Chapter II

Synthesis of Novel Flavones and Chromones
Synthesis of

- 2-(3, 5-difluorophenyl)-4H-chromen-4-ones
- 2-(3-(5-bromothiophen-2-yl)-1-phenyl-1H-pyrazol-4-yl)-4H-chromen-4-ones
- 2-(3-(4-fluorophenyl)-1-phenyl-1H-pyrazol-4-yl)-4H-chromen-4-ones
- 2-(3-(5-bromothiophen-2-yl)-1-phenyl-1H-pyrazol-4-yl)-3-chloro-4H-chromen-4-ones
2.1 Introduction

Flavonoids are a group of naturally occurring polyphenolic compounds that are widely found in the plant kingdom. They serve as dietary supplements and occur naturally as plant pigments in a broad range of fruits, nuts, seeds, flowers, barks and vegetables as well as beverages such as tea, coffee, beer and red wine [1]. According to an estimate, almost 4000 different flavonoids to date are part of daily human diet [2].

Flavonoids are C15 compounds composed of two aromatic rings linked through three carbon bridge with a carbonyl function located at one end of the bridge. They can be subdivided into several classes of flavonoids and flavonoids related compounds such as dihydrochalcone (1), chalcone (2), flavanones (4), isoflavones (5) and aurones (6) [3]. Structure (3), which forms the skeleton of a large class of flavonoids are known as flavone. (Fig. 1)

\[ \text{Fig. 1: Flavonoids and their sub-structures.} \]

As one of the most representative families of plant secondary metabolites, flavonoids have been found to be associated with a remarkable spectrum of biological and pharmacological activities. Flavonoids have been reported to exert multiple biological effects including antimicrobial [4], cytotoxicity [5], anti-inflammatory [6]. In last decades, medicinal chemists have paid great attentions on the isolation, screening and structural modifications of new flavonoids.
Most interestingly, it has been found recently that some flavonoids displayed anticancer activity with novel mechanisms, such as carcinogen inactivation, antiproliferation, cell cycle arrest, induction of apoptosis and differentiation, inhibition of angiogenesis, antioxidation and reversal of multidrug resistance [7]. The work of Hertog and co-workers showed the inverse correlation between flavonoids intake and coronary heart disease mortality [8]. Flavonoids have attracted the interest of researchers because they showed promising antioxidant activity which can protect the human body from free radicals [9-11]. Many flavonoids such as quercetin, luteolin, and catechins are better antioxidants than the nutrient antioxidants such vitamin C, Vitamin E and β-carotene [12]. The function of antioxidants is to intercept and react with free radicals at a faster rate than the substrate. Since free radicals are able to attack at a variety of targets including lipids, fats and proteins, it is believed that they may damage organisms, leading to disease, poisoning and in the form of ageing [13]. Several reviews have been written on the interaction between flavonoids and mammalian cells including comprehensive articles by Harborne and Williams [14] and Middleton et al. [15]. An extensive review on biochemistry and medical significance of flavonoids has recently been produced by Havsteen [16].

Heterocyclic compounds are widely distributed in natural products and comprise a huge number of biologically active compounds. Amongst the various heterocyclic systems, chromones are the most widely investigated. Chromones [17] have been the subject of the considerable chemical interest in the past decades. Chromones constitute one of the major classes of naturally occurring compounds and interest in their chemistry continues unabated because of their usefulness as biologically active agents [18] as well as pharmacological active agents [19]. Some of the biological activities attributed to chromone derivatives include cytotoxic (anticancer) [20-22], neuroprotective [23], HIV-inhibitory [24], antimicrobial [25, 26], antifungal [27] and antioxidant activity [28]. Due to their abundance in plants and their low mammalian toxicity, chromone derivatives are present in large amounts in the diet of humans [29]. Flavonoids [30] are the chromones that are also most abundantly distributed in nature. Peucenin [31], Eugenitol [32] and Isoeugenitol [33] are some commonly occurring chromones. The chromones are also well known for their antioxidant [34], biocidal [35], wound healing [36], anti-inflammatory [37], antiulcer [38], and immune stimulatory [39] activities.
Recently, some chromones are also reported as anti-HIV agents [40]. Khellin [41] (A) and 2,4-thiazolidinedione [42] (B) shown in (Fig. 2) are the chromones that are used as antispasmodic agents, in the treatment of angina pectoris and antidiabetic agents that improve peripheral insulin resistance in type-II diabetic patients.

