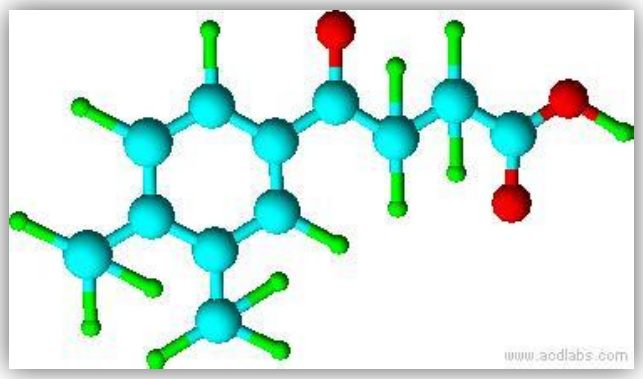
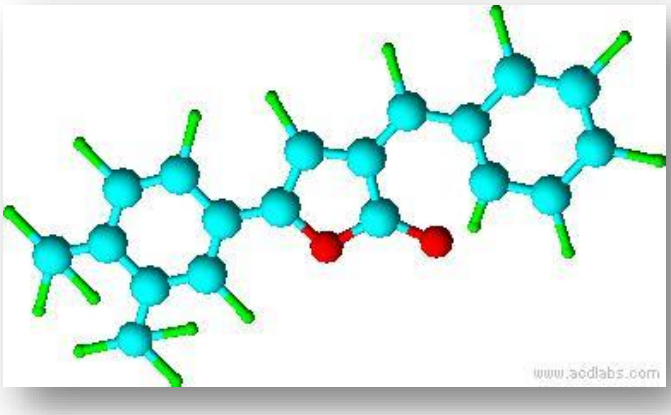
"SYNTHESIS OF 2(3*H*)-FURANONE DERIVATIVES FROM γ-OXOBENZENEBUTANOIC ACID DERIVATIVES"





GUIDE:
MS. SIDDHALI V. GIRKAR

BY:
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SCHOOL OF CHEMICAL SCIENCES, GOA UNIVERSITY

A project report entitled

"Synthesis of 2(3*H*) - furanone derivatives from γ-oxobenzenebutanoic acid derivatives"

Dissertation submitted to Goa University in partial fulfillment of the requirement for the degree of

MASTER OF SCIENCE
IN
CHEMISTRY

By

Monisha Nair
BSc

School of Chemical Sciences
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Taleigao Plateau
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INDIA

April 2020

STATEMENT

I hereby declare that the matter presented in this dissertation entitled **"Synthesis of 2(3*H*)- furanone derivatives from γ-oxobenzenebutanoic acid derivatives"** is based on the result of investigations carried out by me in the School of Chemical Sciences, Goa University under the supervision of **Ms. Siddhali V. Girkar** and the same has not been submitted elsewhere for the degree or diploma.

MONISHA NAIR
CH-18-048

CERTIFICATE

This is to certify that the dissertation entitled **"Synthesis of 2(3*H*)- furanone derivatives from γ-oxobenzenebutanoic acid derivatives"** is bonafide work carried out by Ms. Monisha Nair under my supervision in partial fulfillment of the requirements for the award of the degree of Master of Science in Chemistry at the School of Chemical Sciences, Goa University.

Ms. SIDDHALI . V. GIRKAR
Guiding Teacher
School of Chemical Sciences
Goa University

CERTIFICATE

This is to certify that the dissertation entitled **"Synthesis of 2(3*H*)- furanone derivatives from γ-oxobenzenebutanoic acid derivatives"** is bonafide work carried out by Ms. Monisha Nair under my supervision in partial fulfillment of the requirements for the award of the degree of Master of Science in Chemistry at the School of Chemical Sciences, Goa University.

Dean,
School of Chemical Sciences
Goa University

ACKNOWLEDGEMENT

It gives me an immense pleasure to present the project entitled **"Synthesis of 2(3*H*)-furanone derivatives from γ-oxobenzenebutanoic acid derivatives" .**

I extend my whole- hearted thanks to our project guide Ms. Siddhali V. Girkar, Assistant professor, School of Chemical Sciences, Goa University, for her valuable guidance and encouragement without which the project would not have been successfully executed.

My sincere thanks to Prof. V.S. Nadkarni, Dean of the School of Chemical Sciences, for providing all the necessary facilities for the dissertation work.

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Last but not the least, I wish to thank my parents for their moral support and financial assistance, without whom I would have not been able to pursue my studies. Their encouragement has given me a lot of confidence during the project work as it could successfully reach the completion.

Monisha Nair

CONTENTS

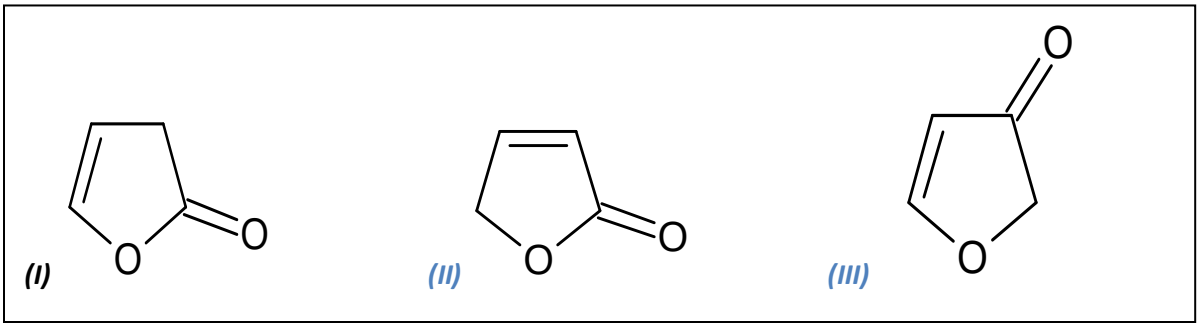
CHAPTER –I

INTRODUCTION

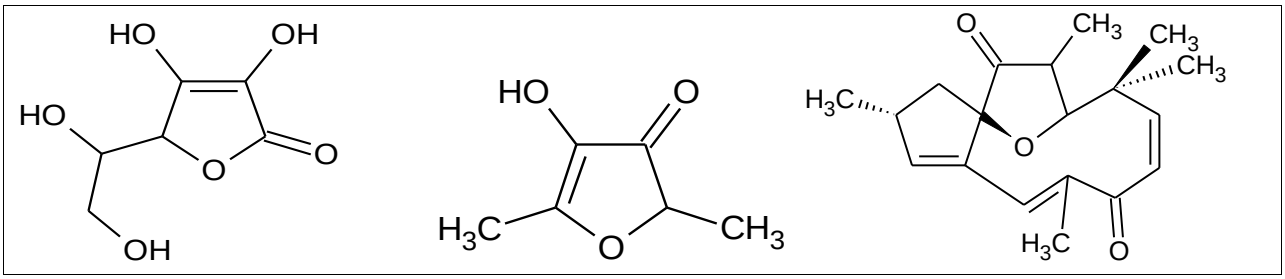
INTRODUCTION

Heterocycles form by far the largest of classical divisions of organic chemistry and are of immense importance biologically and industrially. The vital interest of the pharmaceutical and agrochemical industries in heterocycles is often connected with their natural occurrence. Heterocyclic nucleus is present as a core structural component in an array of drug categories such as antimicrobial, anti-inflammatory, analgesic, antiepileptic, antiviral, antineoplastic, antihypertensive, antimalarial, local anaesthetic, antianxiety, antidepressant, and antidiabetic, etc[1]. An important feature of the structure of many heterocyclic compounds is that it is possible to incorporate functional groups either as substituent or as a part of the ring system itself.

Furanones represent an interesting class of heterocyclic compounds, which constitute the central ring system of many of the natural products**.** They are derivatives of furan and, depending on structure, are divided into three main types: 2(3*H*)-furanones (I), 2(5*H)*-furanones (II), and 3(2*H*)-furanones(III).

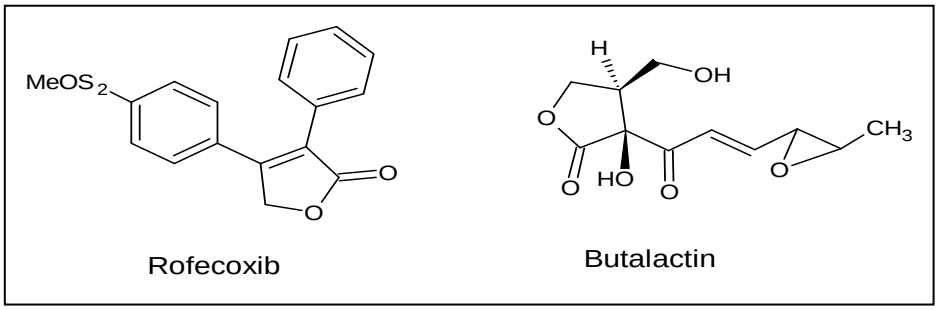


Systems (I) and (II) are unsaturated γ-Iactones known as 'butenolides'. Compounds of this type are also known as 'crotonolactones' based on the parent crotonic acid. On the other hand, (III) is a cyclic α,β-unsaturated ketone. The best known and most widely studied of naturally occurring furanones is ascorbic acid (vitamin C). For human beings, furanones are important, as they are major attractive components of many food flavors such as strawberry, pineapple, roasted meat, nuts, and soy sauce [2].



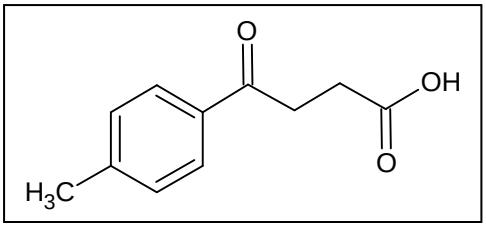
L- Ascorbic acid 2,5-Dimethyl-4-hydroxy-3(2*H*)-furanone Jatrophone

The efficacy of several butyrolactone derivatives against mycobacteria suggests that these structures could serve as a new template for tuberculosis drug development[3]. Among a wide variety of compounds that have been explored for developing pharmaceutically important antimicrobial agents, unsaturated γ-lactones have played an important role. Moreover, furanone ring derivatives (α,β unsaturated lactones) acquire a special place in natural chemistry and in heterocyclic chemistry, as the furanone system is a frequently encountered structural motif in many pharmacologically relevant compounds[4].There are marketed drugs using furanone rings, e.g., basidalin as anticancer, ascorbic acid as an antioxidant, narthogenin and butalactin as antibiotic, rofecoxib as a specific COX-2 inhibitor[5].



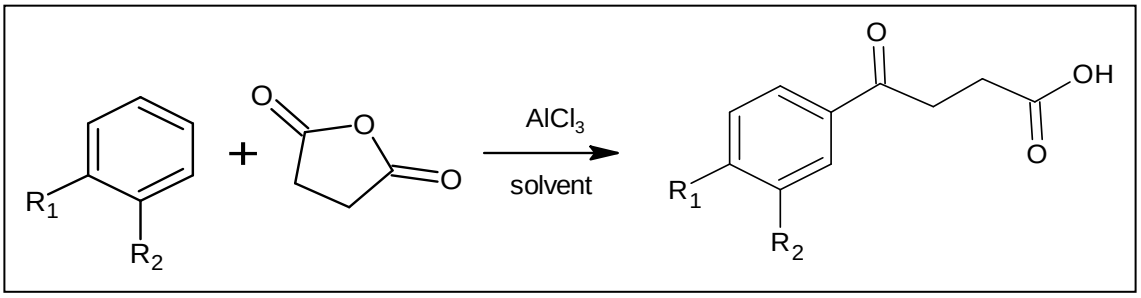
Rofecoxib Butalactin

Even the simpler butyrolactone, 3,3-diethylbutyrolactone, shows anticonvulsant activity.The reactivity of the γ -lactone ring present in furanone derivatives has been further exploited for the synthesis of nitrogen heterocycles of potential pharmacological interest.3-(4-Methylbenzoyl)propanoic acid is an example of the aroylpropanoic acid class of non-steroidal anti-inflammatory drugs (NSAIDs). Aroylpropanoic acids are good anti-inflammatory agents [6].



