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SYNTHESIS AND ANTI-MICROBIAL ACTIVITY OF 4-ACETYL MORPHOLINE CHALCONES

Gudivada Sridevi[*1], Mrs. Kattepogu Naga Kumari[2], SK. Shakeela[2], Mrs.Chowpati Ramya[3], Pedamallu Niharika[4], Mrs. Syed Meraj Sultana[5], Mrs. Jasmine Shaik[6]

[1&3]Victoria College of Pharmacy, Guntur-522002, Nallapadu. Andhra Pradesh, India.
[2]Hindu College of Pharmacy, Amaravati Road, Guntur-, Andhra Pradesh, India.
[2]Hindu College of Pharmacy, Guntur-522002, Andhra Pradesh, india.
[4]Sim's College of pharmacy, Guntur-522002, mangaldasnagar.andhra Pradesh, India.
[5&6]St. Mary's College of Pharmacy, Chebrolu, Guntur-522212, Andhra Pradesh, India.

Abstract:
The current study examined that the Chalcones are abundant in edible plants and are considered as the precursors of flavonoids and iso-flavonoids. Claisen–Schmidt condensation is a method used for preparing Chalcones, which is an important class of flavonoids. They have a wide range of biological operations and industrial applications. Due to the excessive importance of β-unsaturated carbonyl moiety and due to a broad range of natural and synthetically designed products, the development of novel synthetic methods remains interested in the research area to synthesize chalcones and their derivatives. According to the results, all the title compounds were purified by recrystallization method using methanol as a solvent. Five compounds were synthesized whose yield generally ranges from 68-95%. So, the 4-dimethyl amino benzaldehyde and salicylaldehyde derivatives were obtained in highest yields, p-hydroxy benzaldehyde, 2-chloro and p- chlorobenzaldehyde derivatives show lowest yield. The chalcone derivatives in the present study were characterized through IR, NMR spectral analysis. Bacillus subtilis was used to screen the compounds for their Anti-bacterial activity using cup-plate method. Compounds-2, 4 and 5 (p-hydroxy benzaldehyde, 2-chloro and p-chlorobenzaldehydes) showed the highest inhibition, while 4-dimethyl amino benzaldehyde showed moderate inhibition and tetracycline was selected as a standard drug.

Keywords: *Chalcones derivatives, Claisen–Schmidt condensation technique, Bacillus Subtilis, Tetracycline, Anti-bacterial activity.*

Corresponding author:
Gudivada Sridevi,
Assistant Professor,
Department of Pharmaceutical Sciences,
Victoria College of Pharmacy,
Email ID: gudivadasridevi1996@gmail.com

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INTRODUCTION:

Chalcones (1,3-Diphenyl-2-propen-1-one) are-unsaturated ketones containing the reactive keto ethylenic group CO-CH=CH. The chemistry of chalcones has generated intensive scientific studies throughout the world. A special interest has been focused on the synthesis and biodynamic activities of chalcones[1]. The name "Chalcones" was given by Kostanecki and Tambor. These compounds are also known as benzal acetophenone or benzylidene acetophenone. In chalcones, two aromatic rings are linked by an aliphatic three carbon chain. Chalcones bear very good synthon framework so that, a variety of novel heterocycles with good pharmaceutical profile can be designed. Chalcones are well known intermediates for synthesizing various heterocyclic compounds and have been reported to exhibit a variety of biological activities[2]. They have been reported to possess anti-bacterial, anti-ulcerative, anti-malarial, anti-cancer, anti-viral, anti-hyperglycemic, anti-inflammatory, and cytotoxic activity[3]. The presence of reactive chalcone is found to be responsible for their anti-microbial activity which may be altered depending on the type and position of substituent on the aromatic rings.

Chalcone is a unique template that is associated with several biological activities and they are the versatile intermediates for the development of various heterocyclic systems[4]. Chalcone nucleus is one of the most important and well-known intermediate, and is an integral feature of a variety of flavonoids and medicinal agents. The naturally occurring secondary metabolites such as flavonoids and iso-flavonoids are biosynthesized from this precursor unit[4]. They have the potential to be developed as lead compounds for the discovery of antioxidant, anti-inflammatory and anticancer agents. The formation of the nucleus is mainly constituted with the cyclization reaction of α, β unsaturated carbonyl unit of chalcone. The chemistry involved in the formation of these heterocyclic systems can be explained via hydrazone or Michael type addition.

In 2013, a new report has been shown that chalcones are able to inhibit tubulin polymerization, giving cytotoxicity and destruction of tumoral vasculature. In 2012, analyzed the detailed exploration of the pharmacological significance of chalcone scaffold[5]. They highlighted that variously substituted natural and synthetic chalcones have shown significant pharmacological potential and many of them were not toxic to normal cells[6]. In fact, many natural chalcones have shown one or more pharmacological activity. Sharmaetrecently highlighted the potential of various heterocyclic chalcone analogues as anticancer agents with a brief summary about therapeutic potential of chalcones mechanism of anticancer action of various chalcone analogues, current and prospects related to the chalcones derived anticancer research[7].

