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Research Article

Overview of Diverse Pharmacological Activities of Substituted Coumarins: Compounds with Therapeutic Potentials

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Abstract

Coumarins are well known plant derived natural product which is extensively used as a biological active compound. Coumarins have attracted considerable attention of medicinal chemists and pharmacologists and have been demonstrated to bear many pharmacological activities. Natural and synthetic coumarins were verified to have antioxidant, antiinflammatory, anticoagulation, estrogenic, dermal photosensitizing, vasodilator, molluscicidal, anti helmentic, sedative, hypnotic, analgesic, hypothermic, antimicrobial, anticancer, anticonvulsant, antihyperlipidemic, tyrosinase inhibitor and anti-parkinsonism and antiulcer activities. This review is based on recent studies of coumarins and coumarin related compounds. Therefore the focus will be on their pharmacological importance along with the various synthesis methods. The aim of the paper is to review the available information on substituted coumarins.

Keywords: Pharmacological activities; synthesis, benzopyrone; antioxidant; anti-inflammatory; antimicrobial; anticancer; anticonvulsant; anticoagulant; substituted coumarins

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Introduction

Coumarins are well-known naturally occurring oxygen-heterocyclic compounds isolated from various plants. They belong to the family of lactones having 1-benzopyran-2-one system (**1**) that can be isolated from plants as well as synthesis. Many coumarins have been isolated from the plant parts and reported to possess many pharmacological activities like anti-inflammatory & antipyretics, antioxidant, brochodialator, vasodialator, antiamoebic, antibacterial and antifungal activities. Synthesis of coumarins and their derivatives has attracted considerable attention of organic and medicinal chemists from many years as the large number of natural products contain this heterocyclic nucleus. Coumarins are widely used ngas additives in food, perfumes, cosmetics, pharmaceuticals, optical brighteners, dispersed fluorescent and laser dyes. Thus the synthesis of this heterocyclic nucleus is of much interes coumarins were first synthesized via the Perkin reaction (1868), and many simple coumarins are still prepared through this method. In the early nineties, the Knoevenagel reaction emerged as an important synthetic method to synthesize coumarin derivatives with carboxylic acid at the 3-position. Many other synthetic methods for coumarins have been reported, including the Pechmann, Reformatsky and Wittig reactions. The pharmacological properties as well as therapeutic applications of coumarins depend upon the pattern of substitution and recently they are reported to possess many pharmacological activities [Backhouse et al., 2001; Torres et al., 2006; Piao et al., 2004; Ramanitrahasimbola et al., 2005; Dongmoa et al., 2007; Iqbal et al., 2009; Tadaa et al., 2002; Stein et al., 2006; Rajithaa et al., 2006; Shaabani et al., 2009].

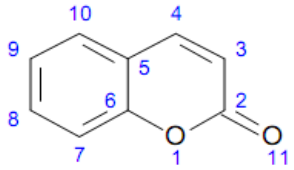
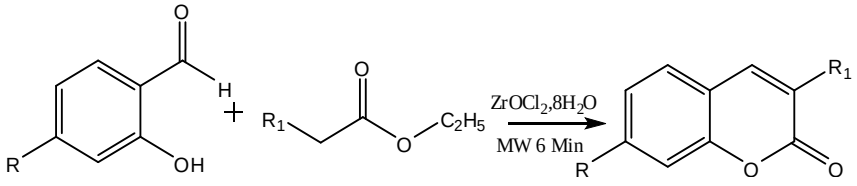


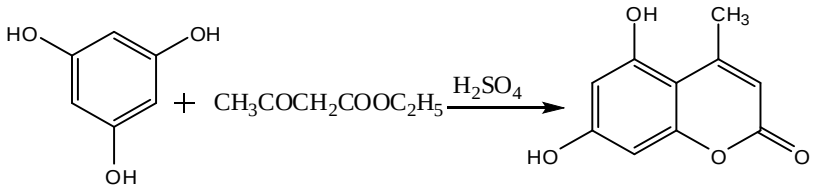
Figure 1 Molecular scaffold of 1-benzopyran-2-one (coumarin nucleus)

General synthesis of coumarin

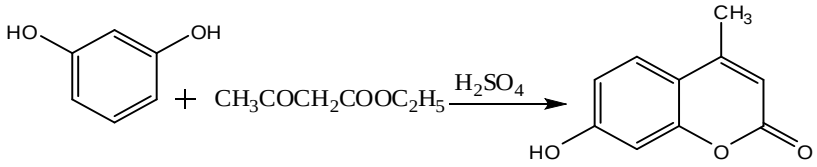
Synthesis of substituted coumarins: The $ZrOCl_2.8H_2O$ shows high catalytic activities for the synthesis 3-subsituted coumarins via knoevenagel condensation under solvent free conditions by microwave heating. The procedure offers several advantages including the low loading of catalyst, high yields clean reaction and the use of a variety of substrate which makes it a useful of attractive strategy for the synthesis of 3-substituted coumarins [Moghaddam et al., 2009].