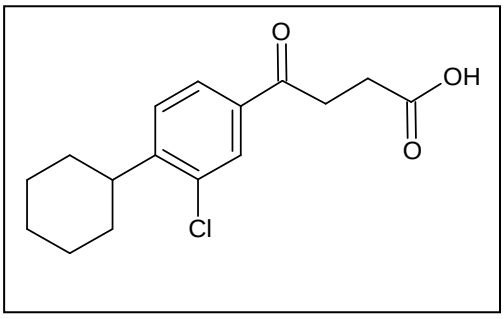
3-(4-Methylbenzoyl)propanoic acid

The structural moiety, **γ-oxobenzenebutanoic acid**, with suitable substitution on benzene nucleus and side chain is a useful structural moiety in the synthesis of several biologically active compounds such as fenbufen, bucloxic acid, menbutone, trepibutone, florantyrone,etc. The same moiety, γ-oxobenzenebutanoic acid, is also an important precursor for the preparation of aromatic lactones in organic synthesis. Among the γ-oxobenzenebutanoic acid analogues, fenbufen occupies a special place due to its biological activity. Fenbufen is a non-steroidal antiinflammatory drug (NSAID), used to relieve the pain, stiffness, and inflammation that may accompany a number of disorder.

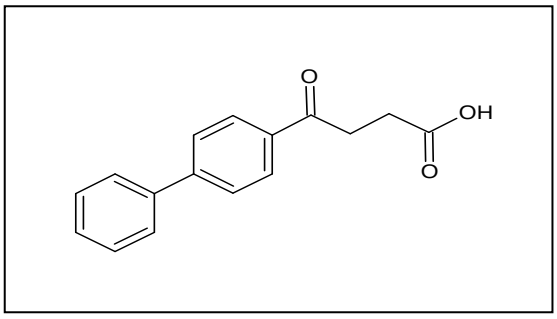


γ-Oxobenzenebutanoic acid analogues are generally prepared using Friedel-Crafts acylation of the corresponding aromatic hydrocarbon with succinic anhydride. Although Friedel-Crafts reaction of succinic anhydride with toluene using Lewis acid reagents such as aluminum chloride is known in the literature, the procedure has its own disadvantages.

Disadvantages. The literature procedures uses carcinogenic solvents such as benzene. The isolation of the material is also cumbersome , involves azeotropic distillation and high-temperature operations. The material is generally isolated in low yields and also requires multiple extractions with organic solvents[7] .



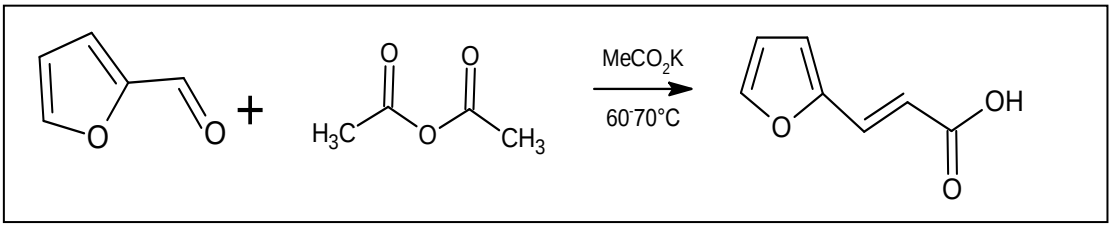
BUCLOXIC ACID



FENBUFEN

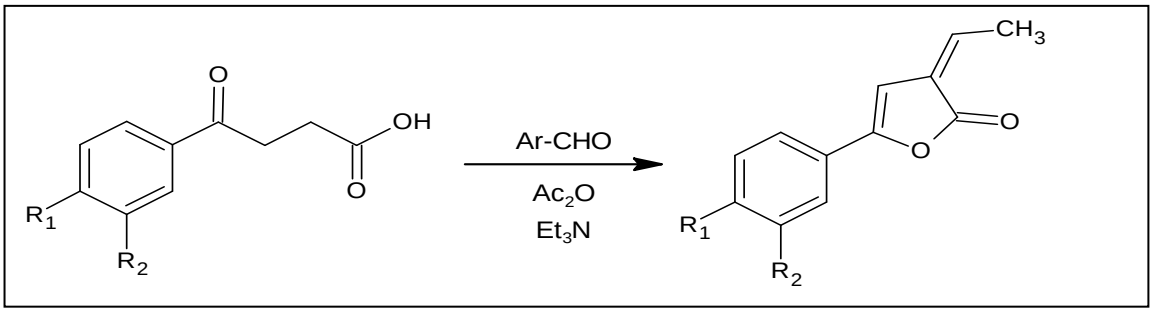
PERKIN REACTION:

Perkin reaction involves the condensation of acidic anhydride and aldehyde in the presence of weak base (i.e., Sodium and potassium salt of the acid or trimethylamine) to give unsaturated carboxylic acid.



In 1968 Perkin described the very first example of such type condensation reaction, involve the synthesis of coumarin by condensing the sodium or potassium salt of salicylaldehyde with acetic anhydride. In 1883 a very important variation was done by Plöchl, which involve the heating of benzaldehyde and hippuric acid in presence of acetic anhydride. Erlenmeyer determined the Azalactone structure of the product and extended the scope of Perkin reaction to other aldehydes (Erlenmeyer Azalactone synthesis)[8] .

This modified perkin reaction can be applied to the synthesis of substituted 2(3*H)*-furanones by reacting aromatic aldehydes with γ-oxobenzenebutanoic acid derivatives in presence of acetic anhydride and triethylamine acting as a base.



The mechanism basically involves formation of anhydride enolates and aldol type condensation. Recently, many results have been published showing that the initial condensation at least in presence of trimethylamine, may not be only aldol type but also indicate a pathway involving the formation and subsequent cycloaddition of ketene to form a β-lactone intermediate that breaks to give the cinnamic acid[8].

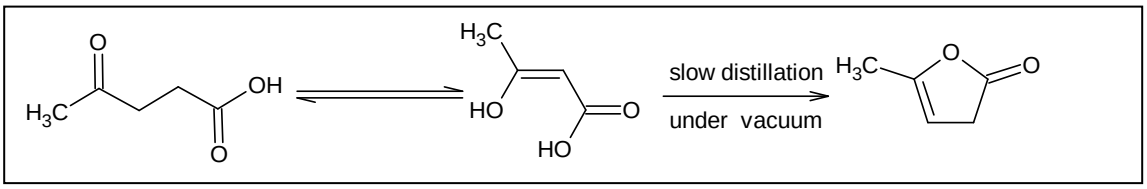
CHAPTER - II

LITERATURE REVIEW

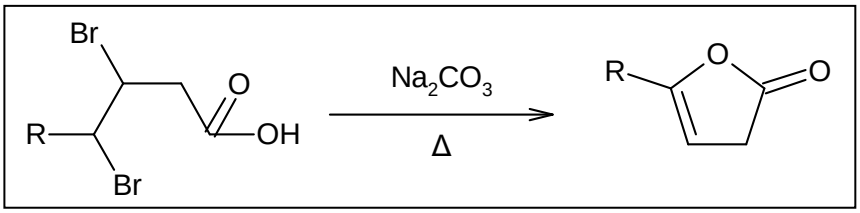
LITERATURE REVIEW

Among butenolides, 2(3*H)*-furanones are most widely employed as useful synthetic units for C-C bond formation and introduction of functional groups. Various methods for the preparation of these lactones are well known of which some of them are listed below:

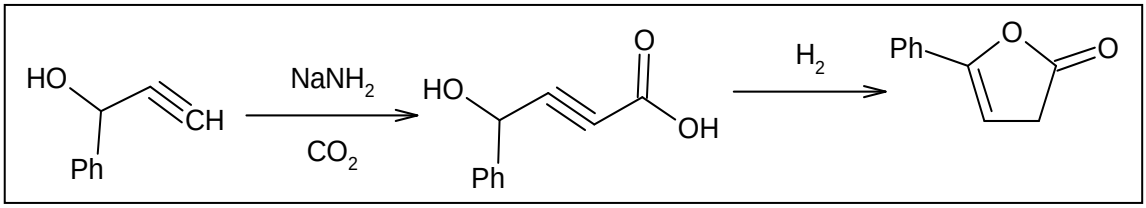
- From γ-Keto Acids: One of the common methods for the synthesis of 2(3*H*)-furanone involves the intramolecular dehydration of the corresponding γ-keto acids. Levulinic acid which can enolise readily, gives uangelica lactone on slow distillation. The cyclisation can also be effected by heating with acetic anhydride, acetyl chloride or a mixture of acetic anhydride and sulphuric acid.



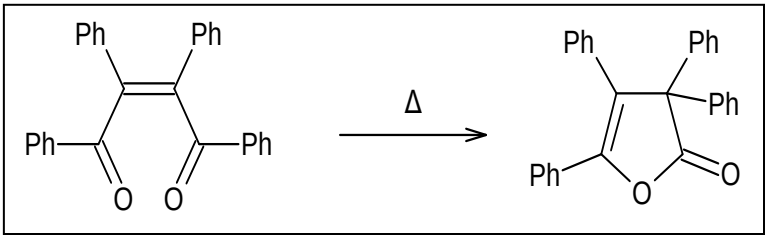
- From β,γ-Dibromo Acids: 2(3*H)*-Furanones can be prepared from β,γ-dibromo acids by treating with water or sodium carbonate solution. The reaction proceeds through a hydrolysis - cyclisation - dehydrobromination sequence to give the furanone product. Thermal decomposition of 4 in presence of quinoline also led to the formation of these furanones.



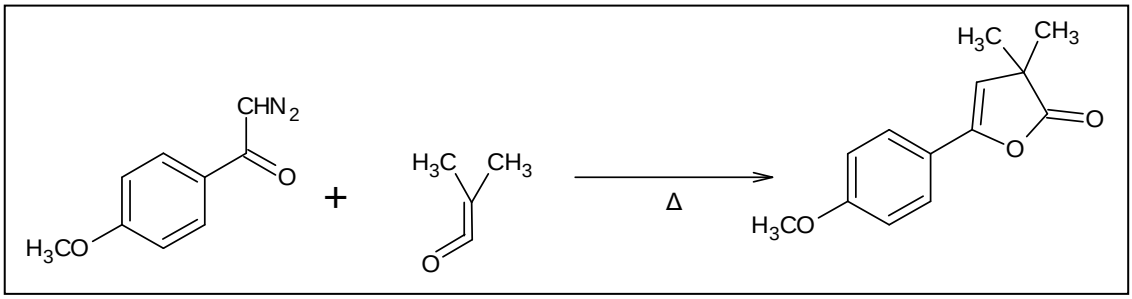
- From Acetylenic Acids:Nineham et al. in 1949 have reported the synthesis of 2(3*H*)-furanones from acetylenic acids. Carboxylation of phenylethynylcarbinol in presence of sodamide gives 4-hydroxy-4-phenylbut2-ynoic acid. Upon hydrogenation, gives the corresponding 2(5*H*)-furanone, which isomerizes to 5-phenyl-2(3*H*)-furanone.



