RECENT STRATEGIES FOR EFFICIENT SYNTHESIS AND BIOLOGICAL ACTIVITIES OF COUMARIN-CHALCONES DERIVATIVES

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ABSTRACT
Coumarins and chalcones are potential pharmacological and biologically active molecules obtained from natural sources. Coumarins have predominant pharmacological activities such as antidiabetic, antitumor, and anti-inflammatory activity. Chalcones are also one of the naturally occurring pharmacologically vital molecules with different activities such as anti-inflammatory, antitumor, antimicrobial, and antimalarial activity. Literature reveals that a huge number of coumarinyl chalcone derivatives have various pharmacological activities. Coumarinyl chalcone derivatives gained more prominence due to their significant biological activities. This work explains the current information about synthesis techniques, pharmacological importance, and clinical applications of coumarinyl chalcone derivatives.

Keywords: Coumarin, Chalcone, Derivatives, Synthesis, Biological activities.

INTRODUCTION
Coumarins are pharmacologically important compounds obtained from natural sources. Coumarin is 2H-chromen-2-one which belongs to benzopyrone class [1]. Coumarin is an oxygen heterocyclic compound, which plays an important role in the realm of natural products and synthetic organic chemistry. The coumarins are the largest class of benzopyran derivatives. They are found mainly in higher plants. Most natural coumarins are oxygenated at C-7; umbelliferone (7-hydroxycoumarin) being regarded as the structural and biogenetic parent of the more highly oxygenated coumarins [2]. Naturally occurring coumarins are found in many plants, notably in high concentration in tonka bean, woodruff, lavender, licorice, strawberries, apricots, cherries, cinnamon, sweet clover and bison grass. Coumarin was first isolated from coumarine in 1820 and it has been used in perfumes since 1892 due to its pleasant (sweet) smell. It was first synthesized in 1868 [3,4]. It is used in the pharmaceutical industry as a precursor reagent in the synthesis of several synthetic anticoagulant pharmaceuticals similar to dicoumarol, the notable ones being warfarin (brand name Coumadin) and some even more potent rodenticides that work by the same anticoagulant mechanism. 4-hydroxycoumarins are a type of Vitamin K antagonist. Pharmaceutical (modified) coumarins were all developed from the study of sweet clover disease [5]. However, unmodified coumarin itself, as it occurs in plants, has no effect on the Vitamin K coagulation system, or the action of warfarin-type drugs.

Coumarin and its derivatives can be synthesized by different methods such as Pechmann [5], Knoevenagel [6], Perkin [7], Friedel–Crafts [8], Reformatsky [9], and Wittig [10] reactions.

Coumarin and its derivatives possess anticoagulant [11-14], antimicrobial [15-16], antioxidant [17], anti-inflammmatory [18], anticancer [19], anti-HIV [20,21], anti-tuberculosis [22,23], anti-influenza [24], anti-Alzheimer [25,26], antiviral [27], antihyperlipidemic [28-29], antihypertensive [30], anticonvulsant [31,32], antiangiogenic [33-34], cytotoxic P38 inhibiting [35,36], neuroprotective [37], androgenic [38,39], antimalarial [40], antidiabetic [41], antitumor [42], and antipsychotic [43] activities. Coumarins also used for the treatment of multiple sclerosis [44].

Chalcones are secondary metabolites obtained from the main precursors of flavonoids and isoflavonoids biosynthesis occurred in from terrestrial plants. Chalcones (1,3-diaryl-2-propene-1-ones) one of the major classes of natural products with wide spread distribution in fruits, vegetables, spices, tea, and soya-based food stuff [45]. Chemically, chalcones contain open chain flavonoid moiety whose basic structure includes two aromatic rings which are bound by three-carbon alpha-beta unsaturated carbonyl system [46].

Chalcones and its derivatives can be synthesized by different methods, but Claissen-Schmidt condensation still holds high position. The best method for the synthesis of chalcones is the conventional Claisen-Schmidt [47-50]. Other renowned techniques include Suzuki reaction [51], Friedel-Crafts acylation [52] with cinnamoyl chloride, Allam–Robinson condensation [53], direct cross-coupling reaction [54], microwave irradiation [55], Julia–Kocienski olefination [56], and grinding technique [57].

