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VARIOUS PHARMACOLOGICAL ASPECTS OF COUAMRIN DERIVATIVES: A REVIEW

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Abstract: Coumarin-2H-chromen-2-one and its derivatives are widely distributed in nature. Coumarin belongs to a group as benzopyrones, which consists of a benzene ring joined to a pyrone nucleus. Coumarins exhibit a broad pharmacological profile. Coumarins are regarded as a promising class of bioactive heterocyclic compounds that exhibit a range of biological activities like anti-microbial, anti-viral, anti-diabetic, anti-cancer activity, anti-oxidant, anti-parasitic, anti-helmintic, anti-proliferative, anti-convulsant, anti-inflammatory and anti-hypertensive activities etc. The coumarins are of great interest due to their pharmacological properties. In particular, their physiological, bacteriostatic and anti-tumor activity makes these compounds attractive backbone derivatisation and screening as novel therapeutic agents.

Keywords: Coumarin-2H-chromen-2-one, Coumarin, benzopyrones, coumarin derivatives, biological activities.

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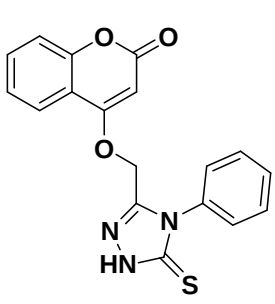
INTRODUCTION

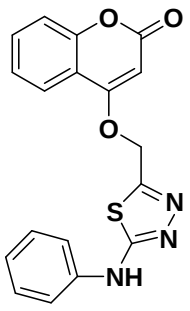
Coumarins have been established as a well known naturally occurring heterocyclic compounds isolated from various plants. Coumarins comprise a very large class of compounds found throughout the plant kingdom. They are found at high levels in some essential oils, particularly *cinnamon* bark oil (7,000 ppm), *cassia* leaf oil (up to 87,300 ppm) and *lavender* oil. Coumarin is also found in fruits (e.g. *bilberry, cloudberry*), green tea and other foods such as *chicory*. Most of the coumarins occur in higher plants, with the richest sources being *Rutaceae* and *Umbelliferone*[1]. They belong to the family of lactones having 1-benzopyran-2-one system that can be isolated from plants as well as can be carried out in the laboratory[2]. Coumarin is versatile pharmacophore which exhibits a wide variety of biological activities like antibacterial[3] and antimicrobial[4]. Coumarins occupy a special role in nature. They belongs to the flavonoid class of plant secondary metabolite, which exhibit a variety of biological activities, associated with low toxicity and have achieved considerable interest due to their beneficial potential effects on human health[5]. Coumarin derivatives have been reported for anticoagulant, anti-inflammatory[6], antimicrobial[7], antiHIV, antioxidant[8], antiallergic, anticancer[9] and anti proliferative and antiviral[10] activities. Isoxazole derivatives have analgesic[11], anti inflammatory, antimicrobial, anti tumour, antiHIV, herbicidal, fungicidal and CNS stimulant[12] activities. 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.

ANTI MICROBIAL ACTIVITIES

Al-Amiery et al. have synthesized 4-[(5-mercapto-4-phenyl-4H-1,2,4-triazol-3-yl)-methoxy]-2H-chromen-2-one as coumarin derivatives and their antifungal activity was determined based on the growth inhibition rates of the mycelia of strains of *Aspergillus niger* and *Candida albicans* in Potato Dextrose Broth medium (PDB) against concentrations ranging from 10 to 100μgml^{-1}. Two compounds **(1a-1b)** showed good activity as antifungals against fluconazole standard drug[13].

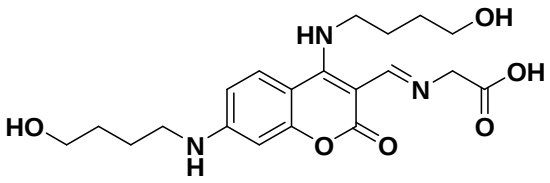


1a



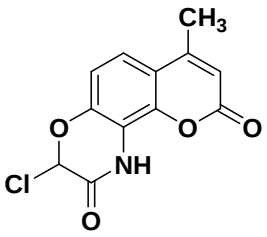
1b

Behrami et al synthesized some novel coumarin derivatives**,** antibacterial activity of synthesized compounds and standard drugs (streptomycin and cefalexine) at concentrations of 2mgml^{-1}, 3mgml^{-1} and 5mgml^{-1} were evaluated against three strains of bacterial culture, *Staphylococcus aureus*, *Escherichia coli* and *Bacillus cereus*. One compound **(2)** showed a significant antibacterial effect against *S. aureus, Escherichia coli* and *Bacillus cereus*[14].



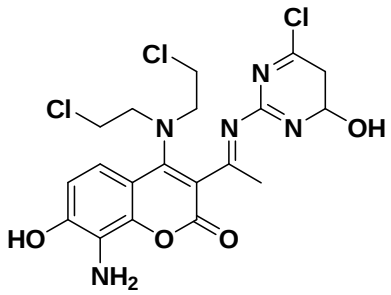
2

Novel coumarin derivatives were synthesised by Sahoo et al. and antibacterial activity was tested against Gram positive bacteria i.e. *Staphylococcus aureus* and Gram negative bacteria i.e. *Escherichia coli*. DMSO was used as a control. One compound **(3)** possessed maximum antibacterial activity as compared to standard drug amoxicillin which may be due to presence of chlorine on aromatic ring of coumarins. Other compounds also showed mild to moderate activity at 0.1ml concentration level on both organisms[15].