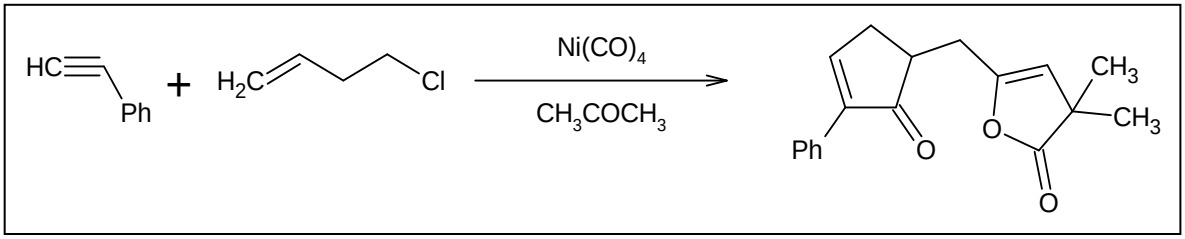
- Thermal Rearrangement of Dibenzoylalkenes: Dibenzoylalkenes undergo bond reorganization process thermally to give corresponding 2(3*H*)-furanones. This remarkable rearrangement was first observed by Zenin in 1872 when he established that pyrolysis of cis dibenzoylstilbene led to the formation of tetraphenylcrotonolactone.



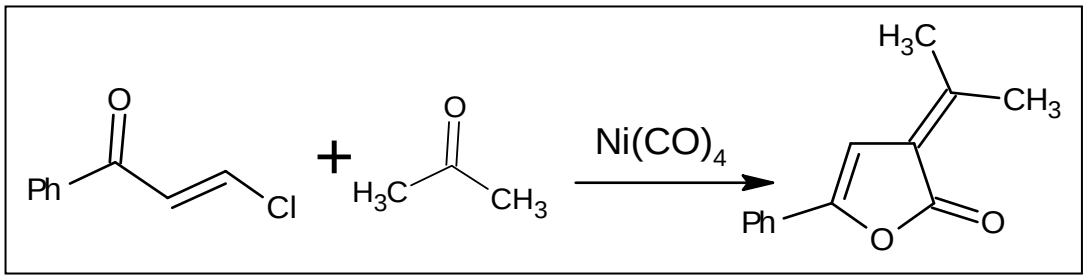
- From Diazoketones and Ketene Derivatives: The reaction of diazoketones with ketenes in ether in N_2 atmosphere at room temperature has reported to give 2(3*H*)-furanones through 1,3-cycloaddition. Dimethyl ketene on reaction with substituted diazoketones gives corresponding 2(3*H*)-furanone.



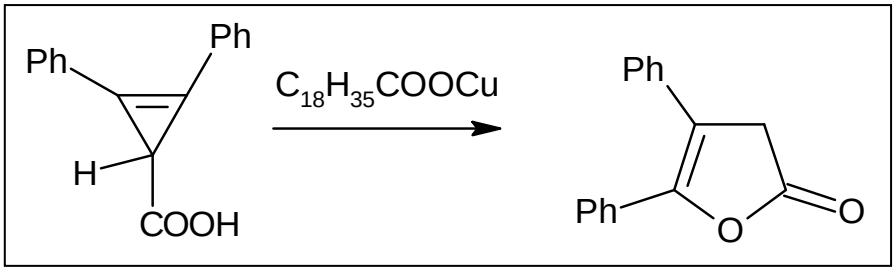
- Metal Carbonyl Catalysed Reactions: Chiusoli and coworkers reported the synthesis of2(3*H*)-furanones from phenyl acetylene and allyl halides in presence of nickel tetracarbonyl in acetone .



In an alternate method allyl halides are treated with acetylene and carbon monoxide in the presence of nickel chloride and Mn-Fe alloy. The yield of lactones is about 25 %. In a more recent method, ß-chlorovinylphenyl keton has been reacted with acetone, with $Ni(CO)_4$ added as a catalyst.

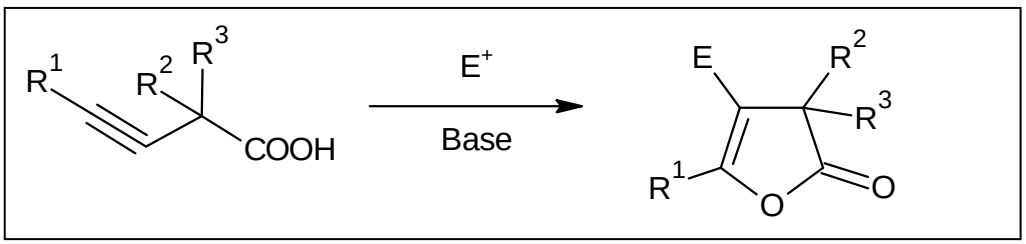


- From Cyclopropane Derivatives: When 2,3-diphenyl-2-cyclopropene-1-carboxylic acid is heated in benzene in the presence of a catalytic amount of copper stearate, it rearranges to give β,γ-diphenyl-$\Delta^{\beta,\gamma}$-butenolide[2],[9].



- By electrophilic cyclization of 3-alkynoate esters and acids:

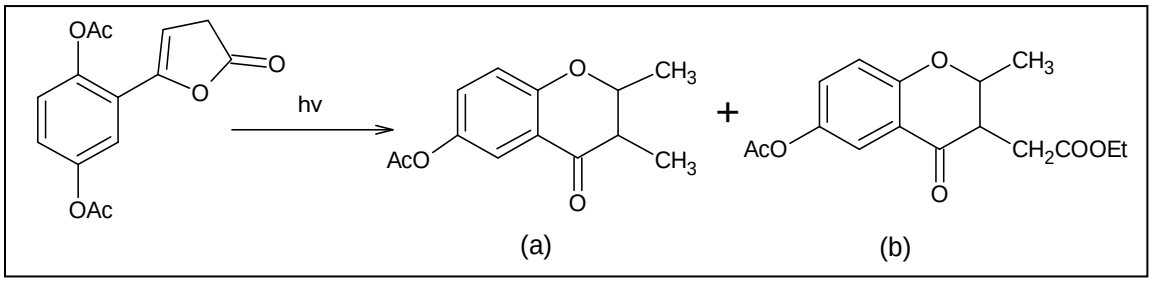
It is basically the cyclization of the 3-alkynoate esters proceed by coordination of the carboncarbon triple bond to the electrophile, followed by nucleophilic attack by the oxygen of the carbonyl group of the ester to produce an intermediate A, which undergoes removal of the alkyl group of the ester group via SN_2 displacement by nucleophiles present in the reaction mixture[10].



PHOTOCHEMISTRY OF 2(3*H*) –FURANONES:

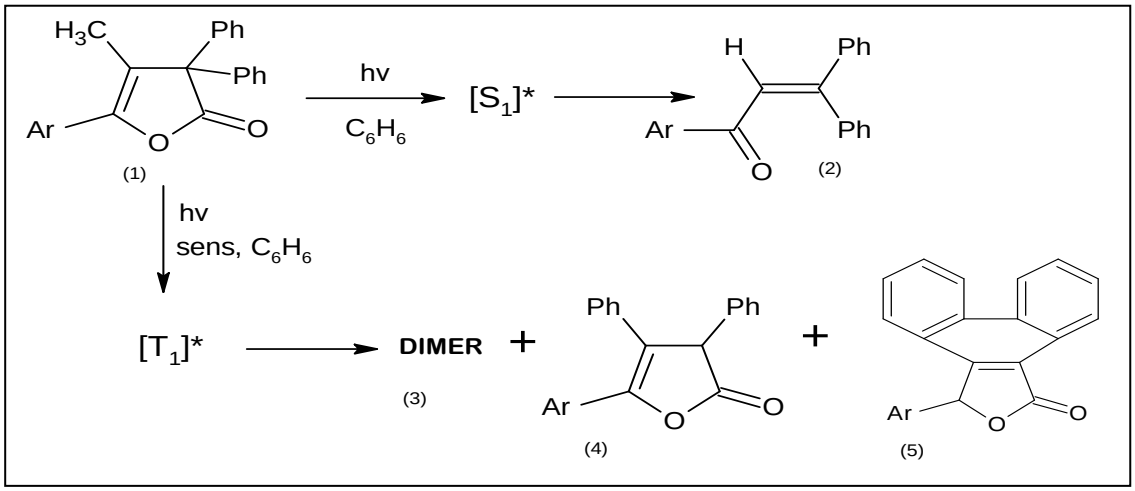
The photochemistry of lactones has been extensively investigated over the last few years. Photochemical behaviour of unsaturated lactones is largely dependent on the double bond location. Although ring opening of α,β-unsaturated lactones is possible upon irradiation in vapour phase, their condensed phase photochemistry can be related to that of the enone system, the ring remaining intact. In contrast to this behaviour, the breaking of the lactonic O-CO bond is the main primary photoprocess in enol lactones.

Irradiation of 5-(2',5'diacetoxy- phenyl)-2(3*H*)-furanone afforded the corresponding chromones (a) and (b). Chromone formation can be rationalized by assuming that the cleavage of the lactonic O-CO bond is also the primary photochemical step in these o-acetoxyaryl furanones[11].



Direct photolysis of solutions of substituted 2(3*H*)-furanones (1) in benzene gave the decarbonylation products l-aryl-3,3-diphenyl- prop-2-en-1-ones(2) in high yields (87-96%).When the photolysis was performed in benzene in the presence of p-methoxyacetophenone, rearrangement products resulting from $C_3 \longrightarrow C_4$ phenyl group migration (that is, 5-aryl- 3,4-diphenyl-2(5*H*)-furanones,) (4)as well as 3-aryl- phenantrho[9,10-c]furan-l(3*H*)-ones (5) were obtained in 12-52 % and 9-40% yields, respectively. Photodimers (3) were also obtained under sensitized irradiation conditions. Except for the photodimers, the structures of the products were established by spectral data and compared with authentic samples prepared through well- defined routes. The spectral characterization of the dimers was not possible because of their insolubility in suitable solvents. Apparently, these are products of (2 + 2) $\longrightarrow$ 4 reactions from the triplet states of 2(3*H*)-furanones.

