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Review Article

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

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ABSTRACT

Coumarins and chalcones are potential pharmacological and biologically active molecules obtained from the natural source. 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.

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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 largestclassof1-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 coumarone in 1820 and it has been used in perfumes since 1882 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 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-inflammatory [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], antiadipogenic [33,34], cytochrome P_{450} inhibiting [35,36], neuroprotective [37], analgesic [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-propane-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 α, β-unsaturated carbonyl system [46].

Chalcones and its derivatives can be synthesized by different methods, but Claisen–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, Allan–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 [30], and antimalarial [77] activities.

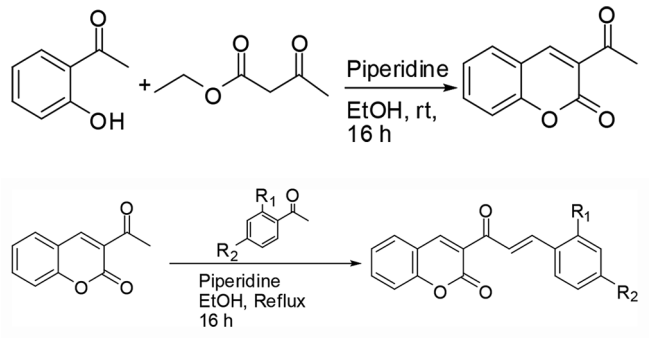
IMPORTANCE OF COUMARINYL CHALCONE

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.

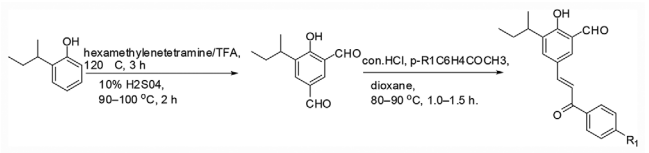
Recent research suggests that the fusion of a chalcone moiety with the coumarin ring may be promising for the synthesis of derivatives with enhanced two-photon absorption cross-sections [78,79].

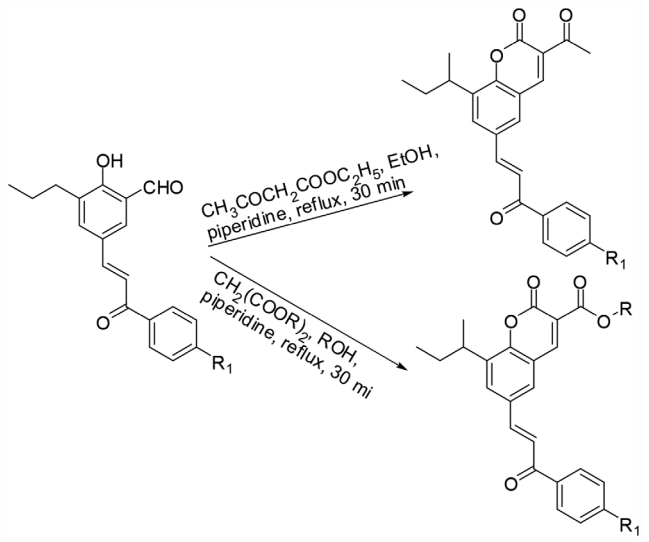
SYNTHESIS OF COUMARINYL CHALCONES

Thrineshen M, *et al*, [80] reported the synthesis of 2- and 4-substituted-coumarinyl chalcones by refluxing the phenolic aldehyde with ethyl acetoacetate in methanol 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 catalyst to get the coumarinyl-chalcones.

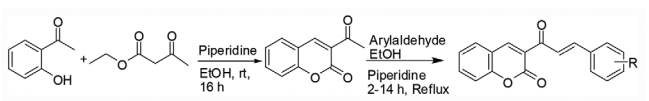


Sashidhara *et al*. [81] reported the synthesis of novel coumarin-chalcone hybrids by treating 2-*sec*-butylphenol with hexamethylene triamine or TFA at 120°C about 3 h to get 5-*sec*-butyl-4-hydroxyisophthalaldehyde. Then, it was converted to chalcone derivative by treating with p-substituted acetophenone in dioxane at 80–90°C about 1–1.5 h. Then, it was fused with coumarin by refluxing with ethyl acetoacetate 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.

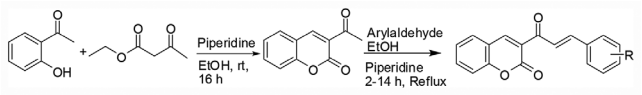




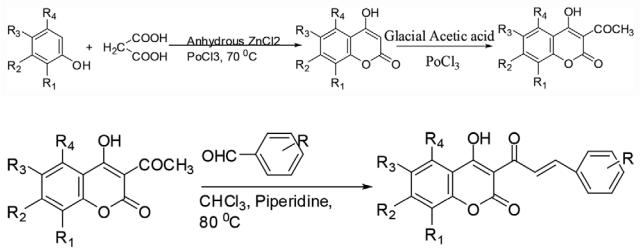
Vazquez-Rodriguez *et al*. [82] reported synthesis of coumarin-chalcones using Knoevenagel reaction for the preparation of 3-acetylcoumarin (salicylaldehyde ethyl acetoacetate and a few drops of piperidine were mixed for 5 min at room temperature without any solvent) and Claisen-Schmidt aldol condensation 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.



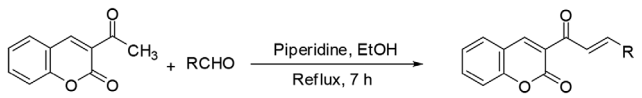
Patel *et al*. [83] reported synthesis of some coumarinyl chalcones by reacting the 4-hydroxy coumarin with phosphorus oxychloride and glacial acetic acid to get 4-hydroxy-3-acetyl coumarin and the second step involved the Knoevenagel condensation between the same molar amount of 4-hydroxy-3-acetyl coumarin (**3**) and substituted benzaldehydes with chloroform in the presence of piperidine catalyst.



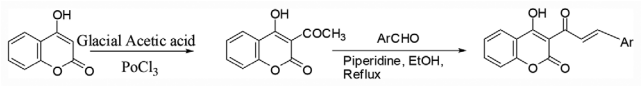
Trivedi *et al*. [84] reported the synthesis of coumarinyl chalcones by reacting the aromatic phenol with malonic acid in the presence of phosphorus oxychloride and zinc chloride at 70°C about 20 h, and the resulting compound was acetylated with glacial acetic acid and phosphorus oxychloride. Then, the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



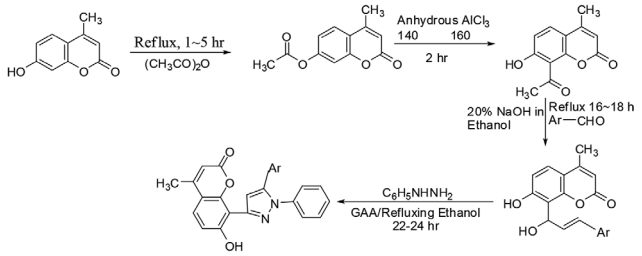
Prasad *et al*. [85] reported the synthesis of coumarinyl chalcones by refluxing the 3-acetyl coumarin and substituted aromatic aldehydes in ethanol with piperidine about 1–7 h.



