SYNTHESIS, BIOACTIVITY SCREENING AND DOCKING ANALYSIS OF THIAZOLE DERIVATIVES CONTAINING QUINOLINE MOIETIES

By

Aongchainu Marma

Student ID: 19MCHEM003P

A thesis submitted in partial fulfilment of the requirements for the degree of Master of Philosophy in Chemistry.

Department of Chemistry

CHITTAGONG UNIVERSITY OF ENGINEERING AND TECHNOLOGY

May, 2024

CERTIFICATION

The thesis titled **"SYNTHESIS, BIOACTIVITY SCREENING AND DOCKING ANALYSIS OF THIAZOLE DERIVATIVES CONTAINING QUINOLINE MOIETIES."** submitted by **Aaongchainu Marma**, Student ID. 19MCHEM003P, Session: 2019-2020 has been accepted as satisfactory in partial fulfillment of the requirement for the degree of **Master of Philosophy** in Chemistry on 15 May, 2024.

BOARD OF EXAMINERS

15.5.24

1. **Dr. Ranajit Kumar Sutradhar** — Chairman (Supervisor)
Professor
Department of Chemistry
Chittagong University of Engineering and Technology

15/5/24

2. **Dr. Ranjit Kumar Nath** — Member (Ex-Officio)
Professor & Head
Department of Chemistry
Chittagong University of Engineering and Technology

15.5.24

3. **Dr. Md. Rezaul Karim** — Member
Professor
Department of Chemistry
Chittagong University of Engineering and Technology

15.5.24

4. **Dr. Yunus Ahmed** — Member
Associate Professor
Department of Chemistry
Chittagong University of Engineering and Technology

5. **Dr. Dipen Debnath** (On line participant) — Member (External)
Professor
Department of Chemistry
Shahjalal University of Science and Technology
Sylhet -3114

CANDIDATE'S DECLARATION

I hereby declare that the work contained in this Thesis has not been previously submitted to meet the requirements for an award at this or any other higher education institution. To the best of my knowledge and belief, the Thesis contains no material previously published or written by another except where due reference is cited. Furthermore, the Thesis complies with the PLAGIARISM and ACADEMIC INTEGRITY regulations of CUET.

Aongchainu Marma
19MCHEM003P
Department of Chemistry
Chittagong University of Engineering and Technology

Copyright Declaration

I hereby declare that I am the sole author of the thesis titled **"SYNTHESIS, BIOACTIVITY SCREENING AND DOCKING ANALYSIS OF THIAZOLE DERIVATIVES CONTAINING QUINOLINE MOIETIES"**. Along with this, submitted a softcopy is true copy of my final hardcopy thesis including any required final revisions, as accepted by the board of examination.

I hereby release my copyright to Chittagong University of Engineering and Technology (CUET) for uploading the electronic version of the same to the `Digital Repository (Institutional Repository)' of CUET after one year from the day of submission. Apart from this, the existing or to be approved Open Education Resources (OER) policies and procedures of Chittagong University of Engineering and Technology (CUET) shall be applicable to this research work.

I also acknowledge my sincere delivering of copyright to Chittagong University of engineering and Technology (CUET) to reproduce this thesis by reprography or by other means, in total or by part at the necessity of individuals for the purpose of scholarly research.

Signature of the Author

Declaration by the Supervisor

This is to certify that Aongchainu Marma has carried out this research work under my supervision and that he has fulfilled the relevant Academic Ordinance of the Chittagong University of Engineering and Technology so that he is qualified to submit the following Thesis in the application for the degree of MASTER OF PHILOSOPHY IN CHEMISTRY. Furthermore, the Thesis complies with the PLAGIARISM and ACADEMIC INTEGRITY regulations of CUET.

Dr. Ranajit Kumar Sutradhar
Professor
Department of Chemistry
Chittagong University of Engineering and Technology

Dedication

I would like to dedicate this thesis to

My parents and wife

Table of Contents

Chapter – 1

Introduction

Chapter – 2

Experimental

Chapter – 3

Results and Discussions

Chapter – 4

Conclusion and Future Plan

Chapter – 5

List of Figures

List of Tables

Abbreviations

COSY	Correlated Spectroscopy
DEPT	Distortionless Enhancement by Polarization Transfer
DPPH	2,2-diphenyl-1-picrylhydrazil
HMBC	Hetero-Nuclear Multiple Bonds Correlation
HSQC	Hetero-Nuclear Single Quantum Coherence
Hz	Hertz
IR	Infrared
J	Coupling Constant
NMR	Nuclear Magnetic Resonance
ppm	Parts Per Million
Rf	Retardation factor
TLC	Thin Layer Chromatography
TMS	Tetramethyl Silane
DMSO	Dimethyl Sulphoxide

ACKNOWLEDGEMENT

First of all, I pray God Buddha for successfully completion of my thesis.

I am extremely delighted to express my deepest sense of gratitude and grateful thanks to my supervisor **Dr. Ranajit Kumar Sutradhar**, Professor, Dept. of Chemistry, Chittagong University of Engineering and Technology (CUET). He provided information, suggestions, criticism and encouragement that inspired me to carry out this study.

I am very much grateful to Mr. Md. Din Islam, Assistant Professor, Dept. of Chemistry, Chittagong University of Engineering and Technology (CUET) for his cordial support, valuable suggestions and over all guidance to complete the thesis work.

I am grateful to Professor Ranajit Kumar Nath, Head of Dept. of Chemistry for his valuable advices and all faculty members and staffs, Dept. of Chemistry, CUET for their kind support and assistance during my thesis work.

I am very much pleased and grateful to M Noor E Alam Siddiki, Commander, Bangladesh Navy, Ex-Principal of Bangladesh Noubahini School and College Kaptai(BNSCK); Mahbub Ahmed Shahjalal, Commander, Bangladesh Navy, Principal of BNSCK; Rakibul Hasan Sarkar, Lieutenant Commander, Bangladesh Navy, Ex-Principal of BNSCK and Md. Jahangir Alam, Vice-Principal of BNSCK for their support and encourage to me.

I gratefully acknowledge to the Ministry of Science and Technology, Peoples Republic of Bangladesh for awarding this research grant. I am also thankful to the CUET authority for giving permission and support to complete this research work.

At last, my sincere grateful is specially extended to my beloved parents, wife and family members for their heartfelt blessing, immeasurable sacrifice and continuous inspiration which lead me to all my success in study.

May, 2024

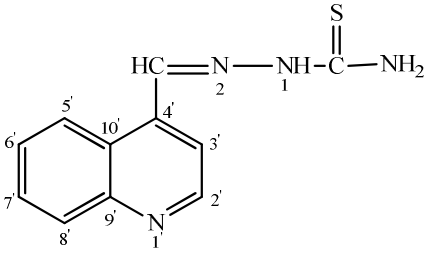
The Author
(Aongchainu Marma)

Abstract

Thiazole, the heterocyclic compound is an important scaffold of azaheterocycles family. Heterocyclic nucleus containing thiazole Schiff bases imparts an important function in medicinal chemistry and serves as a key template for the development of various therapeutic agents. In our present work, three thiazole Schiff base derivatives containing quinoline moieties **1b-3b** were synthesized by two step reactions. Firstly, three thiosemicarbazone derivatives **la-3a** were synthesized using aldehydes substituted quinoline and thiosemicarbazide. Cyclization of **la-3a** with 3-chloroacetylacetone afforded the corresponding thiazoles Schiff bases **1b-3b**. The synthesized analogs characterization was elucidated by spectral analyses (IR, ^{1}H NMR, ^{13}C NMR, COSY, HSQC and HMBC). All the synthesized compounds were screened for their antimicrobial activity towards three gram-positive bacteria *Bacillus Cereus, Staphylococcus aureus* and *Bacillus magaterium*, three gram-negative bacteria *Klebsiella pneumonia, Pseudomonas aeruginosa* and *Escherichia coli* and two fungal strains *Trichoderma harzianum* and *Aspergillus niger* were used in this study revealed that some compounds displayed moderate to good antimicrobial activities compared to standard Ampicillin & Amphotericin B in Agar disc diffusion technique. Compounds **1b & 3b** revealed comparable antibacterial activities against *S. aureus, B. Cereus, K. pneumonia* and *E. coli*, compound **2b** showed potential antibacterial activities against *S. aureus, K. pneumonia,* and *E. coli* with standard ampicillin. In antifungal screening, compounds **1b** & **3b** showed moderate to potential antifungal activities against the fungi *Aspergillus niger* with standard amphotericin b. From our research, we observed that compounds **1b** & **3b** might be used as potential antibacterial and antifungal drugs in future.

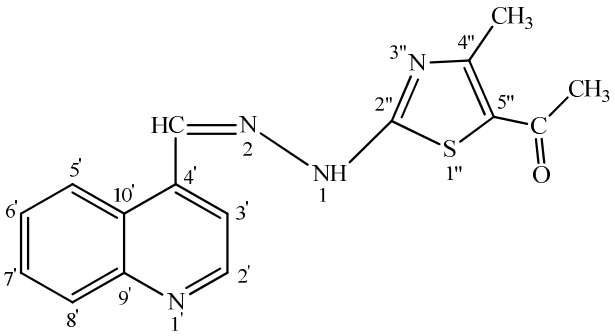
বিমূর্ত

Thiazole নামক হেটেরোসাইক্লিক যৌগটি Azaheterocycles শ্রেণির একটি গুরুত্বপূর্ণ এবং অপরিহার্য সদস্য। Thiazole Sciff Base হেটেরোসাইক্লিক নিউক্লিয়াস ঔষধ রসায়নে একটি গুরুত্বপূর্ণ অংশ দখল করে আছে, যারা বিভিন্ন Therapeutic Agent এর বিকাশের জন্য প্রধান নির্ণায়ক হিসাবে কাজ করে। আমাদের বর্তমান এই গবেষণায় তিনটি Quinolinothiazole জাতক **(1b-3b)** দুটি ধাপে সংশ্লেষণ করা হয়। প্রথম ধাপে, Quinolinoaldehyde এবং Thiosemicarbazide - এর বিক্রিয়ায় তিনটি Thiosemicarbazone জাতক **(1a-3a)** সংশ্লেষণ করা হয়। দ্বিতীয় ধাপে, Thiosemicarbazone জাতক -এর সাথে 3-chloroacetylacetone এর বিক্রিয়ায় কুইনোলিনযুক্ত থায়াজোল জাতক **(1b-3b)** সংশ্লেষণ করা হয়। এরপর, সংশ্লেষিত Thiosemicarbazone জাতক **(1a-3a)** এবং Thiazole জাতকগুলো **(1b-3b)** বর্ণালী বিশ্লেষণ যন্ত্র দ্বারা বিশ্লেষণ (IR, ^{1}H NMR, ^{13}C NMR, COSY, HSQC এবং HMBC) করে যৌগগুলোর গঠন নির্ণয় করা হয়। সকল সংশ্লেষিত যৌগ Agar Disc Diffusion পদ্ধতিতে তিনটি gram-positive bacteria যথা *Bacillus Cereus, Staphylococcus aureus*, *Bacillus magaterium*, তিনটি gram-negative bacteria যথা bacteria *Klebsiella pneumonia, Pseudomonas aeruginosa*, *Escherichia coli* এবং দুটি ছত্রাকের নমুনা *Trichoderma harzianum* and *Aspergillus niger* দ্বারা জীবাণুরোধী কার্যকলাপ পর্যবেক্ষণ করা হয়। কিছু যৌগ Agar Disc Diffusion পদ্ধতিতে স্ট্যান্ডার্ড ampicillin এবং amphotericin b-এর তুলনায় মাঝারি থেকে ভাল মানের জীবাণুরোধী কার্যকলাপ প্রদর্শন করেছে। আদর্শ যৌগ Ampicillin এর সাথে তুলনায় **1b** এবং **3b** যৌগ *S. aureus, B. Cereus, K. pneumonia* এবং *E. coli* বিরুদ্ধে তুলনীয় ব্যাকটেরিয়ারোধী কার্যকলাপ প্রদর্শন করেছে এবং **2b** যৌগ *S. aureu, K. pneumonia* এবং *E. coli* বিরুদ্ধে সম্ভাব্য ব্যাকটেরিয়াবিরোধী কার্যকলাপ প্রকাশ করেছে। ছত্রাকবিরোধি কার্যকলাপে, আদর্শ যৌগ amphotericin b এর সাথে তুলনায় **1b** এবং **3b** যৌগ *Aspergillus niger* ছত্রাকের বিরুদ্ধে মাঝারি থেকে ভালো মানের ছত্রাকবিরোধী কার্যকলাপ দেখিয়েছে। আমাদের গবেষণা থেকে আমরা লক্ষ্য করেছি যে, **1b** এবং **3b** যৌগ ভবিষ্যতে সম্ভাব্য antibacterial এবং antifungal ওষুধ হিসাবে ব্যবহার করা যেতে পারে।



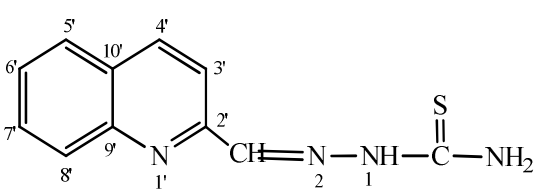
1a (1)

2-(quinolin-4'-ylmethylene) hydrazine carbathioamide



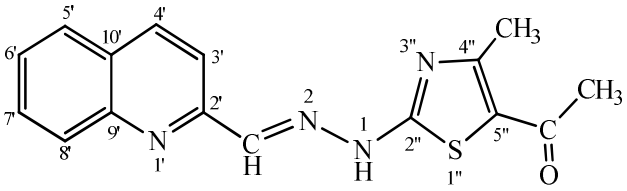
1b (2)

5"-aceto-4"-methyl-2"-(2-(quinolin-4'-ylmethylene) hydrazine) thiazole



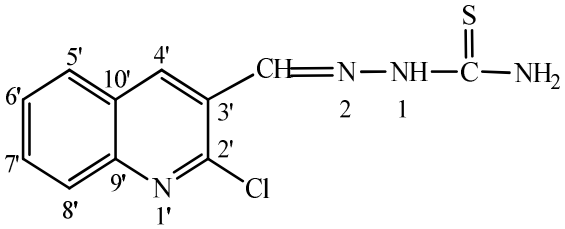
2a (3)

2-(quinolin-2'-ylmethylene) hydrazine carbathioamide



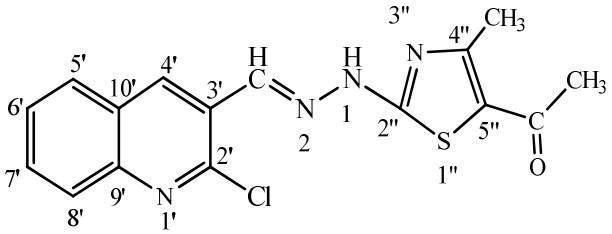
2b (4)

5"-aceto-4"-methyl-2"-(2-(quinolin-2'-ylmethylene)-hydrazine) thiazole



3a (5)

2-(2'-chloro-quinolin-3'-ylmethylene) hydrazine carbathioamide



3b (6)

5"-aceto-4"-methyl-2"-(2-(2'-chloro-quinolin-3'-yl methylene))-hydrazine thiazole

Chapter - 1

Introduction

1.1 General

(a) Heterocyclic Compounds

Molecules containing nitrogen, oxygen or sulfur atoms in a ring structure of carbon are called heterocyclic compounds. The hetero-atoms in the carbon cycle are caused for increasing large number of organic compounds and most of the heterocyclic molecules are considered as very valuable and useful for human being due to presence of their biological activities.

Heterocyclic compounds are two types such as aliphatic and aromatic heterocyclic compounds. (1) aziridine, (2) thiirane, (3) oxetane, (4) thietane, (5) tetrahydrofuran (THF), (6) pyrrolidine, (7) piperidine etc. are the some examples of aliphatic heterocyclic compounds and the aromatic heterocyclic compounds are (8) furan, (9) pyrrole, (10) pyridine, (11) indole, (12) quinoline, (13) isoquinoline, (14) imidazole, (15) oxazole, (16) pyrazole, (17) purine etc. (Quin and Louis D. 2010).

Many heterocyclic compounds are observed in biological molecules. For examples, purine and pyrimidine bases are found in DNA (Alberts B et al. 2002), indoles and pyrolidine moieties present in tryptophan and proline which are very essential to human's life (Konopelski P and Ufnal M. 2018). In fact, medicinal chemistry, biochemistry, agricultural science etc. life science fields are based on heterocyclic compounds and these compounds have been observed showing greater activity as antibacterial, antifungal, anticancer, anti-inflammatory, antimalarial, antiviral, anti-diabetic etc. (Gupta and Monika 2015). A variety of natural occurred drugs such as quinine, codeine, emetine, atropine, reserpine, theophylline and vice versa are heterocyclic compounds. Practically, the most synthetic drugs such as sunitinib, eribulin, citalopram, dasatinib etc. contains pyrrole, furan, benzofuran, thiazole, pyrazole respectively (Wu and Yong-Jin 2012).

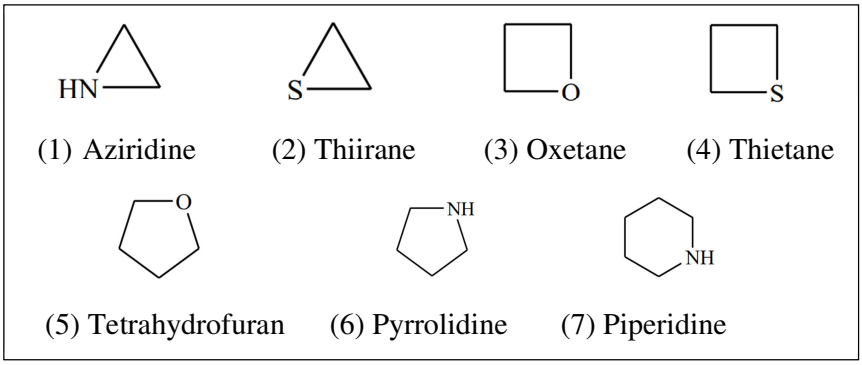


Figure 1.1 : Aliphatic heterocyclic compounds

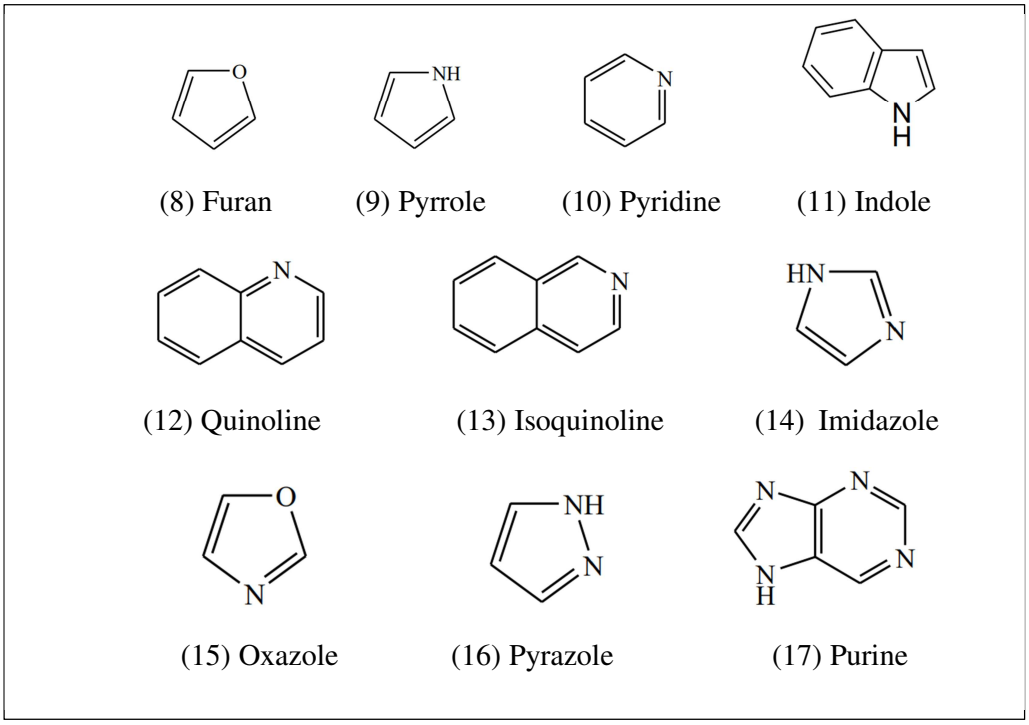


Figure 1.2: Aromatic Heterocyclic Compounds

(b) Thiazole

Among the heterocyclic compounds, thiazoles occupy an important place of interest to researchers and scientists for their biological activity. Basically, thiazole contains three carbons, nitrogen and sulfur in five-membered ring (Figure 1.3). It was first discovered by Hantzschand and Weber in 1887. The Physical properties of thiazole are boiling point 116-118 °C, pale yellow color, liquid, sparingly soluble in H_2O and specific gravity 1.2 (Eicher et al. 2012).

Figure 1.3: 5-Membered ring skeleton of Thiazole

Thiazoles are the member of azole family which also includes imidazoles and oxazoles. The thiazole ring is planar. Delocalization of lone pair's pi-electrons of sulfur and four pi-bonding electrons in the ring structure satisfies the Huckel's rule. The presence of the delocalization of such lone pair and pi-bonding electrons reveals thiazole compound as aromatic in nature (Ji Ram and Vishnu 2019).

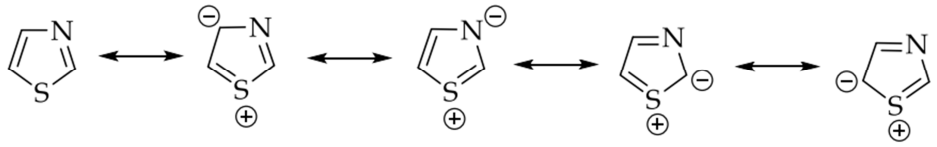


Figure 1.4: Resonating structure of Thiazole

Thiazoles are generally basic compound. But it is greatly affected by substituting electron donating groups or withdrawing groups at 2, 4 and 5 number carbons to arise acidic or basic strength. The basicity of thiazole increases with introducing electron donating group such as $–CH_3$, Cl^-, F^-, OH^-, CN^-. Maximum effect of adding substituent is observed when $-CH_3$ is placed at carbon-2 position of thiazole ring. It might be occurred due to the center positioned carbon between N and S heteroatoms. Again, when strong electron withdrawing group i.e. NO_2 is introduced the basicity or nucleophilicity of the thiazole ring is decreases (Dong Chan Kim et al. 1997).

The heterocyclic ring of thiazole is very significant as a part of pharmacologically active drugs that makes the thiazole as widely studied heterocyclic compounds (Nadeem Siddiqui et al. 2009). Having pharmacologically active properties most uses drugs contain thiazole moiety, for examples (18) sulfathiazol as antimicrobial drug (David et al 2009), (19) nitazoxanide as antiparasitic agent (Leanne M. and Louis 2005), (20) ravuconazole as anti-fungal (A. C Pasqualotto and K O Thiele 2010), (21) thiamethoxam as insecticide (Maienfisch and Peter 2006), (22) ritonavir as anti-HIV (Hull MW and Montaner JS 2011), (23) meloxicam as antiinflammatory (Barnette, Dustyn A et al. 2021) etc.

Thiazole moiety in natural products are found in vitamin B1 (thiamin), erythrazole B, firefly luciferin, marine natural products and other various compounds (Jacques-Henry Julliard & Roland Douce 1991, Sunil Kumar and Ranjana Aggarwal 2019, Jin, Zhong). Thiazole and its derivatives exhibit wide range and important bioactivities i.e. antioxidant, antibacterial, anticancer, antifungal, anti-HIV, anti-inflammatory effects (Anthi Petrou & et al. 2021, V. Jaishree & et al. 2012, El-Gamal & Kamal M. 2017). Thiazole moiety has vital roles utilizing in leading identification and optimization as it contains pharmacophoric and bioisosteric components. Drugs containing thiazole moiety can be considered as determinant for its physiochemical and pharmacokinetic properties.

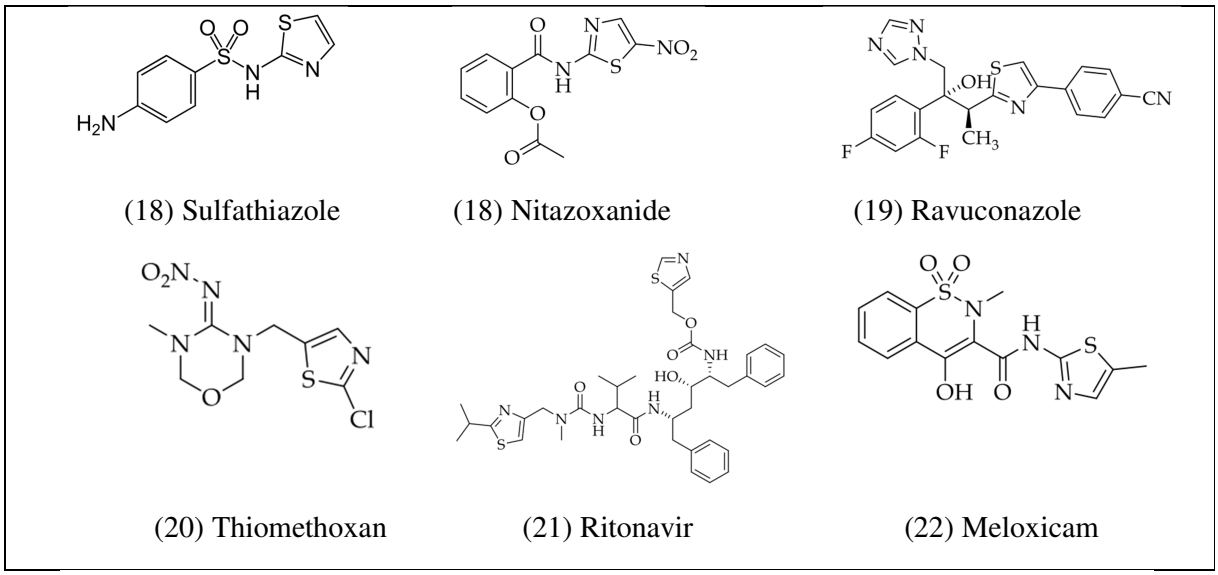


Figure 1.5: Some examples of commercial drugs containing thiazole ring

(c) Quinoline

Quinoline, another type of heterocyclic compounds consisting of the composition of benzene and pyridine rings as a double-ring structure that have the molecular formula C_9H_7N, the simplest member of the series.

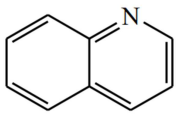


Figure 1.6: Structural formula of Quinoline

It is also known as benzopyridine or benzazine. It is yellowish color, oily like liquid, hygroscopic, soluble in many organic solvents such as water, alcohol and ether. Quinoline alkaloids extracted from natural products show observable and distinctive biological activities and due to its simple structure and their significant properties, researchers have great interest to extract or synthesize quinoline and its derivatives (Michael and Joseph P. 2008).

Quinoline alkaloids are observed and derived from many organism i.e. animals and plants (Attygalle et al., Guamán Ortiz et al. 2014) those have numerous pharmacological and biological activities such as antibacterial effects against bacterial infections, antifungal effects against fungal infections, antitumor, anti-inflammatory, antioxidant, antiviral activities (Shang et al. 2018).

(d) Thiazole and Quinoline: Biological Importance

In the 21st century, antibiotic resistance (ABR) occurred by most of the microorganisms i.e. virus and bacteria is widely recognized as a threat to human health around the world. Due to expansive and repeated uses of antibiotics, drug-resistant and multidrug resistant viral and bacterial infections are increasing in alarming rate that have brought out difficult to treat using previous antibiotic and take much time to cure (Shankar and Balasubramanium 2014). Multidrug resistant grown up by accumulating multiple genes in bacteria and virus cell that code resistance to the drug or increasing the expression of genes coding for multidrug efflux (Nikaido and Hiroshi 2009). This multidrug resistance caused by bacteria and virus accumulated genes drives the researchers to improve new and potential antibiotic agents to specific target. The synthesis of thiazole derivatives containing quinoline moiety is an attractive field in synthetic organic chemistry and therapeutic science. Thiazole and quinoline nuclei are exist in many natural products and both of them have significant biological activities as antimicrobial agents that already reported separately. The combination of two or more bioactive molecules i.e. thiazole and quinoline moiety in a molecular scaffold shows good antimicrobial activity (Eissa et al. 2021). Moreover, in the research, has been found that thiazole and quinoline moieties have minimum cytotoxicity to hepatocyte cells (Sheng-Feng et al. 2016).

Again, the compounds those contain imine or azomethine functional group (-C=N-) are called Schiff bases. Azomethine (-C=N-) group is obtained by condensation of 1^{o} amine ($R–NH_2$) with carbonyl (= CO) compounds that was first reported by Hugo Schiff. Because of antioxidant, analgesic, anti-inflammatory, antimicrobial, anticancer, anti-tubercular and anthelmintic activities, these bases have important applications in pharmaceutical fields (Brodowska et al. 2014, Anouar et al. 2013 and Shaikh et al. 2016).

It has been also studied that, in human respiration process, reactive oxygen species (ROS) is generated in presence of free radicals that leads to damage bacteria and human cells and caused for several diseases like autoimmune, inflammatory, cardiovascular neurodegenerative, diabeties and cancer diseases (H. Nohl et al. 2003, Sahdeo Prasad et al. 2017, H Kaneto et al. 2010). Antioxidants are found as neutralizing free radicals to protect the cells and tissues from fatal diseases. Thiazole Schiff bases are evaluated as important antioxidant agents that protect tissues from DNA oxidative damage and produce stable DPPH fragments by free-radical scavenging (E.N. Bentz et al. 2017, Aswathanarayanappa et al. 2013).

Considering above biological significance as core structure of several drugs, preventing capability of reactive oxygen species (ROS) formation, antibacterial and antifungal activities of thiazole containing quinoline moiety, a new series of thiazole Schiff base derivatives containing quinoline Schiff bases were synthesized and characterized. All synthesized quinolinothiazole derivatives were evaluated antibacterial and antifungal effects using agar disc diffusion method (N. G. Heatley, 1944). In these experiments, gram-positive bacteria called *S. aureus, B. Cereus* and *B. magaterium*, gram-negative bacteria called *E. coli, K. pneumonia* and *P. aeruginosa* and fungal strains called *T. harzianum* and *A. niger* were used in the experiments.

1.2 Literature Review

In 2018, Mickevicius et al. synthesized a new series of bis(thiazol-5-yl)methane derivatives and they evaluated the antibacterial, antioxidant activities of the synthesized products. The antioxidant evaluation of **3,3'-((Methylenebis(4-(4-bromophenyl)thiazole-5,2-diyl))bis((4-hydroxyphenyl) azanediyl)) bis(2-methyl-propanoic acid)** compound by free-radical scavenging method was found highly scavenging abilities (80.12%). All of the synthesized thiazole derivatives were screened antibacterial activities by diffusion method against *Escherichia coli*, *Xanthomonas campestris*, *Rhizobium radiobacter* comparing to ampicillin (50μg/mL). Several derivatives showed most active against the tested bacteria (Mickevicius et al. 2018).

N C Desai et al. synthesized **2-(5-(2-chloro-6-methylquinolin-3- yl)-3-aryl-4,5-dihydro-1H-pyrazol-1-yl) thiazol-4(5H)ones** derivatives. The synthesized compounds were characterized by using ^{1}H NMR, ^{13}C NMR, IR & mass spectroscopy. Then antimicrobial activities of synthesized thiazolinone derivatives were tested against Escherichia coli and et al. The antimicrobial study showed that some of synthesized thiazolinone derivatives were identified as remarkable results against *E. coli* (N. C. Desai et al. 2013).

Kamal M. and El-Gamal evaluated the anticancer activity of some new heterocyclic compounds containing pyrimido [4, 5-b] quinoline moiety against breast cancer cell (MCF-7). Several compounds were found potential cancer activity (IC_{50}= 48.54 μM) as compared to reference drug doxorubicin (IC_{50}= 71.80 μM) (El-Gamal and Kamal 2017).

Noor Barak Almandila et al. developed a series of thiadiazole containing quinoline those were characterized by ^{1}H NMR, ^{13}C NMR and MS. From the antileishmanial activity studies of synthesized compounds it had been found that, some compounds showed excellent antileishmanial activities in presence of hydroxyl groups in phenyl ring with the values IC_{50} ranged from 0.04 ± 0.01 - 3.60 ± 0.20μM as compared to pentamidine (standard drug, 7.02 ± 0.09μM) (N. Barak et al. 2018).

Sally I. Eissa et al. evaluated a series of hybrid quinoline and thiazole moieties as antifungal and antibacterial activities by in vitro process. The evaluation studies reported that several synthesized compounds were found minimum inhibitory concentrations (MIC) against experimental fungal and bacterial strains and the significant inhibition of the growth of such experimental strains. From the study, they suggested that hybrid

quinoline and thiazole moieties are interesting scaffolds for improvements of novel antifungal and antibacterial agents (Sally I. Eissa et al. 2021).

Samir Bondock et al. reported thiazole derivatives as new and potential anti-microbial agents those were characterized by ^{1}H NMR, ^{13}C NMR and IR. By evaluating in vitro antimicrobial activity, the studies had been confirmed that **5-acetyl-4-methyl-2-(3-pyridyl) thiazole** compound among the developed compounds showed as good inhibitor to grow up *S. epidermidis.* The studies of structure-activity relationship (SAR) were also found that the increase of the substituents in thiazole at position 4 or 5 decreased the antimicrobial activities (Samir Bondock et al. 2013).

S.A. Khan et al. Synthesized Quinoline-3-carbonitrile derivatives and observed potential antibacterial activities. They observed that, synthesized compound **[4-(furan-2-yl)-8-methoxy-2-oxo-1,2,5,6-tetrahydrobenzo[h]quinoline-3-carbonitrile]** among the others showed better antibacterial activities. The studies also reported that the synthesized compound had low lying LUMO and band gap energy of 3.40 eV that increased antibacterial activity by interacting with target (S.A. Khan et al. 2019).

Guofan Jin et al. characterized a series of quinoline derivatives by ^{13}C NMR, ^{1}H NMR, HR-mass Spectroscopy and IR spectroscopy. They also studied anticancer properties, cytotoxicity, antibacterial effects against *S. aureus* and *E. coli* bacteria. **8-((4-(benzyloxy) phenyl) amino)-7-(ethoxycarbonyl)-5-propyl- [1,3]dioxolo[4,5-g]quinolin-5-ium** compound was observed as comparatively potential active antibacterial agents than other synthesized compounds. The compound was observed MIC value 3.125 $mmol \cdot mL^{-1}$, lower than amoxicillin and ciprofloxacin (reference agents) and IC_{50} values 4.45±0.88, 4.74±0.42, 14.54±1.96, and 32.12±3.66 against human cancer cells (Guofan Jin et. al. 2020).

1.3 Objectives of this research work:

Epidemiological analysis reported that the diseases infected by microorganisms are mentioned as the cause of death from known periods. At present, the increasing rate of drug resistance by microorganism to antibiotics is being a threat to human health that drives researchers to improve new and effective antibiotics against such strains of microorganisms. Our research work focused on synthesize of thiazole containing quinoline moiety which is pharmacologically interesting heterocyclic compound. Aims and objectives of this research works are summarized as below:

(a) Synthesis of thiosemicarbazone and thiazole derivatives containing quinoline moieties.

(b) Characterization of thiosemicarbazones and thiazole derivatives by IR, ^{1}H NMR, ^{13}C NMR, COSY, HSQC and HMBC spectroscopy,

(c) Studies of anti-fungal and anti-bacterial activities of the synthesized analogs.

(d) Studies of ADMET, pharmacokinetic prediction and also the molecular docking.

Chapter - 2

Experimental

Part A: Chemical Studies

2.1 Reagents and solvents

(i) 4-quinolinecarboxylaldehyde

(ii) 2-quinolinecarboxylaldehyde

(iii) 2-chloro-3-quinolinecarboxylaldehyde

(iv) Thiosemicarbazide

(v) 3-chloroacetylacetone

(vi) Ethanol

(vii) Methanol

(viii) Acetone

(ix) Ethyl acetate

2.2 Synthesis of thiazole derivatives

Step-1: Synthesis of thiosemicarbazone derivatives

3 mmol of thiosemicarbazide was taken in a 250 mL two neck flask and dissolved in 10 mL ethanol. 3 mmol of respective quinolinealdehyde was dissolved in 5 mL ethanol and the solution was added drop wise to thiosemicarbazide solution. The mixture was refluxed with stirring for six to eight hours at 78-80^{o}C. Continuous stirring was maintained until the reaction complete. TLC was used to visualize the reaction progress using ultraviolet light. Then, a crude product was obtained by cooling and filtering the reaction mixture. The crude precipitate was recrystallized from ethanol (99%) to afford intermediate thiosemicarbazone analogs **1a-3a.**

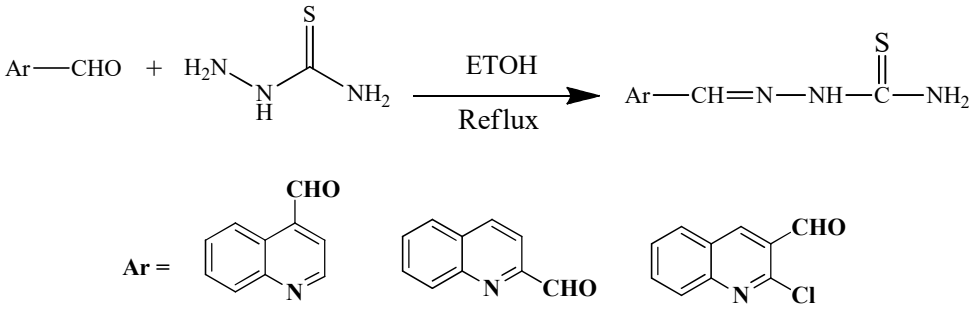


Figure 2.1: Procedure for thiosemicabazone synthesis

Step-2: Synthesis of thiazole derivatives

550 mg of 3-chloroacetyleacetone was dissolved in 10 mL of acetone at 0°C in an ice bath. On the other hand, 3 mmol of thiosemicarbazone dissolved in 10 mL of absolute acetone in 250 mL two neck flask. Ice cooled 3-chloroacetyleacetone solution was then added to thiosemicarbazone solution at room temperature. The mixture was kept stirred for twenty four hours and followed by reflux for three hours at 60°C. Then the mixture was poured to a conical flask and kept in ice cold water for precipitation. The crude precipitate was recrystallized from ethanol (99%) to afford thiazole derivatives **1b- 3b**.

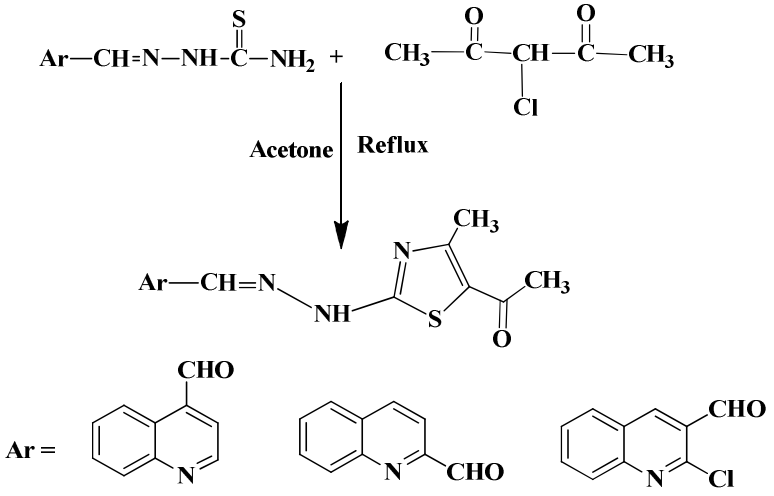


Figure 2.2: Procedure for hydrazinylthiazole synthesis

2.3 Purification Technique

2.3.1 Purification of the reagents and solvents

Distillation method was applied to purify solvent that used in during investigation at the boiling point of the respective solvents. After distillation had been done, the solvent was removed from the media using vacuum rotary evaporator.

2.3.2 Glassware cleaning, washing and drying procedure

Glassware was carefully washed and cleaned before employing in laboratory and specific purpose used glassware was dried in oven. Detergent and washing powder i.e. Wheel

Powder, VIM Liquid (those not affect glass) were used for washing purposes. The detergent powder was used by moistening with a little water or directly introduced into the glassware or applied to the dirty area with a test-tube brush that dipped into the moistened powder. Then the apparatus was rinsed with dist. water thoroughly. If necessary, the operation was performed repeatedly. Finally, dilute acetone was used for proper cleaning. For 1-3 hours, all types of glassware were dried in electrical oven maintaining temperature at 100-120°C.

2.4 Experimental techniques employed

2.4.1 Chromatographic techniques

Chromatography is a separation technique depending on distributions of components from mixture solution into differential concentrations. The technique is formulated on the basis of that, the relative amounts of solutes in mobile phase are distributed when it passed through stationary phase. The chromatographic techniques are used for separating and purifying the components in the mixture. The following chromatographic techniques were used for the separation and purification of compounds

2.4.2 Thin layer chromatographic (TLC) technique

TLC is a chromatographic technique used to identify substances from mixtures of non-volatile compounds after separation and test purity of the compounds. The Separation technique on TLC involves the distribution of two or more substances from the mixture between a mobile phase (solvent) and a stationary phase (sample mixture) that is carried out by plastic or aluminium foil or glass plate which is coated with a fine and thin layer of aluminium oxide (alumina) or silica gel or cellulose adsorbent materials. This layer of adsorbent coated on the sheet is called the stationary phase. A drop of sample taken with capillary tube has been applied on the sheet and kept in a solvent or solvent mixture (mobile phase) so that the mobile phase can drew up the sheet via capillary action. If there are present different analytes, they ascend on the TLC plate at different rates. This technique is very simple, quick in use and in fact, inexpensive procedure. Organic researchers and chemists get answer quickly as to how many compounds are there in experimental mixture. Unknown compounds can be identified in a mixture by determining R_f value compared with known compound's R_f value. The progress of a

reaction is most easily and efficiently followed by this technique. Again, a single and round spot in TLC plate indicates the purity of a compound.

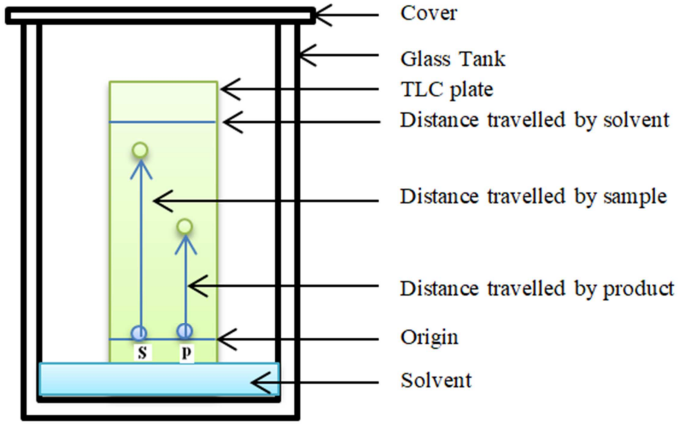


Figure 2.3: TLC Determination Technique

2.4.3 Steps involved in TLC

(i) Sample application on TLC plates

A drop of sample was applied on TLC plate by capillary tube with intense care to avoid the creation of a hole on the film.

(ii) Development of plates

After spotting the sample on the plate (stationary phase, it was placed in solvent tank at a time. The plate was put in the solvent tank in such a way that the spotting point was somewhat upper than solvent and kept for solvent risen up on the TLC plate.

(iii) Location of spots

The spots on the plates were located by placing it in ultraviolet light or an iodine chamber and marked by pencil.

(iv) R_f value determination on TLC plate

R_f value means retardation factor value of any compound is calculated from TLC plate according to the equation as fallow:

$$R_f = \frac{\text{Distance travelled by the solute}}{\text{Distance travelled by the solvent}}$$

2.4.4 Column chromatography

Column chromatography is also very important separation technique that is used to separate into different compounds from the mixture. This technique also involves mobile phase (sample mixture) and stationary phase as adsorbent i.e. silica. Small or large scale of chemical compounds can be used in this technique.

2.4.5 Principle of column chromatography

Mobile phase containing sample mixture is allowed to flow through stationary phase in a vertically kept column. The compounds in the mixture flow in different rates according to their affinity to stationary phase in where higher affinity component to stationary phase travel slow and lower affinity component fast one. Finally, the components can be separated out in different concentrations.