The radical center at the C_5 position in the intermediate produced as a result of $C_3 - C_4$ phenyl group migration is expected to be stabilized by both electron-withdrawing and -releasing groups at the para position of the phenyl group at this position[12].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Ph
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(1)
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C6H6
[S1]*
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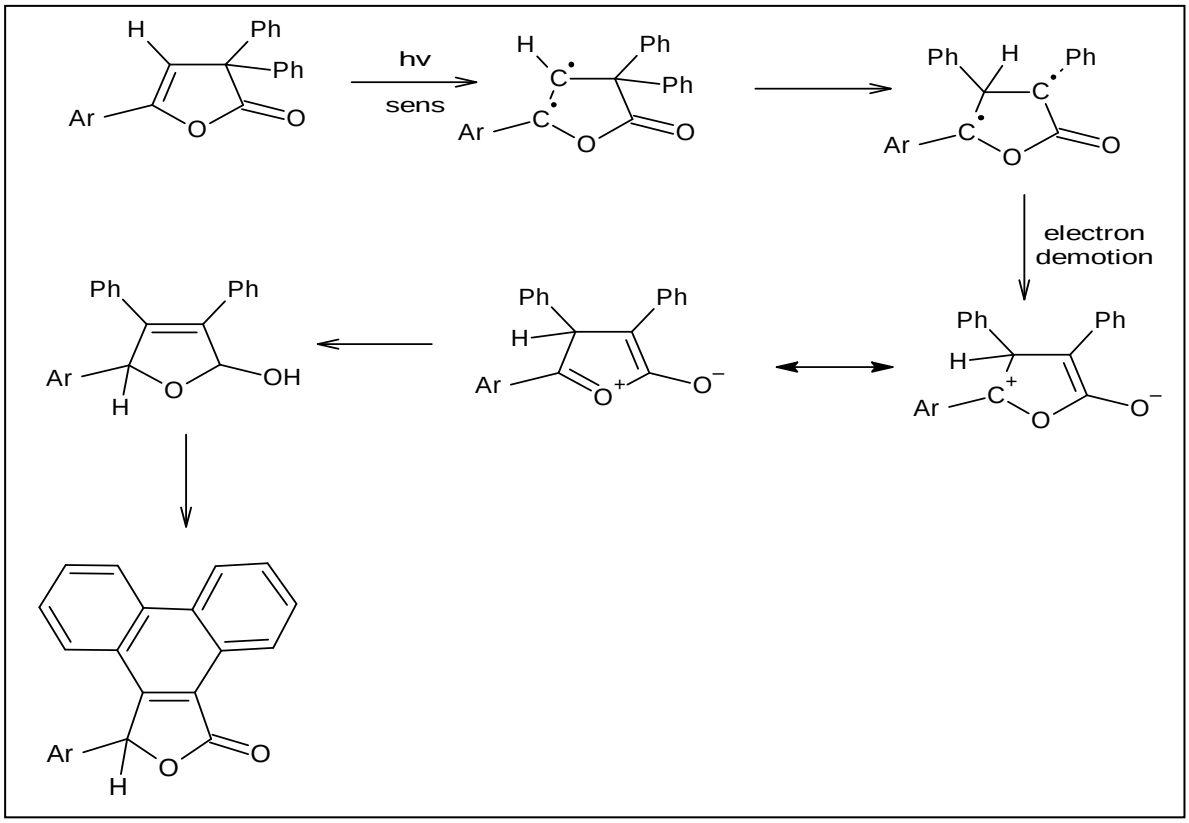
Mechanism: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O−
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OH
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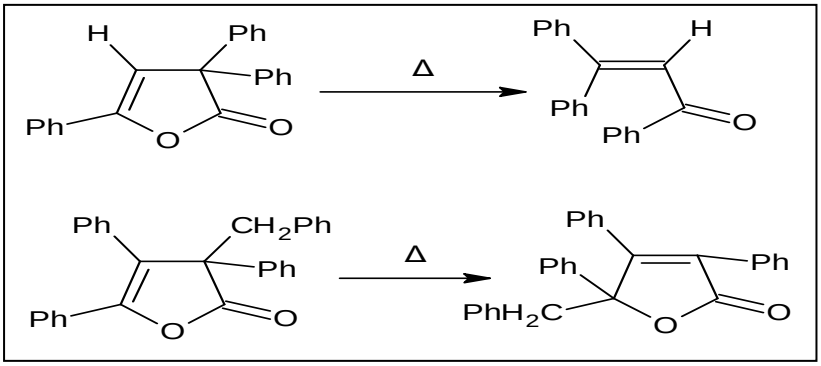
H

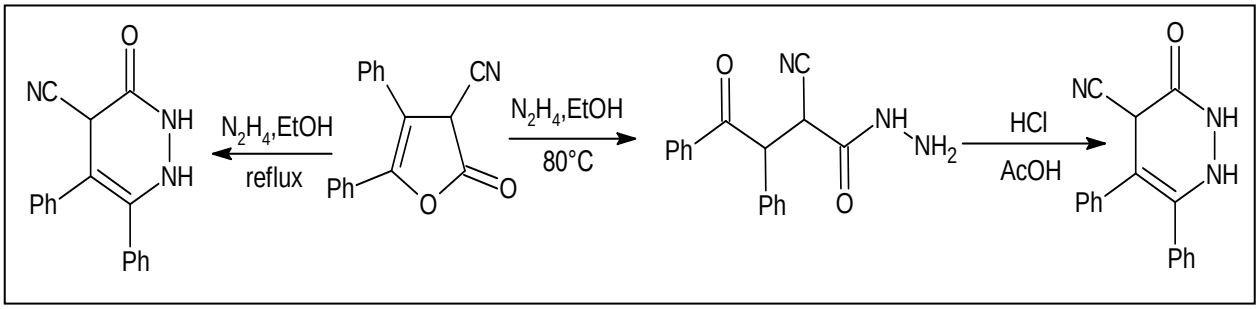
Thermal Transformations:

In contrast to the photochemical transformation, the thermal transformations of 2(3*H*)-furnanones lead to decarbonylation products and, in some cases, rearrangement products, arising through a [1,3]sigmatropic shift of the substituent groups[2].

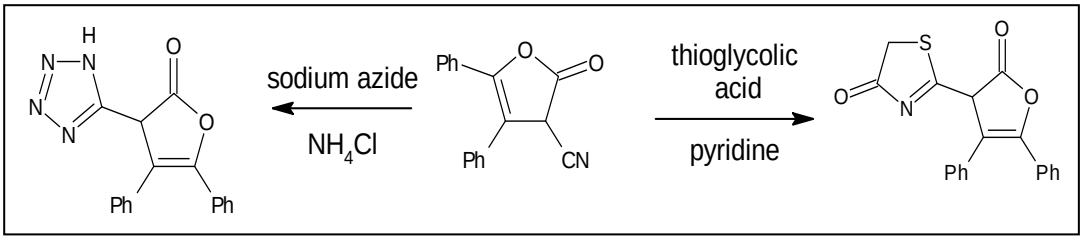


Other reactions 0f 2(3H) furanones:

2(3*H*)-Furanone with hydrazine hydrate in ethanol at 80°C undergoes ring opening to give the open chain hydrazide(propionic acid hydrazide) , and with hydrazine hydrate in refluxing ethanol it gave pyridazinone derivative. When the hydrazide was reacted with hydrochloride/AcOH mixture it led to the ring closure to give the pyridazinone[13].



The presence of cyano group at position-3 in the 2(3*H*) furanones is used to construct thiazolidinone and tetrazole rings at this position. Thus 2 (3*H*) furanone reacted with thioglycolic acid gives the thiazolidinone derivatives . The tetrazolyl derivatives were obtained by reacting the 2(3*H*)- furanones with sodium azide in the presence of ammonium chloride[13].



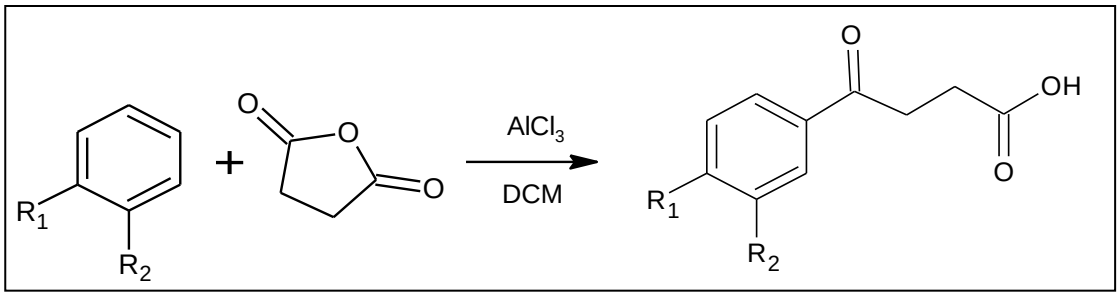
CHAPTER - III

PRESENT WORK

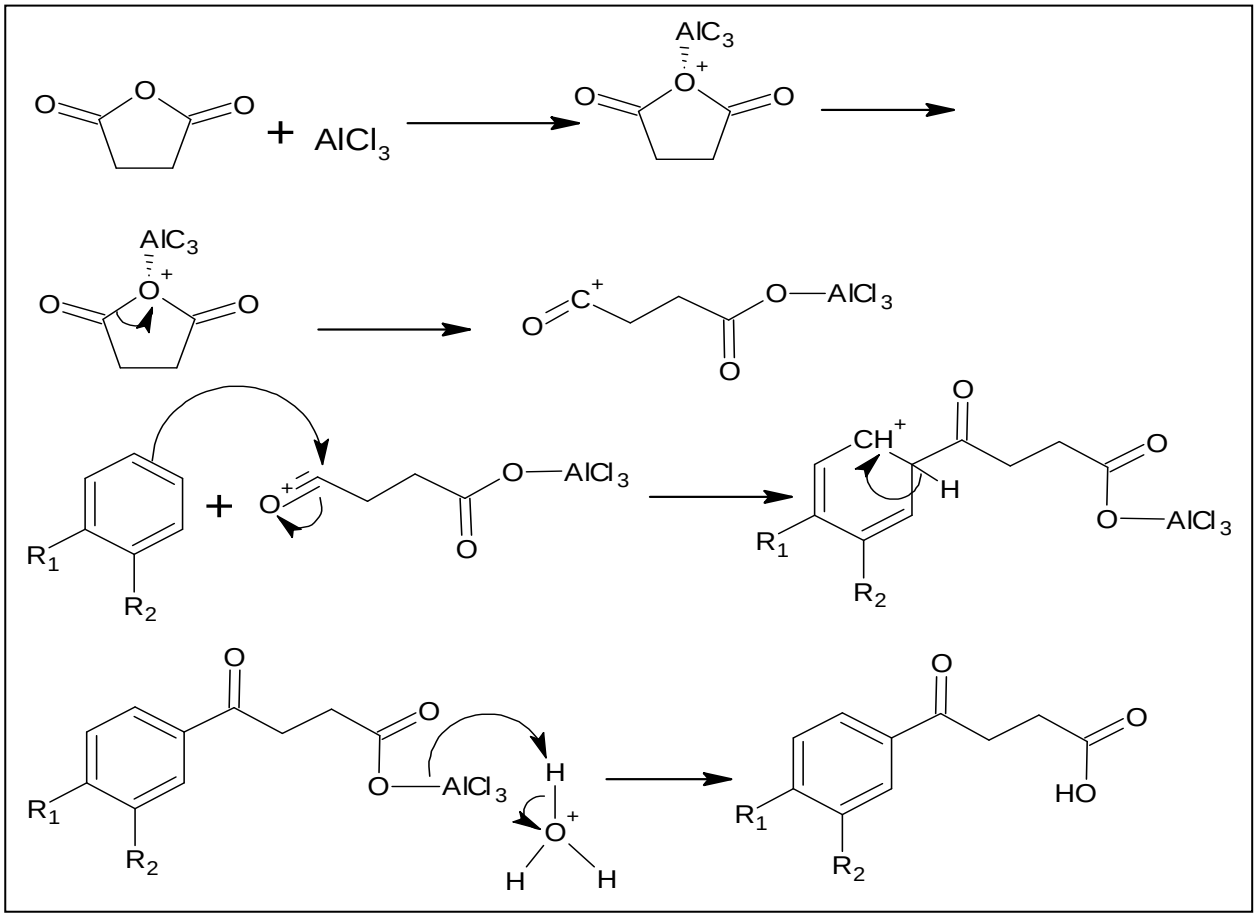
Step I:

Synthesis of γ-oxobenzenebutanoic acid derivatives:

By employing Friedel crafts acylation reaction , few derivatives of γ-oxobenzenebutanoic acid were prepared using succinic anhydride . Aromatic compounds such as Toluene , Xylene , Anisole , Biphenyl and Chlorobenzene were used and the reaction mixture was stirred for 24 hours at room temperature .



