Section A-Research paper

Recent Advancement and Futuristic Approaches of Various Derivatives of Chromones : A Comprehensive Review

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Abstract

The chromone and its derivatives are the most important heterocyclic compound showing a lot of pharmacological activities. these heterocyclic derivatives offer a variety of pharmacological activities with change in the structures offers a numerous diversity with beneficial synthesis of members of new compounds. A huge volume of research has been done in this specific area but this review emphasizes on the recent advancements of heterocyclic compounds having pharmacological activities, i.e., antiviral, antifungal, anti – inflammatory activities of last five years. so, this review will be beneficial for the researchers doing work on this specific areanowadays. this review analysis a keen wide study of chromone derivative of last 10 years at least.

Keywords): Chromones, chemo preventive, chemotherapeutic, anticancer, structure-activity relationships (SAR)

INTRODUCTION

The Greek term "chroma," from which the English word "chromones" is derived." which means "color," and it denotes that a large number of chromone derivatives display a variety of colors. In 1900, Bloch and Krosnick adopted the tribal name "Chromone." Chromone, an isomer of coumarin, is a chromone benzopyran derivative. which has a keto group replaced on the Pyron ring. Other names for chromone include 1,4 benzopyran. having a benzo annulated pyrone ring, chromones are heterocyclic compounds that include oxygen. The chromone belongs to natural occurring substances co flavone which one responsible for provide colors and protect from uv radiation and fungus disease .In addition to providing plants with an alluring coloration for pollinators, chromones also assist plants survive by shielding them from UV radiation and fungus diseases.(1)Figure 1

Figure 1. Various chromone Derivatives

Therefore, the most crucial task in the medical field is to regulate or restore the homeostatic oxidative balance.Humans cannot produce essential antioxidants like ascorbic acid and tocopherol; instead, they need to be obtained outside the body. As a result, antioxidant defense systems vary depending on the species and are strongly influenced by diet.(2)

Chemically Chromones are a class of heterocyclic chemicals that include oxygen (benzo-pyrones, benzo-1-benzopyran-4-ones, or 4H-chromen-4-ones). The flavones are the participants inthe primary class of natural flavonoids chemicals thatcontain a chromone structure because they have a 2-aryl substitution (3-4)

Chromones and a number of other organic materials, support Pollinators to attracted forwards to the color of plants because of their pigmentation. They also protect the plant from UV radiation and fungus, protecting its life and capacity for reproduction(4-5)

Chromone-based chemicals have been linked to a number of significant biological consequences the ability to block a number of enzymes and possess antiviral, antifungal, antibacterial, antiallergenic, anti-tubulin, antiviral, antihypertensive, and antitumoral properties(4,5)

Chromanones

Chromanones are the name for the derivative of chromone 2, 3-dihydroA double bond formed by C-2/C-3 is absent from every molecule in this group and contains different chromones as see compounds (1–11). Since small groups likemethyl, hydroxyl, isopentenyl, propenyl, and othersthe C-2, C-5, and C-7 positions is replaced inthe, compounds **(1–8)** have relatively simple structures. Compounds (9–11) are unique variations of chromanones having have a pyran ring connected at C-6/C-7

