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Coumarins and Chromones : A Remarkable Scaffolds for Anti-inflammatory Activity

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Abstract

The significance of Coumarin and Chromone nucleus was highlighted by several literature reports as a source of potential candidates for anti-inflammatory drug development. Various natural coumarins such as umbelliferone, scopoletin, visnadin, marmin and esculetin demonstrated potent anti-inflammatory activity through various mechanisms. And various natural chromones such as Amoora rohituka, Dysoxylum binectariferum Schumanniophyton magnificum showed potent anti-inflammatory activity. Keeping in view the importance of naturally occurring coumarins and chromones researchers have extensively explored these by synthesizing various derivatives as anti-inflammatory agents. The present review describes the different synthetic methods and the importance of Coumarin and Chromone nucleus, as anti-inflammatory lead molecules. So it may help the medicinal chemists in rational design of future anti-inflammatory molecules based on Coumarin and Chromone scaffold.

Keywords: Coumarins, Chromones, Anti-inflammatory effects, COX-1, COX-2, 5-LOX

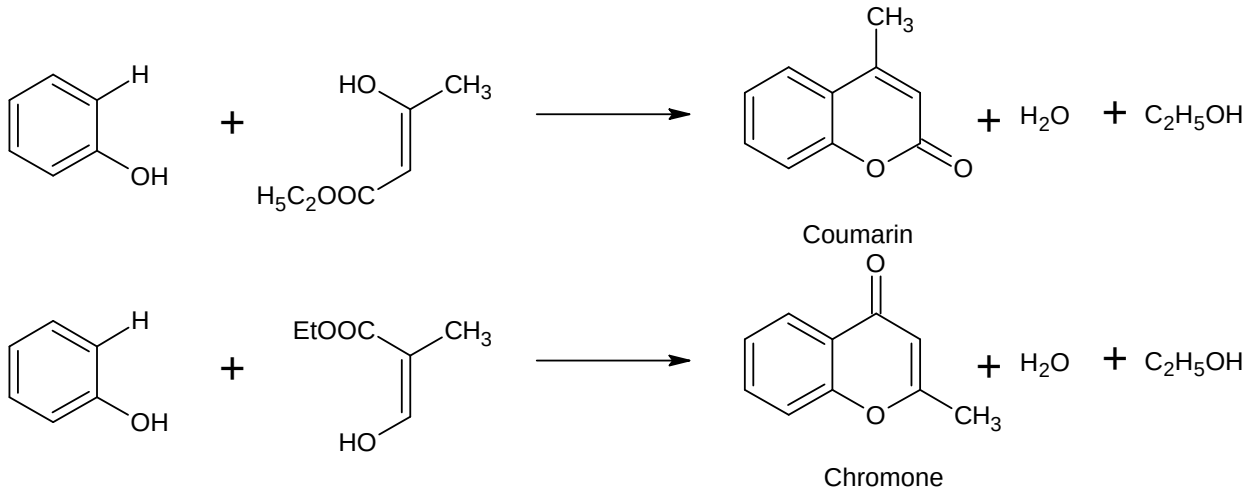
INTRODUCTION

Inflammation is caused by a variety of stimuli including physical damage, microbial invasion, ultra violet irradiation, and immune reactions. Redness, heat, swelling, and pain are classical symptoms of inflammation. Redness and heat are caused by the increased blood flow whereas swelling occurs due to the increased movement of fluid and white blood cells into the area of inflammation. Release of chemical mediators and compression of nerves in vicinity of the inflammatory process causes pain [1]. If not controlled; inflammation cascades can lead to the development of diseases such as rheumatoid arthritis, chronic asthma, multiple sclerosis, inflammatory bowel disease, and psoriasis. Many of these diseases are debilitating and are becoming increasingly common in our aging society. Rheumatoid arthritis, an inflammatory condition of multiple joints, affects 0.3–1.0% of the general population and is more prevalent among women in developed countries. Osteoarthritis affects 9.6% of men and 18% of women aged more than 60 years. Increases in life expectancy and aging populations are expected to make osteoarthritis the fourth leading cause of disability by the year 2020 [2,3]. Chronic inflammation leads to cancer, which is witnessed by recent experimental and clinical studies. It has been estimated that 15–20% of all cancer deaths resulted from underlying infections and inflammatory reactions. The inflammatory cascade involves a series of events and various inflammatory mediators. The major anti-inflammatory targets include enzymes, cyclooxygenase (COX-1 and COX-2), 5-lipooxygenase (5-LOX), inducible nitric oxide synthase (iNOS), inosine monophosphate dehydrogenase; cytokines and cytokine receptors, tumor necrosis factor (TNF)-α and TNF-RII, interleukin (IL)-1b and IL-1RA, IL-2 and IL-2R, interferon (IFN)-a2, IFN-b1, and IFN-g [4,5]. Natural products being structurally most diverse compounds have engrossed substantial attention from medicinal chemists for the development of anti-inflammatory agents [6-8]. Coumarins (also known as 1,2-benzopyrone) and chromones (also known as 1,4-benzopyran) constitute an important class of natural products. These compounds have been reported to possess a wide range of biological activities including, antimicrobial, antiviral, anticancer, anti-inflammatory, antioxidant, and anticoagulant. To date, more than 1300 such compounds have been identified [9]. Coumarin and Chromone derivatives recognized as inhibitors of not only LOX and COX enzymes, but also of the neutrophil-dependent superoxide anion generation. Many research groups had reported that various Coumarin and Chromone derivatives block inflammation by inhibiting various targets. However, no such molecule has made its way to the clinics so far [10]. Fylaktakidou et al (2004) reviewed the potential of various natural and synthetic coumarin derivatives as anti-inflammatory and antioxidant molecules [11]. Curini et al. (2006) described an array of biological activities of prenyloxycoumarins and prenyloxyfuranocoumarins [12]. Recently, Bansal et al. (2013) discussed coumarin as a potential nucleus for development of anti-inflammatory molecules [13].

