Review Article

Biological importance of 4H-1-benzopyran and derivatives

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Abstract

Compounds containing pyran, benzopyran and benzo thiopyran ring systems display interesting biological activities such as antiallergic, antitumor, antiviral, antioxidant and antiinflammatory etc. The aim of the present paper was to review the available information on this field.

Key Words: 4H-1-Benzopyran and derivatives, Biological importance

Introduction

Six-membered oxygen and sulfur containing heterocycles are widespread through both the domains of natural and synthetic compounds. Compounds containing pyran, benzopyran and benzo thiopyran ring systems display interesting biological activities, which have motivated the chemical community towards the studies on their isolation, structure, reactivity and synthesis. The important group of natural benzopyran compounds is the flavonoids which abundantly occur in the plant kingdom. Their intake takes place through foods and they perform many important biological functions. The main objectives of synthesis of chromones and related compounds are not only for the development of more diverse and complex compounds having wide range of biological activities and their structure-activity relationship (SAR) studies but also for other applications in medicinal chemistry and material science, such as development of various fluorescence probes due to interesting photophysical and photochemical properties of these compounds. Benzo thiopyrans are mainly synthetic compounds and in the recent past the studies on their syntheses have experienced a surge due identification of a number of biological activities of compounds containing this ring system.
Biological Importance of Chroman [≡ 2,3-Dihydro-4H-1-benzopyran] Derivatives

Chromans have considerable biological importance, especially as potentially useful pesticides and drugs\(^{1a}\). Chromans have gained recent interest because of their broad biological and pharmacological activities. Disodium cromoglycate marked as Intal or Cromolyn sodium bears some structural resemblance to khelin, the spasmolytic component of seeds of *Ammivisnaga*. Intal is one of the successful drugs for the prevention of asthmatic attacks, though it is not effective in the treatment of an acute attack of asthma. It appears to prevent the release of histamine and other substances which mediate hypersensitive reactions but is ineffective once these substances have been released\(^{1b-c}\).

![Intal](image)

A number of 3-(1H-tetrazol-5-yl)chromones were synthesized and found to have antiallergic activity\(^2\). Yang *et al.* synthesized series of chromanones and chromones analogues of diacylhydrazine derivatives which have broad insecticidal activities\(^3\). The insecticidal activity of such compounds against *Aphis medicaginis*, *Nilaparvata legen*, *Mythima separata*, *Tetranychus cinnabarinus* etc. were investigated. Heilmann *et al.* isolated chromanone acids from *Calophyllum brasiliense* Cambers. All compounds showed moderate to strong antibacterial\(^4\) activity against *Bacillus cereus* and *Staphylococcus epidermidis*. Bis-chromans 1 show potential biological activity against human pathogenic bacteria\(^5\). Bis-chromanones have been found to exhibit significant activity towards *S. aureus* and *S. faecalis*.

![Bis-chromans 1](image)

Park *et al.* synthesized\(^6\) a new series of compounds with chromone and chromanone which have ability to inhibit HIV-1. A series of chroman and chromanone derivatives have antioxidant activities. Lee *et al.* synthesized and evaluated\(^7\) 6-hydroxy-7-methoxy-4-chromanone and chroman-2-carboxamides as antioxidant. Gamal-Eldeen *et al.* isolated\(^8\) a
chromone derivative, 2-(hydroxymethyl)-8-methoxy-3-methyl-4H-chroman-4-one, which has modulatory effect on carcinogen metabolizing enzyme CYP1A (Cytochrome P-450 1A). The results indicate that the chroman is a promising inhibitor of CYP1A activity up to 60% of the stimulated-CYP1A in murine hepatoma cells and significantly reduced GST (Glutathione S-transferases). The isolated chroman possesses a potent specific radical scavenging activity against hydroxyl radicals and induced DNA damage. Prakash et al.\(^9\) synthesized 3-hydroxy-2-(1-phenyl-3-aryl-4-pyrazolyl) chromone 2 which has antifungal activity against three phylopathogenic fungi, namely Helminthosporium species, Fusarium oxysporum and Alternaria alternata. Ishar et al. synthesized novel 6-chloro/flurochromone derivatives 3\(^10\) as potential topoisomerase inhibitor anticancer agents.