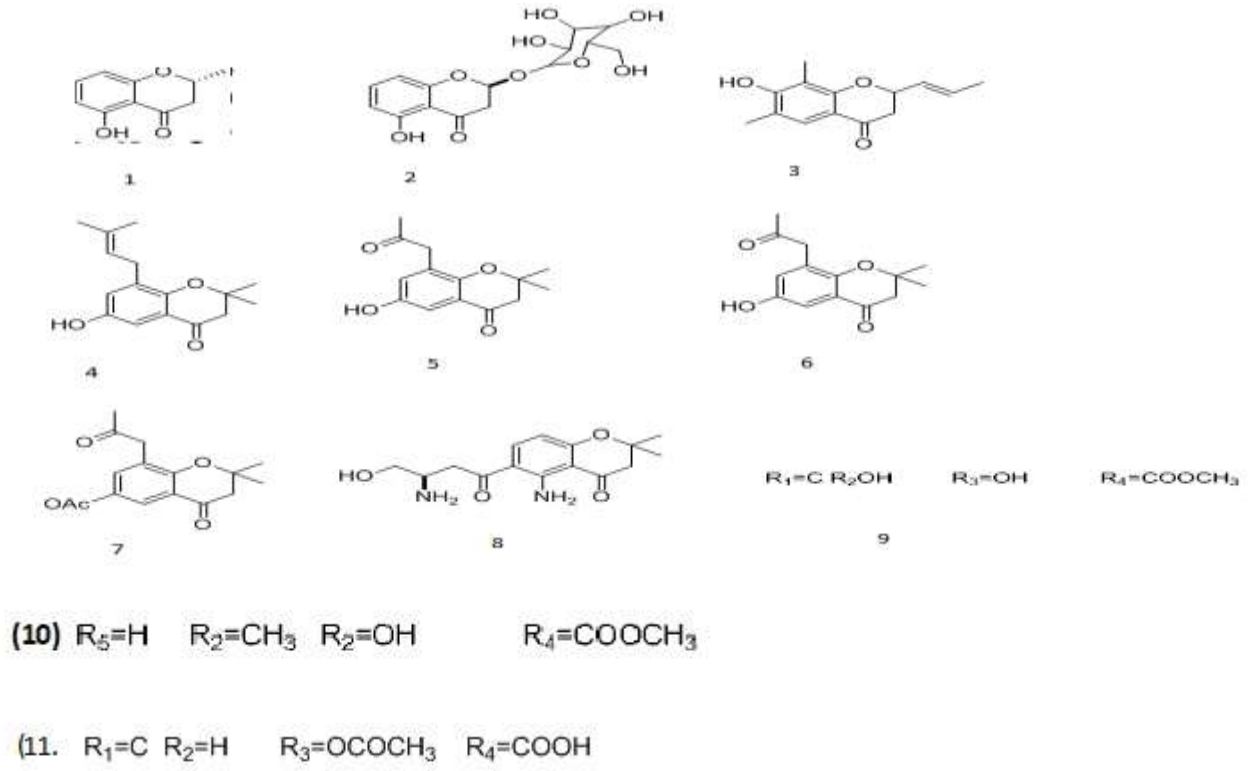


Figure 2. Structures of Chromanones

Synthesis of Chromones

Synthesis of chromone has great interest and long history (4) in research field. There are a number of techniques have been created to create chromone derivatives: Using an intra-molecular Wittig method, for instance, and the Allan-Robinson strategy for chalcones (7,8)

A popular technique is the conversion of an o-hydroxy to an acyl acetophenone utilizing an aromatic acid chloride, resulting an aryl ester. then a foundation repositions the ester group (Bakare Venkataraman rearrangement) during cyclocondensation, a 2-arylchromone is produced froma substance known as a 1,3-diaryl 1,3-diketone. (5) as shown in **Figure 2**

Reactions out across media with the addition of too much sulfuric acid to glacial acetic acid was one of the reaction conditions used (6) isopropanol (7) Anhydrous sodium acetate or aqueous potassium carbonate in glacial acetic acid are examples of cationic exchange resins. (8)Using CuC_{12} in ethanol, greener processes have recently been described. (9) Heteropoly acids and ionic liquid exposed to microwave radiation (10)and ortho-fluorobenzyl chloride condenses a 1,3-keto ester, where the displacement of the fluoride by a bisenolate oxygen and chromone occurs in an intramolecular reaction. Whenever carbon monoxide is present, ortho hydroxyaryl iodides are coupled to alkynes by palladium to chromones in situ, ring-closing. Takes place using ortho – hydroxyaryl alkynyl as an intermediate.(1) as shown in **Figure 3 and 4**

