SYNTHESIS AND CHARACTERIZATION OF SCHIFF BASE LIGANDS WITH BENZENE RING, THEIR Pd(II) AND Pt(II) METAL COMPLEXES

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Master D. Thesis

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I certify that in my opinion the thesis submitted by Ahmed Sultan Sameer AL-ISSWI titled "SYNTHESİS AND CHARACTERİZATİON OF SCHİFF BASE LİGANDS WİTH BENZENE RİNG, THEİR Pd(II) AND Pt(II) METAL COMPLEXES" is fully adequate in scope and in quality as a thesis for the degree of Master Degree.

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This thesis is accepted by the examining committee with a unanimous vote in the Department of Chemistry as a Master of Science thesis. 17/01/2024

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Ahmed Sultan Sameer AL-ISSWI

ABSTRACT

Master Thesis

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In this study, three bidentate Schiff base ligands obtained from the reactions of 2-aminomethyl thiophene, 2-aminomethyl pyridine, and 2-aminomethyl piperidine amines with benzaldehyde were synthesized, and their corresponding platinum (II) and palladium (II) metal complexes were prepared. Ligands coordinate with the metal center through the S and N atoms to form a square-planar complex [$MLCl_2$]. The ligands and the corresponding Pd (II) and Pt (II) complexes were characterized using FT-IR, ^{1}H-NMR, ^{13}C-NMR, ESI-MS, and MALDI TOF-MS methods.

Key Word **:** Schiff base, Ligand synthesis, Metal complex, Platinum, Palladium.
Science Code : 20103

ÖZET

Yüksek Lisans Tezi

BENZEN HALKALI SCHİFF BAZI LİGANDLARIN Pd(II) VE Pt(II) METAL KOMPLEKSLERİNİN SENTEZİ, YAPILARININ AYDINLATILMASI

Ahmed Sultan Sameer AL-ISSWI

Karabük Üniversitesi
Lisansüstü Eğitim Enstitüsü
Kimya Anabilim Dalı

Tez Danışmanı:
Dr. Öğr. Üyesi İsmail YILMAZ
Ocak 2024, 65 sayfa

Bu çalışmada 2-aminometil tiyofen, 2-aminometil piridin ve 2-aminometil piperidin aminlerin benzaldehit ile reaksiyonlarından elde edilen üç adet iki dişli Schiff bazı ligandı sentezlendi ve platin (II) ve paladyum (II) ile metal kompleksleri hazırlandı. Ligandlar kare-düzlem [$MLCl_2$] formunda kompleks oluşturmak için S atomu ve N atomu aracılığıyla metal merkezine koordine olur. Ligandlar ve Pd (II) ve Pt (II) komplekslerinin yapıları, FT-IR, ^{1}H-NMR, ^{13}C-NMR, ESI-MS ve MALDİ TOF-MS metodları kullanılarak karakterize edildi.

Anahtar Sözcükler : Schiff bazı, Ligand sentezi, Metal kompleksi, Platin, Paladyum.
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ABBREVITIONS

NMR : Nuclear magnetic resonance spectroscopy
FT-IR : Fourier Transform Infrared Spectroscopy
DMF : N, N-dimethylformamide
DMSO : dimethyl sulfoxide
M.W : Molecular Weight

SYMBOLS

°C : Degrees Celsius
g : Gram
mL : milliliter
DCM : dichloromethane
MS : Mass spectrometry
ppm : parts per million
Al : Aliphatic
Ar : Aromatic
Pd : Palladium
Pt : Platinum

PART 1

THE AIM AND IMPORTANCE OF THE STUDY

Schiff bases and them derivatives are essential in coordination chemistry because of their adaptability and capacity to create stable coordination compounds with transition metals. Schiff bases, organic compounds containing the imine functional group (-C=N), have been extensively studied for their remarkable capacity to serve as very efficient chelators for various metal ions. Much work has been focused on creating and studying Schiff bases with many binding sites, allowing them to attach to metal centers and form coordination compounds with exceptional structural design.

Schiff bases are manufactured using heterogeneous aromatic rings containing sulfur and nitrogen into important coordination complexes with biological activity. On the other hand, the aim of synthesizing heterocyclic Schiff base complexes containing platinum or palladium is to create innovative compounds with potentially superior activity against cancer cells, especially resistant ones, compared to conventional cisplatin derivatives and exhibiting a more comprehensive range of anti-cancer properties. Platinum complexes are frequently used to treat approximately 50% of patients undergoing cancer therapy. *Cis*-platinum was the first platinum compound discovered for its anti-cancer properties. Palladium complexes also show similar properties to platinum complexes, and their cancer drug potential is being highly investigated.

Bi-dentate Schiff bases with their palladium and platinum complexes were successfully synthesized. As in previous studies, the chelating ligands form square-plane complexes with palladium (II) and platinum (II) ions, usually in the *cis* structure. The biological properties of the obtained compounds will be examined in further studies.

PART 2

INTRODUCTION

2.1. THE IMPORTANCE OF COORDINATION CHEMISTRY IN BIOLOGICAL SYSTEMS

Inorganic chemistry has a vast and expanding application in medicine, particularly concerning inorganic complexes, which are extremely important.[1]. Progress in bio-coordination chemistry is essential for enhancing the formulation of molecules to minimize harmful side effects and comprehend their modes of operation [2]. Coordination chemicals have a crucial role in biological systems. The presence of chlorophyll in hemoglobin, which is essential for sustaining life, relies on this molecule [3]. The role of hemoglobin in carrying oxygen and the function of chlorophyll in producing oxygen in green plants are vitally important. Myoglobin, phthalocyanine, and vitamin B12 are examples of coordination compounds in living systems. In the hemoglobin structure Figure 2.1. The complexes formed by metal ions within the biological body are biological catalysts. Likewise, platinum and palladium complexes have biological activity in the body and are also used as a treatment for cancer [4]. The binding of Fe^{3+} with morphine and histamine demonstrates the significance of hemoglobin as a prominent illustration of coordination chemistry within our bodies [5].

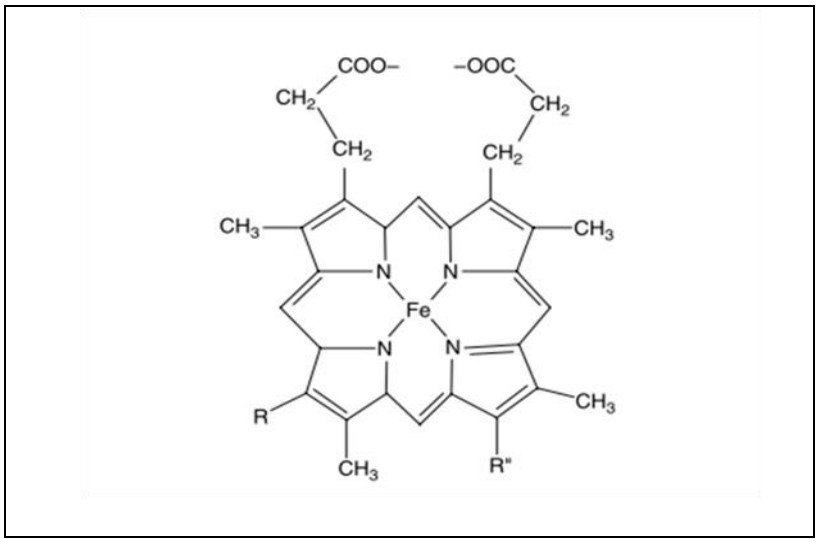

Figure 2.1. Iron complexes hemoglobin structure [6].

2.2. SCHIFF'S BASES

Schiff bases contain an azomethane group (-HC=N-). Schiff bases usually consist of the reaction of aldehydes and ketones with primary amines. They were first discovered in 1864 by the scientist Hugo Schiff. The formation of Schiff bases often occurs through acid or base catalysis [7]. Schiff bases serve as ligands to form metal complexes of diverse forms and as intermediates in the synthesis of amino acids [8]. Schiff base ligands, which are flexible, have an essential place in coordination chemistry thanks to azomethine nitrogen and other donor atoms in their structure [9]. The Schiff bases formed by the reaction of amines or aliphatic or aromatic amino acids with aromatic aldehydes have significant thermal stability. In their solid form, these compounds maintain this stability. Conversely, the molecules resulting from the condensation of aliphatic amines are predominantly in liquid state [10,11]. Schiff bases are generally bi, tri dentate chelate ligands Figure 2.2.

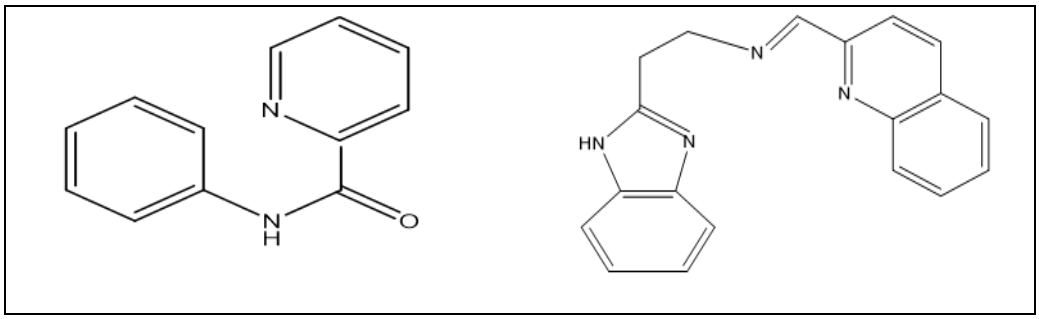

Figure 2.2. Examples of monodentate, bidentate Schiff bases[12].

Numerous researchers have thoroughly investigated these chemicals to analyze their chemical and physical characteristics across disciplines. The domains encompassed in this study involve applying preparation techniques, identification methods, protective measures, and determination procedures for aldehydes or ketones. It also includes the purification of carbonyl and amino compounds and synthesizing these compounds in intricate or delicate reactions [13]. The condensation products produced by the process by which primary amines react with carbonyl compounds is referred to as Schiff bases formation. As an analog of a ketone or aldehyde, a Schiff base, sometimes called an imine or azomethine group, is created by substituting an imine or azomethine group for the carbonyl group (C=O). A Schiff base is a chemical molecule where the nitrogen atom forms a connection with an aryl or alkyl group (R) rather than hydrogen. The chemical possesses a functional group in the form of a carbon-nitrogen double bond [14].

The Schiff base, also known as an azomethine, has a general structure that can be described as follows. Figure 2.3 illustrates that R represents either a phenyl or alkyl group, which contributes to the stability of the Schiff base by forming a stable imine [15].

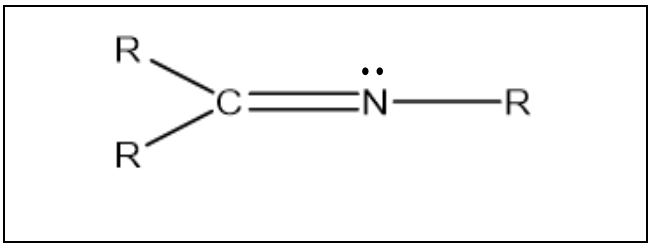

Figure 2.3. Schiff base general structure [16].

Sulfur or nitrogen atoms can replace the oxygen atoms. The production often occurs via combining an aldehyde or ketone with a primary amine to form a condensation product, as depicted by the provided process [17]. Schiff bases are a widely recognized group of chemical substances, primarily synthesized by combining primary aromatic amines with carbonyl compounds. Their excellent stability is attributed to the presence of the azomethine group, and they exhibit ligand functionality in the field of coordination chemistry [18,19].

2.3. SCHIFF BASE METAL COMPLEXES

Schiff bases are crucial ligands in metallic complexes by coordinating with metal ions. This coordination results in the formation of stable structures, which can enhance the biological activity of the ligand [20]. These ligands can form complexes with metal ions by interacting with another functional group and the imine nitrogen. The Schiff base ligands provide a framework for forming coordination complexes, including significant transition metals such as Pd^{2+}, Pt^{2+}, Cu^{2+}, Zn^{2+}, Ni^{2+}, and Co^{2+}, as in Figure 2.4 [21].

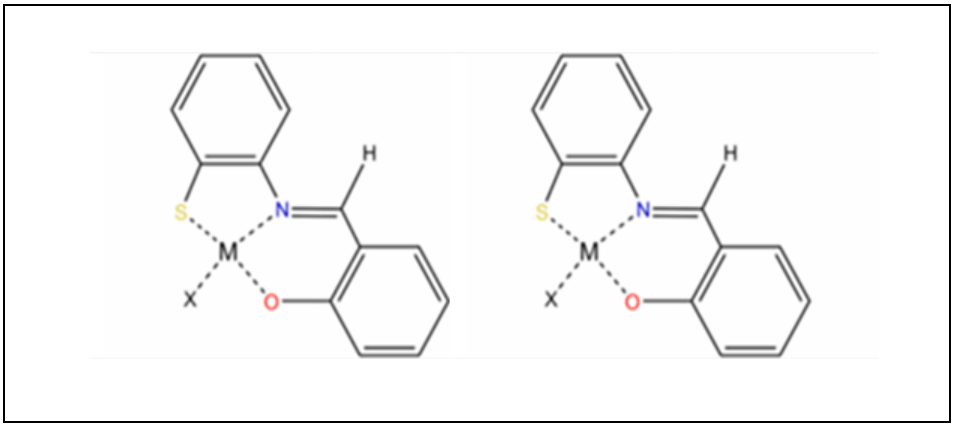

Figure 2.4. Bi and tridentate Schiff bases coordination to the transition metal. M=Pd, Pt, X=Cl [22].

The Schiff base ligands can form coordination complexes with typical transition metal ions by utilizing nitrogen and sulfur donor sites. The metal chelates of the Schiff base have improved biological and DNA binding characteristics [23,24]. Following the accidental discovery of *cis*-platin in 1965 and its remarkable effectiveness in treating

cancer, researchers became interested in exploring the potential of developing new metal-inorganic complexes as chemotherapeutic medicines [25,26]. The metal complexes that have been most extensively studied so far involve core metal ions of platinum and palladium [27]. However, because of their high cost and the adverse side effects linked to the previously stated metal centers, second-row transition metal complexes are considered promising candidates for designing possible anti-cancer drugs [28]. The binding ability of these compounds is enhanced by their definite coordination geometries and specific photophysical characteristics [29]. Most inorganic medicines used as antifungal, antibacterial, and antineoplastic treatments contain these metal ions [30]. This context focuses on developing possible metal-organic compounds with chemotherapeutic capabilities using platinum (II) and palladium (II) transition metals. Their metal complexes, which possess identical ligands, exhibit varying affinity for DNA interaction. The uneven allocation of electrons in the d subshell may explain the spectral, magnetic, redox activity variations and structural properties observed among their analogs [31]. Transition metal complexes featuring planar aromatic side groups are particularly intriguing because they can interact with DNA by coordinating with metal ions and intercalating the aromatic side chains. For a complex to exhibit these characteristics, it must possess vacant coordination sites, the ability to expand its coordination shell, or ligands that can be easily replaced [32]. Dyson Liu and Sadler have recently documented some compounds that possess the potential to form both covalent and non-covalent bonds with DNA. These complexes have more activity than covalent binders using nitrogen and sulfur atoms [33].

2.4. NEW TRENDS IN PLATINUM AND PALLADIUM COMPLEXES AS ANTINEOPLASTIC AGENTS

The coordination modes and chemical characteristics of platinum (II) and palladium (II) are highly analogous, resulting in similar behavior of their complexes. Pd (II) has garnered significant interest as a potential substitute for platinum in the quest for novel cisplatin analogs for anti-cancer therapies [34]. Platinum (II) complexes have garnered significant interest from researchers due to their potent effectiveness as anti-cancer agents. The study revealed that the ligands' characteristics and organization can impact

the medication's mechanism of action and metabolism throughout its passage through the cell membrane and intracellular space [35]. However, *cis*-platin is commonly employed as an anti-cancer medication. Although there is a growing interest in exploring other metal ions, platinum complexes are currently the sole metal-based pharmaceuticals utilized in medical environments. Figure 2.5, along with approximately ten additional platinum complexes, are presently undergoing clinical studies [36].

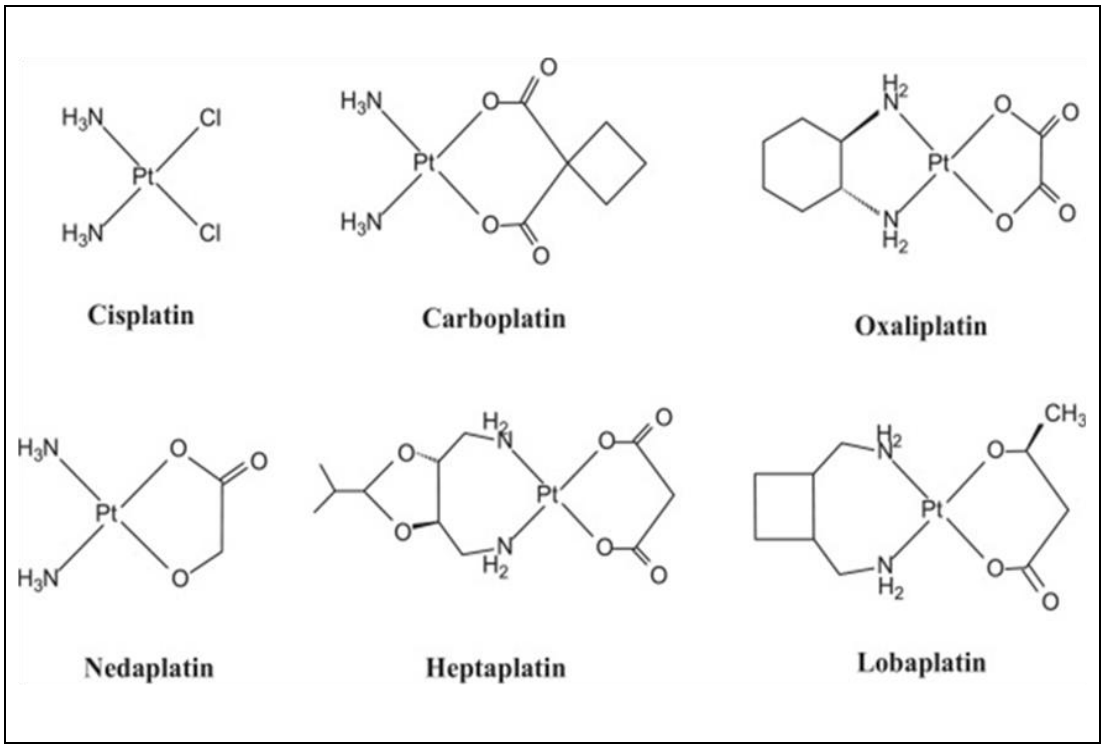

Figure 2.5. Commonly used medications for the treatment of cancer [37].

Carboplatin, a second-generation platinum-based anti-cancer medication, is commonly used due to its substitution of chloro ligands with carboxylate groups. This alteration pertains to the chemical compound *cis*-diamine(1,1cyclobutanedicarboxylate) platinum (II) results in reduced side effects compared to *cis*-platin [38]. The emergence of many novel platinum-based anti-cancer medications, such as Carboplatin, Nedaplatin, Lobaplatin, and Oxaliplatin (as shown in Figure 2.5), continues to face limitations and does not provide any additional clinical benefits compared to the already available cisplatin [39]. Moreover, the development of resistance to *cis*-platin is commonly reported as a result of chemotherapy [40]. There

is considerable interest in Pd (II) analogs due to their typical isostructural nature with Pt (II) analogs. This similarity allows for a comparable coordination mechanism and geometry [41].

Nevertheless, Pd (II) systems achieve equilibrium significantly faster than Pt (II) systems, with kinetics approximately 10^4-10^5 times faster. The sluggish rate of production for Pt (II) complexes typically precludes the calculation of stability constants [42]. Thus, Pd (II) complexes are commonly employed as representative models to investigate the interaction between Pt (II) and DNA, as well as to imitate the binding characteristics of different platinum (II) species [43]. Additionally, it has been proposed that the more rapid substitution of ligands in palladium (II) compared to platinum (II) in laboratory conditions makes palladium a more suitable model for investigating platinum (II) reactions in living organisms [44]. Biological processes involving platinum (II) complexes always initiate with the process of aquation. Multiple palladium complexes have been documented [45]. Bidentate amine ligands have demonstrated anti-cancer activity that is equivalent to or surpasses that of cisplatin.

Furthermore, a sequence of unstable Pd (II) complexes has demonstrated their utility as analogs for comprehensively understanding the thermodynamics of processes involving closely related Pt (II) complexes. Furthermore, there is a suggestion that these palladium complexes could be beneficial in treating gastrointestinal cancers resistant to cisplatin [46]. Mono-dentate ligands can attach to a metal in either a *cis*- or trans-configuration, and various circumstances determine the stability of these isomers. As a result, bidentate ligands are more dependable for creating *cis*-complexes, especially with palladium (II) and platinum (II) [47]. Studying the interaction between DNA bases and Pd (II)/Pt (II) complexes, which possess chelating N, N'-donors and a *cis*-MCl_2 configuration, provides a model system for understanding the mechanism behind the anti-tumor effects of cisplatin. We aim to clarify the coordination chemistry of mixed-ligand palladium complexes that consist of bidentate amines and biologically active ligands, due to their potential as effective anti-cancer drugs [48]. The platinum complexes formed by combining aniline and 2-pyridine carboxaldehyde have shown significant efficacy against the hormone-independent human cell line derived from

breast cancer. The cellular lineage is the cell line MDA-MB 231 [49]. One such complex is [dichloro-N-(pyridine-2-yl) methylene benzamine platinum (II) Figure2.6. which is the primary. *Cis*-platin derivatives containing an aliphatic amine moiety have demonstrated significant cytotoxicity in cell lines resistant to *cis*-platin [50]. The challenges occur due to the inability of anti-cancer medications to distinguish between healthy and malignant cells. This has prompted significant research on creating platinum complexes that demonstrate increased selectivity towards [51].