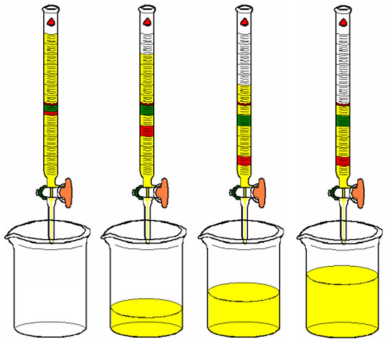


Figure 2.4: Column Chromatography

2.5 Recrystallization techniques

Solid organic compounds are seldom pure, because of some other compounds in small amount are also produced at the time of isolated from organic reactions. The purification desired products is carried out through crystallization process.

The crystallization process is given in following:

(a) Impure products are dissolved with suitable solvent in a suitable vial or a conical flask; heat is applied if required.
(b) Filtered out Dust and insoluble materials from the solution to obtain the clear solution.
(c) The hot solution is to be cooled and dissolved substance is allowed to recrystallize out.

(d) The crystals are separated from the mother liquor.

(e) The resulting crystal products are dried and tested for to determine purity. The purity tests are usually performed by determining melting point and observing behavior in the thin layer chromatography.

2.6 Determination of melting points (m.p.)

All melting points were recorded in m.p. apparatus of Fisher John (Model no. 1A 9000) and were uncorrected. The heating was done carefully in order to maintain a uniform and a steady temperature.

2.7 Characterization of Products (Spectroscopic methods)

i) Infrared (IR) spectroscopy: Infrared spectra were measured in KBr disk on FTIR spectrophotometer (Model FTIR- IR Affinity-1) and printed in cm^{-1}. Spectra were recorded at WazedMiah Scientific Research Centre, Jahangirnagar University, Savar, Dhaka,

ii) Nuclear magnetic resonance (NMR) spectroscopy: ^{1}H-NMR,^{13}C-NMR, DEPT-135, COSY, HSQC and HMBC spectra of the samples were recorded on a BRUKER Advance-III HD spectrometer operating at 400 MHz and 100 MHz at WazedMiah Scientific Research Centre, Jahangirnagar University, Savar, Dhaka, Bangladesh. Chemical shifts (δ values) are recorded in ppm that is relative to TMS and *J* values are recorded in hertz (Hz) unit. The multiplicities of spins were expressed as singlet (s), doublet (d), double doublet (dd), triplet (t), quartet (q) and multiplet (m).

2.8 Physical properties of compound la

Physical appearance: Yellow cotton like solid

Solubility: Soluble in methanol and DMSO

Melting point: 260-263ºC

TLC: Single spot with R_f value 0.57 in *n*-C_6H_{14} **:** EtOAc (1**:**1) solvent system

Amount: 940 mg

Yield: 76% (on dry weight basis)

IR: $\bar{\upsilon}_{max}$ (KBr) 3439 cm^{-1} (N-H stretching), 1610cm^{-1} (N-H bending)

^{1}H NMR (DMSO) δ: 8.94 (1H, d, *J* = 4.4 Hz, H2'), 8.19 (1H, d, *J* = 4.4 Hz, H3'), 8.09 (1H, d, *J* = 8.0 Hz, H5'),7.72 (1H, t, *J* = 7.2 Hz, H6'), 7.82 (1H, t, *J* = 7.2 Hz, H7'), 8.31 (1H, d, *J* = 8.4 Hz, H8'), 8.88 (1H, s, H11), 11.70 (1H, s, H-N) and 8.48 (2H, s, H_2-N)

^{13}C NMR (DMSO) δ: 150.5(C2'), 118.3(C3'), 125.4(C4'), 130.2(C5'), 127.8(C6'), 130.0(C7'), 123.4(C8'), 148.7(C9'), 137.7(C10'), 138.2(C̲H=N), 178.9(C̲=S).

2.9 Physical properties of the compound 1b

Physical appearance: Reddish orange crystal

Solubility: Soluble in acetone, methanol and DMSO

Melting point: 275-278ºC

TLC: Single spot with R_f value 0.63 in *n*-C_6H_{14} **:** EtOAc (2**:**3) solvent system

Amount: 288 mg

Yield: 68% (on dry weight basis)

IR: $\bar{\upsilon}_{max}$ (KBr) 3430 cm^{-1} (N-H stretching), 1627cm^{-1} (N-H bending)

^{1}H NMR(DMSO) δ: 9.04 (1H, d, *J* = 2.0 Hz, H2'), 8.42 (1H, d, *J* = 4.4 Hz, H3'), 8.16 (1H, d, *J* = 8.0 Hz, H5'), 7.85 (1H, t, *J* = 6.8 Hz, H6'), 7.96 (1H, t, *J* = 7.2 Hz, H7'), 8.36 (1H, d, *J* = 8.4 Hz, H8'), 8.92 (1H, s, C̲H=N), 11.85 (1H, s, H-N), δ2.55 (3H, s, CO-C̲H_3) and 2.46 (3H, s, C̲H_3).

^{13}C NMR (DMSO) δ: 148.3(C2'), 118.1(C3'), 125.6(C4'), 127.4(C5'), 128.7(C6'), 131.7(C7'), 123.8(C8'), 148.3(C9'), 136.9(C10'), 137.0(C̲H=N), 179.0(C2''), 128.8(C4''), 168.1(C5''), 189.7(C̲=O), 29.9(CO-C̲H_3), 19.5(C̲H_3).

2.10 Physical properties of the compound 2a

Physical appearance: Yellow powder

Solubility: Highly Soluble in methanol and DMSO

Melting point: 217-220ºC

TLC: Single spot with R_f value 0.75 in *n*-C_6H_{14} **:** EtOAc (1**:**1) solvent system

Amount: 440 mg

Yield: 70% (on dry weight basis)

IR: $\bar{\upsilon}_{max}$ (KBr) 3394 cm^{-1} (N-H stretching), 1605cm^{-1} (N-H bending)

^{1}H NMR (DMSO) δ: 8.44 (1H, d, *J* = 8.8 Hz, H3'), 8.35 (1H, d, *J* = 8.4 Hz, H4'), 8.00 (1H, d, *J* = 4.8 Hz, H5'), 7.61 (1H, t, *J* = 7.2 Hz, H6'), 7.77 (1H, t, *J* = 7.2 Hz, H7'), 7.99 (1H, t, *J* = 8.0 Hz, H8'), 8.24 (1H, s, C̲H=N), 11.79 (1H, s, H-N) and 8.32 (2H, s, H_2-N).

^{13}C NMR (DMSO) δ: 154.3(C2'), 118.5(C3'), 136.7(C4'), 129.2(C5'), 127.6(C6'), 130.3(C7'), 128.3(C8'), 147.7(C9'), 128.2(C10'), 143.0(C̲H=N), 178.9(C̲=S).

2.11 Physical properties of the compound 2b

Physical appearance: Reddish orange crystal

Solubility: Soluble in methanol and DMSO

Melting point: 222-225ºC

TLC: Single spot with R_f value 0.56 in *n*-C_6H_{14} **:** EtOAc (1**:**1) solvent system

Amount: 361 mg

Yield: 71% (on dry weight basis)

IR: $\bar{\upsilon}_{max}$ (KBr) 3445 cm^{-1} & 3285 cm^{-1} (N-H stretching), 1635cm^{-1} (N-H bending)

^{1}H NMR (DMSO) δ: 8.14 (1H, d, *J* = 8.0 Hz, H3'), 7.92 (1H, d, *J* = 7.6 Hz, H4'), 8.18 (1H, d, *J* = 6.4 Hz, H5'), 7.74 (1H, t, *J* = 7.6 Hz, H6'), 7.92 (1H, t, *J* = 7.6 Hz, H7'), 8.18 (1H, d, *J* = 6.4 Hz, H8'), 8.86 (1H, s, C̲H=N), 12.16 (1H, s, H-N), 2.53 (3H, s, CO-C̲H_3) and 2.45 (3H, s, C̲H_3).

^{13}C NMR (DMSO) δ: 152.0(C2'), 118.0(C3'), 132.5(C4'), 128.9(C5'), 128.6(C6'), 132.3(C7'), 128.9(C8'), 140.5(C9'), 128.3(C10'), 141.7(C̲H=N), 169.8(C2''), 128.2(C4''), 168.3(C5''), 189.7(C̲=O), 29.9(CO-C̲H_3), 18.1(C̲H_3)

2.12 Physical properties of the compound 3a

Physical appearance: Yellow powder

Solubility: Soluble in methanol, ethanol and acetone

Melting point: 209-212ºC

TLC: Single spot with R_f value 0.56 in *n*-C_6H_{14} **:** EtOAc (1**:**1) solvent system

Amount: 388 mg

Yield: 69% (on dry weight basis)

IR: $\bar{\upsilon}_{max}$ (KBr) 3392 and 3261 cm^{-1} (N-H stretching), 1602cm^{-1} (N-H bending)

^{1}H NMR (DMSO) δ: 8.51 (1H, s, H4**'**), 7.94 (1H, d, J = 8.4 Hz, H5**'**), 7.70 (1H, t, *J* = 6.8 Hz, H6**'**), 7.84 (1H, t, *J* = 7.2 Hz, H7**'**), 7.99 (1H, d, *J* = 8.0 Hz, H8**'**), 8.27 (1H, s, C̲H=N), 11.81 (1H, s, H-N) and 8.47 (2H, s, H_2-N)

^{13}C NMR (DMSO) δ: 148.8(C2'), 126.6(C3'), 137.2(C4'), 128.3(C5'), 128.2(C6'), 132.0(C7'), 128.9(C8'), 147.3(C9'), 127.4(C10'), 136.5(C̲H=N), 178.8(C̲=S).

2.13 Physical properties of the compound 3b

Physical appearance: Brown powder

Solubility: Soluble in methanol and acetone

Melting point: 232-235ºC

TLC: Single spot with R_f value 0.63 in *n*-C_6H_{14} **:** EtOAc (1**:**1) solvent system

Amount: 302 mg

Yield: 62% (on dry weight basis)

IR: $\bar{\upsilon}_{max}$ (KBr) 3439 cm^{-1} (N-H stretching), 1616cm^{-1} (N-H bending)

^{1}H NMR (DMSO) δ: 8.50 (1H, s, H4'), 7.84 (1H, d, *J* = 8.4 Hz, H5'), 7.20 (1H, t, *J* = 6.8 Hz, H6'), 7.32 (1H, t, *J* = 7.2 Hz, H7') and 7.52 (1H, d, *J* = 8.0 Hz, H8'), 8.35 (1H, s, C̲H=N), 12.06 (1H, s, H-N), 2.50 (3H, s, C̲O-CH_3) and 2.42 (3H, s, C̲H_3).

^{13}C NMR (DMSO) δ: 147.5(C2'), 125.6(C3'), 136.1(C4'), 128.1(C5'), 128.0(C6'), 131.3(C7'), 127.8(C8'), 146.9(C9'), 127.7(C10'), 136.3(C̲H=N), 178.2(C2''), 127.6(C4''), 168.5(C5''), 189.1(C̲=O), 29.3(CO-C̲H_3), 19.3(C̲H_3).

Part B: Biological Studies

2.14 Antimicrobial activity assay

All the synthesized thiazole derivatives were tested *In vitro* anti-bacterial and anti-fungal effects by Agar disc diffusion method (N. G. Heatley, 1944). The media of Potato Dextrose Agar (PDA) (HIMEDIA, India) and Mueller Hinton Agar (MHA) (HIMEDIA, India) were taken as basal media for antimicrobial screening of experimental bacterial and fungal strains.

Following steps are involved in the experiments:

(1) In this method, the incubations of PDA and MHA were done for twenty four hours and then the contaminations were observed.
(2) After incubation, the bacterial and fungal strains were inoculated on media with sterile cotton bar.
(3) Then, the sample disc was put very carefully on agar medium that was pre-inoculated.
(4) The agar plates were aerobically incubated for twenty four hours at 37^{o}C for antibacterial and for forty eight hours at 26°C for antifungal screening.
(5) The media were controlled by adding Dimethyl sulfoxide (DMSO). 25µL of sample solution in DMSO were added each disc that contain 300 µg of thiazole derivatives.
(6) 25µL of Ciprofloxacin and iconazole solution in DMSO was added on per disc as positive control of antibacterial and antifungal screening respectively.
(7) Finally, after 24 h incubation, the inhibition zone's diameter was measured by circling the disc.

All the tests were performed for three times according to above steps. In the study, gram-positive bacterial strains *Bacillus cereus, Staphylococcus aureus* and *Bacillus magaterium*, gram-negative bacterial strains *Klebsiella pneumonia, Pseudomonas aeruginosa* and *Escherichia coli* and *Trichoderma harzianum* and *Aspergillus niger* fungal strains were used.

Part C: Docking Studies

2.15 Molecular docking studies

In silico molecular docking studies is conducted to support the design and invention of new drug molecule for the effective inhibition of target protein of disease development. Molecular docking studies of thiazole analogs were carried out by Gaussian 09, PyRx 0.8, and Pymol software package. Structure optimization of the synthesized analogs were performed by Gaussian 09 software based on B3LYP/6- 31G (+, d, p) basis set up in the DFT method. Hetero atoms, water molecules, and unwanted chain were removed from the protein chain by utilizing PyMOL (Version 1.7.4) software package and energy minimization of the protein structure were performed to remove bad contacts of the protein atoms utilizing Swiss-PdbViewer (Version 4.1.0) software. Finally, using the PyRx-Virtual Screening Tool (Version 0.8) followed by auto dock wizard. Further, Biovia Discovery Studio (Version 4.1) was used for performing the calculation of nonbonding interaction and to display and analyze the docking results.

2.16 *In silico* ADMET Prediction

Pharmacokinetic properties of synthesized thiazole compounds were studied by *In silico* ADMET Prediction method. ADMET stands for Absorption, Distribution, Metabolism, Excretion and Toxicity. Absorption, Distribution, Metabolism and Excretion are the four steps of Pharmacokinetic properties. Toxicity studies are also performed as a part of pharmacokinetic properties where acronym stands ADMET prediction.

The mode of entry of a chemical substance into the body is described by absorption. It indicates the chemical moving from the administration site to the blood stream. Administrations are mainly performed by digestive tract ingestion, respiratory tract inhalation, dermal application and direct injection into the bloodstream. These mediums affect bioavailability that measures how much of a drug is absorbed in an unchanged form. Only intravenous injection was observed in 100% where other routes of administration reduce bioavailability. After absorption of drugs into the bloodstream, it is distributed to tissues around the body. This distribution of drug is typically accomplished

by bloodstream and transfer in cell-to-cell. Metabolism or biotransformation is the process of chemically converting pro-drugs or drugs into metabolites that occurs before or after the drugs reached to the site of action. Metabolism can inactivate a drug or convert a pharmacologically inactive pro-drug into an active drug. The process of elimination of metabolized drug compound from the body is called excretion. Most of the drugs are excreted as feces or urine. It may be excreted through lungs or sweat too. Molecular size and charge of metabolized drugs influence the excretion process.

Toxicity determines how toxic or harmful a chemical is to the body. Toxicity of a drug occurs when a person accumulates an excess amount in his blood that causes a negative effect on the body. Usually after high absorption of a drug, if the kidney or liver is not able to excrete all the metabolites, it accumulates in the blood causing toxicity. In this case, even a much-needed drug can have harmful and unintended side effects due to overdose or toxicity.

The pharmacokinetic properties of synthesized thiazole derivatives were assessed by ADME online tool SwissADME (http://www.swissadme.ch). In the ADME study, numerous parameters have been calculated including molecular weight, hydrogen bond donor and acceptor, blood brain barrier, human intestinal absorption, central nerve system, P-glycoprotein inhibitor, oral rat acute toxicity, hERG etc.

Chapter - 3

Results and discussions

Part A : Chemical Studies

3.1 Characterizations of compounds 1a and 1b:

Compound **1a** (940 mg) was yellow amorphous solid, m.p 260-263°C. The IR spectra of compound **1a** showed sharp absorptions at $\bar{\upsilon}_{max}$ 3439 cm^{-1} and 1610 cm^{-1} for N-H stretching and bending respectively. The ^{13}C NMR spectra of compound **1a** showed that 11 carbons are present in the molecule (Table 3.1). The ^{13}C DEPT spectrum of **1a** revealed the presence of no methylene carbons in the compound. The absorption positions of all 11 carbons in ^{13}C NMR spectrum are given in Table 3.1. The ^{1}H NMR spectrum of 1a showed the presence of 6 aromatic protons at δ 8.94 (1H, d, *J* = 4.4 Hz, H2'), 8.19 (1H, d, *J* = 4.4 Hz, H3'), 8.09 (1H, d, *J* = 8.0 Hz, H5'), 7.72 (1H, t, *J* = 7.2 Hz, H6'), 7.82 (1H, t, *J* = 7.2 Hz, H7') and 8.31 (1H, d, *J* = 8.4 Hz, H8'). The absorption positions of one olifinic proton attached to carbon H-C=N is at δ 8.88 (1H, s, H-C=N), one NH proton δ 11.70 and two NH_2 protons δ 8.48 are appeared in ^{1}H NMR spectrum. The important homo-nuclear correlations (H-H) in 2D COSY spectrum and hetero-nuclear (H-C) correlations in HMBC spectrum are presented in Figure 3.1 and Table 3.1. On the basis of IR, ^{1}H NMR and ^{13}C NMR spectra, structure **1** was confirm to the compound **1a.** Compound **1a** is characterized as **2-(4'-quinolinylmethylene) hydrazine carbathioamide (1).**

Compound **1b** (288 mg) was reddish orange amorphous solid, m.p. 275-278°C. The IR spectra of compound **1b** showed sharp absorptions at $\bar{\upsilon}_{max}$ 3430 cm^{-1} for N-H stretching and for N-H bending at $\bar{\upsilon}_{max}$ 1627 cm^{-1}. The ^{13}C NMR spectra of compound **1b** showed that 16 carbons are present in the molecule (Table 3.1). The absorption positions of 16 carbons in ^{13}C NMR spectrum are given in Table 3.1. The ^{1}H NMR spectrum of **1b** showed the presence of 6 aromatic protons at δ 9.04 (1H, d, *J* = 2.0 Hz, H-2'), 8.42 (1H, d, *J* = 4.4 Hz, H-3'), 8.16 (1H, d, *J* = 8.0 Hz, H-5'), 7.85 (1H, t, *J* = 6.8 Hz, H-6'), 7.96 (1H, t, *J* = 7.2 Hz, H-7') and 8.36 (1H, d, *J* = 8.4 Hz, H-8') in the molecule. The absorption positions of one olifinic proton attached to carbon H-C=N appeared at δ 8.92 (1H, s, H-C=N) and one NH proton appeared at δ 11.85 (1H, s, H-N) and two sets methyl protons appeared at δ 2.55 (3H, s, CO-CH_3) and 2.46 (3H, s, CH_3). The important homo-nuclear correlations (H-H) in 2D COSY spectrum and hetero-nuclear (H-C) correlations

in HMBC spectrum are presented in Figure 3.1 and Table 3.1. Thus on the basis of IR, ^{1}H NMR and ^{13}C NMR spectra, structure **2** was confirm to the compound **1b**. Compound **1b** is thus characterized as **5''-aceto-4''-methyl-2''-(2-(4'-quinolinylmethylene) hydrazine) thiazole (2).**

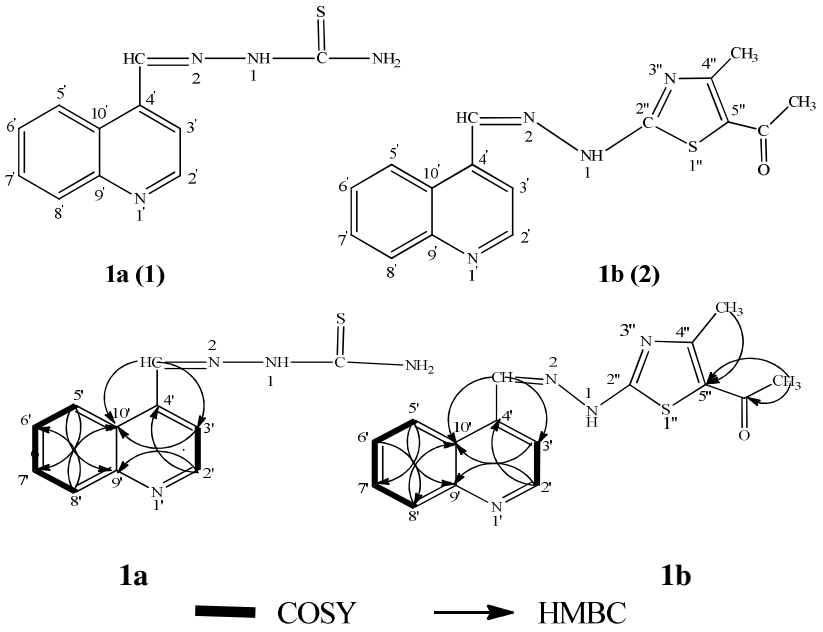


Figure 3.1: Important COSY and HMBC correlations of compound **1a** and **1b**

Table 3.1: ^{13}C NMR and ^{1}H NMR data of compounds 1a & 1b (DMSO, δ, ppm, J/Hz)*

C atom	^{13}C, δ	^{1}H, δ	COSY	HMBC	^{13}C, δ	^{1}H, δ	COSY	HMBC
2'	150.5	8.94,d,*J*=4.4	H3'	C4',9'	148.3	9.04,d,*J*=2.0	H3'	C4',9'
3'	118.3	8.19, d, *J*=4.4	H2'	C10', CH=N	118.1	8.42,d, *J*=4.4	H2'	C10', CH=N
4'	125.4				125.6			
5'	130.2	8.09,d, *J*=8.0	H6'	C7',9'	127.4	8.16,d,*J*=8.0	H6'	C7',9'
6'	127.8	7.72,t, *J*=7.2	H5',7'	C8',10'	128.7	7.85,t,*J*=6.8	H5',7'	C8',10'
7'	130.0	7.82,t, *J*=7.2	H6',8'	C5',9'	131.7	7.96,t, *J*=7.2	H6',8'	C5',9'
8'	123.4	8.31,d, *J*=8.4	H7'	C6',10'	123.8	8.36,d,*J*=8.4	H7'	C6',10'
9'	148.7				148.3			
10'	137.7				136.9			
CH=N	138.2	8.88,s		C3',10'	137.0	8.92,s		C3',10'
2"					179.0			
C=S	178.9							
4"					128.8			
5"					168.1			
C=O					189.7			
CO-CH_3					29.9	2.55,s		C=O
CH_3					19.5	2.46,s		
NH		11.70,s				11.85,s		
NH_2		8.48,s						

*The assignment was based on DEPT (135), COSY, HSQC and HMBC experiments.

