Med Chem Res (2013) 22:3049–3060
DOI 10.1007/s00044-012-0321-6

MEDICINAL CHEMISTRY RESEARCH

REVIEW ARTICLE

Coumarin: a potential nucleus for anti-inflammatory molecules

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Received: 4 August 2012 / Accepted: 25 October 2012 / Published online: 10 November 2012

Abstract Numerous research reports have indicated the coumarin nucleus as a potential candidate for development of anti-inflammatory drugs. Various phytoconstituents such as umbelliferone, scopoletin, columbiatnetin, visniadin, marmin, and many more derived from coumarin nucleus are found to have potent anti-inflammatory as well as antioxidant activities. A large number of coumarin derivatives have also been designed, synthesized, and evaluated to have mild-to-very potent anti-inflammatory activity through different mechanisms. However, despite the continuing efforts in search of these drugs, no major breakthrough has been achieved so far. In the present review, a critical analysis of various reports on naturally as well as the synthetically derived coumarin derivatives having anti-inflammatory activity has been carried out and a structural–activity relationship around the coumarin nucleus has been proposed to assist the medicinal chemists in rationally designing the anti-inflammatory drugs.

Keywords Coumarin · Anti-inflammatory · Structure–activity relationship · TNFα inhibitor

Introduction

Inflammation is a dynamic biological process which occurs as a result of chemical, physical, immunological, and/or biological stimuli to human body (Khan *et al*., 2005). It is characterized by five cardinal signs i.e., *rubor* (redness), *tumor* (swelling), *calore* (heat), *dolore* (pain), and *function laesa* (disturbance of function) (Medzhitov, 2011). The four components of a typical inflammatory process include inflammatory inducers (like infection, wound or tissue injury, or any other diseased state), sensors (like mast cells, macrophages, dendritic cells, etc.), inflammatory mediators (like various cytokines, biological amines, etc.), and the target tissues (Dinarello, 2010). A moderate inflammation is essentially an adaptive response of human body to restore the homeostasis through countering the antigens/inducers by phagocytosis or immigration of leukocytes at the site of injury. This acute inflammatory response is normally terminated (resolution of inflammation) after the inducer is eliminated (Li *et al*., 2011). However, if inducer is not eliminated or persists because of any diseased states, such as Alzheimer's disease, asthma, atherosclerosis, Crohn's disease, gout, multiple sclerosis, osteoarthritis, psoriasis, rheumatoid arthritis, diabetes mellitus, carcinoma, bacterial or viral infections, etc., then the resolution phase may not be induced leading to chronic inflammation (Kontogiorgis and Hadjipavlou-Litina, 2005; Symeonidis *et al*., 2009) usually localized to the site of inducers and results in local tissue remodeling. Such chronic inflammatory states generate a vicious cycle between inflammation and the accompanying pathological state. For instance, obesity can lead to inflammation, and the chronic inflammation can promote obesity-associated diabetes by inducing insulin resistance (Grivennikov *et al*., 2010). Therefore, control of inflammation becomes more important in all pathological conditions, and it has occupied a central position in many branches of pharmacology.

The inflammatory response can be controlled by eliminating the inducers, by blocking the sensors, by inhibiting the mediators, or by directly acting on the target tissues (Medzhitov, 2008). Elimination of inducer, especially diseased states mentioned earlier, may need long-term drug

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treatments, and in such cases, control of inflammation by the use of anti-inflammatory agents becomes important to prevent tissue remodeling (Nathan, 2002). The most widely explored targets for controlling inflammation are the inflammatory mediators such as plasma proteases, arachidonic acid metabolites (like PGE2 and leukotrienes), histamine, serotonin, nitric oxide, cytokines (such as lipoxins, interleukins 1–16, and tumor necrosis factor-α), chemokines (such as those belonging to the CXC, CC, and C subsets), and colony-stimulating factors (CSFs) (Khan *et al*., 2010; Cronstein and Weissmann, 1995). These mediators are produced through various processes involving cyclooxygenases, caspases, and kinases (like cyclin-dependent kinases, mitogen-activated protein kinase 38, c-jun N-terminal kinase, mitogen-activated protein kinase/extracellular signal regulated kinase, serine threonine kinases, interleukin receptor-associated kinase 4, Janus kinases, kinase insert domain receptor, NF-kβ, lymphocyte specific kinase, spleen tyrosine kinase, and TNFα kinase as result of activation of sensors cells and bind to specific receptor to orchestrate the inflammatory response (Bhagwat, 2009; Feghali and Wright, 1997; Sebban and Courtois, 2006)).

A large number of chemical compounds derived from diverse group of heterocyclic nuclei are reported to inhibit inflammatory process at one or the other stage. Coumarin analogs constitute an important class of anti-inflammatory molecules. Many research groups have reported that various coumarin derivatives block inflammation at various levels as depicted in Fig. 1. However, no such molecule has made its way to the clinics so far. Fylaktakidou *et al*. (2004) have reviewed various natural and synthetic coumarin derivatives as anti-inflammatory and antioxidant molecules. Curini *et al*. (2006) have also reviewed the biological potential of prenyloxycoumarins and prenyloxyfuranocoumarins which are generally considered as a family of secondary plant metabolites only used as intermediates in coumarin-based compounds. The present review is a comprehensive update and critical analysis of various reports on naturally as well as synthetically derived coumarin derivatives till date having anti-inflammatory activity culminating to structural–activity relationships (SARs). These SARs around the coumarin template may help medicinal chemists in designing and synthesizing novel compounds with improved anti-inflammatory and other pharmacological activities.

