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Research Article

SYNTHESIS OF CHROMONES AND THEIR APPLICATIONS DURING THE LAST TEN YEARS

Hanaa A. Tawfik[1], Ewies F. Ewies[2] and Wageeh S. El-Hamouly[1]

[1]Department of Chemistry of Natural and Microbial Products, Pharmaceutical Industries Division, National Research Centre, Cairo, Egypt.
[2]Department of Organometallic and Organometalloid Chemistry, Chemical Industrial Division, National Research Centre, 12622, Dokki, Cairo, Egypt.

ABSTRACT

The present review represents a board description for the methods used in the synthesis of chromones and some of its derivatives. The rigid bicyclic chromone fragment has been classified as a privileged structure in drug discovery, due to its use in a wide variety of pharmacologically active compounds; few examples as therapeutic agents chromones are used as scaffolds for the development of bioactive compounds, the application in medicinal chemistry, such as preparation of fluorescence probes, due to photochemical properties of chromones have been also mentioned. This review is limited to the work done during the last ten years.

Keywords: Chromone, Synthesis, Reactions, Biological Activity, Applications, Drugs.

GENERAL INTRODUCTION

Chromone chemistry has been widely explored and extensively reviewed over the past few years. The following review is intended to give a broad overview of the synthesis of chromones and is by no means exhaustive. Particular attention has been given to the synthesis of chromones, since their uses and applications in last ten years.

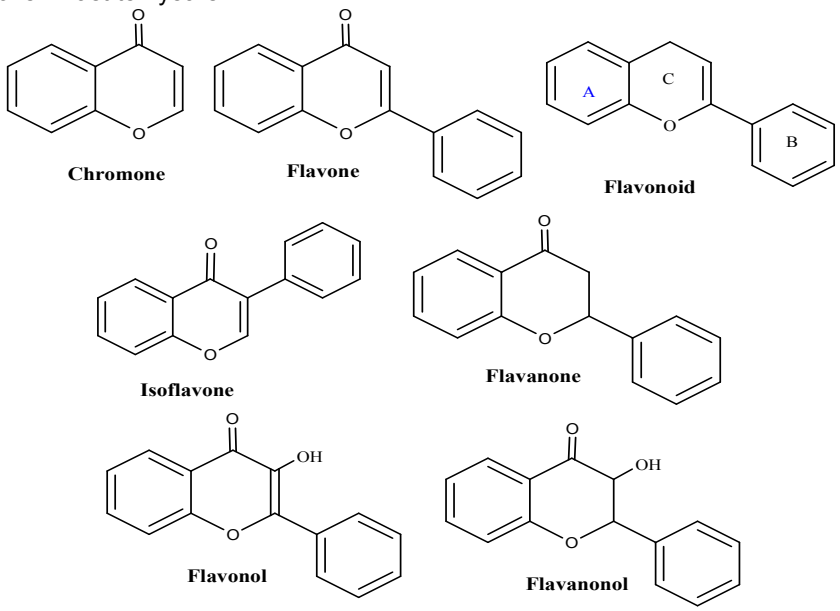


Fig. 1: Examples of common chromones(flavonoids) and their derivatives

1.1 Chromones

The chromone ring system, 1-benzopyran-4-one (Figure 2), is the core fragment in several flavonoids, such as flavones, flavonols and isoflavones[1]. The word chromones is derived from the Greek word chroma, meaning "color", which indicates that many chromone derivatives exhibit a broad variation of colors. The rigid bicyclic chromone fragment has been classified as a privileged structure in drug discovery, due to its use in a wide variety of pharmacologically active compounds such as anticancer[2], anti-HIV, antibacterial and anti-inflammatory agents[3-12]. Several chromone derivatives have also been reported to act as kinase inhibitors, to bind to benzodiazepine receptors and as efficient agents in the treatment of cystic fibrosis[13-15].

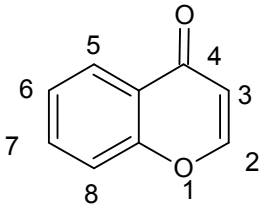


Fig. 2: The general structure and numbering of chromones

Although there are a large number of chromone derivatives known for their pharmacological properties there are only a few examples that have been or that are used as therapeutic agents today. Khellin (Figure 3)as an example extracted from the seeds of the plant *Ammi visnaga*, was the first chromone in clinical practice and it has been used for centuries in the Mediterranean area as a diuretic to relieve renal colic[16]. Around the 1950s, khellin was used as a smooth muscle relaxant in the treatment of angina pectoris and asthma[17]. However, present use of khellin as a therapeutic agent focuses on the treatment of vitiligo, a pigmentation disorder[18]. Other current medical treatments with chromone derivatives is exemplified by sodium cromoglycate (Lomudal®) used as a mast cell stabilizer in allergic rhinitis, asthma and allergic conjunctivitis; diosmin (Daflon®) for the treatment of venous diseases; flavoxate as smooth muscle relaxant to treat urge incontinence (Figure 5)[16,19-23].

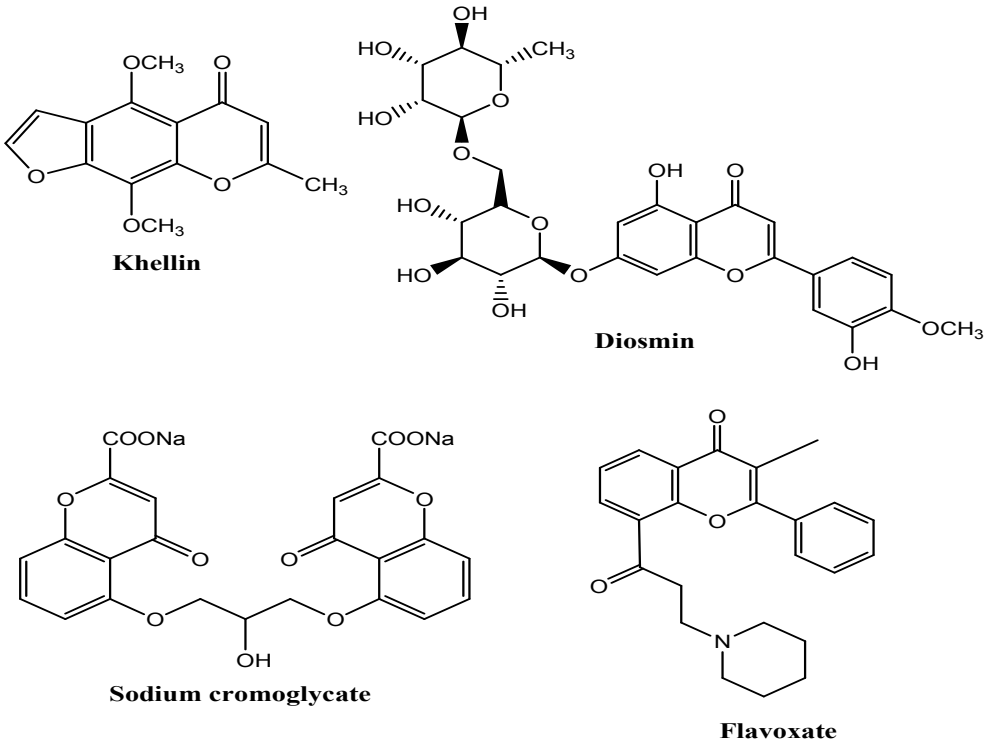


Fig. 3: Examples of chromone-based compounds that have been or that are used as pharmaceutical agents

Beside their diversity as structural scaffolds possible to modify to achieve different pharmacological activities, several chromone derivatives exhibit a wide range of fluorescent properties. In particular, the 3-hydroxyflavones have been used as hydrogen bonding sensors, fluorescent probes for DNA-binding affinity studies and as fluorophores for protein labeling and apoptosis[24-27].

1.2. Chromones as scaffolds for bioactive compounds

Chromones are used as scaffolds for the development of bioactive compounds. These frameworks are naturally occurring derivatives containing anoxa-pyran ring[28,29]. General structures of chromone moieties are illustrated in Figure 1. The most frequently found chromone-based natural products are the 2-arylsubstituted chromones (flavonoids) carrying hydroxy and/or methoxy groups on the Aand/or B rings[30,31]. They are constituents of pigments in leaves and are present in a range of food sources such as olive oil, tea, fruits, and red wine[32]. Flavonoids are well represented inthe literature[33,34].
The substitution pattern of the chromone scaffolds determines their different biological effects. Known effects of these types of compounds are antioxidant[35,36], antiviral[37], antibacterial[38], or kinase inhibition [39,40]. Hence, chromones can be considered privileged structures, defined as "*a single molecular framework ableto provide ligands for diverse receptors*"[41-43].

2. Synthesis of chromones

One of the first methods for the synthesis of chromones was introduced by Heywang and Kostanecki [44,45], which involved the decarboxylation of chromone-2-carboxylic acid. Since then, several other routes with higher yields and less drastic experimental conditions have been developed.

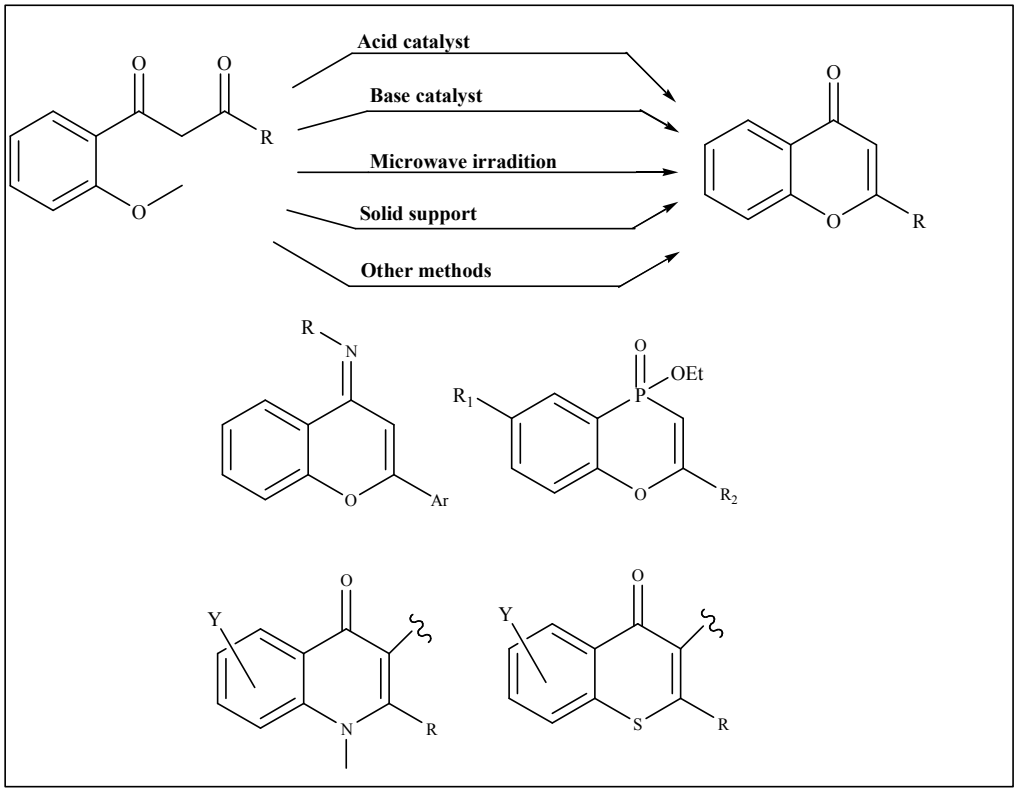
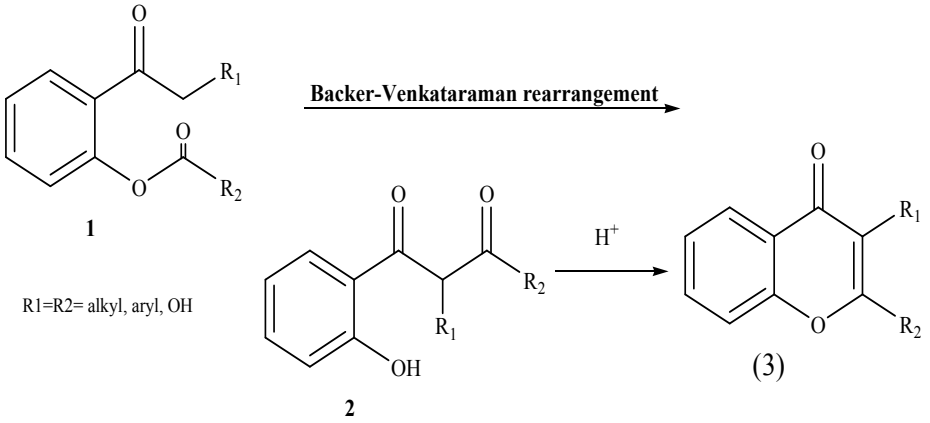


Fig. 4: Systematic diagram illustrate different synthetic methods of chromones derivatives

Chromones could be synthesized under either acidic or basic conditions. The classical, 3-disubstituted benzopyranone **3** synthesis utilized acidic conditions (Scheme 1) and was by far the most common method[46]. It proceeded through an intramolecular condensation of molecules such as **2**, which were usually obtained through a Baker–Venkataraman[47] rearrangement of compound **1**, or via a Claisen ester condensation[48] (Scheme 1). Most synthesis required harsh acidic conditions as the final step. On the other hand, synthesis utilizing basic conditions typically consisted of piperidine in

refluxing pyridine for several hours to affect ring closure. This was far less common[48]. Recently, microwave heating has also been used to affect ring cyclization[49].



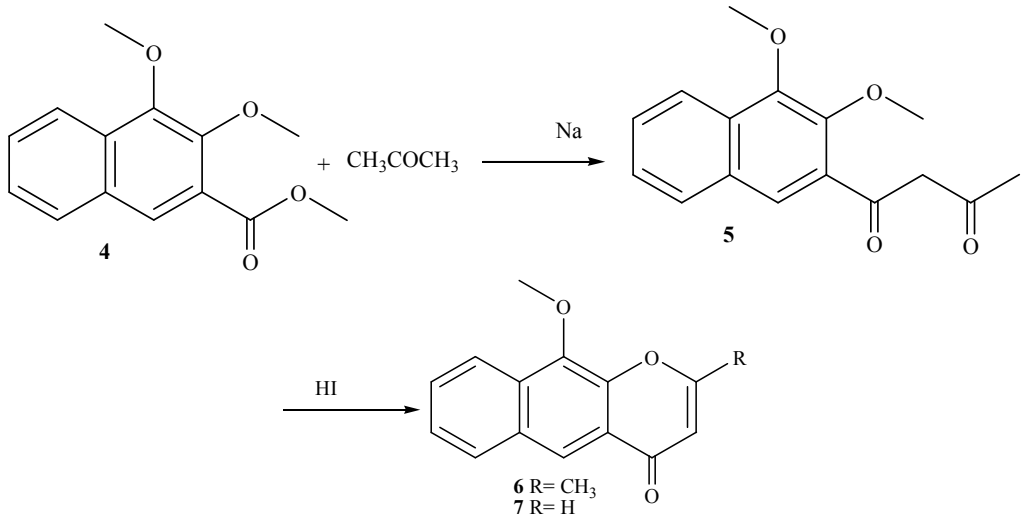
Scheme. 1:

2.1. Acid as catalyst in chromone ring closure.

Acid comprised a major catalyst in chromone ring closure, and many acids can be used including hydriodic acid, polyphosphoric acid (PPA), acetic acid, methanesulfonylchloride, hydrochloric acid, para toluene sulfonic acid (PTS), triflic anhydride, phosphorus oxychloride, perchloric acid, and sulfuric acid.

