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COMPARATIVE STUDY ON SYNTHESIS OF α, β-UNSATURATED CARBONYL COMPOUNDS AND THEIR PHARMACOLOGICAL SCREENING

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Abstract:
α β-Unsaturated carbonyl compounds are organic compounds with the general structure (O=CR)−Cα=Cβ-R. Such compounds include enones and enals. In these compounds the carbonyl group is conjugated with an alkene (hence the adjective unsaturated). Unlike the case for carbonyls without a flanking alkene group, α,β-unsaturated carbonyl compounds are susceptible to attack by nucleophiles at the β-carbon. This pattern of reactivity is called vinylogous. Examples of unsaturated carbonyls are acrolein (propenal), mesityl oxide, acrylic acid, and maleic acid. Unsaturated carbonyls can be prepared in the laboratory in an aldol reaction and in the Perkin reaction and Claisen condensation. B -keto esters are abundant in edible plants and consider for a precursor for flavonoids and iso-flavonoids of life cycle of a human being, Which is fully contaminated and polluted. It is evident that people are prone to be various kinds of diseases, hence it is forced that researchers and scientists for the Synthesis of novel drugs. The claisen reaction refers to an organic coupling reaction that results in the formation of a carbon-carbon bond either between two esters or between a single ester and one carbonyl compound. Beta ketoesters are having various pharmacological activities like antimicrobial, antioxidant, antimalarial, antifungal, antiHIV, Anti diuretic, anti-cancer, antitubercular, etc

Keywords: *α,β-Unsaturated carbonyl compounds, antimicrobial, antioxidant, antimalarial, antifungal.*

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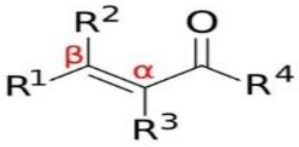
INTRODUCTION:

A **α**,β-Unsaturated carbonyl compounds are organic compounds with the general structure (O=CR)−Cα=Cβ-R. Such compounds include enones and enals. In these compounds the carbonyl group is conjugated with an alkene (hence the adjective unsaturated). Unlike the case for carbonyls without a flanking alkene group, α,β-unsaturated carbonyl compounds are susceptible to attack by nucleophiles at the β-carbon. This pattern of reactivity is called vinylogous. Examples of unsaturated carbonyls are acrolein (propenal), mesityl oxide, acrylic acid, and maleic acid. Unsaturated carbonyls can be prepared in the laboratory in an aldol reaction and in the Perkin



reaction and claisen condensation.

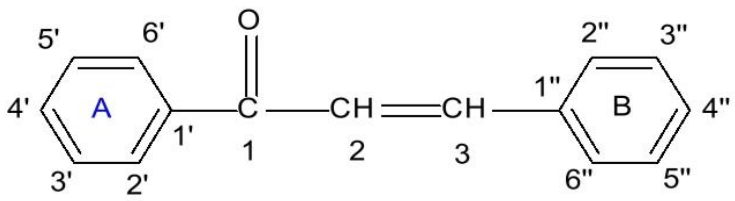
B -keto esters are abundant in edible plants and consider for a precursor for flavonoids and iso-flavonoids of life cycle of a human being, Which is fully contaminated and polluted. It is evident that people are prone to be various kinds of diseases, hence it is forced that researchers and scientists for the Synthesis of novel drugs.A,β-unsaturated carbonyl compound is versatile molecule possess a wide range of biological activities. A,β-unsaturated carbonyl compounds are organic compounds characterized by the presence of both carbonyl and alkene functional groups within their molecular structure. Their unique chemical properties, such as the ability to undergo diverse chemical transformations, make them valuable intermediates in the synthesis of various bioactive compounds. Furthermore, their structural resemblance to essential metabolites found in microbial cells allows them to interfere with vital biological processes, resulting in potent antimicrobial effects.

In organic chemistry, the Claisen -Schmidt condensation is the reaction between an aromatic aldehyde or ketone having an alpha -H atom with an aromatic carbonyl compound lacking an alpha -hydrogen.The desirable product of this reaction is usually β-ketoesters, the antimicrobial activity of β -ketoesters is attributed to their ability to disrupt key cellular processes in microorganisms, such as cell wall biosynthesis, protein synthesis, and DNA replication. By inhibiting vital enzymatic pathways or altering the structural integrity of microbial cells β -ketoesters effectively impede microbial growth, replication, and survival. Moreover, their broad-spectrum activity against, a reaction of an aromatic aldehyde with an aromatic ketone in the presence of base(KOH) to form an α,β-unsaturated carbonyl compounds with high chemo selectivity.