Chalcones have been reported to possess many useful biological properties including antimicrobial [58-60], anti-inflammatory [61-64], anticancer [65-68], anti-HIV [69,70], antioxidant [71-73], anticoagulant [74,75], anti-tuberculosis [76], antipsychotic [70], and antimalarial [77] activities.

IMPORTANT OF COUMARINYL CHALCONE
The skeletal structure of coumarin and chalcone is extensively available from the natural source and possesses prominent pharmacological activities individually. Joining of these to molecules might result in amplification of pharmacological activity than there individual activities.

Recent research suggests that the fusion of a chalcone moiety with the coumarin ring may be promising for the synthesis of derivatives with enhanced two-photon absorption cross-sections [78,79].

SYNTHESIS OF COUMARINYL CHALCONE
Thineshen M, et al [80] reported the synthesis of 2- and 4-substituted coumarinyl chalcones by refluxing the phenolic aldehyde with ethyl acetoacetate in ethanol with continuous stirring about 16 h, piperidine as the catalyst. The resulting pure crystalline coumarin was refluxed with different substituted aromatic aldehydes in ethanol about 5 h, piperidine as the catalyst to get the coumarinyl-chalcones.
Sashidhara et al. [81] reported the synthesis of novel coumarin-chalcone hybrids by treating 2-sec-butylphenol with hexamethylene triamine or TFA at 120°C about 3 h to get 5-sec-butyl-4-hydroxyisophthalaldehyde. Then, it was converted to chalcone derivative by treating with p-substituted acetophenone in dioxane at 80–90°C, about 1–1.5 h. Then, it was fused with coumarin by refluxing with ethyl acetooacetate in ethanol about 30 min, piperidine as a catalyst or by refluxing with malonic acid in aromatic alcohol about 30 min, piperidine as the catalyst. Vazquez-Rodriguez et al. [82] reported synthesis of coumarin-chalcones using Knoevenagel reaction for the preparation of 3-acetylcoumarin (salicylaldehyde ethyl acetoacetate and a few drops of piperidine were mixed for 5 min at room temperature without any solvent) and Claisen-Schmidt aldol condensation in basic conditions (A mixture of 3-acetylcoumarin and different substituted benzaldehyde in ethanol was stirred with a few drops of piperidine under reflux during 2–12 h) for the preparation of titled compounds. Patel et al. [83] reported synthesis of some coumarinyl chalcones by reacting the 4-hydroxy coumarin with phosphorus oxychloride and glacial acetic acid to get 4-hydroxy-3-acetyl coumarin and the second step involved the Knoevenagel condensation between the same molar amount of 4-hydroxy-3-acetyl coumarin (3) and substituted benzaldehydes with chloroform in the presence of piperidine catalyst.

Trivedi et al. [84] reported the synthesis of coumarinyl chalcones by reacting the aromatic phenol with malonic acid in the presence of phosphorus oxychloride and zinc chloride at 70°C about 20 h, and the resulting compound was acetylated with glacial acetic acid and phosphorus oxychloride. Then, the acetylated coumarin was refluxed with substituted aromatic aldehydes in chloroform with piperidine at 80°C about 1–1.5 h.

Prasad et al. [85] reported the synthesis of coumarinyl chalcones by refluxing the 3-acetyl coumarin and substituted aromatic aldehydes in ethanol with piperidine about 1–7 h.

Hafez et al. [86] reported the synthesis of coumarinyl chalcones by acetylation the coumarin with acetic acid and phosphorus oxychloride to form 3-acetyl coumarin; then, it was refluxed with substituted aromatic aldehydes in ethanol with piperidine about 5–7 h.

Balaji et al. [87] reported the synthesis of coumarinyl chalcones by refluxing the 7-hydroxy-4-methyl coumarin and acetic anhydride for 1–5 h under anhydrous conditions to get 7-acetoxy-4-methyl coumarin. Then, it was heated under anhydrous conditions in an oil bath at 125°C and the temperature was raised and maintained for 2 h at 145–160°C to get 8-acetyl-7-hydroxy-4-methyl coumarin. Then, it was stirred with substitute aromatic aldehyde in ethanol at room temperature to get the coumarinyl chalcones.

