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Crystal Structure and DNA Binding Properties of A Sulfide Bridged Dimeric Schiff Base Compound

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ABSTRACT

In this research, a novel 4,4'-Diaminodiphenyl sulfide-based Schiff base compound [**6,6'-((1E,1'E)-((thiobis (4,1-phenylene)) bis(azaneylylidene)) bis(methaneylylidene)) bis(3-(diethylamino) phenol)** (**A**)], which is known to have good biological activity and forms the basis of anticancer drugs, was successfully synthesized. Structural characterization of the synthesized Schiff base compound was determined by FT-IR and ^{1}H-^{13}C NMR, spectroscopies. Also, the molecular structure of the compound was determined by a single-crystal X-ray diffraction study. The DNA binding ability of the compound was measured using UV-vis spectroscopy. Using the spectral changes, the DNA binding constant of the compound was calculated as K_b (M^{-1})= 6.25x10^5. The K_b value found suggests the existence of an intercalative interaction.

4,4'-Diaminodifenil Sülfür Bazlı Imin Bileşiğinin Spektral ve DNA Bağlama Özellikleri

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ÖZ

Bu araştırmada, antikanser ilaçların temelini oluşturan ve iyi derecede biyolojik aktiviteye sahip olduğu bilinen, yeni bir 4,4'-Diaminodifenil sülfit bazlı Schiff bazı bileşiği [**6,6'-((1E,1'E)-((thiobis (4,1-phenylene)) bis(azaneylylidene)) bis(methaneylylidene)) bis(3-(diethylamino) phenol)** (**A**)] başarıyla sentezlenmiştir. Sentezlenen Schiff bazı bileşiğinin yapısal karekterizasyonu, FT-IR ve ^{1}H-^{13}C NMR, spektroskopileri ile belirlenmiştir. Ayrıca, bileşiğin moleküler yapısı, tek kristalli bir X-ışını kırınım çalışmasıyla belirlenmiştir. Bileşiğin DNA bağlama yeteneği, UV-*vis* spektroskopisi kullanılarak ölçülmüştür. Spektral değişimlerden faydalanılarak bileşiğe ait DNA bağlama sabiti Kb (M^{-1})= 6.25x10^5 olarak hesaplanmıştır. Bulunan K_b değeri interkalatif bir etkişimin varlığını önermektedir.

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1. Introduction

Cancer, one of the leading causes of death globally and is first among them, is a type of disease that causes the spread of cellular disorder in the body in the region aberrant cell enlargement with the ack demand to spread. If the DNA structure of the cancerous cell is treated, cancer disappears (Jamshidvand et al. 2018). Compounds bearing Schiff bases, an azomethine group ordinarily achieved from the condensation of primary amines and activated carbonyl groups (Puchtler and Meloan, 1981),

are frequently investigated by pharmaceutical researchers for their anti-cancer effects. Schiff bases are the essential materials in coordination chemistry and medicinal chemistry (Habibi and Askari 2013; Jamshidvand et al. 2018). Schiff bases are compounds formed by bonding the aldehyde or ketone structure with the primary amine. The azomethine group carried by these structures plays a role in many medical activities, for instance, antibacterial, herbicide, anti-inflammatory, antifungal, anti-cancer, anti-diabetic and antitumor activities (Jamshidvand et al. 2018). Deoxyribonucleic acid (DNA), which examines the construction and duty of cells, is an important destination for antiviral, anti-cancer and antibiotic drugs (Li and Dong 2009; Radi et al. 2014). The interplay between their molecules and DNA is based on size, conformation, and the capabilities of molecules' functional groups. These interactions are empirically studied (UV-*vis* absorption and emission properties) and placement works (Tümer et al. 2017; Güngör et al. 2021). Hyperchromic shifts in the absorption bands indicate the change in major or minor distortions in the DNA sequence, and changes in the absorption wavelengths because of interaction between DNA and the molecule provide information about the binding status (Güngör et al. 2020).

Schiff bases are vital in producing new anti-cancer drugs in the pharmaceutical field since Schiff bases are linked with DNA based on anti-cancer drug molecules (Jamshidvand et al., 2018; Abu-Dief et al. The binding between DNA and molecule can be in three different ways (Radi et al. 2014; Jamshidvand et al. 2018); In the form of electrostatic coupling with the negative charge of the sugar-phosphate structure (Wang et al. 2005; Radi et al. 2014; Jamshidvand et al. 2018), in the form of interaction over the corrugated DNA double helix (Radi et al. 2014; Jamshidvand et al. 2018), a hydrogen bond or van der Waals interplay in the form (intercalative bonding) (Radi et al. 2014; Jamshidvand et al. 2018). Among these three different types of bonding, intercalative bonding is the strongest. The surface of the interlocutory molecule is sandwiched among them aromatically, heterocyclic DNA base couples. The molecule's skill to bind to DNA depends on the size and electron density of the aromatic rings it is expected to interact with and the strength of the hydrophobic/hydrophilic interactions (Jayamani et al. 2014; Shokohi-Pour et al. 2016; Jamshidvand et al. 2018; Abu-Dief et al. 2021).