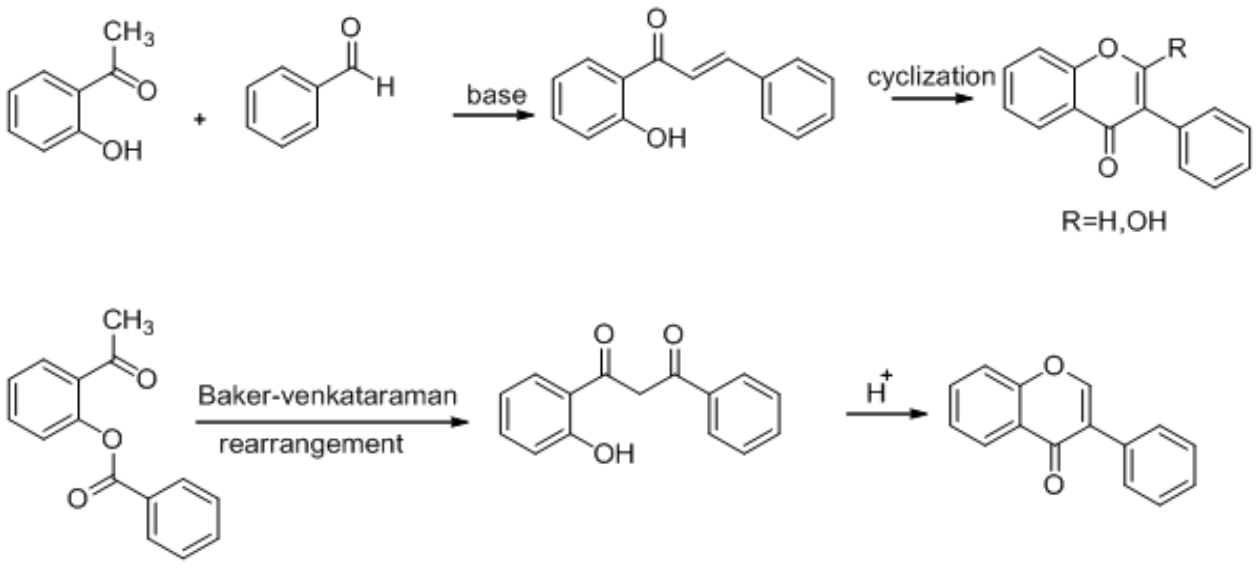


Fig. 3. Common methods for obtaining the structure of a chromone: (I) cyclization after a chalcone; (II) Bake-Venkatraman rearrangement

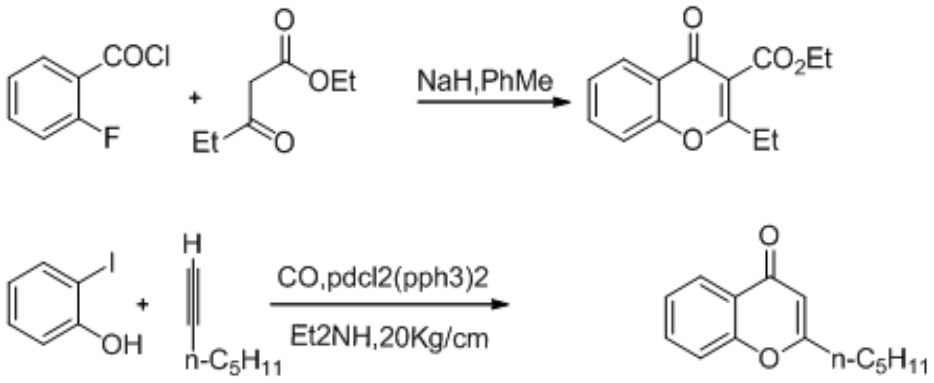
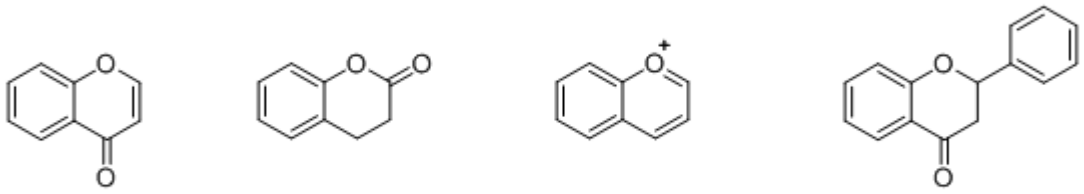


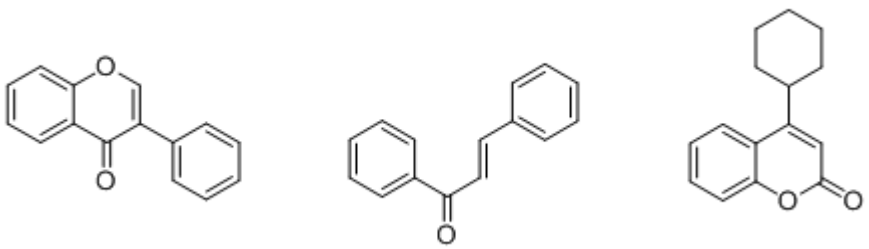
Fig.4. Chromone structure is often obtained by two different synthetic processes: (I) Enolate oxygen provides an intramolecular sensing., and II) palladium as a catalyst.

THE CHROMONES NUCLEUS'S CHEMISTRY

In the benzo-Pyron network, chromones (1) are heterocyclic substances. It's a benzopyrone. derivative with an overlying keto group on the Pyron ring.'(12).Benzo fusedsimilar to both the Pyron and the Pyrilliumcations ring. system in a number of key natural compounds. These systems (13),which include chromone (1), coumarin (2), and benzyopriliumcation (3) There have also been reports of many flavones(4),isoflavones(5), chalcones(6), neoflavones(7), glycosides, and flavones.(14)



(1) (2) (3) (4)



(5) (6) (7)

Pharmacological actions with efficacy

1. Anticancer activity: One of the major priorities in pharmaceutical research is the discovery and development of new anticancer drugs with strong cytotoxic action. The use of currently available chemotherapeutic agents has several limitations, including differences in efficacy, poor toxicity profiles, and side effects(15)