SYNTHETIC ASPECTS OF CHALCONES:

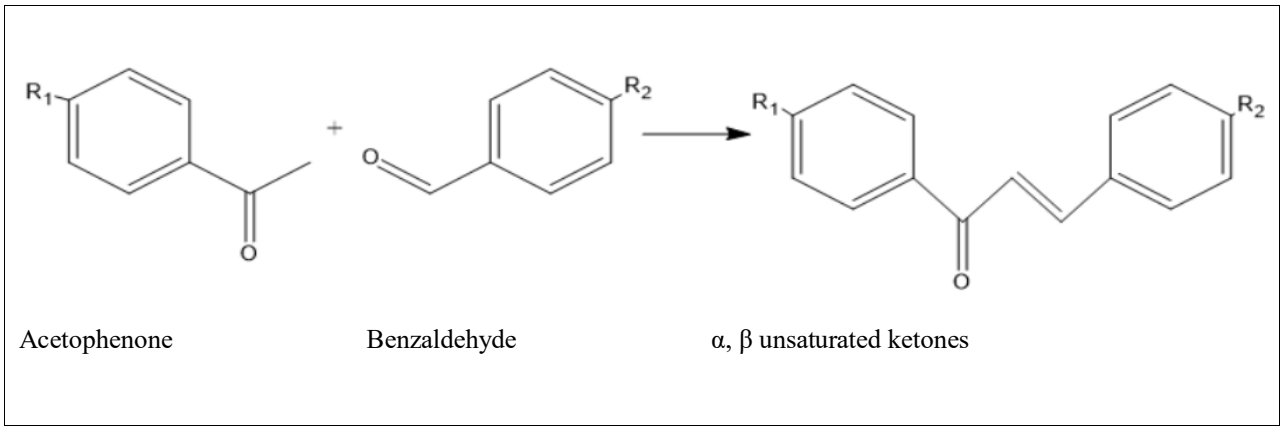
Different methods are reported in the literature for the preparation of chalcones. The chalcones are versatile reactive intermediates which are used to synthesize several heterocyclic rings systems like five-membered (e. g. pyrroles, pyrazoles, imidazole, isoxazoles, oxazole, thiazoles, etc.)[8], six-membered (e. g. pyridines, pyrimidines, triazines, etc.), seven-membered (e.g., benzodiazepines, benzoxazepines, benzothiazepines, etc.).

CONVENTIONAL METHODS:

Synthesis of E-chalcones:

Claisen-Schmidt condensation:

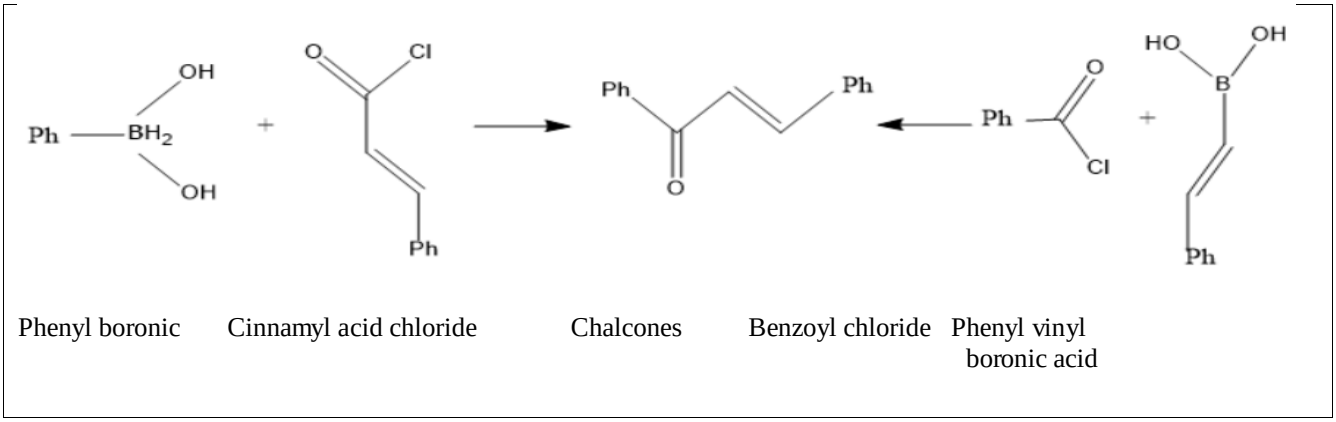
The Claisen-Schmidt condensation between acetophenone (1.01) and benzaldehyde (1.02) is a valuable C-C bond forming reaction which allows α, β-unsaturated ketones called chalcones (1.03) to be obtained[9]. Traditionally, the Claisen-Schmidt condensation is carried out at 50°Cusing 10-60% of alkali hydroxide or sodium ethoxide over a period of 12-15 hrs[9, 10].