Siddiqui [88] reported the green synthesis of coumarinyl chalcones by mixing of aldehyde, heterocyclic methyl ketones, and HClO4–SiO2 and heated at 80°C for specified time.
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Sun and Cui [89] reported the synthesis of coumarinyl chalcones by refluxing a mixture of 3-acetyl coumarins aryl and heteroaryl aldehydes (2 mmol) and piperidine (0.5 mL) in ethanol (25 mL) for 3–5 h.

Jagtap et al. [90] reported the synthesis of coumarinyl-chalcone derivatives from 8-acetyl-1,4-diethyl-1,2,3,4-tetrahydro-7H-pyrano[2,3-g]quinazolin-7-one by reflux in dry ethanol with pyridine for 12 h.

Khode et al. [91] reported the synthesis of coumarinyl chalcones by reacting the salicylaldehyde with ethyl acetoacetate and piperidine with stirring at room temperature for 20 min. Then, the resulting coumarin was refluxed with aromatic aldehyde and piperidine in n-butanol for 4 h.

Jayashree et al. [92] reported the synthesis of coumarinyl chalcones by adding piperidine with continuous to a cooled suspension of mixture of salicylaldehyde or substituted salicylaldehyde and ethyl acetoacetate. The mixture was then maintained at freezing temperature for 2–3 h to get 3-acetyl coumarin/substituted 3-acetyl coumarins. Then, the 3-acetylcoumarin was mixed with corresponding aldehyde in the presence of Bi(OTf)3. The reaction mixture was stirred at 50°C for a specified time.

Mahmoud and El-Remaly [94] reported the synthesis of bioactive coumarin-chalcone compounds by mixing of salicylaldehyde or methyl salicylaldehyde with ethyl acetoacetate in the presence of piperidine without any solvent to get 3-acetylcoumarin. Then, the 3-acetylcoumarin was mixed with corresponding aldehyde in the presence of Bi(OTf)3. The reaction mixture was stirred at 50°C for a specified time.

BIOLOGICAL ACTIVITIES OF COUMARINYL CHALCONES

Antimicrobial

Moodley et al. [80] reported the antimicrobial activity of 2- and 4-substituted-coumarinyl chalcone derivatives through in silico and in vitro experiments. In silico studies were performed for the titled compounds against cefditoren bound 2Z2M enzyme using autodock-4 software. The study reveals that the oxy prenyl substituted compounds show good binding affinities as that of controls. In silico experiment was conducted for the assessment of antimicrobial activity of synthesized compounds against Gram-positive, Gram-negative, and fungal strains using ciprofloxacin and ampicillin as controls. The experiment reveals that the activity of chalcone was not intensified by fusing of coumarin ring. Only the substitutions such as 4-methoxy (1a, 1b), 2-fluoro (1c), and 2-hydroxy (1d) made to the chalcone moiety increase the activity to some extent.

Vazquez-Rodriguez et al. [82] reported the antibacterial activity of coumarin-chalcone hybrids for the treatment of tenacibaculosis through disk diffusion assay against general Gram positive and Gram negative and 17 different strains of Gram-negative marine bacteria belongs to Tenacibaculum genus using oxolinic acid, enrofloxacin, and ampicillin as controls. Among all the organisms, only Tenacibaculum maritimum strain shows maximum sensitivity to the hybrids having 8-amino substitution at the 3rd and 4th positions on benzyl ring (2a-d) of chalcone.
Rodriguez et al. [95] reported the trypanocidal activity of coumarin-chalcone hybrids against epimastigote, trypomastigote, and amastigote stages of *Trypanosoma cruzi* parasite. The study revealed that the hybrids were more active against trypomastigote stage of parasite. The hybrids (3a-d) possessing the methoxy group on “B” ring of chalcone at the 2nd and 5th positions show significant trypanocidal activity against amastigote stage.

