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Synthesis and characterization of new gallic acid derivatives complimented with antibacterial activity

A Thesis

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in partial fulfillment of the requirements for

the Degree of Master of Science in Chemistry

By

Safa Ammer Yehia

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Supervised By
Assist. Prof. Dr. Nasreen R. Jber

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﴿ بِسْمِ اللّهِ الرَّحْمَنِ الرَّحِيمِ ﴾

إِنَّا فَتَحْنَا لَكَ فَتْحًا مُّبِينًا﴿١﴾لِّيَغْفِرَ لَكَ اللَّه ُمَاتَقَدَّمَ مِن ذَنبِكَ وَمَاتَأَخَّرَ

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Dr.Nasreen R. Jber

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Dr. Mehdi Salih Shihab
Head of the Department of Chemistry
College of Science
Al-Nahrain University

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We the examining committees, certify that we read this thesis and examined the student ***safa ammer yehia*** , in its contents and that, according to our opinion, is accepted as a thesis for the degree of Master of Science in chemistry.

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Professor
Dr. Hadi M. A. Abood
Dean of College of Science
Al- Nahrain University

Dedicated To you …

Safa ammer

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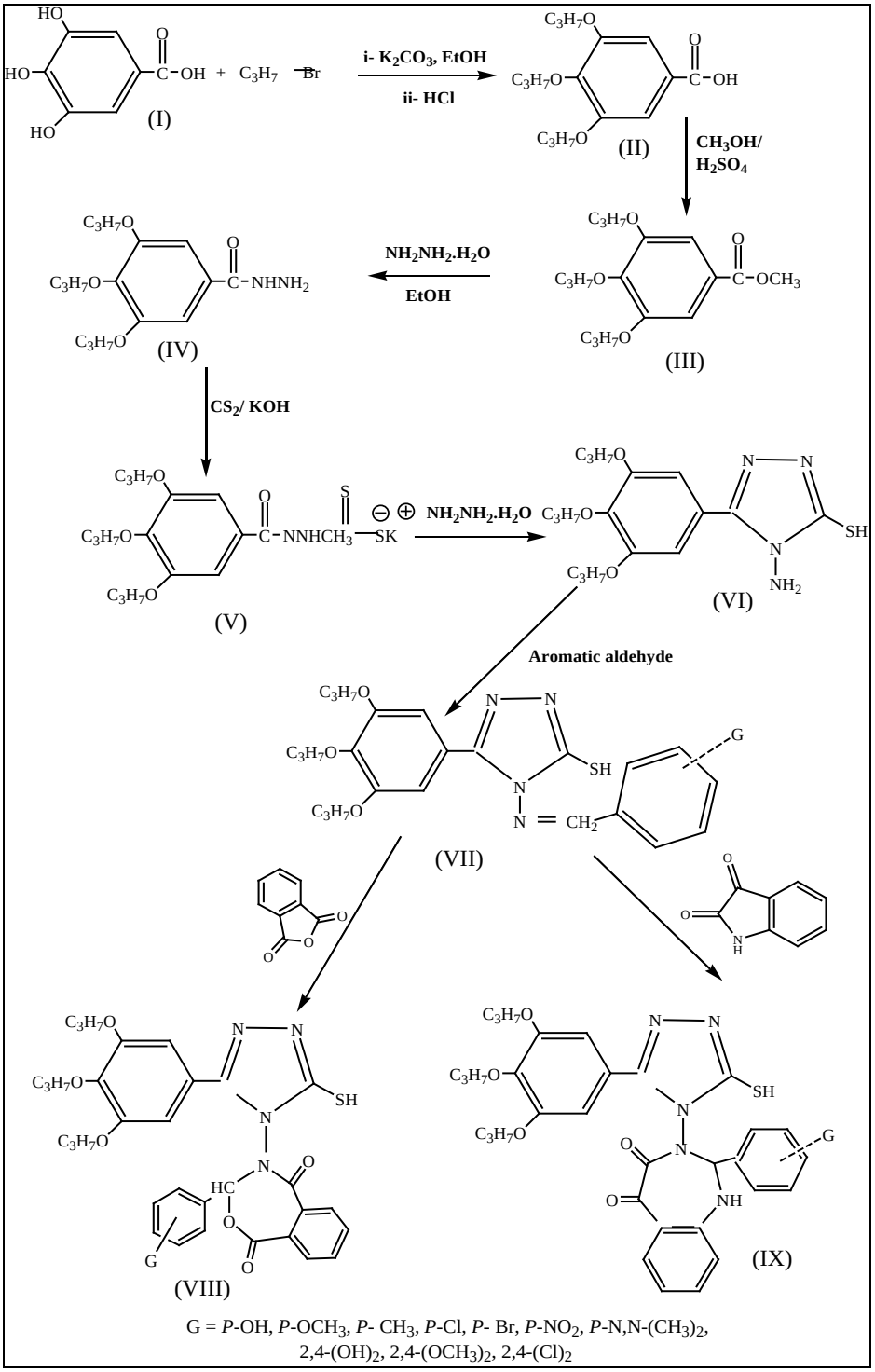
Summary

This work consists of synthesis of new oxazepine and diazepine compounds according to the Schemes shown below.

In order to obtain the target compounds, the following routes were adopted:-

- Preparation of 3,4,5-tripropoxy benzoic acid (II) by the reaction of gallic acid (I) with propylbromide.
- Preparationofmethyl-3,4,5-tripropoxybenzoate(III) via direct esterfication of compound (II) with methanol in presence of sulfuric acid as catalyst.
- Preparation of 3,4,5-tripropoxybenzoic hydrazide (IV) from the reaction of ester compound (III) with hydrazine hydrate.
- The reaction of hydrazide compound (IV) with carbon disulfide in basic media leads to the formation of thio carbazinate salts (V) which undergoes cyclization in excess of hydrazine hydrate to give 3-thio-{5-yl-(3`,4`,5`-tripropoxyphenyl)}-4-amino-1,2,4-triazole (VI).
- Shiff`s bases $(VII)_{\mathbf{a-j}}$ were synthesized through the condensation reaction of 3-thio-{5-yl-(3`,4`,5`-tripropoxyphenyl)}-4-amino-1,2,4-triazole (VI) with different aromatic aldehydes in absolute ethanol and in presence of few drops of glacial acetic acid.
- 1,3-Oxazepine-4,7-dione derivative compounds $(VIII)_{\mathbf{a-j}}$ were synthesized by the reaction of Schiff`sbase compounds $(VII)_{\mathbf{a-j}}$ with phthalic anhydride in dry benzene.
- [1,3] diazepine $(IX)_{\mathbf{a-j}}$ was prepared by the reaction of schiff`s bases $(VII)_{\mathbf{a-j}}$ with isatin in ethanol.



Synthetic route for synthesized compounds.

All the synthesized compounds were characterized using FTIR and CHNS-O analysis and some of them by ^{1}HNMR.

Some of the synthesized compounds were assayed for their antibacterial activity against four representative Gram-positive bacteria *viz*. ***(Staphylococcus aureus***, ***Bacillus subtilis)*** and Gram-negative bacteria *viz*. ***(Pseudomonas aeruginosa***, ***Enterobacter iaceae***) by disc diffusion method. The investigation of antibacterial screening data reveal that almost all the compounds **(VIII)$_{a,b,e,f,j}$** and **(IX)$_{a,b,e,f,j}$** are active and showing moderate to good antibacterial activity with concentrations (10, 25, 50, 100) μg/ml.

Abbreviations

DMSO	Dimethyl sulfoxide.
HATU	1H Benzotriazole Tetramethyl uoronium.
EIPEA	Ethyl isopropyl ethyl amine.
TFA	Tetrahydrofuran.
NEt_3	Triethyl amine
PTSA	Paratulenesulfonic acid
FTIR	Fourier Transform Infrared Spectrophotometer.
1HNMR	Proton Nuclear MagneticResonance Spectrometer.
TLC	Thin Layer Chromatography.

CHAPTER ONE

INTRODUCTION

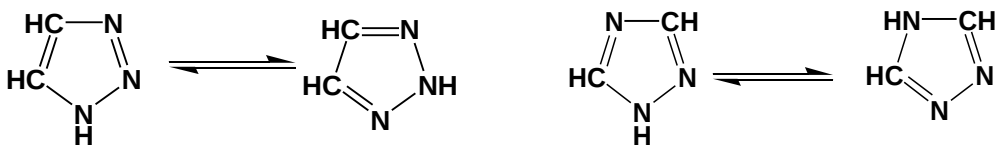
INTRODUCTION

1.1 Heterocyclic compounds

Heterocyclic compounds are cyclic compounds containing at least one atom of carbon and at least one element other than carbon. A ring with only heteroatom is called homocyclic compound and heterocycles are the counterparts of monocyclic compounds. Thus incorporation of oxygen, nitrogen, sulphur or an atom of a related element into an organic ring structure in place of a carbon atom gives rise to a heterocyclic compounds[(1).] In the recent years, the incidence of fungal and bacterial infections has increased dramatically. The widespread use of antifungal and antibacterial drugs in resistance to drug therapy against fungal and antibacterial infections which led to serious health hazards[(2).] It is well-known that heterocyclic compounds having azole nucleus are important pharmacophore that appear extensively in various types of pharmaceutical agents, widely implicated in biochemical processes and display diversity of pharmacological activities. These heterocyclic compounds form a major part of organic chemistry; they are widely distributed in nature and play a vital role in metabolism of living cells. For Their practical applications range from extensive clinical use to fields as diverse as medicine, agriculture, photochemistry, biocidal formulation and polymer science[(3).]

1.2 Triazoles

Triazoles are five memberd heterocyclic compounds containing three nitrogen and two carbon atoms. There are two types of combination for the atoms the 1,2,3-triazoles or vic- (vicinal) triazoles(I) and the 1,2,4-triazoles (II) known as sym-(symmetrical)[(4)] triazoles.



I II

Figure 1.1: Types of 1,2,3- and 1,2,4 Triazoles

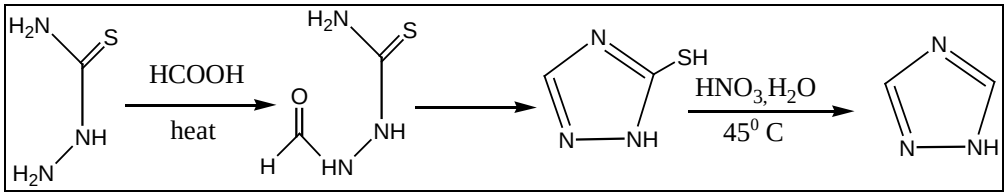
The name of triazole was first given to the carbon-nitrogen ring system $C_2N_3H_3$ by ***Potts***, who described it's derivatives early as 1885.Triazole ring is planar with 6π-electron aromatic system with distortion of the π-system induced by the annular nitrogen atoms[5].

1,2,4-Triazole derivatives usually exist in solid forms at room temperature. 3,4,5-substituted 1,2,4-triazole derivatives melt with thermolysis at high temperature when heated at 316 C°for 30 minutes"**[6]**. "They have color ranging form white to dark brown. They mostly soluble in polar solvents like ethanol, chloroform, dimethyl sulfoxide and dimethyl formamide, but insoluble in non-polar solvents like ethers, the solubility in non-polar solvents can be increased by substitution on the nitrogen atom. 1,2,4-triazole are soluble in acidic and basic media due to salt formation by protonation and deprotonation, respectively"**[7]**. Many triazole compounds possess good fungicidal and plant growth regulating activity [8]. The 1,2,4-triazole is an ubiquitous feature of many pharmaceutical and agrochemical products. The substituted 1,2,4-triazole nucleas is particularly common, and can be found in marketed drugs such as fluconozole, terconazole, and rizatriptan alperazolam[9]. As drugs, triazole compounds are highly efficient, low poisonous and inward –absorbent. The studies on triazole derivatives are mainly concentrated on compounds with the triazole as the only active group, the reports of triazole compounds that contain both triazole group and other active group in the single molecule has rarely been found [10].

1.3.1 Synthesis of 1,2,4-triazole and its derivatives

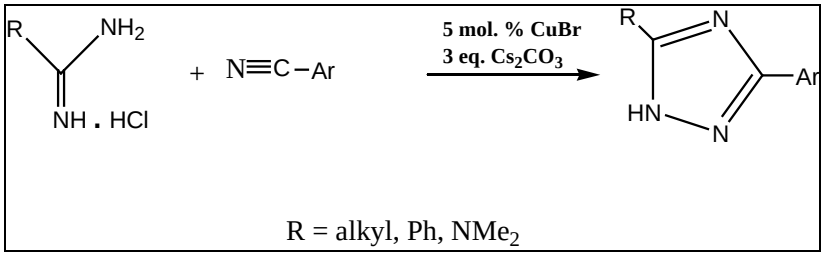
Severl methods have been used for the synthesis of 1,2,4-triazole. C. Ainsworth and co-workers[11] reported synthesis of 1, 2, 4-triazole nucleus by the reaction of thiosemicarbazide with formic acid forming 1-Formyl-3-thiosemicarbazide as an intermediate. The reaction of 1-Formyl-3-thiosemicarbazide with aqueous sodium hydroxide and hydrochloric acid yield

1,2,4-Triazole-3(5)- thiol which on treatment with a mixture of water, concentrated nitric acid, and sodium nitrite finally produce 1,2,4-triazole nucleus, as shown in scheme 1.1.



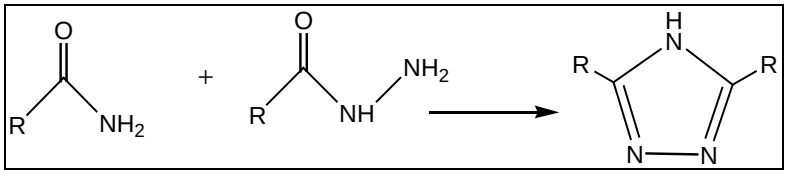
Scheme 1.1: Synthesis of 1, 2, 4-triazole nucleus by the reaction of thiosemicarbazide with formic acid

Ueda, Nagasawa[12] synthesized 1,2,4-triazole derivatives by treatment of substituted amidine and benzonitrile in presence of copper-catalyst under an atmosphere of air by sequential N-C and N-N bond-forming oxidative coupling reactions.



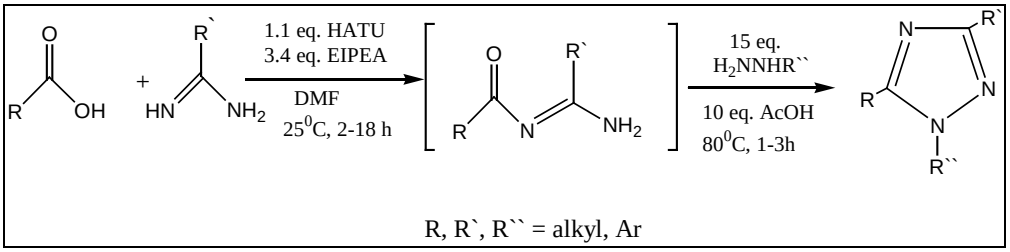
Scheme 1.2: Synthesized 1,2,4-triazole derivatives by treatment of substituted amidine and benzonitrile in presence of copper-catalyst

Pellizzar and co-workers[13] synthesis of substituted 1, 2, 4-triazole by the reaction of an amide and a hydrazide.



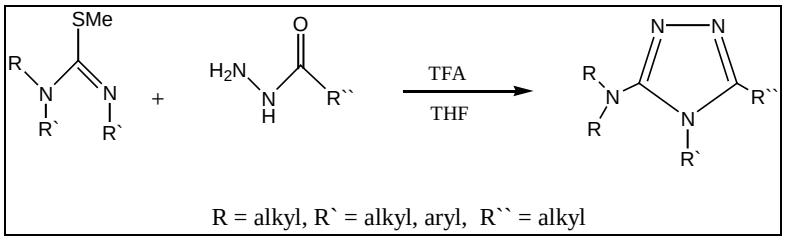
Scheme 1.3: Synthesis of substituted 1, 2, 4-triazole by the reaction of an amide and a hydrazide.

Castanedo, and co-workers[14] , provided a highly regioselective one-pot process which provides rapid access to highly diverse 1,3,5-trisubstituted 1,2,4-triazoles from reaction of carboxylic acids and primary amidines.



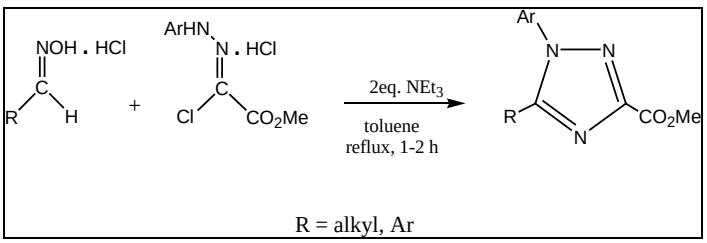
Scheme 1.4: Synthesis 1,2,4-triazoles from reaction of carboxylic acids and primary amidines.

Batchelor and co-workers[15] synthesis of 3-N, N-Dialkylamino- 1, 2, 4-triazole from S-methylisothioureas and acyl hydrazides in presence of trifluoroacetaldehyde and tetrahydrofuran.



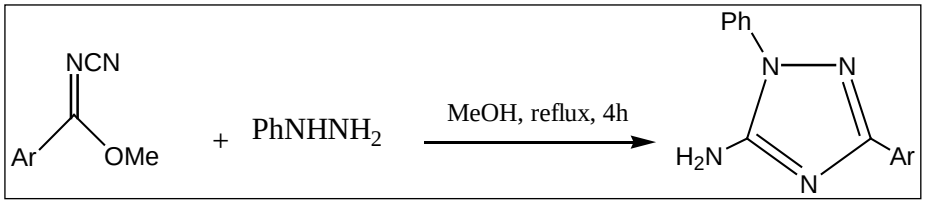
Scheme 1.5: Synthesis of 3-N, N-Dialkylamino- 1, 2, 4-triazole from S-methylisothioureas and acyl hydrazides

Wang and co-workers[16] carried out an effective 1,3-dipolar cycloaddition for the synthesis of 1,3,5-trisubstituted 1,2,4-triazole derivatives by reaction of oximes with hydrazonoyl hydrochlorides using triethylamine as a base gave the desired 1,3,5-trisubstituted 1,2,4-triazolesin good yields.



Scheme 1.6: Synthesis of 1,3,5-trisubstituted 1,2,4-triazole derivatives by reaction of oximes with hydrazonoyl hydrochlorides

P. Yin and co-workers[17] synthesized 1, 2, 4-triazole derivatives by the reaction of substituted methyl N-cyanoarylimidate and phenylhydrazine.



Scheme 1.7: Synthesized 1, 2, 4-triazole derivatives by the reaction of substituted methyl N-cyanoarylimidate and phenylhydrazine.

1.3.2 Biological importance of 1,2,4-Triazoles derivatives

1,2,4-Traizole moiety is of great importance to chemists as well as biologist as it is chemically useful molecules having diverse biological activities. Triazole, a heterocyclic nucleus has attracted a wide attention of the medicinal chemist in search for the new therapeutic molecules. Out of its two possible isomers, 1,2,4- triazole is which posses almost all types of biological activities. Some of the drugs which are having Triazole as core molecule are given below. several 1,2,4-Traizole containing compounds are used as drugs for instance Fluconazole is used as an antimicrobial drug, while Vorozole**,**Letrozole and Anastrozoleare used as non steroidal drugs used for the treatment of cancer. Loreclezole is used as an antifungal agent[18].

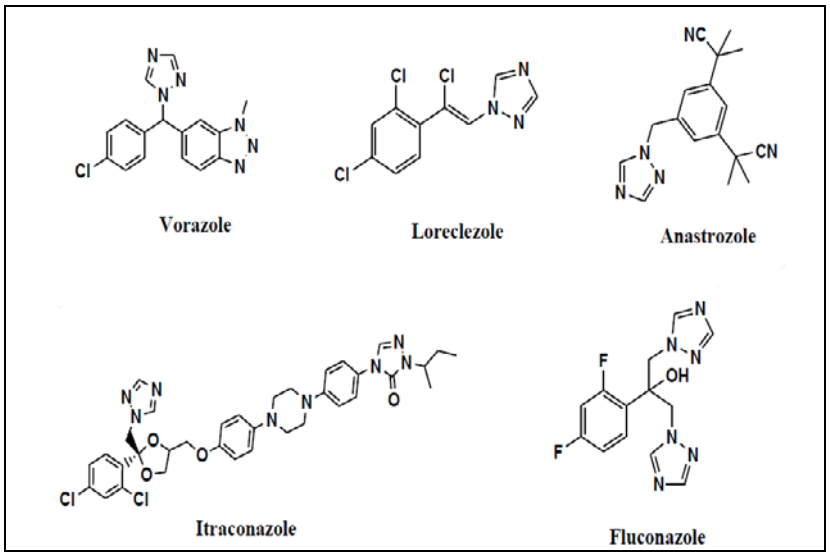
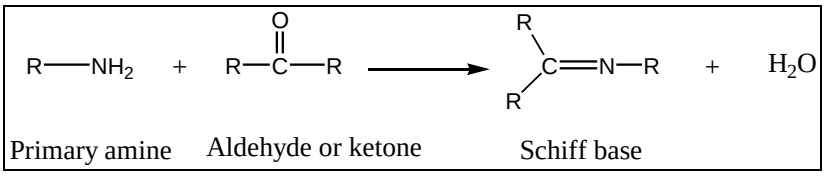


Figure 1.2: Drugs containing 1,2,4-Traizole moiety.

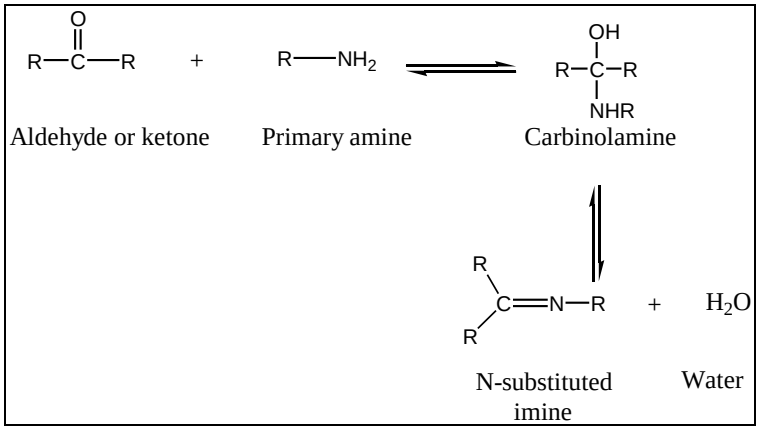
1.4 Schiff bases

A Schiff base is a nitrogen analog of an aldehyde or ketone in which the C=O group is replaced by C=N-R group. It is usually formed by condensation of an aldehyde or ketone with a primary amine according to the following scheme:



Scheme 1.8: General equation for synthesis of Schiff bases

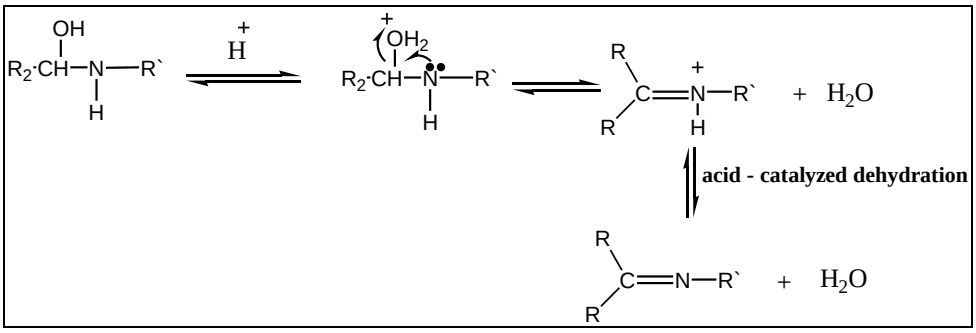
Where R, may be an alkyl or an aryl group. Schiff bases that contain aryl substituents are substantially more stable and more readily synthesized, while those which contain alkyl substituents are relatively unstable. Schiff bases of aliphatic aldehydes are relatively unstable and readily polymerizable[19,20] while those of aromatic aldehydes having effective conjugation are more stable[21]. The formation of a Schiff base from an aldehydes or ketones is a reversible reaction and generally takes place under acid or base catalysis, or upon heating.



Scheme 1.9: Reaction of aldehyde or ketone with amine to form Schiff base.

The formation is generally driven to the completion by separation of the product or removal of water, or both. Many Schiff bases can be hydrolyzed back to their aldehydes or ketones and amines by aqueous acid or base.

The mechanism of Schiff base formation is another variation on the theme of neucleophilic addition to the carbonyl group. In this case, the neucleophile is the amine. In the first part of the mechanism, the amine reacts with the aldehyde or ketone to give an unstable addition compound called carbinolamine.The carbinolamine loses water by either acid or base catalyzed pathways. Since the carbinolamine is an alcohol, it undergoes acid catalyzed dehydration[22].



Scheme 1.10: Mechanism of synthesis of Schiff base.

1.4.1 Reactions of Schiff`s Bases

Schiff`s bases undergo addition reactions of azomethine, the reagents add to polarized double bond (-N=C),) therefore, nucleophilic reagents attack the carbon atom of the azomethine linkage[23]**:**

1.Alkyl halide

2. Carboxylic acid chloride

3.Grignared Reagents

4.Hydrogenation

5.Maleic anhydride , succinic anhydride

1.4.2 Cycloaddition Reactions of Schiff`s Bases

For several years, the Diels-Alder reactionwas the only widely useful example of the so-called cycloaddition reactions. The extensive generalization by Huosgen and his schoolof the concept of 1,3-dipolar cycloadditions, first recognized by Smith, has opened new avenues for investigations[24]. The dimerization of olefins, as well as the addition of carbenes and nitrenes to unsaturated centers has extended the seriesto include three-,five and six-membered ring systems. Huosgen ,Grashey and Sauer[25] have reviewed cycloaddition reactions of alkenes.

1.5 1,3 Oxazepine

Oxazepine belongs taking non-homologus structure which has 7-membered that contains 2-non-homologous atoms (oxygen and nitrogen) and structure formula compounds[26].

