International Research Journal of Multidisciplinary Scope (IRJMS), 2024; 5(3):321-330 IRJMS

Review Article | ISSN (O): 2582-631X DOI: 10.47857/irjms.2024.v05i03.0719

Coumarin Chalcone Hybrids: Molecular Hybridization Strategy for Drug Design

Sumita Kumari[1]*, Amit Sharma[1], Sonia Yadav[2]

[1]Jagannath University, Jaipur, Rajasthan, India, [2]SGT College of pharmacy, SGT University, Gurugram, Haryana, India. *Corresponding Author's Email: sumitabajia87@gmail.com

Abstract

Naturally occurring and synthetically produced hybrid compounds are potential reservoir for development of novel drug regimen because of various benefits including effectiveness, minimal side effects, receptor interactions and pharmacokinetic features. Coumarin and chalcone are perfect building blocks for creating hybrid scaffolds that can be used as bioactive agents. These are essential classes of synthetic chemistry with wide range of pharmacological properties. Encouraged by potential therapeutic and medicinal significance of these hybrids, the scientists have reported dozens of coumarin chalcone hybrids with a broad range of biological properties like antioxidant, analgesic, antimicrobial, antiviral, anticancer, antianxiety, antimalarial, anti-inflammatory etc. It is intended to support to medicinal researchers in the efficient, fruitful development of coumarin chalcone hybrids to maximize their biological potential. In view of these findings, we present here some literature review, synthetic methods and pharmacological efficacy, molecular targets.

Keywords: Coumarin-Chalcone Hybrids, Molecular Hybridization, Molecular Targets, Pharmacological Properties, Synthesis.

Introduction

The goal of medicinal chemistry is to create, assemble, refine new bioactive compounds; various drug research approaches can be applied for this purpose (1). From last few years, medicinal chemists used molecular hybridization approach or strategy for new lead compounds design and development. Through various unique molecular interactions molecular hybridization tactic will yield new molecules with improved pharmacokinetic profile that cause interaction with multiple sites (2). In the past few years, concept of hybrid molecules designed by mixing of two or more pharmacophore has gained attention in the field of drug development and medicinal chemistry as well. Coumarin is most valuable medicinal pharmacophore. It found in natural compounds as an integral structural element and also has gained attention because of its therapeutic applications like antimycobacterial efficacy. Mainly, it found in flavonoids, natural alkaloids, anthocyanins, tocopherols. Various coumarin derivatives possess significant biological actions (3, 4). Another phytoconstituents having enone and aromatic ketone as functional group collectively called chalcones. Claisen-Schmidt reaction is general synthetic method for chalcones. It can also be prepared by Aldol condensation (5, 6). In 21st century, the chemistry of chalcones remains interest for various therapeutic activities such as anticancer, antigout, anti-inflammatory, antioxidant, antimicrobial (7, 8). In view of this biological significance of both scaffolds approach of molecular hybridization is being used. Basic skeletons of coumarin and chalcone shown in Figure 1. The molecular hybrids of coumarin - chalcones by Konidala *et al.,* (2021) and Vazquez-Rodriguez *et al.,* (2015) were examined for T. maritimum strains by using well diffusion method for fungal treatment (9, 10). Coumarin chalcone hybrids also tested for cancer by Amin *et al.,* against HCT-116 human colon lung cancer cell lines and the compounds generated by molecular hybridization process showed excellent anticancer activity with IC50 of 0.01μM (11). These hybrids were investigated for the inhibition of PI3K (P110α/p85α), and the IC50 value was found to be 50.78 μM (12, 13). Chalcone–coumarin hybrids developed by Pingaew *et al.,* (2014) possessed the

(Received 07th March 2024; Accepted 15th July 2024; Published 30th July 2024)

highest anticancer activity against HuCCA1, HepG2, A549, and MOLT-3, with IC50 values of 11.13 ± 0.40 μM, 15.70 ± 2.00 μM, 31.40 ± 1.00 μM, and 5.16 ± 0.69 μM, respectively (14). Molecular docking a tool of molecular modelling was also preferred to investigate the binding of the ligands to potential targets and for designing of hybrids. The highest binding energy was used to predict the hybrid characteristics. The coumarin–chalcone derivatives developed by Hu *et al.,* (2022) as α-glucosidase inhibitors, compounds displayed the highest IC50 value (15). Therefore, chalcone coumarin hybridization may produce appealing scaffolds for generation of novel anti-cancer and antimicrobial drugs. Here we quoted about various literature of coumarin chalcone hybrids for different potentials.

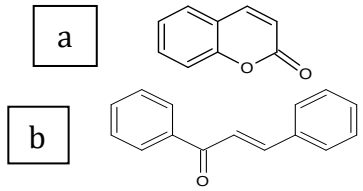


Figure 1: Coumarin (a) Chalcone (b) Skeleton

Mukusheva G K *et al.,* (2014) observed coumarin chalcone hybrid synthesis with a triazole linker (Figure 2) (16). Perenz- cruz *et al.,* (2015) synthesised hydroxy coumarin chalcone hybrids and screened for biological and electrochemical studies (Figure 3) (17). 2- and 4- substituted chalcone coumarin hybrids synthesized and observed for antibacterial activity by Moodley *et al.,*, (2016) and also explored the effect of methoxy, chloro, phenyl, flouro groups on antibacterial activity (Figure 4) (18). Zavrsnik *et al.,* (2017) reported coumarin synthesis and tested for antimicrobial activity against many species. He found that 4-chloro substitution is most effective for staphyloccocus aureus (Figure 5) (19).

