 |
| **5b** | H | 3,4-$(MeO)_2C_6H_3$ | 4-$MeOC_6H_4$ | 188 |
| **5c** | H | 4-$N(CH_3)_2C_6H_4$ | 4-$MeOC_6H_4$ | 238 |
| **5d** | H | $C_4H_3O$ | 4-$MeOC_6H_4$ | 180 |
| **5e** | Cl | $C_6H_5$ | 4-$MeOC_6H_4$ | 182 |
| **5f** | Cl | 4-$MeOC_6H_4$ | 4-$MeOC_6H_4$ | 254 |
| **5g** | Cl | 3,4-$(MeO)_2C_6H_3$ | 4-$MeOC_6H_4$ | 188 |
| **5h** | Cl | $C_4H_3O$ | 4-$MeOC_6H_4$ | 178 |
| **5i** | Cl | 4-$FC_6H_4$ | 4-$MeOC_6H_4$ | 205 |
| **5j** | H | $C_6H_5$ | $C_4H_3S$ | 150 |
| **5k** | Cl | 4-$FC_6H_4$ | $C_4H_3S$ | 194 |
| **5l** | H | 4-$ClC_6H_4$ | $C_4H_3S$ | 176 |
| **5m** | H | 3-$MeOC_6H_4$ | $C_4H_3S$ | 144 |
| **5n** | H | 4-$ClC_6H_4$ | 2-$BrC_6H_4$ | 182 |
| **5o** | H | $C_6H_5$ | 2-$BrC_6H_4$ | 176 |
| **5p** | Cl | 4-$MeOC_6H_4$ | 2-$BrC_6H_4$ | 213 |
| **5q** | Cl | $C_4H_3O$ | 2-$BrC_6H_4$ | 132 |
| **5r** | H | 3-$MeOC_6H_4$ | 2-OH,3-$MeC_6H_3$ | 154 |
| **5s** | H | $C_6H_5$ | 2-OH,3-$MeC_6H_3$ | 98 |
| **5t** | Cl | $C_4H_3O$ | 2-OH,3-$MeC_6H_3$ | 178 |
| **5u** | H | 4-$FC_6H_4$ | 2-OH,3-$MeC_6H_3$ | 189 |
| **5v** | H | $C_6H_5$ | $C_6H_5$ | 170 |
| **5w** | Cl | $C_4H_3O$ | $C_6H_5$ | 211 |

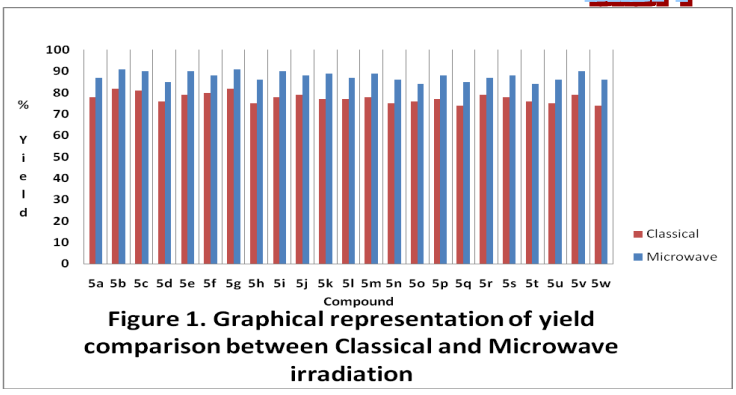


**Figure 1. Graphical representation of yield comparison between Classical and Microwave irradiation**

**In vitro antibacterial activity**

The newly synthesized esters (**5a-w**) were tested in *vitro* on a panel of selected Gram-positive (*Bacillus subtilis*, *Staphylococcus aureus*) and Gram-negative (*E. coli*, *Pseudomonas aeruginosa*) bacterial strains (**Table 2**).

**Table 2.** Antimicrobial-screening results of 3-aroyloxychromones (**5a-w**)

| Compound | Micro-bacteria (MIC at 100 µg/mL) | | | | Mycobacterium tuberculosis MIC (ug/ml) |
|---|---|---|---|---|---|
| | Gram (+) ve | | Gram (-) ve | | |
| | BS | SA | EC | PA | |
| **5a** | + | ++ | + | ++ | - |
| **5b** | +++ | ++ | +++ | +++ | - |
| **5c** | + | + | ++ | ++ | 50 |
| **5d** | ++ | ++ | ++ | ++ | - |
| **5e** | + | - | ++ | + | - |
| **5f** | ++ | ++ | + | ++ | - |
| **5g** | +++ | ++ | ++ | +++ | 50 |
| **5h** | ++ | + | + | ++ | - |
| **5i** | ++ | ++ | ++ | ++ | - |
| **5j** | ++ | + | ++ | ++ | - |
| **5k** | ++ | ++ | ++ | + | - |
| **5l** | +++ | +++ | +++ | +++ | - |
| **5m** | +++ | ++ | +++ | ++ | - |
| **5n** | + | + | - | + | - |
| **5o** | + | + | ++ | - | - |
| **5p** | ++ | ++ | ++ | ++ | - |
| **5q** | +++ | +++ | ++ | +++ | 50 |
| **5r** | ++ | ++ | ++ | ++ | - |
| **5s** | + | ++ | + | - | - |
| **5t** | +++ | +++ | +++ | ++ | 50 |
| **5u** | ++ | ++ | ++ | ++ | - |
| **5v** | ++ | ++ | + | ++ | - |
| **5w** | +++ | +++ | +++ | +++ | - |
| Ampicillin | +++ | ++ | +++ | +++ | - |
| Pyrazinamide | - | - | - | - | 50 |