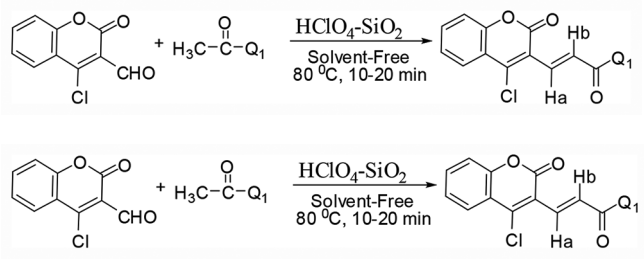
Hafez *et al*. [86] reported the synthesis of coumarinyl chalcones by acetylating the coumarin with acetic acid and phosphorus oxychloride to form 3-acetyl coumarin; then, it was refluxed with substituted aromatic aldehydes in ethanol with piperidine about 5–7 h.



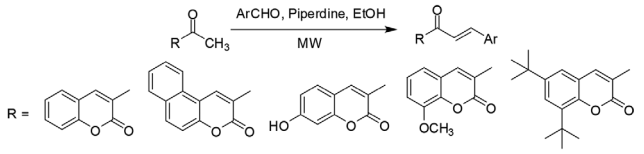
Balaji *et al.* [87] reported the synthesis of coumarinyl chalcones by refluxing the 7-hydroxy-4-methyl coumarin and acetic anhydride for 1–5 h under anhydrous conditions to get 7-acetoxy-4-methyl coumarin. Then, it was heated under anhydrous conditions in an oil bath at 125°C and the temperature was 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.



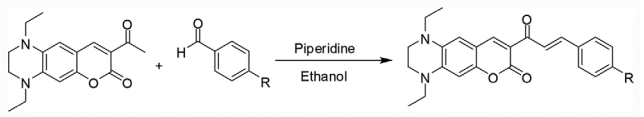
Siddiqui [88] reported the green synthesis of coumarinyl chalcones by mixing of aldehyde, heterocyclic methyl ketones, and $HClO_4$–SiO_2 and heated at 80°C for specified time.



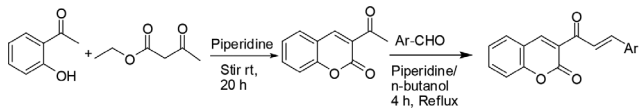
Sun and Cui [89] reported the synthesis of coumarinyl chalcones by refluxed a mixture of 3-acetyl coumarins aryl and heteroaryl aldehydes (2 mmol) and piperidine (0.5 mL) in ethanol (25 mL) for 3–5 h.



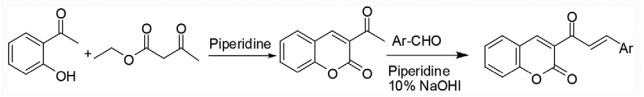
Jagtap *et al*. [90] reported the synthesis of coumarinyl-chalcone derivatives from 8-acetyl-1,4-diethyl-1,2,3,4-tetrahydro-7H-pyrano[2,3-g]quinoxalin-7-one by refluxed with benzaldehyde in dry ethanol with pyridine for 12 h.



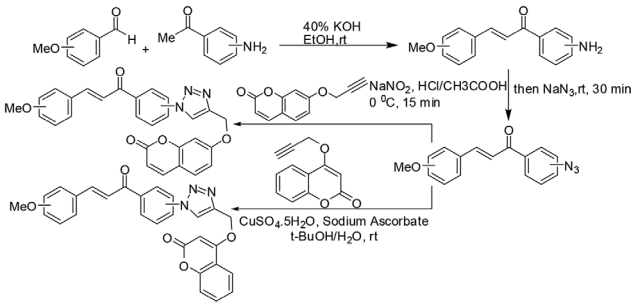
Khode *et al*. [91] reported the synthesis of coumarinyl chalcones by reacting the salicylaldehyde with ethyl acetoacetate and piperidine with stirring at room temperature for 20 min. Then, the resulting coumarin was refluxed with aromatic aldehyde and piperidine in n-butanol for 4 h.



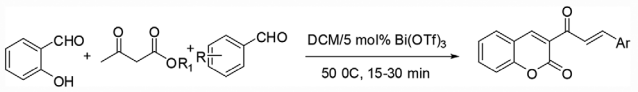
Jayashree *et al*. [92] reported the synthesis of coumarinyl chalcones by adding piperidine with continuous to a cooled suspension of mixture of salicylaldehyde or substituted salicylaldehyde and ethyl acetoacetate. The mixture was then maintained at freezing temperature for 2–3 h to get 3-acetyl coumarin/substituted 3-acetyl coumarins. Then, the resulting compound was dissolved in with 30% and added aromatic aldehyde with ethanol, allowed the mixture stand for 24 h, diluted with distilled water, and acidified with dilute hydrochloric acid.



Pingaew *et al*. [93] reported chalcone-coumarin hybrids by condensation of various aromatic aldehydes with two aminoacetophenones (3- or 4-NH_2). Subsequently, azotization reaction of the aminochalcones using sodium nitrite and sodium azide in a mixture of glacial acetic acid and concentrated hydrochloric acid afforded the corresponding azidochalcones. Then, dipolar cycloaddition of azide/alkyne to the synthesis of 1,2,3-triazole linkage. Finally, the azides subjected to cycloaddition with alkynes to afford the novel desired hybrid molecules.



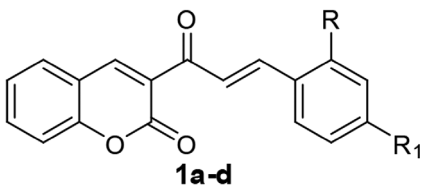
Mahmoud and El-Remaily **[**94] reported the synthesis of bioactive coumarin-chalcone compounds by mixing of salicylaldehyde or methyl salicylaldehyde with ethyl acetoacetate in the presence of piperidine without any solvent to get 3-acetylcoumarin. Then, the 3-acetylcoumarin was mixed with corresponding 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

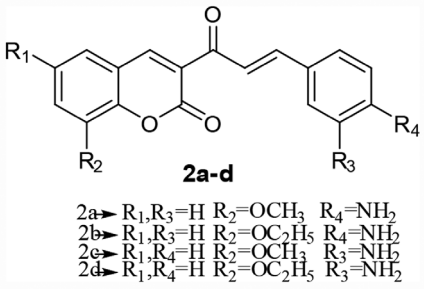
Moodley *et al*. [80] reported the antimicrobial activity of 2- and 4-substituted-coumarinyl chalcone derivatives through *in silico* and *in vitro* experiments. *In silico* studies were performed for the titled compounds against cefditoren bound 2Z2M enzyme using autodock-4 software. The study reveals 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.



1a-d

1a► R = H R_1=OCH_3
1b► R = OCH_3 R_1=OCH_3
1c► R = F R_1=H
1d► R = OH R_1=H

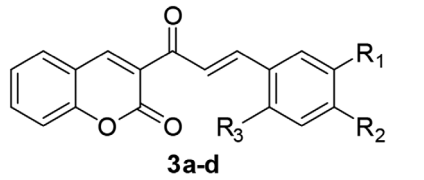
Vazquez-Rodriguez *et al*. [82] reported the antibacterial activity of coumarin-chalcone hybrids for the treatment of tenacibaculosis through disk diffusion assay against general Gram positive and Gram negative and 17 different strains of Gram-negative marine bacteria belongs to *Tenacibaculum* genus 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.



