Review Article CODEN: IJPRNK IMPACT FACTOR: 4.278 ISSN: 2277-8713
Bhinder CK, IJPRBS, 2014; Volume 3(4): 560-585 IJPRBS

INTERNATIONAL JOURNAL OF
PHARMACEUTICAL RESEARCH AND BIO-SCIENCE

REVIEW: 3-SUBSTITUTED COUMARIN AS ANTICANCER AGENT

BHINDER CK, KAUR A, KAUR A
Department of Pharmaceutical Chemistry, ASBASJSM COP, Bela, Punjab.

Accepted Date: 22/07/2014; Published Date: 27/08/2014

Abstract: In recent years, researchers hunt for a novel anticancer agent mainly from plants. Among various phytochemicals, coumarins have attracted considerable interest in the past few years due to their potential health benefits. Coumarin belongs to a group as benzopyrones, which consists of a benzene ring joined to a pyrone nucleus. Coumarins possess a number of biological activities like anticoagulant, antimicrobial, anti-inflammatory, analgesic, antioxidant, anticancer, antiviral, antimalarial etc. The present review describes the Chemistry, sources, synthetic review and pharmacological profile of 3-substituted coumarin. The aim of the present paper is to review the available information on 3-substituted coumarins.

Keywords: Coumarin, Anticancer, Benzo-pyrones, Cytotoxic.

PAPER-QR CODE

Corresponding Author: MS. CHAMANDEEP KAUR BHINDER

Access Online On:

www.ijprbs.com

How to Cite This Article:

Bhinder CK, Kaur A, Kaur A; IJPRBS, 2014; Volume 3(4): 560-585

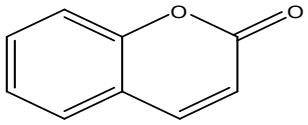
INTRODUCTION

Cancer is the second leading cause of death in Europe and North America. Discovery and development of anticancer agents are the key focus of several pharmaceutical companies as well as non-profit government and non-government organizations, like the National Cancer Institute (NCI) in the United States, the European Organization for Research and Treatment of Cancer (EORTC), and the British Cancer Research Campaign (CRC) [1]. Cancer is a class of disease in which a group of cells display uncontrolled growth, invading adjacent tissues and sometimes metastasis or spreading to other locations in the body via lymph or blood. Every year, at least 200,000 peoples die worldwide from cancer related to their workplace. Currently, most cancer deaths caused by occupational risk factor occur in developed world [2]. A variety of herbs and herbal extracts contain different photochemical and biological activity that can provide therapeutic effects. Several herbs can help to provide some protection against cancer & stimulate the immune system. Coumarin comprises a group of natural compounds found in a variety of plant sources. The synthesis of coumarin is an important reaction in organic chemistry because of their wide application in medicinal chemistry. Coumarin comprises a group of natural compounds found in verity of plant sources [3]. Coumarin is the parent substance of the benzo-α-pyrone group which was first isolated from tonka beans in 1820. The name comes from a French word, coumarou, for the tonka bean. It is the simplest compound of a large class of naturally occurring phenolic substances made of fused benzene and α-pyrone ring [4]. Coumarins are naturally occurring as well as synthetic derivatives, and having widespread applications as HIV protease inhibitors, anticoagulant, spasmolytic and bacteriostatic agents. However, the most widely reported activities for coumarin derivatives are their anti-inflammatory and anti-cancer activities [5]. Coumarin derivatives (CDs) are often discussed because of their diverse biological properties. CDs have attracted considerable attention from organic and medicinal chemists, as they are widely used as fragrances, pharmaceuticals and agrochemicals. Their antioxidant, bacteriostatic and anti-cancer activities make these compounds attractive for investigators for further backbone derivatization and screening as novel therapeutic agents and other foremost topics of this field of research. Some reports have emphasized the efficacies of pure coumarins against Gram-positive and Gram-negative bacteria as well as fungi. In addition CDs have been shown to inhibit cell proliferation in a cancerous cell line. Experimental investigations as well as clinical and epidemiological findings have provided evidence supporting the role of reactive oxygen metabolites or free radicals in the etiology of cancer. Certain aldehydes such as malonyldialdehyde, the end product of lipid peroxidation arising from free radical degeneration of polyunsaturated fatty acids, can cause cross-linking in lipids, proteins and nucleic acids leading to cellular damage. The human body is equipped with certain enzymatic and non-enzymatic antioxidants which can counteract the deleterious actions of free radicals and radical-induced cellular and molecular

damage. Disruption of this sensitive balance between the free radicals and the antioxidants may lead to cellular damage and trigger carcinogenesis. The circumstantial literature concerning CDs cited above inspired us to undertake the present studies on selected CDs and evaluate them as possible antioxidant and anticancer agents. Different physicochemical descriptors have been calculated in silico to discuss the possible structure activity relationship[6].

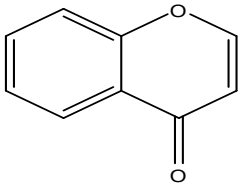
CHEMISTRY OF COUMARIN

The fusion of pyrone ring with benzene nucleus gives rise to a class of heterocyclic compound known as benzopyrone, of which two distinct types are recognized: Benzo-α-pyrone (Figure 1) commonly called as coumarin. Benzo-γ-pyrone (Figure 2) commonly called as Chromon.



Benzo-α-pyrone

(Figure **1)**



Benzo-γ-pyrone

(Figure **2)**

They are differing from each other only in the position of carbonyl group in heterocyclic ring. Several methods were developed for the synthesis of coumarin, such as the Pechmann, Perkin, Knoevegel, Witting and Reformastsky reaction. Among these, the Pechmann reaction has been the most widely used method, since it proceeds from very simple starting materials and gives good yield of variously substituted coumarin. Pechmann reaction consists of condensation of β-ketonic ester with phenol to give coumarin [7].

SYNTHETIC ROUTES FOR COUMARINS

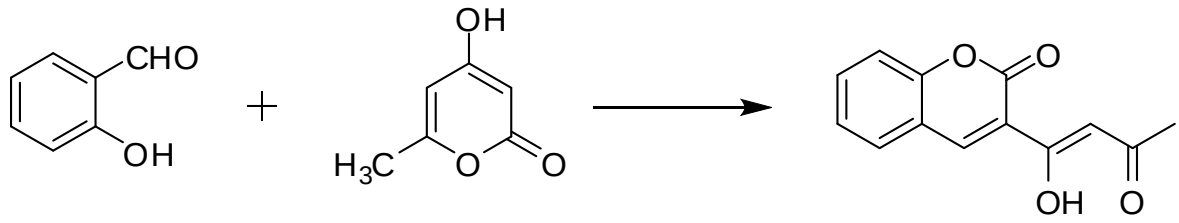
The synthesis of coumarins has been the subject of extensive study over many decades and is usually synthesized by several methods as follow:

i) Knoevenagel Condensation:

Shanmuganathan, S. *et al.*; (2010) reported the catalytic scope of the silica-immobilized piperazine was assessed for the Knoevenagel Condensation between salicylaldehyde and diethyl malonate.

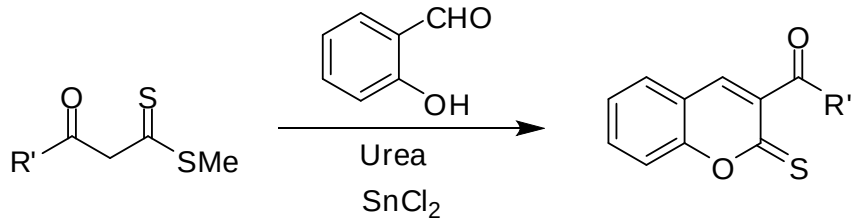
Valizadeh, H. *et al.*; (2010) carried out synthesis of various coumarins by using a task specific ionic liquid (IL, $OPPh_2$), bearing a phosphinite weak Lewis base group in an imidazolium cation, which was found to efficiently catalyze the Knoevenagel Condensation of salicylaldehydes with ethyl cyanoacetate.