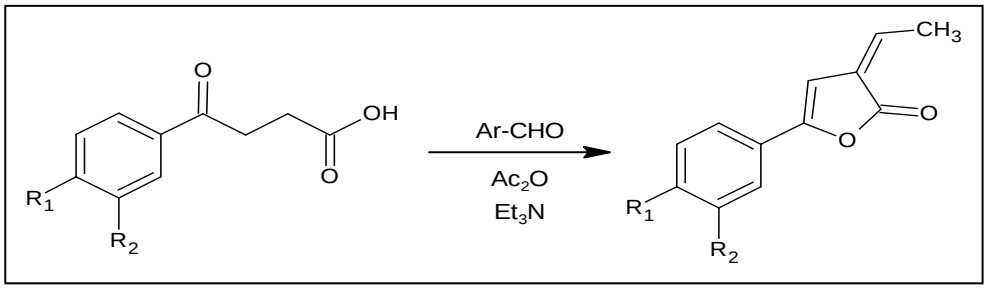
MECHANISM



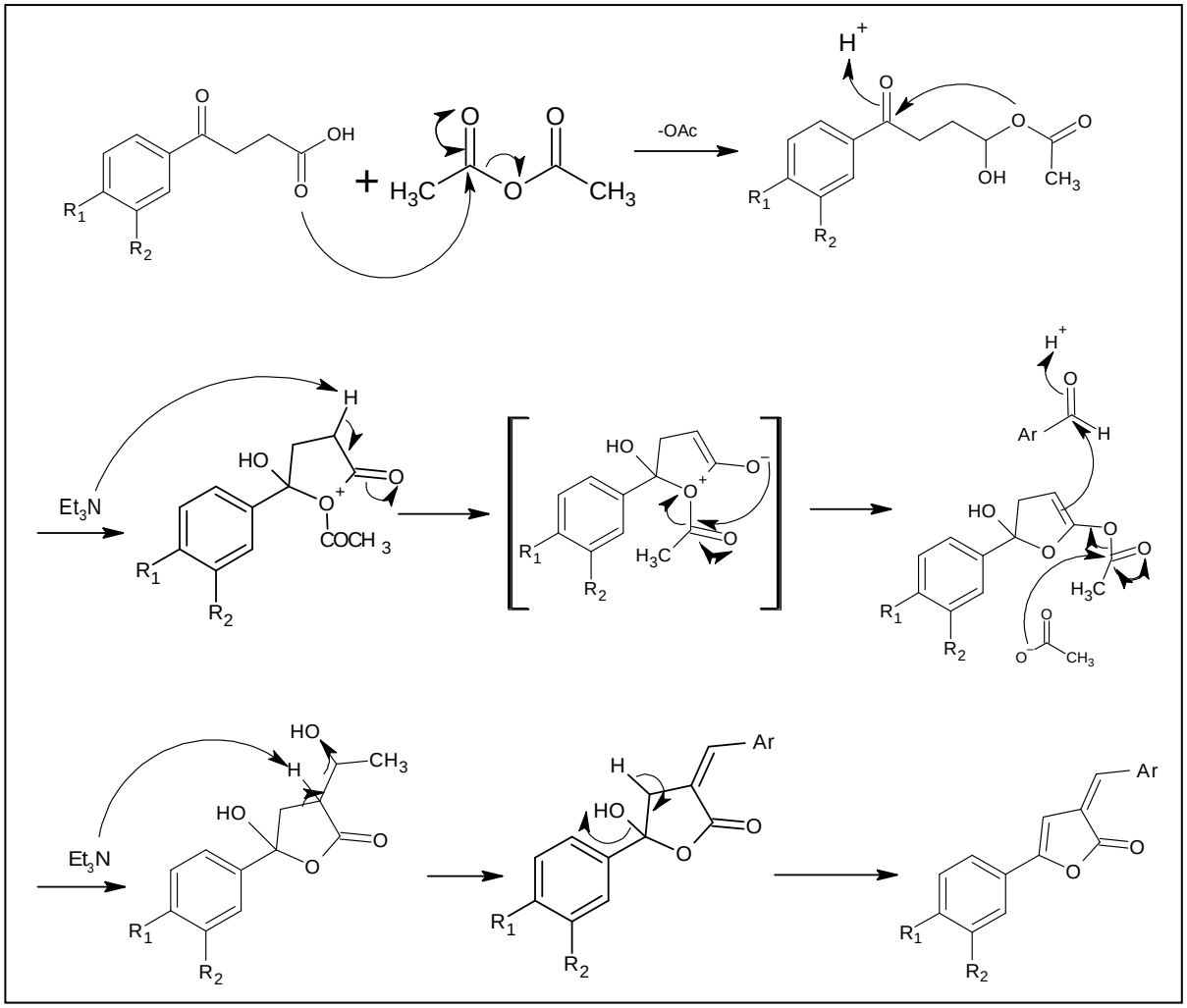
Step II :

Synthesis of 3-arylidines-5-(4'-disubstituted phenyl)-2(3*H*)-furanones;

By employing Perkin reaction few derivatives of 3-arylidine-5-(4' substituted phenyl)-2(*3H*)-furanones were prepared. Three different aldehydes namely banzaldehyde, p-dimethylaminobenzaldehyde and 4- chlorobenzaldehyde were reacted with acetic anhydride and triethylamine to give the desired product.[5]



MECHANISM



CHAPTER - IV

EXPERIMENTAL WORK

EXPERIMENTAL WORK

Step I,

Synthesis of γ-oxobenzenebutanoic acid derivatives:

Scheme A

In a round bottom flask 1g (0.0104 mol) of succinic anhydride was taken and to it 6.5mL (0.061 mol) of dry toluene was added. To the round bottom flask a reflux condenser was fit with a attached calcium guard tube. The reaction was supported over a water bath, and to it 3.2g (0.024 mol) of $AlCl_3$ was added in small portions. The contents were refluxed for about 30 minutes. The mixture was poured in a beaker containing crushed ice and to it 50% HCl was added. The solid compound thus obtained was filtered using Büchner funnel. The filtered compound was washed with dilute HCl and dried .The compound was recrystallized from boiling water and the melting point was determined.

Scheme B

In a round bottom flask 1g (0.1 mol) of succinic anhydride was mixed with 4mL (0.3680 mol) of anisole . The flask was kept in a ice bath . 3g (0.224 mol) of powdered $AlCl_3$ was added in small quantities with constant shaking . A vigorous reaction set in. Once the solution color turned red , the flask was fitted with a air condensor with a calcium chloride guard tube at the top. It was left at room temperature for about 24 hours with stirring. The contents were then poured in a beaker containing 10mL of ice cold HCl . The product obtained was filtered using a büchner funnel and washed with cold water .It was then dissolved in sodium bicarbonate solution by boiling and a small quantity of charcoal was added .This was then filtered. The filtration on acidification gave the crude sample of oxo-acid. It was then recrystallized from boiling water and dried. The melting point of the recrystallized compound was determined.

Step II,

Synthesis of 3-arylidines-5-(4'-disubstituted phenyl)-2(3*H*)-furanones:

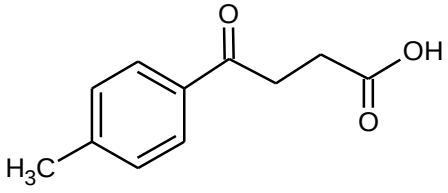
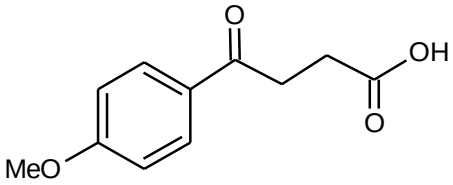
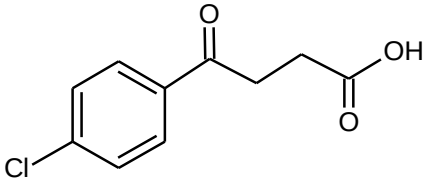
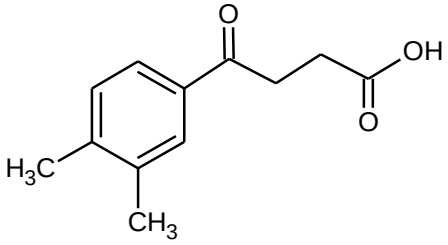
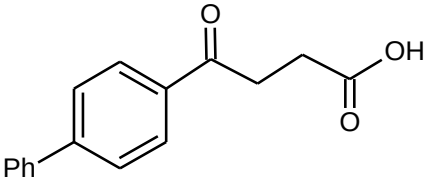
In a round bottom flask, (3.0mmol) γ-oxobenzenebutanoic acid and equimolar of aromatic aldehyde (3.0 mmol) in 5 drops of acetic anhydride were fused together. Then 2 drops of triethylamine was added to it and the contents were refluxed for about 15-20 minutes. A colored solid mass was formed which as then further crystallized from a mixture of methanol/chloroform (1:1).

CHAPTER -V

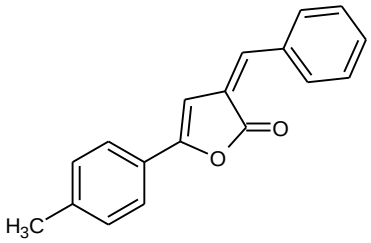
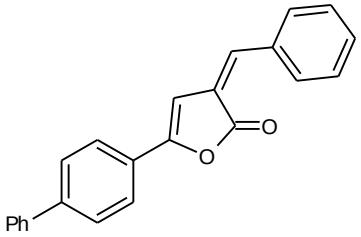
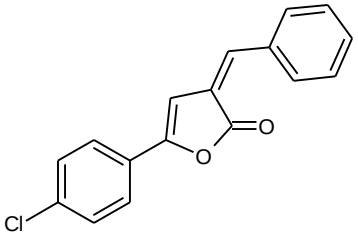
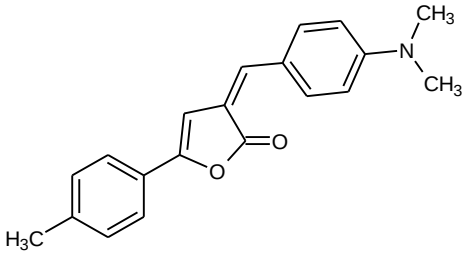
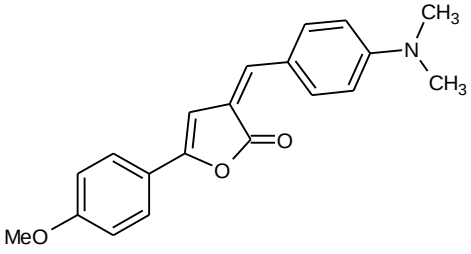
RESULTS AND DISCUSSION

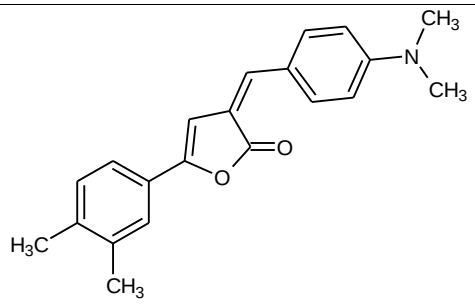
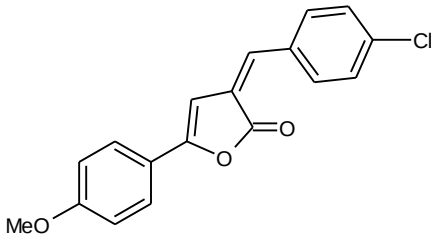
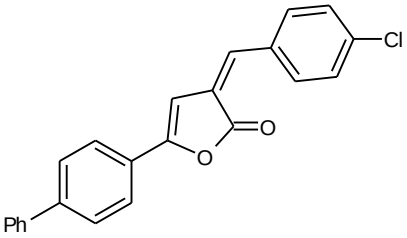
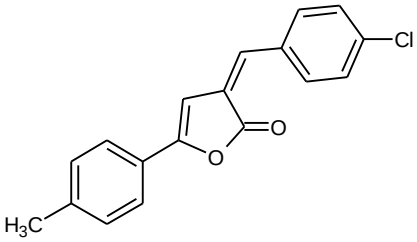
RESULTS AND DISCUSSION