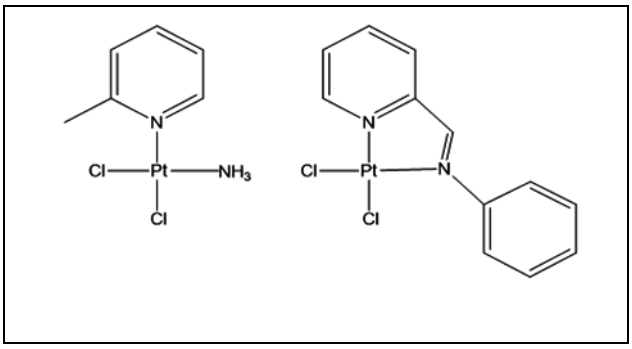

Figure 2.6. Structure of picoplatin (ZD0473) (a) and dichloride-N-(pyridine-2-methylene) aniline platinum (II) [50].

2.4.1. Complexes' Mechanisms of Binding DNA

Most drugs used in clinical settings, including anti-cancer ones, interact with DNA by taking on a covalent or non-covalent binding mode. Through alkylation or intera/interstrand cross-linking, those that engage through covalent binding create covalent adducts with DNA. Covalent interactions produce a compound-DNA complex that is irreversible and ultimately inhibits cell functions, leading to cell death. Covalent binders with large sizes form large adducts that distort the DNA backbone, leading to the inhibition of transcription and replication and the disruption of intricate proteins. These effects ultimately lead to the death of cells [52].

Megaliter ablators are created when tiny organic intercalators (ligands) form a covalent connection with transition metals. The dual function of side chain-containing metal complexes is demonstrated by their ability to bind DNA through metal coordination and side arm intercalation [53]. Covalent binders are also known as alkylating agents because they generate adducts when they bind an alkyl group to DNA. The well-known

covalent linker cis-platin is a molecule that targets DNA by forming intra- or inter-chain cross-links through chloro groups. It is utilized in the treatment of cancer. This is because it can covalently bind to purine nucleotides in DNA. Given that guanine is the most nucleophilic DNA base, guanine-N7 is the most favored location for the Pt (II) complex to attach Figure 2.7. The Hard, Soft Acid Base (HSAB) theory explains the interaction on the seventh site of guanine.

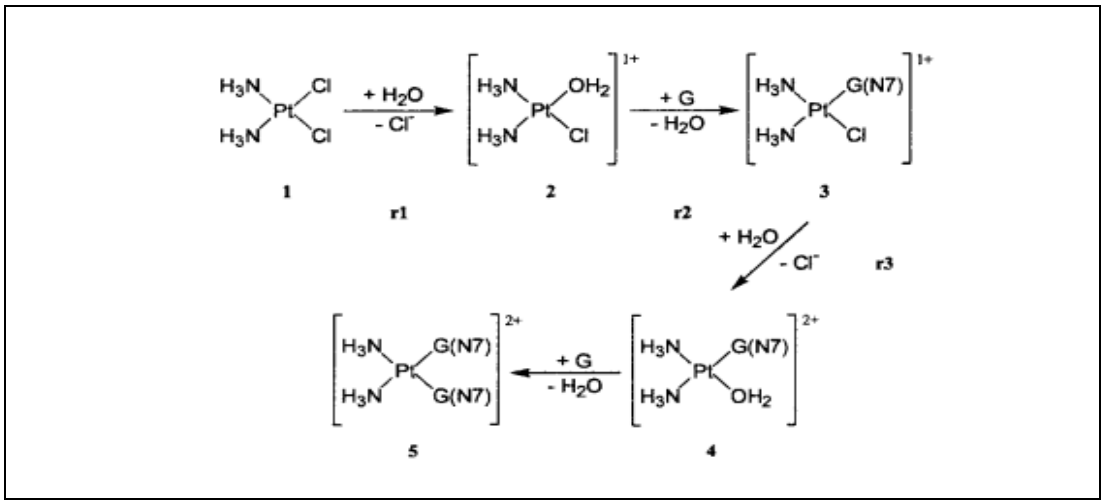

Figure 2.7. The scheme for cis-platin reaction with DNA [53].

Two classifications of complexes consist of anionic leaving groups with low reactivity, for example, the dicarboxylate group present in carboplatin, which undergoes hydrolysis at a slow rate. Two categories of platinum complexes are considered less toxic. The first category is water-soluble, meaning it can dissolve in water. This type is stable and remains in the bloodstream for a more extended period. The second category is water-insoluble or lipophilic, meaning it does not dissolve in water but can dissolve in fats. This type hydrolyzes slowly and is easily removed from the bloodstream through tissue penetration. As a result, the use of platinum complexes can lead to typical toxic side effects [54].

2.4.2. Anti-Cancer Platinum Medications That Start With Cisplatin and Substitute Amine or Chloride Ligands

The reasoning behind creating cisplatin analogs is based on basic coordination chemistry principles and the findings of mechanistic studies [55]. The general formula

for these neutral complexes is [PtX_2(A)n]. The compound has a square planar structure with two departing groups (X) positioned in the cis configuration. The last two sites are occupied by either two monodentate ligands (A, n=2) or one bidentate chelating diamine (A, n=1) that supplies the amine nitrogen atom [56]. Upon entering the cell, either one or both of the X ligands undergo substitution with water molecules. The complex's high lipophilicity and chemical neutrality make the substitution easier. The X anion commonly establishes chemical connections with atoms that act as electron donors, such as oxygen, iodide, and chloride atoms [56]. Nitrogen, as the donor atom in ligand A, is the primary cause for the platinum to form thermodynamically stable bonds, which remain intact even in the adduct produced with DNA. The latter is created by removing water molecules as the platinum ion of the corresponding species makes a covalent bond with the nitrogen atom at the purine 7-position. The resultant adduct exhibits high kinetic stability because of the low transaction of amines and heterocyclic nitrogen ligands. This is an essential consideration in developing novel cisplatin analogs [57]. 1,2- and 1,3-intrastrand cross-links can develop between neighboring guanines due to the metal complex's cis geometry; the trans isomer cannot produce these types of cross-links due to geometric constraints. The resultant intrastrain adduct bends and distorts DNA, causing various biological reactions, including death, DNA repair, transcription inhibition, replication, and cell-cycle halt [58].

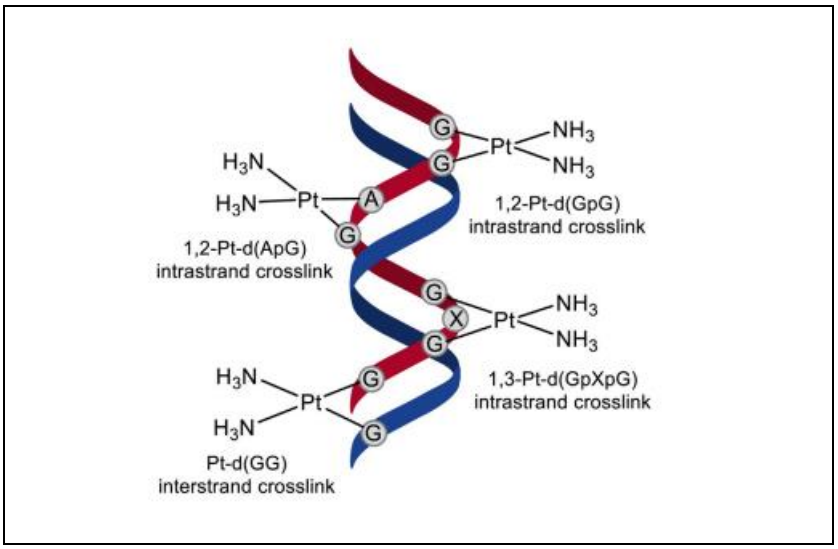

Figure 2.8. In this form, cisplatin creates bonds with DNA through the amino group on the platinum atom [59].

PART 3

PREVIOUS STUDIES

A Schiff base, designated as HL_2, was produced through the condensation reaction between the compounds mentioned are 4-(2-amino-ethyl)benzene-1,2-diol and 2-hydroxy-benzaldehyde. Consequently, transition metal complexes were synthesized and analyzed using the general formulas $Ni(L)_2$, $Pd(L)_2$, and $Pt(L)Cl_2$. An array of techniques was employed to analyze the ligand and its metal complexes, specifically nickel (II), palladium (II), and platinum (II), including FT-IR spectroscopy, ^{1}H-NMR spectroscopy, elemental analysis, determination of metal and chloride content, assessment of magnetic susceptibility, and mass spectrometry (MS) [59].

The process of creating and analyzing compounds containing palladium(II) and platinum(II) [MLX_2] has been performed. The complexes consist of L, which represents 2-(4'-methyl-2'-pyridyl) benzimidazole. Additionally, the specified compounds are 2-(4'-methyl-2'-pyridyl)benzoxazole(mpbo), 2-(4'-methyl-2'-quinolyl)benzoxazole(mqbo), and 2-(4'-methyl-8'-quinolyl)benzoxazole (mq'bo). X is also included, which represents either C1 or Br. The characterization process encompassed conductivity and magnetic measurements, in addition to i.r. and electronic spectra. Furthermore, $M(mqbo)_2Br_2$ and $Pt_2(mpbt)C1_4$, where mpbt denotes 2-(4'-methyl-2'-pyridyl)benzothiazole, have been synthesized and characterized using the same methods. The ligands form bidentate chelates by binding to the nitrogen atoms of pyridine or quinoline, as well as isoxazole or imidazole. The derivatives of [MLX_2] exhibit a *cis* conformation and possess a square planar structure [60].

Schiff base ligands were utilized to produce complexes (C1-C5) consisting of palladium in its+2 oxidation state and platinum in its +2 oxidation state. The ligands employed in this investigation are R-(phenyl) methenamine (L1), R-(pyridin-2-yl) methenamine(L2), and R-(furan-2-yl) methenamine(L3), specifically R-(E)-N-((1H-

pyrrol-2-yl)methylene). The complexes (C1–C5) were analyzed using Fourier Transform Infrared Spectroscopy and Proton Nuclear Magnetic Resonance. An X-ray crystallography investigation was conducted on the ligands (L1-L2) and a platinum complex. L1 and L2 are categorized inside the P21/n monoclinic and P-1 triclinic space systems. The C5 complex is categorized within the P21/c monoclinic space group. The log P values were more than or equal to 1.2692 ± 0.004, suggesting the presence of lipophilicity. The complexes were analyzed to determine their effectiveness in inhibiting cancer and the mechanism by which they operate on various human cancer cell lines (Caco-2, HeLa, HepG2, MCF-7, and PC-3), as well as a noncancerous cell line (MCF-12A) [61].

The work entails the production of Pd(II) and Pt(II) compounds by combining four Schiff base ligands containing phosphorus and four hydrazonoic-phosphines. The complexes B1 and B2 consist of Phosphorus Schiff base ligands coordinated with Pd (II) ions, have been effectively developed and characterized. These complexes have the strongest affinity for DNA binding, has been accomplished. An empirical investigation evaluates the DNA-binding affinities of these recently found Pd(II) complexes. The modalities via which these metal complexes induce apoptosis in the designated cells via various methods are ascertained by performing flow cytometry analysis to examine apoptosis and conducting a colony formation investigation [62].

The platinum (II) complexes $[Pt(L1H)_2]Cl_2$, $[Pt(L2H)]Cl_2$, and $[Pt(L)_2]$ are formed through the combination of reactive Schiff's base ligands. The chemical abbreviation L1H refers to hydrazinecarbothiamide of 5-bromoindolinedione, while L2H indicates hydrazine carboxamide of 5-bromoindolinedione. The characterization of all compounds in this study was performed using ^{1}H-NMR and IR spectroscopy. The molar conductance experiments provide evidence that supports the 1:1 stoichiometry of these substances. Pt(II) complexes have diamagnetic properties and a square planar structure. The IR spectrum data indicates that Schiff's bases act as bidentate ligands, forming a bond with the Pt(II) metal through the sulfur and hydrogenic nitrogen atom [63].

The formation of a Pd(II) complex was achieved by reacting $PdCl_2$ with pyridine-2-benzotriazole, which was dissolved in toluene. The molecular structures and vibrational characteristics of a Pd(II) complex were examined using FT-IR analysis. The structural characteristics were ascertained utilizing nuclear magnetic resonance (NMR) methodologies. Moreover, an NMR spectrum was employed to ascertain the specific nitrogen atom to which the Pd atom established a chemical bond [64].

Pd(II) and Pt(II) complexes containing phenylalanine ester groups, the pyridyl amino group is attached to a metal center by utilizing the production of Schiff bases via amino acids as an intermediary step. Distinct crystals of each chemical were successfully produced, and their molecular structures were thoroughly ascertained. The Pd (II) complex exhibited significant cytotoxicity in comparison to the Pt(II) complex [65].

Pd(II) and Pt(II) complexes were synthesized and examined. The amines employed in the process were o-toluidine, m-toluidine, and p-toluidine, and 4-hydroxy aniline to ascertain their properties, the compounds underwent elemental analysis, FT-IR spectroscopy, ^{1}H-NMR spectroscopy and MALDI-TOF mass spectrometry. DNA adduct formation was evaluated using circular dichroism and electrophoretic mobility analysis. In addition, atomic force microscopy captured photos of the compounds containing DNA. Pd(II) or Pt(II) ions induce notable alterations in DNA's secondary and tertiary configuration in every instance by binding to the nitrogen atoms of the nucleobases. The findings exhibited a robust capacity to inhibit cell proliferation and a significant augmentation in apoptosis [66].

Pd(II) and Pt(II) were reacted with basic aromatic diamines to investigate their potential anti-cancer effects. The selected diamines consist of 2,3-diamino toluene (2,3 dat), 3,4-diamino toluene(3,4 dat), 4,5-diamino xylene(4,5 dax), and 2,3-diaminophenol(2,3 dap) are all compounds that exhibit aromatic characteristics. The complexes, specifically called *cis*-[MCl_2(diamine)], were examined using chemical analysis, conductivity testing, and NMR spectroscopy utilizing ^{1}H and ^{13}C. The X-ray crystallography technique was employed to establish the crystal structure of the Pd(II) complexes that incorporate 2,3-diamino toluene and 4,5-diaminoxylene. In addition, atomic force microscopy was employed to capture images of the alterations induced

by the complexes on plasmid DNA pBR322. The IC50 values were determined for the four platinum complexes against the A2780cisR cancer cell line, which exhibits resistance to *cis*-platin [67].

Pd(II) and Pt(II) complexes that inhibit cell growth were created, incorporating biomolecular connections to utilize them as medications for treating cancer. The metals used are platinum and palladium, which are bonded with either a single (imidazoline-2-imine) or double (imidazoline-2-imine) chelating bond. The compounds [Pd(DMEAImiPr)Cl_2], [Pd(DACH(ImiPr)2)Cl_2], and [Pt(DMEAImiPr)Cl_2] are being referred to. the metal complexes display a range of cytotoxicity against certain cancer cell lines, varying from modest to powerful. The spectrophotometric approach investigated the interactions between these complexes and the model DNA oligos or protein molecules. The ESI-MS findings unequivocally establish the presence of approximations. The UV-Vi metal complexes were employed to investigate their interaction with CT-DNA, specifically calf thymus DNA, by analyzing their absorption and emission spectra [68].

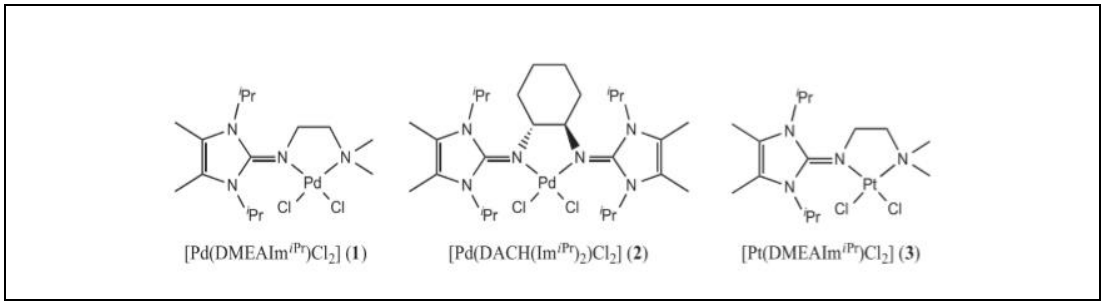

Figure 3.1. Some Platinum and Palladium schiff base complexes [69].

PART 4

CHEMICALS AND MATERIALS

4.1. USED DEVICES

- NMR: AGILENT 400/54, 400 MHz, Chemistry Department of the Faculty of Basic Sciences at Recep Tayyip Erdogan University.
- FT-IR(ATR): Thermo Scientific, Nicolet™ iS™, iD7, Department of Chemistry in Karabuk University.
- ESI-MS: Thermo Scientific TSQ Quantum Access MAX, Research Laboratory of Recep Tayyip Erdogan University (MERLAB).
- MALDI TOF-MS: Bruker Micro flex LT MALDI-TOF MS at Gebze Technical University, Faculty of Basic Sciences, Department of Chemistry.

4.2. CHEMICALS USED

Table 4.1. Chemicals used.

	Chemical	Source
1	ethanol	Merck
2	methanol	Merck
3	acetone	Merck
4	Thiophene-2-ylmethanamine	Sigma Aldrich
5	pyridine-2-ylmethanamine	Across
6	piperidine-2-ylmethanamine	Sigma Aldrich
7	Benzaldehyde	Fluka
8	$PdCl_2$	Sigma Aldrich
9	$PtCl_2$	Ambeed
10	Silica gel	Merck
11	DCM	Erba
12	DMF	Merck
13	DMSO	Merck

PART 5

EXPERIMENTAL

5.1. SYNTHESIS OF THE LIGAND

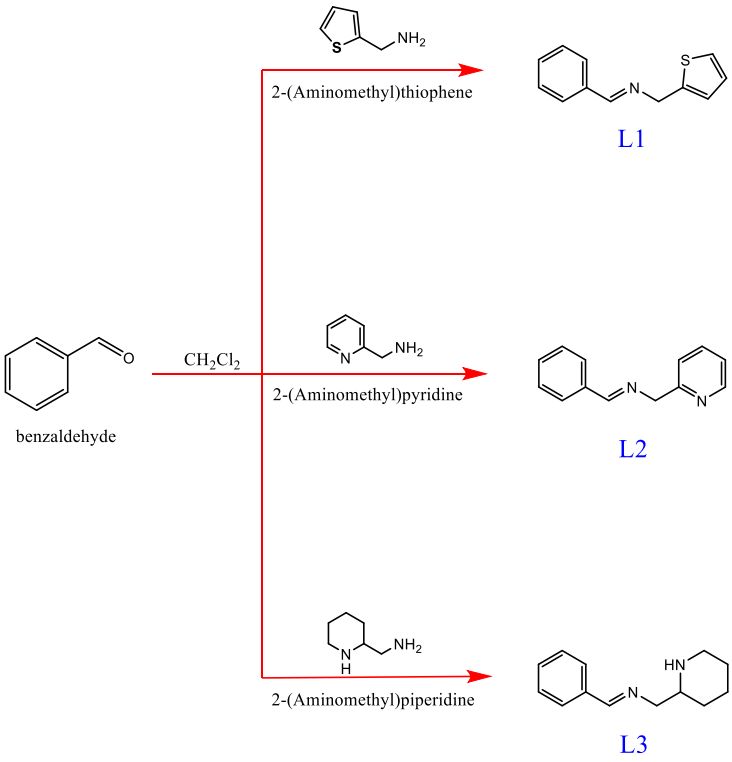

Figure 5.1. Synthesis Scheme of Ligands.

Benzaldehyde (10 mmol) was dissolved in 15 mL of dichloromethane, and a primary amine (10 mmol) was also dissolved in 15 mL of dichloromethane. Subsequently, the two solutions were gradually amalgamated by introducing tiny droplets while maintaining continuous agitation at ambient temperature. Upon completion of the addition, a solution with a yellow hue was generated. The solution underwent continuous reflux at 65°C for five hours. After the reaction, extraction was carried out by introducing a 1 M NaOH solution to the reaction mixture. The DCM phase was collected and dehydrated using $MgSO_4$. The solvent was eliminated through

evaporation with a rotary evaporator. The ligands (L1, L2, and L3) that were in the form of yellow or orange gels were dehydrated in a desiccator.

5.1.1. (E)-1-phenyl-N-(thiophen-2-ylmethyl)methanimine (L1)

FT-IR (ATR, cm-1): 3062, 2829, 1641, 1579, 1495, 1450,1431, 1377, 1360, 1307, 1292, 1218, 1169, 1074, 1025, 849, 825, 757, 689, 495.

^{1}H NMR (400 MHz, cdcl$_3$) δ 8.39 (t, *J* = 1.5 Hz, 1H), 7.87 – 7.76 (m, 2H), 7.51 – 7.38 (m, 2H), 7.30 – 7.23 (m, 1H), 7.07 – 6.98 (m, 2H), 5.01 (d, *J* = 1.8 Hz, 2H).

^{13}C NMR (101 MHz, cdcl$_3$) δ 162.30, 142.13, 135.99, 130.99, 128.68, 128.42, 126.94, 125.02, 124.78, 59.34.

ESI-MS (m/z): 201.84 (L), calculated 201.29.

5.1.2. (E)-1-phenyl-N-(pyridin-2-ylmethyl)methanimine (L2)

FT-IR (ATR, cm-1): 3059, 3027, 2821, 1642, 1588, 1568, 1491, 1472, 1454, 1432, 1308, 1205, 1148, 1069, 1047, 1026, 994, 906, 845, 745, 698, 618,517,

^{1}H NMR (400 MHz, cdcl$_3$): δ 8.60 – 8.50 (m, 1H), 8.35 – 8.24 (m, 1H), 7.74 – 7.58 (m, 2H), 7.48 (td, *J* = 7.7, 1.8 Hz, 1H), 7.40 – 7.35 (m, 2H), 7.31 – 7.17 (m, 3H), 5.12 (s, 2H).