METHODS USED FOR THE SYNTHESIS OF COUMARINS AND CHROMONES

Many methods have been devised so far for the synthesis of coumarin derivatives, under conventional, microwave and sound assisted strategies. The two most important methods for the synthesis of Coumarin derivatives are Perkin [14] and Pechmann [15]. The naturally occurring coumarins have been obtained either (i) by the closure of the lactonic ring with the necessary substitutents in the benzene nucleus, or (ii) by the introduction of the substituents in the requisite Coumarin. The action of the sodium salt of an aliphatic acid and its anhydride on an o-hydroxy aldehyde with the intermediate formation of the o-hydroxy cinnamic acid (Perkin method) and the action of malic acid on phenols in the presence of sulphuric acid (Pechmann's method) have been convenient methods for the synthesis of naturally occurring coumarins.

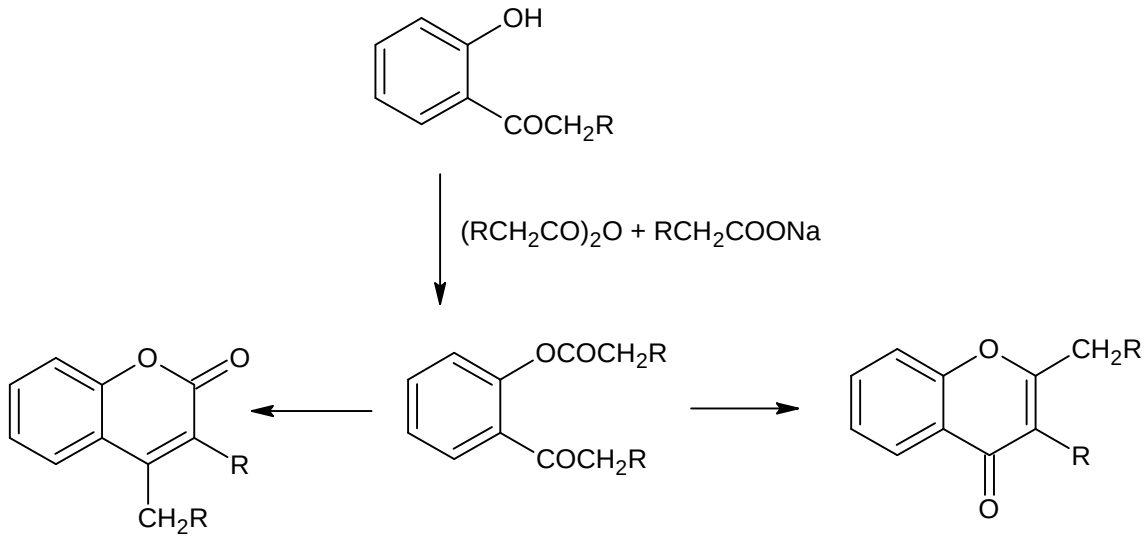
Pechmann condensation: The condensation of a phenol with β-ketonic ester may lead to two different products either a Coumarin or a Chromone.

