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Research Article

Evaluation of Pro-Drug Properties in a Novel Schiff Base-Incorporated Pt(II) Complex

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Abstract

The present investigation involved the synthesis of a new Schiff base and its platinum complex. The chemical structures of both the ligand and the complex were determined using various analytical techniques, including ^{1}H-NMR, ^{13}C-NMR, FT-IR, and elemental analysis. Moreover, the interaction between the synthesized complex and Amyloid-Beta, a crucial factor in the pathogenesis of Alzheimer's disease, was explored. This interaction was assessed by employing fluorescence spectrophotometry. Additionally, the influence of the histidine amino acid, which has been reported in the literature to play a significant role in the interaction between Amyloid-Beta and coordination compounds, was monitored using ^{1}H-NMR. These investigations could improve our comprehension of ligands and complexes' chemical structure and biological effects. Furthermore, they may contribute to the advancement of knowledge regarding important neurodegenerative disorders such as Alzheimer's disease, as well as the development of potential therapeutic strategies.

Keywords: Alzheimer's Disease, Amyloid Beta, Platinum Complexes, Schiff Bases, Cytotoxic Activity.

Yeni Schiff Bazı İçeren Pt(II) Kompleksinin Pro-İlaç Özelliklerinin Değerlendirilmesi

Öz

Bu çalışma, yeni bir Schiff bazının sentezi ve platin kompleksinin incelenmesini içermiştir. Hem ligandın hem de kompleksin kimyasal yapıları, ^{1}H-NMR, ^{13}C-NMR, FT-IR ve elementel analiz gibi çeşitli analitik teknikler kullanılarak belirlenmiştir. Ayrıca, Alzheimer hastalığının patogenezinde önemli bir faktör olan Amiloid-Beta ile sentezlenen kompleks arasındaki etkileşim araştırılmıştır. Bu etkileşim, floresan spektrofotometre kullanılarak değerlendirilmiştir. Ek olarak, Amiloid-Beta ve koordinasyon bileşikleri arasındaki etkileşimde önemli bir rol oynadığı literatürde bildirilen histidin amino asidinin etkisi, ^{1}H-NMR kullanılarak izlenmiştir. Bu araştırmalar, ligand ve komplekslerin kimyasal yapıları ve biyolojik etkileri hakkındaki anlayışımızı artırma potansiyeline sahiptir. Ayrıca, Alzheimer hastalığı gibi önemli nörodejeneratif bozukluklar hakkındaki bilgi ilerlemesine ve potansiyel terapötik stratejilerin geliştirilmesine katkıda bulunabilir.

Anahtar Kelimeler: Alzheimer Hastalığı, Amiloid Beta, Platin Kompleksleri, Schiff Bazları, Sitotoksik Aktivite.

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1. Introduction

Schiff Bases are a class of compounds that follow the general formula RR'C=NR" (where R represents an aryl group, R' represents a hydrogen atom, and R" represents an alkyl or aryl group). Interestingly, even when R" is an alkyl or aryl group and R' is an alkyl or aromatic group, the compound is still referred to as a Schiff Base. These compounds exhibit versatility due to the presence of different substituents and the potential inclusion of N-N' bridges or the absence of bridges altogether.

The synthesis of Schiff Bases can be achieved through various reaction methods, with the most employed method being the acid-catalyzed condensation reaction between an amine and an aldehyde or ketone under reflux conditions. In the initial step of this reaction, the nitrogen atom of the amine undergoes a nucleophilic attack on the carbonyl carbon, resulting in the formation of an unstable carbinolamine intermediate. It is worth noting that the starting materials can be interchanged in this reaction. Upon elimination of water, a C=N bond is formed. These bases are typically synthesized from carbonyl compounds such as aldehydes and ketones, along with aromatic amines. The process involves nucleophilic addition, semi-aminal formation, and subsequent dehydration, ultimately leading to the formation of an imine [1].

The pH dependence of imine formation is a crucial factor to consider. In the initial step, non-protonated free amines are added to carbonyl groups. If the solution becomes excessively acidic, the concentration of amines decreases, resulting in a slowdown of the normally rapid step. This step plays a significant role in determining the overall reaction rate. In the subsequent step, protonated groups, such as OH, are eliminated. Consequently, a decrease in acidic concentration promotes the progression of the second step, facilitating the easy elimination of H_2O. Under acidic conditions, basic amines are typically protonated, making them non-nucleophilic and impeding the reaction's advancement. Moreover, the reaction is hindered under highly basic conditions. For instance, there is a lack of suitable protons available to catalyze the separation of the hydroxyl group in carbinolamine. In general, the reactivity of aldehyde is more than ketone in the formation of Schiff base.

Schiff bases are a class of ligands that play a crucial role in chemistry [2]. They are highly versatile and can be easily prepared, making them valuable in transition metal coordination chemistry. In recent years, there have been significant advancements in the chemistry of transition metal complexes with metallo-rings [3]. Bidentate N-donor ligands form chelate complexes by coordinating with one of the metal centers using each nitrogen atom. These metallochelates are commonly used in regiospecific organic and organometallic syntheses, including addition reactions and catalytic materials. Ruthenium complexes containing bidentate Schiff bases are particularly useful in catalytic processes such as Kharasch addition, enol-ester synthesis, alkyne dimerization, olefin metathesis, and polymerization. Chiral Schiff base metal complexes are employed for achieving stereoselective organic transformations. Tetradentate Schiff base complexes of oxovanadium exhibit potential for multi-electron transfer. Schiff bases have shown potential as anticancer agents, but their activity is further enhanced when

they form metal complexes. Schiff bases with an azomethine bridge have been found to possess antitumor, antibacterial, and antifungal properties. In drug research, it has been observed that small molecules interacting with DNA can cause DNA damage, leading to cell death. Therefore, compounds with anticancer, antiviral, and antiseptic properties often exhibit biological activity by interacting with DNA. Numerous studies have demonstrated that transition metal complexes can bind to DNA through intercalation.

