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SYNTHESIS AND MICROBIOLOGICAL EVALUATION OF SOME NOVEL CHALCONE DERIVATIVES

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Abstract:

Chalcones are among the most extensively investigated class of organic compounds. Chalcones has been considered as magic moiety, which is a core structure in various synthetic pharmaceuticals displaying a broad-spectrum of biological activities.

They are widely used as anti-inflammatory, anticonvulsant, analgesic, antimicrobial, anti-HIV, etc

In view Of the wide spectrum activities of condensed Chalcones, it was thought worthwhile to undertake the synthesis of (1,3 diphenyl-2- propen-1-one) chalcones nucleus is linked to another biologically active moiety.3-methyl-4hydroxy acetophenone and respective aromatic aldehyde where mixed and dissolved in minimum amount of alcohol.To this aqous potassium hydroxide Solution added slowly and mixed occasionally for 24Hrs at room temperature Completion of reaction is identified by TLC using silica gel-G.

The purity of compounds synthesised was established by TLC the synthesised derivatives by were characterised by FT-IR, ^{1}HNMR and mass spectral analyses. All the derivatives synthesised were screened for their antibacterial and antifungal activities using cup plate method against gram positive bacillus subtilis and staphylococcus and gram negative is Escherichia coli and prototeus vulgaris at 100mg/ml.Benzyle penicillin was used as reference standard for comparing results.

The compound belongs to (A1 to A6) have shown promising antibacterial and fungal activity compounds A4,A5,A6 were found to be potent activity and A1,A2,A3 Shows moderate activity.

Keywords: *3-Methyl-4-hydroxy acetophenone Chalones, Antimicrobial, Antifungal.*

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INTRODUCTION:

Pharmaceutical Chemistry is a science that makes use of general laws of chemistry to study drugs, i.e. their preparation, chemical nature, composition, structure, quality control and the conditions of their storage as well as their biological activities.

Pharmaceutical Chemistry occupies the most important place among the related sciences e.g. Drug technology, Toxicological Chemistry and Pharmacognosy.

At the same time Pharmaceutical Chemistry and studies of the physical and chemical properties of drugs, the method being a specialized science, depends on their chemical (inorganic, organic, analytical, physical and colloidal chemistry) and also on medico biological (pharmacology, physiology, biological chemistry) disciplines.

Medicinal Chemistry, according to Burger, "tries to be based on the ever increasing hope that biochemical rationales for drug discovery may be found".

The first use of synthetic molecules for interference with the life process, when chloroform and ether were introduced for anaesthesia in the first half of 19th century. Phenacetin probably is the first drug to be designed as a result of knowledge of biochemical transformations.

Chemotherapeutic agents combine with receptor areas of the cells by ordinary chemical reactions, although modified to include more types of bond formations.

Ehrlich concluded that drug resistance developed, when the drug was no longer absorbed by the parasite. His ideas have supported experimental facts. Chemical modifications of drug molecules to locate the number of series having optimal effects, and will probably continue to be a factor necessary to drug discovery to establish the effect of drug molecules the new invention in physicochemical directions such as X-ray analysis, UV, IR, and NMR have immensely helped the medicinal chemist. In thebiochemical view, the knowledge of drug receptor interactions, pharmacokinetic advancements in enzymology, have helped medicinal chemist in hypothesizing the correct mechanism of action of drug molecule.

The approach to practice Medicinal Chemistry was developed from an empirical one involving organic synthesis of new compound, based largely on modification of structures of known activity.

According to Manfred Wolf, present development of Medicinal Chemistry has resistance, stating that "underlying the new age in foundation that includes explosive development of molecular biology since 1960, the advances in physical chemistry and physical organic chemistry has made possible by high speed computers and new powerful analytical methods".

In view of the above considerations we have selected a tailor made approach of drug design in search of new potent bioactive drug molecules.Heterocycles are abundant in nature and are of great significance to life because their structural subunits exist in many natural products such as vitamins, hormones, antibiotics etc[1]. Hence, they have attracted considerable attention in the design of biologically active molecules [2].

