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Antimicrobial activity of Mixed Ligand Transition Metal Complexes: A Review

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ABSTRACT

Heteroleptic, or mixed-ligand complexes are coordination compounds in which a central metal ion is bound to two or more chemically distinct ligands, and this diversity of coordination creates a synergistic environment that enhances the properties of the complexes. By combining ligands of different electronic and structural natures, these complexes exhibit improved electronic characteristics, greater catalytic efficiency and heightened biological activity compared to simpler homoleptic systems. Their versatility makes them valuable across disciplines such as in medicinal chemistry, they display a wide spectrum of antimicrobial effects, including antibacterial, antitubercular, antimalarial, and antifungal activity. This ability to fine-tune the behavior of a metal center through ligand diversity positions heteroleptic complexes as powerful tools for both fundamental research and practical applications in medicine, industry, and environmental science.

KEYWORDS Digital Entrepreneurship, Digital Learning, Higher Education..

1. INTRODUCTION

Unlike traditional coordination complexes, mixed ligand complexes feature at least two different types of ligands bound to a single central metal ion. The presence of multiple ligand types heightens the chance that the complex will exhibit properties deviating from theoretical predictions. This variability piques researchers' interest in designing such complexes, as their structural diversity plays a vital role in biological systems1.The mixed chelation in these complexes yields distinctive structures that facilitate the diffusion and retention of active species across cell membranes2. The synthesis and characterization of these compounds remain areas of growing importance. Studies have convincingly shown that certain complexes demonstrate potent biological activity against various pathogenic bacteria3,4.

Mixed ligand complexes serve as models for metalloenzymes, while also activating enzymes and aiding in the transport and storage of bioactive molecules5. The metal ions coordinated by these ligands are essential in key biological processes6.7. As a prominent subset of organometallic compounds, they are widely evaluated for their biological properties8. Their potential in medicine has captured significant research attention due to the array of therapeutic possibilities9,10. This review examines the antimicrobial activity and inhibitory effects of mixed-ligand complexes.

Biological phenomena of Mixed ligand complexes

Antimicrobial activity

Mixed ligand complexes exhibit enhanced antimicrobial properties, particularly in antibacterial and antitubercular activities. This improvement arises from synergistic ligand effects that boost potency against pathogens.

Antibacterial activity

The complex with mixed ligands of 4-(Benzeneazo)salicylaldehyde and 2-amino-4-nitrophenol (See 1.1, Fig 1) demonstrated antibacterial action in opposition to the range of bacterial pathogens. .With an inhibitory zone ranging in diameter from 18 to 24 mm, the Cu(II) complex demonstrated impactful wide ranging action in opposition to Bacillus subtilis, Pseudomonas aeroginosa, Staphylococcus aureus and Escherichia coli. The bacterial lawn plate

utilized for the comparison analysis showed the zone diameter represented percentage inhibition when positive control tetracycline was employed. There was no distinctive inhibitory effect against most of negative control of the pathogen tested11. The antibacterial resistance feature of gram positive/gram negative bacterial species were conducted out for palladium metal(II) ofloxacin drug and amino acid protein ligands (See 1.2,1.3,1.4, Fig 1) The palladium complexes illustrated significantly increased level against Klebsiella and Escherichia coli12. The enhanced antimicrobial activity of palladium complexes against the bacterial strain is imputable to the concept of chelation. The subsequent sharing of positive charges throughout the ligands and the metals, along with the potential of π-electron delocalization through the formation of a more lipophilic metal complex that makes the system for accurate penenetration of the lipid coating for the microorganisms13.

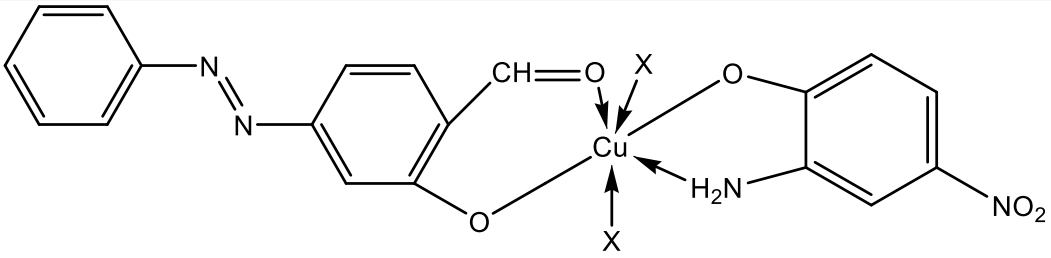
Oxovanadium(IV) complex of 8-hydroxy quinoline and 3-acetyl-6-methyl-2H-pyran-2,4,(3H)-dione (See 1.5, Fig 1) was screened for the antibacterial effectiveness against E.coli(MTCC16799) and S.pyogenes (MTCC1925) at a concentration of 300-µg cm^3 in DMSO by the agar well diffusion method. The complex is less active against E.coli but shows considerable activity against S. pyogenes in comparison with the drug[14].