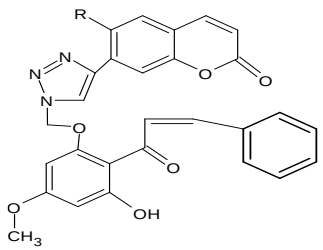


Figure 2: Coumarin Chalcone Hybrids with Triazole Linker

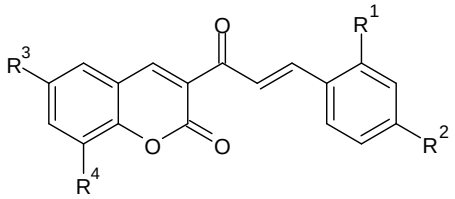


Figure 3: Hydroxy Coumarin Chalcone Hybrids

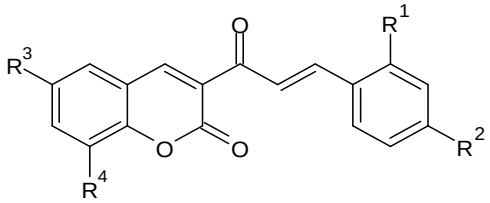


Figure 4: 2- and 4- substituted Coumarin Chalcone

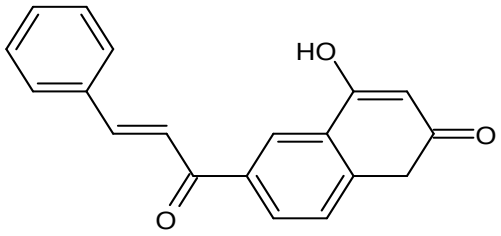


Figure 5: Coumarin Hybrid

Importance of Coumarinyl Chalcones

Coumarin and chalcone skeletons are widely available from natural sources and both have notable biological properties on their own, combining and hybridization of these two molecules results in desired effects. Recent review tells that joining of coumarin moiety alongwith chalcone ring may be important for derivatization (20).

Synthesis of Coumarinyl Chalcones

New synthesised chalcone coumarin hybrids observed by Shashidhara et.al by combining 2-sec-butyl phenol alongwith hexamethylene triamine at 120°C for 3 hrs. The product obtained was 5-sec-butyl-4-hydroxyisophthaldehyde, reacting with p-acetophenone for 1.5hrs at 90˚C. Then, mix with coumarin after refluxing with ethyl acetoacetate (ethanolic) (30 mins) using piperidine as catalyst (Figure 6) (21).

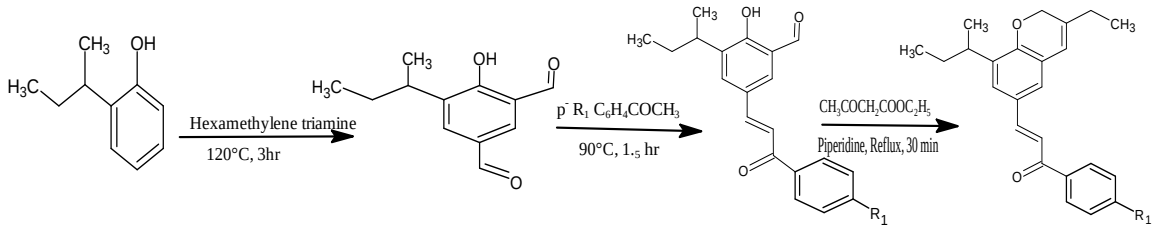


Figure 6: Synthetic Strategy of Coumarin Chalcones by Shashidhara *et al.,* (21)

Thrineshen *et al.,* reported of 2-and 4- substituted coumarinyl chalcones synthesis by reflux aldehyde (phenolic) with ethyl acetoacetate (methanolic) for 16 hrs, using piperidine as catalyst. Resulted coumarin refluxed with ethanolic aromatic aldehyde (substituted) for 5hr, piperidine act as catalyst (Figure 7) (22).

Prasad *et al.,* observed coumarinyl chalcone formation by refluxing 3-acetyl coumarin with ethanolic aromatic aldehyde (substituted) for 7 hrs, catalyst was piperidine (Figure 8) (9).

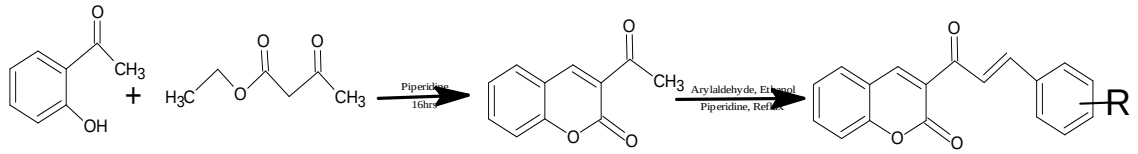


Figure 7: Coumarin Chalcone Synthesis by Thrineshen *et al.,* (22)

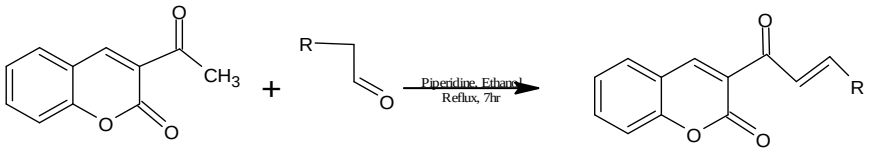


Figure 8: Synthetic Procedure by Prasad *et al.,* (9)

Patel *et al.,* reported the coumarinyl chalcones by reaction of $PoCl_3$ and CH_3COOH with 4-hydroxy coumarin to found 4-hydroxy-3-acetyl coumarin then further reacted with benzaldehydes (substituted) and $CHCl_3$ by Knoevenagel condensation by using piperidine as catalyst (Figure 9) (23).