Alzheimer's disease (AD) is a prevalent form of dementia, accounting for approximately 60-80% of dementia cases. Dementia is a neurodegenerative condition that impacts various cognitive functions such as memory, language, attention, problem-solving, and decision-making. This impairment arises from brain damage. Alzheimer's disease poses significant challenges globally, requiring costly and labor-intensive treatment, second only to heart and cancer diseases. The primary culprit behind this disease is believed to be the accumulation of $A\beta_{1-42}$, resulting in the formation of insoluble plaques. These plaques consist of amyloid-β (Aβ) peptides and are thought to disrupt neuronal communication between cells. In the pursuit of effective treatment, organic molecules with aromatic rings and suitable chelating ligands containing nitrogen donors play a crucial role. The development of these ligands and the synthesis of coordination compounds formed with them are essential for combating Alzheimer's disease.

Despite the numerous Schiff base-Pt complexes that have been reported [5-11], their impact on Alzheimer's disease has not yet been explored. In a recent study, F. Collin and colleagues [12] synthesized several Pt complexes, including Pt(Φ-MePy)(DMSO)Cl, $Pt(DMSO)_2Cl_2$, $Pt(bpy)Cl_2$, $Pt(Phen)Cl_2$, and $Pt(\Phi\text{-}Phen)Cl_2$, with the aim of reducing the interaction of Zn and Cu with Aβ aggregation and ROS production, respectively. The structures of these complexes were elucidated, and their interaction with the Aβ28 peptide was examined. Similarly, Sasaki and colleagues [13] investigated the interaction of Pt(Φ-MePy)(DMSO)Cl and $Pt(DMSO)_2Cl_2$ complexes with Cu(II)-Aβ28 using EPR measurements. The results indicated that the Pt complex did not displace Cu(II), but it did bind to specific regions of the Aβ peptide. In another study, Kenche and colleagues [14] determined the structure of a complex formed between an N,N-dimethyl-2-[2-(quinolin-8-yl)-1H-benzimidazol-1-yl] ligand and $Pt(dmso)_2Cl_2$. They then investigated the interaction of this complex with mouse Aβ fibrils and found that it inhibited aggregation. Additionally, Satra synthesized a Pt(IV) complex with the same ligand and demonstrated that its efficacy was higher than that of the Pt(II) complex. Based on these findings, our study aims to synthesize a new Schiff base and characterize its four-coordinated Pt(II) complexes. Furthermore, we plan to investigate the interactions of these complexes with histidine.

2. Materials And Methods

2.1. Chemicals

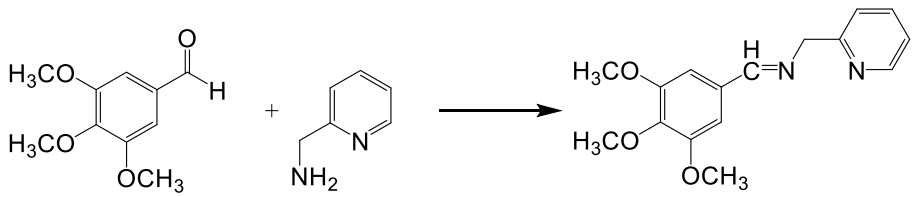
To synthesize the Schiff base, 2-picolamine and 3,4,5-trimethoxybenzaldehyde were obtained from Sigma Aldrich and Alfa Easer companies. L-Histidine, PBS buffer (phosphate buffer), and Tioflavin-T were also acquired from the same suppliers. The $A\beta_{1-42}$ fluorescent kit was purchased from Anaspec. The starting complex $Pt(DMSO)_2Cl_2$ was synthesized based on the literature data [15].

2.2. Instrumentations

^1H NMR and ^{13}C NMR spectra were recorded on the Vairian AS 400 NMR spectrometer in $CDCl_3$ and DMSO-d6 with tetramethylsilane (TMS) as an internal reference. Chemical shifts are reported in ppm (δ). Coupling constants, *J*, are reported in Hz. FT-IR analyses were conducted using the Perkin Elmer Spectrum 100 FTIR spectrophotometer with CsI (4000-250 cm^{-1}). Furthermore, the facilities at İnönü University were utilized for elemental analysis.

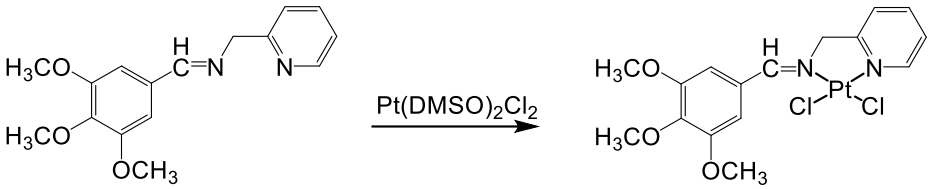
2.3. Synthesis of Ligand and its Platinum Complex

