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Pharmacological Importance and Synthesis of Chromone and its Derivatives : A Short Review

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ABSTRACT:

The search for safer drugs is always the main focus of various medicinal chemistry researchers. Chromones (4H-chromen-4-ones) represents a group of naturally occurring compounds pervasive in plants, and the chromone core has been proved to be a precious scaffold in pharmacological chemistry. This review paper is therefore done on purpose to orient the researchers for the design and synthesis of novel chromone core based compounds and development of more efficient and safer drugs. Many efforts are done for searching these compounds from natural sources as well as for synthesising compounds containing chromone core having enhanced biological activities and synthesising them in high yield to make pharmacological studies and clinical uses. Molecules containing the chromone core possess wide range of biological properties like antifungal, antibacterial, anti-allergic, anti-inflammatory, antiviral,etc.This review represent the medicinal importance and various procedure regarding the synthesis of chromones and their derivatives.

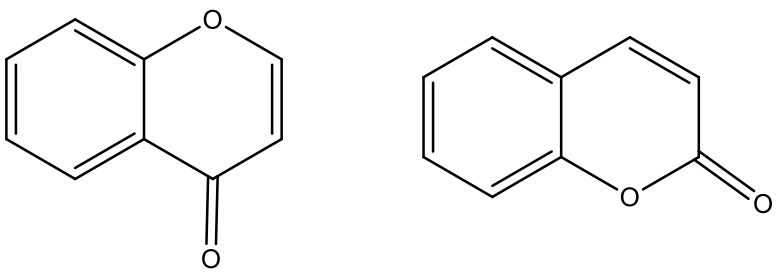
Keywords: ***Chromone, anti-inflammatory, analgesic, antifungal, antibacterial.***

INTRODUCTION:

Although there are a wide variety of antibiotics available that are used commercially as medicines, but synthesis of new compounds is always of great use due to increasing drug resistance. Heterocyclic compounds having nitrogen, oxygen or sulphur possess numerous biological activities.

Chromones represent a group of compounds that are naturally present almost everywhere specially in plants [1]. Chromone skeleton containing molecules were found to possess various biological activities including antimicrobial, antiallergesic, antiviral, antihypertensive, anti-inflammatory, antitumor etc. as well as these compounds were having the potential of inhibiting various enzymes that are involved in causing broad range of diseases [2,3].

Chromone **1** is a derivative of benzopyran with a substituted ketone group on the pyran ring. It is an isomer of coumarin **2**.



1 **2**

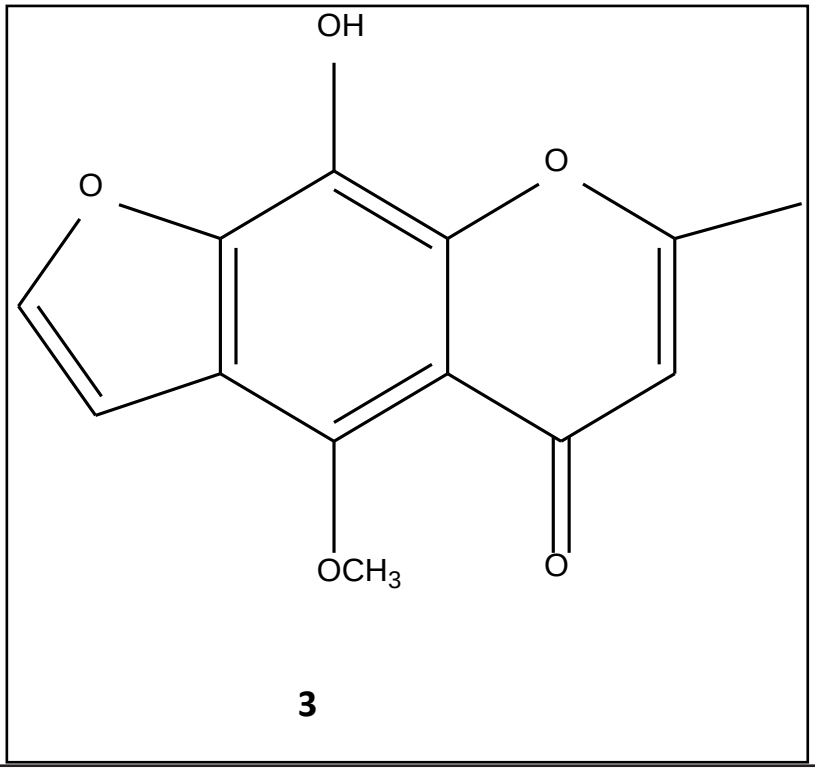
Structure of chromone[4,5]

PHARMACOLOGICAL VALUES OF CHROMONES AND THEIR DERIVATIVES:

Chromones as well as other heterocyclic compounds bearing it at different positions are found to have various biological activities. Chromones substituted heterocyclic compounds are found to have antibacterial and antifungal activities [6-9].

A large number of heterocyclic compounds having chromone moiety were reported to actvariously on central nervous system. It was found in literature that khellin (2-Methyl-5,9di-methoxyfuro[3',2',6,7] Chromone) **3** was the first known heterocyclic compound that was having chromone moiety. It was extracted from Ammi viisnaga L. (khellah plant). Khellin [10] and 2,4-thiazolidinedione derivatives of chromone [11-13] are the chromone derivatives reported as antispasmodic agent. Khellin has also been found to be vasodilator [14-22], and bronchiodilator [23-25]. This compound was reported to possess a number of pharmacological activities that created interest of researchers in the studies of this compound [26-34]. Khellin has also been used for centuries in the Mediterranean area as diuretic [35]. It was also used in the treatment of angina pectoris and asthma [36]. Presently Khellin is used in the treatment of vitiligo a pigmentation disorder [37].

Although Khellin was considered to have broad pharmacological activity, but high toxicity and low water solubility were its major drawbacks. Henceforth, its analogues were synthesized with the objective of synthesizing its substitutes that can overcome these drawbacks. For example, 2-methyl-5-(2-dimethyl-aminoethoxy)-9-methoxyfuro[3',2',6, 7]chromone methotheophylline **4** [38] and 9-(2-diethylaminoethoxy-5-hydroxy-2-methylfuro[3',2',6,7]chromone hydrochloride **5** [39] were synthesized and examined. These compounds were found slightly useful although these were less potent than Khellin.



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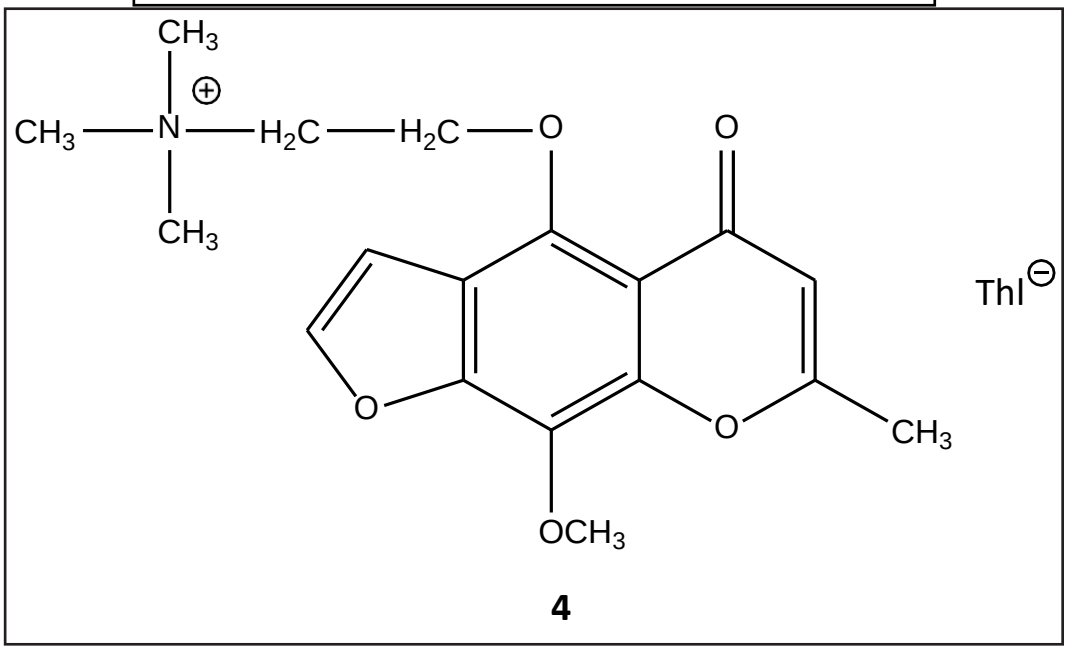

