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Chromone As A Versatile Nucleus

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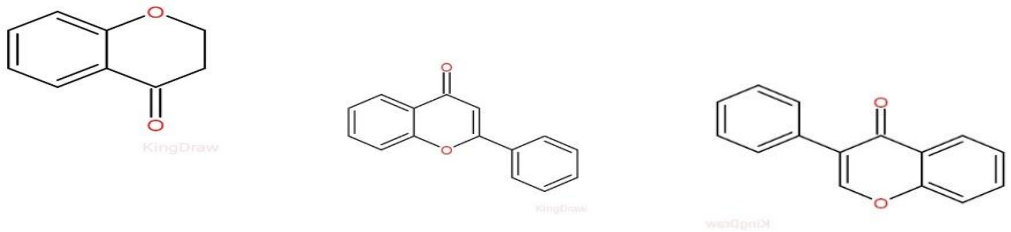
ABSTRACT: The present review represents a broad description about Chromone. Chromone nucleus and its derivatives occur in nature widely. Chromone are benzopyran and they contain 4H- benzopyran moiety. Chromone molecule performs many important biological activities such as anti-inflammatory, anti-allegetic, anti-oxidants , anti-cancer due to this reason they are known as versatile nucleus. In plant Chromone nucleus are present which give attractive coloration for pollinators and protects plants from UV radiation and fungus.Chromones can be classified into three groups chromanones, simple Chromone and fused chromone. There are different methods for synthesis of the Chromone derivatives such as Bakevenkatraman rearrangement, Cyclocondensationetc, firstly the synthesis of theChromone was introduced by Heywang and Kostanecki.

KEYWORDS: Chromone, versatile, Bakevenkatraman rearrangement, Heywang and Kostanecki.

I. INTRODUCTION

The word Chromone derived from Greek word chroma, which means , “color” and it indicates that many Chromone derivative exhibits a broad variation of colours .The “Chromone” tribal name was first used by Bloch and Kostaniecki in 1900. Chromone is derivative of Chromone benzopyran which has substituted keto group on the pyron ring and it is isomer of the coumarin. Chromone is also known as1,4 benzopyran. Chromones are oxygen containing heterocyclic compounds with a benzo annelated pyrone ring. The Chromone ring is as shown in fig.1.

Chromones are naturally occurring which are present in several members of flavones. Chromones play an important role in plant, which makes attractive coloration for pollinators they also protect plants from fungi pathogens or UV radiation which help in plant survival. [1-2]



Chromone Flavone Isoflavone

Fig .1. Chromone core and flavonoids.

II. STRUCTURES

Chromone molecule is a group of oxygen-containing heterocyclic compounds. Chromones can be classified on the basis of differences of structure, they can be classified into three large groups, chromanones, simple chromones and fused chromones [3]

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2.1. Chromanones

The derivativeof chromone 2, 3-dihydro is called chromanones. All compounds of this group contain various chromones without C-2/C-3 double bond; see compounds **(1–15)**. The structures of compounds **(1–8)** are comparatively simple, as the C-2, C-5, and C-7 position are replace by small groups, such as methyl, hydroxyl, isopentenyl, propenyl, and so forth. Compounds **(9–11)** are special types of chromanones identify by the presence of pyran ring linked at C-6/C-7. Compounds **(12−13)** are particular chromanone derivatives featured in being composed of two chromanone units, whose connection location makes a difference. Compounds **(14, 15)** are tetrahydro chromanone derivatives. The chemical structures are shown below in Fig. 2.