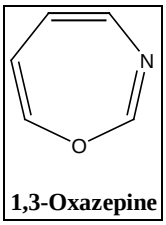
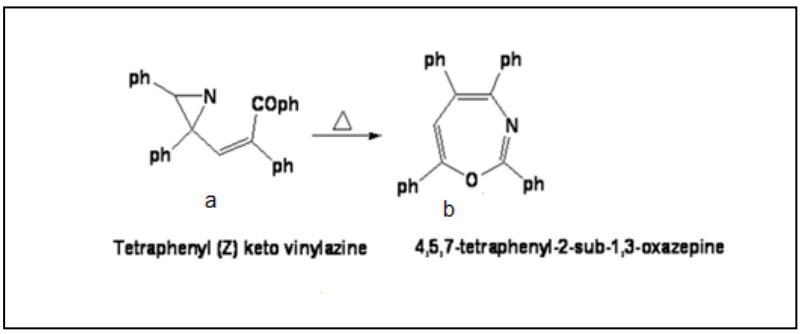
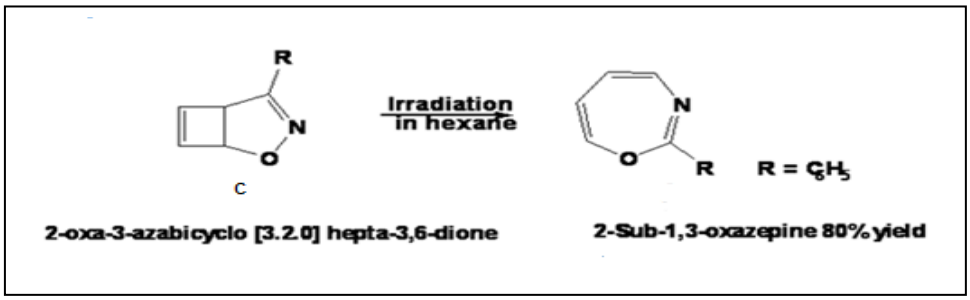


Figure 1.3: 1,3-oxazepine

Le Roux et.al.[27],synthesized oxazepine in 90% **(b)** through heating of **(a)** in 100° C**.**

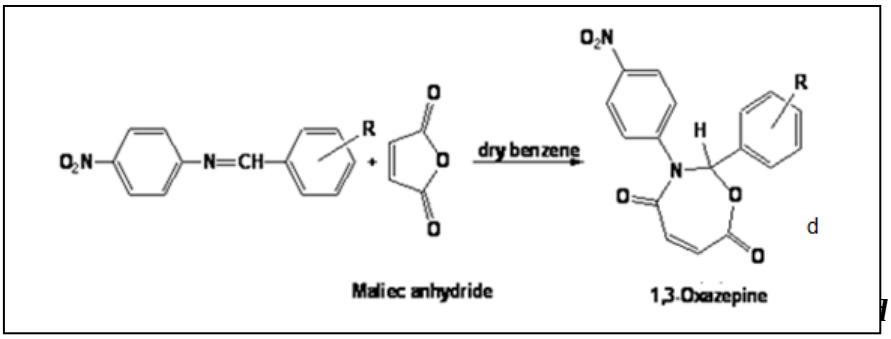


kumagai et al.,[28]**,**synthesized oxazepines through photochemical reaction of **(c).**

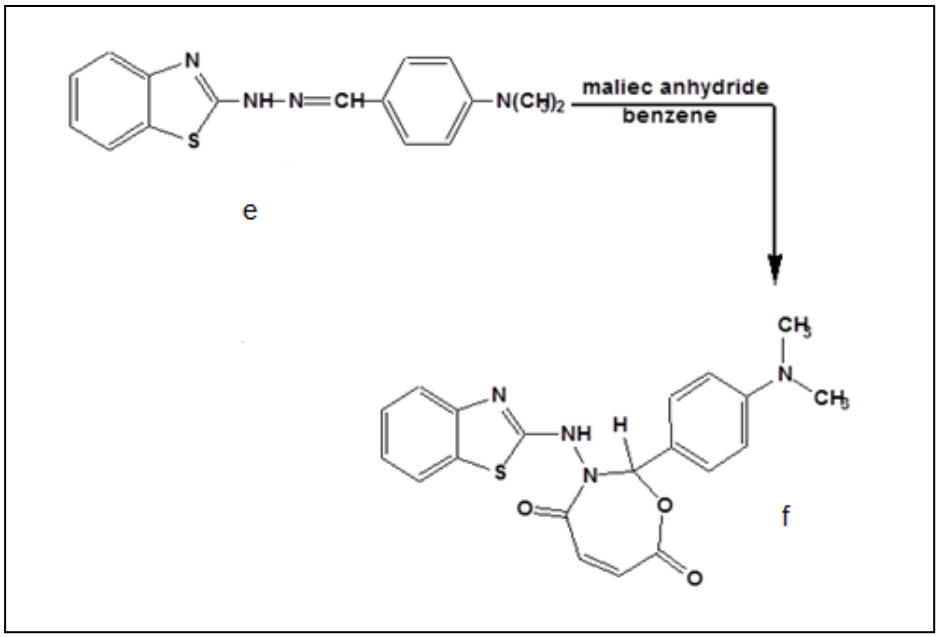


Scheme 1.12: Synthesized oxazepine by kumagai et al.

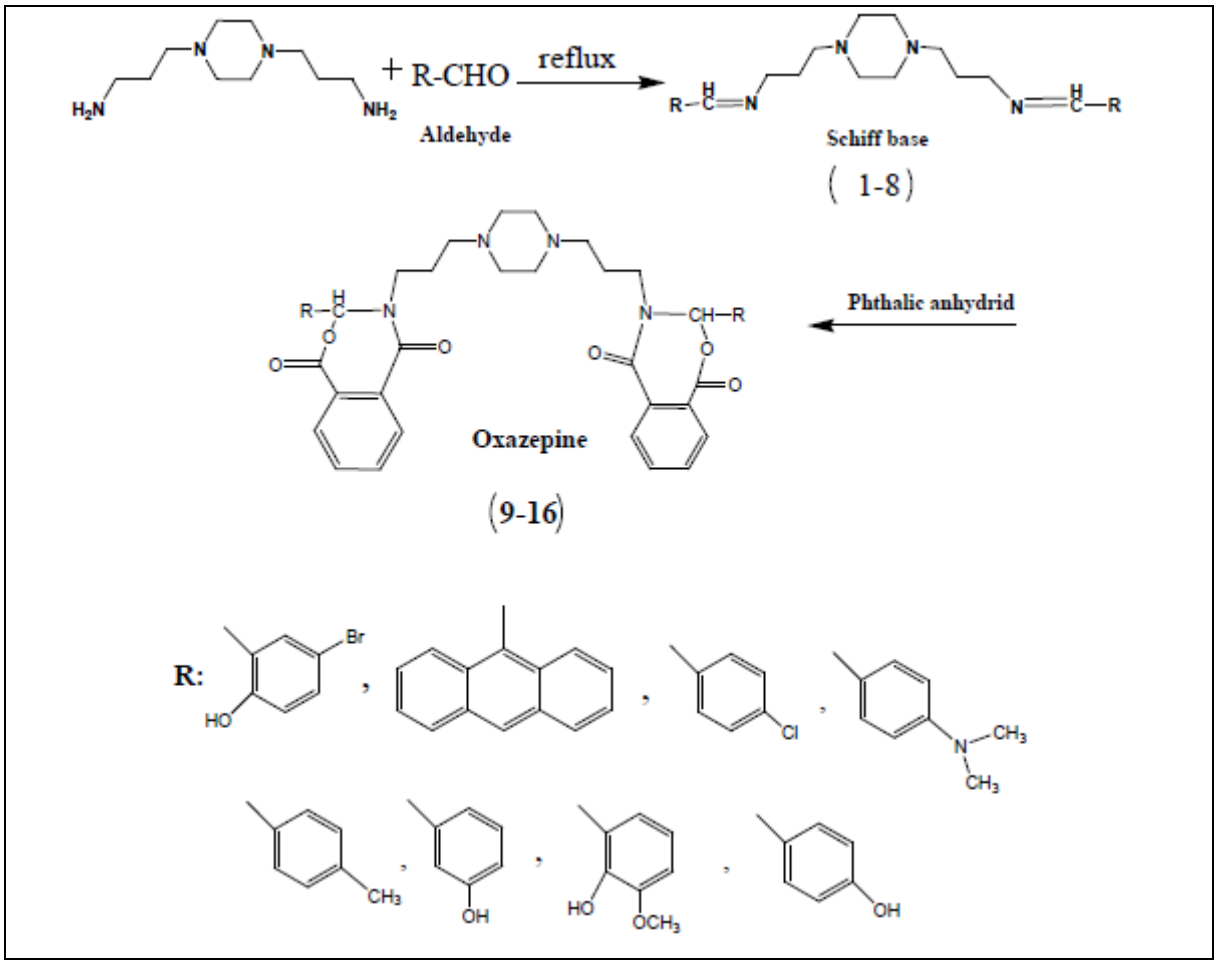
Hussein and Obaid[29]prepared oxazepindion**(d)** from the reaction of Schiff's bases with maleic or phthalic anhydride in dry benzene**.**



AL-Juburi[30], prepared 2-[(2′-(4′- (dimethylamino) phenyl)-4,7-dione-2,2-dihydro-1,3-oxazepine-3′(2H)] benzothiazol hydrazine **(f)** from the reaction of 2-(4-dimethyl amino) benzylidene) hydrazine benzothiazole**(e)** and maleic anhydride**.**

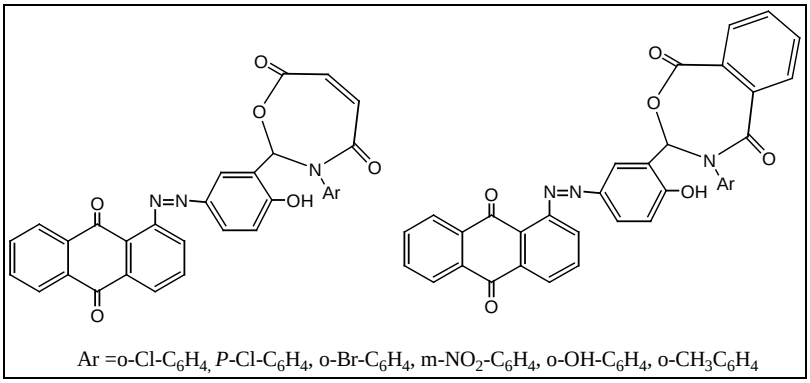


Hamak and Eissa[31] synthesizesd a series of Schiff base and their derivative (oxazepine), 1,4-Bis (3- aminopropyl)-piperazine was condensed with various aromatic aldehyde in ethanol in the presence of acetic acid as catalyst to yield the Schiff base(1-8). These Schiff's bases on treatment with phthalic anhydride gave substituted oxazepine(9-16).



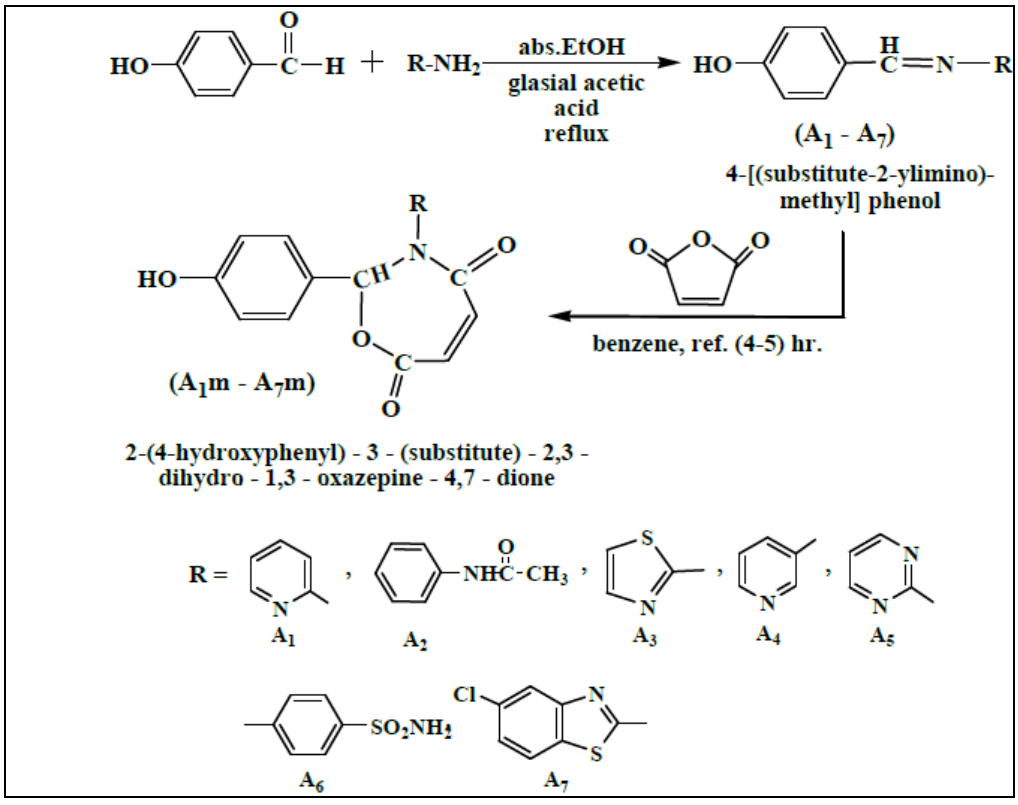
Scheme 1.15: Synthesized oxazepine by Hamak and Eissa

Khan et al.[32] design of new derivatives for anthraquinone azo compounds bearing 1,3-oxazepine rings with different saromatic moieties.



Scheme 1.16: Synthesized oxazepine by Khan et al.

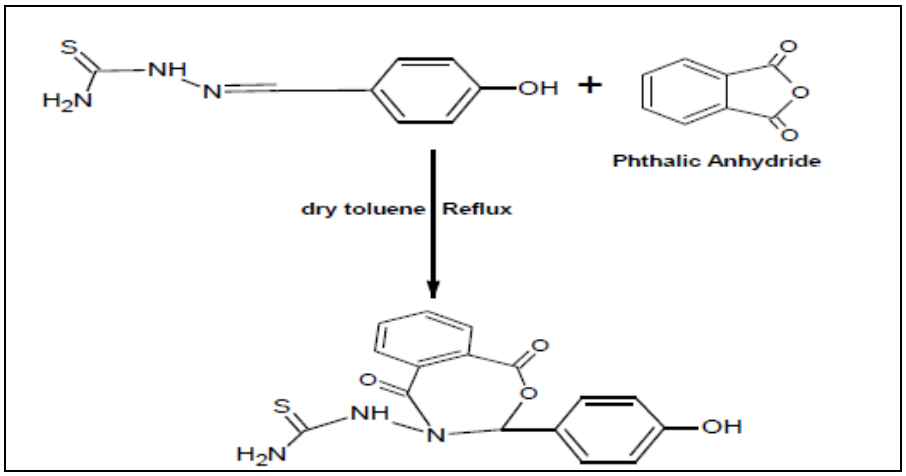
Abdul – Wahid et al. [33] synthesized a series of 1, 3-oxazepine derivatives throughout two steps. First step synthesis of imines derivatives (A1-A7) via the condensation reaction of 4-hydroxy benzaldehyde with different substituted amines by using catalytic amount of glacial acetic acid, while the second step involves reactions of the prepared imines (A1-A7) via maleic anhydride by [2+5] cycloaddition in dry benzene and refluxing it to produce 1, 3 - oxazepine - 4, 7 - dione derivatives (A1m-A7m) respectively.



Scheme 1.17: Synthesized oxazepine by Abdul – Wahid et al.

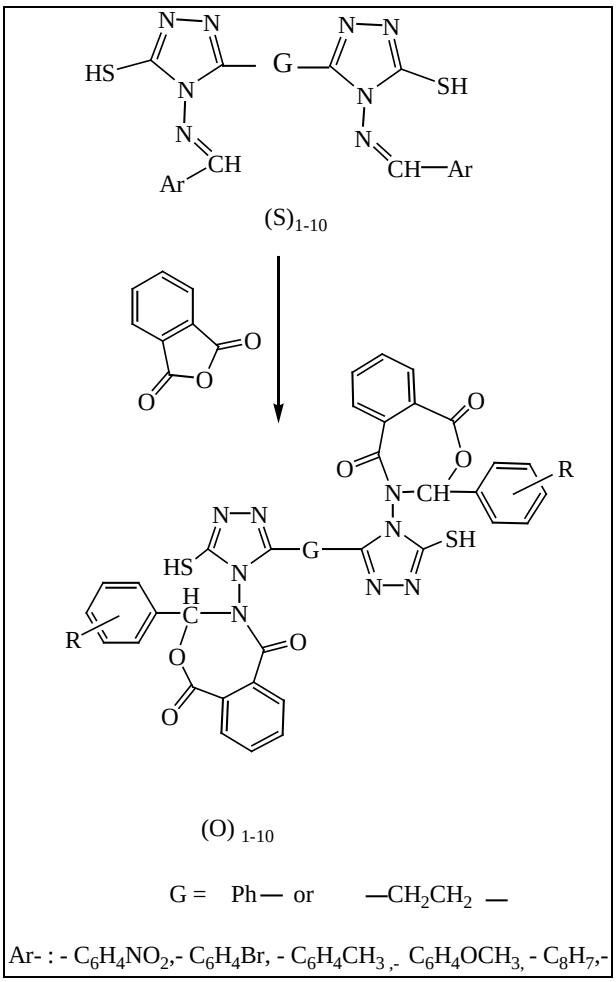
Abdulridha[34] synthesized a Schiff base and its derivative (oxazepine) by the reaction between thio-semicarbazide and aromatic aldehyde 4-hydroxybenzaldehyde in ethanol in the presence of acetic acids to yield the

Schiff base. This Schiff base on treatment with phthalic anhydride to give seven-member heterocyclic ring called oxazepine. Oxazepineas di-dentate ligand treated with hydrated metal chlorides CuCl2 and FeCl2 in the presence of ethanol as solvent to yield tetrahedral complexes.



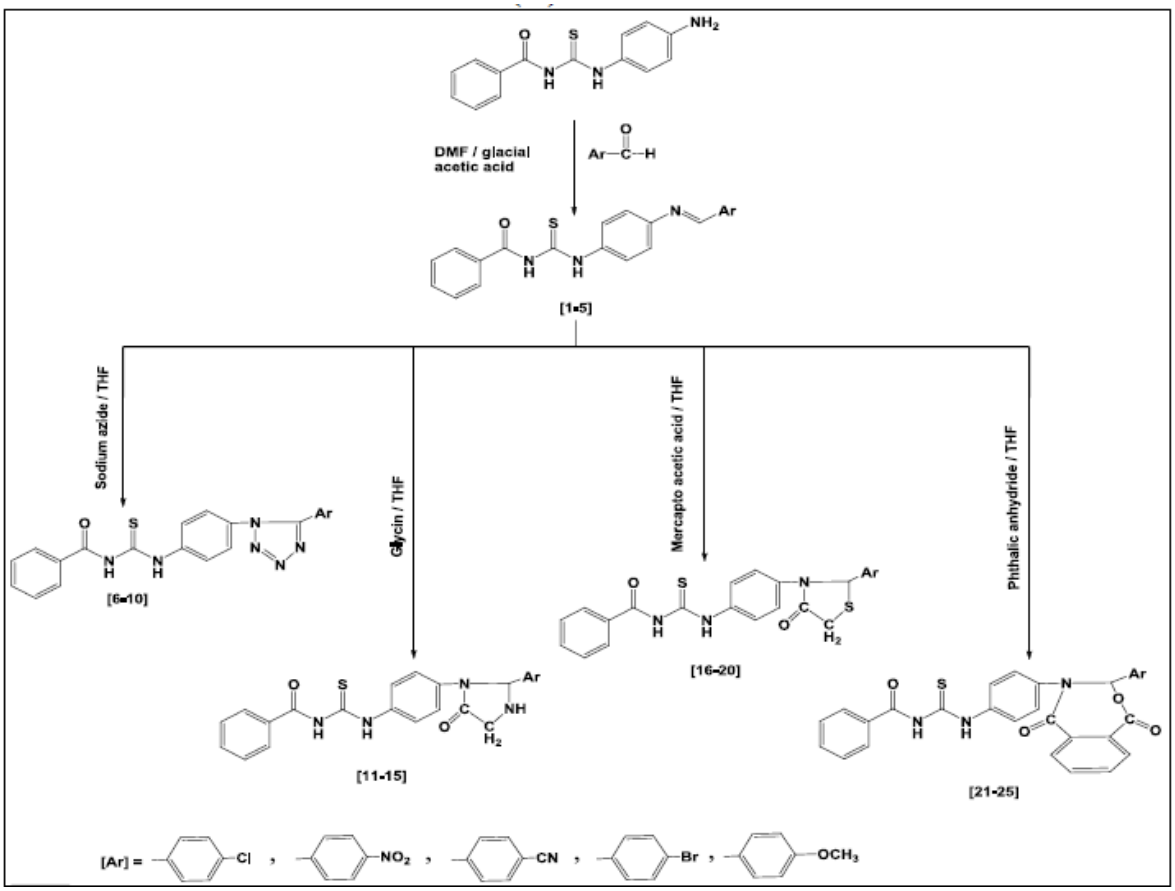
Scheme 1.18: Synthesized oxazepine by Abdulridha

Younus and Jber[35] synthesized new derivatives of 4-amino-3-mercapto-1,2,4-triazol containing 1,3-oxazepine ring by reaction of new synthesis compounds containing imine group (S)1-10 with phthalic anhydride, in dry benzene to give compounds (O)1-10.



Scheme 1.19: Synthesized oxazepine by Younus and Jber

Al-Sultani[36] synthesized some of new tetrazole, imidazolinone, thiazolidinone, and oxazepine derivatives. The first step includes formation Schiff bases (1-5) from condensation N-[(4-aminophenyl) carbamothioyl] benzamide with different aromatic aldehydein the presence of glacial acetic acid in DMF as a solvent. Four route with different reagents used for the cyclization of the prepared Schiff bases by reagent (sodium azide, 2-amino acetic acid, 2-mercapto acetic acid and phthalic anhydride) to form tetrazole (6-10), imidazolinone (11-15), Thiazolidinone (16-20), oxazepine(21-25) derivatives respectively.



Scheme 1.20: Synthesized oxazepine by Al-Sultani

1.6 Diazepine compounds:

Diazepines are seven membered heterocycles consisting of two nitrogen atoms. Their name and activities change depending on position of nitrogen atoms. For instance, they are named as 1,2- diazepine, 1,3-diazepine or 1,4-diazepine.

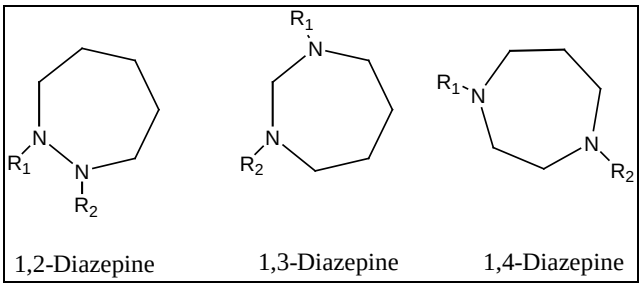


Figure 1.4: Diazepine compounds

The benzodiazepines are consisting of benzene ring fused with the diazepine ring to give the three analogous[37] . The most common, benzodiazepine is a heterocyclic compound where benzene and diazepine rings are fused. There are different isomers depending on the position of nitrogen atoms. Benzodiazepines are widely used in clinics and for medicinal purposes[38]. So these molecules are very popular since they are used as drugs.[39]

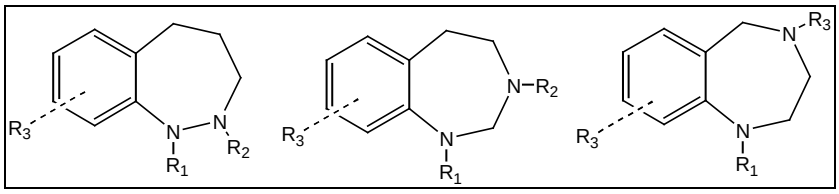
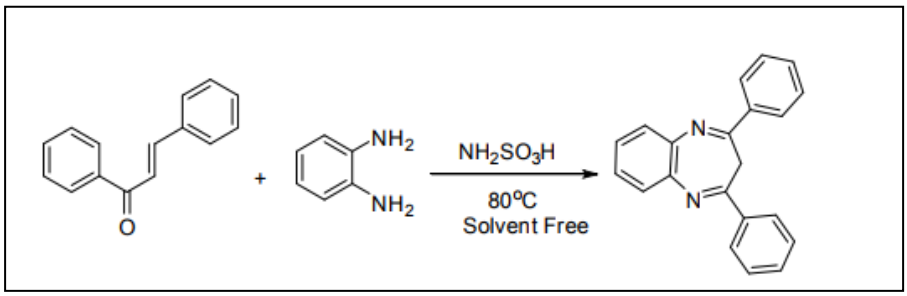


Figure 1.5: Benzodiazepine compounds

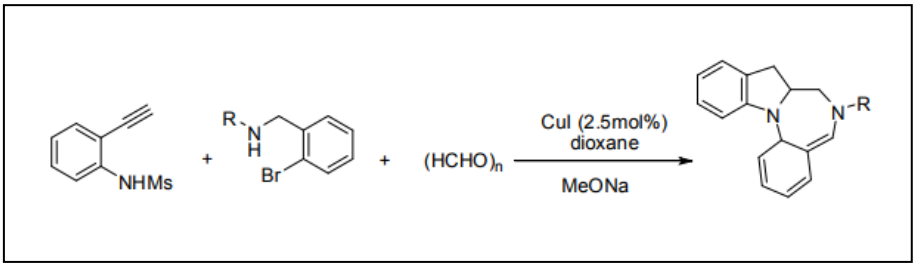
1.6.1 Synthesis of benzodiazepines

Attempts have been made in the field of synthetic chemistry to synthesize the various benzodiazepines and related compounds of pharmacological interest. Reaction of chalcone with ortho-phenylenediamine in presence of sulfamic acid (10mol %) as catalyst gave benzodiazepine[40].



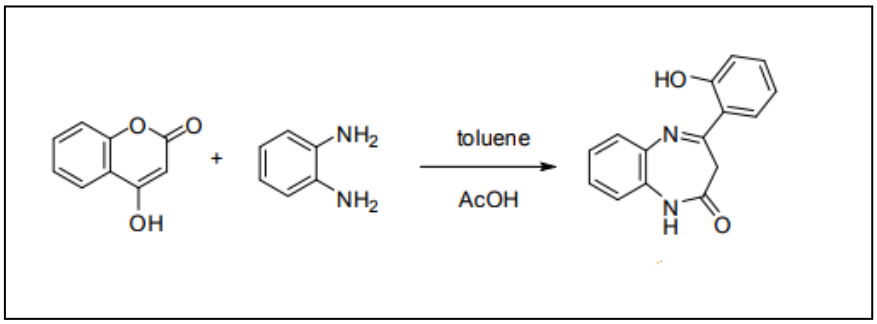
Scheme 1.21: Synthesis of benzodiazepine by Reaction of chalcone with ortho-phenylenediamine

Reaction of N-mesyl-2-ethynylaniline ,benzylamines and paraformadehyde by three component coupling/cyclization in presence of copper iodide catalyst gave indole fused diazapines[41].



