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PHYSICO-CHEMICAL PROPERTIES AND DIFFERENT METHOD OF SYNTHESIS OF CHROMONES AND ITS DERIVATIVES: A REVIEW

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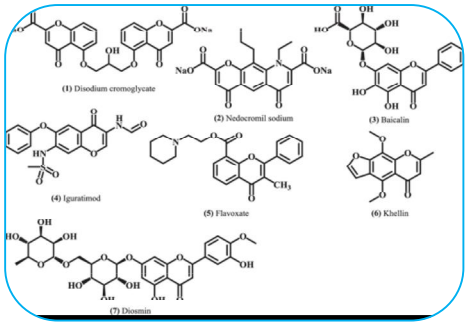
ABSTRACT:

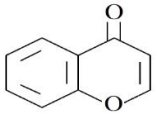


The present review is about the methods used to synthesize chromonesand its derivatives. Chromone is a rigid bicyclic moiety i.e., 4H-Benzopyran-4-one (1) and its derivatives are collectively known as Chromones. Their structural diversity of chromones (type, number and position of substituent attached to the main core) is responsible for their physical, chemical and biological properties. These are classified as privilegedstructure in drug discovery, Because of its use in a wide variety of pharmacologically active compounds.It is also used as scaffolds for the development of bioactivecompounds and have considerable applications in medicinal chemistry, due to their abundance in nature and biological cycles.

KEY-WORDS: *Chromone,drug, scaffolds, biological cycles, BiologicalActivity.*

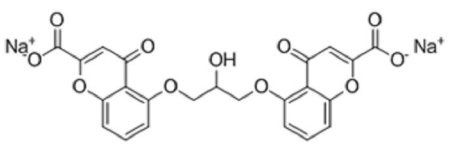
INTRODUCTION:

Chromone is a rigid bicyclic moiety i.e., 4H-Benzopyran-4-one (1) [1] and its derivatives are collectively known as Chromones. The word chromones is derived from the Greek wordchroma, meaning *color*, which indicates that many chromone derivatives exhibit a broad variation ofcolors.



(1)

The chromone moiety is an active pharmacophore and found in different drugs[4,6] such as Cromolyn (2), Nedocromil (3), Diosmin (4), Flavoxate (5), etc. Chromones are also valuable intermediates in the synthesis of novel bioactive compounds[3,7]. The word chromone was derived from Greek word *chroma* (means color) and many chromone derivatives exhibit a broad variation of colors.



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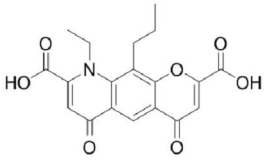

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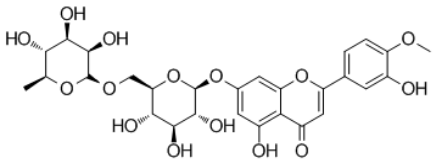

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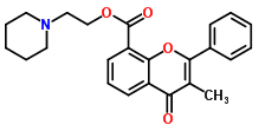
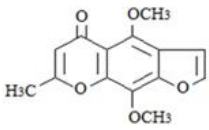


(5)

Chromones play very important roles in plant cycles and their abundance with different pharmacological activities[8a-d], made them research subject for drug discovery. They exhibit a wide range of biological and pharmacological activities like anti-bacterial[9], anti-fungal[10], anti-viral[11], anti-depressant[12a], anti-hypertensive[12b], anti-obesity[13], anti-ulcer[14], anti-cancer[15], anti-oxidant[16], anti-HIV[17], anti-inflammatory[18], immunostimulators[19], biocidal[20], wound healing[21] and immune-stimulatory[22]. There derivatives also possess enzymatic inhibition properties towards different systems like oxidoreductase, kinase, lipoxigenase and cycloxigenase[23].

The first chromone derivative *Khellin* (6) was extracted from seeds of plant *Ammi visnaga*. It was found antispasmodic and used in the treatment of angina pectoris[24]. Its 2,4-thiazolidenedione derivatives[25] (7)was found antidiabetic and used to improve peripheral insulin resistance in type-II diabetic patients. Their two analogues have also been synthesized to improve water solubility, i.e. *2-Methyl-5-(dimethylaminoethoxy)-9-methoxyfuro[3',2',6,7]chromonephylline* (8) and *9-(2-Diethylaminoethoxy)-5-hydroxy-2-methylfuro[3',2',6,7]chromone* (9)[26,27].



