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SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF NOVEL CHALCONE DERIVATIVE

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ABSTRACT

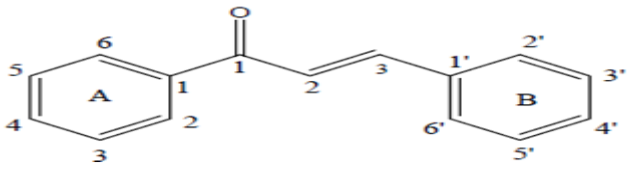
Chalcones are 1,3-diphenyl-2-propene-1-one, in which two aromatic rings are linked by a three carbon α, β- unsaturated carbonyl orgenic compound and report to possess a wide spectrum of biological activity such as antibacterial, antifungal, anticancer, antioxident e.t.c. the biological activity of chalcon derivative is due to enonepharmacophor in their structure. These are abundant in edible plants and are considered to be precursors of flavonoids and isoflavonoids. In an effort to develop antimicrobial agents, a series of chalcones were prepared by Claisen-Schmidt condensation of appropriate. Acetophenones with aromatic Aldehydes in the presence of aqueous solution of potassium hydroxide and ethanol at room temperature. Benzaldehyde and an Acetophenone in the presence of sodium hydroxide as a catalyst, chalcones can also be prepared by an aldol condensation. the structure of this compound is well supported by U.V, NMR, IR, MASS Spectral data. the compound has been evaluated for their antimicrobial activities.

KEYWORDS: antimicrobial, chalcone, synthesis.

INTRODUCTION

Chalcone

Chalcones are 1,3-diphenyl-2-propene-1-one, in which two aromatic rings are linked by a three carbon α,β-unsaturated carbonyl system.



General Structure of Chalcone.

IUPAC Name: (2E)1,3-Diphenylprop-2-en-1-one

Chemical Formula: $C_{15}H_{12}O$

Molar Mass: 208.26 g·mol^{-1}

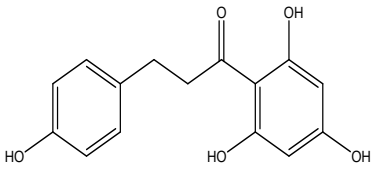
Density: 208.26 g·mol^{-1}

Melting Point: 55 to 57 °C (131 to 135 °F; 328 to 330 K)

Boiling Point: 345 to 348 °C (653 to 658 °F; 618 to 621 K)

Magnetic susceptibility: -125.7·10^{-6} cm^3/mol

Chalcone represent an important group of natural or synthetic compound with an array of biological activity. They are intermediate in biosynthesis of flavonoids. chalcone are abundant in commonly consumed fruits and vegetable such as apple pears, strawberry and tomatoes respectively. they are also present in wheat and wheat product the most common chalcone that occurce in the fruit and vegetable include **phloretin**, phloridzinchalconoringenin and arbutin.



Phloretin

Chalcone play an important role in a number of biological activity for example they show significant activity towards verity of tumors and display chemoprotectives properties. This can be attributed to their antioxidant properties. Among another important properties chalcone inhibits bacterial growth and posses antifungal and antivirus properties. Further more. They have anti inflammatory and capillarity strengthing properties. Hence chalcone may provide novel therapeutic approach in treatment of inflammatory disorder.

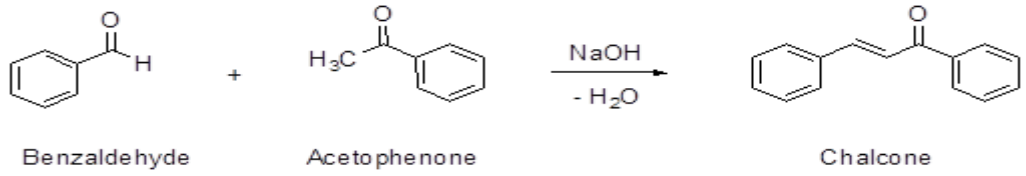
Most research in organic chemistry involves multifunctional molecules. Indeed, most organic compounds found in nature, as well as modern pharmaceutical agents, are multifunctional molecules. Determining which functional groups react in a chemical reaction is critical to the success of synthetic organic chemistry. Another goal of organic synthesis is to discover environmentally-friendly reactions, called **green chemistry**, where a minimum of waste is produced and the reactions have high atom economy.

