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Synthesis , characterization and antibacterial activity of new series of sulfamethoxazole derivatives

A Thesis

Submitted to the Department of Pharmaceutical Chemistry and the Committee of Graduate Studies of the College of Pharmacy-University of Al-Mustansiriyah in Partial Fulfillment of the Requirement for the Degree of Master in Pharmacy "Pharmaceutical Chemistry"

By

Zainb Mohammed abd al-khaliq

(B.Sc. Pharmacy 2012)

Supervised by

Assist. Prof.

Dr. Monther Faisal Mahdi

Assist. Prof.

Dr. Rafah Al-Smaism

2015 AD **1436 AH**

Certification

We certify that this thesis, ***"Synthesis , characterization and antibacterial activity of new series of sulfamethoxazole derivatives"****, was prepared under our supervision at the Department of pharmaceutical Chemistry, College of Pharmacy-University of AL-Mustansiriyah as a partial fulfillment of the requirements for the degree of Master in Pharmacy (Pharmaceutical chemistry).*

Signature:

Name: ***Assist. Prof. Dr. Monther Faisal Mahdi***

Address: Department of Pharmaceutical Chemistry

College of Pharmacy-University of Al-Mustansiriyah

Date: / /2015

Signature:

Name: ***Assist. Prof. Dr. Rafah Al-Smaism***

Address: Department of Pharmaceutical Chemistry

College of Pharmacy- University of Al-Mustansiriyah

Date: / /2015

In view of the available recommendation, we forward this thesis for debate by examination committee.

Signature:

Name: ***Dr.Inam S.Arif***

Chairman of the Committee of Graduate Studies in the College of Pharmacy

Date: / /2015

Certification

We, the examining Committee after reading this thesis, ***"Synthesis , characterization and antibacterial activity of new series of sulfamethoxazole derivatives",*** *and examining the student* ***Zainb Mohammed abd al-khaliq*** *in its contents, find it adequate as a Partial Fulfillment of the requirements for the Degree of Master in Pharmacy (Pharmaceutical Chemistry).*

Signature:

Name:

(Chairman)

Date: / /2015

Signature:

Name:

(Member)

Date: / /2015

Signature:

Name:

(Member)

Date: / /2015

Approved for the University Committee for the Graduate Studies.

Signature:

Name: Assistant. Prof. Dr. Monther Faisal Mahdi

Dean of College of Pharmacy

University of Al- Mustansiriyah

Date: / /2015

﴿ وَمَا أُوتِيتُمْ مِنْ الْعِلْمِ إِلاَّ قَلِيلاً ﴾

صَدقَ الله الْعَلِيُّ العَظِيم

سورةالإسراء/الآية ٨٥

Dedication

TO

Those Who Live With Me Day And Night…..

The Spirit Of My Father…

The Loving Heart Of My Mother…

The Pride Of My Life…

My Elder Brother , Zaid ;

My Teachers…

My Friends…

Sisters And Brothers

With My Love

Zainb Mohammed abd al-khaliq

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List of Abbreviations

Comp	Compound
COX	Cyclooxygenase
CFU	Colony forming units
DNAs	Deoxyribonucleic acid
DMF	Dimethylformamide
FT-IR	Fourier transform infrared spectroscopy
G-VE	Gram negative
G+VE	Gram positive
HIV	Human Immunodeficiency Virus
MIC	Minimum inhibitory concentration
NO	Number
PABA	Para-aminobenzoic acid
^{1}H -NMR	Proton nuclear magnetic resonance
R_f	Relative to front

RNA	***Ribonucleic acid***
SAPs	***Serine amide phosphates***
S.aureus	***Staphylococcus aureus***
Str	***Stretching***
SMX	***Sulfamethoxazole***
Sym	***Symmetric***
THF	***Tetrahydrofuran***
TLC	***Thin layer chromatography***
TMP	***Trimethoprim***

Abstract

Sulfamethoxazole (SMX) belong to the sulfonamide group of antibiotic.It was chosen to be the representative of this group due to its widespread use and detection frequency in the aquatic environment. The thiazolidinones ring has been integrated into a widespread range of known biologically energetic compounds , either as a substituent group or as a replacement of another ring inspired researchers to produce several compounds containing this moiety. Furthermore the chemistry of chalcones has produced serious scientific readings during the world . Chiefly interest has been concentrated on the creation and biodynamic actions of chalcones , so that diversity of novel heterocycles with good pharmaceutical shape can be designed.

Synthetic procedures have been successfully developed for the generation of the target compounds were used six different aromatic para benzaldehydes of (H ,OH , OCH_3 , NO_2 , Cl & $N(CH_3)_2$), and following multi steps reaction procedure. The purity of the products was checked by using thin layer chromatography (TLC). The chemical structure of intermediate and final compounds were characterized and confirmed by measuring their melting points, FT-IR spectroscopy, elemental microanalysis (CHNS) and ^{1}HNMR of final compounds.

The preliminary study of antimicrobial activity were done on 3 different strains of bacteria and showed that the final compounds $M_{3(a-f)}$ have significant activity compared with standard drug (Sulfamethoxazole), have moderate to good activity.

CHAPTER ONE

INTRODUCTION

1.1 Background of Antibacterial agents:

From the time when the discovery of the penicillin by Alexander Fleming in 1929 and the first starter of the sulpha medications by Domagk in 1932, the number of new antimicrobials existing has enlarged vastly between 1940 and 1960. 'The period of antibiotics' lead to positivity till the early of 1970s, that infectious diseases can be well-ordered and stopped and mankind felt self-confident that new medicine would overcome. But, infections are still the second-chief reason of death worldwide, producing over 13 million deaths each year. This point is the outcome of the appearance of new diseases, the comeback of diseases once organized and more specially of the progress of antimicrobial resistance.(1) In history, antibiotics are chemical substances produced by various species of micro-organisms that suppress the growth of other micro-organisms and may eventually destroy them. In modern usage the term antibiotic has been extended to include both chemically modified natural antibiotics and entirely manmade substances which would more technically be referred to as semi synthetic or synthetic antimicrobial agents. (2,3) Antibiotics antimicrobial can be classified grounded on their aim specificity"narrow-spectrum" antibiotics aim certain kinds of bacteria, such as gram positive or gram negative bacteria, however wide antibiotics spectrum disturb a wide variety of bacteria. (4)The finding and improvement of the antibiotics are amongst the most potent and effective attainments of up-to-date science and technology for the controller of infectious diseases. However, the growing antimicrobial resistance appearance and its distribution among bacterial strains reduced the efficacy of treatment achievement of big quantity of medications. (5) Antimicrobial mediators can be categorized as bacteriostatic, represented by chloramphenicol or bactericidal represented by penicillin. Bactericidal agents

reason bacterial cell death, while bacteriostatic agents inhibit the bacteria from growing. (6)

1.1.1. Mechanisms of action of antibacterial agents

Antimicrobial agents are classified as stated by their mechanism of action that excludes:

A. **Interfering with the cytoplasmic membrane:** (Polymyxins, Daptomycin) these agents diffuse through the outer membrane and cell wall of susceptible cells to the cytoplasmic membrane. They bind to the cytoplasmic membrane and disrupt and destabilize it. This causes the cytoplasm to leak out of the cell resulting in cell death (they are bacteriocidal). (7)

B. **Interference with nucleic acid synthesis is caused by two classes of drugs:** Fluoroquinolones (e.g. nalidixic acid, ciprofloxacin, levofloxacin and gemifloxacin) interfere with DNA synthesis by blocking the enzyme DNA gyrase. Fluoroquinolones fix to the DNA gyrase-DNA complex and let the fragmented DNA strands to be out into the cell, which leads to cell death. Rifampin binds to DNA-in need of RNA polymerase, which blocks the production of RNA and results in cell death (they are bacteriocidal). (8)

C. **Interfering with cell wall synthesis:** Antibacterial treatments that effort by preventing bacterial cell wall creation exclude the β-Lactams, for example the carbapenems , monobactams ,penicillins and cephalosporins, and the glycopeptides, as well as vancomycin and teicoplanin. β -lactams mediators inhibit production of the bacterial cell wall by the interfering with enzymes necessary for creation of the peptidoglycan coat. Glycopeptides as well impede with the cell wall creation, by connection to the terminal D-alanine

remains of emerging peptidoglycan series, thus avoiding the cross linking stages essential for firm cell wall creation (they are bacteriocidal). (9)

D. Reserve of a metabolic pathway: sulfonamides and trimethoprim block the way for folic acid production, which initially inhibits DNA creation. The common antibacterial drug mixture of trimethoprim, (a folic acid similarity) and more sulfamethoxazol (asulfonamide) hinders 2 steps in the enzymatic passageway for the bacterial folate production (they are bacterioststic). (10)

E. Inhibition of protein synthesis: chloramphenicol,tetracyclines ,aminoglycosides, Macrolides,and oxazolidinones yield their antibacterial effects special by inhibiting protein production. Ribosomes of the bacteria vary in configuration from their complements in eukaryotic cells. Mediators of the antibacteria take benefit of these variances to selectively stop bacterial growing. Aminoglycosides , tetracyclines and macrolides bind to the 30S subunit of the ribosome, while chloramphenicol binds to the 50S subunit (they are bacterioststic).(7)

1.1.2 The antimicrobial resistance

For the duration of the latest five eras, the usage and sometimes mismanagement of antimicrobials in together human and veterinary treatment has give rise to the appearance of straining of bacteria that no longer reaction to antimicrobial treatment (11). Antimicrobial fight progresses over and done with a number of dissimilar mechanisms : (1) alterations of the penetrability in the bacterial cell membrane/ wall, limiting the entree of the antimicrobials to objective positions ; (2) energetic efflux of the antimicrobials out of the cell; (3) modification in the aim site; (4)The degradation of enzymes or alteration in antimicrobial

mediator; and (5) achievement of another metabolic paths to those withdrawn by the antimicrobial mediator (table 1-1).

Table (1-1) mechanisms of antimicrobial resistance [11]

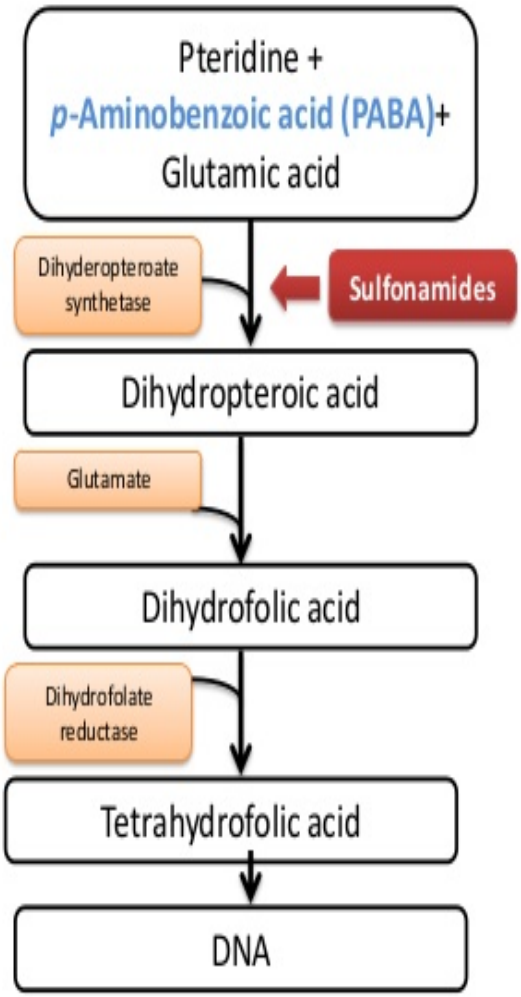
Mechanisms of resistance		Antimicrobial (s) affected
1	Alteration of the antimicrobial agent	Beta-lactams, aminoglycosides,and chloramphenicol.
2	Modification or defense of the target site	Macrolides, beta lactams, aminoglycosides, quinolones ,rifampicin, trimethoprim, as well tetracycline
3	Reduced antibiotic accretion • Declined uptake • Greater than before efflux	• Various antibiotics like(quinolones) • Chloramphenicol, quinolones, macrolides , and tetracycline
4	Change of the metabolic path	Trimethoprim and sulfonamides.

1.2 introduction of the sulfa drugs

The development of sulfanilamide is an informative area in medicine. However , the pharmacological importance of sulfanilamide nucleus is well established in pharmaceutical chemistry.The sulfanilamide pharmacophore has several important applications in drug design (12). Antibacterial sulfanilamide comprise a large group of compounds that are structural analogues of para-aminobenzoic acid

(PABA),they interfere with the microbial growth through competitive inhibition of dihydropetroate synthase enzyme,through the prevention of incorporation of PABA into folic acid which is essential coenzyme in the biosynthesis of bacterial thymdine, purines and some amino acids ,as shown in the figure (1)(13).Therefore , sulfanilamides are bacteriostatic drugs and are active against G+ve and G-ve bacteria(14-16). Then the starter of prontosil over 70 years past, the sulfa drugs have been broadly used to treat a wide spectrum of microbial diseases(17).sulfanilamide especially N1 substituted sulfonamide derivatives as the first effective antibacterial drugs to cure human bacterial infection, then after they are followed by the introduction and wide use of penicillines during 1940s that occupy great infections(18). The researchers efforts have focused on seeking for naturally occurring inhibitors for bacterial growth and persistence , biochemical targets for antimicrobials and improvements on the exciting agents found in nature primarily in 1950s and 1960s that continues until 1990(19). The need for alternative antibacterial drugs and new development strategies are greater than it has been in a quarter of a century. Despite , the considerable efforts that have been done, a little progress have been observed in the development of novel antimicrobial agents(20).

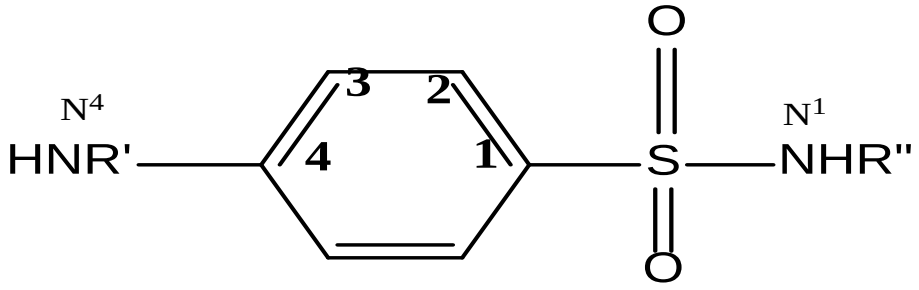
- Bacteria synthesize their own folic acid (FA) of which *p*-aminobenzoic acid (PABA) is a constituent, and is taken up from the medium.
- Sulfonamides, are structural analogues of PABA, inhibit bacterial folate synthase and formation of folate get inhibited.
- Sulfonamides competitively inhibit the PABA with pteridine residue to form dihydropteroic acid which conjugates with glutamic acid to produce dihydrofolic acid.
- Sulfonamide altered folate an which is metabolically injurious



Figure(1-1): Mechanism of action of antibacterial sulphonamide drugs.

1.2.1 Structural activity relationship of sulfonamides

The large numbers of synthetic antibacterial sulfonamides with their various modifications have permitted to investigate the influence of structural alteration on the antibacterial activity. Since, sulfonamides are rather small molecules (as shown in the key structure) and there are n't too many variation that can be carried out without changing the basic nucleus, these have led to the following conclusions[21,22a].



The key structure

1- The (N^4) amine and sulfonamide groups should be on the benzene ring in the 1,4 para positions for antibacterial activity. However , the N^4 should be unsubstituted or substituted to form azo or amide prodrugs or new analouges. Prodrugs are inactive unless they could be hydrolysed in vivo to regenerate the parent drugs.
2- Replacement of benzene ring with other ring system or its substitution on position other than 1,4 position will decrease or abolish the antibacterial activity.
3- Exchanging of the sulfonamide group SO_2NHR with the sulfone SO_2Ph-p-NH_2 will retain the activity.

4- Sulfonamide group is essential for biological activity and the amide should be secondary (N^1)[22a].

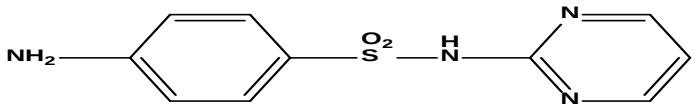
The presence of p-aminobenzensulfonyl moiety have an important role for maintaing antibacterial activity. Therefore ,all of the attention is focused on the N^1-substituents. These substituents seem to affect the physicochemical and pharmacokinetic characteristics of the drug. The already established substitution sites are:

A- N^1 substitution with various heteroaromatic and non heteroaromatic (R") influence the extent of plasma protein binding that in turn affects on the drugs' plasma concentration in addition to their onset and duration of action as shown in figure(1-2). Further more the nature of (R")group influences the drug's pka, its lipophilic-lipophobic solulbilty behavior , its excretion and toxicity profile.

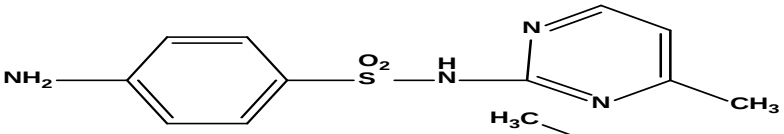
B- N^4 azo and acyl derivatives as prodrugs[21.22b].

Short-Acting systemic sulphonamides

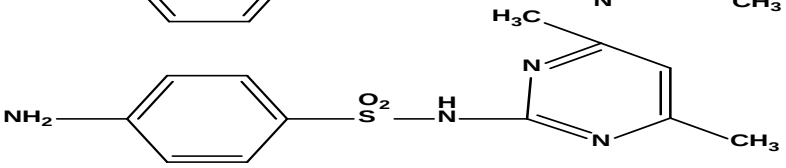
Sulfadiazine



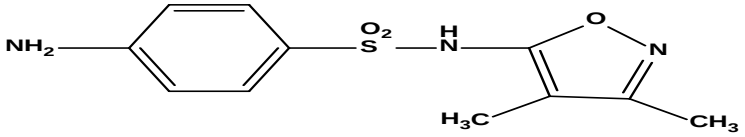
Sulfamerazine



Sulfamethazine

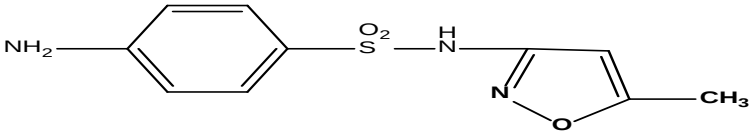


Sulfisoxaole

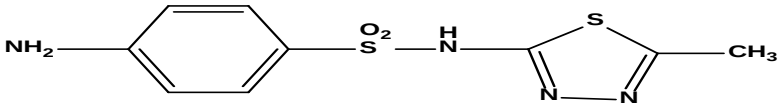


Intermediate- acting systemic sulfonamides

Sulfamethoxazole

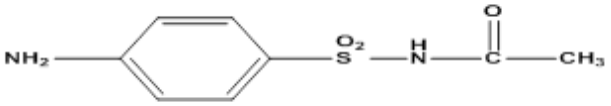


Sulfamethizole

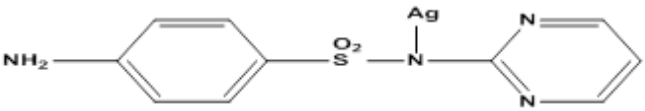


Topical sulfonamides

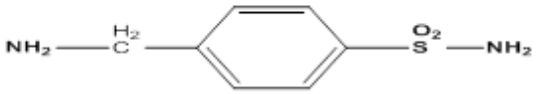
sulfacetamide



Silver sulfadiazine



Mafenide



Phthalylsulfathiazole

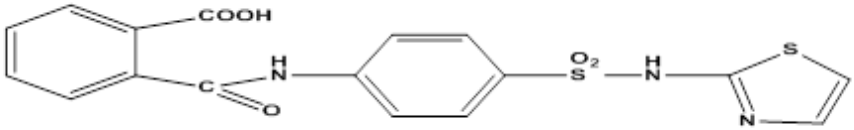


Figure (1-2): Structure and characteristics of some sulfonamide drivatives[15-23].

1.2.2. Sulfamethoxazole

Sulfamethoxazole (SMX) belong to the sulfonamide group of antibiotic.It was chosen to be the representative of this group due to its widespread use and detection frequency in the aquatic environment. It is effective against both gram-positive and gram negative bacteria and inhibits growth by a competitive binding into dihydropteroate synthetase which stops the conversion of para-aminobenzoic acid (PABA) to dihydropteroate, a precursor to tetrahydrofolic acid, which is essential for the synthesis of nucleic acids. An additional mechanism of action is that sulfonamides block cross-membrane transport of glutamic acids which also is an essential component for synthesizing folic acid[24]. Co-trimoxazole (sulfamethoxazole /trimethoprim, SMX/TMP), an antibiotic in usage for numerous periods, has been shown to be active in contrast to S. aureus in vitro [25]. Its workings have synergistic bactericidal action in contrast to S. aureus[26]. (TMP-SMX) is a broadspectrum antibiotic used to delicacy a variety of infections. Due to its effectiveness, its simplicity of dosing, and to the reasonably low expense, it has converted a popular choice among several physicians. However, as with any drugs, a side effects may be expert. Gastrointestinal upset and rash are the furthermost usually reported side effects accompanying with TMP-SMX[27].

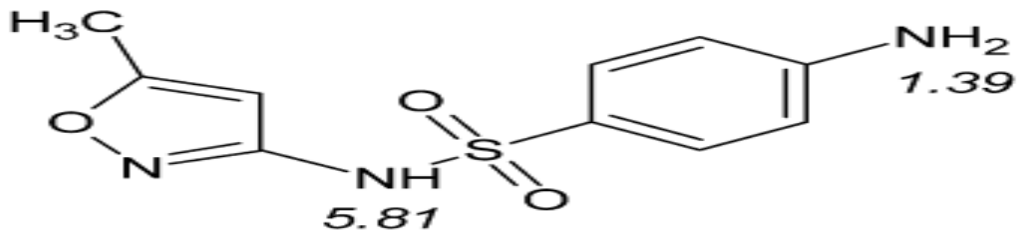


Figure (1-3): Chemical structure and pKa-values[28] of Sulfamethoxazole

SMX is metabolized trough hydroxylation, acetylation and glucuronidation, with only the acetylated metabolite N4-acetylsulfamethoxazole being detectable in plasma[29]. SMX acts both as acid and base, with the primary amine having pKa1.39 acting as base, and the secondary amine being acidic with pKa5.81[28].

1.3.Schiff bases

The schiff bases are summarizing yields of carbonyl compounds with primary amines & they were initial informed by Schiff [30]. in 1864. These compounds have the corporate structural feature by the azomethine group with a overall formula $RHC=NR_1$, anywhere R and R_1 are aryl, cyclo alkyl,alkyl or heterocyclic groups which may be variously exchanged. Schiff bases are also knows as azomethines , imines or anils [31-33]. Several studies displayed that existence of the single pair of electrons in an sp^2 hybridized orbital of nitrogen atom of the imines cluster is of significant biological and chemical importance(which can be changed depending upon the type of substituent existent on the aromatic rings). For the reason that of the relative easiness of artificial flexibility, preparation, and the distinct things of C=N group, schiff bases are commonly excellent chelating mediators[33-35], specifically when a functional cluster like –SH or –OH is existent close to the azomethine group so as to procedure a five or six membered ring with the metal ion. Changeability of schiff base ligands , analytical ,biological and manufacturing uses of their complexes create additional researches in this region highly needed. At the present time, the investigation playing field dealing with the schiff base coordination chemistry has extended extremely. The significance of the schiff base complexes of biomedical applications , catalysis, bioinorganic chemistry and science material ,supramolecular chemistry, separation and encapsulation processes, and formation of composites with rare properties and configurations has been well documented and studied[36].