![Structures of Khellin and 2, 4-thiazolidinedione](image)

\[ Y = S, \text{ NH, NMe, NEt}; Z = O, S \]

**Fig.2.** Structures of Khellin and 2, 4-thiazolidinedione

Chromones can be readily converted into a broad range of heterocyclic systems, *e.g.*, xanthones [43] and pyranobenzopyranones [44] by cycloaddition strategies, pyrazolopyrimidines [45], pyridopyrimidines [46], pyrimidopyrimidines [47], benzopyranobenzothiazepines, oxazepines, diazepines [48], furobenzopyranones [49], o-hydroxyphenyl substituted pyrazoles [50] and pyrimidines [51,52] can be accomplished by the reaction with several nucleophiles and particularly bis-nucleophiles.

Chromones constitute an important class of oxygen heterocycles [53]. 2-substituted chromones i.e. Flavonoids are widely distributed in nature in plant kingdom. Quercetin (1) (Fig. 3), the major individual nonpolymeric molecule among the polyphenols represents 60–75% of the flavonoid intake [53]. Quercetin is a very efficient antioxidant [54] and appears to be active against many diseases related to ageing such as cancer [55], cardiovascular [56] and neurodegenerative [57] diseases. In blood, quercetin is found mainly in metabolized form. The non-degradative metabolism of quercetin involves three main modifications of the phenolic hydroxyl groups: methylation, sulfation and glucuronidation [58]. Plasma analysis of pigs fed with quercetin-rich diets show that quercetin is absent and only methylated metabolites such as
4′-O-methylquercetin (2, tamarixetin) and 3′-O-methylquercetin (3, isorhamnetin, Fig. 2), mainly conjugated as glucuronides or sulfates [59], are present. Increasingly, the chromone or flavonoid chemistry is the subject of medical research due to the inherent biological properties displayed by them. They have been reported to possess many useful properties, including oestrogenic activity, enzyme inhibition, antimicrobial activity [60, 61], antiallergic activity, antioxidant activity [62], vascular activity and cytotoxic antitumor activity [63].

Fig. 3. Structures of quercetin and methylated metabolites.

Some of the chromones, especially those having heterocyclic substituents at C-2 and C-3 positions have good pharmacological activities viz. coronary spasmolytic and bronchodilatory activities useful in the treatment of asthma [64-69]. The synthesis of 3-substituted chromones appears worthy of study because they are important natural products like isoflavones and in medicines such as ipriflavone, an antiosteoporosis drug [70].
2.2 Methods of Synthesis of Flavones, Chromones and Chlorochromones.

Chromones and C-3 bearing chromones have been synthesized and investigated for long time. Chromones are in general synthesized by oxidative cyclization of respective chalcones. In literature various reagents were described which can brought about this cyclization. Some of the reagents include SeO$_2$ in amyl alcohol, sodium hypobromite, and catalytic iodine in DMSO. 3-halogenated chromones were obtained using different halogenating agents [71-75] shown in (Fig.4).

![Fig.4. Synthesis of chromones from chalcones using various reagents.](image-url)
i. Auwers Synthesis of Chromones

The Auwers synthesis is a series of organic reactions forming flavanols from a coumarone [76-78] (Scheme 2.01).

![Scheme 2.01](image)

ii. Algar-Flynn-Oyamada Reaction for the synthesis of Chromones

In this method a chalcone was oxidatively cyclized to flavanol [79, 80] (Scheme 2.02).

![Scheme 2.02](image)

iii. Synthesis of Chromone in Sealed Tube

Jawed Iqbal and co-workers [81] described an unusual protocol for 3-methyl sulphide chromone using I$_2$-DMSO-H$_2$SO$_4$ system in a sealed tube. 2'-hydroxy-4,4',6'-trimethoxychalcone was first heated at 100°C for 15 min. with dimethyl sulphoxide and a small amount of sulfuric acid, then a catalytic amount of iodine was added, and the mixture was heated in a sealed tube at 100°C for 2 hr to get 3-methylthio-5, 7, 4'-trimethoxyflavone (Scheme 2.03).

![Scheme 2.03](image)
iv. **Synthesis of chlorochromone under reflux condition**

Gill *et al.* [82] have reported the synthesis and antimicrobial screening of chlorochromones bearing pyrazoles (Scheme 2.04).

![Scheme 2.04]

v. **Synthesis of chromones under Microwave irradiation**

Mezene *et al.* [83] described the synthesis of flavones under microwave irradiation (Scheme 2.05).

