Chapter II

Synthesis of
3-arylidenechromanones
CHAPTER-II

3-Arylidenechroman-4-ones

Introduction

3-Arylidenechroman-4-ones belong to homoisoflavanoid, a class of naturally occurring oxygen heterocyclic compounds with C-16 skelton\(^1\). Homoisoflavanoids include biogenetically and structurally related 3-benzylidenechroman-4-ones (1), 3-benzylchromones (2), 3-benzyl chroman-4-ones (3) and 3-benzyl-3-hydroxychroman-4-ones (4).

![Chemical structures](image1)

These compounds were found to differ in their structures from those of isoflavanones in having a benzyl group instead of a phenyl group at 3-position of the chroman-4-one skelton. Because of the presence of an extra carbon in their basic skelton as compared to isoflavones these compounds have acquired the name homoisoflavanone derivatives.

Chroman-4-one derivatives have been found to exhibit a broad range of pharmacological activities\(^1\)\(^-\)\(^2\) but have drawn much attention due to their anti-human-immunodeficiency-virus (HIV-I)\(^2\) properties, that causes acquired immune deficiency syndrome.

3-Benzylidenechroman-4-ones inhibit the growth, the sporogenesis and the enzymes involved in the infection mechanism of phytophthora parasitica\(^3\) and show antifungal activity\(^4\). Some substituted 3-benzylidenechroman-4-ones have also been found to display anti-inflammatory, analgesic, platelet anti-aggregating\(^5\) and hypocholesterolemic activities\(^6\). Sim et al. have used 3-benzylidenechroman-4-one derivatives for the synthesis of some selective ligands required for antiestrogen-binding sites.\(^7\)

Recently a series of substituted 3-benzylidene-7-alkoxychroman-4-ones have been synthesized and evaluated for their antioxidant activities (Fig. 1). 3-Benzylidene-7-alkoxychroman-4-one derivatives bearing catecholic group on benzylidene moiety exhibited excellent antioxidant activity.\(^8\)
In another recent report bis(arylidene)chroman-4-one derivatives (Fig. 2) have been synthesised which displayed bathochromic shifts and showed potential biological activity against human pathogenic bacteria.\(^9\)

The natural origin of the homoisoflavanoids came into picture when the first two members namely eucomin (5), and eueomol (6) were first isolated in the year 1967 from bulbs of Eucomis bicolar BAK by Boehler and Tamm.\(^10\)

Five more compounds, belonging to the same class were reported by Finckh & Tamm\(^11\) from Euconus punctuate. These are punctatin (7), 3,9-dihydropunctatin (8) 4′-O-methyl-3,9-dihydro punctatin (9), 4′-demethyleucomin (10) and 4′-demethyl-5-O-methyl -3,9-dihydroeucomin(11). All the plants from which these compounds have been isolated belong to family, ‘Liliaceae’
Sindwell and Tamm\textsuperscript{12} in the same year isolated three more compounds belonging to homoisoflavanone series from Eucomis Autumnalis Graeb. Two of them 4'-O-methyl punctatin (12) and eucomalin (13) were found to be 3-benzylidenechroman-4-one derivatives while the third one 3,9-dihydroeucomalin (14) was identified as 3-benzyl derivative.

Purushothaman et al.\textsuperscript{13} isolated another 3-benzylidenechroman-4-one namely bonducellin (15) from Caesalpinia bonducella.

Recently two new homoisoflavonoids, (E)-7-methoxy-3-(4'-methoxybenzylidene)chroman-4-one (16) and (E)-7-hydroxy-3-(3',4',5'-trimethoxybenzylidene)chroman-4-one (17) have also been isolated from the whole plant of Caesalpinia pulcherrima\textsuperscript{14}.

3-Benzylidenechroman-4-ones have also been used to prepare their isomeric 3-benzyl chromones by the isomerisation of their exocyclic double bond into pyranone ring using potassium tert. butyrate\textsuperscript{15}, rhodium chloride\textsuperscript{16}, or potassium carbonate in N,N-dimethyl formamide medium\textsuperscript{17} (Fig. 3).
Past work on the synthesis of 3-arylidenechroman-4-ones

Synthetic 3-arylidenechroman-4-ones are known from the early twentieth century. Traditional synthesis of 3-arylidenecharoman-4-ones is based on the condensation of chroman-4-ones with aromatic aldehyde in the presence of acidic or basic catalyst. But earlier in most of the cases acid catalyzed condensation of the two components i.e. chroman-4-ones and aldehydes was used to synthesise the title compounds because the chroman-4-one ring is normally stable to acidic reagents. However, the acid catalysed condition is not always convenient, so the use of basic catalyst such as potassium hydroxide, sodium hydroxide, sodium methoxide have also been reported. A brief description of the various catalysts used for synthesis of 3-arylidenechroman-4-ones is given below.

Basic catalysts

Preparation of 3-arylidenechroman-4-ones was first studied by Robinson et al. They prepared 3-benzylidenechroman-4-ones by carrying out the condensation between chroman-4-one and appropriate aryl aldehydes using alcoholic potassium hydroxide (scheme 1).