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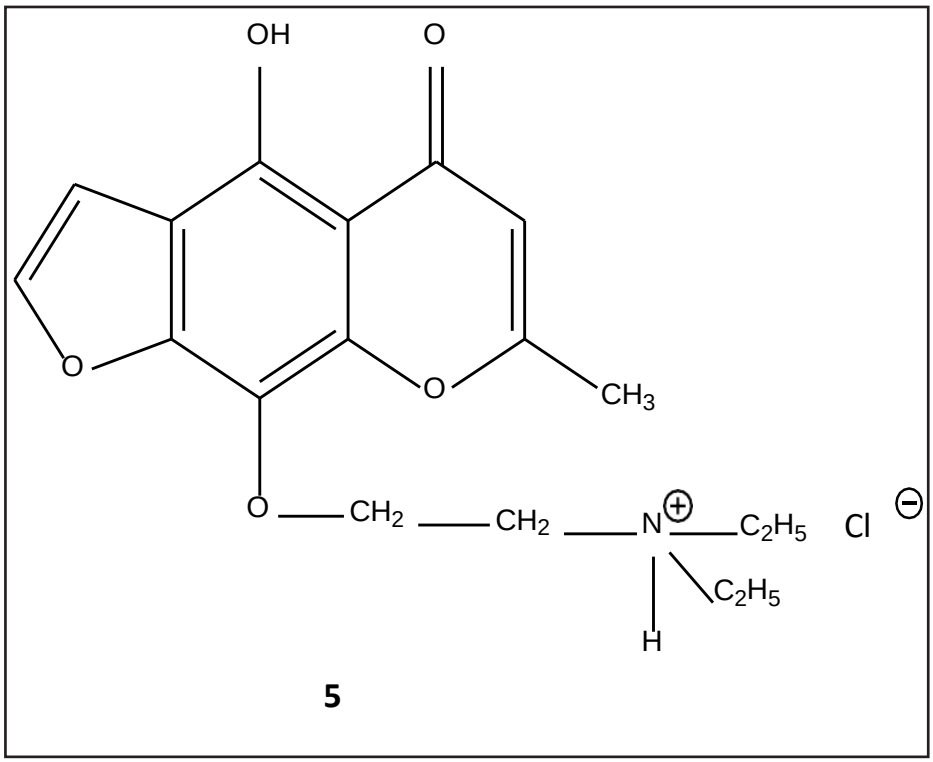

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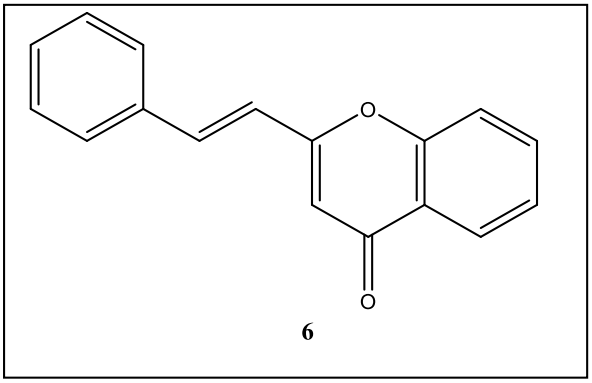
A large number of compounds having chromone moiety are reported time to time for possessing various pharmacological activity. 2-Styryl chromone **6** is a group of natural and synthetic chromones possessing therapeutic applications in the treatment of allergies [40], cancers [41-45], gout [46], and oxidative stress related damage [47]. The antioxidant behaviour of 2-styrylchromone is of great interest. 3',4'-dihydroxy-2-styrylchromone derivatives **7** were found to possess good scavanging activities [48] against reactive oxygen species (ROS) and reactive nitrogen species (RNS).



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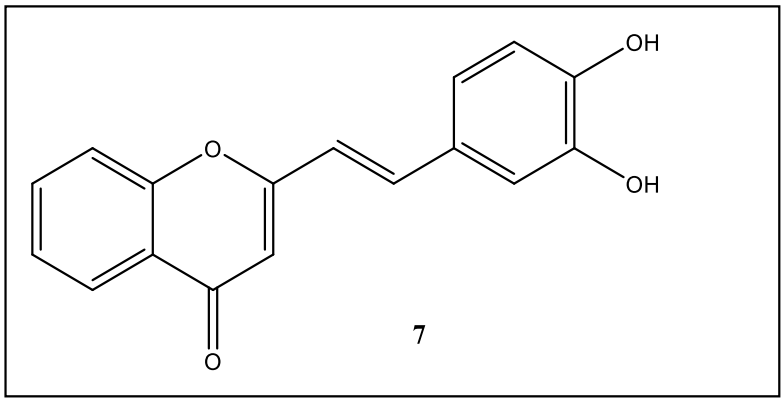

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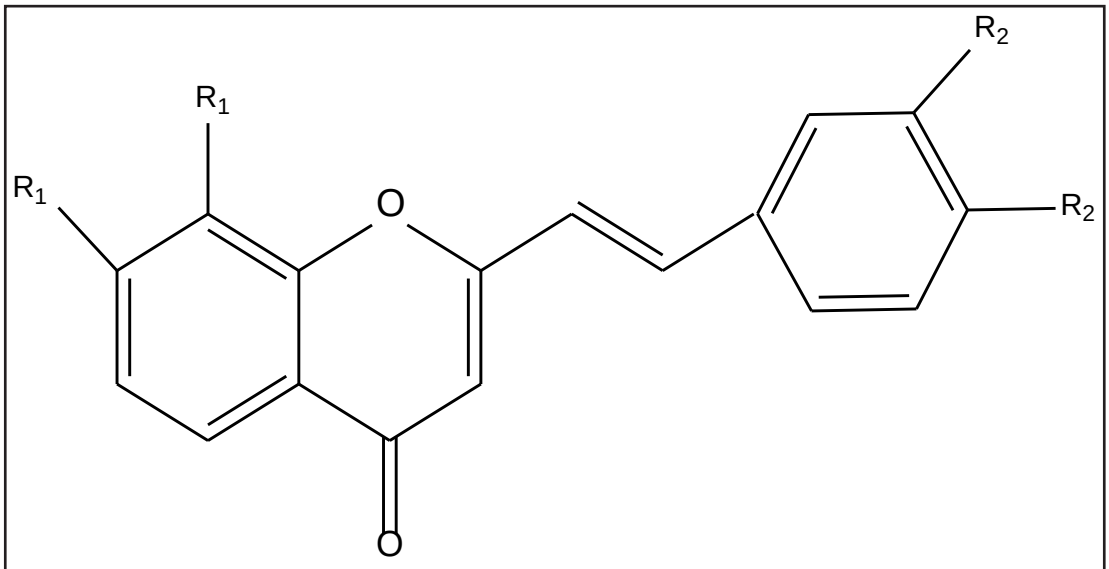
Ana Gomes et al. have synthesized new compound **8(a-c)** and tested these compounds to show scavanging activities against (ROS) and (RNS), although these were less effective than already tested compound **7** for the same activity [49].



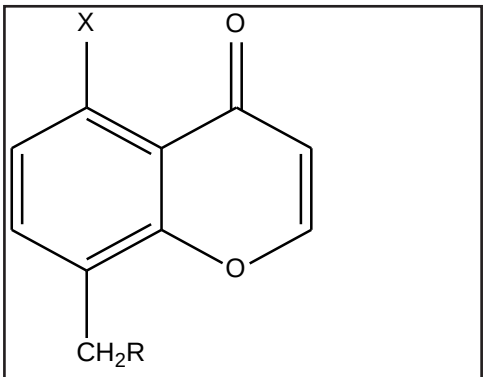
8a) R_1=OMe;R_2=OH

8 b) R_1=OH;R_2=OH

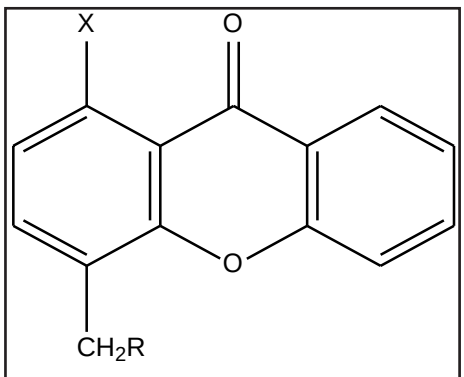
8 c) R_1=OH;R_2=OMe

Maurizio Recanatini et al. [50] synthesized compound **9(a-c)** and also compounds **9(d- f)** having Nimidazolyl methyl substituent in position 8 of chromone ring in **9(a-c)** and in position 4 of Xanthone nucleus in **9(d-f)** driven by the fact that chromone nucleus can be used as a carrier of pharmacophoric group in many pharmacological fields like bradycardic [51], adrenergic beta blocking agent [52], analeptics[53], acetylcholinesterase inhibitors [54].