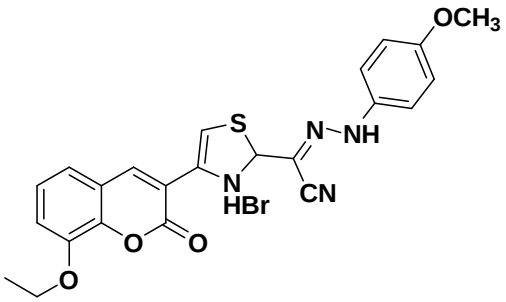
3

Behrami et al. synthesized 8-amino-4,7-dihydroxy-chromen-2-one coumarin derivatives. The antibacterial activities of all the compounds and standard streptomycin and cefalexine at concentractions of 2mgml^{-1}, 3mgml^{-1} and 5mgml^{-1} were studied against *Staphylococcus aureus*, *Bacillus subtilis* and *Escherichia coli*. One compound **(4)** was more active than cefalexine and lesser active than streptomycin and it was most active among synthesized compounds[16].



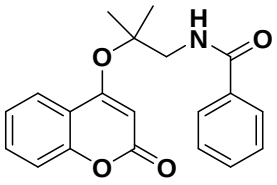
4

Mohamed et al. derivatised some novel 8-ethoxycoumarin and screened for their in-vitro antimicrobial activities against two Gram negative *Bordetella bronchiseptica* (ATCC 4617) and *Escherichia coli* (ATCC 14169) and four Gram positive *Bacillus pumilus* (ATCC 14884), *Bacillus subtilis* (ATCC 6633), *Staphylococcus aureus* (ATCC 29737) and *Staphylococcus epidermidis* (ATCC 12228) pathogenic bacteria and two fungi *Candida albicans* (ATCC 10231) and *Saccharomyces cervesia* (ATCC 9080). One compound **(5)** resulted in wide spectrum antimicrobial activity against all tested bacteria and fungi compared to ampicillin (25µgml^{-1}) and mycostatin (25µgml^{-1}) by replacing the hydrogen atom attached to the coumarin nucleus at C-3 with a side chain, while the other compounds with other side chains showed moderate to weak activity[17].



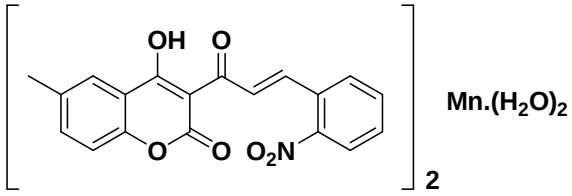
5

Lin et al. synthesized acyl coumarins, 4-hydroxy, and 7-hydroxycoumarins and coumaric amide dimers and were tested against stains of *Bacillus subtilis* (BCRC 10029), *Staphylococcus aureus* (BCRC 11863), *Escherichia coli* (BCRC 11758), and *Pseudomonas aeruginosa* (BCRC 11733) and Penicillin G potassium salt (CAS 113-98-4, USP grade) was used as a reference drug. One compound **(6)** was the most potent compound out of the tested compounds against *Bacillus subtilis* with MIC value of 8µgml^{-1}[18].



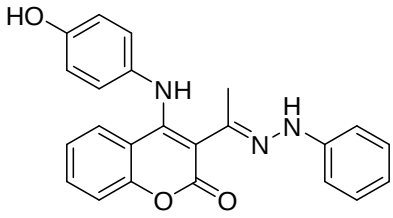
6

Vyas et al. synthesized some novel 3-[{(3-(2'-Nitrophenyl)}-prop-2-enoyl]-4-hydroxy-6-methyl-2H-chromene-2-ones **(7)** and their in-vitro antimicrobial activity screened against four strains of bacteria such as *Staphylococcus aureus*, *Bacillus megaterium*, *Escherichia coli*, and *Proteus vulgaris* and one fungi *Aspergillus niger*. Zone of inhibition of highly active compound was 25mm as antibacterial agent against *Escherichia coli* compared with standards ampicillin (16mm), amoxicillin (17mm), ciprofloxacinin (26mm), erythromycin (22mm) and was 23mm as antifungal agent against *Aspergillus niger* compared with standard drug griseofulvin (21mm)[19].



7

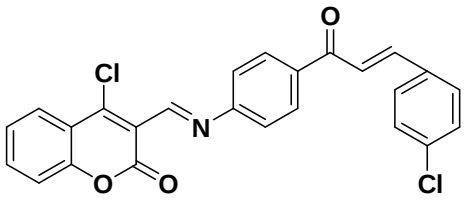
Vaso et al. reported the organic synthesis of some new 2H-[1]-benzopyran-2-one(coumarin) derivatives at concentrations of 2mgml^{-1}, 3mgml^{-1} and 5mgml^{-1} and their antibacterial activity against three bacterial cultures Gram positive bacteria i.e. *Staphylococcus aureus* and *Bacillus aureus* and Gram negative bacteria i.e. *Escherichia coli* was compared with standard antibiotics Cephalexine and Streptomycine. One compound **(8)** was weaker than that of Streptomycine and stronger as compared to Cephalexine in antibacterial activity against Staphylococcus aureus[20].