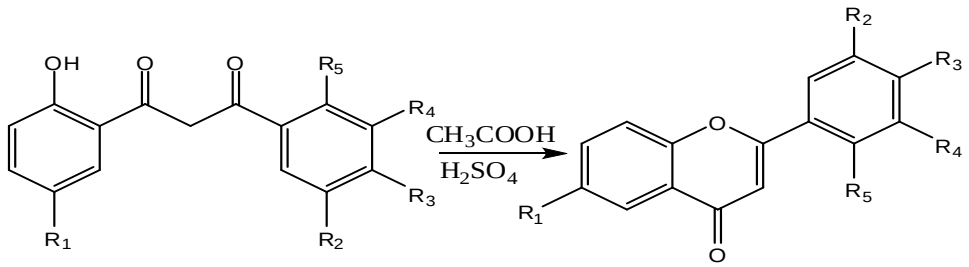
Conventional synthesis of Coumarins



Phloroglucinol ethyacetoacetate 4-Methyl-5,7- Dihydroxy Coumarin



Phloroglucinol ethyacetoacetate 4-Methyl-7-hydroxy Coumarin

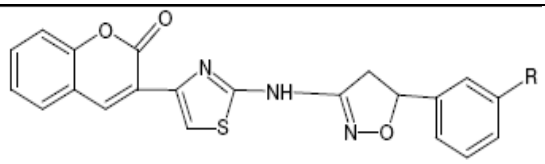
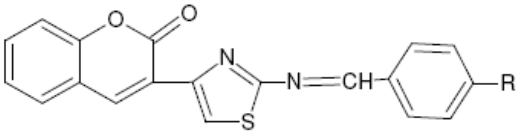
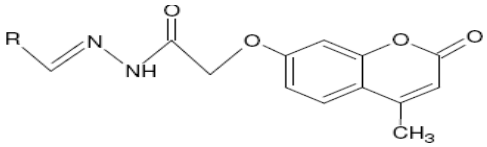
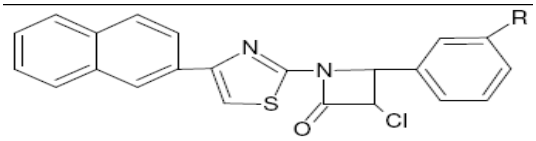
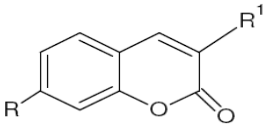
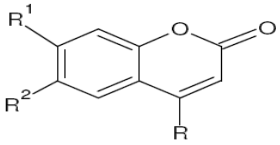
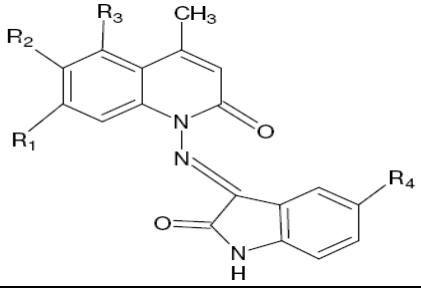


Pharmacological activities

Coumarin agents (known as 1,2-benzopyrone), consisting of fused benzene and α-pyrone rings are present in significant amounts in plants and more than 1300 coumarins were identified from natural sources [Hoult and Paya. 1996]. These natural compounds serve as important models for advanced design and synthesis of more active analogous coumarins that possess were shown to have potent biological activities [Mei-Hsiang, et al., 2011]. The synthesis of coumarins and their derivatives has attracted considerable attention from organic and medicinal chemists as a large number of natural products contain this nucleus [Rajitha et al., 2006; Murreey et al., 1982]. They are widely used as additives in food, perfumes, cosmetics, pharmaceuticals [O'kennedy and Thornes. 1997] and optical brighteners5 and dispersed fluorescent and laser dyes [Zabradnic. 1992]. Thus the synthesis of this heterocyclic nucleus is of much interest. Coumarins have been synthesized by several routes including pechmann, perkin, knoevenagel, reformatsky and wittig reactions [Paramjeet et al., 2012]. Coumarins also exhibits anticoagulant activity and some coumarin drugs are widely used as anticoagulants-warfarin and acenocoumarol [Nikhil et al., 2012; Venkataraman et al., 2014]. The investigation have revealed their potentials as versatile biodynamic agent for example 3-heteroaryl substituted coumarins and benzocoumarins of potential interest as pharmaceutical and, photochromic dyes [Al-Zaydi. 2003]. Similarly substituted coumarins were exhibit high potency as antimicribial agent [Ajani and Nwinyl. 2010; Martinz-palou. 2007]. Introduction of fluoro and sulfonamide moieties into coumarin side chain improve the biological activity of compound

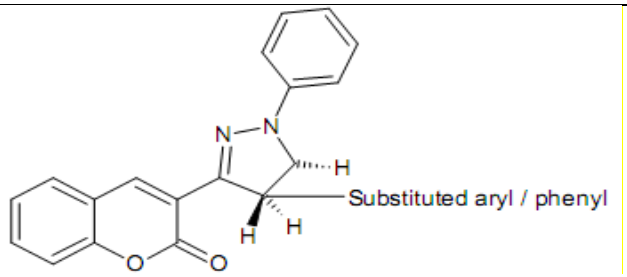
[Zuo et al., 2008]. Specifically 1,5 substituted benzothiazepine [Raval et al., 2008] are well known compounds for diverse therapeutically properties like antimicrobial, antihypertensive, calcium channel blocker, blood platelet aggregation inhibitory, and coronary vasodilatory effects [Gurdeep and Sham Anand. 2008; Khoobia et al., 2011; Benkabelia. 2005; Iiahmi et al., 2005; Prieto et al., 1999; Kunchandy and Rao. 1990; Padma et al., 1998]. Furthermore derivative of coumarins possesses antibacterial activity against bacteria and antifungal activity and also possess a broad spectrum of biological importance. The coumarins containing a Schiff base are expected to have enhanced antitumor and other biological activity [Desai et al., 2008; Naik and Desai. 2006; Satynarayana et al., 2008; Siddiqui et al., 2010; Moghaddam et al., 2009; More and Mahulikar. 2011; Dighe et al., 2010].

