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A review on “Recent advances in Coumarin derivatives with their multidisciplinary actions”

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ABSTRACT

Coumarins are an entity which is being synthesized in many of its derivative form from past few years; the entity is major source of interest for many of medicinal chemist to explore its various pharmacological potentials especially anti coagulant activity. In present article we review recent derivatives of coumarin that are synthesized with their pharmacological activities like anti oxidant, anti inflammatory, anti microbial activity, anti hepatitis and hepatoprotective, anti cancerous, anti pyretic and analgesic activity . Literature study of various research papers and other publications which provide detailed work and recent study of its derivatives is taken into consideration. Present data suggests that coumarin apart from anti coagulant activity is widely used in many of pathological conditions. Various combinations of coumarin with other heterocyclic rings with their respective activities are being reviewed in present article.

Key Words: Coumarin, anti oxidant, anti hepatitis, anti cancerous.

INTRODUCTION

Coumarin in itself possess much of broad range of biological activities namely anticoagulation, antibiotic, antifungal, antipsoriasis, cytotoxic, anti-HIV, anti-inflammatory. Especially 7-hydroxycoumarin has antioxidant[11,12,13] properties and cytostatic,[14,15] antibacterial,[12] antiviral,[12] xanthine oxidase inhibitor,[12] antihyperglycemic, [16] casein kinase 2 inhibitor[17] activities, vasorelaxant[18], antitubercular [19]. Recently, coumarin derivatives have been evaluated in the treatment of human immunodeficiency virus, due to their ability to inhibit human immunodeficiency virus integrase [20, 21, and 22]. It's been revealed that efficacy of coumarins for MAO-A and MAO-B affinity and selectivity can be efficiently modulated by appropriate substitutions in the coumarin ring [23]. Apart from their therapeutical activities, it is

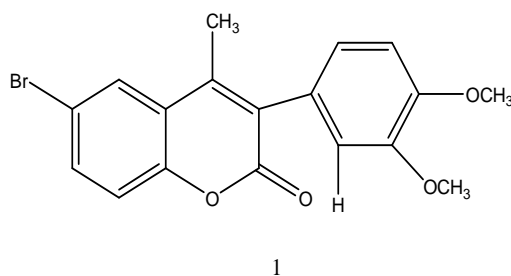
also an important analytical agent. Regarding their high fluorescence ability, they are widely used as optical whitening agents, brighteners, laser dyes and also as fluorescent probes [24] in biology and medicine [25].

Being synthetically important their biosynthetic derivatives like, phytoalexins, which are hydroxylated derivatives of coumarins, produced in carrots in response to fungal infection and can be presumed to have antifungal activity [26]. General antimicrobial activity was provided in Woodruff (*Galium odoratum*) extracts [27].

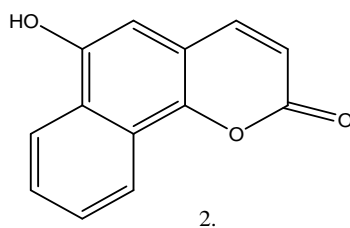
Now when coumarin ring fused with other rings, a synergistic effect of both the rings in their biological activities are obtained, such compounds are exploited in development of various important molecule which provides scaffolds for drug development. Various moieties when combined with coumarin can produces same or different effects but with different potencies. Details are review here for such recent derivatives of coumarins with different activities. Various activities which are specifically studied here are:

Anti oxidant activity. [28, 29, 30]

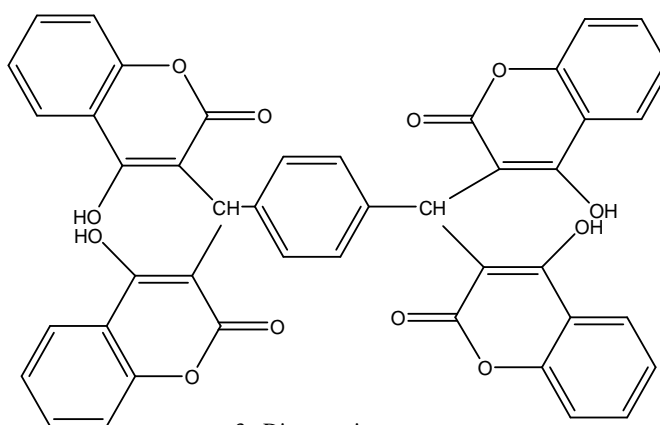
peroxidation activity, substituent on the aromatic ring of the benzopyranone moiety, the presence of electron-withdrawing groups on the phenyl ring of position 3 favours activity. The best combined pharmacological profile is exhibited by compound 1. [28]