Key to symbols:
Gram (+) ve Bacteria: BS: *Bacillus subtilis*; SA: *Staphylococcus aureus*;
Gram (-) ve Bacteria: EC: *Escherichia coli*; PA: *Pseudomonas aeruginosa;*
Inactive = - (inhibition zone < 5 mm); Slightly active = + (inhibition zone 5-12 mm);
Moderately active = + + (inhibition zone 13-17 mm); Highly active = + + + (inhibition zone > 17 mm). - = Inactive.

Most of the compounds showed moderate to good bacterial inhibition. Compounds **5b**, **5g**, **5i**, **5m**, **5q**, **5t** and **5w** found to be active against *B.subtilis*, **5l**, **5q**, **5t** and **5w** for *S. aureus*, **5b**, **5l**, **5m**, **5t** and **5w** *E. coli*, **5b**, **5g**, **5l**, **5q** and **5w** *P. aeruginosa* showed very good activity almost equivalent to that of standard against all the bacterial strains. The compounds **5d**, **5f**, **5h**, **5i**, **5j**, **5q**, **5p**, **5r**, **5u** and **5v** showed moderate active against *B.subtilis*, **5a**, **5b**, **5d**, **5f**, **5g**, **5i**, **5k**, **5m**, **5p**, **5r**, **5s**, **5u** and **5v** for *S. aureus*, **5c**, **5d**, **5e**, **5g**, **5i**, **5j**, **5k**, **5o**, **5p**, **5q**, **5r** and **5u** for *E. coli*, **5a**, **5c**, **5d**, **5f**, **5h**, **5i**, **5j**, **5m**, **5p**, **5i**, **5t**, **5u** and **5v** for *P. aeruginosa*. The activity of compounds **5e** (SA), **5n** (EC), **5o** (PA), and **5s** (PA) against selected set of bacterial strains could not be precisely determined since the MICs were generally higher than the standard used in our in *vitro* screen. These compounds could be considered as antibacterially inactive.

**Antitubercular activity**

The antimicrobial study prompted us for further anti-tubercular evaluation against *M. tuberculosis*. All compounds (**5a-w**) were evaluated for antitubercular activity against clinically isolated *M. tuberculosis* strains with L-J slants. The stated compounds were screened against the clinically isolated *M. tuberculosis* at concentrations 50 ug/ml. This study showed that the compounds **5c**, **5g**, **5q**, and **5t** were active whereas the remaining compounds were inactive (**Table 2**).

**Molinspiration calculation of molecular physicochemical properties**

A large number of molecules having high probability to show biological activity can be virtually screened and selected by using Molinspiration miscreen engine.[21] According to Lipinski rule, the first property log P (octanol/water partition coefficient) is a key parameter which is calculated as a sum of fragment based contribution and correction factors (**Table 3**). The second property molecular polar surface area (TPSA) is another useful parameter which predicts drug transport properties as well as it characterizes drug absorption, including intestinal absorption, bioavailability, Caco-2 monolayer permeability and blood-brain barrier penetration. TPSA is calculated as a sum of polar atoms (O, N and attached H) in a molecule.[22,23] Log P value and polar surface area (PSA) values are two important properties for the prediction of per oral bioavailability of drug molecules.[24,25] The properties of the compounds (**5a-w**) were studied using molinspiration software and the values were compared to that of the standard drugs Ampicillin and Streptomycin. As per the 5 rule properties the log P and PSA values for compounds (**5a-w**) show appreciable values, (i.e. log P <= 5) except compounds **5e**, **5f**, **5j**, **5n**, and **5p**. Also, the properties like molecular weight (<=500), number of hydrogen bond acceptors (<=10) and number of hydrogen bond donors (<=5) fall in the acceptable range for the compounds (**5a-w**), except for compounds **5e**, **5f**, **5i**, **5n**, **5p** other compounds have log P values around 5 which is the upper limit for the drugs to be able to penetrate through bio membranes according to the Lipinski's rules. However, **5d**, **5j**, and **5m** exhibit low degree of lipophilicity among the other compounds. Lipinski's rule suggests that two or more violations in a compound show probability of problems in bio availability.[26] All the compounds have only one violation of the Rule except **5d** which shows zero violation.