Shi, D. *et al.*; (2009) have synthesized novel 3-acetoacetylcoumarin derivatives by reaction between substituted salicylaldehyde and 4-hydroxy-6-methyl-2*H*-pyran-2-one *via* Konevenagel Condensation in good yields using [bmim]Br as a catalyst at 90°C [Scheme 1].



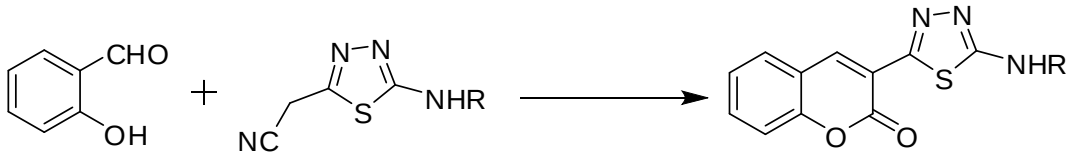
Scheme 1

Singh, O. M. *et al.*; (2009) carried out reaction of substituted salicylaldehyde and oxodithioesters using $SnCl_2$ as a catalyst for the synthesis of 2*H*-chromene-2-thiones in high yields [Scheme 2].



Scheme 2

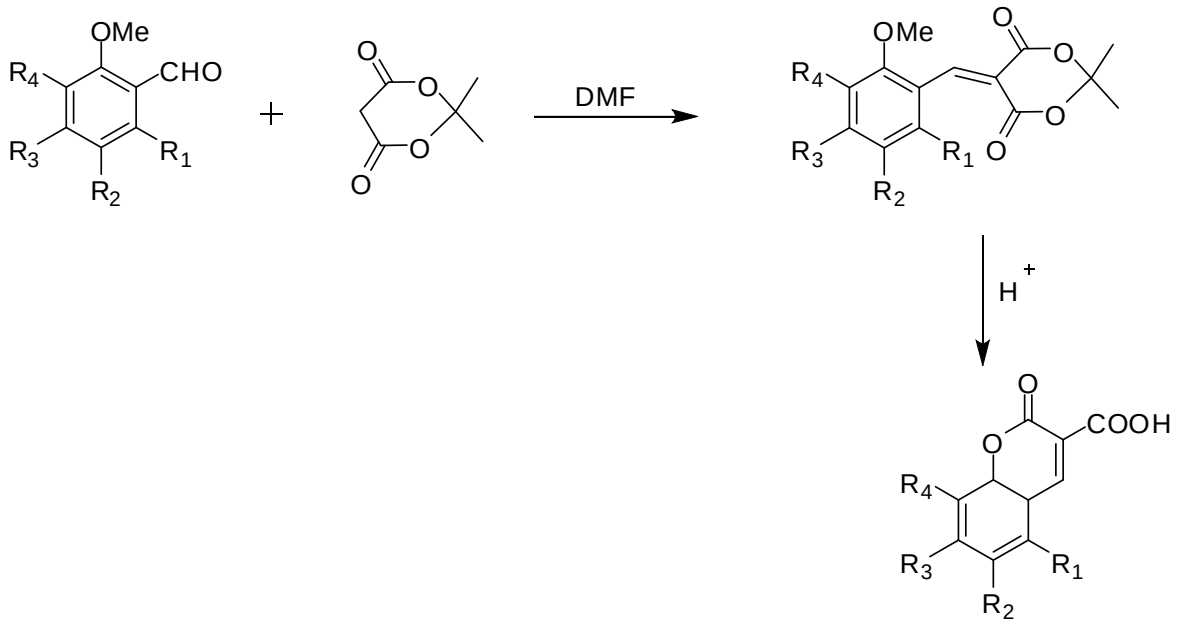
Wardakhan, W. W. *et al.*; (2009) synthesized coumarin moiety containing 1,3,4-thiadiazole derivatives having anti-microbial activity [Scheme 3].



Scheme 3

Armstrong, V. *et al.*; (1988) reported a two step method for the synthesis of coumarin-3-carboxylic acids *via* sulphuric acid catalyzed Knoevenagel Condensation of 2-

methoxybenzaldehyde with Meldrum's acid in dimethylformamide followed by cyclization [Scheme 4].

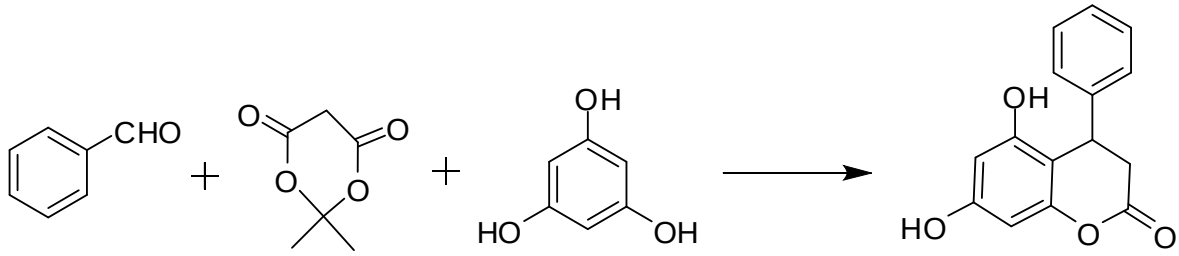


Scheme 4

A solid-phase synthesis has also been reported for condensation of 2-methoxy benzaldehyde with Meldrum's acid in the presence of an excess of ZnO at 80^{o}C followed by cyclization in the presence of cold H_2SO_4. Recently many one-pot methods have been reported involving condensation of *ortho*-hydroxyarylaldehyde and Meldrum's acid in the presence of a solid acid catalyst under microwave irradiation, by grinding a reaction mixture with ammonium acetate and keeping it overnight and by use of piperidinium acetate in ethanol under reflux conditions. Some uncatalyzed routes have also been developed involving heating the reaction mixture in an aqueous medium.

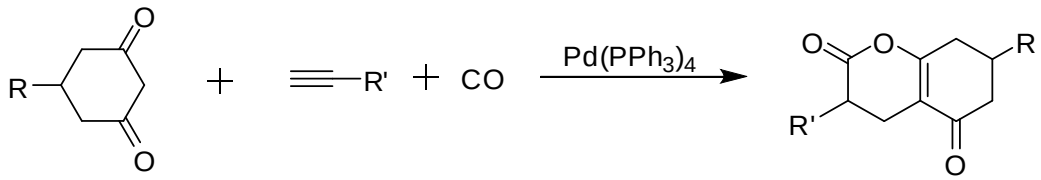
Although large number of reports available on the synthesis of coumarin-3- carboxylic acid, to the best of our knowledge there is no report for the synthesis of coumarin-3-carboxylic acid by Knoevenagel Condensation of Meldrum's acid and salicylaldehyde using basic catalyst.

Nair, V. *et al*.; (1987) synthesized coumarin by using three components, which proceeds *via* a domino Knoevenagel–*hetero*-Michael-type addition sequence [Scheme 5].



Scheme 5

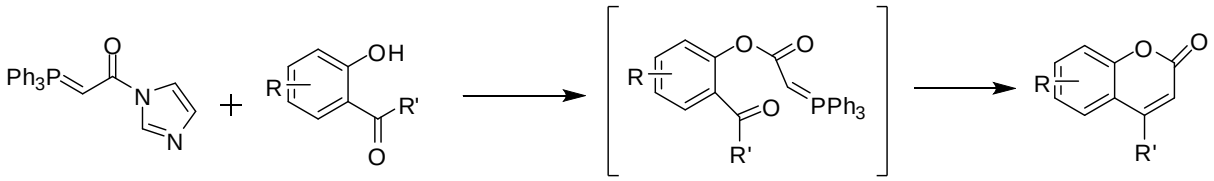
ii) Hua, R. *et al.*; (2010) co-workers synthesized 3,4,7,8-tetrahydro-2*H*-chromene-2,5(6*H*)-dione derivatives with excellent selectivity *via* a [3+2+1] cyclocarbonylative coupling of 1,3-cyclohexanediones, terminal alkynes and CO catalyzed by $Pd(PPh_3)_4$ [Scheme 6].