These comp. are described by the (N=CH) (imine) cluster which imports in explaining the transamination mechanism and rasemination reaction in biological system[37,38]. An remarkable use of these comp. is their application as an active corrosion inhibitor, which is established on their capability to suddenly form a monolayer on the surface to be secure. Several viable inhibitors include amines or aldehydes, but furthermost probably due to the (C=N) bond the Schiff bases role more powerfully in a lot of cases[39]. The literature clearly displays that the study of Schiff base ligand systems is linked with several of the key advances made in inorganic chemistry[40-42]. They played a important role in the progress of new coordination chemistry[43].

Schiff bases derived from sulfonamides drug have been acquired interest due to their biological system. Compounds containing sulfonamide group have been used as drug for diseases[44]. They are the essential compound due to their industrial application and wide range of biological activities , they have been found to have the pharmacological actions such as antimalarial[45]. Anticancer[46]. Antibacterial[47,48] . Antifungal[49] . Antitubercular[50] ,antiviral[51] ,and antiinflammatery[52] . They also work as a back bone for the production of different heterocyclic compounds.

1.4. Heterocyclic compounds

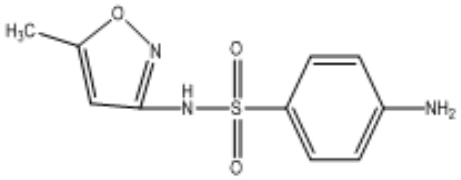
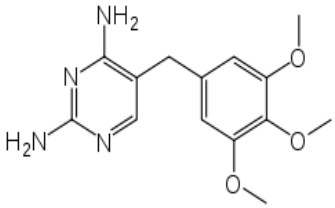
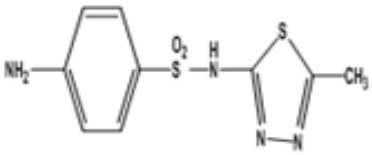
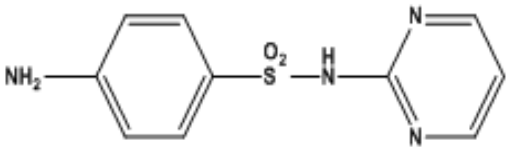
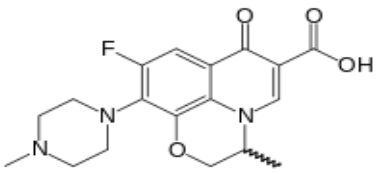
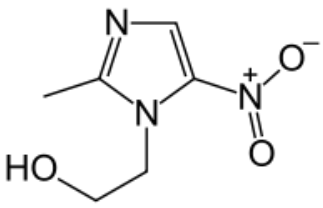
Organic chemists create hundreds of different heterocyclic compounds in each week. In furthermost circumstances the chemist has specific causes for creating a particular compound, commonly based on theoretical concerns, biological mechanisms ,medicinal chemistry, or a mixture of all three. The heterocyclic compounds are very broadly spread in nature and are very necessary to living organisms. They show a vital part in the metabolism of all the active cells. Among large number of heterocycles found in nature, nitrogen heterocycles are the most

abundant specially those containing oxygen or sulfur[53], due to their wide distribution in nucleic acid illustration and their involvement in almost every physiological process of plants and animals. Heterocyclic compounds possess great applicability in industry as well as in our life in different ways. For example greatest of the sugars and their derivatives, excluding vitamin C[54], be present largely in the formula of five membered (Furanosied structure) or six membered (Pyranosied structure) ring having one oxygen atom. Further most members of the vitamin B group have heterocyclic rings involving nitrogen. e.g., vitamin B6 (Pyridoxine)[55,56],which is a derived from the pyridine essential in amino acid metabolism. The heterocyclic compounds also occupy key position in the area of drugs and pharmaceuticals. Almost 80% of the drugs in clinical use are based on heterocyclic constitution because they have specific chemical reactivity.

Majority of the drugs being introduced in pharmacopeias are heterocyclic compounds, such as chlordiazepoxide (tranquillizer)[57,58], imipromine (antidepressant)[59], guanethidine (antihypertensive)[60], indapamide (diuretic and antihypertensive)[61,62],etc.

Many antibiotics including penicillin[63], cephalosporin[64], norfloxacin[65], streptomycin[66,67], etc., also contain heterocyclic ring. Many veterinary products like pyrantel and morantel are the drug of choice as broad spectrum anthelmintics[68]. The herbicides atrazine and Simazine are well known example of heterocyclic agrochemicals[69,70]. Plant pigments such as indigo[71], hemoglobin[72], and anthiocyanins[73], chlorophyll[74], has contributed much to colour chemistry and all these contain heterocyclic ring. Further, many other heterocyclic colouring matters are in use since prehistoric times. Further, the heterocyclic tetra selena fulvalene was the first ionic molecular crystal to demonstrate superconductivity[75]. Heterocyclic chemistry is one of the biggest regions of research in organic

chemistry and it is developing rapidly. Of all available organic chemistry literature, published research on heterocyclic creation accounted for about 60 % in 1998, but at the present time the portion is much larger allowing for that novel heterocyclic compounds are available in different fields such as pharmaceuticals, biochemistry, materials and others. [76] Figure (1.4) shows structures of some chemotherapeutic agents on the bases of heterocyclic rings.

 **sulfamethoxazole**	 **Trimethoprim**
 **Sulfamethizole**	 **Sulfadiazine**
 **Ofloxacin**	 **Metronidazole**

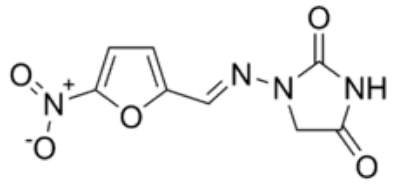
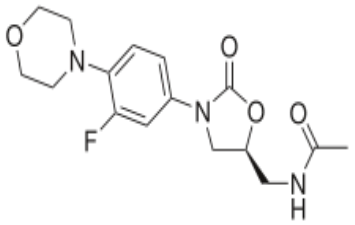
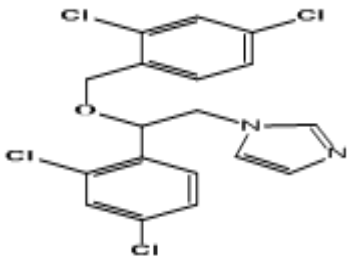
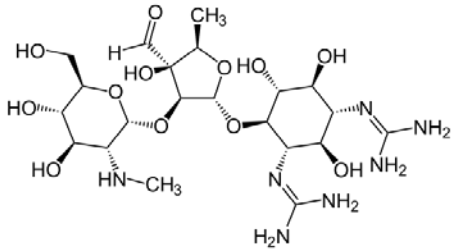
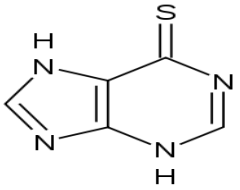
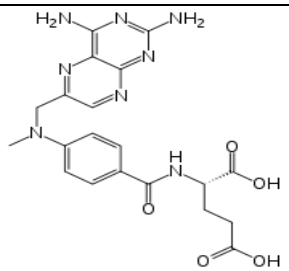
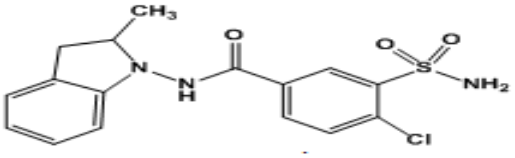
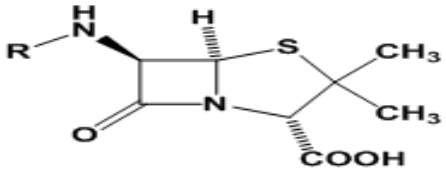
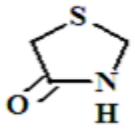
 **Nitrofurantoin**	 **Linezolid**
 **Miconazole**	 **Streptomycin**
 **Mercaptopurin**	 **Methotrexate**
 Indapamide	 Penicillin

Fig.1.4 Structures of some chemotherapeutic agents on the bases of heterocyclic rings.

1.5. Thiazolidinone

There are various biologically active molecules which contain different hetero atoms such as nitrogen, sulphur and oxygen, always drawn the consideration of chemist over the years mainly because of their biological importance. Thiazolidinones are thiazolidine derivatives and have an atom of sulfur at position 1, an atom of nitrogen at position 3 and a carbonyl group at position 2, 4, or 5 [(77)]. However, its derivatives belong to the most frequently studied moieties and its presence in penicillin was the first recognition of its occurrence in nature. The 4-thiazolidinone scaffold **(1)** is very versatile and has featured in a number of clinically used drugs. They have found uses as antibacterial [(78)], antitubercular [(79)], anti-inflammatory [(80)] and as antiviral agents, especially as anti-HIV agents [(81)].



(1)

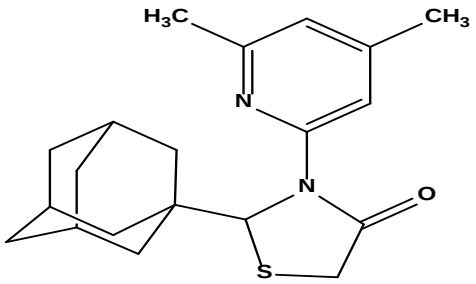
1.6.Biological Activities of 4-thiazolidinones

The thiazolidinones ring has been integrated into a wide range of known biologically active compounds, either as a substituent group or as a replacement of another ring inspired researchers to produce several compounds containing this moiety.

1.6.1 . Antiviral Activity

Jan Balzarini *et al*. synthesized a series of novel thiazolidin-4-ones behavior a lipophilic adamantyl substituent at location 2, and numerous substituents on the nitrogen atom of the thiazolidine ring were produced where as a

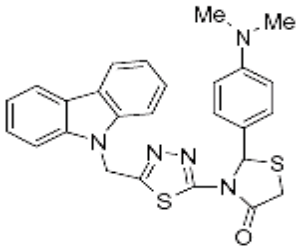
number of compounds exhibited a modest anti-HIV-1 activity, compound **(2)** was endowed with a remarkable antiviral potency [82].



(2)

1.6.2. Antidepressant and Anticonvulsant Activity

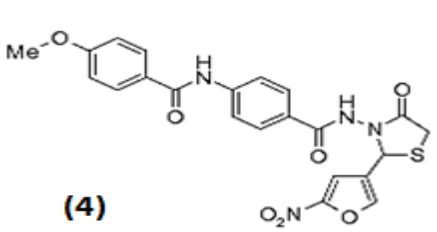
A number of replaced thiazolidinonyl carbazol derivatives are effective anticonvulsant and antipsychotic agent. Compounds ensuring thiazolidinone ring confirmed more potent antipsychotic as well as anticonvulsant activities as compared to compounds having azetidinone ring. Among these, compound **(3)** showed very good response in contrast to psychotic diseases by cassette their responses towards amphetamine induced stereotyped, cataleptic behavior by Rota rod performance and Maximal Electroshock Seizure test for anticonvulsant activity [83]



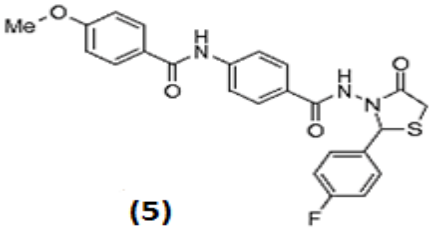
(3)

1.6.3. Antitubercular Action

Kucukguzel et al. described antimycobacterial action against Mycobacterium tuberculosis $H37_{Rv}$ of substituted 4-thiazolidinones and found that only compounds **(4)** and **(5)** showed 90 and 98% inhibitions at 6.25µg mL^{-1}, respectively [84].



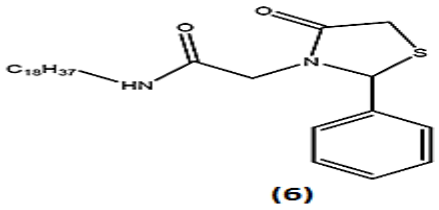
(4)



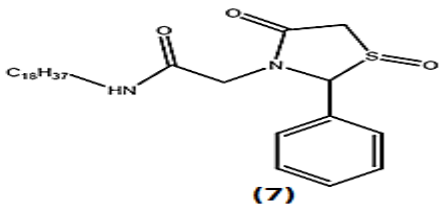
(5)

1.6.4. Anticancer Activity

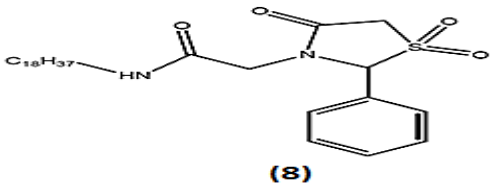
Gududuru *et al.* described the synthesis and biological evaluation of new 2-aryl-4-oxothiazoilidin- 3-yl amides against prostate cancer cells. Three potent compounds have been identified (**6, 7** and **8)**, which are effective in killing Prostate malignant cells with enhanced selectivity compared to serine amide phosphates (SAPs) [85].



(6)



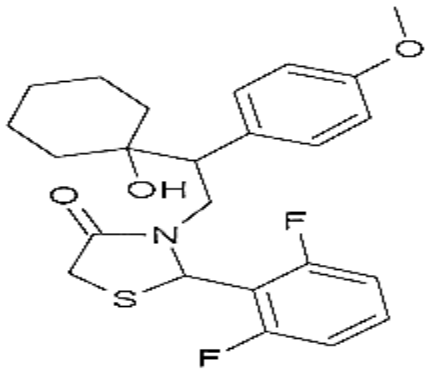
(7)



(8)

1.6.5.Antibacterial Activity

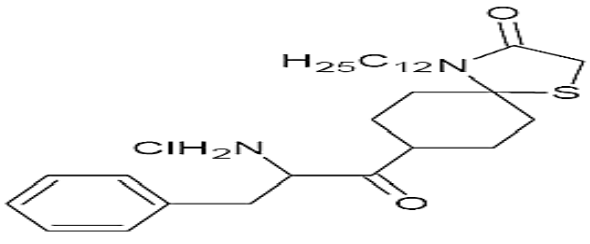
Studies have shown that thiazolidinones were more active than thiazoles against some common bacteria. Kavitha reported more than 20 thiazolidinone derivatives were tested against *Bacillus subtilis* and *Escherichia coli*. He concluded that synthesized compounds exhibited powerful activity.This significant inhibitory activity can be attributed to fluorine atoms and has been observed in thiazolidinone derivatives with different positions **(9)** [86].



(9)

1.6.6. Antifungal Activity

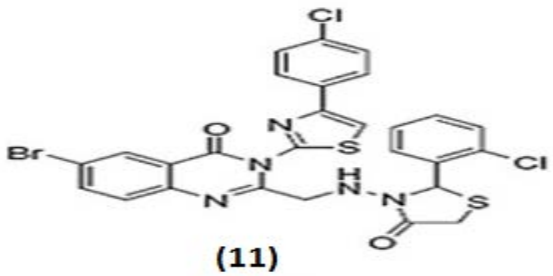
Compound **(10)** and its derivatives were prepared and screened by Katti *et al*. against two strains of *candida albicans* and one strain of *Cryptococcus neoformans* , and found that the antifungal activity was of average to higher level against the various fungal strains [87] .



(10)

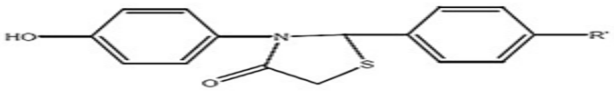
1.6.7. Anti-inflammatory and Analgesic Activity

Arylalkanoic acids constitute the basis for the widely used nonsteroidal anti- inflammatory agents such as ibuprofen and naproxen ; these medications hinder the COX enzymes, the mode of action of these drugs is correlated with unwanted side- effects such as gastrointestinal and renal toxicities, to overcome these side effects anti-inflammatory and analgesic activity of new series of quinazolinone derivatives having thiazolidinone at 2nd position was reported by Kumar *et al*. Interestingly compound **(11)** which was substituted with chloro group at 2nd position of phenyl ring, showed almost equal anti-inflammatory activity to that of phenylbutazone at 50 mg/kg, it was also tested for ulcerogenic activity and the UD(50) value was found to be 195.6mg/kg [(88)].



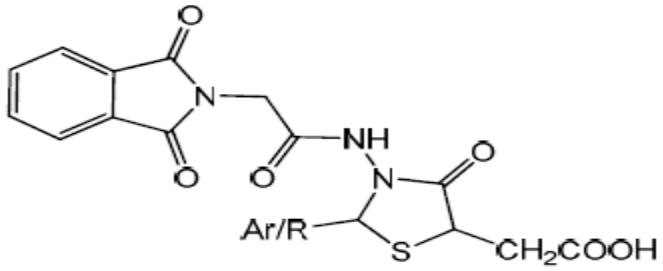
(11)

Taranalli AD *et al.* synthesized a series of thiazolidine-4-one derivatives from sulfanilamide and evaluated for anti-inflammatory, analgesic and anti-ulcer activity. The compound **(12)** and compound **(13)** showed potential activity [(89)].



(12) R'= H
(13) R' = CH_3

A series of 2-(3-(2-(1,3-dioxoisoindolin-2- yl) acetamido)- 4 -oxo- 2 -substituted thiazolidin-5- yl) acetic acid **(a-l) .** The compound **a** found to be most significant as shows highest inhibition in *in-vivo* anti-inflammatory evaluation. Other compounds **c**, **f** and **j** also showed enhanced biological activity. The compounds **a, b** and **e** had shown more inhibition as compared to diclofenac in *in-vivo* anti-inflammatory evaluation. The ulcerogenic toxicity study had shown minimum toxicity effects of selected synthesized compounds. The ulcerogenic toxicity was performed[90,91], for selected compounds which have shown better anti-inflammatory activity in compounds **a, b, c, f** and **j**.



2-(3-(2-(1,3-dioxoisoindolin-2-yl)acetamido)-4-oxo-2-substituted thiazolidin-5-yl)acetic acid (a-l)

Where
R= $-CH_3$,$-C_2H_5$
Ar =1) = Aromatic
2) = Heteryl
R'= Cl, OH, CH_3, OCH_3

Fig. 1.5 Substituded thiazolidin-5- yl as anti-inflammatory agent

1.7. Chalcone

The chalcones chemistry has made serious scientific readings all over world. Chiefly importance has concentrated on production & biodynamic actions of the chalcones. The name "Chalcones" was given by Tambor and Kostanecki[92]. Chalcones are as well famous as benzylidene acetophenone or benzalacetophenone. In these compound , an aliphatic three carbon series connected the two aromatic rings. Chalcone allows a actual good work so range of new heterocycles with good pharmaceutical shape can be planned. Chalcones are unsaturated ketone having the reactive ketoethylenic group(CO-CH=CH). Chalcones are colored compounds for the reason that of existence of the chromophore (CO-CH=CH), which rest on in the existence of other auxochromes. Dissimilar ways are existing for establishment of chalcones[93-95].The furthermost suitable method is the Claisen-Schimdt condensation of equimolar quantities of aryl aldehyde with arylmethylketone in the existence of alcoholic alkali[96]. These compounds are used to create a number of products like pyrimidines, pyrazolines isoxazoles and cyanopyridines having dissimilar heterocyclic ring systems.[97-100]

1.7.1.Industerial importance of the chalcones

They have nearby correlation with tetralones ,flavones, aurones and aziridines. Chalcones and their products find use as artificial sweeteners[101-103], 3,2',4',6'-tetrahydroxy-4-propoxy-dihydrochalcone-4-β'-neohesperdoside[104] ,this has been used as artificial sweetener& is 2200 times sweeter compare to the glucose. Chalcones derivatives may performance as scintillator [105], polymerization catalytic agent [106,107], fluorescent whitening mediator [108], organic brightening mediator [109,110], stabilizer in contrast to heat, ultraviolet light, visible light and aging[111-113] **.** As well the these comp. have been establish beneficial in elucidating

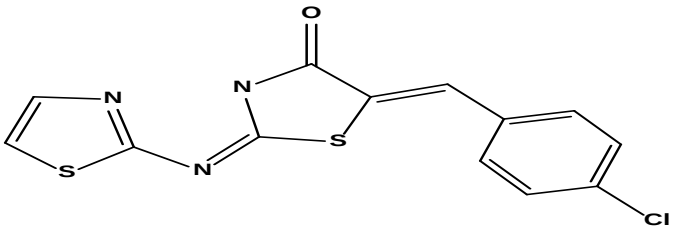
configuration of natural products similar to hemlock tannin[(114)], cyanomaclurin[(115)], ploretin[(116)], eriodictyol and homoeriodictyol[(117)], naringenin[(118)] .

1.7.2. Biological importance

The existence of -unsaturated carbonyl system of chalcone creates it biologically active [(119)]. They have displayed antibacterial activity in contrast to *candida albicans ,Staphylococcus aureus, Wettinia anomala , Escherichia coli* and some other organisms[(120)]. Nuhrich , Devaux, and Dargelos[(121)] created some nitrofuryl chalcones and tested for their antibacterial activity. These compunds are connected with dissimilar biological actions like insecticidal[(122)], anticancer[(123,124)], anti-inflammatory[(125)], bactericidal[(126)], fungicidal[(127)], antiviral[(128)], antimalarial[(129)] and antiulcer[(130)]. Literature displays that lieochalcone and oxygenated chalcone has strong antileishmanial action [(131,132)].

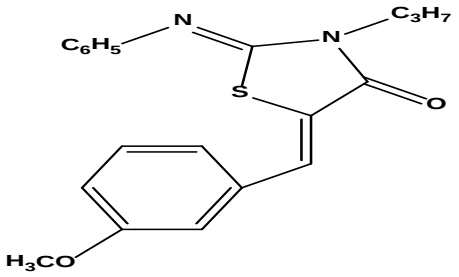
1.8. pharmacological activity of substituted 5-arylidene-4-thiazolidinones

Antibacterial action is powerfully reliant on the nature of the substituents at C-2 & N-3 of the thiazolidinone ring. Substituted 5-arylidene moiety shows an essential role in enhancing the antimicrobial things of 2-(thiazol-2-ylimino) thiazolidin-4-one. Substitution with chloro group at 2^{nd}, 3^{rd} or 4^{th} position on benzene ring enhanced antibacterial activity (p-Cl substitution is greatest energetic) associated to arylidene products exchanged with hydrophilic hydroxyl or methoxy group or nitro group[(133)].