Drug likeness is defined as a complex balance of various molecular properties and structure features which determine whether particular molecule is similar to the known drugs. The behaviour of a molecule in a living organism like bioavailability, transport properties, affinity to proteins *etc*. are influenced by various drug properties such as hydrophobicity, electronic distribution, hydrogen bonding characteristics, molecule size and presence of various pharmacophoric features. Drug likenesses of the compounds were calculated in terms of GPCR ligands, ion channel modulators, kinase inhibitors and nuclear receptors ligands using Molinspiration testing.

All compounds (**5a-w**) have consistent negative values except for a few compounds which show positive KI score (**Table 4**). These numerical values conform and are comparable to that of the standard drugs used. It is important to note that the score for the above mentioned parameters follow the rule that "larger the score value greater is the probability of the molecule to be active."

**Table 3.** Molinspiration calculation of 3-aroyloxychromones (**5a-w**)

| Compound | Mi logP | TSPA | OH-NH | MW | N viol | Vol. |
|---|---|---|---|---|---|---|
| **5a** | 5.59 | 65.75 | 0 | 375 | 1 | 324.92 |
| **5b** | 5.24 | 84.22 | 0 | 432.43 | 1 | 376.01 |
| **5c** | 5.69 | 68.99 | 0 | 415.44 | 1 | 370.82 |
| **5d** | 4.73 | 78.89 | 0 | 362.34 | 0 | 306.49 |
| **5e** | 6.24 | 65.75 | 0 | 406.82 | 1 | 338.45 |
| **5f** | 6.3 | 74.98 | 0 | 436.85 | 1 | 363.99 |
| **5g** | 5.89 | 84.22 | 0 | 466.87 | 1 | 389.54 |
| **5h** | 5.39 | 78.89 | 0 | 396.78 | 1 | 320.02 |
| **5i** | 6.41 | 65.75 | 0 | 424.81 | 1 | 343.38 |
| **5j** | 5.09 | 56.52 | 0 | 348.38 | 1 | 290.08 |
| **5k** | 5.91 | 56.52 | 0 | 400.81 | 1 | 308.55 |
| **5l** | 5.77 | 56.52 | 0 | 382.82 | 1 | 303.62 |
| **5m** | 5.13 | 65.75 | 0 | 378.40 | 1 | 315.63 |
| **5n** | 6.63 | 56.52 | 0 | 455.69 | 1 | 330.79 |
| **5o** | 5.95 | 56.52 | 0 | 421.25 | 1 | 317.26 |
| **5p** | 6.66 | 65.75 | 0 | 485.72 | 1 | 356.34 |
| **5q** | 5.75 | 69.66 | 0 | 445.65 | 1 | 312.36 |
| **5r** | 5.78 | 85.98 | 1 | 402.40 | 1 | 349.49 |
| **5s** | 5.75 | 76.74 | 1 | 372.38 | 1 | 323.95 |
| **5t** | 5.54 | 89.88 | 1 | 396.78 | 1 | 319.05 |
| **5u** | 5.91 | 76.74 | 1 | 390.37 | 1 | 328.88 |
| **5v** | 5.53 | 56.52 | 0 | 342.35 | 1 | 299.37 |
| **5w** | 5.33 | 69.66 | 0 | 366.76 | 1 | 294.48 |
| AMP | -0.87 | 113 | 4 | 349 | 0 | 299 |
| STREP | -5.35 | 336 | 16 | 581 | 3 | 497 |

**Table 4**. Drug likeness of 3-aroyloxychromones (**5a-w**)

| Compound | GPCR | ICM | KI | NRL |
|---|---|---|---|---|
| **5a** | -0.48 | -0.60 | 0.03 | -0.59 |
| **5b** | -0.42 | -0.56 | 0.05 | -0.53 |
| **5c** | -0.41 | -0.57 | 0.05 | -0.50 |
| **5d** | -0.44 | -0.88 | -0.21 | -1.13 |
| **5e** | -0.45 | -0.59 | 0.01 | -0.74 |
| **5f** | -0.42 | -0.55 | 0.01 | -0.69 |
| **5g** | -0.40 | -0.58 | 0.04 | -0.66 |
| **5h** | -0.41 | -0.85 | -0.22 | -1.26 |
| **5i** | -0.38 | -0.53 | 0.07 | -0.67 |
| **5j** | -0.70 | -0.78 | -0.17 | -0.99 |
| **5k** | -0.58 | -0.68 | -0.10 | -1.06 |
| **5l** | -0.67 | -0.74 | -0.16 | -1.03 |
| **5m** | -0.65 | -0.78 | -0.14 | -0.93 |
| **5n** | -0.70 | -0.66 | -0.13 | -0.98 |
| **5o** | -0.73 | -0.69 | -0.13 | -0.94 |
| **5p** | -0.64 | -0.68 | -0.14 | -1.02 |
| **5q** | -0.66 | -0.95 | -0.38 | -1.65 |
| **5r** | -0.42 | -0.55 | 0.05 | -0.54 |
| **5s** | -0.45 | -0.54 | 0.04 | -0.57 |
| **5t** | -0.39 | -0.78 | -0.20 | -1.25 |
| **5u** | -0.39 | -0.47 | 0.10 | -0.51 |
| **5v** | -0.51 | -0.59 | 0.04 | -0.63 |
| **5w** | -0.44 | -0.86 | -0.22 | -1.36 |
| AMP | -0.57 | -0.55 | -0.90 | -0.10 |
| STREP | -0.56 | -0.43 | -0.78 | -0.04 |

