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Scientific Research
University of Baghdad
College of Education for Pure Science / Ibn Al-Haitham
Department of Chemistry

Synthesis and study biological activities of some new amic acid and their derivatives of Mefenamic acid

A Thesis

Submitted to council of the College of Education for Pure Science / Ibn AI- Haitham University of Baghdad in Partial Fulfillment of the Requirements for the Degree of Master in Organic Chemistry

By

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2019 A.C **1441 A.H**

بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

أَقِمِ الصَّلَاةَ لِدُلُوكِ الشَّمْسِ إِلَىٰ غَسَقِ اللَّيْلِ

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Supervisor Certification

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Date 20 / 11 / **2019**

Department of Chemistry

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In view of the available recommendations, I forward this thesis for debate by the examining committee.

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This is

Dedicated to

My Family

Ali

Acknowledgment

Praise be to God, and God's blessing and peace be on our prophet Mohammed who rescued mankind from darkness to light.

I present my deepest gratitude and greatest appreciation to the virtuous lecturer *Assit Prof. Dr. Muna Sameer Al-rawi* whom obliged me by suggesting the subject of the research and bore the responsibilities of supervision. Therefore I wish to her everlasting health, happiness, success and long life.

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Ali

Abstract

Amic acid represent a major class of organic compounds and some of its derivatives were used in drug industry , Therefore modification structure of the amic acid derived from mefenamic acid have allowed using multistep processes to the synthesize of new derivatives that may be having a broad spectrum of biological activity and fewer side effects than the original compound.

For this purpose in this work, mefenamic acid was used as a starting material for the preparation of amic acid and its derivatives via multistep synthesis as fallowing:

First: compound [I] which was prepared by the reaction between the carboxylic acid group in mefenamic acid and methanol in acidic medium, which was converted to a corresebonding acid hydrazide [II].

Second: the key intermediate amic acids $[III]_{a-e}$ were synthesized by refluxing of acid hydrazid of mefenamic acid[II] with different anhydrides (maleic, succinic, phthalic, 3-nitrophthalic, or naphthalic anhydride) in acetone.

Third: dehydration of the synthesized amic acid $[III]_{a-e}$ by acetic anhydride and anhydrous sodium acetate producing the new type of imide compound $[IV]_{a-e}$.

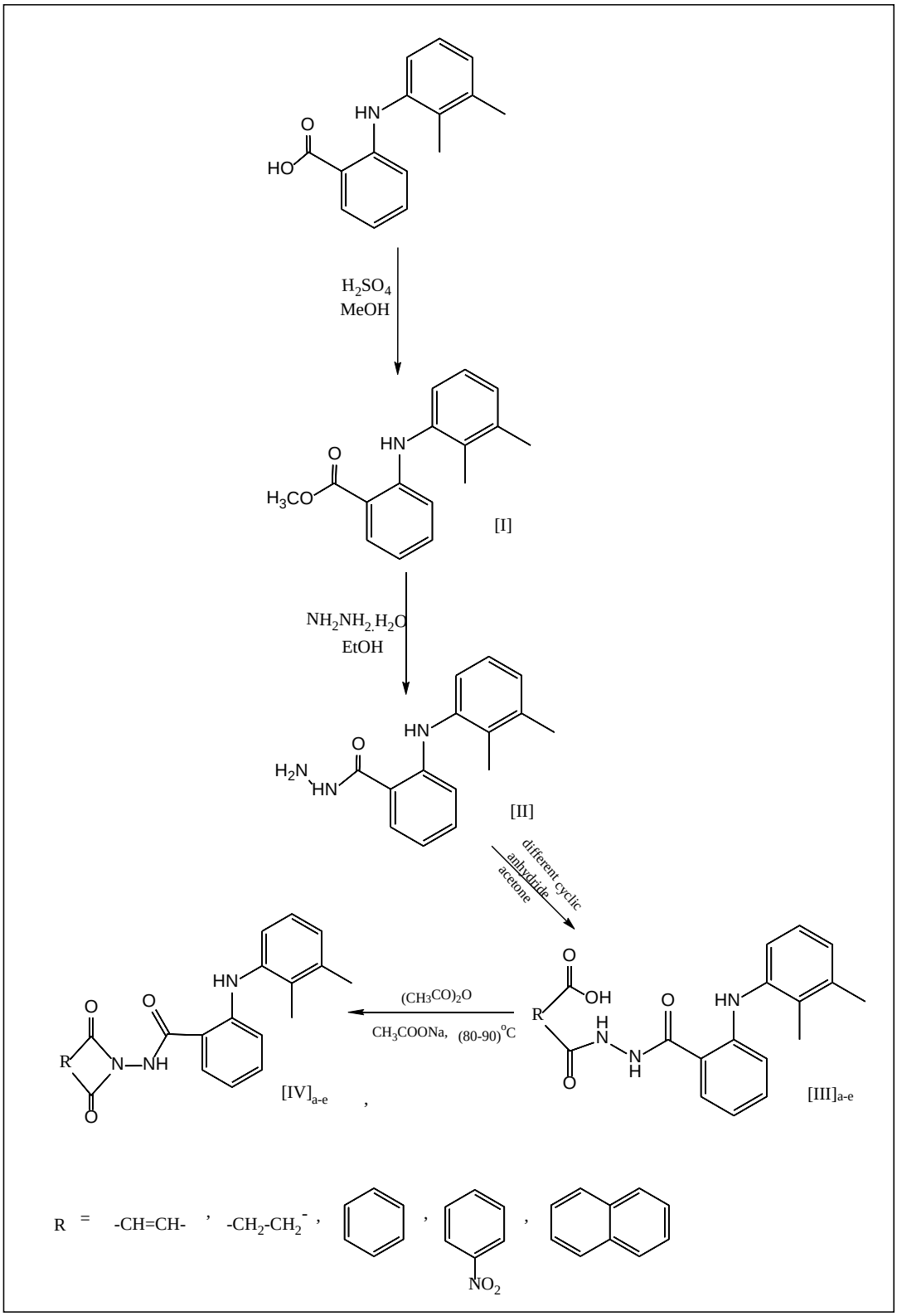
Fourth: the esterification of hydroxyl groups of amic acid $[III]_a$ to produce corresponding new ester[V], which was condensed with hydrazine hydrate to give acid hydrazide [VI], then the later compound reacted with substituted aromatic aldehydes (syringaldehyde, 4-

nitrobenzaldehyde or vaniline) in ethanol using glacial acetic acid as a catalyst under reflux producing the target schiff bases[VII]$_{a-c}$.

Fifth: the new derivatives containing heterocyclic unit four and five member ring were formed such as azetidin-2-one [VIII]$_{a-c}$, imidazolidin-4-one [IX]$_{a-c}$, and thiazolidin-4-one [X]$_{a-c}$. The reaction of Schiff base [VII]$_a$ with chloroacetylchloride in the presence of triethylamine led to the formation of the new target azetidin-2-one [VIII]$_{a-c}$. While the imidazolidin-4-one [IX]$_{a-c}$ and thiazolidin-4-one [X]$_{a-c}$ derivatives were produced by heating the mentioned schiff bases [VII]$_{a-c}$ with glycine in triethylamine , and thioglycolic acid in dry benzene, respectively.

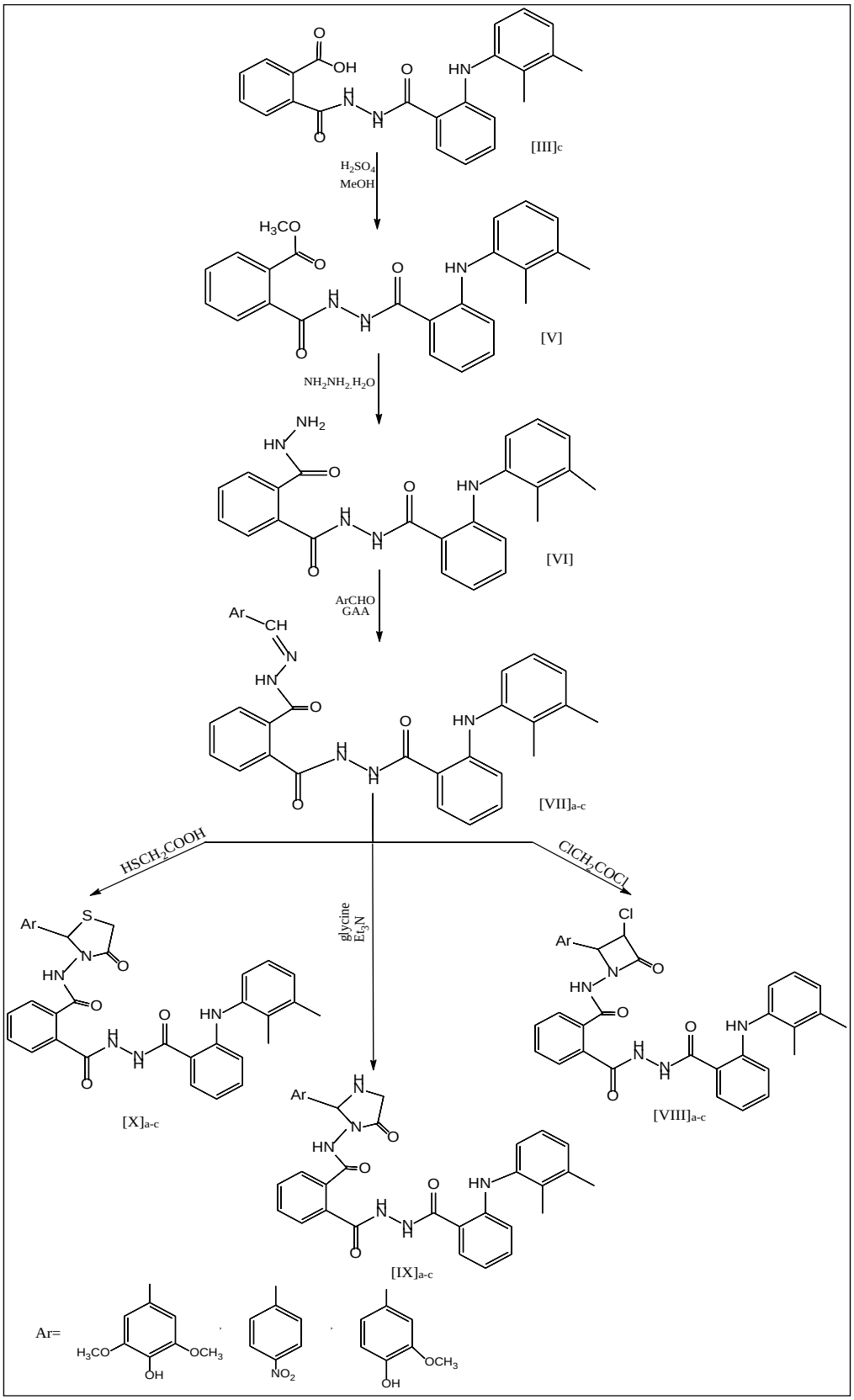
The structures of the synthesized compounds were confirmed using FTIR, ^{1}HNMR, mass and CHN-S (some of them) techniques .

Sixth: antimicrobial activity for some of the synthesized compounds were examined against different types of bacteria and the results showed that most of them have a good anti bacterial activity. Also, the cytotoxic effect of some the synthesized compounds was tested against MCF-7 cell line (human breast carcinoma cells) and positive results were obtained for some of them, which encouraged us to study the toxicity using living organisms (mice) to evaluate its acute toxicity and proved the results of non-toxicity of the derivatives.


HN
O
HO
H_2SO_4
MeOH
HN
O
H_3CO
[I]
$NH_2NH_2.H_2O$
EtOH
HN
O
H_2N
HN
[II]
different cyclic anhydride
acetone
O
OH
R
H
N
N
H
O
O
HN
$(CH_3CO)_2O$
CH_3COONa, $(80\text{-}90)^oC$
O
O
R
N
NH
O
HN
$[IV]_{a\text{-}e}$,
$[III]_{a\text{-}e}$
R = -CH=CH- , $-CH_2-CH_2^-$,
,
NO_2
,

Scheme(1)

III


[III]c
H2SO4
MeOH
[V]
NH2NH2.H2O
[VI]
ArCHO
GAA
[VII]a-c
HSCH2COOH
ClCH2COCl
glycine
Et3N
[X]a-c
[VIII]a-c
[IX]a-c
Ar=

Scheme(2)

IV

List of Abbreviation

Symbol	Full name	Symbol	Full name
^{0}C	Celsius degree	ppm	Part per million
cm^{-1}	Reciprocal centimeters	G.A.A	Glacial acetic acid
DMF	Dimethyl formamide	AcOH	Acetic acid
DMSO	Dimethyl sulfoxide	Aliph.	Aliphatic
Fig.	Figure	C.H.N-S	Elemental analysis
^{1}H-NMR	Proton Nuclear magnetic resonance	gm	gram
hrs.	Hours	δ	Chemical shift
M.P.	Melting point	Calc.	Calculated
mL	Milliliter	EtOH	Ethanol
FT-IR	Fourier Transform Infrared	R.T	Room temperature
Comp.	compound	Ar.	Aromatic
NSAID	non-steroidal anti-inflammatory drugs	THF	Tetrahydrofuran
MeOH	methanol	P.T	Proton transfer

Contents

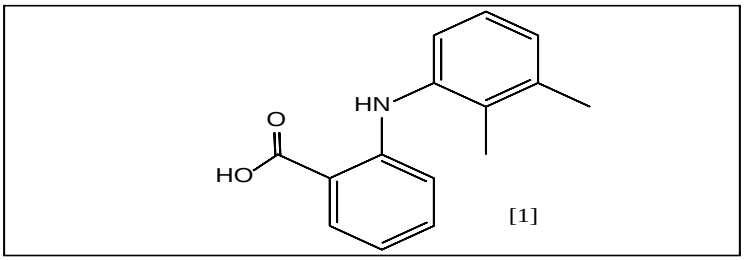
Chapter One

Introducation

1.1 Mefenamic acid

Mefenamic acid is one of the anthranilic acid derivatives with high stability due to the presence of aromatic group. Mefenamic acid represent one of non-steroidal anti-inflammatory drugs (NSAID) belonging to the N-aryl amino benzoic acid(1). Mefenamic acid [1] has a very widely utilized fenamatesa class for pain treatment. It is considered to be working via blocking cyclo-oxygenasecyclo (COX1 and COX2) action which is involved in producing prostaglandins (which have been generated as a response to injuries or some disease and result in pain, inflammation, and swelling) or prostaglandins right after already forming them there by they relieve inflammation and pain(2).

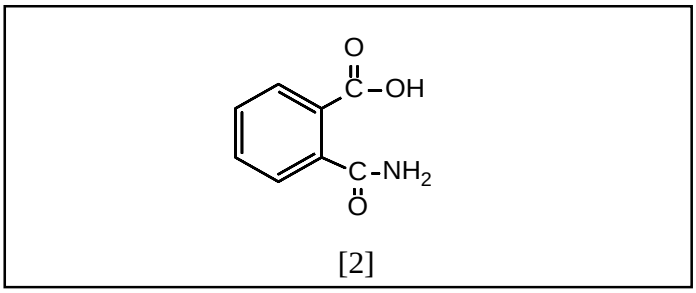
The prodrugs including mefenamic acid are bio-reversible drug molecule derivatives which experience inter-molecular or intra-molecular reactions via the chemical or enzymatic bio-transformation in body for giving the mapping active parent medications and a nontoxic pro-moiety. Pro-drugs were successfully and extensively utilized as chemical tools for modifying the physico-chemical, pharmacokinetic in addition to the pharmaco-dynamic properties of widely utilized medications and new medications. Exploiting the pro-drug method will potentially accomplish reducing of the mefenamic acid (gastro-intestinal) intolerance to improve its bio-availability(3).



[1]

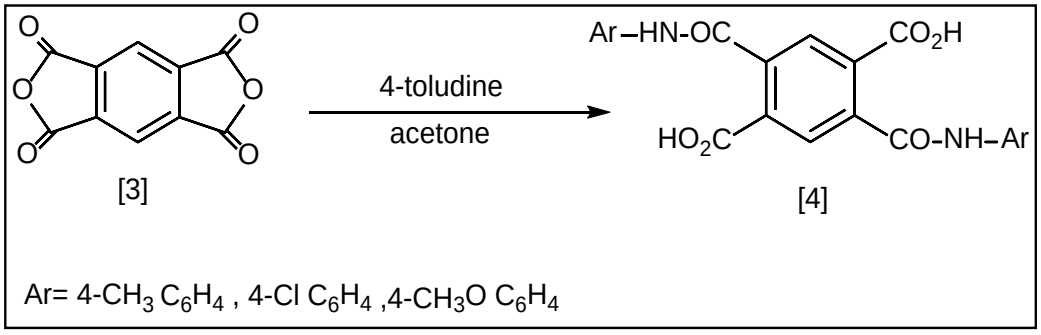
1.2 Amic acids

Amic acids [4] are organic compounds containing carboxyl group and amide group in their molecules. They can be prepared by the reaction of primary or secondary aliphatic or aromatic amines with different anhydrides such as maleic, phthalic, and succinic anhydride .



[2]

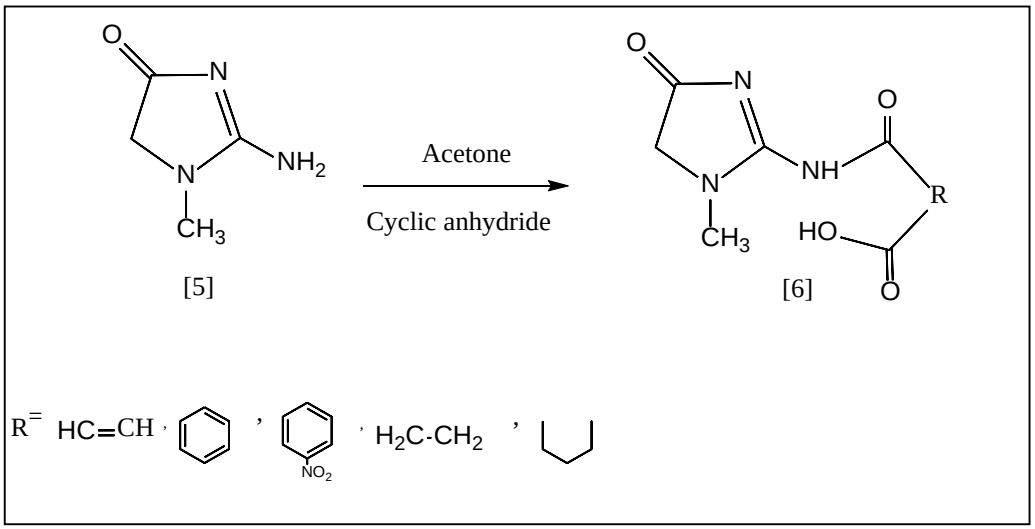
The symmetrical diamic acid N,N¯-bis-(4-methyl phenyl) pyromellitamic diacid [4] was synthesized from the reaction of 4-toludine with pyromellitic dianhydride [3] in dry acetone at room temperatur for 24 hrs[5] .



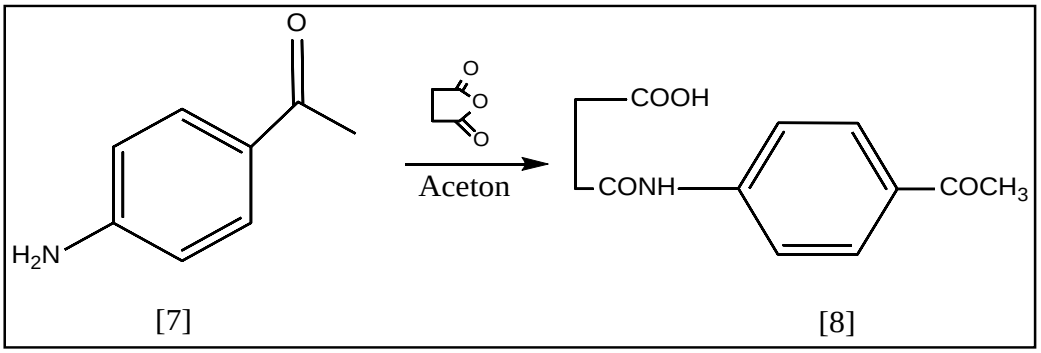
[3] [4]

Ar= 4-CH_3 C_6H_4 , 4-Cl C_6H_4 ,4-CH_3O C_6H_4

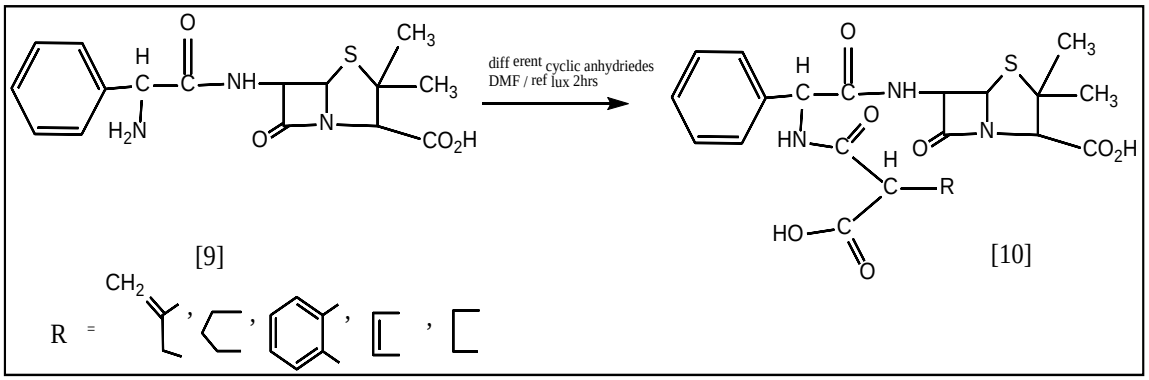
The new amic acid [6] from the reaction between creatinine[5] and different cyclic anhydrides (maleic, phthalic ,3-nitro phthalic, succinic, and glutaric) in THF under cooling condations $(0\text{-}5)^0C$ and continuous stirring under room temperature for 2 hrs [6].



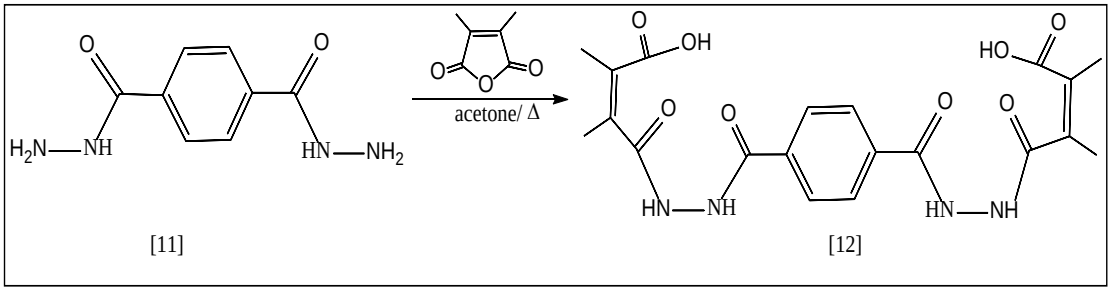
On the other hand, N-(4-acetophenyl)succinamic acid[8] was produced via reaction of equimolar amounts of succinic anhydride with 4-amino acetophenone [7] in excess of acetone[7,8].



Also some new amic acid are prepared by the reaction of ampicillin drug with different cyclic anhydrides in tetrahydrofuran (THF) and refluxed for 2 hrs[9].



Finally[10] 2,3-dimethyl malic anhydride reacted with terephthalo - hydrazide [11] in acetone and stirring overnight at room temperature to prouduce new amic acid [12].

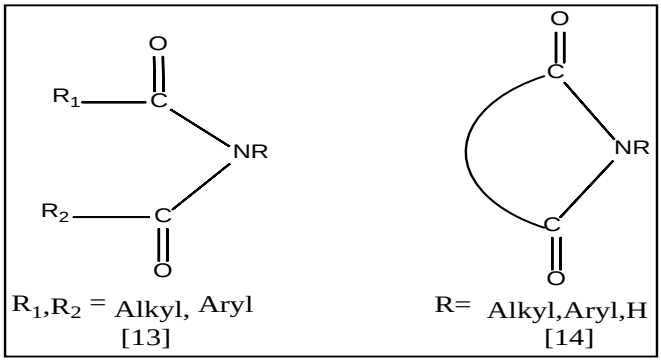


1.3 Imides

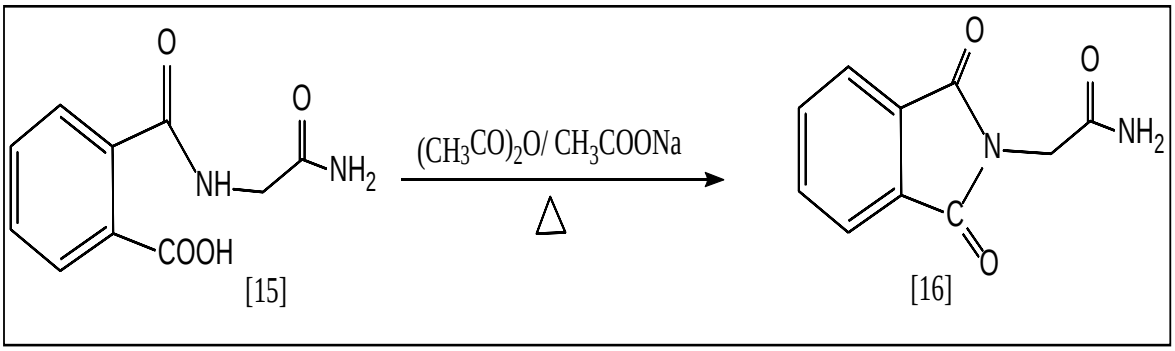
Cyclic imides and their N-derivatives [11] are an important class of organic compounds that contain bis-amide[8] linkages with a general structure of [-CO-N(R)-CO-]. They could be taken under consideration as monoacyl derivation of the amides or as diacyl derivatives of ammonia or a primary amine[12].

Imides are organic compounds classified into main groups: open chain imides [13] and cyclic imides [14], They have many implementa - tions in medicinal, biological, polymer, and synthetic chemistry. particularly, cyclic imides, which are considered as significant bases for

the natural products and medications, like palasimides, migrastatin, thalidomide, salfredins, and phensuximide[12].



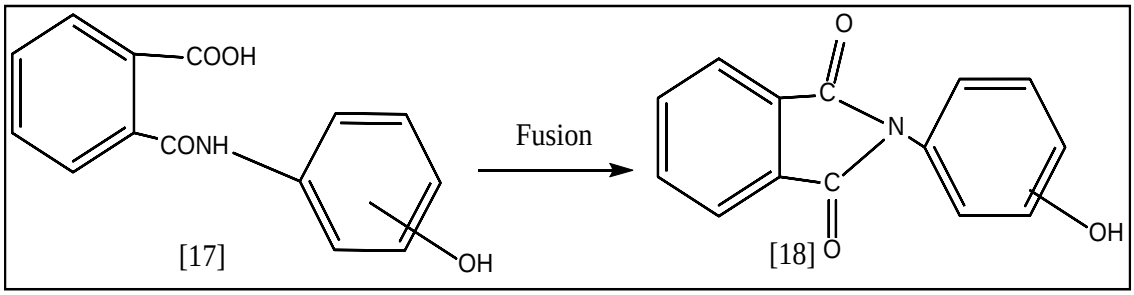
Many researchers found one or more approachs to the cyclic of imides using different reagents as follows: the cyclic imide 2- (1, 3-di-oxoisoindolin-2-yl) acetamide [16] are produced by a reaction from amic acid of phthalic anhydride [15] with dehydrating agents acetic anhydride and anhydrous sodium acetate and heating with stirring for 4 hrs to give cyclic imide compound [8].



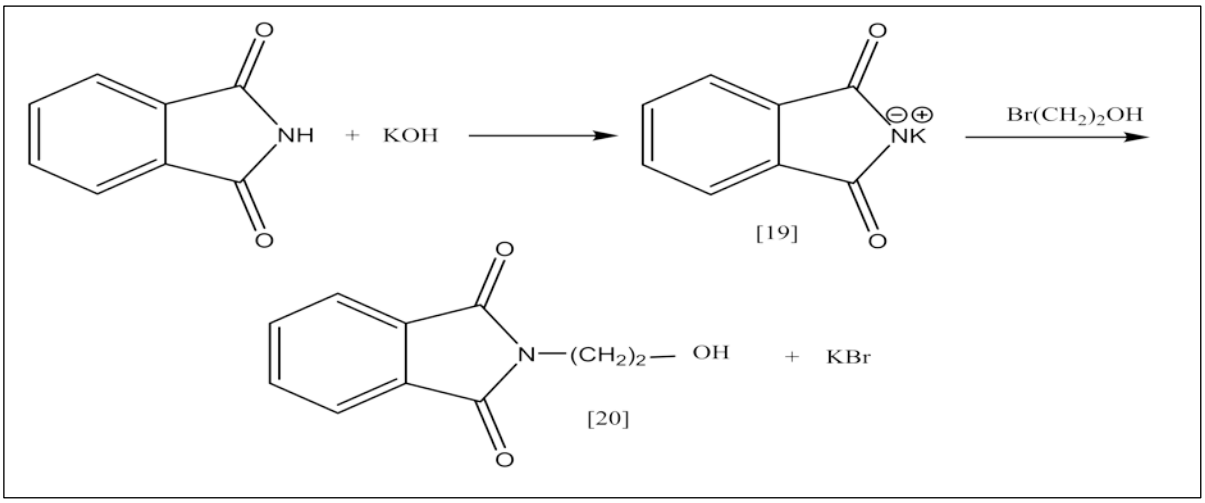
The most important dehydrating agents used in dehydrating of amic acids to the corresponding imides include: acetic anhydride with anhydrous sodium acetate[13,14], thionyl chloride[15,16], acetyl chloride with

triethylamine[17,18], phosphorus trichloride[19,20], and phosphorus pentaoxide[21].

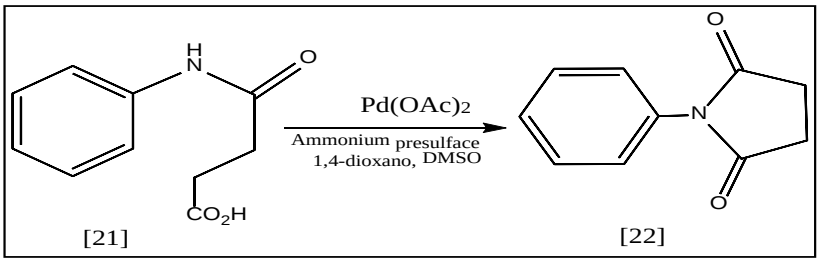
Another method for the preparation of imides is thermal dehydration. Al-Azzawi[22] applied this method successfully in the preparation of N-substituted citraconimides[18] in high yields from compound [17] .



Early scientists[23] found that using potassium salt of unsubstituted phthalimide [19] with different alkyl halides producing the corresponding N-substituted imides[20].

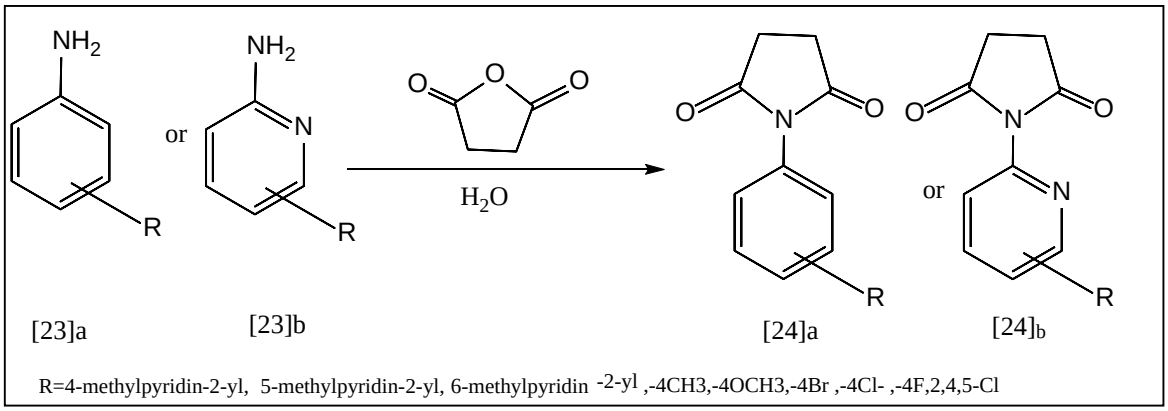


From the succinanilic [21] acid dehydrative cyclization for prepared the N-phenyl succinimide[24] [22] has been observed.



