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SUBSTITUTED COUMARIN AS PROMISING ANTIMICROBIAL AGENTS - A REVIEW

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ABSTRACT

One of the main issues and the driving force behind developing a new class of antimicrobial drugs with potent activity compared to conventional therapy is the emergence of resistance by bacterial and fungal stains to existing antimicrobial agents. Coumarin or 2H-chromen-2-one is a well-known compound with a wide range of pharmacological properties in therapeutics. It exhibits anticoagulant, antioxidant, anticancer, antimicrobial and antiulcer properties. The importance of coumarin and its derivatives in preventing antimicrobial resistance has been highlighted by recent research that demonstrates its potent antibacterial action. In the present paper, different coumarin derivatives and the effect of substituents on their antimicrobial activity were reviewed. The study showed that carboxylic and ester substituents in the coumarin can enhance antimicrobial activity whereas phenolic groups show reduced activity. Hence, the nature and position of substituents have a significant effect on the antimicrobial activity of coumarin.

KEYWORDS: Coumarin, Coumarin derivatives, Antimicrobial activity.

1. INTRODUCTION

Nowadays, bacterial infections epitomize significant health threats globally with an increased morbidity and mortality. Antimicrobial drugs are the greatest contribution of 20th-century therapeutics. Drugs in this class differ from all others in that they are designed to inhibit or kill the infecting organism and to have no or minimal effect on the recipient. Antimicrobial resistance is the major problem faced by the chronic use of antibiotics. Annual death worldwide due to antimicrobial resistance continues to increase by around 750,000 and are expected to reach as high as 10 million by 2050. Some microbes have always been resistant to certain antimicrobial agents, while others have acquired resistance due to their use over a while. However, the development of resistance is dependent on the microorganism as well as on the drug molecule. Staphylococci, coliforms, and tubercle bacilli show rapid resistance to penicillin and Strep. Pyogenes whereas spirochetes have not developed significant resistance. Gonococci quickly developed resistance to sulfonamides and other antibiotics.[1]

All the information mentioned above highlights the need to develop novel antibacterial agents to prevent cross-resistance to marketed antibiotics.

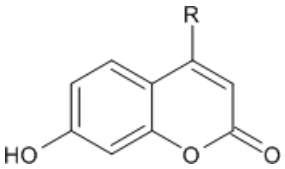
Coumarin or 2H-chromen-2-one is an organic chemical compound with the formula $C_9H_6O_2$ considered to be a privileged structure due to its wide range of biological properties including anticoagulant, antioxidant, anticancer, anti- neurodegenerative, antimicrobial and estrogenic dermal photosensitivity.

Various coumarin derivatives were synthesized and proved to be an effective antimicrobial agent. The different substituents on the coumarin ring possess a significant effect on its antimicrobial activity.[2] So in the present review, we aim to attain a detailed highlight on the antimicrobial activity of substituted coumarins.

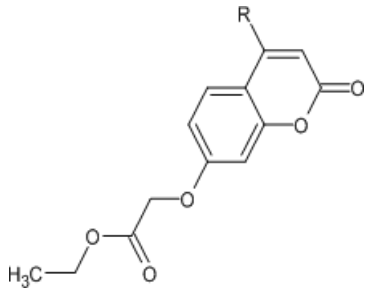
2. Antimicrobial activity

Gabriel Tatarinya et al, synthesized various coumarin derivatives starting from 4-methyl-7-hydroxy coumarin prepared by Pechmann synthesis and evaluated them for their antimicrobial and antioxidant activity. Different compounds of coumarin esters (11a–11b) and coumarin thiazole derivatives (Va–Vb) were synthesized by several reactions. All the synthesized compounds were tested for their antibacterial and antifungal activity. Antimicrobial activity was evaluated by the agar disc diffusion method (CLSI, 2014) using Gram-positive bacteria (*Staphylococcus aureus, Sarcina lutea, Bacillus cereus*), Gram-negative bacteria (*Escherichia coli, Pseudomonas aeruginosa*), and pathogenic yeasts (*Candida albicans, Candida glabrata, Candida parapsilosis*). All the synthesized compounds were found to be more active against Gram-positive bacteria than those exhibited against Gram-negative bacteria. The compounds 1b, 11b, 111b, and 1Vb showed more

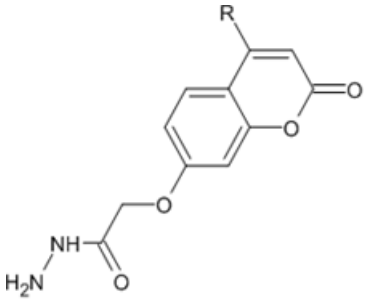
activity against *S. aureus*. It takes into account that the replacement of the methyl group in the fourth position with the propyl group was correlated to increased activity against *S. aureus*. The results also show that the umbelliferone derivatives 11a, 1a, and 1Va bearing a methyl group attached to C4 showed moderate action against *B.cereus*. The compound Vb, which contains a thiadiazole ring, was found active against *Escherichia coli*.