![Structure of chromone derivative](image)

Tkaishi et al. isolated\(^11\) chromone glucosides, takanechromones 4 and chromanone glucosides, named takanechromanones 5 from the methanolic extracts of Hypericum sikokumontanum together with twenty seven compounds. The isolated compounds were assayed for antimicrobial activity against Helicobacter pylori and cytotoxicity against human cancer cell line.

![Structure of glucosides](image)

The significant antipyretic activity of 2-methylchromones has been recognized fifteen years ago. They have the same antipyretic effect as paracetamol and analgesic effect as novalgin. Also, 2-methylchromones 6 and 7 play vital role in the replication cycle of AIDS virus and thus act as HIV-1 protease inhibitors\(^12\)

![Structure of antipyretic compounds](image)
Khellin 8 is the principal constituent of *Ammivisnaga L.* It is 2-methyl-chromone with a linearly fused furan ring system and has been found to be a potent coronary vasodilator in bronchial action on bronchial muscle, gall bladder and bile duct. Additionally, it has been reported to be used as antispasmodic13. 5,6,7-Trihydroxy-2-methylchromone 9 showed a high inhibition activity towards α-glycosidase (the α-glycosidase enzyme catalyses the final step in the digestive process of carbohydrate, hence, α-glycosidase inhibitors can retard the decomposition and absorption of dietary carbohydrates to suppress postprandial hyperglycemia14. Chromone derivatives have capacity to act as antioxidant. Many chromone derivatives

![chemical structures](image)
such as luteolin 10, quercetin 11, catechins 12 are better antioxidants than the nutrients antioxidants such as vitamin C, vitamin E and β-carotene15. The function of antioxidant is to intercept and react with free radicals at a rate faster than the substrate. Since free radicals are able to attack at variety of targets including lipids, fats, and proteins, it is believed that they may damage organisms leading to disease poising including aging. Quercetin 11, kaempferol, morin, myricetin and rutin, by acting as antioxidants, exhibited anti-inflammatory, antiallergic, antiviral as well as anticancer activity. They have also protective role in liver and cardiovascular disease. Quercetin and silybin act as radical scavengers and protect liver from reperfusion ischemic tissue damage16,17. Quercetin has been reported to completely inhibit the growth of *Staphylococcus aureus*18. Chromone derivatives have been investigated for their antibacterial, antifungal and antiviral activities. Y. B. Vibhute *et al.* showed that chromones of the type 13 available from a new class of chalcones have antibacterial activity against *Xanthomonas citri, Erwinia carotovora, Escherichia coli, Bacillus subtilis* using ampicillin as a standard drug19. Murty *et al.* synthesized 7,4′-dihydroxy-3′-methoxyflavone 14, a chromone

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derivative, which has antibacterial activity against gram positive bacteria like \textit{Staphylococcus aureus}, \textit{Bacillus subtilis} and \textit{Staphylococcus griseus} and gram negative bacteria like \textit{Escherichia coli} and \textit{Psuedomonas aureagionsa}. 

Subramanyam \textit{et al.} isolated the trimethoxyflavone 15 from \textit{Andrographis viscosula} and used it in the treatment of dyspepsia, influenza, malaria, respiratory functions and as an astringent and antidote for poisonous stings of some insects. B. S. Dawane \textit{et al.} synthesized chromone derivatives 16 of the type containing substituted naphthalene moiety having antibacterial activities against \textit{Staphylococcus aureus} and \textit{Escherichia coli}, by disk diffusion method, using tetracycline antibiotic for comparison of activity.

A number of chromones were isolated from the peelings of tangerine orange, having fungistatic activity against \textit{Deuterophoma tracheiphila}. Nobiletin 17, a citrus flavonoid, isolated from tangerine orange exhibited strong activities. Chlorflavonin was the first chlorine-containing flavonoid-type antifungal antibiotic produced by strains of \textit{Aspergillus candidus}. 

Naturally occurring chromone derivatives with antiviral activity have been recognized since the 1940s, but only recently attempts have been made to make synthetic modification of natural compounds to improve antiviral activity. Quercetin, morin, rutin, dihydroquercetin, apigenin, catechin, hesperidin have been reported to possess antiviral activity against some of the 11 types of viruses. It has been found that flavonols are more active than flavones against \textit{Herpes simplex} virus type 1. \textit{Calsalpinia pulcherrima} showing antiviral activity has been found to possess quercetin. The mode of action of quercetin against HSV-1(herpes virus) and ADV-3 (adeno-virus) was found to be at the early state of multiplication, and this compound can be used for the treatment of infection caused by these two virus. Because of world-wide
spread of HIV, the investigation of antiviral activity of chromanone and chromone derivatives was focused mainly on HIV\textsuperscript{25}. There have been several recent reports on anti-AIDS activity of such derivatives\textsuperscript{26}.

