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CHROMONES : THE HEALTH FRIENDLY MOLECULES

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Heterocycles are eminent molecules of high medicinal value. Chromones which are also heterocyclic molecules are being used pharmacologically for a long time. They are starting materials for the synthesis of medicines in the modern era too. Their pharmacological activities range from antibacterial, antifungal and anti-inflammatory activities to anti-cancer and anti-HIV activities. They are eco-friendly molecules as they are natural products and are extensively distributed in various parts of plants which constitute our food items. This publication reviews health friendly nature of chromones as concluded from their diverse medicinal utility which has made it a revolutionary molecule in organic synthesis.

KEYWORDS : Chromones, medicinal value, pharmacological activity, green chemical synthesis, diuretic activity, cardiovascular activity, antibacterial, antifungal and anti-inflammatory activities, anti-cancer and anti-HIV activities.

INTRODUCTION

Diseases have been major obstacle in the smooth running of human life. Man has always been in quest to find cures for one disease or other since the beginning of human civilization. Research on medicinal plants revealed that heterocycles are important as medicinally active molecules. Chromones [the benzopyran-4-ones] which are also heterocyclic molecules have been of considerable interest in past few decades [1, 2]. They occur in nature and exhibit biological functions in addition to pharmacological activities [3, 4]. Chromones are also photochemically active and lead to active heterocyclic derivatives [5]. Flavonoids [6], [*i.e.* 2-phenylchromones] are widely distributed in nature. To mention few : eugenitol [7], isoeugenitol [8] and querecetin [9]. Various medicinal activities associated with benzopyrones are : biocidal [10], anti-inflammatory [11], wound healing [12], anti-oxidant [13], anti-ulcer [14], etc. Recently, anti-HIV activity has also been found in chromones [15].

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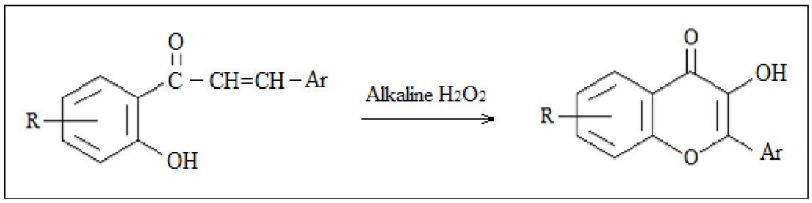
GREEN CHEMICAL SYNTHESIS OF SOME CHROMONES AND THEIR DERIVATIVES

Green chemical aspect of synthesis of drugs is relevant in present context to avoid nuisance in environment as well as from the point of view of good health. Green chemical synthesis of some chromones are known as well as can be designed. A few are discussed below:

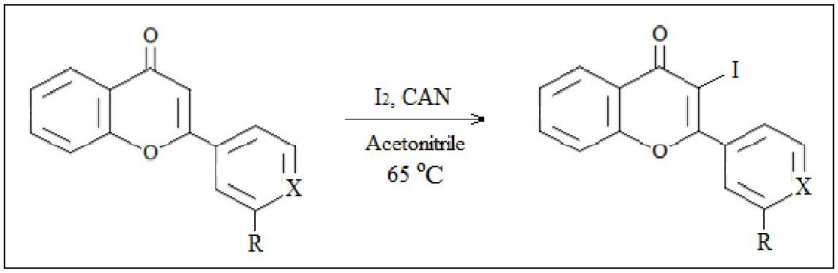
(1) Synthesis of 3-hydroxy-2-arylchromones: Chalcones can be converted to 3-hydroxy-2-arylchromones in presence of alkaline hydrogen peroxide [16, 17]. [Scheme-1]. This reaction is known as Alger, Flymn and Oyamada reaction.

SCHEME- 1



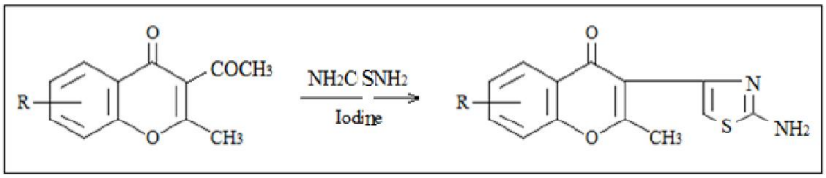
(2) Synthesis of 3-iodo-2-heteroarylchromones: Iodine can be introduced at 3- position of chromone by reacting them with iodine and ceric (IV) ammonium nitrate in acetonitrile solvent at 65°C [18]. [Scheme-2].