Complexes of Ni(II) with triphenyl phosphine (pph_3), imidazole, 4-picoline and bipyridine containing 4-(p-phenyl)thiosemicarbazones of salicylaldehyde have been assessed in comparison to E.coli and the complex containing imidazole (See 1.6, Fig 1) was observed to be most intensive[15]. The anti bacterial activities of Zn(II) complexes of 2-acetylpyridine-4-phenylsemicarbazone and N and S containing hetero ligands such as thiophene, pyridine, picoline, aniline and ammonia were evaluated against S. aureus, and B. anthracis. The most active complexes were thiophene and aniline[16].

The mixed ligands of 2,6-pyrimidinedicarboxaldehydebis(o-hydroxyphenylimine), 2,6-pyridinedicarboxaldehydebis(p-hydroxyphenylimine) and 2-aminopyridine with Ni(II) and Zn(II) metal ions showed moderate activity towards Pseudomonas aeroginosa similar to that of Ampicillin antibiotic[17]. The more electron donating group (OMe) of the [$RuCl(CO)(C_{17}H_{16}ON)(py)(pph_3)$] complex showed higher inhibition action against E.coli and Salmonella typhi of 1% and 2% DMSO solution in potato dextrose agar medium. Elevation in the accumulation of the compounds increases the inhibition activity[18]. This is consistent with Tweedy's theory of chelation, which states that partial sharing of the positive charge and potential π-electro delocalization throughout the entire ring are the main justifications of the decrease in chelation with the mutual opposition of the metal atom. This enhances the lipophilic depiction of the metal chelates, which enables them to more easily infiltrate the lipid folds of the bacterial membranes[19]. The copper complex with mixed bipyridine and phenanthroline (See 1.7, Fig 1) showed increasing activity as attributed to the free metal ion. The complexes with mixed ligands represented greater antibacterial activity contrasted to the uncoordinated ligand and free metal ion and hence they are more potent antimicrobial agents[20,21]. The mixed ligands of ciprofloxacin and 4'-(4-benzyloxyphenyl)-2,2':6',2"- terpyridine with Copper chloride (See 1.8, Fig 1) exhibited more activity against E. coli, P. aeruginosa, S. marcescens, B. subtilis and S. aureus and the MIC data of these complexes featured that the Cu complex had absolute capacity than ciprofloxacin[22]. The good antimicrobial activity was examined with the chelate effect, aspect of the ligands, the total charge of the complex, the aspect of the ion neutralizing the ionic complex, the nuclearity concerning the metal center in the complex[23,24].

The isatinmonohydrazone with 2-hydroxynapthaldehyde and 8-hydroxy quinoline as primary and secondary ligands (See 1.9, Fig 1) combined with the copper metal displayed maximum inhibitory zone of 24 mm limiting the expansion of P. medocina with MIC of 3.12 µg/mL. The variability concerning the effectiveness of distinct biocidal entities against diverse species is interdependent upon the impermeability of the cell, metal ion size and dipole moment, which may change as a potential outcome of metal ion presence[25]. The Copper complex of imino-oxalato mixed ligands (See 1.10, Fig 1) exhibited higher antimicrobial efficacy in comparison to Cobalt, Nickel and Zinc complexes and have MIC values of 1.7-2.8 µg/mL and it may be contributed as a outcome of the atomic radius and the electronegativity of Cu(II) ion[26]. Larger atomic radii and higher electronegativity reduce the effective positive charges on the metal complex molecules, facilitating their interaction with the charged particle and extremely sensitive biological membranes[27].