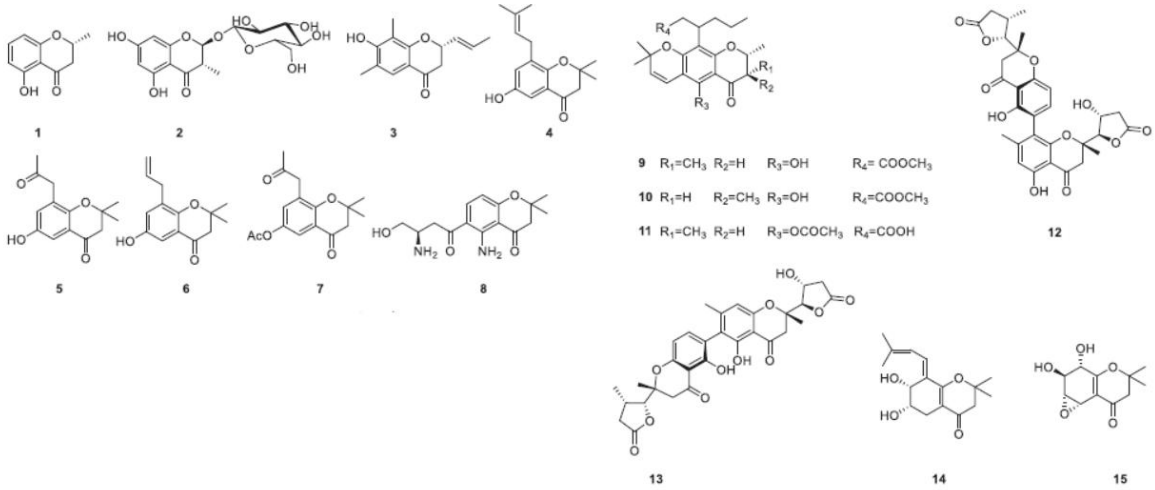

Fig.2. Structures of chromanone

2.2. Simple Chromones

If the substituent groups at basis skeleton of chromones can't undergo cyclization to appointpyran ring, furan ring, or other ring, these compounds belong to simple chromones. Compounds **(16–70)** fall into this type. Their chemical structures are shown in fig .3.The structures of compounds **(16–29)** are comparatively simple, as the interchange groups are hydroxyl, methyl, and so on. Compounds **(16–20)** having same structures with the difference of substituent group at C-6. Compounds **(27–28)** are chromones presenting in a linear alkyl sidechain replace at C-2, and the linear alkyl owns 20 carbons in compound **(28)**. Compounds **(30–37, 67–68)** belong to chromone. Glycosides, amid them compound **(33)** is a rhamnoside and compounds **(34–35)** are rutinosides. Compounds **(36–37),** as C-glycosides, are change from other chromone glycosides as O-glycosides. Compounds **(38–44)** belong to 2-styrylchromones. Compounds **(45–57)** are 2-(2-phenylethyl) chromones, which differ from 2-styrylchromones in the double bond at C-1’/C-2′. Compounds **(58–59),** as a tiny type, create more awareness to be paid for the presence of nitrogen groups and compound **(58)** is an isomer of compound **(59).**

The piperidine ring position of the Chromone nucleus in compound **(58)** is C-8 while that in compound **(59)** is C-6, create a change between them. Capillarisin **(60)** belongs to phenoxyl chromones. Compounds **(61–64)** are appropriate in the existence of five-membered ring in substituent groups. Compounds **(65–66)** are chromone gallates which are also related to tannins. Compounds **(69–70)** are highly oxygenated chromones.

