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Review Article

PHARMACOLOGICAL ACTIVITIES OF CHROMENE DERIVATIVES: AN OVERVIEW

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ABSTRACT

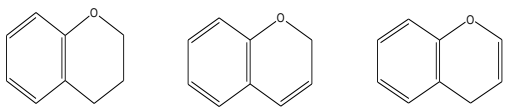
Chromene (Benzopyran) was one of the privileged scaffold which appears as an important structural component in various natural products and also possess useful photochemical properties. The derivatives of benzopyran moiety can be capable of interacting with a variety of cellular targets which leads to their wide ranging biological activities such as antitumor, antihepatotoxic, antioxidant, anti-inflammatory, diuretic, anticoagulant, antispasmolytic, estrogenic, antiviral, antifungal, antimicrobial, anti-helminthic, hypothermal, vasodilatory, anti-HIV, antitubercular, herbicidal, anticonvulsant and analgesic activity. The potency of these clinically useful pharmacophore in treatment of cancer and inflammation and other activities encouraged the development of some more potent and significant compounds. The SAR studies reported that the substitution in the chromene nucleus with the specific groups increases the ability of the molecule to prevent diseases. This review is summarized to know about the different pharmacological activities of chromene nucleus with the extended knowledge about its anticancer and anti-inflammatory activity.

Keywords: 2*H*-chromene, 4*H*-chromene, anticancer activity and anti-inflammatory activity.

INTRODUCTION

Chromene (Benzopyran) is one of the privileged medicinal pharmacophore which appears as an important structural component in natural compounds and generated great attention because of their interesting biological activity. It is a heterocyclic ring system consisting of a benzene ring fused to a pyran ring. Chromene constitute the basic backbone of various types of polyphenols and widely found in natural alkaloids, tocopherols, flavonoids, and anthocyanins[1]. It is known that certain natural and synthetic chromene derivatives possess important biological activities such as antitumor, antivascular[2], antimicrobial[3], antioxidant[4], TNF-α inhibitor[5], antifungal[6], anticoagulant, antispasmolytic, estrogenic[7], antiviral[8], anti-helminthic, anticancer[9], anti-HIV[10], antitubercular[11], anti-inflammatory[12], herbicidal, analgesic and anticonvulsant[13] activity. A key feature is that the lipophilic nature of the benzopyran derivatives helps to cross the cell membrane easily[14]. Chromene derivatives are also plays a important role in the production of highly effective fluorescent dyes for synthetic fibers, daylight fluorescent pigments and electro photographic and electroluminescent devices[15]. Among the all heterocyclic compounds, oxygen heterocycles are special because of their wide occurrence and broad pharmaceutical significance.

The benzopyran nucleus include some structural skeletons such as chromane, 2*H*-chromene and 4*H*-chromene[16] (Fig 1).



Chromane 2*H*-Chromene 4*H*-Chromene

Figure: 1

Vitamin E (Fig. 2) was an evident example for the naturally occurring chromane, which possess antioxidant activity[17].

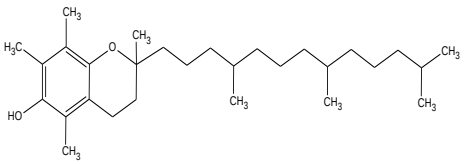
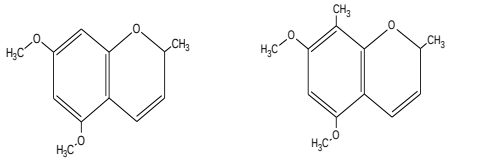


Fig. 2 : Vitamin E

The isolation of naturally occurring 2*H*-chromenes have been reported in vast number of publications. Examples of recently reported compounds include 5,7-dimethoxy-2-methyl-2*H*-chromene and 5,7-dimethoxy-2,8-dimethyl-2*H*-chromene (Fig 3), both were isolated from the leaf essential oil of *Calyptranthes tricona* which possess potential antifungal activity.



5,7-dimethoxy-2-methyl-2*H*-chromene 5,7-dimethoxy-2,8-dimethyl-2*H*-chromene

Figure: 3

In contrast to 2*H*-chromenes, 4*H*-chromene compounds are rather unusual and only a few examples of natural products containing this structure have been isolated. 7-hydroxy-6-methoxy-4*H*-chromene (Fig 4) was an example for naturally occurring 4*H*-chromene, which was obtained from the flower of *Wisteria sinensis* that exhibit organoleptic property[16]. An additional naturally occurring 4*H*-chromene was uvafzlelin (Fig 5) that isolated from the stems of *Uvaria ufielii* which shows broad spectrum of antimicrobial activity against gram-positive and acid-fast bacteria[18].