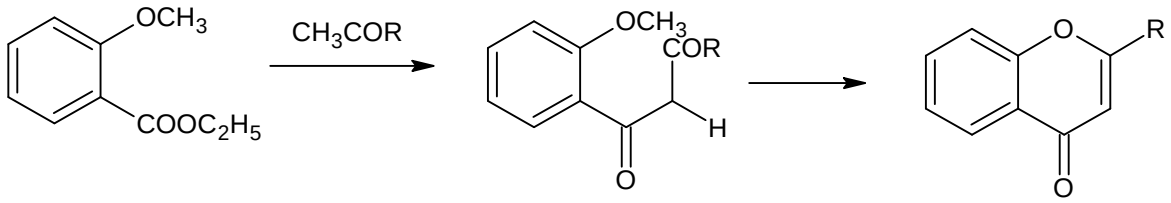


Pechmann showed that coumarins are obtained by using sulphuric acid as the condensing agent and Simonis [16] showed that chromones are obtained by using phosphorus pentoxide. These two reactions have been extensively studied by Chakravarti and co-workers [17] and Robertson and others [18] with special reference to the part played by the condensing agent and the influence of any substituent in the molecule of the β-ketonic ester or the phenol. The halogen and nitro groups exert an inhibiting effect in pechmann's reaction in the formation of coumarins and a favourable influence in chromone formation in Simonis' reaction. Neutral, basic or acidic condensing agents like sodium acetate, sodium ethoxide, hydrochloric acid, boric anhydride, zinc chloride, phosphoric acid bring about Coumarin condensation [19]. Goodall and Robertson [20] have found that phosphoryl chloride in some cases bring about chromone condensation.

Conventionally, the Pechmann reaction is also carried out in presence of phosphorous pentoxide, trifluoroacetic acid and aluminum chloride. Homogeneous metal chlorides such as $ZnCl_2$, $TiCl_4$, triflates, sulfonic acid and ionic liquids are reported to produce 7-hydroxy coumarin derivatives in high yield at ambient temperature. Due to non-reusability of these homogeneous catalysts different solid acid catalysts such as amberlyst ion-exchange resins, zeolites, montmorillonite K-10, polyaniline sulfate salt, heteropoly acids, nafion resin/silica nanocomposites and nano-crystalline sulfated-zirconia have been studied for the synthesis of coumarin derivatives. Microwave irradiation has been found more useful for synthesis of these coumarin derivatives in order to minimize the reaction time. Recently, ultrasound assisted Pechmann synthesis has also been reported producing good yields of 7- hydroxy -4-methyl coumarin, however, with homogenous $BiCl_3$ catalyst. Ruhemann [21] condensed sodium phenolates with ethyl chloro-fumarate, ethyl phenyl-propiolate and ethyl B-chloro-crotonate and treated the intermediate products, thus obtained, with concentrated sulphuric acid or better with phosphorus pentachloride and aluminium chloride whereby the desired chromones were obtained.

Nagai and Tahara [22] heated resacetophenone and phenol with sodium acetate and acetic anhydride and prepared the derivatives of chromones.





Ketone used	Acid anhydride used	Product obtained
o-Hydroxy-acetophenone	Acetic anhydride + Sodium acetate	Chromone
o-Hydroxy-acetophenone	Propionic anhydride + Sodium propionate	Coumarin
o-Hydroxy-propiophenone	Acetic anhydride + Sodium acetate	chromone
o-Hydroxy-propiophenone	Propionic anhydride + Sodium propionate	Chromone
o-Hydroxy-propiophenone	Butyric anhydride + Sodium butyrate	Chromone
o-Hydroxy-acetophenone	Phenyl acetic anhydride+ Sodium phenyl acetate	Coumarin
o-Hydroxy-propiophenone	Phenyl acetic anhydride+ Sodium phenyl acetate	Coumarin

Chromones synthesized from o-hydroxy acid was made by Kostanecki [23] by condensation of ethyl-o-methoxy-benzoate with acetone and acetophenone on heating the intermediate B-diketones with hydroiodic acid.

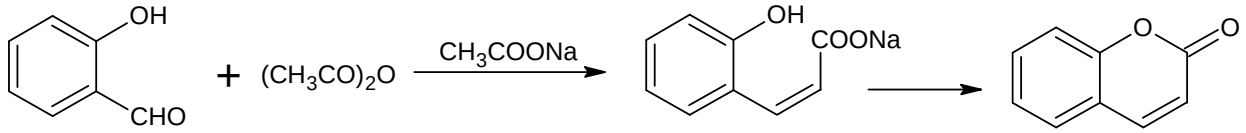
Hekiborn and co-workers have found that the nature of the product in this reaction depends on (i) the nature of the o-hydroxy ketone and the acid anhydride and the salt used.

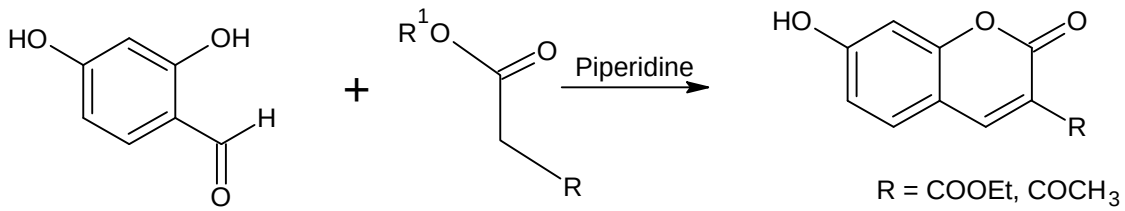
Other methods for the synthesis of coumarins

Perkin reaction: This classical method has entered into every textbook of organic chemistry. As stated above, Perkin [24] first synthesized coumarin from salicylaldehyde by heating it with acetic anhydride and anhydrous sodium acetate. This reaction occurs with the formation of an intermediate o-hydroxycinnamic acid derivative which passes spontaneously into the lactone when liberated from its sodium salt.