Novel Mn(III) mixed ligand complexes of ciprofloxacin with various bis-pyrazolone based bidentate ligands (See 1.11, Fig 1) possess increase in cell permeability and hence they are more potent bacteriostatics. Only lipid soluble substances may passs through the lipid membrane that envelops the cell and liposolubility is anticipated to be a key element in regulating antimicrobial action[28]. The overtone concept suggests that the chelation reduces the core atom's polarity mostly due to potential electron delocalization along the whole chelation ring and partial positive charge sharing with the contributing groups and this makes the core manganese atom to be lipophilic, which facilitates its penetration of the lipid folds of the cell membrane[29,30.]



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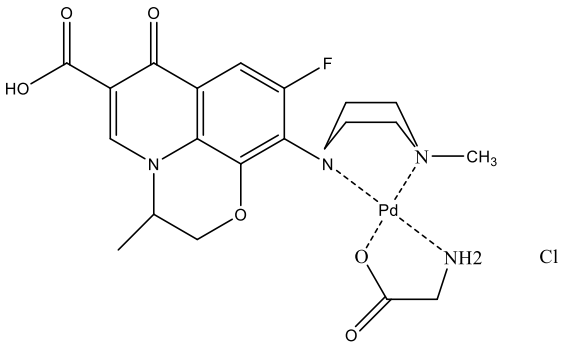

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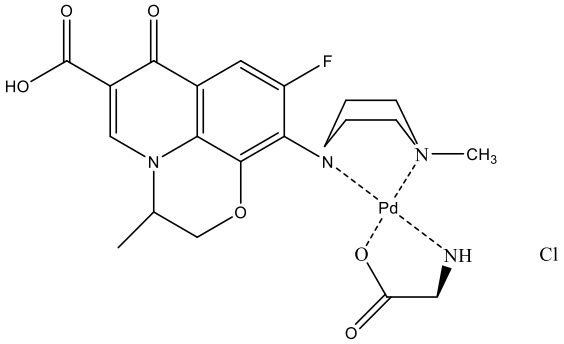

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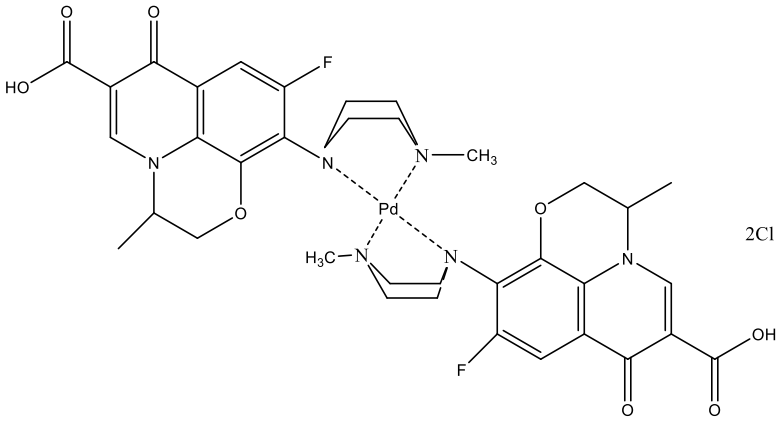

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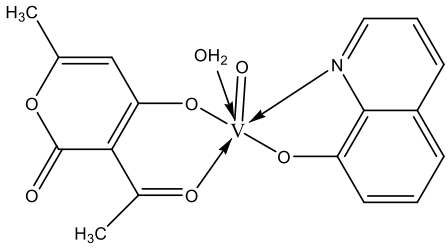

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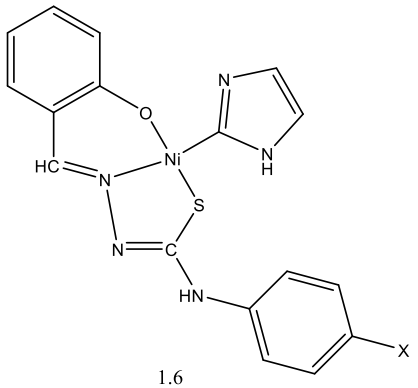

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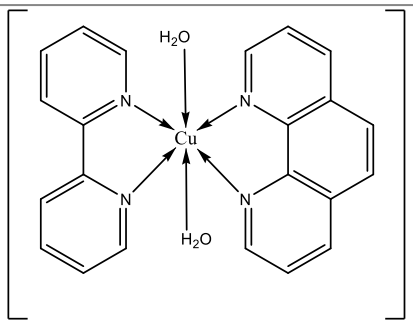

