Pharmacologically potentials of different substituted coumarin derivatives

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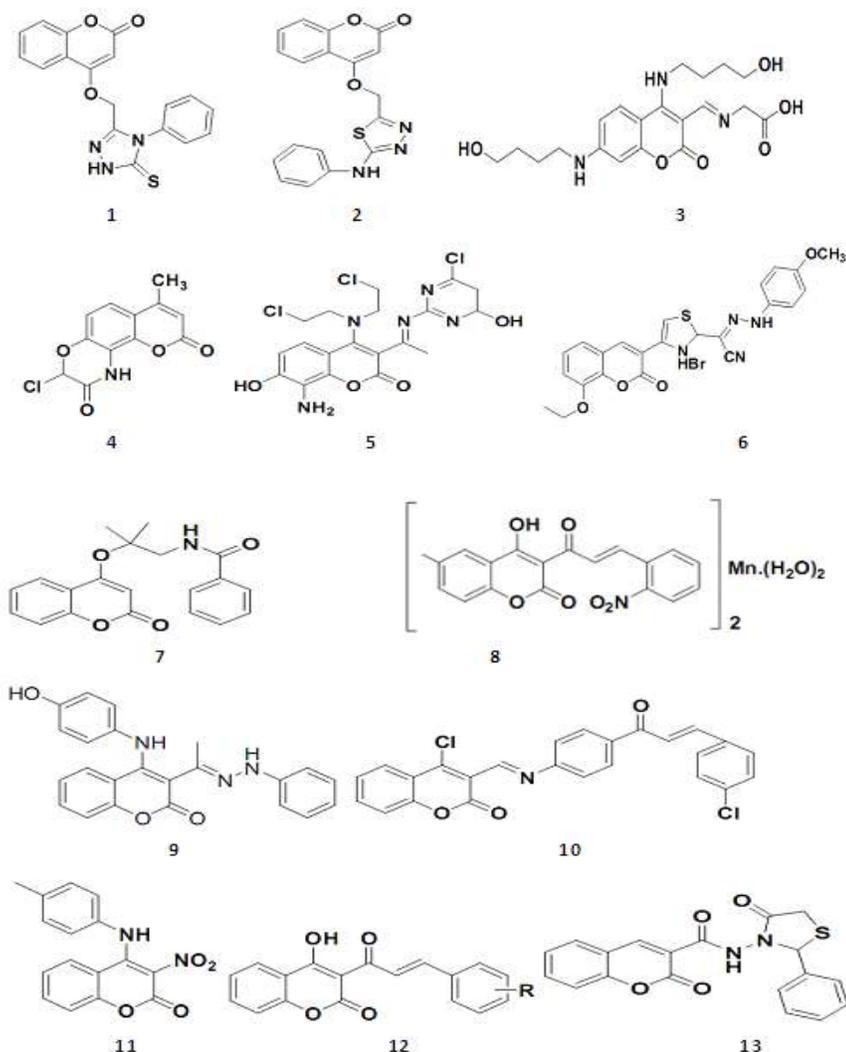| A R T I C L E I N F O	A B S T R A C T
Article type: Review article **Article history:** Received October 2014 Accepted December 2014 January 2015 Issue **Keywords:** Coumarins Benzopyrones Biological activities	Coumarin and its derivatives are widely spread in nature. Coumarin goes to a group as benzopyrones, which consists of a benzene ring connected to a pyrone moiety. Coumarins displayed a broad range of pharmacologically useful profile. Coumarins are considered as a promising group of bioactive compounds that exhibited a wide range of biological activities like anti-microbial, anti-viral, antiparasitic, anti-helmintic, analgesic, anti-inflammatory, anti-diabetic, anti-cancer, anti-oxidant, anti-proliferative, anti-convulsant, and antihypertensive activities etc. The coumarin compounds have immense interest due to their diverse pharmacological properties. In particular, these biological activities make coumarin compounds more attractive and testing as novel therapeutic compounds.

Capsule Summary: Coumarin derivatives are considered as promising bioactive compounds that exhibited a wide range of biological activities.

INTRODUCTION

Coumarins are well recognized naturally occurring compounds which isolated and present in large number of compounds in the plant kingdom. Mostly occur in higher plants, richest sources being *Rutaceae* and *Umbelliferone* (Jain and Joshi, 2012). They are present in high level in some essential oils, like *cinnamon* bark oil, *cassia* leaf oil and *lavender* oil. Coumarin is also present in fruits like *bilberry, cloudberry*, green tea and other foods like *chicory*. Coumarin contains the lactone ring having 1-benzopyran-2-one ring system (Batra et al., 2012). 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 (Sandeep et al., 2009).

Coumarin is multipurpose pharmacophore which exhibits a wide variety of biological activities (Olayinka et al., 2010). Coumarin derivatives have been reported for anticoagulant (Abdelhafez et al., 2010; Bhatia et al., 2009), anti-inflammatory (Kontogiorgis and Hadjipavlou-Litina. 2005; Li et al., 2013), antimicrobial (Keri et al., 2010), antifungal (Khan et al., 2004; Brooker et al., 2007), anti-HIV, antioxidant (Kontogiorgis et al., 2006; Kontogiorgis and Hadjipavlou-Litina. 2003), antiallergic, antidepressant (Gnerre et al., 2000), antidiabetic (Han et al., 2014), anticancer (Chen et al., 2013), anti-proliferative, antiviral (Yang et al., 2011), various enzyme and receptor inhibiting activities and other biological activities (Chen et al., 2006; de Marchi et al., 2004; Gupta et al., 2010; Han et al., 2005; Jalal et al., 2012; Kathuria et al., 2009; Kumar et al., 2005; Lee et al., 2014; Liu et al., 2012). Therefore, the pharmacological properties as well as therapeutic applications of coumarins depend upon the pattern of substitution to possess many pharmacological

against *Aspergillus niger* and *Candida albicans* in concentrations ranging from 10 to 100μg/ml. Two compounds (1 and 2) showed good antifungal activity and fluconazole used as standard drug (Al-Amiery et al., 2012). Some coumarin derivatives showed antibacterial activity and standard drugs (streptomycin and cefalexine) at concentrations of 2mg/ml, 3mg/ml and 5mg/ml were evaluated against *Staphylococcus aureus*, *Escherichia coli* and *Bacillus cereus*. Compound (3) showed a significant antibacterial effect against *S. aureus, E. coli* and *B. cereus* (Behrami et al., 2012).