Schiff bases, known to have good biological activities, form the basis of materials such as catalysts, intermediates in organic synthesis, dye, pigment, polymer stabilisers and corrosion inhibitors. According to the information in the literature, complex structures of Schiff bases are more bioactive than their ligands. Schiff base materials have an essential place in coordination chemistry, paving the way for biochemistry and optical materials (Kajal et al. 2013)**.**

Schiff bases show strong affinity for transition metal ions. They are known as excellent ligands because imine groups can chelate with metal ions (Ghosh, et al., 2018; Xia, et al., 2015). Schiff bases can coordinate strongly with metals, with active imine groups and the desire to bind hetero elements in their structure (Sönmez et al., 2019; Kalantari and Asadi, 2020). Schiff base metal complexes, which form the basis of anti-cancer drugs and are known as the most suitable candidates for these drugs,

fasten with DNA through non-covalent bonding, for instance, electrostatic, intercalation and gutter bonding (Kalantari and Asadi, 2020). Non-covalent binding anticancer drugs have proven to have less side effects when compared to covalently bound anticancer drugs (Kalantari & Asadi, 2020: Kumalo, et al. 2015). The chelated complex increases the biological activity of many compounds (Chohan, et al. 2002). It is reported that Schiff bases demonstrate a considerable increase in pharmacological characteristics after interacting with metal ions (Abu-Dief and Mohamed, 2015).

The calf thymus, fish sperm and herring sperm DNA are ofted used as models in the DNA bindinding studies of binder molecules. These three DNA models are structurally similar regarding the number of base pairs and base sequences (Magdy, et al. 2021).

In this study, we synthesised a new imine compound based on 4,4′-diaminodiphenyl sulfide. The spectral and DNA binding properties of the obtained compound were studied. The structure of the compound obtained within the scope of the study was characterised by UV–*vis*, FTIR, $^{1}H^{13}C$ NMR and photoluminescence spectroscopy. Moreover, the DNA binding properties of the compound were determined. Additionally, the synthesised material's molecular edifice was characterised by a single-crystal X-ray diffraction study.

2. Material and Method

Chemicals employed in synthesis and analysis were obtained from company firms (Aldrich or Merck). The structure of the produced imine bond material was characterised using spectroscopic c such as FTIR and $^{1}H^{13}C$ NMR. In the structural analysis of the compound, FTIR (ATR) measurements, Perkin Elmer Spectrum 400 Spectrophotometer, light absorption properties, Hitachi U3900h Spectrophotometer UV-*vis* spectrophotometer, determination of emission characteristics Perkin Elmer, Photoluminescence Spectrophotometer, structure determination of the molecule, ^{1}H and ^{13}C NMR Bruker AVANCEIII 400 Mhz NMR Spectrophotometer and melting point of the material was obtained employing the Elektrothermal LTD 9200 instrument. All material was prepared with spectrophotometric grade solvents and treated using a one cm optical path quartz cuvette.

2.1. Synthesis of Schiff Base Compound

6,6' - ((1E,1'E) - ((thiobis (4,1-phenylene)) bis (azaneylilidene) bis (methanililidene)) bis (3-(diethylamino) phenol) (A) containing imine bond during the synthesis of the compound; First, 2.82 mmol of 4-(diethylamino)-2-hydroxybenzaldehyde was dissolved in methanol in a flask. Refluxing was continued until the dissolution of the substance was complete. 1.41 mmol, 4,4'-thiodianilin was included in the prepared solution, and the concoction was refluxed on a magnetic stirrer for 48 hr. The resulting mixture was kept at room condition to crystallise (Fig.1).

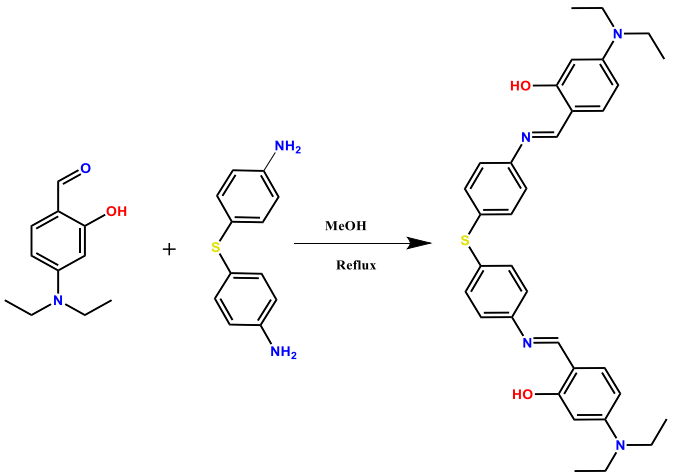

Figure 1. Compound **A**'s synthesis reaction.

2.2. X-ray Crystal Structure solution and refinement details

A single crystal of the compound with 0.15 × 0.08 × 0.06 mm^3 dimensions was attached to a glass fibre, and crystal diffraction data were obtained on a Supernova, Single source at the offset, Eos diffractometer at ambient temperature. Using Olex2 (Dolomanov et al. 2009), the structure was solved with the SHELXT (Sheldrick 2015a) and refined with the SHELXL (Sheldrick 2015b) refinement package using Least Squares minimisation. The crystals of the compound gave weak diffraction data, yet reasonable structure solution and refinement values were obtained. X-ray crystallographic data are provided in Table 1. The *cif* file containing structural info was deposited to Cambridge crystallographic data centre with CCDC number with 2209648.