Knoevenagel reaction: Knoevenagel [25] developed a method for the synthesis of coumarin derivatives from o-hydroxyaldehydes by condensation with ethyl malonate, ethyl acetoacetate, ethyl cyanoacetate etc. in the presence of piperidine, pyridine, and other organic bases.

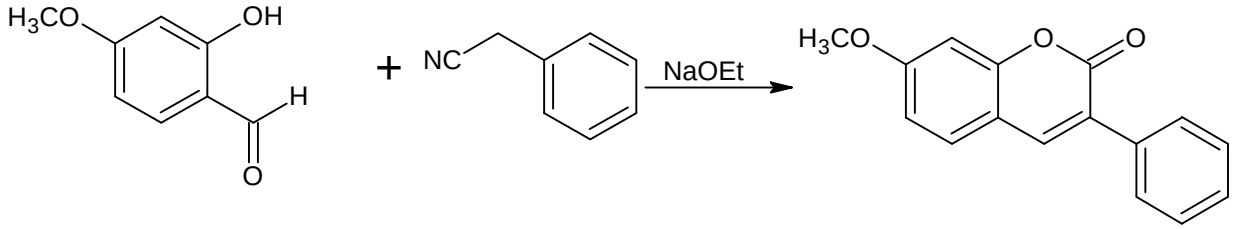
Various workers have successfully used this reaction by suitably changing the reactants, reagents and experimental conditions to improve the yield and reduce the complexity of the reactions [26].