2a-d

2a ➤ R_1,R_3=H R_2=OCH_3 R_4=NH_2
2b ➤ R_1,R_3=H R_2=OC_2H_5 R_4=NH_2
2c ➤ R_1,R_4=H R_2=OCH_3 R_3=NH_2
2d ➤ R_1,R_4=H R_2=OC_2H_5 R_3=NH_2

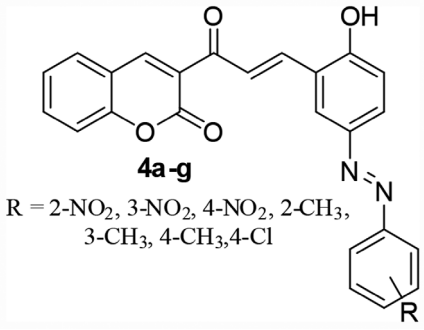
Rodriguez *et al*. [95] reported the trypanocidal activity of coumarin-chalcone hybrids against epimastigote, trypomastigote, and amastigote stages of *Trypanosoma cruzi* parasite. The study revealed that the hybrids were more active against trypomastigote stage of parasite. The hybrids (**3a-d**) possessing the methoxy group on "B" ring of chalcone at the 2nd and 5th positions show significant trypanocidal activity against amastigote stage.



3a-d

3a ➤ R_1,R_3=H R_2=OCH_3
3b ➤ R_2=H R_2,R_3=OCH_3
3c ➤ R_1,R_2,R_3=OCH_3
3d ➤ R_1,R_3=OCH_3 R_2=H

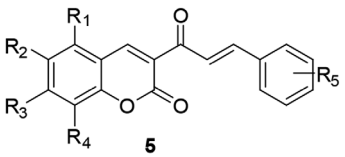
Deshpande *et al*. [96] reported the antibacterial activity of coumarin-chalcone hybrids (**4a-g**) against five human pathogens. The hybrid (**4g**) with para chloro substitution on benzyl ring of chalcone shows potent activity against Gram-positive bacteria.



4a-g

R = 2-NO_2, 3-NO_2, 4-NO_2, 2-CH_3, 3-CH_3, 4-CH_3,4-Cl

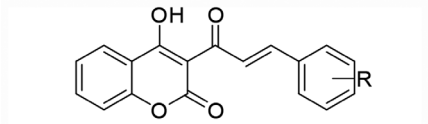
Trivedi *et al*. [84] reported screening of anti-HIV for coumarinyl chalcones (**5**). Unfortunately, no compound shows positive result for anti-HIV activity.



5

R_1=H/CH_3 R_2= H/CH_3 R_3=H/CH_3
R_4= H/$CH(CH_3)_2$,
R_5=H/4-OH/4-OCH_3/3-OC_6H_5/
2-NO_2/3-NO_2/4-$N(CH_3)_2$/3-OCH_3/4-OH/3,4-DiOCH_3

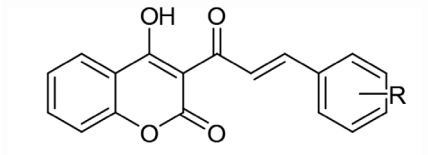
Hamdi *et al*. [97] reported that the coumarin-chalcone hybrids (**6**) with electron-withdrawing and electron donating groups on "B" ring of chalcone show moderate antibacterial activity.



6

R = H, 2/3/4-Cl, 4-Br/F/CH_3/OCH_3/NO_2/$N(CH_3)$ C_4H_4, 3,4,5-TriCH_3

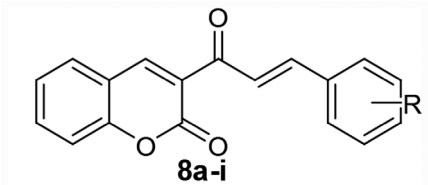
Spirtovic-Halilovic *et al*. [98] reported the *in vitro* and *in silico* experiments for screening the antibacterial activity of coumarin-chalcone hybrids (**7a-d**). The *in vitro* method reveals that the hybrids (**7d**) with bromine substitution on "B" ring of chalcone show the highest potency against 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 able and least reactive.



7a-d

7a ➤ R =2-Cl **7b** ➤ R =3-Cl
7c ➤ R =4-Cl **7d** ➤ R =4-Br

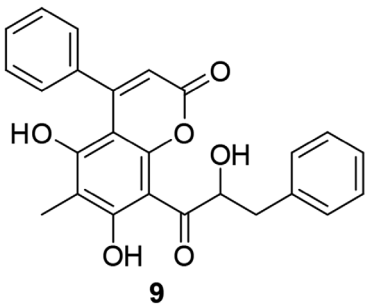
Naruka *et al*. [99] reported the antimicrobial activity of coumarin-chalcone hybrids (**8a-i**). The study reveals the hybrid (**8h**) with dimethoxy substitution at para and meta position and hybrid (**8i**) with para dimethyl amino substitution on "B" ring of chalcone shows better activity than control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



8a-i

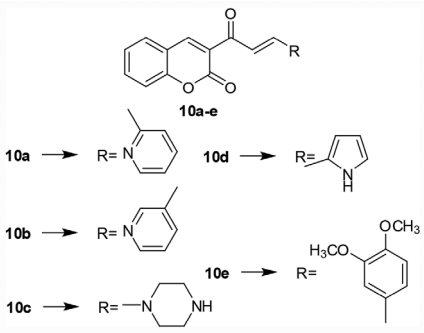
R = H, 2-OH, 4-OH, 2,3-Cl, 4-F, 4-OCH_3, 2,4,6-TriOCH_3, 3,5-OCH_3 4-$N(CH_3)_2$

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.

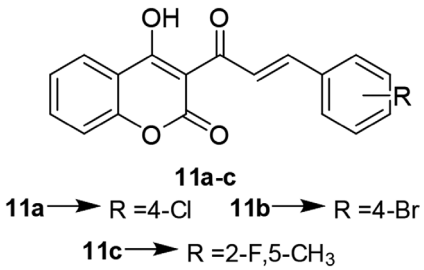


9

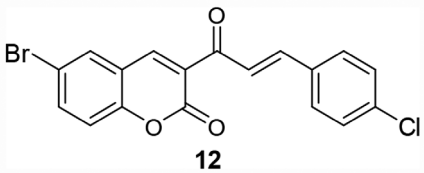
Prasad *et al*. [85] reported the antimicrobial activity of coumarin-chalcones (**10a-e**). The study reveals that the compound (**10e)** with dimethoxy substitution on "B" ring of chalcone shows potent antimicrobial activity.



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.

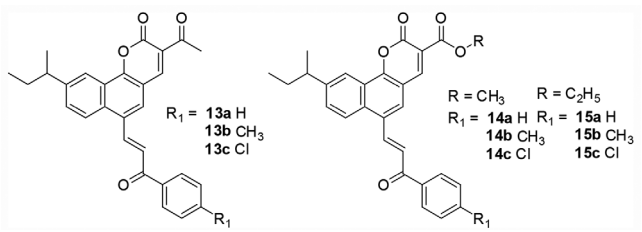


The antibacterial screening for coumarinyl chalcones indicates that the compound (**12**) with bromo substitution at the 6th position of coumarin ring and ortho-chloro substitution on "B" ring of chalcone has proved to be potent antibacterial activity.