Acetophenone Benzaldehyde α, β unsaturated ketones

Fig.no:1

Suzuki reaction:A general method for the synthesis of chalcones based on Suzuki reaction between phenyl boronic acid (1.08) and cinnamyl chloride (1.09) or between benzoyl chloride (1.11) and phenyl vinyl boronic acid (1.12) is described[11].



Phenyl boronic Cinnamyl acid chloride Chalcones Benzoyl chloride Phenyl vinyl boronic acid

Fig.no:2

Heck reaction:

Coupling of an aryl vinyl ketone (1.13) with an aryl iodide (1.14) in heck reaction condition also resulted chalcones (1.15) and other flavonoids.

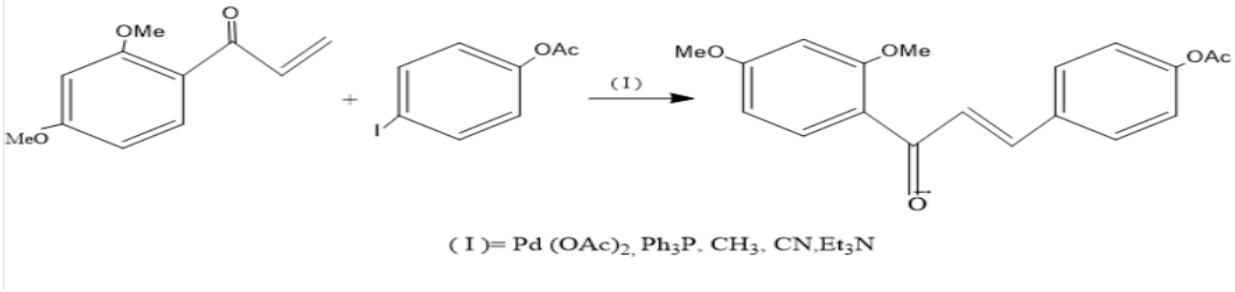


Fig.no:3

Chalcones from cinnamic acid and its derivatives:

Cinnamic acid and phenol, cinnamic anhydride, cinnamoyl chloride and benzene cinnamoyl chloride and phenol have been used for the synthesis of chalcones and their analogues[12].

Chalcones from O-iodophenyl acetate and palladium:

A convenient palladium catalysed procedure for the synthesis of O-hydroxy chalcones, flavanone and benzo furans has been described where O-iodophenyl acetates were used as a common precursor.

Chalcones from Schiff bases:
In presence of acid, aryl amino ketones derived from Schiff bases undergo hydramine cleavage to yield primary aromatic amine and chalcones[13].

Chalcones from enamines:
The synthesis of chalcones has been affected by the interaction of benzaldehyde with N-α-styryl morpholine.

Chalcones from organometallic compounds:
Chalcones have also been synthesized by acetylenic Grignard reagents, cadmium derivatives and cinnamyl chloride in ether, phenyl magnesium bromide and cinnamon nitrile in presence of ammonium chloride and methyl magnesium iodide with benzaldehyde[13].

Chalcones from critical water:
Recently has carried out Clines-Schmidt condensation reaction of aromatic aldehyde and ketone in critical water.

NON-CONVENTIONAL METHODS:
During the last few decades, chemical application of microwave and ultrasound irradiation has received a lot of attention and widespread research is going on in these areas[14]. Significant enhancement of selectivity, rate of reactions and yield in synthesis of chalcones has been achieved by means of microwave and ultrasound irradiation.

Microwave irradiated synthesis of chalcones:
The following heterogeneous catalysts have been used for the synthesis of chalcones and their analogous under microwave irradiation.

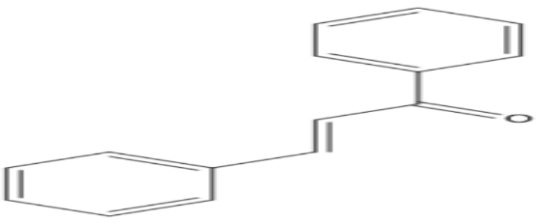
- Potassium carbonate
- Barium hydroxide
- P-Toluene sulphonic acid
- KF-Aluminium oxide
- Zirconium tetrachloride
- Piperidine
- Aqueous alkali

Ultrasound irradiated synthesis of chalcones:
Recently, following heterogenous catalysts have been successfully used for the synthesis of chalcones and their analogues under ultrasound irradiation.

- Potassium carbonate
- Basic Aluminium oxide
- Amino grafted Zeolite
- Barium hydroxide
- Pulverized Potassium hydroxide
- KF-Aluminium oxide

Chemistry:
The chemistry of chalcones has generated intensive scientific studies throughout the world. Chalcones (1, 3-Diphenyl-2-propen-1-one) are constituted of a three carbon α, β unsaturated carbonyl system. This conjugated double bond always produces the delocalisation of π electrons towards carbonyl carbon and reduces its electrophilic character[15]. Chemically they consist of open chain flavonoids in which the two aromatic rings are joined by a linker of three carbonα, β unsaturated carbonyl system.