The claisen reaction refers to an organic coupling reaction that results in the formation of a carbon-carbon bond either between two esters or between a single ester and one carbonyl compound. Beta ketoesters are having various pharmacological activities like antimicrobial, antioxidant, antimalarial, antifungal, anti-HIV, anti-diuretic, anti-cancer, anti-tubercular, etc. Chalcone is an α,β-unsaturated carbonyl system and acts as a chemical synthon for synthesis of different N,S,O-Heterocycles by abridgment with a variety of bi-nucleophilic reagents . The chalcone compounds have been cited to possess varied biological and pharmacological importance,like antimicrobial,anti-HIV,anti-inflammatory,antitubercular,antileishmanial, antiviral,antiprotozoal,antitumor,analgesic,cytotoxic,immunomodulatory,antimalarial, anti-ulcerative, antioxidant, antihyperlipidemic, Antihistaminic, antifeedant, anticonvulsant, antiplatelet, and antihyperglycemic activities .besides that, hepatitis A virus (HAV) infects the liver, belongs to the genus hepatoviral within the picornaviridae family, and is a single RNA strand covered by icosahedral-shaped protein shell . The Search of new synthetic compounds to overcome HAV continues during the last decades . Also, naphthalene nucleus is present in a wide variety in the field of medicinal chemistry because of their wide applications in drug discovery.

Flavonoids are an important group of naturally occurring bioactive compounds. This field of investigation was initiated in 1936 by the discovery of Citrin, known as“ Vitamin P or Permeabilities vitamin”. It has since been claimed that many other flavonoids have similar pharmacological properties. Chalcones belong to an important class of flavonoids, which may be prepared by Claisen reaction. They possess a wide range of biological activities and industrial applications. Kostanecki was the first to give the term chalcone and who did pioneering work in the synthesis of naturally coloring compounds.

Chalcones are 1,3-diphenyl-2-propene-1-one, in which aromatic rings are linked by a three carbon α, β-unsaturated carbonyl system. These are abundant in edible plants and are considered to be the precursors of flavonoids and isoflavonoids.



These diverse biological activities initiated our interest to synthesize some naphthalene–benzofuran derivatives bearing various heterocyclic compounds. Some of the newly synthesized derivatives were tested as antiviral agents against HAV. In addition, the cytotoxic activity of Some prepared derivatives against HepG2 and MCF-7 Cell lines was evaluated.A,β-Unsaturated carbonyl compounds are key building blocks in organic chemistry. Their catalytic synthesis has received significant attention during the past decades. Among the known methodologies, carbonylation reactions represent an atom-efficient tool box to convert a variety of easily available Substrates into valuable α β -unsaturated carbonylated products including aldehydes, ketones, esters, Amides, and carboxylic acids. Herein, we summarize the most important achievements in this field with a special focus on results from the last decade.The term "alpha beta" refers to the positions of the carbon atoms adjacent to the carbonyl group. The general structure of an alpha beta unsaturated carbonyl compound is R-C(=O)-C=C-R', where R and R' can be various substituents such as alkyl groups, aryl groups, or hydrogen atoms. This structure gives these compounds unique reactivity and properties.

One of the key characteristics of alpha beta unsaturated carbonyl compounds is their ability to undergo conjugate addition or Michael addition reactions. The presence of the double bond adjacent to the carbonyl group allows nucleophilic attack at the beta carbon, leading to the formation of a new bond with the nucleophile. This reactivity makes these compounds versatile building blocks in organic synthesis.A,β- unsaturated carbonyl compounds are widely found in nature and have significant biological activity. They can be natural products or synthetic molecules. Many pharmaceuticals, natural pigments, and flavoring agents contain this functional group. Some examples include chalcones, curcumin, and steroids.

Synthesizing α,β-Unsaturated carbonyl compounds by microwave irradiation method is type of green chemistry, having some importance like green chemistry is a newly emerging field to design, synthesize and implement chemical products by scientists and engineers that would protect and benefit the economy, people, and our planet by finding creative and innovative methods to reduce waste, conserve energy, and discover replacements for hazardous substances. It is a sustainable method that would protect our ecosystem from hazardous and toxic chemicals.

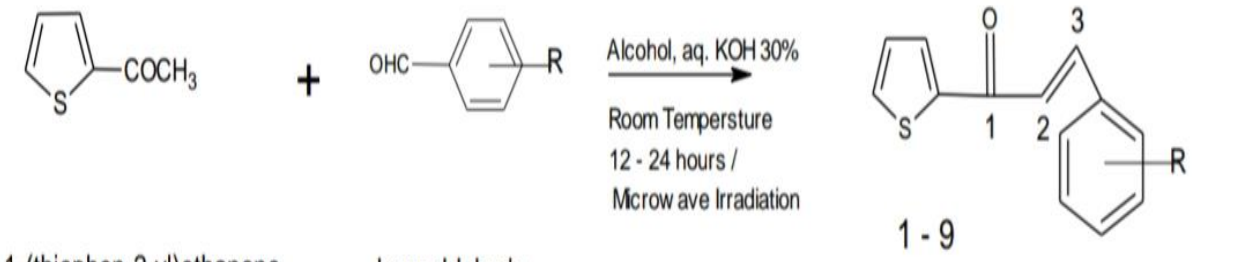
Experimental part:

All chemical reagents and solvents are purchased from commercial suppliers (HIMIDIA) and were without further purification. Melting points were determined on a capillary melting point apparatus and are uncorrected. The IR spectra were recorded in KBr on Perkin Elmer BX spectrophotometer. The purity of the compounds was checked by TLC using Silica gel-G(Merck).

