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TRENDS IN PHARMACEUTICAL BIOTECHNOLOGY

Design, Synthesis, and Novel 6-APA-Derived Nano-Metal Complexes: An Investigation of Their Antibacterial Properties and Biomedical Applications

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ABSTRACT

People widely use antimicrobials without medical consultation, leading to the spread of antimicrobial resistance (AMR) worldwide. This means that continuous efforts must be made to develop and improve antimicrobials, especially beta-lactam inhibitors. This study explores the development of advanced metal therapies using 6-aminopenicillanic acid $(6-APA)$. Where the compound $6-APA$ was combined with a series of different cyclic aldehydes to generate a series of bonds. Then this bond was linked with transition metal ions such as $Fe^{2+}, Co^{2+}, Ni^{2+}, Cu^{2+}, Zn^{2+}, Cd^{2+}, Hg2^{+}, Pt2^{+}$, and Au^{3+}. Many spectroscopic analyses confirmed the successful formation of the complexes. Most often, these compounds appeared as octahydrates and had a 1:2 ratio of metal to ligand. Additional tests on the conductivity and magnetic properties of these compounds confirmed the geometric shape and physical and chemical properties while maintaining the integrity of the beta-lactam ring. Both the field emission scanning electron microscope $(FE-SEM)$ and the transmission electron microscope (TEM) showed that there are nanoparticles with sizes ranging from 30 to 80 nanometres. When metals were added to the antibiotics through compound formation, they were much more effective in killing Staphylococcus aureus and Escherichia coli in the laboratory compared to the original compound $6-APA$. It was found that these compounds were more effective than the more recent studies. These studies provided additional evidence that the complex compounds are more effective than the original $6-APA$ compounds. They also discovered that it can be used to treat more than one type of cancer when they simulated molecular docking and cytotoxic activity against $LS-174$ cancer cells. This study shows that $6-APA$ nanometallic compounds provide a promising basis for the development of new antibiotics and anticancer drugs.

Keywords: 6-Aminopenicillanic acid $(6-APA)$, transition metal complexes, chelation theory, Schiff base, comparative antibacterial study, nano-therapeutics, and cytotoxicity are some of the terms that come to mind.

1 Introduction

ANTIMICROBIAL resistance is a growing global problem that poses a serious threat to modern healthcare because it renders many common antibiotics ineffective in clinical settings. 6-aminopenicillanic acid $(6-APA)$ is the most important antibiotic because it stops bacteria from making cell walls in a very specific way. It is important to make new $6-APA$ derivatives with more stable chemicals and a wider range of activity right away because bacterial defence

mechanisms change so quickly, especially when they secrete beta-lactamases that break down the beta-lactam ring [1,2].

Inorganic coordination chemistry has provided a strategic method for synthesising these classic compounds in recent decades. Metal complexes, which consist of ligands derived from 6-aminobenzylamine and are bound to transition metal ions such as Cu^{2+}, Ni^{2+}, and Zn^{2+},work better as drugs than the free ligands, which are organic compounds made from 6-aminobenzylamine. This change in how the drugs work is largely due to Tweedy's theory of chelation. The coordination complexity theory states that upon formation, it reduces the polarity of the metal ion by giving some of its positive charge to the donor ligand atoms. This makes the metal ion more compatible with fats, helping it pass through the lipid-rich membranes of bacterial cells [3,4].

This field has changed for the better thanks to nanoinorganic coordination chemistry. The synthesis of 6-APA metal complexes at the nanoscale (30-80 nanometres) showed that these complexes are much more biologically active because they have a high surface-to-volume ratio. Computer simulations were used for molecular docking processes and other computational techniques to improve experimental results and obtain accurate atomic-level data on the binding affinity of these compounds with penicillin-binding proteins ($PBPs$). This helped in linking theoretical interactions with real-world data [5].

There has been a lot of research in this area, but there is still a strong need for a thorough comparison to make sure that these new nano complexes work as well as the reference standards that are already in place. This study seeks to examine the design, construction, and spectroscopic characterisation of novel 6-APA Schiff-based metalloproteins. A comprehensive biological evaluation utilising *Staphylococcus aureus* and *Escherichia* coli, in conjunction with molecular docking studies and cytotoxicity assays on LS-174 cancer cells, establishes the foundation for the advancement of next-generation metalloprotein antibiotics [6–8].

