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Ministry of Higher Education
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University of Baghdad
College of Education for Pure Science-
Ibn-Al-Haitham
Department of Chemistry

Synthesis, Characterization and Evaluation The Biological Activity of New Five and Seven Heterocyclic Compounds Derived from L-Ascorbic Acid

A thesis
submitted to the council of College of
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By

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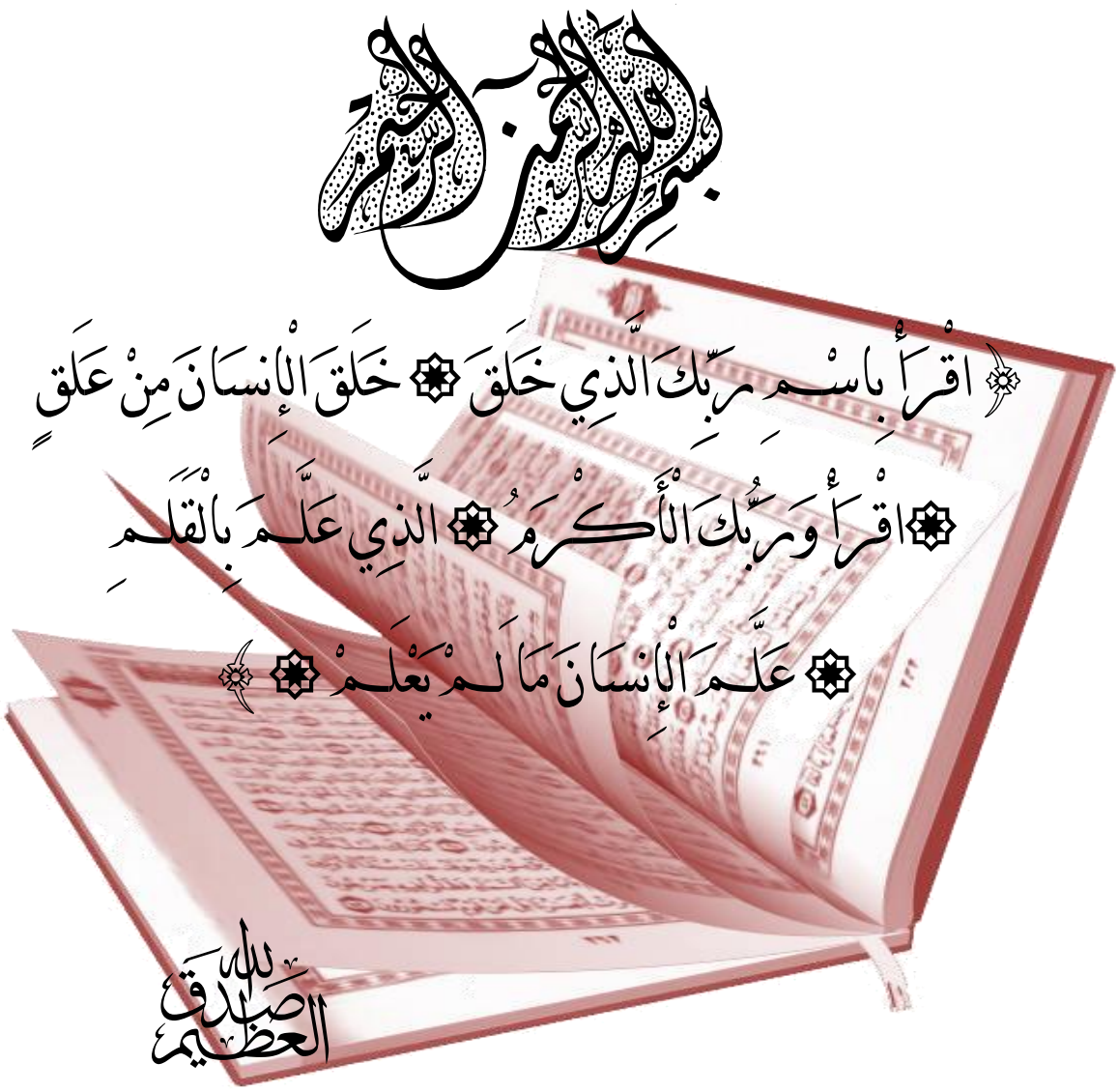

﴿ سورة العلق/الآية 1-5 ﴾

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Dedication

To whom the mind gave me, To the mystery of my presence my dear father, To whom gave me tenderness and care beloved my dear mother ….

To my repose, and my heart always remembers them to my sisters...

Israa

Acknowledgement

Thanks God Who granted me love of science and helped me to overcome the obstacles and paved the way for me to acquire more knowledge, and the prayer and peace be upon the prophet Mohammad and his good family and companions.

The honor is mine to express my sincere thanks and gratitude to my supervisor **Assist. Prof. Dr. Rasmia Mahmoud Rumez** for her generously to provide me with her great support and scientific notification for the completion of this thesis. Therefore I desire her everlasting verdure, gladness, success and extended life.

Sincerely gratitude are "also to the Dean of College of Education for Pure Science (Ibn-Al-Haitham)" and the staff of Chemistry Department.

Israa

Summary

L-Ascorbic acid, and its derivatives are very important compounds used in different field such as biological activity. Therefore some compounds have been synthesized by many methods.

This study includes the synthesis of five and seven membered ring heterocyclic compounds derived from L-ascorbic acid.

They are includes the following routes:-

1. The first route includes synthesis of aldehyde (5) from several steps. The first step is prepared the acetal (2) from reactions of (L-AA) in dry acetone entity of dry hydrogen chloride gas gave. Reaction of the acetal (2) with *p*-chlorobenzoyl chloride in pyridine to formation the ester (3), which was dissolved in (65%) acetic acid and ethanol to give the corresponding glycol compound (4). Aldehyde compound (5) was prepared by oxidation of glycol with sodium periodate in distilled water, Scheme (I).

2. The second route includes synthesis of 2-amino-5-(3-chlorophenyl)-1,3,4-thiadiazole (6) using thiosemicarbazide with 3-chlorobenzoic acid in presence of phosphorus oxychloride, and synthesis of esters 7(a,b) by the esterification of derivative benzoic acid with abs. ethanol in acidic medium, then conversion esters 7(a,b) to hydrazide 8(a,b) by using hydrazine hydrate. Finally ring closure of hydrazide 8(a,b) with 4-aminobenzoic acid in presence of phosphorus oxychloride to afford oxadiazole [(3,5-dinitrophenyl)-5-(4-aminophenyl)-1,3,4-oxadiazole] (9a) and [2-(4-nitrophenyl)-5-(4-aminophenyl)-1,3,4-oxadiazole] (9b), Scheme (I).

3. Schiff bases (10c), (10d) and (10e) were synthesized by reacted of amines (6), (9a) or (9b) with aldehyde (5) in DMF as a solvent with drops of glacial acetic acid, Scheme (I).

4. 2,5-Dihydrotetrazole compounds (11c), (11d) and (11e) were synthesized by 1,3-dipolar cycloaddition of Schiff bases (10c), (10d) or (10e) with sodium azide in DMF as a solvent, Scheme (II).

5. 1,3-Oxazepine derivatives (12-14)c,d,e were synthesized by cycloaddition reaction of Schiff bases (10c, 10d or 10e) with different anhydrides such as (maleic, phthalic or 3-nitrophthalic) anhydride, Scheme (II).

6. The diazepine derivatives (15-17)c,d,e were synthesized by reacted each one of oxazepine compounds (12c-14e) with 4-methoxyaniline in DMF as a solvent, Scheme (II).

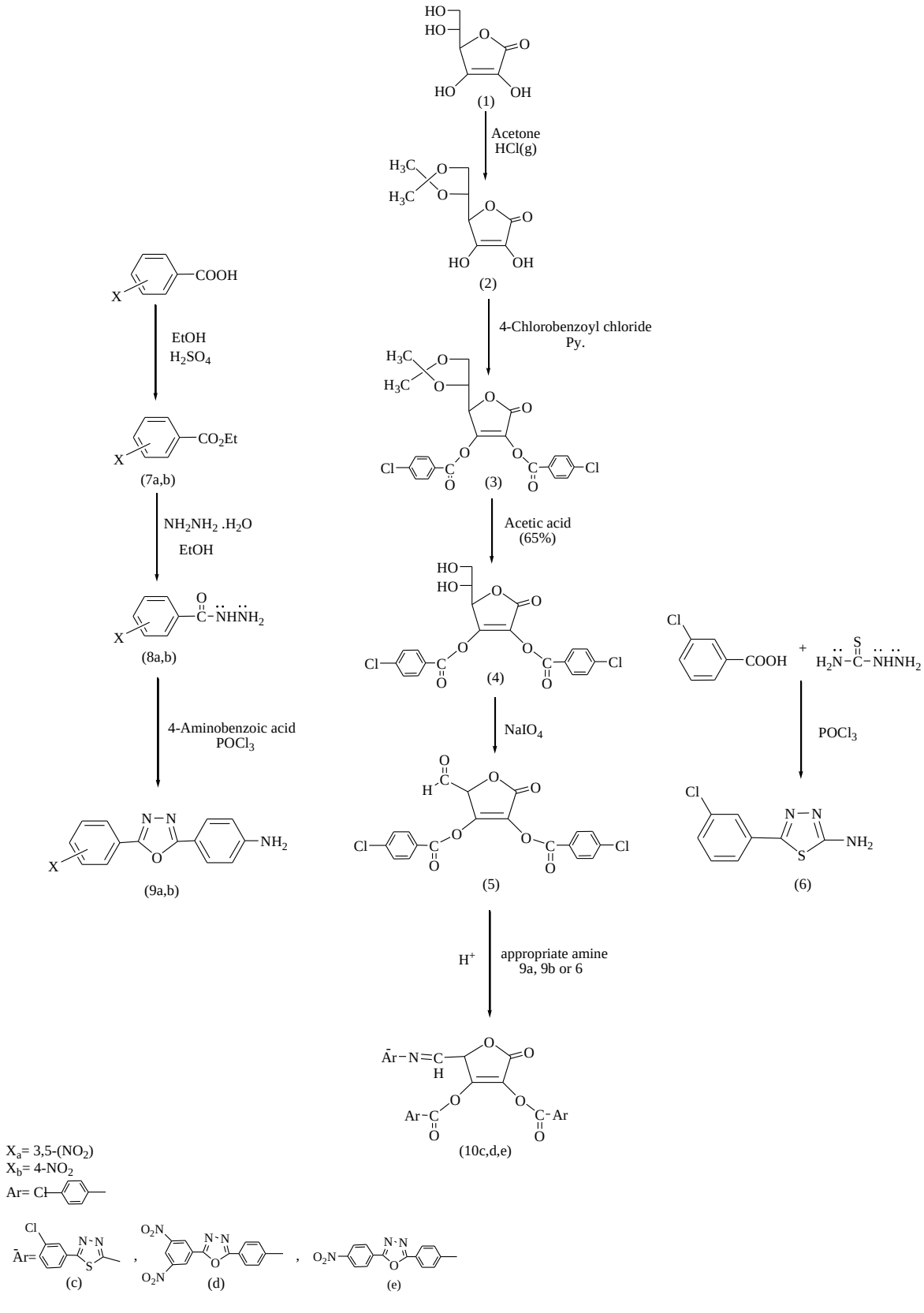
7. The Schiff base (18) was synthesized by reaction of aldehyde (5) with thiosemicarbazide and two drops of G.A.A. in abs. ethanol as a solvent, Scheme (III)..

8. The 1,3-thiazolidin-4-one (20) was synthesized by reaction of Schiff base (18) together with 2-chloroacetic acid in ethanol as a solvent, derivatives of 1,3-thiazolidin-4-one (21)i-m were synthesized by reaction of compound (20) with aromatic aldehydes in the presence of piperidine as a base, Scheme (III).

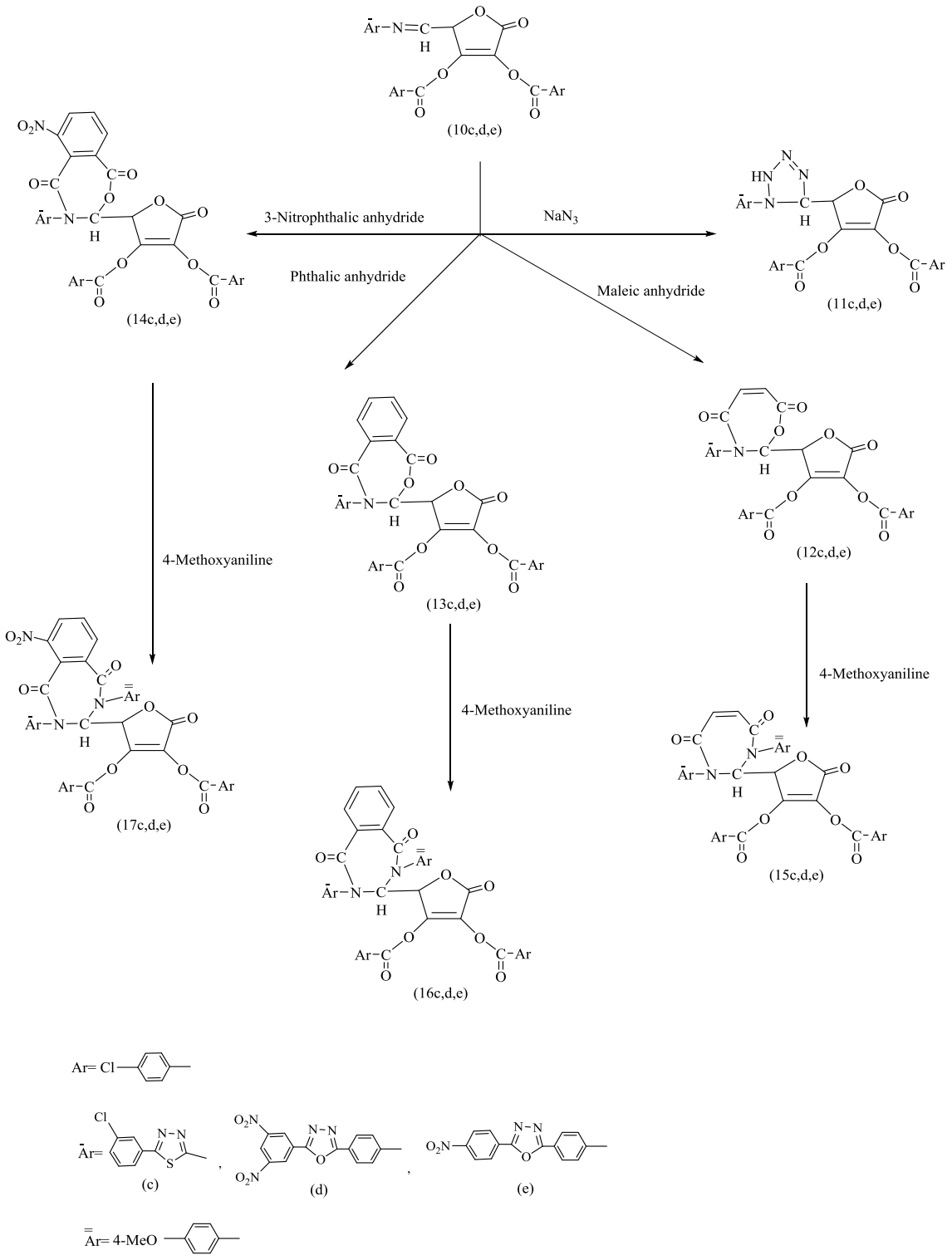
9. The 2,5-dihydrotetrazole compounds (22f,g,h) were synthesized from polar cycloaddition reaction of hydrazones (19f, 19g or 19h) with sodium azide in DMF as a solvent while the compounds (19f,g,h) were synthesized by reaction of phenylhydrazine or substituted phenylhydrazine with aldehyde (5), Scheme (III).

10. The synthesized compounds were characterized by spectral methods such as FTIR and several of them via Mass spectroscopy, ^{1}H-NMR, ^{13}C-NMR and measured its physical properties (melting point, color, molecular formula and yield).

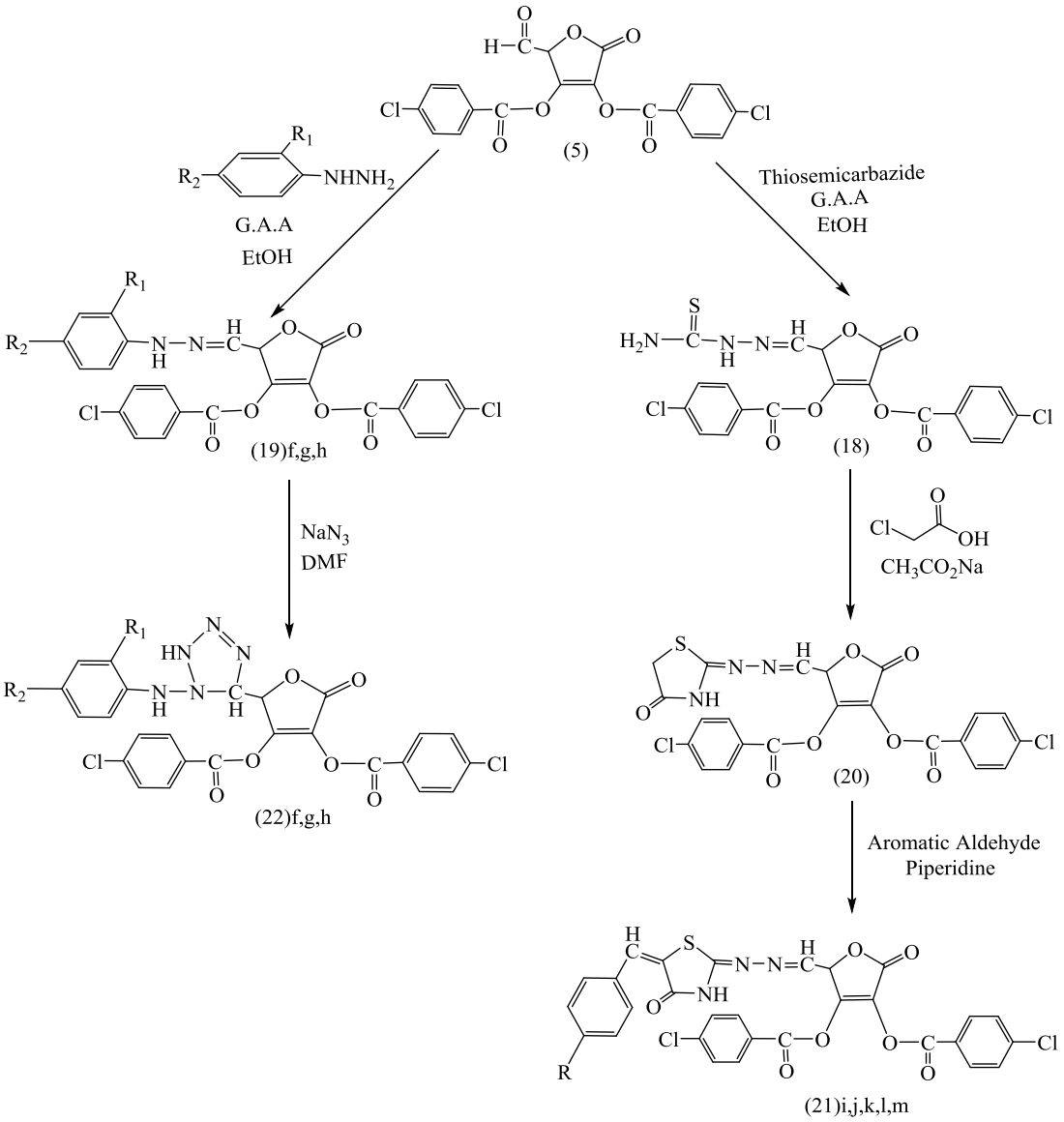
11. All these new compounds have been screened for their anti bacterial efficiencies, using two types of pathological bacteria, the (*Escherichia coli*) (G-) and (*Staphylococcus aureus*) (G+).


(1)
Acetone
HCl(g)
(2)
4-Chlorobenzoyl chloride
Py.
(3)
Acetic acid
(65%)
(4)
NaIO4
(5)
H+
appropriate amine
9a, 9b or 6
(10c,d,e)
EtOH
H2SO4
(7a,b)
NH2NH2 .H2O
EtOH
(8a,b)
4-Aminobenzoic acid
POCl3
(9a,b)
POCl3
(6)
Xa= 3,5-(NO2)
Xb= 4-NO2
Ar= Cl
(c)
(d)
(e)

Scheme (I)


(10c,d,e)
3-Nitrophthalic anhydride
NaN3
Phthalic anhydride
Maleic anhydride
(14c,d,e)
(11c,d,e)
(12c,d,e)
(13c,d,e)
4-Methoxyaniline
4-Methoxyaniline
4-Methoxyaniline
(17c,d,e)
(16c,d,e)
(15c,d,e)
Ar= Cl
(c)
(d)
(e)
Ar= 4-MeO

Scheme (II)



R= H, CH_3, OCH_3, NO_2, NMe_2
(f): R_1= H, R_2= H
(g): R_1= NO_2, R_2= NO_2
(h): R_1= H, R_2= NO_2

Scheme (III)

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List of Abbreviation

Symbol	*Name*
L.A.A	L-Ascorbic acid
USD	United states dollar
N	Normality
Fig.	Figure
R.T.	Room temperature
AcOH	Acetic acid
$POCl_3$	Phosphorus oxychloride
HCl	Hydrogen chloride
MS	Mass spectrometry
Anhy.	Anhydrous
MHz	Megahertz (10^6 Hz)
DMSO	Dimethyl sulfoxide
TLC	Thin-layer chromatography
M	Molarity
DMF	Dimethylformamide
R_f	Retention factor
Comp.	Compound
M.p.	Melting point
FTIR	Fourier Transform Infrared
O.O.P.	Out of plane
^{1}H-NMR	Proton Nuclear Magnetic Resonance
^{13}C-NMR	Carbon Nuclear Magnetic Resonance
EtOH	Ethanol
G.A.A.	Glacial acetic acid
T.S	Transition state
P.T.	Proton transfer
Ar.	Aromatic
Ali.	Aliphatic

Asy.	Asymmetric
Sy.	Symmetric

Chapter One

Introduction

1.1 L-Ascorbic acid

Vitamin C, also known as ascorbic acid and L-ascorbic acid, is a vitamin found in food and used as a dietary supplement. It is best known for its antioxidant properties, vitamin C lack is caused the disease scurvy and can be banned and medicated together with L-AA comprising dietary supplements or foods. Early symptoms are malaise and lethargy, progressing to shortness of breath, bone pain, bleeding gums, susceptibility to bruising, poor wound healing, and finally fever, convulsions and eventual death. Until quite late in the disease the damage is reversible, as with vitamin C repletion, healthy collagen replaces the defective collagen. Treatment can be orally or intramuscular or intravenous injection. [1] There is no evidence to boost the use of the public people for the forbidding of colds. [2, 3] It can be taken orally or by blueness. Overall good tolerances. [1] Large doses may cause discomfort in the digestive system, headaches, sleep disorders, and the expulsion of the skin. [1, 3] Natural dosing is safe during pregnancy. [4] Vitamin C is one of the fundamental nutrients involved in tissue repair. [1] Nutriments comprising vitamin C embody fruits of raw bell peppers, citrus, broccoli, strawberries & brussels sprouts. [2] May decrease vitamin C content in nutriments motive via long storage or concoction. [2] Vitamin C was discovered in 1912, separated in 1928, and first made in 1933. [5] It is included in the World Health Organization's List of Essential Medicines, the most effective and safe drugs required in the health system. [6] Vitamin C is available as a general medicine without a prescription. [1] "The wholesale cost in the developing world was about 0.003 to 0.007 USD per tablet. [7] In some countries, ascorbic acid may be added to foods such as breakfast cereal". [2]

"Ascorbic acid is a weakly sugar acid structurally regarding to glucose. In biological systems, ascorbic acid could be found only in lower pH, but in neuter solutions at a higher level of pH 5 is found mainly in the ionized form, ascorbate". "All these molecules have vitamin C activity and therefore

simultaneously it is used together with L-AA, Unless otherwise specific. Several analytical methods have been developed to detect ascorbic acid. For example, Vitamin C content for a nutritional sample such as fruit juice can be calculated by measuring the sample size required to remove the color of dichlorophenolidophenol (DCPIP) solution and then calibrate the results compared to a known concentration of vitamin C". [8, 9]

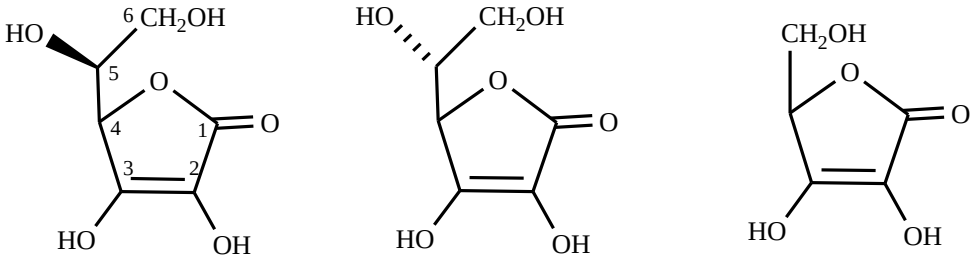
"A 2010 review find no role to complement vitamin C in the therapy of rheumatoid arthritis. [10] Studies testing the influence of vitamin C ingestion on the hazard of Alzheimer's sickness have reached discordant conclusions. [11, 12] Maintaining healthy food intake may be more important than supplements to achieve any possibility utility". [13]

A 2013 Cochrane review did not find any evidence that vitamin C supplements reduce the risk of lung cancer in healthy or high-risk persons (smokers exposed to asbestos). [14]

A meta-analysis for 2014 found that taking vitamin C may be safeguard against the risk of lung cancer. [15] A second meta-analysis did not find any influence on the danger of prostate cancer. [16]

A 2014 review shows that, "presently, the use of elevated-dosage IV vitamin C [as an anticancer factor] cannot be recommended outside of a clinical experiment". [17]

Structurally, (L-AA) is one from the easiest vitamins. It is close of the C_6 sugars, existence the aldono-1,4-lactone of a caproic acid (L-gulonic or L-galactonic acid), and comprises an enediol set on carbons (2 & 3). The stereoisomer of (L-AA; D-isoascorbic acid, D-araboAA, D-erythorbic acid), has modicum if any antiscorbutic efficacy, and must not be mixed with D-erythro AA, that is the C_5 analogous of L-ascorbic acid discovered in fungi and numerous of yeasts, Fig. (1.1).



L-ascorbic acid

D-isoascorbic acid
(D-araboascorbic acid,
D-erythorbic acid)

D-erythroascorbic acid

Fig. (1.1): Chemistry of ascorbic acid

Delocalization of the π-electrons over the C_2-C_3 conjugated enediol method settles the compound and the hydrogen of the hydroxyl group at C_3 to be very acidic, and to come apart with a pKa of 4.13. Thus at the pH physiological, L-AA occurs as a monoequivalent anion (L-ascorbate). Dismantling the second hydroxyl occur in pH 11.6. [18]

Ascorbic acid appears as white or somewhat yellow, crystalline solid with squeaky acidic taste, its melting point (190-192) ºC, it's scentless and progressively obfuscate at subjection to light. [19] High dissoluble in water and minimal in alcohol, propylene glycol and glycerol indissoluble by ether, benzen, petroleum ether, and chloroform. [20, 21]

1.2 Cyclic acetals

Cyclic acetals are more stable towards hydrolysis than other acyclic ones, also much easier to make. Cyclic acetals are readily formed by the reaction of two molecules, a ketone and a diol. The reaction produces two products, acetal plus water, the usually unfavourable entropy of acetal formation is not a factor. Formation is also kinetically favoured because the intramolecular ring-closing reaction is fast, Fig. (1.2). [22]

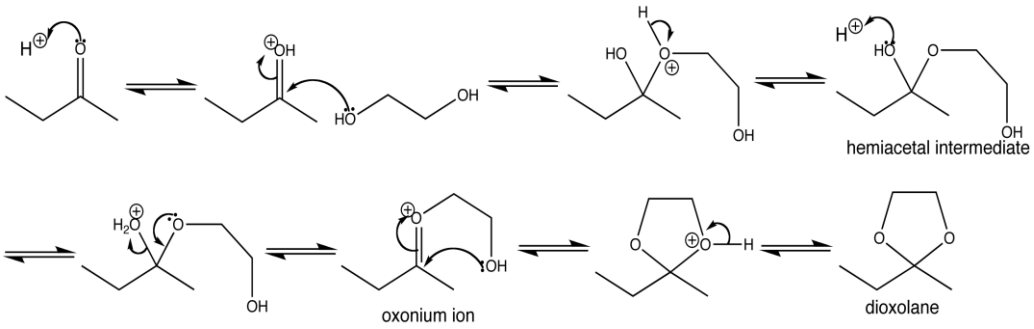
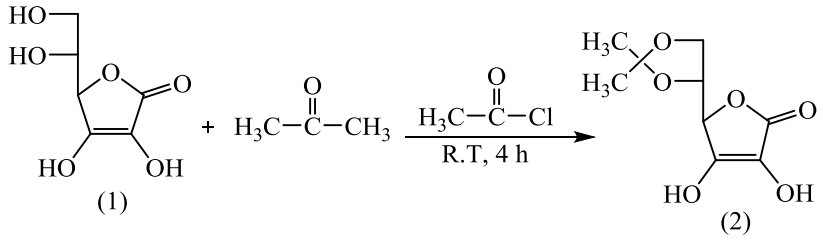


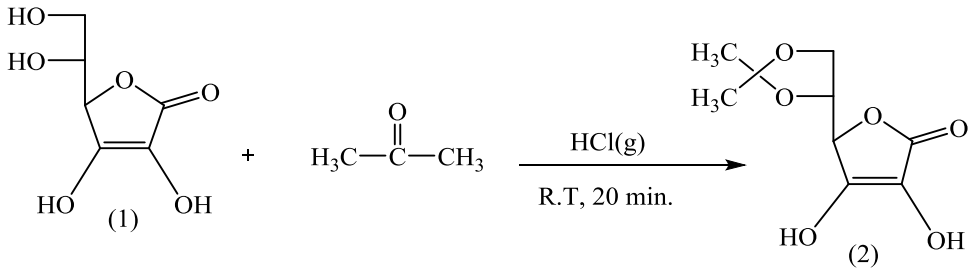
Fig. (1.2): Cyclic acetal formation

1.3 (5, 6-*O*-Acetal) derivatives of L-Ascorbic Acid

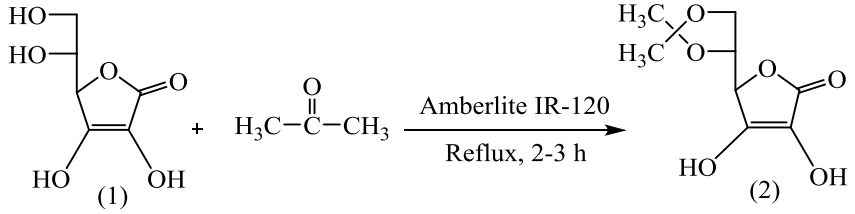
Taking consideration the acidity of the four hydroxyl groups [pKa value] and the stereochemistry in L-ascorbic acid. Alkylation studies were performed under various experiential conditions. The four hydroxyl groups exhibit a various reaction to the electrophiles beneath the basic reaction conditions. These hydroxyl groups give very much hydrophilic feature to it and thence, unable to dissolve in organic solvents. Because of its granular nature to water, it has been modified into an industrially useful mediums which are dissoluble in organic solvents. One of these derivatives, 5,6-*O*-ketal or 5,6-*O*-acetal, are dissoluble in organic solvents. Preserving groups 5 and 6 -OH also limits their intervention during reaction, containing the C-2 and C-3 enol hydroxyls. The derivatives of 5,6-O-isopropylidene-L-ascorbic acid (2) were prepared, by various methods, But the easiest way is to solve the L-ascorbic acid (1) in excess acetone that contains a catalytic amount of acetyl chloride to yield (80-85) % of (2). [23]



L. L. Salomon [24] prepared (2) in 1963, by flowing gas (HCl) during a solution of (1) and dry acetone $(CH_3)_2CO$, to yield (85-90) % of (2).

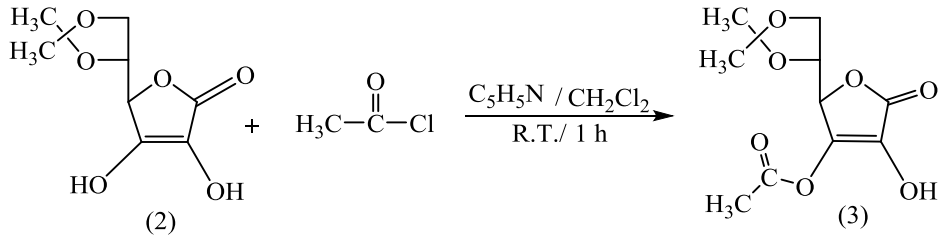


P. J. H. Carlsen et al. [25] found a practical alternative for synthesis of compound (2) involving the reaction of L-ascorbic acid in refluxing acetone in the presence of an acidic ion-exchange resin (Amberlite IR-120) as catalyst.

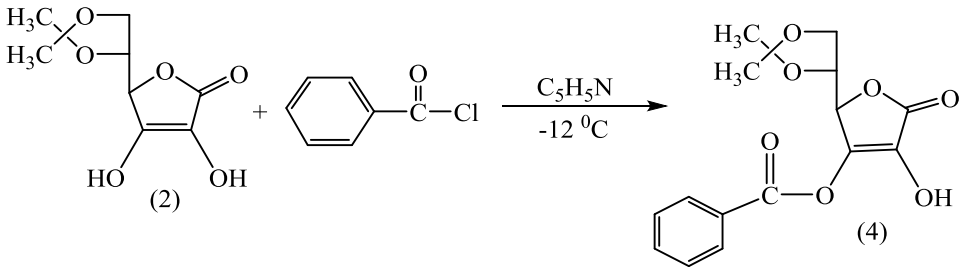


1.4 L-Ascorbic acid esters derivatives

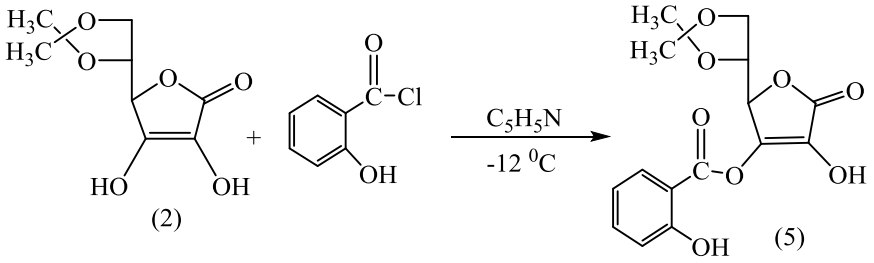
Four hydroxyl groups of ascorbic acid that are oversensitive to acylation. Nevertheless, through working with compound 2, the (5,6-*O*-isopropylidene) derivative of L-AA, the condition is streamlined in that lone the (C2 & C3) hydroxyls stay open to acylation. The colossal hole in the pKa of (C2 OH & C3 OH) aggregates synthetically supports a (C3-*O*-acyl) yield (3), that is dominatingly created on the pH scope from (4-7) beneath state of adding an acyl group. [26] so as to form 3-*O*-acyl derivatives (3) and not to formation (2,3-*O*-di-acyl & 2-*O*-acyl) was used (C_5H_5N) pyridine, as a feeble organic base with (pKa) near to (9). [27]



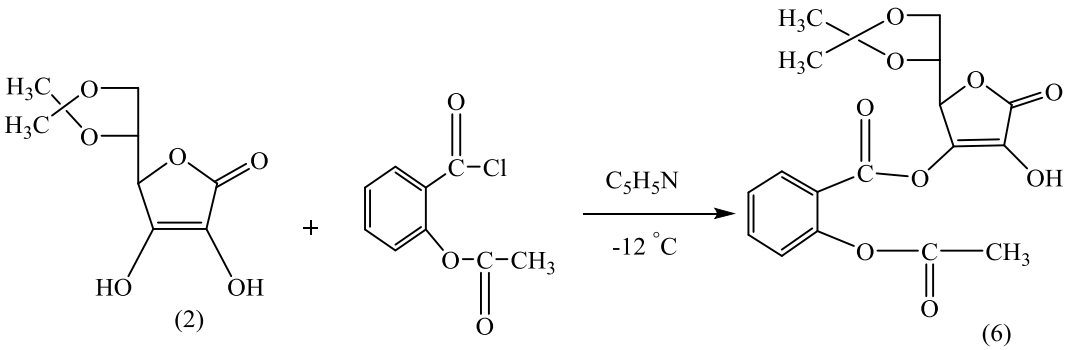
The reaction of (5,6-*O*-isopropylidene-L-AA) together with benzoyl chloride at existence the pyridine and cooling to -12^{o} C gave the compound (4) in a good yield (72%). [28]



Compound (5) was prepared by treatment of salicyloyl chloride along with acetal (2) in dry pyridine at (-12^{o} C). [29]

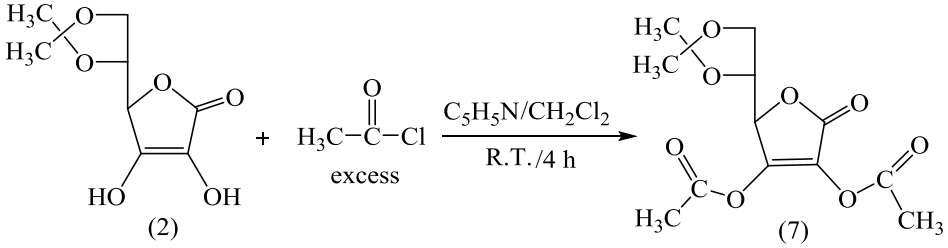


Compound (6) was prepared by treatment of acetylsalicyloyl chloride along with acetal (2) in dry pyridine at (-12^{o} C). [29]



A specific description for (C2-*O*-acetyl & C3-*O*-acetyl) esters of (5,6-*O*-isopropylidine-L-AA) has been beforehand announced. Synthesis of generality disubstituted results of (2), are basically accomplished by the utilization of abundance electrophilic reagents beneath the suitable reaction situations to straightway produce (2,3-*O*-disubstituted products of 2). [26] The (5,6-*O*-isopropylidene-2,3-*O*-diacetyl-L-AA) (7) was synthesized by reaction of

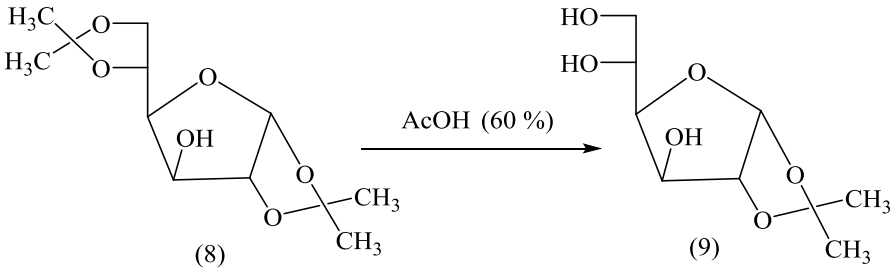
compound (2) with two equivalent of (C_5H_5N) and overabundance of acetyl chloride at existence the dichloromethane.



1.5 Acetals hydrolysis

Since the fashioning of acetals is volatile, acetals in the existence of acid and abundances of water were changed quickly back for alcohols and correspondent compounds that contain carbonyl group; that procedure termed acetal decomposition in water. The hydrolysis is a chemical reaction in which a molecule of H_2O ruptures one or more chemical bonds. Therefore, acetal become steady when the solutions are neutral and basic. [30]

Acetyl carbohydrates are degraded by treatment using one of their accompanied reactants: perchloric acid, tartaric acid, hydrochloric acid (2N), acidic ion exchange resin, CF_3CO_2H (TFA), (I_2) in (CH_3OH), acetic acid 50%, concentricity of hydrochloric acid in THF. 1,2-*O*-isopropylidene-α-D-glucofuranose (9) was prepared from hydrolysis of 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (8). [31]



1.6 Periodate oxidation

Periodate oxidation reaction is used in carbohydrate chemistry and is also applicable to wood polysaccharides. Periodic acid is mainly capable of

leaning alpha and beta glycols quantitatively from wood polysaccharides. Compounds containing an aldehyde or ketonic group adjacent to an alcoholic group are also attacked by periodic acid in similar manner as glycols. The estimation of the periodic acid used and the formic acid or formaldehyde produced will indicate the number, in pairs, of free oxidizable groups (-CHOH, -CHO or -CO). Since periodic acid can easily be estimated volumetrically, oxidations with H_5IO_6, or $HIO_4.2H_2O$ are very useful in analytical chemistry. [32]

"HIO_4 or $NaIO_4$ can be used to cleave vicinal glycols into two carbonyl compounds or into a single compound with two carbonyl groups. The formation of a diester of iodo (VII) acid as an intermediate is decisive for the success of this reaction. The diester intermediate decomposes in a one-step reaction in which three valence electron pairs are shifted simultaneously. One of these shifted electron pairs ends up as a lone pair on iodine, and the iodine (VII) initially present is thereby reduced to iodine (V)", Fig. (1.3). [33]

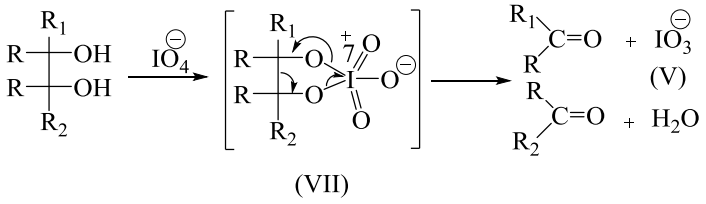


Fig. (1.3): The mechanism of the diol oxidation

The oxidative cleavage of D-(+)-mannitol-diacetonide with sodium periodate lead to a mixture of D-(+)-glyceraldehyde, its hydrate and oligomeric derivatives. [34] In the case of glycerol, the carbon chain is cleaved twice, and two molecules of formaldehyde and one molecule of formic acid are liberated; in the process, two molecules of periodate are consumed. [31]

1.7 Oxadiazoles

Oxadiazole is a five membered heterocyclic compound having two carbon, two nitrogen and one oxygen atoms and two double bonds, having

general formula $C_2H_2ON_2$. Oxadiazole is a very weak base due to the inductive effect of the oxygen. The replacement of two (-CH=) group in furan by two pyridine type nitrogen (-N=) reduces aromaticity of the resulting oxadiazole ring to such an extent that the oxadiazole ring exhibit character of conjugated diene.

There are four possible isomers of oxadiazole depending on the position of nitrogen atom in ring and are numbered as (a) 1,2,3-oxadiazole, (b) 1,2,4-oxadiazole, (c) 1,2,5-oxadiazole, and (d) 1,3,4-oxadiazole, Fig. (1.4).

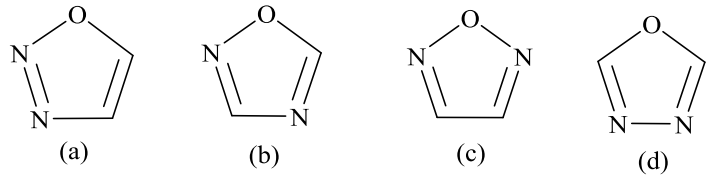
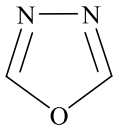


Fig. (1.4): Structures of oxadiazole isomers

Among these four isomers of oxadiazole an attempt is to synthesize some 1,3,4-oxadiazoles. Now we restrict to discuss about 1,3,4-oxadiazoles. 1,3,4-Oxadiazole is a five membered heterocyclic ring containing one oxygen and two nitrogen atoms at the position 1,3 and 4 respectively. As azoles, this is also an electronegative ring system with weak basic characteristics due to the inductive effects of the hetero atoms. [35]

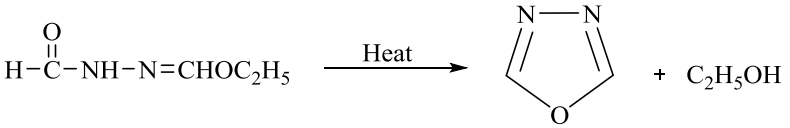
The nucleus of 1,3,4-oxadiazole ring is symmetrical and planer (d).



(d)

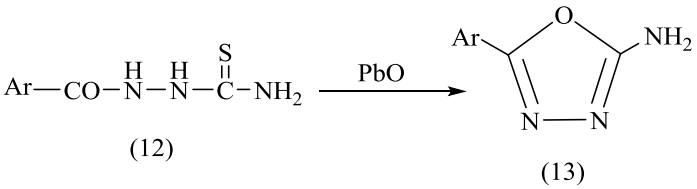
1.8 Synthesis of 1,3,4-oxadiazole derivatives

Ainsworth first prepared 1,3,4-oxadiazole (11) in 1965 by the thermolysis of ethyl formate formlyhydrazone (10) at atmospheric pressure. [36]



(10) (11)

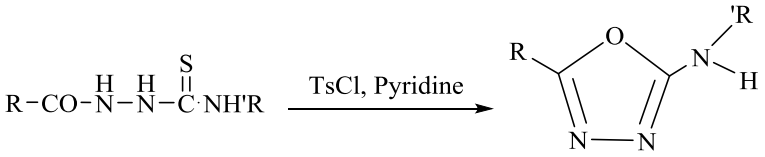
2-Amino-5-substitutedphenyl-1,3,4-oxadiazoles (13) was made appropriately of 1-benzoyl-thiosemicarbazide (12) via cyclization through PbO. [37]



(12) (13)

Ar = C_6H_5, 4-HOC_6H_4, 4-ClC_6H_4, 4-$CH_3OC_6H_4$, 4-$NO_2C_6H_4$

The thiosemicarbazides were cyclised too in the existence of tosyl chloride (TsCl) and pyridine to produce 2-amino-5-substituted-1,3,4-oxadiazole (14). [38]

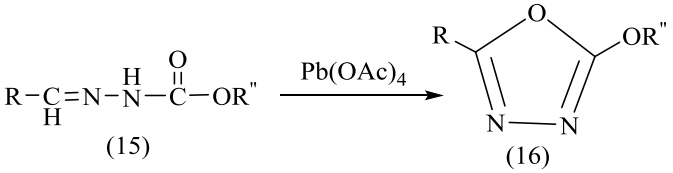


(14)

R = Me-, Me_3C-, F_3C-, $C_6H_5CH_2$-, 2-FC_6H_4, 4-FC_6H_4, 2-MeC_6H_4, 2-$MeOC_6H_4$, 4-$Me_2NC_6H_4$, 2-furyl, 4-pyridyl

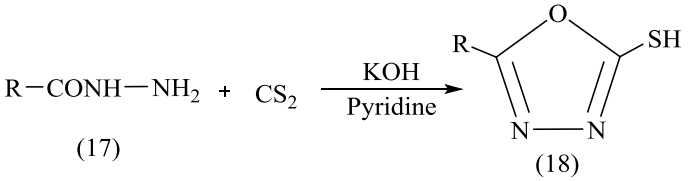
'R = $C_6H_5CH_2$-

Hydrazone derivatives (15) was cycled in an oxidized manner through $Pb(OAc)_4$ to production the analogous disubstituted 1,3,4-oxadiazoles (16). [39]



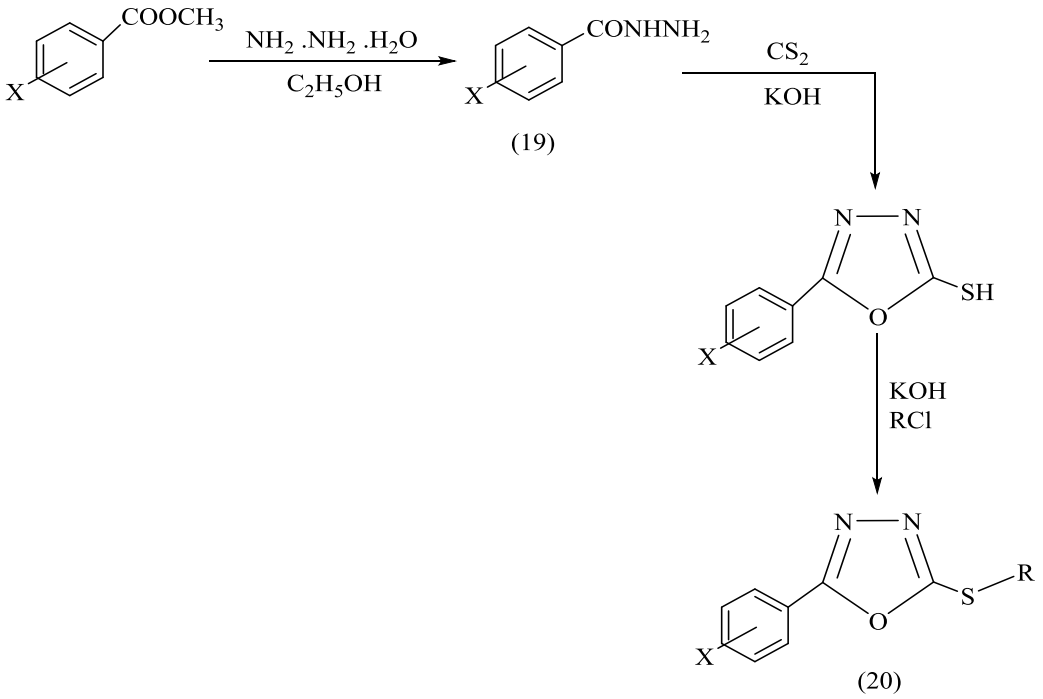
(15) (16)

Hydrazide derivatives (17) were recycled by using carbon disulfide to produce 2-mercapto-1,3,4-oxadiazole (18). [40]



(17) (18)

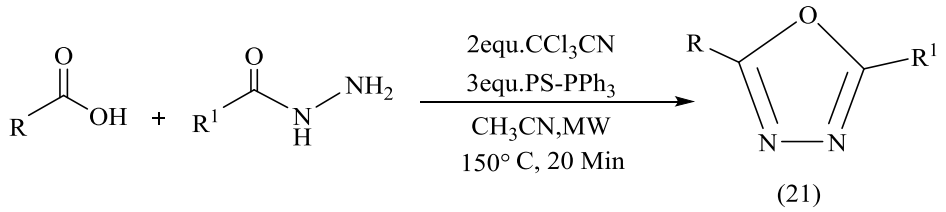
2-Mercapto derivatives of 1,3,4-oxadiazoles (20) have been prepared by reaction of substituted benzohydrazide (19) via carbon disulphide followed by condensation reaction. (41)



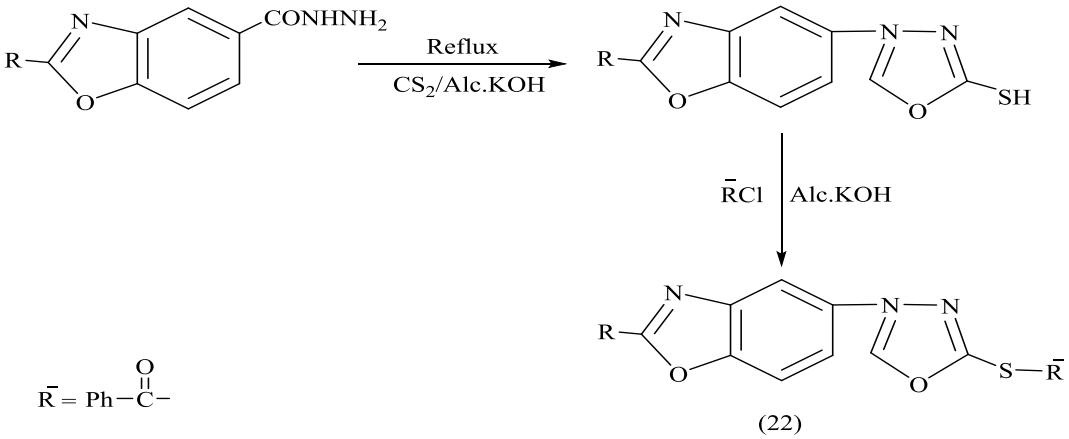
X = 2-Cl, 3-Cl, 4-Cl, 2,4-$(Cl)_2$

R = $-CH_2COOH$, $-CH_2CH_2COOH$

1,3,4-Oxadiazole (21) can be prepared from carboxylic acid and hydrazide with $PSPPh_3/CCl_3CN$. (42)

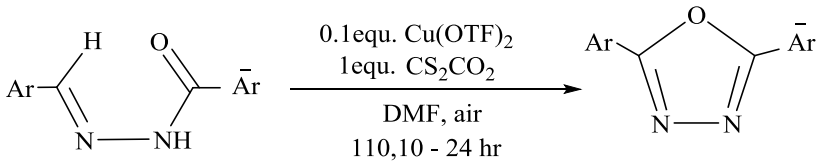


Compounds (22) were prepared by the reaction of 5-(2-substituted benzo oxazol-5-yl)-1,3,4-oxadiazolin-2-thione with benzyl chloride in alcoholic KOH. (43)



(22)

A direct access to symmetrical 2,5-disubstituted [1,3,4]-oxadiazoles (23) have been accomplished through a catalytic quantity of $Cu(OTF)_2$. [44]

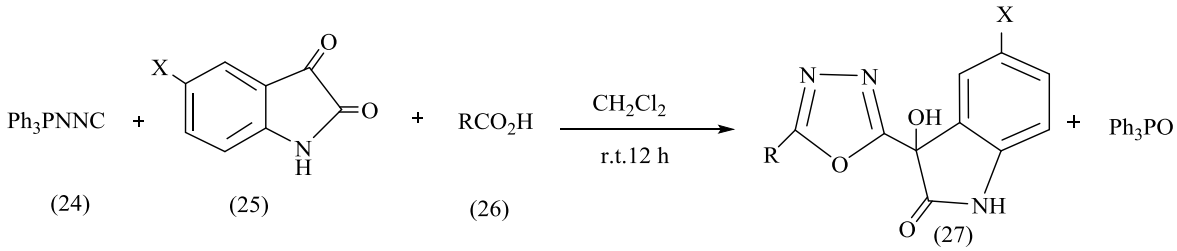


(23)

Ar = C_6H_5, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-$BuOC_6H_4$, 3,4-$(MeO)_2C_6H_3$, 4-FC_6H_4, 3-FC_6H_4, 4-ClC_6H_4, 4-BrC_6H_4, 4-$MeO_2CC_6H_4$, 2-pyridyl, 2-furyl, 2-thiophyl

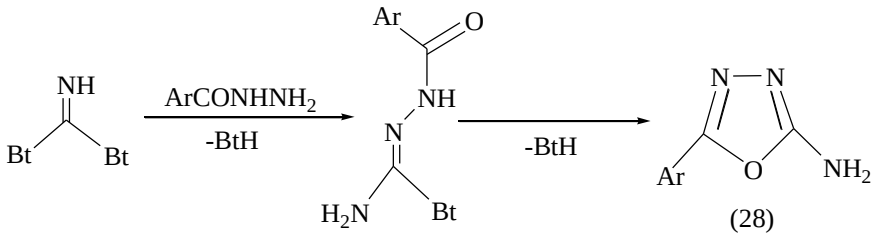
$\bar{Ar}$ = C_6H_5

The 3-(1,3,4-oxadiazol-2-yl)-3-hydroxy-1,3-dihydro-2H-indol-2-ones (27) have been prepared by the reaction of N-isocyanimino triphenyl phosphorane (24), an isatin (25) and a carboxylic acid (26) in ratio 1:1:1 under mild conditions to give in excellent yield. [45]



(24) (25) (26) (27)

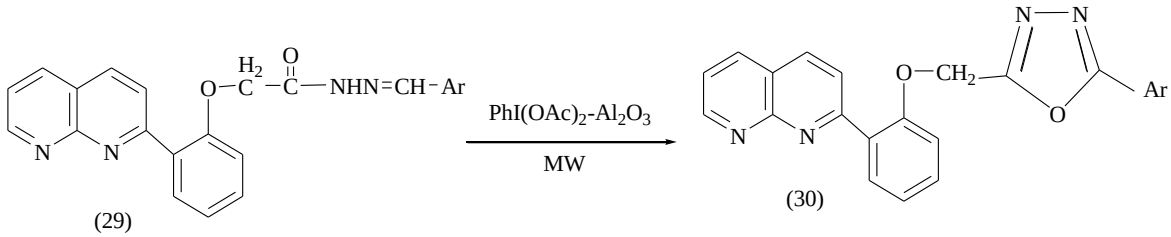
2-Amino-5-aryl-1,3,4-oxadiazole (28) was prepared from di(benzotriazolyl)methanimine. [46]



(28)

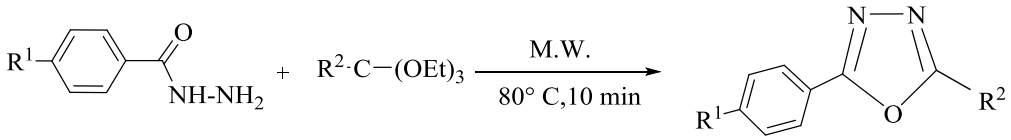
Ar = Ph, 4-t-BuC_6H_4, 4-$NH_2C_6H_4$, 4-HOC_6H_4, 4-$NO_2C_6H_4$, 3-$NO_2C_6H_4$, 4-ClC_6H_4, 2-ClC_6H_4, 2-pyridinyl

Alumina-supported iodobenzen diacetate is a highly efficient reagent for the oxidative cyclization of compound (29) to (30) in solvent-free conditions under microwave irradiation. [47]



(29) (30)

One pot, solvent free using microwave mediated synthesis of 1,3,4-oxadiazoles (31) were also reported by V. Polshettiwar. [48]



(31)

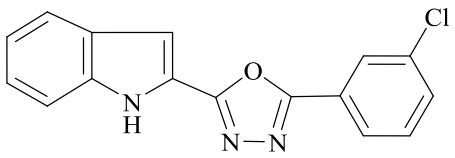
R^1 = H, F, OMe, 2-furyl, 2-thienyl

R^2 = H, Et, Ph

1.9 Biological activity of 1,3,4-oxadiazole derivatives and its importance

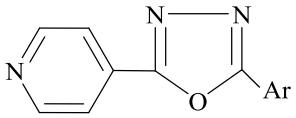
The 1,3,4-oxadiazoles have large scope of vitality efficiencies, viz, antimicrobial, antiinflammatory, antioxidant, antibacterial, antifungal, antiviral activities, etc. The derivatives of 1,3,4-oxadiazoles are also used in medicinal therapy as anti-cancer, anti-convulsent, anti-tubercular, etc. Some material applications of 1,3,4-oxadiazole derivatives lie in the field of liquid crystals, photoluminescent polymers etc. used in the field of industry.

The compound 2-(3-chlorophenyl)-5-(1H-indol-2-yl)-1,3,4-oxadiazole (32) have anti-bacterial activity against *E. coli* and *S. aureus*. [49]



(32)

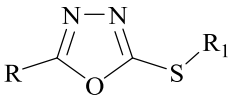
A series of some 1,3,4-oxadiazole derivative (33) have anti-microbial activity. They showed antifungal and antibacterial activity against the fungi viz *A. niger* and *C. albicans* and bacteria viz. *B. subtilis* and *S. aureus*. [50]



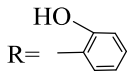
(33)

Ar= *p*-HOC_6H_4,
p-ClC_6H_4
p-FC_6H_4

A series of 2-alkylthio-5-aryl-1,3,4-oxadiazole (34) showed antibacterial and antifungal activity against the bacteria, *E. coli* and *S. aureus* and *fungi A. niger*. [51]

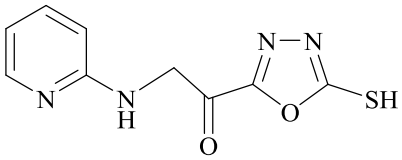


(34)



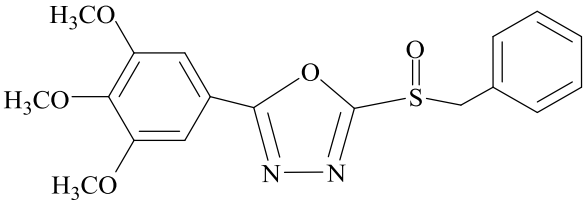
R_1= H, C_2H_5, $-CH_2Ph$
$-CH_2CO_2C_2H_5$

1-(5-mercapto-1,3,4-oxadiazol-2-yl)-2-(pyridine-2-yl-amino)ethanone (35) are potential antimicrobial agents. [52]



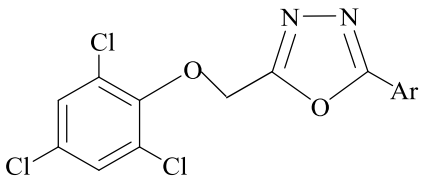
(35)

The group of new sulfoxide derivatives having 1,3,4-oxadiazole (36) have been reported as antifungal agents. [53]



(36)

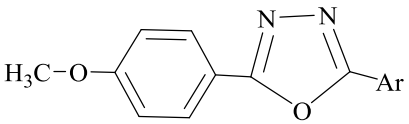
2-Substituted-aryl-5-(2,4,6-trichlorophenoxymethyl)-1,3,4-oxadiazoles (37) showed anti-inflammatory activity. [54]



Ar = Phenyl, 2– chlorophenyl, 4– chlorophenyl

(37)

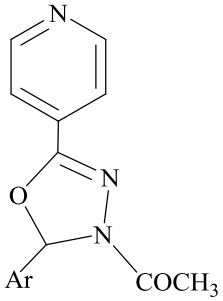
2,5-Disubstituted-1,3,4-oxadiazoles (38) are reported for example the factors to reduce inflammation. [55]



(38)

Ar = C_6H_5, 4-MeC_6H_4, $CH{=}CHC_6H_5$, 3-$NH_2C_6H_4$, 4-$NH_2C_6H_4$, 4-$NO_2C_6H_4$, 3,5-$(NO_2)_2C_6H_3$, 4-HOC_6H_4, 2,4-$(HO)_2C_6H_3$, 2-HO-3-MeC_6H_3

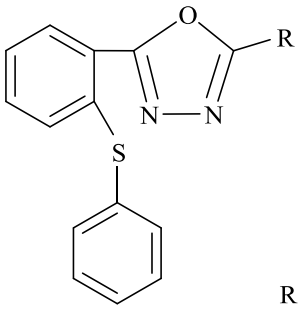
A series of isonicotinic acid hydrazide incorporated derivatives of 1,3,4-oxadiazoles (39) have anti-convulsant activity. [56]



(39)

Ar = *o*-ClC_6H_4, *p*-ClC_6H_4, *o*-HOC_6H_4, *m*-HOC_6H_4, *p*-$CH_3OC_6H_4$, *p*-FC_6H_4, *o*-$NO_2C_6H_4$, *p*-$(CH_3)_2NC_6H_4$

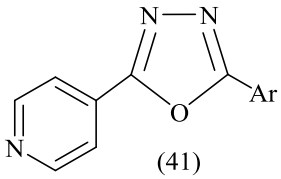
5-[2-(phenylthio)phenyl]-1,3,4-oxadiazole (40) showed anti-convulsant activity. [57]



R = OH, SH, -S-CH_3

(40)

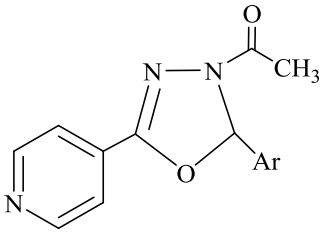
A series of 1,3,4-oxadiazoles (41) showed analgesic activity. [58]



Ar = C_6H_5, 2-ClC_6H_4

(41)

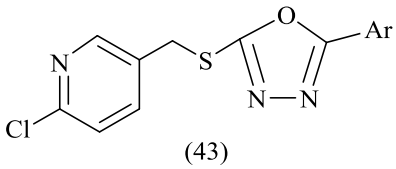
2-Aryl-5-pyridine-1,3,4-oxadiazole (42) have analgesic agents. [59]



(42)

Ar = 4-HOC_6H_4
4-ClC_6H_4, 3-$NH_2C_6H_4$
2-ClC_6H_4, 3-$MeOC_6H_4$
3,4-$Me_2C_6H_3$
4-FC_6H_4

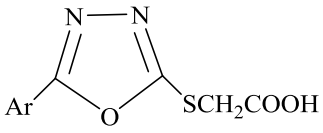
2-Chloropyridine derivatives having 1,3,4-oxadiazole (43) moiety were reported as anti-cancer agents against gastric cancer cell. [60]



(43)

Ar = 2-HO-4-MeO-C_6H_3
Naphthyl

Substituted-1,3,4-oxadiazole-2-thiones (44) are reported as anti-cancer agents. [61]

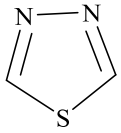


(44)

Ar= C_6H_5, 4-HOC_6H_4, 4-ClC_6H_4
4-$NO_2C_6H_4$, 4-$NH_2C_6H_4$

1.10 Thiadiazoles

Thiadiazole is a versatile moiety that exhibits a wide variety of biological activities. It acts as "hydrogen binding domain" and "two electron donor system" with a constrained pharmacophore. The first 1,3,4-thiadiazole was described by Fischer in 1882 but the true nature of the ring system was demonstrated first in 1890 by Freund and Kuh.



Many drugs containing thiadiazole nucleus are available in the market such as acetazolamide, methazolamide, sulfamethazole, etc.

Thiadiazole is a five membered heterocyclic compounds that show various types of biological activity. It contains two nitrogen atoms and one sulphur atom as hetero atoms. There are four isomers of thiadiazole, Fig. (1.5), that is

a- 1,2,3- Thiadiazole

b- 1,2,4- Thiadiazole

c- 1,2,5- Thiadiazole

d- 1,3,4- Thiadiazole [62]

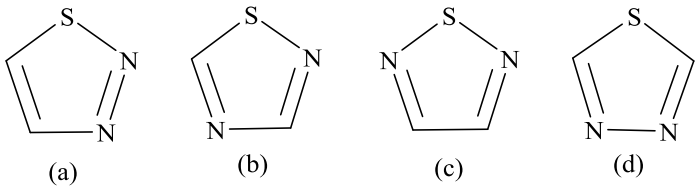
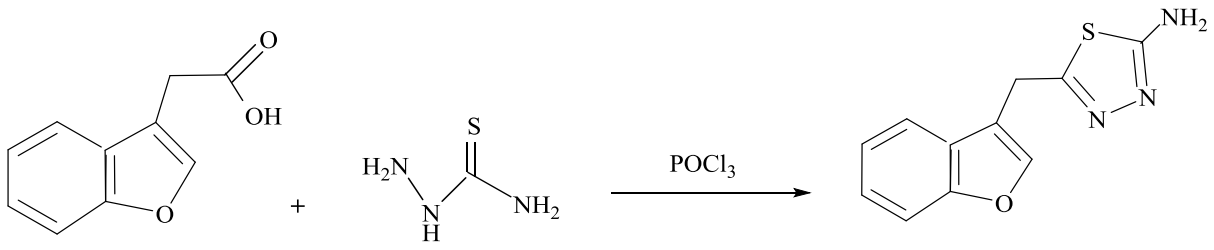


Fig. (1.5): Structures of thiadiazole isomers

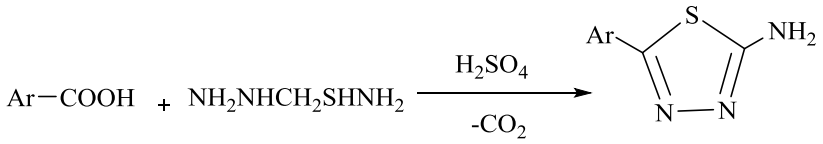
1.11 Synthesis of 1,3,4-thiadiazole derivatives

Benzofuran-3-acetic acid (45) react with thiosemicarbazide (46) to yield {5-(benzofuran-3-ylmethyl)-[1,3,4]-thiadiazol-2-yl-amine} (47) in presence of $POCl_3$. [63]



(45) (46) (47)

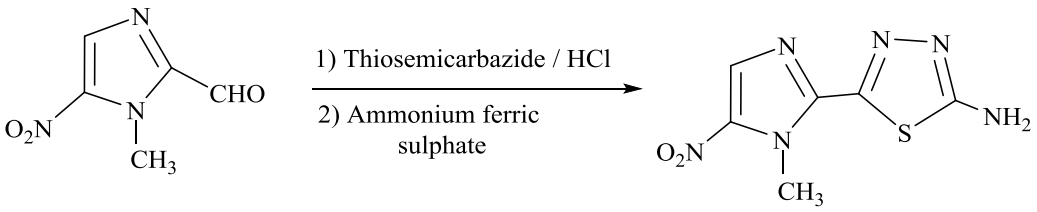
S. R. Pattan et al. [64] reported synthesis and biological evaluation of some 1,3,4-thiadiazole derivatives (50). A mixture of aryl carboxylic acid (48), thiosemicarbazide (49), in the presence of sulphuric acid was refluxed for 1 hr.