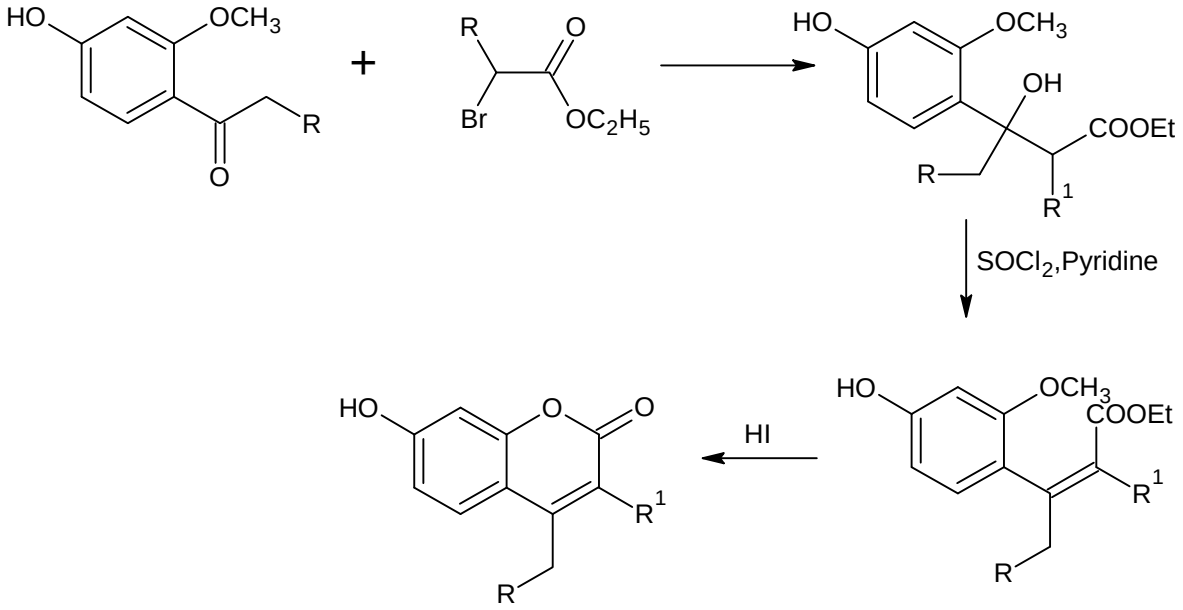




R = H, Me, Et

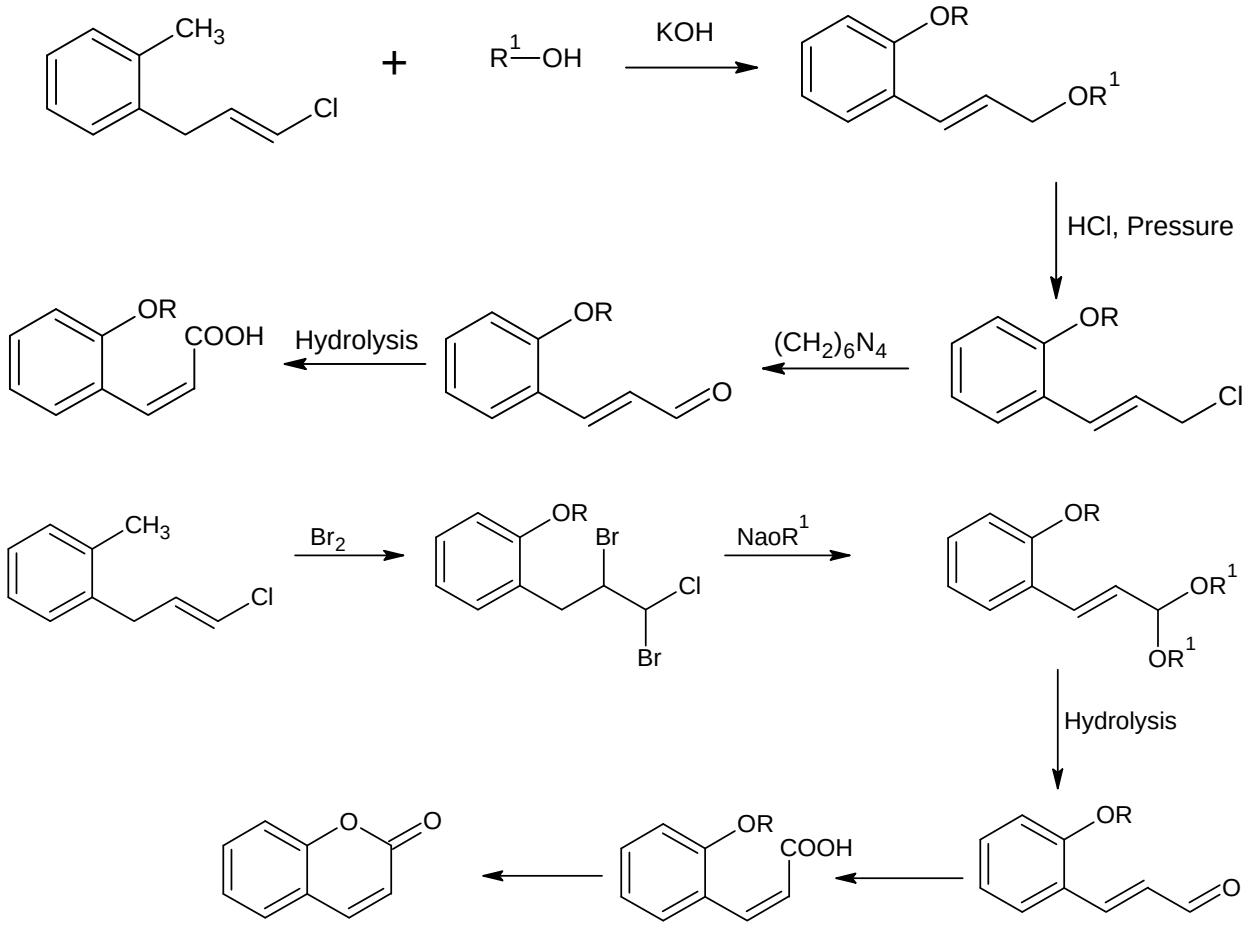
R = COOEt, $COCH_3$





Reformatsky reaction: Chakravarti and Majumdar [27] have developed a method by which 3,4-dialkyl-substituted coumarins not available by the usual methods may be synthesized, in which o-hydroxyaryl alkyl ketones, under the conditions of the Reformatsky reaction, are ultimately converted into coumarin derivatives.

Friedel-Crafts reaction: Bert [28] has developed a general method for synthesizing coumarins, which consists in condensing phenolic ethers with CH2C1CH=CHC1 either by the Friedel-Crafts reaction or in the presence of zinc dust to obtain ROC6H4CH2CH=CHCl, which can also be synthesized by condensing CH2ClCH=CHCl with o-bromophenolic ether through the Grignard reaction. This is then converted into the corresponding coumarin in two ways, as shown below.



Allan and Robinson [29] further developed this method for the synthesis of a large number of chromones and chromonols occurring in nature. It has been found, however, that this method is not exclusively applicable for chromone formation, inasmuch as chromones or coumarins or a mixture of both may result from the above reaction, since there are two ways, in which the intermediate acyl derivative may lose water, giving a chromone or a coumarin. In addition to the above-mentioned methods, other reactions used for the coumarin synthesis are Claisen rearrangement [30] Wittig [31] and catalytic cyclization reactions [32]. An approach via ring-closing metathesis (RCM) to synthesize versatile coumarin scaffolds have been described recently [33].