[21] [22]

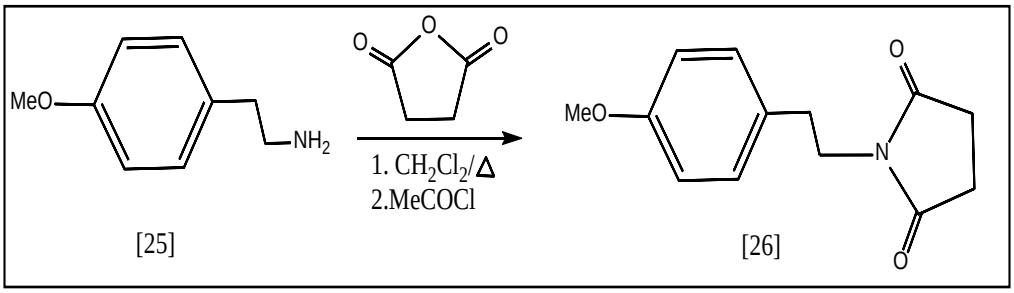
A simple and clean green approach was performed for preparing different N-phenyl or N-methylpyridin-2-yl succinimides [24_a,24_b] by means of the N-substituted anilines[$23]_a$ or N-substituted 2-aminopyridines [$23]_b$ with succinic anhydride with the heating in aqueous medium with simultaneous distillation of water[25] .



[23]a [23]b [24]a [24]$_b$

R=4-methylpyridin-2-yl, 5-methylpyridin-2-yl, 6-methylpyridin -2-yl ,-4CH3,-4OCH3,-4Br ,-4Cl- ,-4F,2,4,5-Cl

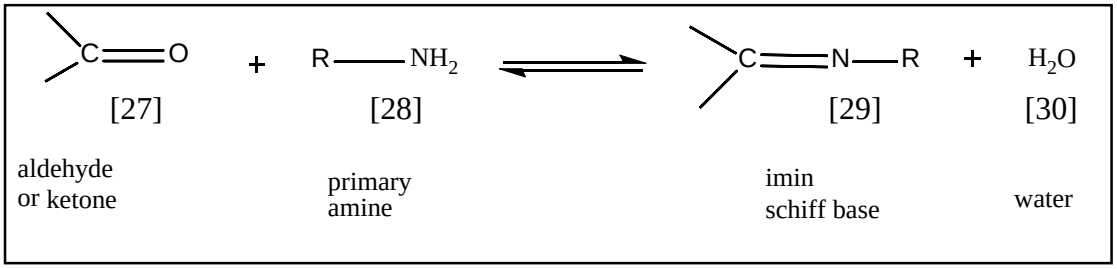
In addition, imide 1-(4-methoxyphenylethyl) pyrrolidine -2,5-dione [26] was prepared by the treatment of 4- methoxyphenylethylamine [25]with succinic anhydride followed by acetyl chloride under reflux[26].



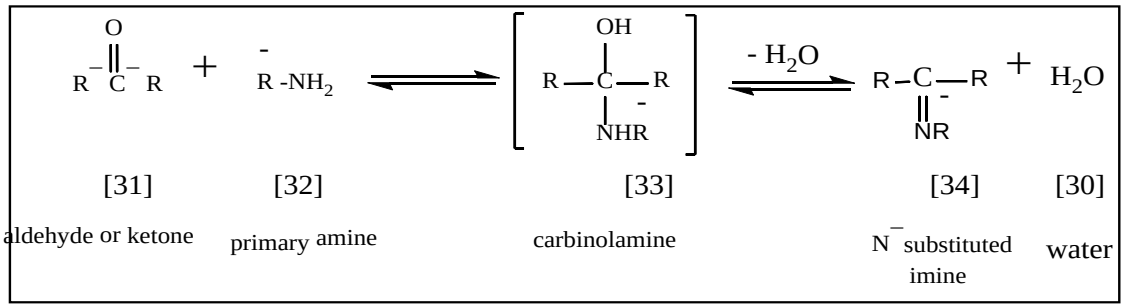
[25] [26]

1.4. Schiff bases

Schiff bases are compounds that contain the group of azomethine with a formula $R_1R_2C = N\text{-}R_3$ was initially stated by Hugo Schiff bases has been produced via primary amines' reactions with aldehyde or ketone, which is placed under base catalysis, heat, or acid [27].



Schiff bases containing substitutes of aryls are more readily synthesized and have considerably higher stability, whereas schiff bases containing substituents of alkyl are rather unstable[28]. Schiff base formation from ketone or aldehyde is shown in the following reversible equation.



In the case where amine is protonated and turns non-nucleophilic, equilibrium is pulled to left and the formation of the carbinol-amine cannot happen. Which is why, the synthesis of numerous Schiff bases are optimally performed at slightly acidic medium[29]. Schiff bases are

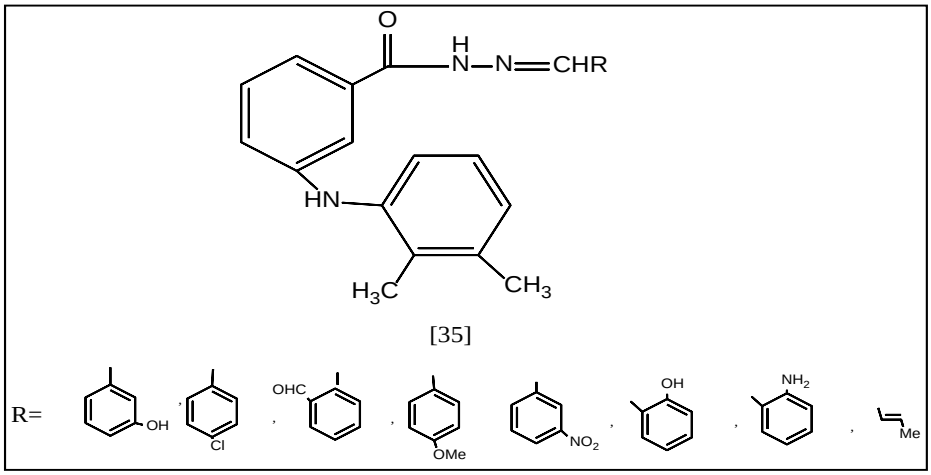
indicated and characterized with azomethene, which is very important group in organic chemistry. The azomethene or imine group in the shciff bases is analogue to the carbonyl groups in the carbonyl compounds but the oxygen atom is replaced by nitrogen atom[30].

Schiff bases have been reported for showing a range of biological actions, as well as cytotoxic[31], anticancer[32], antibacterial[33], antifungal[34], antimalarial[35], anti-inflammatory agents[36]and antitumor activities [37].

1.4.1. Schiff Bases Synthesis

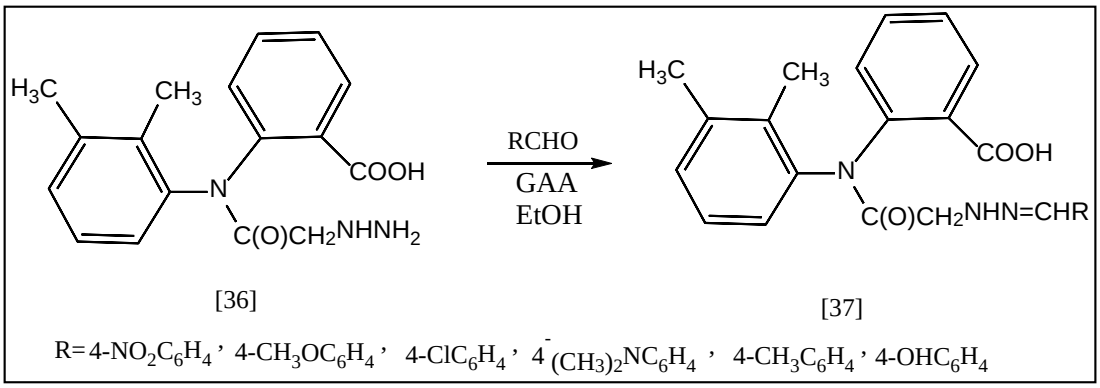
In general, Schiff base was synthesis is by the condensation between equimolar carbonyl compound and primary amine in pure alcohol in the existence of the hydrochloric acid or the glacial acetic acid drops.The group that form in condensation called azomethine group[38,39].

In 2010, Lingam et.al[40] synthesized 1-aroyl-2-(alkenyl /aryl)idene hydrazines [35] derived from the mefenamic acid in good yields.The reaction of 2-(2,3-dimethylphenylamino) benzohydrazide with different aldehydes under traditional and microwave conditions of irradiation and some of them showed moderate cytotoxic activities (in vitro) against the cell line of human lung (A-549) .



[35]

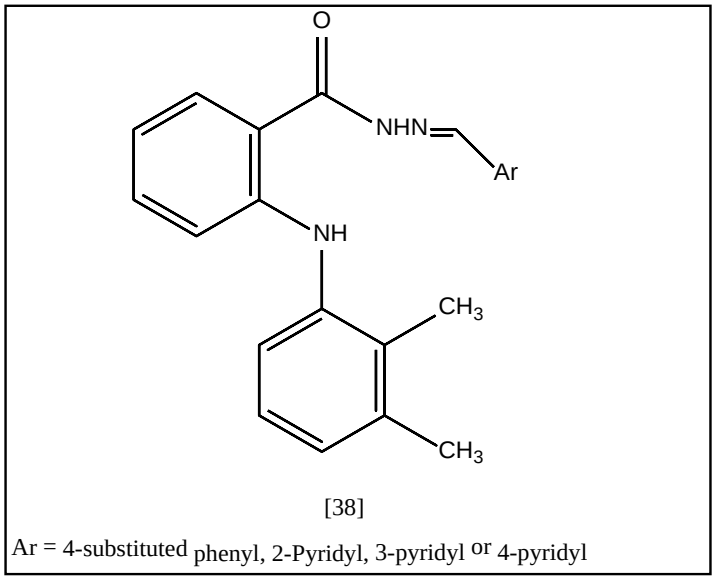
While, Ayad M.R.[(41)]were synthesized a new series of the Schiff bases, 2-[N-(2,3-di-methylphenyl)-2-(2-aryl-hydrazinyl)acetamido] benzoic acid [37] from the reaction between 2-[N-(2,3-di-methylphenyl)-2-hydrazinyl-acetamido] benzoic acid [36] and various aldehydes in absolute ethanol at room temperature for 4hrs. two drops of GAA were added as a catalyst.



[36] [37]

R= 4-$NO_2C_6H_4$, 4-$CH_3OC_6H_4$, 4-ClC_6H_4, 4-$(CH_3)_2NC_6H_4$, 4-$CH_3C_6H_4$, 4-OHC_6H_4

Recently, Asif [(42)] synthesized derivatives of the N-arylhdyrazone of the mefenamic acid [1] from refluxing of a mix of the hydrazide derivative [38] with various aldehyde in pure ethanol, and stirred at a room temperature for 1/2 to 1 hr. Two drops of the hydrochloric acid present as a catalyst, and yield was studied for analgesic and anti-inflammatory activity.



[38]

Ar = 4-substituted phenyl, 2-Pyridyl, 3-pyridyl or 4-pyridyl

1.5. Heterocyclic Compounds

The cyclic systems which contain carbons and a minimum of one or more hetro atom are referred to as hetero-cyclic. Several heteroatoms are common as heterocyclic rings part and the most widely known hetero-atoms are sulphur, nitrogen, or oxygen[(43)]. A heterocyclic ring could be containing one or several hetero-atoms that could be the same or not. In addition to that, the rings could be saturated or otherwise, the structures of heterocyclic derivatives could be consisting of aromatic or non-aromatic rings[(44,45)].

Heterocyclic chemistry is a very complicated and interesting organic chemistry branch and constitutes the most varied and the largest organic compounds family[(46,47)].

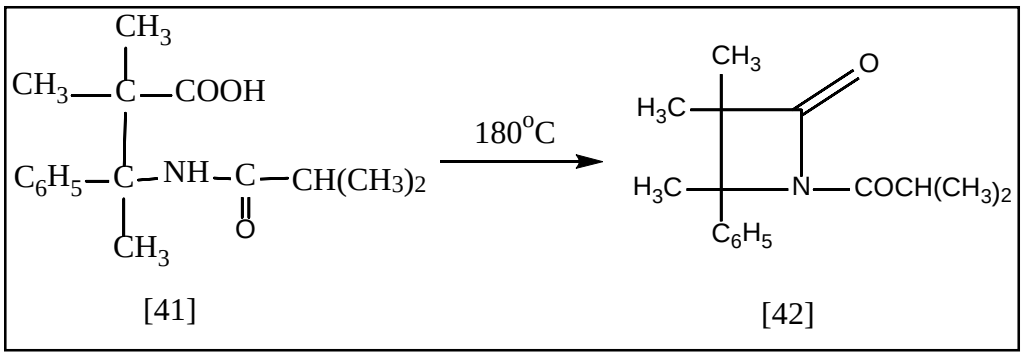
1.5.1 2-Azetidinone

Azetidine[39] is a four membered cyclic compound that containing one nitrogen atom , but 2- azetidinone differs[40] from azetdine by the presence of carbonyl group at carbon number two (β- lactam), skeleton was identified as an important component for synthesizing many of antibiotics which are utilized in the area of medicine like cephalosporin, penicillin, thienamycine, and aztreonam [(48)].

[39] [40]

1.5.1.1 Synthesis of 2-Azetidinone

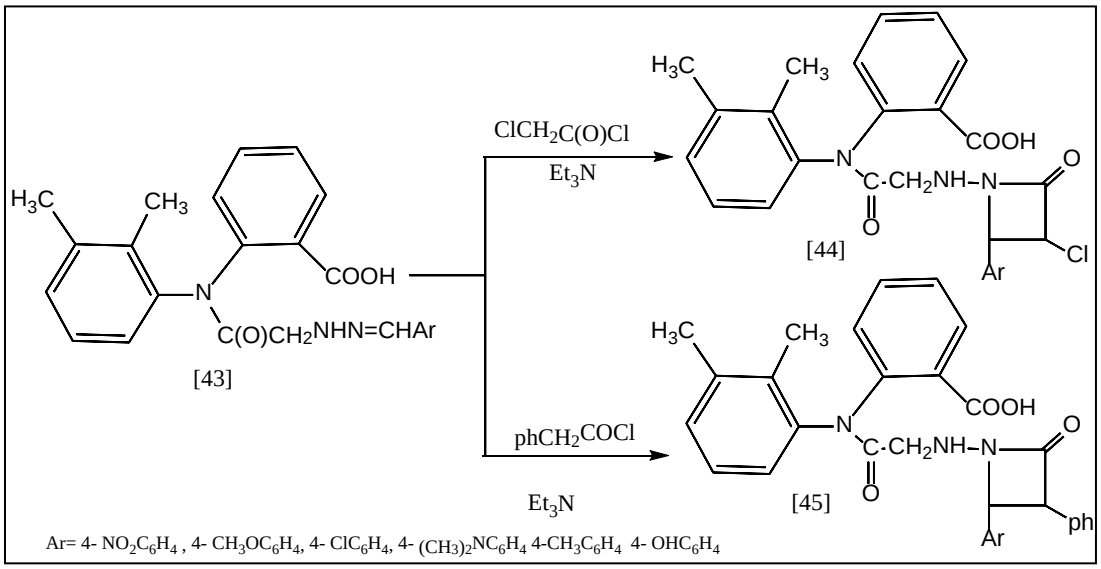
β - Amino propionic[(49)] acid does not yield 2-azetidinone(β – lactam), while acyclic derivatives of such acid can easily be transformed into heterocycles by heating. The chemical reactions to synthesis compound[42] from β - Amino propionic derivative[41] is shown in the following:



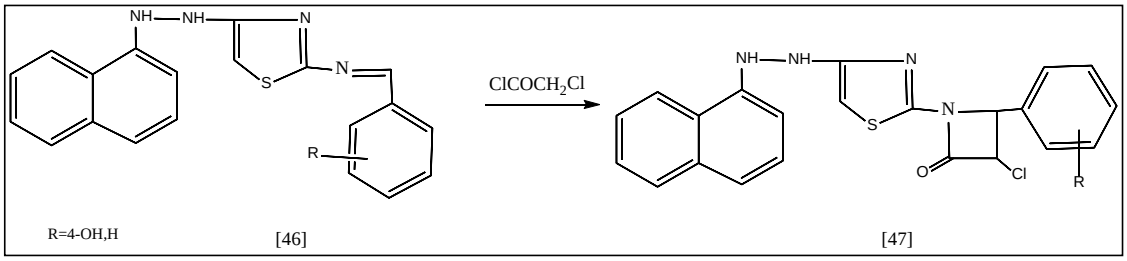
[41] [42]

Reagents such as acetyl chloride, phosphorus trichloride and thionyl chloride have been successfully used for ring closure of 3 –amino acids[50].

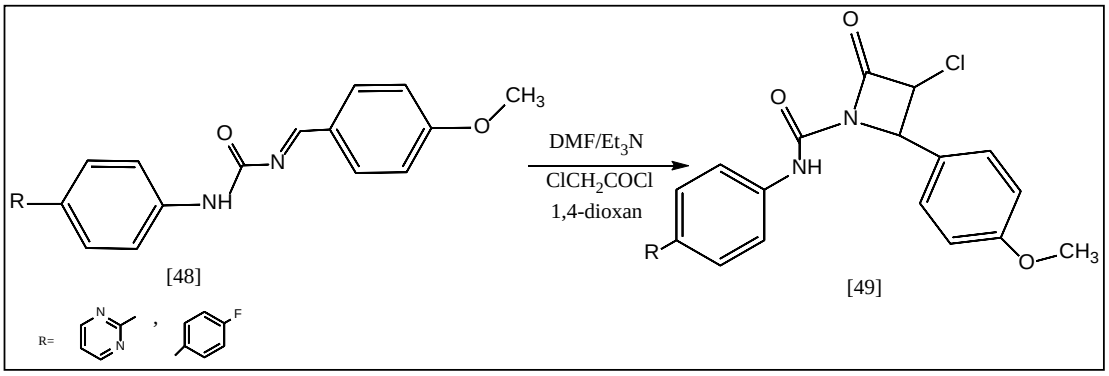
Ayad [41], has recently synthesized a series of 2-[2-{(2-chloro-3-(4-aryl- 4-oxoazetidin-1-yl)amino} -N-(2,3-dimethylphenyl) acetamido] benzoic acid [44] and 2-[2-{(4-aryl-4-oxo-3-phenyl-azetidine-1-yl) amino}-N-(2,3-dimethylphenyl)acetamido] benzoic acid [45] from the cyclocondensation of a variety of Schiff bases [43] with chloroacetyl chloride or phenylacetyl chloride and the existence of dry benzene and triethyl amine, respectively.



Ravitas et. al.[51] have concluded that the reaction of variously substituted Schiff base[46] in 1,4-dioxane with chloroacetyl chloride with triethylamine present gives 3-chloro-4-(4-substituted)-1-(4-(2-(naphthalene-1-yl) hydrazinyl) thiazole-2-yl) azetidine-2-one [47], which showed inflammation inhibitory and analgesic activities .



In 2017, Veera et.al.[52] have synthesized 3-chloro-2-(4-methoxy phenyl) - 4-oxo- N- (4-aryl) azetidine-1-carboxamide [49] in N, N-dimethylformamide, chloroacetyl chloride and triethyl amine by nucleophilic addition and cycloaddition reactions. It had displayed moderate to significant antioxidant effects.



1.5.2 Imidazoles

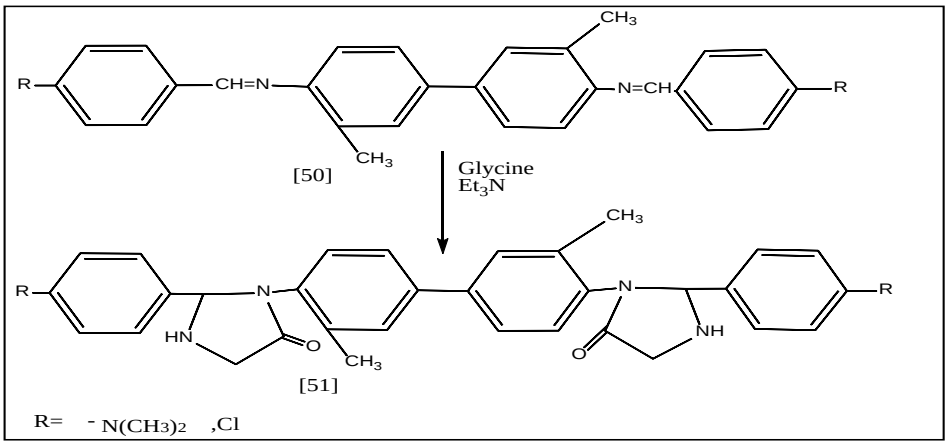
Heterocycles which contain nitrogen are ubiquitous in several bio-molecules. Particularly, motifs of imidazole is a vital class of compound as a result of the fact that they are prevalent in numerous bio-molecules like purines, biotin, histamine, histidine, and in the natural products. Imidazole is a five membered planar ring. It is an organic compound that has the formula $C_3H_4N_2$, It is soluble in water and other polar solvents [53,54]. Imidazole is a heterocyclic aromatic compound. Imidazole states to

the parental compound, 1-3-diazole. Numerous medications include a ring of imidazole, like nitro-imidazole that used as antifungal drug.

1.5.2.1 Imidazol-4-one

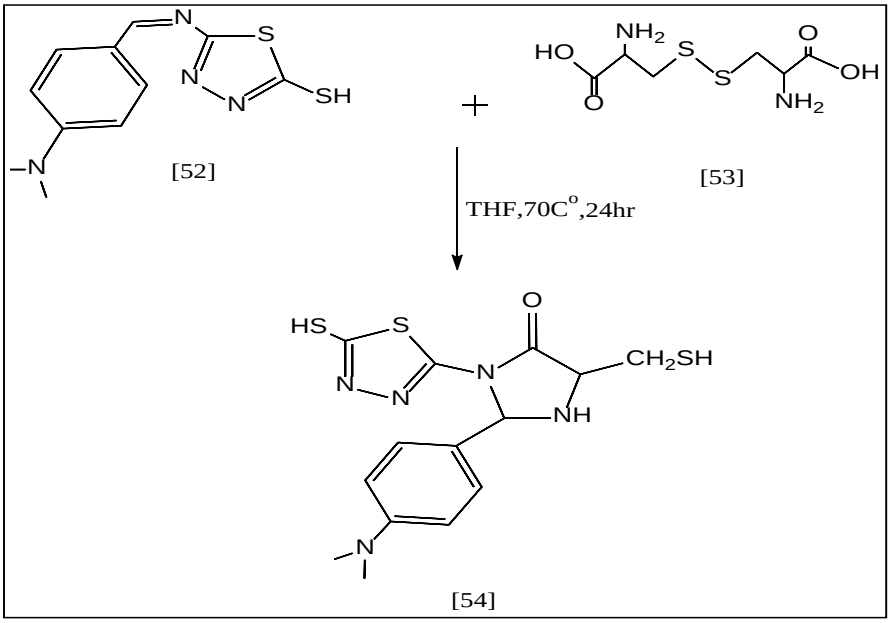
Imidazol-4-one is one of imidazoles contained carbonyl group at atom carbon in position-4. Imidazol-4-ones can also be regarded as cyclic amine and used as antimicrobial, antioxidant, anti-inflammatory, antifungi and anticancer. Also, imidazole-4-one derivatives are commonly utilized as intermediates in synthesizing organic target compound including pharmaceuticals, dyes and photographic chemicals[55,56].

Al-Rawi M. et. al.[57] synthesized bis imidazolidin-4-one derivatives [51] from the reaction of N,N'-(3,3'-dimethyl-[1,1'-biphenyl]-4,4'-diyl)bis(1-p-tolylmethanimine) [50] with glycine and trimethylamine , using ethanol as a solvent under refluxing conditions. This compound has exhibited moderate inhibition against two types of anti-bacterials.

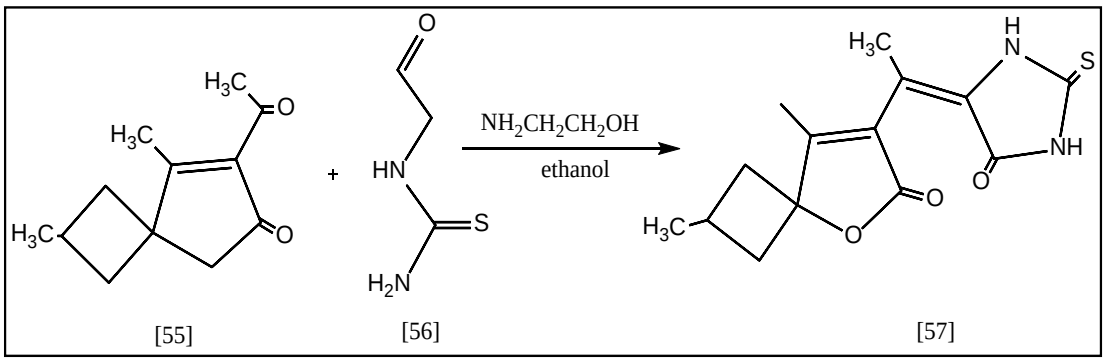


Furthermore, in 2015 the 2-(4-(dimethylamino)phenyl)-3-(5-mercapto-1,3,4-thiadiazol-2-yl)-5-(mercaptomethyl)imidazolidin-4-one

[54] was synthesized from the reaction of (Z)-5-[(4-(dimethylamino) benzylidene) amino]-1,3,4-thiadiazole-2-thiol [52] with cysteine [53] in THF under reflux condition [(58)] .

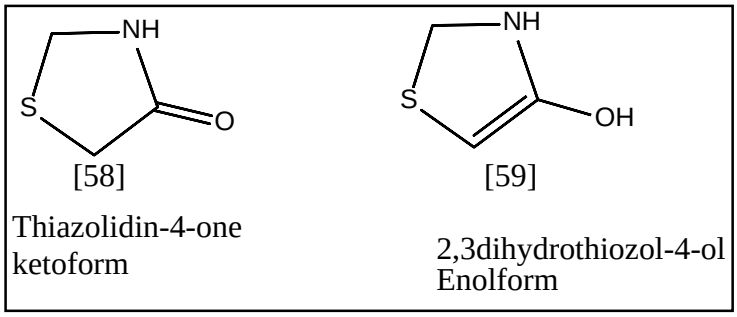


There is another method[(59)] for the preparation of (E)-5-(1-(2,8-dimethyl-6-oxo-5-oxaspiro[3.4]oct-7-en-7-yl)ethylidene)-2-thioxoimid-azolidin-4-one [57]. This based on the reaction of 7-acetyl-2,8-dimethyl-5- oxaspiro [3.4]oct-7-en-6-one [55] with 1-(2-oxoethyl)thiourea [56] and hydroxyl ethylamine in ethanol.



1.5.3 Thiazolidin-4-one

Thiazolidin-4-ones are a class of heterocyclic organic complexes which have a sulfur atom at position1, a nitrogen atom at the position3, and a group of carbonyl at the position 4. Thiazolidin-4-one is one of the most intensively researched classes of a 5-member ring. The derivatives of thiazolidin-4-one is known as well as marvel nucleus due to the fact that it provides various derivations with a range of biological actions [60,61]. Thiazolidin-4- one can be found in one form and two tautmerisum [62,63].



[58] Thiazolidin-4-one ketoform

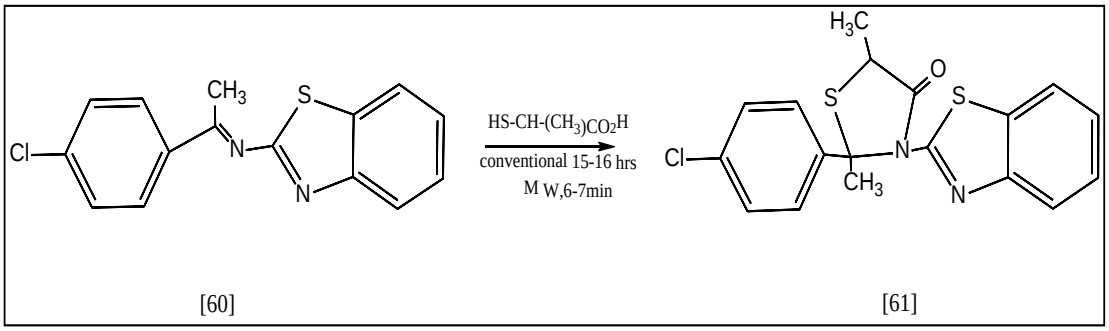
[59] 2,3dihydrothiozol-4-ol Enolform

Thiazolidin-4-one ring system is a fundamental structure in a variety of synthetic pharmaceutical factors, that display a wide variety of biological actions like anti-cancer[64], local anesthetic[65], antitumor[66], anticonvulsant[67], anti-inflammatory[68], antioxidant[69], anthelmintic[70], antimicrobial[71], anti-HIV[72], antiphlogistics[73] and antimalarial [74].

1.5.3.1 Synthesis of thioazolidin-4-ones

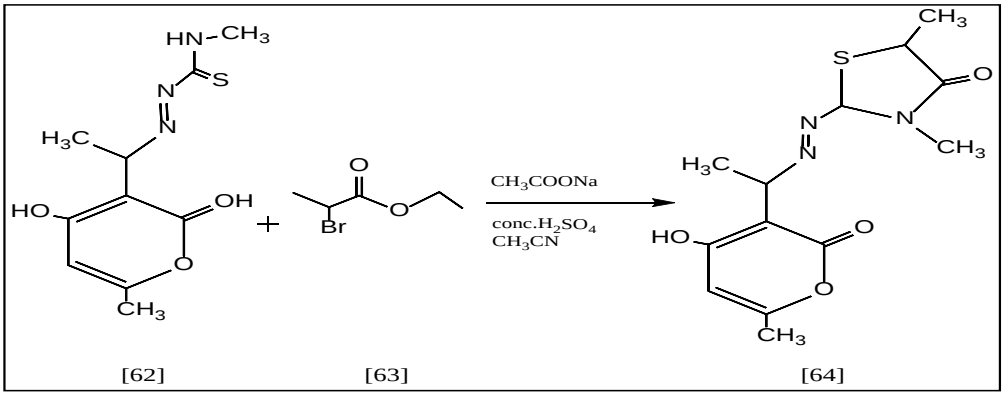
The typical approach for preparing 1,3-thiazolidin-4-one includs schiff bases reaction with thioglycolic acid in dry benzene.

In 2009 Abhinit et. al.[75] have been reported the synthesis of thiazolidin-4-one derivative [61] form the reaction of Schiff base [60] with thioglycolic acid using a conventional mothed and the microwave, irradiation They concluded that the yield from microware irradiated synthesis was higher than the conventional.



[60] [61]

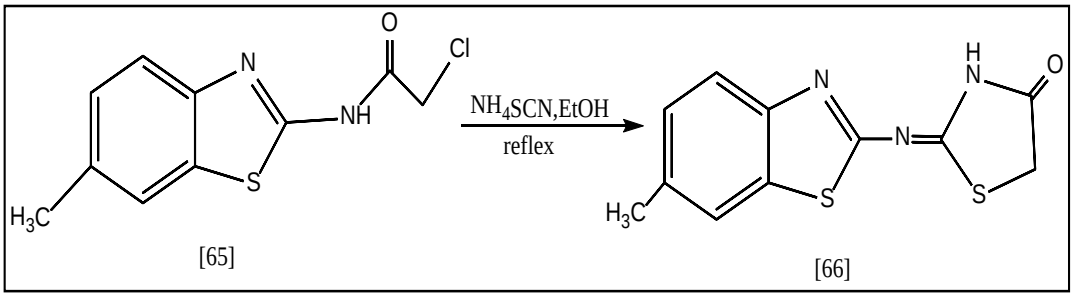
Nechak et. al. [76] synthesized 2-((1-(4-hydroxy-6-methyl-2oxo-2H-pyran-3yl)ethyl)diazenyl)-3,5-dimethylthiazolidin-4one [64] by the reaction of 2-(1-(4hydroxy-6-methyl-2oxo-2H-pyran-3yl)ethyl)-N-methyl-diazene-1-carbothioamide [62] with ethyl 2-bromopropionate[63] with anhydrous sodium acetate, concentrated H_2SO_4 and CH_3CN.