![Scheme 2.05]

vi. **Cyclization of α-haloketones**

Jedidiah M. Hastings and co-workers recently, reported the synthesis of 3-chloro chromones from α-haloketones and mesityl chloride BF₃-Et₂O. Due to its unique architectural scaffold and proposed rapid assembly, the synthesis of this natural product was pursued with the aim of identifying structure activity relationships. Synthesis of the natural product was accomplished in eight highly convergent steps, which led to a facile method for the construction of related compounds. Biological evaluation of derrubone and its analogues identified several compounds that exhibit low micromolar inhibitory activity against breast and colon cancer cell lines [84] (Scheme 2.06).
vii. Microwave induced oxidative cyclization of chalcones

Gill and co-workers recently, reported microwave induced synthesis of Flavones and 3- chloro chromones by using DMSO/I₂ and DMSO/CuCl₂ under the influence of microwave irradiation [85]. (Scheme 2.07)

viii. By halogenations of β-diketone

Makrandi and co-workers reported Selective chlorination and bromination of 1-(2-hydroxyphenyl)-3-phenylpropane-1,3-diones with ammonium chloride/ammonium bromide and hydrogen peroxide in biphasic medium using phase transfer catalysis [86] (Scheme 2.08).

ix. Microwave- assisted synthesis of flavones and chromones

George W. Kabalka and Arjun R. Mereddy reported a high yield synthesis of flavones and chromones via dehydrative cyclization of 1, 3-propanediones in ethanol, in presence of CuCl₂ under microwave irradiation[87] (Scheme 2.09).
Scheme 2.09

x. Synthesis of chromones from 1, 3 diketone under microwave irradiation

J. Jayashankaran et al. reported a high yield synthesis of chromones via Knoevenagel hetero Diels–Alder reactions between 3-methyl/phenyl-5-(3-methyl-but-2-enylsulfanyl)-1-phenyl-1H-pyrazole-4-carbaldehyde and unsymmetrical 1, 3-diones and K-10 Montmorillonite clay was thoroughly ground in a mortar. The reaction mixture was irradiated using a domestic microwave oven [88] (Scheme 2.10).

Scheme 2.10

xi. Synthesis of flavones and chromones using a Wells-Dawson heteropolyacid as catalyst

Daniel O. Bennardi et al described the use of bulk and silica-supported Wells-Dawson acid (H_2P_2W_{18}O_{62}.24H_2O) as reusable, heterogeneous catalysts to obtain substituted flavones and chromones for the cyclization of 1-(2-hydroxyphenyl)-3-aryl-1,3-propanediones [89] (Scheme 2.11).
xii. Transition-metal-free intramolecular Ullmann-type O-arylation leading to chromones

Jie Zhao et al synthesized chromone derivatives using substituted 1-(2-bromophenyl)-1,3-diones by intramolecular O-arylation under optimized reaction conditions (one equivalent of K$_2$CO$_3$, DMF, 100°C, under air), to give the products in good to excellent yields [90] (Scheme 2.12).

\[
\begin{align*}
\text{X} &\quad= \text{Br, Cl} \\
\text{Y} &\quad= \text{CH, N}
\end{align*}
\]

Scheme 2.12

xiii. Synthesis of Chromones via Palladium-Catalyzed Ligand-Free Cyclocarbonylation of o-Iodophenols with Terminal Acetylenes in Phosphonium Salt Ionic Liquids

Qian Yang and Howard Alper synthesized chromone derivatives by the highly efficient and selective palladium-catalyzed ligand-free cyclocarbonylation reaction of o-iodophenols with terminal acetylenes and CO in the phosphonium salt ionic liquid, C$_{14}$H$_{29}$(C$_6$H$_{13}$)$_3$P$^+$Br$^-$, in good to excellent yields under atmospheric CO pressure [91] (Scheme 2.13).

\[
\begin{align*}
\text{R} &\quad= \text{Phenyl, Furfuryl, 1-Naphthyl, 2-Naphthyl}
\end{align*}
\]

Scheme 2.11
Synthesis of 4H-Chromen-4-ones via Intramolecular Wittig Reaction

Pradeep Kumar et al reported new and simple route to chromones via intramolecular ester carbonyl olefination using (trimethylsilyl)methylenetriphenylphosphorane [92]

(Scheme 2.14).

\[
\begin{align*}
\text{R} & \quad \text{OCOR}_1 \\
\text{O} & \quad \text{OTBDMS} \\
\end{align*}
\]