A practical method for the synthesis of such compounds is of great interest in synthetic organic chemistry.

The chemistry of chalcones generated intensive scientific studies throughout the world, especially interesting for their biological and industrial applications. Chalcones are colored compounds because of the presence of the chromophore and auxochromes. They are known as benzal acetophenones or benzylidene acetophenones. Kostanecki and Tambor gave the name Chalcone. The alternative names given to chalcones are phenyl styryl ketones, *β*-phenyl acrylphenone, - and *α* - phenyl-- *β*benzoethylene.

The chalcones are α, β-unsaturated ketones containing the reactive ketoethylenic group - CO - CH= CH -.Presence of α, β-unsaturated carbonyl system in chalcone makes it biologically active.

Some substituted chalcones and their derivatives have been reported to possess some interesting biological properties such as antifungal[3],antimicrobiall[4],antimalarial[5],antiHIV[6]antitubercular[7]Chalcones, considered as the precursor of flavonoids and isoflavonoids, are abundant in edible plants and have also been shown to display a diverse array of pharmacological activities, such as anticancer[8],anti-inflammatory[9]and Consequently, the chalcone backbone could be a versatile scaffold for drug design. A survey of the literature revealed that some natura[53,54] and synthetic chalcones[108]showed significant ALR2 inhibitory activities, and this prompted us to investigate potential ARIs derived from chalcone based compounds.

Thus, we focused on the compounds having a carboxylic acid moiety that was incorporate the

chalcone backbone and synthesized these compounds.

SYNTHETIC ASPECT:

A considerable variety of methods are available in literature for the synthesis of chalcones. The most convenient method is the one, that involves the Claisen-Schimidt[10,12]condensation of equimolar quantities of an aryl methyl ketone with aryl aldehyde in presence of alcoholic alkali.

Chalcones possess conjugated double bonds and a completely delocalized Π-electron system on both benzene rings. Molecules possessing such system have relatively low redox potentials and have a greater probability of undergoing electron transfer reactions. Chalcones are synthesized by Claisen-Schmidt condensation of aldehyde and ketone by base catalyzed or acid catalyzed followed by dehydration to yield chalcones.

THERAPEUTIC IMPORTANCE

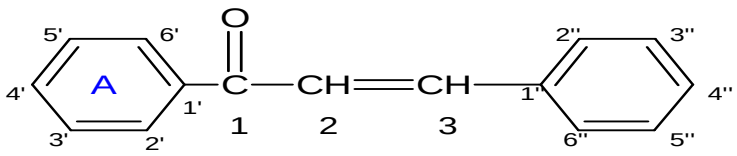
Chalcone derivatives have been found to possess wide range of therapeutic activities as shown below.

1. AntiBacterial[5,6,7]
2. Antifungal[8,9,10]
3. Antimalarial[11,12]
4. Anti HIV[13,14,15]
5. Antileishmanial[16,17,18]
6. Antitubercular[19,20]
7. Antitumor[21,22,23,24]
8. Anticancer[25]
9. Antiinflammatory[33,34,35]
10. Antioxidant[36,37,38]

Chalcone (1) is a generic term given to compounds bearing the 1, 3 diphenyl -2-propen-1-one frame work and belong to the flavonoid family.[39]
Chemically they are open chain flavonoids in which the two aromatic rings are joined by a three carbon unsaturated carbonyl system. Chalcones are abundantly present in nature starting from ferns to higher plants and a number of them are poly hydroxylated in the aryl rings.

In plants, chalcones are converted to the corresponding (2S) - flavanones in a stereospecific reaction catalyzed by the enzyme chalconeisomerase. This close structural and biogenetic relationship between chalcones and flavanones explains why they often co-occur as natural products.