[62] [63] [64]

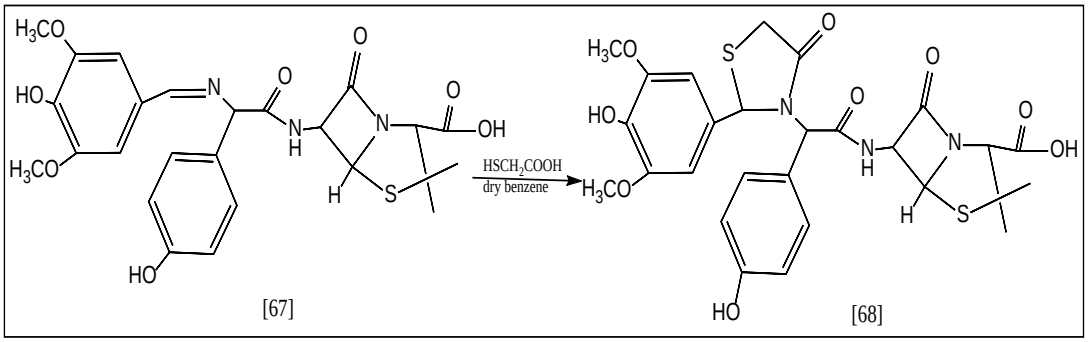
On the other hand, new compound 2-((6- methylbenzo[d]thiazol-2-yl) imino)thiazolidin-4one [66] was synthesized from the reaction of 2-

chloro-N-(6-methylbenzo[d]thiazol-2yl)acetamide [65] with ammonium thiocyanate in refluxing ethanol. This new compound exhibited antimicrobial activity and anti-fungal activity[77].



[65] [66]

Recently, Al-Rawi M. et.al[78] synthesized a new thioazolidin-4-one derivative 6-{2- [(4-Hydroxy-3,5-dimethoxyphenyl) -1,3-thiazolidin-4-one]-2- (4-hydroxyphenyl) acetyl] amino}-3,3-di-methyl-7-oxo-4-thia-1-aza-bicyclo [3.2.0] heptane-2-carboxylic acid [68] containing amoxicillin unit from the reaction of Schiff base [67] with thioglycolic acid in dry benzene.



[67] [68]

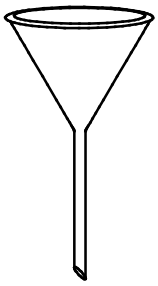
Aim of the work

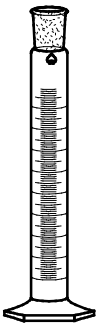
Synthesis and characterization of new amic acid and their derivatives containing heterocyclic units starting material with Mefensmic acid as follows:

1. Synthesis and characterization of new derivative of amic acids.
2. Synthesis and characterization of new derivative of imide compounds.
3. Synthesis and characterization of new Schiff bases.
4. Synthesis and characterization of new four member rings: azetidin-2-one.
5. Synthesis and characterization of new five member rings : imidazolidin-4-one derivative, and thiazolidin-4-one derivatives .
6. Study the biological activities of some synthesized compound as follows:
   a. Antibacterial activities against four types of bacteria
   b. The cytotoxic effect was tested against MCF-7cell line (human breast carcinoma cell).
   c. The toxicity using living organisms(mice).

Chapter Two

Experimental Part





Chemicals and techniques

2.1. Chemicals

Table (2-1) lists every utilized chemical and their supplies.

Name of material	Name of company	Purity %
Acetic anhydride	BHD	98%
Acetone	BHD	99%
Benzene	Riedel-De Haën	99%
Chloroacetyl chloride	Merck	99%
Chloroform	BHD	99%
Diethyl ether	GPR	99%
Ethanol absolute	GCC	99%
Ethyl acetate	Aldrich	99%
Glycine	Aldrich	99%
Hydrochloric acid	CDH	98%
Maleic anhydride	Aldrich	99%
Mefenamic acid	Micro Company	97%
4-Nitrobenzaldehyde	Aldrich	98%
Sodium acetate	Aldrich	99%
Syringaldehyde	Aldrich	98%
Thiosemicarbizd	Merck	99%
Triethylamine	BDH	99%
Vaniline	Aldrich	99%

2.2. Instruments

1- Melting Points measurement

Uncorrected points of melting have been specified with the use of Hot-stage, Gallen Kamp apparatus of the melting point.

2- Fourier Transformation Infrared Spectrophotometer- FTIR

The spectra of FTIR were recorded using discs of potassium bromide on Shimadzu 400 S (Ir prestige-21) FT-IR spectroscopy, and Shimadzu (8300) infrared spectrophometer of FT-IR in the College of Education for Pure Sciences, Ibn Al-Haitham.

3- Nuclear magnetic resonance spectrometer (^{1}HNMR)

^{1}H NMR spectra were recorded on a Bruker Ultra Shield 300 MHz, Gaziantep University Turkey, and Ultra Shield 400 MHz, Bruker, Switzerland, at Central lab, Tahran University - Iran . Chemical shifts have been reported in ppm(δ), with the use of DMSO or $CDCl_3$ as solvent with TMS as the internal standard.

4- Elemental microanalysis (C.H.N-S)

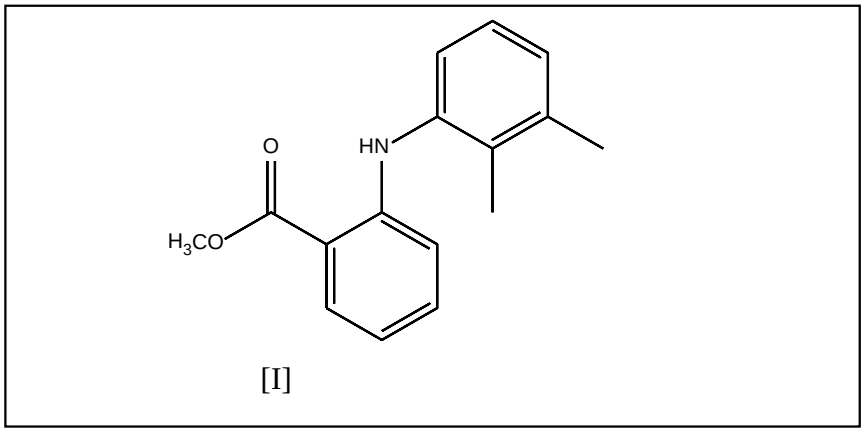
The elemental analyses were carried out using EuroEA Elemental Analyzer model E.A 3000 (Italy) at the Central Service Lab - College of Education For Pure Science (Ibn Al- Haitham).

5-Mass spectroscopy

Mass spectra were measured using of Electron Impact (EI),Italy,70eVmass ,with the use of a Model of MS: 5973 spectrometer at Central lab, Tahran University - Iran .

2.3. Synthesis methods

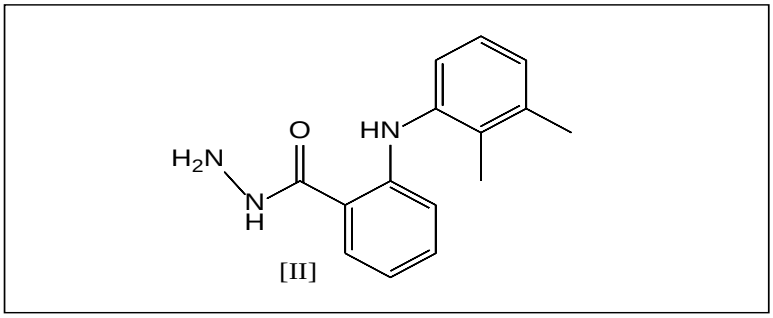
2.3.1 Preparation of methyl 2-(2,3-di-methylanilino) benzoate[I]



[I]

To a solution of mefenamic acid (2.41g, 0.01 mol) in methanol (15mL), conc. H_2SO_4 (1.5mL) was added guardedly. The solution was refluxed for 16hrs. and the reaction has been monitored using thin layer chromatography. After completion of the reaction, solvent was evaporated. The crude was added onto water, neutralized (pH =7) by 40% NaOH and finally extracted with chloroform (3×25mL). The combined layer of $CHCl_3$ was washed, dried over anhydrous Na_2SO_4 and concentrated. The white solid that was formed, filtered, and dried to give compound [I]. Rf = 0.80 (3:2 ethyl acetate/n-hexane), yield 80% and m.p (97-99^{0}C), (Lit., m.p 96-98^{0}C) [40].

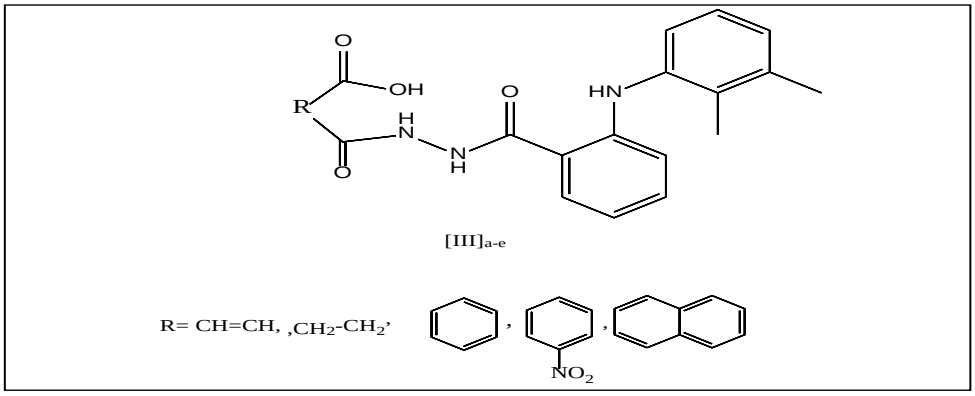
2.3.2 Preparation of 2-(2,3–dimethylphenylamino) benzohydrazide [II].



[II]

To a solution of ester [I] (2.56g, 0.01mol) in EtOH (15mL) was added 80%hydrazine hydrate (0.01mol) dropwise and the solution was stirred. . The temperature of the mixture was raised gradually to (95-100) ºC and was maintained for (12 hrs). This mixture was concentrated and the residue was diluted by water (10mL). The aqueous layer was extracted with chloroform (3x25mL). The organic layers were collected, combined, washed and dried over anhydrous Na_2SO_4. The yellow solid was purified by crystallization from EtOH, filtered and dried in order to produce the compound [II]. Rf = 0.3 (3:2ethyl acetate/n-hexane), yield 80%, and m.p (116-118) ºC, (Lit. m.p118-120ºC) [40].

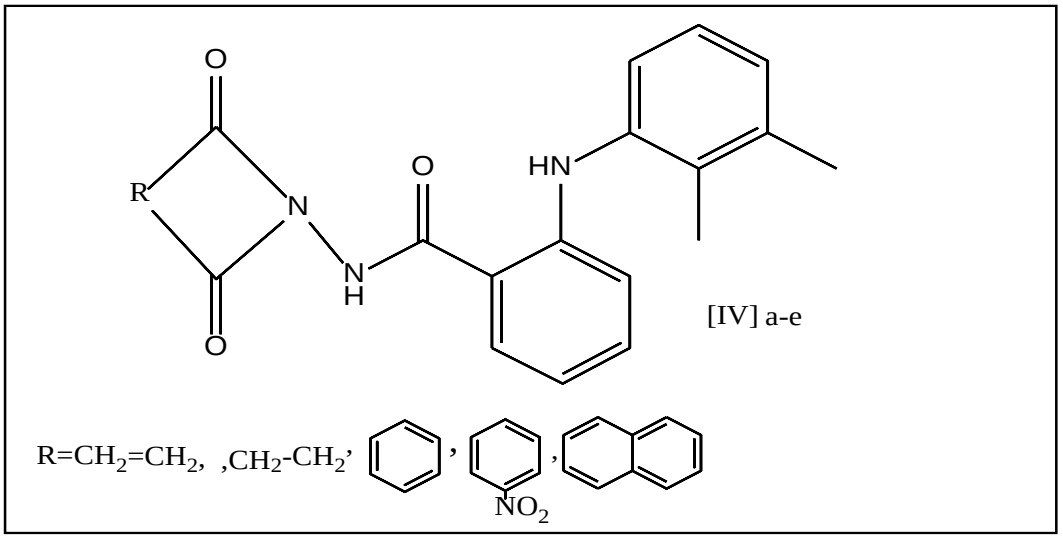
2.3.3. Synthesis of amic acid[79][III]$_{a-e}$



[III]$_{a-e}$

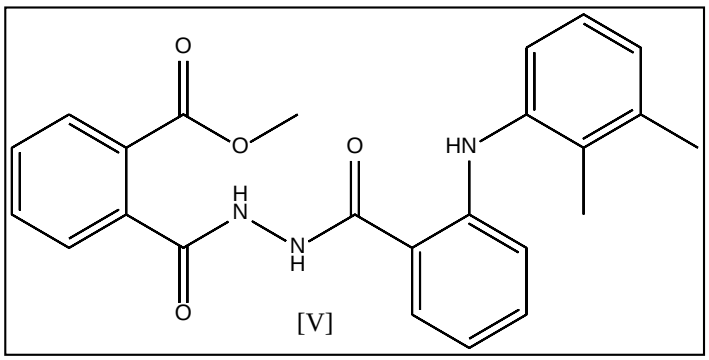
To a solution of different cyclic anhydrides (0.01mole) in 15mL acetone , a solution of acid hydrazid [II] (2.56 g, 0.01mole) in 15mL of acetone was added dropwise during one hour. The mixture was afterwards left at room temperature with continuous stirring for 24 hrs. The product was filtered off , and recrystallized from acetone to give amic acid derivetives $[III]_{a-e}$. The nomenclature, structural formula, physical data, and molecular formula of the compounds $[III]_{a-e}$ are given in Table(2-2).

2.3.4. Synthesis of N- substituted- imide $[IV]_{a-e}$.



Amic acid (0.01 mol) [80] $[III]_{a-e}$ was placed in 50mL round bottom flask and a mixture of sodium acetate (0.82g,0.01mol) and acetic anhydride(0.01mol) was added . The mixture was maintained between 80-90 ^{o}C by means of water-bath and stirred for 30 minutes. The mixture has been allowed to stirring for one hour at room temperature. After that, the mixture was poured on ice-water (100mL) and filtered off, then, recrystallized from the acetone. The physical data are given in Table(2-3). The elemental analysis of compound $[IV]_{b}$:Cal: C%=67.65 , H%= 5.63 ,N%=12.46; Found: C%=67.89 ,H%=5.91 ,N%=12.22

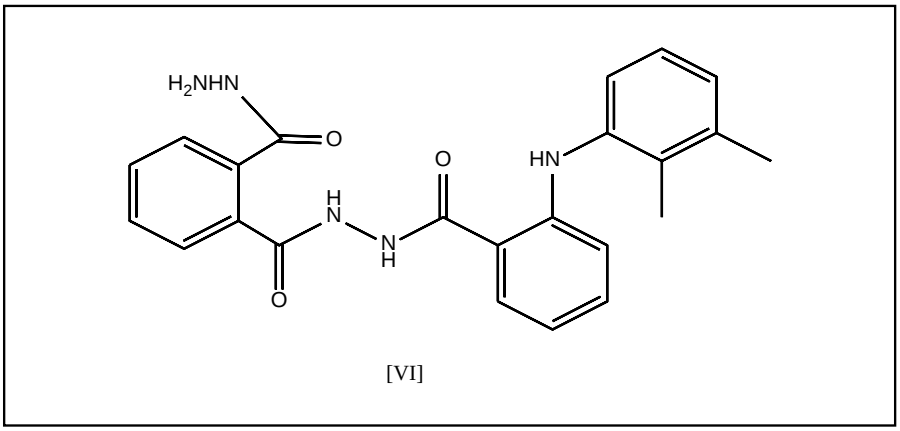
2.3.5 Synthesis of methyl 2-(2-(2-((2,3-dimethylphenyl) amino) benzoyl) hydrazine-1-carbonyl)benzoate[V]



[V]

A mixture of compound [5] $[III]_c$ (4.03g, 0.01 mol), absolute methanol (25mL) and conc. H_2SO_4 (1.5 mL) was refluxed for 6 hrs. After, The mixture was cooling and washed with a solution of sodium bicarbonate, The resulting of a white crystals solid was filtered off, washed with water, dried and recrystallized by ethanol in order to produce compound [V] , yield 70% and m.p (188-190)^oC .

2.3.6 Synthesis of N'-(2-((2,3-dimethylphenyl) amino) benzoyl) phthalohydrazide [VI].

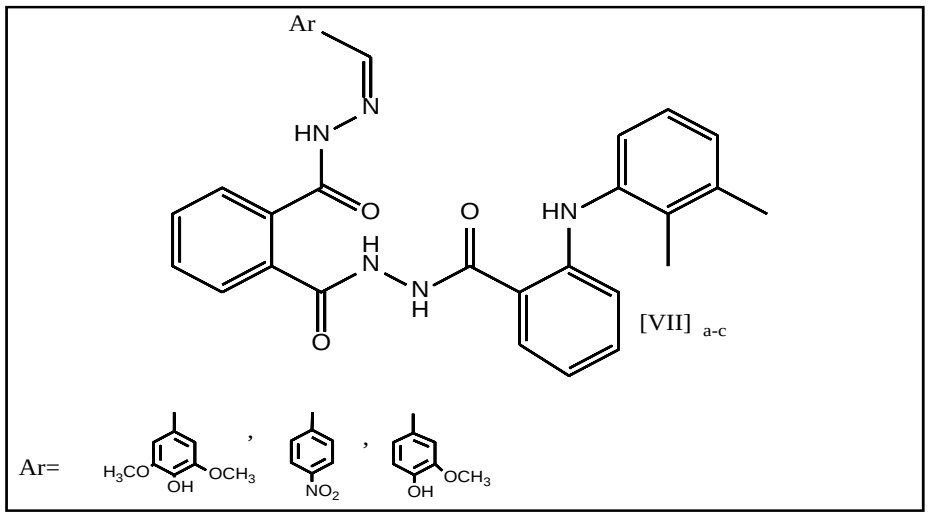


[VI]

A mixture of new ester [V] (4.17g, 0.01mol) was dissolved in absolute ethanol (20mL). Hydrazine hydrate (0.01mol) was slowly added and the mixture

was refluxed for 6hrs. The mixture was cooled and the pale yellow solid has been filtered, then used ethanol to recrystallized, yield 71%; m.p (137°C -139) °C**.**

2.3.7 Synthesis of Schiff bases [VII]$_{a-c}$



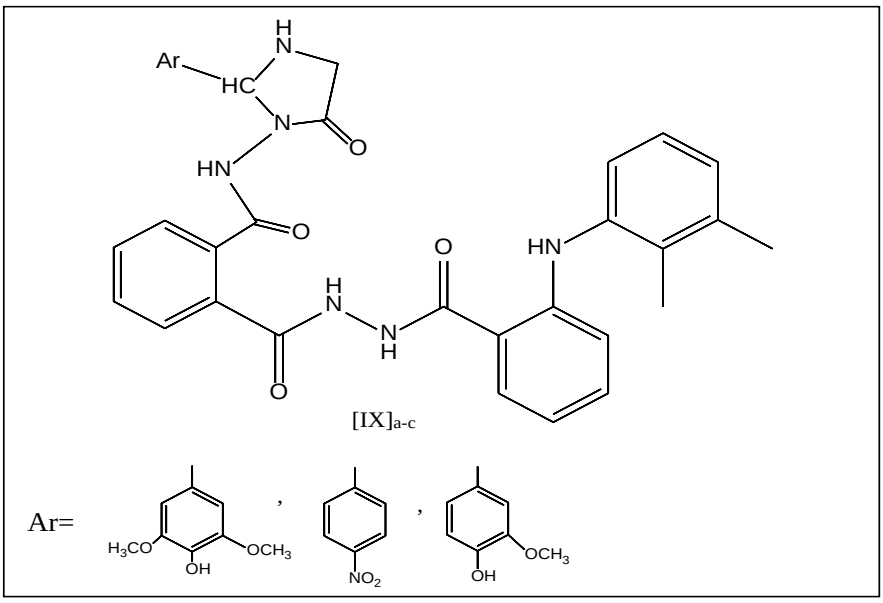
A mixture of new acid hydrazide [VI] (4.18g, 0.01mol) (Syringaldehyde, 4-Nitrobenzaldehyde, and Vaniline) (0.01mol) with EtOH (15mL) and four drops of GAA were refluxed for 6hrs, cooled and after that filtered the product, and crystallized from the ethanol[(9)] . The nomenclature, structural formula, physical data, and molecular formula of the compounds [VII]$_{a-c}$ are given in Table(2-4).

2.3.8 Synthesis N-(3-chloro-2-(substituted)-4-oxoazetidin-1yl)-2-(2-(2-((2,3-dimethylphenyl)amino)benzoylhydrazine-1- carbonyl) benzamide [VIII]$_{a-c}$

Chloroacetylchloride[(81)] (0.01 mol) in 10mL of dry benzene cooled at (0 -5ºC) , to this flask Et_3N (0.01 mol) was added, and solution of Schiff base [VII]$_{a-c}$ (0.01 mol) in 10 mL benzene was added slowly and refluxed in a water bath for 12 hrs. After completing the reaction, the mixture was poured onto water which is ice-cold in order to allow precipitation that which is filtered and dried**.** The

nomenclature, structural formula, physical data, and molecular formula of the compounds $[VIII]_{a-c}$ detail in Table(2-5).

2.3.9 Synthesis of N-1-((2-((2,3 dimethylphenyl)amino) phenyl) carbamoyl)-N-2-(2-(substituted)-5-oxoimidazolidin-1-yl) phthalamide[81] $[IX]_{a-c}$

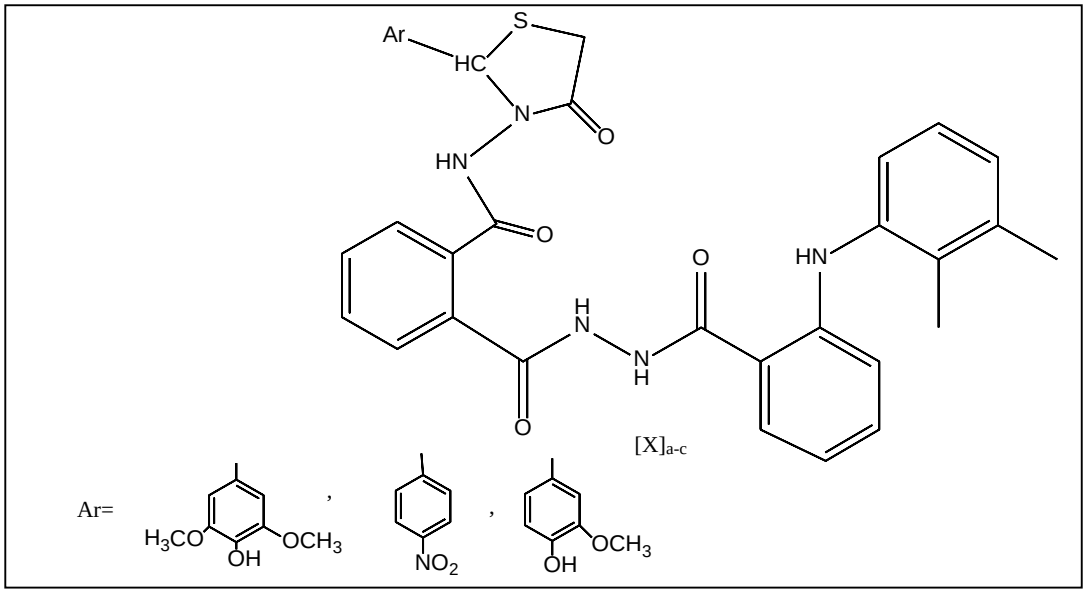


$[IX]_{a-c}$

Amixture of schiff bases $[VII]_{a-c}$ (0.01 mol), glycine (0.75g,0.01mol) and Et_3N (1 mL) in ethanol (15 mL) has been refluxed for 9hrs. The reaction mixture was neutralized by diluted hydrochloric acid and after that, poured to water that is ice-cold. The precipitate was filtered off, washed with water and recrystallizes from ethanol. The nomenclature, structural formula, physical data, and molecular formula of the compounds $[IX]_{a-c}$ are given in Table(2-6).

Elemental analysis of $[IX]_b$ Calac : C%=63.26 ,H%= 4.77 N%= 16.14; Found : C%=63.68 ,H%= 4.90 N%=16.00.

2.3.10. Synthesis of N-1-((2-((2,3- dimethylphenyl)amino)phenyl) carba mmoyl) –N-2-(2-(substituted)-4-oxothiazolidin-3-yl)phthalamide[81] $[X]_{a-c}$



The new schiff bases $[VII]_{a-c}$ (0.01 mol) and thioglycolic acid (0.01mol) were refluxed in dry benzene (20mL) for 8hrs. The solvent has undergone evaporation and reaction mixture has been neutrilized by a solution of sodium bicarbonate, and recrystallized from petroleum ether. The nomenclature, structural formula, physical data, and molecular formula of the compounds $[X]_{a-c}$ are given in Table(2-7).

2.4 Biological Evaluation

This study involves evaluate antibacterial activity, cytotoxic effect, and toxicity *(in vivo)* of some new amic acid and their derivatives of mefenamic acid.

2.4.1 Antibacterial activity

Four pathogenic bacteria species were utilized in this study as test organisms *(in vitro)* for some synthesized compounds. These are: *Staphylo coccus*

aureus(G+), Bacillus subtilisa (G+), Klebsiella pneumoniae (G-), and Escherichia.coli (G-) according to the agar diffusion method[82].

Fresh bacterial cltures suspension of approximately 108 colony cell/ml was incubated at 37°C for 24hrs, then spread on the Muller-Hintone agar plates with the use of sterilized swabs. 6 mm diameter wells have been cut in the solidified agar and filled by 10mg/ml solution of some synthesized derivatives in DMSO, and placed into with occulted plates. The plates have been aerobically incubated at a temperature of 37°C for 24hrs, and after that, the diameter of the inhibition zone was measured (in mm).

2.4.2 Anticancer screening

The cytotoxic effect of some new amic acid and their derivatives of mefenamic acid against a cell line of breast cancer MCF7 for 48 hrs. The cells of MCF7 were seeded in 96-well culture plates at 200µl/ cell suspension was filled to each one of the wells and the plates have been covered by plate and sealed using parafilm and placed in an incubator, then incubated for 24hrs in humidified chamber at a temperature of 37ºC with 5% CO_2 gas and medium fill up with 10% bovine serum and 1% of penicillin /streptomycin mixture until the cells reached confluence. The plate was checked out for contamination, and cultured at different concentrations 10 - 500 µg/mL, whereas 200 µl medium of maintenance have been added into every monitoring group well, then plates were tighter by parafilm and regressed to incubator. Cytotoxicity evaluation was performed after 48 hrs, the supernatant was removed, 150µL DMSO was added into the solution followed with incubation at a temperature of 37ºC for 15minutes with shaking, and absorbance values(OD) was read using a micro-plate reader at 450nm wave-length to calculated the rate of inhibition of the cell growth. The cell growth inhibition rate has been computed based on [82] follow formula:

$$\text{Inhibition rate} = \frac{control\ mean - treatment\ mean}{control\ mean} \times 100$$

2.4.3 The test of Acute Toxicity

In the presented research, three groups of 45 albino mice (each consisting of 15 mice) were utilized for the evaluation of acute toxicity of some of the synthesized compounds, using the Lorke-written method[82]. Mice were fasted for 18 hrs with free arrival to water prior to the experiment. The compounds were dissolved in distilled water and treated through injection (5g/kg and 10g/kg). Post treatment, the mice have been fed, and after that, their weights were registered followed by observing for general toxicity symptoms signs, mortality, and behavior for 14 days. In this study the treatment group and the control group were compared with doses of the injection. The mice behaviors were recorded over the next 14 days. Moreover, some mice have been sacrificed with cervical dislocation and liver, kidneys, and heart have been weighed.

Table (2-2): The nomenclature, structural formula, physical data, and molecular formula of Amic acid $[III]_{a-e}$.

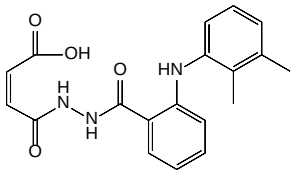
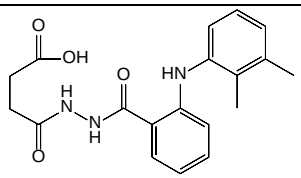
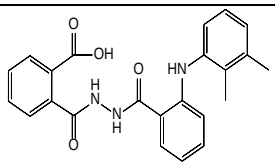
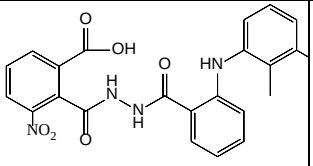
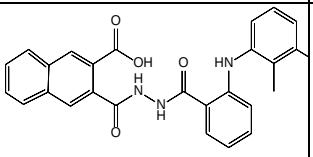
Comp. No.	Name	Structure	Yield %	Color	M.P. ℃	Chemical Formula
[III] a	4-(2-(2-((2,3-dimethyl phenyl)amino) benzoyl) hydrazineyl)-4-oxobut-2-enoic acid		83	Yellow dark	202-204	$C_{19}H_{19}N_3O_4$
[III] b	4-(2-(2-((2,3-dimethyl phenyl)amino)benzoyl)hydazineyl)-4-oxo butanoic acid		65	Yellow light	148-150	$C_{19}H_{21}N_3O_4$
[III] c	(2-(2-(2-((2,3-di-methyl phenyl) amino) benzoyl) hydrazine-1-carbonyl) benzoic acid		81	brown	210-212	$C_{23}H_{21}N_3O_4$
[III] d	2-(2-(2-((2,3-dimethyl phenyl) amino) benzoyl) hydrazine-1-carbonyl)-3-nitrobenzoic acid		73	Yellow light	186-188	$C_{23}H_{20}N_4O_6$
[III] e	3-(2-(2-((2,3-dimethyl phenyl)amino)benzoyl) hydrazine-1-carbonyl)-2-naphthoic acid		62	baige	207-209	$C_{27}H_{23}N_3O_4$

Table (2-3): The nomenclature, structural formula, physical data, and molecular formula of Imides $[IV]_{a-e}$.