Table 1 Pharmacological activities of some coumarin derivatives

Structure and Pharmacological Activity	
	
Anti microbial, antifungal, anti-inflammatory agent, anti HIV [Desai at. el. 2008]	Antimicrobial, fungicidal, antibacterial, anticoagulant, antiallergic [Naik et. al. 2006]
	
Antibacterial, antifungal, antitumor activity [Satyanarayana et. al. 2008]	Antimicrobial, fungicidal, antibacterial, anticoagulant, antiallergic [Naik Et. al. 2006]
	
Antimicrobial and anti chemotherapeutics [Moghaddm et. al. 2009]	Cancer therapy, Anti inflammatory, Antiviral [More et. al. 2011]
	Anti asthmatic, antibacterial, antifungal, antimalarial, antiviral, antiinflammatory [Siddiqui et.al. 2010]

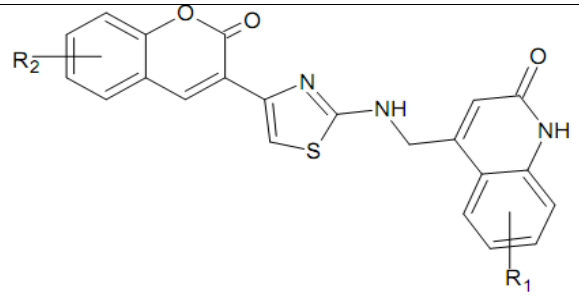
Anti-inflammatory and Analgesic Activity: A series of 5-(substituted)aryl-3-(3-coumarinyl)-1-phenyl-2-pyrazolines (**2**) by reacting various substituted 3-aryl-1-(3-coumarinyl)propan-1-ones with phenylhydrazine in the presence of hot pyridine. These compounds were screened for *in vivo* anti-inflammatory and analgesic activities at a dose of 200 mg/kg

b.w. All compounds exhibited significant anti-inflammatory activity compared with diclofenac (13.5 mg/kg b.w.) as a standard drug. These compounds were also found to have significant analgesic and antipyretic activity with minimum ulcerogenic index [Khode et al., 2009]. The tri-heterocyclic thiazoles containing coumarin and carbostyril (1-aza coumarin) (**3**) by the reaction of the *in situ* generated 4-thioureidomethyl carbostyril and 3-bromoacetyl coumarins. These compounds were evaluated for their *in vivo* analgesic and anti-inflammatory activities. The 7-chloro substitution in carbostyril and 6,8-dibromo substitution in the coumarin ring enhanced anti-inflammatory activity [Kalkhambkar et al., 2007]. A series of N-aryl substituted 2-imino -2*H*-1-benzopyran-3-carboxamides (**4**) and 2-oxo-2*H*-1-benzopyran-3-carboxamides (**5**) were evaluated for anti-inflammatory activity in albino rats. The results were found to be comparable with piroxicam taken as the reference drug. The efficacy of the compounds, 2-imino/oxo-2*H*-1-benzopyran-3-carboxamides were further studied in albino mice and were found to be essentially non-toxic at the highest dose tested [Bylov et al., 1999].



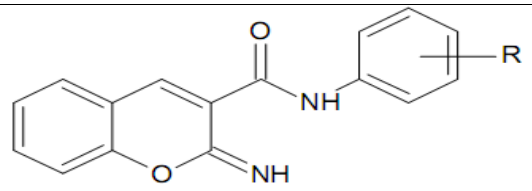
Aryl/phenyl=C_6H_5, 4-OCH_3-C_6H_4, -CH=CH-C_6H_5, 4-Cl-C_6H_5, 2,4-$(Cl)_2$-C_6H_3, 4-$N(CH_3)$2-C_6H_4, 3-NO_2-C_6H_4, 4-CH_3-C_6H_4, 4-F-C_6H_4, 2-NO_2-C_6H_4, 4-OH-C_6H_4

Figure 2 Structure of 5-(substituted) aryl-3-(3 coumarinyl)-1- phenyl-2-pyrazolines



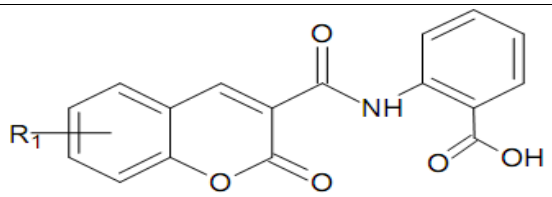
R_1=6-Cl, 7-Cl, 8-CH_3, **R_2**=H, 6'Br, 6'8'-Br

Figure 3 Structure of triheterocyclic thiazoles containing coumarin and carbostyril



R=2-$COOCH_3$, 4-$COOCH_3$

Figure 4 Structure of N-aryl substituted 2-imino-2H-1- benzopyran-3-carboxamides



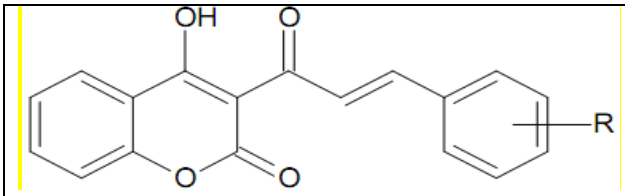
R=H, 5-OCH_3, 3-OCH_3, 5-NO_2, 5-Cl, 3-ally

Figure 5 Structure of N-aryl substituted 2-oxo-2H-1- benzopyran-3-carboxamides

Antimicrobial Activity: A series of 3-cynnamoyl-4-hydroxycoumarins (**6**) by the reaction of nucleophilic addition of 3-acetyl-4-hydroxycoumarin acting on appropriate aromatic aldehydes. The microbiological activities of the compounds were on species of bacteria *Pseudomonas aeruginosa*, *Echerichia coli*, *Salmonella typhimurium*, *Bordatella bronchiseptica*, *Bacillus subtilis* and *Staphyloccocus aureus*. All the compounds showed larger or smaller growth inhibition zones when they came in contact with Gram-positive aerobe bacteria *B. subtilis* and *S. aureus*. These compounds showed resistance to Gram-negative types of bacteria. The compounds having halogens showed the best microbiological

