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"Biological Pertinences of Cardanol-Infused α-Naphthylamine Ligand in Coordination with Four Metal Complexes"

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ABSTRACT:

The pursuit of innovative therapeutic agents, especially Schiff bases, is capturing the keen interest of medicinal chemists around the globe. Cardanol-derived Schiff bases, which are synthesized extensively from cashew nut shell liquid (CNSL) and combined with four different metals, show significant promise in pharmaceutical science. By synthesizing and characterizing cardanol-based Schiff base ligands and their complexes with metals like Cu, Co, Ni, and Zr, a new class of tetradentate ligands is identified. For elucidating a thorough understanding of the complexes' structural and electronic properties as well as the stereochemistry and binding interactions of these experimental complexes, an exhaustive suite of analyses was employed utilizing a range of advanced physicochemical and spectroscopic techniques. These methods included elemental analysis and advanced spectral studies such as 1H NMR, 13C NMR, and high-resolution mass spectrometry (HRMS). Additionally, the antibacterial and antioxidant properties of these complexes were assessed. The findings distinctly indicate that the copper complexes exhibit superior antibacterial and antifungal activities compared to the other tested complexes of Co, Ni, and Zr. This superiority accentuates the prospective viability of copper-based Schiff base complexes as formidable contenders for future antimicrobial therapies.

Keywords: Therapeutic agents, Cardanol Schiff bases, Metal complexes, Tetradentate ligands, Biological pertinences.

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1. Introduction

Bioinorganic chemistry, an interdisciplinary field, examines the roles of metals and non-metals in biological systems. This area has attracted significant global research interest due to its importance in life sciences and its critical contributions to medicine (Jesmin et al., 2010; Yang et al., 2012; Annapoorani and Krishan, 2013). The current study falls within this domain, focusing on Schiff base complexes and ligands to explore their physical, chemical, and medicinal properties.

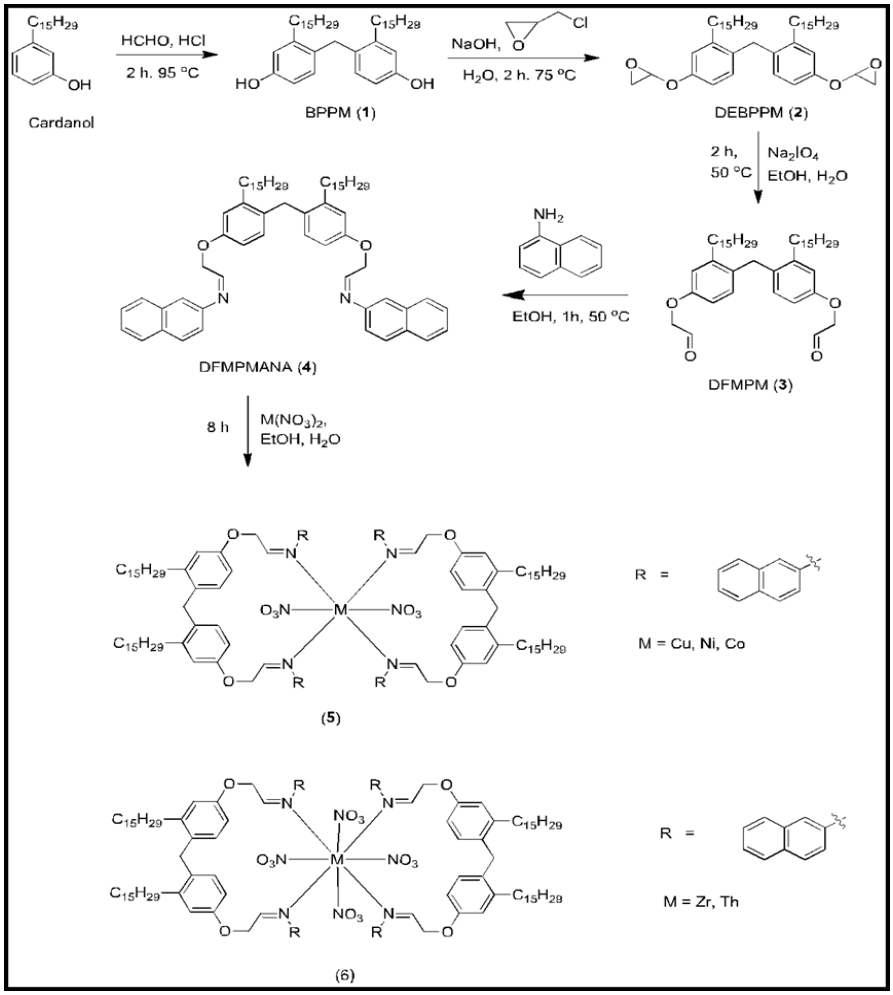
Natural products play a crucial role in the prevention and treatment of diseases, especially in developing countries where traditional medicine is a primary healthcare system (Farnsworth NR, 1993; Houghton P, 1995). Higher plants, in particular, may serve as a new source of antimicrobial agents with unique mechanisms of action (Runyoro D et al., 2006; Shahidi BH, 2004). However, the misuse of these agents has led to the rise of multiple drug-resistant bacteria, presenting significant challenges in infection treatment. Despite the development of numerous new antibiotics, resistance among microorganisms continues to escalate (Towers GH et al., *2001*).The synthesis and design of organic compounds for medicinal purposes are vital aspects of medicinal chemistry. When these compounds are complexes with metals, their therapeutic efficacy often increases (Prajapat P, 2018; Orvig C and Abrams MJ, 1999; Jones MR et al., 2014; Sumrra SH et al., 2020; Zafar W et al., 2021). Medicinal inorganic chemistry is thus an expanding research area with significant potential for discovering the therapeutic applications of Schiff base compounds and their metal complexes (Jones MR et al., 2014; Varol M, 2016). Schiff bases, featuring an azomethine group (–C=N–), are synthesized by the condensation of primary amines with active carbonyl groups (Sadigova S et al., 2008). These compounds exhibit various pharmacological activities, including antibacterial (Login CC, 2019), antifungal (Bharti S et al., 2010), and antioxidant (de Santana TI et al., 2018; Taha M et al., 2013) properties.