Scheme 6

iii) Wittig reaction

Upadhyay, P. K. *et al.*; (2009) reported a novel one-pot synthesis of coumarins *via* intramolecular Wittig cyclization from the reaction of phenolic compounds containing *ortho*-carbonyl group and triphenyl(α-carboxymethylene)phosphorane imidazolide [Scheme 7].

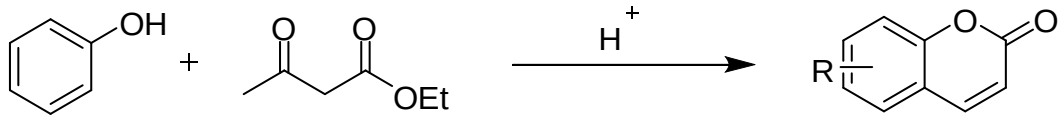


Scheme 7

iv) Von Pechmann reaction:

The Pechmann condensation is one of the most common procedures for the preparation of coumarin and its derivatives. This method involves the reaction between phenol and β-ketoester in the presence of an acidic catalyst.

Maheswara, M. *et al.*; (2006) applied $HClO_4$–SiO_2 under solvent-free conditions to carry out Pechmann condensation [Scheme 8].

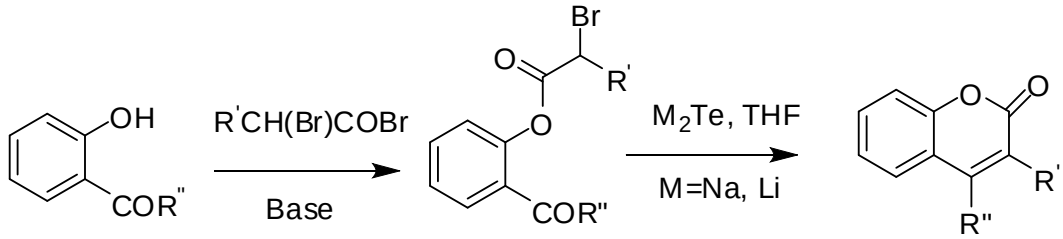


Scheme 8

The reaction can also be catalyzed by different Brønsted and Lewis acids *viz* PPA, $InCl_3$, $ZrCl_4$, $Yb(OTf)_3$, *p*-TsOH, $BiCl_3$, and I_2 or AgOTf .

v) Reformatsky Reaction

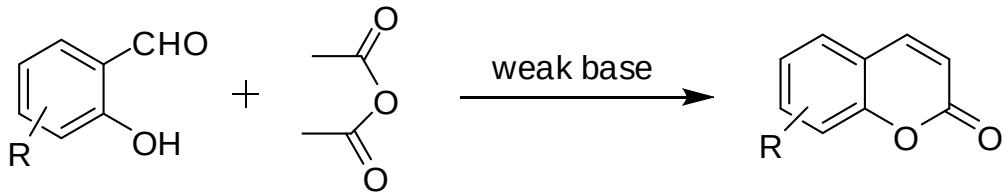
Dittmer, D. C. *et al.*; (2005) have achieved the sodium telluride-triggered cyclization of the bromoacetate of salicylaldehyde to coumarin *via* modified Reformatsky reaction. The cyclization proceeds by formation of the phenolate ester enolate, elemental tellurium and bromide ion. The enolate anion either attacks the *ortho* carbonyl group leading to cyclization or eliminates a phenolate ion to give a ketene [Scheme 9].



Scheme 9

vi) Perkin reaction:

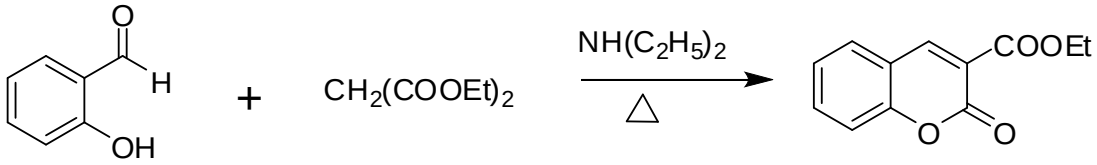
Perkin, W. H. *et al.*; (1868) reported the synthesis of coumarin by the reaction of sodium salt of salicylaldehyde with Ac_2O. The Perkin reaction provides a useful method for the synthesis of α,β-unsaturated aromatic acids and involves the condensation of a carboxylic anhydride with an aromatic aldehyde in presence of a weak base such as sodium or potassium acetate or triethylamine [Scheme 10] [8].



Scheme 10

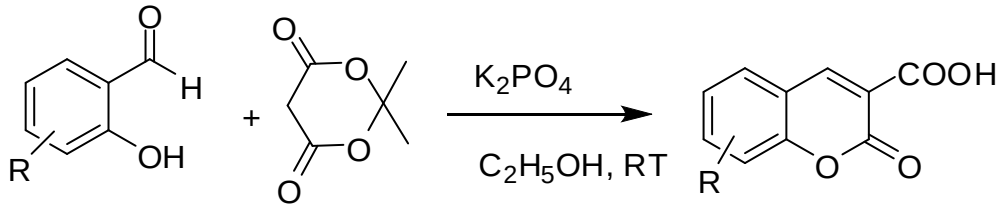
SYNTHETIC REVIEW OF 3-SUBSTITUTED COUMARIN

Li-Mei, S. *et al.*; (2014) reported the synthesis of ethylcoumarin-3-carboxylate by refluxing (2 hr.) salicylic aldehyde, diethyl malonate and diethylamine in anhydrous ethanol. After the mixture was cooled to room temperature, it was poured into 60 ml of ice-water. The resulting crystals were filtered and washed with iced 50% ethanol solution for three times [Scheme 11] [9].



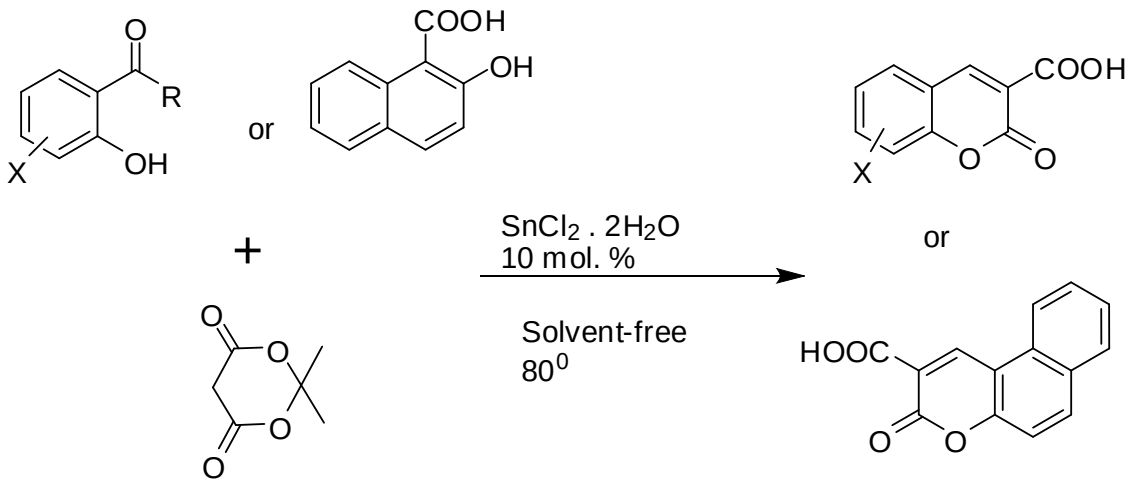
Scheme 11

Undale, K. A. *et al.;* (2012) reported the synthesis of 3-substituted coumarins by using potassium phosphate as a catalyst. The 3-substituted coumarins were prepared by the stirring of salicylaldehyde and meldrums acid using catalytic amount of potassium phosphate at room temperature in ethanol [Scheme 12] [10].