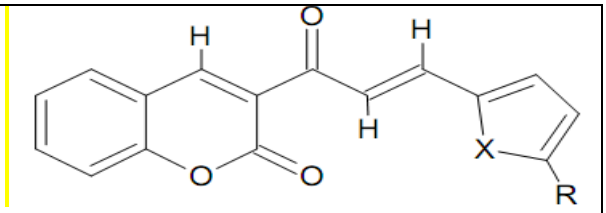
activity. Compounds having 4-Br and 4-Cl were found to be the most effective against *B. subtilis*. Compound having 4-Cl was found to be the most effective against *S. Aureus* [Zavrsnik et al., 2011]. The 3-[3-(s-aryl and s-heteroaromatic)acryloyl]-2*H*-chromen-2-one derivatives (**7**) synthesis was carried out by condensation of 3-acetylcoumarin with aromatic andheteroaromatic aldehydes to afford the corresponding aromatic chalcones and heteroaromatic chalcones. All the compounds were screened for antibacterial activity against five gram positive bacteria (*Bacillus anthracis*, *B. Stearothermophilus*, *B. Subtilis*, *B. cereus* & *S. aureus*) and five gram negative bacteria (*E. coli*, *Klebsiella pneumonia*, *P. aeruginosa*, *P. fluorescence* & *Shigella dysenteriae*) and results were compared with the standard drug-streptomycin. 3-[3-(4- dimethylaminophenyl)acryloyl]-2*H*-chromen-2-one was found to the most active compound at minimum inhibitory concentration (MIC) value of 7.8 µg/ml [Ajani and Nwinyi. 2010]. Some 4-aryl-2,6-di(coumarin-3- yl) pyridines by the reaction of 3-coumarinoyl methyl pyridinium salts (**8**) with 1-[2*H*-1-benzopyran-2-on-3-yl]-3-aryl-prop-2-en-1-ones in the presence of ammonium acetate and acetic acid under the Krohnke reaction conditions. All the compounds were screened for antimicrobial activity. None of the compounds showed antifungal activity against *A. niger*. Most compounds showed moderate activity against the Gram-positive bacteria. *B. subtilis*. The results towards this bacteria revealed that the incorporation of the substituents either in the coumarin nucleus or in a phenyl ring did not affect the antibacterial activity much more and all the compounds had almost same activity. Activity of other compounds indicated that the presence of an additional fused benzene ring between the C-5' and C-6' positions inhibited the antibacterial activity towards *E. Coli* [Patel et al., 2010]. The 3-coumrinoyl pyridinium bromides (**9**) prepared by reaction of methyl and ethyl esters of nicotinic acid with isonicotinic acid and 3-coumarinoyl quinolinium bromides by reaction of methyl and ethyl esters of nicotinic acid with quinoline. Most of the compounds possessed significant antimicrobial activity when compared with that of gentamycin and amoxycillin. These compounds were showing good qualitative antimicrobial property [Porwal *et al*., 2009]. The N-substituted-2-oxo-2*H*-1-benzopyran-3-carboxamide (coumarin-3-carboxamides) (**10**) in order to develop new anti-*Helicobacter pylori* agents and evaluated them for antibacterial activity. All the compounds showed little or no activity against different species of Gram-positive and Gram-negative bacteria of clinical relevance and against various strains of pathogenic fungi. Compounds in which the 3-amidic function is substituted with a phenyl bearing fluorine, methyl and cyano groups, showed very low or no activity against all strains. Among these compounds having 4-acyl phenyl group showed the best activity against *H. pylori* metronidazole resistant strains in the 0.25-1 µg/ml MIC range, indicating that the presence of an acyl function is an important feature for activity [Chimenti et al., 2006]. The 4-[1-(2*H*-[1]-4-hydroxy-2-oxo-benzopyran-3-yl)methylidene]-2-phenyl-4*H*-oxazol-5- ones and [1,2,4]triazine -6-one and its derivatives by acetylation reaction. All the compounds were screened for antimicrobial activity and found to exhibit significant activity [Mulwad and Satwe. 2006]. The 1,3-dipolar cycloadducts of 3-azidoacetylcoumarins with dimethyl acetylene dicarboxylate (DMAD). These compounds were synthesized by reaction of 3-bromoacetylcoumarins with sodium azide in aqueous acetone to give 3-azidoacetylcoumarins which on further reaction with DMAD in dry xylene produced 1,3-dipolar cycloadducts. All the compounds and their adducts were screened for antimicrobial activity and good results were obtained. This activity was carried out against two pathogenic bacteria *E. coli*, *B. subtilis* and *A. niger* as the fungal strain [Kusanur and Kulkarni. 2005]. Some heterocycles by incorporating isoxazoles, pyromidines and 1,5- benzothiazeoine in a parent 4-hydroxycoumarin molecule which enhanced the biological properties of these molecules. These compounds were tested for *in vitro*

antibacterial activity [Mulwad and Pawar. 2003]. The coumarin derivatives containing sulphanilamide group were synthesized refluxing 6-H/6-bromo/6-chloro/salicylaldehydes with sodium salt of substituted *p*-acetamidobenzene sulphonylglycine in the presence of acetic anhydride for 4-5 hrs and by hydrolysing the product with 50% sulphuric acid and acetic acid. They also synthesized 3-amino-(N-arylsubstituted)-6-bromo-2*H*-1-benzopyran-2-ones and 6-bromo-3-phenoxy substituted-2*H*-1-benzopyran-2-ones. This synthesis involved the condensation of 5-bromo salicylaldehyde with sodium salt of substituted N-aryl glycine and sodium slat of substituted phenoxy acetic acid respectively. All the compounds were screened for *in vitro* antitubercular activity against highly virulent *Mycobacterium tuberculosis* HRv strains and compared to that of streptomycin and isoniazid [Gupta and Phull. 1996; Gupta and Prabhu. 1996].



