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Review Article

DIVERSE PHARMACOLOGICAL ACTIVITIES OF 3-SUBSTITUTED COUMARINS: A REVIEW

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ABSTRACT
Coumarins belong to the family of lactones having benzopyrone system that can be isolated from plants as well as total synthesis can be carried out in the laboratory. To date, 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 pharmacologists in recent years as they have been demonstrated to bear many pharmacological activities like anti-inflammatory & analgesic, antimicrobial, antioxidant, anticancer, analgesic & ulcerogenic, anticonvulsant, antihyperlipidemic, tyrosinase inhibitor and anti-parkinsonism activity. The aim of the present paper is to review the available information on 3-substituted coumarins.
KEYWORDS: Coumarins, benzopyrone, anti-inflammatory, antimicrobial, antioxidant, anticancer, anticonvulsant

INTRODUCTION

Over the years, coumarins have been established as the well-known naturally occurring oxygen-heterocyclic compounds isolated from various plants. They belong to the family of lactones having 1-benzopyran-2-one system (Figure 1) that can be isolated from plants as well as total synthesis can be carried out in the laboratory[1]. Many coumarins have been isolated from the plant parts and reported to possess many pharmacological activities like anti-inflammatory & antipyretic[2], antioxidant[3,4], bronchodilator[5], vasodilator[6], antiamoebic[7], antibacterial[8] and antifungal[9] activities.

The 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 as additives in food, perfumes, cosmetics, pharmaceuticals, optical brighteners, dispersed fluorescent and laser dyes. Thus the synthesis of this heterocyclic nucleus is of much interest[10]. Coumarins were first synthesized via the Perkin reaction in 1868, and many simple coumarins are still prepared through this method. In the early 1900s, the Knoevenagel reaction emerged as an important synthetic method to synthesize coumarin derivatives with carboxylic acid at the 3-position. To date, many other synthetic methods for coumarins have been reported, including the Pechmann, Reformatsky and Wittig reactions[11].

Furthermore, 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.

PHARMACOLOGICAL ACTIVITIES

Anti-inflammatory and Analgesic Activity

Khode S *et al.* synthesized a novel series of 5-(substituted)aryl-3-(3 coumarinyl)-1-phenyl-2-pyrazolines (Figure 2) by reacting various substituted 3-aryl-1-(3-coumarinyl)propan-1-ones with phenylhydrazine in the presence of hot pyridine. Structures of all new synthesized compounds were characterized on the basis of elemental analysis and spectral data (IR, 1H 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[12].

Kalkhambkar RG *et al.* synthesized triheterocyclic thiazoles containing coumarin and carbostyril (1-aza coumarin) (Figure 3) 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[13].

Bylov IE *et al.* synthesized a series of N-aryl substituted 2-imino-2*H*-1-benzopyran-3-carboxamides (Figure 4) and 2-oxo-2*H*-1-benzopyran-3-carboxamides (Figure 5) 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 (ALD_{50}) in albino mice and were found to be essentially non-toxic at the highest dose tested[14].

Antimicrobial Activity

Zavrsnik D *et al.* synthesized a series of new 3-cynnamoyl-4-hydroxycoumarins (Figure 6) by the reaction of nucleophilic addition of 3-acetyl-4-hydroxycoumarin acting on appropriate aromatic aldehydes. The microbiological activity of the synthesized compounds was tested by the diffusion and dilution methods on species of bacteria *Pseudomonas aeruginosa*, *Echerichia coli*, *Salmonella typhimurium*, *Bordatella bronchiseptica*, *Bacillus 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*[15].

