The Review: Antimicrobial Activity of Coumarin

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Abstract- *Drug resistance has become a growing problem in the treatment of infectious diseases caused by bacteria and fungi. Given their wide range of biological activity and clinical applications, coumarin and its derivatives—which are heterocyclic compounds made from benzene and an oxygen-containing pyrone ring—are well known. These compounds are remarkably potent in terms of both their inhibitory activity and their advantageous selectivity ratio. The class of bioactive heterocyclic compounds known as coumarinsis thought to hold great promise because of its wide range of biological effects, including anti-microbial, anti-viral, anti-diabetic, anti-cancer, anti-oxidant, anti-parasitic, anti-helmintic, and anti-proliferative, anti-convulsant, anti-inflammatory, and anti-hypertensive activities. The data presented in this publication might be useful in the pursuit of better antimicrobial drugs with lower levels of microbial resistance and an enhanced antimicrobial profile.*

Keywords- Coumarin, Coumarin derivatives, Antibacterial and antifumgal activity, pyrone ring, fluoro coumarin..

I. INTRODUCTION

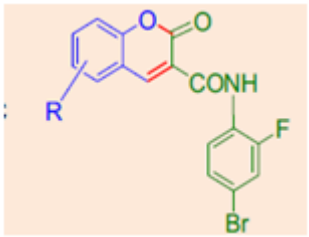
In the field of organic synthesis and natural goods, coumarin chemicals are a crucial class. Natural products that are biologically active have coumarin skeletons and are employed as an intermediary step in the synthesis of bioactive heterocyclic compounds and revealed its antimicrobial [1], antifungal [2], anti-inflammatory[3,5], anti-cancer[4,5], anti-tubercular [6], anti-oxidant[7] and anticoagulant

Properties [8]. A freshpotential to produce innovative multicyclic. Molecules with enhanced biological activity is provided by the Combination of heterocyclic [9, 10]. The production of several biologically active molecules, including coumarone and fluorocoumarin, uses coumarin as an intermediate [11].the pharmaceutical sector uses coumarin derivatives widely and they act as good chelating agents with many metal ions especially transition metals [12-14].The most creative and abundant sources of leading structures comprising of coumarin system includes plants from the families Rutaceae, Rubiaceae, Asteraceae, Apiaceae, Oleaceae, Fabaceae, Solanaceae and Hippocastanaceae,as well as microorganisms from the Asperigillus and Streptomyces strains[15-18].

II. ANTIMICROBIAL ACTIVITY

- Khan et al were synthesized their invitro antimicrobial activity against the two bacterial strains, *Escherichia coli* (gram –ve) and *Bacillus Cereus* (gram +ve). One compound was compared with ciprofloxacin Which shows good activity. For antifungal activity the compound were screened against 7 fungal strains *Aspergillusniger, Aspergillusfumigatus, Aspergillusflavus, Rhizopus, Mucor, Penicillium* and *Candida albicans*Which shows good activity. One compound (1) was compared with Fluconazole which shows good activity *against Rhizopus, Mucor, Penicillium, Candidaalbicans* and *Aspergillus flavus* by placing amide moiety at C3 position and substitution at c6/c8 position [19-22].
- Olayinkao .Ajani et al reported biological activity and synthesis of certain coumarin all the compounds (2, 3, 4, 5) demonstrated good efficacy against *Escherichia coli, Bacillus subtilis, Staphylococcusaureus* [23].
- Abdul Raheem et al synthesized a new coumarin derivatives and screened their antibacterial activity against two gram positive bacteria S.aureus and *Streptococcus pneumonia*, two gram negative bacteria *Pseudomonas aeruginosa* and *Escherichia coli* show high activity towards (G +ve) and (G –ve) bacteria when compared with amoxicillin. All the tested compound (6) shows high activity against *Candida*albicans compared to fluconazole and miconazole. [24]
- Regini Anthony et al synthesized a compound and screened their antimicrobial activity by broth dilution method. For antibacterial activity (ATCC 10148), Staphylococcus aureus (NCTC 3750), *Pseudomonas aeruginosa* (Fishers immunotype) test fungi species are *Aspergillus.niger* (ATCC 16404) and *Candidaalbicans* (ATCC 10231) with different concentration starts from 25ppm. Test compound (7) is compared with standard reference Ampicillin/Fluconazole at 100ppm in the same Condition.(7)
- Haseen Buvabi et al were developed a coumarin derived Schiff base ligand synthesis. This demonstrated that the free Schiff base ligand had greater antibacterial action against the gram –ve.Bacteria *Escherichia coli* than did the metal complex of copper(II) metal ion. This demonstrates that the freshly created Schiff base ligand compound (8, 9) is physiologically active substance.(8)(9)