THE IUPAC NAMES OF SYNTHESUIZED COMPOUNDS ARprop-2-en-1-on

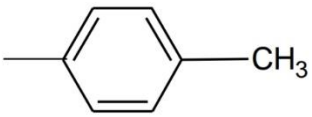
1. 3-(4-methylphenyl)-1-(thiophen-2-yl)prop-2-en-1-one
2. 3-(4-nitrophenyl)-1-(thiophen-2-yl)prop-2-en-1-one
3. 3-(4-methoxyphenyl)-1-(thiophen-2-yl)prop-2-en-1-one
4. 3-(4-ethoxyphenyl)-1-(thiophen-2-yl)prop-2-en-1-one

SCHEME

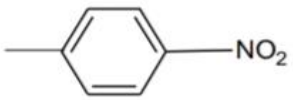


1-(thiophen-2-yl)ethanone benzaldehyde 3-phenyl-1-(thiophen-2-yl)prop-2-en-1-one

General structures of benzaldehydes:



1.



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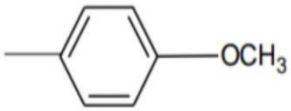

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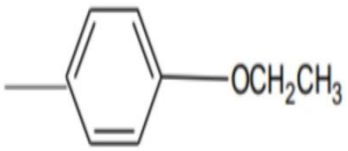
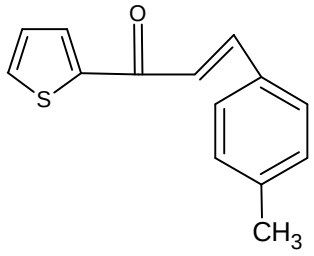


4.

General procedure for the synthesis of chalcones by Claisen-Schmidt condensation Synthesis of the chalcones using 2-acetylthiophene (1-9):-
Conventional:
Equimolar quantities (0.001mol) of 2-acetylthiophene and respective aldehydes (0.001mol), were mixed and dissolved in minimum amount (3ml) of alcohol, to this aqueous potassium hydroxide solution (30%) was added slowly and mixed occasionally for 24 hrs, at room temperature. Completion of the reaction was identified by observing on precoated TLC plates of Merck. After completion of the reaction, the reaction mixture was poured into crushed ice, if necessary acidified with dil HCl. The solid separated was filtered and dried. It was purified by recrystallization or by column chromatography performed on silica gel (100-200 Mesh, Merck), using ethyl acetate and hexane mixture as mobile phase.

MWI:
Equimolar quantities (0.001mol) of 2-acetylthiophene and respective aldehydes (0.001mol) were mixed and dissolved in minimum amount (3ml) of alcohol; to this aqueous potassium hydroxide solution (30%) was added slowly and mixed. The entire reaction mixture was microwave irradiated for about 2-6 minutes at 180 watts, then kept aside for 1-3 hrs. Completion of the reaction was identified by observing on precoated TLC plates of Merck. After completion of the reaction, the reaction mixture was poured into crushed ice, if necessary acidified with dil HCl. The solid separated was filtered and dried. It was purified by recrystallization or by column chromatography performed on silica gel (100-200 mesh, Merck), using ethylacetate and hexane mixture as mobile phase.

1. 3-(4-methylphenyl)-1-(thiophen-2-yl) prop-2-en-1-one



MOLECULAR FORMULA	M. Wt	M.P	TIME AND (%) YIELD			
			CONVENTIONAL		MICROWAVE IRRADIATION	
			T	%Y	T	%Y
$C_{14}H_{12}OS$	228 ± 2	110 ± 5°c	24 hrs	78%	5 min	88%
10% Ethyl acetate / Hexane TLC-Rf : 0.54						

IR (cm^{-1}): 1732 (C=O),
1645 (HC=CH),
652(C-S)