Birch et al. modified the above method and used 10% aqueous sodium hydroxide as condensing agent for the synthesis of 3-veratrylidene-6,7-dimethoxychromanone, 3-furfurylidene-6,7-dimethoxychromanone and 3-veratrylidene-5,7-dimethoxychromanone. Later on Sim et al. obtained 3-benzylidenechroman-4-ones by refluxing desired chroman-4-ones with aryl aldehydes in ethanol medium using catalytic amount of sodium hydroxide (scheme 2).
Piperidine has also been used as catalyst for the synthesis of \(E\)-3-arylidenechroman-4-ones\(^{26-28}\). However, in case where piperidine is used as catalyst, an exo-endo double bond migration takes place if the benzaldehyde has strong electron acceptor substituents\(^{27,29}\) (scheme 3). In such a case 3-benzyl-4-chromone is the sole isolable product instead of expected \(E\)-3-arylidene chromon-4-one. The use of pyrrolidine has also been reported for this condensation\(^{30}\).

\[\text{Dry hydrogen chloride in acetic acid}\]

Robinson et al.\(^{31}\), who have used earlier alcoholic potassium hydroxide\(^{32}\) as condensing agent, later on found that dry hydrogen chloride in acetic acid, is a better condensing agent. He obtained 3-anisalidene-7-methoxychroman-4-one and 3-veratrylidene-7-methoxychroman-4-one in 79% yield (scheme 4) by passing dry hydrogen chloride gas through alcoholic solution of the two reactants i.e. chroman-4-ones and appropriate aryl aldehydes at room temperature and then leaving at room temperature.

Later on 5,7-di-O-methyleucomin was synthesized by Boehler and Tamm\(^{10}\) from 5,7-dimethoxychroman-4-one and anisaldehyde using dry hydrochloric acid in acetic acid as condensing agent (scheme 5).
Krishnamurthy et al.\textsuperscript{32} have reported improved yields of 3-benzylidenechroman-4-one by using dry hydrogen chloride in dry ether medium as condensing agent. However, in this reaction a by product containing chlorine was also obtained, which required purification by elaborate column chromatography of the crude product.

George C Wright\textsuperscript{33} used dry hydrogen chloride gas in absolute ethanol for condensation of 6-methoxychroman-4-one with 6-nitroveratraldehyde. But he got along with the expected product, an unexpected product which was identified as 2,3-dihydro-3-(α-ethoxy-4,5-dimethoxy-2-nitrobenzyl)-6-methoxy-4H-benzopyran-4-one (scheme 6).

3-Cinnamylidenechroman-4-one has also been obtained in 50% yield by refluxing chroman-4-one with cinnamaldehyde in presence of glacial acetic acid and conc. hydrochloric acid for 2 hours (scheme 7).\textsuperscript{34}

**Acetic anhydride**

During the work on the synthesis of homoisoflavanoids, Farkas et al.\textsuperscript{35} synthesised eucomin by prolonged refluxing of 5,7-dihydroxycromonone with anisaldehyde in acetic
anhydride medium for 80 hours, when eucomin diacetate was obtained in 24% yield. Eucomin was then obtained by saponification of diacetate with alkali at room temperature (scheme 8).

\[
\begin{align*}
\text{HO-} & \quad \text{CHO} \quad \text{Ac}_2\text{O} \quad \text{AcO} \quad \text{OAc} \quad \text{AcO} \\
\text{HO-} & \quad \text{OCH}_3 \\
\text{HO} & \quad \text{O} \\
\end{align*}
\]

scheme 8

Though this method is very simple and convenient but due to prolonged refluxing (80 hours.) it could not become a widely accepted method.

Woods and Dix\textsuperscript{36} heated a mixture of 4-chromanone, benzaldehyde and anhydrous potassium acetate for 2 hours at 120-130\degree C, and obtained 3-benzylidene-4-chroman-4-one in 78% yield by acidification of the reaction mixture.

Later on acetic anhydride was used for the synthesis of imidazole derivative by reacting 7-hydroxy-4-chromanone with 1-methyl-5-nitro-imidazole-2-carboxaldehyde in the presence of sodium acetate at 100\degree C for 1.5 hours\textsuperscript{37} (scheme 9).

\[
\begin{align*}
\text{HO} & \quad \text{N} \quad \text{N} \quad \text{Me} \\
\end{align*}
\]

scheme 9

**Other methods**

Basavaiah et al.\textsuperscript{38} has reported the synthesis of the title compound i.e. 3-arylidene-chroman-4-ones by the ring closure of an acrylic acid derivative with trifluoroacetic anhydride in dichloromethane (scheme 10).

\[
\begin{align*}
\text{MeO-} & \quad \text{H-} \quad \text{R} \quad \text{CH}_2\text{Cl}_2 \quad \text{R} \\
\text{MeO-} & \quad \text{O-} \quad \text{COOH} \\
\end{align*}
\]

scheme 10

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PRESENT WORK

3-Arylidenechroman-4-ones, a sub group of naturally occurring homoisoflavanoids, have been obtained by the condensation of aryl aldehydes with chroman-4-ones (chromanones). Various condensing agents have been used for this reaction, description of which has already been given but these methods have the limitation of longer reaction period, low yields, or formation of the side products.

We have now observed (chapter-1) that condensation of active methylene group with aryl aldehydes can be carried out much more effectively using anhydrous barium hydroxide under solvent free conditions, using grinding technique. The reaction is completed within few minutes at room temperature and the product is formed in high yields, therefore, it was proposed to synthesise 3-arylidenechroman-4-ones by condensation of chroman-4-ones and aryl aldehydes under similar conditions with the view to get the required compounds in high yields. The chroman-4-ones required for the reaction have now been obtained by the cyclisation of phenoxy propanoic acids using the modified conditions, making use of microwave irradiations. The required chroman-4-ones were obtained in higher yields in much shorter time.