Maurizio Recanatini et al. [50] found that compounds **9(a-f)** behave as aromatase inhibitors that can be considered for development as anticancer drugs.

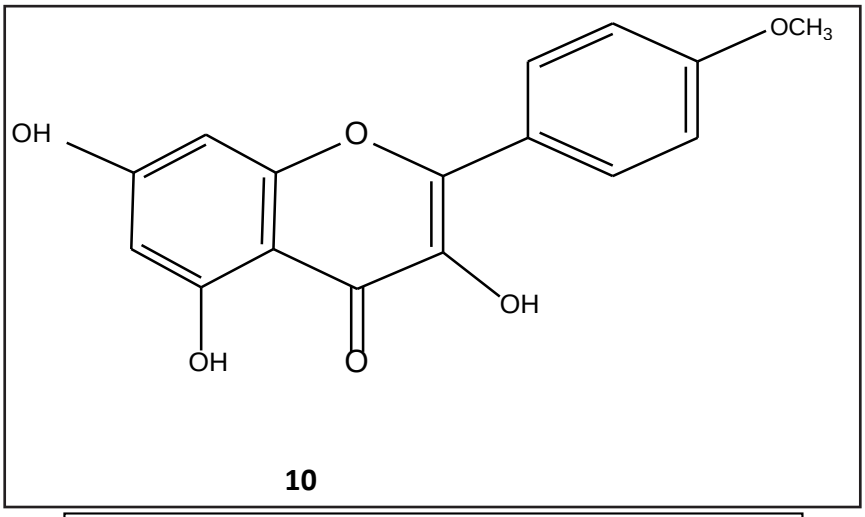


9.a):X=CN;R=imidazol-1-yl
9.b)X=NO_2;R=imidazol-1-yl
9.c)X=Br;R=imidazol-1-yl



9.d):X=CN;R=imidazol-1-yl
9.e)X=NO_2;R=imidazol-1-yl
9.f)X=Br;R=imidazol-1-yl

Gao and his colleagues [55] isolated the components of a health liquor Zhuyeqing liquor. It is a famous Chinese functional health liquor. This liquor was studied to have number of components but two were isolated named Kaempferide**10** and 5- hydroxy- 3',4',7,8- tetramethoxy-flavonol **11**. These two compounds were found to possess NO inhibitory activity.



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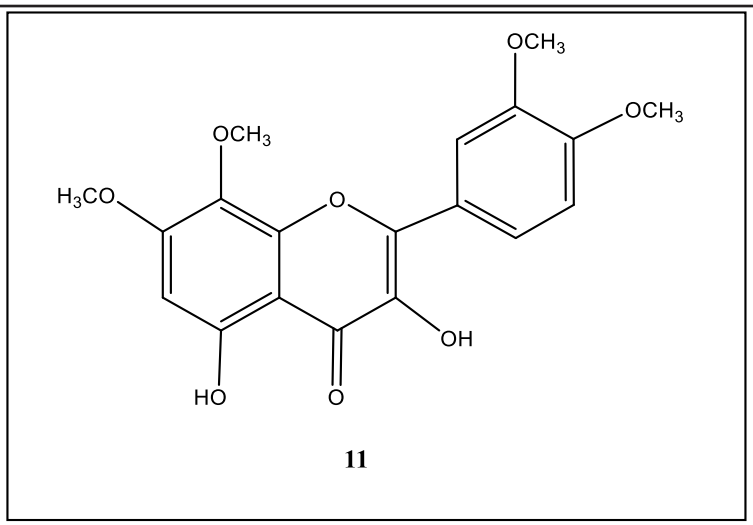

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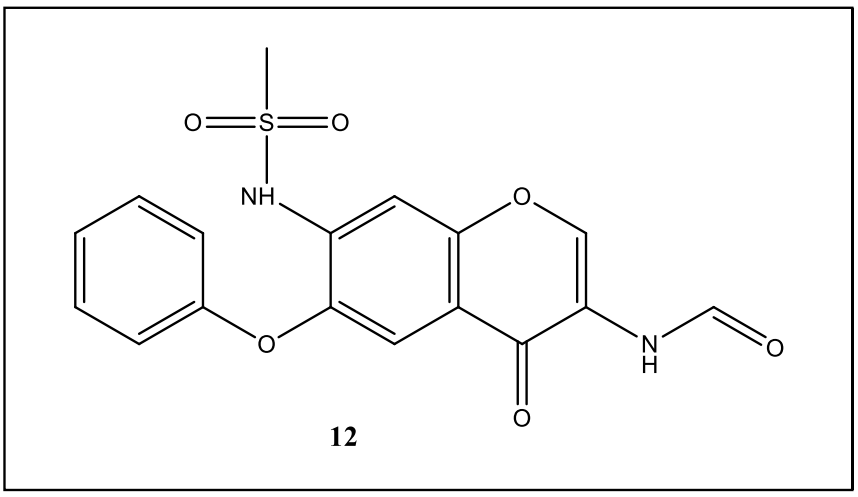
N-(3-formamido-4-oxo-6-phenoxy-4H-chromen-7-yl)methanesul-fonamide **12** also known as iguratimod was the first chromone identified to show Cox inhibitory activity amongst many chromone based compounds that showed considerable inhibitory activities towards both Cox-1 and Cox-2 [56]. The chromone core has been considered useful for synthesizing new anti-inflammatory agents [57,58] since several novel compounds that shown capacity to inhibit Cox enzyme were found to have chromone moiety [59,60].



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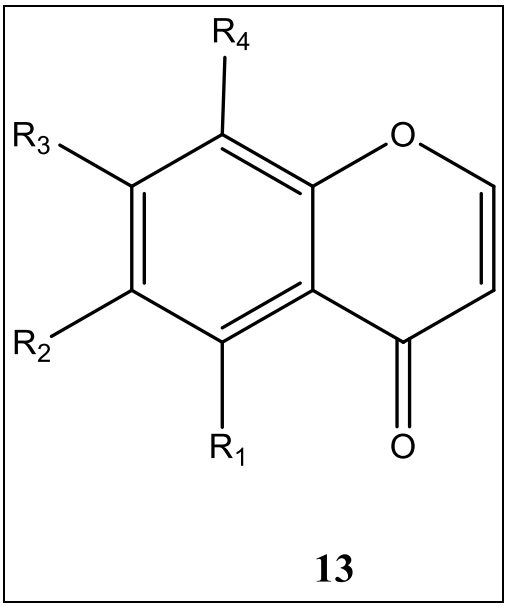
Anti-inflammatory activity were discovered in stellatin that is a major proportion of *Dysophylla stellate* Benth. Ex wall. It was found to show antiinflammation action as COX inhibitor [59]. This research worked as inspiration for developing new analogues of chromone. Studies of structure activity relationship (SAR) of chromones by causing inhibition of COX established a basic pharmophore **13** having a C_2=C_3 double bond, 5-hydroxysubstituent and 4-carboxyl group as necessary features for causing inhibition of COX [57].



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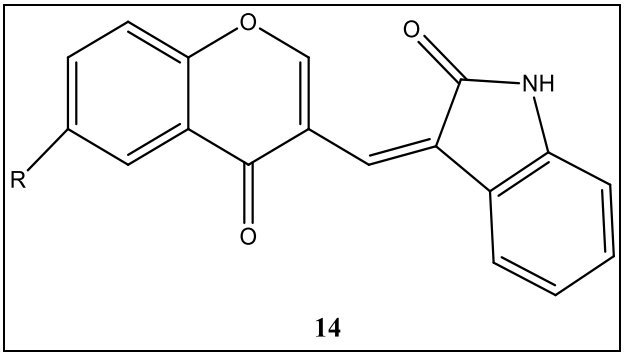
Designing of new COX inhibitors promoted synthesis of various hybrid molecule by combining different biologically active molecule. Hybrids were supposed to possess higher biological activities than their components. Several hybrid molecules containing chromone and indole groups were synthesized and evaluated for their COX inhibiting potential [61]. Combination of chromone with oxindole **14** showed considerable inhibition and selectivity for COX-2 over COX. These hybrid compounds were having higher COX inhibition for COX-2 and better selectivity for COX-2 over COX-1 as compared to the parent compound Wogonin **15**. This study was done by Shaveta et al and it has proved that these hybrid molecules obtained by combining two biologically active groups show considerably greater activity than the components from which these are derived [61].