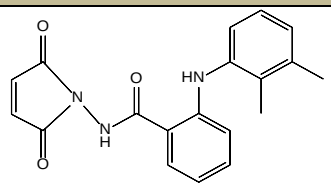
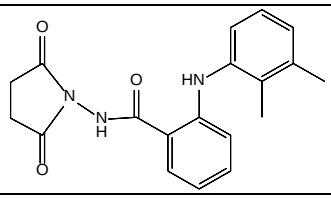
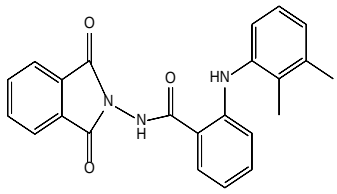
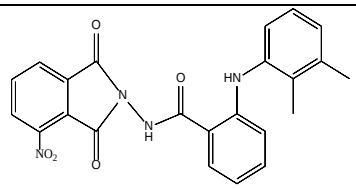
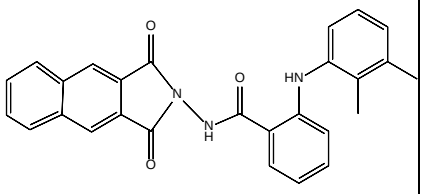
Comp. No.	Name	Structure	Yield %	Color	M.P .℃	Chemical Formula:
$[IV]_a$	2-((2,3-dimethyl phenyl) amino)-N-(2,5dioxo-2,5-di-hydro-1H-pyrrol-1yl) benzamide		80	light gray	178 - 180	$C_{19}H_{17}N_3O_3$
$[IV]_b$	2-((2,3-dimethyl phenyl)amino)-N-(2,5-di-oxopyrrolidin-1yl) benzamide		68	Brown dark	164 - 166	$C_{19}H_{19}N_3O_3$
$[IV]_c$	2-((2,3-dimethyl phenyl) amino) -N-(1,3-di-oxoisoindolin-2yl)benzamide		70	baige	188 - 190	$C_{23}H_{19}N_3O_3$
$[IV]_d$	2-((2,3-di-methyl phenyl)amino)-N-(4nitro-1,3-dioxo isoindolin-2yl) benzamide		77	light green	250 - 252	$C_{23}H_{18}N_4O_5$
$[IV]_e$	2-((2,3-dimethyl phenyl)amino)-N-(1,3dioxo-1,3-di-hydro-2H-benzo[f]isoindol-2yl) benzamide		73	orange	270 decom.	$C_{27}H_{21}N_3O_3$

Table (2-4):) The nomenclature, structural formula, physical data, and molecular formula of Schiff bases $[VII]_{a-c}$

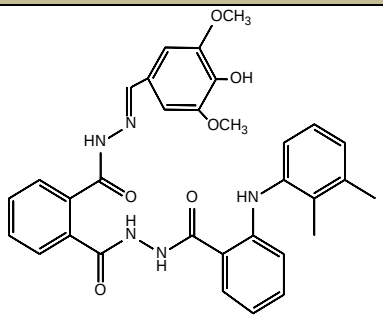
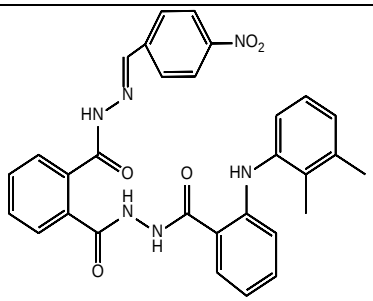
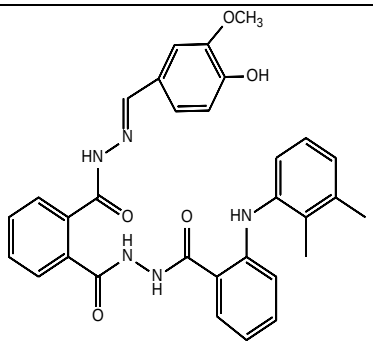
Comp. No.	Name	Structure	Yield %	Color	M.P .℃	Chemical Formula
$[VII]_a$	N'-1-(2-((2,3-dimethyl phenyl) amino) benzoyl) -N'-2-(4-hydroxy-3,5-dimeth oxybenzylidene) phthalohydrazide		68	Peal yellow	101 - 102	$C_{32}H_{31}N_5O_6$
$[VII]_b$	N'-1-(2-((2,3-dimethyl phenyl)amino) benzoyl)-N'-2-(4-nitrobenzylidene) phthalohydrazide		77	Yellow Light	189 - 191	$C_{30}H_{26}N_6O_5$
$[VII]_c$	N'-1-(2-((2,3-dimethyl phenyl)amino) benzoyl)-N'-2-(4-hydroxy-3-methoxy benzylidene)phthalohydrazide		81	Yellow Light	168 - 171	$C_{31}H_{29}N_5O_5$

Table (2-5):): The nomenclature, structural formula, physical data, and molecular formula of azitidon-2-one [VIII]$_{a-c}$

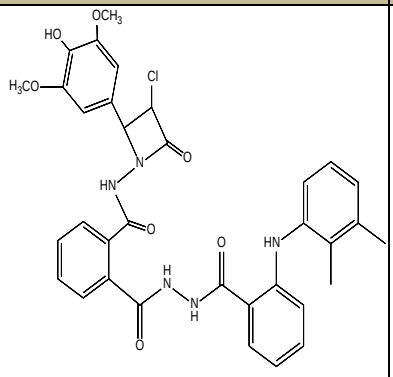
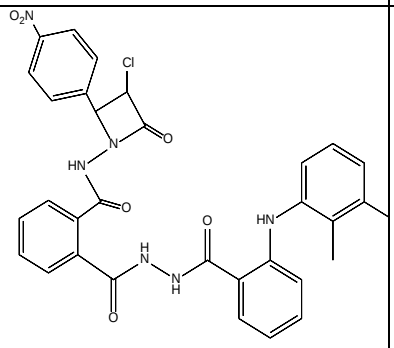
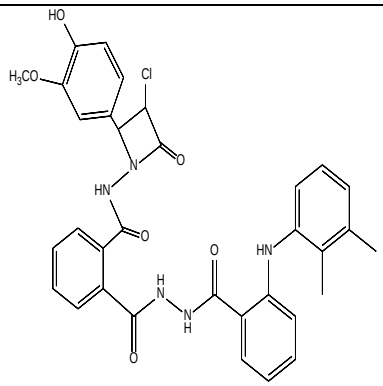
Comp. No	Name	Structure	Yield %	Color	M.P. ℃	Chemical Formula
[VIII]$_a$	N-(3-chloro-2-(4-hydroxy-3,5-dimethoxyphenyl)-4-oxo-azetidin-1-yl)-2-(2-(2-((2,3-dimethylphenyl) amino)benzoyl)hydrazine-1-carbonyl) benzamide		65	Light Brawn	146-148	$C_{34}H_{32}ClN_5O_7$
[VIII]$_b$	N-(3-chloro-2-(4-nitro-phenyl)-4-oxo-azetidin-1-yl)-2-(2-(2-((2,3-dimethylphenyl)amino) benzoyl)hydrazine-1-carbonyl)benzamide		87	Light yellow	213-215	$C_{32}H_{27}ClN_6O_6$
[VIII]$_c$	N -(3-chloro-2-(4-hydroxy-3-methoxy)-4-oxo-azetidin-1-yl)-2-(2-(2-((2,3-dimethylphenyl amino)benzoyl) hydrazine-1-carbonyl)benzamide		90	Dark brawn	184-186	$C_{33}H_{30}ClN_5O_6$

Table (2-6):): The nomenclature, structural formula, physical data, and molecular formula of of imidazal-4-one[IX])$_{a-c}$.

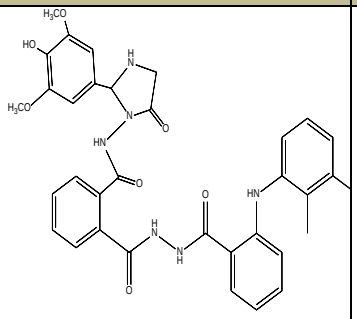
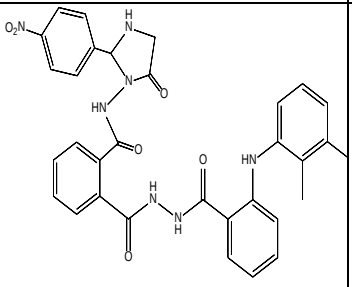
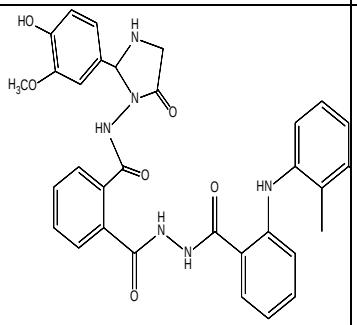
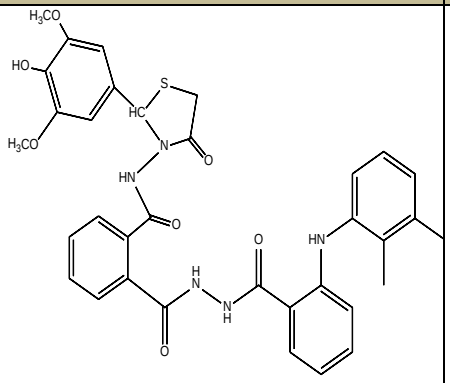
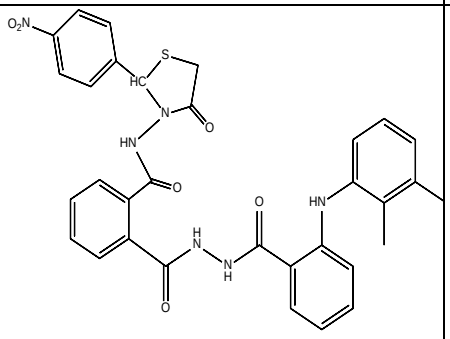
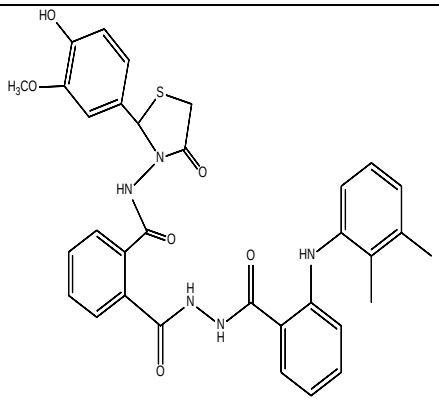
Comp. No	Name	Structure	Yield %	Color	M.P .℃	Chemical Formula
$[IX]_a$	2-(2-(2-((2,3-di-methyl phenyl) amino)benzoyl)hydrazine-1-carbonyl)-N-(2-(4-hydroxy-3,5-di methoxyphenyl)-5-oxo-imidazolidin-1-yl)benz amide		70	Light yellow	144 - 146	$C_{34}H_{34}N_6O_7$
$[IX]_b$	2-(2-(2-((2,3-dimethyl phenyl)amino)benzoyl)hyd razine-1-carbonyl)-N-(2-(4-nitrophenyl)-5-oxo-imid azolidin-1-yl) benzamide		66	Dark yellow	221 - 223	$C_{32}H_{29}N_7O_6$
$[IX]_c$	2-(2-(2-((2,3-dimethyl phenyl)amino)benzoyl)hyd razine-1-carbonyl)-N-(2-(4-hydroxy-3-methoxy phenyl) -5-oxo-imidazolidin-1yl) benzamide		61	White	182 - 184	$C_{33}H_{32}N_6O_6$

Table (2-7): The nomenclature, structural formula, physical data, and molecular formula of of Thiozolidenon-4-one $[X]_{a-c.}$

Comp. No	Name	Structure	Yield %	Color	M.P. ℃	Chemical Formula
$[X]_a$	2-(2-(2-((2,3-dimethyl phenyl)amino)benzoyl)hydrazine-1-carbonyl)-N-(2-(4-hydroxy-3,5-dimethoxyphenyl)-4-oxo-thiazolidin-3-yl) benzamide		55	yellow	225-227	$C_{34}H_{33}N_5O_7S$
$[X]_b$	2-(2-(2-((2,3-dimethyl phenyl)amino)benzoyl) hydrazine-1-carbonyl)-N-(2-(4-nitrophenyl)-4-oxo-thiazolidin-3-yl) benzamide		62	Light yellow	215-217	$C_{32}H_{28}N_6O_6S$
$[X]_c$	2-(2-(2-((2,3-dimethyl phenyl)amino)benzoyl) hydrazine-1-carbonyl)-N-(2-(4-hydroxy-3-methoxyphenyl)-4-oxo-thiazolidin-3yl) benzamide		57	white	195-197	$C_{33}H_{31}N_5O_6S$

Chapter Three

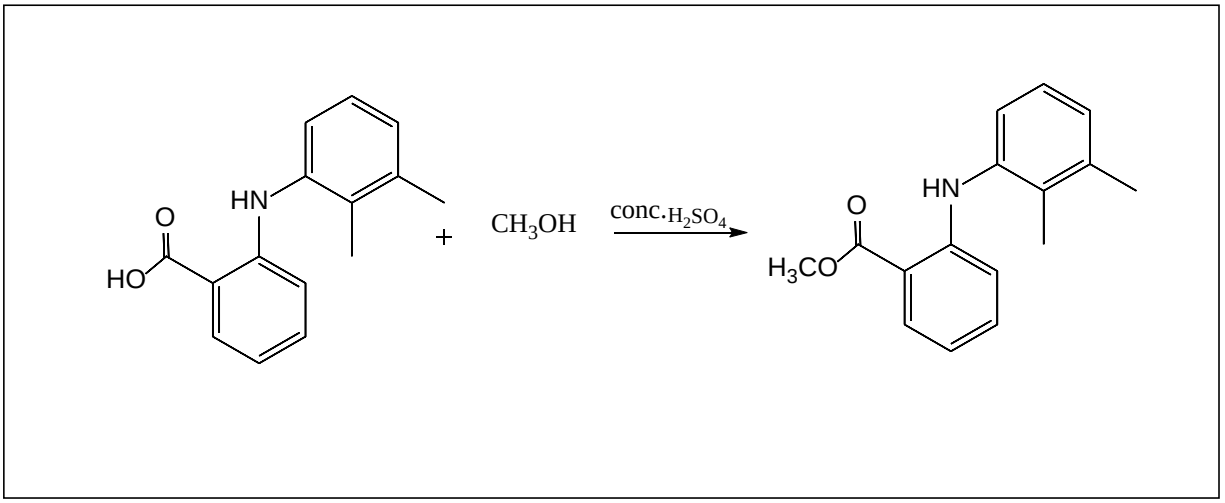
Results & Discussion

3.1 Synthesis and characterization

Mefenamic acid is a compound which belongs to N-aryl anthranilic acid family. The FT-IR spectrum of mefenamic acid, showed the following bands: a broad band of (O-H) stretch vibration observed at (3300-2974) cm^{-1}, stretching band C-H aromatic at (3010)cm^{-1}, stretching band at (2974-2940) cm^{-1} for (C-H) aliphatic, stretch band at (1650) cm^{-1} for (C=O) carboxylic acid, stretch band at (1575,1547) cm^{-1} for (C=C) aromatic ring. ^{1}HNMR spectrum data of mefenamic acid display (s.6H) for aliphatic methyl protons at δ(2.18-2.35), (m,7H) for aromatic ring protons at δ(6.65-8.04) and (s,1H) for carboxylic group at δ(9.39ppm)[83].

3.1.1 Prepartion and characterization of methyl 2-(2,3-dimethyl anilino) benzoate [I]

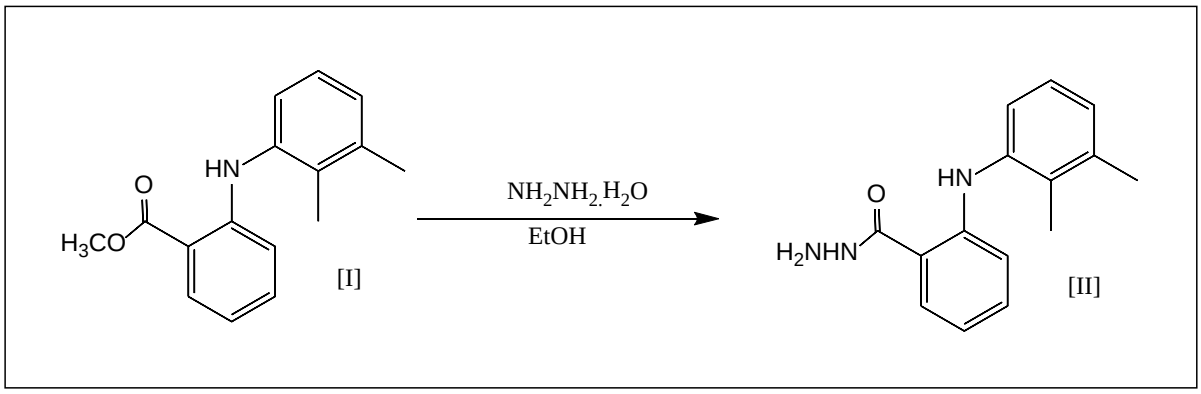
A number of ester derivatives of the mefenamic acid were synthesized via a reaction between the carboxylic group and methanol with the concentrated sulphuric acid present in 80% yield, m.p 96-98°C (Lit., m.p96-98°C)[40] as shown in the equation (3-1).



Equation (3-1)

The spectrum of the FT-IR, Figure (3-1) for ester [I] exhibited absorptions due to stretching vibration of C=O ester at(1684)cm^{-1}, and disappearance of the stretching bands for C=O and O-H of the carboxylic moiety of mefenamic acid. Also, showed a new bands at 1255 cm^{-1} for C-O stretching of ester group.

3.1.2. Prepartion and characterization of 2-(2,3-di-methyl phenyl amino) benzohydrazide[II]

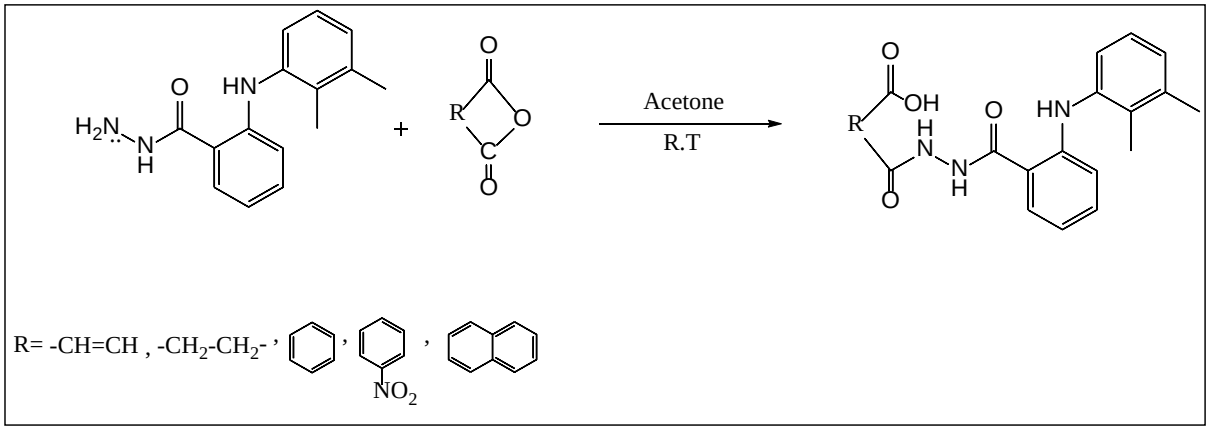


Equation (3-2)

Condensation ester [I] with 80% hydrazine hydrate in ethanol resulted in the acid hydrazide [II], that is characterized by melting point[40] (116-118°C) (Lit., 118-120) °C and FT-IR spectrum, Figure (3-2), revealed three stretching bands of absorption in the region (3329-3190) cm^{-1} which is assigned to bands of NH and NH_2 groups. Also IR spectrum showed a new band of stretching vibration due to the amide group C=O at (1641)cm^{-1} for hydrazide moiety.

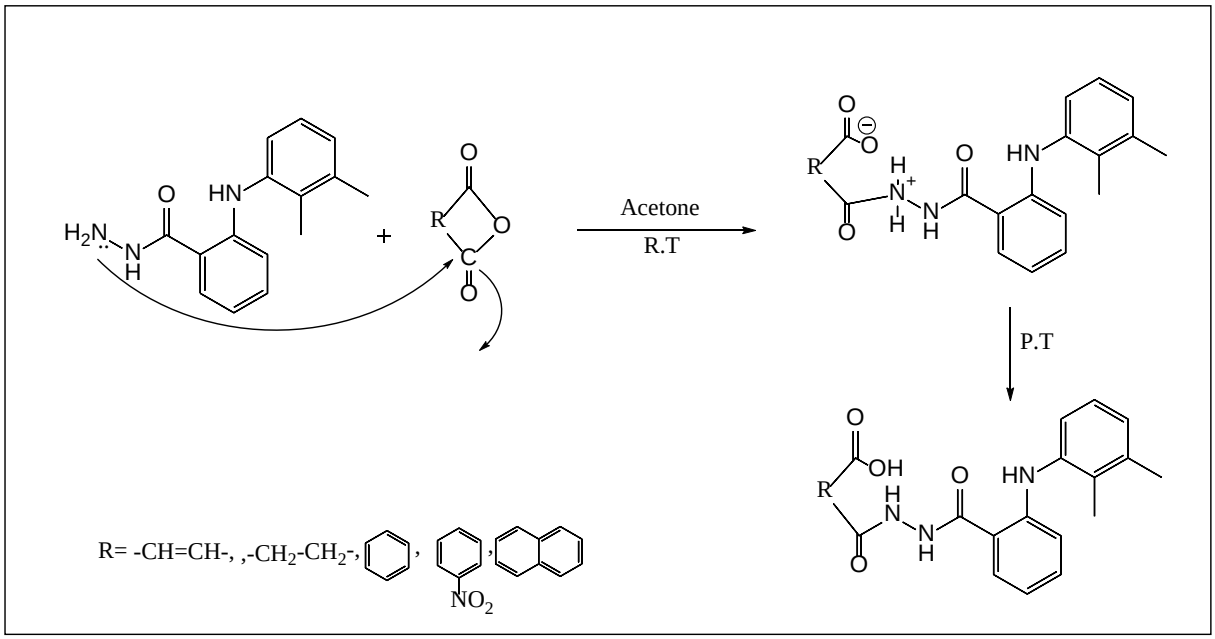
3.1.3. Synthesis and Characterization of amic acids $[III]_{a-e}$

The amic acids $[III]_{a-e}$ were synthesized by the reaction between one mole of acid hydrazide [II] and a similar mole of various cyclic anhydrides (maleic, succinic, phthalic, 4-nitro phthalic, or naphthalic anhydride) in dry acetone as a solvent at room temperature.



Equation (3-3)

This reaction's mechanism[79] proceeds through nucleophilic addition reaction as in the following, Scheme (3-3) :



Scheme (3-1)

The synthesized amic acids $[III]_{a-e}$ were identified FTIR, ^{1}HNMR and mass spectrometry. The spectra of FTIR for compound $[III]_a$ and $[III]_c$, Figure. (3-3), and Figure (3-4) have shown the disappearance of absorption bands of NH_2 and other peaks that are identified of cyclic anhydride of starting materials together with new absorption bands of stretching that appear as a result of the O-H of carboxylic moiety in range between (3390 and 2374) cm^{-1}, (C=O)

appeared at (1712-1678) cm^{-1}, while the band of stretching for amid group (C=O) become clear at(1653-1623) cm^{-1}. The functional groups of FT-IR data of amic acids $[III]_{a-e}$ are listed in Table (3-1).

Table 3- 1: The FTIR spectra of amic acids $[III]_{a-e}$

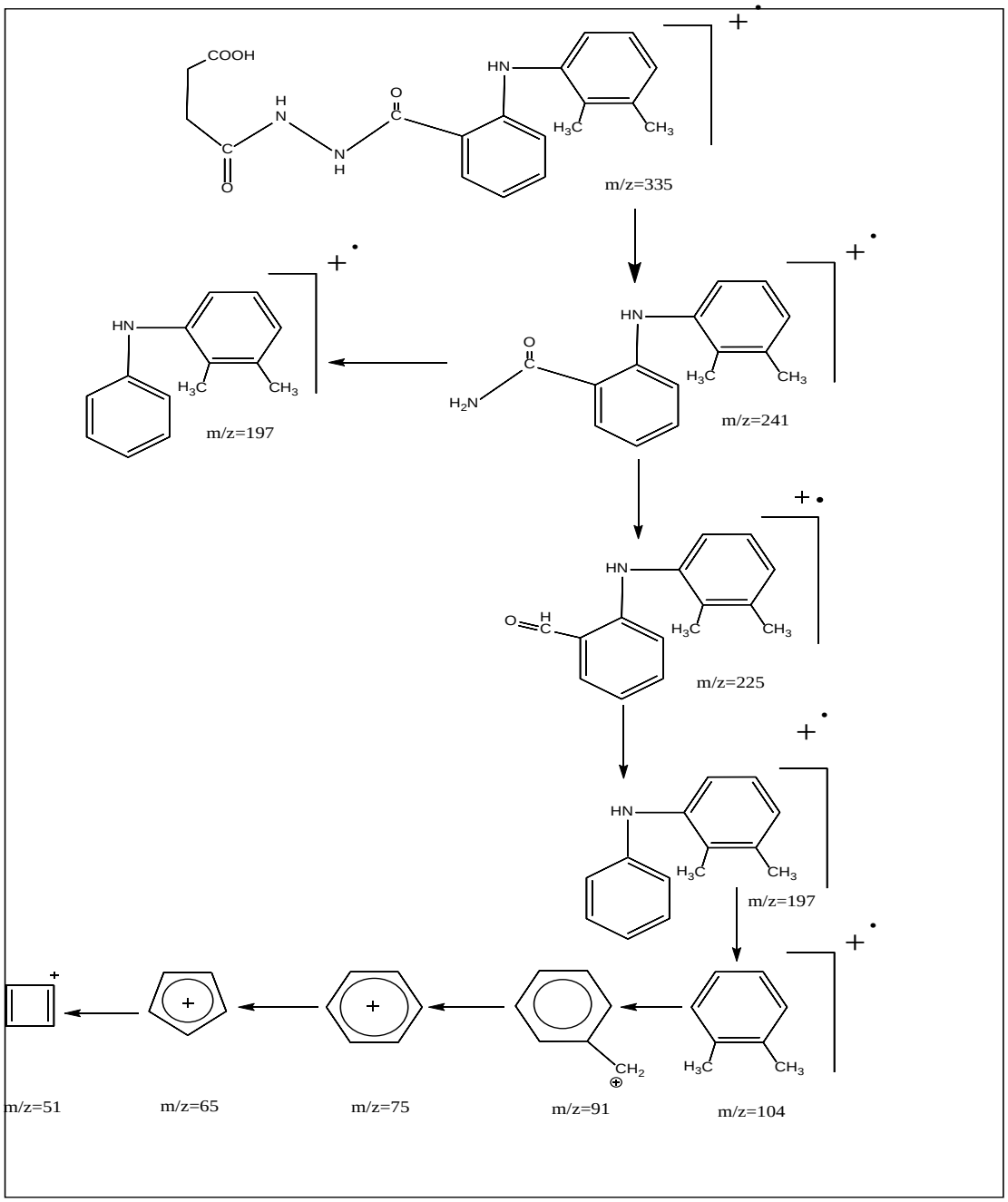
Comp NO.	ν(O-H)	ν(N-H)	ν(C-H) aromatic	ν(C-H) aliphatic	ν(C=O) Carboxylic	ν(C=O) amide	ν(C=C) aromatic
$[III]_a$	3309	3280, 3203	3095	2974-2864	1701	1651	1576, 1508
$[III]_b$	3360	3298, 3309	3093	2981-2870	1701	1681	1570, 1504
$[III]_c$	3390	3309, 3250	3012	2974-2912	1712	1653	1576, 1504
$[III]_d$	3346	3313, 3228	3018	2923-2866	1707	1651	1576, 1531
$[III]_e$	3311	3291, 3100	3018	2927-2862	1739	1650	1577, 1510

^{1}HNMR spectra for compound $[III]_c$, Figure (3-5) showed the characteristic chemical shift (DMSO-d_6 as a solvent): two singlet signals appeared at δ (2.09,2.28) ppm might be a result of six aliphatic protons of the 2 groups of the CH_3. Many signals of eleven aromatic protons at δ (6.66-8.08) ppm. A good sharp signal at δ (9.45) might be a result of three protons NH groups. Finally, a carboxylic moiety proton has seemed as broad band at δ(12.06 -12.50) ppm[(84)].

^{1}HNMR spectra for compound $[III]_d$, Figure (3-6) showed two singlet signals appeared at δ (2.04– 2.27) ppm which might be a result of six protons of 2 groups of the CH_3. Multiplet signals of ten aromatic protons at δ (6.66-8.44)

ppm. A good sharp signal at δ (9.45) might be a result of three NH group protons. Finally, a carboxylic moiety proton has seemed as broad weak band of δ (12.00 -12.40) ppm.

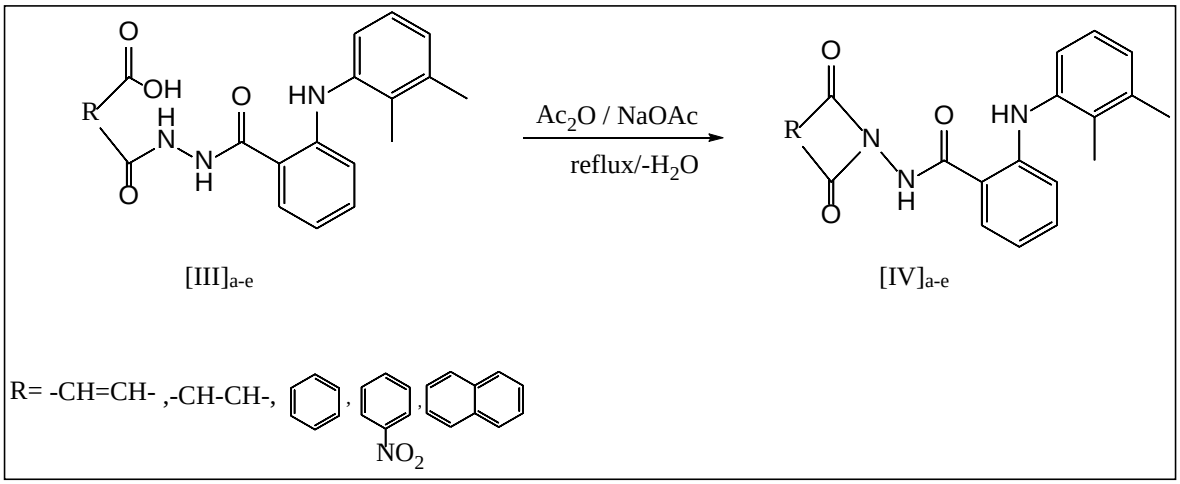
Finally[85], the mass spectra of compound $[III]_b$, Fig.(3-7),showed a character is fragmentation at m/z=(241, 208,194 ,104,75, and 51), as in the Scheme (3-5).



Scheme (3-2)

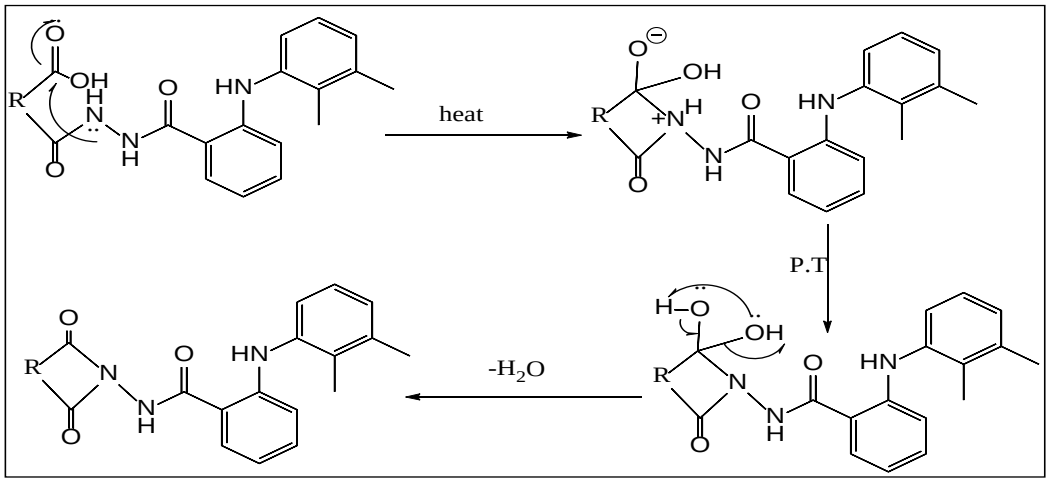
3.1.4. Synthesis and characterization of imides $[IV]_{a-e}$

A series of imide compounds$[IV]_{a-e}$ of mefenamic acid were obtained by intramolecular cyclization of amic acid $[III]_{a-e}$ in acetic anhydride and sodium acetate at(80-90)^{o}C. The proposed means for the synthesis of the titled derivatives can be explained as follows in Equation (3-4).



Equation (3-4)

The reaction was performed via amino group nucleophilic attack in acid hydrazide on the atom of the carbon of a carbonyl group in anhydride leads to the formation imide compounds by cyclization with losing water molecule [85], as show in Scheme (3-3).



Scheme (3-3)

The synthesized imids deivatives $[IV]_{a-e}$ structure was confirmed using the spectroscopy of FT-IR , ^{1}HNMR, CHN-S.

The spectra of the FT-IR of compound $[IV]_e$ and $[IV]_d$, Figures (3-8) ,and (3-9), exhibited significant two bands symmetry and asymmetry vibration of stretching of the carbonyl group (imide cyclic)[86] in the range (1800-1700) cm^{-1} indicating the success of reaction which lead to imide formation, and two absorption bands at (1439-1128)$cm^{-1}$for asymmetry and symmetry stretching vibration of C-N-C(cyclic imide)[87-88]. Table(3-2) lists the FTIR of the new imids $[IV]_{a-e}$.