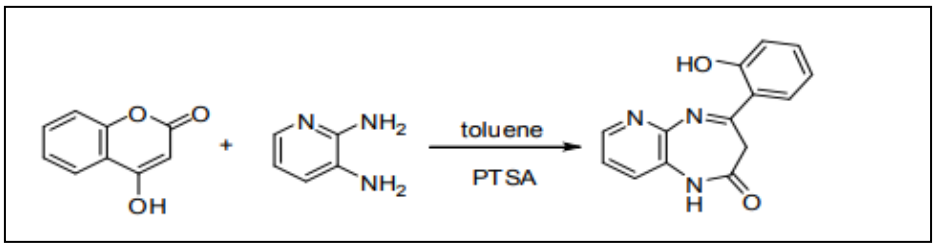
Scheme 1.22: Synthesis of benzodiazepine by Reaction of N-mesyl-2-ethynylaniline ,benzylamines and paraformadehyde

Condensation of 4-hydroxy-2H-chromen-2-one with o-phenylenediamine in presence of acetic acid afforded benzodiazepine[42].



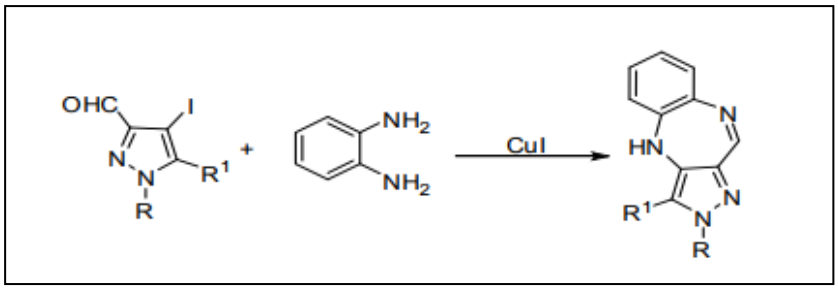
Scheme 1.23: Synthesis of benzodiazepine by Condensation of 4-hydroxy-2H-chromen-2-one with o-phenylenediamine

Condensation of 4-hydroxy-2H-chromen-2-one with pyridine-2,3-diamine in presence of PTSA afforded diazepine[43].



Scheme 1.24: Synthesis of benzodiazepine by Condensation of 4-hydroxy-2H-chromen-2-one with pyridine-2,3-diamine in presence of PTSA.

Reaction of halogen containing pyrazole-3-carbaldehyde with o-phenylenediamine in ethanol and triethylamine gave 4-Pyrazole-1,4-diazepines[44].



Scheme 1.25: Synthesis of benzodiazepine by Reaction of halogen containing pyrazole-3-carbaldehyde with o-phenylenediamine

1.6.2 Biological activity of benzodiazepines

Benzodiazepines serve as cholecystokinin A and B antagonists,[44] opioid receptor ligands,[45] platelet-activating factor antagonists,[46] HIV trans-activator (Tat) antagonists,[47] HIV reverse transcriptase inhibitors.[48] Benzodiazepines having effect on central nervous system for example clozapine (1), olanzapine (2) and quetiapine (3) are used in the clinic for treating schizophrenia, while clonazepam (4), diazepam (5), lorazepam (6), nitrazepam (7) and oxazepam (8) are used as antianxiety drugs.

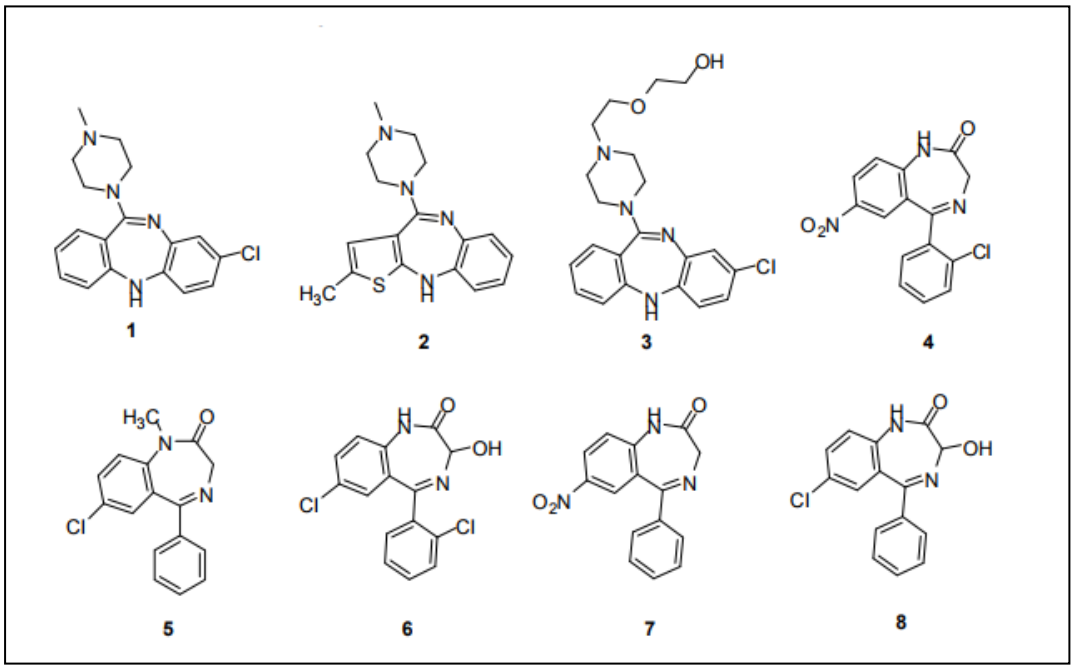


Figure 1.6: Biological activity of benzodiazepines compounds

1.7 Aim of the work

1- Synthesis of Oxazepine derivatives containing 1,2,4-triazole ring.

2- Synthesis of Diazepine derivatives containing 1,2,4-triazole ring.

3- Study the biological activity for some of the synthesized compound against Gram-positive bacteria *viz*. ***(Staphylococcus aureus***, ***Bacillus)*** and Gram-negative bacteria *viz*. ***(Pseudomonas***, ***Enterobacter***).

4- Deduce the structures of the synthesized compounds using elemental analysis and spectroscopic technique (FT-IR and ^{1}HNMR).

CHAPTER TWO

EXPERIMENTAL PART

2. EXPERIMENTAL

2.1 Chemicals

All chemicals were used directly from Fluka, BDH and Merck suppliers, without further purification.

2.2 Techniques

2.2.1 Fourier Transform Infrared Spectrophotometer (FT-IR)

FT-IR spectra in the range (4000-400) cm^{-1} were recorded using potassium bromide disc on FT-IR instrument Model 8300 Shimadzu Spectrophotometer, Japan. The analyses were carried out in department of chemistry, college of Science, Al-Nahrain University.

2.2.2 Proton Nuclear magnetic resonance spectrometer (^1H -NMR)

Proton Nuclear Magnetic Resonance (^1H-NMR) spectra were recorded on Brüker ACF 300 spectrometer at 300 MHz, using deuterated DMSO and deuterated Acetone as solvent with TMS as an internal standard, in the University of Exeter, England.

2.2.3 Melting point

Uncorrected melting points were recorded on hot stage Gallenkamp melting point apparatus (U.K.).

2.2.4 Elemental analysis (CHNS-O)

Elemental analysis (CHNS-O) was carried out using EURO EA elemental analyzer instrument. The analyses were carried out in department of chemistry, college of Science, Al-Nahrain University.

2.3 Preparation procedures

2.3.1 Synthesis of 3,4,5-tripropoxy benzoic acid (II):

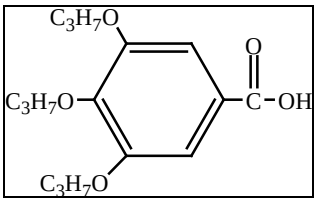


Figure (2.1): 3,4,5-tripropoxy benzoic acid

Dissolving of 3,4,5-Trihydroxy benzoic acid (1.7 g, 0.01 mol) in (20 mL) ethanol. K_2CO_3 (2.76 g, 0.03mol) was added with stirring, the mixture was placed in (100 mL) round bottom flask and cooled to room temperature, then (0.033 mol) of propyl bromide was added drop wise. The solution was refluxed overnight. K_2CO_3 (2.78 g, 0.03 mol) dissolved in a little amount of water (~ 5mL) was added to the reaction mixture and heated for (1-3) hrs. The solvent was evaporated and equal volume of water was added. The solution was heated till became clear. Acidification with conc. HCl yielded precipitate[50]. Recrystallization from ethanol gave the desired product with yield 89%, m.p.=171-173 .

2.3.2 Preparation of methyl 3,4,5-tripropoxy benzoate(III)

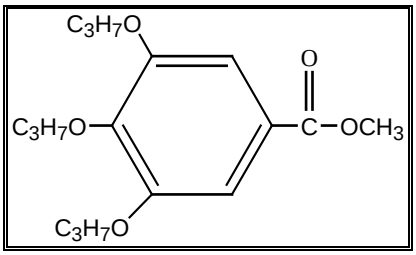


Figure (2,2): methyl 3,4,5-tripropoxybenzoate (III).

A mixture of 3,4,5-tripropoxy benzoic acid (2.96g, 0.01 mol) and methanol (10 mL, 0.25 mol) and concentrated sulphuric acid (2.7 mL) were placed. The reaction mixture was refluxed for 4 hrs., the excess of alcohol was distill off on a water bath (rotary evaporator) and allowed to cool[51]. Pour the residue into

about 25 mL of water. The obtained solid was filtered, Recrystallization from ethanol yielded 92 % , (m. p. = 93-95 ºC).

2.3.3 Preparation of 3,4,5-tripropoxybenzhydrazide (IV) :

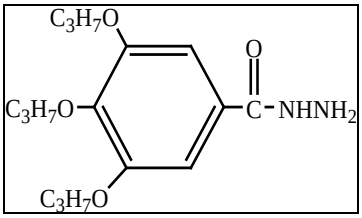


Figure (2.3): 3,4,5-tripropoxybenzhydrazide (IV).

Hydrazine hydrate 15 mL were added to a (1.94g ,0.01 mol) of methyl 3,4,5-trialkoxy benzoate. The mixture refluxed for 4 hrs., then 30 mL of ethanol were added and the reflux continued over night. The ethanol was distilled off. The obtained solid was filtered and washed with cold water. Recrystallization from ethanol yielded 90%, (m.p.= 168-170ºC) [52].

2.3.4 Preparation of 3,4,5-tripropoxyphenylthiocarbazinate (V)

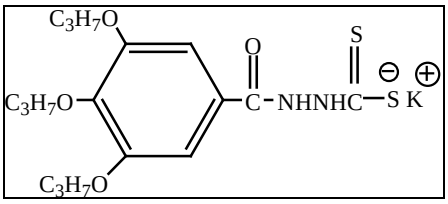


Figure (2.4): 3,4,5-tripropoxyphenylthiocarbazinate (V)

KOH(0.015 mol, 0.89 g) were dissolved in absolute ethanol (7.5 mL) then added to a mixture of 3,4,5-tripropoxybenzhydrazide (0.01 mol , 1.5 g) and carbon disulfide (1.5 mL), in ice bath till the yellow precipitate was obtained which was dissolved in absolute ethanol (10 mL), then stirred about 7hrs., the obtained solid was filtered and dried to obtain the desired product[52] .

2.3.5 Preparation of 3-thio-{5-yl-(3`,4`,5`-tripropoxyphenyl)}-4-amino-1,2,4-triazole (VI)

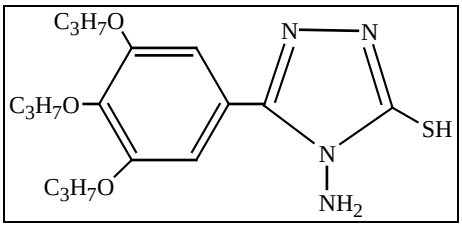
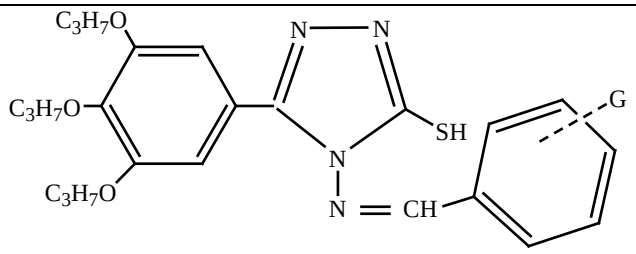


Figure (2.5): 3-thio-{5-yl-(3`,4`,5`-tripropoxyphenyl)}-4-amino-1,2,4-triazole (VI)

Suspension of potassium salt was used directly because it was non stable, hydrazine hydrate (2 mL) and water (8 mL) was refluxed for 4 hrs. The color of the reaction mixture changed to green, hydrogen sulfide was evolved and a homogenous solution resulted, the advance from the reaction is monitored through TLC (hexane:ethylacetate, 7:3). A white solid was precipitated by dilution with cold water (10 mL) and acidification with concentrated hydrochloric acid. The product was filtered, washed with cold water and recrystallized from ethanol yielded 88% (m.p. = 204-206) [52].

2.3.6 General procedure for preparation of Schiff`s bases 3-thio-{5-yl-(3`,4`,5`-tripropoxy phenyl)}-4-substituted benzelidineamino-1,2,4-triazole (VII)$_{a-j}$



G = *P*-OH, *P*-OCH_3, *P*- CH_3, *P*-Cl, *P*- Br, *P*-NO_2, *P*-N,N-$(CH_3)_2$, 2,4-$(OH)_2$, 2,4-$(OCH_3)_2$, 2,4-$(Cl)_2$

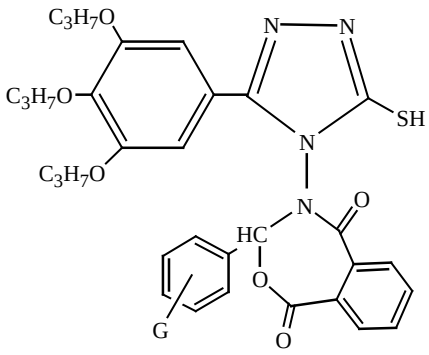
Figure(2.6): 3-thio-{5-yl-(3`,4`,5`-tripropoxyphenyl)}-4-substituted benzelidineamino-1,2,4-triazole (VII)$_{a-j}$

A mixture of the Benzaldehyde derivatives (0.01 mol) and compound (VI) (0,01 mol, 0.94 g) was dissolved in 15 mL absolute ethanol containing a drops of glacial acetic acid and refluxed for 4 hrs., the progress of the reaction was monitored by TLC (hexane:ethylacetate, 7:3). The reaction mixture was then allowed to cool to room temperature, the solid was filtered, washed with (2%) HCl solution then with distilled water, recrystallized from ethanol to yield colored crystals[53].

Table (2.1): Physical properties of compounds (VII)$_{a-j}$

COMP NO.	G	MOLECULAR FORMULA	MW.	YIELD %	COLOR	M.P.°C
(VII)$_a$	**4-OH**	$C_{24}H_{30}N_4O_4S$	470.5	82	Yellow	208-210
(VII)$_b$	**4-OCH$_3$**	$C_{25}H_{32}N_4O_4S$	484.6	78	Yellow	167-170
(VII)$_c$	**4-CH$_3$**	$C_{25}H_{32}N_4O_3S$	468.6	75	Light yellow	152-154
(VII)$_d$	**4-Cl**	$C_{24}H_{29}N_4O_3SCl$	489	80	Light yellow	176-178
(VII)$_e$	**4-Br**	$C_{24}H_{29}N_4O_3SBr$	533.4	85	Light yellow	188-191
(VII)$_f$	**4- NO$_2$**	$C_{24}H_{29}N_5O_5S$	499.5	87	Yellowish orange	204-206
(VII)$_g$	**4- N,N(CH$_3$)$_2$**	$C_{26}H_{35}N_6O_3S$	511.6	86	Light yellow	193-195
(VII)$_h$	**2,4- (OH)$_2$**	$C_{24}H_{30}N_4O_5S$	486.5	74	Yellow	212-215
(VII)$_i$	**2,4- (OCH$_3$)$_2$**	$C_{26}H_{34}N_4O_5S$	514.6	78	Yellow	158-161
(VII)$_j$	**2,4-(Cl)$_2$**	$C_{24}H_{28}N_4O_3SCl_2$	523.4	82	Yellow	198-200

2.3.7 General procedure for synthesis of 2-(substituted phenyl)3-(5-yl-(3`,4`,5`-tripropoxyphenyl)-3-thio-[1,2,4] triazolo [1,3] Oxazepine-4,7-dione(VIII)$_{a-j}$:



G = *P*-OH, *P*-OCH_3, *P*- CH_3, *P*-Cl, *P*- Br, *P*-NO_2, *P*-N,N-$(CH_3)_2$, 2,4-$(OH)_2$, 2,4-$(OCH_3)_2$, 2,4-$(Cl)_2$

Figure (2.7): 2-(substituted phenyl)3-(5-yl-(3`,4`,5`-tripropoxyphenyl)-3-thio- [1,2,4] triazolo [1,3] Oxazepine-4,7-dione(VIII)$_{a-j}$

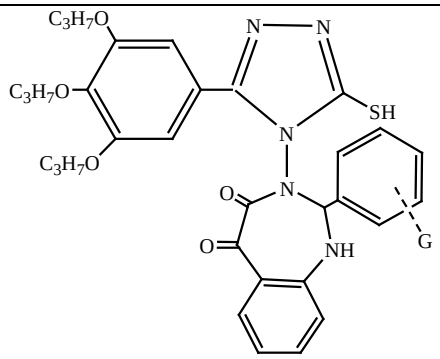
A mixture of corresponding Schiff`s bases (0.001 mol) and phthalic anhydride (0.001 mol) in dry benzene (30 mL) was heated for 5hrs. in water bath at (70 C◦), excess solvent was distilled, the precepitate was filtered and recyrstallized from ethanol [(54)].

Table (2.2) Physical properties of compounds (VIII)$_{a-j}$.

COMP NO.	G	MOLECULAR FORMULA	MWT.	YIELD %	COLOR	M.P.̊C
(VIII)$_a$	**4-OH**	$C_{32}H_{34}N_4O_7S$	618.7	60	White	223-225
(VIII)$_b$	**4-OCH_3**	$C_{33}H_{36}N_4O_7S$	632.7	63	Yellow	187-190
(VII)$_c$	**4-CH_3**	$C_{33}H_{36}N_4O_6S$	616,7	61	Light yellow	170-173
(VIII)$_d$	**4-Cl**	$C_{32}H_{33}N_4O_6SCl$	637.1	72	White	178-180
(VIII)$_e$	**4-Br**	$C_{32}H_{33}N_4O_6SBr$	681.5	74	Brown	179-182
(VIII)$_f$	**4- NO_2**	$C_{32}H_{33}N_5O_8S$	647.6	72	Yellow	190-192
(VIII)$_g$	**4-N,N$(CH_3)_2$**	$C_{34}H_{39}N_6O_6S$	659.7	70	White	202-204

(VIII)$_h$	**2,4- (OH)$_2$**	$C_{32}H_{34}N_4O_8S$	634.6	63	White	217-220
(VIII)$_i$	**2,4-(OCH$_3$)$_2$**	$C_{34}H_{38}N_4O_8S$	662.7	62	Brown	183-185
(VIII)$_j$	**2,4-(Cl)$_2$**	$C_{32}H_{32}N_4O_6Cl_2$	639.5	68	White	205-208

2.3.8 General procedure for synthesis of 2-(substituted phenyl)3-(5-yl-(3`,4`,5`-tripropoxyphenyl)-3-thio- [1,2,4] triazolo [1,3] diazepine-4,5-dione (IX)$_{a-j}$



G = *P*-OH, *P*-OCH$_3$, *P*- CH$_3$, *P*-Cl, *P*- Br, *P*-NO$_2$, *P*-N,N-(CH$_3$)$_2$, 2,4-(OH)$_2$, 2,4-(OCH$_3$)$_2$, 2,4-(Cl)$_2$

Figure (2.8): 2-(substituted phenyl)3-(5-yl-(3`,4`,5`-tripropoxyphenyl)-3-thio- [1,2,4] triazolo [1,3] diazepine-4,5-dione (IX)$_{a-j}$

A mixture of corresponding Schiff`s bases (0.001 mol) and isatine (0.001 mol) in ethanol (30 mL) was refluxed for (4 hr). The reaction mixture cooled and filtered, the solid separate was recrystallized from ethanol[(54)].

Table (2.3) Physical properties of compounds(IX)$_{a-j}$.

COMP. NO.	G	MOLECULAR FORMULA	MWT	YIELD %	COLOR	M.P.°C
(IX)$_a$	**4-OH**	$C_{32}H_{35}N_5O_6S$	615.6	78	Light Yellow	228-231
(IX)$_b$	**4-OCH$_3$**	$C_{33}H_{37}N_5O_6S$	631.7	82	Light Yellow	215-217
(IX)$_c$	**4-CH$_3$**	$C_{33}H_{37}N_5O_5S$	615.7	74	Yellow	187-190
(IX)$_d$	**4-Cl**	$C_{32}H_{34}N_6O_7SCl$	682.1	76	Yellow	143-145
(IX)$_e$	**4-Br**	$C_{32}H_{34}N_5O_5SBr$	680.6	83	Yellow	160-162

(IX) $_f$	**4- NO_2**	$C_{32}H_{34}N_6O_7S$	646.7	80	Red	188-190
$(IX)_g$	**4- $N,N(CH_3)_2$**	$C_{34}H_{40}N_7O_5S$	658.7	70	Yellow	182-184
$(IX)_h$	**2,4- $(OH)_2$**	$C_{32}H_{35}N_6O_7S$	647.7	72	Light Yellow	231-234
$(IX)_i$	**2,4- $(OCH_3)_2$**	$C_{34}H_{39}N_5O_7S$	661.7	64	Yellow	245-247
$(IX)_j$	**2,4-$(Cl)_2$**	$C_{32}H_{33}N_5O_5Cl_2$	670.7	58	Yellow	218-220

2.4 Antibacterial activities

The antibacterial activities of the synthesized compounds were studied against gram-positive bacteria (***Staphylococcus aureus***, ***Bacillus***) and gram-negative bacteria (***Pseudomonas***, ***Enterobacter***) the microorganism was supplied as ready bacterial cultures by Biotechnology Department, College of Science, Baghdad University, at a concentration of 10, 25, 50, 100 µg/ML by Agar well Diffusion method as follow:

1. Bacterial media was prepared by using a touch of bacterial culture to a test tube contains (5 mL) of the sterilized distilled water.
2. Mueller Hinton (MH.) was prepared by dissolving (9.5 g) MH. in (250 mL) distilled water and sterilized by autoclave at 121°C, 1.5 atmosphere for 30 min., then cooled to (40-45) min.
3. In each (25 mL) MH., (250 µL) of bacterial was added and mixed gently, then it has been poured into a Petri dish and wait till solidification.
4. In each medium, five pores were made by the use of a sterile dry rod with a diameter of 5 mm. The inhibition zones test [(55)] was applied by using solutions of prepared compounds dissolved in DMSO. These solutions were added using fixed amount (50 µL) of each compound with concentrations of (10, 25, 50, 100) µg/mL in pores. The control (DMSO) was added to the fifth pore. The plates were incubated at 37 ^oC for 24 hrs.

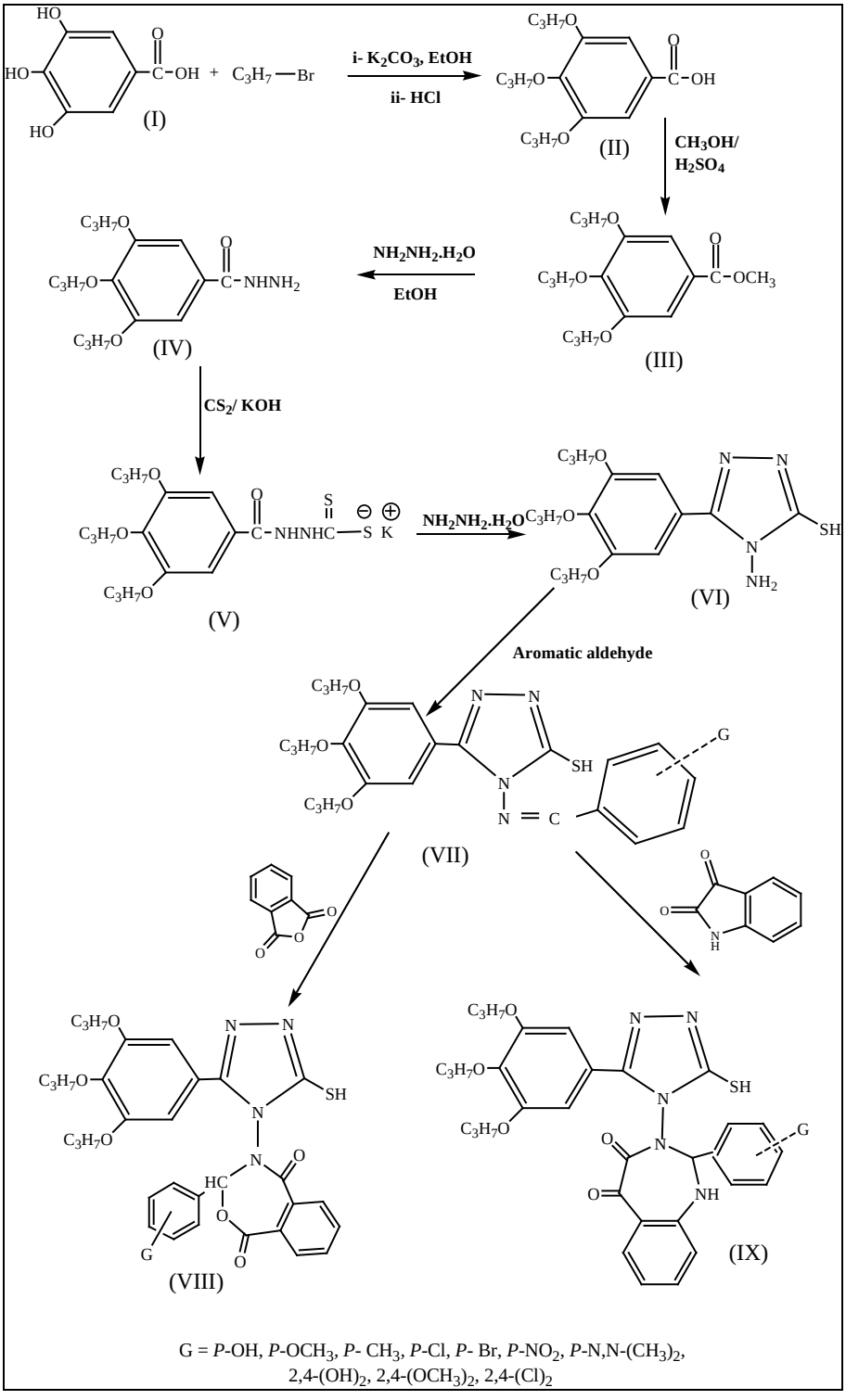
Finally the inhibition diameter was measured for each pore using a ruler. The translucent area which surrounds the disc (including the diameter of the disc that lacks bacterial growth) considered as the zone of inhibition.