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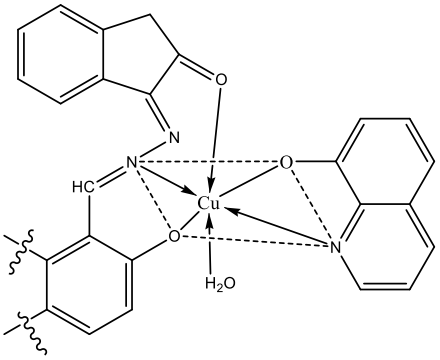

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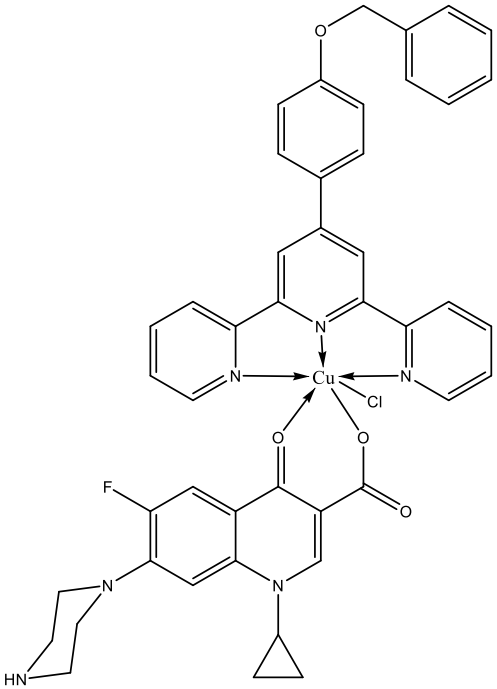

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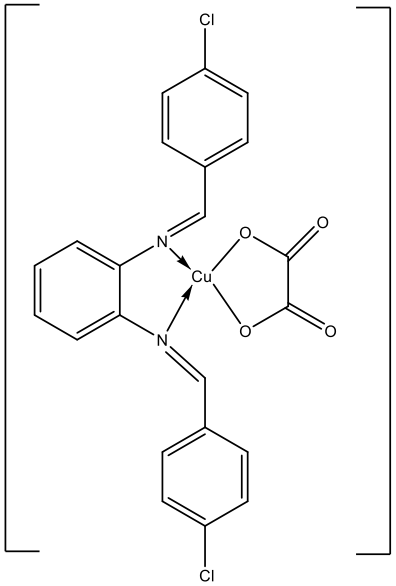

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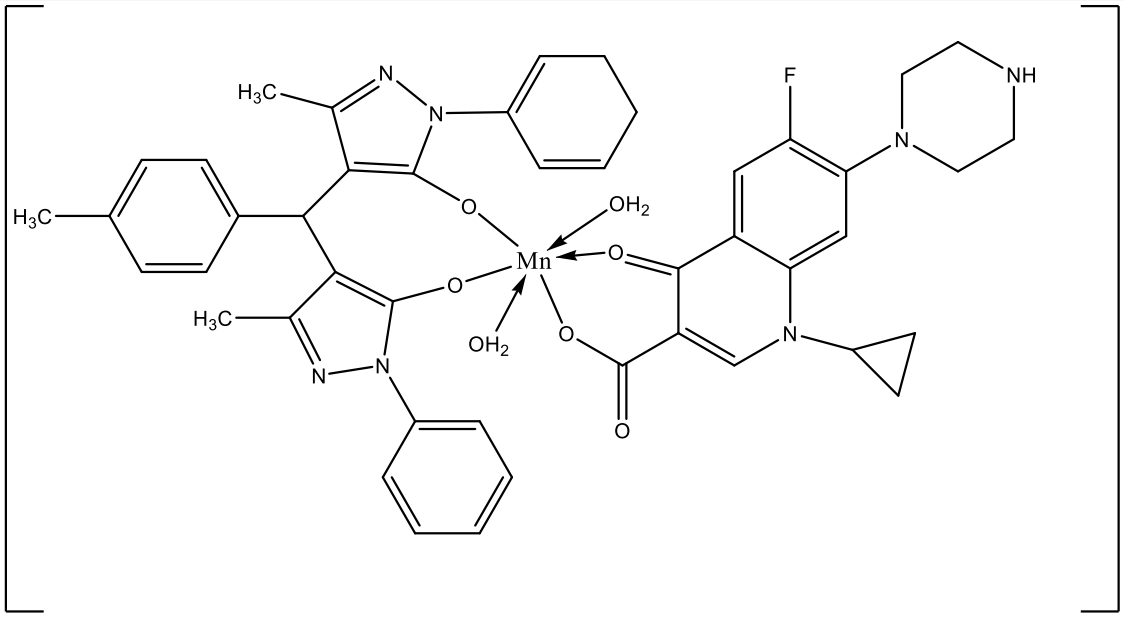

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Fig 1: Antibacterial activity of transition metal complexes.