Table 1. X-ray crystallographic information and refinement details for **A.**

Experimental formula	$C_{34}H_{38}N_4SO_2$
Formulation weight	566.74
Temperature/K	293(2)
Crystal scheme	Monoclinic
Space group	C2/c
a/Å	13.2473(12)
b/Å	5.8157(8)
c/Å	38.884(3)
α/°	90
β/°	91.322(8)
γ/°	90
Volume/$Å^3$	2994.9(6)
Z	4
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection/°	7.526 to 57.87
Index ranges	$-16 \le h \le 16$, $-7 \le k \le 6$, $-30 \le l \le 52$
Reflections collected	6244
Independent reflections	3369 [R_{int} = 0.0373, R_{sigma} = 0.0888]
Data/limits/parameters	3369/103/189
Goodness-of-fit on F^2	1.278
Ultimate R indexes [I>=2σ (I)]	R_1 = 0.1490, wR_2 = 0.3929
Ultimate R indexes [all data]	R_1 = 0.2312, wR_2 = 0.4570

3. Results and Discussion

Structural characterisation analysis of synthesised compound was concluded using spectroscopic approaches, for instance, $^{1}H^{13}C$-NMR, FTIR and UV-*vis*. The spectroscopic results meet expectations about the compounds and confirm the structure.

6,6'-((1E,1'E)-((thiobis(4,1-phenylene))bis(azaneylylidene))bis(methaneylylidene))bis(3-(diethylamino) phenol) (**A**): **$C_{34}H_{38}N_4O_2S$**. **Yield**: %81, **Color**: Yellow-Red

3.1. Compound A's FTIR Spectrum

Looking at the FTIR spectrum of the compound "A" is checked; FTIR data (ν, cm^{-1}): 2928- 2967 (C-H) aliphatic, 1615 (C=N), 1190 (C-N), 1484-1514 (C=C), 1256 (C-O), 815,790 (C-H) aromatic. FTIR Spectrum of A structure is given in (Fig.2**)**. The presence of the imine bond stretching at 1615 cm^{-1} as a sharp peak showed that the compound favoured the phenol-imine form in the solid state. This was further investigated by single crystal X-ray diffraction study.

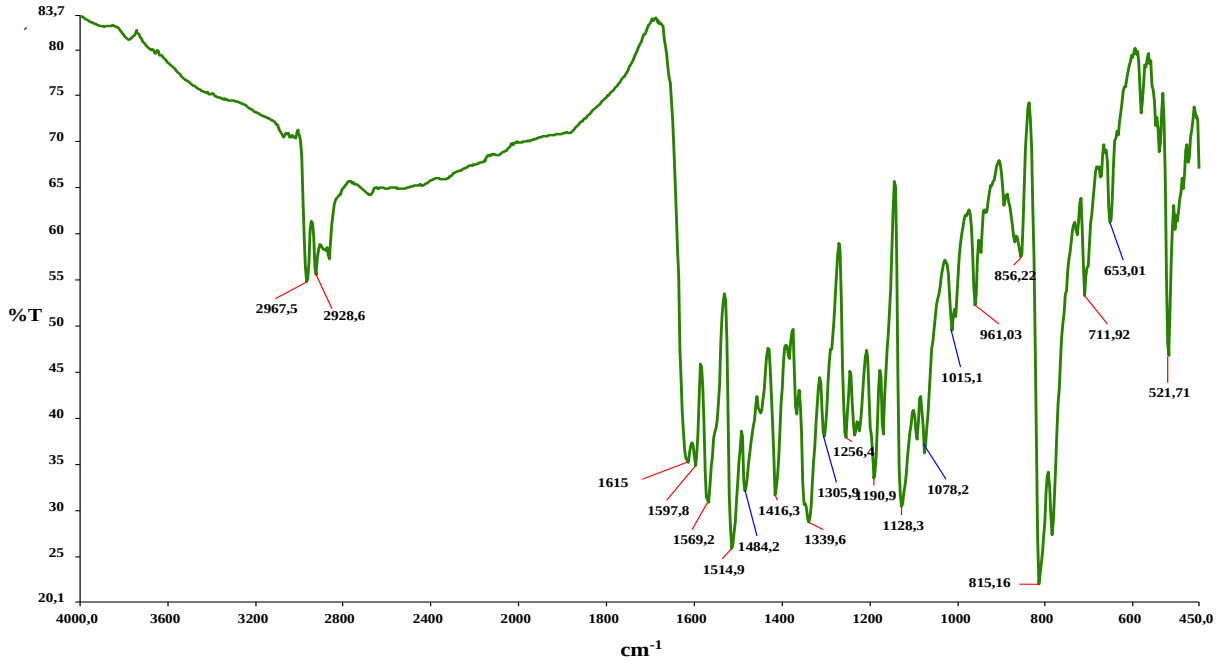

Figure 2 Compound **A**'s FTIR spectrum.

3.2. Compound A's Crystal Structure

The crystal structure of material A was defined using the single-crystal X-ray diffraction method. The material's structure was solved in a monoclinic unit cell with C2/c space group. In its crystalline structure, the two portions of the molecule are connected by a two-fold rotation axis passing through the central sulphur atom, and thus asymmetric unit contains half of the structure. The crystal structure of the material is given in (Fig.3). In the material, the imine bond length (N1-C7) is 1.294 (7) Å showing a characteristic C=N double bond distance. The C9-O1 distance is 1.338(10) Å, which is in the expected C-O single bond distance range. The N1-C7 and C9-O1 bond distances showed that the compound favours phenol-imine tautomeric form in the crystal. The S1-C1 bond showed a

characteristic S-C bond length (1.772(6) Å). In each half of the compound, phenyl and phenol rings are nearly co-planar by a twist angle of 4.85º. The molecular structure shows projected intramolecular phenol-imine hydrogen bonds [O1-H·····N1 with D····A distance of 2.595 Å. In the structure, molecules are connected by C-H·····O and π-π stacking interactions (Fig.4).