CHAPTER THREE

RESULTS AND DISCUSSION

Results and Discussion

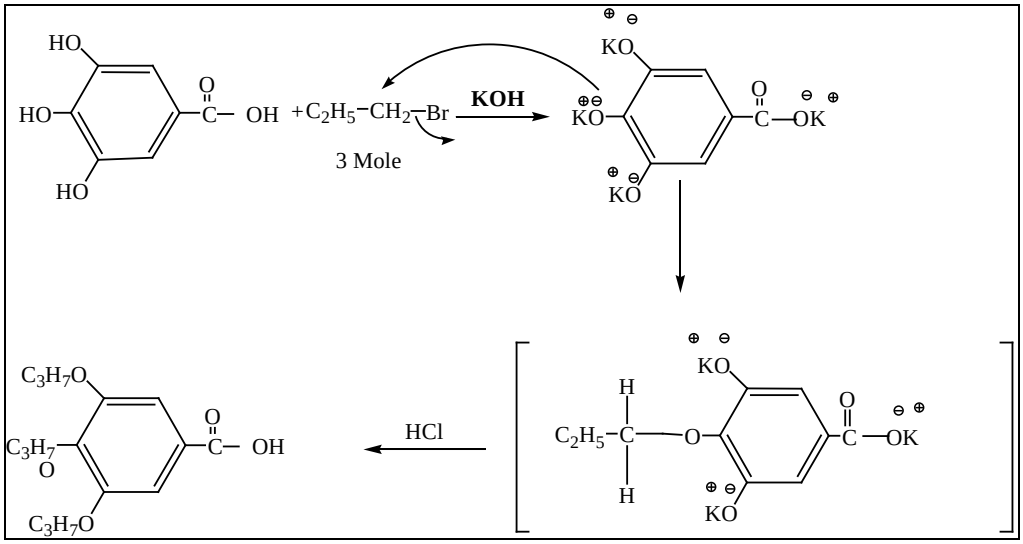
This work involves the synthesis of heterocyclic compounds with seven membered rings derived from gallic acid as shown in scheme (3.1):



Scheme (3.1): Synthetic route for synthesized compounds.

3.1 Preparation of 3,4,5-tripropoxybenzoic acid (II):

3,4,5-tripropoxy benzoic acid (II) was prepared by the reaction of gallic acid with propylbromide as shown below scheme (3.2)[57]:



Scheme 3.2: Mechanism steps for preparation of 3,4,5-tripropoxybenzoic acid(II).

The structure of prepared compound was identified via FTIR spectroscopy. Figure 3.1 shows the FTIR spectrum of 3,4,5-tripropoxybenzoic acid (II) using KBr disc which showed the following characteristic absorption bands: broad band at 3361 cm^{-1} and 1716 cm^{-1} that could be attributed to O – H stretching and carbonyl of carboxyl group respectively and bands at 2921 and 2873 cm^{-1} due to aliphatic C – H stretching of alkyl group, while the C = C stretching occurs at 1595 cm^{-1}.

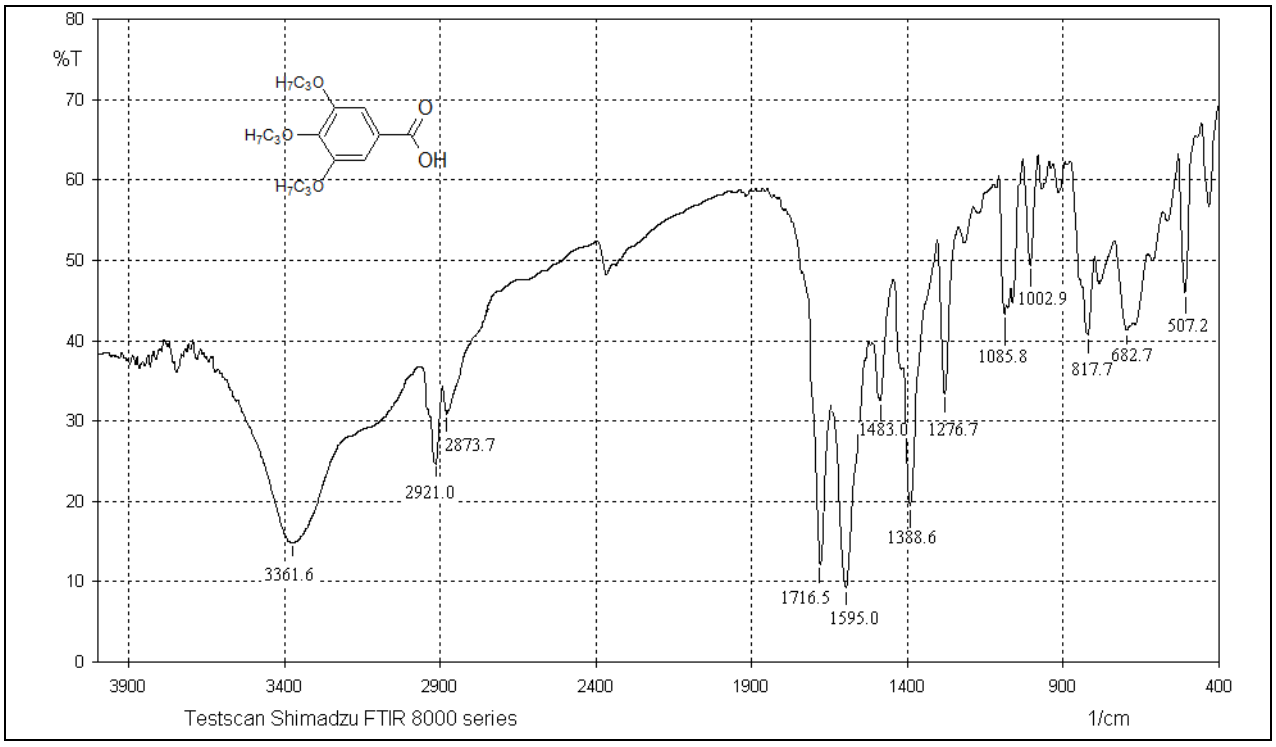
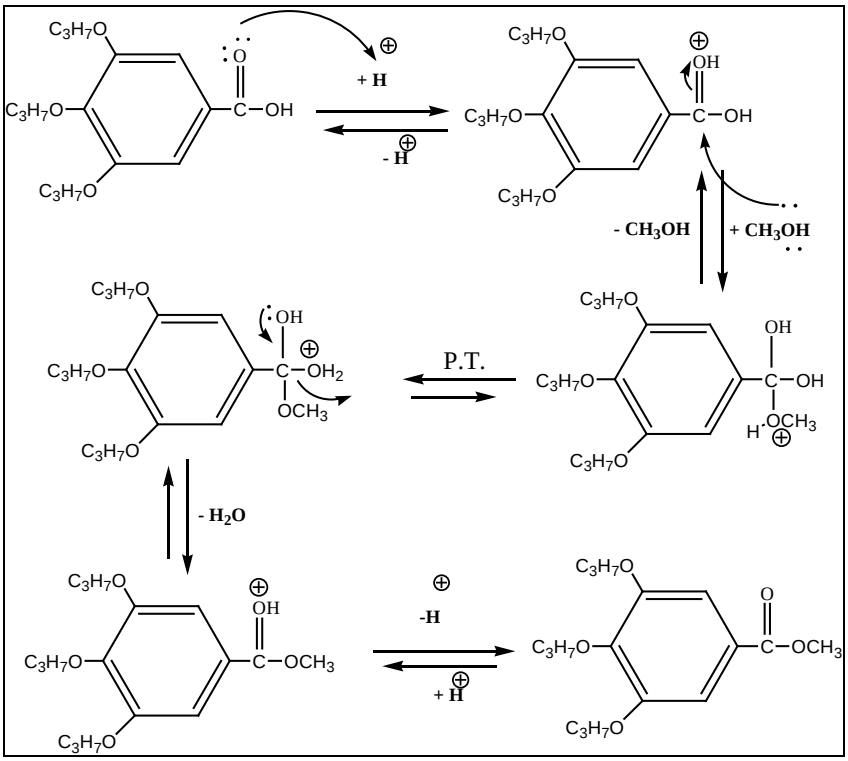


Figure 3.1: FTIR spectrum of 3,4,5-tripropoxybenzoic acid (II).

3.2 Preparation of methyl 3,4,5-tripropoxybenzoate (III):

The titled compound was prepared via direct esterfication of compound (II) with methanol in presence of sulfuric acid as catalyst as shown below[(58)]:



Scheme 3.3: Mechanism steps for preparation of methyl- 3,4,5-tripropoxybenzoate(III).

Figure 3.2 represent the FTIR spectrum of compound (III), which show the following characteristic absorption bands (cm^{-1}): disappearance the broad band of the hydroxyl group stretching at 3361 with the appearance of strong C – H aliphatic stretching bands at 2977 and 2847 and also the appearance of ester carbonyl strtching at 1743.

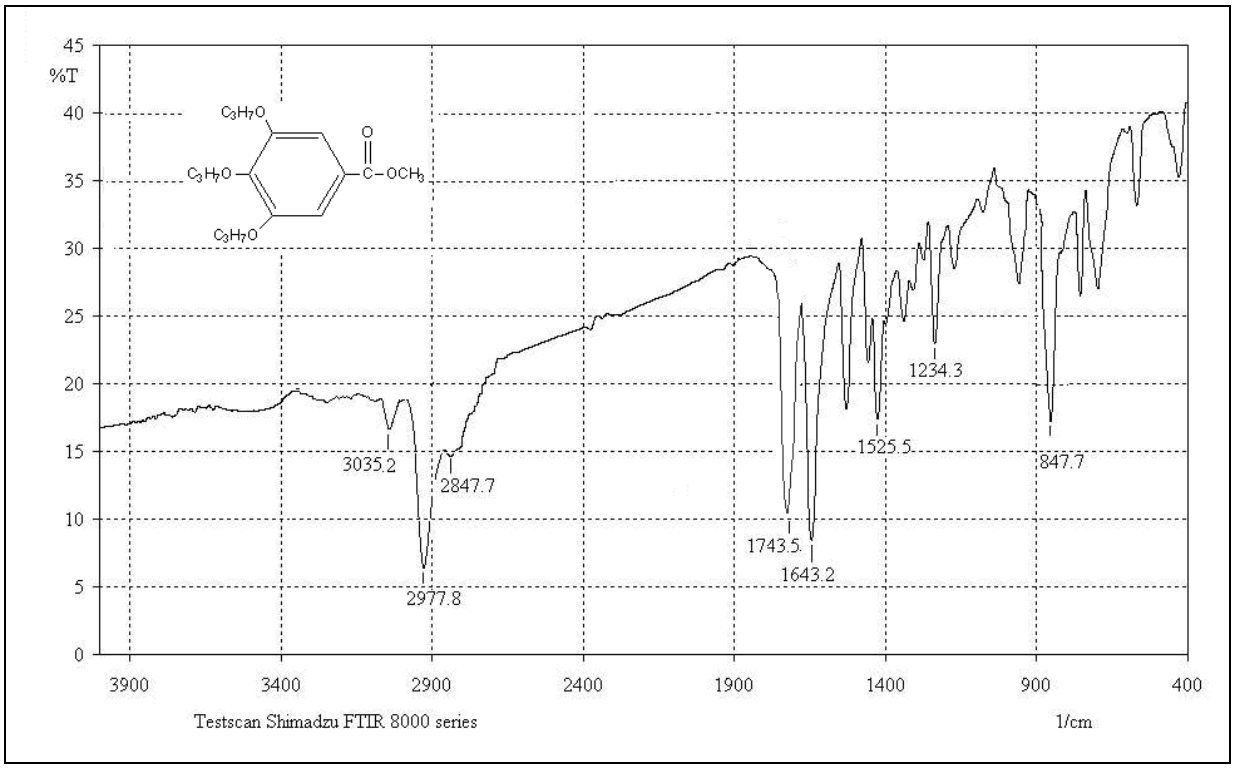
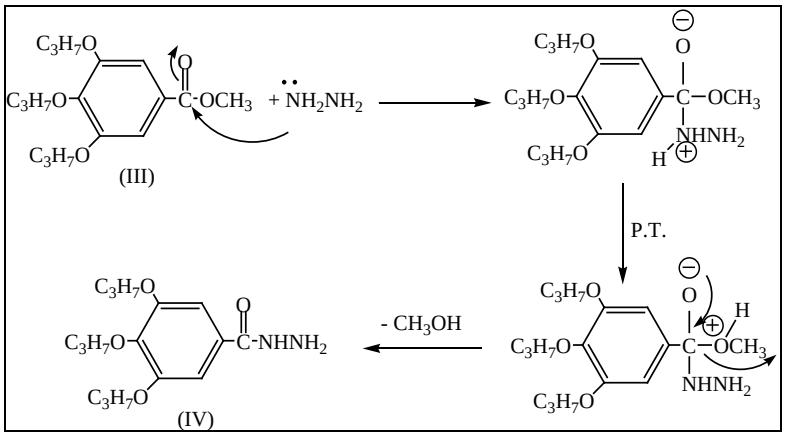


Figure 3.2: FTIR spectrum of methyl-3,4,5-tripropoxybenzoate (III).

3.3 Preparation of 3,4,5-tripropoxybenzoic hydrazide (IV):

Compound (IV) was prepared from the reaction of ester compounds (III) with hydrazine hydrate[(59)].



Scheme 3.4: Mechanism steps for preparation of 3,4,5-tripropoxybenzoic hydrazide(IV).

The structure of prepared compounds was confirmed using FTIR spectroscopy.

The FTIR spectrum show the appearance of bands at 3411, 3364, 3113, 1686, 1613, 751 and 822which could be assigned to ν N – H (asymm. and symm.), ν C = O (amide), ν C = C and out of plane bending of sustituted benzene ring.

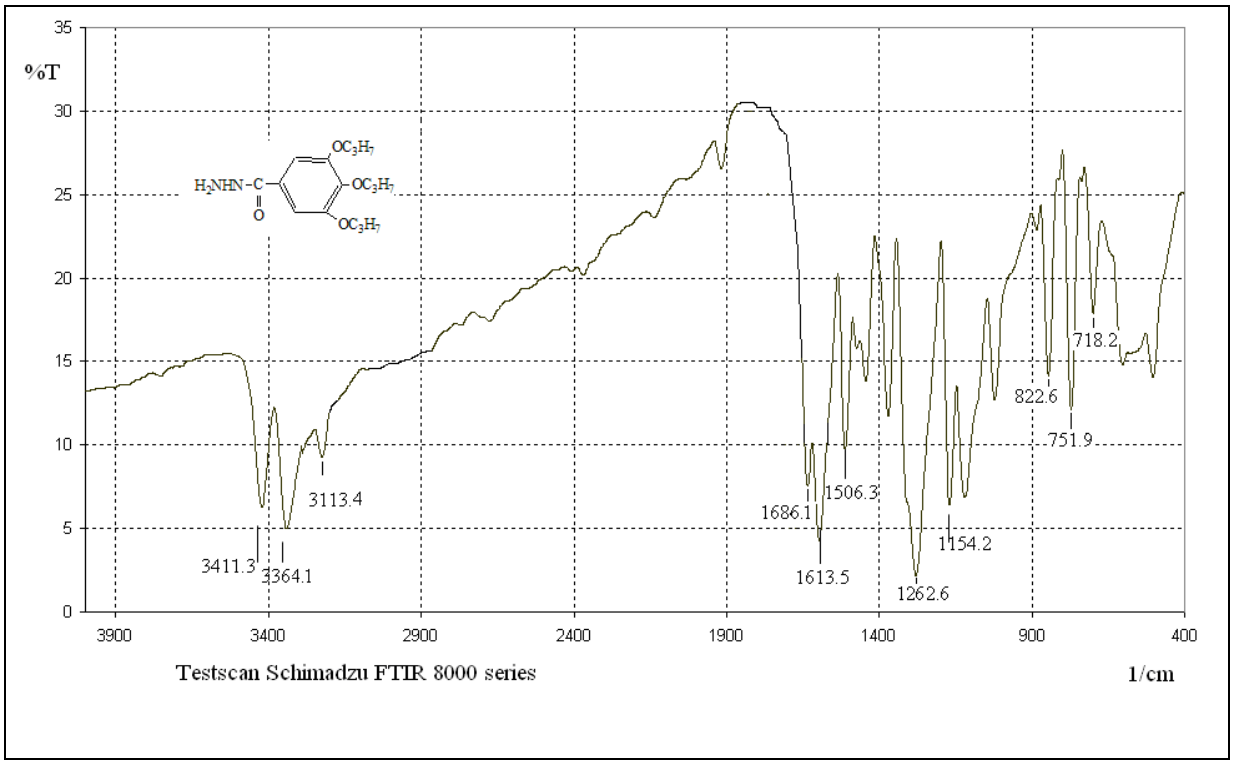
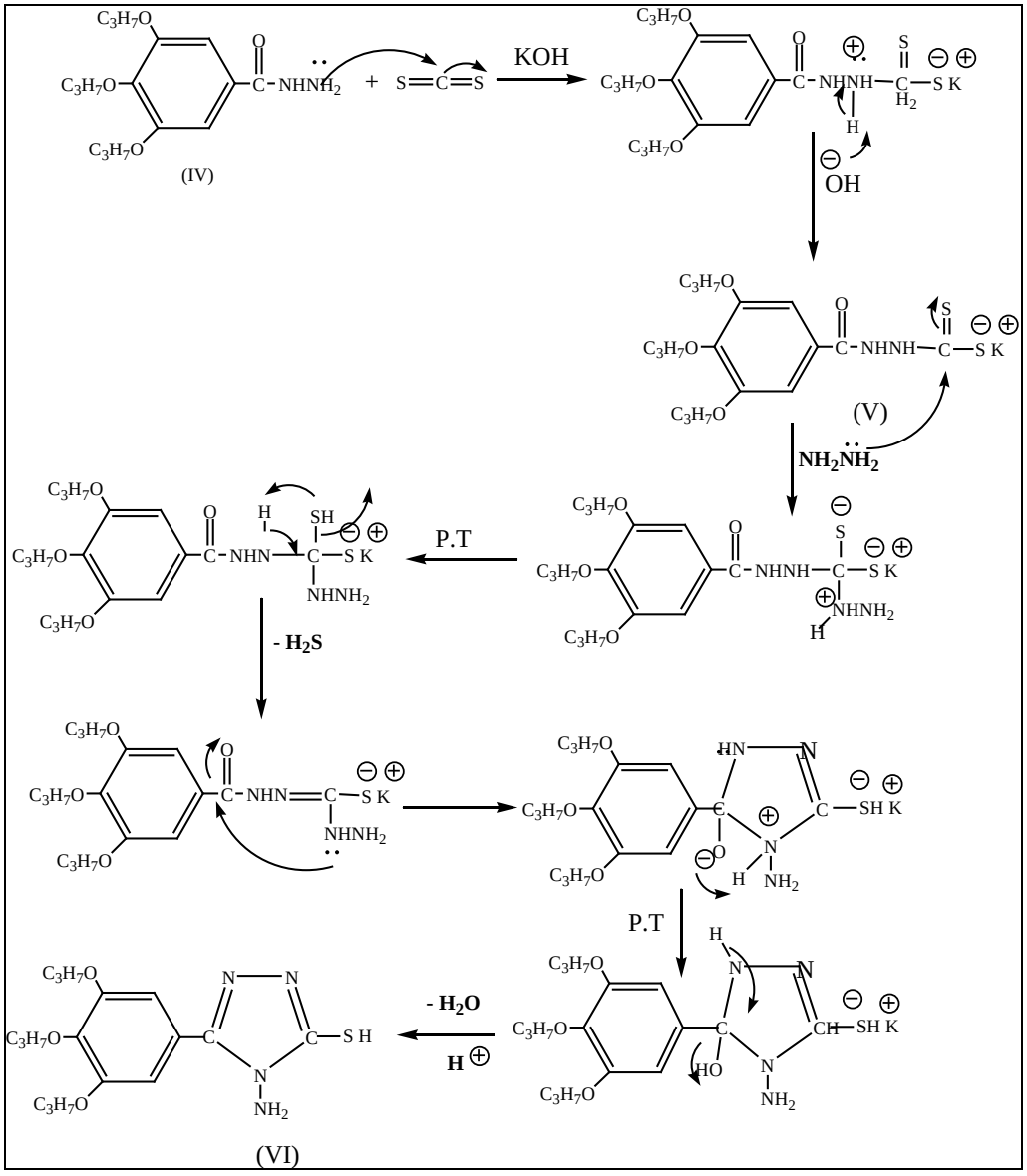


Figure 3.3: FTIR spectrum of 3,4,5-tripropoxybenzoic hydrazide (IV).

3.4 Synthesis of 3-thio-{5-yl-(3`,4`,5`-tripropoxyphenyl)}-4-amino-1,2,4-triazole (VI)

The reaction of hydrazide compounds (IV) with carbon disulfide in basic media leads to the formation of thio carbazinate salts (V) which undergo cyclization in excess of hydrazine hydrate to give 3-thio-{5-yl-(3`,4`,5`-tripropoxyphenyl)}-4-amino-1,2,4-triazole (VI).



Scheme 3.5: Mechanism steps for preparation of 3-thio-{5-yl-(3`,4`,5`-tripropoxyphenyl)}-4-amino-1,2,4-triazole (VI).

The structure of compound (VI) was characterized using FTIR, ^{1}HNMR spectroscopic technique. The purities of compounds were confirmed by using an elemental analysis. The elemental analysis of compound (VI) is listed in Table (3.1).

Table 3.1: Elemental Analysis (CHNS-O) for compounds (VI)

COMP. NO.	FORMULA	%C		% H		%N		%S	
		Calc.	Found	Calc.	Found	Calc.	Found	Calc.	Found
(VI)	$C_{17}H_{26}N_4O_3S$	55.73	55.69	7.10	6.98	15.30	15.32	8.74	8.65

The FTIR spectrum of compound (VI) figure (3.4), (KBr disc cm^{-1}), show the appearance of bands at 3452, 3252, 3165, 3050, 1628, 1598, 825, 751 and 713 which could be assigned to ν N – H (asymm. and symm.), ν C-H (aromatic), ν C=N, ν C= C and out of plane bending of trisubstituted benzene ring.

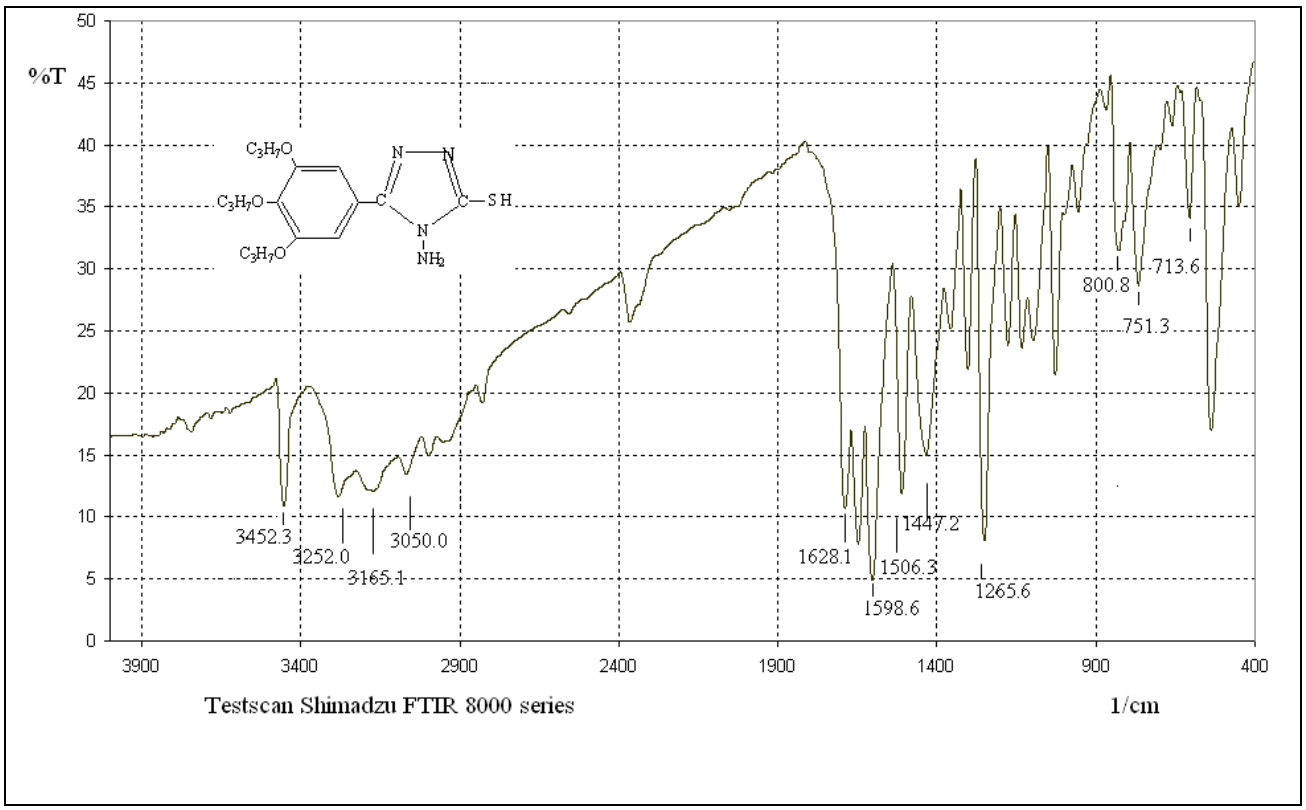


Figure 3.4: FTIR spectrum of 3-thio-{5-yl-(3`,4`,5`-tripropoxyphenyl)}-4-amino-1,2,4-triazole (VI).