Synthesis of 3-benzylidenechroman-4-one was taken as the first example. Chroman-4-one and benzaldehyde were thus ground with anhydrous barium hydroxide in a mortar with pestle and the required compound i.e. 3-benzylidenechroman-4-one was obtained in 89% yield. Following this method differently substituted 3-arylidenechroman-4-ones were obtained.

This appears to be a simple and highly efficient procedure for the synthesis of 3-arylidene chroman-4-ones as it requires much shorter time (5 minutes grinding time + 5 to 10 minutes digestion time) for the completion of the reaction and yields of the product are also high. Moreover it is an eco-friendly protocol. Details of the work are presented below.

Reaction of chroman-4-one with benzaldehyde: synthesis of 3-benzylidenechroman-4-one

Chroman-4-one required for the reaction was obtained by cyclisation of phenoxy propanoic acid with polyphosphoric acid (PPA) under microwave irradiations. A mixture of chroman-4-one (20; 4 mmol), benzaldehyde (21; 4.1 mmol) and anhydrous barium hydroxide (C-200, 2.5 g) was taken in a mortar and ground well with pestle for 5 minutes. Progress of the reaction was checked on TLC, when a new product was found to have formed. For the completion of the reaction, reaction mixture was left at room temperature and chroman-4-one was found to have reacted completely after five minutes. Reaction mixture was acidified after...
adding ice cold water (30 ml) to it. A solid product that obtained on recrystallisation from petroleum ether-diethyl ether mixture as a colourless crystalline solid m.p. 111-112°C in 89% yield. The compound showed in IR a peak at 1664 cm⁻¹ showing the presence of α,β-unsaturated carbonyl group. In its \(^1\)H-NMR it showed a doublet at δ 5.35 for two protons, J=1.84 Hz (-CH₂), a multiplet between δ 6.82 to δ 6.98 for eight protons (H-6, H-7, H-8, H-2', H-3', H-4', H-5', H-6'), a singlet at δ 7.88 for one proton (olefinic) and a double doublet with J values, 1.72 and 7.88 Hz due to one proton (H-5). Based on this data the compound was identified as 3-benzylidenechroman-4-one (1). Further confirmation was made by m.p. comparison with literature value\(^{41}\).

Synthesis of 3-(4'-methoxybenzyldiene) chroman-4-one (23)

Chroman-4-one (20), anisaldehyde (22) and anhydrous barium hydroxide were ground well in a mortar with pestle for 5 minutes and reaction mixture was left at room temperature for 5 minutes and worked up as described in the previous case to give 3-(4'-methoxy benzylidene)chroman-4-one (23) in 87% yield whose structure was confirmed by its IR, \(^1\)H-NMR and by comparison of m.p. with literature value\(^{34}\).

Synthesis of 3-(3'-methoxybenzyldiene)chroman-4-one (25)

A mixture of chroman-4-one (20), 3-methoxybenzaldehyde (24) and anhydrous barium hydroxide was ground in a mortar with pestle for 5 minutes. Reaction mixture was left at room temperature for 10 minutes and worked up as described earlier to give 3-(3'-methoxy
benzylidene)chroman-4-one (25) in 85% yield, whose structure was confirmed based on its IR, 
$^1$H-NMR data and by comparison of its m.p. with literature value.$^{42}$

Synthesis of 6-methyl-3-benzylidenechroman-4-one (29)

6-Methylchroman-4-one (28), obtained by cyclisation of 4-methylphenoxy propanoic acid (27) with PPA using microwave irradiation, was ground well with benzaldehyde (21) and anhydrous barium hydroxide in the mortar using pestle for 5 minutes. Reaction mixture was left at room temperature for 10 minutes and worked up as described in earlier cases to give 6-methyl-3-benzylidenechroman-4-one (29) in 87% yield, whose structure was confirmed by its IR, $^1$H-NMR and comparison of m.p. with literature value.$^{45}$

Synthesis of 6-methyl-3-(4'-methylbenzylidene)chroman-4-one (31)

A mixture of 6-methylchroman-4-one (28), 4-methylbenzaldehyde (30) and anhydrous barium hydroxide was ground with pestle in a mortar for 5 minutes and left at room temperature for another 10 minutes. It was worked up as described earlier to give 6-methyl-3-(4'-methylbenzylidene)chroman-4-one (31) in 83% yield, whose identity was confirmed by its IR, $^1$H-NMR and spectral data.
Synthesis of 6-methyl-3-(4′-methoxybenzylidene)chroman-4-one (32)

A mixture of 6-methylchroman-4-one (28), anisaldehyde (22) and anhydrous barium hydroxide on grinding with pestle in a mortar for 5 minutes and then keeping the reaction mixture for another 10 minutes followed by working up as described earlier gave 6-methyl-3-(4′-methoxybenzylidene)chroman-4-one (32) in 88% yield. Identity of the product obtained was confirmed by its IR and $^1$H-NMR spectral data.

Synthesis of 8-methyl-3-(4′-methoxybenzylidene)chroman-4-one (36)

8-Methylchroman-4-one (35), obtained by cyclisation of 2-methylphenoxy propanoic acid (34) with PPA using microwave irradiations, anisaldehyde (22) and anhydrous barium hydroxide were ground together in a mortar with pestle for 5 minutes. The reaction mixture was kept at room temperature for another 5 minutes and worked up as described earlier to give 8-methyl-3-(4′-methoxybenzylidene)chroman-4-one (36) in 84% yield, whose structure was confirmed by its IR and $^1$H-NMR spectral data.