One of the goals of green chemistry is the use of less hazardous solvents. The synthesis of Chalcones can even be done with no solvent. However, the use of water as a solvent of the aldol condensation followed by dehydration to form a conjugated ketone. Chalcones are an important class of naturally occurring compounds of interest to the pharmaceutical industry for their potential antitumor, antibacterial, antifungal, and anti-inflammatory activity.

In an effort to develop antimicrobial agents, a series of Chalcones were prepared by Claisen-Schmidt condensation of appropriate acetophenones with aromatic aldehyde in the presence of aqueous solution of potassium hydroxide and ethanol at room temperature. Benzaldehyde and an acetophenones in the presence of sodium hydroxide as a catalyst Chalcones can also be prepared by an aldol condensation.

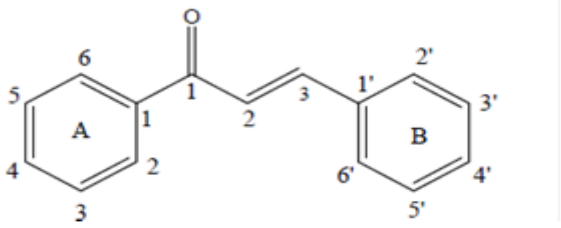
MATERIALS AND METHOD OF ANTIBACTERIAL ACTIVITY

Synthesis of Chalcone



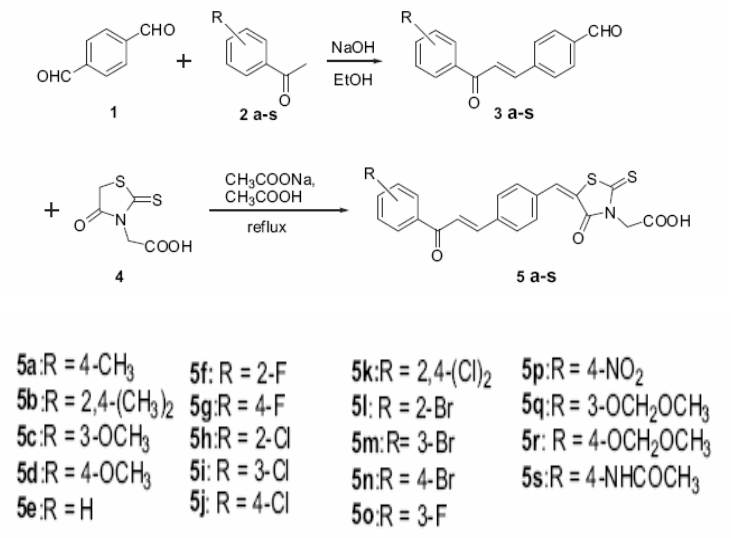
The treatment of bacterial infections remains a challenging therapeutic problem because of emerging infectious diseases and the increasing number of multidrug-resistant microbial pathogens. Despite the many antibiotics and chemotherapeutics available, the emergence of old and new antibiotic-resistant bacterial strains in the last decades constitutes a substantial need for new classes of anti-bacterial agents.[1]

Chalcones, considered to be the precursor of flavonoids and isoflavonoids, are abundant in edible plants. They consist of open-chain flavonoids in which the two aromatic rings are joined by a three carbon α, β-unsaturated carbonyl system (Scheme 1).



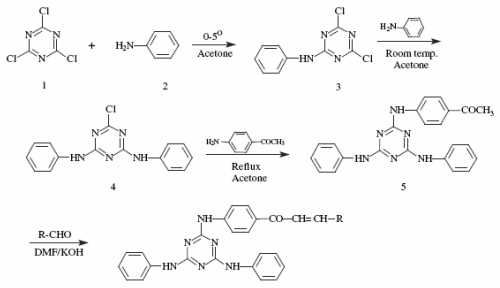
Scheme 1. General Structure Of Chalcone.

Studies revealed that compounds with a chalcone-based structure have anti-oncogenic[2], anti-inflammatory[3], anti-ulcerative[4], analgesic[5], antiviral[6], anti-fungal[7], anti-malarial[8] and anti-bacterial activities.[9] Chen et al[10] synthesized chalcone derivatives (5) containing a rhodanine-3-acetic acid (4) moiety with potential anti-bacterial activity.