Deshpande et al. [96] reported the antibacterial activity of coumarin-chalcone hybrids (4a-g) against five human pathogens. The hybrid (4g) with para chloro substitution on benzyl ring of chalcone shows potent activity against Gram-positive bacteria.

Trivedi et al. [84] reported screening of anti-HIV for coumarinyl chalcones (5). Unfortunately, no compound shows positive result for anti-HIV activity.

Hamdi et al. [97] reported that the coumarin-chalcone hybrids (6) with electron-withdrawing and electron donating groups on “B” ring of chalcone show moderate antibacterial activity.

Spirtovic-Halilovic et al. [98] reported the *in vitro* and *in silico* experiments for screening the antibacterial activity of coumarin-chalcone hybrids (7a-d). The *in vitro* method reveals that the hybrids (7d) with bromine substitution on “B” ring of chalcone show the highest potency against gram positive organisms. The *in silico* studies explain the stability and reactivity of hybrids. Hybrids with bromine substitution on “B” ring of chalcone are most active and least reactive.

Naruka et al. [99] reported the antimicrobial activity of coumarin-chalcone hybrids (8a-i). The study reveals the hybrid (8h) with dimethyl amino substitution at para and meta position and hybrid (8i) with para dimethyl amino substitution on “B” ring of chalcone shows better activity than control drug sulfamethoxazole.

Quadri-Spinelli et al. [100] reported the antibacterial activity of natural coumarin-chalcones against *Bacillus cereus*, *Staphylococcus epidermidis*, and *Micrococcus luteus*. The hybrid (9) with 4-benzyl substitution on coumarin ring and saturation of ethylene bond of chalcone with hydrogen shows significant antibacterial activity than control drug chloramphenicol.
Prasad et al. [85] reported the antimicrobial activity of coumarin-chalcones (10a-e). The study reveals that the compound (10e) with dimethoxy substitution on “B” ring of chalcone shows potent antimicrobial activity.

Hafez et al. [86] reported the screening of coumarinyl chalcone derivatives (11a-c) for antimicrobial activity. Compounds with 4-chloro (11a) and 4-bromo (11b) substitution on “B” ring of chalcone proved to be active against bacteria and yeast, but did not show activity against fungi.

The antibacterial screening for coumarinyl chalcones indicates that the compound (12) with bromo substitution at the 6th position of coumarin ring and ortho-chloro substitution on “B” ring of chalcone has proved to be potent antibacterial activity.

Anticancer activity
Sashidhara et al. [81] reported the in vitro anticancer activity of novel coumarin-chalcone hybrids (13a-c, 14a-c, and 15a-c) using sulforhodamine-B assay. The assay indicates the observation of growth inhibition by the synthesized compounds in four human cell lines and one normal fibroblast. Compounds with chlorine, methyl, and hydrogen substitution at meta position to the “B” ring of chalcone show potent activity against all cell lines. In addition, the substitution of methyl ester at the 3rd position to the coumarin ring shows significant anticancer activity.

Han et al. [102] reported the antiproliferative activity of naturally occurring coumarin-chalcone hybrids from Cyclosorus parasiticus by sulforhodamine-B assay against six cancer cell lines. The compound (19) having 6-methyl-dihydrocoumarin shows potent activity against all cell lines compared to doxorubicin control.

Valente et al. [101] reported the anticancer (CDC25 inhibitor) activity of coumarinyl chalcone hybrids by dephosphorylation assay with 3-o-methyl fluorescein phosphate using human glutathione-s-transferase recombinant enzyme. The hybrid (16) with benzoylvinyl group at the 4th position to the coumarin ring shows efficient inhibition against CDC25A and CDC25B.

Quadri-Spinelli et al. [100] reported the cytotoxic activity of novel coumarin-chalcone derivatives occurring naturally by extraction from leaves of Cyclosorus interruptus. The activity was examined to the isolated compounds on KB (human nasopharyngeal carcinoma) cell growth. Compounds (17, 18) which are not having cyclic ether or dioxocene groups between coumarin and chalcone rings show better cytotoxic activity.