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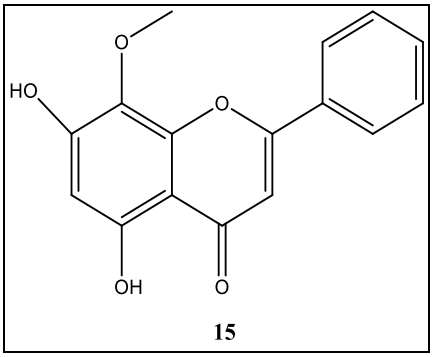

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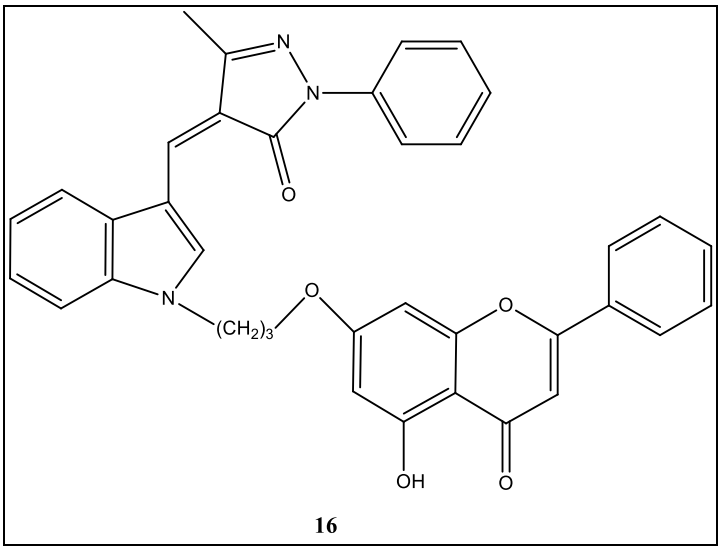
Shaveta and co-workers combined chrysin with indole and pyrazole rings. By proper combination of these three rings, a number of hybrid molecules were synthesized and their COX inhibitory activities were evaluated [62]. One of the synthesized compound **16** showed considerable COX inhibitory activity and good selectivity for COX-2 than COX-1.



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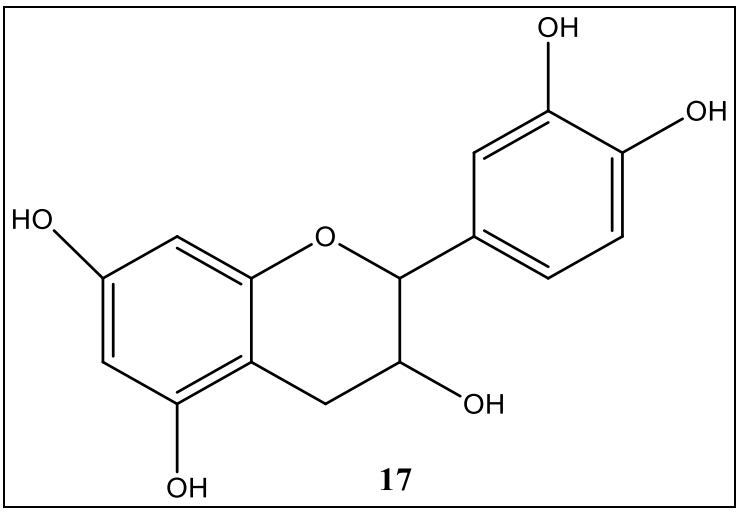
Many plants that were found to contain chromone derivatives were used in traditional medicine [63]. For example, flavocoxid which is marketed as Limbrel, contain naturally existing compounds catechin **17** and baicalin **18.** This acts as inhibitor of COX as well as 5- LOX [64].



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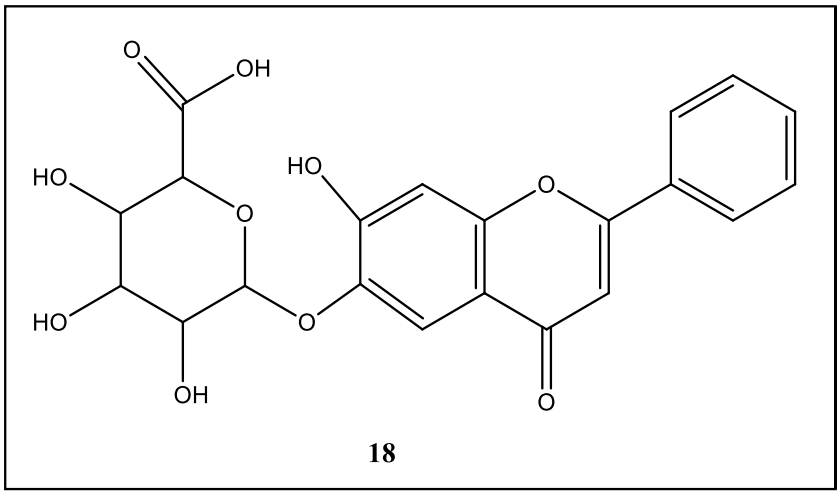

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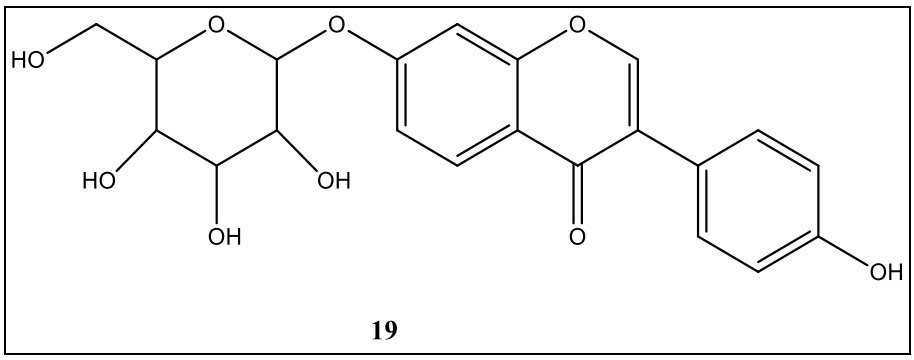
Zhao et al. studied selected chinese herbs of medicinal properties and evaluated these for 5-LOX inhibitory activity [65]. Among the constituents of these herbs various chromone derivatives like daidzin **19**, 3'-hydroxypuerarin **20** and daidzein **21** showed considerable medicinal properties.



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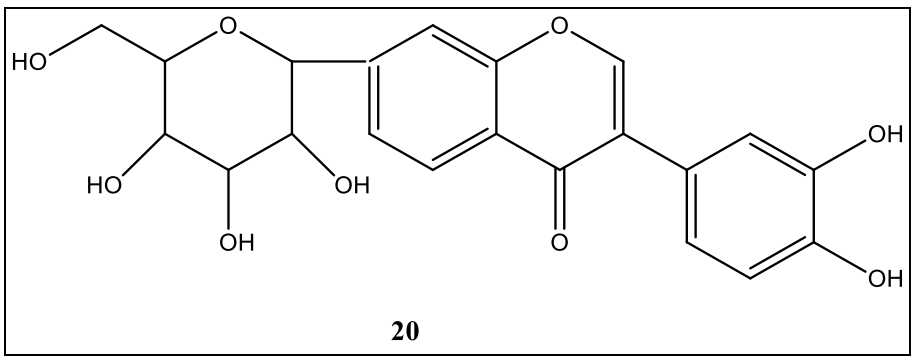

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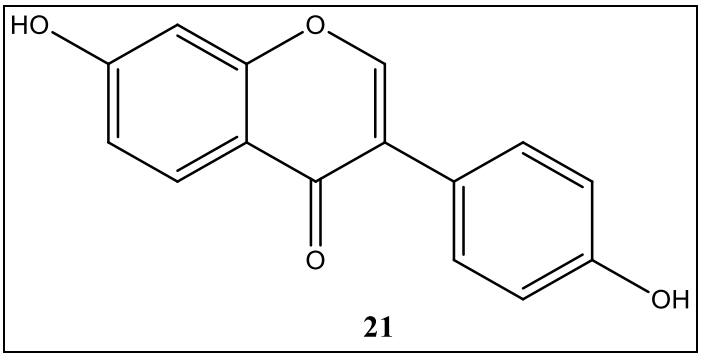