Coumarin derivatives as anti-inflammatory compounds

Marina Roussaki [34] synthesized a series of coumarin analogues bearing a substituted phenyl ring on position 3 were synthesized via a novel methodology, through an intermolecular condensation reaction of 2-hydroxyacetophenones and 2-hydroxybenzaldehyde, with imidazolyl phenylacetic acid active intermediates. The in vitro antioxidant activity of the synthesized compounds was evaluated using two different antioxidant assays (radical scavenging ability of DPPH stable free radical and inhibition of lipid peroxidation induced by the thermal free radical AAPH). Moreover, the ability of the compounds to inhibit soybean lipoxygenase was determined as an indication of potential anti-inflammatory activity. Wenchen Pu [35] prepared 3-arylcoumarins through Perkin condensation and further acid-promoted hydrolysis if necessary. In lipopolysaccharide-activated mouse macrophage RAW264.7 cells, 6,8-dichloro-3-(2-methoxyphenyl)coumarin and 6-bromo-8-methoxy-3-(3-methoxyphenyl)coumarin exhibited nitric oxide production inhibitory activity. B. Sandhya [36] synthesized new aminosubstituted derivatives of coumarin and evaluated for analgesic, anti-inflammatory and antimicrobial activity.

Mehrdad Iranshahi [37] synthesized the mono isopentenyloxy, -geranyloxy and -farnesyloxy derivatives of coumarin and the compounds were evaluated for their inhibitory potency against soybean 15-lipoxygenase (SLO) and human 15-lipoxygenase-1 (HLO-1). Amongst the synthetic analogs, 5-farnesyloxycoumarin showed the most potent inhibitory activity against SLO. Ranjana Aggarwal [38] synthesized novel 2-(5-hydroxy-5-trifluoromethyl-4,5-dihydropyrazol-1-yl)-4-(coumarin-3-yl)thiazoles by condensing 3-(2-bromoacetyl)coumarins with various 5-hydroxy-5-trifluoromethyl-4,5-dihydropyrazol-1-thiocarboxamides, obtained by the reaction of thiosemicarbazide with trifluoromethyl-β-diketones. All the tested compounds displayed significant to moderate *in vivo* anti-inflammatory activity when compared to the standard drug indomethacin. A series of new ethers of quinolinone linked with different substituted coumarins and benzofurans were synthesized from 4-(bromomethyl)quinolinones by Rajesh G. Kalkhambkar [39] . In pharmacological evaluations, some of these chloroquinolinones also showed 70–77% inhibition of inflammation after 8 h, whereas the other compounds showed 51–55% inhibition. Most of the compounds showed potent analgesic activity compared to the standard and control.

The PEGylated coumarins were synthesized by Mukesh K. Pandey [40] in two different ways. In the first approach, diesters of 4-methyl and 4,8-dimethylcoumarin were co-polymerized, separately with poly(ethylene glycol) using *Candida antarctica* lipase under solventless conditions. In the other approach, 4-methyl and 4,8-dimethylcoumarins were suitably converted to their bromo analogues and were tethered to already synthesized PEGylated polymers. Synthesized derivatives were evaluated for anti-inflammatory activities with respect to their ability to inhibit the TNF-α induced ICAM-1 (intercellular cell adhesion molecule-1) on human endothelial cells. It was found that PEGylated 4-methyl and 4,8-dimethylcoumarin derivatives were more effective than their non-PEGylated analogues to inhibit ICAM-1 expression.

Kuldip Upadhyay [41] synthesized a series of 4-styrylcoumarin have been by Knoevenagel condensation between substituted 4-methylcoumarin-3-carbonitrile and different heterocyclic or aromatic aldehydes. 4-Methylcoumarin-3-carbonitrile has been synthesized by the base catalyzed reaction between substituted 2-hydroxyacetophenone and ethyl cyanoacetate. The compounds were evaluated for their anti-inflammatory activity (against TNF-α and IL-6) and anti-tubercular activity. Some compounds showed potent activity against TNF-α with 73% inhibition at 10 μM concentration. Koneni V. Shashidhara [42] synthesized novel biscoumarin–chalcone hybrids were evaluated for their anti-inflammatory and antioxidant activity. Radha Krishan Arora [43] Inspired from occurrence of anti-inflammatory activity of 3-substituted coumarins and antiulcer activity of various 2-substituted benzimidazoles, novel compounds have been designed by coupling coumarin derivatives at 3-position directly or through amide linkage with benzimidazole nucleus at 2-position. The resultant compounds are expected to exhibit both anti-inflammatory and antioxidant activities along with less gastric toxicity profile.

Xiu-Yun Song [44] designed therapeutic stratagies to inhibit the activation of microglia may lead to significant advancement in the treatment of most neurodegenerative diseases. 7-hydroxy-5-methoxy-4-methyl-3-(4-methylpiperazin-1-yl)-coumarin (IMM-H004) is a novel compound and has been reported exerting potent neuroprotective effects which may be related to anti-inflammation. In this study, the anti-inflammatory effects of IMM-H004 were investigated in lipopolysaccharide (LPS)-treated BV2 microglia. The observations indicated that treatment with IMM-H004 significantly inhibited BV2 microglia activation, protected PC12 cells and primary neurons against indirect toxicity mediated by exposure to conditioned medium (CM) from LPS-treated BV2 cells. Additionally, IMM-H004 significantly suppressed the release of TNF-α, IL-1β and NO, and suppressed the expression of pro-inflammatory mediators and cytokines such as iNOS, COX-2, and IL-6 in LPS-stimulated BV2

microglia. The nuclear translocation of NF-κB and the phosphorylation level of JNK and p38 MAPK pathways were also inhibited by IMM-H004 in LPS-treated BV2 microglia. Moreover, IMM-H004 also was a strong selective OH , scavenger whose effect was similar with vitamin C. Overall, the findings suggested that IMM-H004 might be a promising therapeutic agent for alleviating the progress of neurodegenerative diseases associated with microglia activation.