2.3.1. Synthesis of Ligand



The synthesis was carried out using the melting technique at a temperature of 80°C in the presence of N_2 gas, without a solvent. The reactants used were 3,4,5-trimethoxybenzaldehyde (36 mg; 0.184 mmol) and 2-picolamine (20 mg; 0.184 mmol). The reaction occurred in an oil bath for approximately 15 minutes. After the reaction was complete, a yellow-colored oil-like product was obtained. The volatile components were then removed under vacuum. The overall yield of the reaction was determined to be 80%. FT-IR (Ʊ, cm^{-1}); 1586.1 (C=N). ^1H (400 MHz, $CDCl_3$) δ (ppm): 8.48 (d, 1H, *J*=4.7 Hz, Py-*H*), 8.29 (s, 1H, N=C*H*), 7.58 (t, 1H, *J*=7.7 Hz, Py-*H*), 7.32 (d, 1H, *J*=7.8 Hz, Py-*H*), 7.09 (t, 1H, J=6.0 Hz, Py-*H*), 6.99 (s, 2H, Ar-*H*), 4.86 (s, 2H, N-CH_2), 3.81 (s, 6H ,OCH_3), 3.80 (s, 3H ,OCH_3).^{13}C (100 MHz, $CDCl_3$) δ (ppm): 162.7 (*C*=N), 159.1 (Py-*C*), 153.4 (Ar-*C*), 149.2 (Py-*C*), 140.5 (Ar-*C*), 136.6 (Py-*C*), 131.5 (Ar-*C*), 122.2 (Py-*C*), 122.0 (Py-*C*), 105.4 (Ar-*C*), 66.5 (N-*C*H_2), 60.8 (O*C*H_3), 56.1 (O*C*H_3).

2.3.2. Synthesis of Complex (Pt-L)



L (20.3 mg; 0.071 mmol) was refluxed with $Pt(DMSO)_2Cl_2$ (30 mg; 0.071 mmol) in a 1:1 molar ratio in chloroform for 2 hours. At the end of this period, a dark yellow-orange precipitate formed, which was separated and washed with diethyl ether. The resulting material was dried under vacuum to obtain a yellow-orange solid product. Yield: 52%, Decomposition Point: 220-240°C. Elemental analysis: Calculated ($C_{16}H_{18}CI_2N_2O_3Pt$, 552.32): C,34.79; H, 3.28; N, 5.07; Found: C, 33.98; H, 3.16; N, 5.07. FT-IR (U, cm^{-1}); 1647.0 (C=N), 322-293 (Pt-CI). ^{1}H (400 MHz, DMSO-d_6) δ (ppm): 9.07 (d, 1H, *J*=5.9 Hz, Py-*H*), 8.92 (s, 1H, N=C*H*), 8.10 (t, 1H, *J*=7.7 Hz, Py-*H*), 7.62 (d, 1H, *J*=7.9 Hz, Py-*H*), 7.46 (t, 1H, J=6.7 Hz, Py-H), 7.40 (s, 2H, Ar-*H*), 6.16 (s, 2H, N-CH_2), 4.08 (s, 3H, OCH_3), 4.06 (s, 6H , OCH_3). ^{13}C (100 MHz, DMSO-d_6) δ (ppm): 166.0 (*C*=N), 162.4 (Py-*C*), 156.7 (Ar-*C*), 152.5 (Py-*C*), 143.8 (Ar-*C*), 139.9 (Py-*C*), 134.9 (Ar-*C*), 125.6 (Py-*C*), 125.3 (Py-*C*), 108.7 (Ar-*C*), 69.9 (N-*C*H_2), 61.4 (O*C*H_3), 59.5 (O*C*H_3).

2.4. NMR Measurement of $Pt(L)Cl_2$-Histidine Interaction

The $Pt(L)Cl_2$ complex underwent solvolysis through vigorous stirring in a mixture of DMSO and H_2O with a ratio of 2:1 for a duration of 15 minutes. Subsequently, histidine was meticulously weighed and combined with the complex solution in a molar ratio of 1:2 (complex to histidine) in the presence of HCl. The resulting mixture was then incubated at a temperature of 37°C for 15 minutes, while PBS buffer was added. Following this, the ^{1}H-NMR spectrum of the sample was acquired, revealing discernible differences in the signals resulting from the interaction.

2.5. Fluorescence Measurements

The $A\beta_{1-42}$, ThT, and the complex formed with 1% DMSO in water were initially diluted to the desired concentration (final concentration 10 micromolar) using the provided assay buffer. To conduct fluorescence measurements, a black well plate was used, with each well adjusted to a volume of 100 µl. The aggregation inhibition of the complex was evaluated by adding $A\beta_{1-42}$ to the system both individually and in combination with the complex. Additionally, the fluorescence properties of the complex alone and the assay buffer were examined. Measurements were recorded using the Thermo Fisher Scientific Varioskan Flash microplate reader, with excitation at 480 nm and emission at 484 nm.

3.Results and Discussion

3.1. NMR Evoluation

Figures 1 and 2 present the ^{1}H-NMR and ^{13}C-NMR spectra, respectively, of the L ligand. The imine proton of the ligand is detected as a singlet at 8.29 ppm. The -OCH_3 groups exhibit multiplet signals at 3.81 and 3.80 ppm. Additionally, the ^{13}C-NMR values of the ligand align with the anticipated structure. The imine carbon is observed at 162.7 ppm and the carbons of the methoxy group at 60.8 and 56.1 ppm.