Scheme 2 Chalcone derivatives (5) containing a rhodanine-3-acetic acid (4).

The s-triazine based Chalcones and their derivatives demonstrate a range of biological activities and in general have been studied extensively because of their wide range of biological activity.[11–24] They are found to be effective as local anaesthetics[11], antibacterial[12,13], antimalarial[14–16], Solankee et al[25] synthesized of some new S-triazine based Chalcones and their derivatives for evaluation of their antimicrobial activity.

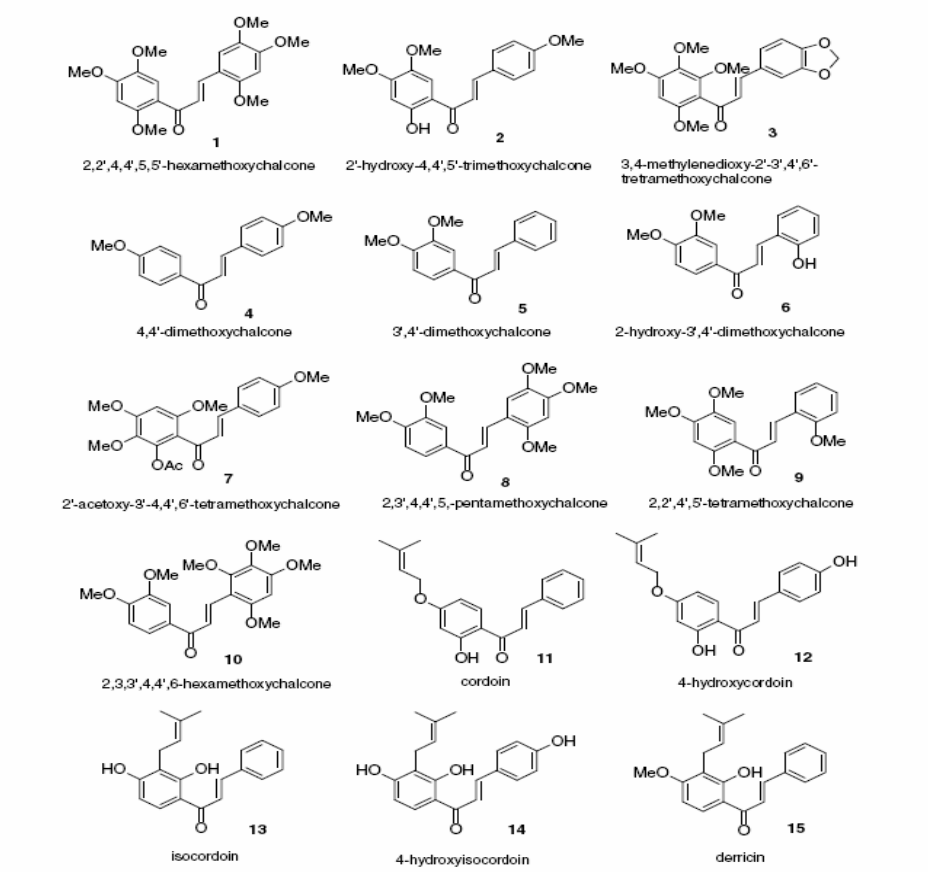


Scheme 3: Triazine based Chalcones (R = Aryl or heteroaryl).

Although Chalcones possess an widen range of biological activities, the antibacterial activity of Chalcones is being increasingly documented. Depending on the substitution of the two aromatic rings, the Chalcones can display different spectra of activity. For instance, (E)-Chalcones containing 4-alkylthio- or 4-alkoxy side chains and 4'-N-piperidine or 4'-N-

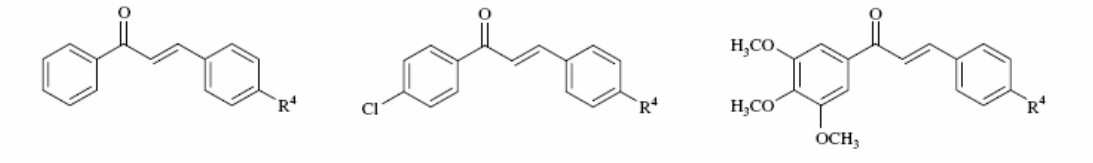
methylpiperidine groups, as Para substituents, exhibited a narrow spectrum of antibacterial activity, being affective against Gram-positive bacteria.[26] Conversely, broad-spectrum compounds, effective against Gram-positive and Gram-negative bacteria, were obtained by introduction of piperazine or 2,5-dichlorothiophene on the basic skeleton of the Chalcones[27].