Table (3- 2): The spectra of FTIR of imids $[IV]_{a-e}$

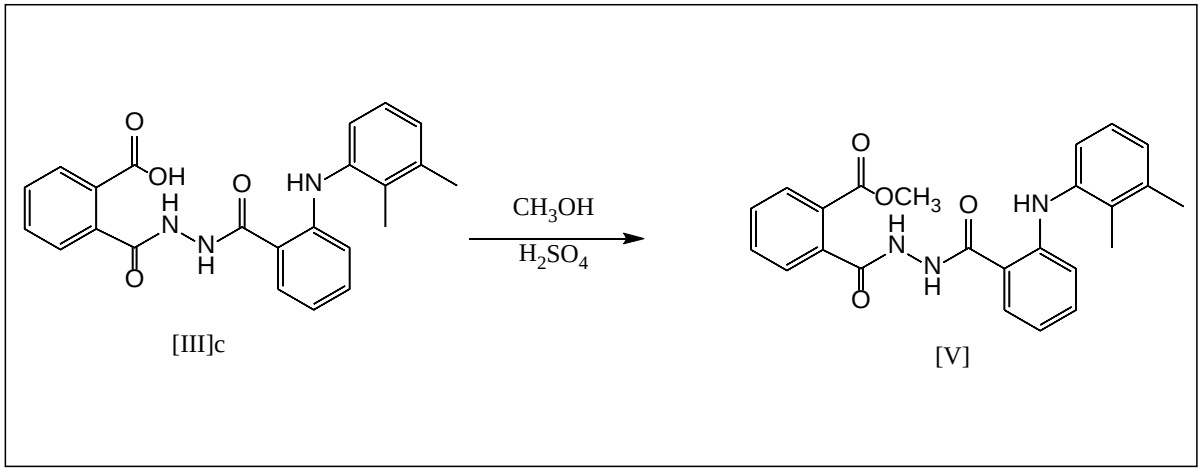
Comp No.	ν(N-H)	ν(C-H) arom.	ν(C-H) aliph.	ν(C=O) imide cyclic asy, sy.	ν(C=O) amide	ν(C-N-C)asy., sy.	ν(C=C) arom.
$[IV]_a$	3435	3030	2999-2856	1765-1745	1643	1315-1248	1574
$[IV]_b$	3344	3062	2941-2916	1790-1739	1651	1439-1244	1570
$[IV]_c$	3406	3159	2978-2945	1766-1685	1635	1404-1242	1543
$[IV]_d$	3342	3010	2910-2880	1795-1761	1662	1334-1112	1568
$[IV]_e$	3465	3006	2939-2893	1736-1714	1641	1414-1223	1570

^{1}H-NMR spectra of compound $[VI]_c$, Figure (3-10) showed the appearance of many signals: two singlet signals at δ (2.09, 2.27) ppm might be a result of the six protons of the two groups of the CH_3. Many signals of eleven aromatic protons at δ (6.66-7.90) ppm. A good sharp signal at δ(9.57) might be a result of two protons of the groups of the NH.

^{1}H-NMR spectra of the imid $[VI]_e$, Figure (3-11) showed two sharp singlet signals display at δ (2.08, 2.27) ppm that could be attributed to the six protons of two groups of CH_3, while many signals of thirteen aromatic protons at δ (6.66-8.44) ppm. A good sharp signal at δ (9.59) might be a result of two protons of the groups of NH. The elemental analysis of imid$[IV]_b$ is in good agreement with the theortical data.

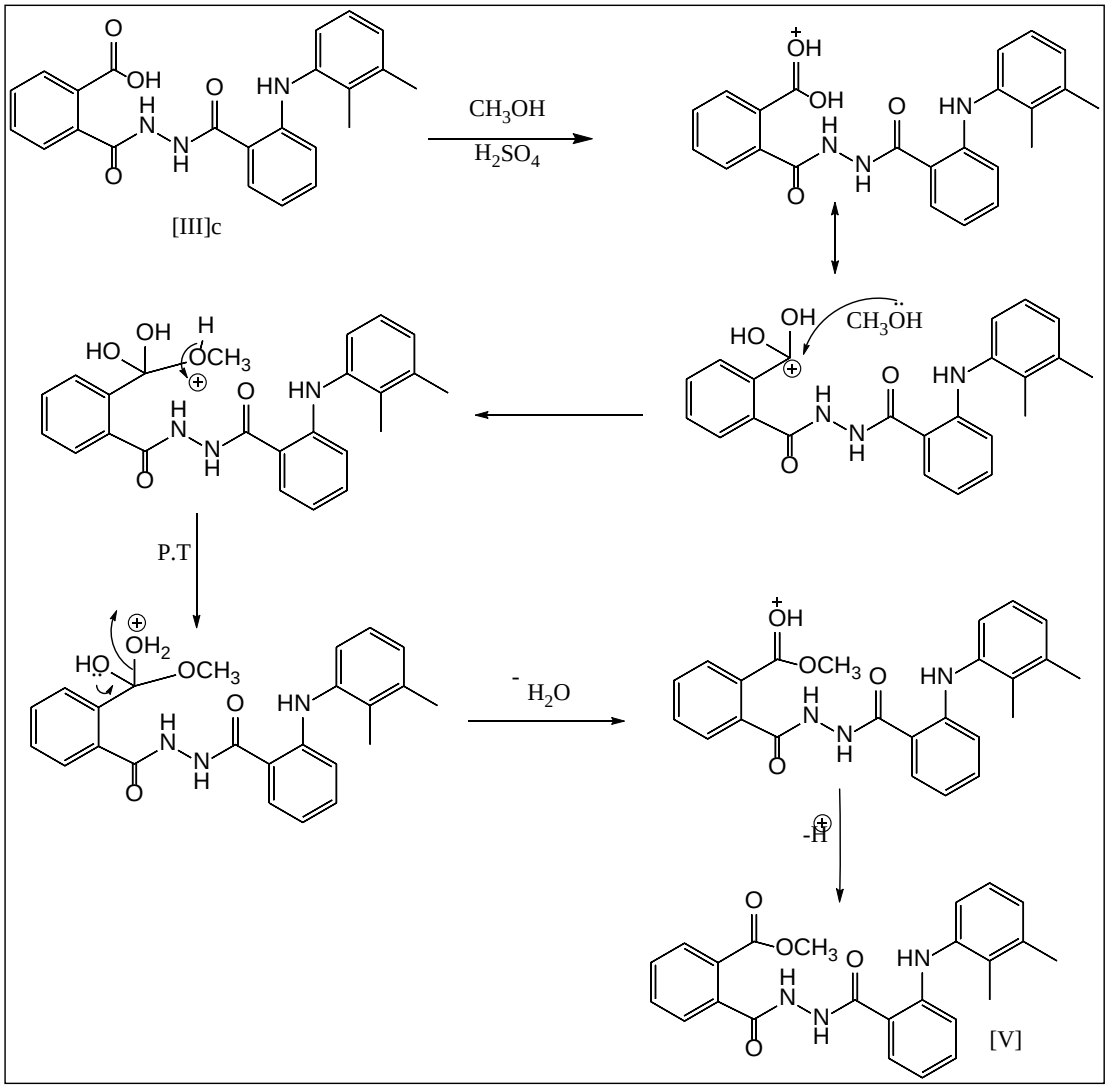
3.1.5. Synthesis and characterizing of methyl 2-(2-(2-((2,3-di-methylphenyl)amino)benzoyl)hydrazine-1-carbonyl)benzoate[V]

The new ester [V] was obtained from esterification of the carboxylic acid moiety of amic acid $[III]_c$, using absolute methanol in an acidic medium[89], this structure has been characterized with FTIR and^{1}HNMR spectroscopy.



Equation (3-5)

The mechanism[89] of this reaction may be outlined as showed in Scheme (3-4).



Scheme(3-4)

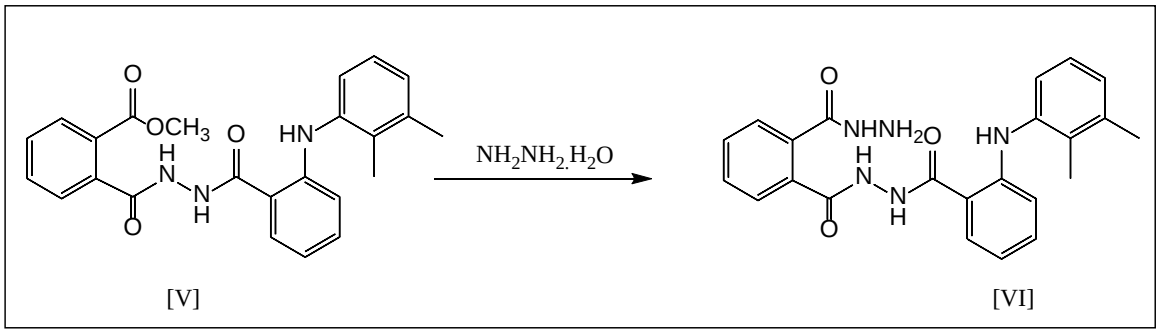
The spectra of the FT-IR, as it has been illustrated in Figure (3-12) showed the a band of absorption at 1732cm^{-1} as a result of the vibrationof stretching of (C=O) for the ester, also, a new band appearance at 1227cm^{-1} is a result of the (C-O) ester group bending, as well as a disappearing of two O-H and C=O bands of the cearboxylic moiety.

The ^{1}HNMR spectra of the compound [V], Figure (3-13) showed next characteristic chemical shifting (DMSO –d_6) showed a sharp two singlet signals display at δ (2.08, 2.27) ppm that could be attributed to the six protons of two groups of CH_3, a singlet signal at δ 3.86 ppm as a result of three protons of

OCH_3 groups, two signals have emerged in the range of δ (6.66-8.09) ppm for the aromatic protons and a singlet signal at δ 9.66 ppm as a result of three protons of the groups of NH.

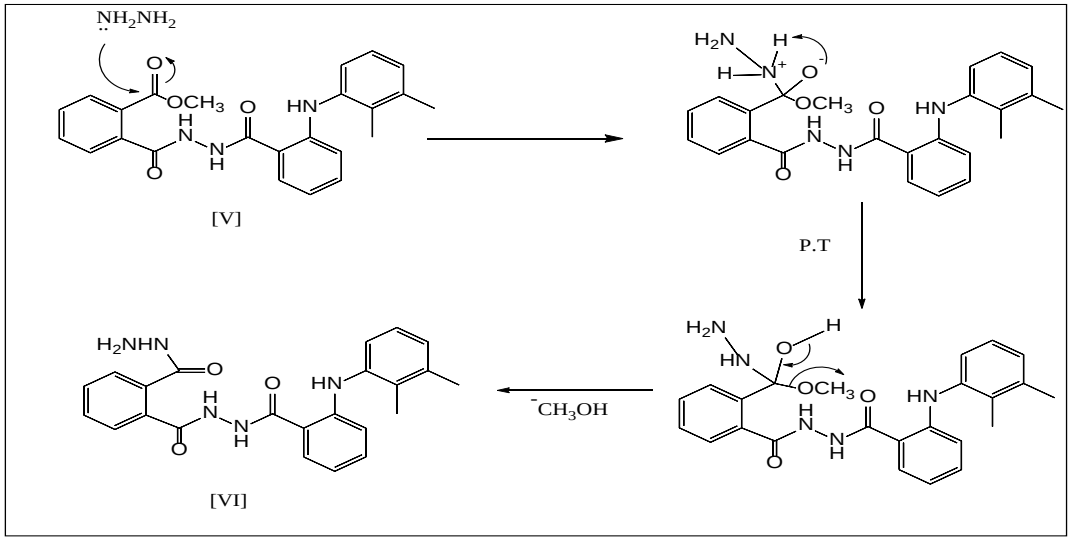
3.1.6. Synthesis and characterizing of N'-(2-((2,3-dimethyl phenyl) amino)benzoyl) phthalohydrazide [VI]:

The new acid hydrazides [VI] was synthesized from the reaction of ester [V] with 80% hydrazine hydrate in absolute ethanol, which has undergone the characterization of the spectroscopy of FTIR and ^{1}HNMR .



Equation (3-6)

The mechanism[89] for the synthesis of this derivative [VI] may be outlined in Scheme (3-5).



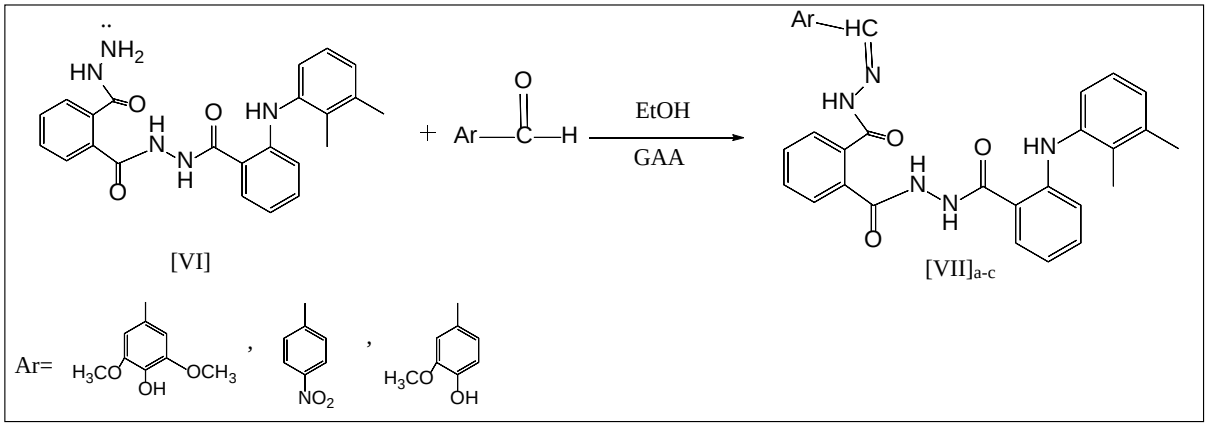
Scheme (3-5)

FT-IR spectra of the compound [VI], Figure (3-14) showed two strong bands of absorbing at (3309,3151)cm^{-1} to the groups of (NH and NH_2) and this is an excellent proof for successfully forming the acid hydrazine. Other absorption bands have emerged at (1660cm^{-1}) due to(C=O) amid group, and absorption (1442cm^{-1} – 1384cm^{-1}) for (C-N).

^{1}HNMR spectra of the compound [VI], Figure (3-15) showed some of the properties of the chemical shifting (DMSO –d_6) such as: a sharp two singlet signals appeared at δ (2.11, 2.28) ppm might be a result of the six protons of the aliphatic methyl groups, a sharp signals between δ (5.56-5.58) ppm of the two protons of the NH_2 group, and numerous signals have emerged in the range between δ (6.56 and 8.09) ppm for eleven aromatic protons and singlet signal at δ (11.13)ppm as a result of the NH groups protons**.**

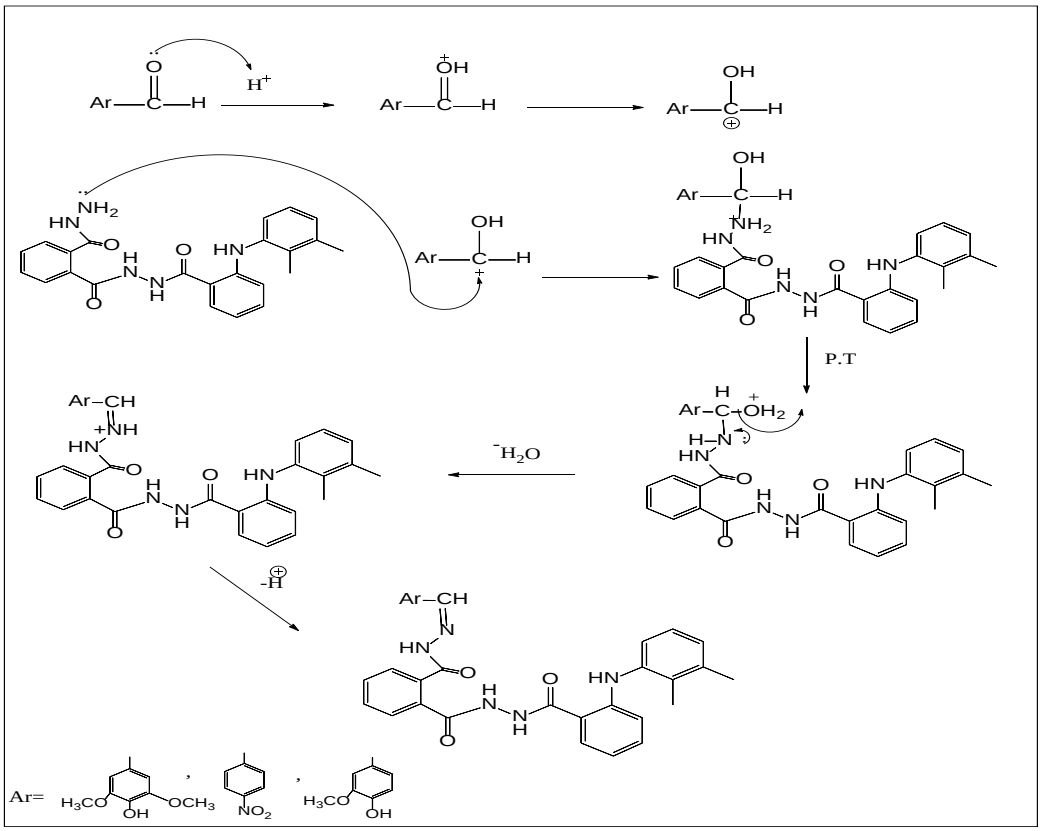
3.1.7. Synthesis Schiff base $[VII]_{a-c}$ and characterization

The new Schiff bases were undergone synthesis via refluxing equemolare of acid hydrazid [VI] with aromatic aldehydes (Syringaldehyde, 4-Nitrobenzaldehyd or Vaniline) in absolute ethanol with some drops of glacial acetic acid, Equation (3-7):



Equation (3-7)

The mechanism of Schiff bases $[VII]_{a-c}$ formation is a nucleophile addition reaction[(90)]Scheme (3-6):



Scheme (3-6)

These Schiff bases $[VII]_{a-c}$ were characterized using FT-IR, and ^{1}HNMR spectroscopy.

A new stertching band of absorption at (1626cm^{-1}) assigned to the group of the azomethine group (C=N), Figure(3-16) for $[VII]_a$, A stretching band at (3548) cm^{-1} as a result of the O-H of aromatic ring, and a good peak at (3419-3313) cm^{-1} for a stretching NH overlap with OH group beside to peak at (1651cm^{-1}) as a result of the C=O, Table (3-3) shows the spectral data of the FTIR of new Schiff bases$[VII]_{a-c}$.

Table(3-3): spectral data of FTIR of Schiff bases $[VII]_{a-c}$

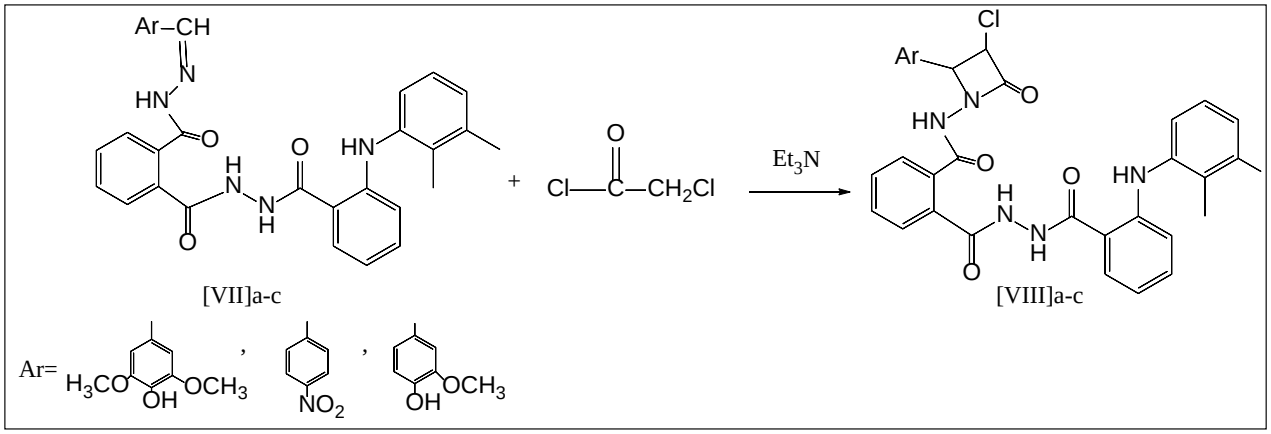
Com. No.	υ(NH) and OH overlap cm^{-1}	υ(C-H) arom.cm^{-1}	υ(C-H) aliph.cm^{-1}	υ(C=N) cm^{-1}	υ(C=O) cm^{-1}	υ(C=C) arom. cm^{-1}	others
$[VII]_a$	3419-3313	3016	2968-2935	1626	1651	1599,1579	OH:3546
$[VII]_b$	3423-3329	3008	2922-2858	1653	1682	1577,1512	NO_2:1512-1327
$[VII]_c$	3344-3313	3016	2920-2856	1653	1653	1599,1574	OH:3550

The ^{1}HNMR spectrum (in $CDCl_3$) for the compound $[VII]_a$, Fig. (3-17) ,showed two sharp singlet signals at δ (2.10, 2.29) ppm which might be a result of six protons of two groups of CH_3, a singlet signal at δ3.84ppm as a result of the six OCH_3 groups protons, also many signals in range between δ(6.68-7.88) ppm for thirteen aromatic protons. Also a sharp signal at δ6.71ppm for one proton could be attributed to the group of OH ring, a singlet signal at δ(8.55)ppm as a result of one proton of the group of (CH=N). Finally a singlet signal at δ (9.70)ppm due to NH group protons was appeared .

The ^{1}HNMR spectrum for the compound $[VII]_c$ (in DMSO-d_6), Figure (3-18) showed two sharp singlet signals appeared at δ (2.10,2.29) ppm as a result of two methyl groups. Many signals appeared in range between (δ6.69 and 7.89) ppm for the aromatic protons, a sharp signal at δ(6.71)ppm for one proton could be attributed to the group of OH ring, a singlet signal at δ(8.37)ppm a result of one of (CH=N) group proton and a signal of singlet at δ (9.48) ppm due to NH group protons.

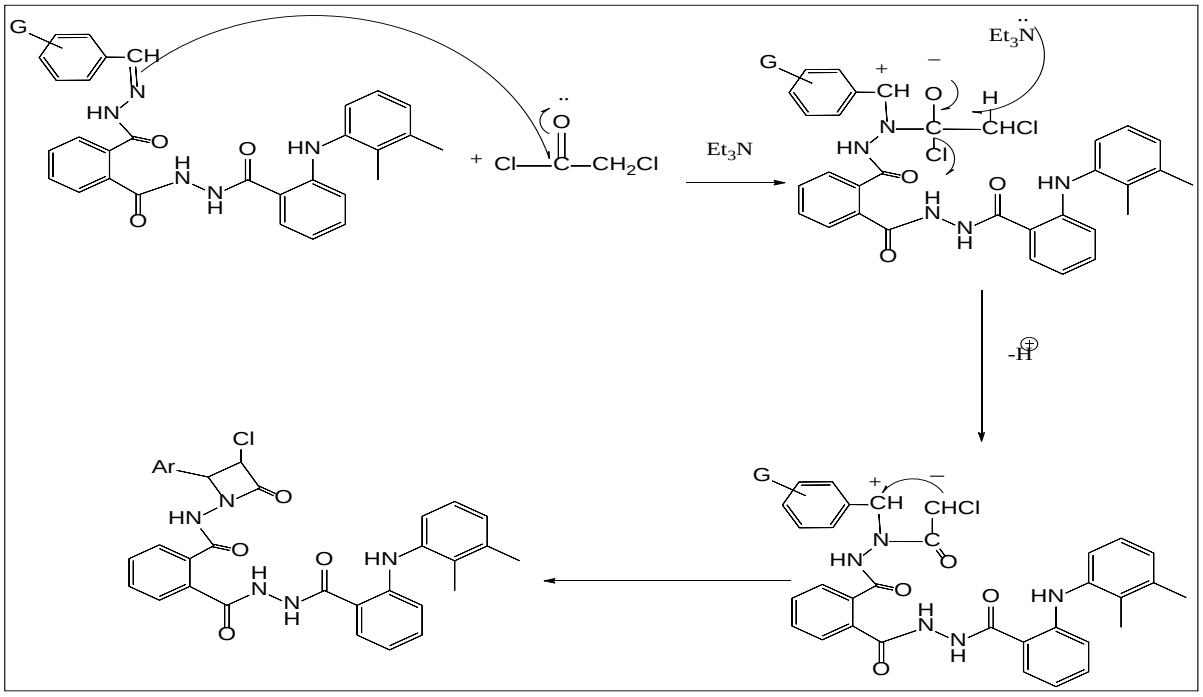
3.1.8. Synthesis of 2-azetidinone[VIII]$_{a-c}$ and characterization

The most widely employed approach for in situate producing of the derivatives of ketene is an acyl chloride simple reaction with a base, in general, a tertiary amine, the conditions of the reaction are usually slight (between -10ºC and room temperatures). The novel 2-azetidinone [VIII]$_{a-c}$ was synthesized via Schiff base[VII]$_{a-c}$ reaction with chloroacetyl chloride, with the triethyl amine[81] present, as in the Equation (3-8):



Equation (3-8)

The suggested mechanism[81] of the desired product is outlined below:



Scheme(3-7)

These compounds $[VIII]_{a-c}$ were characterized for FT-IR, ^{1}HNMR and Mass spectrmetery.

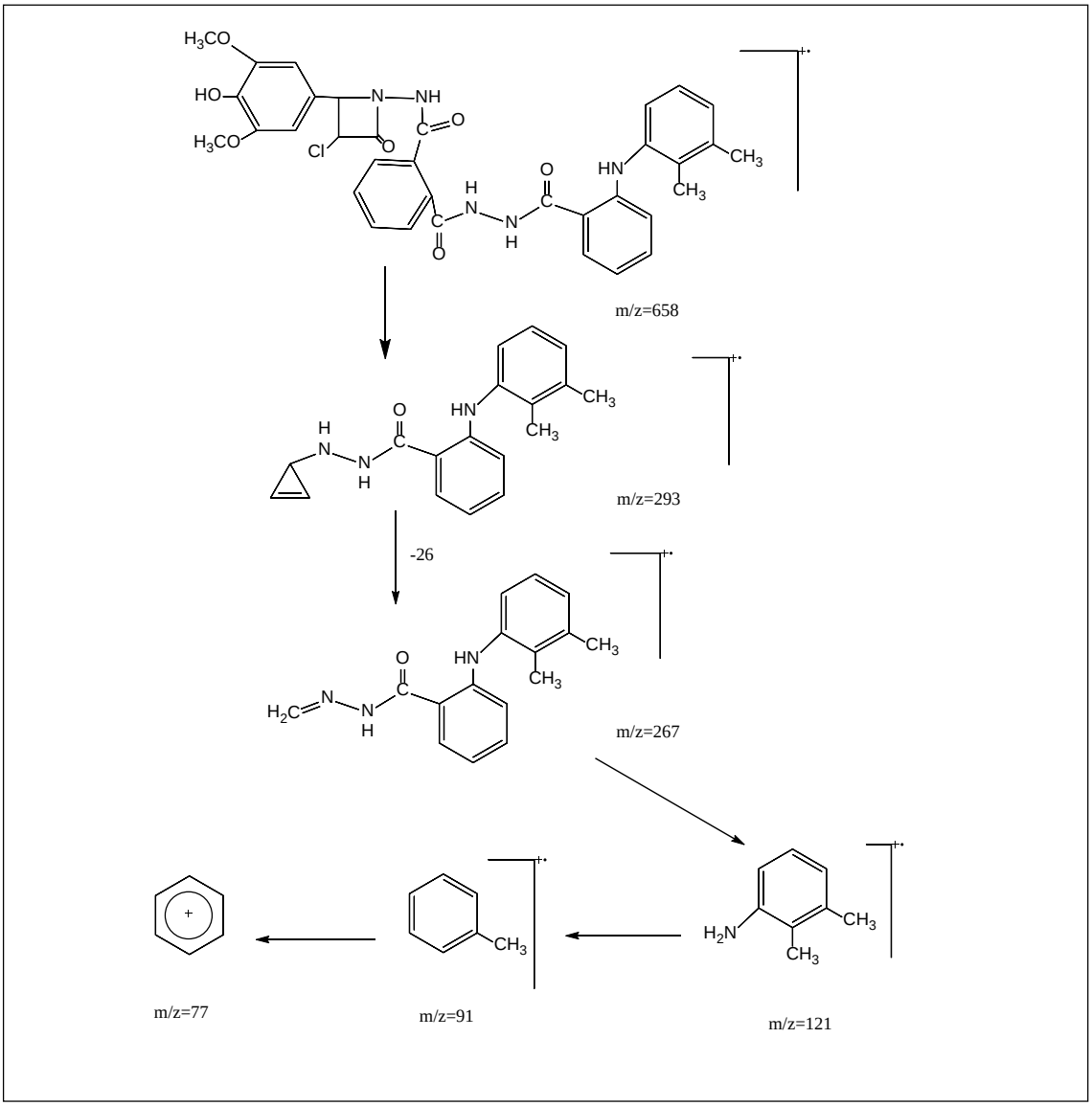
The spectrum FT-IR compound $[VIII]_c$, Figure (3-19) showed disappearance of the group of the azomethine group with the emerging of new absorption stertching band at (1732cm^{-1}) due to group (C=O) in 2-azetidinone ring, a band of stretching at (3514) cm^{-1} as a result of the O-H in aromatic ring, and another peaks have been stated in Table(3-4).

Table (3-4): FTIR spectral of 2-azetidinone $[VIII]_{a-c}$

Com. No.	ν(N-H)	ν(C-H) aromatic	ν(C-H) aliphatic	ν(C=O)	ν(C-Cl)	Others cm^{-1}
$[VIII]_a$	3450-3371	3001	2945-2811	1730	850	OH:3556
$[VIII]_b$	3335-3201	3005	2925-2854	1748	783	NO_2:1508, 1387
$[VIII]_c$	3438-3408	3080	2947-2844	1732	839	OH:3514

The^{1}H-NMR spectra for the compound$[VIII]_c$, Figure (3-20) showed some chemical shifts, a sharp two singlet signals appeared at the range between δ (2.10 and 2.29) for six protons of the methyl groups, signal at δ (3.33) ppm for (CH-CHCl) protons in azetidione ring, also showed a singlet signal at δ3.84ppm for three protons due to OCH_3, and many signals have emerged in the range between δ (6.68 and 7.89) ppm for fourteen aromatic protons, and signals at δ (9.45) ppm which could be three protons of groups NH ,finally a signal at δ (12.97)ppm for one proton OH group tautomeric with NH group[91,92].

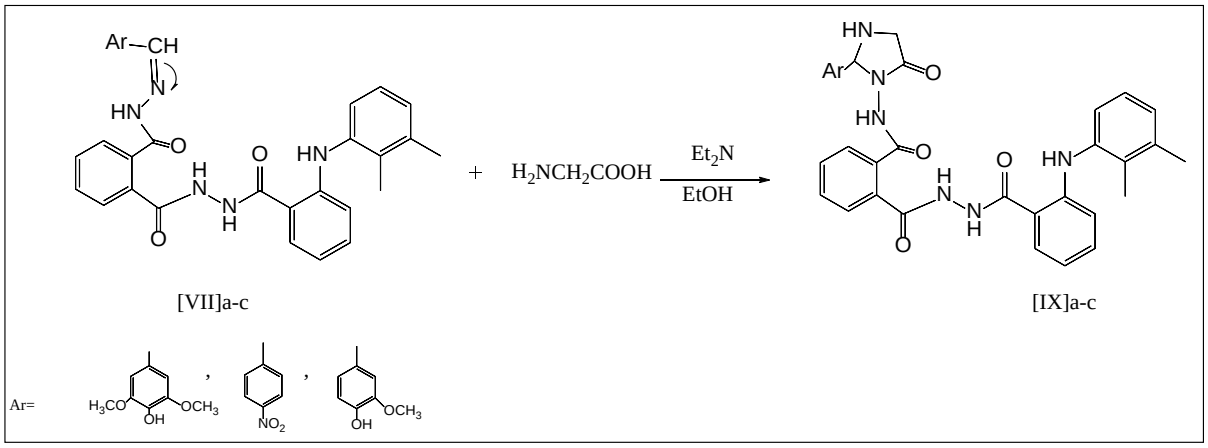
The mass spectra of compound $[VIII]_a$, figure (3-21) showed a molecular ion peaks recorded at m/z=658(20%), 557(18%), 293(100%), 267(50%), 163(30%), 91(12%), and 77(8%), respectively, Scheme(3-8).