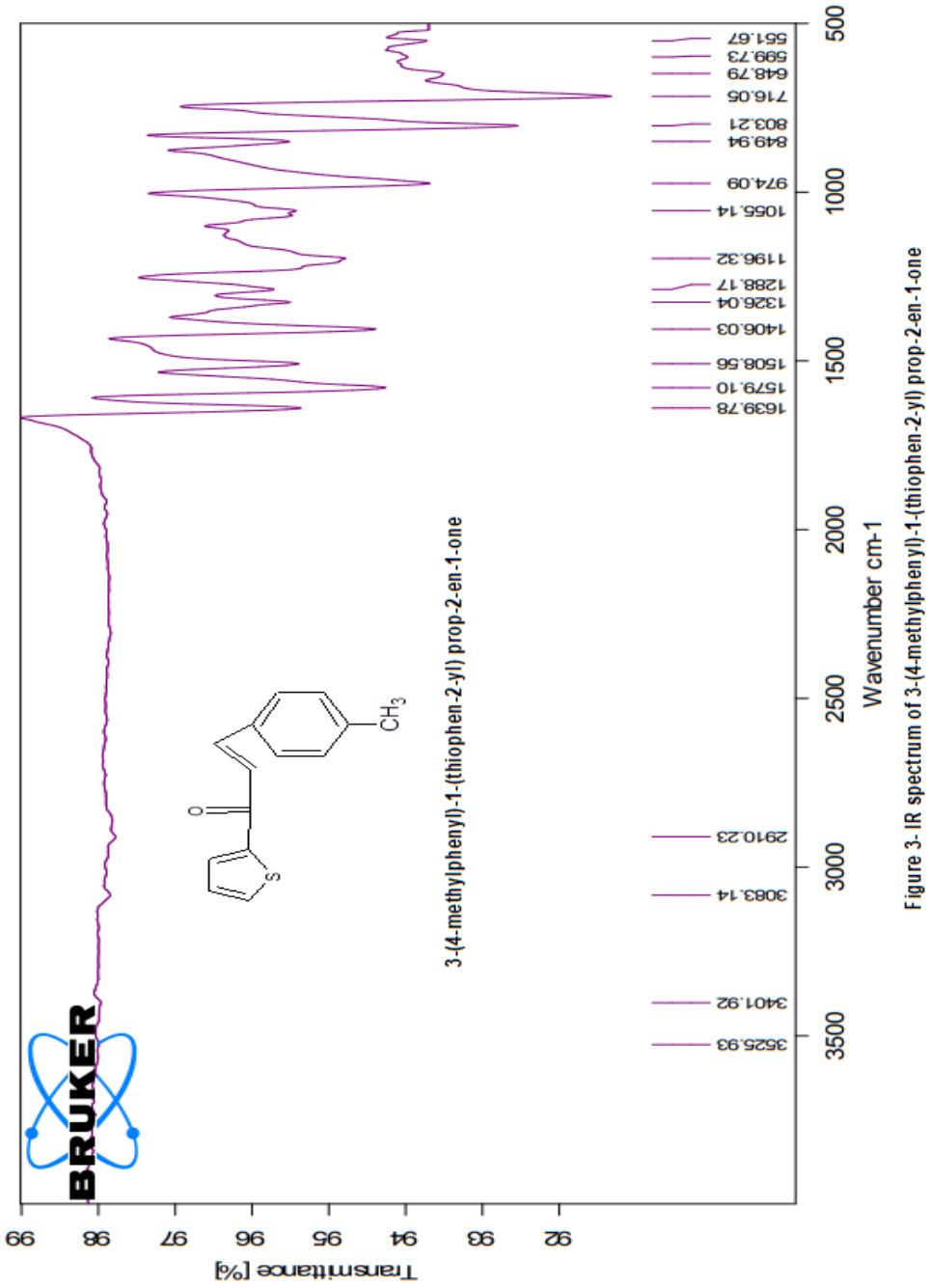
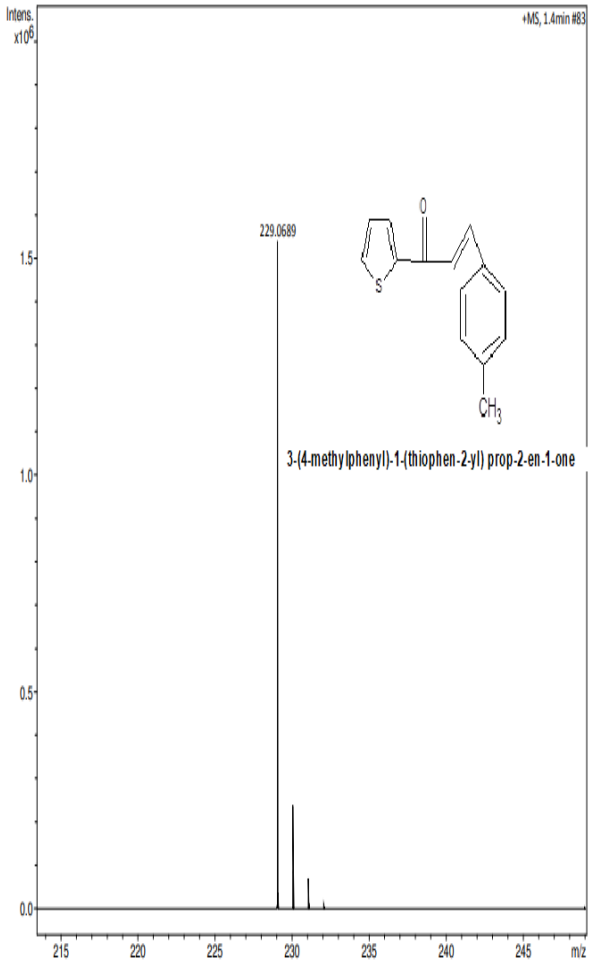