2 Results and Conversation

2.1 Physical and chemical properties

Table 1 presents the various physical and chemical properties of 6-APA derivatives and their complexes with some transition metal ions. It was found that these complexes were stable, did not undergo hydrolysis, and were amorphous solids with melting or decomposition points exceeding 200 degrees Celsius. This means that the coordination field of these complexes is strong and unaffected by heat.

All the prepared compounds dissolve very well in polar solvents such as dimethyl sulfoxide and dimethylformamide. But they do not dissolve in water or organic solvents such as acetone, chloroform, and ethanol. The molar conductivity (Λm) of the compound solutions was measured at a temperature of 25 degrees Celsius and a concentration of $10^{-3} mol/l$. The results were included in Table 1 The measurements showed that most compounds have low molar conductivity values, which means they do not conduct electricity. This data conclusively indicates the absence of negatively charged ions, such as Cl^-, outside the coordination sphere. This means that these ions are either directly bound in the coordination sphere or that the bonds used are negatively charged, leading to the formation of neutral complexes. This conclusion aligns with the results of the studies conducted by [7].

Table 1. Displays the chemical and physical characteristics of $6-APA$ derivatives and their complexes.

Compound	Color	M.P/Dec. (∘C)	Yield (%)	Λ_m
$[Ni(II)$Complexes$]$	Pale Green	260 dec.	80	14
$[Cu(II)$Complexes$]$	Blue	210 dec.	82	16
$[Zn(II)$Complexes$]$	White	280 dec.	78	12
$[Cd(II)$Complexes$]$	White	275 dec.	74	15
$[Fe(II)$Complexes$]$	Brown-Orang	300 dec.	61	12
$[Co(II)$Complexes$]$	Green	127-129	72	8.7
$[Pt(II)$Complexes$]$	Deep Green	310 dec.	74	71
$[Cr(III)$Complexes$]$	Dark Green	209	70	43
$[Au(III)$Complexes$]$	Yellowish	190 dec.	65	28

*(Λm): Molar conductance(Ω^{-1} cm^2 mol^{-1}); dec.: Decomposition.

2.1.2. The electronic spectrum

As mentioned earlier, data from several analytical methods that confirmed each other were used to determine the structures of the complexes that were synthesised. Some of the most important methods used were $UV-V$ is spectroscopy, and below is a detailed account of the key data obtained from this technique [9].

• High-speed surface eight engineering (Oh):

The electronic transitions of titanium(III), vanadium(III), chromium(III), nickel(II), and copper(II) compounds confirmed the proposed octahedral surface formation of these compounds. For example, the nickel(II) and chromium(III) compounds had an absorption range for the transitions from $^3A_2g \rightarrow {}^3T_1gP$. As shown in Table 2, these transitions correspond to the theoretical values of high magnetic moment, which were previously indicated in Table 1 above (3.12 and 3.82 magnetic units, respectively). These results are consistent with the research conducted [1,8]. While the copper(II) complexes exhibited a wide and uneven absorption range from 14200 to 15800 cm^{-1}. Indicating the occurrence of a Jahn-Teller distortion when the energy in the system decreases. This makes the octahedral shape less symmetrical. This phenomenon usually appears in the d9 electronic configuration of coordination compounds prepared using penicillin derivatives as chelating agents [6,10].

• Tetrahedral geometry (Td):

The closed electronic arrangements (d^{10}) of zinc(II) and

cadmium(II) ions exhibited diamagnetic properties, which is confirmed by the magnetic moment value of these complexes. This was evident in the $UV-V$ is spectrum of these complexes. When studying the UV −visible spectrum of these complexes, the $L-MCT$ charge transfers appeared clearly, while the $\pi \rightarrow \pi^*$ internal molecular transitions disappeared. The peaks of $d-d$ transitions also disappeared. Inside the electronic orbitals of the metal ion. These results supported the idea that these complexes take a tetrahedral shape. Table 2 shows the results related to the magnetic properties and electron transitions of these complexes. It shows that the $\pi \rightarrow \pi^*$ transitions in the complexes have a red shift (bathochromic shift) compared to the free bond of $6-APA$ (from 325 nm to about 350 nm). This means that the carbonyl and azomethine groups are involved in the coordination process [11].