2.1.1. Hydriodic acid as a catalyst

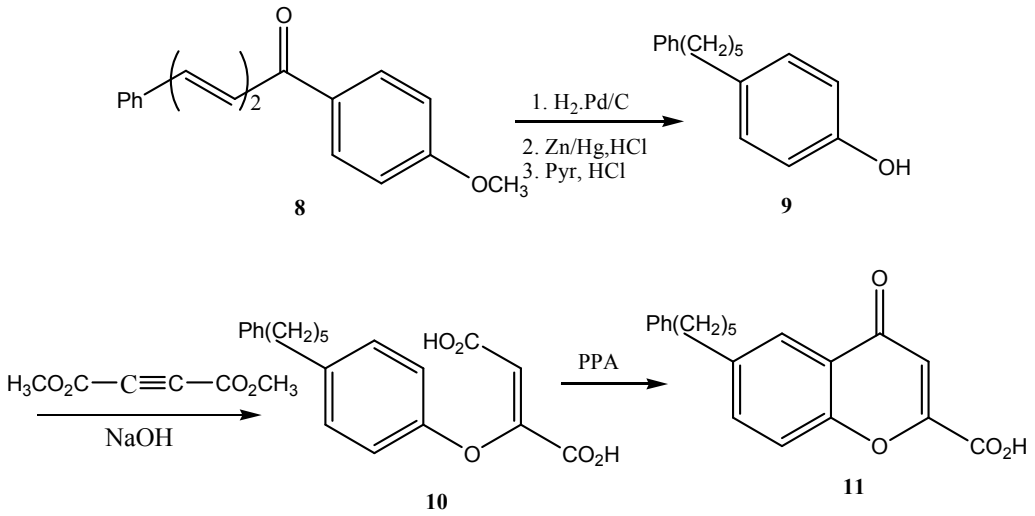
It has been reported[50] that synthesis of a mixture of 2-methyl-8-hydroxy-6,7-benzochromone (**7**) and 2-methyl-8-methoxy-6,7-benzochromone (**6**) using hydriodic acid as a catalyst in the ring closure (Scheme 2).



Scheme. 2:

2.1.2. Polyphosphoric acid as a catalyst.

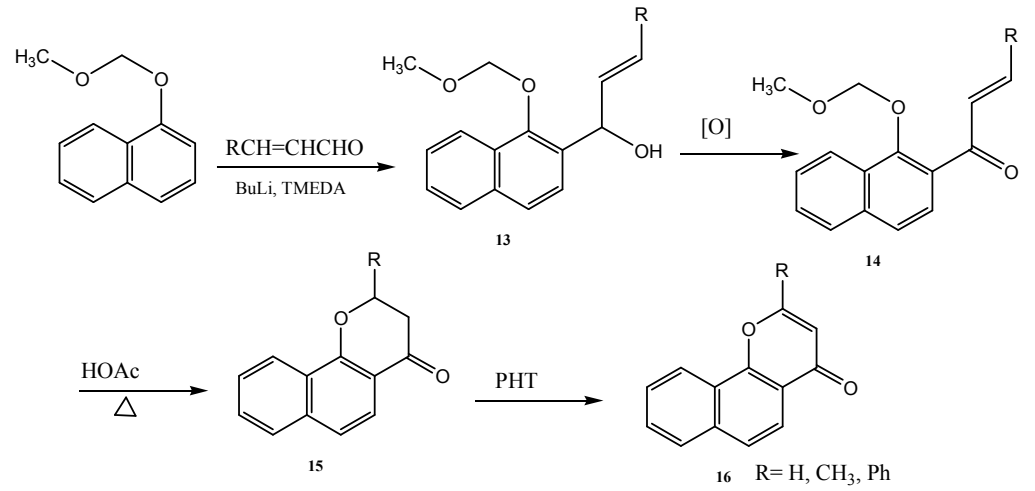
Polyphosphoric acidwas taken as a catalyst in the chromone ring closure for the formation of chromone-2-carboxylic acids from phenols, which was converted to the chromone **11** through Polyphosphoric acidas the catalyst in the last step. This method was more suitable in the phenolic hydroxyl side chain in a carboxylic acid of the cyclization[51].



Scheme. 3:

2.1.3. Acetic acid as a catalyst.

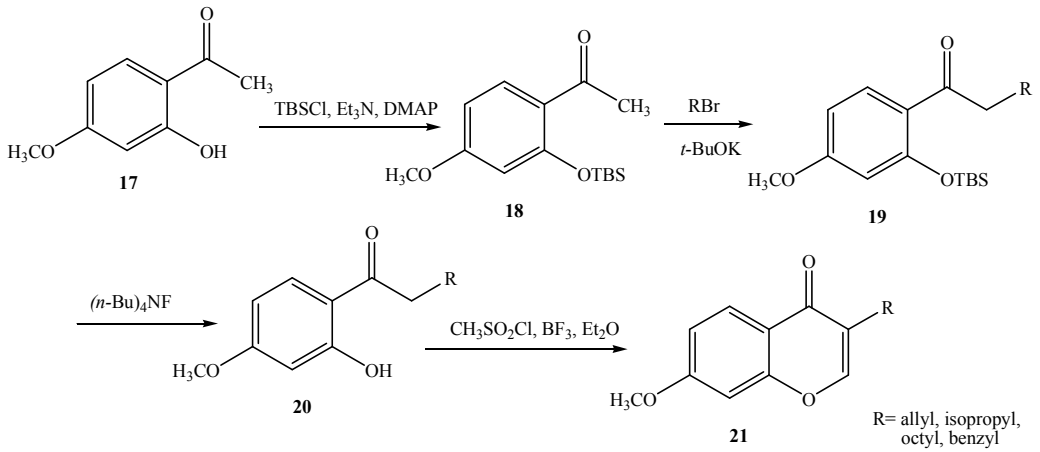
A new synthesis of chromones **16** and flavones[52] was based on the *ortho*-directed metalation of methoxymethyl aryl ethers with alkyl lithium reagents (Scheme 4), using acetic acid as catalyst in the chromone ring closure. This synthetic approach appeared general in its applicability. It has been applied to the synthesis of a series of polycyclic chromone and flavone compounds containing the naphthalene and pyrene ring systems that hold promise as agents for the chemoprevention of cancer.



Scheme. 4:

2.1.4. Methane sulfonyl chloride as a catalyst

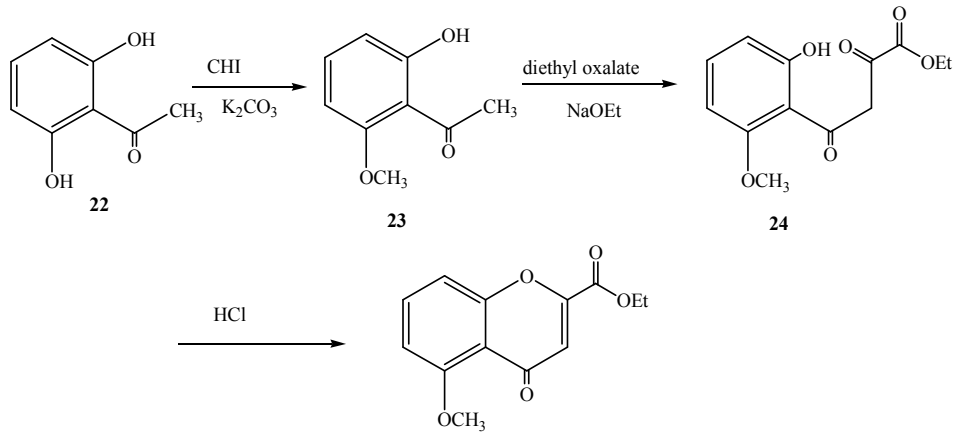
In 2001, Ismail and Abd El Aziem[53] reported the synthesis of the new 3-substituted-7-methoxy-4H-1-benzopyran-4-ones (**21**) starting from 2-hydroxy-4-methoxyacetophenone (**17**) according to Scheme 5 the key step in this synthesis involved alkylation of2-(t-butyldimethylsilyloxy)-4-methoxyacetophenone (**18**) with alkyl halide using potassium tertiary butoxide was prepared from **17** by using *t*-butyldimethyl silylchloride. The *o*-silyl protected alkylacetophenone derivatives (**19**) were, therefore, treated with tetra-n-butylammonium fluoride to produce the corresponding 2'-alkyl-2-hydroxy-4-methoxyacetophenone (**20**) was synthesized in good yield. Cyclization of the alkyl derivatives **20** was achieved via methane sulfonyl chloride using boron trifluoride diethyl ether at 0^{o}C to give the desired 3-substituted-7-methoxy-4*H*-1-benzopyran-4-ones. This reaction conditions was relatively mild, and the reaction yield was also relatively high.



Scheme. 5:

2.1.5. Hydrochloric acid as a catalyst.

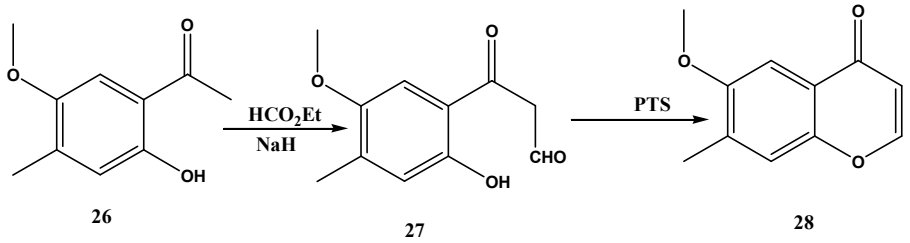
In 2003, Boumendjel and coworkers[54] obtained chromone **25** in three steps starting from 2,6-dihydroxyacetophenone (Scheme 6); they used concentrated hydrochloric acid as a catalyst in the ring closure.



Scheme. 6:

2.1.6. Para toluene sulfonic acid as a catalyst

In 2004, Sabui and Venkateswaran[55] synthesized the 6-methoxy-7-methyl chromone **28** using *para*-toluene sulfonic acid (PTS) as a catalyst in the ring closure (Scheme 7). This catalyst was especially suitable in the phenolic hydroxyl and aldehyde condensation cyclization.

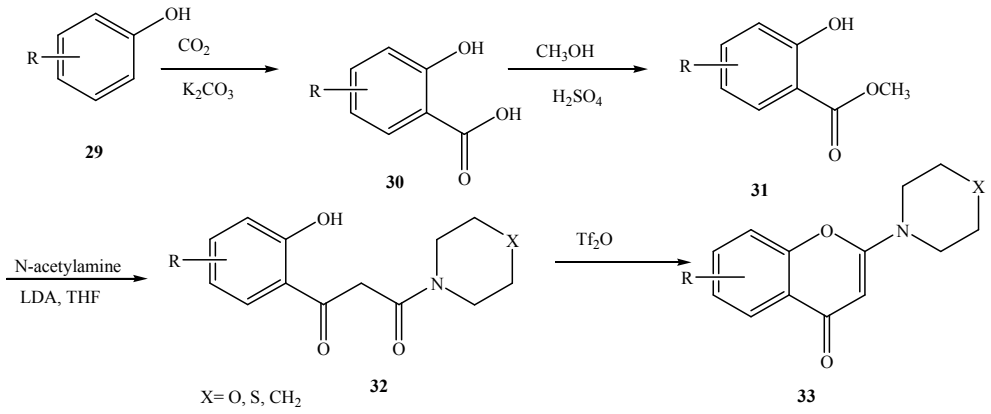


Scheme. 7:

2.1.7. Triflic anhydride as a catalyst

In 2005, Griffin et al.[56] used triflic anhydride as a catalyst to construct the chromone ring (Scheme 8). Ring closure to the required chromones **33** was readily affected with triflic anhydride. Although the

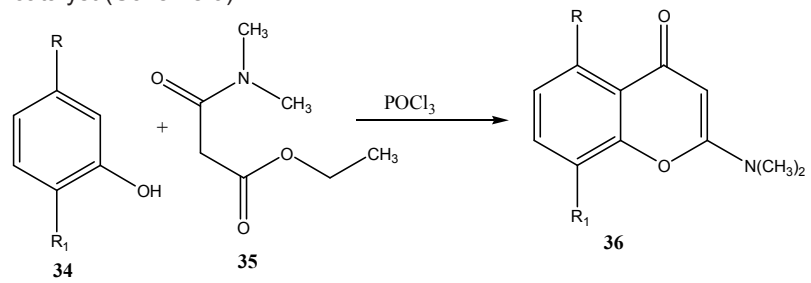
effect of this catalyst was better, but higher prices due to trifluoroacetic anhydride, making its practical application being limited.



Scheme. 8:

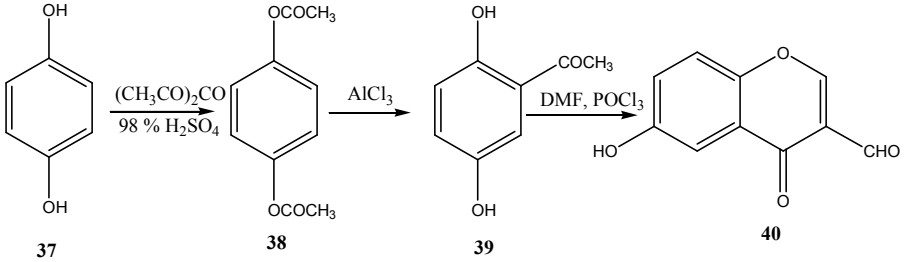
2.1.8. Phosphorus oxychloride as a catalyst

This catalyst is most widely used in the chromone ring closure, and there are two ways in construction the chromone ring. One approach is that phenolic compounds and carbonyl compounds are refluxed in phosphorus oxychloride, another approach is that the phenolic compounds with the acyl side chain is refluxed in phosphorus oxychloride.In 2005, Balbi and coworkers[57] synthesized thechromone ring *via* $POCl_3$ as a catalyst (Scheme 9).



Scheme. 9:

In 2008, Yang and coworkers[58] prepared the 6-hydroxy-3-carbaldehyde chromone *via* a Vilsmeier reaction in another way (Scheme 10). 6-hydroxy-4-chromone-3-carbaldehydes **40** were easily prepared by the reaction of 2,5-dihydroxy-acetophenone **39** with DMF in $POCl_3$ solution[59].

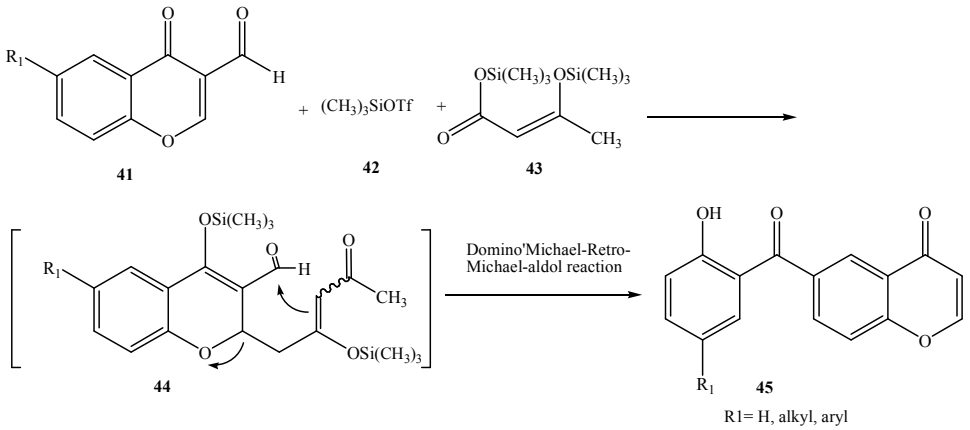


Scheme. 10:

2.1.9. Perchloric acid as a catalyst

In 2006, Langer and coworkers[60] synthesized novel chromone using perchloric acid as a catalyst (Scheme 11). The reaction of 3-formylchromones **41** with Me_3SiOTf (**42**) and 1,3-bis(silyl enol ether) **43** afforded the 4-(2-hydroxybenzoyl)phenols **44**. The formation of the products could be explained by

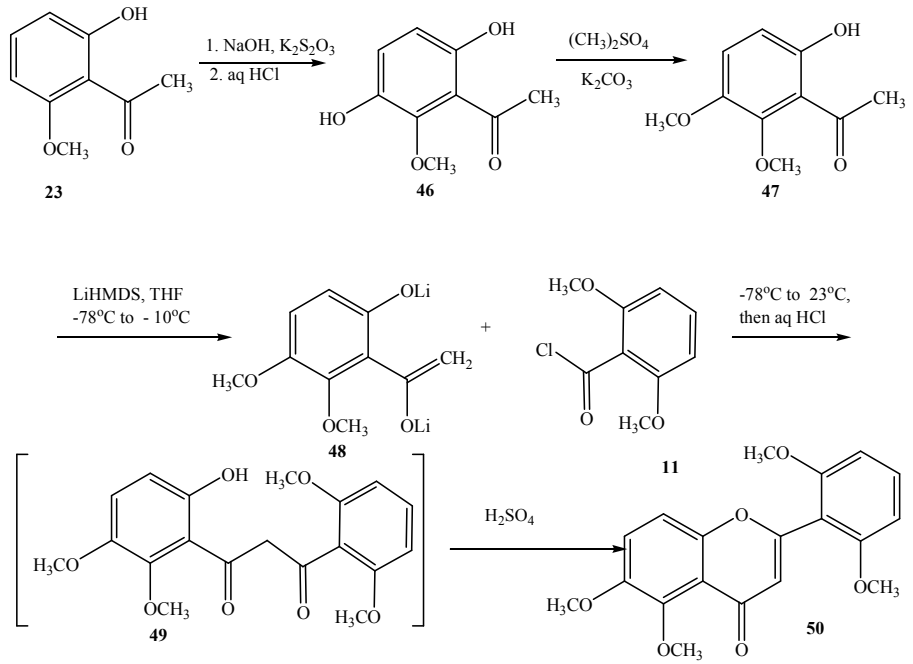
a domino ‘‘Michael–retro-Michael–Aldol’’ reaction. Compounds **44** were transformed into the novel chromones **45** by treatment with triethyl orthoformate and perchloric acid[61-67].