+ \[
\text{Ph}_3\text{P} = \text{CHSiMe}_3
\]

\[
\begin{align*}
\text{R} & \quad \text{O} \\
\text{R} & \quad \text{R}_1
\end{align*}
\]

Scheme 2.14
2.3 Present Work

**Scheme A**

4(a-h) & 14(a-h)

**Scheme B**

9(a-h) & 15(a-h)

**Scheme C**

13(a-h) & 16(a-h)
Scheme D
2.4 Experimental

2.4A General procedure for the synthesis of 6-bromo-2-(3, 5-difluorophenyl)-4\textit{H}-chromen-4-one (14g) : Compound 4g was taken in 10ml ethanol and to this 4-5 drops of conc. hydrochloric acid was added. Reaction mixture was then heated under reflux for 1 hr, cooled and poured over crushed ice. The resulting product was separated by filtration and crystallized from ethanol. The compounds 14(a-h) were prepared by following the general procedure. Physical data are recorded in Table 4. Their structures have been confirmed by IR, $^1$HNMR and Mass spectral data.

2.4B General procedure for the synthesis of 2-(3-(5-bromothiophen-2-yl)-1-phenyl-1\textit{H}-pyrazol-4-yl)-6-chloro-4\textit{H}-chromen-4-one (15c): (0.25 gm, mmole) of chalcone 9c was dissolved in 15 mL of DMSO. To this reaction mixture catalytic amount of iodine (I$_2$) was added. The reaction mixture was heated in an oil bath for 4 hr at 120$^\circ$C. After completion of reaction (monitored by TLC), reaction mass was left overnight. 10 mL cold water was slowly added to the flask and the separated product was filtered, washed with water followed by dil. sodium thiosulphate solution for several times. It was again washed with water, dried under vacuum and crystallized from ethanol to yield 15c. The compounds 15(a-h) were prepared by following the general procedure. Physical data are recorded in Table 5. Their structures have been confirmed by IR, $^1$HNMR and Mass spectra.

2.4C General Procedure for the synthesis of 6-chloro-2-(3-(4-fluorophenyl)-1-phenyl-1\textit{H}-pyrazol-4-yl)-4\textit{H}-chromen-4-one (16c): The compounds 16(a-h) were prepared by following the above procedure. The physical data of the compounds 16(a-h) were recorded in Table 6. Their structures have been confirmed by $^1$H NMR, Mass and IR spectra.
2.4D General Procedure for the synthesis of 2-(3-(5-bromothiophen-2-yl)-1-phenyl-1H-pyrazol-4-yl)-3-chloro-4H-chromen-4-one (17c): (0.25 gm, 0.0007 mmole) of chalcone 9c was dissolved in 15 mL of DMSO. To this reaction mixture catalytic amount of cuprous chloride (CuCl₂) was added. The reaction mixture was heated in an oil bath for 4 hr at 120°C. After completion of reaction (monitored by TLC) reaction mass was left overnight. 10 mL cold water was slowly added to the flask and the separated product was filtered, washed with water followed by dil. HCl for several times. It was again washed with water, dried under vacuum and crystallized from ethanol to afford 17c. The physical data of the compounds 17(a-h) is recorded in Table 7. Their structures have been confirmed by ¹H NMR, Mass and IR spectra.
Table 4: Physical data of compounds (14a-h)

<table>
<thead>
<tr>
<th>Comp.</th>
<th>R₁</th>
<th>R₂</th>
<th>R₃</th>
<th>M.P. (°C)</th>
<th>Yield (%)</th>
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<tbody>
<tr>
<td>14a</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>164-166</td>
<td>79</td>
</tr>
<tr>
<td>14b</td>
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<td>H</td>
<td>CH₃</td>
<td>182-184</td>
<td>67</td>
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<td>14d</td>
<td>Cl</td>
<td>H</td>
<td>Cl</td>
<td>278-280</td>
<td>73</td>
</tr>
<tr>
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<td>H</td>
<td>F</td>
<td>188-190</td>
<td>71</td>
</tr>
<tr>
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<td>248-250</td>
<td>78</td>
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<tr>
<td>14g</td>
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<td>H</td>
<td>Br</td>
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<td>68</td>
</tr>
<tr>
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Table 5: Physical data of compounds (15a-h)

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<th>Comp.</th>
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<th>R₃</th>
<th>M.P. (°C)</th>
<th>Yield (%)</th>
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<td>86</td>
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<td>15b</td>
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<td>CH₃</td>
<td>248-250</td>
<td>87</td>
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<tr>
<td>15c</td>
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<td>H</td>
<td>Cl</td>
<td>240-242</td>
<td>52</td>
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<td>F</td>
<td>280-282</td>
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Table 6: Physical data of compounds (16a-h)