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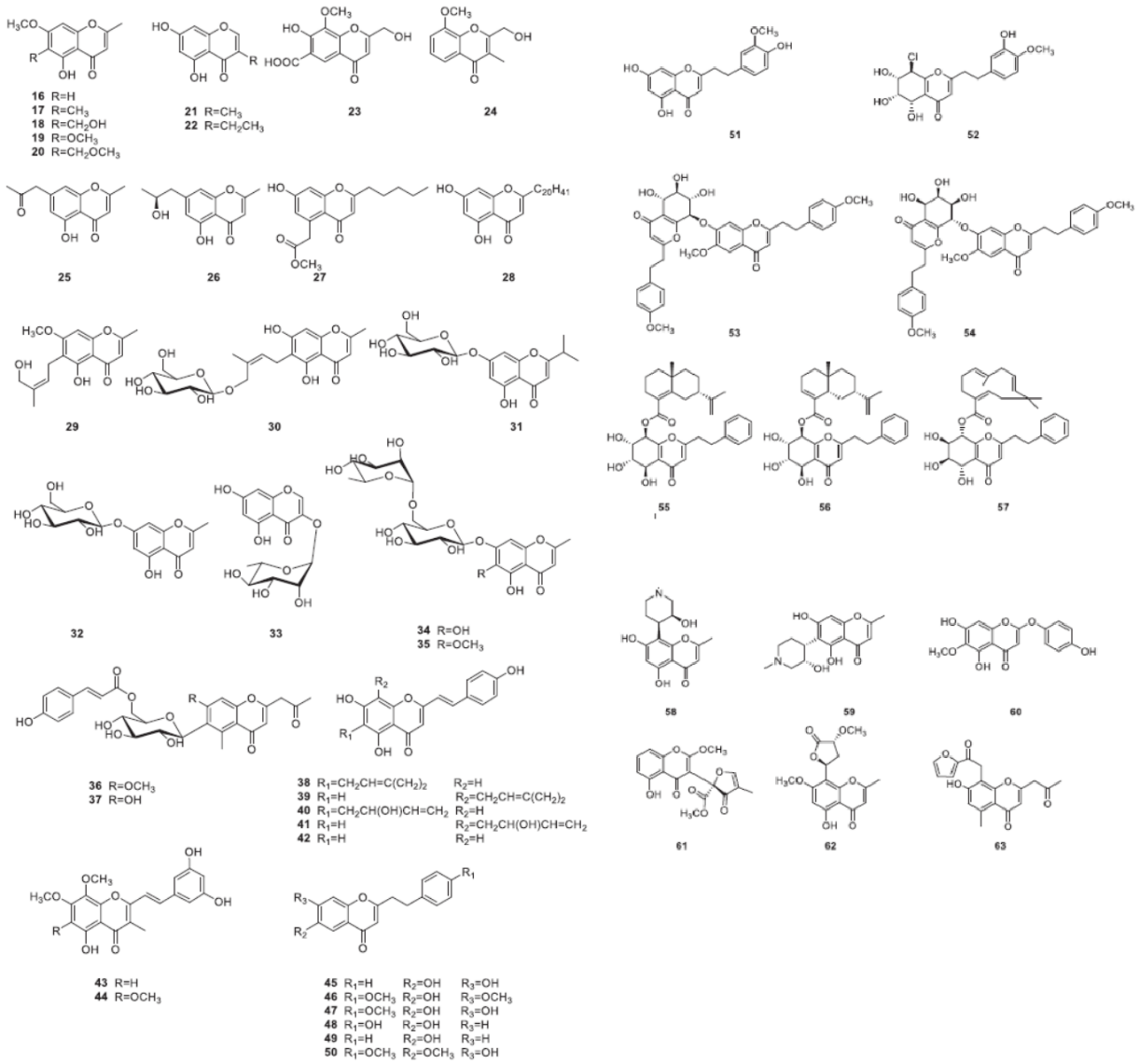

Fig. 3. Structures of Simple Chromones.

2.3. Fused Chromones

If substituent groups on the basis skeleton of chromones will undergo cyclization to get pyran rings, furan rings or other rings, these compounds related to fused chromones, including furanochromones, pyranochromones, and so on. The chemical structure are shown below fig.4.Furanochromones, are important class of active components, commonly found in the families of Umbelliferae [4-5] and Ranunculaceae [6-7] Compounds **(71–83)** are members of furanochromone derivatives. Different from compounds **(71–77),** there is a dihydrofuran attached to the chromone moiety in compounds **(78–83).** Cimitriteromone B and D **(82–83)** gives attention towards the triterpene group. Coniochaetone H **(84)** is a unique cyclopentachromone with a chlorine substitution at C-6, could not isolated from a natural source. Compounds **(85–88)** are dihydrothiophene-condensed chromones and Oxalicumone A **(85)** is a configurational isomer of oxalicumone B **(86).** Compounds **(89–102),** having the core structure of pyran or dihy-Dropyran joined to chromone skeleton which belong to pyranochromone derivatives. The position of pyrano or dihydropyrano attached with chromone skeleton is at C-