Ajani OO *et al.* synthesized 3-[3-(s-aryl and s-heteroaromatic)acryloyl]-2*H*-chromen-2-one derivatives (Figure 7) by exploration of potential utilization of microwaves as an energy source. This synthesis was carried out by condensation of 3-acetylcoumarin with aromatic and heteroaromatic aldehydes to afford the corresponding aromatic chalcones and heteroaromatic chalcones. All the synthesized compounds were screened for antibacterial activity by *in vitro* agar well diffusion technique against five gram positive bacteria (*Bacillus anthracis*, *B. Stearothermophilus*, *B. Subtilis*, *B. cereus* & *Staphylococcus aureus*) and five gram negative bacteria (*Escherichia coli*, *Klebsiella pneumonia*, *Pseudomonas 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 value of 7.8 μg/mL[1].

Patel AK *et al.* synthesized some 4-aryl-2,6-di(coumarin-3-yl)pyridines by the reaction of 3-coumarinoyl methyl pyridinium salts (Figure 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 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*[16].

Porwal B *et al.* synthesized 3-coumrinoyl pyridinium bromides (Figure 9) 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 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[17].

Chimenti F *et al.* prepared five new and three already known N-substituted-2-oxo-2*H*-1-benzopyran-3-carboxamides (coumarin-3-carboxamides) (Figure 10) 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[18].

Mulwad VV *et al.* synthesized 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. 3-Formyl-2*H*-[1]-4-hydroxy-2-oxo-benzopyrans and N-benzoyl glycine were taken as the starting material. All the compounds were screened for antimicrobial activity and found to exhibit significant activity[19].

Kusanur RA *et al.* developed the new 1,3-dipolar cycloadducts of 3-azidoacetylcoumarins 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[20].

Mulwad VV *et al.* 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[21].

Gupta AS *et al.* 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*-acetamidobenzenesulphonylglycine 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-aryl substituted)-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 title compounds were screened for *in vitro* antitubercular activity against highly virulent $H_{37}Rv$ strains of mycobacterium tuberculosis var hominis using Youman's liquid method as compared to that of streptomycin and INH[22,23].

Antioxidant Activity

Singh OM *et al.* developed a facile, convenient and high yielding synthesis of a combinatorial library of 3-alkanoyl/aroyl/heteroaroyl-2*H*-chromene-2-thiones (Figure 11) 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)[24].

Roussaki M *et al.* synthesized a series of coumarin analogues (Figure 12) 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[25].

Melagraki G *et al.* synthesized a series of novel coumarin-3-carboxamides (Figure 13) and their hybrids (Figure 14) 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[26].

Stanchev S *et al.* 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-trimethoxyphenyl)(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^{-4}mol/L)[27].

Anticancer Activity

Budzisz E *et al.* determined the cytotoxic effects and alkylating activity of a series of 3-[1-(alkylamino)-ethylidene]-chroman-2,4-dione (Figure 15), 2-methoxy-3-[1-(alkylamino)-ethylidene]-2,3-dihydro-2,4-dioxo-2λ^5-benzo[e][1,2] oxaphosphinane (Figure 16) and [2-oxo-4-phenyl(alkyl)-2*H*-chromen-3-yl]-phosphonic acids dimethyl ester (Figure 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_{50} data are 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 test compounds was established. Their 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[28].

Reddy NS *et al.* synthesized coumarin 3-(N-aryl) sulphonamides (Figure 18) 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 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_2 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[29].

Analgesic and Ulcerogenic Activity

Gupta JK *et al.* synthesized a novel series of 3-(2-amino-6-pyrimidin-4-yl)-6-bromo-2*H*-chromen-2-one (Figure 19) 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[30].

Anticonvulsant Activity

Siddiqui N *et al.* prepared several heteroaryl semicarbazones (Figure 20) 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[31].

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. Following this paradigm, Sashidhara KV *et al.* 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 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 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[32].

Tyrosinase Inhibitor Activity

Fais A *et al.* resynthesized coumarin-resveratrol hybrids (Figure 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 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[33].

Anti-parkinsonism Activity

Matos MJ *et al.* synthesized a new series of 8-bromo-6-methyl-3-phenylcoumarin derivatives (Figure 23) 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)[34].