Substituted hydroxycoumarins and 7- or 8-hydroxybenzo[f]coumarins were prepared by the treatment of phenols and naphthalenediols, respectively, with malic acid and H_2SO_4 under microwave irradiation. It has been identified that phenolic compounds present antioxidant activity. The presence of the phenolic hydroxyl group (6-, 7- or 8-) seems to support the antioxidant activity but the effect on activity is independent of the position of hydroxyl group. It is generalized that the benzo derivative compound 2 is more potent than any of the cyclohexyl derivatives. Compound 2 shows higher anti oxidant activity among various hydroxybenzocoumarins being synthesized. [29].

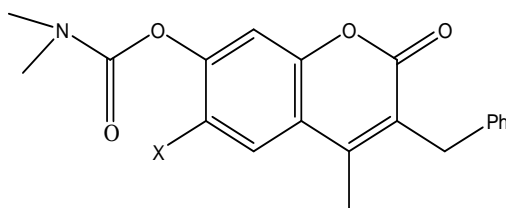


Different substituted 3, 3'-arylidenebis-4-hydroxycoumarins and tetrakis-4-hydroxycoumarin derivative (compound 3) were synthesized by 4-hydroxycoumarin and aromatic aldehydes containing different groups in *ortho*, *meta* or *para* positions and condensing them in boiling ethanol or acetic acid. A possible relationship between intermolecular hydrogen-bonded structures and the antioxidant activities of these compounds are analyzed. The compounds which contain intermolecular hydrogen bonds is uncoupler and inhibitor of mitochondrial oxidative phosphorylation, while compounds which can only form intermolecular hydrogen bonds, is only uncoupler of oxidative phosphorylation. Thus, the formation of hydrogen bonds may be an important factor in assisting the synthesized dicoumarols (specifically compound 3) to attain the correct configuration for antioxidant activities.[30]

3. Dicoumarins

Anti inflammatory activity. [32, 33]

A novel series of coumarin-based carbamates were synthesized, which exhibited potent inhibitory activity of TNF- α (Tumor necrosis factor) which is a proinflammatory cytokine secreted by a variety of cells, including monocytes and macrophages, in response to many inflammatory stimuli or external cellular stress[31]. Substitution at C-6 position of the coumarin ring system was found to have the most influence on TNF- α inhibitory activity. This observation led to the discovery of 6-halo derivatives with influential activity.[32]

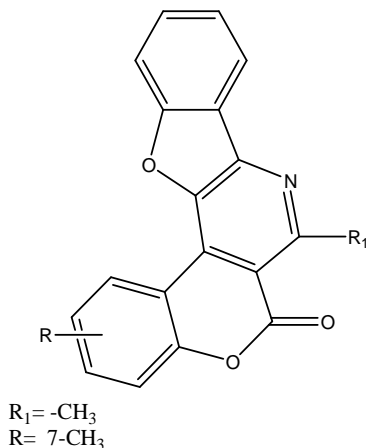


X= Cl, Br, I, F

4.

An array of angularly fused polycyclic heterocycles with coumarin, benzofuran and pyridine rings by N-C-C3 annealation, were synthesized from 4-bromomethylcoumarins and salicylonitrile. These derivatives have wider applicability to create new fused heterocyclic

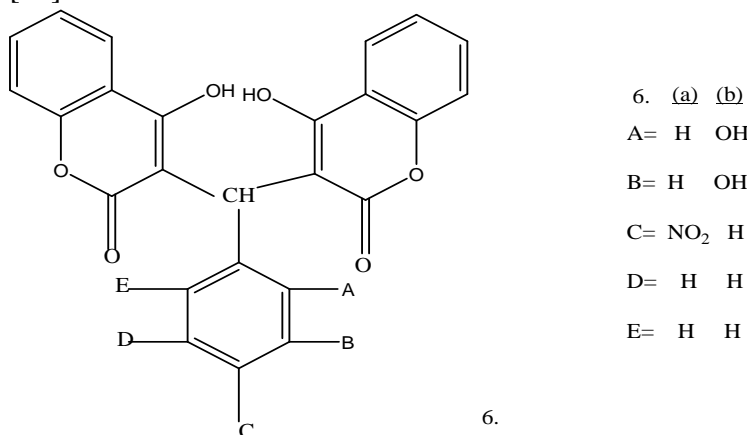
systems for their anti inflammatory activity. Among the compounds tested, compound 5 showed significant inhibition of inflammation at various doses, and it has been summarized that in this angularly fused system substitutions of electron donating groups are preferential for inflammatory inhibitions. [33]