^{13}C NMR (101 MHz, cdcl$_3$) δ 163.17, 159.44, 149.31, 148.39, 136.15, 135.28, 130.90, 128.31, 128.25, 127.92, 122.40, 121.45, 70.69.

ESI Mass (m/z): 196.91(L), calculated 196.25; 214.77 (L+H_2O), calculated 214.27.

5.1.3. (E)-1-phenyl-N-(piperidin-2-ylmethyl)methanimine (L3)

FT-IR (ATR, cm-1): 3060, 3026, 2929, 2847, 2794, 1644, 1491, 1452, 1392, 1369, 1324, 1291, 1259, 1226, 1196, 11481068, 1050,1026, 987, 939, 915, 860, 812, 770, 751, 696, 640, 621, 605, 578, 561, 492, 438.

^{1}H NMR (400 MHz, cdcl$_3$) δ 8.31 – 8.26 (m, 1H), 7.86 (dt, *J* = 6.9, 1.5 Hz, 2H), 7.75 – 7.66 (m, 1H), 7.59 – 7.39 (m, 2H), 3.63 – 3.34 (m, 2H), 2.94 – 2.74 (m, 3H), 1.78 – 1.11 (m, 6H).

^{13}C NMR (101 MHz, cdcl$_3$) δ 163.31, 139.32, 132.21, 128.73, 128.64, 128.51, 128.02, 63.18, 49.85, 48.58, 28.78, 24.96, 23.90.

ESI Mass (m/z): 202.38 (L), calculated 202.30.

5.2. SYNTHESIS OF COMPLEXES

A solution of L (5 mmol) in DMF (10 ml) was added dropwise to a stirred solution of Pd (MeCN)$_2$Cl$_2$ or Pt (COD)Cl$_2$ (5 mmol) in DMF (10 ml). The solution was refluxed for 24 hours at 100 °C. During this time, the colors of the solutions became yellow, orange, and dark orange. The complexes were purified by column chromatography on Silica gel using DMF solvent. The obtained solutions were concentrated and allowed for crystallization. Since suitable crystals could not be obtained, the solvent was removed, and the complexes were dried in a desiccator.

5.2.1. Synthesis of palladium (II) complexes (C1, C3 and C5)

5.2.1.1. Pd-L1 Complex (C1)

FT-IR (ATR, cm-1):

3281, 3106, 2922, 2852, 2190, 1651, 1576, 1537, 1488, 1472, 1384, 1346, 1246, 1176, 1119, 1073, 1039, 983, 850, 833, 748, 694, 661, 564, 476.

MALDI-TOF MS:

225.55 L+Na

305.97 PdL

379.98 $PdLCl_2$

393.81 $[PdLCl_2]+H_2O$

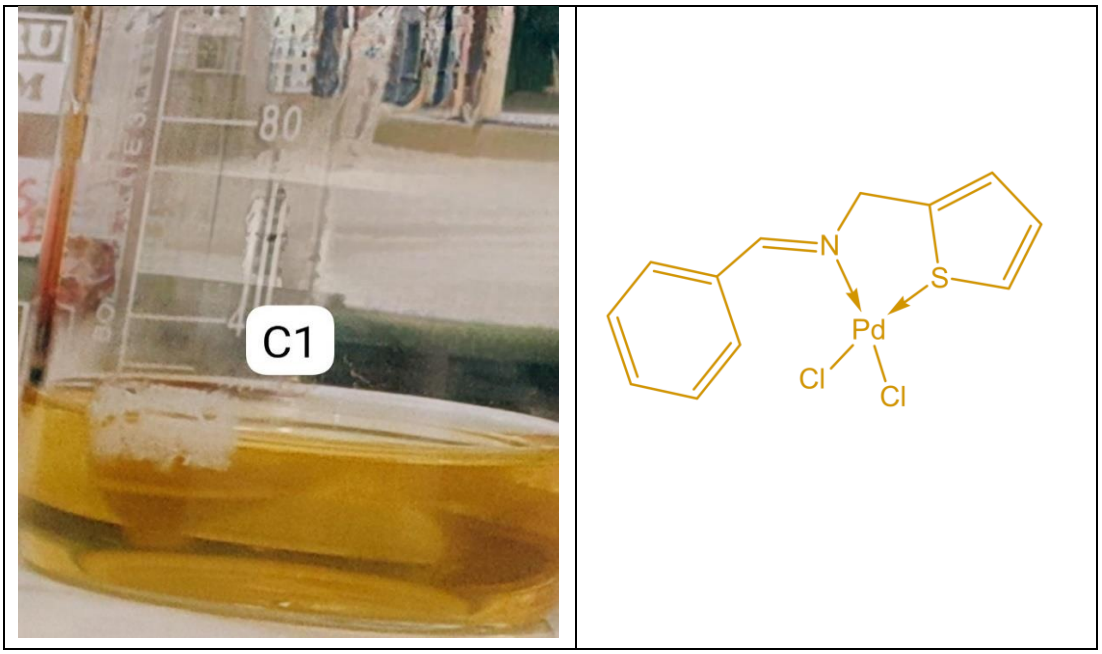

Figure 5.2. C1-Pd (II) See the job method of the complex.

5.2.1.2. Pd-L2 Complex (C3)

FT-IR (ATR, cm-1):

3471, 3233, 3208, 3005, 2980, 2924, 2189, 1634, 1451, 1420, 1386, 1251, 1137, 1125, 1050, 1012, 896, 813, 759, 701,509,435

MALDI-TOF MS :

303.67 PdL

373.04 $[PdLCl_2]$

389.91[$PdL_2Cl_2]+H_2O$

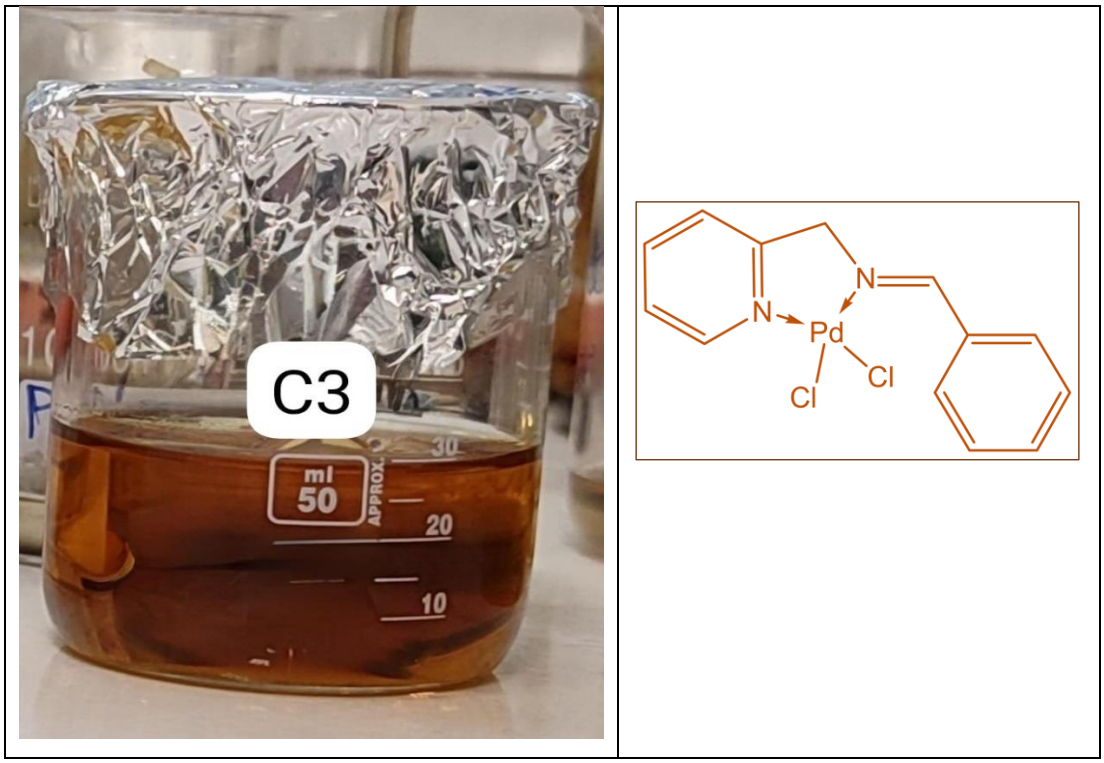

Figure 5.3. C3-Pd (II) See the job method of the complex.

5.2.1.3. Pd-L3 Complex (C5)

FT-IR (ATR, cm-1):

3274, 3193, 3099, 2923, 2858, 2182, 1658, 1566, 1445, 1341, 1271, 1211, 1158, 1135, 1088, 1073, 1052, 1034, 964, 935, 902, 873, 858, 789, 754, 702, 670, 641, 556, 516, 469, 418.

MALDI-TOF MS:

312.26 PdL

380.44 $[PdLCl_2]$

389.59 $[PdLCl_2]+0.5\ H_2O$

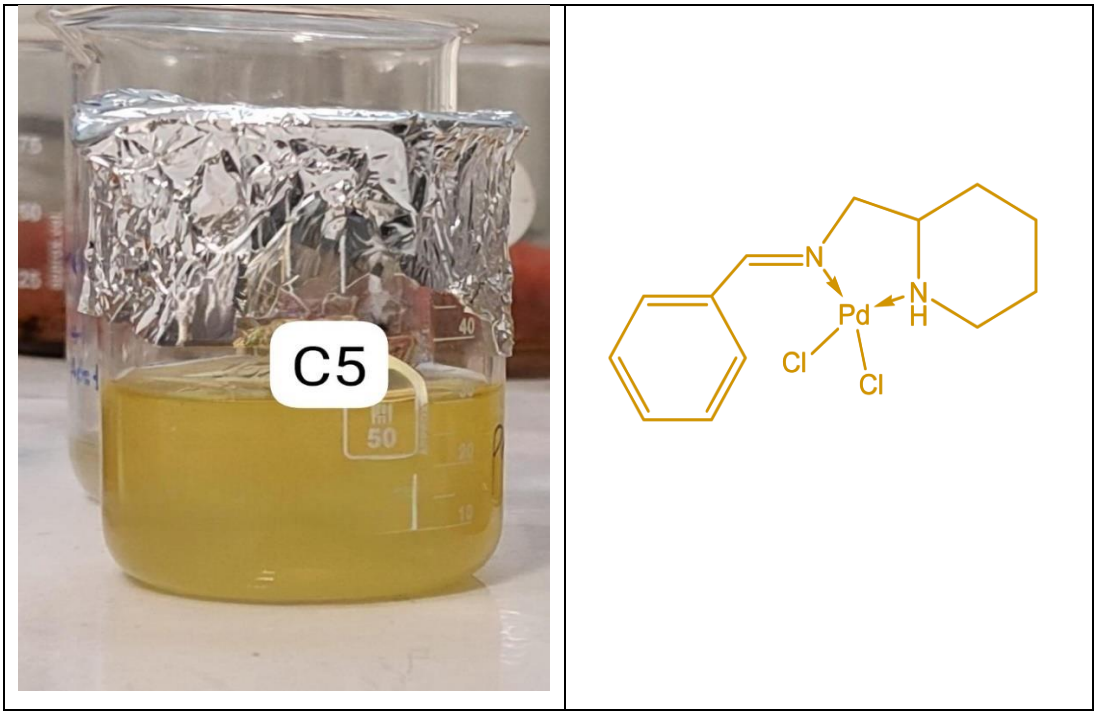

Figure 5.4. C5-Pd (II) See the job method of the complex.

5.2.2. Synthesis of Platinum complexes (C2, C4andAC6)

5.2.2.1. Pt-L1 Complex (C2)

FT-IR (ATR, cm-1):

3213, 3075, 2920, 2851, 2186, 1651, 1445, 1377, 1331, 1292, 1053, 762, 698, 462.

MALDI-TOF MS :

396.51 PtL

466.56 [$PtL1Cl_2$]

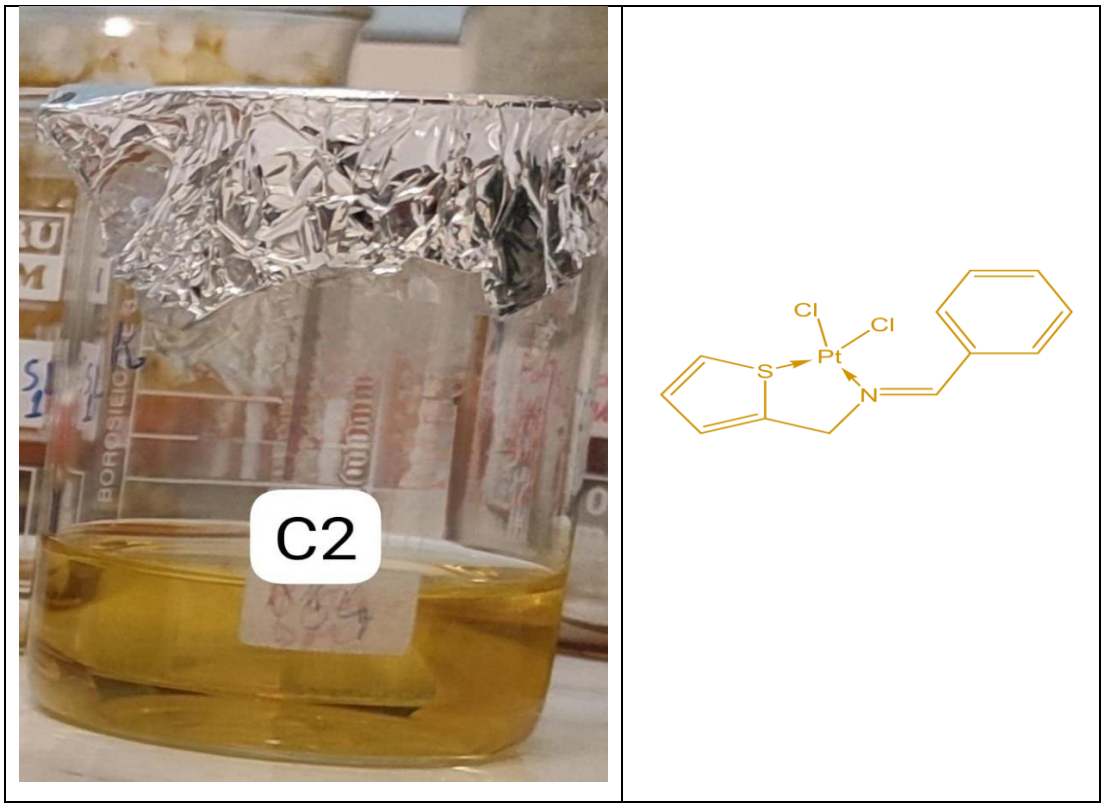

Figure 5.5. C2-Pt (II) See the job method of the complex.

5.2.2.2. Pt-L2 Complex(C4)

FT-IR (ATR, cm-1):

3367, 3220, 3009, 2923, 2852, 2178, 1652, 1446, 1398, 1339, 1247, 1138, 1082, 1037, 1011, 897, 871, 831, 763,701,

MALDI-TOF MS:

391.89 PtL

463.71 [$PtLCl_2$]

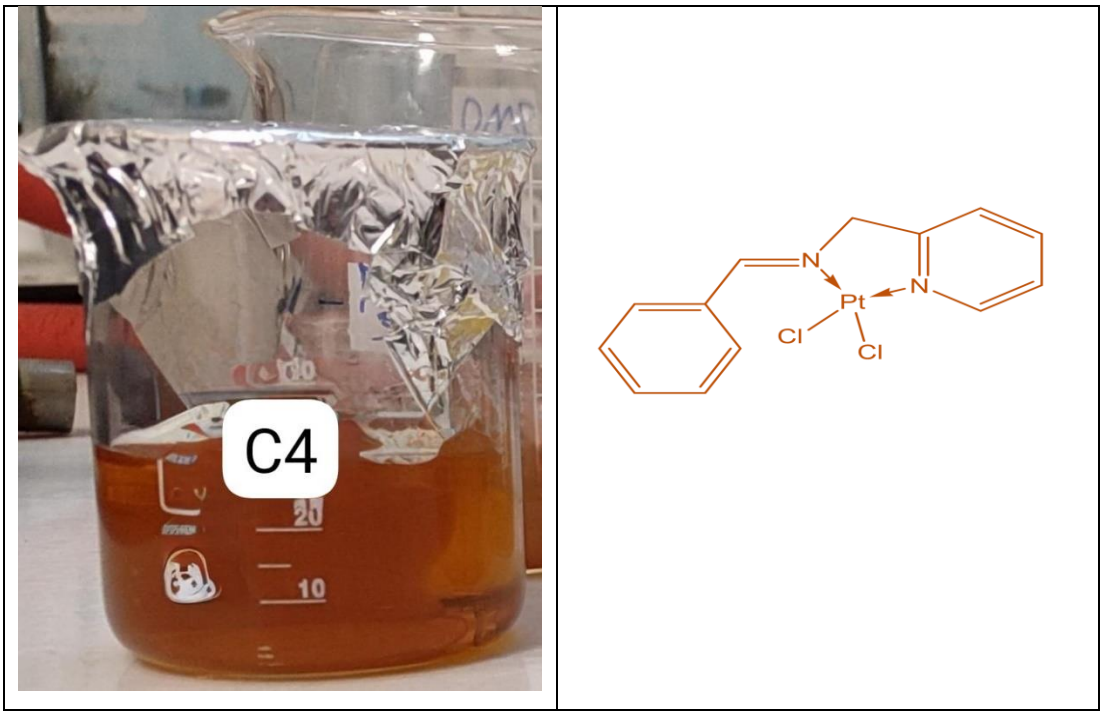

Figure 5.6. C4-Pt (II) See the job method of the complex.

5.2.2.3. Pt-L3 Complex(C6)

FT-IR (ATR, cm-1):

3181, 3129, 2922, 2852, 2182, 1651, 1573, 1444, 1385, 1335, 1252, 1174, 1095, 1057, 873, 768, 700, 660, 473.

MALDI-TOF MS:

420.43 [PtL]+Na
469.88 [$PtLCl_2$]

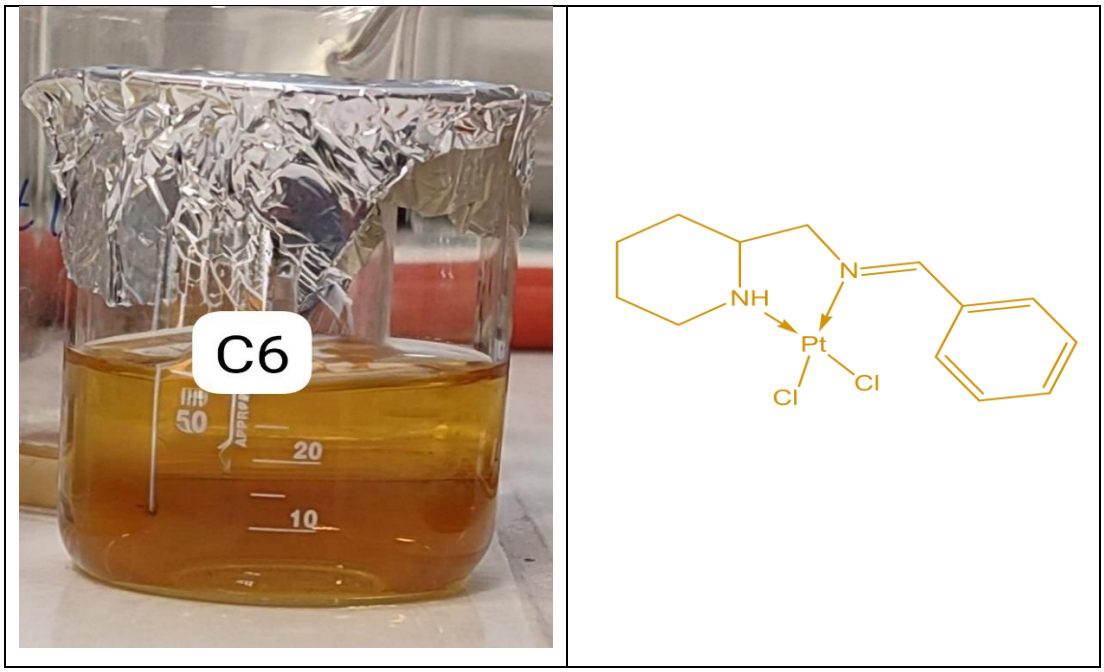

Figure 5.7. C6-Pt (II) See the job method of the complex.