Coumarinyl chalcone synthesis via green synthesis process reported by Siddiqui *et al.,* (24). Ethyl acetoacetate with salicylaldehyde in presence of piperidine for 20 minutes at room temperature yield coumarinyl chalcones then obtained product refluxed for 4 hrs with aromatic aldehydes, reported by Khode *et al.*, (25) (Figure 10).

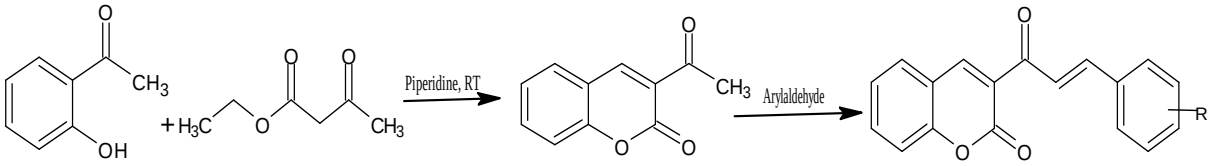


Figure 9: Knoevenagel Condensation

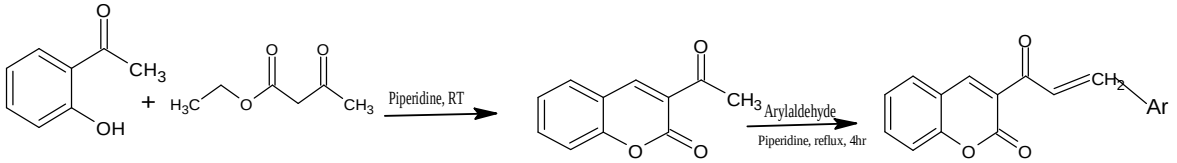


Figure 10: Synthesis by Khode *et al.,* (25)

Pharmacological Applications

Hybrids are discussed on basis of biological effects, natural sources, SAR, structural features, mechanism of action and hybridization strategies, in this review. This review expected the potential development of chalcone coumarin derivatives as potential therapeutic agent.

Antitumour Activity: Nowadays cancer is a deadly disease throughout the world. Because of their drug like efficacy, molecular hybrids have become

more popular. In last ten to fifteen years numerous anti-neoplastic drugs as per principles of molecular hybridization have been mentioned (26). Anticancer potential of synthetic coumarin chalcone hybrids is discussed or covered here. By using Sulforhodamine-B-assay, found antitumour activity of coumarin chalcone hybrids. In four human cell lines this assay predicts growth inhibition by hybrids. Potent activity against all cell lines shown by methyl and chlorine substituted hybrids (Table 1, Figure 11) (21, 27). Coumarinyl chalcones shows antitumour activity against MCF-7 cell lines for breast cancer. OCH_3 group at chalcone ring gives better result (Table 1, Figure 12) (28).

Coumarinyl chalcone derivatives showed anticancer activity against hepato carcinoma cell lines. Compounds bearing bromo, methyl substituents result weak anticancer activity (Table 1, Figure 13) (29-31).

Nikalje *et al*., observed coumarin chalcone hybrids for in vitro cytotoxic activity against cancer cell lines(human). Compound given below showed potent efficacy for HeLa and MCF-7 cell lines. He found on aromatic ring electron releasing groups lowered cytotoxic action and electron withdrawing groups increased it. Docking results revealed good binding affinity towards topoisomerase II for all synthesised compounds as compared to reference drug (etoposide) (Table1, Figure 14) (32,33). Shang *et al.,* provided cytotoxicity of human lung adenocarcinoma cells for two series of coumarin chalcone synthetics. He found that presence of hydroxyl group on B ring gives more cytotoxic activity as compared to non-substitution (34).

Antimalarial Activity: Various chalcone and coumarins observed in past for antimalarial efficacy (35, 36). Different findings for coumarin and chalcone as antimalarials reported in this section. Coumarinyl chalcone hybrids reported antimalarial activity against chloroquine resistant *plasmodium falciparum,* compounds with electron withdrawing groups shows effective antimalarial activity (Table 1, Figure 15) (23). By using in sillico and in vitro studies coumarinyl chalcone derivatives showed antimalarial activity. Trimethoxy substitution at chalcone ring gives potent compounds (Table 1, Figure 16) (26).

The antimalarial activity of the anti-tumour coumarin chalcone hybrids generated by Pingaew et al was also assessed. It was observed that molecule having trimethoxy group on B ring more potent.

Antimicrobial Activity: Fungal and bacterial infections are becoming major health issues around through world (37). Using cup plate method, the antibacterial properties of coumarin chalcones were assessed by Gholap *et al.,* 24 hours cultured three bacterial strains were subjected for in vitro antibacterial activity. Nystatin and streptomycin used as reference drugs. Every substance examined showed good to moderate antibacterial activity with zone of inhibition in range of 5-26mm (38).

Using streptomycin as reference compound Ajani *et al.,* assessed synthesized coumarin chalcone hybrids for antimicrobial activity against five series of gram negative and gram-positive bacteria. Most of the produced compounds showed zones of inhibition on different bacterial growth were found to vary between 10mm to 23 mm. Compound shown in Table 1 (Figure 17) was found to be the most active, with MIC value of 7.8g μ/ml (39, 40).

Spirtovic- Halilovic et al evaluated antibacterial activity of 4 coumarin chalcone hybrids against two gram-positive bacteria (aerobic). Each of the four hybrids possessed the capacity to prevent bacterial development. Compound given in Figure determined to be most effective. For all the four compounds reactivity and stability descriptors were predicted by using density function theory (DFT; Table 1, Figure 18) (41).