5. Polycyclic coumarin

Anti microbial activity. [30,33]

Different substituted 3, 3'-arylidenebis-4-hydroxycoumarins derivatives were synthesized when 4-hydroxycoumarin and aromatic aldehydes containing different groups in *ortho*, *meta* or *para* positions condense in boiling ethanol or acetic acid. A relationship between intermolecular hydrogen-bonded structures and their anti microbial activities are analyzed. These compound forms intermolecular hydrogen bonding, and in biological systems, the formation of these intermolecular hydrogen bonds may hold these compounds (dicoumarols) in a suitable configuration for binding to an enzyme and hence may be an important factor in assisting the molecule to attain the correct configuration for antimicrobial activities. The two most active compounds 6a and 6b were tested on *P. acnes* and *S. epidermidis*, and showed the low acute toxicity.[30]

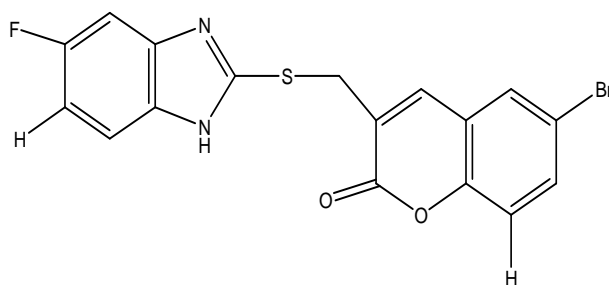


Derivatives of fused polycyclic heterocycles with, coumarin, benzofuran and pyridine rings by N-C-C3 annealation were synthesized. Literatures have suggested that benzopyranopyridines are essential in compound to have anti-bacterial activity studies revealed that on the mode of

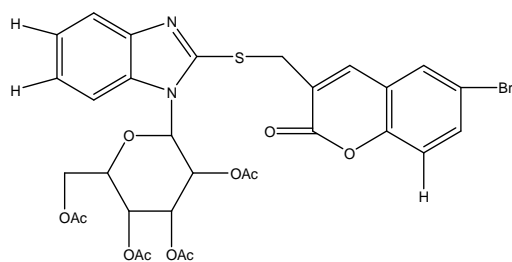
action of the anti-bacterial action of benzopyranopyridine esters act via the DNA gyrase inhibition pathway. In the anti-microbial screening all the derivatives had a MIC of 25 g/ml against *Pseudomonas chinchori*, whereas at the same concentration they were inactive against *Micrococcus aureus*. In the anti-fungal screening, all the compounds inhibited the growth of *Aspergillus fumigatus* at 25 g/ml, whereas against *Penicillium wortmanni* they were active at a concentration of 100 g/ml. [33]

Anti hepatitis and hepatoprotective activity. [35]

A series of substituted benzimidazole– coumarin conjugated compounds were synthesized and their potential antiviral activity was evaluated in the Huh 5-2 replicon system. Among the various synthesized derivatives of benzimidazole–coumarin conjugates some were found to inhibit HCV subgenomic replicon replication in the Huh 5–2 cell line, conjugates 7a and glucoside 7b inhibited HCV replication with EC₅₀ values of 3.4 μM and 4.1 μM, respectively. In conclusion it was found that enhancement of the selectivity from substituents in the coumarin nucleus was found of the order OMe<H<Br; attachment of the –CH₂–coumarin moiety onto the benzimidazole-2-thione nucleus connected with a pyranose enhanced the HCV inhibitory activity by >9.4-fold and selectivity by 6.7-fold; incorporation of a β-d-glucose peracetate moiety into the benzimidazole–coumarin conjugate resulted in a 4.8-fold increase in anti-HCV activity. Thus compounds 7a and 7b may be considered as potential lead anti-HCV compounds for further selectivity optimization against hepatitis-C virus. [35]