General structure of chalcone:

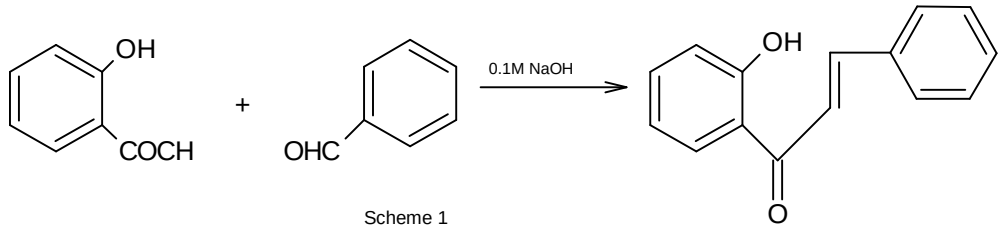


All the chalcones give pink coloration with concentrated sulphuric acidin Wilson's test[5] and when a phenolic hydroxyl group is present, they give violet coloration withalcoholic ferric chloride solution.

Chalcones on heating with traces of iodine in dimethyl sulphoxide (DMSO) for two hours give the corresponding flavones. Chalcones were converted into the corresponding flavonols by their oxidation using hydrogen peroxide in methanolic sodium hydroxide solution and these flavonols showed a characteristic greenish yellow fluorescence in ethanolic solution as well as with concentrated sulphuric acid.

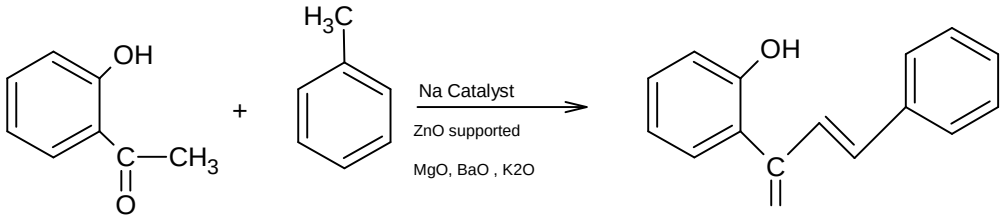
General Methods of Synthesis of Chalcones

Chalcones can be obtained by the acid or base catalyzed aldol condensation of acetophenones with aromatic aldehydes[40-42].1.2'-hydroxyacetophenone react with benzaldehyde in the presence of 0.1M NaOH to give the chalcone[26] (Scheme 1).



Scheme 1

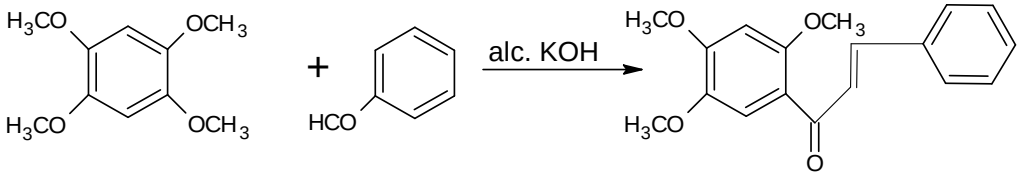
2. Liquid phase Claisen-Schmidt condensation between 2-hydroxyacetophenone and benzaldehyde was carried out over a zinc oxide supported metal oxide catalyst under solvent free conditions to form 2'-hydroxychalcone[10](Scheme 2)



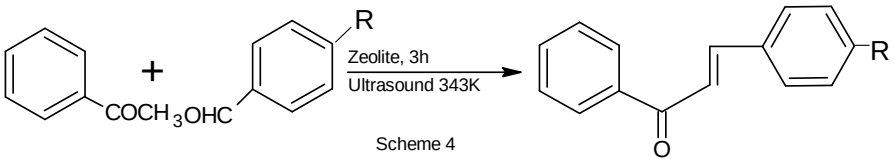
Scheme 2

3.2',4',5'-trimethoxyacetophenone, when condensed with equimolar proportions of aromatic aldehydes in the presence of 30 % alcoholic alkali at room temperature yield chalcones[38](Scheme 3).

Claisen-Schmidt condensation between benzaldehyde and acetophenone by sonochemical and thermally activated reactions over zeolite as catalyst under solvent free conditions give chalcone[39] (Scheme 4).