Naturally derived coumarin derivatives

Flavonoids constitute an important class of coumarin-based phytoconstituents and are found in abundant amounts in

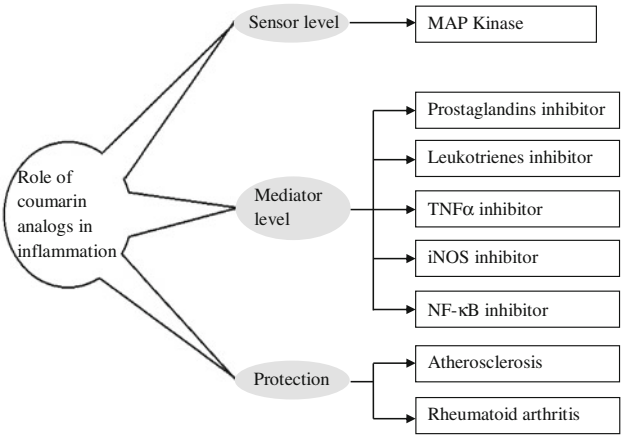


Fig. 1 Inflammatory targets of coumarin derivatives

essential oils, fruits, green tea, and other foods such as chicory (Lake, 1999; Lacy and Kennedy, 2004). The richest sources of coumarin-based molecules are the plants of Rutaceae and Umbelliferae families. Although distributed throughout all parts of the plant, their maximum contents are found in fruits, followed by roots, stems, and leaves (Keating and Kennedy, 1997). Various coumarin derivatives isolated from plants (Table 1) have been reported to possess anti-inflammatory activities. These act by reducing tissue edema, altering the functions of enzymatic systems, such as cyclooxygenase and lipoxygenase, and preventing the generation of free radicals. A detailed analysis of structures of these coumarin-based constituents has helped in postulating a brief SAR around the coumarin nucleus (Table 1):

- An α,β-unsaturated carbonyl group or free hydroxyl at the C-8 increases the activity.
- Most of the constituents are 6-/7-monosubstituted, 6,7-disubstituted, or 6,7-fused coumarins. In general, any substituent at any of these two positions are found to contain an oxygen atom (–OH or –OR). Hence, a polar moiety is very well tolerated at these positions.
- The C-4 remains unsubstituted in all the plant-derived coumarins.
- A linear long chain hydrophobic moiety is well tolerated at C-3.

Synthetically derived coumarins derivatives

Many reports on synthesis and exploration of numerous coumarin analogs for anti-inflammatory, analgesic, and/or antioxidant activities are available in the literature. These are discussed in chronological order herein. One of the