Synthesis of 6-bromo-3-benzylidenechroman-4-one (40)

6-Bromochroman-4-one (39) obtained by polyphosphoric acid catalyzed, microwave assisted cyclisation of 4-bromophenoxy propanoic acid (38), benzaldehyde (21) and anhydrous barium hydroxide were ground together in a mortar for 5 minutes and reaction mixture was left at room temperature for another 10 minutes. Reaction mixture on working up
as described earlier gave 6-bromo-3-benzylidenechroman-4-one (40) in 92% yield, whose identity was confirmed on the basis of its IR and $^1$H-NMR spectral data.

![Chemical structure](image)

**Synthesis of 6-bromo-3-((4'-methoxybenzylidene)chroman-4-one (41)**

A mixture of 6-bromochroman-4-one (39), anisaldehyde (22), and anhydrous barium hydroxide was ground with pestle in a mortar for 5 minutes and left at room temperature for another 10 minutes. It was worked up as described earlier to give 6-bromo-3-((4'-methoxybenzylidene)chroman-4-one (41) in 91% yield, whose structure was confirmed by its IR and $^1$H-NMR spectral data.

![Chemical structure](image)

**Synthesis of 6-bromo-3-((3'-methoxybenzylidene)chroman-4-one (42)**

A mixture of 6-bromochroman-4-one (39), 3-methoxybenzaldehyde (24), and anhydrous barium hydroxide was ground together in a mortar with pestle for 5 minutes and left at room temperature for another 10 minutes. It was worked up as described earlier to give 6-bromo-3-((3'-methoxybenzylidene)chroman-4-one (42) in 88% yield, whose structure was confirmed by its IR and $^1$H-NMR spectral data.
Synthesis of 6-bromo-3-(4'-methylbenzylidene)chroman-4-one (43)

A mixture of 6-bromochroman-4-one (39), 4-methylbenzaldehyde (30), and anhydrous barium hydroxide on grinding in a mortar with pestle at room temperature followed by working up as described above gave 6-bromo-3-(4'-methylbenzylidene)chroman-4-one (43) in 86% yield. Identity of the compound was confirmed by its IR and $^1$H-NMR spectral data.

\[
\begin{array}{c}
\text{Br} \\
\text{O} \\
\text{39} \\
\end{array}
+ 
\begin{array}{c}
\text{CHO} \\
\text{CH}_3 \\
\text{30} \\
\end{array}
\xrightarrow{\text{anhydrous Ba(OH)$_2$; r.t.}}
\begin{array}{c}
\text{Br} \\
\text{O} \\
\text{43} \\
\end{array}
\]

Synthesis of 6-bromo-3-(2',4'-dimethoxybenzylidene)chroman-4-one (45)

A mixture of 6-bromochroman-4-one (39), 2,4-dimethoxybenzaldehyde (44), and anhydrous barium hydroxide was ground well in a mortar with pestle for 5 minutes and left at room temperature for another 15 minutes. It was worked up as described earlier to give 6-bromo-3-(2',4'-dimethoxybenzylidene)chroman-4-one (45) in 89% yield, whose Identity was confirmed by its IR and $^1$H-NMR spectral data.

\[
\begin{array}{c}
\text{Br} \\
\text{O} \\
\text{39} \\
\end{array}
+ 
\begin{array}{c}
\text{CHO} \\
\text{OCH}_3 \\
\text{OCH}_3 \\
\text{44} \\
\end{array}
\xrightarrow{\text{anhydrous Ba(OH)$_2$; r.t.}}
\begin{array}{c}
\text{Br} \\
\text{O} \\
\text{OCH}_3 \\
\text{45} \\
\end{array}
\]

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Experimental

Phenoxy propanoic acid (19)

A solution of 3-chloropropanoic acid (60 g, 0.5 mol), neutralized with 10% sodium bicarbonate solution was added in small quantities to a hot solution (80-90°C) of phenol (18; 47 g, 0.5 mol) dissolved in aqueous potassium hydroxide (60 g dissolved in 200 ml H₂O) during one hour. The reaction mixture was further heated for 3 hours on oil bath at 80 to 90°C, cooled, and acidified with conc. HCl. It was extracted with ether and the ethereal layer repeatedly washed with aqueous NaHCO₃ solution. The aqueous layer was acidified with conc. HCl. The solid that precipitated out was filtered, washed with water and dried to give 3-phenoxy propanoic acid (19; 30 g), m.p. 97-98°C (lit. m.p. 98-100°C).

Polyphosphoric (PPA)

Phosphorous pentoxide (10 g) and phosphoric acid (5 g) thoroughly mixed by glass rod were irradiated with microwaves in a round bottom flask for 30 seconds (6 x 5 sec.) using 40% power (360W) of the oven with shaking after each interval of 5 seconds. The mixture was then cooled to room temperature, when polyphosphoric acid was obtained as a yellow creamish viscous liquid.

Chroman-4-one (20)

Phenoxy propanoic acid (19; 15 g) was added to freshly prepared polyphosphoric acid (10 ml) in a round bottom flask fitted with guard tube and was thoroughly mixed by glass rod. The resulting mixture was then irradiated with microwaves for 30 seconds (6 x 5 sec.) using 40% power of the oven with shaking after each interval of 5 seconds. Pasty residue so obtained was decomposed with crushed ice (50 g). Cold suspension was then extracted with diethyl ether, washed with 10% aqueous sodium bicarbonate (2 x 25 ml) followed by water and dried over magnesium sulphate. The solvent was removed by distillation and residue thus obtained was recrystallised form petroleum ether-diethyl ether mixture to give chroman-4-one (20; 10.5 g) m.p. 38-40°C (lit. m.p. 38.5°C).