8

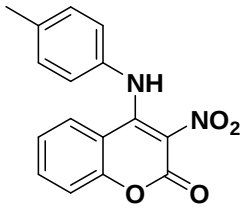
A series of the Schiff's bases, 3-(4-(4-(substituted phenyl)prop-1-ene-3-one)phenylimino) methyl)-4-chloro-2H-chromen-2-ones were synthesized by Kudale et al. and these compounds

were investigated in-vitro against gram positive bacteria, *Staphylococcus aureus* (ATCC 9144), *Bacillus subtilis* (ATCC 6633) and *Staphylococcus epidermis* (ATCC 12228) and gram negative bacteria, *Escherichia coli* (ATCC 25922), *Salmonella typhi* and *Psuedomonas aeruginosa* (ATCC 9027) and the antifungal activity was evaluated against *Aspergillus niger* (ATCC 10594) and *Clostridium albicans* (ATCC 10231) using amoxicillin and fluconazole as standard drugs for antibacterial and antifungal activities respectively. One compound **(9)** was found to be most active with an MIC of 20µgml^{-1}against all the tested organisms[21].



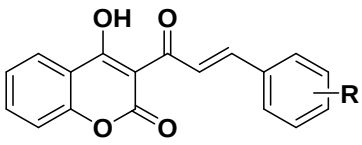
9

Dekic et al. synthesized 4-arylamino-3-nitrocoumarins and were evaluated for their in-vitro antibacterial and antifungal activities against pathogenic strains *Staphylococcus aureus* ATCC 6538, *Bacillus cereus*, *Bacillus subtilis* ATCC 6633, *Escherichia coli* ATCC 8739, *Escherichia coli*, *Klebsiella pneumoniae* ATCC 10031, *Salmonella enterica* ATCC 13076 and yeast *Candida albicans* ATCC 10231 and *Aspergillus niger* ATCC 16404. One compound **(10)** was found greatest anticandidal as compared with other compounds of the series. Tetracycline and Nystatine were used as the reference drugs [22].



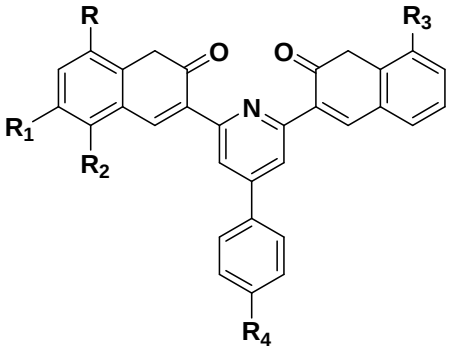
10

Zavrsnik D et al. prepared a series of new 3-cynnamoyl-4-hydroxycoumarins **(11)**. The microbial activity of the synthesized compounds was tested on species of bacteria *Pseudomonas aeruginosa*, *Echerichia coli*, *Salmonella typhimurium*, *Bordatella bronchiseptica*, *Bacillus subtilis* and *Staphyloccocus aureus*. The compounds having halogens showed the best microbial activity. Compounds having 4-Br and 4-Cl were found to be the most effective against *Bacillus subtilis*. Compound having 4-Cl was found to be the most effective against *Staphyloccocus aureus* [23].



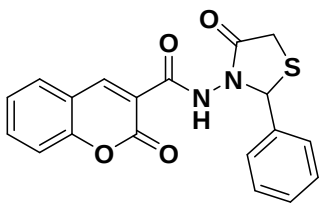
11

Patel AK et al. synthesized some 4-aryl-2,6-di(coumarin-3- yl)pyridines **(12)** and were tested for antimicrobial activity. None of the compounds showed antifungal activity against *Aspergillus niger*. The results revealed that the incorporation of the substituents like -CH_3 or -OCH3 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 some compounds indicated that the presence of an additional fused benzene ring between the C-5' and C-6' positions inhibited the antibacterial activity towards *Escherichia coli*[24].



12

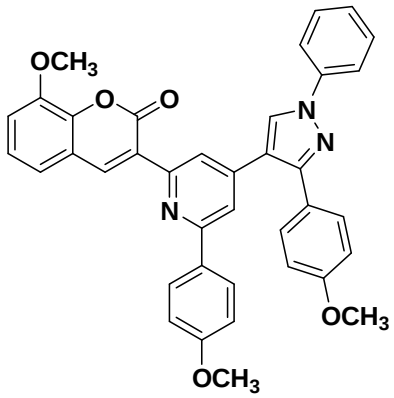
Some coumarin derivatives containing thiazolidin-4-one ring were synthesized by Rama Ganeshet al. and were screened for their antibacterial activity against Gram positive bacteria *Staphylococcus aureus, Bacillus subtilis* and Gram negative bacteria *Klebsiella pneumonia, and Escherichia coli* at the concentration of 0.001molml^{-1} compared with standard drug Ciprofloxacin. Zone of inhibition of highly active compound **(13)** was 20mm against Staphylococcus aureus and Bacillus subtilis[25].



13

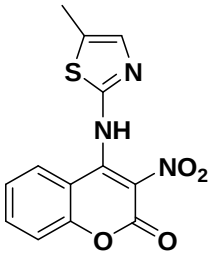
Brahm Bhatt et al. synthesized 4-methyl-3-phenyl-6-[4-(3-aryl-1-phenyl-1H-pyrazol-4-yl)-6-aryl-pyridin-2-yl]coumarin derivatives **(14)** and were screened for anti-bacterial activity against

Escherichia coli, Bacillus subtillis and anti-fungal activity against Candida albican by agar cup diffusion method. DMF was used as blank, Streptomycin was used as anti-bacterial standard and Clotrimazole as anti-fungal standard drug at concentration of 1000µgml^{-1}. All the synthesized compounds showed activity against both gram positive and gram negative bacteria but lesser activity compared to standard drug[26].