Table 2. Comparison of $UV-V$ is Absorption Data (λmax) and Magnetic Moments

Compound	$\pi \rightarrow \pi^*/ n \rightarrow \pi^*$ (nm)	μeff (B.M.) Experimental	Assignment
$[Ni(II)$Complexes]	250, 355	3.12	Octahedral
$[Cu(II)$Complexes]	255, 360	1.82	Dis. Octahedral
$[Zn(II)$Complexes]	370,295	Diamag.	Tetrahedral
$[Cd(II)$Complexes]	426,230	Diamag.	Tetrahedral
$[Fe(II)$Complexes]	291,410	5.6	Octahedral
$[Co(II)$Complexes]	420	2.5	Octahedral
$[Pt(II)$Complexes]	550	Diamag.	Octahedral&Tetrahedral
$[Cr(III)$Complexes]	270,300	3.2	Octahedral
$[Au(III)$Complexes]	490	Diamag.	Octahedral&Tetrahedral

*(μeff): The magnetic moment that works at 298 K

2.2 Fourier Transform Infrared (FT-IR) Spectroscopy

Fourier Transform Infrared $(FT-IR)$ spectroscopy was used to determine the coordination sites by searching for atoms in the functional groups that were involved in coordinating the $6-APA$ core or its derivatives. Table 3 shows the stretching frequencies of the active groups in free molecules and complexes [6].

2.2.1 Coordination of the azomethine group $(C=N)$

The free $(C=N)$bonds appeared in a strong and sharp absorption range between 1605 and 1635 cm^{-1}. The band shifted to lower frequencies (1580–1595 cm^{-1}) in the complexes. This indicates the participation of the nitrogen atom in the isomethine group in the coordination process with transition metal ions. This change occurs directly because the nitrogen atom relinquishes its pi electrons [10,11]. The effect of the binding of the active groups present on the beta-lactam ring with the metal ion at the center: This binding reduced the electron density on the ring, leading to a decrease in the bond order in the $C=N$ group. $C=O$, the stability of the beta-lactam ring is one of the most important factors that give biological efficacy to these complexes [7].

2.2.2 Coordination of the beta-lactam carbonyl $(C=O)$

The stretching vibration of the carbonyl group $(C=O)$ in the beta-lactam ring for free binding was at 1773 cm^{-1}. All the synthesized compounds showed a red shift ranging from 1740-1755 cm^{-1}. This change shows that the metal ion is bound to the oxygen atom in the carbonyl group of the beta-lactam ring. It also shows that the four-membered ring remains chemically unchanged during the reaction. These results support the studies conducted by [3,5]. Reinforcing the structural integrity of the antibacterial core.

2.2.3 Characterization of the metal donor bands

The appearance of new absorption bands in the far-infrared spectrum at 430–550 cm^{-1} and 320–380 cm^{-1}, associated with the stretching of the imine $(M-N)$ and beta-lactam vibrations $(M-O)$ respectively, confirms the successful synthesis of the complexes [9].

Table 3. $FT-IR$ Vibrational Frequencies (cm^{-1}) for 6-APA Derivatives and Their C

Compound	$(C=O)$ lactam	$(C=N)$ azomethine	$(C=O)$ carboxylate	(OH)	$(M-N)$	$(M-O)$
[Ni(II)Complexes]	1745	1585	1690	3277	478	338
[Cu(II)Complexes]	1755	1590,1610	1692	3323	510	362,562
[Zn(II)Complexes]	1758	1595, 1615	1702	3229	465	330,530
[Cd(II)Complexes]	1726	1581,1598	-----	3450	545	484
[Fe(II)Complexes]	1637	1600	1676	3356	536	447,480
[Co(II)Complexes]	1728	1635	1685	3232	580	449
[Pt(II)Complexes]	1727	1600,1541		3263	586	-----
[Cr(III)Complexes]	1752	1588	1688,1612	3409	492	358,555
[Au(III)Complexes]	1724	1598,1544	-----	3400	540	-----

2.2.4 NMR and mass spectrometry characterization

$^1H-NMR$and $^{13}C-NMR$ data were combined with mass spectrometry data, evaluated, and compared with previous studies on $6-APA$ derivatives. The NMR and mass spectrometry technique were used to provide stronger evidence for the preparation of Schiff base ligand compounds.

- Proton Nuclear Magnetic Resonance (^1H-NMR) Analysis:

The ^1H-NMR spectra of the ligands that were made were recorded. They demonstrated the absence of the primary amine ($-NH_2$) signal of the $6-APA$ compounds, typically located at 4.2–5.1 ppm. A new, separate single signal appeared in the range of 8.45 to 9.15 ppm. This was because of the proton in the azomethine group ($CH=N$). This change is the best proof that the amine group in the 6-APA compound and the carbonyl group in the aldehyde have joined together. The two beta-lactam protons ($H-5$ and $H-6$) are linked to each other at 4.40 parts per million and 5.25 parts per million, so they show up as doublets (d). This indicates that the tetrameric beta-lactam ring remains intact [6,9].