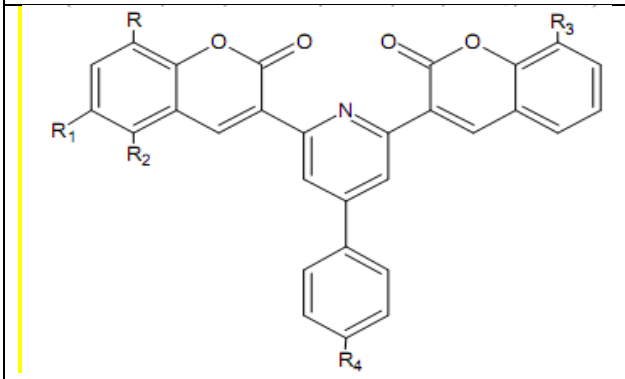
R=2-OH, 5Br, 4-CH_3, 4-OCH_3, 4-OH, 4-Br, 4-Cl, 2-F, 2-NO_2

Figure 6 Structure of 3-cynnamoyl-4-hydroxy coumarins



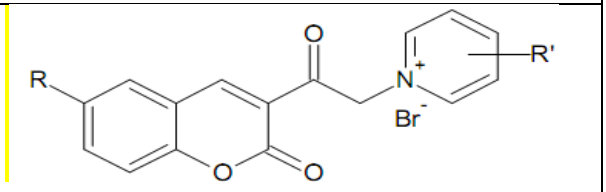
X=O, NH, **R**= H, NO2, Cl, CH_3, C_2H_5

Figure 7 Structure of 3 -[3-(s-aryl and s-heteroaromatic)acryloyl]-2H-chromen-2-ones



R=H, OCH_3, **R_1=R_2**=H/Benzo, **R_3**=H, OCH_3, **R_4**=H, OCH_3

Figure 8 Structure of 4-aryl-2,6-di(coumarin-3-yl)pyridines



R=H, Cl, Br, **R'**=4$COOC_2H_5$, 3$COOC_2H_5$,4-$COOCH_3$, 3-$COOCH_3$

Figure 9 Structure of 3-coumrinoyl pyridinium bromides

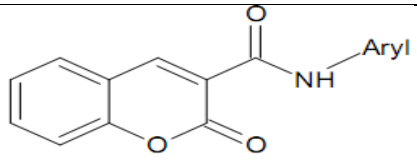
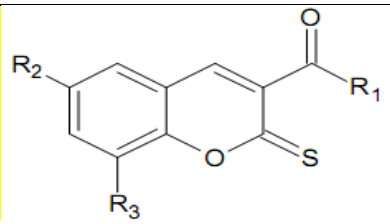


Figure 10 Structure of N-substituted-2-oxo-2H-1-benzopyran-3-carboxamides

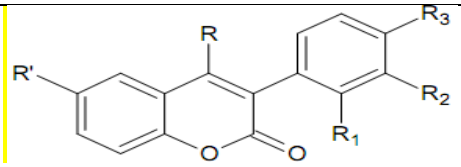
Antioxidant Activity: A combinatorial library of 3-alkanoyl/aroyl/heteroaroyl-2*H*-chromene-2-thiones (**11**) by the condensation of easily accessible β-oxodithioesters and salicylaldehyde/ substituted 2-hydroxybenzaldehydes under solvent-free conditions. The free radical scavenging capacity of the compounds towards the stable free radical 2,2-diphenyl-1-picrylhydrazyl (DPPH) was measured and these compounds were found to scavenge DPPH free radicals efficiently. These compounds exhibited profound antioxidant activity. Some selected compounds were able to protect curcumin from the attack of sulfur free radical produced by radiolysis of glutathione (GSH) [Singh et al., 2010]. A series of coumarin

analogues (**12**) bearing a substituted phenyl ring on position 3, through an intermolecular condensation reaction of 2-hydroxyacetophenones and 2-hydroxyl benzaldehyde with imidazolylphenylacetic acid active intermediates. *In vitro* antioxidant activity of the synthesized compounds was evaluated using two different antioxidant assays (DPPH stable free radical and inhibition of lipid peroxidation induced by the free radical AAPH). The compounds were inhibited soybean lipoxygenase and were exhibited potential anti-inflammatory activity [Roussaki et al., 2010]. A series of coumarin-3-carboxamides (**13**) and their hybrids (**14**) with the α-lipoic acids were evaluated for their *in vitro* antioxidant activity and *in vivo* anti-inflammatory activity. These compounds were found to possess the both activities [Melagraki et al., 2009]. Some 4-hydroxy-coumarin derivatives, ethyl 2-[(4-hydroxy-2-oxo-2*H*-chromen-3-yl)(4-hydroxyphenyl)methyl]-3-oxo-butanoate, 4-[1-(4-hydroxy-2-oxo-2*H*-chromen-3-yl)-2-(ethoxycarbonyl)-3-oxobutyl] benzoic acid, ethyl 2-[(4-hydroxy-2-oxo-2*H*-chromen-3-yl) (3-nitrophenyl)methyl]-3-oxo-butanoate and ethyl 2-[(3,4,5-trimethoxyphenyl)(4-hydroxy-2-oxo-2*H*- chromen-3-yl)methyl]-3-oxobutanoate were tested for *in vitro* antioxidant activity in hypochlorous system. The assay was based on the luminal-dependent chemiluminescence of free radicals, which decreased in the presence of 4-hydroxycoumarin derivative. Ethyl 2-[(4-hydroxy-2-oxo-2*H*-chromen-3-yl)(4-hydroxyphenyl)methyl]-3-oxobutanoate expressed the best scavenger activity at the highest concentration (10 mol/L) [Stanchev et al., 2009].



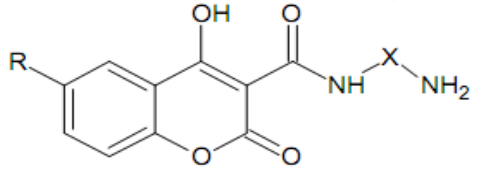
R$_1$=Substituted phenyl/heterocyclic nuclei, **R**$_2$=H, Br, **R**$_3$=H, OCH_3

Figure 11 Structure of 3-alkanoyl/aroyl/ heteroaroyl- 2H- chromene-2-thiones



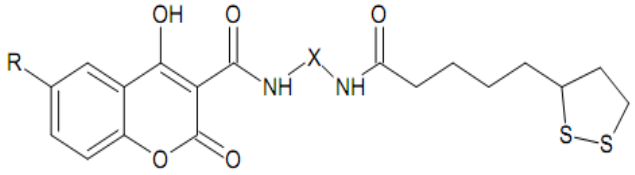
R=H,CH_3, R'=H, Cl, Br, **R**$_1$=H, Br, OCH_3, **R**$_2$=H, OCH_3, **R**$_3$=OCH_3, NO_2, OH, Br, H

Figure 12 Structure of coumarin analogues



R=H, CH_3, X=$(CH_2)_2$,$(CH_2)_6$, $(CH_2)_8$, o-phenylene gr.