Table 1 Coumarin-based anti-inflammatory phytoconstituents

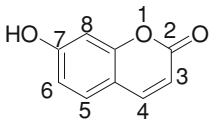
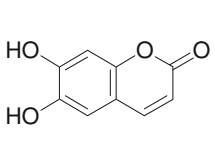
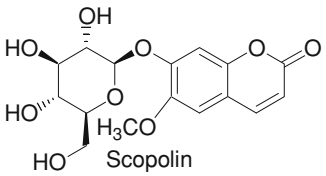
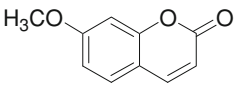
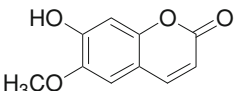
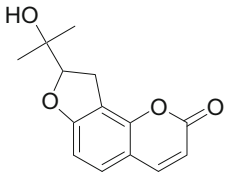
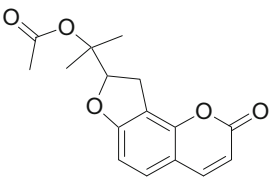
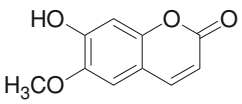
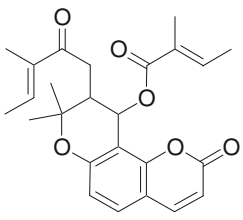
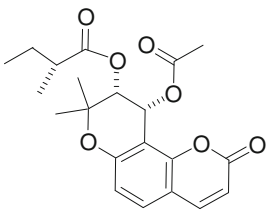
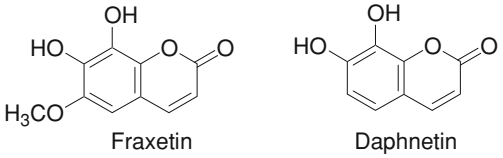
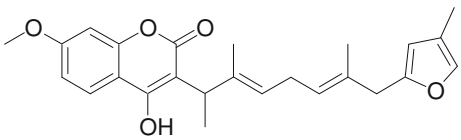
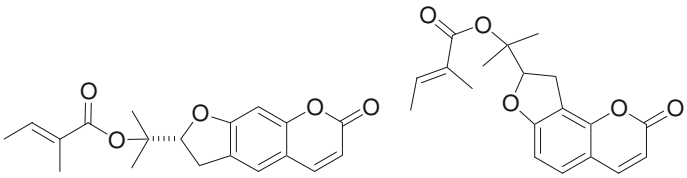
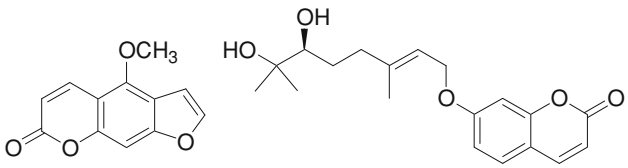
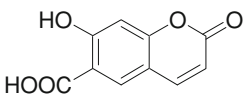
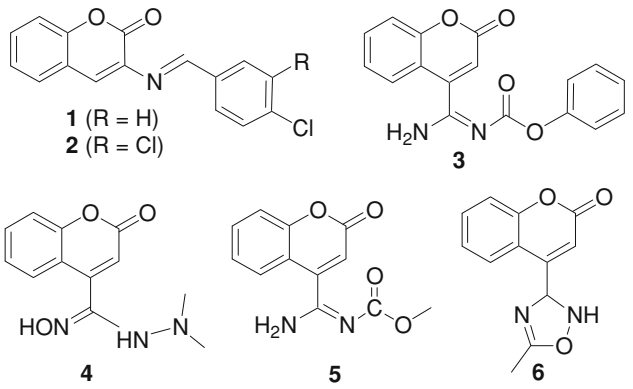
Source	Chemical constituent	References
Hydroalchoholic extract fromaerial part of *Justicia pectoralis*	 Umbelliferone	Lino *et al*., (1997)
Ethyl acetate extract of *Santolina oblongifolia*	 Aesculetin  Scopolin  Herniarin  Scopoletin	Silvan *et al*., (1998)
Aqueous extract of *Corydalis heterocarpa*	 Columbianetin  Libonoridin	Kang *et al*., (2009)
Petroleum benzene/ acetoacetate fraction of powdered stems of *Erycibe obtusifolia*	 Scopoletin	Pan *et al*., (2010)
Dry extract of aerial parts of *Lingusticum lucidum*	 Praeruptorin  Visnadin	Menghini *et al*., (2010)

Table 1 continued

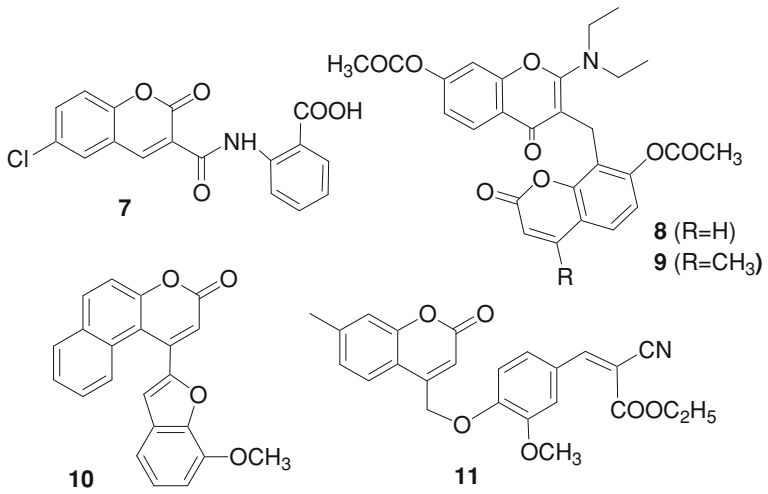
Source	Chemical constituent	References
Aqueous infusion of aerial parts of *Bidens tripartite*	 Fraxetin Daphnetin	Pozharitskaya *et al*., (2010)
Extract from roots of *Ferula fukanensis*	 Fukanemerin	Nazari and Ironshahi (2011)
n-Hexane extract of aerial parts and roots of *Zosima absinthifolia*	 (+)-Columbiandin (-)-Deltoin	Bahadir *et al*., (2011)
Roots of *Aegle marmelos* and *H. laciniatum*	 Marmin Sphondin	Shoeb *et al*., (1973), Ling *et al*., (2002)
Methanolic extract of whole plants of *Angelica decursiva*	 Umbelliferone-6-carboxylic acid	Zhao *et al*., (2012)

earliest reports on synthetic coumarin derivatives appeared in 1992 wherein Maddi *et al*. (1992) have reported a series of substituted 3-(benzylideneamino)coumarins and their evaluation for anti-inflammatory activity at an oral dose of 100 mg/kg. The compounds 1 and 2 exhibited, respectively 75 and 60 % inhibitions of carrageenan-induced paw edema (CPE). These also showed significant analgesic activity in acetic acid-induced writhing model in mice. Subsequently, Nicolaides *et al*. (1998) synthesized varied coumarin-4-carboxamidoximes and 4-oxadiazolyl coumarins. From these series, the compounds 3 and 4 produced maximum inhibition of CPE (more than 80 %), whereas the compounds 5 and 6 inhibited lipoxygenase with IC_{50} value of 76 and 77 %, respectively. The study suggested an unsaturated substituent as an important feature at C-4 of the coumarin nucleus.