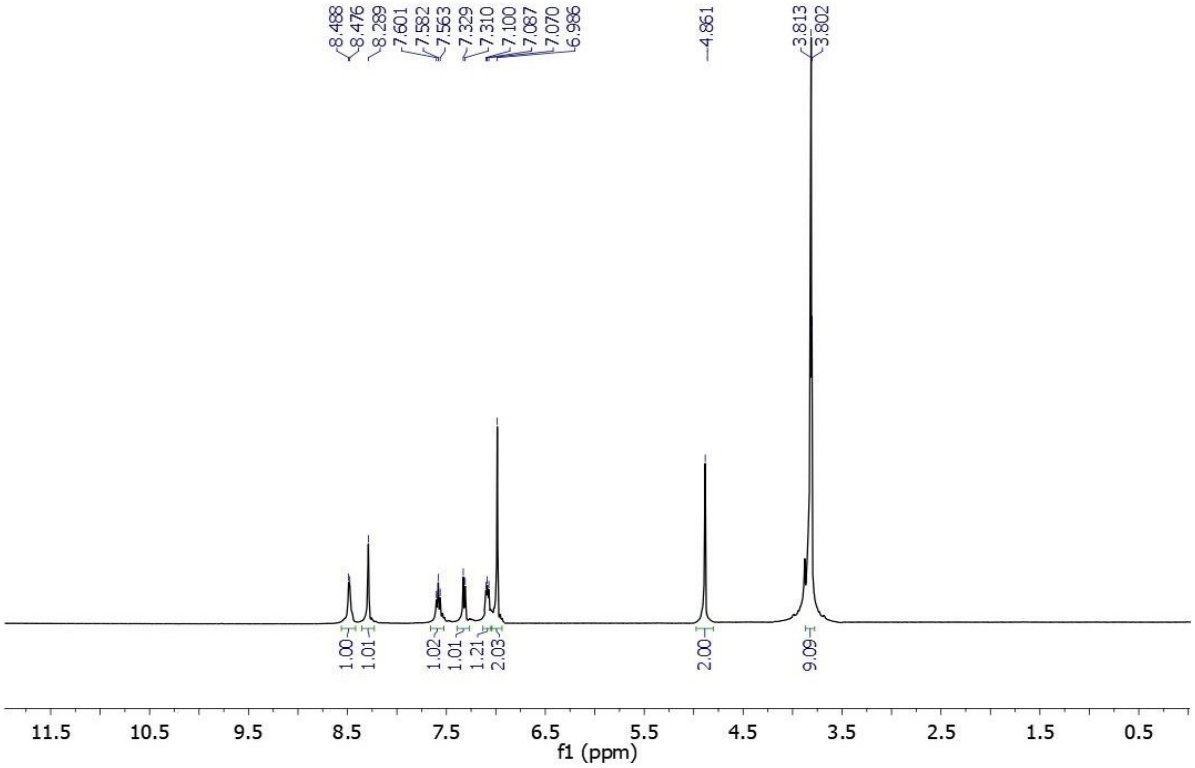


Figure 1. ^{1}H-NMR Spectrum of **L**.

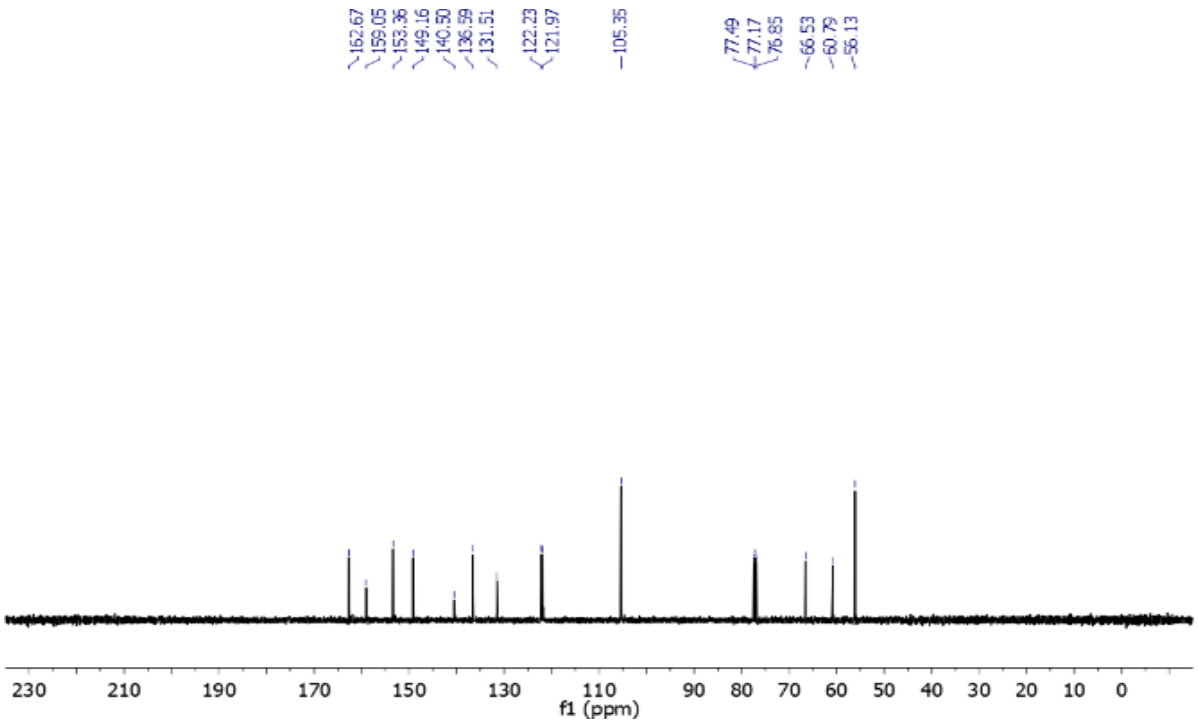


Figure 2. ^{13}C-NMR Spectrum of **L**.

The ^{1}H-NMR and ^{13}C-NMR spectra of the synthesized Pt(L)Cl_2 complex are given in Figures 4 and 5. NMR data related to the ligand and comples are shown in Table 1.