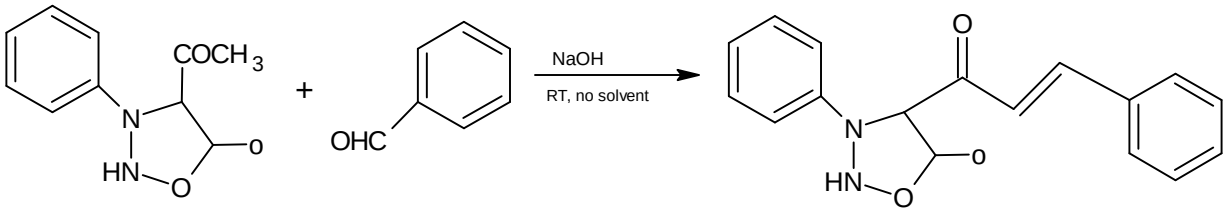


Scheme 3



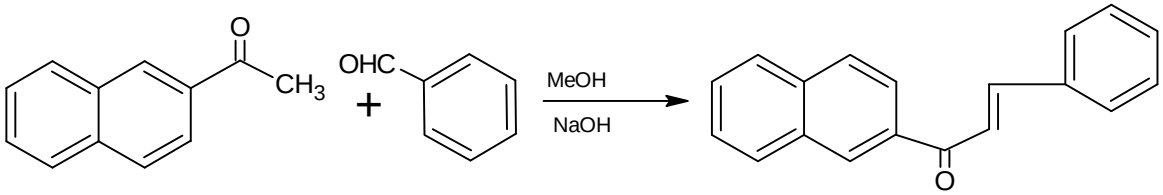
Scheme 4

5.4-acetyl-3-aryl-syndones when subjected to grinding with various aryl aldehydes in the presence of a base catalyst under solvent free conditions yield syndonechalcones[40] (Scheme 5).

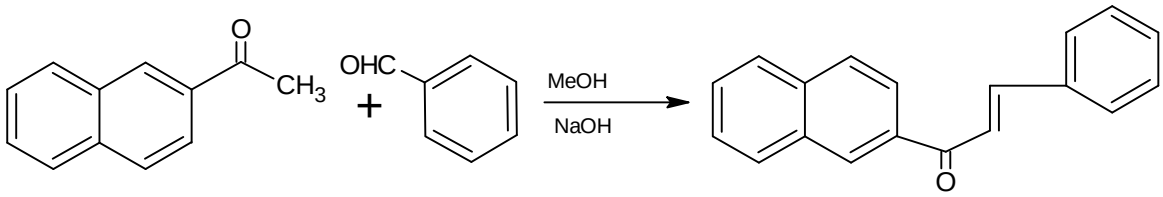


Scheme 5

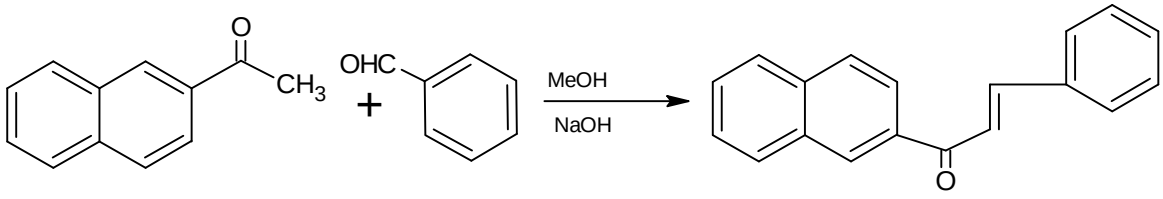
Condensation of 2-naphthylmethyl ketones with substituted aryl aldehydes in the presence of NaOH under methanol as solvent gave the corresponding chalcones[41] (Scheme 6).