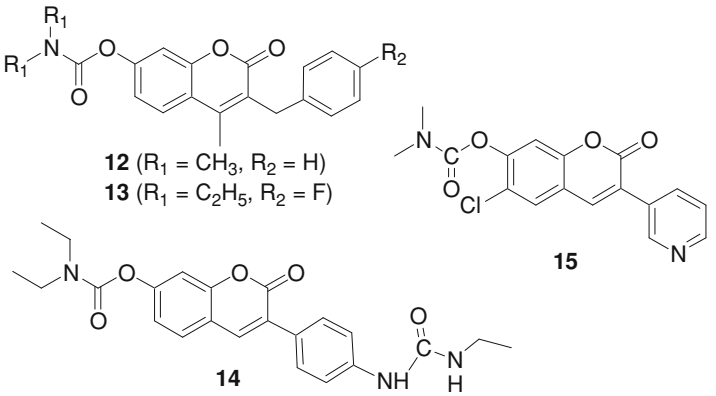


From a series of 2-oxo-2H-1-benzopyran-3-carboxamides, the compound 7 is reported to produce 54 % reduce the O_2^- production. The study revealed the importance of an acetoxy group at C-7 in coumarin nucleus as its replacement decrease the activity (Mazzeia *et al*., 2001). Potent anti-inflammatory activities of benzofuranyl and aryloxy derivatives of coumarins (10 and 11) (Ghate *et al*., 2003) have further supported the importance of an unsaturated functional group at C-4 as discussed earlier for the compounds 3–6.

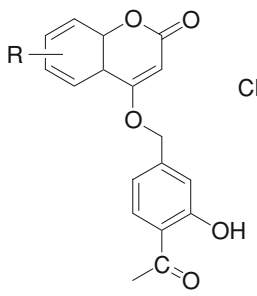
Cheng *et al*. (2004) have developed a series of carbamic acid esters of 7-coumarinol from which the compound 12 is reported as a moderate TNF-α inhibitor. Various modifications were carried out at C-3 and C-7 to enhance the activity. The *N*,*N*-diethyl carbamate and *N*,*N*-dimethyl thiocarbamate analogs are found to have activities higher than the *N*,*N*-dimethyl carbamate analog. Placement of a



inhibition in CPE and also found to be non-toxic at the higher dose levels (Bylov *et al*., 1999). The unsymmetrically bis-coumarin derivatives (8 and 9) are found to possess protein kinase C inhibitory activity and capacity to fluorine at *para*-position of the benzyl (13), replacement of benzyl with phenyl (14) or with pyridine (15) at C-3 greatly enhanced the TNFα inhibitory activity (IC_{50} 2.4, 0.32, and 0.45 μM, respectively).



Nicolaides *et al*. (2004) have synthesized and reported a series of Benzo[l]khellactone derivatives. Among these, compounds 16 and 17 exhibit the maximum activity with 59 % inhibition of CPE and 100 % inhibition of lipoxygenase. Kontogiorgis and Hadjipavlou-Litina (2004) have synthesized several coumarin derivatives possessing azomethine substituents at C-7 and evaluated for in vivo anti-inflammatory and in vitro antioxidant activities. Of these, compounds 18 and 19 exhibit 54–58 % inhibition of CPE, which suggests that the minimum requirement for in vivo and in vitro activities include a coumarin ring bearing a polar substitution at 7-position similarly as noted in various plant-derived coumarin derivatives. Subsequently, the same authors explored various Mannich bases at C-8 of 7-hydroxy coumarin and found compounds 20 and 21 to exhibit 75–77 % inhibition of CPE in comparison to 47 % inhibition by indomethacin. In addition, the compounds 21 and 22 inhibit LOX and exert good antioxidant activities (Kontogiorgis and Hadjipavlou-Litina, 2005).



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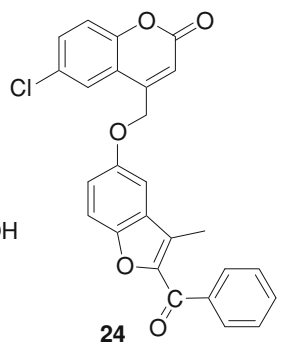

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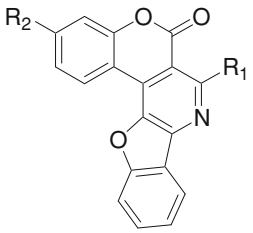
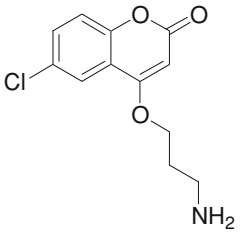


25 (R_1 = CH_3, R_2 = Cl)
26 (R_1 = C_2H_5, R_2 = OCH_3)



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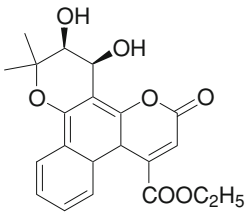

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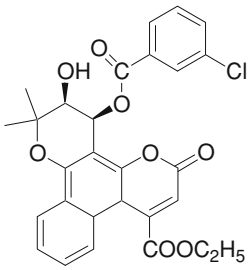