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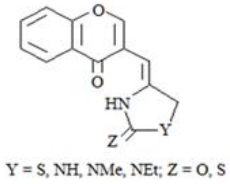
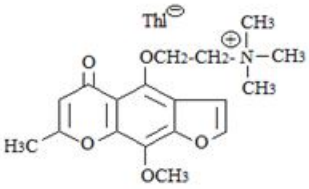


Y = S, NH, NMe, NEt; Z = O, S

(7)



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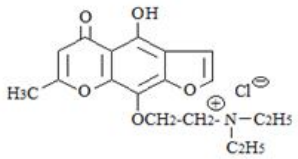
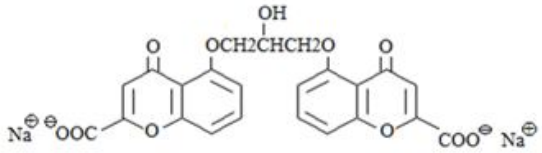


(9)

Other examples are Disodium cromoglycate (10) used as asthma drug, Chromone-3-carbaldehyde (11) used in the treatment of T-cell leukemia, lymphomas and rheumatoid arthritis, Diosmin (12) used for the treatment ofvenous diseases and flavoxate (13) is used as smooth muscle relaxant to treat urge incontinence[28-31].



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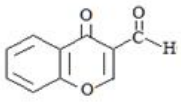

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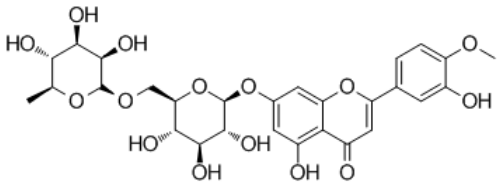

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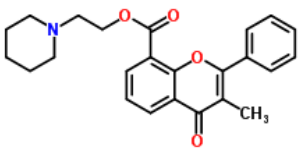
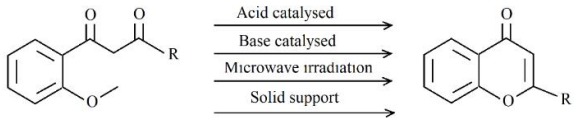


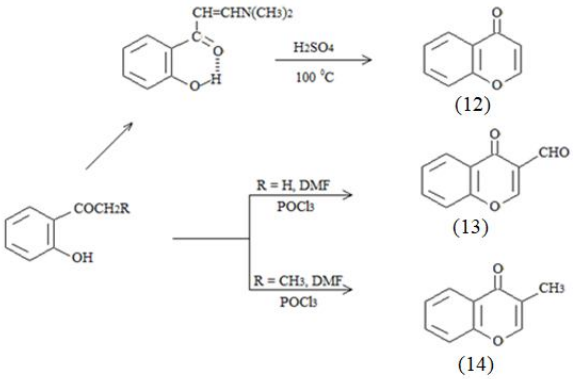
(13)

Synthesis of chromones: Depending on the starting materials and required chromone, there are a number of synthetic routes are reported time to time. The first method to synthesize chromones was developed by Heywang and Kostanecki[32].



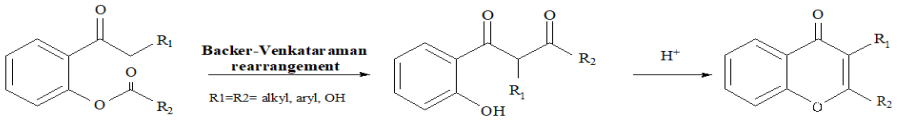
(10) (11)

Condensation of o-hydroxyacetophenone with dimethylformamide (DMF) and its acetal or triethyl orthoformate yields 2-unsubstituted chromones, chromone (12), 3-formylchromone (13) and 3-methylchromone (14) have already been synthesized[33,34].