Schiff bases, known for their carbon-nitrogen double bond (-HC=N-), are key compounds in pharmacology due to their strong chelating properties, ease of synthesis, and diverse applications (Ghosh et al., 2020; da Silva et al., 2011). They have been extensively studied for their antibacterial, antitubercular, antifungal, antiparasitic, antiviral, antioxidant, anticancer, analgesic, catalytic, and anti-inflammatory properties (Ghosh et al., 2020; da Silva et al., 2011; Noor et al., 2020). The ongoing research interest in these compounds, especially in medicine, underscores their therapeutic potential (Muhammad et al., 2020; Mohkles et al., 2019).

The rising incidence of microbial infections and increasing resistance to existing antibiotics highlight the need for novel antimicrobial agents. Despite the promising antimicrobial properties of Schiff bases, there is limited research on metal complexes derived from Schiff base ligands synthesized from cardanol and α-naphthylamine. This study has initiated an antimicrobial assessment of the various biological activities of synthesized complexes of Co, Ni, Cu, and Zr. Additionally, an in-vitro analysis of the antibacterial and antifungal activities of the synthesized ligands and complexes is conducted. A comparative study of these experimental compounds against commercially available antibacterial and antifungal drugs, such as Amikacine and Nystatin, is also undertaken. The insights gained from this research contribute noteworthy part to the development of new therapeutic agents, advancing our understanding of their potential applications in medicine.

Synthesis of Cardanol-Based α-Naphthylamine Schiff Base Ligand

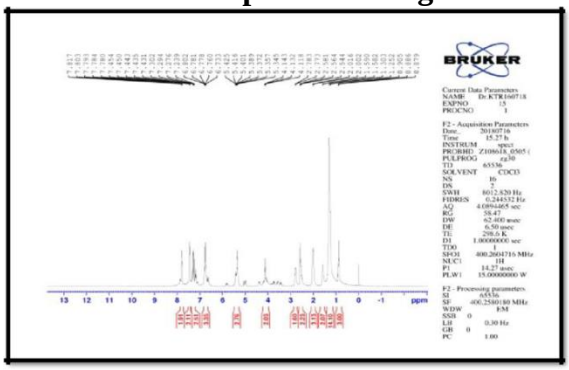
Adhering to the methodology delineated by Isac et al. (2011), the synthesis initiates with the combination of cardanol (497 mmol, 150 g) and formaldehyde (8 mL) in the presence of HCl (20 mL). This reaction mixture is sustained at 95 ºC for 2 hours, resulting in the formation of a red-colored liquid with an 85% yield, identified as bis(3-pentadecenylphenol)methane (BPPM).Subsequently, BPPM (100 mmol, 61.5 g) is reacted with epichlorohydrin (18.6 mL) in the presence of NaOH (200 mmol, 8 g) at 75 ºC for 2 hours. This reaction produces a red-colored liquid with a 90% yield, known as the diglycidyl ether of bis(3-pentadecenylphenol)methane (DEBPPM).The DEBPPM (100 mmol, 72.8 g) is then subjected to oxidation with sodium periodate (185 mmol, 42.8 g) dissolved in water. The reaction is conducted at 50 ºC for 2 hours, yielding a red-colored liquid with an 85% yield, identified as di-α-formylmethoxy bis(3-pentadecenylphenyl)methane (DFMPM). Finally , DFMPM (10 mmol, 7 g) is heated in a beaker for 30 minutes. Sequentially, α-naphthylamine (20 mmol, 2.86 g) is dissolved in 20 mL of ethanol, and the resulting mixture is refluxed at 90 ºC for 1 hour. The reaction mixture is then poured into a beaker containing ice cubes, leading to the precipitation of a black semi-solid. This product, DFMPMANA, is subsequently filtered and dried, achieving a yield of 94% of the desired Schiff base ligand.



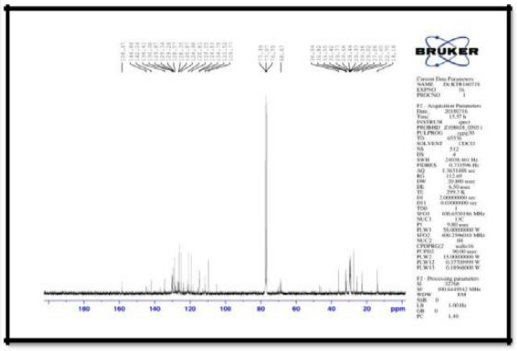
Synthetic route for cardanol based α-Napthylamine ligand and four experimental metal complexes

DFMPMANA was obtained as a black semisolid with a yield of 6.58 g (94%) which has a melting point of 185°C. The infrared spectrum (ATR) showed absorption bands at ν/cm−1: 3375 (H2O), 2852 (C-H, aliphatic), 1581 (imine C=N), 1450 (C-H, methyl), and 1255 (C-O, aromatic ester) (Fig 8.1). High-resolution mass spectrometry (EI) indicated a calculated m/z for [M]+ [C67H86N2O2]+ of 951.4085, and the found value was 951.4082 (Fig 3).