IR (KBr): 1692 cm⁻¹ (C=O).

3-Benzylidenechroman-4-one (1)

Chroman-4-one (20; 0.6 g), benzaldehyde (21; 0.42 ml) and anhydrous barium hydroxide (2.5 g) were ground together in mortar with pestle for 5 minutes and the resulting mixture in mortar was left at room temperature for 5 minutes. Progress of the reaction was checked on TLC, and the reaction was found to be completed. Ice cold water (30 ml) was
added to the reaction mixture and acidified with conc. HCl. The solid that separated out was filtered, washed with water and recrystallised from petroleum ether-diethyl ether mixture, to give 3-benzylidenechroman-4-one (1; 0.85 g), m.p. 111-12°C (lit. m.p. 112°C). IR (KBr): 1664 cm⁻¹ (C=O).

H-NMR (CDCl₃): 6 5.35 (d, J = 1.84 Hz, 2H, -O-CH₂-), 6.82-6.98 (m, 8H, H-6, H-7, H-8, H-2', H-3', H-4', H-5', H-6'), 7.88 (s, 1H, = CH-), 8.03 (dd, J = 1.72 Hz & 7.88 Hz, 1H, H-5).

3-(4'-Methoxybenzylidene)chroman-4-one (23)

A mixture of chroman-4-one (20; 0.6 g), anisaldehyde (22; 0.5 ml) and anhydrous barium hydroxide (2.5 g) was ground well in a mortar with pestle for 5 minutes and reaction mixture was left at room temperature for 5 minutes. The reaction was found to be completed when checked on TLC. Ice cold water (30 ml) was added to the reaction mixture and acidified with conc. HCl. The solid that separated out was filtered, washed with water and recrystallised from petroleum ether-diethyl ether mixture to give 3-(4'-methoxybenzylidene)chroman-4-one (23; 0.92 g), m.p. 130-32°C (lit. m.p. 133-34°C). IR (KBr): 1664 cm⁻¹ (C=O).

H-NMR (CDCl₃): 6 3.86 (s, 3H, OCH₃), 5.38 (d, J = 1.80 Hz, 2H, -OCH₂-), 6.95-7.50 (m, 7H, H-6, H-7, H-8, H-2', H-3', H-5', H-6'), 7.84 (s, 1H, = CH-Ph), 8.02 (dd, J = 1.64 Hz & 7.84 Hz, 1H, H-5).

3-(3'-Methoxybenzylidene)chroman-4-one (25)

A mixture of chroman-4-one (20; 0.6 g), 3-methoxybenzaldehyde (24; 0.5 ml) and anhydrous barium hydroxide (2.5 g) was ground well in a mortar with pestle for 5 minutes and reaction mixture was left at room temperature for another 10 minutes. The completion of the reaction was checked on TLC. Ice cold water (30 ml) was added to the reaction mixture and acidified with conc. HCl. The solid that separated out was filtered washed with water and recrystallised from petroleum ether-diethyl ether mixture to give greenish yellow crystals of 3-(3'-methoxybenzylidene)chroman-4-one (25; 0.9 g), m.p. 103-04°C (lit. m.p. 103-04°C). IR (KBr): 1665 cm⁻¹ (C=O).

H-NMR (CDCl₃): 6 3.84 (s, 3H, OCH₃), 5.35 (d, J = 1.84 Hz, 2H, -OCH₂-), 6.84-6.98 (m, 5H, H-8, H-2', H-4', H-5', H-6'), 7.26-7.51 (m, 2H, H-6, H-7), 7.84 (s, 1H, = CH-Ph), 8.02 (dd, J = 1.72 Hz & 7.88 Hz, 1H, H-5).
4-Methylphenoxy propanoic acid (27)

A solution of 3-chloropropanoic acid (60 g) neutralized with 10% aqueous sodium bicarbonate solution was added in small quantities to a hot solution (80-90°C) of p-cresol (26; 52 ml) dissolved in aqueous potassium hydroxide (60 g dissolved in 200 ml H₂O) during one hour. The reaction mixture was further heated for 3 hours on oil bath at 80 to 90°C, cooled and acidified with conc. HCl. It was extracted with ether and the ethereal layer was repeatedly washed with aqueous NaHCO₃ solution. The aqueous layer was acidified with conc. HCl. The solid that precipitated out was filtered, washed with water and dried to give 4-methylphenoxy propanoic acid (27; 36.0 g), m.p. 145-46°C (lit. m.p. 145-48°C).43

6-Methylchroman-4-one (28)

4-Methylphenoxy propanoic acid (27; 15 g) was added to freshly prepared polyphosphoric acid (10 ml) in a round bottom flask fitted with guard tube and the reaction mixture was thoroughly mixed by glass rod. The resulting mixture was then irradiated with microwaves in an oven for 30 seconds (6 × 5 sec.) using 40% power of the oven with shaking after each interval of 5 seconds. Pasty residue so obtained was decomposed with crushed ice (50 g). Cold suspension was extracted with diethyl ether, washed with 10% aqueous sodium bicarbonate (2 × 25 ml) followed by water and dried over magnesium sulphate. The solvent was removed by distillation and residue obtained was recrystallised from petroleum ether-diethyl ether mixture to give 6-methylchroman-4-one (28; 10.0 g), m.p. 35-36°C (lit. m.p. 35-36°C).44

IR (KBr): 1698 cm⁻¹ (C=O).