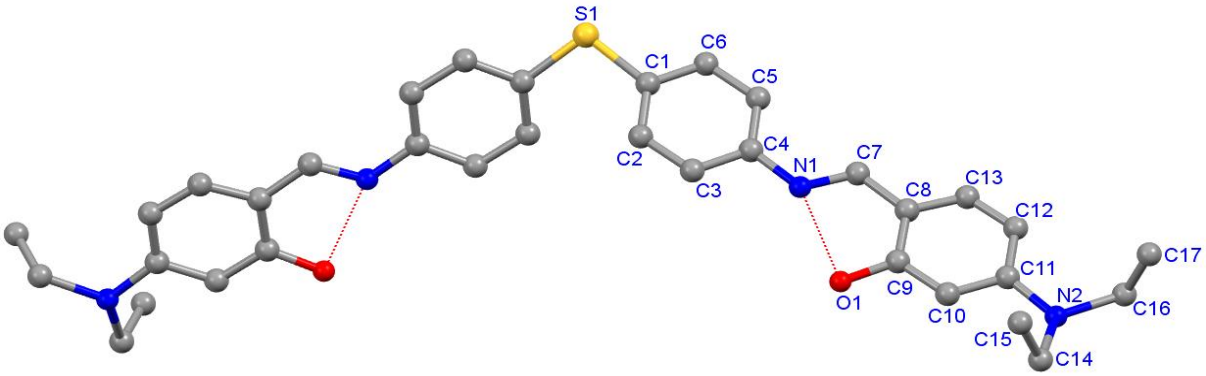

Figure 3. Compound **A**'s Crystal structure. Symmetry-related atoms are not labelled. The phenol-imine hydrogen bond O1-H·····N1 is shown as dashed lines.

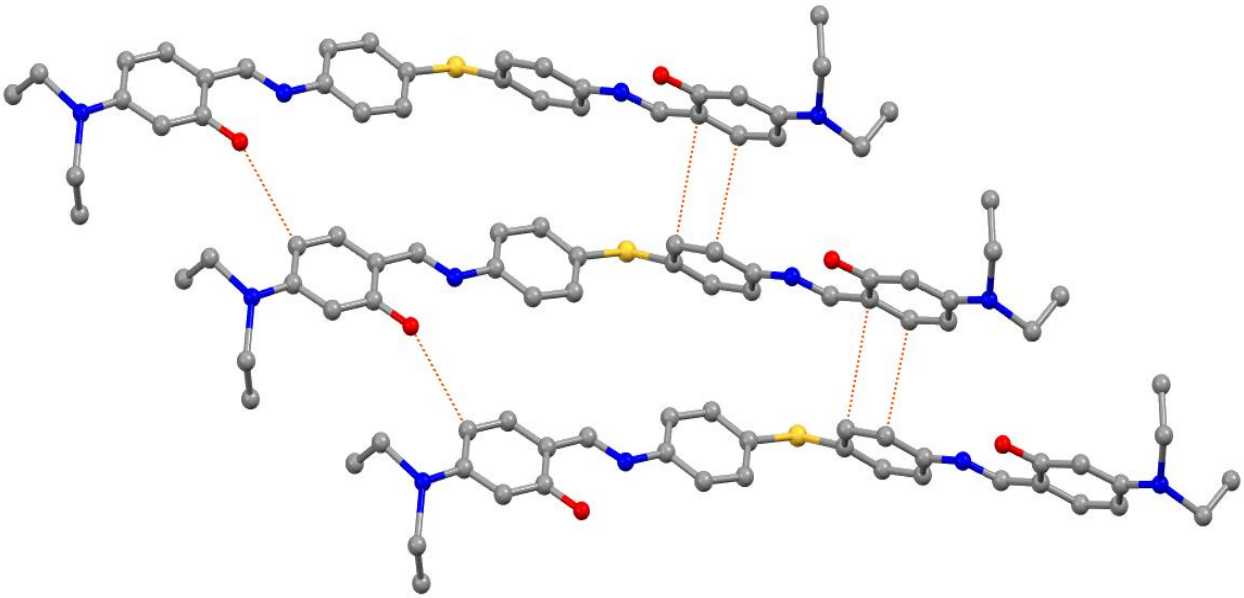

Figure 4. C-H·····O and π-π contacts in compound **A**' structure

3.3. Compound A's UV-*vis* spectra

The electronic spectra of the structurally characterised compound A were investigated in $CHCl_3$, EtOH, Diethylether and DMSO solution (10^{-5} M). The absorption spectra of compound A are given in (Fig.5). Compound A dissolved in DMSO gave a broad absorption band around 385 nm, indicating π-π* transitions of cyclic structures. The diethylether solution of compound a showed a similar absorption band around 390 nm with a wider and partially redshifted tendency, increasing the absorption density compared to the DMSO solvent. The $CHCl_3$ and EtOH solution decreased the absorption density and showed absorption bands showing π-π* transitions at 395 nm and 410 nm, respectively, with a redshift tendency relative to DMSO.