Hugo et al[28] investigated the influence of the substitution pattern, involving hydroxyl, methoxyl, acetoxyl and methyledioxy groups as well as isoprenoid substituents, of both A and B rings of 31 chalcones on their antibacterial activity against human pathogenic microorganisms.



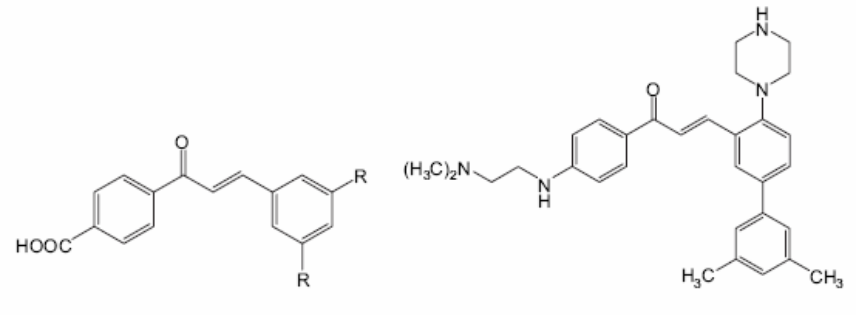
Scheme 4: Structures of tested chalcones.

Daniela et al[29] prepared some novel hydroxylated compounds and chalcone derivatives with altered linker between the two aryl rings. Antibacterial effects of all the compounds were investigated towards the most widely distributed pathogens in humans - *S. aureus* and *E. coli*. The MIC of the compounds was determined by the method of serial dilution in meat-peptone broth. Based on the results some structure activity relationships were predicted.



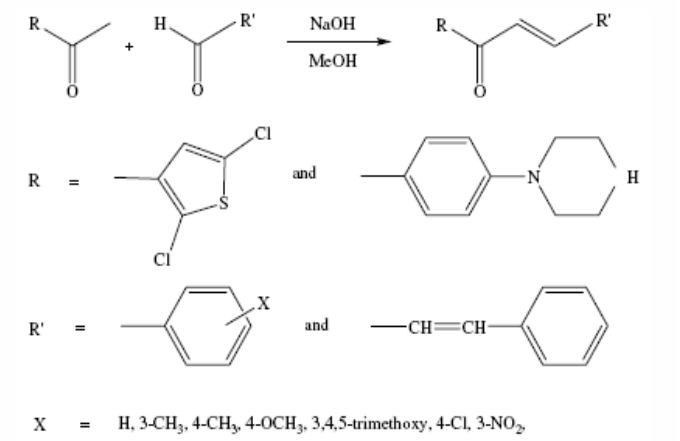
Scheme 5: Structures of designed and synthesized Chalcones (R = CH_3,OCH_3,OH etc).

Liu et al[30] synthesized a library of chalcones with basic functionalities by introducing rings like piperazine, piperidine and pyridine to evaluate antibacterial activity against drug sensitive strains of *Staphylococcus aureus* and *Escherichia coli.*