PART 6

RESULTS AND DISCUSSIONS

The ligands L1−L3 are synthesized by reacting Schiff bases derived from benzaldehyde with thiophene-2-methenamine (L1), pyridine-2-methenamine (L2), or piperidine-2-methenamine (L3), as depicted in Figure 6.1. The ligands were analyzed using ^{1}H NMR, ^{13}C NMR, mass spectrometry, and FT-IR spectroscopy. Synthesis of Schiff bases involves the reaction between aliphatic or aromatic aldehydes or ketones and aliphatic or aromatic primary amines, following the conventional method for synthesizing Schiff base ligands, as illustrated in Figure 6.1. The amine group acts as a nucleophile in the first step of the process, where it reacts with the carbonyl group by nucleophilic addition to generate a Schiff base. The electrons of the amine nitrogen undergo nucleophilic assault on the aldehyde or ketone, resulting in the formation of carbinolamine, an intermediate molecule. This carbinolamine is then catalyzed by an acid or base, leading to the elimination of water. The dehydration of carbinolamine is the primary factor that restricts the rate at which a Schiff base can form [69,70]

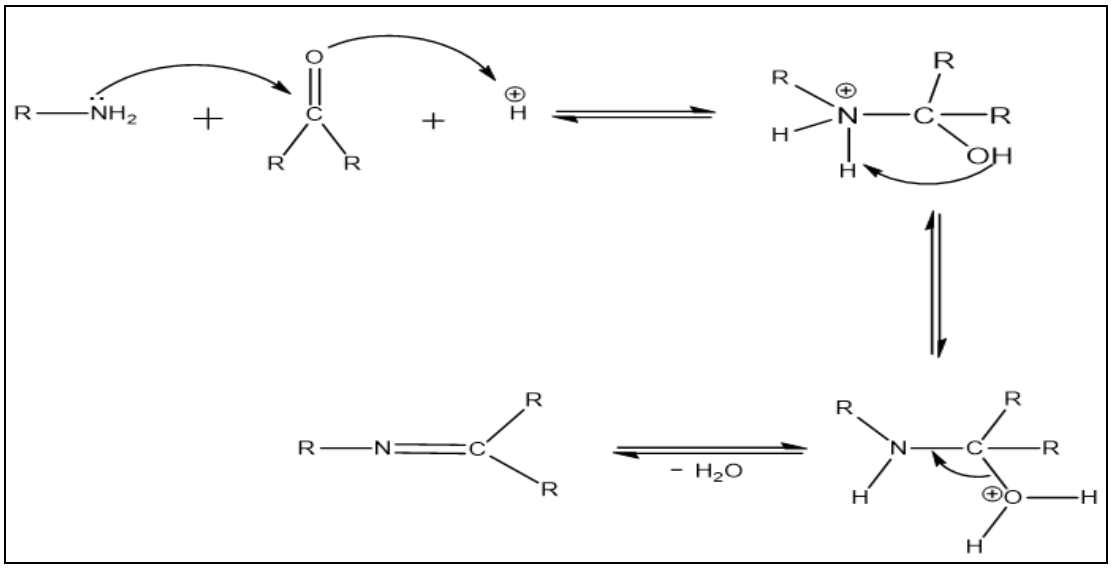

Figure 6.1. Schiff bases preparation mechanism [71].

The formation of metal complexes (C1-C6) was achieved by reacting Pd $(MECN)_2Cl_2$ or Pt $(COD)Cl_2$ salts with ligands in a DMF solution. The complexes (C1, C2, C3, C4, C5, and C6) were synthesized using the ligands L1, L2, and L3. The complexes displayed square planar geometries with a metal-to-ligand ratio of 1:1. Complexes with this stoichiometry exhibited similar tones solubility in DMF. However, it is insoluble in acetone, methanol, and water.

6.1. FT-IR SPECTRUMS

Table 6.1 provides the FT-IR vibrational frequencies of selected ligands and complexes. The compounds thiophene-2-methenamine, pyridine-2-methenamine, and piperidine-2-methenamine displayed distinct bonding of the $(-NH_2)$ group within the stretching vibration range of 3367, 3361, and 3285 cm^{-1}, respectively. The presence of the carbonyl group (C=O) in benzaldehyde was determined by observing its distinctive frequency of 1696 cm^{-1}. The values are shown in Figure 6.2.

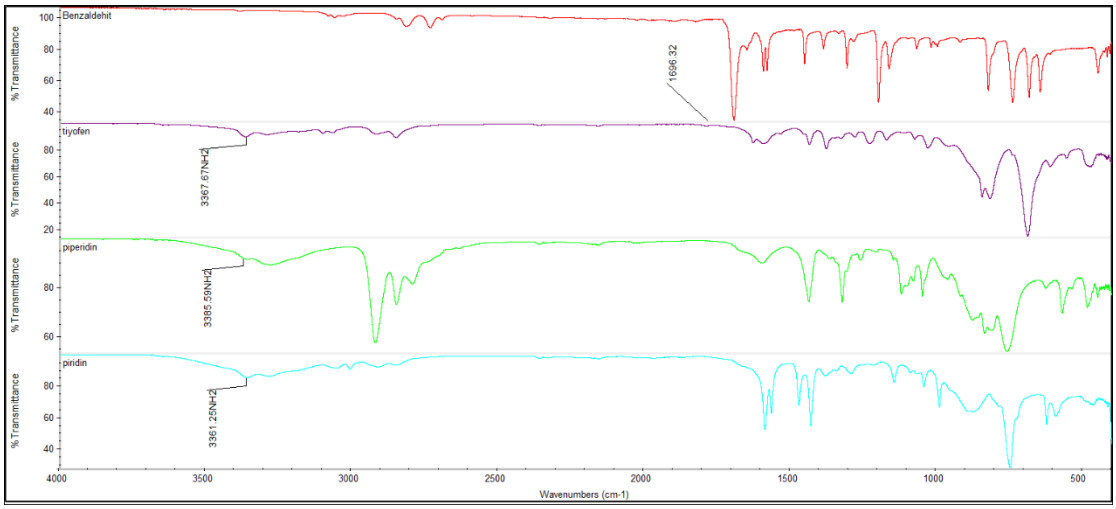

Figure 6.2. FT-IR for benzaldehyde, thiophene-2methenamine, pyridine-2-methenamine, and piperidine-2-methenamine

The characteristic vibrational peaks of ligands and complexes containing the azomethine (C=N) functional group were determined between 1634-1652 cm^{-1}. In addition, C-H_{ar} group peaks were observed in the range 3005 - 3106 cm^{-1} and C-H_{al} group vibrations in the range 2821-2980 cm^{-1}. The disappearance of the aldehyde C=O group and amine NH peaks in the synthesized ligands indicates the formation of the

C=N bond. The modifications seen in the azomethine vibration bands in the complexes, as depicted in Figure 6.3, suggest the formation of a link between the electron pair of the nitrogen atom in the azomethine group and the central metal atom. This confirms the coordination of Pd and Pt ions to the sulfur atoms of the thiophene ring [71] This evidence suggests that the Schiff base ligand functioned as a neutral bidentate ligand, establishing bonds with the metal ions via sulfur and nitrogen atoms [72] Figures 6.3, 6.4, and 6.5 show comparative FT-IR spectra of ligands and complexes.

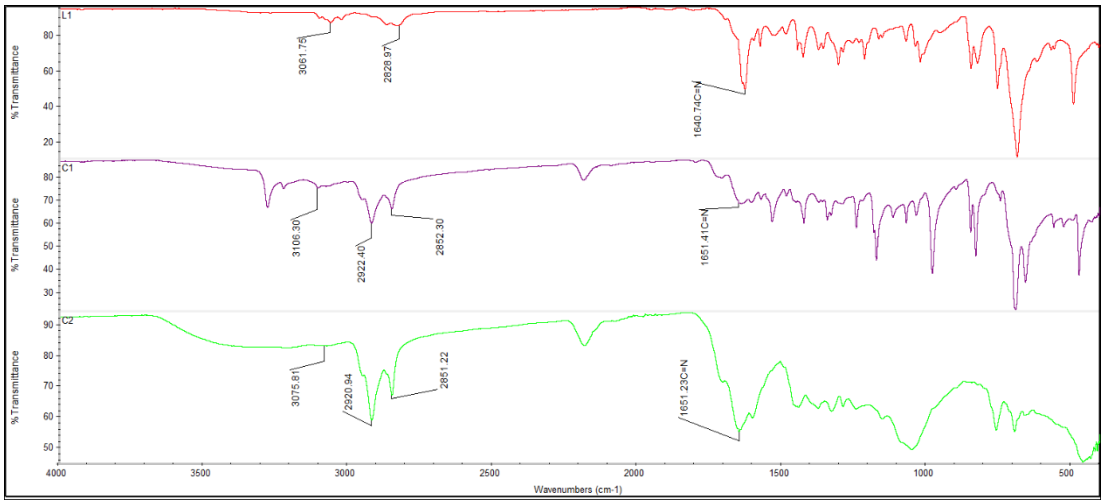

Figure 6.3. FT-IR for L1 ligand, C1 and C2 complexes.

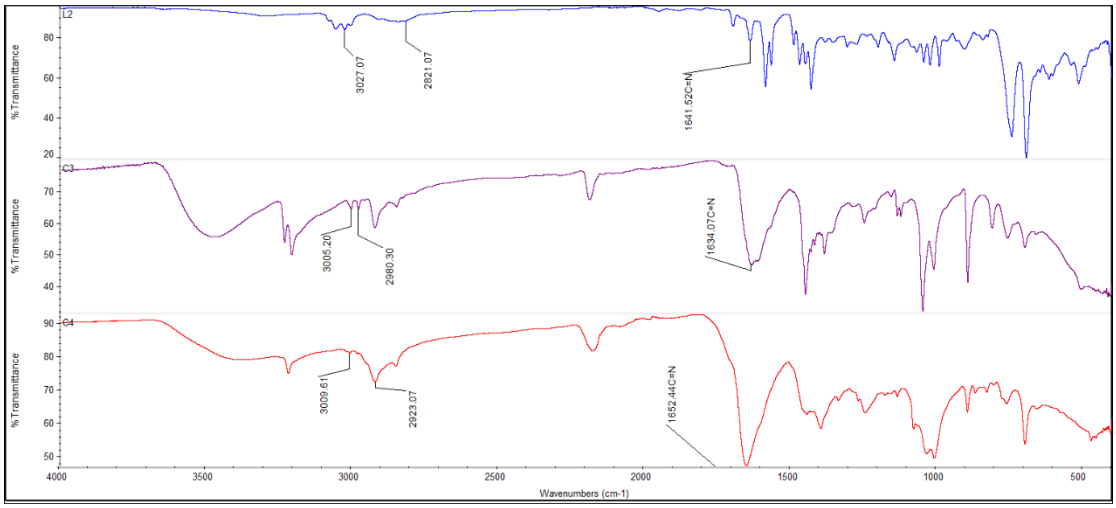

Figure 6.4. FT-IR for L2 ligand, C3 and C4 complexes.

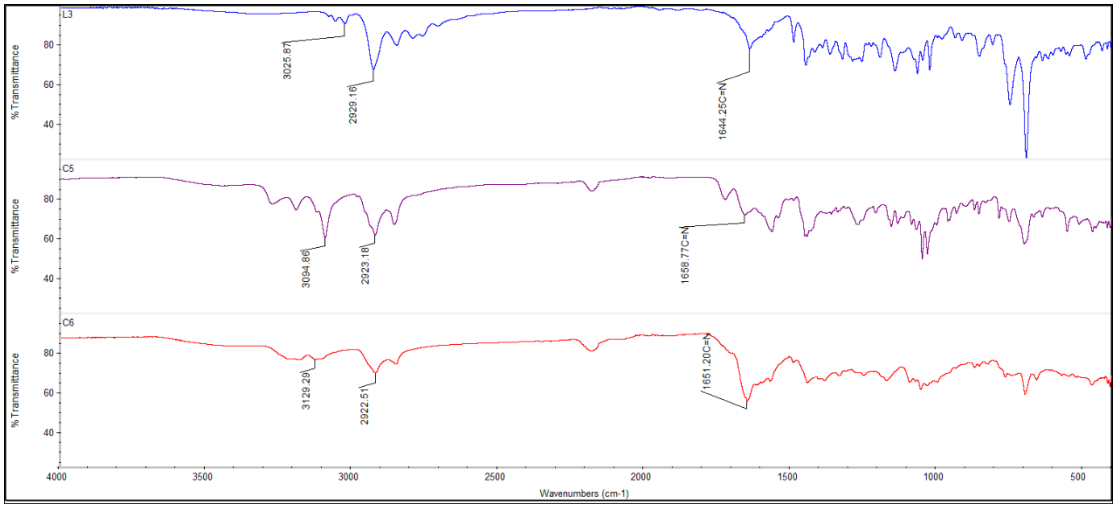

Figure 6.5. FT-IR for L**3** ligand, C**5** and C**6** complexes.

Detected changes in the frequencies of azomethine vibration bands indicate electronic transitions, specifically related to the interaction between the unoccupied π-antibonding orbitals of the azomethine group and the d-orbitals of the metal ion. During this coordination, electrons in the azomethine π-antibonding orbitals can shift to higher-energy metal d-orbitals. The process involves the transfer of electrons from the unoccupied pi-antibonding orbitals of azomethine to the d-orbitals of a metal, which is responsible for this transformation. The observed alterations in the vibration patterns of the azomethine group suggest electronic shifts, namely in the interaction between the vacant π-antibonding orbitals of the azomethine group and the d-orbitals of the metal ion. During coordination, electrons in the π-antibonding orbitals of the azomethine group can shift to higher-energy metal d-orbitals. The shift is caused by the electronic transition that arises from the unoccupied pi-antibonding orbitals of the azomethine group towards the d-orbitals of the metal [73]. Table 6.1 displays the remaining functional groups.

Table 6.1. FT-IR frequency values of ligands and complexes.

	υ$(CH)_{ar}$	**υ $(CH)_{al}$**	**υ (C=N)**	**υ (C=C)**	**υ (Pd-N)**	**υ (Pt-N)**
L1	3062	2829	1641	1579 1495 1450		
C1	3106	2922	1651	1576 1537 1488	476 [74]	
C2	3076	2921	1651	1446		462[75]
L2	3027	2821	1642	1588 1568 1491		
C3	3005	2980	1634	1452 1421	509[76]	
C4	3010	2923	1652	1447		474[77]
L3	3026	2929	1644	1491 1452		
C5	3095	2923	1659	1566 1446	469[74]	
C6	3129	2923	1651	1573 1444		473[77]

6.2. ^{1}H NMR SPECTRA

Figure 6.6 shows selected specific ^{1}H NMR peaks of the ligands. The L1 ligand exhibits a peak at 8.39 ppm corresponding to the H -C=N- group and another peak at 5.01 ppm corresponding to the -CH_2- group. The L2 ligand displays a peak at 8.60 ppm, corresponding to the H -C=N- group, and another peak at 5.12 ppm, corresponding to the -CH_2- group. In the spectrum of the L3 ligand, a peak at 8.31 ppm for the H-C=N group and peaks at 3.63 and 3.34 ppm for the -CH2- group were detected.

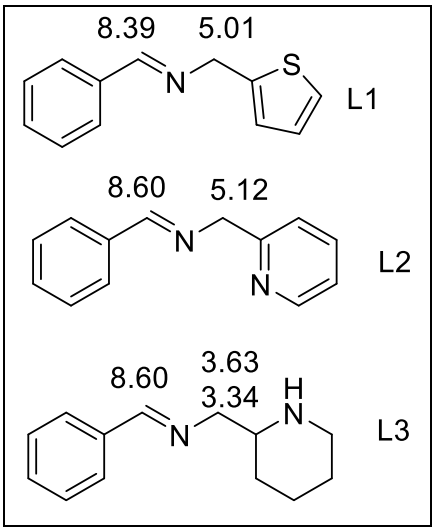

Figure 6.6. Selected ^{1}H NMR peaks of the ligands.

6.3. ^{13}C NMR SPECTRA

In the ^{13}C NMR peaks of the ligands, 12 carbon peaks were seen in the L1 ligands. The azomethine peak was detected at the expected chemical shift of 162.30 ppm, whereas the (-CH_2-) group peak was located explicitly at 59.34 ppm. The other peaks: 142.13,135.99, 130.99, 128.68, 128.42, 126.7, 125.5, 125.2.

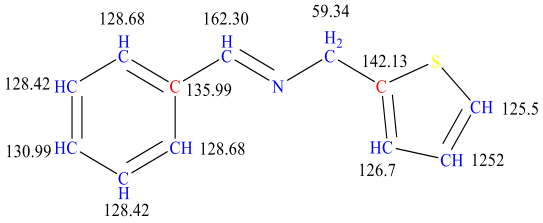

Figure 6.6. ^{13}C-NMR peaks of L1.

The L2 ligands exhibited the anticipated 13 carbon peaks. A peak corresponding to azomethine is detected with a chemical shift of 163.17 ppm. The chemical shift of the (-CH_2-) group was 70.69 ppm. The other peaks are 159.44, 149.31, 135.28, 130.90, 128.31, 136.15, 148.39, and 122. 40.

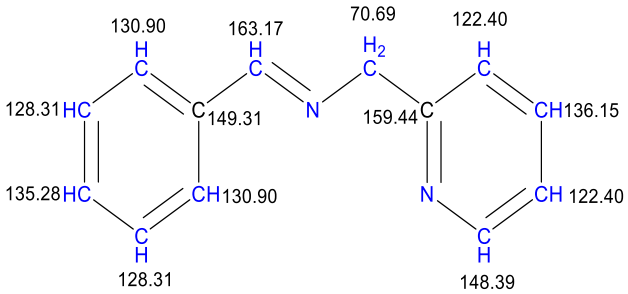

Figure 6.7. ^{13}C-NMR peaks of L2

The L3 ligands exhibited 13 carbon peaks, by expectations. A peak corresponding to an azomethine group was detected with a chemical shift of 163.31 ppm. The chemical shift of the (-CH_2-) group was measured to be 63.18 ppm. The other peaks are 139.32, 132.21, 128.51, 128.64, 128.73, 128.2; CH_2 peaks 48.58, 24.96, 48.78, 23.90.

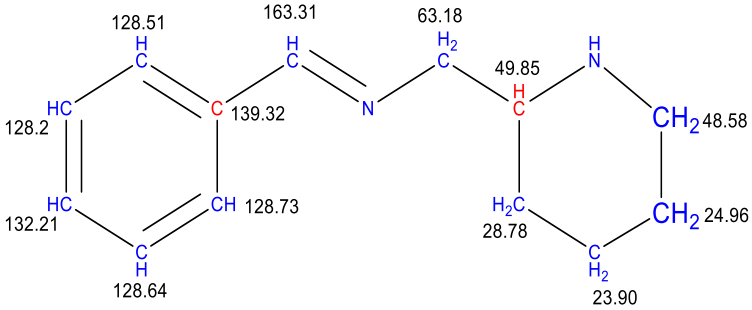

Figure 6.**8**. ^{13}C-NMR peaks of L3.

6.4. MASS SPECTRUMS

The molecular weights of compounds L1, L2, and L3 were determined as 201.29, 196.25, and 202.30 g/mol, respectively. The ligands L1, L2, and L3, displayed in Table 6.2, have an identical composition to that determined from theoretical calculations.

Table 6.2. ESI-Mass Peaks of The Ligands.

Ligands	Molecular Weights	ESI-Mass Peaks
L1	201.29	201.84
L2	196.25	196.91
L3	202.30	202.38

6.5. MALDI-TOF MASS ANALYSIS OF THE COMPLEXES

Table 6.3 displays the theoretical and experimental MALDI-TOF MS data for complexes C1-C6.

Table 6.3. MALDI-TOF Mass results of the complexes.

	Complex	**Theoretical molecular weight**	**MALDI-TOF Peaks**
C1	$[PdL1Cl_2]$	378.61	379.98
C1	$[PdL1Cl_2]+H_2O$	394.91	393.81
C3	$[PdL2Cl_2]$	373.57	373.04
C3	$[PdL2Cl_2]+H_2O$	389.95	389.91
C5	$[PdL3Cl_2]$	379.62	380.44
C5	$[PdL3Cl_2]+0.5H_2O$	388.62	389.59
C2	[PtL1]	396.37	396.51
C2	$[PtL1Cl_2]$	467.27	466.56
C4	[PtL2]	391.34	391.89
C4	$[PtL2Cl_2]$	462.24	463.71
C6	[PtL3]+Na	420.37	420.43
C6	$[PtL3Cl_2]$	468.29	469.88

PART 7

CONCLUSION

- The aim of the work carried out in this thesis was to synthesise and characterise three ligands containing benzene ring in Schiff base (imine) structure and their complexes with Pd(II) and Pt(II) transition metals.
- The ligands were obtained by boiling benzaldehyde with the amines 2-aminomethyl thiophene, 2-aminomethyl pyridine, and 2-aminomethyl piperidine in anhydrous dichloromethane using anhydrous magnesium sulphate. All ligands were obtained as yellow-orange gels and dried in a desiccator.
- The complexation reactions were carried out by boiling the ligands and metal salts in DMF and purified by silica-gel column.
- The ligands were characterised by FT-IR, 1H-NMR, 13C-NMR and ESI-MS and the complexes were characterised by FT-IR and MALDI TOF-MS.
- The structures of the complexes obtained were determined to be in the structure of [MLCl2].

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APPENDIX A.