6-Methyl-3-benzylidenechroman-4-one (29)

6-Methylchroman-4-one (28; 0.65 g), benzaldehyde (21; 0.42 ml) and anhydrous barium hydroxide (2.5 g) were ground together in a mortar with pestle for 5 minutes and reaction mixture was left at room temperature for another 10 minutes. Completion of the reaction was checked on TLC. Ice cold water (30 ml) was added to the reaction mixture and acidified with conc. HCl. Solid that separated out was filtered, washed with water and recrystallised form petroleum ether-diethyl mixture to give 6-methyl-3-benzylidenechroman-4-one (29; 0.87 g) m.p. 146-47°C (lit. m.p. 147-48°C).45

IR (KBr): 1668 cm⁻¹ (C=O).
6-Methyl-3-(4'-methylbenzylidene)chroman-4-one (31)

6-Methylchroman-4-one (28; 0.65 g) 4-methylbenzaldehyde (30; 0.48 ml) and anhydrous barium hydroxide (2.5 g) were ground together in a mortar with pestle for 5 minutes and the reaction mixture was left at room temperature for another 10 minutes. Completion of the reaction was checked on TLC. Ice cold water (30 ml) was added to the reaction mixture and acidified with conc. HCl. Yellow solid that separated out was filtered, washed with water and recrystallised form petroleum ether-diethyl ether mixture to give 6-methyl-3-(4'-methylbenzylidene)chroman-4-one (31; 0.87 g), m.p. 126-28°C.

IR (KBr): 1667 cm⁻¹ (C=O).

Found: C, 81.72; H, 6.08; C₁₈H₁₆O₂ requires: C, 81.79; H, 6.10.

1H-NMR (CDCl₃): δ 3.04 & 3.30 (each s, 6H, 2 × CH₃), 5.33 (d, 2H, -OCH₂-, J = 1.84 Hz), 6.86 (d, J = 8.4 Hz, 1H, H-8), 7.20-7.31 (m, 5H, H-7, H-2', H-3', H-5', H-6'), 7.81 (d, J = 1.80 Hz, 1H, H-5), 7.55 (s, 1H, = CH - Ph).

6-Methyl-3-(4'-methoxybenzylidene)chroman-4-one (32)

6-Methylchroman-4-one (28; 0.65 g), anisaldehyde (22; 0.5 ml), and anhydrous barium hydroxide (2.5 g) were ground well in a mortar with pestle for 5 minutes and the reaction mixture was left at room temperature for another 10 minutes. Completion of the reaction was checked on TLC. Ice cold water (30 ml) was added to the reaction mixture and acidified with conc. HCl. The yellow solid that separated out was filtered, washed with water and recrystallised from petroleum ether-diethyl ether mixture to give 6-methyl-3-(4'-methoxybenzylidene)chroman-4-one (32; 0.98 g), m.p. 108-10°C.

IR (KBr): 1667 cm⁻¹ (C=O).

Found: C, 77.10; H, 5.71; C₁₈H₁₆O₃ requires: C, 77.12; H, 5.75.

1H-NMR (CDCl₃): δ 2.34 (s, 3H, CH₃), 3.84 (s, 3H, OCH₃), 5.35 (d, J = 1.8 Hz, 2H, -O-CH₂), 6.87 (d, J = 8.4 Hz, 1H, H-8), 6.8 - 7.59 (m, 5H, H-7, H-2', H-3', H-5', H-6'), 7.74 (d, 1H, H-5, J = 1.8 Hz), 7.85 (s, 1H = CH - Ph).

2-Methylphenoxy propanoic acid (34)

A solution of 3-chloropropanoic acid (60 g) neutralized with 10% aqueous sodium bicarbonate solution was added in small quantities to a hot solution (80-90°C) of o-cresol
(33; 51 ml) dissolved in aqueous potassium hydroxide (60 g dissolved in 200 ml H₂O) during one hour. The reaction mixture was further heated for 3 hours on oil bath at 80 to 90°C, cooled and acidified with conc. HCl. It was extracted with ether and the ethereal layer was repeatedly washed with aqueous NaHCO₃ solution. The aqueous layer was acidified with conc. HCl. The solid that precipitated out was filtered, washed with water and dried to give 2-methylphenoxy propanoic acid (34; 20 g), m.p. 85-86°C.

8-Methylchroman-4-one (35)

2-Methylphenoxy propanoic acid (34; 15 g) was added to freshly prepared polyphosphoric acid (10 ml) in a round bottom flask fitted with guard tube and the reaction mixture was thoroughly mixed with glass rod. The resulting mixture was then irradiated with microwaves in an oven for 30 seconds (6 x 5 sec.) using 40% power of the oven with shaking after each interval of 5 seconds. Pasty residue so obtained was decomposed with crushed ice (50 g). Cold suspension was extracted with diethyl ether, washed with 10% aqueous sodium bicarbonate (2 x 25 ml) followed by water and dried over magnesium sulphate. The solvent was removed by distillation and residue obtained was recrystallised from petroleum ether-diethyl ether to give 6-methylchroman-4-one (35; 7.0 g), m.p. 30-31°C (lit. m.p. 29.5°C).⁴⁶ IR (KBr): 1695 cm⁻¹ (C=O).