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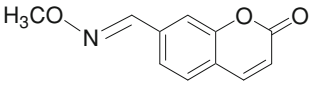

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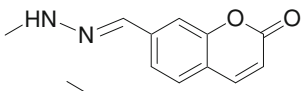

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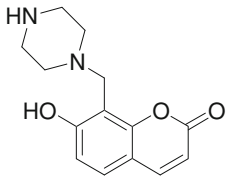

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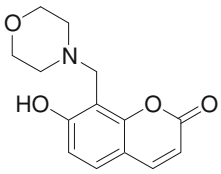

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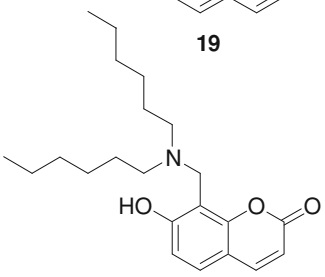

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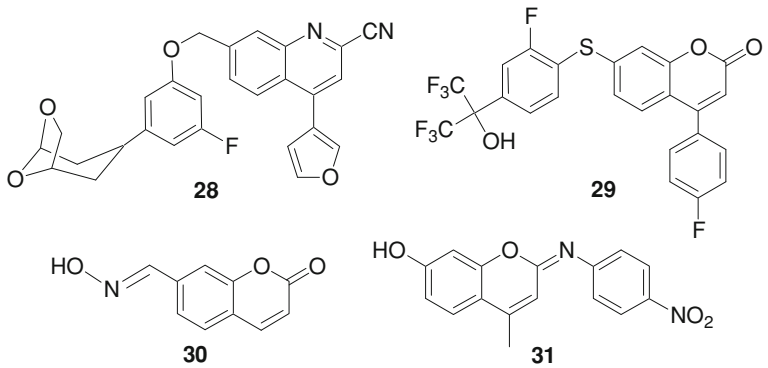
Ghate *et al*. (2005) have synthesized various coumarinyl ethers exemplified by compounds 23 and 24. The benzofuranyl derivative (24) is reported to have analgesic and anti-inflammatory activities comparable with indomethacin. A chlorine substituent at C-6 further increased the activity. Fusion of coumarin nucleus with benzofurans through pyridine ring produces compounds with good anti-inflammatory, analgesic, and antimicrobial activities. Among these, compounds 25 and 26 show anti-inflammatory activity in a dose-dependent manner with maximum inhibition (97 %) at 300 mg/kg (Khan *et al*., 2005). Taking thiocoumarins as lead inducible nitric oxide synthase (iNOS) inhibitor, Jackson *et al*. (2005) have synthesized many compounds among which compound 27 is found to have IC_{50} of 60 nM for iNOS.

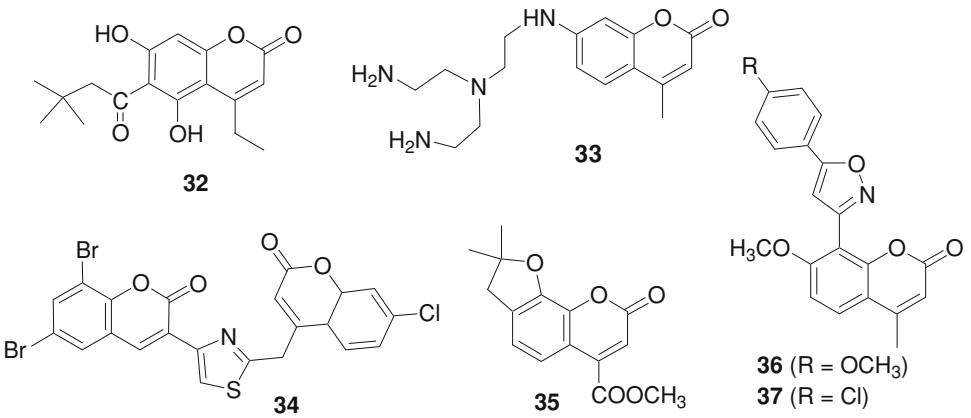
Taking compound 28 (a quinoline derivative) as lead, various coumarin derivatives were developed by replacing 2-cyanoquinoline moiety with fluorophenyl coumarin and dioxabicylcooctanyl moiety with hexafluorocarbinol. The resultant molecule (29) exhibited lower toxicity with increasing anti-inflammatory activity. Prodrugs of 29 synthesized by derivatization at C-2 of coumarin ring further increase the activity (Grimm *et al*., 2006). In the continuing attempts to develop potent anti-inflammatory and antioxidant molecules, Kontogiorgis *et al*. (2006) have also synthesized a series of coumarin derivatives with 7-azomethine linkage. The compound 30 emerged as the most potent COX-1 inhibitor (78.6 % inhibition). Gacche *et al*. (2006) have synthesized coumarin Schiff bases (CSBs) possessing

different substituents and evaluated for in vitro anti-inflammatory activity through inhibition of β-glucuronidase. The SAR studies revealed that the presence of a nitro group and the overall steric effect of CSBs may be the contributing factors for the inhibition of β-glucuronidase. The compound 31 was reported to be the most potent with 39 % inhibition.