In general, cancer is associated with the extentcellular mitochondria and metabolic disturbances such as the provision of cellular energy and cell death Reactive oxygen species are products of metabolic processes (ROS) formation, impaired enzymatic action and increased aerobic glycolysis in tumor cells it can be measured by measuring abnormalities in lipid metabolism, an imbalanced pH, and values (16)

2. Antibacterial activity Pongagrabol 1 showed activity against Shigella, Streptococcus hemolytic us and A streptococcus aureus. Minimal concentration that inhibits the first two microbes is 64 µg/ml(17)Extracts in methanol and ethyl acetate(18)combined with carangin from the pogonia pinnata plant showed antibacterial efficacy. Flavonoids in an extract fromLonchocarpolscontain 8% and 19% of ping Amol in Montana's plants in dichloromethane.The action of oblanceolate B. Pong Amol itself proved effective against Bacillus subtilis and Cladosporium cladosporioides against Staphylococcus aureus. (19)

3 Psychotropic activity Karang in is known to boost the neurological system, as a tranquillizer is pong Amol tranquilizer (With respective LD50 values and 17.14 mg/kg, respectively(20).derivatives in the pyran (2,3)-indole 4(7H) (3) system are artificial counterparts of natural chromones that do not occur in nature.The vanilloid receptor TRPV 1 serves as series' analogue. (21)This is of specific significance in the therapy for osteoarthritis, fibromyalgia pain, cancer-related pain, and pain associated with surgery of a general and gynecological nature. (IC50 = 0.068 RM).

4 Antiviral properties Militia erythrocalyx's isolated Pongol 4 methyl ether showed action against the HSV-1 and HSV-2 strains of the herpes virus (22).A piperidine ring and an unsubstituted hydroxyl group are presentwithin the molecule are responsible for its anti-HIV-139 activity,having no anti-H. pylori activity in 8-bibromo-3-formylchromone, but it had strong urease inhibitory action.(23).

5 Antifungal activity Chromone 3-hydroxy-2-(1-phenyl-3-aryl-4-pyrazolyl) (7),a derivative used as an antifungal medication. preventing the growth of fungus hyphal. (24)Angelicin (8), a furanocoumarin found in nature has antifungal properties vs Aspergillus, Cryptococcus neoformans, and Candida albicans nigricans(25)The coumarin derivative esculetin (9) exhibits Cryptococcus neoformans and Saccharomyces cerevisiaeboth targets of antifungal action. (26)

6 Antituberculosis action: Newly developed 1,2,3-triazole-fused Spiro chromone (10) conjugates were created and inhibited the developmentof(27)(chromenylium) (3-thienyl) methyl]-2H-2-chromenone against Mycobacterium tuberculosis in vitro& was tested with (11) inhibition) is the most effective active ingredient action promised against Mycobacterium tuberculosis(28)

7 Anti- inflammatory action Asthma is treated with nedocromil sodium (12), which also has anti-inflammatory effects.It functions by preventing inflammatory cells from becoming active such as platelets, mast cells, eosinophils, macrophages, neutrophils, and monocytes(29)Homoisoflavanones (13) and the chemically related substances (14) have been cited as antibacterial and anti-inflammatory compounds act against the COX-1 enzyme(30)