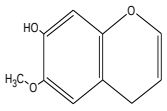


Fig. 4 : 7-hydroxy-6-methoxy-4*H*-chromene

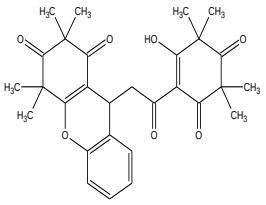


Fig.5 : Uvafzlelin

conrauinone A (Fig 6), was a naturally occurring fused ring chromene, has been isolated from the bark of the tree *Millettia conraui* and potentially utilized for the treatment of intestinal parasites[19]. Another natural compound was erysenegalensein C (Fig 7) which has been extracted from the bark of *Erythrina senegalensis* and found potential use in the treatment of stomach pain, female infertility and gonorrhoea[20].

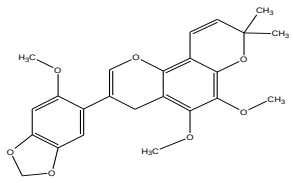


Fig. 6 : Conrauinone A

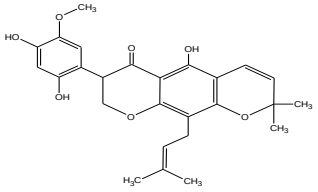


Fig. 7 : Erysenegalensein C

6-substituted-2*H*-chromenyl compounds shows highest 5-HT_{1A} receptor affinity and potential antidiabetic activity as a Na^+-glucose co-transporter inhibitor[16]. In the SAR studies, N-2-[[(6-Fluorochroman-8-yl)oxy]ethyl]-4-(4-methoxyphenyl)butylamine (Fig 8) selected as a lead compound and the structural modifications made on the chromene ring, the middle aliphatic portion, amine and the terminal aromatic ring to get more potential 5-HT_{1A} receptor antagonists[21].

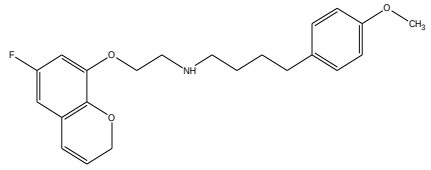


Fig. 8 : N-{2-[(6-fluoro-2*H*-chromen-8-yl)oxy]ethyl}-4-(4-methoxyphenyl)butan-1-amine

In recent studies, 2*H*-chromene especially 2,2-dimethylchromene derivatives are classified under the family of potassium-channel activating drugs which have anti-ischemic behavior and antihypertensive activity[22,23]. Cromakalim, (f)-trans-6-cyano-3,4-dihydro-2,2-dimethyl-4-(2-oxo-l-pyrrolidinyl)-2H-1-benzo[b]pyran-3-ol (Fig 9) was a antihypertensive agent which relaxes the vascular smooth muscle by activation of potassium ion channels[24].

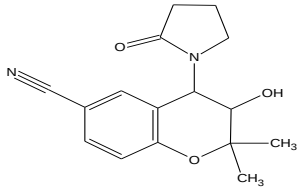


Fig. 9 : Cromakalim

2-amino-4-aryl-4*H*-chromene compound was act as an insulin-regulated amino peptidase (IRAP) inhibitor which exhibit a wide range of therapeutic applications include enhancing memory and learning functions[1]. Most potent inhibitors include either a 4-(pyridin-3yl) or a 4-(isoquinolin-3-yl) substituent at the benzopyran and also a 2-amino or 2-acetamido substitution. Some of the examples for IRAP inhibitors[25] (Fig 10) are:

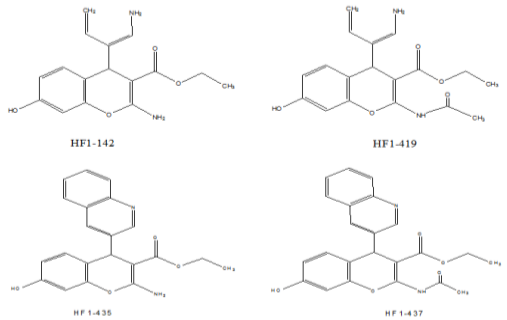


Figure 10:

In addition, amino chromene derivatives are widely used as cosmetics, pigments and potential biodegradable agrochemicals.

Dihydropyrano[3,2-c]chromenes (Fig 11) are another family of important heterocycles that have been used as cognitive enhancers, for the treatment of neurodegenerative diseases, including Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, Down's syndrome , AIDS associated dementia and Huntington's disease as well as for the treatment of schizophrenia and myoclonus[23].