SPECTRUMS

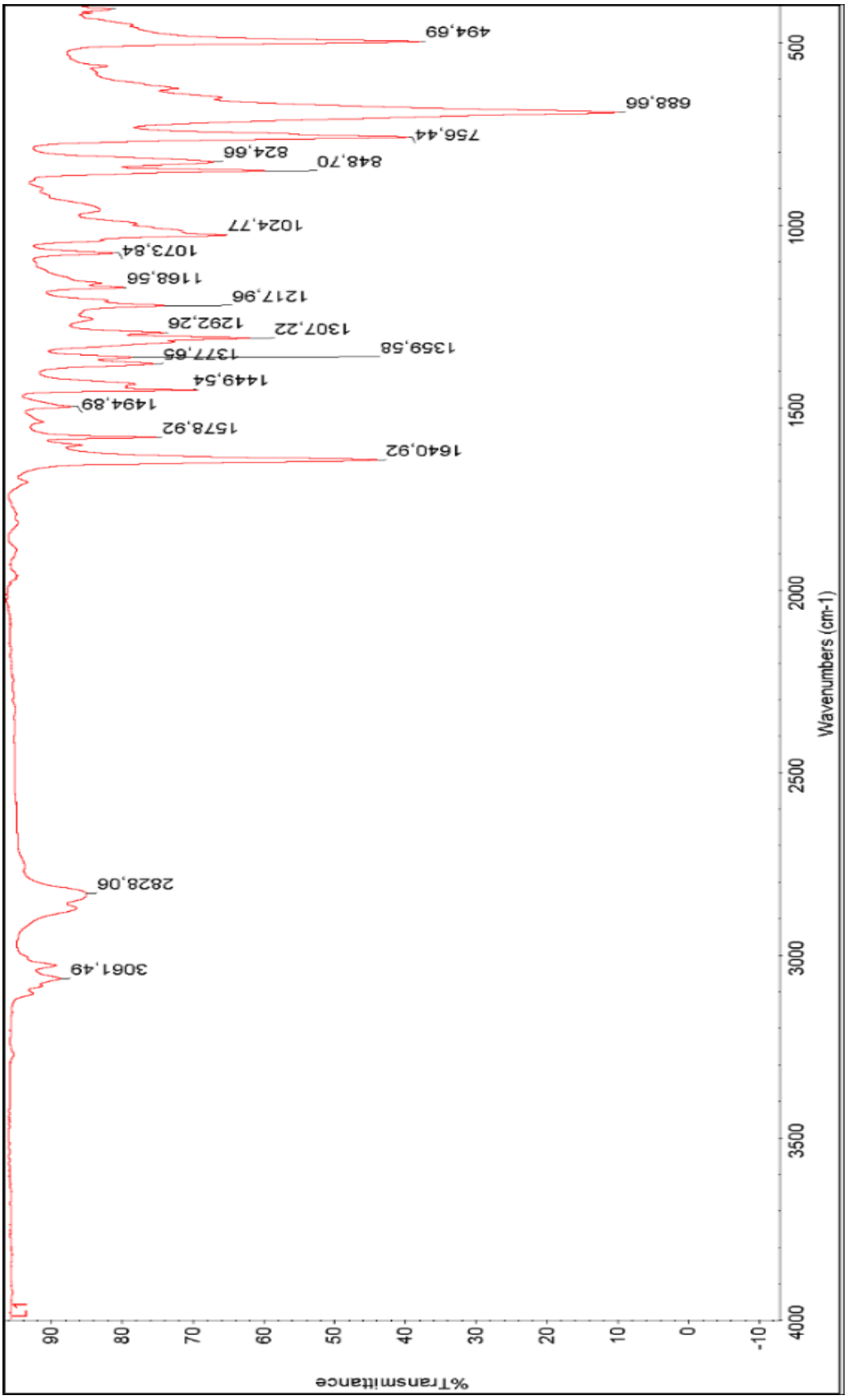

Figure Appendix A.1. FTIR spectrum of (E)-2-(((thiophen- 2ylmethyl) imino) methyl) phenol (L1).

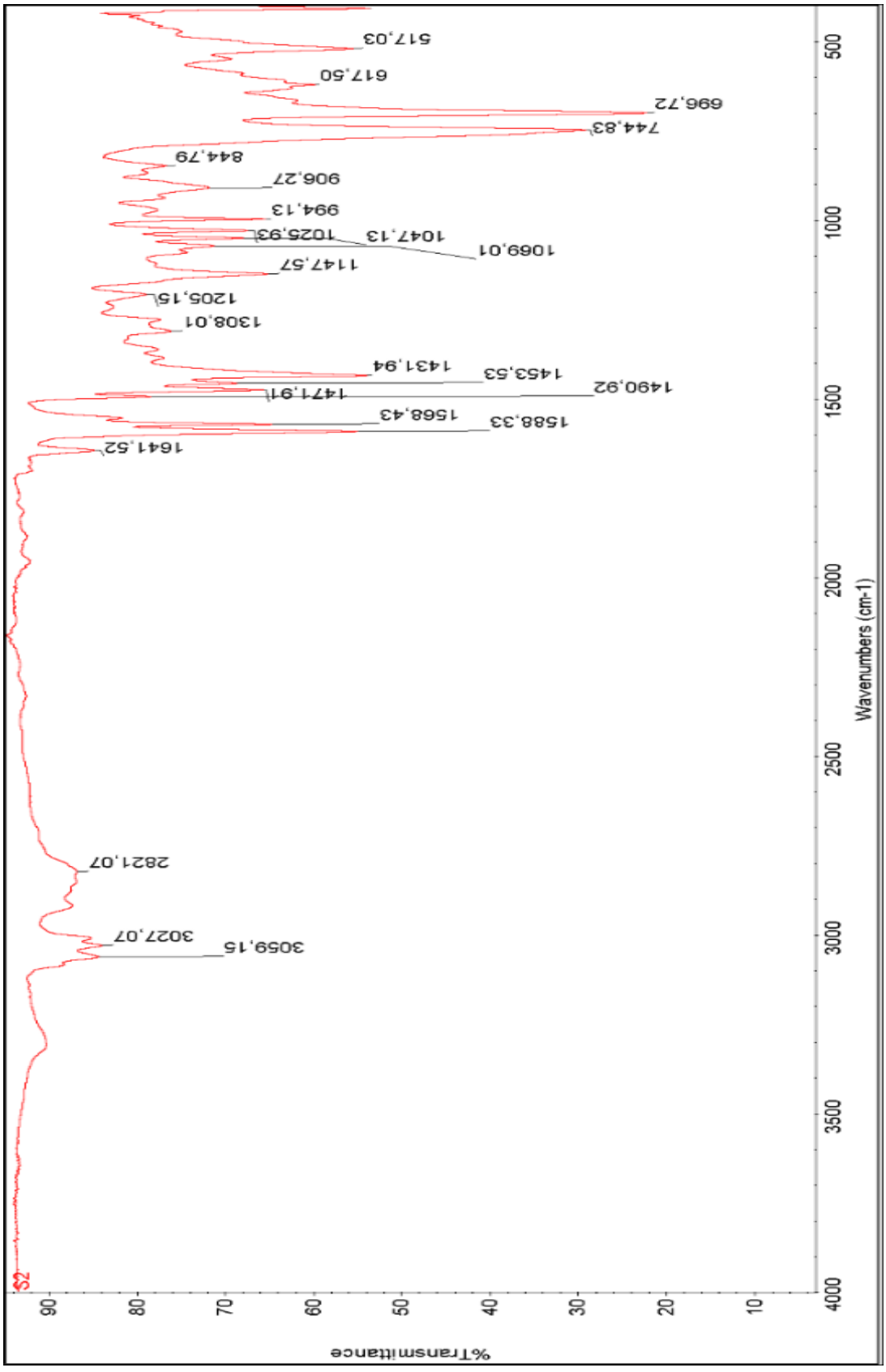

Figure Appendix A.2. FTIR spectrum of (E)-2-(((pyridin-2-ylmethyl) imino) methyl) phenol (L2).

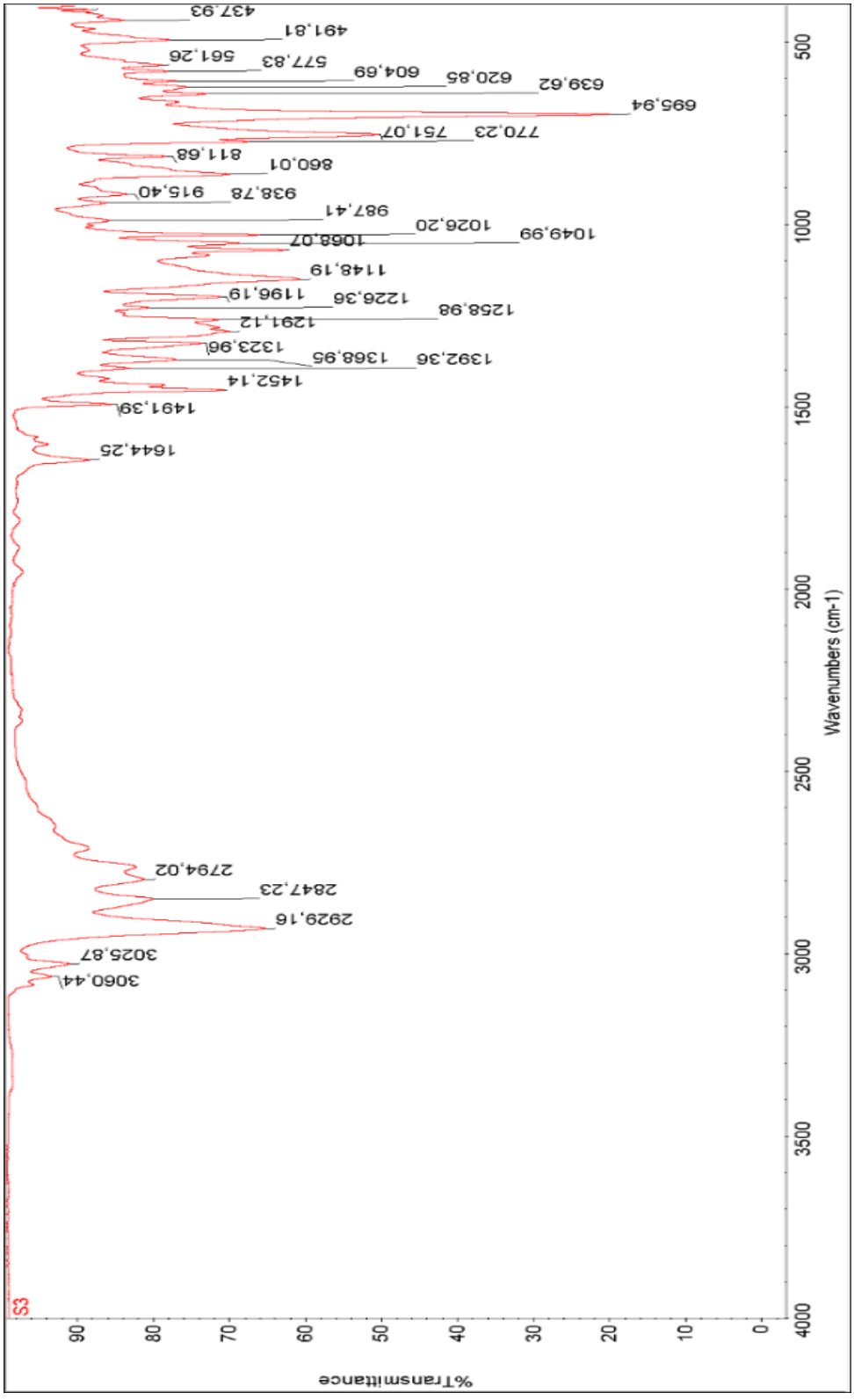

Figure Appendix A.3. FTIR spectrum of (E)-2-(((piperidin-2ylmethyl) imino) methyl) phenol (L3).

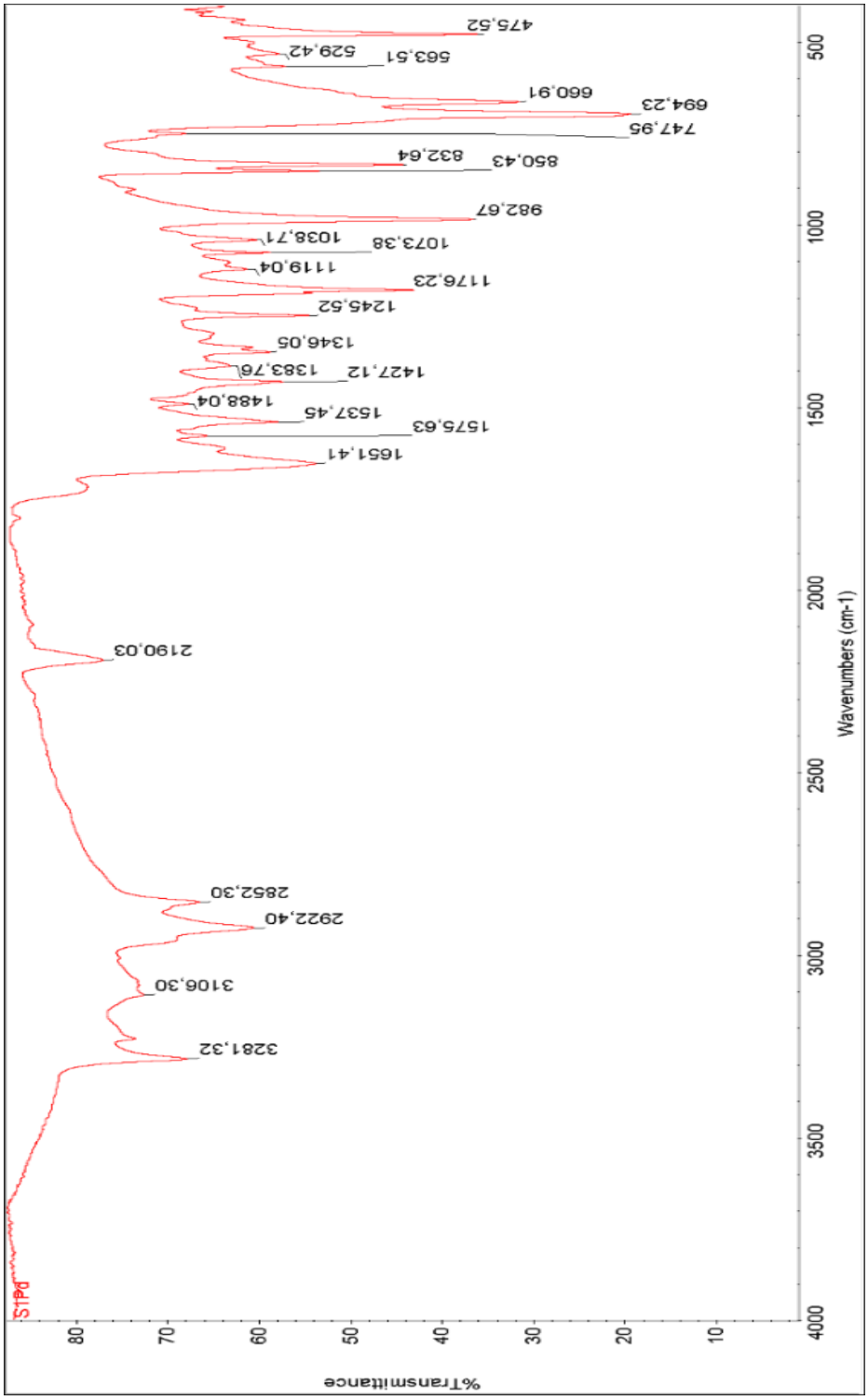

Figure Appendix A.4. FTIR spectrum of C1.

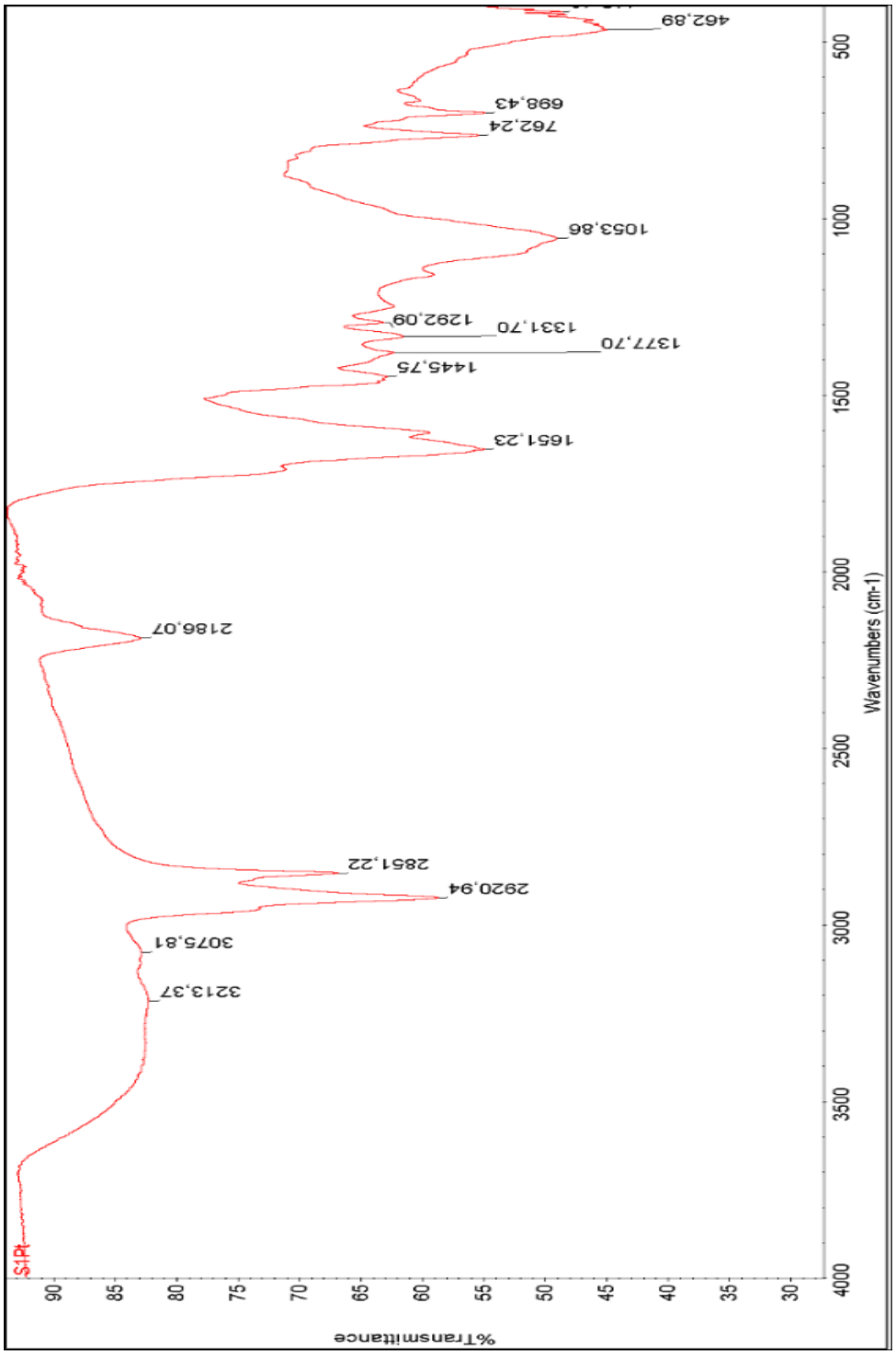

Figure Appendix A.5. FTIR spectrum of C2.

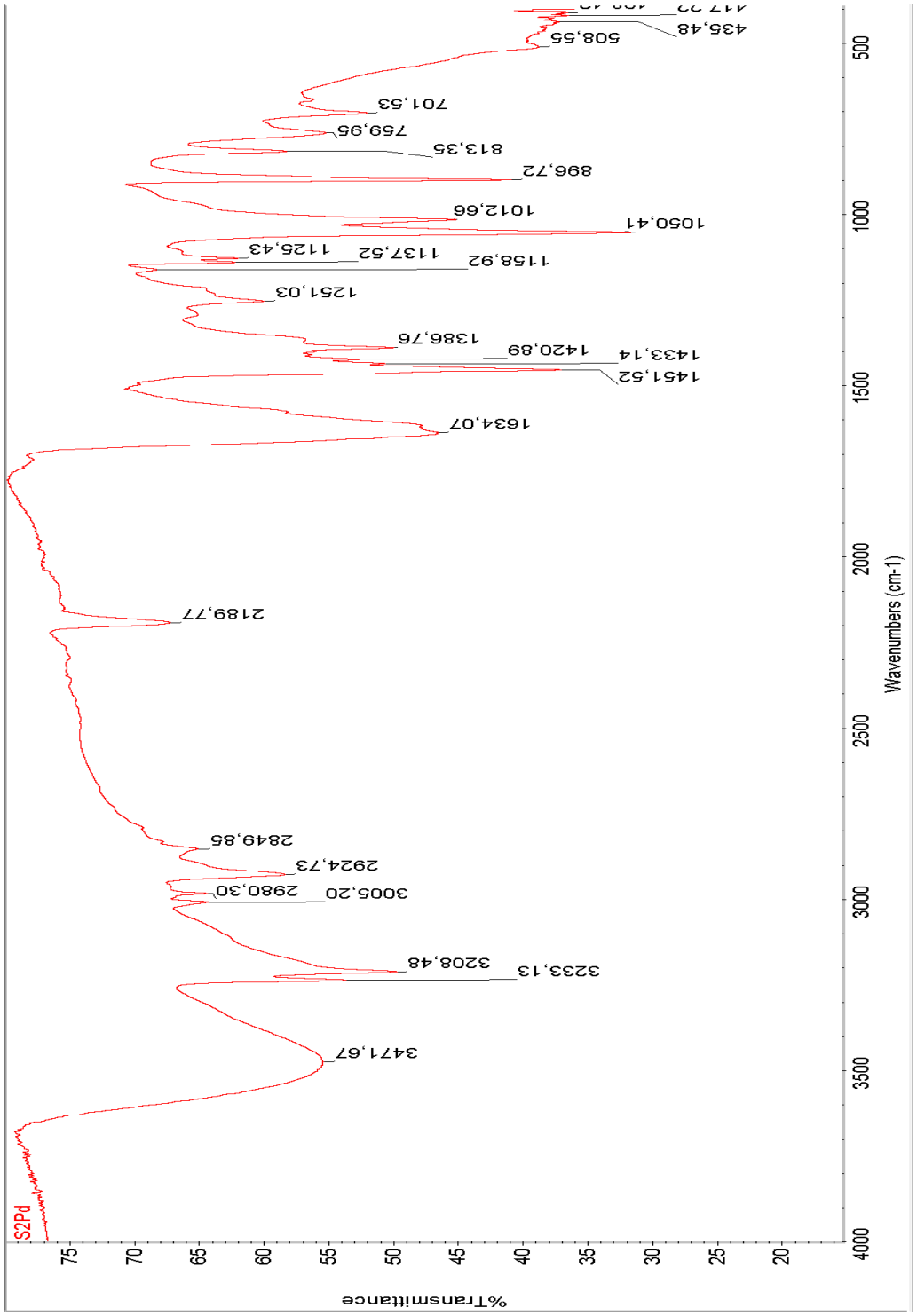

Figure Appendix A.6. FTIR spectrum of C3.