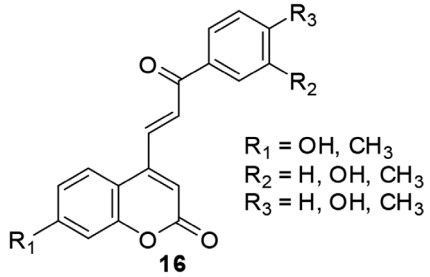


Anticancer activity

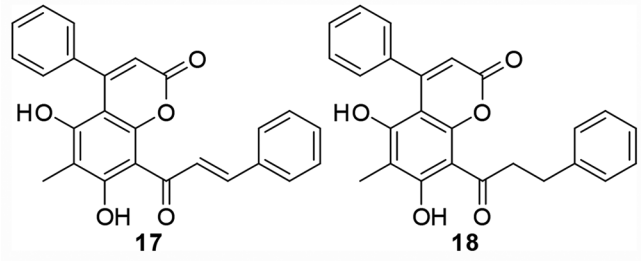
Sashidhara *et al*. [81] reported the *in vitro* anticancer activity of novel coumarin-chalcone hybrids (**13a-c, 14a-c, and 15a-c**) using sulforhodamine-B assay. The assay indicates the observation of growth inhibition by the synthesized compounds in four human cell lines and one normal fibroblast. Compounds with chlorine, methyl, and hydrogen substitution at para 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.



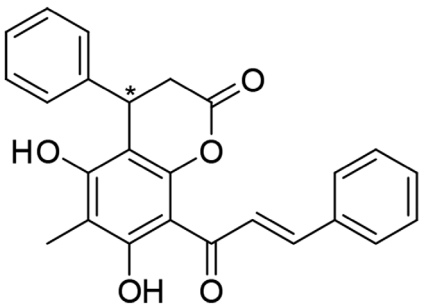
Valente *et al*. [101] reported the anticancer (CDC25 inhibitor) activity of coumarinyl chalcone hybrids by dephosphorylation assay with 3-o-methyl fluorescein phosphate using human glutathione-s-transferase recombinant enzyme. The hybrid (**16**) with benzoylvinyl group at the 4th position to the coumarin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



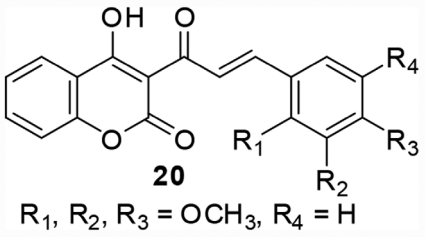
Quadri-Spinelli *et al*. [100] reported the cytotoxic activity of novel coumarin-chalcone derivatives occurring naturally by extraction from leaves of *Cyclosorus interruptus*. The activity was examined to the isolated compounds on KB (human nasopharyngeal carcinoma) cell growth. Compounds (**17, 18**)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



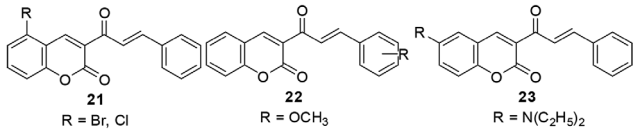
Han *et al*. [102] reported the antiproliferative activity of naturally occurring coumarin-chalcone hybrids by from *Cyclosorus parasiticus* by sulforhodamine-B assay against six cancer cell lines. The compound (**19**) having 6-methyl-dihydrocoumarin shows potent activity against all cell lines compared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



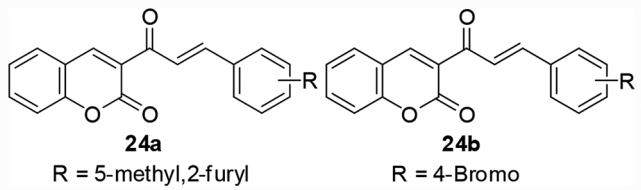
Kuladeep *et al*. [83] reported the antiproliferative activity of coumarinyl chalcones against breast cancer cell lines. Compound (**20**) with methoxy substitution at 2,3,4 carbons of "B" ring of chalcone proved to be potent antiproliferative agents.



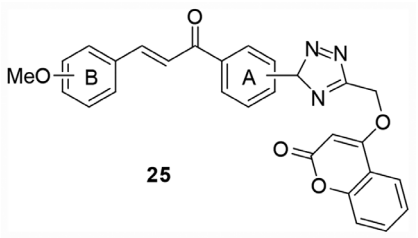
Delel *et al*. [103] reported the anticancer activity of coumarin-chalcones against CDC25 phosphatase. Hybrids with chlorine and bromine at the 6th position on coumarin ring (**21**) inhibit CDC25A than hybrids with methoxy group at the 6th position of coumarin ring. However, in case of CDC25B, the activity 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 hepato carcinoma 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.

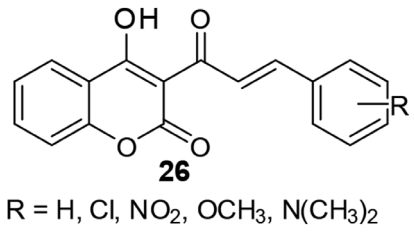


Pingaew *et al*. [93] reported the anticancer activity of chalcone-coumarin hybrids against HuCCA-1, HepG2, A549, and MOLT-3. The hybrids which possess triazole show potent anticancer activity against MOLT-3 and HuCCA-1. Hybrid (**25**) with tri-substituted methoxy group selectively inhibits MOLT-3. Hybrids with 2,3-dimetoxy 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).

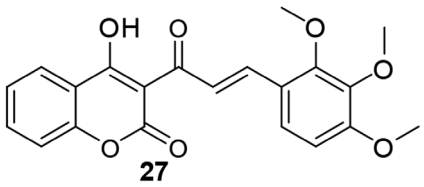


Antimalarial activity

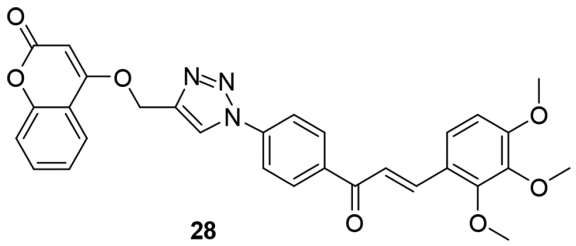
Patel *et al*. [83] reported the antimalarial activity of coumarinyl chalcone hybrids against chloroquine susceptible (3D7) and chloroquine-resistant (W2) *Plasmodium falciparum*. The substitutions at meta and para positions to the "B" ring of chalcone moiety (**26**) are essential for antiplasmodial activity. The compound possessing the electron-withdrawing group (NO_2) 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.

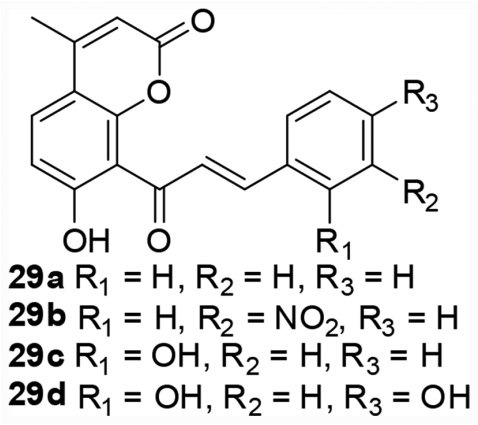


Pingaew *et al*. [93] reported the antimalarial activity of coumarinyl-chalcone hybrids by *in vitro* and *in silico* studies. The compound (**28**) linked by 1,2,3-triazole and substitution of trimethoxy group on "B" ring of chalcone was proved as the most potent compounds. *In silico* studies show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

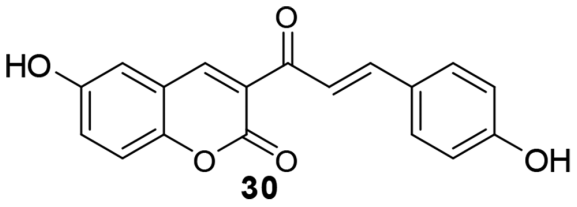


Antioxidant activity

Xi and Liu [104] reported the antioxidant activity of coumarin-chalcone hybrids through screening of inhibitory activity against Cu^{+2}/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.

