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Al-Nahrain University
College of Science
Department of Chemistry


# Synthesis and Characterization of Some Amino Acid Derivatives and Studying Its Antibacterial Activity

## A Thesis

Submitted to the College of Science/ Al-Nahrain University as a Partial Fulfillment of the Requirements for the Degree of Master of Science in Chemistry

**By**

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2017 A.C. 1438 A.H.

بسم الله الرحمن الرحيم

"قالُواْ سُبْحَانَكَ لاَ عِلْمَ لَنَا إِلاَّ مَا عَلَّمْتَنَا

إِنَّكَ أَنتَ الْعَلِيمُ الْحَكِيمُ "

صدق الله العظيم

سورة البقرة / الآية (32)

# Supervisor Certification

I certify that this thesis entitled "Synthesis and Characterization of Some Amino Acid Derivatives and Studying Its Antibacterial Activity" was prepared by "Dina Ziad Qassim" under our supervision at the College of Science, Al-Nahrain University as a partial fulfillment of requirements for the Degree of Master of Science in Chemistry.

Signature:

Name: **Dr. Jawad K. Shneine**

Scientific Degree: Assistant Professor

Date: / / 2017

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In view of the available recommendation, I forward this thesis for debate by the Examining Committee.

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Name: **Prof. Dr. Emad Al-Sarraj**

Title: Head of Chemistry Department, College of Science,

Al Nahrain University

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We, the examining committee, certify that we have read this thesis entitled "**Synthesis and Characterization of Some Amino Acid Derivatives and Studying Its Antibacterial Activity**" and examined the student "**Dina Ziad Qassim**" in its contents and that in our opinion, it is accepted for the degree of Master of Science in organic chemistry.

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I, hereby certify upon the decision of the examining committee.

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Scientific Degree: Professor
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Date: / /2017.

# الأهداء

إلى سيدي ومولاي صاحب الخلق العظيم الذي انزله الله رحمة للعالمين
خير البشر الرسول النبي **محمد صلى الله عليهِ والهِ وسلم.**

إلى الينبوع الذي لا يمل العطاء, إلى من حاكت سعادتي بخيوط منسوجة
من قلبها إلى **والدتي العزيزة.**

إلى من سعى وشقى لأنعم بالراحة والهناء الذي لم يبخل بشئ من أجل
دفعي في طريق النجاح الذي علمني أن أرتقي سلم الحياة بحكمة وصبر
إلى
**والدي العزيز.**

إلى الروح التي سكنت روحي **زوجي الغالي.**

إلى من حبهم يجري في عروقي ويلهج بذكراهم فؤادي إلى
**أخواتي وأخي.**

إلى من سرنا سوياً ونحن نشق الطريق معاَ نحو النجاح والإبداع إلى من
تكاتفنا يداً بيد ونحن نقطف زهرة وتعلمنا إلى
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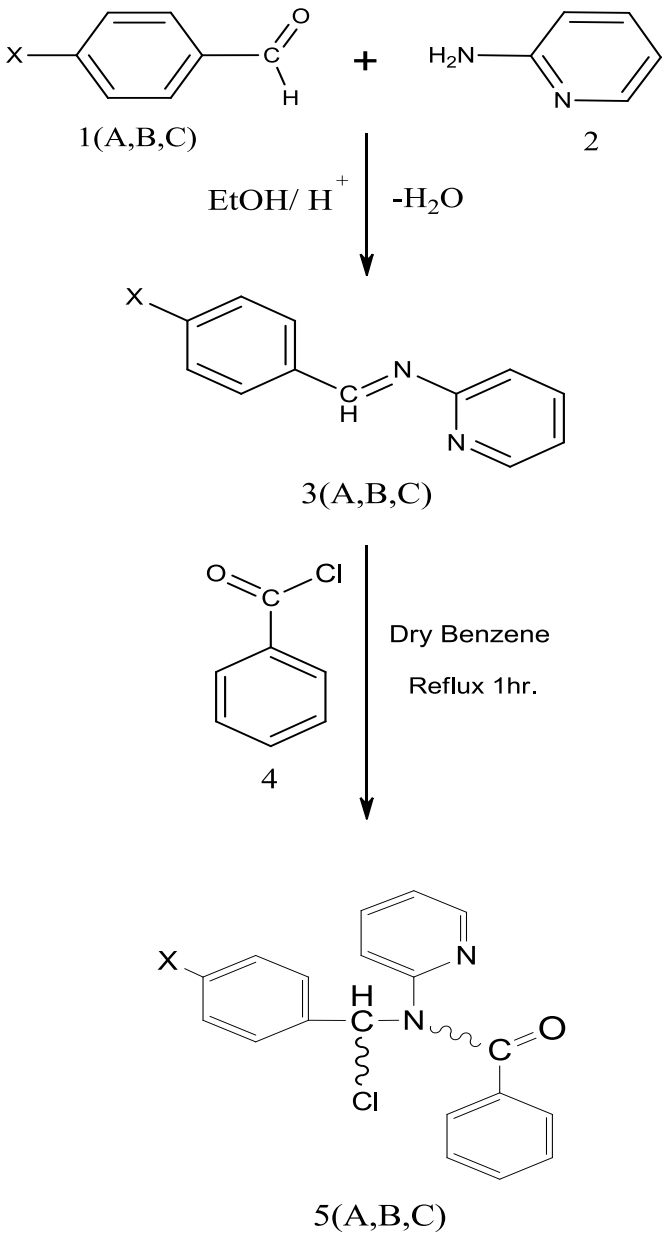
***Dina Ziad***

# Summary

The present work includes the synthesis of different Schiff's bases [3(A-C)] by the reaction of 2-Aminopyridine [2] with benzaldehyde and its derivatives [1(A-C)]. These Schiff's bases react with benzoyl chloride [4] to yield benzamide derivatives [5(A-C)]. The synthesis of L-amino acid derivatives [6(A-C)–10(A-C)] has been performed by the reaction of benzamide derivatives [5(A-C)] with (Glycine, L-Alanine, L-Phenylalanine, L-Asparatic acid and L-Asparagine). FTIR, $^{1}$H-NMR and $^{13}$C-NMR spectroscopy were used to characterize the prepared compounds. The biological activity of compounds were evaluated toward gram negative bacteria (*Klebsiella pneumoniae*) and gram positive bacteria (Staphylococcus aureus).

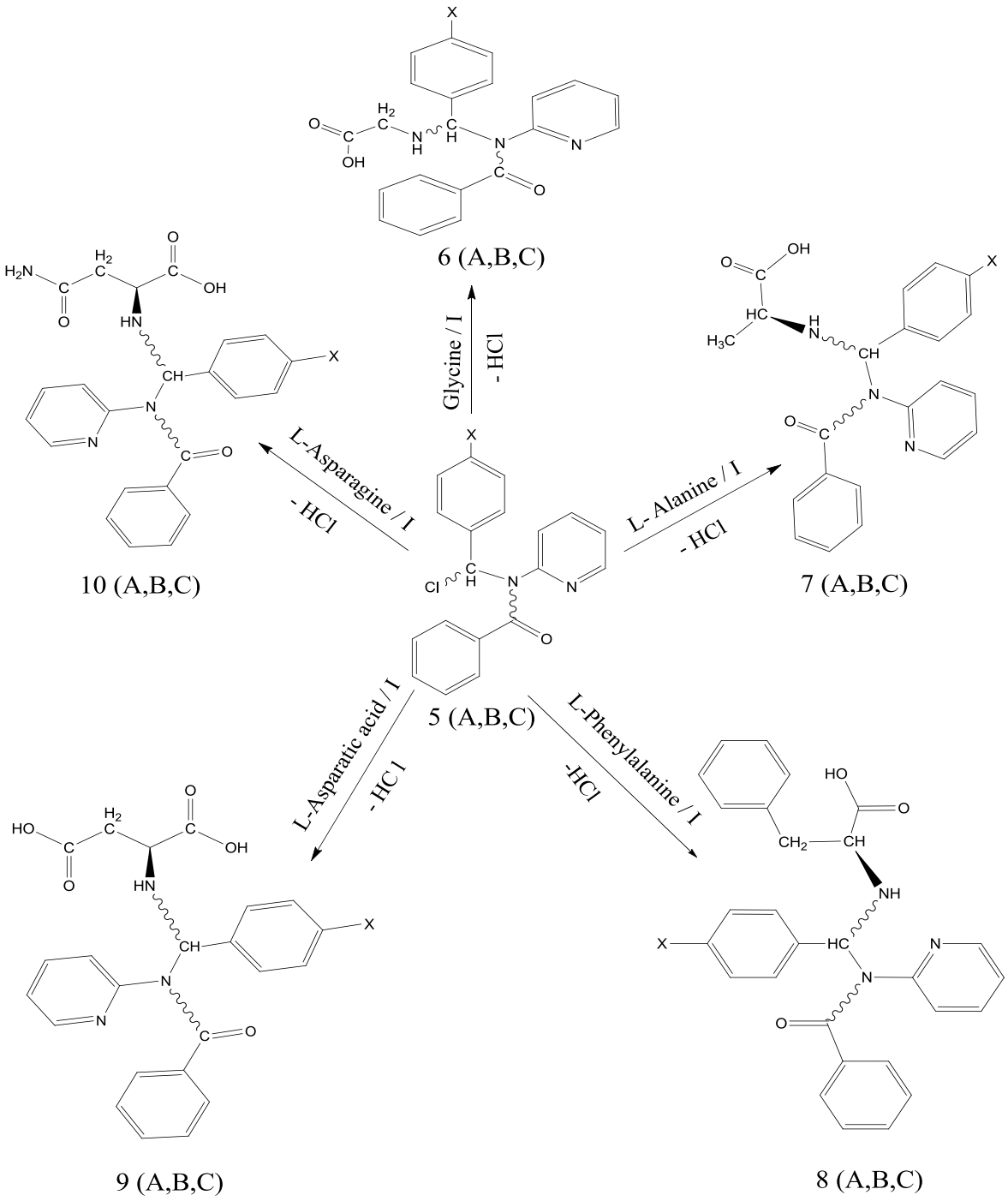
The synthesized compounds [6(A-C) – 10(A-C)] showed a lower anti-bacterial activity compared with Meropenem as a reference against both (*Staphylococcus aureus*) and (*Klebsiella pneumoniae*).

The compounds 6A, 7B and 8C were found as the best anti-bacterial activity among the synthesized compounds against both bacteria at the concentration of 50 (µg/ml).




X: H, Cl, Br.

**Scheme 1:** Synthetic route of *N*-[chloro-(4-monosubstituted-phenyl) methyl]-*N*-(pyridin-2-yl) benzamide.




X: H, Cl, Br.

I: Dioxan / $H_2O$, reflux 4hr.

**Scheme 2:** Synthetic route of (2S)-2-*N*-[(benzoyl-pyridin-2-yl-amino)-(4-monosubstituted-phenyl)-methyl]-L-amino acid from *N*-(Chloro-(4-monosubstituted-phenyl methyl)-*N*-(pyridin-2-yl)benzamide.

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# Abbreviations

| Symbol | Full meaning |
|---|---|
| **°C** | Centigrade |
| **cm** | centimeter |
| **DMSO** | Dimethyl sulfoxide |
| ***E. coli*** | *Escherichia coli* |
| **FTIR** | Fourier Transform Infrared Spectroscopy |
| **Hrs.** | Hours |
| ***K. pneumoniae*** | *Klebsiella pneumoniae* |
| **L** | Left |
| **m.p.** | Melting point |

| | |
|---|---|
| **µg** | Microgram |
| **µL** | Microliter |
| **mL** | Milliliter |
| **mm** | Millimeter |
| **min.** | Minutes |
| **MH.** | Muller Hinton |
| **Mero.** | Meropenem |
| **NMR** | Nuclear magnetic resonance |
| **ppm** | Part per million |
| **R** | Right |
| ***S. aureus*** | *Staphylococcus aureus* |
| **SEM** | Scanning electron micrograph |

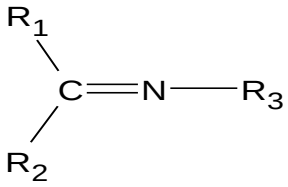
# CHAPTER ONE

## INTRODUCTION

## 1.1 Schiff's bases

A Schiff's base (imine or azomethine), named after Hugo Schiff, contains a carbon-nitrogen double bond with the nitrogen connected to an aryl or alkyl but not hydrogen. Schiff bases are of general formula $R_1R_2C=NR_3$, where $R_3$ is an aryl or alkyl group that makes the Schiff's bases a stable imine [(1)], Fig (1-1).

A Schiff's base derived from aniline, where $R_3$ is a phenyl or a substituted phenyl, can be called an anil [(2)]. Schiff's bases that contain aryl substituents are substantially more stable and more readily synthesized, while those which have alkyl substituents are relatively unstable. Schiff's bases of aliphatic aldehydes are relatively unstable and readily polymerizable whereas those of aromatic aldehydes containing effective conjugation are more stable [(3)].

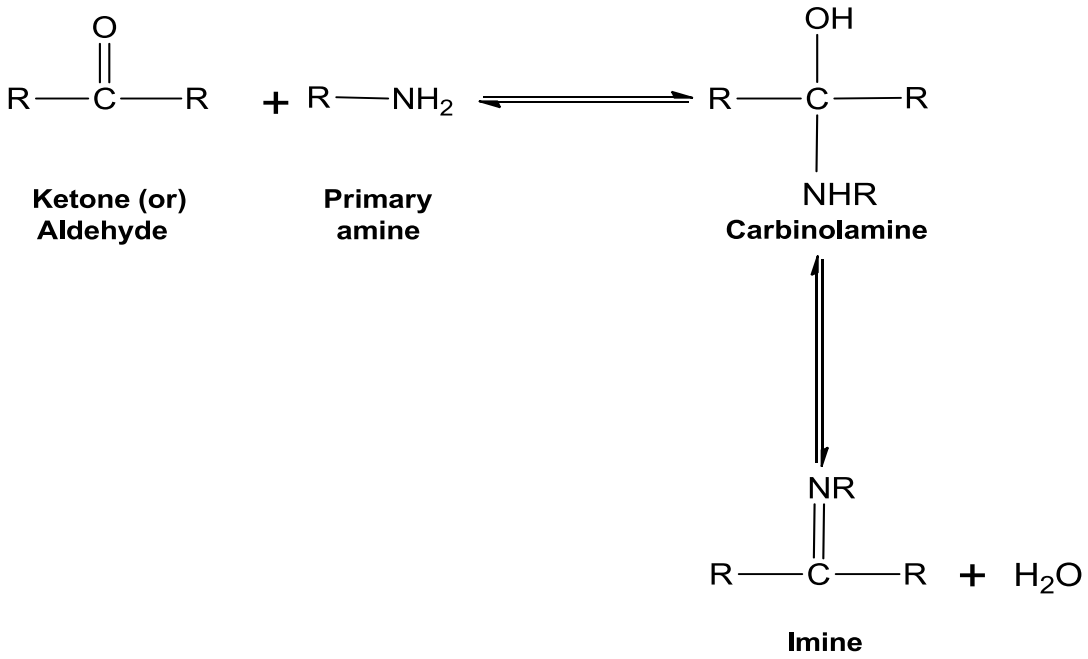



$R_1$, $R_2$, $R_3$: Aryl or Alkyl group.

Fig (1-1): Structure of Schiff base.

The formation of a Schiff's base from aldehydes (or) ketones is a reversible reaction and usually takes place under acid (or) base catalysis, or upon heating. The formation is usually driven to the completion by split-up of the product or removal of water, or both. Many Schiff's bases can be hydrolyzed back to their aldehydes or ketones and amines by aqueous acid or base [(4)], Scheme (1-1).

The dehydration of carbinolamine is also catalyzed by a base. This reaction is somewhat analogous to the $E_2$ elimination of alkyl halides except that it is not a concerted reaction. It proceeds in two steps through an anionic intermediate. The Schiff's base formation is really a sequence of two types of reactions, i.e. addition followed by elimination [(4)].

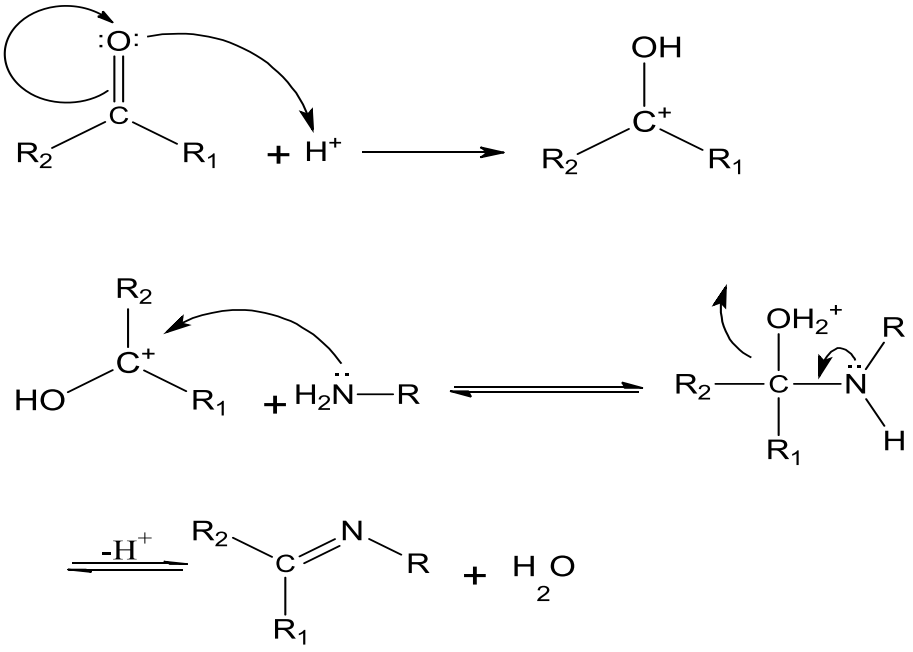



R: Aryl or Alkyl group.

Scheme (1-1): The chemical equations of Schiff's base formation.

However the acid concentration cannot be too high because amines are basic compounds. If the amine is protonated and grow into non-nucleophilic, equilibrium is pulled to the left and carbinolamine formation cannot occur. Therefore, many Schiff's bases synthesis are best carried out at mild acidic pH. The mechanism of Schiff's base formation is another variation on the theme of nucleophilic addition to the carbonyl group. In this case, the nucleophile is the amine. In the first part of the mechanism, the amine reacts with the aldehyde or ketone to give an unstable addition compound called carbinolamine. The carbinolamine loses water by either acid or base catalyzed pathways. Since the carbinolamine is an alcohol, it undergoes acid catalyzed dehydration [(4)], Scheme (1-2).

Schiff's bases are considered as starting materials for synthesis of heterocyclic compounds [(5)], and metal complexes [(6)]. Also Schiff's bases are as important organic compounds for polymerization reactions [(7)], wherever they considered as catalyst of reaction [(8)].

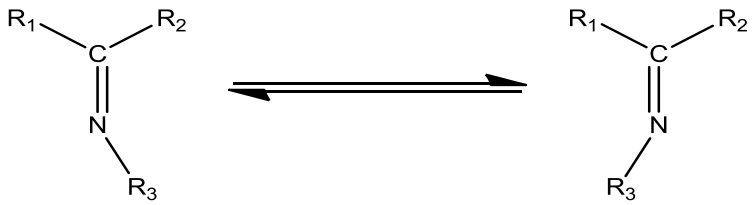


R, $R_1$, $R_2$: Aryl or Alkyl group.

Scheme (1-2): The mechanism of Schiff's base formation.

Schiff's bases show good anti-proliferative [9], antiviral [10], antimicrobial [11], anti-inflammatory [12], activities and play as antimalarial [13], anticancer [14], antibacterial [15], antifungal [16], and anti-tubercular [17].

Schiff bases have two geometric isomers result from stereo distribution of groups attached to double bond which known as cis-trans isomerism. One of these isomers is more stable than the other result from type of group's distribution about carbon and nitrogen atom [18], Scheme (1-3).



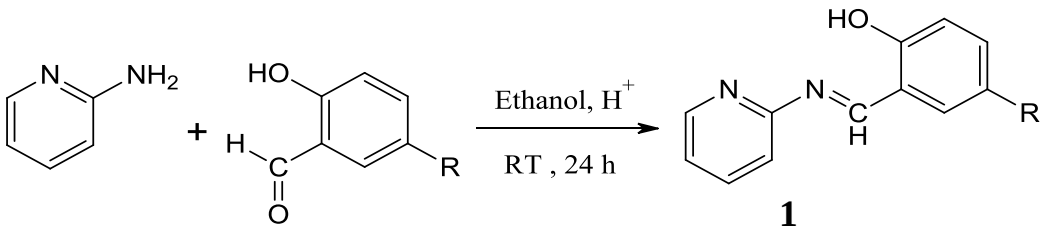
Trans Cis

$R_1$, $R_2$, $R_3$: Aryl or Alkyl group.

Scheme (1-3): geometric isomer of Schiff's bases.

### 1.1.1 Schiff's base of 2-Aminopyridine

In 2013 ***Vinita et al.*** [19]**,** prepared 2-Aminopyridine Schiff's bases [1] by the reaction of 2-aminopyridine with substituted Salicylaldehyde and showed that they capable to prevent the growth of *S. aureus* and *E. coli* in different concentrations.

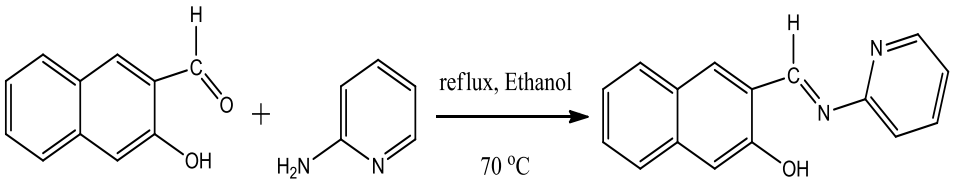



**1**

R: H, $NO_2$, Br, $OCH_3$.

Scheme (1-4): The formation of compounds [1].

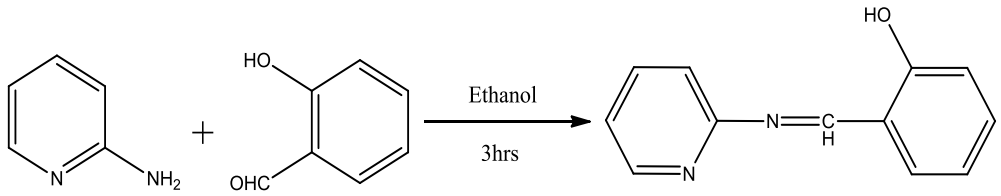
In 2015 ***Hamdan et al.*** [20], Synthesized complexes of Fe (II) and Cu (II) with a tridentate Schiff 's base [2], 2-((z)-(pyridine-2-ylimino)methyl) naphthalene-1-ol resulting from 2-hydroxy-1-napthaldehyde and 2-Amino pyridine and evaluated the Antibacterial and antifungal activities in vitro against three types of G+ and G- bacteria, *Escherichia coli*, *Pseudomonas aeruginosa*, *Staphylococcus aureus* and three types of fungi, *Aspergillus flavus*, *Trichophyton rubrum* and *Candida albicans* with determination of minimum inhibitory concentrations of ligand and metal complexes.




**2**

Scheme (1-5): The formation of compound [2].

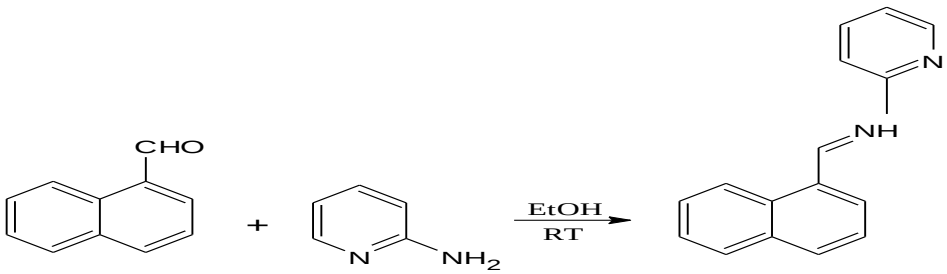
In 2016 ***Ramachandran et al.*** [21]**,** Synthesized a new series (Z)-2-(pyridine-2-ylimino) methyl phenol derivative [3] by the reaction of 2-aminopyridine with 2-Hydroxybenzaldehyde. This compound showed mild antibacterial activity against *Staphylococcus aureus* and *Escherichia coli*.




**3**

Scheme (1-6): The formation of compound [3].

In 2016 ***Santhoshkumar et al.*** [22]**,** have synthesized and studied the selective fluorescent probe for $Fe^{2+}$ of naphthalene pyridine Schiff's base [6] derived from 1-Naphthaldehyde and 2-aminopyridine.

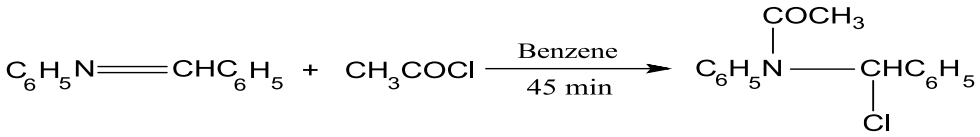



**4**

Scheme (1-7): The formation of compound [4].

### 1.1.2 Reactions of Schiff's base

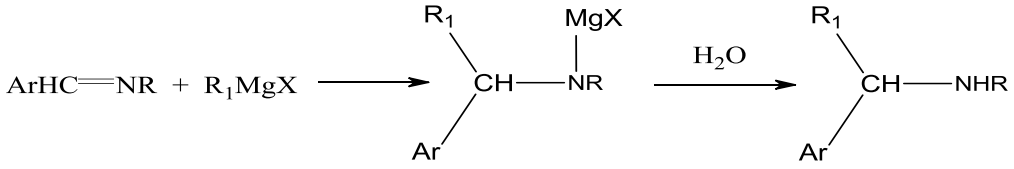
Aromatic Schiff's bases are weak bases and weak nucleophiles. This is supported by the fact that they do not react with simple alkyl halides, allyl halides or benzyl halides but they react with the relatively more reactive acid halides. Acetyl chloride, for example, react with N-Benzylideneaniline to give N-[chloro(phenyl)methyl]-N-acetanilide [7] [18], Scheme (1-8).




**5**

Scheme (1-8): The formation of compound [5].

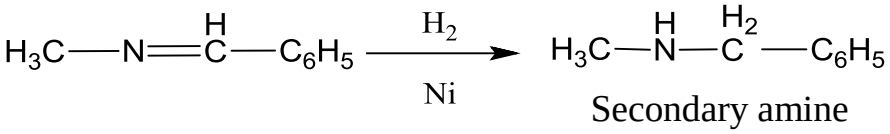
Grignard reagent reacts with azomethine compounds to form product which on hydrolysis result secondary amines. The reaction is usually applied to the Schiff bases which are prepared from aryl aldehydes [(18)], Scheme (1-9).




R, $R_1$: Aryl or Alkyl group.

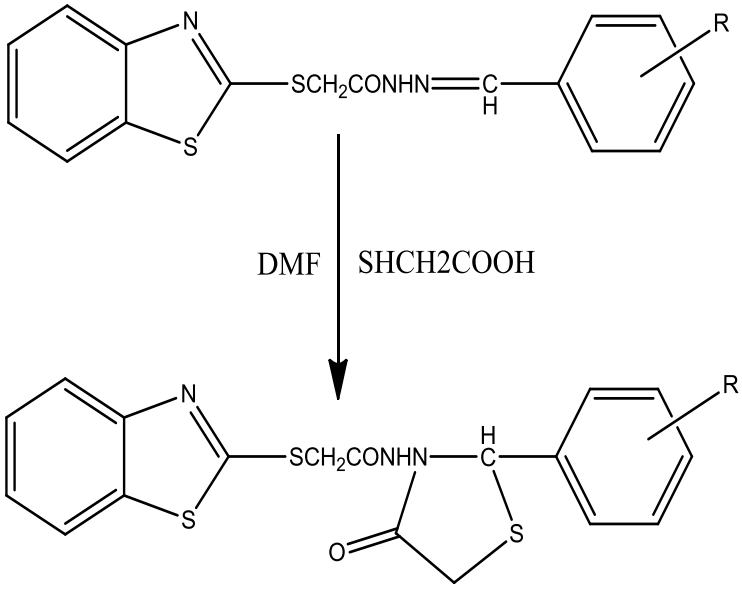
Scheme (1-9): The formation of secondary amines.

Schiff's bases can be hydrogenated in the presence of catalyst to give the corresponding secondary amines [(18)], Scheme (1-10).




Scheme (1-10): The formation of secondary amines.

In 2006 ***Desai et al.*** [(23)], synthesized 4-thiazolidinones [6] in a good yields from the heterocyclization reaction of 2-(benzothiazol-2-ylthio)-N'-benzylideneacetohydrazide with mercaptoacetic acid in DMF in the presence of catalytic amount of anhydrous $ZnCl_2$ under microwave irradiation and compared with conventional methods, Scheme (1-11).

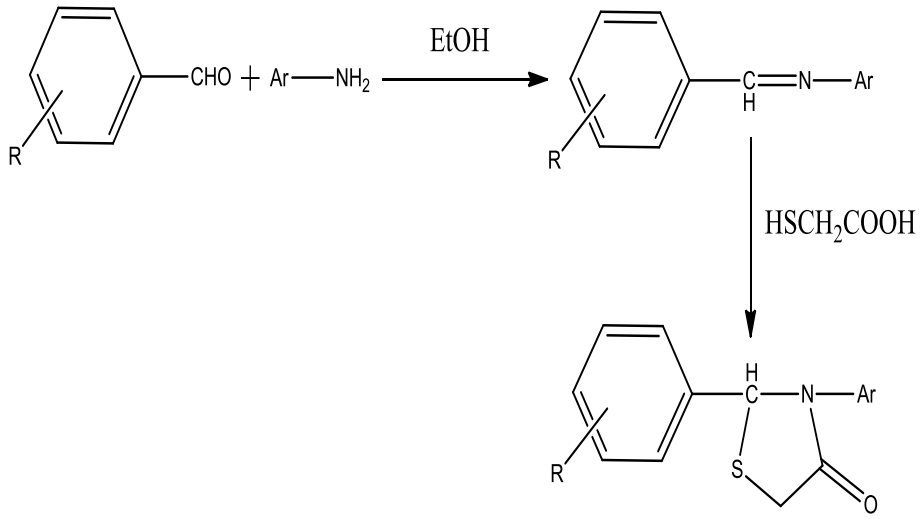



**6**

R: 4-$NO_2$, $CH_3$.

Scheme (1-11): The formation of compounds [6].

In 2006 ***Sahu et al.*** [24], reported that condensation of substituted benzaldehydes with primary aryl amines gave a series of Schiff bases which, on reaction with mercaptoacetic acid, resulted in the formation of the corresponding 4-thiazoldinones [7], Scheme (1-12).




**7**

Ar=4-$NO_2$ , Phenyl, 4-Cl and Naphthyl, R=2-OH, 4-$N(CH_3)_2$ , 4-$NO_2$, 4-Cl and 4-$OCH_3$.

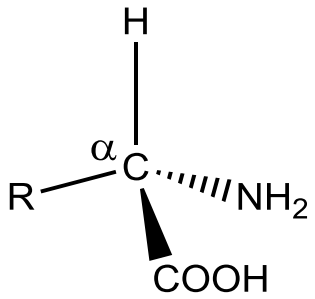
Scheme (1-12): The formation of compounds [7].

## 1.2 Amino acid derivatives

Amino acids play central parts both as construction blocks of proteins and as intermediates in metabolism. The 20 amino acids that are originate within proteins carry a vast array of chemical adaptability. The precise amino acid content, and the sequence of those amino acids, of a specific protein, is determined by the sequence of the bases in the gene that encodes that protein. The chemical properties of proteins amino acids determine the biological activity of the protein. Proteins not only catalyze all (or most) of the reactions in living cells, they control virtually all cellular process. In addition, proteins contain within their amino acid sequences the necessary information to determine how that protein will fold into a three dimensional structure, and the stability of the resulting structure [(25)].

Humans can produce 10 of the 20 amino acids. The others must be supplied by food. Failure to obtain enough of even 1 of the 10 essential amino acids, those that we cannot make, results in degradation of the body's proteins—muscle and so forth—to obtain the one amino acid that is needed. Unlike fat and starch, the human body does not store excess amino acids for later use, the amino acids must be in the food every day [(26)].

The 10 amino acids that produce are alanine, asparagine, aspartic acid, cysteine, glutamic acid, glutamine, glycine, proline, serine and tyrosine. Tyrosine is produced from phenylalanine, so if the diet is deficient in phenylalanine, tyrosine will be required as well. The essential amino acids are arginine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, threonine, tryptophan, and valine [(27)]. The general structure of an amino acid is:




R: Side chain group

Fig (1-2): General structure of amino acid.

With the R group indicating the side chain [27]. All amino acids having a free α-amino group except proline, the structure differs slightly from general formula because the amino group and (R) group are part of ring, and this give strength to the proline in peptides that contain it [18], Fig (1-3).

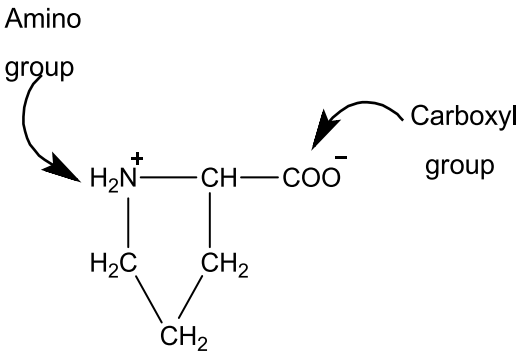
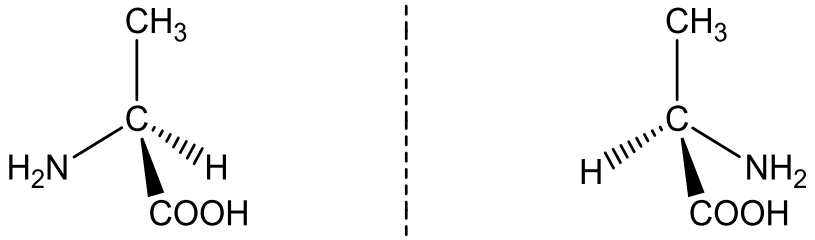



Fig (1-3): Structure of Proline.

All amino acids in nature except glycine contain an asymmetric carbon (chiral carbon) and so amino acids are optically active. There are two possible arrangements for molecules with chiral carbon. Molecules that have only in special arrangement of their atoms are called (stereoisomer). There are two types of stereoisomer of molecules with chiral carbon, D-isomers, L-isomers. The atoms of two isomers are bonded together in the same pattern except for position of amino group and hydrogen atom [18].

Careful examination reveals that the two isomers in Fig (1-4) are mirror images to each other, such molecules called (enantiomers), cannot be superimposed on each other [18].

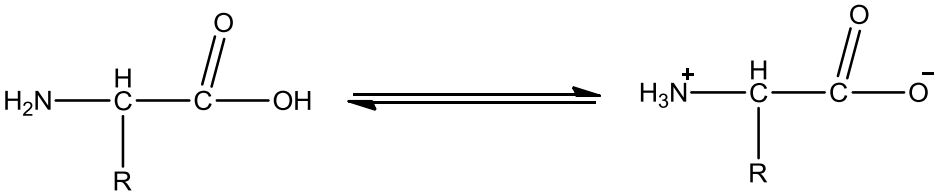



L-Alanine D-Alanine

Fig (1-4): The structural formula (L, D) for alanine.

Some of amino acids contain equal quantity from (D) and (L) and this mixture called (Racemic Mixture). The genetic code use only (L-amino acids) in constructing proteins, although (D-amino acids) may occur as a modification after the genetic code has been transcribed into proteins, or they are formed by nongenatically directed processes into (D-amino acids) occur mainly in the lower organisms such as bacteria [18].

Bjerrume suggest that nearly the whole of neutral aliphatic amino acid is present in solution in the form of the dipolar ion (Zwitter ion), as shown in figure (1- 4) that carries both a positive and negative charge as result of internal acid-base reaction in amino acid molecules [18].




non ionized form dos not exist

Zwitter ion present in soilds state and solution

Scheme (1-13): The Zwitter ion for Amino Acid.

A solution of glycine, for example, i.e., $NH_2CH_2CO_2H$ is compared with one of ammonium acetate; if a strong acid is added to the latter, the reaction is with basic $CH_3CO_2^-$ ion and $CH_3CO_2H$ is formed, but a strong base reacts with the acidic $^+NH_3$ ion to yield $NH_2$ [18].

In the same way, the addition of strong acid to glycine consisting mainly of the dual ion $^+NH_3CH_2CO_2^-$, result in the reaction [18].

$$^+NH_3CH_2CO_2^- + H_3O^+ \rightleftharpoons {}^+NH_3CH_2CO_2H + H_2O$$

While reaction with alkali is:

$$^+NH_3CH_2CO_2^- + OH^- \rightleftharpoons NH_2CH_2CO_2^- + H_2O$$

There are several other properties of amino acids which are in agreement with the dipolar ion type of structure. These are the high melting point, the sparing solubility in alcohol and acetone, and increased solubility in presence of natural salts, all of these properties associated with ionized substance [18].

Amino acids have long played an important role in both human and animal nutrition and health maintenance. On account of its functionality and the special features arising from chirality, this class of compounds is biochemically extremely important and of great interest for the chemical industry [28].

In this industry, amino acids are also used to chelate metal cations in order to improve the absorption of minerals from supplements, which may be required to improve the health or production of these animals [29].

The most closely studied flavor enhancer is monosodium glutamate, the sodium salt of glutamic acid. Glutamate is a frequently used as flavor enhancer in foods, enhances the savory flavors imparted by glutamic acid, which occurs naturally in proteinaceous foods e.g. meats, seafood, stews, soups, sauces,[30] and aspartame (aspartyl-phenylalanine-1-methyl ester) is considered to be the first generation of sweeteners [31].

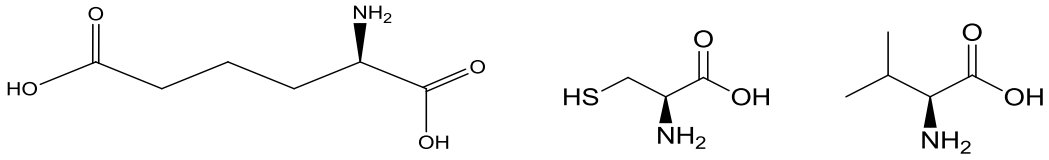
The remaining proteinogenic amino acids are required in the pharmaceutical and cosmetics industries and are also ideal raw materials for synthesis of chiral

active ingredients, which in turn find application in such sectors as pharmaceuticals, cosmetics, and agriculture [28].