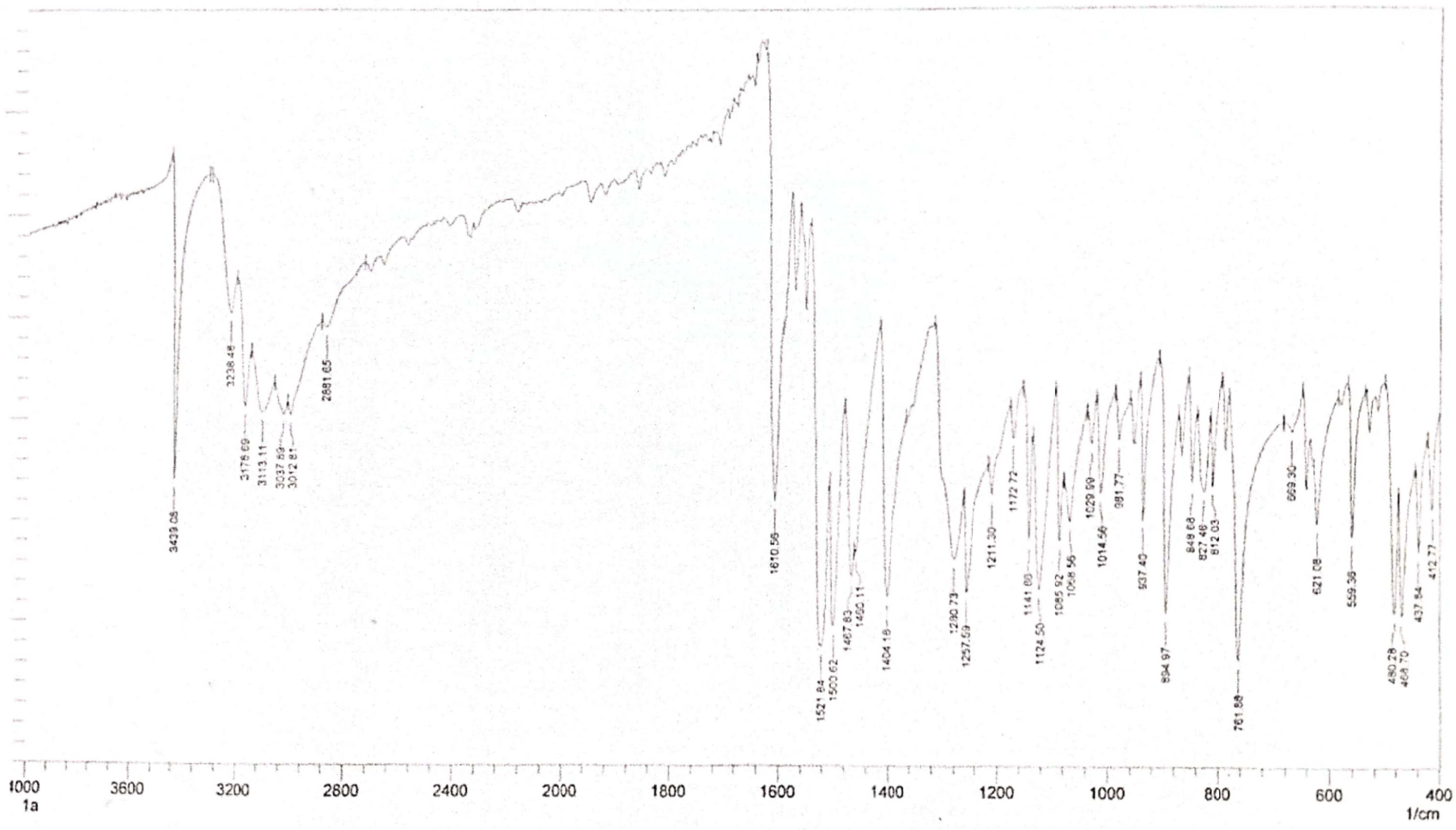


Figure 3.2 IR Spectrum of compound 1a

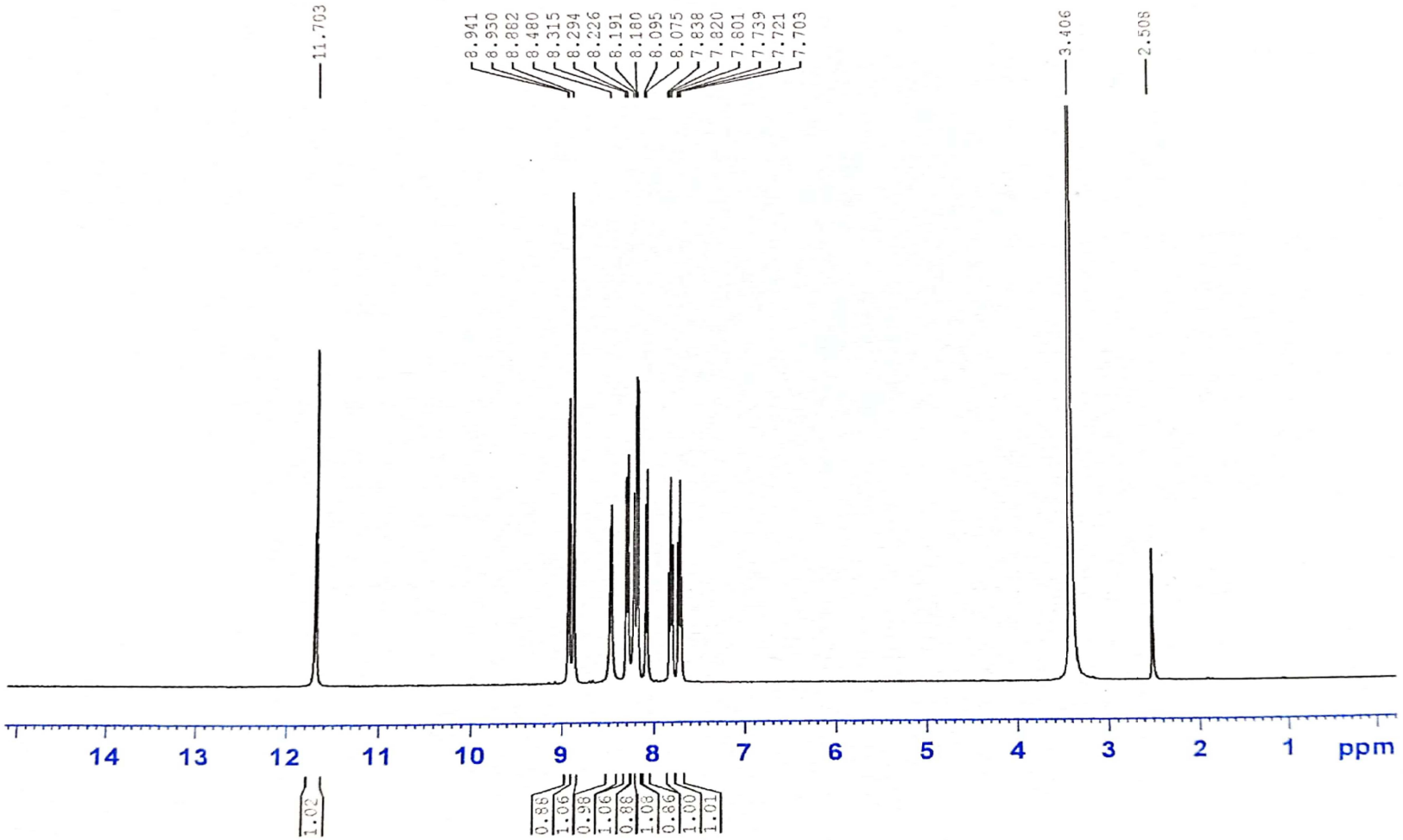


Figure 3.3 ^{1}H NMR Spectrum of compound 1a

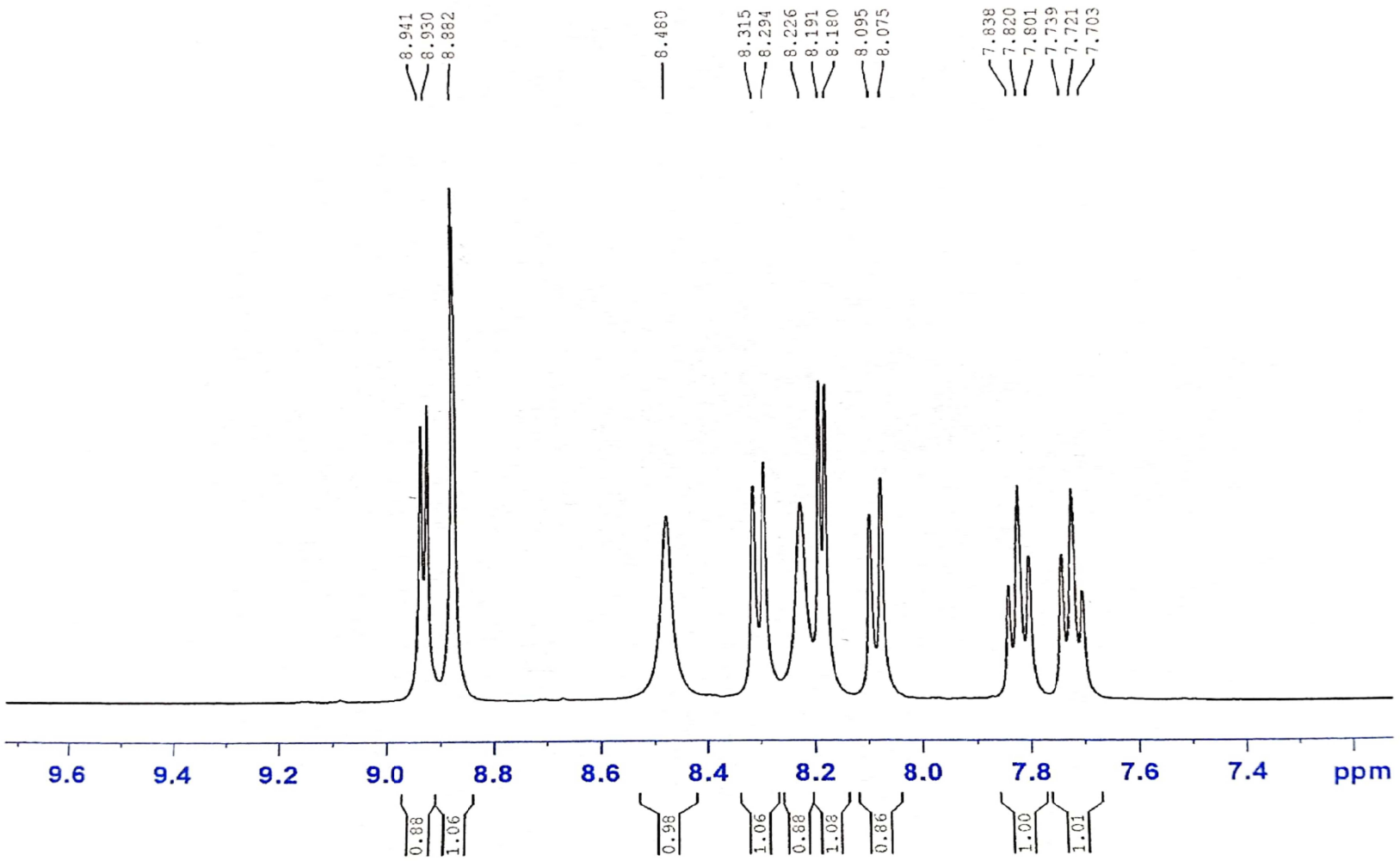


Figure 3.3a ^{1}H NMR Spectrum (Expd.) of compound 1a

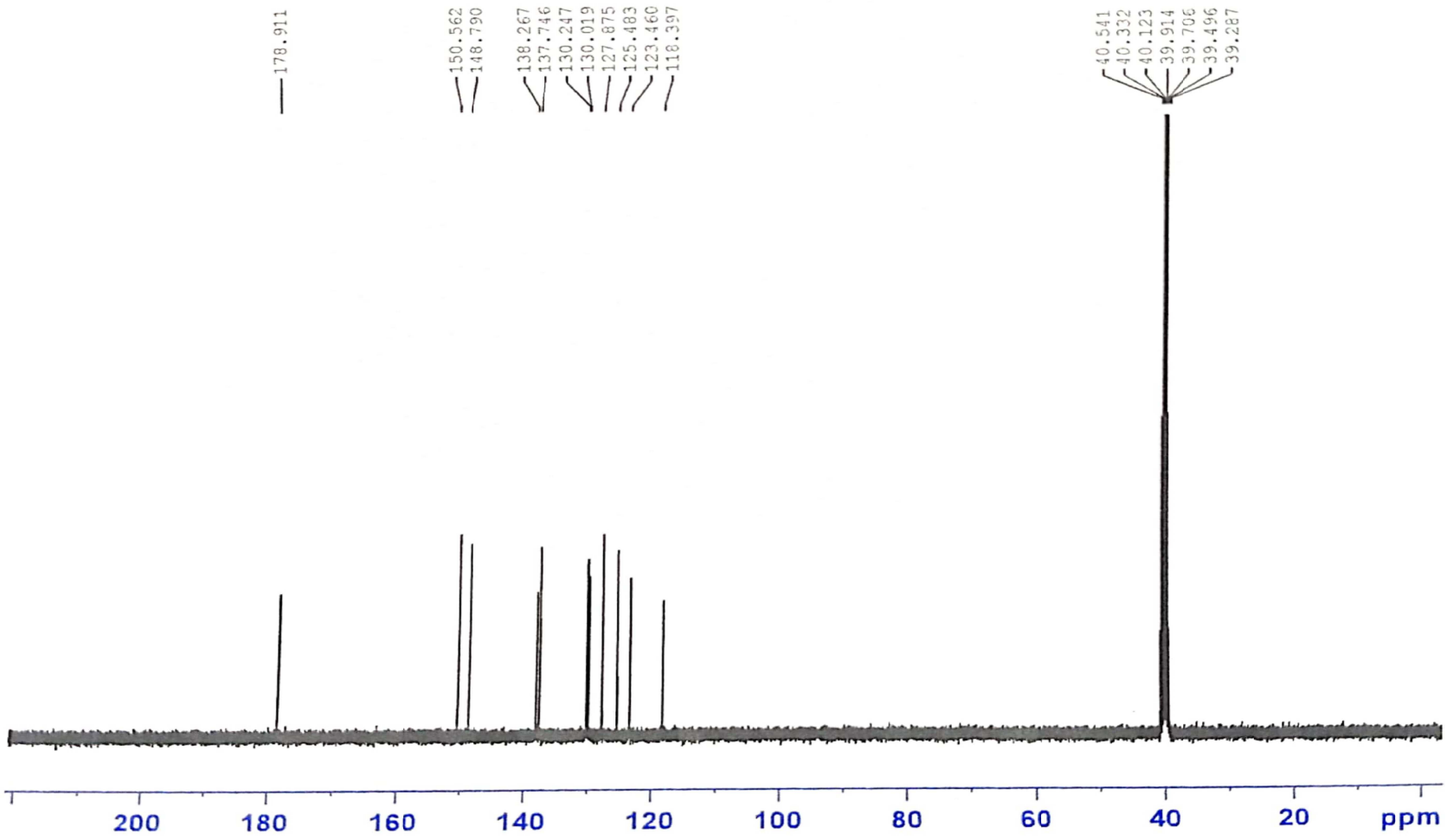


Figure 3.4 ^{13}C NMR Spectrum of compound 1a

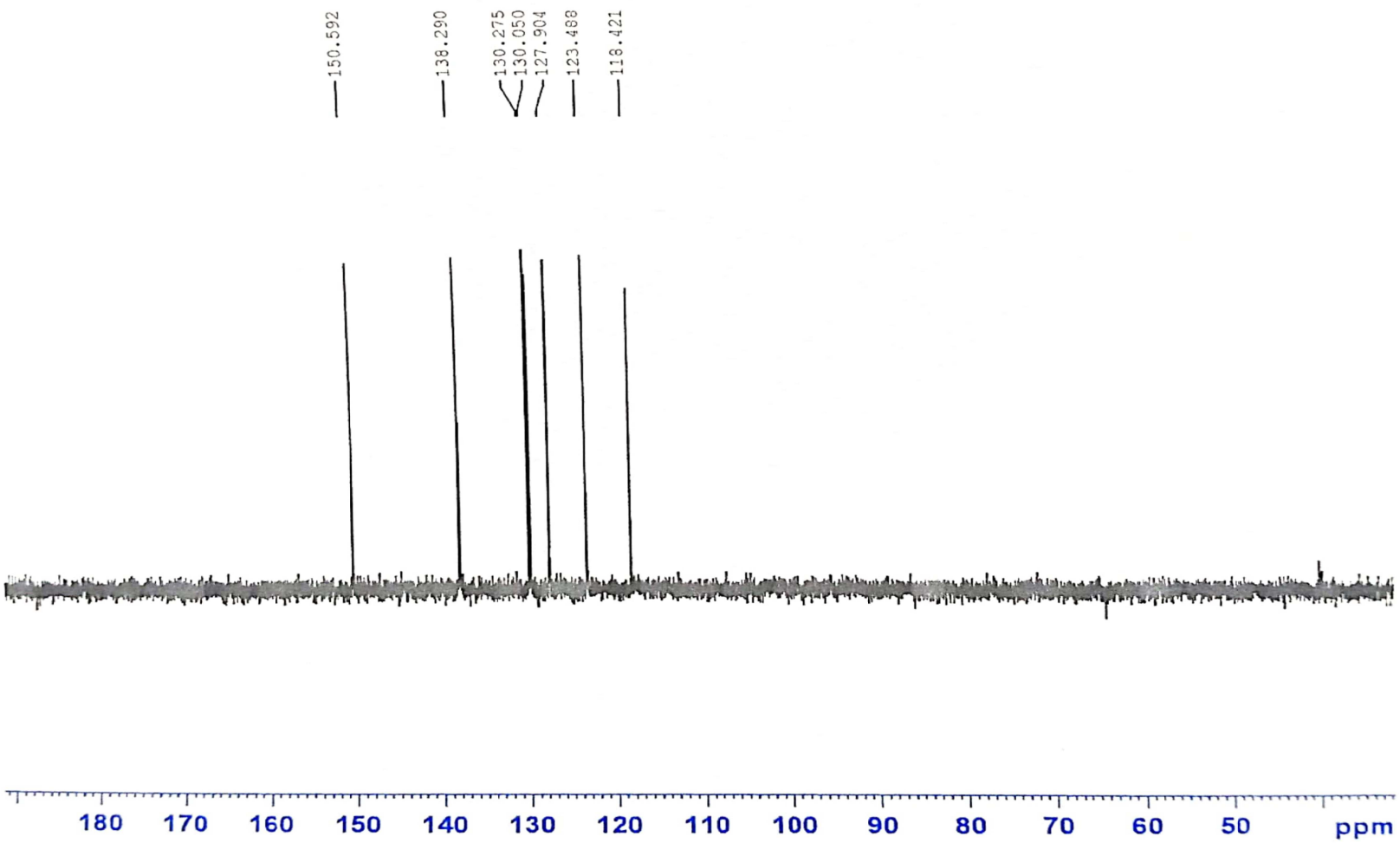


Figure 3.5 DEPT-135 Spectrum of compound 1a

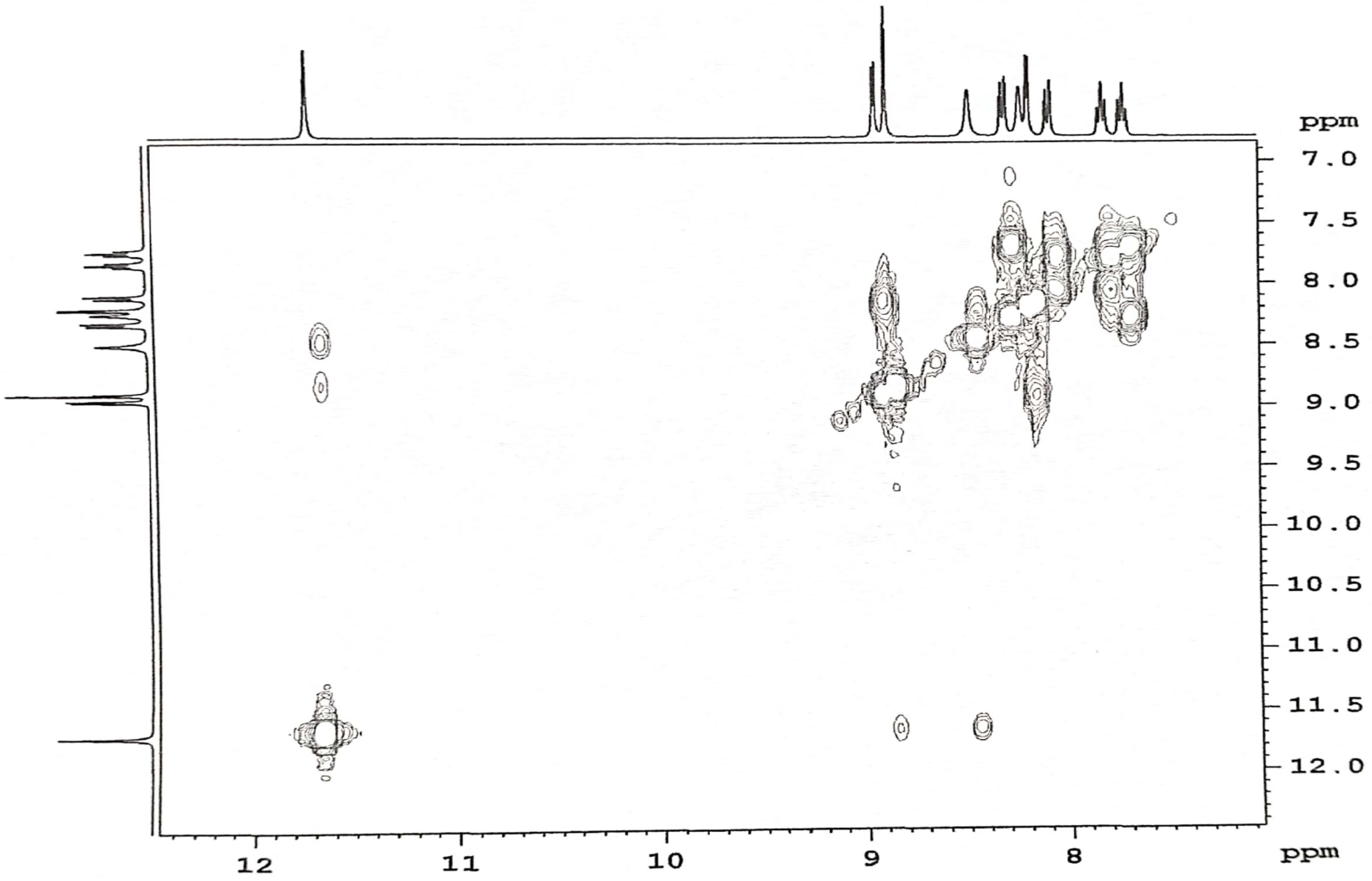


Figure 3.6 2D COSY Spectrum of compound 1a

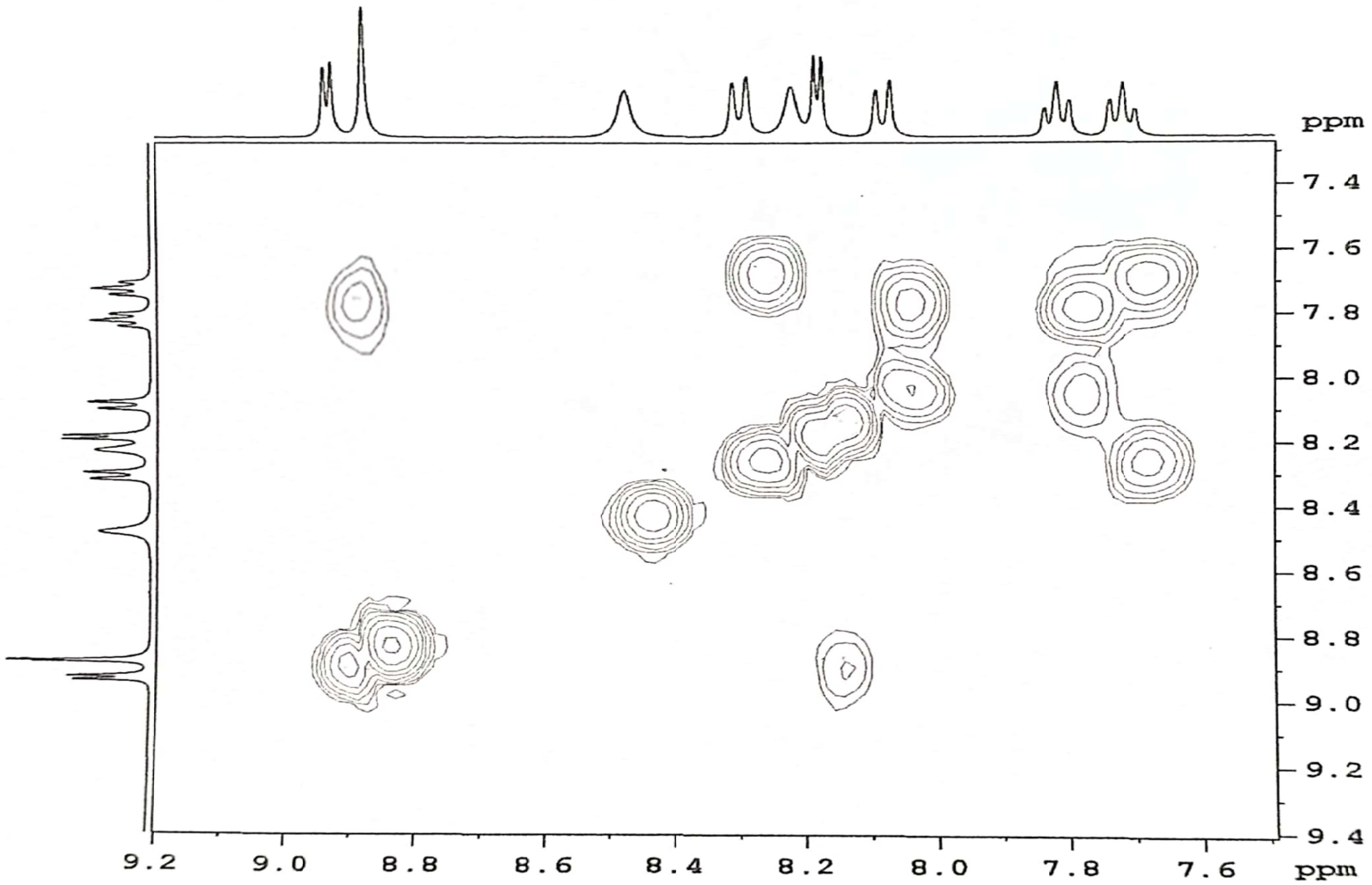


Figure 3.6a 2D COSY Spectrum (Expd.) of compound 1a

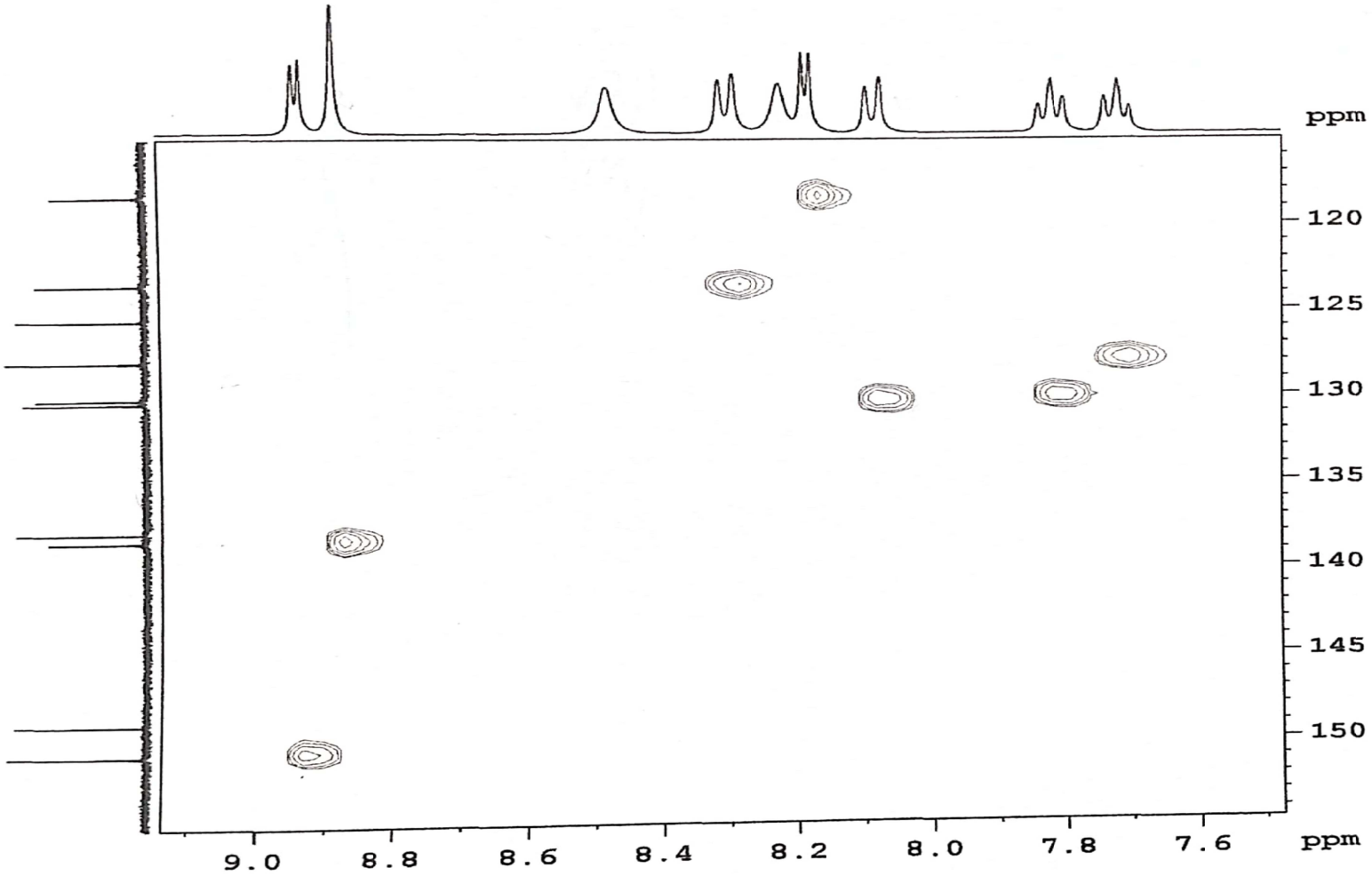


Figure 3.7 HSQC Spectrum of compound 1a

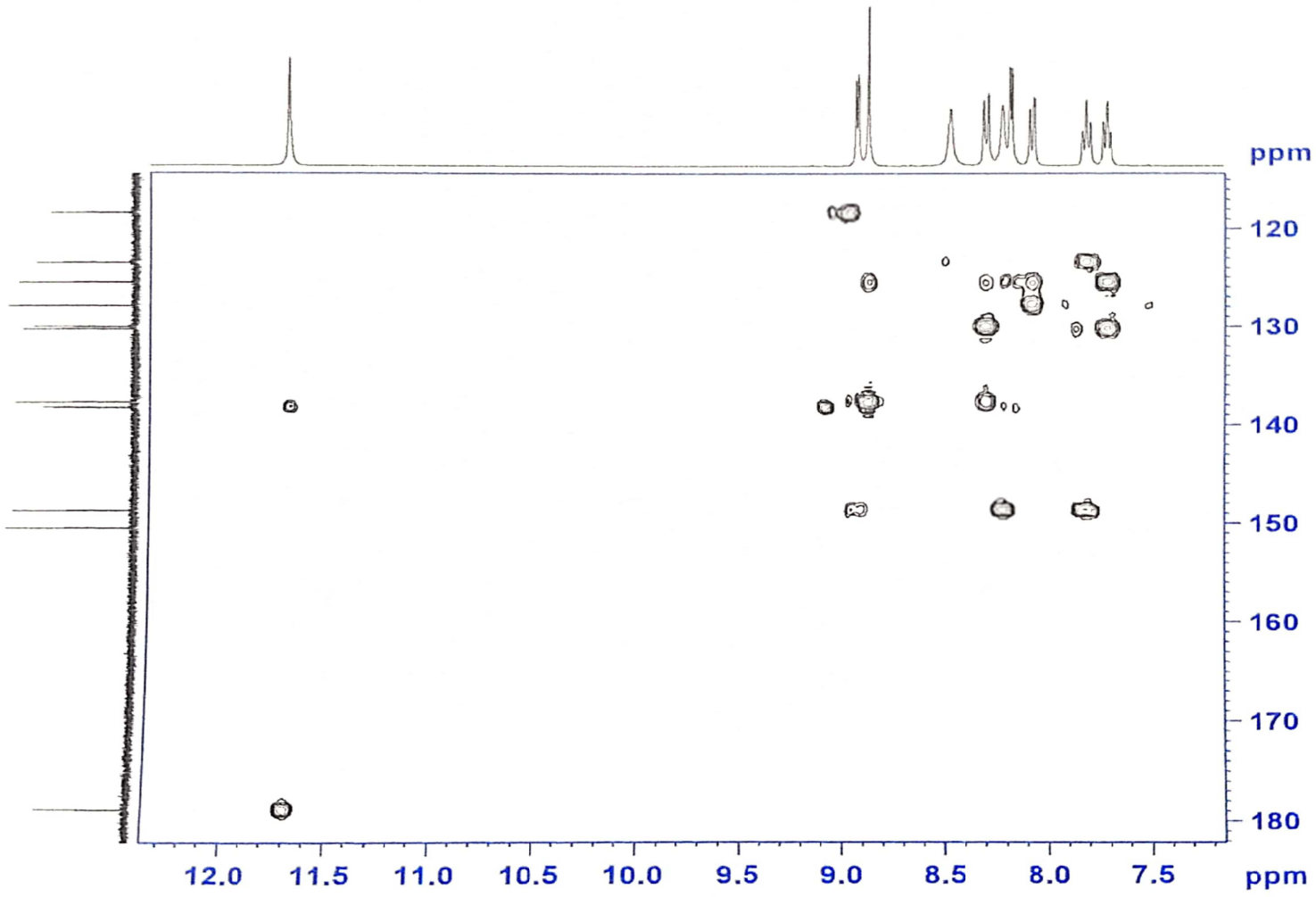


Figure 3.8 HMBC Spectrum of compound 1a

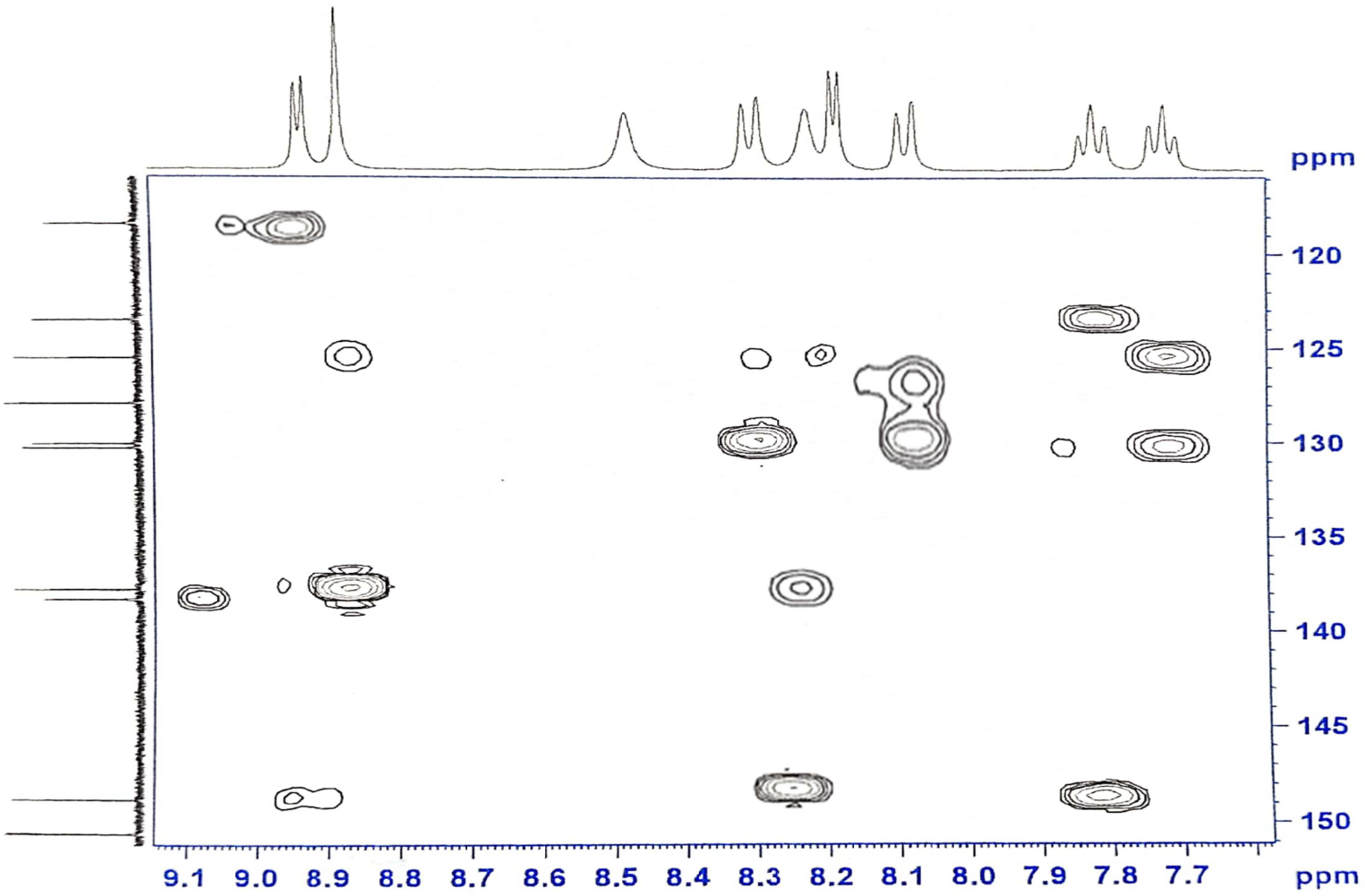


Figure 3.8a HMBC Spectrum(Expd.) of compound 1a

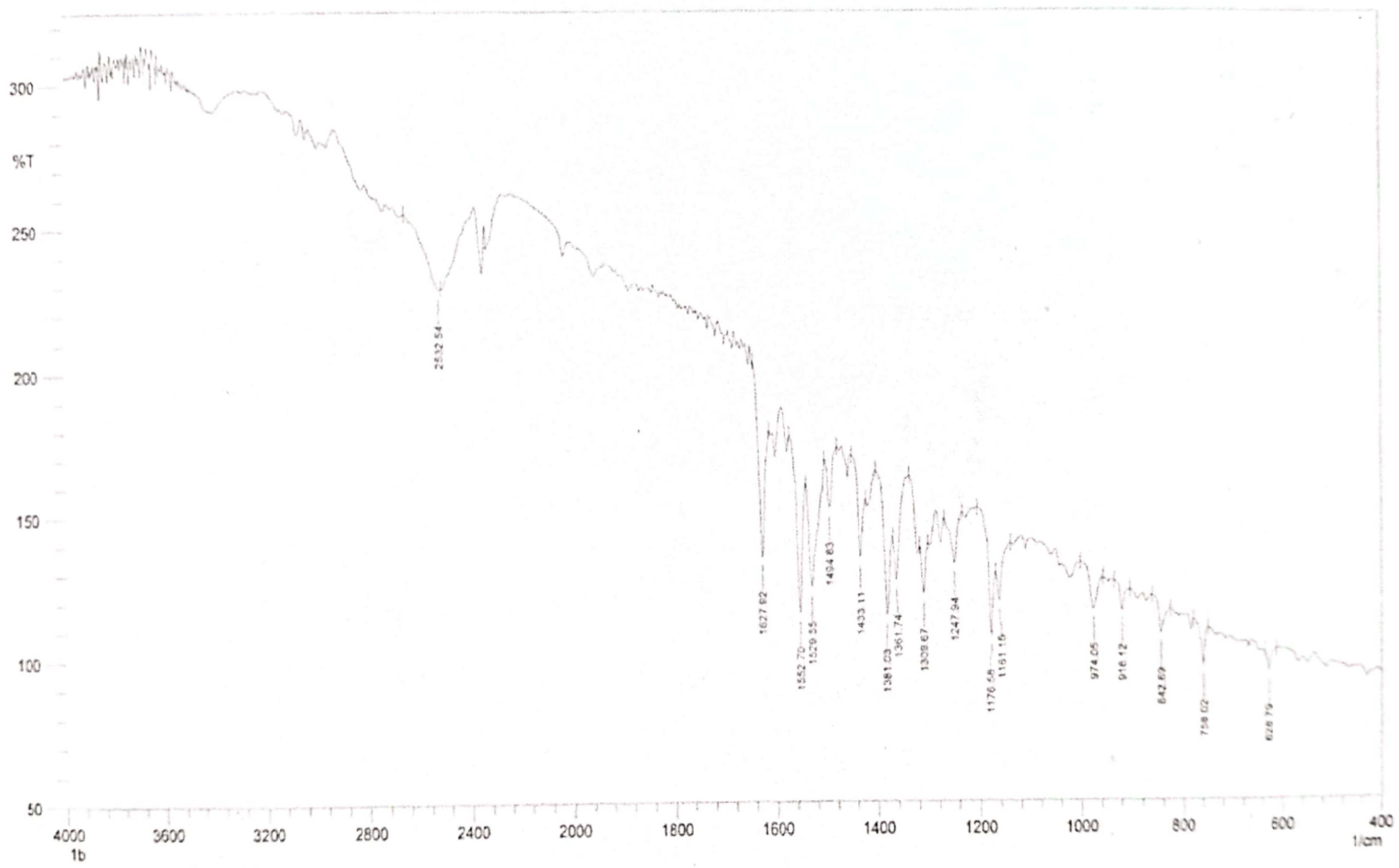


Figure 3.9 IR Spectrum of compound 1b

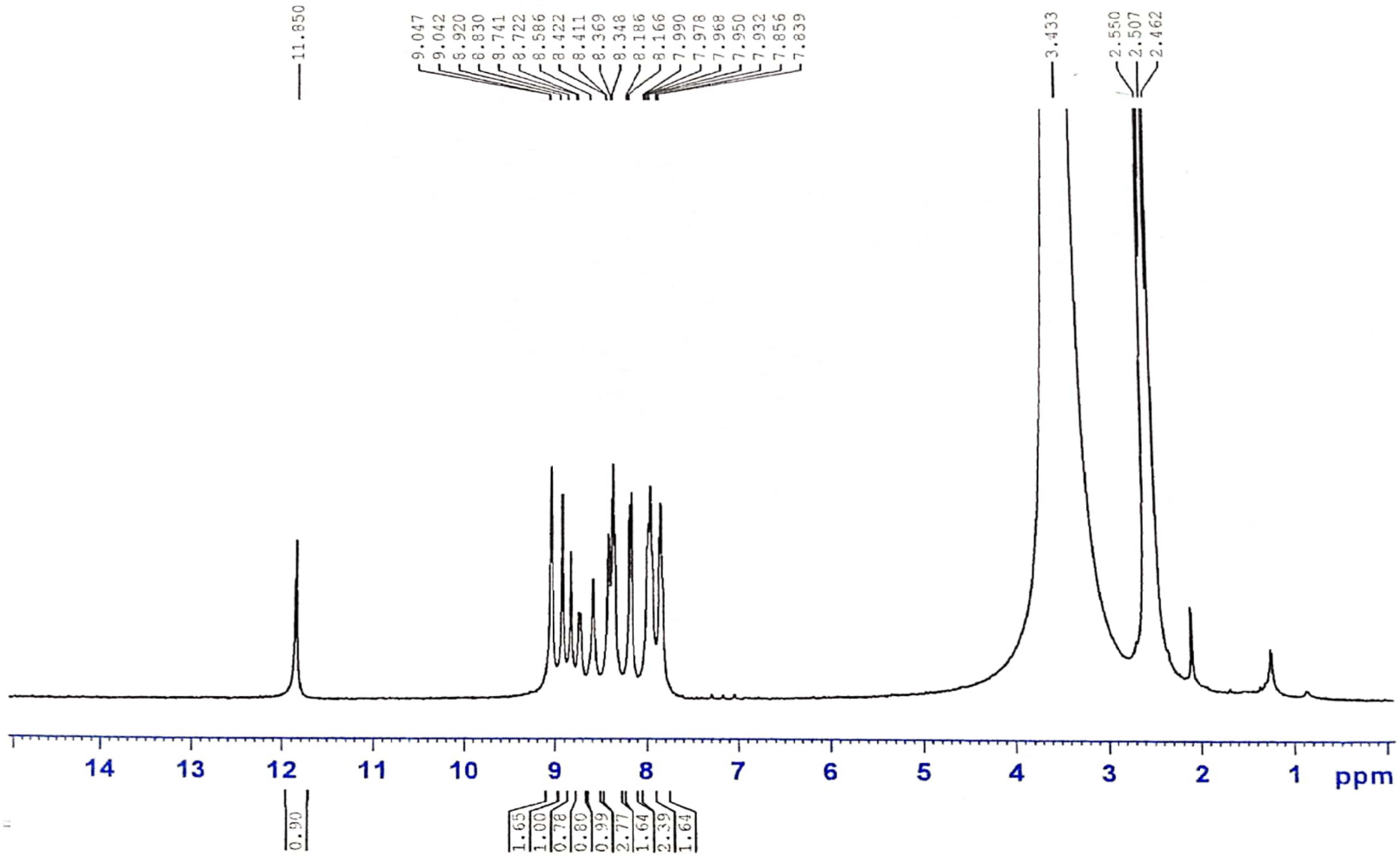


Figure 3.10 ^{1}H NMR Spectrum of compound 1b

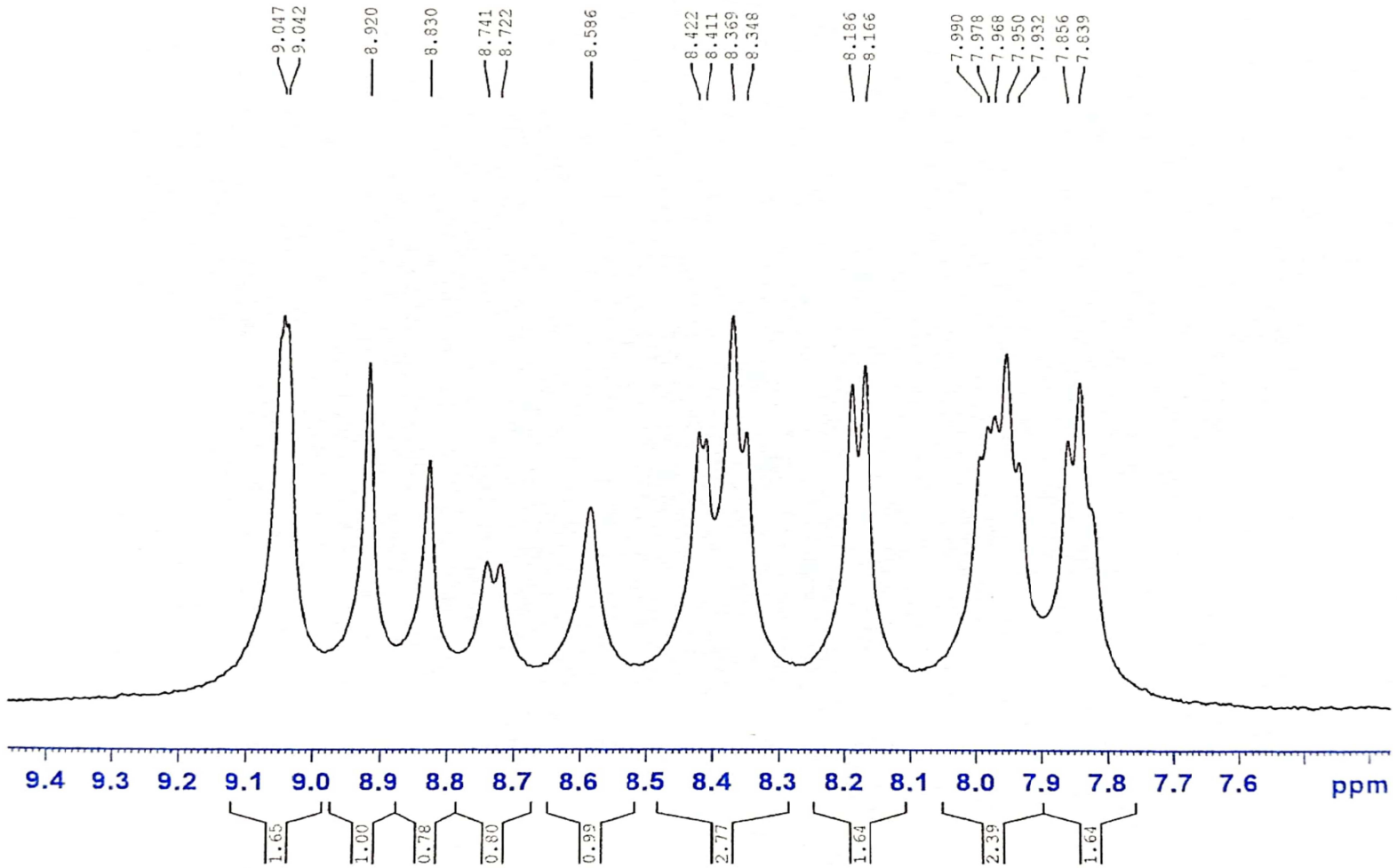


Figure 3.10a ^{1}H NMR Spectrum(Expd.) of compound 1b

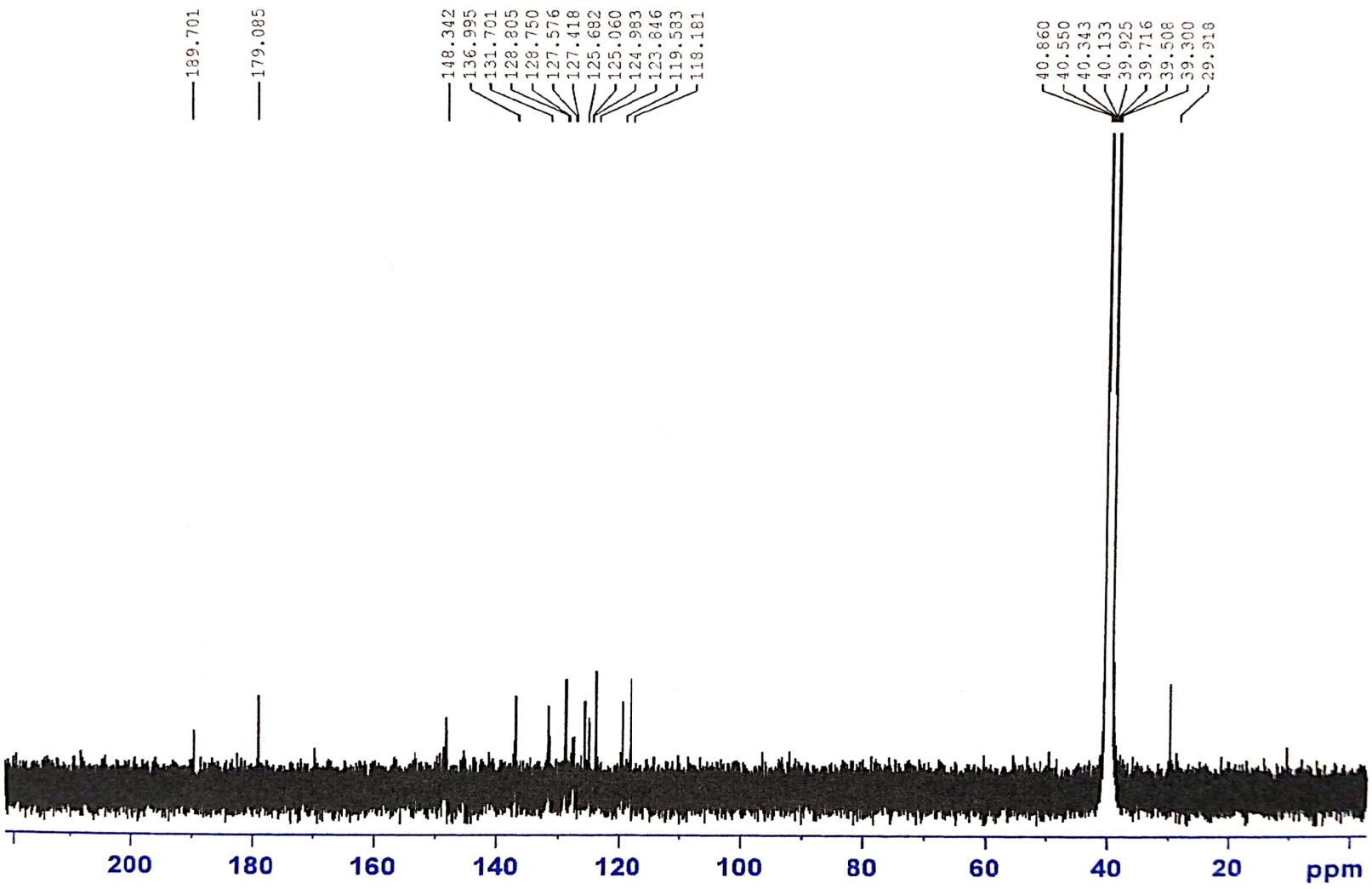


Figure 3.11 ^{13}C NMR Spectrum of compound 1b

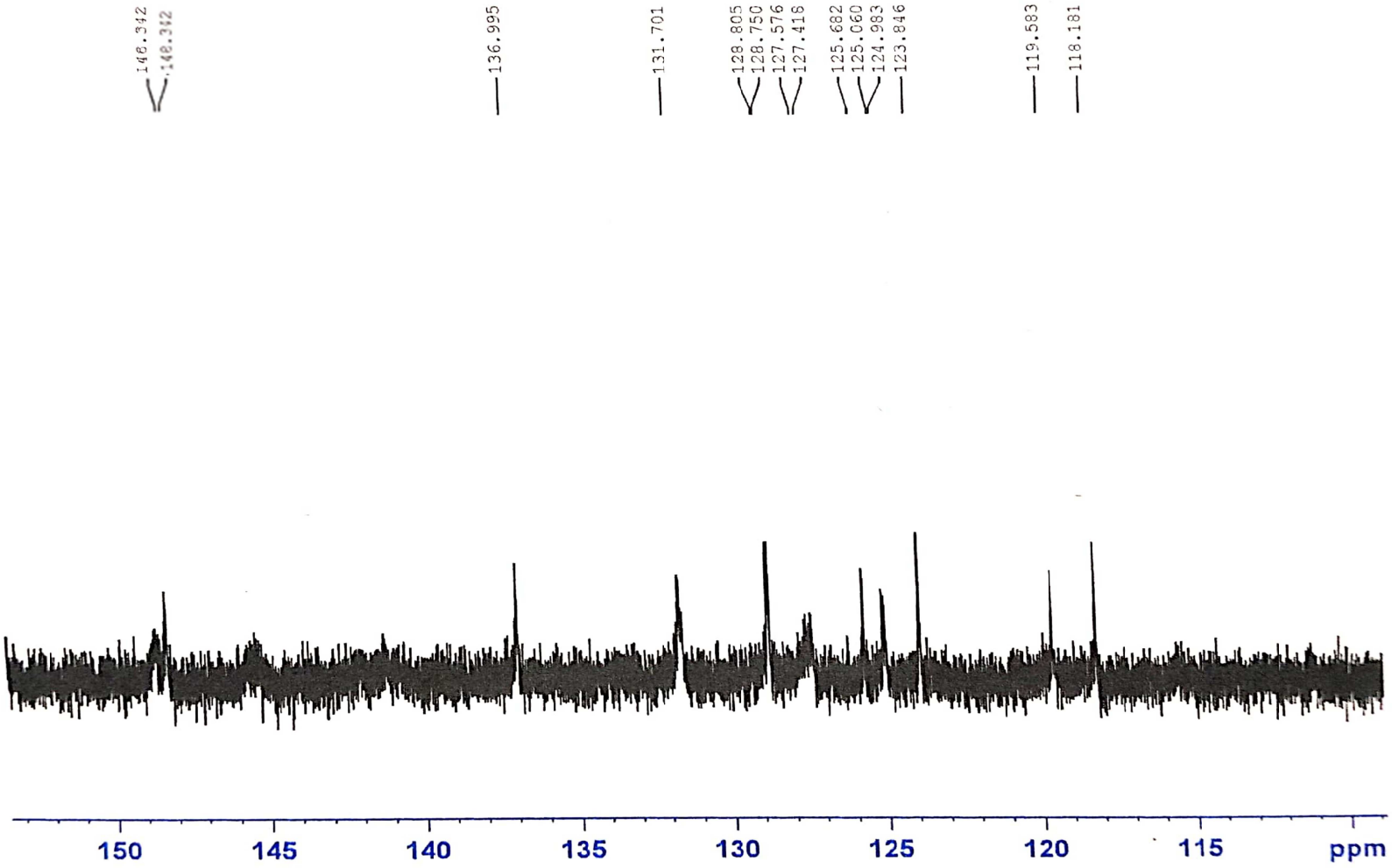


Figure 3.11a ^{13}C NMR Spectrum (Expd.) of compound 1b

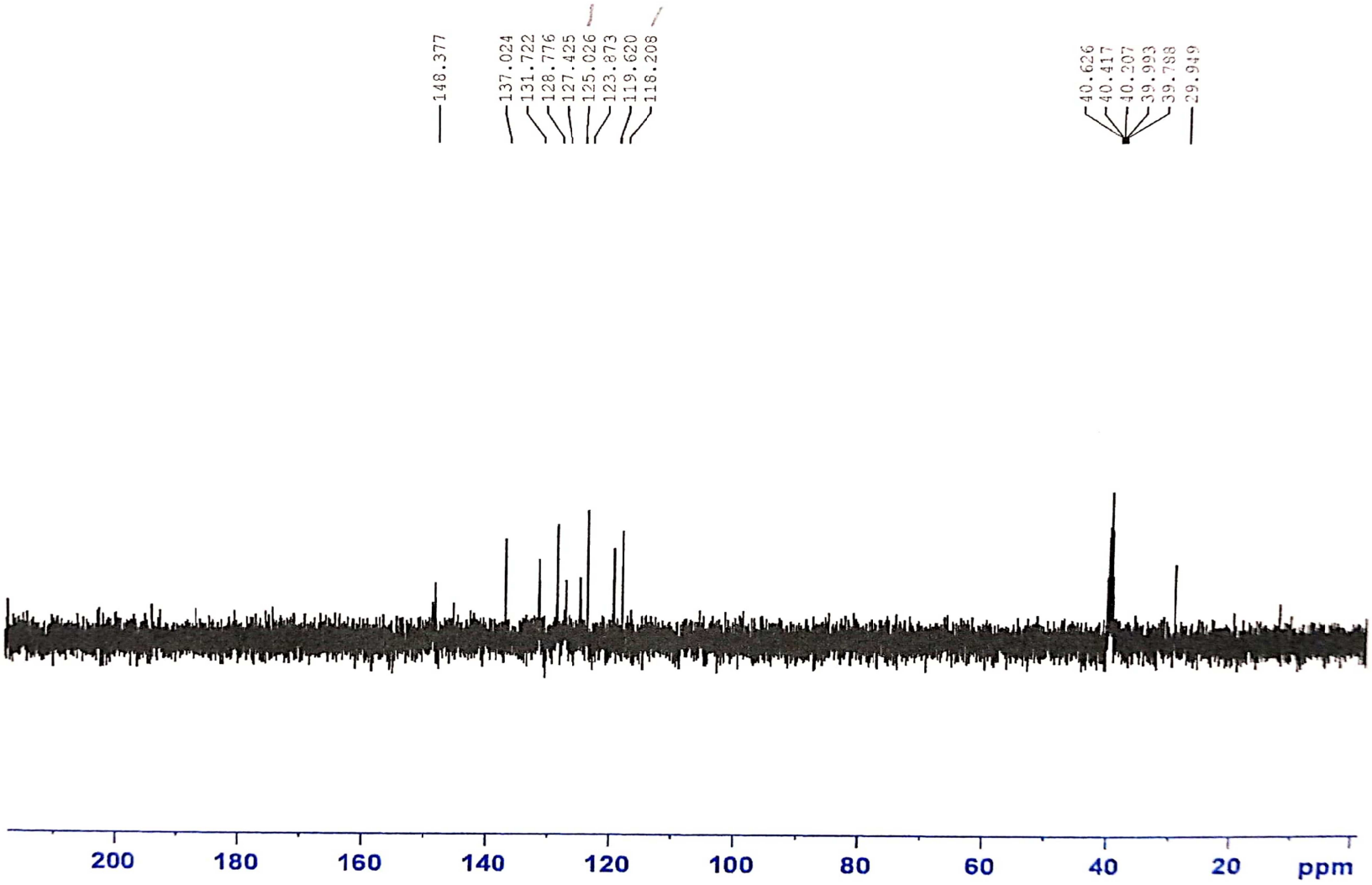


Figure 3.12 DEPT-135 Spectrum of compound 1b

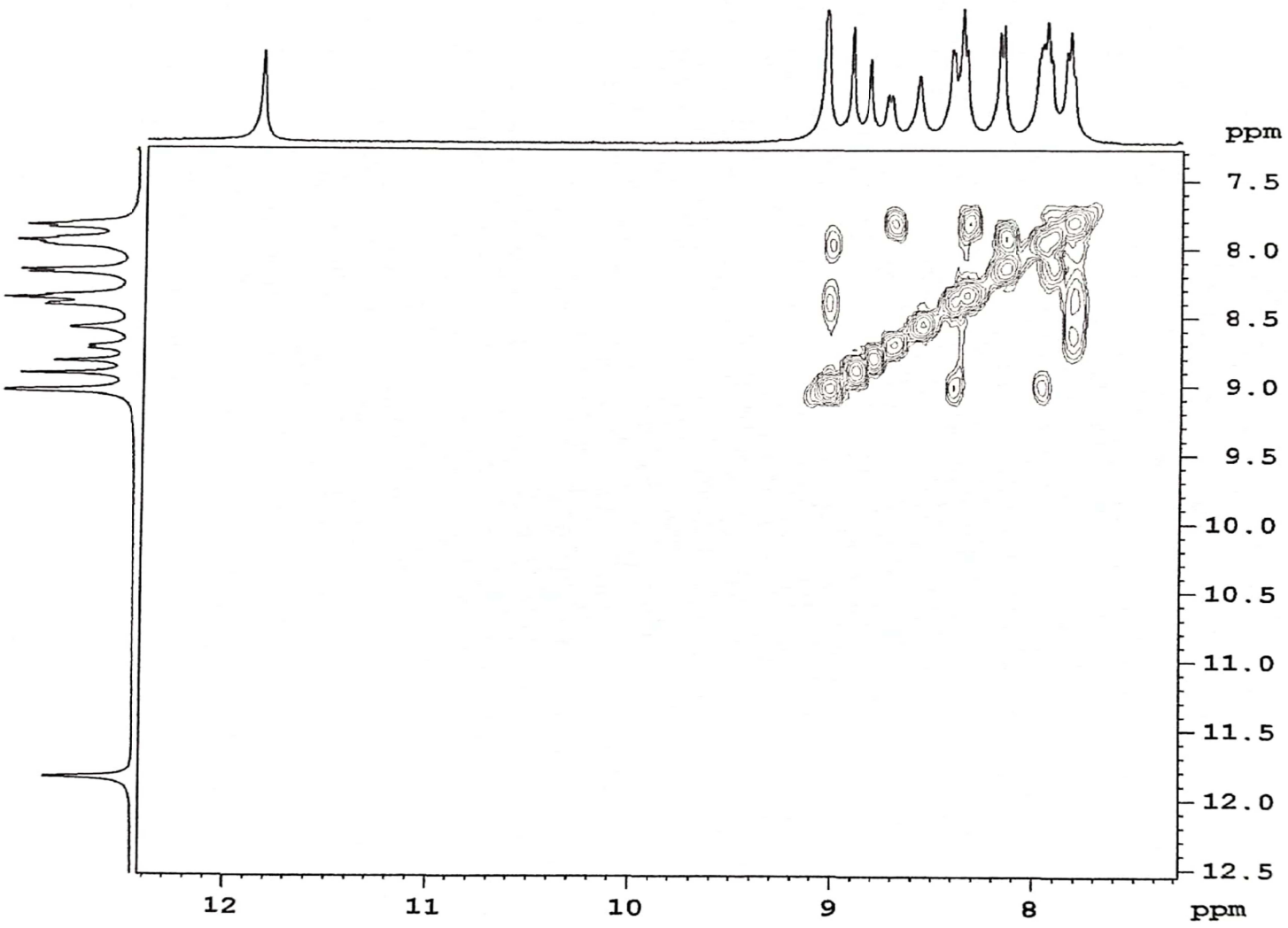


Figure 3.13 2D COSY Spectrum of compound 1b

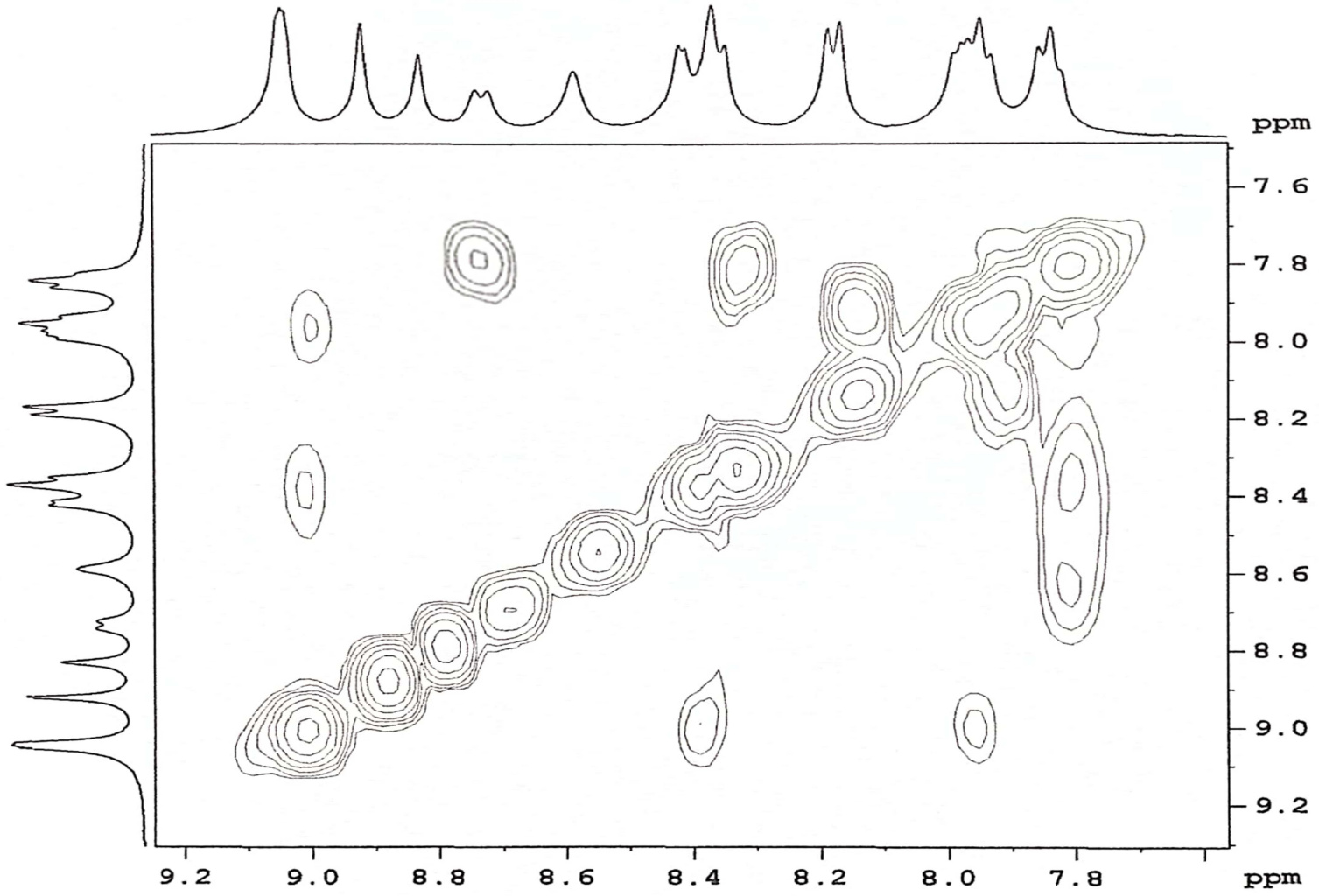


Figure 13a 2D COSY Spectrum(Expd.) of compound 1b

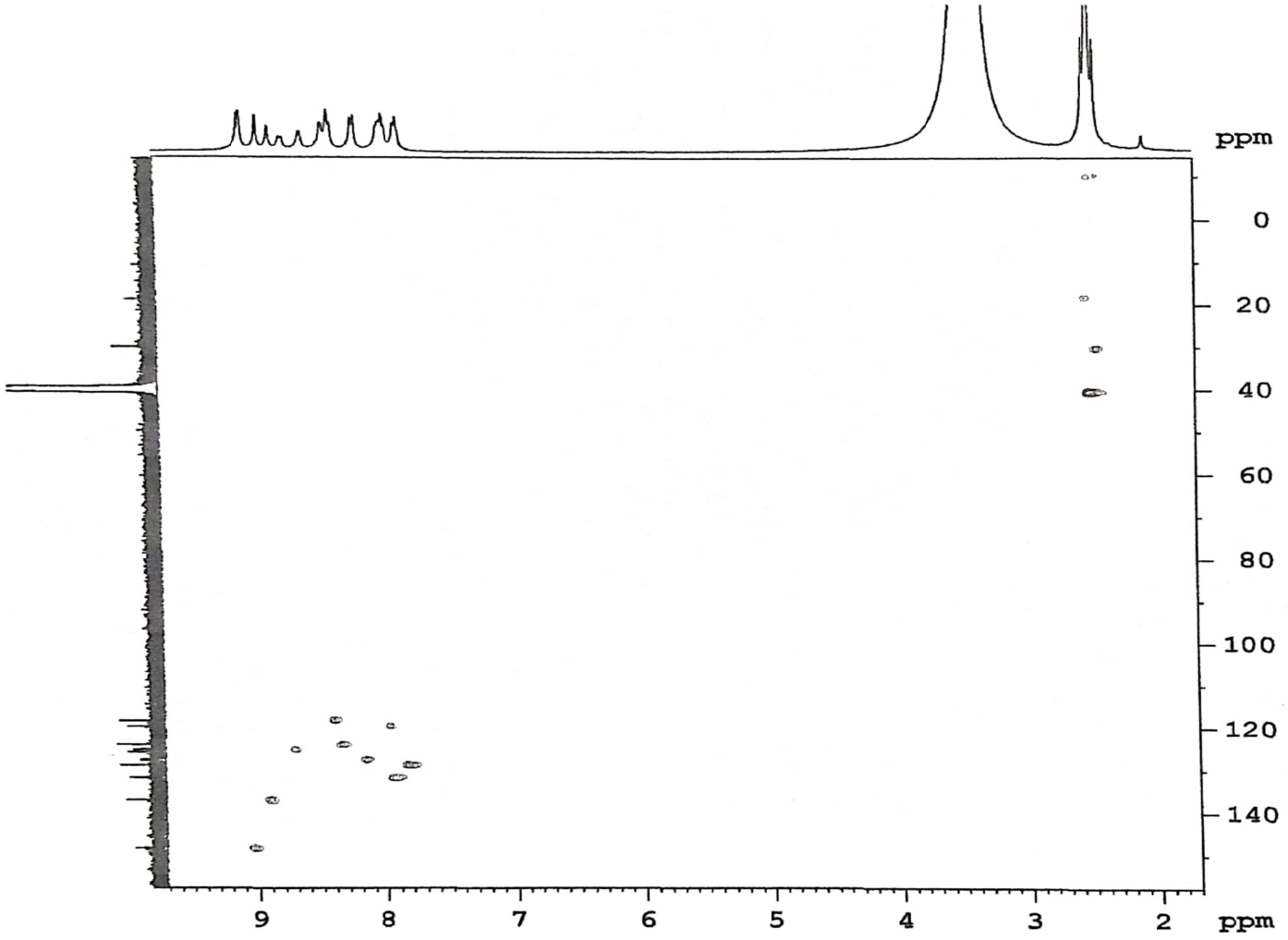


Figure 3.14 HSQC Spectrum of compound 1b

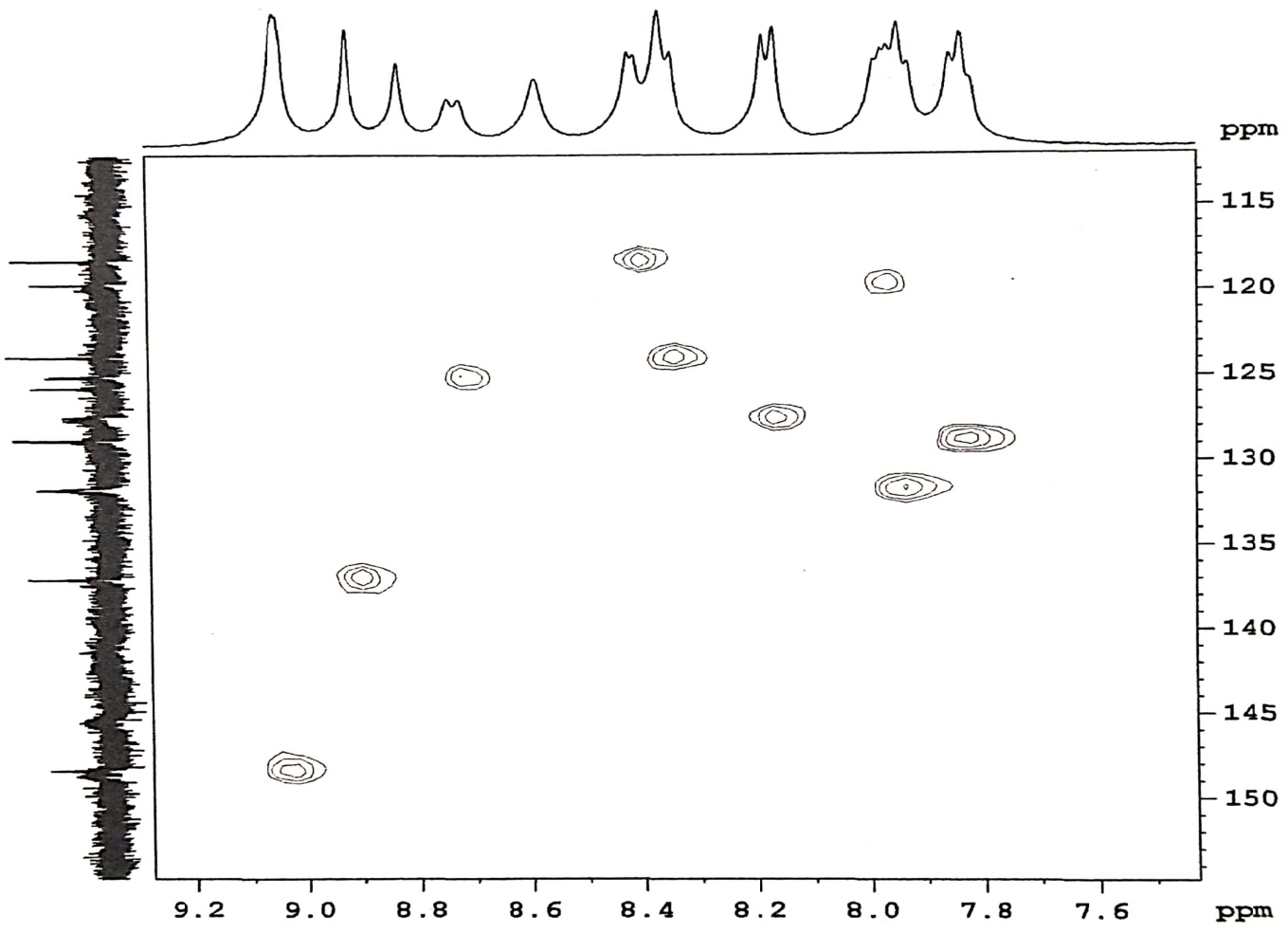


Figure 3.14a HSQC Spectrum(Expd.) of compound 1b

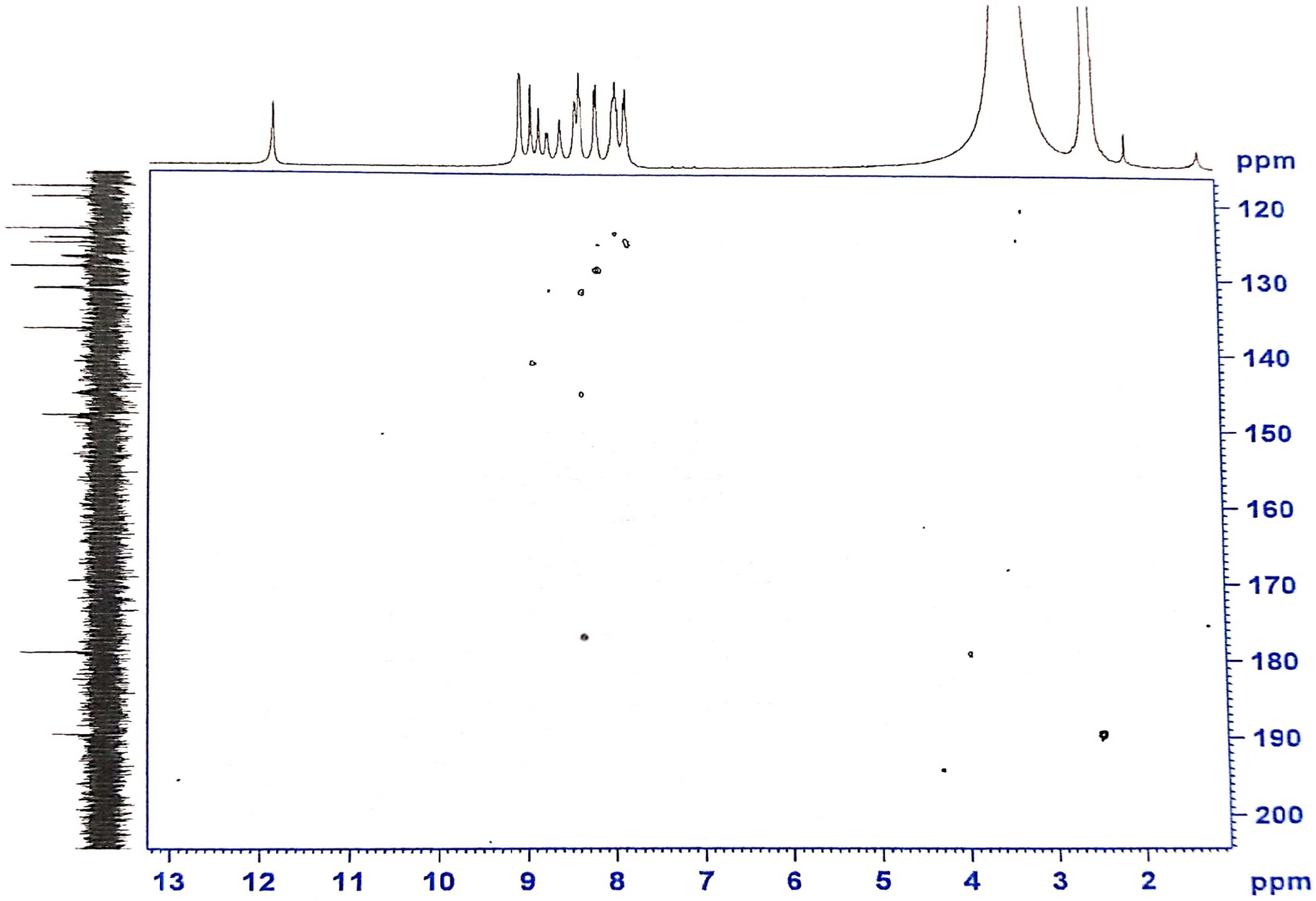


Figure 3.15 HMBC Spectrum of compound 1b

3.2 Characterization of compound 2a and 2b:

Compound **2a** (440 mg) was yellow amorphous solid, m.p 217-220°C. The IR spectrum of compound **2a** showed sharp absorptions at $\bar{\upsilon}_{max}$ 3349 $cm^{-1}$for N-H stretching and 1605 $cm^{-1}$for N-H bending. The ^{13}C NMR spectrum of compound **2a** showed that 11 carbons are present in the molecule (Table 3.1). The ^{13}C DEPT spectrum of **2a** revealed that there is no methylene carbons present in the molecule. The absorption positions of all 11 carbons in ^{13}C NMR spectrum are given in Table 3.2. The ^{1}H NMR spectrum of **2a** showed the presence of 6 aromatic protons at δ 8.44 (1H, d, *J* = 8.8 Hz, H3'), 8.35 (1H, d, *J* = 8.4 Hz, H4'), 8.00 (1H, d, *J* = 4.8 Hz, H5'), 7.61 (1H, t, *J* = 7.2 Hz, H6'), 7.77 (1H, t, *J* = 7.2 Hz, H7') and 7.99 (1H, t, *J* = 8.0 Hz, H8'). The absorption positions of one olifinic proton attached to carbon H-C=N is at δ 8.24 (1H, s, H-C=N), one NH proton at δ 11.79s and two NH_2 protons at δ 8.32s appeared in ^{1}H NMR spectrum. The important homo-nuclear correlations (H-H) in 2D COSY spectrum and hetero-nuclear (H-C) correlations in HMBC spectrum are presented in Figure 3.16 and Table 3.2. On the basis of IR, ^{1}H NMR and ^{13}C NMR spectra, structure **3** was confirm to the compound **2a**. Compound **2a** is thus characterized as **2-(2'-quinolinylmethylene) hydrazine carbathioamide (3).**