(48) (49) (50)

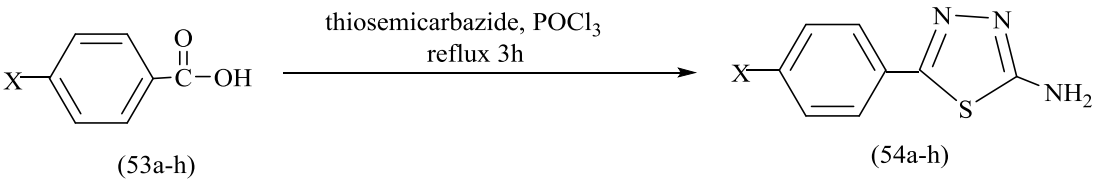
Ar= 4-$NH_2C_6H_4$, 4-$NO_2C_6H_4$

F. Poorrajab et al. [65] reported the synthesis of some nitroimidazoyl-1,3,4 thiadiazoles. Treatment of 1-methyl-5-nitroimidazole-2-carboxaldehyde (51) with thiosemicarbazide in the presence of HCl results in corresponding thiosemicarbazone which upon cyclization with ammonium ferric sulphate gave 2-amino-1,3,4-thiadiazole (52).



(51) (52)

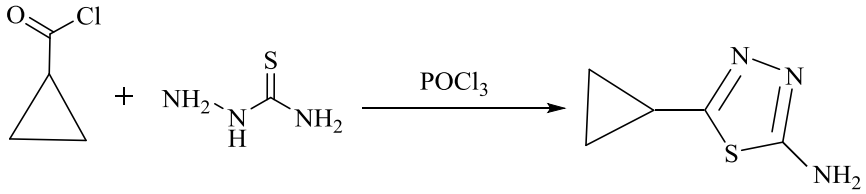
J. Salimon et al. [66] were prepared 2-amino-5-substituted-1,3,4-thiadiazole (54a-h) starting the interaction between the different substituted aromatic acids that contain a carboxyl group (53a-h) with thiosemicarbazide in phosphorus oxychloride.



(53a-h) (54a-h)

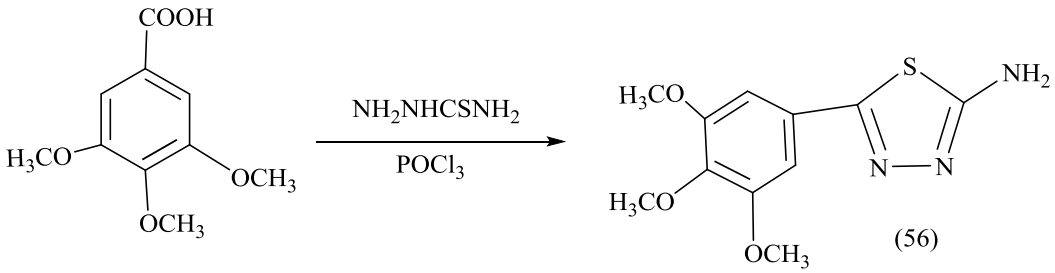
X= a= H, b= -NO_2, c= -OCH_3, d= Br, e= I, f= Cl, g= -CH_3, h= -CH=CH-Ph

M. N. Noolvi et al. [67] has reported the synthesis of 2-amino-5-cyclopropyl-1,3,4-thiadiazole (55) by refluxing of cyclopropanecarbonyl chloride with thiosemicarbazide in presence of $POCl_3$.



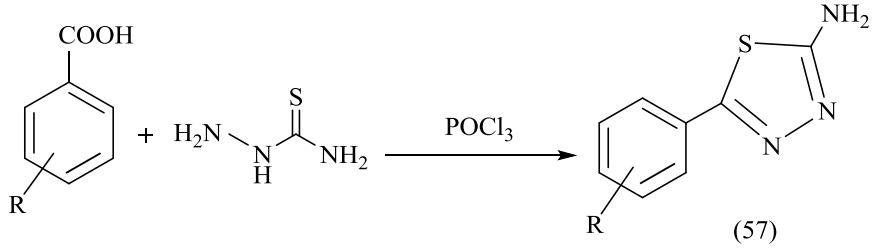
(55)

S. G. Alegaon et al. [68] noted the preparation of {2-amino-5-[3,4,5-trimethoxyphenyl]-1,3,4-thiadiazole} (56) was acquired via immediate cyclization of thiosemicarbazide and 3,4,5-trimethoxybenzoic acid in the entity of $POCl_3$.



(56)

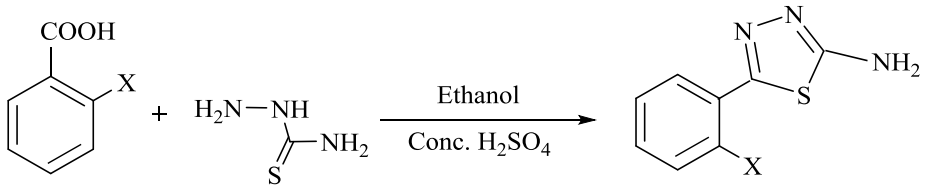
S. Sharabassapa et al. [69] has reported the synthesis of 2-amino-5-substitutedphenyl-1,3,4-thiadiazole (57) by refluxing of carboxylic acid with thiosemicarbazide in presence of $POCl_3$.



(57)

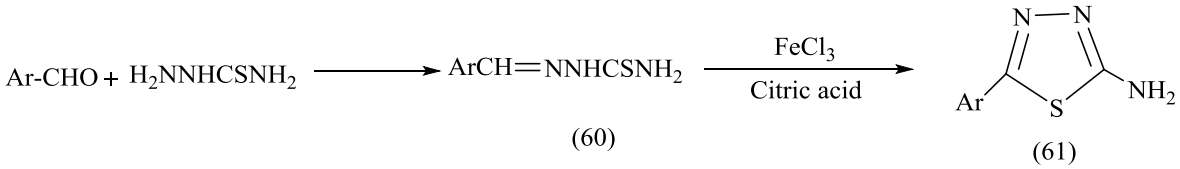
R= H, 4-Cl, 4-F, 4-CH_3O, 4-NO_2

M. M. Raj et al. [70] were synthesized novel thiadiazoles by reaction of benzoic and 2-hydroxybenzoic acid with thiosemicarbazide to synthesize {5-phenyl-1,3,4-thiadiazol-2-amine} (58) and {2-(5-amino-1,3,4-thiadiazole-2-yl) phenol (59)}.



X = H: (58)
X = OH: (59)

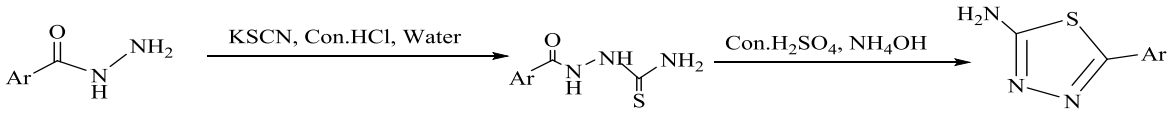
B. Mathew et al. [71] were synthesized thiosemicarbazone (60) by the reaction between aromatic aldehyde and thiosemicarbazide. This thiosemicarbazones undergo oxidative cyclization with $FeCl_3$ in presence of citric acid medium to form 5-phenyl and 5-substituted phenyl 2-amino-1,3,4-thiadiazole (61).



(60) (61)

Ar = C_6H_5, 4-ClC_6H_4, 4-$MeOC_6H_4$, 2-$NO_2C_6H_4$, 3-$NO_2C_6H_4$

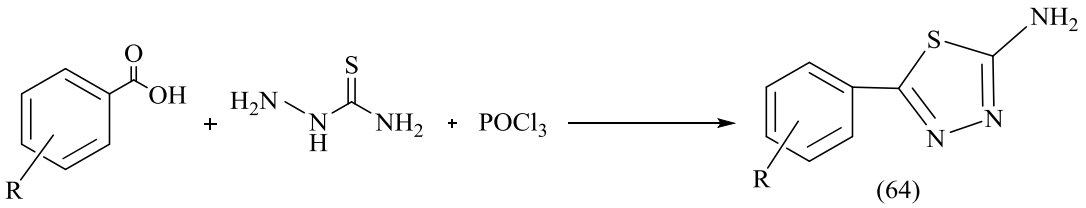
B. Gadhiya et al. [72] were synthesized compounds (63) via thiosemicarbezides (62) in presence of conc. sulphuric acid.



(62) (63)

Ar = -C_6H_5, 4-ClC_6H_4, 4-$CH_3C_6H_4$, 4-$CH_3OC_6H_4$, -$CH_2C_6H_5$, -CH_2(4-FC_6H_4), -CH_2(4-ClC_6H_4), -CH_2(4-$CH_3C_6H_4$)

K. T. Waghmode et al. [73] were synthesized amino thiadiazole derivatives (64) from cyclocondensation of substituted benzoic acid and thiosemicarbazide at existence the phosphoryl trichloride beneath the condensation of vapours and the return of this condensate to the system from which it originated state.



(64)

R= H, *p*-CH_3O, *p*-NO_2, 4-Cl, 4-OH, 2-Cl, -CH═CH_2, 2-OH, 4-CH_3, 3-CH_3

1.12 Biological activity of 1,3,4-thiadiazole derivatives

"1,3,4-Thiadiazole is the isomer of thiadiazole series. A glance at the standard reference works shows that more studies have been carried out on the 1,3,4-thiadiazole than all the other isomers combined. Members of this ring system have found their way in to such diverse applications as pharmaceuticals, oxidation inhibitors and metal complexing agents". [74] During last few long time there has been large fulfillment of diverse modules of thiadiazole compositions, several of that known to hold exciting biological possessions such as antimicrobial, [75] antituberculosis, [76] anti-inflammatory, [77] analgesic, [78] anticonvulsants, [79] antihypertensive, [80] antileshmanial, [81] antioxidant, [82] anticancer, [83] antitubercular, [84] antidiabetic, [85] antifungal, [86] antiviral, [74] antidepressant, [87] activity.

Among them 2,5-disubstituted-1,3,4-thiadiazoles are responsible for diverse biological activity probably due to –N=C–S grouping. "1,3,4-Thiadiazole derivatives possess remarkable biological activity probably conferred to them due to strong aromaticity of the ring system which leads to great *in vivo* stability and generally, a lack of toxicity for higher vertebrates, including humans when diverse functional group that interact with biological receptor are attached to aromatic ring". [88, 89]

1.13 Schiff bases

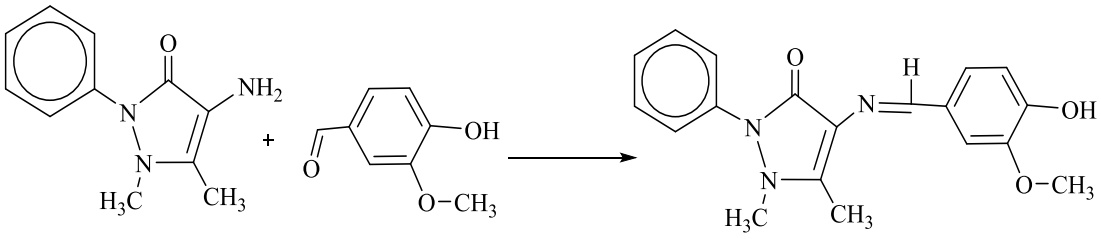
Schiff base was invented by Hugo Schiff, who was named after him. There are essentially compounds with a functional group with a double bond

of carbon - nitrogen, nitrogen atom connected to the aryl or alkyl group, not by hydrogen. The general meaning of the rules of Schiff bases, can be symbolize for the general formula $R_1R_2C=NR_3$, where R is an organic sideway chain. Some are limited to secondary aldimines (Such as azomethines as carbon is associated with a hydrogen atom) with the common form RCH = NR'. [90- 92] Carbon - nitrogen double bond affords a significant role in various developments of chemical sciences. Azomethine compounds are likely to be used as fine chemicals and medical essentials.

1.14 Synthesis of Schiff bases

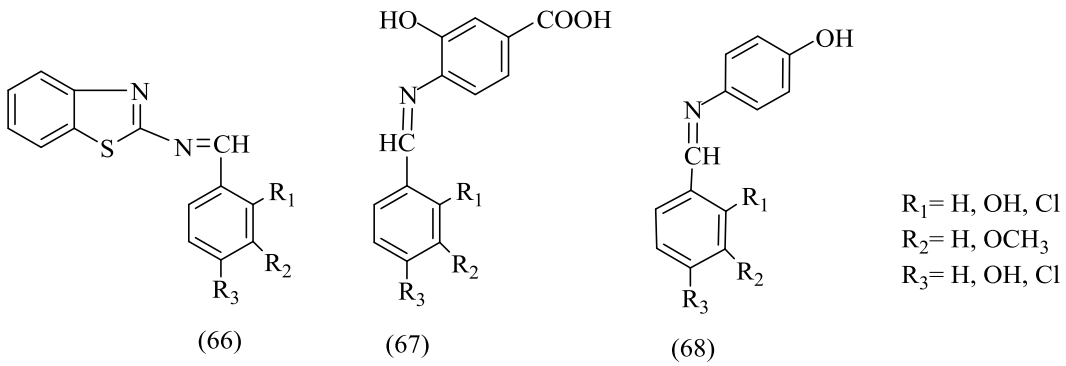
There are a number of application methods for preparation of Schiff bases. In classic manner of synthesis also known as the organic synthesis, Which typically involves solvent removal from the reaction mix or abstraction of liquid exclusively in the case of high boiling aprotic dipolar solvents, or isolation of the product through the extraction of liquid- liquid. [90, 93]

M. S. Suresh et al. [94] were synthesized Schiff base (65) from reaction of 1-phenyl-2,3-dimethyl-4-aminopyrazol-5-one (4-aminoantipyrine) with vanillin. The mixture was refluxed for 5 h.



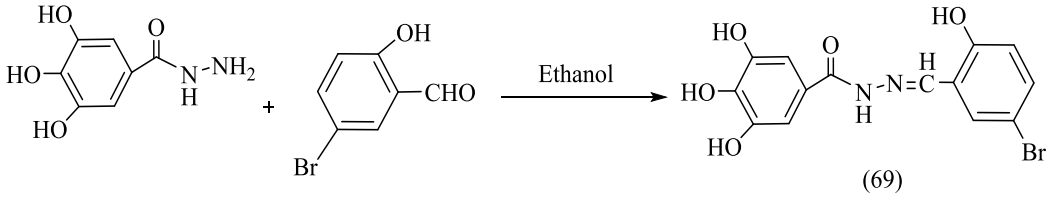
(65)

A series of new Schiff bases resulted from the acid catalyzed condensation of aryl aldehydes with aromatic and heteroaromatic amines. The structures of the Schiff bases synthesized from starting material mentioned above are 2-amino-benzthiazole (66), 4-aminosalicylic acid (67) and 4-aminophenol (68) are shown in below. [95]



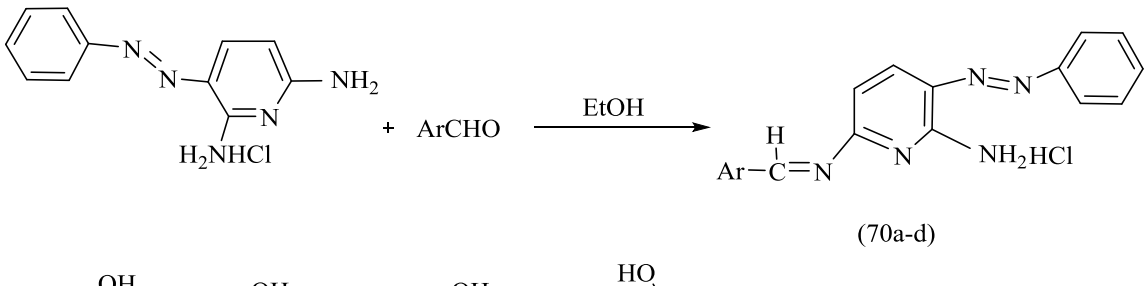
(66) (67) (68)

A new hydrazide Schiff base (5-bromo-2-hydroxybezylidene)-3,4,5-trihydroxybenzohydrazide (69) was prepared by refluxing 3,4,5-trihydroxybenzhydrazide with an ethanolic of 5-bromo-2-hydroxybenzaldehyde. [96]

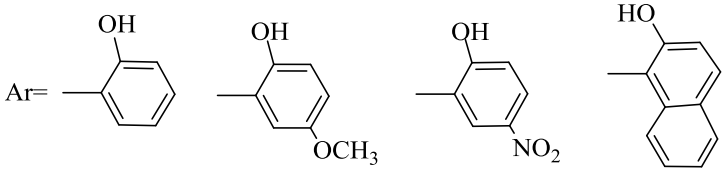


(69)

The Schiff bases (70a-d) were synthesized and investigated by elemental analysis, FT-IR, ^{1}H-NMR, ^{13}C-NMR, UV–Vis and MS spectroscopic techniques. [97]

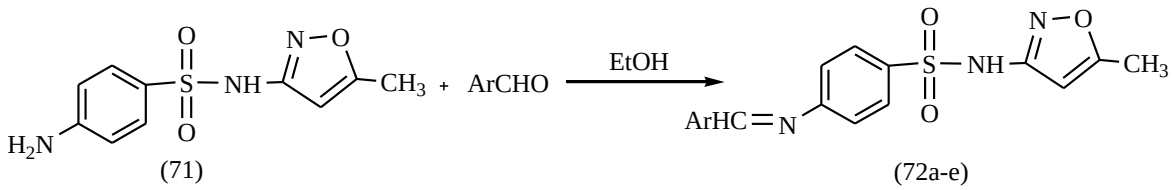


(70a-d)



(a) (b) (c) (d)

Z. Hussain et al. [98] were synthesized five new series of Schiff bases. Schiff bases (72a-e) were produced by the reaction of sulfamethoxazole (71) and aldehydes in ethanol. These compounds were characterized through different physical chemical techniques such as m.p (melting point), elemental analysis, FTIR spectroscopy, and multinuclear ^{1}HNMR.

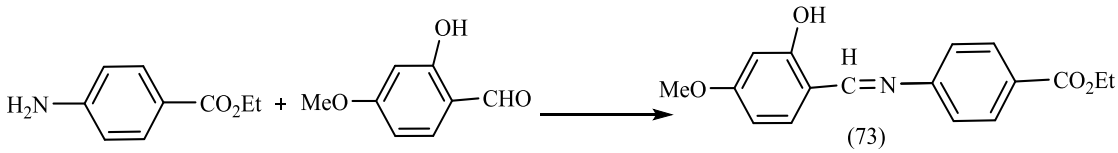


(71) (72a-e)

Ar= 2-HOC_6H_4, 4-N,$N^-(Me)_2C_6H_4$, 3-$NO_2C_6H_4$, 4-BrC_6H_4, C_6H_5

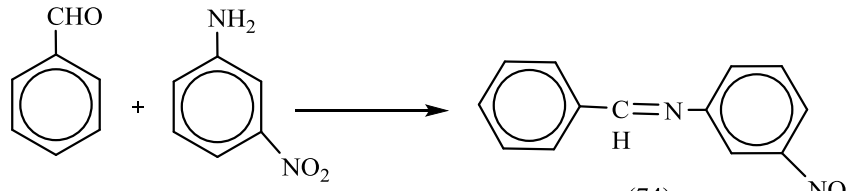
(a) (b) (c) (d) (e)

The Schiff base (73) was prepared by refluxing in ethanol an equimolar mixture of ethyl-4-aminobenzoate with 2-hydroxy-4-methoxybenzaldehyde. (99)



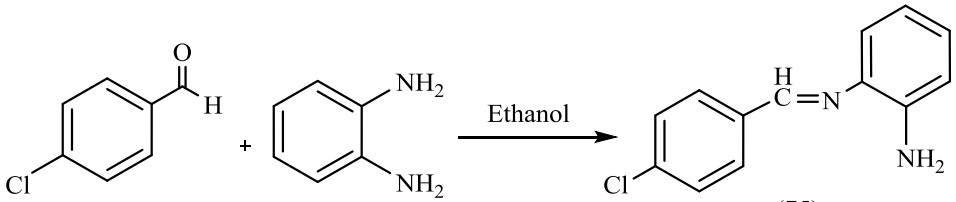
(73)

The Schiff base of *m*-nitroaniline (74) was prepared by reaction of benzaldehyde with *m*-nitroaniline. (100)



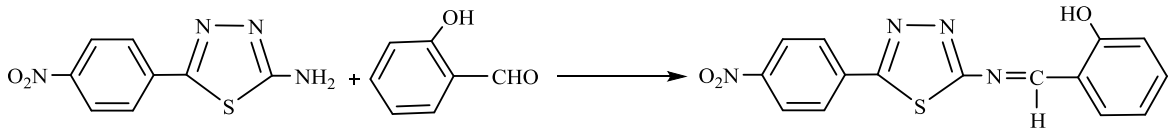
(74)

A Schiff base [(E)-N^1-(4-chlorobenzylidene)benzene-1,2-diamine] (75) was synthesized by microwave irradiation from reaction of *p*-chlorobenzaldehyde and *o*-phenylenediamine. (101)



(75)

E. Yousif et al. (102) were synthesized Schiff base (76) via reaction of 5-(*p*-nitrophenyl)-1,3,4-thiadiazole-2-amine with salicyaldehyde.



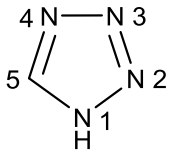
(76)

1.15 Biological activity of Schiff bases

Imines also demonstrate a large extent of biological efficiencies; containing antimycotic, antibacterial, antimalarials, anti proliferative, antiinflammatory, anti viral, anticancer, antitumor and anti pyretic properties. [103, 104] Imine or azomethine groups exist in natural, natural derivatives and non natural compounds. The amino group found in these compounds has proven to be of great importance in their biological activities. [105, 106] Schiff bases are significant compounds because they have wide range of industrial applications. [107]

1.16 Tetrazoles

Tetrazoles are class of synthetic organic heterocyclic compounds consisting of five-member ring of four nitrogen and one carbon atom (plus hydrogen).The simplest is tetrazole itself CN_4H_2. It is white to pale yellow crystalline solid with weak characteristic odour, soluble in water and alcohol. It is acidic in nature due to presence of four nitrogen atoms. Numbering of tetrazoles is as shown below. [108, 109]



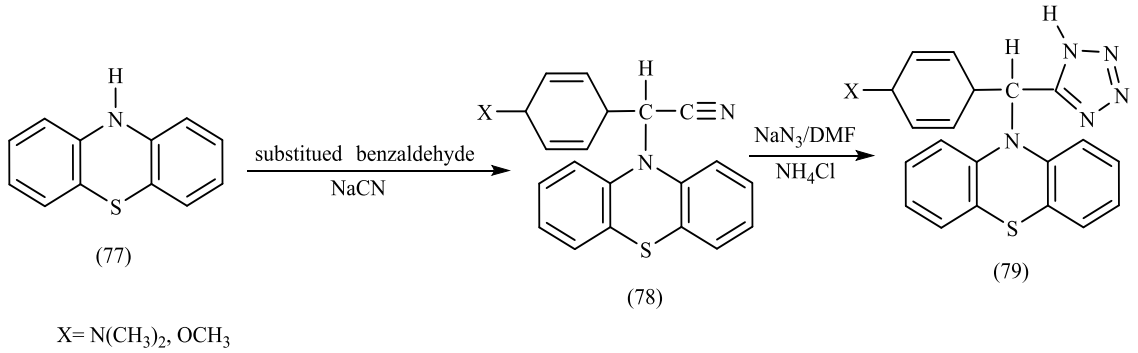
1H-tetrazole

1.17 Synthesis of tetrazole derivatives

The proton acid-catalyzed cycloaddition between hydrazoic acid and nitriles has long been one of the main routes to 5-substituted tetrazoles. However, this standard procedure suffers a dangerous potential explosion with large excess amounts of harmful hydrazoic acid. Consequently, it is

urgent to improve the synthetic method of obtaining 5-substituted-1H-tetrazoles. A number of catalytic systems of [3+2] reaction of sodium azide and nitriles were reported by various research teams, such as Zn(II) salts, [110–112], $AlCl_3$. [113]

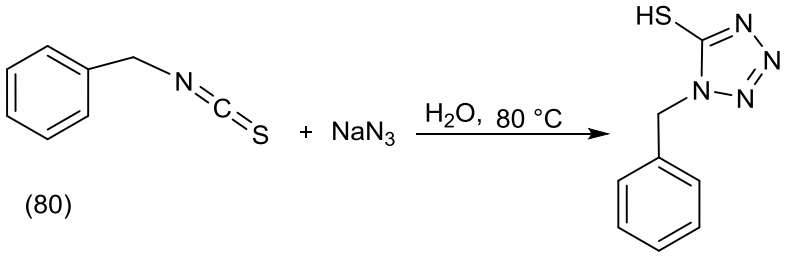
S. Arulmurugan et al. [114] were synthesized novel tetrazole derivatives from phenothiazine. Phenothiazine (77) is first converted into corresponding nitrile by reacting it with aldehyde, sodium metabisulphite and sodium cyanide. The nitrile (78) on treatment with NaN_3/DMF yielded the tetrazole derivative (79).



(77) (78) (79)

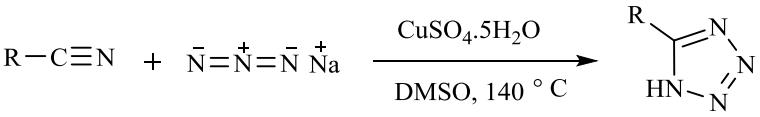
X= $N(CH_3)_2$, OCH_3

Reaction between commercially available benzyl isothiocyanate (80) and sodium azide in water provided 1-benzyl-1H-tetrazole-5-thiol (81) in good yield. [115]



(80) (81)

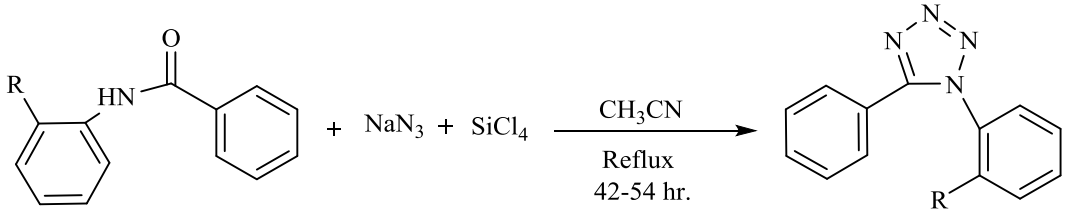
B. Akhlaghinia et al. [116] have been synthesized a series of 5-substituted-1H-tetrazoles (RCN_4H) (82) by cycloaddition reaction of different aryl and alkyl nitriles with sodium azide in DMSO using $CuSO_4.5H_2O$ as catalyst.



(82)

R= Ph, 4-BrC_6H_4, 4-ClC_6H_4, 4-CNC_6H_4, 2-$NO_2C_6H_4$, 2-NH_2-5-NO_2-C_6H_3, 4-$EtOC_6H_4$, 3,5-di-$MeOC_6H_3$, 3-MeC_6H_4, 4-HOC_6H_4, 9-phenanthrene, 2-thiophene, 4-pyridine, 2-pyridine, $(CH_3)_2CHCH_2$, $(CH_3)_2CH(CH_2)_2$, $PhCH_2$

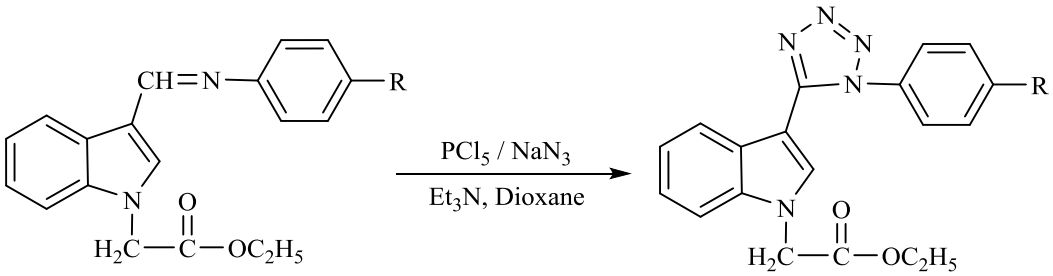
P. Najafi et al. [117] used a one-step method for the conversion of bulky secondary N-benzoyl amides (83) to sterically hindered 1,5-disubstituted tetrazoles (84) in 83%-88% yields using silicon tetrachloride in the presence of sodium azide and acetonitrile as solvent.



(83) (84)

R= CF_3, F, Cl

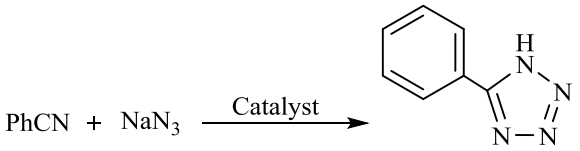
S. Muralikrishna et al. [118] were synthesized (86) by reaction of Schiff base (85) with sodium azide in PCl_5 and Et_3N.



(85) (86)

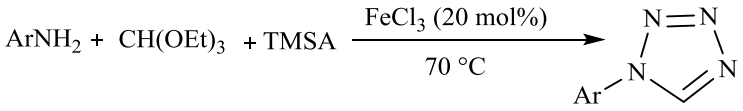
R= H, CH_3, OCH_3, Br, NO_2, CF_3

L. Zamani et al. [119] were synthesized 5-phenyl-1H-tetrazole (87) via the reaction of benzonitrile by sodium trinitride in the presence of nano-$TiCl_4.SiO_2$ in various solvent.



(87)

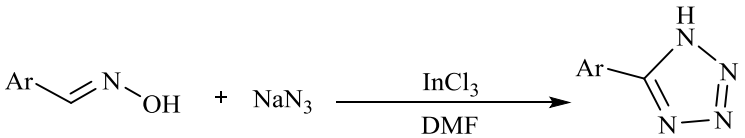
An efficient procedure for the preparation of 1-substituted-1H-1,2,3,4-tetrazoles (88) via a three-component condensation of triethyl orthoformate, amine, and trimethylsilyl azide (TMSA) using inexpensive and environment-friendly $FeCl_3$ as catalyst under solvent-free conditions has been reported. [120]



(88)

Ar = C_6H_5, 4-MeO-C_6H_4, 4-Et-C_6H_4, 3,4-Me_2-C_6H_3, 4-Br-C_6H_4, 4-Cl-C_6H_4, 3-NO_2-C_6H_4, 4-NO_2-C_6H_4, 2-C_5H_4N

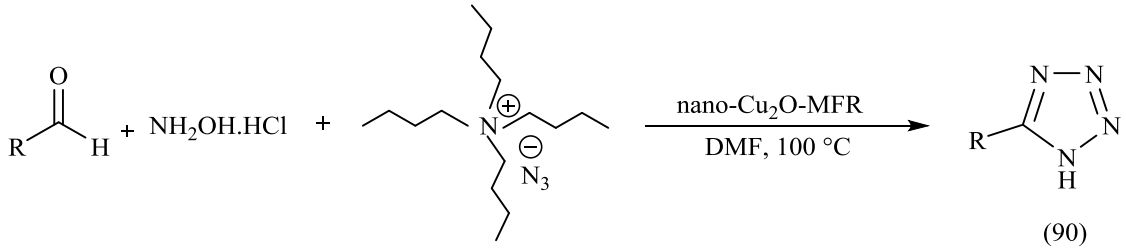
5-Substituted-1H-tetrazole derivatives (89) can be prepared in good to excellent yields from various oximes and sodium azide by using indium(III) chloride as a Lewis acid catalyst. [121]



(89)

Ar= 4-Br-Ph, 3-F-Ph, 4-F-Ph, 4-O_2N-Ph, 4-Meo-Ph

5-Substituted-1H-tetrazole (90) were synthesized form the reaction of benzaldehyde with hydroxylamine hydrochloride and tetrabutylammonium azide (TBAA) in the presence of nano-Cu_2O–MFR. [122]



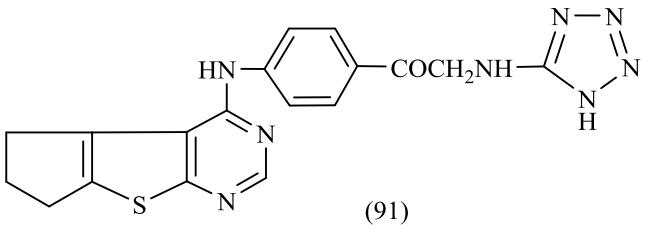
(TBAA) (90)

R= alkyl and aryl

1.18 Biological activity of tetrazole derivatives

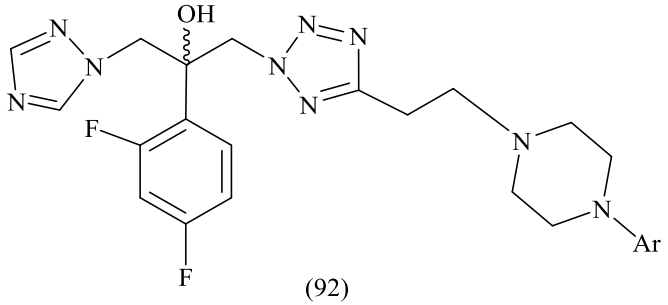
Tetrazole compounds and their derivatives were applied in biological activities like antifungal; antibacterial; antitubercolous; antiviral; cyclo-oxygenase inhibitors; antinociceptive; anticancer and hypoglycemic efficiencies. They are consumed like catalyst in the phosphonates synthesis.

M. D. Salahuddin et al [(123)] were synthesized several new {benzothieno[2, 3-d] pyrimidines} and prepared compounds are effective versus the bacteria like *Escherichia coli*, *Staphylococcus aureus*, *Bacillus subtilis*, and *Bacillus pumilis* however the {thieno[2,3-d] pyrimidine derivatives} including tetrazole ring (91) displays mild anti-bacterial efficiency.



(91)

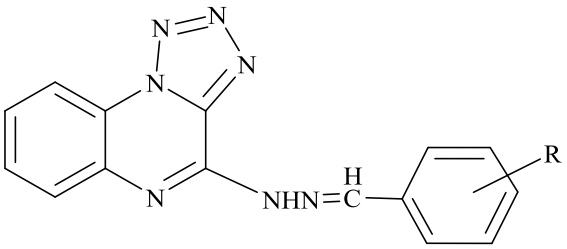
R. S. Upadhyaya et al. [(124)] were prepared new substituted tetrazoles (92) possessing anti-fungal efficiency. The derivatives holding piperidine are found to be extremely effective.



(92)

U. Natarajan et al. [(125)] a new synthetic methodology has been reported from imines integrating {tetrazolo quinoxalines} (93). All newly synthesized heterocycles were examined their anti-inflammatory and antimicrobial effectivenesses *in vitro*. Few of them showed promising efficiency. Ambient conditions, exceptional product yields and easy working ways make this

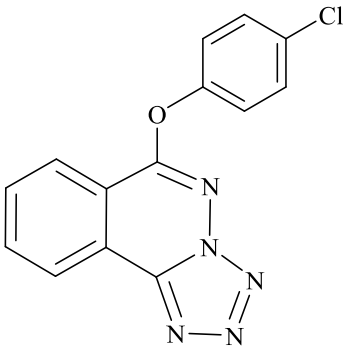
synthetic strategy the best protocol for synthesizing newer Schiff bases derivatives.



(93)

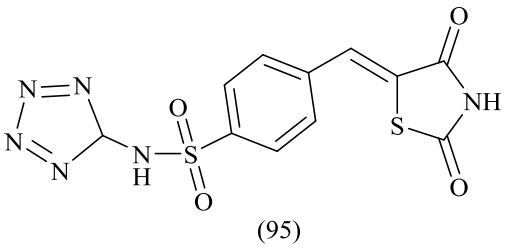
R = 2-OH, 3-OH, 4-OH, 2-NO_2, 3-NO_2, 4-NO_2, 2-Cl, 4-Cl, 2-$N(CH_3)_2$, 3,4,5-OCH_3

X-Y Dun et al. [126] noted the anti-convulsant efficiency of {6-(4-chlorophenoxy)-tetrazolo[1,5-a] phtalazine} (94) in various experimental seizure models.



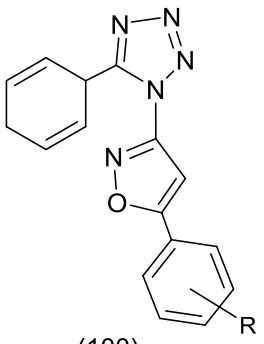
(94)

Pataan S. R. and its workers [127] has produced novel 2,4-thiazidolidione compounds having the tetrazole (95) due to of their anti-diabetic activity. Most compounds appeared good anti-diabetic efficiency while compared by glibenclamide.



(95)

V. H. Bhaskar et al. .[129] a synthesis, identification and assessment of anti-cancer efficiency were reported for several tetrazole derivatives in that dissimilar tetrazole derivatives comprising isoxazole (100) were prepared.

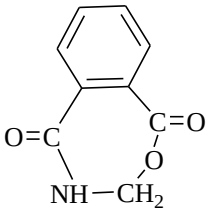


(100)

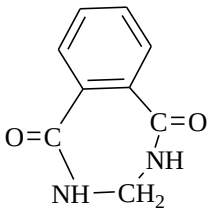
R= H, 2-Cl, 4-Cl, 4-Br, 4-OCH_3, 3-NO_2, 4-CH_3, 4-N-$(CH_3)_2$

1.19 Oxazepines and diazepines

"Oxazepine" refers to any seven-membered ring was containing an oxygen and nitrogen atom but diazepine was containing two nitrogen atoms. The 1,3-oxazepine is a branch of many types of the heterocyclic oxazepine. [129, 130] The core structure of 1,3-oxazepine and diazepine-4,7-diones consists of a seven memebred ring along with two carbonyl group. through the years, the synthesis of oxazepine and diazepine compounds were inspected and documented.



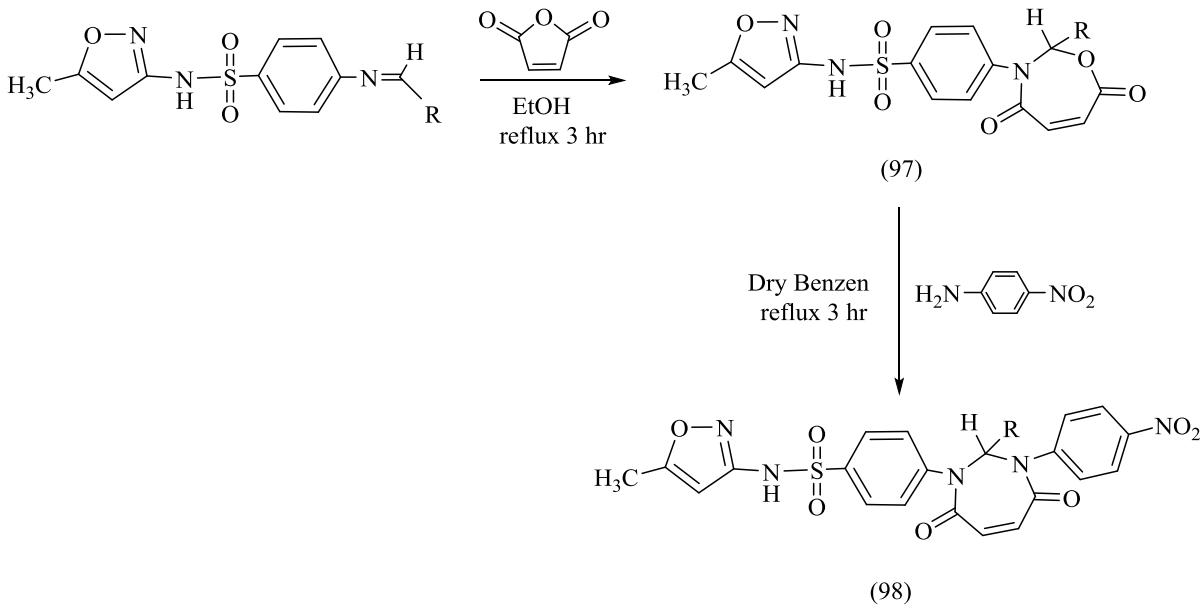
1,3-oxazepine-4,7-dione



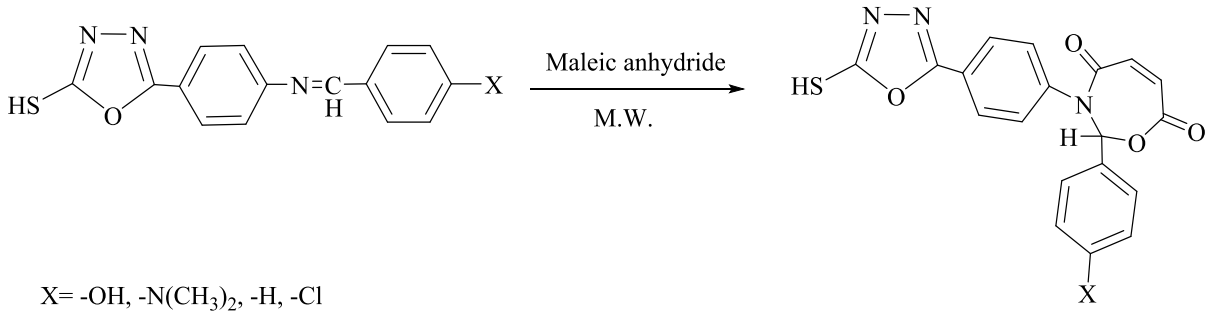
1,3-diazepine-4,7-dione

1.20 Synthesis of oxazepine and diazepine derivatives

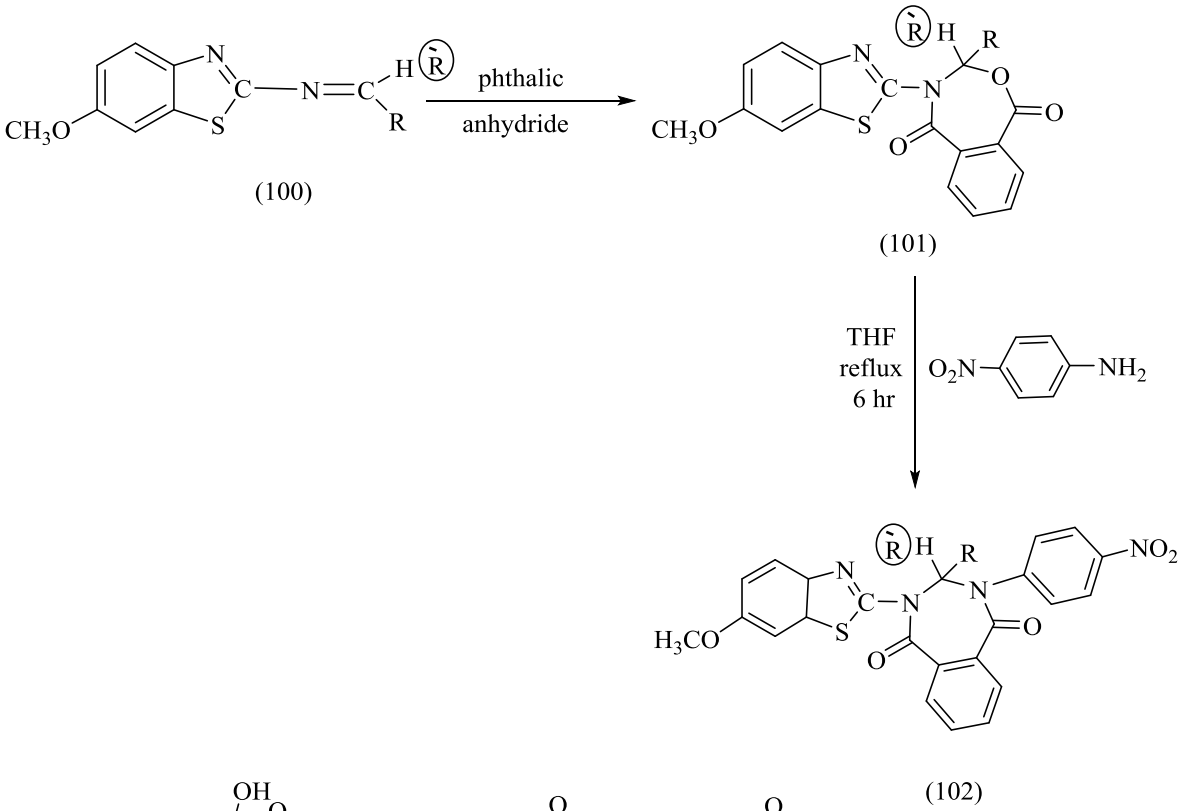
Schiff base reacted with phthalic anhydride, maleic anhydride and substituted phathalic anhydride to give oxazepine derivatives that were reacted with primary aromatic amines to produce diazepine derivatives. Azomethine compounds react with maleic anhydride, to give 1,3-oxazepine-4,7-dione derivatives (97) which react with primary aromatic amines to give the corresponding 1,3-diazepine-4,7-dione (98). [131]



A. Hameed [132] was prepared 1,3-oxazepine compounds (99a-d) by microwave irradiation.



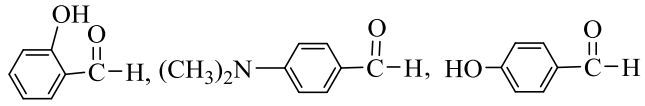
Schiff bases (100) reacted with phthalic anhydride to give oxazepine derivatives (101) that were reacted with primary aromatic amines to give diazepine derivatives (102). [133]

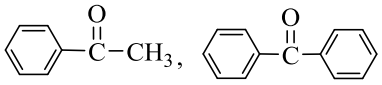


(100)

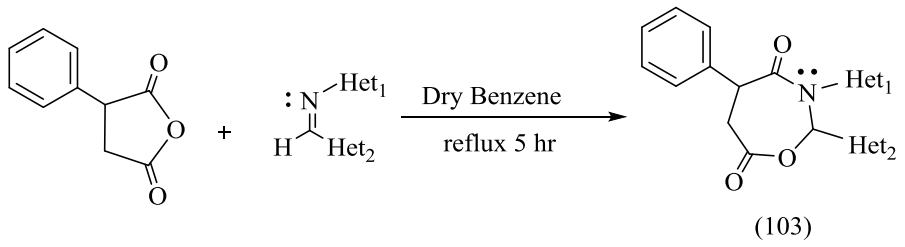
(101)

(102)

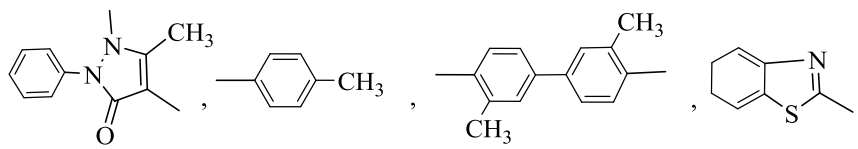
RCHO= 

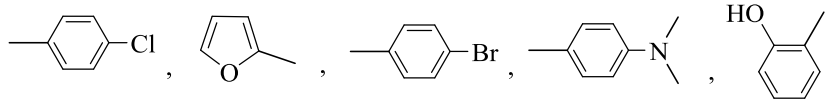
RCOR= 

The synthesis of novel 1,3-oxazepane-4,7- dione (103) were achieved by the polar cycloaddition reaction of imines with phenyl succinic anhydride fairly anhydrous benzene at reflux condition. [134]



(103)

Het_1= 

Het_2= 

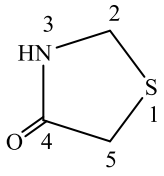
1.21 Biological activity of oxazepine and diazepine derivatives

Oxazepines as a "privileged scaffold". They were a recognized class of seven-membered heterocycles together with (2) heteroatoms. The molecular properties of this pharmaceutically important nucleus have been extensively studied due to its presence in some natural products and biologically active compounds. [135] Among the biological activities, it is worth mentioning antithrombotic, [136] antiepileptic, [137] anticonvulsant, [138] anti-inflammatory, [139] progesterone agonist, [140] antifungal, [141] antagonist and analgesic, [142] antipsychotic, [143] anxiolytics, [144] antihistaminic, [145] antiaggregating, [146] and epidermal growth factor receptor (EGFR) tyrosine kinase inhibitory [147] activities.

Many of the benzodiazepines and their oxides showed interesting sedatives, muscle relaxant and anticonvulsant properties, in animals. Diazepine (valium) are a class of drugs used as relaxants, minor tranquilizers, hypnotics and muscle relaxant because it is often seen in forensic and clinical cases. [148- 154]

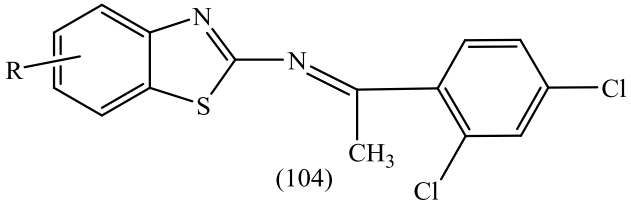
1.22 Thiazolidinones

Thiazolidinones were the derivatives of thiazolidine and possess a sulfur atom in location 1, a carbonyl group in site 2, 4, or 5 and a nitrogen atom in position 3 . Nevertheless, its derivatives related to the most repeatedly studied moieties and their existence in penicillin was the first avowal of its appearance in nature. [155] Similary {1,3–thiazolidin-4-ones} were heterocyclic nucleus containing an atom of sulfur and nitrogen in positions 1 and 3, respectively and the carbonyl group in position 4 have been widely studied in recent years.



1.23 Synthesis of thiazolidinone derivatives

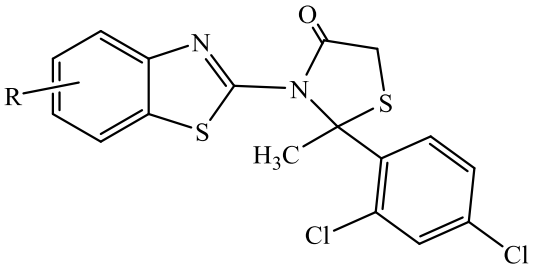
K. Mistry et al. [156] has carried out the microwave assisted synthesis of thiazolidinone (105) from the Schiff bases (104) by using 2-mercaptopropionic acid**.**



(104)

Conventional 15-16 hr
Microwave 6-7 min

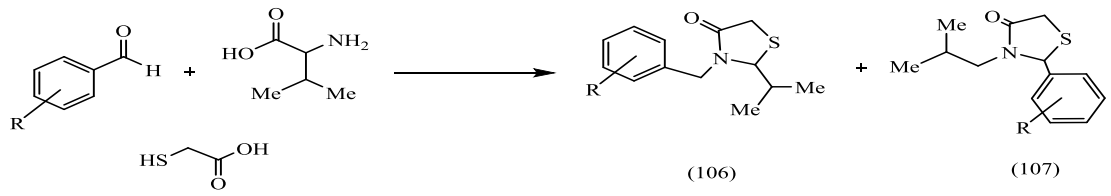
$HSCH(CH_3)COOH$



(105)

R= 6-NO_2, 6-SO_3H, 6-OH, 4-NO_2, 5-Cl, 6-OCH_3, 6-CH_3, 4-OCH_3, 4,6-$(NO_2)_2$, 6-$NHCOCH_3$

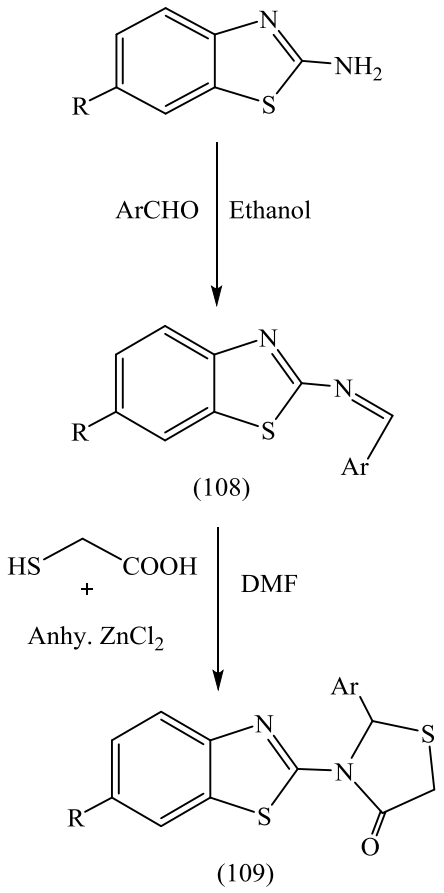
Novel route to the synthesis of 2-isopropyl-3-benzyl-1,3-thiazolidin-4-ones (106) and 2-phenyl-3-isobutyl-1,3-thiazolidin-4-ones (107) by using 1:1:3 mole ratio of valine, arenealdehyde and mercaptoacetic acid was reported by W. Cunico et al. [157] and suggested that the insertion of strong withdrawing group, NO_2, present on benzaldehyde favored the synthesis of hetero-cycle (106) in good yields, whereas the methoxy and fluoro groups produces the type (107) thiazolidinones.



(106) (107)

R = F, NO_2, MeO

Some 2-aryl-3-(substituted benzothiazolyl)-1,3-thiazolidine-4-ones (109) have been synthesized by the reaction of substituted-2-aminobenzothiazole with aromatic aldehyde (benzaldehyde, *p*-chlorobenzaldehyde, anisaldehyde, salicylaldehyde) to give (108) followed by cyclic condensation with mercaptoacetic acid. [158]

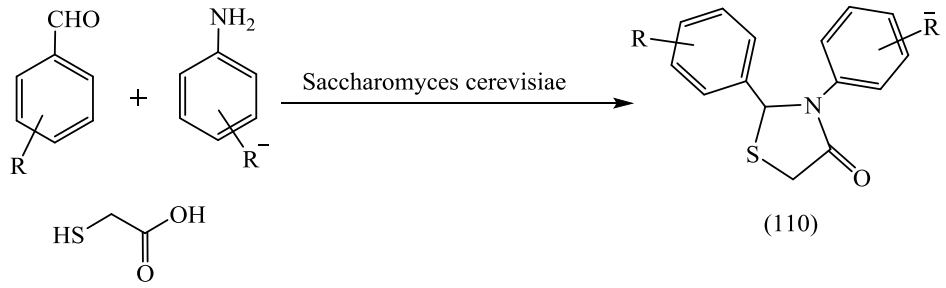


(108)

(109)

R = Cl, OC_2H_5, CH_3
Ar = C_6H_5, *o*-HOC_6H_4, *p*-$CH_3OC_6H_4$, *p*-ClC_6H_4

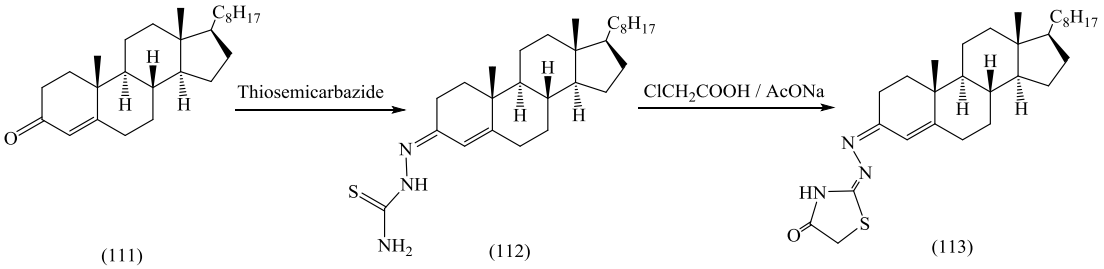
Another method was reported by U. R. Pratap et al. [159] to synthesize {2,3-diaryl-4-thiazolidinones} (110) where in {Saccharomyces cerevisiae} (baker'ssourness) which contains lipase enzyme has been used as a catalyst that quicker the construction of azomethines as well cyclo-condensation of the amines, aryl aldehydes and thioglycolic acid.



(110)

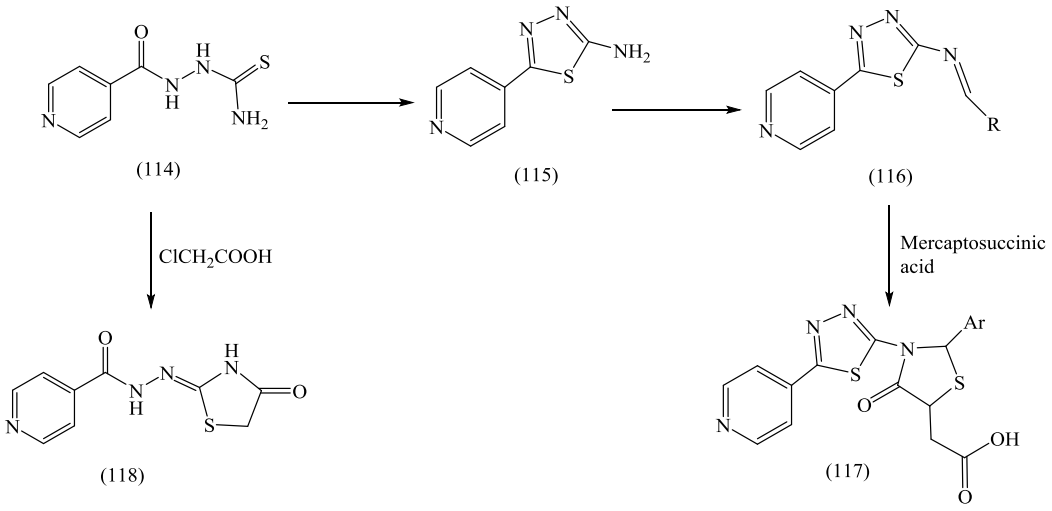
R= H, *p*-OCH_3, *m*-Cl, *m*-NO_2, *p*-OH, *p*-*Cl*
$\bar{R}$= H, *p*-CH_3, *p*-Cl

S. Shamsuzzaman et al. [160] informed the preparation of {3-diazo (4'-thiazolidinone)cholest-4-ene} (113) from {cholest-4-ene-3-one thiosemicarbazone} (112) and $ClCH_2CO_2H$ in the existence of CH_3CO_2Na. The compound (112) was gotten via interaction between thiosemicarbazide and a {chlost-4-en-3-one} (111) in the entity of hydrochloric acid concentrated.



(111) (112) (113)

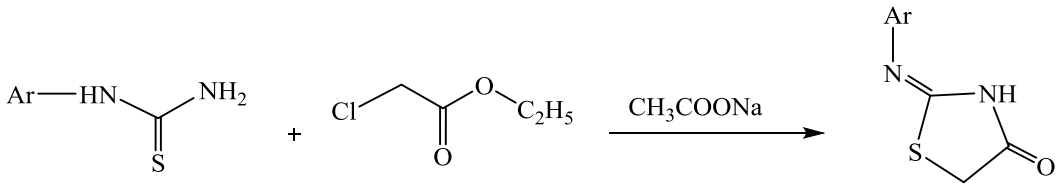
R. Sharma et al. [161] were prepared {2-amino-5-(4'-pyridyl)-1,3,4-thiadiazole} (115) via cyclization of {isonicotinoyl thiosemicarbazide} (114) along with H_2SO_4 concentrated. while (115) was refluxed with different aldehydes. The corresponding erylidene derivatives (116) were given and on which furthermore dealing with mercaptosuccinic acid supplied thiazolidinone derivative (117). Other derivative of thiazolidinone [2-isonicotinoylhydrazido-1,3-thiazolidinone] (118) was gotten via sequential treatment of isonicotinoyl thiosemicarbazide (114) with chloroethanoic acid in the existence of sodium ethanoate.



(114) (115) (116) (118) (117)

Ar= 4-$CH_3OC_6H_4$, 4-ClC_6H_4, 3,4,5-$CH_3OC_6H_2$, 3-$NO_2C_6H_4$, 4-$NO_2C_6H_4$, 4-$(CH_3)_2NC_6H_4$, C_6H_5, C_4H_3O (2-furyl)

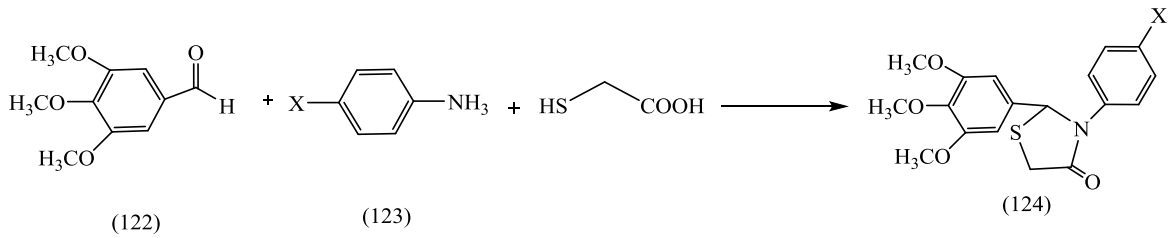
M. R. Shiradkar et al. [162] were reported that many of {aryl-thioureas} (119) on treatment with ethyl chloroacetate (120) and fused (CH_3CO_2Na) in an (C_2H_5OH) provided 2-arylimino-4-thiazolidinones (121).



(119) (120) (121)

Ar = C_6H_5, 2-HOC_6H_4, 4-ClC_6H_4, 4-MeC_6H_4, 3-$NO_2C_6H_4$

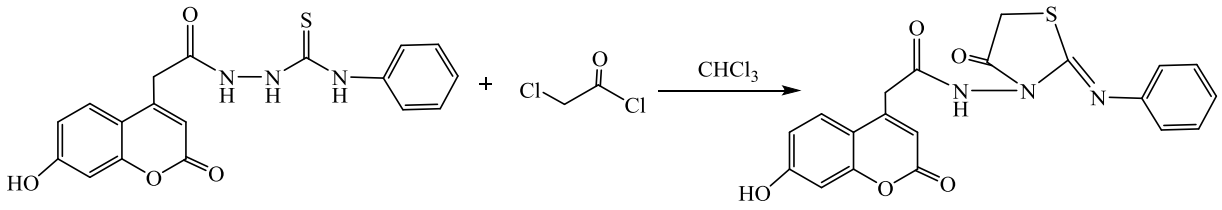
Z. Turgut et al. [163] preparation of {4-thiazolidinones} (124) via the Katti cabodiimide (DCC) by the one-pot three component condensation reaction of an aldehyde (122), an aromatic amine (123) and mercaptoacetic acid.



(122) (123) (124)

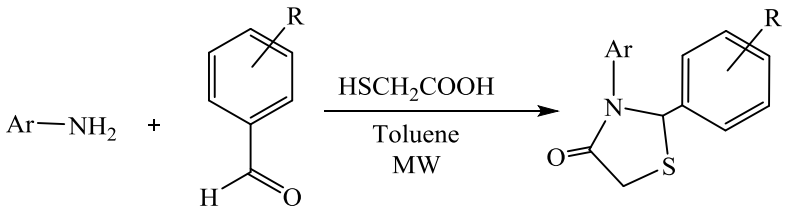
X= CH_3, Cl, OC_6H_5, OCH_3, OC_2H_5

M. Cacic et al. [164] recorded the cyclization of thiosemicarbazide derivative (125) with chloroacetyl chloride in ($CHCl_3$) that awarded thiazolidinone derivative (126).



(125) (126)

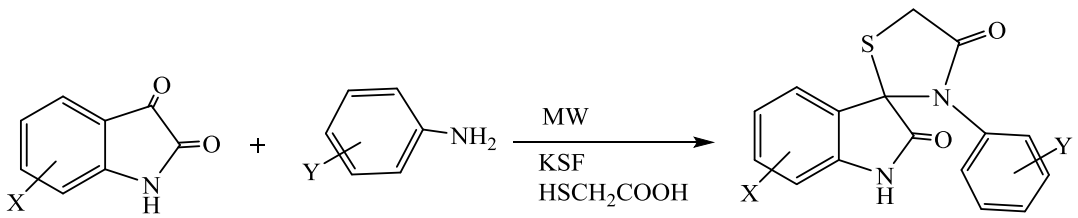
D. Sriram and others [165] reported that the synthesis of the 2,3-diaryl-1,3-thiazolidin-4-ones (129) has been accomplished by reacting substituted benzaldehyde (128) with equimolar quantity of the suitable substituted aromatic amine (127) in the entity of excess of mercaptoacetic acid in toluene beneath microwave radiation. versa from conventional methods (period of the reaction 48 h and yields of (30-70)%); microwave-assisted interactions were very simplistic (6-8 min.) and given very good yields (64-82%).



(127) (128) (129)

Ar= 4-F-C_6H_4-, R=4-Cl, 2-Cl

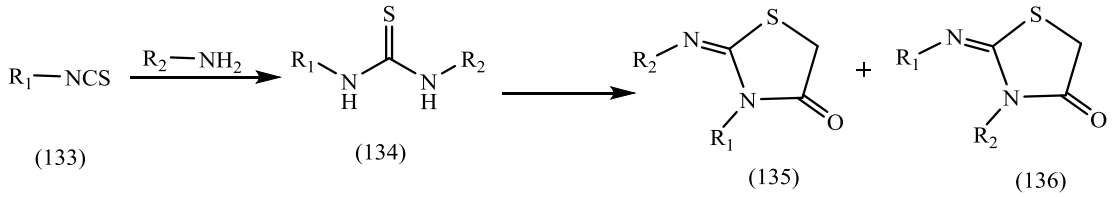
K. Arya et al. [166] prepared *spiro*[indole-thiazolidinones] (132) by the multi ingredient condensation through indole-2,3-dione (130), amines (131) and ($HSCH_2CO_2H$) consuming montmorllonite KSF such as solid support in 85-90%, yield in (4-5 min) below MW interaction provisions.