Scheme(3-8)

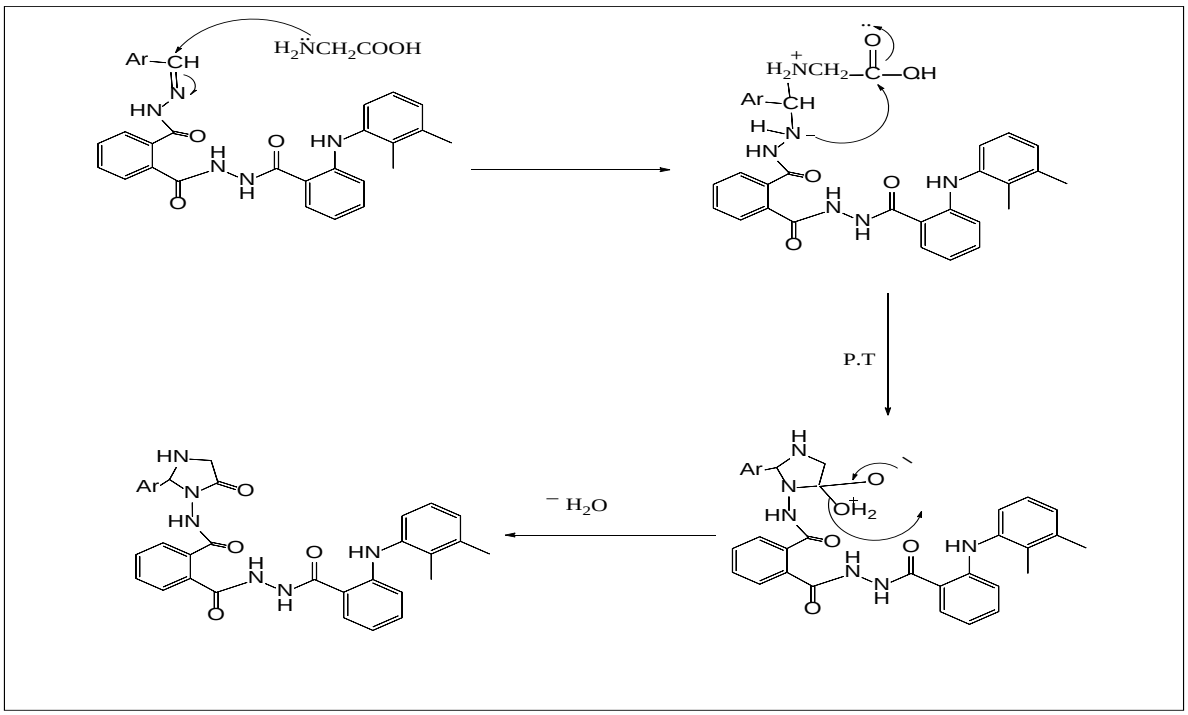
3.1.9. Synthesis and characterization of imidazol-4-one $[IX]_{a-c}$

New imidazole-4-one derivations $[IX]_{a-c}$ have undergone synthesis by refluxing schiff bases $[VII]_{a-c}$ with glycine and triethylamine (Et_3N) in absolute ethanol, Scheme(3-9):



Equation (3-9)

The suggested mechanism[81] of the desired product is outlined below:



Scheme (3-9)

Those complounds $[IX]_{a-c}$ structures were indicated through FT-IR, ^{1}H-NMR spectroscopy.

The FT-IR absorption spectrum of the compound $[IX]_c$, Figure (3-22) showed disappearance of the group of imin with the emerging a new characteristic of absorption due to imidazole ring[92] in a range between (1736 - 1722) cm^{-1} that was given to the stretching band of C=O in imidazole-4-one ring, a band of stretching at (3410-3313) cm^{-1} as a result of the groups of N-H. All the spectral data for compounds $[IX]_{a-c}$ were stated in Table(3-5).

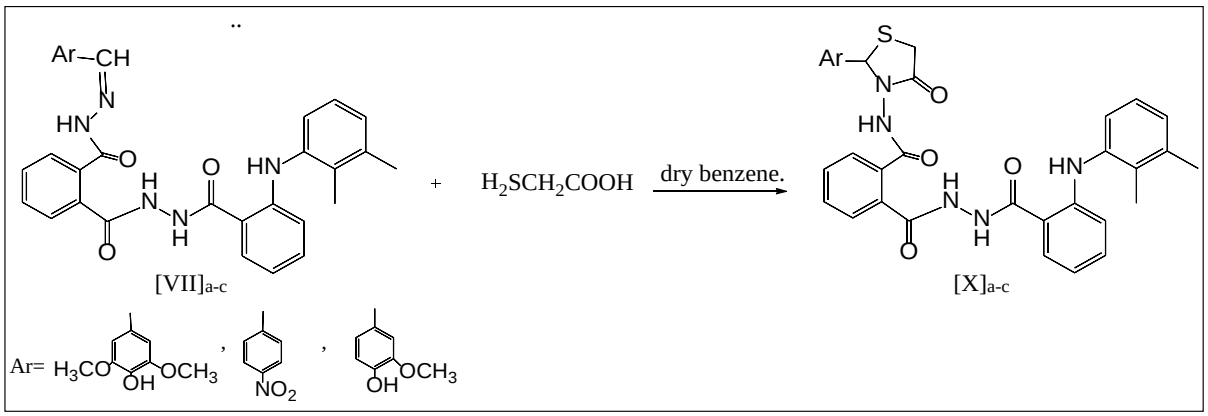
Table (3-5): FTIR spectral of imidazolidon-4-one $[IX]_{a-c}$

Comp. Number	ν(N-H)	ν(C-H) aromatic	ν(C-H) aliphatic	ν(C=O)	ν(C-N)	Others cm^{-1}
$[XI]_a$	3410-3170	3012	2933-2843	1736,1610	1336	OH:3550
$[XI]_b$	3425-3167	3008	2897-2844	1722,1604	1338	NO_2:1550,1300
$[XI]_c$	3344-3313	3008	2922-2862	1738	1331	OH:3558

The spectra of ^{1}HNMR (in DMSO) of $[IX]_c$, Figure (3-23), showed two singlet at δ (2.09 and 2.29)ppm that attributed to the six protons of two groups of the CH_3, also two signals at δ(3.43-3.45)ppm have been assigned to two protons of CH_2 imidazolidin-4-one ring, also singlet signal of two methoxy groups at δ(3.82)ppm, a singlet signal of OH group at δ (6.59)ppm, many signals at δ (6.41 -7.91)ppm due to fourteen aromatic protons[93,94]. Furthermore, sharp singlet signals at δ (11.12ppm) might be a result of NH group protons.

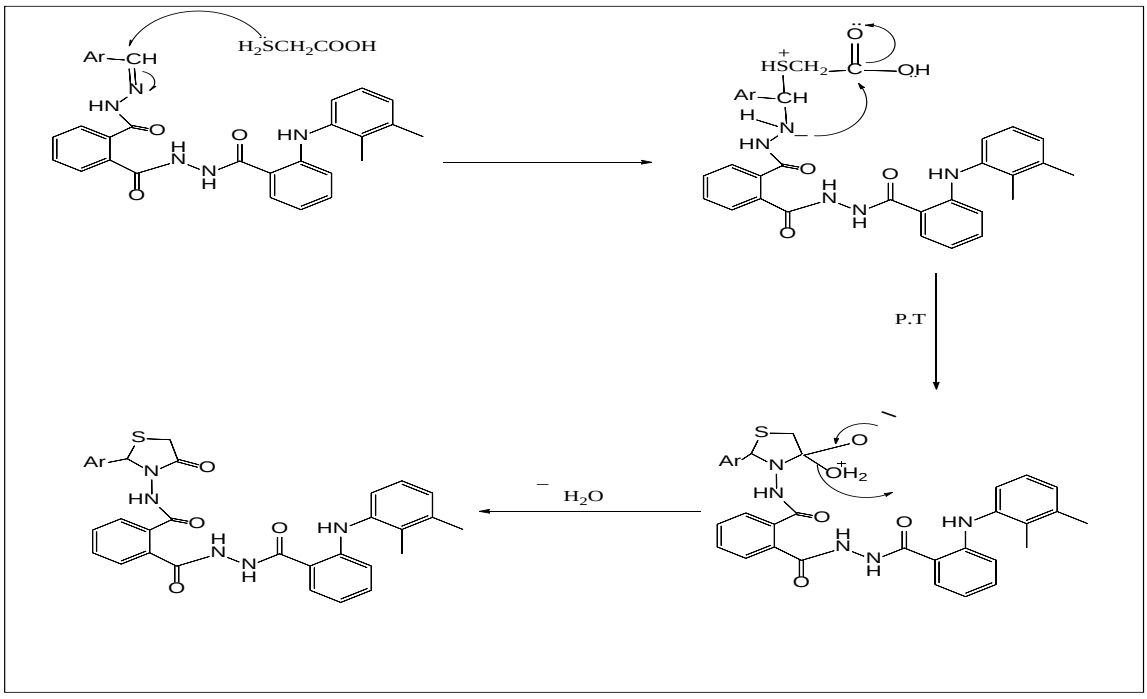
3.1.10. Synthesis and characterization of Thiazolidin-4-one $[X]_{a-c}$

The new thiazolidin-4-ones derivatives $[X]_{a-c}$ have undergone synthesis via refluxing equimolar amounts of the compounds $[VII]_{a-c}$ with the thioglycolic acid in dry benzene, Equation(3-10).



Equation (3-10)

The suggested mechanism[81] of the desired product is outlined below Scheme(3-10):



Scheme (3-10)

These compounds $[X]_{a-c}$ structures were identified by their melting points, FT-IR, and ^{1}HNMR spectroscopy.

FT-IR absorption spectra of the compound $[X]_b$, Figure (3-24) showed the emerging of a new absorption characteristic to thiazolidin-4-one ring in the region (1745-1732) cm^{-1} that is assigned to the stretching of C=O, a stretching band at the range between (3311, 3195cm^{-1}) due to N-H groups this was the most characteristic proof on cyclization process success. All the spectral data for compounds $[X]_{a-c}$ are stated in Table(3-6).

Table (3-6): FTIR spectral thiazolidin-4-one $[X]_{a-c}$

Comp. Number	ν(N-H)	ν(C-H) aromatic	ν(C-H) aliphatic	ν(C=O)	ν(C-S)	Others cm^{-1}
$[X]_a$	3313	3016	2920-2858	1653	748	OH:3421
$[X]_b$	3311	3014	2970-2862	1651	752	NO_2:1508,1333
[X]c	3336	3049	2918-2804	1635	739	OH:3504

The ^{1}H-NMR spectra of the compound $[X]_b$, (in DMSO-d_6), Figure (3-25) showed two signal of methyl groups detected at δ (2.10, 2.29)ppm, a singletrelated to CH_2 thiazolidin-4-one ring appeared at δ 3.87 ppm, signal at δ7.37ppm as a result of the proton of (S-CH-N), multiplet signals at δ (6.68 - 7.87)ppm could be equivalent to fifteen protons that were assigned to the aromatic ring. Furthermore, a sharp singlet signal at δ (9.45ppm) for NH group protons[(94)].

3.2. Biological Activity

Mefenamic acid has analgesic action three times more than that of aspirin. However, like all classical NSAIDs It was found to increase the risks of gastrointestinal ulcers. A series of amic acid derivatives of mefenamic acid were synthesized with the aim of inhibitting topical gastrointestinal toxicity of mefenamic acid. This study involves evaluation antibacterial activity, cytotoxic effect, and toxicity *in vivo* of new amic acid and their derivatives of mefenamic acid.

3.2.1 Antibacterial activity

The antibacterial activity of some synthesized compounds was examined (*in vitro*) against *Staph.aureus (G+), Bacillus subtilisa (G+), Klebsiella pneumoniae (G-), and E.coli (G-)* based on the approach of agar diffusion[82]. Most of derivatives showed the high biological activity or low biological activity against bacteria, the data are listed in Table(3-7) . Compound $[VIII]_c$ showed good inhibition against *Staphylococcus aureus*, this could be related to the presence of azetidin-2-one(β-lactam), while compound $[X]_c$ showed slightly active against *Klebsiella pneumonia* and *E.coli*.

Table(3-7) : anti-bacterial activity of some synthesized compounds

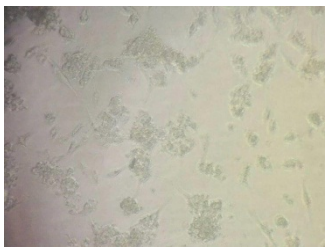
Comp. No.	*Zone of inhibition in millimeter*			
	Staphyl ococcus aureus	*Bacillus sabtilis*	*Klebsiella pneumoniae*	*Escherichis coli*
[III]c	12	13	17	11
[IV]c	11	5	12	11
[VIII]c	26	13	15	11
[IX]c	12	13	15	12
[X]c	13	13	5	5

3.2.2 Anticancer screening

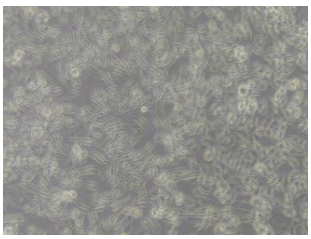
The cytotoxicity of new amic acid and their derivatives of mefenamic acid ($[III]_c$, $[IV]_c$, $[VII]_c$, $[VIII]_c$, $[IX]_c$)was studied against cancer cell line of MCF7 [14-15] for 48 hrs. Cytotoxicity assay of this synthesized compounds ($[III]_c$,$[VII]_c$, and $[VIII]_c$) caused good inhibitory effect on the growth of cell line except compounds ($[IV]_c$, and[$IX]_c$). Table (3-8). Compound $[III]_c$ showed more than 50% inhibition for MCF-7and compound $[VII]_c$ less than 50% inhibition for MCF-7cell line.

Table (3-8): The inhibition of cells growth of some synthesized compounds µl/well

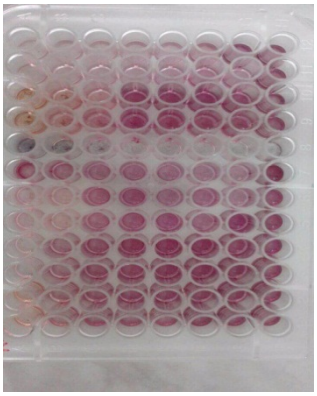
Comp.	inhibition of cells growth forMCF-7
$[III]_c$	53.1%
$[IV]_c$	0%
$[VII]_c$	31.1%
$[VIII]_c$	10.1%
$[IX]_c$	0%



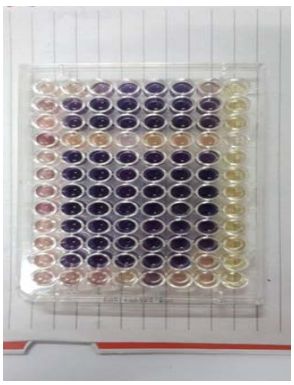
A



B



C



D

A: Images of well (L20B) after Staining
B: Images of well (L20B) before Staining
C: Image of plate after Staining
D: Image of plate before Staining

3.2.3. The Test of Acute Toxicity

The news synthesized compounds derivatives from mefenamic acid exhibit no toxicity signs, mortality and behavior, for two weeks mice.There showed no change any contrasts in weights of(mice that have been measured daily) between the control group and groups that have been treated, there were no any modifications in the behaviors of mice, nor any symptoms of toxicity were noticed after 14 days. At the end some mice have been sacrificed with cervical dislocation and organs such as liver, kidneys, and heart have been weighed. Moreover, visual evaluation of organs of mice showed normal appearance. Some amic acid and their derivatives of mefenamic acid were screened for their antibacterial, anticancer activity and acute toxicity test[82].We need for further investigation to know mechanism by which the heterocyclic compounds act to give a potent cytotoxic effectthat might get the mefenamic derivatives an attention for being promise anticancer product.

Suggestions for future work

1 - Synthesis of new Schiff base by the reaction of the ester[V]with thiosemicarbazide.

2 - Synthesis of new heterocyclic derivatives by the reaction of Schiff bases with different anhydride to form seven memberd ring.

3 - Synthesis of new fused rings from the synthesized compounds.

4 - Study the liquid crystalline properties of the synthesized compounds.

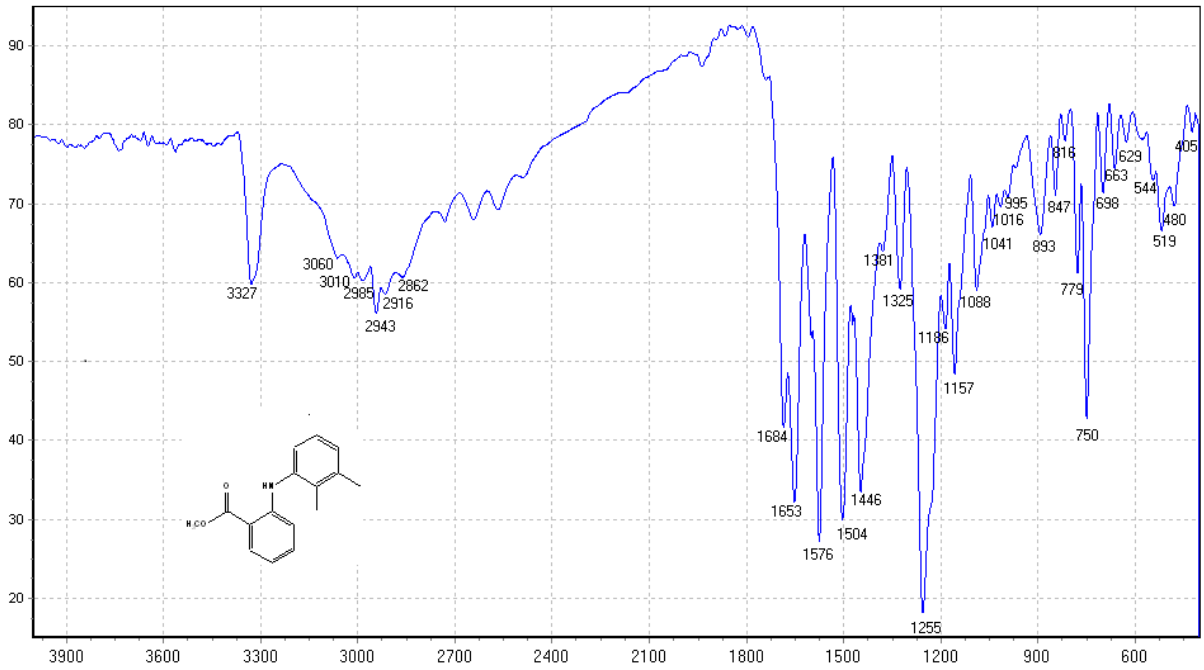


Figure : (3-1) FT-IR Spectrum of compound[I]

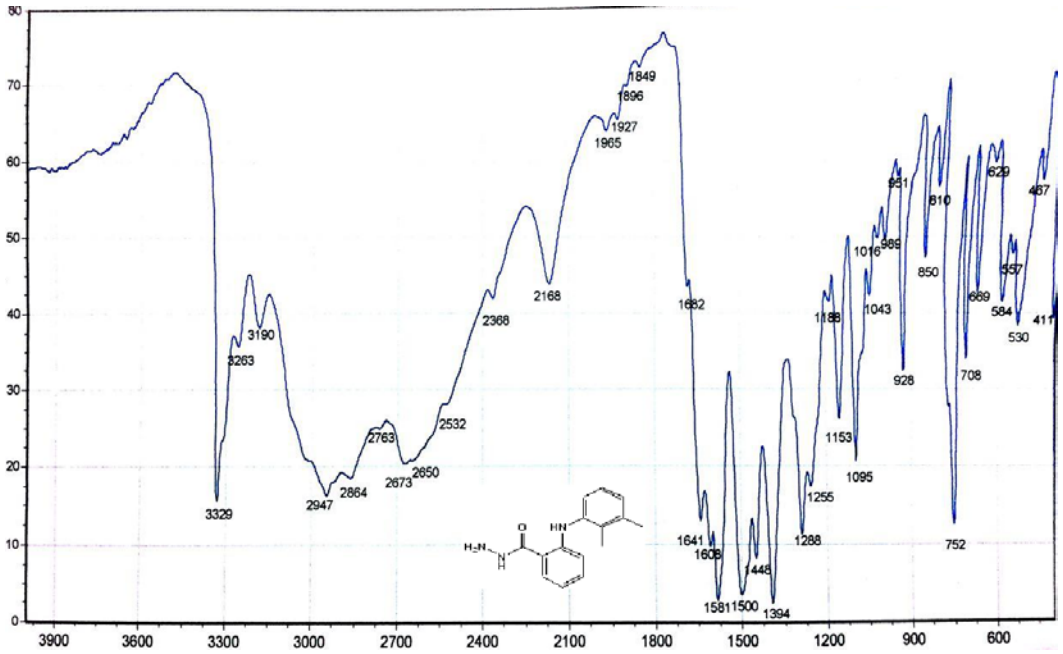


Figure: (3-2) FT-IR Spectrum of compound [II]