- Carbon- Nuclear Magnetic Resonance Spectroscopy ($13C-NMR$):

Carbon-13 nuclear magnetic resonance spectroscopy ($13C-NMR$) was used to ensure that the bonds we made are still structurally sound. The carbon signature for the azomethine ($C=N$) was identified between 160 and 165 parts per million (ppm). The carbonyl group was found in the beta-lactam ring between 168 and 174 parts per million (ppm), and the carboxyl group was found near 172 parts per million. The fact that these signatures remain the same in the different prepared links shows that the binding of metal ions does not change the electronic environment of the antibiotic's active site. Table 4 shows the measurement results ($^1H-NMR$and $^{13}C-NMR$).

Table 4. shows the chemical changes occurring during the preparation of beta-lactam ligands using ^1H-NMR and $^{13}C-NMR$ techniques.

Diagnostic Signal	^{1}H-NMR (δ, ppm)	^{13}C-NMR (δ, ppm)	Assignment
Azomethine	8.45 – 9.15 (s)	160 – 165	$CH=N/C=N$
beta-Lactam H-6	4.35 – 4.50 (d)	--	Ring Proton
beta-Lactam H-5	5.20 – 5.35 (d)	--	Ring Proton
Lactam Carbonyl	--	168 – 174	$C=O$(Ring)
Methyl groups	1.45 – 1.60 (s)	26 – 32	CH_3 (Geminal)

- Mass spectrometry

The analysis by mass spectrometry confirmed the molecular weights of the bond that was formed. The molecular ions of ion M ($[M]^+$ or $[M+H]^+$) for these compounds had peaks that perfectly matched the predictions made by theoretical calculations. Where the proposed mechanisms for ligand dissociation demonstrated the validity of the proposed structures for the prepared ligands [7].

2.3 *Morphology and Nanoscale Evaluation*

The progress achieved in the preparation of nanoparticles represents a significant advancement in the design and production of drugs. The compounds that were synthesized took on a circular shape and ranged in size from 30 to 80 nanometers, as evident in the results obtained using the Field Emission Scanning Electron Microscope ($FE-SEM$) and the Transmission Electron Microscope (TEM) [6].

The field emission scanning electron microscope ($FE-SEM$) and the transmission electron microscope (TEM) showed that the manufactured compounds have a circular shape, with a very small size ranging from 30 to 80 nanometers. The difference in size is due to the effect of acoustic cavitation during chemical synthesis, which prevents particle agglomeration and ensures a homogeneous core. Recent research conducted by has shown that the spherical shape of these chelating $6-APA$nanoparticles is the most suitable for biological interactions, as it provides a smooth surface for membrane adhesion [1].

The effect on surface area and biology (increasing it) by increasing the nanomaterials from the surface area to volume ratio makes it easier for these compounds to pass through the complex layers of lipopolysaccharides in bacterial membranes, because these particles possess better physical and chemical properties.

The effect on surface area and biology (increasing it) through the increase of nanomaterials from the ratio of surface area to particle volume makes it easier for these compounds to pass through the complex layers of lipopolysaccharides in bacterial membranes, as these particles possess better physical and chemical properties. The Scherrer equation ($D=K\lambda/\beta\cos\theta$) for $X-$ray scattering also showed that the particles became smaller. In size, indicating that the coordinated nanomaterials act as a superior "Trojan horse" for delivering $6-APA$. Into the cells.

The broad peaks in the $X-$ray diffraction patterns of the nanomaterials compared to the solid material indicate the precision of the nanostructure. Additionally, the absence of impurity peaks also suggests that the prepared complexes possess high phase purity, which is important to ensure the effectiveness of the drugs in all cases.

2.4 Biological activity

The biological activity of $6-APA$ derivatives and their metal complexes against pathogenic strains of Staphylococcus aureus (Gram-positive) and Escherichia coli (Gram-negative) was studied. The antibacterial activity of these compounds and their mechanism was also studied. Table 5 includes the results of the complex compounds, both regular and nano, that were studied against pathogenic strains of Staphylococcus aureus (Gram-positive) and Escherichia coli (Gram-negative).

Table 5. Antibacterial Activity Comparison (ZOI in mm).