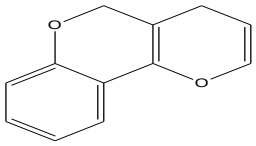
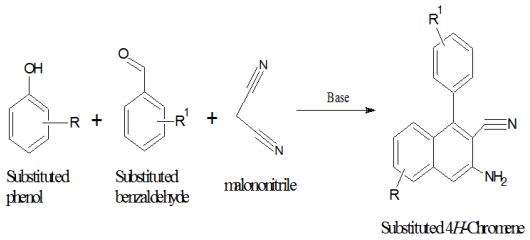


Fig. 11 : Dihydropyrano[3,2-*c*]chromene

In the synthesis, chromenes are generally prepared by reacting malononitrile, aldehyde and activated phenol in the presence of hazardous organic bases (piperidine, pyridine, ammonia, potassium carbonate, triethylamine, magnesium oxide, etc) for several hours[26] (scheme).



Scheme

But the conventional procedures for the synthesis of chromene derivatives are not found to be satisfactory because of less effectiveness and yield. So the most suitable method for the synthesis of these compounds would be the multicomponent reaction (MCR) due to the fact that the synthesis can be performed without the isolation of the intermediates and within a short reaction time[3].

Anticancer Activity Of Chromene

Cancer constitutes the second main mortality cause in the world[27]. Cancer is a disease characterized by the uncontrolled growth of abnormal cells. It is now documented that the most cytotoxic anticancer agents induce apoptosis which is the programmed cell death. Chromene derivatives are an attractive template for the identification of potential anticancer agents[28]. In recent years, there has been much interest in this class of compounds and their potential utility as anti-cancer drugs.

Many of the natural compounds contain chromene moiety have been reported with anticancer activity. These compounds are isolated from plants, sea fish, etc. Some of the examples of natural anticancer compounds include tephrosin[29](lung cancer) (Fig 12), calanone[30,31](leukemia and cervical carcinoma) (Fig 13), acronycine[32](lung, colon and ovary cancer) (Fig 14), seselin[33](skin cancer) (Fig 15).

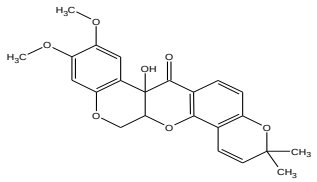


Fig.12 : Tephrosin

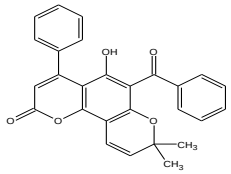


Fig.13 : Calanone

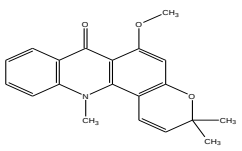


Fig.14 : Acronycine

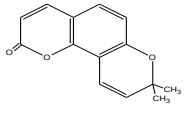
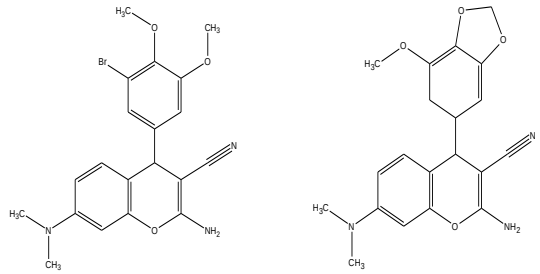


Fig.15 : Seselin

The potential proapoptotic chemotherapeutic agents using tubulin as one of the best cancer target so inhibition of the tubulin

polymerization was useful in the cancer therapy[34]. Anticancer agents can bind to different sites of tubulin and inhibit tubulin polymerization. This leads to the discovery of new structural classes of compounds of colchicine binding site of tubulin. The drugs coming under this category that binds to the colchicine binding site of tubulin results the deformation of α, β- dimer structure of tubulin, which prevents the tubulin assembly into microtubules leading to apoptotic cell death[2,9]. Substituted 4-aryl-4*H*chromene compounds belongs to a novel class of microtubule inhibitors and the systematic change in the substitution of 4-aryl group increases the anticancer activity of the compound[34]. Examples for compounds that coming under this category were 2-amino-4-(3-bromo-4,5-dimethoxyphenyl)-7-(dimethylamino)-4*H*-chromene-3-carbonitrile and 2-amino-7-(dimethylamino)-4-(7-methoxy-1,3-benzodioxol-5-yl)-4*H*-chromene-3-carbonitrile (Fig 16).