Figure 3- IR spectrum of 3-(4-methylphenyl)-1-(thiophen-2-yl) prop-2-en-1-one

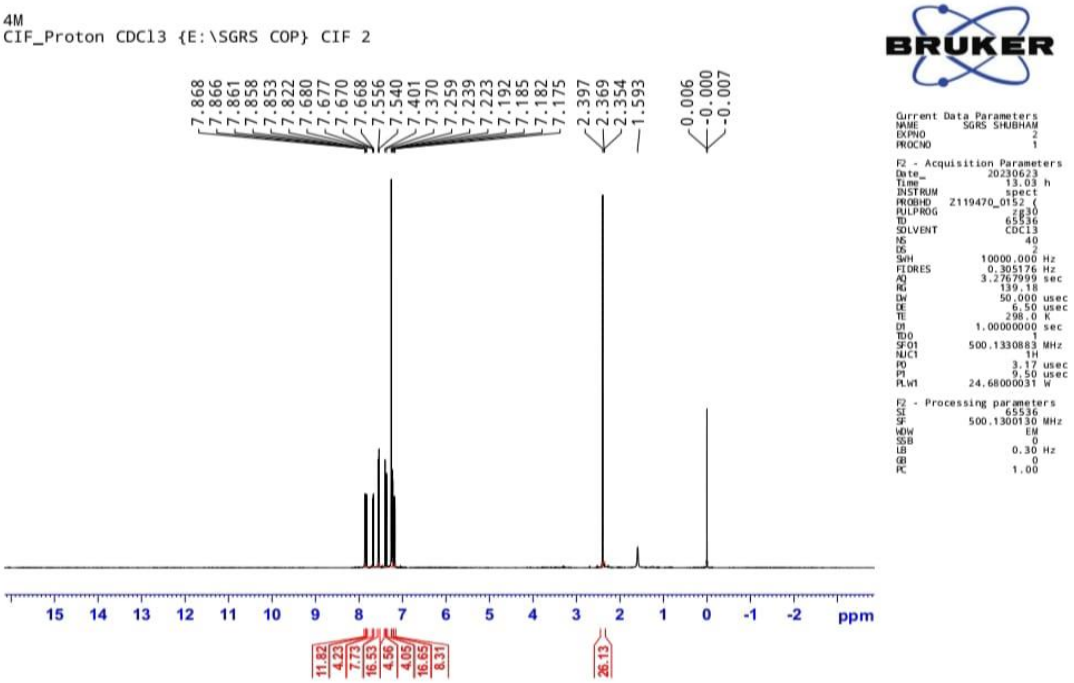


Mass spectrum of 3-(4-methylphenyl)-1-(thiophen-2-yl) prop-2-en-1-one and MW 229.0689 was found.

1H NMR (CDCl3,ppm), spectra was recorded in the indicated solvent on Bruker WM 400 MHz Spectrometer with TMS as internal standard.

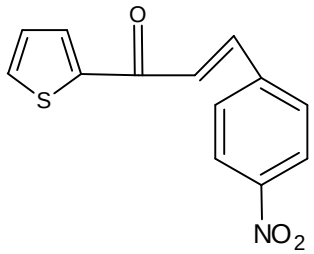
When 2- acetylthiophene reacted with 4-Methylbenzaldehyde, It show following spectral data of NMR

7.39(1H, d, J=16Hz , −CO−CH=), 7.56 (1H, d, J=16Hz, =CH−Ar), 7.88 (1H, d, J=9Hz, −C−51−H), 7.68 (2H, d, −C−2−H, −C−6−H), 7.58 (1H, d, J=8Hz, −C−31−H), 7.23 (2H, d, −C−3−H, −C−5−H), 7.19 (1H, m, −C−41−H).



NMR spectrum of 3-(4-methylphenyl)-1-(thiophen-2-yl) prop-2-en-1-one .

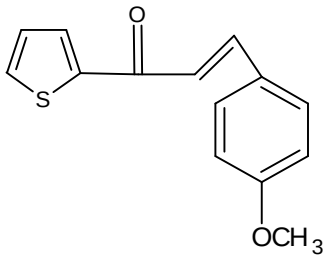
2. 3-(4-nitrophenyl)-1-(thiophen-2-yl) prop-2-en-1-one



MOLECULAR FORMULA	M. Wt	M.P	TIME AND (%) YIELD			
			CONVENTIONAL		MICROWAVE IRRADIATION	
			T	%Y	T	%Y
$C_{13}H_9O_3NS$	259	110 ± 5°c	24 hrs	60%	5 min	78%
10% Ethyl acetate / Hexane TLC-Rf : 0.54						

IR (cm^{-1}): 1720 (C=O),
1640 (HC=CH)
650 (C-S).
450(NO_2)

3. **3-(4-methoxyphenyl)-1-(thiophen-2-yl) prop-2-en-1-one**



MOLECULAR FORMULA	M. Wt	M.P	TIME AND (%) YIELD			
			CONVENTIONAL		MICROWAVE IRRADIATION	
			T	%Y	T	%Y
$C_{14}H_{12}O_2S$	244	110 ± 5°c	24 hrs	70%	5 min	80%
10% Ethyl acetate / Hexane TLC-Rf : 0.53						

IR (cm^{-1}): 1720 (C=O),

1648 (HC=CH),
1170 (-OCH3).
666 (C-S)