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6/C-7, C-7/C-8, C-7/C-8, C-2/C-3 in compounds **(89–97), (98–99), (100–101), (102),** respectively. Compounds **(93–97)** are dihydropyran-condensed chromones. Different with compounds **(89–102),** compound **(103)** having two benzo-γ-pyrano rings. Preusso chromone a **(104)** is a special compound which specify in the thiopyran moiety attached to the chromone skeleton at C-2/C-3.There is an oxepin moiety having double bond linked with the chromone skeleton through C-6 and C-7 in ptaeroglycol **(105).**

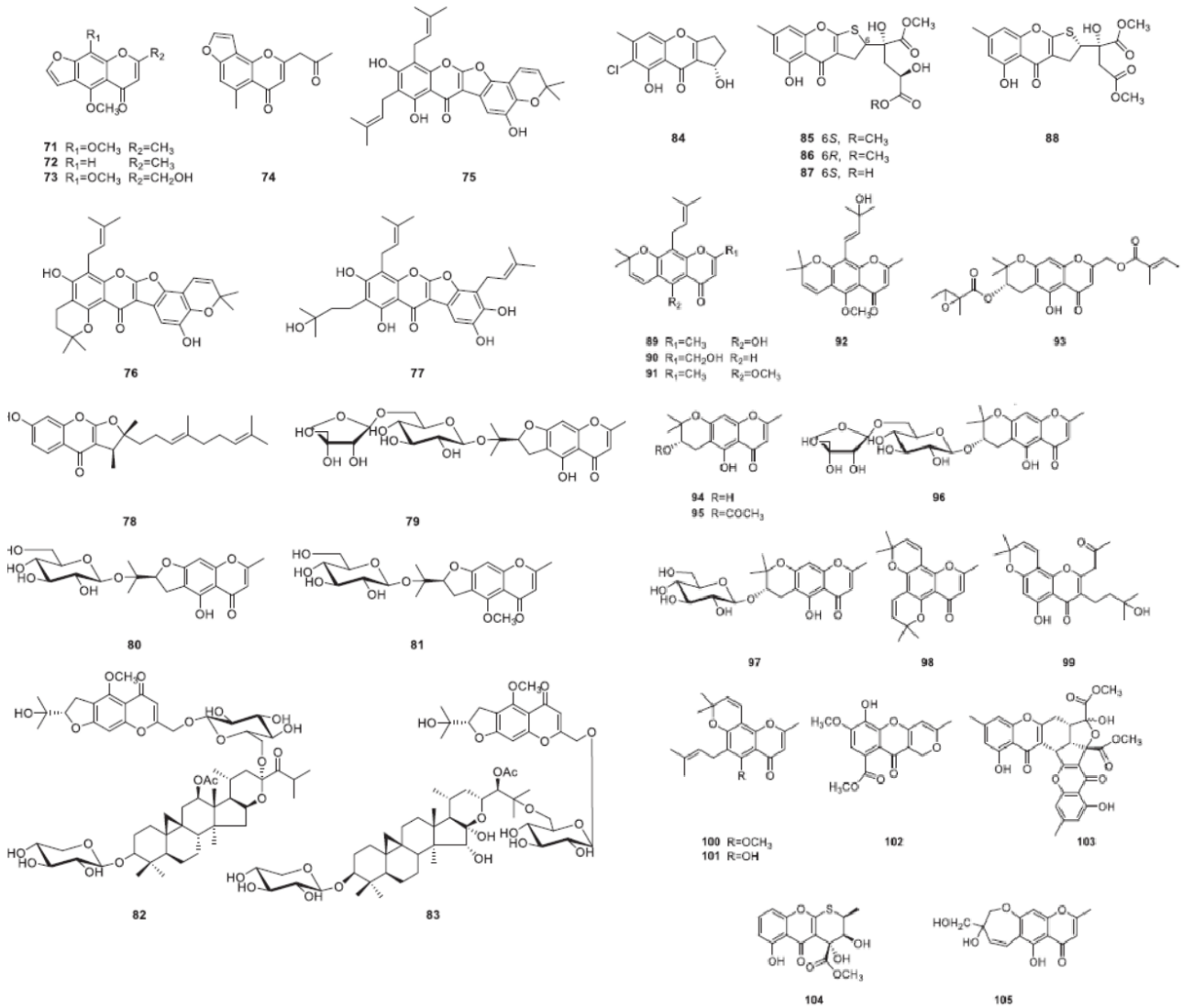

Fig.4. Structures of Fused chromanones.