The antibacterial and antifungal properties of 11 coumarin chalcones were explored by Naruka *et al.,* Majority of synthesized affiliates have strong antibacterial activity for more than one strains of bacteria. However, sulfa-methoxazole as standard found less effective than three hybrids. The QSAR model suggested the strong relationship between the parameter of WPSA and log Zol values against E. coli for coumarin hybrids. QSAR results show that higher antibacterial activity for lower WPSA value. This QSAR model can be used to rationally design antibacterial drugs in future that based on coumarin chalcone hybrids (42, 43).

Antioxidant Activity: It is commonly known that excessive formation of reactive oxygen species as well as oxidative stress brought on by free radicals significantly contributes to inflammatory and cardiovascular diseases. It has been demonstrated that hybrid compounds are promising antioxidants against illnesses caused by oxidative stress. Many

hybrids of coumarin chalcones are designed by medicinal chemists. This section gives a quick summary of these innovations. Coumarinyl chalcone hybrids were found to have antioxidant activity by Rodreguez *et al.,* through electrochemical analysis, hybrids having bromine and hydroxyl group in coumarin ring at 6th and 8th position respectively demonstrate radical scavenging activity (Table 1, Figure 19) (44).

Xi *et al.,* reported seven coumarin chalcones for inhibitory effects on AAPH-induced oxidation of DNA, cu2+/GSH. GSH induced destruction of DNA caused by all seven compounds. Compound given in Figure 20 (Table 1) shown excellent scavenging property due to hydroxyl group present at benzene ring (45).

Sashidhara *et al.,* reported three series of biscoumarin-chalcones for radical scavenging potential and lipid peroxidation reduction capacity of microsomes. Screened three hybrids identified as optimum efficacy in superoxide anions inhibition by 29%, 24%, 30% inhibition of microsomal lipid peroxidation by 23%, 27%, 24%, hydroxyl radical inhibition by29%, 26%, 21% respectively (Table 1, Figure 21) (46).

Antitubercular Activity: Ahmad et al proposed antitubercular action of chalcone coumarin hybrids against H37RV mycobacterium tuberculosis, by using multiple regression linear based QSAR model and activity increased by incorporating nitrogen moiety on B ring of chalcone (Table 1, Figure 22) 47-49).

Antihyperlipidemic Activity: Cardiovascular diseases are one of main cause for mortality worldwide. Numerous coumarin and chalcones have been shown capable to lower cholesterol. As lipid lowering agent 16 hybrids of coumarin chalcone reported by Sashidhara *et al.,* (50, 51). Screening results showed that compound in Figure 23 (Table 1) had the most powerful ability to reduce the triglycerides, total cholesterol and phospholipids of hyperlipidaemic rats by 25%, 26%, 24% respectively at 100mg/kg body weight in Wistar rats (52).

Anti-inflammatory Activity: The normal response of body to any injury is known as inflammation involves accumulation of exudates and cells in inflammed tissues. Redness, warmth, pain and swelling are four common indicators of inflammation. The anti-inflammatory efficacy of biscoumarin chalcone analogues was examined for ability to prevent carageenan-induced paw edema in albino rats by giving dose 100mg/kg body weight against ibuprofen used as reference drug. These analogues showed 33% reduction in volume of paw (45).

Fluorescent Activity: Compounds containing coumarin and chalcone scaffolds demonstrated potential use as fluorescent probes (52). Photophysical and spectroscopic properties of hybrids reported by Al-Sehemi *et al.,* Study revealed that polarity of solvent directly affect the fluorescent properties of chalcone coumarin hybrids (Figure 24) (53).

The potential of four coumarin chalcones have evaluated as chemical sensors for copper and cyanide ions by Shan *et al.,* The finding shows that majority of compounds give sharp colour change. Copper ions form complex with target and cyanide ions bonded with C=C bond. Absorbance peak of target compound shown at 486nm and 431nm due to cyanide and cupric ions respectively. Compound's fluorescence spectrum response to cyanide and copper ions was also investigated. It was found that target molecules in presence of copper and cyanide ions exhibits fluorescence turn off response sensors (54).

Anti-neurodegenerative Activity: Several compounds obtained from chalcocoumarins were synthesised and tested against both monoamine oxidase enzyme isoforms i.e. MAO-A and MAO-B. These hybrids exhibited affinity towards MAO-B in micromolar concentration with effective IC50 value. These hybrids have adequate solubility in gastrointestinal tract and good indication for fitting in active site of MAO and form an interaction necessary for inhibition of rMAO-B and also could be promising agents to treat parkinson's disease (neurodegenerative disorder; Table 1, Figure 25) (55). Zhu *et al.,* (2023) designed, synthesized coumarin chalcone hybrid derivatives based on structure hybridization principle and evaluated for their biological potential as PDE2 inhibitors. These hybrids exhibited significant inhibitory effects on PDE2 with potential IC50 value (56).