(130) (131) (132)

X= H, 5-Cl, 5-CH_3 Y= OCH_3

The reaction between the aryl or alkyl isothiocyanate (133) and primary amine were providing the matching {thiourea derivative} (134), that was immediately cyclized by treating with halo acetic acid to the analogous two isomeric {2-imino-thiazolidin-4-ones} of the common structures 135 and 136. (167)

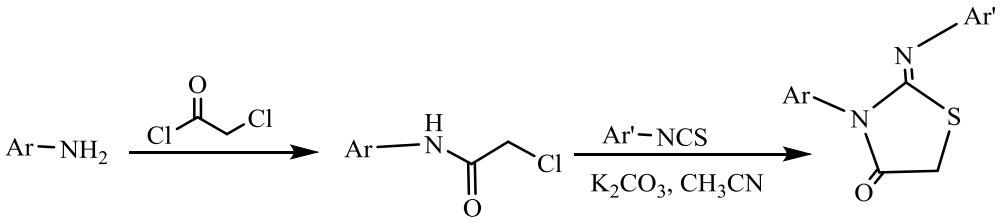


(133) (134) (135) (136)

R_1 = 2-MeC_6H_4, 3-MeC_6H_4, 4-MeC_6H_4, 2,6-$Me_2C_6H_3$, 2-ClC_6H_4, 2-$MeOC_6H_4$, 3-pyridyl, cyclohexyl, $C_6H_5CH_2$-

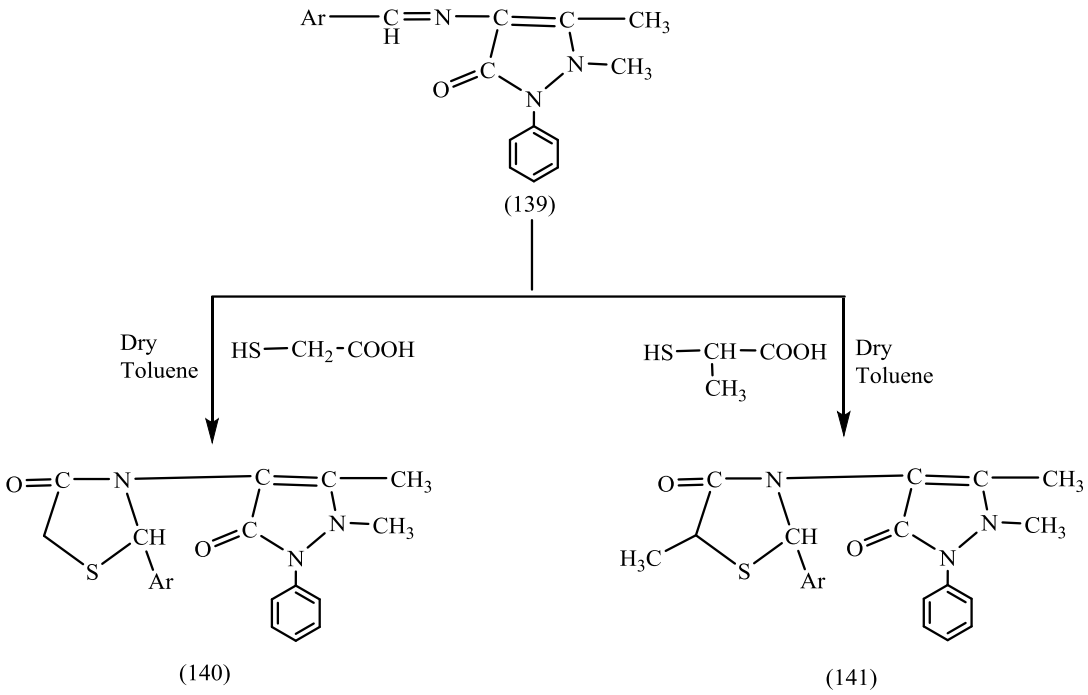
R_2 = Me_2CH-, $MeCH_2CH_2$-

Coupling reaction among of the α-chloroamide derivatives (137) with isothiocyanate in existence of a slight base awarded the iminothiazolidinone derivatives (138). (168)



(137) (138)

Condensation of 4-amino-2,3-dimethyl-1-phenyl-3-pyrazoline-5-one with different aromatic and heterocyclic aldehydes in dry toluene gave azomethines (139), that on reaction with mercaptoacetic acid and 2-methylmercaptoacetic acid in dry toluene give the corresponding 2,3-disubstituted-4-thiazolidinones (140) and 2,3-disubstituted-5-methyl-4-thiazolidinones (141). (169)

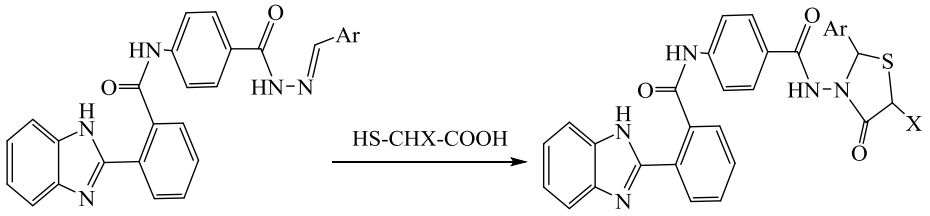


(139)

(140) (141)

Ar = 2,5-$(MeO)_2C_6H_3$, 2,4-$(Cl)_2C_6H_3$, 4-FC_6H_4, 2-HOC_6H_4, 4-N,N-$(Et)_2$-2-HOC_6H_3, 3-Br-4-HO-5-$MeOC_6H_2$, 6-C_9H_6N

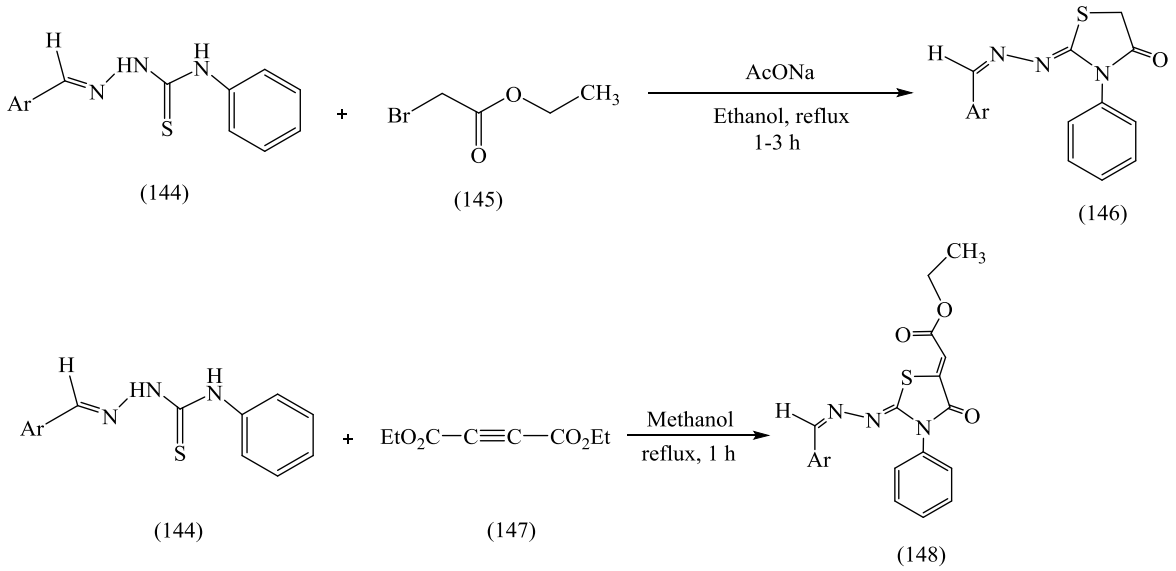
Synthesis of new thiazolidinone derivatives (143) were possessing benzimidazole nucleus by condensation reaction of various substituted Schiff bases, (142) and mercapto acids in presence of anhydrous $ZnCl_2$. [170]



(142) (143)

X = H, CH_3, CH_2COOH
Ar = C_6H_5, 4-$NH_2C_6H_4$, 2-ClC_6H_4, 3,4-$(Me)_2C_6H_3$, 3,4-$(MeO)_2C_6H_3$, 2-$C_4H_3OC_6H_4$, 2-HOC_6H_4, 4-$MeOC_6H_4$, 4-$N(Me)_2C_6H_4$

They present here the synthesis in good yields of two series of highly functionalized thiazolidinone derivatives (146, 148) from the reactions of various 4-phenyl-3-thiosemicarbazones (144) with ethyl 2-bromoacetate (145) or diethyl acetylenedicarboxylate (147), respectively. [171]

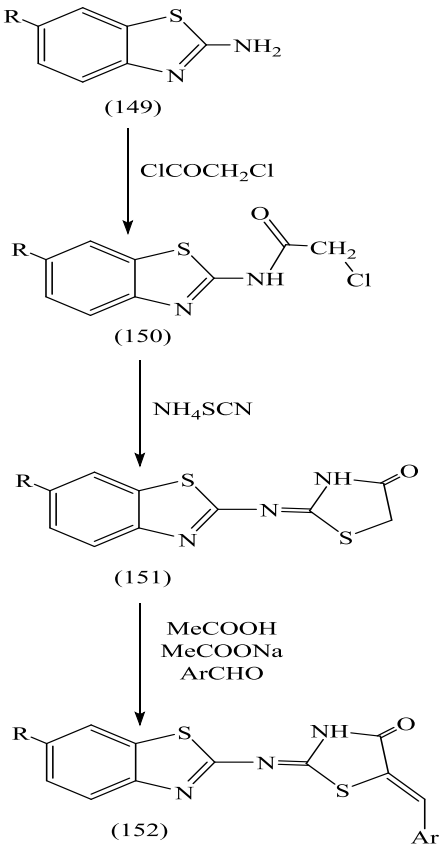


(144) (145) (146)

(144) (147) (148)

Ar = 4-$NO_2C_6H_4$, 2,3-$(NO_2)_2C_6H_3$, 3,4,5-$(MeO)_3C_6H_2$, 4-$CH_3SO_2C_6H_4$, $CH_3SC_6H_4$, 4-$CF_3C_6H_4$

5-Substituted-4-thiazolidinone derivatives (152) were synthesized through chloroacetylation of 2-aminobenzothiazole derivatives (149) to give (150) and further cyclised by the use of ammonium thiocyanate to afford (151) then subjected to different aryl and heteroaryl aldehydes. [172]

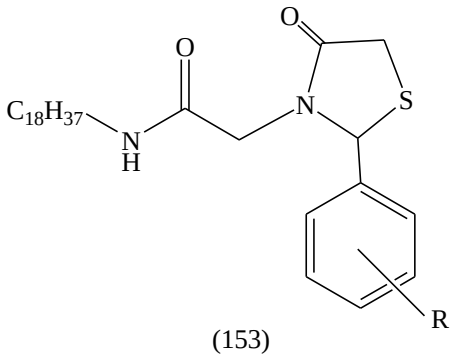


(149) (150) (151) (152)

R= H, $COOC_2H_5$
Ar= 2-thionyl, 3-$CH_3OC_6H_4$, 3-pyridyl, 2-furyl

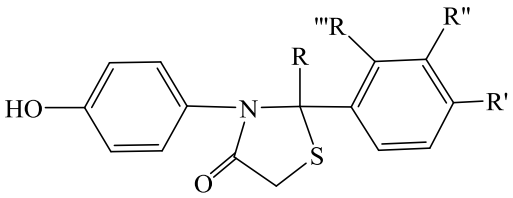
1.24 Biological activity of thiazolidinone derivatives

V. Gududuru et al. [173] description the preparation and vitality were estimation of novel {2-aryl-4-oxothiazolidin-3-yl amides} (153) counter to the prostate cancer cells.



(153)

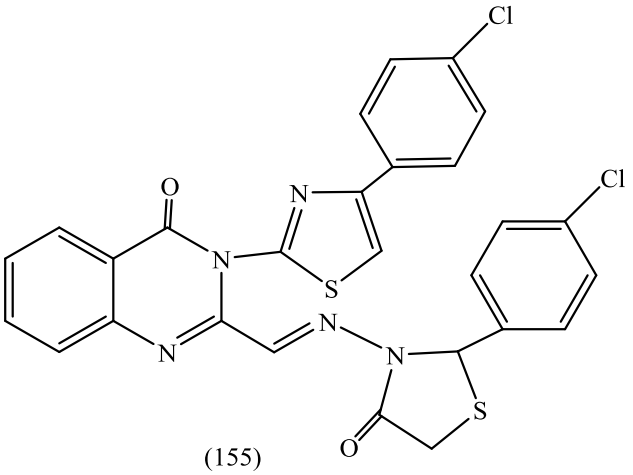
A. D. Taranalli et al. [174] prepared a concatenation of {thiazolidine-4-one derivatives} (154a,b) of sulfanilamide and appraised for antiinflammatory, analgesic and anti-ulcer efficiency. The compound (154a) and the compound (154b) with substitution R'-CH_3 displayed potential effectiveness.



(154)a,b

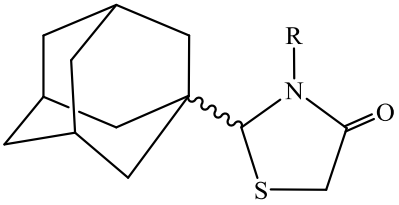
(154a) R= H, R'= H, R''= H, R'''= H
(154b) R= H, R'= CH_3, R''= H, R'''=H

A. Kumar et al. [175] prepared a combination of {3-[4'-(*p*-chlorophenyl)thiazol-2'-yl]-2-[(substitutedazetidinone/thiazolidinone) aminomethyl]-6-bromoquinazolin-4-ones} (155) and estimated them for analgesic and anti-inflammatory efficiencies.

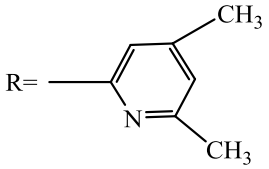


(155)

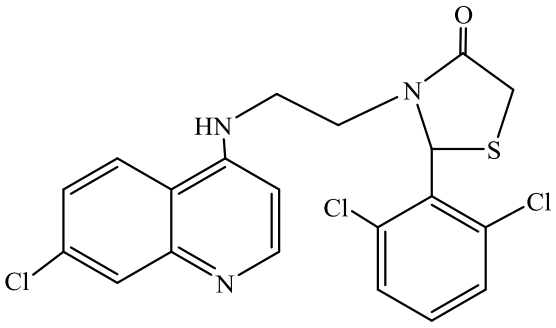
J. Balzarini and its workers [176] prepared a chain of new {thiazolidin-4-one} (156) bearing a lipophilic adamantyl substituent in location 2, and versatile alternatives on the nitrogen atom of the thiazolidine ring; while many compounds showed a modest HIV-1 activity.



(156)

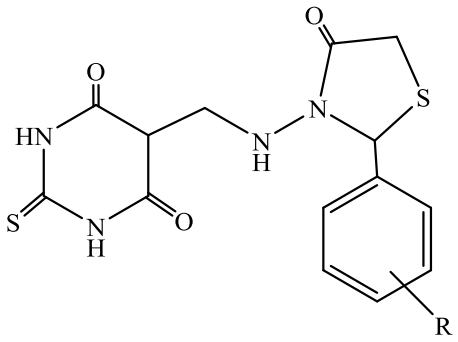


V. R. Solomon et al. [177] were reported to synthesis chloroquine analogues containing 1,3-thiazolidin-4-one nucleus with the amino group in the side chain of the 4-aminoquinoline (157). All compounds were assessed for their antimalarial activing against *P. Falciparum in-vitro* and several compounds that have exhibited their activing comparable to standard drug were too estimated versus *P. Yoelli in-vivo*.

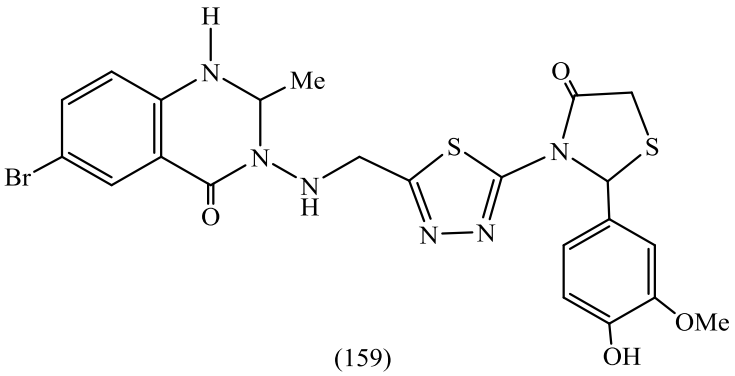


(157)

Numerous5-[(2-phenyl-4-oxo-thiazolidin-3-yl)amino]-2-oxo-thiobarbituric acids (158a,b) [178] and 3-({4-[2-alkylphenyl)-4-oxo-1,3-thiazolidin-3-yl]-1,3,4-thiadiazol-2-yl}methylamino)-2-methyl-6-monosubstituted-quinazolin-4(3H)-one (159) [179] have been synthesized by way of Cunico and its workers and estimated *in-vivo* for their anti-convulsant action.



(158a) R= *p*-OCH_3
(158b) R= *m*-OCH_3, *p*-OH



(159)

Aim of the work

L-Ascorbic acid induce researchers for further developments in organic synthesis because of their biological activity.

This work includes:-

1) Synthesis of aldehyde derived from L-ascorbic acid and three amine compounds.
2) Synthesis of Schiff bases.
3) Synthesis of tetrazole, oxazepine, diazepine and thiazolidinone derivatives.
4) Screening of biological activity for synthesized compounds against two kinds of bacteria (G+ and G-).

Chapter Two

Experimental Part

2.1 Chemicals

The chemicals used are listed in Table (2.1):

Table (2.1): Chemicals and their manufactures

Company supplied	Material	Purity %
BDH	4-Aminobenzoic acid	99.5
	4-N,N-dimethylbenzaldehyde	99.5
	Ethyl acetate	99
	4-Methoxyaniline	99
	4-Nitrophenylhydrazine	96
	Piperidine	98
	Sodium periodate	99
	Thiosemicarbazide	98
CDH	Maleic anhydride	97
	Sulfuric acid	98
CHEM-SUPPLY	Sodium azide	99
Merck	Benzene	99.7
	2,4-Dinitrophenylhydrazine	99.5
	Phosphoryl chloride	99
Riedel-de Haen	3-Chlorobenzoic acid	99
	Chloroform	99.4
	3,5-Dinitrobenzoic acid	99
	Hydrochloric acid	37
	Absolute methanol	97
	4-Methylbenzaldehyde	99
	4-Nitrobenzoic acid	99
	3-Nitrophthalic anhydride	98
	Petroluim ether	90
Romil	Anhydrous magnesium sulfate	97
	n-Hexane	99.5
	Dimethylformamide	99.9
Scharlau	Hydrazine hydrate	80
Sigma-aldrich	Absolute ethanol	99.9
	Glacial acetic acid	99.8
	Acetone	99.8
	Anisaldehyde	97
	L-Ascorbic acid	99
	Benzaldehyde	98
	Chloroacetic acid	99
	4-Chlorobenzoyl chloride	99

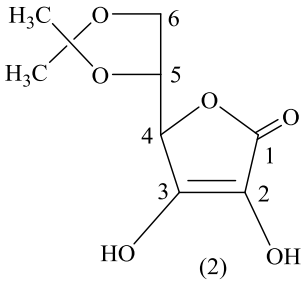
	Diethyl ether	99
	4-Nitrobenzaldehyde	98
	Phenylhydrazine	97
	Phthalic anhydride	99.5
	Pyridine	99.5
	Sodium acetate anhydrous	99.9

2.2 Instruments

1. Melting points were registered by using Hot-Stage, Gallen Kamp melting point apparatus and DigiMelt MSRS.
2. FTIR spectra were recorded using KBr discs on a Shimazu FTIR-8400S spectrophotometer at Ibn-Sina company, and Shimadzu IR Affinity-1-Fourier Transform Infrared spectrophotometer, University of Baghdad, College of Education for Pure Science (Ibn Al-Haitham), Chemistry Department and Shimadzu FTIR-600 spectrophotometer, University of Baghdad, College of Education for Pure Science (Ibn Al-Haitham), Central Service Laboratory.
3. Mass spectroscopy were recorded on Agilent mass spectrometer model 5975C VL MSD at the Tehran University, Iran and by Electron Impact (EI) at Mashhad University of Medical Sciences, Mashhad, Iran.
4. ^{1}H-NMR (400 MHz) and ^{13}C-NMR (75 MHz) spectra were recorded in DMSO-d_6 on Bruker BioSpin GmbH, University of Kashan, Iran and on Varian (500 MHz), Inova NMR spectrometer, at University of Kashan, Iran.
5. Thin Layer chromatography (TLC) was completed on aluminum glazy with layer of silica gel, provided via (Merck). The compounds were appeared by iodine vapour.
6. Biological activity for synthesized compounds have been screened for antibacterial activity against (*Escherichia coli* and *Staphylococcus aureus*) in nutrient agar medium in University of Baghdad, College of Science,

Department of Biology and in University of Baghdad College of Education for Pure Science (Ibn Al-Haitham), Central Service Laboratory.

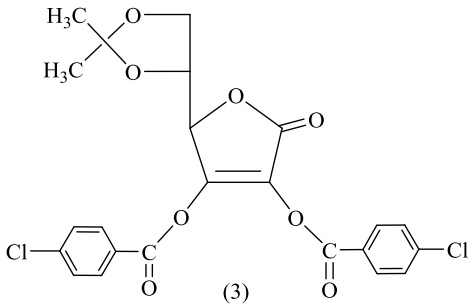
2.3 Preparation of 5,6-*O*-isopropylidene-L-ascorbic acid (2) [24]



(2)

Dry hydrogen chloride was quickly bubbled with stirring for (20) minutes into a (250mL) flask including (10g, 57mmol) of powdered L-ascorbic acid (1) and dry acetone (100mL) at room temperature. After addition of n-hexane (80mL), mixing and cooling in an ice-water, the supernatant was poured. The precipitate was washed (4 times) with (154) mL of hexane-acetone mixture (7:4) (v/v), with mixing, cooling in an ice-water and removal of supernatant after each addition. The last precipitate was dried under reduced pressure to yield acetal (2) (93%) as a white crystalline, m.p. (210-212 ºC), (lit. 210-212 ºC). R_f (0.69) (methanol: benzene) (1:1) (v/v).

2.4 Synthesis of 2,3-*O*-di(4-chlorobenzoyl)-5,6-*O*-isopropylidene-L-ascorbic acid (3) [180]



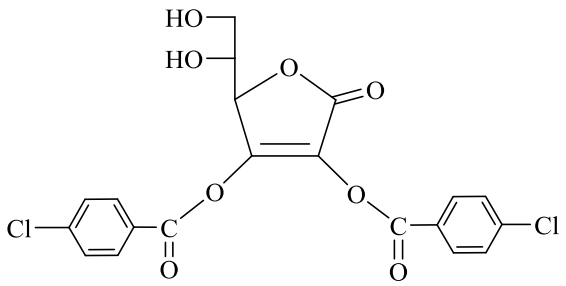
(3)

Added of 4-chlorobenzoyl chloride (15mL, 115mmol) to a cold solution of (compound 2) (10g, 46mmol) in pyridine (50mL) with mixing. The

production mixture was stirred period (2 hrs.), then kept in dark place at room temperature for (22) hours.

The mixture was poured into (ice-water) and mixing period (20 minutes). The oil layer was extracted with chloroform (2×150mL), then washed with water, dilute hydrochloric acid (HCl) (5%) (2×100mL), saturated aqueous ($NaHCO_3$) (100mL), and water, dried by (anhy. $MgSO_4$). Chloroform was evaporated. The residue recrystallized from abs. ethyl alcohol to yield ester (3) (87%) as a brown solid, m.p. (110-112 ºC). R_f (0.78) (benzene: methanol) (3:2) (v/v).

2.5 Synthesis of 2,3-*O*-di(4-chlorobenzoyl)-L-ascorbic acid (4) [180]

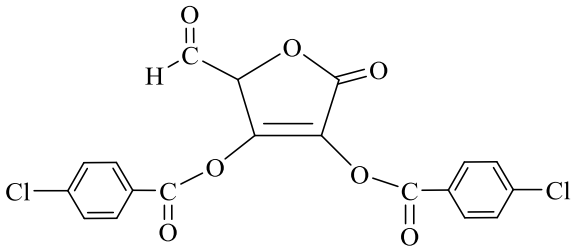


(4)

Compound (3) (10g, 19.45mmol) was dissolved in mixture of absolute ethanol (10mL) and (65%) acetic acid (30mL) and mixing for (48 hrs.) at (R. T.). The (TLC) appeared that the reaction was completed (benzene: methanol, 3:2).

The reaction mixture was filtered and (40mL) of benzene was added to the filtrate, repeat this procedure (4 times). The product recrystallized from abs. ethyl alcohol to give glycol (4) (85%) as a deep brown solid, m.p. (150-152 ºC). R_f (0.58) (benzene: methanol, 3:2) (v/v).

2.6 Synthesis of pentulosono-γ-lactone-2,3-enedi (4-chlorobenzoate) (5) [180]

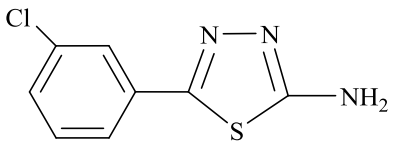


(5)

To the mixing solution of ($NaIO_4$) (4.7g, 22mmol) in (60mL) of distilled water at (0 °C), a solution of (compound 4) (10g, 22mmol) in (60mL) of absolute ethanol was added dropwise. After moving for (15 minutes), added (0.5mL) of ethylene glycol dropwise, stirring was continued at (R. T.) for (2 hours).

The mixture was filtered and to the filtrate, (40mL) of water was added then the yield was extracted by (3×50mL) of (ethyl acetate), the product dried by (anhy. $MgSO_4$), then filtered and the solvent was evaporated and the product recrystallized from chloroform to produce aldehyde (5) (74%) as a yellow solid, (m.p.: 198-200 ºC). R_f (0.76) (benzene: methanol, 3:2) (v/v).

2.7 Synthesis of 2-amino-5-(3-chlorophenyl)-1,3,4-thiadiazole (6) [181]

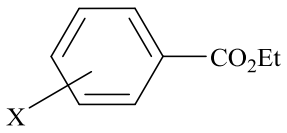


(6)

Phosphorus oxychloride (10mL) was added to a mixture of thiosemicarbazide (0.91g, 10mmol) and 3-chlorobenzoic acid (1.5g, 10mmol). The reaction mixture was heated at (90-100 ºC) for (6) hours. The ice-cold water was added to the reaction medium and the precipitate was

filtered, washed with water and recrystallized from abs. ethyl alcohol to afford the desired product amine (6), (57%) as a white powder, (m.p.: 220-223 ºC).

2.8 Preparation of compounds (7a,b) [182]



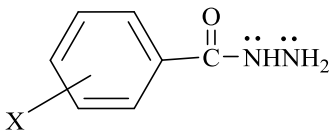
(7a,b)

Xa=3,5-di(NO_2)

Xb=4-NO_2

Conc. H_2SO_4 (5 drops) was added dropwise to a solution of substituted aromatic acid (10mmol) in absolute ethanol (10mL). The mixture was refluxed for (5) hours. After completing reaction, the solvent was removed under reduced pressure. The crude product was extracted with ethyl acetate (2×25mL), the organic layer was washed with saturated solution of sodium hydrogen carbonate, then with distilled water and dried under anhydrous magnesium sulfate. The solvent was removed under reduced pressure and the residue was recrystillized from absolute ethanol to afford compounds (7a,b) as a white crystals, yield (52%), m.p. (94-95 ºC), lit. (94-95 ºC) for 7a and (74%), m.p. (55-59 ºC), lit. (55-59 ºC) for 7b.

2.9 Preparation of compounds (8a,b) [182]



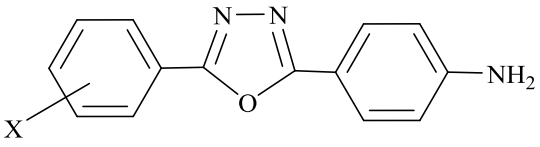
(8a,b)

Xa= 3,5-di(NO_2)

Xb= 4-NO_2

A mixture of compounds (7a or 7b) (10mmol) and (50mmol) of hydrazine hydrate (80%) in absolute ethanol (10mL) was refluxed for (20) hours. After cooling the solvent and excess hydrazine hydrate were removed under reduced pressure, then recrystallized from abs. ethanol to give compound (8a) as a deep brown solid, yield (61%), m.p. (215-217 ºC) and compound (8b) as a brown solid, yield (67%), m.p. (210-214 ºC) lit. (210-214 ºC).

2.10 Synthesis of compounds (9a,b) [183]

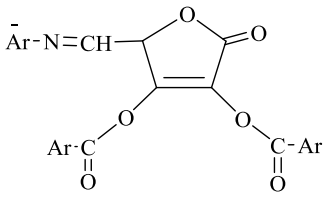


(9a, b)

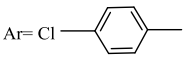
Xa= 3,5-di(NO_2)
Xb= 4-NO_2

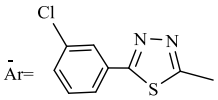
To a mixture of (8a or 8b) (3.3mmol) and 4-aminobenzoic acid (3.3mmol) was added phosphorus oxychloride (10mL). The reaction mixture was refluxed at (90-100 ºC) for (5) hours. The reaction mixture was cooled to room temperature, the excess of $POCl_3$ was concentrated through high vacuum, the residue was quenched with ice and the separated solid was filtered, dried and recrystallized from absolute ethanol to afford compound (9a) as a green solid, yield (71%), m.p. (263-265 ºC) and compound (9b) as a yellow solid, give (67%), m.p. (250-252 ºC).

2.11 Synthesis of Schiff bases (10c,d,e) [180]

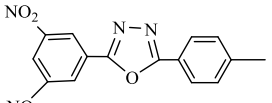


(10c,d,e)

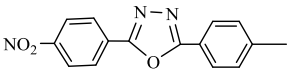




(c)



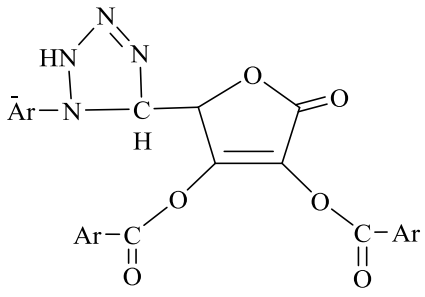
(d)



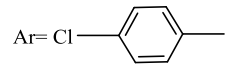
(e)

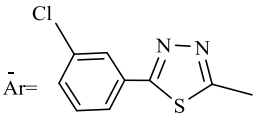
A mixture of appropriate compounds 6, 9a or 9b (0.5mmol) with aldehyde (5) (0.21g, 0.5mmol) in DMF (10mL) and 3 drops of glacial acetic acid was heated (48) hours, the DMF was evaporated and the product recrystallized from abs. ethyl alcohol to produce the Schiff bases (10c,d,e). The nomenclature and their physical properties for synthesized Schiff bases were illustrated in (Table 2.2).

2.12 Synthesis of 2,5-dihydrotetrazoles (11c,d,e) [184]

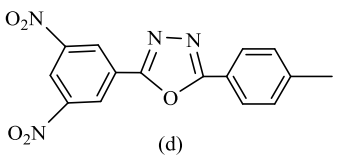


(11c,d,e)

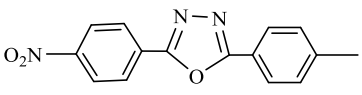




(c)



(d)

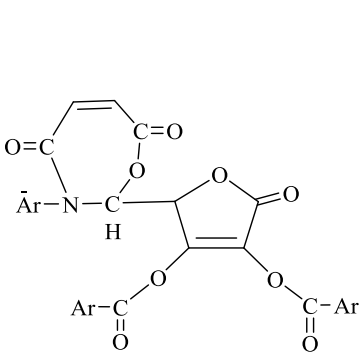


(e)

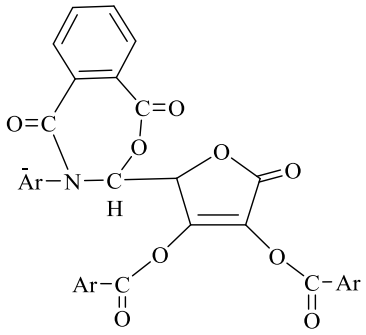
An equimolar quantities (0.3mmol) of azomethines (10c, 10d or 10e) with sodium azide and DMF (5mL) was refluxed for (48) hours. The mixture

was added to the ice-cold water, the compounds were filtered and washed with water, dried and recrystallized from absolute ethanol to give 2,5-dihydrotetrazoles (11c,d,e). The nomenclature and their physical properties for synthesizing 2,5-dihydrotetrazoles were awarded in (Table 2.2).

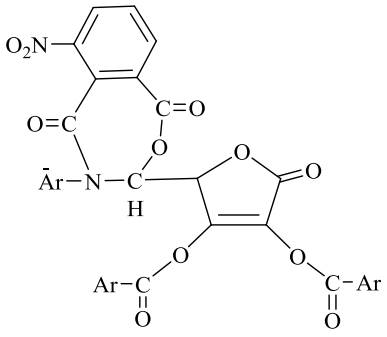
2.13 Synthesis of 1,3-oxazepine compounds (12,13,14)c,d,e [180]



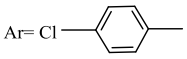
(12c,d,e)

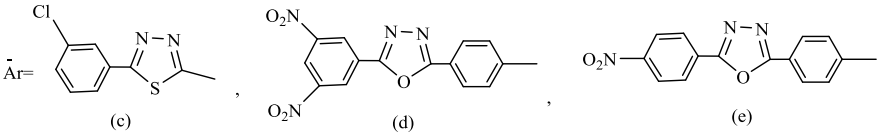


(13c,d,e)



(14c,d,e)

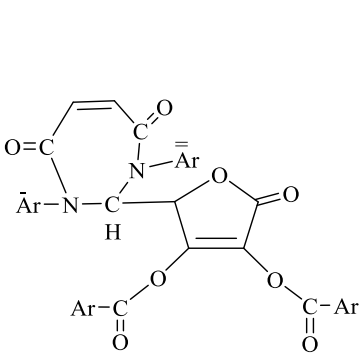




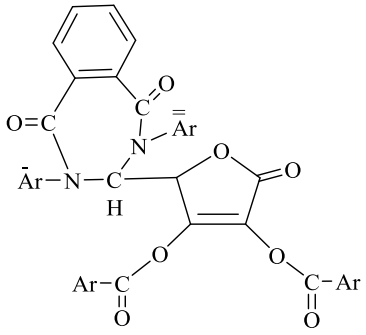
(c) (d) (e)

An equimolar quantities (0.3mmol) of azomethines (10c, 10d or 10e) with different acid anhydrides such as (maleic, phthalic or 3-nitrophthalic) anhydride (0.3mmol) in (10mL) of DMF was refluxed for (24) hours. The DMF was removed and the solid recrystallized via absolute ethyl alcohol to give 1,3-oxazepines (12,13,14)c,d,e. The nomenclature and physical properties of 1,3-oxazepines were shown in (Table 2.2).

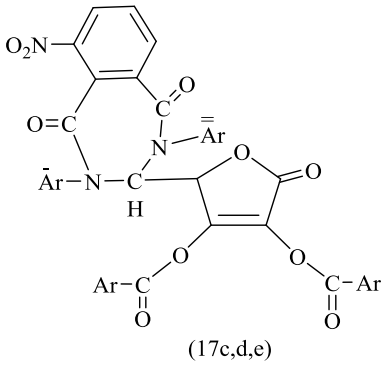
2.14 Synthesis of 1,3-diazepine compounds (15,16,17)c,d,e [185]



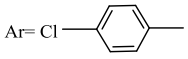
(15c,d,e)

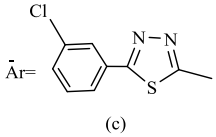


(16c,d,e)

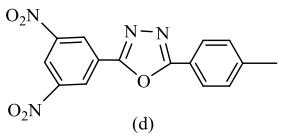


(17c,d,e)

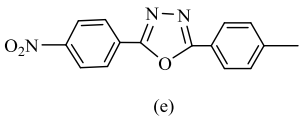




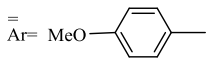
(c)



(d)

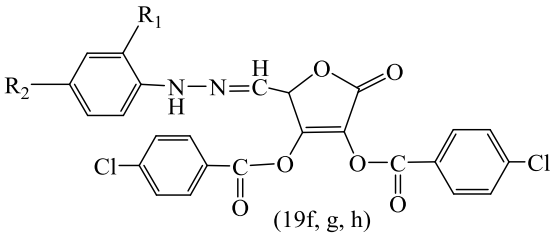


(e)

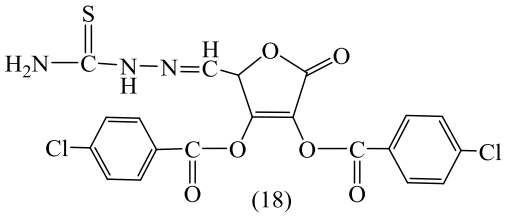


A mixture of equimolar amounts (0.3mmol) of each one of 1,3-oxazepines (12c-14e) with 4-methoxyaniline (0.3mmol) in 5mL of DMF was refluxed for (48) hours. The solvent was removed and the resulting colored solid recrystallized from absolute ethanol to obtained 1,3-diazepines (15,16,17)c,d,e. The nomenclature and physical properties of 1,3-diazepines were given in Table (2.2).

2.15 Synthesis of thiosemicarbazone (18) and hydrazone derivatives (19f,g,h) [186]



(19f, g, h)

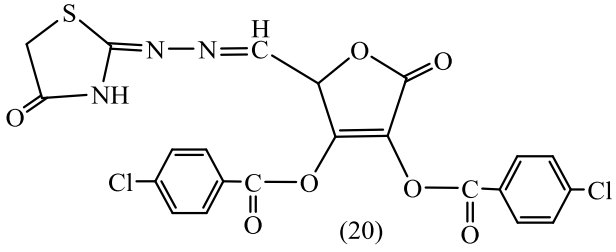


(18)

(19f)= R_1= H, R_2= H
(19g)= R_1= NO_2, R_2= NO_2
(19h)= R_1= H, R_2= NO_2

Thiosemicarbazide, phenylhydrazine or substitutedphenylhydrazine (1mmol) was added to a solution of aldehyde (5) (0.421g, 1mmol) in abs. ethyl alcohol (4mL) and (2) drops of (gla. CH_3CO_2H). The reactants were heated period (6 hrs.). Cooled the product to (R. T.) and the solid was filtered, dried and recrystallized from abs. ethanol to afford compounds (18) and (19f,g,h). The nomenclature and their physical properties of compounds (18) and (19f,g,h) were illustrated in (Table 2.2).

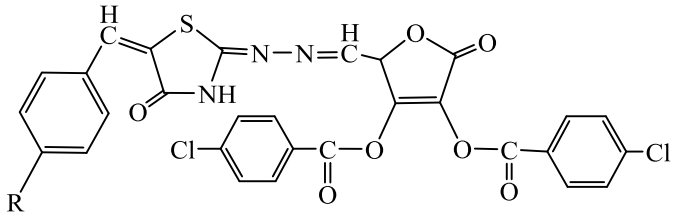
2.16 Synthesis of 1,3-thiazolidin-4-one (20) [186]



(20)

A mixture of thiosemicarbazone (18) (0.16g, 0.3mmol), chloroacetic acid (0.09g, 1mmol) and sodium acetate (0.25g, 3mmol) in abs. ethyl alcohol (5mL) was heated for (6 hrs.). The reaction mixture poured onto ice-water and filtered the solid, washed with water, dried and recrystallized from abs. ethyl alcohol to yield compound (20) as a brown solid. The nomenclature and its physical properties of this compound was demonstrated in (Table 2.2).

2.17 Synthesis of 1,3-thiazolidin-4-one derivatives (21i,j,k,l,m) (186)

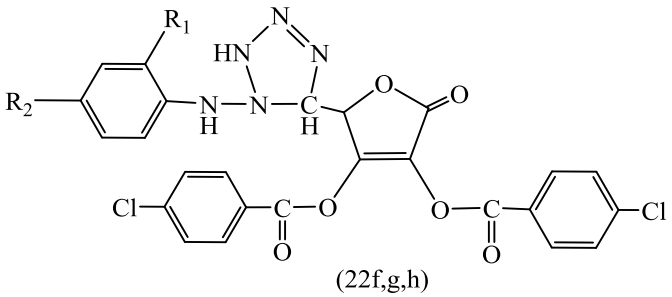


(21i,j,k,l,m)

R= H, CH_3, OCH_3, NO_2, NMe_2

A mixture of compound (20) (0.1g, 0.2mmol) with benzaldehyde or substituted benzaldehyde (0.2mmol) was refluxed in presence of ($C_5H_{11}N$) piperidine (0.5mL) for (3 hrs.). The reaction mixture was cooled to (R. T.), and poured onto ice-water. The yield was extracted by (10mL) of chloroform with washing of diethyl ether (10mL), evaporated the chloroform to yield compounds (21i,j,k,l,m) as a brown oil. The nomenclature and physical properties for compounds (21i,j,k,l,m) were illustrated in (Table 2.2).

2.18 Synthesis of 2,5-hydrotetrazole derivatives (22f,g,h) (184)



(22f,g,h)

(f): R_1= H, R_2= H
(g): R_1= NO_2, R_2= NO_2
(h): R_1= H, R_2= NO_2

To the mixture of azomethines (19f, 19g or19h) (0.2mmol) and sodium azide (0.01g, 0.2mmol), DMF (2mL) was added. The mixture was refluxed for 10 hrs., with stirring, then cooled to room temperature and the precipitate was filtered, washed with cold water and then recrystallization from abs.

ethanol to produce compounds (22f,g,h) as a brown solid. The nomenclature and physical properties of 2,5-dihydrotetrazole derivatives (22f,g,h) were listed in Table (2.2).

2.19 Biological evaluation

Synthesized compounds have been screened for antibacterial activities using cup-plate agar diffusion method. [187] The compounds were screened for antibacterial activity against (*Escherichia coli and Staphylococcus aureus*) in nutrient agar medium. These sterilized agar media were poured into Petri-dishes and allowed to solidify. On the surface of the media microbial suspensions were spread with the help of sterilized triangular loop. A stainless steel cylinder of 8mm diameter (pre-sterilized) was used to bore cavities. All the synthesized compounds (0.01 M) were placed serially in the cavities with the help of micropipette and allowed to diffuse for 1 hr. DMSO was used as a solvent for all the compounds, and as a control. These plates were incubated at 37 ^{o}C for 24 hr. for antibacterial activities. The zone of inhibition observed around the cups after respective incubation was measured in mm.

Table (2.2): Nomenclature and physical properties for prepared compounds

Comp. No.	Nomenclature	Molecular formula	M.p. °C or °dec	Yield %	Color
2	5,6-*O*-isopropylidene-L-ascorbic acid	$C_9H_{12}O_6$	210-212	93	White
3	2,3-*O*-di(4-chlorobenzoyl)-5,6-*O*-isopropylidene-L-ascorbic acid	$C_{23}H_{18}O_8Cl_2$	110-112	87	Brown
4	2,3-*O*-di(4-chlorobenzoyl)-L-ascorbic acid	$C_{20}H_{14}O_8Cl_2$	150-152	85	Deep brown
5	pentulosono-γ-lactone-2,3-enedi(4-chlorobenzoate)	$C_{19}H_{10}O_7Cl_2$	198-200	74	Yellow
6	2-amino-5-(3-chlorophenyl)-1,3,4-thiadiazole	$C_8H_6N_3SCl$	220-223	57	White
7a	ethyl 3,5-dinitrobenzoate	$C_9H_8O_6N_2$	94-95	52	White
7b	ethyl 4-nitrobenzoate	$C_9H_9O_4N$	55-59	74	White
8a	3,5-dinitrobenzohydrazide	$C_7H_6O_5N_4$	215-217	61	Deep brown
8b	4-nitrobenzohydrazide	$C_7H_7O_3N_3$	210-214	67	Brown
9a	2-(3,5-dinitrophenyl)-5-(4-aminophenyl)-1,3,4-oxadiazole	$C_{14}H_9O_5N_5$	263-265	71	Green
9b	2-(4-nitrophenyl)-5-(4-aminophenyl)-1,3,4-oxadiazole	$C_{14}H_{10}O_3N_4$	250-252	67	Yellow
10c	5-(3-chlorophenyl)-2-[pentulose-γ-lactone-2,3-enedi(4-chlorobenzoate)-imine]-1,3,4-thiadiazole	$C_{27}H_{14}O_6N_3Cl_3S$	138-140	67	Deep brown
10d	4-{4-[5-(3,5-dinitrophenyl)-1,3,4-oxadiazol-2-yl]phenyl-imine}-pentulose-γ-lactone-2,3-enedi(4-chlorobenzoate)	$C_{33}H_{17}O_{11}N_5Cl_2$	240	75	Pale brown
10e	4-{4-[5-(4-nitrophenyl)-1,3,4-oxadiazol-2-yl]phenyl-imine}-pentulose-γ-lactone-2,3-enedi(4-chlorobenzoate)	$C_{33}H_{18}O_9N_4Cl_2$	250	62	Brown
11c	1-[(3-chlorophenyl)-1,3,4-thiadiazol-2-yl]-5-[pentulose-γ-lactone-2,3-enedi(4-chlorobenzoate)]tetrazole	$C_{27}H_{15}O_6N_6Cl_3S$	220	55	Deep brown
11d	1-{4-[5-(3,5-dinitrophenyl)-1,3,4-oxadiazol-2-yl]phenyl}-5-[pentulose-γ-lactone-2,3-enedi(4-chlorobenzoate)]tetrazole	$C_{33}H_{18}O_{11}N_8Cl_2$	280	50	Brown

11e	1-{4-[5-(4-nitrophenyl)-1,3,4-oxadiazol-2-yl]phenyl}-5-[pentulose-γ-lactone-2,3-enedi(4-chlorobenzoate)]tetrazole	$C_{33}H_{19}O_9N_7Cl_2$	270	52	Deep brown
12c	2-[pentulose-γ-lactone-2,3-enedi(4-chlorobenzoate)]-5-[(3-chlorophenyl)-1,3,4-thiadiazol-2-yl]-2,3-dihydro[1,3]-oxazepine-4,7-dione	$C_{31}H_{16}O_9N_3Cl_3S$	198-200	50	Deep brown
12d	2-[pentulose-γ-lactone-2,3-enedi(4-chlorobenzoate)]-3-{˙4-[5-(3,5-dinitrophenyl)-1,3,4-oxadiazol-2-yl]phenyl}-2,3-dihydro[1,3]oxazepine-4,7-dione	$C_{37}H_{19}O_{14}N_5Cl_2$	158-160	43	Brown
12e	2-[pentulose-γ-lactone-2,3-enedi(4-chlorobenzoate)]-3-{˙4-[5-(4-nitrophenyl)-1,3,4-oxadiazol-2-yl]phenyl}-2,3-dihydro[1,3]-oxazepine-4,7-dione	$C_{37}H_{20}O_{12}N_4Cl_2$	220	52	Brown
13c	2-[pentulose-γ-lactone-2,3-enedi(4-chlorobenzoate)]-5-[(3-chlorophenyl)-1,3,4-thiadiazol-2-yl]-2,3-dihydrobenz[1,2e][1,3]-oxazepine-4,7-dione	$C_{35}H_{18}O_9N_3Cl_3S$	128-130	55	Brown
13d	2-[pentulose-γ-lactone-2,3-enedi(4-chlorobenzoate)]-3-{˙4-[5-(3,5-dinitrophenyl)-1,3,4-oxadiazol-2-yl]phenyl}-2,3-dihydrobenz[1,2e][1,3]-oxazepine-4,7-dione	$C_{41}H_{21}O_{14}N_5Cl_2$	222	58	Deep brown
13e	2-[pentulose-γ-lactone-2,3-enedi(4-chlorobenzoate)]-3-{˙4-[5-(4-nitrophenyl)-1,3,4-oxadiazol-2-yl]phenyl}-2,3-dihydrobenz[1,2e][1,3]-oxazepine-4,7-dione	$C_{41}H_{22}O_{12}N_4Cl_2$	238-240	42	Brown
14c	2-[pentulose-γ-lactone-2,3-enedi(4-chlorobenzoate)]-5-[(3-chlorophenyl)-1,3,4-thiadiazol-2-yl]-2,3-dihydro(3-nitrobenz)[1,2e][1,3]-oxazepine-4,7-dione	$C_{35}H_{17}O_{11}N_4Cl_3S$	197-199	52	Brown
14d	2-[pentulose-γ-lactone-2,3-enedi(4-chlorobenzoate)]-3-{˙4-[5-(3,5-dinitrophenyl)-1,3,4-oxadiazol-2-yl]phenyl}-2,3-dihydro(3-nitrobenz)[1,2e][1,3]-oxazepine-4,7-dione	$C_{41}H_{20}O_{16}N_6Cl_2$	260	53	Deep brown

14e	2-[pentulose-γ-lactone-2,3-enedi(4-chlorobenzoate)]-3-{˙4-[5-(4-nitrophenyl)-1,3,4-oxadiazol-2-yl]phenyl}-2,3-dihydro(3-nitrobenz)[1,2e][1,3]-oxazepine-4,7-dione	$C_{41}H_{21}O_{14}N_5Cl_2$	230	58	Deep brown
15c	1-(4-methoxyphenyl)-2-[pentulose-γ-lactone-2,3-enedi(4-chlorobenzoate)]-5-[(3-chlorophenyl)-1,3,4-thiadiazol-2-yl]-2,3-dihydro[1,3]-diazepine-4,7-dione	$C_{38}H_{23}O_9N_4Cl_3S$	235	48	Deep brown
15d	1-(4-methoxyphenyl)-2-[pentulose-γ-lactone-2,3-enedi(4-chlorobenzoate)]-3-{˙4-[5-(3,5-dinitrophenyl)-1,3,4-oxadiazol-2-yl]phenyl}-2,3-dihydro[1,3]-diazepine-4,7-dione	$C_{44}H_{26}O_{14}N_6Cl_2$	255	46	Brown
15e	1-(4-methoxyphenyl)-2-[pentulose-γ-lactone-2,3-enedi(4-chlorobenzoate)]-3-{˙4-[5-(4-nitrophenyl)-1,3,4-oxadiazol-2-yl]phenyl}-2,3-dihydro[1,3]-diazepine-4,7-dione	$C_{44}H_{27}O_{12}N_5Cl_2$	260	47	Deep brown
16c	1-(4-methoxyphenyl)-2-[pentulose-γ-lactone-2,3-enedi(4-chlorobenzoate)]-5-[(3-chlorophenyl)-1,3,4-thiadiazol-2-yl]-2,3-dihydrobenz[1,2e][1,3]-diazepine-4,7-dione	$C_{42}H_{25}O_9N_4Cl_3S$	153-155	52	Deep brown
16d	1-(4-methoxyphenyl)-2-[pentulose-γ-lactone-2,3-enedi(4-chlorobenzoate)]-3-{˙4-[5-(3,5-dinitrophenyl)-1,3,4-oxadiazol-2-yl]phenyl}-2,3-dihydrobenz[1,2e][1,3]-diazepine-4,7-dione	$C_{48}H_{28}O_{14}N_6Cl_2$	210	50	Deep brown
16e	1-(4-methoxyphenyl)-2-[pentulose-γ-lactone-2,3-enedi(4-chlorobenzoate)]-3-{˙4-[5-(4-nitrophenyl)-1,3,4-oxadiazol-2-yl]phenyl}-2,3-dihydrobenz[1,2e][1,3]-diazepine-4,7-dione	$C_{48}H_{29}O_{12}N_5Cl_2$	200	47	Brown
17c	1-(4-methoxyphenyl)-2-[pentulose-γ-lactone-2,3-enedi(4-chlorobenzoate)]-5-[(3-chlorophenyl)-1,3,4-thiadiazol-2-yl]-2,3-dihydro(3-nitrobenz)[1,2e][1,3]-diazepine-4,7-dione	$C_{42}H_{24}O_{11}N_5Cl_3S$	250	46	Deep brown

17d	1-(4-methoxyphenyl)-2-[pentulose-γ-lactone-2,3-enedi(4-chlorobenzoate)]-3-{¯4-[5-(3,5-dinitrophenyl)-1,3,4-oxadiazol-2-yl]phenyl}-2,3-dihydro(3-nitrobenz)[1,2e][1,3]-diazepine-4,7-dione	$C_{48}H_{27}O_{16}N_7Cl_2$	270	44	Deep brown
17e	1-(4-methoxyphenyl)-2-[pentulose-γ-lactone-2,3-enedi(4-chlorobenzoate)]-3-{¯4-[5-(4-nitrophenyl)-1,3,4-oxadiazol-2-yl]phenyl}-2,3-dihydro(3-nitrobenz)[1,2e][1,3]-diazepine-4,7-dione	$C_{48}H_{28}O_{14}N_6Cl_2$	230	45	Brown
18	pentulosono-γ-lactone-2,3-enedi(4-chlorobenzoate) thiosemicarbazone	$C_{20}H_{13}O_6N_3Cl_2S$	130-133	57	Pale brown
19f	pentulosono-γ-lactone-2,3-enedi(4-chlorobenzoate)phenylhydrazone	$C_{25}H_{16}O_6N_2Cl_2$	123-125	59	Brown
19g	pentulosono-γ-lactone-2,3-enedi(4-chlorobenzoate)-2,4-dinitrophenylhydrazone	$C_{25}H_{14}O_{10}N_4Cl_2$	116-120	60	Orange
19h	pentulosono-γ-lactone-2,3-enedi(4-chlorobenzoate)-4-nitrophenylhydrazone	$C_{25}H_{15}O_8N_3Cl_2$	138-140	63	Orange
20	2-[pentulose-γ-lactone-2,3-enedi(4-chlorobenzoate) hydrazono]-1,3-thiazolidin-4-one	$C_{22}H_{13}O_7N_3Cl_2S$	167-170	58	Brown
21i	(5-benzylidene)-2-(pentulose-γ-lactone-2,3-enedi(4-chlorobenzoate)hydrazono)-1,3-thiazolidin-4-one	$C_{29}H_{17}O_7N_3Cl_2S$	-	72	Brown
21j	(5-(4-methylbenzylidene)-2-(pentulose-γ-lactone-2,3-enedi(4-chlorobenzoate)hydrazono)-1,3-thiazolidin-4-one	$C_{30}H_{19}O_7N_3Cl_2S$	-	81	Brown
21k	(5-(4-methoxybenzylidene)-2-pentulose-γ-lactone-2,3-enedi(4-chlorobenzoate)hydrazono)-1,3-thiazolidin-4-one	$C_{30}H_{19}O_8N_3Cl_2S$	-	75	Brown

21l	(5-(4-nitrobenzylidene)-2-(pentulose-γ-lactone-2,3-enedi(4-chlorobenzoate)hydrazono)-1,3-thiazolidin-4-one	$C_{29}H_{16}O_9N_4Cl_2S$	-	83	Brown
21m	(5-(4-N,N-dimethylbenzylidene)-2-(pentulose-γ-lactone-2,3-enedi(4-chlorobenzoate)hydrazono)-1,3-thiazolidin-4-one	$C_{31}H_{22}O_7N_4Cl_2S$	-	75	Brown
22f	1-phenylamino-5-pentulose-γ-lactone-2,3-enedi(4-chlorobenzoate)tetrazole	$C_{25}H_{17}O_6N_5Cl_2$	108	90	Brown
22g	1-(2,4-dinitrophenylamino)-5-pentulose-γ-lactone-2,3-enedi(4-chlorobenzoate)tetrazole	$C_{25}H_{15}O_{10}N_7Cl_2$	130	66	Brown
22h	1-(4-nitrophenylamino)-5-pentulose-γ-lactone-2,3-enedi(4-chlorobenzoate)tetrazole	$C_{25}H_{16}O_8N_6Cl_2$	305	72	Brown

Chapter Three

Results and Discussion

3.1 Synthesis and characterization of the precursors

L-Ascorbic acid (vitamin C) is a water soluble vitamin which acts as an oxidizer and free radical scavenger. It was called antioxidant because of its ability of quenching or stabilizing free radicals that lead overtime to degenerative diseases, including cardiovascular cancer, cataracts and other diseases. (188)

The FTIR spectrum of L-AA (1), Fig. (3.1) indicated the next peaks, the stretching bands at (3525, 3410, 3315, 3215) cm^{-1} for (O-H) groups at positions (C-6), (C-5), (C-3), and (C-2) respectively, indicating that, the four (O-H) are non-equivalents, stretching peak at (2916) cm^{-1} for (C-H) aliphatic, stretching peak at (1755) cm^{-1} for (C=O) lactone ring, stretching band at (1672) cm^{-1} for (C=C), stretching bands at (1140) cm^{-1} for (C-O), and bending band at (758) cm^{-1} for (O-H) (O.O.P.).

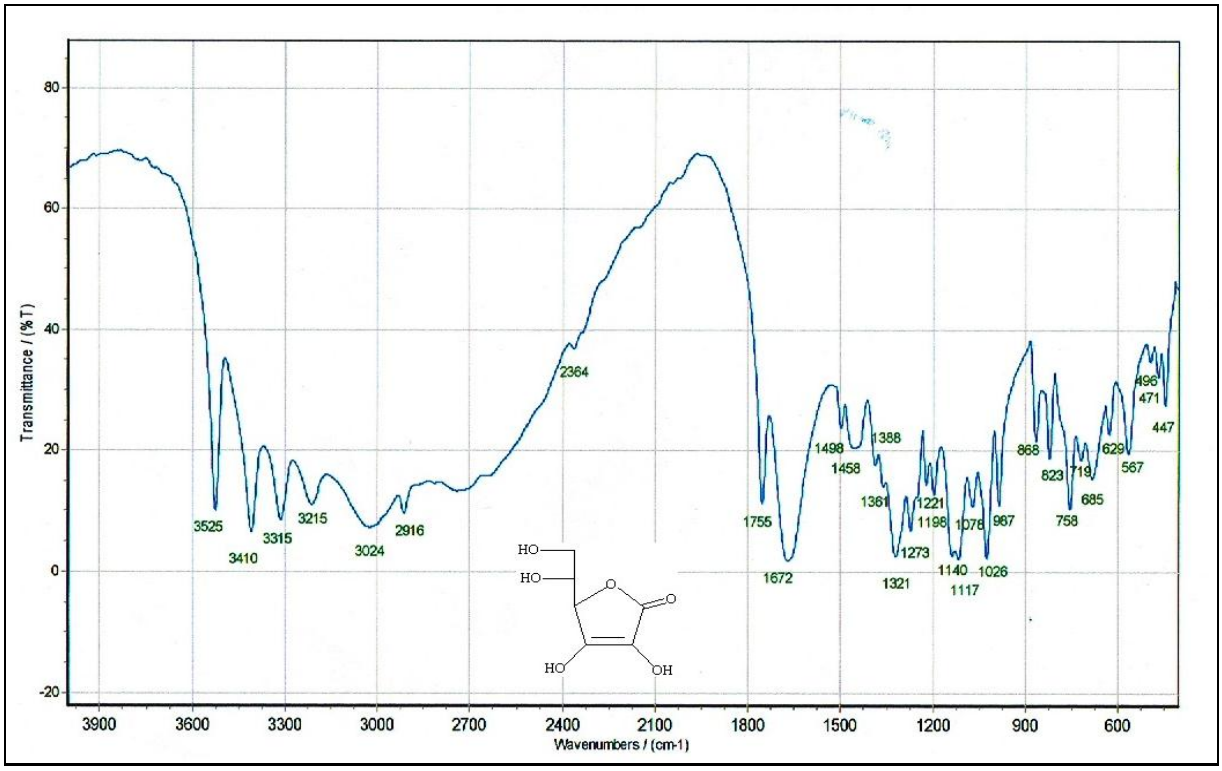
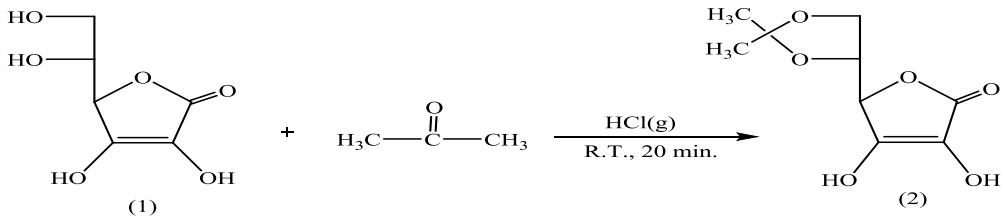


Fig. (3.1): FT-IR spectrum of L-AA (1)

The protocol includes protecting of hydroxyl groups at the positions 5,6-C-atoms of L-ascorbic acid and then the (OH) groups upon C-2 and C-3 sites was esterificated.

3.1.1 Preparation of 5,6-*O*-isopropylidene-L-ascorbic acid (2)

Acetal (2) was prepared via following Salomon method from the reaction of L-AA (1) with acetone in acidic media. [24]



The FTIR spectrum of acetal (2), Fig. (3.2) showed the following bands, the stretching bands at (3240) cm^{-1} for (O-H) vinylic, vibrating peaks at (2995, 2908) cm^{-1} for (C-H) aliphatic, acetal linkage, stretching peak at (1755) cm^{-1} for (C=O) lactone ring, vibrating band at (1664) cm^{-1} for (C=C), bending bands symmetrical and asymmetrical at (1381, 1431) cm^{-1} for (C-H) aliphatic, stretching bands at (1140) cm^{-1} for (C-O), and bending band at (768) cm^{-1} for (O-H) (O.O.P.).

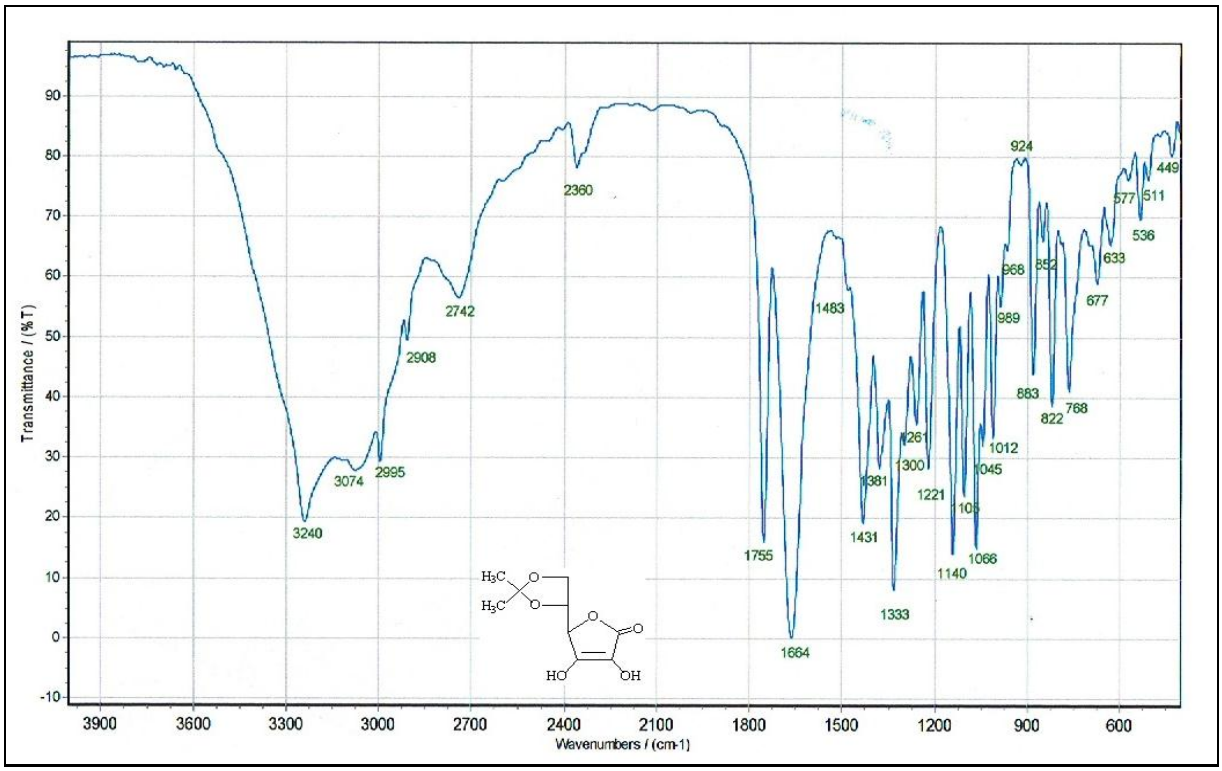
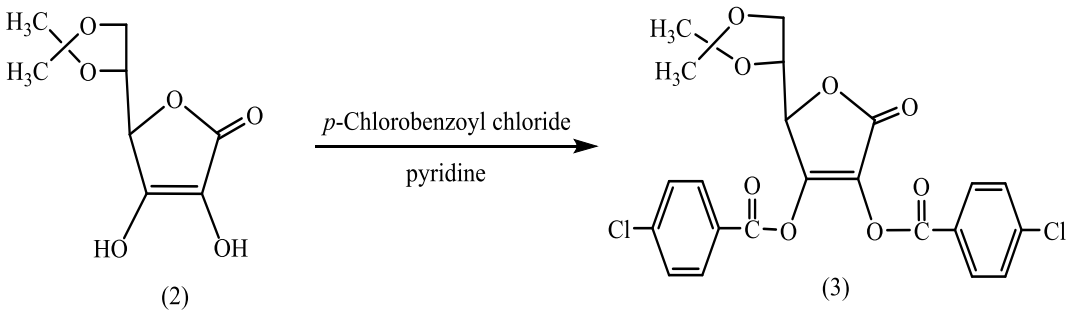


Fig. (3.2): FT-IR spectrum of acetal (2)

3.1.2 Synthesis of 2,3-*O*-di(4-chlorobenzoyl)-5,6-*O*-isopropylidene-L-ascorbic acid (3)

Acetal (2) reacts with excess of 4-chlorobenzoyl chloride in dry pyridine to give ester (3).



The FT-IR spectrum of ester (3), Fig. (3.3) demonstrated stretching peak upon (1685 cm^{-1}) related to (C=O) of the ester, and evanescence of the stretching peaks for (O-H) of acetal (2), stretching peak at (3091) cm^{-1} for (C-H) aromatic, vibrating peaks at (2985, 2937) cm^{-1} due to (C-H) aliphatic,

acetal linkage, stretching peak at (1743) cm^{-1} for (C=O) lactone ring, stretching bands at (1593) cm^{-1} for (C=C) aromatic, stretching bands at (1279) cm^{-1} belong to (C-O) of ester and (850) cm^{-1} related to (C-H) aromatic bending (O.O.P.).

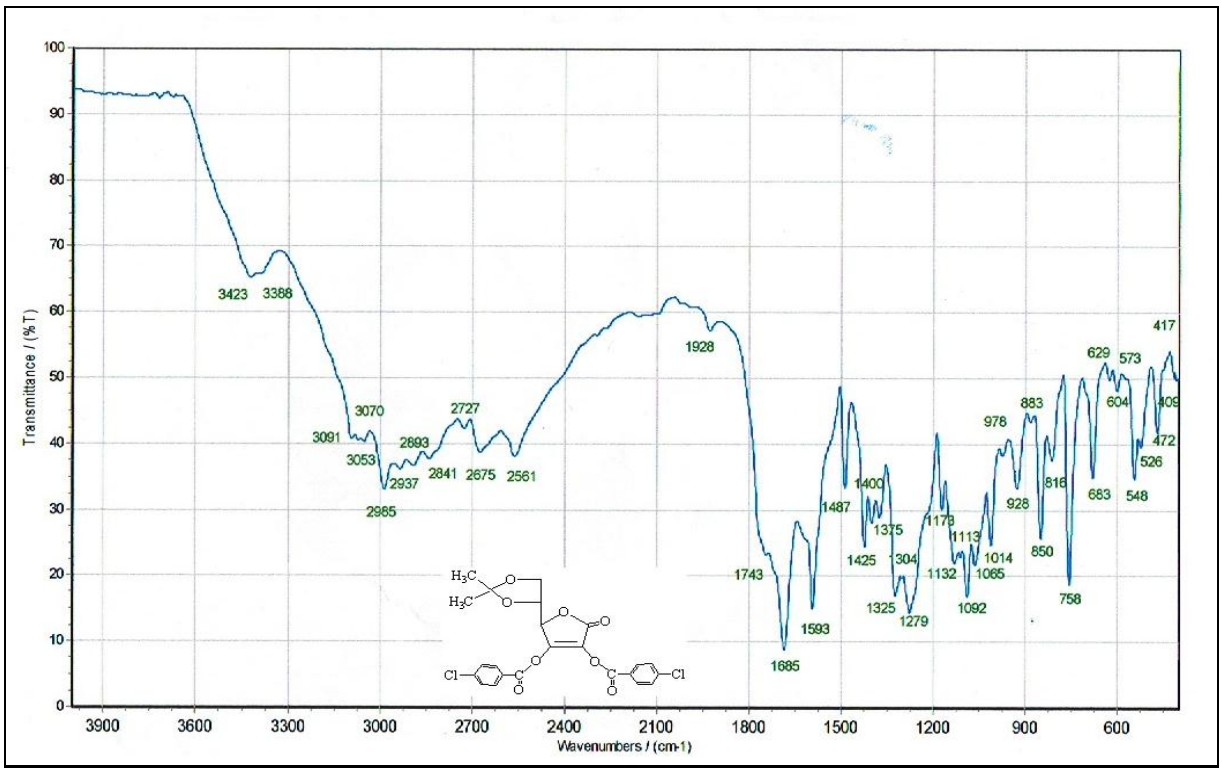
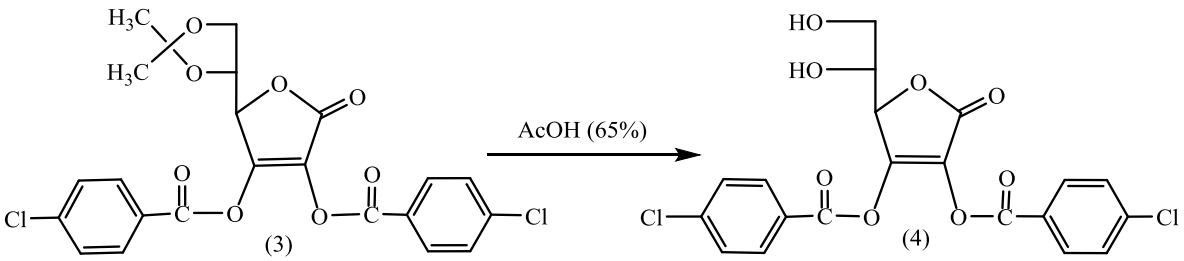


Fig. (3.3): FTIR spectrum of ester (3)

3.1.3 Synthesis of 2,3-*O*-di(4-chlorobenzoyl)-L-ascorbic acid (4)

Isopropylidene ring hydrolyzed in acidic media easily as mentioned in the introduction; we used (65%) acetic acid to hydrolyze the acetal's ring.



The FTIR spectrum of glycol (4), Fig. (3.4) showed stretching broad peak at (3415) cm^{-1} belong to (O-H), stretching band at (3095) cm^{-1} for (C-H) aromatic, stretching band at (2985, 2895) cm^{-1} due to (C-H) aliphatic, stretching peak at (1720) cm^{-1} belong to (C=O) lactone ring, stretching peak at (1685) cm^{-1} for (C=O) of the ester, (1593, 1487) cm^{-1} for (C=C) aliphatic and aromatic. Stretching bands at (1275) cm^{-1} related to (C-O) of ester, and (850) cm^{-1} assigned to (C-H) aromatic bending (O.O.P.).