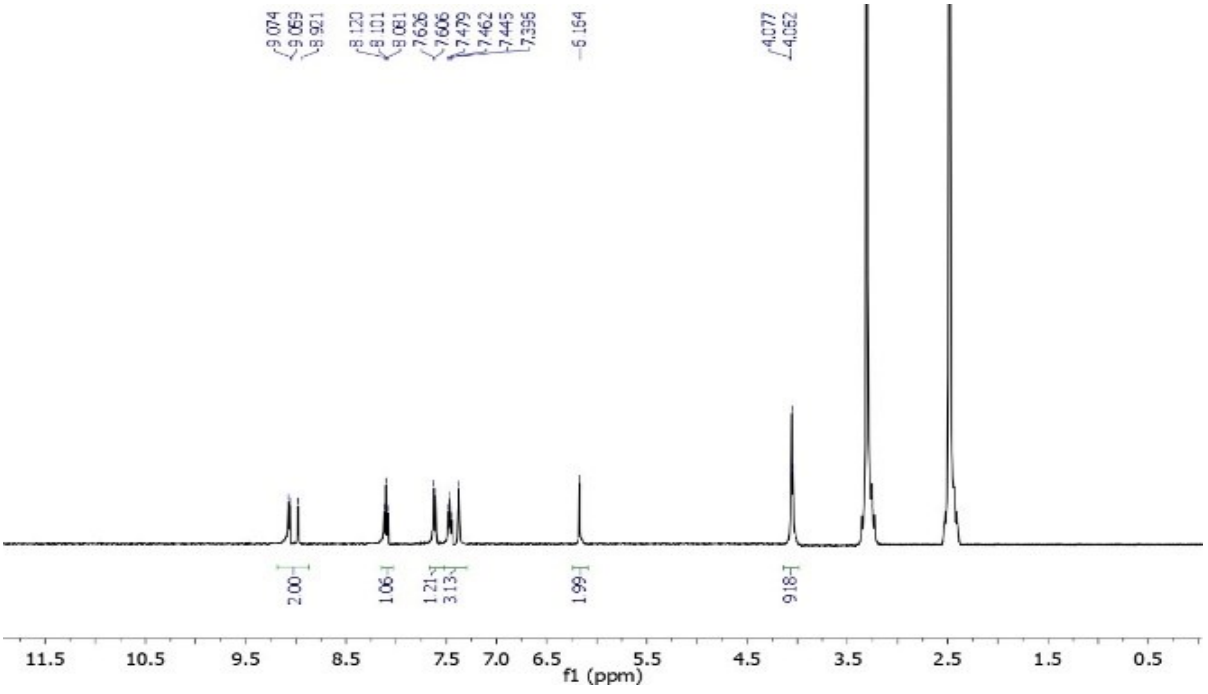


Figure 3. ^{1}H-NMR Spectrum of Pt(L)Cl_2.

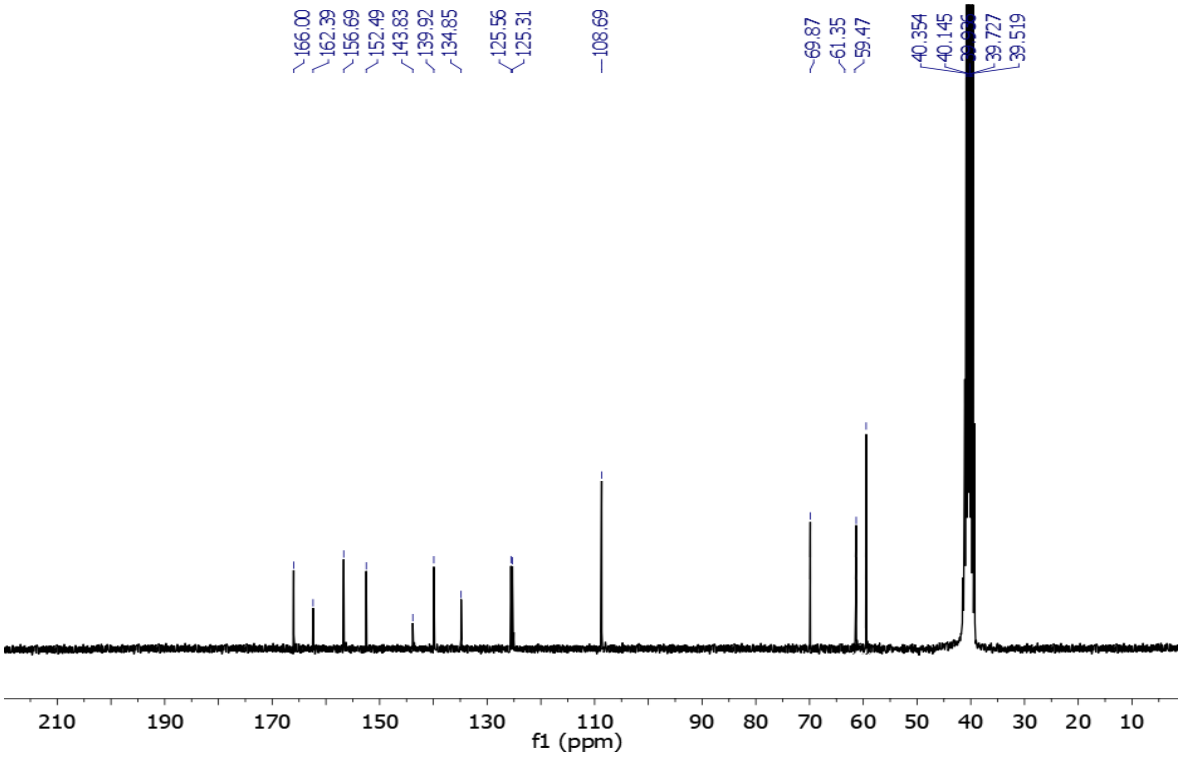
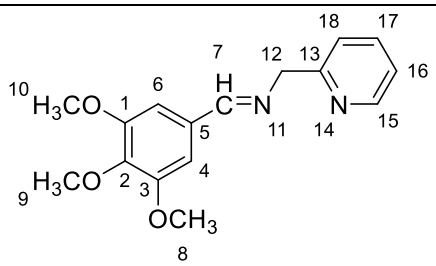
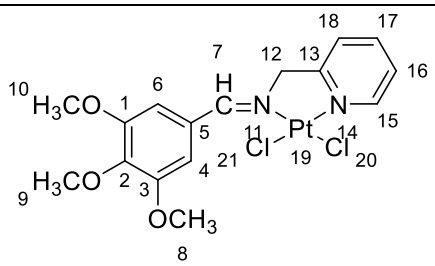