Especially interest has been focussed on the synthesis and biodynamic activities of chalcones. These compounds are also known as benzal acetophenone or benzylidene acetophenone. In chalcones, two aromatic rings are linked by an aliphatic three carbon chain. Chalcone bears a very good synthon so that variety of novel heterocycles with good pharmaceutical profile can be designed[16]. The structure of a chalcone contains, two benzenoid rings with are joined by an aliphatic chain of three carbons. They have keto-ethylenic moiety (-CO-CH=CH-) in their structure. They have a conjugated double bond and an entirely delocalized π-electron-containing order on aromatic rings.



1, 3-Diphenyl-2-propen-1-one

Fig.no:4

are prepared by two ways. Firstly, Claisen-Schmidt condensation between acetyl derivative of heterocyclic nucleus and substituted aromatic aldehyde nucleus. Secondly, substituted derivatives of acetophenone and various heterocyclic aldehydes in presence of alcoholic basic medium.

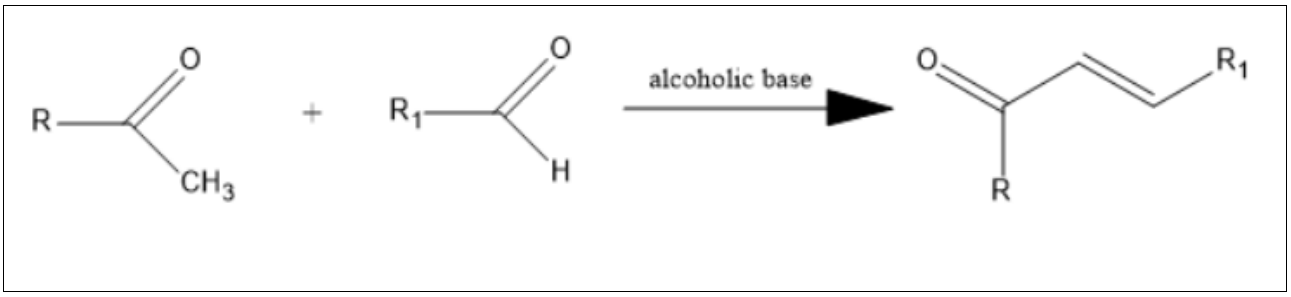
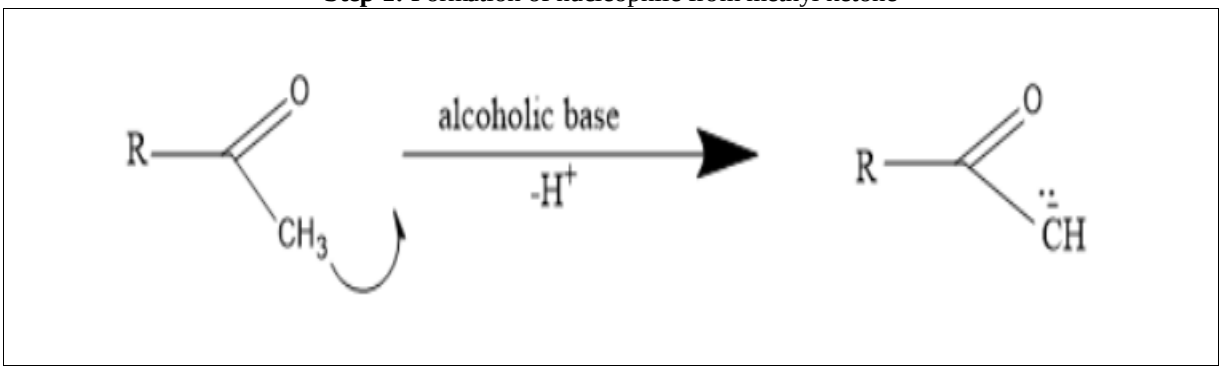


Fig.no:5

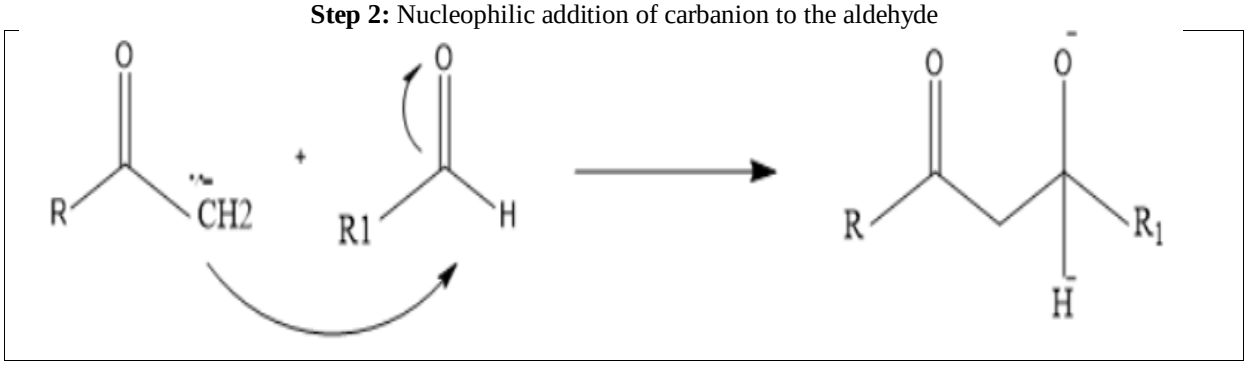
R = phenyl or heterocyclic;R_1 = phenyl or heterocyclic