Compound (VI) also characterized using ^{1}HNMR. Figure (3.5) show the ^{1}HNMR spectrum of the compound (DMSO-d6, δ in ppm): 7.33-7.49 (s, 2H, arom. H) for the benzene ring, 12.53 (s, 1H, SH), 9.81 (s, 2H, N – H), 3.96 (t, 6H, O – CH_2), 1.75 (m, 6H, - CH_2), and 0.92 (t, 9H, - CH_3).

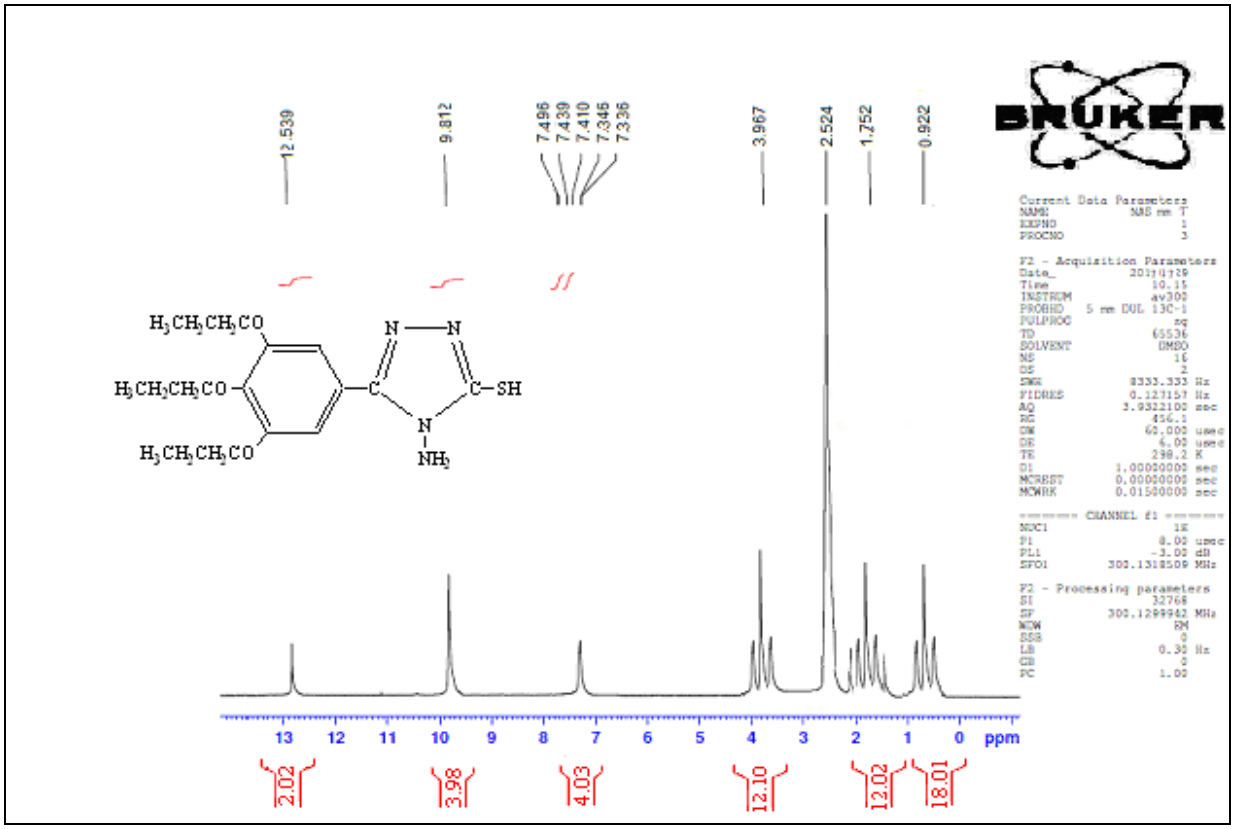
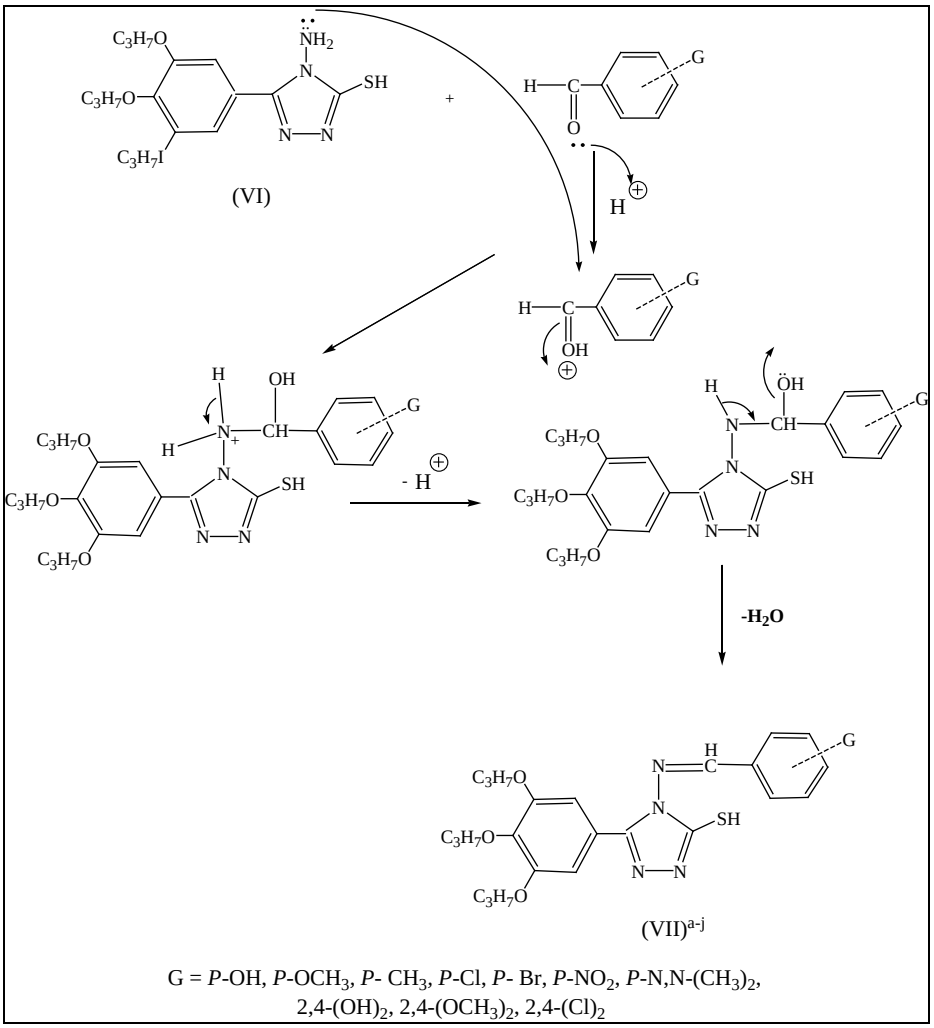


Figure 3.5: FTIR spectrum of 3-thio-{5-yl-(3`,4`,5`-tripropoxyphenyl)}-4-amino-1,2,4-triazole (VI).

3.5 Synthesis of 3-thio-{5-yl-(3`,4`,5`-tripropoxyphenyl)}-4-substituted benzelidineamino-1,2,4-triazole (VII)$_{a-j}$:

Shiff`s bases (VII)$_{a-j}$ were synthesized through the condensation reaction of 3-thio-{5-yl-(3`,4`,5`-tripropoxyphenyl)}-4-amino-1,2,4-triazole (VI) with different aromatic aldehydes in absolute ethanol and in presence of few drops of glacial acetic acid as shown below:



Scheme 3.6: Mechanism steps for preparation of 3-thio-{5-yl-(3`,4`,5`-tripropoxyphenyl)}-4- substituted benzelidineamino-1,2,4-triazole (VII)$_{a-j}$.

The structures of all products were identified using FT-IR and ^{1}H-NMR for some of them. The all resultant spectral were in correspondence with expected values. The purities of compounds were confirmed by using an elemental analysis. The elemental analysis of compounds (VII)$_{a-j}$ are listed in Table (3.2). The observed values are in well agreement with theoretical values indicating structure of respective compounds.

Table 3.2: Elemental Analysis (CHNS-O) for compounds $(VII)_{a,c,f\&g}$

COMP. NO.	FORMULA	%C		% H		% N		% S	
		Calc.	Found	Calc.	Found	Calc.	Found	Calc.	Found
$(VII)_a$	$C_{24}H_{30}N_4O_4S$	61.27	61.20	6.38	6.34	11.91	11.87	6.80	6.77
$(VII)_c$	$C_{25}H_{32}N_4O_3S$	64.10	64.12	6.83	6.79	11.96	11.88	6.83	6.78
$(VII)_f$	$C_{24}H_{29}N_5O_5S$	57.71	57.68	5.81	5.78	14.02	13.92	6.41	6.39
$(VII)_g$	$C_{26}H_{35}N_5O_3S$	62.77	62.73	7.04	7.01	14.08	14.10	6.43	6.39

The spectroscopic observation of $(VII)_e$ is given: FT-IR (KBr, cm^{-1}) figure (3.7): show the appearance of bands at 3180, 2931, 2881, 1628, 1600, 841.1, 756 and 712 which could be assigned to ν C – H of azomethane group[60], ν CH aliphatic, ν CH =N, ν C = C and out of plane bending of trisubstituted benzene ring. Table 3.3 shows the FT-IR absorption bands for synthesizes compounds.

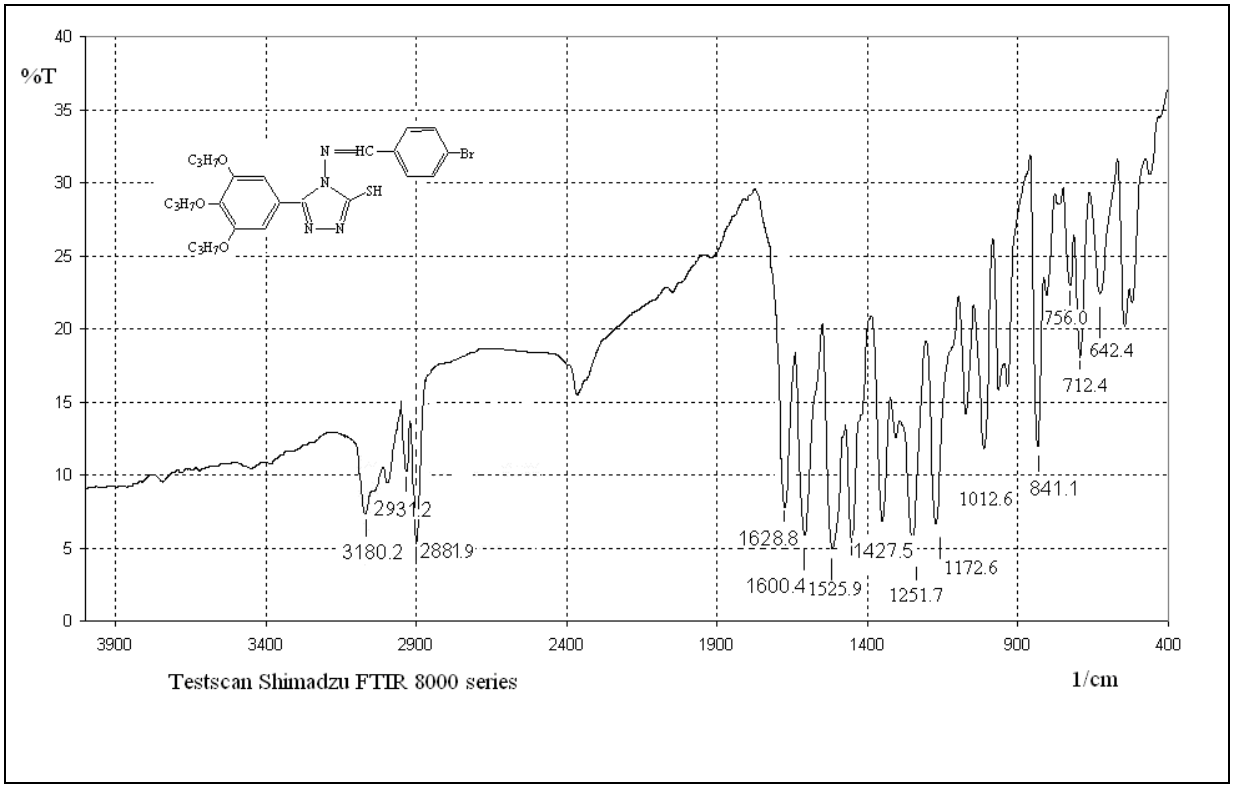


Figure 3.6: FTIR spectrum of 3-thio-{5-yl-(3`,4`,5`-tripropoxyphenyl)}-4- (4``-bromo benzelidineamino)-1,2,4-triazole $(VII)_e$.

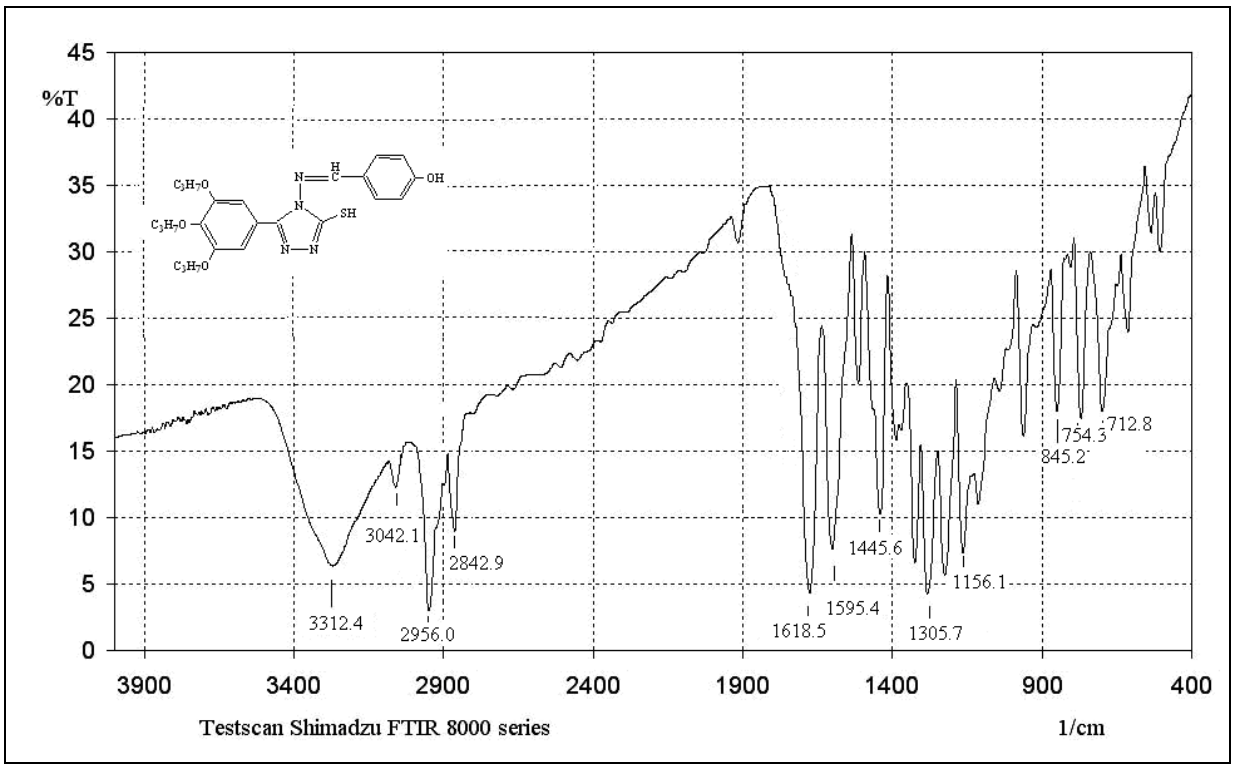


Figure 3.7: FTIR spectrum of 3-thio-{5-yl-(3`,4`,5`-tripropoxyphenyl)}-4- (4``-hydroxy benzelidineamino)-1,2,4-triazole (VII)$_a$.

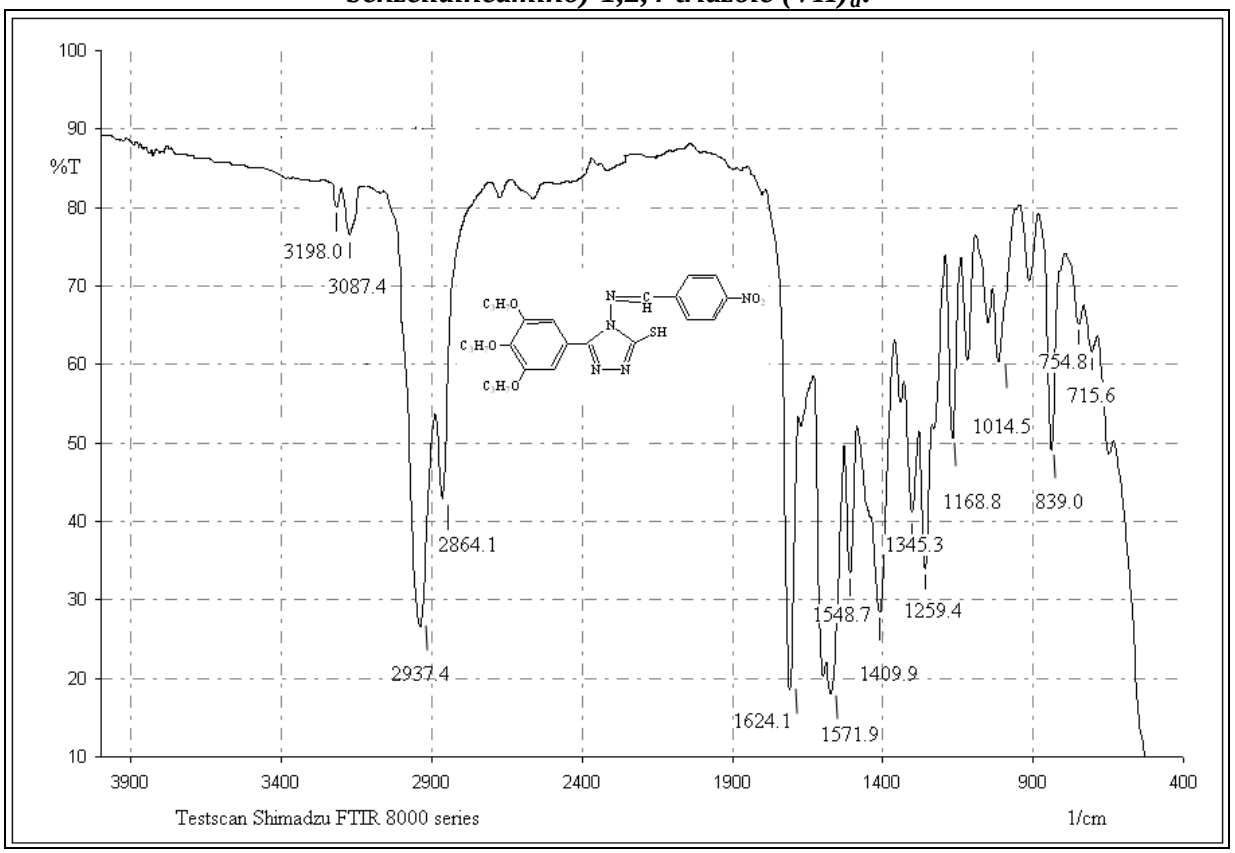


Figure 3.8: FTIR spectrum of 3-thio-{5-yl-(3`,4`,5`-tripropoxyphenyl)}-4-(4``-nitro benzelidineamino)-1,2,4-triazole (VII)$_f$.

^{1}HNMR (DMSO-d_6), δ in ppm) figure (3.10) for compouns $(VII)_b$: 7.43-7.53 (d, 4H, arom. H), 7.60 – 7.62 (s, 2H, arom.), 8.2 (s, 1H, CH = N), 12.6(s, 1 H, SH), 3.81 (s, 3H, OCH_3), 3.96 (t, 6H, (-OCH_2), 1.96 (m, 6H, CH_2), 0.96 (t, 9H, CH_3).

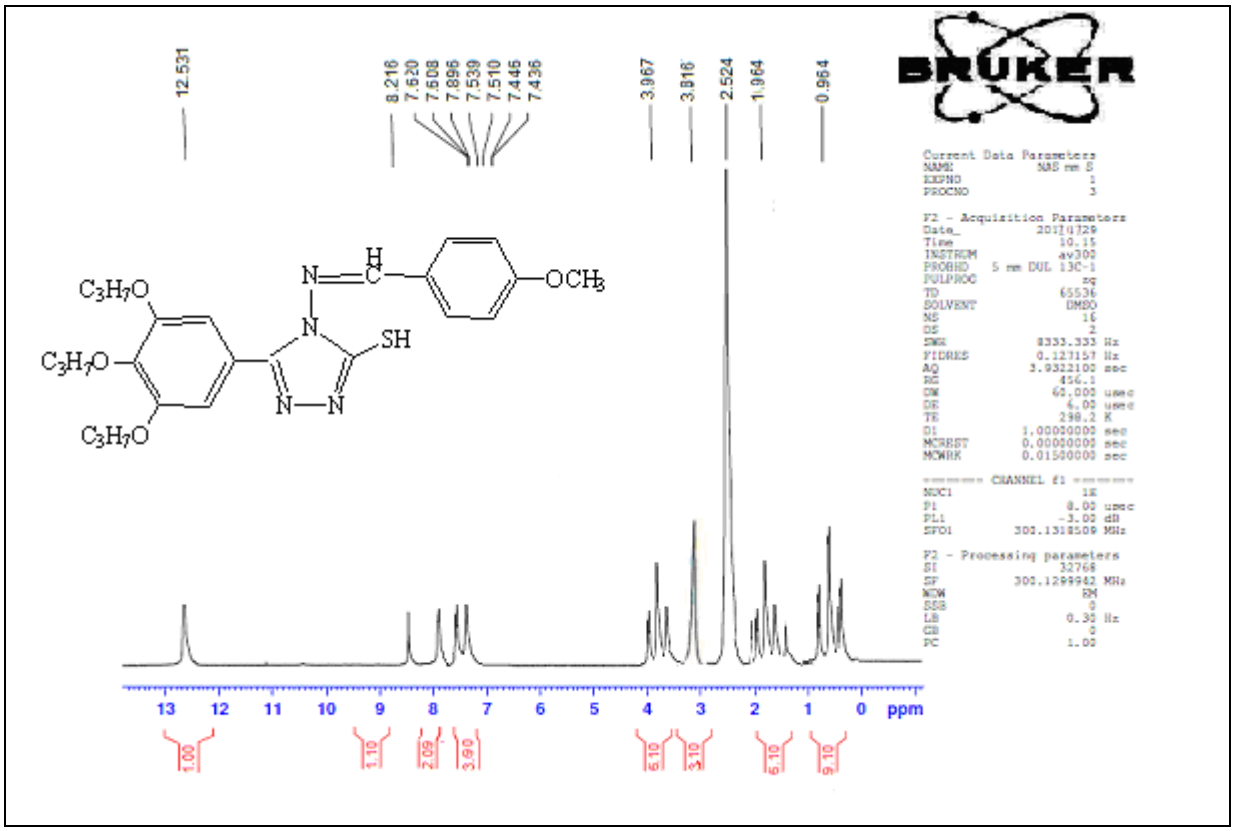


Figure 3.9: ^{1}HNMR spectrum of 3-thio-{5-yl-(3`,4`,5`-tripropoxyphenyl)}-4-(4``methoxybenzelidineamino)-1,2,4-triazole $(VII)_b$

^{1}HNMR (DMSO-d_6), δ in ppm) figure (3.11) for compouns $(VII)_f$: 7.33-7.4 3 (s, 2H, arom. H), 7.49 – 7.52 (d, 4H, arom.), 8.3 (s, 1H, CH = N), 12.6(s, 1 H, SH), 3.91 (t, 6H, (-OCH_2), 1.96 (m, 6H, CH_2), 0.93 (t, 9H, CH_3). Table (3.3) shows the FT-IR absorption bands for synthesizes compounds.