Chromone derivatives as anti-inflammatory compounds

The p38 MAPK signaling pathway plays a pivotal role in inflammation. Targeting p38 MAPK may be a potential strategy for the treatment of inflammatory diseases. Hailiang Liu [45] showed that a novel chromone derivative, DCO-6, significantly reduced lipopolysaccharide (LPS)-induced production of nitric oxide, IL-1β and IL-6, decreased the levels of iNOS, IL-1β and IL-6. John A. Hutter [46] identified a new antiinflammatory agent as 8-[*C*-β-D-[2-*O*-(*E*)-cinnamoyl]glucopyranosyl]-2-[(*R*)-2-hydroxypropyl]-7-methoxy-5-methylchromone which was isolated from *Aloe barbadensis*.

Siwattra Choodej [47] also isolated two new rearranged limonoids, harperforatin and harperfolide and a new chromone, harperamone from fruits and roots of *Harrisonia perforata*, together with eight known compounds. Their structures were elucidated on the basis of spectroscopic data. Harperfolide exhibited potent anti-inflammatory activity by suppressing nitric oxide (NO) production from activated macrophages. *Aloe* has long been used in food products, beverages and cosmetics, and as a traditional medicine to treat various diseases in many countries. Ya Nan Sun [48] isolated a new chromone, aloe resin E, and a new pyrone, aloenin C, together with thirteen known compounds aqueous dissolved *Aloe* exudates and their structures were identified by spectroscopic analysis. Nuclear factor kappa B (NF-κB) inhibitory activity of the isolated compounds was evaluated using an NF-κB luciferase assay in HepG2 cells. Among them, 7-hydroxy-5-(hydroxymethyl)-2-methylchromone, 5-((*S*)-2′-oxo-4′-hydroxypentyl)-2-hydroxymethylchromone and aloenin aglycone showed significant inhibitory effects against TNFα-induced NF-κB. Fatima Bousejra-ElGarah [49] synthesized a series of 21 chromone carboxamide derivatives bearing diverse amide side chains. Chromone carboxamide derivatives revealed that the presence of a 6-fluoro substituent on the chromone nucleus or propyl and 3-ethylphenyl groups on the amide side chain has a positive impact on the anti-inflammatory activity. Hydrophilic chromone carboxamide derivatives also showed greater 5-lipoxygenase inhibition.

CONCLUSION

Coumarins and chromones has long been known as antiinflammatory compounds. So many derivatives of these compounds were synthesized by various methods like pechmann condensation, perkin reaction, reformatsky reaction and Knoevenagel reaction. But there is still necessary for effective anti-inflammatory agents with less side effects. This review helpful in understanding what are the compounds that already synthesized and which positions of the coumarin and chromone are effective for substitution as anti-inflammatory compounds. And more research should be done on establishment of exact mechanism of these compounds so that to develop these derivatives with more specific action and with least side effects.