4-R-7-hydroxy-coumarin (1a-1b)



2-ethyl-((4-R-2-oxo-2H-chromen-7-yl) oxy) acetate (11a-11b)



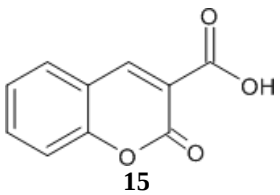
4-R-2-oxo-2H-benzopyran-7-oxyacetic acid hydrazide (111a-111b)

No R
1a CH_4
11a CH_4
1b C_3H_8
11b C_3H_8
111b C_3H_8

Figure 1: Compounds showing significant antimicrobial activity.

The presence of a methyl group in the fourth position of the coumarin ring is correlated with increased activity against Pseudomonas ATCC 27853, while the 4-propyl coumarin derivatives were found to be inactive, and the introduction of a sulphur atom appeared to be correlated with good anti-candida activity.[3]

Mesami Kawase et al., synthesized different coumarin derivatives and tested their activity against several microorganisms, including Helicobacter pylori.All the compounds synthesized were tested on Gram-negative bacteria *Escherichia coli*, *Shigella sonnei*, *Shigella dysenteriae*, *Salmonella typhi*, *Salmonella typhimurium*, *Vibrio cholerae*, and Gram-positive bacteria *S. aureus*, *Bacillus licheniformis* and *H. pylori*. The microdilution broth method was used to determine the MIC. Among the synthesized coumarin derivatives, 3 compounds (15, 16, and 17) bearing carboxylic acid or ester groups could exhibit potent antibacterial activities. While derivatives of 1, 2, 11, and 14 bearing a phenolic hydroxyl group were found to be less active.



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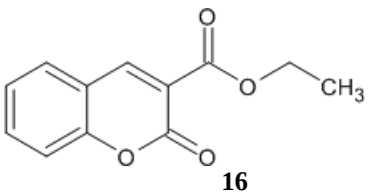

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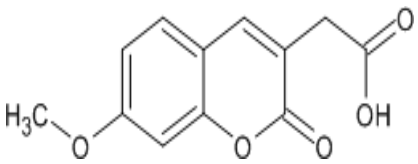
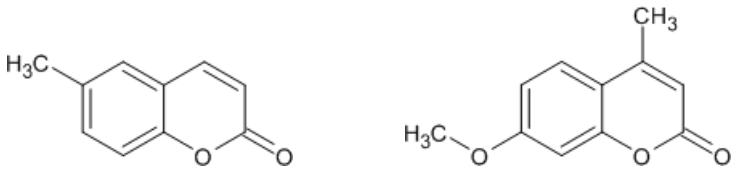


17

Figure 2: Synthesized compounds 15-17 with significant antimicrobial activity.

Compounds 16 and 17 show good anti H. pylori activity. It reveals that one active site of compounds might be carboxylic acid function, and it also shows that compound 15 with carboxylic acid was not active against H. pylori, which remains an exception.[4]

Fauzia Anjum Chattha et al., synthesised different coumarin-3-acetic acid derivatives, and all the synthesised compounds were screened for their antimicrobial activity using the agar dilution method. The study investigated against two Gram-negative bacteria *Shigella sonnei, Escherichia coli* and two Gram-positive bacteria, *Bacillus subtilis, Staphylococcus aureus,* along with the standard drugs ciprofloxacin and moxifloxacin. The MIC values show that all the synthesised compounds exhibit good activity against *Bacillus subtilis*. The compounds 6-methyl coumarin (5) and 7-methoxy-4-methylcoumarin (8), with MIC values (µ*g*/*ml*) 10. 53 and 11.7, respectively, showed better activity than the standard drug ciprofloxacin. It is seen that fewer polar groups on coumarin exhibit good antimicrobial activity as compared the coumarin groups with polar substituents.[5]



6-methyl-2*H*-1-benzopyran-2-one7-methoxy-4-methyl-2H-1-benzopyran

Figure 3: Compound showing significant antimicrobial activity.