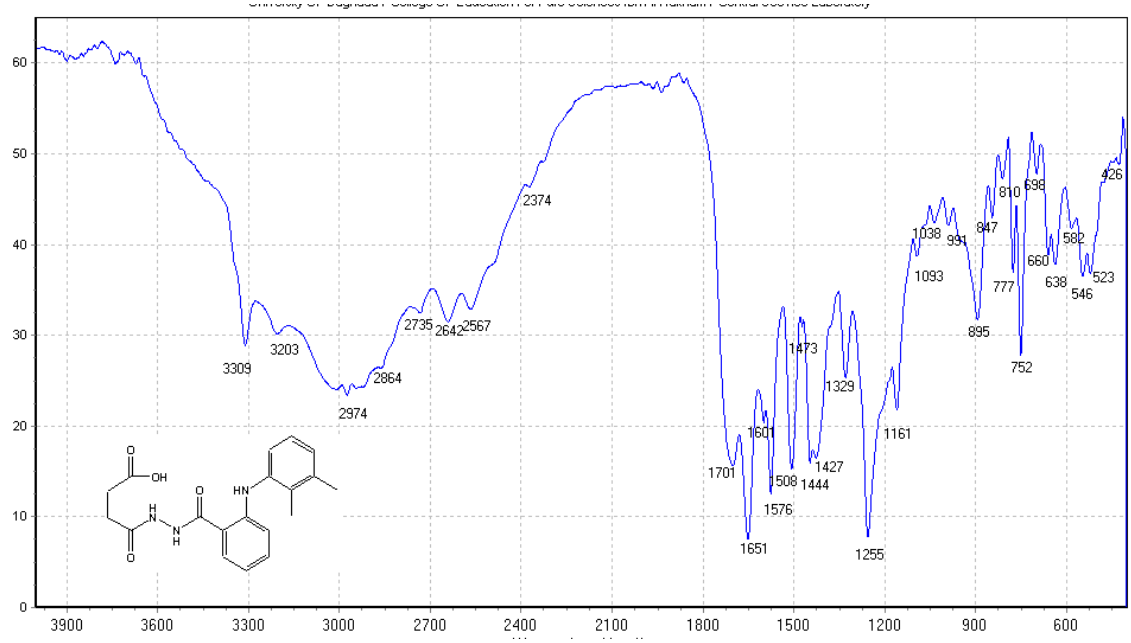


Figure: (3-3) FT-IR Spectrum of compound $[III]_b$

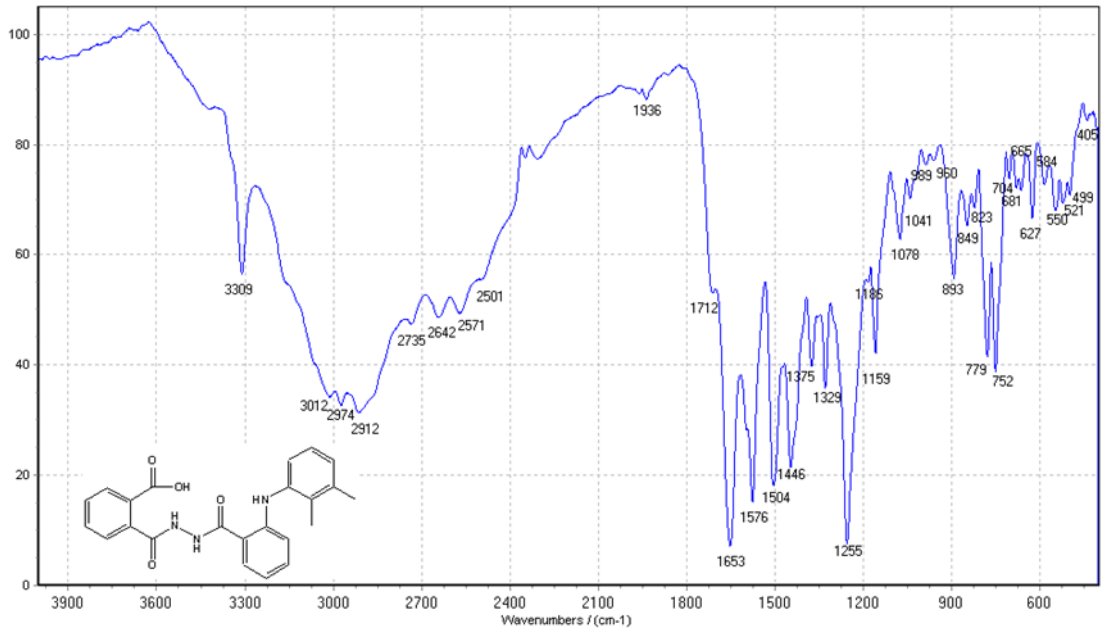


Figure : (3-4) FT-IR Spectrum of compound$[III]_c$

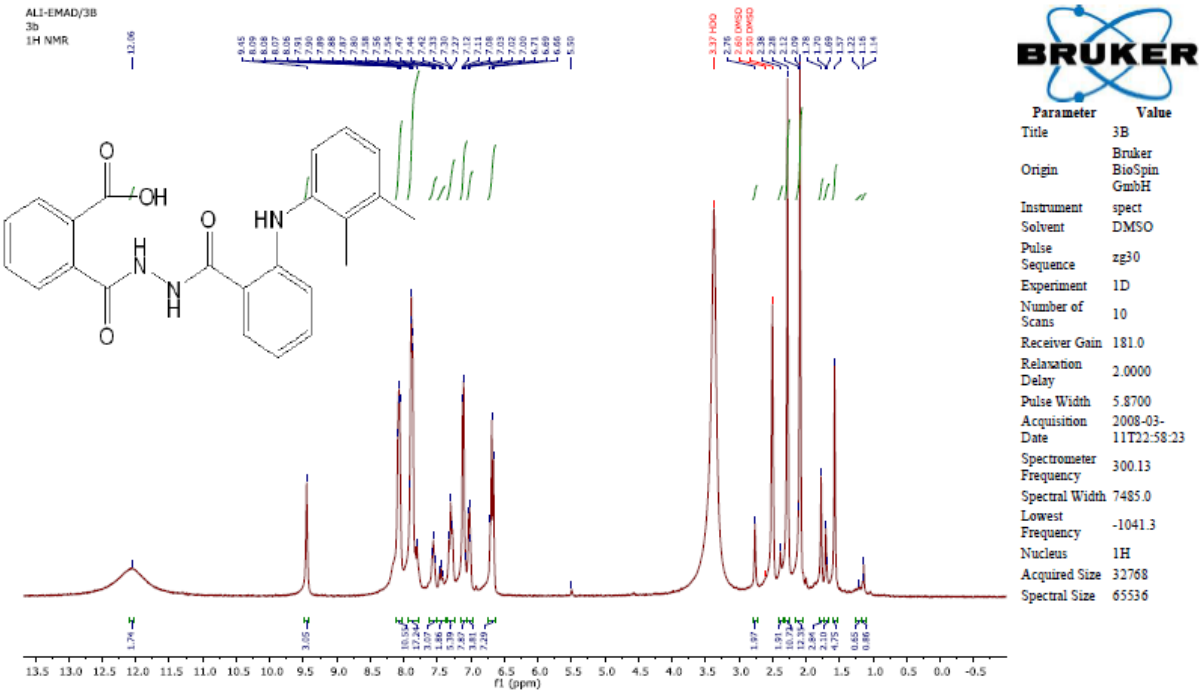


Figure : (3-5) ^{1}HNMR Spectrum of compound[III]$_{c}$

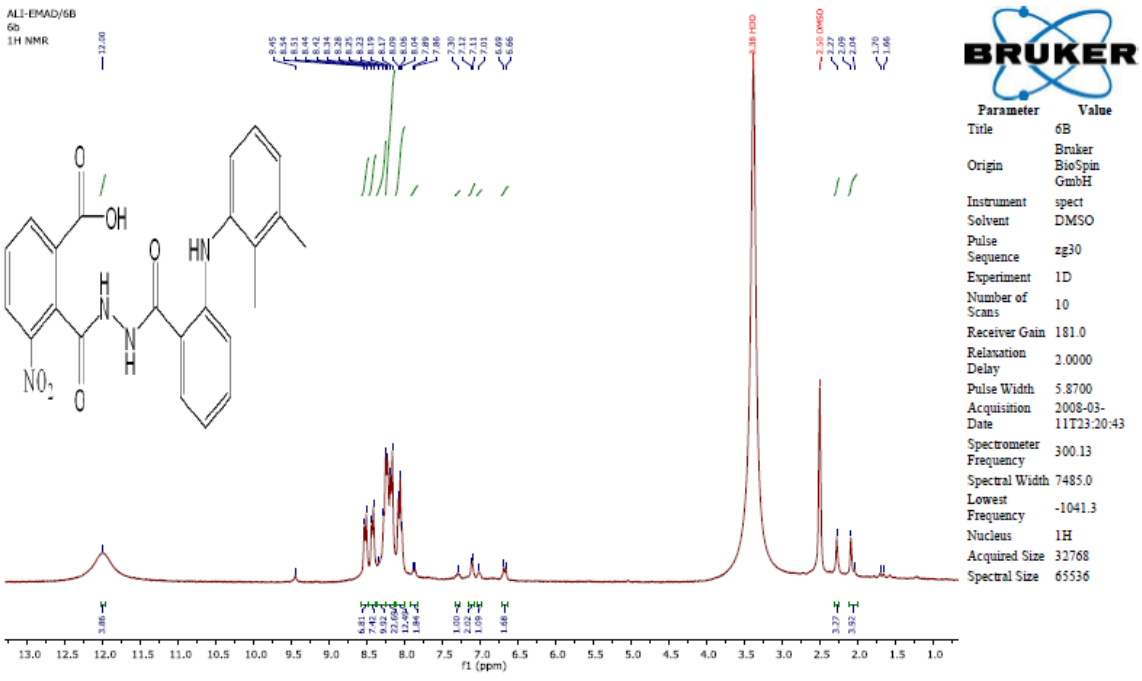


Figure : (3-6) ^{1}HNMR Spectrum of compound [III]$_{d}$

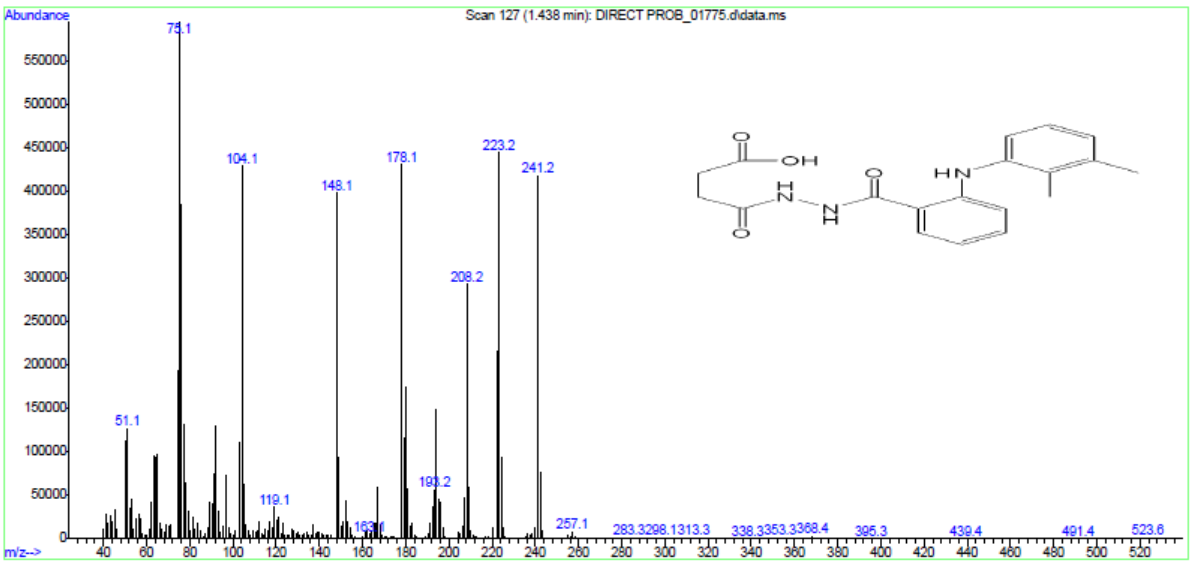


Figure:(3-7) Mass spectrum of compound $[III]_b$

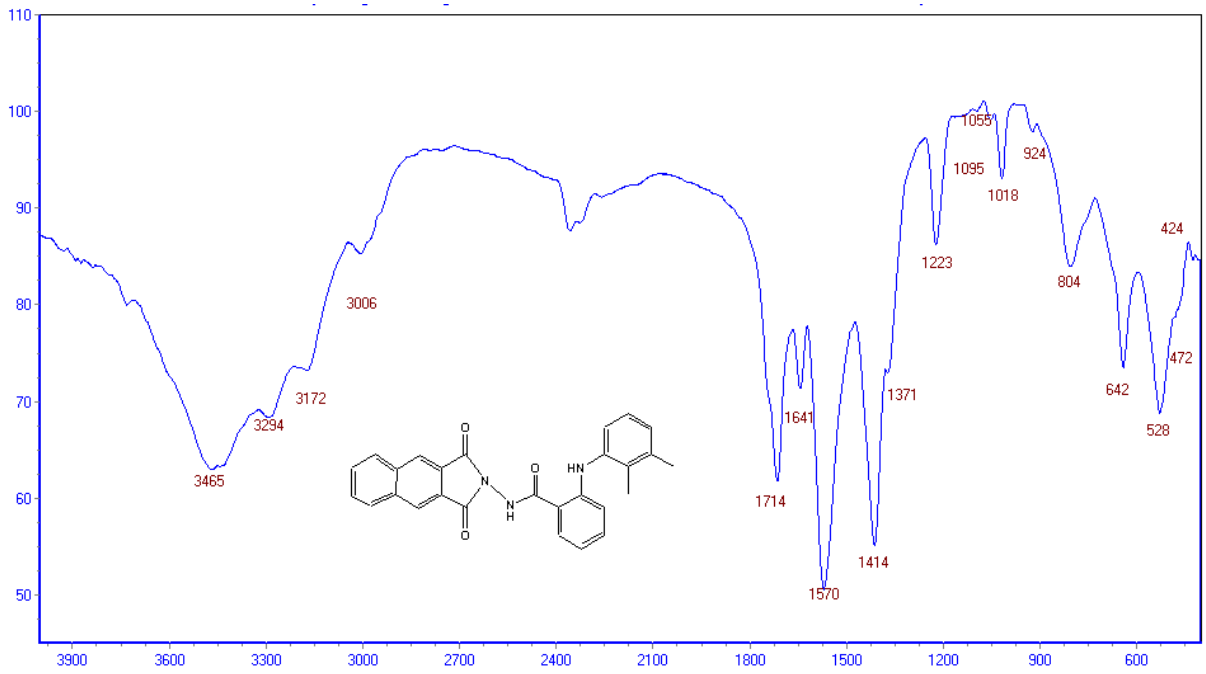


Figure : (3-8) FT-IR Spectrum of compound$[IV]_e$

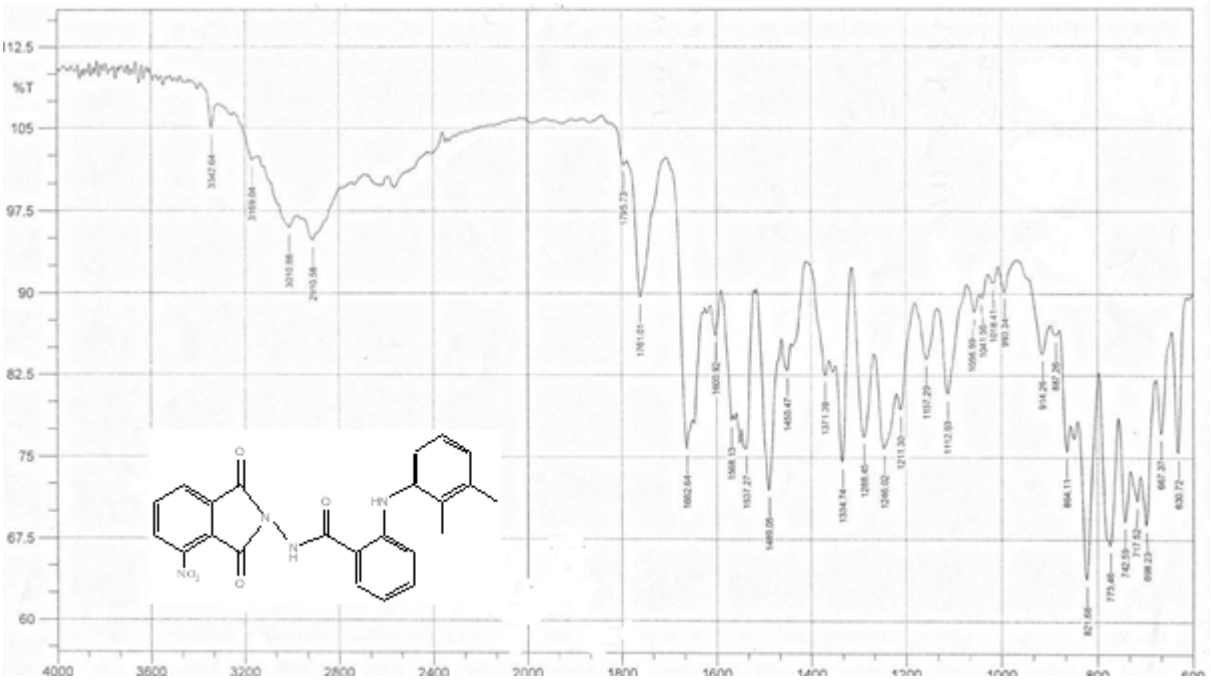


Figure : (3-9) FT-IR Spectrum of compound$[IV]_d$

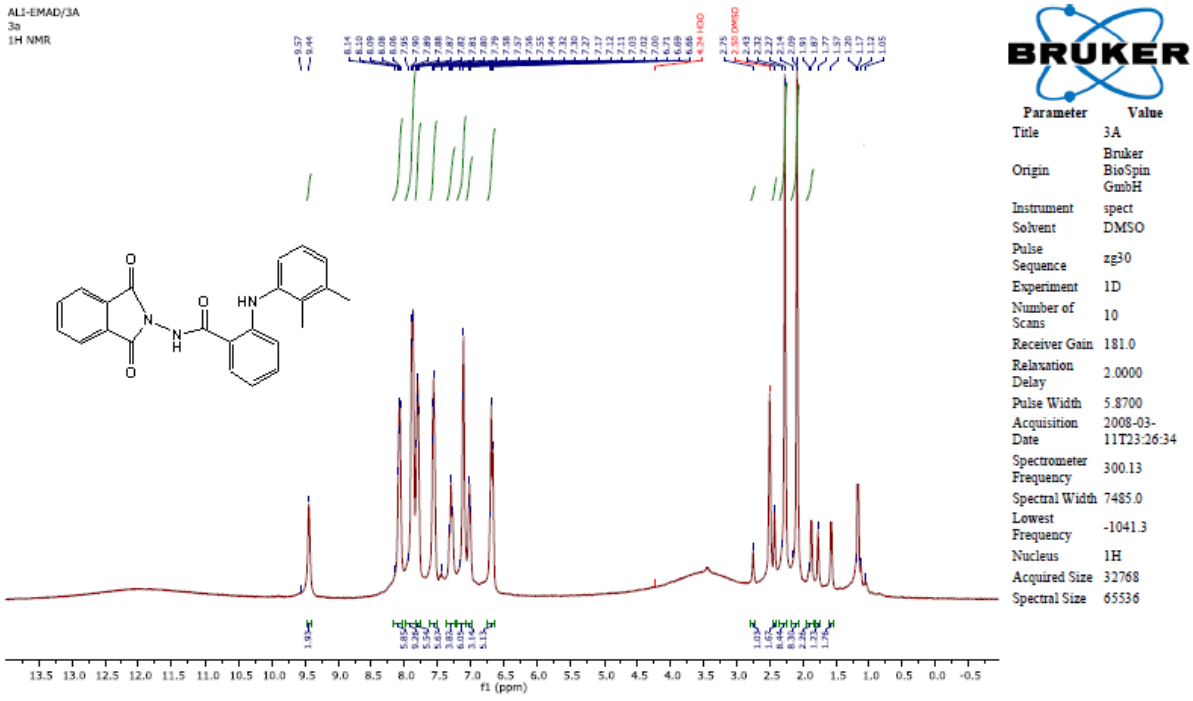


Figure : (3-10) ^{1}HNMR Spectrum of compound$[IV]_c$

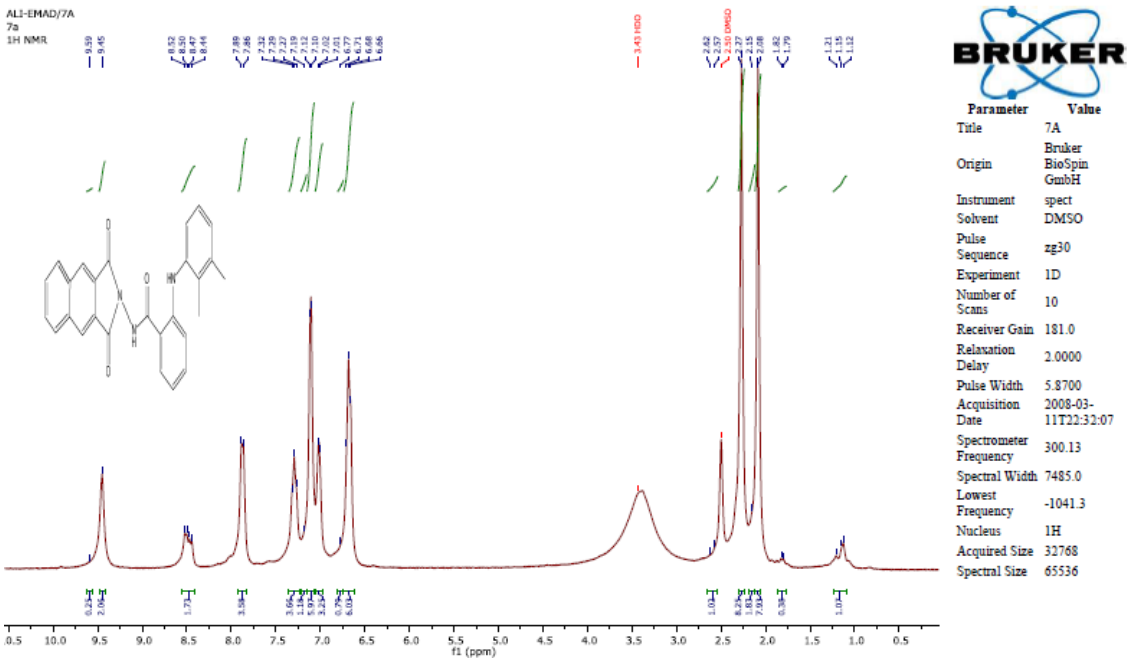


Figure : (3-11) ^{1}HNMR Spectrum of compound [IV]e

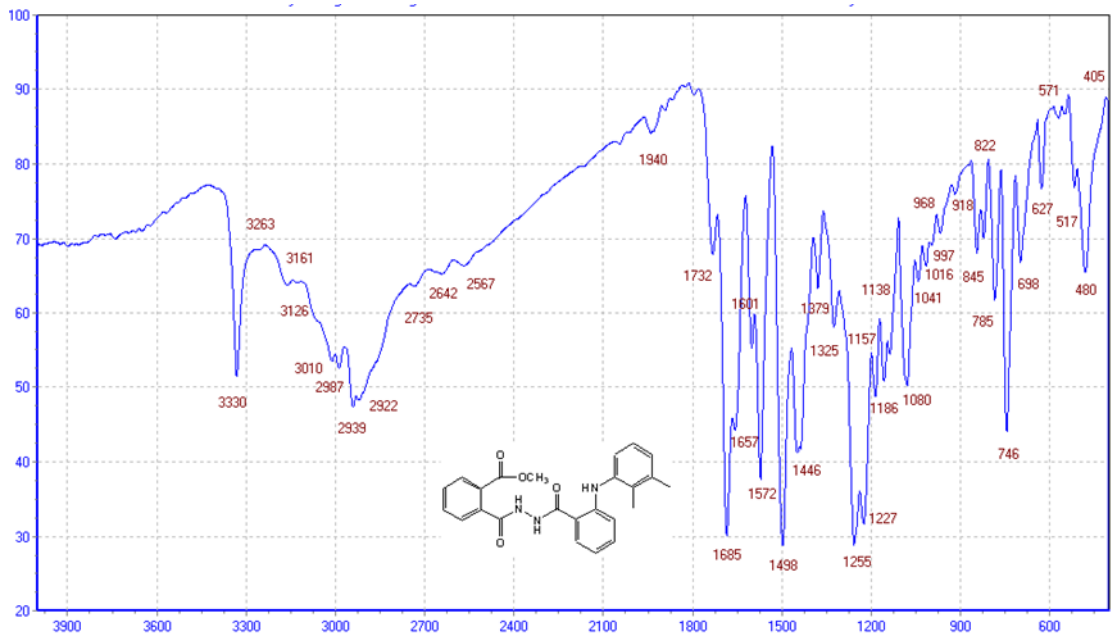


Figure : (3-12) FT-IR Spectrum of compound [V]

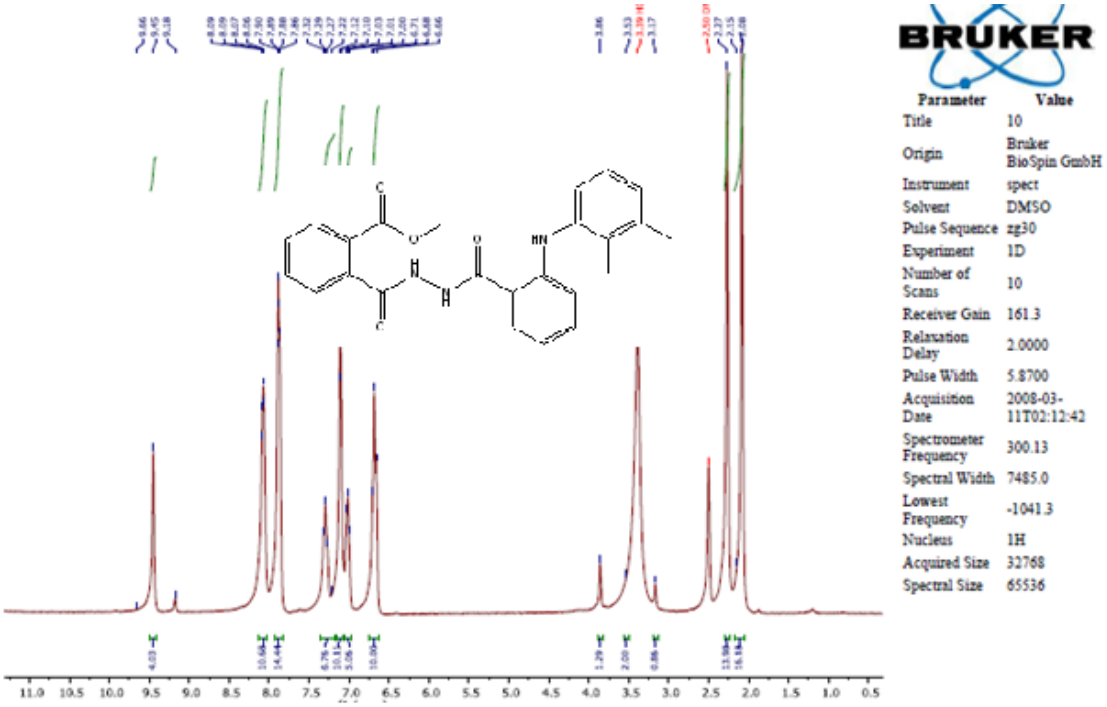


Figure : (3-13) ^{1}HNMR Spectrum of compound [V]

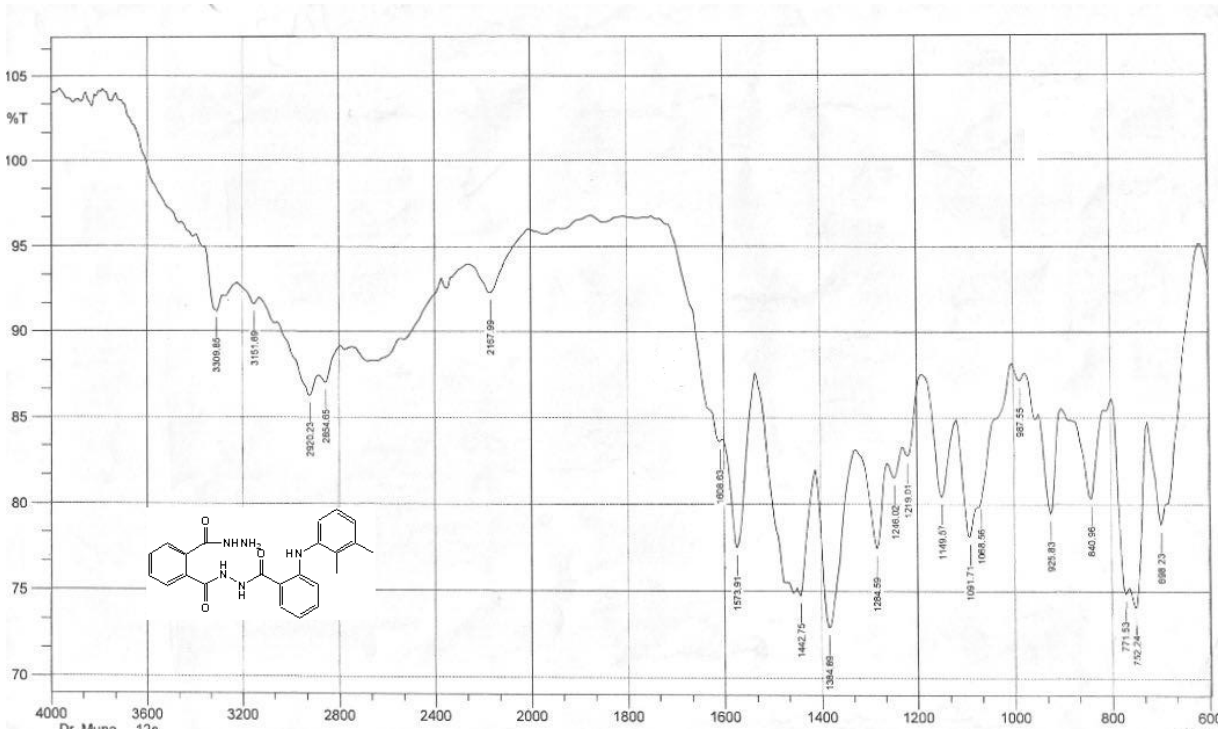


Figure : (3-14) FT-IR Spectrum of compound[VI]

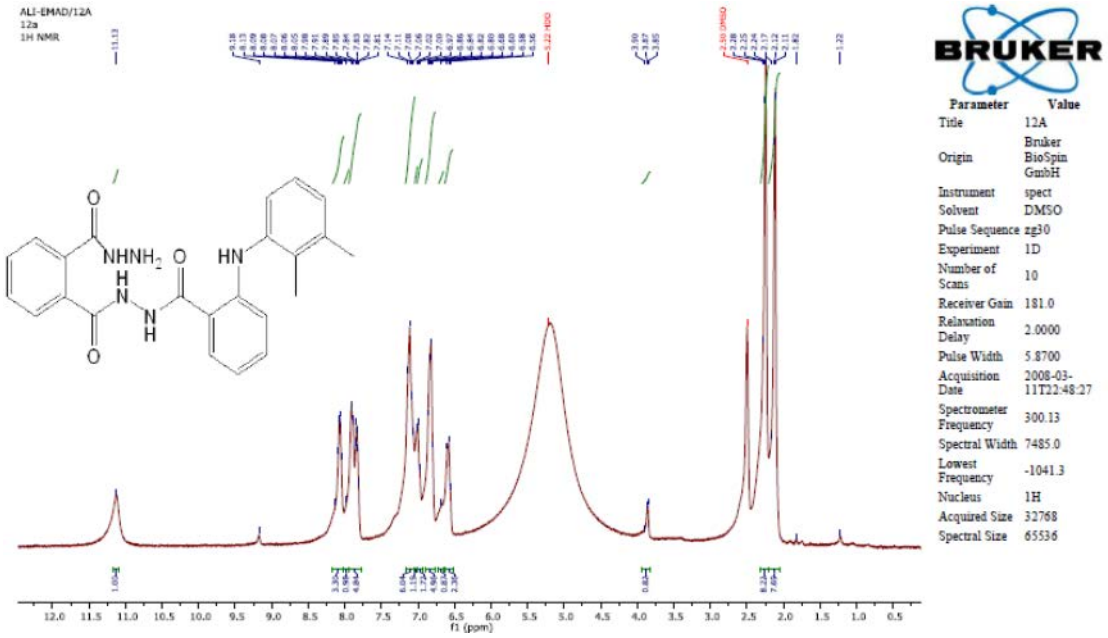


Figure : (3-15) ^{1}HNMR Spectrum of compound[VI]