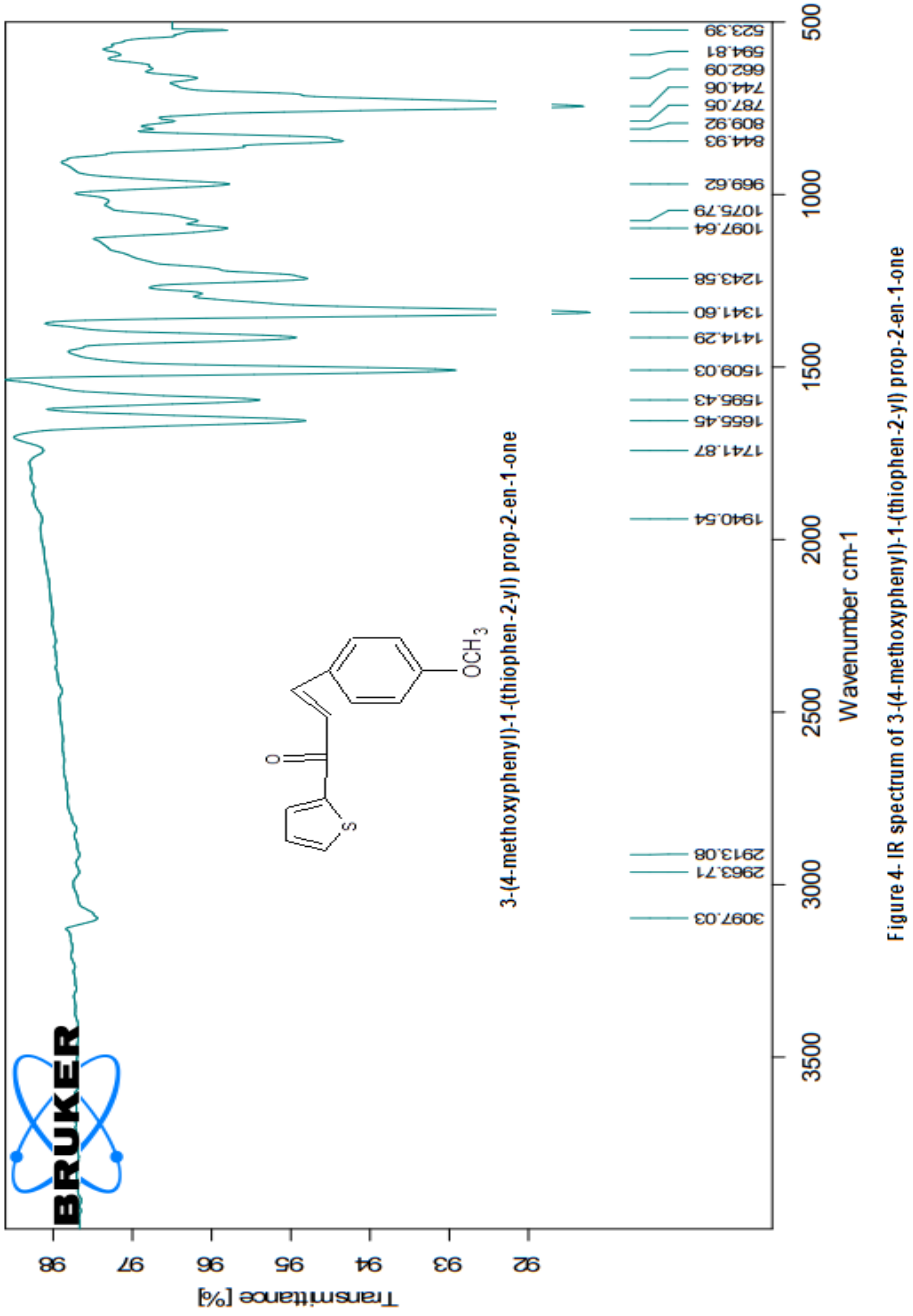
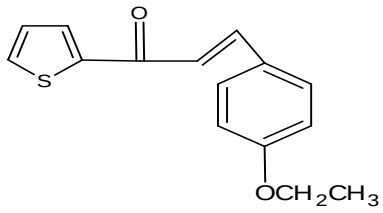


Figure 4- IR spectrum of 3-(4-methoxyphenyl)-1-(thiophen-2-yl) prop-2-en-1-one

4. 3-(4-ethoxyphenyl)-1-(thiophen-2-yl) prop-2-en-1-one



MOLECULAR FORMULA	M. Wt	M.P	TIME AND (%) YIELD			
			CONVENTIONAL		MICROWAVE IRRADIATION	
			T	%Y	T	%Y
$C_{15}H_{14}O_2S$	258	110 ± 5°c	24 hrs	76%	5 min	87%
10% Ethyl acetate / Hexane TLC-Rf : 0.57						

IR (cm^{-1}): 1720 (C=O),
1640 (HC=CH),
650 (C-S).