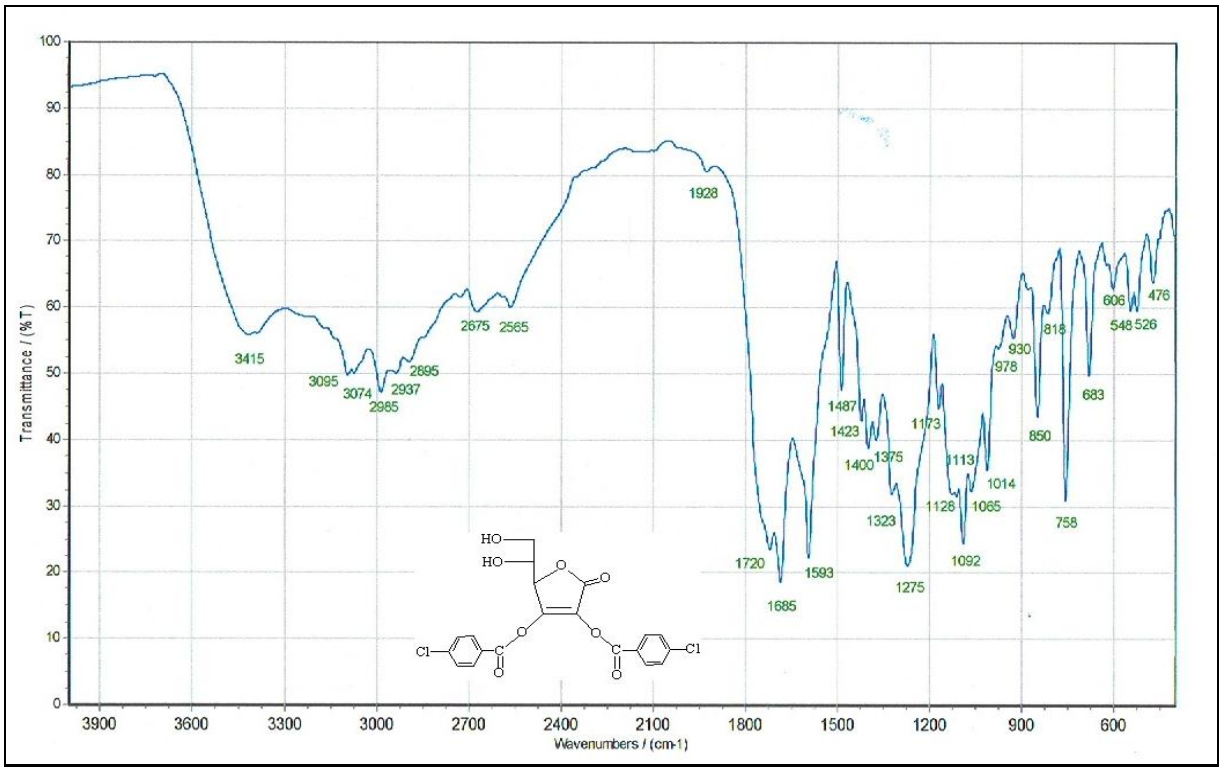
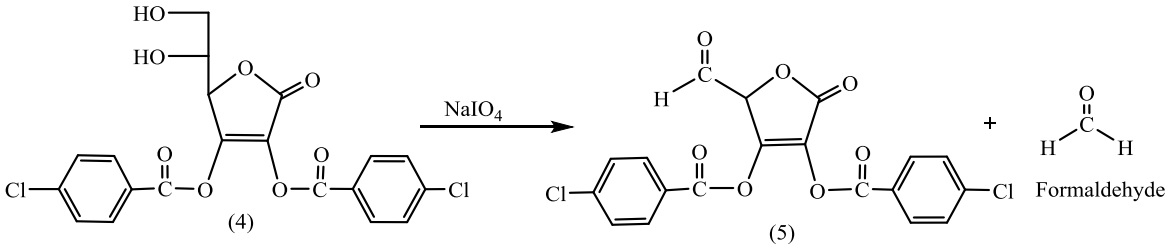


Fig. (3.4): FTIR spectrum of glycol (4)

3.2 Synthesis and characterization of pentulosono-γ-lactone-2,3-enedi (4-chlorobenzoate) (5)

Glycols (compounds contain two vicinal hydroxyl groups) oxidized by periodate, which was cleaved the carbon-carbon (bearing OH groups) bond and formation of two compounds containing carbonyl groups.



The compound (5) was featured by FT-IR, ^{1}H-NMR and ^{13}C-NMR, compound (5) occurrence a silver mirror by Tollen's test. [189] The FT-IR spectrum of aldehyde (5), Fig. (3.5), showed the following bands, vibrating peaks at (2843, 2727) cm^{-1} belong to (C-H) aldehydic, vibrating peaks at (3093, 2983) cm^{-1} for (C-H) aromatic, aliphatic, stretching band at (1793) cm^{-1} for (C=O) lactone ring, vibrating band at (1728) cm^{-1} for (C=O) aldehydic, and (850) cm^{-1} due to (C-H) aromatic bending (O.O.P).

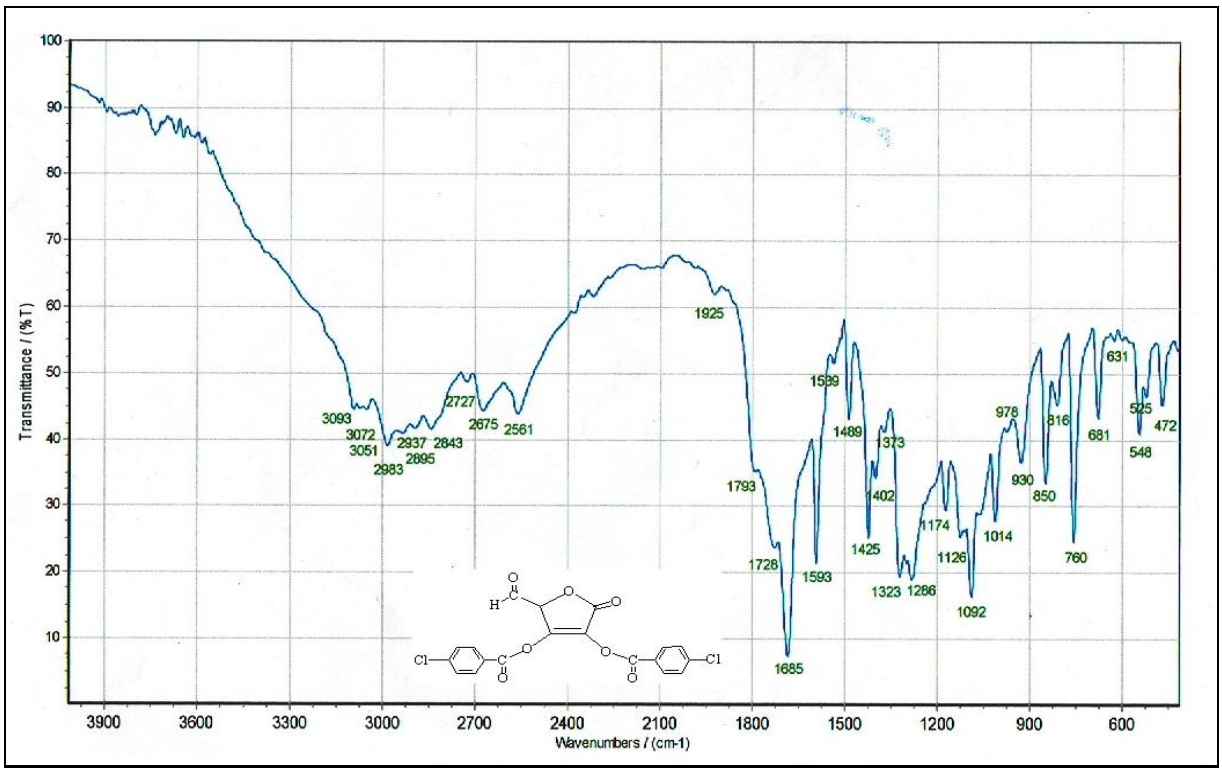


Fig. (3.5): FTIR spectrum of aldehyde (5)

The ^{1}H-NMR spectrum of compound (5) in DMSO-d_6, Fig. (3.6) showed the following signals: singlet signal at δ(2.5) ppm for DMSO, signal at δ(4) ppm for one proton of lactone ring (H-4), doublet doublet signals at δ(7.56-

7.99) ppm for aromatic protons, singlet signal at δ(13.19) ppm for one proton of (C-H) aldehydic.

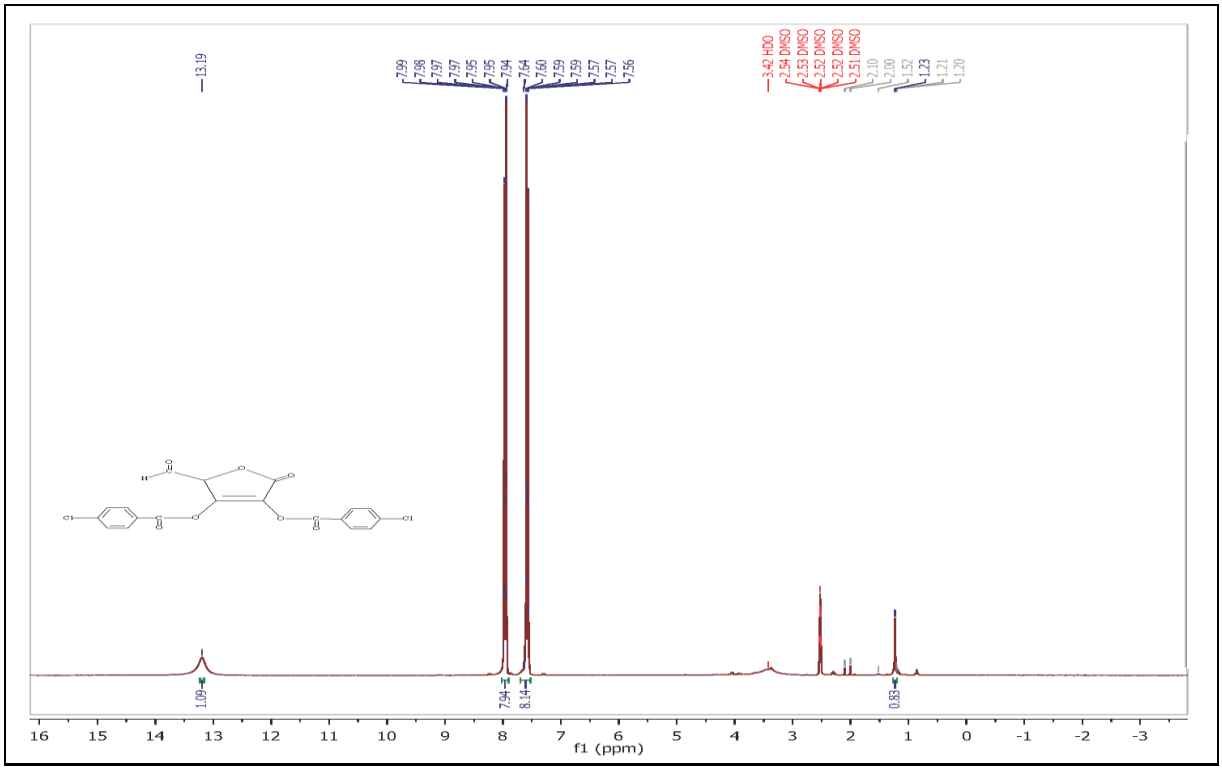


Fig. (3.6): ^{1}H-NMR spectrum of aldehyde (5)

The ^{13}C-NMR spectrum of aldehyde (5) in DMSO-d_6, Fig. (3.7) indicated the following signals: signal at δ(39.15-40.82) ppm belong to the solvent, signals at δ(129.20-131.60) ppm for aromatic carbons and C-2, signal at δ(138.26) ppm for C-3, signal at δ(166.92) ppm for (C=O) lactone ring and ester. The signal of C-4 with signals of DMSO-d_6, and the signal of aldehydic carbonyl was disappeared because of it showed out of the scale. (190)

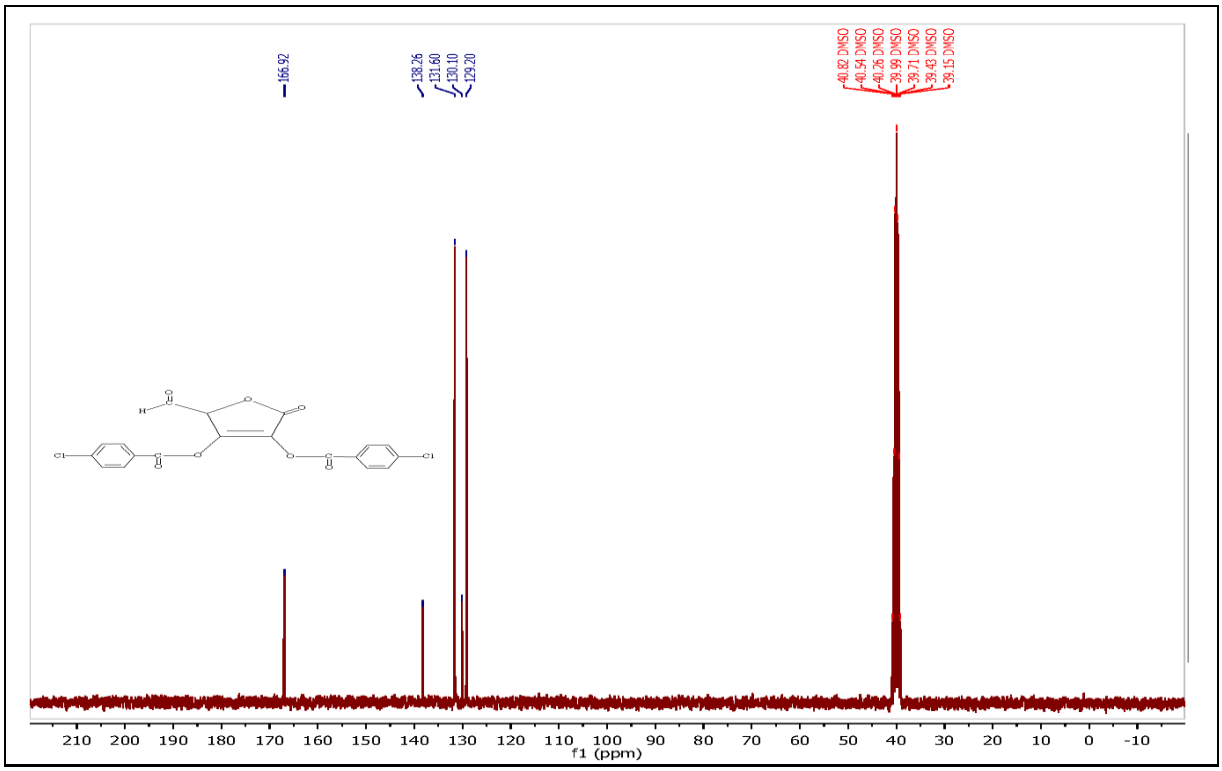
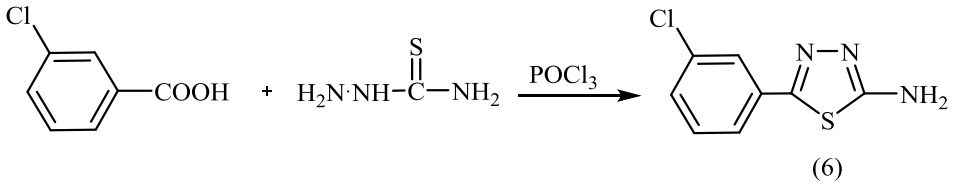


Fig. (3.7): ^{13}C-NMR spectrum of aldehyde (5)

3.3 Synthesis and characterization of compounds (6 and 9a,b)

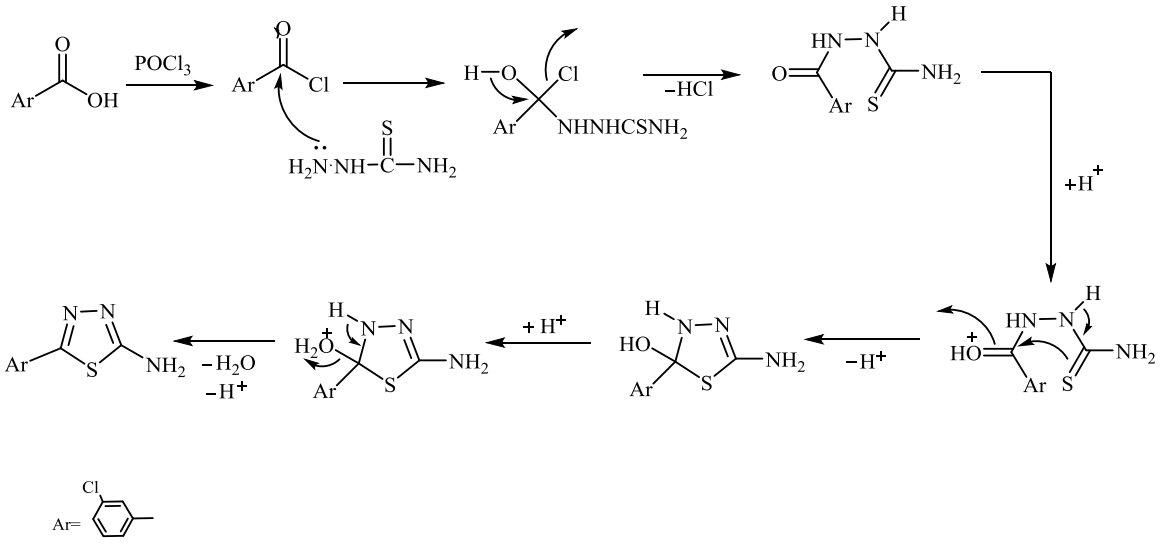
3.3.1 Synthesis and characterization of 2-amino-5-(3-chlorophenyl)-1,3,4-thiadiazole (6)

The reaction of 3-chlorobenzoic acid along with thiosemicarbazide in the presence of $POCl_3$ under reflux for 6 hrs leaded to formation of 2-amino-5-(3-chlorophenyl)-1,3,4-thiadiazole (6).



(6)

The mechanism [191] of this reaction outlined in Scheme (3.1).

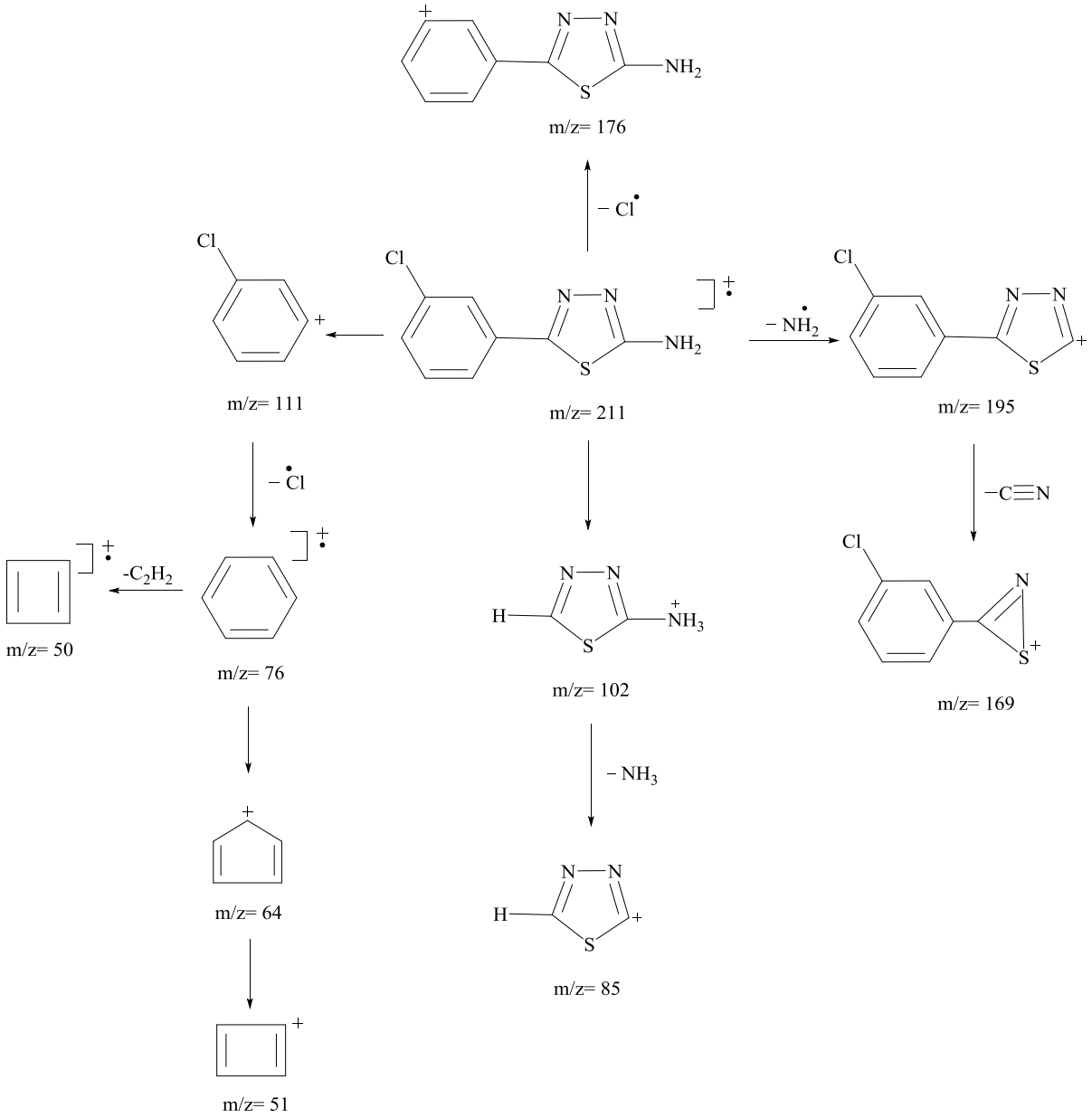


Scheme (3.1): The mechanism of prepared compound (6)

The reaction was initiated by conversion of acid to the acid chloride, followed by nucleophilic attacking of the most nucleophilic nitrogen of thiosemicarbazide on the carbonyl carbon of the acid chloride in a nucleophilic substitution reaction to form intermediate. The latter compound suffers from internal nucleophilic attacked by the sulfur atom of the thiol to form the thiadiazole ring (6).

The structural diagnosis for amine (6) was based on spectral data FTIR, ^{1}H-NMR and Mass spectroscopy. The FT-IR absorption spectrum, Fig. (3.8) demonstrated two peaks at (3265, 3168) cm^{-1} attributed to the NH_2 group, peak at (3060) cm^{-1} for CH aromatic, peak at (1630) cm^{-1} due to C=N of thiadiazole ring and peak at (785) cm^{-1} of bending meta substituted benzene ring.

^{1}H-NMR spectrum of this compound (in DMSO-d_6 as solvent), Fig. (3.9) showed signals at δ(7.53-8.04) ppm related to four aromatic protons, broad signal at δ(9.27) ppm could be imputed for NH_2 group. The mass spectrum of the amine (6) indicated m/z= 211 (M^+), Fig. (3.10). Characteristic fragments which identified this compound were showen in Scheme (3.2).



Scheme (3.2): The characteristic fragments of amine (6)

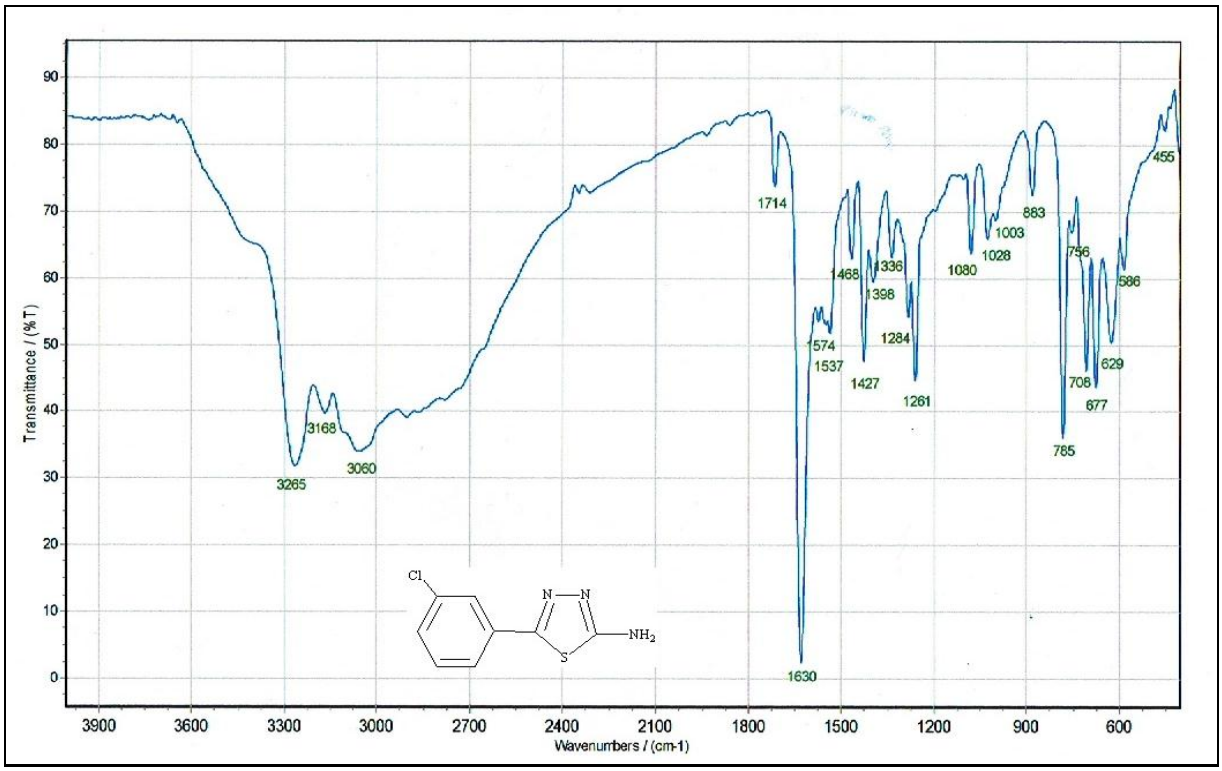


Fig. (3.8): FTIR spectrum of amine (6)

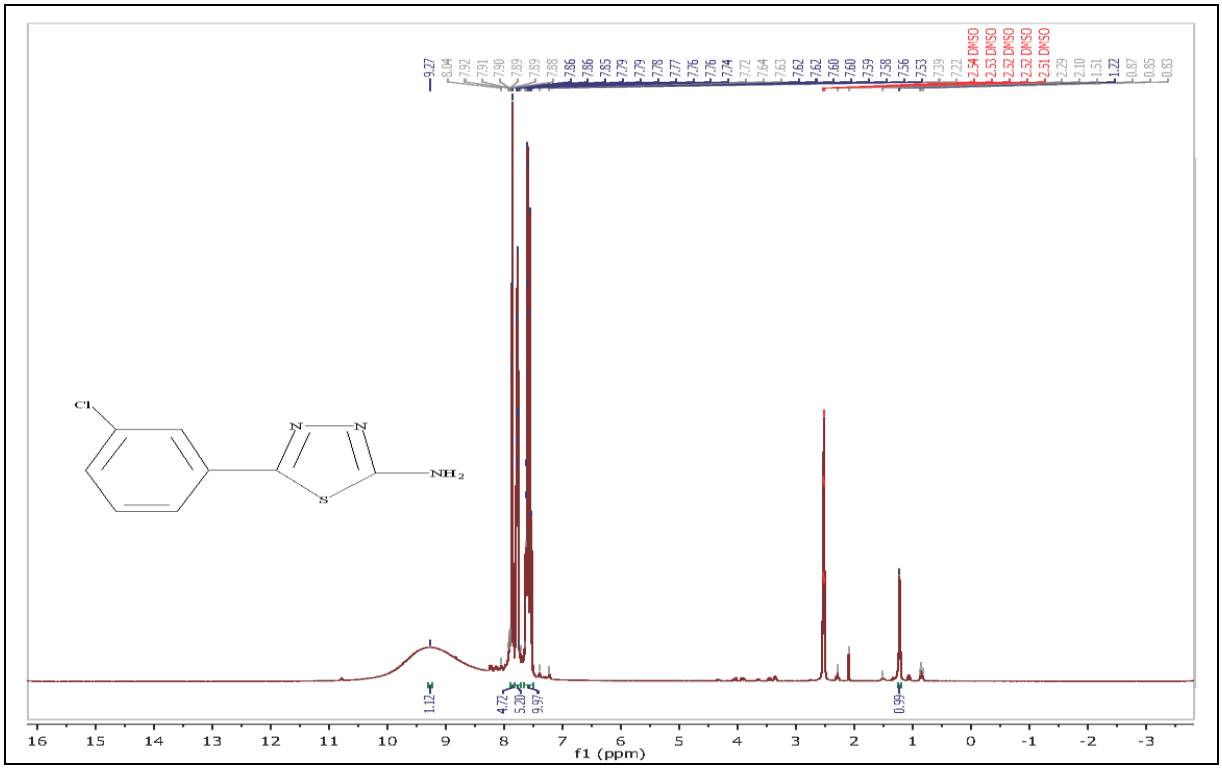


Fig. (3.9): ^{1}H-NMR spectrum of amine (6)

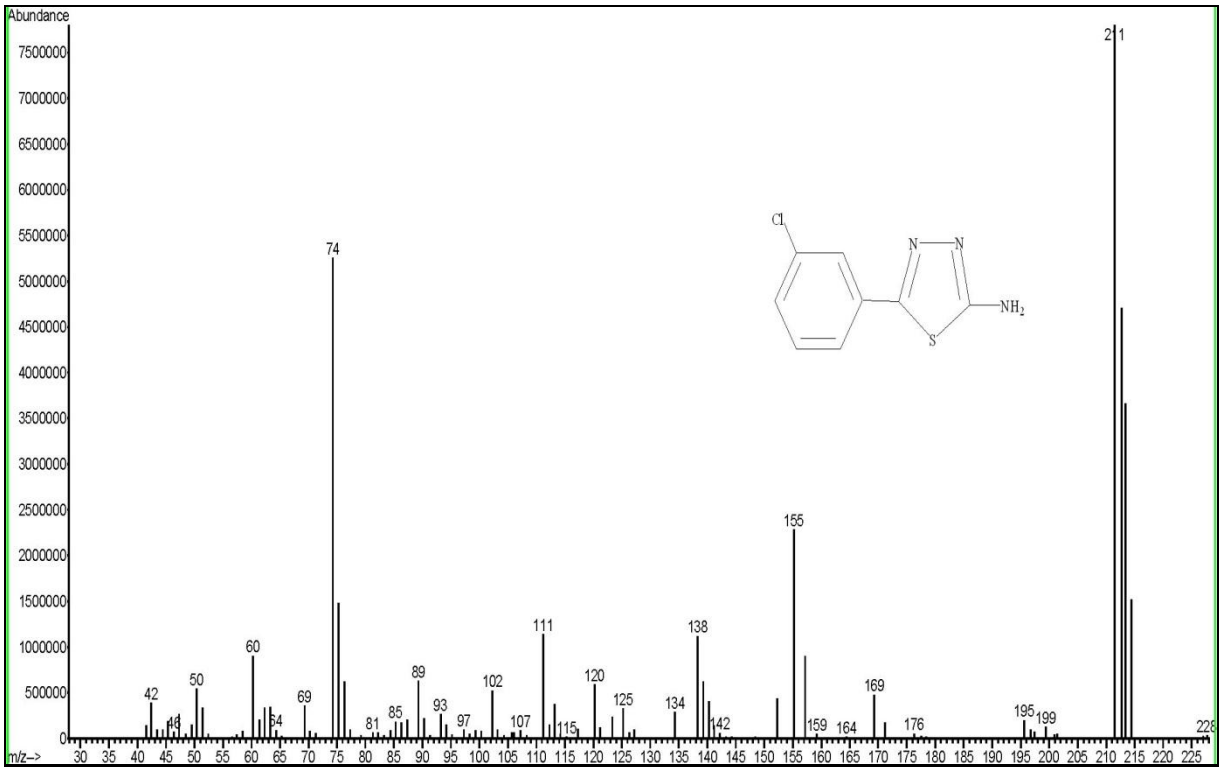
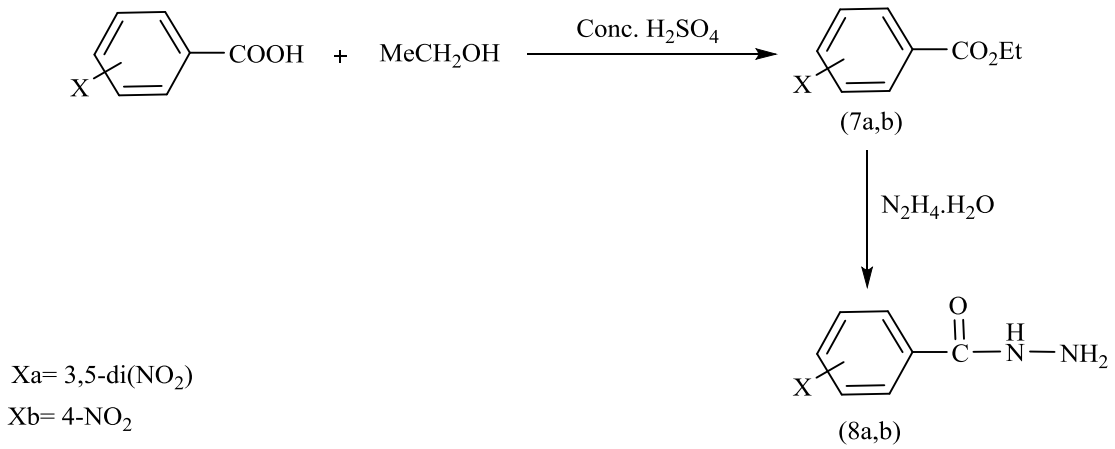


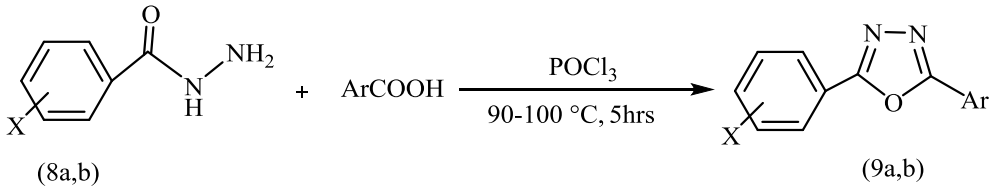
Fig. (3.10): Mass spectrum of amine (6)

3.3.2 Synthesis and characterization of 2-(3,5-dinitro and 4-nitro(phenyl)-5-(4-aminophenyl)-1,3,4-oxadiazole (9a,b)

To prepared these compounds, we prepared the ester (7a,b) from reaction of appropriate aromatic acid with ethyl alcohol in presence of con. sulphuric acid and then preparation of acid hydrazide (8a,b) from treatment of ester with hydrazine hydrate.



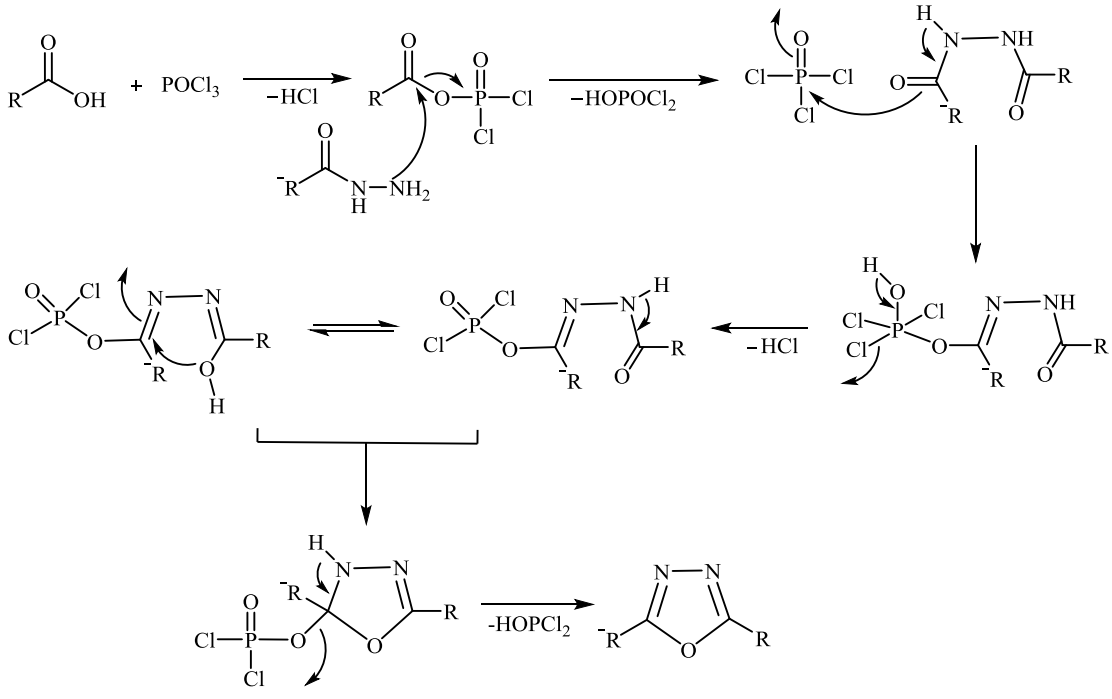
Two of newly 1,3,4-oxadiazoles (9a,b) were synthesized by the cyclization of acid hydrazide (8a,b) with 4-aminobenzoic acid in the presence of $POCl_3$.



(8a,b) (9a,b)

Xa= 3,5-di(NO_2)
X_b= 4-NO_2
Ar= H_2N–C$_6$H$_4$–

The mechanism of cyclization by carboxylic acid and acid hydrazide were shown in Scheme (3.3). [192]



R= X–C$_6$H$_4$–
X_a= 3,5-di(NO_2)
X_b= 4-NO_2
R^-= H_2N–C$_6$H$_4$–

Scheme (3.3): Suggested mechanism of cyclization in the presence of $POCl_3$

The compounds (7a,b) were detected by melting points and FT-IR spectra. The F-TIR spectra Figs. (3.11) and (3.12) showed the absorption bands at (1730 and 1718) cm^{-1} due to (C=O) of ester of compounds (7a and 7b) respectively.

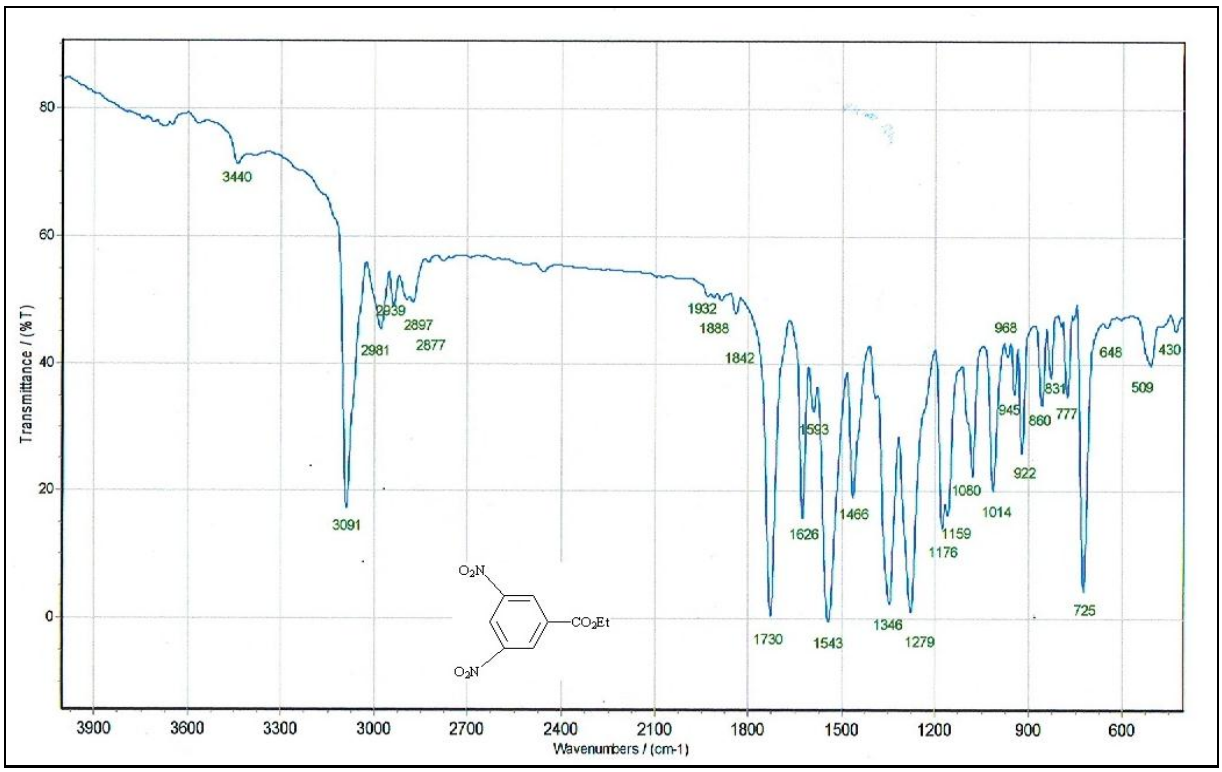


Fig. (3.11): FTIR spectrum of compound (7a)

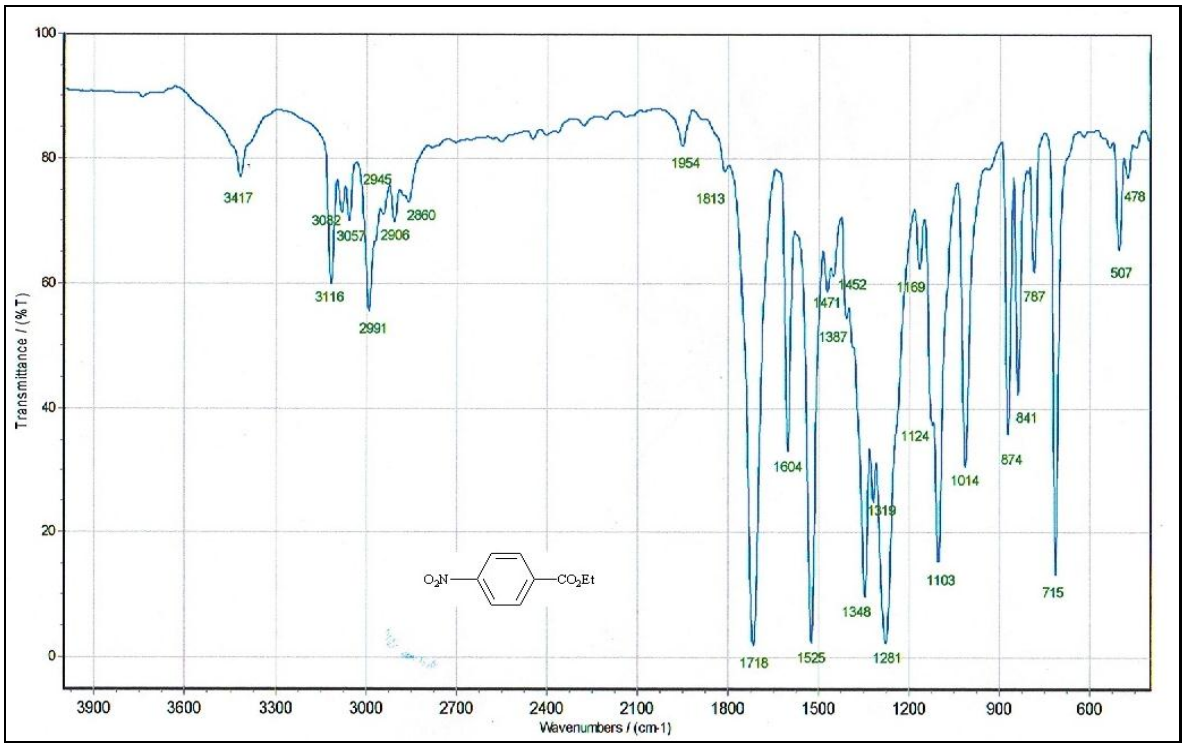


Fig. (3.12): FTIR spectrum of compound (7b)

The acid hydrazide (8a,b) were characterized by melting points and FT-IR spectra. The FT-IR spectra, Figs. (3.13) and (3.14) showed the following bands for (8a), (3394) cm^{-1} for (N-H), (3317, 3207) cm^{-1} for (NH_2) group, (3103) cm^{-1} for (C-H) aromatic, (1641) cm^{-1} for sec. amide, (1608) cm^{-1} for (C=C) aromatic and (1520, 1348) cm^{-1} for (NO_2) group and the FTIR for (8b) showed bands, (3330) cm^{-1} for (N-H), (3259, 3151) cm^{-1} for (NH_2) group, (3072) cm^{-1} for (C-H) aromatic, (1643) cm^{-1} for (C=O) sec.amide, (1595) cm^{-1} for (C=C) aromatic and (1510, 1346) cm^{-1} for (NO_2) group.

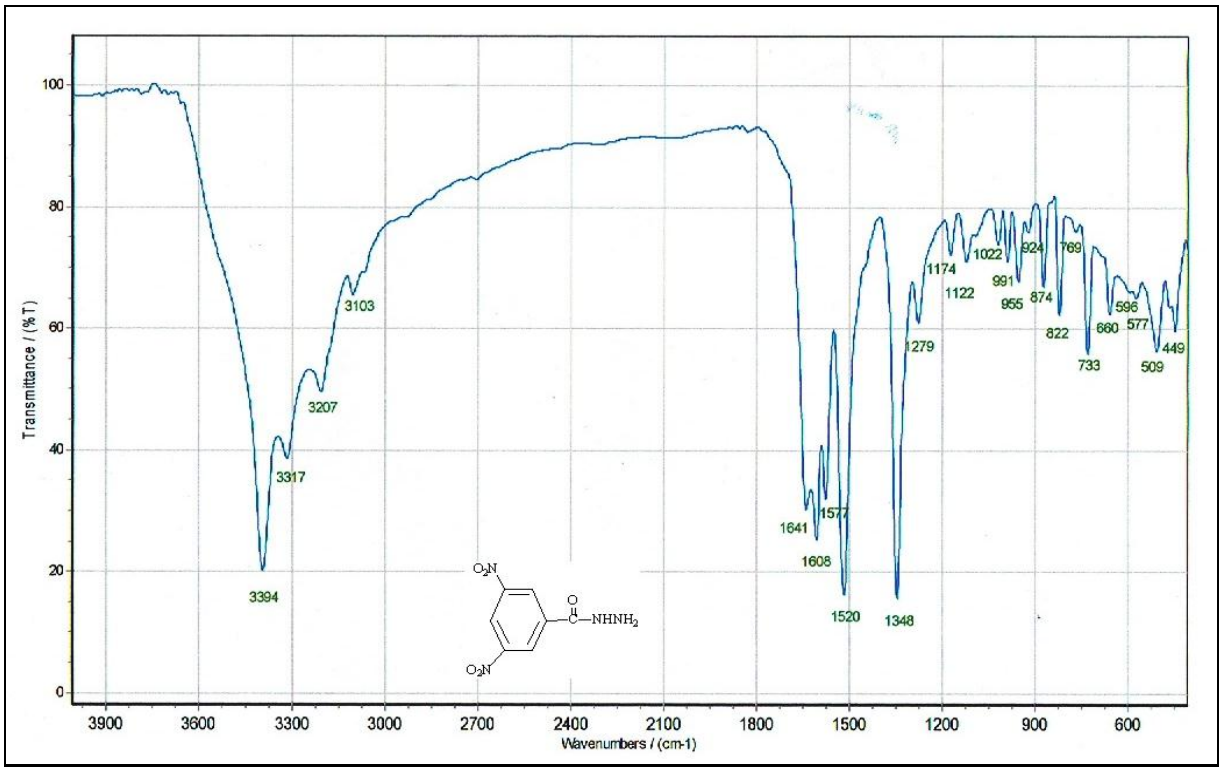


Fig. (3.13): FTIR spectrum of acid hydrazide (8a)

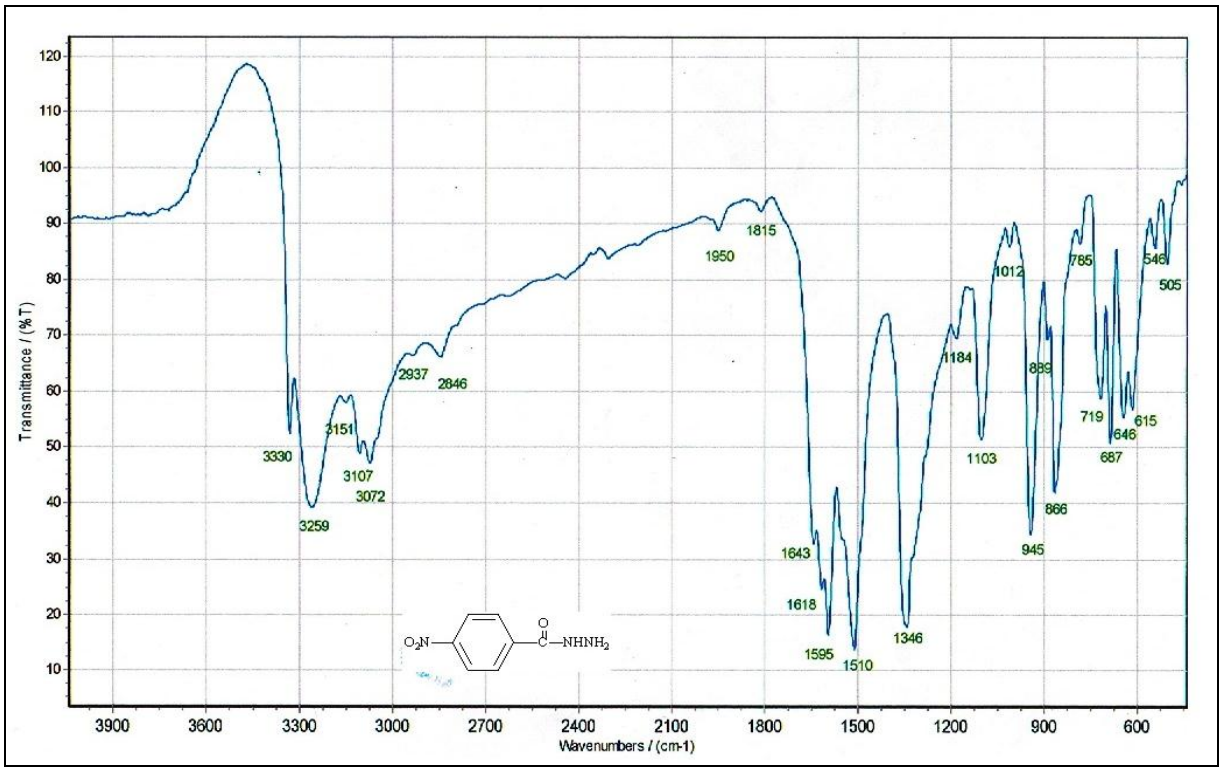


Fig. (3.14): FTIR spectrum of acid hydrazide (8b)

The amine (9a) was identified via FT-IR and mass spectroscopy. The FT-IR spectrum of (9a) Fig. (3.15) indicated the (NH_2) group at (3356, 3224) cm^{-1}, (C-H) aromatic at (3089) cm^{-1}, (C=N) at (1603) cm^{-1}, (C=C) at (1533) cm^{-1}, (C-O) at (1184) cm^{-1} and at (1504, 1344) cm^{-1} for (NO_2).

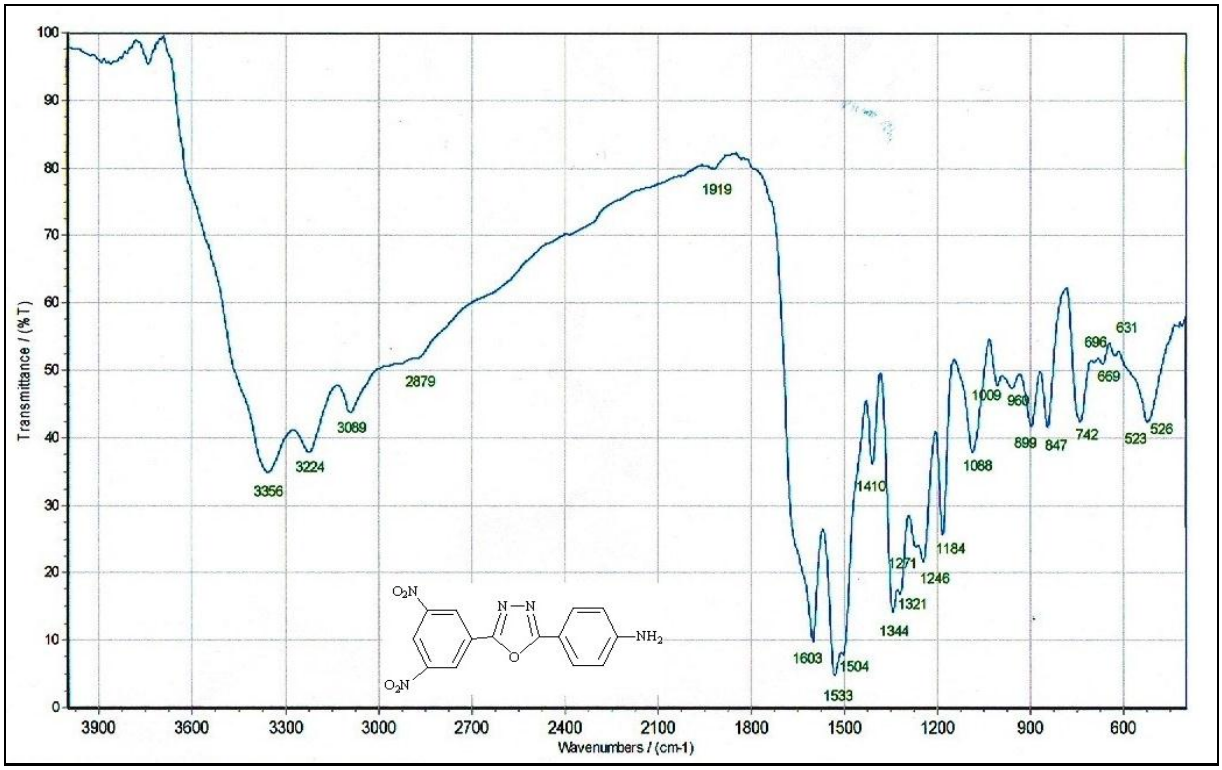
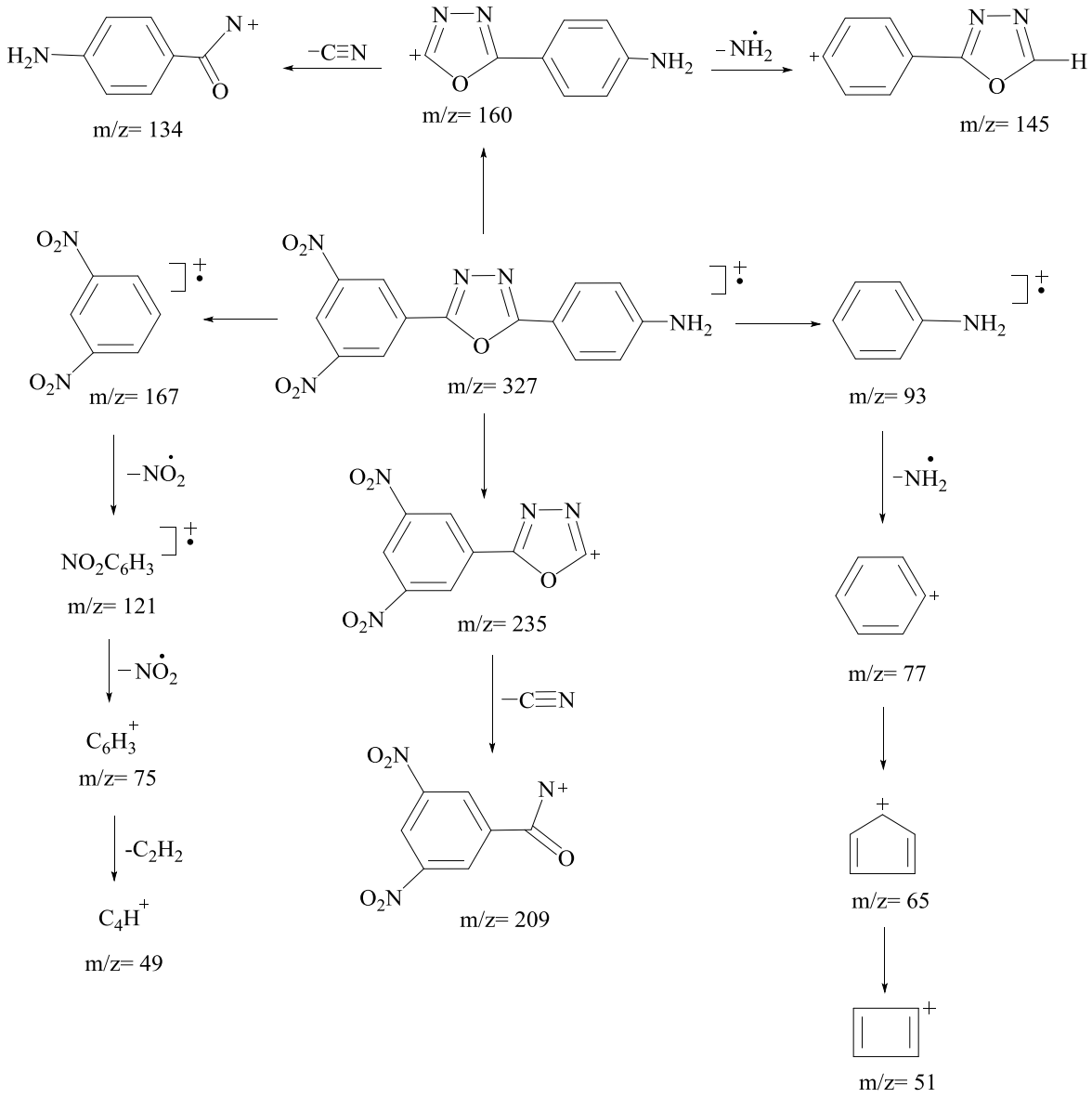


Fig. (3.15): FT-IR spectrum of amine (9a)

The mass spectrum of amine (9a), Fig. (3.16) exhibited m/z= 327 (M^+) and characteristic fragments of this compound showed in Scheme (3.4). Whereas the FT-IR spectrum of compound (9b), Fig. (3.17) demonstrated the (NH_2) group at (3338, 3217) cm^{-1}, (C-H) aromatic at (3072) cm^{-1} and (C=N) at (1601) cm^{-1}, (C=C) at (1556) cm^{-1}, at (1105) cm^{-1} for C-O and at (1520, 1342) cm^{-1} for (NO_2) group.



Scheme (3.4): The characteristic fragments of amine (9a)

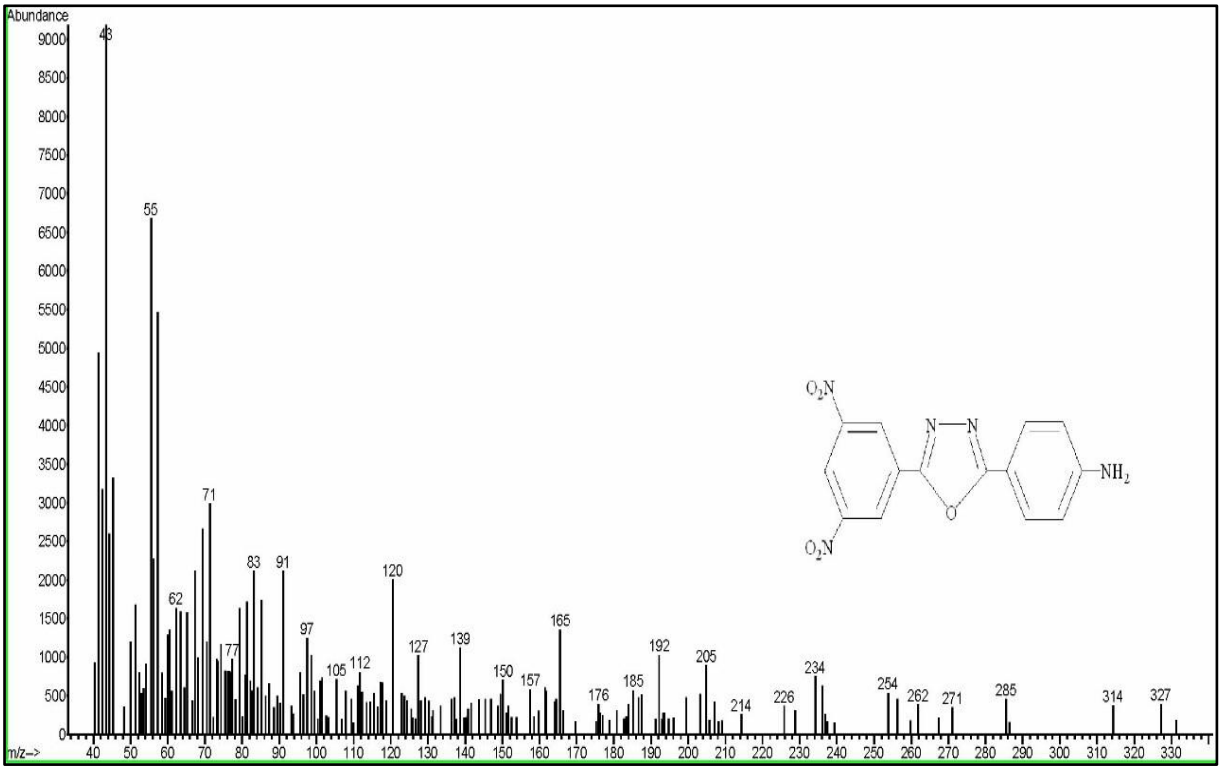


Fig. (3.16): Mass spectrum of amine (9a)

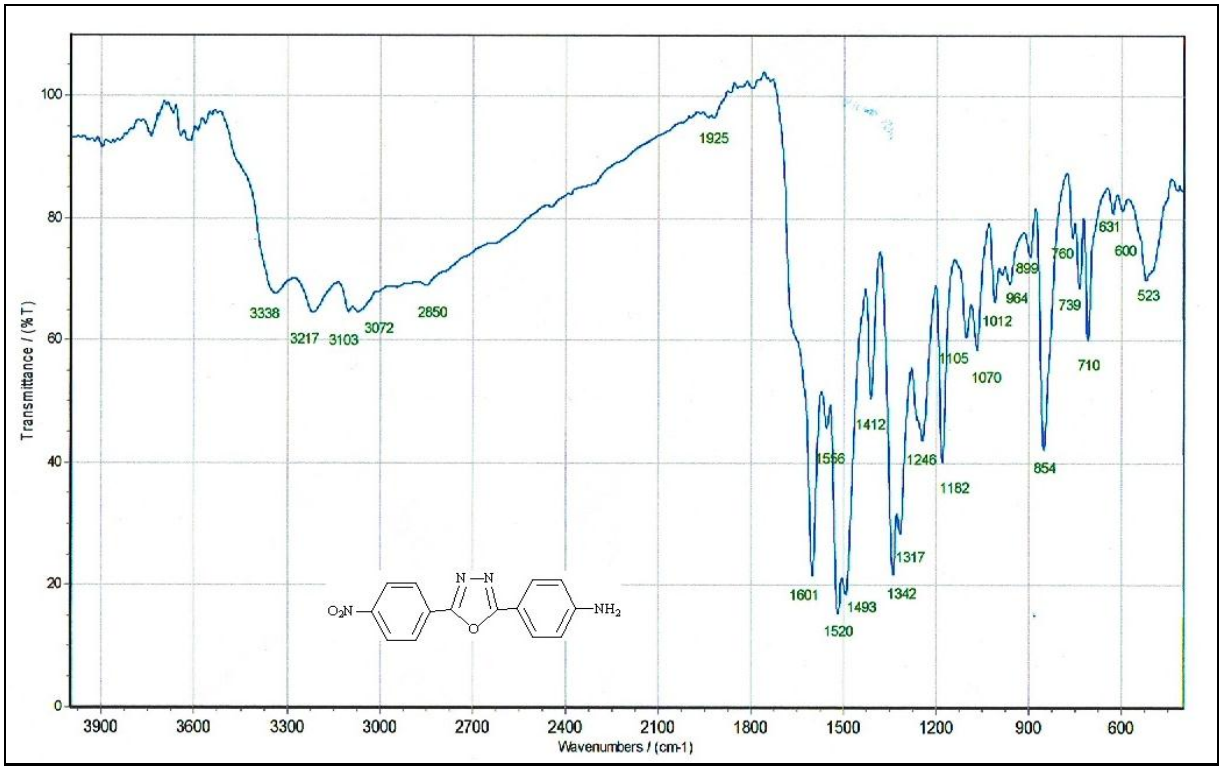


Fig. (3.17): FTIR spectrum of amine (9b)

The ^{1}H-NMR spectrum of compound (9b), Fig. (3.18) exhibited that the NH_2 signal at δ(11.05 ppm) and showed a doublet doublet signals among in the range δ(7.74-8.51) ppm related to aromatic protons. The mass spectrum of amine (9b), Fig. (3.19) exhibited m/z= 282 (M^+) and characteristic fragments of this compound were shown in Scheme (3.5).