SCHEME- 2



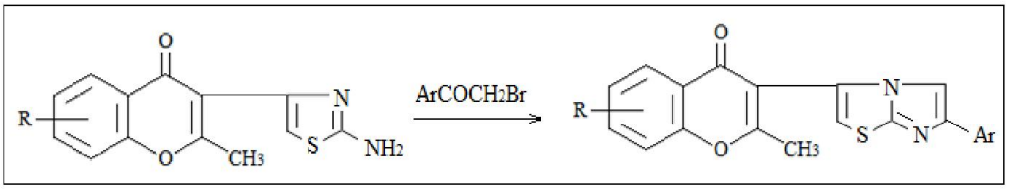
(3) Synthesis of 3-(2-aminothiazol-4-yl)-2-methylchromones: 3-Acetyl-2-methylchromones upon heating with thiourea and iodine under solvent free condition on water bath for 24-36 hrs. yield these compounds [19, 20]. [Scheme-3].

SCHEME- 3



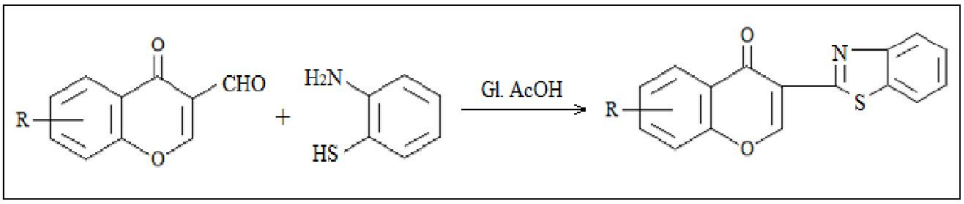
(4) Synthesis of 3-(6-arylimidazo[2,1-b]thiazol-3-yl)-2-methyichromones: 3-(2-aminothiazol-4-yl)-2-methylchromones condense with phenacyl bromides in alcohol to provide this chromonyl system which is a lead for diuretic activity [19, 20]. [Scheme-4].

SCHEME- 4



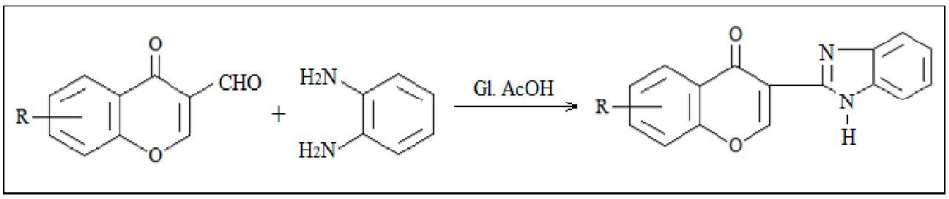
(5) Synthesis of 3-(2-benzothiazolyl)chromones: 3-Formyl chromones yield this system upon reaction with o-aminothiophenol in glacial acetic acid [21]. [Scheme-5].

SCHEME- 5



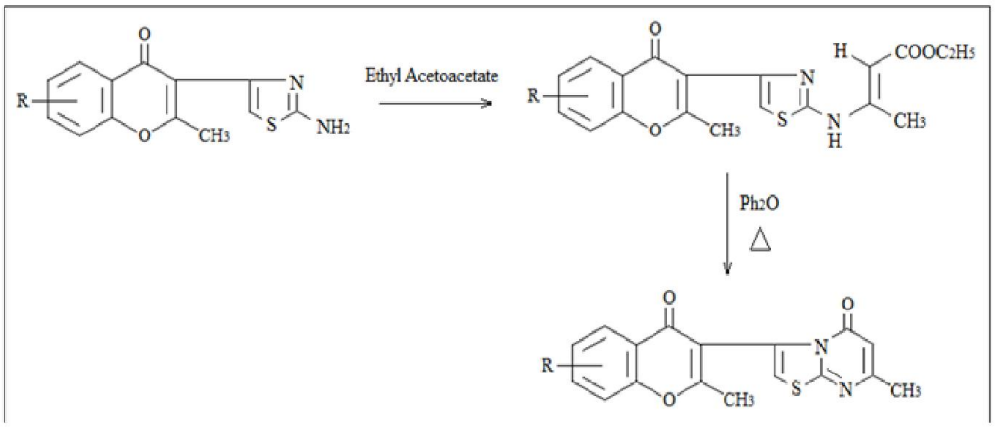
(6) Synthesis of 3-(2-benzimidazolyl)chromones: This system can be obtained by the condensation of 3-formyl chromones with o-phenylenediamine in glacial acetic acid [22]. [Scheme-6].