- Behrami et al. synthesized a coumarine derivatives from 4, 7-dihydroxy-chromen-2-one and antibacterial activity was determined based on disc method with 3 bacterial cultures S.aureus, E.coli and B.cereus. The study offers the first concrete proof that the substance categorically prevents the growth of S.aureus, E.coli and B.cereus. (10)
- Al-Amiery et al. have synthesized 4-[(5-mercapto-4-phenyl-4H-1, 2, 4-triazol-3-yl)-methoxy]-2-ones as coumarin derivatives. Based on the growth inhibition rates of mycelia of A.niger and C.albicans strains in potato Dextrose Broth Medium (PDC) against doses ranging from 10 to 100gml, antifungal activity was identified. Two compound (10, 11) shown good Antifungal activity when compared with standard fluconazole [28-33] (11)
- G.Naik et al. were synthesized a novel coumarin derivatives using nutritional agar media. Two gram +ve and two gram –ve bacteria, S.aureus (MTCC 96), B.subtilis (MTCC 441) and E.coli (MTCC 443), P.aeruginosa (MTCC 688), the antibacterial activity of the produced compounds was evaluated. The antifungal activity was evaluated against the C.albicans (MTCC 227).One compound (12) was less active than the Ampicillin 100µgml and fluconazole (10µg) is compared for antifungal activity shows less activity[34-37].(12)
- Milan cocic et al. have synthesized some derivatives of (7-Hydroxy-2-oxo-2H-chromen -4yl)-acetic acid hydrazide. One compound (13, 14, and 15) wereScreened for their antimicrobial activity against S.pneumonia which shows high antimicrobial activity and were slightly less active against P.aeruginosa,B.subtilis, B.cereus and S.panama.(13)(14) (15)
- Ravinder et al. were synthesized a novel coumarins containing substituted 1, 3, 4-oxadiazole derivatives by the agar diffusion method.The antibacterial activity were screened against S.aureus gram (+ve) and E.coli gram (-ve) bacteria. All compound (16) show good activity when compared with ciprofloxacin. For antifungal activityA.niger and C.albicans are the bacterial strains. One compound is compared with Fluconazole which shows good activity. (16)
- Vasantha et al.have synthesized 8, 9-di-Hydro-7H-benzo-N-(Benzyloxy) - 2-(4-mwthyl coumarin-4/6-yloxy)-Acetamidederivatives. All the compounds (17) were screened for the antibacterial activity against E.coli gram (-ve) and S.aureus gram (+ve) bacteria. All compounds activities are almost equal to the standard drug. (17)
- Mohamad et al. synthesized a new compounds were screened for their antimicrobial activities *in vitro* against two Gram-negative *Bordetellabronchiseptica*(ATCC 4617) and *Escherichia coli* (ATCC 14169) and four Gram positive *Bacillus pumilus*(ATCC 14884), *Bacillus subtilis*(ATCC 6633), *Staphylococcusaureus*(ATCC 29737) and *Staphylococcus epidermidis*(ATCC 12228) pathogenic bacteria and two fungi *Candida albicans*(ATCC 10231) and *Saccharomyces cervesia*(ATCC 9080). The activities of these compounds (18, 19) were tested using the disc diffusion method for Bacteria and the paper disk diffusion method for fungi. The area of zone of inhibition was measured using Ampicillin (25 µg mL−1) as standard antibiotic Micostatin (25 µg mL−1) was used as a reference antifungal. The screening results demonstrated that replacing the hydrogen atom attached to the coumarin nucleus at C-3 with a side chain and results in wide spectrum antimicrobial activity against all tested bacteria and fungi compared to ampicillin and mycostatin, while the other compounds with other side chains showed moderate to weak activity[41,42]. (18)(19)
- Yang et al. antifungal assays were performed against A. solani and F. axysporum in vitro by the plate growth rate method Studies on their antifungal activity against *A. Solani, F. Oxysporum*and *F.moniliforme*show that all coumarin-chitosan derivatives have higher antifungal activity than chitosan.The introduction of halogen substituents to the phenyl ring of coumarin is more favorable to antifungal activity. (20)



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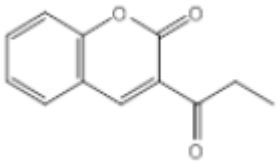