III. SOURCE OF CHROMONE NUCLEUS

Chromone is a naturally occurring has been used as traditional medicine and is rich source of bioactive compounds. Chromones are widely distributed oxygen containing natural heterocyclic compounds from the plant of polygonaceae, Sterculiaceae, Rhamnaceae, Umbeliferaceae, Liliaceae, Astraceae etc.

Chromones from natural food sources are berries, vegetables, tea and wine showed significant inhibitory activity against DNA topoisomerase [8-10]. Peucenin and Eugenin were the first compounds containing chromone nucleus

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were isolated from rhizome of the peucedgnumostrthium[11] and the wild cleveegeniacaryophythunbg [12] respectively.

IV.THE PRESENT: CHROMONE-BASED APIS

This scaffold's biological potential, are related to a low mammalian toxicity, prompted the development of several chromone-based drugs with different applications, particularly as anti-inflammatory agents [13-15] (Figure 5). Disodium cromoglycate **(106)** is one such example, used as a mast cell stabilizer for the treatment of allergic rhinitis, asthma, and allergic conjunctivitis commercialization faced some challenges due to the response of asthmatics to cromoglycate therapy is highly variable and it must be administrated by inhalation due to poor oral absorption. Likewise, Nedocromil sodium **(107)** is marketed for the prevention of wheezing, shortness of breath and other breathing problems caused by asthma. Also, flavocoxid, an extract containing the naturally occurring compound Baicalin **(108)** as one of its major APIs, it issued as an anti-inflammatory drug acting in the molecular pathways responsible for the production of both prostaglandins and leukotrienes, through the dual inhibition of COX and 5-LOX [16] Finally, Iguratimod **(109)** is a disease-modifying anti-rheumatic drug, accumulating its anti-inflammatory effects with the ability to inhibit immunoglobulin and cytokine production and inducing an anabolic effect on bone metabolism [17]. Besides the aforementioned anti-inflammatory chromones, a number of other derivatives presented in Figure 5, including Flavoxate **(110)**, Khellin **(111)**, and Diosmin **(112)**, were marketed for distinct pharmacological applications. It is also effective for the treatment of chronic venous insufficiency and Hemorrhoidal disease, of urinary bladder spasms (through anticholinergic activity with antimuscarinic effects) and of angina pectoris and asthma (through smooth muscle-relaxation) respectively.

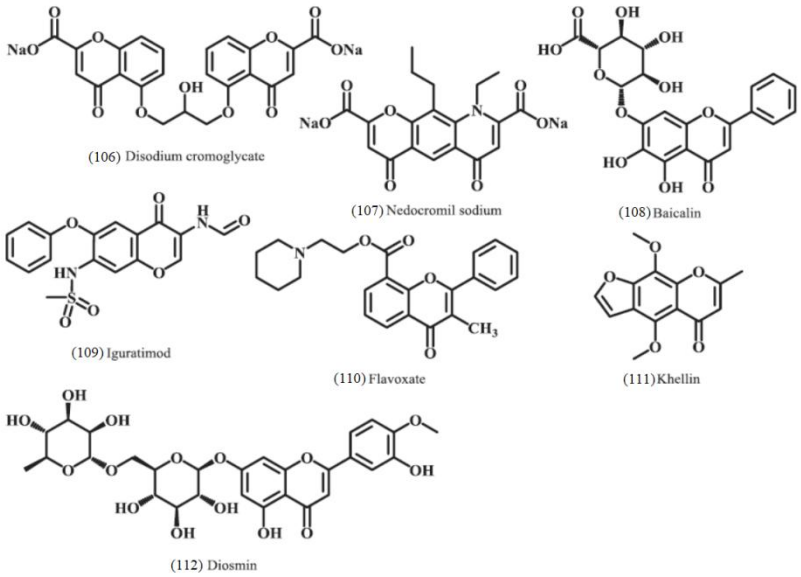

Fig .5. Chromone derivatives in pharmaceutical industry

V. CHEMISTRY

The synthesis of chromone has great interest and long history [18] in research field. There are many number of methods have been developed for the synthesis of chromone derivatives: for example, the Allan-Robinson strategy, for chalcones and via an intra- Molecular Wittig strategy [19-20]. One of the most common methods involves acylation of an o-hydroxyacetophenone with an aromatic acid chloride gives an aryl ester. The ester group is then rearranged by a base (Bakere Venkataraman rearrangement) to a 1,3-diaryl 1,3-diketone,