Scheme 6



Scheme 6



Scheme 6

Objectives:

1. It is proved from the literature that apart from possessing several biological activities, chalcones are also useful intermediates for the synthesis of several chemical and pharmacological classes of therapeutic agents having heterocyclic structures in them. Also a number of chalcones with novel substituent were earlier isolated from a number of tephrosia species in our laboratories. These chalcones were endowed with significant biological activities. Based on these observations, it was considered worthwhile to synthesize some new substituted chalcones by claisen Schmidt condensation reaction in the present study.
2. To synthesize some new chalcones of 3'-methyl-4'-hydroxyacetophenone by reaction with various aromatic and hetero aromatic aldehydes.
3. To characterize the synthesized chalcones using IR, 1H NMR, Mass spectra and Elemental analysis data. The data related to structural characterization are given individually.
4. To screen the synthesized chalcones for their antimicrobial antifungal activities
5. To identify the active compounds for further exploitation

METHODOLOGY

The importance of Chalcones moiety has been discussed in the previous chapter. Among the many methods available for the synthesis of chalcones derivatives , in the present chapter a convenient and versatile methodology has been adopted for the synthesis of Chalcones derivatives.

In the present case all the reactions were carried out under prescribed laboratory conditions and we are monitored by TLC technique using Pre coated TLC plates.The products were purified by re crystallization. Melting points were determined by capillary method and were uncorrected.

^{1}HNMR spectra of the final compounds were recorded on Bruker Avance II 300 NMR spectrometer (300 MHZ).

All spectra were obtained in a mixture of DMSO. Further evidence about the structure was obtained by recording the mass spectrum of few typical compounds, along with their IR spectra and ^{1}HNMR.

MATERIAL AND METHODS

1. The entire chemicals used were procured from Qualingens, Himedia and Loba-chemicals.
2. Purity of starting materials used for reaction was confirmed by checking their melting point or boiling point and by thin layer chromatography
3. Melting points were determined in open capillary tube using precision melting point apparatus and uncorrected.
4. The FT-IR a spectra of the synthesized compounds has been obtained from NGSM Institute of Medical Sciences Deralakatte, Mangalore. The IR spectra were carried out by SHIMADZU PERKIN EKMER 8201 PC IR SPECTROMETER using a thin film on potassium bromide pellets.
5. The ^{1}HNMR spectra of the selected compounds has been obtained from Indian Institute of Chemical Technology Hyderabad. The PMR spectra were recorded on BRUKER AVANCE II 300 NMR SPECTROMETER in a mixture of DMSO. Chemical shift values are reported as values in ppm relative to TMS (d=0) as internal standard.
6. The Mass spectrum of the selected synthesized compounds has been performed in Indian Institute of Chemical Technology Hyderabad. The FAB mass spectra were recorded on JEOL SX-102/DA-6000 Mass Spectrometer using Argon/Xenon (6Kv, 10Ma) as the FAB gas.
7. Purity of compounds was checked on “Silica Gel G” coated on laboratory micro slides prepared by dipping method or pre coated plates, eluent was the mixture of different polar and non-polar solvents in varying proportions and detection was done either by observing in UV (ultra-violet) light or exposure to iodine vapours as required. The absence of TLC spots for starting materials and appearance of new TLC spot at different R_F value ensured the completion of reaction.

A brief description of the solvents, chemicals procured, the instruments and the conditions employed for the characterization of the synthesized compounds are presented here.

The organic solvents such as methanol, acetone,cholorofrom and ethyl acetate were of spectral grade and used as such without further purification. Anhydrous methanol was obtained by fractional distillation and storing over type 4A molecular sieves. The acetone present in methanol was removed by using the following procedure.

A mixture of 500 ml of methanol,25ml of furfural and 60 ml of 10% sodium hydroxide solution was refluxed for 12 hours, then the mixture was distilled

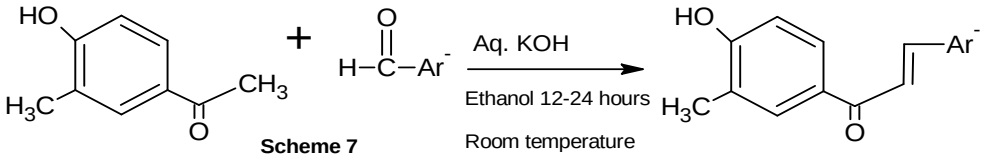
and the first few milliliters of the distillate was rejected as it contains trace amount of formaldehyde.