Antitubercular activity

Latent tuberculosis, also known as non replicating Mycobacterium tuberculosis, is more resistant to most anti tuberculosis medications than replicating TB and necessitates a longer course of treatment[31].

It was found that 5-chloro-7-iodo-8-hydroxy quinoline metal complexes displayed anti tubercular activity. In particular, many derivatives of mixed ligand complexes are indeed developed and examined for the anti tubercular property. The complex interconnected with metal ions embracing 1,10-phenanthroline and 5-chloro-7-iodo-8-hydroxy quinoline as ligands. The Mn(II) complex (See 2.1, Fig 2) had equivalent MIC values of 45µg/mL and 40 µg/mL to the conventional medicine rifampicin, against tuberculosis (TB) (MTCC200). On the other hand, the Co(II) complex (See 2.2, Fig 2) shown more potent activity, with a MIC that was 6.4 times lower than that of rifampicin. Based on this study, metal complexes and free ligands have more antitubercular efficacy than metal salts[32].

The silver(I) complex of thiosemicarbazide, 2-(propan-2-ylidene)hydrazinecarbothioamide and thiazolidine-2-thione shows better activity against M. tuberculosis when compared with the second-line drugs of tuberculosis[33]. The clioquinol with (E)-2-(3-(4-chlorophenyl)acryloyl)-3H-benzo[f]chromen-3-one as primary and secondary ligands with Cu(II) complex (See 2.3,2.4,2.5 Fig 2) have shown enhancement in activity with MIC of 3.125 µg mL^{-1} was emerged as the most promising anti-tubercular element due to its superior action especially compared to streptomycin[34].

Vanadium complexes like [$V^{V}O$(L-pheolnaph-im)(5-Cl-8HQ)], [$V^{V}O$(OMe)$(8HQ)^{2}$] and [$V^{IV}O$(pic)(8HQ)] (See 2.6,2.7,2.8, Fig 2) are more active than the currently used drugs such as p-aminosalicylic acid (0.5-2.0 µg/mL), ethinamide (0.63-1.25 µg/mL), gentamicin (2.0-4.0 µg/mL), ethambutol (0.94-1.88 µg/mL). tobramycin (4.0-8.0 µg/mL), clarithromycin (8.0-16 µg/mL) in comparison with the molar basis[35]. Mixed ligand Cu(II) complexes (See 2.9, Fig 2) based on bromo-coumarins with clioquinol has an enhancement of activity and it showed that the complexation of ligand with Cu(II) metals has doubled its activity[36].