14

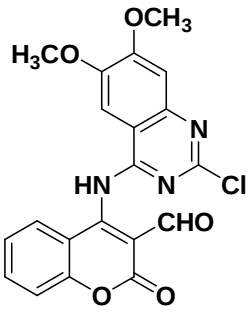
4-heteroarylamino coumarin derivatives containing nitrogen and sulfur were synthesized by Dekic et al. and tested for their in-vitro antimicrobial activity, against thirteen strains of bacteria, *Bacillus subtilis* (ATCC 6633), *Clostridium pyogenes* (ATCC 19404), *Enterococcus sp.* (ATCC 25212), *Micrococcus flavus* (ATCC 10240), *Sarcinalutea* (ATCC 9341), *Staphylococcus aureus* (ATCC 6538), *Klebsiella pneumoniae* (ATCC 10031), *Proteus vulgaris* (ATCC 8427), *Escherichia coli* (ATCC 8739), *Escherichia coli* (ATCC 25922), *Pseudomonas aeruginosa* (ATCC 27857), *Pseudomonas aeruginosa* (ATCC 9027) and *Salmonella enteritidis* (ATCC 13076) and three fungal strains *Aspergillus niger* (ATCC 16404), *Candida albicans* (ATCC 10231) and *Saccharomyces cerevisiae* (ATCC 9763). One compound **(15)** was the most active which showed reduction of bacterial and fungal growth comparable with the standards drugs like tetracycline and nystatine[27].



15

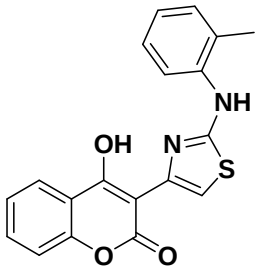
Govori et al. synthesized 4-Heteroaryl-coumarin-3-carbaldehydes and antimicrobial properties of these new coumarins were investigated against *Staphylococcus aureus*, *Escherichia coli*,

Hafnia alvei, *Pseudomonas aeruginosa* and *Enterobacter cloacae*. The Agar disc diffusion technique measured the diameters of the inhibition zone around discs which were previously wetted with N,N-DMF solution of compounds at concentrations of 1,3 and 5mgml^{-1}. One compound **(16)** was more active against Staphylococcus aureus, *Escherichia coli* and *Enterobacter cloaco* and not active as antimicrobial agent against *Hafnia alvei* and *Pseudomonas aeruginosa*[28].



16

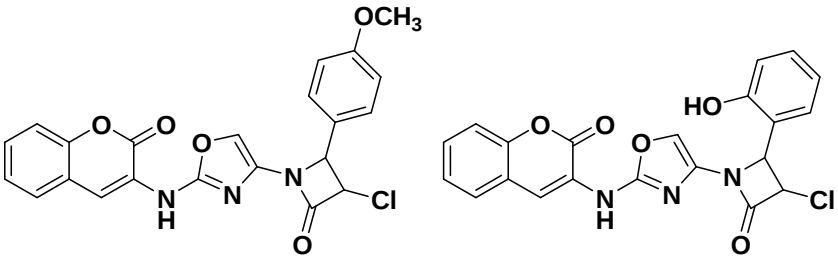
Novel 4-hydroxy-chromene-2-one derivatives were synthesized by Mladenovic et al. and screened for their antibacterial activity against Gram positive bacteria *Staphylococcus aureus, Bacillus subtili* and Gram negative bacteria *Klebsiella pneumonia, Escherichia coli* and their antifungal activity against *M. mucedo, C. albicans*. Streptomycin was used as standard anti-bacterial drug and ketoconazole as standard antifungal drug. One compound **(17)** had activity equal to that of standard drug ketoconazole (31.25µgml^{-1}) against *M. mucedo*[29].



17

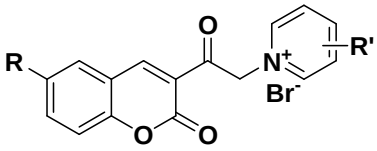
A novel series of 3-[(2'-Substituted benzylidene amino thiazol-4'-yl)amino]coumarins **(18a-18b)** was prepared by Singh et al. and evaluated for antibacterial activity against various bacteria, *Staphylococcus aureus* 209 P, *E. Coli* ESS2231, *Proteus vulgaris*, *K. Pneumoniae* were used and antifungal activity was performed against *Candida albicans* ATCC10231 and results were compared with gattifloxacin and ciprofloxacin for antibacterial and fluconazole for antifungal activities respectively and propylene glycol treated group served as control. One compound

showed potent antibacterial activity while the other compound exhibited most potent antifungal activity[30].



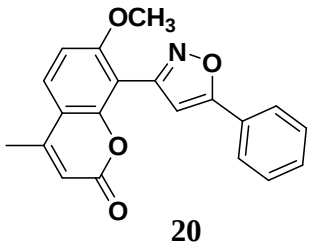
18a **18b**

Porwal B et al. synthesized 3-coumrinoyl pyridinium bromides **(19)** 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-COOC2H5, R = -Cl & R' = 4-COOC2H5, R = -H & R' = 3-COOC2H5 and R = -Cl & R' = 4-COOCH3 were found to be more active than that of other test compounds[31].



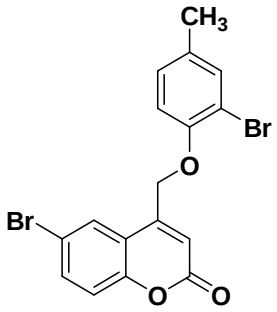
19

A new series of 7–methoxy-4-methyl-8-[5-(substituted aryl)isoxazol-3-yl]–2H–benzopyran-2-ones were synthesized by Sandeep et al. Antimicrobial activity was carried out against 24 hr old cultures of *Escherichia coli, Pseudomonas aeruginosa, Staphylococcus aureus* and *Bacillus subtilis*. The fungi used were *Aspergillus niger, Aspergillus flavus* and *Candida albicans*. The compounds were tested at concentrations of 25µg/ml in dimethylformamide against all the organisms. Ciprofloxacin (25µgml^{-1}) and fluconazole (25µgml^{-1}) were used as standard drugs for antibacterial and antifungal activities respectively. Among the compounds tested for antibacterial activity, one compound **(20)** showed highest zone of inhibition against *S. aureus* and *B. subtilis* and minimum inhibition against *E. coli* and *P. aeruginosa*. The remaining compounds exhibited moderate activity[32].