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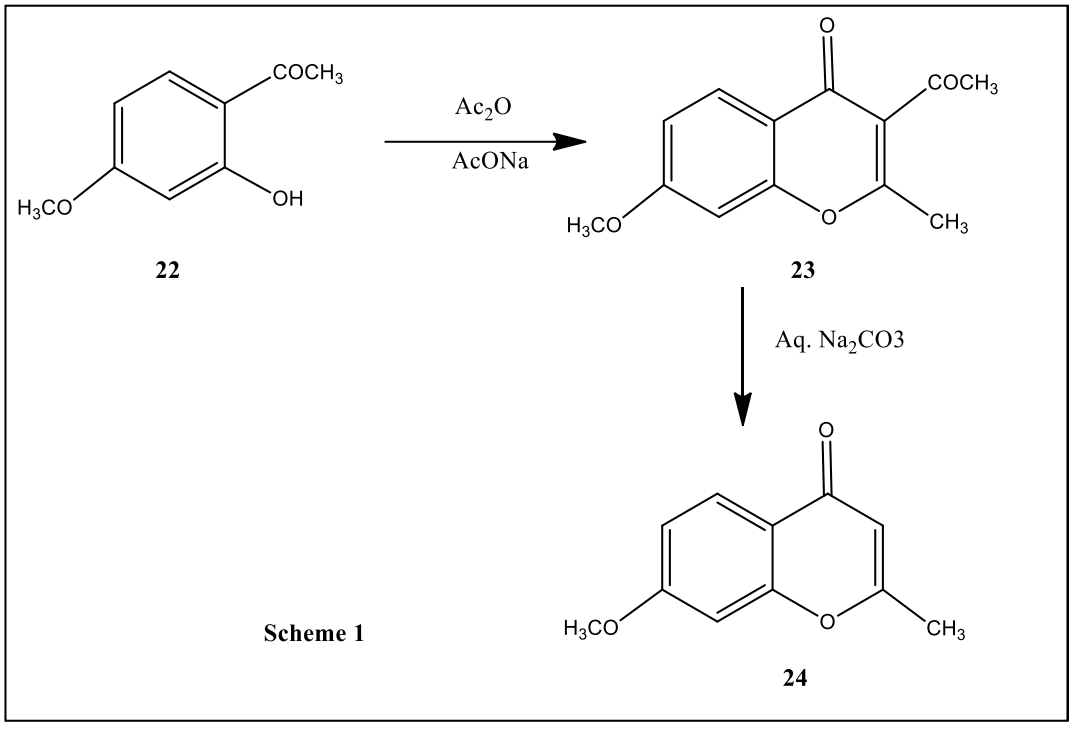
VARIOUS SYNTHETIC ROUTES OF CHROMONES AND THEIR DERIVATIVES:-

Throughout the years various methods have been used for the synthesis of chromones. A brief description of various methods for synthesis of chromones is described as below:

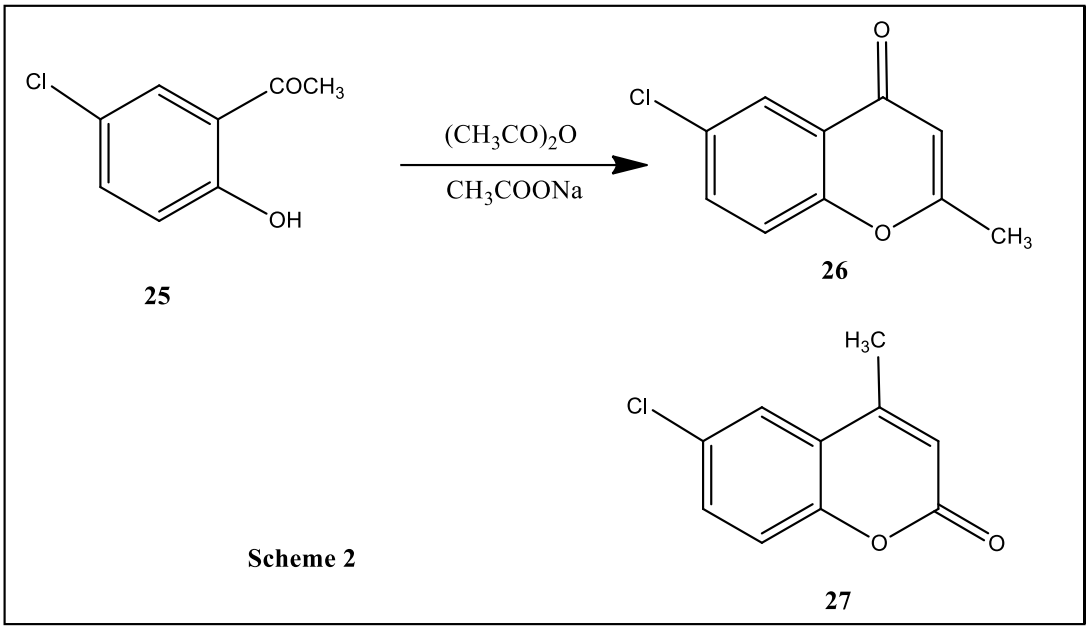
1. Kostanecki-Robinson method: One of the first method was developed by Heywang and Kostanecki. In this method 2'-hydroxy -acetophenone **22** was allowed to react with an anhydride resulting into the synthesis of chromone core **24** through intermediate **23** [66]. (Scheme-1)

Robinson et al [67] extended this procedure further. They synthesized flavones by treating o-hydroxyacetophenones with sodium salts of aromatic acids and acid anhydrides. This reaction is named as kostanecki-Robinson synthesis. But in this reaction along with chromone side product coumarin was also produced. 2-hydroxy-5-chloroacetophenone **25** on reaction with acid anhydride and sodium salts of aromatic acids gave chromone **26** as well as coumarin **27** [68] (Scheme-2)



22 **23** **24**

Scheme 1



25 26 27

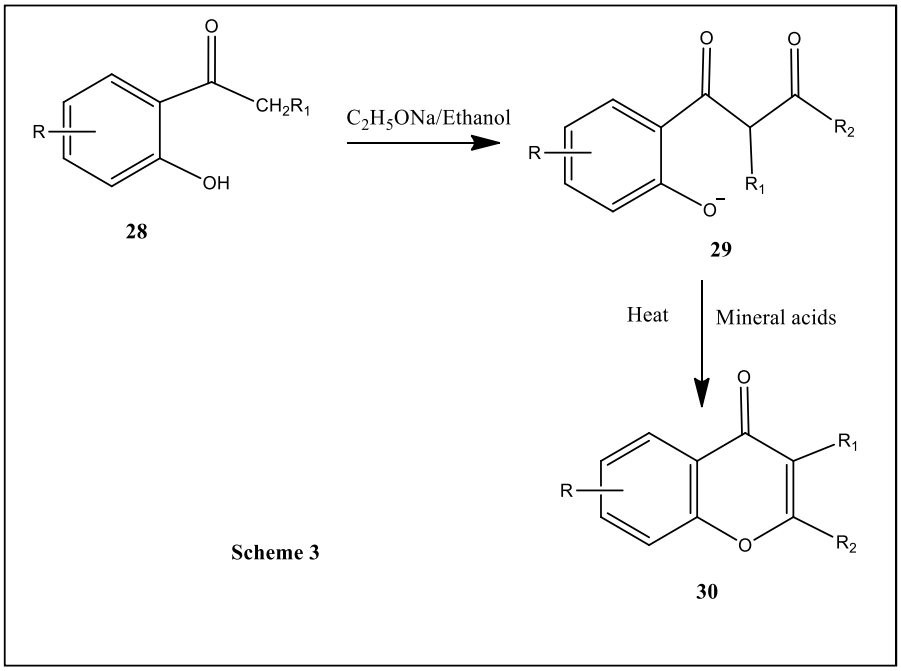
Scheme 2

2. **Classic Claisen condensation method:** This method was first used by Kostanecki, Paul and tambor [69] for the synthesis of 7-ethoxychromone-2-carboxylicacid. The starting compound is o-hydroxyarylalkyl ketone **28**. The reaction occurs in two steps. The first step uses a strong base generally sodium ethoxide in ethanol to give enolate that reacts with a carboxylic ester giving 1,3-dioxo-phenoxy intermediate **29**. In second step this intermediate undergoes cyclization under acidic conditions using heating to give chromone **30** [70-72] (Scheme-3).