Ethanol obtained by distillation of commercial ethyl alcohol was refluxed over ignited calcium oxide for 6 hours and distilled at atmospheric pressure and then used for column chromatography.The column was subjected to gradient elution using n-hexane, mixtures of hexane and ethyl acetate (5%, 10%, 15 %, 25%, 50% and 75% hexane in ethyl acetate),ethyl acetate and mixtures of ethyl acetate and methanol (1%, 2%, 5% and 10% ethyl acetate in methanol). Fractions each of 100ml were collected. The separation of the compounds was checked on TLC under UV lamp and also by spraying the plates with 10% sulphuric acid.

General procedure for the synthesis of chalcones by Claisen- Schmidt condensation [42-47]:

Synthesis of the chalcones of 3'-methyl-4'-hydroxy acetophenone (A1-A6):

Equimolar quantities (0.005mol) of 3'-methyl-4'-hydroxyacetophenone and respective aldehydes were mixed and dissolved in minimum amount of alcohol. To this, aqueous potassium hydroxide solution (50%, 7.5 ml) was added slowly and mixed occasionally for 24 hours, at room temperature. Completion of the reaction was identified by TLC using silica gel-G. After completion of the reaction, the mixture was poured onto crushed ice, acidified if necessary with dilute hydrochloric acid, and the solid that separated was isolated by filtration, dried and purified by column chromatography on silica gel (100- 200 mesh, Merck), with a mixture of ethyl acetate and hexane as the mobile phase. The overall reaction involving the formation of chalcones and the mechanism of formation are shown in Schemes 7.



Scheme 7

Characterization of new chalcones

Table 1. Physical characterization data of chalcones

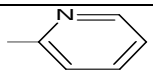
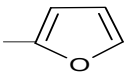
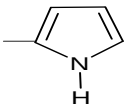
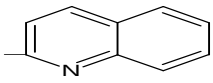
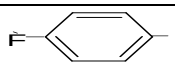
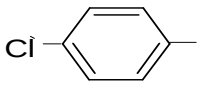
Compound	Ar	Molecular Formula	Relative Molecular Mass(RMM)	Melting Point (^{0}C)	Yield (%)
A_1		C15H13NO2	239	180-181	85
A_2		$C_{14}H_{12}O_3$	228	162-163	63
A_3		C14H13NO2	227	205-207	64
A_4		C19H15NO2	289	70-72	84
A_5		C16H13FO2	256	181-183	78
A_6		C16H13ClO2	272.5	213-214	75

Table 2. Elemental analysis data of chalcones

Compound	(% Calculated)			(% Found)		
	C	**H**	**N**	**C**	**H**	**N**
A1	75.30	5.48	4.85	75.21	5.43	4.82
A2	73.67	5.30	-	73.58	5.24	-
A3	73.99	5.77	6.16	74.01	5.74	6.20
A4	78.80	5.18	4.39	78.77	5.22	4.42
A5	75.00	5.10	-	74.20	4.70	-
A6	70.50	4.80	-	70.10	4.10	-

Antimicrobial activity:

In view of varied biological and pharmacological importance of different substituted chalcones, it is felt worthwhile to evaluate them for possible activities.

The compounds obtained in the present study were screened for antibacterial and antifungal activities since several reports were available in literature on these activities. Moreover, the results obtained on the chalcones either isolated or synthesized in our laboratory possessed significant antibacterial and antifungal activities.

The details of each of the methods are presented in the experimental section along with the results in tables followed by discussion.

Antibacterial Activity [5,6,7]

The synthesized chalcones were screened for the antibacterial activity against three Gram-positive bacteria viz., Bacillus pumilis, Bacillus subtilis and Staphylococcus aureus and two Gram-negative bacteria viz., Escherichia coli and Proteus vulgaris by using the cup plate method[95-97]. Benzyl penicillin was used as reference standard for comparing the results.