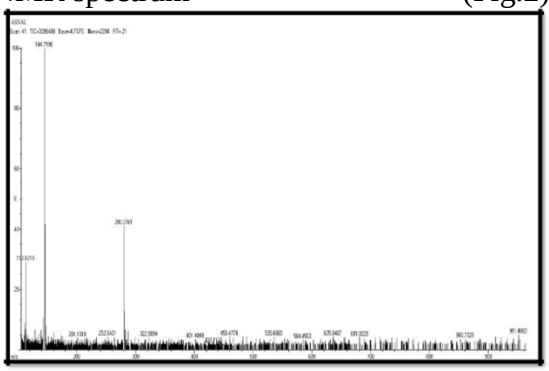
Structural view of experimental ligand DFMPMANA by



(Fig.1). ^{1}HNMR spectrum



(Fig.2). ^{13}C NMR spectrum



(Fig.3). HRMS spectrum

The ^{1}H NMR spectrum (400 MHz, CDCl3) shows the following signals: δ 0.88 - 0.87 (d, 3H, free methyl group), δ 1.58 - 1.25 (m, 14H, Al-CH2),

δ 4.11 (s, bridging), δ 4. 14 - 4.13 (d, 2H, O - CH2), δ 6.80 - 6.73 (m, Ar –aldehyde H),

δ 7.79 - 7.30 (t, 4H, -Ar napthy- H), δ 7.8 (d, 2H, N=CH) (Fig.1).

The **^{13}C** NMR (100 MHz, CDCl3): δ 14.16, 22.70, 25.60, 27.26, 29.02, 29.26, 26.33, 29.44, 29.66, 29.77, 31.42, 31.55, 31.82, 36.04, 68.67, 109.77, 111.52, 114.75, 114.83, 119.05, 120.81, 124.90, 125.87, 126.35, 128.57, 129.28, 129.34, 130.00, 134.41, 142.04, 144.86, 158.47 (Fig. 2).

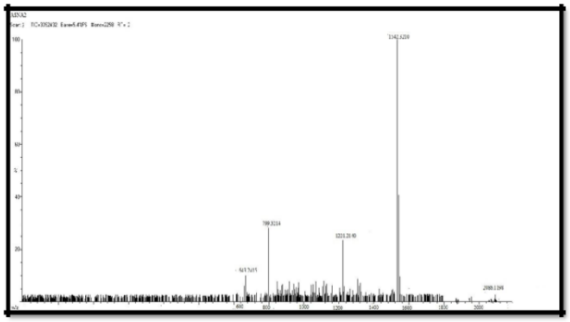
Synthesis of α-Naphthylamine Schiff Base Metal Complexes Slot in Cardanol

On the molar ratio of 1:2, aqueous solutions containing metal nitrate salts of Cu(II) (2.5 mmol, 0.6025 g), Co(II) (2.5 mmol, 0.7275 g), Zr(IV) (2.5 mmol, 0.8475 g), and Ni(II) sulfate (2.5 mmol, 0.61 g) were meticulously introduced into a stirred mixture of Cardanol-based Schiff base ligand (DFMPMANA) (5 mmol, 4.75 g) dissolved in 30 mL of ethanol. The resulting amalgamation underwent reflux for 9 hours at 85°C. Subsequently, the mixture

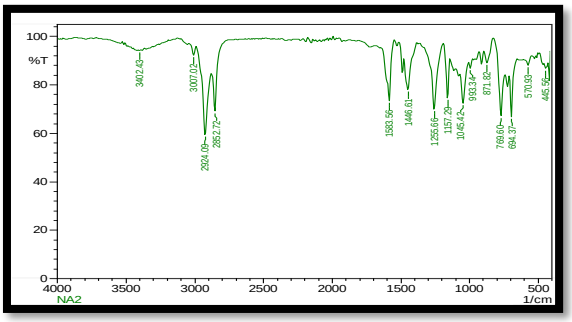
was filtered, and the filtrate was allowed to cool to room temperature. The ensuing precipitate underwent thorough washing with ethanol and diethyl ether to eliminate impurities, culminating in final drying in a desiccator to yield the stable product.

DFMPMANA-Co was isolated as a black solid with a yield of 3.85 g (81%) and has a melting point of 218°C. Analysis by infrared spectroscopy (ATR) revealed characteristic absorption bands at ν/cm−1: 3402 (H2O), 2852 (C-H, aliphatic), 1583 (imine C=N), 1446 (C-H, methyl), 1255 (C-O, aromatic ester), 570 (Co-N), and 445 (Co-O) (Fig. 5). High-resolution mass spectrometry (EI) indicated a calculated m/z for [M]+ [C134H172N6O10Co]+ of 2086.1200, with an observed value matching closely at 2086.1200 (Fig. 4).