Coumarin derivatives were evaluated as antibacterial activity against Gram positive bacteria *S. aureus* and Gram negative bacteria *E.* Compound (4) exhibited highest antibacterial activity and amoxicillin used as standard drug which may be due to existence of chlorine on aromatic ring of coumarins. Other compounds were also showed mild to moderate activity at 0.1ml concentration level on both these organisms (Sahoo et al., 2012). The 8-amino-4,7-dihydroxy-chromen-2-one coumarin derivatives were exhibited antibacterial activities and standard drugs were streptomycin and cefalexine at concentractions of 2mg/ml, 3mg/ml and 5mg/ml against *S. aureus*, *B. subtilis* and *E. coli*. Compound (5) was more active than cefalexine and less active than streptomycin (Behrami and Krasniqi, 2012). Some 8-ethoxycoumarin were screened for their in-vitro antimicrobial activities against two Gram negative *Bordetella bronchiseptica* and *E. coli* and four Gram positive *Bacillus pumilus*, *B. subtilis*, *S. aureus* and *Staphylococcus epidermidis* pathogenic bacteria and two fungi *Candida albicans* and *Saccharomyces cervesia*. Compound (6) resulted in wide spectrum antimicrobial activity against all tested bacteria and fungi compared to ampicillin (25μg/ml) and mycostatin (25μg/ml) (Mohamed et al., 2012).
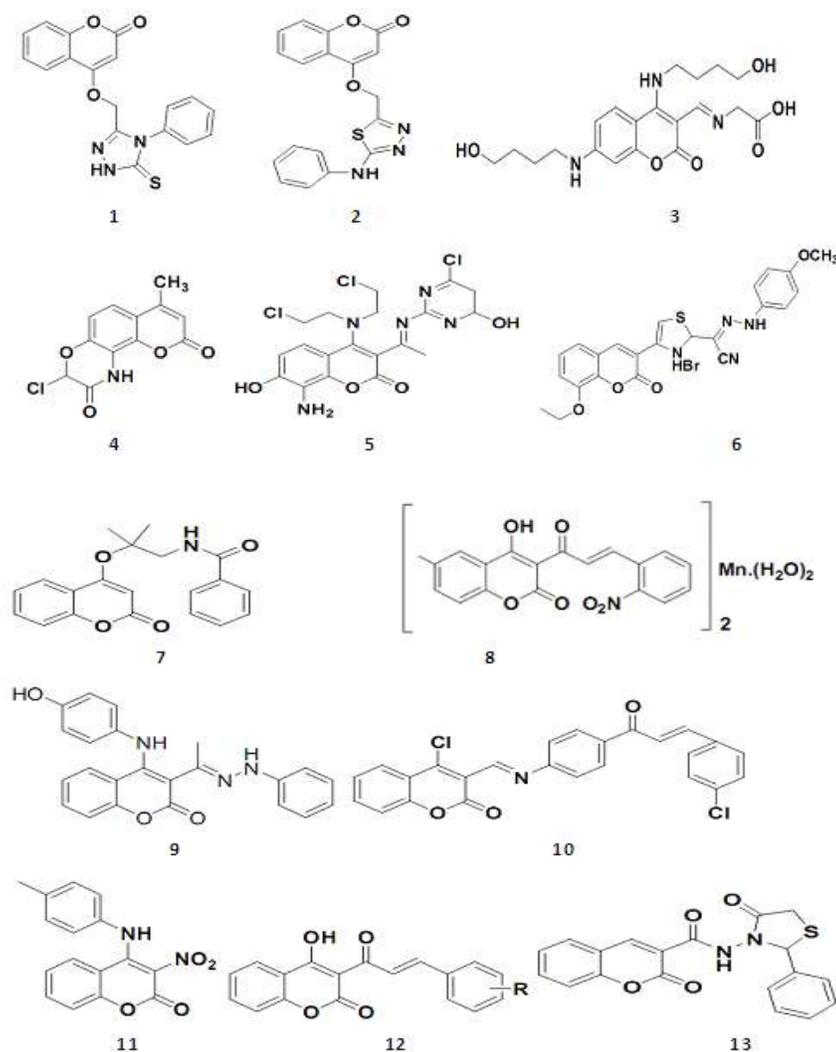
The acyl coumarins, 4-hydroxy, and 7-hydroxycoumarins and coumaric amide dimers were tested against *B. subtilis*, *S. aureus*, *E. coli*, and *Pseudomonas aeruginosa* and Penicillin G potassium salt was used as a reference drug. Compound (7) was the most potent compound out of the tested compounds against *Bacillus subtilis* with MIC value of 8μg/ml (Lin et al., 2012). Some 3-[{(3-(2'-Nitrophenyl)}-prop-2-enoyl]-4-hydroxy-6-methyl-2H-chromene-2-ones (8) were evaluated for their in-vitro antimicrobial activity against four strains of bacteria, *S. aureus*, *Bacillus megaterium*, *E. coli*, and *Proteus vulgaris* and one fungi *A. niger*. Zone of inhibition of highly active

activities (Doss et al., 2001; Abd Elhafez et al., 2003). An agent that is used to avoid the formation of blood clots called anticoagulants and have various uses such as for the prevention or treatment of disorders differentiated by abnormal blood clots and emboli (Aurora et al., 2001). Anticoagulant drugs comprise intravenous heparin, which acts by inactivating thrombin and several other clotting factors that are required for a clot to form, and oral anticoagulants such as warfarin and dicumarol, which act by inhibiting the liver's production of vitamin K dependent factors that are crucial to clotting. Anticoagulants are also used for the preservation of stored whole blood and blood parts and to maintain laboratory blood samples from clotting (Venkataraman et al., 2014).

Antimicrobial activities

4-[(5-mercapto-4-phenyl-4H-1,2,4-triazol-3-yl)-methoxy]-2H chromen-2-one was evaluated for their antifungal activity

compound was 25 mm as antibacterial agent against *E. coli* compared with standards drug ampicillin (16mm), amoxicillin (17mm), ciprofloxacinin (26mm), erythromycin (22mm) and was 23 mm as antifungal agent against *A. niger* compared with standard drug griseofulvin (21mm) (Vyas et al., 2012). Some 2H-[1]-benzopyran-2-one derivatives at concentrations of 2 mg/ml, 3 mg/ml and 5mg/ml were evaluated for their antibacterial activity against three Gram positive bacteria, *S. aureus* and *B. aureus* and Gram negative bacteria, *E. coli* was compared with standard drugs Cephalexine and Streptomycine. Compound (9) was weaker than Streptomycine and stronger than Cephalexine in antibacterial activity against *S. aureus* (Vaso et al., 2012). A series of 3-(4-(4-(substituted phenyl)prop-1-ene-3-one)phenylimino) methyl)-4-chloro-2H-chromen-2-ones were investigated in-vitro against gram positive bacteria, *S. aureus*, *B. subtilis* and *S. epidermis* and gram negative bacteria, *E. coli*, *S. typhi* and *P. aeruginosa* and the antifungal activity was evaluated against *A. niger* and *Clostridium albicans* using amoxicillin and fluconazole as standard drugs for antibacterial and antifungal activities respectively. Compound (10) was found to be most active with an MIC of 20μg/ml against all the tested organisms (Kudale and Deodhar. 2012). The 4-arylamino-3-nitrocoumarins were evaluated for their antibacterial and antifungal activities against pathogenic strains *S. aureus*, *B. cereus*, *B. subtilis*, *E. coli*, *Klebsiella pneumoniae*, *Salmonella enterica* and yeast *C. albicans* and *A. niger*. Compound (11) was found greatest anticandidal as compared to other compounds and Tetracycline and Nystatine were used as the reference drugs (Dekic et al., 2011). A series of 3-cynnamoyl-4-hydroxycoumarins (12) were tested on bacteria *P. aeruginosa*, *E. coli*, *Salmonella typhimurium*, *Bordatella bronchiseptica*, *B. subtilis* and *S. aureus*. The compounds having halogens showed the highest antimicrobial activity. Compounds having 4-Br and 4-Cl were found to be the most effective against *B. subtilis*. Compound having 4-Cl was found to be the most effective against *S. aureus* (Zavrsnik et al., 2011). Some coumarin derivatives containing thiazolidin-4-one ring were screened for their antibacterial activity against Gram positive bacteria *S. aureus, B. subtilis* and Gram negative bacteria *Klebsiella pneumonia, and E. coli* at the concentration of 0.001mol/ml compared with standard drug Ciprofloxacin. Zone of inhibition of highly active compound (13) was 20 mm against *S. aureus* and *B. subtilis* (Rama Ganesh et al., 2010).

Some 4-aryl-2,6-di(coumarin-3- yl)pyridines (14) and were tested for antimicrobial activity. None of the compounds showed antifungal activity against *A. niger*. The results showed that the incorporation of the substituents like -CH₃ 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 *E. coli* (Patel et al., 2010).