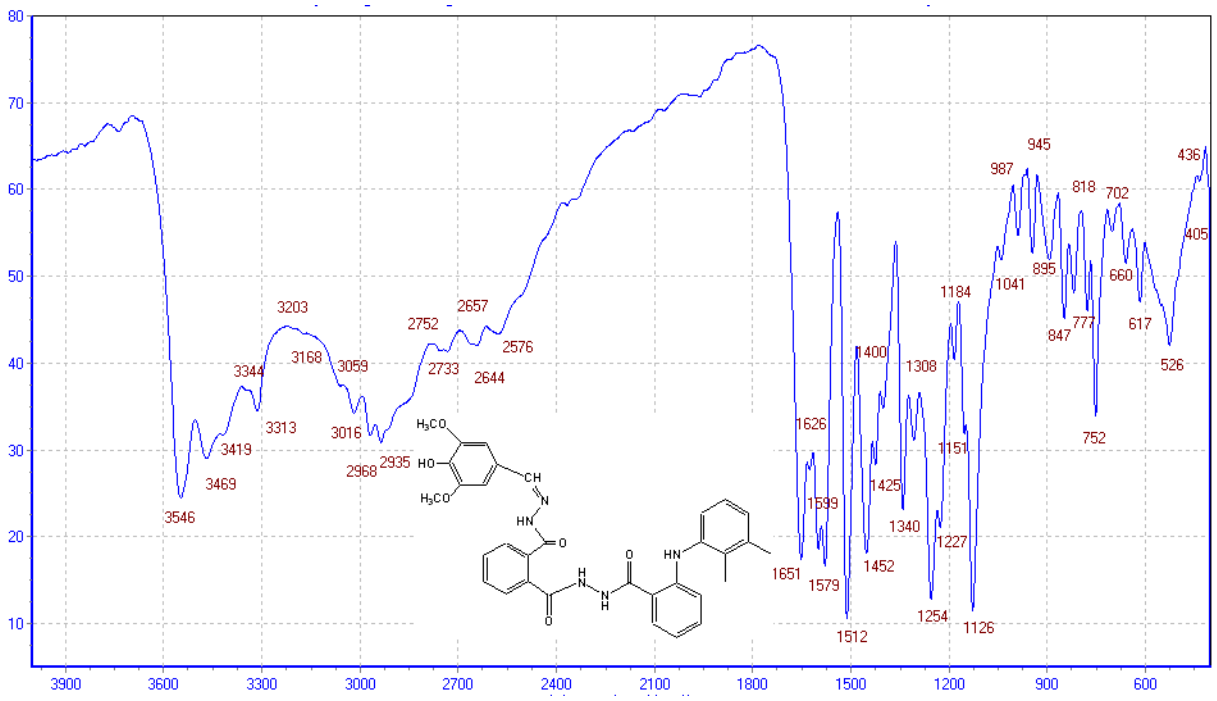


Fig : (3-16) FT-IR Spectrum of compound[VII]a

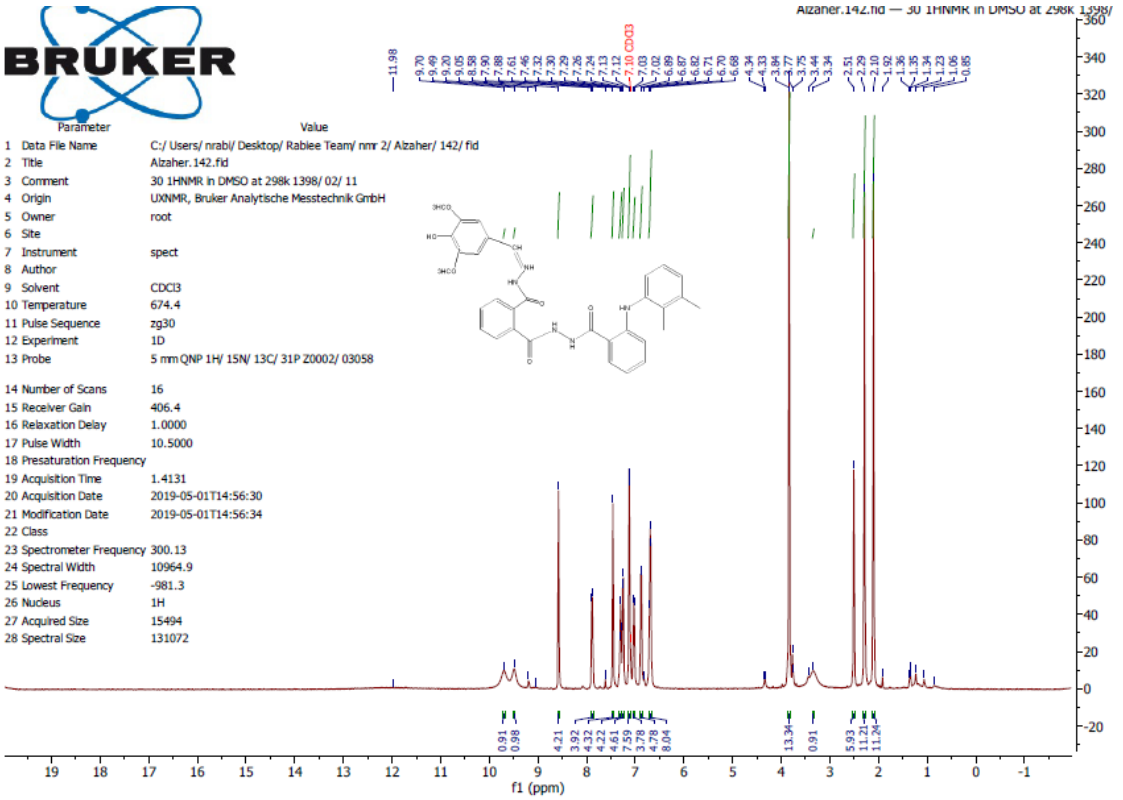


Figure : (3-17) ^{1}HNMR Spectrum of compound [VII]$_a$

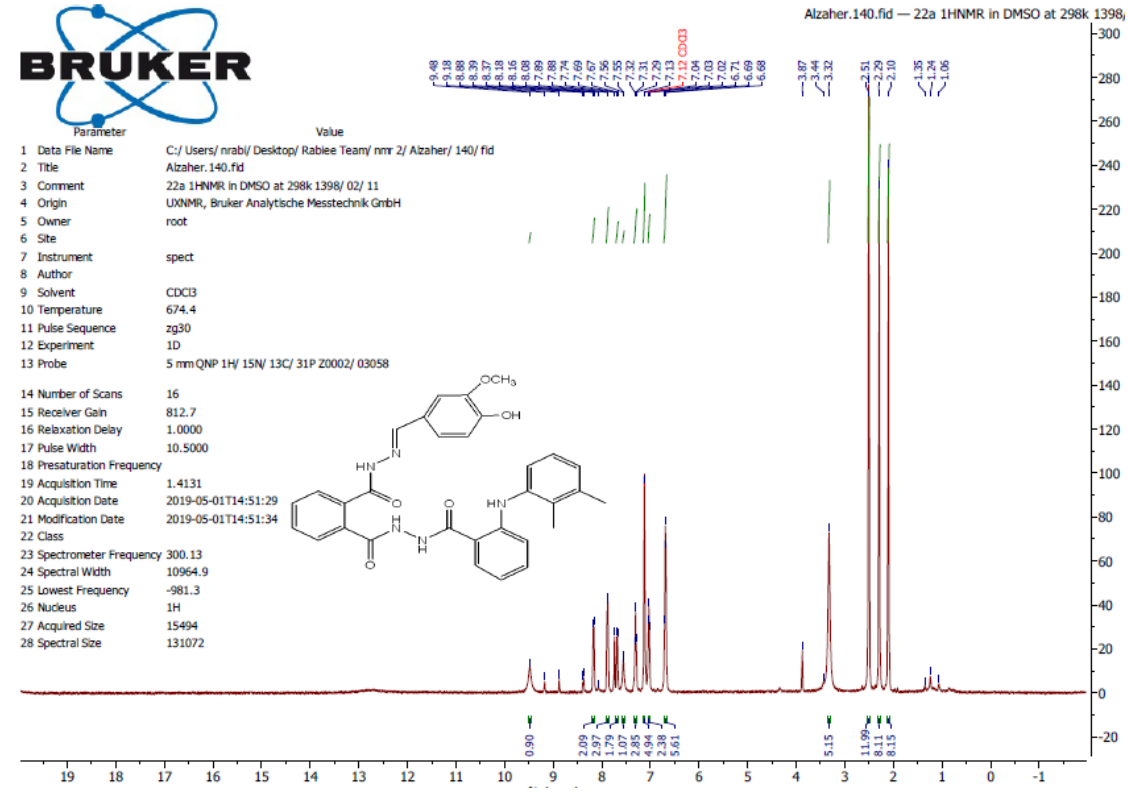


Figure : (3-18) ^{1}HNMR Spectrum of compound[VII]$_c$

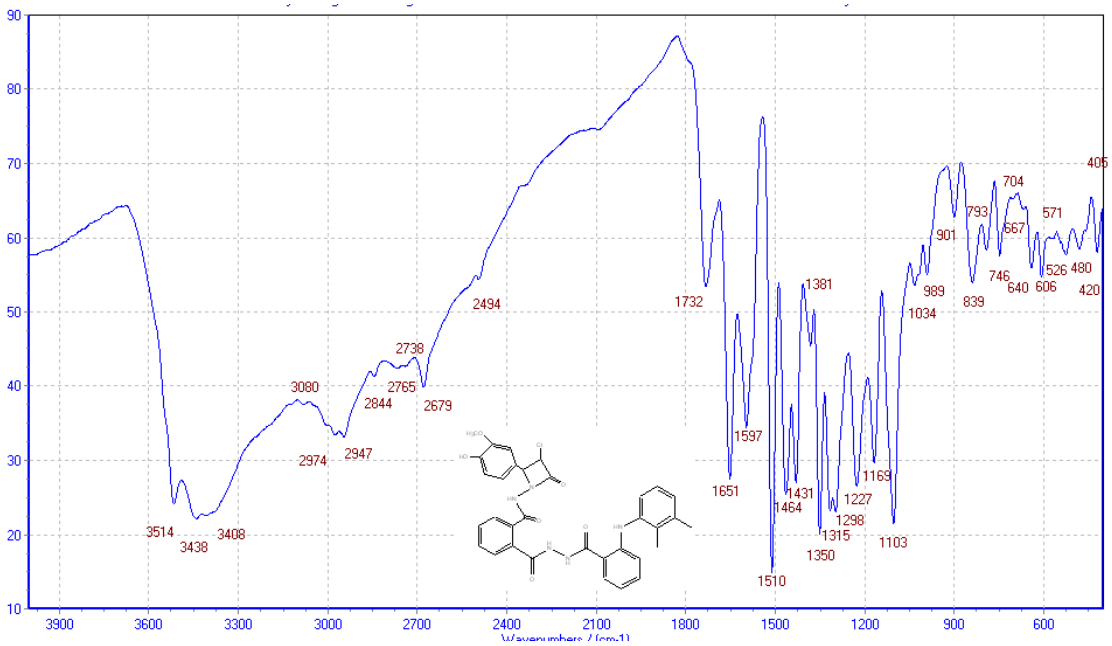


Figure : (3-19) ^{1}HNMR Spectrum of compound[VIII]$_{c}$

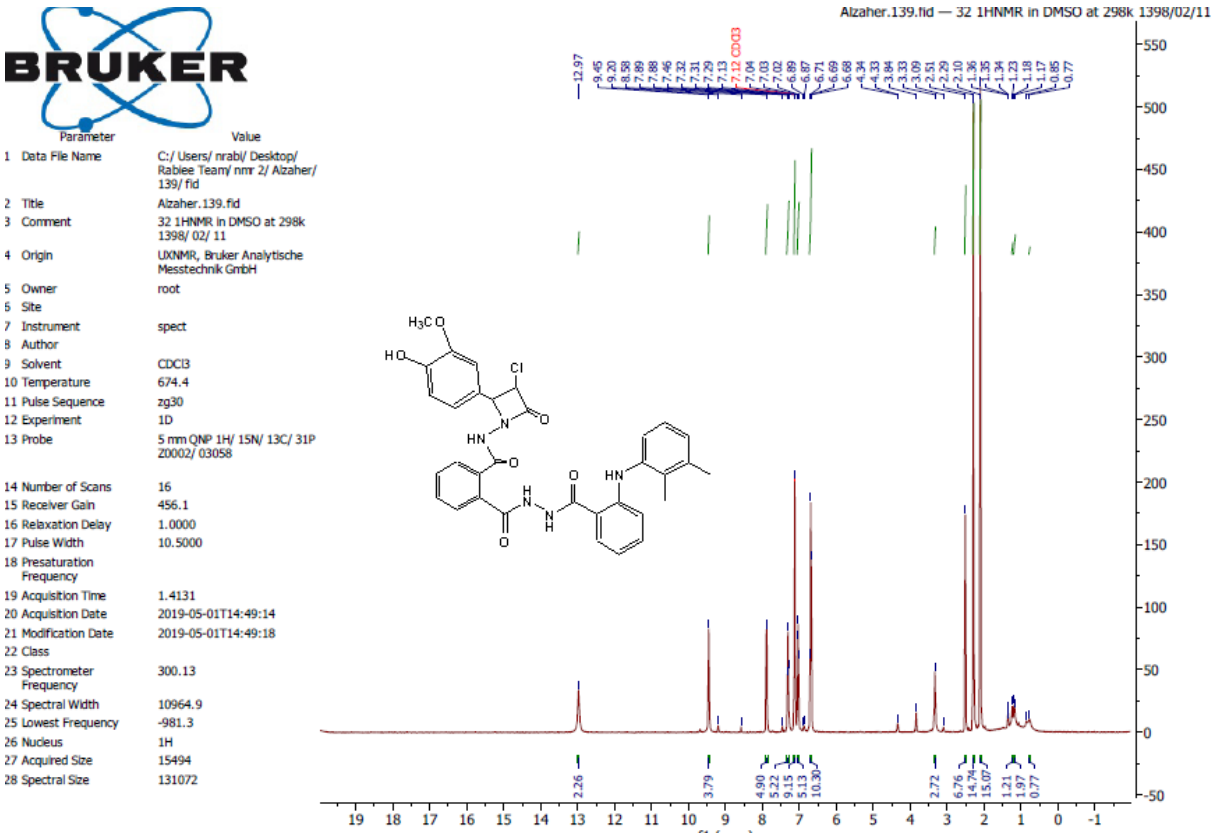


Figure: (3-20) ^{1}HNMR Spectrum of compound[VIII]$_{C}$

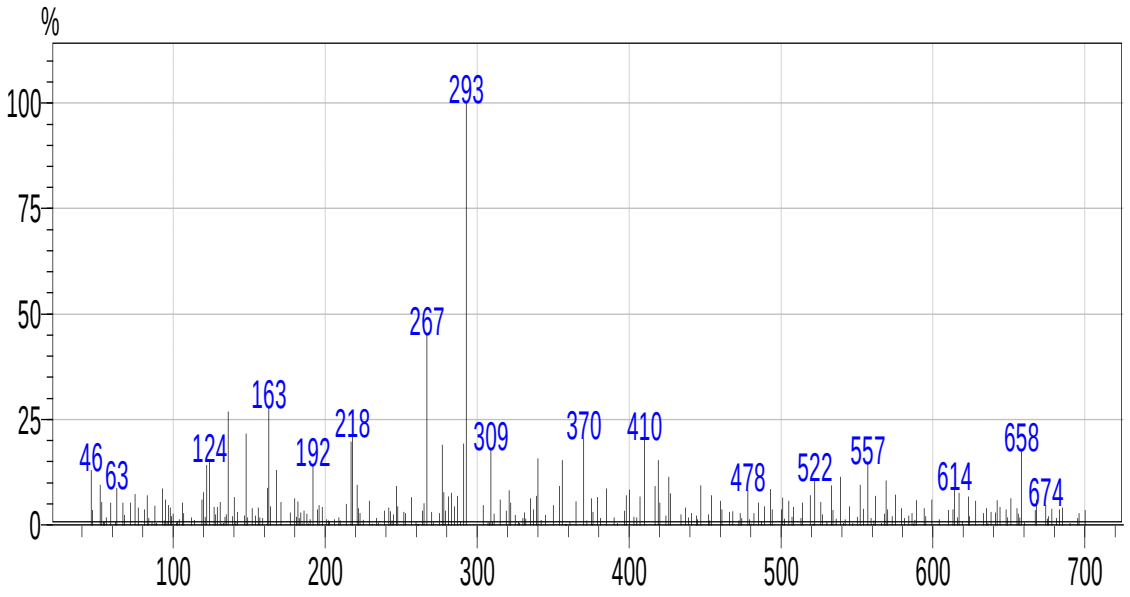


Figure.:(3-21) Mass spectrum of compound [VIII]$_a$

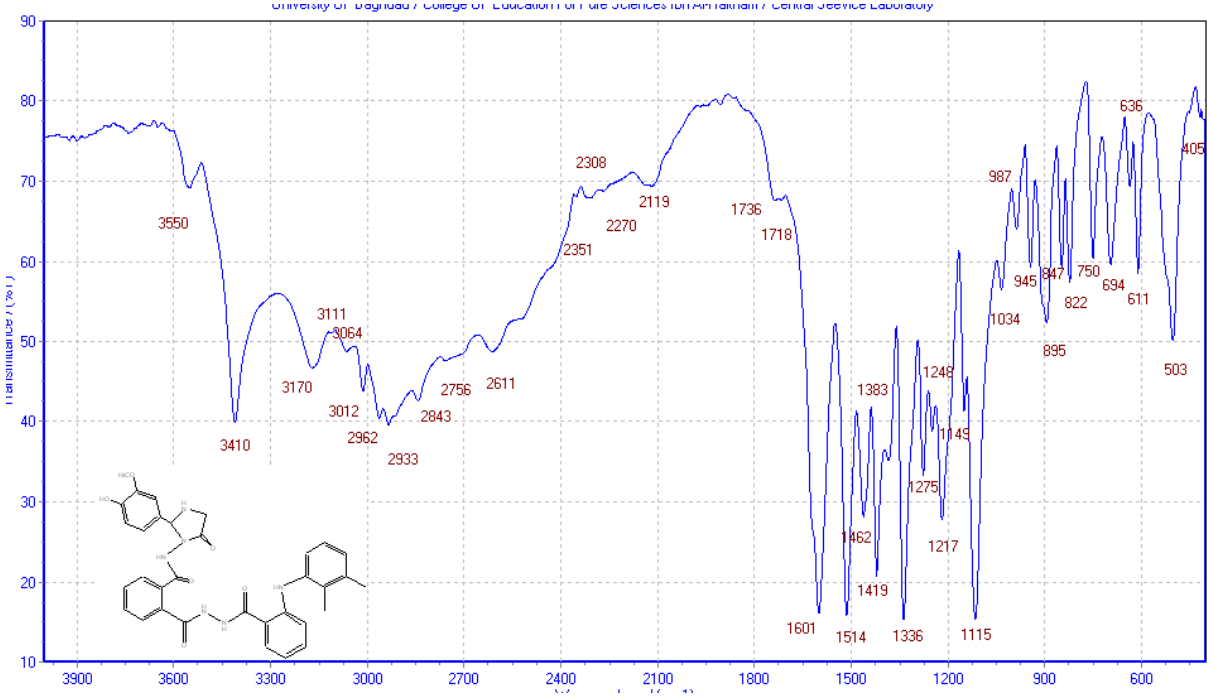


Figure : (3-22) FT-IR Spectrum of compound [IX]$_c$

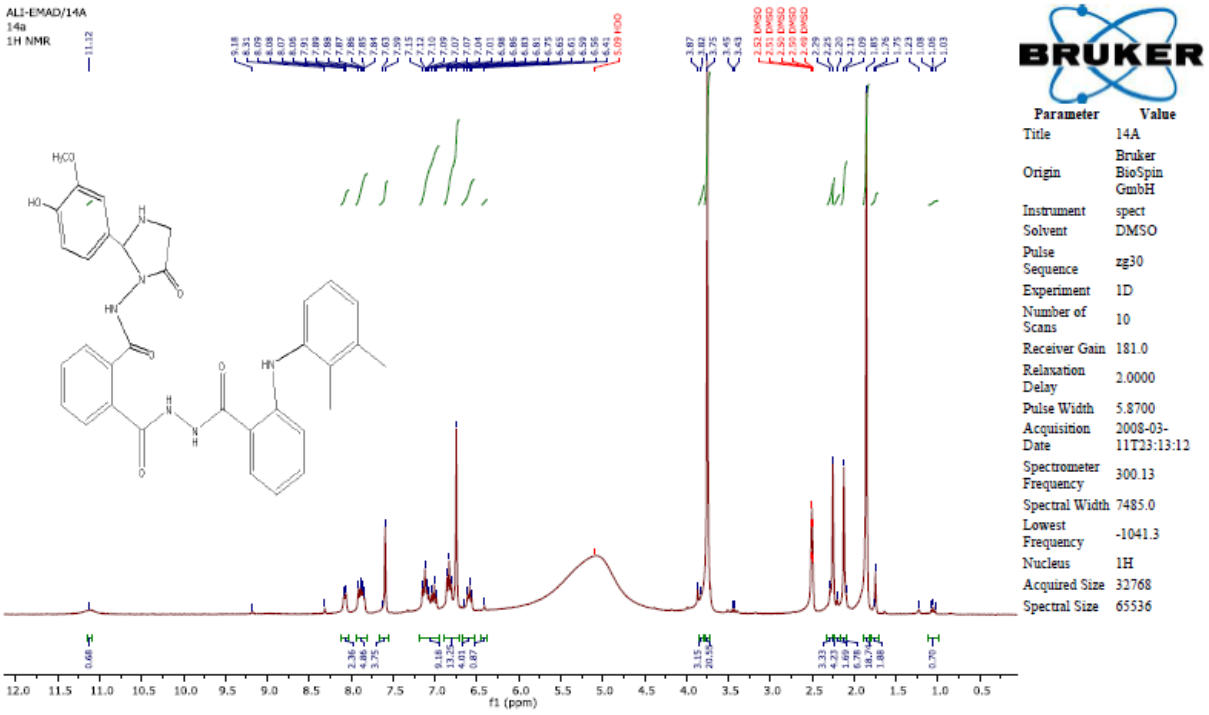


Figure : (3-23) ^{1}HNMR Spectrum of compound[IX]$_c$

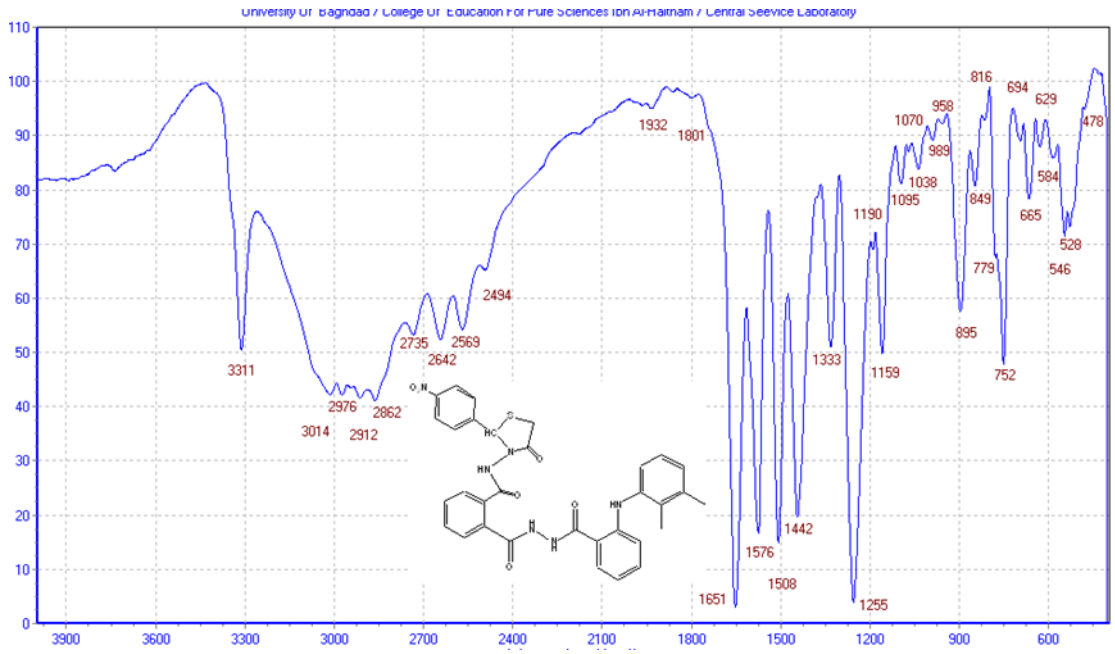


Figure : (3-24) FT-IR Spectrum of compound[X]$_b$

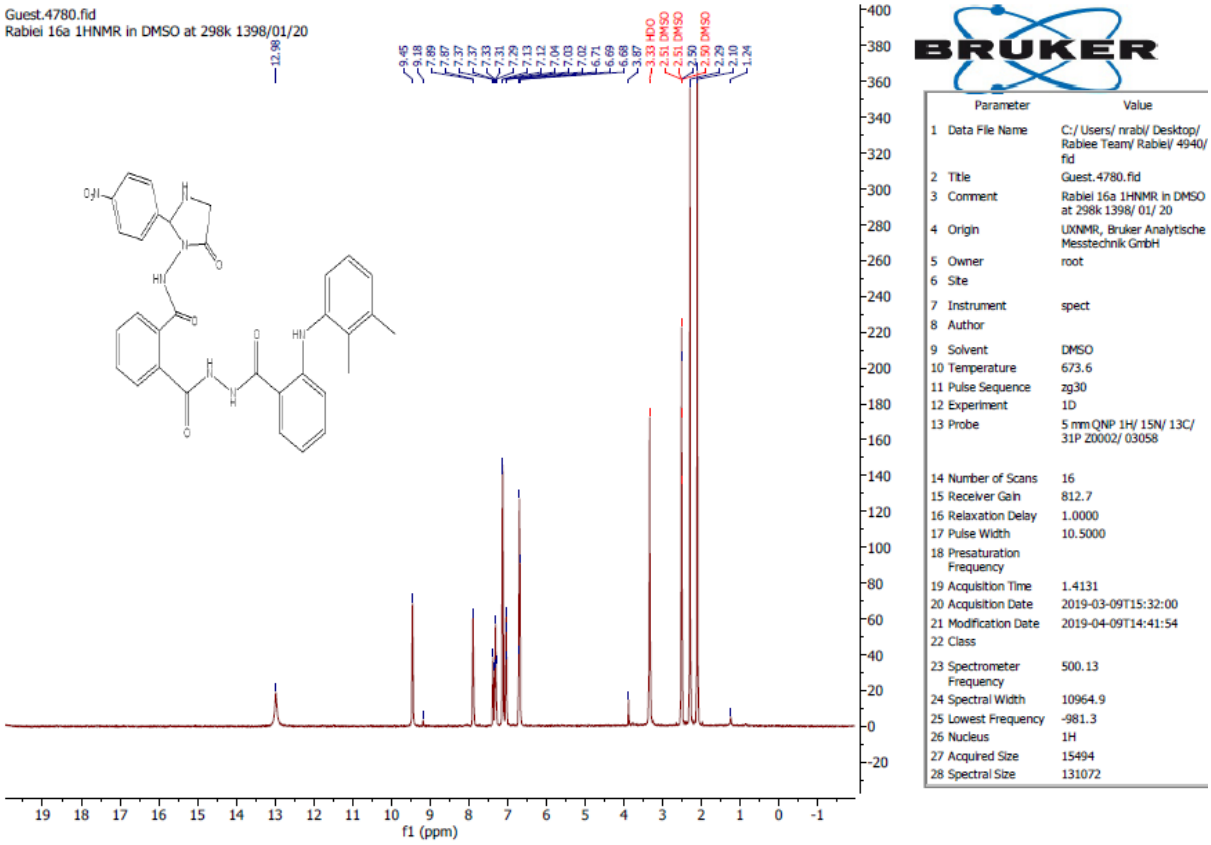


Figure : (3-25) ^{1}HNMR Spectrum of compound$[IX]_b$

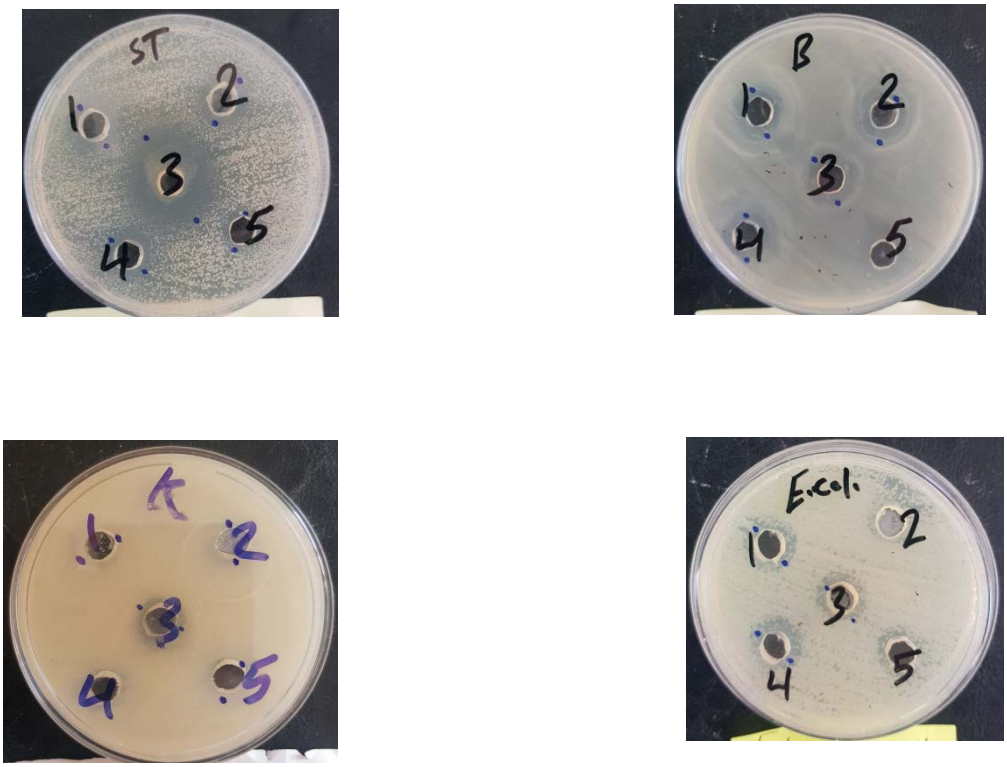


Figure (3-26)Antibacterial activities of compounds *against Staphylococcus* , *Bacillus* ,*Klebsieua pheumoiae* , and *E. coli*.

Conclusions

1-The new amic acids compounds can be synthesized (in a good yield) by the reaction of acid hydrazid of mefenamic acid with different anhydrides in acetone. These amic acids used as starting material to synthesis new derivatives.

2- Dehydration of the synthesized amic acid by acetic anhydride and anhydrous sodium acetate producing the corresponding imide compounds.

3- The esterification of hydroxyl groups of amic acid to produce corresponding new ester.

4- The acid hydrazide compound can be prepared by condensation of ester compound with hydrazine hydrate in absolute ethanol.

5- The Schiff base compounds can be prepared by condensation of acid hydrazide with substituted aromatic aldehydes in ethanol using glacial acetic acid as a catalyst .

6-The new azetidin-2-one derivatives were synthesized from the reaction of Schiff bases with chloroacetylchloride in the presence of triethylamine in dry benzene.

7-The new imidazolidin-4-one derivatives were synthesized by the reaction of Schiff base with glycine in the presence of triethylamine in ethanol.

8-The new thiazolidin-4-one derivatives were synthesized from the reaction of Schiff bases with thioglycolic acid in dry benzene.

9- The structure of the synthesized compounds characterized using TLC, elemental analysis (C.H.N-S) and spectral data (FTIR, ^{1}HNMR and Mass spectrometry). These data give a good evidence for the formation of the suggest structure to these compounds.

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الخلاصة

يمثل حامض الأميك صنف رئيسي من المركبات العضوية ويستخدم بعض مشتقاته في صناعة الأدوية ، وبالتالي فإن التعديل على حامض الأميك المشتق من حمض الميفيناميك الذي ينتج باستخدام عدة خطوات لتحضير مشتقات جديدة والتي يمكن ان تمتلك طيف واسع من النشاط البيولوجي وآثار جانبية أقل من المركب الأصلي.

ولهذا الغرض، فأن حامض الميفيانااميك يستخدم في هذا العمل كمادة أولية في التحضير لحامض الاميك ومشتقاته عن طريق التخليق في عدة خطوات :

أولا: المركب [I] والذي تم تحضيره عن طريق التفاعل بين مجموعة الحامض الكاربوكسيلي في حامض الميفيانااميك والميثانول في وسط حامضي والذي تم تحويله الى حمض الهايدرازيد المقابل .[II]

ثانيا: حوامض الاميك $[III]_{a-e}$ كوسطيات تم تحضيرها عن طريق التكثيف للهايدرازايد المشتق من حامض الميفيناميك .[II] مع انهايدرات مختلقة مثل : الماليك، السكسينيك، الفثالك، النتروفثالك وانهدريد النفثالك) بوجود الاستون.

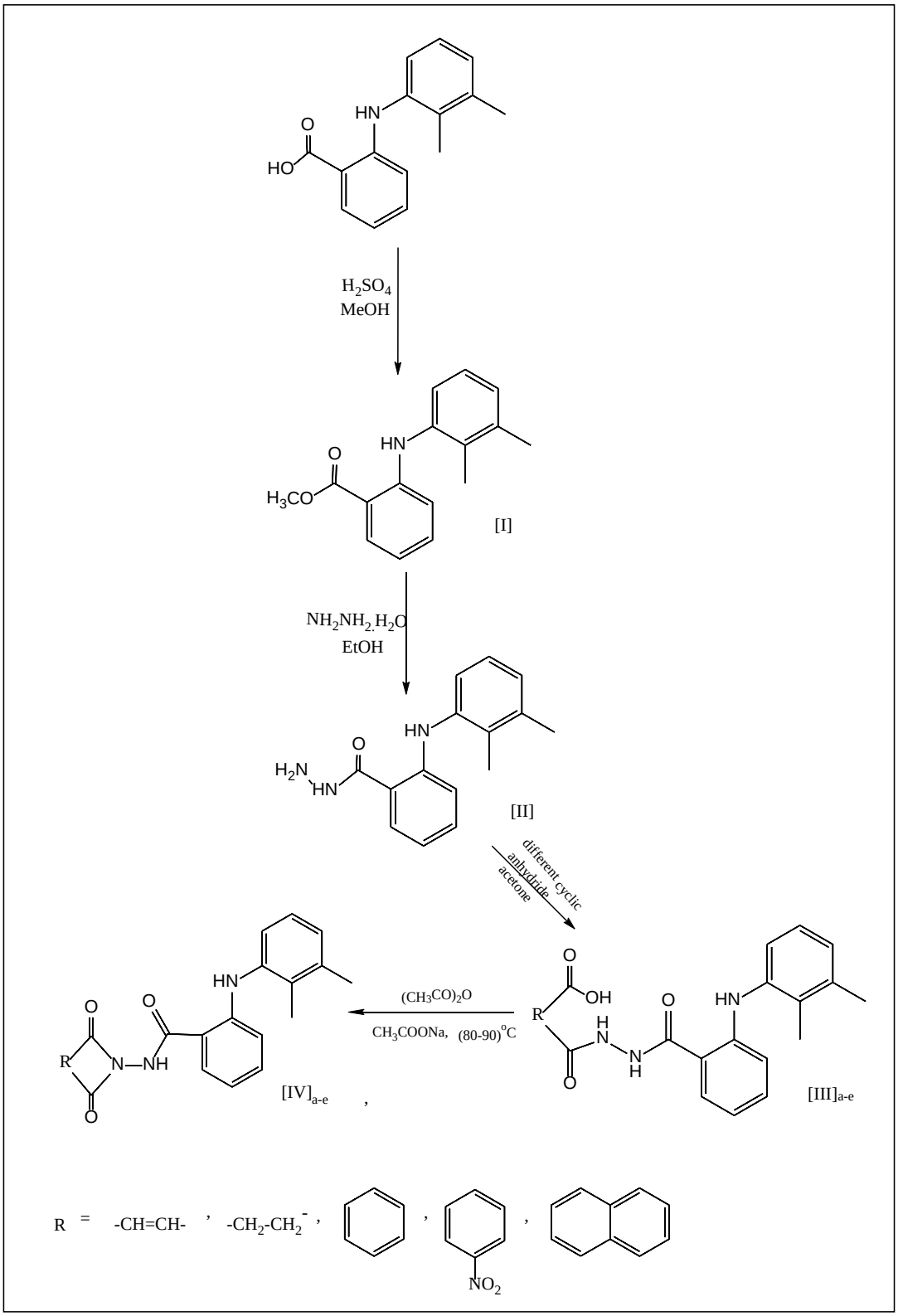
ثالثا: الغلق الحلقي الضمني لحوامض الاميك المحضرة $[III]_{a-e}$ باستعمال انهايدريد الخليك وخلات الصوديوم اللامائية عند درجة حرارة (٨٠-٩٠)^{o}م منتجاً نوعا جديدا من مركب الايميد $[IV]_{a-e}$.

رابعا: عملية الاسترة لمجموعة لحامض الاميك $[III]_{a}$والتي تنتج الاستر المقابل[V] والذي تم تكثيفه مع الهايدرازايد[VI] ثم يتفاعل المركب الاخير مع الديهايدات اروماتية معوضة (سيرينج الديهايد ، نيتروبنزالديهايد أو الفانيلين) في كحول الايثانول بأستخدام حامض الخليك الثلجي كمادة محفزة تحت التسخين لأنتاج قاعدة شف $[VII]_{a-c}$.

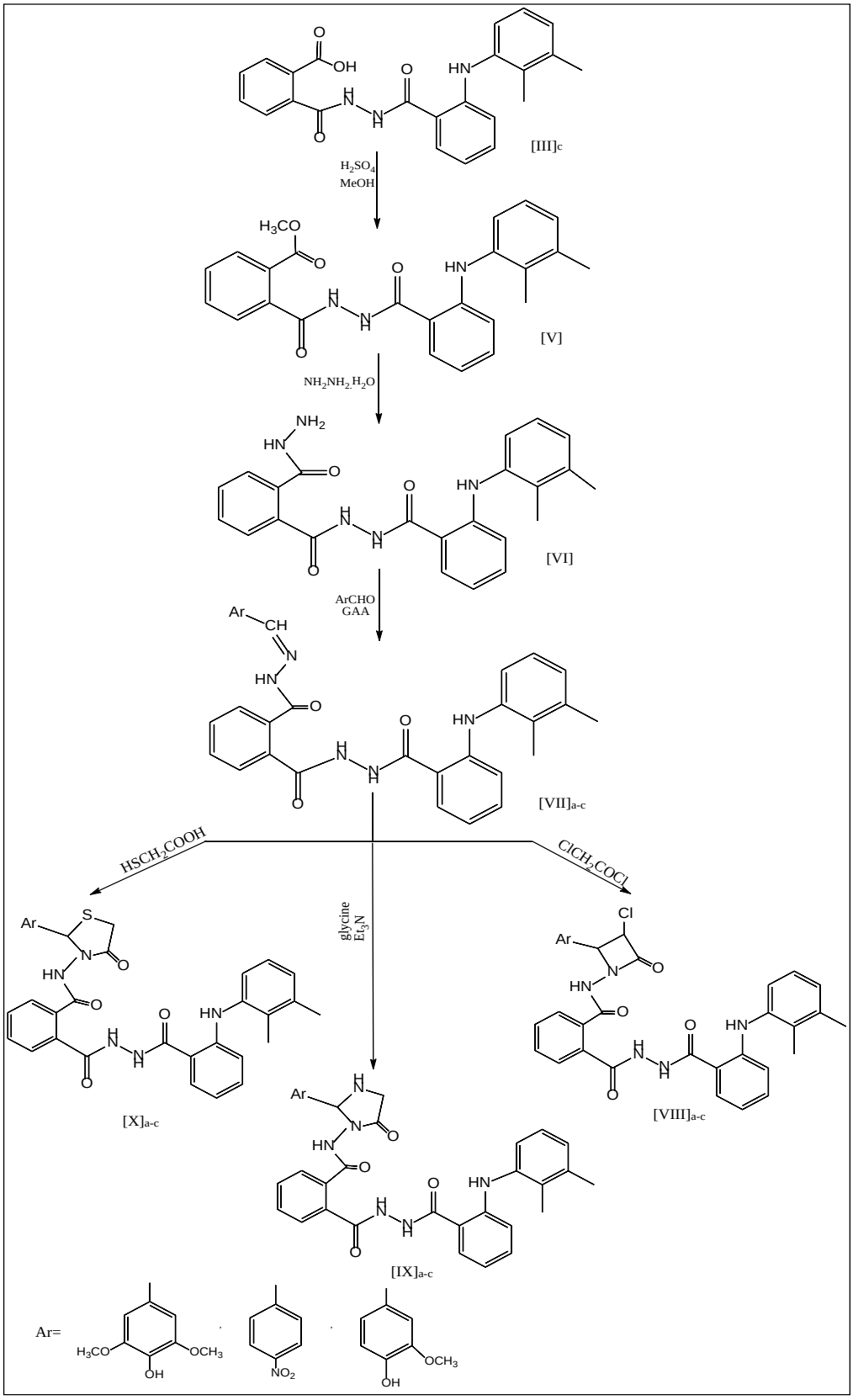
خامسا: أن المشتقات الجديدة تحتوي تحتوي حلقات رباعية وخماسية كأزيتيدين $[VIII]_{a-c}$ و أيميدازولدينون وثايازولدينون $[IX]_{a-c}$ وقد أدى تفاعل القاعدة شيف $[VII]_{a}$ مع الكلورواسيتيل كلورايد بوجود التراي اثيل امين الى تكوين أزيتيدين جديد $[VIII]_{a-c}$ وبينما تم انتاج ألايميدازولدينون $[X]_{a-c}$ والثايازولدينون $[XI]_{a--c}$ عن طريق تصعيد قاعدة شف المذكورة $[VII]_{a}$عن طريق الكلايسين في التراي اثيل امين وحامض الثايوكلايكولك في البنزين الجاف على التوالي.

شخصت جميع المركبات المحضرة باستخدام FTIR و^{1}HNMR وطيف الكتلة و CHNS لبعض منها.

سادسا: تم فحص النشاط المضاد للميكروبات لبعض المركبات المحضرة ضد أنواع مختلفة من البكتيريا وأظهرت النتائج أن لمعظمها نشاط جيد مضاد للبكتيريا. أيضا ، تم اختبار التأثير السام للخلايا لتركيزات مختلفة من بعض المركبات المخلقة على خط خلايا MCF-7 (خلايا سرطان الثدي البشرية) وتم الحصول على نتائج إيجابية لبعضها ، مما شجعنا على دراسة السمية باستخدام الكائنات الحية (الفئران) لتقييم سميته الحادة وثبت نتائج عدم سمية المشتقات.


HN
O
HO
H2SO4
MeOH
HN
O
H3CO
[I]
NH2NH2.H2O
EtOH
HN
O
H2N
HN
[II]
different cyclic
anhydride
acetone
O
OH
R
H
N
N
H
O
HN
[III]a-e
(CH3CO)2O
CH3COONa, (80-90)°C
HN
O
O
R
N—NH
O
[IV]a-e
R = -CH=CH- , -CH2-CH2- ,
NO2

Scheme(1)


[III]c
H2SO4
MeOH
[V]
NH2NH2.H2O
[VI]
ArCHO
GAA
[VII]a-c
HSCH2COOH
ClCH2COCl
glycine
Et3N
[X]a-c
[VIII]a-c
[IX]a-c
Ar=

Scheme(2)

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

تحضير ودراسة الفعالية البايولوجية لبعض حوامض الاميك الجديدة ومشتقاتها من حامض الميفيناميك

رسالة
مقدمة الى مجلس كلية التربية للعلوم الصرفة-ابن الهيثم ــ جامعة بغداد
وهي جزء من متطلبات نيل درجة الماجستير في علوم الكيمياء

من قبل
علي عماد صباح الحسناوي
بكالوريوس علوم كيمياء / جامعة بغداد / ٢٠١٢

بإشراف
أ.م د. منى سمير سعيد الراوي

١٤٤١ هـ ٢٠١٩ م