Structural view of experimental complex DFMPMANA-Co by



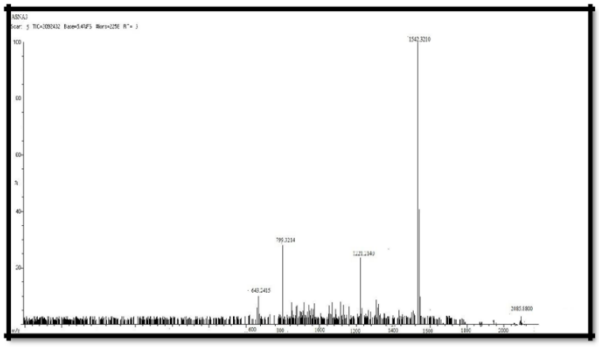
(Fig.4). HRMS spectrum



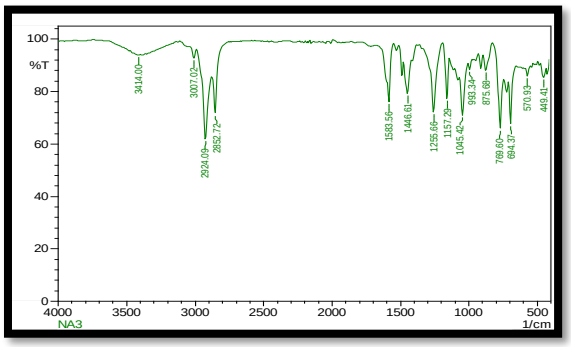
(Fig.5). IR spectrum

DFMPMANA-Ni has been obtained as a black solid. Yield: 3.61 g; 76% with Melting point: 207 °C. IR (ATR) (ν/cm^{-1}): 3414 (H2O), 2852 (C-H) (aliphatic), 1583 (imine C=N), 1446 (C-H) (methyl), 1255 (C-O) (aromatic ester), 570 (Ni-N), 449 (Ni-O) (Fig.7). HRMS (EI): m/z is calculated for [M]$^+$ [C134H172N6O10Ni]$^+$ calculated 2085.8802, found 2085.8800 (Fig 6).

Structural view of experimental complex DFMPMANA-Ni by



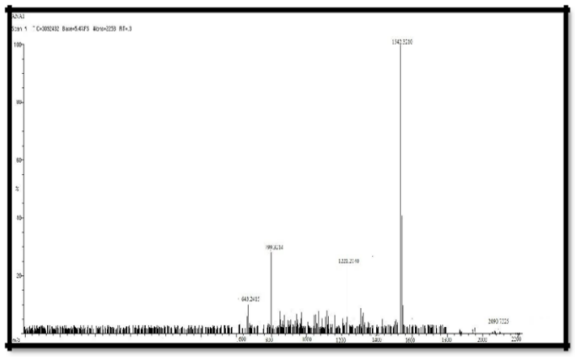
(Fig.6). HRMS spectrum



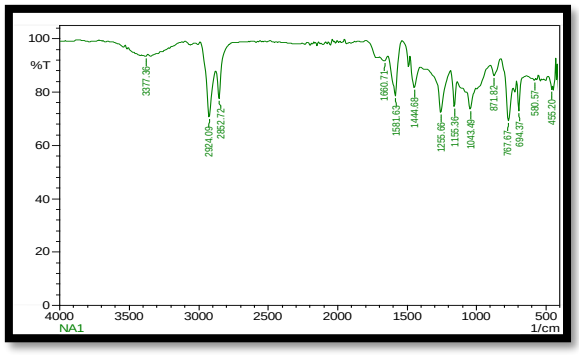
(Fig.7). HRMS spectrum

DFMPMANA-Cu has been obtained as a black solid. Yield: 3.705 g; 78%. Melting point: 193°C. IR (ATR) (ν/cm^{-1}): 3377 (H2O), 2852 (C-H) (aliphatic), 1660 (imine C=N), 1444 (C-H) (methyl), 1255 (C-O-C) (aromatic ester), 580 (Cu-N), 455 (Cu-O) (Fig.9). HRMS (EI): m/z is calculated for [M]$^+$ [C134H172N6O10Cu]$^+$ 2090.7328, found 2090.7325 (Fig. 8).

Structural view of experimental complex DFMPMANA-Cu by



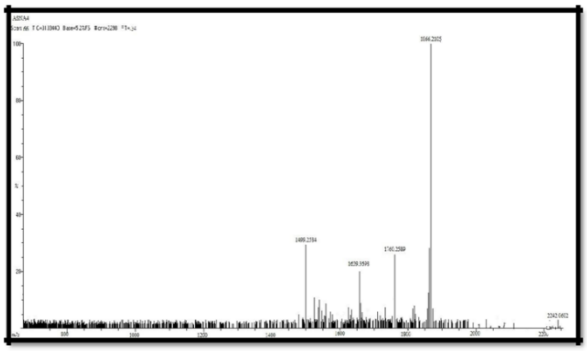
(Fig.8). HRMS spectrum



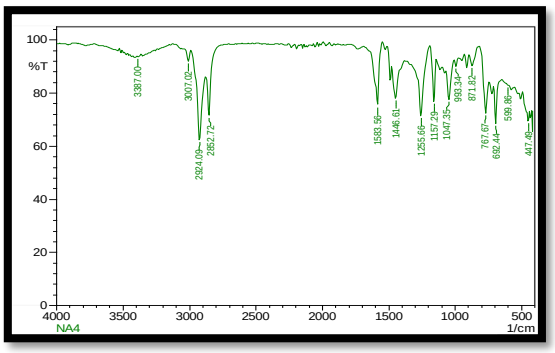
(Fig.9). IR spectrum

DFMPMANA-Zr has been obtained as a black solid. Yield: 3.467 g; 73%. Melting point: 213°C. IR (ATR) (ν/cm^{-1}): 3387 (H2O), 2852 (C-H) (aliphatic), 1583 (imine C=N), 1446 (C-H) (methyl), 1255 (C-O) (aromatic ester), 599 (Zr-N), 447 (Zr-O) (Fig.11). HRMS (EI): m/z is calculated for $[M]^+$ $[C134H172N8O16Zr]^+$ calculated 2242.0606, found 2242.0602 (Fig. 10).

Structural view of experimental complex DFMPMANA-Zr by



(Fig.10). HRMS spectrum



(Fig.11). IR spectrum

2. Results

The current study focuses on the experimental synthesis of ligands and complexes, as outlined in Scheme 8.1. Initially, five unique Schiff base complexes derived from cardanol were synthesized by reacting the DFMPMANA ligand with different metal salts such as Co, Ni, Cu, and Zr with the objective to explore the coordination chemistry and properties of these complexes. Furthermore, comprehensive physical data, including melting points, infrared spectra, and elemental analyses, for all synthesized ligands and complexes are presented and discussed in detail in Table 1.