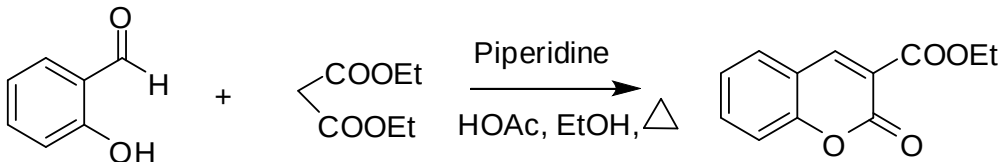
Scheme 12

Karami, B. *et al.*; (2012) reported the synthesis of comarin-3-carboxylic acid in good yield by using catalytic amount of $SnCl_2.H_2O$ under solvent free conditions. It efficiently catalyzes the Knoevengel condensation and intramolecular cyclization of 2-hydrobenzaldehyde or acetophenone with Meldrum's acid [Scheme 13] [11].



Scheme 13

Horning, E. C. *et al.;* (1955) reported the synthesis of 3-substituted coumarins by using salicylaldehyde and ethyl malonate. The 3-substituted coumarins were prepared by condensation of salicylaldehyde with ethyl malonate the presence of piperidine and acetic acid under reflux conditions in ethanol [Scheme 14] [12].



Scheme 14

PHARMACOLOGICAL PROFILE OF 3-SUBSTITUTED COUMARIN

Anticancer Activity

Nasr, T. *et al.*; (2014) reported synthesis of sixteen coumarins bearing hydrazide-hydrazone moiety and evaluated them against human drug-resistant pancreatic carcinoma (Panc-1) cells and drug-sensitive (hepatic carcinoma; Hep-G2 and leukemia; CCRF) cell lines in vitro. The 6-brominated coumarin hydrazide-hydrazone derivatives (Figure 3) were more potent than doxorubicin (DOX) against resistant Panc-1 cells and also showed significant cytotoxicity against all tested cells (IC_{50}: 3.60-6.50 mM) on comparison with all other coumarin hydrazide-hydrazone derivatives [13].

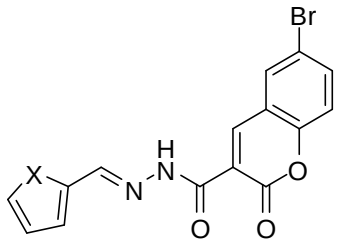


Figure 3: General structure of 6-brominated coumarin hydrazide-hydrazone derivatives

Avin, B. R. V. *et al*.; (2014) reported sequence of coumarin analogs (Figure 4) were obtained by multi step synthesis from hydroxy benzophenones and the *in vitro* antiproliferative effect of the title compounds were tested against Ehrlich Ascites Carcinoma (EAC) and Daltons Lymphoma Ascites (DLA) cell lines. Among the series, compound with bromo group in the benzophenone moiety was endowed with excellent antiproliferative potency with significant IC_{50} value. These compounds should be used as a lead for developing a potent anticancer drug in the near future [14].

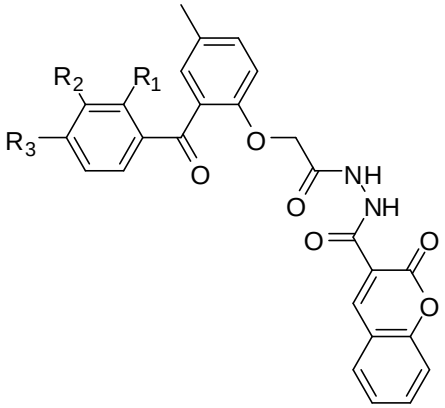


Figure 4: General structure of coumarin conjugated benzophenone analogs.

Wu, Q. X. *et al.*; (2014) reported a series of novel 1-(3-substituted-5-phenyl-4,5-dihydropyrazol-1-yl)-2-thio-ethanone derivatives (Figure 5) as potential telomerase inhibitors. The bioassays demonstrated that compounds occupied high antiproliferative activity against SGC-7901, MGC-803, Bcap-37 and HEPG-2 cell lines. By a modified TRAP assay, some compounds were tested against telomerase, and showed the most potent inhibitory activity with IC_{50} value at 0.92-0.09 mM. The mechanism of antitumor action indicated that the compounds suppress cell proliferation through inducing cell cycle arrest in G_0/G_1 phase [15].

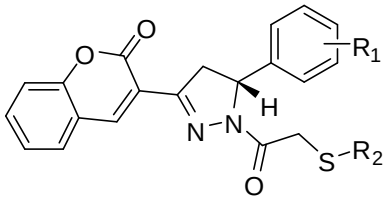


Figure 5: General structure of 1-(3-substituted-5-phenyl-4,5-dihydropyrazol-1-yl)-2-thio-ethanone derivatives

Sashidhara, K. V. *et al.*; (2013) reported the development of new, targeted antibreast cancer drug which can treat both the hormone receptor (positive and negative) breast cancers. The concept of molecular hybridization led to discover a novel class of coumarin-monastrol hybrid (Figure 6), as a novel breast cancer agent, which selectively induce apoptosis in both primary and metastatic breast cancer cell lines [16].

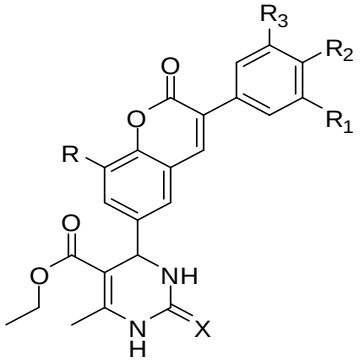


Figure 6: General structure of coumarin-monastrol hybrid

Kim, S. N. *et al.*; (2009) reported a novel synthetic microtubule inhibitor 7-diethylamino-3-(20-benzoxazolyl)-coumarin (DBC, Figure 7). DBC causes destabilization of microtubules, leading to a cell cycle arrest at G_2/M stage. In addition, human cancer cells are more sensitive to DBC (IC_{50} 44.8–475.2 nM) than human normal fibroblast (IC_{50} 7.9 mM), and DBC induces apoptotic cell death of cancer cells. Furthermore, the data showed that DBC is a poor substrate of drug efflux pumps and effective against multidrug resistant (MDR) cancer cells. Taken together, these results described a novel pharmacological property of DBC as a microtubule inhibitor, which may make it an attractive new agent for treatment of MDR cancer [17].

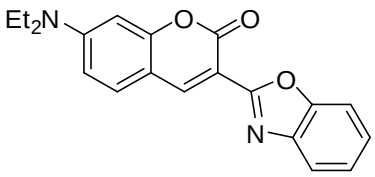


Figure 7: General structure of 7-diethylamino-3-(20-benzoxazolyl)-coumarin (DBC)

Reddy, N. S. *et al.*; (2004) synthesized coumarin 3-(N-aryl) sulphonamides (Figure 8) by Knoevenagel condensation of anilinosulfonylacetic acids with suitable salicylaldehydes and by the reaction of methyl anilinosulfonylacetates with substituted salicylaldehydes in the presence of a catalytic amount of a base. The effect of all the compounds on the growth of human tumor cells in culture were 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 NH2 terminal kinase1) by these compounds as shown in immune complex kinase assay, clearly showed that they activate JNK pathway either by interacting with JNK1 or with one of the upstream kinases in this pathway. Current efforts were focused on identifying the target kinase for these compounds [18].