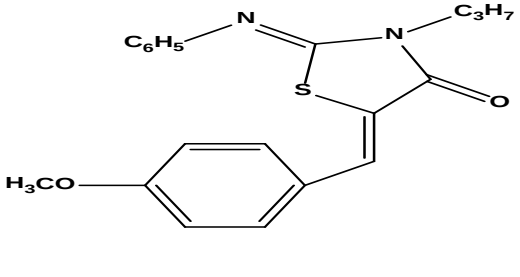


(14)

Chains of 5 -arylidene- 2 -imino -4- thiazolidinoness displayed important action altitudes in carrageenan-encouraged paw & rats pleurisy edema models of severe inflammation.5-(3-methoxyphenylidene) -2- phenylimino-3-propyl-4 thiazolidinone (15) displayed decreases in the level (85% at the 3rd h) like to that of indomethacin. 5- (4- Methoxyphenyl) methylidene-2phenylimino-3-propyl-4-thiazolidinonee (16) exposed great levels of carrageenan-encouraged paw edema decrease as good as to those of indomethacin. Docking study of compound (16) exhibited that 4-methoxyarylidene moietycan simply occupy the area of the COX-2 secondary pocket & create hydrogen bonds contact with Tyr 355 , Arg 120 and Arg513.[(134)]



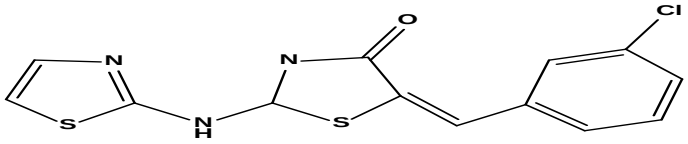
(15)



(16)

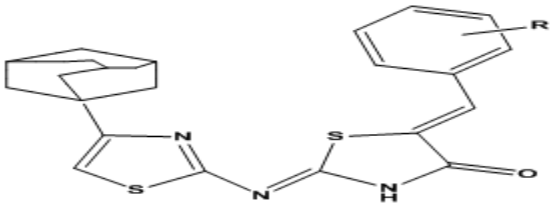
The product 2- (thiazole-2- ylamino)- 5 -(m-chlorophenylidene)-4-thiazolidinone (17) displayed maximum COX-1 & COX-2 inhibitory action however altering the site of chloro group from meta to other sites reduced the actions in a chains of 2-thiazolylimino/ heteroarylimino- 5- arylidene- 4- thiazolidinones. Replacement with hydroxygroup at the para position or nitro group at the meta or para position

acts to be unfavorable for their COX selective action and reduced the efficiency of replaced products .[135]



(17)

4- Adamantyl- 2- thiazolylimino-5- arylidene-4 -thiazolidinones as displayed in the fig.(1.5)was established to show a significant decrease of a broad spectrum of gram negative and gram positive bacteria. The greatest significant action was saw for compounds having p-OH and 3,5-OCH_3 group on arylidene moiety in contrast to recognized strains. It has been displayed that the introduction of arylidene moieties at dissimilar locations of the thiazolidinone ring improved the antimicrobial action. In addition, studies have shown that the existence of electron-withdrawing nitro group at para and meta position of arylidene moiety encourages the action profile. The starter of methoxy group at location 3 and 3, 5 in the 4-hydroxy derived in overall lead to compounds with greater action, whereas replacement of hydroxyl group with methoxy in 4th site typically reduced action.[136]



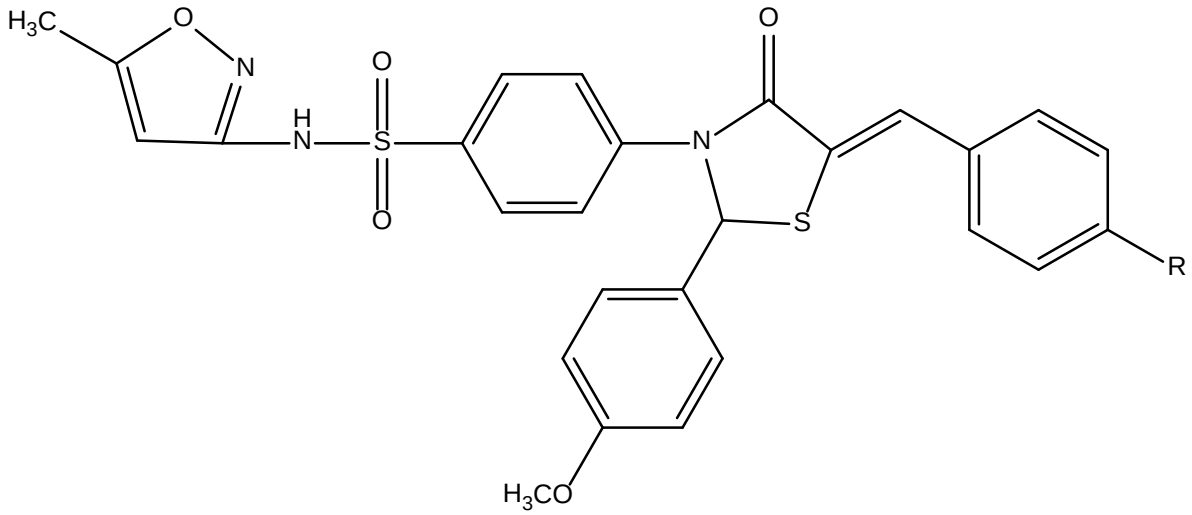
R=*p*-Cl ,*m*-Cl, *o*-Cl, *p*-NO_2, *m*-NO_2 ,*o*-NO_2 , *p*-OH ,*m*-OH ,*o*-OH , *p*-OCH_3, *m*-OCH_3 and 3,5-OCH_3

Fig. 1.6. Substituded 5-arylden-4-thiazolinones as antibacterial agent.

1.9. Aim of work

Synthesis of new series of sulfa drugs derived from sulfamethoxazole containing substituted 5-arylidene -4-thiazolidinone, these compounds expected to have higher antimicrobial than sulfamethoxazole , due to their pharmacophore .

The general structure of these compounds:



Compound	R
M_3	**-H**
M_4	**-OH**
M_5	**-OCH_3**
M_6	**-NO_2**
M_7	**-Cl**
M_8	**-$N(CH_3)_2$**

CHAPTER TWO

EXPERIMENTAL

CHAPTER TWO

Experimental work

2.1 Chemicals and Equipments

2.1.1: Chemicals

The specific chemicals used in this work are listed below with their suppliers:

Table (2-1): The chemicals and reagents with their origins.

Materials	Company	Origin
Absolute Ethanol	GCC	India
Absolute Methanol	GCC	India
Acetone	GCC	India
Benzaldehyde	Himedia	India
Benzene	BDH	England
Chloroform	GCC	India
Diethyl ether	BDH	England
Ether	Scharlau	Spain
Ethyl acetate	BDH	England
Hydrochloric acid (HCl)	BDH	England
Magnesium sulfate (anhydrous)	Fluka AG	Switzerland
N, *N* dimethylformamide	Scharlau	Spain
p –chlorobenzaldehyde	Fluka AG	Switzerland
p –hydroxybenzaldehyde	Fluka AG	Switzerland
p –methoxybenzaldehyde	Himedia	India
p –nitrobenzaldehyde	Himedia	India

p-dimethylaminobenzaldehyde	Himedia	India
Petroleum spirit	BDH	England
Petroleum spirit (40-60)	BDH	England
Piperidene	BDH	England
Silica gel GF254 (type 60)	Merck	Germany
Sodium bicarbonate ($NaHCO_3$)	Sigma	spain
Sulfamethoxzaole	Virchow Laboratories Limited(VLL)	India
Sulfuric acid (H_2SO_4)	BDH	England
Tetrahydrofuran (THF)	BDH	England
Triethylamine	BDH	England
$ZnCl_2$	Laboratory chemical	India

2.1.2 Equipments

The equipments used in this work are enumerated below in table (2-2).

Table (2-2): Equipments with their origins

Equipments	Company	Country
Electric melting points apparatus	**Electro thermal 9300**	**USA**
Elemental analyzer	**Perkin–Elmer model 2400**	**U.K.**
FTIR spectrophotometer	**Schimadzu**	**Japan**
Chiller Julabo VC (F30)	**GMBH**	**Germany**
Vacuum pump	**Bibby sterilin LTD**	**U.K.**
Proton Nuclear Magnetic Resonance(^{1}H -NMR)(300MHZ)	**Bruker**	**Germany**

2.2 Methods of characterization and identifications

Common methods were used for the characterization and identification of the created compounds which includes the following:

2.2.1 Thin layer chromatography (TLC)

Arising Thin Layer Chromatography was ride on Kieslgel GF_{254} (60) aluminum plates, E. Merck (Germany), to check the clarity of the synthesized compounds and to monitor the development of the reactions.

Compounds detected by exposuring to iodine vapor or to UV_{254} light.

Chromatograms were eluted by the following solvent systems :[137]

a/ Petroleum ether: ethyl acetate (7:3)
b/ toluene: ether (3:1)

2.2.2 Melting points

Thomas Hoover Electronic Apparatus of melting point measurements were hand-me-down for determination of the (melting points) stated by the following work.

2.2.3 Infrared bands

Determinations of infrared bands were done and documented as a KBr picture using FTIR Shimadzu (Japan), in University of Al-Mustansiriyah, at college of pharmacy.

2.2.4 Elemental Microanalysis

The elemental microanalysis of the created final products was done in chemistry department, AL-Byat University, Jordan, by using a Perkin–Elmer model 2400 instrument.

2.2.5 Proton Nuclear Magnetic Resonance (^{1}H -NMR)

^{1}HNMR bands (solvent DMSO-d_6) were documented on 300 MHZ spectrometer . Bruker DMX-500 spectrophotometer with TMS as internal standard which were made in AL-Byat University, Jordan, at chemistry department.

2.3 Chemical synthesis

The synthesis of compounds were achieved following procedures registered in unit (2.3.1) through unit (2.3.3) and the steps were shown in scheme (3-1).

2.3.1 Synthesis of schiff base [4-((4-methoxybenzylidene)amino)-N-(5-methylisoxazol-3-yl)benzenesulfonamide] (M_1)

The schiff-base was set by the usual condensation reaction, in which equimolar (0.01 mol ,1.362 g) of *p*- methoxybenzaldehyde and the amine (Sulfamethoxazole) (0.01 mol, 2.533 g) were liquefied in least possible quantity of ethanol ,also glacial acetic acid(1 mL) was added and refluxed for about 5-8 hrs , the response was tested by TLC using petroleum ether/ ethyl acetate (7:3)

,after that cools at room temperature and the contented was transferred on crushed ice. The crystals product was collected through filteration .yield (88%) with melting point at 234-236°C.

The physical properties, percent yield and R_f values of schiff base are listed in table (3-1), The FT-IR spectrum for the synthesized compounds are listed in table (3-2) figure (3-2). The ^{1}H-NMR data for compound [M_1] is in table (3-3) and figure (3-10).

2.3.2 Synthesis of 4-(2-(4-methoxyphenyl)-4-oxothiazolidin-3-yl) -N-(5-methylisoxazol-3-yl) benzene sulfonamide (M_2).

A combination of Schiff base (0.01 mol, 2.98g), thioglycolic acid (0.022 mol, 2.5 mL) in DMF (20 mL) with a touch of the anhydrous $ZnCl_2$, was refluxed for 12 hrs , the progress of the reaction was checked by TLC using ether: toluene (1:3) as an eluent. The reaction mixture was cooled to the room temperature and then transferred into crussed ice. The solid thus separated was filtered, washed a several times with water. Yield 95% with m.p.136-137°C.

The physical properties, percent yield and R_f values of M_2 are listed in table (3-1), The FT-IR spectrum for the synthesized compounds are listed in table (3-2) figure (3-3). The ^{1}H-NMR data for compound [M_2] are recorded in table (3-4) and figure (3-11).

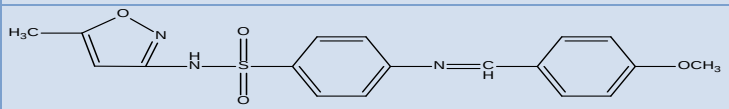
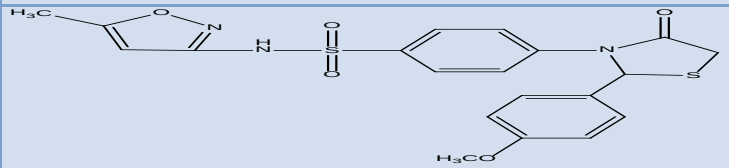
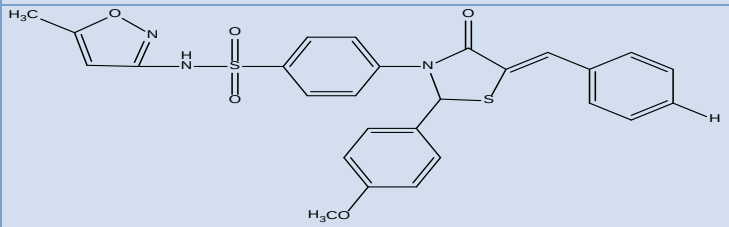
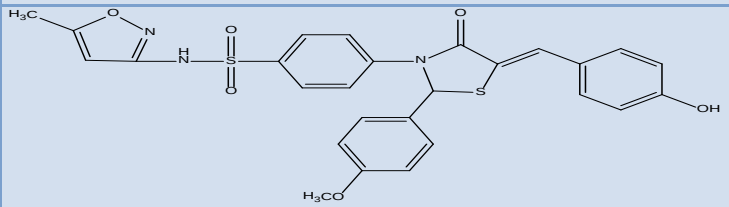
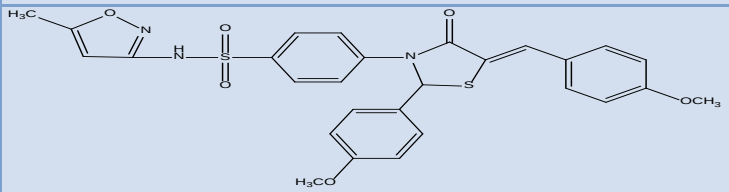
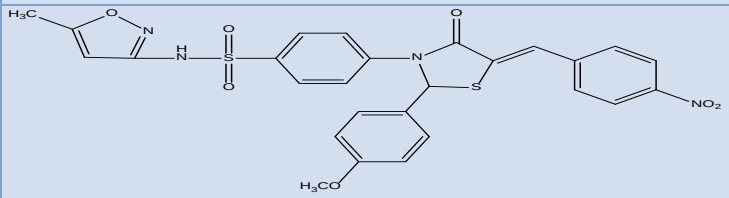
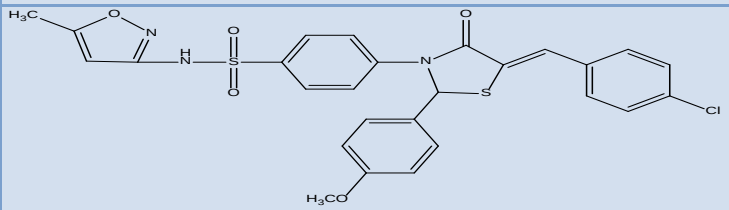
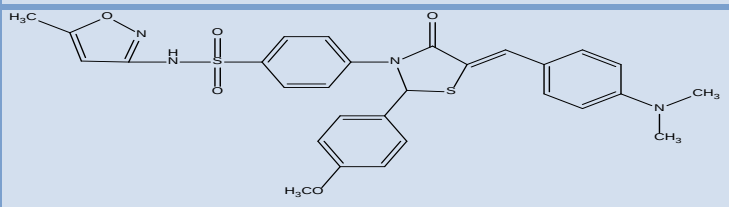
2.3.3 Synthesis derivatives of M_3 ($_{a-f}$)

In a 250 ml round bottom flask , put a mixture of compound M_2 (0.01 mol, 4.455 g) and an aromatic aldehyde (0.012 mol) in absolute ethanol (50-55 ml) was refluxed with piperidine (1-3 drops) for range 6-14 hrs according to type of derivarives .the progress of the reaction was tested by TLC using Methanol/ Chloroform/ Ether (4: 3: 3) . The composite was filtered and washed with cold, dry toluene or dry ethanol and after that recrystallized form ethanol[138-140].

The physical properties, percent yield and R_f values of compounds **[$M_{3(a-f)}$]** are recorded by table (3-1), and FT-IR spectrum data were recorded in table

(3-2) figures (3- 4) to (3- 9). The ^{1}H-NMR data for compounds [**$M_{3\ a\text{-}f}$**] figures (3-12) to (3-17) are summarized in tables (3-5) to (3-10).

Table (2-3): Structures and names of the synthesized compounds

Comp.	Structure	Name
M_1		4-((4-methoxybenzylidene)amino)-N-(5-methylisoxazol-3-yl)benzenesulfonamide
M_2		4-(2-(4-methoxyphenyl)-4-oxothiazolidin-3-yl) -N-(5-methylisoxazol-3-yl)benzenesulfonamide
M_{3a}		(Z)-4-(5-benzylidene-2-(4-methoxyphenyl)-4-oxothiazolidin-3-yl)-N-(5-methylisoxazol-3-yl)benzenesulfonamide.
M_{3b}		(Z)-4-(5-(4-hydroxybenzylidene)-2-(4-methoxyphenyl)-4-oxothiazolidin-3-yl)-N-(5-methylisoxazol-3-yl)benzenesulfonamide.
M_{3c}		(Z)-4-(5-(4-methoxybenzylidene)-2-(4-methoxyphenyl)-4-oxothiazolidin-3-yl)-N-(5-methylisoxazol-3-yl)benzenesulfonamide.
M_{3d}		(Z)-4-(2-(4-methoxyphenyl)-5-(4-nitrobenzylidene)-4-oxothiazolidin-3-yl)-N-(5-methylisoxazol-3-yl)benzenesulfonamide.
M_{3e}		(Z)-4-(5-(4-chlorobenzylidene)-2-(4-methoxyphenyl)-4-oxothiazolidin-3-yl)-N-(5-methylisoxazol-3-yl)benzenesulfonamide.
M_{3f}		(Z)-4-(5-(4-(dimethylamino)benzylidene)-2-(4-methoxyphenyl)-4-oxothiazolidin-3-yl)-N-(5-methylisoxazol-3-yl)benzenesulfonamide.

2.4. Biological study

2.4.1. Antimicrobial study :[141,142]

The antimicrobial activity of the final compounds was done in City of Medicine / educational laboratories section.

A preliminary antibacterial have been carried out according to Well Diffusion Method:

The synthesized compounds have been studied for their antimicrobial activity in vitro against three tested bacteria (*Escherichia coli, Pseudomonas aeruginosa*,as gram negative bacteria and *Staphylococcus aureus.*,as gram positive bacteria) were clinical activated and maintained on nutrient agar medium for testing antibacterial activity

Sulfamethoxazole was used as a standard drug for antibacterial activity.

2.4.2. Sensitivity Assay:

The antibacterial activities of the each derivatives compound were determimed by agar well diffusion assay was carried out by using pure isolates of three type of bacteria was first subcultured in Brain heart infusion broth at temperature 37°C for 18-24 hour. select 3-5 colonies of bacteria isolates by loop and transfer them to tube containing 3 mL normal saline and vortex well.

Approximately one hundred microliters of the standardized inoculum bacterial suspension of around (1.5×10^8 CFU/mL) gained from McFarland turbidity standard (number 0.5). of each bacteria was used to inoculated by use glass spreader on the surface of Mueller Hinton Agar (MHA) plates. The additional liquid was airdried under a sterile hood or repeat the spreading process. the plate were allowed to dry and punched wells (five)in diameter 6 mm. into agar. Subsequently,In each agar plate of tested bacteria five wells were made and (100µl) of dilutions of derivatives compound (500,250,125 and 62.5) introduced into wells on MHA plate. DMSO used as the negative controller.

The plates were incubated at 37 °C for 24 hours and the antimicrobial action was estimated by determining the diameter of the inhibition zone (IZ) all over the place the disc in mm.

The valuation of antibacterial action was based on extent of the diameter of inhibition zone formed all over the place the well.

2.4.3.Preparation of serial dilutions of new synthesized compounds

- Take 0.01 g from each compounds and put it in test tube ,dissolve it in 10mL DMSO solvent (this is the stock solution 1000µg/mL)
- Take 2.5 mL from the stock solution put it in another test tube and add 2.5 mL from DMSO solvent here made (500µg/mL)(1^{st} dilution)
- Take 2.5 mL from the first dilution solution put it in another test tube and add 2.5 mL from DMSO solvent here made (250µg/mL)(2^{nd} dilution)
- Take 2.5 mL from the 2^{nd} dilution solution put it in another test tube and add 2.5 mL from DMSO solvent here made (125µg/mL)(3^{rd} dilution)
- Take 2.5 mL from the 3^{rd} dilution solution put it in another test tube and add 2.5 mL from DMSO solvent here made (62.5µg/mL)(4^{th} dilution)

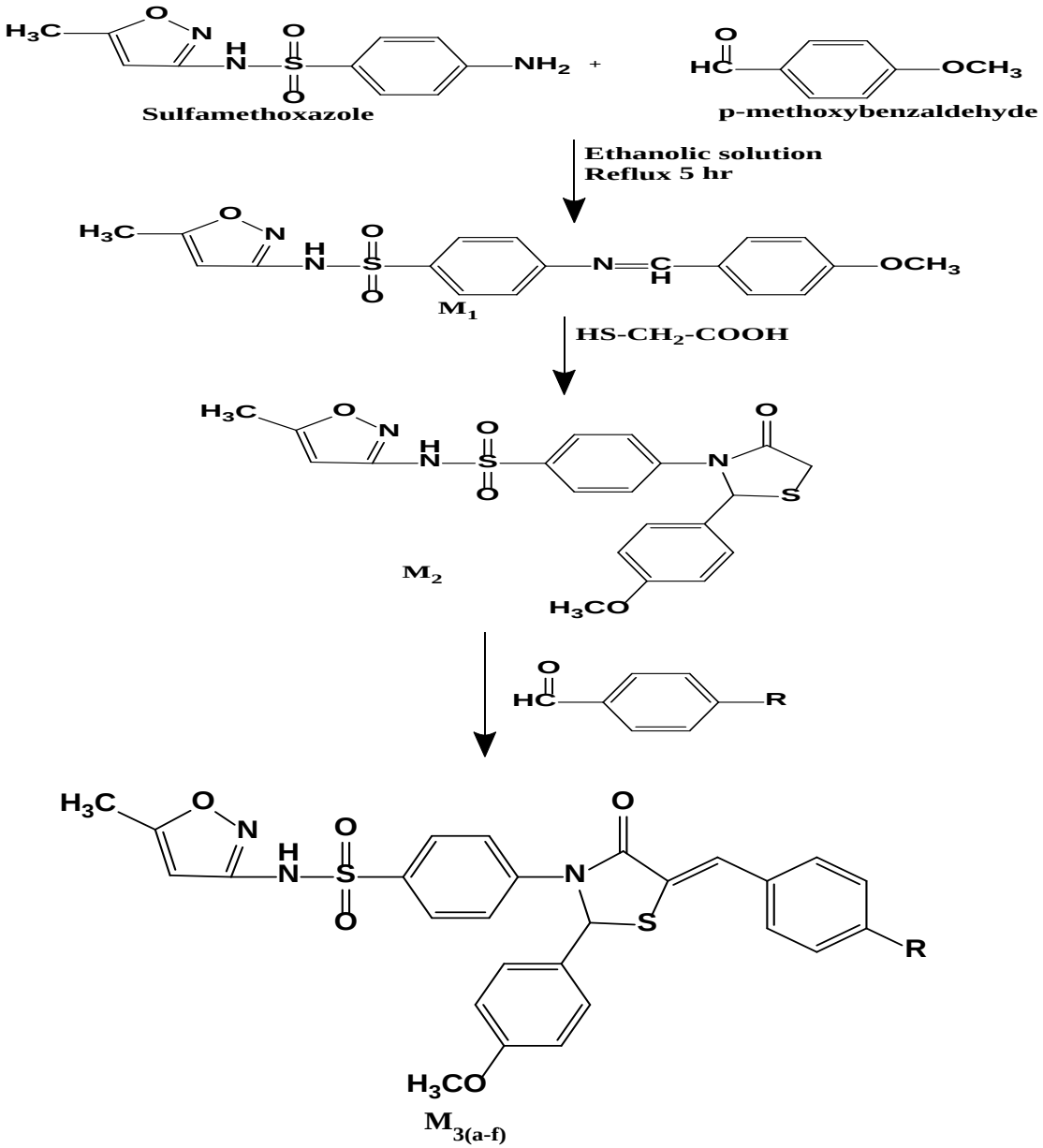
This process repeated for all the synthesized compounds (M_{3-8}) also for Sulfamethoxazole was used as a standard drug.