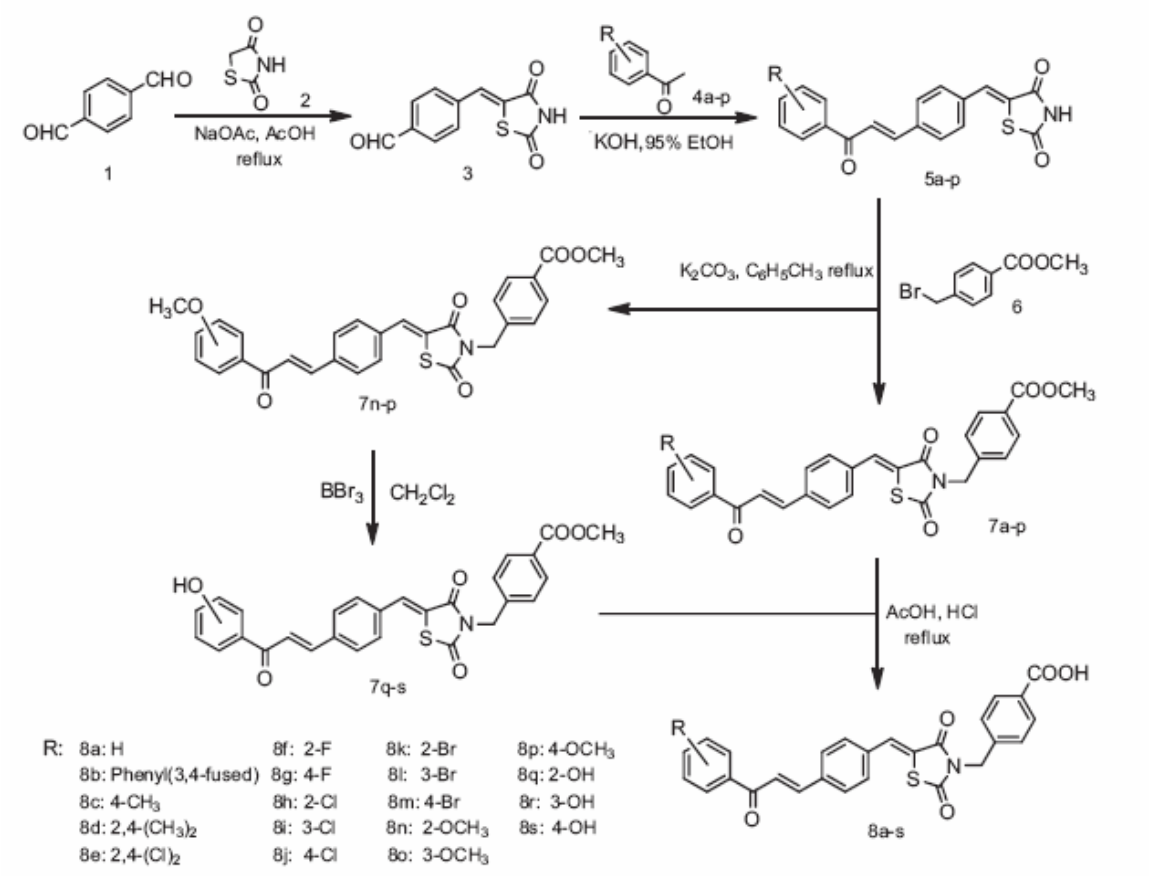
Scheme 6: Chalcones with basic functionalities.

Tomar et al[31] synthesized two new series of Chalcones by reacting 1-(4-piperazin-1-yl-phenyl)ethanone and 1-(2,5-dichloro- 3-thienyl)-1-ethanone with different substituted Benzaldehyde by Claisen–Schmidt condensation. All the synthesized compounds have been evaluated for antimicrobial activity and some of these derivatives were found to be potentially active against Gram-positive bacteria, *Staphylococcus aureus and Escherichia coli.*