Molecular Targets

Different enzymes are available as molecular targets for coumarin chalcone hybrids to show their biological effects against diseases. Described as:

Xanthine Oxidase inhibitor: Xanthine oxidase catalyses hypoxanthine and xanthine by oxidative

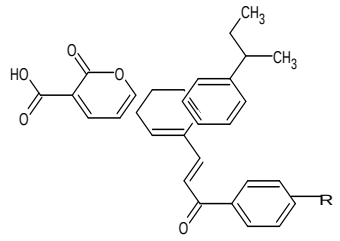
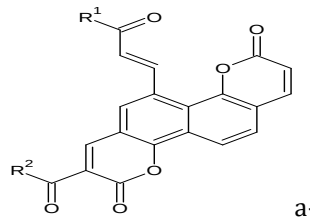
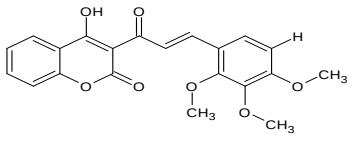
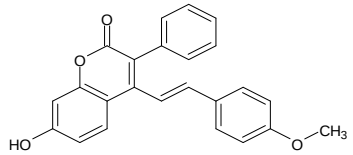
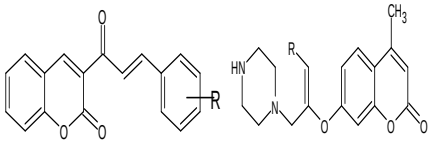
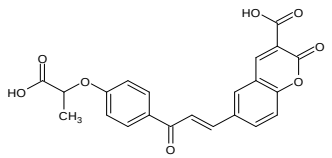
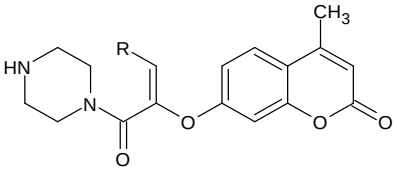
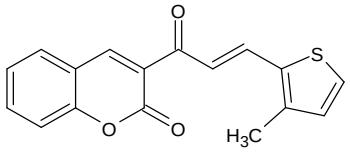
hydroxylation to produce reactive oxygen species and uric acid as well which results gout. Hence, xanthine oxidase inhibition resulted anticancer and antigout profile. Virdi et al reported coumarin chalcone hybrids synthesis for their xanthine oxidase inhibitory property by using pyran as linker. Bovin milk XO enzymatic assay used for in vitro evaluation of hybrids having allopurinol as standard. Compound in figure shown effective inhibition of xanthine oxidase and found to be most effective and potent compound due to lower molecular volume and clog P value. It was observed that by enhancing these values XO inhibition decreased (Table 1, Figure 26) (57).

Adenosine receptor antagonists (AR): Adenosine is an ATP component and building block for nucleic acid. Adenosine signals by activation of four receptors A1, A2A, A2B, A3 that act as drug targets. Adenosine receptor antagonists play important role in cancer. Vazquez-Rodriguez *et al.,* reported that compound given in fig potent inhibitor for hA_3AR with dissociation constant value 5160. Its binding affinity was compared with theophylline (Table 1, Figure 27) (58).

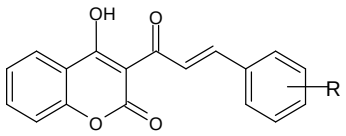
Histone deacetylases (HDACs): Removal of acetyl groups from lysine catalysed by histone deacetylases enzymes, these are important targFets for anticancer therapy. Sediel et al reported 8 coumarin chalcone hybrids for cell proliferation effect and HDAC potential in leukemia cell lines. Compound given in figure shown 50% inhibition of HDAC3 (Table 1, Figure 28) (59).

Monoamine oxidase inhibitors (MAOIs): Two isoforms of FAD containing enzyme MAO-A and MAO-B identified. Inhibitors of these isoforms found to be useful in Alzheimer and Parkinson's disease treatment. Potential of coumarin as MAO inhibitory molecule described in many studies. Vazquez-Rodriguez found MAO inhibition of coumarin chalcone hybrids by molecular docking. Compounds shown in figure was found more selective for MAO-A against neurodegenerative disorders (Table 1, Figure 29, 30) (60).

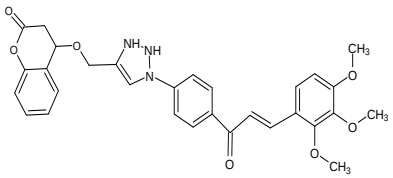
Table 1: Structure of Some Coumarin Chalcone Hybrids

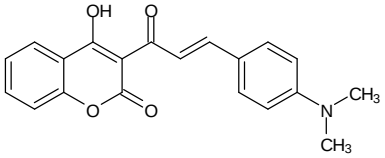
Figure No.	Structure	Figure No.	Structure
11	 R—CH_3, C_2H_5	21	 a-c a-- R^1= C_6H_5, R^2= OCH_3 b-- R^1= 2-thiophenyl, R^2= OC_2H_5 c-- R^1= 2-furyl, R^2= OC_2H_5
12		22	
13	 R= 5-CH_3, 4- Br, 2-furyl	23	
14		24	