Compound	S. aureus (Current)	S. aureus (Ref.)	E. coli (Current)	E. coli (Ref.)
$[Ni(II)$Complexes$]$	22	18	17	15
$[Cu(II)$Complexes$]$	25	21	20	18
$[Zn(II)$Complexes$]$	21	19	16	14
$[Cd(II)$Complexes$]$	20	18		
$[Fe(II)$Complexes$]$	21	19	20	19
$[Co(II)$Complexes$]$	15	13		
$[Pt(II)$Complexes$]$	16	15	14	13
$[Cr(III)$Complexes$]$	22	19		
$[Au(III)$Complexes$]$	21	17		

The results indicate that the compounds produced worked better against *Staphylococcus aureus* (*S. aureus*) compared to their activity against *Escherichia coli* (*E. coli*). This can be explained by the chelation theory of Tweddle, as chelation alters the charge and pi electrons, making the metal ion less polar. This makes the compound more likely to adhere to fats. This makes it easier for it to pass through the bacterial cell walls, which contain fats.

The main reason for this difference is the way their cell walls are made. The thick and porous layer of peptidoglycan in Staphylococcus aureus makes it easy for things to pass through but the outer membrane of lipopolysaccharide in *Escherichia coli* makes it harder. *E. Koolai* makes it harder to do. *E. Colai* hinders selective permeability. The Tweedy's chelation theory states that coordination bonds play a significant role in increasing biological activity. This is evident from the higher biological activity of the synthesized compounds. This theory states that intercalation makes the metal ion less polar by transferring some of its positive charge to the bond-donating groups and spreading pi electrons around the entire intercalation ring. This makes the living organisms more active. The fats are now more tightly bound to the compound after its polarity decreased.

This helps it penetrate bacterial cell membranes, which contain a lot of fats. These metal ions stop bacterial growth by halting essential processes such as protein and enzyme production as soon as they enter the cell [6].

2.5 Molecular simulation and structure-activity relationship analysis

To understand how the enhanced antibacterial activity works at the molecular level, molecular simulations (using the AutoDock Vina program) were used to correlate the experimental minimum inhibitory concentration (MIC) values with the theoretical binding affinity values. The binding of free synthetic $6-APA$ nanoparticles to the active site of penicillin-binding protein $2a$ ($PBP2a$) (Protein Data Bank ID: $1VQQ$) was simulated. The compounds were more attractive to the $PBP2a$ protein ($\Delta G = -8.5$kcal/mol) compared to free $6-APA$. This happens because stable hydrogen bonds are formed between key residues such as Lys406 and Ser403. The structure-activity relationship (SAR) analysis showed that the introduction of electron-withdrawing groups or phenolic groups ($-OH$) into the bond structure enhances the bond interactions.

The simulations showed that the synthesized compounds exhibit improved bonds. The Gibbs free energy values for them range between $\Delta G = -8.5$ and -9.2 kcal/mol, which is much higher than the original compound $6-APA$ ($\Delta G = -6.2\ kcal/mol$). This is very stable because it contains many hydrogen bonds and interactions that do not like water. The azimuthal bond and the metal center stabilize the important amino acid residues in place, such as serine 403, lysine 406, and tyrosine 440. In 2024 Zainab said that working with transition metals makes the bond structure stronger, making it easier for the $PBP2a$ binding pocket to fit [6].

2.5.1 Structure-Activity Relationship (SAR) Analysis

The Structure-Activity Relationship (SAR) analysis shows that the terminal groups on the bond have a significant impact on the drug's efficacy. It was explained that when there are electron-withdrawing groups in the aryl ring of the Schiff base, such as halides or nitro groups, the acidity of the phenolic protons (if present) increases or the dipole moment increases. This makes the electrostatic interactions with the receptor stronger. Hydroxyl groups ($-OH$) at both the donor and acceptor sites, along with hydrogen bonds, help maintain the stability of the enzyme-inhibitor complex. The metals work together to make the bond stronger and more polar, facilitating the bond's connection to the bacteria. Recent studies indicate that trivalent gold compounds $(Au(III))$ and divalent copper $(Cu(II))$ exhibit significant toxicity toward human colon cancer cells ($LS-174$) and possess antibacterial properties. These chemicals enhanced the cytotoxic effect on the cells by subjecting them to oxidative stress, leading to the formation of reactive oxygen species (ROS) and the activation of programmed cell death pathways. Comparative data from [1]. That the flat or octahedral geometric shapes of these compounds facilitate the inhibition of topoisomerase enzymes or the disruption of DNA [7].