Some 4-methyl-3-phenyl-6-[4-(3-aryl-1-phenyl-1H-pyrazol-4-yl)-6-arylpyridin-2-yl]coumarin derivatives (15) were screened for anti-bacterial activity against *E. coli, B. subtillis* and anti-fungal activity against *C. albican*. Streptomycin was used as anti-bacterial standard and Clotrimazole as anti-fungal standard drug at concentration of 1000μg/ml. All the compounds showed activity against both gram positive and gram negative bacteria but lesser activity compared to standard drug (Brahmbhatt et al., 2010). The 4-heteroarylamino coumarin derivatives containing nitrogen and sulfur were tested for their in-vitro antimicrobial activity, against thirteen strains of bacteria, *B. subtilis*, *Clostridium pyogenes*, *Enterococcus sp.*, *Micrococcus flavus*, *Sarcinalutea*, *S. aureus*, *K. pneumoniae*, *Proteus vulgaris*, *E. coli*, *P. aeruginosa*, and *Salmonella enteritidis* and three fungal strains *A. niger, C. albicans* and *Saccharomyces cerevisiae*. Compound (16) was the most active which showed reduction of bacterial and fungal growth comparable with the standards drugs like Tetracycline and Nystatine (Dekic et al., 2010). The 4-Heteroaryl-coumarin-3-carbaldehydes were tested for antimicrobial properties against *S. aureus*, *E. coli*, *Hafnia alvei*, *P. aeruginosa* and *Enterobacter cloacae*. The compounds at concentrations of 1,3 and 5 mg/ml. Compound (17) was more active against *S. aureus, E. coli* and *E. cloaco* and not active as antimicrobial agent against *H. alvei* and *P. aeruginosa* (Govori et al., 2010). Novel 4-hydroxy-chromene-2-one derivatives were screened for their antibacterial activity against Gram positive bacteria *S. aureus, B. subtili* and Gram negative bacteria *K. pneumonia, E. coli* and their antifungal activity against *M. mucedo, C. albicans*. Streptomycin was used as standard antibacterial drug and ketoconazole as standard antifungal drug. Compound (18) had activity equal to that of standard drug ketoconazole (31.25μg/ml) against *M. mucedo* (M ladenovic et al., 2010). A series of 3-[(2'-Substituted benzylidene amino thiazol-4'-yl)amino]coumarins (19 and 20) were evaluated for antibacterial activity against various bacteria, *S. aureus*, *E. Coli*, *Proteus vulgaris*, *K. Pneumoniae* were used and antifungal activity was performed against *C. albicans* 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 (Singh et al., 2010).

A series of 7–methoxy-4-methyl-8-[5-(substituted aryl)isoxazol-3-yl]–2H–benzopyran-2-ones were evaluated as antitubercular agents. Antimicrobial activity was carried out against 24 hr old cultures of *E. coli, P. aeruginosa, S. aureus* and *B. subtilis*. The fungi used were *A. niger, A. flavus* and *C. albicans*. The compounds were tested at concentrations of 25μg/ml against all the organisms. Ciprofloxacin (25 μgm/l) and fluconazole (25 μg/ml) were used as standard drugs for antibacterial and antifungal activities respectively. Among the compounds tested for antibacterial activity, compound (21) showed highest zone of

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against *Clostridium albicans*. Ciprofloxacin and ketoconazole were used as the standard antibacterial and antifungal drugs respectively. These compounds and standards drugs were evaluated at concentration of 100μg/ml. Compound (23) showed 92%, 80% and 90% growth inhibition against *S. aureus, E. coli* and *C. albicans* respectively (Bhat et al., 2009). The 3-coumrinoyl pyridinium bromides (24) and 3-coumarinoyl quinolinium bromides were 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. Coumarinoyl pyridinium salts having R = -H & R'= 4-COOC$_2$H$_5$, R = -Cl & R' = 4-COOC$_2$H$_5$, R = -H & R' = 3-COOC$_2$H$_5$ and R = -Cl & R' = 4-COOCH$_3$ were found to be more active than that of other test compounds (Porwal et al., 2009).

The 4-chloro-3-((substituted-phenylimino)methyl)-2H-chromen-2-ones were tested for antimicrobial activity in-vitro against Gram positive *S. aureus* and *B. subtilis* and Gram negative bacteria *E. coli* and fungi *A. niger* and *C. albicans*. Compound (25) was found to be most active against all the tested organisms with an MIC of 15μg/ml. Amoxicillin was standard for antibacterial activity and fluconazole for antifungal activity (Bairagi et al., 2009). N-substituted-2-oxo-2H-1-benzopyran-3-carboxamides (coumarin-3-carboxamides) (26) as anti-*Helicobacter pylori* agents and evaluated them for antibacterial activity. All the compounds showed little or no activity against different species of Gram positive and Gram negative bacteria and against various strains of pathogenic fungi. Compounds having 4-acyl phenyl group showed the best activity against *H. pylori* metronidazole resistant strains in the 0.25–1μg/ml range, indicating that the presence of an acyl function is an important feature for activity (Chimenti et al., 2006).

A series of Schiff bases and Cu (II) complexes (27), 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 standard drugs (Creaven et al., 2009). The 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 were screened for antimicrobial activity and found to exhibit significant activity (Mulwad and Satwe. 2006). A 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 (28) were screened for their
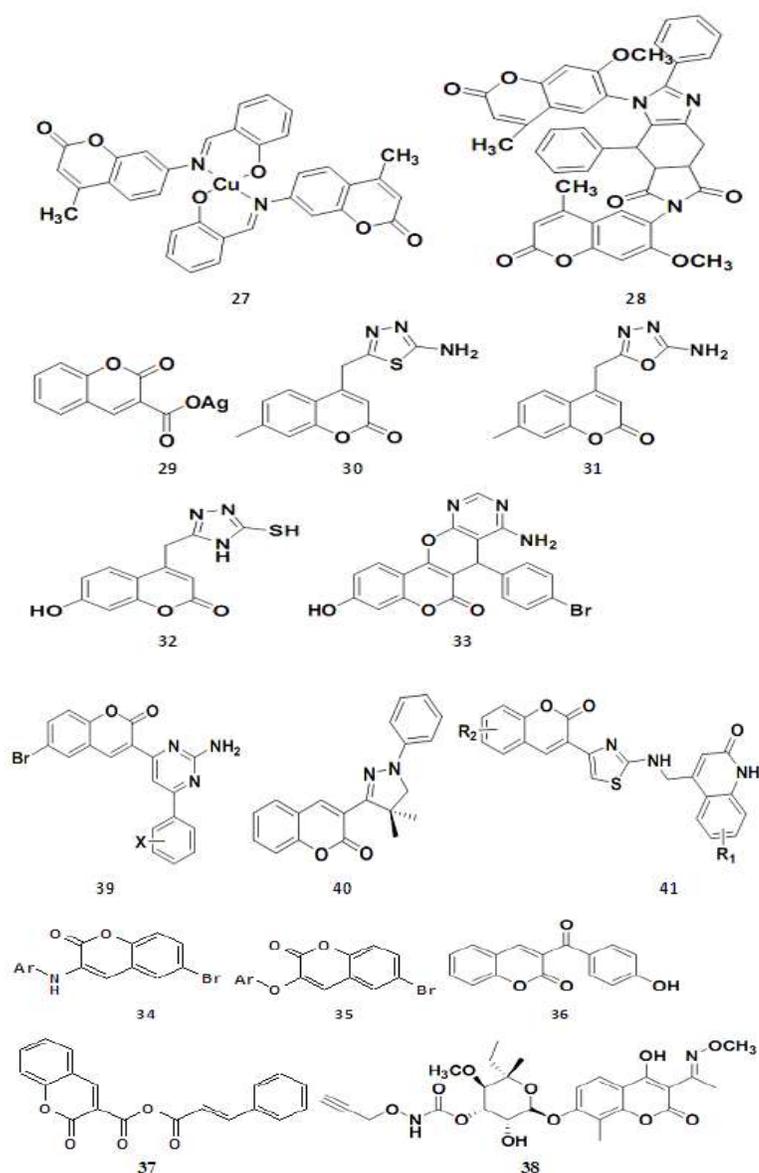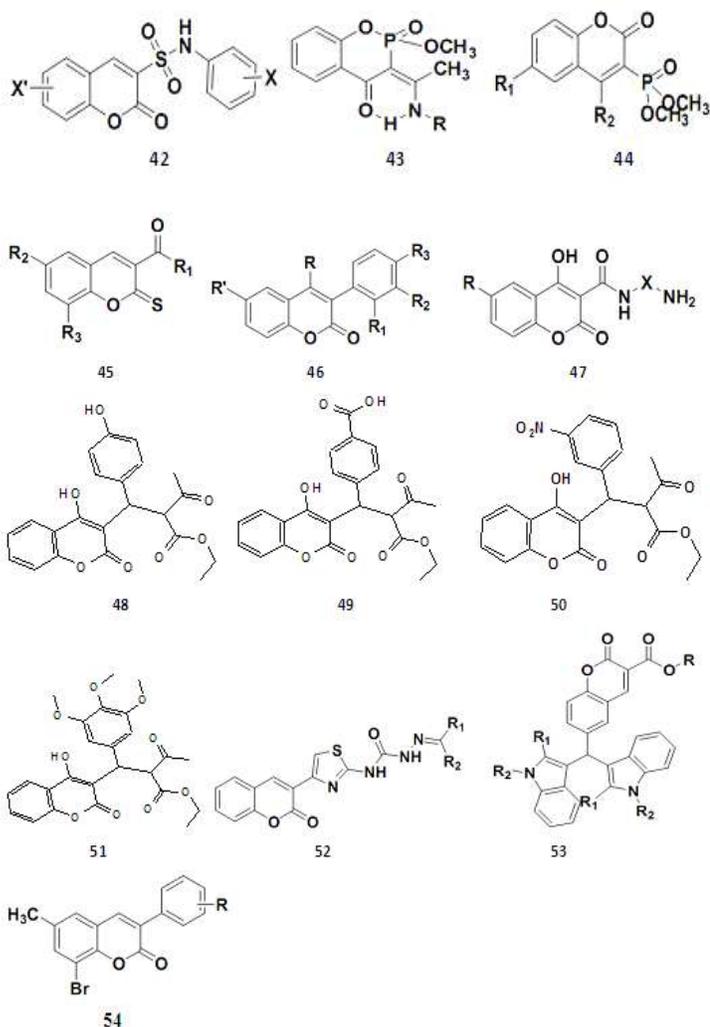
inhibition against *S. aureus* and *B. subtilis* and minimum inhibition against *E. coli* and *P. aeruginosa*. The remaining compounds exhibited moderate activity (Sandeep et al., 2009). Some 4-aryloxmethylcoumarins (22) were screened for their antibacterial and antifungal activity at different concentrations of 500, 250, 100 and 50μg/ml. Antibacterial activity was carried out against two Gram positive bacteria, viz. *S. aureus*, and *Streptococcus faecalis* and three Gram negative bacteria, viz. *E. coli*, *P. aeruginosa*, *K. pneumonia*. Antifungal activity was carried out against five fungi, viz. *A. flavus*, *A. fumigatus, C. 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 (Basanagouda et al., 2009). 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 were screened for their antimicrobial activity against Gram positive *S. aureus* and Gram negative *E. coli* stains and antifungal activity