Scheme. 11:

2.1.10. Sulfuric acid as a catalyst

In 2007, Cushman and coworkers[68] reported the synthesis of chromone zapotin[50] using H_2SO_4 as a catalyst (Scheme 12)[69,70]. This H_2SO_4 as catalyst and HCl as catalyst means were basically the same.



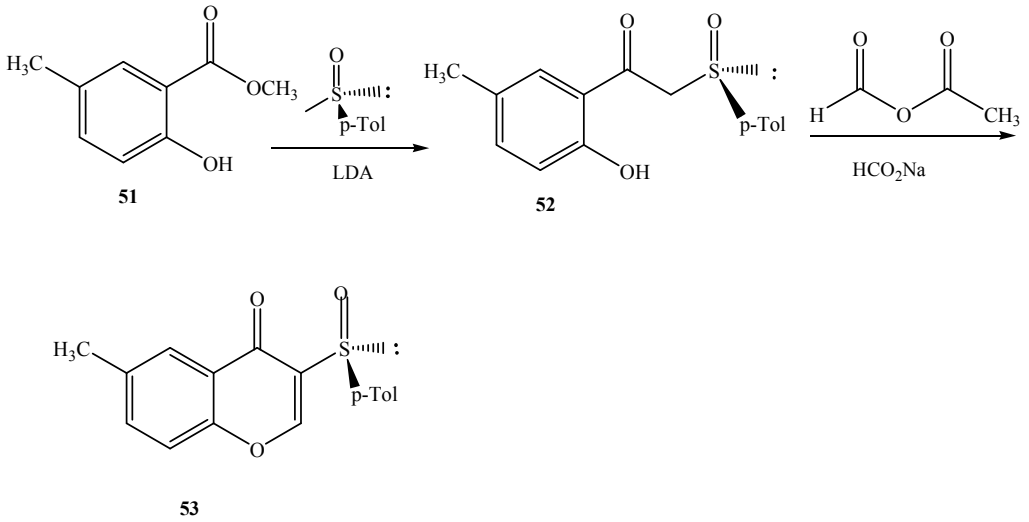
Scheme. 12:

2.2. Base as catalyst in chromone ring closure

Although base as catalyst in the chromone ring closure is not common compared with acid, sometimes it can really bring some satisfactory results.

2.2.1. Sodium formate as a catalyst

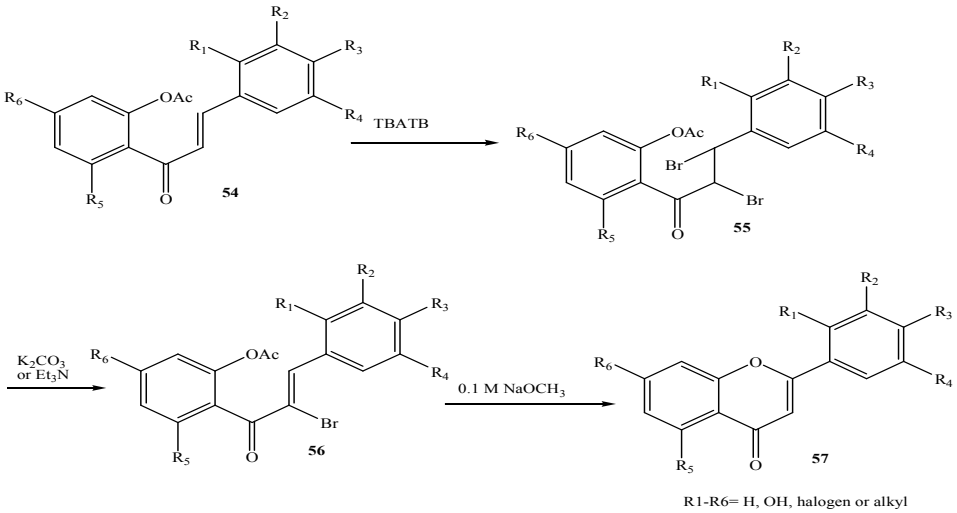
In 2001, Wallace and coworkers[71] reported the synthesis of enantiomerically pure (S)-2-methylchroman-4-one **53** based on the following procedure (Scheme 13). The formation of the chromone **53** was achieved conventionally using acetic formic anhydride and sodium formate[72], but this method is only applicable to compounds with ketosulfoxide.



Scheme. 13:

2.2.2. Sodium methoxide as a catalyst.

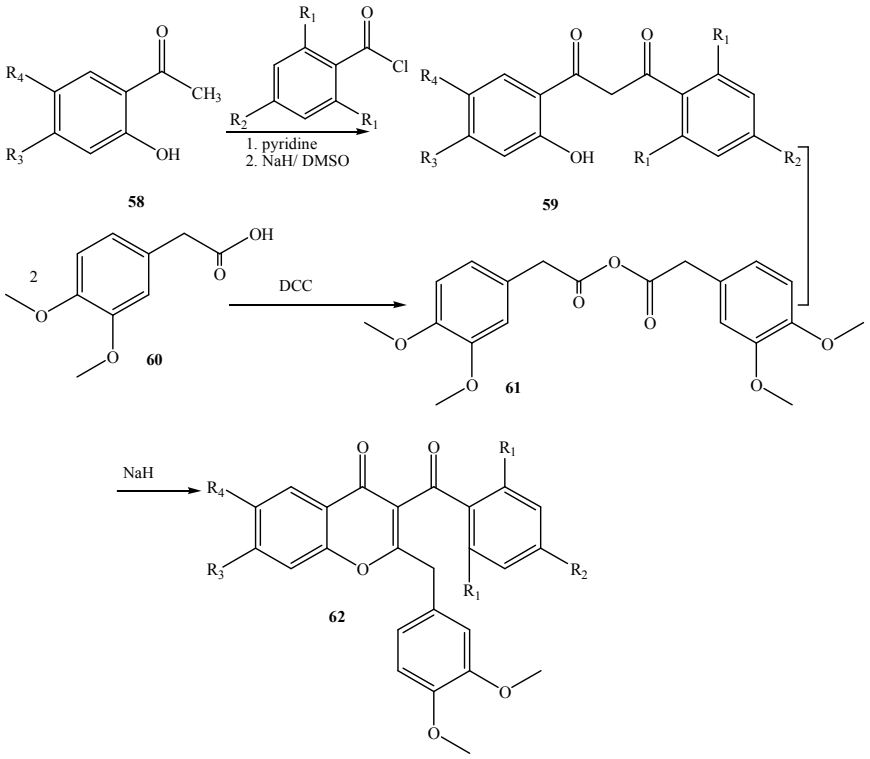
In 2001, Khan and coworkers[73] synthesized the chromone ring **57** *via* cyclization on treating with 0.1M NaOMe solution (Scheme 14). The main feature of this reaction was the bromination of the unsaturated olefinic bond.



Scheme. 14:

2.2.3. Sodium hydride as a catalyst

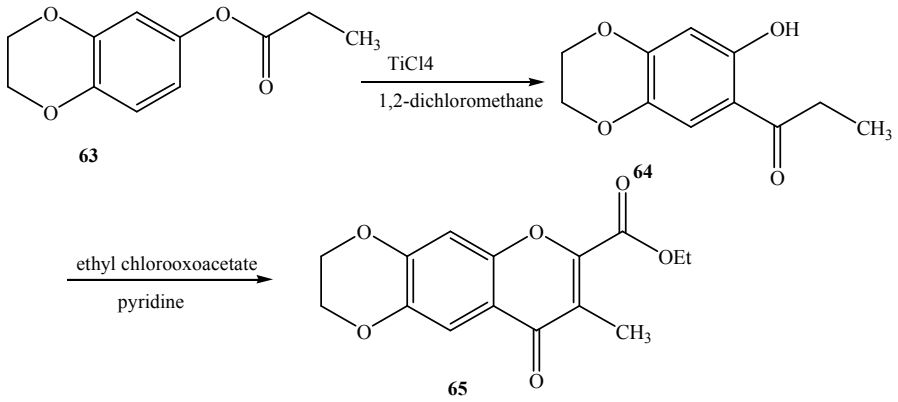
In 2003, Samat and coworkers[74] developed the synthesis of a series of 3-benzoyl-2-benzylchromones through a classical and an optimized Kostanecki–Robinson method involving an o-hydroxyphenyl-b-diketone **59** and an acid anhydride **61** (Scheme 15). In last reaction, sodium hydride was used also as base to favor the formation of the expected chromone **62** instead of byproducts. However, this method had one drawback; the anhydride was not easy to prepare, especially for the aromatic acid anhydride.



Scheme. 15:

2.2.4. Pyridine as a catalyst

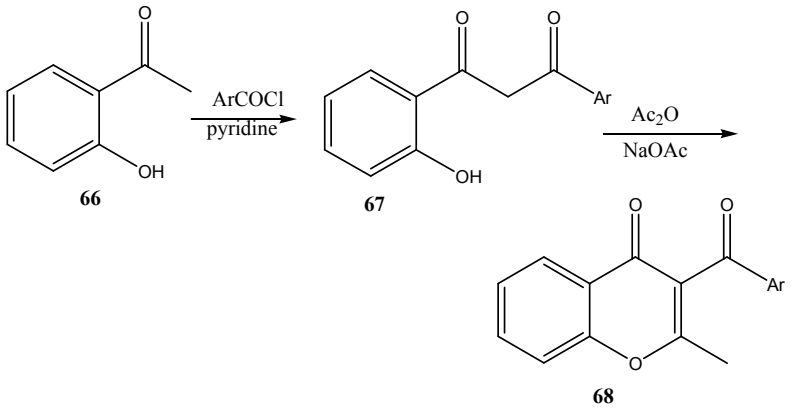
In 2005, Lee et al.[75] synthesized the chromone**65** using pyridine as a catalyst in the ring closure (Scheme 16). This method of using pyridine as a catalyst was more suitable to acyl phenols and chloroacetyl carboxylic acid esters in the chromone ring closure.



Scheme. 16:

2.2.5. Sodium acetate as a catalyst.

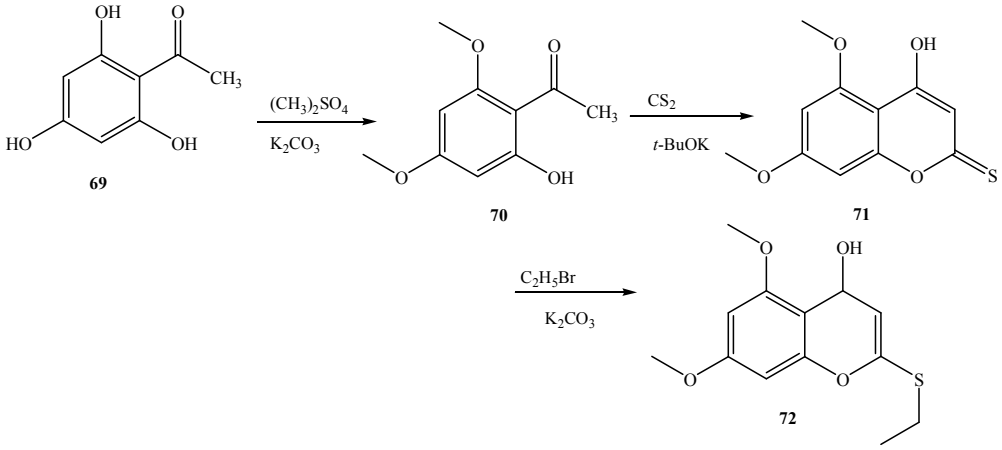
In 2005, Gabbutt and coworkers[76] synthesized 3-acylchromones **68**by acylation of 2'-hydroxydibenzoylmethane with acid anhydrides in the presence of sodium acetate (Scheme 17). This condensation reaction was not only applicable to acetic anhydride but also for other acid anhydride such as propionic anhydride and butyric anhydride.



Scheme. 17:

2.2.6. Potassium *tert*-butoxide as a catalyst.

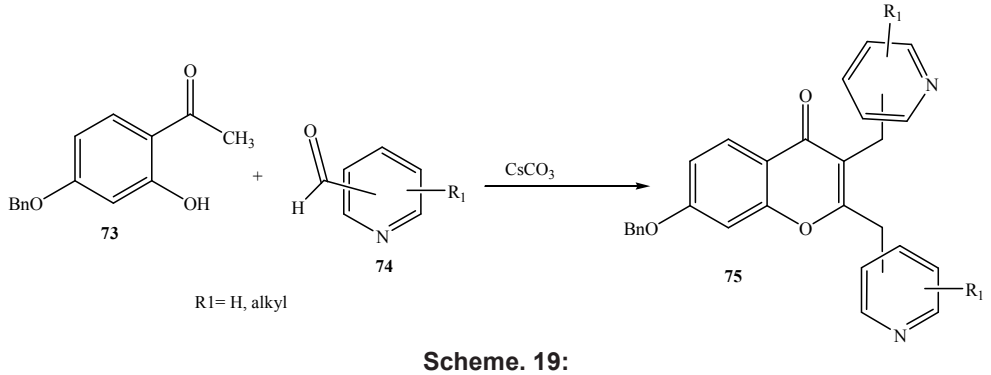
In 2007, Wu and coworkers[77] prepared the chromone ring **72** using potassium tert-butoxide in the ring closure during their total synthesis 6-demethoxycapillarisin (Scheme 18). This reaction was very useful, which laid the foundation to expand the SAR of chromone ring with sulfur atom in the side chain.



Scheme. 18:

2.2.7. Caesium carbonateas a catalyst

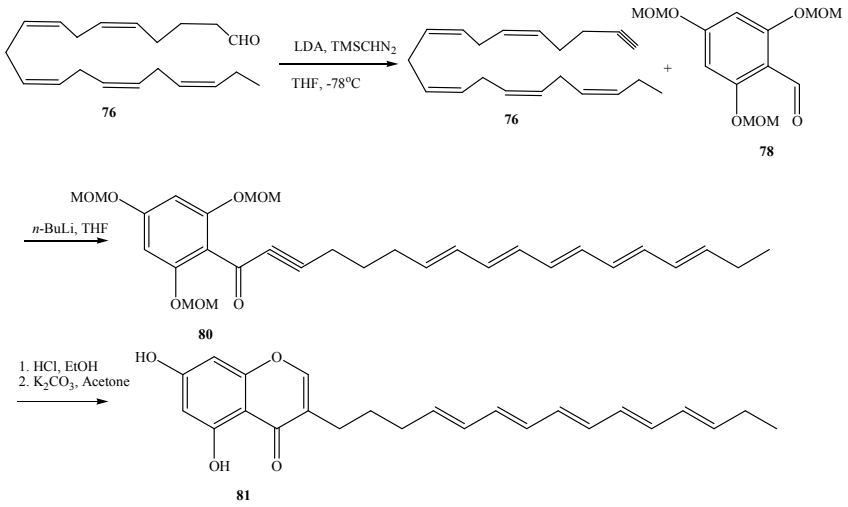
In 2008, Arai *et al.*[78] described a practical and useful synthesis of heterocyclic substituted chromones (Scheme 19) and also developed a one-pot synthesis by Michael aldol reaction of chromone derivatives bearing heterocycle units. The 2,3-heterocyclic-substituted chromones **75** were obtained in one step, as shown in scheme 19, 4-benzyloxy-2-hydroxyacetophenone (**73**) reacted with heterocyclic aldehydes **74** to give 2,3-disubstituted chromone **75** in high yield under Cs_2CO_3conditions.