Figure 13 Structure of novel coumarin-3-carboxamides

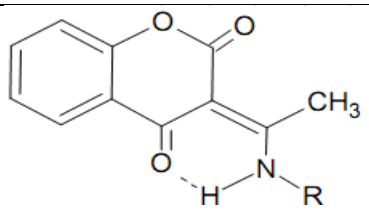


R=H, CH_3 X=$(CH_3)_2$, $(CH_2)_6$, $(CH_2)_8$

Figure 14 Structure of hybrid of novel coumarin-3-carboxamides with α-lipoic acid

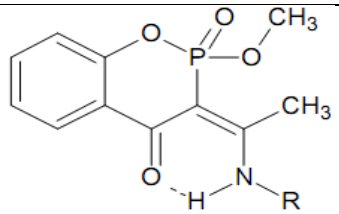
Anticancer Activity: The cytotoxic effects and alkylating activity of a series of 3-[1-(alkylamino)ethylidene]-chroman-2,4-dione (**15**), 2-methoxy-3-[1-(alkylamino)-ethylidene]-2,3-dihydro-2,4-dioxo-2λ-benzo[e][1,2]oxaphosphinane (**16**) and [2-oxo-4-phenyl(alkyl)-2*H*-chromen-3-yl]-phosphonic acids dimethyl ester (**17**) on the two leukemia cell lines HL-60 and NALM-6. The test compounds were much more toxic to NALM-6 cells than to

HL-60 cells. IC data are up to nine times lower for the NALM-6 than for the HL-60 cell lines. The *in vitro* Preussmann test, phosphonic derivatives possessed very high alkylating activity; phosphoric derivatives were less active while the chroman-2,4-dione derivatives could be included in the group of low activity alkylating agents. The cytotoxic effect increased with an increase of the hydrophobic parameters in the region of the substituents at the 2-, 3- and 4-positions of the benzopyrone skeleton of these compounds [Budzisz et al., 2003]. The coumarin 3-(N-aryl) sulphonamides (**18**) by Knoevenagel condensation of anilinosulfonylacetic acids with suitable salicylaldehydes and by the reaction of methyl anilinosulfonylacetates with substituted salicylaldehydes. The effect of all the compounds on the growth of human tumor cells in culture was evaluated using androgen receptor negative prostate (DU145), colorectal (DLD-1), non-small cell lung carcinoma (H157), estrogen receptor negative breast (BT20), and chronic myeloid leukemia (K562) cell lines. The dose response of each cell line was established by determining the number of viable cells after 96 hr. of continuous treatment against five different concentrations (1-100 µM range) of each compound. The activation of JNK1 (c-Jun NH terminal kinase1) by these compounds as shown in immune complex kinase assay and they activate JNK pathway either by interacting with JNK1 or with one of the upstream kinases in this pathway [Reddy et al., 2004].



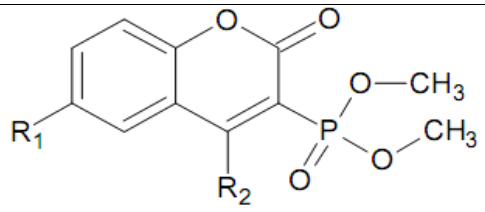
R= CH_3, CH_2CH_2OH, $CH_2C_6H_5$

Figure 15 Structure of 3-[1-(alkylamino)-ethylidene]-chroman-2,4-dione



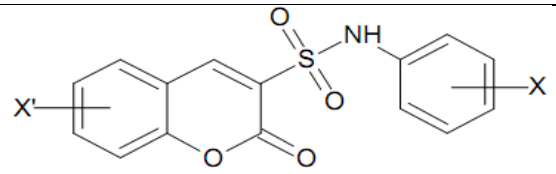
R= CH_3, CH_2CH_2OH, $CH_2C_6H_5$

Figure 16 Structure of 2-methoxy-3-[1-(alkylamino)-ethylidene]-2,3-dihydro-2,4-diox o-2λ-benzo[e][1,2] oxaphosphinanes



R= CH_3, CH_2CH_2OH, $CH_2C_6H_5$

Figure 17 Structure of [2-oxo-4-phenyl (alkyl)-2H-chromen-3-yl]-phosphonicacids dimethyl esters

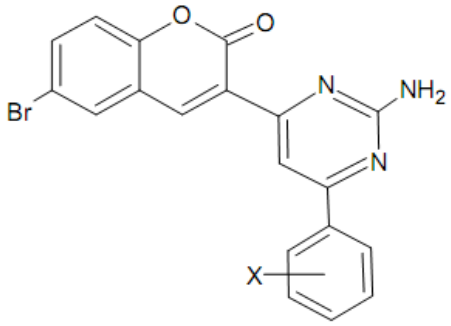


X= 4-OCH_3, 4-F, 4-Br, **X'**=6-Cl, 8-Cl, 8-Br,6-OCH_3,8-OC_2H_5

Figure 18 Structure of coumarin 3-(N-aryl) sulphonamides

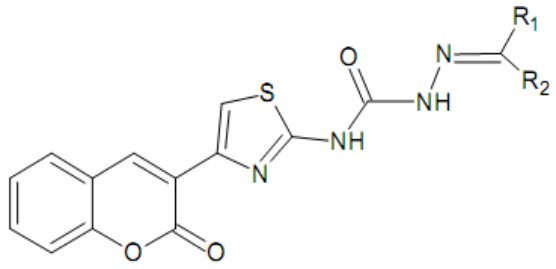
Analgesic and Ulcerogenic Activity: A series of 3-(2-amino-6-pyrimidin-4-yl)-6-bromo-2*H*-chromen-2-one (**19**) from 3-acetyl-6-bromo-2*H*-chromen-2-one. These compounds were screened for *in-vivo* analgesic activity at a dose of 20 mg/kg body weight. Among them, compounds having *o*-chloro, *m*-chloro and *m*-bromo phenyl exhibited significant analgesic activity and compounds having 2,4-dichloro and 2,6-dichloro phenyl exhibited highly significant activity comparable