Include 5-HTP (5-hydroxytryptophan) used for experimental treatment of depression [32], L-DOPA (L-dihydroxyphenylalanine) for Parkinson's treatment [33], and eflornithine drug that inhibits ornithine decarboxylase and used in the treatment of sleeping sickness [34].

Amino acid derivatives were also used in production of drugs for antimicrobial [35], antifungal [36], anticancer [37], antibodies [38].

The compounds α-Aminoadipic acid [8], L-cysteine [9] and L-Valine [10] were used in biosynthesis of penicillin and cephalosporin [39].

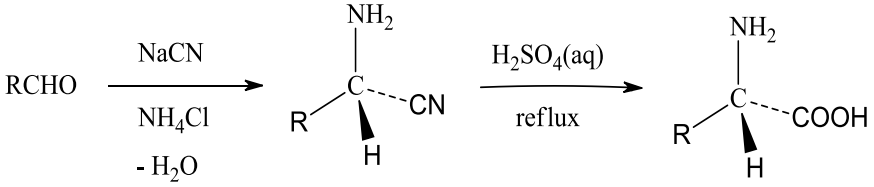



**8** **9** **10**

Fig (1-5): The structure of compounds [8], [9], [10].

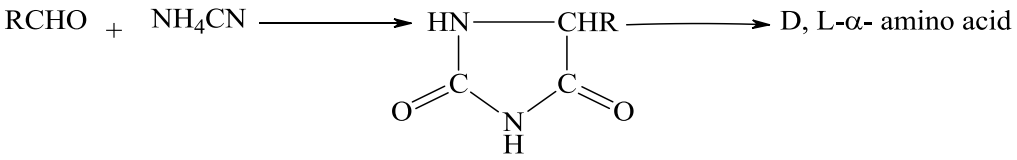
### 1.2.1 Chemical synthesis of Amino acids

The α-amino-acid grouping, —NH—CHR—CO—O—, can be built up from its components through the Strecker synthesis [40]:




Scheme (1-14): The formation by Strecker synthesis.

Or by the Bucherer–Bergs synthesis [40]:

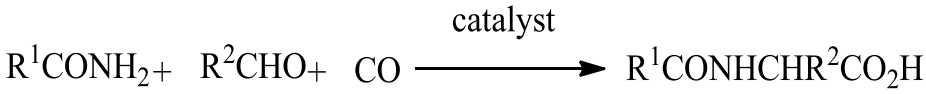



Scheme (1-15): The formation by Bucherer–Bergs synthesis.

An even simpler synthesis, the Miller–Urey experiment in which some of the presumed atmospheric components in prebiotic eras were shown to combine, is not of practical interest since it gives mixtures with low yields and it cannot be directed towards a predominant target amino acid [(40)].

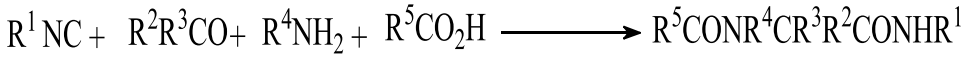

Scheme (1-16): The formation by Miller–Urey experiment.

Further general syntheses such as carboxylation or carbonylation of alkylamide [(40)].




Scheme (1-17): The formation by carboxylation of alkylamide..

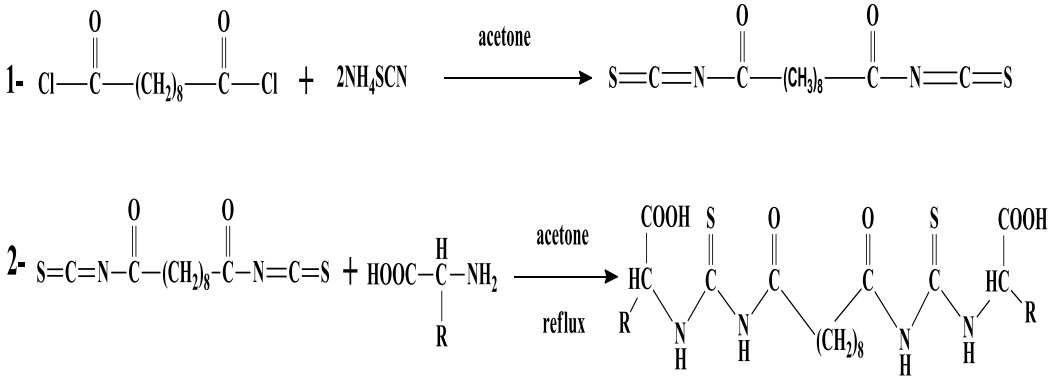
And the Ugi ‘four-component condensation [(40)].




Scheme (1-18): The formation by Ugi.

These are useful methods capable of development in certain cases for large-scale syntheses of simple amino acids [(40)].

In 2012 ***AL-Haidery*** [41], synthesized a new series of *N*-[(sebacoylamino) thioxomethyl]-amino acid [11] were prepared by the reaction of sebacoylisothiocyanate with various amino acids namely L-histidine, L-glutamic acid, L-tryptophan, L-lysine.



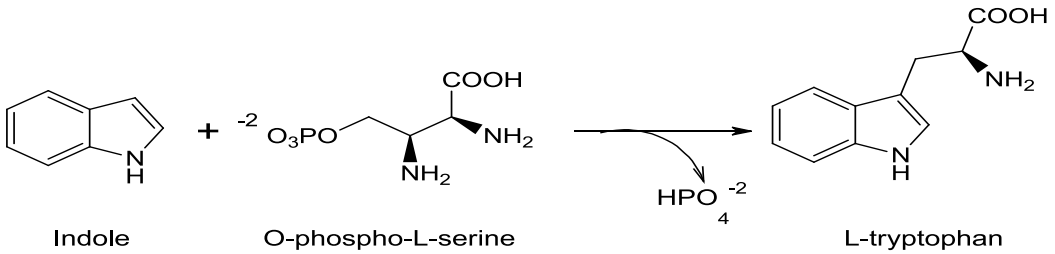

N-[(Sebacoylamino)thioxomethyl]-amino acid

**11**

R: L-Histidine, L-Glutamic acid, L-Tryptophan, L-Lysine.

Scheme (1-19): The formation of compounds [11].

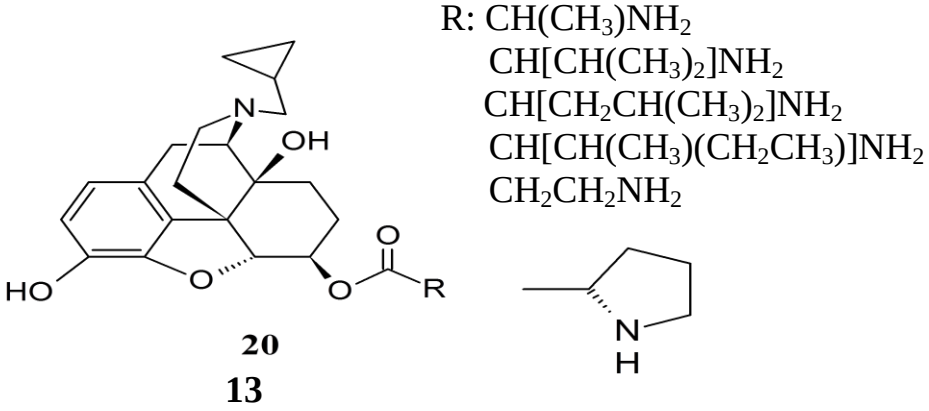
In 2014 ***Busch et.al*** [42], synthesized L-tryptophan [12] from O-phospho-L-serine and indole by using TrpB2 Enzymes.




**12**

Scheme (1-20): The formation of compound [12] [43].

In 2014 ***Eldridge et.al*** [43], Synthesized six amino acid ester prodrugs. A small library of amino acid ester prodrugs of 6-β-naltrexol (NTXOL, 1) [13] was prepared in order to investigate the candidacy of these prodrugs for microneedle-enhanced transdermal delivery.




**20**

**13**

Scheme (1-21): The formation of compounds [13].

## 1.3 Biological activity

### 1.3.1 Antimicrobials [44]

In recent years, drug resistance by human pathogenic bacteria is being commonly reported from all over the world. However, the situation is alarming in developing as well as developed countries due to indiscriminate use of antibiotics, although pharmacological industries have produced large number of newer antibiotics in the last three decades. Reason behind this is that microorganisms are becoming resistant to both older and newer antibiotics. In addition, bacteria have the genetic ability to transmit and acquire resistance to drugs which are utilized as therapeutic agents and transferring the resistance from one bacteria to another. Antibiotics provide the main basis for the therapy of microbial infections. Since the discovery of these antibiotics and their uses as chemotherapeutic agents there was a belief in the medical fraternity that this would lead to the eventual era dictation of infectious diseases. However, overuse of antibiotics has become the major factor for the emergence and dissemination

of multidrug resistant strains of several groups of microorganisms. The antimicrobial agents are of great value for devising curative measures against bacterial infections. The indiscriminate use of antibiotics has led to the emergence of antimicrobial resistance in various isolates of bacteria.

Resistant bacteria impacts the public health in such a way that it increases morbidity and mortality from treatment failures and increases healthcare costs as newer and more expensive antibiotics are needed to treat infections. Resistant bacteria are emerging worldwide as a threat to the favorable outcome of common infections in community and hospital settings. *Staphylococcus aureus* showed resistant due to the production of penicillinase with the ability to hydrolyze penicillin; first generation resistant due to β-lactamases and third-generation cephalosporins are resistant due to the production of extended-spectrum β-lactamases (ESBLs). Microorganisms are the concealed enemies to the mankind and cause a very profound damage in human body as well as other living organism. The agents, which have the capacity to kill the microbes or arrest the multiplication, are called the antimicrobial agents or drugs. There are a lot of antimicrobial drugs of which some are discovered or established.

### 1.3.2 *Staphylococcus aureus*[45]

They are gram positive spherical cell. Usually arranged in grape like irregular clusters. They grow readily on many types of media and are active metabolically, fermenting carbohydrates and producing pigments that vary from white to deep yellow. Some are members of normal flora of skin and mucous membranes of humans, a variety of pyogenic infections, and even fatal septicemia.

The pathogenic staphylococci often hemolyse blood, coagulate plasma and produce a variety of extra cellular enzymes and toxins. The most common type of food poisoning is caused by a heat-stable *staphylococci* rapidly develop resistance to many antimicrobial agents and present difficult therapeutic

problems. *S. aureus* is a major pathogen for human. Almost every person will have some type of *S. aureus* infection during a poisoning or minor skin infection to serve life threatening infections. *S. aureus* infection can also result from direct contamination and a wound like the post-operative *staphylococcoal*.

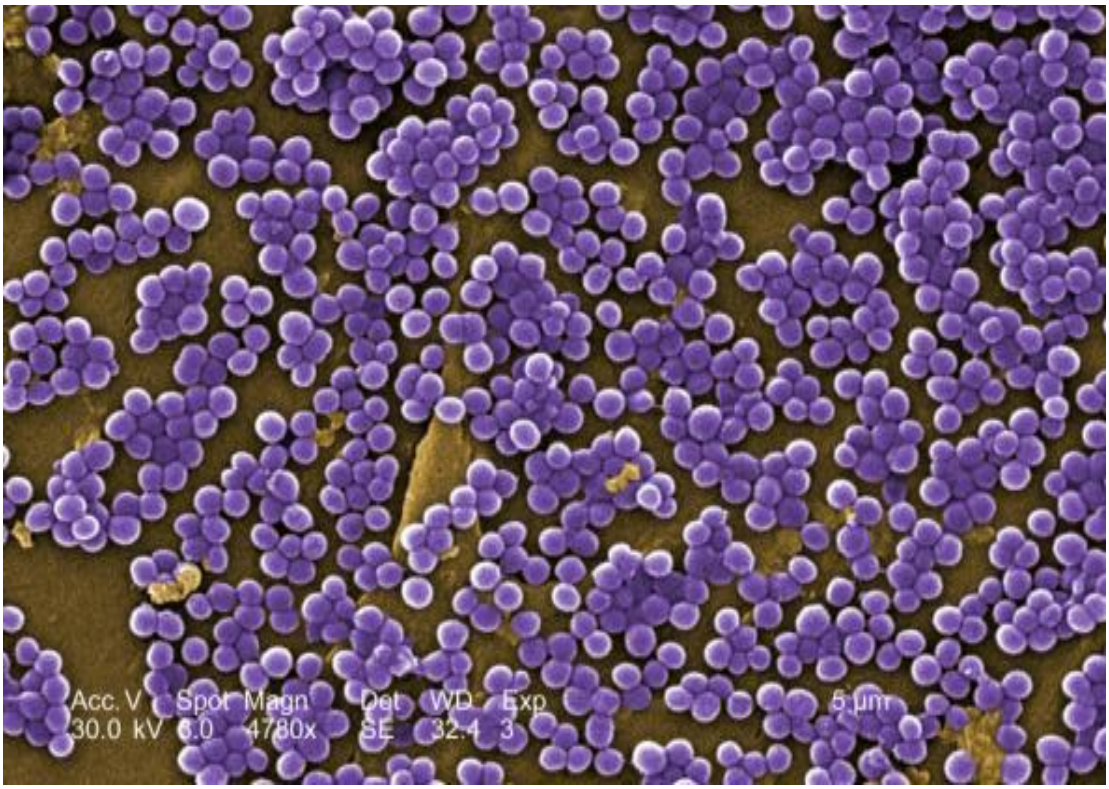



Fig (1-6): Colorized scanning electron micrograph (SEM) depicted numerous clumps of *Staphylococcus aureus* bacteria [(46)].

### 1.3.3 *Klebsiella pneumoniae*[(47)]

*Klebsiella* is a gram negative, non-motile, encapsulated, lactose fermenting, facultative anaerobe belonging to the Enterobacteriaceae family. It is the second most popular member of the aerobic bacterial flora of the human intestine. It is the most common causative agent of nosocomial and community acquired infections.

It causes pneumonia, urinary tract infection, other pyogenic infections, septicemia and rarely diarrhea. Biochemically typical strains of *Klebsiella*

*pneumoniae* are resistant to a wider range of antibiotics than are most *Escherichia coli* strains. They are nearly always naturally resistant to ampicillin. Resistance of *Klebsiella* to previously sensitive antibiotics is also increasing in the recent years due to overuse and misuse of antimicrobial agents and or natural causes, of particular concern is the Extended Spectrum Beta Lactamase (ESBL) producing *Klebsiella pneumoniae* that have been steadily increasing over the past years and rapidly spreading worldwide that pose a serious threat for healthcare associated infections.

Increasingly the ESBL *Klebsiella pneumoniae* are also showing co-resistance to other antimicrobial agents like quinolones and aminoglycoside antibiotics. Both morbidity and mortality is increased when infection is caused by these drug resistant organisms. Antibiotic sensitivity pattern may change from time to time and place to place.

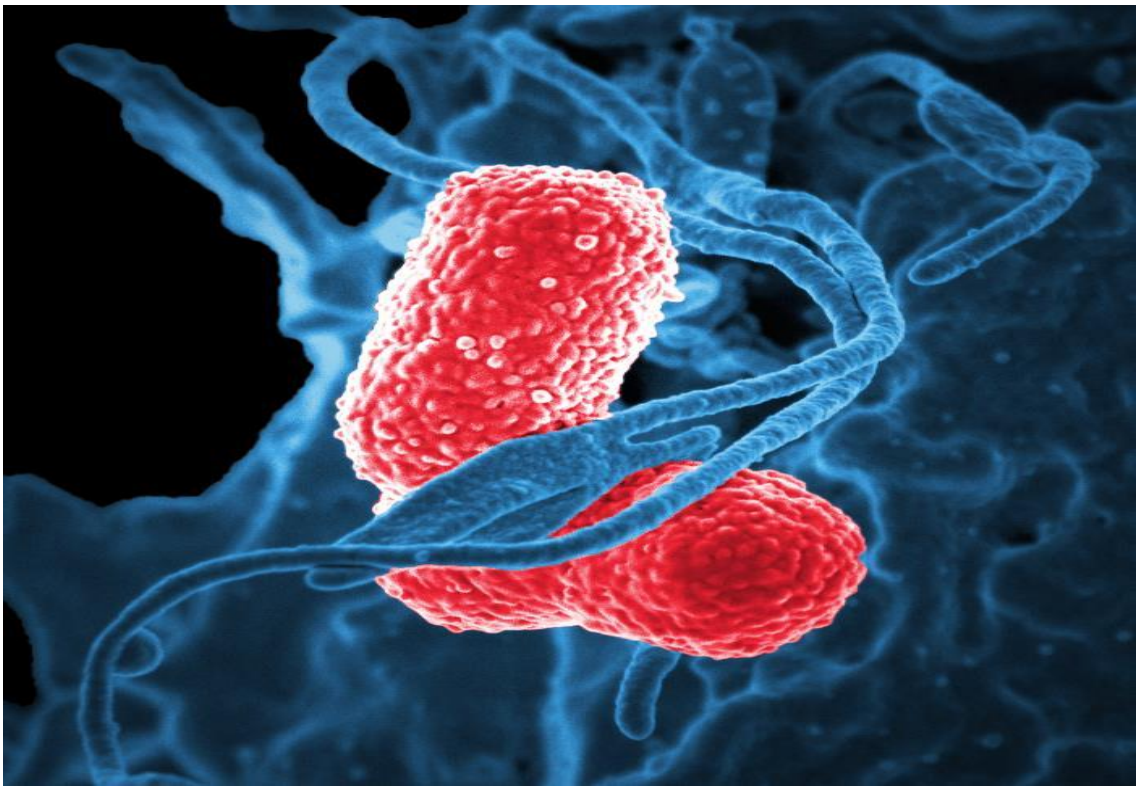


Fig (1-7): Colorized scanning electron micrograph (SEM) depicted a blue-colored of Klebsiella pneumoniae bacteria [(48)].

## 1.4 The aims of the present work

Amino acid derivatives are of great importance because many of these compounds have been found to show biological active, chemotherapeutic and antibiotic.

Schiff's base derivatives are considered as important class of compounds having a wide spectrum of biological activity.

This work was designed to inquire the following targets:

1. Synthesis of amino acid derivatives via Schiff's bases starting from benzaldehyde derivatives and 2-Aminopyridine.
2. Characterization of the products by using melting points, FTIR, $^{1}$H-NMR and $^{13}$C-NMR spectroscopy.
3. Exploration the biological activity of synthesized compounds aganist two kinds of Bacteria *Staphylococcus aureus* and *Klebsiella pneumoniae.*

# CHAPTER TWO

## EXPERIMENTAL PART

## 2.1 Chemicals

The following table shows the chemicals with their purity and companies.

**Table (2-1) showed all the used chemicals**

| Chemicals | purity | Supplied from |
|---|---|---|
| 2-Aminopyridine | 99% | GPR |
| Benzaldehyde | 99% | BDH |
| Benzene | 99.7% | ROMIL |
| Benzoyl chloride | 98% | SYNCHEMICA |
| Calcium chloride | - | BDH |
| 1,4-Dioxane | 99% | Thomas Baker |
| DMSO | 99.58% | POISON |
| Ethanol absolute | 99.9% | Scharlau |
| Hydrochloric acid | 37% | CDH |
| L-Alanine | 99.9% | AAG |
| L-Aspartic acid | 99% | Fluka |
| L-Asparagine | - | - |
| L-Phenyl alanine | 99% | Fluka-Garantie |
| *P*-Bromobenzaldehyde | 98% | Himedia |
| *P*-Chlorobenzaldehyde | 98% | Himedia |
| Glacial acetic acid | 90% | Hopkins & Williams |
| Glycine | 99.5% | ROMIL |
| Sodium carbonate | 99% | GPR |

## 2.2 Apparatus

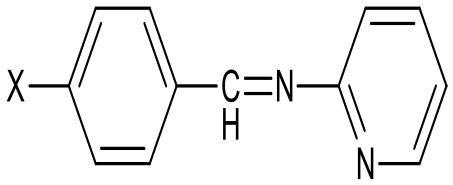
The following apparatus were mainly used in this work:

1. Melting points were determined on electro thermal capillary apparatus, Chachan, MLP-01, and were uncorrected.
2. Fourier Transform Infrared Spectroscopy **(**FT-IR) spectra in the range of (400-4000) $cm^{-1}$ were recorded by KBr disc on FT-IR, 8300 Shimadzu Spectrophotometer, (Ibn-Sena, Ministry of Industry).
3. Nuclear Magnetic Resonance spectroscopy (NMR), $^{1}H$ NMR and $^{13}C$ NMR by using DMSO as solvent in NMR Spectrometer 400 MHz, Avance III 400, Bruker, Germany, (Isfahan University, Isfahan, Iran).
4. Autoclave, Fanem MOD. 415 (Sao Paulo - Brazil). Biotechnology Department, College of Science, Baghdad University.
5. Incubator, Memmert (Germany). Biotechnology Department, College of Science, Baghdad University.

## 2.3 Procedures

### 2.3.1 Synthesis of *N*-(4-monosubstituted benzylidene)-pyridin-2-amine 3(A-C) [49]

A mixture (0.01 mol) of the Benzaldehyde derivatives and (0,01 mol, 0.94 gm) of 2-aminopyridine was dissolved in 15 mL absolute ethanol containing a drop of glacial acetic acid and refluxed for 10 hrs. The reaction mixture was then allowed to cool to room temperature, the solid was filtered, washed with (2%) HCl solution then with distilled water, recrystallized from ethanol to yield colored crystals.



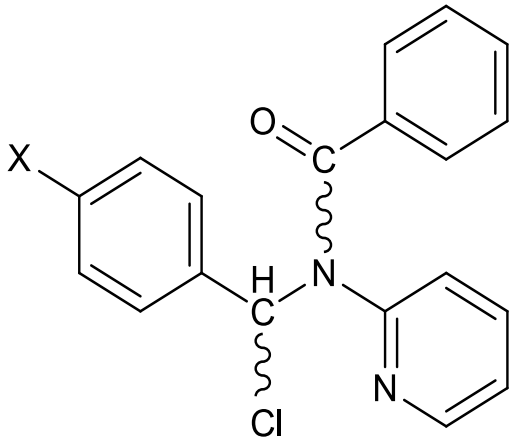

X: H, Cl, Br.

**Table (2-2) Physical properties of 3(A-C)**

| Comp. | X | Formula | Yield% | Melting Point | Color |
|---|---|---|---|---|---|
| **3A** | **H** | $C_{12}H_{10}N_2$ | 67% | 89-91 °C | Pale yellow |
| **3B** | **Cl** | $C_{12}H_9N_2Cl$ | 64% | 78-80 °C | Pale yellow |
| **3C** | **Br** | $C_{12}H_9N_2Br$ | 84% | 43-45 °C | Pale yellow |

### 2.3.2 Synthesis of *N*-[chloro (4-monosubstituted phenyl) methyl]-*N*-(pyridine-2-yl) benzamide 5(A-C) [49]

In a 50 mL round bottom flask equipped with a magnetic stirrer bar, was dissolved (0.005 mol) of Shiff 's bases 3(A-C) in 10 ml of dry benzene. In the dropping funnel (0.005 mol, 0.6 ml) of benzoyl chloride was placed in 10 ml of dry benzene. The benzoyl chloride solution was added dropwise to the reaction mixture and refluxed for 1hr. The solvent was evaporated and the precipitated colored product was filtered, washed with dilute solution of sodium carbonate (2%) then with distilled water, and recrystallized from ethanol and dried.



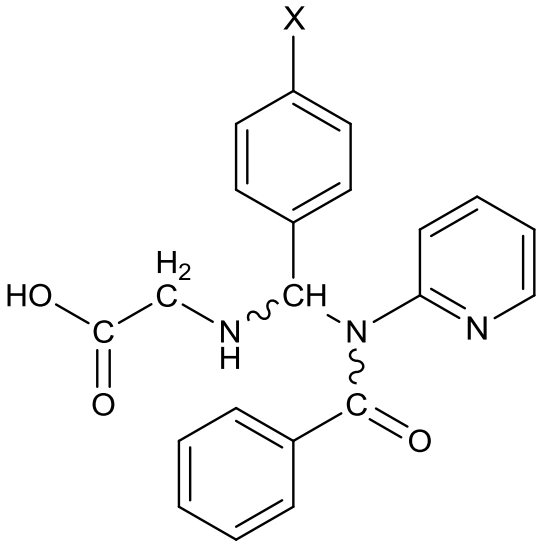

X: H, Cl, Br.

**Table (2-3) Physical properties of 5(A-C)**

| Comp. | X | Formula | Yield% | Melting Point | Color |
|---|---|---|---|---|---|
| **5A** | **H** | $C_{19}H_{14}N_2OCl$ | 63% | 99-101 °C | White |
| **5B** | **Cl** | $C_{19}H_{13}N_2OCl_2$ | 74% | 115-117 °C | White |
| **5C** | **Br** | $C_{19}H_{13}N_2O_2BrCl$ | 55% | 84-86 °C | Pale yellow |

### 2.3.3 Synthesis of *N*-[(benzoyl-pyridin-2-yl-amino)-(4-mono substituted phenyl)-methyl]-L-Amino acid [6(A-C) – 10(A-C)] [18]

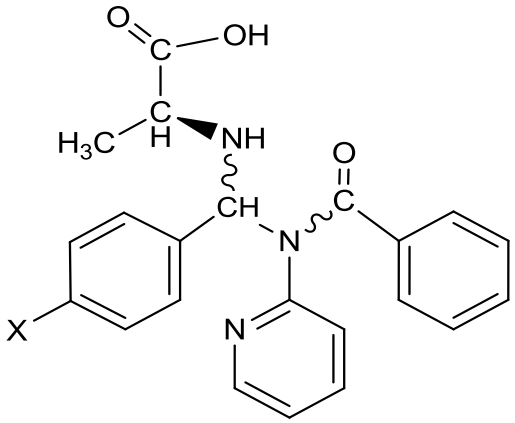
A mixture of (0.005 mol) acid halide 5(A-C) and (0.005 mol) amino acid were dissolved in 10 ml (2:1) 1, 4-dioxane-water, and was refluxed with stirring for 4 hrs. The resulting mixture was cooled and a few drops of distilled water were added, the crystals were separated out, filtered, washed with distilled water. The product was recrystallized from (2:1) 1, 4-dioxane: water and dried.




X: H, Cl, Br.

**Table (2-4) Physical properties of 6(A-C)**

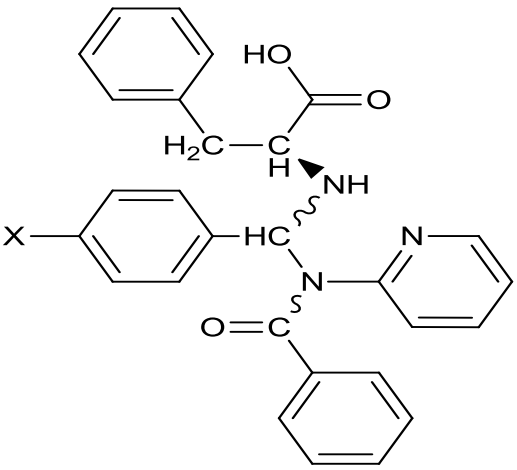
| Comp. | X | Formula | Yield% | Melting Point | Color |
|---|---|---|---|---|---|
| **6A** | **H** | $C_{21}H_{19}N_3O_3$ | 72% | 73-75 °C | Pale white |
| **6B** | **Cl** | $C_{21}H_{18}ClN_3O_3$ | 72% | 75-77 °C | White |
| **6C** | **Br** | $C_{21}H_{18}BrN_3O_3$ | 68% | 72-74 °C | White |



X: H, Cl, Br.

**Table (2-5) Physical properties of 7 (A-C)**

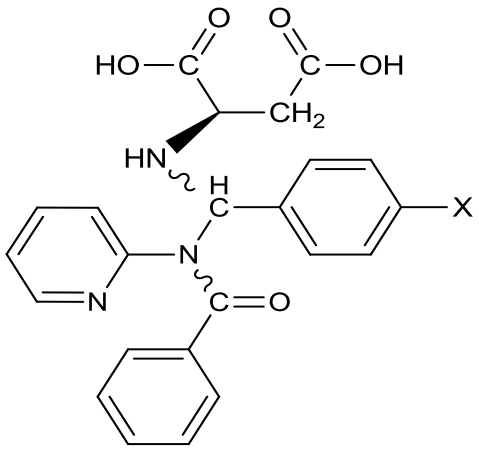
| Comp. | X | Formula | Yield% | Melting Point | Color |
|---|---|---|---|---|---|
| **7A** | **H** | $C_{22}H_{21}N_3O_3$ | 72% | 74-76 °C | Pale white |
| **7B** | **Cl** | $C_{22}H_{20}ClN_3O_3$ | 72% | 71-73 °C | Pale white |
| **7C** | **Br** | $C_{22}H_{20}BrN_3O_3$ | 77% | 70-72 °C | White |



X: H, Cl, Br.

**Table (2-6) Physical properties of 8(A-C)**

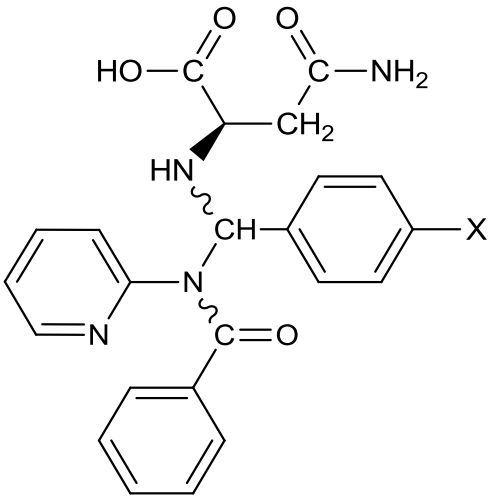
| Comp. | X | Formula | Yield% | Melting Point | Color |
|---|---|---|---|---|---|
| **8A** | **H** | $C_{28}H_{25}N_3O_3$ | 68% | 69-71 °C | Pale white |
| **8B** | **Cl** | $C_{28}H_{24}ClN_3O_3$ | 71% | 72-74 °C | Pale yellow |
| **8C** | **Br** | $C_{28}H_{24}BrN_3O_3$ | 77% | 76-78 °C | Pale yellow |



X: H, Cl, Br.

**Table (2-7) Physical properties of 9(A-C)**

| Comp. | X | Formula | Yield% | Melting Point | Color |
|---|---|---|---|---|---|
| **9A** | **H** | $C_{23}H_{21}N_3O_5$ | 72% | 76-78 °C | Pale white |
| **9B** | **Cl** | $C_{23}H_{20}ClN_3O_5$ | 72% | 75-77 °C | Pale white |
| **9C** | **Br** | $C_{23}H_{20}BrN_3O_5$ | 80% | 68-70 °C | White |



X: H, Cl, Br.

**Table (2-8) Physical properties of 10(A-C)**

| Comp. | X | Formula | Yield% | Melting Point | Color |
|---|---|---|---|---|---|
| **10 A** | **H** | $C_{23}H_{24}N_4O_3$ | 72% | 75-77 °C | Pale white |
| **10 B** | **Cl** | $C_{23}H_{23}ClN_4O_3$ | 75% | 70-72 °C | Pale white |
| **10 C** | **Br** | $C_{23}H_{23}BrN_4O_3$ | 81% | 76-78 °C | White |

## 2.4 Biological Activity

### 2.4.1 Antimicrobial Activity

In this study, the synthesized compounds were evaluated for their *invitro* antimicrobial activity against the gram negative bacteria and gram positive bacteria. The microorganism was supplied as ready bacterial cultures by Biotechnology Department, College of Science, Baghdad University.

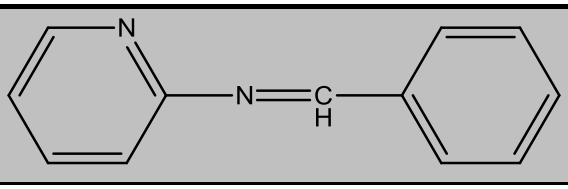
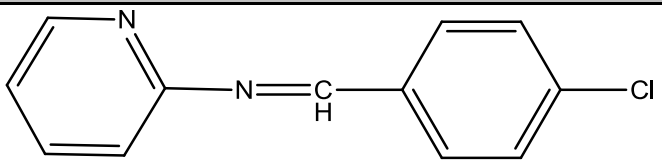
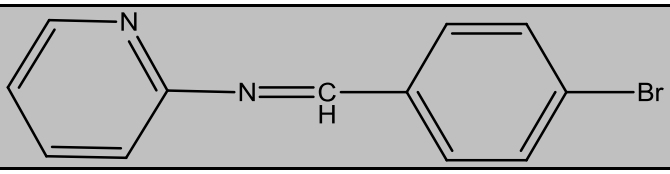
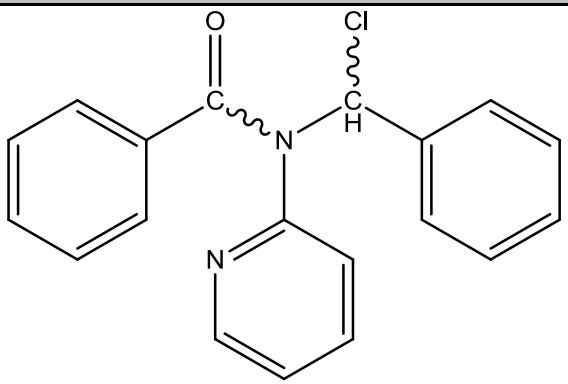
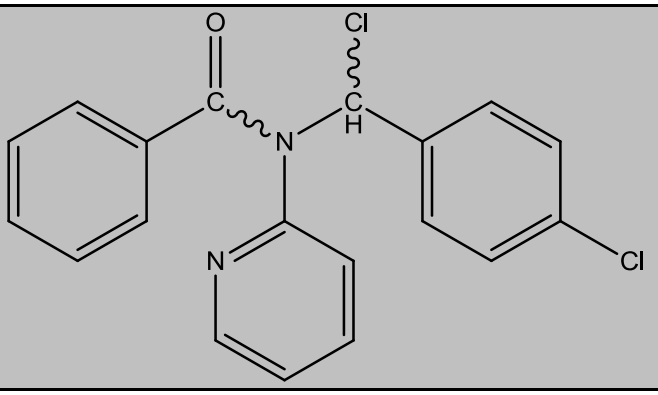
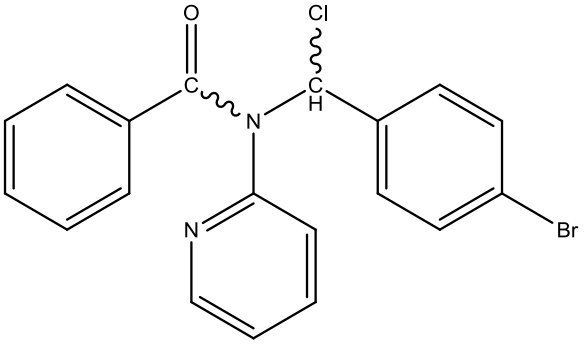
Well diffusion method [(50)] was used to determine the inhibiting potential of the prepared compounds against two strains of bacteria, one of them was gram negative (*Klebsiella pneumoniae*) and the other was gram positive (*Staphylococcus aureus*). Meropenem was used to compare the power of inhibition, by using the following steps:

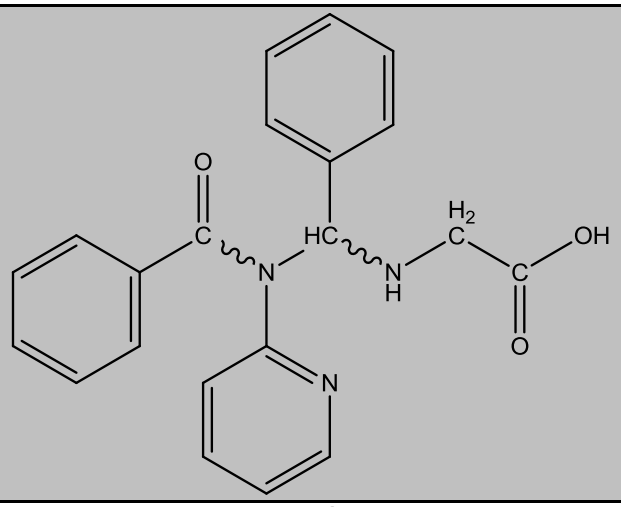
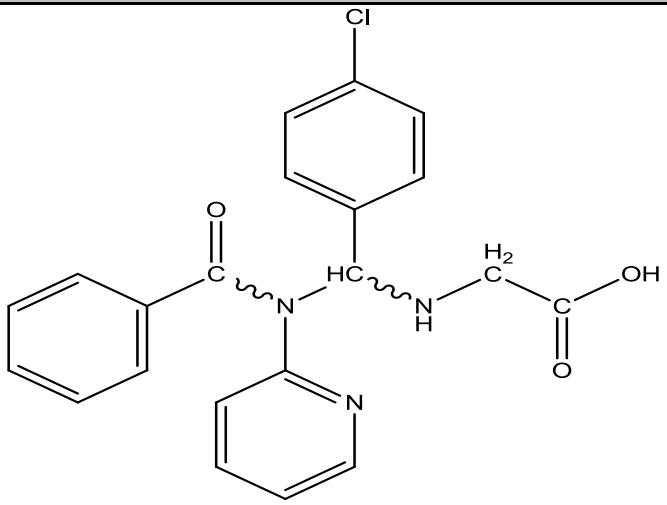
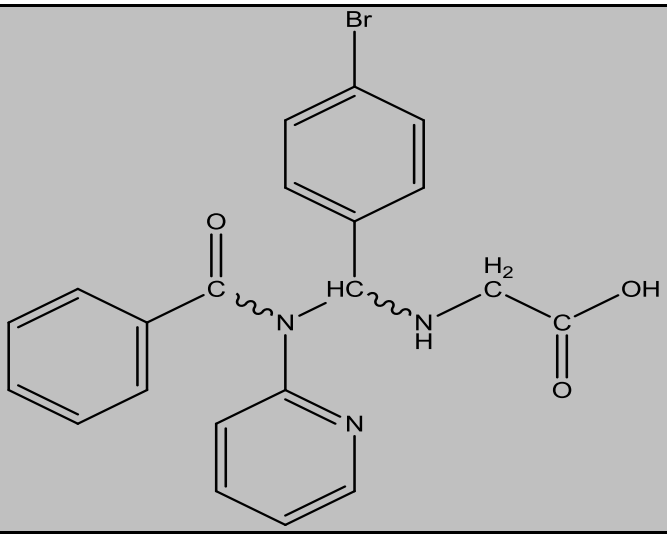
1. Bacterial media was prepared by using a touch of bacterial culture to a test tube contains (5 mL) of the sterilized distilled water.
2. Mueller Hinton (MH.) was prepared by dissolving (38 g) MH. in (1000 mL) distilled water and sterilized by autoclave at 121°C, 1.5 atmosphere for 15 min., then cooled to (40-45) min.
3. In each (25 mL) MH., (250 μL) of bacterial media (*Staphylococcus aureus* or *Klebsiella pneumoniae*) was added and mixed gently, then it has been poured into a Petri dish and wait till solidification.