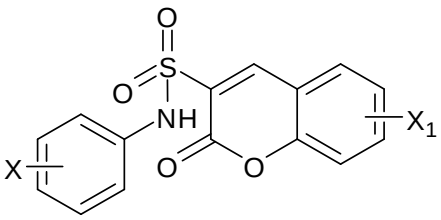


Figure 8: General structure of coumarin-3-(N-aryl)sulphonamides

Budzisz, E. *et al.*; (2003) determined the cytotoxic effects and alkylating activity of a series of 3-[1-(alkylamino)-ethylidene]-chroman-2,4-dione (Figure 9), 2-methoxy-3-[1-(alkylamino)-ethylidene]-2,3-dihydro-2,4-dioxo-2λ5-benzo[e][1,2]oxaphosphinane (Figure 10) and [2-oxo-4-phenyl(alkyl)-2*H*-chromen-3-yl]-phosphonic acids dimethyl ester (Figure 11) on the two leukemia cell lines HL-60 and NALM-6. The tested compounds were much more toxic to NALM-6 cells than to HL-60 cells. IC_{50} data were up to nine times lower for the NALM-6 than for the HL-60 cell lines. As determined in an *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. Using regression analysis QSAR, a relationship between biological activity and the physicochemical properties of the tested compounds were established. Their cytotoxic effect increased with an increase of the hydrophobic parameters in the region of the substituent at the 2-, 3- and 4-positions of the benzopyrone skeleton of these compounds [19].

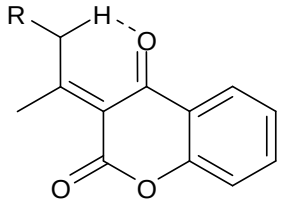


Figure 9: General structure of 3-[1-(alkylamino)-ethylidene]-chroman-2,4-dione

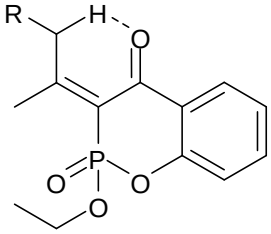


Figure 10: General structure of 2-methoxy-3-[1-(alkylamino)-ethylidene]-2,3-dihydro-2,4-dioxo-2-benzo[e][1,2]oxaphosphinanes

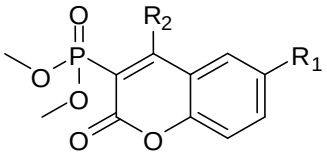


Figure 11: General structure of [2-oxo-4-phenyl(alkyl)-2*H*-chromen-3-yl]-phosphonic acids dimethyl esters

Antimicrobial Activity

Zavrsnik, D. *et al.*; (2011) synthesized a series of new 3-cynnamoyl-4-hydroxycoumarins (Figure 12) by the reaction of nucleophilic addition of 3-acetyl-4-hydroxycoumarin acting on appropriate aromatic aldehydes. The microbiological activity of the synthesized compounds were tested by the diffusion and dilution methods on species of bacteria *Pseudomonas aeruginosa, Echerichia coli, Salmonella typhimurium, Bordatella bronchiseptica, Bacillu subtilis and Staphyloccocus aureus*. All the synthesized compounds showed larger or smaller growth inhibition zones when they came in contact with Gram-positive aerobe bacteria *Bacillus subtilis* and *Staphyloccocus aureus*. The tested 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* [20].

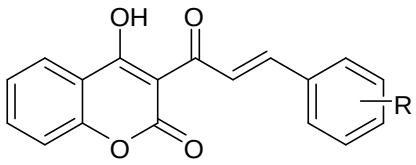


Figure 12: General structure of 3-cynnamoyl-4-hydroxycoumarins

Patel, A. K. *et al.*; (2010) synthesized some 4-aryl-2,6-di(coumarin-3-yl)pyridines by the reaction of 3-coumarinoyl methyl pyridinium salts (Figure 13) 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 synthesized compounds were screened for antimicrobial activity. None of the compounds showed antifungal activity against *A. niger*. Eighteen compounds showed moderate activity against the Gram-positive bacteria *B. subtilis*. The results towards this bacteria revealed that the incorporation of the substituents like $-CH_3$ or $-OCH_3$ 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* [21].

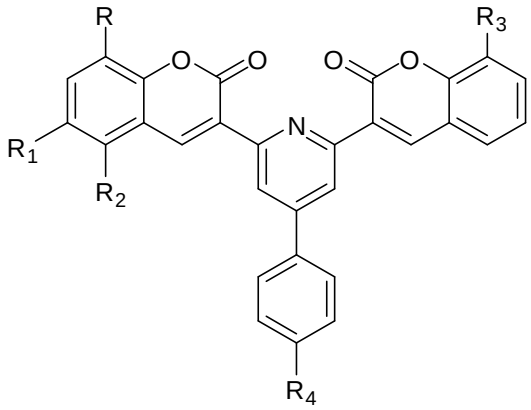


Figure 13: General structure of 4-aryl-2,6-di(coumarin-3-yl)pyridines

Porwal, B. *et al.*; (2009) synthesized 3-coumrinoyl pyridinium bromides (Figure 14) by reaction of methyl and ethyl esters of nicotinic acid with isonicotinic acid and 3-coumarinoyl quinolinium bromides and by reaction of methyl and ethyl esters of nicotinic acid with quinoline. Most of the tested compounds possessed significant antimicrobial activity when compared with that of gentamycin and amoxycillin. The test compounds showing good qualitative antimicrobial property were further screened for their quantitative antimicrobial study by 96-well plate (Two fold dilution technique) using an ELISA Reader. Coumarinoyl pyridinium salts having R = -H & R' = 4-$COOC_2H_5$, R = -Cl & R' = 4-$COOC_2H_5$, R = -H &R' = 3-$COOC_2H_5$ and R = -Cl & R' = 4-$COOCH_3$ were found to be more active than that of other test compounds [22].

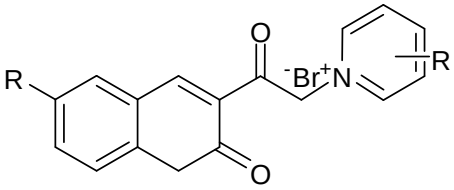


Figure 14: General structure of 3-coumrinoyl pyridinium bromide

Chimenti, F. *et al.*; (2006) prepared five new and three already known N-substituted-2-oxo-2*H*-1-benzopyran-3-carboxamide-(coumarin-3-carboxamides) (Figure 15) in order to develop new anti-*Helicobacter pylori* agents and evaluated them for antibacterial activity. All the synthesized 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 the prepared 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 [23].

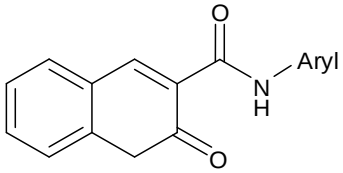


Figure 15: General structure of N-substituted-2-oxo-2*H*-1-benzopyran-3-carboxamides

Mulwad, V. V. *et al.*; (2006) synthesized 4-hydroxy-2-oxo-2*H*-[1]-benzopyran-3-aldehydesemicarbazone and its derivatives by acetylation reaction. 3-formyl-4-hydroxycoumarin and semicarbazide were taken as the starting material. All the compounds were screened for antimicrobial activity and found to exhibit significant activity [24].

Kusanur, R. A. *et al.*; (2005) developed the new 1, 3-dipolar cycloadducts of 3-azidoacetyl coumarins with dimethyl acetylene dicarboxylate (DMAD). They 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 newly synthesized 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 [25].

Mulwad, V. V. *et al.*; (2003) synthesized 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 [26].

Gupta, A. S. *et al.*; (1996) developed one pot synthesis of coumarin derivatives containing sulphanilamide group. They synthesized these derivatives by refluxing 6-H/ 6-bromo/ 6-chloro/ salicylaldehydes with sodium salt of substituted *p*-acetamido benzene sulphonyl glycine 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 by the condensation of 5-bromosalicylaldehyde with sodium salt of substituted N-aryl glycine and sodium salt of substituted phenoxy acetic acid respectively. All the title compounds were screened for *in vitro* antitubercular activity against highly virulent H37Rv strains of *Mycobacterium tuberculosis var hominis* using Youman's liquid method as compared to that of streptomycin and INH [27].

Antioxidant Activity

Singh, O. M. *et al.*; (2010) developed a facile, convenient and high yielding synthesis of a combinatorial library of 3-alkanoyl/aroyl/heteroaroyl-2*H*-chromene-2-thiones (Figure16) by the condensation of easily accessible β-oxodithioesters and salicylaldehyde/ substituted 2-hydroxybenzaldehydes under solvent-free conditions. The assessment of 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. The newly synthesized compounds exhibited profound antioxidant activity. Five selected compounds were able to protect curcumin from the attack of sulfur free radical generated by radiolysis of glutathione (GSH) [28].