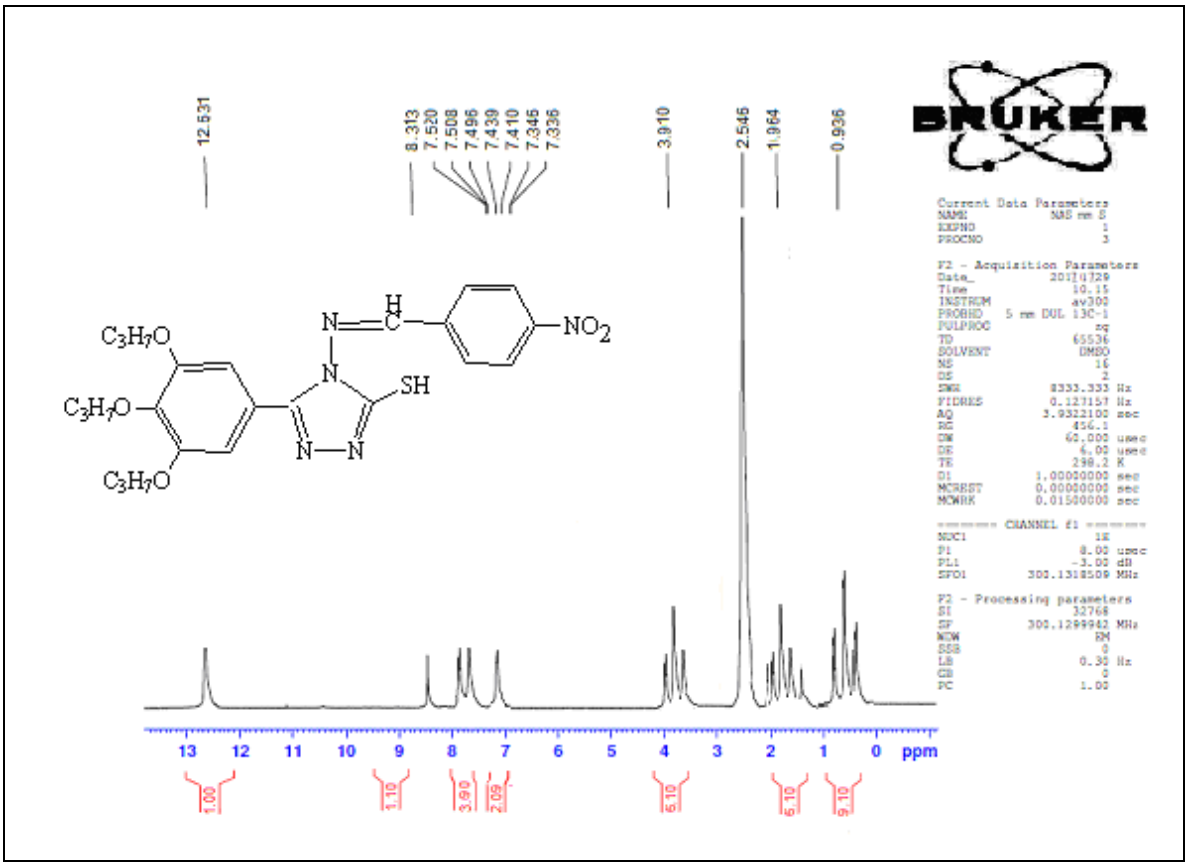


Figure 3.10: ^{1}HNMR spectrum of 3-thio-{5-yl-(3`,4`,5`-tripropoxyphenyl)}-4-(4``-nitrobenzelidineamino)-1,2,4-triazole (VII)$_f$

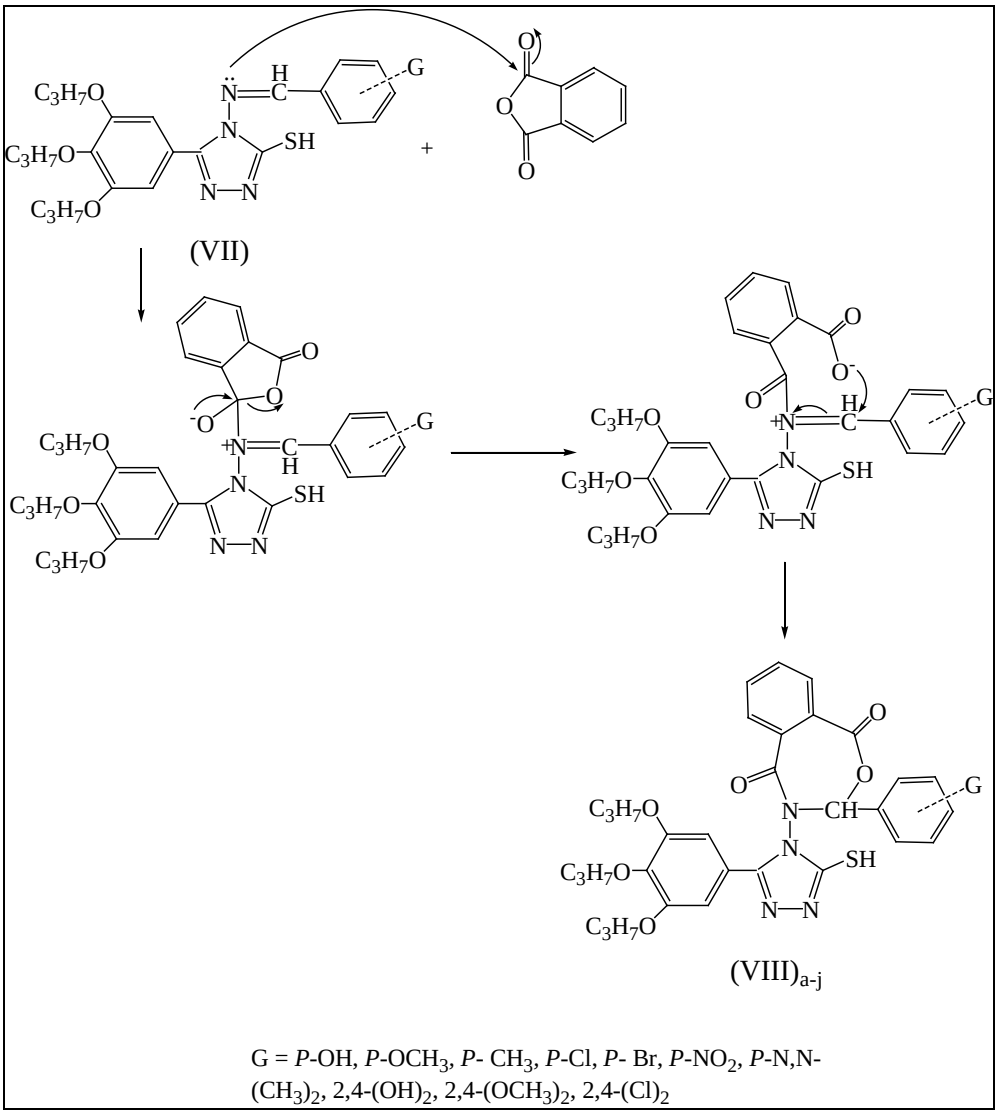
Table 3.3: Characteristic FTIR absorption bands of synthesizes compounds (VII)$_{a-j}$.

COMP. NO.	G	νAR H	ν C- H ALIPH.	ν CH = N	ν C =C	γ - SUB.BENZENE	OTHER
(VII)$_a$	4-OH	3042	2956 2842	1618	1595	845, 754, 712	3312 (O – H)
(VII)$_b$	4-OCH_3	3087	2957 2867	1621	1587	842, 755, 714	1100 (C – O)
(VII)$_c$	4-CH_3	3068	2973 2881	1620	1592	834, 751, 714	-
(VII)$_d$	4-Cl	3080	2976 2882	1623	1597	835, 754, 720	623 (C – Cl)
(VII)$_e$	4-Br	3040	2931 2881	1628	1600	841, 756, 712	642(C – Br)
(VII)$_f$	4- NO_2	3087	2937 2864	1624	1571	839, 754. 715	1548, 1345 (NO_2)
(VII)$_g$	4- N,N$(CH_3)_2$	3065	2986 2876	1618	1589	834, 751, 718	1143 (C – N)
(VII)$_h$	2,4- $(OH)_2$	3072	2981 2865	1621	1600	835, 755, 715	3342(O – H)
(VII)$_i$	2,4-$(OCH_3)_2$	3056	2977 2861	1623	1598	837, 756, 720	1157 (C – O)
(VII)$_j$	2,4-$(Cl)_2$	3068	2970 2851	1620	1597	841, 758, 718	626 (C – Cl)

3.6 Syntheses of 2-(substituted phenyl)3-(5-yl-(3`,4`,5`-tripropoxyphenyl)-3-thio- [1,2,4] triazolo [1,3] Oxazepine-4,7-dione(VIII)$_{a-j}$:

Compounds $(VIII)_{a-j}$ were synthesized by the reaction of Schiff base compounds $(VII)_{a-j}$ with phthalic anhydride in dry benzene to give 1,3-Oxazepine-4,7-dione derivative compounds. Cycloaddition is achieved by ring formation that results from the addition of π electrons either δ π bonds with formation of new δ bonds[61].

The reaction mechanism involve two steps, firstly nucleophilic substitution (tetrahydral mechanism) by the addition of nucleophile (nitrogen of imine group) to the carbon of the anhydride carbonyl group (ring opening), and secondly; nucleophilic addition of oxygen nucleophile to the carbon of the azo-methine group (ring closer) as shown below scheme (3.7):



Scheme 3.7: Mechanism steps for synthesis of substituted [1,2,4] triazolo [1,3] Oxazepine-4,7-dione(VIII)$_{a-j}$

The structures of all products were identified by using FT-IR and ^{1}H-NMR for some of them. The purities of compounds were confirmed by using an elemental analysis. The elemental analysis of compounds (VIII)$_{a-j}$ are listed in Table (3.4).

Table 3.4: Elemental Analysis (CHNS-O) for compounds (VIII)$_{a,h,I\ \&\ j}$

COMP .NO.	FORMULA	%C		% H		% N		% S	
		Calc.	Found	Calc.	Found	Calc.	Found	Calc.	Found
(VIII)$_a$	$C_{32}H_{34}N_4O_7S$	62.13	62.18	5.50	5.48	9.06	9.01	5.17	5.19
(VIII)$_h$	$C_{32}H_{34}N_4O_8S$	60.56	60.51	5.36	5.32	8.83	8.85	5.04	5.00
(VIII)$_i$	$C_{34}H_{38}N_4O_8S$	61.63	61.59	5.74	5.70	8.45	8.48	4.83	4.81
(VIII)$_j$	$C_{32}H_{32}Cl_2N_4O_6S$	57.22	57.18	4.76	4.71	8.34	8.31	4.76	4.72

Spectroscopic observation of $(VIII)_a$ for example is given: FT-IR (KBr, cm^{-1}) figure (3.12): 3276 (O – H stretching), 1736 (C = O of lactone stretching), 1651 (C = O of lactame stretching)[61], 3033 (Ar–H), 2987–2876 (*v* C–H, aliphatic stretching), 1567 (*v* C=C), 1232 (*v* C−O), 831 (out of plane bending for *para*-substituted benzene ring). Table (3.5) shows the FT-IR absorption bands for synthesizes compounds.

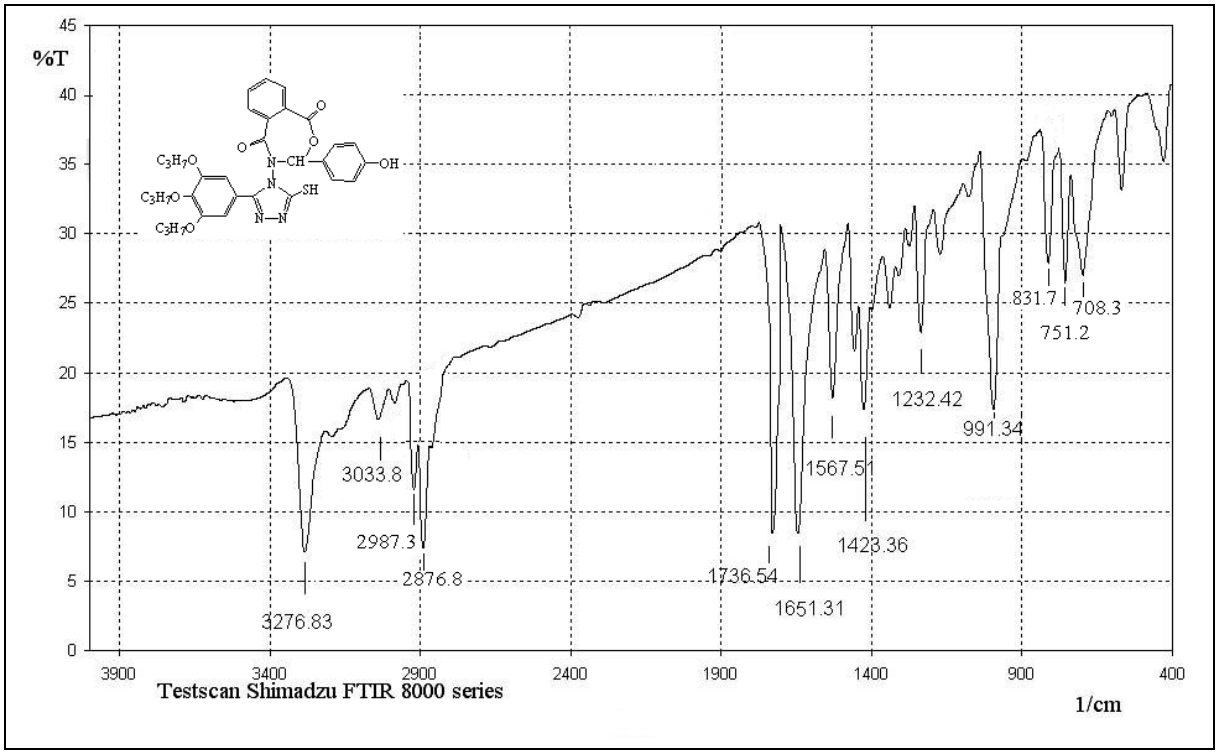


Figure 3.11: FTIR spectrum of 2-(4``-hydroxyphenyl)3-(5-yl-(3`,4`,5`-tripropoxyphenyl)-3-thio- [1,2,4] triazolo [1,3] Oxazepine-4,7-dione(VIII)$_a$

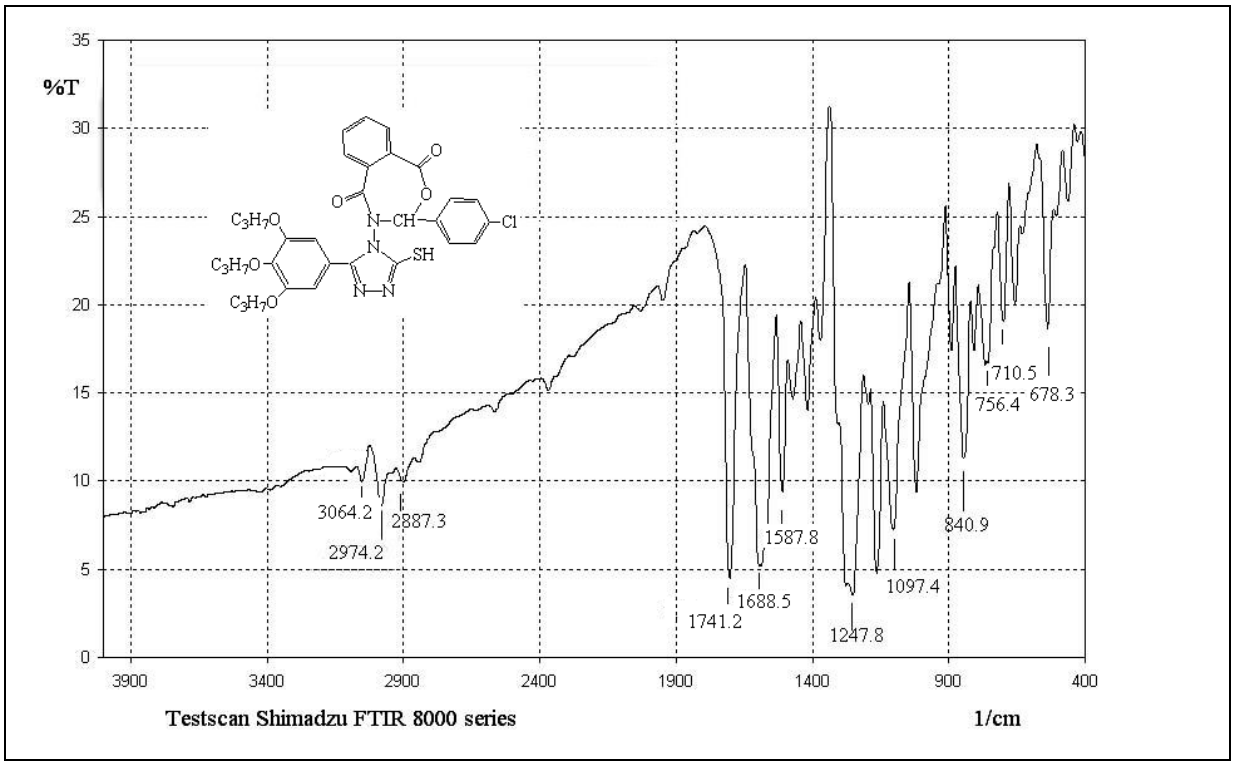


Figure 3.12: FTIR spectrum of 2-(4``-chlorophenyl)3-(5-yl-(3`,4`,5`-tripropoxyphenyl)-3-thio- [1,2,4] triazolo [1,3] Oxazepine-4,7-dione(VIII)$_d$

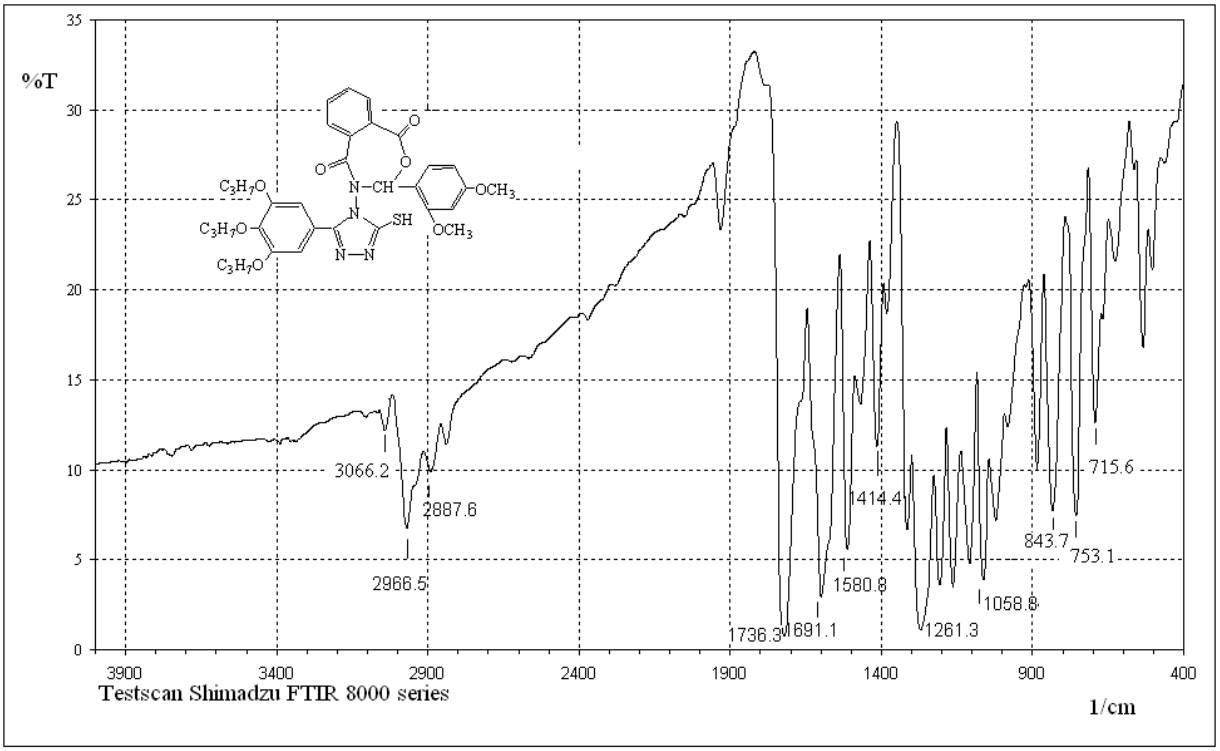


Figure 3.13: FTIR spectrum of 2-(2``,4``-dimethoxyphenyl)3-(5-yl-(3`,4`,5`-tripropoxyphenyl)-3-thio- [1,2,4] triazolo [1,3] Oxazepine-4,7-dione(VIII)$_i$

^{1}HNMR spectrum of compound (VIII)$_h$ (DMSO-d$_6$, δ in ppm) figure (3.15): 11.53(s, 1H, SH), 9.5 (s, OH), 7.92 -7.94 (s, 2H, arom. H), 7.53 – 7.59(d, 4H,

arom. H), 7.08 – 7.14 (3H, arom. H), 4.06 – 4.13 (t, 6H, (-OCH_2), 1.41 – 1.86 (m, 6H, CH_2), 0.9 – 1.0 (t, 9H, CH_3).

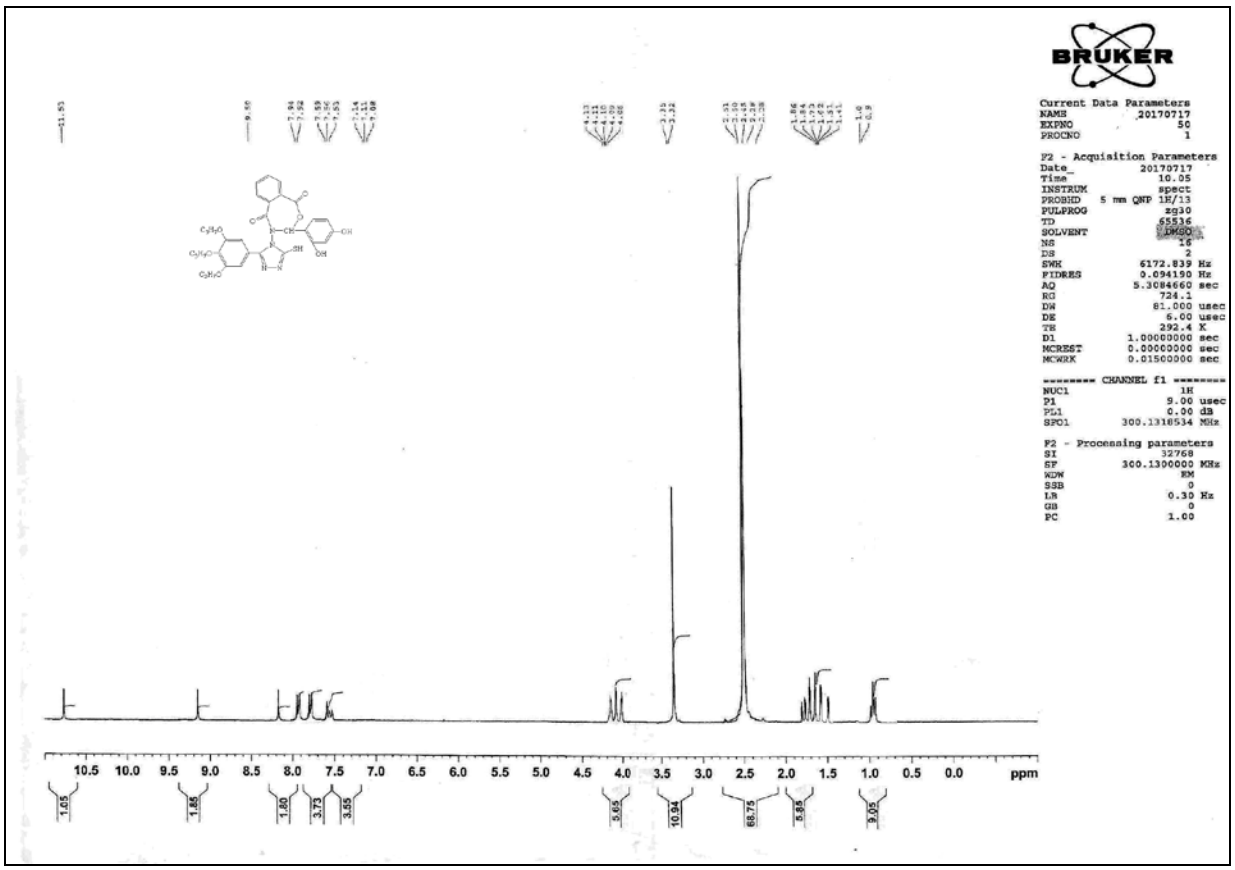


Figure 3.14: ^{1}HNMR spectrum of 2-(2``,4``-dihydroxyphenyl)3-(5-yl-(3`,4`,5`-tripropoxyphenyl)-3-thio- [1,2,4] triazolo [1,3] Oxazepine-4,7-dione(VIII)$_h$

^{1}HNMR spectrum of compound $(VIII)_f$ (DMSO-d_6, δ in ppm) figure (3.16): 10.91(s, 1H, SH), 6.95 -8.3 (10H, arom. H), 3.7 – 3.91 (t, 6H, (-OCH_2), 1.91 – 1.96 (m, 6H, CH_2), 1.09 – 1.14 (t, 9H, CH_3).

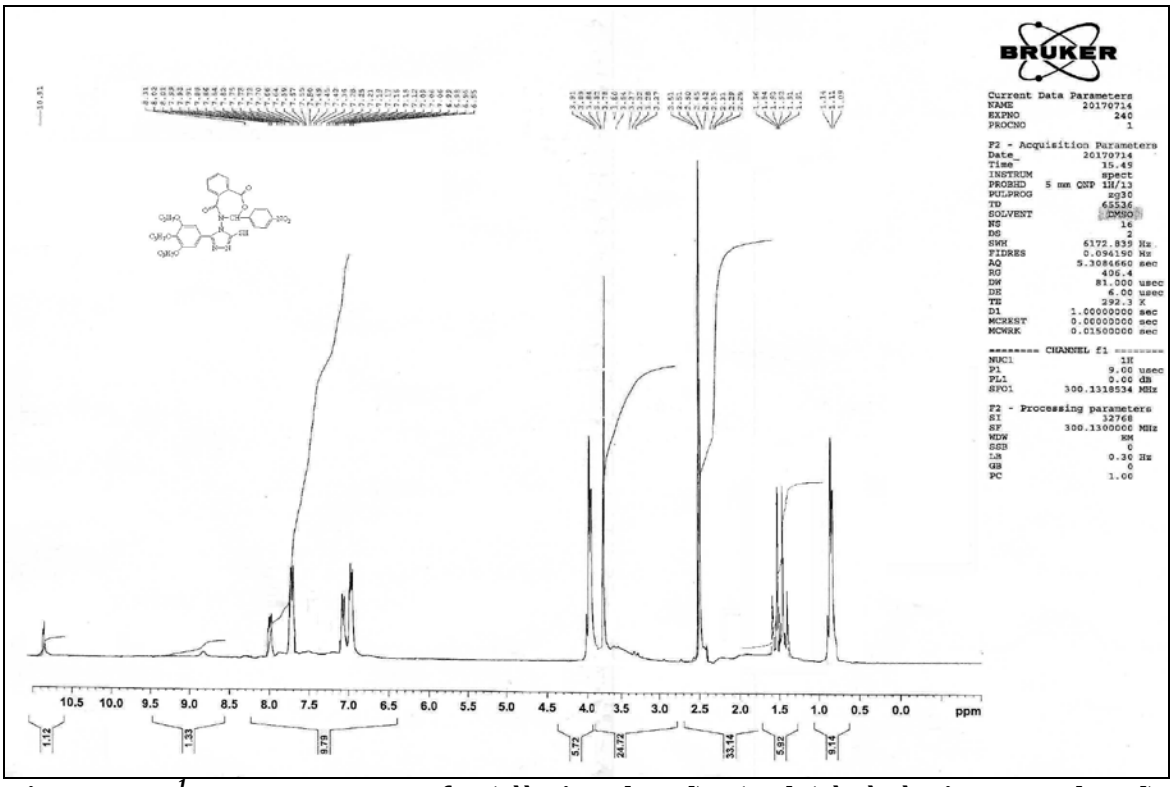


Figure 3.15: ^{1}HNMR spectrum of 2-(4``-nitrophenyl)3-(5-yl-(3`,4`,5`-tripropoxyphenyl)-3-thio- [1,2,4] triazolo [1,3] Oxazepine-4,7-dione(VIII)$_f$

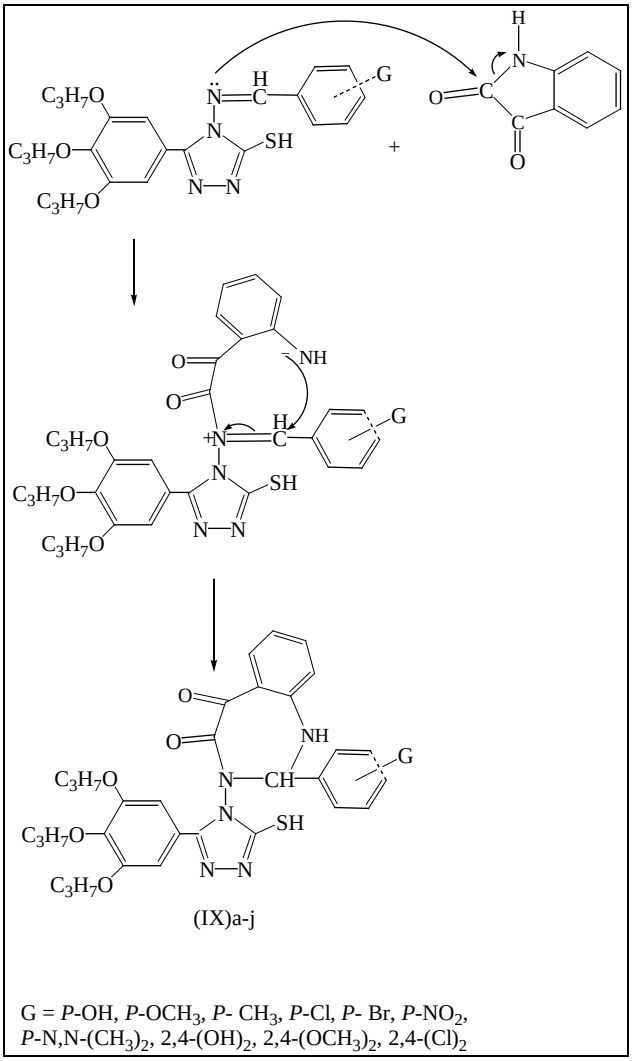
Table 3.5: Characteristic FTIR absorption bands of synthesizes compounds (VIII)$_{a-j}$.