Table: 1: Physiological characterization data for the experimentally synthesized α-Naphthylamine-based ligand and the four corresponding metal complexes.

Compounds	Yield %	Colour	Mol. Formula	M. Weight	Melting Point
DFMPMANA	85	Black	C67H86N2O2	951.4085	185

(Ligand)					
DFMPMANA - Co	72	Black	C134H172N6O10Co	2086.1200	218
DFMPMANA- Ni	68	Black	C134H172N6O10Ni	2085.8802	207
DFMPMANA - Cu	68	Black	C134H172N6O10Cu	2090.7328	193
DFMPMANA - Zr	75	Black	C134H172N8O16Zr	2242.0606	213

Infrared spectra of the experimentally synthesized DFMPMANA ligand and its four metal complexes

The infrared spectra of the DFMPMANA ligand and its four metal complexes, synthesized experimentally, exhibit distinct characteristics. The strong band observed at 1660 cm-1, attributed to ν (CH=N) in the Schiff base ligand, indicates the conversion of the free NH2 group of semicarbazide into an azomethine group. Additionally, the presence of an IR absorption band in the range of 3414 cm-1 to 3200 cm-1 signifies the presence of water molecules in both the ligand and complexes (Chellaian & Madhavan, 2009). In the complexes, the C=N band appears shifted, suggesting the coordination of the azomethine nitrogen atom with the metal ion, facilitated by electron donation from nitrogen to the metal's empty d-orbitals. Bands at 2852 cm-1 indicate the presence of alkane groups, while those at 1450 cm-1 - 1444 cm-1 confirm the presence of alkyl methyl groups. The aromatic ether group is identified by a band at 1255 cm-1. New bands appearing in the regions of 580 cm-1 - 569 cm-1 and 455 cm-1 - 447 cm-1 indicate M-N and M-O coordination in the complexes (Emin Erdem et al., 2009).

NMR spectral data for the experimentally synthesized DFMPMANA ligand

The NMR spectral data for the experimentally synthesized DFMPMANA ligand reveal further insights. In the ^{1}H NMR spectrum (400 MHz, CDCl3), a doublet at δ = 7.8 ppm corresponds to HC=N, while a triplet in the range of δ = 7.79 - 7.30 ppm is attributed to aromatic naphthyl protons. A multiplet observed at δ = 6.80 - 6.73 ppm corresponds to aromatic aldehyde protons, and a doublet due to ester protons appears around δ = 4.14 - 4.13 ppm. A singlet at δ = 4.11 ppm is attributed to bridging protons, accompanied by a multiplet of aliphatic protons in the range of δ = 1.58 - 1.25 ppm. Additionally, a doublet due to free methyl groups is observed at δ = 0.88 - 0.87 ppm.

In the ^{13}C NMR spectrum (100 MHz, CDCl3), signals are observed at 158.47 ppm for the imine (HC=N) group and at 130 ppm for the (Ar-N=C) group. Additionally, singlets at 68.67 ppm and 36.04 ppm have also been observed corresponding to O-CH2 and bridging CH2 groups, respectively.

(Table. 2) Antibacterial effect of experimentally synthesized α-Napthylamine based ligand and four metal complexes against the clinical pathogens

SAMPLE	***Tested Clinical Pathogens***							
	S. aureus **(mm)**	***B. subtilis*** **(mm)**	***E. faecalis*** **(mm)**	***P. aeruginosa*** **(mm)**	***E. coli*** **(mm)**	***P. mirabilis*** **(mm)**	***B. species*** **(mm)**	***K. pneumoniae*** **(mm)**
Amikacin	15±0.0	15±0.01	12±0.0	15±0.001	12±0.01	14±0.01	17±0.01	17±1.36
DFMPMANA (Ligand)	0	0	0	**8±0.62****	0	0	0	0
Amikacin	27±0.0	16±0.01	13±0.01	20±0.00	27±0.01	16±0.01	21±0.01	19±0.01
DFMPMANA - Co	7±1.03	9±2.22	9±3.75	**12±1.65****	**10±1.05***	**9±0.08****	7±3.50^{IS}	0
DFMPMANA - Ni	0	**9±0.34****	9±1.42	**13±0.53****	**11±1.41****	**9±1.05****	8±1.30	0
DFMPMANA - Cu	**7±0.36****	**9±1.72****	0	**12±0.82****	**11±2.37***	9±2.06	**7±1.68***	0
DFMPMANA - Zr	0	9±3.02^{IS}	**9±0.83****	**7±1.04****	**12±1.33***	**9±0.61***	**0**	0

Is--- stands for Insignificant

*----stands for significant at the level of p<0.05%

**----stands for highly significant at p<0.001% level

The present findings explicitly demonstrate that the ligand and its four experimental complexes exhibit substantial activity against the tested P. aeruginosa strains. Notably, the copper and nickel complexes display notable antibacterial efficacy across all six pathogenic isolates, surpassing the other four DFMPMANA complexes.Specifically, the copper complex emerges as an exceptionally effective bactericidal agent against the experimental pathogenic bacterial organisms (refer to Table 2).