Variety of acidic catalysts were used in this reaction with passage of time such as hydrochloric acid, polyphosphoric acids, hydroiodic acid, sulphuric acid, per chloric acids and also organic acids like acetic acids , p-toluene sulphonic acids and also the dehydrating agents like methanesulfonyl chloride, phosphorous oxy chloride etc. [73]. Later on with the passage of years various other catalysts were used focusing on mild reaction condition for synthesizing 1,3-dioxo-phenoxy intermediate **29**, like triethylamine [74], LiH [75], NaH in pyridine [76-78].

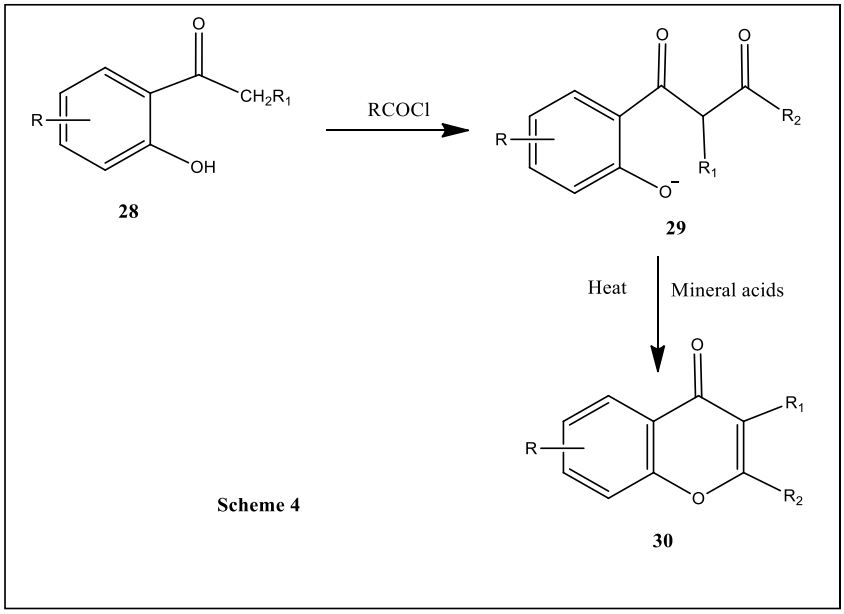
Several chromone derivatives like 2,6-dimethylchromone and 2-methyl-6-Chloro chromone were synthesized using microwave irradiation to reduce reaction time [79]. Mozingo et al. [80] synthesized alkyl chromones like 2-ethyl chromone by modifying claisen condensation. In their method o-hydroxy acetophenone was condensed with an ester using Na as catalyst to get 1,3-diketone intermediate. The intermediate was treated with inorganic acids like HCl to cause intramolecular cyclization resulting in chromone product.

Later on several modifications were reported. Several chromones were obtained from o-hydroxy acetophenone by condensing it with tertbutyl-ethyl oxalate. Condensation was followed by cyclodehydration using concentrated HCl [81]. Reaction time was reduced and yield was improved with the use of tertbuty-lethyloxalate.



Scheme 3

3. **Baker Venkataraman Rearrangement:** Baker- Venkataraman done the acylation of o-hydroxyl alkyl aryl ketones **28** with acyl chlorides in basic medium to give 1,3-dioxophenoxy salt intermediate. It then undergoes cyclization under severe acidic conditions like in presence of H_2SO_4 (Scheme-4).



Scheme 4

Originally the Baker-Venkataraman rearrangement [82,83] was used for synthesizing a flavone. Starting material for that reaction was an o-benzoyloxyacetophenone that undergoes intramolecular rearrangement in the presence of a base like potassium carbonate, resulting in the formation of o-hydroxydibenzoyl methane intermediate. The intermediate was isolated and subjected to cyclization in the presence of strong acids.

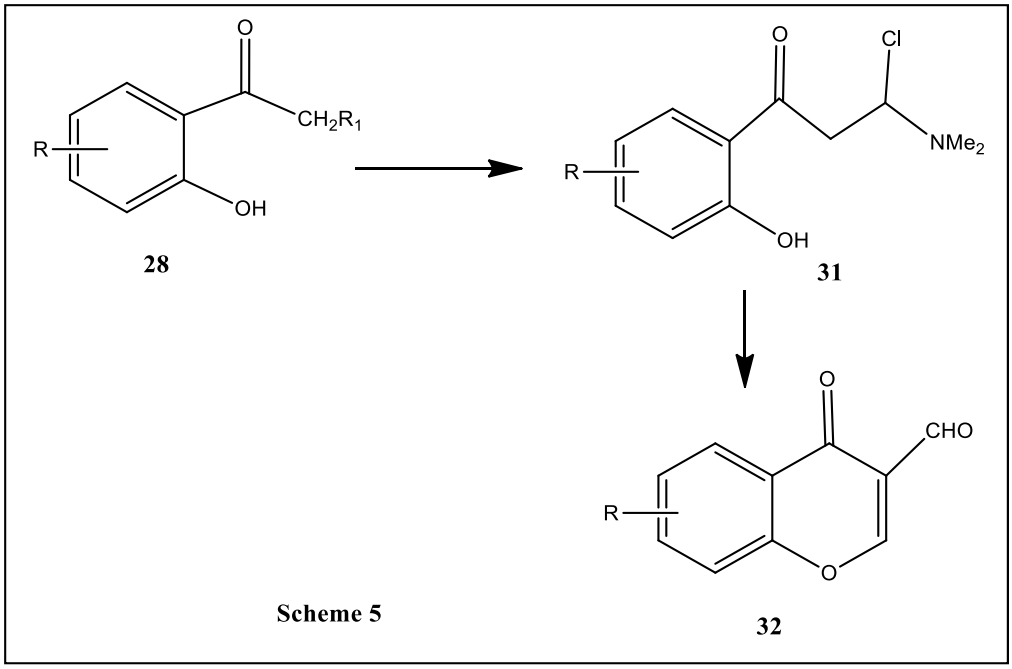
2-styrylchromones are synthesized by Baker-Venkataraman rearrangement [84-88].

Later on several modifications were made in this method, like performing cyclization process in situ, using pyridine as catalyst [89,90]. For example, synthesis of 2, 8-disubstituted chromone derivatives using pyridine for cyclization step was based on this approach [91]. In some other methods instead of using acyl chloride, carboxylic acids [92] or acid anhydrides [93] were also used as starting substance. Along with this, use of different bases like sodium hydride [77], sodium alkoxide [94-96], potassium or sodium hydroxide [97] were also reported.

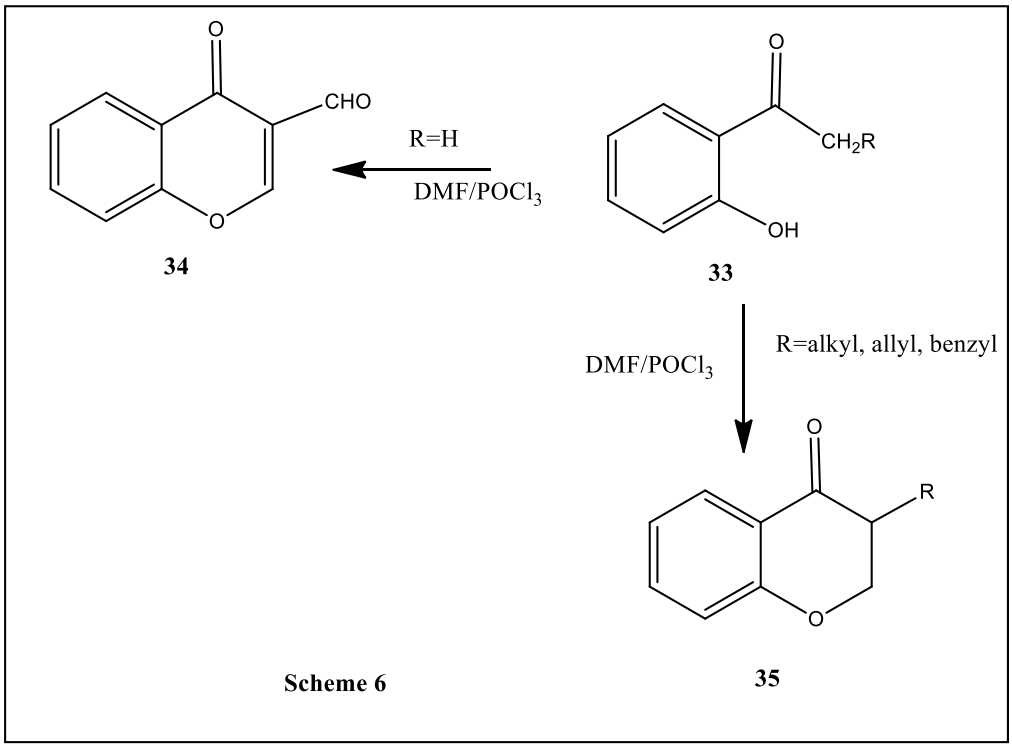
4. **Vilsmeier-Haack reaction**: Typically 3 -substituted chromones are synthesized by vils meier-haack reaction (also called vilsmeier reaction) [69]. In this reaction o-hydroxyarylalkyl ketone is allowed to react with a formylating agent known as vilsmeier haack reagent. In this reaction a chloroiminium ion is formed in situ, by the reaction between formylating reagent like DMF with $POCl_3$ that reacts with ketone enolate which is obtained from o-hydroxy alkylaryl ketone **28** during the progress of reaction.