COMP NO.	G	νAR H	νALIPH. C – H	ν C= O LACTONE	ν C = O LACTAME	γ *PARA-SUB.*	OTHER
(VIII)$_a$	4-OH	3033	2987 2876	1736	1651	831	3276 (O – H)
(VIII)$_b$	4-OCH_3	3072	2977 2885	1741	1685	834	1157 (C – O)
(VIII)$_c$	4-CH_3	3066	2965 2878	1739	1681	831	-
(VIII)$_d$	4-Cl	3064	2974 2887	1741	1688	840	678(C- Cl)
(VIII)$_e$	4-Br	3084	2951 2841	1734	1676	835	621 (C- Br)
(VIII)$_f$	4- NO_2	3058	2973 2870	1736	1672	832	1554 1345(NO_2)
(VIII)$_g$	4-N,N(CH_3)$_2$	3071	2966 2871	1739	1684	841	1045 (C – N)
(VIII)$_h$	2,4-(OH)$_2$	3081	2949 2863	1742	1688	837	3456
(VIII)$_i$	2,4-(OCH_3)$_2$	3066	2966 2887	1736	1691	843	1058 (C – O)
(VIII)$_j$	2,4-(Cl)$_2$	3078	2961 2881	1737	1692	844	683(C- Cl)

3.7 Synthesis of 2-(substituted phenyl)3-(5-yl-(3`,4`,5`-tripropoxyphenyl)-3-thio- [1,2,4] triazolo [1,3] diazepine (IX)$_{a-j}$:

The title compound was prepared by the reaction of schiff`s bases (VII)$_{a-j}$ with isatine in ethanol is turn collapses to the 7- membered heterocyclic system to give substituted [1,2,4] triazolo [3,4-b][1,3] diazepine derivatives compounds.

The reaction mechanism involve two steps, firstly nucleophilic substitution (tetrahydral mechanism) by the addition of nucleophile { nitrogen of imine group of compounds (VII)$_{a-j}$} to the carbon of the amide carbonyl group of isatin (ring opening), and secondly; nucleophilic addition of nitrogen nucleophile to the carbon of the azo-methine group (ring closer) as shown below scheme (3.8):



Scheme 3.8: Mechanism steps for synthesis of [1,2,4] triazolo [3,4-b][1,3] diazepine derivatives(IX)$_{a-j}$.

The structures of all products were identified by using FT-IR and some of them by ^{1}H-NMR and mass spectroscopy. The purities of compounds were confirmed using an elemental analysis. The elemental analysis of compounds $(IX)_{a-j}$ are listed in Table (3.6).

Table 3.6: Elemental Analysis (CHNS) for compounds $(IX)_{b, c, e \& f}$

COMP. NO.	FORMULA	%C		% H		% N		% S	
		Calc.	Found	Calc.	Found	Calc.	Found	Calc.	Found
$(IX)_b$	$C_{33}H_{37}N_5O_6S$	62.75	62.78	9.34	9.37	11.09	11.11	5.07	5.10
$(IX)_c$	$C_{33}H_{37}N_5O_5S$	64.39	64.42	6.01	6.06	11.38	11.42	5.20	5.27
$(IX)_e$	$C_{32}H_{34}N_5O_5S$	64.00	64.06	5.66	5.71	11.66	11.69	5.33	5.38
$(IX)_f$	$C_{32}H_{34}N_6O_7S$	59.44	59.50	4.95	5.01	13.00	13.04	4.95	5.02

Spectroscopic observation of $(IX)_c$ is given: FT-IR (KBr, cm^{-1}) figure (3.10): 3287, 2965, 2852, 1722, 1687 and 1604 which assign to (ν N-H), (ν C–H, aliphatic stretching), (C = O of ketone stretching), (C = O of lactam stretching) and (ν C=C stretching) respectively. Table (3.7) shows the FT-IR absorption bands for synthesizes compounds.

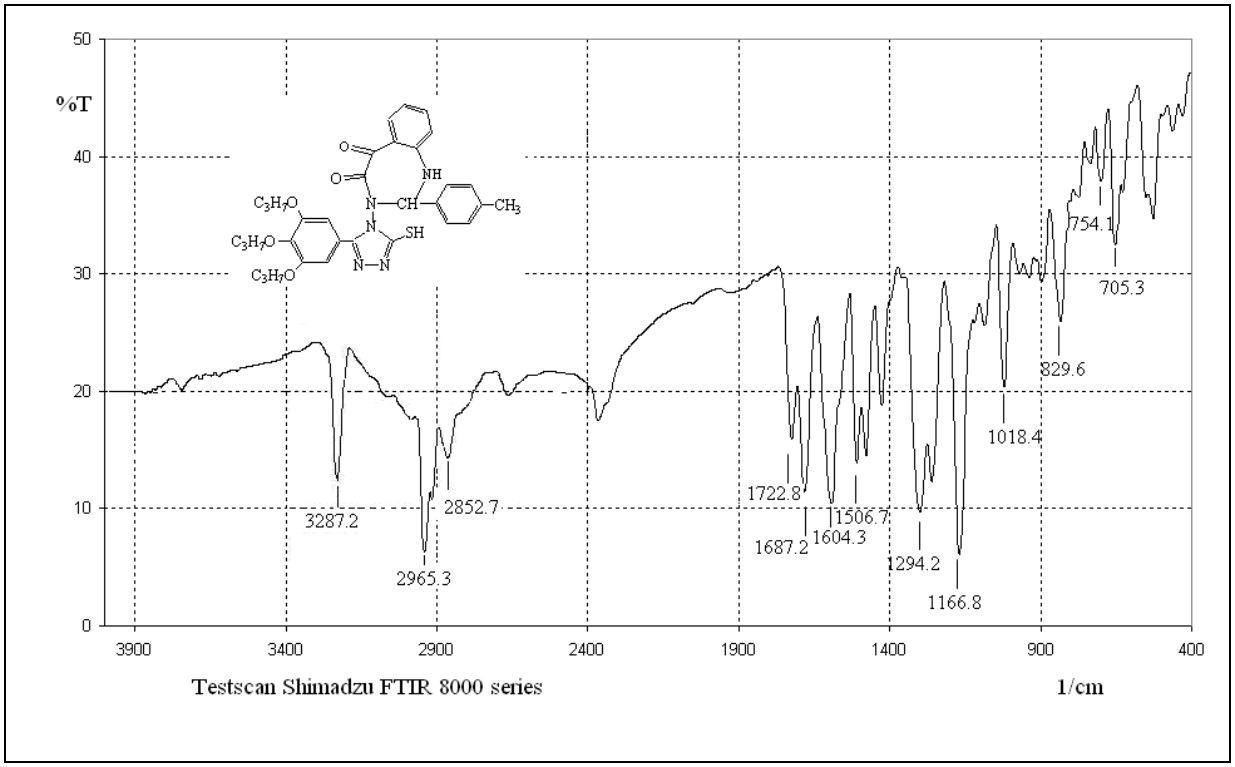


Figure 3.16: FTIR spectrum of 2-(toluyl)3-(5-yl-(3`,4`,5`-tripropoxyphenyl)-3-thio- [1,2,4] triazolo [1,3] diazepine $(IX)_c$

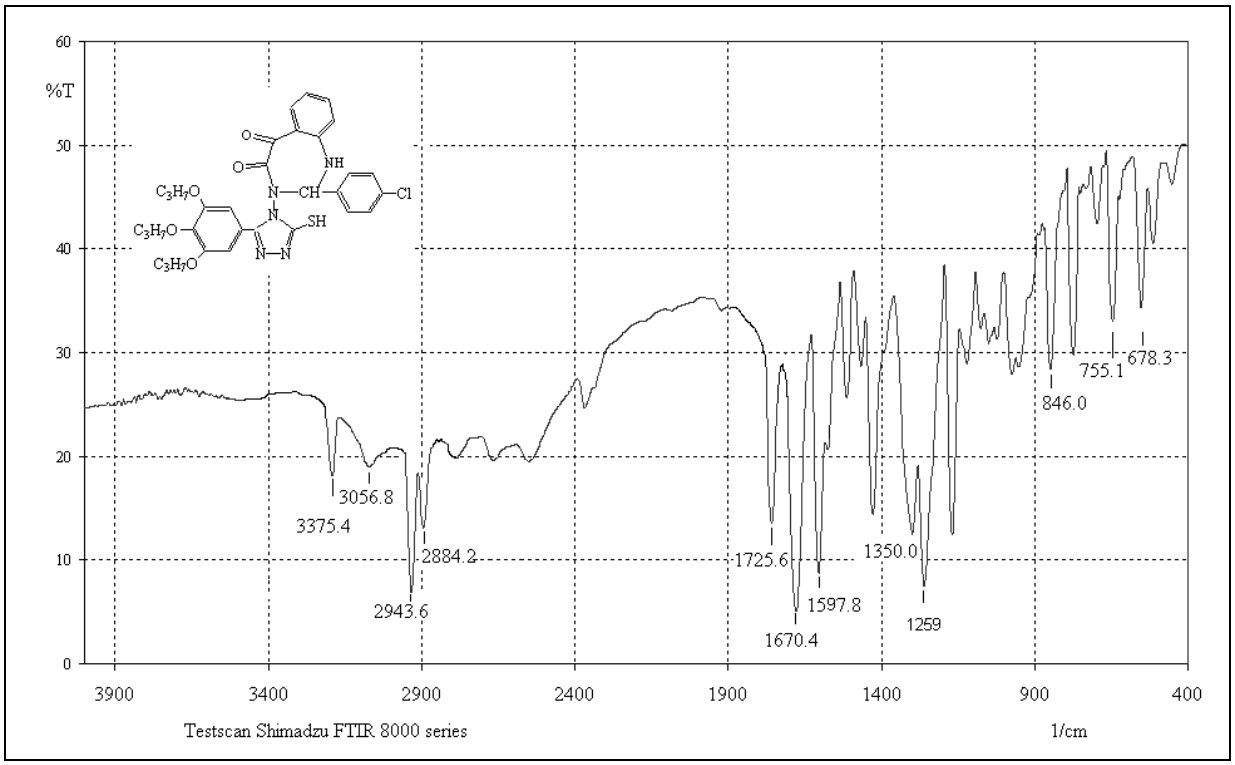


Figure 3.17: FTIR spectrum of 2-(4``-chlorophenyl)3-(5-yl-(3`,4`,5`-tripropoxyphenyl)-3-thio- [1,2,4] triazolo [1,3] diazepine (IX)$_d$

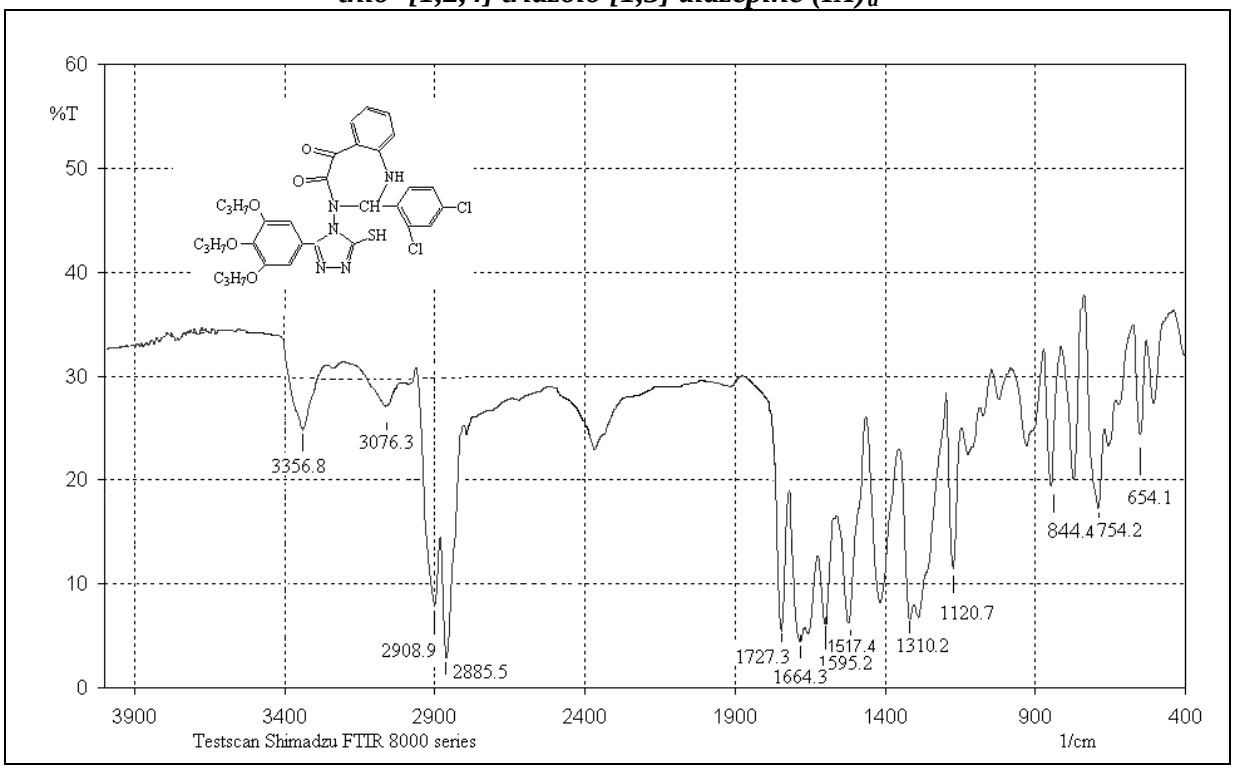


Figure 3.18: FTIR spectrum of 2-(2``,4``-dichlorophenyl)3-(5-yl-(3`,4`,5`-tripropoxyphenyl)-3-thio- [1,2,4] triazolo [1,3] diazepine (IX)$_j$

^{1}HNMR spectrum of compound $(IX)_b$ (Aceton-d_6, δ in ppm) figure (3.13): 10.88 (s, 1H, SH), 7.00 – 8.06 (s & d, 10 H, arom. H), 6.57 – 6.72 (s, 1H, N – H), 4.37 – 4.58 (t, 6 H, OCH_2), 3.83 – 3.88 (s, 3H, OCH_3), 1.91 – 2.10 (m, 6H, CH_2), 0.90 – 1.10 (t, 9H, CH_3).

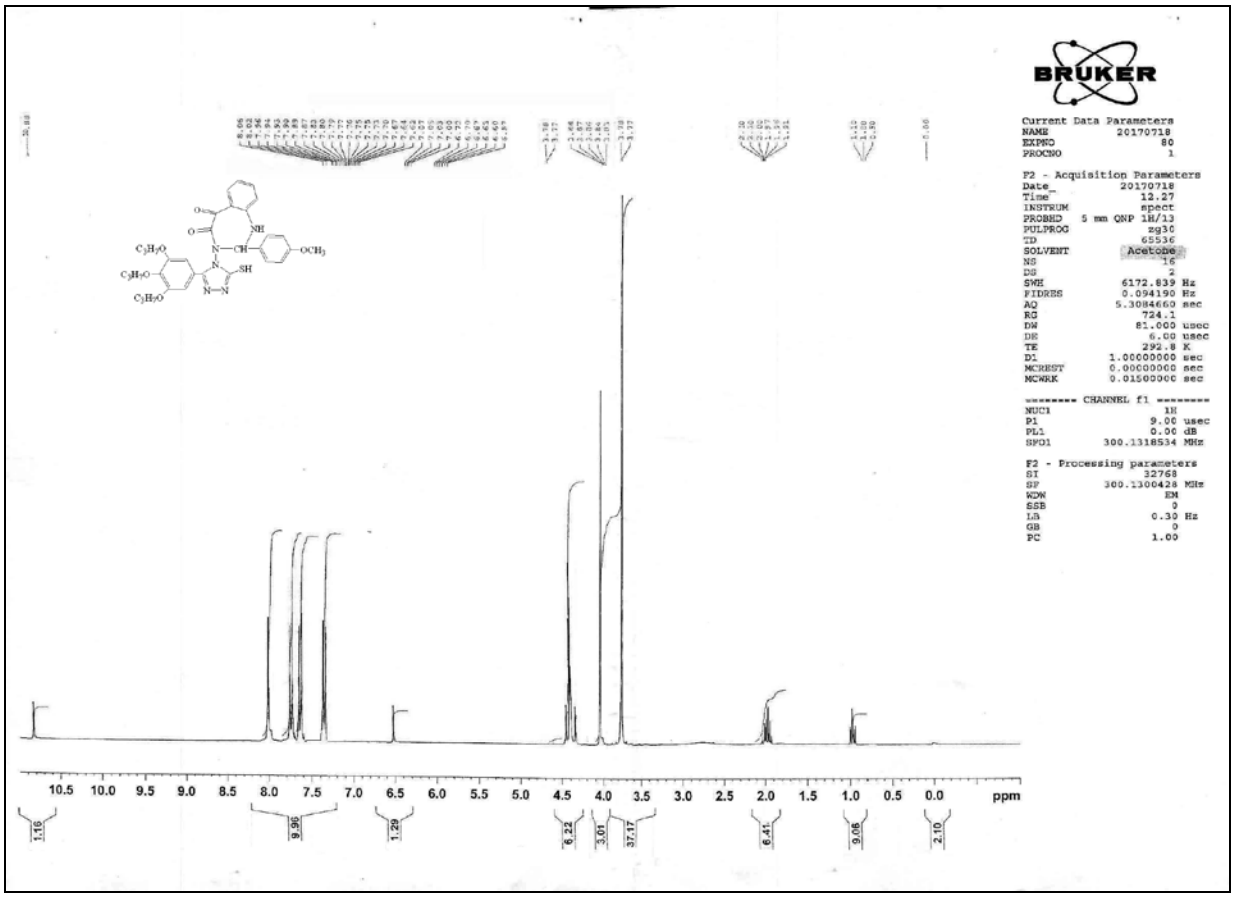


Figure 3.19: ^{1}HNMR spectrum of 2-(4``-methoxyphenyl)3-(5-yl-(3`,4`,5`-tripropoxyphenyl)-3-thio- [1,2,4] triazolo [1,3] diazepine $(IX)_b$

^{1}HNMR spectrum of compound $(IX)_e$ (DMSO-d_6, δ in ppm) figure (3.14): 11.10 (s, 1H, SH), 6.85 – 8.02 (s & d, 10 H, arom. H), 6.49 – 6.54 (s, 1H, N – H), 3.78 – 3.91 (t, 6 H, OCH_2), 1.91 – 1.96 (m, 6H, CH_2), 1.09 – 1.14 (t, 9H, CH_3).

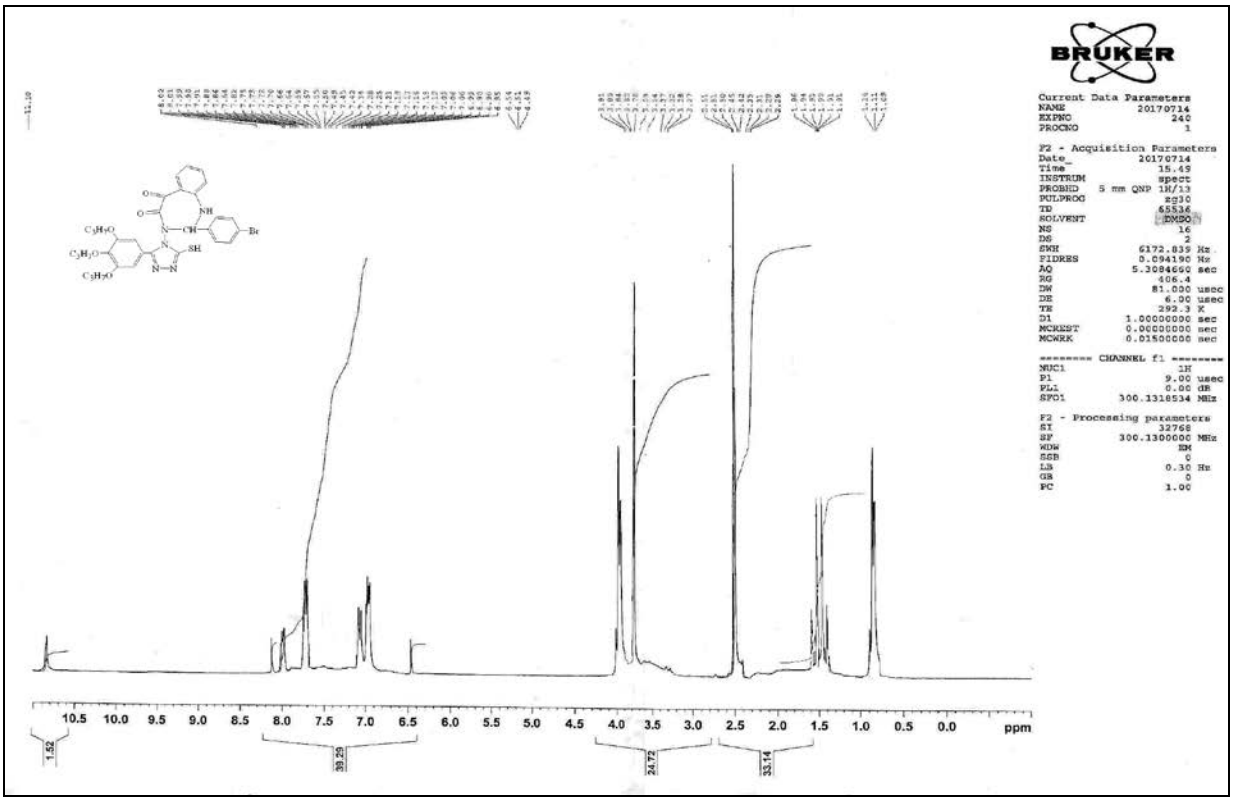


Figure 3.20: ^{1}HNMR spectrum of 2-(4``-bromophenyl)3-(5-yl-(3`,4`,5`-tripropoxyphenyl)-3-thio- [1,2,4] triazolo [1,3] diazepine $(IX)_e$

Table 3.7: Characteristic FTIR absorption bands of synthesizes compounds $(IX)_{a-j}$.

COMP. NO.	G	ν (N – H)	ν (C – H) ALIPHATIC	ν (C = O) KETONE	ν (C = O) LACTAME	OTHERS
$(IX)_a$	4-OH	3280	2931& 2865	1724	1693	
$(IX)_b$	4-OCH_3	3282	2989 & 2877	1726	1693	1089 ν (C – O)
$(IX)_c$	4-CH_3	3398	2939 & 2845	1714	1672	1083 ν (C – O)
$(IX)_d$	4-Cl	3219	2917 &2876	1721	1686	628 ν (C – Cl)
$(IX)_e$	4-Br	3268	2952 & 2871	1732	1685	931 ν (C – Br)
$(IX)_f$	4- NO_2	3307	2970 & 2845	1729	1643	1552&1325ν (NO_2)
$(IX)_g$	4- N,N$(CH_3)_2$	3310	2932 &2861	1722	1658	-
$(IX)_h$	2,4- $(OH)_2$	3263	2973& 2829	1726	1660	-
$(IX)_i$	2,4- $(OCH_3)_2$	3238	2980& 2860	1739	1700	1089 ν (C – O)
$(IX)_j$	2,4-$(Cl)_2$	3196	2939& 2854	1719	1649	628 ν (C – Cl)

3.8 Antibacterial Studies

Some of the synthesized compounds were assayed for their antibacterial activity against four representative Gram-positive bacteria *viz*. ***(Staphylococcus aureus***, ***Bacillus)*** and Gram-negative bacteria *viz*. ***(Pseudomonas***, ***Enterobacter***) by disc diffusion method[62], and the mean inhibition zone data are reported in Table 3.8. All assays included the solvent and reference controls. ***Erythro Mycin*** was used as standard drug. The investigation of antibacterial screening data reveal that almost all the compounds **(VIII)$_{a,b,e,f,j}$** and **(IX)$_{a,b,e,f,j}$** are active and showing moderate to good antibacterial activity with concentrations (10, 25, 50, 100) µg/ml.

The results were listed in Table (3.8), and shown in Figures [(3.21) - (3.25)], including the reference drug (Erythro Mycin).