Antifungal efficacy, as illustrated in Table 3, reveals that the ligand and four experimental complexes were tested against four fungal species: A. flavus, A. niger, C. albicans, and R. species. The ligand exhibits minimal inhibition against A. flavus (8 ± 1.06 mm) and C. albicans (9 ± 0.56 mm), while showing no effect on A. niger and R. species. Among the experimental complexes, A. niger exhibits notable susceptibility to all five complexes, with copper, cobalt, and nickel showing significant zones of inhibition (7 ± 0.78 mm, 8 ± 1.02 mm, and 8 ± 0.87 mm, respectively). Zirconium also demonstrates significant inhibition

zones (8 ± 1.10 mm and 7 ± 2.01 mm). The copper complex exhibits significant activity against R. species (20 ± 1.85 mm) and C. albicans (9 ± 0.03 mm), while A. flavus shows no response to any of the synthesized complexes. Except for the copper complex, the other complexes show no effect on Rhizopus species, and similarly, all complexes except copper show no inhibition zone against C. albicans. DFMPMANA-Cu, based on antimicrobial studies, displays significantly higher activity against the tested clinical pathogens compared to the commercialized standard antibiotic drugs Amikacin/Streptomycin and Nystatin.

(Table. 3) Antifungal effect of experimentally synthesized α-Napthylamine based ligand and four metal complexes against the clinical pathogens.

SAMPLE	***Tested fungal organisms***			
	***A. flavus* (mm)**	***A. niger* (mm)**	***Rhizopus species* (mm)**	***C. albicans* (mm)**
NYSTATIN	22±0.03	24±0.01	12±0.001	19±0.045
DFMPMANA (Ligand)	8±1.06	0	0	9±0.56
NYSTATIN	14±2.14	16±1.44	12±1.32	16±1.84
DFMPMANA - Co	0	**8±1.02****	0	0
DFMPMANA - Ni	0	**8±0.87****	0	0
DFMPMANA - Cu	0	**7±0.78****	**20±1.85****	**9±0.03****
DFMPMANA - Zr	0	8±1.10*	0	0

Is--- stands for Insignificant
*---- stands for significant at the level of p<0.05%
**---- stands for highly significant at p<0.001% level

Anti-oxidant activity of experimentally synthesized α- napthylamine ligand and four metal complexes

The antioxidant properties of the ligand and its four experimental complexes are meticulously detailed in Table 4, where their efficacy in the DPPH scavenging assay is thoroughly examined. Among the tested compounds, DFMPMANA-Cu displayed the highest antioxidant activity with a measured value of 55.55 ± 1.69 µg/mg. Following closely, DFMPMANA-Ni exhibited a significant antioxidant capacity of 42.7 ± 1.45 µg/mg. DFMPMANA-Co and DFMPMANA also demonstrated notable antioxidant capabilities, with values of 33.2 ± 0.85 µg/mg and 31.90 ± 4.81 µg/mg, respectively. Conversely, DFMPMANA-Zr exhibited the lowest observed antioxidant efficiency at 16.09 ± 1.07 µg/mg.

DFMPMANA-Cu emerges with the highest observed antioxidant capacity, underscoring its robust ability to scavenge free radicals compared to the other complexes. DFMPMANA-Ni follows closely behind, exhibiting substantial antioxidant activity, while DFMPMANA-Co

and DFMPMANA also demonstrate considerable antioxidant potential, albeit to a lesser extent. DFMPMANA-Zr shows the least observed antioxidant efficiency among the tested compounds.

These results establish a clear ranking of antioxidant performance among the ligand and its complexes, showcasing DFMPMANA-Cu as the most effective antioxidant followed by DFMPMANA-Ni, DFMPMANA-Co, DFMPMANA, and DFMPMANA-Zr. This hierarchical order underscores the varying degrees of antioxidative potential inherent in these compounds, providing valuable insights for potential applications in antioxidant therapies or related biomedical fields.

(Table. 4) Anti-oxidant effect of experimentally synthesized α-Napthylamine based ligand and four metal complexes

Sl. No.	Sample	Concentration of antioxidants in µg/mg of sample
1	**DFMPMANA**	31.90 ± 4.81 Is
2	**DFMPMANA - Co**	**33.2 ± 0.85****
3	**DFMPMANA - Ni**	**42.7 ± 1.45***
4	**DFMPMANA - Cu**	**55.55 ± 1.69***
5	**DFMPMANA - Zr**	**16.09 ± 1.07***

Is-- stands for Insignificant

*----stands for significant at the level of p<0.05%

**---- stands for highly significant at p<0.001%level.

3. Discussion

The quest for anti-pathogenic complexes, essential for safeguarding human health, has ignited a global pursuit into diverse complexes and ligands, aimed at unraveling their biological activities. Notably, research by Kotwal et al. (2010) underscores the heightened bioactivity of metal complexes relative to their corresponding ligands.

Since 1798, the study of coordination complexes has evolved significantly within both inorganic and organic chemistry, particularly in the synthesis of pharmaceutically significant compounds (Chellaian and Madhavan, 2008). This exploration has focused on constructing complex structures that define the unique characteristics and functionalities of these compounds (Saranya et al., 2004). Coordination chemistry involves the strategic pairing of a central atom with surrounding ligands—ions, atoms, or neutral molecules—that act as donors of electron pairs (Silverman, 1992). Ligands, which can be neutral molecules or mono-/polyatomic anions possessing unshared electron pairs, can form chelates—complexes characterized by cyclic structures. Many naturally occurring substances, including amino acids, peptides, proteins, and hormones, serve as ligands due to the presence of donor atoms such as nitrogen, oxygen, sulfur, and phosphorus (Shukla et al., 2013).