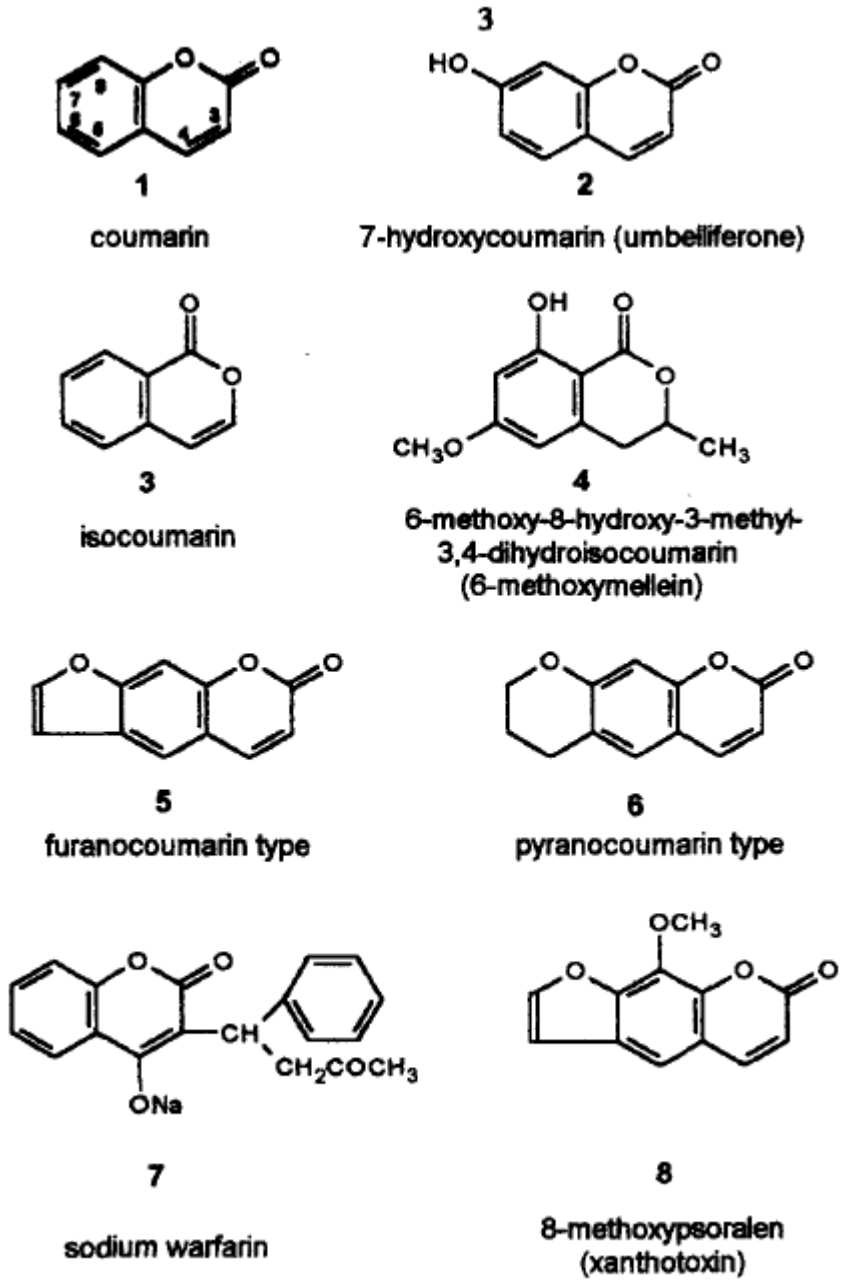
Scheme 7: Syntheses of designed Chalcones with variation in R and R'.

Liu et al[32] synthesized a series of chalcone derivatives bearing the 2,4 thiazolidinedione and benzoic acid moieties and evaluated their anti-bacterial activity. Among the tested compounds, five compounds were found to be effective against six Gram-positive bacteria (including multidrug-resistant clinical isolates). None of the compounds exhibited any activity against the Gram-negative bacteria.



Scheme 8: Chalcone derivatives bearing the 2,4 thiazolidinedione and benzoic acid moieties.

Coumarins comprise a very large class of phenolic substances found in plants and are made of fused benzene and pyrone rings (representative structures shown below). At least 1300 have been identified, principally as secondary metabolities in green plants. The prototypical compound is coumarin itself (1, 2- benzopyrone). Coumarin is a pleasant smelling compound which gives a characteristic odour. Coumarins are found in many families of plants such as Apiaceae, Asteraceae, Fabiaceae, Rosaceae, Rubiaceae, Rutaceae and Solanaceae. Coumarins vary greatly in their structural diversity and this can influence their biological activity. Several papers have been published on the various biological and pharmacological properties of coumarin derivatives.



Scheme 9. Some naturally occurring coumarins.

Smyth et al[33] studied the antimicrobial activities of 43 naturally occurring and synthetic coumarins. The coumarins exhibiting good bioactivity (i.e. a low minimum inhibitory concentration) against two *S. aureus* strains were then assessed for their antimicrobial activities against a range of eight clinically, isolaled MRSA strains.