antibacterial activity against *S. aureus* at a concentration of 106CFC/ml on the surface of a Mueller-Hint on gelose plate. One compound exhibited the strongest antibacterial activity (Hamdi et al., 2006). Some 4-substituted coumarins were evaluated as in vitro screening against Gram positive *S. aureus* and Gram negative *Salmonella typhi*. Ampicillin and trimethoprim were used as standard drugs. Two compounds (30 and 31) were showed significant antibacterial activity at concentration levels of 10 to 200 µg/ml against *S. aureus* and *S. typhi* (Mashelkar and Audi. 2006). Some (7-hydroxy-2-oxo-2H-chromen-4-yl)-acetic acid hydrazides (32) were found to possess high antimicrobial activity against *S. pneumoniae* and were slightly less active against *P. aeruginosa*, *B. subtilis, B. cereus* and *Salmonela panama* (Cacic et al., 2006). The 1,3-dipolar cycloadducts of 3-azidoacetylcoumarins with dimethyl acetylene dicarboxylate. All the compounds and their adducts were screened for antimicrobial activity and good results were obtained (Kusanur and Kulkarni. 2005). Pyrimidino[5',4'-6,5]-,pyridino[3',2'-6,5] and pyrrolo[3',2'-5,6]4H-pyrano-[3,2-c][1] benzo-pyran-6-one derivatives were screened for their activity against Gram positive bacteria, *S. aureus, B. subtilis, B. cereus*, Gram negative bacteria, *P. aurignosa, E. coli, Enterobacter aerogenes* as well as fungi *A. niger, Penicillium italicum, Fusarium oxysporum*. Standard drugs amoxicillin for bacteria and mycostatin for fungi were used at a concentration of 1000 ppm for comparisons. Compound (33) exhibited excellent antibacterial activity towards *E. aerogenes* (Al-Haiza et al., 2003).

Some heterocycles by incorporating isoxazoles, pyromidines and 1,5-benzothiazeoine in a parent 4-hydroxycoumarin molecule which enhanced the in vitro antibacterial activity of these molecules (Mulwad and Pawar, 2003). The 3-amino-(N-aryl substituted)-6-bromo-2H-1-benzopyran-2-ones (34) and 6-bromo-3-phenoxy substituted-2H-1-benzopyran-2-ones (35) were screened for antitubercular activity against highly virulent H37Rv strains of *Mycobacterium tuberculosis* as compared to streptomycin and Isoniazid (Gupta and Phull, 1996; Gupta and Prabu, 1991) Some substituted 3-(4-hydroxybenzoyl)-1H-isochromen-1-one (36), 2-benzopyran-1H-2-one,1H-2-oxo-benzopyran-3-carboxylic acids (37) and 2-benzofuran-1H-one showed good activity against *S. aureus* and *E. coli* (Purohit, 2001). Antibacterial activities of coumarin inhibitors of DNA gyrase B bearing a N-propargyloxycarbamate at C-3' of various 5',5'-di-alkylnoviose including RU79115 (38) were defined. In-vitro, RU79115 bactericidal activity against *Escherichia faecium* and *S. aureus* was time dependent and similar to standard drug vancomycin in case of *S. aureus* (Musicki et al., 2000). A series of coumarin 7-substituted cephalosporins and sulfones were tested against *S. aureus*, *E. coli* and *P.*

antibacterial activity against *S. aureus* and *Salmonella typhi* and antifungal activity against *A. 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 50 µg/ml to 200 µg/ml (Choudhari and Mulwad. 2006). A series of coumarin derived carboxylate ligands and their silver (I) complexes (29) were screened for their in-vitro antibacterial activity against a range of Gram positive and Gram negative stains 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 confirmed potent activity (Creaven et al., 2006). The bis[N-(4-oxocoumarinylmethylene)]-1,4-diamines were exhibited as

aeruginosa with varying concentrations of the associated antibiotic cefotaxime (0.125-256 μg/ml) 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 bacteria with a lower MIC value than for ampicillin alone (Bonsignore et al., 1998).

Anti–inflammatory and analgesic activity

A series of 3-(2-amino-6- pyrimidin-4-yl)-6-bromo-2H chromen-2-ones (39) were tested for analgesic activity at a dose of 20 mg/kg body weight. Among them, compounds having o-chloro, m-chloro and mbromo phenyl exhibited significant analgesic activity and compounds having 2,4-dichloro and 2,6-dichloro phenyl exhibited highly significant activity comparable with Diclofenac sodium. Compounds having o-chloro phenyl, 2,4-dichloro and 2,6-dichloro phenyl were further screened for acute-ulcerogenic activity. Compound having 2,6-dichloro phenyl was found to be most

promising analgesic agent devoid of ulcerogenic effects (Gupta et al., 2010).

A series of 5-(substituted)aryl-3-(3coumarinyl)-1-phenyl-2-pyrazolines (40) were screened for in vivo anti-inflammatory and analgesic activities at a dose of 200 mg/kg. Among these compounds, compounds having 4-Cl-C6H4, 2,4-(Cl)$_2$-C$_6$H$_3$, 3-OMe-C$_6$H$_4$ and 4-F-C$_6$H$_4$ exhibited significant anti-inflammatory activity while compounds having 4-Cl-C$_6$H$_4$ and 2,4-(Cl)$_2$-C$_6$H$_3$ showed significant activity in chronic inflammation such as adjuvant induced arthritis and compared with diclofenac (13.5 mg/kg). These compounds were also exhibited significant analgesic activity and antipyretic activity with minimum ulcerogenic index (Khode et al., 2009). The triheterocyclic thiazoles containing coumarin and carbostyril(1-azacoumarin) (41) were evaluated for their analgesic and anti-inflammatory activities. The 7-chloro substitution in carbostyril and 6,8-dibromo substitution in the coumarin ring improved anti-inflammatory activity (Kalkhambkar et al., 2007). A series of N-aryl substituted 2-imino-2H-1-benzopyran-3-carboxamides and 2-oxo-2H-1-benzopyran-3-carboxamides were screened for anti-inflammatory activity in albino rats. These compounds were found to be comparable with piroxicam and these compounds were found to be essentially non-toxic at the highest dose tested (Bylov et al., 1999).