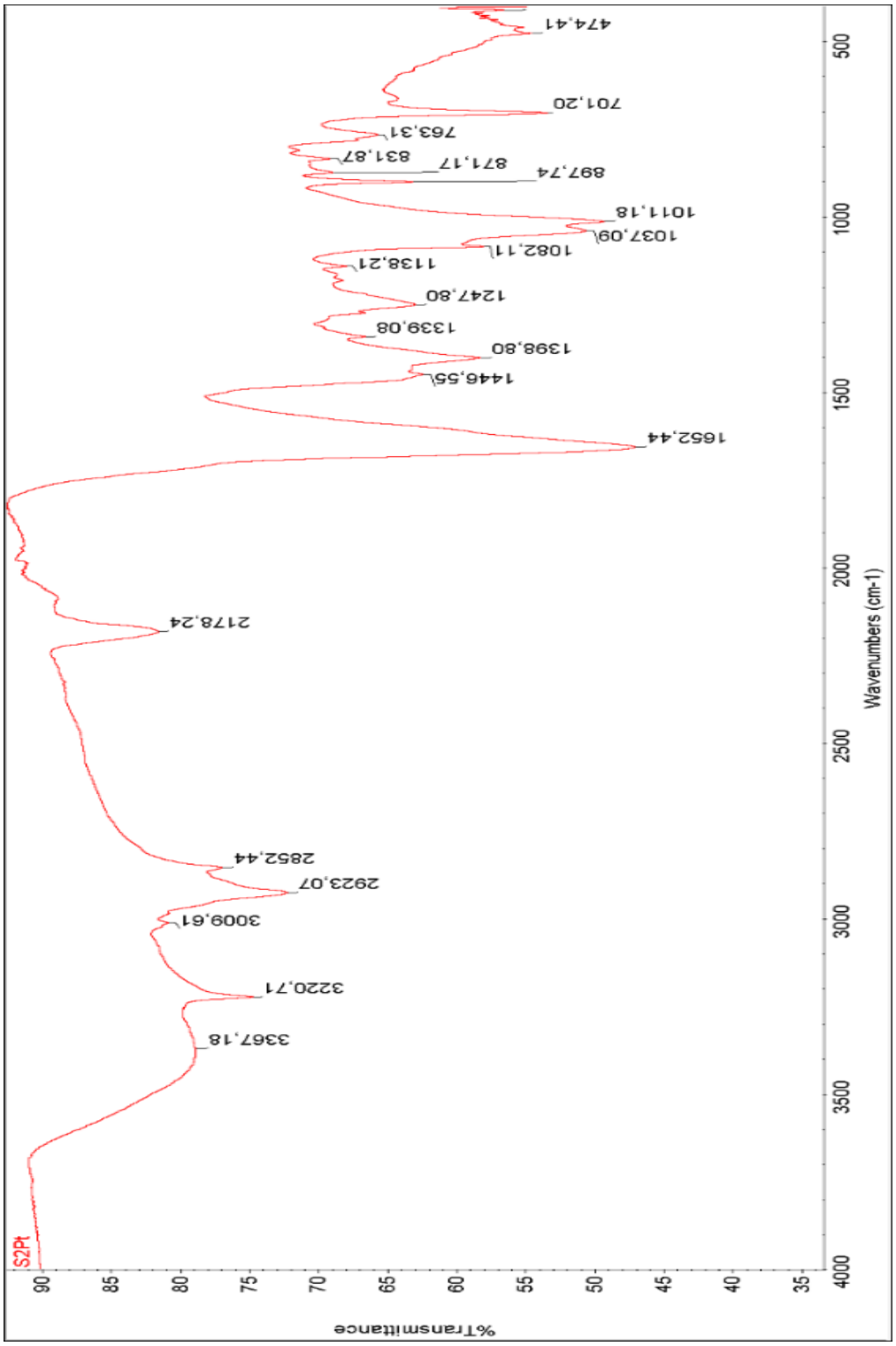

Figure Appendix A.7. FTIR spectrum of C4.

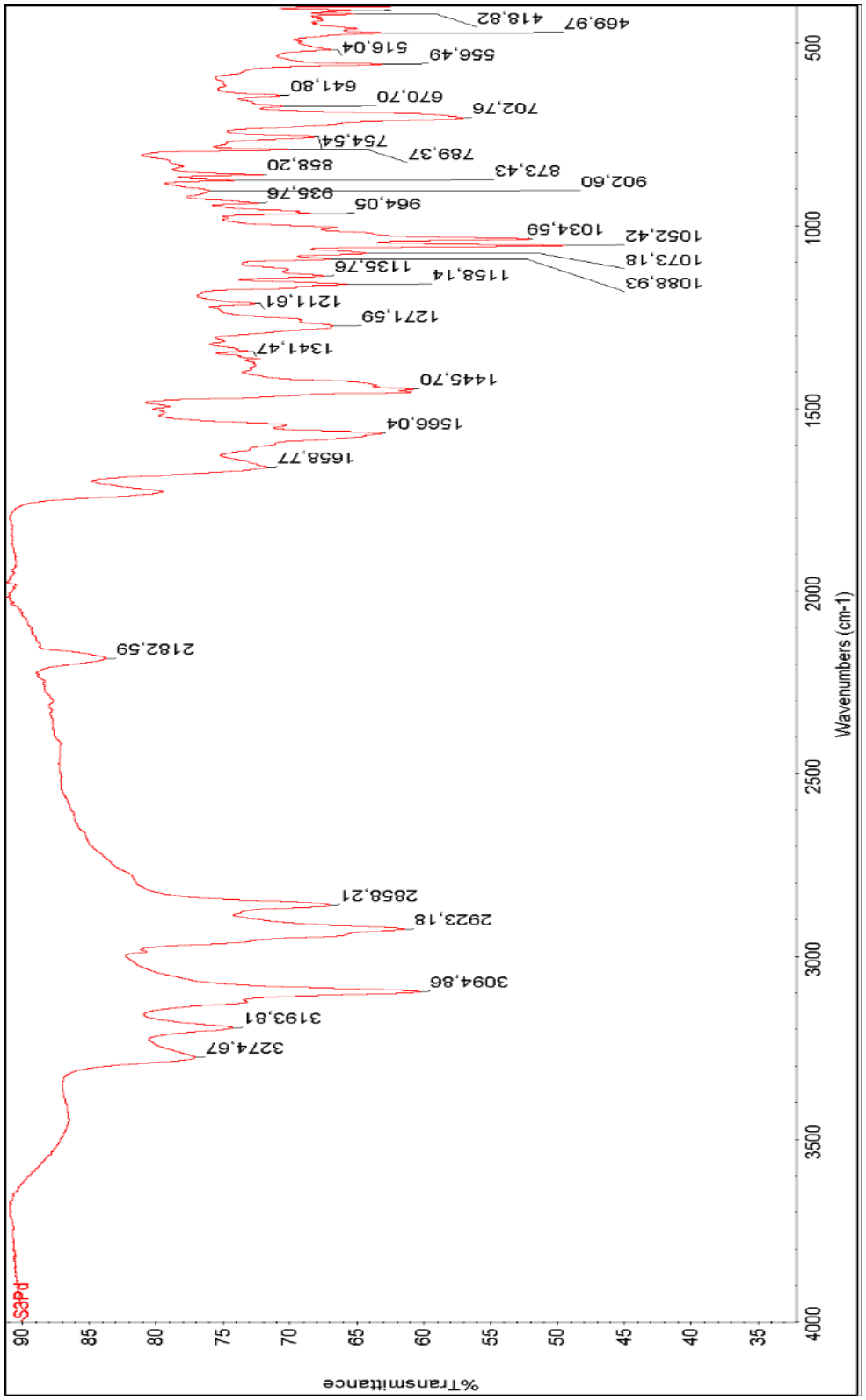

Figure Appendix A.8. FTIR spectrum of C5.

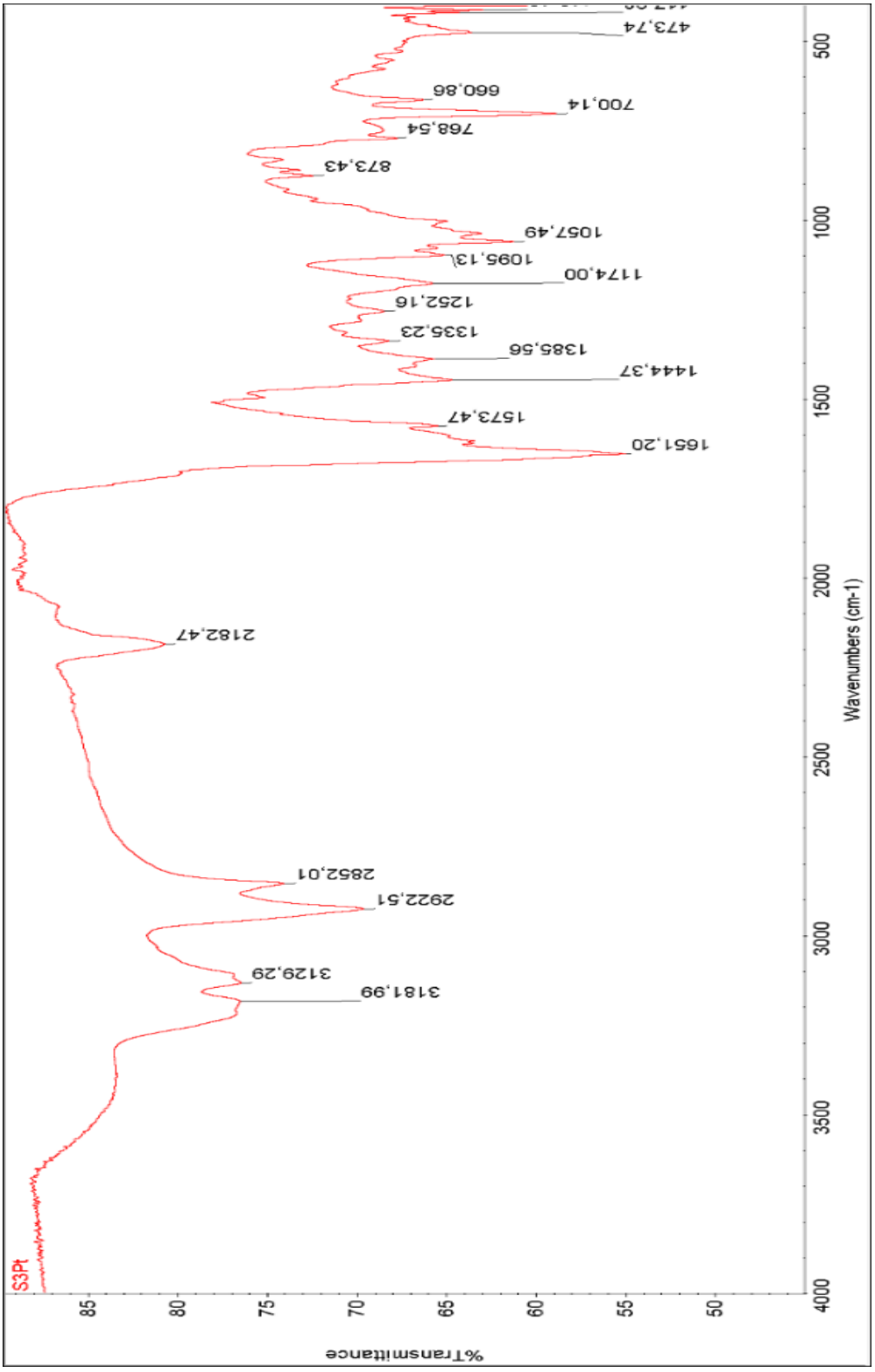

Figure Appendix A.9. FTIR spectrum of C6.

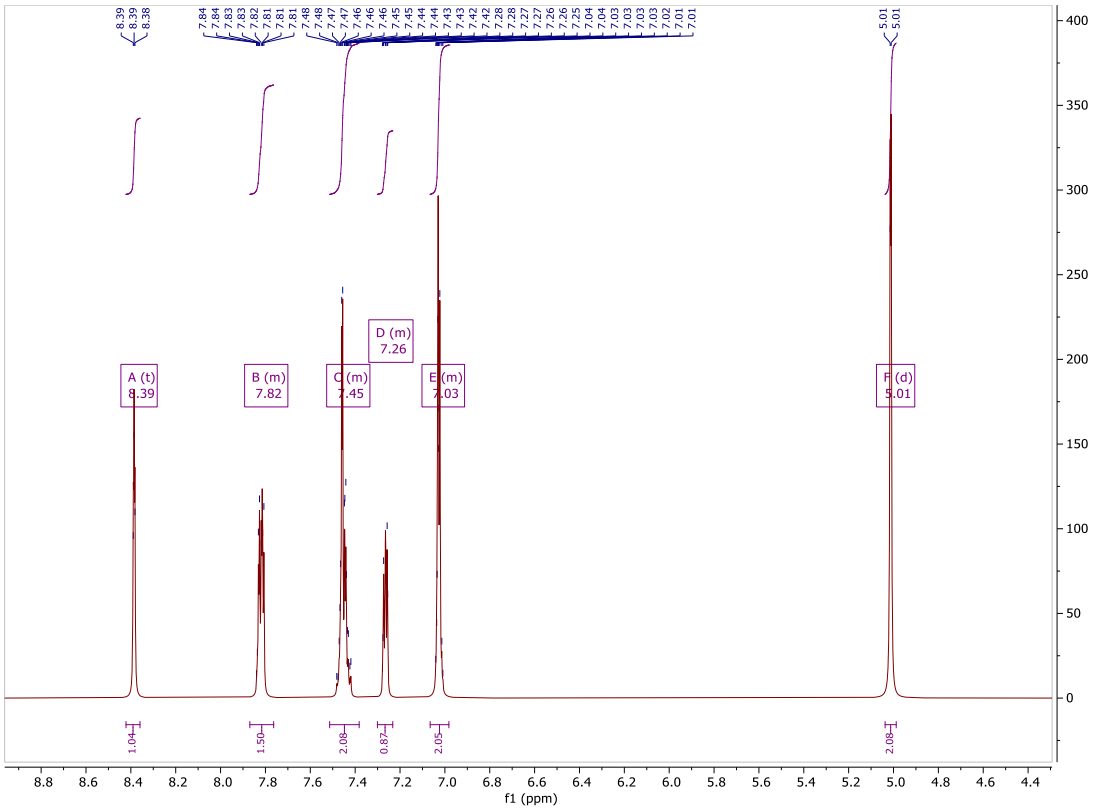

Figure Appendix A.10. ^{1}H NMR spectrum of ligand L1.

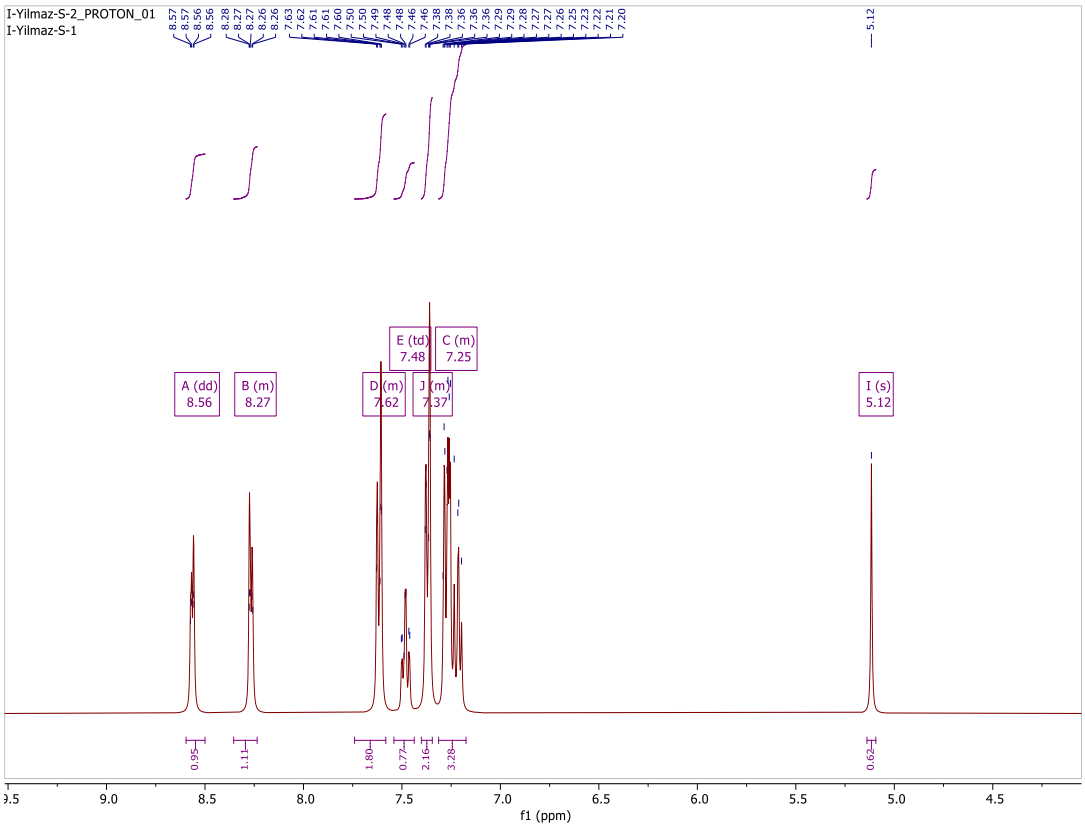

Figure Appendix A.11. ^{1}H NMR spectrum of ligand L2.

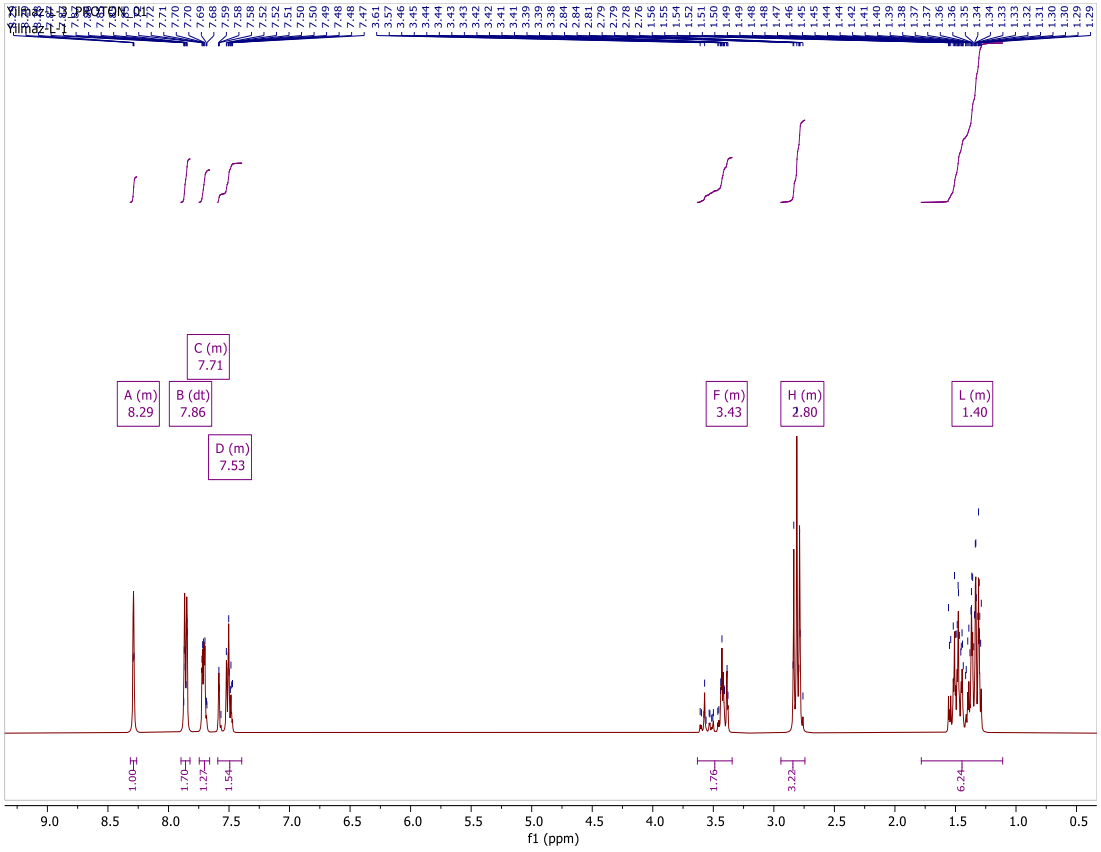

Figure Appendix A.12. ^{1}H NMR spectrum of ligand L3.

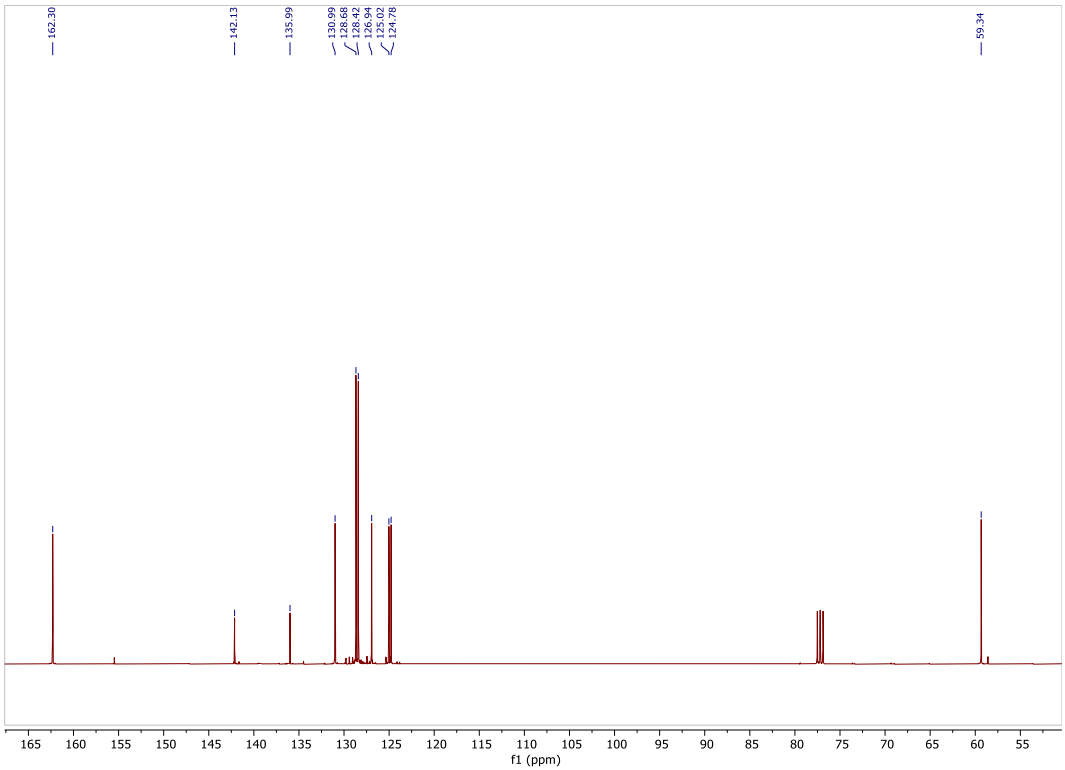

Figure Appendix A.13. ^{13}C NMR spectrum of ligand L1.