SCHEME- 6



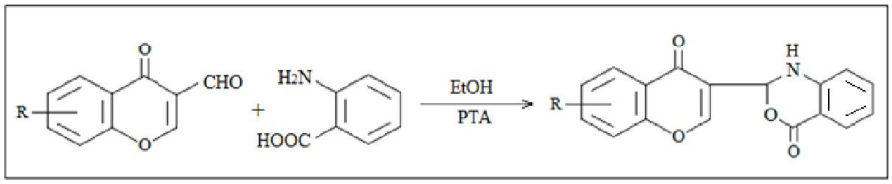
(7) Synthesis of 3-(7-methyl-5H-thiazolo[3,2-a]pyrimidin-5-one-3-yl)-2-methyl chromones: 3-(2-aminothiazol-4-yl)-2-methylchromones condense with ethyl acetoacetate to give 3-(7-methyl-5H-thiazolo[3,2-a]pyrimidin-5-one-3-yl)-2-methyl chromones through the intermediacy of Ethyl (E)-3-[4-(2-methyl-4-oxo-4H-1-benzopyran-3-yl)-2-thiazolyl] aminocrotonates contrary to intermediate 2-acetoacetylaminothiazoles reported in literature [23]. The intermediates undergo cyclization upon refluxing in diphenyl ether [24]. [Scheme-7].

SCHEME- 7



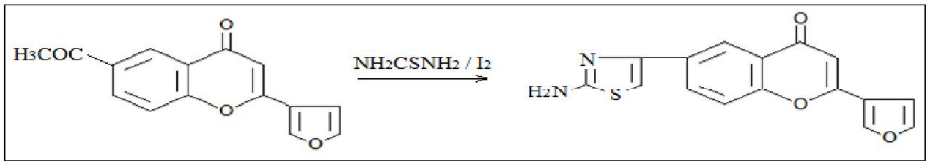
(8) Synthesis of 3-(dihydro-1, 3-benzooxazin-4-one-2-yl) chromones : 3-Formyl chromones undergo condensation with anthranilinic acid in alcohol in presence of catalytic amount of *p*-toluene sulphonic acid to create this system [25]. [Scheme-8].

SCHEME- 8



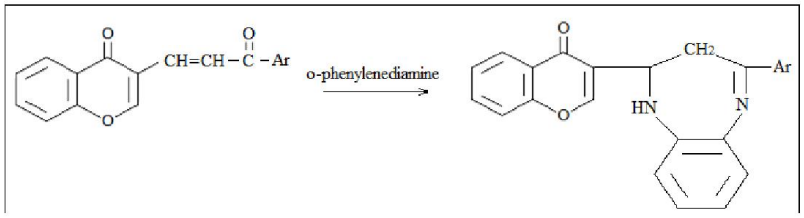
(9) Synthesis of 6-(2-aminothiazol-4-yl)-2-furylchromone: 6-Acetyl-2-furyl chromone can be converted to 6-(2-aminothiazol-4-yl)-2-furylchromone by condensing the former with iodine and thiourea on water bath [26]. [Scheme-9].

SCHEME- 9



(10) Synthesis of 3-(4-Phenyl-2,3-dihydro-1,5-benzodiazepin-2-yl)chromone: This compound has been obtained by reacting 1-phenyl-3-(chromon-3-yl)-2-propene-1-one [chalcone of chromone] with o-phenylenediamine in ethanol [27]. [Scheme-10].

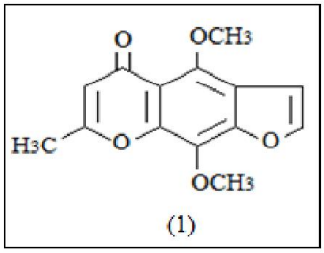
SCHEME- 10



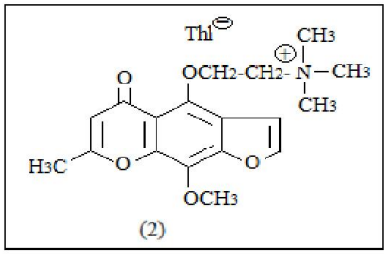
BIOLOGICAL AND MEDICINAL VALUE OF CHROMONES

Chromones as well as other flavonoids are of considerable importance in the development of pharmaceuticals as they are considered non-toxic on account of their distribution in plants and plant products which constitute the human diet. Chromone system *i.e.* benzopyran-4-one moiety is basic structure of flavonoids like flavones, flavonols and isoflavones [28]. This moiety is a unit in several drugs. For example, it possesses anti-cancer [29], anti-HIV [30-31], anti-inflammatory [32] and antibacterial [33] activities.