L Ravithej Singh et al., synthesised a new series of novel coumarin benzimidazole derivatives and tested them for their broad-spectrum antimicrobial activity against ESKAPE pathogens as well as cytotoxicity against eukaryotic cells. ((E)-3-(2-(1H-benzo[d]imidazol-1-yl)-1-((4-chlorobenzyl)oxy)imino)ethyl)-2H-chromen-2-one (compound 12) showed remarkable broad-spectrum antimicrobial activity against the target strains of microorganisms *Pseudomonas aeruginosa, Staphylococcus aureus,* and *Bacillus subtilis* with MIC values (g/ml) of 3.12, 1.56, and 3.12, 0.95, respectively, compared to the reference drug ampicillin (MIC = 25 µg/ml).

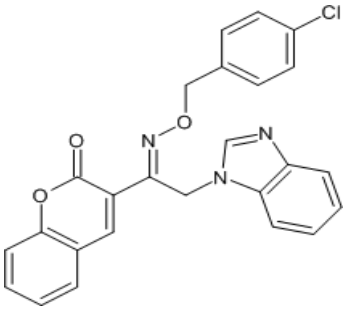


Figure 4: Compound 12.

The test results take into account that the compound with a halogen atom shows better antimicrobial activity than others, and its position and number of halogen atoms in the molecular structure have a significant effect as they enhance thetarget binding ability of the compound. Also found that coumarin-benzimidazole conjugates with chlorine atom at the para position show higher broad-spectrum activity than chlorine at both the ortho and para positions.[6]

Sonia Yadav et al., synthesised a new series of 4-aniline coumarins through the Schiff base reaction and screened them for antimicrobial activity. The study was conducted through a zone inhibition assay or well diffusion assay against *Staphylococcus aureus, Escherichia coli* and *Pseudomonas aeruginosa*. The test results showed that among the synthesized compounds (4a-4j) the compounds 4a (R^1:H, R^2:H, R^3:H), 4d (R^1:NH_2, R^2:H, R^3:H), and 4h (R^1:OCH_3, R^2:OCH_3, R^3:OCH_3) showed good activity against the targeted strains of microorganisms.

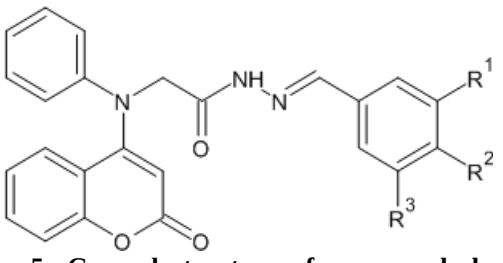
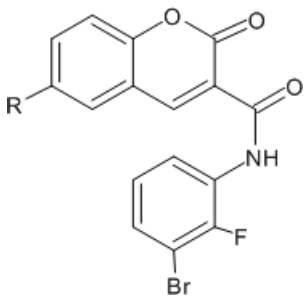


Figure 5: General structure of compound showing significant antimicrobial activity.

Mohd. Shahnawaz Khan et al., synthesised a new series of substituted chromene-3-carboxamide derivatives through a green approach, and all the synthesised

compounds were screened for antimicrobial activity. The study investigated against *Escherichia coli* and *Bacillus cereus* using the agar-well diffusion method. The test results show that compounds 3-6 (R:NO_2, Br, Cl, NO) and 10 have broad-spectrum antibacterial activity because of the presence of bromo, chloro, or nitro group substituents at the 6th and 8th carbon positions of the chrome ring. And compound 5 with dichloro substitution exhibits remarkable growth inhibition against targeted strains of microorganisms with MIC values (µg/ml*) Bacillus cereus*- 250 and *Escherichia coli* -250.[8]



Compound 3-6 Compound 10

Figure 6: Derivatives and Substituents.

Samija Muratovic et al., synthesised a new series of benzylidene-bis-(4-hydroxy coumarin) derivatives and fused benzopyran coumarin derivatives and screened them for their antimicrobial and antifungal activity using the disc diffusion assay and dilution method. The MIC values of all the synthesised compounds were determined. The test results indicate that the compounds 5c and 6b exhibit significant antibacterial activity with MIC (µg/ml) of 7.8, 3.9 against *Bacillus subtilis* and *Staphylococcus aureus* respectively.