AMP: Ampicillin; STREP:Streptomycin; GPCRL: GPCR ligand;ICM: Ion Channel modulator; KI: Kinase inhibitor; NRL: Nuclear receptor ligand.L

## CONCLUSIONS

3-Aroyloxy chromones (**5a-w**) were synthesized (75-90%) and characterised by chemical tests and spectral analysis. The o-aroylation reactions were carried out both under conventional and microwave irradiation. Only a few minutes were needed to obtain the desired product under microwave irradiation in comparison to the several hours required by the conventional method. All the compounds were screened against the panels of certain gram positive and gram negative bacteria. Good results were obtained using molinspiration testing against standard compounds Streptomycin and Amoxicillin. It is observed that the esters possess a broad range of lipophilic character.

## Experimental Section

**General.** All the chemicals and solvents were obtained from Merck (AR grade) and were used without further purification. Melting points were taken in an open capillary tube and are uncorrected. The microwave assisted syntheses of 3-aroyloxyflavones were carried out in a 300W laboratory microwave reactor, bench mate model CEM - 908010. IR spectra were recorded on Shimadzu DR-8031 and $^{1}$H NMR spectra were recorded on Bruker Avance II 400MHz liquid state NMR spectrometer in solvent $CDCl_3$ using tetramethylsilane as an internal standard. Mass spectra were recorded on water Micromass Q-T of Micro spectrometer equipped with an ESI source. All the elemental analyses were done using Perkin Elmer 2400 CHN analyzer. The reactions were monitored on pre-coated TLC plates (Silica gel 60 F254, Merck), visualizing the spots under ultraviolet light and iodine chamber.

## Biological screening

Antimicrobial activity of 3-aroyloxy chromones (**5a-w**) was determined by agar diffusion method. All human pathogenic bacteria viz. *Bacillus subtilis*, *Staphylococcus aureus*, *Escherichia coli*, *Pseudomonas Aeruginosa* were obtained from the department of Pharmacy RTM Nagpur University, Nagpur, India. Stock solutions of compounds were diluted in dimethyl formamide (DMF) to give a final concentration for determining the Minimum inhibitory concentration (MIC) value. MIC was defined as the lowest concentration of compound required for a complete inhibition of the bacterial growth after incubation time. For antibacterial activity Muller Hinton agar was used. The wells of 6 mm diameter were filled with 0.1 mL of the test compounds separately for each test of bacterial strain. The antibiotic Ampicillin was used as a reference antibacterial agent, for comparison. Inoculated plates were then incubated at 37$^{o}$C for antibacterial activity. The antimicrobial activity was measured in terms of the zone of inhibition in mm and categorised, as 0–5 mm for mild, 6–12 mm for moderate and 13–17 mm for efficacy, respectively (**Table 2**).

Evaluation of in vitro antituberculosis $H_{37}Rv$ strain was carried out with recommended protocol using Middle Brook (MB) 7H10 agar medium. A 100 µL of serial two fold dilutions of the stock (1.0 mg/mL in DMF) of test compound and standard antitubercular drug (Pyrazinamide) were incorporated in the medium. Compounds/drug containing tubes were kept in slanting position till the medium solidified. Culture of M. Tuberculosis $H_{37}Rv$ grown on Lowenstein-Jensen (L-J) was harvested in N-saline containing 0.05% Tween-80.

The culture was vigorously agitated with glass beads to make a single cell suspension. Working inoculums (10 µL/tube) of mycobacterium was spread on the surface of the medium and the tubes were kept at $37^0$C for 4 weeks for the appearance of colonies. Tubes containing no drug served as control. The minimum concentration of the drugs /compounds that completely inhibited the growth of mycobacterium was recorded as Minimum Inhibitory Concentration (MIC) with respect to the used inoculums.