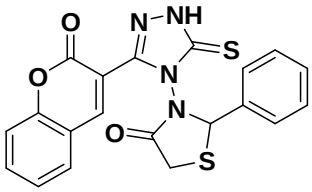
20

Basanagouda et al. synthesized 4-aryloxmethylcoumarins **(21)** and screened for their antibacterial and antifungal activity at different concentrations of 500, 250, 100 and 50µgml^{-1} by the disc diffusion method. Antibacterial activity was carried out against two Gram positive bacteria, viz. *Staphylococcus aureus*, and *Streptococcus faecalis* and three Gram negative bacteria, viz. *Escherichia coli*, *Psuedomonus aeruginosa*, *Klebsiella pneumonia*. Antifungal activity was carried out against five fungi, viz. *Aspergillus flavus*, *Aspergillus fumigatus, Candida albicans, Penicillium notatum* and *Rhizopus*. Ciprofloxacin and Fluconazole were used as standard antibacterial and antifungal drug respectively. The compounds possessing methoxy, chloro, bromo substituents at C-6 position of coumarin showed higher activity[33].



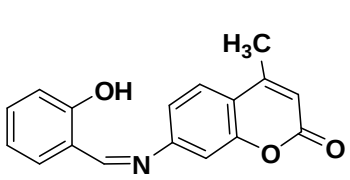
21

Bhatt et al. synthesized a series of 2-(substitutedphenyl)-3-[3-(2-oxo-2H-coumarin-3-yl)-5-thioxo-1,5-dihydro-4H-1,2,4-triazol-4-yl]-1,3-thiazolidin-4-ones and screened for their antimicrobial activity against Gram positive *Staphylococcus aureus* and Gram negative *Escherichia coli* stains and antifungal activity against *Clostridium albicans*. Ciprofloxacin and ketoconazole were used as the standard antibacterial and antifungal drugs respectively. The test compounds and standards drugs were evaluated at concentration of 100µg/mL. DM F (N,N-dimethylformamide) was used as solvent and control. One compound **(22)** showed 92%, 80% and 90% growth inhibition against *Staphylococcus aureus, Escherichia coli* and *Clostridium albicans* respectively[34].

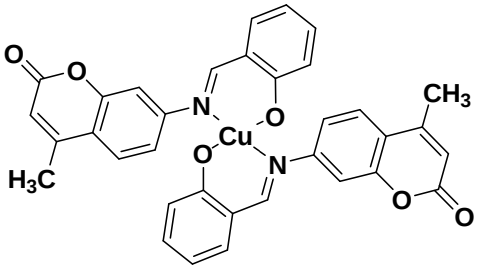


22

Creaven et al. prepared a series of Schiff bases and Cu(II) complexes **(23a-23b)**. All of the free ligands and their metal complexes were tested for their antifungal activity compared with ketoconazole and amphotericin B. The ligands showed no antimicrobial activity whereas a number of the metal complexes exhibited potent antimicrobial activity when compared with their respective standard drugs[35].

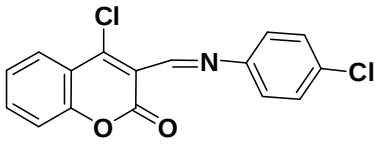


23a



23b

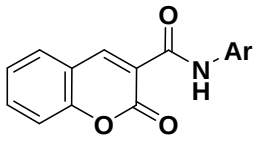
4-chloro-3-((subst it ut ed-phenylimino)methyl)-2H-chromen-2-ones were synthesized by Bairagi et al. and tested for antimicrobial activity in-vitro against Gram positive *Staphylococcus aureus* (ATCC 29737) and *Bacillus subtilis* (ATCC 2063) and Gram negative bacteria *Escherichia coli* (ATCC 20931) and fungi *Aspergillus niger* (ATCC 16404) and *Candida albicans* (ATCC 10231). One compound **(24)** was found to be most active against all the tested organisms with an MIC of 15µgml^{-1}. Amoxicillin was standard for antibacterial activity and fluconazole for antifungal activity[36].



24

Chimenti F et al. prepared N-substituted-2-oxo-2H-1-benzopyran-3-carboxamides (coumarin-3-carboxamides) **(25)** as 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 and against various strains of pathogenic fungi.

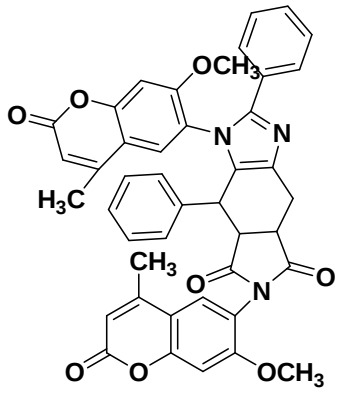
Among the prepared compounds having 4-acyl phenyl group showed the best activity against *Helicobacter pylori* metronidazole resistant strains in the 0.25–1μgml^{-1} range, indicating that the presence of an acyl function is an important feature for activity[37].