An unsubstituted chromone intermediate **31** is generated which is then attacked by chloroiminium ion to give 3-substituted chromone **32**. (Scheme-5).

This method was used for the synthesis of chromones for first time in 1973 [98] and since then it has been used for synthesizing 3-formyl chromones **34** or 3-alkyl chromones **35** [98,99], this process depend on which type of *o*-hydroxyl alkyl aryl ketone **33** is taken as starting substance for the process. (Scheme-6).



Scheme 5

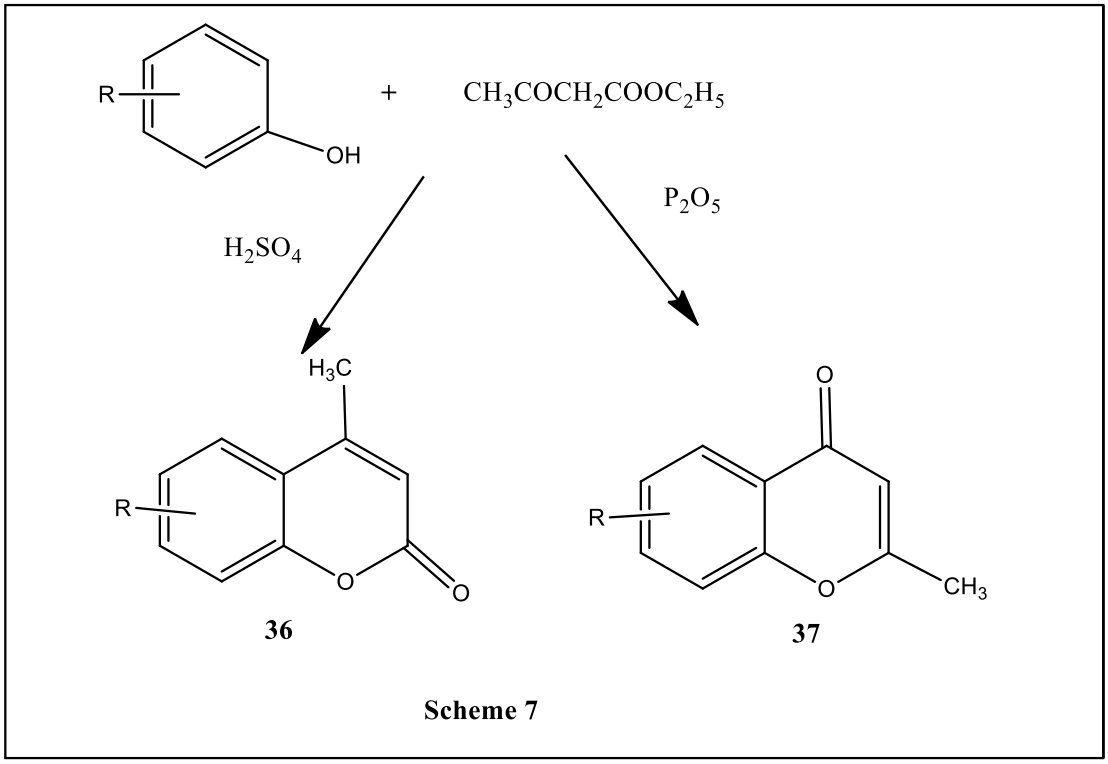


Scheme 6

However this method was having some short comings like poor yield, side products and long reaction time. Therefore some modifications were done like use of boron trifluoride diethyl etherate that gives dioxoborin intermediate [100-103] and variety of vilsmeier haack reagent like phosgeneiminium chloride, triphosgene (bis-(trichloromethyl)carbonate)/DMF-dimethyl acetal (DMf-DMA) [104]. It results in the synthesis of 2-amino chromones [105] and 3-halochromones [106].

In past few years vilsmeier haack reaction is improved by using microwave promoted synthesis of 3-formyl chromones [107,108].

5. **Simonis Reaction:** Phenols on condensation with β-keto esters can yield a coumarin, a chromone or both. Formation of coumarin **36** was reported by Pechman if condensation was carried out in presence of sulphuric acid [109]. However Simonis et al. used Phosphorous pentaoxide in place of sulphuric acid. They reported the formation of chromone **37** [110]. This procedure is known as Simonis condensation [111] (Scheme-7).



Scheme 7

It was found that if alkyl groups are present on the α-position of the β-ketoester, then formation of chromone is favoured.

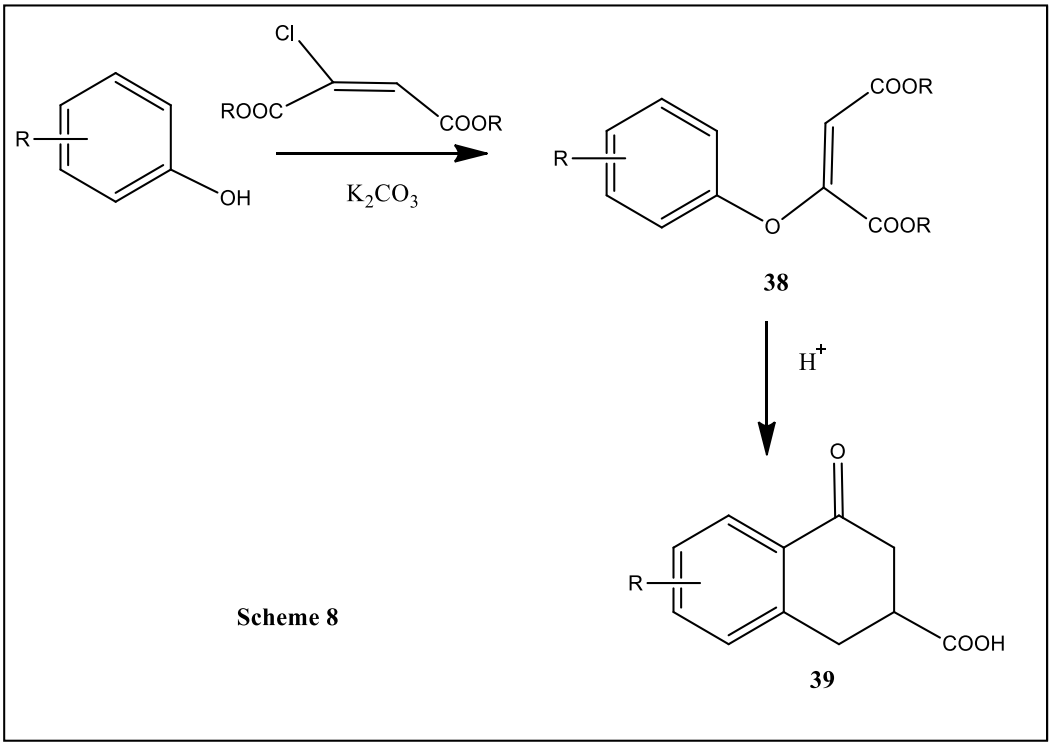
6. **Ruheman Reaction:** This method is largely used for synthesis of chromone-2-carboxylic acids and derivatives [112]. In this method chromones are obtained by reacting phenol with acetylinic dicarboxylic acids or esters in basic conditions. The intermediate formed **38** is subjected to H_2SO_4 or $HClO_4$ or HF to give chromone **39** (Scheme-8).