CONCLUSION

The synthesis and biological activities of coumarin derivatives have been focused recently due to potential activities exhibited by them. Modifications on the 3-position of coumarin nucleus have resulted in a large number of compounds having diverse pharmacological activities. Some of the ascertained properties of 3-substituted coumarins are fairly 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.

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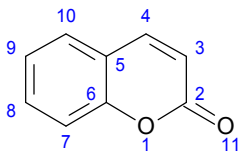

Figure 1: Molecular scaffold of 1-benzopyran-2-one (coumarin nucleus)

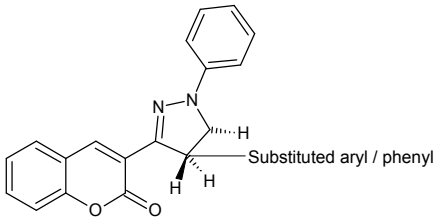

Figure 2: General structure of 5-(substituted) aryl-3-(3 coumarinyl)-1-phenyl-2-pyrazolines

(Aryl/ phenyl = -C_6H_5, 4-OMe-C_6H_4, -CH=CH-C_6H_5, 4-Cl-C_6H_4, 2,4-$(Cl)_2$-C_6H_3, 4-NMe_2-C_6H_4, 3-NO_2-C_6H_4, 4Me-C_6H_4, 3-OMe-C_6H_4, 4-F-C_6H_4, 2-NO_2-C_6H_4, 4-OH-C_6H_4)

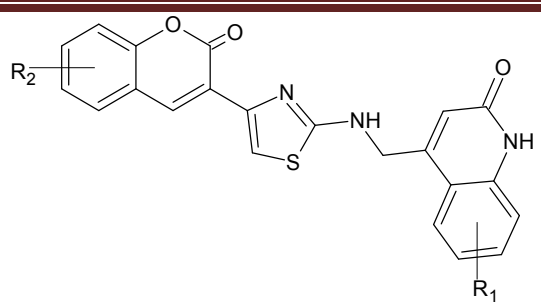

Figure 3: General structure of triheterocyclic thiazoles containing coumarin and carbostyril

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

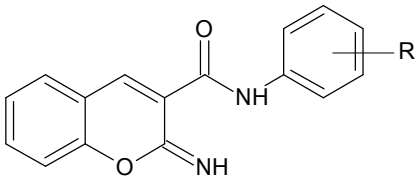

Figure 4: General structure of N-aryl substituted 2-imino-2*H*-1-benzopyran-3-carboxamides

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

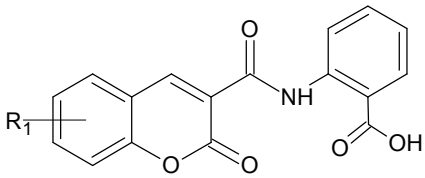

Figure 5: General structure of N-aryl substituted 2-oxo-2*H*-1-benzopyran-3-carboxamides

(R = -H, 5-OCH_3, 3-OCH_3, 5-NO_2, 5-Cl, 3-allyl)

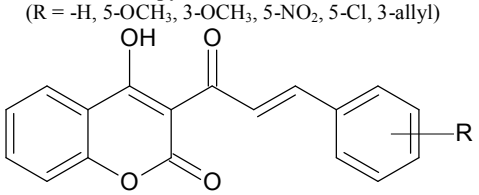

Figure 6: General structure of 3-cynnamoyl-4-hydroxycoumarins

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

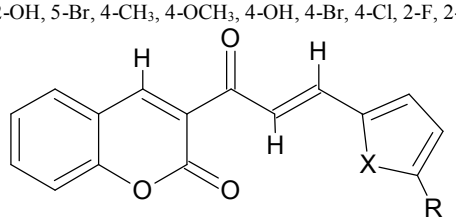

Figure 7: General structure of 3-[3-(s-aryl and s-heteroaromatic)acryloyl]-2*H*-chromen-2-one derivatives

(X = -O-, -NH; R = -H, -NO_2, -Cl, -CH_3, -C_2H_5)