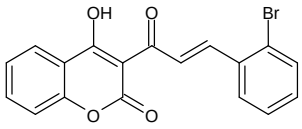
R= aryl or heteroaryl

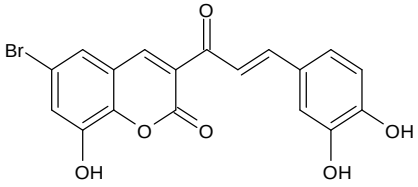
15 

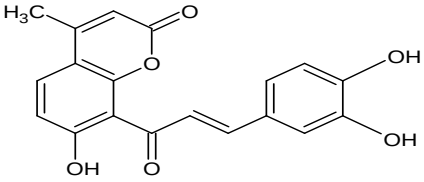
R= electron withdrawing group

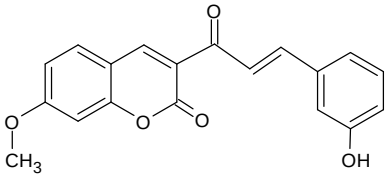
16 

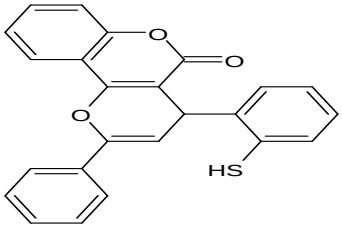
17 

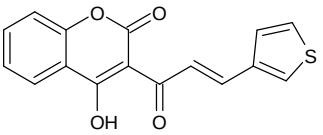
18 

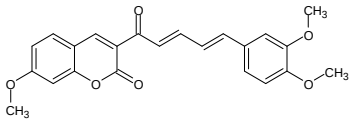
19 

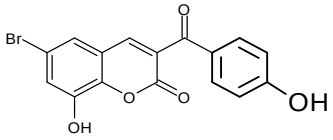
20 

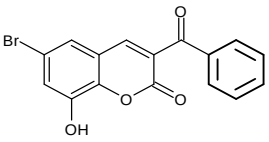
25 

26 

27 

28 

29 

30 

Conclusion

Coumarin and chalcone hybrids have drawn more attention for their diverse pharmacological activities. We outlined anticancer, antimicrobial, antioxidant, anti-inflammatory, fluorescent, antimalarial properties of synthesised hybrids. The review is crucial for the creation of innovative lead compounds. In this review, a focus is on investigation of novel methods for synthesis of hybrids of coumarin chalcones including diverse array of medicinal, biological activities of these hybrids and another topic that covered is molecular targets also.

Abbreviations

Nil.

Acknowledgement

Nil.

Author Contributions

The authors confirm sole responsibility for the study conception and design, data collection, manuscript preparation.

Conflict of Interest

The authors declare no conflict of interest.

Ethics Approval

Not applicable.

Funding

This study has not been supported by any external funding.

References

1. Riedl S, Zweytick D, Lohner K. Membrane-active host defence peptides–challenges and perspectives for the development of novel anticancer drugs. Chemistry and Physics of Lipids. 2011; 164(11): 766–781.
2. Burch JD, Farand J, Colucci J, Sturino C, Ducharme Y, Friesen RW, *et al.* Naphthalene/quinoline amides and sulfonylureas as potent and selective antagonists of the EP4 receptor. Bioorganic *&* Medicinal Chemistry Letters. 2011; 21(12):1041–1046.
3. Tandel H, Chikhalia KH, Patel SK. Synthesis and antibacterial activity of novel coumarin –chalcone hybrids. Indian Journal of Chemistry. 2019; 58B (5): 594-602.
4. Kucukislamoglu K. Synthesis and biological evaluation of novel coumarin-chalcone derivatives containing urea moiety as potential anticancer agents. Arabian Journal of Chemistry. 2020;13(1): 1120-1129.
5. Sokmen M, Khan MA. The antioxidant activity of some curcuminoids and chalcones. Inflammopharmacology. 2016; 24(5)*:* 81–86.
6. Maheswari U. Flavonoids: Therapeutic Potential of Natural Pharmacological agents. International Journal of Pharmaceutical Sciences an d Research. 2017; 7(10): 3924-3930.
7. Chavan A. Molecular Docking Study and Antibacterial Activity of Chalcones Derivatives. The Pharma Innovation Journal. 2020; 9(1): 39-42.
8. Hseieh HK. Chalcone synthesis, properties and medicinal application: A review. Environmental Chemistry Letters. 2020; 18(6): 433-458.
9. Konidala SK, Kotra V, Danduga RCSR, Kola PK, Bhandare RR, Shaik AB *et al.,* Design, multistep synthesis and in-vitro antimicrobial and antioxidant screening of coumarin clubbed chalcone hybrids through molecular hybridization approach. Arabian Journal of Chemistry. 2021; 14(6): 103154.
10. 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. Bioorganic & Medicinal Chemistry Letters. 2015; 23(9): 7045-52.
11. Amin KM, Eissa AAM, Abou-Seri SM, Awadallah FM, Hassan GS. Synthesis and biological evaluation of novel coumarin– pyrazoline hybrids endowed with phenylsulfonyl moiety as antitumor agents. European Journal of Medicinal Chemistry. 2013; 60(3): 187–198.
12. Kurt BZ, Kandas NO, Dag A, Sonmez F, Kucukislamoglu M. Synthesis and biological evaluation of novel coumarin-chalcone derivatives containing urea moiety as potential anticancer agents. Arabian Journal of Chemistry. 2020; 13(1): 1120–1129.
13. Pavic K, Beus M, Poje G, Uzelac L, Kralj M, Rajic Z, *et al.,* Synthesis and biological evaluation of harmirins, novel harmine– coumarin hybrids as potential anticancer agents. Molecules. 2021; 26(10): 64-90.
14. 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. European Journal of Medicinal Chemistry. 2014; 85(10): 65–76.
15. Hu CM, Luo YX, Wang WJ, Li JP, Li MY, Zhang YF, *et al.,* Synthesis and Evaluation of Coumarin-Chalcone Derivatives as α-Glucosidase Inhibitors. Frontier Chemistry. 2022; 10(6): 926543.
16. Mukusheva GK, Lipeeva AV, Zhanymkhanova PZ. The flavanone pinostrobin in the synthesis of coumarin chalcone hybrids with a triazole linker. Chemistry of Heterocyclic Compounds. 2015; 51(4): 146–152.
17. Patel PB, Patel TK, Baxi SN, Acharya HR, Tripathi C. Antitubercular effect of 8- [(4-Chloro phenyl) sulfonyl]-7- Hydroxy-4-Methyl-2H-chromen-2-One in guinea pigs. Journal of Pharmacology and Pharmacotherapeutic. 2018; 2: 253- 60.
18. Moodley T, Momin M, Mocktar C, Kannigadu C, Koorbanally NA. The synthesis, structural elucidation and antimicrobial activity of 2-and 4-substituted-coumarinyl chalcones. Magnetic Resonance in Chemistry. 2016; 54(7): 610-617.
19. Zavrsnik T, Al-Amiery AA, Al-Majedy YK, Kadhum AAH, Mohamad AB. Synthesis of new coumarins complemented by quantum chemical studies. Research on Chemical Intermediates. 2016; 10(7): 3905-18.
20. Li X, Zhao Y, Wang T, Shi M, Wu F. Coumarin derivatives with enhanced two-photon absorption cross-sections. Dyes and Pigments. 2007; 74(1): 108-12.
21. Sashidhara KV, Kumar A, Kumar M, Sarkar J, Sinha S. Synthesis and in vitro evaluation of novel coumarin chalcone hybrids as potential anticancer agents. Bioorganic & Medicinal Chemistry Letters*.* 2010; 20(24): 7205-11.
22. Moodley T, Momin M, Mocktar C, Kannigadu C, Koorbanally NA. The synthesis, structural elucidation and antimicrobial activity of 2-and 4-substituted-coumarinyl chalcones. Magnetic Resonance in Chemistry. 2016; 54(7): 610-627.
23. 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. Medicinal Chemistry Research*.* 2012; 21(8): 1780-84.
24. Siddiqui ZN. A convenient synthesis of coumarinyl chalcones using HClO4 -SiO2: A green approach. Arabian Journal of Chemistry. 2015; 43(12): 2788-97.
25. 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. European Journal of Medicinal Chemistry. 2019; 44:1682-8.
26. Nepali K, Sharma S, Sharma M, Bedi PMS, Dhar KL. Rational approaches, design strategies, structure activity relationship and mechanistic insights for anticancer hybrids. European Journal of Medicinal Chemistry. 2014; 77: 422–487.