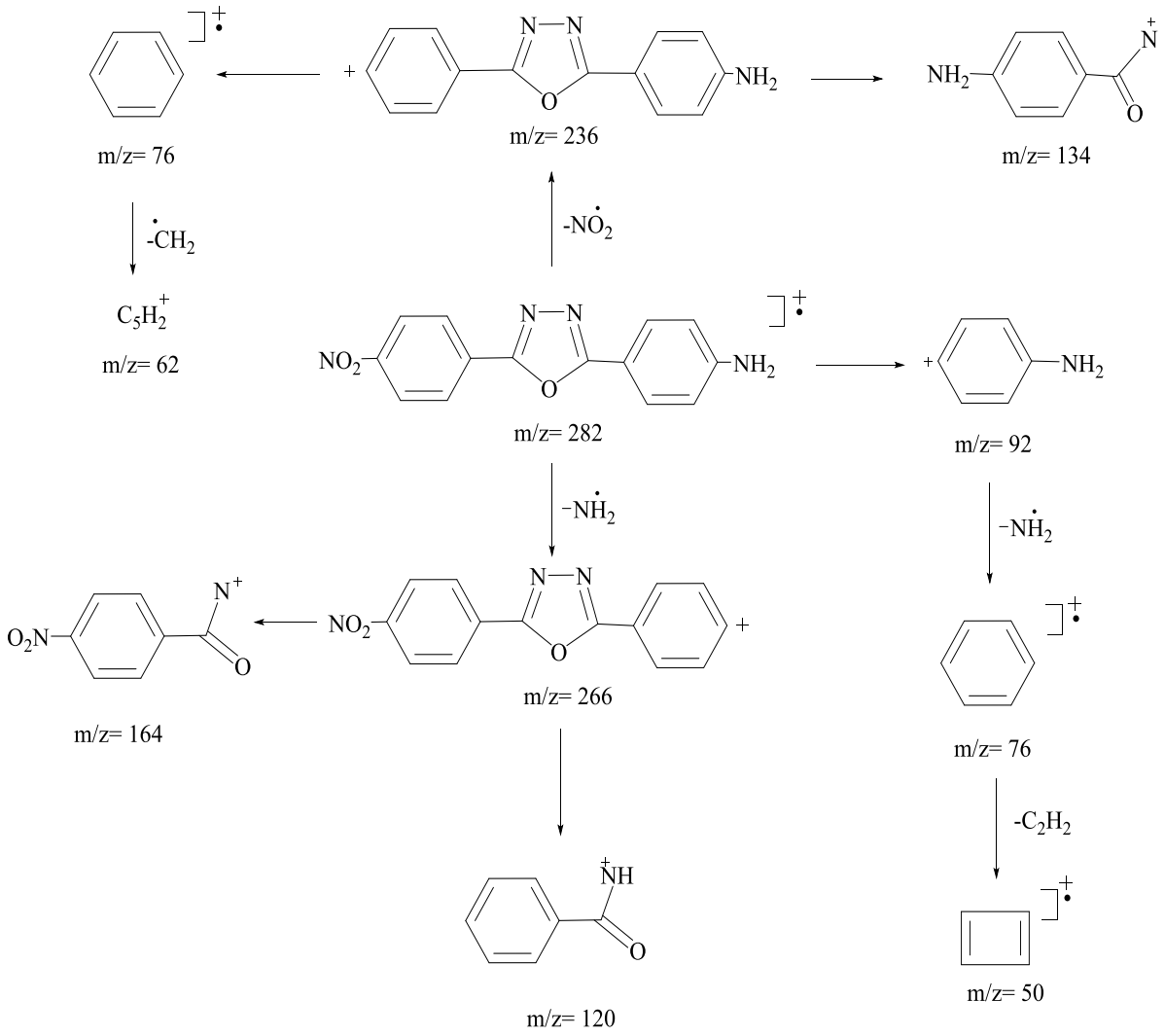


Diagram (3.5): The characteristic fragments of amine (9b)

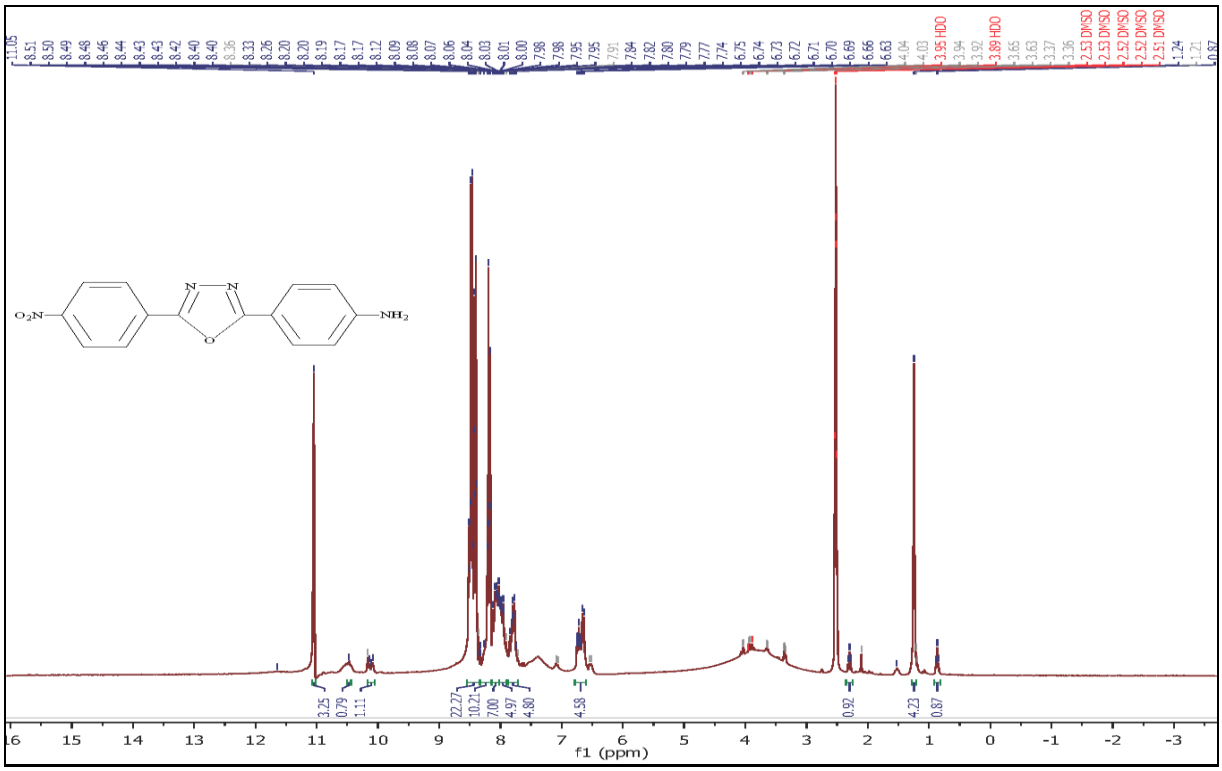


Fig. (3.18): ^{1}H-NMR spectrum of amine (9b)

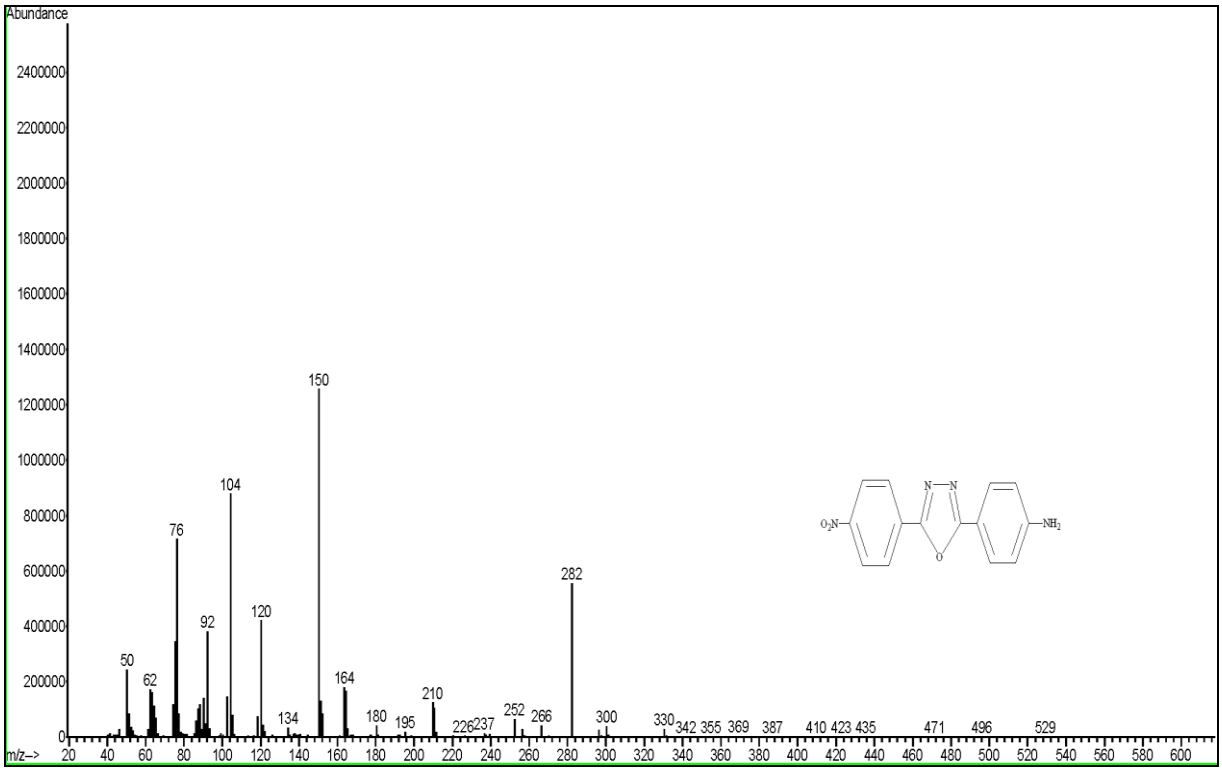
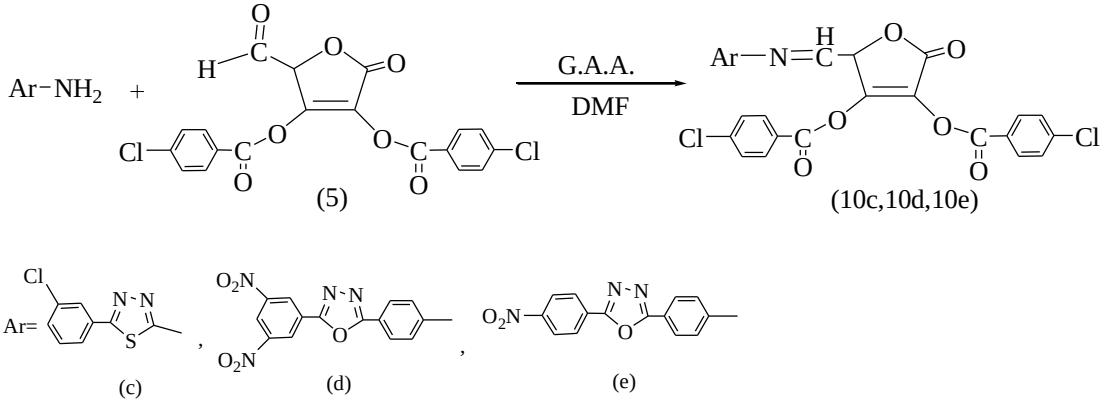


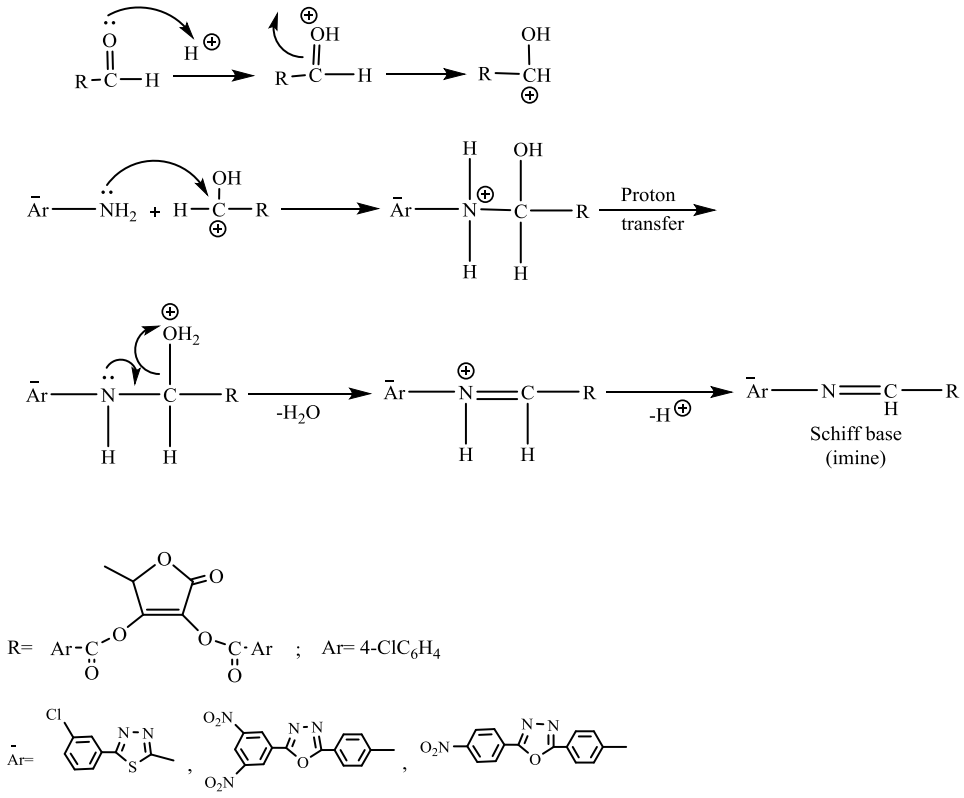
Fig. (3.19): Mass spectrum of amine (9b)

3.4 Synthesis and characterization of Schiff bases (10c), (10d) and (10e)

The new Schiff bases were synthesized by refluxing equimolar of aldehyde derived from L-ascorbic acid (5) with amino compounds (6), (9a) or (9b) in DMF with some drops of glacial acetic acid (G.A.A.).



The mechanism of this reaction was outlined as follows, Scheme (3.6). [193]



Scheme (3.6): The mechanism for Schiff base formation

These Schiff bases (10c), (10d) and (10e) were detected via FT-IR, ^{1}H-NMR and mass spectroscopy.

FT-IR absorption spectrum of Schiff base (10c), Fig. (3.20) indicated the disappearance of absorption peaks at (3265, 3168) cm^{-1} of NH_2 and C=O group at (1728) cm^{-1} of the starting materials together with emergence new absorption stretching peak at (1645) cm^{-1} that is belong to azomethine group (C=N stretching), a stretching bands at (3097, 2927, 1680, 1618, 1591) cm^{-1} due to (C-H) aromatic, (C-H) aliphatic, (C=O) of ester, (C=N) in thiadiazole ring and (C=C) aromatic respectively.

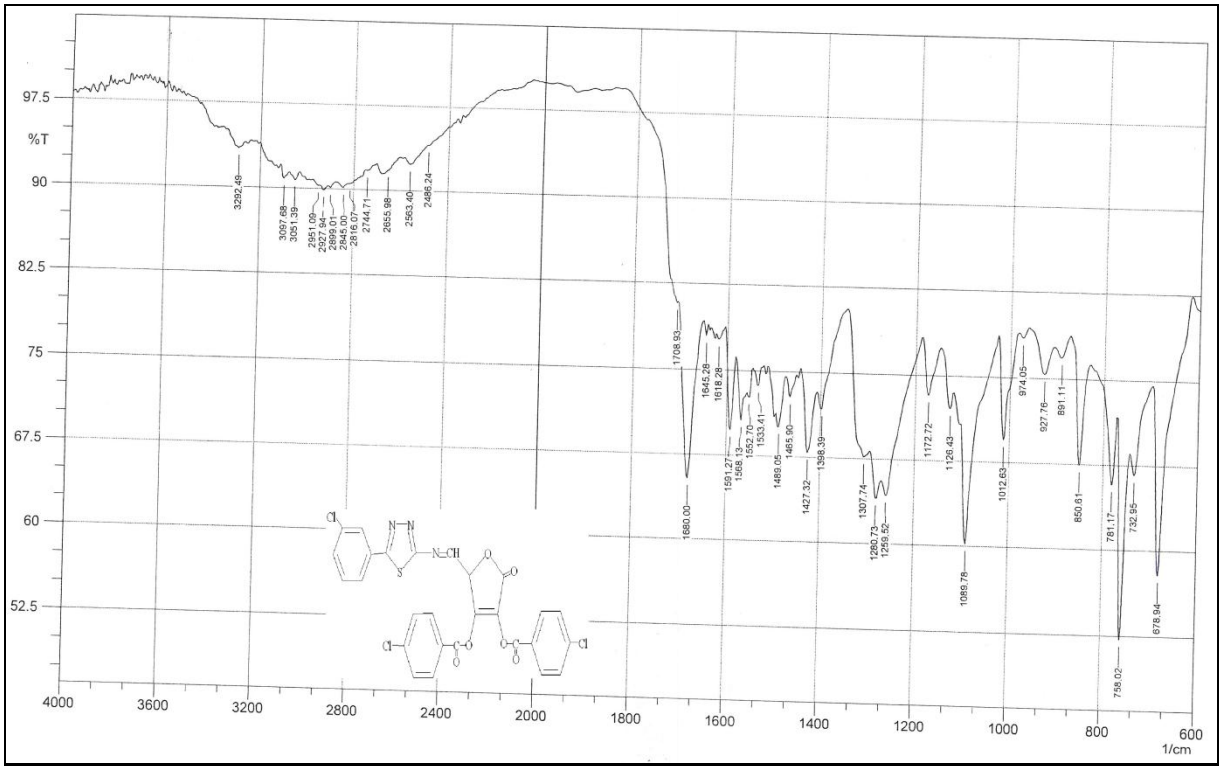
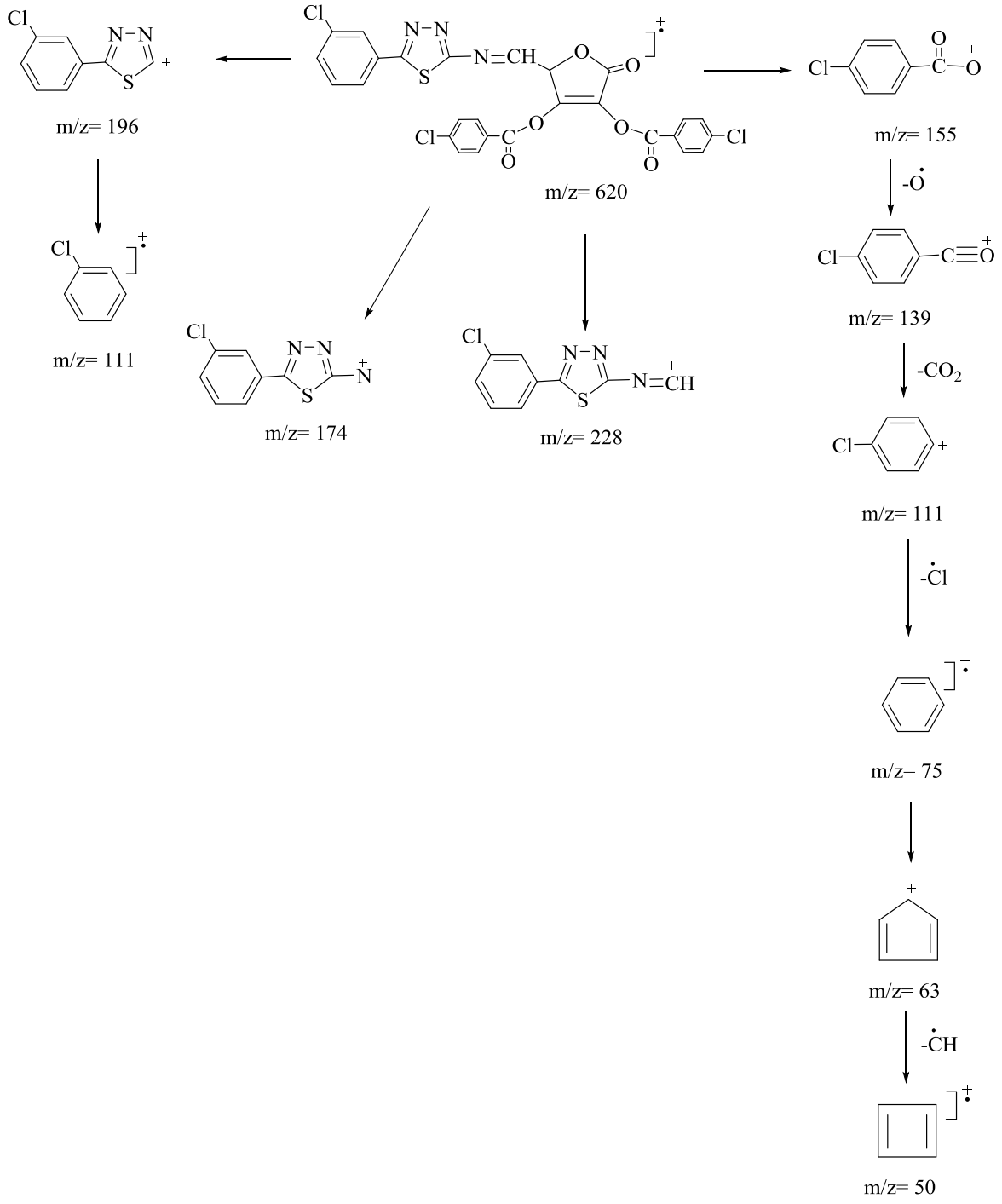


Fig. (3.20): FTIR spectrum of Schiff base (10c)

The ^{1}H-NMR spectrum of Schiff base (10c) (in DMSO-d_6), Fig. (3.21) demonstrated a singlet signal at δ(8.62 ppm) related to one proton of the (CH=N) group. Multiplet signals at δ(7.50-8.11) ppm that could be imputed to the tweleve aromatic protons and a signal at δ(4.5 ppm) is assigned to one proton of lactone ring (H-4).

The mass spectrum of Schiff base (10c), Fig. (3.22) exhibited m/z= 620 (M^+) where some of sulphur atom is atomic weight (34) as well as three nitrogen atoms are atomic weight (15) and characteristic fragments of this compound showed in Scheme (3.7).



Scheme (3.7): The characteristic fragments of Schiff base (10c)

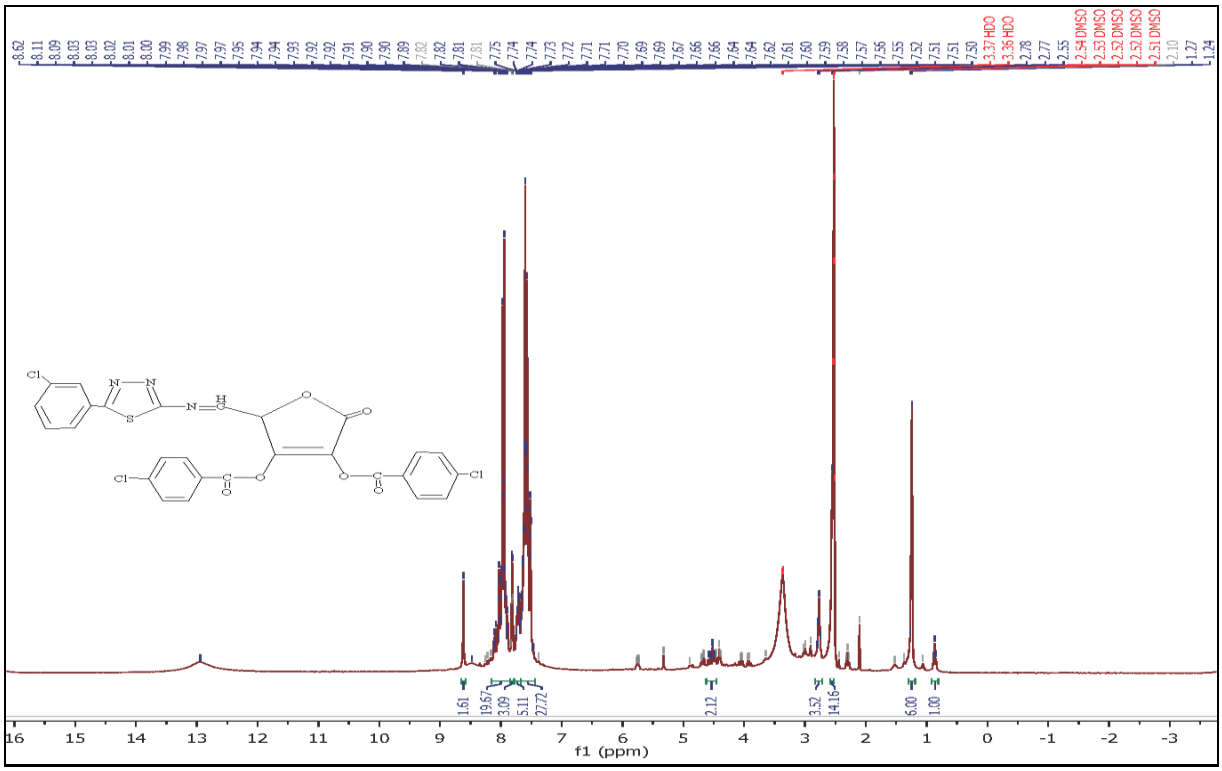


Fig. (3.21): ^{1}H-NMR spectrum of Schiff base (10c)

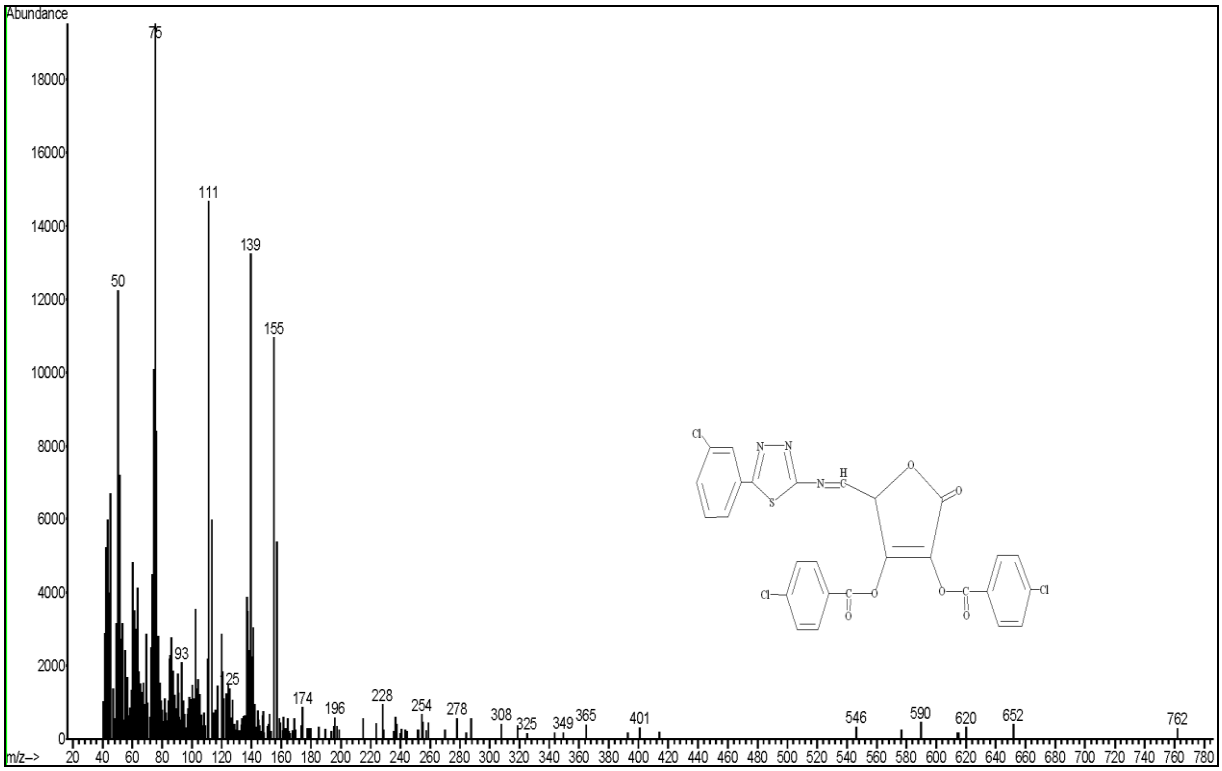


Fig. (3.22): Mass spectrum of Schiff base (10c)

FTIR absorption spectrum of Schiff base (10d), Fig. (3.23) showed the disappearance of absorption bands of NH_2 at (3356, 3224) cm^{-1} and C=O group at (1728) cm^{-1} of the starting materials together with emergence new absorption stretching peak at 1645 cm^{-1} that is belong to azomethine group (C=N stretching), a stretching bands at (3095, 2924, 1676, 1627, 1591, 1531 and 1317) cm^{-1} related to (C-H) aromatic, (C-H) aliphatic, (C=O) of ester, (C=N) in oxadiazole ring, (C=C) aromatic and (NO_2) groups (asymmetric and symmetric stretching) respectively.

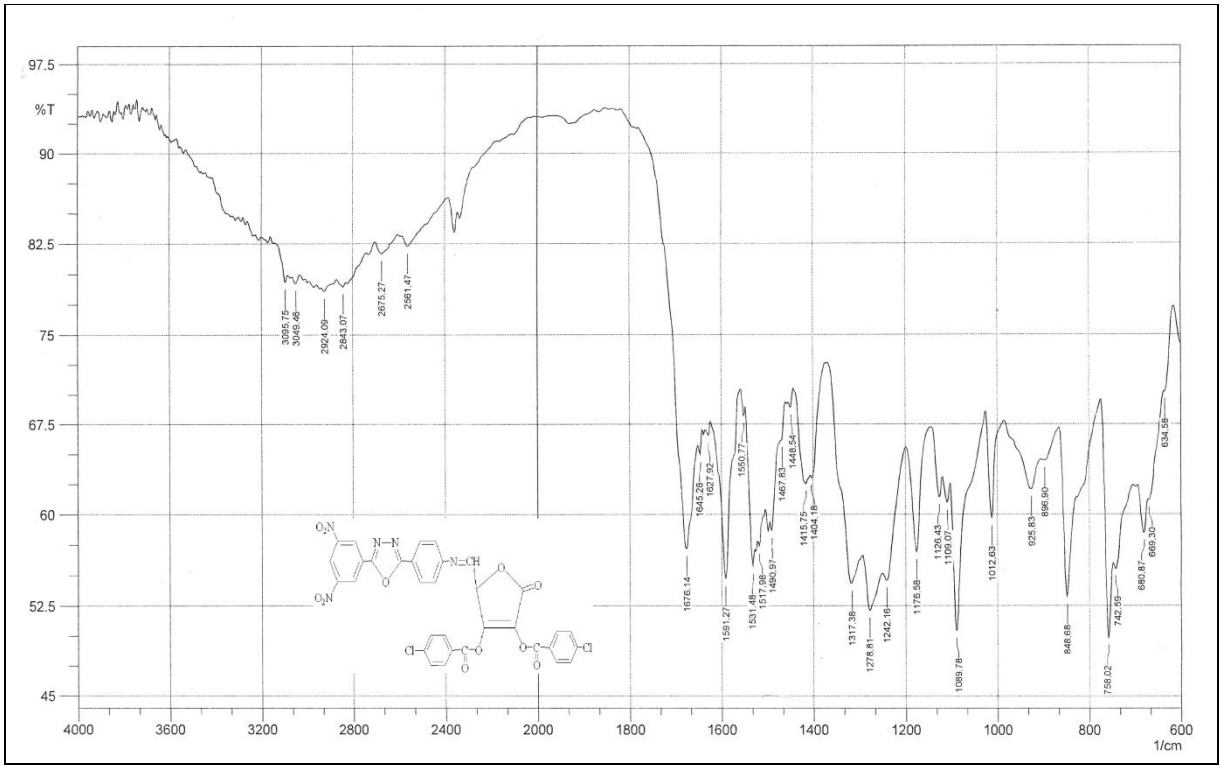


Fig. (3.23): FTIR spectrum of Schiff base (10d)

The ^{1}H-NMR spectrum of Schiff base (10d) (in DMSO-d_6), Fig. (3.24) indicated a signal at δ(8.10 ppm) could be imputed to one proton of the (CH=N) group. Multiplet signals at δ(7.40-8.08) ppm that could be attributed to the aromatic protons and a signal at δ(4.04 ppm) is assigned to one proton of lactone ring (H-4).

The mass spectrum of Schiff base (10d), Fig. (3.25) exhibited m/z= 730 (M^+) and characteristic fragments of this compound were shown in Scheme(3.8).

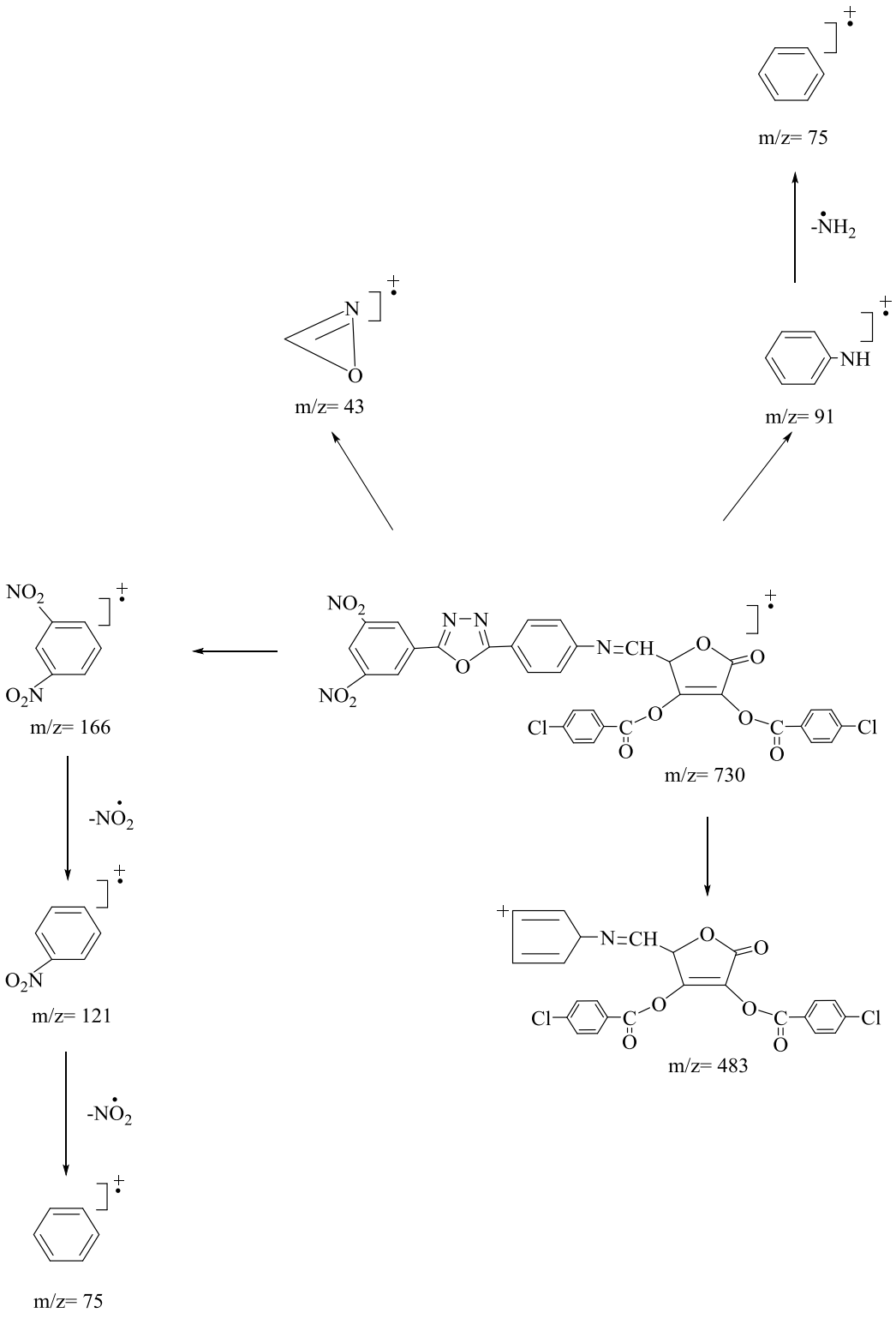


Diagram (3.8): The characteristic fragments of Schiff base (10d)

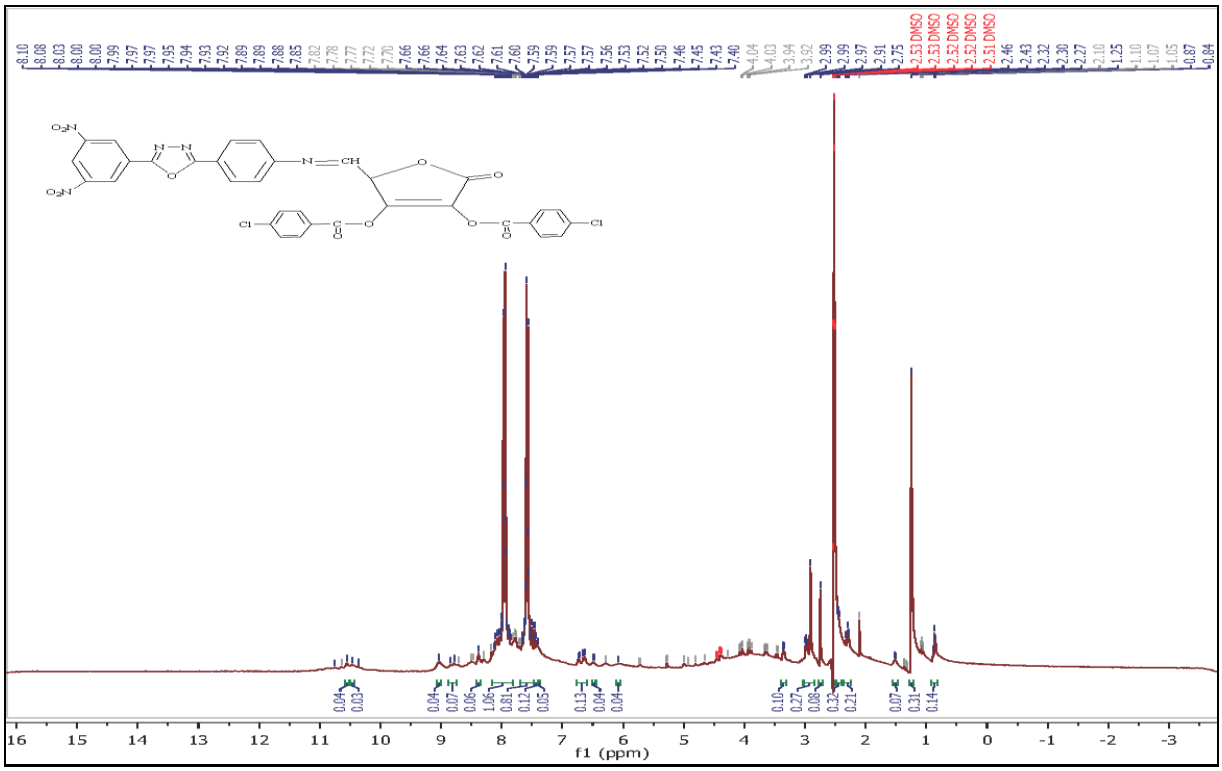


Fig. (3.24): ^{1}H-NMR spectrum of Schiff base (10d)

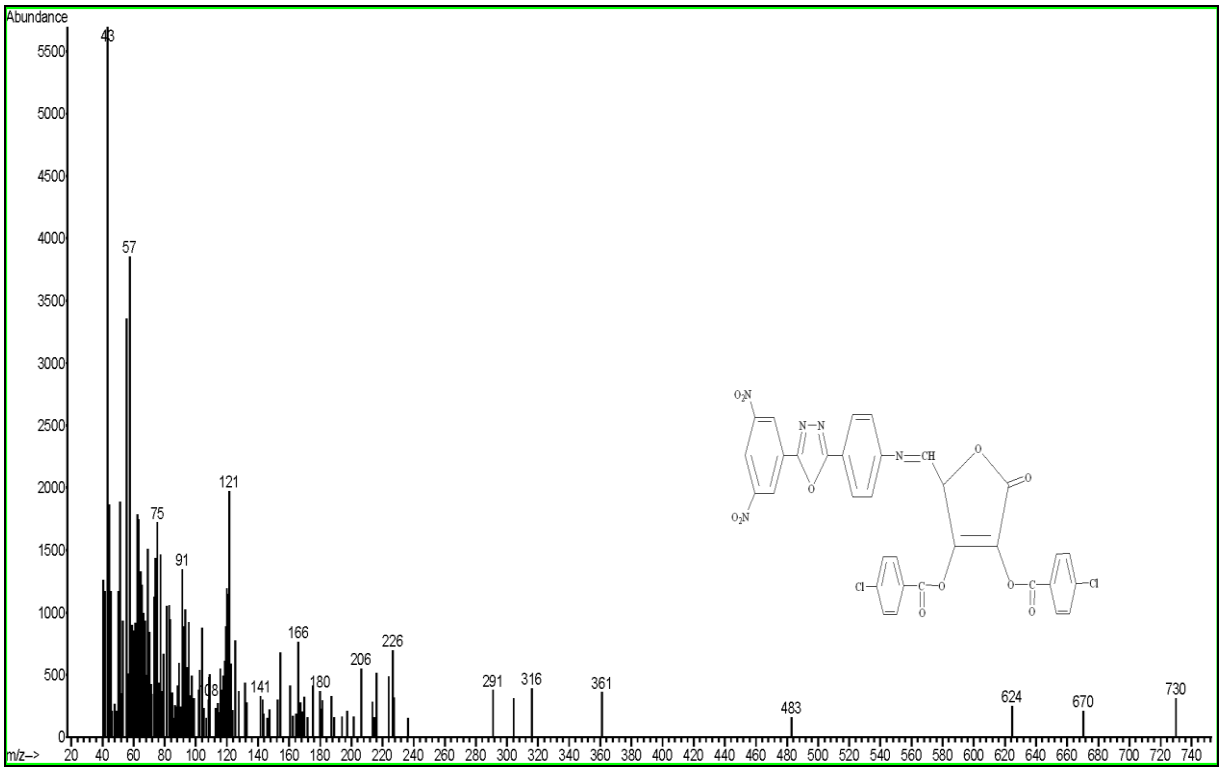


Fig. (3.25): Mass spectrum of Schiff base (10d)

FTIR absorption spectrum of Schiff base (10e), Fig. (3.26) showed the disappearance of absorption bands of NH_2 at (3338, 3217) cm^{-1} and C=O group at (1728) cm^{-1} of the starting materials together with appearence new absorption stretching peak upon (1635) cm^{-1} that is assigned to azomethine group (CH=N vibrating), a stretching band at (3074, 1654, 1604, 1519 and 1342) cm^{-1} related to (C-H) aromatic, (C=O) of ester, (C=C) aromatic, (NO_2) group asymmetric and symmetric stretching, (C=N) group in oxadiazole ring is overlap with (C=N) group for Schiff base.

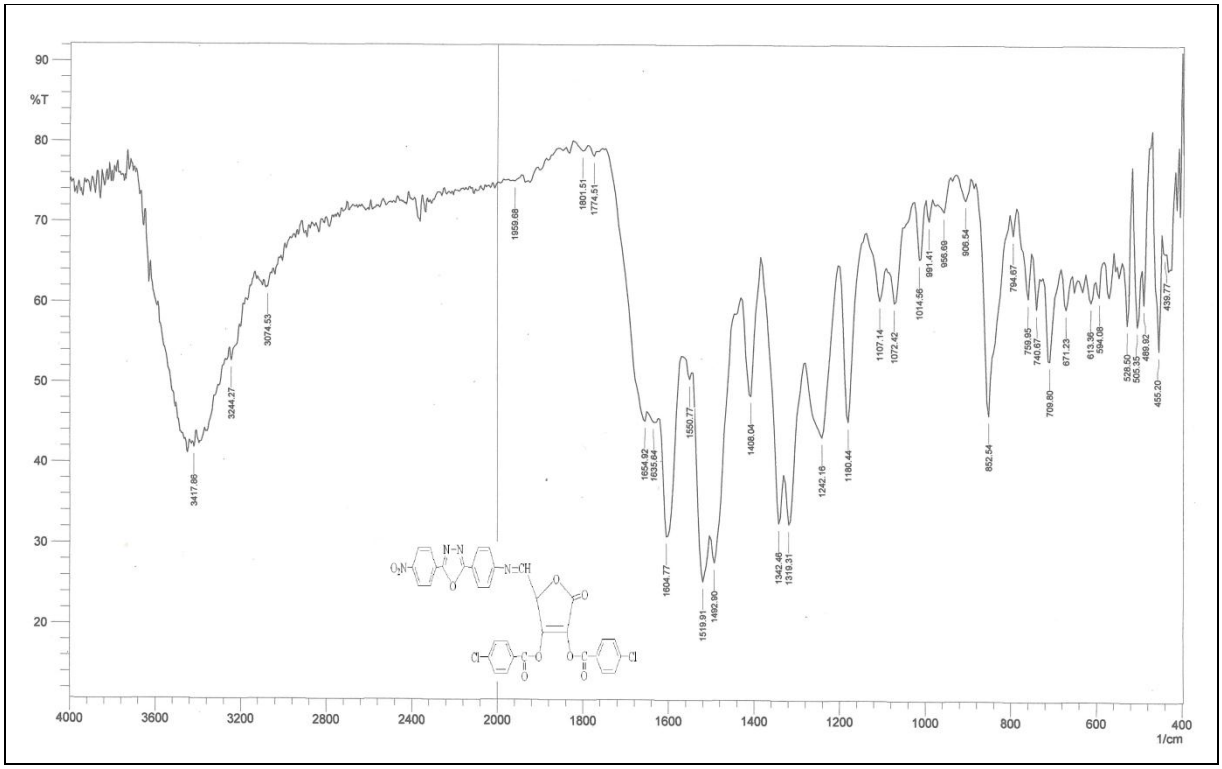
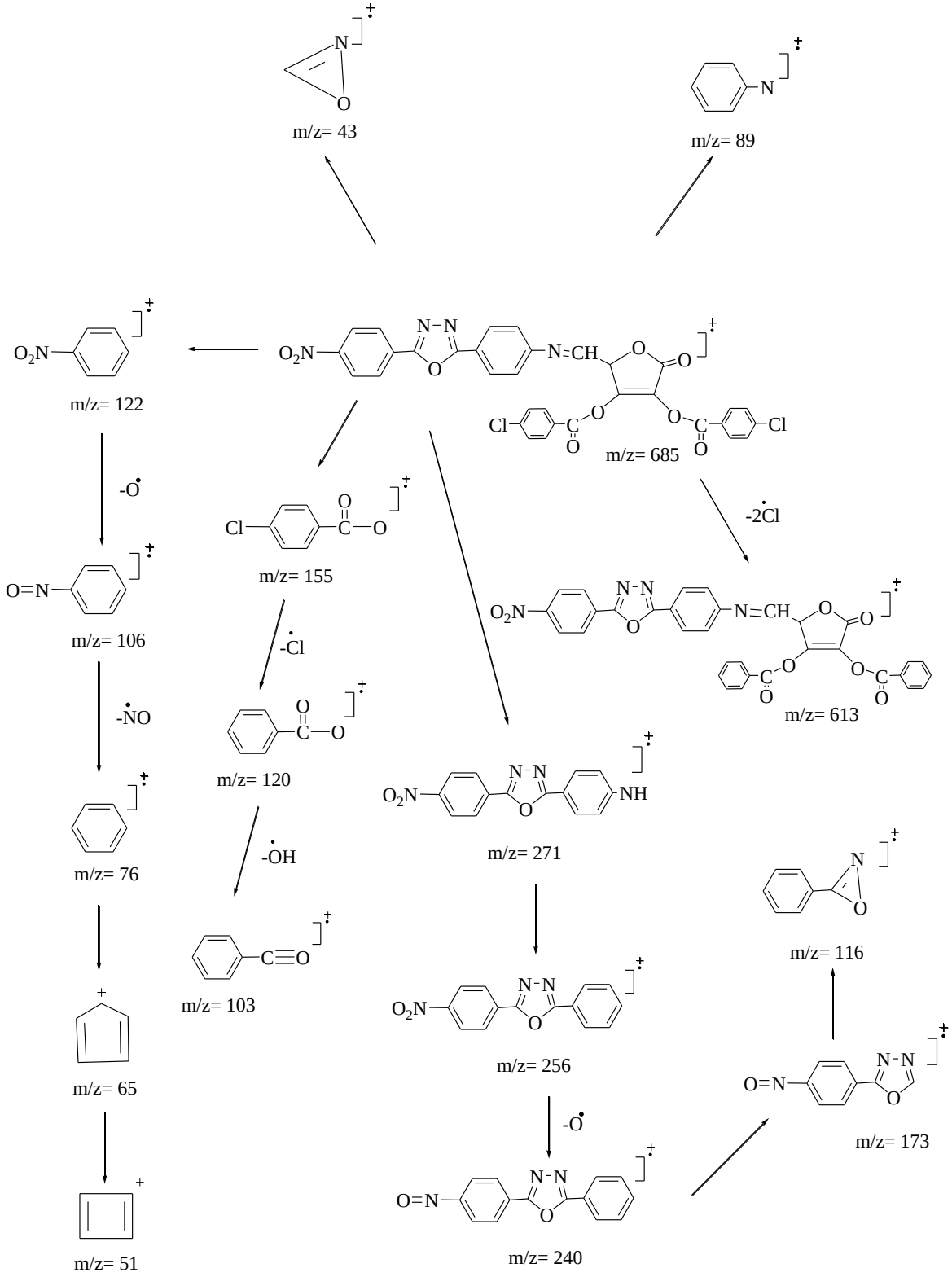


Fig. (3.26): FTIR spectrum of Schiff base (10e)

The ^{1}H-NMR spectrum of Schiff base (10e) (in DMSO-d_6), Fig. (3.27) indicated two doublet pairs at δ(7.57-8.52) ppm that could be imputed to the aromatic protons and for one proton of the (CH=N) group and a signal at δ(3.47 ppm) was assigned to one proton of lactone ring (H-4).

The mass spectrum of Schiff base (10e), Fig. (3.28) indicated m/z= 685 (M^+) and characteristic fragments of this compound were shown in Scheme (3.9).



Scheme (3.9): The characteristic fragments of Schiff base (10e)

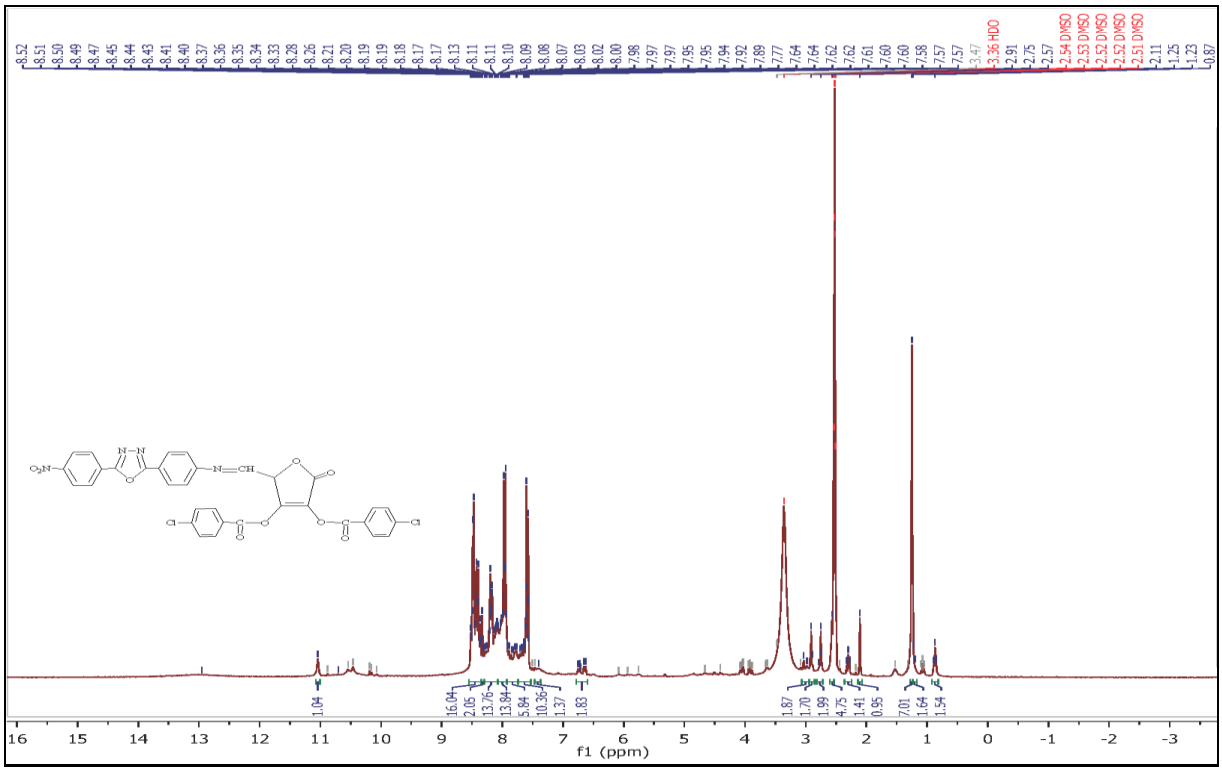


Fig. (3.27): ^{1}H-NMR spectrum of Schiff base (10e)

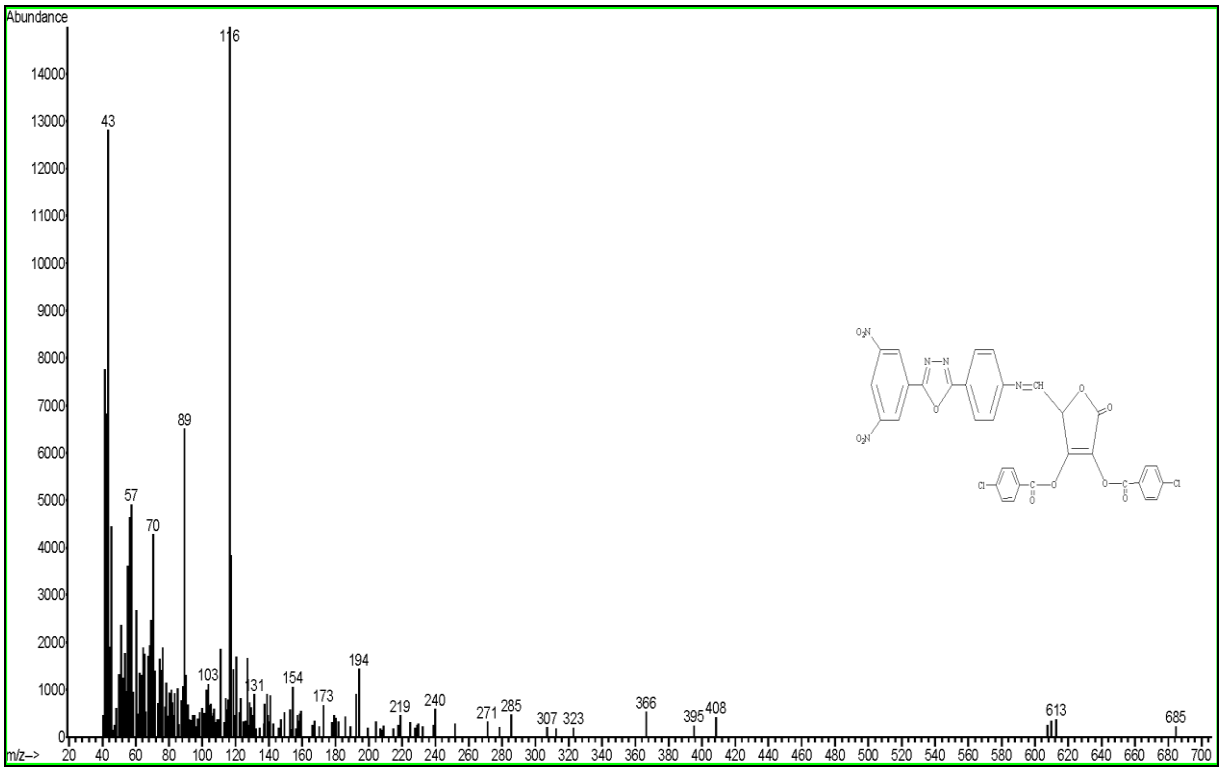
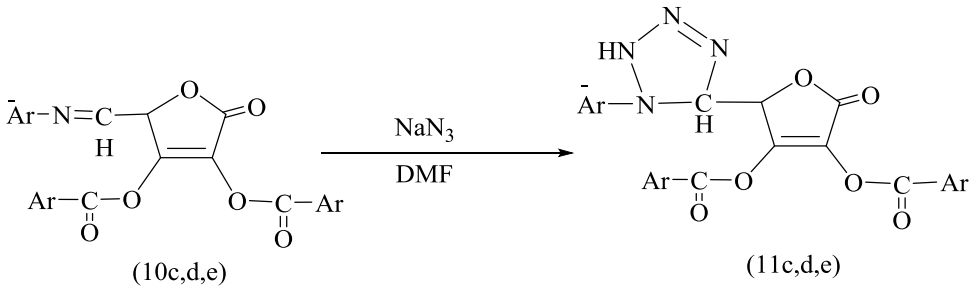
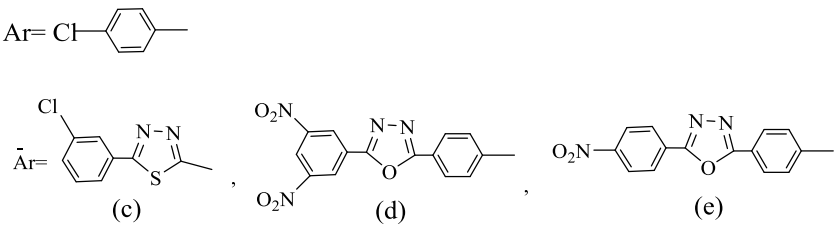


Fig. (3.28): Mass spectrum of Schiff base (10e)

3.5 Synthesis and characterization of 2,5-dihydrotetrazole compounds (11c, 11d and 11e)

2,5-Dihydrotetrazole derivatives (11c, 11d and 11e) were obtained by addition reaction of NaN_3 to imines (10c, 10d or 10e) in dimethyl formamide.





This reaction is a (3+2) cycloaddition reaction [194], which implied the addition of 1,3-dipoles like azides to the unsaturated system like imine bond as dipolarphiles. The result is a five-membered ring [195] showed in the Fig (3.29).

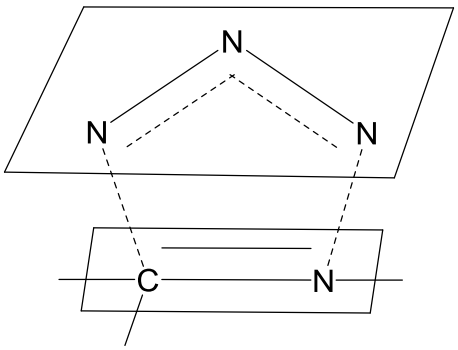
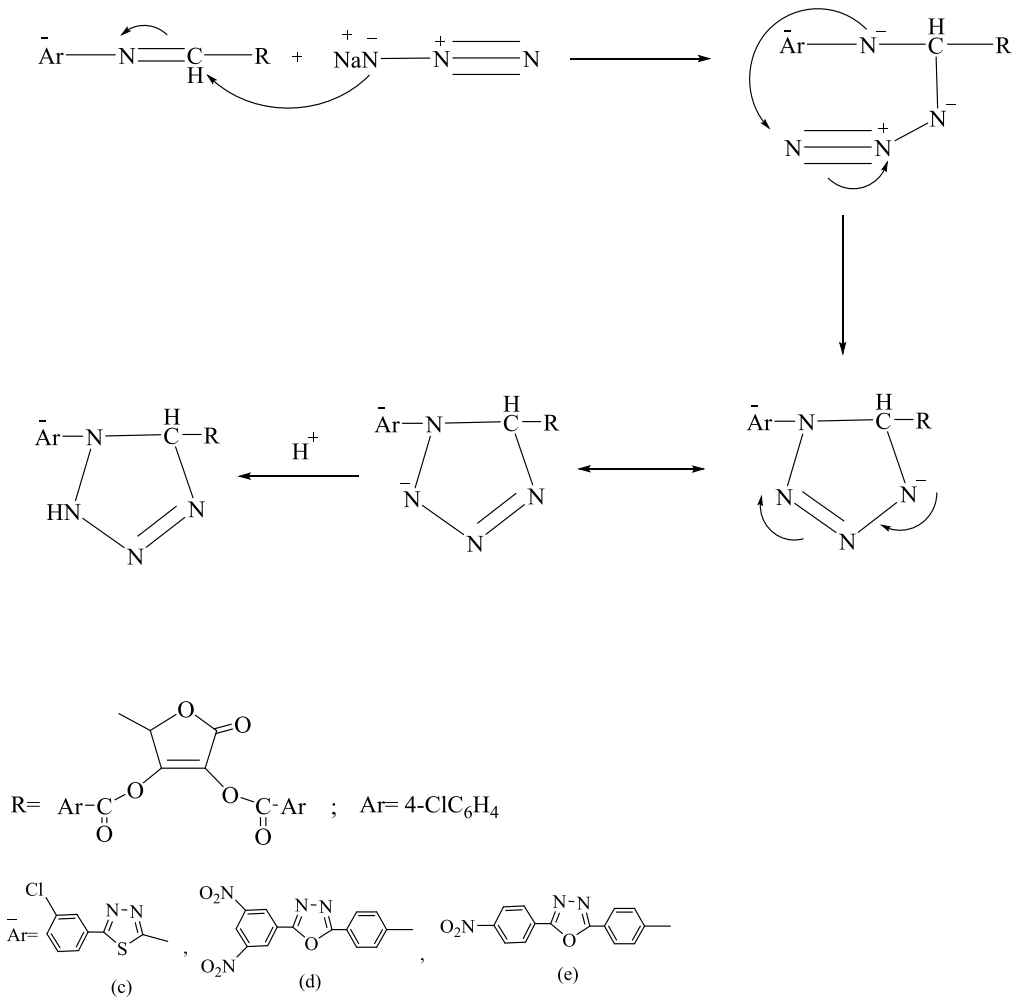


Fig. (3.29): Transition state of tetrazole

The mechanism of this reaction was outlined as follows in Scheme (3.10). [196]



Scheme (3.10): The mechanism for 2,5-dihydrotetrazole formation

These compounds were detected by FT-IR and ^{1}H-NMR spectroscopy for 2,5dihydrotetrazole (11e). The FTIR spectra, Figs (3.30), (3.31), (3.32) respectively showed the appearance of new absorption vibrating peak in the range(1550-1560) cm^{-1} that are belong to N=N vibrating [197]. The FTIR characteristic data for 2,5dihydrotetrazole compounds (11c,11d,11e) were given in Table (3.1).

Table (3.1): The FTIR spectral data of compounds (11c, 11d, 11e)

Comp. no.	ν(N-H)	ν(C-H) ar.	ν(C-H) ali.	ν(C=O) est.	ν(C=N) in ring	ν(C=C) ar.	ν(N=N)	ν(NO_2) asy.	ν(NO_2) sy.
11c	3354	3072	2926,2864	1693	1625	1568	1550	-	-
11d	3392	3057	2995,2839	1662	1643	1598	1560	1510	1359
11e	3369	3074	2931,2852	1662	1645	1595	1550	1516	1313

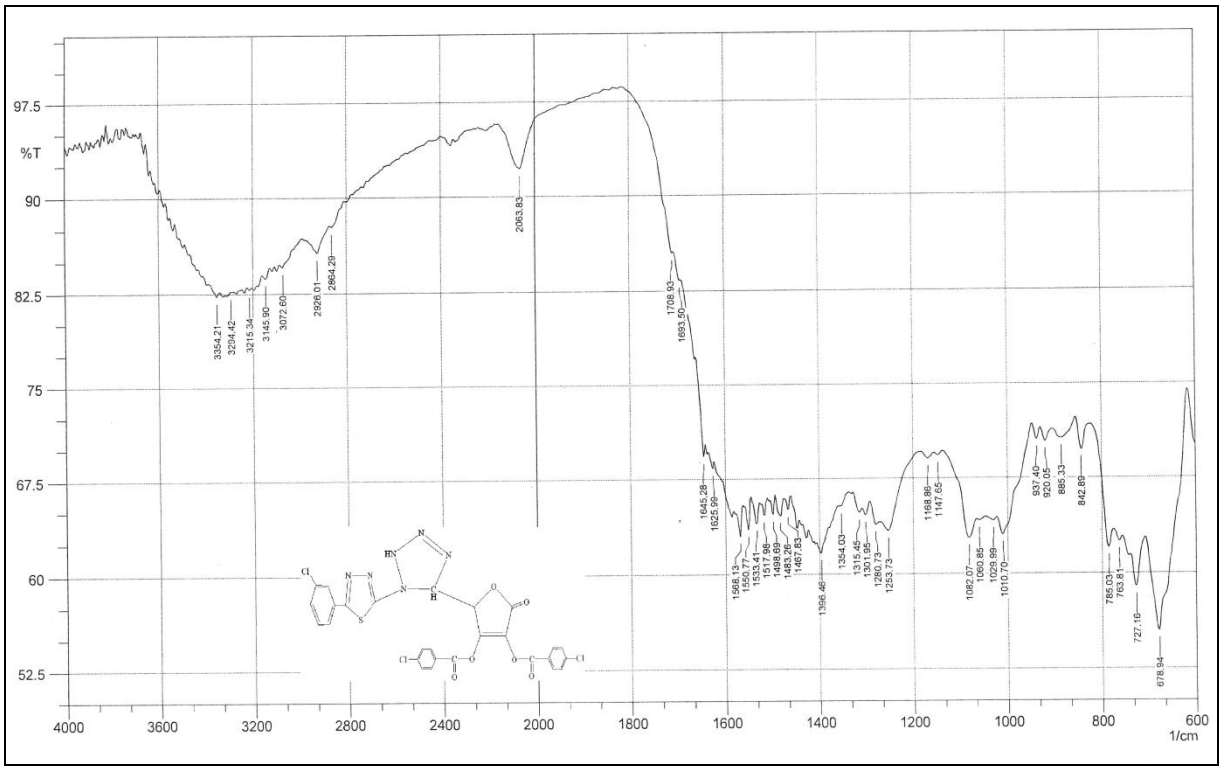


Fig. (3.30): FTIR spectrum of 2,5dihydrotetrazole (11c)

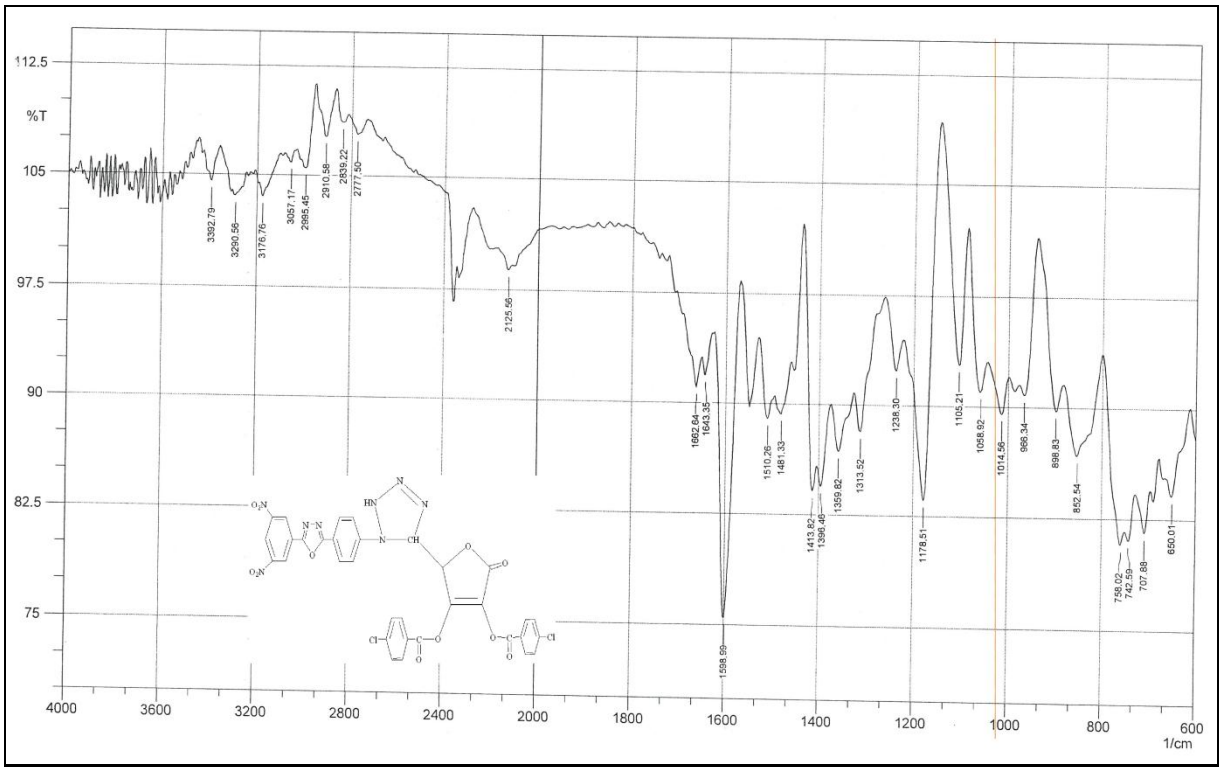


Fig. (3.31): FTIR spectrum of 2,5dihydrotetrazole (11d)

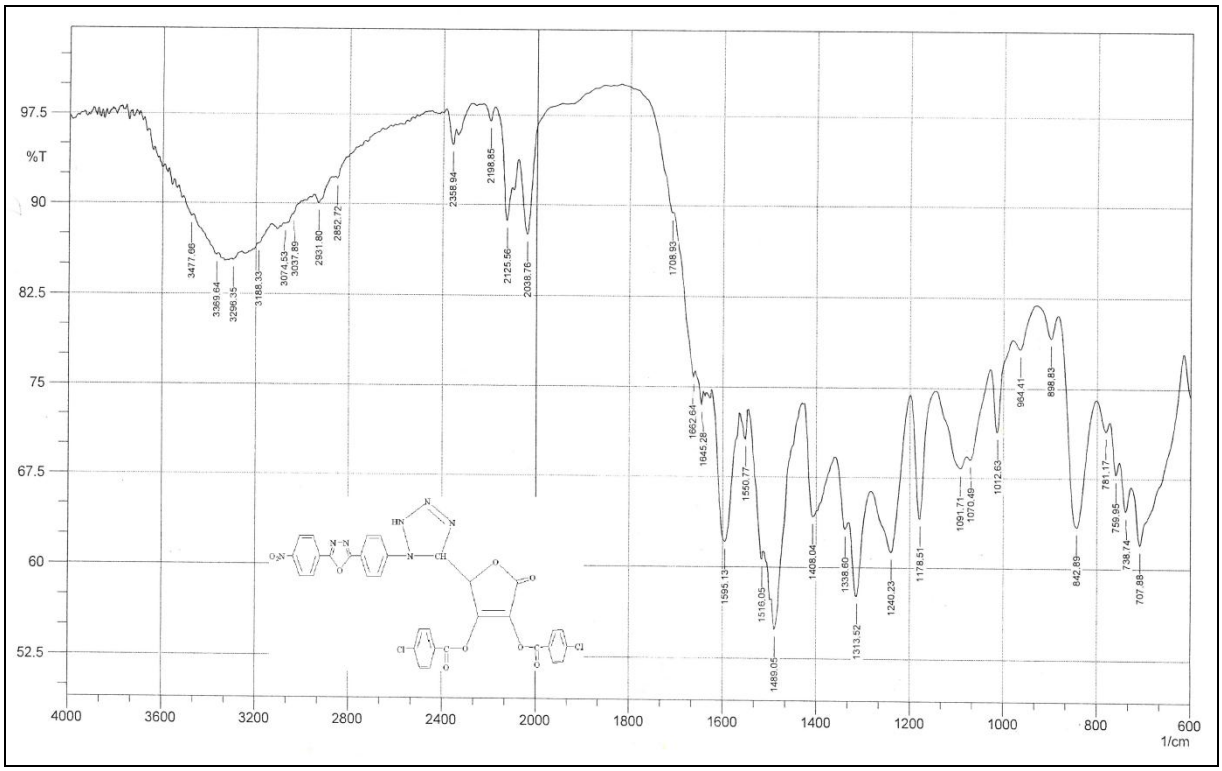


Fig. (3.32): FTIR spectrum of 2,5dihydrotetrazole (11e)

^{1}H-NMR spectrum of 2,5dihydrotetrazole (11e) (in DMSO-d_6), Fig. (3.33) indicated the singlet signal at δ(6.61) ppm for one proton of NH for 2,5dihydrotetrazole ring, and doublet doublet signals for aromatic protons appeared in the range δ(7.34-8.45) ppm. Also the spectrum showed two signals at δ(5.87) and δ(6) ppm for CH of 2,5dihydrotetrazole ring and lactone ring, respectively.