CHAPTER THREE

RESULTS & DISCUSSION

3.1 General Methodology

For the synthesis of the target sulfamethoxazole derivatives, the reaction series are drawn in schemes **(3-1)**



R= H(M_{3a}) , OH(M_{3b}) , OCH_3(M_{3c}) , NO_2(M_{3d}) , Cl(M_{3e}) & $N(CH_3)_2$(M_{3f}).

Scheme (3-1): Synthesis of intermediates and target compounds

3.2. Synthetic Studies

The synthetic ways for the designed target compounds, are illustrated in schemes (3-1). The characterization and the purity of the intermediates and the target compounds (melting point percent yield and R_f values) were summarized in table (3-1). The functional groups of the synthesized compounds were identified using FT-IR spectroscopy, as shown in figures (3-2) to (3-9) and their interpretations were presented in table (3-3). The chemical structures were confirmed using elemental microanalysis (CHNS) as presented in table (3-2) and ^{1}H-NMR spectra as shown in figures (3-10) to (3-17) and their interpretations were presented in tables (3-4) to (3-11).

The overall synthesized compounds are designed to be as follows:

1-Synthesis Schiff base from sulfamethoxazole with the para methoxy benzaldehydes under reflux conditions .

2-Synthese 4- thiazolidinone derivatives of sulfamethoxazole

3- Synthesis of the final cpds. containing substituted 5-arylidene -4-thiazolidinone pharmacophore.

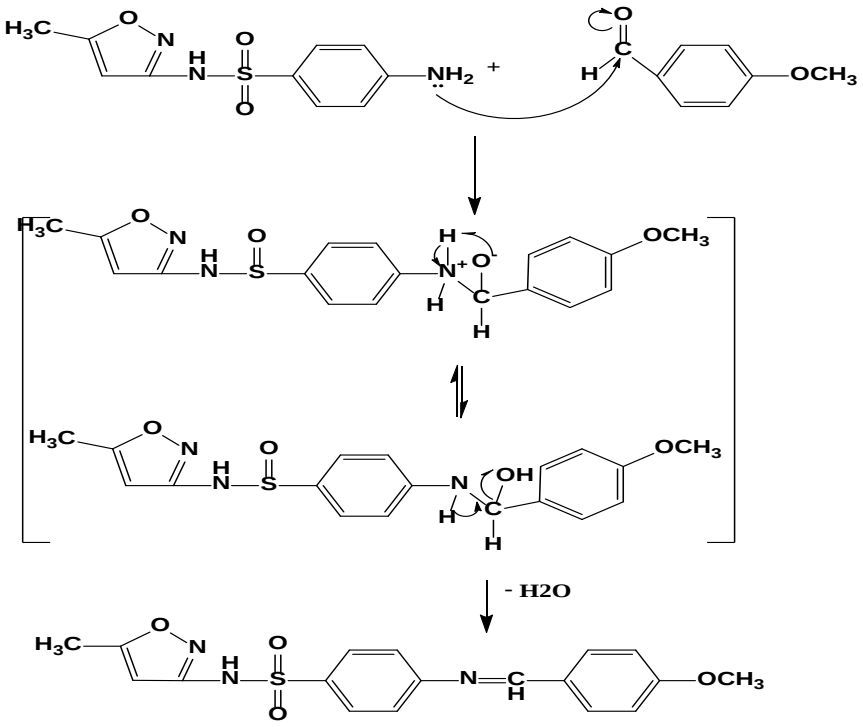
3.2.1 Synthesis of Schiff base(M_1)

The reaction of aromatic aldehyde with sulfamethoxazole (amine) is the most common reactions to synthesize hydrazone compound (Schiff base or imine). Imines were made by using acid catalysis by reversible process which begins with nucleophilic addition of a primary amine to the carbonyl group, then transferring the proton to the oxygen from nitrogen to produce carbinolamine or

which is neutral amino alcohol. Protonation of the carbinolamine oxygen through the use of an acid catalyst after that converts the (–OH) into a better leaving group (-OH2), and loss of water produces an iminium ion. Loss of a proton from nitrogen gives the final product and regenerates the acid catalyst as shown in Scheme (3- 2) [(143)].

The structure of compound of Schiff base was identified by melting point and R_f values given in Table (3-1). FT-IR characteristic absorption bands of compound of schiff base, presented in figure (3-2) & table (3-3). The IR spectrum clearly shows the characteristic absorption band at 3400 cm^{-1} is for υ_{NH} stretching of amide , bands in region 2854.74cm^{-1} refer to methyl υ_{C-H} stretching of and $\upsilon_{C=N}$ stretching at region 1658.84-1600.97 cm^{-1},and disappear of primary amine υ_{NH2} stretching at region 3468.13 cm^{-1} .

^{1}H-NMR spectra of compound [M_1] ,figure (3-10) , table (3-4) , showed the broad singlet at (11.41- ppm) integrated for NH amide proton ,The spectrum also shows signal at (8.97- ppm) integrated for one proton assigned for the proton of imine (CH=N) group.

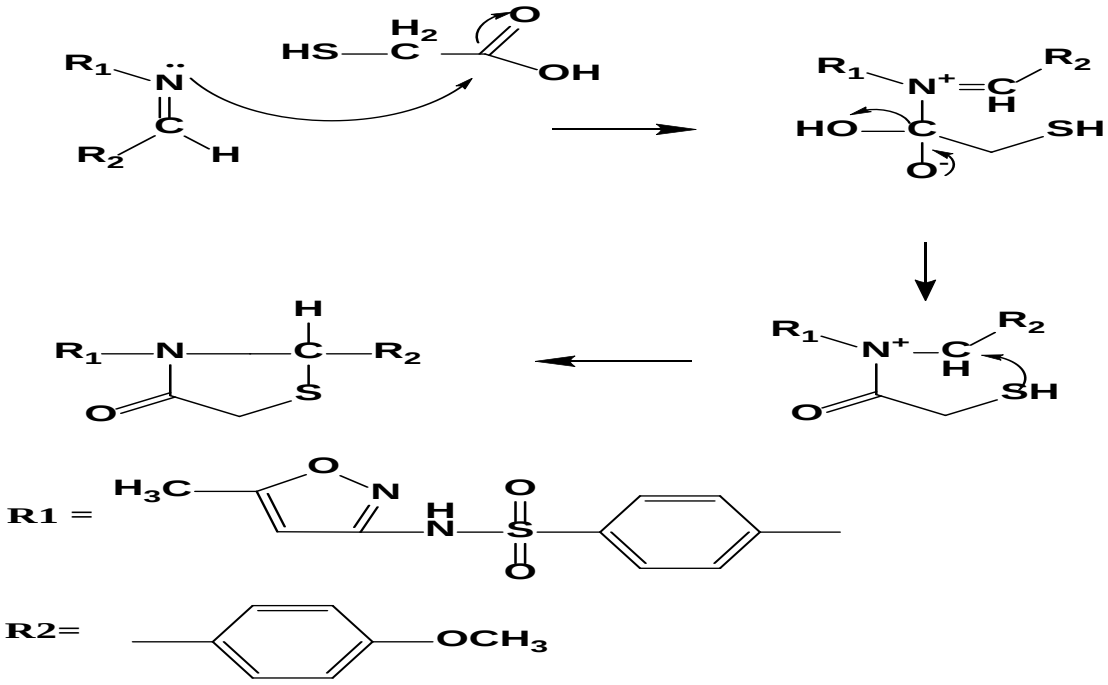


Scheme (3-2): Mechanism of Schiff base synthesis

3.2.2 Synthesis of 4- thiazolidinone (M_2)

The compound containing 4- thiazolidinone were obtained by A mixture of Schiff base , thioglycolic acid in *N*, *N* dimethylformamide with a pinch of anhydrous $ZnCl_2$, under refluxing for 12 h.

The suggested mechanism for the formation of compounds were proposed as follow in Scheme (3-3) [144].It was more probable through the formation of the compound containing 4- thiazolidinone than other mechanism , sine the carbon of carbonyl more electrophilic than carbon of imine, so unshared pair of electron of nitrogen atom will attack carbon atom of carbonyl faster than the probability of attack of imine carbon by unshared pair of electron of sulfhydryl group



Scheme (3-3): Mechanism of 4-thiazolidinone synthesis

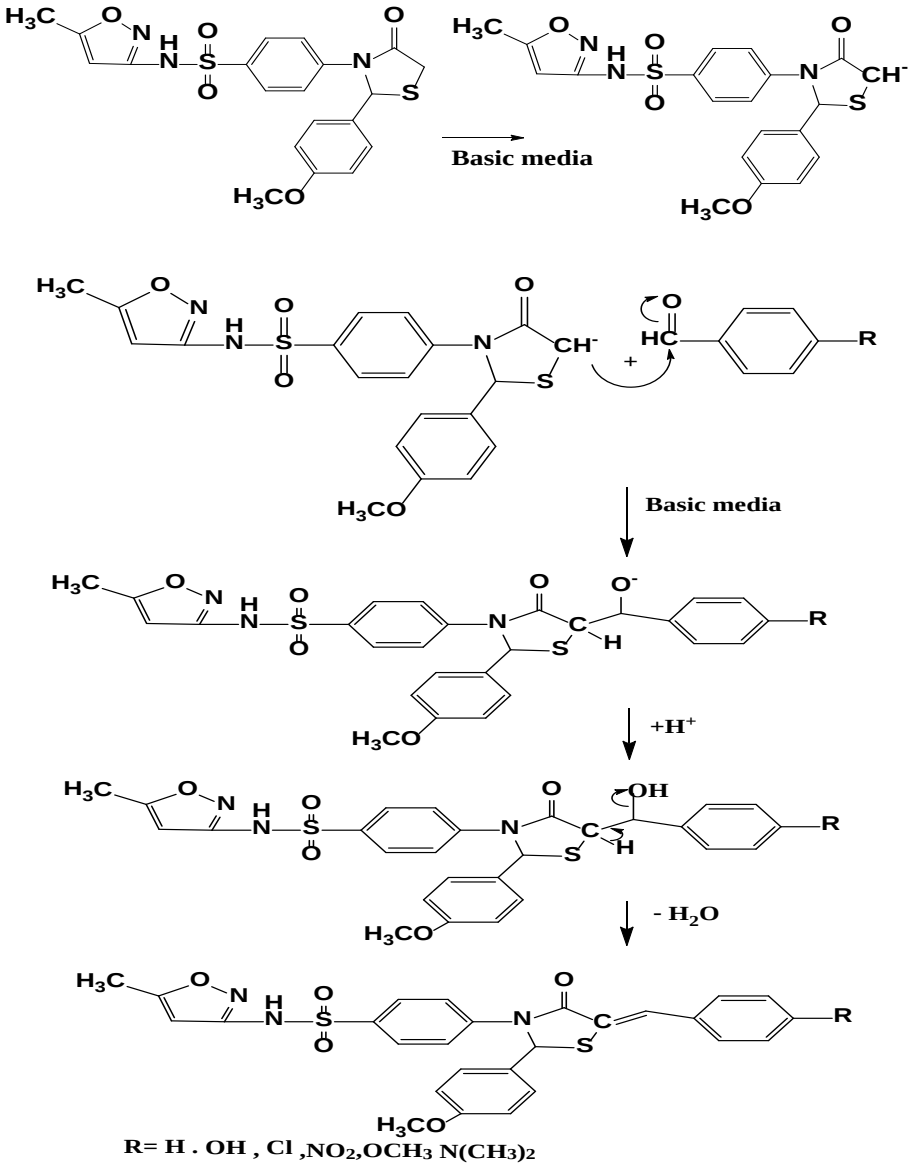
The structure of compounds (M_2) was characterized by melting point and R_f values given in Table (3-1)

FT-IR characteristic absorption bands of compound (M_2), presented in figure (3-3) &table (3-3). The IR spectrum clearly show characteristic absorption band at 3377.47 cm^{-1} is for υ_{NH} stretching of amide , bands in region 2968.55cm^{-1} refer to methyl a symmetric υ_{C-H} stretching of and $\upsilon_{C=0}$ stretching at region 1702.13 cm^{-1},and disappear of $\upsilon_{C=N}$ stretching at region 1658.84 cm^{-1} .

^{1}H-NMR spectra of compound [M_2] ,figure (3-11) , table (3-4) to , showed the broad singlet at (10.97- ppm) integrated for NH amide proton ,The spectrum also shows disappeared of signal at (8.9- ppm) integrated for one proton assigned for the proton of imine (CH=N) group, and appearance of CH_2 ,CH of thiazolidinone signal at (6.02-ppm)and (6.51) respectively.

3.2.3 Synthesis of chalcones $M_{3(a-f)}$

The compounds containing chalcone obtained by The main method for the synthesis of chalcones is the classical Claisen-Schmidt condensation in the presence of aqueous alkaline bases [145-147]. (our work in basic media)as follow in scheme (3-4) .



Scheme (3-4) mechanism of chalcone synthesis in basic media[145]

3.3 Characterization and identification of the target compounds and their interpretation

The physical properties, melting points and the R_f values of the synthesized compounds and their intermediates were listed in the tables (3-1),and the TLC were performed in two different solvent systems in order to follow up the reactants conversa into products without side reaction as revealed by the presence of one spot with different retardation factor (R_f) values as shown in table (3-1).

3.3.1 Elemental microanalysis (CHNS)

Elemental microanalysis was done for target compounds (M_{3-8}),to confirm their basic chemical structures. The results were offered in table (3-2) & revealed good covenant with calculated percentages. The percentage deviation of the observed / calculated values was found to be submitted with the exact analysis.

3.3.2 interpretation of the results of FT-IR spectral data

The FT-IR spectra of the synthesized compds and their intermediates, showed a characteristic bands of absorption which were in consistence with the proposed structure of the compounds. the values of the characteristics bands of these spectra were discussed according to the literature survey of an analogues compounds and reference book[(148)] and summarized in table (3-3).

3.3.3 Interpretation of the results of the ^{1}H-NMR

The ^{1}H-NMR analysis was used to identify the synthesized compounds and their intermediates. The spectra were recorded using DMSO solvent the values of the characteristics of the chemical shift were discussed according to the literature survey of an analogues compounds and reference book[(148)] and summarized in tables (3-4) to (3-11).

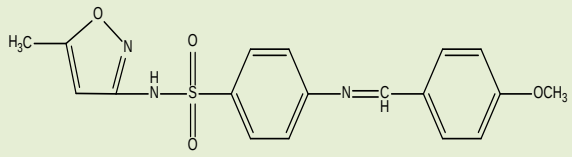
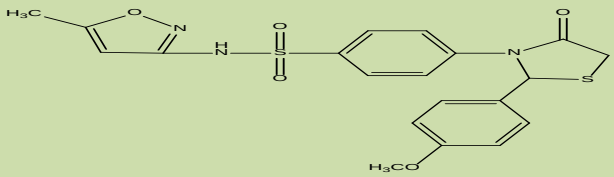
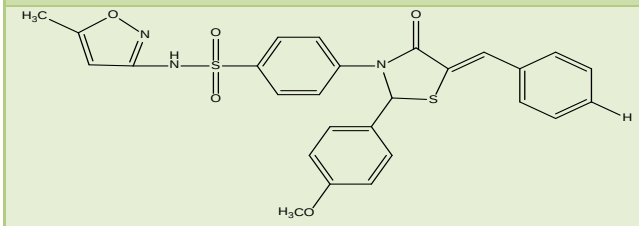
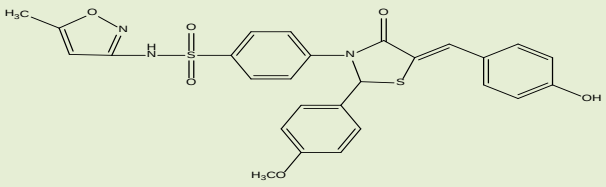
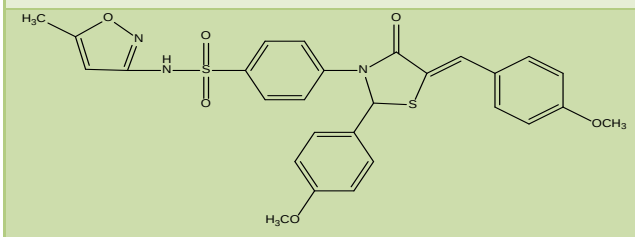
Table (3-1): Charachterizayion and physical properties of the intermediates and the final compounds

Comp No.	R	Mol. Formula	Yield %	Color, physical appearance	M.P / °C	R_f value
M_1	-	$C_{18}H_{17}N_3O_4S$	88	Yellow crystalline	234-235	A: 0.54 B: 0.52
M_2	-	$C_{20}H_{19}N_3O_5S_2$	90	Off white powder	136-137	A: 0.64 B: 0.62
M_{3a}	H	$C_{27}H_{22}N_3O_5S_2$	67	Pale-yellow powder	244-245	A: 0.71 B: 0.70
M_{3b}	OH	$C_{27}H_{22}N_3O_6S_2$	62	Yellowish brown powder	180-181	A: 0.52 B: 0.49
M_{3c}	OCH_3	$C_{28}H_{24}N_3O_6S_2$	73	Brown powder	118-120	A: 0.68 B: 0.66
M_{3d}	NO_2	$C_{27}H_{21}N_4O_7S_2$	74	Pale-green	214-215	A: 0.88 B: 0.86
M_{3e}	Cl	$C_{27}H_{21}N_3O_5S_2Cl$	75	Yellow powder	262-263	A: 0.81 B: 0.78
M_{3f}	$N(CH_3)_2$	$C_{29}H_{27}N_4O_5S_2$	74	Orange powder	198-199	A: 0.77 B: 0.74

Table (3-2): ***Elemental microanalysis of the final compounds(CHNS).***

Compound	*Molecular weight*	*Empirical formula*	*Elemental microanalysis %*		
			Element	***Calculated***	*Observed*
M_{3a}	532.61	$C_{27}H_{23}N_3O_5S_2$	***C***	*60.77*	***60.45***
			H	*4.34*	***4.17***
			N	*7.87*	***7.78***
			S	*12.02*	***12.05***
M_{3b}	548.61	$C_{27}H_{23}N_3O_6S_2$	***C***	*59.00*	***59.28***
			H	*4.22*	***4.05***
			N	*7.65*	***7.77***
			S	*11.67*	***11.56***
M_{3c}	562.64	$C_{28}H_{25}N_3O_6S_2$	***C***	*59.67*	***59.46***
			H	*4.47*	***4.415***
			N	*7.46*	***7.51***
			S	*11.38*	***11.58***
M_{3d}	577.6	$C_{27}H_{22}N_4O_7S_2$	***C***	*56.05*	***56.06***
			H	*3.83*	***3.72***
			N	*9.68*	***9.78***
			S	*11.08*	***11.05***
M_{3e}	567.06	$C_{27}H_{22}N_3O_5S_2Cl$	***C***	*57.09*	***57.12***
			H	*3.90*	***3.71***
			N	*7.40*	***7.39***
			S	*11.29*	***11.3***
M_{3f}	575.68	$C_{29}H_{28}N_4O_5S_2$	***C***	*60.40*	***60.22***
			H	*4.89*	***5.06***
			N	*9.72*	***9.52***
			S	*11.12*	***11.15***

Table (3-3): FT-IR Spectral data for intermediate and final compounds

Compounds	Characteristics bands of IR spectra (cm-1,KBr disk)	
	Bands	**Interpretation**
 M_1	3400	**NH** Stretching vibration of 2°sulfonamide
	2854	**CH** Stretching vibration of methyl
	1658	**C=N** Stretching vibration of Imine
	1600	**C=N** stretching of isoxazole ring
	1585	Aromatic **C=C** stretching
	1093 1274	**C-O-C** symmetric Str. **C-O-C** a symmetric Str.
	775.	**CH** bending vibration out of plane
 M_2	3377	**NH** Stretching vibration of 2°sulfonamide
	3049	**CH** Stretching vibration of aromatic
	2968	**CH** asymmetric stretching of CH
	1705	**C=O** Stretching vibration of thiazolidinone
	1612	**C=N** stretching of isoxazole ring
	1504	Aromatic **C=C** stretching
	1251	**C-OCH3** stretching
 **M_{3a}**	3367	**NH** Stretching vibration of 2°sulfonamide
	3190	**C-H** stretching of aromatic
	2951	**CH** asymmetric stretching of CH_3
	1668	**C=O** stretching of thiazolidinone
	1589	Aromatic **C=C** stretching
	1163	**C-S** stretching
 **M_{3b}**	3452	Phenolic **O-H** stretching
	3223	**NH** Stretching vibration of 2°sulfonamide
	3076	**C-H** stretching of aromatic
	2928	**CH** asymmetric stretching of CH_3
	1680	**C=O** stretching of thiazolidinone
	1612	Aromatic **C=C** stretching
	1222	**C-S** stretching
 **M_{3c}**	3452	**NH** Stretching vibration of 2°sulfonamide
	3078	**CH** stretching of aromatic
	2929	**CH** asymmetric stretching of CH_3
	1701	**C=O** stretching of thiazolidinone
	1637	**C=N** stretching of isoxazole ring
	1595	Aromatic **C=C** stretching
	1251	**C-OCH3** stretching
	1130	**C-S** stretching