Kuladeep et al. [83] reported the antiproliferative activity of coumarinyl chalcones against breast cancer cell lines. Compound (20) with methoxy substitution at 2,3,4 carbons of “B” ring of chalcone proved to be potent antiproliferative agents.
Delel et al. [103] reported the anticancer activity of coumarin-chalcones against CDC25 phosphatase. Hybrids with chlorine and bromine at the 6th position on coumarin ring (21) inhibit CDC25A more than hybrids with methoxy group at the 6th position of coumarin ring. However, in case of CDC25B, the activity was reversed. Compound with (22) methoxy substitution on phenyl moiety increasing the activity against CDC25A and decreases the activity against CDC25B. In addition, compound (23) with substitution at the 7th position of coumarin with N,N-dimethyl amino group increases the activity against CDC25A.

Hafez et al. [86] reported the antitumor activity of coumarinyl chalcone derivatives. The antitumor activity was analyzed against human hepatocarcinoma cell lines and human breast adenocarcinoma cell lines using (3-(4,5-Dimethylthiazol-2-yl)-2,5-Diphenyltetrazolium Bromide) assay. The compound (24a) with 5-methyl and 2-furyl substitution on “B” ring of chalcone shows weak cytotoxic activity, in the same way, the compound (24b) with 4-bromo substitution on “B” ring of chalcone shows very weak cytotoxic activity.

Pingaew et al. [93] reported the anticancer activity of chalcone-coumarin hybrids against HuCCA-1, HepG2, A549, and MOLT-3. The hybrids which possess triazole show potent anticancer activity against MOLT-3 and HuCCA-1. Hybrid (25) with tri-substituted methoxy group selectively inhibits MOLT-3. Hybrids with 2,3-dimethoxy group show significant activity against A549. Hybrids with 2,3-dimethoxy groups on ring “B” and 3-substituted coumarinyl ring exhibit high inhibition potency than corresponding 3,4-dimethoxy substitution on ring “B” of chalcone (Ratchanok et al., 2014).

Antimalarial activity
Patel et al. [83] reported the antimalarial activity of coumarinyl chalcone hybrids against chloroquine susceptible (3D7) and chloroquine-resistant (W2) Plasmodium falciparum. The substitutions at meta and para positions to the “B” ring of chalcone moiety (26) are essential for antimalarial activity. The compound possessing the electron-withdrawing group (NO₂⁻) at para position shows potent antimalarial activity.

Wanare et al. [39] reported the antimalarial activity of coumarin-chalcone hybrids using in vitro assay, i.e. microtiter plate-based SYBR-Green-1 against P. falciparum and also by in silico studies against falcipain enzyme. The in vitro assay indicates that the compound (27) having trimethoxy group shows potent antimalarial activity. In silico studies explain the binding affinity of hybrid at active site of falcipain enzyme. More over the lactone ring of coumarins which forms the hydrogen bond with CYS42 of enzyme is essential for antimalarial activity.

Pingaew et al. [93] reported the antimalarial activity of coumarinyl-chalcone hybrids by in vitro and in silico studies. The compound (28) linked by 1,2,3-triazole and substitution of trimethoxy group on “B” ring of chalcone was proved as the most potent compounds. In silico studies show that the hydrophobic interaction of coumarin moiety at Cys42 and Trp206 inhibits the falcipain-2.

Antioxidant activity
Xi and Liu [104] reported the antioxidant activity of coumarin-chalcone hybrids through screening of inhibitory activity against Cu²⁺/GSH, OH⁻, and AAPH-induced oxidation of DNA activity on trapping ABTS and DPPH. Hybrids (29a-c) with no substitution at ortho and para positions show potent OH-induced oxidation of DNA, and compound (29d) with OH group at ortho and para positions shows good activity against AAPH-induced oxidation.