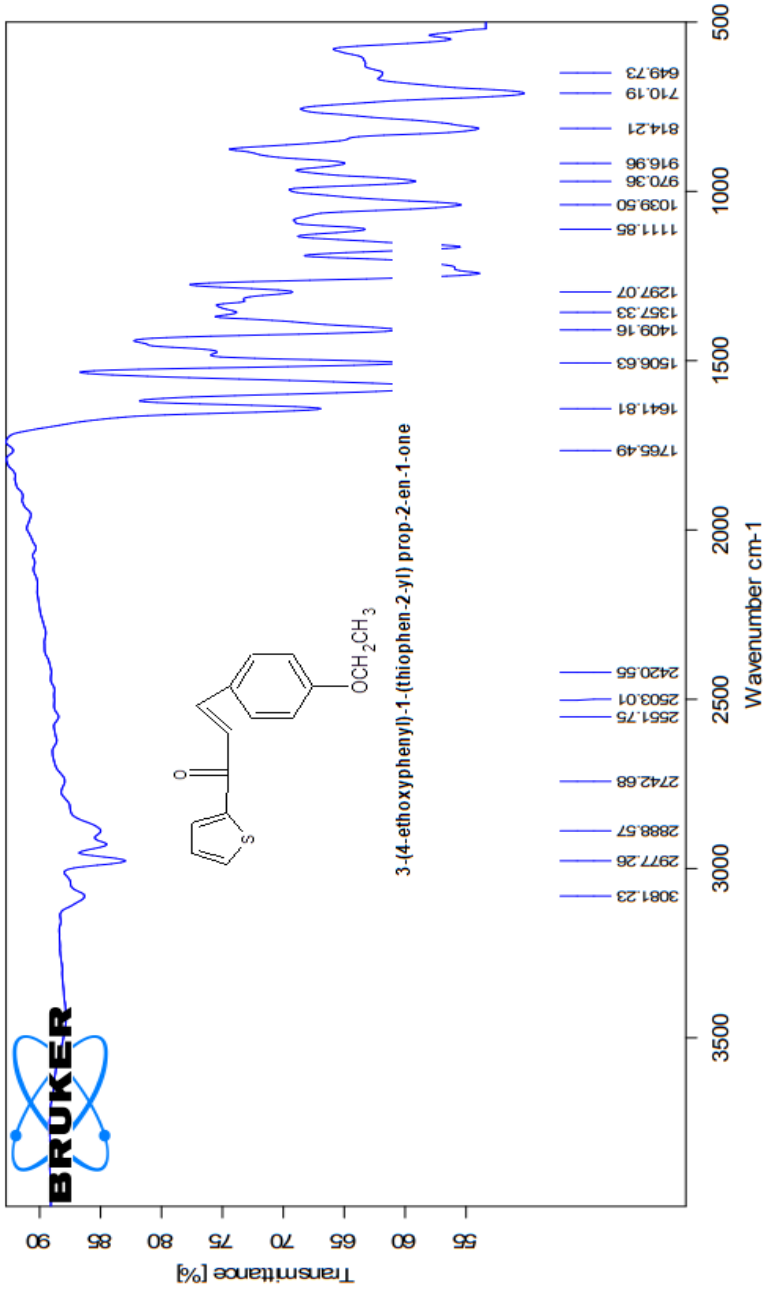


Figure 7- IR spectrum of 3-(4-ethoxyphenyl)-1-(thiophen-2-yl) prop-2-en-1-one

THE SPECTRAL PROPERTIES OF α,β-UNSATURATED CARBONYL COMPOUNDS

UV SPECTRA OF α β UNSATURATED CARBONYL COMPOUNDS:

The UV absorption of oxygenated chalcones in methanol contains a strong absorption band usually in the range 340-390 nm, although chalcones lacking B-ring oxygenation may have their absorption considerably at shorter wavelengths with a minor peak in the range 220-270 nm region 15.

IR SPECTRA OF α β UNSATURATED CARBONYL COMPOUNDS

The IR spectra of chalcones show usually a peak near 1625-1650 cm^3, the characteristic of an a, ß-unsaturated carbonyl group 16,17.

NMR SPECTRA OF α β UNSATURATED CARBONYL COMPOUNDS:

The a-H and B-H of chalcones resonate at 6 6.7-7.4 and 8 7.3-7.7 ppm as two doublets (J-17 Hz) in the 'H NMR spectra 18. In the 13C NMR spectra of chalcones, the carbonyl carbon signal appears between 8 188.6 and 194.6 ppm19. The a- and B- carbon atoms give rise to signals at 8 116.1-128.1 and 8 136.9 145.4 ppm respectively20, and can be readily identified by their characteristic appearance as a six line multiplet in the off-resonance decoupled spectrum. The presence of 2-hydroxyl group shifts the carbonyl carbon shift downfield by **3** ppm relative to corresponding acetoxy and methoxy compounds, presumably owing to hydrogen bonding.

MASS SPECTRA OF α β-UNSATURATED CARBONYL COMPOUNDS:

The mass spectra of the chalcones 21.22 exhibit the molecular ion as the base peak.

Antimicrobial activity:

Beta ketoesters are organic compounds that contain a carbonyl group (C=O) attached to a carbon atom that is adjacent to another carbon-carbon double bond (C=C). These compounds have been of interest in the field of medicinal chemistry due to their potential antimicrobial properties.

The antimicrobial activity of beta ketoesters arises from their ability to interact with the microorganisms' cellular components, such as enzymes or cell membranes, leading to disruption of vital biological processes and ultimately killing or inhibiting the growth of the microorganisms. The synthesis of beta ketoesters typically involves the condensation reaction between a beta-keto acid or ester and an aldehyde or ketone. The resulting compound contains the beta ketoester functional group. To assess the antimicrobial activity of synthesized beta ketoesters, various in vitro and in vivo assays can be performed. These assays involve exposing the target microorganisms, such as bacteria or fungi, to different concentrations of the synthesized compounds and measuring their inhibitory effects on microbial growth.