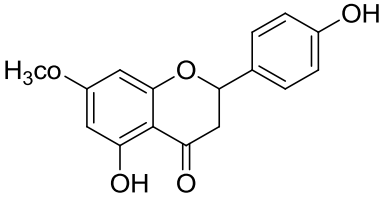
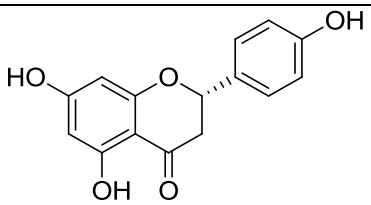
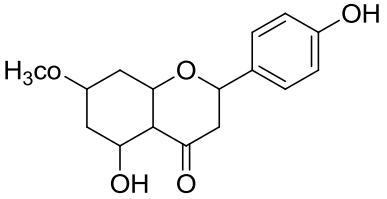
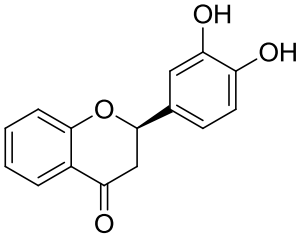
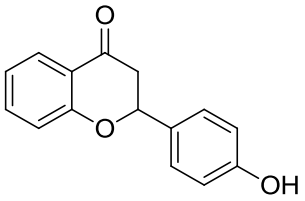
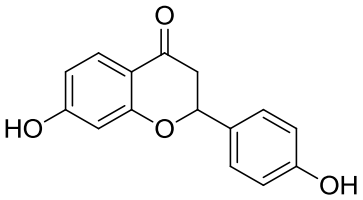
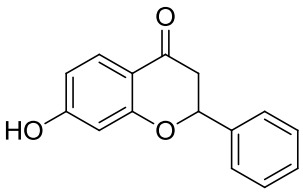
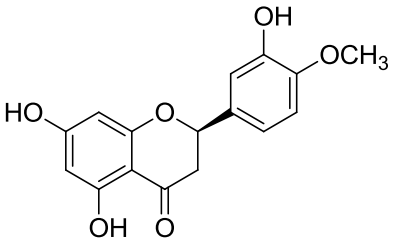
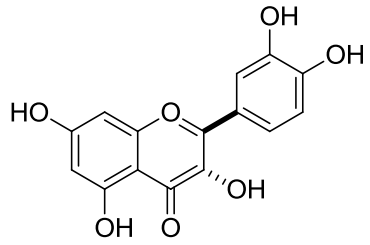
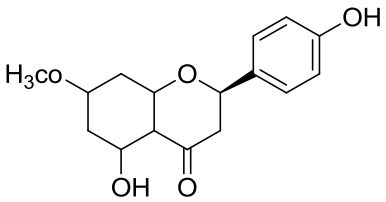
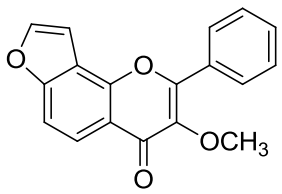
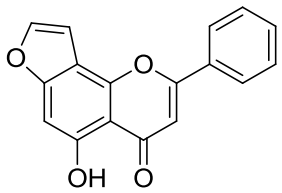
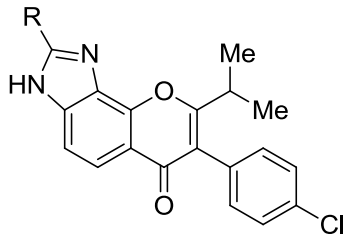
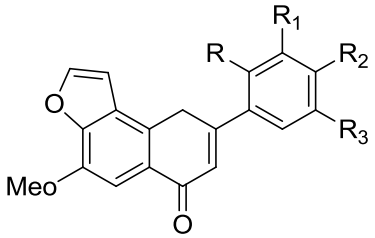
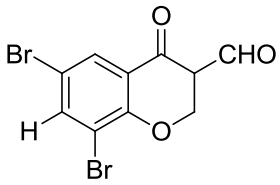
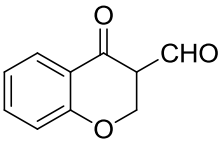
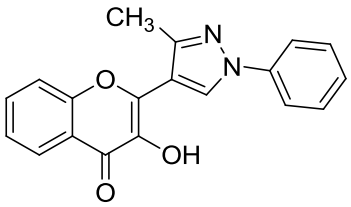
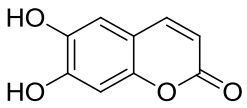
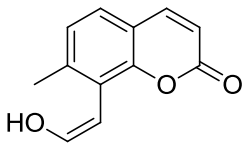
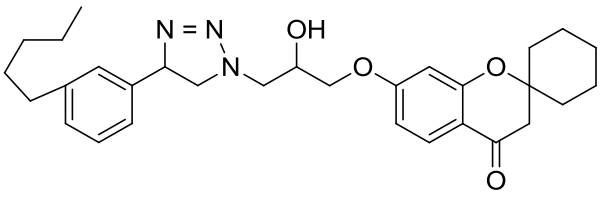
S. No	Name of activity	Structure of the compound
1	Anticancer Activity	 Naringenin
		 Eriodyctiol
		 Sakuranetion
		 Sterubin

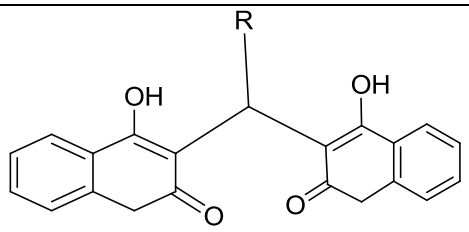
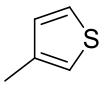
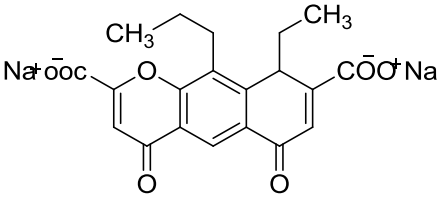
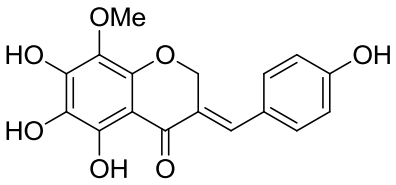
Figure1.Biological flavanones parented by chroman-4-one