25

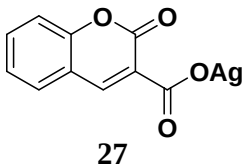
Mulwad VV et al. synthesized 4-[1-(2H-[1]-4-hydroxy-2-oxo-benzopyran-3-yl)methylidene]-2-phenyl-4H-oxazol-5-ones and [1,2,4]triazine-6-one and its derivatives. All the compounds were screened for antimicrobial activity and found to exhibit significant activity[38].

A novel series of 5H,7H-N-(coumarin-6-yl)-2,8-diphenyl-5,7-dioxo-6-(7-methoxy-4-methyl coumarin-6-yl)-4,5,6,7- tetrahydrobenzimidazo[5,6-c]pyrrole derivatives **(26)** was synthesized and screened by Choudhari et al. for their antibacterial activity against *Staphylococcus aureus* and *Salmonella typhi* and antifungal activity against *Aspergillus niger* and *Clostridium albicans*. Ciprofloxacin and miconazole were used as the antibacterial and antifungal standards respectively. All compounds showed antimicrobial activity having MIC values ranging from 50μgml^{-1} to 200μgml^{-1}[39].



26

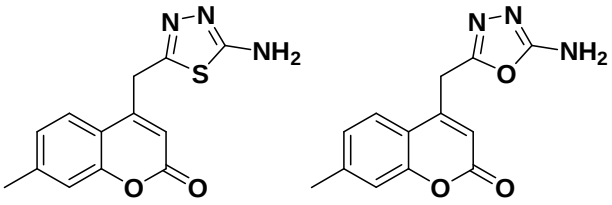
A series of new coumarin derived carboxylate ligands and their silver(I) complexes **(27)** were synthesized, characterized and screened by Creaven et al. for their in-vitro antibacterial activity against a range of Gram positive stains and Gram negative as well as for their antifungal activity. While none of the ligands showed any antimicrobial activity, a number of the Ag(I) complexes exhibited potent activity. In particular, Ag(I) complexes of hydroxy-substituted coumarin carboxylates demonstrated potent activity[40].



27

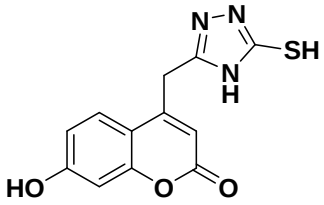
Hamdi et al synthesized bis[N-(4-oxocoumarinylmethylene)]-1,4-diamines and the antibacterial activity tests were carried out using Staphylococcus aureus ATCC 25923 at a concentration of 106CFCml^{-1} on the surface of a Mueller-Hint on gelose plate. One compound exhibited the strongest antibacterial activity[41].

Mashelkar et al. synthesized some novel 4-substituted coumarins and subjected them to in-vitro screening against Gram positive *Staphylococcus aureus* and Gram negative *Salmonella typhi*. Ampicillin and trimethoprim were used as standard drugs. Two compounds **(28a-28b)** showed significant antibacterial activity at concentration levels of 10 to 200µgml^{-1}against *Staphylococcus aureus* and *Salmonella typhi*[42].



28a **28b**

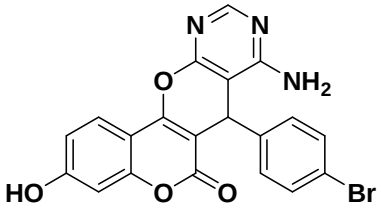
Some derivatives of (7-hydroxy-2-oxo-2H-chromen-4-yl)-acetic acid hydrazide **(29)** were prepared by Cacic et al. and were found to possess high antimicrobial activity against *Staphyloccocus pneumoniae* and were slightly less active against *Pseudomonas aeruginosa*, *Bacillus subtilis, Bacillus cereus* and *Salmonela panama* as compared to standard drug[43].



29

Kusanur RA et al. developed the new 1,3-dipolar cycloadducts of 3-azidoacetylcoumarins with dimethyl acetylene dicarboxylate (DMAD). All the newly synthesized compounds and their adducts were screened for antimicrobial activity and good results were obtained[44].

Pyrimidino[5',4'-6,5]-,pyridino[3',2'-6,5] and pyrrolo[3',2'-5,6]4H-pyrano-[3,2-c][1] benzopyran-6-one derivatives were prepared and screened by Al-Haiza et al. for their activity against Gram positive bacteria, *Staphylococcus aureus, Bacillus subtilis, Bacillus cereus*, Gram negative bacteria, *Pseudomonas aurignosa, Echerichia coli, Enterobacter aerogenes* as well as fungi *Aspergillus niger, Penicillium italicum, Fusarium oxysporum*. Standard drugs amoxicillin for bacteria and mycostatin for fungi were used at a concentration of 1000ppm for comparisons. One compound **(30)** exhibited excellent antibacterial activity towards *Enterobacter aerogenes*[45].

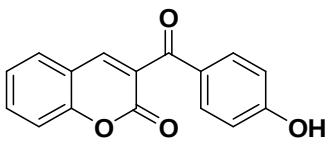


30

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[46].

Gupta AS et al. synthesized 3- amino-(N-aryl substituted)-6-bromo-2H-1-benzopyran-2- ones and 6-bromo-3-phenoxy substituted-2H-1-benzopyran-2-ones. All the title compounds were screened for in-vitro antitubercular activity against highly virulent H37Rv strains of *mycobacterium tuberculosis* as compared to streptomycin and INH[47,48].