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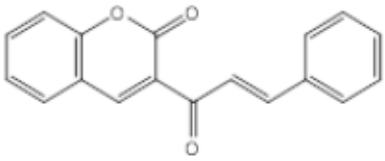

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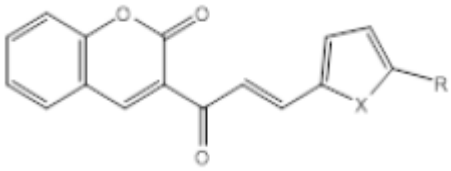

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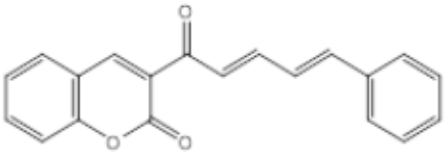

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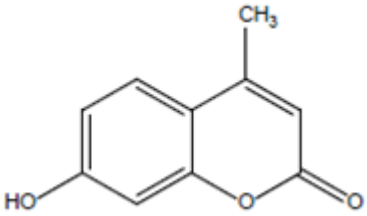

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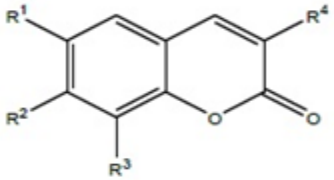

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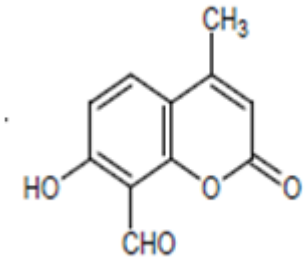

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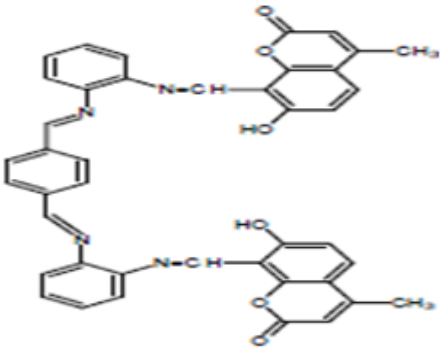

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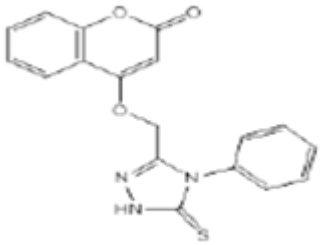

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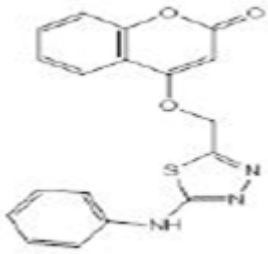

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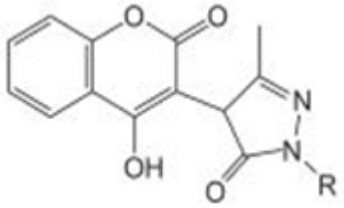

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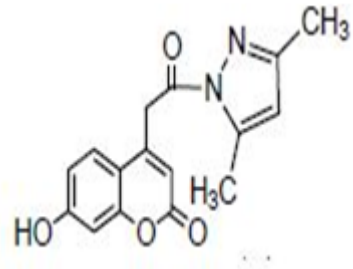

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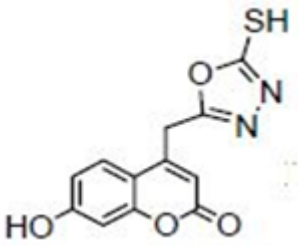

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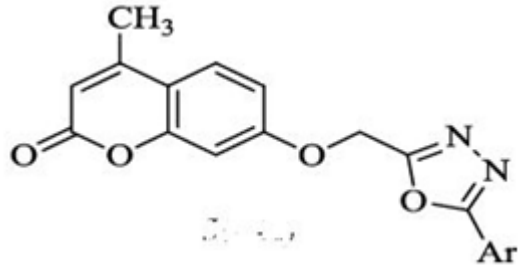

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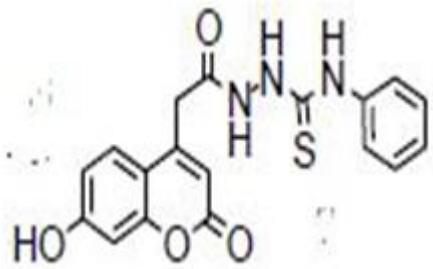