In both laboratory (in vitro) and biological (in vivo) settings, drug molecules frequently function as ligands, competing for essential metal ions vital to enzymatic processes (Shilpa et

al., 2015). The efficacy of pharmaceutical treatments is heavily influenced by the molecular conformation of these drug-ligand complexes and their ability to bind to specific receptors.
Metal complexes hold diverse biomedical applications, including their use in replenishing deficient metal ions within biological systems, countering metal poisoning through the use of ligands as antidotes, and modulating pharmacotherapeutic effects by selectively targeting essential metal ions involved in enzymatic pathways (Ramachandrula et al., 2016). Beyond their biological roles, metal ions also play crucial roles in pharmaceutical analysis and quality control through their detectable complexes, which can be identified using various advanced physicochemical techniques such as spectroscopy, chromatography, and microscopy. This multifaceted approach underscores the pivotal role of coordination chemistry in both understanding biological processes and advancing therapeutic interventions.

4. Conclusion

This comprehensive study delves into the synthesis, characterization, and biological evaluation of twenty novel metal complexes, shedding light on their antimicrobial, antioxidant, and anticancer activities. Medicinal chemists worldwide are engaged in a relentless pursuit to develop novel therapeutic agents capable of combating life-threatening pathogens. This study commences a comprehensive literature survey to ascertain the significance of Schiff base metal complexes in pharmaceutical applications, focusing specifically on five metal salts: Co, Ni, Cu, and Zr. These metal salts were meticulously tested in conjunction with naturally derived cardanol, a meta-substituted phenol sourced from Anacardium occidentale (L) nut shells. The synthesis process involved treating cardanol-derived aldehydes with four distinct amines—2-Aminophenol, 2-Nitroaniline, semicarbazide hydrochloride, and α-Napthylamine—to produce Schiff base ligands, which were subsequently complexed with the aforementioned metal salts.
A total of twenty metal complexes were synthesized and subjected to rigorous characterization through techniques such as FTIR, NMR, and HRMS. The study aimed to evaluate the antibacterial efficacy against a spectrum of pathogens including E. coli, B. subtilis, E. faecalis, P. mirabilis, S. aureus, P. aeruginosa, B. species, and K. pneumonia, as well as antifungal activity against A. flavus, A. niger, C. albicans, and Rhizopus species. Additionally, antioxidant and anticancer activities were assessed using DPPH and MTT assays respectively.
Significant findings emerged from the research, highlighting notable antimicrobial properties, particularly the potent antifungal activity exhibited by napthylamine-based copper complexes. Furthermore, all napthylamine-based complexes demonstrated substantial antibacterial efficacy. These results underscore the potential of Schiff base metal complexes as promising therapeutic agents against a wide range of pathogens.
Comparative studies were conducted between the synthesized complexes and commercially available medicines to validate their medicinal efficacy. The research revealed promising outcomes, suggesting that the synthesized compounds possess competitive efficacy against bacterial, fungal, and cancer cells, potentially at a lower cost compared to existing treatments. This opens new avenues for the widespread application of metal complexes in medicine, paving the way for future developments in anti-pathogenic therapies.
To be brief, this study marks a significant advancement in medicinal chemistry, showcasing the multifaceted potential of Schiff base metal complexes as versatile agents in combating infectious diseases and cancer. The findings not only contribute to the growing body of knowledge on metal-based pharmaceuticals but also advocate for further exploration and development of these compounds for broader therapeutic applications. As researchers continue to refine and expand upon these findings, the prospect of integrating metal

complexes into mainstream medical treatments becomes increasingly promising, offering new hope in the global fight against pathogenic threats.

5. Refferences

1. Annapoorani, S & Krishnan, C 2013, 'Synthesis and spectroscopic studies of trinuclear N4 Schiff base complexes', International J.Chem.Tech. Res., vol.5, no.1, pp.180-185.
2. Bharti S, Nath G, Tilak R, Singh S. Synthesis, anti-bacterial and anti-fungal activities of some novel Schiff bases containing 2, 4-disubstituted thiazole ring. Eur J Med Chem. 2010;45(2):651–60.
3. Chellaian, JD & Madhavan, SN 2009, 'Synthesis and characterization of metal (II) complexes of poly(3-nitrobenzylidene-1-naphthylamine-co-succinic anhydride)', European Polymer Journal, 4.(45), pp. 565-572.
4. Chellaian, JD & Madhavan, SN 2009, 'Synthesis, characterization, and antimicrobial studies of some Schiffbase metal (II) complexes', Journal of Coordination Chemistry, 62 (24): pp. 4018-4028.
5. de Santana TI, de Oliveira BM, de Moraes Gomes PAT, da Cruz ACN, da Silva TG, Leite ACL. Synthesis, anticancer activity and mechanism of action of new thiazole derivatives. Eur J Med Chem. 2018;144:874–86.
6. Emin, E, Eylem, Y, Sari, RK & Nilgun, K 2009, 'Synthesis and characterization of azo-linked Schiff bases and their nickel(II), copper(II), and zinc(II) complexes', Transition Met. Chem., vol. 34, pp. 167-174.
7. Farnsworth NR. Ethno pharmacology and future drug development: The North American experience. *J Ethnopharmacol.* 1993;38:145–52.
8. Ghosh P., Shishir K. D., Mousumath H.A., Kaykobad K., and Nazmul-Islam A. B. M (2020), A review on Synthesis and versatile applications of some selected Schiff bases with their transition metal complexes, Egyptian Journal of Chemistry, 63(2), 523-547
9. Houghton PJ. The role of plants in traditional medicine and current therapy. *J Alter Complement Med.* 1995;1:131–43.
10. Isac Sobana Raj C, Christudhas M and Allen G R G, J Chem Pharm Res., 2011, 3(6), 127.
11. Jesmin, M, Ali, MM & Khanam, JA 2010, 'Antitumour activities of some Schiff bases derived from benzoin, salicylaldehyde, amino phenol and 2,4 dinitrophenyl hydrazine', Thai J. Pharm. Sci., vol. 34, pp. 20-31.
12. Jones MR, Duncan D, Storr T. Introduction to Ligand Design in Medicinal Inorganic Chemistry: John Wiley & Sons Ltd.: Chichester, West Sussex, PO19 8SQ, United Kingdom. 2014
13. Kotwal, DP, Dhoot, BM, Pawar, RP & Jadhav, WN 2010, 'Studies on synthesis of some schiff bases, metal complexes and their antimicrobial activity', Inorganic Chemistry An Indian Journal, 5(1):, pp. 1-3.
14. Login CC, Bâldea I, Tiperciuc B, Benedec D, Vodnar DC, Decea N, Suciu Ş. A novel Thiazolyl Schiff base: antibacterial and antifungal effects and in vitro oxidative stress modulation on human endothelial cells. Oxid Med Cell Longev. 2019;2019:1–11.
15. Mokhles M. A., Ammar A. L., Hanan A. M., Samia A. M., Mamdouh M. A. and Ahmed, A. E (2019): Synthesis, anticancer activity and molecular docking study of Schiff base complexes containing thiazole moiety. Beni - Suef University Journal of Basic and Applied Sciences. 5 (1) Pp. 85 - 96.
16. Muhammad N. U., Sayeda S. A. and Rahatul-alam S. M. (2020), Review: Biomedical applications of schiff base metal complexes, Journal of Coordination Chemistry, 73(23), 3109-3149