γ-oxobenzenebutanoic derivatives were prepared by carrying out Friedel Crafts reaction. In scheme B, DCM was used as a solvent when the aromatic compound used was solid. The formation of the product was confirmed by performing TLC and by determining the melting point. In total 5 acids were prepared as listed below;

Sr . No.	NAME	STRUCTURE	MELTING POINT	YIELD
1	3-(4-methylbenzoyl)-propanoic acid		128℃-130℃	38.2%
2	3-(4-methoxybenzoyl)-propanoic acid		148℃-150℃	72.11%
3	3-(4-chlorolbenzoyl)-propanoic acid		116℃-118℃	41.83%
4	3-(3,4-dimethyllbenzoyl)-propanoic acid		120℃-122℃	81.5%
5	3-(4-phenylbenzoyl)-propanoic acid		180℃-182℃	68.6%

Synthesis of 2(*3H*)-furanone was achieved by employing Perkin condensation. The reaction was carried out without any solvent by just fusing the reactants together for few minutes, followed by addition of triethylamine. The contents were then refluxed for about 20 minutes, thus making it less time consuming. The formation of the product was confirmed by performing the TLC. In total 9 furanone derivatives were prepared as listed below;

Sr . No.	**NAME**	**STRUCTURE**	**MELTING POINT**	**YIELD**
1	3-benzylidene-5-(4-methylphenyl) 2(3*H*)furanone		92℃-94℃	26.66%
2	3-benzylidene-5-([1,1'-biphenyl]-4-yl)-2(3*H*)furanone		-	-
3	3-benzylidene-5-(4-chlorophenyl) -2(3*H*)furanone		208℃-210℃	61.66%
4	3-[4-dimethylaminobenzylidene]-5-(4-methylphenyl) -2(3*H*) furanone		194℃-196℃	40.17%
5	3-[4-dimethylaminobenzylidene]-5-(4-methoxyphenyl)-2(3*H*) furanone		170℃-172℃	55.1%

6	3-[4-dimethylaminobenzylidene]-5-(3,4-dimethylphenyl) -2(3*H*) furanone		188℃-190℃	34.68%
7	3-[4-chlorobenzylidene]-5-(4-methoxyphenyl) -2(3*H*)furanone		230℃-232℃	21.1%
8	5-([1,1'-biphenyl]-4-yl)-3-[(4-chlorobenzylidene] -2(3*H*)furanone		-	
9	3-[(4-chlorobenylidene]-5-(4-methylphenyl) -2(3*H*) furanone		-	

CHAPTER – VI

CONCLUSION

CONCLUSION

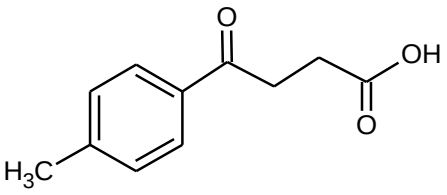
I have tried to carry out a simple, inexpensive and environmentally benign synthesis of derivatives of 2(*3H*)-furanones. The literature procedure makes use of carcinogenic solvents like benzene in Friedel-crafts reaction. I have used dichloromethane as a solvent which is less toxic for few reactions, while the other reactions were carried out without any solvent.

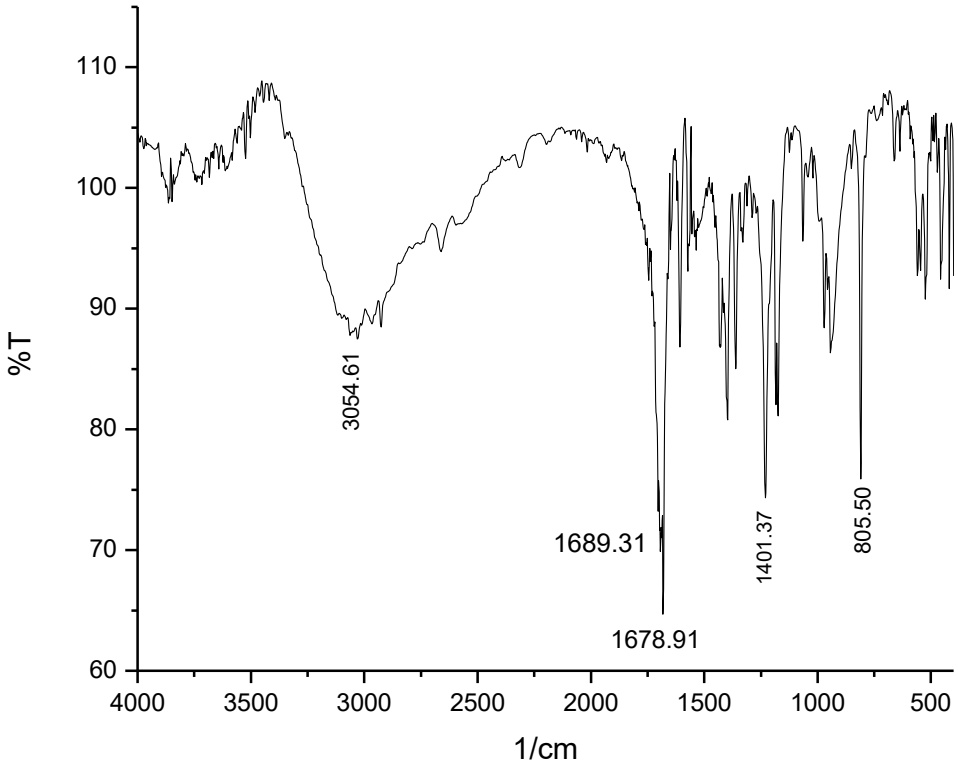
I have tried to carry out the Friedel-Crafts acylation on few representative aromatic compounds like toluene, anisole, xylene, biphenyl and chlorobenzene with succinic anhydride. I have successfully isolated 5 different derivatives of γ-oxobenzenebutanoic acid derivatives. The formation of the product was confirmed by TLC. 4 of the acids were characterized by IR spectroscopy. Compound containing electron withdrawing group like chlorine showed low yield, whereas those with electron donating group like methoxy, phenyl, etc. showed moderate good yield. As the γ-oxobenzenebutanoic acid analogues are known for their biological activity , this derivatives can be further subjected for biological evaluation. By employing modified Perkin reaction . I have tried to synthesize 9 different derivatives of 2(*3H*)-furanones. Out of which 6 furanones were characterized by IR spectroscopy. These can be also be further subjected for biological evaluation.

CHAPTER -VII

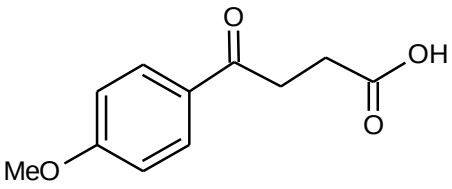
SPECTRAL ATTACHMENTS

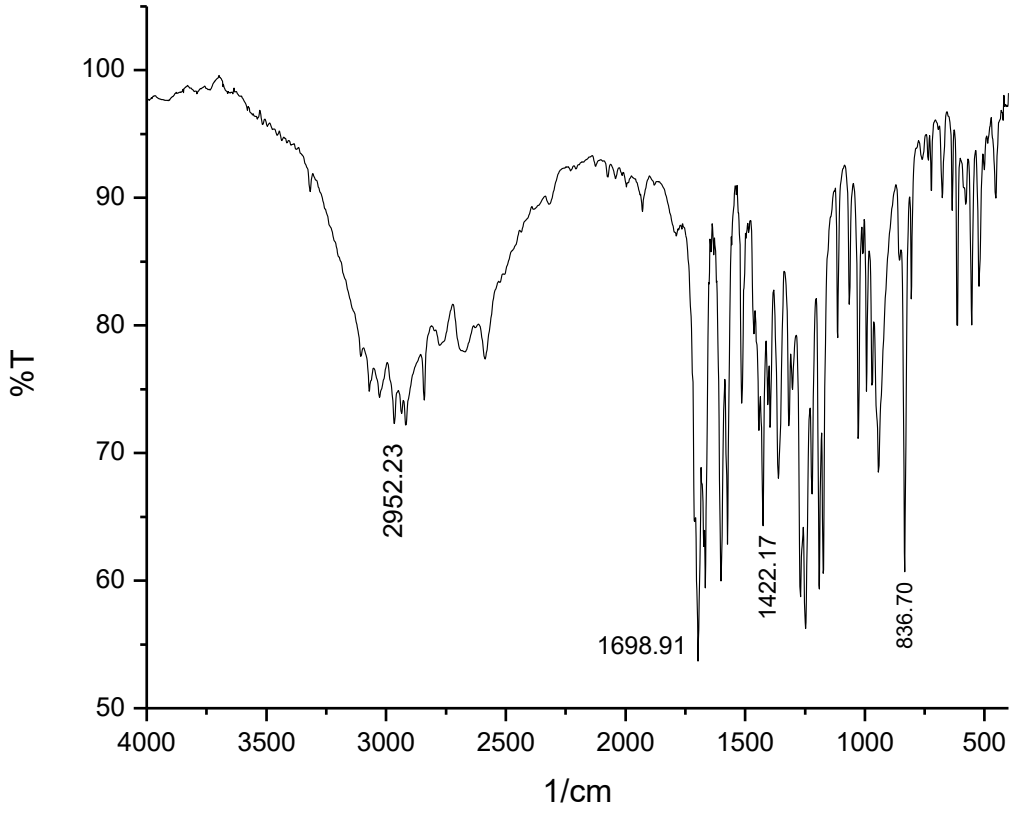
1] **<u>3-(4-methylbenzoyl)-propanoic acid</u>**



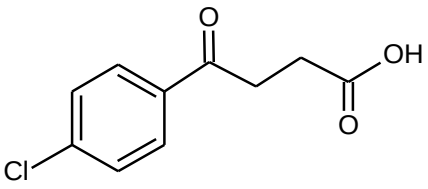


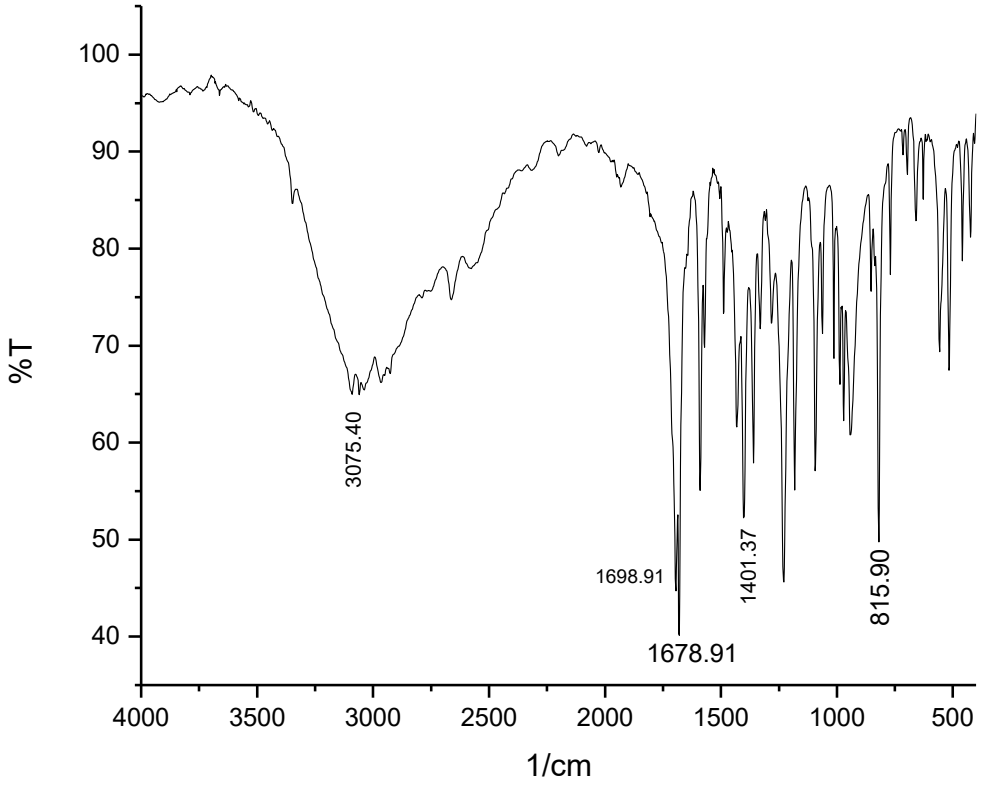
2] **3-(4-methoxybenzoyl)-propanoic acid**