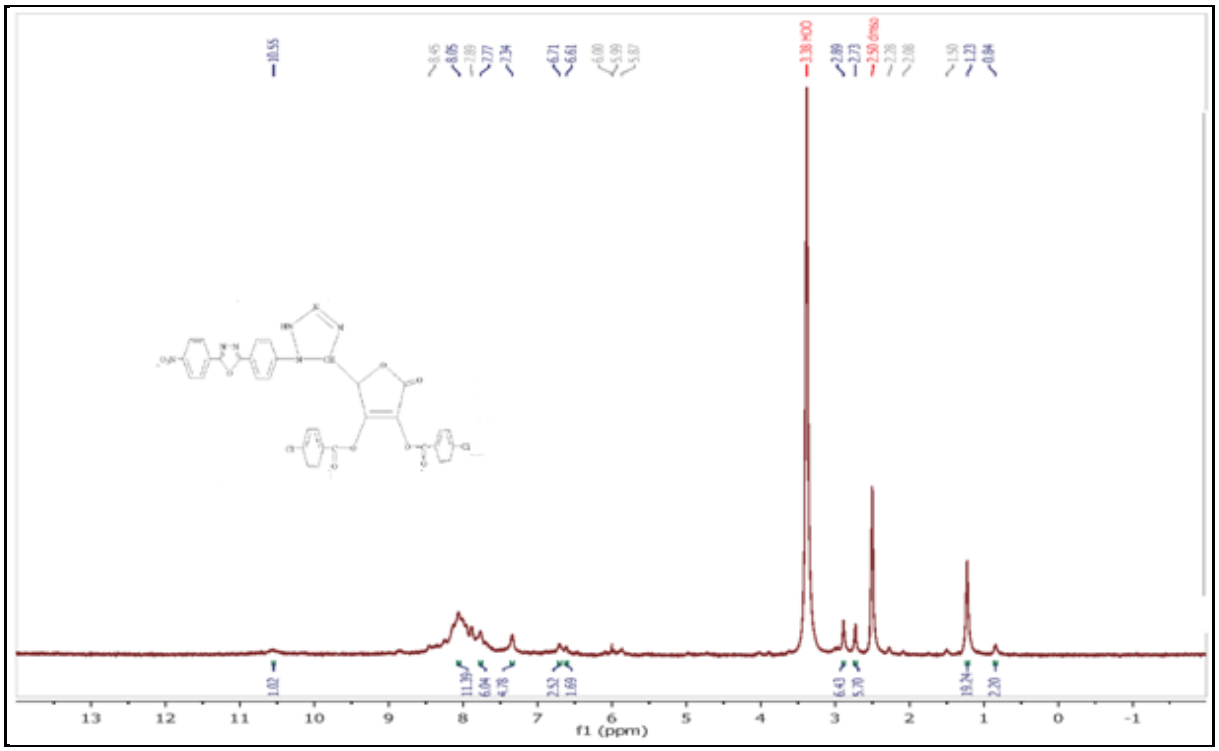
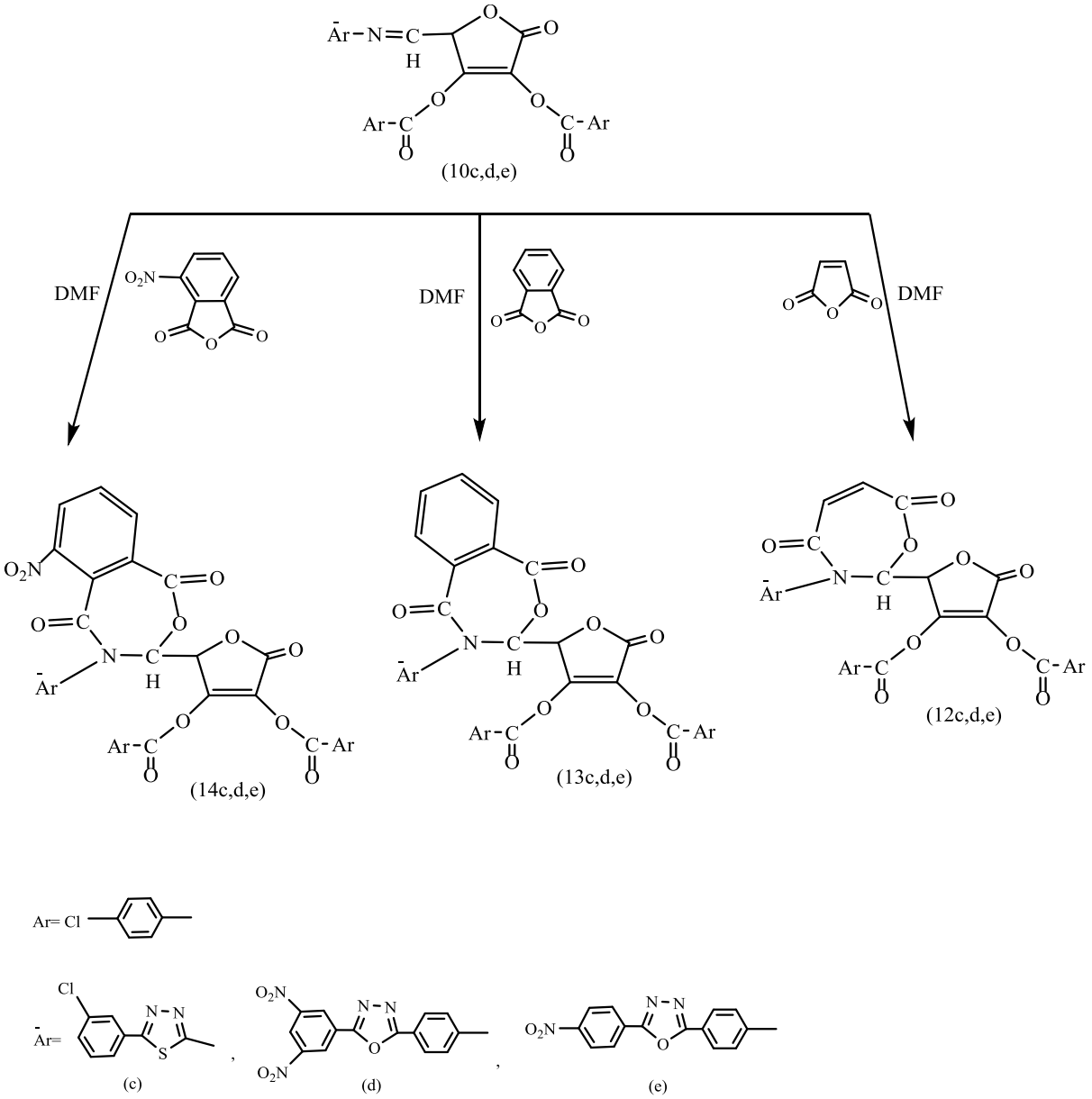


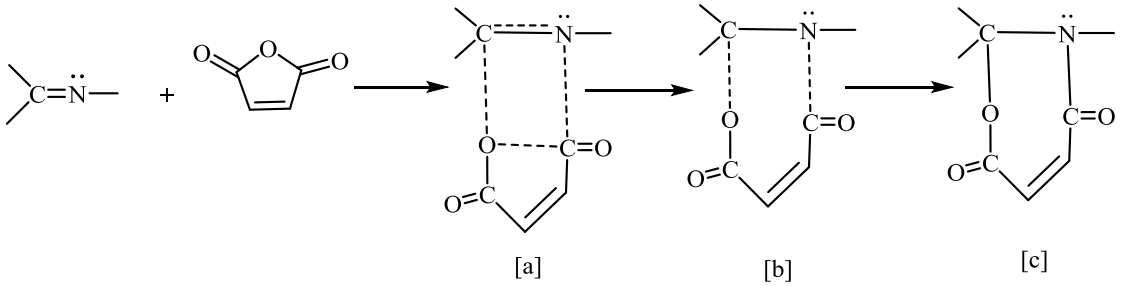
Fig. (3.33): ^{1}H-NMR spectrum of 2,5dihydrotetrazole (11e)

3.6 Synthesis and characterization of 1,3-oxazepine compounds (12-14)c,d,e

Oxazepine derivatives (12-14)c,d,e were synthesized from reaction of azomethines (10c, 10d or 10e) with different acid anhydrides such as (maleic, phthalic or 3-nitrophthalic) anhydride in DMF as a solvent.



The mechanism for this reaction outlined in Scheme (3.11). [198]



Scheme (3.11): The mechanism of formation of 1,3-oxazepine

The mechanism involved the addition of one σ-carbonyl to π-bond (N=C) to give 4-membered cyclic and 5-membered cyclic ring of anhydride in the same transition state [T.S.]a, which opens into (maleic, phthalic and 3-nitrophthalic) anhydride to award 7-membered cyclic ring 1,3-oxazepine [C]. The oxazepine compounds (12-14)c,d,e were detected by FTIR and ^{1}H-NMR spectroscopy for compounds (13)c,d,e. The FTIR spectra, Figs. (3.34) to (3.42) indicated evanescence of absorption band at (1645) cm^{-1} for (C=N) of Schiff bases (10)c,d and (1635) cm^{-1} for (10e). Table (3.2) were listed the absorption bands for lactone and lactam of 1,3-oxazepine compounds (12-14)c,d,e.

Table (3.2): The FTIR spectral data for lactone and lactam of 1,3-oxazepine compounds (12-14)c,d,e

Comp. no.	**ν(C=O) cm^{-1} lactone**	**ν(C=O) cm^{-1} lactam**
12c	1708	1693
13c	1708	1678
14c	1714	1645
12d	1716	1695
13d	1710	1693
14d	1732	1668
12e	1712	1664
13e	1710	1662
14e	1710	1662

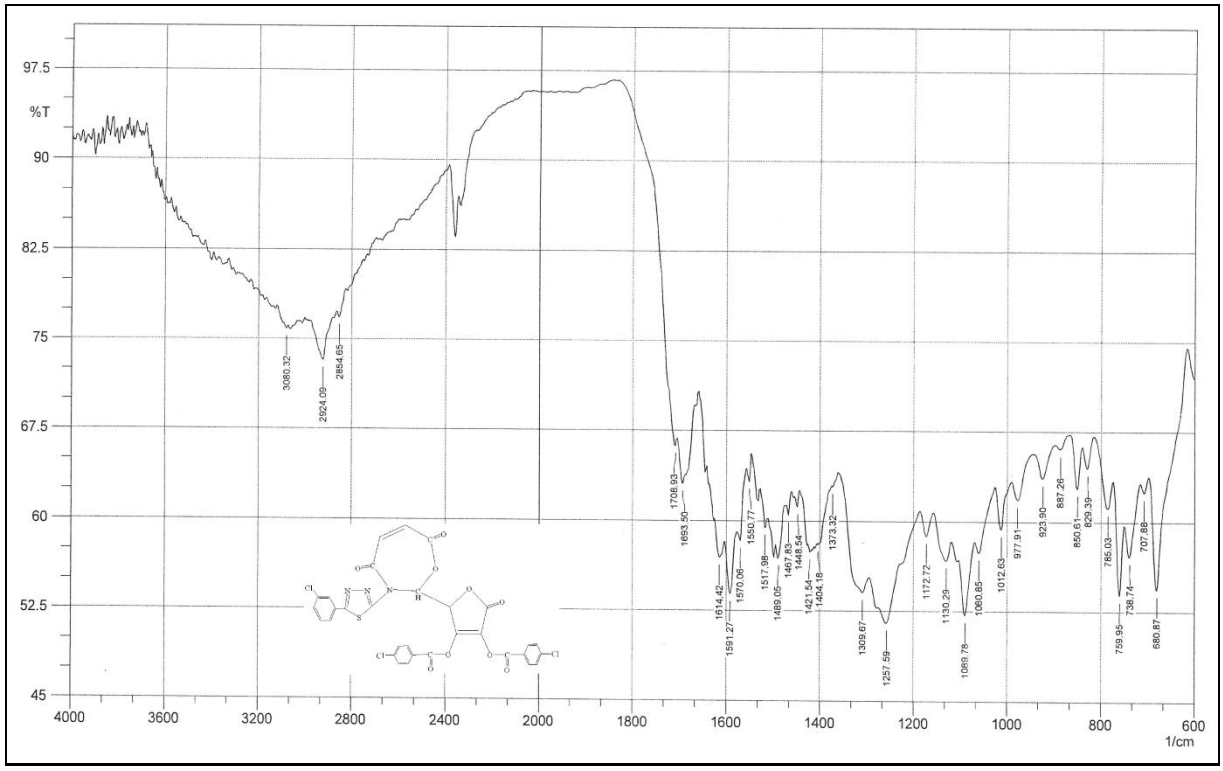


Fig. (3.34): FT-IR spectrum of oxazepine (12c)

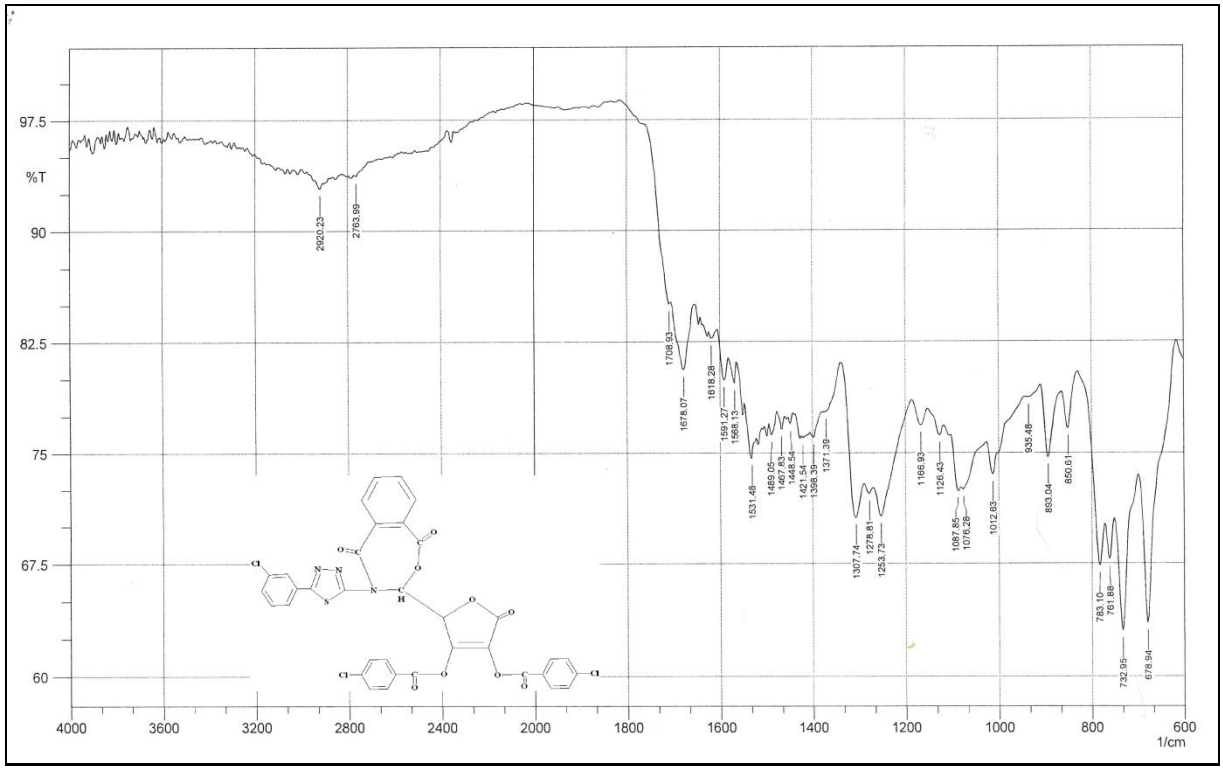


Fig. (3.35): FTIR spectrum of oxazepine (13c)

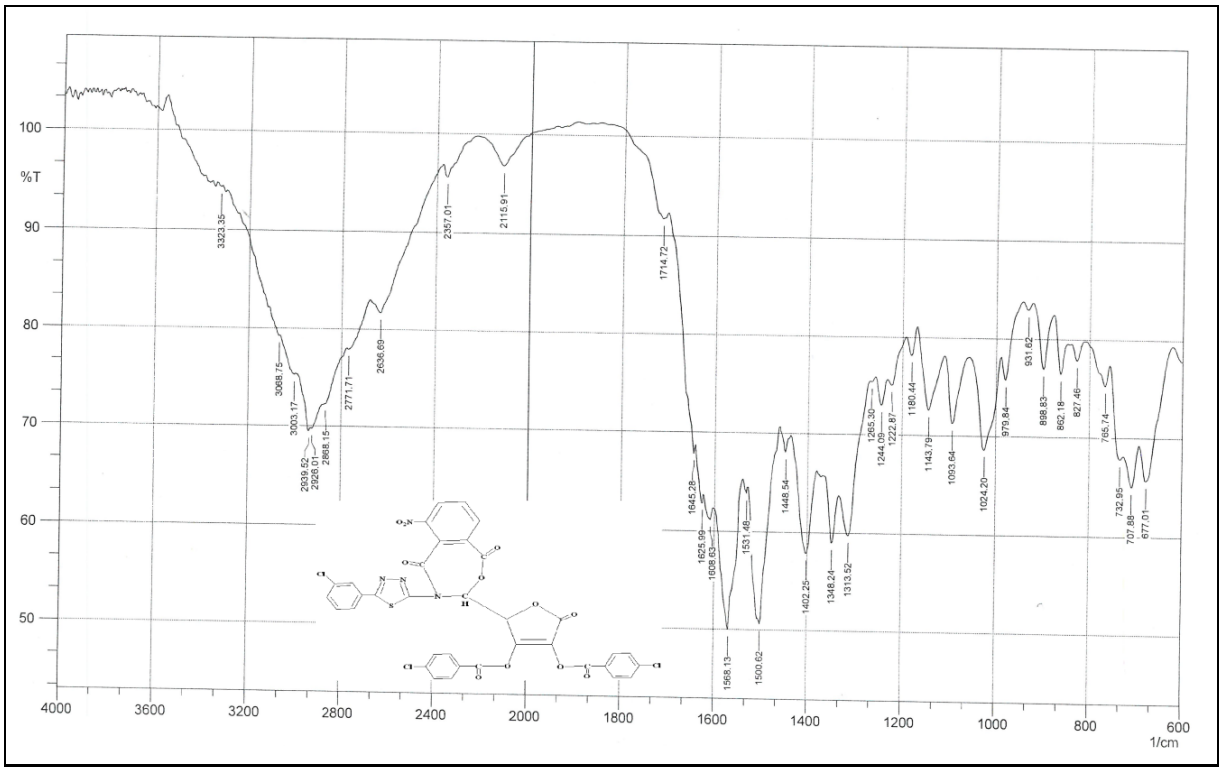


Fig. (3.36): FT-IR spectrum of oxazepine (14c)

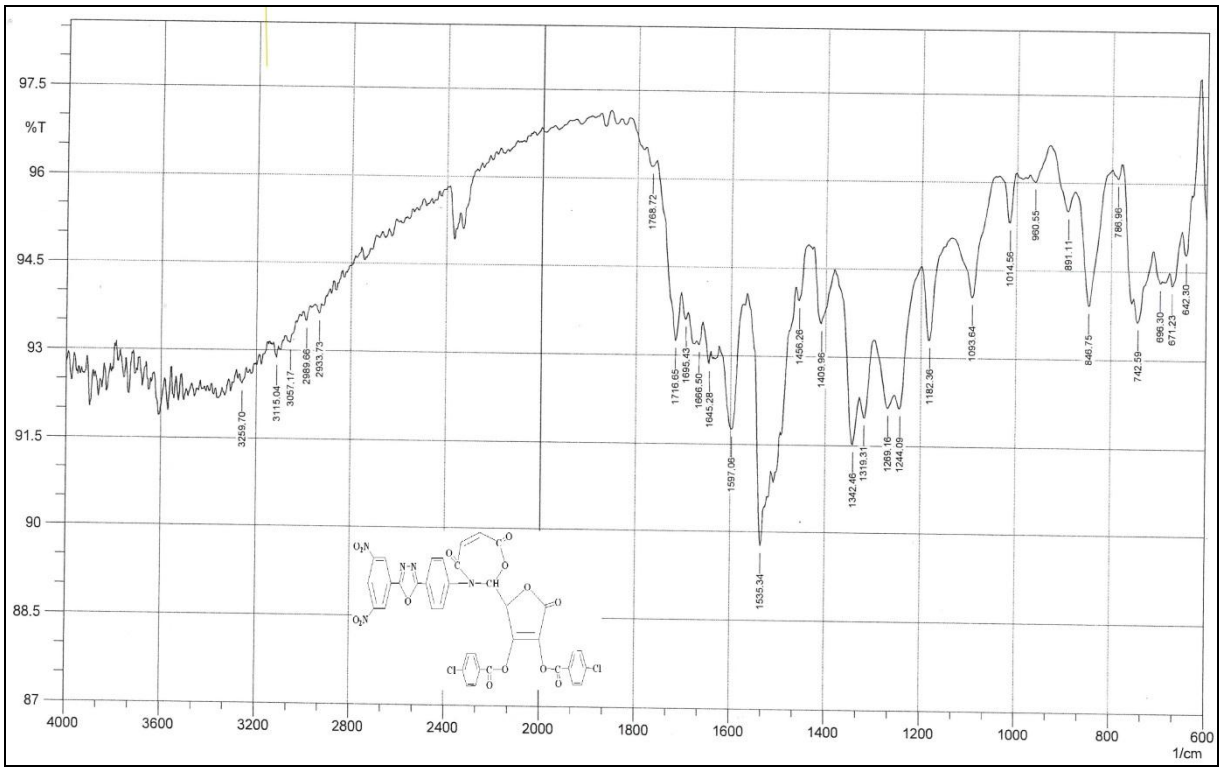


Fig. (3.37): FTIR spectrum of oxazepine (12d)

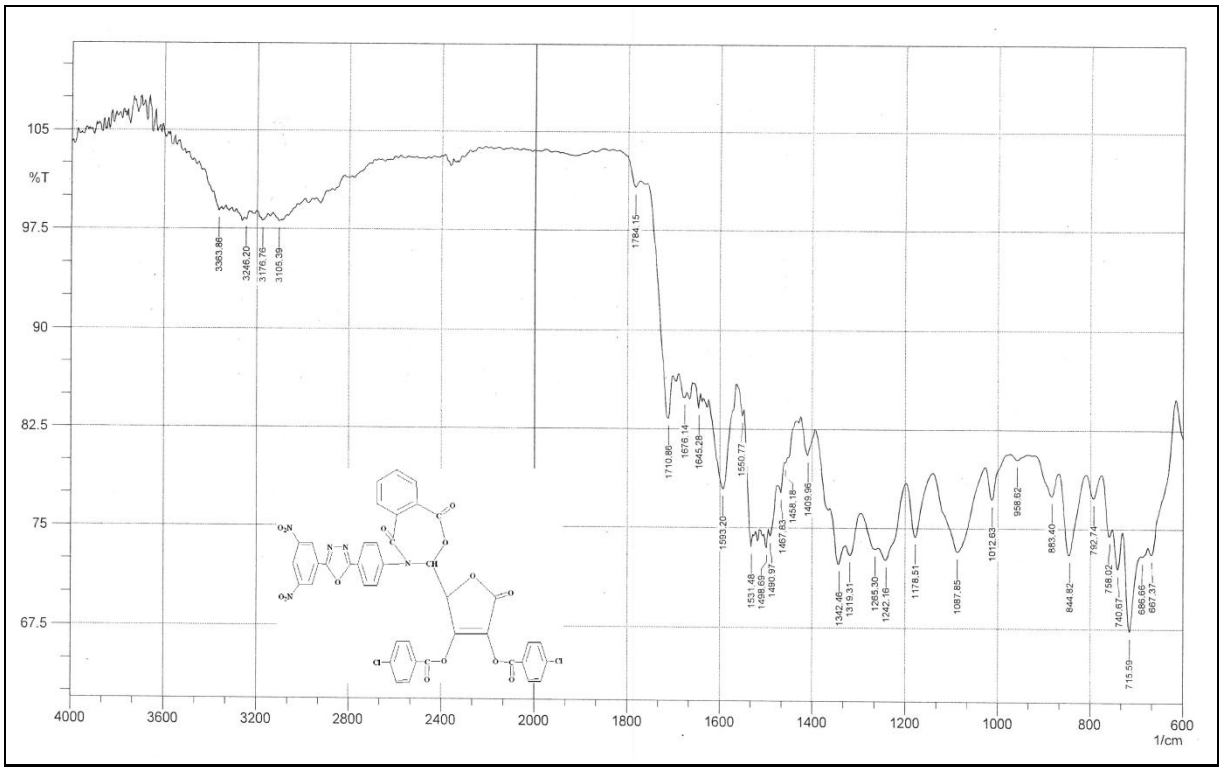


Fig. (3.38): FT-IR spectrum of oxazepine (13d)

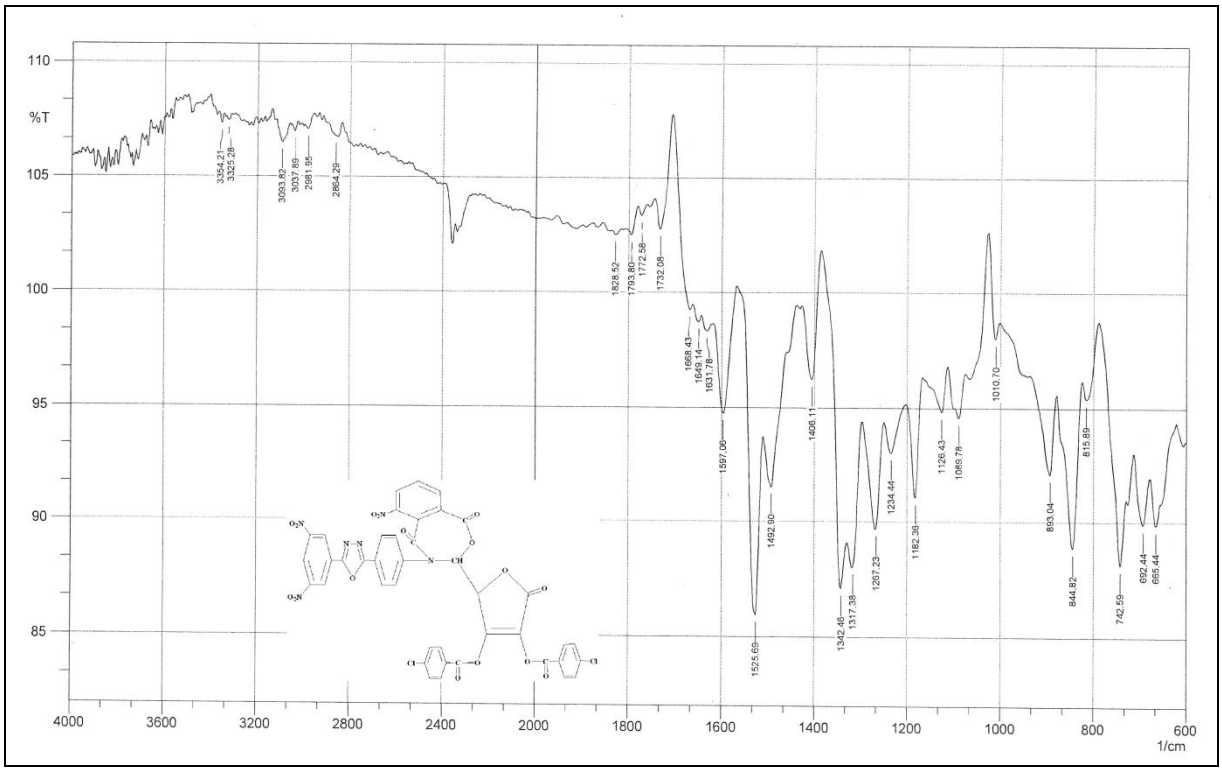


Fig. (3.39): FT-IR spectrum of oxazepine (14d)

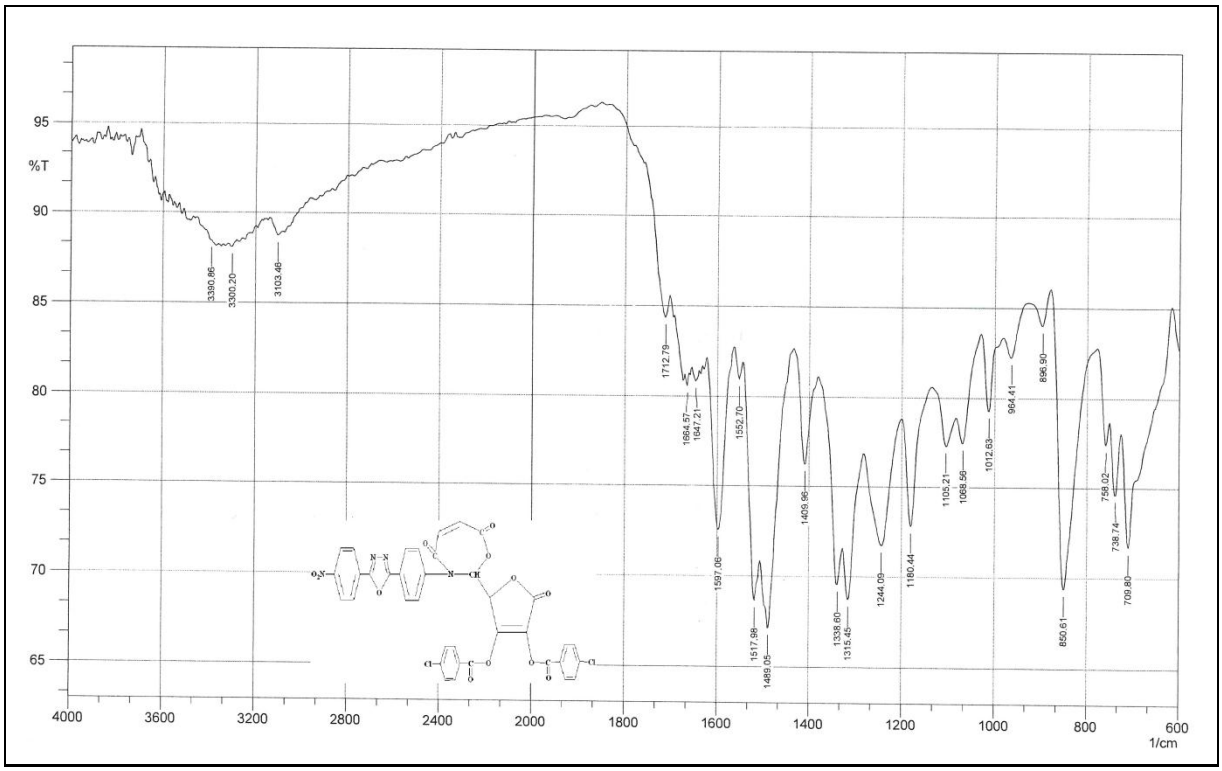


Fig. (3.40): FTIR spectrum of oxazepine (12e)

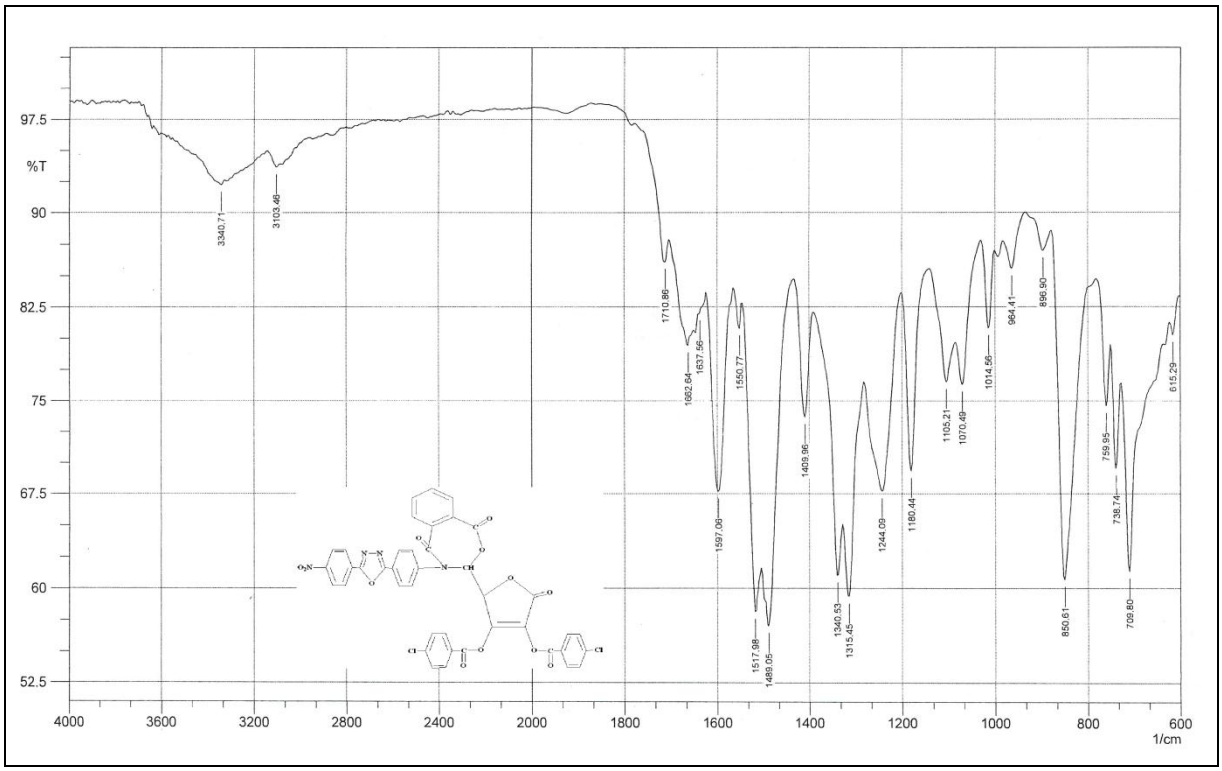


Fig. (3.41): FT-IR spectrum of oxazepine (13e)

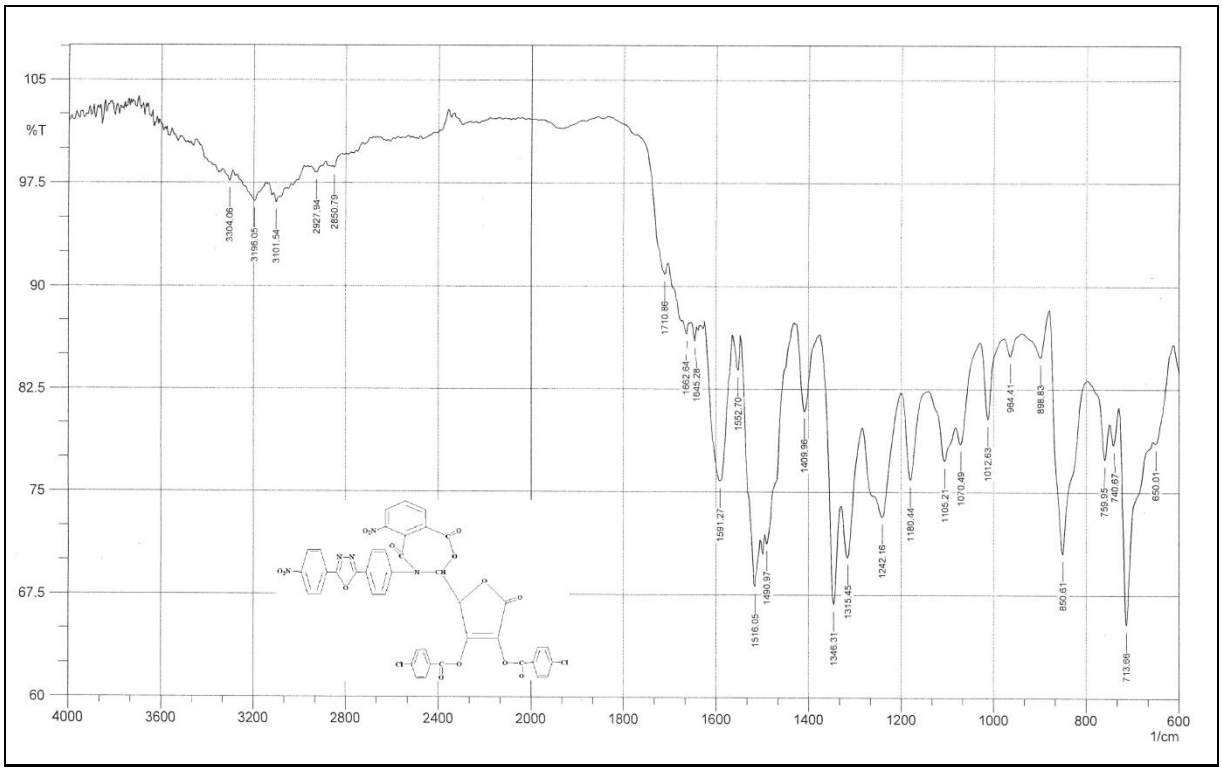


Fig. (3.42): FTIR spectrum of oxazepine (14e)

The ^{1}H-NMR spectrum (in DMSO-d_6 as a solvent) for oxazepine (13c), Fig. (3.43) indicated the following signals: signal at δ(3.90 ppm) for one proton of lactone ring, signal at δ(4.03 ppm) for proton of oxazepine ring and multiplet signals at δ(7.50-8.16) ppm for aromatic protons.

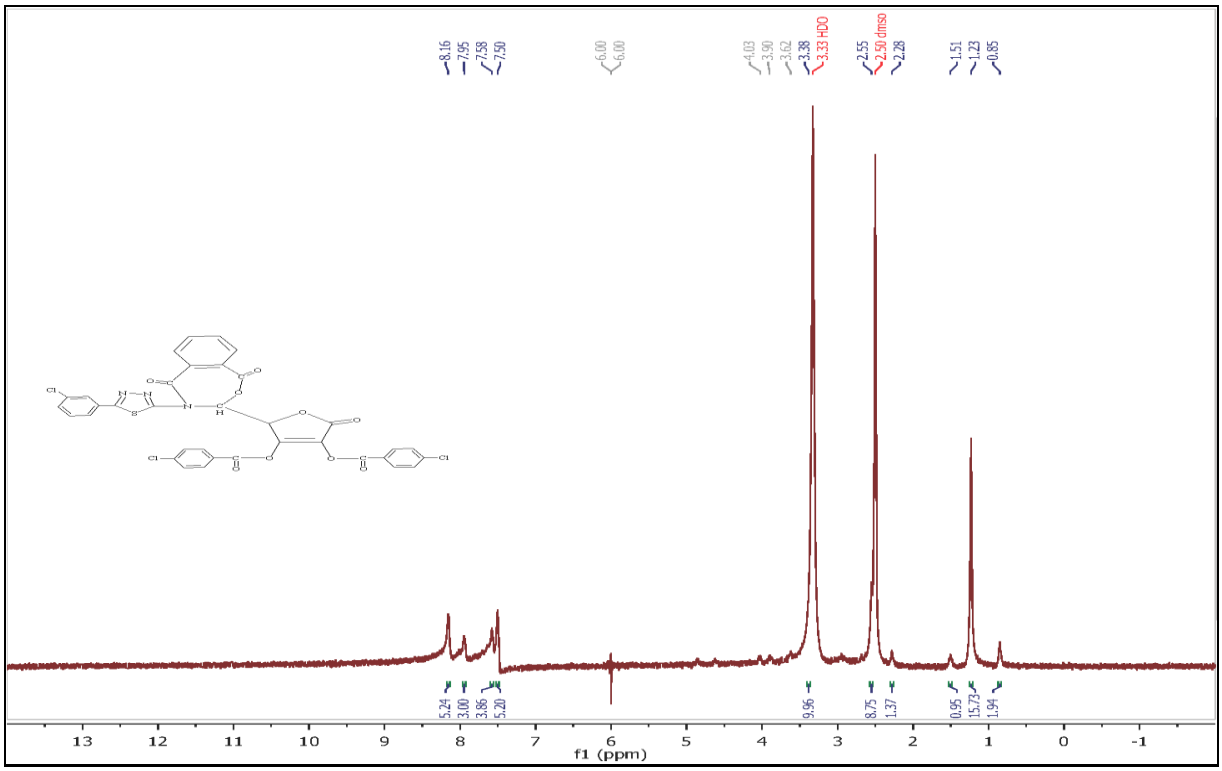


Fig. (3.43): ^{1}H-NMR spectrum of oxazepine (13c)

The ^{1}H-NMR spectrum (in DMSO-d_6 as a solvent) for oxazepine (13d), Fig. (3.44) exhibited the following signals: signal at δ(3.37 ppm) for one proton of lactone ring, signal at δ(3.50 ppm) for proton of oxazepine ring and multiplet signals at δ(7.50-8.20) ppm for aromatic protons.

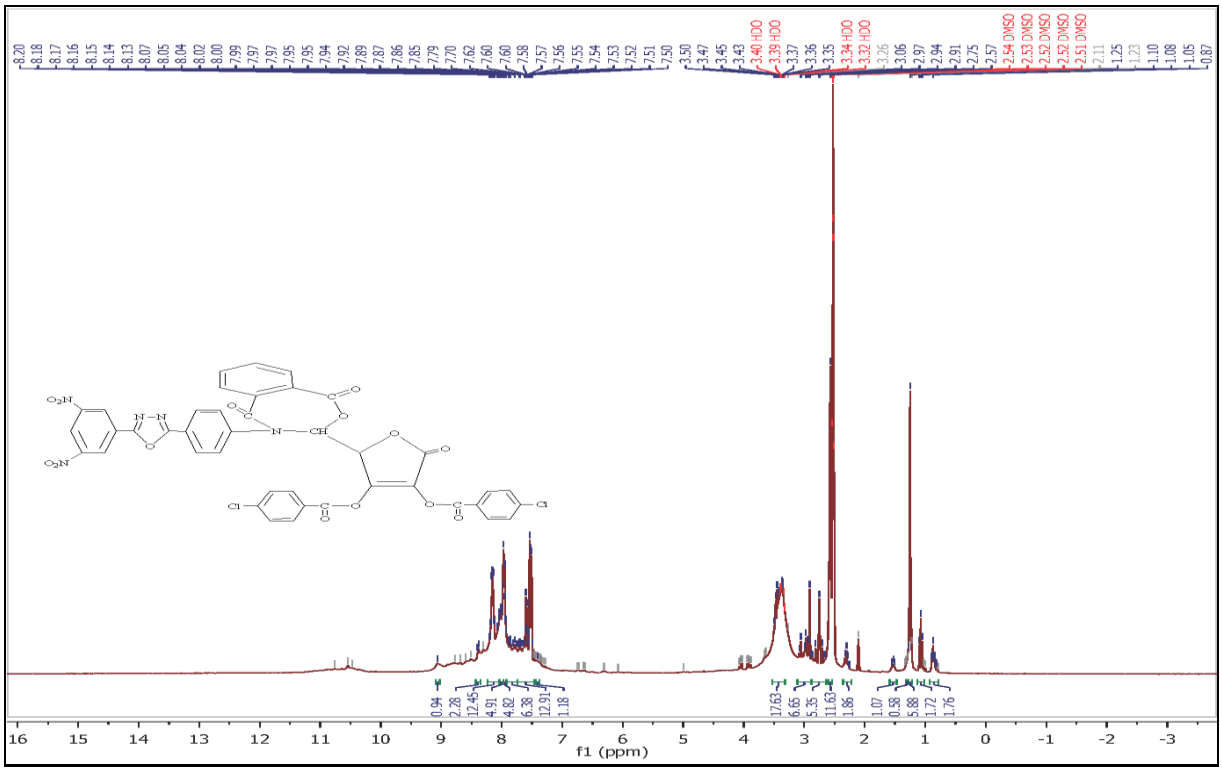


Fig. (3.44): ^{1}H-NMR spectrum of oxazepine (13d)

The ^{1}H-NMR spectrum (in DMSO-d_6 as a solvent) for oxazepine (13e), Fig. (3.45) demonstrated the following signals: signal at δ(3.90 ppm) for one proton of lactone ring, signal at δ(4.02 ppm) for proton of oxazepine ring and multiplet signals at δ(7.13-8.81) ppm for aromatic protons.

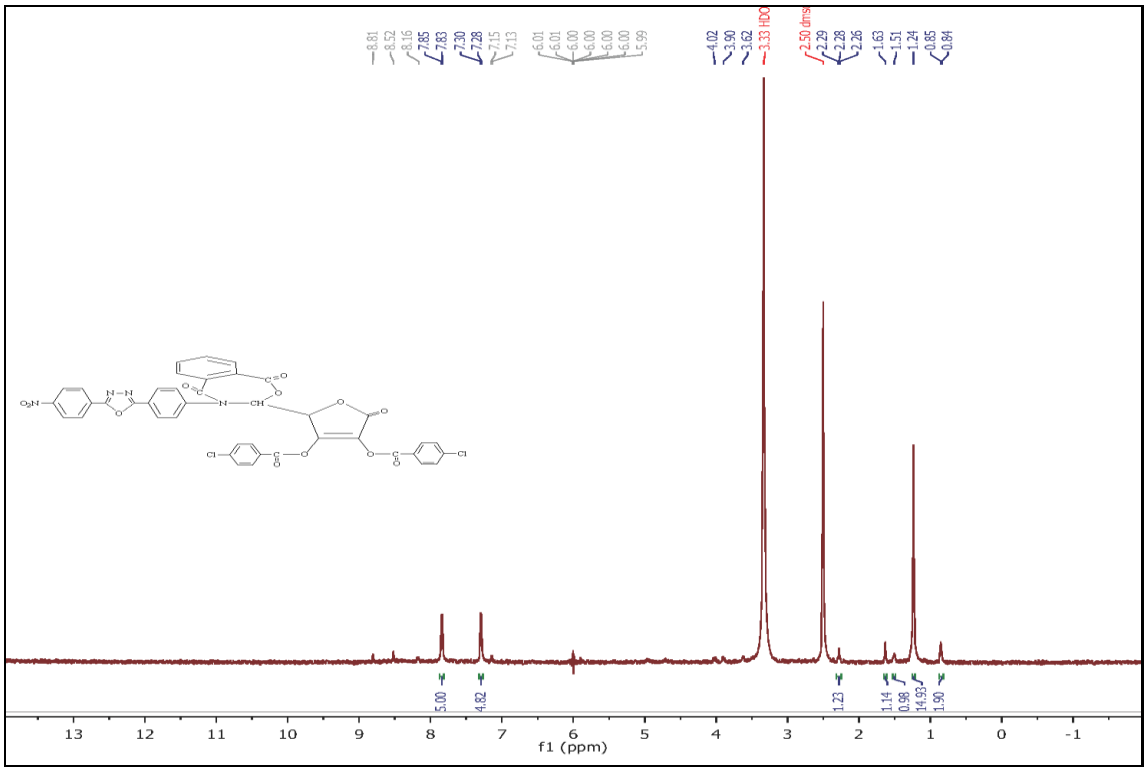
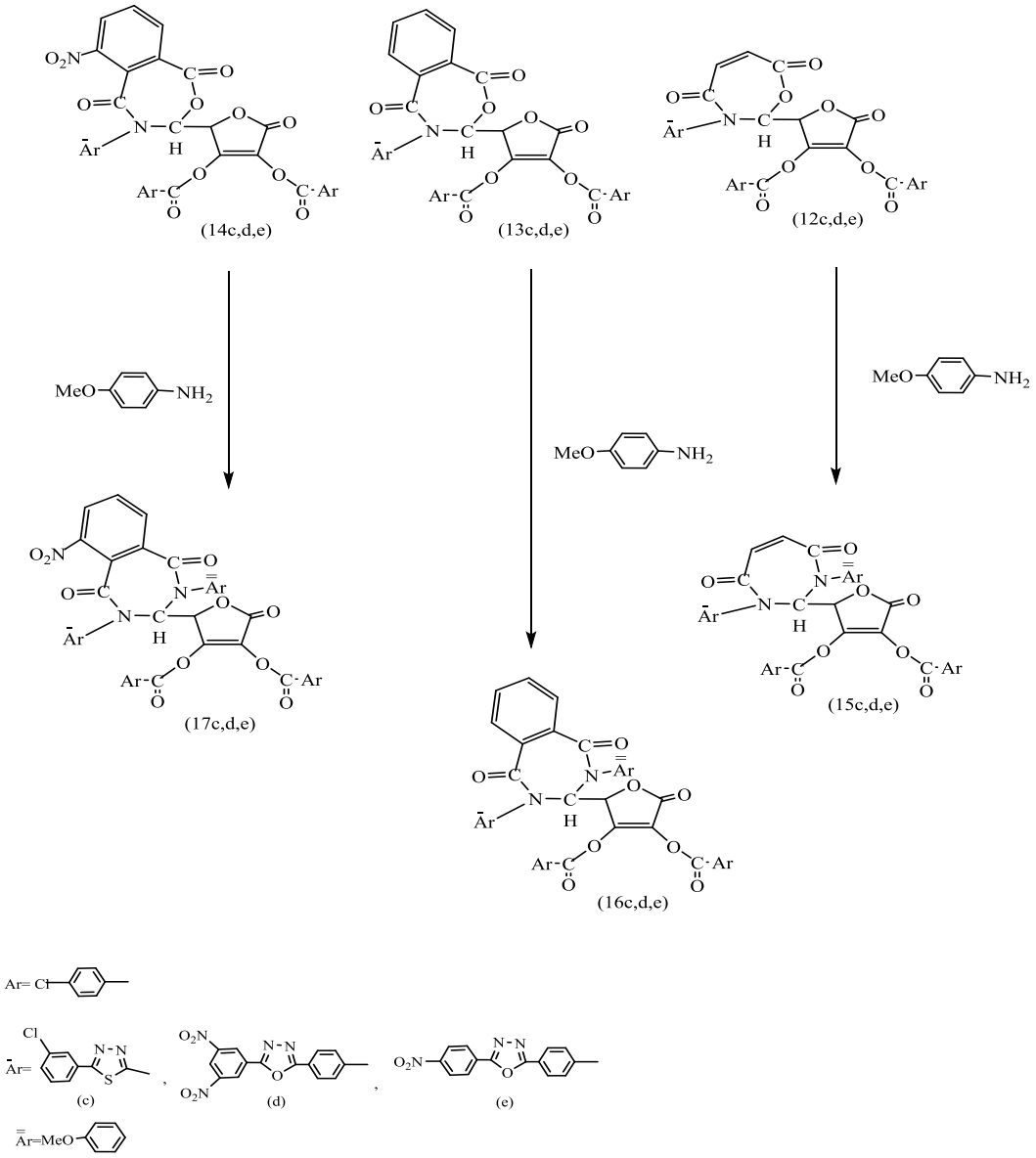


Fig. (3.45): The ^{1}HNMR spectrum of oxazepine (13e)

3.7 Synthesis and characterization of 1,3-diazepine compounds (15-17)c,d,e

Diazepine derivatives (15-17)c,d,e were obtained from each one of compounds (12c-14e) that were reacted with 4-methoxyaniline in presence of DMF as a solvent.



The structures of the new synthesized compounds (15-17)c,d,e have been confirmed by FTIR, ^{1}H-NMR for compounds (16)c,d,e and ^{13}C-NMR for compound (16)d. The FTIR spectra, of compounds Figs. (3.46) to (3.54) showed the disappearance of characteristic bands at (1708-1732) cm^{-1} and at (1645-1695) cm^{-1} related to stretching vibration bands for lactone and lactam groups for oxazepine compounds and appearance of new absorption peaks belong to diazepine compounds at (1705) cm^{-1} of compound (16c), (1708) cm^{-1} of compounds (15)c,d,e, (17e) and (1710) cm^{-1} of compounds (17c), (16, 17)d and (16e).

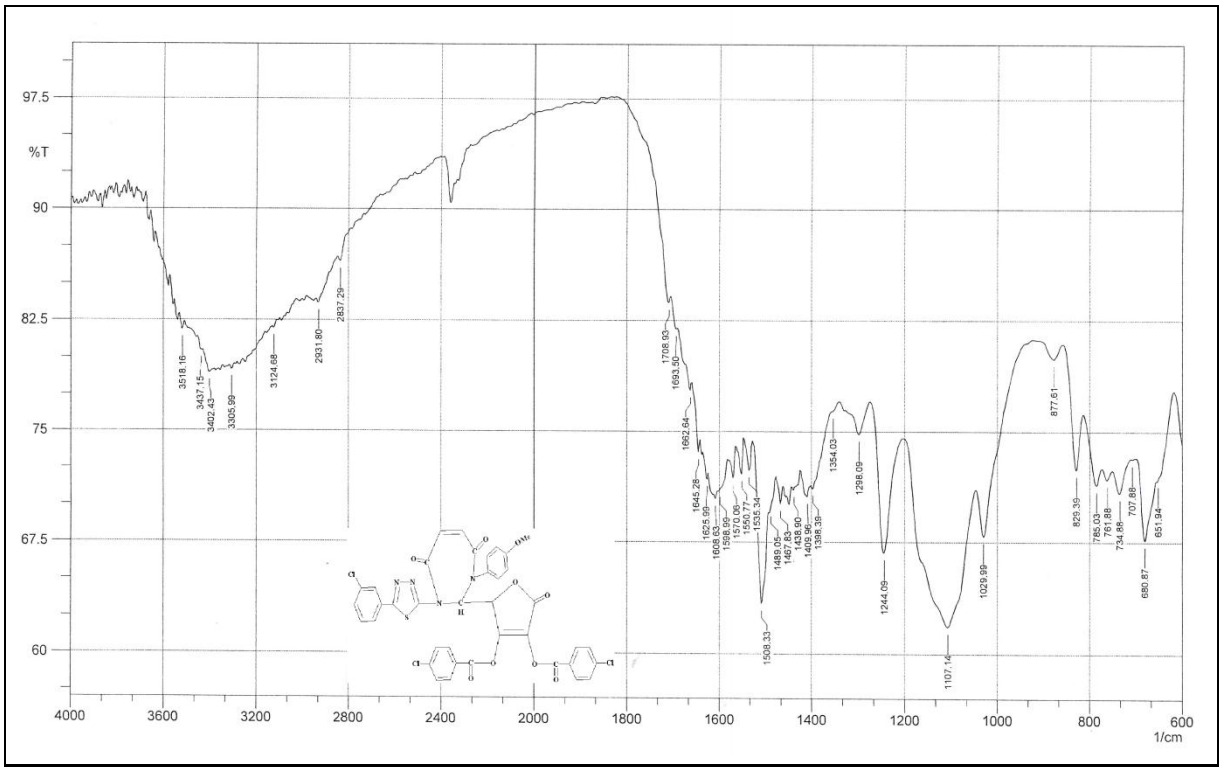


Fig. (3.46): FTIR spectrum of diazepine (15c)

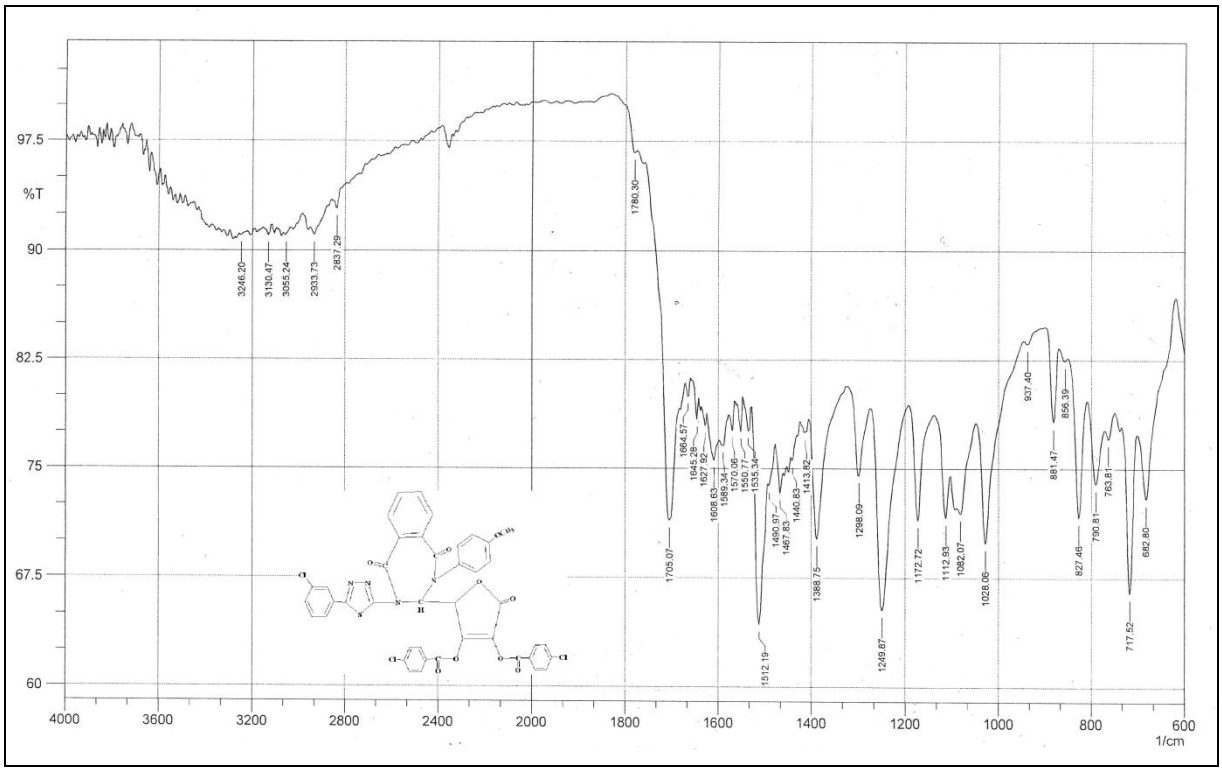


Fig. (3.47): FTIR spectrum of diazepine (16c)

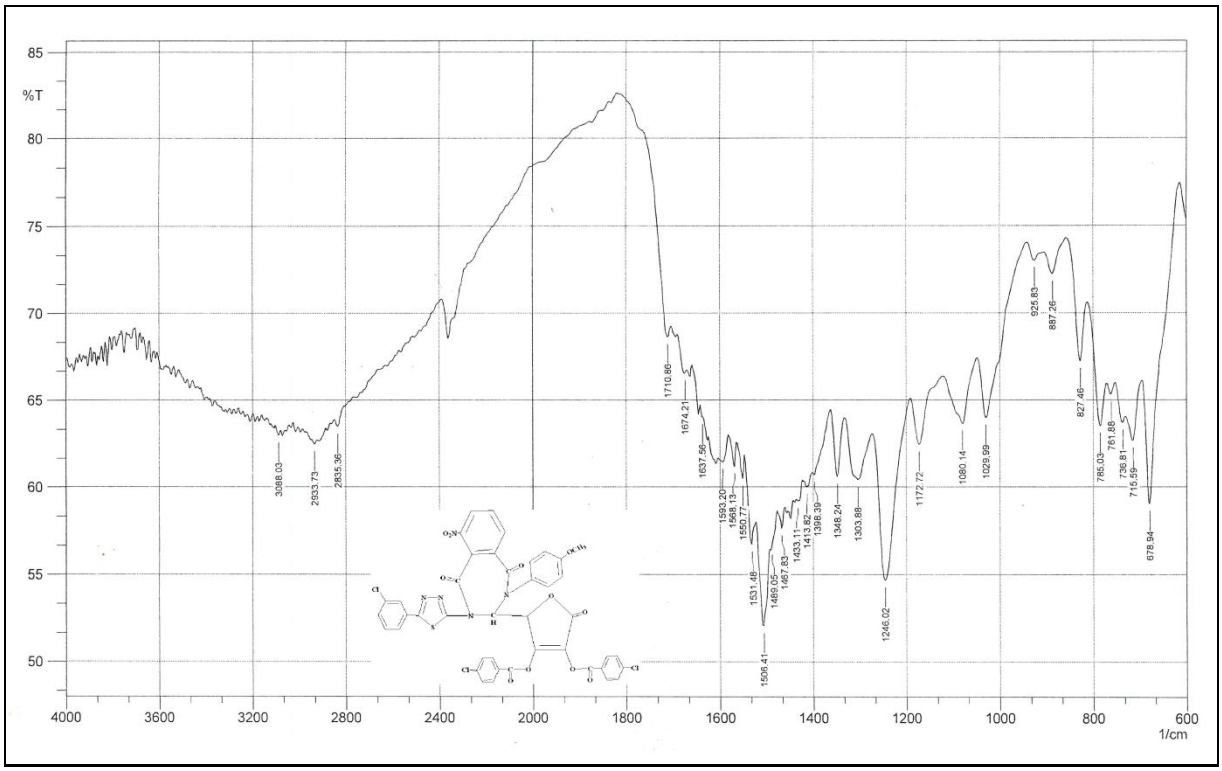


Fig. (3.48): FTIR spectrum of diazepine (17c)

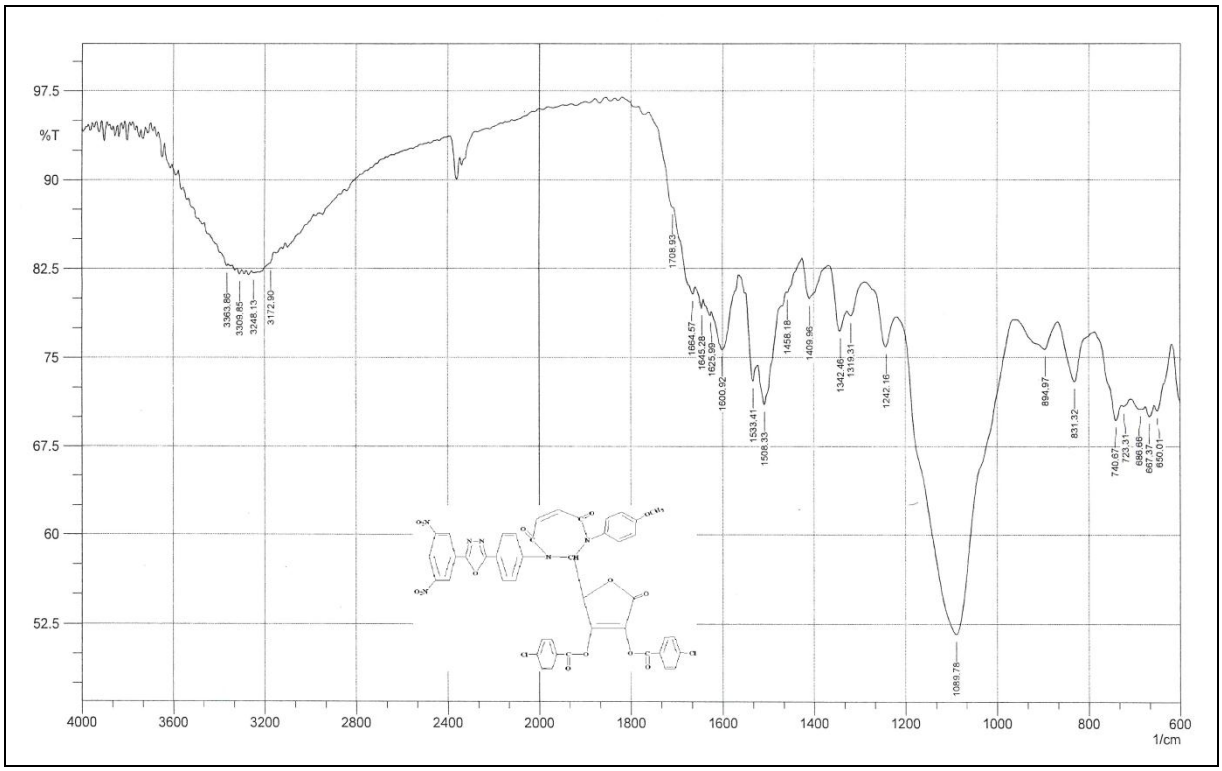


Fig. (3.49): FTIR spectrum of diazepine (15d)

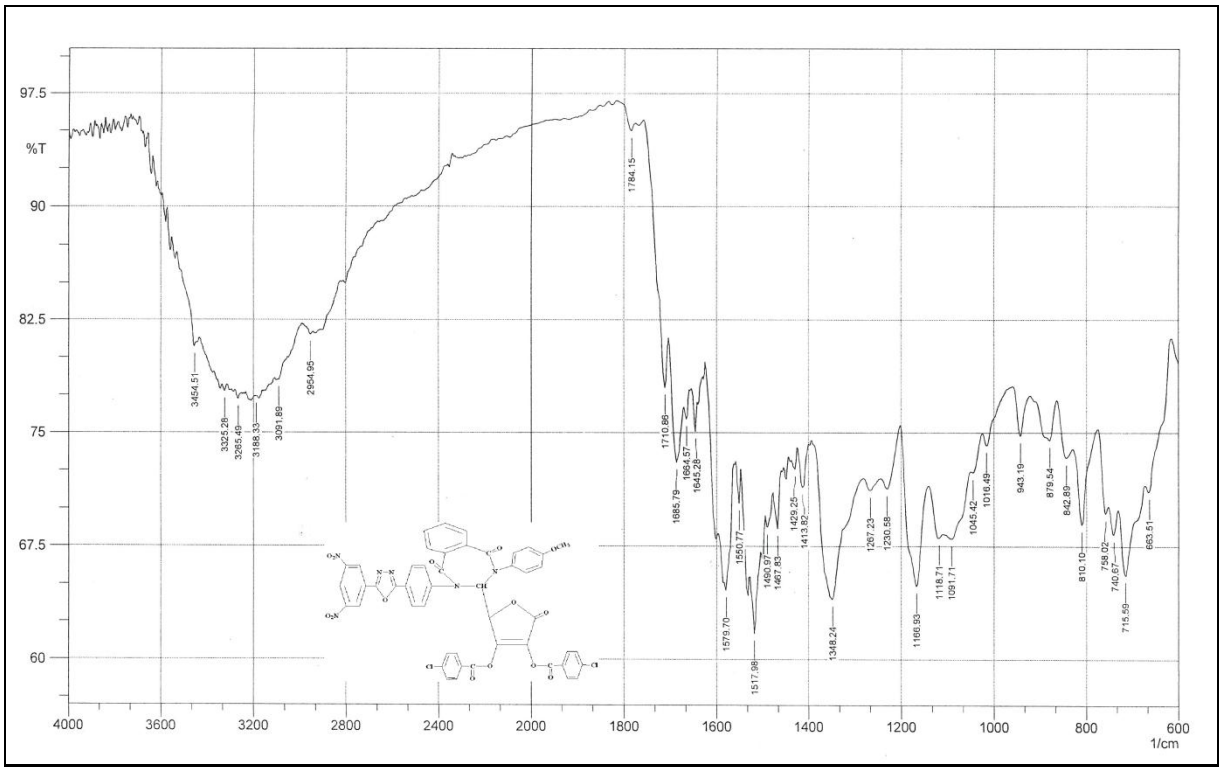


Fig. (3.50): FTIR spectrum of diazepine (16d)

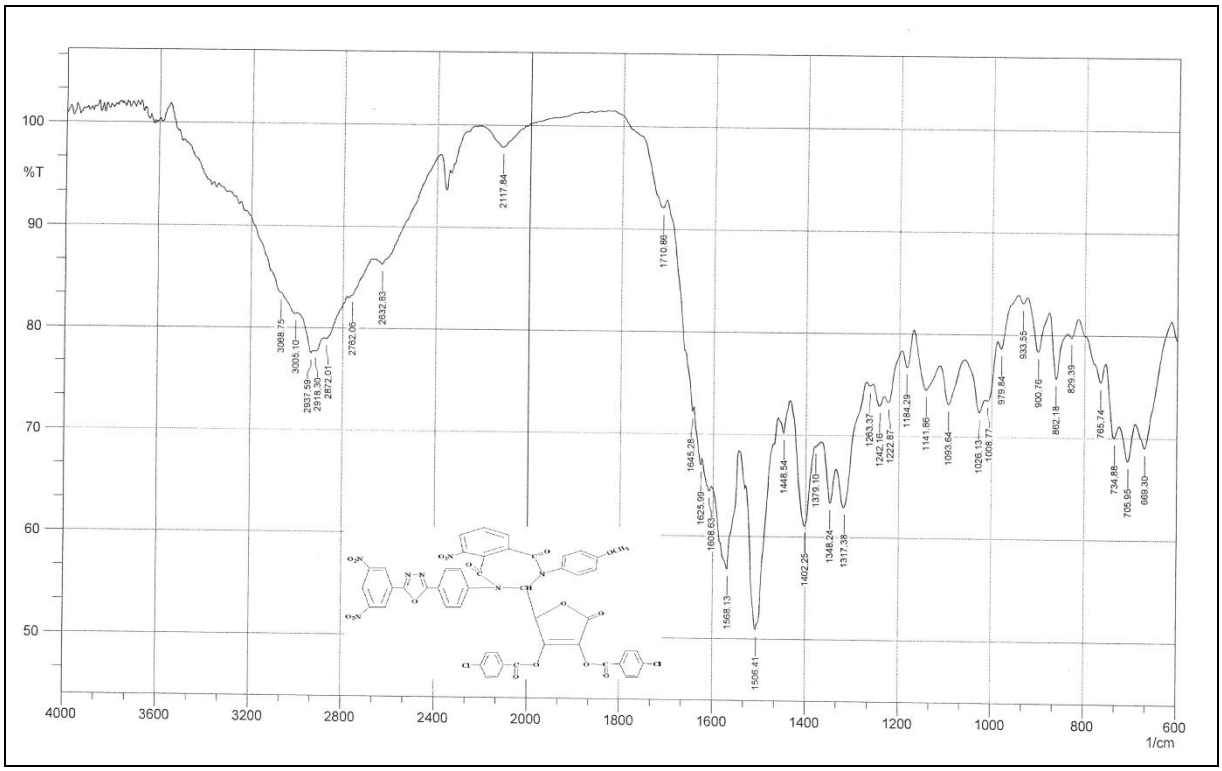


Fig. (3.51): FTIR spectrum of diazepine (17d)

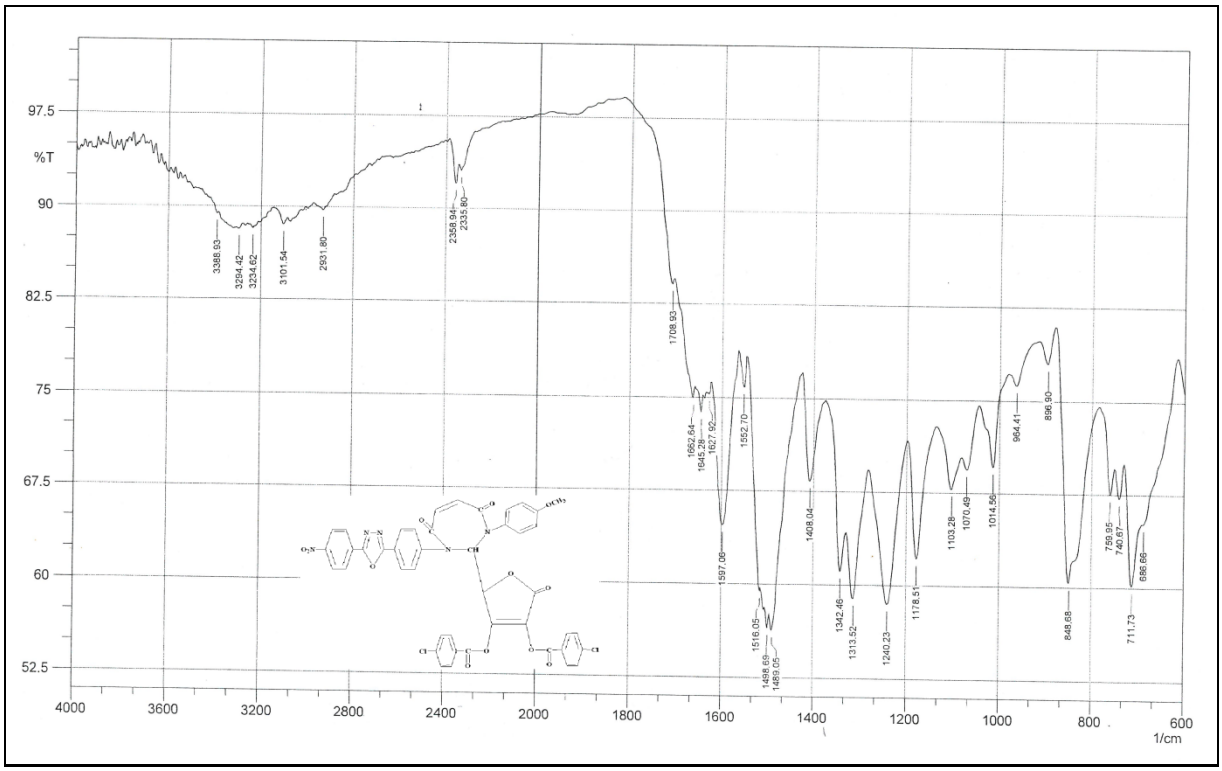


Fig. (3.52): FTIR spectrum of diazepine (15e)

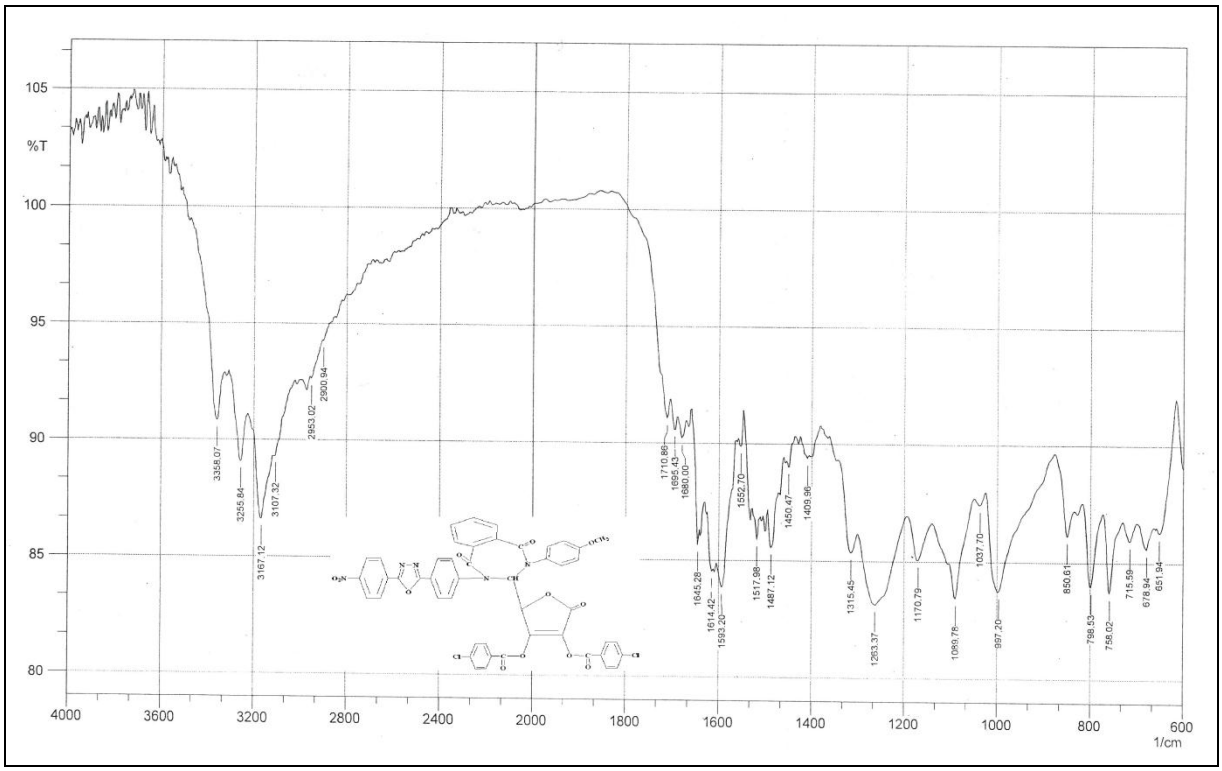


Fig. (3.53): FTIR spectrum of diazepine (16e)

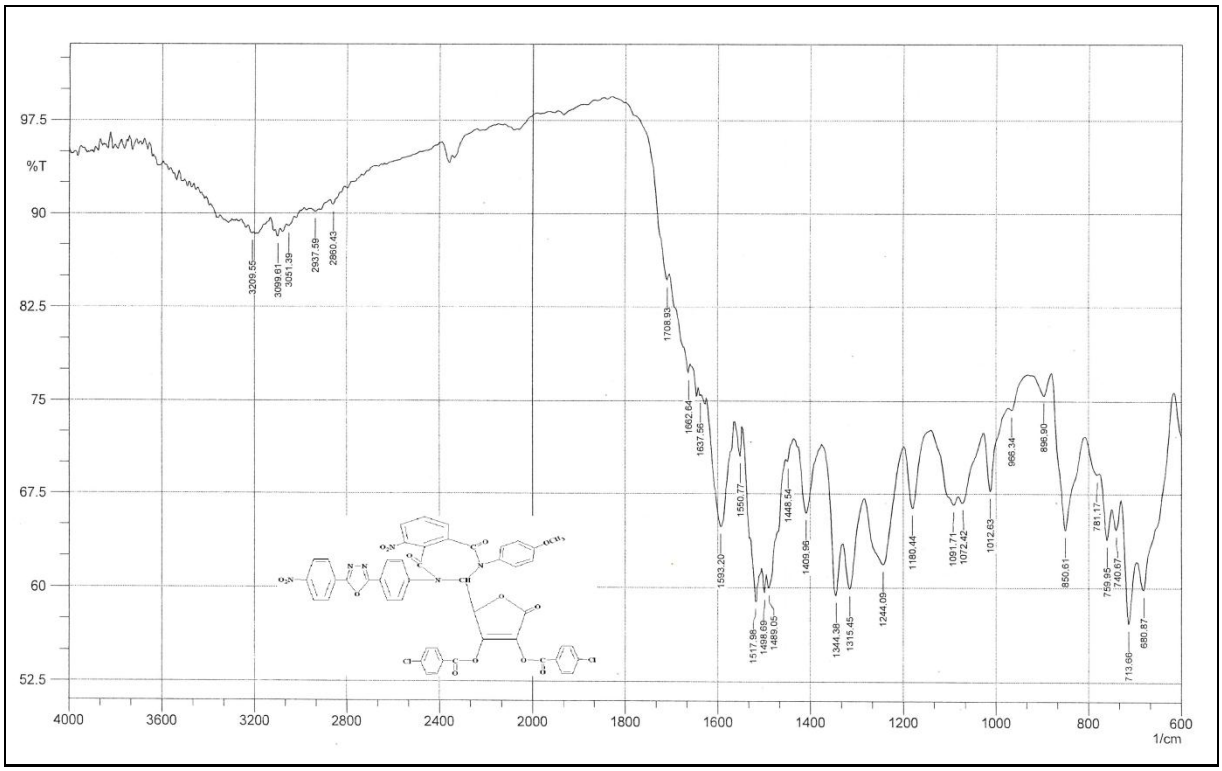


Fig. (3.54): FTIR spectrum of diazepine (17e)

Furthermore, ^{1}H-NMR spectrum of diazepine (16c) (in DMSO-d_6 as a solvent), Fig. (3.55) demonstrated the following signals: singlet signal at δ(3.61) ppm for (OCH_3), signal at δ(4.60 ppm) for one proton of lactone ring, signal at δ(4.84) ppm for proton of diazepine ring and multiplet signals at δ(6.87-8.18) ppm for aromatic protons.