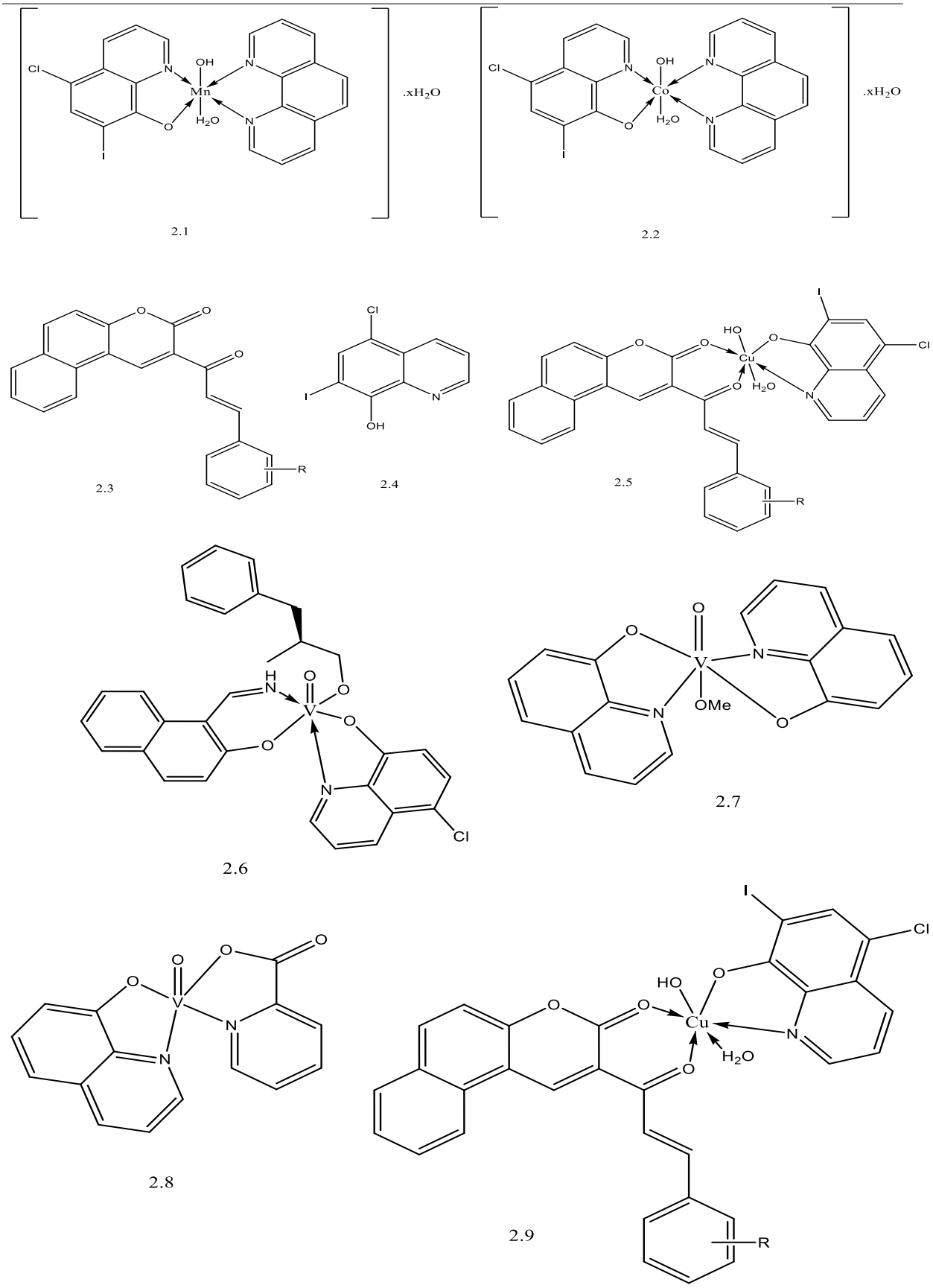


Fig 2: Anti-tubercular activity of Manganese, Cobalt, Vanadium and Copper complexes.

Antiparasitic activity

The persistence of parasitic illness as a highly prevalent concern was attributed to the growing resistance to be readily accessible complexes which were applied for preventing the growth of the parasites.

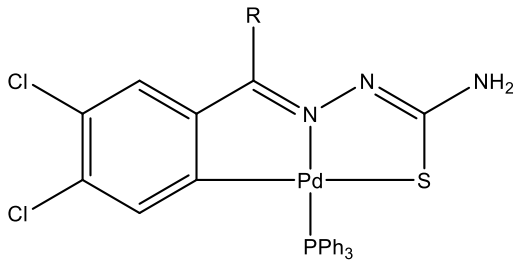
Antimalarial activity:

Globally, Malaria was regarded as a potentially fatal infectious disease[37]. Mixed-ligand complexes were highly useful in treating malarial disease. The chelating capacity of the compounds was shown to be closely related to their capacity for limiting the proliferation of Plasmodium falciparum[38].

It was identified that the mixed ligand complexes of melfloquine hydrochloride and chloroquine phosphate with cobalt(II) and Iron(II) would be a better therapeutic drug for malaria. This can be explained by testing the complexes with mixed ligands and their outcomes were shown as in comparison with the control, the serum ALP activities significantly ($p<0.05$) increased when represented with fluoxetine, chloroquine and $[Ni(Mef)(CQ)]Cl_3$, but the activities of the $[Co(Mef)(CQ)]Cl_2$ and $[Fe (Mef)(CQ)]Cl_3$ groups decreased. In conversely to such control group, kidney ALP activity considerably higher in the $[Co(Mef)(CQ)]Cl_2$ therapeutic group and decreased ($p<0.05$) in the mefloqine and chloroquine therapeutic groups. Hence the mixed ligand complexes $[Co(Mef)(CQ)]Cl_2$ and $[Fe(Mef)(CQ)]Cl_3$ can be utilized as a therapeutic drug for malaria[39].