Culture medium: Nutrient broth was used for the preparation of inoculums of the bacteria and nutrient agar was used for the screening method.

Composition of Nutrient agar medium:

Ingredients	**Quantity**
Peptone	5.0 gm
Sodium chloride	5.0 gm
Beef extract	1.5 gm
Yeast extract	1.5 gm
Agar	15.0 gm
Distilled water (q.s)	1000 ml
pH	7.4± 0.2

The test organisms were sub cultured using nutrient agar medium. The tubes containing sterilized medium were inoculated with the respective bacterial strain. After incubation at 37ºC ±1ºC for 18 hours, they were stored in a refrigerator. The nutrient agar medium sterilized by autoclaving at 121ºC (15 lb/sq.inch) for 15 min. The petriplates, tubes and flasks plugged with cotton were sterilized in hot-air oven at 160 ºC, for an hour. Into each sterilized petriplate (20 cm diameter), was poured about 125 ml of molten nutrient agar medium which was already inoculated with the respective strain of bacteria (5 ml of inoculums to 250 ml of nutrient agar medium) aseptically. The plates were left at room temperature aseptically to allow the solidification. After solidification, the cups of each of 7 mm diameter were made by scooping out medium with a sterilized cork borer from a petridish and labelled accordingly.

Each test compound (5 mg) was dissolved in dimethyl sulfoxide (5 ml Analar grade) to give a concentration of 1000 g/ml. Benzyl penicillin solution was also prepared to give a concentration of 1000g/ml in sterilized distilled water.

The pH of all the test solutions and control was maintained in between 2 to 3 by using conc.HCl. All the compounds were tested at dose levels of 50 g (0.05 ml) and 100 g (0.1 ml) and DMSO used as a control. The solutions of each test compound, control and reference standard (0.05 ml and 0.1 ml) were added separately in the cups and the plates were kept undisturbed for at least 2 hours in a refrigerator to allow diffusion of the solution properly into nutrient agar medium. Petri dishes were subsequently incubated at 37±1 0C for 24 hours. After incubation, the diameter of zone of inhibition surrounding each of the cups was measured with the help of an antibiotic zone reader. All the experiments were carried out in triplicate. The results are presented in Table 3.

Table 3. Antibacterial activity of chalcones

Compound	Ar	Zone of inhibition in mm									
		Quantity in µg/ml									
		B.subtilis		B.pumilis		S.aureus		E. coli		P.vulgaris	
		50	100	50	100	50	100	50	100	50	100
A1	2''-pyridinyl	13	14	10	12	06	09	10	16	07	10
A2	2''-furyl	17	18	15	16	10	15	16	19	12	15
A3	2''-pyrrolyl	15	16	12	14	09	12	13	17	09	13
A4	2''-quinolinyl	18	19	15	17	10	16	17	20	14	16
A5	4''-fluorophenyl	22	23	18	21	16	21	20	22	19	21
A6	4''-chlorophenyl	21	22	17	19	15	18	19	21	18	20
Benzyl penicillin		28	33	31	32	27	30	25	27	28	31
Control (DMSO)		-	-	-	-	-	-	-	-	-	-

DISCUSSION OF THE RESULTS:

All the chalcones (A1-A6) have been evaluated for their antibacterial activity against B. subtilis, B. Pumilis and S. aureus (Gram-positive) and E. coli and P. vulgaris (Gram-negative) using agar cup-plate method. The results of this evaluation were compared with benzyl penicillin as reference standard. It is interesting to note from the results that almost all the compounds exhibited some degree of inhibition zones both at 50 µg and 100 µg dose levels, when compared with the standard drug.

However, the chalcones A5, A6, were found to be more potent on all the bacterial strains. Except A2, A4 all the other three possessed electron withdrawing substituent such as halogen atom, thus revealing the importance of such groups for favourable antibacterial activity. This again is in close agreement with the literature reports on the antibacterial activity of chalcones. A quantitative structure- activity study on a large database of chalcones may reveal the requisite physico-chemical properties for the antibacterial activity.