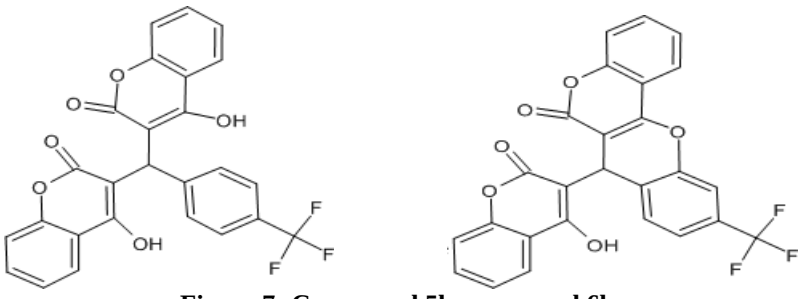
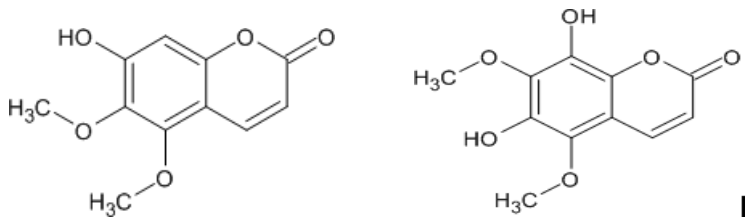


Figure 7: Compound 5b compound 6b.

It was concluded that compound 5c having a strong electron withdrawing effect of the trifluoromethyl group at the C4 position of the phenyl ring contributes to its antimicrobial property, where it enhances the lipophilicity and thus increases the rate of cell permeability of the compound, and bromine at the C5 (6b) position of the phenyl ring was found to increase activity against *S. aureus*.[9]

Oliver Kayser et al., evaluated a series of simple coumarins against several Gram-positive and Gram-negative microorganisms. The compounds 6-hydroxy-7-methoxycoumarin and 7-hydroxy-5,7-dimethoxycoumarin were isolated from Pelargonium sidoides DC (Geraniaceae) and investigated against *Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis, Pseudomonas aeruginosa, Haemophilus influenzae*, and Gram-positive bacteria *Staphylococcus aureus.* The minimum inhibitory concentration values of the samples were determined by a standard two-fold microdilution broth technique using penicillin as a reference agent. The test results indicate that among the active compounds, 7-hydroxy-5, 6-dimethoxy coumarin and 6-8-dihydroxy-5, 7-dimethoxy coumarin showed potent activity with MICs of 0.9-2.1µm. It indicates that the antibacterial activity of coumarin may be correlated to the number of oxygen substituents.[10]



7-hydroxy-5, 6-dimethoxycoumarin 6-8-dihydroxy-5, 7-dimethoxycoumarin

Figure 8: Compounds showing significant antimicrobial activity.

V. V. Mulwad et al., synthesised 4-hydroxycoumarin derivatives with various heterocycles at its 3-position. All the synthesised compounds were screened in vitro for their antimicrobial activity against *S. aureus, S. Typhi* and *E. coli.* The MIC was determined using the tube dilution technique concerning ciprofloxacin, cloxacillin and gentamicin. Test results indicate that all the synthesised compounds showed better antimicrobial activity towards the targeted strains of microorganisms.[11]

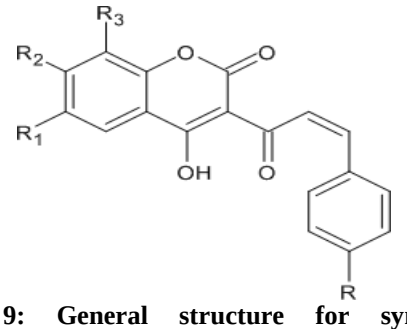


Figure 9: General structure for synthesized derivatives.

Aziz Behrami et al., synthesised different derivatives of coumarin starting from 4, 7-dihydroxy-chromen-2-one and investigated them for antimicrobial activity. The purified synthesised compounds 1a–4a were screened for activity against *Staphylococcus aureus, E. coli* and *B. cereus* with the reference drugs cephalexin and streptomycin. The study indicates that all the synthesised compounds show significant antimicrobial activity.[12]

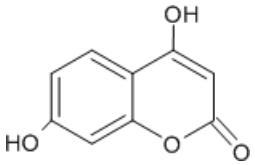


Figure 10: 4, 7-dihydroxy-2*H*-1-benzopyran-2-one (1a).