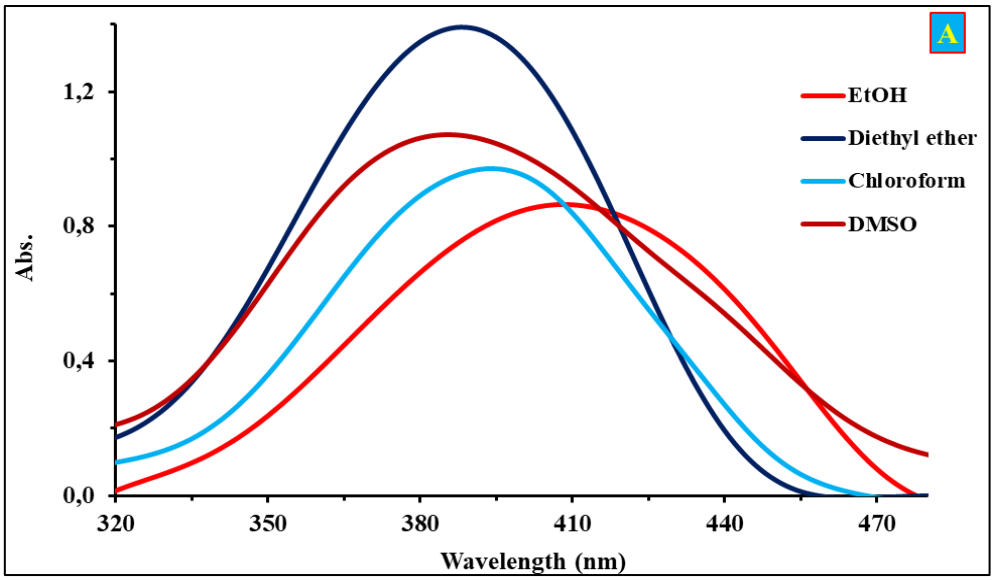

Figure 5. Compound **A**'s UV-*vis* spectrum.

3.4. Compound A's photoluminescence spectra

Within the scope of the study, the excitation and emission values of the Schiff base compound A were measured using DMSO, EtOH, Diethylether and $CHCl_3$ media solutions. The graphs obtained from the solutions prepared at 10^{-5} M values are shown in (Fig.6).

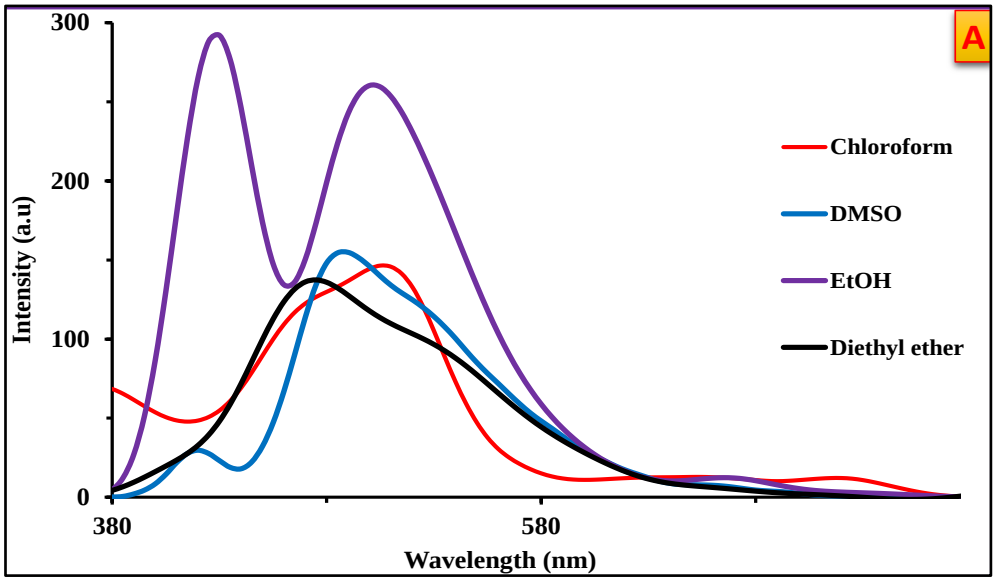

Figure 6. Compound **A**'s photoluminescence spectra.

The stokes shift of the $CHCl_3$ solution of compound A has the largest stokes shift of 115 nm among the solvents determined. It exhibited an emission band at 510 nm with a stokes shift of 115 nm versus 395 nm absorption of the π-π* transition. Diethyl ether and DMSO solutions have a stock shift of 85 and 90 nm, respectively, and exhibit emission bands at 475 nm and 490 nm, respectively. In response to the absorption of EtOH solution at 410 nm, a stokes shift of 15 nm and 85 nm occurred and exhibited two emission bands at 425 nm and 495 nm. Table 2 shows the stokes shifts that occur with the wavelengths of the emission and absorption of compound A in the existence of different solvents.

Table 2. Absorption, emission and stokes shift values of compound **A**.

Compound	λ_{max}, nm			
	Solvents	**Absorption (nm)**	**Emission (nm)**	**Stokes shifts (nm)**
A	EtOH	410	425, 495	15, 85
	$CHCl_3$	395	510	115
	Diethylether	390	475	85
	DMSO	385	490	95

In addition, the Excitation and Emission graphs of the photoluminescence measurements made in MDSO, $CHCl_3$, EtOH and Diethylether environments are given in (Fig.7) to compare the data.