Anti-cancer activity

The effect of coumarin 3-(N-aryl) sulphonamides (42) 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 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, showed that they activate JNK pathway either by interacting with JNK1 or with one of the upstream kinases in this pathway (Reddy et al., 2004). The cytotoxic effects and alkylating activity of 3-[1-(alkyl amino)-ethylidene]-chroman-2,4-dione, 2-methoxy-3-[1-(alkylamino)-ethylidene-2,3-di-hydro-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. IC$_{50}$ 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 factors in the substituents at the 2-, 3- and 4-positions of the benzopyrone moiety of these compounds (Budzisz et al., 2003).

Antioxidant activity

A 3-alkanoyl/aroyl/heteroaroyl-2H-chromene-2-thiones (45) was tested for free radical scavenging capacity towards the stable free radical 2,2-diphenyl-1- picrylhydrazyl (DPPH). These compounds were found to scavenge DPPH free radicals efficiently. These compounds exhibited profound antioxidant activity. Some compounds were able to protect curcumin from the attack of sulfur free radical generated by radiolysis of glutathione (GSH) (Singh et al., 2010). A series of coumarin analogues (46) bearing a substituted phenyl ring on position 3 were evaluated as antioxidant compounds by using two different antioxidant assays. Ability of the compounds to inhibit soybean lipoxygenase was also determined as an indication of potential anti-inflammatory activity (Roussaki et al., 2010). A series of coumarin-3-carboxamides (47) were evaluated for their in-vitro antioxidant activity and in-vivo anti-inflammatory activity. These derivatives were found to possess these activities (Melagraki et al., 2009). Four 4-hydroxycoumarins, ethyl 2-[(4-hydroxy-2-oxo-2Hchromen-3-yl)(4-hydroxy phenyl) methyl]-3-oxobutanoate (48), 4-[1-(4-hydroxy-2-oxo-2H-chromen-3-yl)-2-(ethoxycarbonyl)-3-oxobutyl] benzoic acid (49), ethyl-2-[(4-hydroxy-2-oxo-2H-chromen-3-yl) (3-nitrophenyl)methyl]-3-oxobutanoate (50) and ethyl-2-[(3,4,5-trimethoxyphenyl)-(4-hydroxy-2-oxo-2H-chromen-3-yl) methyl]-3-oxobutanoate (51) were tested for in vitro antioxidant activity. 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 (A) exhibited the best scavenger activity at the highest concentration (10^{-4} mol/l) (Stanchev et al., 2009).

Antihyperlipidemic activity

A series of coumarin bisindole heterocycles (52) were evaluated for antihyperlipidemic activity in hyperlipidemic hamster model. In these compounds, the substitution at position-3 plays a pivotal role and the presence of ethyl ester over methyl is preferred for pronounced activity. On the other hand, the lower indole pharmacophore focused that the unsubstituted indoles have good activity profile compared to substituted indoles. Among compounds tested, compound having R= -C_2H_5 and R_1 =R_2 = -H showed potent activity and was found to decrease the plasma triglyceride levels by 55%, total cholesterol by 20%, accompanied by an increase in HDL-C/TC ratio by 42% in hyperlipidemic rats to a greater degree than some statins (Sashidhara et al., 2010).

Anticonvulsant activity

Some heteroaryl semicarbazones (53) were tested for anticonvulsant activity using pentylenetetrazole (PTZ) induced seizure, maximal electroshock seizure (MES) and Neurotoxicity tests at 30, 100 and 300 mg/kg dose levels. The 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 phenytoin (Siddiqui et al., 2009).

Anti-parkinsonism activity

A series of 8-bromo-6-methyl-3-phenylcoumarin derivatives (54) 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 had one methoxy group in 4' position. Compound with 3-methoxy group, loses activity and selectivity in respect to the mono and dimethoxy derivatives. These compounds did not showed MAO-A inhibitory activity for the highest concentration tested (100μM) (Matos et al., 2009).

DISCUSSION

Several natural compounds with a coumarinic nucleus have been reported to have various biological activities. Isomeric flavonoids, coumarins might affect the development and scavenging of reactive oxygen species (ROS) and influence processes relating free radical-mediated injury. Coumarin can reduce tissue edema and inflammation. Additionally coumarin and its 7-hydroxy-derivative inhibit prostaglandin biosynthesis, which engage fatty acid hydroperoxy intermediates. Natural products such as esculetin, fraxetin, daphnetin and other related coumarin derivatives are accepted as inhibitors not only of the cycloxygenase and lipoxygenase enzymes, but also of the neutrophil-dependent superoxide anions. Due to the high importance of coumarin derivatives extensive efforts have been made by several researchers, to prepare new substituted heterocyclic coumarin rings mainly at 3-, 4- and/or 7-positions. The naturally occurring or synthetically derived coumarin derivatives, which possess anti-inflammatory as well as antioxidant activities (Fylaktakidou et al., 2004). The current progress in the development of coumarin scaffolds for drug discovery as novel anti-cancer agents (Bae et al., 2004; Munakata et al., 2012). Coumarins are a group of plant-derived polyphenolic compounds. They belong to the benzopyrones family and possess a wide variety of cytoprotective and modulatory functions, which may be turned to therapeutic potentials for multiple diseases. Their physicochemical properties seem to define the extent of the biological activity. The coumarins and their derivatives are synthesis, combinatorial techniques, biological evaluation e.g. antimitotic, immunomodulating, antiviral, anticancer and cytotoxic agents, as well as some new biological assays. Acetylcholinesterase (AChE) enzyme inhibition is an important target for the management of Alzheimer disease (AD) and AChE inhibitors are the main reside drugs for its management. Coumarins are the phytochemicals with wide

range of biological activities including AChE inhibition. The afforded to explore the coumarin for developing novel AChE inhibitors with additional biological activities including decrease in β-amyloid (Aβ) deposition and β-secretase inhibition that are also important for AD management. The different coumarin derivatives act as AChE inhibitors for management of AD (Anand et al., 2012). Several natural and synthetic coumarins and derivatives with potent biological responses appear to be promising anticancer activities. Their clinical evaluation will be critical to assess therapeutic utility. The compounds for which the mechanism of action is well defined can serve as lead compounds for the design of new more promising molecules (Kontogiorgis al., 2012).

CONCLUSIONS

Natural as well as synthetic coumarins have drawn much attention due to its broad pharmacological activities. Many coumarins and their derivatives exert anti-coagulant, anti-tumor, antiviral, anti-inflammatory and anti-oxidant effects, anti-microbial and enzyme inhibition properties. The credit of key structural features within coumarin compounds are crucial for the design and development of new coumarin analogues with improved activities and for the characterization of their mechanism of action and potential side effects. The various substituents in the coumarin nucleus strongly influence the biological activities of the resulting compounds. Different derivatives of coumarin which are synthesized by various researchers and their activities are studied and 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. Although some coumarin derivatives have been characterized to suggest a particular biological activity, the challenge would be the design and develop new derivatives with high specific activity for other pharmacological targets and define their mechanism of action to achieve new therapeutic drugs. Various moieties combined with coumarin produces same or different effects but with different potencies.

REFERENCES

Abd Elhafez, O.M., El Khrisy Eel, D., Badria, F., Fathy Ael, D., 2003. Synthesis and biological investigations of new thiazolidinone and oxadiazoline coumarinderivatives. Archives of Pharmaceutical Research 26(9), 686-96.