A polysubstituted coumarin derivative (32) has been reported as a potent anti-inflammatory with IC_{50} of 7.6 μM against NO production in LPS-induced rat paw edema and to reduce hydroxyl radical production by 50 % (Lin *et al*., 2006). The fluorescent zinc probes of coumarin exert anti-inflammatory activity via inhibition of soybean lipoxygenase (LOX) and antioxidant activity via a scavenging superoxide anion radical. The compound 33 is found as the most potent molecule from the series with 92.4 % LOX inhibition (Hadjipavlou-Litina *et al*., 2007a).

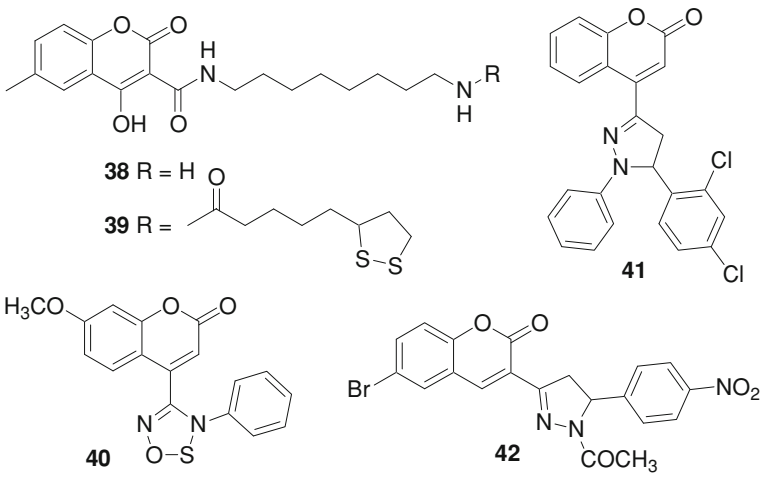
Tricyclic molecules synthesized from two coumarin nuclei connected through thiazoles (34) as well as carbostyril (1-aza coumarin) have been evaluated for in vivo analgesic and anti-inflammatory activities. The SAR studies revealed that a chlorine substituent at C-7 of the carbostyril and 6,8-dibromo substitution in the coumarin ring enhances the anti-inflammatory activity (Kalkhambkar *et al*., 2007). A report on angularly fused coumarins revealed that though the in vitro antioxidant activity of such compounds (35) was low, the in vivo anti-inflammatory activity was good, and the gastrointestinal toxicity was significantly low (Symeonidis *et al*., 2009). Sandeep *et al*. (2009) have developed a series of widely substituted 7-methoxy-4-methyl-8-[5-(substituted aryl)isoxazol-3-yl]-coumarins wherein the compounds 36 and 37 are found to possess good anti-inflammatory activity with 72 and 68 % inhibitions of CPE, respectively. In addition, the compounds were also found to be potently antibacterial.



Melagraki *et al*. (2009) have designed and synthesized various coumarin-3-carboxamides as well as coumarin–lipoic acid conjugates to develop novel hybrid molecules for treatment of human diseases attributed to free radical damage. The compounds 38 and 39 have emerged as the most promising agents exhibiting 100 % hydroxyl radical scavenging activity as well as potent CPE inhibitions (59 and 73 %, respectively). Bansal *et al*. (2009) have designed coumarin derivatives bearing 5-phenyloxathiadiazol-4-yl

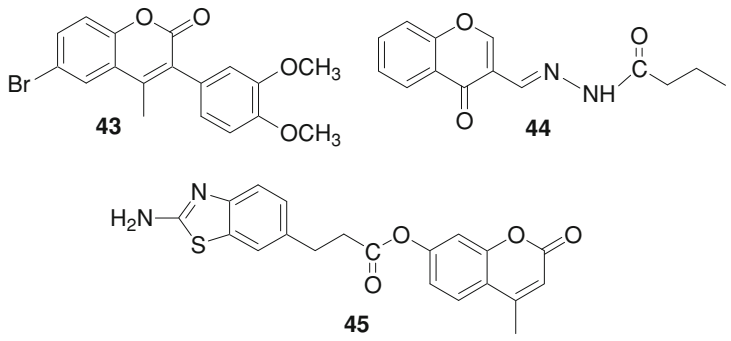
moiety at C-4 of the nucleus on the basis of the pharmacological requirements for binding with p38 MAP kinase. The compound 40 showed anti-inflammatory activity (55.28 % inhibition) comparable with indomethacin (56.52 % inhibition). Superimposition of 40 with the lead p38 kinase inhibitors suggested that the activity may be due to a p38 MAP kinase inhibition. Replacement of oxathiadiazole nucleus with pyrazoline has led to another series of compounds among which the compound 41 proved useful for acute and chronic inflammation with 67.5 and 45.4 % inhibitions, respectively. These compounds also possess analgesic and antipyretic activities with minimum ulcerogenic index (Khode *et al*., 2009). Reddy *et al.* (2010) have synthesized similar kind of derivatives with 3-coumarinyl moieties and found compound 42 exhibiting 66.5 % inhibition in acute inflammatory model in rats as compared to indomethacin (70.99 %).