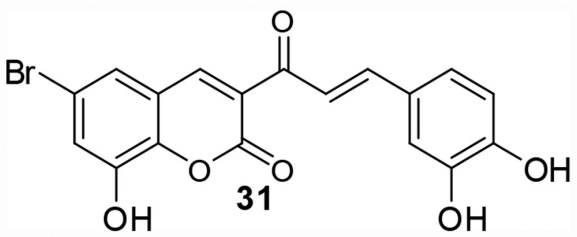


Perez-Cruz *et al*. [105] reported the cytoprotection activity of coumarin-chalcones against reactive oxygen species and reactive nitrogen species on bovine aortic endothelial cell (provine at the endothelial cells by oxygen radical absorbance capacity (ORAC) and electron spin resonance assay. Hybrid (**30**) with OH substitution on B ring of chalcones shows potent activity of ORAC.



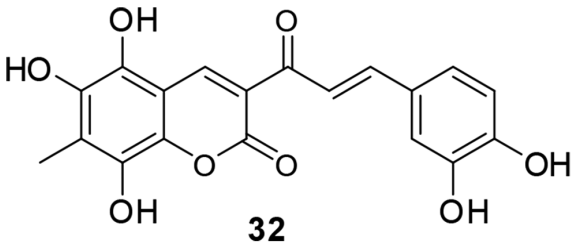
30

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.



31

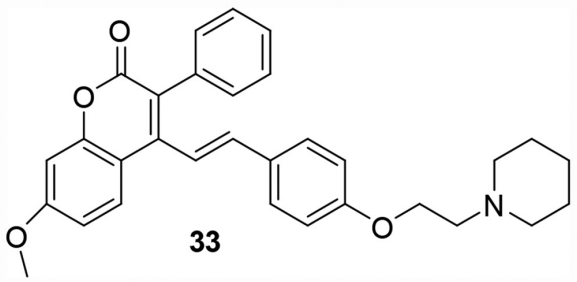
Mazzone *et al*. [106] reported the peroxyl radical stranger activity for coumarinyl chalcones. Compound (**32**) with hydroxyl group on the 5th, 6th, and 8th positions of coumarin ring shows the faster and better peroxyl radical scavenger activity.



32

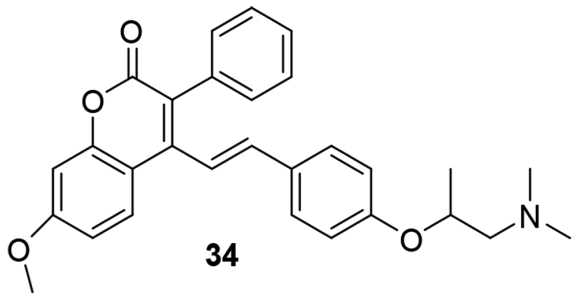
Other activities

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.



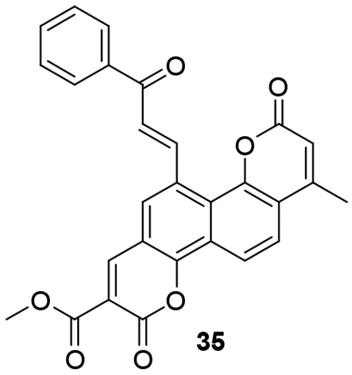
33

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



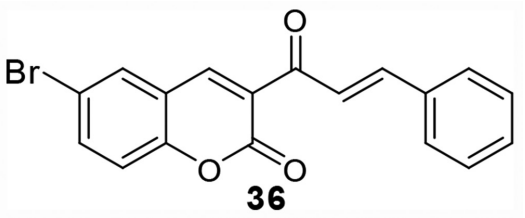
34

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



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.



36

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.

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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 the throughout this work.

CONFLICTS OF INTEREST

Authors have no conflicts of interest in the present work.

AUTHORS' FUNDING

No funding is provided for this work from any organization.