Compound **2b** (361 mg) was reddish orange amorphous solid, m.p 222-225°C. The IR spectra of compound **2b** showed sharp absorptions for N-H stretching at $\bar{\upsilon}_{max}$ 3445 cm^{-1} and for N-H bending at $\bar{\upsilon}_{max}$ 1635 cm^{-1}. The ^{13}C NMR spectra of compound **2b** showed 16 carbons are present in the molecule (Table 3.2). The ^{13}C DEPT spectrum of **2b** revealed that there is no methylene carbon present in the molecule. The absorption positions of all 16 carbons in ^{13}C NMR spectrum are given in Table 3.2. The ^{1}H NMR spectrum of **2b** showed the presence of 6 aromatic protons at δ 8.14 (1H, d, *J* = 8.0 Hz, H3'), 7.92 (1H, d, *J* = 7.6 Hz, H4'), 8.18 (1H, d, *J* = 6.4 Hz, H5'), 7.74 (1H, t, *J* = 7.6 Hz, H6'), 7.92 (1H, t, *J* = 7.6 Hz, H7') and 8.18 (1H, d, *J* = 6.4 Hz, H8') in the molecule. The absorption positions of one olifinic proton attached to carbon H-C=N appeared at δ 8.86 (1H, s, H-C=N) and one NH proton appeared at δ 12.16 (1H, s, H-N) and two sets of methyl protons appeared at δ 2.53 (3H, s, CO=CH_3) and 2.45 (3H, s, CH_3). The important homo-nuclear (H-H) correlations in 2D COSY spectrum and hetero-nuclear (H-C) correlations in HMBC spectrum are presented in Figure 3.16 and Table 3.2. On the basis of IR, ^{1}H NMR and ^{13}C NMR spectra, structure **4** was confirm to the compound **2b**. Compound **2b**

is thus characterized as **5''-aceto-4''-methyl-2''-(2-(2'-quinolinylmethylene) hydrazine) thiazole (4).**

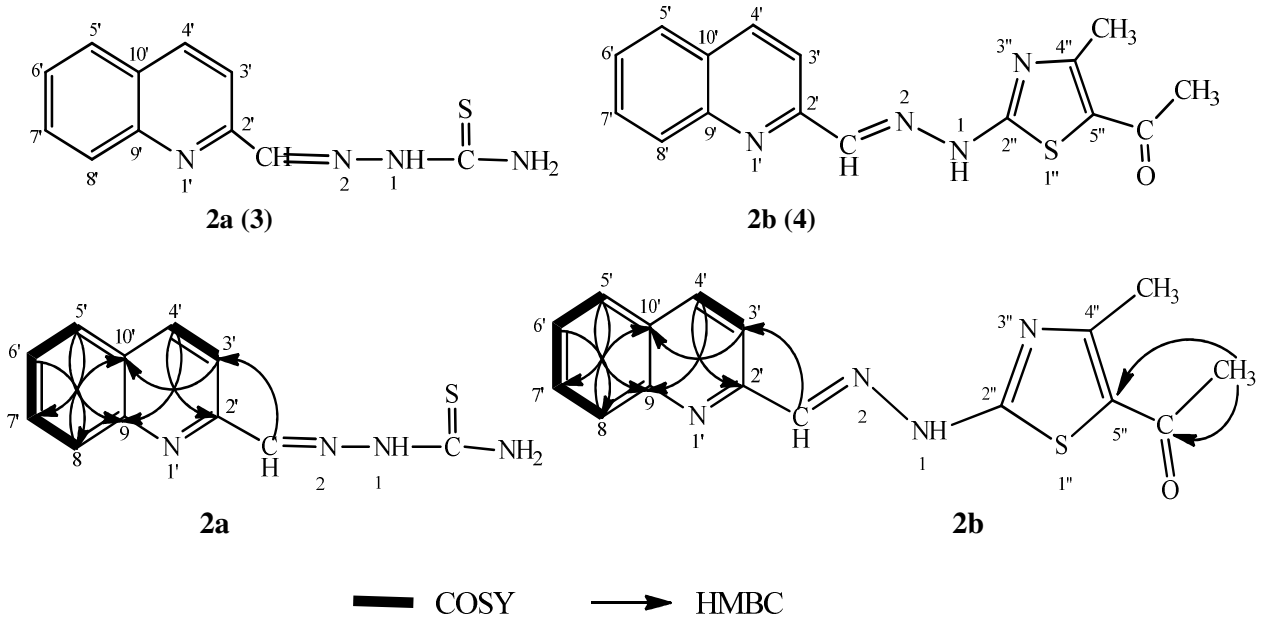


Figure 3.16: Important COSY and HMBC correlations of compound **2a** and **2b**

Table 3.2: ^{13}C NMR and ^{1}H NMR data for compounds 2a and 2b (DMSO, δ, ppm, J/Hz)*

C atom	^{13}C, δ	^{1}H, δ	COSY	HMBC	^{13}C, δ	^{1}H, δ	COSY	HMBC
2'	154.3				152.0			
3'	118.5	8.44,d, *J* =8.8	H4'	C10', CH=N	118.0	8.14,d,*J*=8.0	H4'	C10', CH=N
4'	136.7	8.35,d, *J* =8.4	H3'		132.5	7.92,t, *J* =7.6	H3'	
5'	129.2	8.00,d, *J* =4.8	H6'	C7',9'	128.9	8.18,d, *J* =6.4	H6'	C7',9'
6'	127.6	7.61,t, *J* =7.2	H5',7'	C8',10'	128.6	7.74,t, *J* =7.6	H5',7'	C8',10'
7'	130.3	7.77,t, *J* =7.2	H6',8'	C5',9'	132.3	7.92,t, *J* =7.6	H6',8'	C5',9'
8'	128.3	7.99,t, *J* =8.0	H7'	C6',10'	128.9	8.18,d, *J* =6.4	H7'	C6',10'
9'	147.7				140.5			
10'	128.2				128.3			
CH=N	143.0	8.24,s		C2',3'	141.7	8.86,s		C2',3'
2''					169.8			
C=S	178.9							
4''					128.2			
5''					168.3			
C=O					189.7			
CO-CH$_3$					29.9	2.53,s		C=O
CH$_3$					18.1	2.45,s		
NH$_2$		8.32,s						
NH		11.79,s				12.16,s		