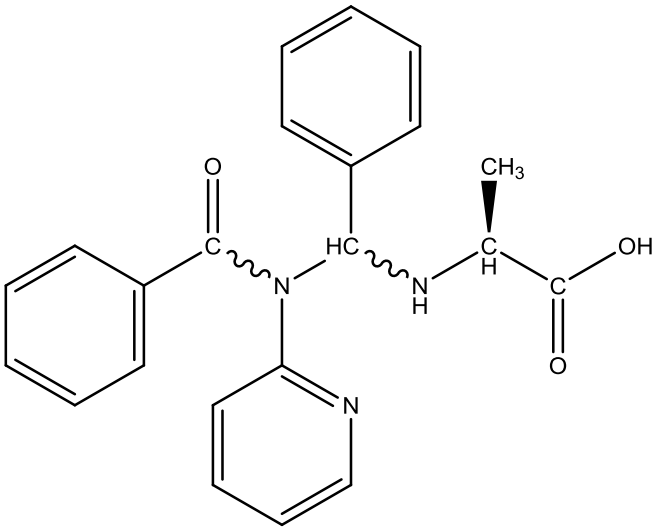
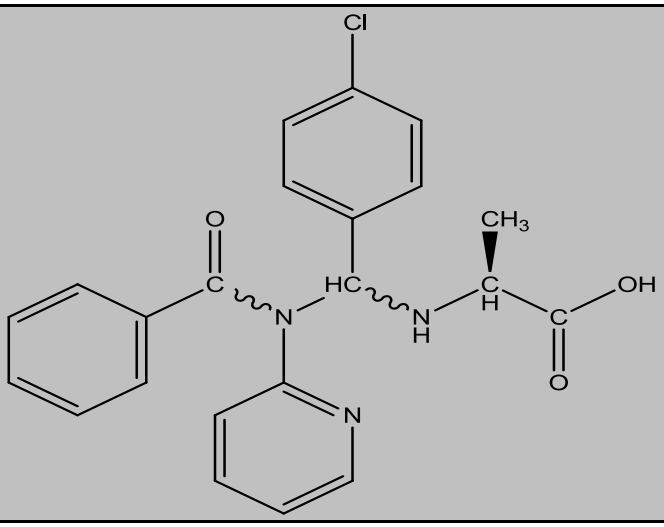
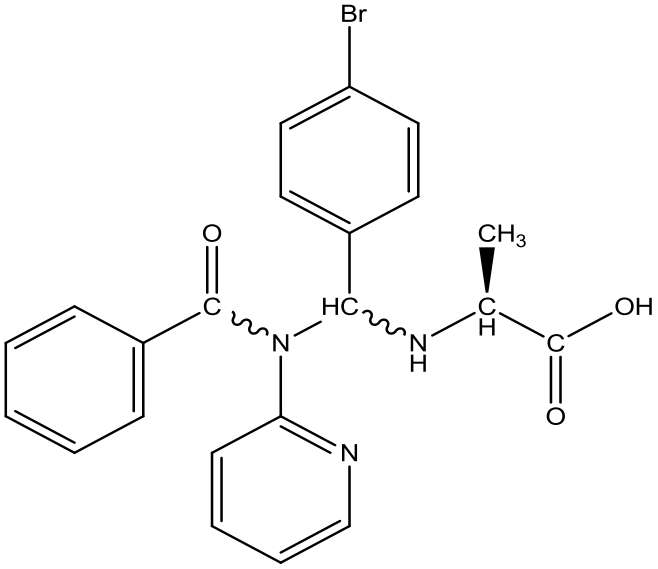
In each medium, five pores were made by the use of a sterile dry rod with a diameter of 5 mm. The inhibition zones test [(46)] was applied by using solutions of prepared compounds dissolved in DMSO. These solutions were added using fixed amount (50 μL) of each compound with concentrations of (5, 10, 25, 50) μg/mL in pores. The control (DMSO) was added to the fifth pore. The plates were incubated at 37 $^{o}$C for 24 hrs.

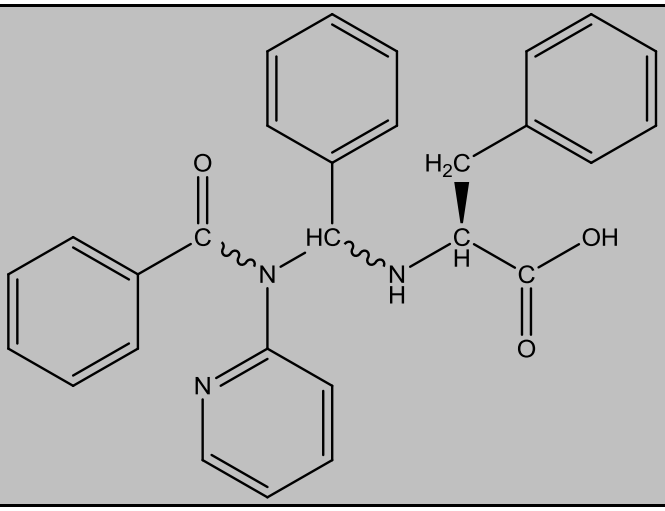
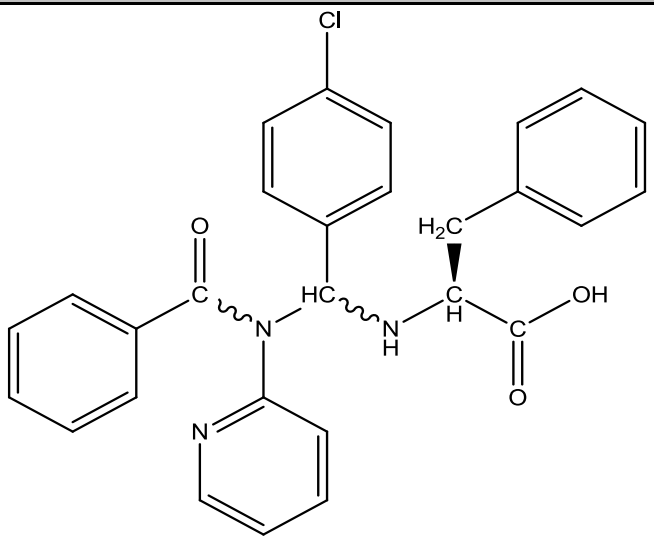
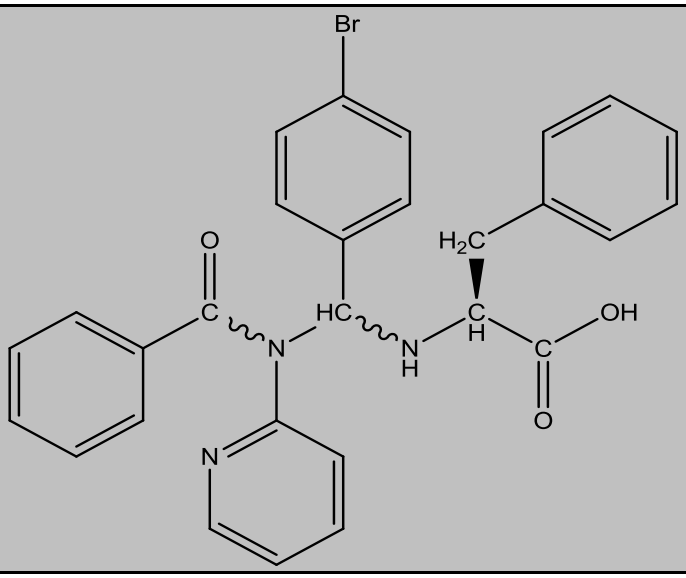
Finally the inhibition diameter was measured for each pore using a ruler. The translucent area which surrounds the disc (including the diameter of the disc that lacks bacterial growth) considered as the zone of inhibition.

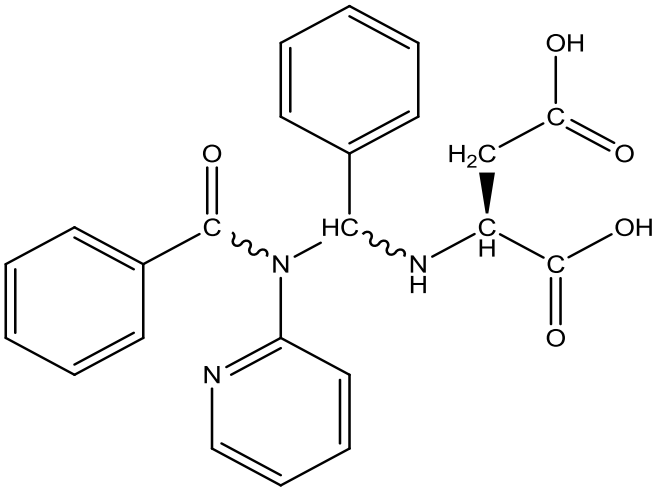
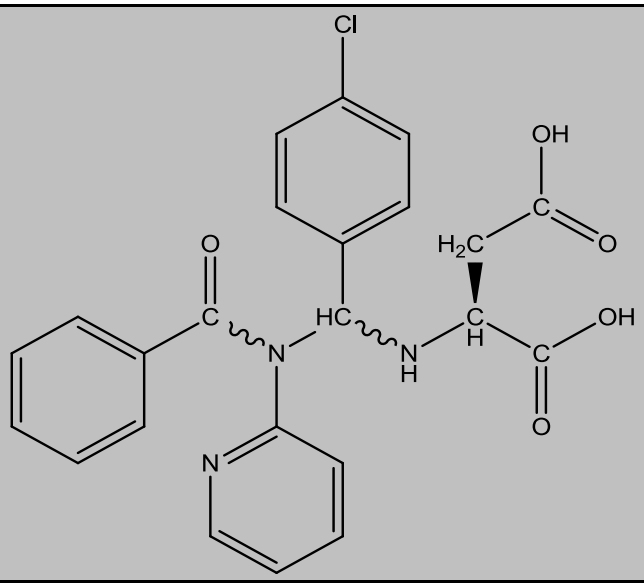
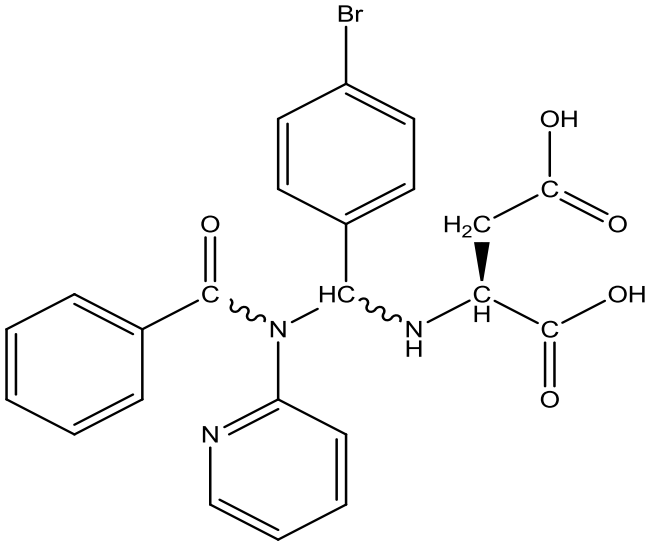
**Table (2-9) Compilation of compounds with their IUPAC names and structures synthesized in this work:**

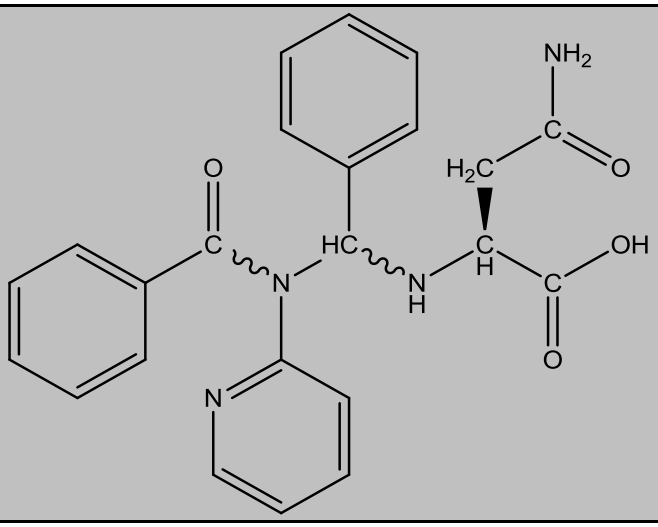
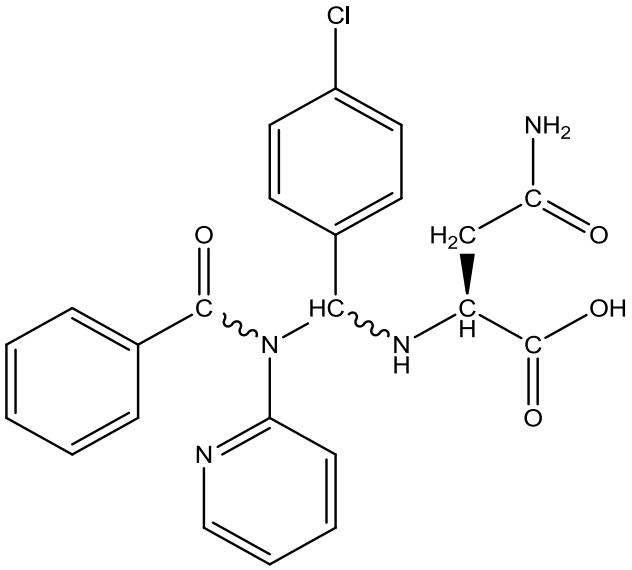
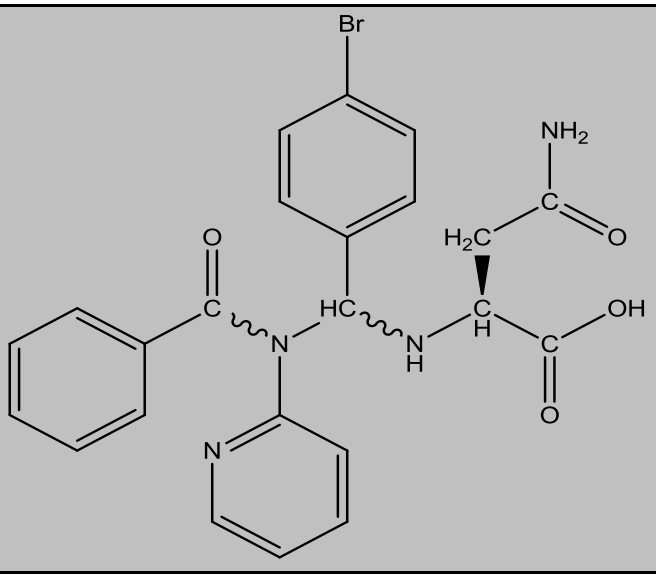
| NO. | Name | structure |
|---|---|---|
| **3A** | *N*-4-benzylidenepyridin-2-amine |  |
| **3B** | *N*-(4-chlorobenzylidene) pyridin-2-amine |  |
| **3C** | *N*-(4-bromobenzylidene) pyridin-2-amine |  |
| **5A** | *N*-[chloro(phenyl) methyl]-*N*(pyridine-2-yl)benzamide |  |
| **5B** | *N*-[chloro(4-chlorophenyl) methyl]-*N*(pyridine-2-yl)benzamide |  |
| **5C** | *N*-[chloro(4-bromophenyl) methyl]-*N*(pyridine-2-yl)benzamide |  |

| | | |
|---|---|---|
| **6A** | *N*-[(benzoyl-pyridin-2-yl-amino)-(phenyl)-methyl]-Glycine |  |
| **6B** | *N*-[(benzoyl-pyridin-2-yl-amino)-(4-chlorophenyl)-methyl]-Glycine |  |
| **6C** | *N*-[(benzoyl-pyridin-2-yl-amino)-(4-bromophenyl)-methyl]-Glycine |  |

| | | |
|---|---|---|
| **7A** | (2S)-2-*N*-[(benzoyl-pyridin-2-yl-amino)-(phenyl)-methyl]-L-Alanine |  |
| **7B** | (2S)-2-*N*-[(benzoyl-pyridin-2-yl-amino)-(4-chlorophenyl)-methyl]-L-Alanine |  |
| **7C** | (2S)-2-*N*-[(benzoyl-pyridin-2-yl-amino)-(4-bromophenyl)-methyl]-L-Alanine |  |

| | | |
|---|---|---|
| **8A** | (2S)-2-*N*-[(benzoyl-pyridin-2-yl-amino)-(phenyl)-methyl]-L-Phenylalanine |  |
| **8B** | (2S)-2-*N*-[(benzoyl-pyridin-2-yl-amino)-(4-chlorophenyl)-methyl]-L-Phenylalanine |  |
| **8C** | (2S)-2-*N*-[(benzoyl-pyridin-2-yl-amino)-(4-bromophenyl)-methyl]-L-Phenylalanine |  |

| | | |
|---|---|---|
| **9A** | (2S)-2-*N*-[(benzoyl-pyridin-2-yl-amino)-(phenyl)-methyl]-L-Asparatic acid |  |
| **9B** | (2S)-2-*N*-[(benzoyl-pyridin-2-yl-amino)-(4-chlorophenyl)-methyl]-L-Asparatic acid |  |
| **9C** | (2S)-2-*N*-[(benzoyl-pyridin-2-yl-amino)-(4-bromophenyl)-methyl]-L-Asparatic acid |  |

| | | |
|---|---|---|
| **10A** | (2S)-2-*N*-[(benzoyl-pyridin-2-yl-amino)-(phenyl)-methyl]-L-Asparagein |  |
| **10B** | (2S)-2-*N*-[(benzoyl-pyridin-2-yl-amino)-(4-chlorophenyl)-methyl]-L-Asparagine |  |
| **10C** | (2S)-2-*N*-[(benzoyl-pyridin-2-yl-amino)-(4-bromophenyl)-methyl]-L-Asparagine |  |

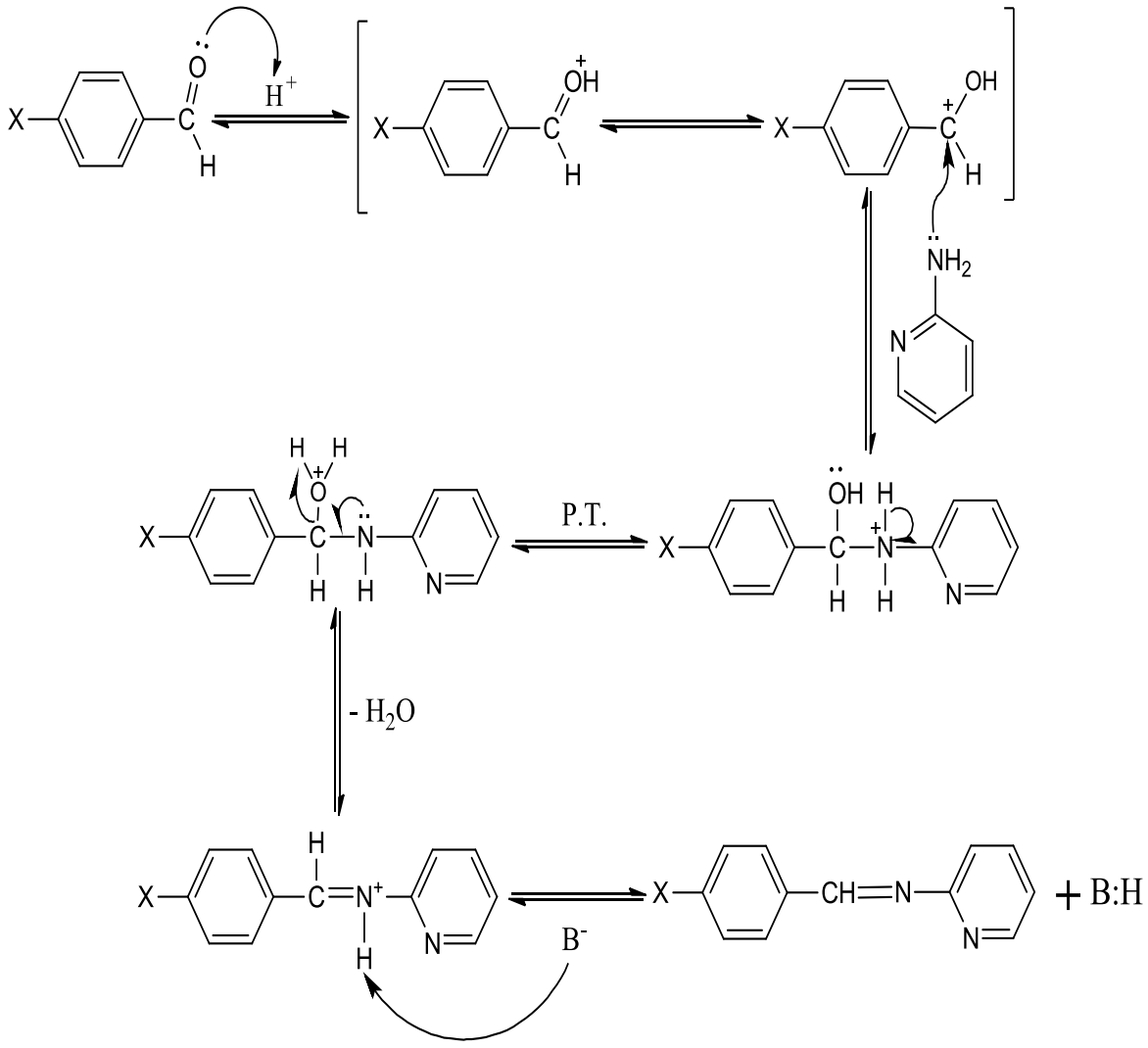
# CHAPTER THREE

## RESULTS & DISCUSSION

# 3 Results and discussion

## 3.1 Synthesis

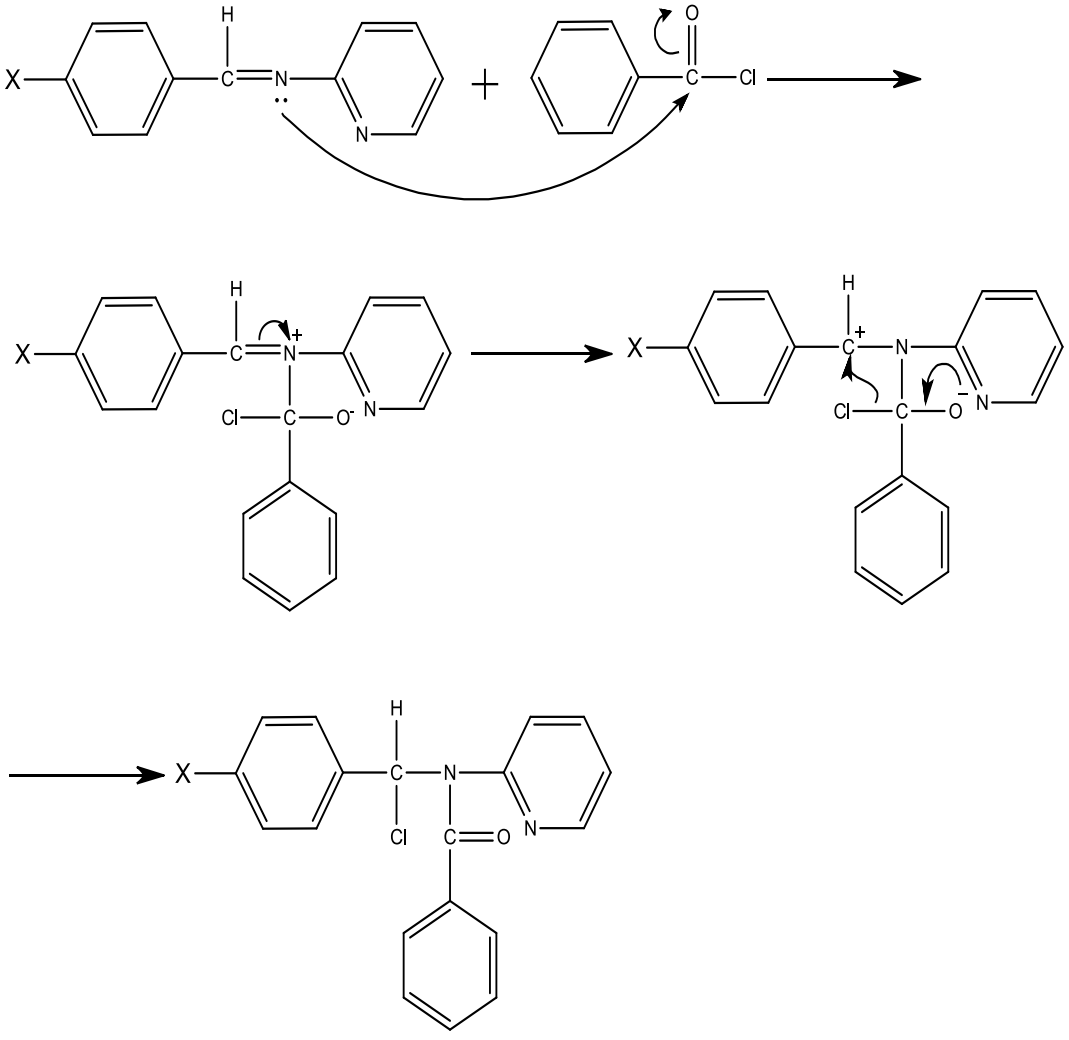
Schiff 's bases of *N*-(4-monosubstituted benzylidene) pyridin-2-amine are synthesized through acid catalyzed condensation reaction of Benzaldehyde derivatives and 2-aminopyridine in ethanol. The formed Schiffs base may be a mixture of cis and trans isomers. The reaction follows an addition-elimination mechanism described below [(49)].




X: H, Cl, Br.

**Scheme (3-1):** The reaction mechanism for the synthesis of 3(A-C).

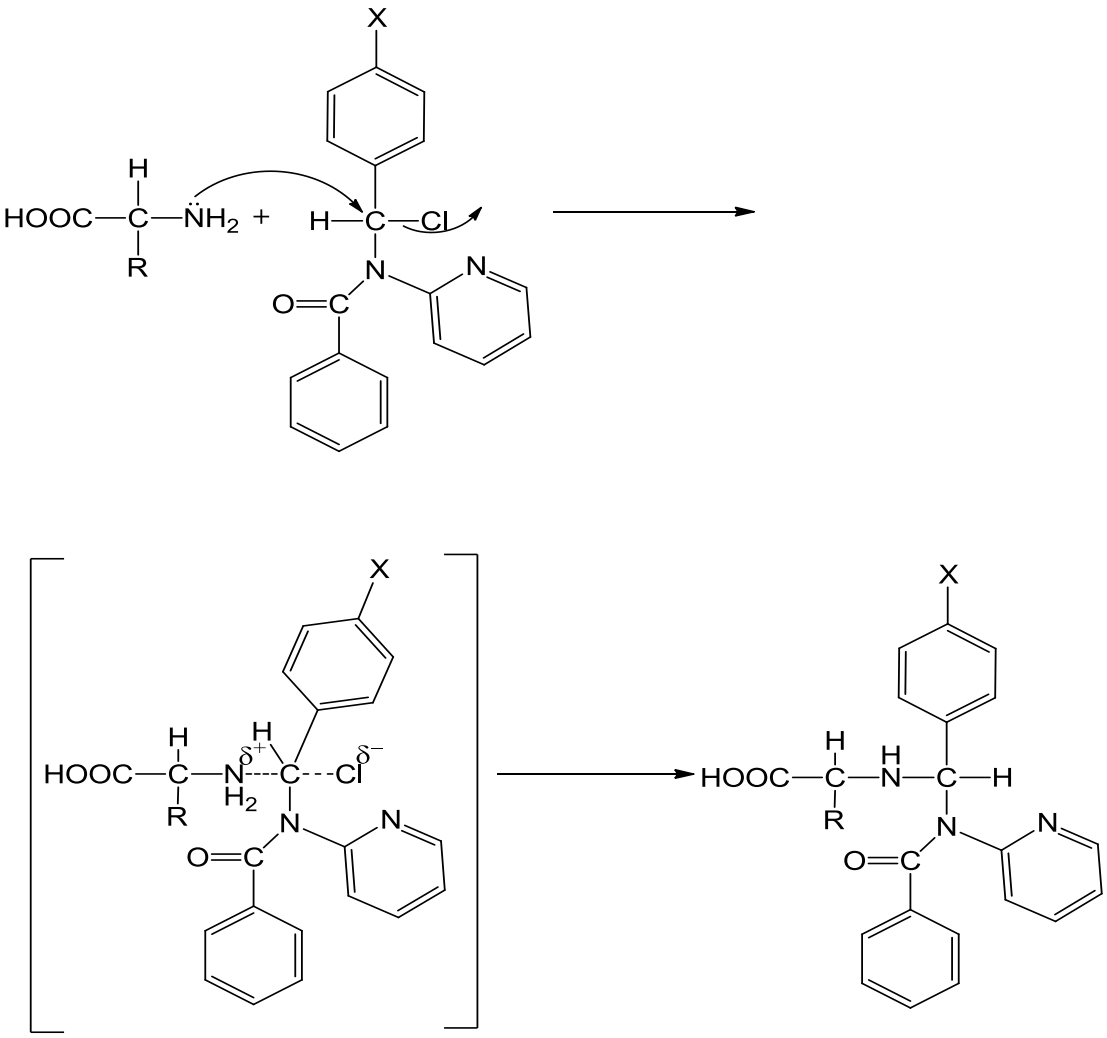
It is found that Schiff 's bases are nucleophiles and weak bases, so they do not react with simple allyl, alkyl or benzyl halides, but they react smoothly with the relatively more reactive acid halides such as benzoyl chloride to give 5(A-C) [49]. The saturation of the double bond produce a new asymmetric carbon atom (stereogenic center) and the product might be a racemic mixture of the two enantiomers. Nucleophilic addition mechanism can be described as follows [51] [52]:



X: H, Cl, Br.

**Scheme (3-2):** The reaction mechanism for the synthesis of 5(A-C).

[6(A-C) – 10(A-C)] have been synthesized by the reaction of L-amino acid with N-[Chloro-(4-monosubstituted-phenyl)-methyl]-N-pyridin-2-yl-benzamide in 2:1 of 1, 4-dioxane-water as a solvent [18]. The product contains two chiral centers, the original carbon and the new coming carbon atom resulted from amino acid. The product is a mixture of diasteriomers. The mechanism of this reaction follows $S_N2$ mechanism as described below [51] [52].




Transition State

X: H, Cl, Br.

R: H, $CH_3$, $CH_2C_6H_5$, $CH_2COOH$, $CH_2CONH_2$.

**Scheme (3-3):** The reaction mechanism for the synthesis of [6(A-C)–10(A-C)].

## 3.2 FT-IR spectrum of prepared compounds

### 3.2.1 Characterization of *N*-(4-monosubstituted benzylidene) pyridin-2-amine 3(A-C)

The Schiff 's bases were characterized by FT-IR spectra fig (3-1), (3-2), (3-3), which showed disappearance of $–NH_2$ absorption band at 3300 $cm^{-1}$ for symmetric and 3443 $cm^{-1}$ for asymmetric band in 2-Aminopyridine, disappearance of carbonyl aldehyde absorption bands was seen in the range of (1689-1699) $cm^{-1}$ and the appearance of the stretching vibration of C=N band at 1678 $cm^{-1}$ indicates the formation of Schiff base. The other informative bands are listed in Table (3-1).

**Table (3-1) FT-IR spectral data for Synthesized 3(A-C)**

| Comp. NO. | X | ν N=C–H arom. | ν C–H arom. | ν C–H aliph. | ν C=N imine | ν C=C arom. | Para sub. |
|---|---|---|---|---|---|---|---|
| **3A** | **H** | 3209 | 3082 | as 3024<br>sy 2970 | 1678 | 1597 | - |
| **3B** | **Cl** | 3147 | 3086 | as 2962<br>sy 2931 | 1678 | 1585 | 767 |
| **3C** | **Br** | 3240 | 3066 | as 2970<br>sy 2935 | 1678 | 1581 | 779 |