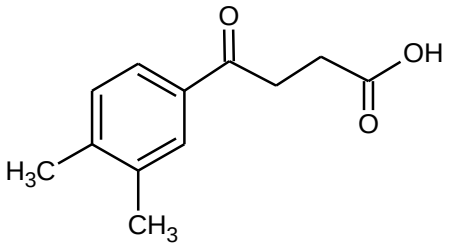


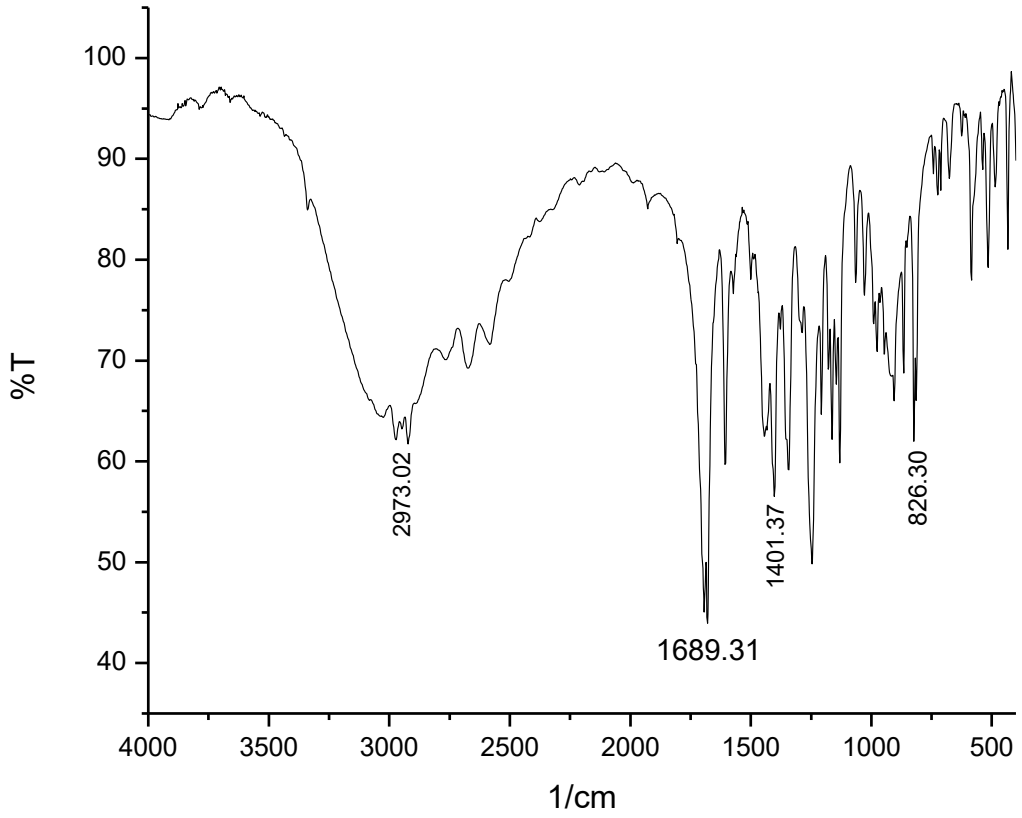
3] 3-**(4-chlorolbenzoyl)-propanoic acid**



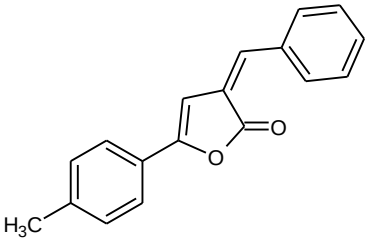


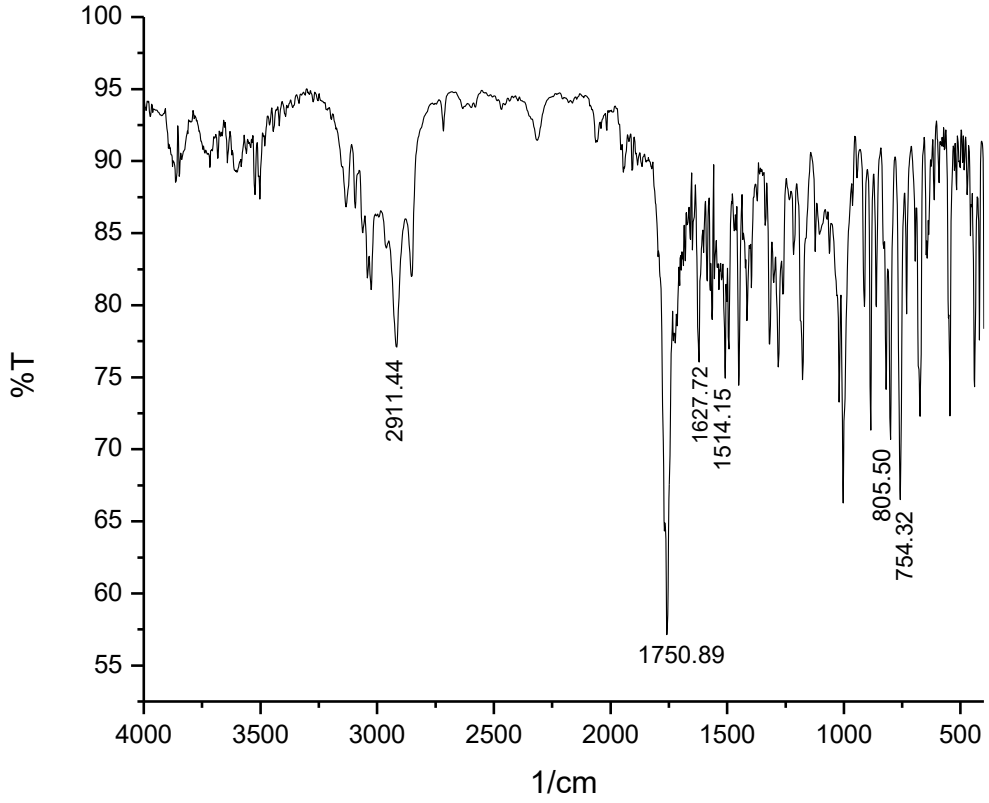
4] **3-(3,4-dimethyllbenzoyl)-propanoic acid**



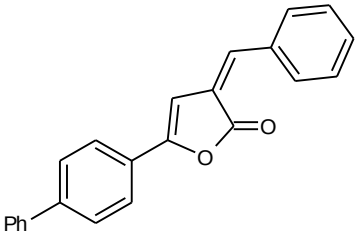


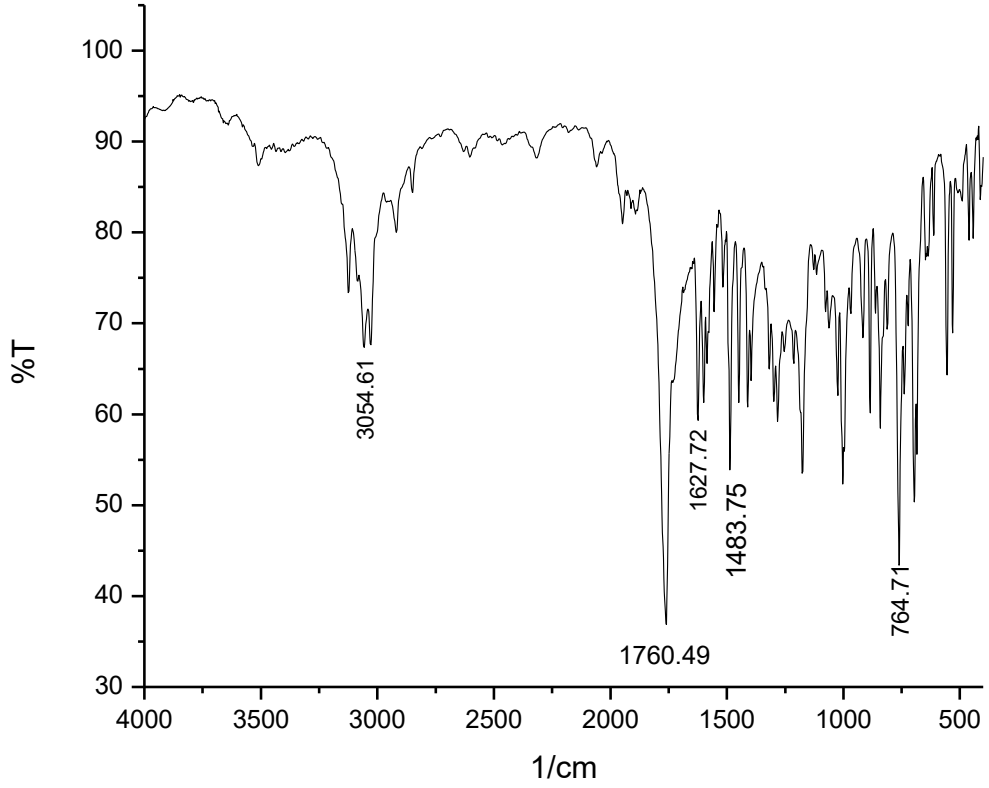
5] **3-benzylidene-5-(4-methylphenyl) 2(3*H*)furanone**