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<th>R₃</th>
<th>M.P. (°C)</th>
<th>Yield (%)</th>
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Table 7: Physical data of compounds (17a-h)

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<th>Comp.</th>
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<th>R₃</th>
<th>M.P. (°C)</th>
<th>Yield (%)</th>
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</table>
2.5 Spectral analysis

![Chemical structure](image)

**14g**

**IR (14g) (cm$^{-1}$):** 1136(C-Br), 1186(C-O), 1265(C-F), 1564(C=C), 1600(Ar C=C), 1635 (C=O).

**$^1$HNMR (14g) (DMSO)$\delta$ ppm:** 7.279(s, 1H, –C=CH), 7.524-7.569(t, 1H, Ar-H, $J$=9.2Hz & 8.8Hz), 7.854-7.945(m, 3H, Ar-H), 8.019-8.047 (dd, 1H, Ar-H, $J$=2.4Hz &2.4Hz), 8.107-8.113(d, 1H, Ar-H, $J$=2.4Hz).

**ES-MS (14g) (m/z):** 336.9(M+1), 339 (M+3).

![Chemical structure](image)

**15c**

**IR (15c)(cm$^{-1}$):** 715(C-Cl), 1076(Ar-Br), 1257(C-O), 1529(C=N), 1560(Ar-C=C), 1602(C=C), 1652(C=O).

**$^1$HNMR (15c) (CDCl$_3$)$\delta$ ppm: 6.626(s, 1H, Chromone-H), 7.077-7.084(d, 1H, Ar-H, $J$=2.8Hz), 7.165-7.172(d, 1H, Ar-H, $J$=2.9Hz), 7.401-7.422(d, 2H, Ar-H, $J$=8.5Hz), 7.512-7.531(t, 2H, Ar-H, $J$=7.6Hz), 7.625-7.646(d, 1H, Ar-H, $J$=8.1Hz), 7.764-7.784(d, 2H, Ar-H, $J$=7.7Hz), 8.196(s, 1H, Ar-H), 8.380(s, 1H, Pyrazole-H).

**ES-MS (15c) (m/z):** 483(M+1), 485(M+3), 487(M+5).
**16c**

**IR (16c) (cm$^{-1}$):** 741(C-Cl), 1235(C=O), 1509(C=N), 1557(Ar C=C), 1620(C=C) 1658(C=O).

**$^1$HNMR (16c) (CDCl$_3$)$\delta$ ppm: 6.406(s, 1H, Chromone-H), 7.134-7.191(m, 2H, Ar-H), 7.275-7.370(d, 1H, Ar-H), 7.394-7.420(m, 1H, Ar-H), 7.526-7.650(m, 5H, Ar-H), 7.784-7.809(m, 2H, Ar-H), 8.125-8.160(m, 1H, Ar-H), 8.449(s, 1H, Pyrazole-H).

**ES-MS (16c) (m/z):** 416.9(M+1), 418.9(M+3).

---

**17c**

**IR (17c) (cm$^{-1}$):** 717(C-Cl), 1080(Ar-Br), 1597, 1612(C=C), 1653(C=O).

**$^1$H NMR (17c) (CDCl$_3$)$\delta$ ppm: 6.955-6.964(d, 1H, Ar-H, $J$=3.6Hz), 7.003-7.012(d, 1H, Ar-H, $J$=3.6Hz), 7.261-7.280(d, 1H, Ar-H, $J$=7.6Hz), 7.393-7.430(m, 1H, Ar-H), 7.516-7.555(m, 1H, Ar-H), 7.638-7.644(d, 1H, Ar-H, $J$=2.4Hz), 7.660-7.667(d, 1H, Ar-H, $J$=2.8Hz), 7.778-7.795(m, 2H, Ar-H), 8.266-8.272(d, 1H, Ar-H, $J$=2.4Hz), 8.591(s, 1H, Pyrazole-H).

**ES-MS (17c) (m/z):** 517(M+1), 519(M+3), 521(M+5), 523(M+7).
IR (14g)

\[ \text{HNMR (14g)} \]
Mass (14g)

IR (15c)
$^1$HNMR (15c)

Mass (15c)
IR (16c)

\[\text{HNMR (16c)}\]
Mass (16c)

IR (17c)
$^1$HNMR (17c)

Mass (17c)
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