8-Methyl-3-(4'-methoxybenzylidene)chroman-4-one (36)

8-Methylchroman-4-one (35; 0.65 g), anisaldehyde (22; 0.5 ml) and anhydrous barium hydroxide (2.5 g) were ground well in a mortar with pestle for 5 minutes and reaction mixture was left at room temperature for another 5 minutes. Completion of the reaction was checked on TLC. Ice cold water (30 ml) was added to the reaction mixture and acidified with conc. HCl. Solid product that separated out was filtered, washed with water and recrystallised form petroleum ether-diethyl ether mixture to give 8-methyl-3-(4'-methoxybenzylidene)chroman-4-one (36; 0.94 g), m.p. 105-06°C.

IR (KBr): 1664 cm⁻¹ (C=O).

**Found:** C, 77.08; H, 5.69; C₁₈H₁₆O₃ requires: C, 77.12; H, 5.75.

¹H-NMR (CDCl₃): δ 2.32 (s, 3H, CH₃), 3.86 (s, 3H, OCH₃), 5.40 (d, J = 1.8 Hz, 2H, O-CH₂-), 6.94-6.98 (m, 3H, H-3', H-5', H-7), 7.26-7.35 (m, 3H, H-6, H-2', H-6'), 7-82-7.88 (m, 2H, =CH-, H-5).
4-Bromophenoxy propanoic acid (38)

A solution of 3-chloropropanoic acid (30 g) neutralized with 10% aqueous sodium bicarbonate solution was added in small quantities to a hot solution (80-90°C) of p-bromophenol (37; 43 g) dissolved in aqueous potassium hydroxide (40 g dissolved in 150 ml H₂O) during one hour. The reaction mixture was further heated for 3 hours on oil bath at 80 to 90°C, cooled, acidified with conc. HCl. and was extracted with ether. The ether layer was repeatedly washed with aqueous sodium bicarbonate solution. The aqueous layer was acidified with conc. HCl. The solid that precipitated out was filtered, washed with water and dried to give 4-bromophenoxy propanoic acid (38; 30 g), m.p. 140-141°C.

6-bromochroman-4-one (39)

4-Bromophenoxy propanoic acid (38; 15 g) was added to freshly prepared polyphosphoric acid (10 ml) in a round bottom flask fitted with guard tube and the reaction mixture was thoroughly mixed by glass rod. The resulting mixture was then irradiated with microwaves in an oven for 30 seconds (6 × 5 sec.) using 40% power of the oven with shaking after each interval of 5 seconds. Pasty residue so obtained was decomposed with crushed ice (50 g) and cold suspension was extracted with diethyl ether, washed with 10% aqueous sodium bicarbonate (2 × 25 ml) followed by water and dried over magnesium sulphate. The solvent was removed by distillation and residue so obtained was recrystallised from petroleum ether-diethyl ether to give 6-bromochroman-4-one (39; 8.0 g), m.p. 78-79°C (lit. m.p. 77-79°C)47.

IR (KBr): 1700 cm⁻¹ (C=O).

6-Bromo-3-benzylidenechroman-4-one (40)

A mixture of 6-bromochroman-4-one (39; 0.8 g), benzaldehyde (21; 0.37 ml) and anhydrous barium hydroxide (2.5 g) was ground well in a mortar with pestle for 5 minutes and reaction mixture was left at room temperature for another 10 minutes. Completion of the reaction was checked on TLC. Ice cold water (30 ml) was added to the reaction mixture and acidified with conc. HCl. Solid that separated out was filtered, washed with water and recrystallised form petroleum ether diethyl ether to give 6-bromo-3-benzylidenechroman-4-one (40; 10 g), m.p. 158-160°C.

IR (KBr): 1670 cm⁻¹ (C=O).

Found: C, 60.95; H, 3.50; C₁₆H₁₁BrO₂ requires: C, 60.98; H, 3.52;
\[^{1}\text{H-NMR (CDCl}_3\text{): } \delta 5.35 \text{ (d, } J = 1.84 \text{ Hz, } 2\text{H, -OCH}_2\text{-), 6.88 \text{ (d, } J = 8.8 \text{ Hz, } 1\text{H, H-8), 7.26-7.32} \text{ (m, } 3\text{H, H-3', H-4', H-5'), 7.44-7.46} \text{ (m, } 2\text{H, H-2', H-6'), 7.55-7.58 \text{ (dd, } J = 2.52 \text{ Hz, & 8.76 Hz, } 1\text{H, H-7), 7.89 \text{ (s, } 1\text{H, = CH-), 8.13 \text{ (s, } 1\text{H, H-5).}}\]

6-Bromo-3-(4'-methoxybenzylidene)chroman-4-one (41)

A mixture of 6-bromochroman-4-one (39; 0.8 g), anisaldehyde (22; 0.44 ml) and anhydrous barium hydroxide (2.5 g) was ground well in a mortar with pestle for 5 minutes and left at room temperature for another 10 minutes. Completion of the reaction was checked on TLC. Ice cold water (30 ml) was added to the reaction mixture and acidified with conc. HCl. Pale yellow solid that separated out was filtered, washed with water and recrystallised form petroleum ether-diethyl ether to give 6-bromo-3-(4'-methoxybenzylidene)chroman-4-one (41; 1.1 g), m.p. 166-68\(^\circ\)C.

IR (KBr): 1670 cm\(^{-1}\)(C=O).