than the non-PEGylated ones (Pandeya *et al*., 2010). Among a series of 3-formyl chromones derivatives, the butanohydrazide derivative (44) has been reported to exhibit potent anti-inflammatory activity (80.78 % inhibition of CPE) higher than aspirin. Hence it can be explored as a novel drug to reduce inflammation (Khan *et al*., 2010). Sandhya *et al*. (2011) have assessed the anti-inflammatory behavior of various coumarin analogs by automated docking studies using a protein–ligand complex constructed on the basis of X-ray structure of COX-2 bound with indomethacin through Molegro Virtual Docker program. The compound 45 emerged as the most active candidate from the series which is found to interact with the enzyme through eight hydrogen bonds (Fig. 2). These include hydrogen bonds of O-1 with Arg^{44} (distance 3.10 and 3.03 Å) and with Arg^{469} (2.79 Å), of O-2 with Arg^{469} (3.16 Å), of ester oxygen with Ser^{471} (2.58 Å) and Tyr^{122} (3.23 Å), of benzothiazole ring nitrogen



Roussaki *et al*. (2010) synthesized 3-aryl coumarin analogs and evaluated for antioxidant and LOX inhibitory activities. The compound 43 caused 86 % LOX inhibition and prevent lipid peroxidation. Evaluation of some PEGylated and non PEGylated 4-methyl and 4,8-dimethyl coumarin derivatives as anti-adhesion molecules for ICAM-1 (intercellular cell adhesion molecule) on human endothelial cells revealed that PEGylated derivatives are more active

with Asn^{43} (3.38 Å) and of NH_2 with Lys^{468} (2.79 Å). These docking studies revealed that the coumarin oxygen is important for binding with Arg^{44} amino acid. The presence of benzthiazole moiety at C-7 increases hydrogen bond formation and thus increases anti-inflammatory activity. The H-bonding involving ester oxygen at C-7 further supports the importance of a polar function at this position (–OH, –OR or –NH) as revealed earlier.



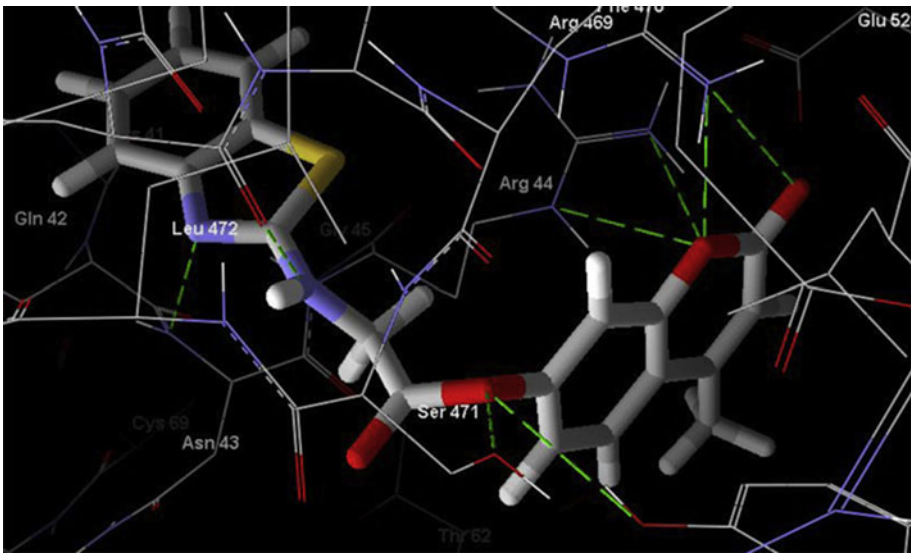
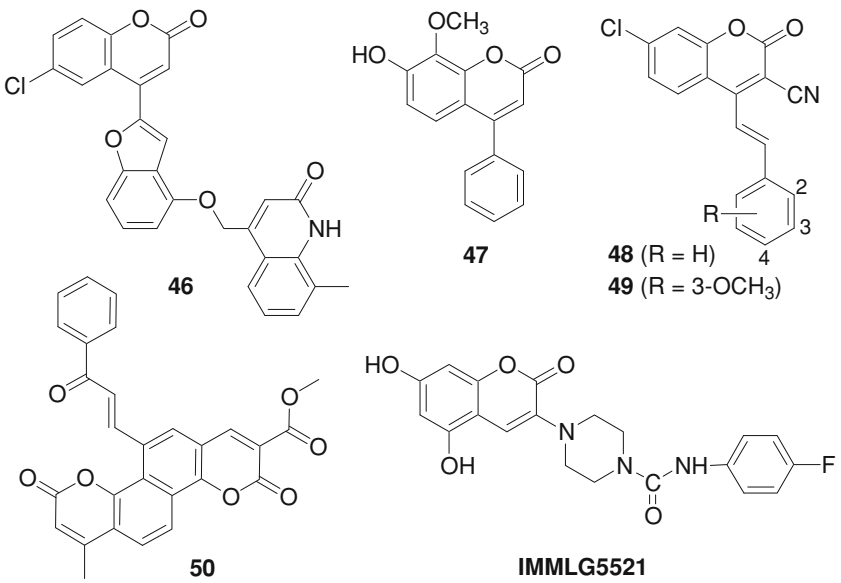