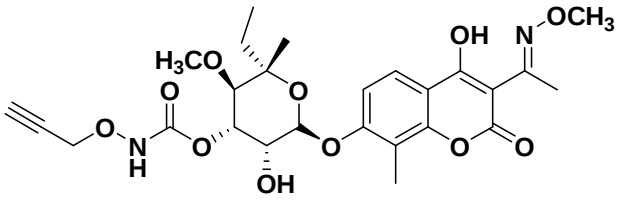
Purohit et al reported synthesis and biological activities of some substituted 3-(4-hydroxybenzoyl)-1H-isochromen-1-one **(31)**,2-benzopyran-1H-2-one,1H-2-oxo-benzopyran-3-carboxylicacids and 2-benzofuran-1H-one. All the compounds showed good activity against *Staphylococcus aureus* and *Escherichia coli*[49].



31

A new series of coumarin inhibitors of DNA gyrase B bearing a N-propargyloxycarbamate at C-3' of various 5',5'-di-alkylnoviose including RU79115 **(32)** were synthesized and their antibacterial activities were delineated by Musicki et al. In-vitro, RU79115 bactericidal activity against

Escherichia faecium and *Staphylococcus aureus* was time dependent and similar to that of standard drug vancomycin in the case of *Staphylococcus aureus*[50].

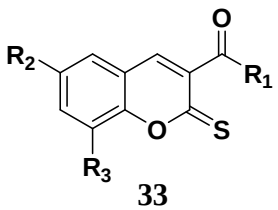


32

Bonsignore et al. synthesized a novel series of coumarin 7-substituted cephalosporins and sulfones. The synthesized compounds were tested against *Staphylococcus aureus* (ATCC 25923), *Escherichia coli* (ATCC 25922) and *Pseudomonas aeruginosa* (ATCC 27853) with varying concentrations of the associated antibiotic cefotaxime (0.125-256µgml^{-1}) Cephalosporins showed a potential activity against Gram positive microorganisms and sulfones showed no significant activity. An association of sulfone with ampicillin was observed to inhibit Gram positive microorganisms with a lower MIC value than for ampicillin alone[51].

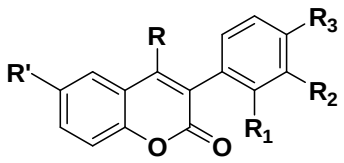
ANTIOXIDANT ACTIVITY

Singh OM et al. developed a facile, convenient and high yielding synthesis of a combinatorial library of 3-alkanoyl/aroyl/heteroaroyl-2H-chromene-2-thiones **(33)**. 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)[52].



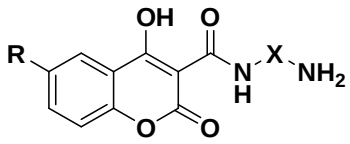
33

Roussaki M et al. synthesized a series of coumarin analogues **(34)** bearing a substituted phenyl ring on position 3. In vitro antioxidant activity of the synthesized compounds was evaluated using two different antioxidant assays. Ability of the compounds to inhibit soybean lipoxygenase was also determined as an indication of potential anti-inflammatory activity[53].



34

Melagraki G et al. synthesized a series of novel coumarin-3-carboxamides **(35)** and 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 (SAR) were developed in order to define the structural features required for activity[54].

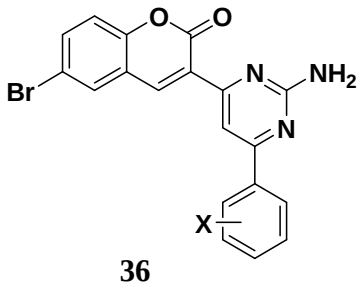


35

Stanchev S et al synthesized four 4-hydroxycoumarin derivatives, ethyl 2-[(4-hydroxy-2-oxo-2H-chromen-3-yl)(4-hydroxyphenyl)methyl]-3-oxobutanoate, 4-[1-(4-hydroxy-2-oxo-2H-chromen-3-yl)-2-(ethoxycarbonyl)-3-oxobutyl]benzoic acid, ethyl-2-[(4-hydroxy-2-oxo-2H-chromen-3-yl) (3-nitrophenyl)methyl]-3-oxobutanoate and ethyl-2-[(3,4,5-trimethoxyphenyl)-(4-hydroxy-2-oxo-2H-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-2H-chromen-3-yl)(4- hydroxyphenyl) -methyl]-3-oxobutanoate expressed the best scavenger activity at the highest concentration (10^{-4}molL $^{-1}$)[55].

ANALGESIC AND ULCEROGENIC ACTIVITY

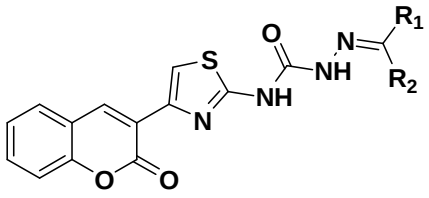
Gupta JK et al. synthesized a novel series of 3-(2-amino-6- pyrimidin-4-yl)-6-bromo-2H-chromen-2-one **(36)**. The synthesized compounds were tested for in-vivo analgesic activity at a dose of 20mgkg^{-1} body weight. Among them, compounds having o-chloro, m-chloro and m-bromo phenyl exhibited significant 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 screened for acute-ulcerogenic activity. Among them, compound having 2,6-dichloro phenyl was found to be most promising analgesic agent devoid of ulcerogenic effects[56].