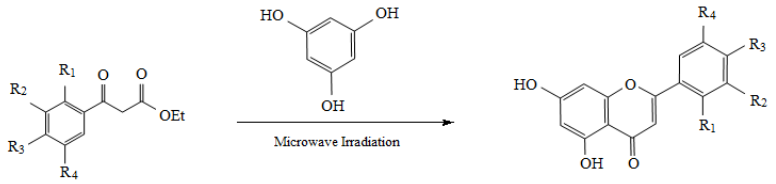
(12) (13) (14)

The 2,3-disubstituted chromones (17) are synthesized by an intramolecular condensation of molecules (16), which were usually obtained through a Baker–Venkataraman[35] rearrangement of compound (15).



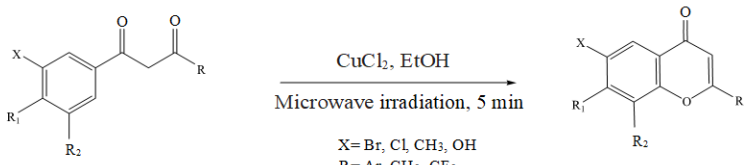
(15) (16) (17)

Microwave irradiation offers a considerable advantage over conventional methods because it enhances the rate and yield of the reaction[36]. The demand for clean and green chemical syntheses increases the use of microwave irradiation. In 2005, Seijas et al.[37] reported a solvent-free synthesis of functionalized flavones (19)under microwave irradiation.



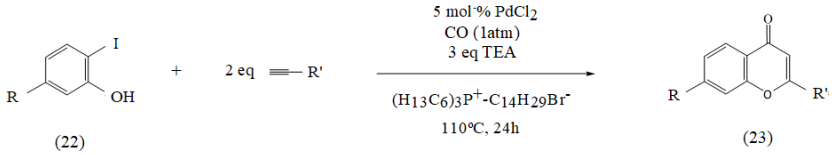
(18) (19)

In same year 2005, Kabalka and Mereddy[38] reported a microwave synthesis of functionalized chromones (21) via the cyclization of 1-(2-hydroxyaryl)-3-aryl-1,3-propanedione (20).



(20) (21)

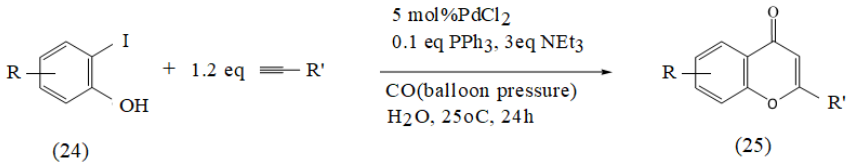
Recently some highly efficient synthetic methods are reported, one is selective palladium-catalyzed ligand-free cyclocarbonylation reaction of oiodophenols (22)with terminal acetylenes under atmospheric CO pressure affords diversified
Chromones (23)[39].



(22) (23)

R= H, CO_2Me
R'= Ar, alkyl

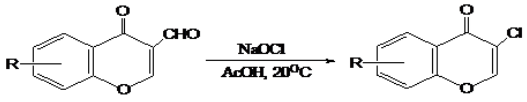
A Pd-catalyzed coupling reaction at room temperature was achieved by using water as a solvent under balloon pressure of CO with Et_3N as a base[40].



(24) (25)

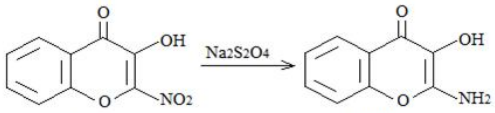
Specific functional group at particular position in chromone framework enhances its biological and pharmacological activities. Some of the important methods are described below:

1. **Halochromones:** When chromne-3-carboxyldehyde (26) is treated with aq. Sodium hypochlorite at room temperature affords 3-chlorochromone (27) [41].



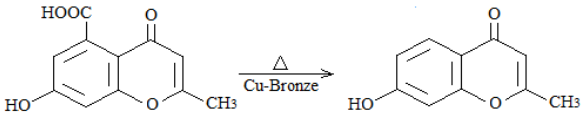
(26) (27)

2. **Aminochromones:** The Reduction of 3-hydroxy-2-nitrochromone (28) with $Na_2S_2O_4$ affords 2-amino-3-hydroxychromone (29)[42].



(28) (29)

3. **Alkylchromones:** TheChromones carboxylic acid (109) give corresponding alkylchromone (110) either heating alone or in quinoline, in presence of copper bronze as catalyst[43-45].