**Chemistry**

**Preparation of 1-(2-hydroxyphenyl)-3-phenylprop-2-en-1-one** (**3a**).

To the mixture of o-hydroxy acetophenone (13.6 gm, 0.1 mol), alcohol (50 mL) and benzaldehyde (12.72 gm, 0.12 mol), NaOH (40%, 19 mL) was slowly added with vigorous stirring (2-3 hrs), till orange solid mass was obtained and left it overnight at ambient temperature. Cold 5N, 42 mL HCl was poured on to it with constant stirring. The yellow solid was filtered, washed with water, dried and crystallised from alcohol (yield 82%). Similarly, other chalcones (**3b-l**) were prepared.

**Preparation of 3-hydroxy-2-phenyl-4H-chromen-4-one** (**4a**).

The mixture of 1-(2-hydroxyphenyl)-3-phenylprop-2-en-1-one (**3a**) (2.24 gm, 0.01 mol), ethanol (50 mL), NaOH (10%, 56 mL) and $H_2O_2$ (30%, 13 mL) was stirred vigorously for 30 minutes and kept for 4 hrs at ice cold condition. It was poured on to cold 5N, 80 mL HCl. The solid was filtered, washed with water, dried and crystallised from alcohol (yield 66%). Similarly, other flavones (**4b-l**) were prepared.

**Preparation of 4-oxo-2-phenyl-4H-chromen-3-yl 4-methoxybenzoate (5a).**

**Esterification;**

(i) Conventional method

The mixture of 3-hydroxyflavone (0.95 gm, 0.004 mol) and p-methoxybenzoyl chloride (1.023 gm, 0.006 mol) was heated on water bath at 50°C for 30 minutes. The progress of reaction was monitored by TLC and $FeCl_3$. The solid obtained was filtered, washed thoroughly with hot water, dried and crystallised from alcohol (yield 78%). Similarly, other esters (**5b-w**) were prepared.

(ii) Microwave irradiation

A mixture of 3-hydroxyflavone (0.95 gm, 0.004 mol) and p-methoxybenzoyl chloride (1.023 gm, 0.006 mol) was irradiated in a microwave oven for 3 minutes. The completion of reaction was monitored by TLC and $FeCl_3$. The solid obtained was filtered, washed thoroughly with hot water, dried and crystallised from alcohol (yield 87%). Similarly, other esters (**5b-w**) were also prepared.

**4-Oxo-2-phenyl-4*H*-chromen-3-yl-4-methoxybenzoate (5a)**. Colourless crystals, yield 87%, mp 168-169 $^0$C; IR ($\nu_{max}$, $cm^{-1}$): 1560.6 (C=O pyrone ring), 1618.5 (C=O). $^1$H NMR (400 MHz, $CDCl_3$): $\delta_H$ 3.04 (s, 3H, $OCH_3$), 6.95-8.16 (m, 13H, Ar-H). MS *m/z*: 372 ($M^{+\cdot}$, 100%). Anal. Calcd for $C_{23}H_{16}O_5$: C, 74.19; H, 4.33%. Found: C, 74.31; H, 4.39%.

**2-(3, 4-Dimethoxyphenyl)-4-oxo-4*H*-chromen-3-yl-4-methoxybenzoate (5b).** Yellow crystals, yield 91%, mp 188-190 $^0$C; IR ($\nu_{max}$, $cm^{-1}$): 1552.6 (C=O pyrone ring), 1608.7 (C=O). $^1$H NMR (400 MHz, $CDCl_3$): $\delta_H$ 3.64 (s, 9H, $OCH_3$), 6.58-8.14 (m, 11H, Ar-H). MS *m/z*: 432 ($M^{+\cdot}$, 100%). Anal. Calcd for $C_{25}H_{20}O_7$: C, 69.44; H, 4.66%. Found: C, 69.53; H, 4.59%.

**6-Chloro-2-(4-(dimethylamino) phenyl)-4-oxo-4*H*-chromen-3-yl-4-methoxybenzoate (5c).**

Yellow crystals, yield 90%, mp 238-239 $^0$C; IR ($\nu_{max}$, $cm^{-1}$):1545.3 (C=O pyrone ring), 1623.4 (C=O). $^1$H NMR (400 MHz, $CDCl_3$): $\delta_H$ 2.52 (s, 6H, $N(CH_3)_2$), 3.38 (s, 3H, $OCH_3$), 6.34-8.11 (m, 11H, Ar-H). MS *m/z*: 449 ($M^{+\cdot}$, 100%). Anal. Calcd for $C_{25}H_{20}ClNO_5$: C, 66.74; H, 4.48; N, 3.11 %. Found: C, 66.65; H, 4.63; N, 3.02%.