D. U. C. Rahayn et al., performed microwave-assisted synthesis of 4-methyl coumarins and investigated their antioxidant and antibacterial activities. Thepurified synthesised compounds were tested for antibacterial activity by disc diffusion assay method against *E .coli* and showed moderate activity with an IC50 value of 99.69 ppm and an inhibition zone of 9mm at 125 ppm, respectively.[13]

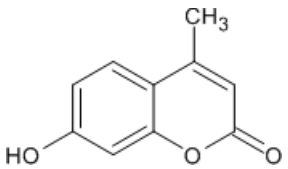


Figure 11: 7-hydroxy-4-methyl-2H-1-benzopyran-2-one.

Kumar S. et al., synthesised substituted 2-(4-methyl-2-oxo-2H-chromen-7-yl) oxy) acetamide derivatives and evaluated their antibacterial and antifungal activity. Antibacterial activity was investigated using two strains, *Staphylococcus aureus* and *Shigella flexneri*, by cup-plate agar diffusion method. The compounds 7a, 7c, 7d, and 7e showed significant activity against targeted microorganisms. It takes into account that compounds having secondary amines with bulkier alkyl substitutions have good activity. Antifungal activity tested for *Candida albicans* showed less activity.[14]

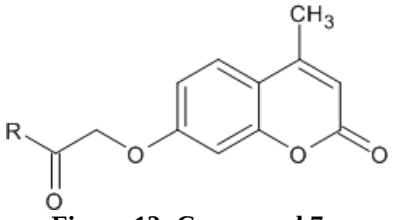


Figure 12: Compound 7a.

Hany M. Mohamed et al., synthesised various 8-ethoxy coumarins and tested them for antimicrobial activity in-vitro against two Gram-negative bacteria, *Bordetella bronchiseptica* and *E .coli* and four gram-positive *Bacillus pumilus, Bacillus substilis, Staphylococcus aureus, S. epidermis* using disc diffusion method. The results reveal that replacing the hydrogen atom on the coumarin nucleus at C3 with a side chain results in significant antimicrobial activity against targeted microorganisms.[15]

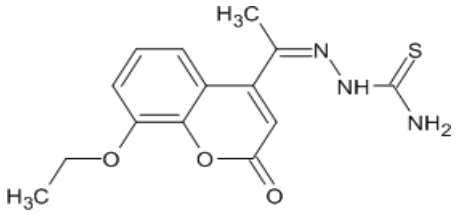


Figure 13: Compound showing significant activity.

Bernadette S. S. Creven et al., synthesized a series of substituted coumarin-3-carboxylate silver (1) complexes and investigated their in vitro antibacterial activity against various Gram-positive bacteria *S. aureus, S. simulans, M. luteus* and gram-negative strains *E. coli, B. olenius.* The results reveal that the hydroxylated derivative (compound 27) showed good activity. It takes into account that hydroxylation of the aromatic ring of the coumarin ligand contributes to antimicrobial activity.[16]

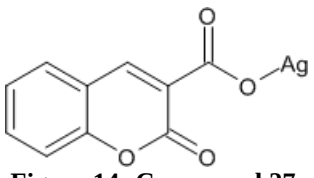


Figure 14: Compound 27.

Anil K. Patel et al., synthesised 4-aryl-2, 6-di (coumarin-3-yl) pyridines and screened them for antimicrobial activity against *E. coli, Bacillus subtilis* by agar diffusion method. The zone of inhibition was measured and

compared with the standard. All compounds 3a–i showed good activity. It reveals that the incorporation of substituent groups like CH_3/OCH_3 either in the coumarin or phenyl ring does not affect the antimicrobial activity.[17]

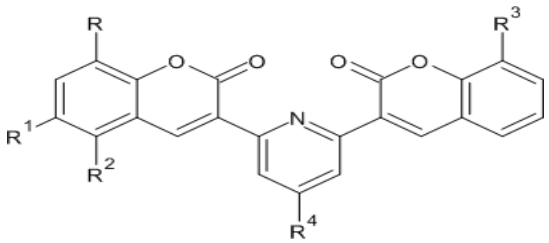


Figure 15: General structure of compound showing significant activity.