Scheme. 19:

2.2.8. Potassium carbonate as a catalyst

In 2009, Anwar and Hansen[79] used K_2CO_3 as a catalyst in the chromone ring closure during their first total synthesis of the marine natural product all-(Z)-5,7-dihydroxy-2-(4Z,7Z,10Z,13Z,16Z-nonadecapentaenyl)chromone **81** (Scheme 20). This reaction using phenol hydroxyl addition to the alkyne bond was relatively classical.

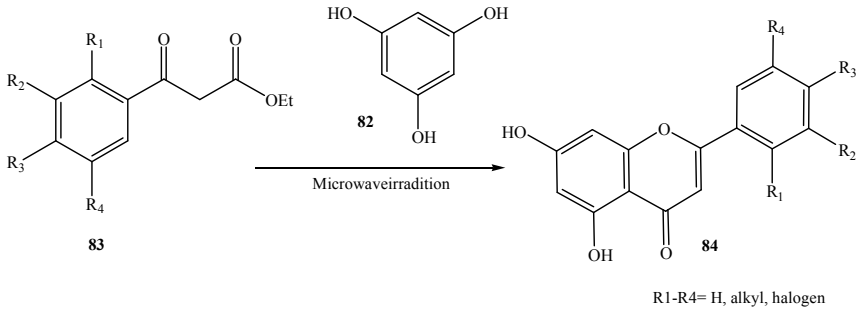


Scheme. 20:

2.3. Chromone ring closure under the microwave irradiation

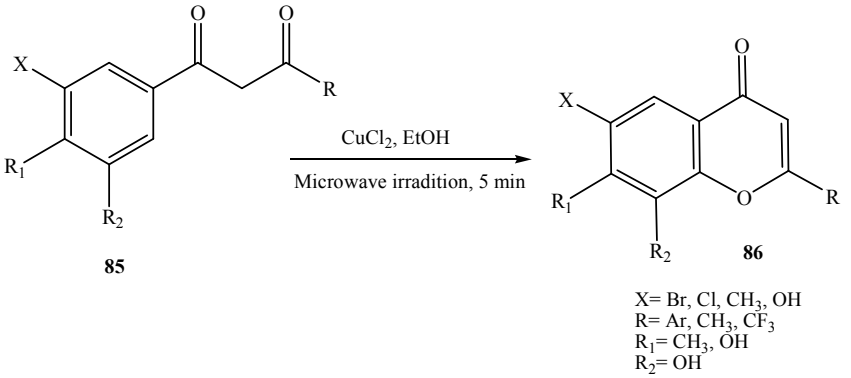
Recently, microwave irradiation[80] offers a considerable advantage over conventional heating because it results in substantial rate enhancements in a wide range of organic reactions. Cleaner reactions are also commonly achieved, together with improvements in yield and selectivity. The increasing demand for clean and ‘‘green’’ chemical syntheses has resulted in increased use of microwave irradiation, so there have been several recent reports, describing the application of microwave irradiation to the synthesis of flavonoids.

In 2005, Seijas et al.[81] reported an eco-friendly direct solvent-free synthesis of functionalized flavones **84** under microwave irradiation (Scheme 21). This method was valid for flavones with or without substitutionin the B ring. Thus, the flavonoids were prepared from the corresponding ethyl benzoyl acetates **83** and phloroglucinol for 2–12 min of irradiation in 66–96% yields. The successful use of microwave irradiation in providing this rapid and direct route to flavones in comparison to classical procedures contributes to confirming the participation of specific effects in some microwave assisted organic synthesis.



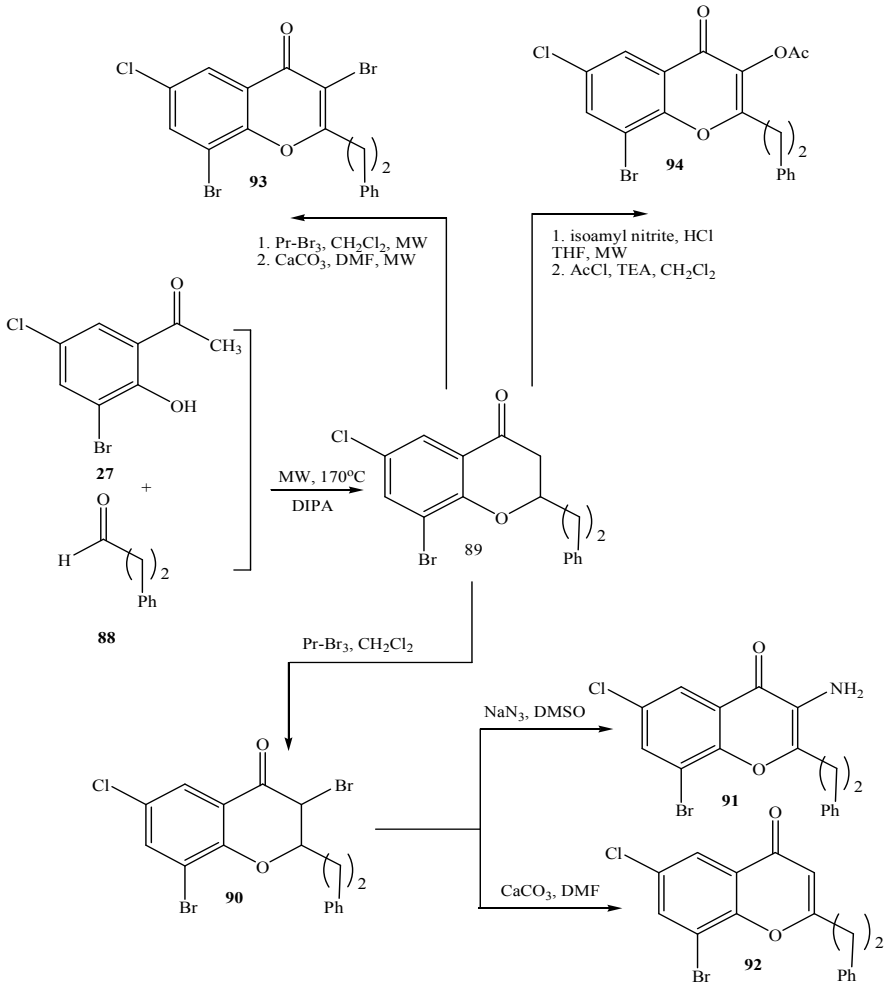
Scheme. 21:

In 2005, Kabalka and Mereddy[82] reported a facile microwave synthesis of functionalized flavones and chromones via the cyclization of 1-(2-hydroxyaryl)-3-aryl-1,3-propanedione (Scheme 22). In their study, the intermediate 1,3-propanediones **85** were synthesized in 5 min via dehydrative cyclization to the corresponding flavones and chromones **86** in ethanol, in the presence of $CuCl_2$ under microwave irradiation.



Scheme. 22:

In 2009, Luthman and coworkers[83] reported a base-promoted condensation between 2-hydroxyacetophenones **87** and aliphatic aldehydes **88** (Scheme 23); they optimized the reaction to afford 2-alkyl-substituted 4-chromanones **89** in an efficient manner using microwave heating. Performing the reaction using diisopropylamine in EtOH at 170 ^{0}C for 1 h gave high yield in 88%. The 4-chromanones could be further converted into highly functionalized 2,3,6,8-tetrasubstituted chromones in which a 3-substituent (acetate, amine, or bromine) was introduced via straightforward chemical transformations.



Scheme. 23:

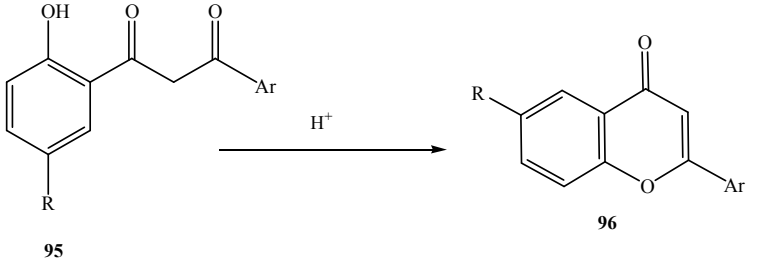
2.4.Chromone ring closure via solid-support

In recent years, solid-phase chemical reaction has appeared many advantages including good selectivity, high yield, simple operation, and no pollution, and some researcher has applied this method in chromone synthesis.

2.4.1. *Via* solid-support catalysts

In 2002, Blanco and coworkers[84] studied the catalytic performance of phosphomolybdic acid (MPA) ($H_3PMo_{12}O_{40}.nH_2O$) and Phosphotungstic acid TPA ($H_3PW_{12}O_{40}\_nH_2O$) (Scheme 24), both bulk or supported on silica (S), to obtain flavones and substituted chromones **96** The result showed that the conversion to flavones and substituted chromones was in general higher in homogeneous phase than that observed for the supported catalysts. Nevertheless, the use of the supported catalysts enabled an easy separation and recovery of the catalyst for its immediate reuse without any important decrease of the catalytic activity.

In addition, the unchanged starting material may be recycled to the reactor because it was almost quantitatively recovered and secondary products were not practically formed.

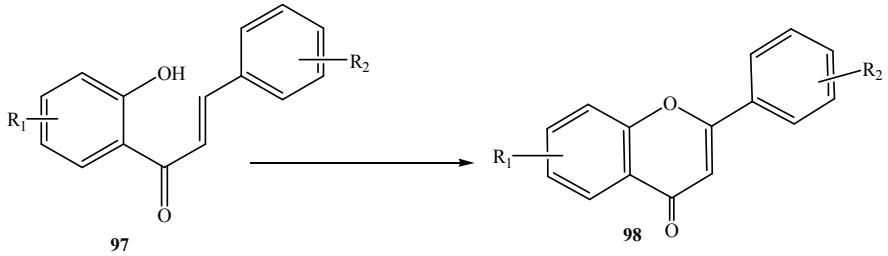


95 **96**

R= Br, Cl, CH_3, OH, Ar, alkyl

Scheme. 24:

In 2005, van Lier and coworkers[85] explored silica gel-supported $InBr_3$ or $InCl_3$ (15–20 mol %) as a new solid-support catalysts for the facile and efficient oxidation, under solvent free conditions (Scheme 25), of 2'-hydroxychalcones **97** to yield the corresponding flavones **98** in >80% yield. The catalysts were easily prepared, stable, and efficient under mild reaction conditions.



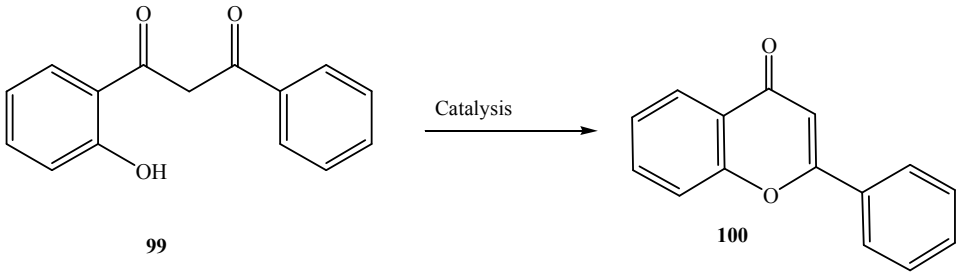
97 **98**

R_1,R_2 = Br, Cl, CH_3, OH, alkyl

Scheme. 25:

Trifluoromethanesulfonic acid (TFMS) is known to be a strong acid, and it is used in many organic reactions such as Friedel Crafts reactions, polymerization, Koch carbonylation, among others [86]. However, the recovery of the triflic acid from the reaction mixture results in the formation of large amounts of waste[86].

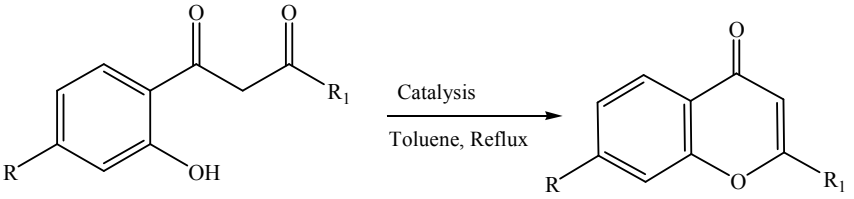
So, in 2007, Romanelli and coworkers described the synthesis and characterization of TFMS supported on mesoporous titania[87] using urea as a low-cost, pore-forming agent (Scheme 26), via HCl catalyzed sol–gel reactions. The acidic characteristics of the solids were determined by potentiometric titration with *n*-butylamine. The use of these solid catalysts provided interesting yields in the cyclization reaction of 1-(2-hydroxyphenyl)-3-aryl-1,3-propanediones **99** to flavone **100**, also leading to an easy separation and recovering of the catalysts for further use.



99 **100**

Scheme. 26:

In 2009, Romanelli and coworkers[88] also prepared the TFMSC1 and TFMSC2 catalysts by adsorption of TFMS on two activated carbons with different textural properties used as supports (Scheme 27). The TFMSC2 catalyst used as solid catalyst provided interesting yields in the cyclization reaction of 1-(2-hydroxyphenyl)-3-aryl-1,3-propanediones **101** to flavones and chromones **102**, also leading to an easy separation and recovery of the catalysts for further use. Moreover, as a significant decrease of the catalytic activity was not observed, they can be recycled without any activity loss.



101

102
R= H, Cl, CH3
R= Phenyl, 1-Naphthyl, 2-Naphthyl

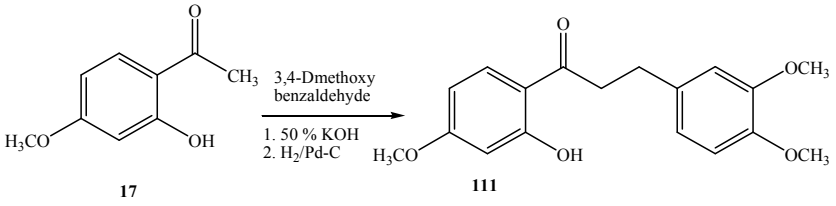
Scheme. 27:

2.5. Chromone ring closure through other methods

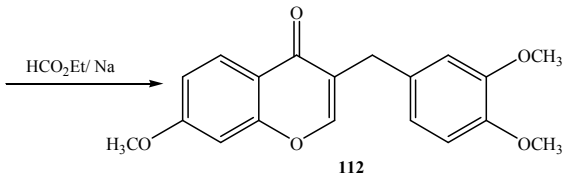
Besides the above acid catalyst, base catalyst, microwave irradiation, and solid-supported synthesis in ring closure, there are many other catalysts and reaction conditions in this chromone construction.

2.5.1 Sodium as a catalyst

The chromone **112** synthesized through a highly efficient procedure catalysted by sodium sand (Scheme 28). This reaction was not practical because the hot sodium sand was very dangerous during the reaction[89].



17 **111**

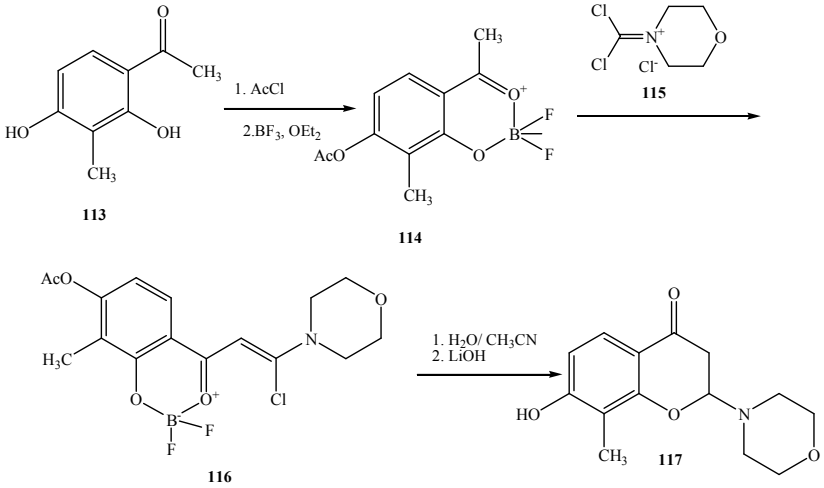


112

Scheme. 28:

2.5.2. Through basic hydrolysis

Morris et al.[90] accomplished the preparation of chromone utilizing a novel synthesis of 2-aminochromones **117** via the condensation of BF_2 complexes of 2'-hydroxyacetophenones with phosgeniminium salts (Scheme 29). Through this method, a side chain containing nitrogen atoms could be introduced into the chromone ring.