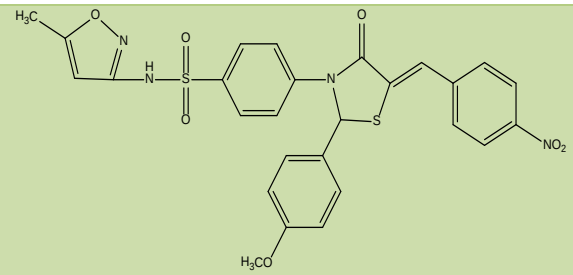
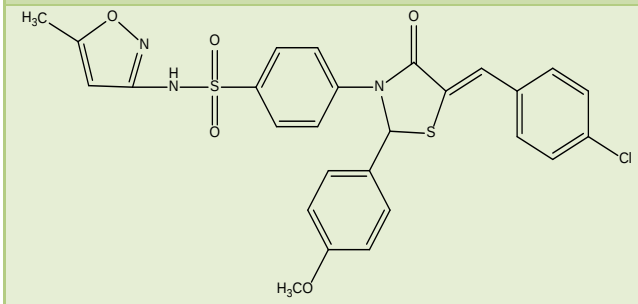
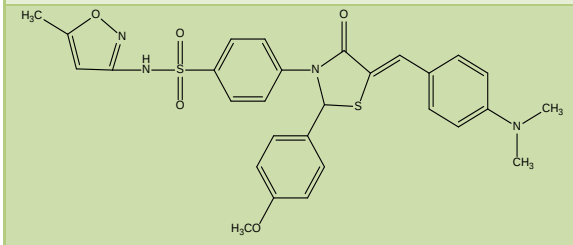
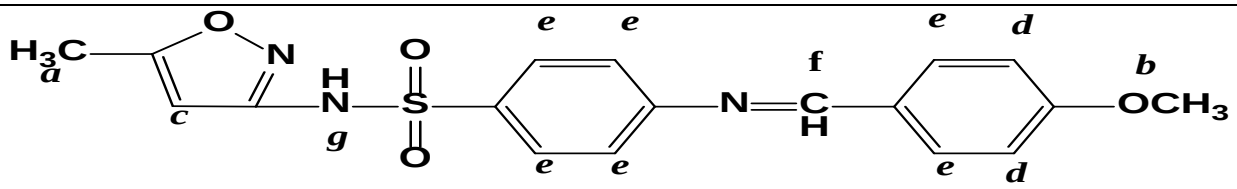
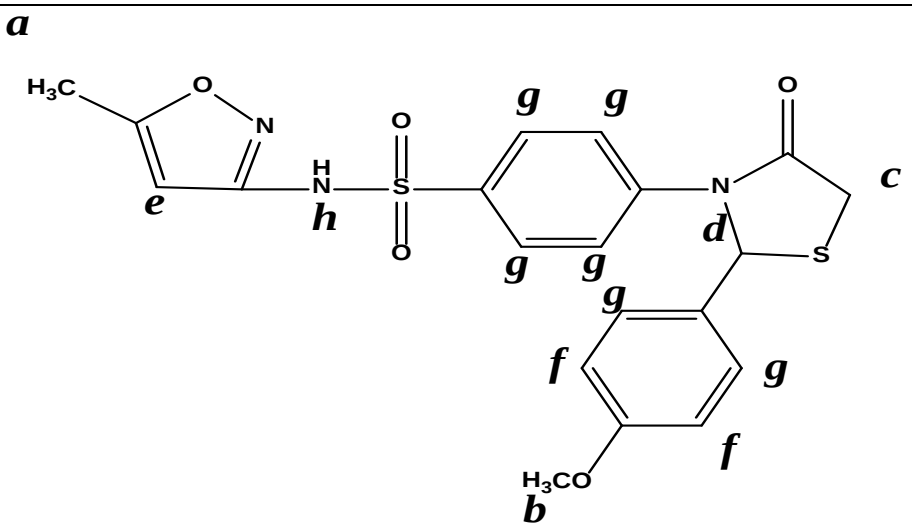
 **M_{3d}**	3452	**NH** Stretching vibration of 2°sulfonamide
	3076	**C-H** stretching of aromatic
	2933	**C-H** asymmetric stretching of CH_3
	1732	**C=O** stretching of thiazolidinone
	1635	**C=N** stretching of isoxazole ring
	1595	Aromatic **C=C** stretching
	1525	NO_2 asymmetric stretching
	1350	NO_2 symmetric stretching
	1174	**C-S** stretching
 **M_{3e}**	3448	**NH** Stretching vibration of 2°sulfonamide
	3288	**C-H** stretching of 2°sulfonamide
	3078	**CH** stretching of aromatic
	2856	**CH** stretching of CH_3
	1732	**C=O** stretching of thiazolidinone
	1637	**C=N** stretching of isoxazole ring
	1604	Aromatic **C=C** stretching
	1174	**C-S** stretching
	1089	**C-Cl** stretching
 **M_{3f}**	3431	**NH** Stretching vibration of 2°sulfonamide
	2951	**C-H** stretching of aromatic
	2845	**CH** asymmetric str. of CH_3
	1720	**C=O** str. of thiazolidinone
	1647	**C=N** str. of isoxazole ring
	1610	Aromatic **C=C** stretching
	1396	**C-N(CH_3)$_2$** stretching
	1168	**C-S** stretching

Table (3-4): ^{1}H-NMR data and their interpretation of compound [M_1]



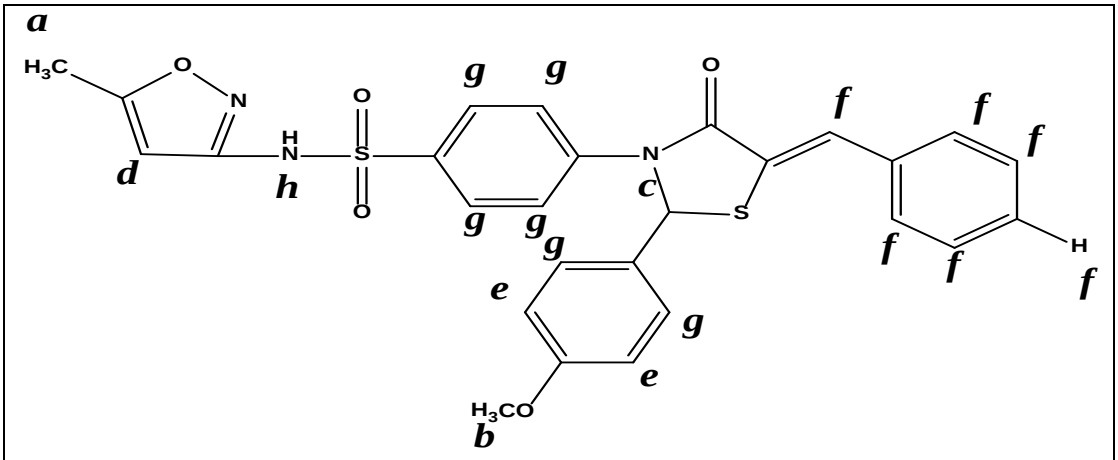
Signal	*Signal Position (δppm)*	*Relative No. of proton*	*Multiplicity*	*Inference*
a	2.131	3H	Singlet	CH_3 of isoxazole ring
b	3.88	3H	Singlet	Para -OCH_3
c	6.17	1H	Singlet	CH- of isoxazole ring
d	7.17	2H	Doublet	Aromatic –H ortho to OCH_3
e	7.6-8.2	6H	Multiplet	Aromatic –H
f	8.9	1H	Singlet	CH=N of Schiff base
g	11.41	1H	Singlet	NH of sulfonamide

Table (3-5): ^{1}H-NMR data and their interpretation of compound [M_2]



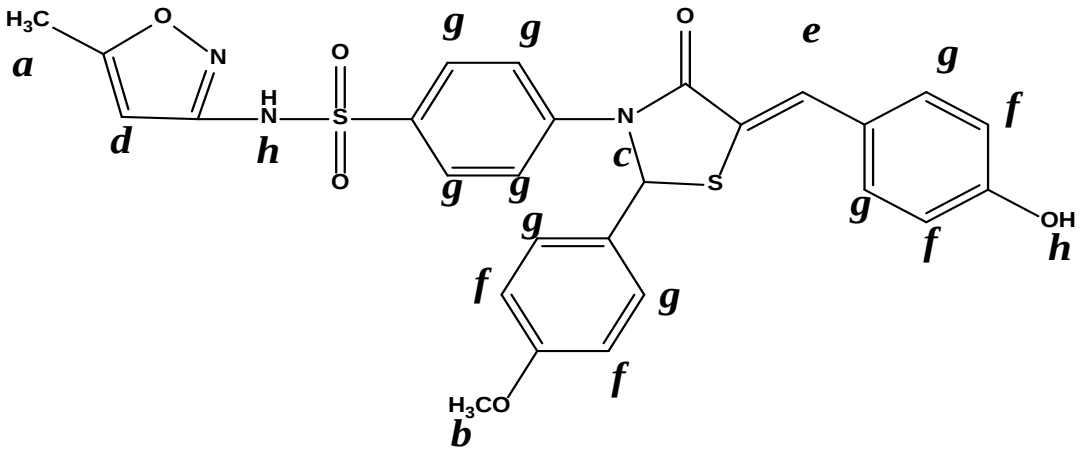
Signal	*Signal Position (δppm)*	*Relative No. of proton*	*Multiplicity*	*Inference*
a	2.28	3H	Singlet	CH_3 of isoxazole ring
b	3.98	3H	Singlet	Para -OCH_3
c	5.31	2H	Singlet	CH_2 of thiazolidinone
d	6.02	1H	Singlet	CH of thiazolidinone
e	6.51	1H	Singlet	CH- of isoxazole ring
f	6.86	2H	Doublet	Aromatic–H ortho to OCH_3
g	7.1-7.47	6H	Multiplet	Aromatic C-H
h	10.97	1H	Singlet	NH of sulfonamide

Table (3-6): ^{1}H-NMR data and their interpretation of compound [M_{3a}]



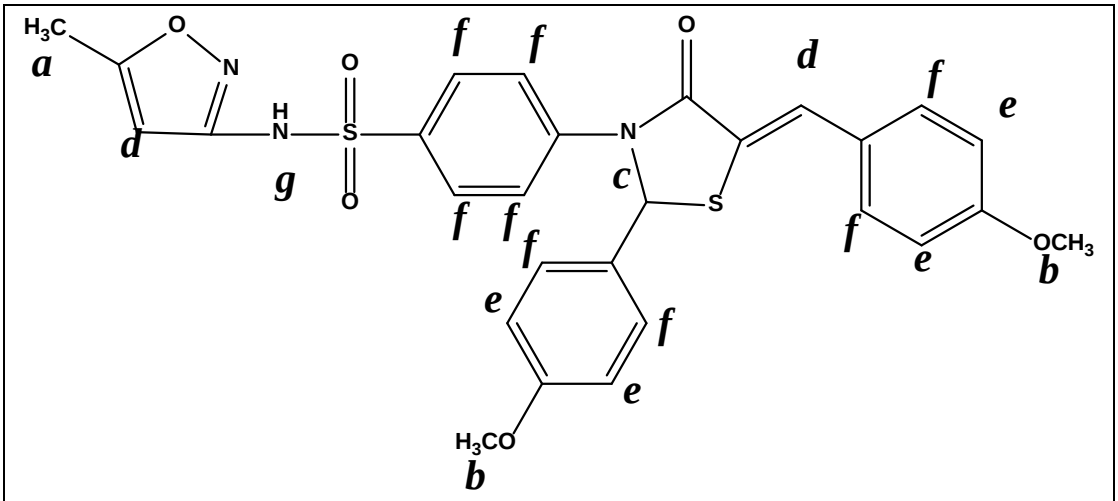
Signal	*Signal Position (δppm)*	*Relative No. of proton*	*Multiplicity*	*Inference*
a	2.40	3H	Singlet	CH_3 of isoxazole ring
b	3.48	3H	Singlet	Para -OCH_3
c	4.11	1H	Singlet	CH of thiazolidinone
d	5.35	1H	Singlet	CH- of isoxazole
e	6.13	2H	Doublet	Aromatic–H(Ortho to OCH_3
f	6.59-6.73	6H	Multiplet	Aromatic –H, CH of chalcone
g	7.41-7.6	6H	Multiplet	Aromatic C-H
h	10.9	1H	Singlet	NH of sulfonamide

Table (3-7): ^{1}H-NMR data and their interpretation of compound [M_{3b}]



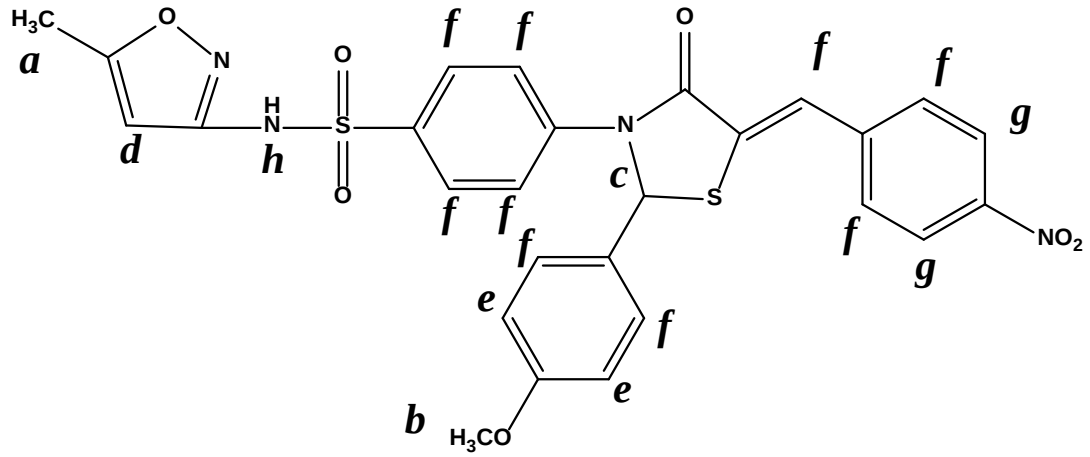
Signal	*Signal Position (δppm)*	*Relative No. of proton*	*Multiplicity*	*Inference*
a	2.2	3H	Singlet	CH_3 of isoxazole ring
b	3.74	3H	Singlet	Para -OCH_3
c	5.49	1H	Singlet	CH of thiazolidinone
d	5.75	1H	Singlet	CH-isoxazole
e	5.82	1H	Singlet	CH of chalcone
f	6.47	4H	Multiplet	Ortho OH & ortho OCH_3
g	6.86-7.76	8H	Multiplet	Aromatic –H
h	10.08	2H	Singlet	NH of sulfonamide Overlaped with phenolic OH

Table (3-8): ^{1}H-NMR data and their interpretation of compound [M_{3c}]



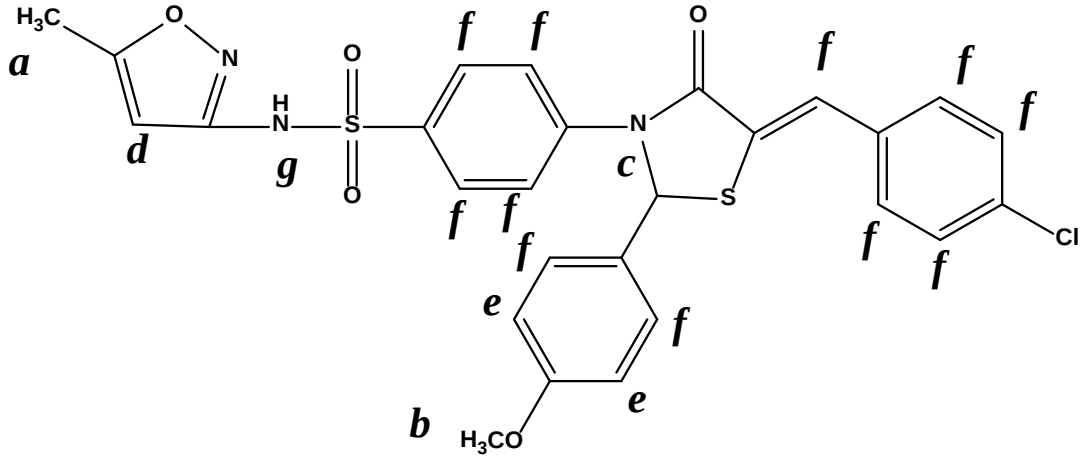
Signal	*Signal Position (δppm)*	*Relative No. of proton*	*Multiplicity*	*Inference*
a	2.31	3H	Singlet	CH_3 of isoxazole ring
b	4.04	6H	Singlet	2(para-OCH_3)
c	5.15	1H	Singlet	CH of thiazolidinone
d	5.72	2H	Singlet	CH of isoxazole & CH-chalcone
e	6.44-6.67	4H	Doublet	Ortho to OCH_3
f	7.31-7.61	8H	Multiplet	Aromatic -H
g	10.9	1H	Singlet	NH of sulfonamide

Table (3-9): ^{1}H-NMR data and their interpretation of compound [M_{3d}]



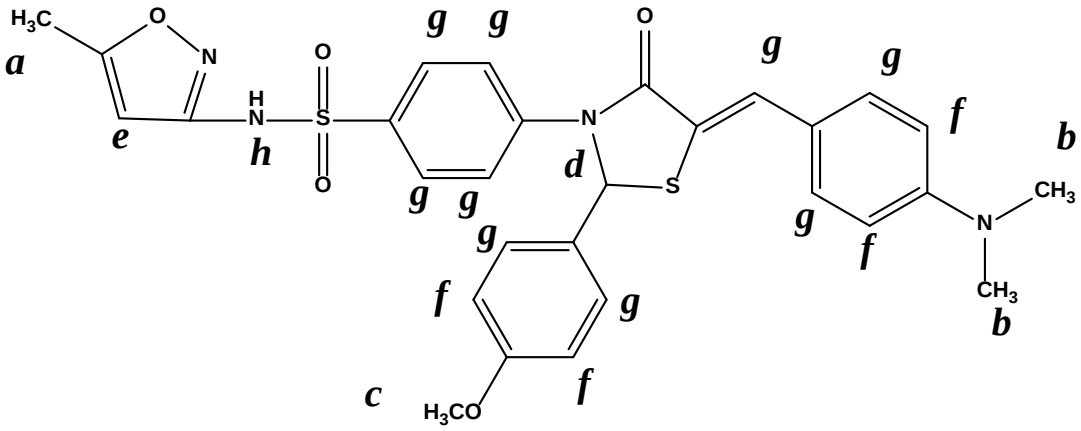
Signal	*Signal Position (δppm)*	*Relative No. of proton*	*Multiplicity*	*Inference*
a	2.10	3H	Singlet	CH_3 of isoxazole ring
b	3.80	3H	Singlet	Para -OCH_3
c	5.33	1H	Singlet	CH of thiazolidinone
d	5.77	1H	Singlet	CH- of isoxazole
e	6.49	2H	Doublet	Aromatic–H(Ortho-OCH_3
f	7.11-7.8	9H	Multiplet	Aromatic –H & CH of chalcone
g	8.2	2H	Doublet	Ortho to NO_2
h	10.98	1H	Singlet	NH of sulfonamide

Table (3-10): ^{1}H-NMR data and their interpretation of compound [M_{3e}]



Signal	*Signal Position (δppm)*	*Relative No. of proton*	*Multiplicity*	*Inference*
a	2.61	3H	Singlet	CH_3 of isoxazole ring
b	3.45	3H	Singlet	Para -OCH_3
c	5.3	1H	Singlet	CH of thiazolidinone
d	5.76	1H	Singlet	CH- of isoxazole
e	6.51	2H	Doublet	Aromatic–H(Ortho-OCH_3
f	6.8-7.19	11H	Multiplet	Aromatic –H & CH of chalcone
g	11.0	1H	Singlet	NH of sulfonamide

Table (3-11): ^{1}H-NMR data and their interpretation of compound [M_{3f}]



Signal	*Signal Position (δppm)*	*Relative No. of proton*	*Multiplicity*	*Inference*
a	2.27	3H	Singlet	CH_3 of isoxazole ring
b	3.03	6H	Singlet	$N(CH_3)_2$
c	3.85	3H	Singlet	Para -OCH_3
d	5.66	1H	Singlet	CH of thiazolidinone
e	6.08	1H	Singlet	CH-isoxazole ring
f	6.77-7.00	4H	Multiplet	Aromatic C–H ortho to OCH_3 & $N(CH_3)_2$
g	7.1-7.96	9H	Multiplet	Aromatic C-H & CH of chalcone
h	10.93	1H	Singlet	NH of sulfonamide

3.4. Antimicrobial activity evaluation

The antibacterial results showed that the effect of tested compounds that as with different concentrations. Also all the tested compounds show activity against gram – ve bacteria *Pseudomonas aeruginosa* unlike the parent compound sulfamethoxazole, with highest activity for para chloro, nitro containing derivatives and lowest activity for the para H and OH derivatives compounds. The assessment of antibacterial was based on dimension of the diameter of inhibition zone formed round the well, and display that the zone of inhibition increased with the increasing of conc. of the tested compds.

Table(3-12) :Antibacterial activity of Sulfamethoxazole and compounds (M_{3a-f}) against tested bacteria:

Compound No.	Concentration (µg/ml)	*Escherichia coli* (Gm-ve) Inhibition zone(mm)	*Pseudomonas aeruginosa* (Gm-ve) Inhibition zone(mm)	*Staphylococcus aureus* (Gm+ve) Inhibition zone(mm)
SMX	500	20	_____	20
	250	15	_____	16
	125	14	_____	15
	62.5	12	_____	_____
DMSO	Pure	_____	_____	_____
M_{3a}	500	20	18	20
	250	20	16	18
	125	18	16	15
	62.5	10	10	13
M_{3b}	500	18	17	20
	250	17	16	19
	125	17	15	16
	62.5	15	12	15
M_{3c}	500	25	24	23
	250	22	20	20
	125	20	18	16
	62.5	15	12	14
M_{3d}	500	20	25	25
	250	20	25	20
	125	18	18	18
	62.5	14	12	15
M_{3e}	500	28	25	25
	250	25	22	22
	125	20	18	20
	62.5	18	15	18
M_{3f}	500	18	23	20
	250	16	20	20
	125	15	20	16
	62.5	13	11	14