*The assignment was based on DEPT (135), COSY, HSQC and HMBC experiments

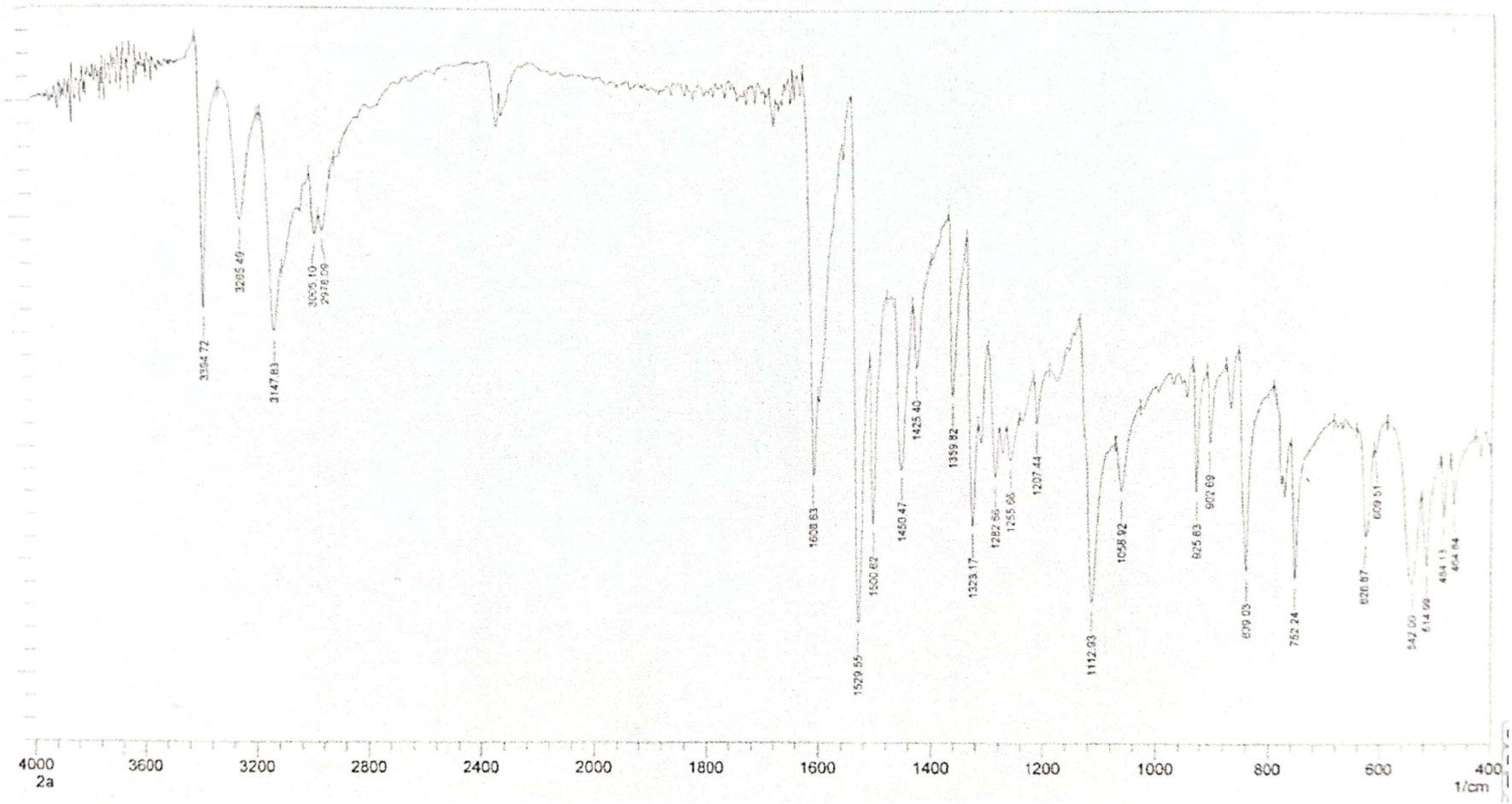


Figure 3.17 IR Spectrum of compound 2a

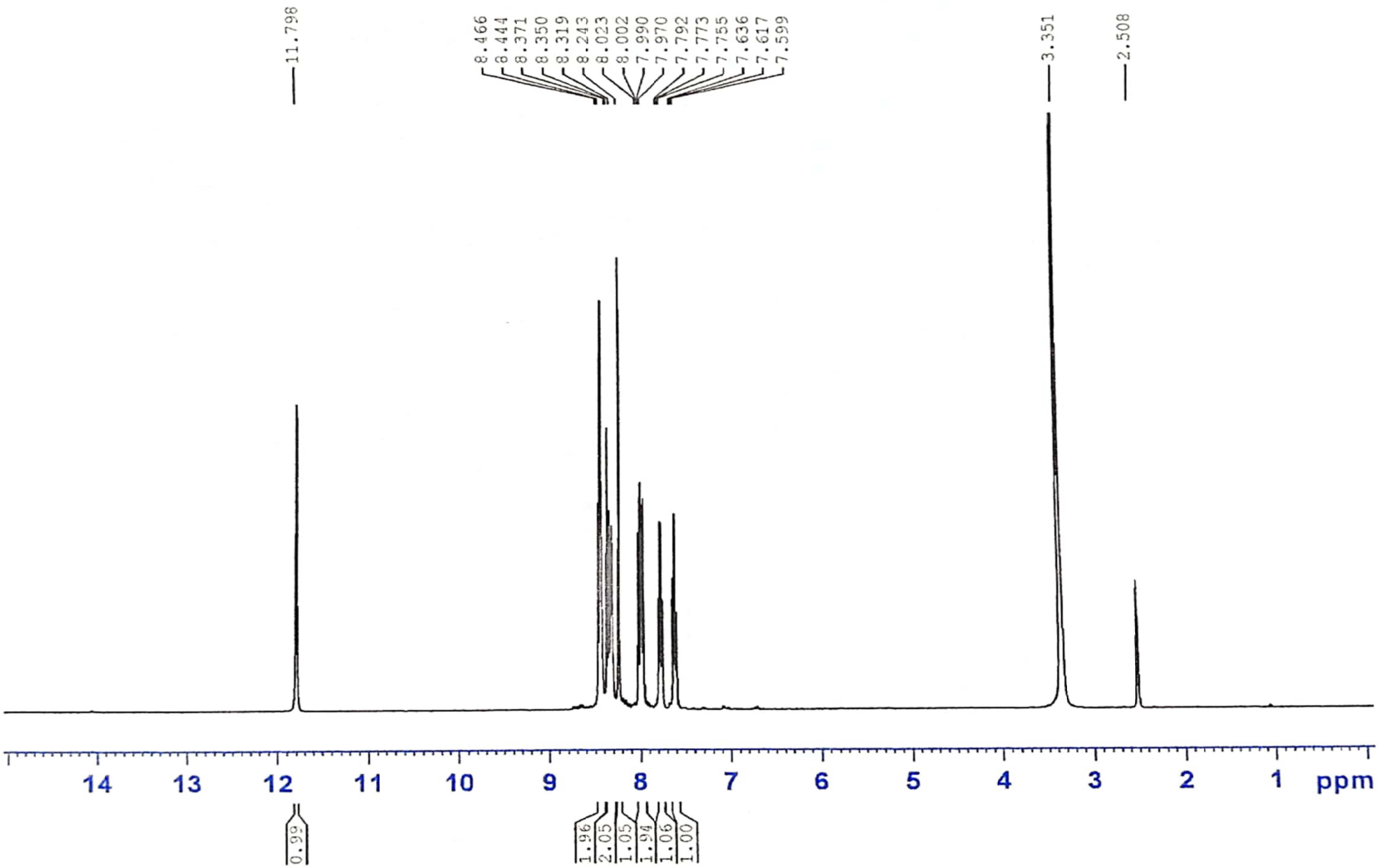


Figure 3.18 ^{1}H NMR Spectrum of compound 2a

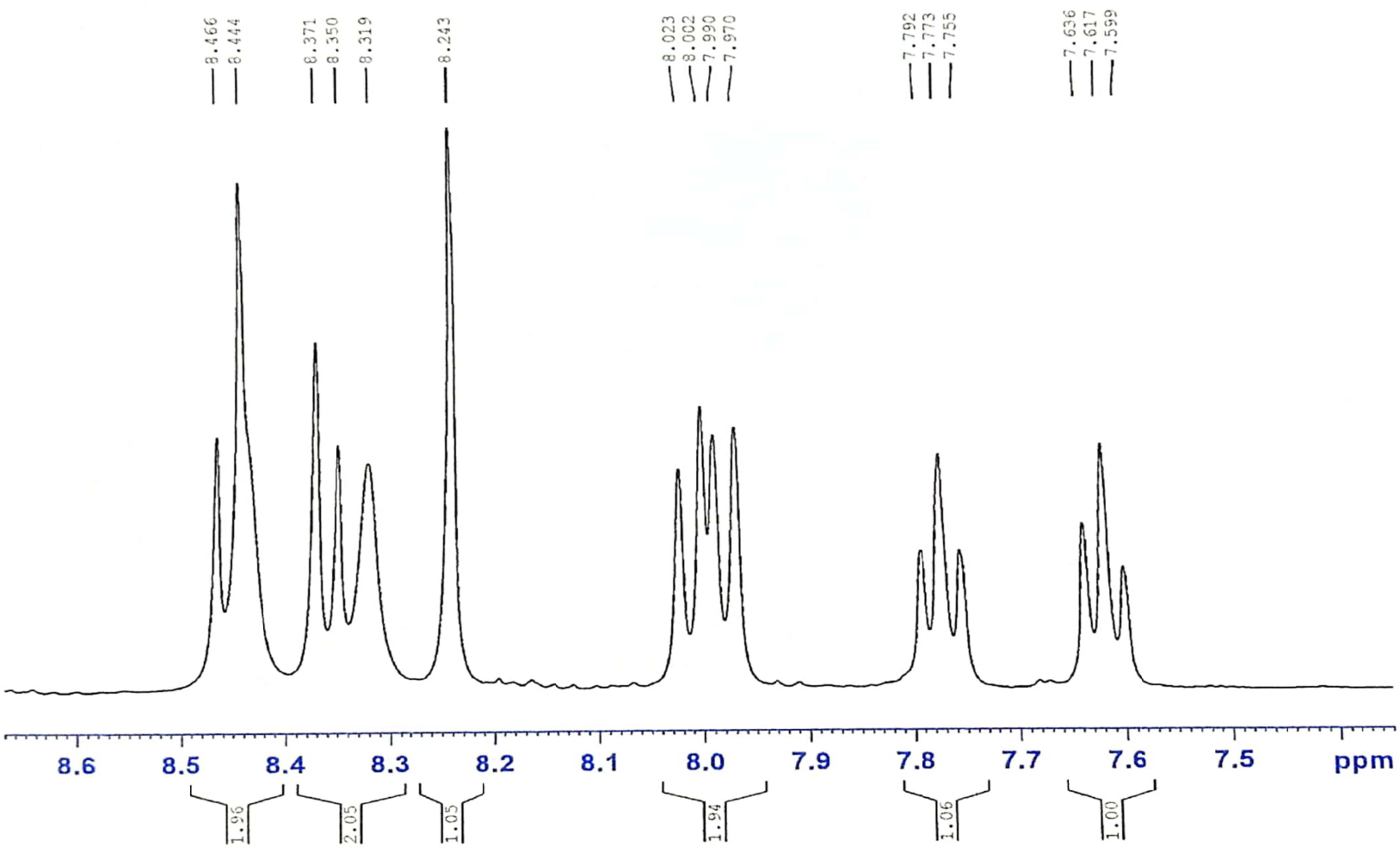


Figure 3.18a ^{1}H NMR Spectrum (Expd.) of compound 2a

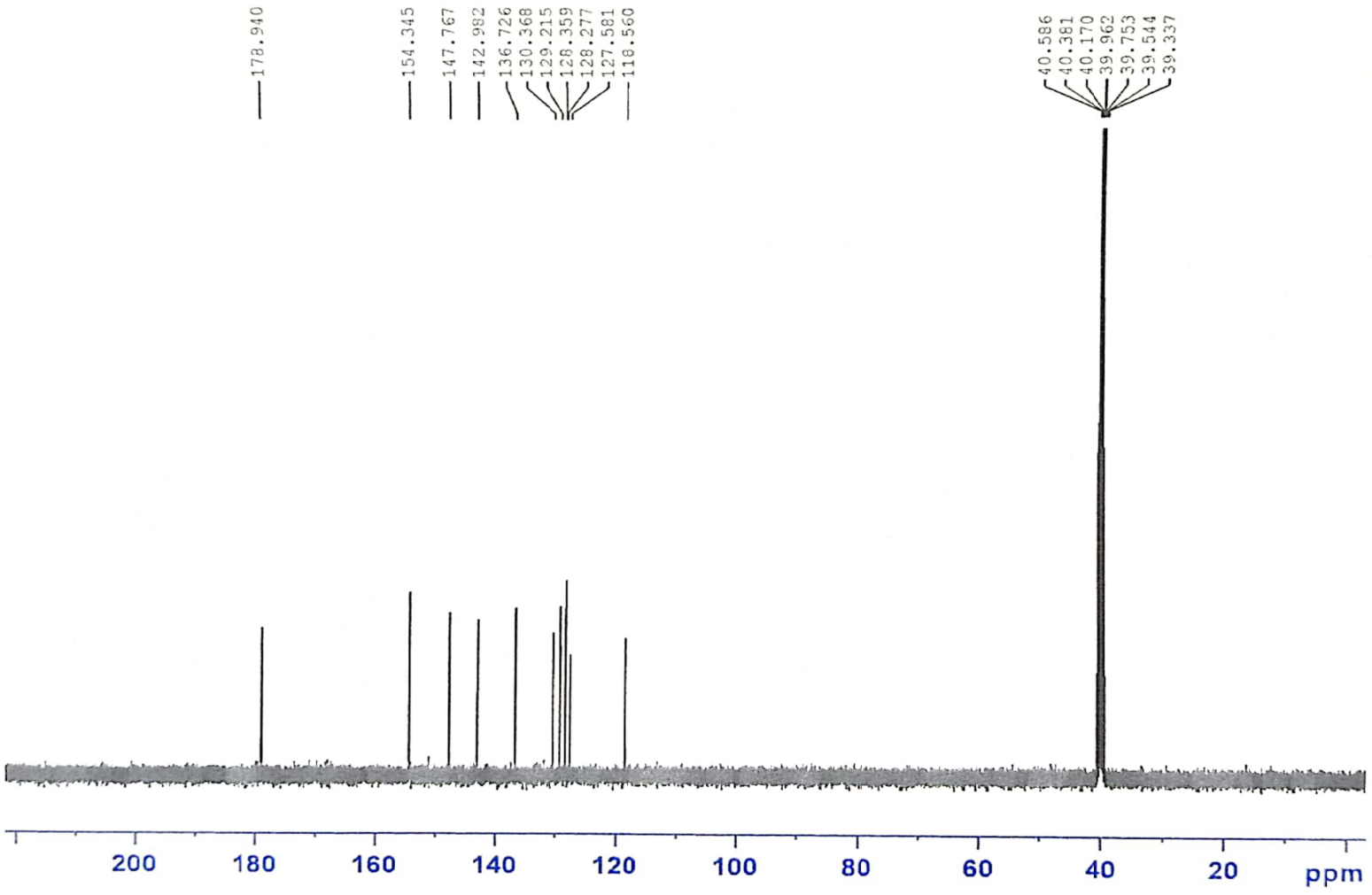


Figure 3.19 : ^{13}C NMR Spectrum of compound 2a

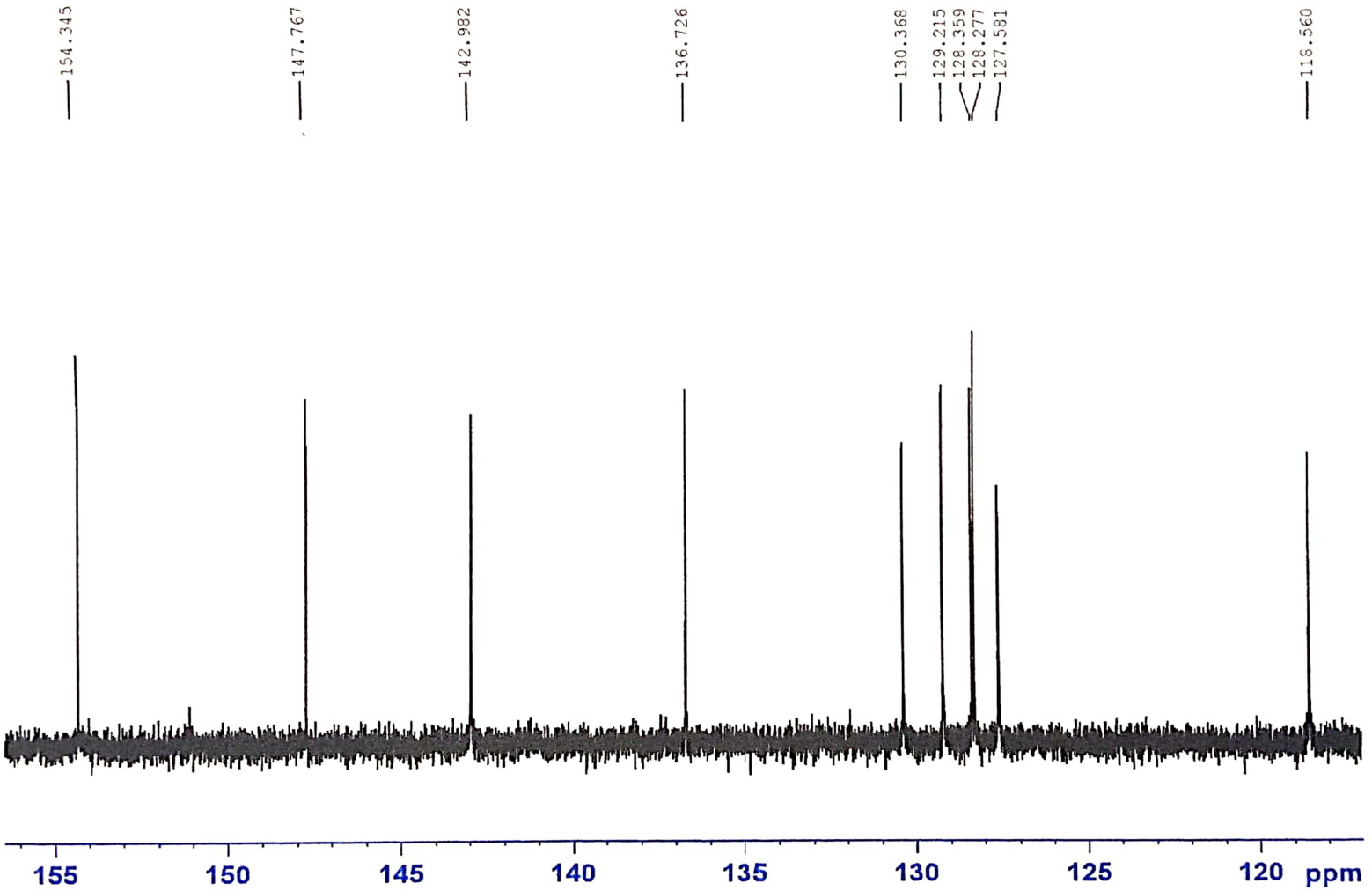


Figure 3.19a : ^{13}C NMR Spectrum (Expd.)of compound 2a

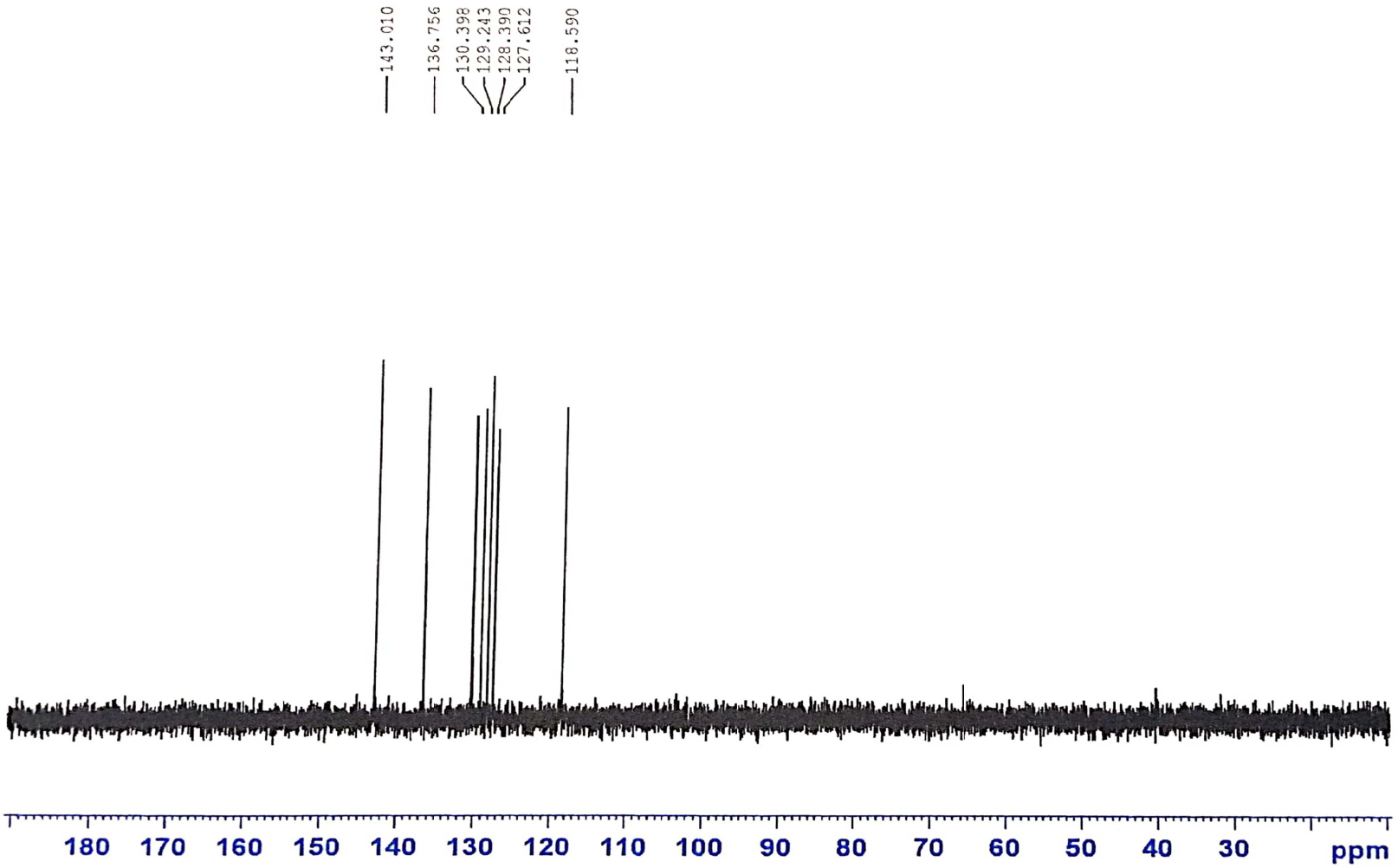


Figure 3.20 DEPT-135 Spectrum of compound 2a

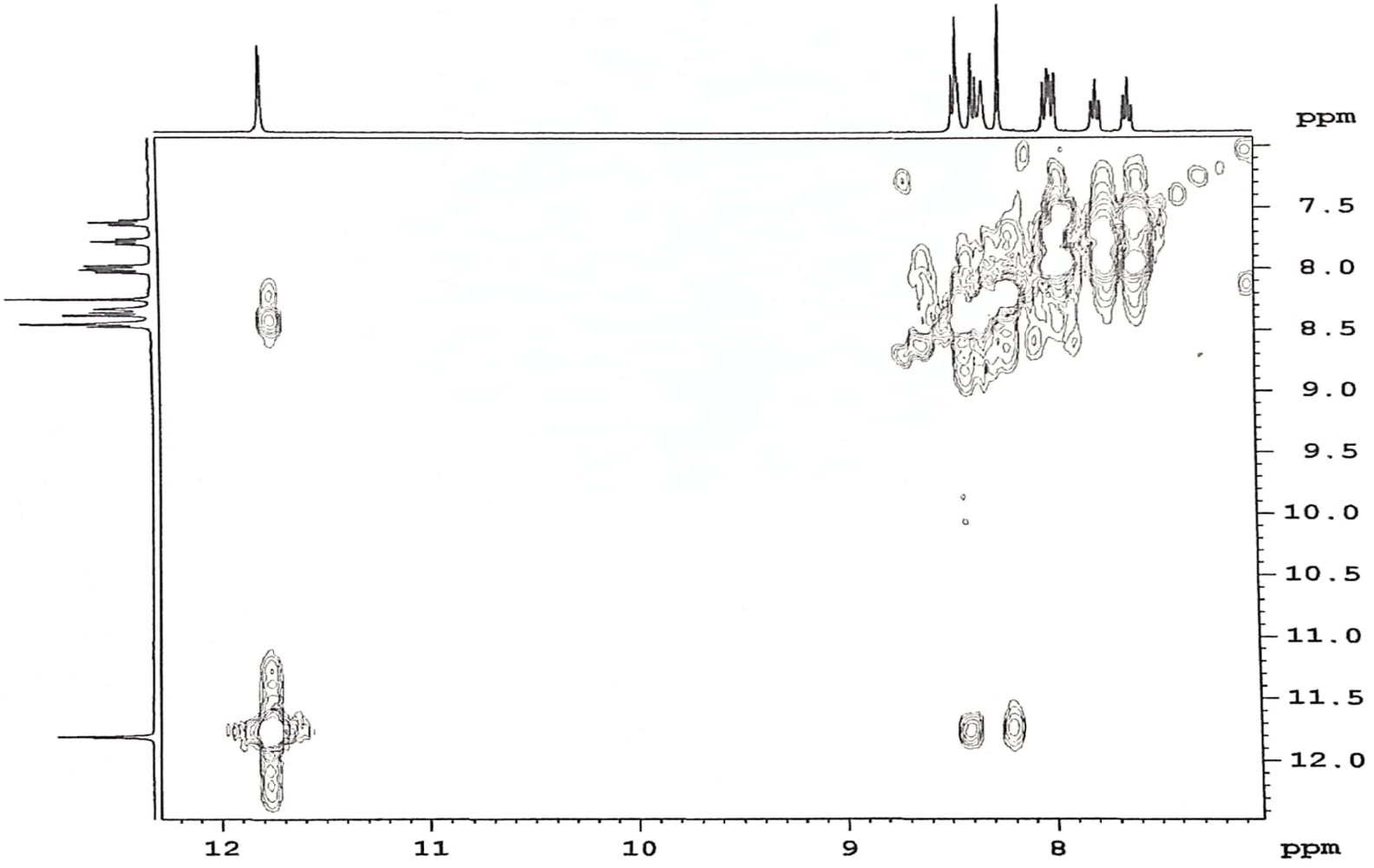


Figure 3.21 2D COSY Spectrum of compound 2a

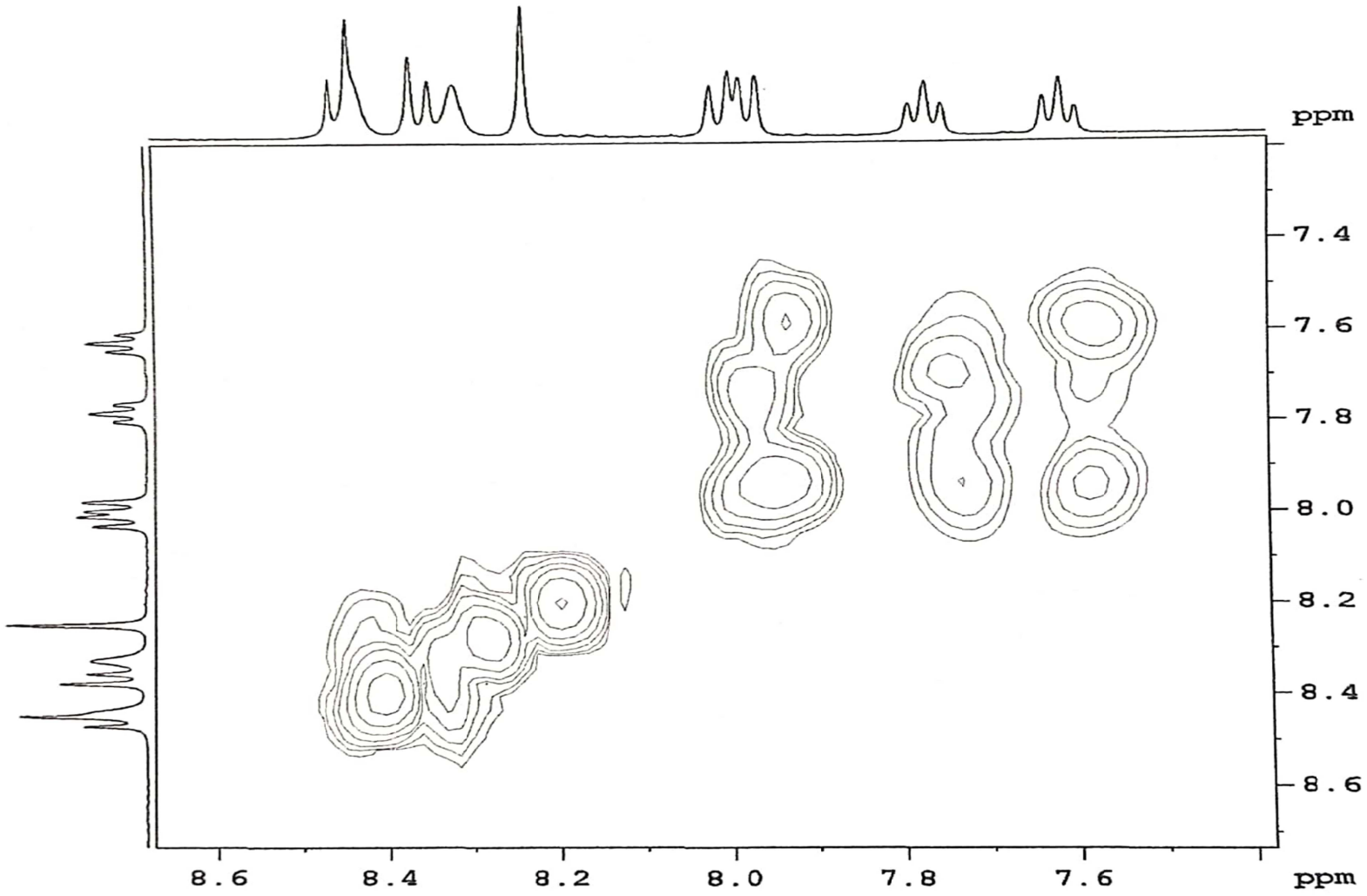


Figure 3.21a 2D COSY Spectrum(Expd.) of compound 2a

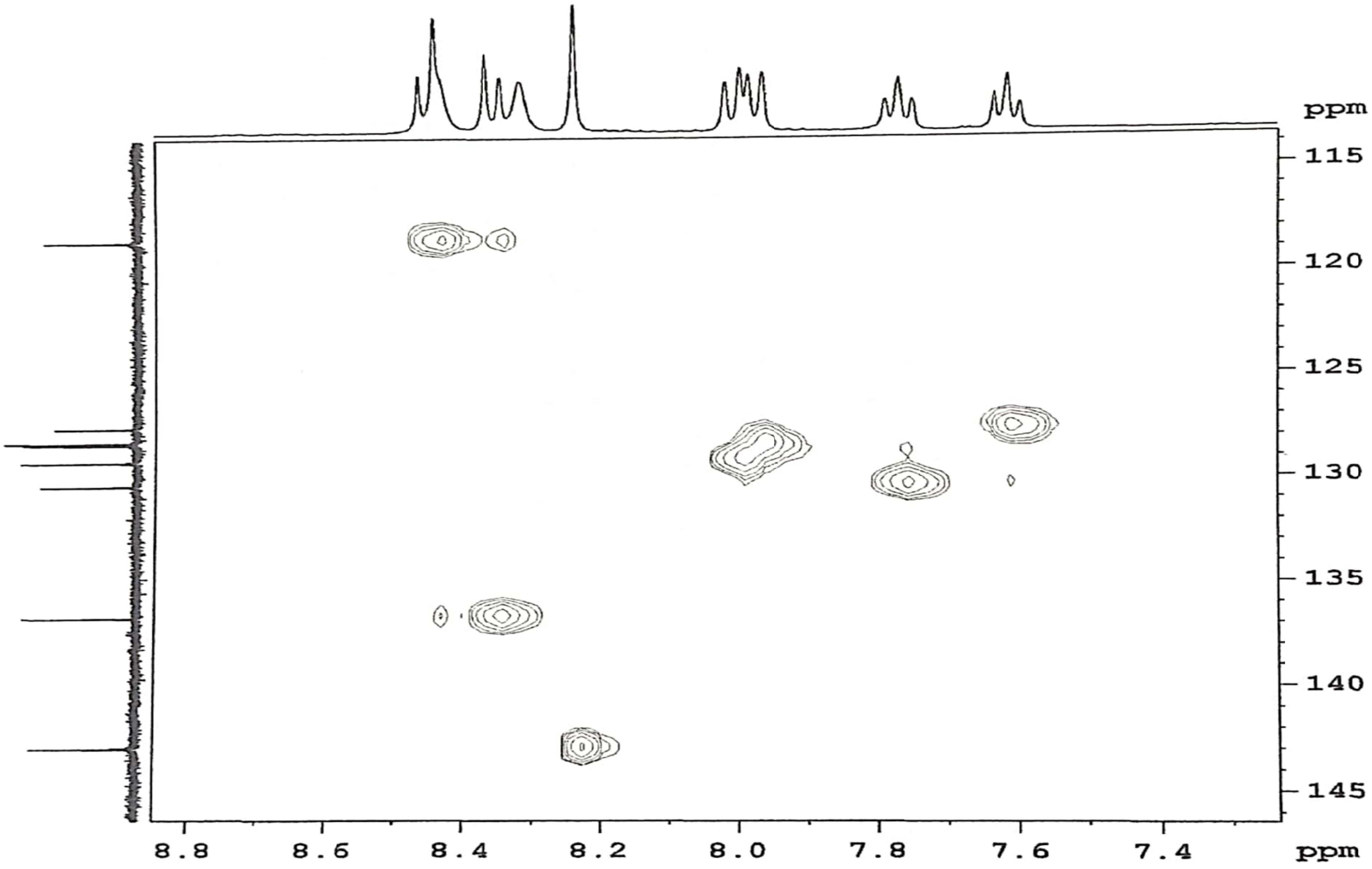


Figure 3.22 HSQC Spectrum of compound 2a

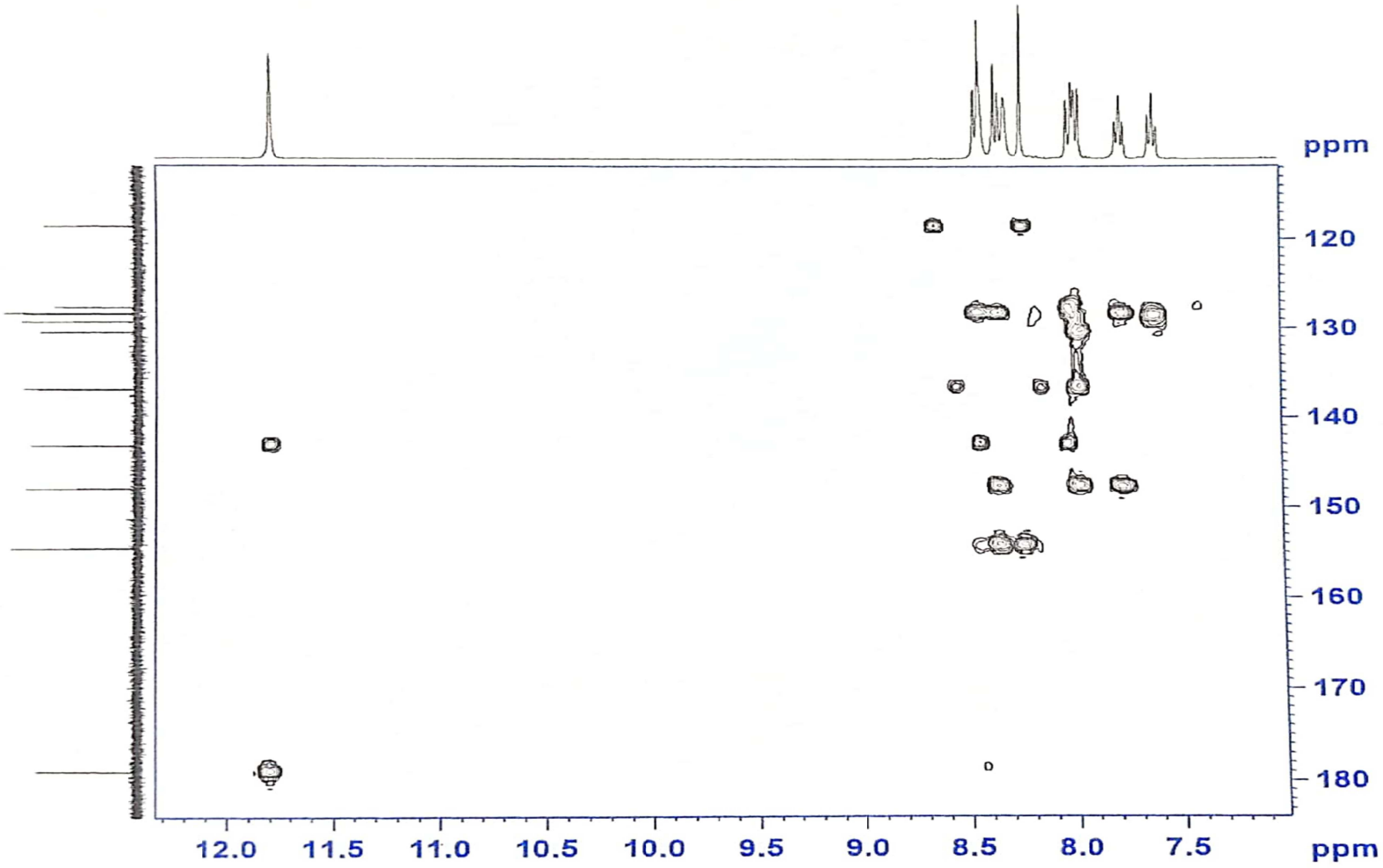


Figure 3.23 HMBC Spectrum of compound 2a

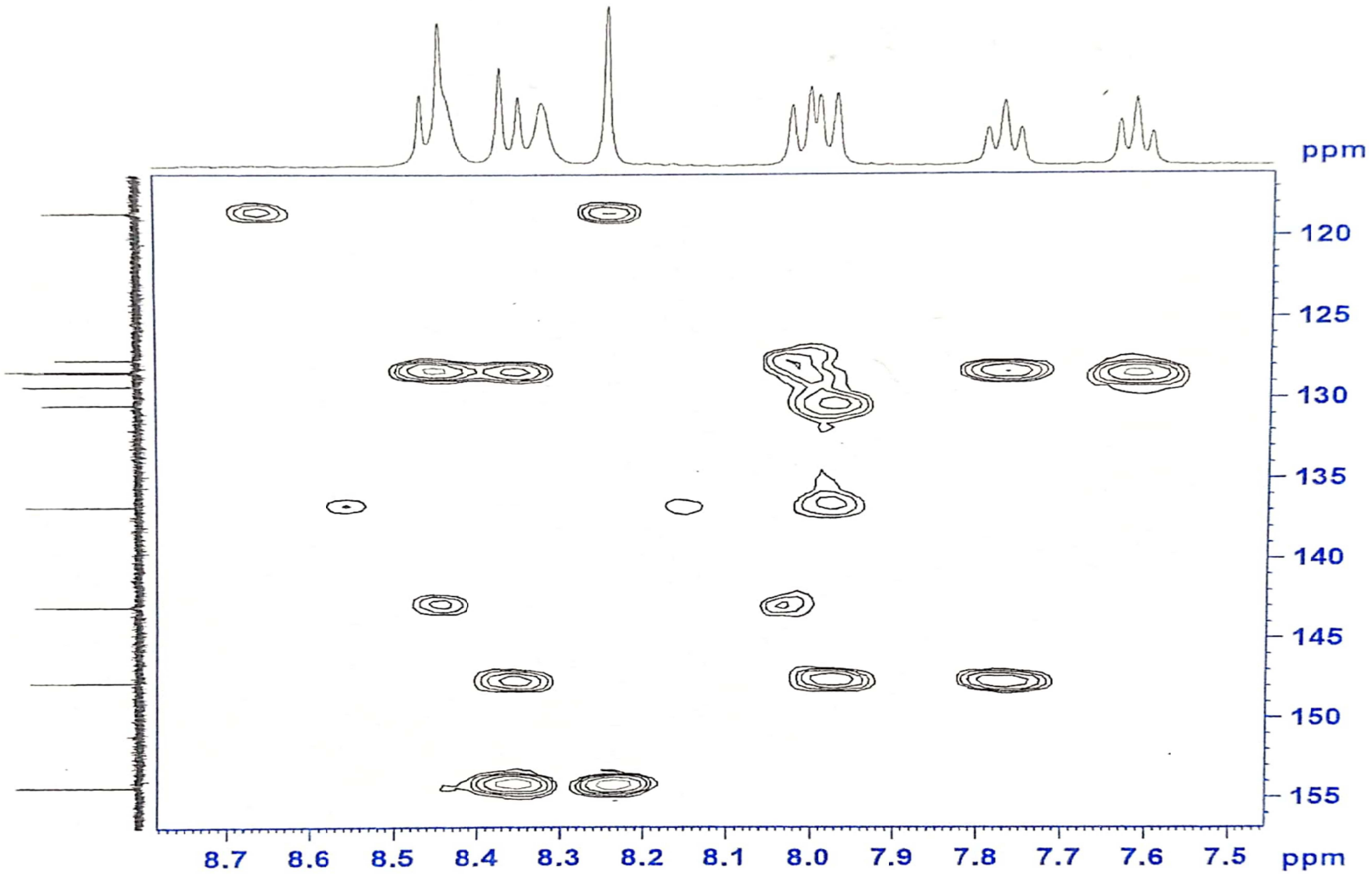


Figure 3.23a HMBC Spectrum(Expd.) of compound 2a

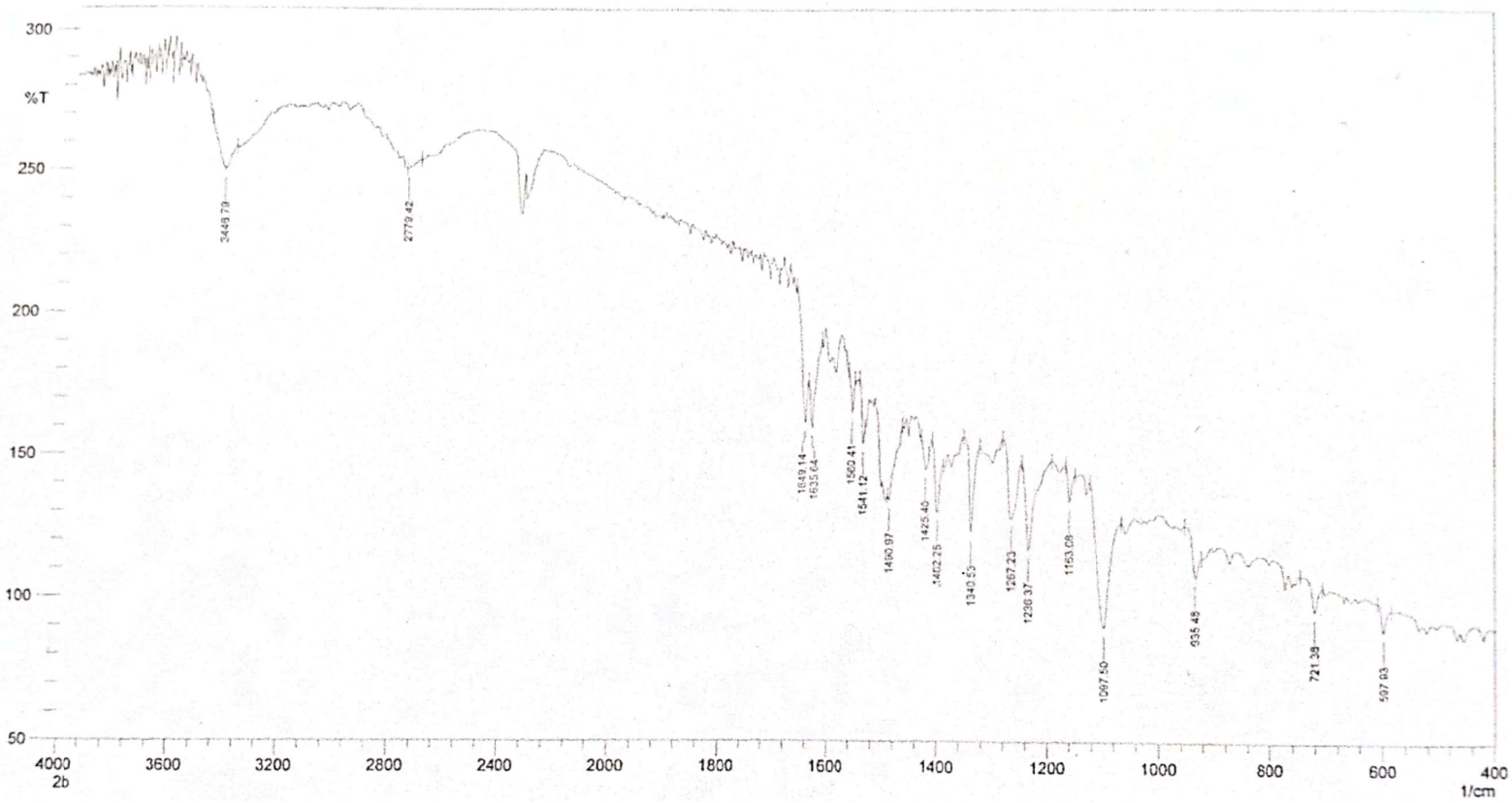


Figure 3.24 IR Spectrum of compound 2a

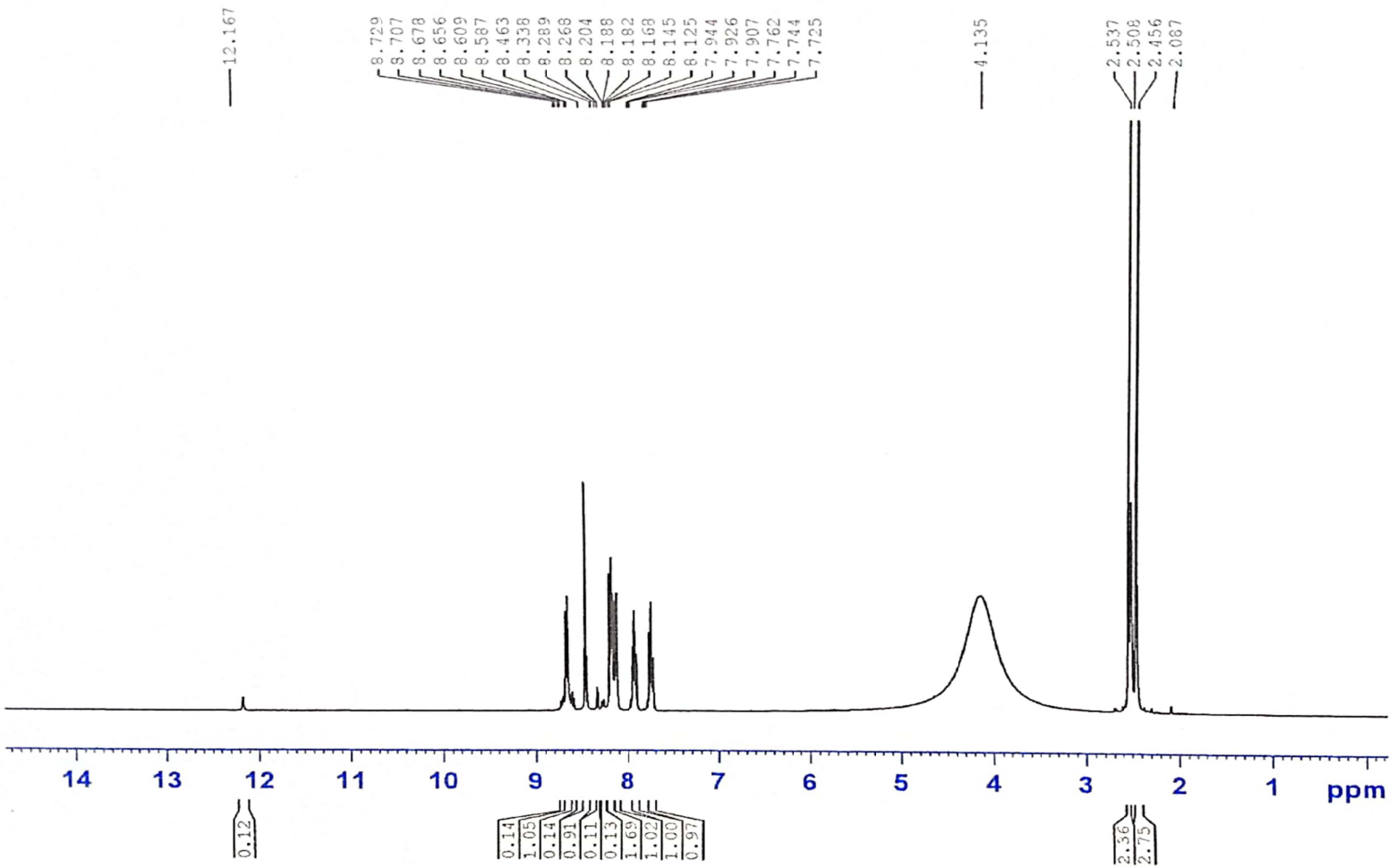


Figure 3.25 ^{1}H NMR Spectrum of compound 2b

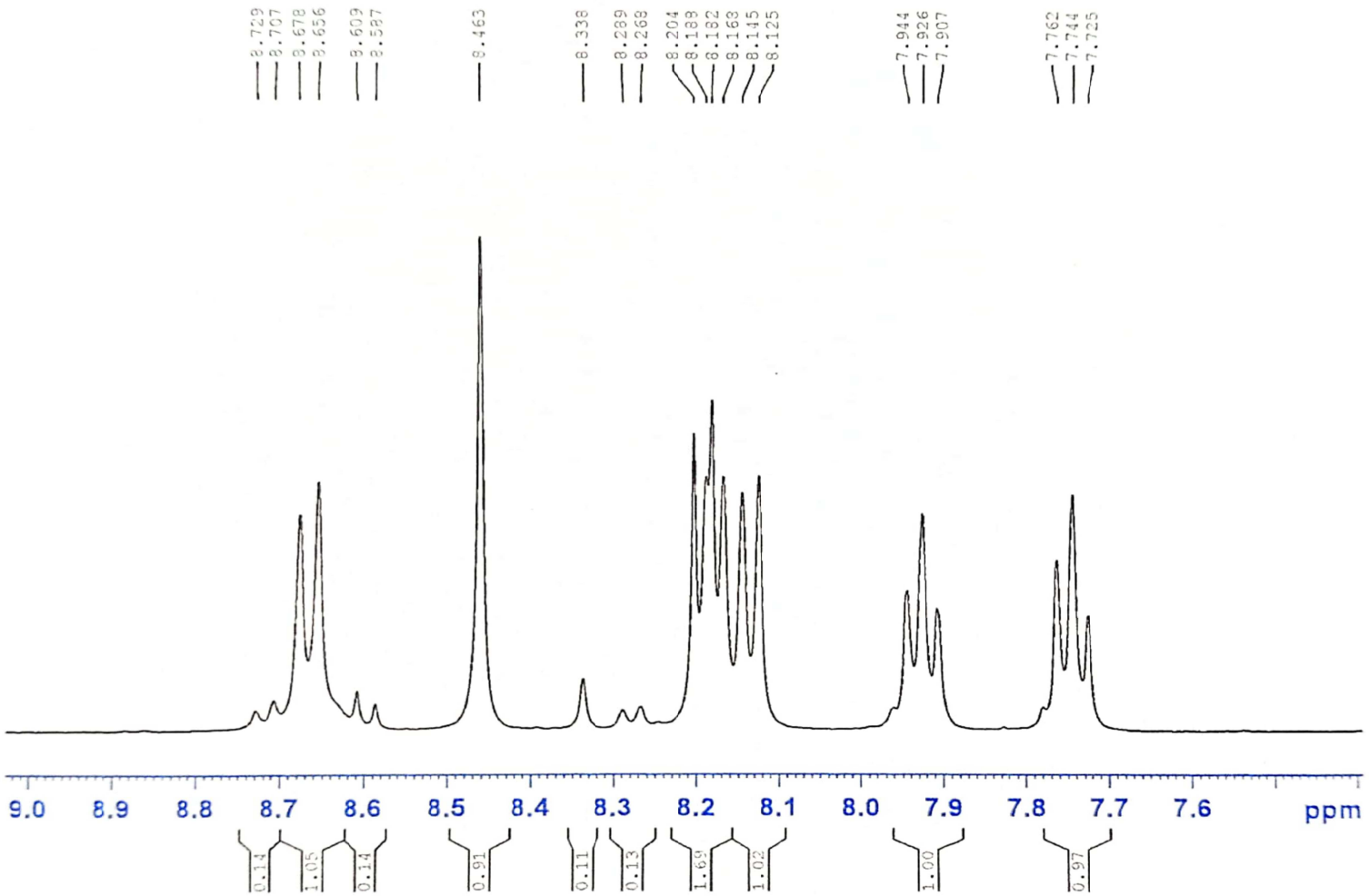


Figure 3.25a ^{1}H NMR Spectrum(Expd.) of compound 2b

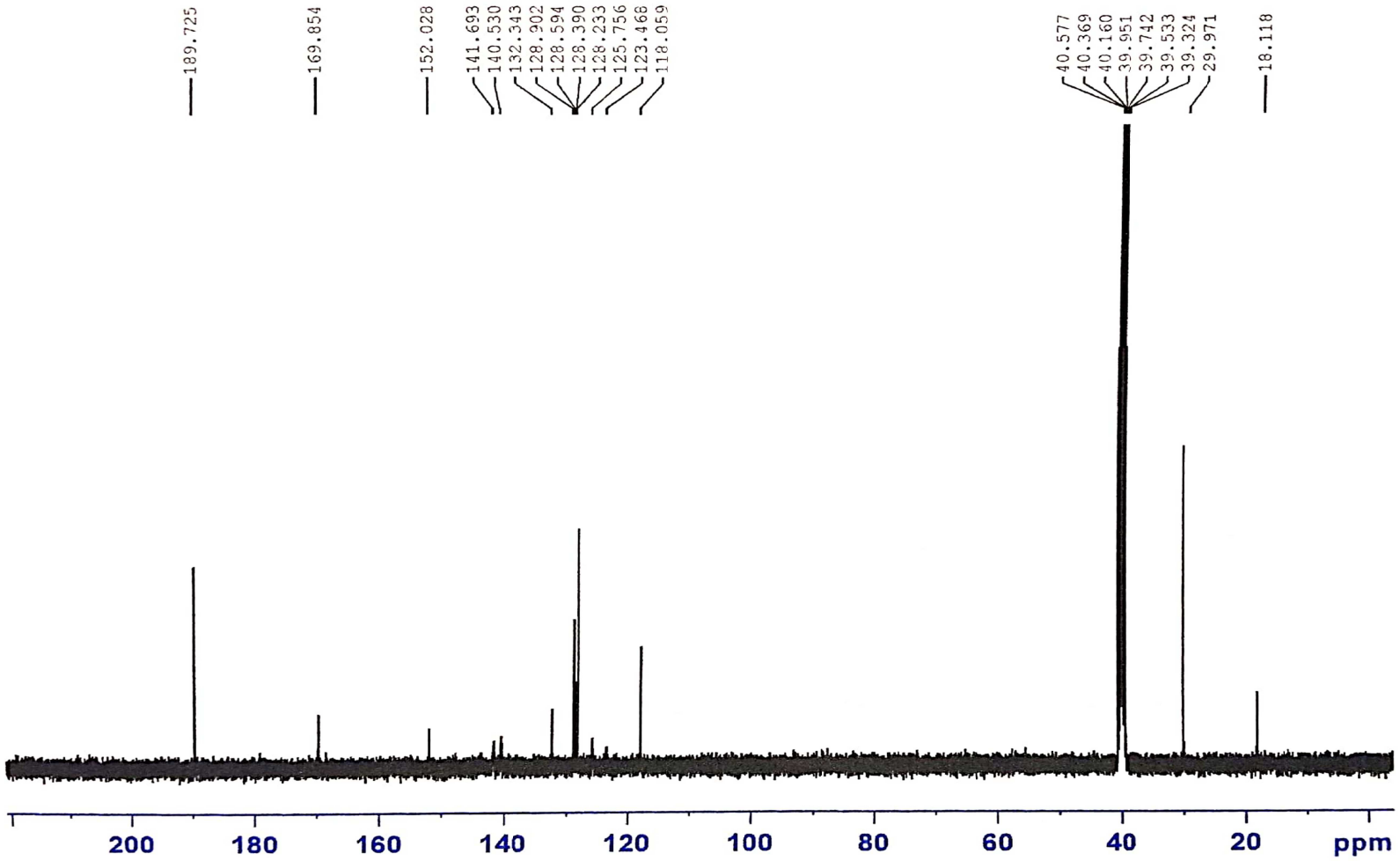


Figure 3.26 ^{13}C NMR Spectrum of compound 2b

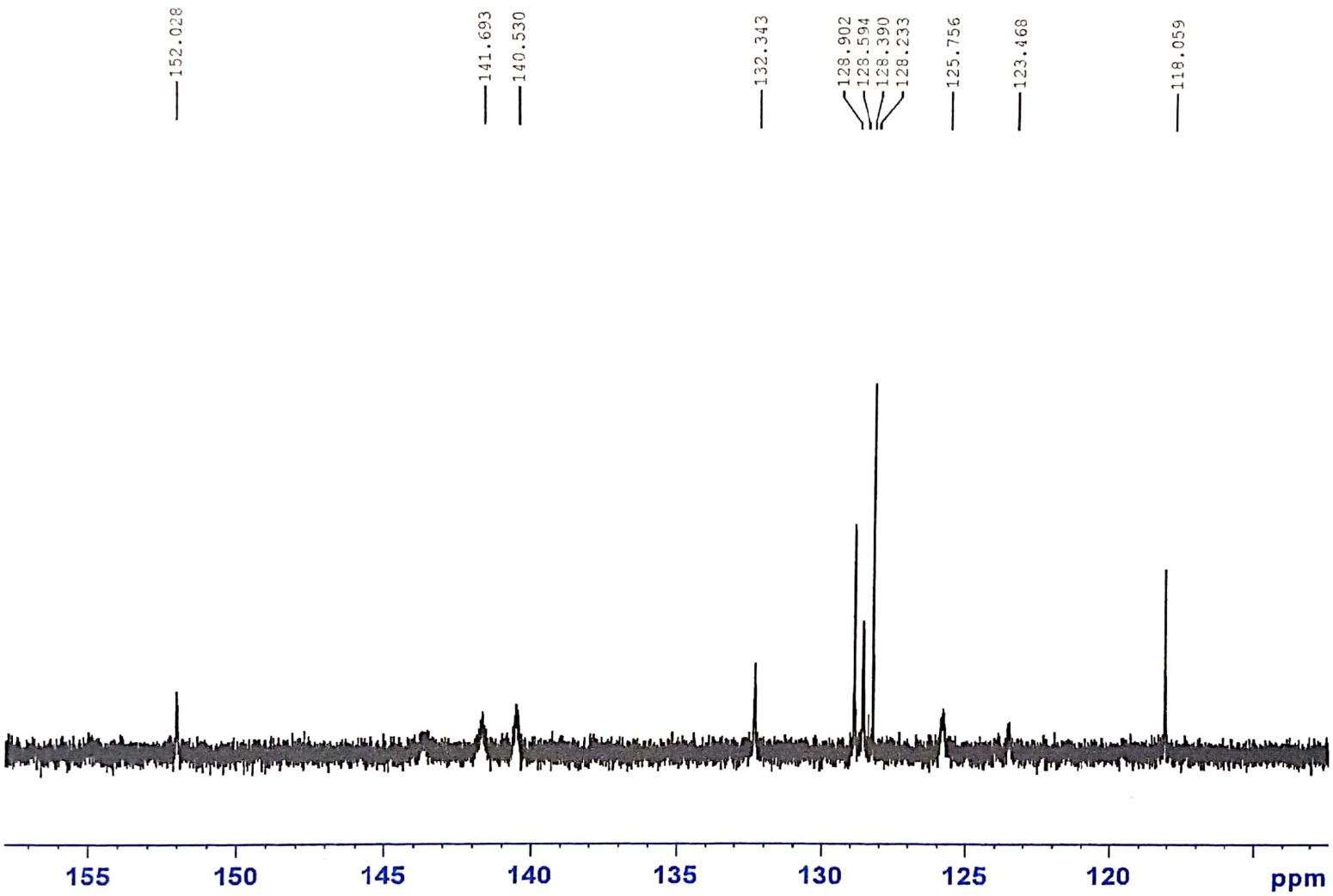


Figure 3.26a ^{13}C NMR Spectrum(Expd.) of compound 2b

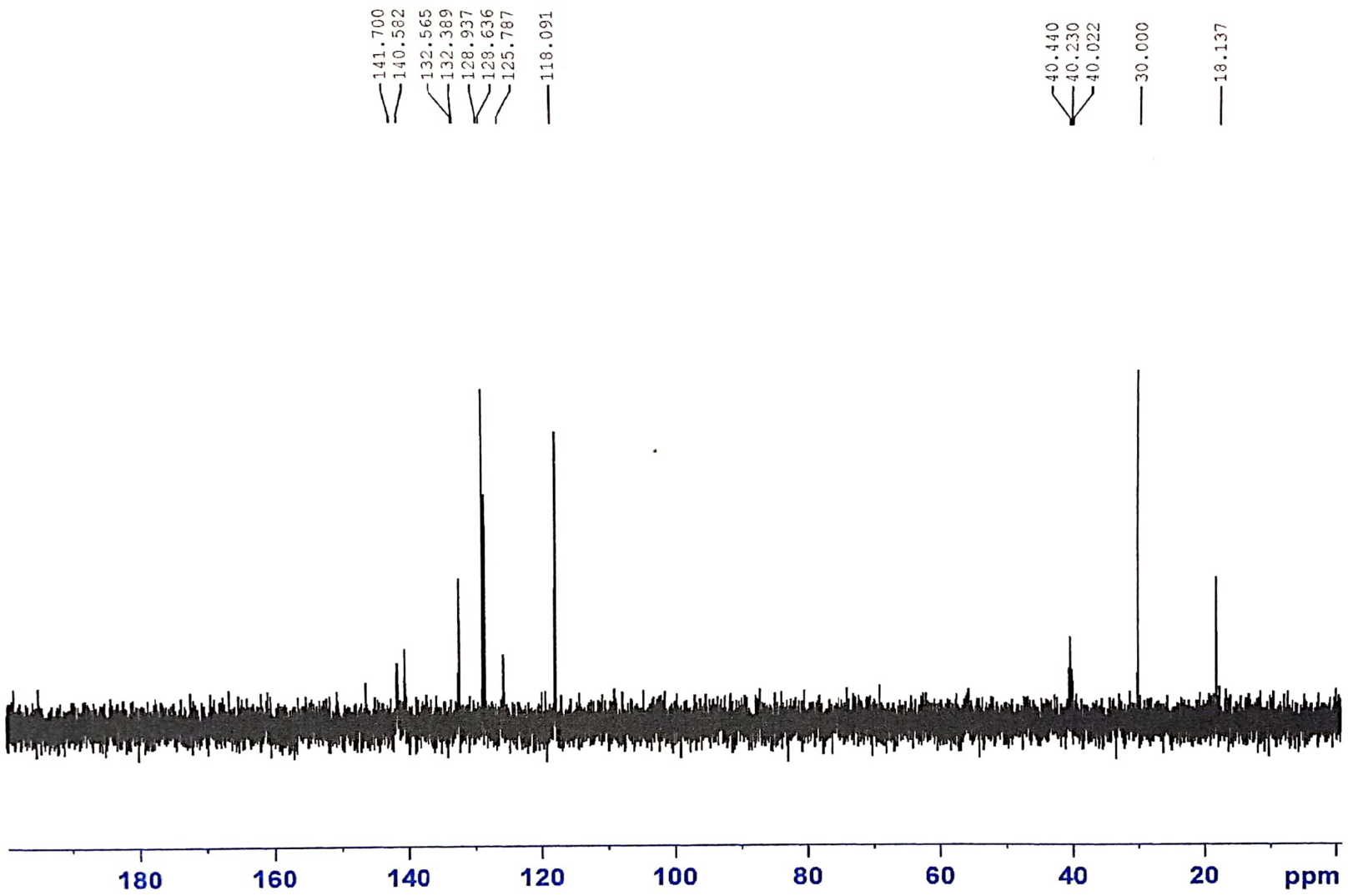


Figure 3.27 DEPT-135 Spectrum of compound 2b

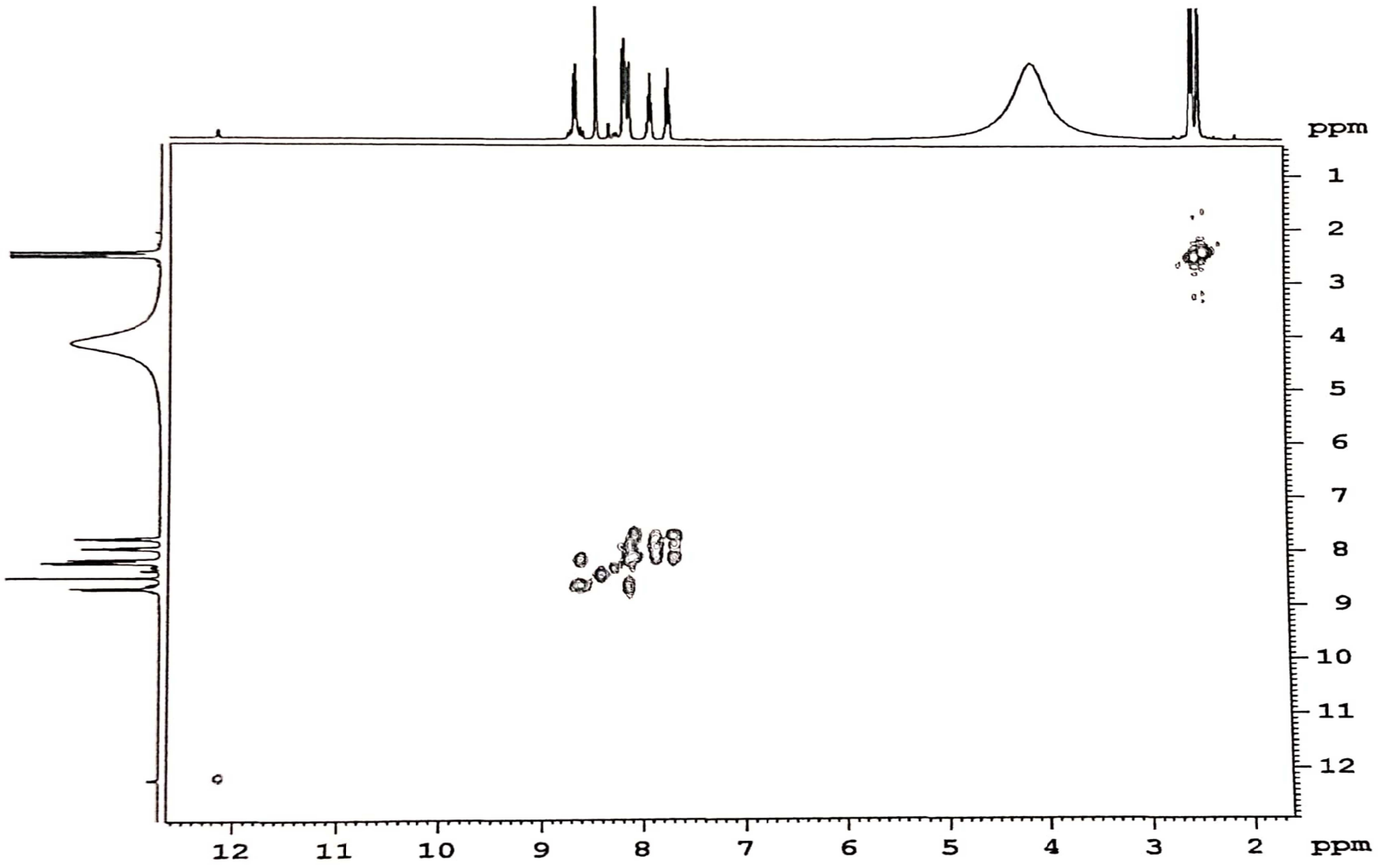


Figure 3.28 2D COSY Spectrum of compound 2b

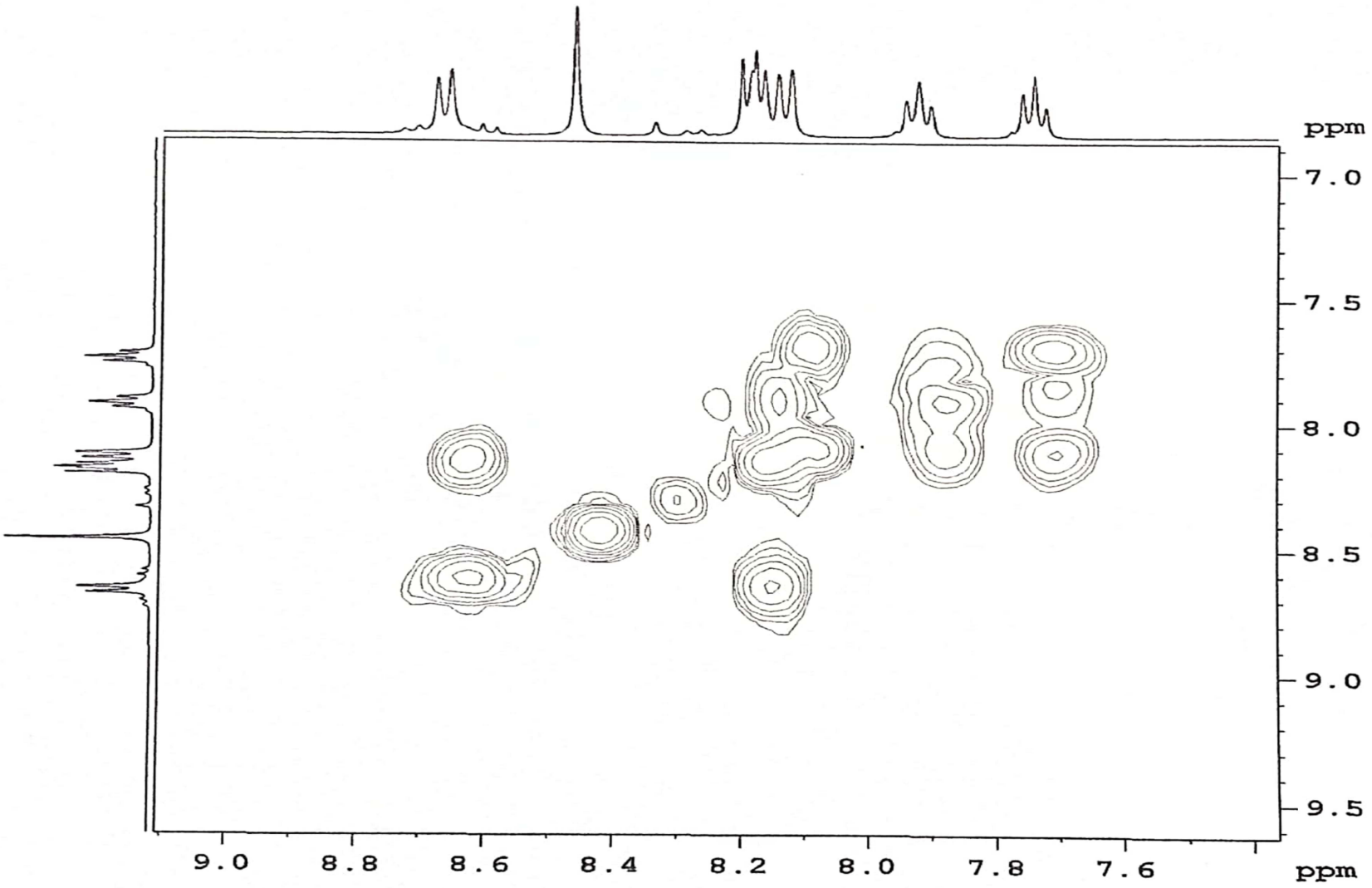


Figure 3.28a 2D COSY Spectrum(Expd.) of compound 2b

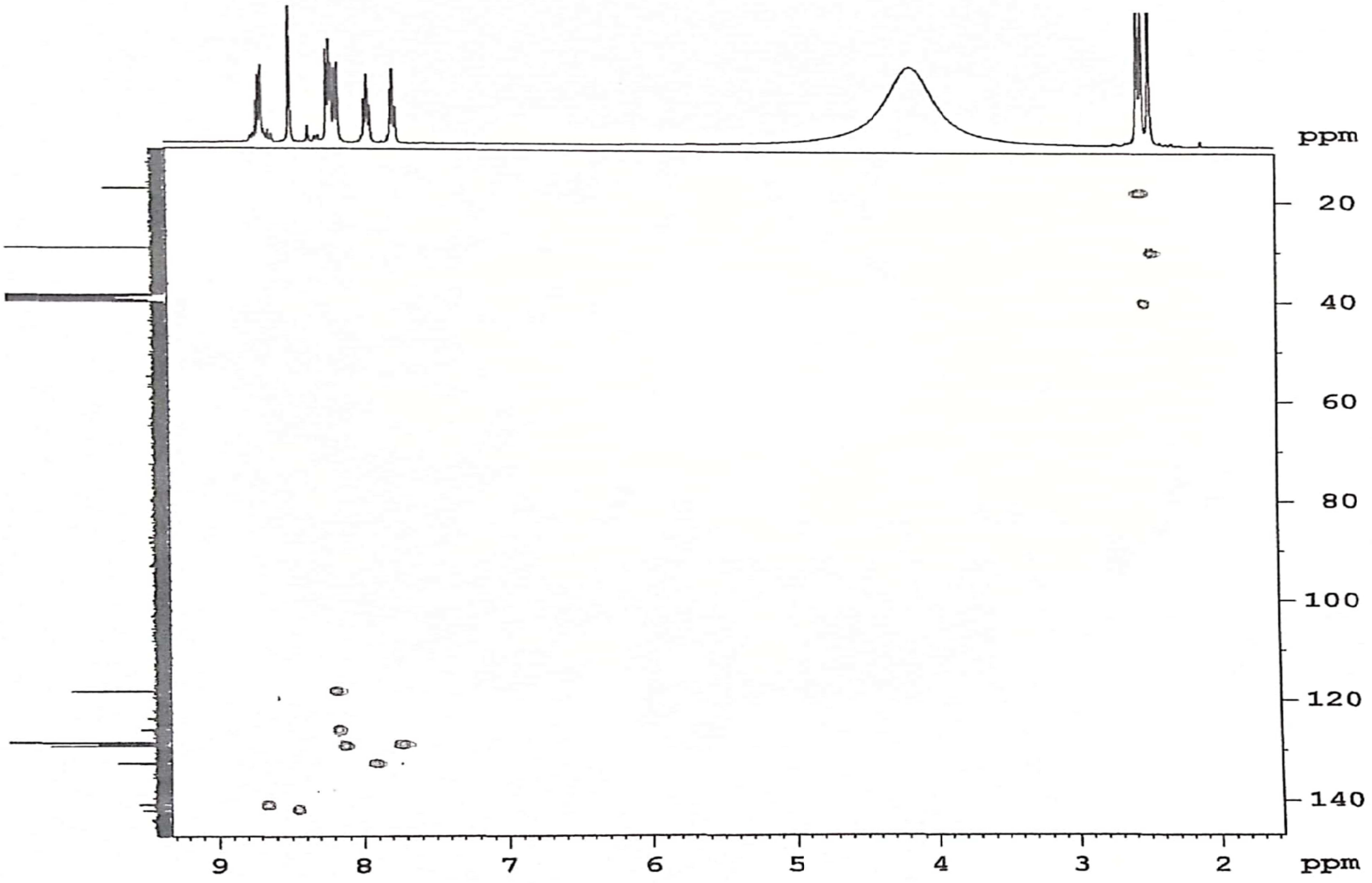


Figure 3.29 HSQC Spectrum of compound 2b

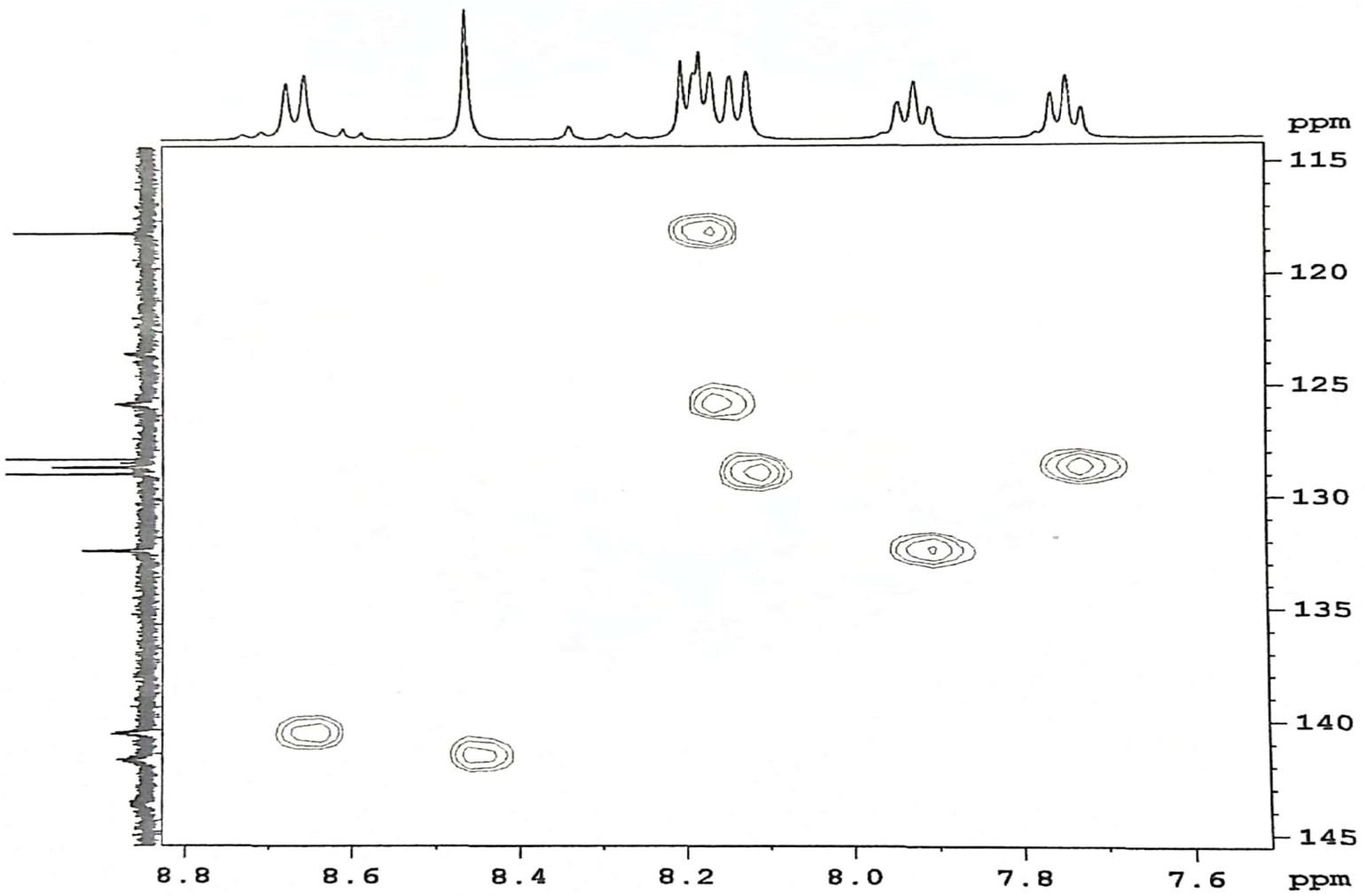


Figure 3.29a HSQC Spectrum(Expd.) of compound 2b

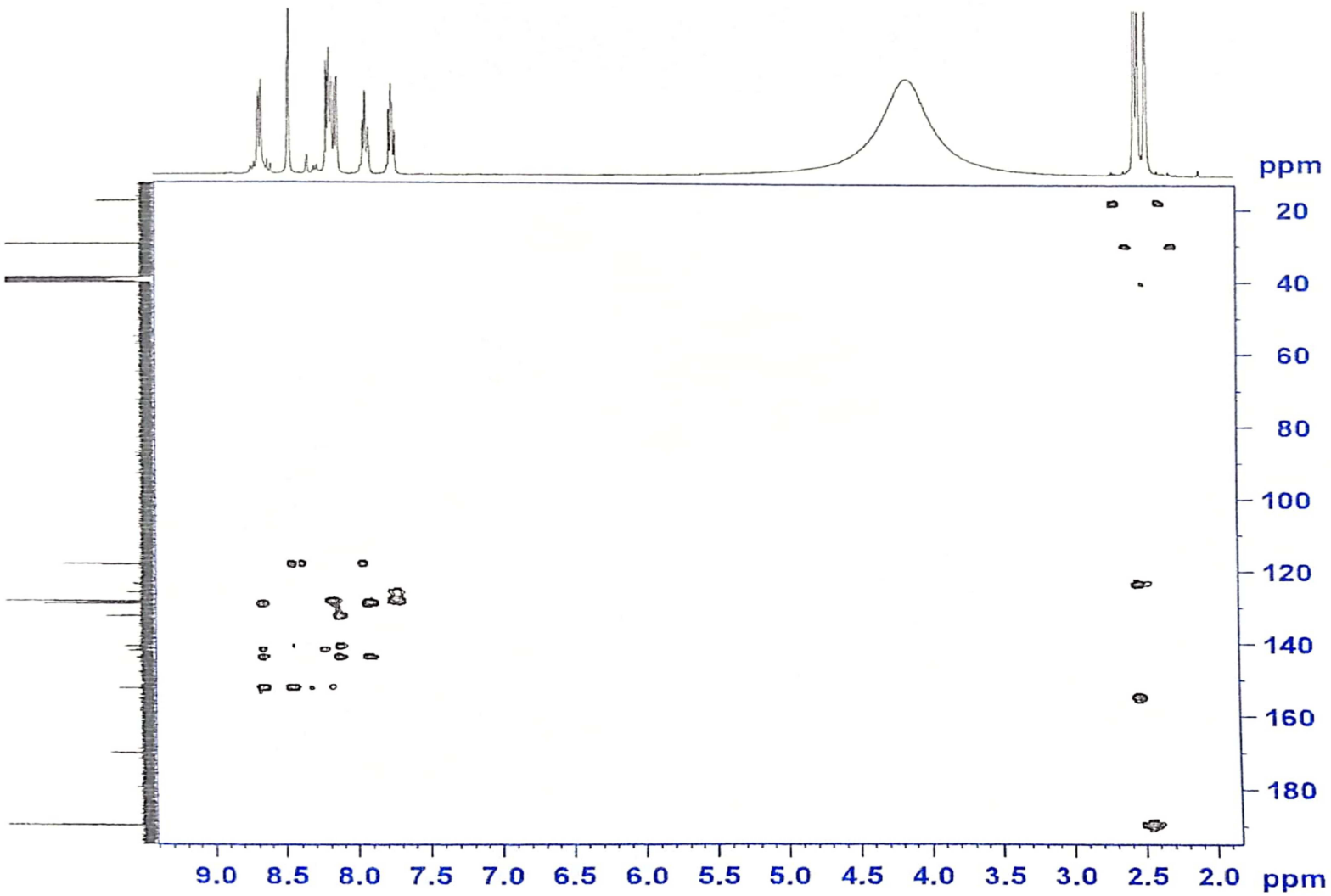


Figure 3.30 HMBC Spectrum of compound 2b

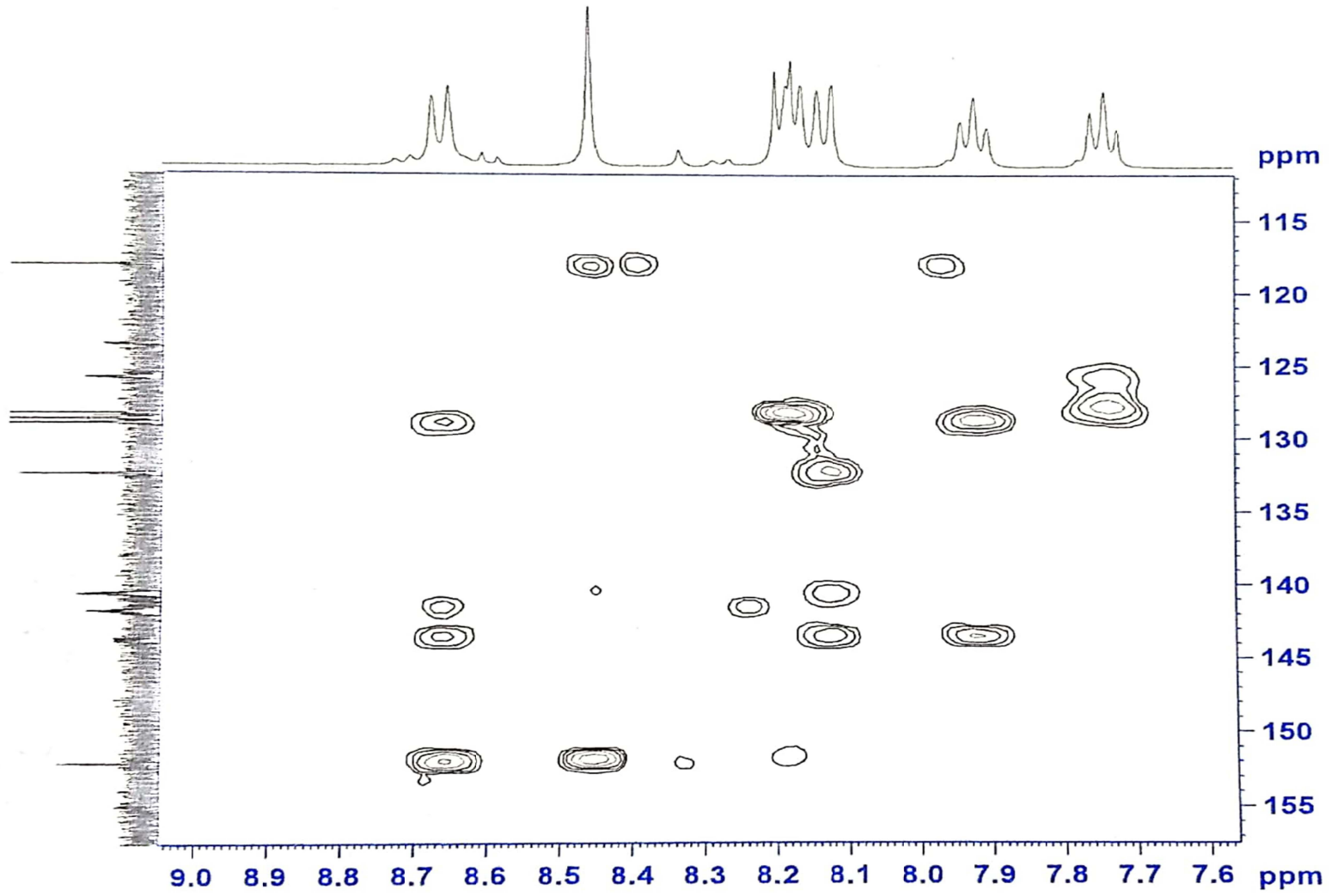


Figure 3.30a HMBC Spectrum (Expd.)of compound 2b

3.3 Characterization of compound 3a and 3b:

Compound **3a** (388 mg) was yellow amorphous solid, m.p 209-212°C. The IR spectra of compound **3a** showed sharp absorptions at $\bar{\upsilon}_{max}$ 3392 $cm^{-1}$for N-H stretching and 1602 cm^{-1} for N-H bending. The ^{13}C NMR spectrum of compound **3a** showed 11 carbons are present in the molecule (Table 3.3). The ^{13}C DEPT spectrum of **3a** revealed that there is no methylene carbons present in the molecule. The absorption positions of all 11 carbons in ^{13}C NMR spectrum are given in Table 3.3. The ^{1}H NMR spectrum of **2a** showed the presence of 5 aromatic protons at δ 8.51 (1H, s, H4'), 7.94 (1H, d, *J* = 8.4 Hz, H5'), 7.70 (1H, t, *J* = 6.8 Hz, H6'), 7.84 (1H, t, *J* = 7.2 Hz, H7') and 7.99 (1H, d, *J* = 