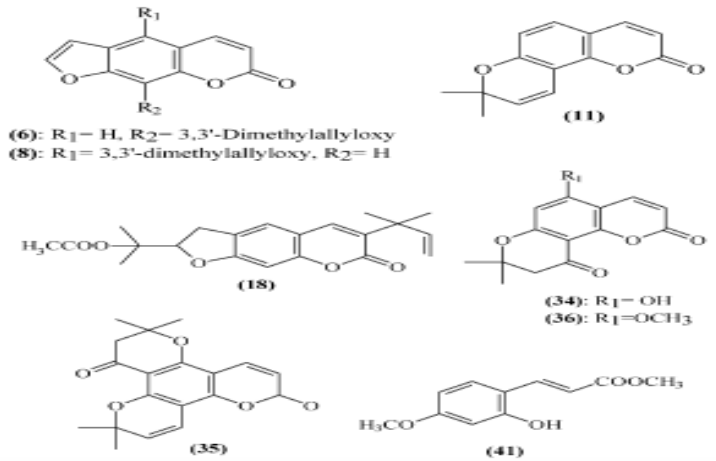
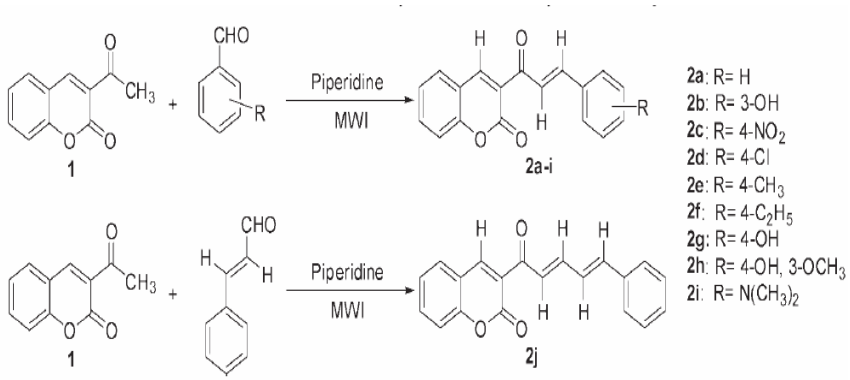


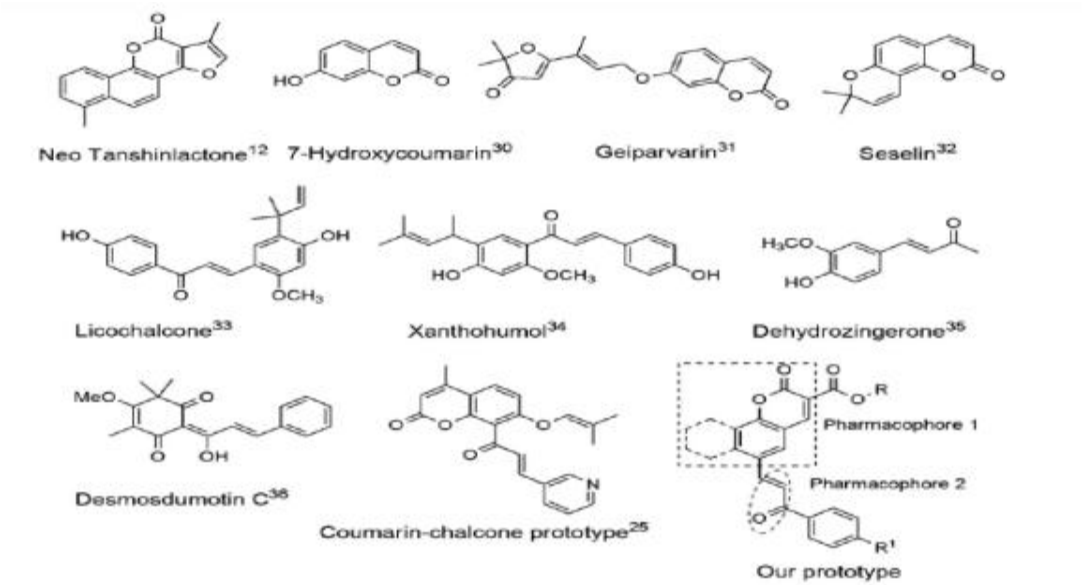
Fig. 1. Structures of the coumarin derivatives.

Scheme 10: Structures of coumarin derivatives.