with standard drug Diclofenac sodium. Compounds having *o*-chloro phenyl, 2,4-dichloro and 2,6-dichloro phenyl were further evaluated for acute-ulcerogenic activity. Among them, compound having 2,6-dichloro phenyl was found to be most promising analgesic agent devoid of ulcerogenic effects [Gupta et al., 2010].



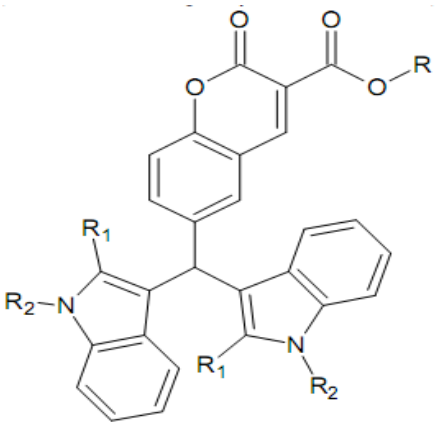
X=2-Cl, 3Cl, 4-Cl, 2-Br, 3-Br, 4-Br, 2-OCH3, 3-OCH3, 2,4,-Cl_2, 2,6Cl_2
Figure 19 Structure of 3-(2-amino-6-pyrimidin-4-yl)-6-bromo- 2H-chromen-2-one

Anticonvulsant Activity: Several heteroaryl semicarbazones (**20**) by the reaction of heteroaryl hydrazine carboxamide with aryl aldehydes or ketones. Compounds were tested for anticonvulsant activity utilizing pentylenetetrazole (PTZ) induced seizure and maximal electroshock seizure (MES) tests at 30, 100 and 300 mg/kg dose levels. Three compounds having exhibited significant anti convulsant activity at 30 mg/kg dose level comparable to the standard drug-phenytoin [Siddiqui et al., 2009].



R=Substituted phenyl, **R_2**=H, CH_3
Figure 20 Structure of heteroaryl semicarbazones

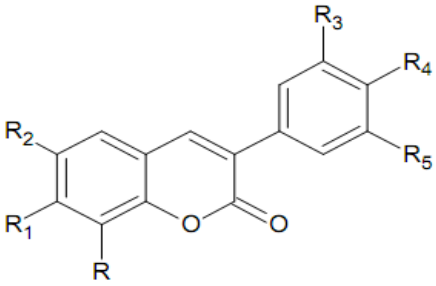
Antihyperlipidemic Activity: A series of coumarin bisindole heterocycles (**21**) by the Duff reaction on naphthalen-1-ol, which was engaged in a Knoevenagel type reaction with appropriate active methylene compounds. Furthermore, an efficient electrophilic substitution of suitable indoles with these coumarin aldehyde derivatives using iodine in acetonitrile furnished coumarin bisindole hybrids. Similarly, another series of coumarin bisindole hybrids were prepared starting from 2-sec- butylphenol resulting in another set of coumarin bisindole hybrids. The compounds were evaluated for antihyperlipidemic activity in hyperlipidemic hamster model. In both the series of compounds, revealed that the substitution at position 3 play a pivotal role and the presence of ethyl ester over methyl is preferred for pronounced activity. On the other hand, the lower indole pharmacophore highlighted that the unsubstituted indoles have good activity profile compared to substituted indoles [Sashidhara et al., 2010].



R=C_2H_5, **R_1**= H, CH_3, R_2= H, CH_3

Figure 21 Structure of synthesized hybrid of coumarin bisindole heterocycles

Tyrosinase Inhibitor Activity: The coumarin-resveratrol hybrids (**22**) by a traditional Perkin reaction carried out in refluxing dimethylsulfoxide (DMSO) between *o*- hydroxybenzaldehydes (or their methoxy substituted derivatives) and the corresponding arylacetic acids, using dicyclohexylcarbodiimide (DCC) as dehydrating agent. Tyrosinase activity assays were performed with L-DOPA as substrate with slight modifications and activity of mushroom tyrosinase was determined and these compounds exhibited tyrosinase inhibitory activity. The 3-(3',4',5'-trihydroxyphenyl)-6,8-dihydroxycoumarin was found to be the most potent compound (0.27 mM) more than umbelliferone (0.42 mM) used as reference compound. The kinetic studies revealed that this compound caused non-competitive tyrosinase inhibition and the number and the position of free hydroxyl groups play an important role in determining the activity [Fais et al., 2009].