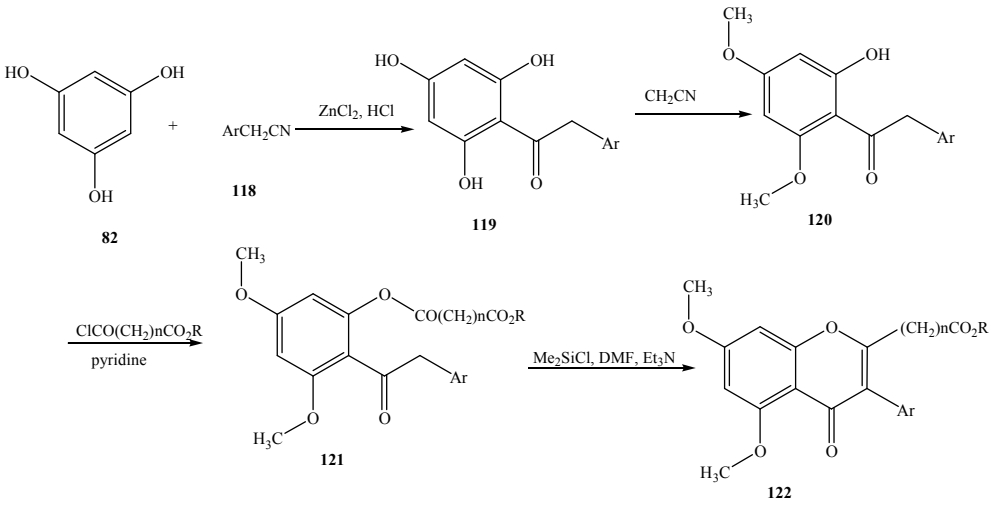


113 114 116 117

Scheme. 29:

2.5.3. Trimethylsilyl chloride as a catalyst

Pelter et al.[91] reported the synthesis of chromone ring **122** via $Me_3SiCl/DMF/Et_3N$ (Scheme 30).

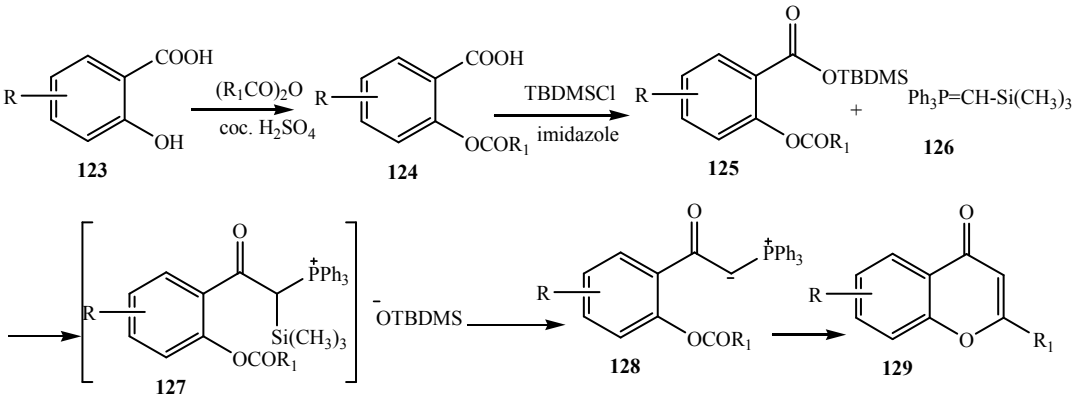


82 118 119 120 121 122

Scheme. 30:

2.5.4. *Via* intramolecular ester carbonyl olefination.

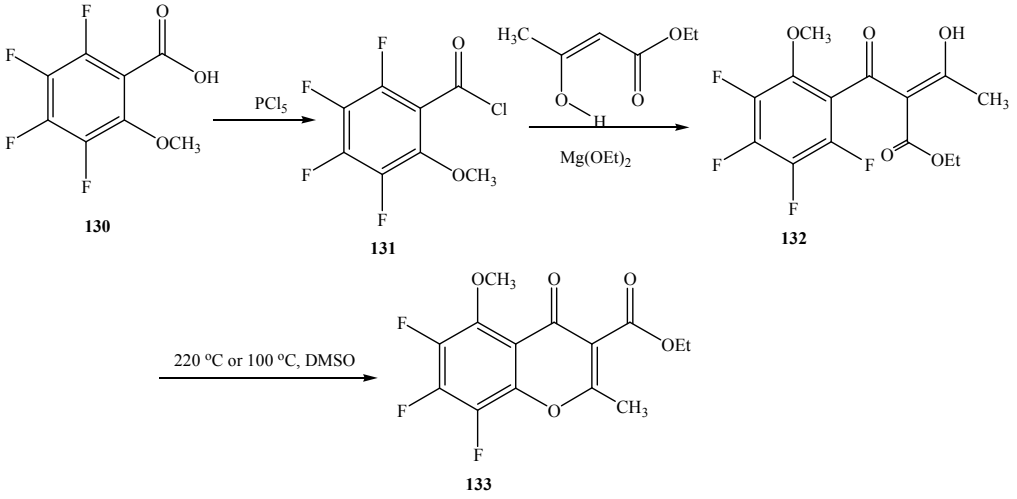
In 2000, Kumar and Bodas[92] reported a new and simple route to 4H-chromen-4-ones **129** via intramolecular ester carbonyl olefination using (trimethylsilyl)methylene triphenyl phosphorane (Scheme 31).



Scheme. 31:

2.5.5. Via heating

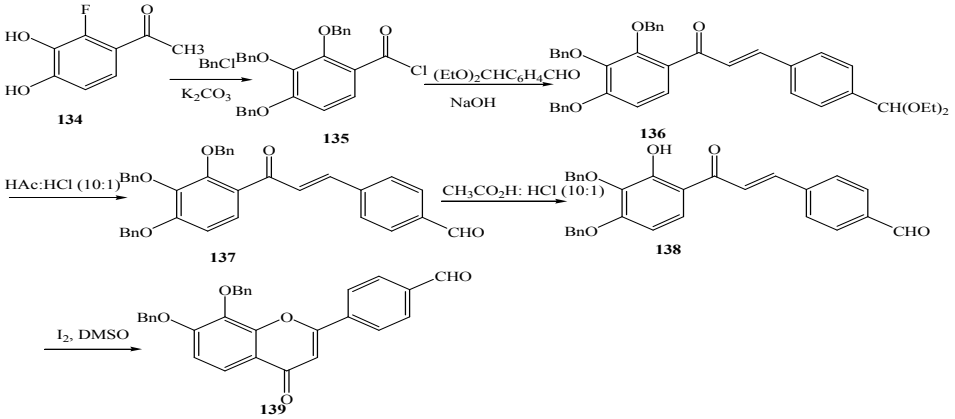
In 2001, Saloutin and coworkers[93] described the acylation of ethyl acetoacetate by the fluorobenzoyl chloride and synthesis of novel flurobenzopyran-2(4)-one (Scheme 32). 2-Dimethoxy-3,4,5,6-tetrafluorobenzoylchloride **131** was obtained by heating the corresponding acid **130** with an excess of phosphorus pentachloride. Then, the interaction of fluorobenzoyl chloride **131** with ethyl acetoacetate in the presence of magnesium ethoxide resulted in β,β'-dioxaester **132**, which readily cyclized into chromone **133** on heating in the absence of solvents or in DMSO. The cyclization proceeded through intramolecular substitution of the ofluorine atom in the fluorophenyl substituent.



Scheme. 32:

2.5.6. Iodine as a catalyst.

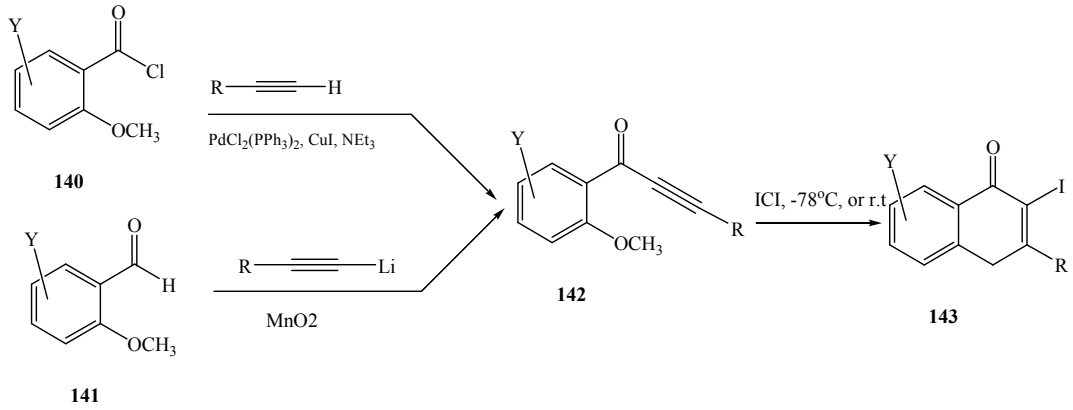
In 2004, Tome´ and coworkers[94] reported the synthesis of chromone**139** through iodine as a catalyst (Scheme 33).



Scheme. 33:

2.5.7. Via ICl-induced cyclization.

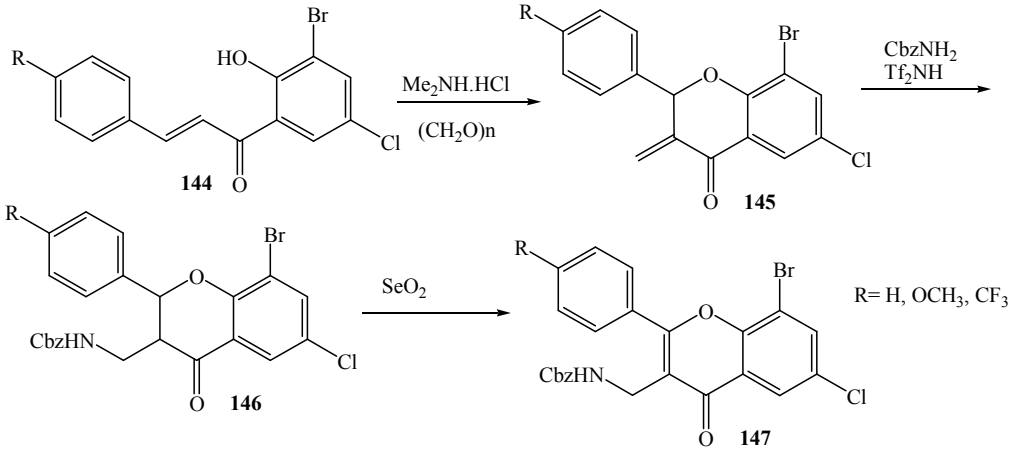
In 2006, Larock and coworkers[95] described the ICl-induced cyclization of heteroatom-substituted alkynones **142** (Scheme 34); this method provided a simple, highly efficient approach to various 3-iodochromones **143**. This process was run under mild conditions, tolerated various functional groups, and generally provided chromones in good to excellent yields.



Scheme. 34:

2.5.8. Under Mannich conditions.

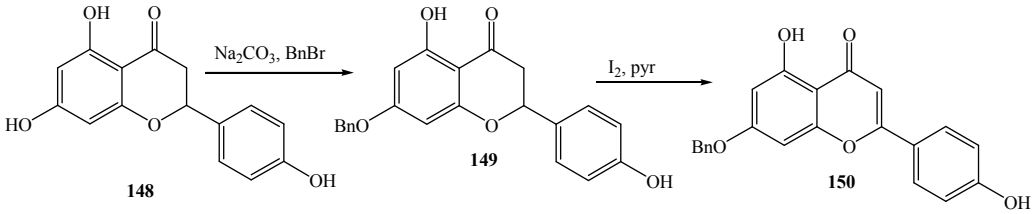
In 2007, Luthman and coworkers[96] developed an efficient synthetic route to Cbz-protected 3-aminomethyl-2-aryl-8-bromo-6-chlorochromones **147** (Scheme 35). This procedure represented a new method to introduce a primary aminomethyl group at the 3-position of a 2-arylchromone scaffold.



Scheme. 35:

2.5.9. Through base-induced elimination

In 2009, Rizzacasa and coworkers[97] described the synthesis of chromone **150** through iodination of naringenin followed by base-induced elimination (Scheme 36).



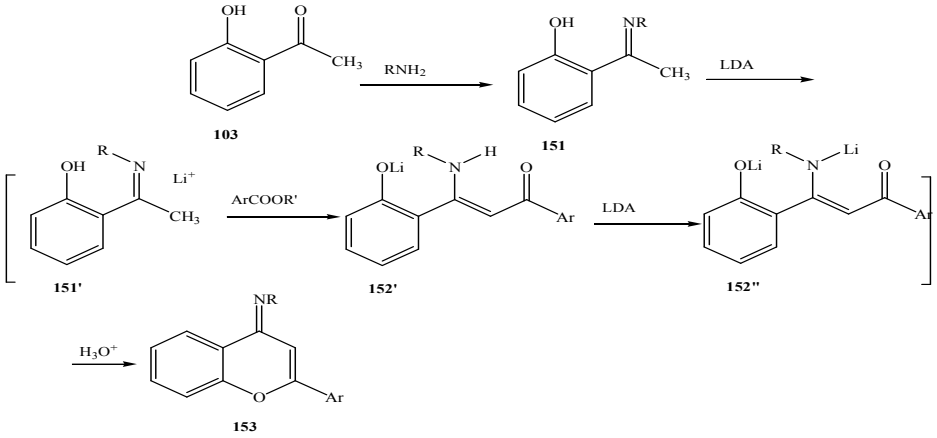
Scheme. 36:

2.6. Synthesis of heterocycle analog of chromone

The chromones have gained considerable synthetic and pharmacological interest for a long time because of their diverse biological activities, and recent studies have indicated that a lot of natural heterocycle analog containing phosphorus, sulphur, and nitrogen also show the expected bioactivity, so many synthesis of heterocycle analog of chromone have been reported with high region selectivity and good yields.

2.6.1. Synthesis of 4H-Chromen-4-ylidenamines

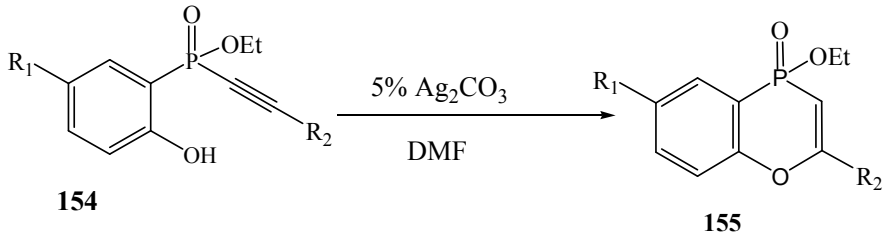
In 2000, Palmieri's group[98] described a method to obtain 4H-chromen-4-ylidenamines **153** because the simplest of them (2-phenyl-4H-chromen-4-imine), has been used for treatment of cell proliferative diseases and for its antihypoxic, hypotensive, and antiallergic properties. (Scheme 37)



Scheme. 37:

2.6.2. Synthesis of phosphachromones

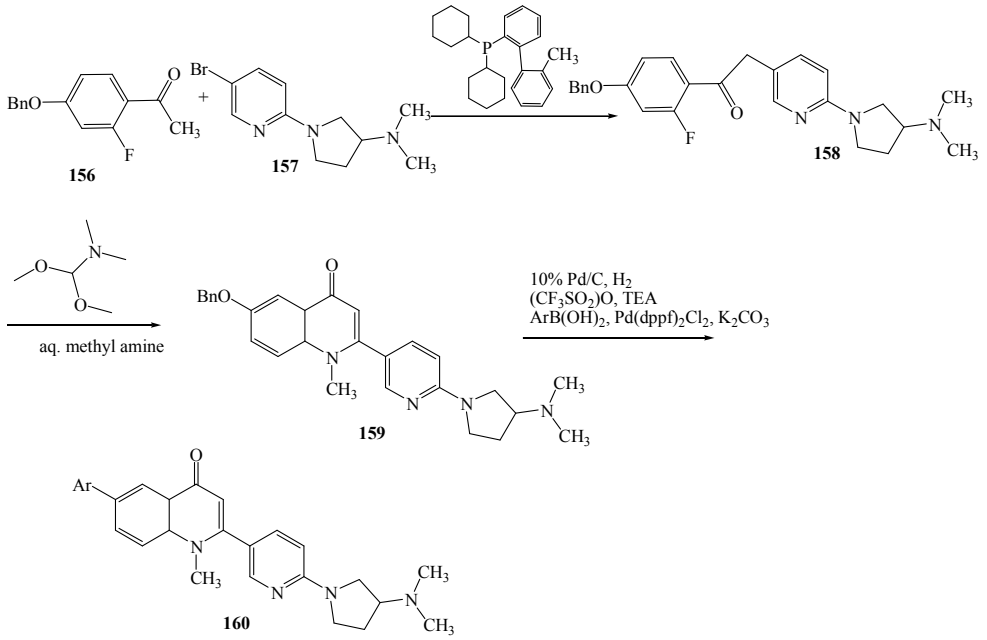
In 2008, Ding and coworkers[99] reported a novel Ag_2CO_3-catalyzed cyclization reaction of *o*-hydroxyphenylethynylphosphinates **154** to phosphachromones **155** with high region selectivity and good yields (Scheme 38), which provided an effective approach to synthesize the new kind of phosphorus heterocycles.