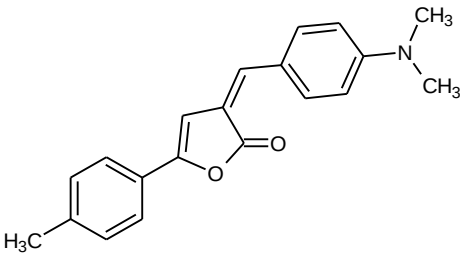


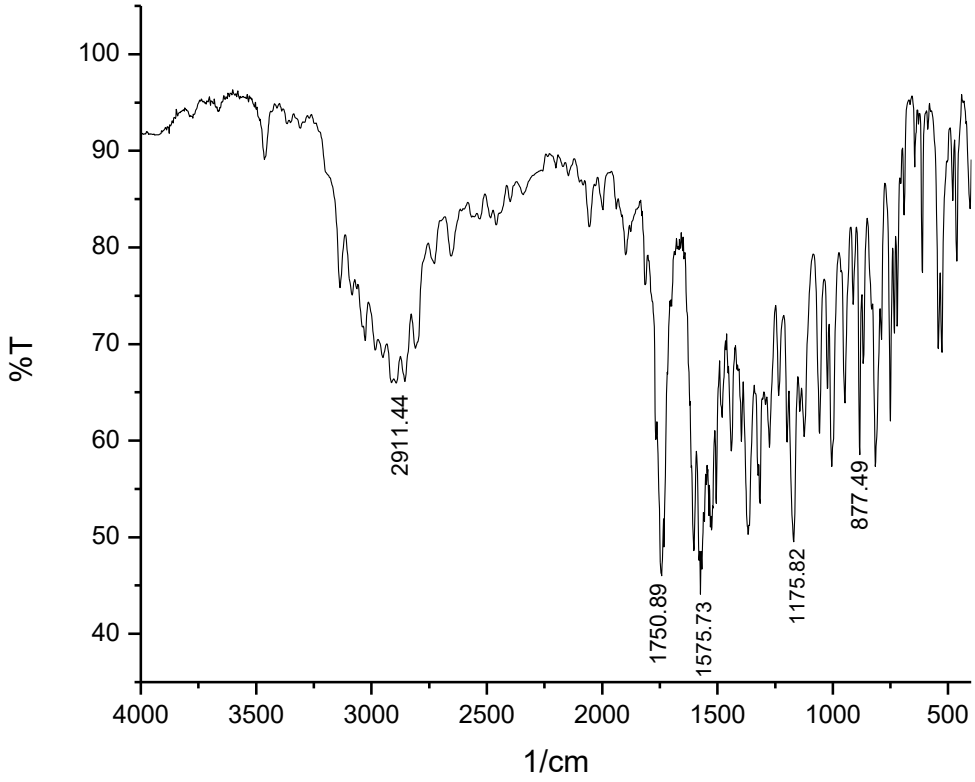
6] **3-benzylidene-5-([1,1'-biphenyl]-4-yl)-2(3*H*)furanone**



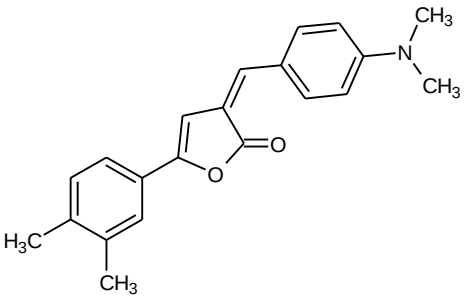


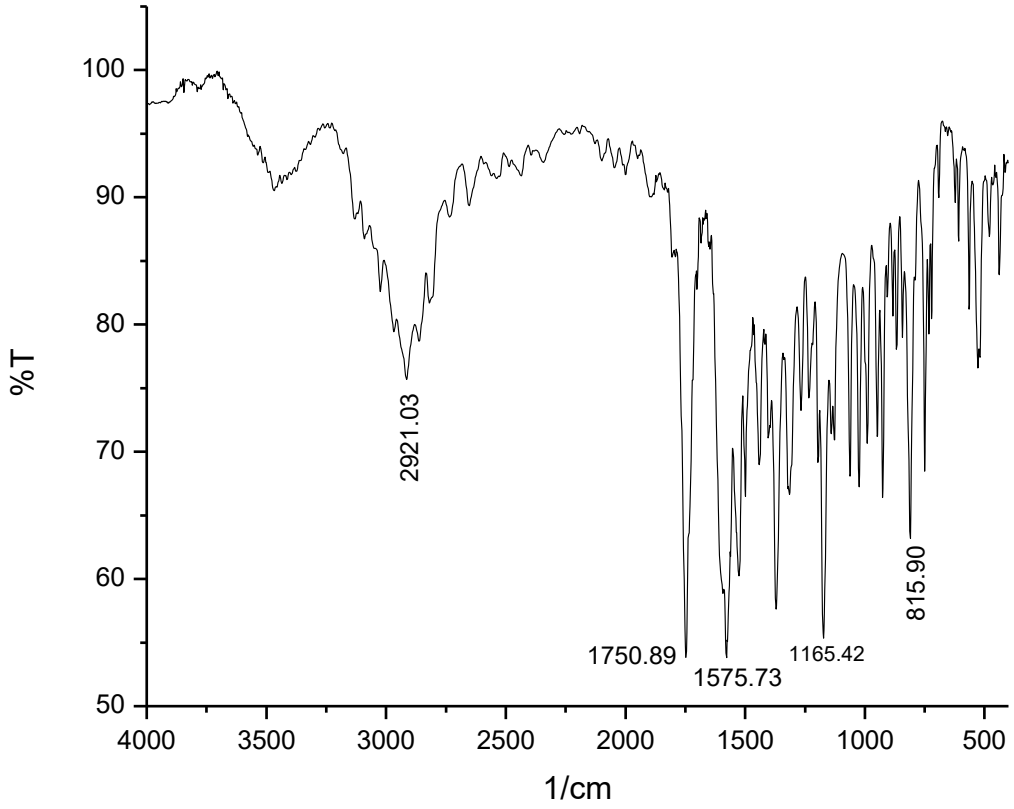
7] **<u>3-[4-dimethylaminobenzylidene]-5-(4-methylphenyl) -2(3*H*) furanone</u>**



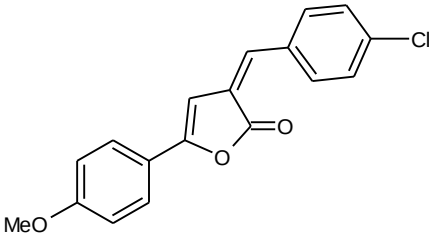


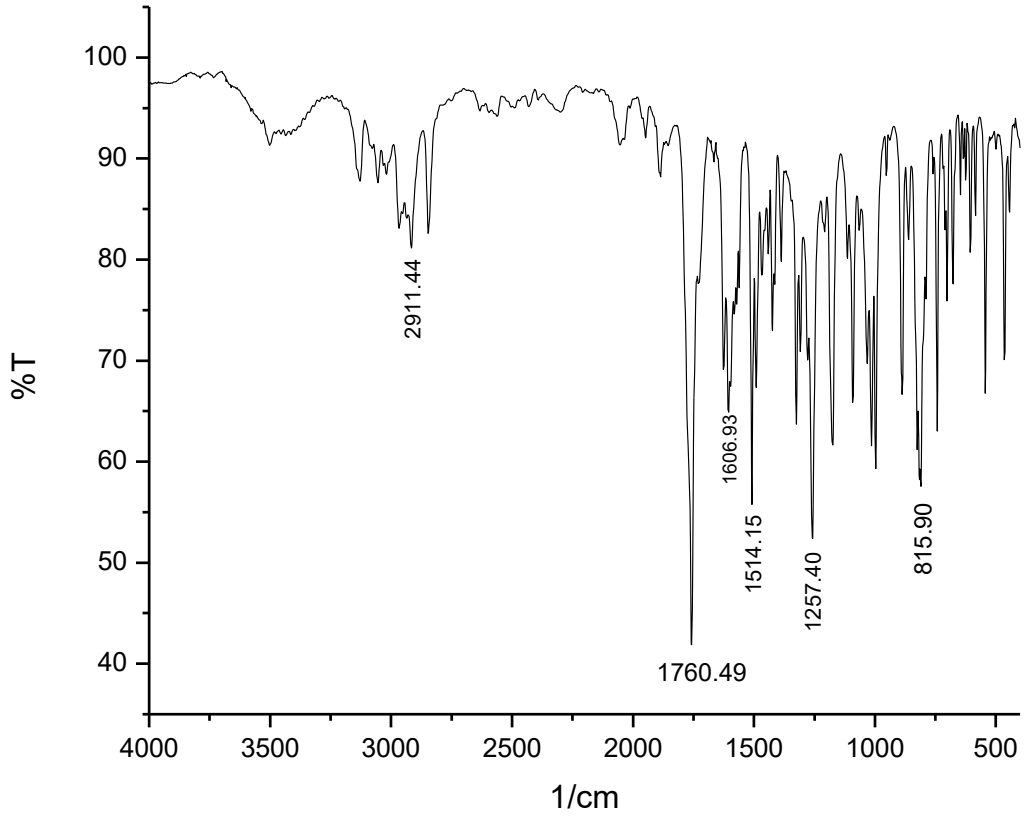
8] **<u>3-[4-dimethylaminobenzylidene]-5-(3,4-dimethylphenyl) -2(3*H*) furanone</u>**



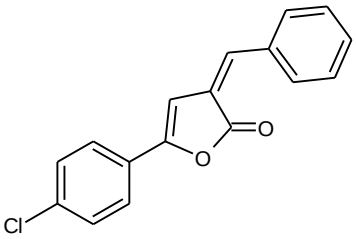


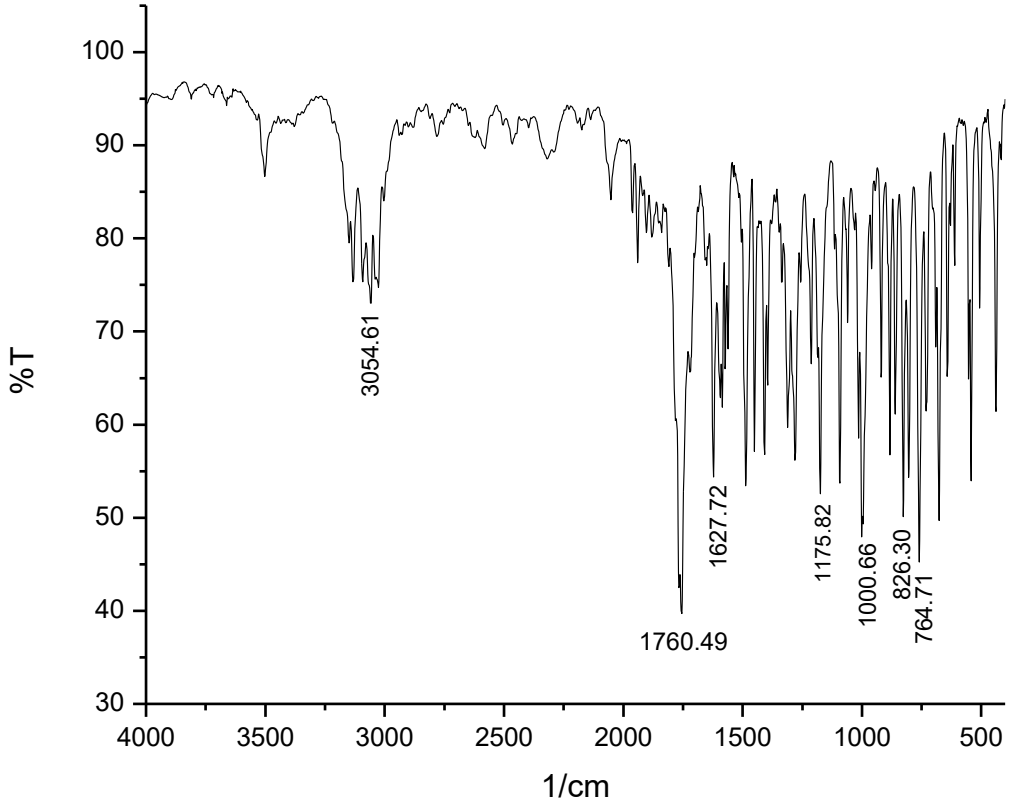
9] **3-[4-chlorobenzylidene]-5-(4-methoxyphenyl) -2(3*H*)furanone**





10] **3-benzylidene-5-(4-chlorophenyl) -2(3*H*)furanone**





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