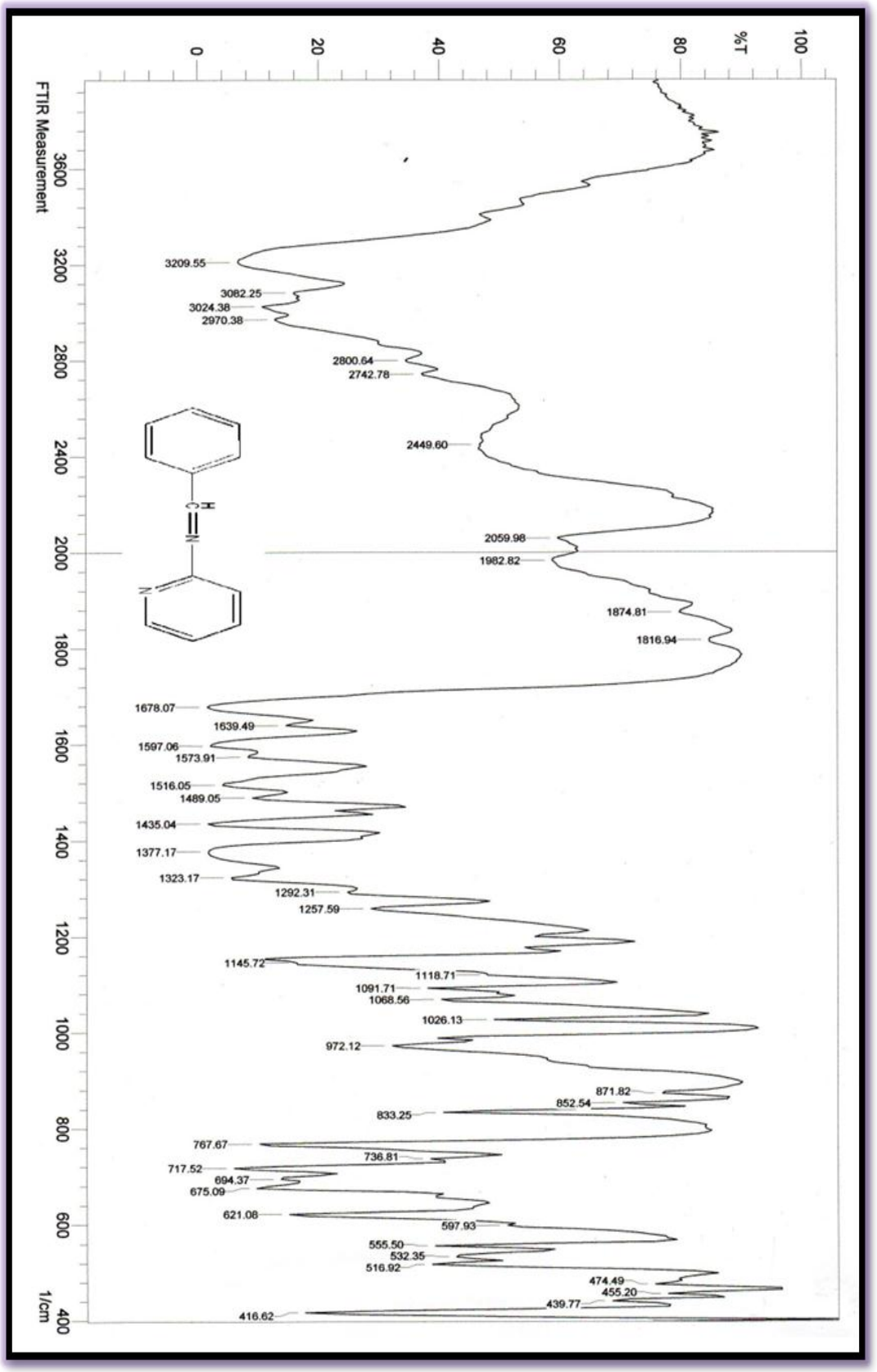



**Fig (3-1): FT-IR ($cm^{-1}$) spectrum of [3A].**

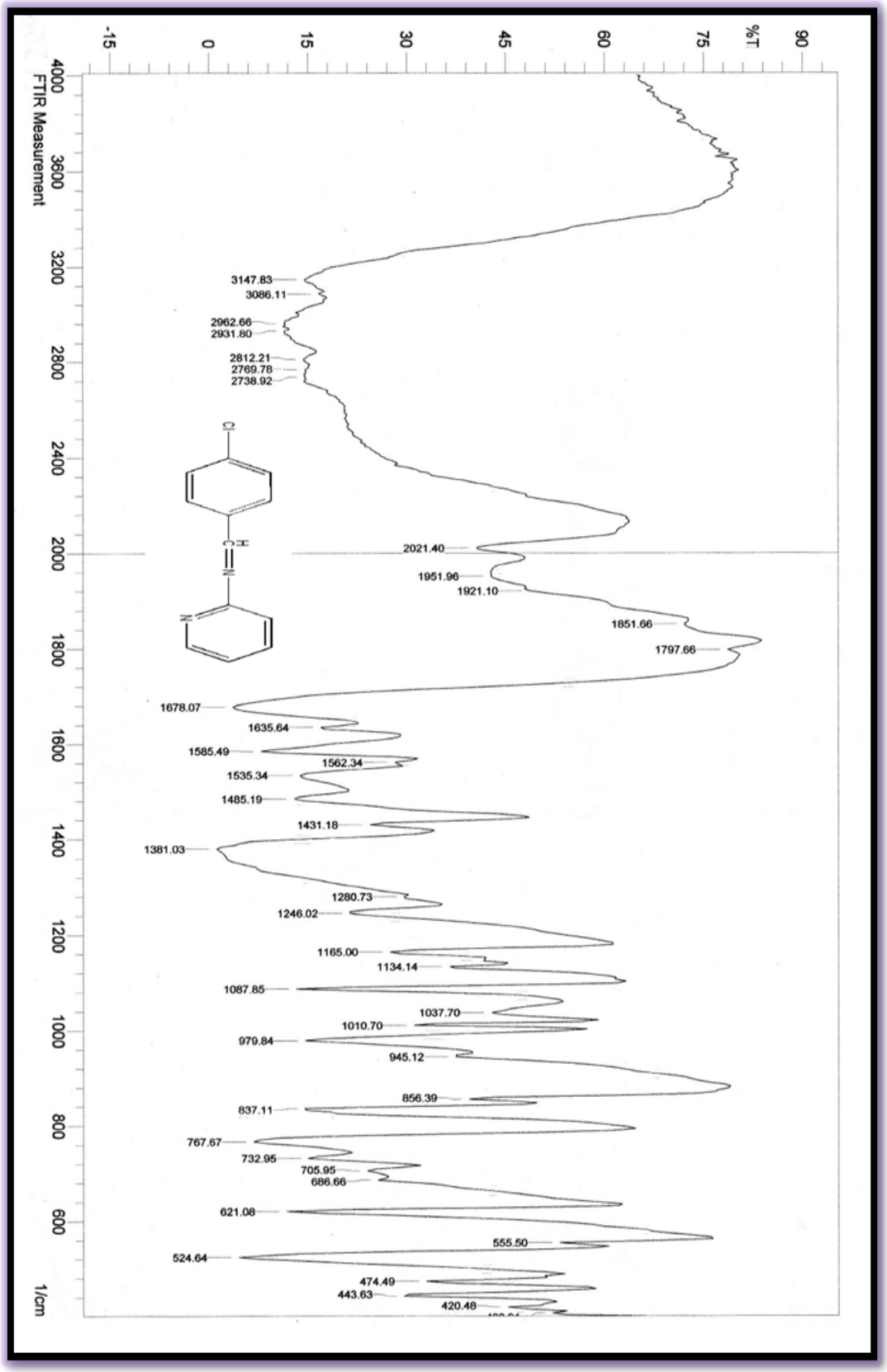



**Fig (3-2): FT-IR ($cm^{-1}$) spectrum of [3B].**

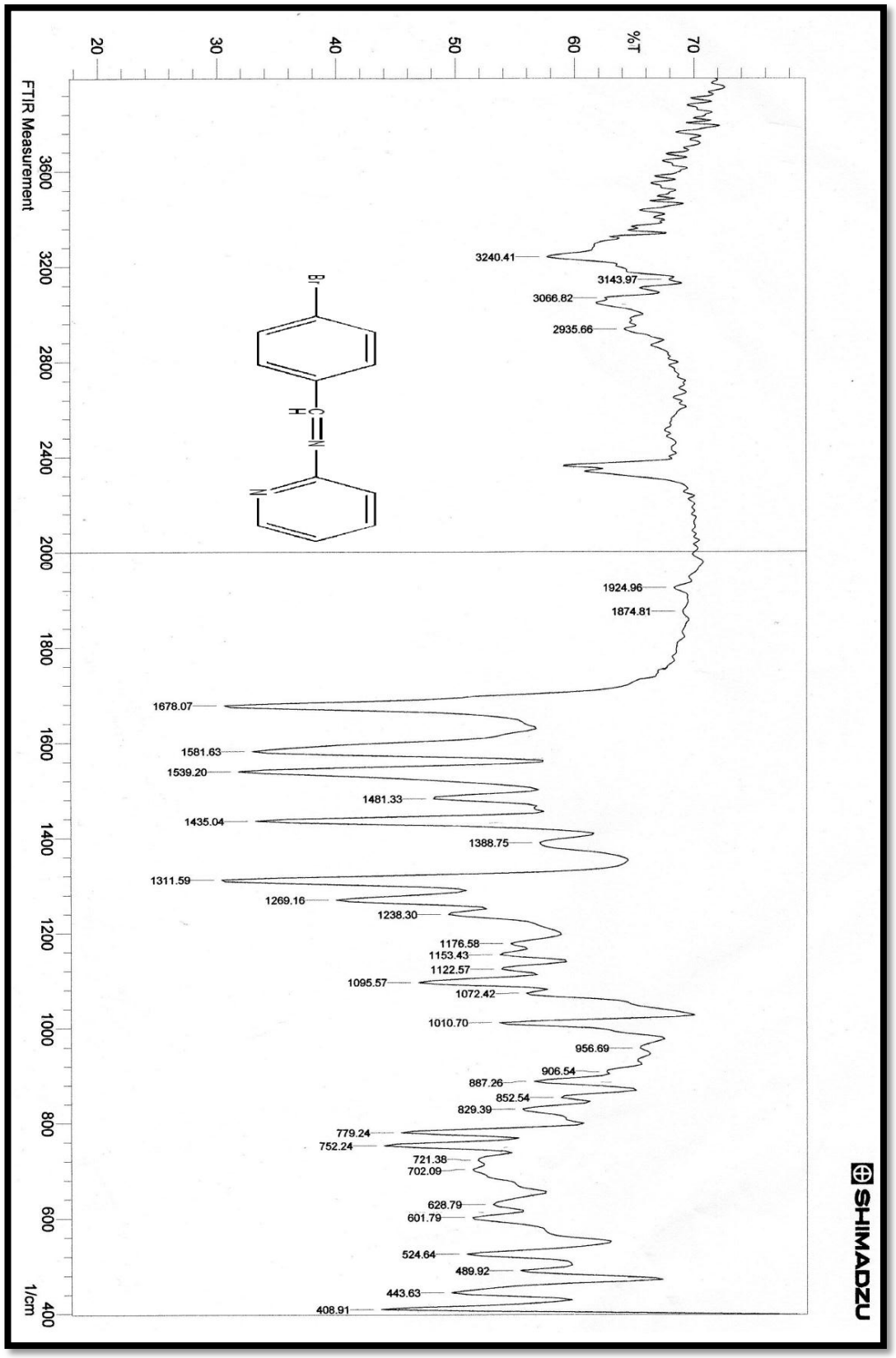



**Fig (3-3): FT-IR ($cm^{-1}$) spectrum of [3C].**

### 3.2.2 Characterization of *N*-[chloro-(4-monosubstitutedphenyl) methyl]-*N*-(pyridin-2-yl) benzamide 5(A-C)

The FT-IR spectra fig (3-4), (3-5), (3-6) show appearance of carbonyl amid absorption band at range (1681-1685) $cm^{-1}$, and disappearance of C=N absorption band at 1678 $cm^{-1}$. The bands at range (659-705) $cm^{-1}$ are attributed to stretching vibration of C-Cl band, the other informative bands are listed in Table (3-2).

**Table (3-2) FT-IR spectral data for synthesized 5(A-C)**

| Comp. NO. | X | ν C–H arom. | ν C–H aliph. | ν C=O amide | ν N=C–H arom. | ν C–N arom. | ν C–Cl aliph. |
|---|---|---|---|---|---|---|---|
| **5A** | **H** | 3062 | as 2927<br>sy 2843 | 1685 | 3240 | as 1296<br>sy 1242 | 659 |
| **5B** | **Cl** | 3070 | as 3005<br>sy 2885 | 1681 | - | as 1296<br>sy 1242 | 705 |
| **5C** | **Br** | 3074 | as 3008<br>sy 2951 | 1685 | - | as 1296<br>sy 1242 | 705 |

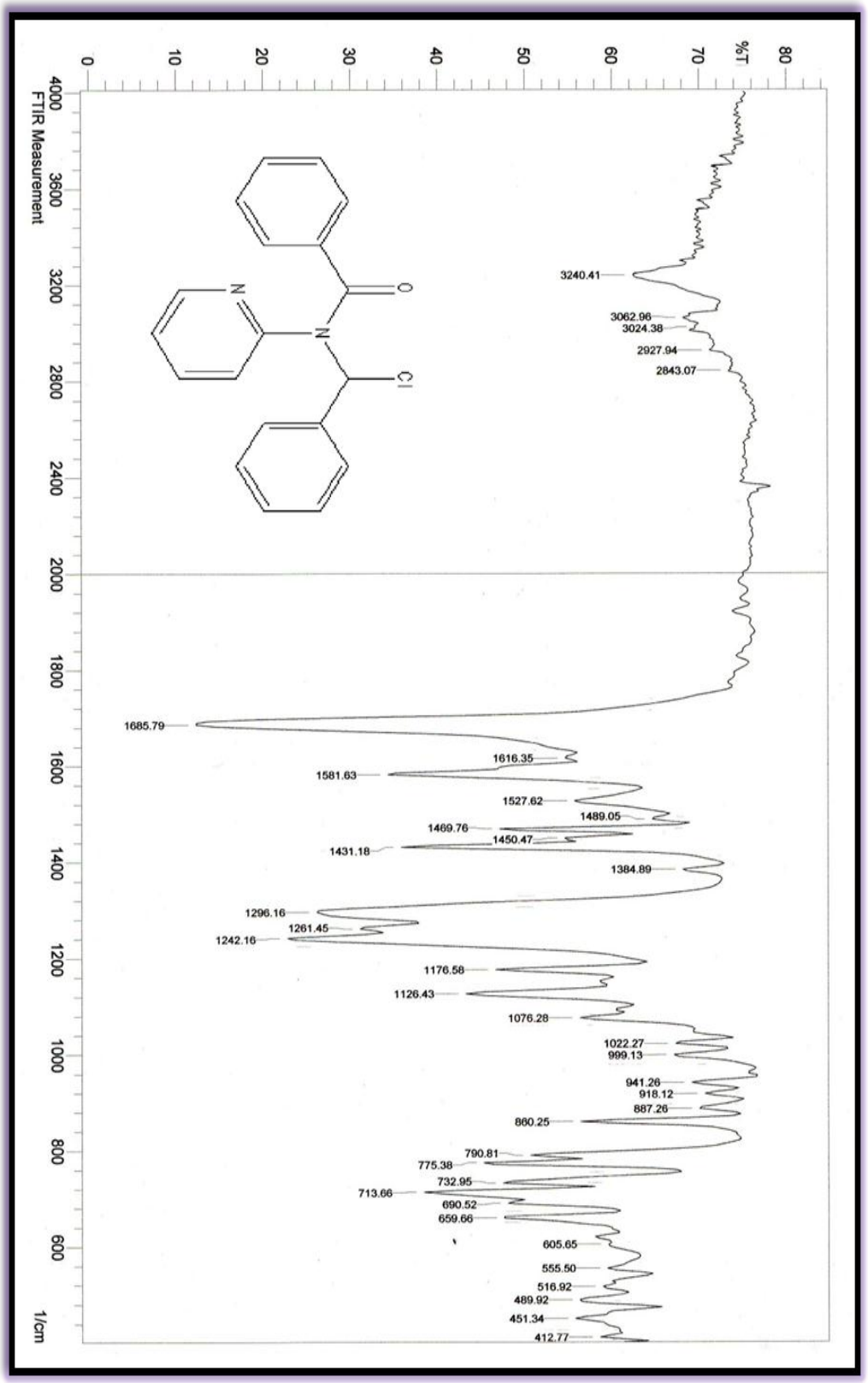



**Fig (3-4): FT-IR ($cm^{-1}$) spectrum of [5A].**

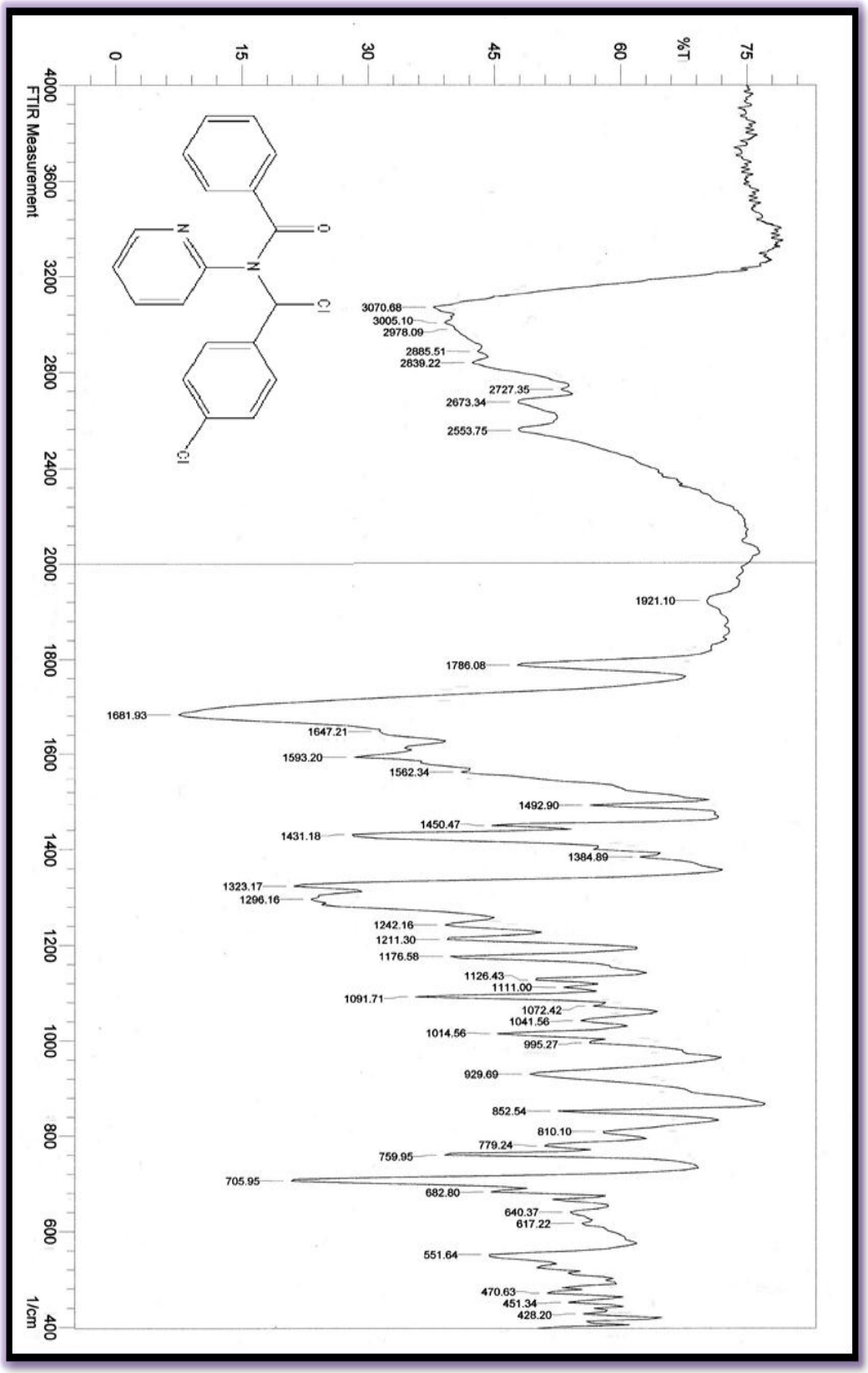



**Fig (3-5): FT-IR ($cm^{-1}$) spectrum of [5B].**

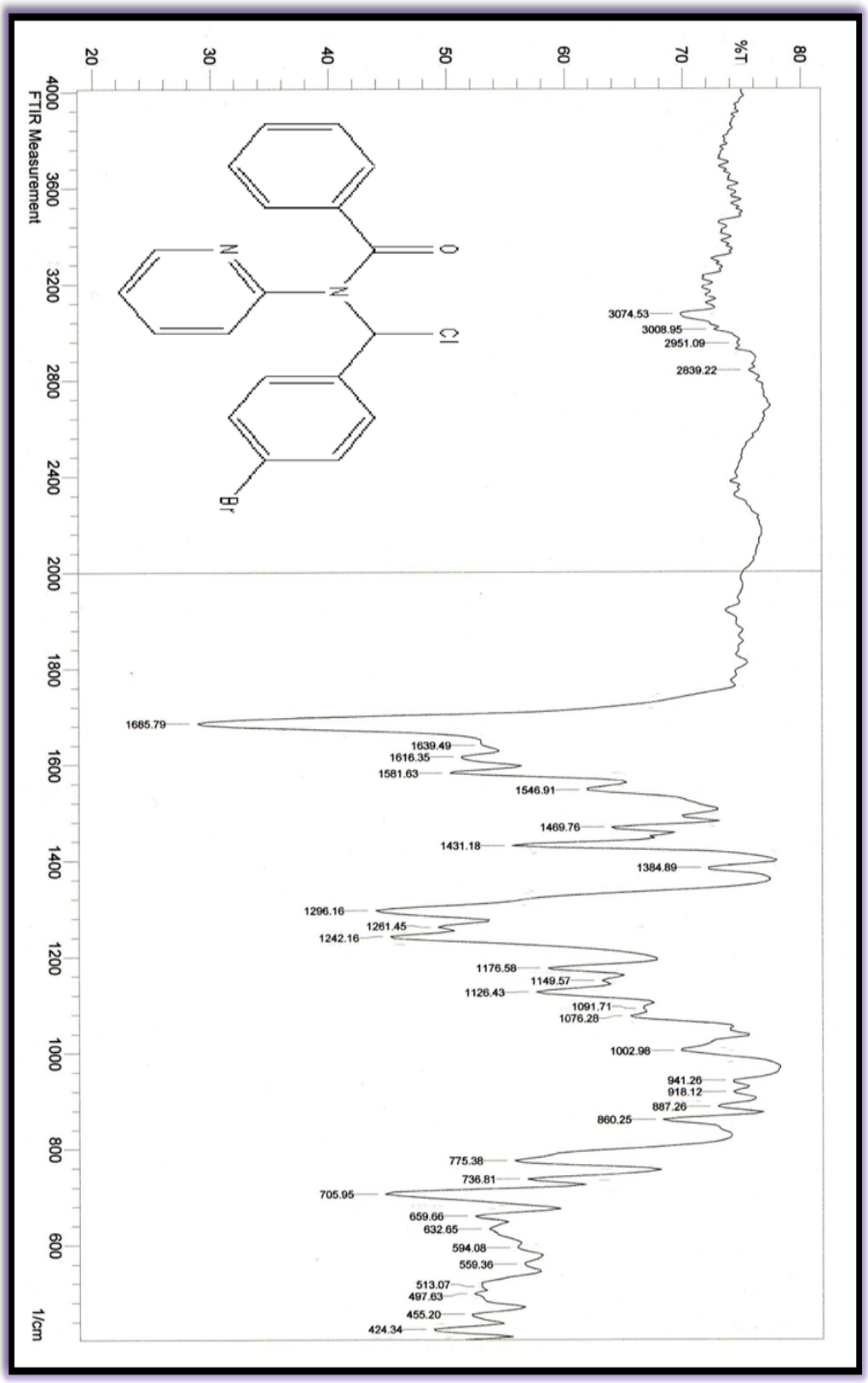



**Fig (3-6): FT-IR ($cm^{-1}$) spectrum of [5C].**

### 3.2.3 Characterization of (2S)-2-*N*-[(benzoyl-pyridin-2-yl-amino) (4-monosubstituted-phenyl)-methyl]-L-Amino acid [6(A-C)-10(A-C)]

The structure of [6(A-B)-10(A-B)] compounds have been confirmed by the appearance of the band at 1678 $cm^{-1}$ and a band at 3275 $cm^{-1}$ and a band at (3294-3302) which were referred to the amide carbonyl overlapped with the carboxylic acid carbonyl, N-H and hydroxyl group. Also the disappearance of band at range (659-705) $cm^{-1}$ confirms the substitution of Chloride with the Amino acid in fig [(3-7)-(3-21)].

**Table (3-3) FT-IR spectral data for synthesized 6(A-C)**

| Comp. NO. | X | υN=C–H arom. | υC–H arom. | υC–H aliph. | υC=O overlap between acid and amide | υNH | υOH carb. acid |
|---|---|---|---|---|---|---|---|
| **6A** | **H** | 3136 | 3074 | as 2927<br>sy 2850 | 1678 | 3275 | ~3300 |
| **6B** | **Cl** | 3132 | 3062 | as 2927<br>sy 2850 | 1678 | 3275 | 3300 |
| **6C** | **Br** | 3136 | 3062 | as 2970<br>sy 2877 | 1678 | 3275 | 3294 |

**Table (3-4) FT-IR spectral data for synthesized 7(A-C)**

| Comp. NO. | X | υN=C–H arom. | υC–H arom. | υC–H aliph. | υC=O overlap between acid and amide | υNH | υOH carb. acid |
|---|---|---|---|---|---|---|---|
| **7A** | **H** | 3116 | 3062 | as 2935<br>sy 2850 | 1678 | 3275 | 3294 |
| **7B** | **Cl** | 3136 | 3062 | as 2931<br>sy 2858 | 1678 | 3275 | 3298 |
| **7C** | **Br** | 3132 | 3066 | as 3005<br>sy 2858 | 1678 | 3275 | ~3300 |

**Table (3-5) FT-IR spectral data for synthesized 8(A-C)**

| Comp. NO. | X | υN=C–H arom. | υC–H arom. | υC–H aliph. | υC=O overlap between acid and amide | υNH | υOH carb. acid |
|---|---|---|---|---|---|---|---|
| **8A** | **H** | 3116 | 3074 | as 2931<br>sy 2843 | 1678 | 3275 | 3298 |
| **8B** | **Cl** | 3136 | 3074 | as 2927<br>sy 2854 | 1678 | 3275 | 3298 |
| **8C** | **Br** | 3132 | 3070 | as 2927<br>sy 2854 | 1678 | 3275 | 3298 |

**Table (3-6) FT-IR spectral data for synthesized 9(A-C)**

| Comp. NO. | X | υN=C–H arom. | υC–H arom. | υC–H aliph. | υC=O overlap between acid and amide | υNH | υOH carb. acid |
|---|---|---|---|---|---|---|---|
| **9A** | **H** | 3132 | 3070 | as 2950<br>sy 2839 | 1678 | 3275 | 3298 |
| **9B** | **Cl** | 3130 | 3062 | as 2927<br>sy 2854 | 1678 | 3275 | 3298 |
| **9C** | **Br** | 3132 | 3070 | as 2935<br>sy 2839 | 1678 | 3275 | 3298 |

**Table (3-7) FT-IR spectral data for synthesized 10(A-C)**

| Comp. NO. | X | υN=C–H arom. | υC–H arom. | υC–H aliph. | υC=O overlap between acid and amide | υNH | υOH carb. acid | $\upsilon NH_2$ overlap with υNH and υOH |
|---|---|---|---|---|---|---|---|---|
| **10A** | **H** | 3136 | 3062 | as 3005<br>sy 2839 | 1678 | 3275 | 3298 | as 3298<br>sy 3275 |
| **10B** | **Cl** | 3132 | 3074 | as 2927<br>sy 2873 | 1678 | 3275 | 3298 | as 3298<br>sy 3275 |
| **10C** | **Br** | 3136 | 3074 | as 3005<br>sy 2839 | 1678 | 3275 | 3302 | as 3298<br>sy 3275 |