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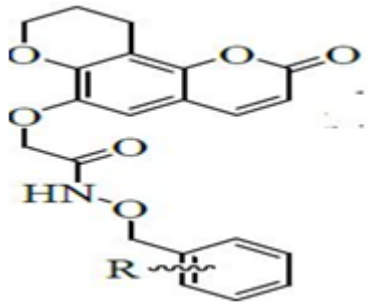

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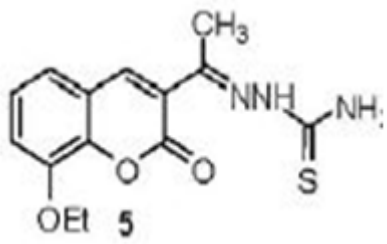

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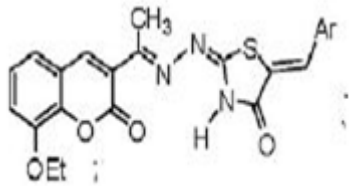

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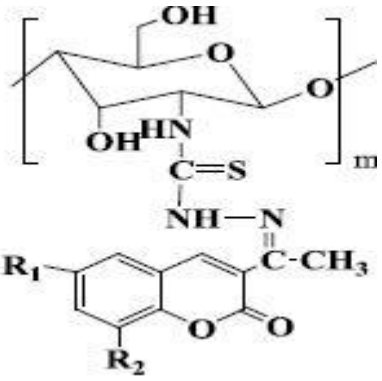

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IV. LITRATURE REVIEW

- **Design, synthesis and validation of anti-microbial coumarin derivatives: Anefficient green approach.**

Mohd.Shahnawaz Khan a,**, Ranu Agrawal b, MohdUbaidullah c, Md. Imtaiyaz Hassan d,

NaziaTarannumb,* (journal homepage: www.heliyon.com). An ecofriendly itinerary for the synthesis of newly substituted chromene-3-carboxamide derivatives was undertaken to avoid impurities, usage of toxic solvents, toxic catalyst, and having improved quantitative yields. The green synthesis involves the condensation of substituted salicyl aldehyde with N-(substituted)phenyl malonic acid in the presence of a base catalyst, piperidine. All reported compounds were assessed for their antimicrobial activities which clearly suggested their therapeutic implications to address antimicrobial pathogenesis. The synthesized coumarin compounds were examined for their antimicrobial activity against 7 fungal strains and 2 bacterial strains at concentration 125–1000 μg/mL. In particular, the compounds 4 and 5 showed lower minimuminhibitory concentration value (125 μg/mL) against maximum microbial strains. Further, docking of all the synthesized compounds was performed with the enzymes lanosterol 14α-demethylase and glucosamine-6-phosphate synthase and a significant binding affinity was observed which supports in vivo antimicrobial study. In addition, the thermal analysis revealed good thermal stability of compounds up to 250 _C. The compounds showed abroad absorption spectrum between 280-550 nm establishing them to be good UV absorbers.

- **Novel Coumarin Derivatives: Synthesis, Characterization and Antimicrobial Activity**

Chirag G. Naika, Gulam M. Malika and Hitesh M.Parekhb,*(<http://journals.sabinet.co.za/content/journal/chem/.). The novel coumarin derivatives (2, 3, 4, 5, 6, 7) have

been synthesized from the reaction of o-acetyloxy benzoic acid with thionyl chloride yielding 2-acetoxy benzoyl chloride, which on further treatment with ethylacetoacetate gave 4-hydroxycoumarin. Substituted pyrazolones and thiazoles reacted with 4-hydroxy coumarin to give pyrazolones and methyl thiazoles related coumarin derivatives. The newly synthesized products were characterized with IR, 1H and 13C NMR, mass spectroscopic techniques and elemental analysis. The synthesized compounds were screened for their antibacterial and antifungal activity. All the compounds were found to have significant activity against the tested microorganisms.