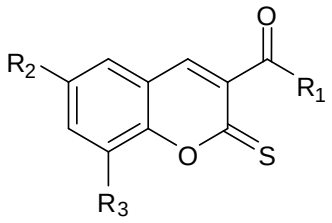


Figure 16: General structure of 3-alkanoyl/aroyl/heteroaroyl-2*H*-chromene-2-thiones

Roussaki, M. *et al.*; (2010) synthesized a series of coumarin analogues (Figure 17) bearing a substituted phenyl ring on position 3 via a novel methodology; through an intermolecular condensation reaction of 2-hydroxyacetophenones and 2-hydroxybenzaldehyde with imidazolylphenylacetic acid active intermediates. *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). Ability of the compounds to inhibit soybean lipoxygenase was also determined as an indication of potential anti-inflammatory activity [29].

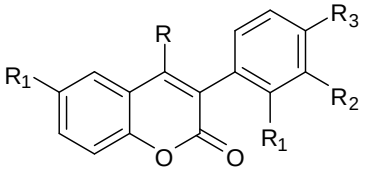


Figure 17: General structure of coumarin analogues

Melagraki, G. *et al.*; (2009) synthesized a series of novel coumarin-3-carboxamides (Figure 18) and their hybrids (Figure 19) with the alpha-lipoic acid. Compounds were evaluated for their *in vitro* antioxidant activity and *in vivo* anti-inflammatory activity. These derivatives were found to possess the mentioned activities and on the basis of results, structure-activity relationships were developed in order to define the structural features required for activity [30].

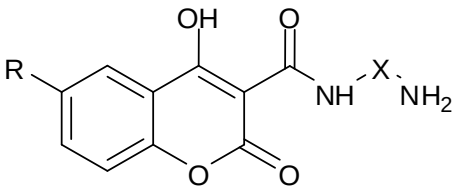


Figure 18: General structure of novel coumarin-3-carboxamide

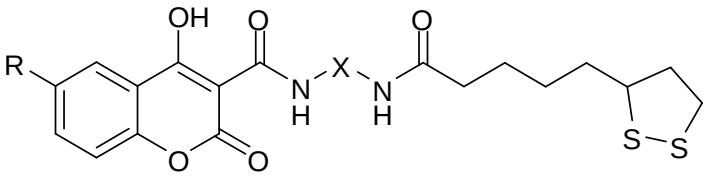


Figure 19: General structure of hybrid of novel coumarin-3-carboxamides with alpha-lipoic acid

Stanchev, S. *et al.*; (2009) synthesized four 4-hydroxycoumarin derivatives: ethyl 2-[(4-hydroxy-2-oxo-2*H*-chromen-3-yl)(4-hydroxyphenyl)methyl]-3-oxobutanoate, 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-oxobutanoate and ethyl 2-[(3,4,5-tri-methoxyphenyl)(4-hydroxy-2-oxo-2*H*-chromen-3-yl)methyl]-3-oxobutanoate. These compounds 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 (10-4mol/L) [31].

Anti-inflammatory and Analgesic Activities

Khode, S. *et al.*; (2009) synthesized a novel series of 5-(substituted)aryl-3-(3-coumarinyl)-1-phenyl-2-pyrazolines (Figure 20) by reacting various substituted 3-aryl-1-(3-coumarinyl)propan-1-ones with phenyl hydrazine in the presence of hot pyridine. Structures of all new synthesized compounds were characterized on the basis of elemental analysis and spectral data (IR, ^{1}H NMR and ^{13}C NMR). The title compounds were screened for *in vivo* anti-inflammatory and analgesic activities at a dose of 200 mg/kg b.w. Among the twelve prepared compounds, compounds having 4-Cl- C_6H_4, 2,4-$(Cl)_2$-C_6H_3, 3-OMe-C_6H_4 and 4-F-C_6H_4 exhibited significant anti-inflammatory activity in model of acute inflammation such as carrageenan-induced rat paw edema while compounds having 4-Cl C_6H_4 and 2,4-$(Cl)_2$-C_6H_3 showed considerable activity in model of chronic inflammation such as adjuvant-induced arthritis and were compared with diclofenac (13.5 mg/kg b.w.) as a standard drug. These compounds were also found to have significant analgesic activity in acetic acid induced writhing model and antipyretic activity in yeast-induced pyrexia model along with minimum ulcerogenic index [32].

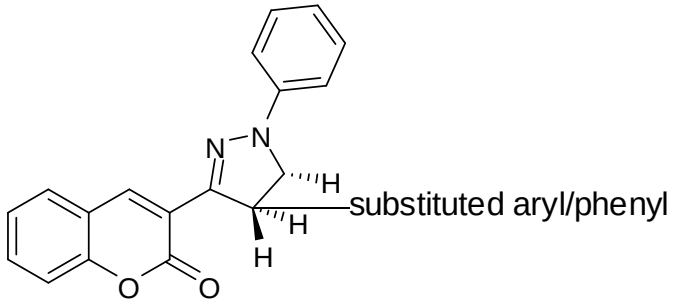


Figure 20: General structure of 5-(substituted) aryl-3-(3-coumarinyl)-1-phenyl-2-pyrazolines

Kalkhambkar, R. G. *et al.*; (2007) synthesized triheterocyclic thiazoles containing coumarin and carbostyril (1-aza coumarin) (Figure 21) by the reaction of the *in situ* generated 4-thioureidomethyl carbostyril and 3-bromoacetyl coumarins. These compounds were tested for their *in vivo* analgesic and anti-inflammatory activities. Qualitative SAR studies indicated that the 7-chloro substitution in carbostyril and 6, 8-dibromo substitution in the coumarin ring enhanced anti-inflammatory activity. These compounds were also found to provide significant protection against acetic acid writhing in animal models [33].

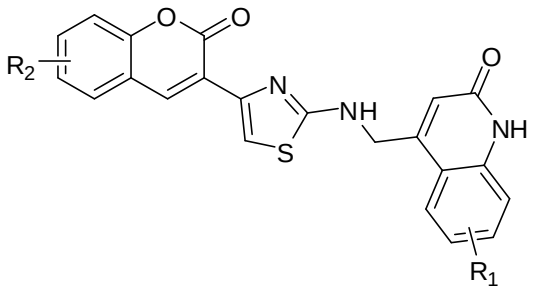


Figure 21: General structure of triheterocyclic thiazoles containing coumarin and carbostyril

Bylov, I. E. *et al.*; (1999) synthesized a series of N-aryl substituted 2-imino-2*H*-1-benzopyran-3-carboxamides (Figure 22) and 2-oxo-2*H*-1-benzopyran-3-carboxamides (Figure 23) and evaluated them for anti-inflammatory activity in carrageenan-induced rat paw edema and in acetic acid-induced peritonitis tests in albino rats. The results were found to be comparable with piroxicam taken as the reference drug. In the consideration of the efficacy of the compounds in these assays, 2-imino/oxo-2*H*-1-benzopyran-3-carboxamides were further studied at graded doses for their acute toxicity (ALD50) in albino mice and were found to be essentially non-toxic at the highest dose tested [34].

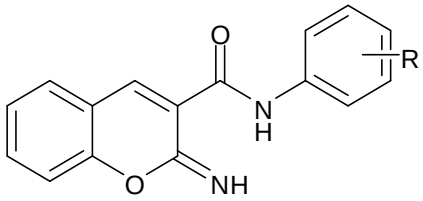


Figure 22: General structure of N-aryl substituted 2-imino-2*H*-1-benzopyran-3-carboamides

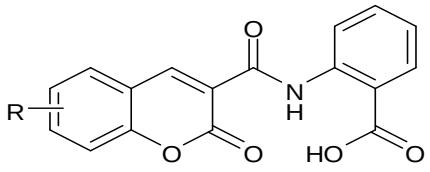


Figure 23: General structure of N-aryl substituted 2-oxo-2*H*-1-benzopyran-3-carboamides

Analgesic and Ulcerogenic Activities

Gupta, J. K. *et al.*; (2010) synthesized a novel series of 3-(2-amino-6-pyrimidin-4-yl)-6-bromo-2*H*-chromen-2-one (Figure 24) from 3-acetyl-6-bromo-2*H*-chromen-2-one. The synthesized 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 using acetic acid induced writhing model. 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 [35].