The basic principle involved in the condensation is nucleophilic addition followed by dehydration. Initially, the abstract of a proton from the methyl ketone is done by the alcoholic basic medium. Usually sodium hydroxide (NaOH) or potassium hydroxide (KOH) of ethanol or methanol medium are used[17]. The abstract of a proton results in the formation of carbanion species and can be act as nucleophilic condensation; nucleophilic addition of carbanion to the aldehyde followed by the addition of proton from corresponding β-hydroxy carbonyl compound. In the final step, dehydration takes place from β-hydroxy carbonyl compound to form corresponding α, β unsaturated carbonyl compound. In the presence of electron-donating group in the aldehyde or presence of hetero nucleus, the final chalcone was achieved by the utilization of mineral acid such as HCl.

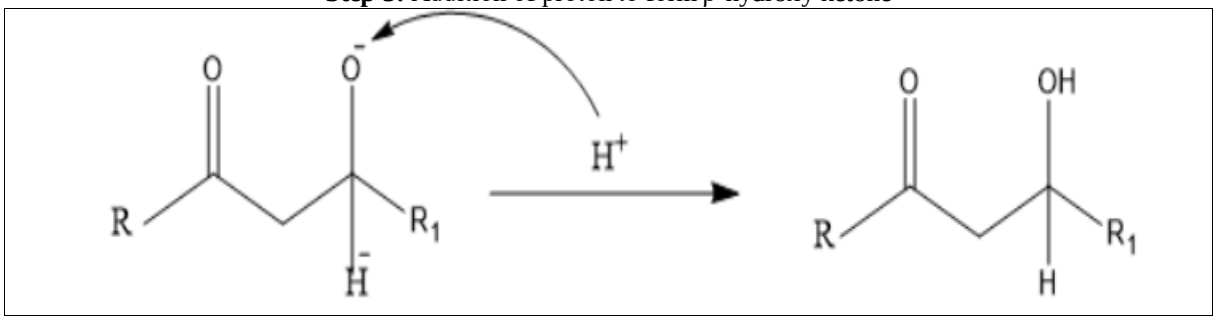
Step 1: Formation of nucleophile from methyl ketone



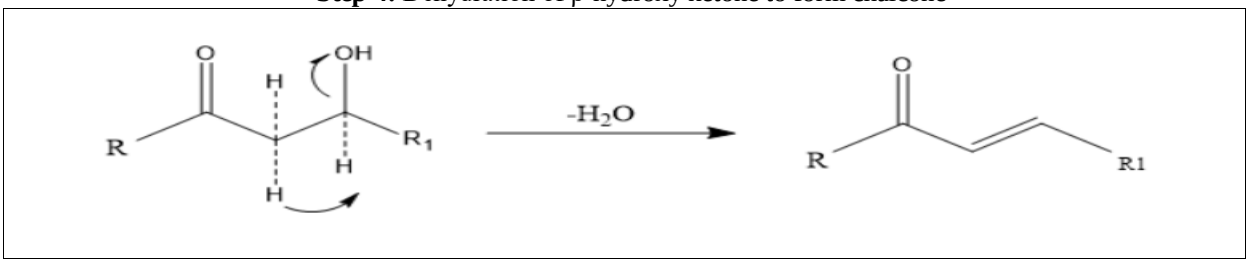
Step 2: Nucleophilic addition of carbanion to the aldehyde



Step 3: Addition of proton to form β-hydroxy ketone



Step 4: Dehydration of β-hydroxy ketone to form chalcone



Importance of chalcones:

Chalcones have been investigated since long due to versatile usefulness.

- ❖ They have close relationship with flavones, aurones, tetralones and aziridines.
- ❖ Chalconesand their derivatives find application as artificial sweeteners, scintillator, polymerization catalyst, fluorescent whitening agent, organic brightening agent, stabilizer against heat, visible light, ultraviolet light and aging.
- ❖ 3, 2', 4', 6'-tetrahydroxy-4-propoxydihydrochalcone-4-β'-neohesperIdose has been used as synthetic sweetener and is 2200 times sweeter than glucose.
- ❖ They contain a keto-ethylenic group and are therefore reactive towards several reagents.e.g. (a) Phenyl hydrazine (b) 2-amino thiophenol etc.
- ❖ The chalcones have been found useful in elucidating structure of natural products like hemlock tannin, cyanmaclurin, phloretin, eriodyctiol and homoeriodyctiol, naringenin.
- ❖ They have been useful as intermediate in the synthesis of certain heterocyclic compound such as flavones, anthocyanins,benzylcoumarins etc.