The Palladium complex (See 3.1,3.2, Fig 3) was tested against 3D7 (chloroquine-sensitive) and K1 (chloroquine and pyrimethamine resistant) P. falciparum strains. The mixed ligand complex of Pd(II) exhibited greater activity in the treatment of malaria[40]. The lowest minimal concentration of 0.11 µM/L was obtained for zinc complex of 4-acyl pyrazolones (See 3.3,3.4,3.5, Fig 3) against P. falciparum[41]. The synthesis of hemozoin, also known as β-hematin was a distinct process that Plasmodium species uses to detoxify free heme. The majority of well known antimalarial medications currently in use have confirmed this target and it was assumed be an ideal location to target potential antimalarial medications[42].

Numerous recent studies have offered proof for a quantitative relationship between the strength of β-hematin formation and antiparasitic activity against the malarial parasite Plasmodium falciparum[43-46]. The efficiency of $[Zn(nap)_2(2\text{-ampy})_2]$ (See 3.6,3.7,3.8, Fig 3) in averting the development of β-Hematin was 75% with the range of concentration between 1-0.6 mg/ml[47]. Platinum(II) complexes of 2,2'-bipyridyl and 1,10-phenanthroline benzoylthiourea inhibit β-hematin development heavily and hence it will comprise the secondary family of platinum antiplasmodials[48]. The cytotoxic effects of $[Ag_2(dppf)(3\text{-benzyl-}1,3\text{-thiazolidine-}2\text{-thione})_2].(NO_3)_2$ complex was assessed to determine the selectivity index to biological activity(SI) and the antiplasmodial activities of the complexes were considered to be specific and safe when the SI was more than 10[49,50]. Due to the highest SI value(more than 12.4) the silver complex can be used for the emergence of antimalarial drug[51].



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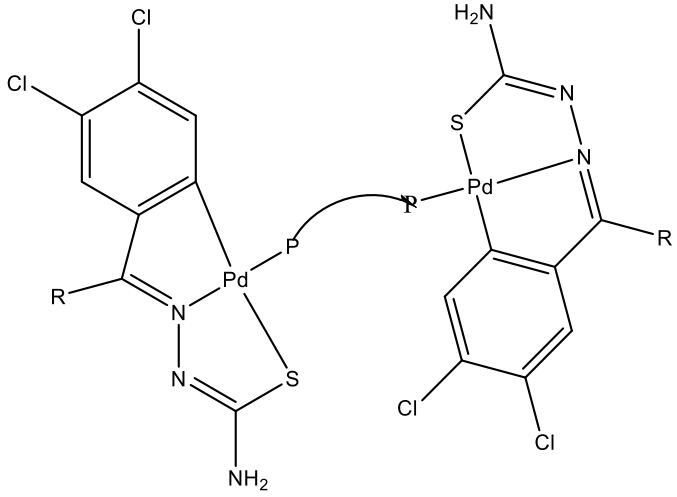