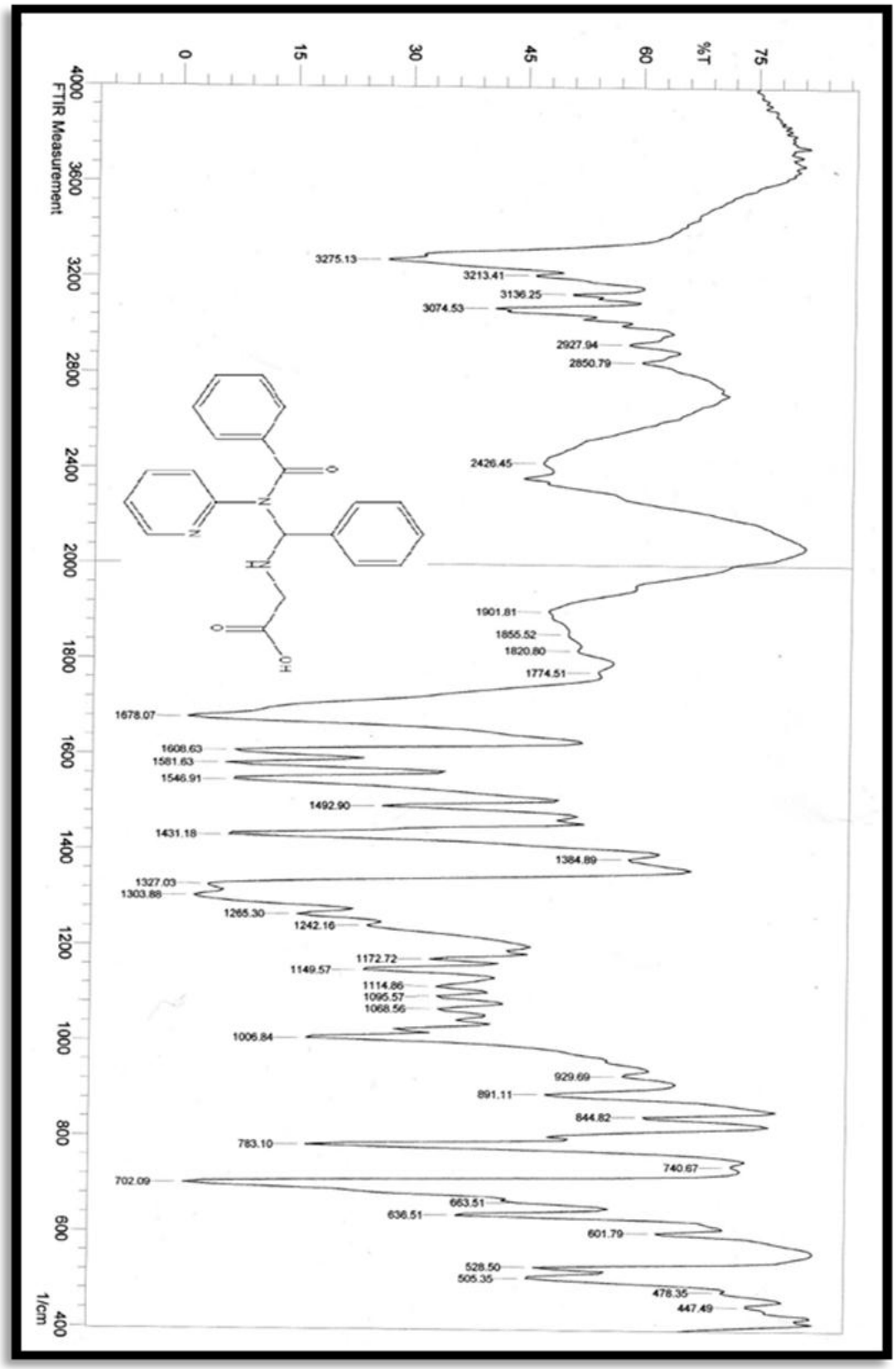



**Fig (3-7): FT-IR ($cm^{-1}$) spectrum of [6A].**

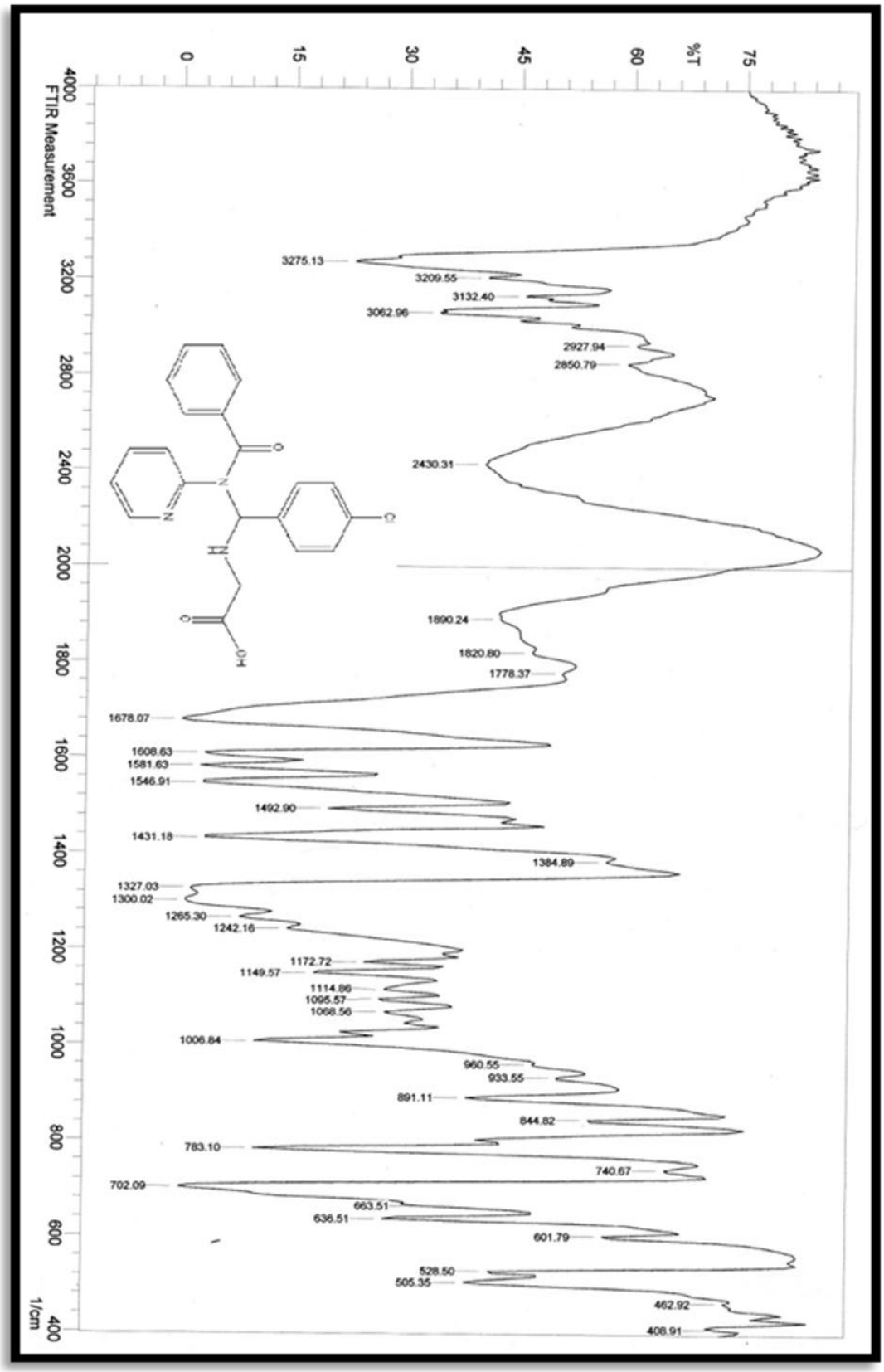



**Fig (3-8): FT-IR ($cm^{-1}$) spectrum of [6B].**

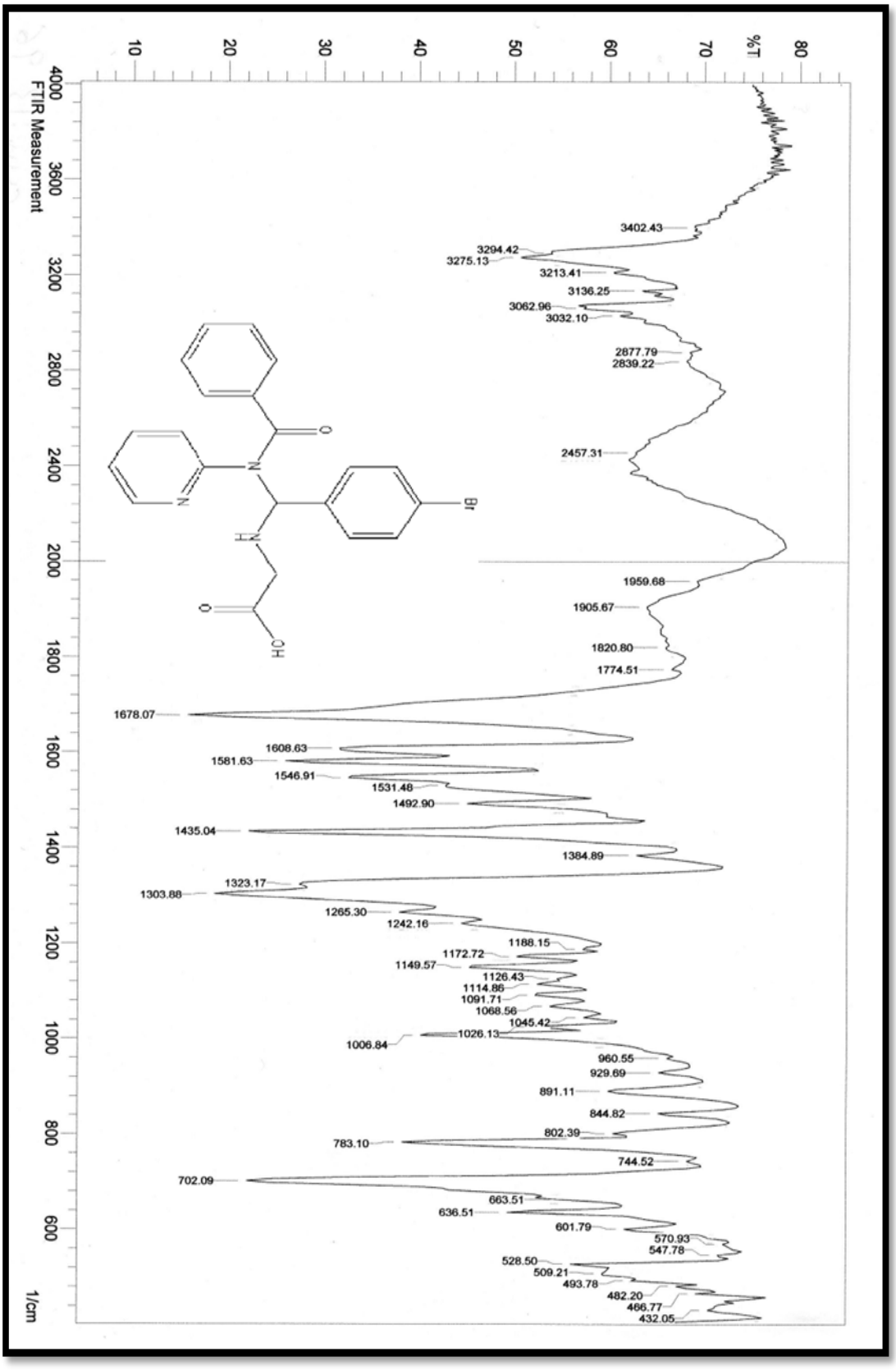



**Fig (3-9): FT-IR ($cm^{-1}$) spectrum of [6C].**

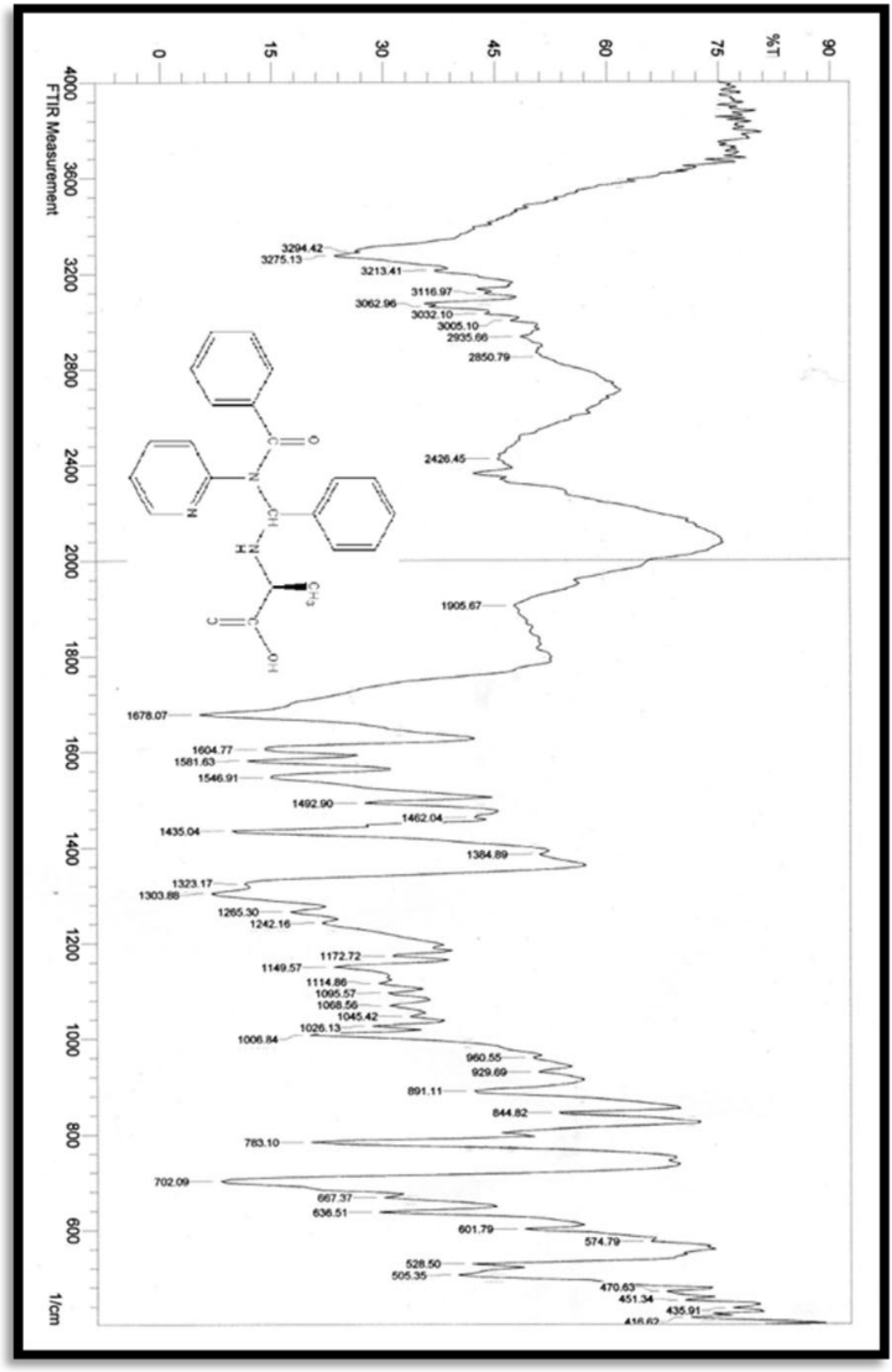



**Fig (3-10): FT-IR ($cm^{-1}$) spectrum of [7A].**

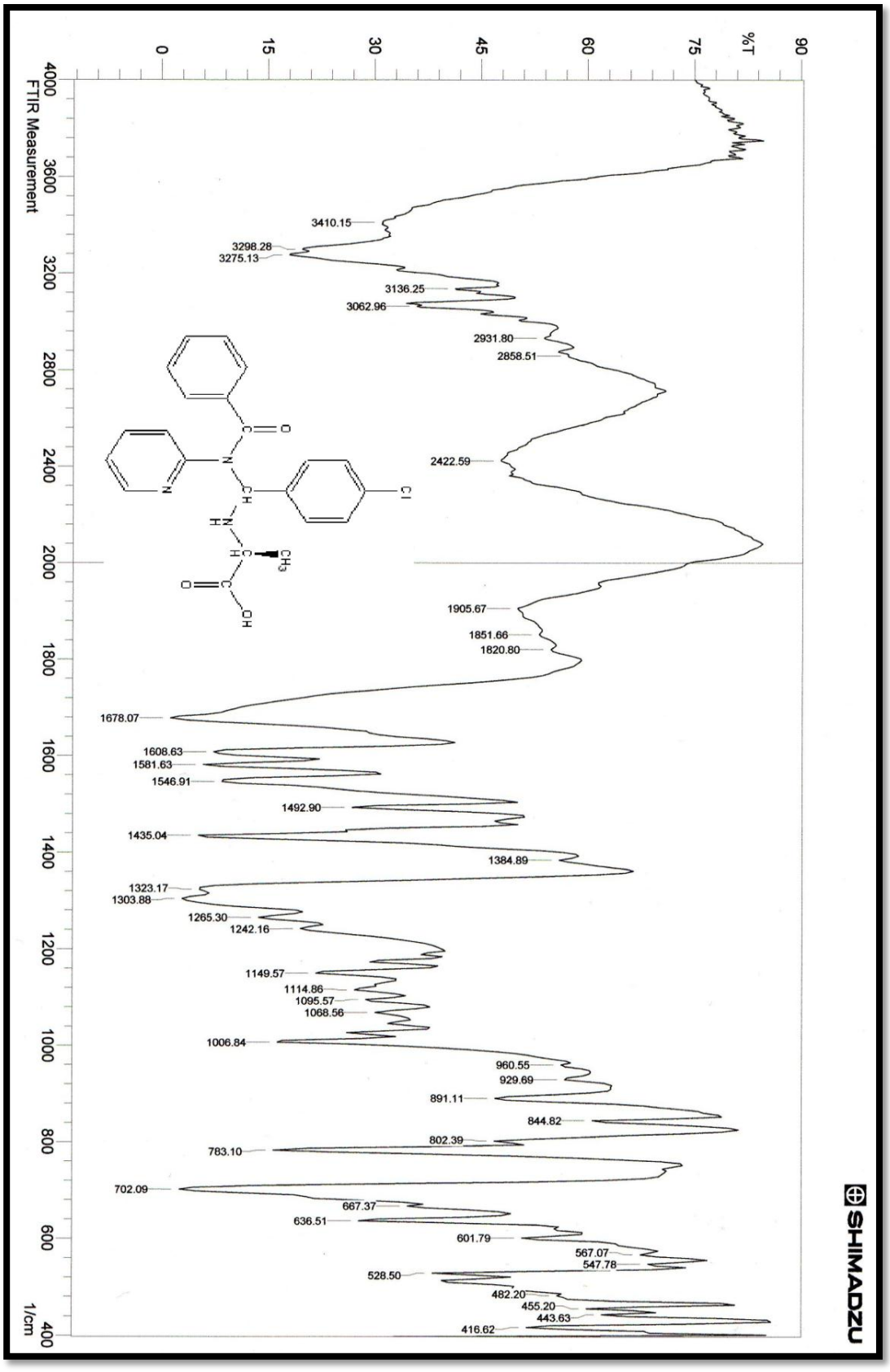



**Fig (3-11): FT-IR ($cm^{-1}$) spectrum of [7B].**

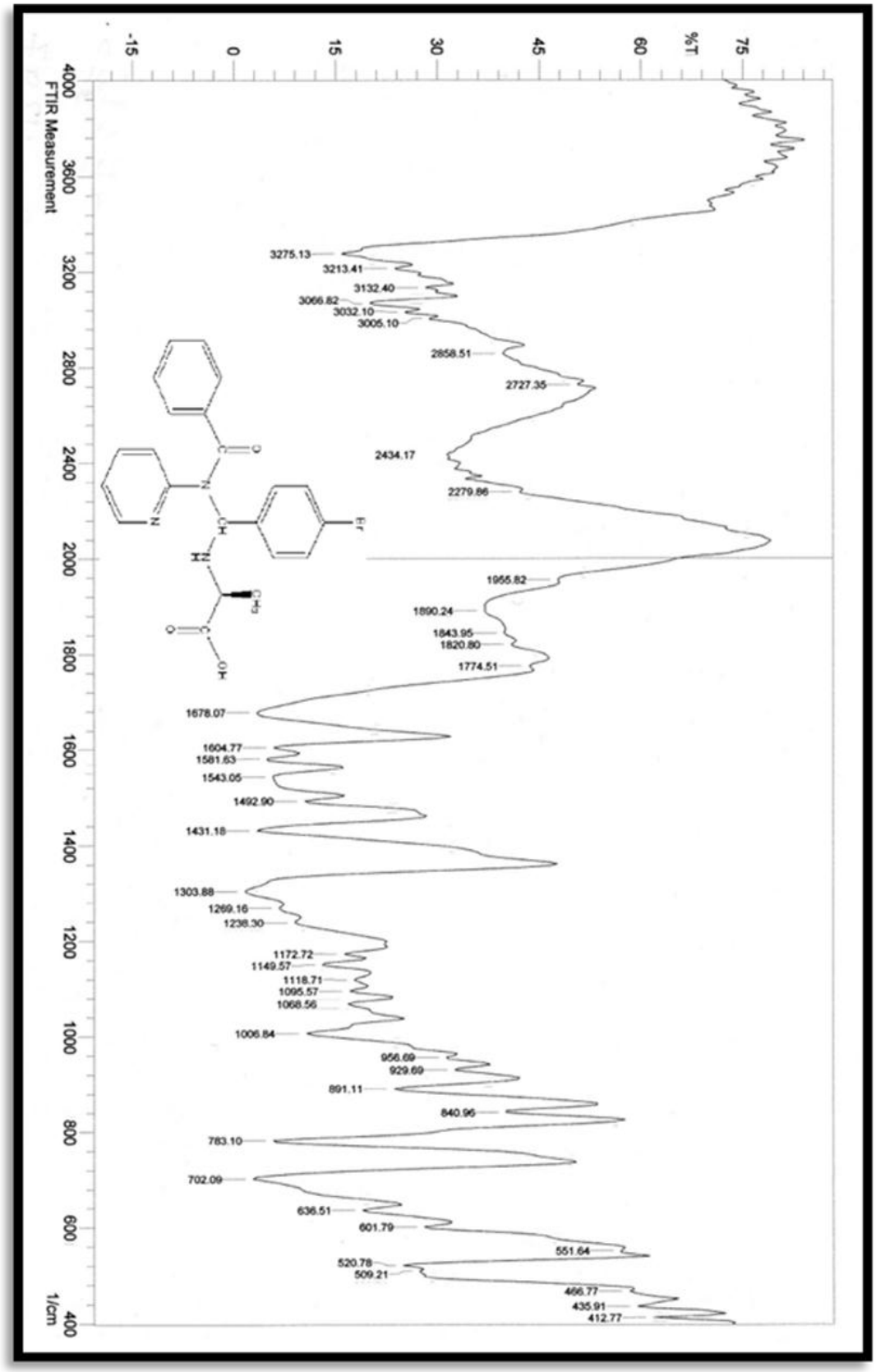



**Fig (3-12): FT-IR ($cm^{-1}$) spectrum of [7Cl].**

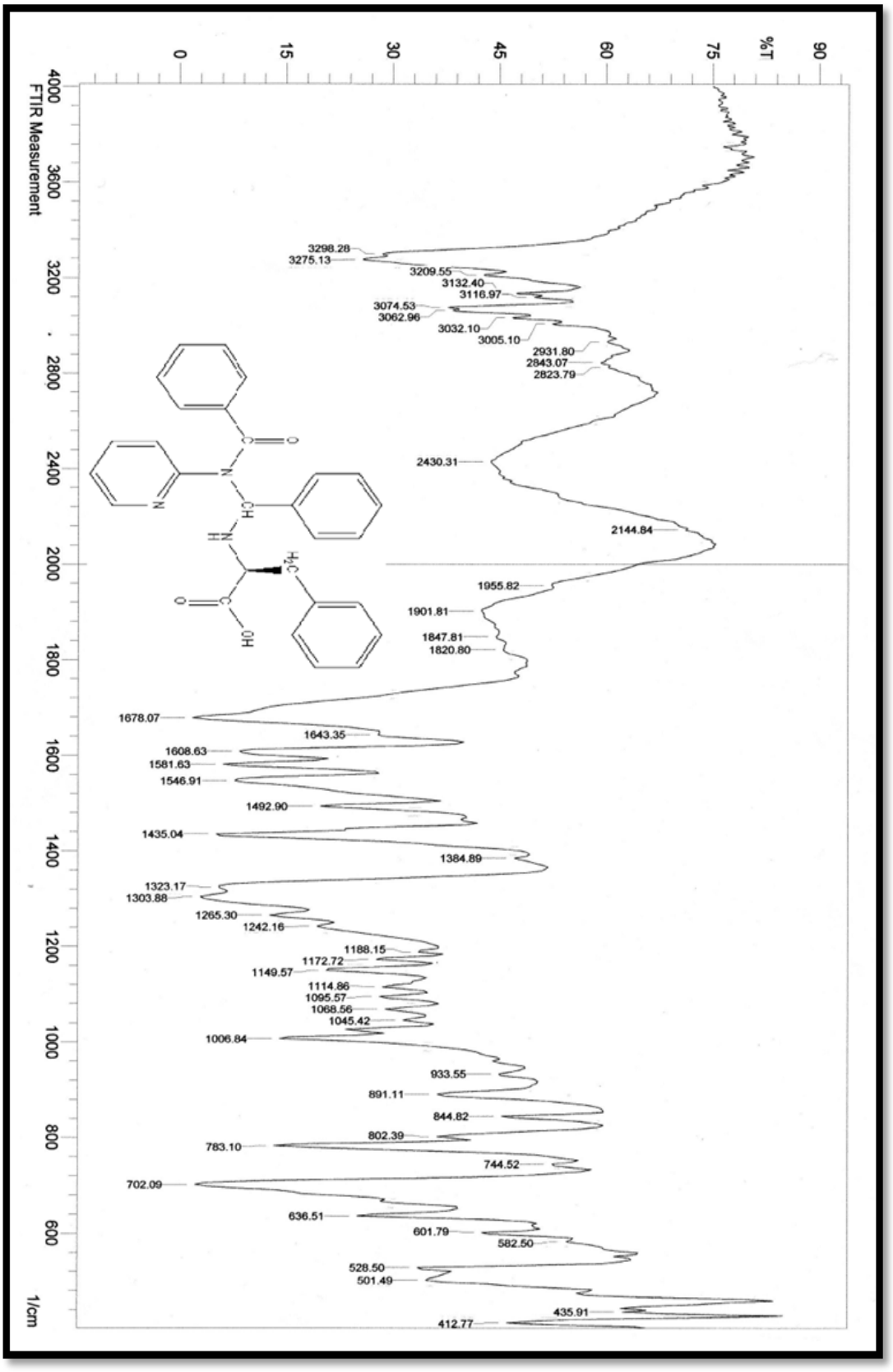



**Fig (3-13): FT-IR ($cm^{-1}$) spectrum of [8A].**

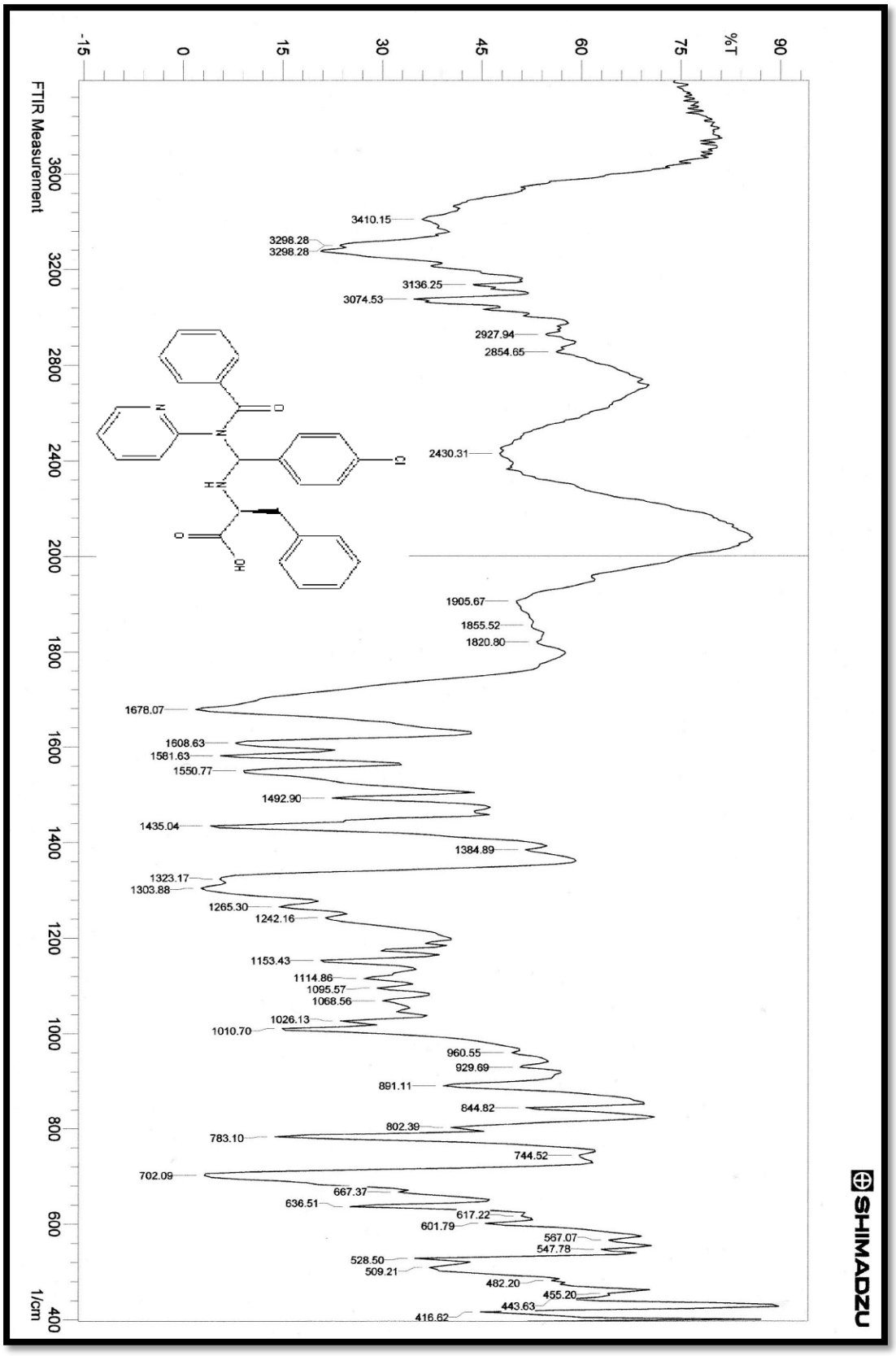



**Fig (3-14): FT-IR ($cm^{-1}$) spectrum of [8B].**

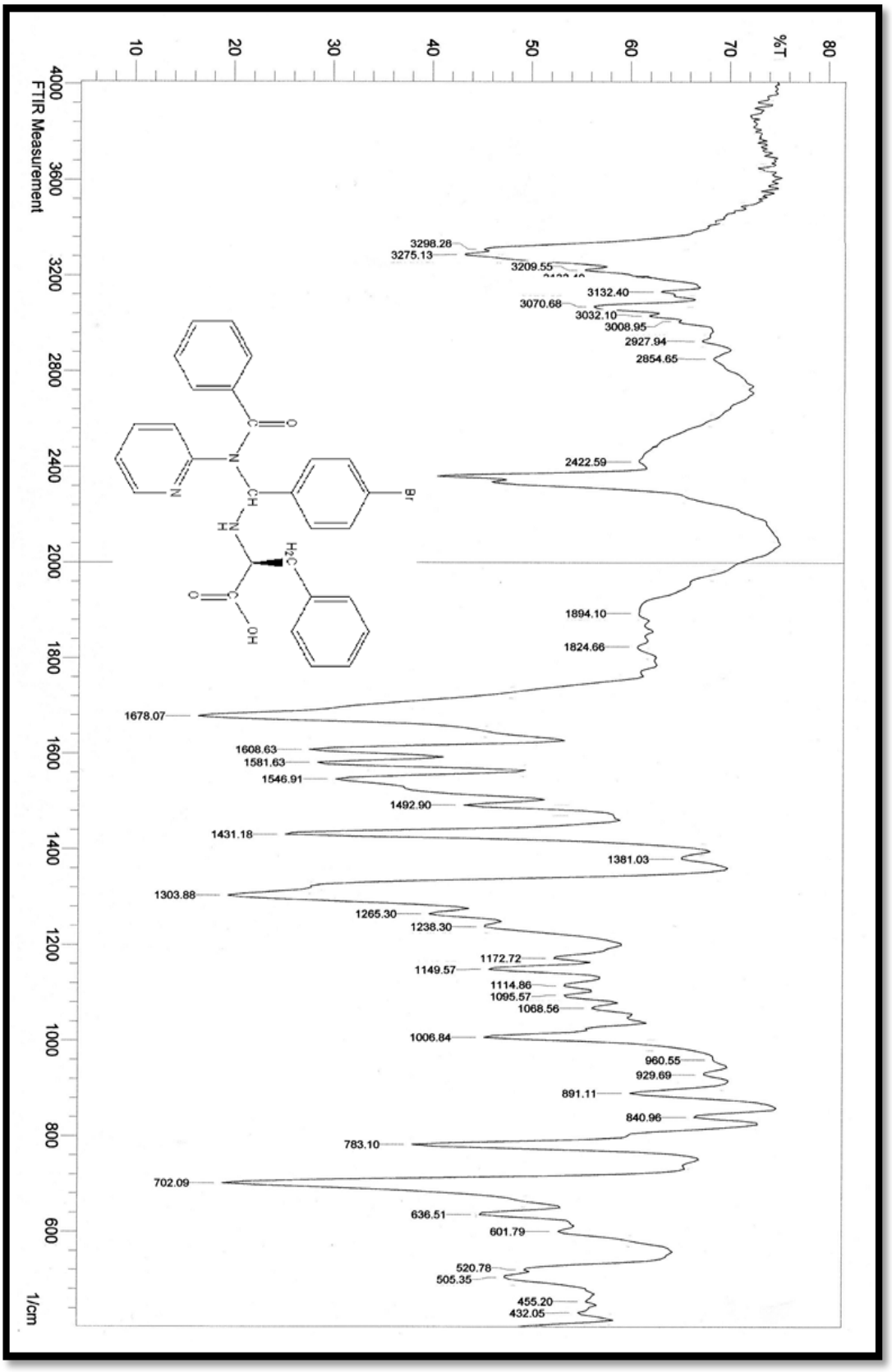



**Fig (3-15): FT-IR ($cm^{-1}$) spectrum of [8Cl].**

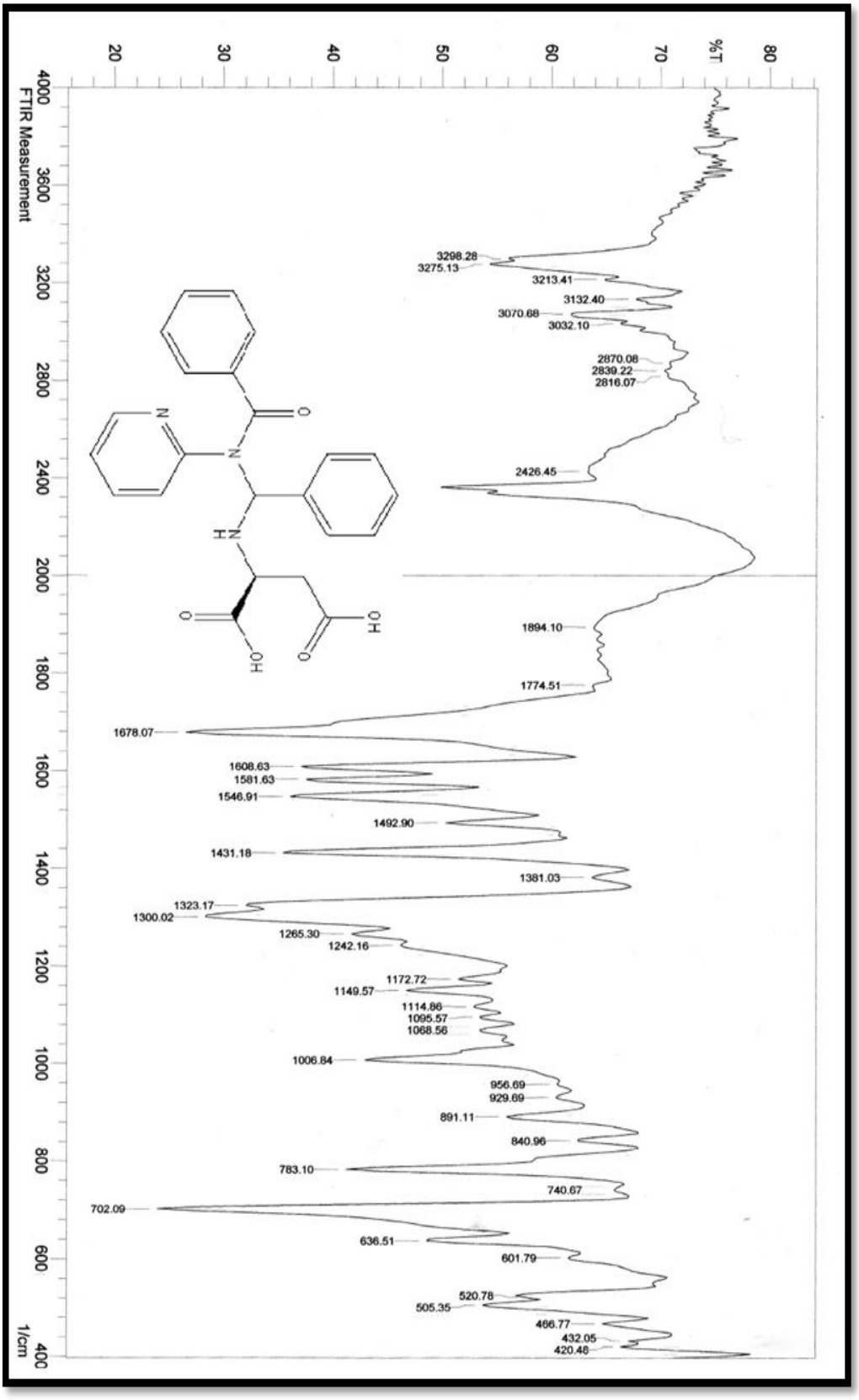



**Fig (3-16): FT-IR (cm-1) spectrum of [9A].**

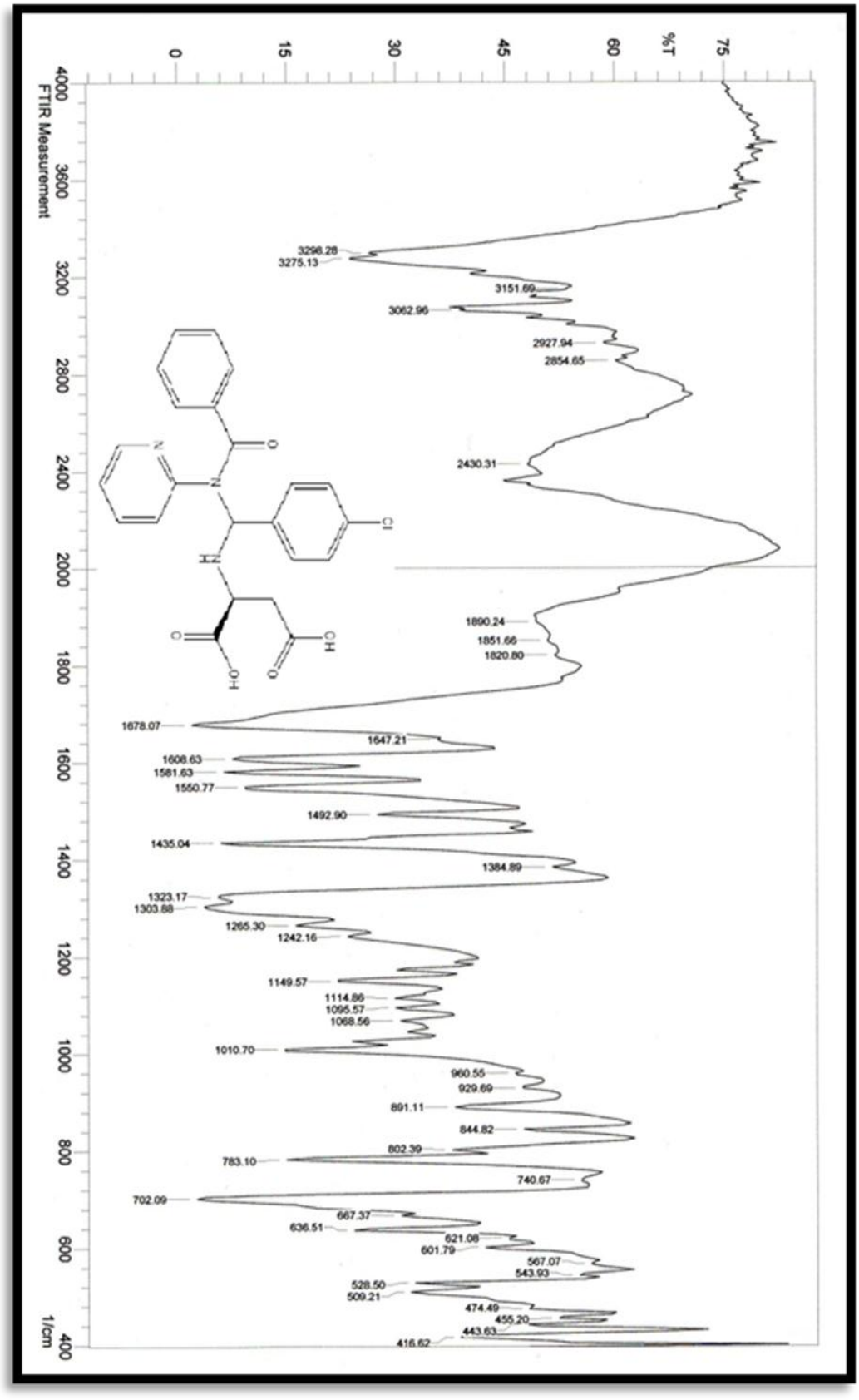



**Fig (3-17): FT-IR ($cm^{-1}$) spectrum of [9B].**

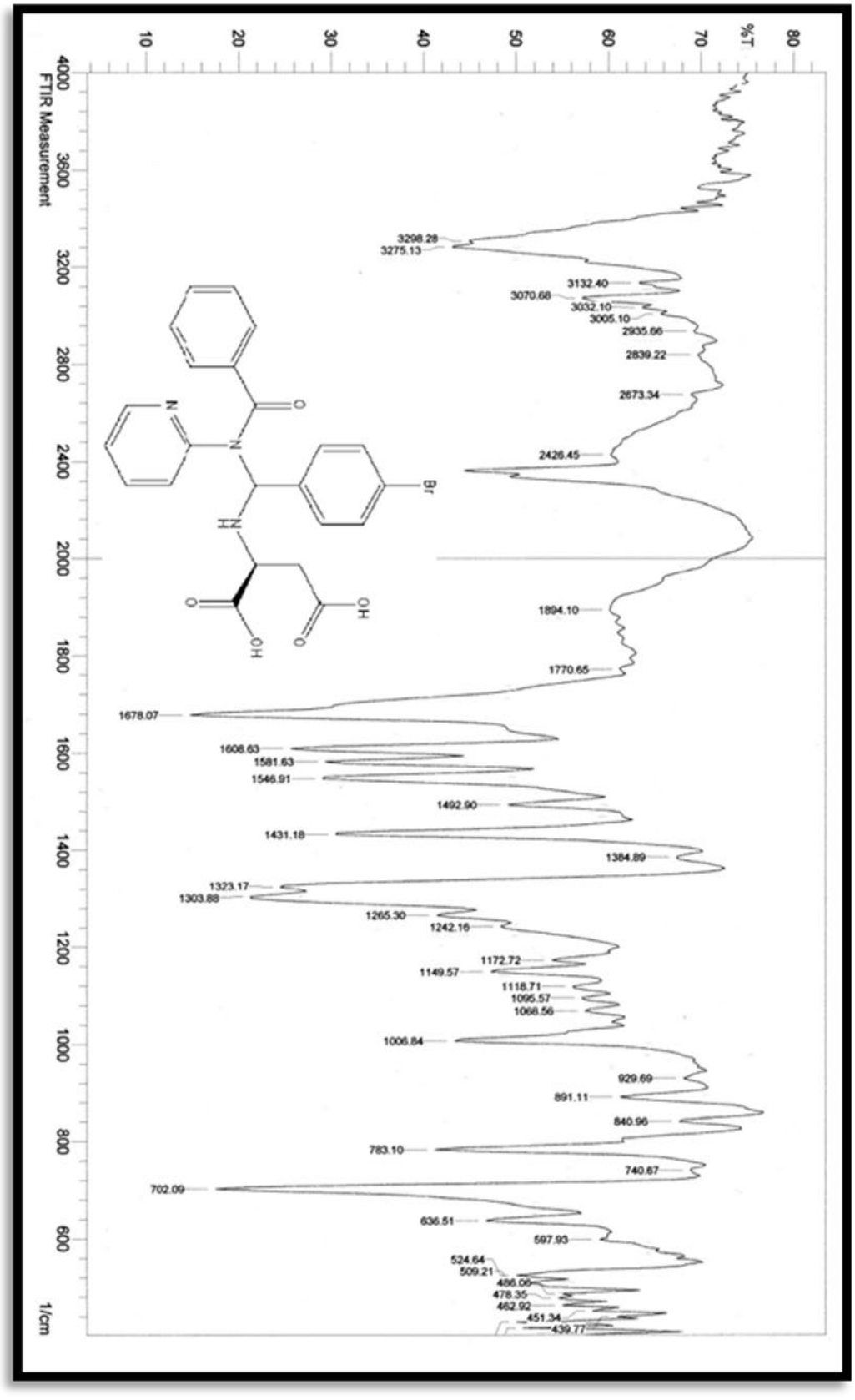



**Fig (3-18): FT-IR ($cm^{-1}$) spectrum of [9C].**

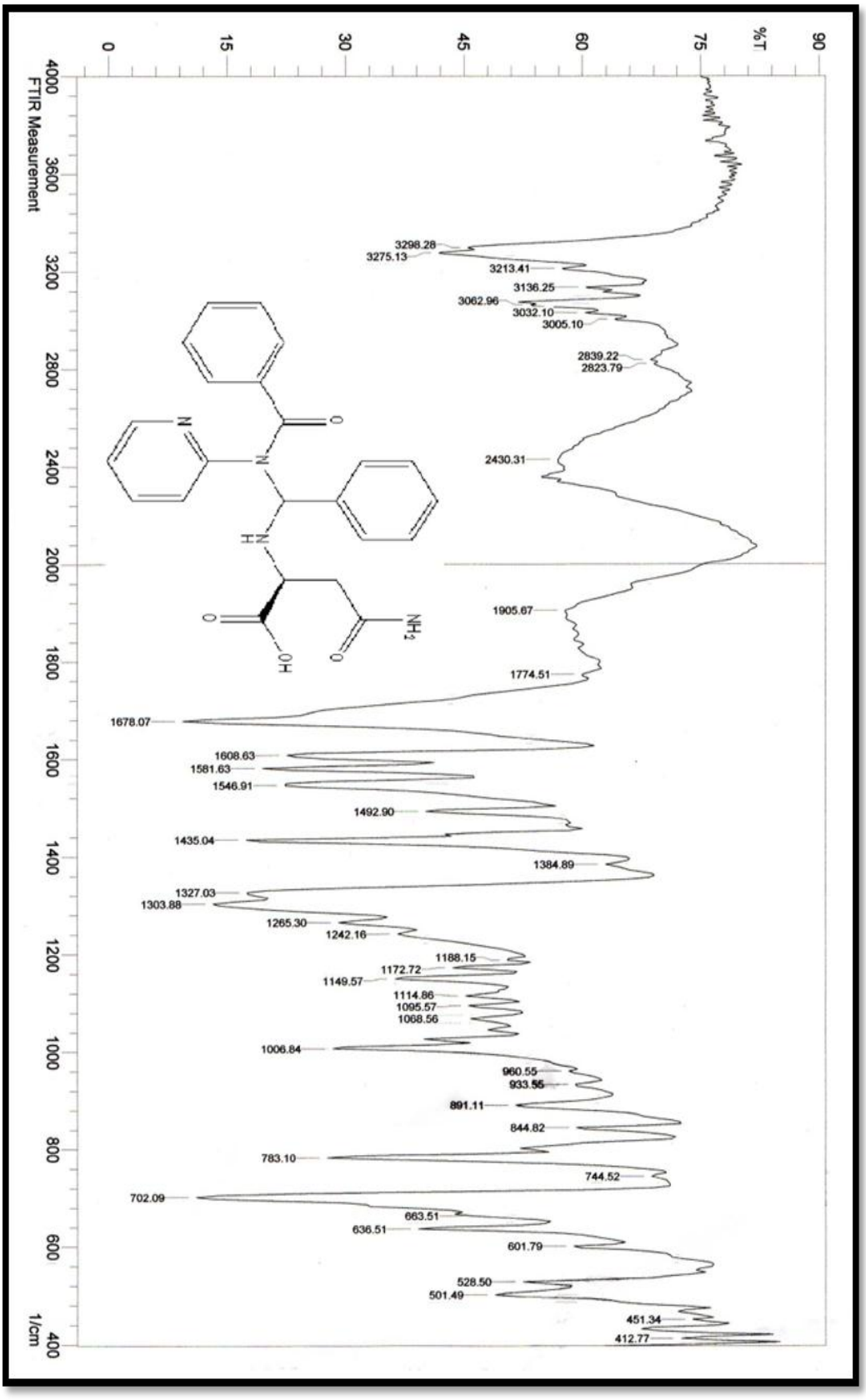



**Fig (3-19): FT-IR ($cm^{-1}$) spectrum of [10A].**

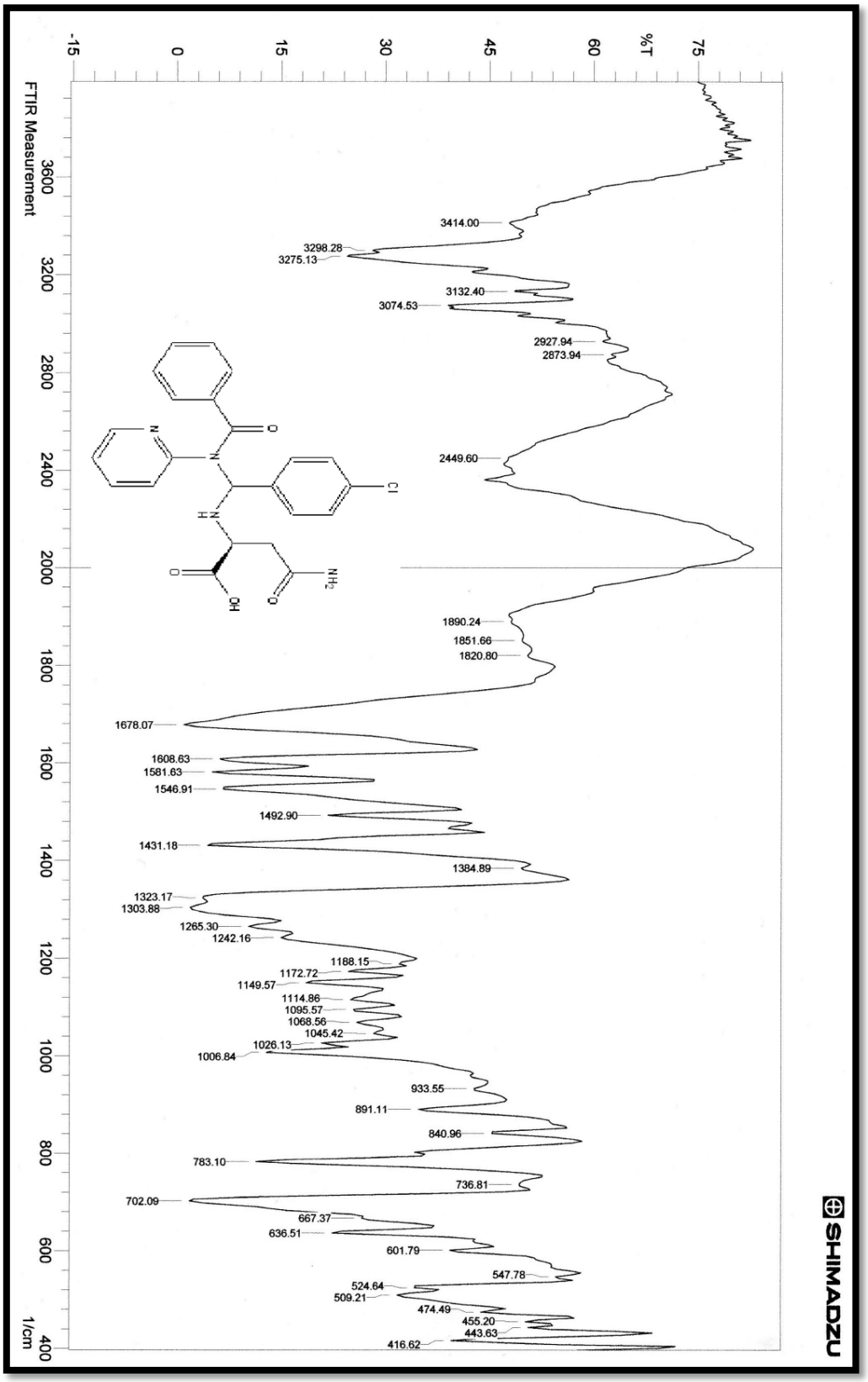



**Fig (3-20): FT-IR (cm-1) spectrum of [10B].**

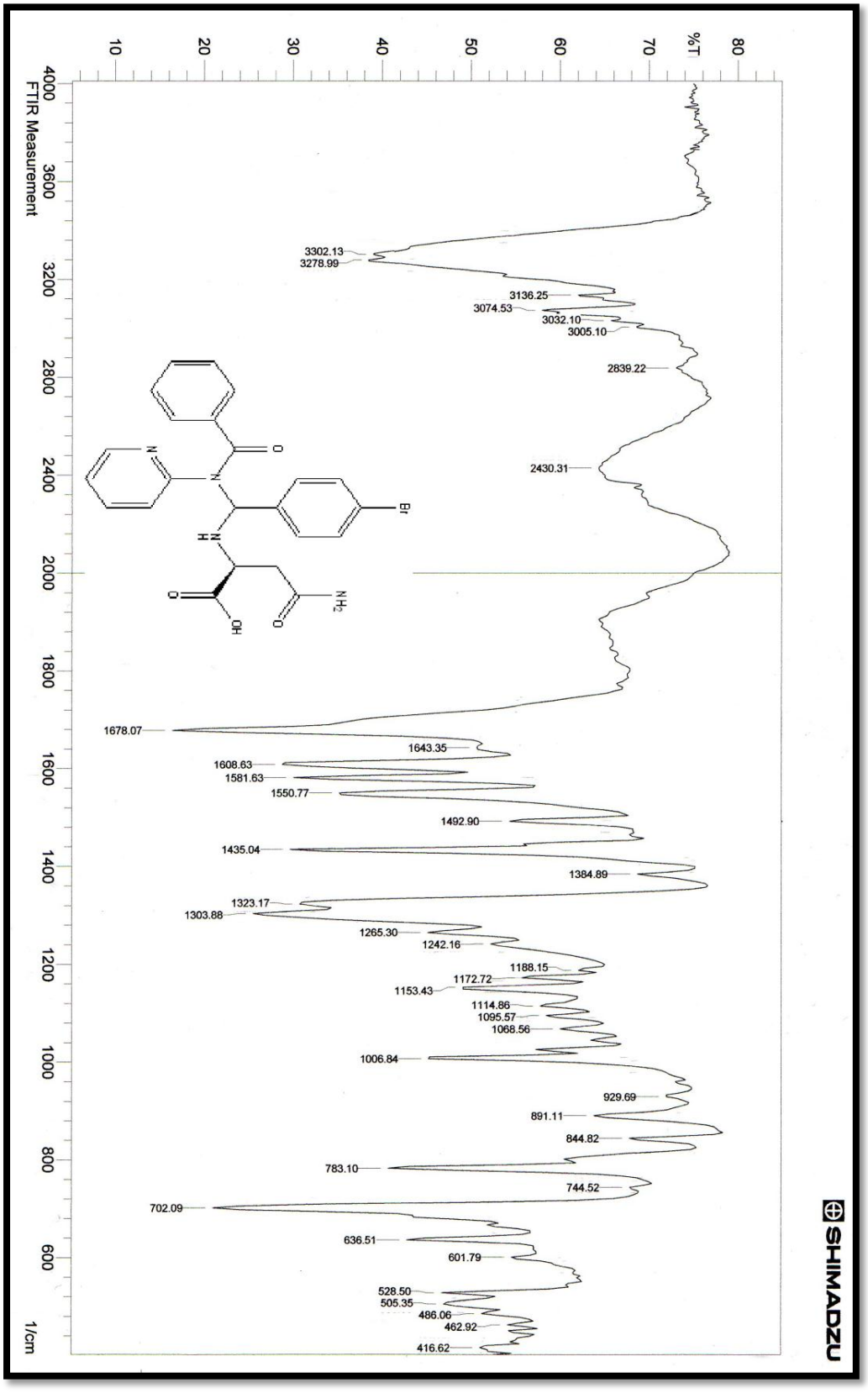



**Fig (3-21): FT-IR ($cm^{-1}$) spectrum of [10C].**

## 3.3 $^{1}$H-NMR and $^{13}$C-NMR spectrum of [6(A-B)-10(A-B)] compounds

$^{1}$H-NMR and $^{13}$C-NMR spectroscopy are also used to elucidate the structure of synthesized L-amino acid derivatives [6(A-B)-10(A-B)]. Table (3-8) shows the characteristic chemical shifts (ppm) for L-amino acid derivatives [6(A-B)-10(A-B)]. DMSO was used as a solvent.