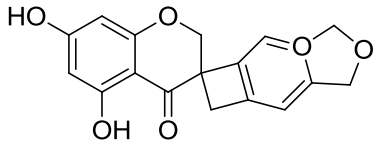
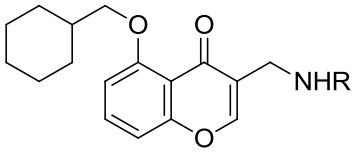
		 4 – Hydroxy flavone
		 5,4 – Dideoxy flavanone
		 5- Dideoxy flavanone
		 Hesperetin

		 (25 ,35) – Trans – dihydroquercetin
		 Sakuranetin **fig. 2 Structure generated from chroman-4-1 (under development phase)**
2	**Antibacterial Activity**	 1 Karangin
		 2 Pongaglabol

3	Psychotropic Activity	 3 R = MeCF2
4	Antiviral Activity	 4 R = R2 = R3 = H, R1 = OH
		 5
		 6

5	Antifungal Activity	 7
		 8
		 9
6	Antituberculosis Activity	 10

		 11
		 R =
7	Anti-inflammatory Activity	 12
		 13

		 14
		 (12 a – d)

API involved furistic approach of chromone

The effectiveness of this scaffold in treating various illnesses has been assessed and improved in numerous research., including illnesses that affect inflammation, the nervous system, cancer, diabetes, and infectious conditions. Numerous novel chromone derivatives have been developed for the pharmaceutical industry and are still being done so. (4,31)For improved or multitarget therapeutic uses, one can pair well-known chromones with other pharmacophores by creating dyads, in addition to developingnovel derivatives with interesting pharmacological properties (32,31)(Figure no 5).

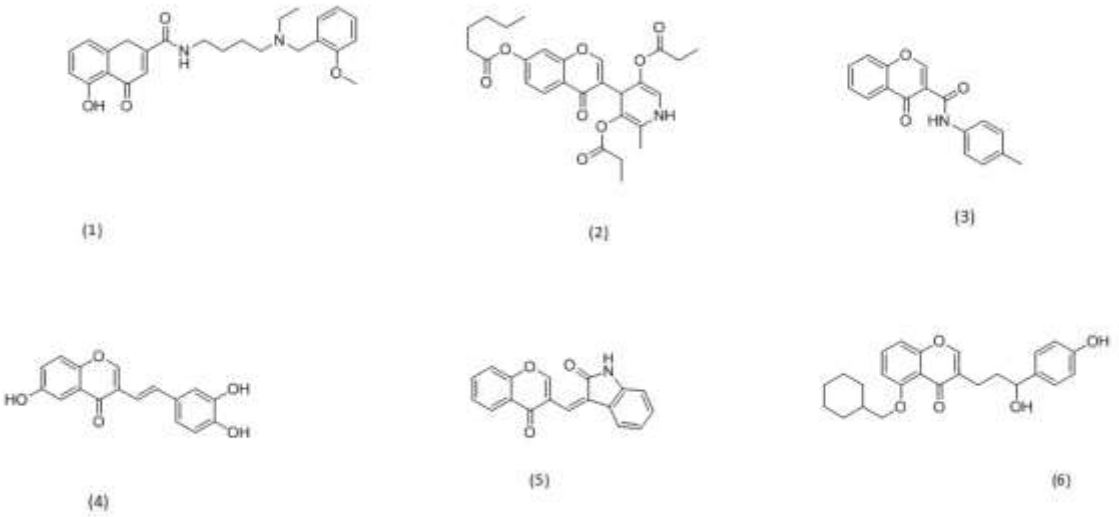


Figure 5. Examples of chromone with interesting biological potential.

APIs that use chromones

Many chromone-based useful pharmaceuticals notably as anti-inflammatory drugs—have been created due to the biological potential of this structure and its low toxicity to mammals (**Figure 6**) [7,8,9] operates at the molecular level as one of its primary APIsinvolves inhibiting COX and 5-LOX simultaneously, which are the mechanisms responsible to create both prostaglandins and leukotrienes (1)