Fig. 2 A model of binding between compound 45 and COX-2 through hydrogen bonds shown as *green dotted lines* (Color figure online)

Coupling of variously substituted coumarins with variously substituted quinolinones through benzofuran nucleus is reported to yield compounds having in vitro anti-inflammatory activity. A chlorine substituent in quinolinone or coumarin moiety (46) enhances anti-inflammatory, analgesic, and antimicrobial activities (Kalkhambkar *et al*., 2011). Timonen *et al*. (2011) have found 7-hydroxy coumarins derivatives inhibit iNOS expression (56 %), NO and IL-6 productions (82 %) in a dose-dependent manner. A phenyl ring at position C-4 (47) or a lipophilic substitution at C-3 further increases the activity. Exploration of polar functional groups around the coumarin nucleus has culminated in compound IMMLG5521 having significant anti-inflammatory activity through inhibition of vascular permeability and leukocyte transmigration (Li *et al*., 2011). Upadhyay *et al.* (2011) have synthesized a series of 4-styrylcoumarins and explored for anti-inflammatory and anti-tubercular activities. The compound bearing unsubstituted styryl group (48) has been found to possess potent IL-6 inhibitory activity (87 %). Substitution with nitro group at 3-position or with hydroxy group at 4-position of the styrylic phenyl slightly decreases the activity. The other substituents (halogens, alkyl, alkoxy, etc.) at all other positions significantly decrease the IL-6 inhibition. On the contrary, a methoxy group at 3-position of the styrylic phenyl (49) confers significant TNFα inhibitory activity (73 %). Recently, Sashidhara *et al.* (2011) have designed bis-coumarins as hybrid molecules by combining pharmacophores of coumarins as well as chalcones with an aim to obtain antioxidant-anti-inflammatory molecules. Of the various compounds in the series, only compound 50 exhibited the best anti-inflammatory activity though less than ibuprofen. However, it also exhibited potent antioxidant activity which provides an important lead in the synthesis of dual-acting drugs.



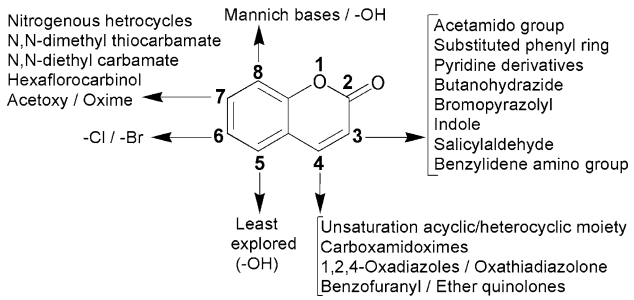


Fig. 3 Substituents explored at different positions (C-3 to C-8) of coumarin nucleus for anti-inflammatory activity

Structure–activity relationship

Many research groups have developed series of compounds to find appropriate functional groups at different positions (from C-3 to C-8) of coumarin nucleus for maximum anti-inflammatory activity. Hadjipavlou-Litina *et al*. (2007b) have studied various hydroxyaryl-substituted coumarin derivatives to develop a SAR and found a polar group at 5-/6-/7-position incurs LOX inhibitory activity on coumarin. These explorations of various functional groups around the coumarin nucleus are summarized in Fig. 3. A critical analysis of the data in Fig. 3 has helped in proposing SAR around the nucleus which shall enable the chemists to rationally design novel anti-inflammatory molecules. The salient features of the proposed SAR are as follows:

- In contrast to the naturally occurring coumarin molecules, most of the synthetic analogs are synthesized by substitutions at C-3 and C-4 of the nucleus. However, C-5 remains unexplored similarly as noted in plant-derived coumarins. Further, the nature of the substituent at C-7 and C-8 is broadly similar in both the synthetic as well plant-derived coumarins.
- An electron-rich hydrophobic group comprising nitrogen containing heterocycles such as indole, pyrimidine, and pyrazole at C-3 potentiates the anti-inflammatory activity.
- An unsaturated heterocyclic rings mainly containing oxygen and nitrogen is well tolerated at C-4.
- A chlorine or bromine at C-6 increases the activity.
- The carbamates and nitrogen-containing heterocycles at C-7 increase the activity by interacting with the receptor through hydrogen bonding.

Conclusions and perspectives

Coumarin-derived compounds (both of natural as well as synthetic origins) posses good to excellent anti-inflammatory activity. Despite this, no such compound has made its way to the clinics. In this article, various reports on exploration of synthetically derived coumarin analogs for anti-inflammatory activity in the literature are critically studied to review the developments in the field in a chronological order. The purpose is to generate a SAR around the coumarin nucleus. The SAR has revealed the suitability of various functional groups or moieties at different positions of the nucleus. The position 5 is found relatively unexplored. Hence, selection of appropriate functional group at C-5 can lead to development of novel clinically useful anti-inflammatory molecules. Conjugation of the coumarin nucleus with lipoic acid has conferred both the antioxidant as well as anti-inflammatory activities which suggest that conjugation of the coumarin nucleus with other class of compounds can also produce hybrid molecules having multiple activities.

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