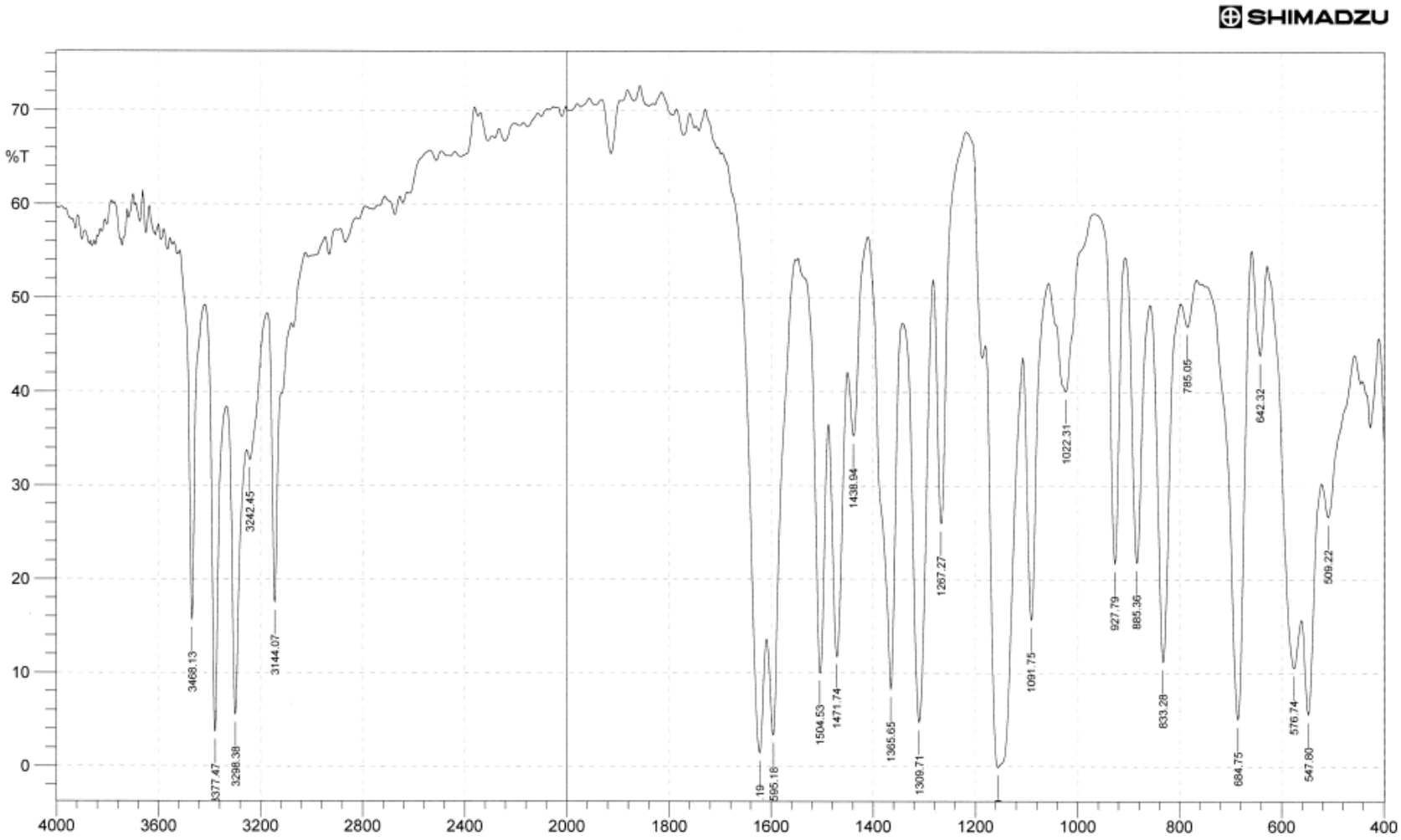
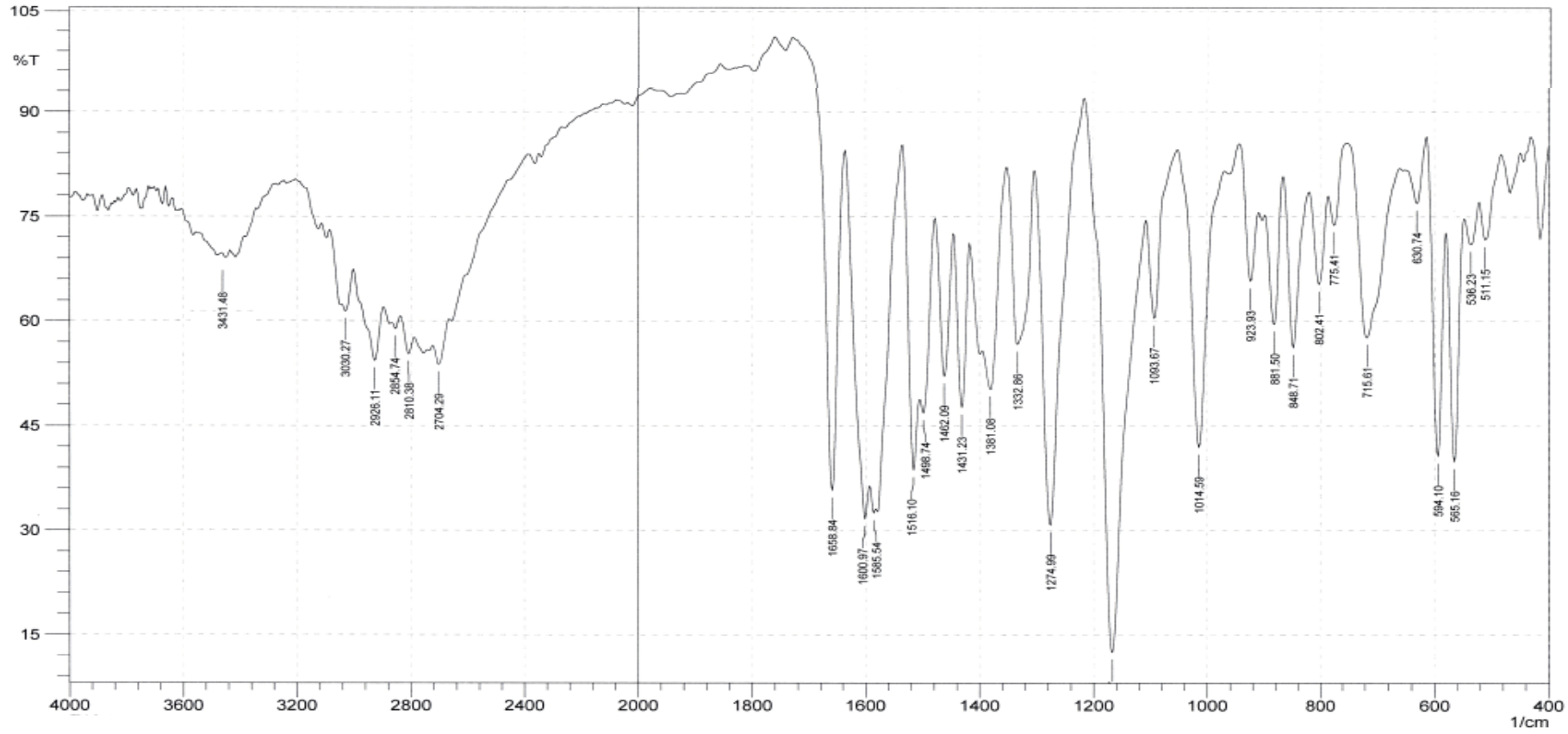
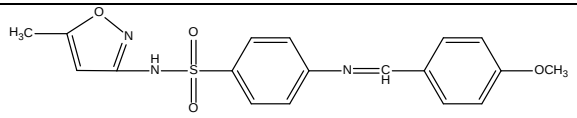


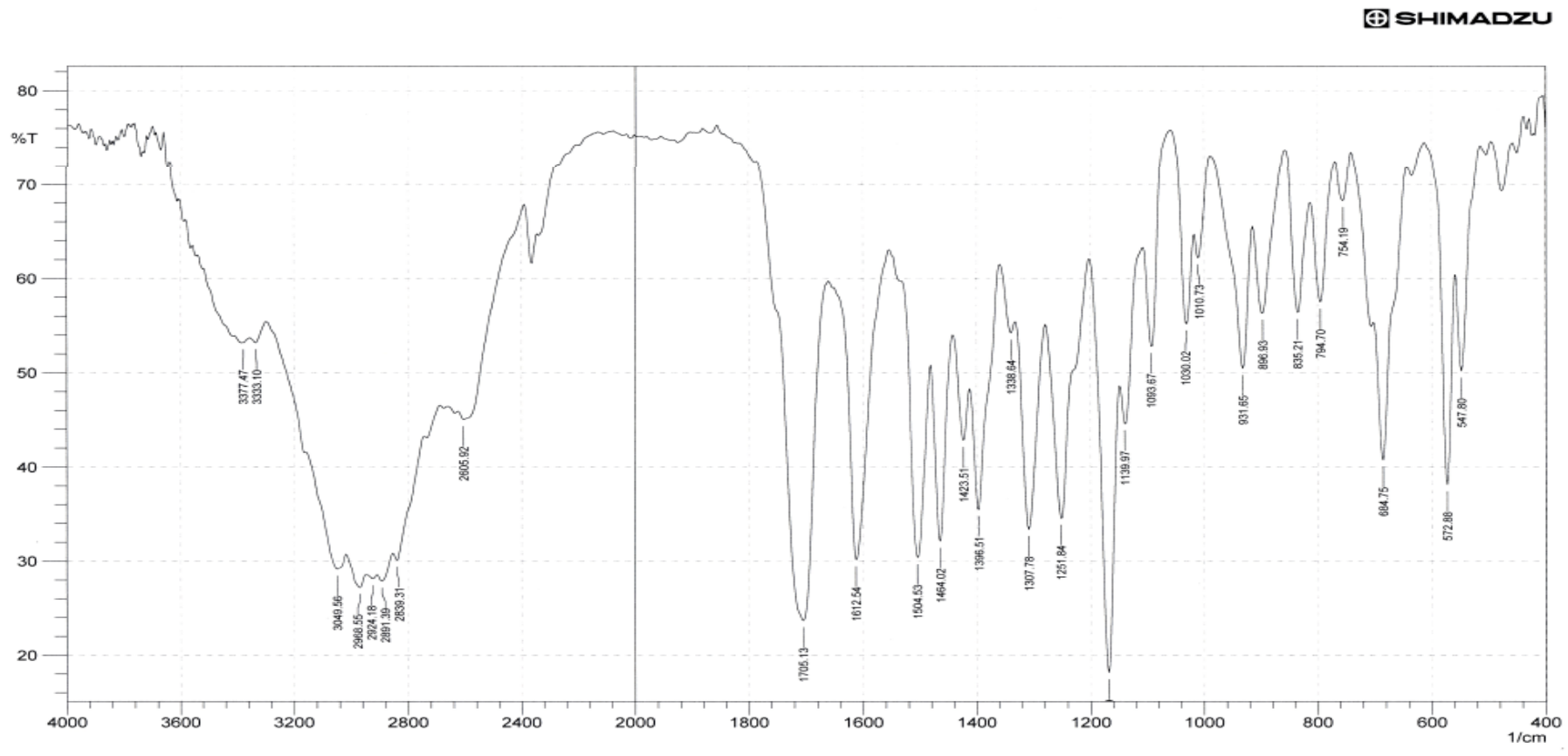
Figure (3-1): FT-IR spectra for sulfamethoxazole

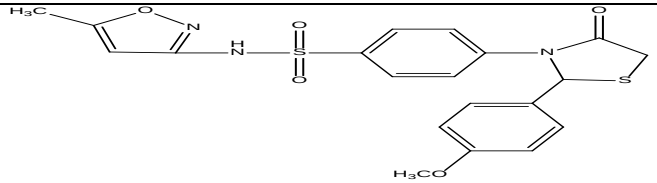




Characteristics bands (cm^{-1})	Mol. Formula: **$C_{18}H_{17}N_3O_4S$**
1658.84 C=N Stretching vibration of imine	M.P. /◦C: **234-235**

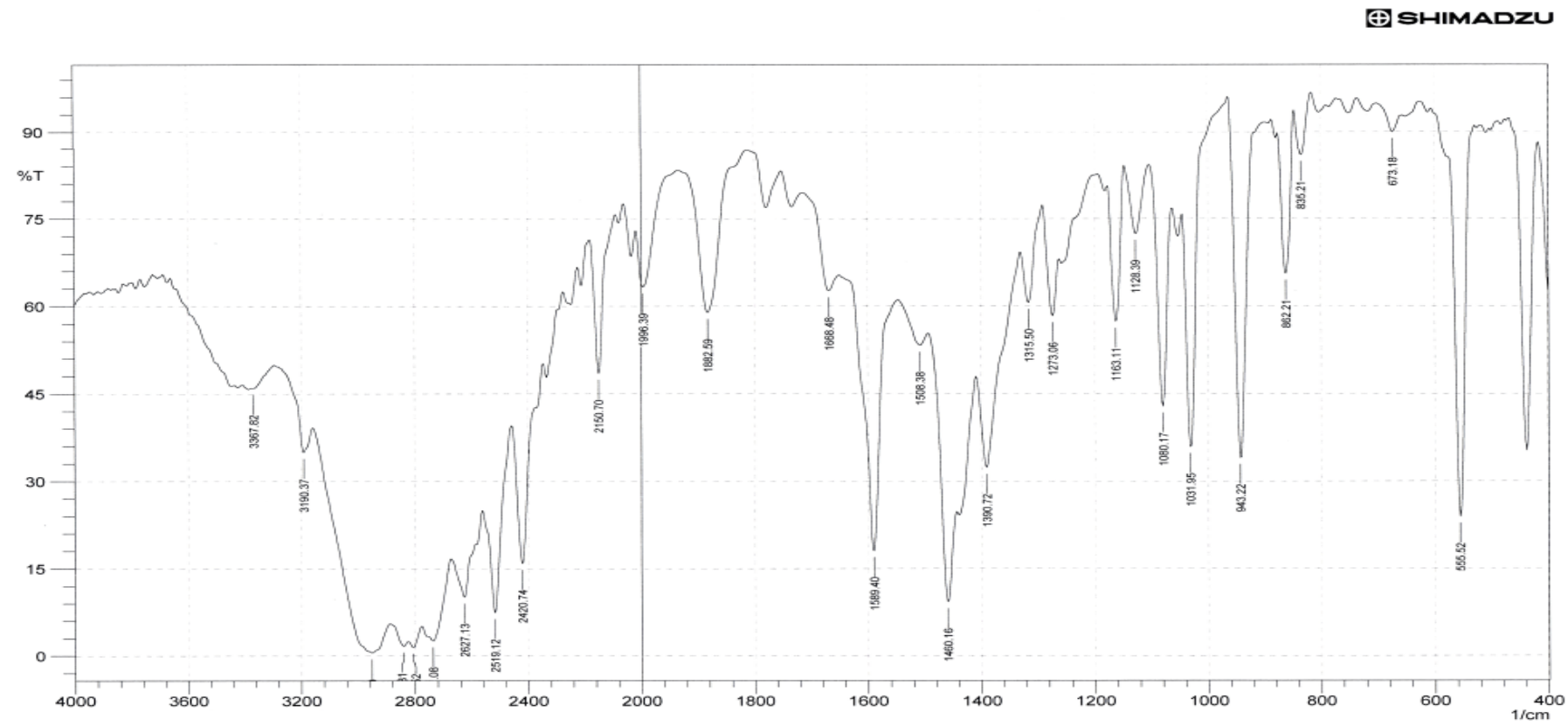
Figure (3-2): FT-IR spectra for compound (M_1)

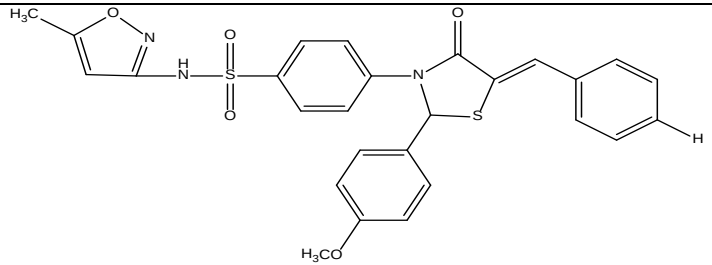




Characteristics bands (cm^{-1})	Mol. Formula: **$C_{20}H_{19}N_3O_5S_2$**
1705.13 C=O Stretching vibration of thiazolidinone 1251.84 C-OCH_3 Stretching	M.P. /◦C: **136-137**

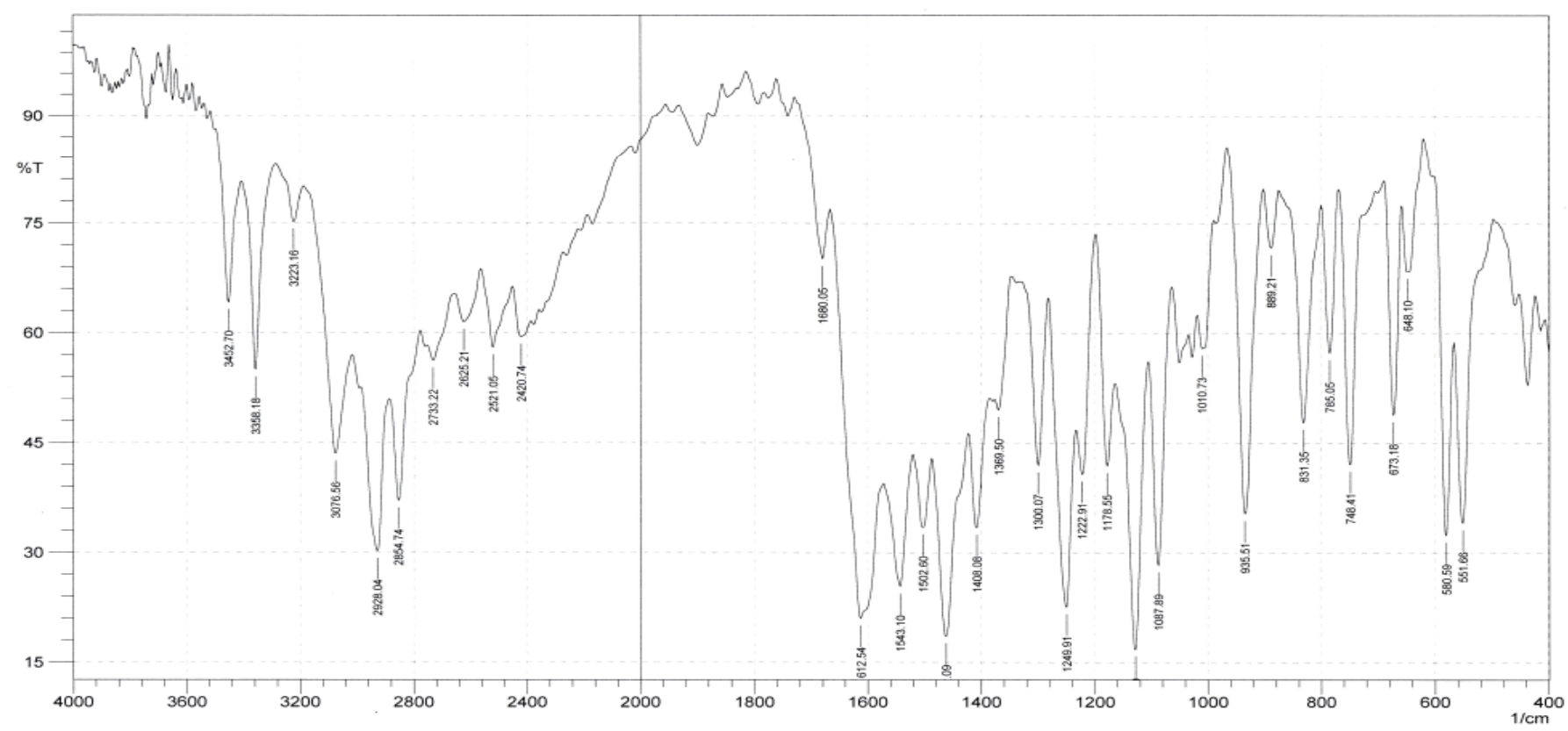
Figure (3-3): FT-IR spectra for compound (M_2)

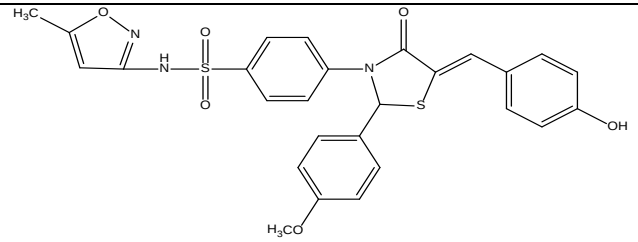




Characteristics bands (cm^{-1})	Mol. Formula: **$C_{27}H_{22}N_3O_5S_2$**
1734.06 C=O Stretching vibration of thiazolidinone 1163.11 C-S Stretching	M.P. /◦C: **244-245**

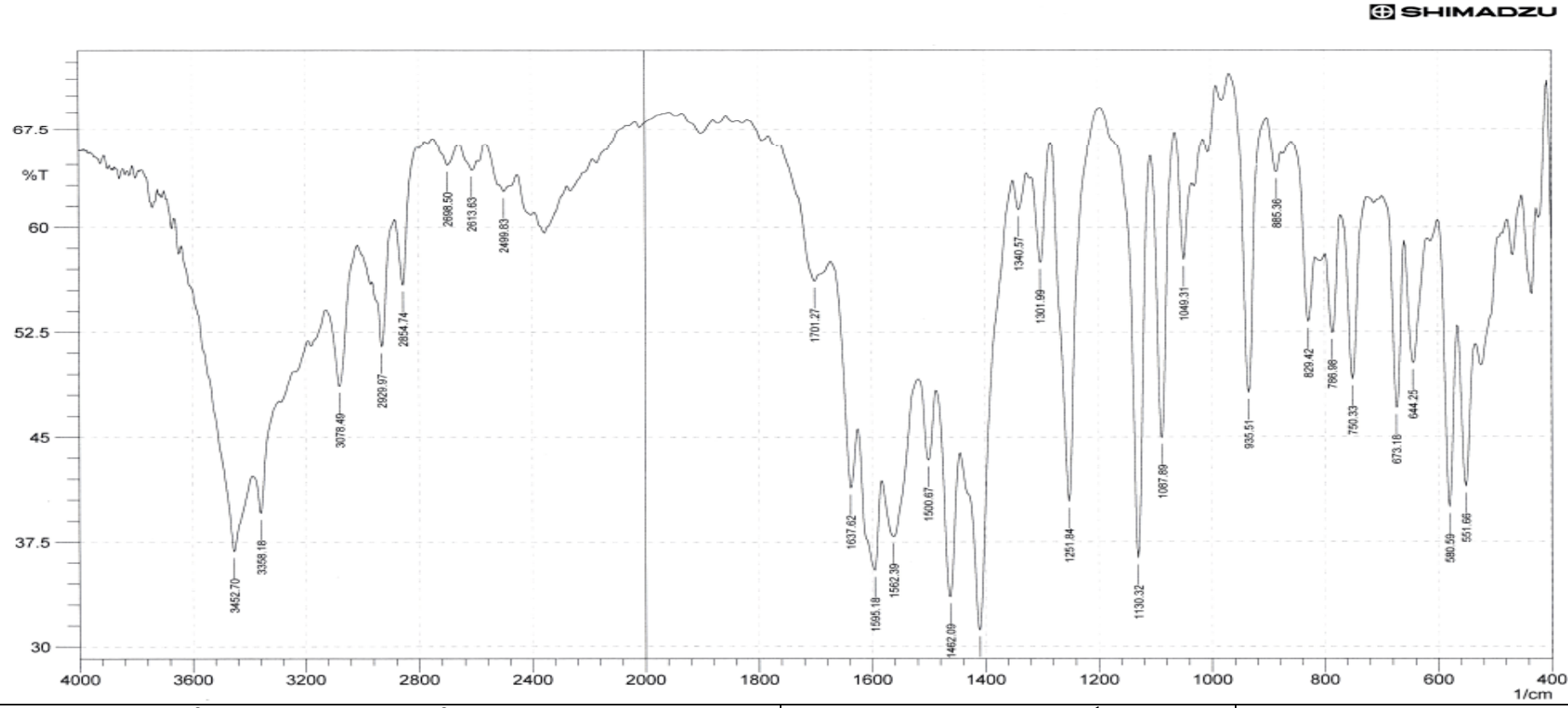
Figure (3-4): FT-IR spectra for compound(M_{3a})

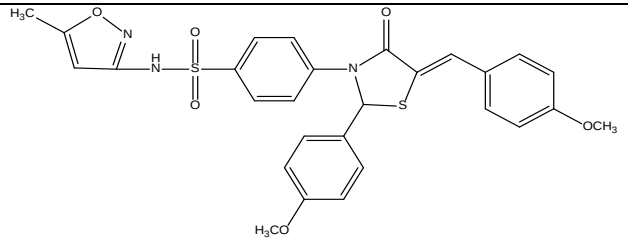




Characteristics bands (cm^{-1})	Mol. Formula: $C_{27}H_{22}N_3O_6S_2$
1739.85 C=O Stretching vibration of thiazolidinone 1222.91 C-S Stretching	M.P. /◦C: **180-181**