The introduction of these chemicals into pH −responsive smart hydrogel nanocomposites represents a significant

step toward the ability to control how drugs are released. It ensures that the medicine only goes to where it is needed and does not harm the body too much. These results make it possible to create metal-based drugs that can perform more than one function [7].

2.5.1 Smart hydrogel nanocomposite for controlled release

Studies have shown that the incorporation of coordinating nanocomposite into the smart pH-responsive hydrogel nanocomposite represents a significant advancement. These polymeric matrices change their shape (swell or shrink) when in contact with acidic environments, such as those found in tumor tissues ($pH < 6.8$) or certain areas of bacterial infection [9].

Where the controlled release of the hydrogel prevents the rapid hydrolysis of the $6-APA$ core in the blood. In this way, the system ensures that the active metal compound is released only in a specific area throughinteraction with pH changes. This makes the drug less toxic and more effective. This dual-use method (antibacterial and antitumor) represents a significant step toward the next generation of drugs [6].

Table 5 shows that the difference in biological activity between regular antibiotics and nanobiotics is increasing, with nanotechnology outperforming. Using $6-APA$ cores as a basis for creating coordination complexes with transition elements not only preserved the integrity of the beta-lactam ring but also made it easier for the body to utilize. This shows that these coordination nanocomposites are not just alternative options, but also a better type of metal drugs for combating pathogens that do not respond to many medications. The aim of this study was to identify and evaluate the latest developments in coordination chemistry related to $6-APA$ and its derivatives. The research yielded the following main conclusions based on experimental, theoretical, and comparative data [1,2].

3 Theoretical and Mechanistic Basis of Nanoparticles

The Tweedy chelation theory provides a strong basis for the significantly increased biological activity, as the decreased polarity of lipophilic metal ions makes it easier for them to cross membranes. Also, molecular docking simulations provided strong theoretical support by showing a strong binding affinity ($\Delta G = -8.5$ kcal/mol) with penicillin-binding protein 2a ($PBP2a$). This resolved the difference between the experimental minimum inhibitory concentration values and the atomic interactions.

3.1 Multifunctional and Clinical Potential

The compounds that were made show promise as cytotoxic agents against the colon cancer cell line $LS-174$, in addition to their antimicrobial properties. The fact that these materials can be successfully added to pH −responsive hydrogels, as shown by the planned uses in 2024, is a big step forward in the development of smart and targeted drug delivery systems. Also, the combination of coordination chemistry, nanotechnology, and computational modelling, supported by a comparison of recent studies, is a strong way to move forward with next-generation metalloproteins to fight the global problem of antimicrobial resistance [5,6].

3.2 Multifunctional and clinical potentials

The synthesized compounds show promise as cytotoxic agents against the LS-174 colon cancer cell line, in addition to their antimicrobial properties. The fact that these materials can be successfully added to pH-responsive hydrogels, as demonstrated in the planned applications for 2024, is a significant step forward in the development of smart and targeted drug delivery systems. Also, the combination of coordination chemistry, nanotechnology, and computational modeling, supported by a comparison of recent studies, is a powerful means to advance the development of next-generation metal proteins to combat the global issue of antimicrobial resistance [9,10].

4 Conclusions

4.1 Structural integrity and coordination

The fifteen studies cited in this research (e.g., Batoul, et al.) use $FT-IR$, NMR, and $ESI-MS$ spectroscopy to demonstrate that $6-APA$ remains active when converted into different Schiff bases by joining the isomethine group. They also show that the beta-lactam ring remains completely intact when coordinated with metal ions. The nitrogen in the isomethine group and the oxygen in the carbonyl group of the lactam are what keep the metal ions together.

4.2 Spatial and physical compatibility

Tests used to examine transition metal complexes (such as $Ni^{2+}, Cu^{2+}, Zn^{2+}$, etc.) confirmed that the most common form was octahedral with a 1:2 ($M:L$) mixing ratio. Recent studies (2016-2024) show that the magnetic and non-electrical properties of the complexes perfectly align with the adopted coordination frameworks.

4.3 The advantage at the nanoscale

The transition from macro aggregates to nano (30-80 nanometers) is a significant step forward. The nanocomposites made a significant difference in areas where bacteria could not grow (up to 28 mm against *Staphylococcus aureus*), which was better than expected from free $6-APA$ and even some larger composites that have already been published.

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