17. Noor U., Faisal R., Saqib A. T., Iqbal A., Sumera Z., Muhammad Z., Paula l. D., Muhammad N T., Jamshed I. and Ali H. (2020), Synthesis, characterization and anticancer activity of Schiff bases, Journal of Biomlecular Structure and Dynamics, 38(11), 3246-3259
18. Orvig C, Abrams MJ. Medicinal inorganic chemistry: introduction. Chem Rev. 1999;99(9):2201–4.
19. Prajapat P. Role of organic, medicinal & pharmaceutical chemistry in drug design: introduction. J Nanomed Res. 2018;7(2):69–70.
20. Ramachandrula, KK, Ramanayam, SK, Sharma, Ravi Kumar, D, Shrikanth, H,Havale1, Basaveswararao, B & Murali Mohan Rao, SV 2016, 'Characterization, synthesis and biological evaluation of naphthalene based piperazines as antibacterial agents', Der Pharma Chemica., 8, (18), pp. 374-379.
21. Runyoro D, Matee M, Olipa N, Joseph C, Mbwambo H. Screening of Tanzanian medicinal plants for anti-Candida activity. *BMC Complement Altern Med.* 2006;6:11. [PMC free article]
22. Sadigova S, Magerramov A, Allakhverdiev M. Synthesis of Schiff bases and oxazolidines from 2-amino-4-phenylthiazole. Russ J Org Chem. 2008;44(12):1821–3.
23. Saranya, M, Subashini, A, Arunagiri, C & Thomas, MP 2004, 'Synthesis, Spectral, Thermal and Antimicrobial Investigation of Some New Co(II), Ni(II) and Cu(II) Schiff Base Complexes', International Journal of Innovative Research in Science & Engineering, 2 pp. 2347-3207.
24. Shahidi BH. Evaluation of antimicrobial properties of Iranian medicinal plants against Micrococcus luteus, Serratia marcescens, Klebsiella pneumonia and Bordetella bronchoseptica. *Asian J Plant Sci.* 2004;3:82–6.
25. Shilpa, P, Idhol & Khadsan, RE 2015, 'Spectral and biological study of some schiff base complexes of Lanthanides', International Journal of Advanced Research in Engineering and Applied Sciences, 4 (3): pp. 122-128.
26. Shukla, S, Srivastava, RS, Shrivastava, SK, Sodhi, A, & Pankaj Kumar 2013, 'Synthesis, characterization, in vitro anticancer activity, and docking of Schiff bases of 4-amino1,2-naphthoquinone', Medicinal Chemistry Research, 22, pp. 1604-1617.
27. Silverman, RB 1992, 'Organic Chemistry of Drug Design and Drug Action', Academic Press, San Diego.
28. Sumrra SH, Habiba U, Zafar W, Imran M, Chohan ZH. A review on the efficacy and medicinal applications of metal-based triazole derivatives. J Coord Chem. 2020;73(20–22):2838–77.
29. Taha M, Ismail NH, Jamil W, Yousuf S, Jaafar FM, Ali MI, Kashif SM, Hussain E. Synthesis, evaluation of antioxidant activity and crystal structure of 2, 4-dimethylbenzoylhydrazones. Molecules. 2013;18(9):10912–29.
30. Towers GH, Lopez A, Hudson JB. Antiviral and antimicrobial activities of medicinal plants. *J Ethnopharmacol.* 2001;77:189–96. [PubMed] [Google Scholar]
31. Varol M. The importance of metal-based drugs in medicinal inorganic chemistry to improve life quality of patients. J Appl Pharm. 2016;8(1):1–2.
32. Yang, X, Wang, Q, Huang, Y, Fu, P, Zhang, J & Zeng, R 2012, 'Synthesis, DNA interaction and antimicrobial activities of copper (II) complexes with Schiff base ligands derived from kaempferol and polyamines', Inorg. Chem. Com., vol. 16, no. 25, pp.55-59.4018-4028.
33. Zafar W, Sumrra SH, Chohan ZH. A review: pharmacological aspects of metal based 1,2,4-triazole derived Schiff bases. Eur J Med Chem. 2021;222:113602.