REFERENCES

1. Venugopala KN, Rashmi V, Odhav B. Review on natural coumarin lead compounds for their pharmacological activity. BioMed Res Int 2013;2013:963248.
2. Gottlieb OR, Murray KR, Ohloff G, Pattenden G. Progress in the Chemistry of Organic Natural Products. Berlin: Springer-Verlag Wein; 1978. p. 200.
3. Vogel A. Darstellung von benzoesäure aus der tonka-bohne und aus den Meliloten Oder steinklee-blumen. [Preparation of benzoic acid from Tonka beans and from the flowers of Melilot or sweet clover]. Ann Physik (in German) 1820;64:161-6.
4. Vogel A. De l'existence de l'acide benzoïque dans la fève de Tonka et dans les fleurs de mélilot. [On the existence of benzoic acid in the Tonka bean and in the flowers of melilot]. J Pharm (in French) 1820;6:305-9.
5. Pechmann HV, and Duisberg C. von Pechmann – Duisberg and Perkin coumarin reactions. Chem Tech Ber 1884;17: 929-79.
6. Knoevenagel E. On the chemistry of the condensing action of ammonia and organic amines in reactions between aldehydes and acetoacetic ester. Ber Dtsch Chem Ges 1898;31:738-48.
7. Johnson JR. Perkin reaction and related reactions. Org React 1942;1:210-65.
8. Bert L. Synthesis of substituted ω-alkoxypropenylbenzenes. Compt Rend 1942;214: 230-2.
9. Shirner RL. Recent Advances in the Reformatsky Reactions. Org React 1942;1: 1.
10. Yavari I, Hekmat-shoar R, Zonouzi A. A new and efficient route to 4-carboxymethylcoumarins mediated by vinyl triphenyl phosphonium salt. Tetrahedron Lett 1998;39:2391-2.
11. Manolov I, Danchev ND. Synthesis, toxicological and phar-macological assessment of some 4-hydroxycoumarin derivatives. Eur J Med Chem Chim Ther 1995;30:531-6.
12. Wu L, Wang X, Xu W, Farzaneh F, Xu R. The structure and pharmacological functions of coumarins and their derivatives. Curr Med Chem 2009;16:4236-60.
13. Kulkarni MV, Kulkarni GM, Lin CH, Sun CM. Recent advances in coumarins and 1-azacoumarins as versatile biodynamic agents. Curr Med Chem 2006;13:2795-818.
14. Ostrov DA, Prada JA, Corsino PE, Finton KA, Le N, Rowe TC. Discovery of novel DNA gyrase inhibitors by high-throughput virtual screening. Antimicrob Agents Chemother 2007;51:3688-98.
15. Gormley NA, Orphanides G, Meyer A, Cullis PM, Maxwell A. The interaction of coumarin antibiotics with fragments of the DNA gyrase B protein. Biochemistry 1996;35:5083-92.
16. Fylaktakidou KC, Hadjipavlou-Litina DJ, Litinas KE, Nicolaides DN. Natural and synthetic coumarin derivatives with anti-inflammatory/ antioxidant activities. Curr Pharm Des 2004;10:3813-33.
17. Bansal Y, Sethi P, Bansal G. Coumarin: A potential nucleus for anti-inflammatory molecules. Med Chem Res 2013;22:3049-60.
18. Riveiro ME, Moglioni A, Vazquez R, Gomez N, Facorro G, Piehl L, *et al*. Structural insights into hydroxycoumarin-induced apoptosis in U-937 cells. Bioorg Med Chem 2008;16:2665-75.
19. Kashman Y, Gustafson KR, Fuller RW, McMahon JB, Currens MJ, Buckheit JR, *et al*. The calanolides, a novel HIV-inhibitory class of coumarin derivatives from the tropical rainforest tree, *Calophyllum lanigerum*. J Med Chem 1992;35:2735-43.
20. Shikishima Y, Takaishi Y, Honda G, Ito M, Takfda Y, Kodzhimatov OK, *et al*. Chemical constituents of prangos tschiniganica; structure elucidation and absolute configuration of coumarin and furanocoumarin derivatives with anti-HIV activity. Chem Pharm Bull 2001;49:877.
21. Manvar A, Bavishi A, Radadiya A, Patel J, Vora V, Dodia N, *et al*. Diversity oriented design of various hydrazides and their *in vitro* evaluation against *Mycobacterium tuberculosis* H37Rv strains. Bioorg Med Chem Lett 2011;21:4728-31.
22. Karal N, Kocabalkanl A, Gursoy A, Ates O. Synthesis and antitubercular activity of 4-(3-coumarinyl)-3-cyclohexyl-4-thiazolin-2-one benzylidenehydrazones. Farmaco 2002;57:589-93.
23. Yeh JY, Coumar MS, Horng JT, Shiao HY, Kuo FM, Lee HL, *et al*. Anti-influenza drug discovery: Structure activity relationship and mechanistic insight into novel angelicin derivatives. J Med Chem 2010;53:1519-33.
24. Anand P, Singh B, Singh N. A review on coumarins as acetylcholinesterase inhibitors for Alzheimer's disease. Bioorg Med Chem 2012;20:1175-80.
25. Piazzi L, Cavalli A, Colizzi F, Belluti F, Bartolini M, Mancinni F, *et al*. Multi-target-directed coumarin derivatives: hAChE and BACE1 inhibitors as potential anti-Alzheimer compounds. Bioorg Med Chem Lett 2008;18:423-6.
26. Curini M, Epifano F, Maltese F, Marcotullio MC, Gonzales SP, Rodriguez JC. Synthesis of collinin, an antiviral coumarin. Aust J Chem 2003;56:59-60.
27. Yuce B, Danis O, Ogan A, Sener G, Bulut M, Yarat A. Antioxidative and lipid lowering effects of 7, 8-dihydroxy-3-(4-methylphenyl) coumarin in hyperlipidemic rats. Arzneimittelforschung 2009;59:129-34.
28. Madhavan GR, Balraju V, Mallesham B, Chakrabarti R, Lohray VB. Novel coumarin derivatives of heterocyclic compounds as lipid-lowering agents. Bioorg Med Chem Lett 2003;13:2547-51.
29. Namba T, Morita O, Huang SL, Goshima K, Hattori M, Kakiuchi N. Studies on cardio-active crude drugs; I. Effect of coumarins on cultured myocardial cells. Plant Med 1988;54:277-82.
30. Baek NI, Ahn EM, Kim HY, Park YD. Furanocoumarins from the root of *Angelica dahurica*. Arch Pharm Res 2000;23:467-70.
31. Luszczki JJ, Wojda E, Andres-Mach M, Cisowski W, Glensk M, Glowniak K, *et al*. Anticonvulsant and acute neurotoxic effects of imperatorin, osthole and valproate in the maximal electroshock seizure and chimney tests in mice: A comparative study. Epilepsy Res 2009;85:293-9.
32. Yusupov MI, Sidyakin GP. Fraxidin and isofraxidin from *Artemisia scotina*. Chem Nat Compd 1975;11:94.
33. Shin E, Choi KM, Yoo HS, Lee CK, Hwang BY, Lee M. Inhibitory effects of coumaris from the stem barks of Fraxinus rhychophylla on adipocyte differentiation in 3T3-L1 cells. Biol Pharm Bull 2010;33:1610-4.
34. Tinel M, Belghiti J, Descatoire V, Amouyal G, Letteron P, Geneve J, *et al*. Inactivation of human liver cytochrome P-450 by the drug methoxsalen and other psoralen derivatives. Biochem Pharmacol 1987;36:951-5.
35. Kharasch ED, Hankins DC, Taraday JK. Single-dose methoxsalen effects on human cytochrome P-450 2A6 activity. Drug Metab Dispos 2000;28:28-33.
36. Wang C, Pei A, Chen J, Yu H, Sun ML, Liu CF, *et al*. A natural coumarin derivative esculetin offers neuroprotection on cerebral ischemia/ reperfusion injury in mice. J Neurochem 2012;121:1007-13.
37. Khan IA, Kulkarni MV, Gopal M, Shahabuddin MS, Sun CM. Synthesis and biological evaluation of novel angularly fused polycyclic coumarins. Bioorg Med Chem Lett 2005;15:3584-7.
38. Ghate M, Kusanur AR, Kulkarni VM. Synthesis and *in vivo* analgesic and anti-inflammatory activity of some bi heterocyclic coumarin derivatives. Eur J Med Chem 2005;40:882-7.
39. Wanare G, Aher R, Kawathekar N, Ranjan R, Kaushik NK, Sahal D. Synthesis of novel α-pyranochalcones and pyrazoline derivatives as *Plasmodium falciparum* growth inhibitors. Bioorg Med Chem Lett 2010;20:4675-8.
40. Tegginamath G, Kamble RR, Kattimani PP, Margankop SB. Synthesis of 3-aryl-4-({2-[4-(6-substituted-coumarin-3-yl)-1, 3-thiazol-2-yl] hydrazinylidene} methyl/ethyl)-sydnones using silica sulfuric acid and their antidiabetic, DNA cleavage activity. Arab J Chem 2016;9:S306-12.
41. Liu XH, Li J, Shi JB, Song BA, Qi XB. Design and synthesis of novel 5-phenyl-N-piperidine ethanone containing 4, 5-dihydropyrazole derivatives as potential antitumor agents. Eur J Med Chem 2012;51:294-9.
42. Chen Y, Wang S, Xu X, Liu X, Yu M, Zhao S, *et al*. Synthesis and biological investigation of coumarin piperazine (piperidine) derivatives as potential multireceptor atypical antipsychotics. J Med Chem 2013;56:4671-90.
43. Chen X, Pi R, Zou Y, Liu M, Ma X, Jiang Y, *et al*. Attenuation of experimental autoimmune encephalomyelitis in C57 BL/6 mice by osthole, a natural coumarin. Eur J Pharmacol 2010;629:40-6.
44. Di Carlo G, Mascolo N, Izzo AA, Capasso F. Flavonoids: Old and new aspects of a class of natural therapeutic drugs. Life Sci 1999;65:337-53.
45. Orlikova B, Tasdemir D, Golais F, Dicato M, Diederich M. Dietary chalcones with chemopreventive and chemotherapeutic potential. Genes Nutr 2011;6:125-5.
46. Guida A, Lhouty MH, Tichit D, Figueras F, Geneste P. Hydrotalcites as base catalysts. Kinetics of Claisen-Schmidt condensation, intramolecular condensation of acetonylacetone and synthesis of chalcone. Appl Catal A Gen 1997;164:251-64.
47. Romanelli G. Pasquale G, Sathicq A, Thomas H, Autino J, Vazquez P. Synthesis of chalcones catalyzed by aminopropylated silica sol–gel under solvent-free conditions. J Mol Catal A Chem 2011;340: 24-32.