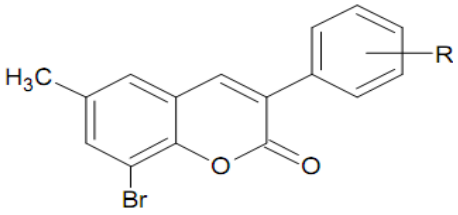


R= H, **R_1**=H, OH, **R_2**=H, **R_3**=H, **R_4**=H, OH, **R_5**=H, OH

Figure 22 Structure of resynthesized coumarin-resveratrol hybrid

Anti-parkinsonism Activity: A series of 8-bromo-6- methyl-3-phenylcoumarin derivatives (**23**) without substituent s and with different number of methoxy substituent in the 3-phenyl ring. The substituent in this scaffold was introduced in the 3', 4' and/ or 5' positions of the 3-phenyl ring of the coumarin moiety. These compounds were evaluated as MAO -A and MAO-B inhibitors using R-(-)-deprenyl (selegiline) and Iproniazide as reference inhibitors, most of them showing MAO-B inhibitory activity in the nanomolar range. The series of compounds proved to be selective inhibitors of the MAO-B isoenzyme. The compound with one methoxy substituent in the phenyl ring was itself very active and selective to MAO-B isoenzyme. Compounds without any substituent and with two methoxy groups showed MAO-B IC on the same activity range. These three compounds had similar inhibitory

activity of the R-(-)-deprenyl. The most potent molecule of this family had one methoxy group in 4' position. Compound with 3-methoxy group, loses activity and selectivity in respect to the mono and dimethoxy derivatives. These compounds did not showed MAO-A inhibitory activity for the highest concentration tested (100 μM) [Matos et al., 2009].



R= H, 4'-CH_3, 3',5'-OCH_3, 3',4',5'-OCH_3
Figure 23 Structure of 8-bromo-6-methyl-3- phenylcoumarin derivatives

Some natural coumarins possessing anti-HIV activity

Dipyranocoumarins-Calanolides (+)-Calanolide A, (+)-[10R, 11S, 12S]-10,11-trans-dihydro-

12-hydroxy-6,6,10,11-tetramethyl-4-propyl-2H, 6H-benzo[1,2-b:3,4-b':5,6b"] tripyran-2-one, is

a novel nonnucleoside RT inhibitor (NNRTI) with potent activity against HIV-1.

Costatolides: Two isomers of calanolide A, (-)-calanolide B (costatolide) and (-)-dihydrocalanolide B (dihydrocostatolide), possess antiviral properties similar to those of calanolide A. These compounds have properties of NNRTIs. The calanolide analogues, exhibit enhanced antiviral activity against drug-resistant viruses after NNRTI treatment. Costatolide and dihydrocostatolide are highly effective inhibitors of clinical strains, including those representing various HIV-1 clades, Sis, NSIs, T-and M-tropic isolates.
Inophyllum: The seeds of *Calophyllum cerasiferum* vesque (Family-*clusiaceae*) and *Calophyllum inophyllum* linn. (Family-*clusiaceae*) contain several known coumarins, among them the potent HIV-1 RT inhibitors costatolide and inophyllum P. calophyllum cerasiferum contained (-)-calanolide B [Dighe et al., 2010].

Discussion

Coumarins and its derivatives have been proved as useful precursors for the synthesis of variety of medicinal agents [Morrison and Boyd. 2008; Lednicer and Mitscher. 2006]. Recent researches with important bioactive compounds in many plant and food materials have received much attention. The oxidation induced by reactive oxygen species (ROS) can result in cell membrane disintegration, membrane protein damage and DNA mutation, which can further initiate or propagate the development of many diseases, like cancer, liver injury and cardiovascular diseases [Sahaa et al., 2008; Anita et al., 2001; Venkateshwarlu et al., 2011]. Although the body possesses such defense mechanisms, as enzymes and antioxidant nutrients, which arrest the damaging properties of ROS continuous exposure to chemicals and contaminants may lead to an increase in the amount of free radicals in the body beyond its capacity to control them, and cause irreversible oxidative damage. Therefore, antioxidants with free radical scavenging activities may have great relevance in the prevention and therapeutics of diseases in which oxidants or free radicals are implicated. Anticoagulants have various uses such as the prevention or treatment of disorders characterized by abnormal blood clots and emboli [Silverstein et al., 1991; Aurora et al., 2001]. Anticoagulant drugs include

intravenous heparin, which acts by inactivating thrombin and several other clotting factors that are required for a clot to form, and oral anticoagulants such as warfarin and dicumarol, which act by inhibiting the liver's production of vitamin K dependent factors that are crucial to clotting. Anticoagulant solutions are also used for the preservation of stored whole blood and blood fractions and to keep laboratory blood specimens from clotting. The synthesis and biological activities of coumarin derivatives have been focused due to potential activities exhibited by them. Modifications on the coumarin nucleus have resulted in a large number of compounds having diverse pharmacological activities. Some of the ascertained properties of substituted coumarins are promising and deserve further investigation in the attempt of finding new therapeutic alternatives. Looking into the medicinal importance of coumarin derivatives, it will be worthwhile to synthesize newer derivatives of coumarins using hybrid approach and screen them for various biological activities. Coumarins belong to the family of lactones having benzopyrone system that can be isolated from plants as well as synthesis. Dietary exposure to benzopyrones is quite significant, as these compounds are found in vegetables, fruits, seeds, nuts, coffee, tea and wine. It is estimated that the average western diet contains approximately 1 gm day of mixed benzopyrones. Many chemical reactions have been established that can be used to synthesize coumarins like Knoevenagel condensation, Perkin, Pechmann, Reformatsky and Wittig reactions. Coumarins have attracted considerable attention of medicinal chemists and have been demonstrated to bear various biological activities. In the development of hybrid molecules through the combination of different pharmacophores in one frame may lead to compounds with interesting biological profiles. Adopting this approach, several research groups have recently reported hybrid molecules by coupling coumarins with different bioactive molecules like: resveratrol, maleimide and alpha-lipoic acid; these studies resulted in new compounds showing antiplatelet, antioxidant and anti-inflammatory activities. Following this paradigm, designed and synthesized a series of compounds that have both coumarin and indole entities in one molecule and evaluated them for antihyperlipidemic activity.

Conclusion

Coumarin and coumarin-related compounds have significant therapeutic potential. They come from a wide variety of natural sources and new coumarin derivatives are being discovered or synthesized on a regular basis. Coumarin is a simple molecule and many of its derivatives have been known for more than a century. However, their vital role in plant and animal biology has not been fully exploited. It is evident from the research described that coumarin compounds are a plentiful source of potential drugs candidate in relation to its safety and efficacy.

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