ANTIFUNGAL ACTIVITY [8,9,10]

All those compounds screened earlier for antibacterial activity were also tested for their antifungal activity. The Fungi employed for the screenings were aspergillus Niger, Rhizopus oryzae and Candida albicans. fluconazole was employed as standard to compare the results. The test organisms were sub cultured using potato dextrose agar (PDA) medium.[51-52]

The tubes containing sterilized medium were inoculated with test fungi and kept at room temperature for obtaining growth. After that, they were stored at 4 ºC in a refrigerator

Composition of Potato-Dextrose-Agar medium:

Ingredients	Quantity
Peeled potato	50.0 gm
Dextrose	5.0 gm
Agar	4.0 gm
Distilled water up to	200 ml

The test organisms were subculture using PDA medium. The tubes containing sterilized medium were inoculated with respective fungal strain and kept aside at room temperature for growing the organism. After confirming the growth, they were stored in a refrigerator.

The inoculums was prepared by aseptically transferring 10 ml of sterile water into freshly sub-cultured slants of the test fungi and making a suspension by scraping the growth with an inoculation medium. The PDA medium was sterilized by autoclaving at 121 ºC (15 lb/Inch) for 15min.

The petri plates, tubes and flasks plugged with cotton, were sterilized in about 125 ml of molten PDA medium which was already inoculated with the respective strain of fungi (5ml of inoculums to 250 ml of nutrient agar medium) aseptically. The plates were left at room temperature aseptically to allow the solidification. After solidification, the cups of each of 7 mm diameter were made by scooping out medium with a sterilized cork borer from a petridish and labelled accordingly.

Each test compound (5mg) was dissolved in dimethyl sulfoxide (5ml, Analar grade) to give a concentration of1000µg/ml. Fluconazole solution was also prepared at a concentration of 1000 µg/ml in sterilized distilled water.

The PH of the test solutions and control was maintained at 2 to 3 by using conc.HCl.

All the compounds were tested at dose levels of 50 µg (0.05 ml) and 100 µg (0.1 ml) and DMSO used as a control. The solutions of each test compound, control and reference standards (0.05 ml and 0.1ml) were added .The solutions of each test compound, control and reference standards (0.05mland0.1ml) were added separately in the cups and the plates were kept undisturbed for at least 2 hours in a refrigerator to allow diffusion of the solution properly into the PDA medium.

Petri dishes were subsequently kept at room temperature for 48 hours. After that, the diameter of zone of inhibition in mm surrounding each of the cups was measured with help of an antibiotic zone reader. All the experiments were carried out in triplicate. The results are presented in Table 4

Table 4. Antifungal activity of chalcones

Compound	Ar	Zone of inhibition in mm					
		Quantity in µg/ml					
		A. niger		C. albicans		R. oryzae	
		50	100	50	100	50	100
A1	2''-pyridinyl	14	16	11	12	11	13
A2	2''-furyl	16	17	16	18	17	18
A3	2''-pyrrolyl	15	16	13	14	14	16
A4	2''-quinolinyl	17	19	16	17	17	19
A5	4''-fluorophenyl	23	25	21	24	18	21
A6	4''-chlorophenyl	22	23	20	23	16	18
Fluconazole (standard)		25	27	23	28	23	26
Control (DMSO)		-	-	-	-	-	-

RESULTS AND DISCUSSION:

Cup-plate method was employed for antifungal activity of chalconesA1 to A6, against A. niger, C. albicans and R. oryzae and fluconazole employed as reference standard to compare the results.

From the results, it was clear that all the chalcones exhibited some degree of inhibition at both the dose levels, when compared with the reference standard. Among the compounds tested, compounds A5, A6were found to be more potent than the other compounds. It is also noticed that the antifungal activity of these compounds was more than the antibacterial activity. This again reveals the importance of the electronic effects of the substituents present on the aromatic ring in enhancing the antifungal activity.

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