Chromanone derivatives have effect on gastrointestinal system. Hesperidine \textsuperscript{18}, citrus flavonoids, possesses significant anti-inflammatory and analgesic effects\textsuperscript{27}. Recently, apigenin \textsuperscript{19}, luteolin \textsuperscript{10} and quercetin \textsuperscript{11} have been reported to exhibit anti-inflammatory activity\textsuperscript{28}. Some recent studies have indicated that flavonoids possess antiulcerogenic activity. Flavonoid lycosides of \textit{Ocimum basilicum} decreased ulcer index and inhibited gastric acid and pepsin secretions in aspirin-induced ulcers in rats\textsuperscript{29}.

\begin{center}
\includegraphics[width=0.5\textwidth]{Hesperidin.png}
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Hesperidin

The liver is subjected to acute and potentially lethal injury by several substances including phalloidin (the toxic constituent of the musroom, \textit{Amanita phalloides}), CCl\textsubscript{4}, galactosamine, ethanol and other compounds. Chromone derivatives have also been found to possess hepatoprotective activity. The derivatives apigenin \textsuperscript{19}, quercetin \textsuperscript{11} and naringenin \textsuperscript{20} can act as putative therapeutic agents against microcrystin LR-induced hepatotoxicity, silymarin was found to be most effective one\textsuperscript{30}. The flavonoid, rutin \textsuperscript{21} and venoruton \textsuperscript{22} showed hepatoprotective effects in experimental cirrhosis\textsuperscript{31}.

\begin{center}
\includegraphics[width=0.5\textwidth]{Apigenin_Naringenin.png}
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\textbf{Apigenin} \hspace{1cm} \textbf{Naringenin}
Chromone derivatives, especially quercetin, have been reported to possess antidiabetic activity. Vessal et al. reported that quercetin brings about the regeneration of pancreatic islets and probably increases insulin release in streptozotocin-induced diabetic rats. Hif and Howell reported that quercetin stimulates insulin release and enhances Ca^{2+} uptake from isolated islets cell, which suggests a place for chromones in non-insulin-dependent diabetes.

The consumption of flavonoids prevents endothelial dysfunction by enhancing the vasorelaxant process leading to a reduction of arterial pressure. Some derivatives of chromones can prevent a number of cardiovascular diseases including hypertension and atherosclerosis.

It was found in the 1960s that tea pigment can reduce blood coagulation, increase fibrinolysis, and prevent platelet adhesion and aggregation. Selected chromanone derivatives such as quercetin, kaempferol, and myricetin were shown to be effective inhibitors of platelet aggregation in dogs and monkeys.

Recent interest in different chromanone derivatives has been stimulated by the potential health benefits arising from the antioxidant activity of these polyphenolic compounds. Some derivatives have been considered as potential protectors against chronic cardiotoxicity caused by the cytostatic drug doxorubicin. Doxorubicin is a very effective antitumor agent but its clinical use is limited by the occurrence of a cumulative dose-related cardiotoxicity, resulting in congestive heart failure. In a recent report, the cardiotoxicity of doxorubicin on the mouse left atrium has been inhibited by flavonoids.

Some chromone derivatives have antineoplastic activity. Quercetin exerted a dose-dependent inhibition of growth and colony formation. The flavonoids, kaempferol, catechin, toxifolin, and fisetin, also suppressed cell growth.
Conclusion

4H-1-Benzothiopyran derivatives show vast array of biologically activity and have been used in traditional eastern medicine for thousands of years. They also constitute unavoidable components of the diet. In the present review, I have reviewed biological properties of 4H-1-Benzothiopyran derivatives. Their widespread occurrence, broad spectrum diversity and natural origin make them appropriate chemical scaffolds for novel therapeutic agents.

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References


12. Ibrahim, M. A.; Ali, T. E.; Alnamer Y. A.; Gabr, Y. A. Synthesis and chemical reactivity of 2-methylchromones. ARKIVOC, **2010** (i), 98.