- **Synthesis of biscoumarin derivatives as antimicrobial agents**

SAMIJA MURATOVIĆ1, KEMAL DURIĆ2, ELMA VELJOVIĆ1, AMAR OSMANOVIĆ1*, DŽENITA SOFTIĆ3, DAVORKA ZAVRŠNIK1. As a further part of our chemical and biological studies in this field, we describe the preparations of the properly substituted benzylidene-bis-(4-hydroxycoumarin) derivatives 5a-h and 3-(6-oxo-(1H)-benzopyrano [4, 3-b] benzopyran-7-yl)-4-hydroxycoumarin derivatives 6a-e. Methods: The synthesized compounds were screened for their in vitro antimicrobial activity against five strains of bacteria and two fungal strains using disk diffusion assay and dilution method. The way in which the substituent group's physicochemical properties influence the antimicrobial activity is discussed in the paper. Results: The in vitro evaluation of their inhibitory properties towards five strains of Gram-positive and Gram-negative bacteria and two fungal strains indicated that the 4trifluoromethylbenzylidene derivative of bis-(4-hydroxycoumarin) (compound 5c) and 3-(6-oxo-(1H)-18-bromobenzopyrano[4,3-b]benzopyran-7-yl)-4-hydroxycoumarin derivative (compound 6b) possess the most potent antibacterial activities, with MIC of 3.9 μg/mL - 7.8 μg/mL against Gram-positive bacteria. Conclusion: The compound 6b has greater antibacterial activity than the standard chloramfenicol (inhibition zone 26 mm and MIC 1.9 μg/mL) against Staphyloccocusaureus and could be considered as leading compound in the future antimicrobial drug development.

- **Molecular Insights into Coumarin Analogues as Antimicrobial Agents: Recent Developments in Drug Discovery**

Rameshwar S. Cheke 1,* ,Harun M. Patel 2, Vaishali M. Patil 3,*, Iqrar Ahmad Ansari 2 , Jaya P. Ambhore 1, (https://www.mdpi.com/journal/antibiotics)

A major global health risk has been witnessed with the development of drug-resistant bacteria and multidrug-resistant pathogens linked to significant mortality. Coumarins are heterocyclic compounds belonging to the benzophenone class enriched in different plants. Coumarins and their derivatives have a wide range of biological activity, including antibacterial, anticoagulant, antioxidant, anti-inflammatory, antiviral, antitumour, and enzyme inhibitory effects. In the past few years, attempts have been reported towards the optimization, synthesis, and evaluation of novel coumarin analogues as antimicrobial agents. Several coumarin-based antibiotic hybrids have been developed, and the majority of them were reported to exhibit potential antibacterial effects. In the present work, studies reported from 2016 to 2020 about antimicrobial coumarin analogues are the focus. The diverse biological spectrum of coumarins can be attributed to their free radical scavenging abilities. In addition to various synthetic strategies developed, some of the structural features include a heterocyclic ring with electron-withdrawing/donating groups conjugated with the coumarin nucleus. The suggested structure□activity relationship (SAR) can provide insight into how coumarin hybrids can be rationally improved against multidrug-resistant bacteria. The present work demonstrates molecular insights for coumarin derivatives having antimicrobial properties from the recent past. The detailed SAR outcomes will benefit towards leading optimization during the discovery and development of novel antimicrobial therapeutics.

- **Coumarin Derivatives with Antimicrobial and Antioxidant Activities**

Gabriela Tataringa and Ana Maria Zbancioc

Coumarin derivatives are structurally interesting compounds for synthesizing antimicrobial and antioxidant agents. Starting from 4-methyl-7-hydroxycoumarin, several derivatives with these properties have been obtained through different reaction steps. Their molecular structures were established by Fourier-transform infrared spectroscopy and nuclear magnetic resonance spectroscopy. The synthesized coumarin derivatives exerted meaningful activities against Gram-positive and Gram-negative bacteria as well as strains of Candida spp. All compounds also exhibited high and moderate antioxidant activity in assays for DPPH inhibition, total reducing power, and nitric oxide (NO) inhibition when compared to ascorbic acid.

V. CONCLUSION

In summary, studies evaluating the antimicrobial activities elicited by coumarins which have currently

expanded and, though there is plenty of *in vitro* evidence to back up the antimicrobial activities of these compounds, the *in vivo* studies available notably indicate the need to interpret data with caution.It is still to be established in vivo if oral consumption of synthetic or natural chemicals truly has an antibacterial effect, and more particularly, what dosage is necessary to produce this effect for various compounds. Recent research points to the rational production of more effective, less harmful chemicals that could be used in clinical settings to treat patients with disorders. However, there are still just a few powerful pharmacological compounds being used as antimicrobicides in clinical phase, despite observable advancements in drug design and medicinal chemistry. The development of fresh, promising prototypes using coumarin has been made possible by the developments in this field.The fact that these compounds have a variety of biological functions and that their structures permit a wide range of substitutions piques interest in the prospect of developing new antimicrobial agents.

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