MATERIALS AND METHODS:

Materials:

4-acetyl morpholine and 4-dimethylaminobenzaldehyde were procured from local market, Methanol,Sodiumhydroxide,p-chlorobenzaldehyde,p-chlorobenzaldehyde, and 2-chloro benzaldehyde, tetracyclinewas obtained from S.D. Fine chemical, Mumbai. Clinical isolates of gram-positive organism growthBacillus subtilis were obtained from Acharya Nagarjuna University, Guntur. All other chemicals were procured were of Analytical grade.

Equipment's:

Maintaining Sterileconditions:

Petri dishes, 6-8 cork bore, inoculum loops, graduated pipettes, conical flask, glass rod, boiling tubes and beakers, test tubes for preparation of sub culture Sterilised test tubes for preparation of test compound solution in a desired concentration, paper disc 18-24 hold growth culture on nutrient medium, fine pointed forceps, cotton wool, Whatman filter paper-No.1.

Antimicrobial Activity:

The antimicrobial activity of synthesized compounds was carried out against bacillus subtilis by cup plate method.

Nutrient agar composition

S.No	Ingredients	Quantity
1	Beef extract	3g
2	peptone	5g
3	Sodium chloride	5g
4	Agar	20g
5	distilled	1000ml

Preparation of culture medium

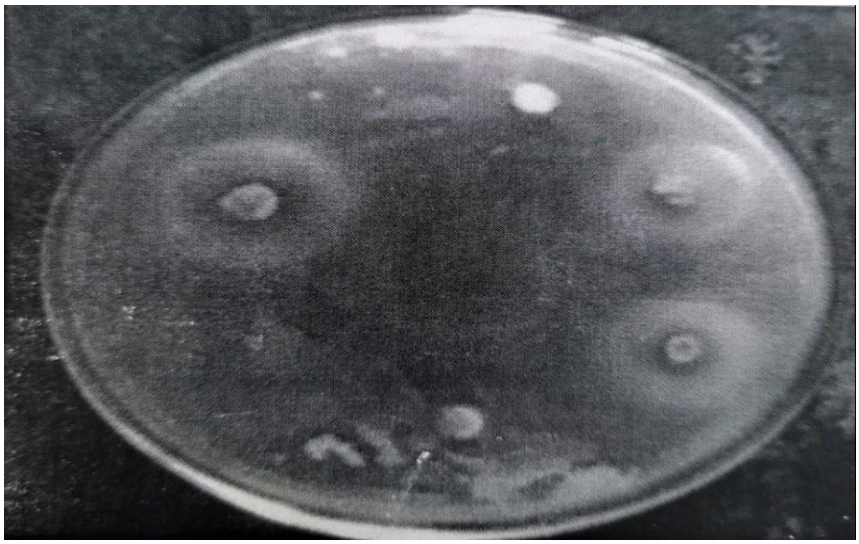
- Nutrient agar medium was prepared as per composition, beef extract, peptone, sodium chloride heated on a water bath until they dissolved. Then agar was addedand heated on a water bath untilit is dissolved, then taken out and a cotton plug was tied it with aluminium foil. Sterilize the medium in autoclave at121℃ temperature and 15 lb pressure for 20 mins. Sterilizedcleaned glass plates in hot air oven at 160 ℃ temperature for 2 hrs in petriplates, 20 ml of aliquor of molten state agar mediumpouredand allowed the plates for solidification of medium.

Preparation of sub-culture

- Nutrient broth was prepared by dissolving all solids ingredients in water and pH was adjusted to 6.2; and sterilize in an autoclave at 15lb/inch pressure for 20 mins.
- One day prior to the test, the above mention stock culture was especially inoculated in 5 ml of sterilized nutrient broth and incubated for 24 hrs at 37 ℃ in an incubator.

RESULTS AND DISCUSIONS:

ANTI-MICROBIAL ACTIVITY- DETERMINATION OF ZONE OF INHIBITION



Zone of inhibition after 24 hrs (in mm):

Compound	Concentration (µg/ml)	Bacillus subtilis (mm)
1	100	6
2	100	8
3	100	10
4	100	3
5	100	9
Standard-Tetracycline	100	5

General Procedures for 5 compounds:

Weigh accurately equimolar concentrations of 4-acetyl morpholine (0.01 M) and substituted aromatic aldehyde (0.01 M) dissolved in 15ml methanol and add 10ml of 10% NaOH and stir for 2 hrs, completion of reaction is monitor by TLC. The mixtures is kept in the refrigerator overnight, acidified using dilute HCl, then add cold water, filter the precipitate, dry and recrystallise with ethanol.

COMPOUND 1: 3-(4-dimethyl amino phenyl)-1-(morpholine) prop-2-ene-1one.