Scheme. 38:

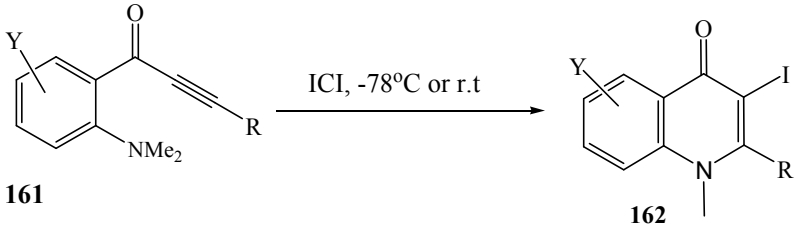
2.6.3. Synthesis of quinolones.

In 2006, Dyck and coworkers[100] reported the synthesis of the quinolone derivatives (Scheme 39).



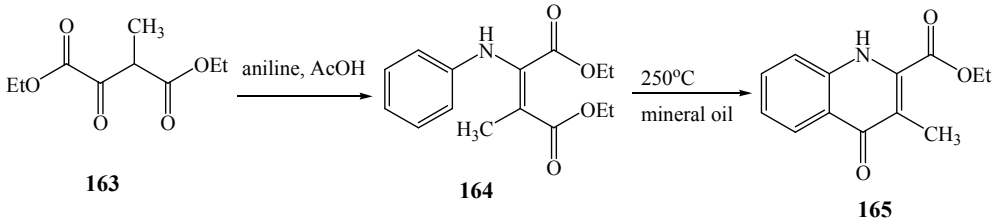
Scheme. 39:

In 2006, Larock and coworkers[95] described the ICl-induced cyclization of nitrogen-substituted alkynones **161** to afford the quinolones **162** in good to excellent yields (Scheme 40).



Scheme. 40:

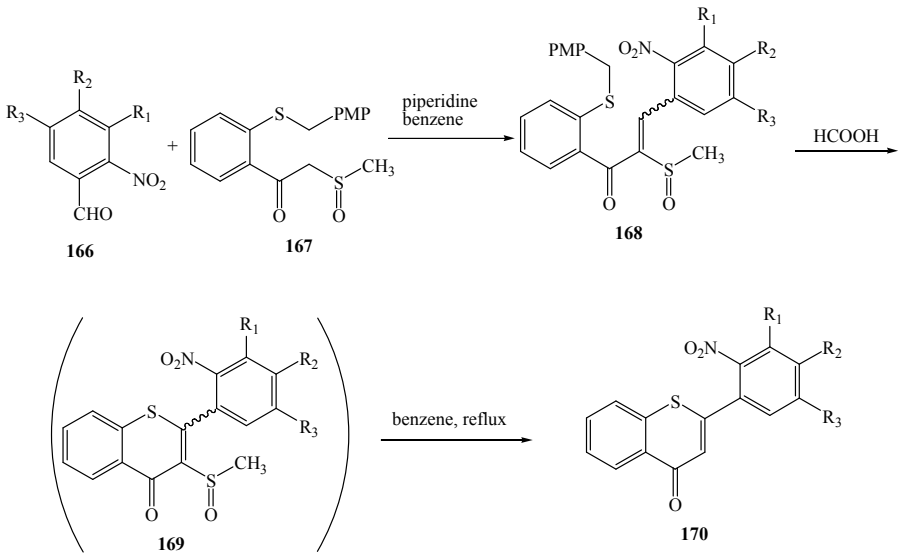
In 2008, Nam and coworkers[101] reported the synthesis of quinolinone **165** as they designed and synthesized the 4-quinolinone 2-carboxamides as calpain inhibitors (Scheme 41).



Scheme. 41:

2.6.4. Synthesis of thioflavones.

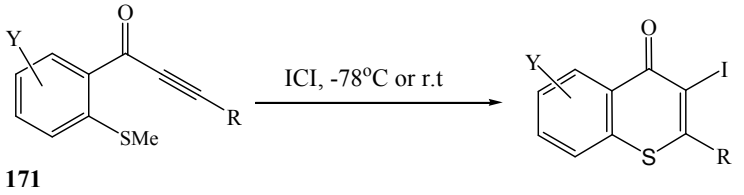
In 2004, Kataoka et al.[102] reported the synthesis of thioflavones as they studied the SARs of thioflavone derivatives as specific inhibitors of the ERK-MAP kinase signaling pathway (Scheme 42).



166 167 168 169 170

Scheme. 42:

In 2006, Larock and coworkers[95] described the ICl-induced cyclization of sulphur-substituted alkynones **171** to give various 3-iodo-thiochromones **172** in good to excellent yields (Scheme 43).

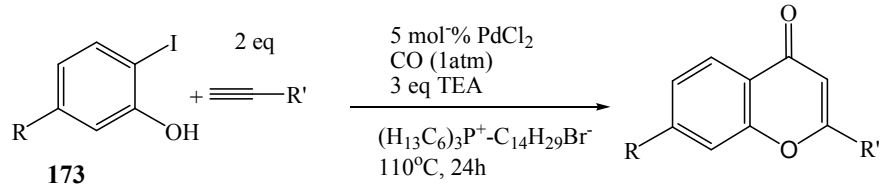


171 **172**

Scheme. 43:

2.7. Recent Synthetic methods of chromones

A highly efficient and selective palladium-catalyzed ligand-free cyclocarbonylation reaction of o-iodophenols **173** with terminal acetylenes under atmospheric CO pressure affords diversified chromones**174** in very good yields. The use of a phosphonium salt ionic liquid as the reaction medium enhances the efficiency of the cyclocarbonylation reaction (Scheme 44)[103].

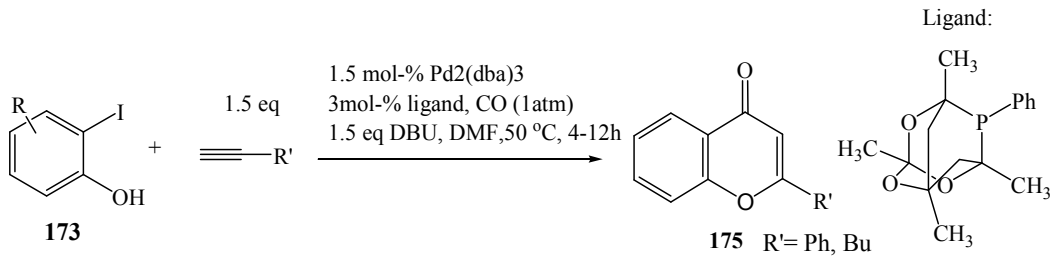


173

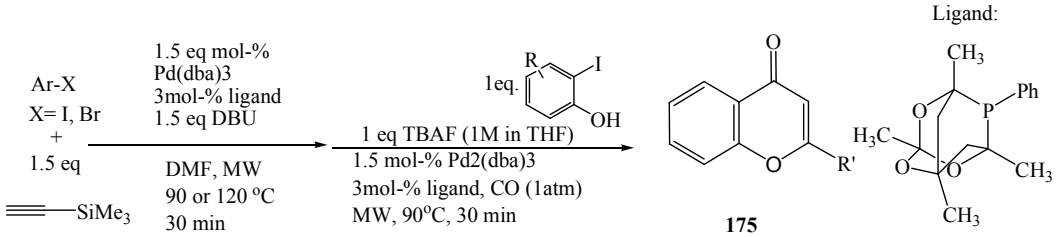
174 R= H, CO_2Me
R'= Ar, alkyl

Scheme. 44:

A palladium complex of 1,3,5,7-tetramethyl-2,4,8-trioxa-6-phenyl-6-phosphaadamantane is an effective catalyst for a sequential microwave-assisted Sonogashira and carbonylative annulation reaction to give substituted flavones**175**(Schemes 45,46)[104].

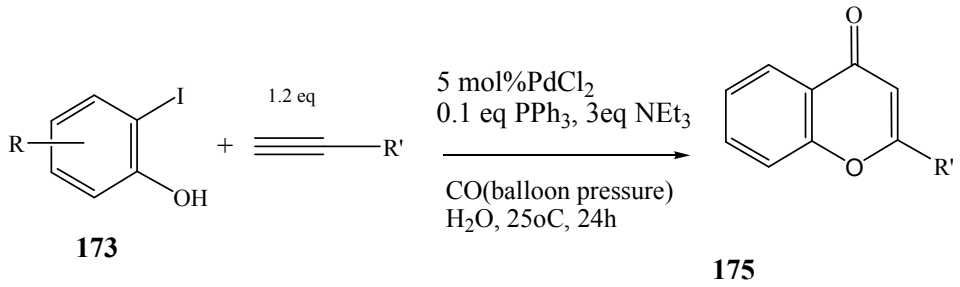


Scheme. 45:



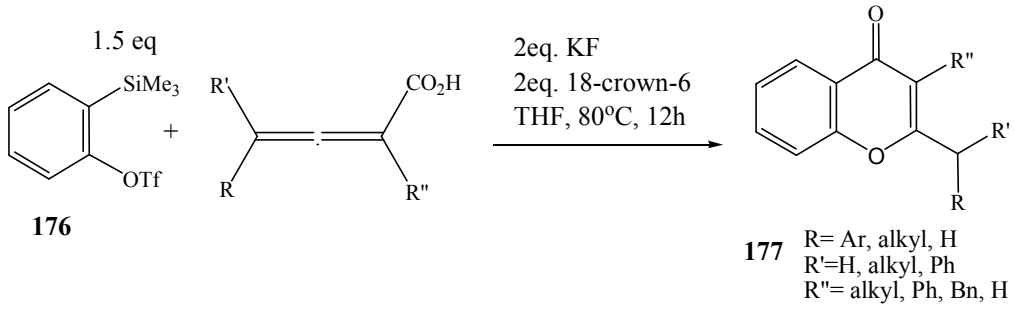
Scheme. 46:

A Pd-catalyzed copper-free carbonylative Sonogashira coupling reaction at room temperature was achieved by using water as a solvent under balloon pressure of CO with Et_3N as a base. The developed method was successfully applied to the synthesis of flavones(Scheme 47)[105].



Scheme. 47:

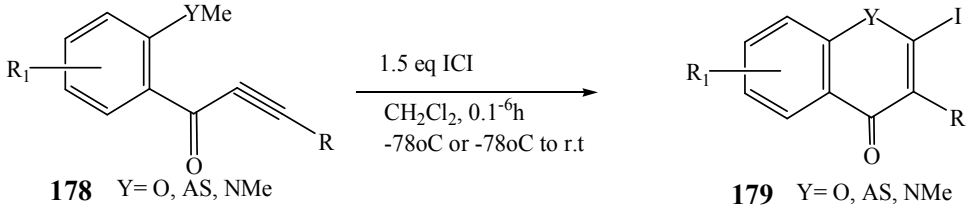
Chromone derivatives **177** were synthesized from 2,3-allenoic acids and benzynes in good yields under mild conditions. The benzyne intermediate undergoes 1,2-addition with the carbonyl group, followed by ring opening, conjugate addition, and protonolysis to afford chromone derivatives. This protocol allows the diversity due to the substituent-loading capability of 2,3-allenoic acids as well as benzynes(Scheme 48)[106].



Scheme. 48:

A mild ICl-induced cyclization of heteroatom-substituted alkynones **178** provides a simple, highly efficient approach to various 3-iodochromones, iodothiochromenones, iodoquinolinones and

analogues**179** in good to excellent yields. Subsequent palladium-catalyzed transformations afford a rapid increase in molecular complexity (Scheme 49) [107].



178 Y= O, AS, NMe **179** Y= O, AS, NMe

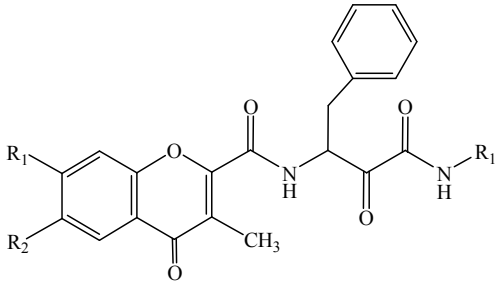
Scheme. 49:

3. Biological Activity

Heterocycles play an important role in the design and discovery of new physiological/pharmacologically active compounds[108]. Chemically, chromones (4H-chromen-4-ones) are heterocyclic compounds with the benzo-c-pyrone framework. Molecules containing the chromone or benzopyranone ring have a wide range of biological activities. They have been shown to be tyrosine and protein kinase inhibitors[109], as well as anti-inflammatory[110], antiviral[111], antioxidant[112,113], antihypertensive agents[111] and Chromone derivatives are also active at benzodiazepine receptors[114]. In addition to this, they have been shown to be anticancer agents[115], and possessing antimutagenic properties[116]. Chromones may also have application in cystic fibrosis treatment, as they activate the cystic fibrosis transmembrane conductance regulator[117]. Therefore, the vast range of biological effects associated with this scaffold has resulted in the chromone ring system being considered as a privileged structure[118]. The main objectives of chromones syntheses are not only for the development of more diverse and complex bioactive compounds for biological activity and structure-activity relationship (SAR) studies but also for other applications in Medicinal Chemistry, such as preparation of fluorescence probes, due to photochemical properties of chromones[119].

3.1. Antioxidant

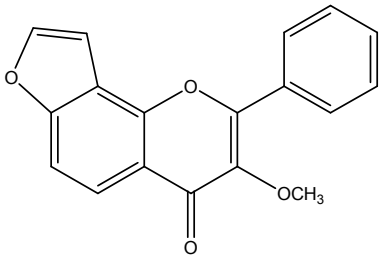
Lee and coworkers (2011), reported that new chromone carboxamide derivatives **179** were synthesized as conformationally constrained structural variants of MDL, to provide alternative μ-calpain inhibitors and antioxidant activities in DPPH scavenging and lipid peroxidation inhibitory effects[120].



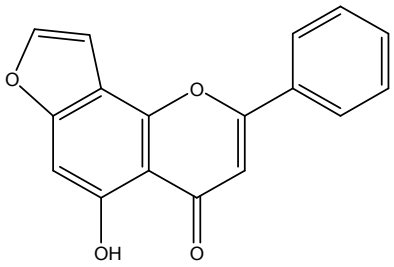
179

3.2. Antibacterial Activity

Pongaglabol **181**exhibited activity against the bacteria *Shigella dysenteriae*, *Streptococcus β-haemolyticus*, and *Staphylococcus aureus*; the lowest concentration for inhibition of the first two types of bacteria amounts to 64 μg/ml[121] Methanol and ethyl acetate extracts from *Pongamia pinnata* plants in mixture with karangin **180**[122] exhibited antibacterial activity. An extract of flavonoids from *Lonchocarpus montanus* plants in dichloromethane, containing 19% of pongamol and 8% of lanceolatin B, exhibited activity against *Staphylococcus aureus*, whereas pongamol itself was active against *Bacillus subtilis* and *Cladosporium cladosporioides*[123].