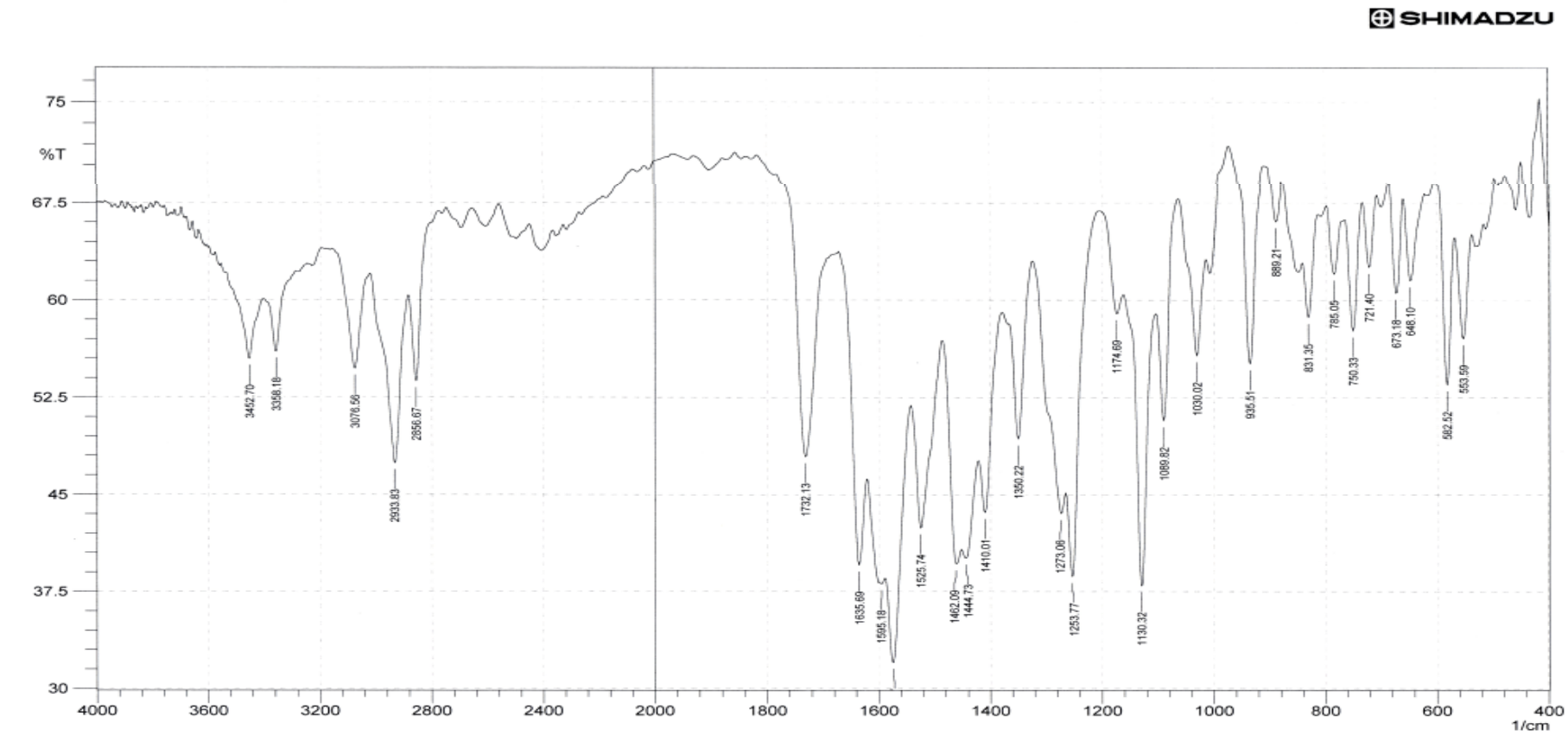
Figure (3-5): FT-IR spectra for compound(M_{3b})

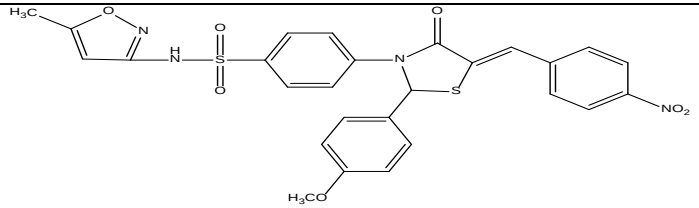




Characteristics bands (cm^{-1})	Mol. Formula: **$C_{28}H_{24}N_3O_6S_2$**
1701.27 C=O Stretching vibration of thiazolidinone	M.P. /◦C: **118-120**

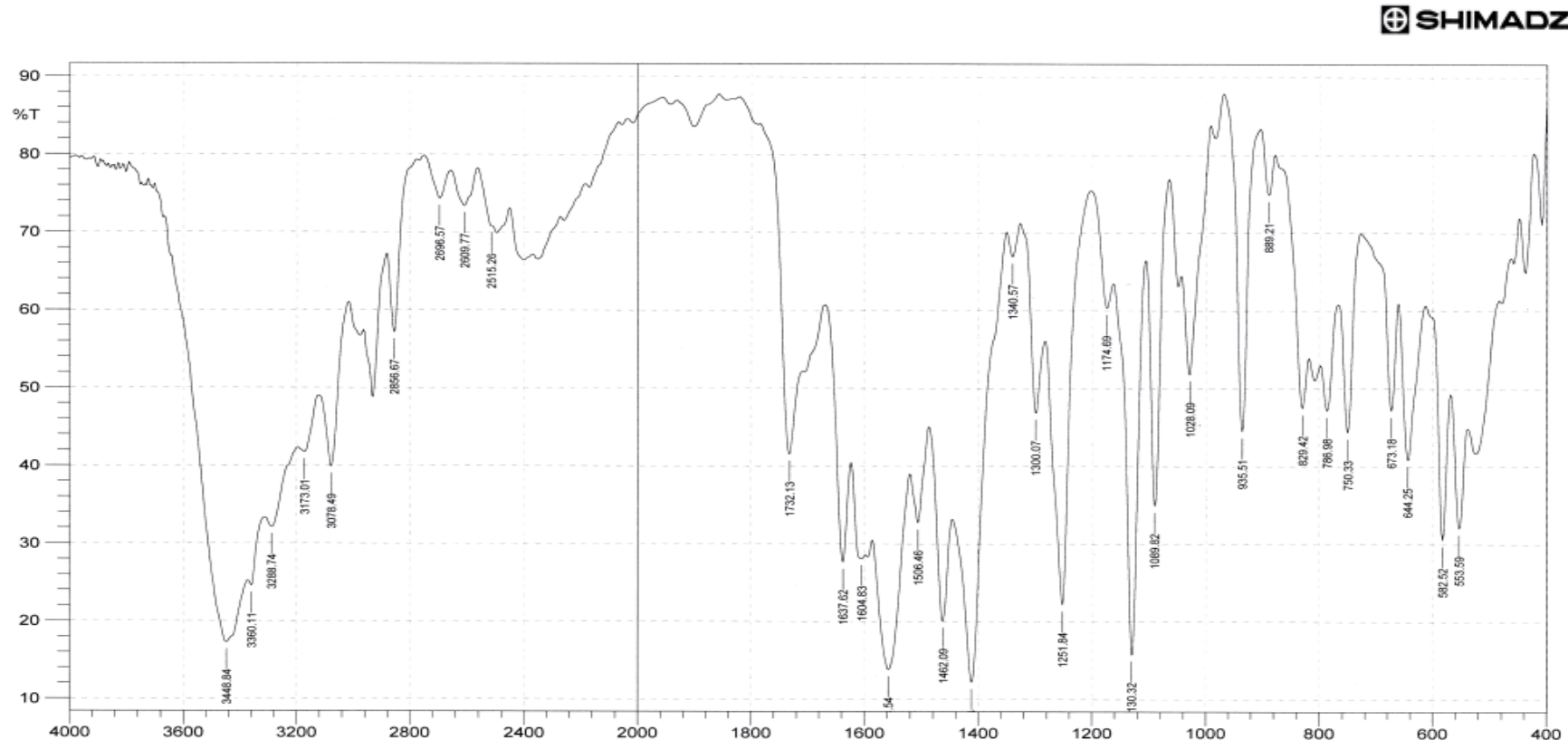
Figure (3-6): FT-IR spectra for compound(M_{3c})

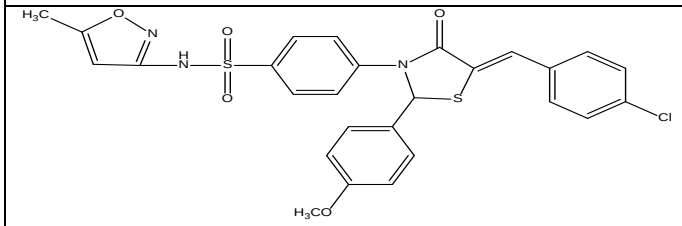




Characteristics bands (cm^{-1})	Mol. Formula: **$C_{27}H_{21}N_4O_7S_2$**
1732.13 C=O Stretching vibration of thiazolidinone 1525.74 NO_2 asymmetric stretching 1350.22 NO_2 symmetric stretching	M.P. /◦C: **214-215**

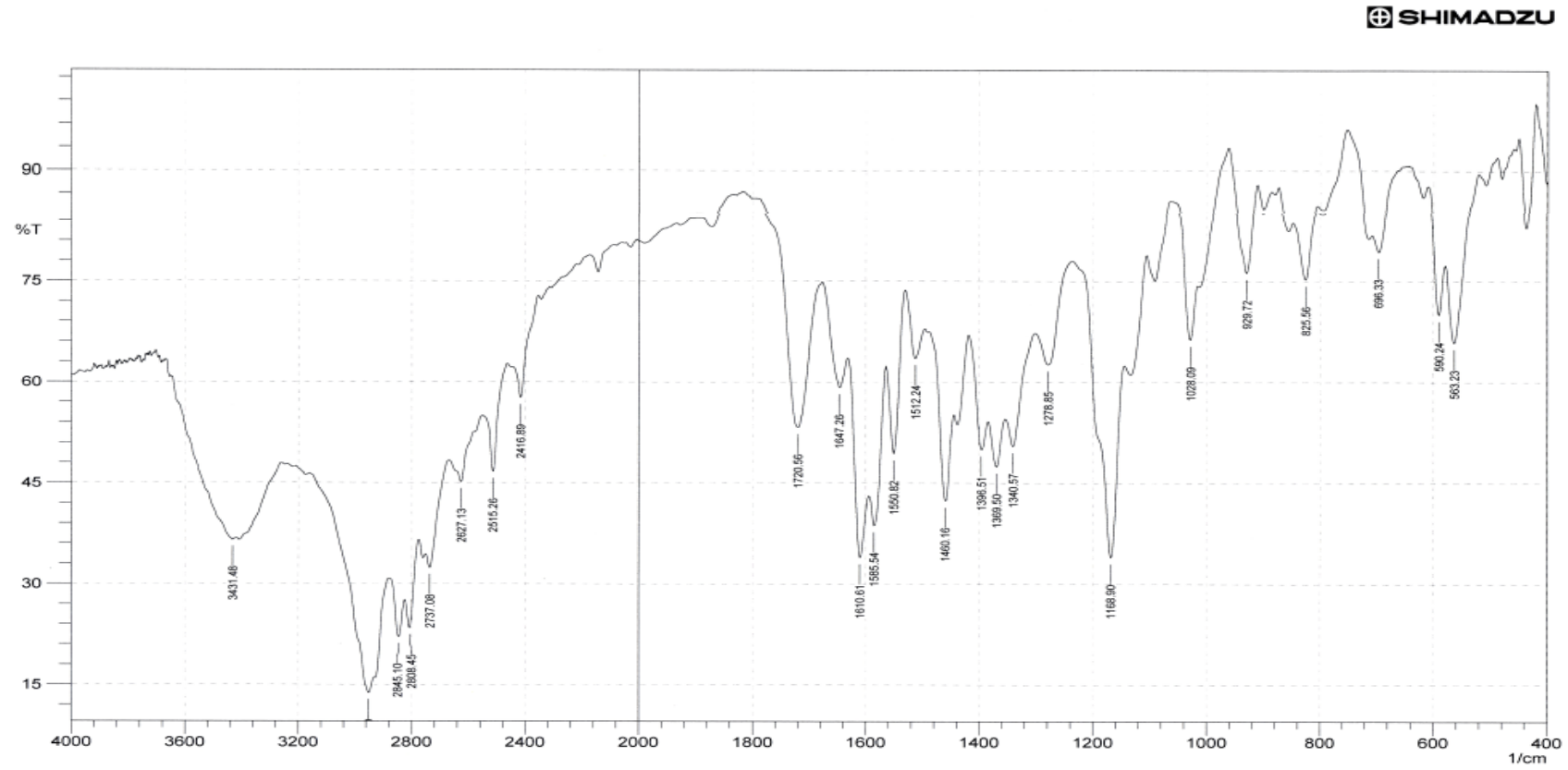
Figure (3-7): FT-IR spectra for compound(M_{3d})

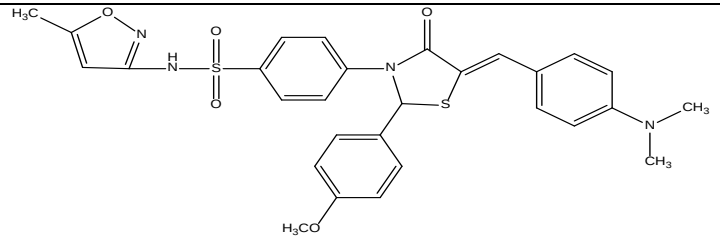




Characteristics bands (cm^{-1})	Mol. Formula: **$C_{27}H_{21}N_3O_5S_2Cl$**
1732.13 C=O Stretching vibration of thiazolidinone 1089.82 C-Cl stretching	M.P. /◦C: **262-263**

Figure (3-8): FT-IR spectra for compound(M_{3e})





Characteristics bands (cm^{-1})	Mol. Formula: **$C_{29}H_{27}N_4O_5S_2$**
1720.56 C=O Stretching vibration of thiazolidinone 1396.51 C-N$(CH_3)_2$ stretching	M.P. /◦C: **198-199**

Figure (3-9): FT-IR spectra for compound(M_{3f})

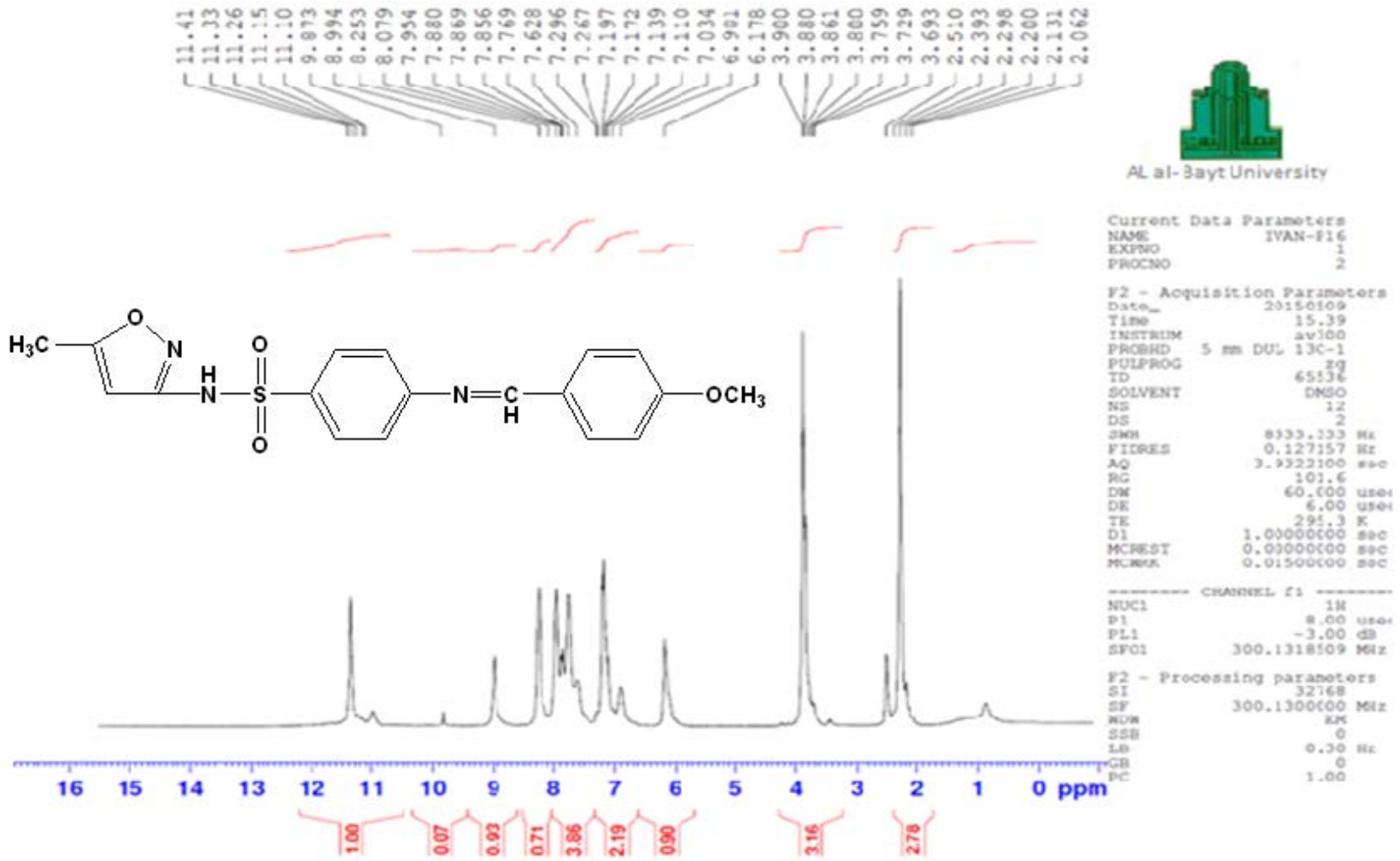


Figure (3-10): ^{1}H-NMR spectra for (M_1)

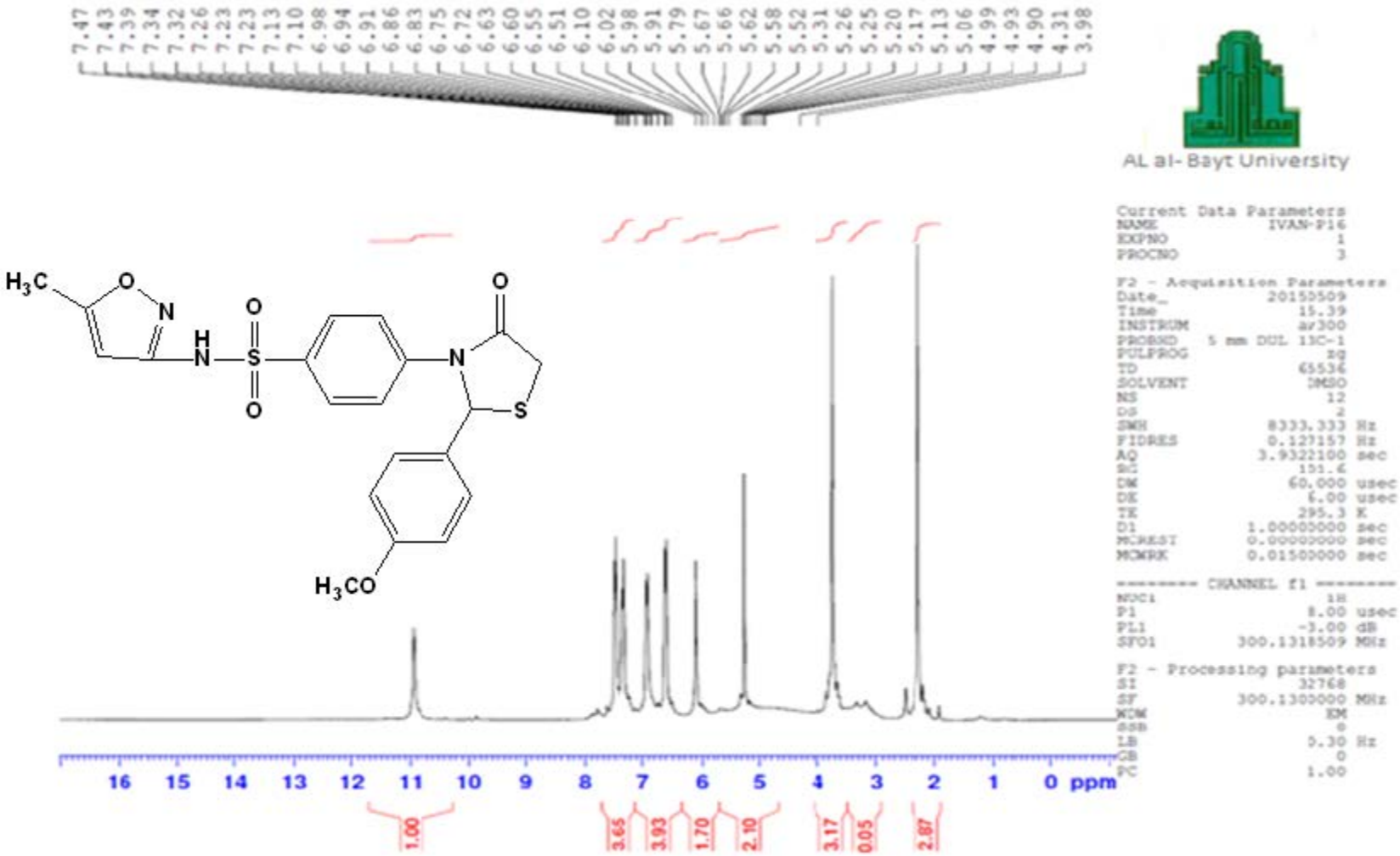


Figure (3-11): ^{1}H-NMR spectra for (M_2)

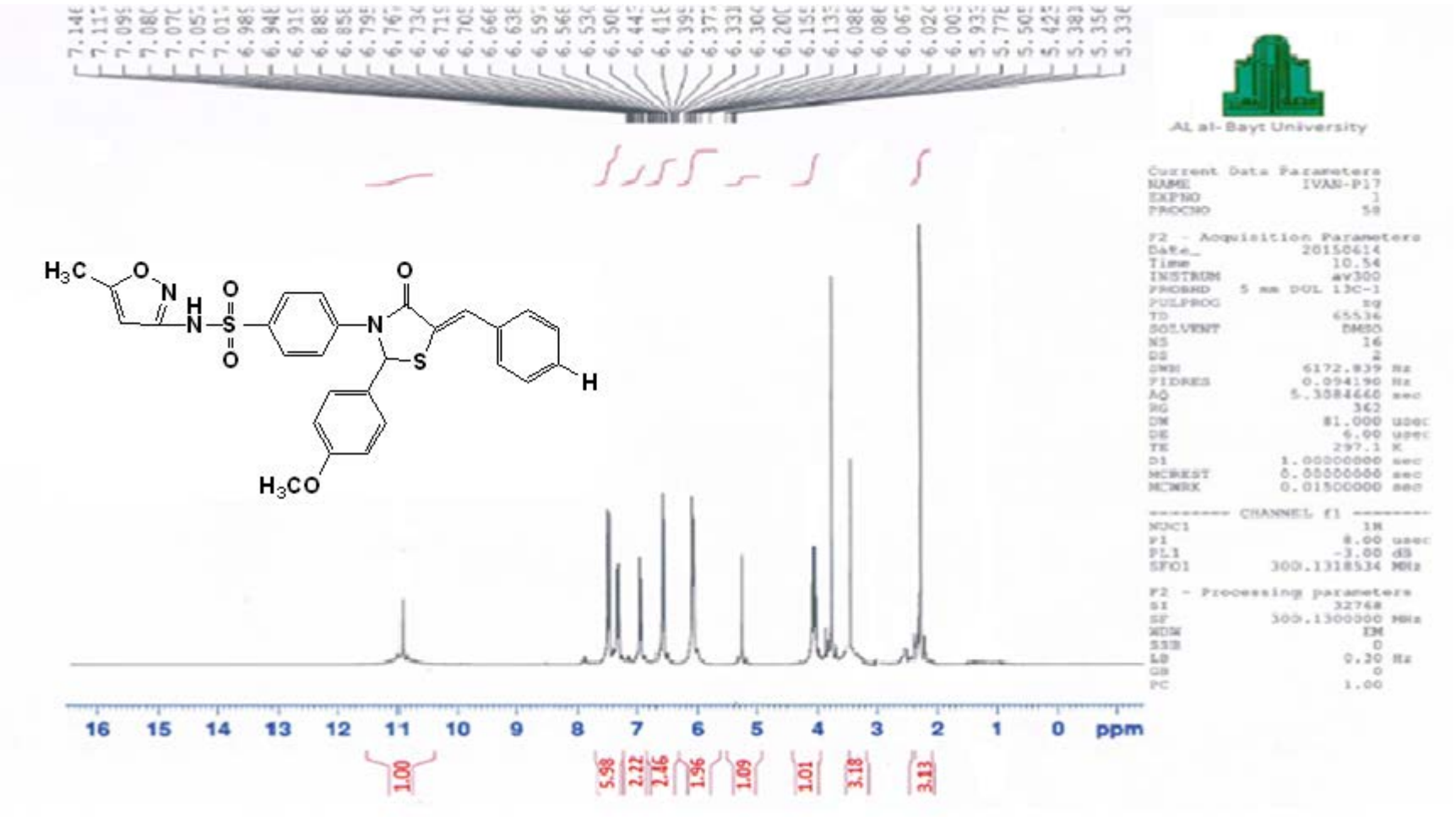


Figure (3-12): ^{1}H-NMR spectra for (M_{3a})