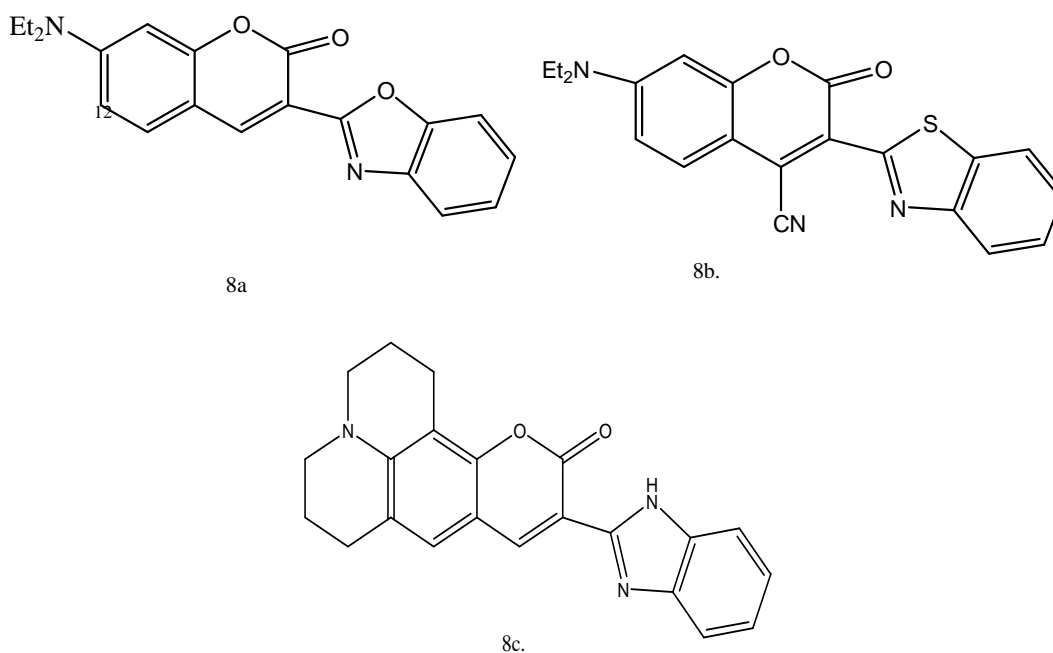
7a. Benzimidazole-SCH₂-coumarin conjugate



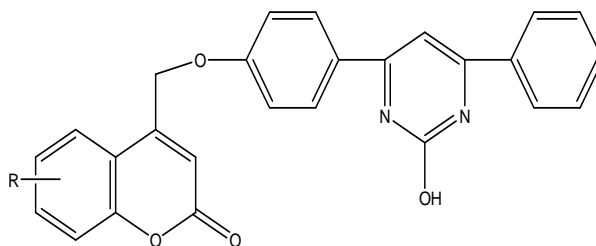
7b. N-glucoside of benzimidazole-SCH₂-coumarin conjugate

Anti cancerous activity. [36]

A series of 7-diethylaminocoumarin compounds were synthesized and the cytotoxicities were tested against human umbilical vein endothelial cell (HUVEC) and some cancer cells. The introduction of benzothiazolyl and analogous groups at 3-position improved the overall inhibition activity and introducing a cyano group at the fourth position afforded the selectivity towards HUVEC. In particular, the inhibition activity of 8a against tested cancer cell lines was comparable to a positive control, paclitaxel, and compounds 8b and 8c showed a high selectivity for HUVEC, which in turn can be potentially utilized as lead compounds to develop nontoxic angiogenesis inhibitors. [36]

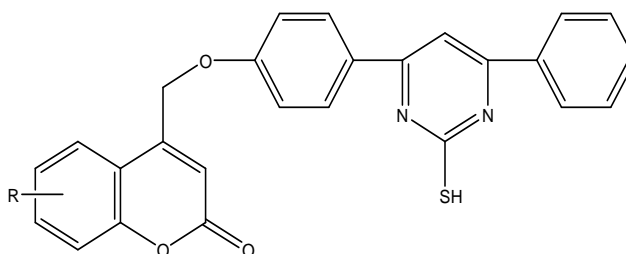
**Analgesic and Anti pyretic activity. [37, 33]**