Figure 4. ^{13}C-NMR Spectrum of $Pt(L)Cl_2$.

Table 1: ^{1}H- and ^{13}C-NMR Peak Assignments for Ligand and Complex

 Ligand (L)		 complex (Pt-L)	
^{1}H-NMR			
Number	ppm	Number	ppm
15	8.48 (d)	15	9.07 (d)
7	8.29 (s)	7	8.92 (s)
16	7.58 (t)	16	8.10 (t)
18	7.32 (d)	18	7.62 (d)
17	7.09 (t)	17	7.46 (t)
4, 6	6.99 (s)	4, 6	7.40 (s)
12	4.86 (s)	12	6.16 (s)
8, 10	3.81 (s)	8, 10	4.06 (s)
9	3.80 (s)	9	4.08 (s)
^{13}C-NMR			
Number	ppm	Number	ppm
7	162,7	7	166.0
13	159.1	13	162.4
1, 3	153.4	1, 3	156.7
15	149.2	15	152.5
2	140.5	2	143.8
17	136.6	17	139.9
5	131.5	5	134.
16	122.2	16	125.6
18	122.0	18	125.3
4,6	105.4	4,6	108.7
12	66.5	12	69.9
9	60.8	9	61.4
8, 10	56.1	8, 10	59.5

*s: singlet; d: doublet; t: triplet; m: multiplet; bs: broad singlet

The imine group in the complex exhibits a shift to 8.92 ppm in the ^{1}H-NMR spectrum, indicating its binding. Conversely, when the pyridylamine's N end binds, it causes a significant shift in the adjacent aromatic ring's protons. Specifically, these protons experience a shift to a

weaker field during complexation, with the proton adjacent to N shifting from 8.49 ppm to 9.07 ppm. Furthermore, the ^{13}C spectrum shows a weak-field shift in the imine group's C atom compared to the ligand spectrum (166.0 ppm) [9, 17].

3.2. FT-IR spectra

The FT-IR spectrum of the ligand is given in figure5. The characteristic vibration signal of the imine group is observed at 1586.1 cm^{-1}. It is observed that the signal related to the carbonyl group in the aldehyde disappears. These assessments collectively confirm the successful synthesis of the ligands. These findings are corroborated by the weak-field shift observed in the imine group vibrations in the FT-IR spectrum of the complex (Fig.6) as well as the elemental analysis results [18, 19]. Additionally, the presence of Pt-Cl stretching vibrations in the FT-IR spectrum of the complex, appearing as a doublet and shifting compared to the starting complex, confirms the occurrence of the anticipated interaction [20]. It was also observed that the signals related to the DMSO group in the initial complex disappeared in the complex spectrum.