27. Zhuang C, Miao Z, Wu Y, Guo Z, Li J, Yao J, *et al.* Double-Edged Swords as Cancer Therapeutics: Novel, Orally Active, Small Molecules Simultaneously Inhibit p53–MDM2 Interaction and the NF-κB Pathway. Journal of Medicinal Chemistry. 2014; 57(3): 567–577
28. Wanare G, Aher R, Kawathekar N, Ranjan R, Kaushik NK, Sahal D, *et al.* Synthesis of novel α-pyranochalcones and pyrazoline derivatives as Plasmodium falciparum growth inhibitors. Bioorganic Medicinal Chemistry Letters. 2010; 20(15): 4675-8.
29. Hafez OM, Nassar MI, El-Kousy SM, Abdel-Razik AF, Sherien MM, El-Ghonemy MM, *et al.* Synthesis of some new carbonitriles and pyrazole coumarin derivatives with potent antitumor and antimicrobial activities. Acta Poloniae Pharmaceutica. 2014; 71(4): 594-601.
30. Sahoo CR, Paidesetty SK, Dehury B, Padhy RN. Molecular dynamics and computational study of Mannich-based coumarin derivatives: potent tyrosine kinase inhibitor. Journal of Biomolecular Structure and Dynamics. 2020; 38 (18): 5419–5428.
31. Sahoo CR, Paidesetty SK, Dehury B, Padhy RN. Nostocine A derivatives as human DNA topoisomerase II-alpha inhibitor. Indian Journal of Pharmaceutical Education and Research. 2020; 54 (3): 669–675.
32. Nikalje PG, Tiwari VS, Tupe VJ, Vyas KV, Qureshi G. Ultrasound assisted-synthesis and biological evaluation of piperazinylprop-1-en-2-yloxy-2h-chromen-2-ones as cytotoxic agents. Letters in Drug & Discovery. 2017; 14: 1195–1205.
33. Pasricha S, Gahlot P. Synthetic strategies and biological potential of coumarin-chalcone hybrids: A new dimension to drug design. Current organic chemistry. 2020; 24(4):1385-1437.
34. Shang Y, Wei Q, Sun Z. Studying the cytotoxicity of coumarin–chalcone hybrids by a prooxidant strategy in A549 cells. Monatshefte fuer Chemie-Chemical Monthly. 2018; 149(12): 2287–2292.
35. Hu XL, Gao C, Xu Z, Liu ML, Feng LS, Zhang GD *et al.* Recent Development of Coumarin Derivatives as Potential Anti-plasmodial and Antimalarial Agents. Current Topics in Medicinal Chemistry. 2017; 17(29): 3219-3231.
36. Yadav N, Agarwal D, Kumar S, Dixit AK, Gupta RD, Awasthi SK *et al.,* In vitro antiplasmodial efficacy of synthetic coumarin-triazole analouges. European Journal of Medicinal Chemistry. 2018; 145: 735–745.
37. Drebes J, Kunz M, Pereira CA, Betzel C, Wrenger C. MRSA infections: From classical treatment to suicide drugs, Current Medicinal Chemistry. 2014; 21(15): 1809–1819.
38. Gholap SS, Deshmukh UP, Tambe MS. Synthesis and in-vitro antimicrobial screening of 3-cinnamoyl coumarin and 3-[3-(1H-indol-2-yl)-3-aryl-propanoyl]-2H-chromen-2-ones. I.J.C. 2013; 3: 171–176.
39. Ajani OO, Nwinyi OC. Microwave-assisted synthesis and evaluation of antimicrobial activity of 3- {3-(s-aryl and s-heteroaromatic) acryloyl} -2H-chromen-2-one derivatives. Journal of Heterocyclic Chemistry. 2010; 47(1): 179–187.
40. Al-Majedy YK, Kadhum AAH, Al-Amiery AA, Mohamad AB. Coumarins: The Antimicrobial agents. Systematic Reviews in Pharmacy. 2017; 8: 62–70. doi: 10.5530/srp.2017.1.11.
41. 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. Journal of the Serbian Chemical Society. 2014; 79(4): 435–443.
42. Naruka SG, Mahajan S, Shah C. Conventional and microwave assisted synthesis and QSAR studies of coumarinylchalcones as potent antimicrobial agents. International Journal of Research in Pharmacy and Chemistry. 2011;1(4): 879–890.
43. Sahoo CR, Patro R, Sahoo J, Padhy RN, Paidesetty SK. Design, molecular docking of synthesized schiff-based thiazole/pyridine derivatives as potent antibacterial inhibitor. Indian Drugs. 2019; 56 (11): 20–25.
44. Rodriguez SV, Guinez RF, Matos MJ, Azar CO, Maya JD. Synthesis and trypanocidal properties of new coumarin-chalcone derivatives. Journal of Medicinal Chemistry. 2015; 5(4):173-7.
45. Xi GL, Li ZQ. Coumarin-Fused Coumarin: Antioxidant Story from N, N-Dimethylamino and Hydroxyl Groups. Journal of Agricultural and Food Chemistry. 2015; 63(13): 3516–3523.
46. Sashidhara KV, Kumar M, Modukuri RK, Sonkar R, Bhatia G, Khanna AK. *et al.* Synthesis and anti-inflammatory activity of novel biscoumarin–chalcone hybrids. Bioorganic Medicinal Chemistry Letters. 2011; 21(15): 4480–4484.
47. Ahmad I, Thakur JP, Chanda D, Saikia D, Khan F, Dixit S *et al.* Synthesis of lipophilic chalcones and their conformationally restricted analogues as antitubercular agents. Bioorganic & Medicinal Chemistry Letters. 2013; 23(5): 1322-5.
48. Yadav DK, Ahmad I, Shukla A, Khan F, Negi AS, Gupta A *et al.,* QSAR and docking studies on chalcone derivatives for antitubercular activity against M. tuberculosis H37Rv. Journal of Chemometrics. 2014; 28(6): 499–507.
49. Patel PB, Patel TK, Baxi SN, Acharya HR, Tripathi C. Antitubercular effect of 8- [(4-Chloro phenyl) sulfonyl]-7-Hydroxy-4-Methyl-2H-chromen-2-One in guinea pigs. Journal of Pharmacology and Pharmacotherapeutics. 2018; 2: 253- 60.
50. Tejada S, Martorell M, Capo X, Tur AJ, Pons A, Sureda A *et al.* Coumarin and Derivates as Lipid Lowering Agents. Current Topics in Medicinal Chemistry Bentham Science. 2017; 17(4): 391–398.
51. Sashidhara KV, Palnati GR, Sonkar R, Avula SR, Awasthi C, Bhatia G. Coumarin chalcone fibrates: a new structural class of lipid lowering agents. European Journal of Medicinal Chemistry. 2013; 64: 422–431.
52. Niu H, Wang W, Li J, Lei Y, Zhao Y, Yang W *et al.* A novel structural class of coumarin-chalcone fibrates as PPARα/γ agonists with potent antioxidant activities: Design, synthesis, biological evaluation and molecular docking studies. European Journal of Medicinal Chemistry. 2017; 138: 212–220.
53. Al Sehemi AG, Pannipara M, Kalam A, Asiri AMA. Combined Experimental and Computational Investigation on Spectroscopic and Photophysical Properties of a Coumarinyl Chalcone. Journal of Fluorescence. 2016; 26: 1357–1365.