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Compound gives a 2-arylchromone on Cyclocondensation [21]. Reaction which has been carried out in different media some reaction conditions employed were the use of excess of sulfuric acid in glacial acetic acid [22], cationic exchange resins in isopropanol [23], glacial acetic acid-anhydrous sodium acetate or aqueous potassium carbonate [24] (Fig. 6). Greener procedures have been recently described, using $CuCl_2$ in ethanol [25], ionic liquid under microwave irradiation, heteropolyacids [26] and ortho-fluorobenzoyl chloride in condensation with a 1,3-keto ester the fluoride is displaced in an intramolecular reaction byenolate oxygen and the chromone obtained directly. Ortho-Hydroxyarylalkynyl ketones are intermediates in palladium catalyzed coupling of ortho-hydroxyaryl Iodides with alkynes in presence of carbon monoxide, ring closing to chromones in situ [27] fig.7.

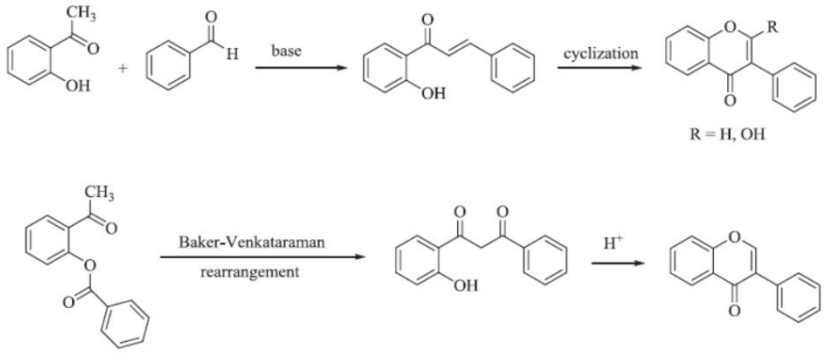

Fig.6.common routes to obtain the Chromone structure, I) Synthesis via a chalcone followed cyclization, II) Synthesis via the Bake -venkatraman rearrangement.

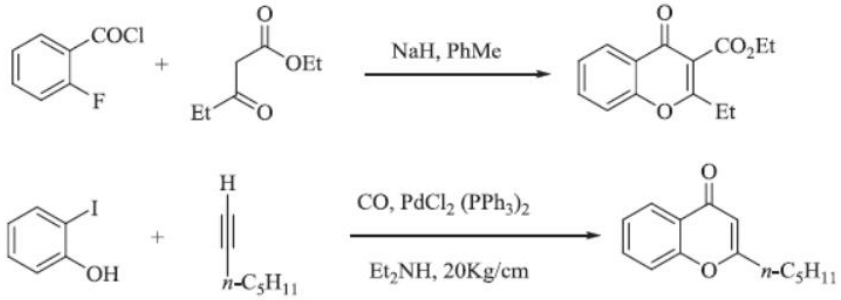

Fig.7. Common synthetic routes to obtain Chromone structure, I) Synthesis via an intramolecular sense by enolate oxygen, II) Synthesis via palladium catalyst.

VI. SYNTHESIS OF CHROMONE

One of the first methods for the synthesis of chromones was introduced by Heywang and Kostanecki [28-29], which involved the decarboxylation of chromone-2-carboxylic acid. Since there are several many other routes which gives higher yields and less drastic experimental conditions have been developed.