Abdelhafez, O.M., Amin, K.M., Batran, R.Z., Maher, T.J., Nada, S.A., Sethumadhavan, S., 2010. Synthesis, anticoagulant and PIVKA-II induced by new 4-hydroxycoumarin derivatives. Bioorganic and Medicinal Chemistry 18(10), 3371-8.

Al-Amiery, A.A., Kadhum, A.A.H., Mohamad, A.B., 2003. Antifungal activities of new coumarins. Molecules 17, 5713- 5723.

Al-Haiza, M.A., Mostafa, M.S., El-Kady, M.Y., 2003. Synthesis and biological evaluation of some new coumarin derivatives. Molecules 8, 275-286.

Anand, P., Singh, B., Singh, N., 2012. A review on coumarins as acetylcholinesterase inhibitors for Alzheimer's disease. Bioorganic and Medicinal Chemistry 20(3), 1175-80.

Aurora, G.M., Jose, G.L., Cristina, L., Consuelo, R.P., 2001. Standardization of rat blood clotting tests with reagents used for humans. Proceedings of the Western Pharmacology Society 44, 153-155.

Bae, H., Kim, H.S., 2004. Solid phase synthesis of 3-(4-hydroxyphenyl)coumarin: preliminary experiments for combinatorial synthesis of substituted 3-phenylcoumarin derivatives. Archives of Pharmaceutical Research 27(8), 811-5.

Bairagi, S., Bhosale, A., Deodhar, M.N., 2009. Design, synthesis and evaluation of schiff's bases of 4-chloro-3-coumarin aldehyde as antimicrobial agents. E-Journal of Chemistry 6(3), 759-762.

Basanagouda, M., Kulkarni, M.V., Sharma, D., Gupta, V.K., Pranesha, Sandhyarani, P., Rasal, V.P., 2009. Synthesis of some new 4-aryloxmethylcoumarins and examination of their antibacterial and antifungal activities. Journal of Chemical Sciences 121(4), 485–495.

Batra, N., Batra, S., Pareek, A., Nagori, B.P., 2012. Diverse Pharmacological Activities of 3-Substituted Coumarins: A Review, International Research Journal of Pharmacy 3(7), 24-29.

Behrami, A., Krasniqi, I., 2012. Antibacterial activity of coumarine derivatives synthesized from8-amino-4,7-dihydroxy-chromen-2-one and comparison with standard drug. Journal of Chemical and Pharmaceutical Research 2012, 4(5), 2495-2500.

Behrami, A., Krasniqi, I., Demaku, S., 2012. Antibacterial activity of coumarinederivatives synthesized from 4,7-dihydroxy-2-oxo-2h-chromene-3-carbaldehyde and comparison with standard drug, International Journal of Research in Pharmacy and Biomedical Sciences 3(3), 1306-1311.

Bhat, M.A., Siddiqui, N., Khan, S.A., Mohamed, M.I, 2009. Synthesis of triazolothiazolidinonederivativesof coumarinwith antimicrobial activity. Acta Polenia Pharmaceutica Drug Research 66(6), 625-632.

Bhatia, M.S., Ingale, K.B., Choudhari, P.B., Bhatia, N.M., Sawant, R.L., 2009. Application quantum and physico chemical molecular descriptors utilizing principal components to study mode of anticoagulant activity of pyridyl chromen-2-one derivatives. Bioorganic and Medicinal Chemistry 17(4), 1654-62.

Bonsignore, L., Cottiglia, F., Elkhaili, H., Jehl, F., Lavagna, S.M., Loy G., Fedele, M.B., Monteil, H., Pompei, D., Secci, D., 1998. Synthesis and antimicrobial activity of coumarin 7-substituted cephalosporins and sulfones. Farmaco 53(6), 425- 430.

Brahmbhatt, D.I., Kaneria, A.R., Patel, A.K., Patel, N.H., 2010. Synthesis and antimicrobial screening of some 3-[4-(3-

aryl-1-phenyl-1H-pyrazol-4-yl)-6-aryl-pyridin-2-yl] and 4-methyl-3-phenyl-6-[4 (3-aryl-1-phenyl-1H-pyrazol-4-yl)-6-aryl-pyridin-2-yl]coumarins. Indian Journal Chemistry 49B, 971-977.

Brooker, N.L., Kuzimichev, Y., Laas, J., Pavlis, R., 2007. Evaluation of coumarin derivatives as anti-fungal agents against soil-borne fungal pathogens. Communication in Agriculture in Applied Biological Sciences 72(4), 785-93.

Budzisz, E., Brzezinska, E., Krajewska, U., Rozalski, M., 2003. Cytotoxic effects, alkylating properties and molecular modelling of coumarin derivatives and their phosphonic analogues. European Journal of Medicinal Chemistry 38, 597-603.

Bylov, I.E., Vasylyev, M.V., Bilokin, Y.V., 1999. Synthesis and anti-inflammatory activity of N-substituted 2-oxo-2H-1-benzopyran-3-carboxamides and their 2-iminoanalogues. European Journal of Medicinal Chemistry 34, 997-1001.

Cacic, M., Trkovnik, M., Cacic, F., Has-Schon, E., 2006. Synthesis and antimicrobial activity ofsome derivatives of (7-hydroxy-2-oxo-2H-chromen-4-yl)-aceticacid hydrazide. Molecules 11, 134-147.

Chen, H., Li, S., Yao, Y., Zhou, L., Zhao, J., Gu, Y., Wang, K., Li, X., 2013. Design, synthesis, and anti-tumor activities of novel triphenylethylene-coumarin hybrids, and their interactions with Ct-DNA. Bioorganic and Medicinal Chemistry Letters 23(17), 4785-4789.

Chen, W., Tang, W., Lou, L., Zhao, W., 2006. Pregnane, coumarin and upane derivatives and cytotoxic constituents from Helicteres angustifolia. Phytochemistry 67(10), 1041-7.

Chimenti, F., Bizzarri, B., Bolasco, A., Secci, D., Chimenti, P., Carradori, S., 2006. Synthesis and invitro selective anti-Helicobacter pylori activity of N- substituted-2-oxo-2H-1-benzopyran-3- arboxamides. European Journal of Medicinal Chemistry 41, 208-212.

Choudhari, B.P., Mulwad, V.V., 2006. Synthesis and antimicrobial screening of 5H,7H-N-(coumarin-6-yl)-2-8-diphenyl-5,7-dioxo-4,5,6,7-tetra-hydrobenzimidazo[5,6-c]-furan and 5H,7H-N (coumarin-6-yl)-2,8-diphenyl-5,7-dioxo-6-(7-methoxy-4-methylcoumarin-6-yl)-4,5,6,7-tetrahydro benzi-midazo [5,6-c]pyrrole. Indian Journal of Chemistry 45B, 314-317.

Creaven, B.S., Devereux, M., Karcz, D., Kellett, A., McCann, M., Noble, A., Walsh, M., 2009. Copper(II) complexes of coumarin-derived Schiff bases and their anti-Candida activity. Journal of Inorganic Biochemistry 103(9), 1196-1203.

Creaven, B.S., Egan, D.A., Kavanagh, K., McCann, M., Noble, A., Thati, B., Walsh, M., 2006. Synthesis, characterization and antimicrobial activity of a series of substituted coumarin-3- carboxyl atosilver(I) complexes. Inorganica Chimica Acta 359, 3976–3984.

de Marchi, A.A., Castilho, M.S., Nascimento, P.G., Archanjo, F.C., del Ponte, G., Oliva, G., Pupo, M.T., 2004. New 3-piperonylcoumarins as inhibitors of glycosomal glyceraldehyde-3-phosphate dehydrogenase (gGAPDH) from Trypanosoma cruzi. Bioorganic and Medicinal Chemistry 12(18), 4823-4833.

Dekic, B.R., Radulovic, N.S., Dekic, V.S., Vukicevic, R.D., Palic, R.M., 2010. Synthesis and antimicrobial activity of new 4-heteroarylamino coumarin derivatives containing nitrogen and sulfur as hetero atoms. Molecules 15, 2246-2256.