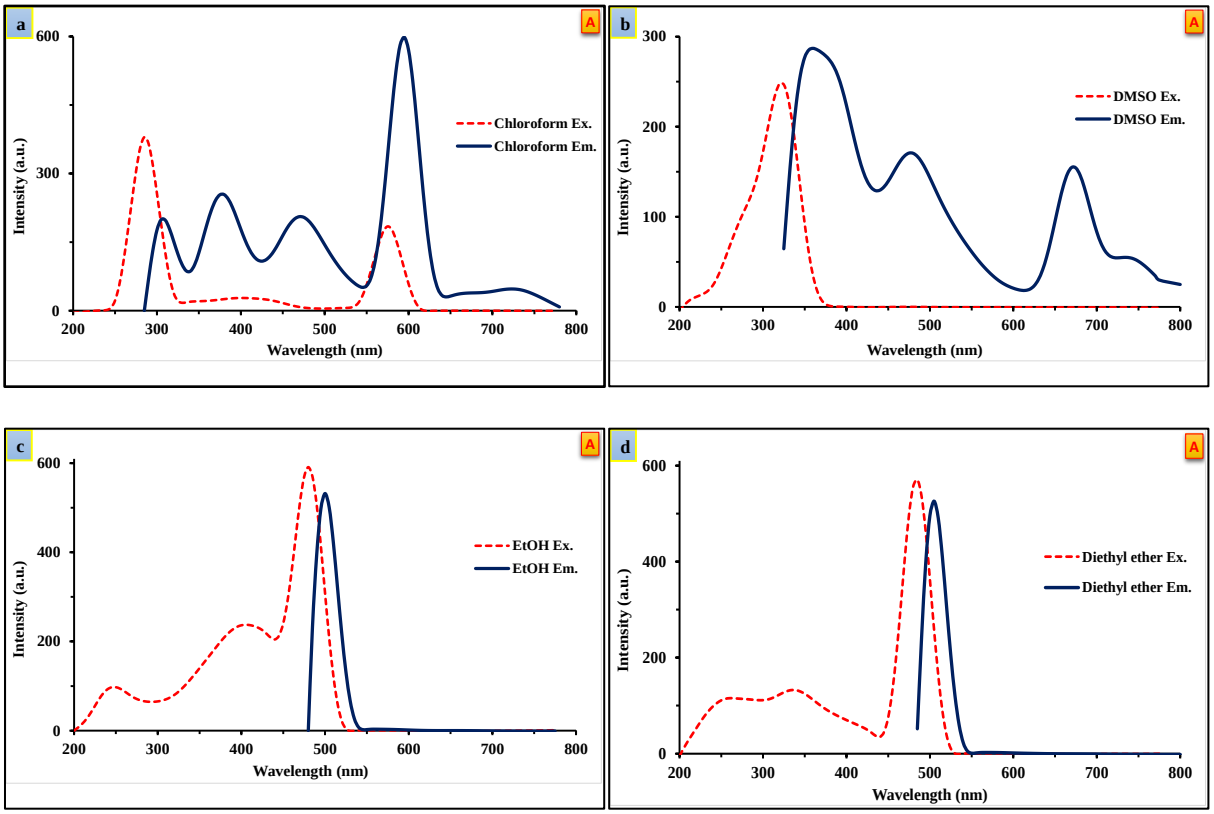

Figure 7. Compound **A**'s **Ex** and **Em** graphs in **a)** $CHCl_3$ **b)** DMSO **c)** EtOH **d)** Diethylether

3.5. Compound A's ^{1}H and ^{13}C NMR Spectra

In the ^{1}H NMR spectrum (^{1}H NMR (400 MHz, $CDCl_3$) δ 13.72, 8.43, 7.39, 7.37, 7.28, 7.22, 7.20, 7.19, 7.16, 6.29, 6.28, 6.26, 6.26, 6.21, 6.21, 3.45, 3.43, 3.42, 3.40, 1.25, 1.23, 1.21.); The signal observed in the δ1.20-1.25 ppm range is the signal of protons belonging to the (-CH_3) group. The signal observed in the range of δ3.40-3.45 ppm is the signal of protons belonging to the (-CH_2-N-) group. The signal observed in the range of δ6.20-7.37 ppm is the signal of protons in the ring structures. The signal of the proton of the azomethine (-HC=N-) group is seen at δ8.43 ppm. Signals of protons belonging to the (-O-H) group attached to the aromatic ring are seen at δ13.72 ppm.

In the ^{13}C-NMR spectrum (^{13}C NMR (101 MHz, $CDCl_3$) δ 164.15, 160.44, 151.95, 147.98, 133.87, 132.63, 132.06, 121.67, 109.10, 103.91, 97.75, 44.63, 12.73); The signal for the "C" atoms of the end

(-CH_3) group is seen at δ12.73 ppm. The signal of "C" atoms belonging to the (N-CH_2-) group is located at δ44.76 ppm. The signal in the range of δ97.75-151.95 ppm is the signal belonging to the "C" atoms in the ring structures. The signal at δ160.44 ppm belongs to the "C" atom of the azomethine (-HC=N-) group. The signal at δ164.15 ppm belongs to the "C" atom of the (-O-C-) group. ^{1}H and ^{13}C NMR data of compound A are given in (Fig.8**)**.