**2-(Furan-2-yl)-4-oxo-4*H*-chromen-3-yl 4-methoxybenzoate (5d).** Dark brown crystals, yield 85%, mp 180-181 $^0$C; IR ($\nu_{max}$, cm$^{-1}$): 1569.3 (C=O pyrone ring), 1620.4 (C=O). $^1$H NMR (400 MHz, $CDCl_3$): $\delta_H$ 3.21 (s, 3H, $OCH_3$), 6.68-8.10 (m, 11H, Ar-H). MS *m/z*: 362 ($M^{+\cdot}$, 100%). Anal. Calcd for $C_{21}H_{14}O_6$: C, 69.61; H, 3.89%. Found: C, 69.48; H, 3.97%.

**6-Chloro-4-oxo-2-phenyl-4*H*-chromen-3-yl-4-methoxybenzoate (5e).** Pink crystals, yield 90%, mp 182-183 $^0$C; IR ($\nu_{max}$, cm$^{-1}$): 1558.3 (C=O pyrone ring), 1615.7 (C=O). $^1$H NMR (400 MHz, $CDCl_3$): $\delta_H$ 3.35 (s, 3H, $OCH_3$), 6.81-8.09 (m, 12H, Ar-H). MS *m/z*: 406 ($M^{+\cdot}$, 100%). Anal. Calcd for $C_{23}H_{15}ClO_5$: C, 67.90; H, 3.72%. Found: C, 67.84; H, 3.87%.

**6-Chloro-2-(4-methoxyphenyl)-4-oxo-4*H*-chromen-3-yl-4-methoxybenzoate (5f).** Colourless crystals, yield 88%, mp 254-255 $^0$C; IR ($\nu_{max}$, cm$^{-1}$):1561.8 (C=O pyrone ring), 1611.5 (C=O). $^1$H NMR (400 MHz, $CDCl_3$): $\delta_H$ 3.22 (s, 6H, $OCH_3)_2$, 6.78-8.18 (m, 11H, Ar-H). MS *m/z*: 436 ($M^{+\cdot}$, 100%). Anal. Calcd for $C_{24}H_{17}ClO_6$: C, 65.99; H, 3.92%. Found: C, 65.91; H, 3.98%.

**6-Chloro-2-(3, 4-dimethoxyphenyl)-4-oxo-4*H*-chromen-3-yl-4-methoxybenzoate (5g).** Yellow crystals, yield 91%, mp 188-189 $^0$C; IR ($\nu_{max}$, cm$^{-1}$): 1565.1 (C=O pyrone ring), 1622.6 (C=O). $^1$H NMR (400 MHz, $CDCl_3$): $\delta_H$ 3.31 (s, 9H, $OCH_3)_3$, 6.63-8.12 (m, 10H, Ar-H). MS *m/z*: 466 ($M^{+\cdot}$, 100%). Anal. Calcd for $C_{25}H_{19}ClO_7$: C, 64.32; H, 4.10%. Found: C, 64.45; H, 4.19%.

**6-Chloro-2-(furan-2-yl)-4-oxo-4*H*-chromen-3-yl-4-methoxybenzoate (5h).** Dark brown crystals, yield 86%, mp 178-180 $^0$C; IR ($\nu_{max}$, cm$^{-1}$): 1567.3 (C=O pyrone ring), 1625.5 (C=O). $^1$H NMR (400 MHz, $CDCl_3$): $\delta_H$ 3.34 (s, 3H, $OCH_3$), 6.43-8.13 (m, 10H, Ar-H). MS *m/z*: 396 ($M^{+\cdot}$, 100%). Anal. Calcd for $C_{21}H_{13}ClO_6$: C, 63.57; H, 3.30%. Found: C, 63.64; H, 3.25%.

**6-Chloro-2-(4-fluorophenyl)-4-oxo-4*H*-chromen-3-yl-4-methoxybenzoate (5i).**
Colourless crystals, yield 90%, mp 205-207 $^0$C; IR ($\nu_{max}$, cm$^{-1}$): 1557.8 (C=O pyrone ring), 1615.3 (C=O). $^1$H NMR (400 MHz, $CDCl_3$): $\delta_H$ 3.39 (s, 3H, $OCH_3$), 6.76-8.11 (m, 11H, Ar-H). MS *m/z*: 424 ($M^{+\cdot}$, 100%). Anal. Calcd for $C_{23}H_{14}ClFO_5$: C, 65.03; H, 3.32%. Found: C, 65.12; H, 3.45%.

**4-Oxo-2-phenyl-4*H*-chromen-3-yl thiophene-2-carboxylate (5j).** Colourless crystals, yield 88%, mp 150-151 $^0$C; IR ($\nu_{max}$, cm$^{-1}$): 1561.6 (C=O pyrone ring), 1617.8 (C=O). $^1$H NMR (400 MHz, $CDCl_3$): $\delta_H$ 6.78-7.94 (m, 12H, Ar-H). MS *m/z*: 348 ($M^{+\cdot}$, 100%). Anal. Calcd for $C_{20}H_{12}O_4S$: C, 68.95; H, 3.47%. Found: C, 68.99; H, 3.32%.