Dekic, V., Radulovic, N., Vukićevic, R., Dekic, B., Stojanovic-Radic, Z., Palic, R., 2011. Influence ofthe aryl substituentidentity in 4-arylamino-3-nitrocoumarins on theirantimicrobial activity. African Journal of Pharmacy and Pharmacology 5(3), 371-375.

Doss, S.H., Wardakhan, W.W., Louca, N.A., 2001. The reaction of digitoxin and digoxin with cyanoacetic acid hydrazide: synthesis of coumarin, thiazole, thiophene and pyridine derivatives with potential biological activities. Archives of Pharmaceutical Research 24(5), 377-84.

Fylaktakidou, K.C., Hadjipavlou-Litina, D.J., Litinas, K.E., Nicolaides, D.N., 2004. Natural and synthetic coumarin derivatives with anti-inflammatory/ antioxidant activities. Current Pharmaceutcal Design 10(30), 3813-33.

Gnerre, C., Catto, M., Leonetti, F., Weber, P., Carrupt, P.A., Altomare, C., Carotti, A., Testa, B., 2000. Inhibition of monoamine oxidases by functionalized coumarin derivatives: biological activities, QSARs, and 3D-QSARs. Journal of Medicinal Chemistry 43(25), 4747-58.

Govori, S., Spahiu, S., Kalaj, V., Leci, O., Haziri, A., Ibrahimi, H., 2010. Antimicrobial properties of newly synthesized derivatives of coumarine. American Journal of Biochemistry & Biotechnology 6(4), 275- 278.

Gupta, A., Priya, N., Jalal, S., Singh, P., Chand, K., Raj, H.G., Parmar, V.S., DePass, A.L., Sharma, S.K., 2010. Specificity of calreticulin transacetylase to acetoxy derivatives of benzofurans: effect on the activation of platelet nitric oxide synthase. Biochimie 92(9), 1180-5.

Gupta, A.S., Phull, M.S., 1996. A convenient onepot synthesis and antitubercular activityof coumarin derivative containing sulphanilamidegroup: Part II. Indian Journal of Chemistry 35, 276-277.

Gupta, A.S., Prabhu, B.S., 1996. Synthesis of 3-amino-(N-aryl substituted)-6-bromo-2H-1-benzopyran-2-ones and 6-bromo-3-phenoxy substituted-2H-1-benzopyran-2-ones aspotential antitubercular agents: Part I. Indian Journal of Chemistry 35, 170-171.

Gupta, J.K., Sharma, P.K., Dudhe, R., Chaudhary, A., Verma, P.K., 2010. Synthesis, analgesic and ulcerogenic activity of novel pyrimidine derivative of coumarin moiety. Analele UniversităŃii din Bucuresti-Chimie (serie nouă) 19(2), 09-21.

Hamdi, N., Lidrissi, C., Saoud, M., Nievas, A.R., Zarrouk, H., 2006. Synthesis of some new biologically active coumarin derivatives. Chemistry of Heterocyclic Compounds 42(3), 320-325.

Han, J., Sun, L., Huang, X., Li, Z., Zhang, C., Qian, H., Huang, W., 2014. Novel coumarin modified GLP-1 derivatives with enhanced plasma stability and prolonged in vivo glucose-lowering ability. British Journal of Pharmacology DOI: 10.1111/bph.12843.

Han, S., Zhou, V., Pan, S., Liu, Y., Hornsby, M., McMullan, D., Klock, H.E., Haugen, J., Lesley, S.A., Gray, N., Caldwell, J., Gu, X.J., 2005. Identification of coumarin derivatives as a novel class of allosteric MEK1 inhibitors. Bioorganic and Medicinal Chemistry Letters 15(24), 5467-73.

Jain, P.K., Joshi, H., 2012. Coumarin: Chemical and Pharmacological Profile. Journal of Applied Pharmaceutical Sciences 2(6), 236-240.

Jalal, S., Chand, K., Kathuria, A., Singh, P., Priya, N., Gupta, B., Raj, H.G., Sharma, S.K., 2012. Calreticulin transacetylase: a novel enzyme-mediated protein acetylation by acetoxy derivatives of 3-alkyl-4-methylcoumarins. Bioorganic Chemistry 40(1), 131-136.

Kalkhambkar, R.G., Kulkarni, G.M., Shivkumar, H., Rao, R.N., 2007. Synthesis of noveltriheterocyclic thiazoles as anti-inflammatory and analgesic agents. European Journal of Medicinal Chemistry 42, 1272-1276.

Kathuria, A., Gupta, A., Priya, N., Singh, P., Raj, H.G., Prasad, A.K., Parmar, V.S., Sharma, S.K., 2009. Specificities of calreticulin transacetylase to acetoxy derivatives of 3-alkyl-4-methylcoumarins: effect on the activation of nitric oxide synthase. Bioorganic and Medicinal Chemistry 17(4), 1550-6.

Keri, R.S., Hosamani, K.M., Reddy, H.S., Shingalapur, R.V., 2010. Synthesis, in-vitro antimicrobial and cytotoxic studies of novel azetidinone derivatives. Archives of Pharmacy (Weinheim) 343(4), 237-47.

Khan, K.M., Saify, Z.S., Khan, M.Z., Zia-Ullah., Choudhary, I.M., Atta-Ur-Rahman., Perveen, S., Chohan, Z.H., Supuran, C.T., 2004. Synthesis of coumarin derivatives with cytotoxic, antibacterial and antifungal activity. Journal of Enzyme Inhibitors & Medicinal Chemistry 19(4), 373-9.

Khode, S., Maddi, V., Aragade, P., Palkar, M., Ronad, P.K., Mamledesai, S., 2009. 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. European Journal of Medicinal Chemistry 44, 1682- 1688.

Kontogiorgis, C., Detsi, A., Hadjipavlou-Litina, D., 2012. Coumarin-based drugs: a patent review (2008-present). Expert Opinion in Therapeutic Patents 22(4), 437-54.

Kontogiorgis, C., Hadjipavlou-Litina, D., 2003. Biological evaluation of several coumarin derivatives designed as possible anti-inflammatory/antioxidant agents. Journal of Enzyme Inhibitors & Medicinal Chemistry 18(1), 63-69.

Kontogiorgis, C.A., Hadjipavlou-Litina, D.J., 2005. Synthesis and antiinflammatory activity of coumarin derivatives. Journal of Medicinal Chemistry 48(20), 6400-8.

Kontogiorgis, C.A., Savvoglou, K., Hadjipavlou-Litina, D.J., 2006. Antiinflammatory and antioxidant evaluation of novel coumarin derivatives. Journal of Enzyme Inhibitors & Medicinal Chemistry 21(1), 21-29.

Kudale, S.D., Deodhar, M.N., 2012. Synthesis and evaluation of some coumarin containing potential antimicrobial agents. E-Journal of Chemistry 9(4), 2493-2500.

Kumar, S., Singh, B.K., Kalra, N., Kumar, V., Kumar, A., Prasad, A.K., Raj, H.G., Parmar, V.S., Ghosh, B., 2005. Novel thiocoumarins as inhibitors of TNF-alpha induced ICAM-1 expression on human umbilical vein endothelial cells (HUVECs) and microsomal lipid peroxidation. Bioorganic and Medicinal Chemistry 13(5), 1605-1613.

Kusanur, R.A., Kulkarni, M.V., 2005. New 1,3-dipolar cycloadducts of 3- azidoacetylcoumarins with DMAD and their antimicrobial activity. Indian Journal of Chemistry 44, 591-594.

Lee, J.H., Kim, Y.G., Cho, H.S., Ryu, S.Y., Cho, M.H., Lee, J., 2014. Coumarins reduce biofilm formation and the virulence of Escherichia coli O157:H7. Phytomedicine 21(8-9), 1037-1042.

Li, Z., Hu, J., Sun, M., Song, X., Li, G., Liu, Y., Li, G., Ji, H., Liu, G., Chen, N., 2013. In vitro and in vivo anti-inflammatory effects of IMMLG 5521, a coumarin derivative. International Immunopharmacology 17(2), 400-403.