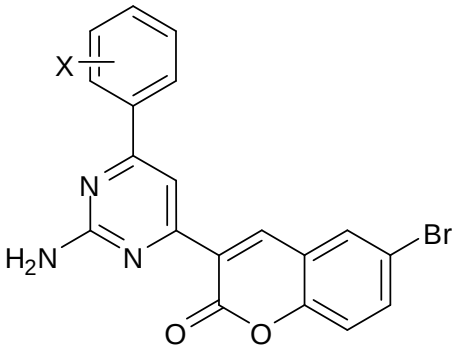


Figure 24: General structure of 3-(2-amino-6-pyrimidin-4-yl)-6-bromo-2*H*-chromen-2-one

Anticonvulsant Activity

Siddiqui, N. *et al.*; (2009) prepared several heteroaryl semicarbazones (Figure 25) by the reaction of heteroaryl hydrazine carboxamide with aryl aldehydes or ketones. Compounds were tested for anticonvulsant activity utilizing pentylenetetrazole induced seizure (PTZ) and maximal electroshock seizure (MES) tests at 30, 100 and 300 mg/kg dose levels. Neurotoxicity of the compounds was also assessed at the same dose levels. Three compounds having 3,4-$Cl.C_6H_3$, 2-$OCH_3.C_6H_4$ and 4-$Br.C_6H_4$ exhibited significant anticonvulsant activity at 30 mg/kg dose level comparable to the standard drug-phenytoin [36].

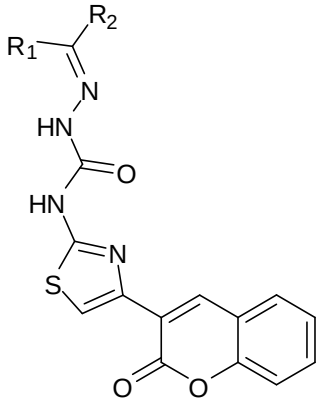


Figure 25: General structure of heteroaryl semicarbazones

Antihyperlipidemic Activity

In the design of new drugs, 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.

Sashidhara, K. V. *et al.*; (2010) designed and synthesized a series of novel compounds that have both coumarin and indole entities in one molecule and evaluated them for antihyperlipidemic activity. They synthesized a series of novel coumarin bisindole heterocycles (Figure 26) 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 which was subjected to same series of above mentioned transformations resulting in another set of coumarin bisindole hybrids. The synthesized compounds were evaluated for antihyperlipidemic activity in hyperlipidemic hamster model. In both the series of compounds, as far as coumarin pharmacophore is considered, it 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, cursory look at the lower indole pharmacophore highlighted that the unsubstituted indoles have good activity profile compared to substituted indoles. Among twelve compounds tested, one compound having R = $-C_2H_5$ and $R_1 = R_2 = -H$ showed potent activity and was found to decrease the plasma triglyceride levels (TG) by 55%, total cholesterol (TC) by 20%, accompanied by an increase in HDL-C/TC ratio by 42% in hyperlipidemic rats to a greater degree than some of the reference statins [37].

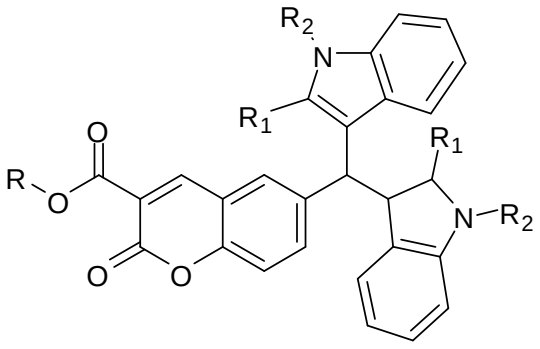


Figure 26: Structure of synthesized hybrid of coumarin bisindole heterocycles

Tyrosinase Inhibitor Activity

Fais, A. *et al.*; (2009) resynthesized coumarin-resveratrol hybrids (Figure 27) 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 to investigate the structure-activity relationships. Tyrosinase activity assays were performed with L-DOPA as substrate with slight modifications and activity of mushroom tyrosinase was determined by spectrophotometric technique. IC_{50} values of these compounds were measured. The results showed that these compounds exhibited tyrosinase inhibitory activity. 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 [38].

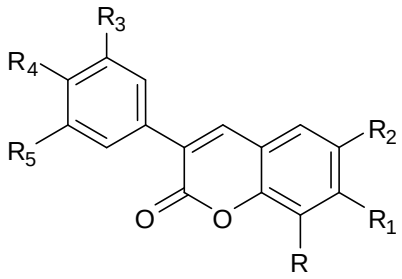


Figure 27: General structure of resynthesiszed coumarin-reseveratrol hybrid

Anti-parkinsonism Activity

Matos, M. J. *et al.*; (2009) synthesized a new series of 8-bromo-6-methyl-3-phenylcoumarin derivatives (Figure 28) without substituents and with different number of methoxy substituent in the 3-phenyl ring. The substituent in this new 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 prepared 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_{50} 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 (IC_{50} = 3.23±0.49nM). 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) [39].

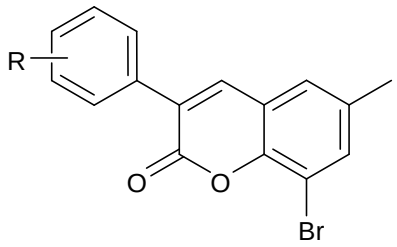


Figure 28: General structure of new series of 8-bromo-6-methyl-3-phenylcoumarin derivatives

CONCLUSION

In the present review, we have attempted to congregate the chemistry, sources, synthetic review and pharmacological review on 3-substituted coumarin. It comprises a vast array of applications such as anticancer, antioxidant, antimicrobial, anti-inflammatory, analgesic, ulcerogenic, anticonvulsant, antihyperlipidemic, tyrosinase inhibitor activity and anti-parkinsonism activities. Modifications on the 3-position of coumarin nucleus have resulted in a large number of compounds, having diverse pharmacological profile; mostly used for the synthesis of compounds having anticancer activity.

REFERENCES

1. Narag AS, Desai DS: Anticancer Drug Development Unique Aspects of Pharmaceutical Development. Pharmaceutical Perspectives of Cancer Therapeutics 2009; DOI 10.1007/978-1-4419-0131-62.

2. Anand P, Kunnumakkara AB: Cancer is a preventable disease that requires major lifestyle change. Pharm. Res. 2008; 25: 2097-2116.

3. Kostova I: Synthesis and natural coumarins as cytotoxic agents. Curr. Med. Chem. 2005; 5: 29-46.

4. Setha SM, Shah NM: The chemistry of coumarins. Chem. Rev. 1945; 36: 1-62.

5. Sandhya B, Vinod Mathew, Lohitha P, Ashwini T, Shravani A: Synthesis, characterization and pharmacological activities of coumarin derivatives. IJCPS. 2010; 1: 16-25.

6. Gacche RN, Jadhav SG: Antioxidant Activities and Cytotoxicity of Selected Coumarin Derivatives: Preliminary Results of a Structure Activity Relationship Study Using Computational Tools. J. Exp. Clin. Med. 2012; 3: 165-169.

7. Shah RC: New synthetical methods in coumarins chemistry. Symposium 1938; 26-27.

8. http://shodhganga.inflibnet.ac.in/bitstream/10603/4343/9/09_chapter%203.pdf

9. Lei-Mei S, Jian-Hua G: Synthesis, crystal structure & photoluminescence of ethyl coumarin-3-carboxylate derivatives. Chinese J. Struct. Chem. 2014; 33, 1: 57-64.