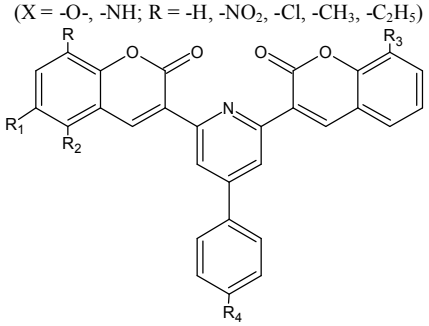

Figure 8: General structure of 4-aryl-2,6-di(coumarin-3-yl)pyridines

(R = -H, -OCH_3, R_1 = R_2 = -H/ Benzo, R_3 = -H, -OCH_3, R_4 = -H, -OCH_3)

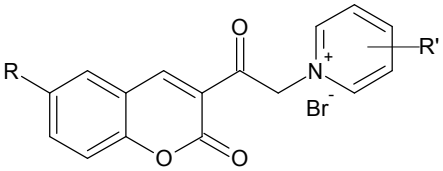

Figure 9: General structure of 3-coumrinoyl pyridinium bromides

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

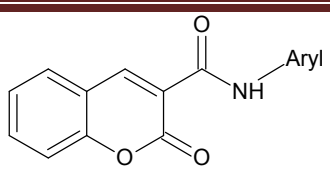

Figure 10: General structure of N-substituted-2-oxo-2H-1-benzopyran-3-carboxamides

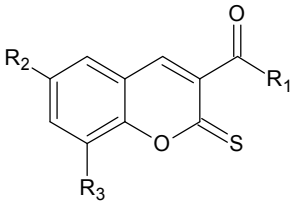

Figure 11: General structure of 3-alkanoyl/aroyl/heteroaroyl- 2H-chromene-2-thiones

(R_1 = substituted phenyls/ heterocyclic nuclei, R_2 = -H, -Br, R_3 = -H, -OCH_3)

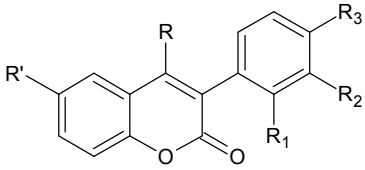

Figure 12: General structure of coumarin analogues

(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)

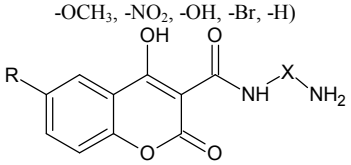

Figure 13: General structure of novel coumarin-3-carboxamides

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

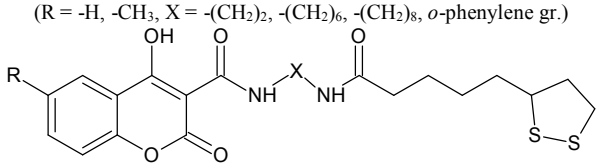

Figure 14: General structure of hybrid of novel coumarin-3-carboxamides with alpha-lipoic acid

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

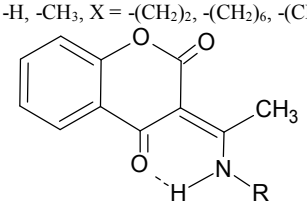

Figure 15: General structure of 3-[1-(alkylamino)-ethylidene]-chroman-2,4-dione

(R = -CH_3, -CH_2CH_2OH, -CH_2Ph)

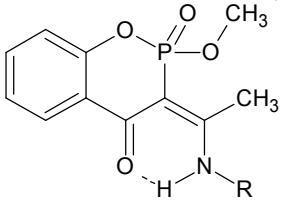

Figure 16: General structure of 2-methoxy-3-[1-(alkylamino)-ethylidene]-2,3-dihydro-2,4-dioxo-2λ^5-benzo[e][1,2] oxaphosphinanes

(R = -CH_3, -CH_2CH_2OH, -CH_2Ph)