The specific mechanism of antimicrobial action can vary depending on the structure of the alpha beta ketoester and the target microorganism. It may involve interference with enzymatic processes, inhibition of cell wall synthesis, disruption of cell membrane integrity, or interference with DNA replication.

Experimental studies, including minimum inhibitory concentration (MIC) assays, time-kill kinetics, and zone of inhibition tests, are commonly employed to evaluate the antimicrobial activity of synthesized beta ketoesters. These studies help determine the effective concentration required to inhibit microbial growth, the rate of microbial killing over time, and the extent of growth inhibition in the vicinity of the compound.

Present Work And Methods :-

The work presented in this chapter deals with the study of antimicrobial activities of newly synthesized compounds against selected pathogens.

Antimicrobial Activity :-

The information regarding the various species of bacteria used to carry out screening is given below.

1. Xanthomonas citri (Xc) :

It is yellow pigmented plant pathogen of the pseudo monodaceae family. It produce yellow colonies. It is gram ±ve bacterium causes citrus cancer on Citrus.

2. Ervinia Caratovora (Ec) :

These species are primary plant pathogens, some cause plant soft-rot Disease, stalk rot on maize. These species produce enzymes that hydrolyse the Pectin between individual plant cells and cause the plant tissue to rot.

3. Escherichia coli (E.coli) :

These are gram ±ve bacilli. E-coli occure in the lower portion of the intestine and urinary tract. They cause urinary tract infection, some strains can cause Gastro-enteritis.

4. Protease vulgerius (Pv) :

It is rod shaped gram ±ve bacteria inhibits the intestinal tracts of human and animals. It is opportunistic pathogen of human. It can found in oil,

water facial Matter. It is grouped with Enterobacteriaceae, It is known to cause urinary tract Infections and wound infections. Optimum conditions of organism is in a Facultative an aerobic environment with an average temperature 37 degree celcius. In 1982 it was separated into 3 biographs on the basis of indole production. Biographs was indole ±ve and represented a new species a p. penneri while biogroup 2 and 3remained together as p.vulgarius.

Experimental :-

For the antimicrobial activities against these pathogens nutrient agar with following composition was used:

Peptone : 5 gm
Beef extract : 3 gm, yeast extract : 1.5 gm
Sodium chloride : 8 gm
Agar : 15 gm
Distilled water : 1000 ml

The diffusion method was employed for determining the antimicrobial activity of the new synthesized compounds. All compounds were tested for antimicrobial activity using the agar diffusion technique on solid media by Pour plate method, for bacteria nutrient agar. Sterile 10 mm diameter stainless steel cylinder placed on respected plates and boar had made which had been poured with respective compounds. Solution of different compounds at concentration of 200 ppm of the compounds in 10% DMSO was poured in the wheels with the help of a sterile micropipette.

The plates where thin incubation at 37ºC for 24 hours. The strength is reported by measuring the diameter of zone inhibition in mm and the results were standardized against Ciprofloxacin. The solution without compound (only10 %). Pyrimidinone was used control the diameter of zone inhibition in mm is given in the following table.

Antimicrobial activities of synthesized compounds Bacteria Shows, Zone of inhibition in diameter (mm)

Compounds	Xanthomonas Citri	Ervinia Carotovora	E.coli	Protease vulgerius
Compound -1	9 mm	10.5 mm	12 mm	-
Compound -2	9 mm	12.5 mm	-	11mm
Compound -3	8 mm	9 mm	11.3 mm	-
Compound -4	9 mm	13 mm	-	7mm
Ciprofloxacin	**20**	**18**	**17**	**18**

RESULT:

Based on the spectral data's like IR, Mass, and NMR it is confirmed that the newly synthesized compounds are formed successfully and were screened for their antimicrobial activity against two gram positive bacteria (Xanthomonas Citri and *Ervinia Carotovora)* and two gram negative bacteria(E.coli and Protease vulgerius) by using cup plate method. out of all synthesized compounds some of them compounds number 1,2,3,4 shows more antimicrobial activity show moderate activity. Zone of inhibition produced by each compounds was measured in mm.

CONCLUSION:

Synthesis of α,β-unsaturated carbonyl compounds was synthesized and their pharmacological screening like antimicrobial activity was done successfully.

Compounds with electron releasing group such as methoxy and ethoxy showed better antimicrobial activity than the others not having such groups. Compound have pharmacophore such as chloro, dichloro,nitro and bromo exhibited moderate antimicrobial activity.

Acknowledgement:

It is with great pleasure that I place on record a deep sense of gratitude and heartfelt thanks to my research guide Dr.Md.Rayees Ahmad (HOD). MPharm Shivlingeshwar College of Pharmacy Almala. for their help, support and constant encouragement throughout the progress of this research work. I am very thankful for giving me the opportunity to be a research student of him. It was really a great experience working under the guidance of him, which was of immense help in my project work without which it would have been an unachievable task.I thank and express my sincere gratefulness to our respected principal sir , Mr. Dharashive V. M. for his goodwill in granting me unlimited facilities for conducting the research. His friendly guidance and cooperation kept me going. I also owe my thanks to managing trustee of our institute for giving the Permission for M. Pharmacy, infrastructure and all other essential facilities and

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