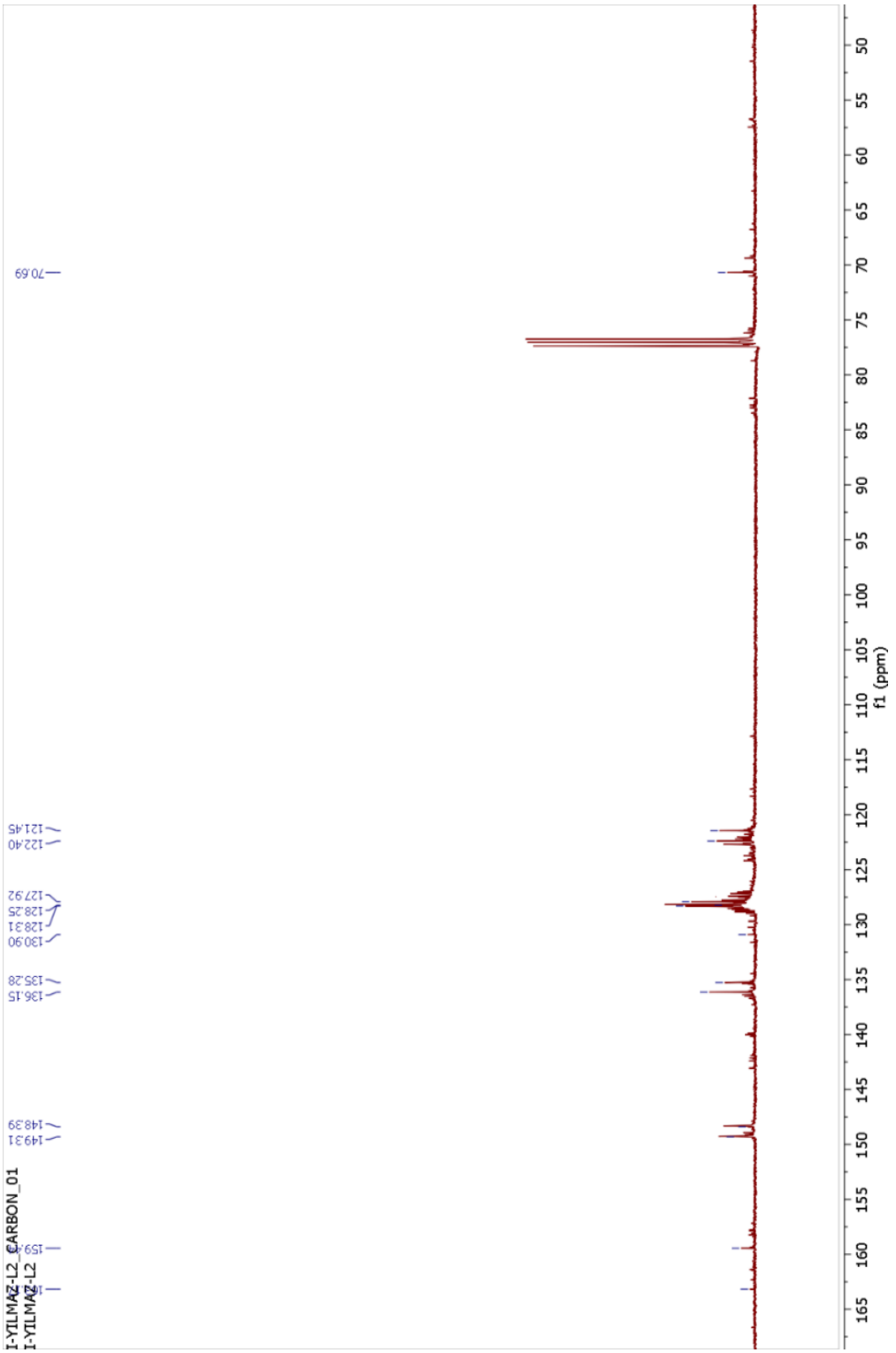

Figure Appendix A.14. ^{13}C NMR spectrum of ligand L2.

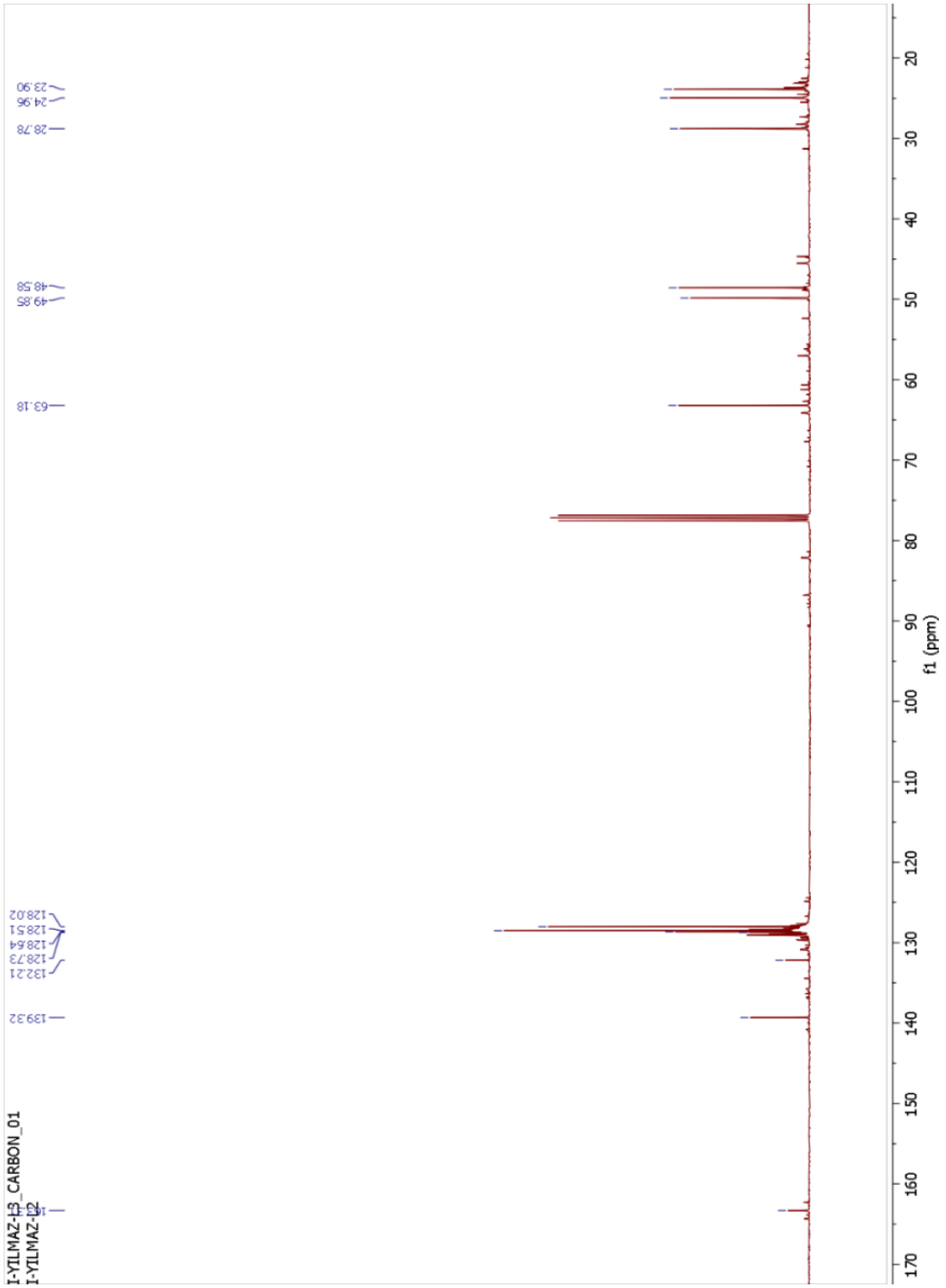

Figure Appendix A.15. ^{13}C NMR spectrum of ligand L3.

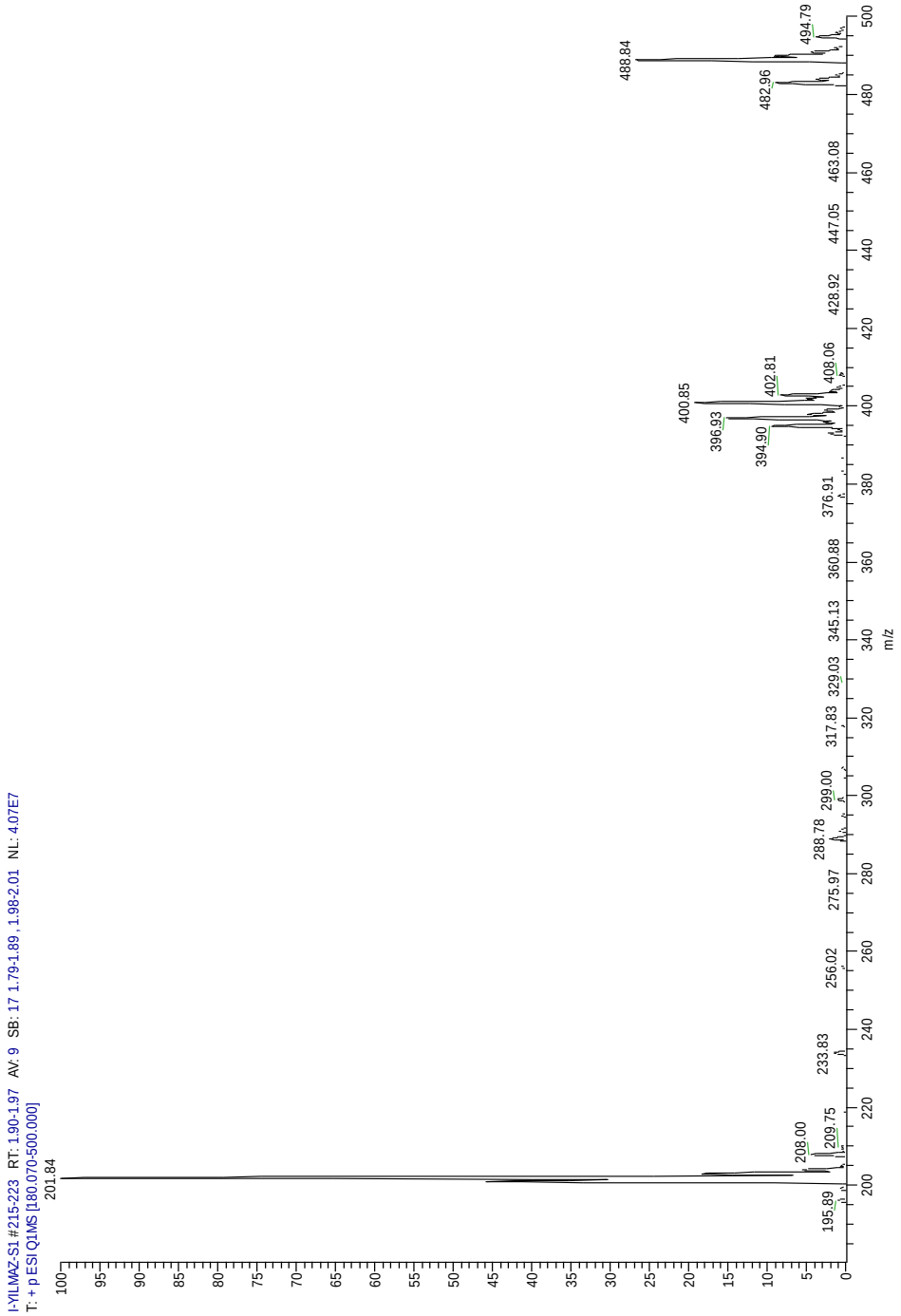

Figure Appendix A.16. Mass spectrum of ligand L1.

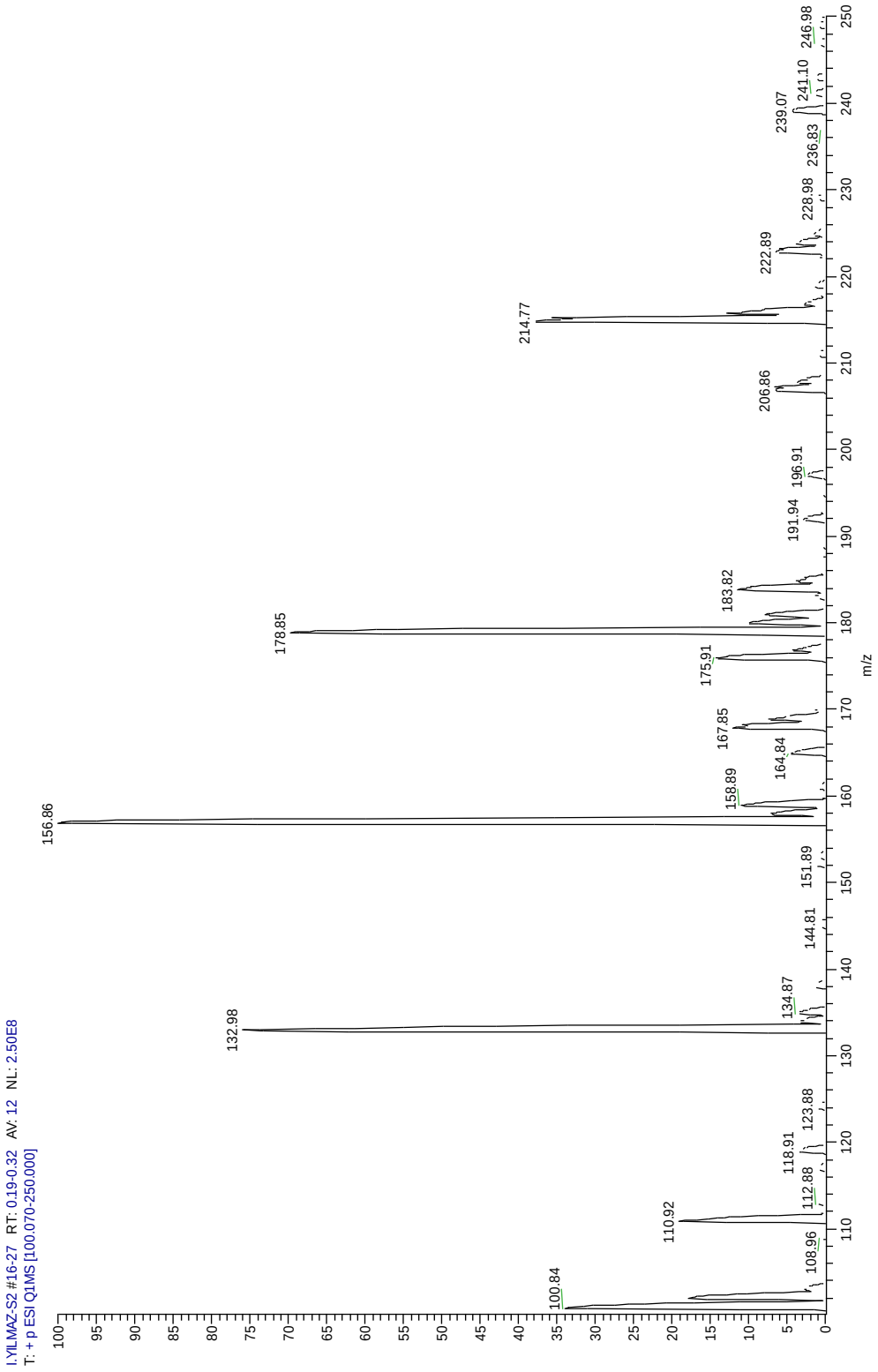

Figure Appendix A.17. Mass spectrum of ligand L2.

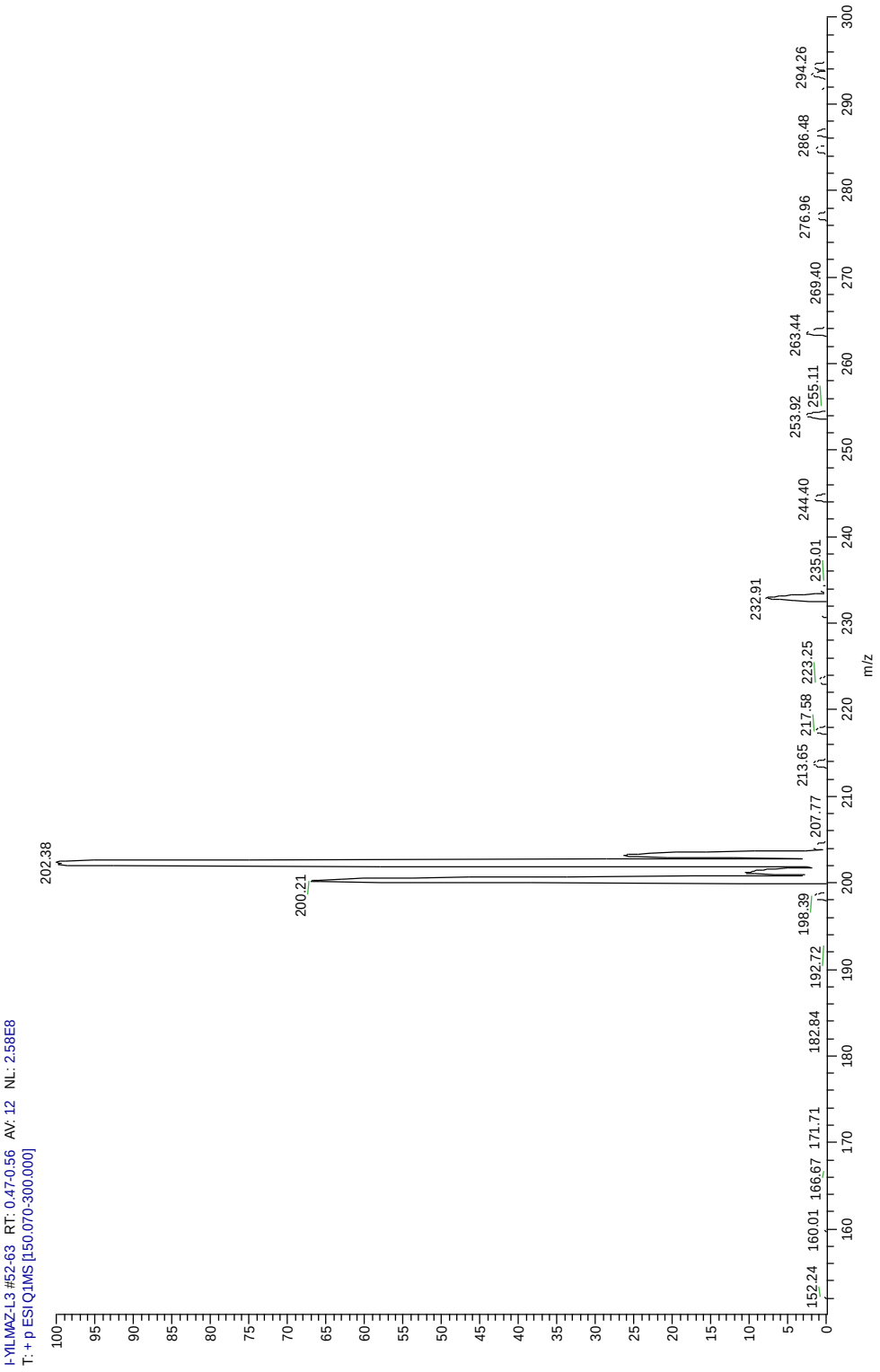

Figure Appendix A.18. Mass spectrum of ligand L3.