For NMR spectra the following notes must be taken in consideration:

Note (1): For all $^{1}$H-NMR spectra, signals at 2.509 ppm are due to the solvent (DMSO) [53].

Note (2): For all $^{13}$C-NMR spectra, signals at (38.796-40.067) ppm are due to the solvent (DMSO) [53].

Note (3): (*s = singlet, d = doublet, trp = triplet, q* = quartet and *m = multiplet*).

In the $^{1}$H-NMR spectra, Fig [(3-22)-(3-35)] the following signals can be seen:

1- The signals with the chemical shifts δ between 1- 4.5 ppm are referred to aliphatic protons.
2- The signals at about 1.2 ppm are referred to the 1H - NH proton.
3- The signals at about 11 ppm are referred to the 1H - OH proton.
4- The signals with the chemical shifts δ between 7.0- 8.5 ppm are referred to aromatic protons derived from the three or four aromatic rings.

In the $^{13}$C-NMR spectra, Fig [(3-26)-(3-39)] the following signals can be seen:

1- The signals with the chemical shifts δ between 36.3- 72.4 ppm are referred to aliphatic carbons.
2- The signals at about 165.9 ppm are referred to the C – amide carbonyl.
3- The signals at about 167.3 ppm are referred to the C –carboxylic acid carbonyl.
4- The signals with the chemical shifts δ between 7.0- 8.5 ppm are referred to aromatic carbons derived from the three or four aromatic rings.

**Table (3-8): $^{1}$H-NMR and $^{13}$C-NMR spectra of [6(A-C)-10(A-C)]**

| Comp. NO. | X | Amino acid group | $^{1}$H NMR Spectra (ppm) | $^{13}$C NMR Spectra (ppm) |
|---|---|---|---|---|
| **6A** | **H** | **Gly.** | ~ 1.25 (1H, *s*, NH), ~ 3.45 (2H, *s*, $CH_2$), ~ 4.15 (1H, *s*, CH), ~ 7.2-8.4 (14H, *m*, CH of three aromatic rings), ~ 11 (1H, *s*, OH). | --- |
| **6B** | **Cl** | **Gly.** | ~1.2 (1H, *s*, NH), 3.442 (2H, *s*, $CH_2$), 4.649 (1H, *s*, CH), 7.14-8.395 (13H, *m*, CH of three aromatic rings), ~ 11 (1H, *s*, OH). | 60.134 (1C, $CH_2$), 72.395 (1C, CH), 114.702-152.165 (17C, 3 aromatic rings), 165.959 (1C, C=O amid), 167.316 (1C, C=O acid). |
| **7A** | **H** | **Ala.** | 1.415 (3H, *d*, $CH_3$), 1.433 (1H, *s*, NH), 3.524-3.536 (1H, *q*, CH), 4.053 (1H, *s*, CH), 7.142-8.391 (14H, *m*, CH of three aromatic rings), 10.787 (1H, *s*, OH). | ~20 (1C, $CH_3$), 60.156 (1C, CH), 72.417 (1C, CH), 114.69-152.17 (17C, 3 aromatic rings), 165.964 (1C, C=O amid), 167.322 (1C, C =O acid). |

| | | | | |
|---|---|---|---|---|
| **7B** | **Cl** | **Ala.** | ~ 1 (3H, *d*, $CH_3$), ~ 1.3 (1H, *s*, NH), 3.527-3.554 (1H, *q*, CH), 4.062 (1H, *s*, CH), 7.135-8.386 (13H, *m*, CH of three aromatic rings), 10.794 (1H, *s*, OH). | --- |
| **8A** | **H** | **Phe.** | 1.201 (1H, *s*, NH), 3.102-3.128 (2H, *d*, $CH_2$), 3.510-3.526 (1H, *trp*, CH), 4.026 (1H, *s*, CH), 7.150-8.396 (19H, *m*, CH of four aromatic rings), 10.790 (H, *s*, OH). | 36.307 (1C, $CH_2$), 54.327 (1C, CH), 114.702-166.273 (23C, 4 aromatic rings), 167.374 (1C, C =O amid), 173.255 (1C, C=O acid). |
| **8B** | **Cl** | **Phe.** | 1.211 (1H, *s*, NH), ~3.2 (2H, *d*, $CH_2$), 3.502-3.520 (1H, *trp*, CH), 4.028 (1H, *s*, CH), 7.153-8.398 (18H, *m*, CH of three aromatic rings), 10.782 (1H, *s*, OH). | --- |

| | | | | |
|---|---|---|---|---|
| **9A** | **H** | **Asp.** | ~ 1.1 (1H, *s*, NH), 3.423 (2H, *d*, $CH_2$), 3.521-3.529 (1H, *trp*, CH), 3.562 (1H, *s*, CH), 7.148-8.394 (14H, *m*, CH of three aromatic rings), 10.789 (2H, *s*, OH). | --- |
| **9B** | **Cl** | **Asp.** | ~ 1.1 (1H, *s*, NH), 3.386-3.435 (2H, *d*, $CH_2$), 3.525-3.558 (1H, *trp*, CH), 4.052 (1H, *s*, CH), 7.142-8.390 (13H, *m*, CH of three aromatic rings), ~ 11 (2H, *s*, OH). | --- |

| | | | | |
|---|---|---|---|---|
| **10A** | **H** | **Asn.** | 0.998-1.045 (1H, *s*, NH), ~ 3.3 (2H, *d*, $CH_2$), ~ 3.5 (1H, *trp*, CH), ~ 4 (1H, *s*, CH), 7.023 (2H, *s*, $NH_2$), 7.002-8.238 (14H, *m*, CH of three aromatic rings), 10.645 (1H, *s*, OH). | 36.307 (1C, $CH_2$), 54.327 (1C, CH), 114.702-166.273 (17C, 3 aromatic rings), 167.374 (2C, C=O amid), 173.255 (1C, C=O acid). |
| **10B** | **Cl** | **Asn.** | ~ 1 (1H, *s*, NH), ~ 3.3 (2H, *d*, $CH_2$), 3.529-3.557 (1H, *trp*, CH), ~ 4 (1H, *s*, CH), 7.168 (2H, *s*, $NH_2$), 7.139-8.389 (13H, *m*, CH of three aromatic rings), 10.795 (1H, *s*, OH). | --- |