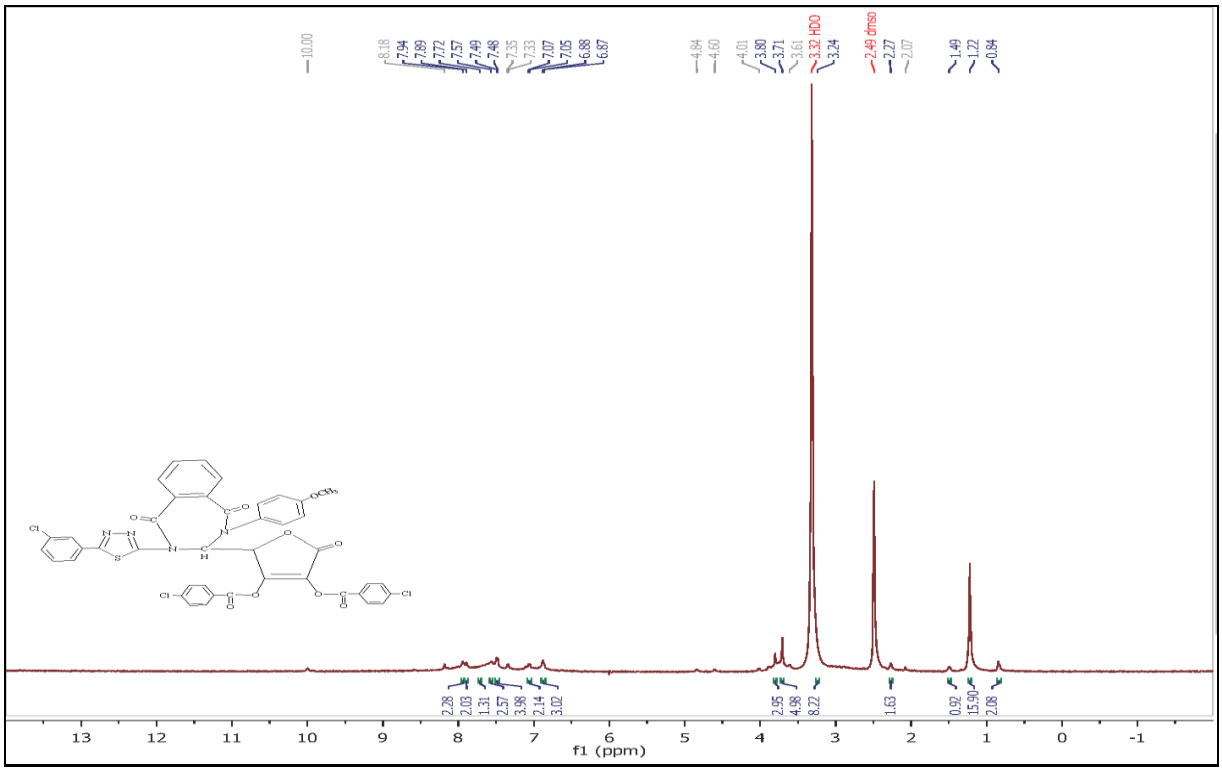


Fig. (3.55): ^{1}H-NMR spectrum of diazepine (16c)

The ^{1}H-NMR spectrum (in DMSO-d_6 as a solvent) of compound (16d), Fig. (3.56), exhibited the following signals: singlet signal at δ(3.63) ppm for (OCH_3), signal at δ(3.77 ppm) for one proton of lactone ring, signal at δ(3.83) ppm for proton of diazepine ring and multiplet signals at δ(6.51-9.05) ppm for aromatic protons.

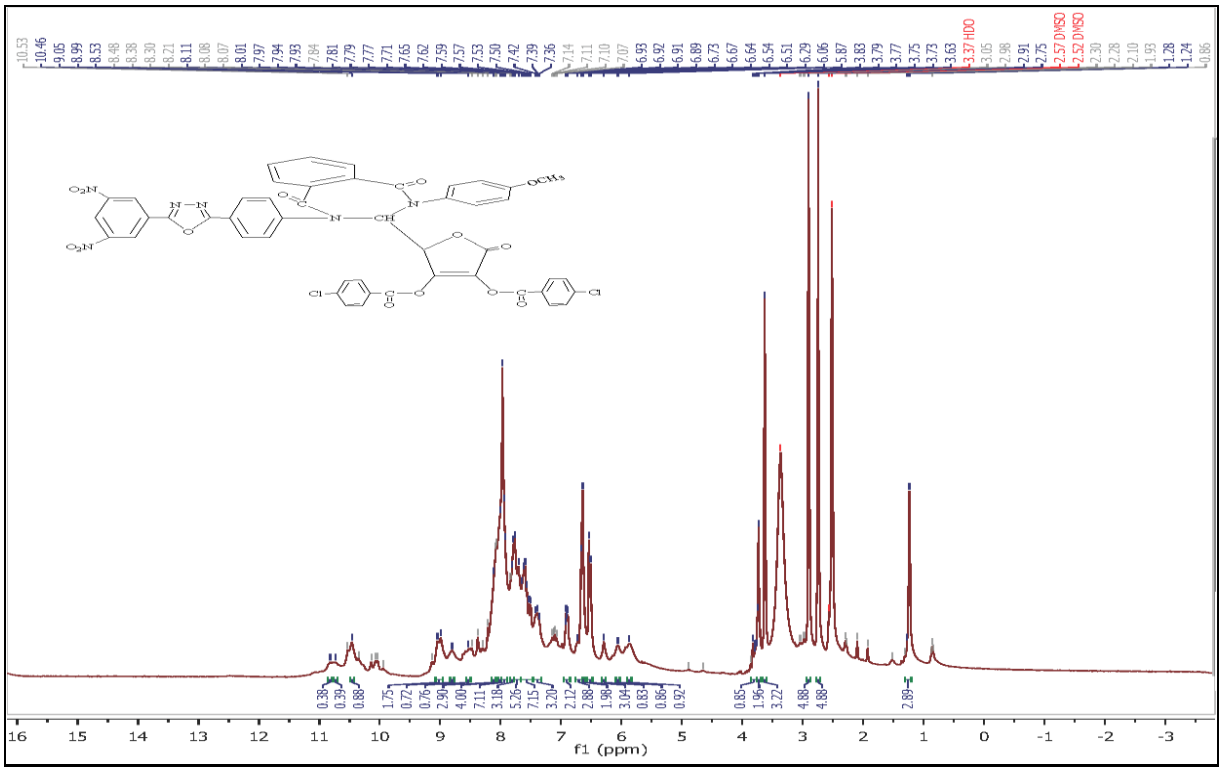


Fig. (3.56): ^{1}H-NMR spectrum of diazepine (16d)

The ^{13}C-NMR spectrum (in DMSO-d_6 as a solvent) of diazepine (16d), Fig. (3.57) demonstrated the following signals: signal at δ(36.26) ppm for (O-CH_3), signals at δ(39.16-40.82) ppm for solvent (DMSO) and C-5 of lactone ring, signal at δ(55.74) ppm for (C-4), signal at δ(99.98) ppm for (C-2), signals at δ(113.04-130.06) ppm for aromatic carbons, signal at δ(131.61) ppm for C-3, signal at δ(151.14) ppm for (C=O) of ester and signal at δ(162.77) ppm for (C=O) of lactam, lactone and (C=N) of oxadiazole ring.

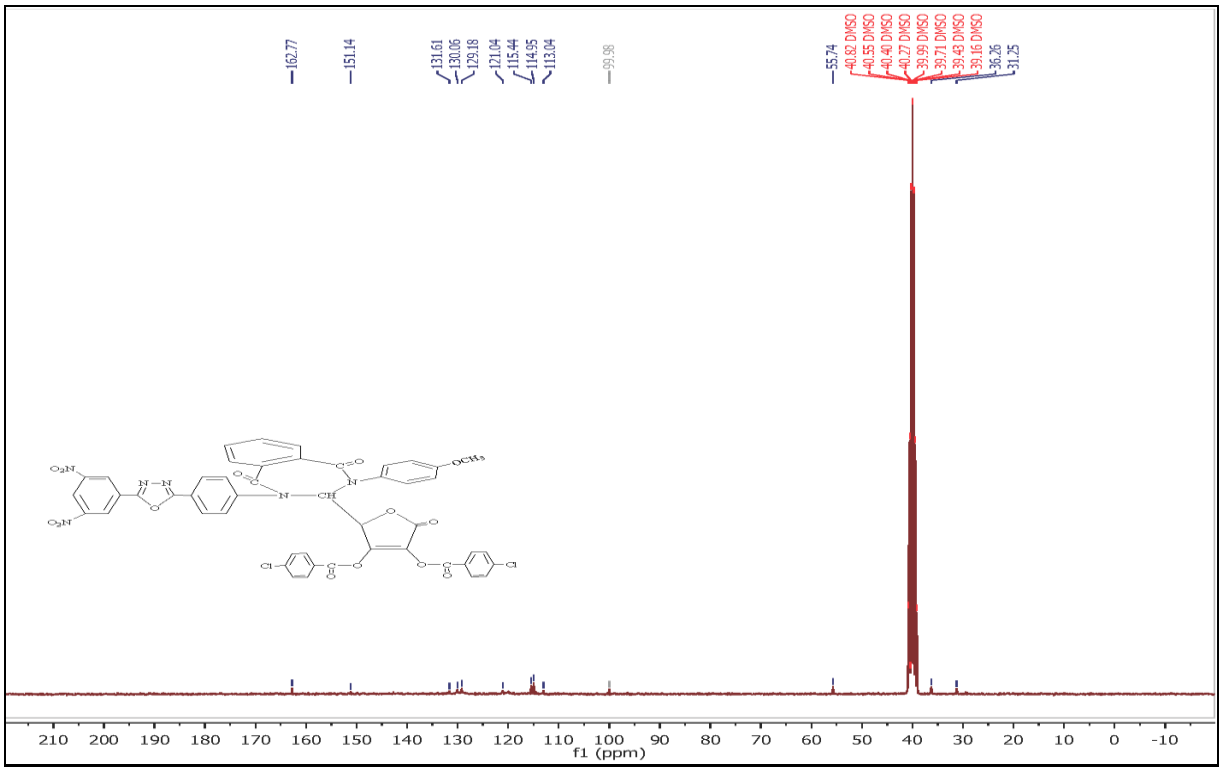


Fig. (3.57): ^{13}C-NMR spectrum of diazepine (16d)

The ^{1}H-NMR spectrum (in DMSO-d_6 as a solvent) of diazepine (16e), Fig. (3.58) demonstrated the following signals: singlet signal at δ(3.67) ppm for (OCH_3), signal at δ(3.71 ppm) for one proton of lactone ring, signal at δ(3.80 ppm) for proton of diazepine ring and multiplet signals at δ(6.50-8.45) ppm for aromatic protons.

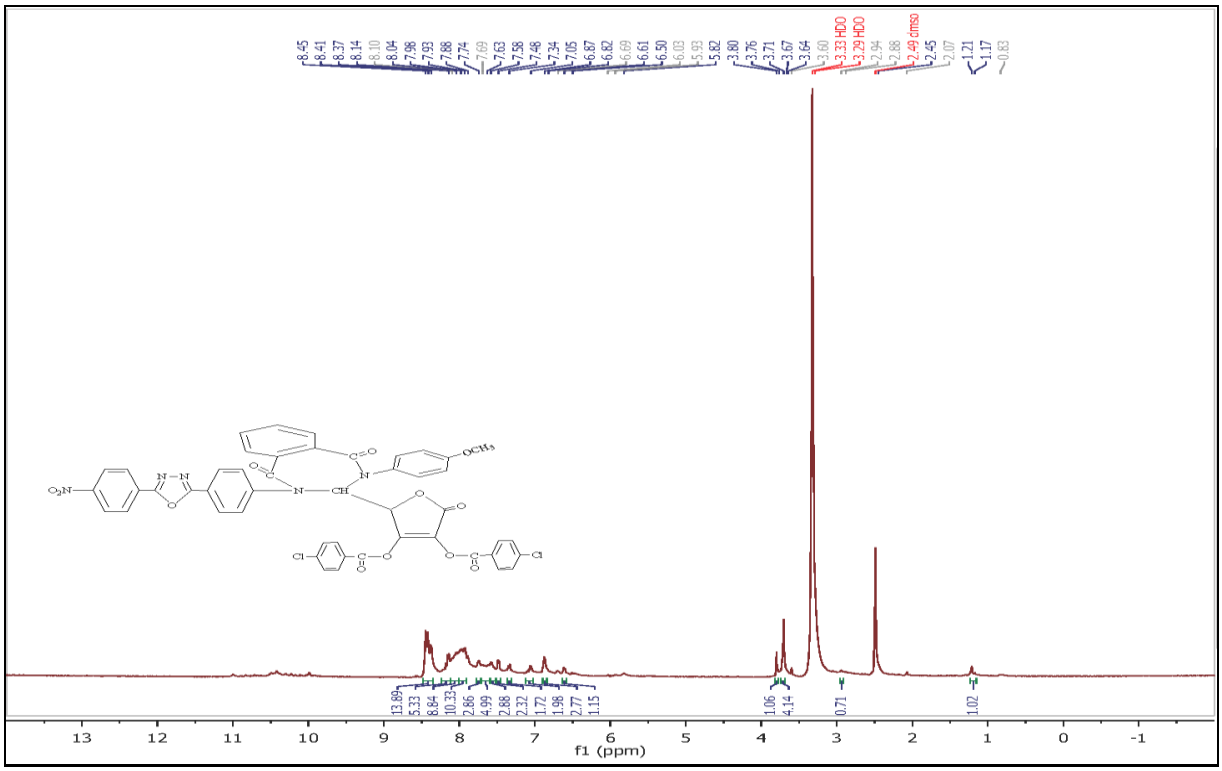
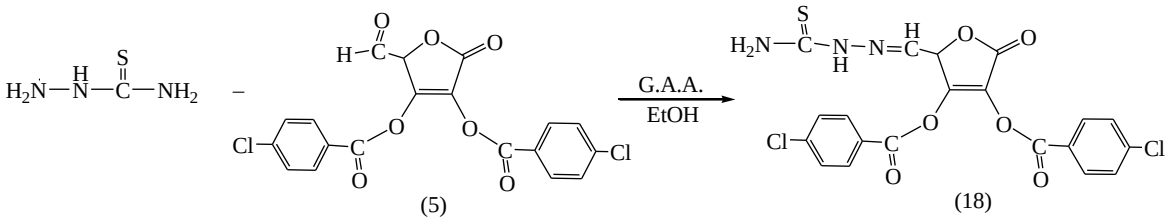


Fig. (3.58): ^{1}H-NMR spectrum of diazepine (16e)

3.8 Synthesis and characterization of 1,3-thiazolidin-4-one and new alkene derivatives of 1,3-thiazolidin-4-one

Thiosemicarbazone (18) which obtained from reaction of aldehyde (5) with thiosemicarbazide in acidic medium.



The thiosemicarbazone (18) was characterized via FT-IR and mass spectroscopy, the FT-IR spectrum for compound (18), Fig. (3.59) showed three new stretching absorption peaks at (3367-3170) cm^{-1} were related to NH and NH_2 groups, whereas the vibrating absorption peak belong to C=N group appeared at (1643 cm^{-1}). The FT-IR characteristic absorption bands of compound (18) were listed in Table (3.3).

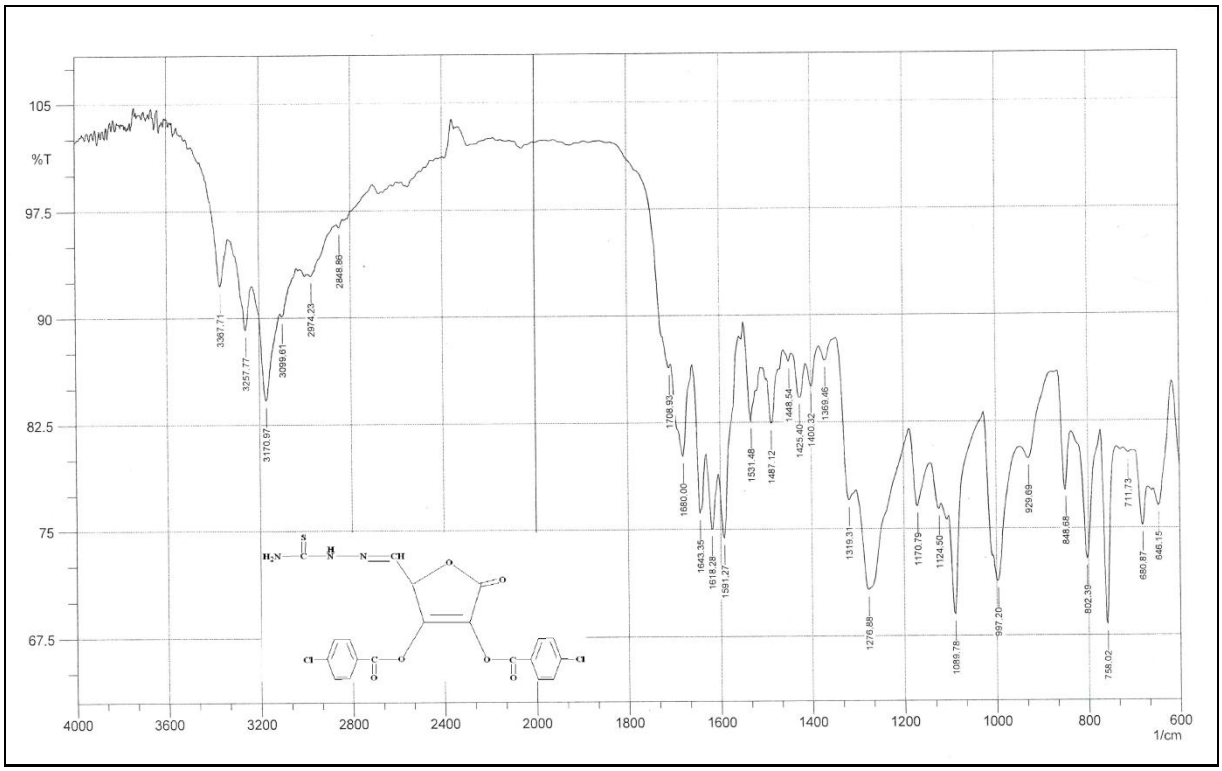
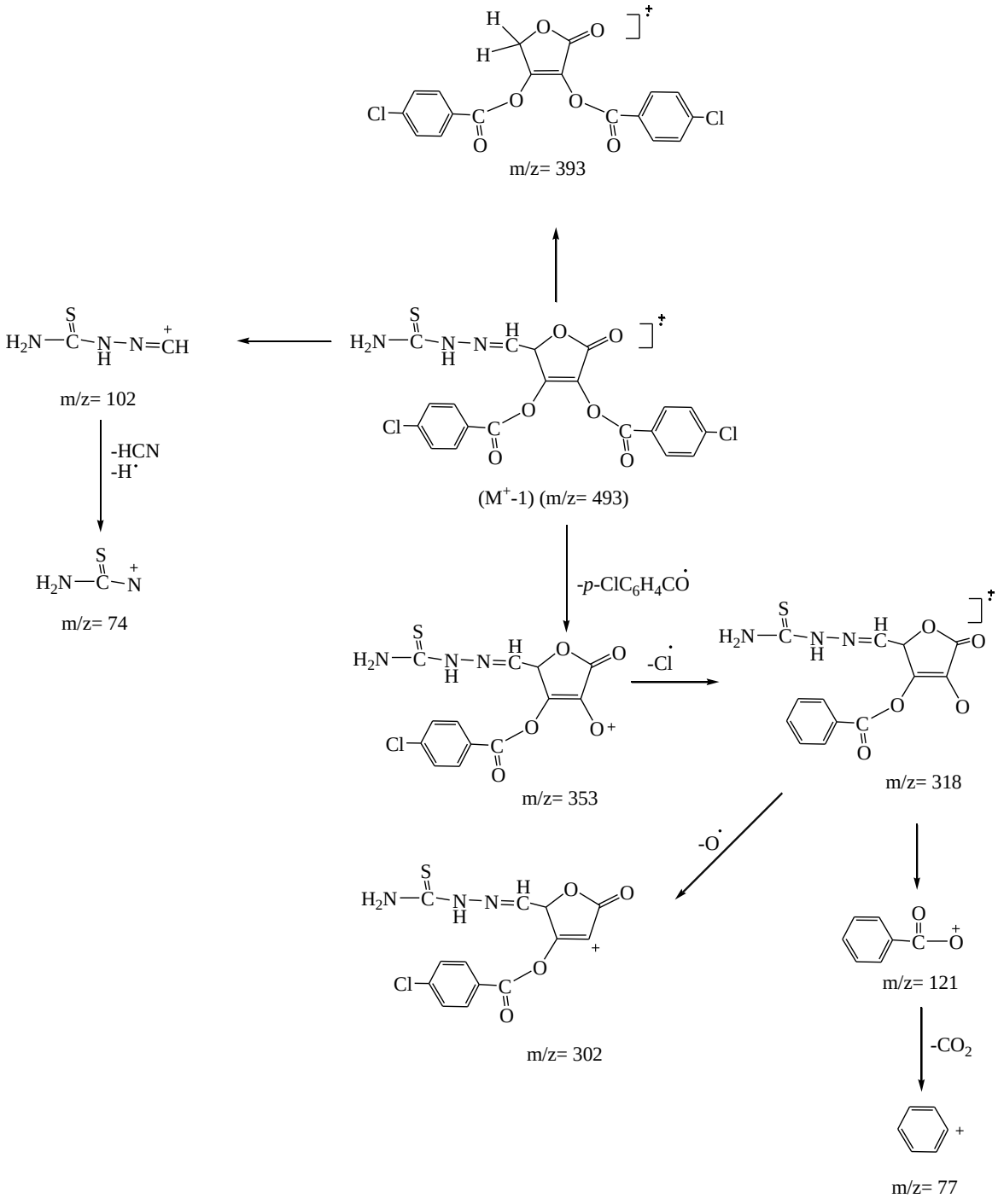


Fig. (3.59): FTIR spectrum of compound (18)

The mass spectrum of Schiff base (18), Fig. (3.60) showed a molecular ion (M^+-1) (m/z=493), and characteristic fragments of this compound were shown in Scheme (3.12).



Scheme (3.12): The characteristic fragments of Schiff base (18)

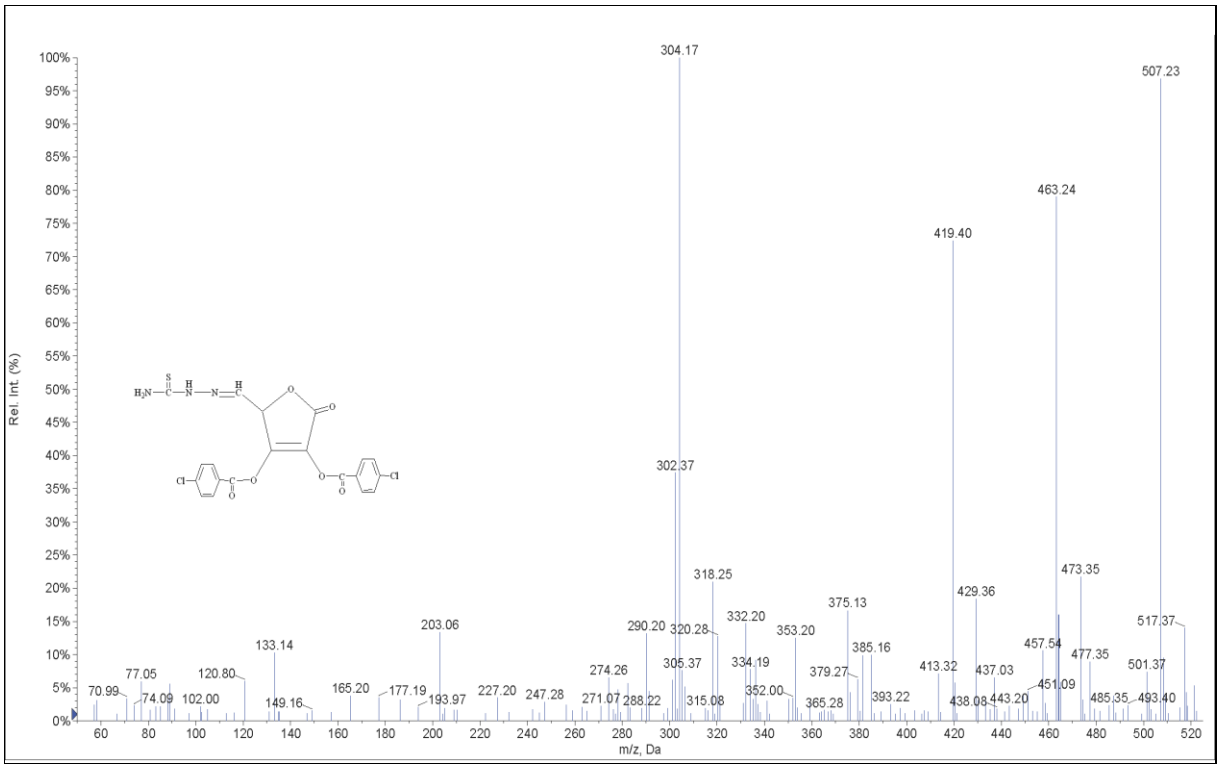
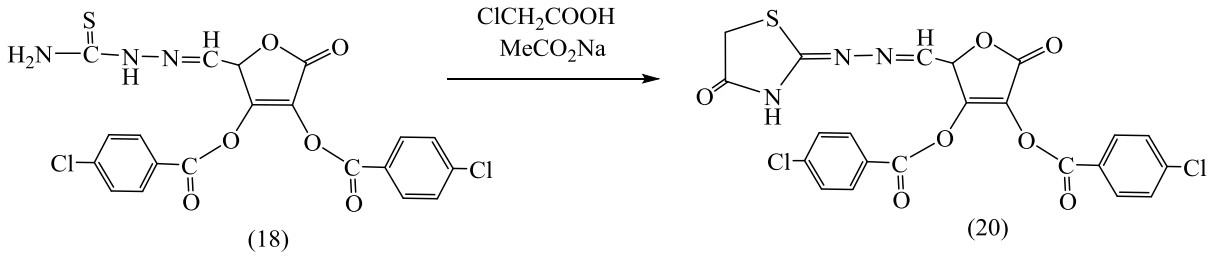


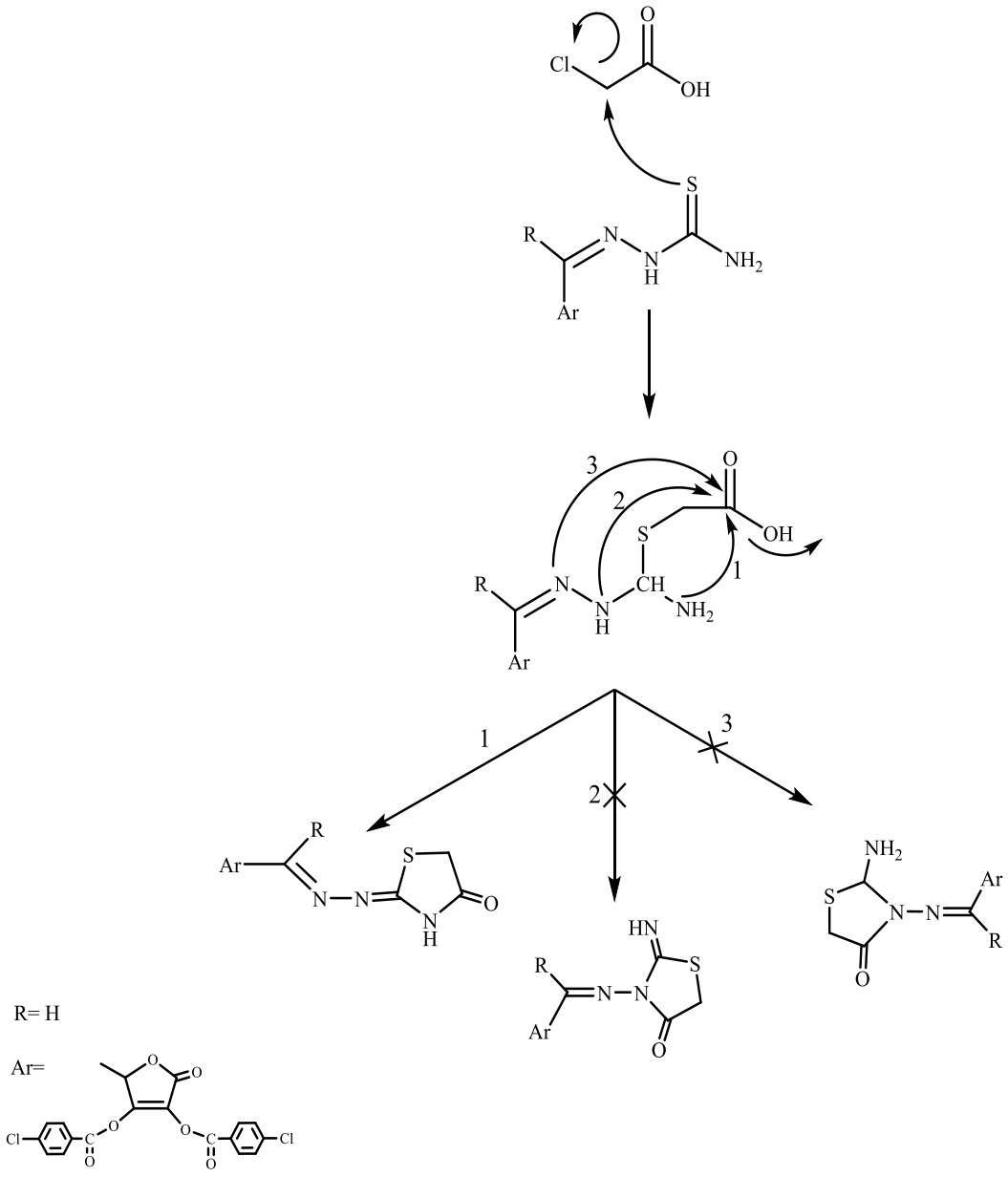
Fig. (3.60): Mass spectrum of compound (18)

The thiosemicarbazone (18) was cyclized successfully to 1,3-thiazolidin-4-one in presence of chloroacetic acid and sodium acetate.



(18) (20)

The cyclization mechanism was outlined in Scheme (3.13). [186]



Scheme (3.13): The suggested mechanism for synthesis 1,3-thiazoldin-4-one

The FTIR spectrum of the product confirmed the formation of the 1,3-thiazolidin-4-one (20), Fig (3.61), showed the disappearance of NH_2 group peaks of thiosemicarbazone (18) with appearance of new characteristic bands at (3325) cm^{-1} and (1714) cm^{-1} related to vibrating of (N-H and C=O) groups of lactam, respectively, Table (3.3).

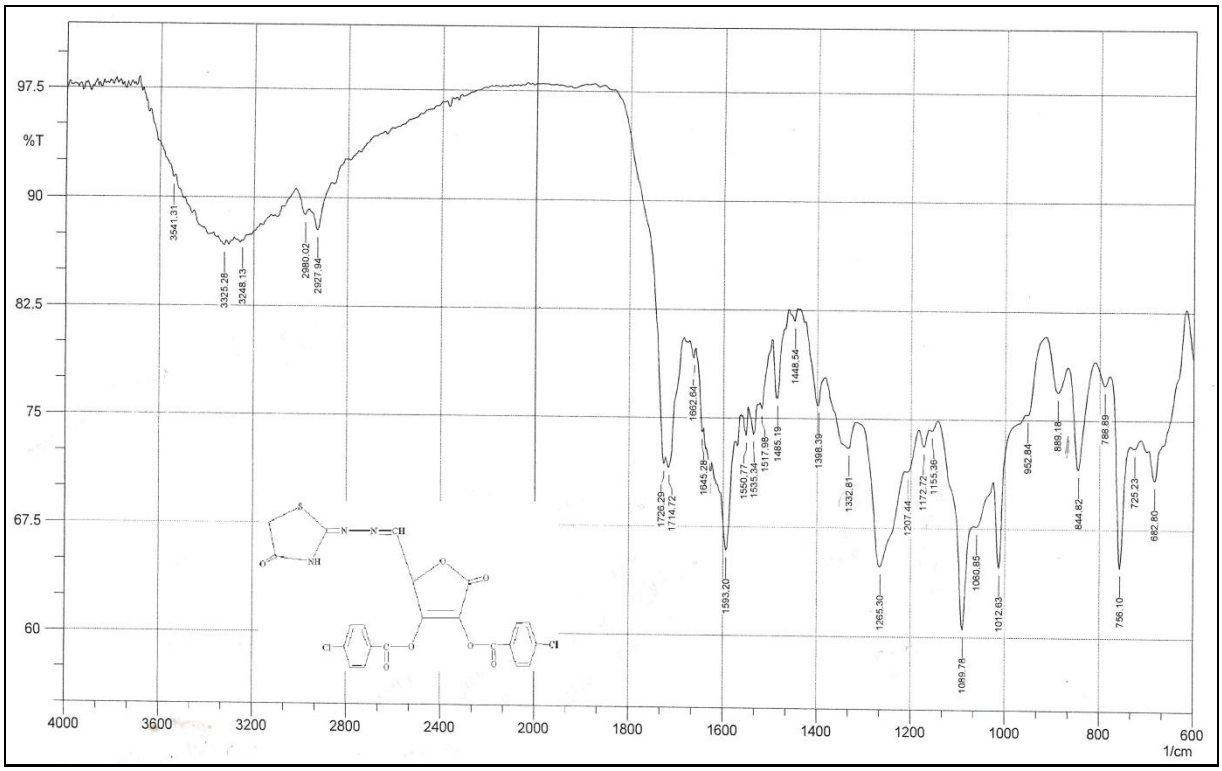
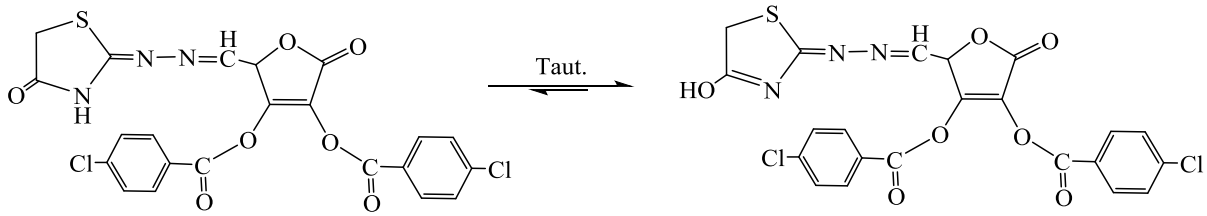


Fig. (3.61): FTIR spectrum of compound (20)

Furthermore, ^{1}H-NMR spectrum of compound (20) (in DMSO-d_6 as a solvent), Fig. (3.62) showed a singlet signal at δ(4.41 ppm) for two protons at C_5 of thiazolidinone ring, signal at δ(4.61 ppm) for (C-H) of lactone ring, likewise singlet signal at δ(3.83) ppm for OH could presence in tautomeric forms, OH due to C=N form, and doublet doublet signals between in the range δ(6.92-8.01) ppm due to aromatic protons and one proton of (CH=N) group.



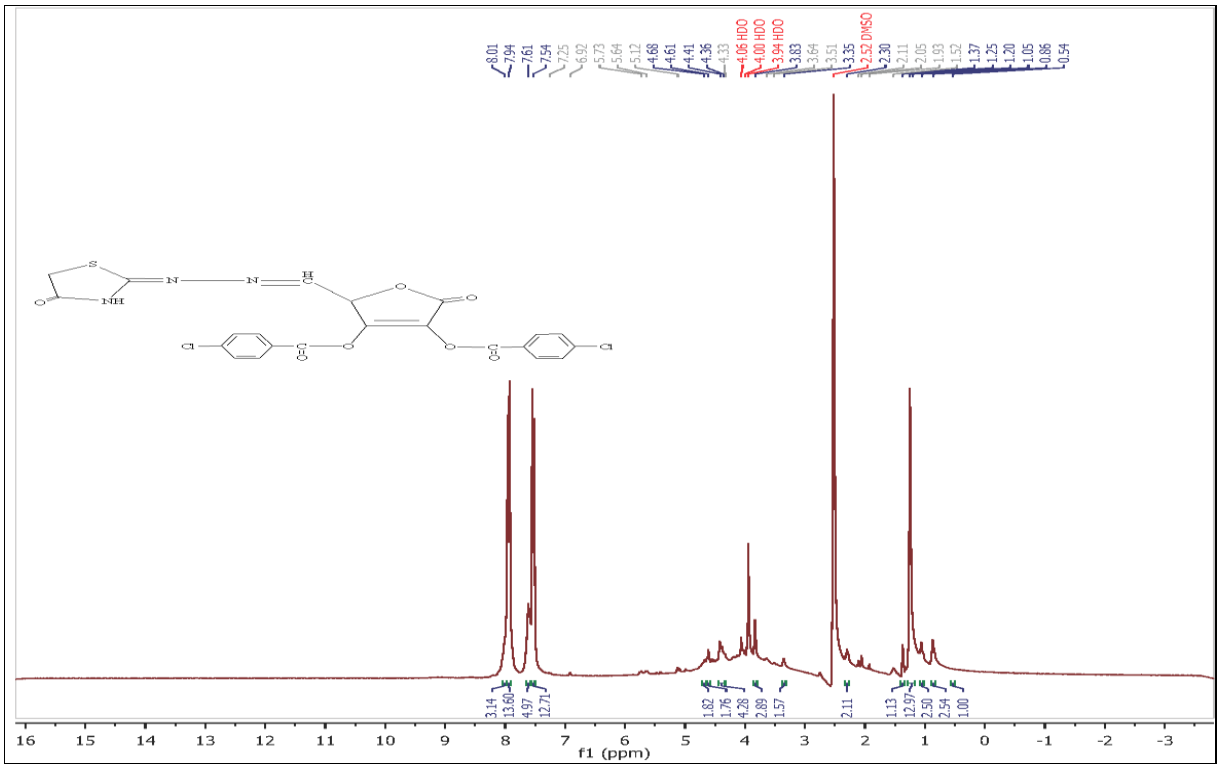
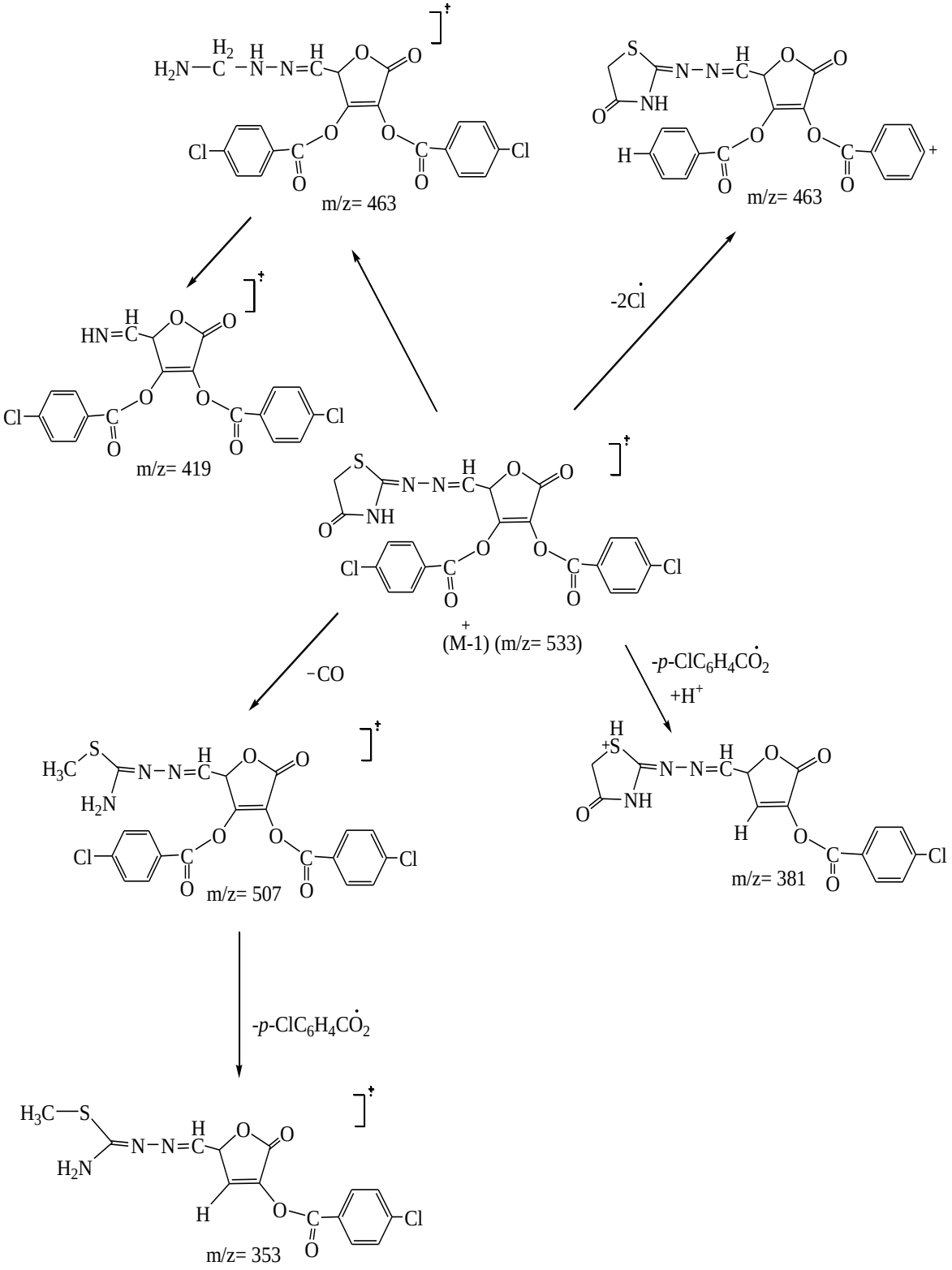


Fig. (3.62): ^{1}HNMR spectrum of compound (20)

The mass spectrum of this compound (20), Fig. (3.63), showed a molecular ion (M^{+}-1+18) (m/z= 551) and characteristic fragments of this compound were shown in Scheme (3.14).



Scheme (3.14): The characteristic fragments of compound (20)

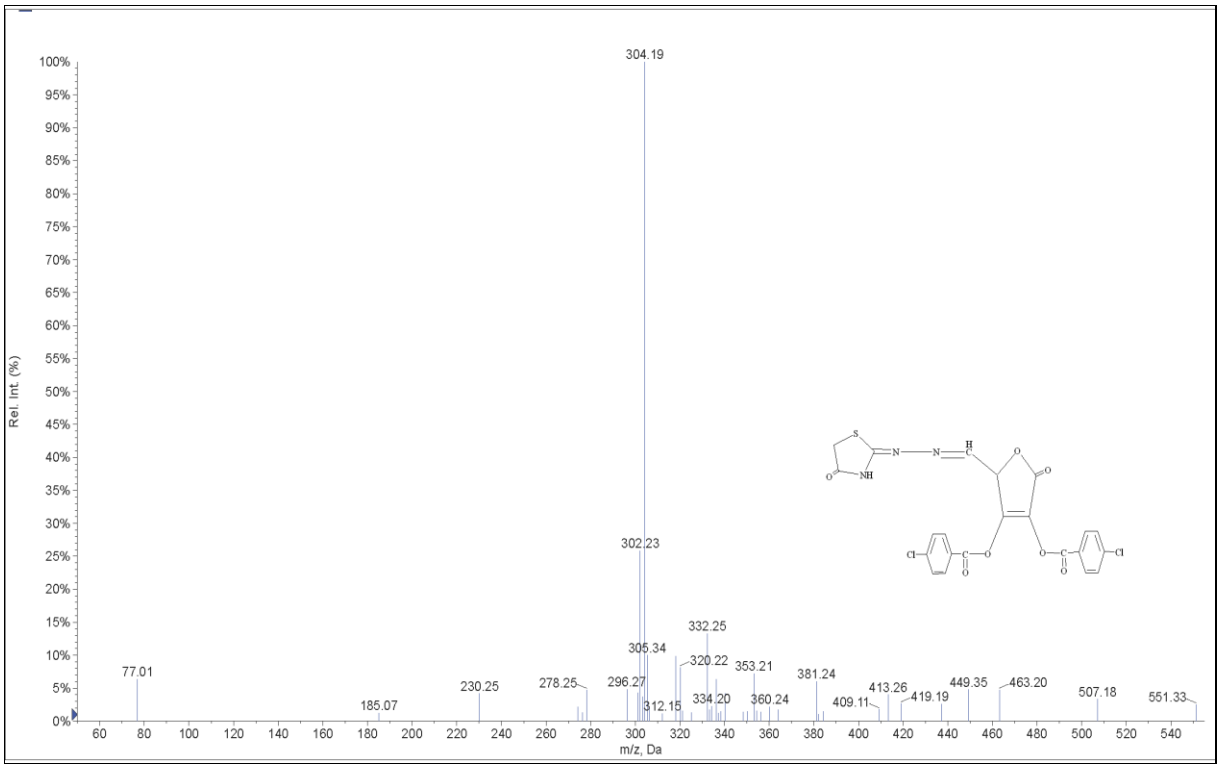
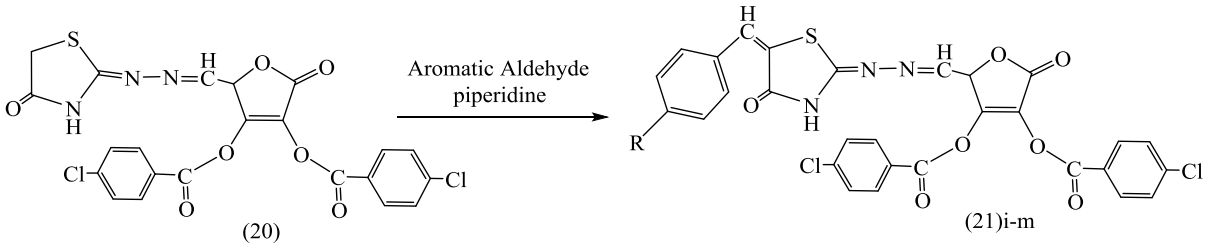


Fig. (3.63): Mass spectrum of compound (20)

By another step of our plan was to introduce a double bond at position 5 of the thiazolidinone ring to give alkene compounds (21)i-m. This step was carried out via reaction of thiazolidinone (20) with benzaldehyde and substituted benzaldehyde in entity of piperidine (which was a base to remove the most acidic proton at position 5 of the ring). The resulted carbanion would easy attack the carbon of the carbonyl group of the benzaldehyde and substituted benzaldehyde to produce the alkene (21)i-m.



R= H, CH_3, OCH_3, NO_2, NMe_2

The structure of the resulted products were confirmed via their FT-IR spectra, Figs. (3.64) to (3.68) that showed a stretching peak for olefinic double bond (C=C) in the range (1616-1593) cm^{-1}. The most characteristic absorption peaks of the products were awarded in (Table 3.3).

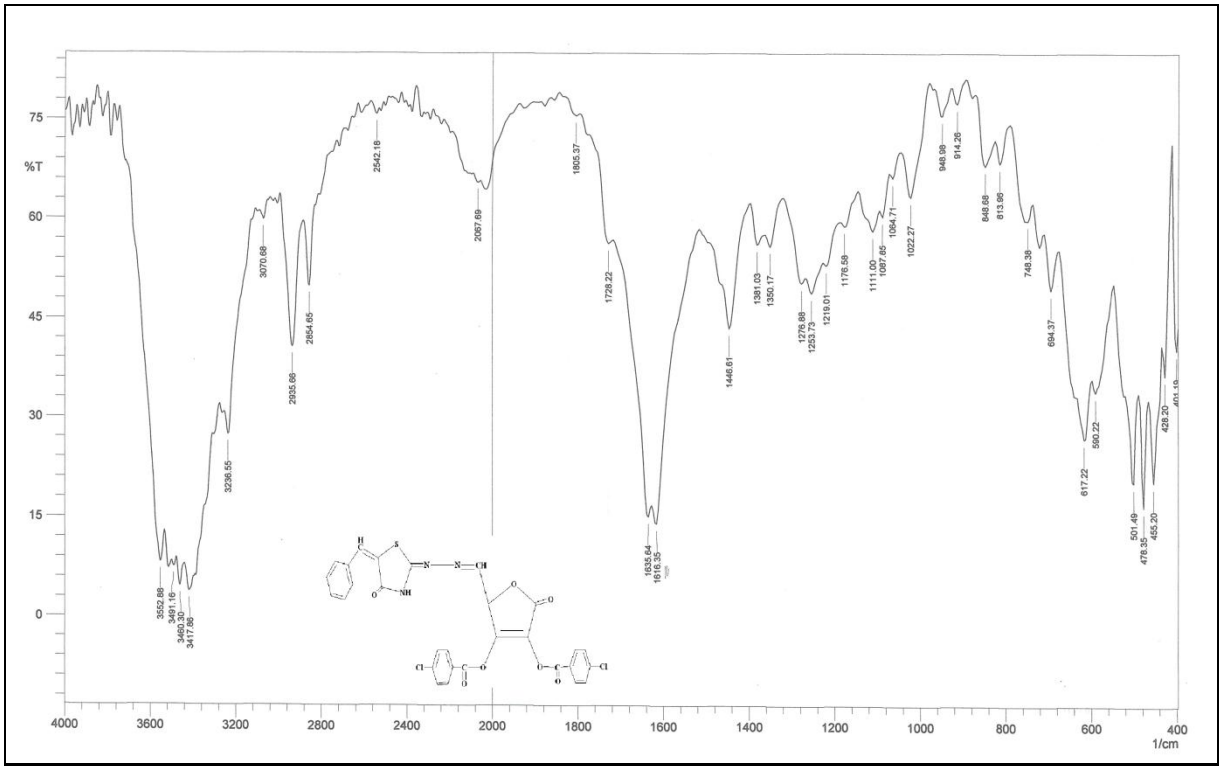


Fig. (3.64): FTIR spectrum of alkene (21i)

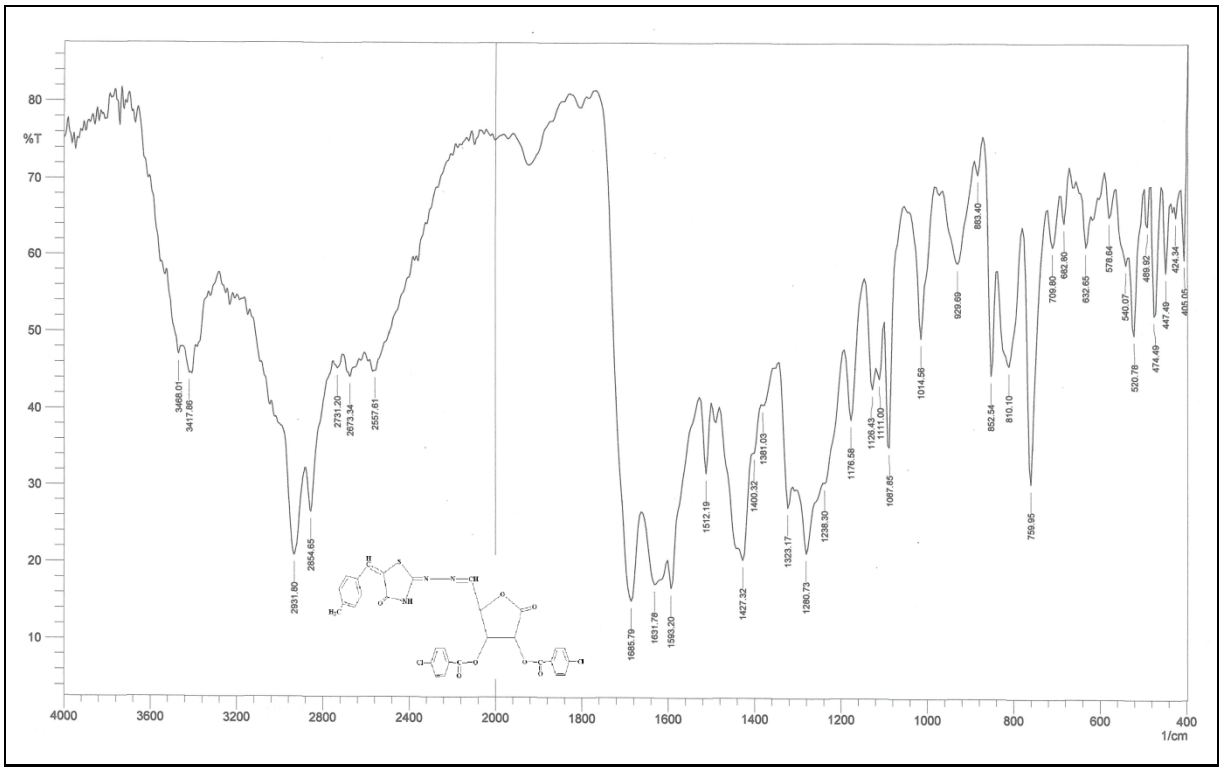


Fig. (3.65): FTIR spectrum of alkene (21j)

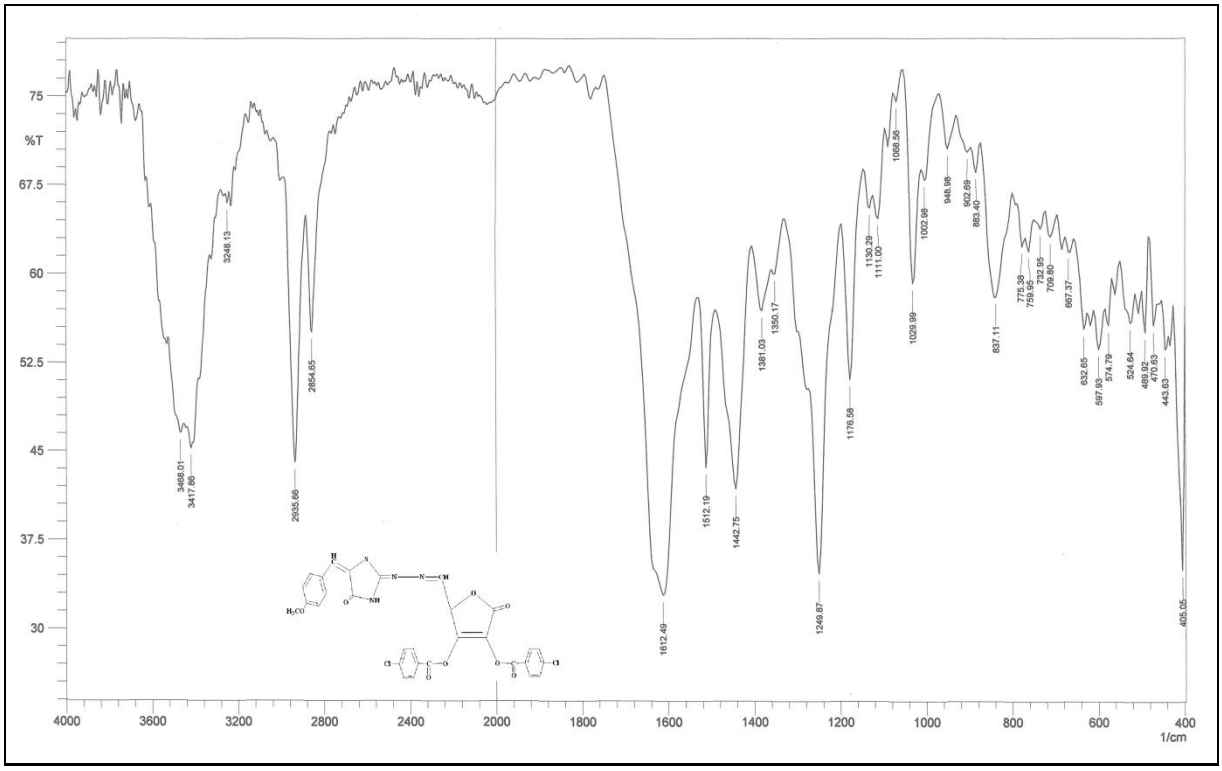


Fig. (3.66): FTIR spectrum of alkene (21k)

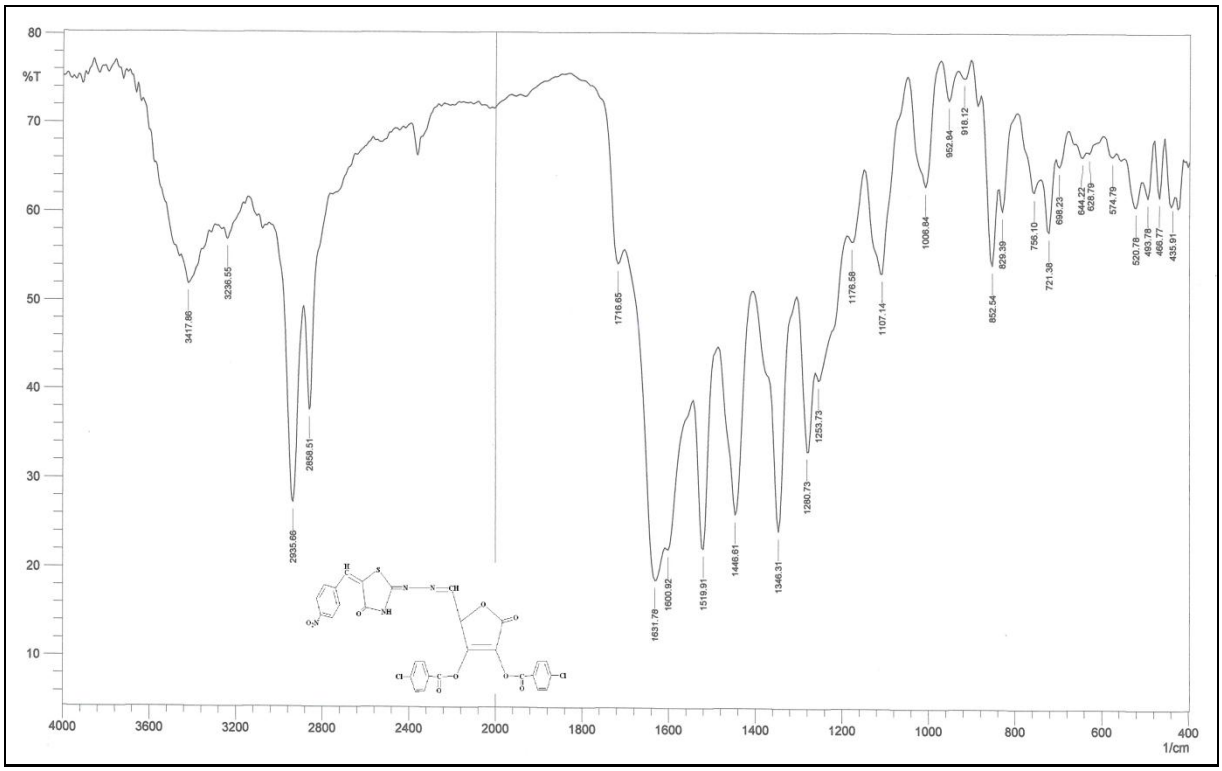


Fig. (3.67): FTIR spectrum of alkene (21l)

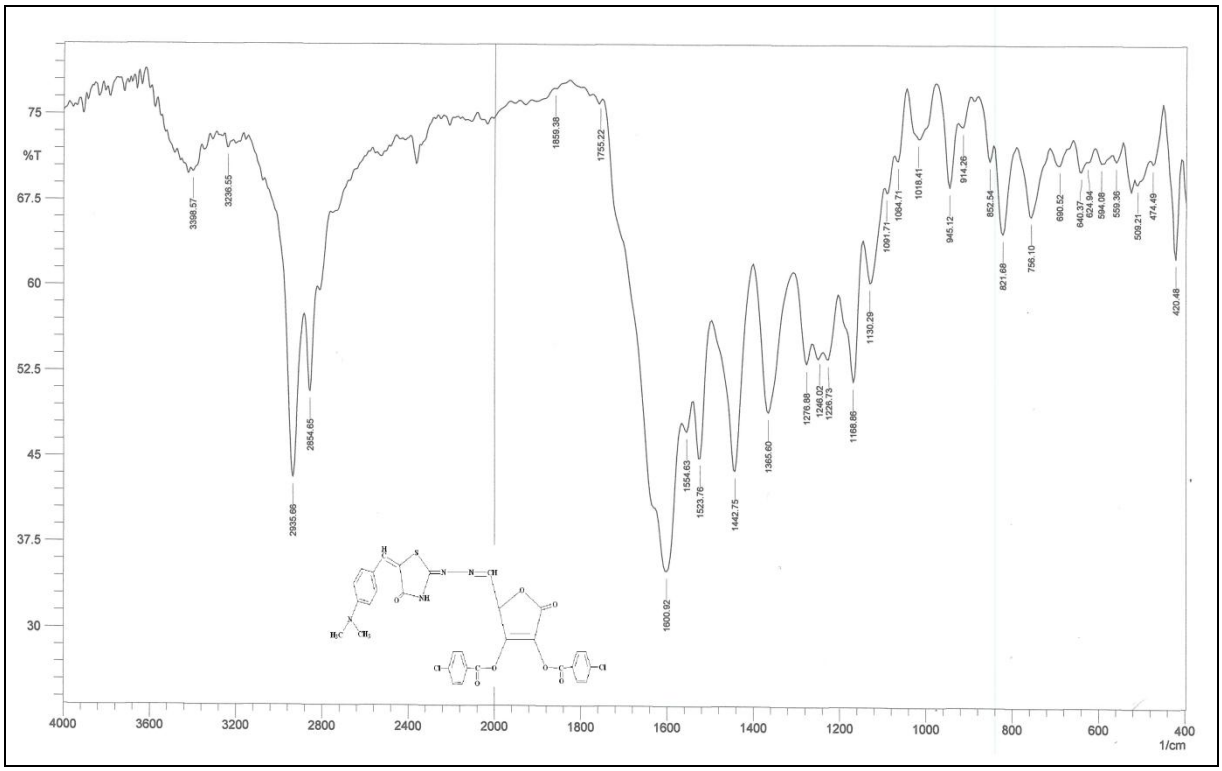


Fig. (3.68): FTIR spectrum of alkene (21m)

Furthermore, ^{1}H-NMR spectrum of alkene (21K) (in DMSO-d_6 as a solvent), Fig. (3.69) showed a singlet signal at δ(8.28 ppm) for one proton of NH group and doublet doublet signals between in the range δ(6.84-7.97) ppm due to fourteen protons. Twelve of aromatic protons, one olefinic proton (CH=) and one proton of imine group (CH=N). A sharp singlet signal appeared at δ(3.85 ppm) belong to three aliphatic protons of methoxy group (OCH_3), so the spectrum showed a signal at δ(4.03 ppm) for one proton of lactone ring.