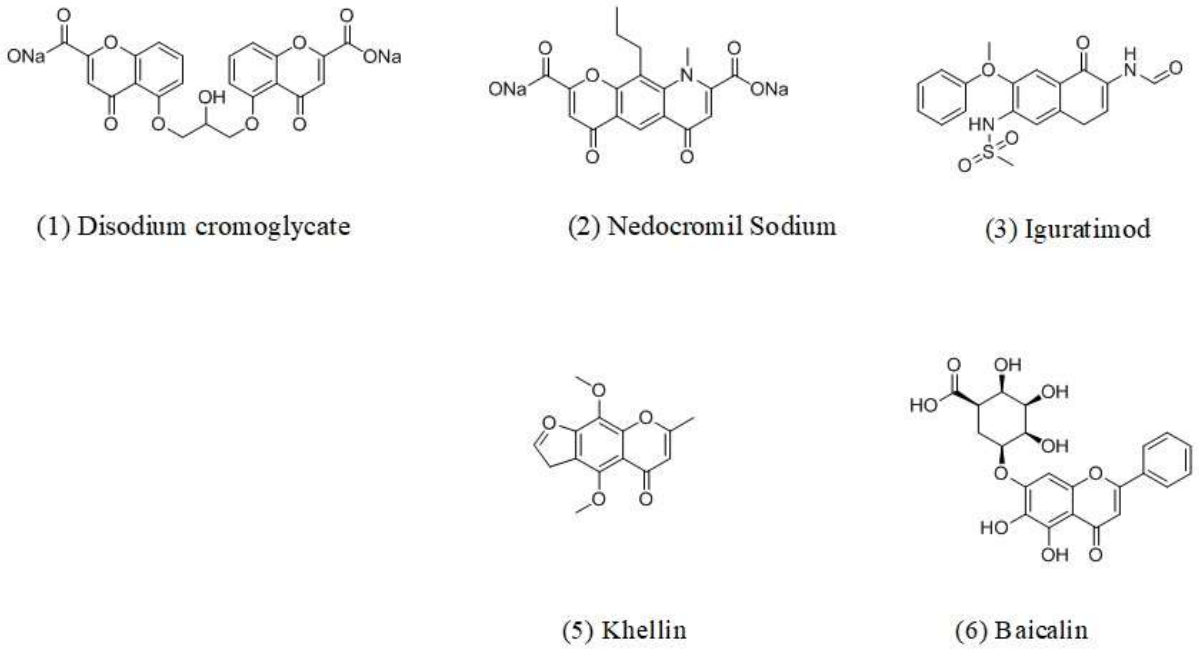


Figure 6: APIs involves inhibiting COX and 5-LOX

CONCLUSION

As chromones and their derivatives are widely distributed throughout the plant kingdom, they are realistically present in a typical human diet. These are compounds that are produced naturally. In order to maximize the benefits of scaffold, a wide range of illnesses, including neurological conditions, inflammatory conditions, diabetes, cancer, and infectious diseases, have been thoroughly researched. Pollinators are attracted to the pigmented colors of plants by chromones and other chemical compounds that aid in pollination. Chromosomes are present in several members of the flavone family.The researchedcompounds of the chromone family that established or potential medicinal activity promote the concept thatwith the help of the chromone nucleus, a desirable framework for the growth of innovative medications.Today, there is a growing interest in finding novel molecules with increased activity as a result of our growing understanding of antioxidant benefits

References:

1. Harborne JB, Williams CA. Advances in flavonoid research since 1992. Phytochemistry. 2000;55(6):481–504.

2. Benzie IFF. Evolution of antioxidant defence mechanisms. Eur J Nutr. 2000;39:53–61.

3. Ellis GP. Chromenes, Chromanones, and Chromones, Volume 31. Vol. 31. John Wiley & Sons; 2009.

4. Horton DA, Bourne GT, Sythe ML. Synthesis, spectroscopic and antimicrobial studies on bivalent Ni (II) and Cu (II) complexes of Bis (thiosemicarbazone). Coord Chem Rev. 2003;103:893–989.

5. Raner KD, Strauss CR, Vyskoc F, Mokbel L. A comparison of reaction kinetics observed under microwave irradiation and conventional heating. J Org Chem. 1993;58(4):950–3.

6. Wheeler TS. Flavone. Org Synth. 2003;32:72.

7. Hoshino Y, Takeno N. A facile preparation of flavones using nonaqueous cation-exchange resin. Bull Chem Soc Jpn. 1987;60(5):1919–20.

8. Saxena S, Makrandi JK, Grover SK. Synthesis of 5-and/or 7-hydroxyflavones using a modified phase transfer-catalysed Baker-Venkataraman transformation. Synthesis (Stuttg). 1985;1985(6/7):697.

9. Kabalka GW, Mereddy AR. Microwave-assisted synthesis of functionalized flavones and chromones. Tetrahedron Lett. 2005;46(37):6315–7.

10. Sarda SR, Pathan MY, Paike V V, Pachmase PR, Jadhav WN, Pawar RP. A facile synthesis of flavones using recyclable ionic liquid under microwave irradiation. Arkivoc. 2006;16(4):43–8.