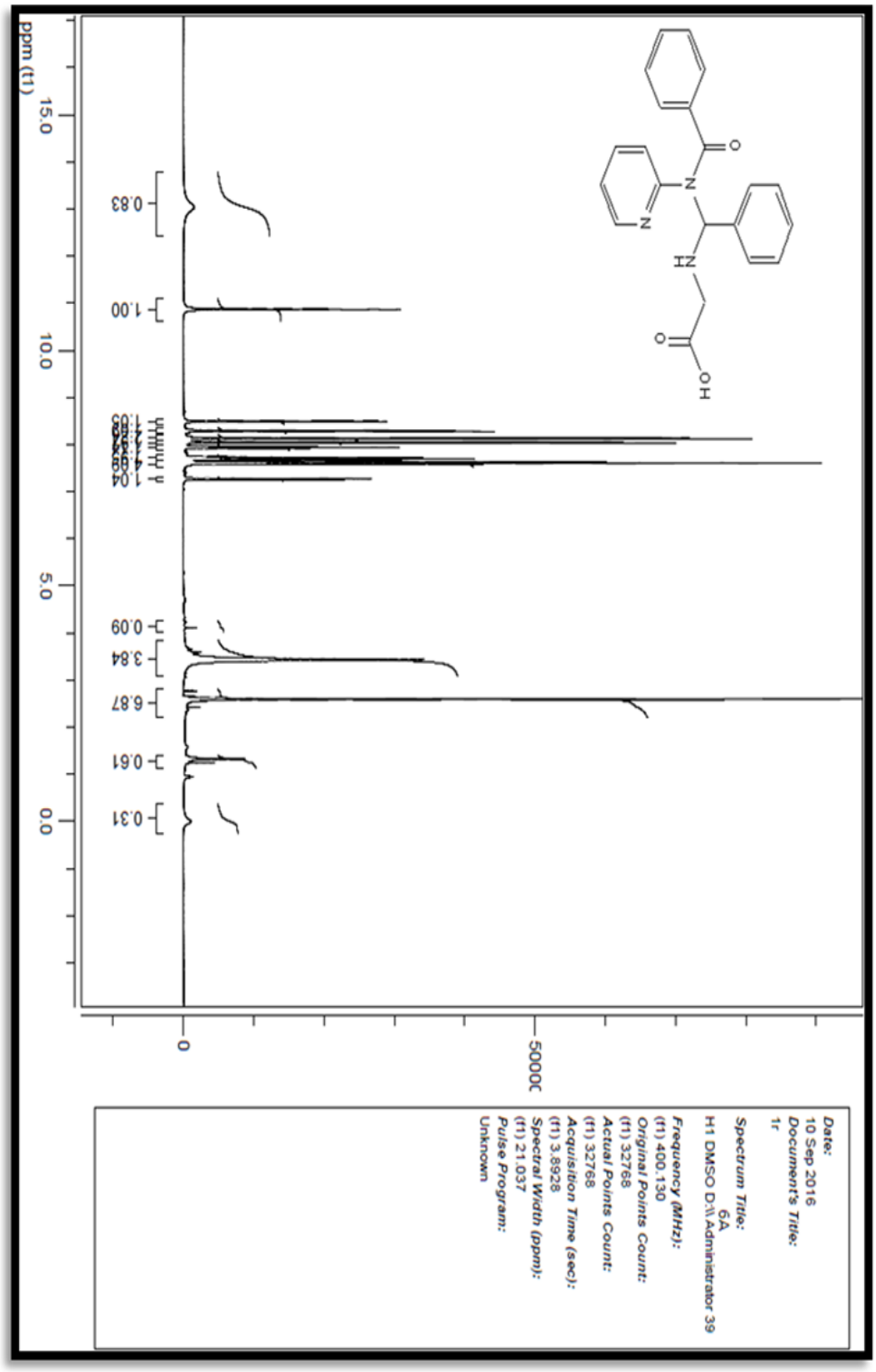



**Fig (3-22): $^{1}$H-NMR (ppm) spectrum of [6A].**

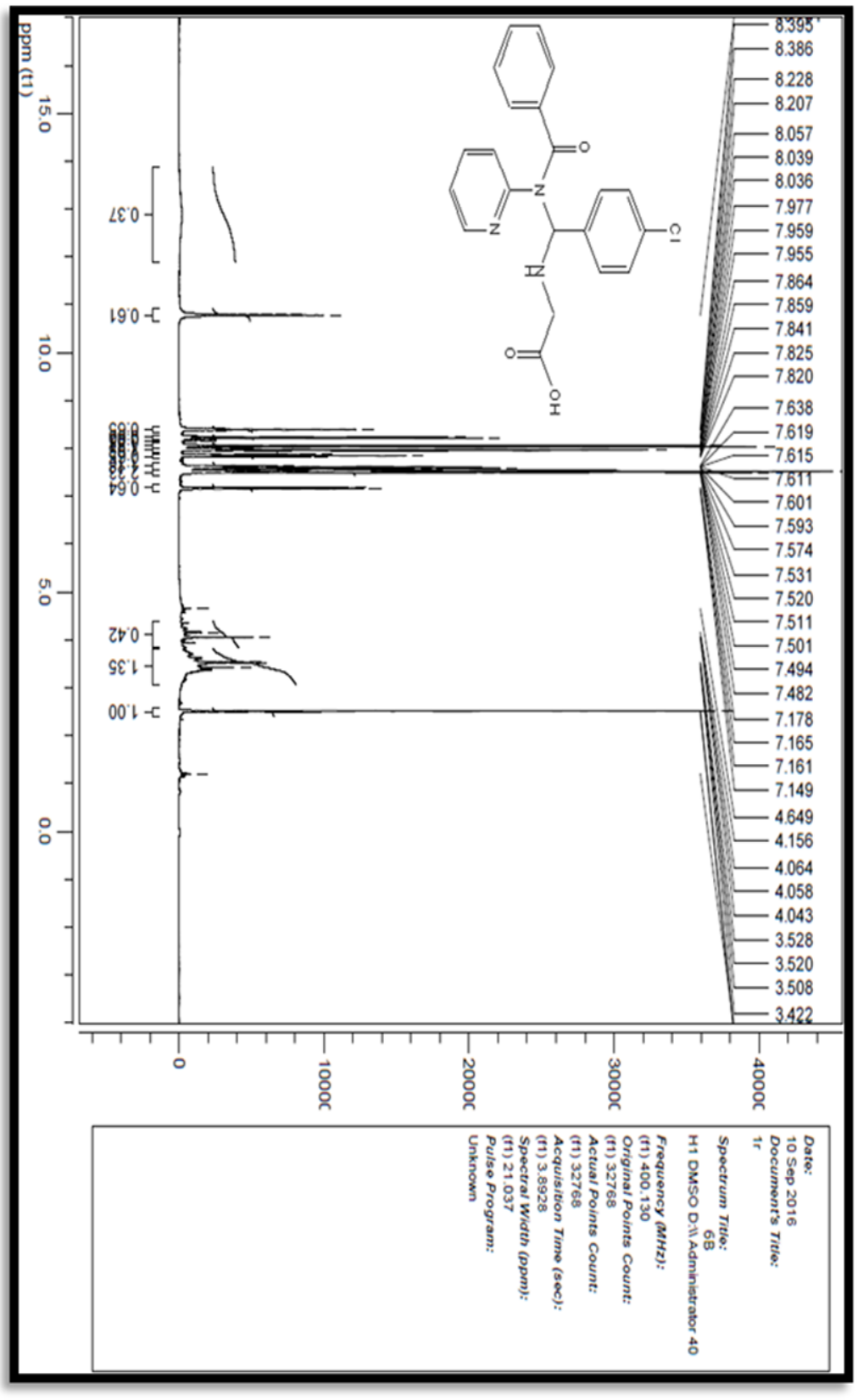



**Fig (3-23): $^{1}$H-NMR (ppm) spectrum of [6B].**

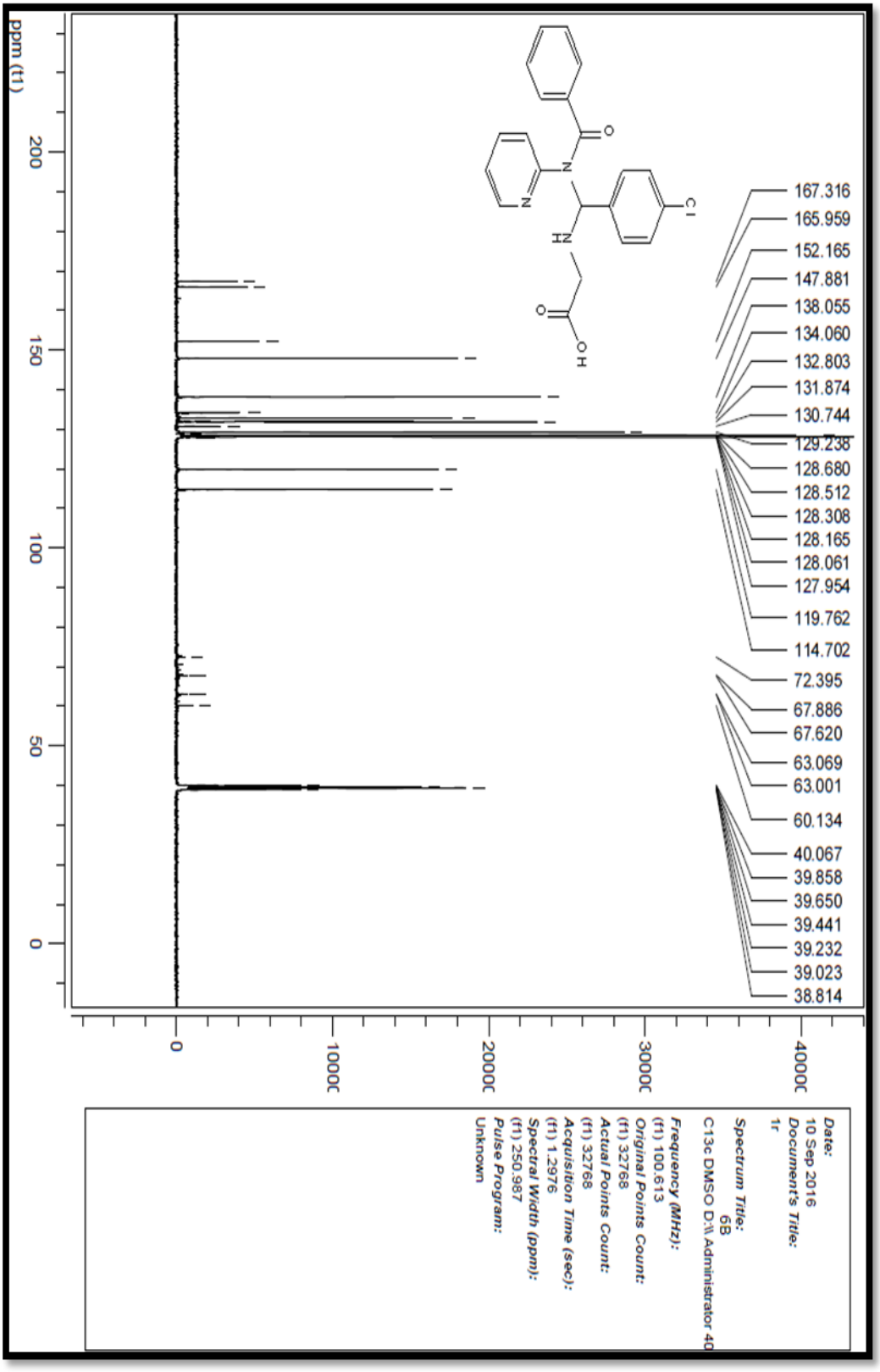



**Fig (3-24): $^{13}$C-NMR (ppm) spectrum of [6B].**

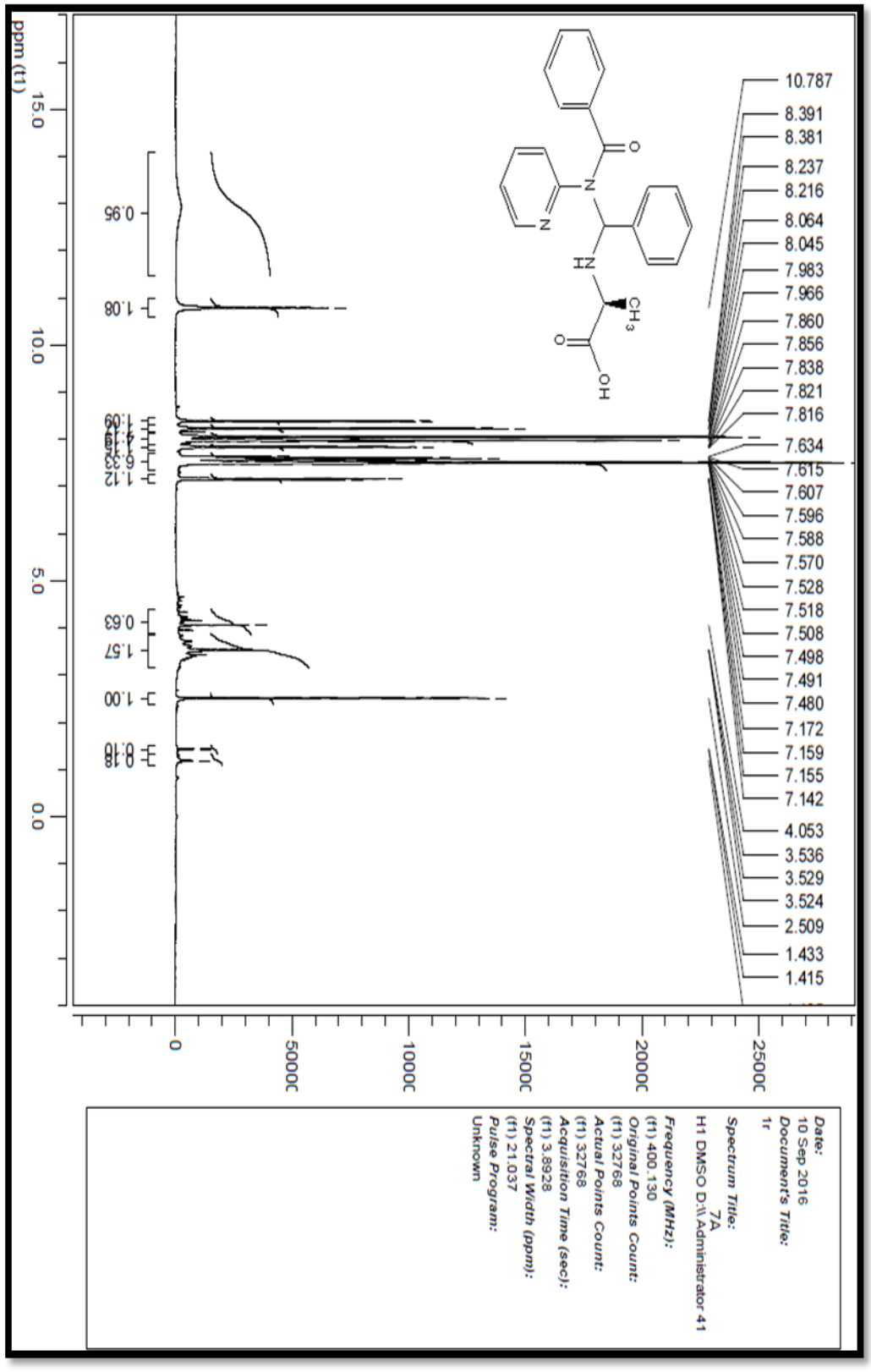



**Fig (3-25): $^{1}$H-NMR (ppm) spectrum of [7A].**

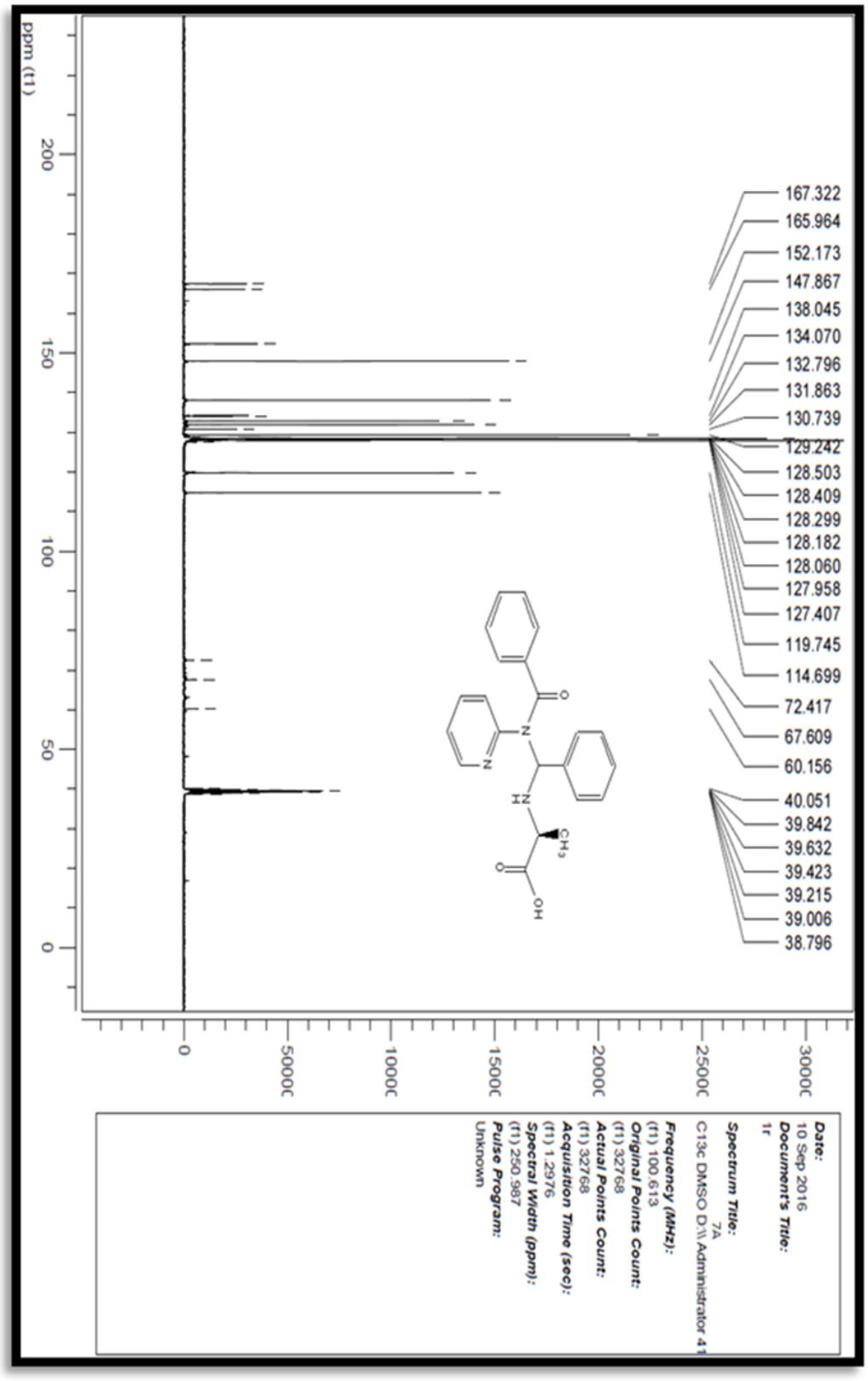



**Fig (3-26): $^{13}$C-NMR (ppm) spectrum of [7A].**

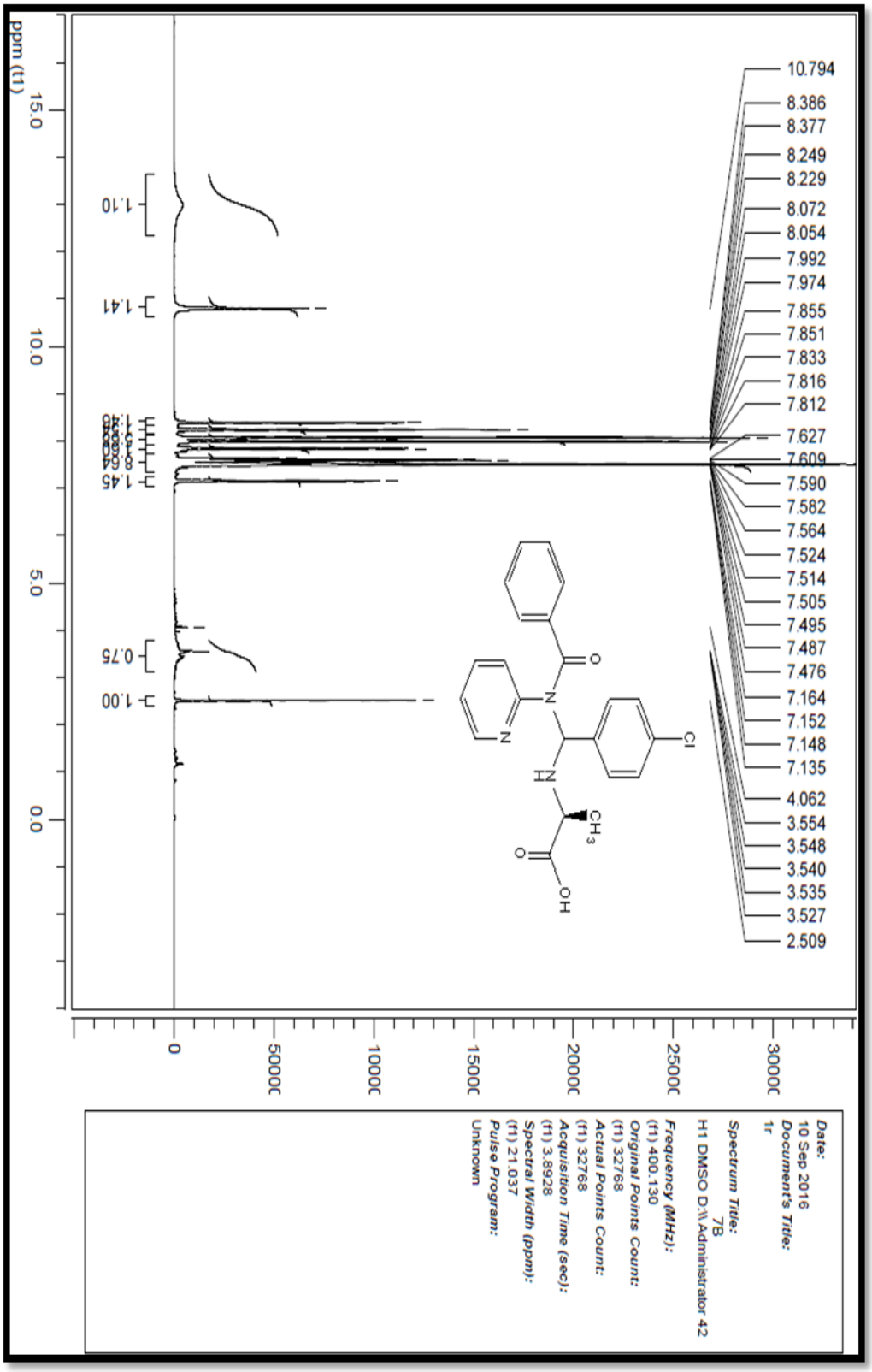



**Fig (3-27): $^{1}$H-NMR (ppm) spectrum of [7B].**

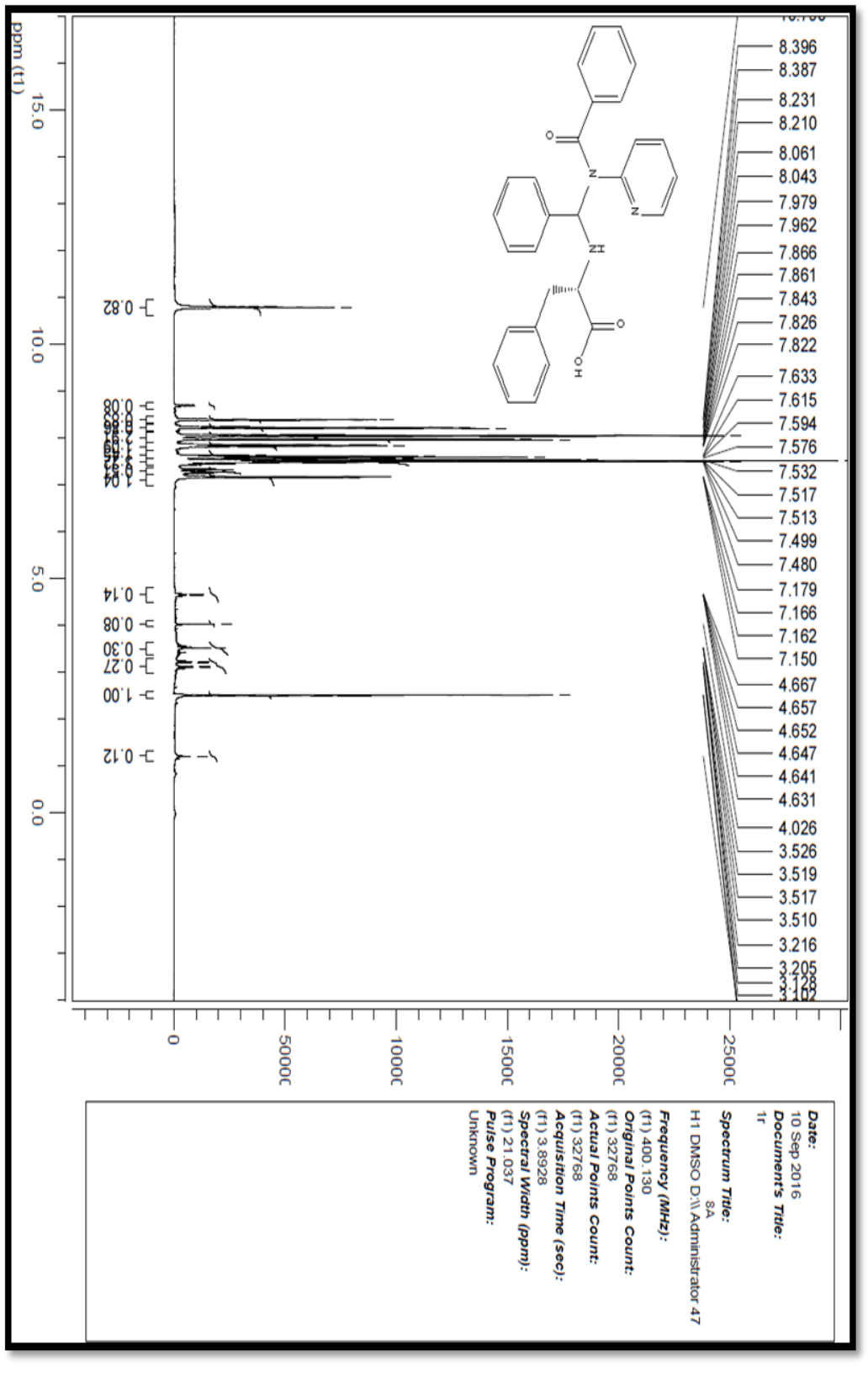



**Fig (3-28): $^{1}$H-NMR (ppm) spectrum of [8A].**

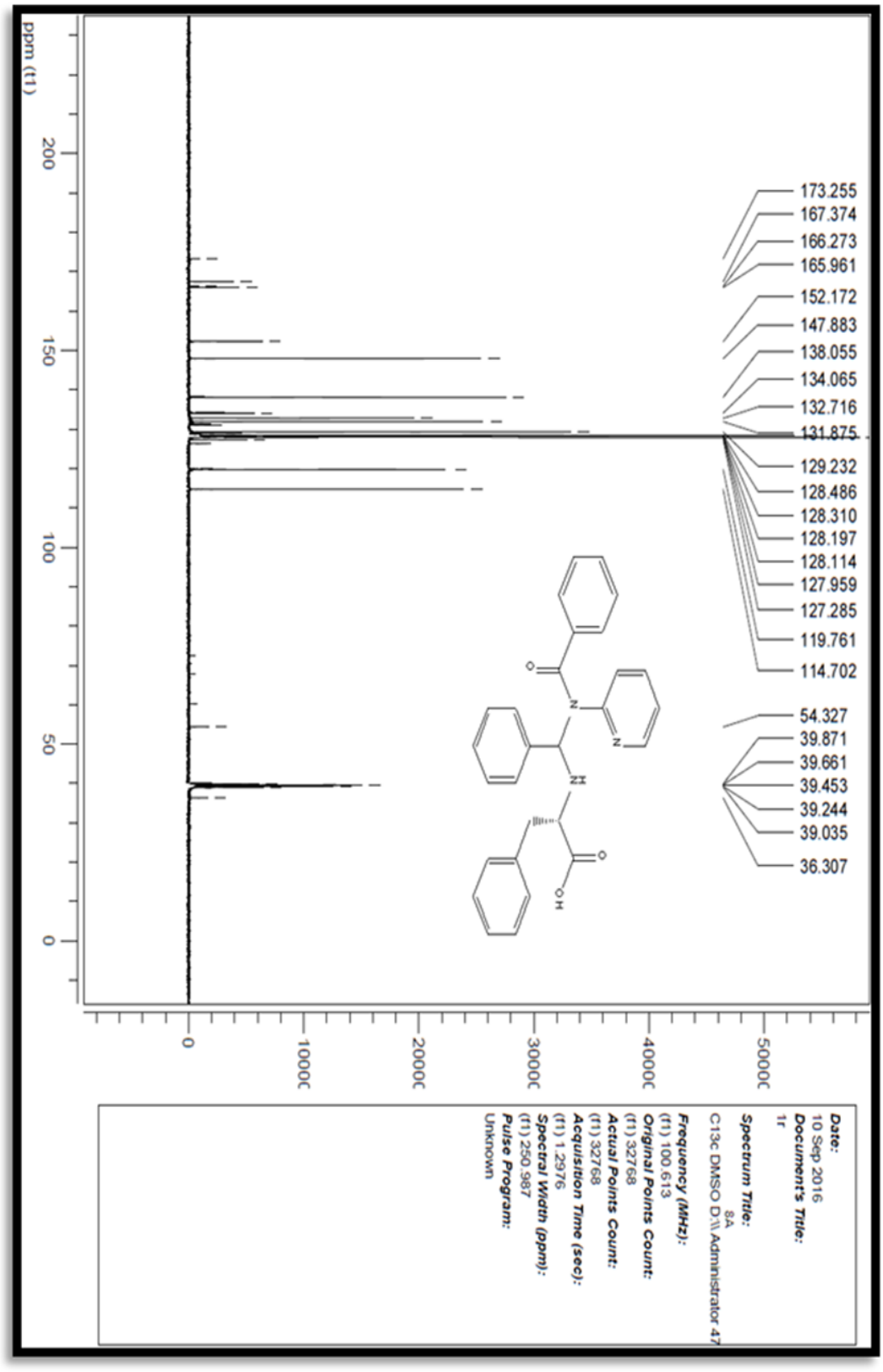



**Fig (3-29): $^{13}$C-NMR (ppm) spectrum of [8A].**

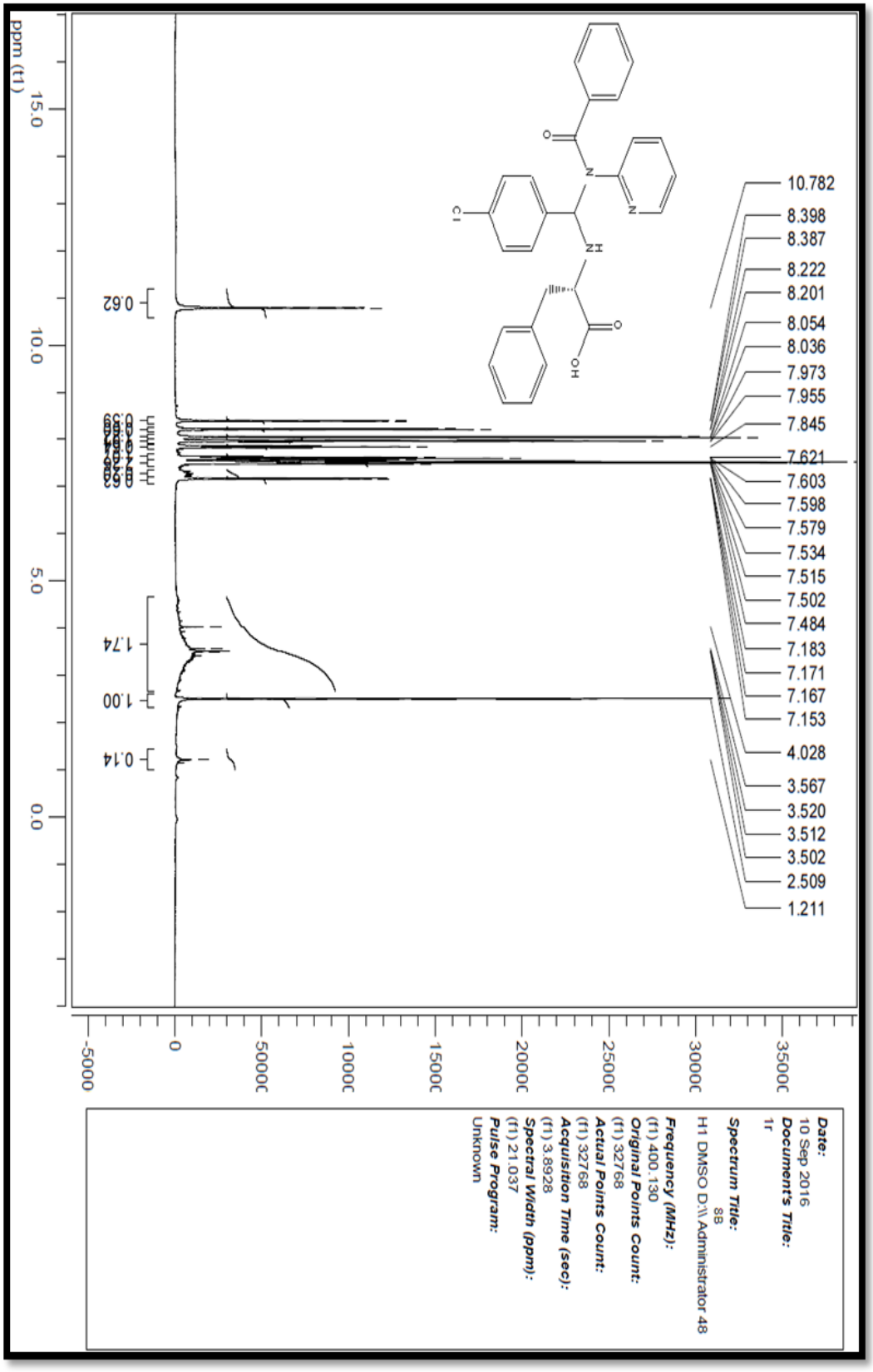



**Fig (3-30): $^{1}$H-NMR (ppm) spectrum of [8B].**

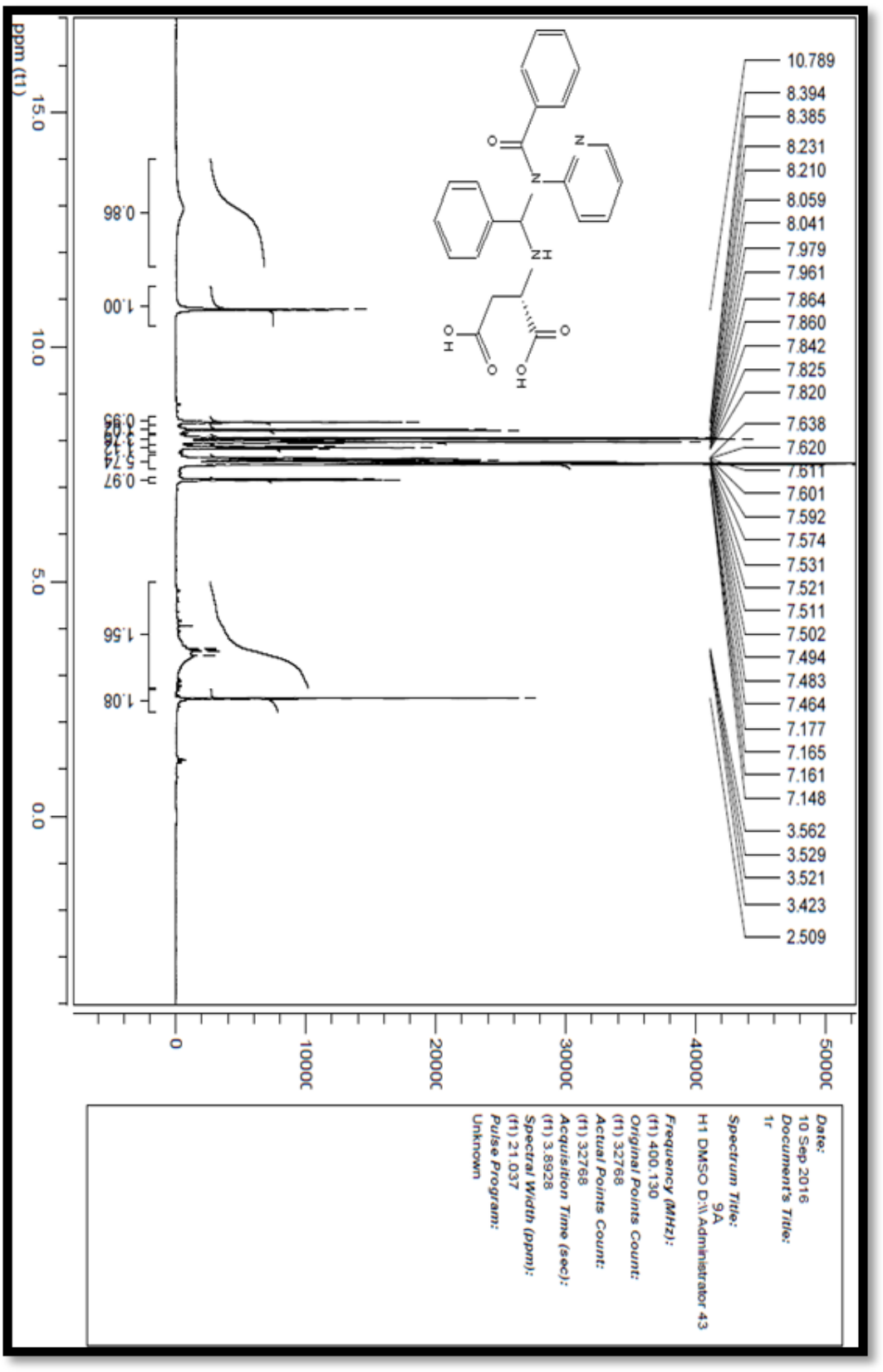



**Fig (3-31): $^{1}$H-NMR (ppm) spectrum of [9A].**

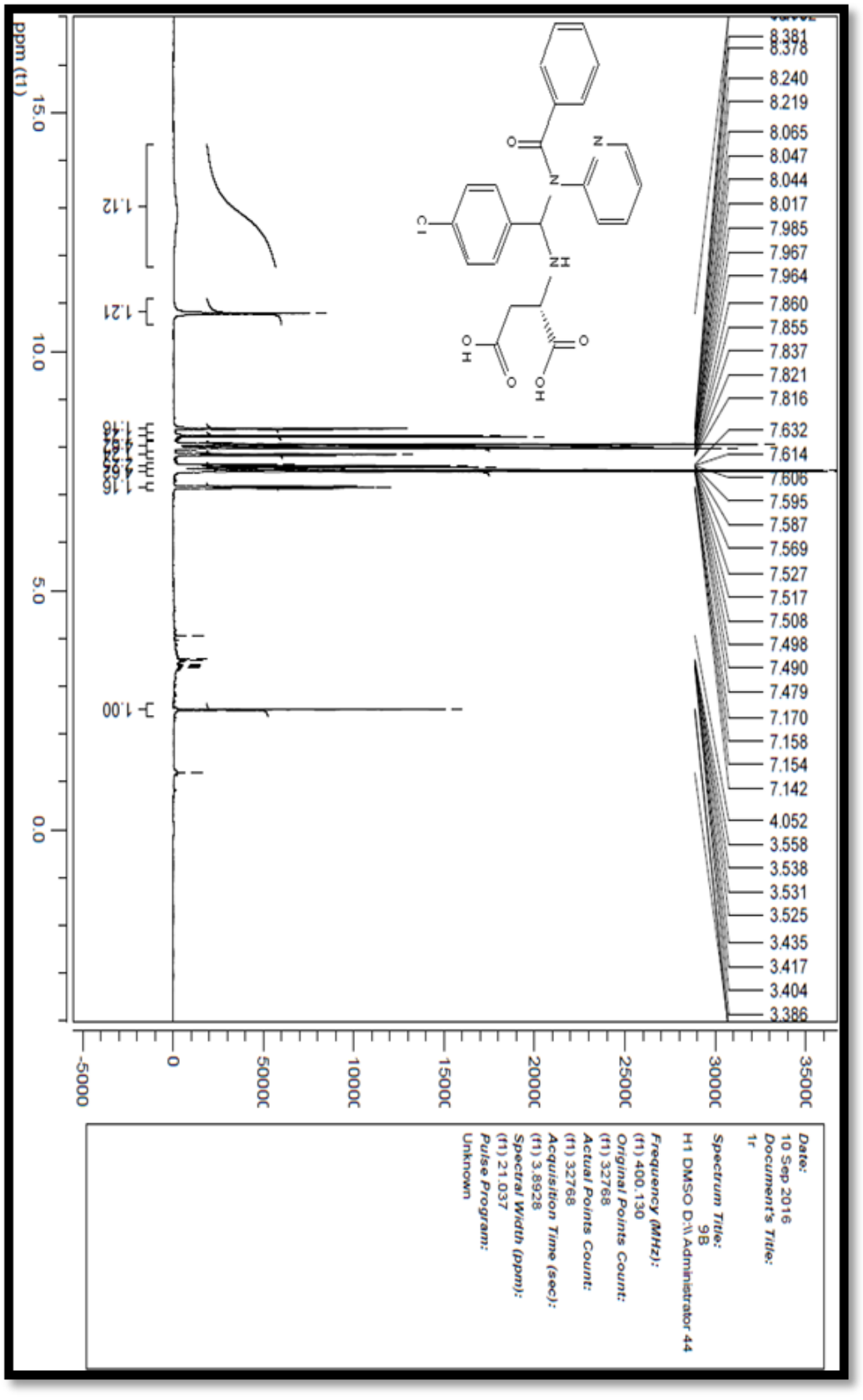



**Fig (3-32): $^{1}$H-NMR (ppm) spectrum of [9B].**

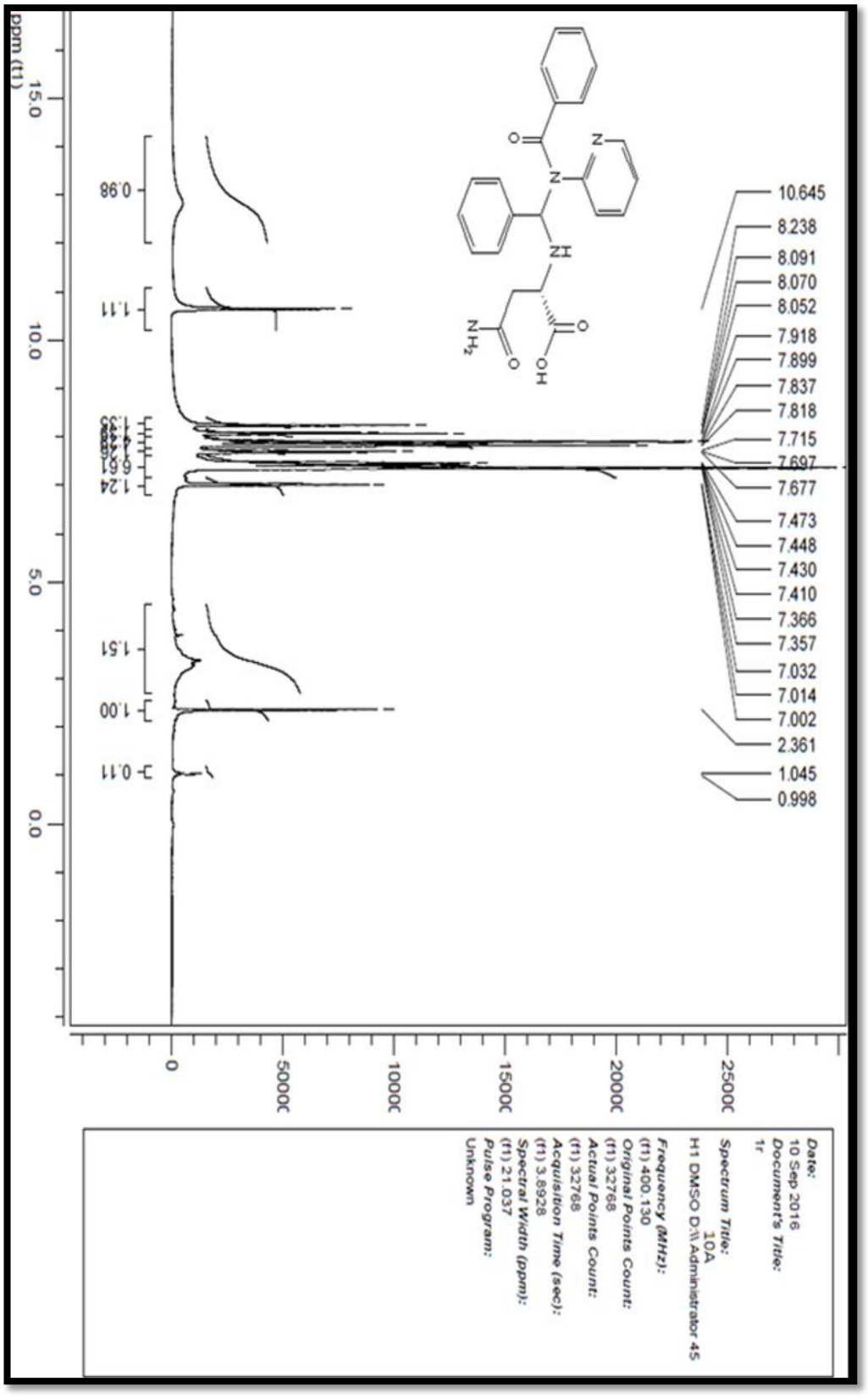



**Fig (3-33): $^{1}$H-NMR (ppm) spectrum of [10A].**

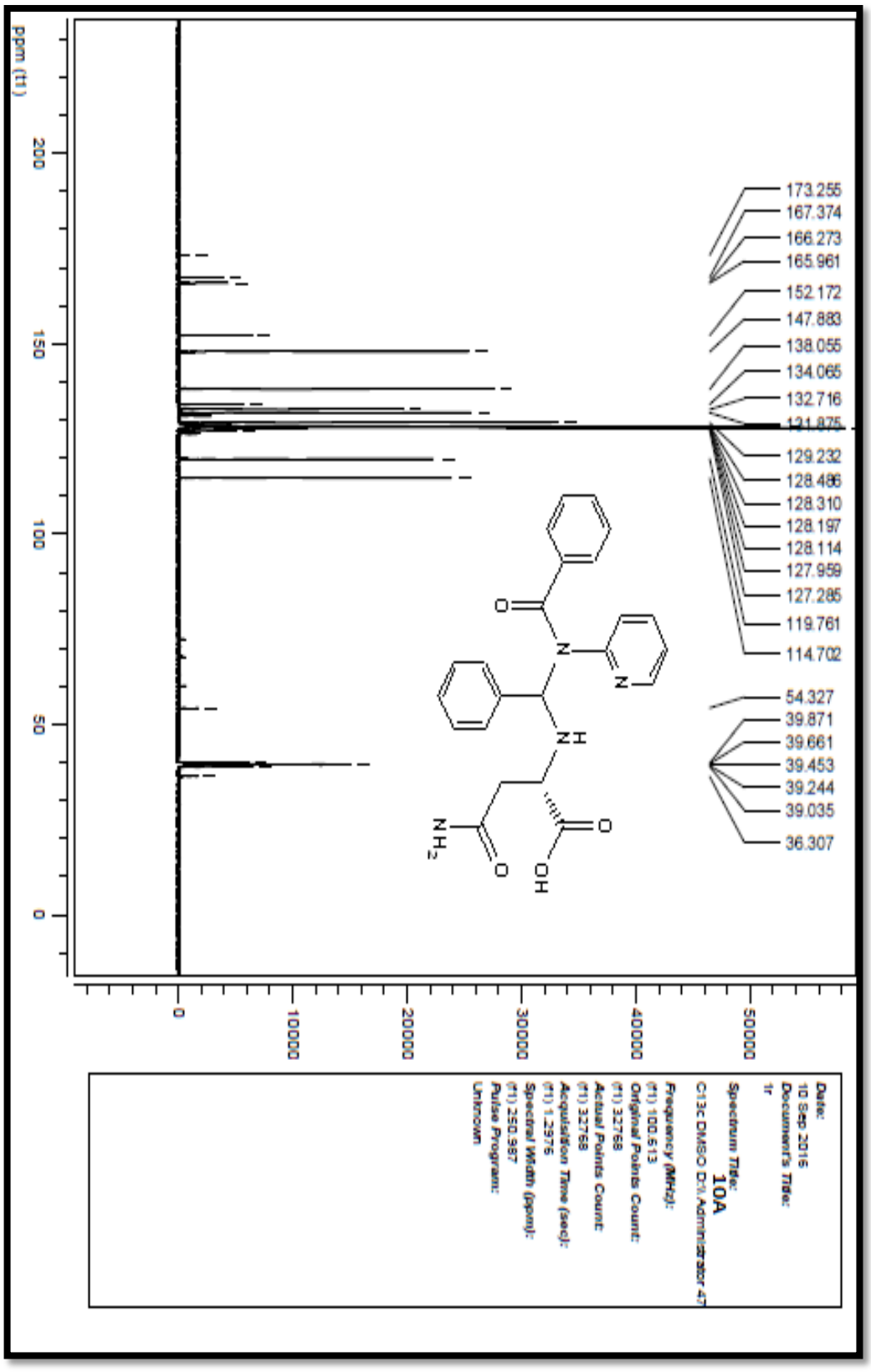



**Fig (3-34): $^{13}$C-NMR (ppm) spectrum of [10A].**

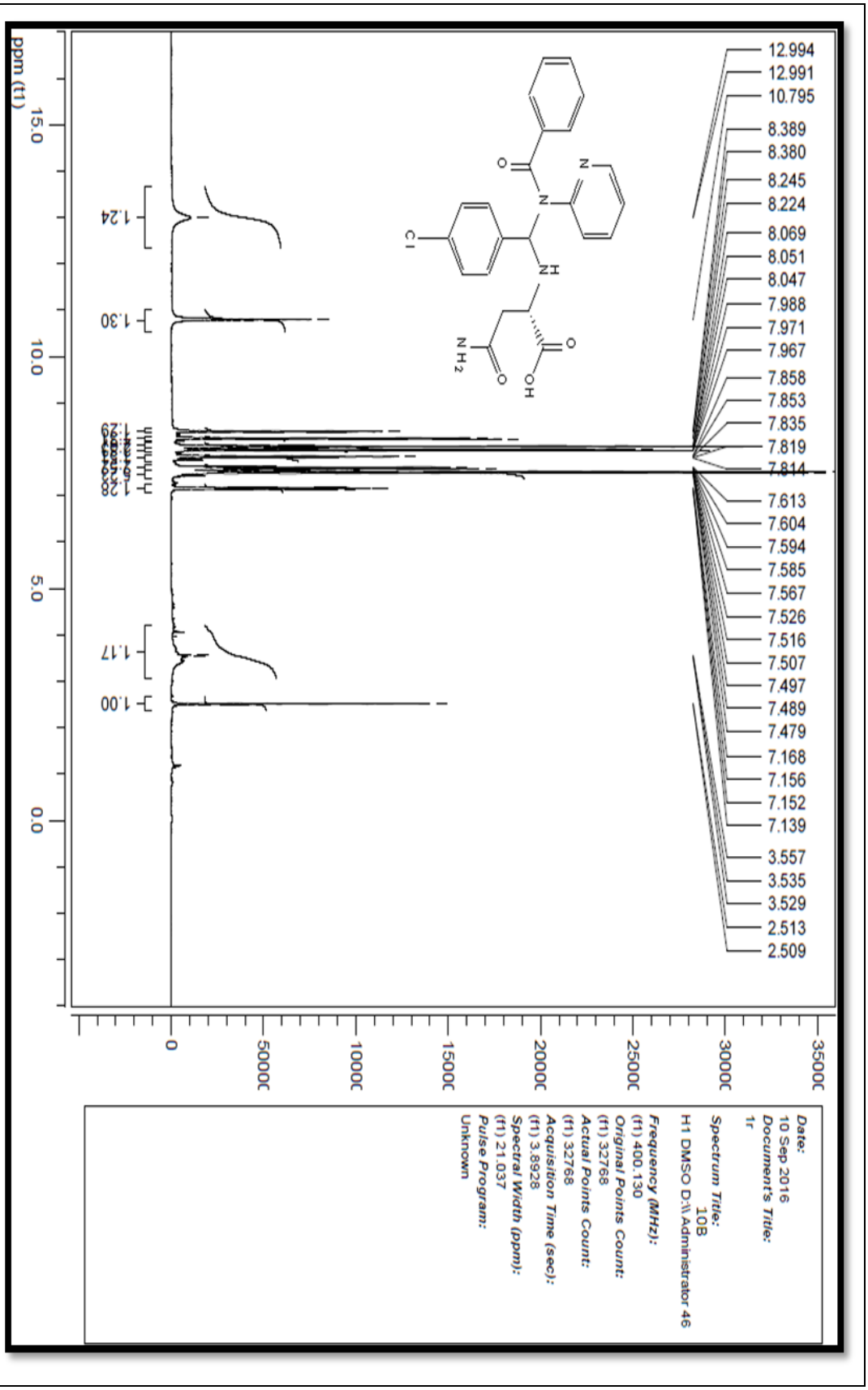



**Fig (3-35): $^{1}$H-NMR (ppm) spectrum of [10B].**

## 3.4 Biological Studies

### 3.4.1 Antibacterial Studies

The inhibition zones caused by the various compounds against two types of bacteria with concentrations (5, 10, 25, 50) µg/ml for all compounds were examined.

The results were listed in Table (3-9), and shown in Fig [(3-38) - (3-45)], including the reference drug (Meropenem).

**Table (3-9): The inhibition zones in (mm) and Minimum inhibition zones (MIC) in (µg/mL) for compounds [6(A-C) – 10(A-C)] and Meropenem against *Staphylococcus aureus* and *Klebsiella pneumoniae***

| Comp. No. | Concentration (µg/mL) | Inhibition Zone in (mm) | |
|---|---|---|---|
| | | *Gram Positive (Staphylococcus aureus)* | Gram Negative (*Klebsiella pneumoniae*) |
| 6A | **5** | 10 | 26 |
| | **10** | 11 | 26 |
| | **25** | 15 | 27 |
| | **50** | 18 | 28 |
| 7A | **5** | - | 11 |
| | **10** | - | 12 |
| | **25** | 14 | 12 |
| | **50** | 15 | 12 |
| 8A | **5** | 12 | - |
| | **10** | 14 | 11 |
| | **25** | 16 | 12 |
| | **50** | 17 | 13 |

| | | | |
|---|---|---|---|
| **9A** | **5** | - | 12 |
| | **10** | - | 13 |
| | **25** | 13 | 13 |
| | **50** | 16 | 13 |
| **10A** | **5** | 11 | - |
| | **10** | 12 | 11 |
| | **25** | 15 | 12 |
| | **50** | 15 | 17 |
| **6B** | **5** | - | - |
| | **10** | 10 | 15 |
| | **25** | 11 | 17 |
| | **50** | 14 | 18 |
| **7B** | **5** | - | - |
| | **10** | 11 | - |
| | **25** | 14 | 14 |
| | **50** | 33 | 24 |
| **8B** | **5** | 12 | 13 |
| | **10** | 13 | 14 |
| | **25** | 14 | 15 |
| | **50** | 15 | 16 |
| **9B** | **5** | - | 10 |
| | **10** | 10 | 11 |
| | **25** | 13 | 12 |
| | **50** | 15 | 13 |
| **10B** | **5** | - | 11 |
| | **10** | 10 | 12 |
| | **25** | 14 | 14 |

| | | | |
|---|---|---|---|
| | **50** | 16 | 15 |
| **6C** | **5** | 11 | 11 |
| | **10** | 12 | 12 |
| | **25** | 13 | 12 |
| | **50** | 14 | 13 |
| **7C** | **5** | 10 | - |
| | **10** | 11 | - |
| | **25** | 15 | 12 |
| | **50** | 17 | 14 |
| **8C** | **5** | - | 11 |
| | **10** | - | 12 |
| | **25** | 13 | 14 |
| | **50** | 14 | 20 |
| **9C** | **5** | - | 11 |
| | **10** | - | 11 |
| | **25** | 12 | 13 |
| | **50** | 14 | 14 |
| **10C** | **5** | - | - |
| | **10** | 11 | - |
| | **25** | 13 | 10 |
| | **50** | 17 | 12 |
| **Mero.** | **5** | 34 | 38 |
| | **10** | 36 | 40 |
| | **25** | 42 | 44 |
| | **50** | 44 | 48 |
| **DMSO** | - | - | - |

The synthesized compounds [6(A-C) – 10(A-C)] showed a lower anti-bacterial activity compared with Meropenem as a reference against both (*S. aureus*) and (*K. pneumoniae*).

From the obtained data in table (3-9), it was found clearly that L-Alanine derivative (7B) has the highest activity against *S. aureus* at Concentration 50 (μg/mL). All other L-Amino acid derivatives have a moderate activity against *S. aurous*.

It was found clearly that Glycine derivative (6A), L-Alanine derivative (7B) and L-Phenylalanine derivative (8C) have the highest activity against *K. pneumonia* at Concentration 50 (μg/mL). All L-Amino acid derivatives have a moderate activity against *K. pneumoniae*.

The synthesized compounds [6(A-C) – 10(A-C)] could destroy the bacteria cell wall. This can be explained by covalently binding to penicillin-binding proteins (PBPs) involved in the biosynthesis of mucopeptides in bacterial cell walls and this lead to rapid bacterial cell death. Bactericidal effects result through inhibition of cellular growth and division and the loss of cell wall integrity, eventually causing cell wall lysis [(54)].

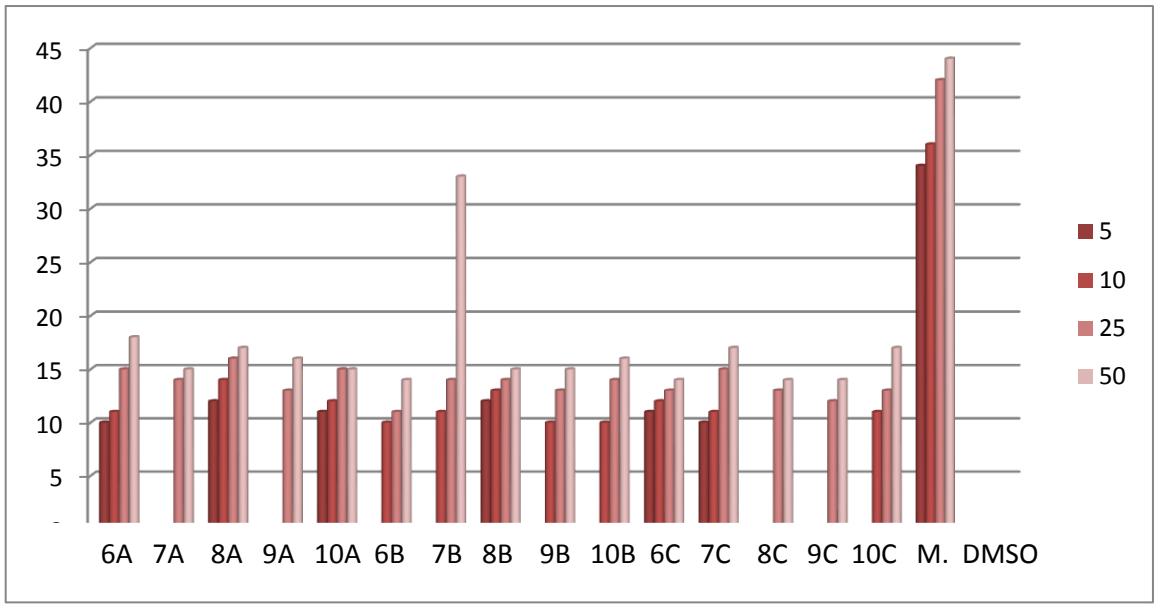



Fig (3-36): The effect of compounds [6(A-C) – 10(A-C)] and Meropenem (M.) on *Staphylococcus aureus* in concentration of 5, 10, 25, 50 (µg/mL) dissolved in DMSO at 37 °C for 24 hrs.

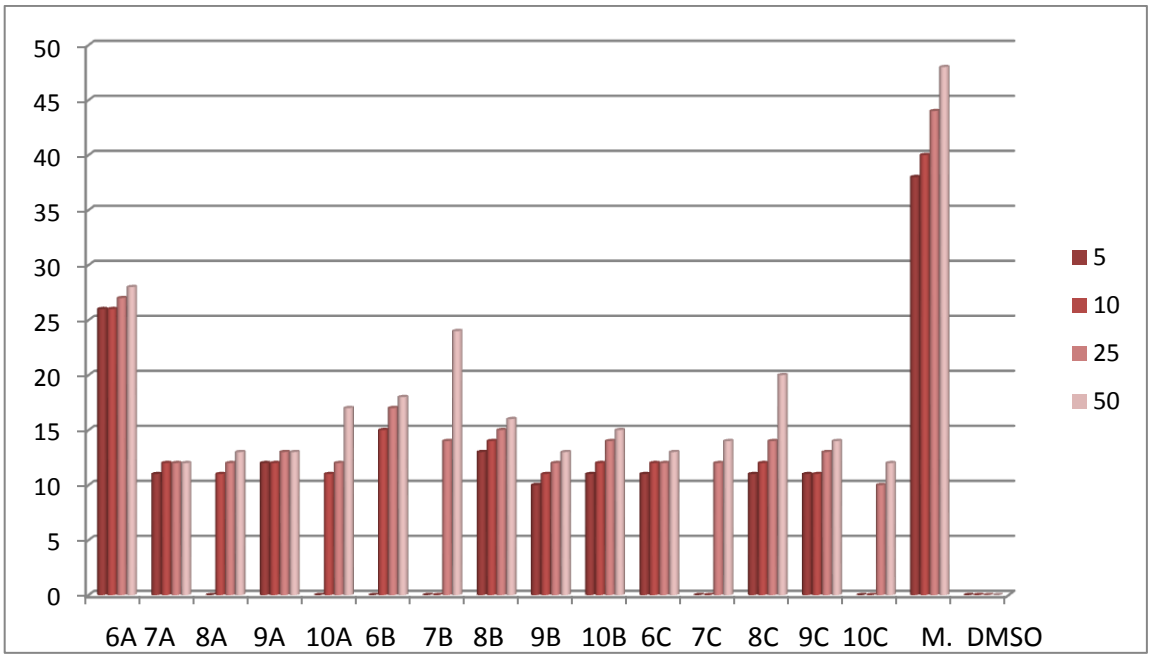



Fig (3-37): The effect of compounds [6(A-C) – 10(A-C)] and Meropenem (M.) on *Klebsiella pneumoniae* in concentration of 5, 10, 25, 50 (µg/mL) dissolved in DMSO at 37 °C for 24 hrs.

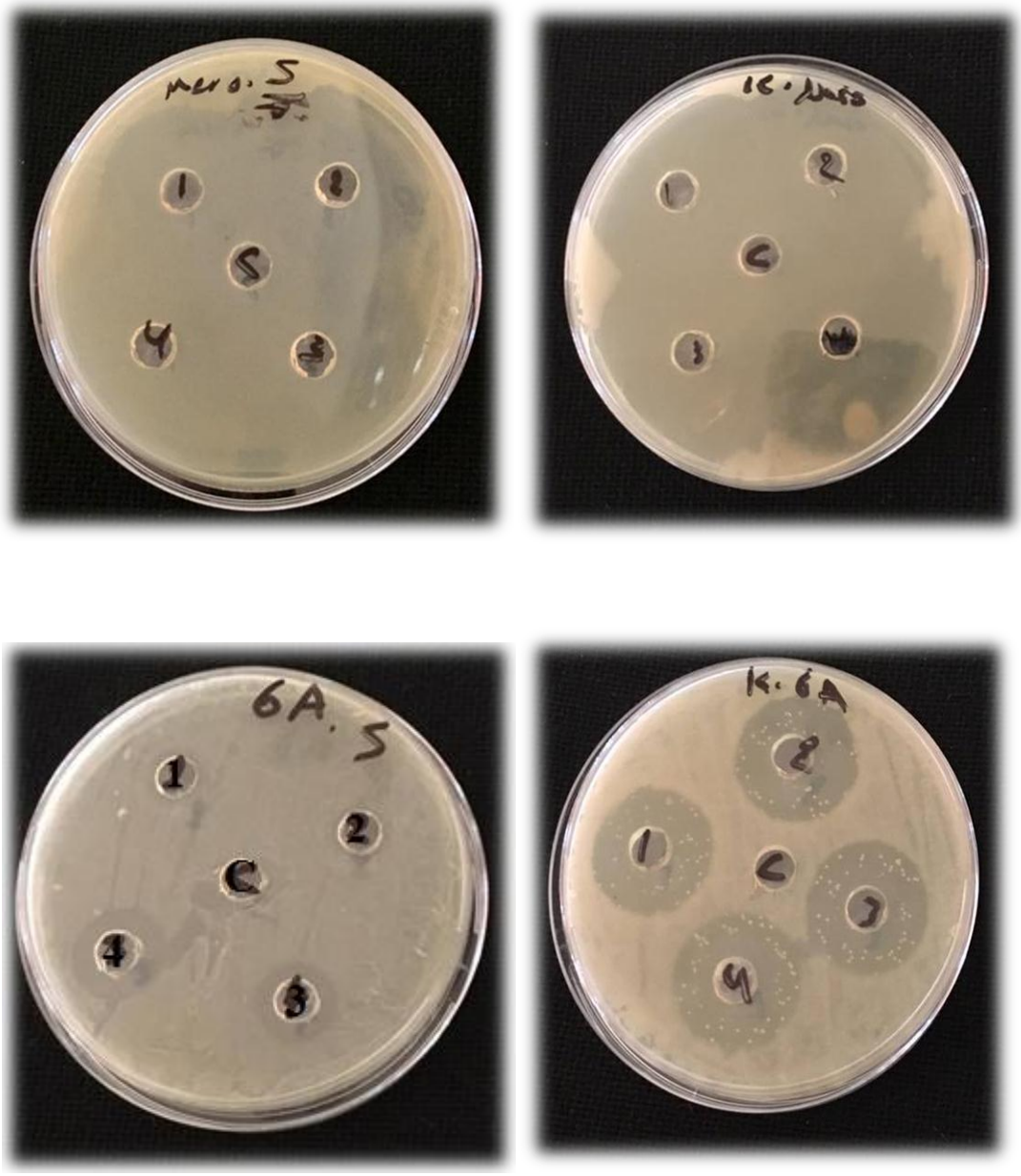



Fig (3-38): Inhibition zones of Meropenem (Mero.) and compound (6A) with concentrations (5, 10, 25, 50) µg/ml against *staphylococcus aureus* (L) and *Klebsiella pneumoniae* (R), with control (DMSO).