48. Climent M, Corma A, Iborra S, Velty A. New one-pot multistep process with multifunctional catalysts: decreasing the E factor in the synthesis of fine chemicals. J Catal 2004;221(2): 474-82.
49. Dhar DN. The Chemistry of Chalcones and Related Compounds. New York: Wiley; 1981.
50. Eddarir S, Cotelle N, Bakkour Y, Rolando C. An efficient synthesis of chalcones based on the Suzuki reaction. Tetrahedron Lett 2003;44:5359-63.
51. Bohm BA. Introduction to Flavonoids. United Kingdom: Harwood Academic Publishers; 1998.
52. Fukui K, Matsumoto T, Nakamura S, Nakayama M, Horie T. Synthetic studies of the flavone derivatives. VII. The synthesis of jaceidin. Bull Chem Soc Jpn 1968;41:1413-7.
53. Al-Masum M, Ng E, Wai MC. Palladium-catalyzed direct cross-coupling of potassium styryltrifluoroborates and benzoyl chlorides a one step method for chalcone synthesis. Tetrahedron Lett 2011;52:1008-10.
54. Srivastava YK. Ecofriendly microwave assisted synthesis of some chalcones. Rasayan J Chem 2008;1:884-6.
55. Kumar A, Sharma S, Tripathi VD, Srivastava S. Synthesis of chalcones and flavanones using Julia Kocienski olefination. Tetrahedron 2010;66:9445-9.
56. Zangade S, Mokle S, Vibhute A, Vibhute Y. An efficient and operationally simple synthesis of some new chalcones by using grinding technique. Chem Sci J 2011;13:1-6.
57. Thati B, Noble A, Rowan R, Creaven BS, Walsh M, McCann M, *et al*. Mechanism of action of coumarin and silver (I)-coumarin complexes against the pathogenic yeast *Candida albicans*. Toxicol *In Vitro* 2007;21:801-8.
58. Bagihalli GB, Avaji PG, Patil SA, Badami PS. Synthesis, spectral characterization, *in vitro* antibacterial, antifungal and cytotoxic activities of co(II), Ni(II) and cu(II) complexes With 1,2,4-triazole schiff bases. Eur J Med Chem 2008;43:2639-49.
59. Rehman SU, Chohan ZH, Gulnaz F, Supuran CT. *In-vitro* antibacterial, antifungal and cytotoxic activities of some coumarins and their metal complexes. J Enz Inhib Med Chem 2005;20:333-40.
60. Piller NB. A comparison of the effectiveness of some anti-inflammatory drugs on thermal oedema. Br J Exp Pathol 1975;56:554-9.
61. Satyajit S, Lutfun N. Text Book of Chemistry for Pharmacy Students: General, Organic and Natural Product Chemistry. England: John Wiley and Sons Ltd.; 2007.
62. Huang GJ, Deng JS, Liao JC. Inducible nitric oxide synthase and cyclooxygenase-2 participate in anti-inflammatory activity of imperatorin from *Glehnia littoralis*. J Agric Food Chem 2012;60:1673-81.
63. Rosselli S, Maggio AM, Faraone N.The cytotoxic properties of natural coumarins isolated from roots of *Ferulago campestris* (*Apiaceae*) and of synthetic ester derivatives of aegelinol. Nat Prod Commun 2009;4:1701-6.
64. Choi J, Lee KT, Ka H, Jung WT, Jung HJ, Park HJ. Constituents of the essential oil of the *Cinnamomum cassia* stem bark and the biological properties. Arch Pharm Res 2001;24:418-23.
65. Portugal JC. Chartreusin, elsamicin A and related anti-cancer antibiotics. Curr Med Chem Anticancer Agents 2003;3:411-20.
66. Whang WK, Park HS, Ham I. Natural compounds, fraxin and chemicals structurally related to fraxin protect cells from oxidative stress. Exp Mol Med 2005;37:436-46.
67. Spino C, Dodier M, Sotheeswaran S. Anti-HIV coumarins from *Calophyllum* seed oil. Bioorg Med Chem Lett 1998;8:3475-8.
68. Patil AD, Freyer AJ, Eggleston DS. The inophyllums, novel inhibitors of HIV-1 reverse transcriptase isolated from the Malaysian tree, *Calophyllum inophyllum* Linn. J Med Chem 1993;36:4131-8.
69. Kashman Y, Gustafson KR, Fuller RW, Cardellina JH, McMahon JB, Currens MJ, *et al*. HIV inhibitory natural products. Part 7. The calanolides, a novel HIV-inhibitory class of coumarin derivatives from the tropical rainforest tree, *Calophyllum lanigerum*. J Med Chem 1992;35:2735-43.
70. Basile A, Sorbo S, Spadaro V. Antimicrobial and antioxidant activities of coumarins from the roots of *Ferulago campestris* (*Apiaceae*). Molecules 2009;14:939-52.
71. Kim SH, Kang KA, Zhang R, Piao MJ, Ko DO, Wang ZH, *et al*. Protective effect of esculetin against oxidative stress-induced cell damage via scavenging reactive oxygen species. Acta Pharmacol Sin 2008;29:1319-26.
72. Hirsch AM, Longeon A, Guyot M. Fraxin and esculin: Two coumarins specific to *Actinidia chinensis* and *A. deliciosa* (kiwifruit). Biochem Syst Ecol 2002;30:55-60.
73. Aoyama Y, Katayama T, Yamamoto M, Tanaka H, Kon K. A new antitumor antibiotic product, demethylchartreusin. Isolation and biological activities. J Antibiot 1992;45:875-8.
74. Hirsh J, Dalen JE, Anderson DR, Poller L, Bussey H, Ansell J, *et al*. Oral anticoagulants: Mechanism of action, clinical effectiveness, and optimal therapeutic range. Chest 2001;119:8S-21S.
75. Cohen AJ. Critical review of the toxicology of coumarin with special reference to interspecies differences in metabolism and hepatotoxic responce and their significance to man. Food Cosmet Toxicol 1979;17:277-89.
76. Chiang CC, Cheng MJ, Peng CF, Huang HY, Chen IS. A novel dimeric coumarin analog and antimycobacterial constituents from *Fatoua pilosa*. Chem Biodivers 2010;7:1728-36.
77. Pushpalatha G, Pramod N, Basha GM, Deepa M, Neelaphar P, Swamy BH. Design, synthesis and anti-malarial activity of coumarin fused quinoline derivatives. J Pharm Res 2016;10:437-41.
78. Beyer H, Hohn H, Lassing W, Studies on compounds consisting thiazole and 2-azetidinone heterocycles. Chem Abstr 1954;47:11183.
79. Li X, Zhao Y, Wang T, Shi M, Wu F. Coumarin derivatives with enhanced two-photon absorption cross-sections. Dyes Pigm 2007;74:108-12.
80. Moodley T, Momin M, Mocktar C, Kannigadu C, Koorbanally NA. The synthesis, structural elucidation and antimicrobial activity of 2-and 4-substituted-coumarinyl chalcones. Magn Reson Chem 2016;54:610-7.
81. Sashidhara KV, Kumar A, Kumar M, Sarkar J, Sinha S. Synthesis and *in vitro* evaluation of novel coumarin chalcone hybrids as potential anticancer agents. Bioorg Med Chem Lett 2010;20:7205-11.
82. Vazquez-Rodriguez S, Lopez RL, Matos MJ, Armesto-Quintas G, Serra S, Uriarte E, *et al*. Design, synthesis and antibacterial study of new potent and selective coumarin chalcone derivatives for the treatment of tenacibaculosis. Bioorg Med Chem 2015;23:7045-52.
83. Patel K, Karthikeyan C, Moorthy NH, Deora GS, Solomon VR, Lee H, *et al*. Design, synthesis and biological evaluation of some novel 3-cinnamoyl-4-hydroxy-2H-chromen-2-ones as antimalarial agents. Med Chem Res 2012;21:1780-4.
84. Trivedi JC, Bariwal JB, Upadhyay KD, Naliapara YT, Joshi SK, Pannecouque CC, *et al*. Improved and rapid synthesis of new coumarinyl chalcone derivatives and their antiviral activity. Tetrahedron Lett 2007;48:8472-4.
85. Prasad YR, Rao AL, Rambabu R. Synthesis and antimicrobial activity of some chalcone derivatives. J Chem 2008;5:461-6.
86. Hafez OM, Nassar MI, El-Kousy SM, Abdel-Razik AF, Sherien MM, El-Ghonemy MM. Synthesis of some new carbonitriles and pyrazolecoumarin derivatives with potent antitumor and antimicrobial activities. Acta Pol Pharm 2014;71:594-601.
87. Balaji PN, Lakshmi LK, Mohan K, Revathi K, Chamundeswari A, Indrani PM. *In-vitro* anti-inflammatory and antimicrobial activity of synthesized some novel pyrazole derivatives from coumarin chalcones. Pharm Sin 2012;3:685-9.
88. Siddiqui ZN. A convenient synthesis of coumarinyl chalcones using $HClO_4$-SiO_2: A green approach. Arab J Chem 2015;12:2788-97.
89. Sun YF, Cui YP. The synthesis, characterization and properties of coumarin-based chromophores containing a chalcone moiety. Dyes Pigm 2008;78:65-76.
90. Jagtap AR, Satam VS, Rajule RN, Kanetkar VR. Synthesis of highly fluorescent coumarinyl chalcones derived from 8-acetyl-1, 4-diethyl-1, 2, 3, 4-tetrahydro-7H-pyrano [2, 3-g] quinoxalin-7-one and their spectral characteristics. Dyes Pigm 2011;91:20-5.
91. Khode S, Maddi V, Aragade P, Palkar M, Ronad PK, Mamledesai S, *et al*. Synthesis and pharmacological evaluation of a novel series of 5-(substituted) aryl-3-(3-coumarinyl)-1-phenyl-2-pyrazolines as novel anti-inflammatory and analgesic agents. Eur J Med Chem 2009;44:1682-8.
92. Jayashree BS, Yusuf S, Kumar DV. Synthesis of some coumarinyl chalcones of pharmacological interest. Asian J Chem 2009;21:5918.
93. Pingaew R, Saekee A, Mandi P, Nantasenamat C, Prachayasittikul S, Ruchirawat S, *et al*. Synthesis, biological evaluation and molecular docking of novel chalcone coumarin hybrids as anticancer and antimalarial agents. Eur J Med Chem 2014;85:65-76.
94. Mahmoud AE, El-Remaily A. Bismuth triflate: A highly efficient catalyst for the synthesis of bio-active coumarin compounds via one-pot multi-component reaction. Chin J Catal 2015;36:1124-30.
95. Rodriguez SV, Guíñez RF, Matos MJ, Azar CO, Maya JD. Synthesis and trypanocidal properties of new coumarin-chalcone derivatives. Med Chem 2015;5:173-7.
96. Deshpande HA, Chopde HN, Pandhurnekar CP, Batra RJ. Synthesis, characterization and testing of biological activity of some novel chalcones derivatives of coumarin. Chem Sci Trans 2013;2:621-7.
97. Hamdi N, Fischmeister C, Puerta MC, Valerga P. A rapid access to new coumarinyl chalcone and substituted chromeno [4, 3-c] pyrazol-4 (1H)-ones and their antibacterial and DPPH radical scavenging activities. Med Chem Res 2011;20:522-30.