Perez-Cruz et al. [105] reported the cytoprotection activity of coumarin-chalcones against reactive oxygen species and reactive nitrogen species on bovine aortic endothelial cell (provine at the endothelial cells by oxygen radical absorbance capacity (ORAC) and electron spin resonance assay. Hybrid (30) with OH substitution on B ring of chalcones shows potent activity of ORAC.
Rodriguez et al. [95] reported antioxidant activity for coumarinyl chalcone hybrids. Hybrids with hydroxyl at the 8th position and bromine group at the 6th position of coumarin ring show potential antioxidant activity through electrochemical study.

Mazzone et al. [106] reported the peroxyl radical stranger activity for coumarinyl chalcones. Compound (32) with hydroxyl group on the 5th, 6th, and 8th positions of coumarin ring shows the faster and better peroxyl radical scavenger activity.

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Sashidhar et al. [81] reported the lipid-lowering activity and anti-inflammatory activity of coumarin-chalcone scaffolds (35).

Jayashree et al. [92] reported the anti-inflammatory activity of coumarinyl chalcones. Compounds with chloro group at the 6th position on coumarin ring and methoxy substitution at meta and para position on “B” ring of chalcone and bromo substitution at the 6th position on coumarin ring show potent anti-inflammatory activity.

Other activities

Ahmad et al. [107] reported the antitubercular activity of coumarin-chalcone compounds against mycobacterium tuberculosis H37RV. The compound (33) with substitution of nitrogen moiety on “B” ring of chalcone significantly increasing the antitubercular activity.

Yadav et al. [108] reported the activity of coumarinyl chalcone derivatives (33,34) against metabolic syndrome.

CONCLUSION

The present paper explains the modern synthetic technique for improving the quality and yield of synthesized derivatives and current biological activities produced by synthesized coumarinyl chalcone derivatives through different mechanisms. This information may be useful for the research society for better understanding of coumarinyl chalcone derivatives regarding their synthetic mechanisms and particular pharmacophore required for exhibit characteristic biological activities through different mechanism of actions.

ACKNOWLEDGMENTS

The authors thank the University Grants Commission, Delhi, India, Acharya Nagarjuna University College of Pharmaceutical Sciences, Acharya Nagarjuna University, Guntur.

AUTHORS' CONTRIBUTIONS

Sathish Kumar Konidala* collected and scientifically represented the data regarding synthesis of coumarin-chalcone derivatives and their pharmacological activities. Dr. Vijay Kotra suggested the topic guided the coauthor throughout this work.
Toxicol evaluation of novel coumarin chalcone hybrids as potential inhibitors of HIV and antibacterial agents. Design, synthesis and antibacterial activity. Review article.

Nitric oxide synthase (NOS) inhibitors are potential therapeutic agents for the treatment of a variety of diseases, including HIV and inflammation. In this review, we focus on the synthesis and biological evaluation of coumarin and chalcone derivatives as potential inhibitors of HIV and antibacterial agents.

The synthesis of coumarin and chalcone derivatives is important for the development of new therapeutic agents. In this study, we synthesized a series of coumarin and chalcone derivatives and evaluated their anti-HIV and antibacterial activities.

The results of this study showed that some of the synthesized coumarin and chalcone derivatives exhibited significant anti-HIV and antibacterial activities.

The anti-HIV activities of the synthesized coumarin and chalcone derivatives were evaluated using the HIV-1 reverse transcriptase (RT) assay and the HIV-1 integrase (INT) assay.

The anti-HIV activities of the synthesized coumarin and chalcone derivatives were compared with those of the standard antiretroviral drugs, lamivudine and zidovudine.

The antibacterial activities of the synthesized coumarin and chalcone derivatives were evaluated using a disc diffusion assay.

The results of this study showed that some of the synthesized coumarin and chalcone derivatives exhibited significant antibacterial activities.

The antibacterial activities of the synthesized coumarin and chalcone derivatives were compared with those of the standard antibiotics, ciprofloxacin and amoxicillin.

The results of this study showed that the synthesized coumarin and chalcone derivatives have potential anti-HIV and antibacterial activities and could be developed as new therapeutic agents.

The synthesized coumarin and chalcone derivatives showed promising anti-HIV and antibacterial activities.

The synthesized coumarin and chalcone derivatives could be used as potential therapeutic agents for the treatment of HIV and inflammation.
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