54. Shan Y, Liu Z, Cao D, Liu G, Guan R, Sun N *et al.* Coumarinic chalcone derivatives as chemosensors for cyanide anions and copper ions. Sensors Actuators B Chemical. 2015; 221: 463–469.
55. Moya-Alvarado G, Yanez O, Morales N, Gonzalez-Gonzaez A, Areche C, Nunez MT *et al.* Coumarin-Chalcone Hybrids as Inhibitors of MAO-B: Biological Activity and In Silico Studies. Molecules. 2021; 26(9): 2430.
56. Zhu Z, Wang FH, Fan J, Zhang C, Song G, Tang L. Design, synthesis and biological activity of coumarin-chalcone hybrid derivatives as phosphodiesterase type II (PDE2) inhibitors. Tetrahedron. 2023; 149(23): 133
57. Virdi HS, Sharma S, Mehndiratta S, Bedi PMS, Nepali K. Design, synthesis and evaluation of 2, 4-diarylpyrano [3, 2-c] chromen-5 (4H)-one as a new class of non-purine xanthine oxidase inhibitors. Medicinal Chemistry Research. 2015; 30: 730–736.
58. Vazquez-Rodriguez S, Matos MJ, Santana L, Uriarte E, Borges F, Kachler S *et al.* Chalcone-based derivatives as new scaffolds for hA3 adenosine receptor antagonists. Journal of Pharmacy and Pharmacology. 2013; 65(5): 697–703.
59. Seidel C, Schneken burger M, Zwergel C, Gaascht F, Mai A, Dicato M *et al.* Novel inhibitors of human histone deacetylases: design, synthesis and bioactivity of 3-alkenoylcoumarines. Bioorganic Medicinal Chemistry Letters. 2014; 24(16): 3797–3801.
60. Ferino G, Matos MJ, Cadoni E, Uriarte E, S. Vilar, Vina D *et al.* Benzopyran-2-Ones as Attractive Scaffold for MAO Inhibitors: Synthesis, Biological Evaluation and Docking Studies. Chem Med Chem. 2013; 8: 956–966.