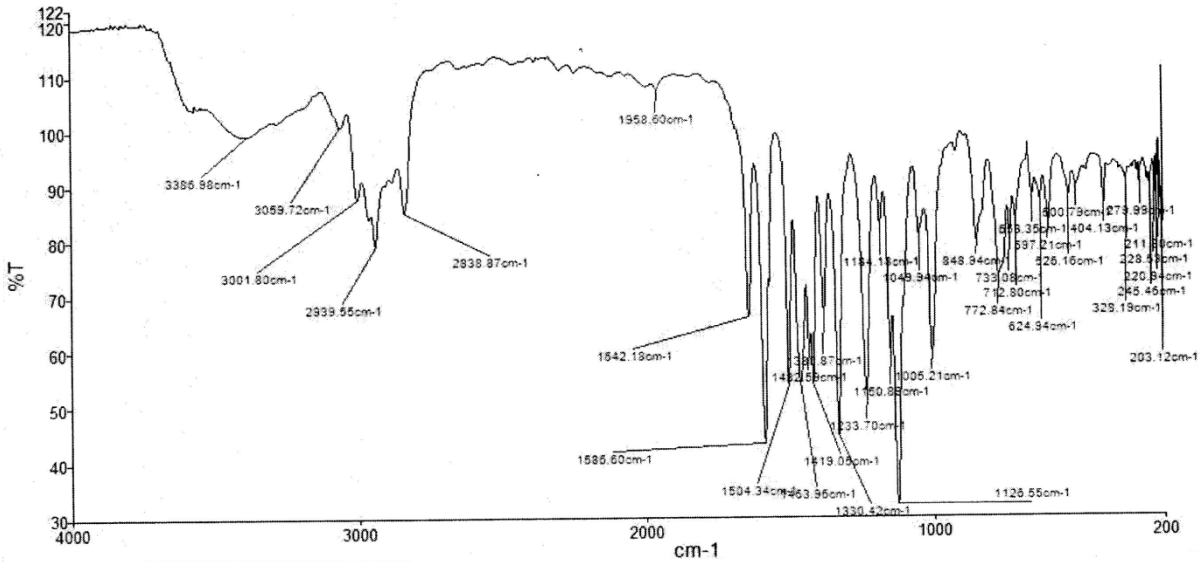


Figure 5.FT-IR spectrum of the Ligand

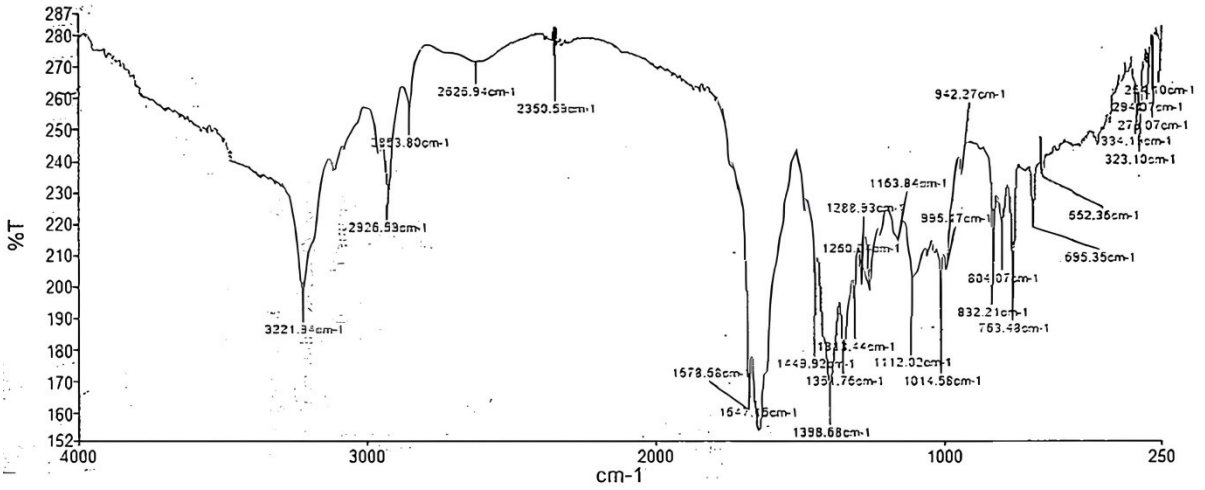


Figure 6. FT-IR spectrum of the $Pt(L)Cl_2$

3.3. Evaluation of $Pt(L)Cl_2$ -Histidine Interaction by NMR Measurements

The determination of the environment for measuring the complex with Histidine was carried out in accordance with the existing literature. To measure the biological activity, it is necessary to first hydrolyze or solvolysis the complex. Initially, an attempt was made to use H_2O, and if the solubility was low, mixtures of DMSO/H_2O were tested [16]. Due to the low solubility of the synthesized complex in water, it was solvolysis with DMSO and then examined for its interaction with Histidine in a DMSO: H_2O (2:1) mixture. Consequently, the spectrum for the complex was initially obtained in DMSO-d6. Upon examination of the spectrum obtained for the complex in DMSO-d6, the peak corresponding to the imine proton was observed at 8.92 ppm. Additionally, the ^{1}H-NMR spectrum of free Histidine in a DMSO/H_2O environment was acquired, revealing the presence of the aromatic protons (Ar-CH) of Histidine hydrochloride (two protons) at 8.57 ppm and 7.27 ppm. The solvolysis complex and Histidine were then incubated in a PBS buffer for 15 minutes at 37°C, and the ^{1}H-NMR spectrum was recorded. The expectation was that one or two solvent molecules would be displaced by Histidine from the solvolysis product. In the resulting spectrum of the interaction, the imine peak associated with the Histidine-bound complex was observed at 8.65 ppm. Furthermore, the (Ar-CH) protons of Histidine shifted to 8.41 ppm and 7.12 ppm due to the interaction with the complex. Based on the observed chemical shift values, it can be inferred that there is an interaction between the complex and histidine. This is further supported by Figure 5, which shows the shift of the imine proton and the shifts in the Histidine peaks during the interaction between the Complex and Histidine. Additionally, according to the literature, the solvolysis of such complexes can result in the formation of numerous adduct products in the interaction with Histidine, indicating interactions with different molar ratios of Histidine [16, 21].