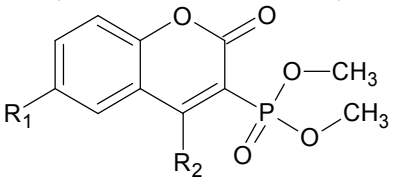

Figure 17: General structure of [2-oxo-4-phenyl(alkyl)-2H-chromen-3-yl]-phosphonic acids dimethyl esters

(R = -CH_3, -CH_2CH_2OH, -CH_2Ph)

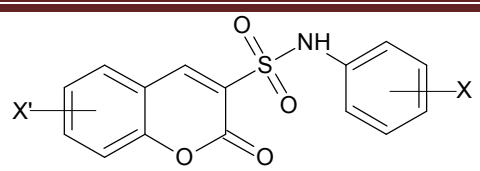

Figure 18: General structure of coumarin 3-(N-aryl) sulphonamides

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

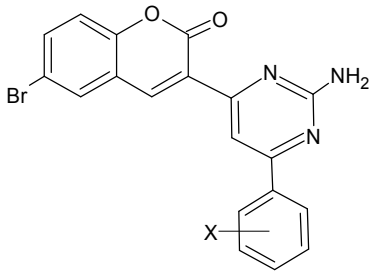

Figure 19: General structure of 3-(2-amino-6-pyrimidin-4-yl)-6-bromo-2H-chromen-2-one

(X = 2-Cl, 3-Cl, 4-Cl, 2-Br, 3-Br, 4-Br, 2-OCH_3, 3-OCH_3, 2,4-Cl_2, 2,6-Cl_2)

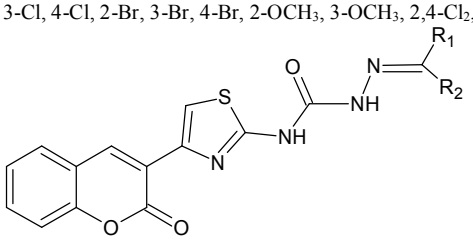

Figure 20: General structure of heteroaryl semicarbazones

(R_1 = substituted phenyl, R_2 = -H, -CH_3)

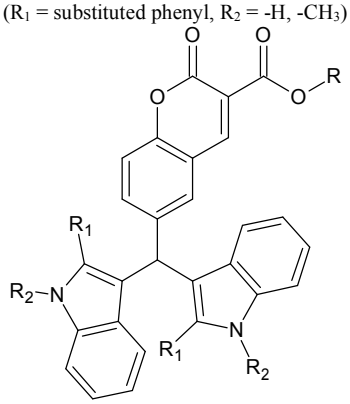

Figure 21: Structure of synthesized hybrid of coumarin bisindole heterocycles

(R = -C_2H_5, R_1 = -H, -CH_3, R_2 = -H, -CH_3)

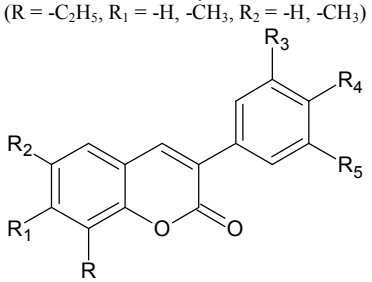

Figure 22: General structure of resynthesized coumarin-resveratrol hybrid

(Different combinations of R = -H, R_1 = -H, -OH, R_2 = -H, R_3 = -H, R_4 = -H, -OH, R_5 = -H, -OH)

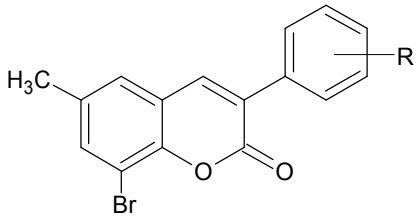

Figure 23: General structure of new series of 8-bromo-6-methyl-3-phenylcoumarin derivatives

(R = -H, 4'-CH_3, 3',5'-OCH_3, 3',4',5'-OCH_3)