2-amino-4-(3-bromo-4,5-dimethoxyphenyl)-7-(dimethylamino)-4*H*-chromene-3-carbonitrile

2-amino-7-(dimethylamino)-4-(7-methoxy-1,3-benzodioxol-5-yl)-4*H*-chromene-3-carbonitrile

Figure 16:

In the above compounds, 2-amino-4-(3-bromo-4,5-dimethoxy-phenyl)-4*H*-chromene-3-carbonitrile induces caspase-mediated apoptosis in tumor cells and more potent than the commonly prescribed anticancer alkaloids. Furthermore, this compound included in the treatment of the drug-resistant cancers and also possessing vascular targeting activity[1,9]. During the process of developing this type of compounds, combretastatin A-4 which was a phosphate prodrug (CA-4P) used as a lead compound because of the simplest structure, potent cytotoxic and vascular disrupting activity[9,34].

Bcl-2 protein binding compounds also provides a satisfactory lead compound for the development of potential anticancer agents. Substituted 4*H*-chromene compounds were bind to Bcl-2 protein (B-cell lymphoma 2) and induce apoptosis in tumor cells[23]. Analogues of 4-aryl-4*H*-chromene also function as potential antagonists for antiapoptotic Bcl-2 proteins. Ethyl 2-Amino-6-bromo-4-(1-cyano-2-ethoxy-2-oxoethyl)-4*H*-chromene-3-carboxylate (HA14-1) (Fig 17), an antagonist for antiapoptotic Bcl-2 proteins was used to overcome drug resistance in cancer[35].

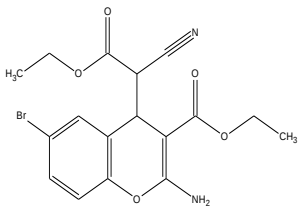
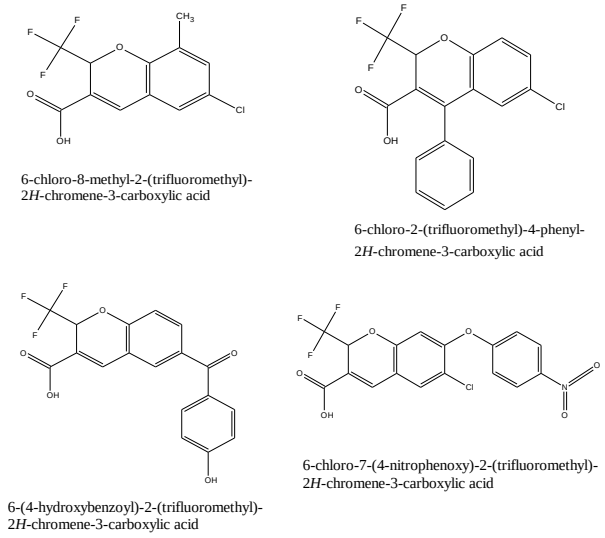


Fig.17: Ethyl 2-amino-6-bromo-4-(1-cyano-2-ethoxy-2-oxoethyl)-4*H*-chromene-3-carboxylate

The SAR studies of chromene nucleus was found that the 4-aryl moiety, 3-cyano group and 2-amino group are essential for the cytotoxic activity[9,36]. The replacement of the 2-amino group with the oxo group exhibit the same activity and helps to remove the chiral center that makes the synthesis more comfortable[37]. Substituting the 7th position with an electron donating group enhances the potency of the compound while an electron withdrawing group in that position decreases the activity[38]. It was found that a methoxy group, dimethylamino group or fused pyrrole ring was preferred at the 7-position[37].

Anti-inflammatory Activity Of Chromene

Inflammation is the first response of the immune system to infection, irritation or foreign substance[39]. The chromene pharmacophore represents a novel class of COX-2 selective inhibitors (coxibs) in non-steroidal anti-inflammatory drugs (NSAIDs) which provide higher potency, efficacy, and selectivity over the existing coxibs (eg: celecoxib, valdecoxib, rofecoxib, and etoricoxib) for the treatment of inflammation[41]. The chromene coxib clinical candidates are SD-8381 and SC-75416. SC-75416 provides a fast onset of action and higher efficacy compared to ibuprofen[42]. Another examples for chromene cyclooxygenase-2 selective inhibitors (Fig 18) include:



6-chloro-8-methyl-2-(trifluoromethyl)-2*H*-chromene-3-carboxylic acid

6-chloro-2-(trifluoromethyl)-4-phenyl-2*H*-chromene-3-carboxylic acid

6-(4-hydroxybenzoyl)-2-(trifluoromethyl)-2*H*-chromene-3-carboxylic acid

6-chloro-7-(4-nitrophenoxy)-2-(trifluoromethyl)-2*H*-chromene-3-carboxylic acid

Figure 18:

Tumor Necrosis Factor α or TNF-α is a pro-inflammatory cytokine secreted in response to many inflammatory stimuli. Binding of TNF-α to its receptors (TNFR1 and TNFR2) initiates the activation of MAP kinase and also causes activation of the transcription factor NF-kB. NF-kB regulates the production of many pro-inflammatory cytokines including TNF-α and related proteins. So decreasing the TNF-α levels or inhibiting NF-kB activation have been shown to be useful for the treatment of many diseases such as rheumatoid arthritis, psoriasis, and inflammatory bowel disease[5]. One of the important approaches to the discovery of inhibitors of TNF-α was the inhibition of zinc containing metalloproteinase, TNF-α converting enzyme (TACE)[42].

The SAR studies shows that the substitution in the benzene ring of the chromene moiety has an important role in the ability of the molecules to block TNF-α production. A methoxy group at the 7th position and 3,4,5-trimethoxyphenyl group at the 2nd position of chromene were the preferred substituents which act as potent inhibitors of TNF-α production[5]. One of the example that coming under this class of compounds was 7-methoxy-2-(3,4,5-trimethoxyphenyl)-2*H*-chromene (Fig 19).

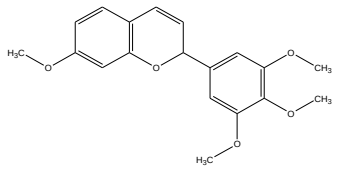


Fig. 19 : 7-methoxy-2-(3,4,5-trimethoxyphenyl)-2*H*-chromene

In addition, 6,7-Dimethyl-3-((methyl-(2-(methyl-(1-(3-trifluoromethyl-phenyl)-1*H*-indol-3-ylmethyl)-amino)-ethyl)-amino)-methyl)-chromen-4-one (Fig 20) was another drug that prevent the TNF-α binding to its receptors. 2-amino-4*H*-chromene derivatives with a nitrile functionality have potential application in the treatment of TNF-α mediated diseases[1].

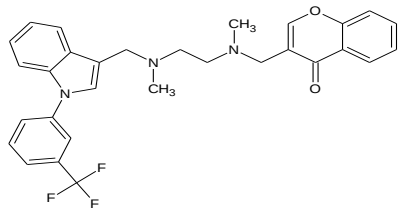


Fig. 20 : 6,7-Dimethyl-3-((methyl-(2-(methyl-(1-(3-trifluoromethyl-pheyl)-1H-indol-3-ylmethyl)-amino)-ethyl)-amino)-methyl)-chromen-4-one

Condensed 4-chloro-2,2-dialkyl chromene-3-carbaldehyde derivatives also have an anti-inflammatory activity and the substitution of thiosemicarbazide group at 3rd position of the pyran ring increases the potency of the compound. One of the example was 1-(4-Chloro-2,2-dimethyl-2H-chromen-3-yl) methylene] thiosemicarbazide (Fig 21) which have better activity compared to indomethacin.

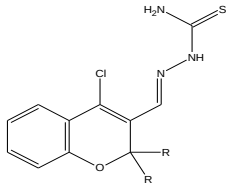


Fig. 21 : 1-[(4-chloro-2,2-dimethyl-2*H*-chromen-3yl)methylene]thiosemicabazide

In case of natural compounds, Cannabichromene (CBC) (Fig 22) was one of four major cannabinoids in *Cannabis sativa* and some of its analogs have high therapeutic potential for the treatment of anti-inflammatory diseases. It was also useful for inducing hypothermia and acts as antimicrobial agent. In the evaluation test, CBC was superior to phenylbutazone[43].

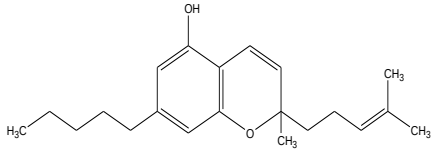


Fig. 22 : Cannabichromene

CONCLUSION

The chromene ring is an important pharmacophore in modern drug discovery. The literature has been given more attention to the chromene nucleus as a source of new anticancer and anti-inflammatory agent. The knowledge gained by various researches has suggested that substituted chromene which interact easily with the receptors and possess different pharmacological activities with lower toxicity. Now the interest of research is to design more potent chromene derivatives having wide diverse of biological activity.

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