**6-Chloro-2-(4-fluorophenyl)-4-oxo-4*H*-chromen-3-yl thiophene-2-carboxylate (5k).** Colourless crystals, yield 89%, mp 194-195 $^0$C; IR ($\nu_{max}$, cm$^{-1}$): 1575.4 (C=O pyrone ring), 1624.2 (C=O). $^1$H NMR (400 MHz, $CDCl_3$): $\delta_H$ 6.81-7.89 (m, 10H, Ar-H). MS *m/z*: 400 ($M^{+\cdot}$, 100%). Anal. Calcd for $C_{20}H_{10}ClFO_4S$: C, 59.93; H, 2.51%. Found: C, 59.87; H, 2.64%.

**2-(4-Chlorophenyl)-4-oxo-4*H*-chromen-3-yl thiophene-2-carboxylate (5l).** Colourless crystals, yield 87%, mp 176-177 $^0$C; IR ($\nu_{max}$, cm$^{-1}$): 1571.2 (C=O pyrone ring), 1622.3 (C=O). $^1$H NMR (400 MHz, $CDCl_3$): $\delta_H$ 6.82-7.86 (m, 11H, Ar-H); MS *m/z*: 382 ($M^{+\cdot}$, 100%). Anal. Calcd for $C_{20}H_{11}ClO_4S$: C, 62.75; H, 2.90%. Found: C, 62.83; H, 2.96%.

**2-(3-Methoxyphenyl)-4-oxo-4*H*-chromen-3-yl thiophene-2-carboxylate (5m).** Brown crystals, yield 89%, mp 144-146 $^0$C; IR ($\nu_{max}$, cm$^{-1}$): 1620.4 (C=O pyrone ring), 1732.3 (C=O), $^1$H NMR (400 MHz, $CDCl_3$): $\delta_H$ 3.78 (s, 3H, $OCH_3$), 7.01 – 8.29 (m, 11H, Ar-H). MS *m/z*: 378 ($M^{+\cdot}$, 100%). Anal. Calcd for $C_{21}H_{14}O_5S$: C, 66.66; H, 3.73%. Found: C, 66.76; H, 3.83%.

**2-(4-Chlorophenyl)-4-oxo-4*H*-chromen-3-yl- 2-bromobenzoate (5n).** Purple crystals, yield 86%, mp 182-184 $^0$C; IR ($\nu_{max}$, cm$^{-1}$): 1632.9 (C=O pyrone ring), 1680.3 (C=O). $^1$H NMR (400 MHz, $CDCl_3$): $\delta_H$ 6.98 – 8.14 (m, 12H, Ar-H). MS *m/z*: 455 ($M^{+\cdot}$, 100%). Anal. Calcd for $C_{22}H_{12}BrClO_4$: C, 57.99; H, 2.65%. Found: C, 57.86; H, 2.74%.

**4-Oxo-2-phenyl-4*H*-chromen-3-yl-2-bromobenzoate (5o).** Purple crystals, yield 84%, mp 176-178 $^0$C; IR ($\nu_{max}$, cm$^{-1}$): 1644.4 (C=O pyrone ring), 1687.5 (C=O). $^1$H NMR (400 MHz, $CDCl_3$): $\delta_H$ 6.94 – 8.09 (m, 13H, Ar-H). MS *m/z*: ($M^{+\cdot}$, 100%). Anal. Calcd for $C_{22}H_{13}BrO_4$: C, 62.73; H, 3.11 %. Found: C, 62.85; H, 3.15%.

**6-Chloro-2-(4-methoxyphenyl)-4-oxo-4*H*-chromen-3-yl-2-bromobenzoate (5p).** Olive green crystals, yield 88%, mp 213-215 $^0$C; IR ($\nu_{max}$, cm$^{-1}$): 1678.7 (C=O), 1639.3 (C=O pyrone ring). $^1$H NMR (400 MHz, $CDCl_3$): $\delta_H$ 3.64 (s, 3H, $OCH_3$), 6.89 – 8.11 (m, 11H, Ar-H). MS *m/z*: 486 ($M^{+\cdot}$, 100%). Anal. Calcd for $C_{23}H_{14}BrClO_5$: C, 56.87; H, 2.91%. Found: C, 56.93; H, 2.79%.

**6-Chloro-2-(furan-2-yl)-4-oxo-4*H*-chromen-3-yl-2-bromobenzoate (5q).** Dark brown crystals, yield 85%, mp 132-133 $^0$C; IR ($\nu_{max}$, cm$^{-1}$): 1528.2 (C=O pyrone ring), 1657.1 (C=O). $^1$H NMR (400 MHz, $CDCl_3$): $\delta_H$ 6.91 – 8.06 (m, 10H, Ar-H). MS *m/z*: 446 ($M^{+\cdot}$, 100%). Anal. Calcd for $C_{20}H_{10}BrClO_5$: C, 53.90; H, 2.26%. Found: C, 53.98; H, 2.34%.