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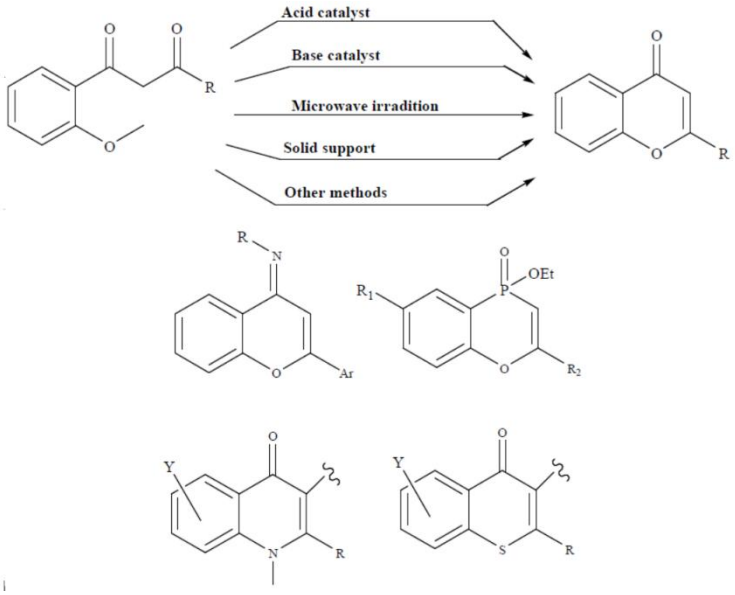
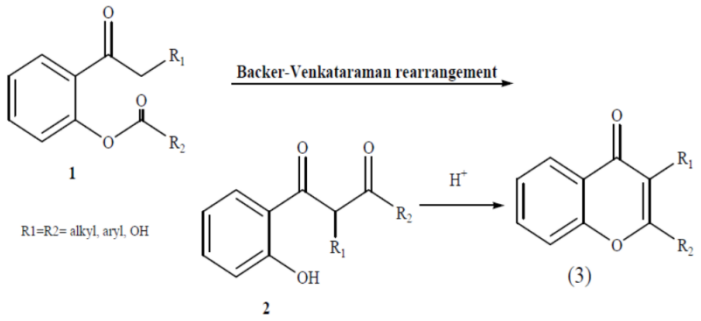


Fig.7.Sytematic diagram illustrate different synthetic method for Chromone derivatives

Chromones can be synthesized by both acidic and basic conditions. The classical, 3-disubstituted benzopyranone **3** synthesized in acidic conditions as shown in (Scheme 1). It proceeded through an intramolecular condensation of molecules such as **2**, which are obtained through a Baker–Venkataraman rearrangement reaction of compound **1**, or Via a Claisen ester condensation (Scheme 1). Most synthesis required harsh acidic conditions as the final step. The synthesis utilizing basic conditions typically consisted of piperidine refluxing pyridine for several hours to affect ring closure. This was far less common. Cyclization can be affected by microwave heating.



Scheme 1

1. Acid as catalyst in chromone ring closure.

Acid comprised a major catalyst in chromone ring closure, and many acids can be used including hydrochloric acid polyphosphoric acid, acetic acid, methane sulfonyl chloride, hydrochloric acid, para toluene sulfonic acid, triflic anhydride, phosphorus oxychloride, perchloric acid, an Sulphuric acid.

Hydroiodic acid as a catalyst for the synthesis of a mixture of 2-methyl-8-hydroxy-6,7-benzochromone and2-methyl-8-methoxy-6,7-benzochromone Scheme 2.