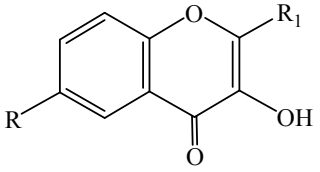


180 Karangin



181 Pongaglabol

Gharpure, et al(2012)[124] synthesized and evaluated 3-hydroxy-2-phenyl-4H-chromen-4-ones**182** asantibacterial activity. 3-Hydroxy-2-phenyl-4H-chromen-4-ones have been synthesized from appropriate 1-(2-hydroxyphenyl)-3-phenylprop-2-en-1-one. All compounds were evaluated for antibacterial activity against *S. Aureus, B. Subtilis, E. Coli* and *P. Aerugenosa* as well as fungi e.g. *C. Albicans* and *A. Niger* and good results were obtained as in comparison with the standards (Std. 1 = Gentamycin and Std. 2 = Clotrimazole).

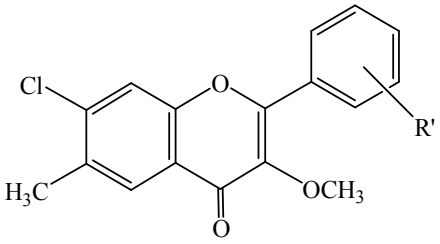


R = i) H, ii) Cl; R_1 = i) C_6H_5 ii) 4-$CH_3C_6H_4$ iii) 3,4-$(OCH_3)C_6H_3$

iv) 4-Cl C_6H_4 v) 4-$N(CH_3)_2C_6H_4$ vi) C_4H_3O vii) 4-F C_6H_5 viii) 4-$OCH_3C_6H_4$

182, 3-Hydroxy-2-phenyl-4H-chromen-4-ones

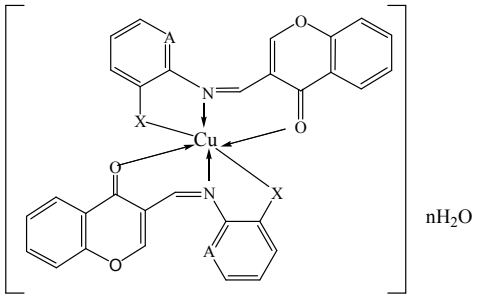
Anjum *et al*(2011)[125] synthesized substituted 3-methoxy-2-phenyl-4-chromones**183**, purified and were screened for their qualitative antimicrobial activity. They were tested against four species of bacteria namely, *Bacillus subtilis* (Gram-positive), *Escheria coli* (Gram-negative), *Pseudomonas aeruginosa* (gram-negative), *Staphylococcus aureus* (Gram-positive). The technique used was Agar Diffusion Method using 100 µg/0.1 mL of Amoxicillin and Gentamycin as standard.



R'= OMe, NMe_2, $(OMe)_2$, CH_3

183

Cu(II) complexes **184** have been synthesized from different Schiff bases, such as 3-((2-hydroxy phenylimino)methyl)-4H-chromen-4-one (HL1), 2-((4-oxo-4H-chromen-3-yl)methylneamino) benzoicacid (HL2), 3-((3-hydroxypyridin-2-ylimino)methyl)-4H-chromen-4-one (HL3) and 3-((2-mercaptophenylimino)methyl)-4H-chromen-4-one (HL4). The complexes were characterized by triclinic system with different unit cell parameters. Antimicrobial, antioxidant and DNA cleavage activities indicate that metal complexes exhibited greater activity as compared with ligands[126].

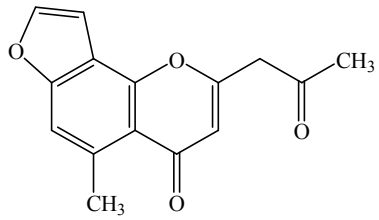


A=C and X=O/S/COO
A=N and X=O

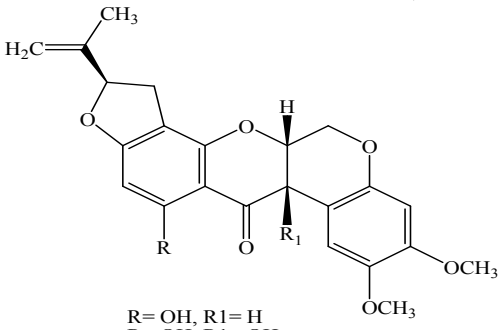
184

3.3. Anticancer Activity

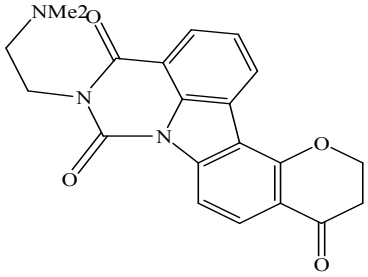
Furoaloesone**185**[127], isolated from the plant *Cape aloe*, is capable to inhibit the growth of cancer cells of the Ehrlich ascitic carcinoma type [127]. (−)-Sumatrol and (±)-villosinol from *Lonchacarpus* aff. *fluvialis*rind exhibited significant cytotoxicity against the cells of human oral epidermal carcinoma. Low toxicity in conjunction with high antitumor activity are also known for the pyrano[2,3-*e*]indol-4(7*H*)-one system[128]. Such properties were found, for example, For compound[128] 12-amino-2-phenylpyrano[2,3-*a*]-acridin-4-one**186** (APPA), investigations of the antiproliferative activity in relation to tyrosine kinase in DHER cells showed that for this compound IC50 = 1.9, while for acronycine IC50 = 3.6 nmol/l. The product APPA also displayed inhibiting activity against more than 60 lines of cancer cells; the IC50 values varied in the range of 0.1-1.4 nmol/l. The best results were obtained for leukemia[128].



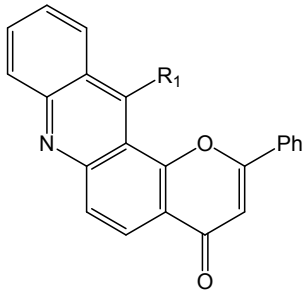
185 , Furoaloesone



R= OH, R1= H
R= OH, R1= OH

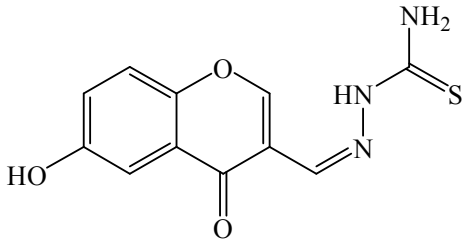


(−)-Sumatrol (±)-villosinol



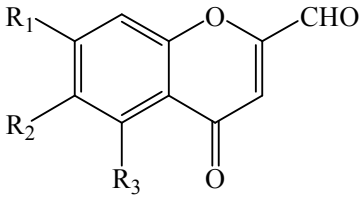
186, 12-amino-2-phenylpyrano [2,3-*a*]-acridin-4-one (APPA)

A new ligand L, 6-hydroxy chromone-3-carbaldehyde thiosemicarbazone**187** and its Ni(II) complex have been synthesized and characterized. Ni(II) complex and ligand L were subjected to biological tests *in vitro* using THP-1, Raji and Hela cancer cell lines. Compared with the ligand, Ni(II) complex showed significant cytotoxic activity against these three cancer cell lines. The interactions of Ni(II) complex and ligand L with calf thymus DNA were then investigated by spectrometric titration, ethidium bromide displacement experiments and viscosity measurements methods. The experimental results indicated that Ni(II) complex bound to DNA by intercalative mode via the ligand L. The intrinsic binding constants of Ni(II) complex and ligand L with DNA were (1.10 ± 0.65) _ 106 M_1 and (1.48 ± 0.57) _ 105 M_1, respectively[129].

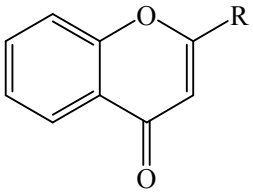


187

Several 3-formylchromone derivatives **188** were examined for their tumor cell-cytotoxic, anti-Helicobacter pylori, urease inhibitory and anti-HIV activity. Comparing their relative cytotoxicity against four human tumor cell lines and three normal human cells, tumor cell-specific cytotoxicity was detected in some 3-formylchromone derivatives. There was no clear-cut relationship between the cytotoxicity and the chemical structures of the compounds. 6,8-Dichloro-3-formylchromone showed comparable anti-H- pylori activity with metronidazole and potent urease inhibition against jack bean urease[130].

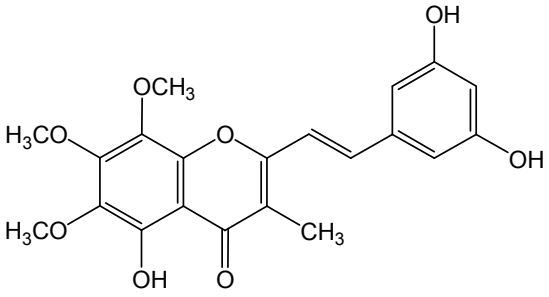


188

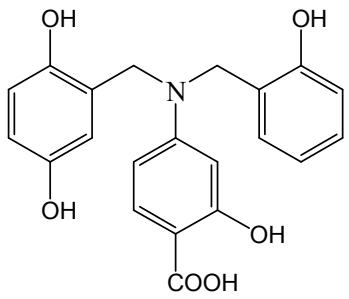


189

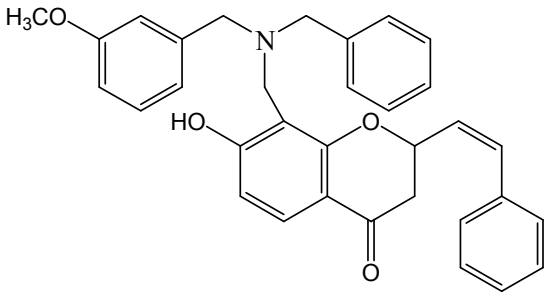
Lavendustin A **191** and hormothamnione **190** were reported to exhibit cytotoxic effects on tumor cell lines. In the present studies, a series of chromone-based lavendustin analogs were synthesized as a simplified hybrid of hormothamnione and lavendustin A by the reductive-amination of formyl-chromone with various amines followed by aminoalkylation. Most compounds synthesized showed significantly improved potencies compared to the standard compound against most of cancer cell lines tested indicating that the removal of styryl group enhanced cancer cell growth inhibitory activities. Compounds **192** and **193** showed the most potent inhibitory activities with GI50 values in the range of 6.01-9.92 mg/ml on A-549 and HCT-15 cells[131].



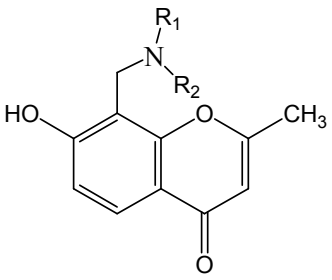
190, hormothamnione



191, Lavendustin A

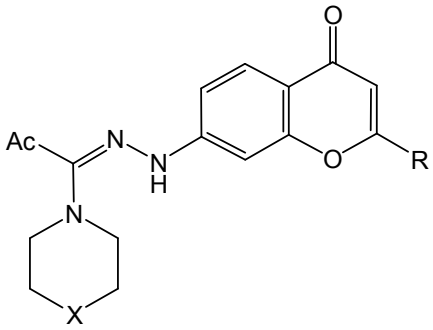


192



193

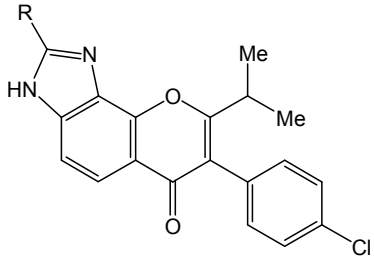
A series of new *N*1-(flavon-7-yl)amidrazones incorporating *N*-piperazines **194**and related congeners were synthesized by reacting the hydrazonoyl chloride derived from 7-aminoflavone and 7-amino-2-methylchromen-4-one with the appropriate piperazine. The antitumor activity of these compounds was evaluated on breast cancer (MCF-7 and T47D) and Leukemic (K562) cell lines by a cell viability assay utilizing the tetrazolium dye 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT). Although with varying degrees, a significant growth inhibitory and cytotoxic effect was observed on all three cancer cell lines[132].



194

3.4. Psychotropic Activity

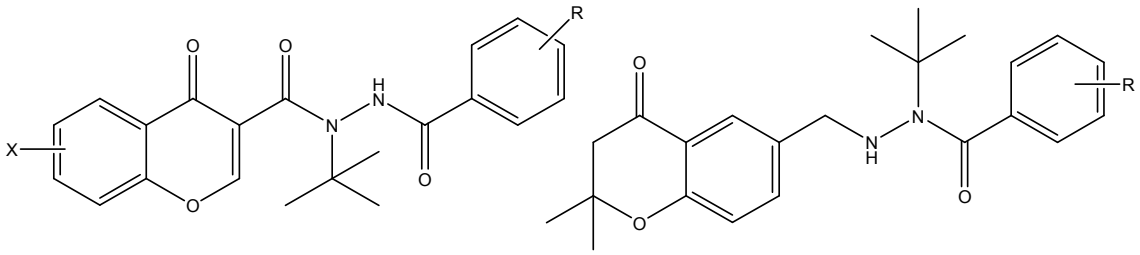
It is known that karangin stimulates the nervous system, whereas pongamol is a sedative agent and depressant (LD50 14.32 and 17.14 mg/kg respectively) [133]. Representatives of the pyrano[2,3-*e*]indol-4(7*H*)-one **195**system are not encountered in nature and are synthetic analogs of natural chromones. The aza analogs of this system showed significant activity as antagonists of vanilloid receptors TRPV-1 [134]. This is important primarily in the treatment of osteoarthritis, pains that accompany cancer, fibromyalgia, and pains during operations of general and gynecological type. Trials carried out on vanilloid receptors TRPV-1 in relation to capsaicin (IC50 = 0.068 μM) showed that this compound is one of the most active antagonists of these receptors (IC50 = 0.054 μM).



195, R = MeCF2

3.5. Insecticidal Activity

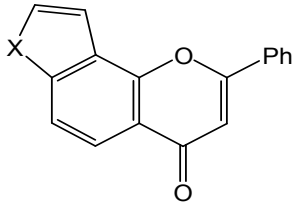
Zhao and coworkers[135] prepared a series of chromanone and chromone analogues of diacylhydrazine derivatives. Some of the chromanone analogues exhibited a good insecticidal activity against Mythima separate at the dosage of 500mg/L.



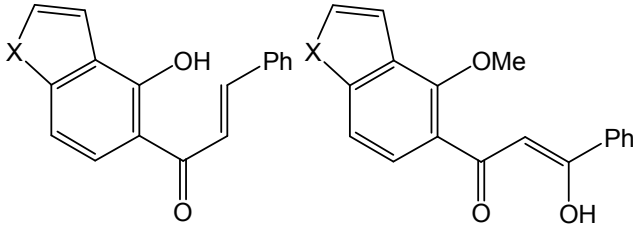
196

3.6. Fungicidal Activity

It is considered that the presence of the methoxyl group at position 5 of the furo[2,3-*h*]chromone system is responsible for the fungicidal activity[136]. The methyl ether of pongaglabol is more active than karangin **180** and lanceolatin B[136]. The latter also displayed fungicidal activity against the fungi *Erysiphe polygoni* and *Ustilago tritici*[136]. Antifungal activity was also found in the *N*-methyl derivatives of pyrano[2,3-*e*]indol-4(7*H*)-ones and the thiophene analogs of karangin and pongamol **181**. The minimum concentration at which the growth of the fungi *Trichophyton mentagrophytes* was inhibited was measured with reference to the fungicide fluconazole as standard. The figure for fluconazole was 2 µg/ml, whereas the value for pongamol and its thiophene analog was 12.5 and 6.25 µg/ml respectively, and for flavone and karangin 12.5 and 6.25 µg/ml respectively[1]. The flavone **197** exhibited fungicidal activity exclusively, while its corresponding chalcone exhibited both fungicidal and antibacterial activity[1]. Antibacterial properties also appeared as a result of replacement of the *N*-methyl group in the β-hydroxychalcone by sulfur in compound **198**[1]. In the series of chalcones the compound with a thiophene ring had higher activity than its aza analog, while the flavone annelated with an *N*-methylpyrrole ring was more active than its thia analog[1].