S.No.	Name of the compound	Weight	Molecular weight	Moles	Equivalence
1	4-acetyl morpholine	1.5 ml	129.16	0.01	1
2	4-dimethylaminobenzaldehyde	1.5 g	149.19	0.01	1
3	Methanol	15 ml	32.04	-	1
4	Sodium hydroxide	10 ml	39.997	-	1

COMPOUND 2: 3-(4-Hydroxy phenyl)-1-(morpholine) prop-2-ene-1one.

S. No.	Name of the compound	Weight	Molecular weight	Moles	Equivalence
1	4-acetyl morpholine	1.5 ml	129.16	0.01	1
2	p-hydroxy benzaldehyde	1.2 g	122.12	0.01	1
3	Methanol	15 ml	32.04	-	1
4	Sodium hydroxide	10 ml	39.997	-	1

COMPOUND 3:3-(2-Hydroxy phenyl)-1-(morpholine) prop-2-ene-1one.

S. No.	Name of the compound	Weight	Molecular weight	Moles	Equivalence
1	4-acetyl morpholine	1.5 ml	129.16	0.01	1
2	Salicylaldehyde	1.4 ml	122.12	0.01	1
3	Methanol	15 ml	32.04	-	1
4	Sodium hydroxide	10 ml	39.997	-	1

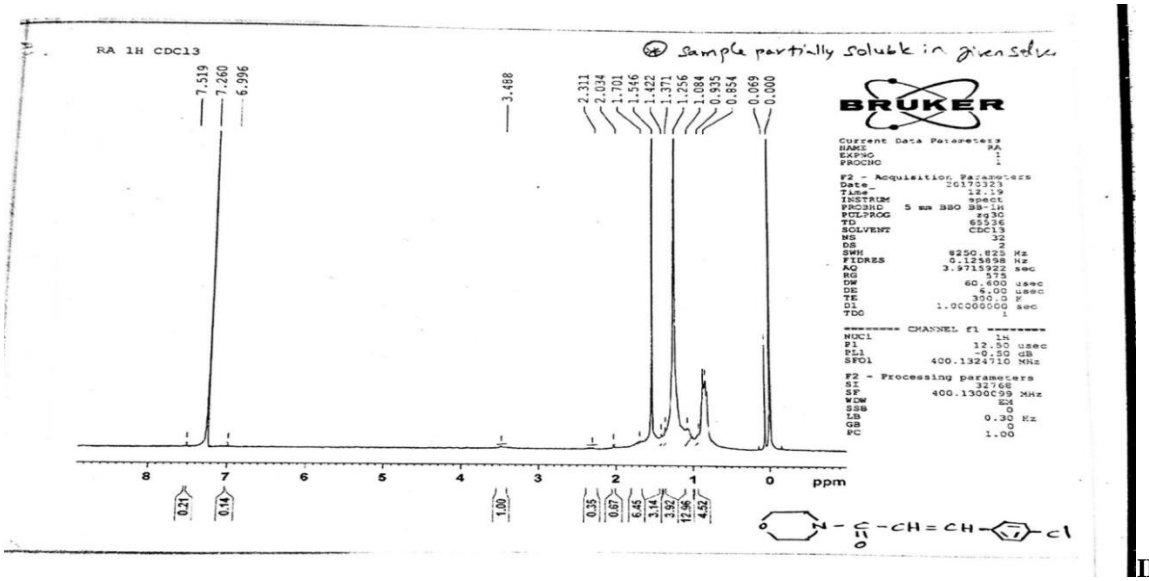
COMPOUND 4: 3-(4-chloro phenyl)-1-(morpholine) prop-2-ene-1one.

S. No.	Name of the compound	Weight	Molecular weight	Moles	Equivalence
1	4-acetyl morpholine	1.5 ml	129.16	0.01	1
2	p-chlorobenzaldehyde	1.4 g	140.5	0.01	1
3	Methanol	15 ml	32.04	-	1
4	Sodium hydroxide	10 ml	39.997	-	1

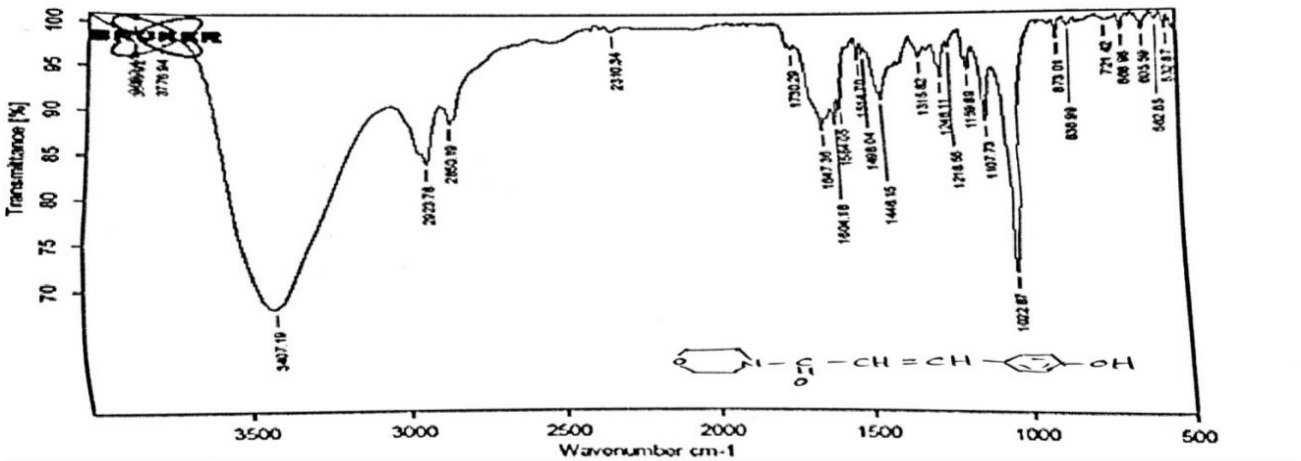
COMPOUND 5: 3-(2-chloro phenyl)-1-(morpholine) prop-2-ene-1one.