Found: C, 59.11; H, 3.78; C\(_{17}\)H\(_{13}\)BrO\(_3\) requires: C, 59.15; H, 3.80;

\[^{1}\text{H-NMR (CDCl}_3\text{): } \delta 3.86 \text{ (s, } 3\text{H, OCH}_3\text{), 5.37 \text{ (d, } J = 1.8 \text{ Hz, } 2\text{H, -OCH}_2\text{-), 6.87 \text{ (d, } J = 8.8 \text{ Hz, 1H, H-8), 6.96-6.98} \text{ (m, } 2\text{H, H-3', H-5'), 7.26-7.29} \text{ (m, } 2\text{H, H-2', H-6'), 7.53 \text{ (dd, } J = 2.56 \text{ & 8.8 Hz, 1H, H-7), 7.84 \text{ (s, } 1\text{H, = CH-), 8.11 \text{ (d, } J = 2.52 \text{ Hz, 1H, H-5).}}\]

6-Bromo-3-(3'-methoxybenzylidene)chroman-4-one (42)

A mixture of 6-bromochroman-4-one (39; 0.8 g), 3-methoxybenzaldehyde (24; 0.44 ml) and anhydrous barium hydroxide (2.5 g) was ground well in a mortar with pestle for 5 minutes and left at room temperature for another 10 minutes. Completion of the reaction was checked on TLC. Ice cold water (30 ml) was added to the reaction mixture and acidified with conc. HCl. Brownish solid that separated out was filtered, washed with water and recrystallised form petroleum ether-diethyl ether to give 6-bromo-3-(3'-methoxybenzylidene)chroman-4-one (42; 1.0 g), m.p. 112-13\(^\circ\)C.

IR (KBr): 1669 cm\(^{-1}\)(C=O).

Found: C, 59.12; H, 3.74; C\(_{17}\)H\(_{13}\)BrO\(_3\) requires: C, 59.15; H, 3.80;

\[^{1}\text{H-NMR (CDCl}_3\text{): } \delta 3.84 \text{ (s, } 3\text{H, OCH}_3\text{), 5.35 \text{ (d, } J = 1.84 \text{ Hz, } 2\text{H, -OCH}_2\text{-), 6.82-6.98} \text{ (m, } 4\text{H, H-8, H-2', H-4', H-5'), 7.37 \text{ (t, } 1\text{H, H-6'), 7.57 \text{ (dd, } J = 2.52 \text{ & 8.76 Hz, 1H, H-7), 7.85 \text{ (s, } 1\text{H, = CH-), 8.13 \text{ (d, } J = 2.51 \text{ Hz, 1H, H-5).}}\]

6-Bromo-3-(4'-methylbenzylidene)chroman-4-one (43)

A mixture of 6-bromochroman-4-one (39; 0.8 g), 4-methylbenzaldehyde (30; 0.42 ml) and anhydrous barium hydroxide (2.5 g) was ground well in a mortar with pestle for 5 minutes
and left at room temperature for another 10 minutes. Completion of the reaction was checked on TLC. Ice cold water (30 ml) was added to the reaction mixture and acidified with conc. HCl. Light yellow solid that separated out was filtered, washed with water and recrystallised form petroleum ether-diethyl ether to give 6-bromo-3-(4'-methylbenzylidene)chroman-4-one (43; 1.0 g), m.p. 156-58°C.

IR (KBr): 1670 cm⁻¹ (C=O).

Found: C, 61.98; H, 3.95; C₁₂H₁₃BrO₂ requires: C, 62.03; H, 3.98;

¹H-NMR (CDCl₃): δ 2.41 (s, 3H, CH₃), 5.36 (d, J = 1.88 Hz, 2H, -OCH₂-), 6.87 (d, J = 8.76 Hz, 1H, H-8), 7.21 (d, J = 8.16 Hz, 2H, H-3', H-5'), 7.25-7.27 (m, 2H, H-2', H-6'), 7.55 (dd, J = 2.52 & 8.8 Hz, 1H, H-7), 7.86 (s, 1H, = CH-), 8.12 (d, J = 2.56 Hz, 1H, H-5).

6-Bromo-3-(2',4'-dimethoxybenzylidene)chroman-4-one (45)

A mixture of 6-bromochroman-4-one (39; 0.8 g), 2,4-dimethoxybenzaldehyde (44; 0.6 g) and anhydrous barium hydroxide (2.5 g) was ground well in a mortar with pestle for 5 minutes and left at room temperature for another 15 minutes. Completion of the reaction was checked on TLC. Ice cold water (30 ml) was added to the reaction mixture and acidified with conc. HCl. Pale yellow solid that separated out was filtered, washed with water and recrystallised form petroleum ether-diethyl ether to give 6-bromo-(2',4'-dimethoxy benzylidene)chroman-4-one (45; 1.1 g), m.p. 166-68°C.

IR (KBr): 1668 cm⁻¹ (C=O).

Found: C, 57.58; H, 4.0; C₁₈H₁₃BrO₄ requires: C, 57.62; H, 4.03;

¹H-NMR (CDCl₃): δ 3.85 (s, 6H, 2 × OCH₃), 5.25 (d, J = 1.72 Hz, 2H, -OCH₂-), 6.49-6.54 (m, 2H, H-3', H-5'), 6.85 (d, J = 8.8 Hz, 1H, H-8), 6.98 (d, J = 8.4 Hz, 1H, H-6'), 7.53 (dd, J = 2.56 & 8.76 Hz, 1H, H-7), 8.01 (s, 1H, = CH-), 8.12 (d, J = 2.52 Hz, 1H, H-5).
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