A novel series of 4-[4-(6-phenyl-pyrimidin-4-yl)-phoxymethyl]-chromen-2-ones were synthesized from various 4-bromomethyl coumarins. The synthesized compounds were screened for *in-vivo* analgesic and anti-pyretic activities. Pyrimidines and coumarins possess their specific biological activities and if these two active pharmacophores, are linked together they would generate novel molecular templates which are likely to exhibit interesting biological activity of analgesic and anti-pyretics. Among them, compounds 9a, 9b and 9c exhibited significant analgesic activity comparable with standard drug analgin and significant anti-pyretic activities comparable with standard drug aspirin. Thus it was concluded that amongst the tested compounds, those containing -NH₂ functional group at 2-position of pyrimidine ring increases their analgesic and anti-pyretic activities. [37]



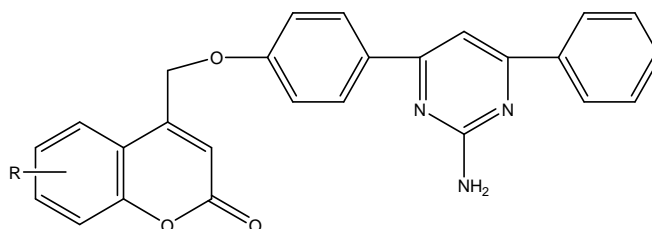
R= 5,6-Benzo

9a.



R= 6-Cl

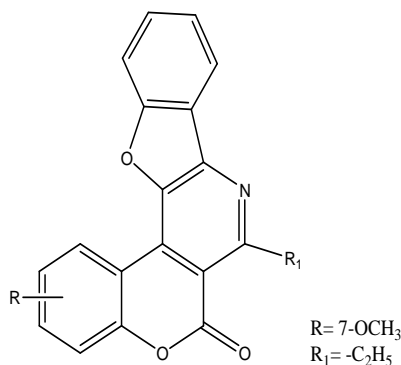
9b.



R= 5,6 benzo

9c.

Derivatives of fused polycyclic heterocycles with, coumarin, benzofuran and pyridine rings by N-C-C3 annealation were synthesized. The most potent compound in the synthesized series was the 7-methoxy derivative, compound 10, which showed 78% inhibition of inflammation and considerable protection against the acetic acid induced abdominal constrictions which gives its effective potency as analgesic agent. [33]



10.

CONCLUSION

Coumarins are the least complex heterocyclic structures having lowest toxicities which could be obtained frequently in nature. Its chief biological activity involves prevention of over grazing by animals, when present in plants due to their bitter taste. In present review emphasis is laid on different derivatives of coumarin which are synthesized by various renowned researchers and their activities are studied. Most widely studied activities are discussed here under separate headings.

Activities like anti oxidants are discussed in which various derivatives having different substitutions shows this activity, here a series of coumarin analogues bearing a substituted phenyl ring on position 3 , 7- or 8-hydroxybenzo[f]coumarins and substituted 3, 3'-arylidenebis-4-hydroxycoumarins and tetrakis-4-hydroxycoumarin derivatives are discussed here which gives the over view that phenyl ring is essential in the substituted coumarins to have an anti oxidant activity. Anti inflammatory activity is considered for coumarin-based carbamates which have inhibitory activity of TNF- α (pro inflammatory agent) and angularly fused polycyclic heterocycles with coumarin derivatives, in which presence of electron withdrawing or accepting substitutions at different positions shows an important role. In case of anti microbial activity substituted 3, 3'-arylidenebis-4-hydroxycoumarins derivatives must have appropriate intermolecular H- bonding ,while fused polycyclic heterocycles with, coumarin, benzofuran and pyridine rings must have proper fusion of the rings to have anti microbial activity and synergizing their overall effects. For anti hepatitis and hepatoprotective activity substituted benzimidazole- coumarin conjugated compounds are studied, for anti cancerous activity a series of 7-diethylaminocoumarin compounds are considered. In last we have discussed series of 4-[4-(6-phenyl-pyrimidin-4-yl)-phenoxy-methyl]-chromen-2-ones and again derivatives of fused polycyclic heterocycles with, coumarin, benzofuran and pyridine rings for their anti pyretic and analgesic activity.

Coumarins have been exploited in recent studies for their various activities and still it can be further utilized for future prospective against various pathological conditions and other uses.

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