S.No.	Name of the compound	Weight	Molecular weight	Moles	Equivalence
1	4-acetyl morpholine	1.5 ml	129.16	0.01	1
2	2-chloro benzaldehyde	1 ml	140.57	0.01	1
3	Methanol	15 ml	32.04	-	1
4	Sodium hydroxide	10 ml	39.997	-	1

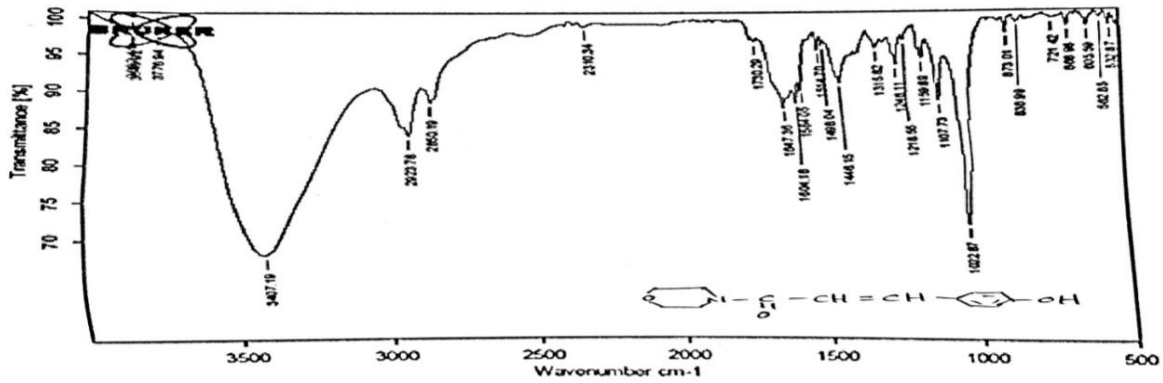
NMR SPCTRUM OF COMPOUND 4



IR SPECTRUM OF COMPOUND 1



IR SPECTRUM OF COMPOUND



SPECTRAL ANALYSIS

INFRARED SPECTROSCOPY:

Infrared spectrum is an important record which gives sufficient information about the structure of an organic compound unlike UV spectrum which comprises of relatively few peaks, this technique provides a spectrum containing a large number of absorption band from which information can be derived about the structure of an organic compound.

When IR is allowed to pass through the sample molecular vibrations namely,

1. Bending vibrations
2. Stretching vibrations

S. No.	Group	Compound 2	Compound 3
1	C=O	647.36	647.79
2	C=C	584.05	13.69
3	Ar-H	3407.19	3419.7

DISCUSSION:

Due to the great importance in the, β unsaturated carbonyl moiety in broad range of natural and synthetically designed products, the development of novel synthetic methods remain interest in research area to synthesize chalcones and their derivatives. All the title compounds were purified by recrystallization using methanol as solvent. 5 compounds were synthesized which yields generally ranging from 68-95%. 4-dimethyl amino benzaldehyde and salicylaldehyde derivatives were obtained in highest yields, p-hydroxy benzaldehyde, 2-chloro and p-chlorobenzaldehyde derivatives show lowest yield. The chalcone derivatives of the present study were characterized through IR, NMR spectral analysis. The compounds were screened for anti-bacterial activity using bacillus subtilis. This was done by cup plate method and compound-2, 4 and 5 (p-hydroxy benzaldehyde, 2-chloro and p-chlorobenzaldehydes) showed highest inhibition and 4-dimethyl amino benzaldehyde showed moderate inhibition. Tetracycline was taken as standard.

CONCLUSION:

In the present investigation, all the synthesized compounds have shown moderate to high anti-bacterial activity. But the biological screening conducted were preliminary. Further structural modifications and screening has to be done to confirm the activity. Long term toxicity studies are to be carried out before on fine conclusion about the activities and safety of the compounds. However, it is an interesting field of studying which can be taken by for more systemic and biolgical studies under controlled conditions.

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Conflict consent

Not applicable

Ethical statement

Not applicable

Author contribution

All authors contributed equally

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