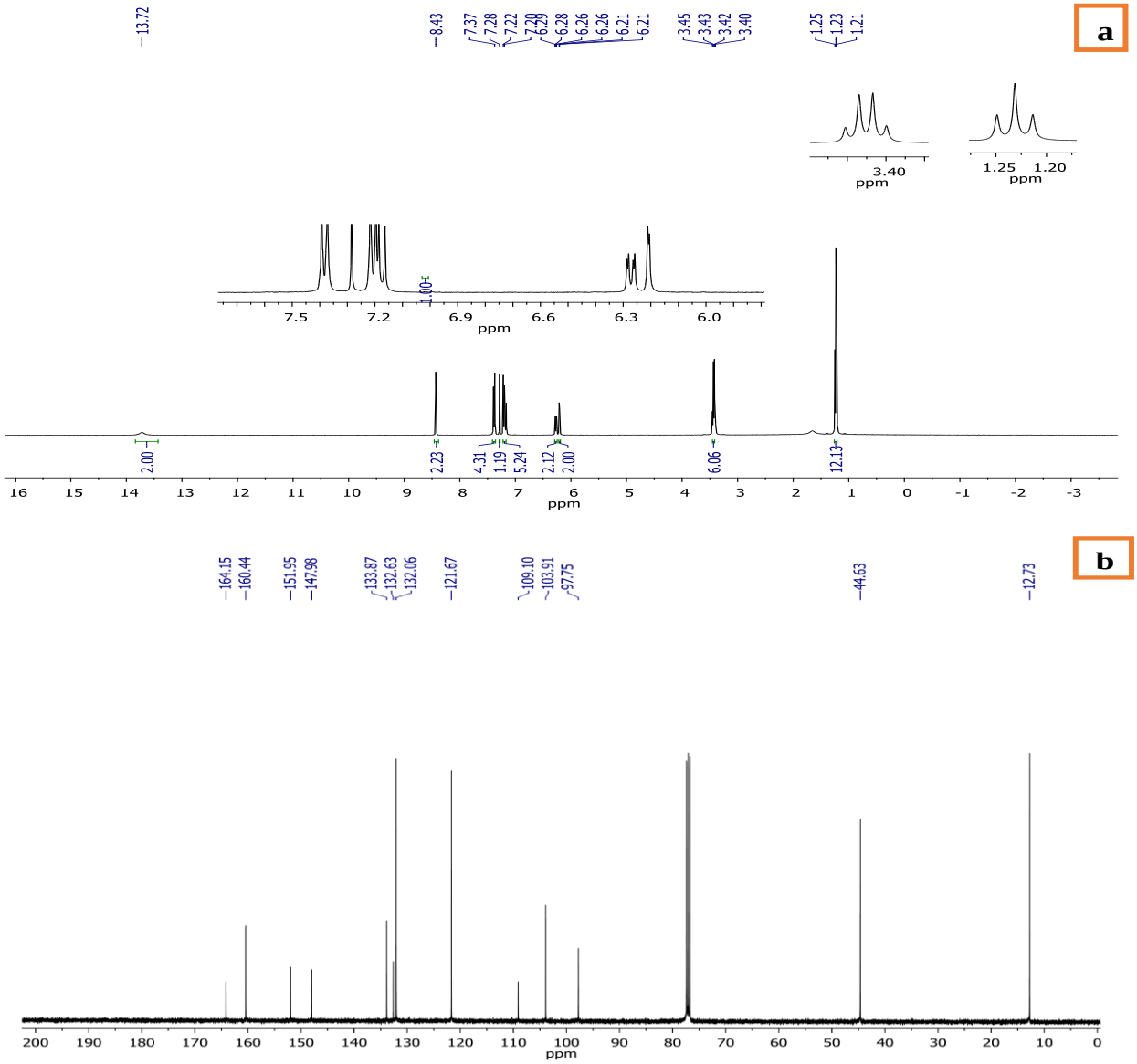

Figure 8. Compound **A**'s **a)** ^{1}H and **b)** ^{13}C NMR spectra

3.6. Interaction of compound A with DNA

3.6.1. DNA interaction studies

To determine the extent of interaction of the newly synthesised Schiff base compound with DNA, double-stranded FSds-DNA (Aldrich) was used without the need for purification. DNA standard solution was prepared in Tris-HCl buffer (20 mM Tris-HCl, 20 mM NaCl, pH 7.0) at room conditions. It was stored in a cold environment (4° C) for not more than seven days. The absorbance ratio at 260 nm and 280 nm wavelengths (A260-A280) was approximately 1.86, indicating that the DNA structure

is free from protein contamination. The ratio of Nucleotide phosphate [NP] in DNA concentration was determined by UV absorbance at 260 nm after dilution of (1/20) using the known ε value of 6600M (Gungor et al. 2020).

UV-*vis* spectrophotometer method is one of the most preferred methods used to investigate the interaction between Schiff base and DNA in terms of quality and quantity and to comment on the type of interaction. The stacking interaction of the aromatic groups of the molecule with DNA results in bathochromism and hypochromism in the UV spectrum. In the UV titration study, the spectra of DNA were recorded for a fixed compound in the presence of the synthesised compound (Tumer et al. 2017). As the DNA solution is added, changes occur in the compound's absorbance band of π- π* transitions. The graphs of hyperchromism, which means an increase in the absorption density, and hypochromism, which means a decrease in the absorption intensity, according to the ratio of the added DNA solution, are generated and shown in (Fig.9). Hyperchromism that occurs with DNA solution added is defined as damage to the double helix structure due to electrostatic binding of the DNA helix structure or partial dissolution (Vijayalakshmi et al. 2000; Anjomshoa et al. 2014; f et al. 2021).