8.0 Hz, H8'). The absorption positions of one olifinic proton attached to carbon H-C=N is at δ 8.27 (1H, s, H-C=N), one NH proton at δ 11.81s and two NH_2 protons at δ 8.47 are appeared in ^{1}H NMR spectrum. The important homo-nuclear (H-H) correlations in 2D COSY spectrum and hetero-nuclear (H-C) correlations in HMBC spectrum are presented in Figure 3.31 and Table 3.3. On the basis of IR, ^{1}H NMR and ^{13}C NMR spectra, structure **5** was confirm to the compound **3a**. Compound **3a** is thus characterized as **2-(2'-chloro-quinolinyl-3'-methylene) hydrazine carbathioamide (5).**

Compound **3b** (302 mg) was brown amorphous solid, m.p 232-235°C. The IR spectra of compound **3b** showed sharp absorptions for N-H stretching at $\bar{\upsilon}_{max}$ 3439 $cm^{-1}$and for N-H bending at $\bar{\upsilon}_{max}$ 1616 cm^{-1}. The ^{13}C NMR spectrum of compound **3b** showed the presence of 16 carbons in the molecule (Table 3.3). The ^{13}C DEPT spectrum of **3b** revealed that there is no methylene carbons present in the molecule. The absorption positions of all 16 carbons in ^{13}C NMR spectrum are given in Table 3.3. The ^{1}H NMR spectrum of **3b** showed the presence of 5 aromatic protons at δ 8.50 (1H, s, H4'), 7.84 (1H, d, *J* = 8.4 Hz, H5'), 7.20 (1H, t, *J* = 6.8 Hz, H6'), 7.32 (1H, t, *J* = 7.2 Hz, H7') and 7.52 (1H, d, *J* = 8.0 Hz, H8'). in the molecule. The absorption positions of one olifinic proton attached to carbon H-C=N appeared at δ 8.35 (1H, s, H-C=N) and one NH proton appeared at δ 12.06 (1H, s, H-N) and two sets of methyl protons appeared at δ 2.50 (3H, s, CO-CH_3) and 2.42 (3H, s, CH_3). The important homo-nuclear (H-H) correlations in 2D COSY spectrum and hetero-nuclear (H-C) correlations in HMBC spectrum are presented in Figure 3.31 and Table 3.3. On the basis of IR, ^{1}H NMR and ^{13}C NMR spectra, structure 6 was confirm to the compound **3b**. Compound **6** is thus characterized as **5''-aceto-4''-methyl-2''-(2-(2'-chloro-quinolinyl-3'-methylene) hydrazine) thiazole (6).**

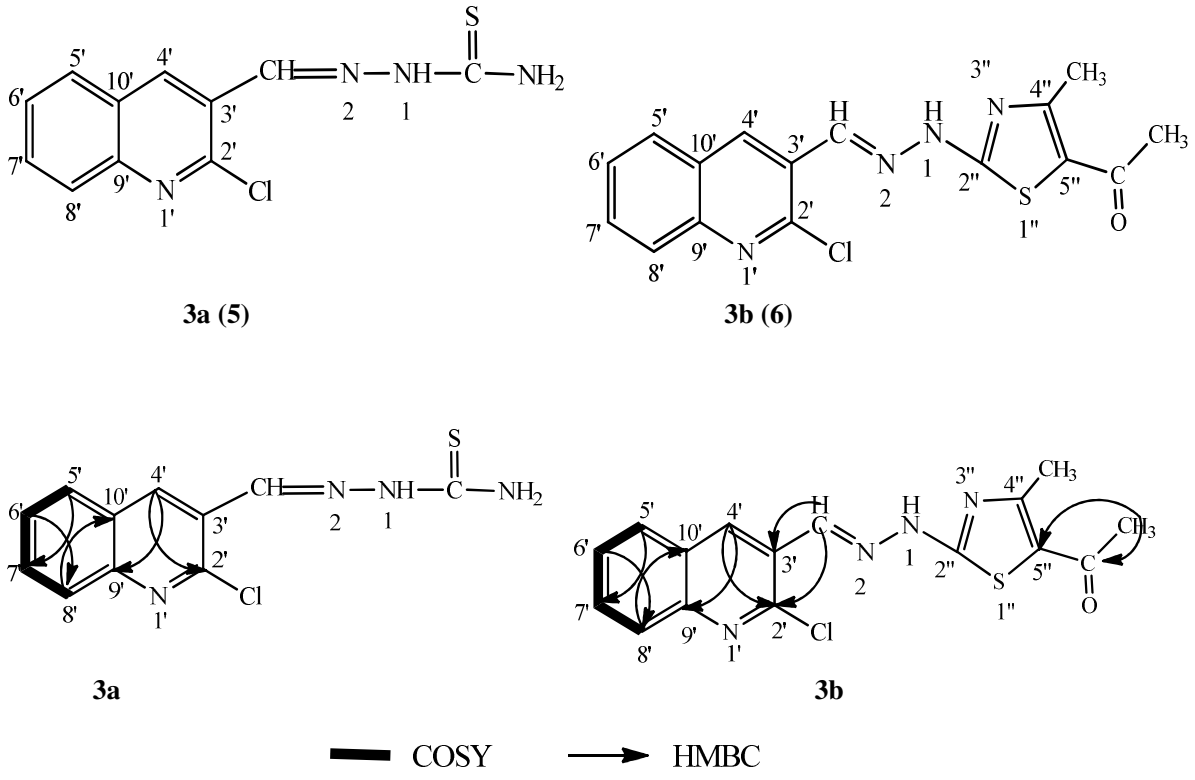


Figure 3.31: Important COSY and HMBC correlations of compound 3a and 3b

Table 3.3: ^{13}C NMR and ^{1}H NMR data for compounds 3a and 3b (DMSO, δ, ppm, J/Hz)*

C atom	^{13}C, δ	^{1}H, δ	COSY	HMBC	^{13}C, δ	^{1}H, δ	COSY	HMBC
2'	148.8				147.5			
3'	126.6				125.6			
4'	137.2	8.51,s		C2',3'	136.1	850,s		C2',3'
5'	128.3	7.94,d, J=8.4	H6'	C9',10'	128.1	7.84,d,J=8.4	H6'	C7',9'
6'	128.2	7.70,t,J=6.8	H5',7'	C8',10'	128.0	7.20,t,J=6.8	H5',7'	C8',10'
7'	132.0	7.84,t, J=7.2	H6',8'	C5',9'	131.3	7.32,t,J=7.2	H6',8'	C5',9'
8'	128.9	7.99,d,J=8.0	H7'	C9',10'	127.8	7.52,d,J=8.0	H7'	C6',10'
9'	147.3				146.9			
10'	127.4				127.7			
CH=N	136.5	8.27,S		C2',4'	136.3	8.35,s		C2',4'
2"					178.2			
C=S	178.8							
4"					127.6			
5"					168.5			
C=O					189.1			
CO-CH_3					29.3	2.50,s		C=O
CH_3					19.3	2.42,s		
NH_2		8.47,s						
NH		11.81,s				12.06,s		