36

ANTICONVULSANT ACTIVITY

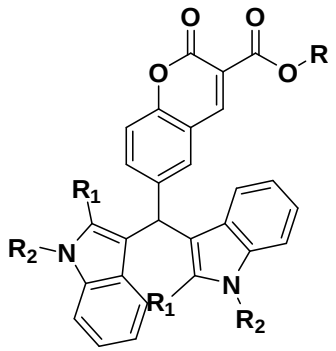
Siddiqui N et al. prepared several heteroaryl semicarbazones **(37)** and compounds were tested for anticonvulsant activity utilizing pentylenetetrazole induced seizure (PTZ), maximal electroshock seizure (MES) and Neurotoxicity tests at 30, 100 and 300mgkg^{-1} dose levels. Three compounds having 3,4-Cl.C_6H_3, 2-OCH_3.C_6H_4 and 4-Br.C_6H_4 exhibited significant anticonvulsant activity at 30mgkg^{-1} dose level comparable to the standard drug-phenytoin[57].



37

ANTIHYPERLIPIDEMIC ACTIVITY

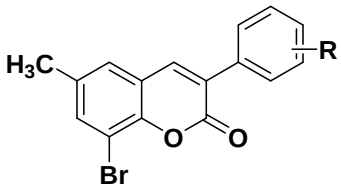
Sashidhara KV et al. synthesized a series of novel coumarin bisindole heterocycles **(38)** and these compounds were evaluated for antihyperlipidemic activity in hyperlipidemic hamster model. In these compounds, as far as coumarin pharmacophore is considered, it revealed that the substitution at position 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 $_{R1}$ = 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[58].



38

ANTI-PARKINSONISM ACTIVITY

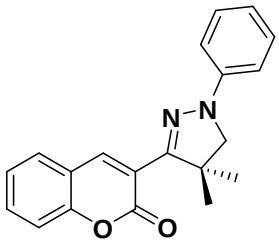
Matos MJ et al. synthesized a new series of 8-bromo-6-methyl-3-phenylcoumarin derivatives **(39)** without substituents and with different number of methoxy substituent in the 3-phenyl ring. The substituent in this new scaffold was introduced in the 3', 4' and/ or 5' positions of the 3-phenyl ring of the coumarin moiety. These compounds were evaluated as MAO-A and MAO-B inhibitors using R-(-)-deprenyl (selegiline) and Iproniazide as reference inhibitors. The most potent molecule of this series had one methoxy group in 4' position (IC50 = 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)[59].



39

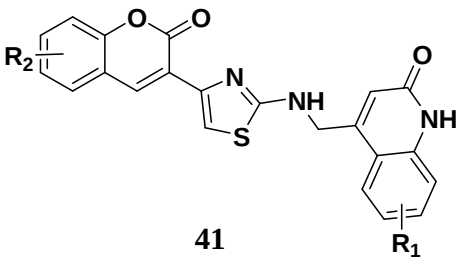
ANTI–INFLAMMATORY AND ANALGESIC ACTIVITY

Khode S et al. synthesized a novel series of 5-(substituted)aryl-3-(3 coumarinyl)-1-phenyl-2-pyrazolines **(40)** and screened for in vivo anti-inflammatory and analgesic activities at a dose of 200mgkg^{-1}. 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 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 chronic inflammation such as adjuvant induced arthritis and were compared with diclofenac (13.5 mgkg^{-1}) 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[60].



40

Kalkhambkar RG et al. synthesized triheterocyclic thiazoles containing coumarin and carbostyril(1-azacoumarin) **(41)** and were tested for their in vivo analgesic and anti-inflammatory activities. Qualitative SAR studies showed that the 7-chloro substitution in carbostyril and 6,8-dibromo substitution in the coumarin ring enhanced anti-inflammatory activity. These compounds were also providing significant protection against acetic acid writhing in animal models[61].

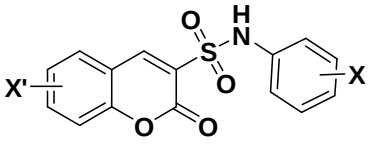


41

A series of N-aryl substituted 2-imino-2H-1-benzopyran-3-carboxamides and 2-oxo-2H-1-benzopyran-3-carboxamides were synthesized by Bylov IE et al. and screened 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. These compounds were found to be essentially non-toxic at the highest dose tested[62].

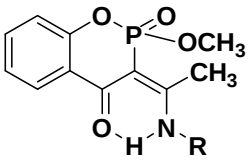
ANTI-CANCER ACTIVITY

Reddy NS et al. synthesized coumarin 3-(N-aryl) sulphonamides **(42)**. 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 hours of continuous treatment against five different concentrations (1-100 µM range) of each compound. The activation of JNK1 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[63].



42

Budzisz E et al. determined the cytotoxic effects and alkylating activity of a series of 3-[1-(alkylamino)-ethylidene]-chroman-2,4-dione, 2-methoxy-3-[1-(alkylamino)-ethylidene-2,3-dihydro-2,4-dioxo-2λ5- benzo[e][1,2] oxaphosphinane **(43)** and [2-oxo-4- phenyl(alkyl)-2H-chromen-3-yl]-phosphonic acids dimethyl ester **(44)** on the two leukemia cell lines HL-60 and NALM-6. These compounds were highly toxic to NALM-6 cells than to HL-60 cells. IC50 data are about nine times lower for the NALM-6 than for the HL-60 cell lines. 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[64].



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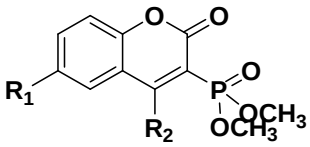

44

CONCLUSION

In present review we focused on different derivatives of coumarin which are synthesized by various researchers and their activities are studied. It can be concluded that coumarin ring fused with other rings, a synergistic effect of both the rings in their biological activities were obtained, such compounds are exploited in development of various important molecule which provides scaffolds for drug development. Various moieties combined with coumarin produces same or different effects but with different potencies.

ACKNOWLEDGEMENT

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