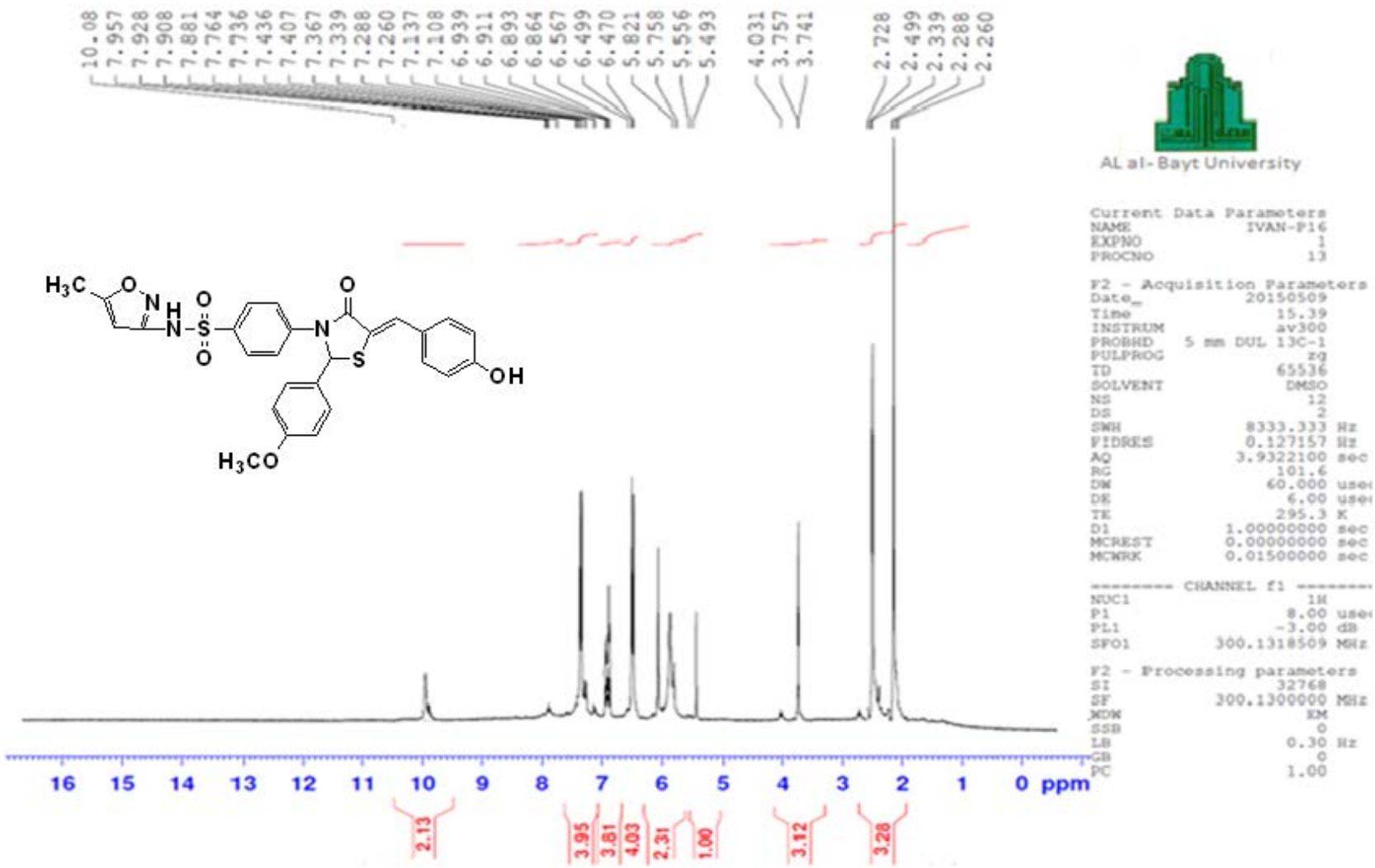


Figure (3-13): ^{1}H-NMR spectra for (M_{3b})

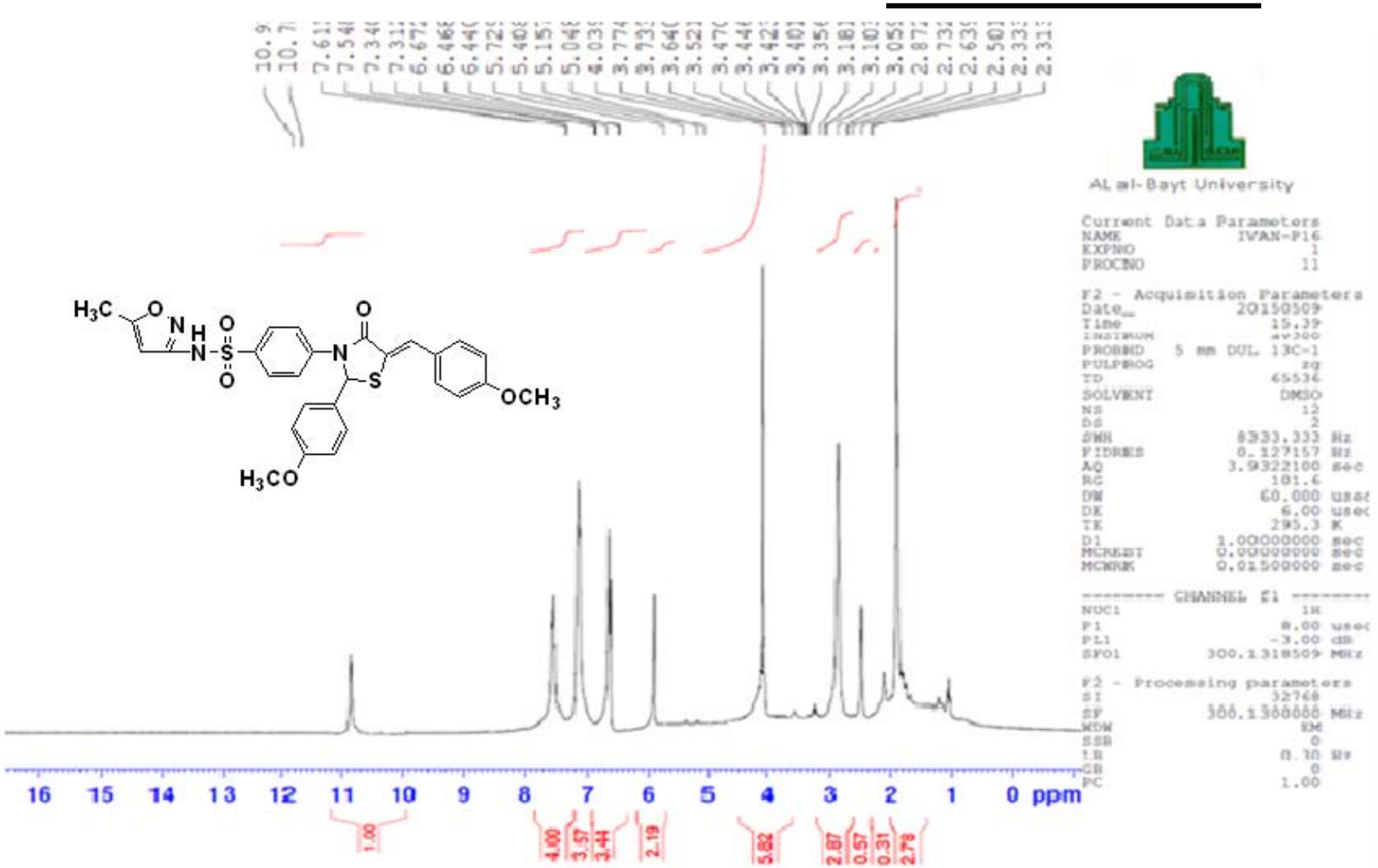


Figure (3-14): ^{1}H-NMR spectra for (M_{3c})

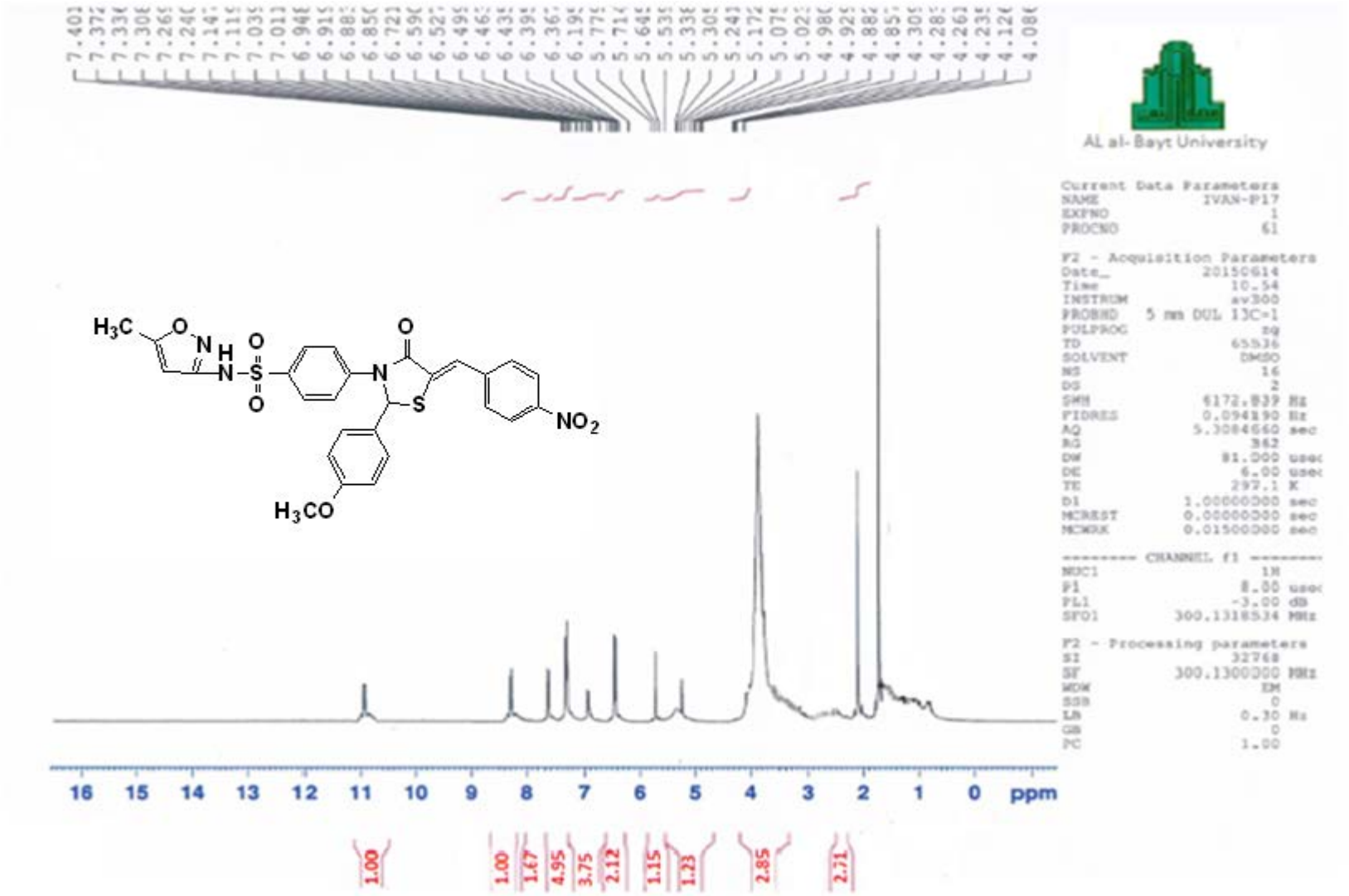


Figure (3-15): ^{1}H-NMR spectra for (M_{3d})

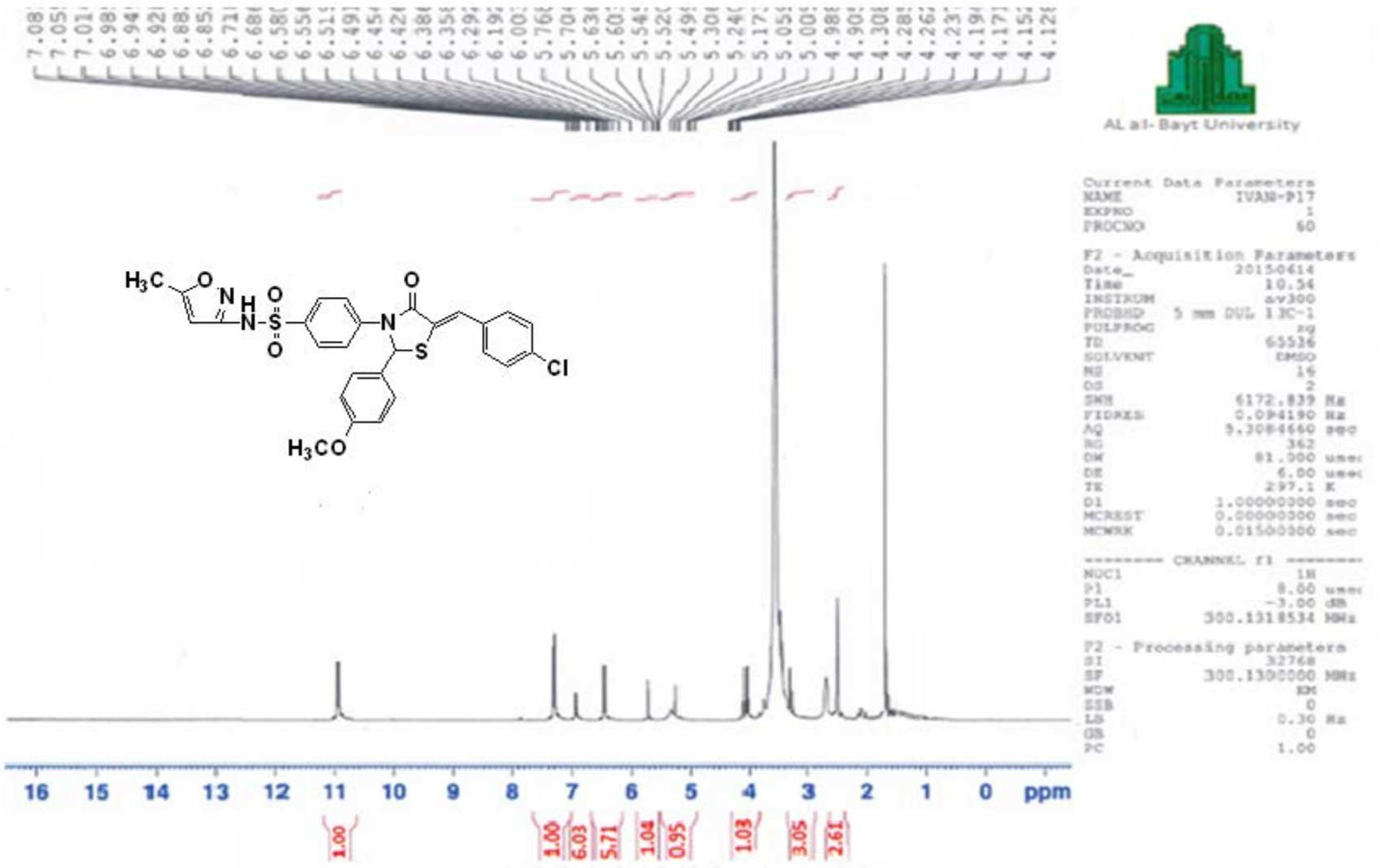


Figure (3-16): ^{1}H-NMR spectra for (M_{3e})

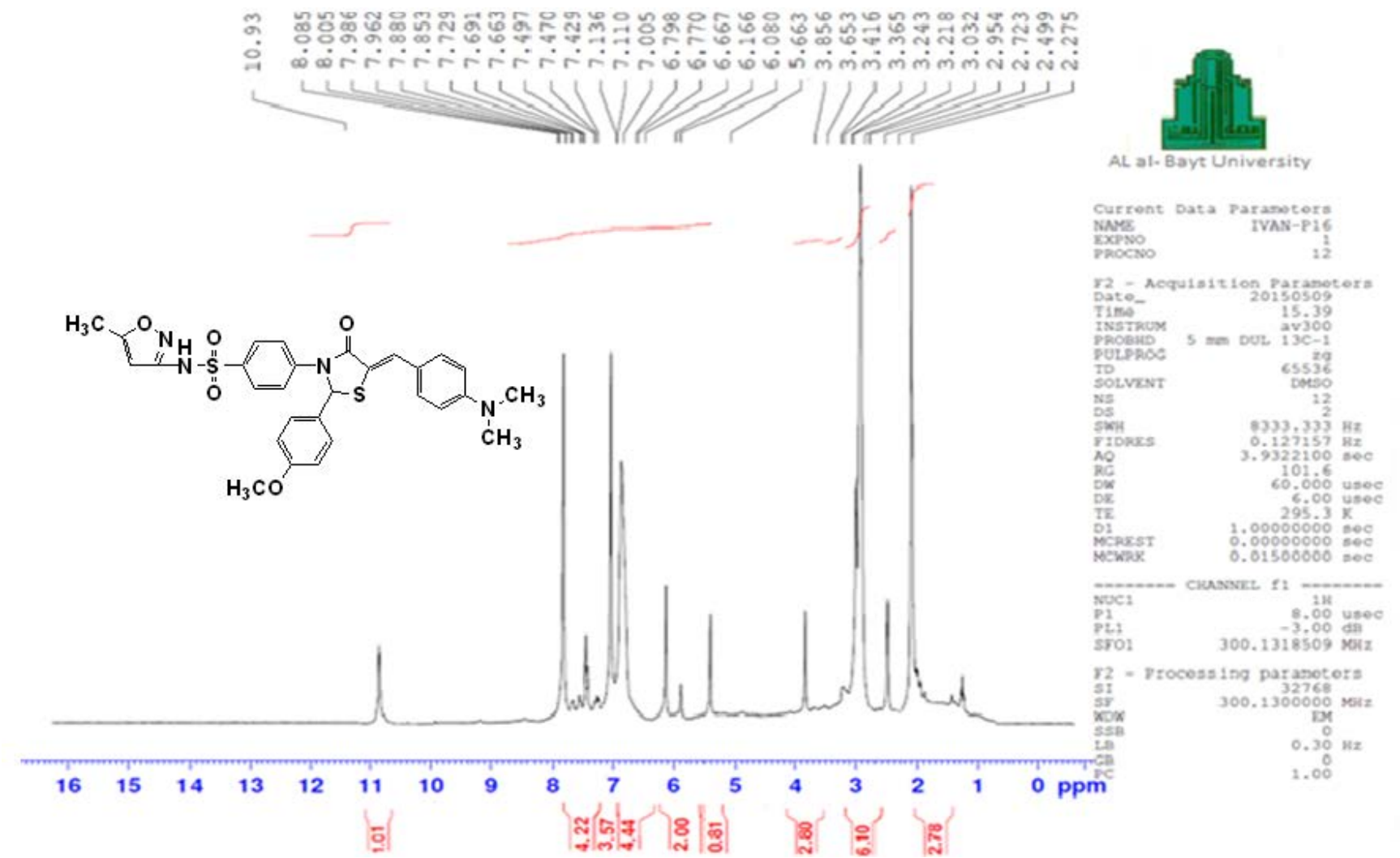


Figure (3-17): ^{1}H-NMR spectra for (M_{3f})

Conclusion

1. The synthesis of the considered compounds has been successfully achieved.
2. Characterization & identification of the target compounds were confirmed by determination of the physical properties, FT-IR spectroscopy ,1H-NMR spectra and elemental microanalysis.
3. Our study of the biological activity indicated that Compounds (**M_{3-8}**) can be further explored as antibiotic agents.

Further study

1. Study other physio-chemical properties of the final compounds like partition coefficient and electronic properties and solubility beaver.
2. Study other antimicrobial activities like antifungal.

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الخلاصة

سلفاميثوكسازول تنتمي إلى مجموعة السلفوناميد من الادوية المضاده للبكترية تم اختياره أن يكون ممثل هذه المجموعة بسبب الاستخدام الواسع النطاق وتيرة الكشف في البيئة المائية. وقد تم دمج الحلقة (4-ثايازوليدينونز) في مجموعة واسعة النطاق من المركبات المعروفة بنشاطها البايولوجي ، سواء كمجموعة المستبدلة أو كبديل للحلقة مستوحاة من الباحثين لإنتاج العديد من المركبات التي تحتوي على هذه النواة.

وعلاوة على ذلك كيمياء الجالكونات قد انتجت دراسات علمية مكثفة في جميع أنحاء العالم. خصوصا وقد تركز الاهتمام على التوليف والأنشطة الدينماكية من الجالكونات، وايضا مركبات حلقية متنوعة وغير متجانسة جديدة ذات شكل دوائي جيد يمكن تصميمه.

ان تخليق المركبات المصممة قد انجز بنجاح ، وبعد إجراء خطوات متعددة. تم فحص نقاوة المنتجات باستخدام كروماتوغرافيا الطبقه الرقيقه. و التركيب الكيميائي للمركبات الوسيطة والنهائية وقد شخص وثبت من خلال قياس (درجة الانصهار)، واطياف الاشعة تحت الحمراء ، والتحليل الدقيق للعناصر واطياف التردد المغناطيسي للمركبات النهائية.

وقد أجريت الدراسة الأولية من النشاط البكتيري على 3 سلالات مختلفة من البكتيريا وأظهرت أن مركبات النهائية (M_{3-8}) لديها نشاط معتمد بالمقارنة مع الدواء القياسي القياسية (سلفاميثوكسازول) حيث ان فعاليتها تتراوح بين المعتدلة الى الجيدة .

جمهوريه العراق

وزارة التعليم العالي والبحث العلمي

الجامعه المستنصريه

كلية الصيدله

تخليق، توصيف والفعالية المضادة للبكتيريا لسلسلة جديدة من مشتقات سلفاميثوكسازول

رسالة مقدمه الى فرع الكيمياء الصيدلانية والى لجنة الدراسات العليا في كلية الصيدله – الجامعه المستنصرية كجزء من متطلبات الحصول على درجة الماجستير في الصيدلة (الكيمياء الصيدلانية)

من قبل

زينب محمد عبدالخالق صبري

بكلوريوس صيدله 2012

باشراف

أ.م.د منذر فيصل مهدي

أ.م.د. رفاه ال سميسم

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