98. Spirtovic-Halilovic S, Salihovic M, Dzudzevic-Cancar H, Trifunovic S, Roca S, Softic D, *et al*. DFT study and microbiology of some coumarin-based compounds containing a chalcone moiety. J Serb Chem Soc 2014;79:435-43.
99. Naruka SG, Mahajan SS. Conventional and microwave assisted synthesis and QSAR studies of coumarinyl chalcones as potent antimicrobial agents. Int J Res Pharm Chem 2011;4:879-90.
100. Quadri-Spinelli T, Heilmann J, Rali T, Sticher O. Bioactive coumarin derivatives from the fern *Cyclosorus interruptus*. Plant Med 2000;66:728-33.
101. Valente S, Bana E, Viry E, Bagrel D, Kirsch G. Synthesis and biological evaluation of novel coumarin-based inhibitors of Cdc25 phosphatases. Bioorg Med Chem Lett 2010;20:5827-30.
102. Wei H, Zhang X, Wu G, Yang X, Pan S, Wang Y, *et al*. Chalcone derivatives from the fern *Cyclosorus parasiticus* and their anti-proliferative activity. Food Chem Toxicol 2013;60:147-52.
103. Dridi D, Abdelwahab AB, Bana E, Chaimbault P, Meganem F, Kirsch G. Synthesis and molecular modeling of some new chalcones derived from coumarine as CDC25 phosphatases inhibitors. Med J Chem 2016;5:323-30.
104. Xi GL, Liu ZQ. Coumarin moiety can enhance abilities of chalcones to inhibit DNA oxidation and to scavenge radicals. Tetrahedron 2014;70:8397-404.
105. Perez-Cruz F, Vazquez-Rodriguez S, Matos MJ, Herrera-Morales A, Villamena FA, Das A, *et al*. Synthesis and electrochemical and biological studies of novel coumarin chalcone hybrid compounds. J Med Chem 2013;56:6136-45.
106. Mazzone G, Galano A, Alvarez-Idaboy JR, Russo N. Coumarin chalcone hybrids as peroxyl radical scavengers: Kinetics and mechanisms. J Chem Inf Model 2016;56:662-70.
107. Ahmad I, Thakur JP, Chanda D, Saikia D, Khan F, Dixit S, *et al*. Syntheses of lipophilic chalcones and their conformationally restricted analogues as antitubercular agents. Bioorg Med Chem Lett 2013;23:1322-5.
108. Yadav DK, Ahmad I, Shukla A, Khan F, Negi AS, Gupta A. QSAR and docking studies on chalcone derivatives for antitubercular activity against *M. tuberculosis* H37Rv. J Chemom 2014;28:499-507.