11. Coppola GM, RW D. An improved synthesis of 2-methylchromone-3-carboxylic acid and its esters. 1981;

12. Bondge SP, Mahalle SR, Burungale AS, Patil LR, Mane RA. A facile synthesis of new 6-acetamido-3-aroyl-2-styryl chromones. 2009;

13. Sandhya B, Mathew V, Lohitha P, Ashwini T, Shravani A. Synthesis, characterization and pharmacological activities of coumarin derivatives. Int J Chem Pharm Sci. 2010;1(1):16–25.

14. Menezes MJ, Manjrekar S, Pai V, Patre RE, Tilve SG. A facile microwave assisted synthesis of flavones. 2009;

15. Jaracz S, Chen J, Kuznetsova L V, Ojima I. Recent advances in tumor-targeting anticancer drug conjugates. Bioorg Med Chem. 2005;13(17):5043–54.

16. Schindler R, Mentlein R. Flavonoids and vitamin E reduce the release of the angiogenic peptide vascular endothelial growth factor from human tumor cells. J Nutr. 2006;136(6):1477–82.

17. Simin K, Ali Z, Khaliq-Uz-Zaman SM, Ahmad VU. Structure and biological activity of a new rotenoid from Pongamia pinnata. Nat Prod Lett. 2002;16(5):351–7.

18. Magalhães AF, Tozzi AMGA, Magalhães EG, Sannomiya M, Soriano M del PC, Perez MAF. Flavonoids of Lonchocarpus montanus AMG Azevedo and biological activity. An Acad Bras Cienc. 2007;79:351–67.

19. Gharpure M, Ingle V, Juneja H, Choudhari R. Synthesis and biological evaluation of 3-hydroxy-2-phenyl-4H-chromen-4 ones. Int J Knowl Eng. 2012;3:148–50.

20. Culshaw AJ, Brain CT, Dziadulewicz EK, Edwards L, Hart TW, Ritchie TJ. Chromone derivatives useful as antagonists of VR1 receptors. Google Patents; 2010.

21. Zhao P-L, Li J, Yang G-F. Synthesis and insecticidal activity of chromanone and chromone analogues of diacylhydrazines. Bioorg Med Chem. 2007;15(5):1888–95.

22. Tawfik HA, Ewies EF, El-Hamouly WS. Synthesis of chromones and their applications during the last ten years during the last ten years. Ijrpc. 2014;4(4):1046–85.

23. Ungwitayatorn J, Wiwat C, Samee W, Nunthanavanit P, Phosrithong N. Synthesis, in vitro evaluation, and docking studies of novel chromone derivatives as HIV-1 protease inhibitor. J Mol Struct. 2011;1001(1–3):152–61.

24. Prakash O, Kumar R, Parkash V. Synthesis and antifungal activity of some new 3-hydroxy-2-(1-phenyl-3-aryl-4-pyrazolyl) chromones. Eur J Med Chem. 2008;43(2):435–40.

25. Ye Y, Zhang L, Fan R. Application of dearomatization strategy on the synthesis of furoquinolinone and angelicin derivatives. Org Lett. 2012;14(8):2114–7.

26. Tien Y-C, Liao J-C, Chiu C-S, Huang T-H, Huang C-Y, Chang W-T, et al. Esculetin ameliorates carbon tetrachloride-mediated hepatic apoptosis in rats. Int J Mol Sci. 2011;12(6):4053–67.

27. Lohray BB, Bhushan V, Rao BP, Madhavan GR, Murali N, Rao KN, et al. Novel euglycemic and hypolipidemic agents. 1. J Med Chem. 1998;41(10):1619–30.

28. Muthukrishnan M, Mujahid M, Yogeeswari P, Sriram D. Syntheses and biological evaluation of new triazole-spirochromone conjugates as inhibitors of Mycobacterium tuberculosis. Tetrahedron Lett. 2011;52(18):2387–9.

29. Borish L, Williams J, Johnson S, Mascali JJ, Miller R, Rosenwasser LJ. Anti- inflammatory effects of nedocromil sodium: inhibition of alveolar macrophage function. Clin Exp Allergy. 1992;22(11):984–90.

30. Rao VM, Damu GLV, Sudhakar D, Siddaiah V, Rao CV. New efficient synthesis and bioactivity of homoisoflavonoids. Arkivoc. 2008;11:285–94.

31. Li S-Y, Wang X-B, Xie S-S, Jiang N, Wang KDG, Yao H-Q, et al. Multifunctional tacrine–flavonoid hybrids with cholinergic, β-amyloid-reducing, and metal chelating properties for the treatment of Alzheimer's disease. Eur J Med Chem. 2013;69:632–46.