S. G. Ovri et al., synthesised some new derivatives of 4-hetero-aryl-coumarin-3-carbaldehydes and investigated their antimicrobial activity against *S. aureus, E. coli, S. aureogenossa* and *Enterobacter cloacea* by agar disc diffusion method. The results indicate that compound 4a shows higher activity against targeted microorganisms.[18]

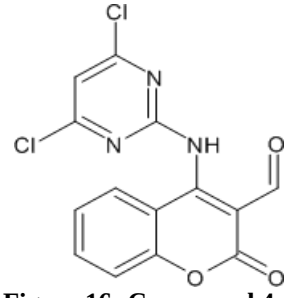


Figure 16: Compound 4a.

Vidoslav Dekic et al., synthesised various 4-arylamino-3-nitrocoumarins and investigated their antimicrobial activity. The synthesised compounds 5a-h were tested against gram-positive strains of *Staphylococcus aureus, Bacillus cereus, Bacillus substilis* and gram-negative *E. coli* using the broth microdilution method and also investigated for antifungal activity. The compound 5h showed the greatest antifungal activity. The study concludes that a significant role in the onset of the antimicrobial activity of these compounds is played by the heteroatoms in the heteroaryl ring substituent bound to the coumarin.[19]

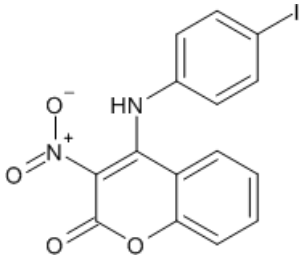


Figure 17: Compound 5h.

Mahantesha Basanagouda et al., prepared 4-aryloxmethylcoumarins and investigated their antimicrobial activity. The study was carried out using two Gram-positive bacteria *Staphylococcus aureus* and *Streptococcus faecalis* and Gram-negative bacteria *E. coli, Pseudomonas aeruginosa, Klebsiella pneumoniae* by disc diffusion method. The results conclude that the compound having methoxy, chloro, or bromo substitutions at the C6 position of coumarin showed higher activity.[20]

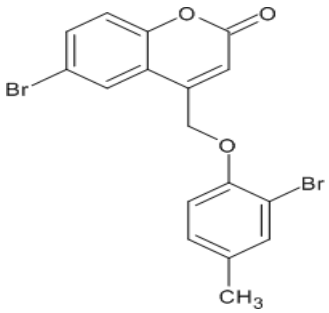


Figure 18: 6-bromo-4-[(2-bromo-4-methylphenoxy) methyl]-2H-1-benzopyran-2-one.

Sayalid kudale et al., prepared a series of Schiff bases incorporating coumarin and chalcone moieties, 3-(4-(4-(substituted phenyl) prop-1-ene-3-one) phenyl amino) methyl) 4-chloro-2h-chromen-2-one 4(a-g) and tested against*B. subtilis, S. aureus, S. epidemis*. The compound 4b showed higher activity against all the tested microorganisms with an MIC of 20 µg/ml.[21]

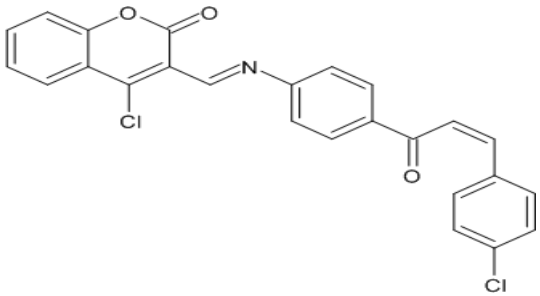


Figure 20: Compound 4b.

Milan Mladenovic et al., synthesized a series of 4-hydroxy-chromene-2-one derivatives and tested against twenty four microorganism cultures. The compound 3b showed higher activity with a MIC range of 130-500 µg/ml. It takes an account that the 4-hydroxy, 3-acetyl and thiazole functional group is important for antimicrobial activity.[22]

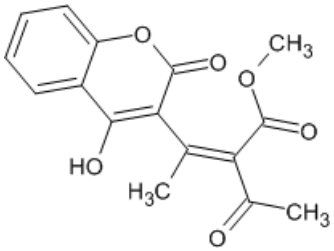


Figure 21: Compound 3b.

3. CONCLUSION

This review depicts the antimicrobial activity of various substituted coumarin derivatives. Coumarin and its derivatives show significant antimicrobial activity against various Gram-positive and Gram-negative microorganisms. The electrondonating and electron-withdrawing nature of substituents and itsposition correlates with the enhanced or diminished antimicrobial activity of coumarin as it effect the membrane permeability and target binding properties of the compounds**.**Heterocyclic substitution on the ring has shown to increase the activity which results in the development of molecules with reduced resistance.

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