**2-(3-Methoxyphenyl)-4-oxo-4*H*-chromen-3-yl-2-hydroxy-3-methylbenzoate (5r).** Light purple crystals, yield 87%, mp 154-155 $^0$C; IR ($\nu_{max}$, cm$^{-1}$): 1532.6 (C=O pyrone ring), 1664.3 (C=O). $^1$H NMR (400 MHz, $CDCl_3$): $\delta_H$ 2.34 (s, 3H, $CH_3$), 3.75 (s, 3H, $OCH_3$), 5.3 (s, 1H, OH), 6.61 – 7.81 (m, 11, Ar-H). MS *m/z*: 402 ($M^{+\cdot}$, 100%). Anal. Calcd for $C_{24}H_{18}O_6$: C, 71.64; H, 4.51%. Found: C, 71.78; H, 4.59%.

**4-Oxo-2-phenyl-4*H*-chromen-3-yl-2-hydroxy-3-methylbenzoate (5s).** Light purple crystals, yield 88%, mp 98-100 $^0$C; IR ($\nu_{max}$, cm$^{-1}$): 1547.6 (C=O pyrone ring), 1638.8 (C=O). $^1$H NMR (400 MHz, $CDCl_3$): $\delta_H$ 2.35 (s, 3H, $CH_3$), 5.2 (s, 1H, OH), 6.89 – 7.86 (m, 12H, Ar-H). MS *m/z*: 372 ($M^{+\cdot}$, 100%). Anal. Calcd for $C_{23}H_{16}O_5$: C, 74.19; H, 4.33%. Found: C, 74.08; H, 4.43%.

**6-Chloro-2-(furan-2-yl)-4-oxo-4*H*-chromen-3-yl-2-hydroxy-3-methylbenzoate (5t).** Dark brown crystals, yield 84%, mp 178-180 $^0$C; IR ($\nu_{max}$, cm$^{-1}$): 1538.6 (C=O pyrone ring), 1645.5 (C=O). $^1$H NMR (400 MHz, $CDCl_3$): $\delta_H$ 2.33 (s, 3H, $CH_3$), 5.4 (s, 1H, OH), 6.81 – 7.97 (m, 9H, Ar-H). MS *m/z*: 396 ($M^{+\cdot}$, 100%). Anal. Calcd for $C_{21}H_{13}ClO_6$: C, 63.57; H, 3.30%. Found: C, 63.48; H, 3.44%.

**2-(4-Fluorophenyl)-4-oxo-4*H*-chromen-3-yl-2-hydroxy-3-methylbenzoate (5u).** Yellow crystals, yield 86-87 %, mp 189 $^0$C; IR (KBr): 1549.1 (C=O pyrone ring), 1643.3 (C=O). $^1$H NMR (400 MHz, $CDCl_3$): $\delta_H$ 2.36 (s, 3H, $CH_3$), 5.1 (s, 1H, OH), 6.89 – 7.84 (m, 11H, Ar-H). MS *m/z*: 390 ($M^{+\cdot}$, 100%). Anal. Calcd for $C_{23}H_{15}FO_5$: C, 70.77; H, 3.87%. Found: C, 70.87; H, 3.71%.

**4-Oxo-2-phenyl-4*H*-chromen-3-yl benzoate (5v).** Colourless crystals, yield 90-92%, mp 170 $^0$C; IR ($\nu_{max}$, cm$^{-1}$): 1551.3 (C=O pyrone ring), 1638.5 (C=O). $^1$H NMR (400 MHz, $CDCl_3$): $\delta_H$ 6.88 – 8.17 (m, 14H, Ar-H). MS *m/z*: 342 ($M^{+\cdot}$, 100%). Anal. Calcd for $C_{22}H_{14}O_4$: C, 77.18; H, 4.12%. Found: C, 77.24; H, 4.19%.

**6-Chloro-2-(furan-2-yl)-4-oxo-4*H*-chromen-3-yl benzoate (5w).** Green crystals, yield 86-87%, mp 211 $^0$C; IR ($\nu_{max}$, cm$^{-1}$): 1565.5 (C=O pyrone ring), 1643.6 (C=O). $^1$H NMR (400 MHz, $CDCl_3$): $\delta_H$ 6.57 – 8.16 (m, 14H, Ar-H). MS *m/z*: 366 ($M^{+\cdot}$, 100%). Anal. Calcd for $C_{20}H_{11}ClO_5$: C, 65.50; H, 3.02%. Found: C, 65.37; H, 3.18%.

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