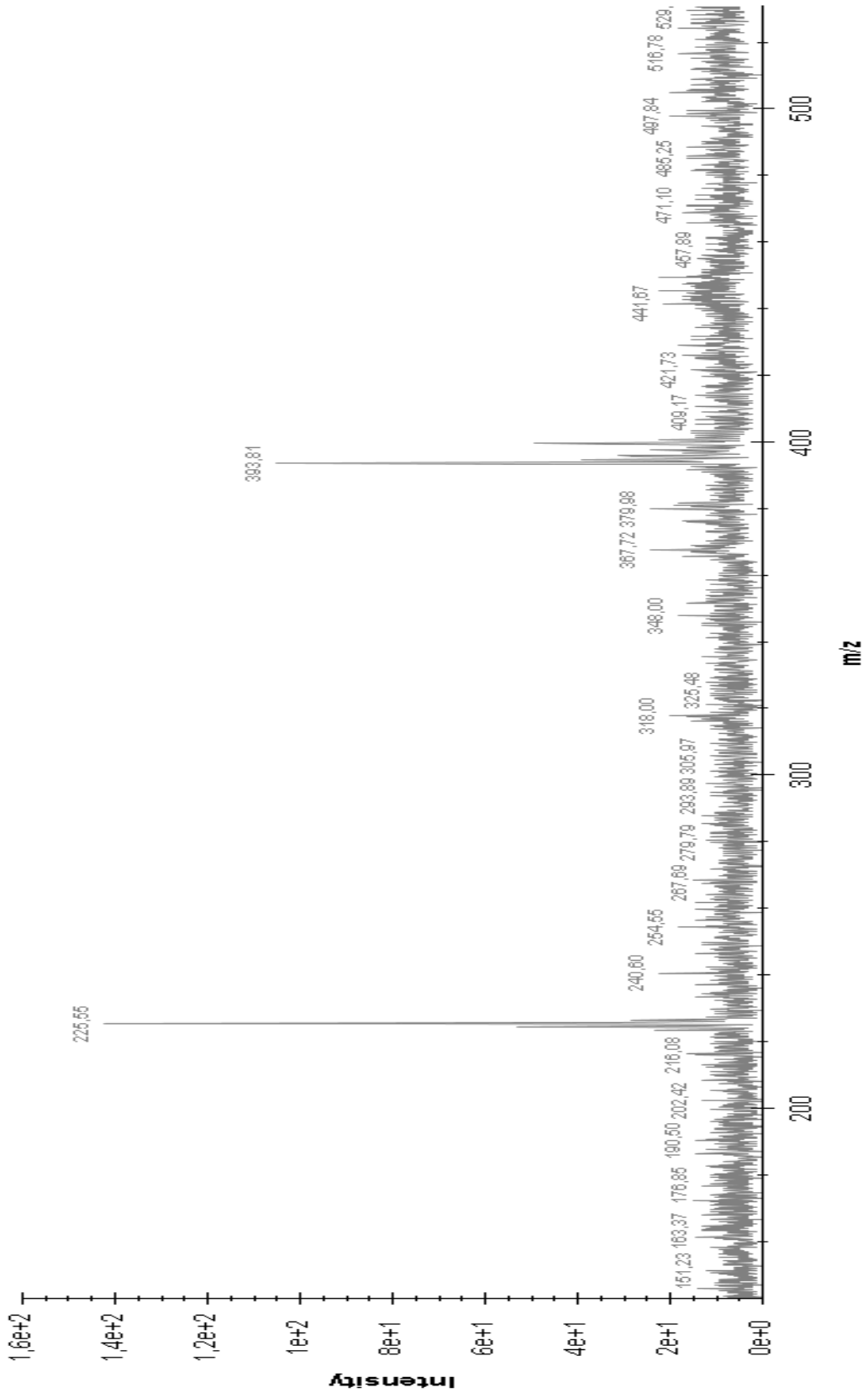

Figure Appendix A.19. MALDI-TOF MS spectrum of complex C1.

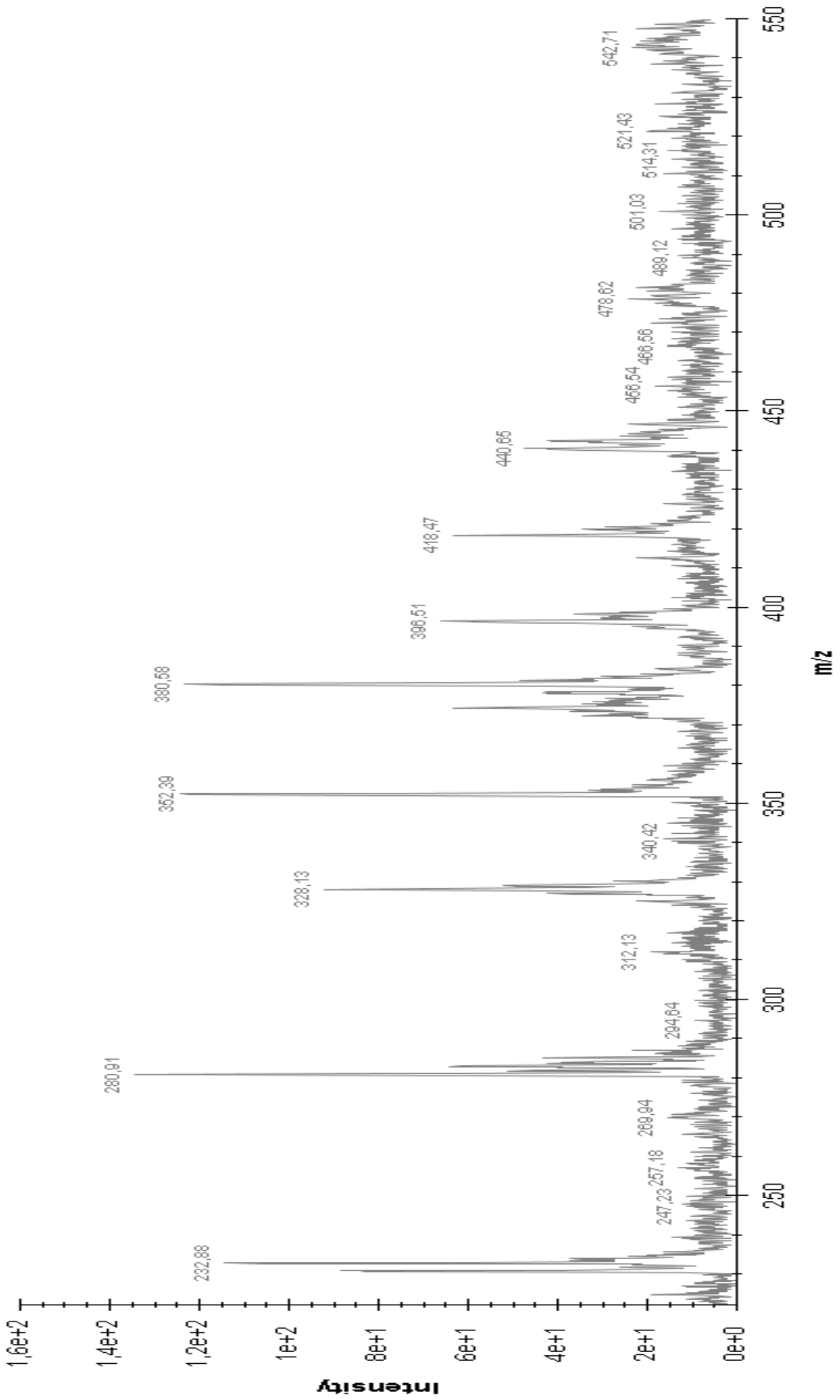

Figure Appendix A.20. MALDI-TOF MS spectrum of complex C2.

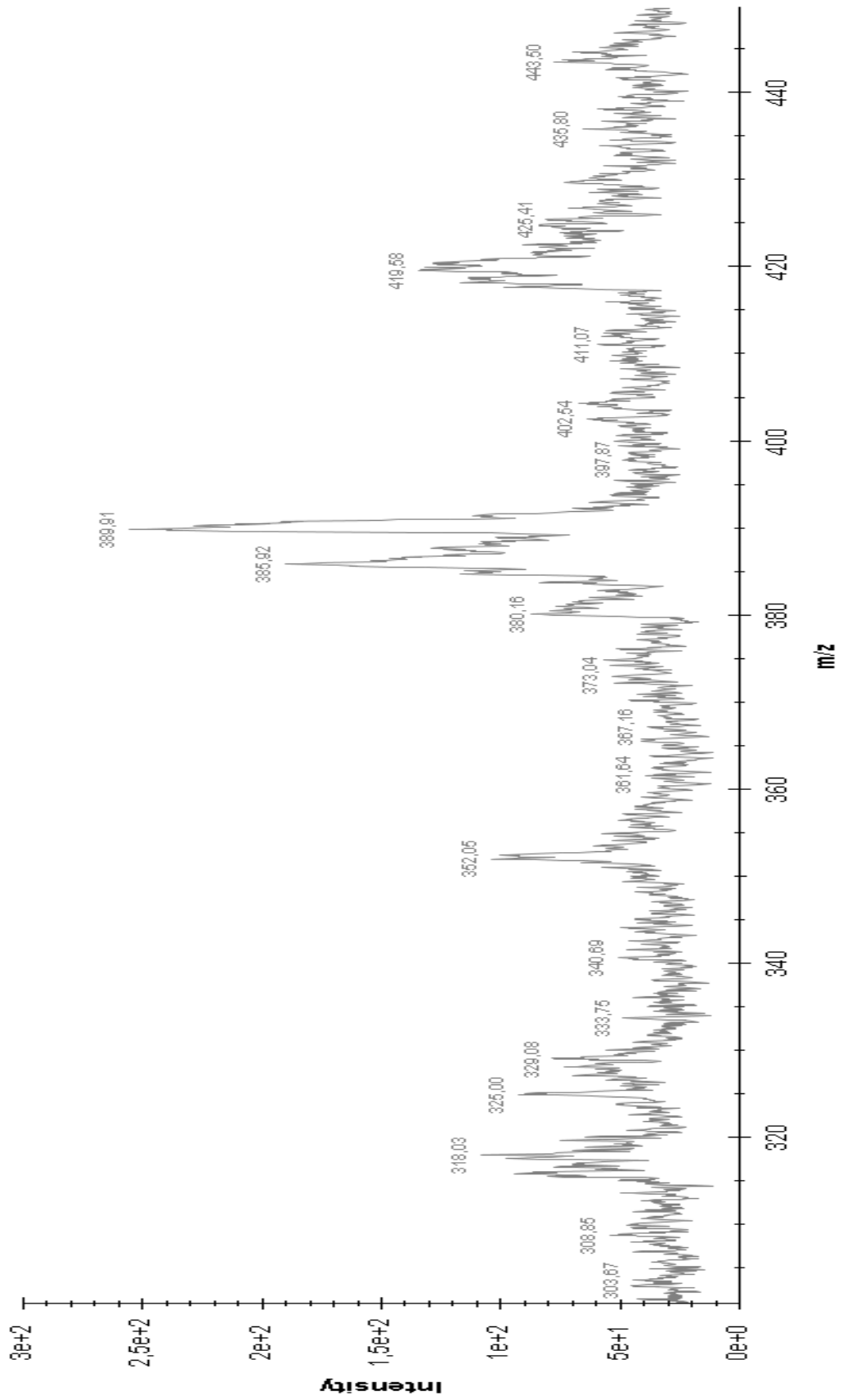

Figure Appendix A.21. MALDI-TOF MS spectrum of complex C3.

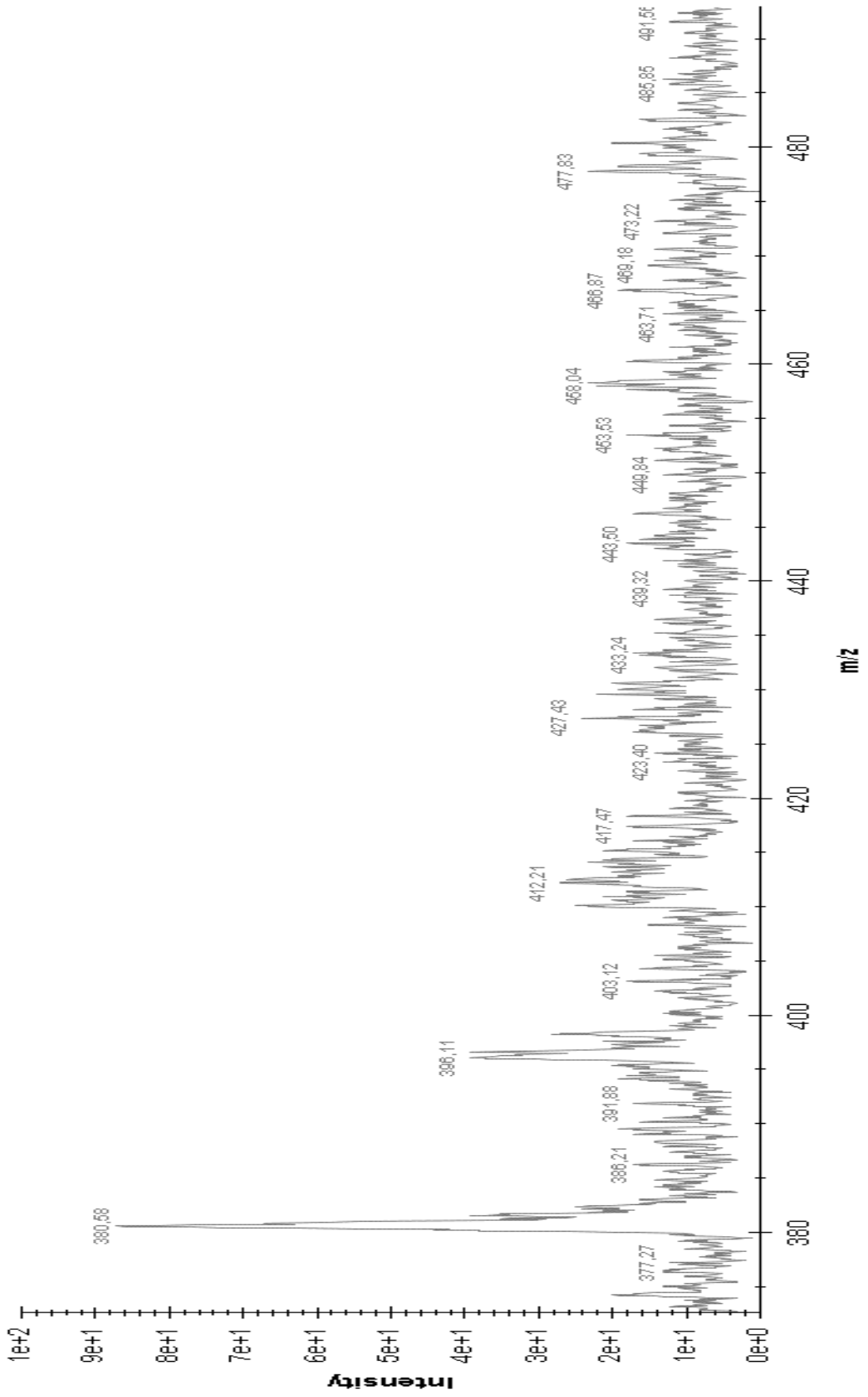

Figure Appendix A.22. MALDI-TOF MS spectrum of complex C4.

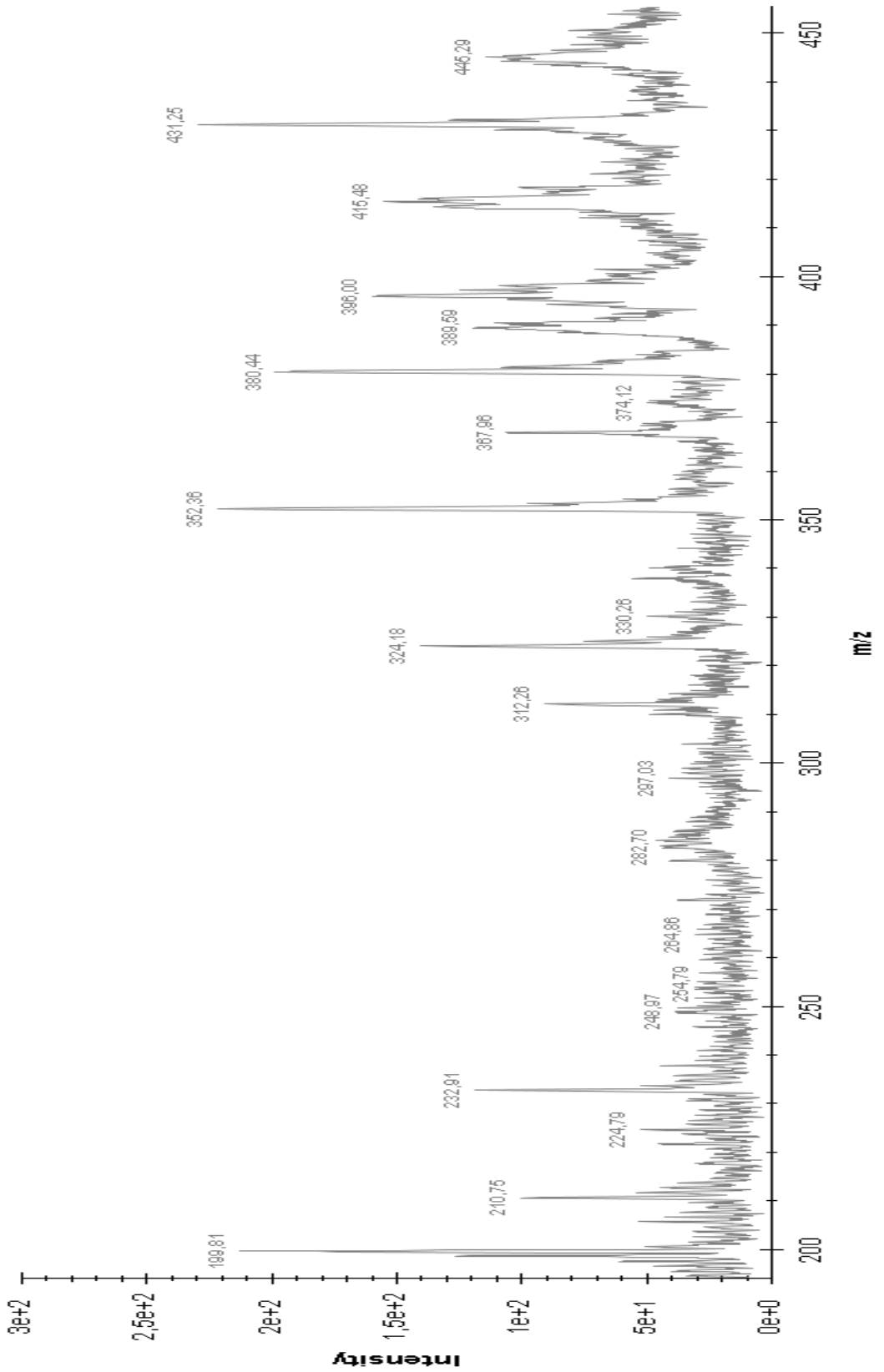

Figure Appendix A.23. MALDI-TOF MS spectrum of complex C5.

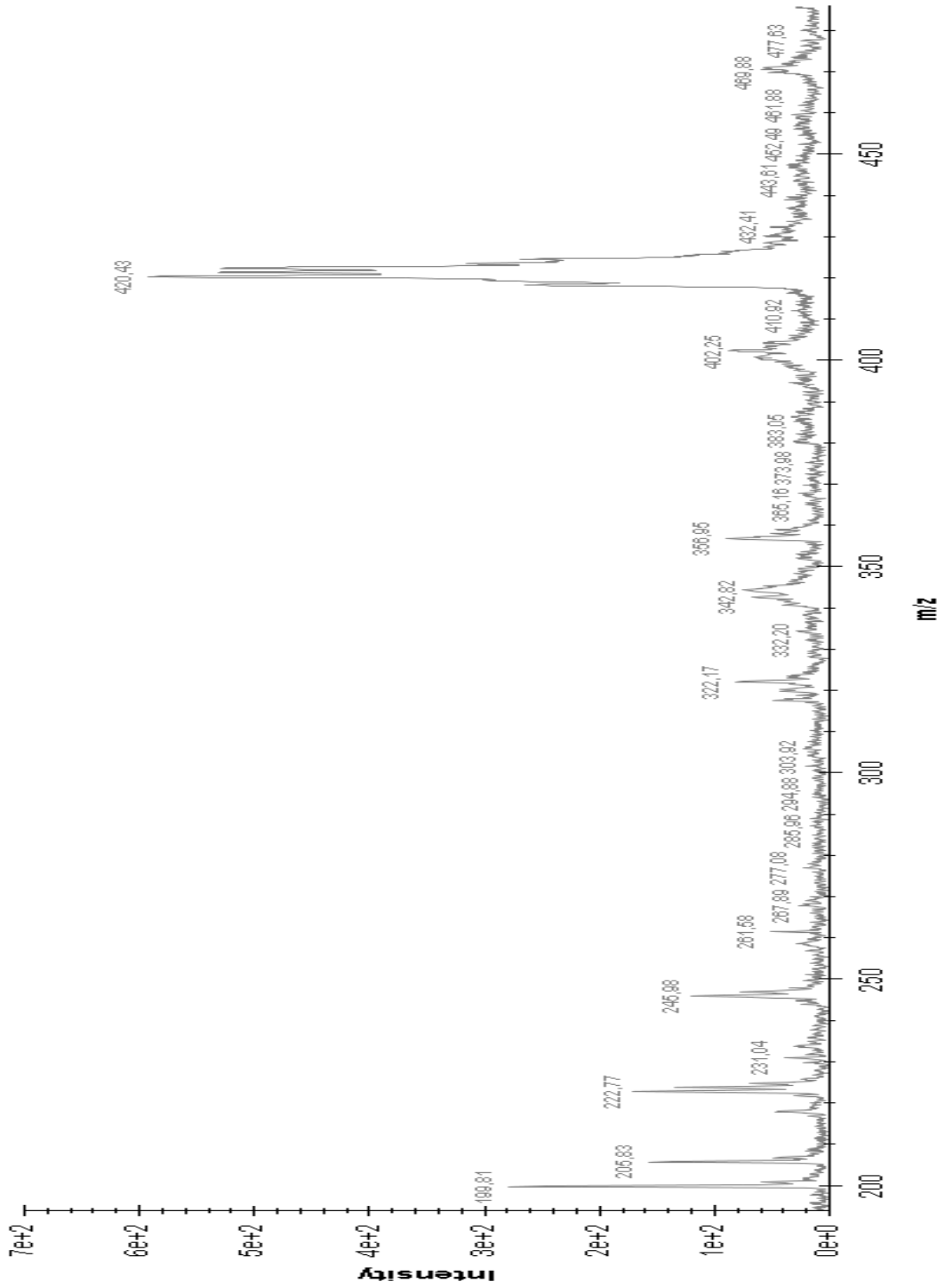

Figure Appendix A.24. MALDI-TOF MS spectrum of complex C6.

RESUME

Ahmed Sultan Samer AL-ISSWE graduated from Ammar bin Yasser High School for Boys in 2011. He began his studies at Al-Anbar University, College of Education for Pure Sciences, Chemistry Department, in 2017 and graduated in 2020. He began his master's studies at the Chemistry Department at Karabuk University, Turkey, in 2021.