7. **Synthesis from salicylic acids and its derivatives:** Salicylic acid derivatives **40** on reaction with tert-butyldimethylsilylchloride and imidazole gave silyl esters that undergoes intramolecular wittig ester carbonyl olefination in presence of (trimethylsilyl) methylene-triphenylphosphorane to give chromone **41** [113] (Scheme-9).

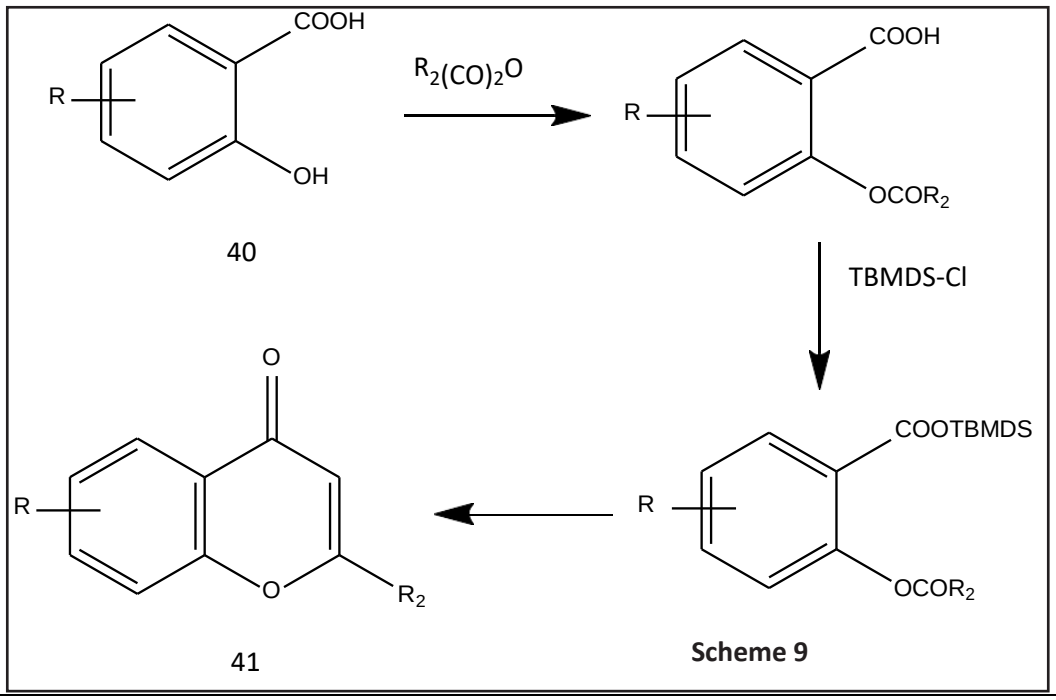
2-methyl chromones **43** can be prepared by reacting salicylic acid derivatives **42** with diethyl malonate and intermediate obtained is then subjected to hydrolysis followed by decarboxylation [114]. Such kind of chromone are also synthesized by reacting methyl salicylate with dimethyl-penta-2,3-diene dioate using tert- potassium butoxide or butanonol [115] (Scheme-10).

Methyl salicylate **42** on Condensation with bromo crotonitrile derivatives followed by cyclization of intermediate in basic medium gives chromones **44**. [116] (Scheme- 11)

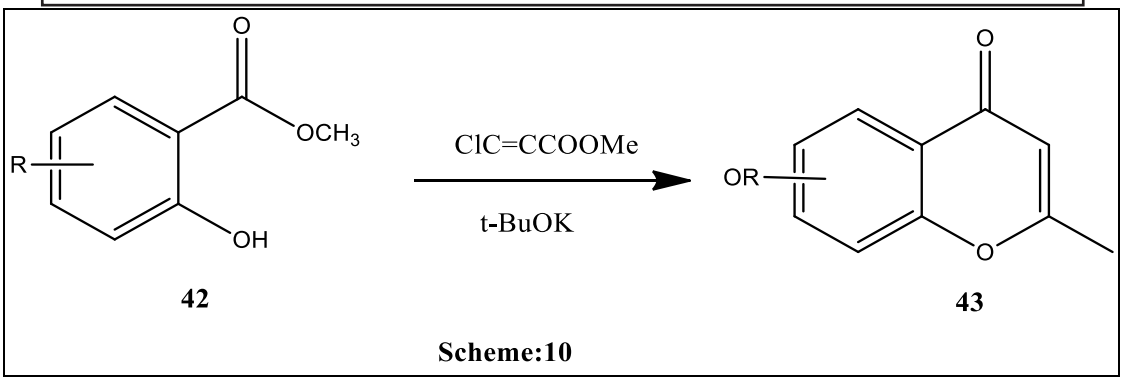
Acetyl salicylic acid derivative **45** on reaction with N- hydroxy benzotriazole (HOBt) and malanonitrle in the presence of NaH followed by cyclization caused by acid catalysts gave 2-amino-3-cyano-4-chromones **46** [117] (Scheme-12).



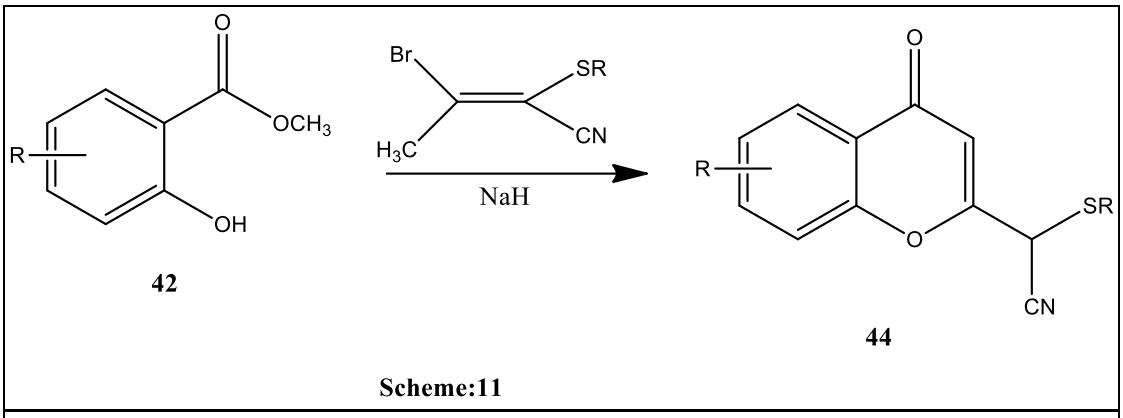
Scheme 8



Scheme 9

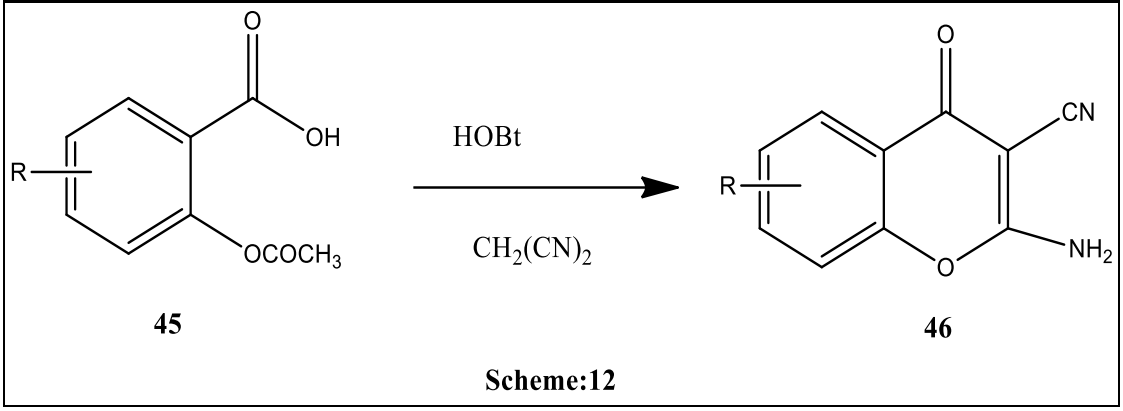


Scheme:10



42 44

Scheme:11



45 46

Scheme:12

CONCLUSION:

A large number of derivatives of chromones have been synthesized and screened for their biological activities. Various modifications can be done with chromone moieties to develop compounds of potential biological importance.This paper develops an interest to explore many more new compounds of biological importance having this system.

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