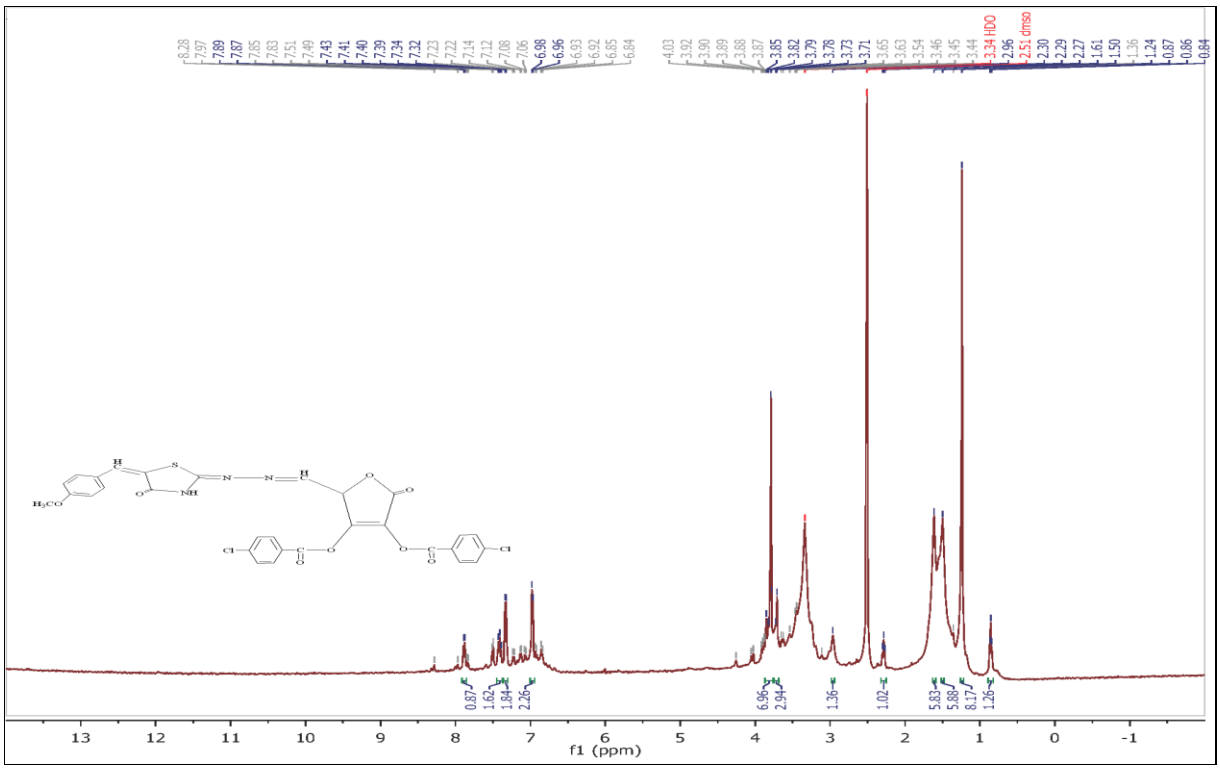


Fig. (3.69): ^{1}H-NMR spectrum of alkene (21k)

While the ^{1}H-NMR spectrum of alkene (21m) (in DMSO-d_6 as a solvent), Fig. (3.70) showed a singlet signal at δ(9.67 ppm) for one proton of NH group, doublet doublet signals between in the range δ(6.56-8.0) ppm related to fourteen protons. Twelve of them were aromatic protons, one olefinic proton (CH=) and one proton of imine group (CH=N). A signal appeared at δ(2.87) ppm belong to six aliphatic protons for (CH_3-N-CH_3) group. As well as, appeared a signal at δ(3.24 ppm) for one proton of lactone ring.

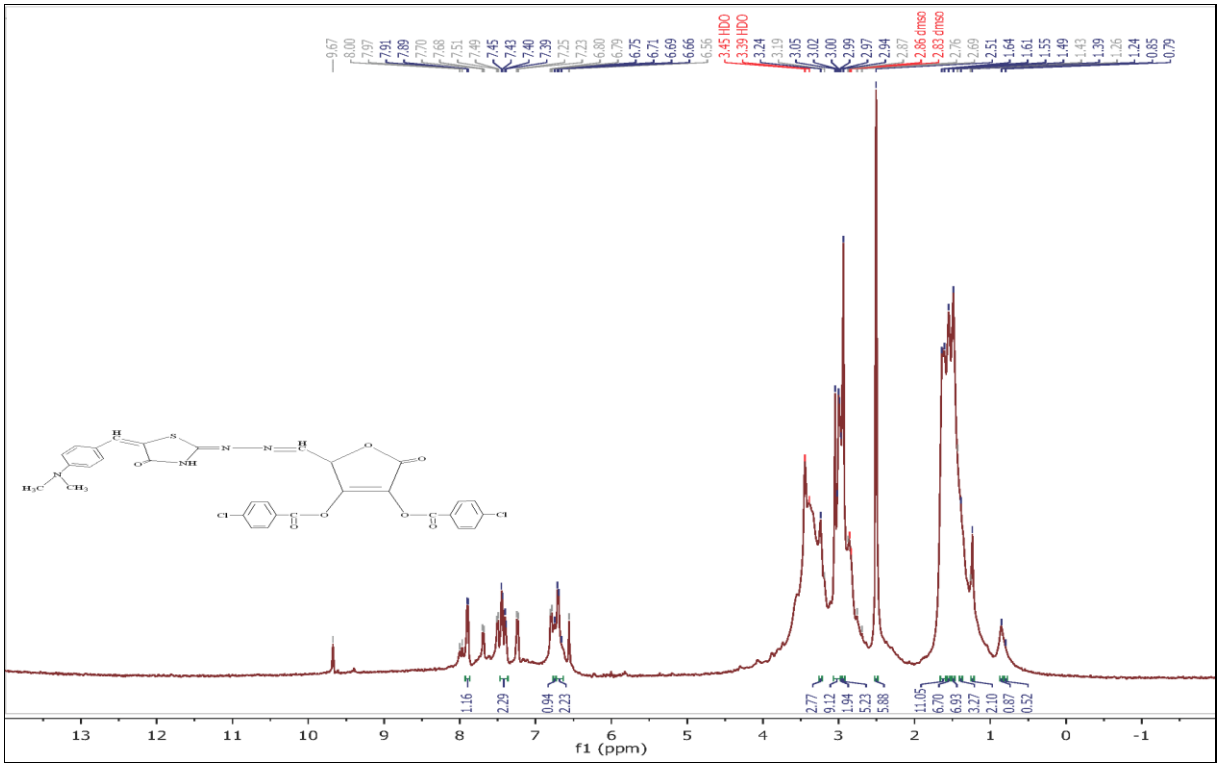
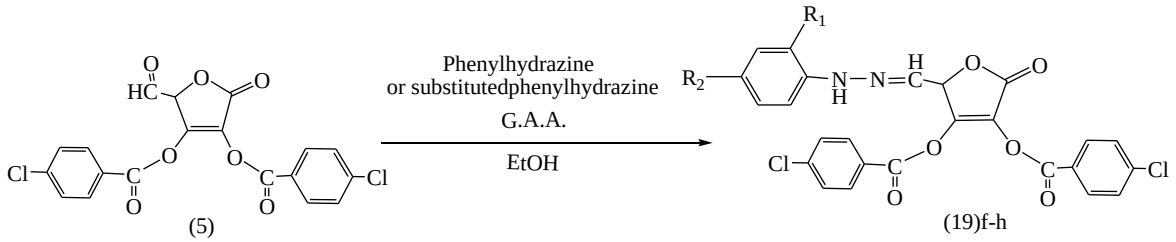


Fig. (3.70): ^{1}H-NMR spectrum of alkene (21m)

3.9 Synthesis of Schiff bases (19)f-h

The new Schiff bases (hydrazones) (19)f-h were synthesized by refluxing equimolar of aldehyde (5) with phenylhydrazine or substituted phenylhydrazine in absolute ethanol with some drops of glacial acetic acid (GAA).



f: R_1= H, R_2= H
g: R_1= NO_2, R_2= NO_2
h: R_1= H, R_2= NO_2

These Schiff bases (19)f-h were detected via FT-IR and ^{1}H-NMR spectroscopy of Schiff base (19g). FT-IR absorption spectra, Figs. (3.71) to (3.73) showed the appearance of new absorption bands in the range (1639-

1612) cm^{-1} that was related to azomethine group (C=N) vibrating. The other FTIR spectral data were listed in Table (3.4).

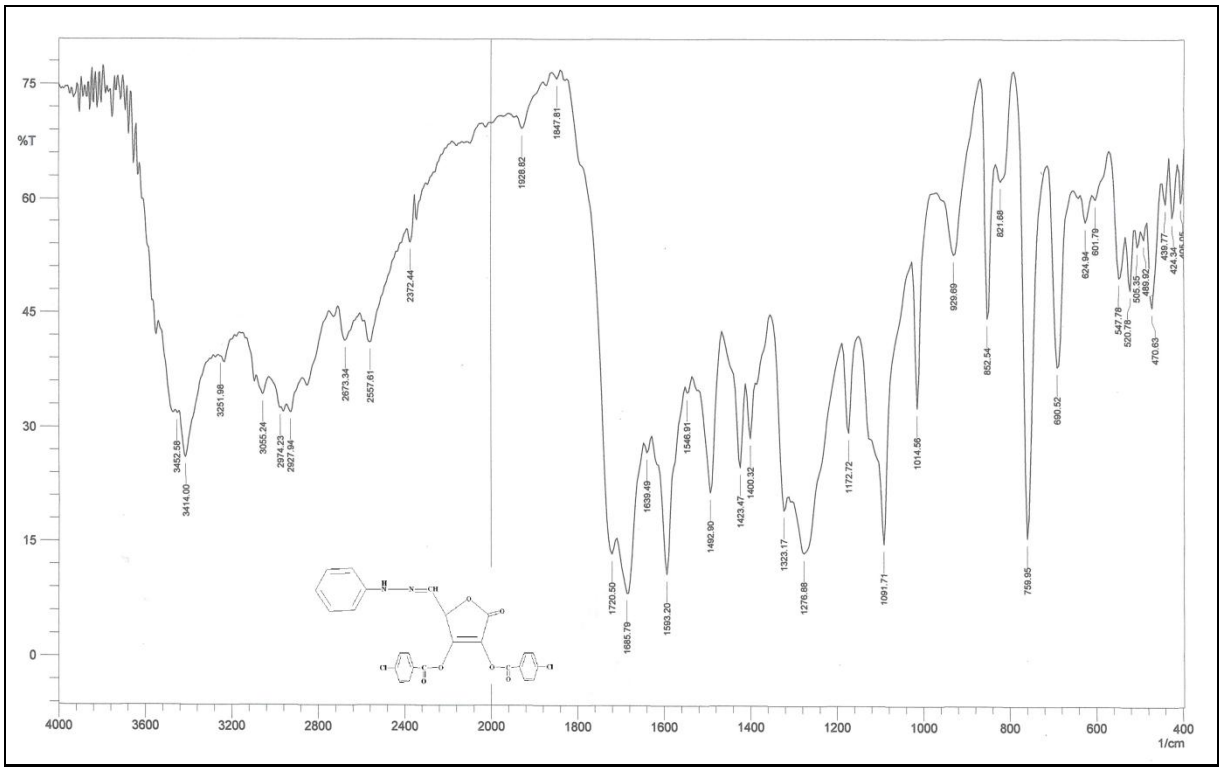


Fig. (3.71): FTIR spectrum of compound (19f)

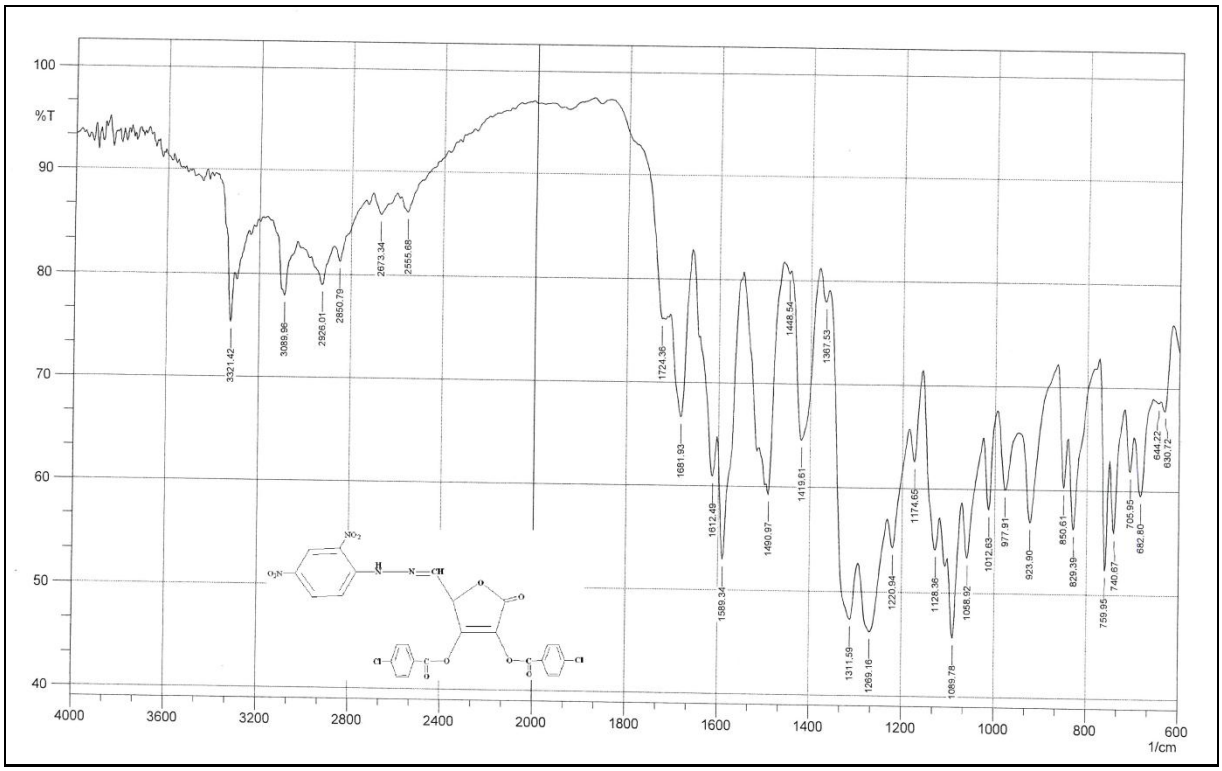


Fig. (3.72): FTIR spectrum of compound (19g)

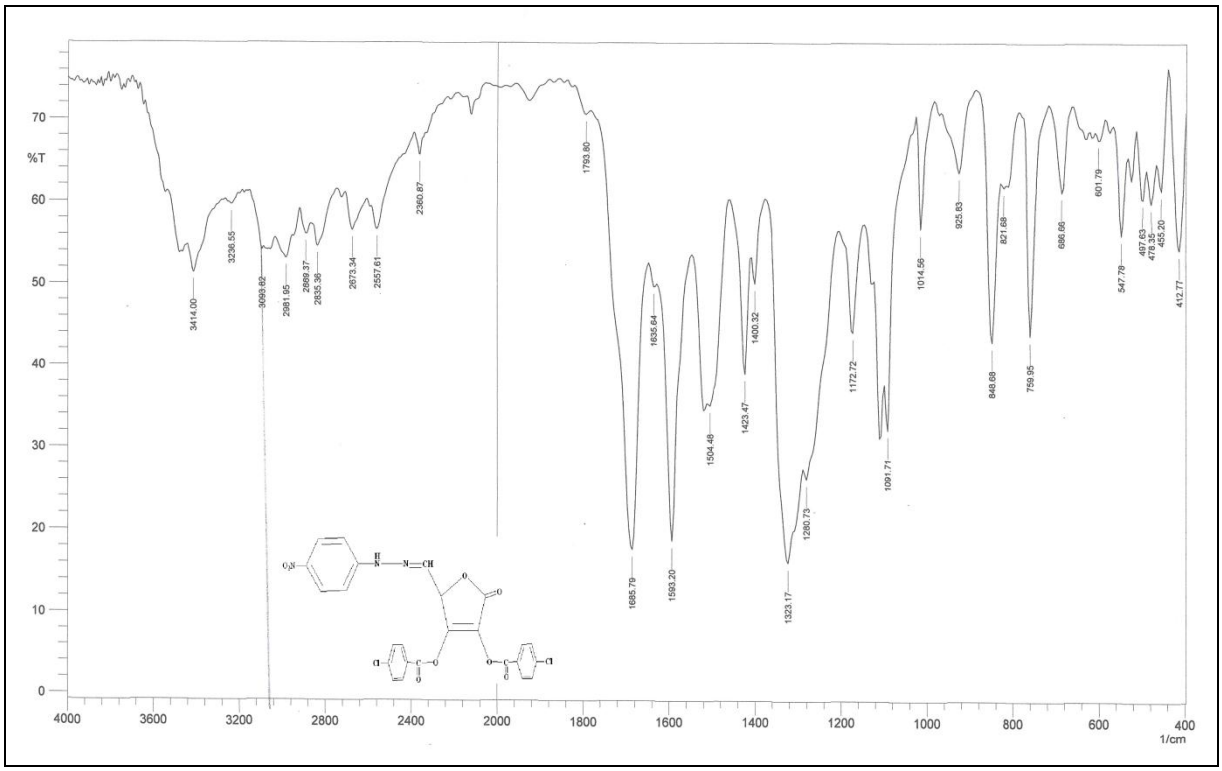


Fig. (3.73): FTIR spectrum of compound (19h)

^{1}H-NMR spectrum in DMSO-d_6 of hydrazone (19g), Fig. (3.74), indicated a sharp signal at δ(9.99 ppm) for one proton could be imputed to the NH group, and multiplet signals between in the range δ(7.55-8.83) ppm that could be imputed to aromatic protons and the one proton of imine group (CH=N) appeared at δ(9.11) ppm. One signal at δ(3.44) ppm for proton of lactone ring.

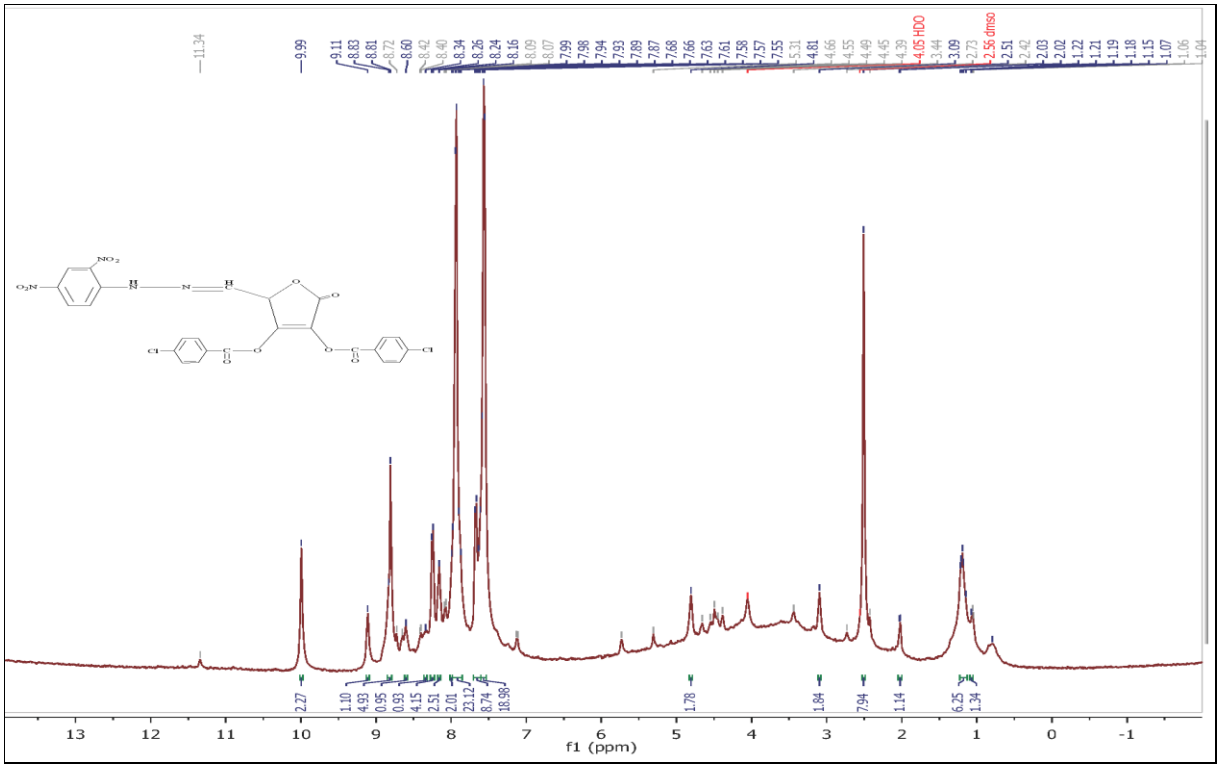
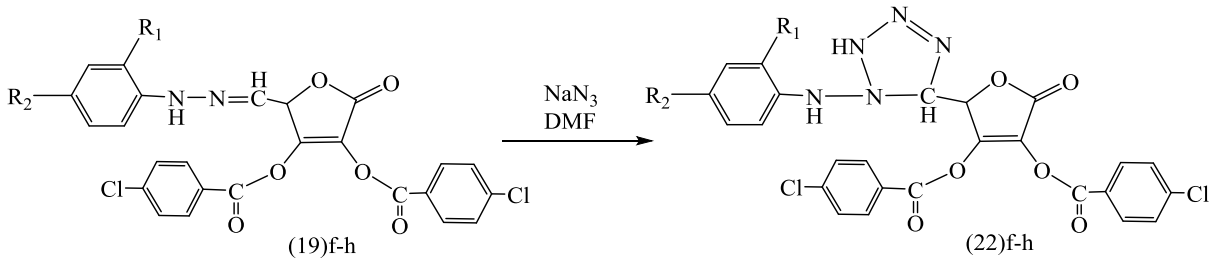


Fig. (3.74): ^{1}H-NMR spectrum of compound (19g)

3.10 Synthesis and characterization of 2,5-dihydrotetrazole compounds (22)f-h

2,5-Dihydrotetrazole derivatives (22)f-h were obtained by addition reaction of NaN_3 to hydrazone (19f, 19g or 19h) in dimethyl formamide.



f: R_1= H, R_2= H
g: R_1= NO_2, R_2= NO_2
h: R_1= H, R_2= NO_2

These compounds were detected via FT-IR and ^{1}H-NMR spectroscopy of 2,5-dihydrotetrazole (22f). The FT-IR spectra, Figs. (3.75) to (3.77) showed the disappearance of absorption stretching bands of imine group with appearance of new absorption stretching band in the rang (1548-1500) cm^{-1} that are related to N=N vibrating. The FT-IR spectral data for 2,5-dihydrotetrazole compounds were shown in Table (3.4).

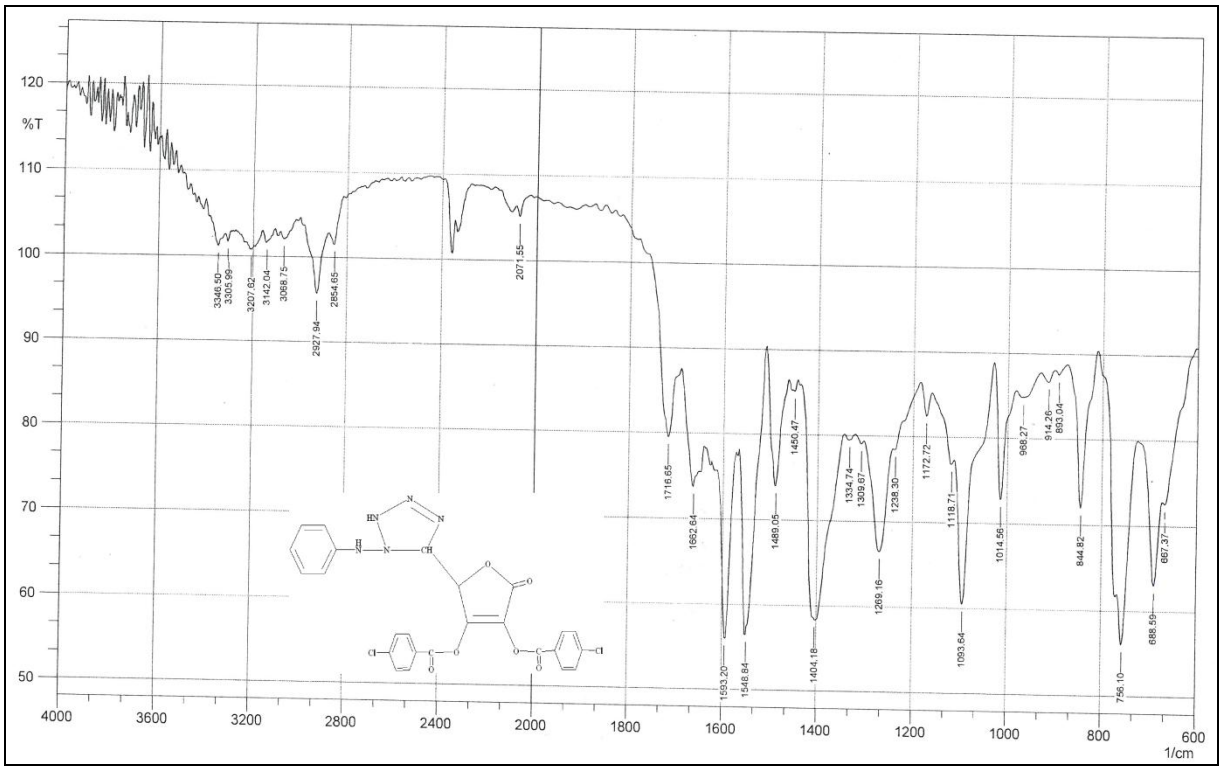


Fig. (3.75): FTIR spectrum of for 2,5-dihydrotetrazole (22f)

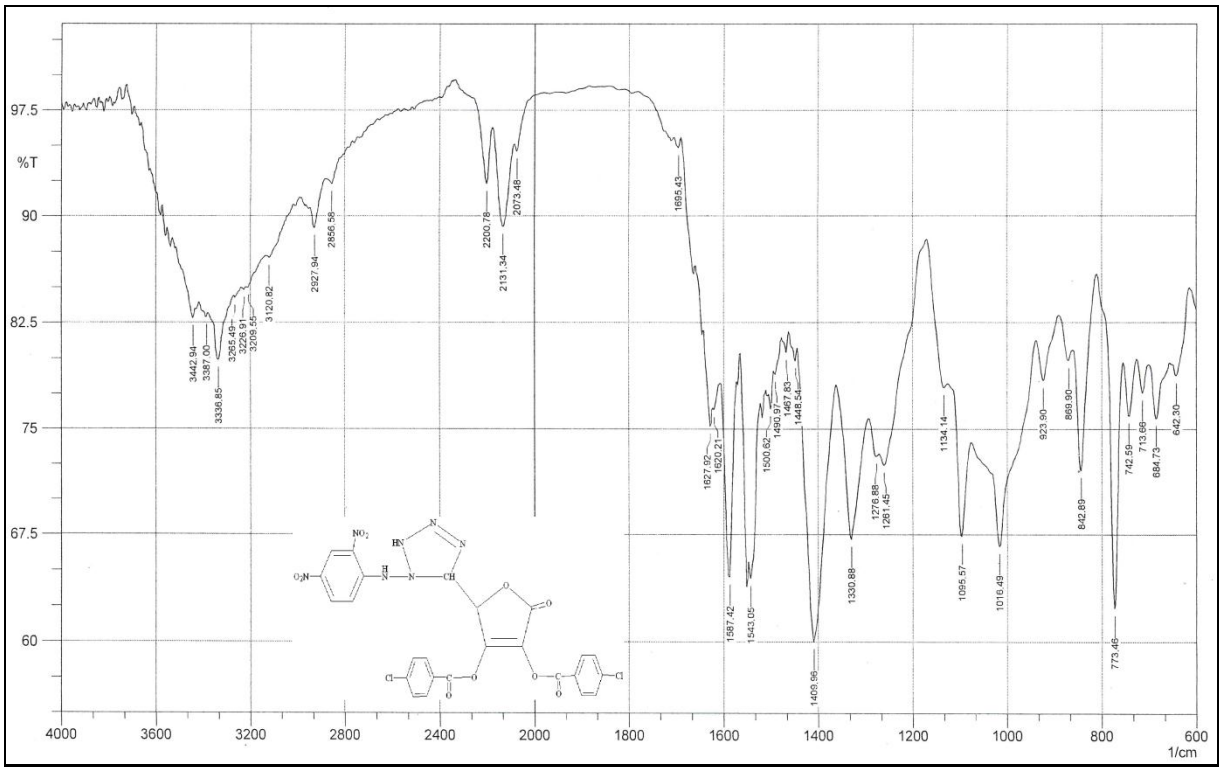


Fig. (3.76): FTIR spectrum of for 2,5-dihydrotetrazole (22g)

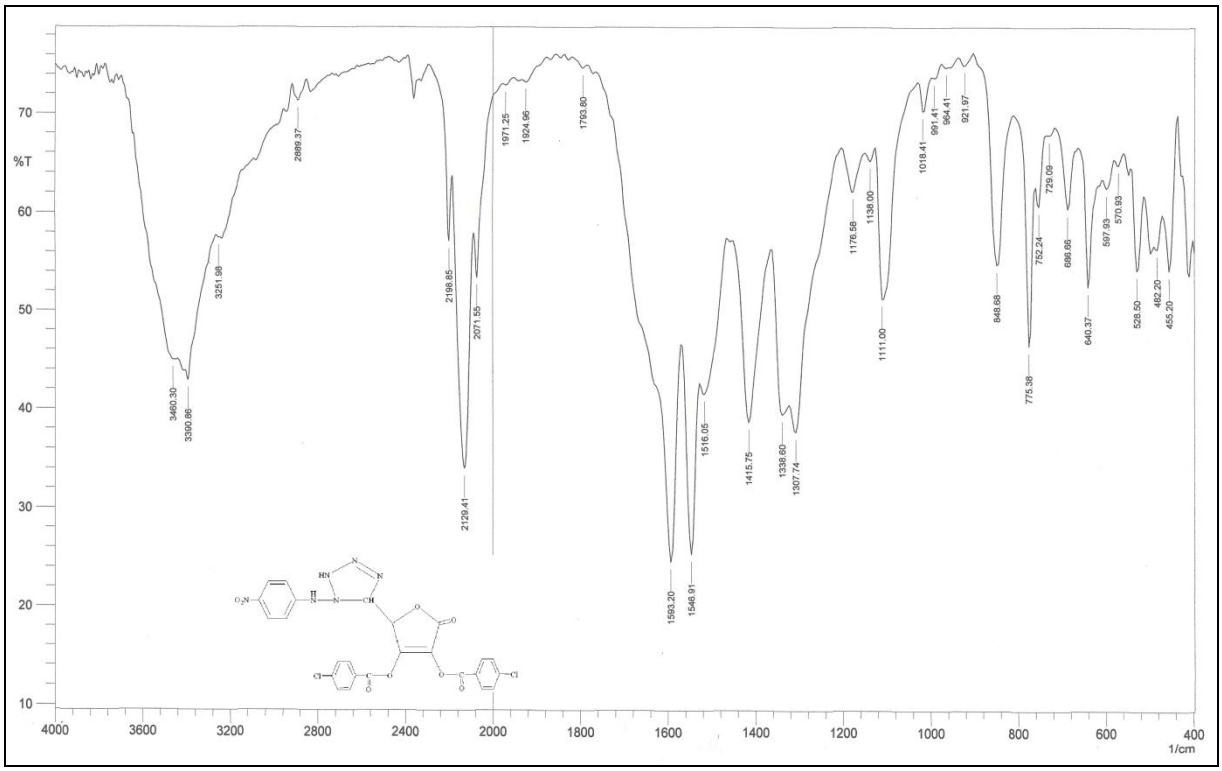


Fig. (3.77): FTIR spectrum of for 2,5-dihydrotetrazole (22h)

^{1}H-NMR spectrum of for 2,5-dihydrotetrazole (22f) (in DMSO-d_6 as a solvent), Fig. (3.78) indicated two singlet signals at δ(8.50) ppm and δ(4.65) ppm for two protons of NH (exocyclic) and NH (endocyclic) respectively and doublet doublet and multiplet signals for aromatic protons appeared in the range δ(7.31-8.01) ppm. Thus the spectrum demonstrated two doublet signals at δ(3.80 ppm) and δ(5 ppm) related to CH for 2,5-dihydrotetrazole ring and lactone ring, respectively.

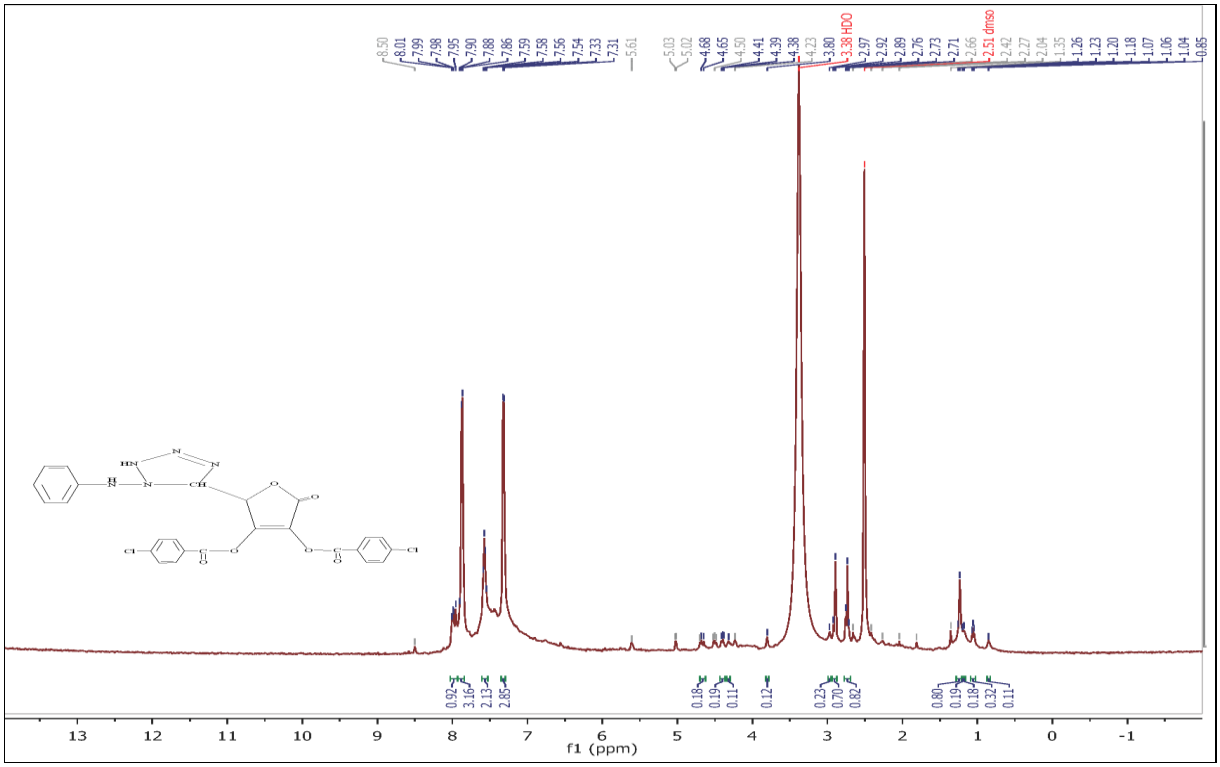


Fig. (3.78): ^{1}H-NMR spectrum of 2,5-dihydrotetrazole (22f)

Table (3.3): FTIR spectral data of compounds (18), (20) and (21)i-m

Comp. no.	νNH	νC-H ar.	νC-H ali.	νC=O est.	νC=N	νC=C ali.	νC=C ar.	νC=S	νC-Cl	νC-S
18	3367	3099	2974,2848	1680	1643	-	1591	1276	1089	-
20	3325	-	2980,2825	1714	1662	-	1593	-	1089	756
21i	3236	3070	2935,2854	1728	1635	1616	1446	-	1087	748
21j	-	-	2931,2854	1685	1631	1593	1512	-	1087	759
21k	3248	-	2935,2854	-	-	1612	1512	-	1088	732
21l	3236	-	2935,2858	1716	1631	1600	1519	-	1107	721
21m	3236	-	2935,2854	-	-	1600	1554	-	1084	756

Table (3.4): FTIR spectral data of compounds (19)f-h and (22)f-h

Comp. no.	νNH	νC-H ar.	νC-H ali.	νC=O est.	νC=N	νC=C ar.	νN=N	νC-Cl	Other
19f	3251	3055	2974,2927	1685	1639	1593	-	1091	-
19g	3321	3089	2926,2850	1681	1612	1589	-	1089	νNO_2: 1490,1311
19h	3236	3093	2981,2835	1685	1635	1593	-	1091	νNO_2: 1504,1323
22f	3142	3088	2927,2854	1682	-	1593	1548	1093	-
22g	3336	-	2927,2856	1695	-	1587	1500	1095	νNO_2: 1543,1330
22h	3251	-	-	-	-	1593	1516	1111	νNO_2: 1546,1307

3.11 Biological activity

The results of antibacterial activities of all synthesized compounds for two microorganisms (*Escherichia coli and Staphylococcus aureus*) were presented in Table (3.5) which the zone of inhibition measured in millimeters (mm). The DMSO was used as control. The Figures (3.77) and (3.78) showed the effect of synthesized compounds on *E. Coli* and *Staph. aureus*.

Table (3.5): The inhibition zone of synthesized compounds (5)-(22h)

Comp. no.	*E. Coli* (G-)	*Staph. aureus* (G+)
DMSO	-	-
5	11	13
6	-	7
9a	-	12
9b	-	13
10c	-	-
10d	-	9
10e	-	9
11c	30	11
11d	-	8

11e	-	13
12c	-	7
12d	-	10
12e	-	9
13c	-	7
13d	-	10
13e	-	8
14c	-	9
14d	14	7
14e	-	8
15c	-	9
15d	-	11
19e=15e	-	9
16c	10	11
16d	-	10
16e	-	10
17c	22	9
17d	-	11
17e	-	9
[II]=18	-	16
[V]a=19f	-	21
[V]b=19g	-	17
[V]c=19h	-	-
[III]=20	-	11
[IV]a=21i	-	20
[IV]b=21j	-	14
[IV]c=21k	-	19
[IV]d=21l	17	20
[IV]e=21m	-	20
[VI]a=22f	-	-
[VI]b=22g	-	-
[VI]c=22h	-	-

Note: Slight activity = (5-10) mm, Moderate activity = (11-15) mm, High activity = (15 and more than 15) mm

Conclusions

1. All compounds didn't show any bacterial activity against *E. coli* (G-) except compounds (5, 11c, 14d, 16c, 17c, 21l) which exhibited compounds (5, 14d) moderate activity while compound (16c) showed low activity and (11c, 17c, 21l) exhibited high activity.
2. For *Staphylococcus aureus*, compounds (10c, 19h, 22f, 22g, 22h) didn't show any activity while compounds (6, 10d, 10e, 11d, 12c, 12d, 12e, 13c, 13d, 13e, 14c, 14d, 14e, 15c, 15e, 16d, 16e, 17c, 17e) showed low activity and compounds (5, 9a, 9b, 11c, 11e, 15d, 16c, 17d, 18, 19f, 19g, 20, 21i, 21j, 21k, 21l, 21m) exhibited high activity.

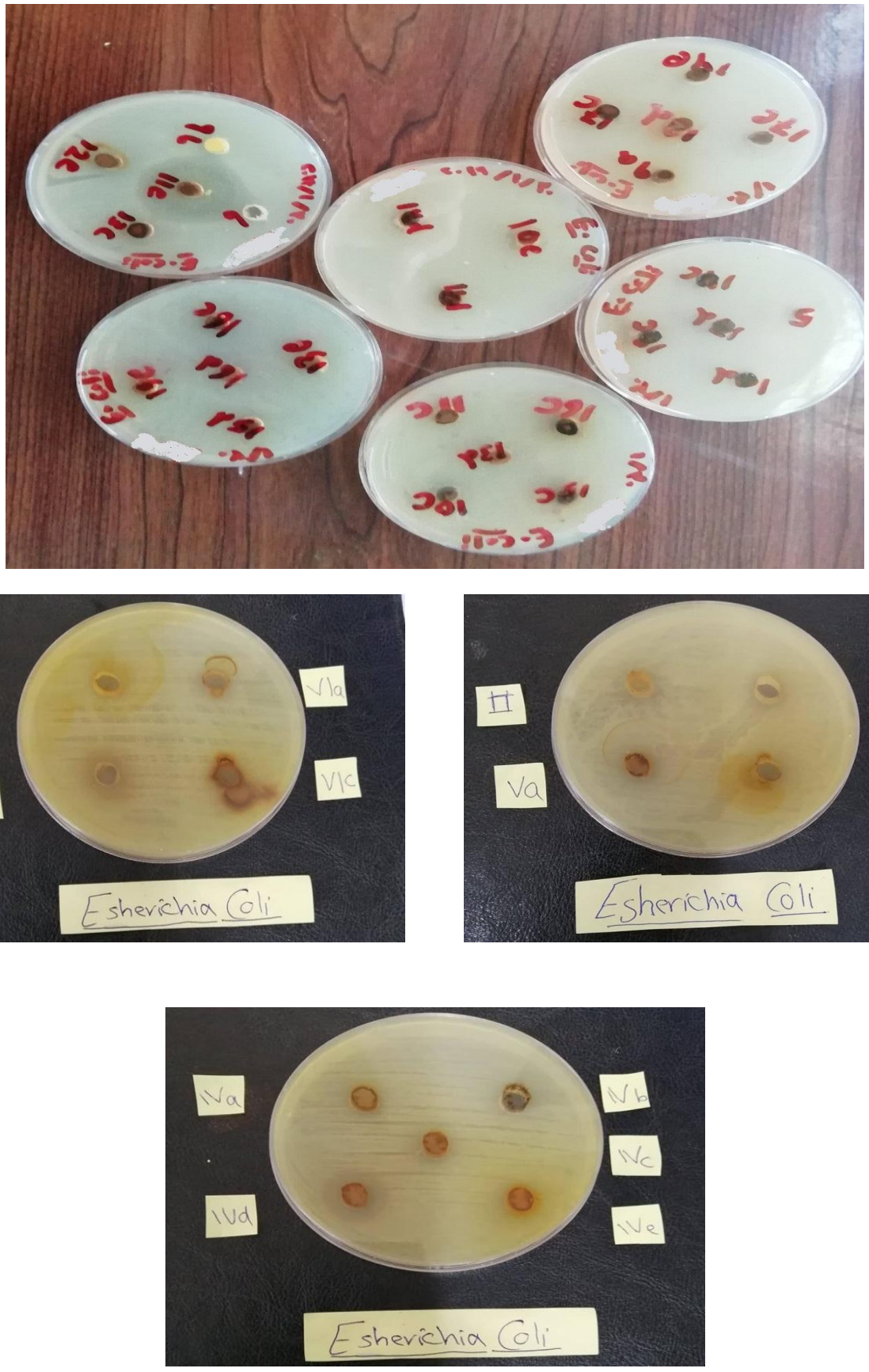
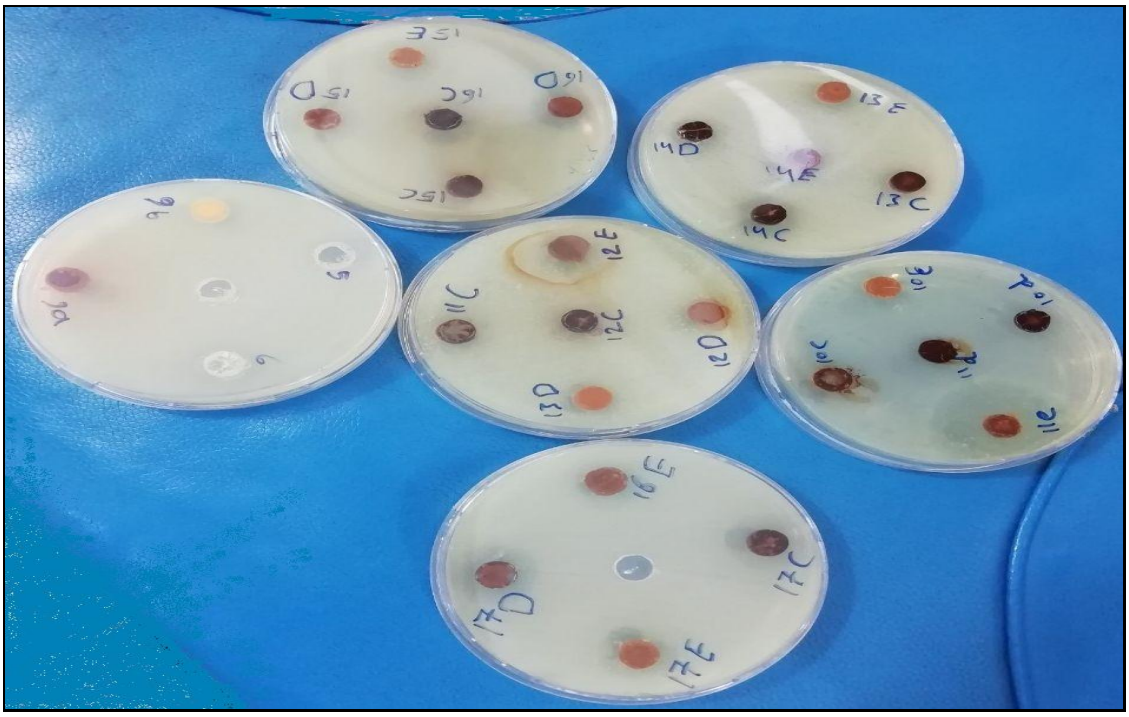
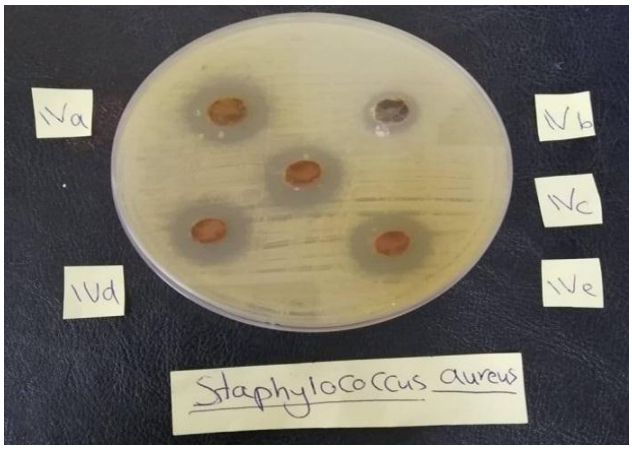


Fig. (3.79): The effect of synthesized compounds on *E. coli*





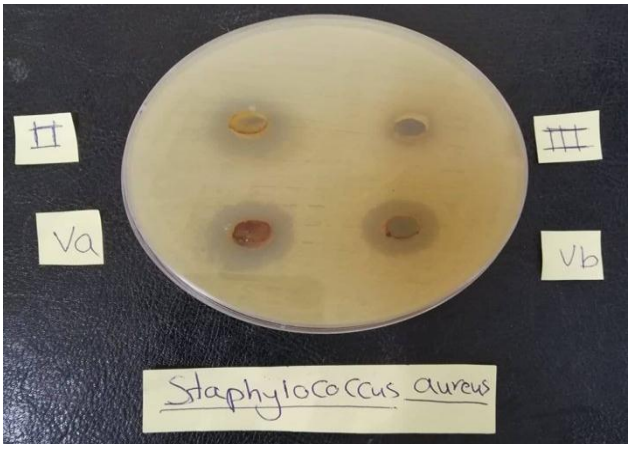
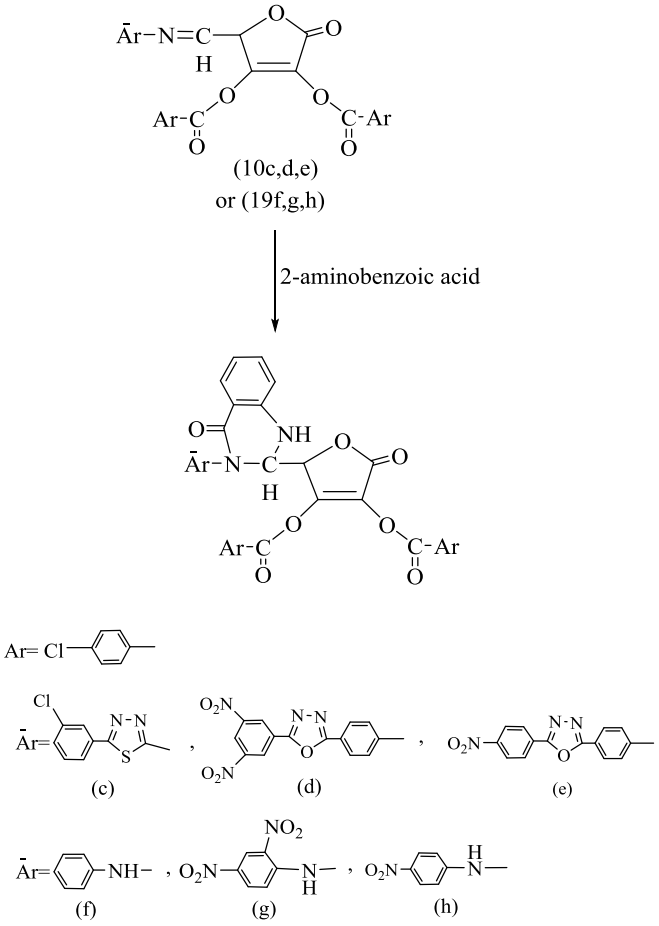


Fig. (3.80): The effect of synthesized compounds on *Staph*. aureus

Suggestion for future work

Because of the highly reactivity of ascorbic acid and their derivatives we describe the synthesis of some new compounds featuring various heterocyclic rings linked with ascorbic acid moiety in order to obtain more biological active compounds such as reaction of Schiff bases (10c, 10d or 10d) and (19f, 19h or 19g) with 2-aminobenzoic acid to afford quinazolin-4-one derivatives and we expected to possess these compounds high biological activity. These derivatives were shown in the following Scheme.



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الخلاصة

L- حامض الأسكوربيك ومشتقاته من المركبات المهمة جدا المستخدمة في المجال البيولوجي. لهذا السبب بعض مركباته تحضر بطرق عديدة.هذه الدراسة تتضمن تحضير مركبات حلقية غير متجانسة خماسية وسباعية مشتقة من L- حامض الاسكوربيك.

هذه الدراسة تتضمن الخطوات الاتية:-

1. يتضمن القسم الاول تحضير الالديهايد من عدة خطوات. الخطوة الاولى هي تحضير الاسيتال (2) الناتج من تفاعل L- حامض الاسكوربيك في الاسيتون الجاف بوجود كلوريد الهيدروجين الجاف. تفاعل المركب (2) مع بارا-كلوروكلوريد البنزويل بوجود البيريدين ليعطي الاستر (3), والذي يذاب في (65%) من حامض الخليك بوسط كحولي ليعطي مركب الكلايكول المقابل (4). مركب الالديهايد (5) يحضر من اكسدة الكلايكول بواسطة بيرايودات الصوديوم بالماء المقطر، مخطط (I).
2. يتضمن القسم الثاني تحضير 2-أمينو-5-(3-كلوروفينيل)-4,3,1-ثادايازول (6) باستخدام ثايوسيميكاربازايد مع 3-كلوروحامض البنزويك بوجود كلوريد الفسفوريل، وتحضير الاسترات (7a,b) من استرة مشتق حامض البنزويك مع الايثانول في وسط حامضي بعد ذلك تحويل الاسترات الى الهايدرازيد (8a,b) باستخدام الهايدرازين المائي. واخيرا الغلق الحلقي للهايدرازيد (8a,b) مع 4-امينو حامض البنزويك بوجود كلوريد الفسفوريل لنحصل على [(2-(5,3-ثنائي نيتروفينيل)-5-(4-أمينوفينيل)-4,3,1-أوكساديازول] (9a) و [2-(4-نيتروفنيل)-5-(4-امينوفينيل)-4,3,1-اوكسادايازول] (9b)، مخطط (I).
3. حضرت قواعد شف (10c), (10d) و(10e) من تفاعل الامينات (6), (9a) أو (9b) مع الالديهايد (5) باستعمال DMF كمذيب مع قطرات من حامض الخليك الثلجي، مخطط (I).
4. حضرت مركبات 5,2-ثنائي هايدروتترازول (11c), (11d) و(11e) من تفاعل الاضافة الحلقية القطبية لقواعد شف (10c), (10d) أو (10e) مع ازايد الصوديوم في مذيب DMF، مخطط (II).
5. حضرت مشتقات 3,1-اوكسازبين c,d,e(14-12) عن طريق تفاعل الاضافة الحلقية لقواعد شف (10c), (10d) أو (10e) مع انهيدريدات مختلفة مثل (الماليك ، الفثاليك أو 3-نيتروفثاليك) انهدريد، مخطط (II).
6. حضرت مشتقات 3,1- دايازبين c,d,e(17-15) من تفاعل كل واحد من مركبات الاوكسازبين (12c-14e) مع 4-ميثوكسي انيلين بوجود المذيب DMF، مخطط (II).

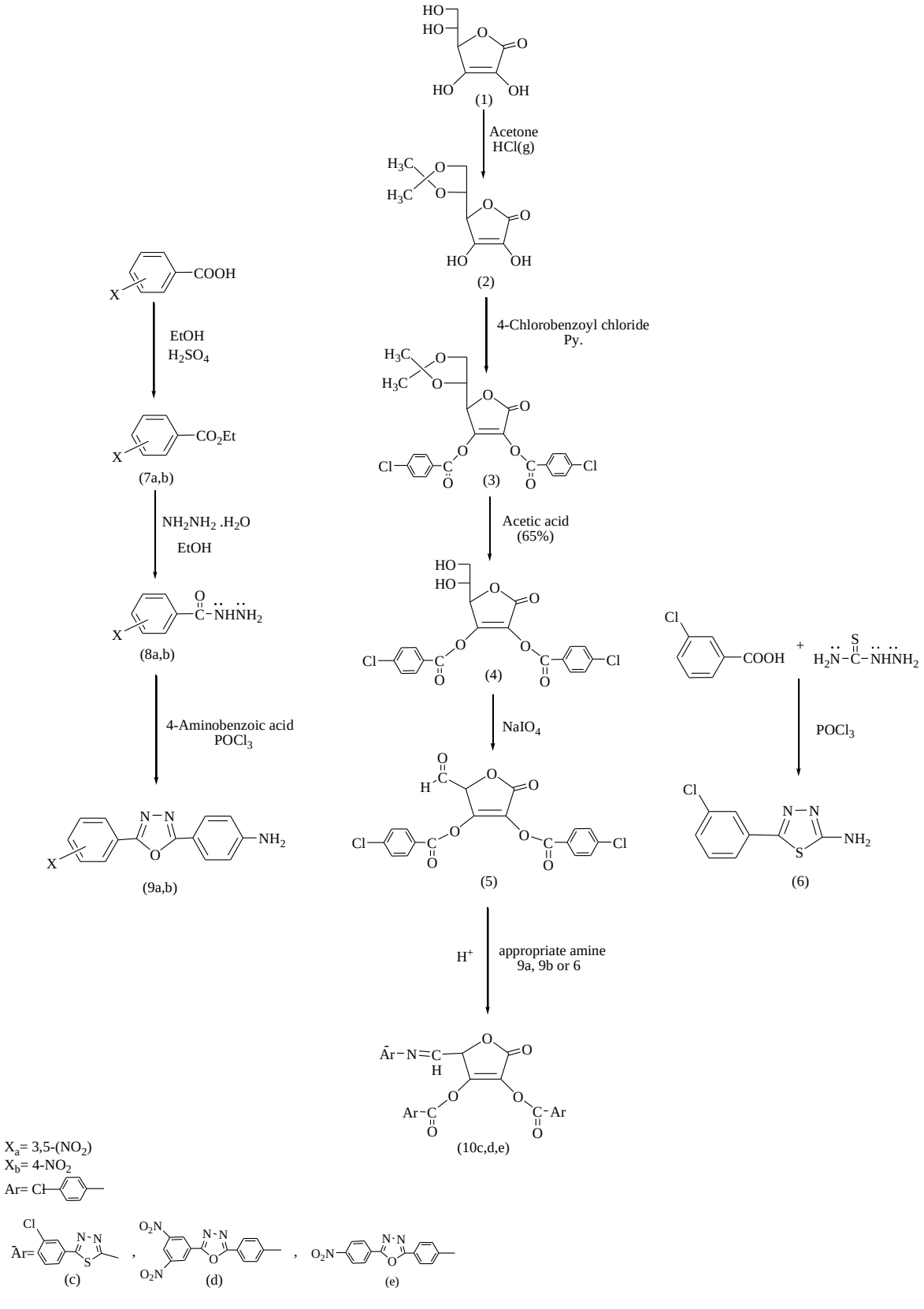
7. حضرت قاعدة شف (18) من تفاعل الالديهايد (5) مع ثايوسيميكاربازيد وقطرتين من حامض الخليك الثلجي في الايثانول المطلق كمذيب، مخطط (III).

8. حضر 3,1-ثايازوليدين-4-اون (20) من تفاعل قاعدة شف (18) مع 2-كلوروحامض الخليك بوجود الايثانول كمذيب، مشتقات 3,1-ثايازوليدين-4-اون (21i-m) (الالكينات) تم تحضيرها بتفاعل المركب (20) مع الديهايدات اروماتية بوجود القاعدة وهي البايبريدين، مخطط (III).

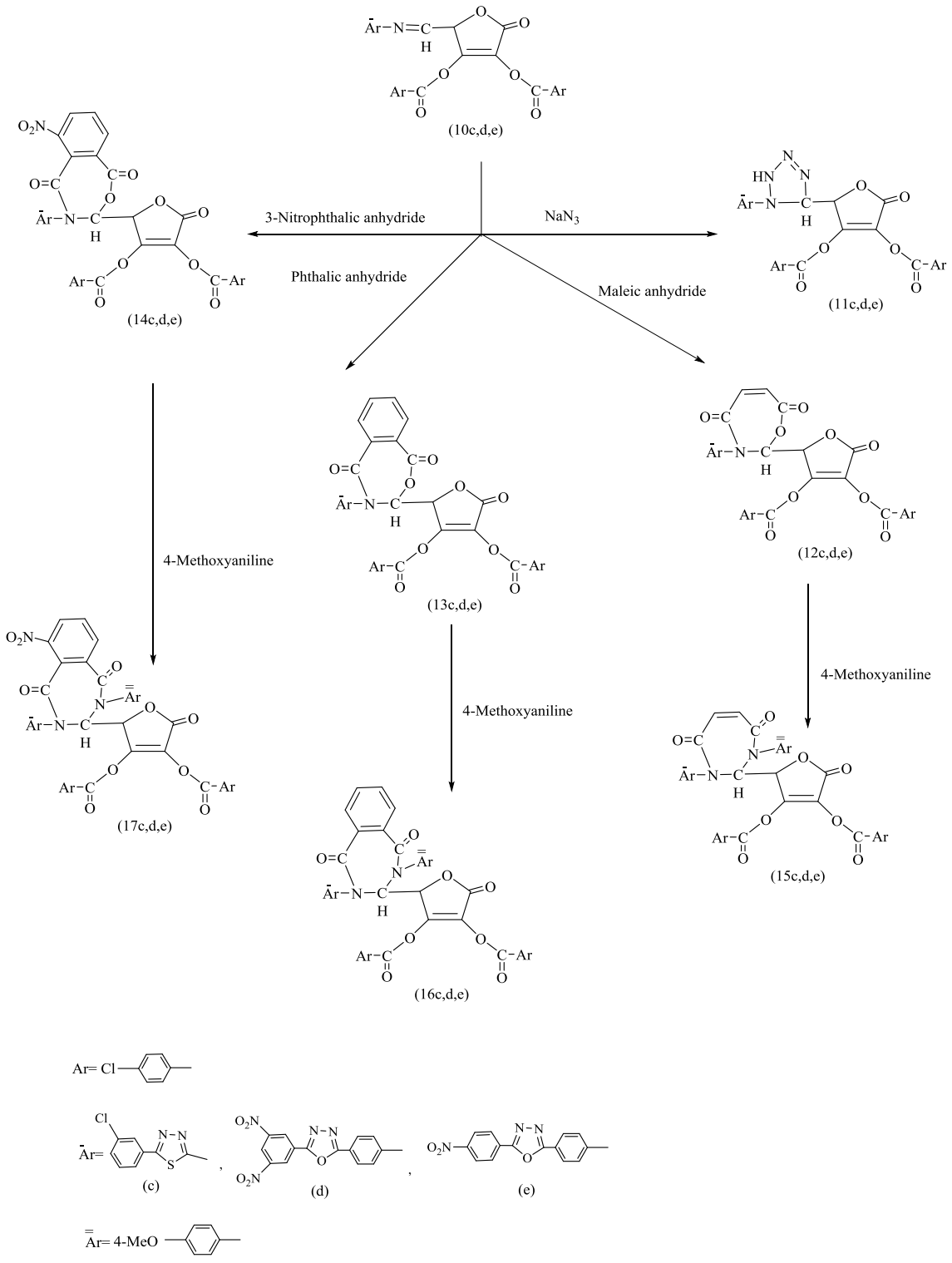
9. حضرت مركبات 5,2-ثنائي هايدروتترازول (22f,g,h) من تفاعل الاضافة الحلقية القطبية لمركبات الهيدرازون (19f، 19g أو 19h) مع ازايد الصوديوم باستعمال المذيب DMF. اما مركبات الهيدرازون (19f,g,h) فحضرت من تفاعل الفنيل هيدرازين اوالفنيل هيدرازين المعوض مع الالديهايد (5)، مخطط (III).

10. المركبات المحضرة شخصت بالطرق الطيفية مثل FTIR و البعض منها بوساطة ^{1}H-NMR ، ^{13}C-NMR ومطيافية الكتلة وتم قياس خواصها الفيزيائية (درجة الانصهار، اللون، الصيغة الجزيئية وحصيلة الناتج).

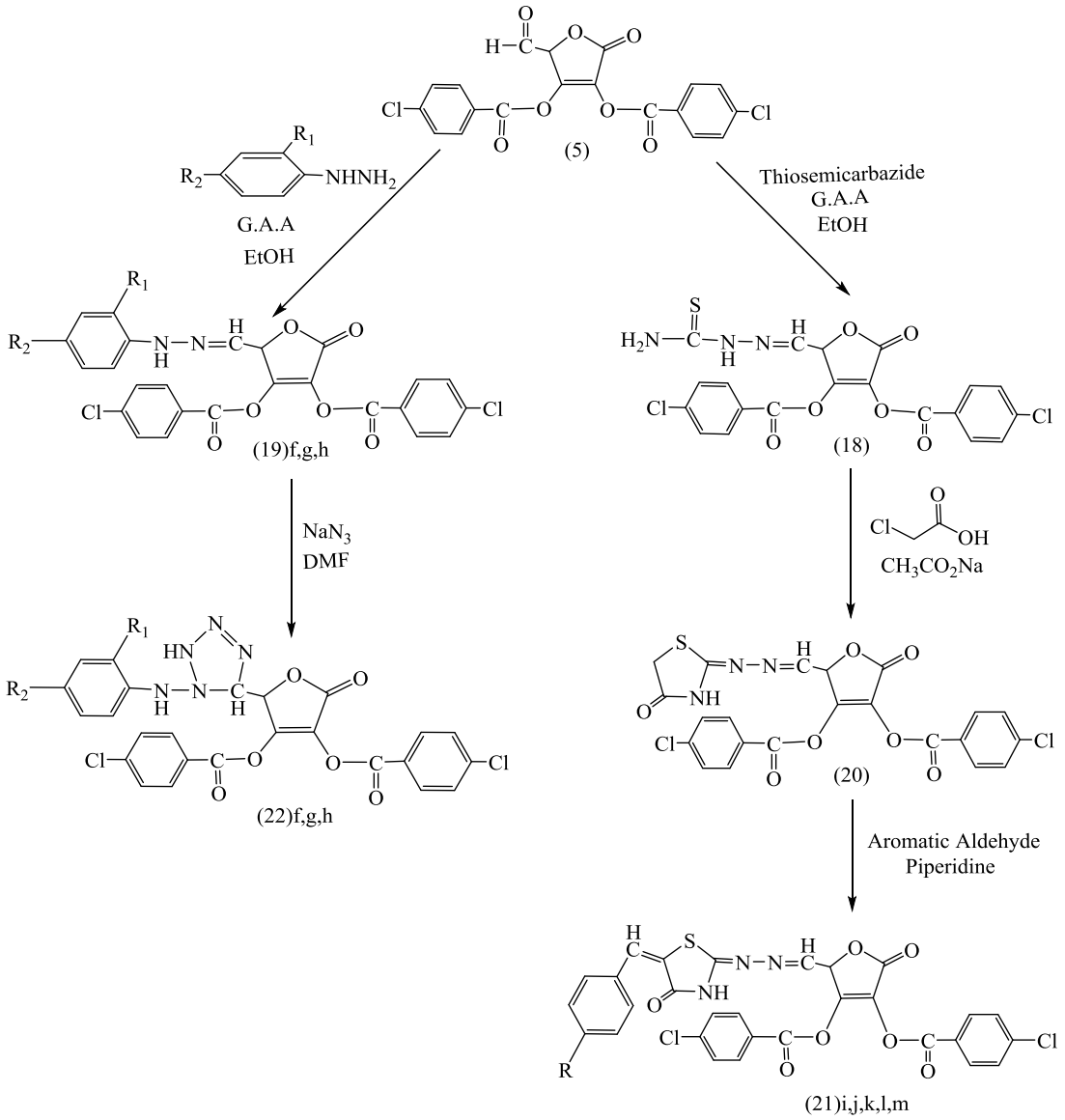
11. تمت دراسة تأثير جميع المركبات المحضرة ضد نوعين من البكتريا المرضية *Echerichia coli* (G-) و*Staphylococcus aureus* (G+).


(1)
Acetone
HCl(g)
(2)
4-Chlorobenzoyl chloride
Py.
(3)
Acetic acid
(65%)
(4)
NaIO4
(5)
H+
appropriate amine
9a, 9b or 6
(10c,d,e)
COOH
EtOH
H2SO4
(7a,b)
NH2NH2 .H2O
EtOH
(8a,b)
4-Aminobenzoic acid
POCl3
(9a,b)
POCl3
(6)
Xa= 3,5-(NO2)
Xb= 4-NO2
Ar= Cl
(c)
(d)
(e)

مخطط (I)


(10c,d,e)
3-Nitrophthalic anhydride
NaN3
Phthalic anhydride
Maleic anhydride
(14c,d,e)
(11c,d,e)
(13c,d,e)
(12c,d,e)
4-Methoxyaniline
4-Methoxyaniline
4-Methoxyaniline
(17c,d,e)
(16c,d,e)
(15c,d,e)
Ar= Cl
(c)
(d)
(e)
4-MeO

مخطط (II)



R= H, CH_3, OCH_3, NO_2, NMe_2
(f): R_1= H, R_2= H
(g): R_1= NO_2, R_2= NO_2
(h): R_1= H, R_2= NO_2

مخطط (III)

جمهورية العراق
وزارة التعليم العالي والبحث العلمي
جامعة بغداد
كلية التربية للعلوم الصرفة / ابن الهيثم
قسم الكيمياء

تحضير, تشخيص وتقدير الفعالية الحيوية للمركبات الحلقية غير المتجانسة الخماسية والسباعية الجديدة المشتقة من L- حامض الاسكوربيك

اطروحة مقدمة إلى
مجلس كلية التربية للعلوم الصرفة - إبن الهيثم -
جامعة بغداد كجزء من متطلبات نيل درجة الدكتوراه
فلسفة في الكيمياء

من قبل
اسراء عبد الزهرة موسى
بكالوريوس علوم في الكيمياء (2004)
ماجستير علوم في الكيمياء (2013)

بإشراف
أ. م. د. رسمية محمود رميز

1441هـ **2019 م**