*The assignment was based on DEPT (135), COSY, HSQC and HMBC experiments

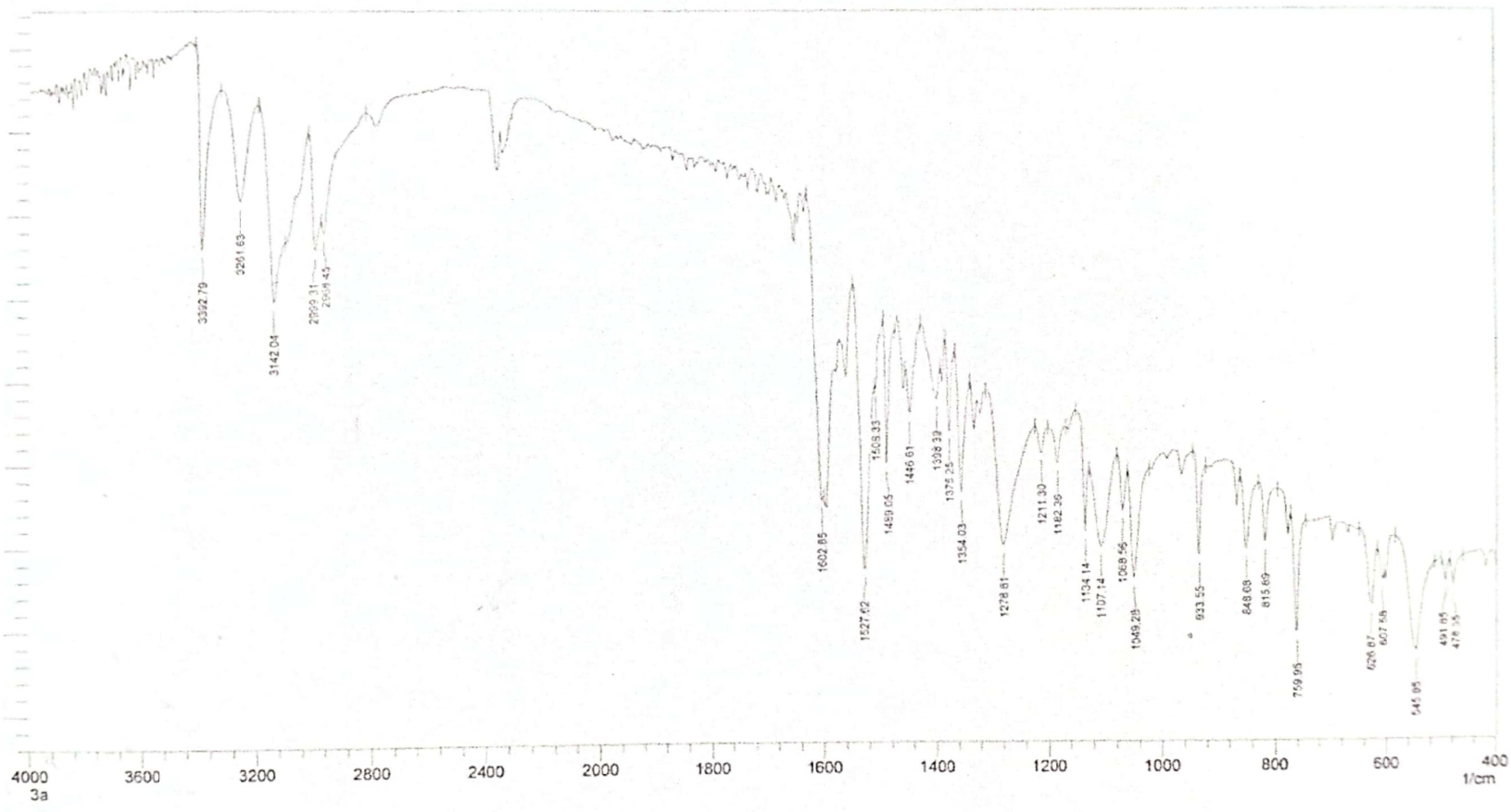


Figure 3.32 IR Spectrum of compound 3a

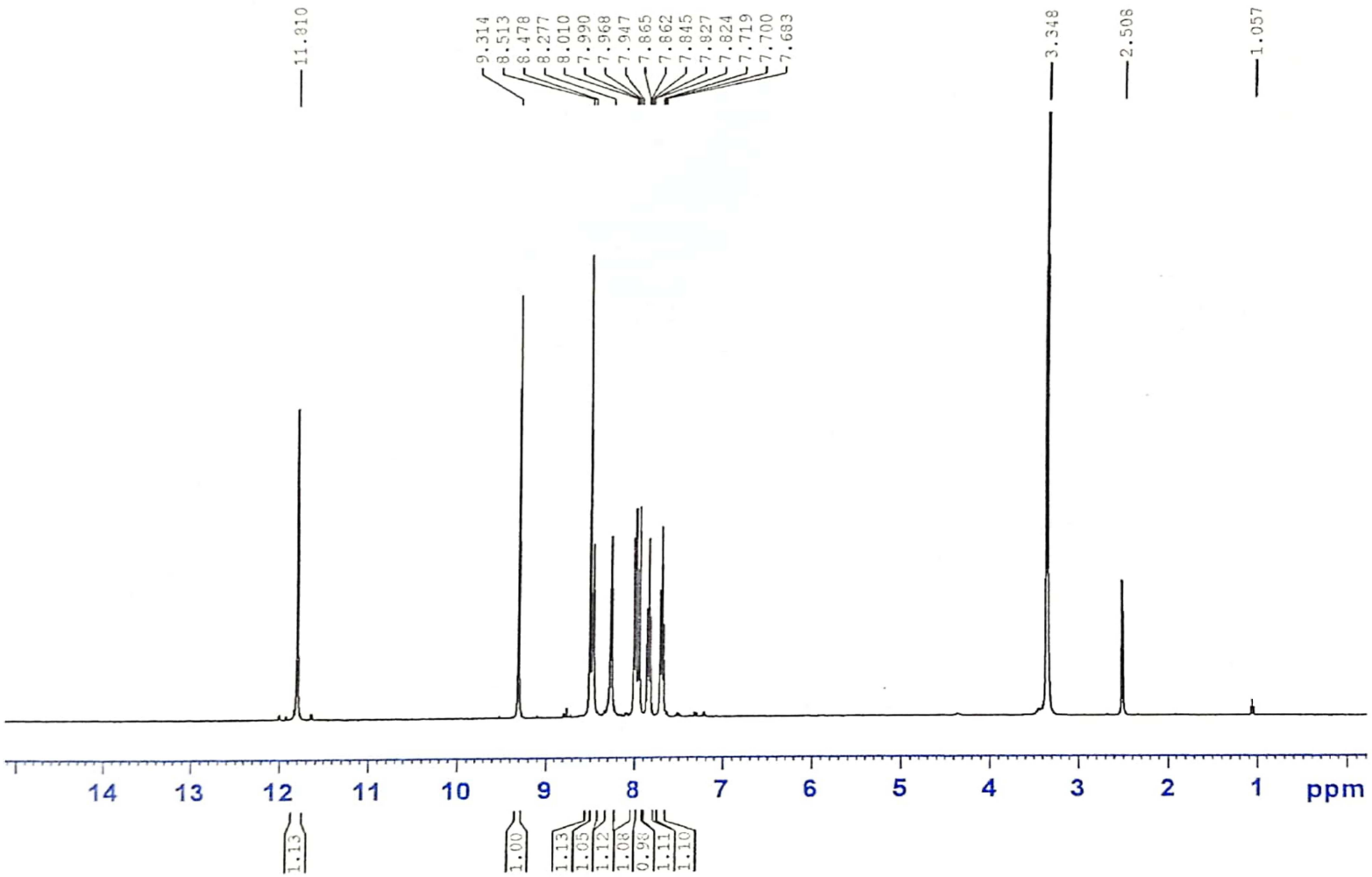


Figure 3.33 ^{1}H NMR Spectrum of compound 3a

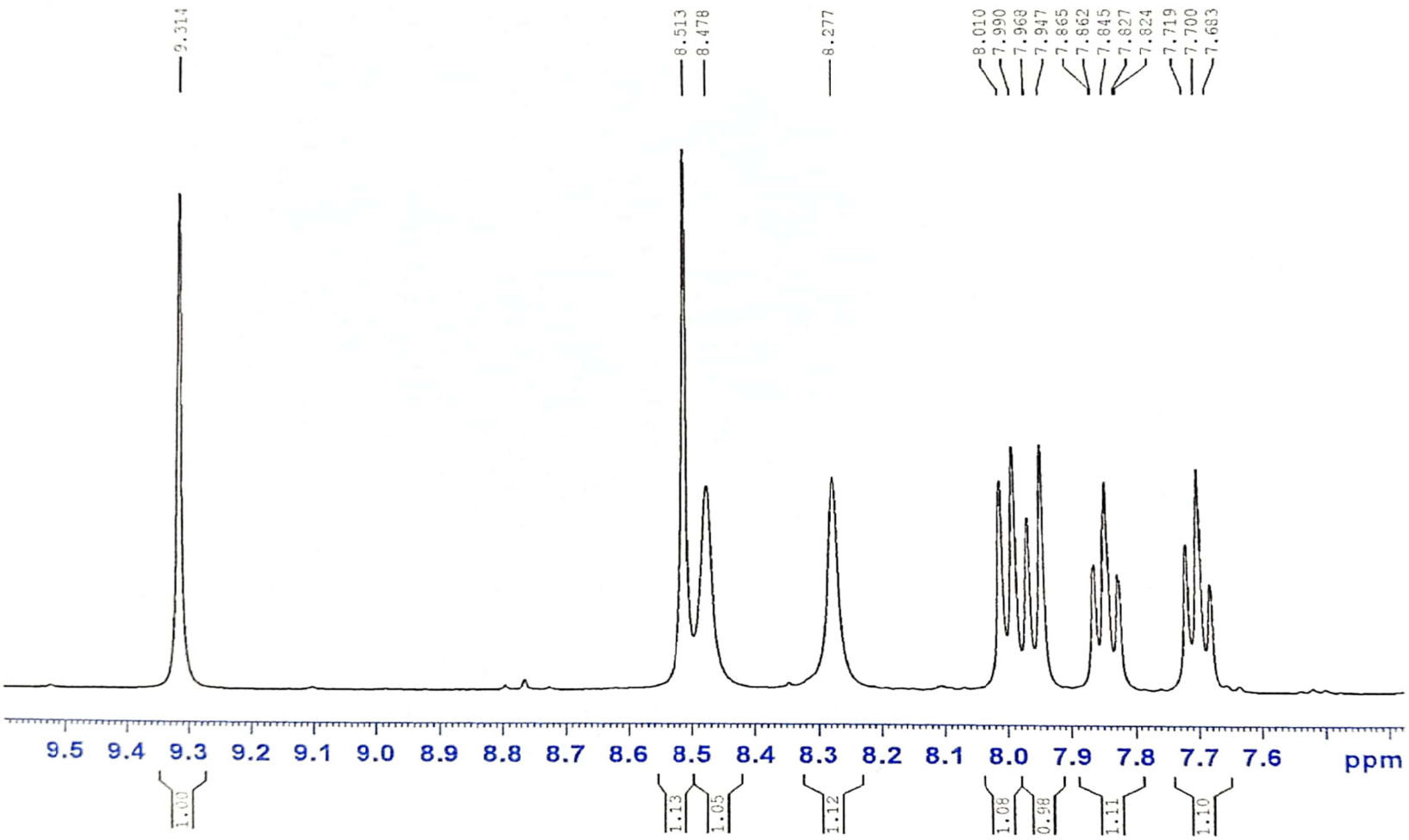


Figure 3.33a ^{1}H NMR Spectrum (Expd.) of compound 3a

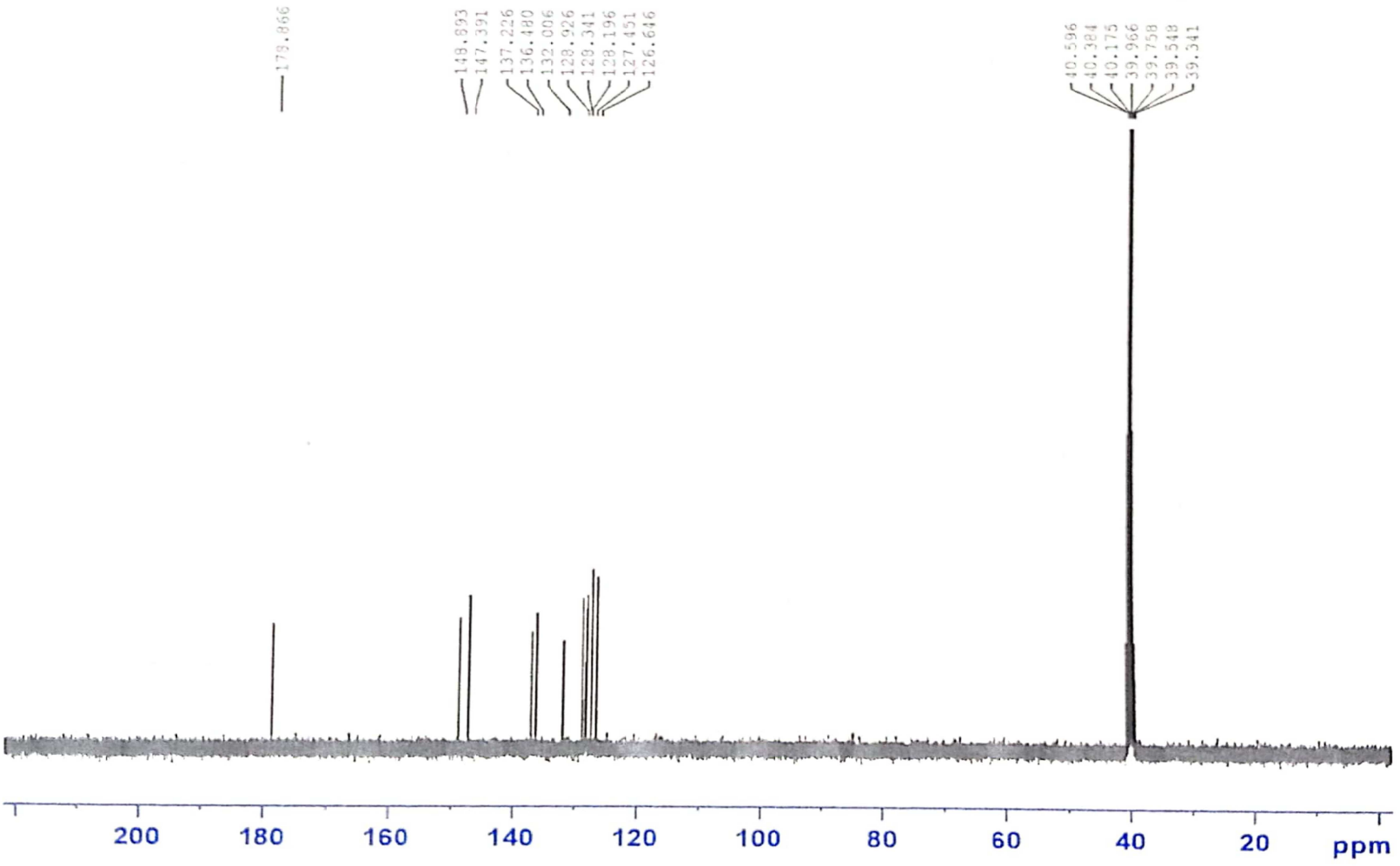


Figure 3.34 ^{13}C NMR Spectrum of compound 3a

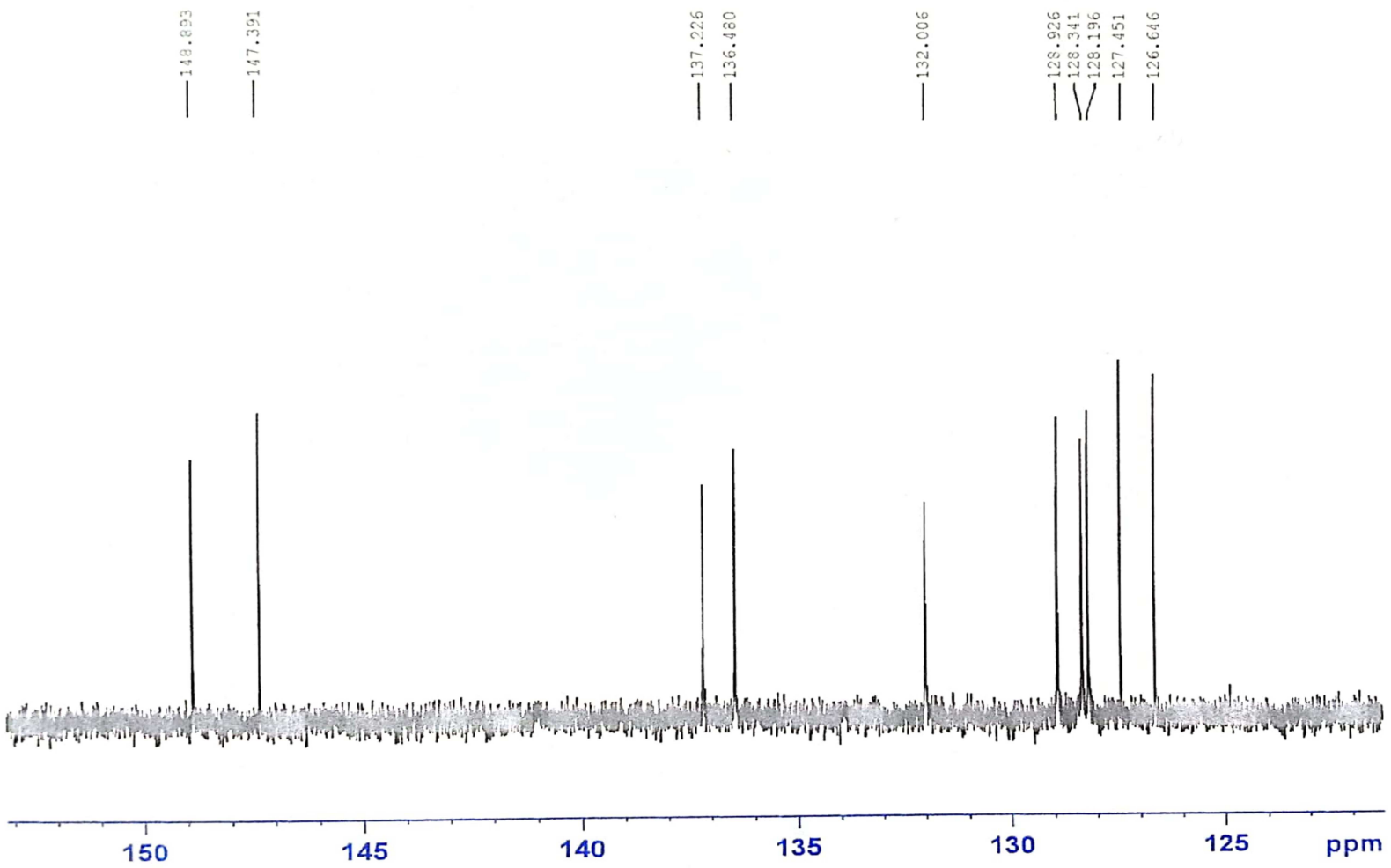


Figure 3.354a ^{13}C NMR Spectrum (Expd.) of compound 3a

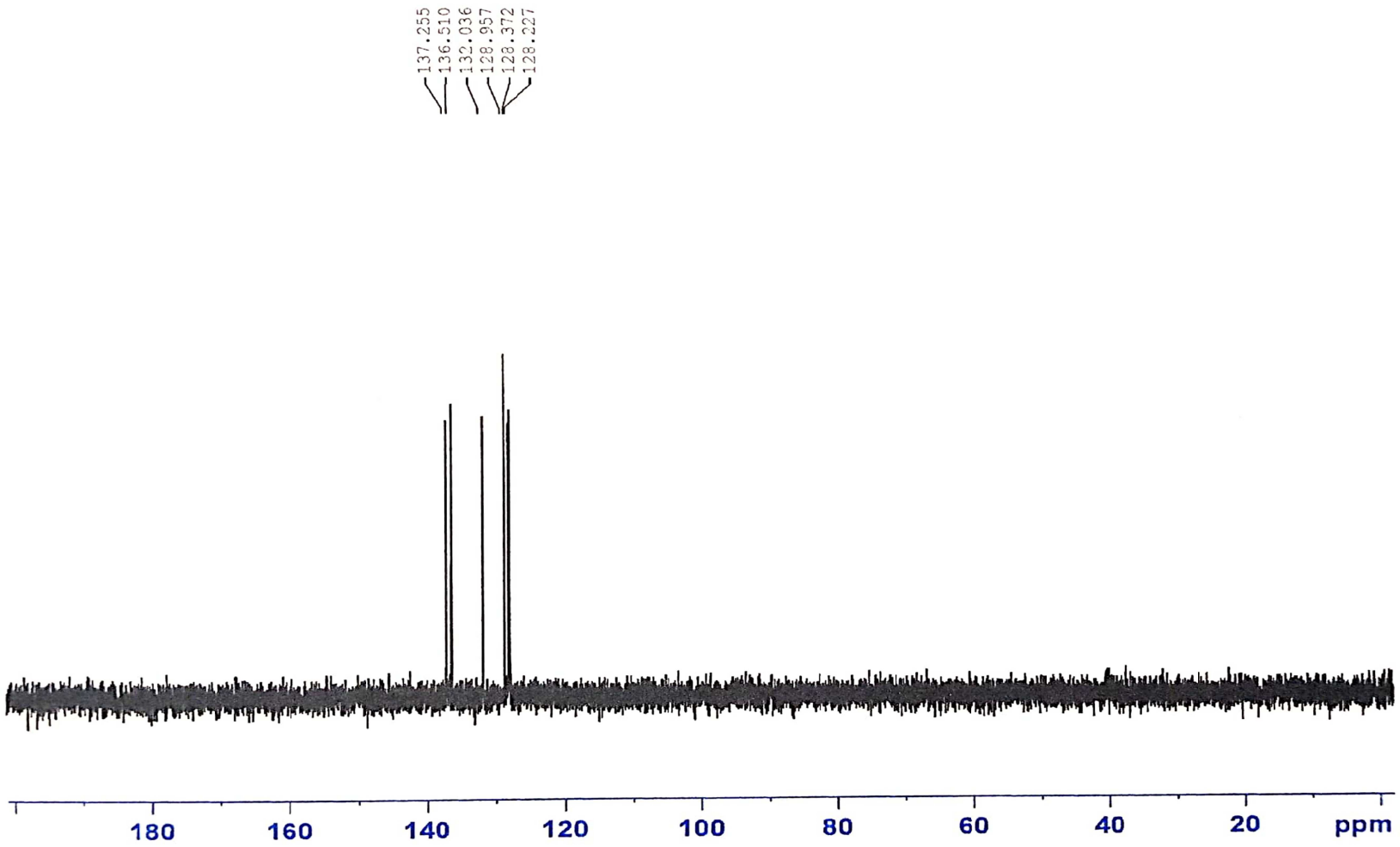


Figure 3.35 DEPT-135 Spectrum of compound 3a

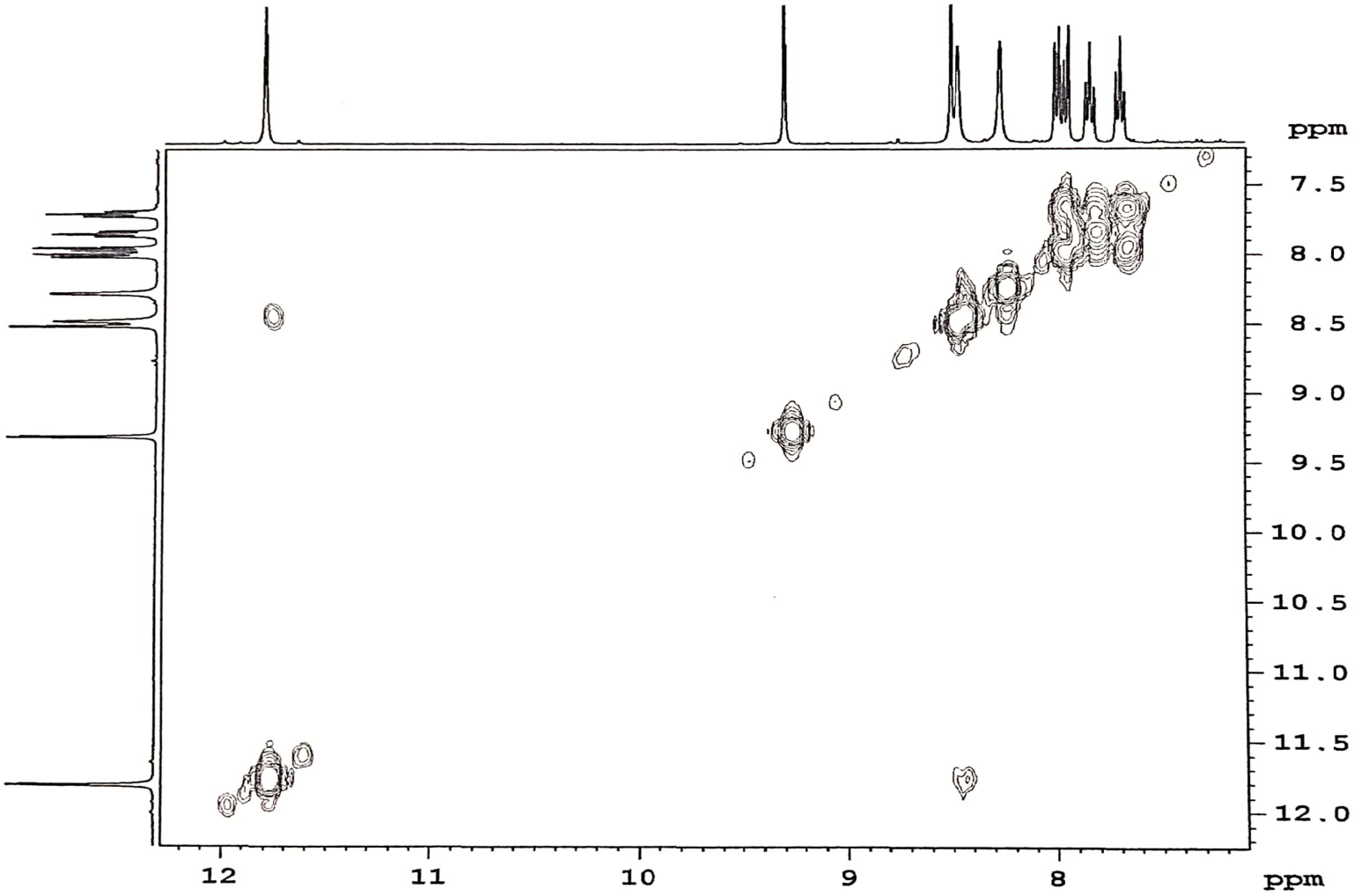


Figure 3.36 2D COSY Spectrum of compound 3a

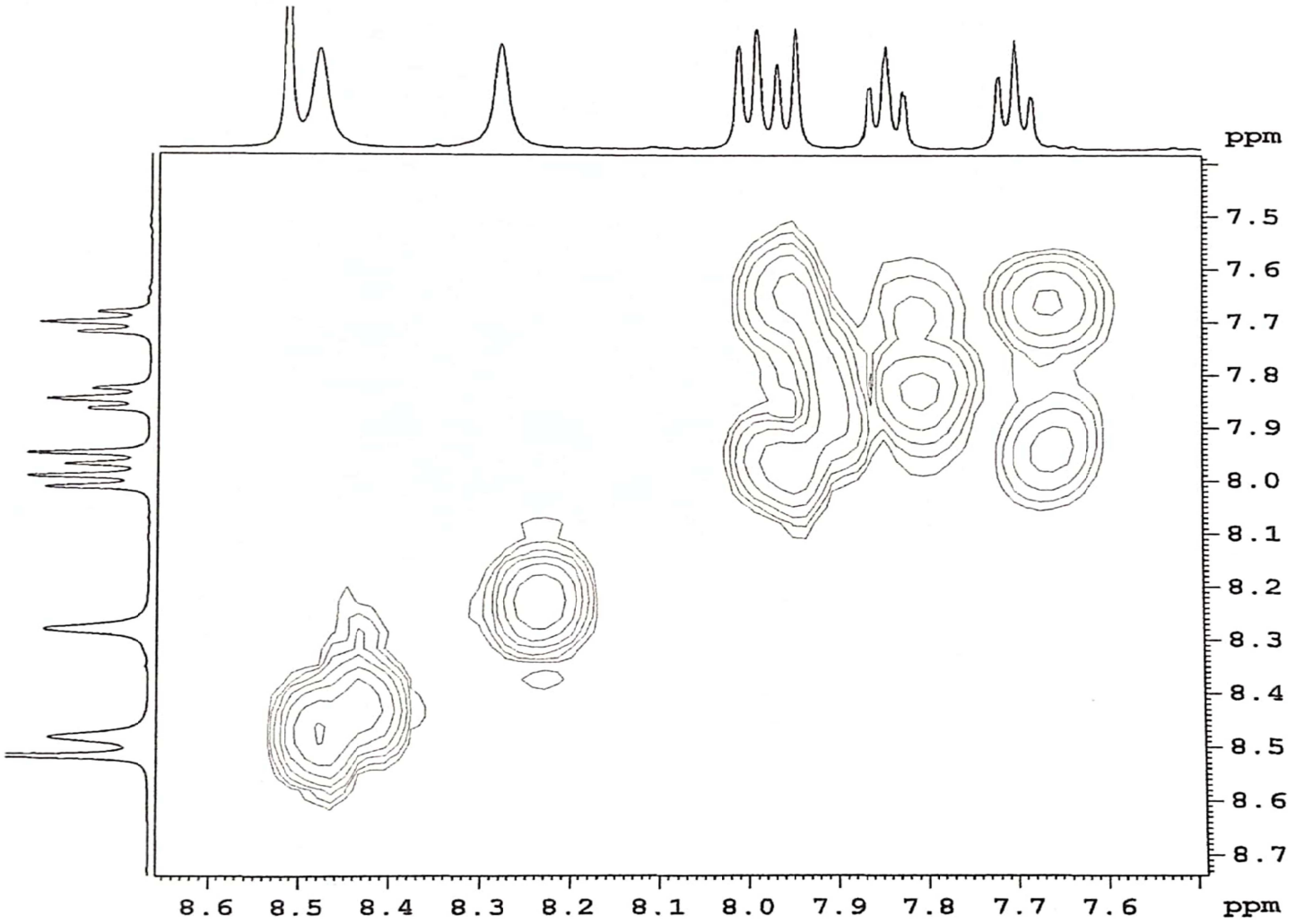


Figure 3.36a 2D COSY Spectrum (Expd.) of compound 3a

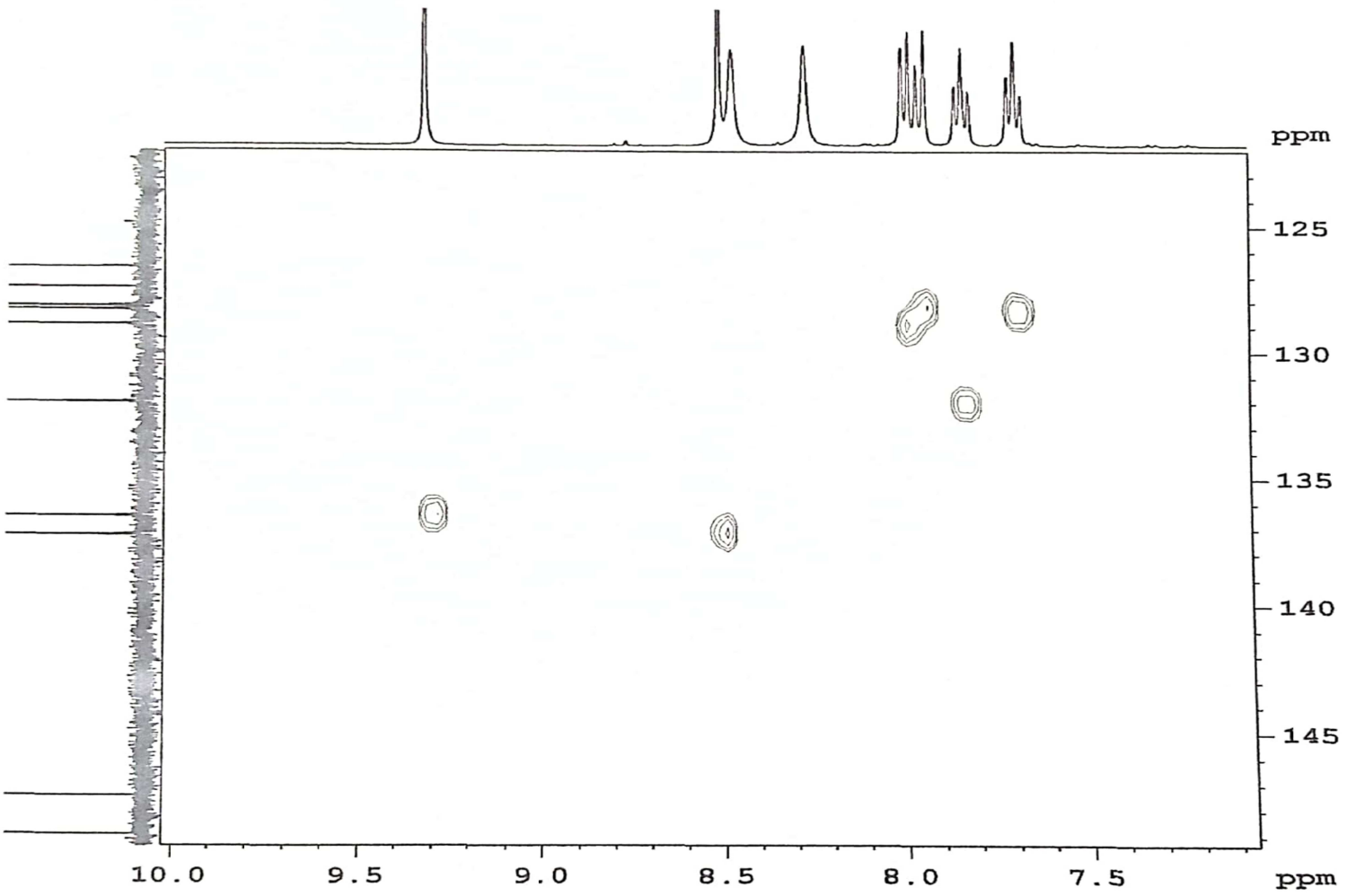


Figure 3.37 HSQC Spectrum of compound 3a

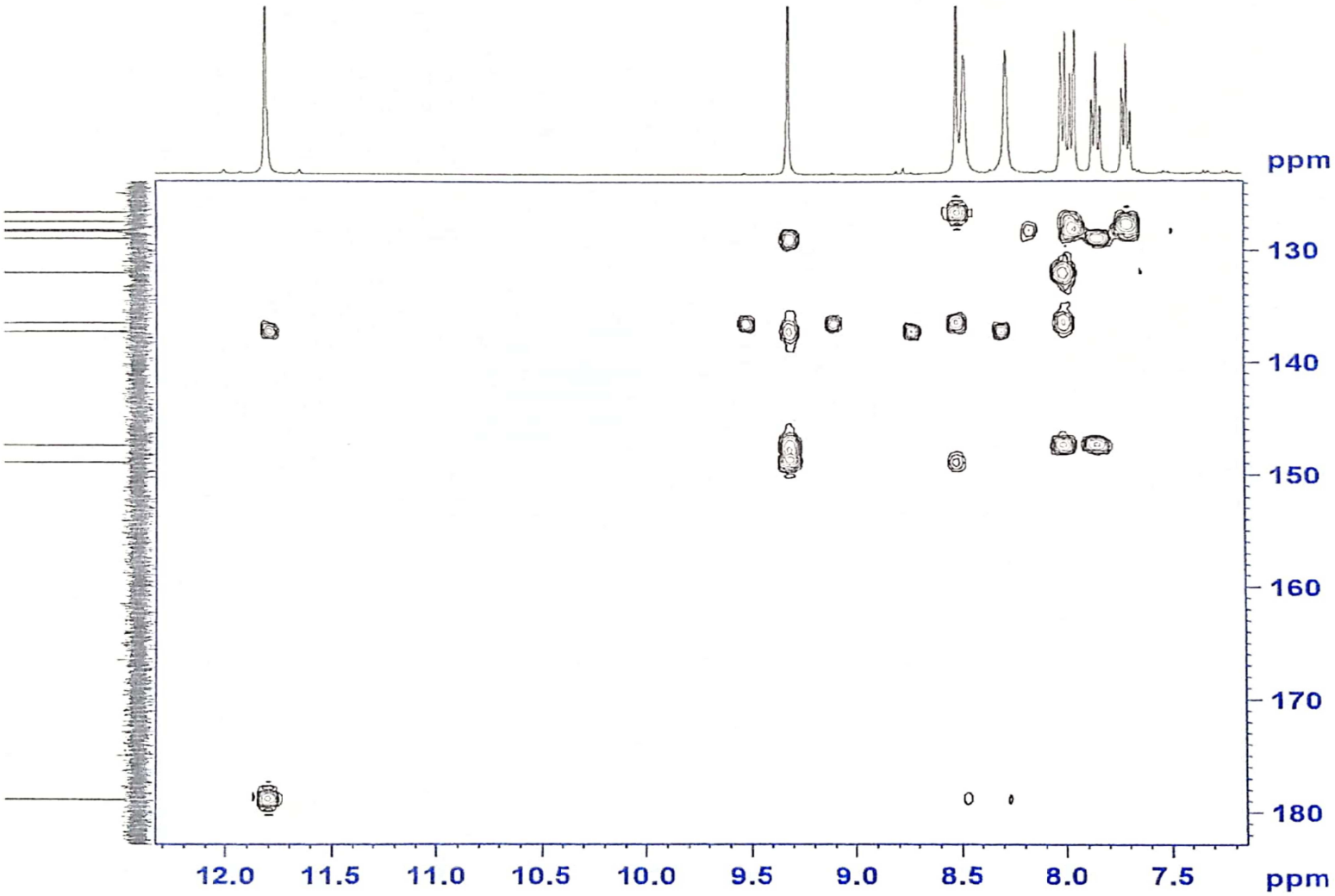


Figure 3.38 HMBC Spectrum of compound 3a

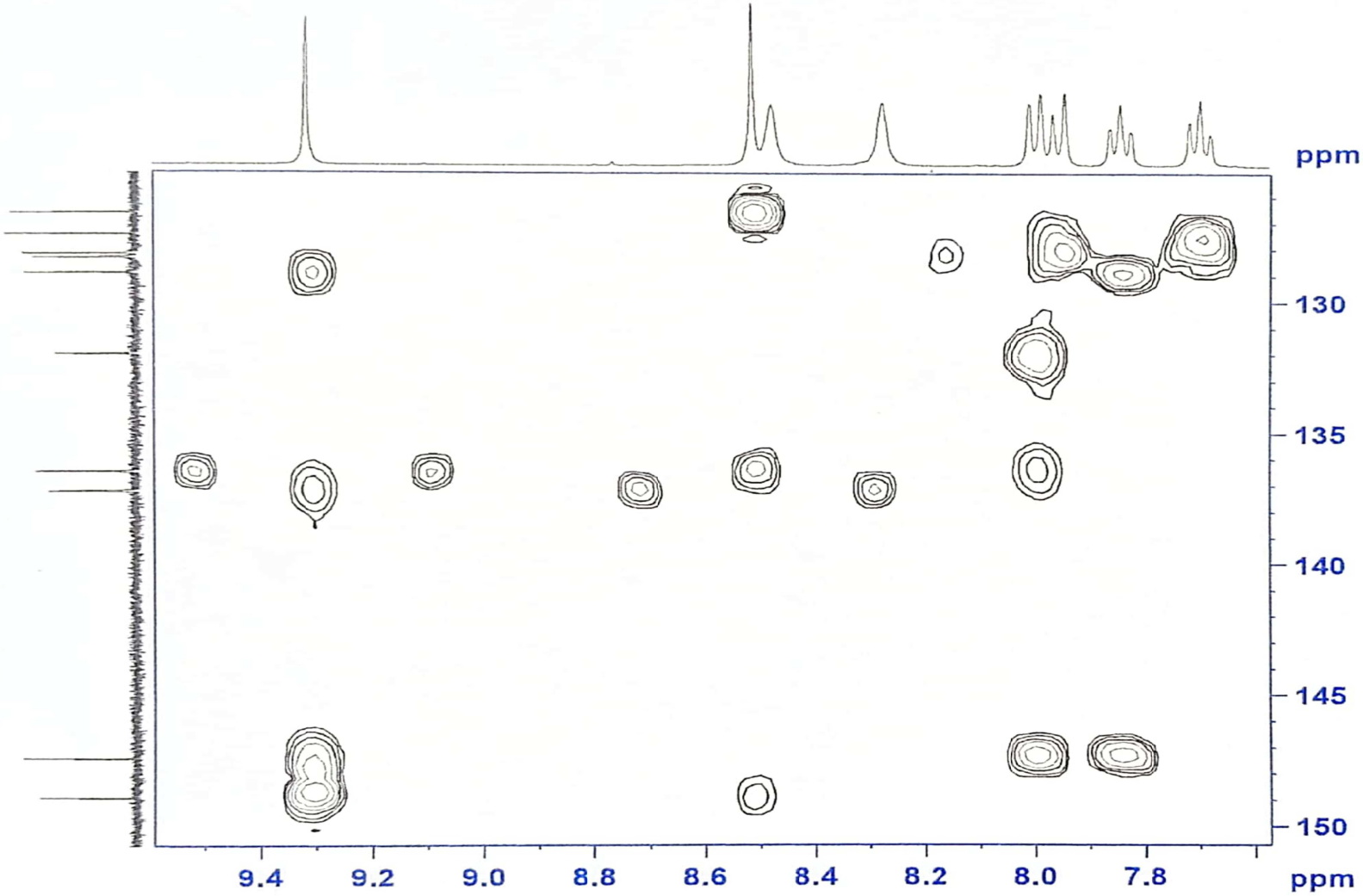


Figure 3.38a HMBC Spectrum(Expd.) of compound 3a

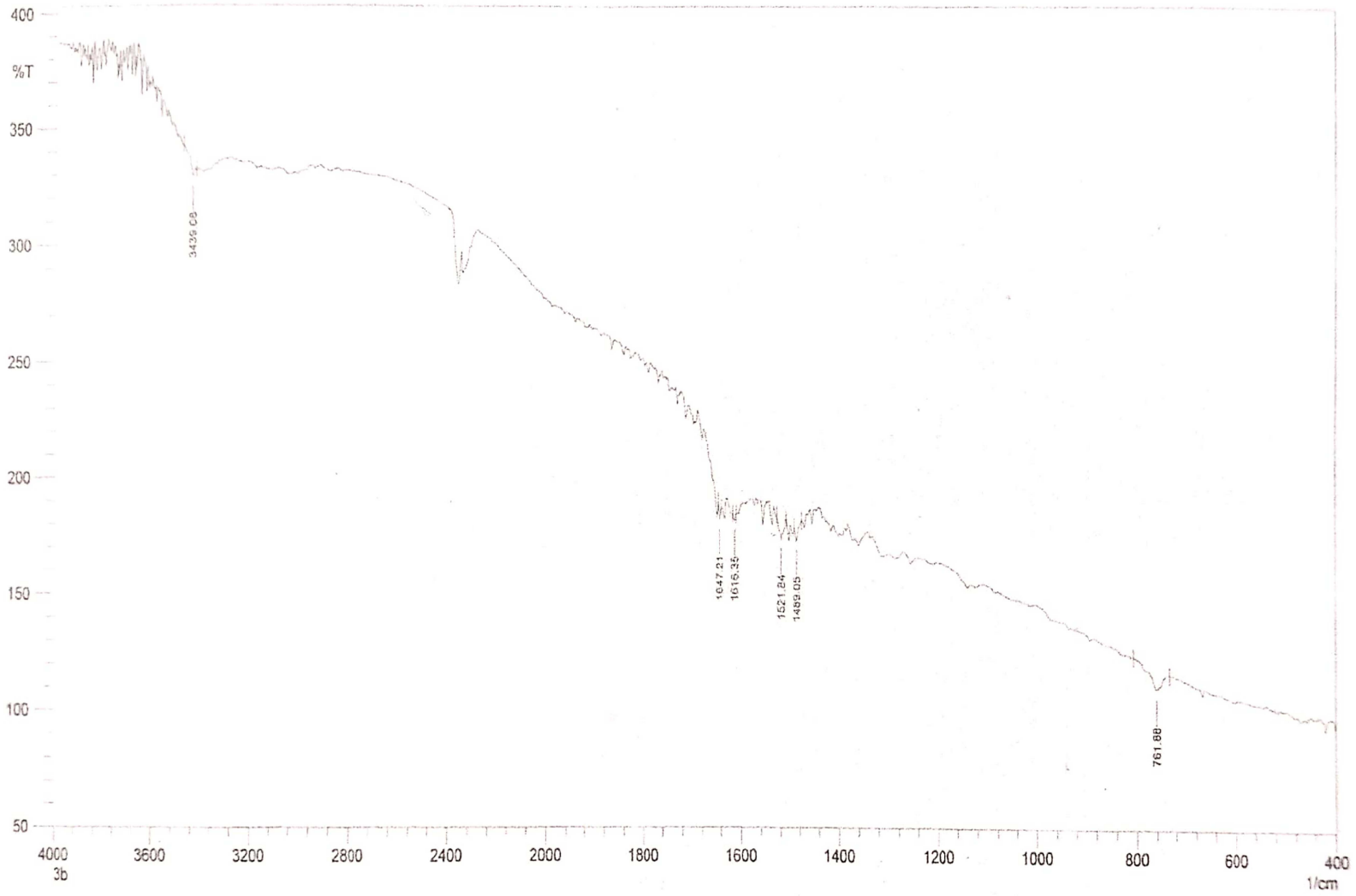


Figure 3.39 IR Spectrum of compound 3b

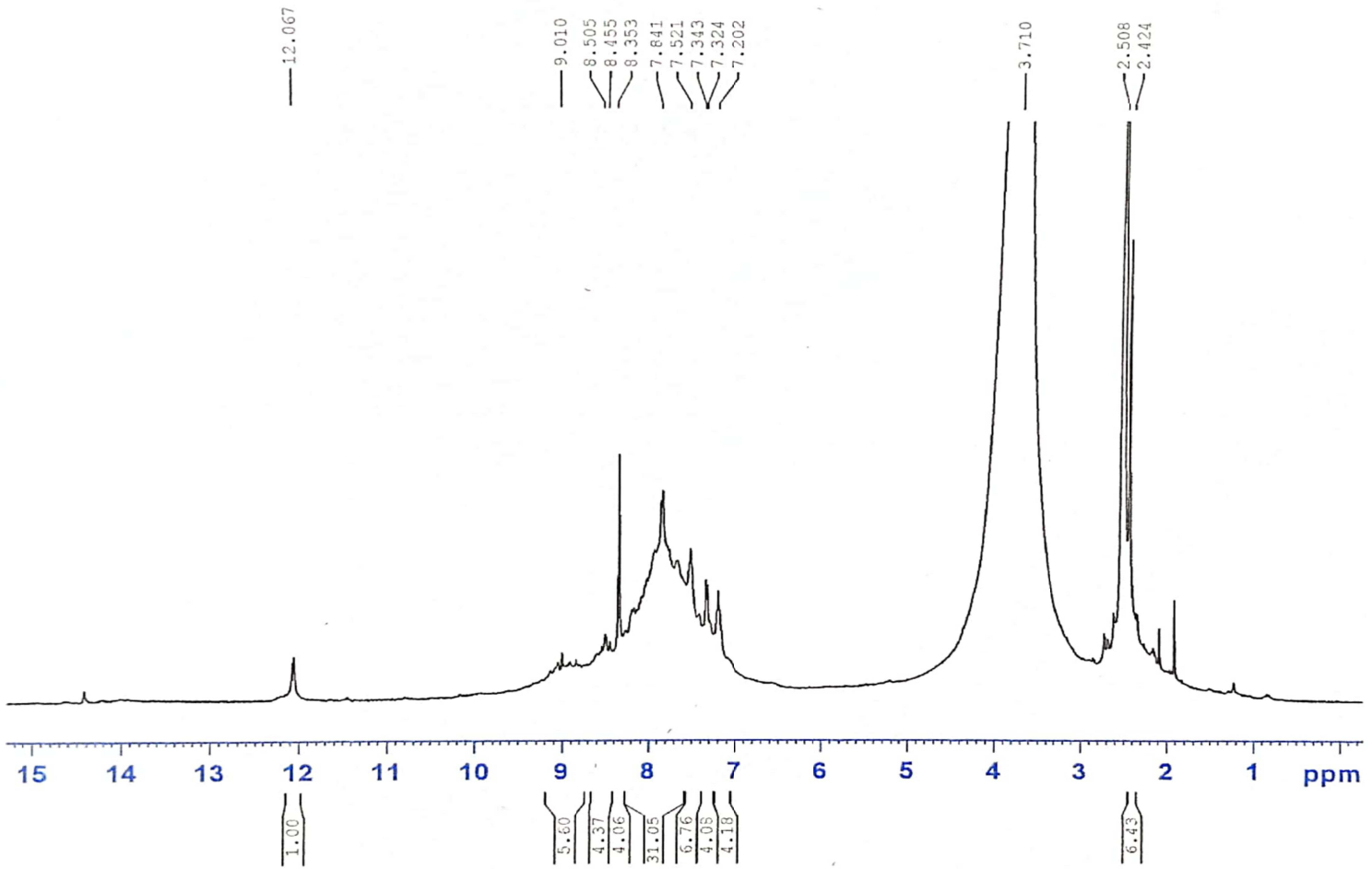


Figure 3.40 ^{1}H NMR Spectrum of compound 3b

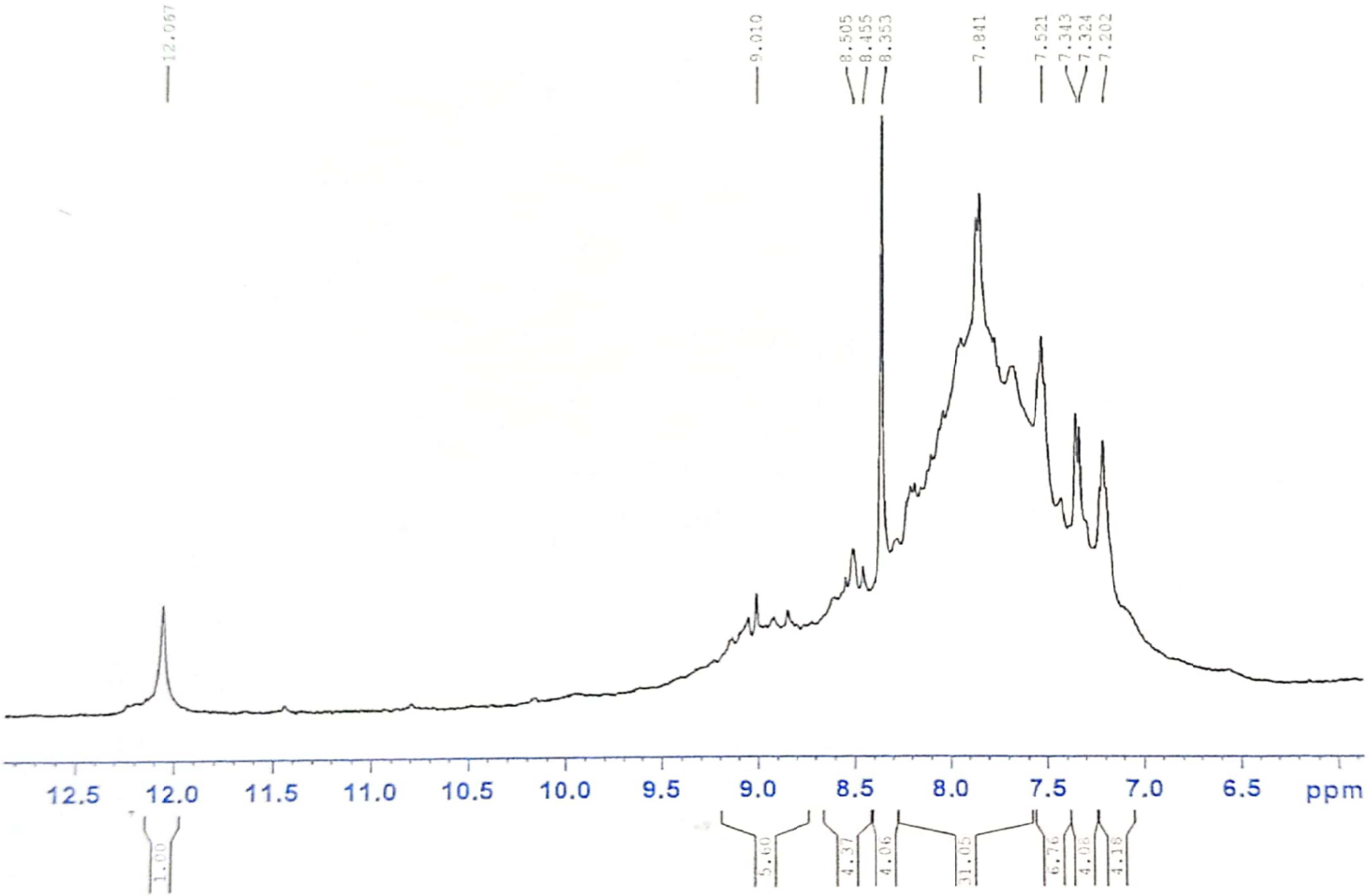


Figure 3.40a ^{1}H NMR Spectrum(Expd.) of compound 3b

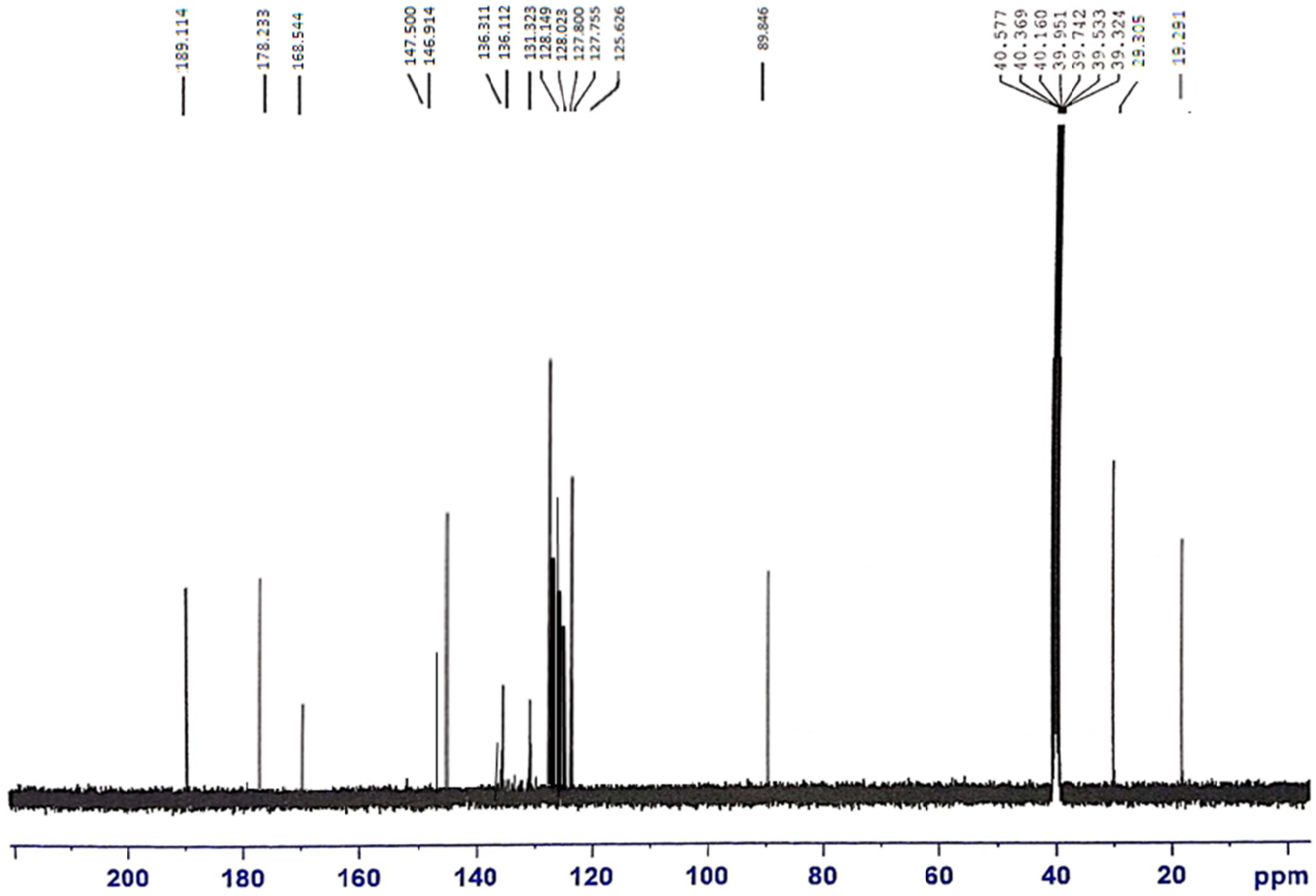


Figure 3.41 ^{13}C NMR Spectrum of compound 3b

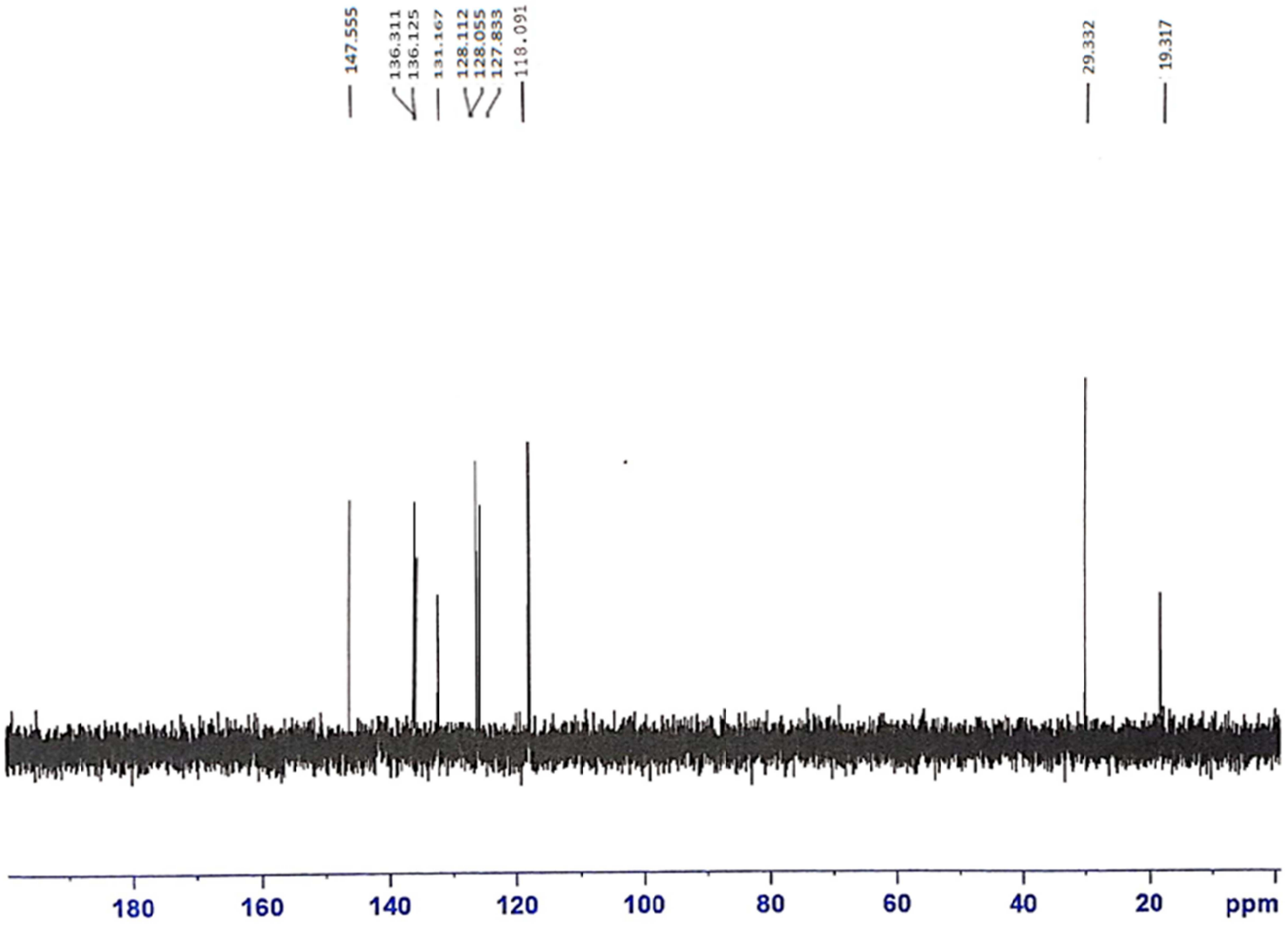


Figure 3.42 DEPT-135 Spectrum of compound 3b

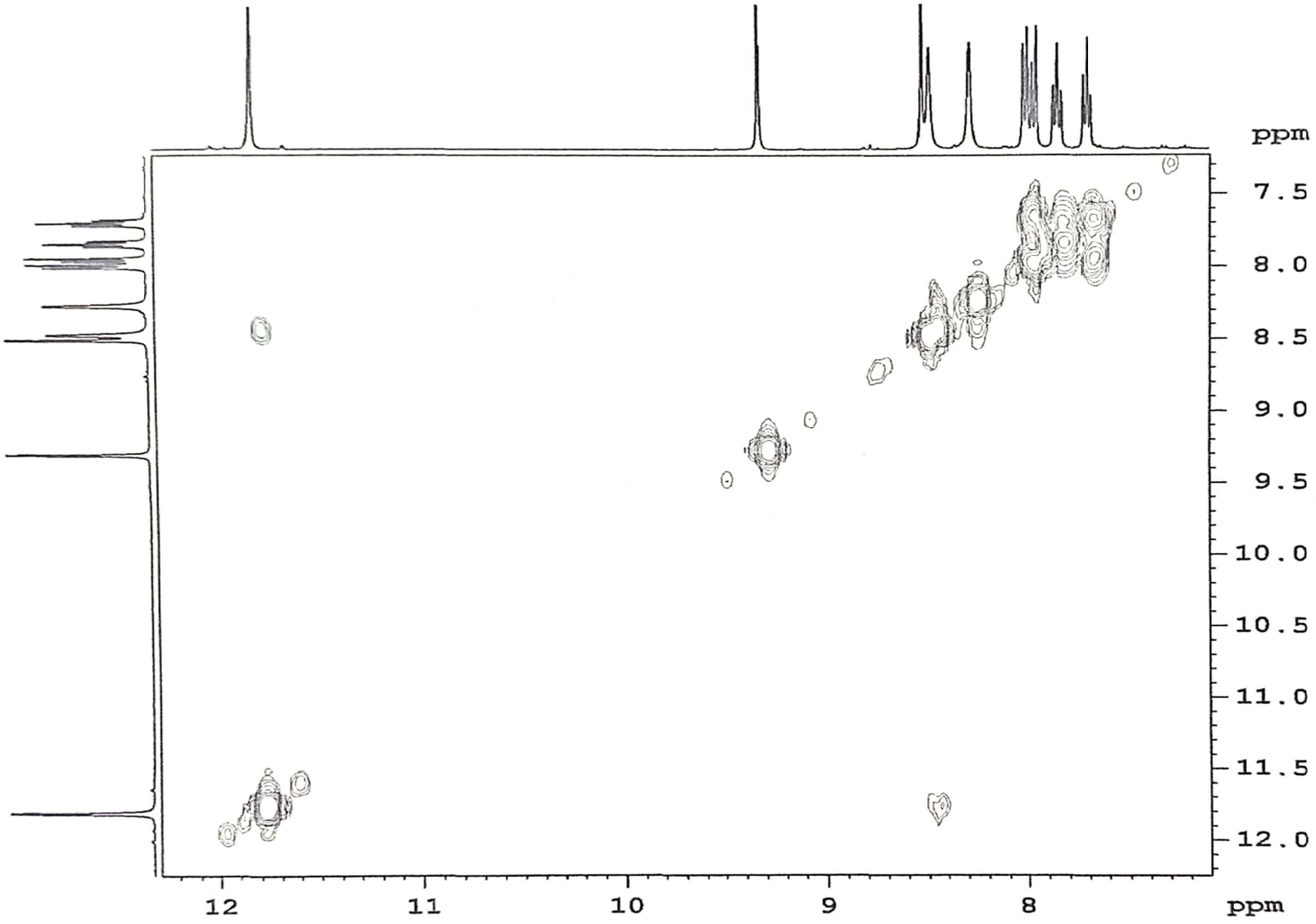


Figure 3.43 2D COSY Spectrum of compound 3b

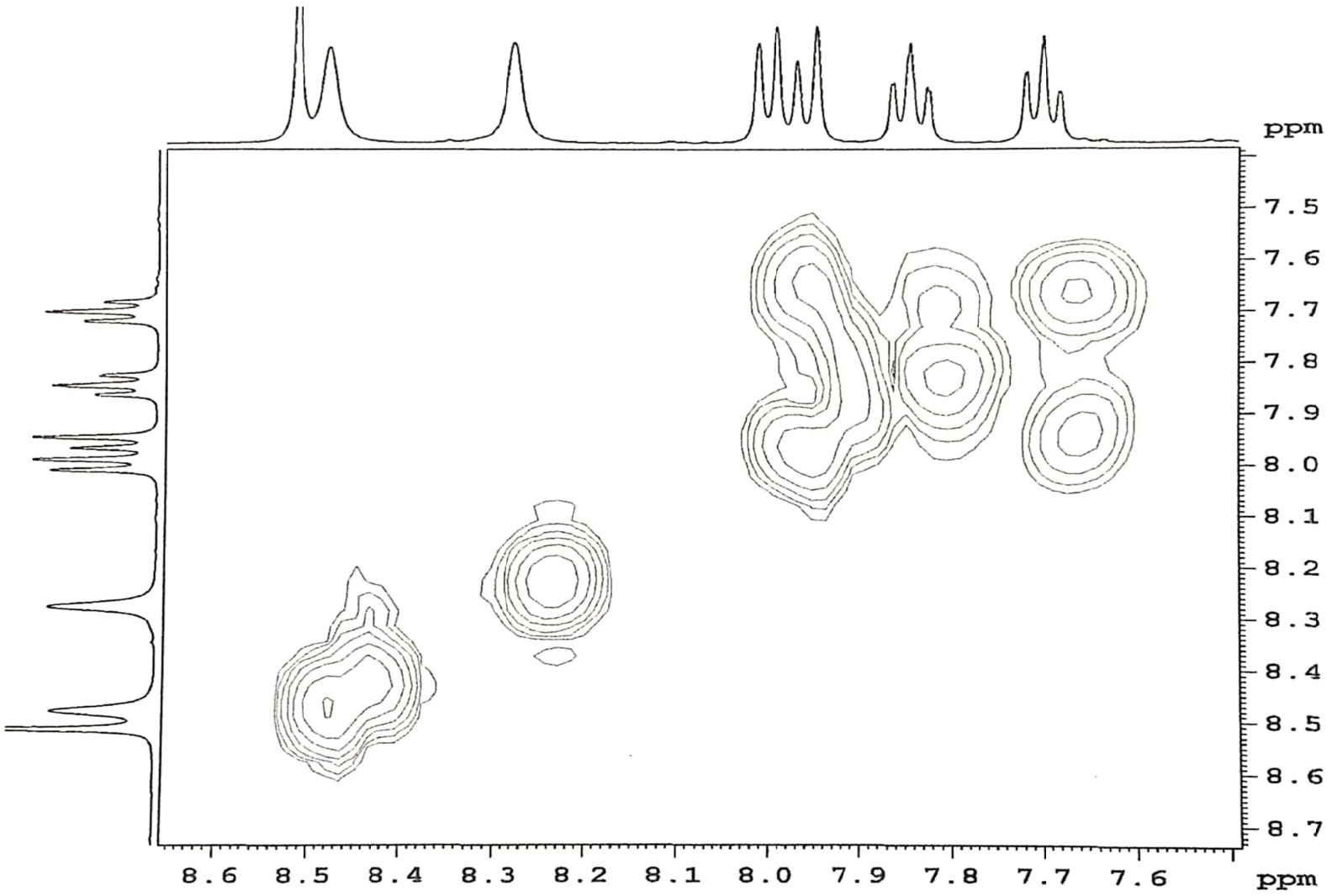


Figure 3.43a 2D COSY Spectrum(Expd.) of compound 3b

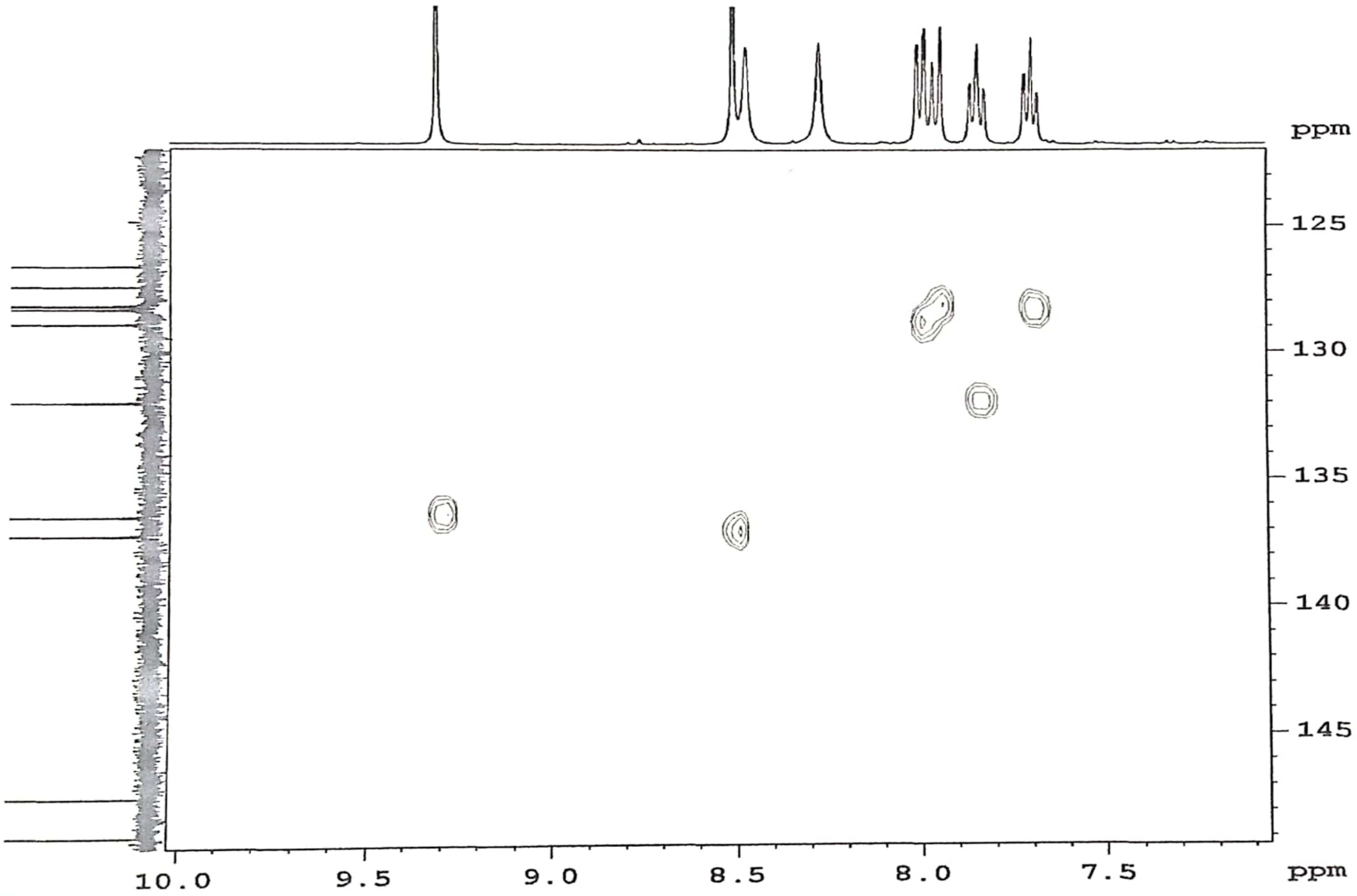


Figure 3.44 HSQC Spectrum of compound 3b

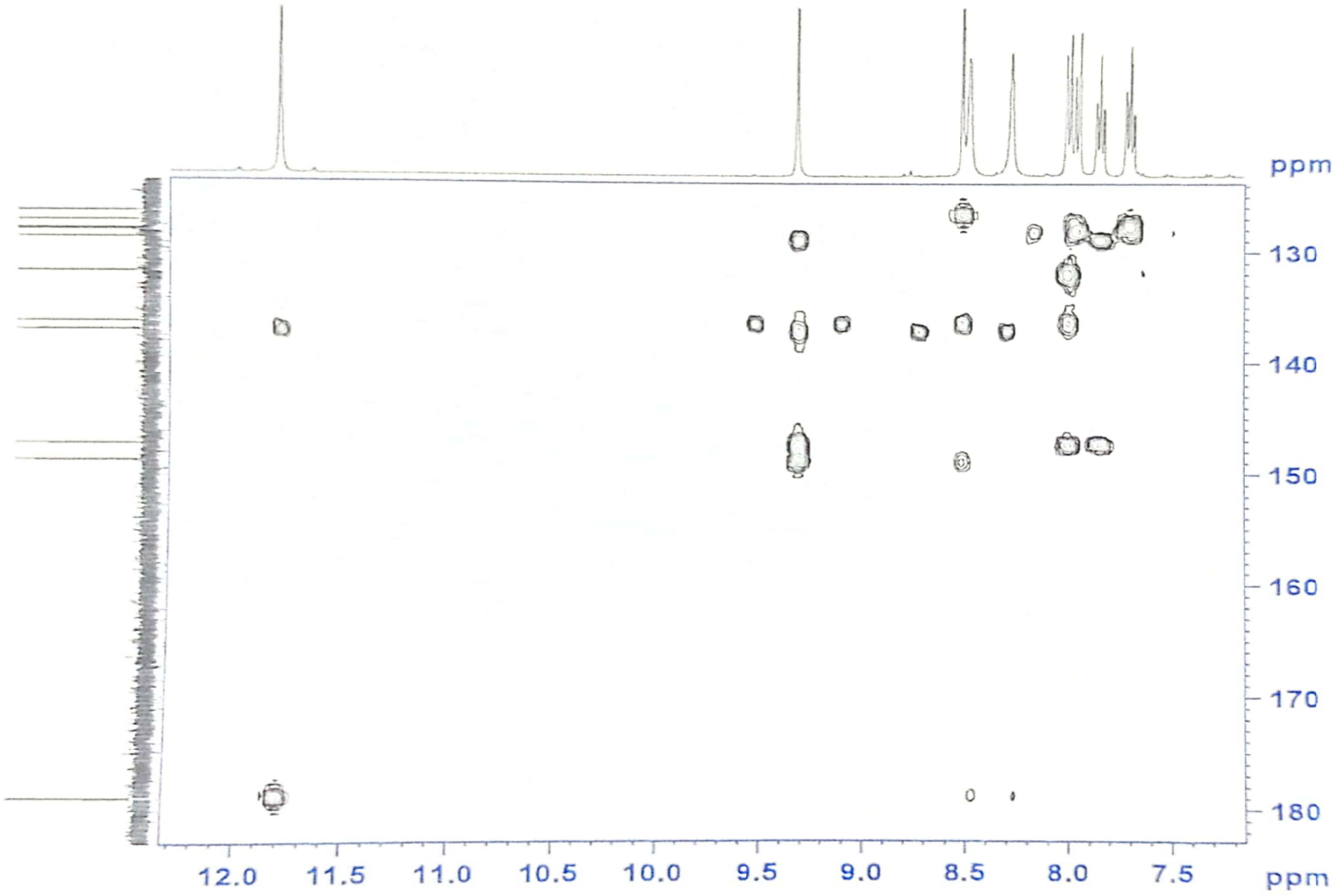


Figure 3.45 HMBC Spectrum of compound 3b

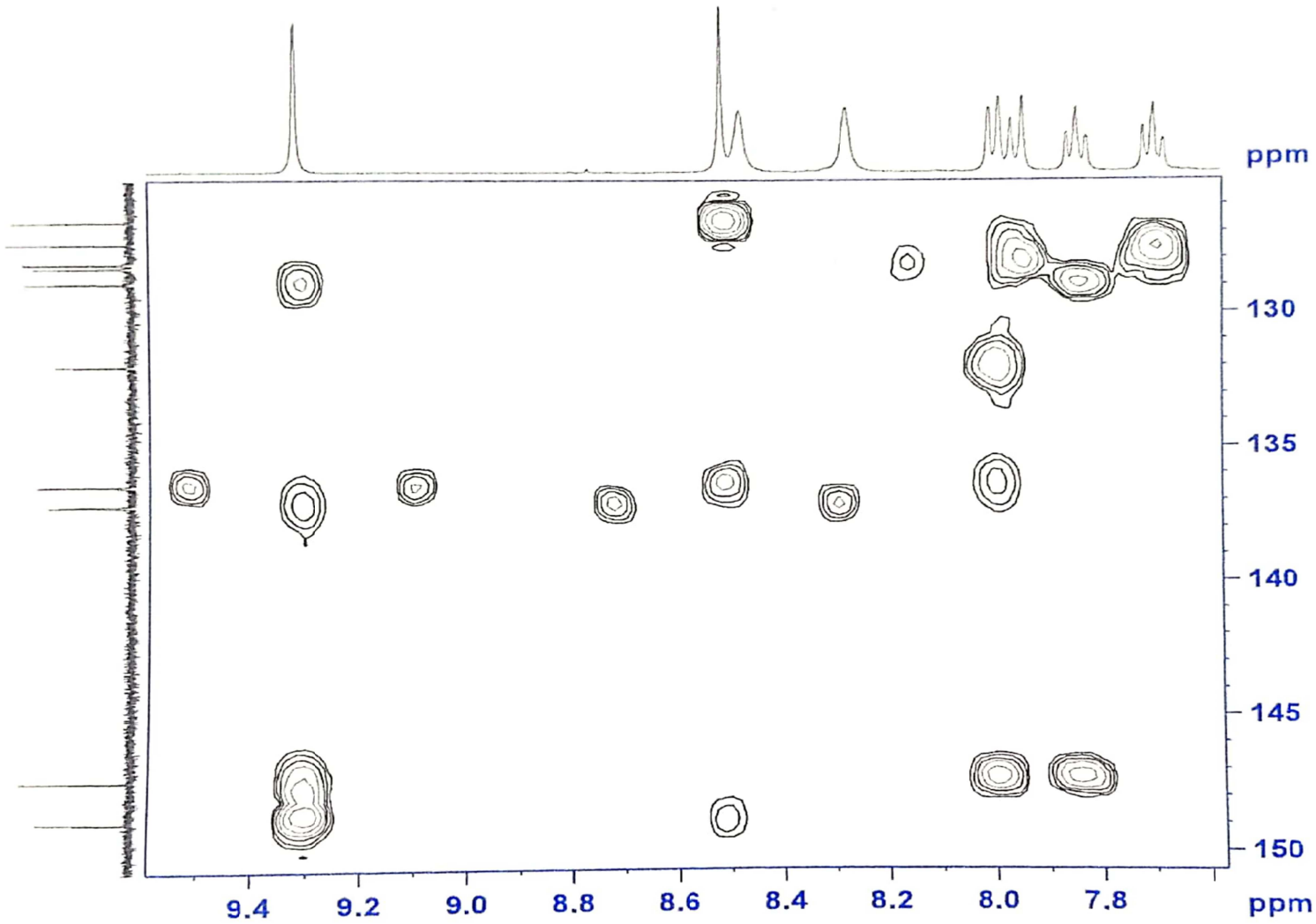


Figure 3.45a HMBC Spectrum (Expd.) of compound 3b

Part B: Biological Studies

3.4 Antibacterial activities assay

Antibacterial activities of the concerned thiazole derivatives have not been studied so far. So it is noteworthy to examine whether these compounds show any such activity or not. For the purpose, investigation on the antibacterial activities of these newly synthesized thiazole derivatives have been carried out against three gram-positive and three gram-negative bacteria which cause different fatal disease. These selected bacteria can cause different fatal diseases. These compounds were found to exhibit different activities against the selected bacteria. All the compounds showed remarkable antibacterial activities against gram-positive bacteria *B. cereus* and *S. aureus* and gram-negative bacteria *K. pneumonia* and *E. coli*. Moreover the compound **1b** revealed comparable antibacterial activities against *S. aureus, B. cereus, K. pneumonia* and *E .coli*, **2b** revealed comparable antibacterial activities against *S. aureus* and *K. pneumonia* and **3b** revealed comparable antibacterial activities against *S. aureus* and *E. coli* with standard. In this study the antibacterial activities of the DMSO as control and Ampicillin as standard have been studied for the comparison. The inhibition zones by different compounds are shown in the Table 3.4. The results are also shown by graphical representation in Figure 3.46.

Table 3.4: Antibacterial activity of the compounds **1b**, **2b** and **3b**

Test Samples	Zone of inhibition in mm					
	Gram positive bacteria			Gram negative bacteria		
	Bacillus Cereus	*Staphylococcus Aureus*	*Bacillus magaterium*	*Klebsiella pneumonia*	*Pseudomonas aeruginosa*	*Escherichia Coli*
1b	20	21	8	22	9	20
2b	16	24	0	24	7	22
3b	18	23	7	21	0	24
DMSO	0	0	0	0	0	0
Ampicillin	32	29	32	34	29	28

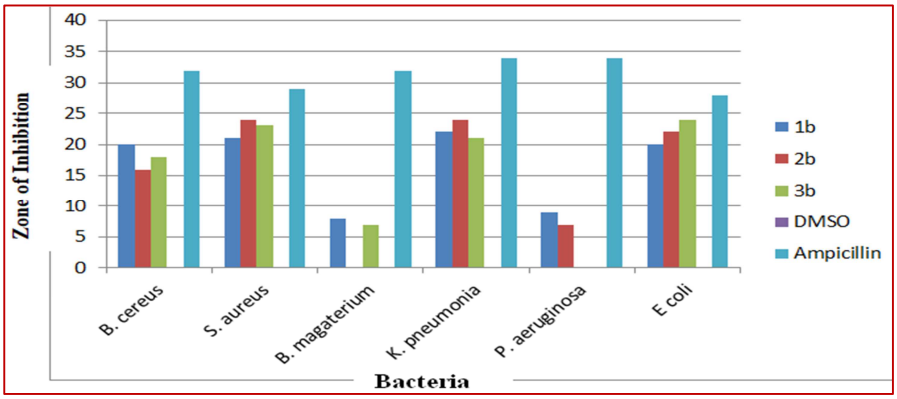


Figure3.46 **:** Graphical representation of antibacterial activities of compounds **1b** - **3b**

3.5 Antifungal activities

To investigate the actual biological activities of these new thiazole derivatives antifungal activities of the concerned thiazole derivatives have also been studied along with the antibacterial activities. In this context, the antifungal activities of these newly prepared thiazole derivatives have been investigated against two selected fungi *Aspergillus niger* and *Trichoderma harzianum*. Most of the compounds were found to inhibit the mycelial growth. All the test samples exhibited significant antifungal activities against the fungi *Aspergillus niger* but compounds **1b** & **3b** showed moderate to potential antifungal activities against the fungi Aspergillus niger and compound **2b** showed moderate antifungal activities against the fungi *Trichoderma harzianum*. However antifungal activities of the solvent DMSO and amphotericin b as standard have also been studies for the comparison. The inhibitions of mycelial growth by different test samples are shown in the Table 3.5 and also shown by a graphical representation in Figure 3.47.

Table 3.5: Antifungal activities of the compounds **1b**, **2b** and **3b**

Test Samples	% Inhibition of mycelialgrowth	
	Aspergillusniger	*Trichodermaharzianum*
1b	20	0
2b	16	15
3b	18	0
DMSO	0	0
Amphotericin B	23	24

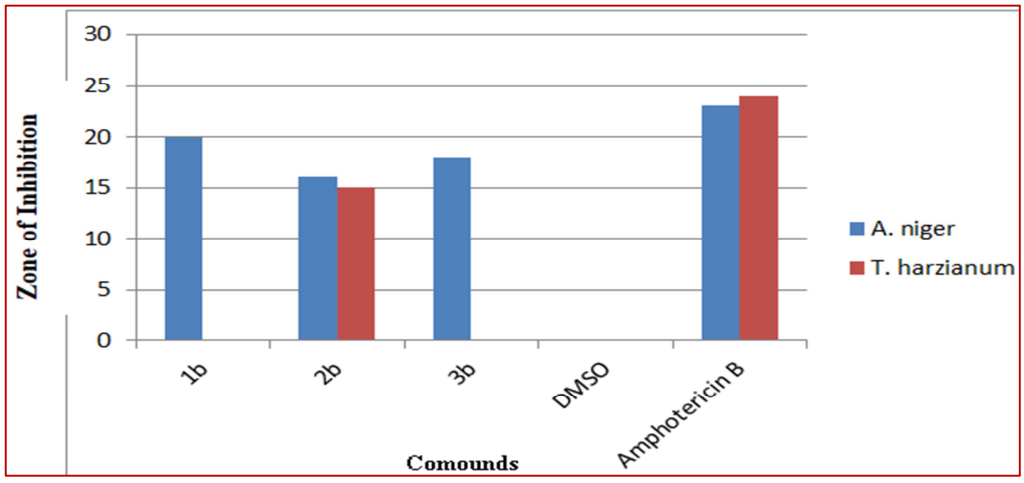


Figure 3.47 : Graphical representation of antifungal activities of compounds **1b** - **3b**.

Part C: Docking studies

3.6 Molecular docking studies

In silico molecular docking studies of synthesized compounds **1b - 3b** were conducted to support the design and invention of new drug molecule for the effective inhibition of target protein of disease development. The non-covalent interactions between the synthesized analogs and target receptors (2D and 3D) are illustrated in Figure 3.49 & Figure 3.50 where poses with the highest negative docking scores were chosen for the ultimate presentation. When docked against 2BTF, compound **1b** and **3b** showed binding score of -7.6 Kcal/mole and -7.9 Kcal/mole.

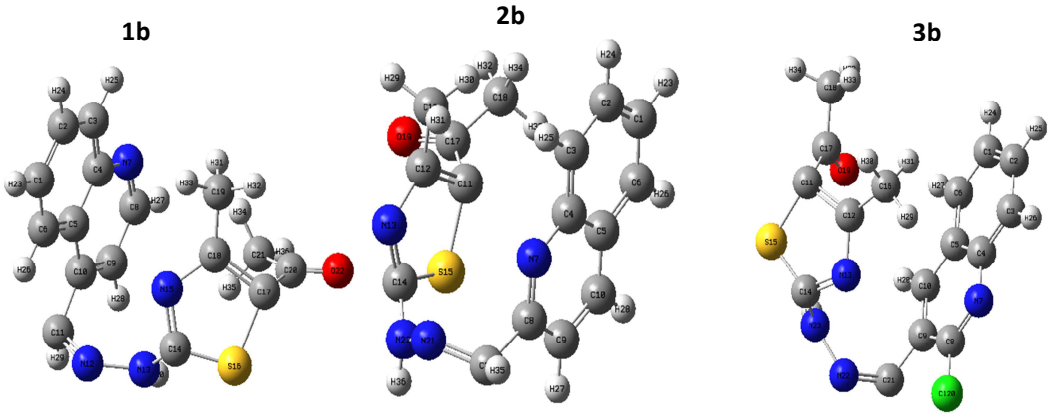


Figure 3.48 : Optimized molecular structures of the synthesized derivatives **1b**-**3b**. Structure optimization was carried out applying DFT/ B3LYP/6-31G(+, d,p) basis setup

Name	Binding affinity (kcal/mol)	Residue in contact	Interaction type	Bond distance (Å)
1b	-7.6	ASP157	Attractive charge	5.27822
		GLU214	Attractive charge	4.83023
		ASP157	Attractive charge	4.40079
		GLU214	Attractive charge	4.44543
		GLY156	Conventional hydrogen bond	2.14822
		GLY302	Conventional hydrogen bond	2.78748
		MET305	Pi- Alkyl	4.71525

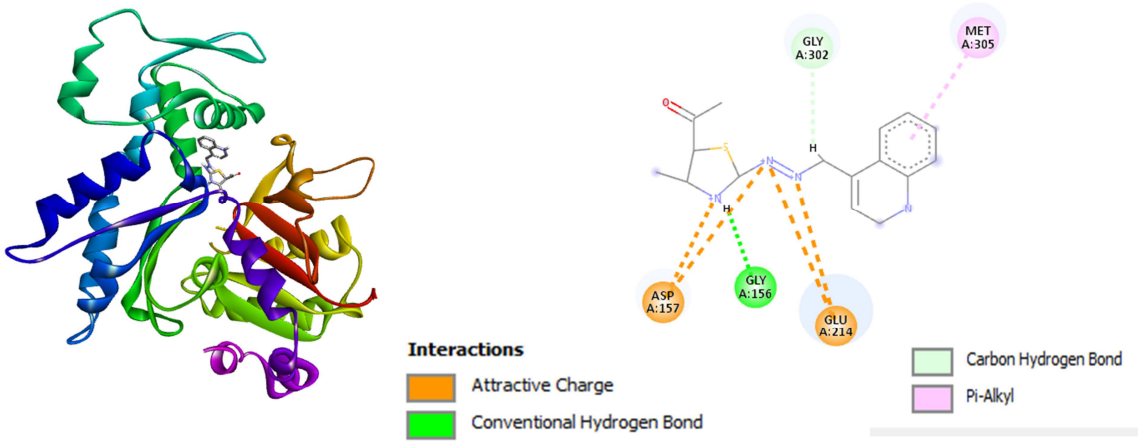


Figure 3.49 : Molecular docking studies of **1b** against receptor 2BTF. (A) 3D docking predictions. (B) 2D interaction sketches.

Name	Binding affinity (kcal/mol)	Residue in contact	Interaction type	Bond distance (Å)
3b	-7.9	PHE375	Salt bridge attractive charge	2.92903
		PHE375	Attractive charge	5.57027
		TYR133	Conventional hydrogen bond	2.16462
		LYS373	Conventional hydrogen bond	2.53984
		MET355	Carbon Hydrogen bond	2.59947
		LYS373	Carbon Hydrogen bond	2.88734
		ALA135	Pi- Alkyl	4.9566
		VAL139	Pi- Alkyl	4.70596
		LEU140	Pi- Alkyl	5.41948
		LEU346	Pi- Alkyl	4.14628

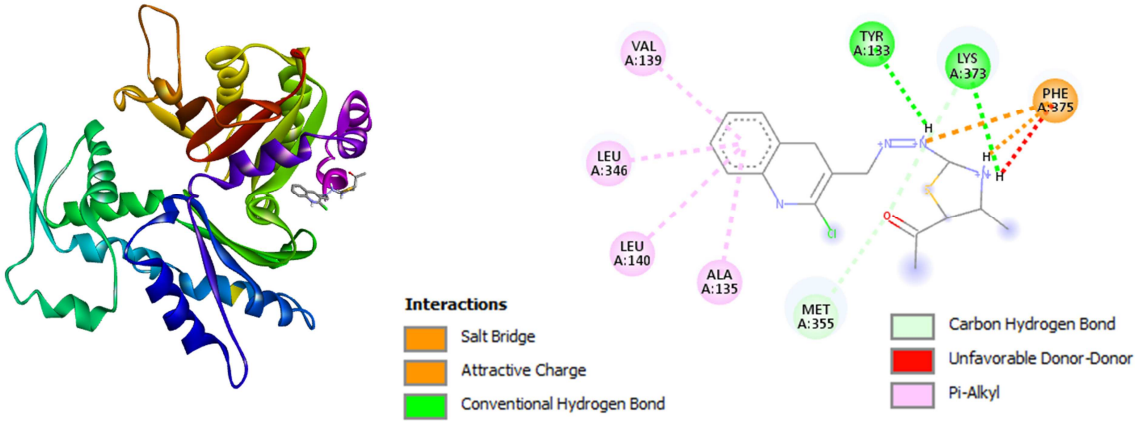


Figure 3.50 **:** Molecular docking studies of **3b** against receptor 2BTF. (A) 3D docking predictions. (B) 2D interaction sketches.

3.7 *In silico* ADMET prediction

The pharmacokinetic properties of synthesized compounds were determined using SwissADME online tool. The determined molecular properties and pharmacokinetic properties are summarized in table 3.6 and table 3.7.

Table 3.6: Molecular properties of synthesized thiazole derivatives

Name	Molecular Weight	LogP	Rotatable H-Bonds	H-Bonds Acceptors	H-Bonds Donors	Surface Area
1b	310.382	3.64832	4	6	1	131.286
2b	310.382	3.64832	4	6	1	131.286
3b	344.827	4.30172	4	6	1	141.590
Ampicillin	349.412	0.3181	4	5	3	143.121

Table 3.7: Pharmacokinetic Properties

Name	Water Solubility (log mol/L)	HIA (%Absorbed)	P-GI I inhibitor	BBB (log BB)	CNS (log PS)	hERG I inhibitor	hERG II inhibitor	ORAT (LD50) (mol/kg)
1b	-4.038	93.099	No	0.168	-2.078	No	Yes	2.407
2b	-3.974	92.875	No	0.295	-2.112	No	Yes	2.417
3b	- 5.018	91.204	Yes	0.202	-1.949	No	Yes	2.358
Ampicillin	**-2.396**	**43.034**	**No**	**-0.767**	**-3.166**	**No**	**No**	**1.637**

BBB= Blood brain barrier, HIA= Human intestinal absorption, CNS=Central nerve system, P-GI= P-glycoprotein inhibitor, ORAT = oral Rat acute toxicity, hERG = human Ether-a- go-go Related Gene

Chapter – 4

Conclusion and Future plan

4.1 Conclusion

Schiff base derivatives and their complexes are the most significant and valuable compounds which have many useful applications because of their chemical versatility, vast synthetic way to different molecular structures and usually these compounds are easy to prepare. Most of the Schiff base thiazole compounds were used as active medicinal agents. As a consequence, the present study focused on the synthesis and characterization of new thiosemicarbazones, thiazole derivatives containing quinolone moieties and screening their antibacterial and antifungal activities. First step newly syntheses compounds **1a - 3a**; thiosemicarbazone derivatives and second step newly syntheses compounds **1b - 3b** thiazole derivatives were characterized by IR, ^{1}H NMR, ^{13}C NMR, DEPT, COSY, HSQC and HMBC spectral analysis. It was visualized that compounds **1b** and **3b** significantly exhibited antibacterial activities and moderate to potential antifungal activities. In the docking studies, compounds **1b** and **3b** showed binding score of -7.6 Kcal/mol and -7.9 Kcal/mol respectively.