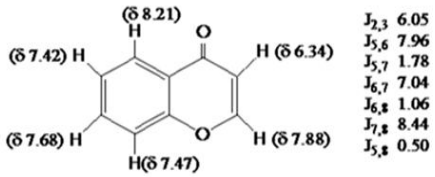
(30) (31)

1.3 Physical and Spectral Properties of Chromones: Chromone is white crystalline solid with bitter taste and aromatic odour when heated[46]. It has melting point 59 ^{0}C and soluble in diethyl ether, ethanol, chloroform, benzene and other organic solvents. The solution of chromone in sulfuric acid gives a blue fluorescence[47-49]. Its Phosphorescence spectra in ethanol[51,52], hexane[52] and 2-methyltetrahydrofuran[50,51] has already been reported.

Ultraviolet spectroscopy: The UV spectra of chromones in various solvents[53-55] suggested the absorption due to n, □* transiton[56] ranges 360 nm (in 3-methylpentane) to 355 nm (in 2-methyltetrahydrofuran) and due to □□□□* transition[57] ranges from 302 nm (in water) to 292 nm (in cyclohexane).

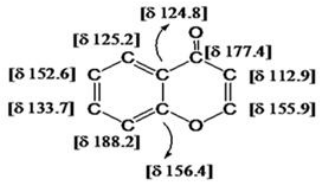
Infrared spectroscopy: In chromones a characteristic absorption band due to C=O stretching vibration appears in the 1670-1575 cm^{-1} region in various solvent systems[58-61].

Proton Magnetic Resonance spectroscopy: PMR spectra of chromones were first recorded by Mathis and Goldstein[62]. The chemical shift value (□) for various protons of chromone in parts per million (ppm) and coupling constant of protons in Hertz are shown in figure (32). An interesting feature of the pmr spectra of chromones is that due to spatial proximity to anisotropic carbonyl group, the signal due to C_5-H appears at 8.21 which separates from those due to other benzene protons. This is characteristic of chromones and is not exhibited by the isomeric coumarins[63-64].



(32)

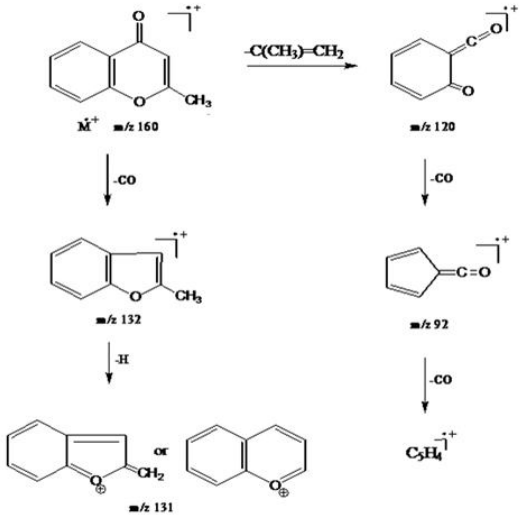
^{13}C-Nuclear Magnetic Resonance spectroscopy: ^{13}C-NMR spectral data of chromones were first reported by Kingsbury and Looker[65]. After that, a number of papers have been published on ^{13}C-NMR of chromones[65-71]. Chemical shift for all the carbon atoms of chromone (in ppm) are shown below.



(33)

Mass spectroscopy: Molecular ion peak constitutes the base peak in the mass spectrum of chromones. Loss of one molecule of CO (path a) affords an abundant ion at M-28[72]. Retro-Diels-Alder reaction is another characteristic fragmentation mode of chromones (arrows) which involves the elision of neutral

acetylene ion undergoes sequential losses of two molecules of CO mass spectral fragmentation of 3-methylchromone is as follows[73].



CONCLUSION: The present review of literature represents a description for the methods used in the synthesis ofchromones and its derivatives. Some of the methods are improvements of the classical synthetic methods and other are non-classical methods to obtain simple oxygenated chromones. They include acid or base catalysed, microwave irradiated or solid-supported synthesis. The chromone framework has been classified as aprivileged structure in drug discovery because it is found in a wide variety of pharmacologically activecompounds. In some examples of therapeutic agents, chromones are used as scaffolds for the development of bioactive compounds

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