Considering the reported findings of various biological activities of coumarins such as anticoagulant[34,35], antitubercular[36], antileucemic[37], antimicrobial[38,39], anti-inflammatory[40,41], anti-HIV[42], analgesic[43,44], anticancer[45], antitumor[46], anticonvulsant[47,48], antiplatelet[49], antifungal[50,51] antiviral[52,53], antibacterial[54-57] and antimalarial[58] activities,. Ajania and. Nwinyi[59] exploited potential utilization of microwaves as an energy source for heterocyclic synthesis and condensed 3-acetylcoumarin with aromatic and hetroaromatic aldehyde to afford the corresponding aromatic Chalcones (2a–j) and hetroaromatic Chalcones (3a–e and 4a–e), respectively, in good to excellent yield within 1–3 min.



Scheme 11: Design and syntheses of coumarinyl chalcones Very recently, Sashidhara et al (60)designed and synthesized a series of novel compounds that have both coumarin and Chalcones entities in one molecule and have evaluated them for their anti-tumour activity.



Scheme 12: Design of Coumarin chalcone prototype for anticancer activity.

RESULT AND DISCUSSION

All the synthesized compounds were evaluated for their in-vitro antibacterial activity against three representative Gram-positive organisms viz. Bacillus subtilis ATCC 8590, streptococcus faecalis ATCC 1157, Staphylococcus aureus ATCC 18590 and three representative Gram-negative organisms viz. Escherichia coli ATCC 10586, Proteus mirabilis ATCC 12453, Pseudomonas aeruginosa ATCC 10662 along with ciprofloxacin as standard and DMSO as solvent control.

The *in vitro* antibacterial assay was carried out by the determination of the minimum inhibitory concentration (MIC) by agar dilution technique recommended by European Committee for antimicrobial susceptibility testing (EUCAST, E. Dif 3.1)[4] and the zone of inhibitionby disk diffusion method (Kirby-Bauer method) recommended byClinical and Laboratory Standards Institute, document M2-A9 [ISBN 1-56238-586-0].[5]

Physico-chemical Characterization of the Compounds

The MIC value of the all synthesized compounds against tested organisms displayed significant activity with degree of variation. It was found that the compounds X, C and D showed generous activity against both Gram-positive and Gram-negative organisms. The A and C have more potent activity because MIC values are less than the other synthesized compounds and closer to the standard.

It was found that the derivatives showed significant antibacterial activity spectrum in comparison to ciprofloxacin. All the synthesized compounds showed the anti-bacterial activity. The compounds B is active against only Gram-negative organisms, but compound X and B showed the activity against *E. coli* and *P. aeruginosa*. The compounds X and D showed broad spectrum of activity against both Gram-positive and Gram-negative organisms. The compounds A, active against only Gram-positive organisms. The compound X active against both *B. subtilis* and s.facealus and compound and the compound X is active against *B. subtilis, s.faecalis and E.coli respectively*. The compound Aactive against only *S.faecalis The* compound D active against both Gram-positive and Gram-negative organisms *viz. S.faecalis and E.coli*. and compound X also active against both Gram-positive and Gram-negative organisms *viz. B.subtilis, S.faecalis* and *E.coli*.

The *B. subtilis* organism sensitive to the compounds D and out of these compounds, The *S.facealus* was susceptible to the compounds X, A and D but the compound A is comparatively more active against *S.faecalis.* The *S. aureus* was susceptible to the compounds C. The *E. coli* organism was susceptible to the compounds X and D but the compound D showed significantly potent activity against *E. coli.* The *P. aeruginosa* sensitive to the compounds B, The *P.aeruginosa*sensitive to the compounds C.Among the above six organisms, S.*faecalis* and E.coli are more susceptible than *S. aureus, B. substalis* and *P. aeruginosa* to the synthesized compounds. The compounds A and D showed the equipotent activity against both Gram-positive than Gram-negative organisms. Among all the synthesized compounds, AC and D have better anti-microbial activity than others.

Antibacterial susceptibility testing result reflects that heterocyclic indole-3-carboxyaldehyde (B) showed the activity against only Gram-negative organisms'*viz. P.aeruginosa.* Heterocyclic 3-acetyl coumarine, p-chlrobenzaldehyde and pyridine-2-carboxyaldehyde showed the activity against only Gram-positive organisms *viz. B. subtilis, s.aeurious* and *S. faecalis*. The heterocyclic indole-3-carboxyaldehyde, 3-acetyl coumarine and pyridine-2-carboxyaldehyde active against Gram-negativeorganisms'*viz. E.coli, P.aeruginosa* and *P.mirabilis.*

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