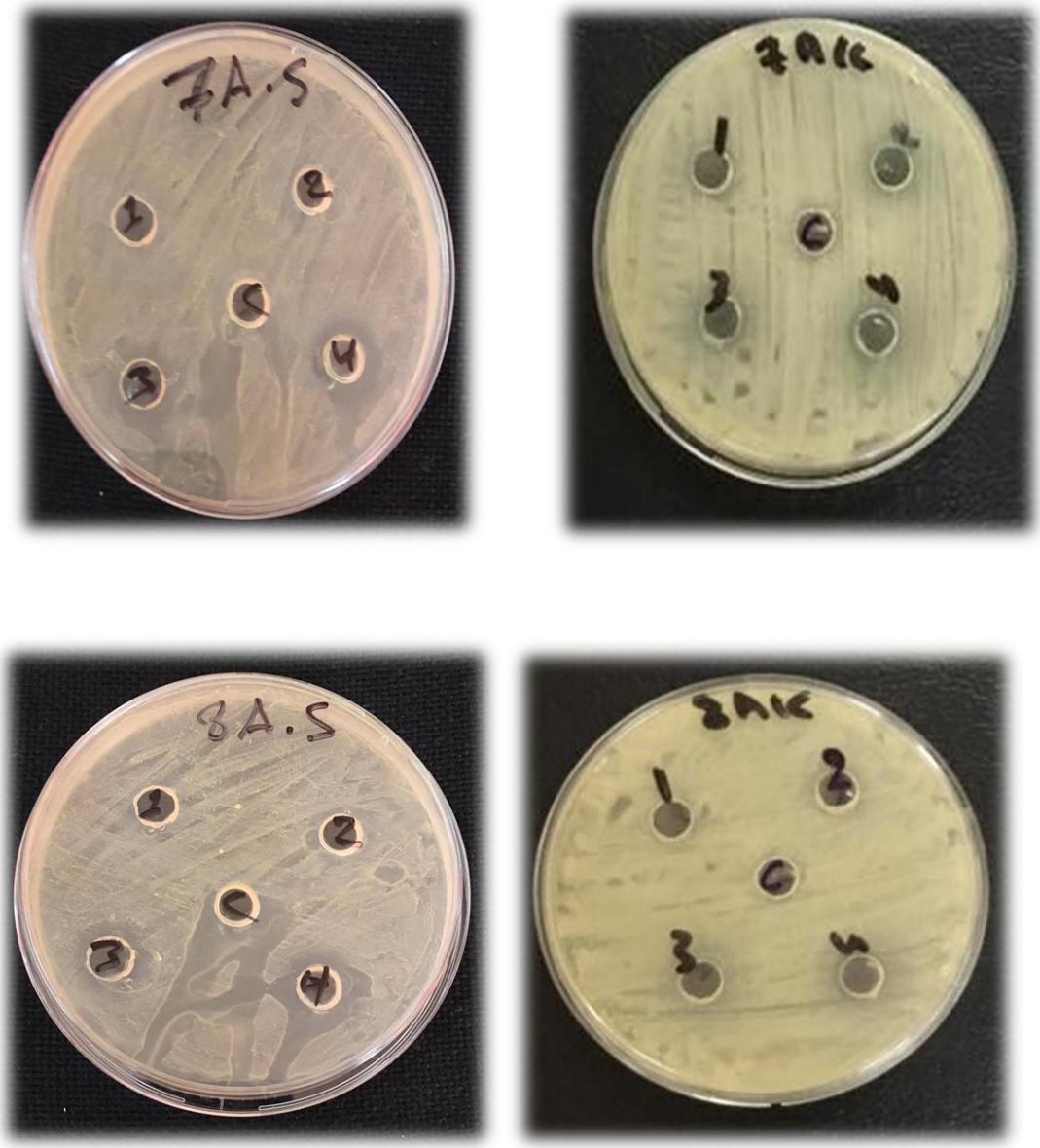



Fig (3-39): Inhibition zones of compounds (7A) and (8A) with concentrations (5, 10, 25, 50) µg/ml against *staphylococcus aureus* (L) and *Klebsiella pneumoniae* (R), with control (DMSO).

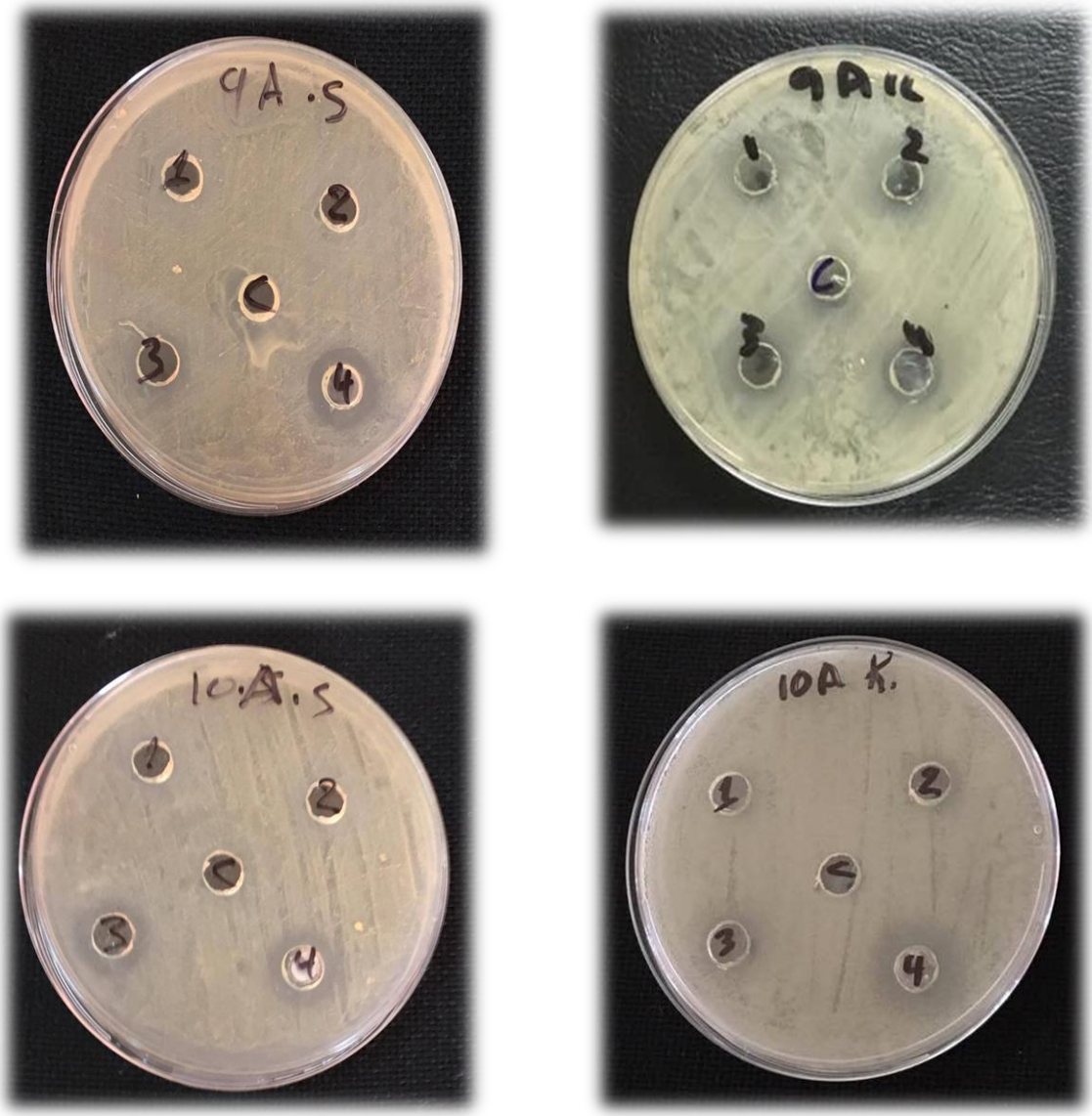



Fig (3-40): Inhibition zones of compounds (9A) and (10A) with concentrations (5, 10, 25, 50) µg/ml against *staphylococcus aureus* (L) and *Klebsiella pneumoniae* (R), with control (DMSO).

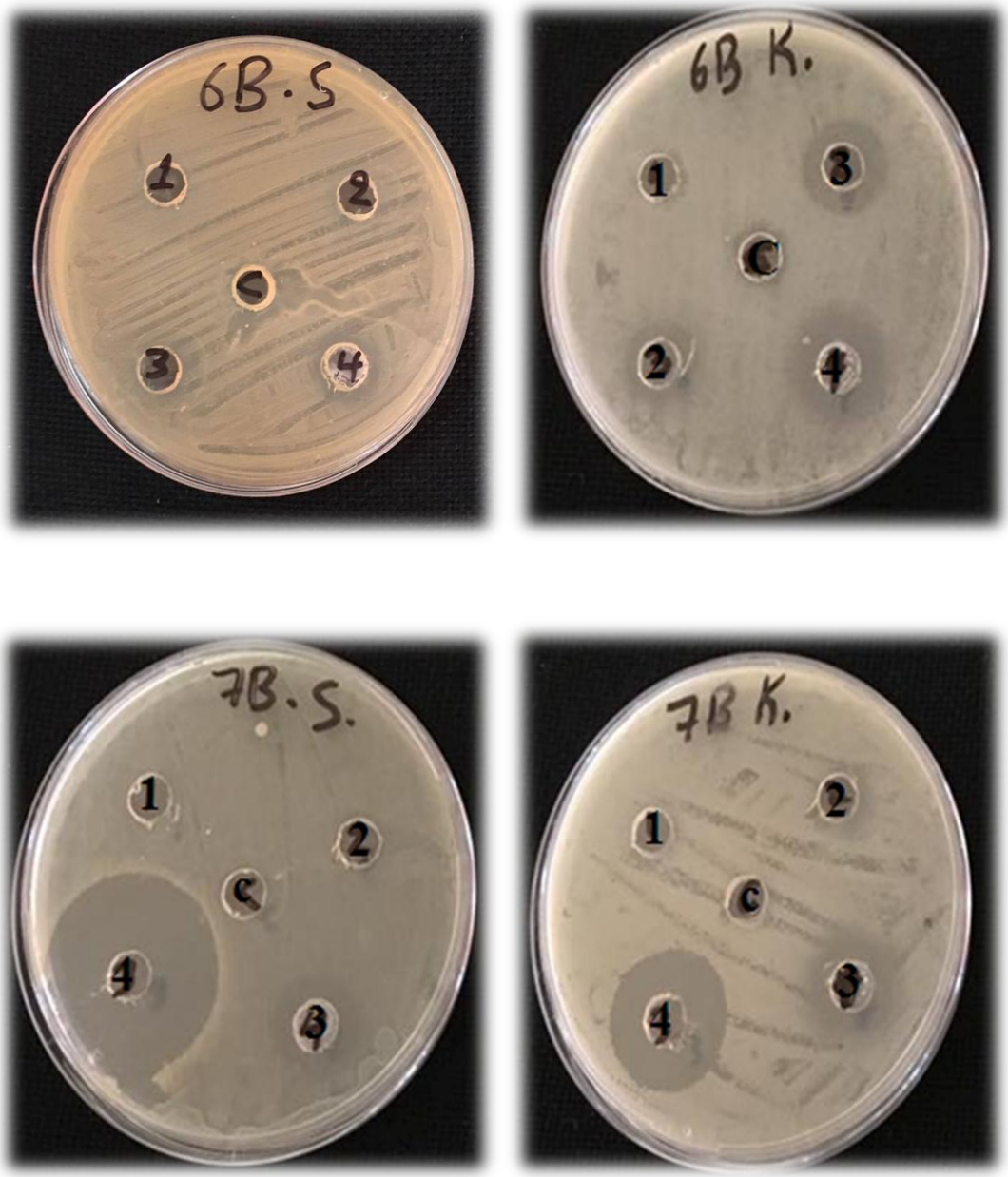



Fig (3-45): Inhibition zones of compounds (6B) and (7B) with concentrations (5, 10, 25, 50) µg/ml against *staphylococcus aureus* (L) and *Klebsiella pneumoniae* (R), with control (DMSO).

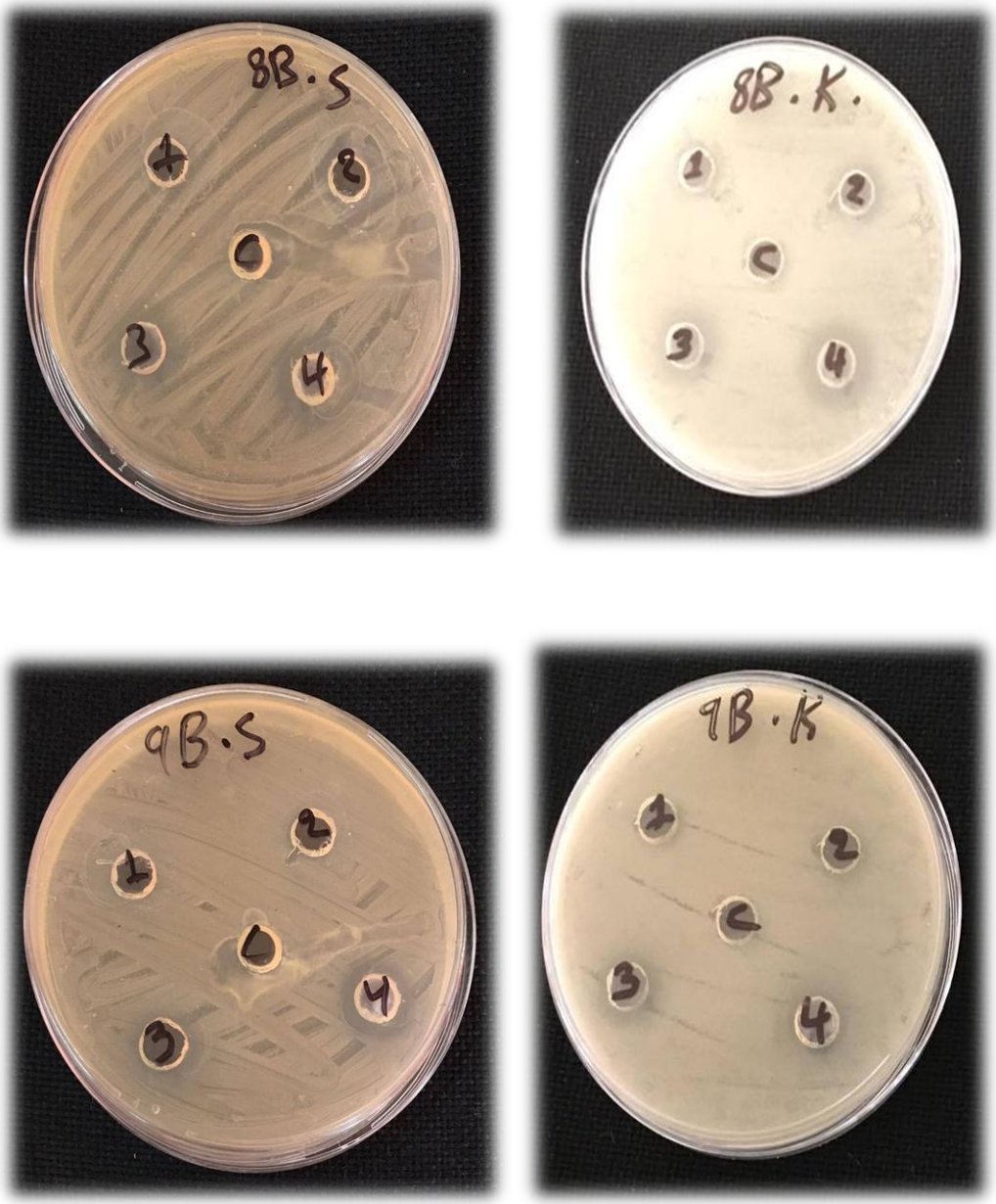



Fig (3-42): Inhibition zones of compounds (8B) and (9B) with concentrations (5, 10, 25, 50) µg/ml against *staphylococcus aureus* (L) and *Klebsiella pneumoniae* (R), with control (DMSO).

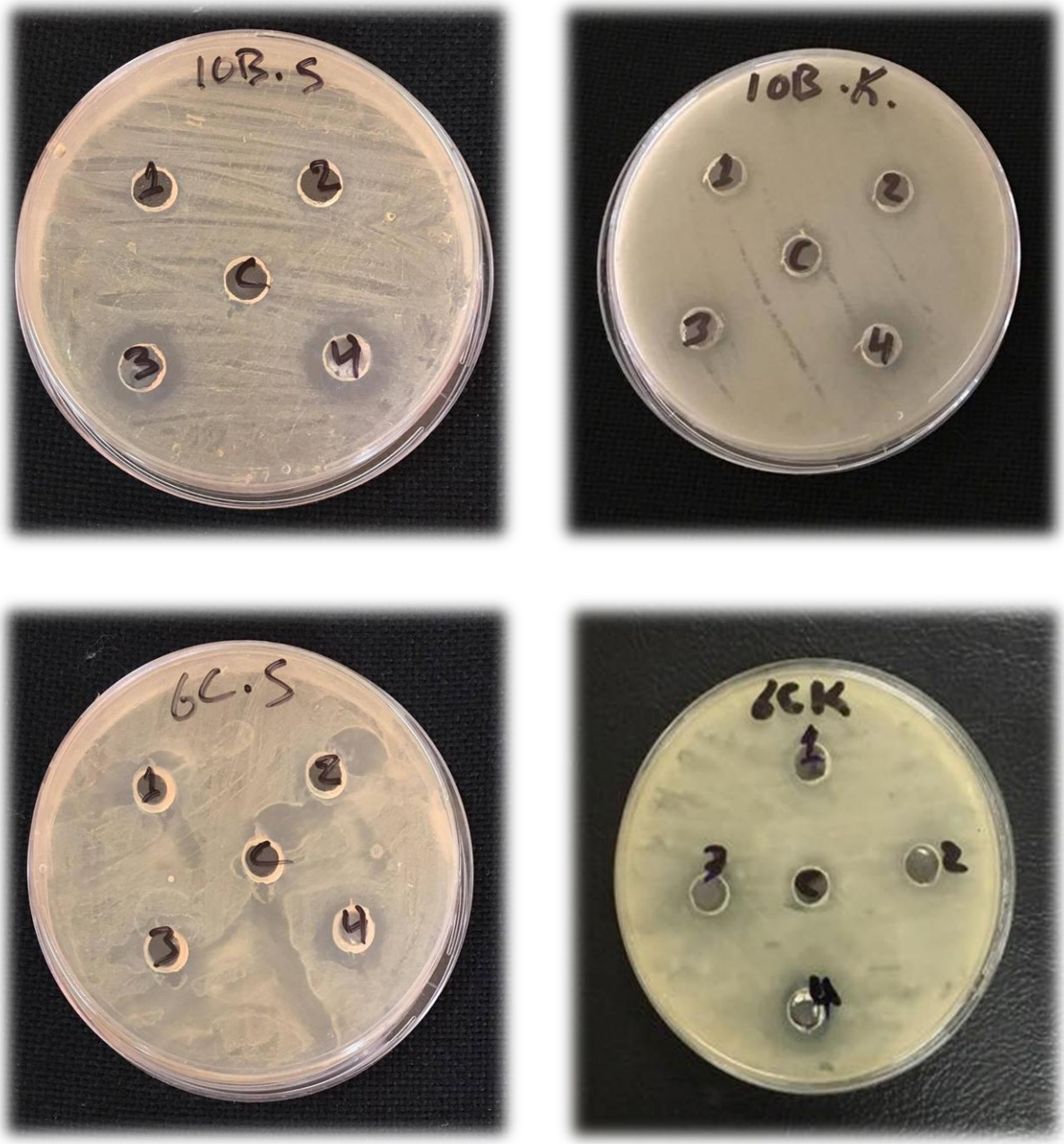



Fig (3-43): Inhibition zones of compounds (10B) and (6C) with concentrations (5, 10, 25, 50) µg/ml against *staphylococcus aureus* (L) and *Klebsiella pneumoniae* (R), with control (DMSO).

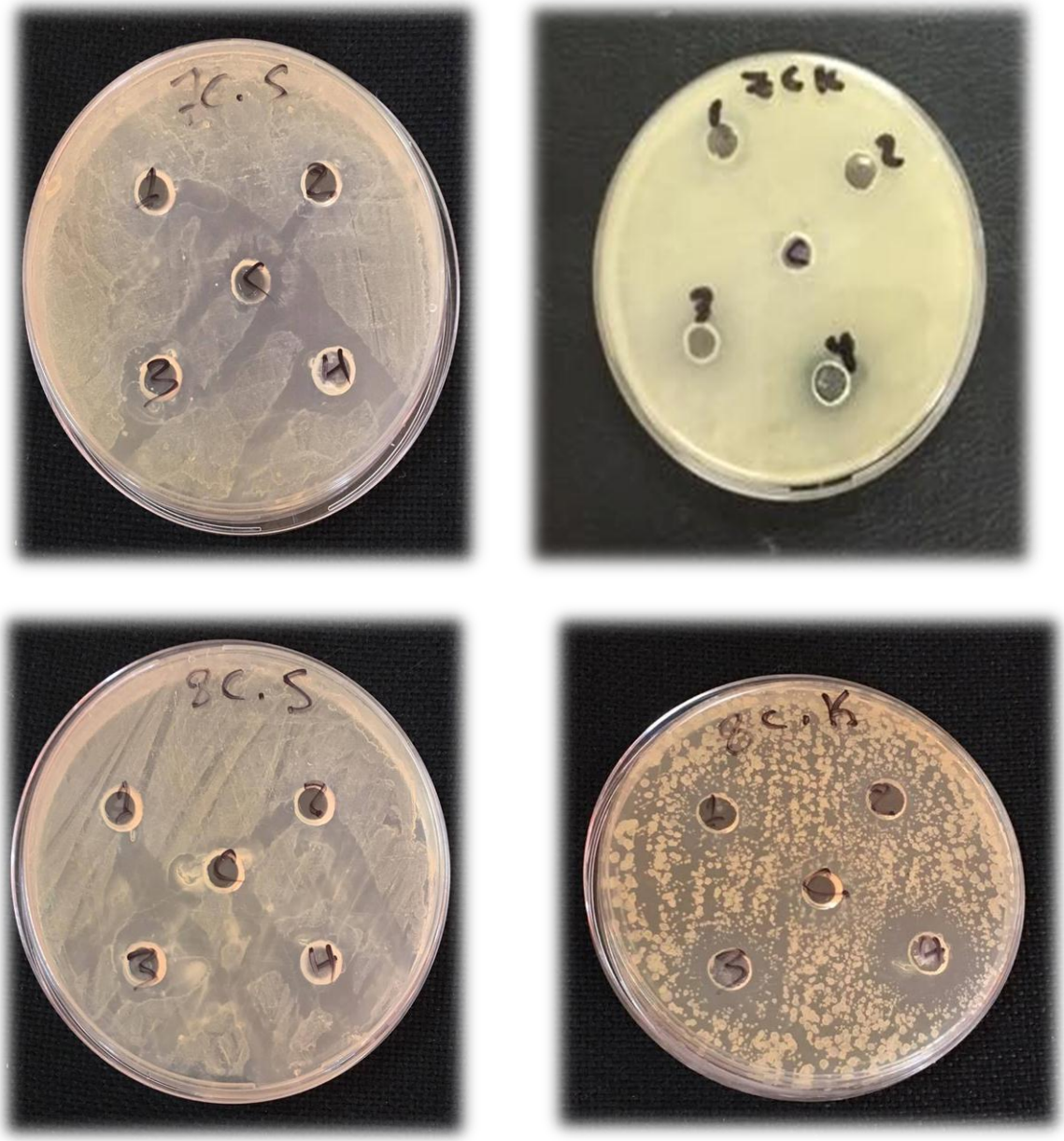



Fig (3-44): Inhibition zones of compounds (7C) and (8C) with concentrations (5, 10, 25, 50) µg/ml against *staphylococcus aureus* (L) and *Klebsiella pneumoniae* (R), with control (DMSO).

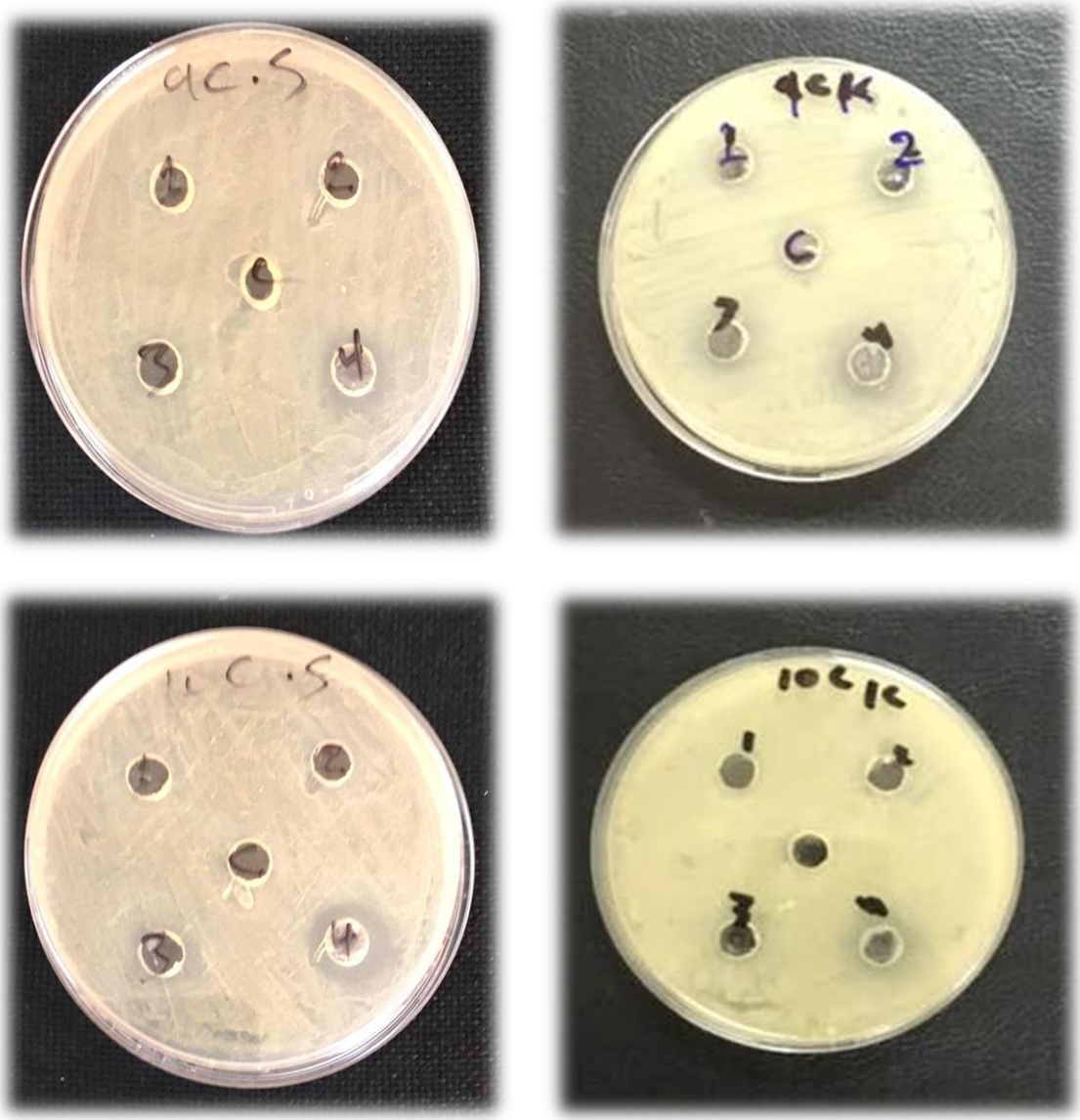



Fig (3-45): Inhibition zones of compounds (9C) and (10C) with concentrations (5, 10, 25, 50) µg/ml against *staphylococcus aureus* (L) and *Klebsiella pneumoniae* (R), with control (DMSO).

## 3.5 Conclusion

Synthesized amino acid derivatives 6A, 7B, and 8C with glycine, L-alanine and L-phenyl alanine, respectively, were the best biological active compounds. It appears that glycine flexibility, and the amino acid side chains: methyl and phenyl were important for their function as biological active compounds. Fundamentally, structural variation and substitution were important factors to be effective on weather Gram positive or negative tested bacteria. Furthermore, it is considerable that more structural substitution and variation will be investigated to reach more favorable results.

## 3.6 Suggestions for further work

1- Derivatives with other L-amino acids and with other benzaldehyde derivatives can be synthesized and tested for their biological activity.
2- Synthesized L-Amino acid derivatives [6(A-C)-10(A-C)] can further react with suitable reagents to obtain different heterocyclic compounds and study their antibacterial, antifungal, or antioxidant activities.
3- Study the antibacterial activity of synthesized compound on other kinds of bacteria.
4- Evaluation the cytotoxicity of the synthesized compounds *In vitro*.

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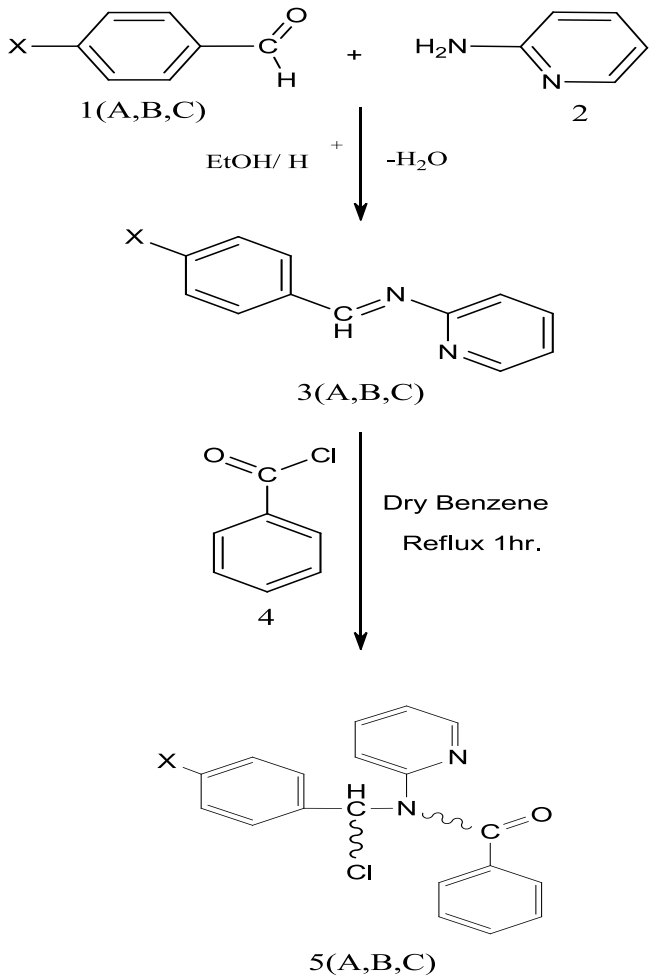
# الملخص


تضمن البحث تحضير قواعد شف مختلفة [3(A-C)] من تفاعل 2- أمينوبريدين [2] مع البنزالديهايد ومشتقاته [1(A-C)] التي تمت مفاعلتها مع بنزوايل كلورايد [4] وبدورها تفاعلت مع L-أحماض أمينيه مختلفه [6(A-C)–10(A-C)] ( كلايسين, L- الأنين, L- فنيل الأنين, L- حامض الاسبارتك, L- الأسبراجين ). تم اعتماد طيف الأشعة تحت الحمراء FT-IR و طيف الرنين النووي المغناطيسي $^{1}$H-NMR , $^{13}$C-NMR لتشخيص المركبات المحضرة. تم تقييم النشاط الحيوي للمركبات النهائية المحضرة ضد جنسين من البكتيريا سالبة الغرام (الكليبسلة الرئوية) و موجبة الغرام (المكورات العنقودية الذهبية).

أظهرت كل المركبات المحضرة [6(A-C)–10(A-C)] فعالية أقل مقارنة بالميروبينم المستعمل كمصدر للمقارنة ضد كل من البكتيريا المكورات العنقورية الذهبية والكليبسلة الرئوية.

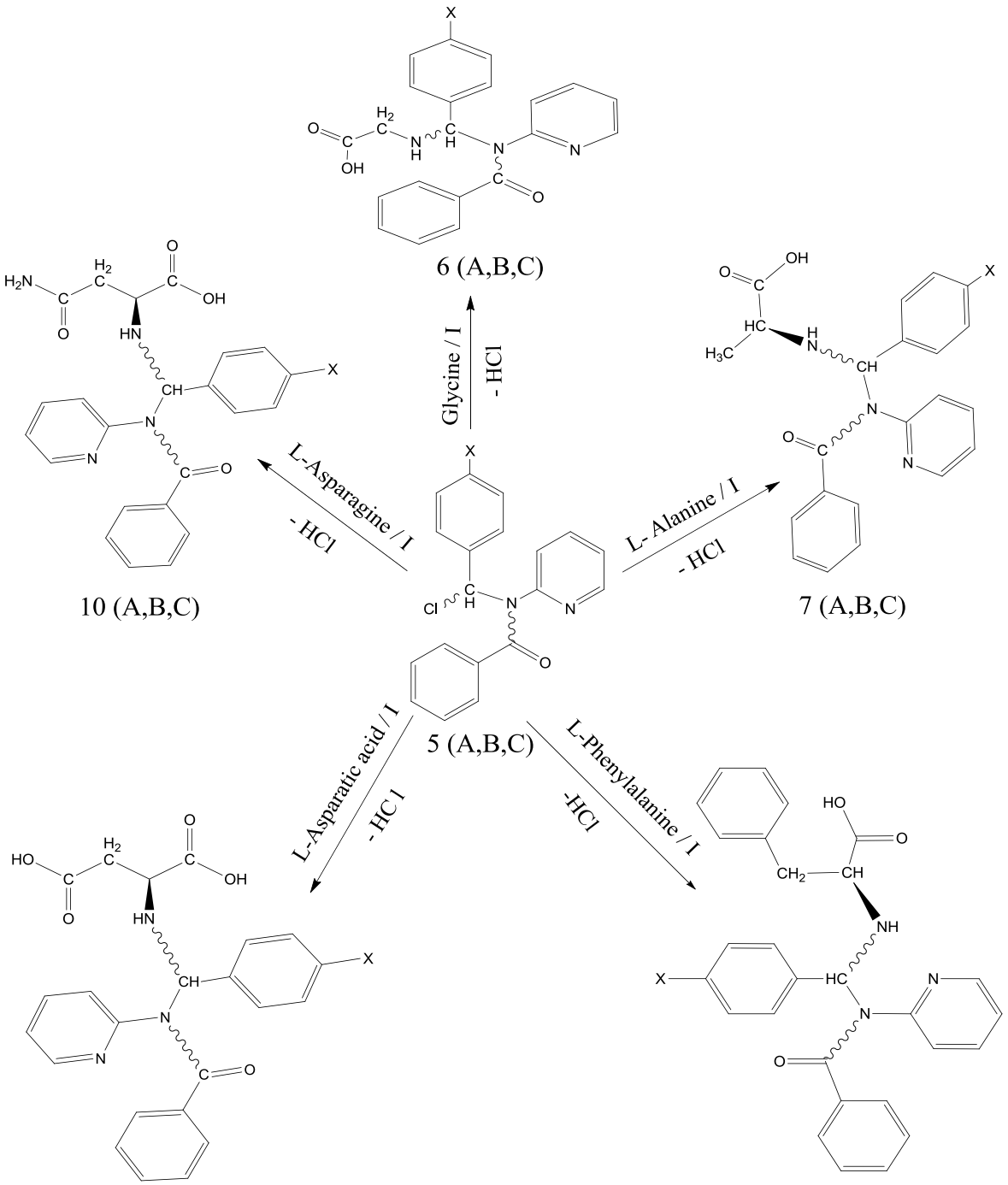
وجد ان هذه المركبات 6A, 7B و 8C لها أفضل فعالية ضد البكتيريا من بين المركبات المحضرة ضد كلا النوعين من البكتيريا عند التركيز 50 (مايكروغرام/مل).


X: H, Cl, Br.

المخطط 1: طريقة تحضير مركب

*N*-[chloro-(4-monosubstituted-benzyl)]-*N*-pyridin-2-yl-benzamide.




X: H, Cl, Br.

I: Dioxan / $H_2O$, reflux 4hr.

المخطط 2 : طريقة تحضير مركب
(2S)-2-*N*-[(benzoyl-pyridin-2-yl-amino)-(4-monosubstituted-phenyl)-methyl]-L-amino acid
*N*-[chloro-(4-monosubstituted-benzyl)]-*N*-pyridin-2-yl-benzamide من

جمهورية العراق
وزارة التعليم العالي والبحث العلمي
جامعة النهرين
كلية العلوم
قسم الكيمياء

# تخليق و تشخيص بعض مشتقات الحوامض الامينية ودراسة الفعالية المضادة للبكتيريا

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

من قبل
**دينا زياد قاسم**
بكالوريوس 2014

**إشراف**
**الاستاذ المساعد**
**د. جواد كاظم شنين**

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2017 م