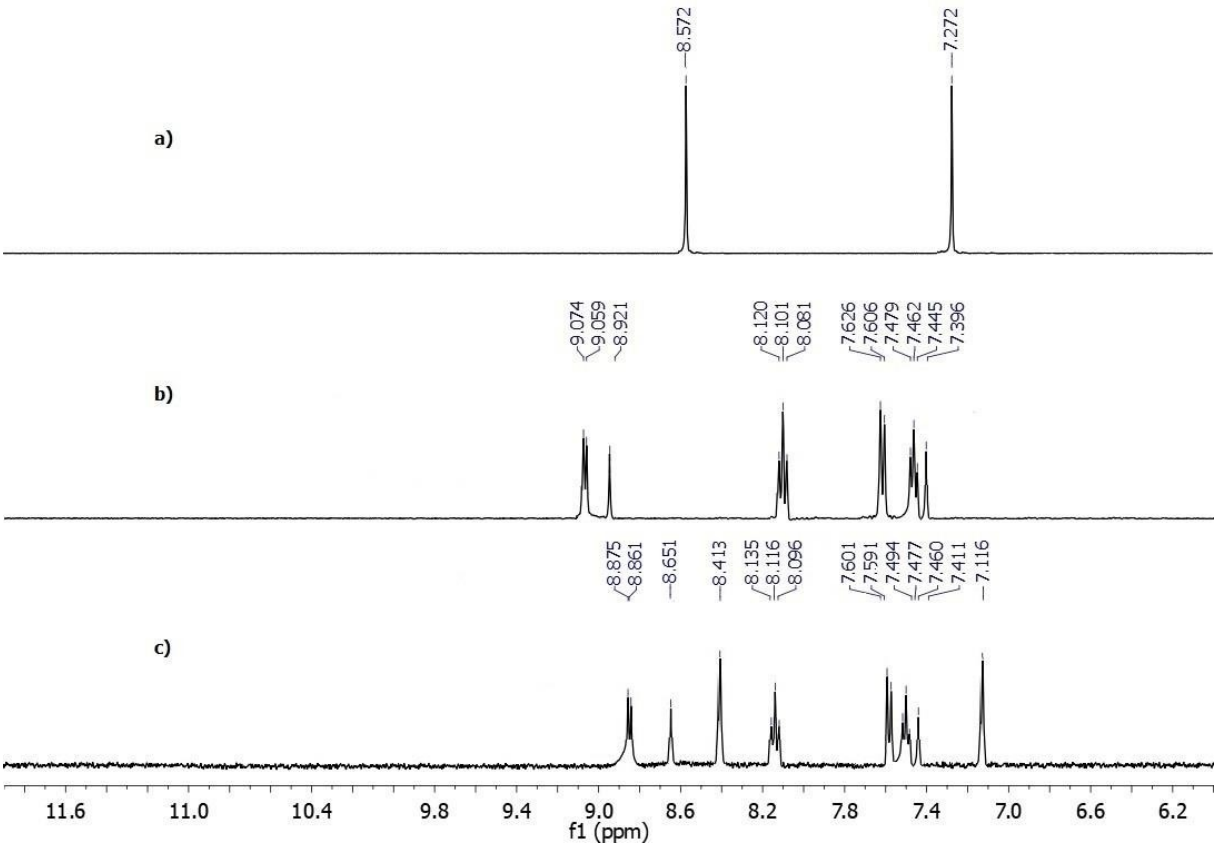


Figure 5. a) ^{1}H-NMR spectrum of Histidine hydrochloride (blind), b) ^{1}H-NMR spectrum of $Pt(L)Cl_2$ complex in DMSO environment, c) ^{1}H-NMR spectrum obtained after 15 minutes of incubation at 37 ºC in a 1:2 ratio of complex to Histidine at pH 7.4.

3.4. Evaluation of Fluorescence Measurements

Although Thioflavin T does not emit fluorescence when it is in its monomeric form and in the presence of $A\beta_{1\text{-}42,}$ it does produce a signal when it is in the presence of aggregated amyloid with ThT (Excitation: 440 nm, Emission: 484 nm). It is anticipated that the complex formed by Thioflavin T and $A\beta_{1\text{-}42}$ will diminish this signal. The measurement results indicate that the $Pt(L)Cl_2$ complex interacts with $A\beta_{1\text{-}42}$ in a 1:1 molar ratio (Figure 6). The decrease in fluorescence values observed when interacting with Amyloid Beta provides evidence that the synthesized compound indeed interacts with Amyloid Beta.

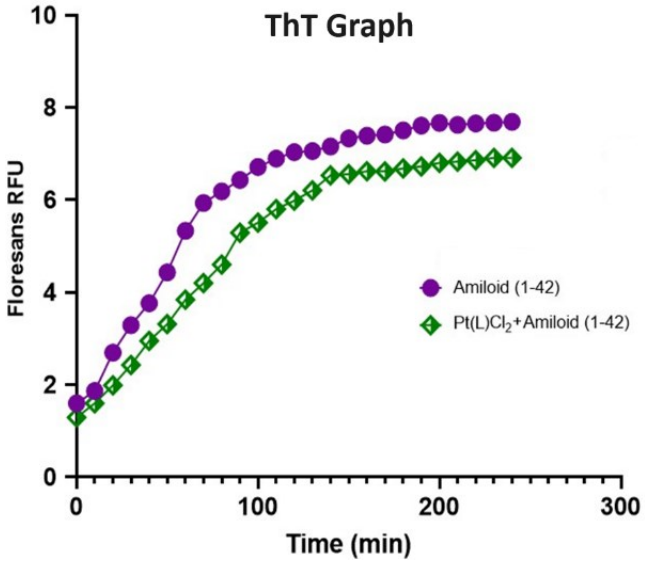


Figure 6. Fluorescence Measurement Graph of $Pt(L)Cl_2$ Complex.

The decrease in the fluorescence intensity of amyloid in the presence of the complex during interaction with Thioflavin T indicates the occurrence of interaction.

4. Conclusion

A Schiff base compound of a novel nature has been successfully synthesized, followed by the synthesis of its platinum complex. The structures of both the ligand and the complex have been thoroughly elucidated through the utilization of various spectroscopic techniques. In the subsequent phase of the research, the compound's potential to exhibit activity against Alzheimer's disease has been investigated by studying its interaction with Amyloid beta in a 1:1 molar ratio. To assess the compound's efficacy, fluorescence measurements have been conducted. Notably, the synthesized complex has displayed significant activity against Alzheimer's disease. Moreover, the interaction between the complex and Histidine, an amino acid predominantly found in Amyloid beta and commonly targeted by coordination compounds, has been meticulously examined. As a result, the study has uncovered the formation of solvolysis products at different molar ratios when one mole of the complex interacts with two moles of Histidine.

Ethics in Publishing

There are no ethical issues regarding the publication of this manuscript.

Author Contributions

Salih Günnaz: Conducted the experiment, analyzed the results, and composed the manuscript.

Khan Mohammad Rahmat: Conducted the experiment.

Sevil İrişli: Oversaw the advancement of the trial, managed the experiment, analyzed the findings, and drafted the written report.

Acknowledgement

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