REFERENCES

[1] R. Gautam and S. M. Jachak, *Med. Res. Rev*., 2009, 29, 767– 820.
[2] G. R. Burmester, E. Feist and T. Dorrner, *Nat. Rev. Rheumatol.,* 2014, 10, 77–88.
[3] R. J. Smith, *Drug Discovery Today,* 2005, 10, 1598–1606.
[4] D. L. Simmons, *Drug Discovery Today*, 2006, 11, 210–219.
[5] C. A. McCulloch, G. P. Downey and H. El-Gabalawy, *Nat. Rev.Drug Discovery*, 2006, 5, 864–876.
[6] J. Grover, V. Kumar, V. Singh, K. Bairwa, M. E. Sobhia and S. M. Jachak, *Eur. J. Med. Chem.,* 2014, 80, 47–56.
[7] K. Bairwa, I. N. Singh, S. K. Roy, J. Grover, A. Srivastava and S. M. Jachak, *J. Nat. Prod.,* 2013, 76, 1393–1398.
[8] S. M. Jachak, *Curr. Med. Chem.,* 2006, 13, 659–678.
[9] F. Borges, F. Roleira, N. Milhazes, L. Santana and E. Uriarte, *Curr. Med. Chem.,* 2005, 12, 887–916.
[10] L. Wu, X. Wang, W. Xu, F. Farzaneh and R. Xu, *Curr. Med. Chem.,* 2009, 16, 4236–4260.
[11] K. C. Fylaktakidou, D. J. Hadjipavlou-Litina, K. E. Litinas and D. N. Nicolaides, *Curr. Pharm. Des.,* 2004, 10, 3813–3833.
[12] M. Curini, G. Cravotto, F. Epifano and G. Giannone, *Curr. Med. Chem.,* 2006, 13, 199–222.
[13] Y. Bansal, P. Sethi and G. Bansal, *Med. Chem. Res.,* 2013, 22,3049–3060.
[14] Perkin, *J.Chem. Soc.,* 1868, 21, 53.
[15] Pechmann, *Ber.,* 1884, 17,929.
[16] Simmons et al., *Ber.,* 1913,46,2015; 1914,47,697, 2229.
[17] Chakravarti, *J.Indian Chem. Soc*., 1931,8,130,407; 1932,9,25,31,389.
[18] Robertson et al*., J.Chem.Soc.,* 1931, 2426; 1932, 1180, 1681; 1936,215.
[19] Chakravarti, *ibid.,* 1935,12,536.
[20] Goodall and Roberton, *J.Chem.Soc.,* 1936, 426.
[21] Ruhemann et al, *J. Chem. Soc.,* 1900, 77, 1185.
[22] Tahara, *ibid.,* 1892, 25, 1292.
[23] Kostanecki, *Ber.,* 1903, 33, 32, 1998.
[24] Perkin, W.H. *J. Chem .Soc*. 1868,53; 1877,388.
[25] Knoevenagel, E, *Ber*. 1898, 31, 2585; 1904,37,4461.
[26] Borsche, W; Streitberger, F; *Ber*. 1904, 37, 3165.
[27] Chakravarti, D; Majundar, B. *J. Indian Chem. Soc.* 1938, 15, 136; 1939,16,389.
[28] Bert, L. *Compt. Rend*. 1942, 214, 230.
[29] Allan, J; Robinson, R. *J. Chem. Soc*. 1924, 2192.
[30] Cairns, N; Harwood, L. M; Astles, D. P. *J. Chem. Soc.* Perkin Trans. 1. 1994, 3101.
[31] Maercker, A. *Org. Synth*. 1934, 14, 270.
[32] Saidi, M. R; Bigdeli, K. *J. Chem. Res*. 1998, 800.
[33] Van, T. N; Debenedetti, S; De Kimpe, N; *Tetrahedron Lett.* 2003, 44, 4199.
[34] Marina Roussaki, Christos A. Kontogiorgis; *Bioorganic & Medicinal Chemistry Letters* 20 (2010) 3889-3892.
[35] Wenchen Pu, Yuan Lin; *Bioorganic & Medicinal Chemistry Letters* 24 (2014) 5432-5434.
[36] Sandhya B, Giles D, Mathew V, Basavarajaswamy G, Abraham R. *European journal of medicinal chemistry.* 2011 Sep 30;46(9):4696-701.
[37]. Iranshahi M, Jabbari A, Orafaie A, Mehri R, Zeraatkar S, Ahmadi T, Alimardani M, Sadeghian H. *European journal of medicinal chemistry*. 2012 Nov 30;57:134-42.
[38] Rajana Aggarwal, Sunil Kumar; *European Journal of Medicinal Chemistry* 62 (2013) 508-514.
[39] Rajesh G. Kalkhambkar, G. Aridoss; *Monatsh Chem* (2011) 142:305-315.
[40] MK Pandey et.al., *European Journal of Pharmaceutical Sciences* 39 (1-3), 134-140. 2009.

[41] K Upadhyay et.al., *Bioorg Med Chem Lett* 21 (8), 2547-2549. 2011.
[42] Sashidhara, Koneni V., et al. *Bioorganic & medicinal chemistry letters* 20.24 (2010): 7205-7211.
[43] Arora, Radha Krishan, et al *Acta Pharmaceutica Sinica B* 4.5 (2014): 368-375.
[44] Song, Xiu-Yun, et al. *Brain research bulletin* 106 (2014): 30-38.
[45]. Liu H, Xu R, Feng L, Guo W, Cao N, Qian C, Teng P, Wang L, Wu X, Sun Y, Li J. *PLoS One*. 2012 Jun 15;7(8):e37168.
[46]. Hutter JA, Salman M, Stavinoha WB, Satsangi N, Williams RF, Streeper RT, Weintraub ST. *Journal of natural products*. 1996 May 22;59(5):541-3.
[47]. Choodej S, Sommit D, Pudhom K. *Bioorganic & medicinal chemistry letters*. 2013 Jul 1;23(13):3896-900.
[48]. Sun YN, Li W, Yang SY, Kang JS, Ma JY, Kim YH. *Journal of Functional Foods*. 2016 Mar 31;21:232-9.
[49]. Bousejra-ElGarah F, Lajoie B, Souchard JP, Baziard G, Bouajila J, El Hage S. *Medicinal Chemistry Research*. 2016 Nov 1;25(11):2547-56.