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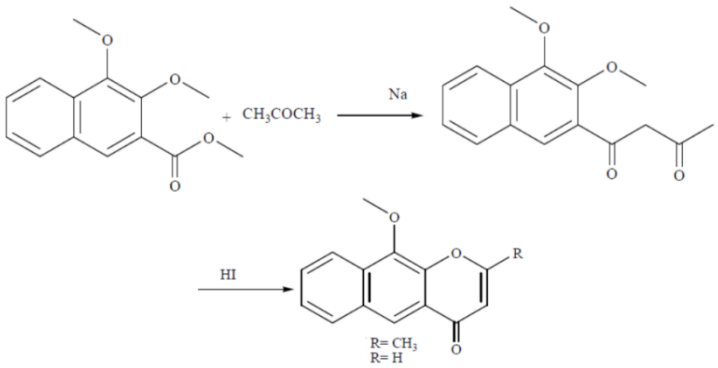
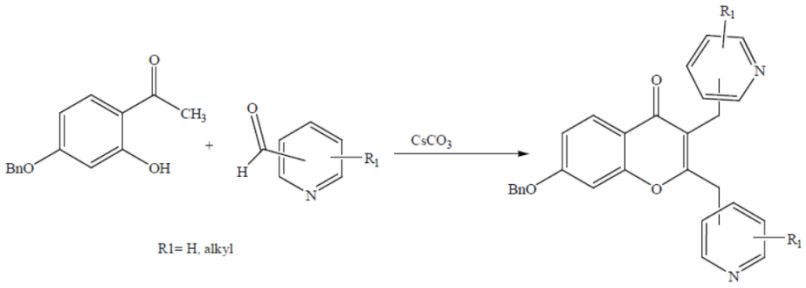


Scheme 2

2. Base as catalyst in chromone ring closure

The base as catalyst in the chromone ring closure is not common compared with acid, Sometimes it can really bring some satisfactory. Base catalysts used are sodium formate, sodium methoxide, sodium hydride, pyridine, sodium acetate, etc.

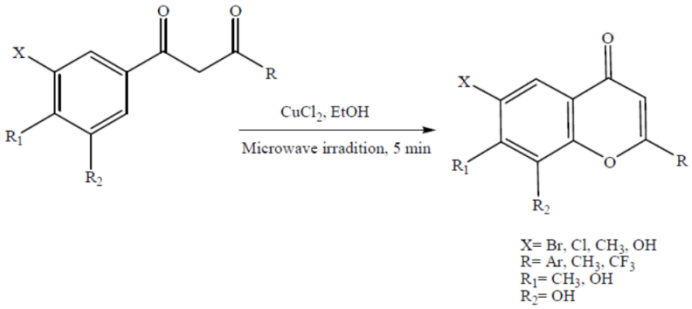
Caesium carbonateas a catalyst for the synthesis of 2,3-disubstituted chromone via Michael aldol reaction Scheme 3.



Scheme 3

3. Chromone ring closure under the Microwave irradiation.

Microwave irradiation 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 the clean and ‘‘green’’ chemical syntheses which has been resulted in increased use of microwave irradiation, so there have been several recent reports, describing the application of microwave irradiation to the synthesis of flavonoid.



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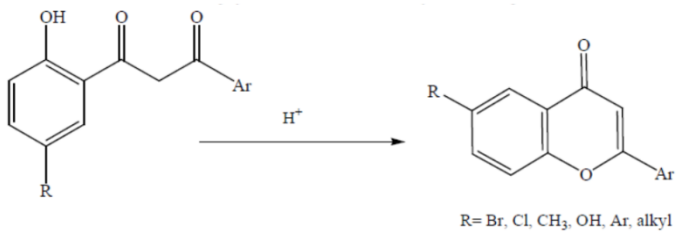
Scheme 4

4. Chromone ring closure via solid-support

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

Via solid-support catalysts

In 2002, Blanco and coworkers84 studied the catalytic performance of phosphomolybdic acid (MPA) ($H_3PMo_{12}O_{40}.nH_2O$) and Phosphotungstic acid TPA ($H_3PW_{12}O_{40}\_nH_2O$), both bulk or supported on silica, to obtain flavones and substituted chromones.



Scheme 5

VII. PHARMACOLOGICAL ACTIVITIES OF THE CHROMONE DERIVATIVES

Chromone and its derivatives has shown many of the pharmacological actions such as [30]

1. Anti-cancer agents
2. Anti-HIV agents
3. Anti-oxidant agents
4. Anti-tubercular agents
5. Anti-inflammatory and Analgesic agents
6. Anti-microbial agents
7. Anti-malarial agents
8. Anti-diabetic agents
9. Anti-convulsant agents
10. Anti-platelet agents
11. Gastroprotective agents
12. Antihistaminic agents
13. Antihypertensive agents
14. Calpain inhibitor
15. Insecticidal activity
16. Enzyme and Receptor Agonists/Antagonists

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