Lin, P.Y., Yeh, K.S., Su, C.L., Sheu, S.Y., Chen, T., Ou, K.L., Lin, M.H., Lee, L.W., 2012. Synthesis and antibacterial activities of novel 4-Hydroxy-7-hydroxy- and 3-Carboxycoumarin derivatives. Molecules 17, 10846-10863.

Liu, J., Wu, F., Chen, L., Zhao, L., Zhao, Z., Wang, M., Lei, S., 2012. Biological evaluation of coumarin derivatives as mushroom tyrosinase inhibitors. Food Chemistry 135(4), 2872-2878.

Mashelkar, U.C., Audi, A.A., 2006. Synthesis of some novel4-substituted coumarins having potential biological activity (Part III), Indian Journal of Chemistry 45B, 1463-1469.

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

Melagraki, G., Afantitis, A., Markopoulou, O.I., Detsi, A., Koufaki, M., Kontogiorgis, C., 2009. Synthesis and evaluation of the antioxidant and anti-inflammatory activity of novel coumarin-3-aminoamides and their alpha-lipoic acid adducts. European Journal of Medicinal Chemistry 44, 3020-3026.

Mohamed, H.M., El-Wahab, A.H.F.A., Ahmed, K.A., El-Agrody, A.M., Bedair, A.H., Eid, F.A., Khafagy, M.M., 2012. Synthesis, reactions and antimicrobial activities of 8-ethoxycoumarin derivatives. Molecules 17, 971-988.

Mulwad, V.V., Pawar, R.B., 2003. Synthesis of some antibacterial compounds from 4- hydroxycoumarin. Indian Journal of Chemistry 42, 2091-2096.

Mulwad, V.V., Satwe, D.S., 2006. Synthesis of biologically active 4-[1-(2H-[1]-4-hydroxy-2-oxobenzopyran-3-yl)methylidene]-2-phenyl-4H-oxazol-5-ones and [1,2,4]triazine-6-one and its derivatives. Indian Journal of Chemistry 45, 1210-1215.

Munakata, R., Inoue, T., Koeduka, T., Sasaki, K., Tsurumaru, Y., Sugiyama, A., Uto, Y., Hori, H., Azuma, J., Yazaki, K., 2012. Characterization of coumarin-specific prenyltransferase activities in Citrus limon peel. Biosciences, Biotechnology and Biochemistry 76(7), 1389-93.

Musicki, B., Periers, A.M., Laurin, P., Ferroud, D., Benedetti, Y., Lachaud, S., Chatreaux, F., Haesslein, J.L., Iltis. A., Pierre, C., Khider, J., Tessot, N., Airault, M., Demassey, J., Dupuis-Hamelin, C., Lassaigne, P., Bonnefoy, A., Vicatc, P., Klicha, M., 2000. Improved antibacterial activities of coumarin antibiotics bearing 50,50-dialkylnoviose: biological activity of RU79115. Bioorganic and Medicinal Chemistry Letters 10, 1695- 1699.

Olayinka, O.A., Nwinyi, O.C., 2010. Microwave-assisted synthesis and evaluation of antimicrobial activity of 3-{3-(s-Aryl and s-Heteroaromatic)acryloyl}-2Hchromen-2-one derivatives. Journal of Heterocyclic Chemistry 47(179), 179-187.

Patel, A.K., Patel, N.H., Patel, M.A., Brahmbhatt, D.I., 2010. Synthesis, characterization and antimicrobial activity of some 4-aryl-2,6-di(coumarin-3-yl)pyridines. ARKIVOC 11, 28-38.

Porwal, B., Jayashree, B.S., Attimarad, M., 2009. Synthesis of some new 3- coumarinoylpyridinium and quinolinium bromides for their antimicrobial activity. Journal of Basic and Clinical Pharmcology 1(1), 29-32.

Purohit, N.V., 2001. Synthesis and studies on biological activities of some substituted 2-benzopyran-1H-one, 1H-2-oxo-benzopyran-3-carboxylic acids and 2-benzof uran-1H-one, Indian Journal of Chemistry 40B, 222-227.

Reddy, N.S., Mallireddigari, M.R., Cosenza, S., Gumireddy, K., Bell, S.C., Reddy, E.P., 2004. Synthesis of new coumarin 3-(N-aryl)sulfonamides and their anticancer activity. Bioorganic and Medicinal Chemistry Letters 14, 4093-4097.

Roussaki, M., Kontogiorgis, C.A., Litina, D.H., Hamilakis, S., Detsi. A., 2010. A novel synthesis of 3-aryl coumarins and evaluation of their antioxidant and lipoxygenase inhibitory activity. Bioorganic and Medicinal Chemistry Letters 20, 3889-3892.

Sahoo, S.S., Shukla, S., Nandy, S., Sahoo, H.B., 2012. Synthesis of novel coumarin derivatives and its biological evaluations. European Journal of Experimental Biology 2(4), 899-908.

Sandeep, G., Ranganath, Y.S., Bhasker, S., Rajkumar, N., 2009. Synthesis and biological screening of some novel coumarin derivatives. Asian Journal of Research in Chemistry 2(1), 46-48.

Sashidhara, K.V., Kumar, A., Kumar, M., Srivastava, A., Puri, A., 2010. Synthesis and antihyperlipidemic activity of novel coumarin bisindole derivatives. Bioorganic and Medicinal Chemistry Letters 20, 6504-6507.

Siddiqui, N., Arshad, M.F., Khan, S.A., 2009. Synthesis of some new coumarin incorporated thiazolyl semicarbazones as anticonvulsants. Acta Polonia Pharm-Drug Research 66(2), 161-167.

Singh, I., Kaur, H., Kumar, S., Kumar, A., Lata, S., Kumar, A., 2010. Synthesis of new coumarin derivatives as antibacterial agents, International Journal of ChemTech Research 2(3), 1745-1752.

Singh, O.M., Devi, N.S., Thokchom, D.S., Sharma, G.J., 2010. Novel 3-alkanoyl/aroyl/heteroaroyl-2Hchromene-2-thiones: Synthesis and evaluation of their antioxidant activities. European Journal of Medicinal Chemistry 45, 2250-2257.

Stanchev, S., Hadjimitova, V., Traykov, T., Boyanov, T., Manolov, I., 2009. Investigation of the antioxidant properties of some new 4-hydroxycoumarin derivatives. European Journal of Medicinal Chemistry 44, 3077-3082.

Vaso, K., Behrami, A., Govori, S., 2012. Synthesis and antibacterial activity of 4-(4 hydroxyphenylamine)-3-[1-(phenylhydrazine]-2H-[1]-benzopyran-2-one. The comparison of the antibacterial activity with standard drugs. Natura Montenegrina 11(1), 93-103.

Venkataraman, S., Meera, R., Ramachandran, V., Devi, P., Aruna, A., Parameswari, S.P.T., Nagarajan, K., 2014. Antioxidant and anticoagulant activity of novel n-substituted-4- methyl-5,7-dihydroxyl coumarin and its ester derivatives. International Journal of Pharmacy Review and Research 4(1), 25-32.

Vyas, K.B., Nimavat, K.S., Joshi, K.M., Jani, G.R., 2012. Synthesis of 3-[{(3-(2'-nitrophenyl)}-prop-2-enoyl]-4-hydroxy-6-methyl-2Hchromene-2-one andits metalcomplexes asanantimicrobial agent, Journal of Chemical and Pharmaceutical Research 4(5), 2720-2723.

Yang, J., Liu, G.Y., Dai, F., Cao, X.Y., Kang, Y.F., Hu, L.M., Tang. J.J., Li, X.Z., Li, Y., Jin, X.L., Zhou, B., 2011. Synthesis and biological evaluation of hydroxylated 3-phenylcoumarins as antioxidants and antiproliferative agents. Bioorganic and Medicinal Chemistry Letters 21(21), 6420-6425.

Zavrsnik, D., Halilovic, S.S., Softic, D., 2011. Synthesis, structure and antibacterial activity of 3- substituted derivatives of 4-hydroxycoumarin. Periodicum Biologorum 113(1), 93-97.