Table 3.8: The inhibition zones in (mm) and Minimum inhibition zones (MIC) in (µg/mL) for compounds [6(A-C) – 10(A-C)] and Erythro Mycin against Staphylococcus aureus, Bacillus, Pseudomonas and Enterobacter Enterobacter

Comp. No.	Concentration (µg/mL)	Inhibition Zone in (mm)			
		Gram Positive		Gram Negative	
		(Staphylococcus aureus)	*(Bacillus)*	*Pseudomonas*	*Enterobacter*
(VIII)$_a$	**10**	30	25	15	22
	25	32	28	18	24
	50	35	31	21	29
	100	43	38	28	33
(VIII)$_b$	**10**	15	10	2	5
	25	18	12	5	8
	50	20	15	8	11
	100	23	18	11	15
	10	25	20	5	23

$(VIII)_e$	**25**	28	23	8	26
	50	30	25	10	28
	100	32	30	14	32
$(VIII)_f$	**10**	27	18	20	24
	25	29	21	22	26
	50	31	23	25	28
	100	37	28	30	33
$(VIII)_j$	**10**	18	15	3	13
	25	20	17	6	15
	50	22	22	8	17
	100	28	25	12	22
$(IX)_a$	**10**	18	12	5	18
	25	22	15	7	20
	50	24	17	9	23
	100	30	21	13	26
$(IX)_b$	**10**	27	20	20	25
	25	29	22	23	26
	50	32	25	25	30
	100	35	30	28	33
$(IX)_e$	**10**	20	18	12	20
	25	22	20	15	23
	50	24	22	18	25
	100	28	27	20	31
$(IX)_f$	**10**	18	12	10	8
	25	20	15	13	11
	50	24	18	15	13
	100	30	23	20	18
	10	18	23	22	15

$(IX)_j$	**25**	22	20	18	18
	50	26	24	22	20
	100	32	30	30	28

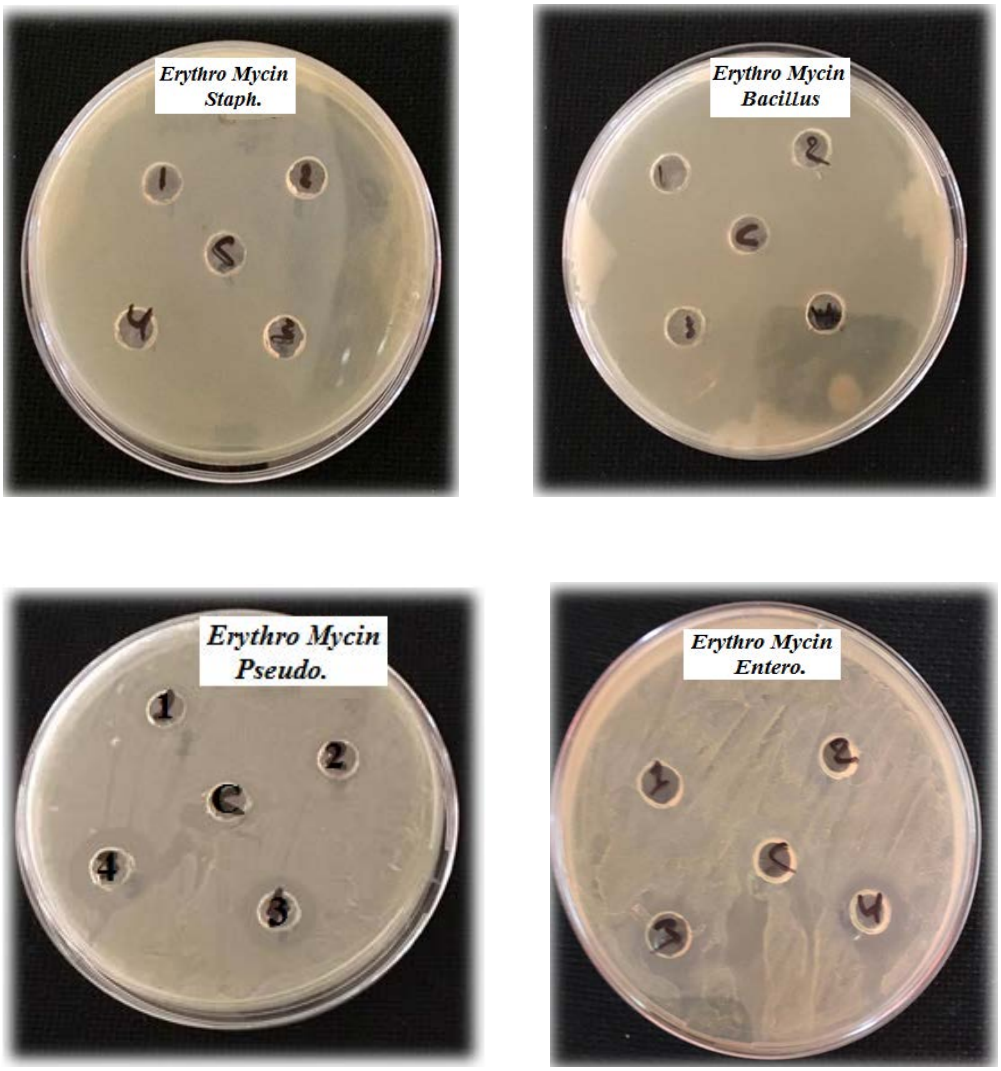


Figure 3.21: Inhibition zones of Erythro Mycin with concentrations (10, 25, 50, 100) µg/ml against staphylococcus aureus, Bacillus, Pseudomonas, and Enterobacter with control (DMSO).

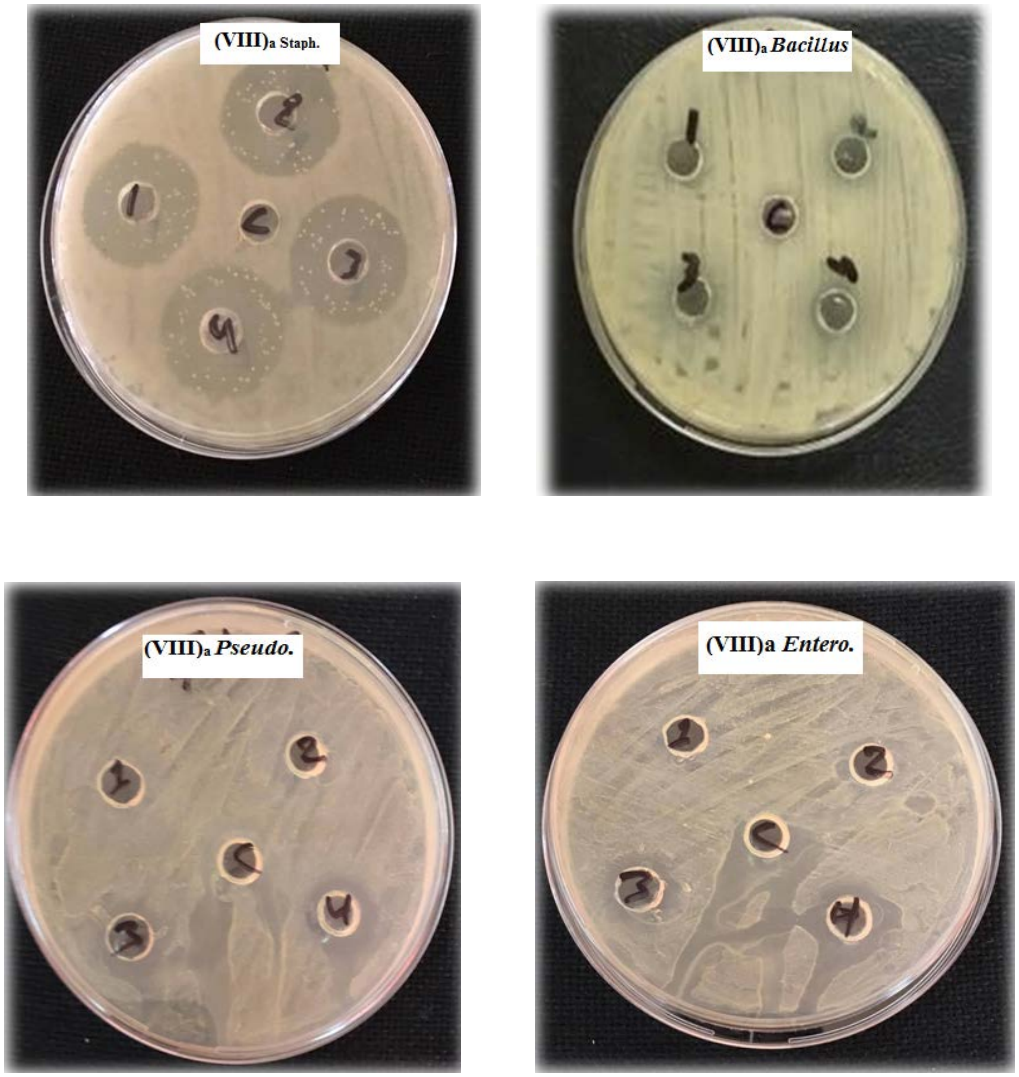


Figure 3.22: Inhibition zones of compound (VIII)$_a$ with concentrations (10, 25, 50, 100) µg/ml against staphylococcus aureus, Bacillus, Pseudomonas, and Enterobacter with control (DMSO).

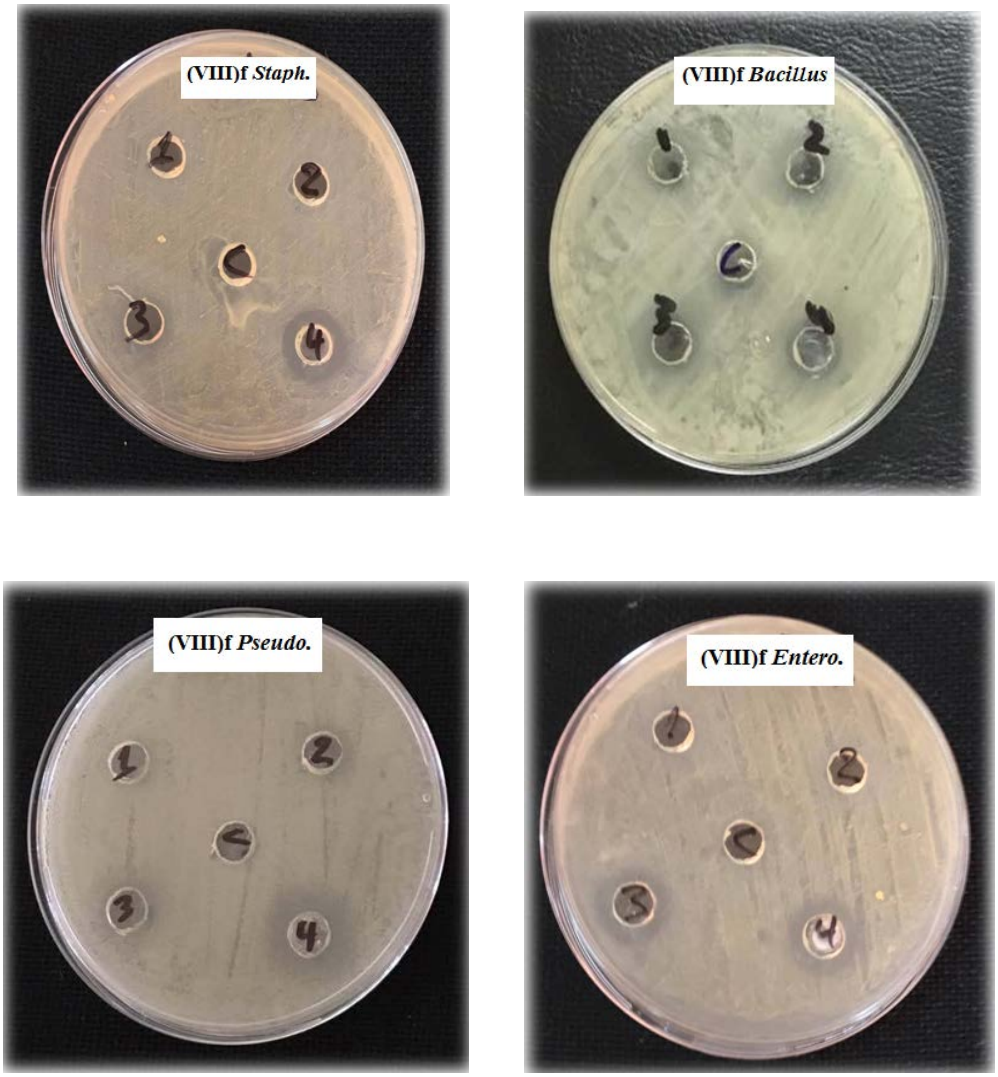


Figure 3.23: Inhibition zones of compound $(VIII)_f$ with concentrations (10, 25, 50, 100) µg/ml against staphylococcus aureus, Bacillus, Pseudomonas, and Enterobacter with control (DMSO).

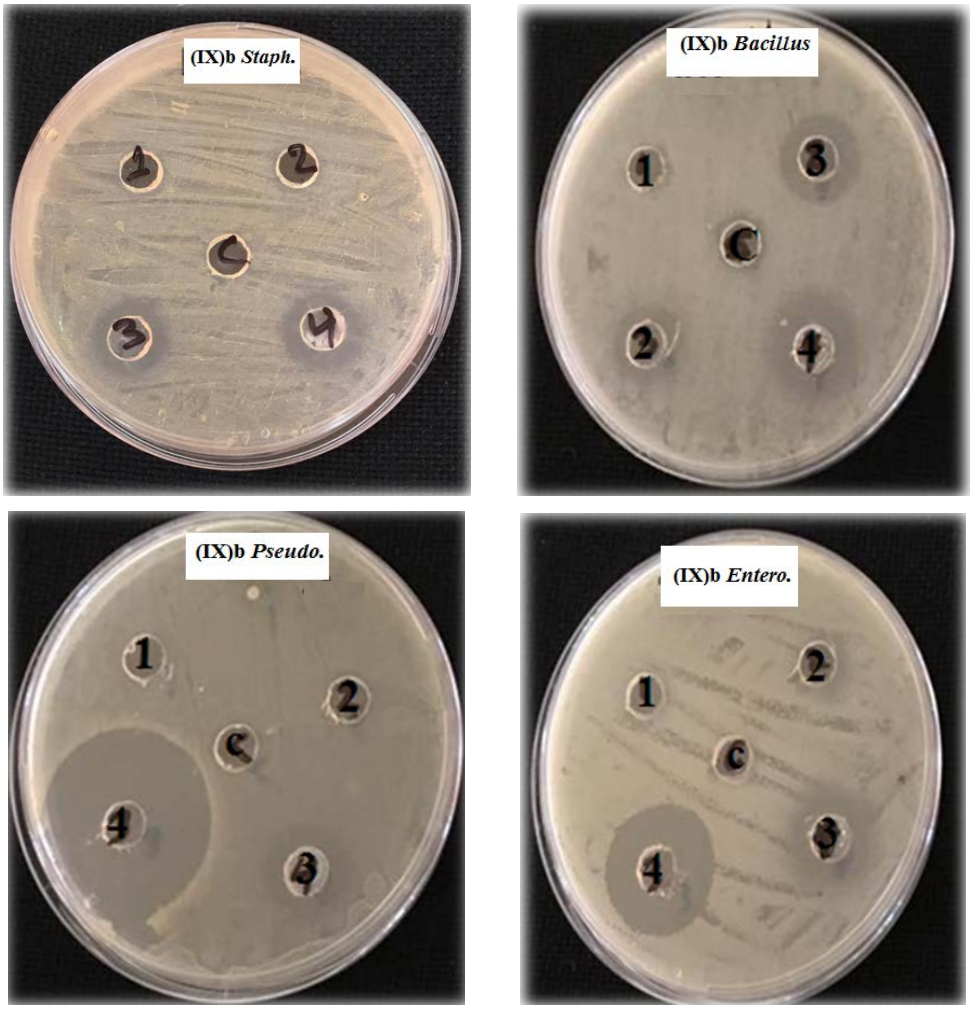


Figure 3.24: Inhibition zones of compound $(IX)_b$ with concentrations (10, 25, 50, 100) µg/ml against staphylococcus aureus, Bacillus, Pseudomonas, and Enterobacter with control (DMSO).

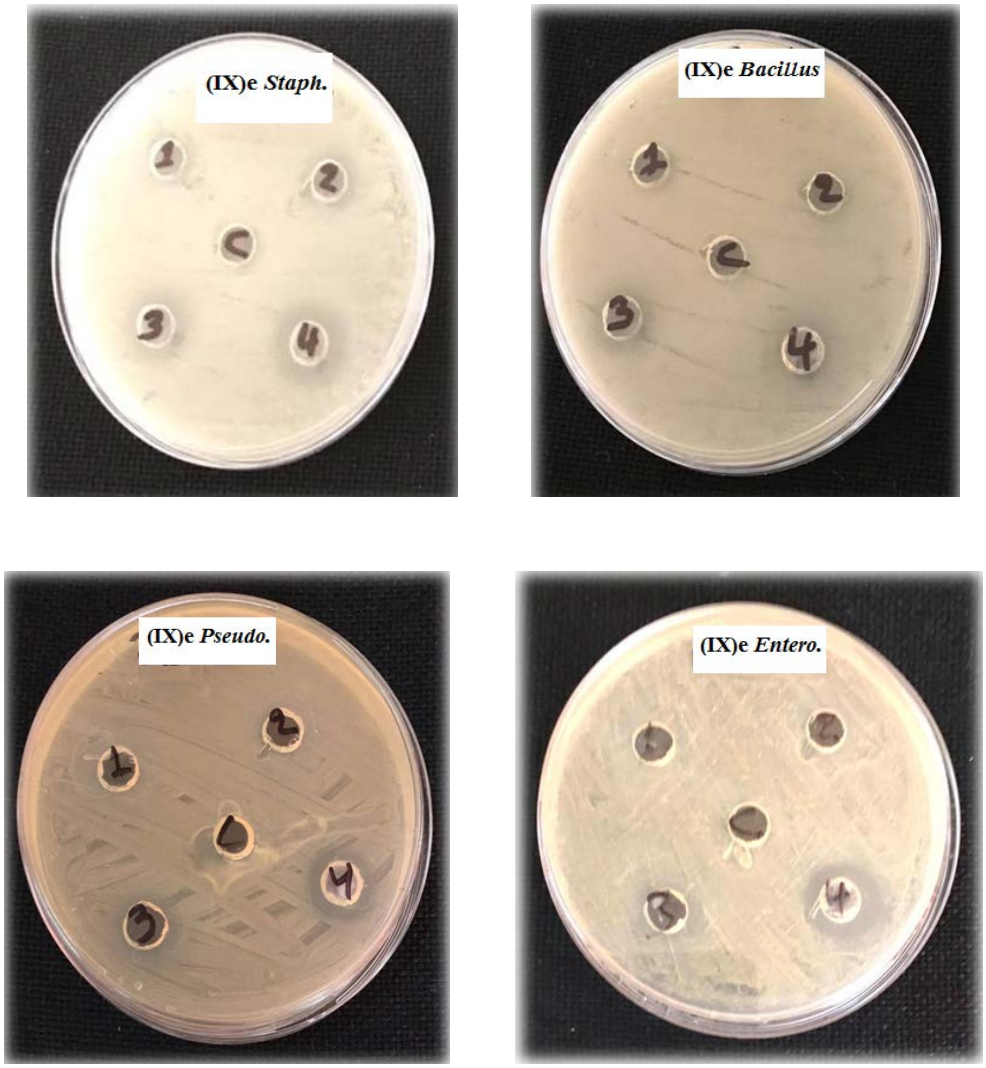


Figure 3.25: Inhibition zones of compound (IX)$_e$ with concentrations (10, 25, 50, 100) µg/ml against staphylococcus aureus, Bacillus, Pseudomonas, and Enterobacter with control (DMSO).

3.9 Conclusions

A new derivatives of ***2-(substituted phenyl)3-(5-yl-(3`,4`,5`-tripropoxyphenyl)-3-thio- [1,2,4] triazolo [1,3] Oxazepine-4,7-dione(VIII)$_{a-j}$*** and ***2-( substituted phenyl)3-(5-yl-(3`,4`,5`-tripropoxyphenyl)-3-thio- [1,2,4] triazolo [1,3] diazepine (IX)$_{a-j}$*** has been synthesized and evaluated for their antimicrobial activity against Gram-positive, Gram-negative bacteria. Most of the compounds showed a moderate degree of antimicrobial activity.

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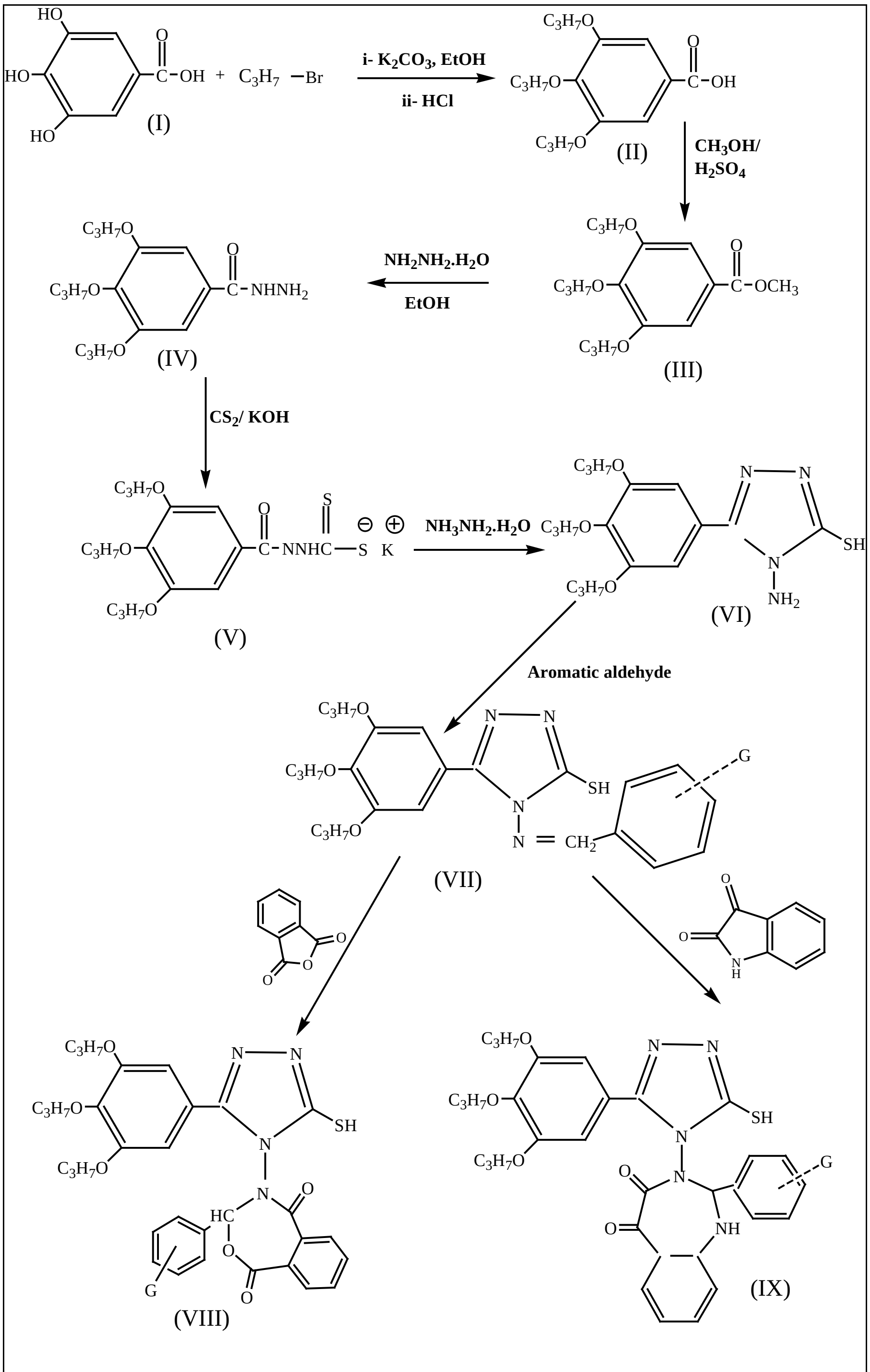
ملخص الاطروحة:

تضمن العمل تحضير مركبات جديدة للاوكسازبين والدايازبين وكما موضح بالمخطط ادناه.

لأجل الحصول على المركبات المستهدفة، تم اعتماد الطرق التالية:

- تحضير ٣،٤،٥–ثلاثي بروبوكسي حامض البنزويك (II) من خلال تفاعل حامض الجاليك (I) مع بروميد البروبيل.
- تم تحضير استر المثيل (III) عن طريق الاسترة المباشرة لـ٣،٤،٥–ثلاثي بروبوكسي حامض البنزويك مع الميثانول بوجود حامض الكبريتيك كعامل مساعد.
- تحضير ٣،٤،٥–ثلاثي بروبوكسي هايدرازيد حامض البنزويك بتفاعل الاستر (III) مع الهايدرازين المائي.
- تفاعل الهايدرازيد (IV) مع ثنائي كبريتيد الكاربون بوسط قاعدي يؤدي الى تحضير ملح الثايوكاربزيت (V) والذي يعاني غلق حلقي بوجود زيادة من الهايدرازين المائي لينتج 5-yl-(3`,4`,5`-tripropoxyphenyl)-3-thio-4-amino-1,2,4-triazole (VI).
- تم تحضير قواعد شف من خلال تفاعل التكاثف بين 3-thio-{5-yl-(3`,4`,5`-tripropoxyphenyl)}-4-amino-1,2,4-triazole (VI). مع الديهايدات اروماتية في الايثانول المطلق وبوجود قطرات قليلة من حامض الخليك الثلجي.
- تم تحضير مشتقات ٣،١–اوكسازبين–٧،٤–دايون $(VIII)_{a-j}$ من تفاعل قواعد شف $(VII)_{a-j}$ مع حامض الفثاليك اللامائي في البنزين الجاف.
- تم تحضير مشتقات ٣،١–دايازبين $(IX)_{a-j}$ من تفاعل قواعد شف $(VII)_{a-j}$ مع الايساتين في الميثانول.
- جميع المركبات المحضرة تم تشخيصها باستخدام مطياف الاشعة تحت الحمراء FTIR والبعض منها تم تشخيصه باستخدام تحليل العناصر CHNS-O ومطيافية الرنين النووي المغناطيسي لذرة الهيدروجين ^{1}HNMR.

- درست الفعالية البايولوجية لبعض المركبات المحضرة كمركبات مثبطة لنمو بعض الجراثيم الموجبة والسالبة لصبغة كرام بطريقة الانتشار، وقد أبدت بعض المركبات فعالية ملحوظة في قتل أو تثبيط هذه الجراثيم.



G = *P*-OH, *P*-OCH_3, *P*- CH_3, *P*-Cl, *P*- Br, *P*-NO_2, *P*-N,N-$(CH_3)_2$, 2,4-$(OH)_2$, 2,4-$(OCH_3)_2$, 2,4-$(Cl)_2$

كلخض ٠: لزئنطخةحصي نلكلنقائ ة

جمهورية العراق

وزارة التعليم العالي والبحث العلمي

كلية العلوم /جامعة النهرين

قسم الكيمياء

تحضير و تشخيص مشتقات جديدة للغاليك اسيد و تشخيص فعاليتها البكتيرية

رسالة

مقدمة الى مجلس كلية العلوم /جامعة النهرين كجزء من متطلبات نيل درجة الماجستير في علوم الكيمياء

من قبل

صفا عامر يحيى

(بكالوريوس ٢٠١٥)

إشراف

أ.م.د. نسرين رحيم جبر

ذي الحجة ١٤٣٨

٢٠١٧ ايلول