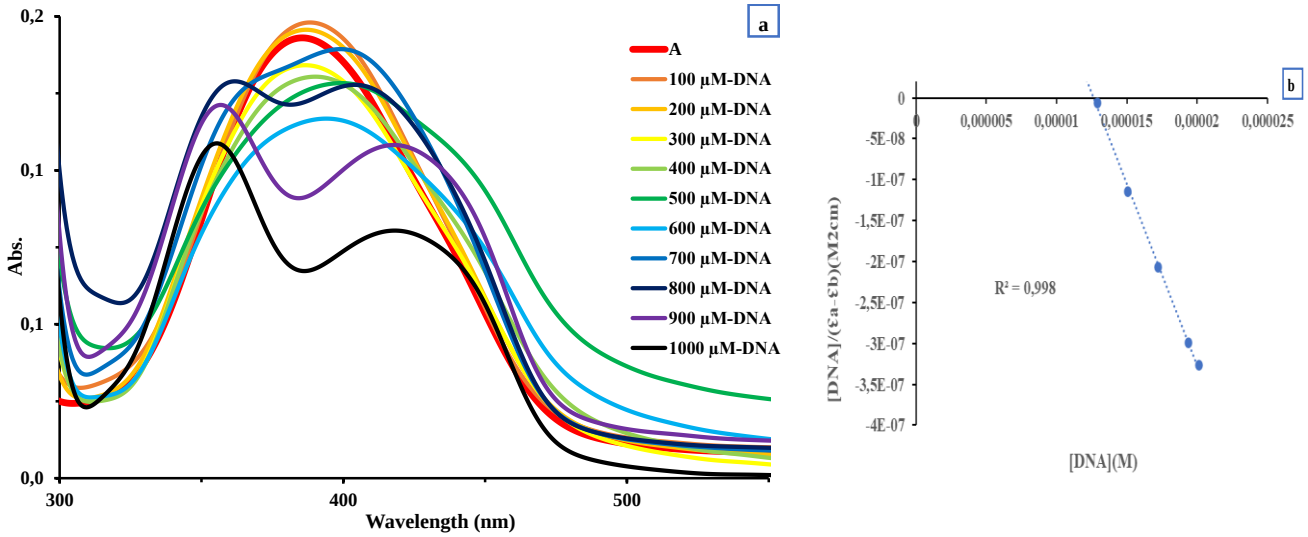

Figure 9 a) UV-*vis* spectrum of the interaction of compound **A** with DNA at certain ratios **b)** The proportional change between [**DNA**] and [**DNA/ εa-εf**] caused by changes in the amounts of FSdsDNA, n = 10.

The interaction of compound A with DNA at certain rates was monitored and recorded. The wide absorbance band of compound A at 385 nm caused an increase in absorbance intensity by showing a partial redshift with the addition of 100 and 200 µM DNA. When DNA amounts in the range of 300-700 µM were added, the absorbance density of compound A decreased at 385 nm and exhibited an absorbance band in the wavelength range of 390-400 nm, showing a redshift tendency. When 800, 900 and 1000 µM DNA amounts were added to Compound A, the absorbance band seen at 385 nm tended to be red and blue shifted with decreasing absorbance density and bifurcation.

The resulting two-peaked new bands were observed at (blueshift) 360,355,355 nm and (redshift) 405, 420, 420 nm, respectively.

The intrinsic binding constant of compound A to FSdsDNA, Kb, was obtained using Equation 1 from data resulting from the shift of absorbance values to different wavelengths with the increase in FSdsDNA concentration (Psomas 2008; Tumer et al. 2017):

[DNA] / (**ε**a-**ε**f) = [DNA] / (**ε**b-**ε**f) + 1/Kb(**ε**a-**ε**f) ……...……(**1**)

εa = A_{obs}/[Complex].

εa = Free complex extinction coefficient.

εb = The extinction coefficient of the fully bound compound

In the graph obtained from [DNA]/(**ε**b-**ε**f) and [DNA] data, **Kb** is demonstrated as the ratio of the slope to the y-intercept (Fig.7b). For compound A, **Kb** (M^{-1})= $6.25x10^5$ was found. The Kb value found showed that the compound exhibited more robust binding connections than ethidium bromide (EB). The fact that the Kb value of the compound is higher than the EB binding affinity for DNA (Kb = $1.23\pm0.07x10^5$) indicates that intercalative interplay may affect EB relocation (Zipper et al. 2004)

4. Conclusion

In this study, compound A containing imine bond (-C=N-) was successfully synthesised following the literature. The material of the synthesised compound was elucidated by FTIR, UV-*vis*, Photoluminescence spectroscopy, $^1H^{13}C$-NMR. According to the FTIR results, the peak belonging to the (-C=N-) group of the compound was observed at 1615 cm-1. In addition, a single-crystal X-ray diffraction study determined the molecular structure of the synthesised compound. The absorbance band of the π- π transitions seen at 285 nm wavelength in the UV-*vis* spectrum of the compound showed a blue and red shift tendency when interacting with the DNA solution. In addition, changes in hypochromism and bathochromism were also observed. Therefore, it is crucial to determine the interaction rate and type of Schiff bases with DNA, which are the basis of anti-cancer drugs. For this reason, UV-*vis* spectroscopy was used to monitor and record the interaction of the new Schiff base we synthesised with DNA in our study. Finally, a new type of Schiff bases, which is considered necessary in many fields such as coordination chemistry, biochemistry, dyes, plastics industry, pharmaceutical chemistry, electronics industry, and pesticides in agriculture, was synthesised within the scope of the study, its structure was clarified, and studies were carried out on its effect on DNA structure.

Conflict of Interest Statement

The article's authors declare that there is no conflict of interest.

Contribution Rate Statement Summary of Researchers

The author declares that each author contributed equally to the article.

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