Out of various known chromone derivatives very few are of medicinal interest. Khellin (2-methyl-5, 9-dimethoxyfuro [3', 2', 6, 7]chromone), **[1]** an active principle of *Ammi Visnaga* was chromone derivative used as drug in Mediterranean area as diuretic agent to cure renal colic [34]. It is also effective anti-spasmodic agent and bronchodilator as well as anti-asthmatic [35-38]. A lot of work has been done on this compound because of broad spectrum of pharmacological activities; but its utility was hampered on account of high toxicity and low water solubility and consequently a number of chromone derivatives came into existence. For instance, other furochromones like 2-methyl-5-(2-dimethylaminoethoxy-9-methoxyfuro [3', 2', 6, 7] chromone methotheophylline **[2] [39]** and 9-(2-diethylaminoethoxy)-5-hydroxy-2-methylfuro[3', 2', 6, 7] chromone hydrochloride **[3] [40]** have also been synthesized and were found to be slightly useful. They are, however, less potent than Khellin.



(1)



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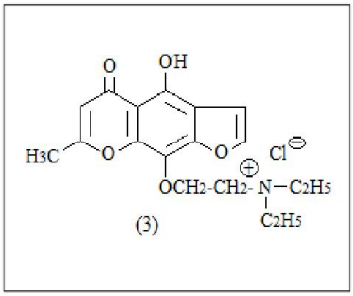

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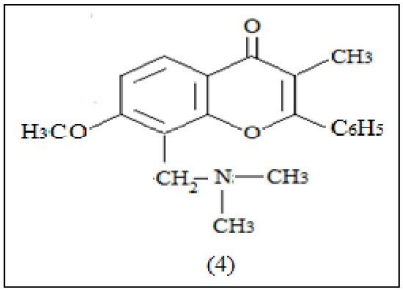
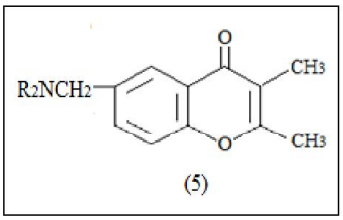


(4)

A number of other compounds possessing chromone moiety have been synthesized and tested pharmacologically. Dimefline, (3-methyl-7-methoxy-8-dimethylaminomethyl flavones), **[4]**, for instance, has been found to show marked stimulating effect on central nervous system (CNS) in general and medulla region in particular [41, 42]. Antispasmodic activity has been found in several types of aminochromones, e.g., 6-N-substituted aminomethyl-2, 3-dimethylchromone **[5] [43]** and 7-N-substituted aminoalkoxy-2-methylchromone **[6]** [44] have this activity.



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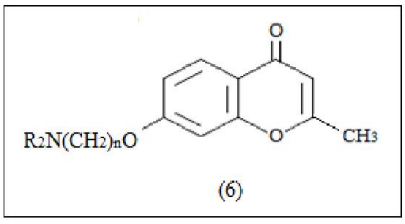
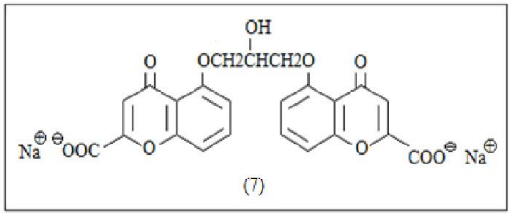


(6)

Anti-asthmatic drug disodium chromoglycate **[7]** is also a chromone derivative. Recognition of O—C=C—C=O group as a structural requirement for activity expedited investigation into chromone bearing a reactive functionality on pyran ring [45]. Simple chromone like that having aldehydic functional group at C-2 or C-3 of chromone act as p56 ^{lck} inhibitor which may have efficacy in the treatment of leukemia and lymphomas as well as autoimmune disorders like rheumatoid arthritis [46]. MAP kinase inhibition activity has been reported recently in chromones [47] which has a role as anti-cancer. Anti-bacterial and antifungal activities have also been reported in chromones [48, 49]. IIeterocycally substituted chromones [8] have been found to be diuretic [19, 20, 50].



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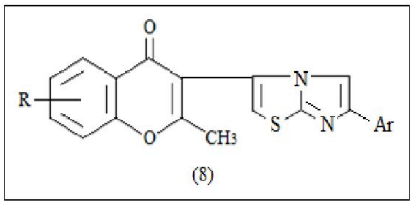

(8)

CONCLUSION

As chromonyl moiety is found in natural products which are part of diet as well as a scaffold in drugs, hence, chromones are health friendly molecules and novel molecules in chemical research.

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