4.2 Future plan

In our study three thiazole derivatives were synthesized and characterized by spectroscopic methods. *In silico* antibacterial and antifungal screening the synthesized compounds showed moderate to good antibacterial and antifungal activities. The studies of antibacterial and antifungal effects are likely to aid the development of new therapeutic agents for diseases caused by microorganisms. Therefore, in the future, more research on thiazole derivatives will play an important role in the synthesis of better quality antibacterial and antifungal drugs against multidrug resistance of microorganisms.

Chapter – 5

References

A. C Pasqualotto, K O Thiele, 2010, Novel triazole antifungal drugs. Current Opinion in Investigational Drugs 11(2):165-174.

Alberts B, Johnson A, Lewis J et al., 2002, The Structure and Function of DNA, Molecular Biology of the Cell. 4th edition, New York : Garland Science.

Anouar, Raweh, Bayach, Taha, Baharudin, F D Meo, Hasan, Aishah, Hadiani, Jean-Fre, Weber, Trouillas, 2013, Antioxidant properties of phenolic Schiff bases: structure–activity relationship and mechanism of action. J Comput Aided Mol Des 27:951–964.

Anthi Petrou, Maria Fesatidou, Athina Geronikaki, 2021, Thiazole Ring—A Biologically Active Scaffold. 26, 3166. https://doi.org/10.3390/molecules26113166.

Aswathanarayanappa, Chandrashekar, Bheemappa, Eswarappa, Bodke, Yadav D, Krishnegowda, Peethambar S, Venkata, Srinivas P, Ningegowda, Raghu, 2013, Synthesis and Evaluation of Antioxidant Properties of Novel 1,2,4-Triazole-Based Schiff Base Heterocycles. Arch. Pharm. Chem. Life Sci. 346, 922–930.

Attygalle, Athula B. et al. Biosynthesis of Quinoline by a Stick Insect. Journal of Natural Products, doi:10.1021/acs.jnatprod.0c00945 .

Barnette, Dustyn A et al., 2021, Meloxicam methyl group determines enzyme specificity for thiazole bioactivation compared to sudoxicam. Toxicology letters vol. 338 : 10-20.

Brodowska, Katarzyna & Lodyga-Chruscinska, Elzbieta, 2014, Schiff bases - Interesting range of applications in various fields of science. Chemik. 68. 129-134.

David B. Bylund S.J. Enna., 2009, Sulfathiazole. [book auth.] xPharm: The Comprehensive Pharmacology Reference, Pages 1-3.

Dong Chan Kim, Kyung Ho Yoo,Kye Jung Shin,Sang Woo Park,Dong Jin Kim, 1997, Basicities of thiazole heterocyclic compounds and the reaction of 3-methyl-2-

methylimino-Δ4-thiazolines with ethyl bromoacetate and 2-bromoacetophenone. J Heterocyclic Chem, Volume 34, Issue 1, Pages 57-63. https://doi.org/10.1002/jhet.5570340110.

Dr P Ravi Shankar, Dr R Balasubramanium, 2014, Antimicrobial resistance: global report on surveillance. WHO.

E.N. Bentz, A.B. Pomilio, R.M. Lobayan, 2017, Donor-Acceptor interactions as descriptors of the free radical scavenging ability of flavans and catechin. Computational & Theoretical Chemistry.

Eicher, T. and Hauptmann, Andreas, 2012, The Chemistry of Heterocycles: Structures, Reactions, Synthesis, and Applications. Wiley-VCH Verlag GmbH, Weinheim: Vols. 3rd, completely revised and enlarged Edition.

Eissa, Farrag, Abbas, shehry et al., 2021, Novel structural hybrids of quinoline and thiazole moieties. Bioorganic Chemistry 110 104803.

El-Gamal, Kamal M., 2017, Synthesis And Anticancer Screening of Heterocyclic Compounds Bearing Pyrimido [4, 5-B] Quinoline Moiety . IJPSR Vol. 8, Issue 2 .

Guamán Ortiz, Luis Miguel, et al., 2014, Multiple Effects of Berberine Derivatives on Colon Cancer Cells. BioMed Research International, Vols. Volume 2014, Article ID 924585, 12 pages.

Guofan Jin, Fuyan Xiao, Zhenwang Li, Xueyong Qi, Lei Zhao, Xianyu Sun, 2020, Design, Synthesis, and Dual Evaluation of Quinoline and Quinolinium Iodide Salt Derivatives as Potential Anticancer and Antibacterial Agents. ChemMedChem vol. 15,7, 600-609. doi:10.1002/cmdc.202000002.

Gupta, Monika, 2015, Heterocyclic Compounds and their Biological Significance: A Review. Department of Chemistry, Vaish College, Rohtak, Haryana, India : International Journal of Physical, Chemical & Mathematical Sciences, Vol. 4. No. 01.

H Kaneto, N Katakami, M Matsuhisa, T Matsuoka, 2010, Role of Reactive Oxygen Species in the Progression of Type 2 Diabetes and Atherosclerosis. Hindawi

Publishing Corporation, Vols. Volume 2010, Article ID 453892, 11 pages. doi:10.1155/2010/453892.

H. Nohl, A.V. Kozlov, L. Gille, K. Staniek, 2003, Cell respiration and formation of reactive oxygen species: facts and artefacts. Biochemical Society Transactions Volume 31, part 6.

Hull MW, Montaner JS, 2011, Ritonavir-boosted protease inhibitors in HIV therapy. Ann Med. Aug;43(5):375-88.

Jacques-Henry Julliard, Roland Douce, March 1991, Biosynthesis of the thiazole moiety of thiamin (vitamin B1) in higher plant chloroplasts. Proc. Nati. Acad. Sci. USA, Vol. 88, pp. 2042-2045.

Ji Ram, Vishnu, 2019, Nomenclature and Chemistry of Three-to-Five Membered Heterocycles. Pages 149-478, Elsevier.

Jin, Zhong. Imidazole, oxazole and thiazole alkaloids. Natural Product Reports,. Vols. 23(3), 464, doi:10.1039/b502166a .

Konopelski P, Ufnal M., 2018, Indoles - Gut Bacteria Metabolites of Tryptophan with Pharmacotherapeutic Potential. Curr Drug Metab;19(10):883-890. doi: 10.2174/1389200219666180427164731. PMID: 29708069.

LeAnne M., Louis, 2005, Wayne State University School of Medicine, Detroit, Michigan : Clin. Infect. Dis. 40, 1173–1180.

Maienfisch, Peter, 2006, Synthesis and Properties of Thiamethoxam and Related Compounds. Zeitschrift für Naturforschung B. 61. 10.1515/znb-2006-0401.

Michael, Joseph P., 2008, Quinoline, quinazoline and acridone alkaloids. Molecular Sciences Institute, School of Chemistry, University of the Witwatersrand, Wits, 2050, South Africa : Royal society of chemistry, 25, 166-187.

Mickevicius, Vytautas & Paraotas, Irmantas & Anusevičius, Kazimieras & Vaickelioniene, Rita & Jonukienė, Ilona & Stasevych, Maryna & Zvarych, Viktor & Komarovska-Porokhnyavets, Olena & Novikov, Volodymyr & Belyakov, Sergey, 2018, Synthesis and evaluation of the antibacterial, antioxidant activities

of novel functionalized thiazole and bis(thiazol-5-yl)methane derivatives. Arkivoc. 240 - 256. 10.24820/ark.5550190.p010.159. .

N. Barak Almandil, M. Taha, F. Rahim, A. Wadood, S. Imran, M.A. Alqahtani, Y.A., 2018, Synthesis of novel quinoline-based thiadiazole, evaluation of their antileishmanial potential and molecular docking studies. Bioorganic Chemistry, doi: https://doi.org/10.1016/j.bioorg.2018.12.025.

N. C. Desai, V. V. Joshi, K. M. Rajpara, 2013, Synthesis of new quinoline-2-pyrazoline-based thiazolinone derivatives as potential antimicrobial agents. Med Chem Res; 22:3663–3674. DOI 10.1007/s00044-012-0377-3.

Nadeem Siddiqui, M. Faiz Arshad, Waquar Ahsan, M. Shamsher Alam, 2009, Thiazoles: A Valuable Insight into the Recent Advances and Biological Activities . Jamia Hamdard (Hamdard University), New Delhi : International Journal of Pharmaceutical Sciences and Drug Research; 1(3): 136-143.

Nikaido, Hiroshi, 2009, Multidrug resistance in bacteria. Annual review of biochemistry vol. 78: 119-46.

N.G. Heatley, 1944, A Method for the Assay of Penicillin, Biochem. J. 38, 61–65.

Quin, Louis D., 2010, Fundamentals of Heterocyclic Compounds. Canada : John Wiley & Sons, Inc., Hoboken, New Jersey.

S.A. Khan, A.M. Asiri, H. Mussa Basisi, M. Asad, M.E.M. Zayed, K. Sharma, M. Younus Wani, 2019, Synthesis and evaluation of Quinoline-3-carbonitrile derivatives as potential antibacterial agents. Bioorganic Chemistry, https://doi.org/10.1016/j.bioorg.2019.102968.

Sahdeo Prasad, Subash C Gupta, Amit K Tyagi, 2017, Reactive oxygen species (ROS) and cancer: Role of antioxidative nutraceuticals. Cancer letters vol. 387: 95-105. doi:10.1016/j.canlet.2016.03.042.

Sally I. Eissa, Amel M Farrag, Samir Y Abbas, Mohamed F El Shehry, Ahmed Ragab, Eman A Fayed, Yousry A Ammar, 2021, Novel structural hybrids of quinoline and thiazole moieties: Synthesis and evaluation of antibacterial and antifungal activities

with molecular modeling studies. Bioorganic chemistry vol. 110 : 104803. doi:10.1016/j.bioorg.2021.104803.

Samir Bondock, Tamer Naser, Yousry A Ammar, 2013, Synthesis of some new 2-(3-pyridyl)-4,5-disubstituted thiazoles as potent antimicrobial agents. European journal of medicinal chemistry vol. 62: 270-9. doi:10.1016/j.ejmech.2012.12.050.

Shaikh, Farooq, Kurjogi, Hosamani, 2016, Antimicrobial And Anti-Inflammatory Activity Of Schiff-Base Derivatives Containing Benzimidazole Moiety. ejpmr,3(7), 457-462.

Shang, Susan, G Yang, Liu, Guo, Xu, Goto, Jun-Cai Li, Ji-Yu Zhang, Kuo-Hsiung, 2018, Biologically active quinoline and quinazoline alkaloids part II. Med Res Rev; 1–47. DOI: 10.1002/med.21492.

Sheng-Feng Cui, Dinesh Addla and Cheng-He Zhou, 2016, Novel 3-Aminothiazolquinolones: Design, Synthesis, Bioactive Evaluation, SARs, and Preliminary Antibacterial Mechanism. J. Med. Chem. 59, 10, 4488–4510.

Sunil Kumar, Ranjana Aggarwal, 2019, Thiazole: A Privileged Motif in Marine Natural Products. Mini-Reviews in Organic Chemistry, 16, 26-34.

V. Jaishree, N. Ramdas, J. Sachin, B. Ramesh, 2012, In vitro antioxidant properties of new thiazole derivatives. Journal of Saudi Chemical Society 16, 371–376.

Wu, Yong-Jin; Heterocycles and Medicine: A Survey of the Heterocyclic Drugs Approved by the U.S. FDA from 2000 to Present, 2012. USA : Neuroscience Discovery Chemistry, Research and Development, Bristol-Myers Squibb Company, Wallingford, CT 06492-7660.