10. Undale AK, Gaikwad DS, Shaikh TS, Desai UV, Pore DM: Potassium phosphate catalyzed efficient synthesis of 3-carboxycoumarin. Indian J. Chem. 2012; 51b: 1039-1042.

11. Karami B, Farahi M, Khodabakhshi S: Rapid synthesis of novel & known coumarin-3-carboxylic acids using stannous chloride dehydrate under solvent free conditions. Hevetica Chimica Acta 2012; 95, 3: 455-460.

12. Horning EC, Horning MG, Dimmig DA: 3-carbethoxycoumarin. Organic Syntheses 1955; 3: 165.

13. Nasr T, Bondock S, Youns M: Anticancer activity of new coumarin substituted hydrazide-hydrazone derivatives. European Journal of Medicinal Chemistry 2014; 76: 539-548.

14. Avin BRV, Thirusangu P, Ranganatha VL, Firdouse A, Prabhakar BT, Khanum SA: Synthesis and tumor inhibitory activity of novel coumarin analogs targeting angiogenesis and apoptosis. European Journal of Medicinal Chemistry 2014; 75: 211-221.

15. Wu XQ, Huang C, Jia YM, Song BA, Li J, Liu XH: Novel coumarin-dihydropyrazole thio-ethanone derivatives: Design, synthesis and anticancer activity. European Journal of Medicinal Chemistry 2014; 74: 717-725.

16. Sashidhara KV, Avula SR, Sharma K, Palnati GR, Bathula SR: Discovery of coumarin-monastrol hybrid as potential antibreast tumor-specific agent. European Journal of Medicinal Chemistry 2013; 60: 120-127.

17. Kim SN, Kim NH, Park YS, Kim H, Lee S, Wang Q, Kim YK: 7-Diethylamino-3(20-benzoxazolyl)-coumarin is a novel microtubule inhibitor with antimitotic activity in multidrug resistant cancer cells. Biochemical Pharmacology 2009; 77: 1773–1779.

18. Reddy NS, Mallireddigari MR, Cosenza S, Gumireddy K, Bell SC: Synthesis of new coumarin 3-(N-aryl) sulphonamides and their anticancer activity. Bioorg. Med. Chem. Lett. 2004; 14: 4093-4097.

19. Budzisz E, Brzezinska E, Krajewska U, Rozalski M: Cytotoxic effects, alkylating properties and molecular modelling of coumarin derivatives and their phosphonic analogues. Eur. J. Med. Chem. 2003; 38: 597-603.

20. Zavrsnik D, Halilovic SS, Softic D: Synthesis, structure and antibacterial activity of 3-substituted derivatives of 4-hydroxycoumarin. Periodicum Biologorum 2011; 113, 1: 93-97.

21. Patel AK, Patel NH, Patel MA, Brahmbhatt DI: Synthesis, characterization and antimicrobial activity of some 4-aryl-2,6-di(coumarin-3-yl)pyridines. ARKIVOC. 2010; 11: 28-38.

22. Porwal B, Jayashree BS, Attimarad M: Synthesis of some new 3-coumarinoyl pyridinium and quinolinium bromides for their antimicrobial activity. J. Basic Clin. Pharm. 2009; 1, 1: 29-32.

23. Chimenti F, Bizzarri B, Bolasco A, Secci D, Chimenti P, Carradori S: Synthesis and in vitro selective anti-Helicobacter pylori activity of N-substituted-2-oxo-2H-1-benzopyran-3-carboxamides. Eur. J. Med. Chem. 2006; 41: 208-212.

24. Mulwad VV, Chaskar A: Synthesis and antibacterial activity of new oxadiazoleo[1,3,5]-triazine, 1,2,4-triazolo and thiadiazolo-1,3,4-oxadiazole derivatives. Indian J. Chem. Section B 2006; 45: 1710-1715.

25. Kusanur RA, Kulkarni MV: New 1,3-dipolar cycloadducts of 3-azidoacetylcoumarins with DMAD and their antimicrobial activity. Indian J. Chem. Section B 2005; 44: 591-594.

26. Mulwad VV, Pawar RB: Synthesis of some antibacterial compounds from 4-hydroxycoumarin. Indian J. Chem. Section B 2003; 42: 2091-2096.

27. Batra N, Batra S, Pareek A, Nagori BP: Diverse Pharmacological Activities of 3-Substituted Coumarins: A Review. International Research Journal of Pharmacy 2012; 3: 24-29.

28. Singh OM, Devi NS, Thokchom DS, Sharma GJ: Novel 3-alkanoyl/aroyl/heteroaroyl-2H-chromene-2-thiones: Synthesis and evaluation of their antioxidant activities. Eur. J. Med. Chem. 2010; 45: 2250-2257.

29. Roussaki M, Kontogiorgis CA, Litina DH, Hamilakis S, Detsi A: A Novel synthesis of 3-aryl coumarins and evaluation of their antioxidant and lipoxygenase inhibitory activity. Bioorg. Med. Chem. Lett. 2010; 20: 3889-3892.

30. Melagraki G, Afantitis A, Markopoulou OI, Detsi A, Koufaki M, Kontogiorgis C: Synthesis and evaluation of the antioxidant and anti- inflammatory activity of novel coumarin-3-aminoamides and their alpha-lipoic acid adducts. Eur. J. Med. Chem. 2009; 44: 3020-3026.

31. Stanchev S, Hadjimitova V, Traykov T, Boyanov T, Manolov I: Investigation of the antioxidant properties of some new 4- hydroxycoumarin derivatives. Eur. J. Med. Chem. 2009; 44: 3077-3082.

32. Khode S, Maddi V, Aragade P, Palkar M, Ronad P K, Mamledesai S: Synthesis and pharmacological evaluation of a novel series of 5-(substituted)aryl-3-(3-coumarinyl)-1-phenyl-2-pyrazolines as novel anti-inflammatory and analgesic agents. Eur. J. Med.Chem. 2009; 44: 1682-1688.

33. Kalkhambkar RG, Kulkarni GM, Shivkumar H, Rao RN: Synthesis of novel triheterocyclic thiazoles as anti-inflammatory and analgesic agents. Eur. J. Med. Chem. 2007; 42: 1272-1276.

34. Bylov IE, Vasylyev MV, Bilokin YV: Synthesis and anti-inflammatory activity of N-substituted-2-oxo-2H-1-benzopyran-3-carboxamide and their 2-iminoanalogues. Eur. J. Med. Chem. 1999; 34: 997-1001.

35. Gupta JK, Sharma PK, Dudhe R, Chaudhary A, Verma PK: Synthesis, analgesic and ulcerogenic activity of novel pyrimidine derivative of coumarin moiety. Analele UniversităŃii din Bucuresti- Chimie (serienouă) 2010; 19: 09-21.

36. Siddiqui N, Arshad MF, Khan SA: Synthesis of some new coumarin incorporated thiazolyl semicarbazones as anticonvulsants. Acta Poloniae Pharmaceutica-Drug Research 2009; 66, 2:161-167.

37. Sashidhara KV, Kumar A, Kumar M, Srivastava A, Puri A: Synthesis and antihyperlipidemic activity of novel coumarin bisindole derivatives. Bioorg. Medicinal Chem. Lett. 2010; 20: 6504-6507.

38. Fais A, Corda M, Era B, Fadda MB, Matos MJ, Quezada E: Tyrosinase Inhibitor Activity of Coumarin-Resveratrol Hybrids. Molecules 2009; 14: 2514-2520.

39. Matos MJ, Vina D, Janeiro P, Orallo F, Uriarte E, Santana L: Synthesis and pharmacological evaluation of coumarins as new scaffold on the Parkinson´s disease. 13th International Electronic Conference on Synthetic Organic Chemistry (ECSOC-13) 1-30 November 2009. Availablefrom: http://www.usc.es/congresos/ecsoc/13/