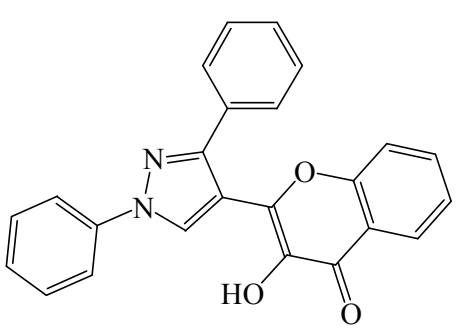


197

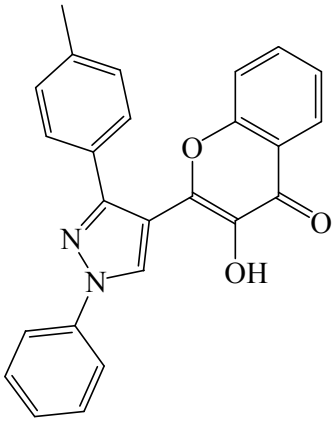


198, X = NMe, X = S

Seven new 3-hydroxy-2-(1-phenyl-3-aryl-4-pyrazolyl) chromones **199, 200** have been synthesized by the oxidation of 2-hydroxychalcone analogues of pyrazole with hydrogen peroxide (H_2O_2) in KOH–MeOH by Algar Flynn Oymanda (AFO) reaction. All the compounds were tested *in vitro* for their antifungal activity against three phytopathogenic fungi, namely*Helminthosporium* species, *Fusarium oxysporum* and *Alternaria alternata*[137].



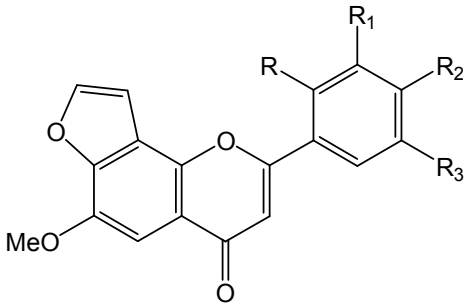
199



200

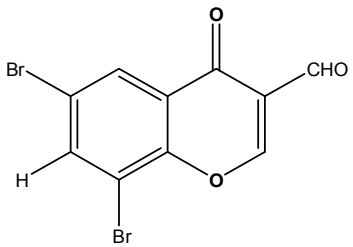
3.7. Antiviral Activity

The methyl ether of pongol**201** isolated from the plant *Millettia erythrocalyx*, exhibited activity against both types of herpes virus HSV-1 and HSV-2[138]. Activity against human immunodeficiency virus (HIV) and herpes virus was found in alkaloids from the *Schumanniophyton* plants. The presence of the piperidine ring and unsubstituted hydroxyl groups in their molecules is responsible for the activity against HIV[139].

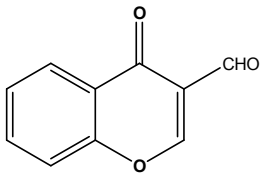


201, R = R2 = R3 = H, R1 = OH

6,8-Bibromo-3-formylchromone exhibited potent inhibitory activity against the urease, but had no anti-H-pylori activity[130].

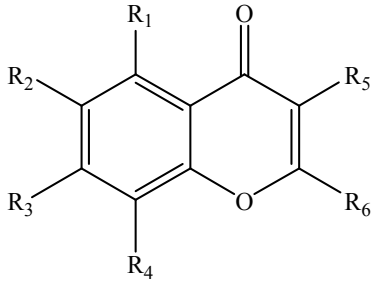


202



189

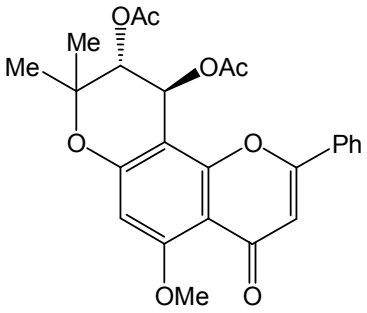
Novel chromone derivatives with a benzopyran-4-one scaffold have been prepared by the one-pot cyclization reaction. The *in vitro* inhibitory activity of these new compounds towards HIV-1 protease has been evaluated using stop time HPLC method as the preliminary screening. The most potent compound, 7,8-dihydroxy-2-(3′-trifluoromethyl phenyl)-3-(3″-trifluoromethylbenzoyl)chromone **203**, showed IC50 = 0.34 μM. The molecular docking study supported results from experimental activity testing and also provided structure–activity relationship of this series[140].



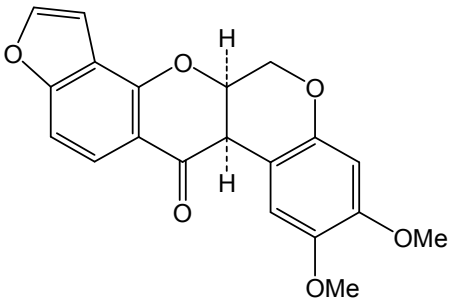
203, R5,R6= 3-(CF3)phenyl or benzoyl, R1-4= H, OH

3.8. Interaction with NADPH-dependent Quinone Reductase

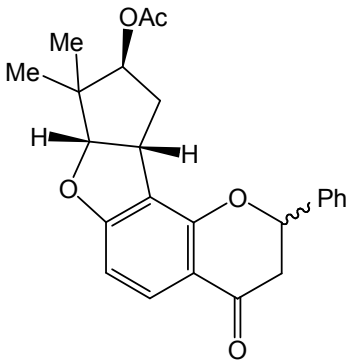
Trials carried out on the action of an extract from the root of the plant *Pongamia pinnata* in petroleum ether, containing a compound (a derivative of 4*H*,8*H*-pyrano[2,3-*f*]chromene-4,8-dione)**204** showed that the substances from the extract activate NADPH-dependent quinone reductase[141]. The inhibition of the latter explains the ability of 1-elliptone **205** present in the plants of the *Tephrosia* genus, to attack neuron mitochondria, which makes it an excellent piscicide (a substance capable of fish poisoning; it is used to control the number of fish in water reservoirs or in the fight against invasions of fish parasites). Trials on an extract from a plant of the *Tephrosia purpurea* genus, containing lanceolatin B, lanceolatin C (pongamol), and also purpurin **206** karangin **180** and kanjone **207**carried out on the cells of rat hepatoma Hepa 1c1c7 showed that it is capable of activating quinone reductase [141].

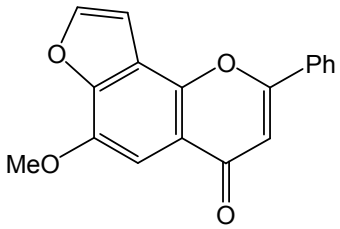


Kanjone



Elliptone





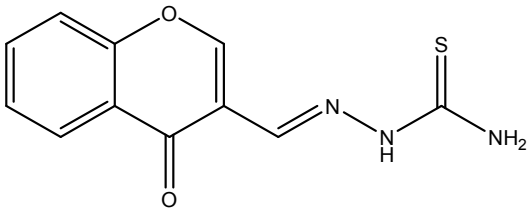
Purpurin

204-207: 4*H*,8*H*-pyrano[2,3-*f*]chromene-4,8-dione derivatives

3.9. DNA binding and fluorescence

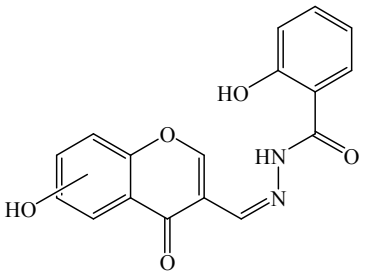
Yong and co-workers[142] (2010) showed that 3-carbaldehyde chromone thiosemicarbazone (L) 208 and its transition metal complexes were synthesized and characterized systematically. Zn(II) and Ni(II) complexes exhibit blue fluorescence under UV light and its fluorescent property in solid state was investigated. Interactions of ligand and Cu(II), Zn(II) and Ni(II) complexes with DNA were investigated

by spectral and viscosity studies, indicating the compounds bind to DNA *via* intercalation and Zn(II) complex binds to DNA most strongly. Antioxidant tests *in vitro* show the compounds possess significant antioxidant activity against superoxide and hydroxyl radicals, and the scavenging effects of Cu(II) complex are stronger than Zn(II), Ni(II) complexes and some standard antioxidants, such as mannitol and vitamin C.



208

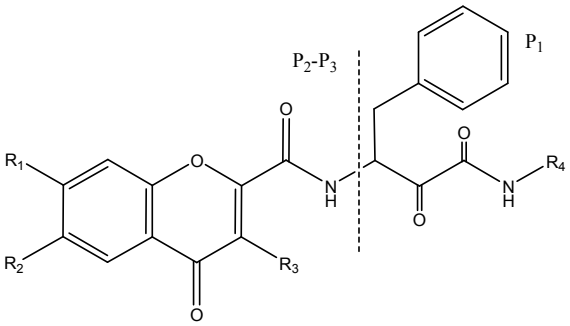
A new ligand, 6-hydroxy chromone-3-carbaldehyde-(2′-hydroxy) benzoyl hydrazone (L) **209** was prepared by condensation of 6-hydroxy-3-carbaldehyde chromone (CDC) with 2-hydroxy benzoyl hydrazine. Its four rare earth complexes have been synthesized. The general formula of the complexes is [LnL2·(NO3)2]·NO3 [Ln = La(**1**), Sm(**2**), Dy(**3**), Eu(**4**)]. Spectrometric titration, ethidium bromide displacement experiments, and viscosity measurements indicate that Eu(III) complex and ligand, especially the Eu(III) complex, strongly bind with calf-thymus DNA, presumably via an intercalation mechanism. The intrinsic binding constants of Eu(III) complex and ligand with DNA were 3.55 × 106 and 1.33 × 106 M−1 through fluorescence titration data, respectively. In addition, the suppression ratio for $O_2^{-\cdot}$ and OH. of the ligand and its complexes was studied by spectrophotometric methods. The experimental results show that La (**1**), Sm (**2**), and Eu (**4**) complexes are better effective inhibitor for OH. than that of mannitol. It indicates that the complexes have the activity to suppress $O_2^{-\cdot}$ and OH. and exhibit more effective antioxidants than ligand alone[143].



209

3.10. Calpain inhibitors

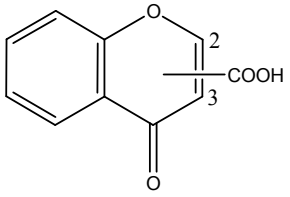
Excessive calpain activations contribute to serious cellular damage and have been found in many pathological conditions. Novel chromone carboxamides **210** derived from ketoamides were prepared and evaluated for μ-calpain inhibition[144].



210

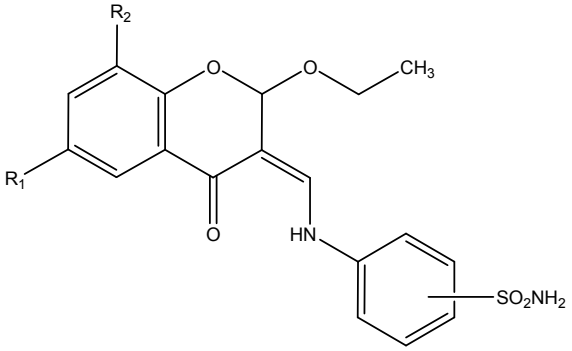
3.10.1. As potent and selectivity MAO inhibitor

Chromone carboxylic acids were evaluated as human monoamine oxidase A and B (*h*MAO-A and *h*MAO-B) inhibitors. The biological data indicated that only chromone-3-carboxylic acid **211**is a potent *h*MAO-B inhibitor, with a high degree of selectivity for *h*MAO-B compared to *h*MAO-A. Conversely the chromone-2-carboxylic acid resulted almost inactive against both MAO isoforms. Docking experiments were performed to elucidate the reasons of the different MAO IC50 data and to explain the absence of activity versus selectivity, respectively[145].



211

Series of chromone containing sulfonamides **212** were prepared by the reaction of (un)substituted 3-formylchromones with 3-aminobenzenesulfonamide and 4-aminobenzenesulfonamide. Bovine carbonic anhydrase (bCA) inhibitory activity of these newly synthesized compounds was determined. All compounds were active and possessed excellent bCA inhibitory activities with IC50 values ranged between 4.31 ± 0.001 and 29.12 ± 0.008 µmol. Compounds derived from 6-fluoro-3-formylchromones were the most active[146].

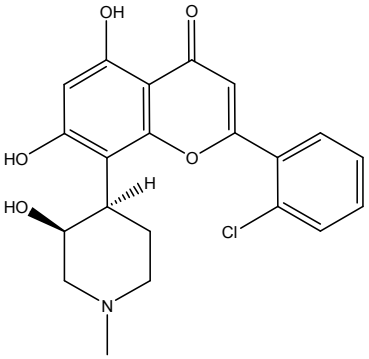


212

4. Recent drugs having chromone structures

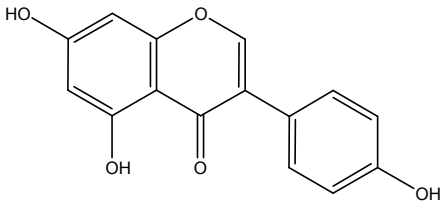
Current medical treatments with chromone derivatives can be exemplified by:

- **Sodium cromoglycate** (Lomudal®): used as a mast cell stabilizer in allergic rhinitis, asthma and allergic conjunctivitis [16, 19-23].It prevents the release of histamine from mast cells and is administrated as a disodium salt[44].
- **Diosmin** (Daflon®): for the treatment of venous diseases[16, 19-23].
- **Flavoxate**: a smooth muscle relaxant to treat urge incontinence[16, 19-23].
- **Nabilone** (Cesamet®): which is a cannabinoid used as an antiemetic drug[45].
- **Alvocidib** (INN; also known as Flavopiridol or HMR-1275) is a cyclin-dependent kinase inhibitor under clinical development for the treatment of chronic lymphocytic leukemia. It has been studied also for the treatment of arthritis[147] and atherosclerotic plaque formation[148]. The target of Flavopiridol is the positive transcription elongation factor P-TEFb. Treatment of cells with Flavopiridol leads to inhibition of P-TEFb and the loss of mRNA production.



IUPAC name: 2-(2-chlorophenyl)-5,7-dihydroxy-8-[(3S,4R)-3-hydroxy-1-methyl-4-piperidinyl]-4-chromenone (Alvocidib)

- **Genistein**
  (5,7-Dihydroxy-3-(4-hydroxyphenyl)chromen-4-one) Isoflavones, such as genistein is found in a number of plants including lupin, fava beans, soybeans, kudzu, and psoralea being the primary food source,[149,150] also in the medicinal plant, *Flemingia vestita*[149] and coffee[150]. Besides functioning as antioxidant and anthelmintic, many isoflavones have been shown to interact with animal and humanestrogen receptors, causing effects in the body similar to those caused by the hormone estrogen. Isoflavones also produce non-hormonal effects.



Genistein is one of several known isoflavones

- **Cromoglicic acid** (INN) (also referred to as cromolyn (USAN), cromoglycate (former BAN), or cromoglicate) is traditionally described as a mast cell stabilizer, and is commonly marketed as the sodium salt sodium cromoglicate or cromolyn sodium. This drug prevents the release of inflammatory chemicals such as histamine from mast cells. Because of their convenience (and perceived safety), leukotriene receptor antagonists have largely replaced it as the non-corticosteroid treatment of choice in the treatment of asthma. Cromoglicic acid requires administration four times daily, and does not provide additive benefit in combination with inhaled corticosteroids[150].
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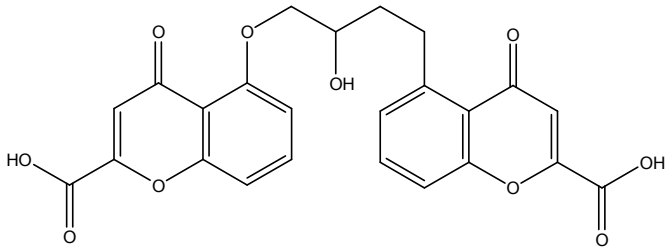

5,5′-(2-hydroxypropane-1,3-diyl)bis(oxy) bis(4-oxo-4*H*-chromene-2-carboxylic acid)

5. CONCLUSION

The present review represents a board description for the methods used in the synthesis of chromones and some of its derivatives. The rigid bicyclic chromone fragment has been classified as a privileged structure in drug discovery, due to its use in a wide variety of pharmacologically active compounds; few examples as therapeutic agents chromones are used as scaffolds for the development of bioactive compounds, the application in medicinal chemistry, such as preparation of

fluorescence probes, due to photochemical properties of chromones have been also mentioned. This review is limited to the work done during the last ten years.

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