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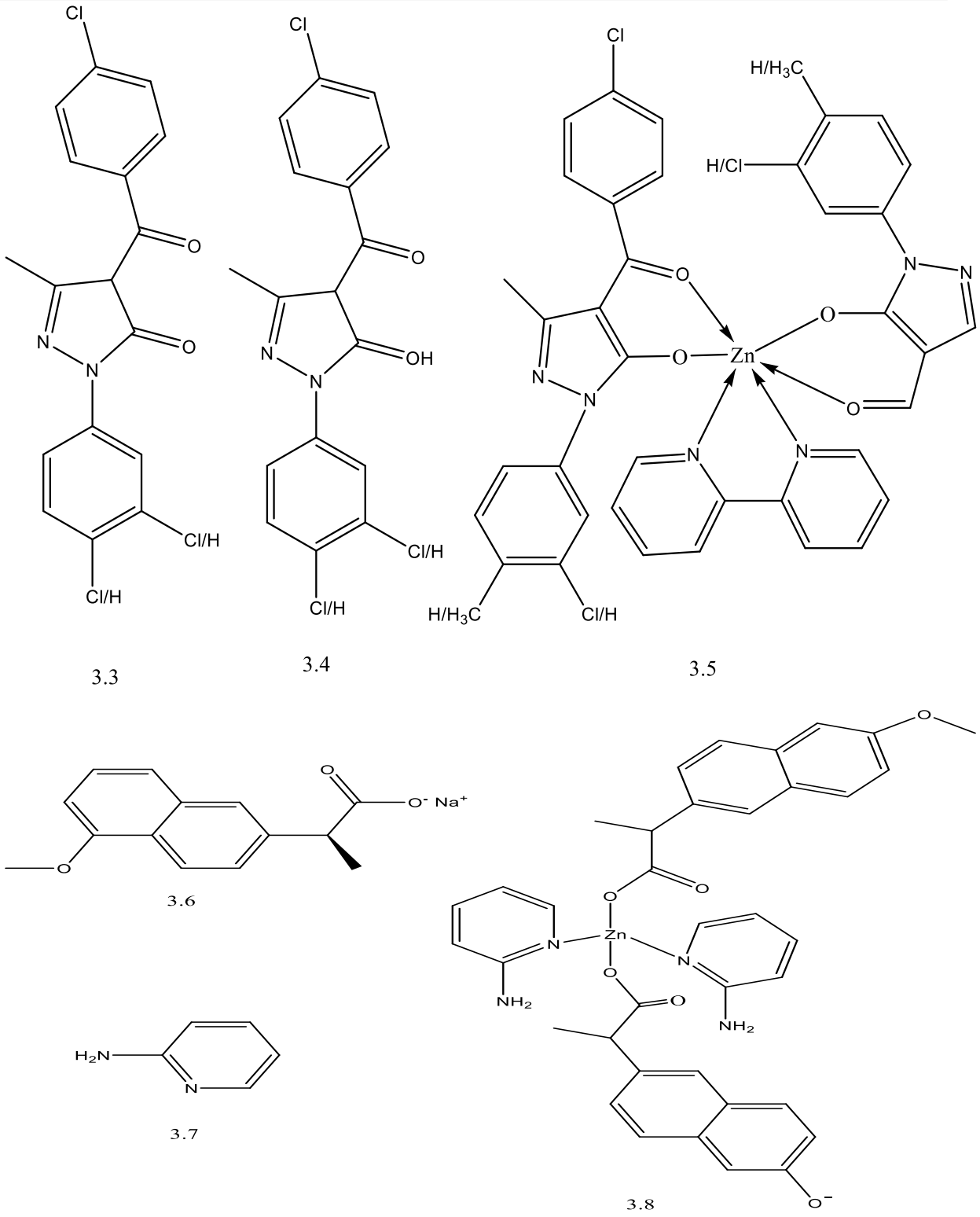

Fig 3: Antimalarial activity of transition metal complexes with its mixed ligands.

Antifungal activity

Mixed ligand complexes had been shown to exhibit greater fungal toxicity compared to their initial organic component(ligand). According to reports, the antifungal action can be significantly associated to the chelation of chemicals[52]. Antifungal action is not just dependent on chelation rather it is a complex combination of various parameters including the kind of metal and ligand, the morphology of the metal compounds, lipophilicity, the availability of co-ligands, steric interactions and pharmacological components[53]. The metal complexes of fluoroquinolone drug enrofloxacin and glycine containing ligands

(See 4.1,4.2,4.3, Fig 4) were evaluated against C. albicans and the sequence of activity is greater for Nickel than Chromium and Copper, through blocking the active sites of the microorganisms, the greater antifungal activity of the mixed ligand complexes prevents the microbes from taking the average[54].

The coordination complexes of 2-hydroxyacetophenone with L-Tyrosine and 4-dimethylaminobenzaldehyde with 2,4-dinitrophenylhydrazine of Fe(III) displayed significant antifungal activity compared to certain complexes when resolved with A. niger, A. flavus, A. alternate and R. stolonifer (See 4.4,4.5,4.6, Fig 4)[55]. The antifungal activities of Mn(III) of mixed ligand complexes were investigated against C. herbarium and A. flavus. In comparison to the complexes using the standard drug fluconazole, $[Mn(acac)_2(NCS)SH_2]$ displayed the maximum percentage of suppression against these fungal strains. This high antifungal activity is described in view of the existence of thiocyanato group[56]. The other complexes $[Mn(acac)_2(Cl)SH_2]$, $[Mn(acac)_2(Br)SH_2]$ and $[Mn(acac)_2(N_3)SH_2]$ showed 49%, 50% and 52% preventing mycelial growth in opposition to C. herbarium respectively[57].

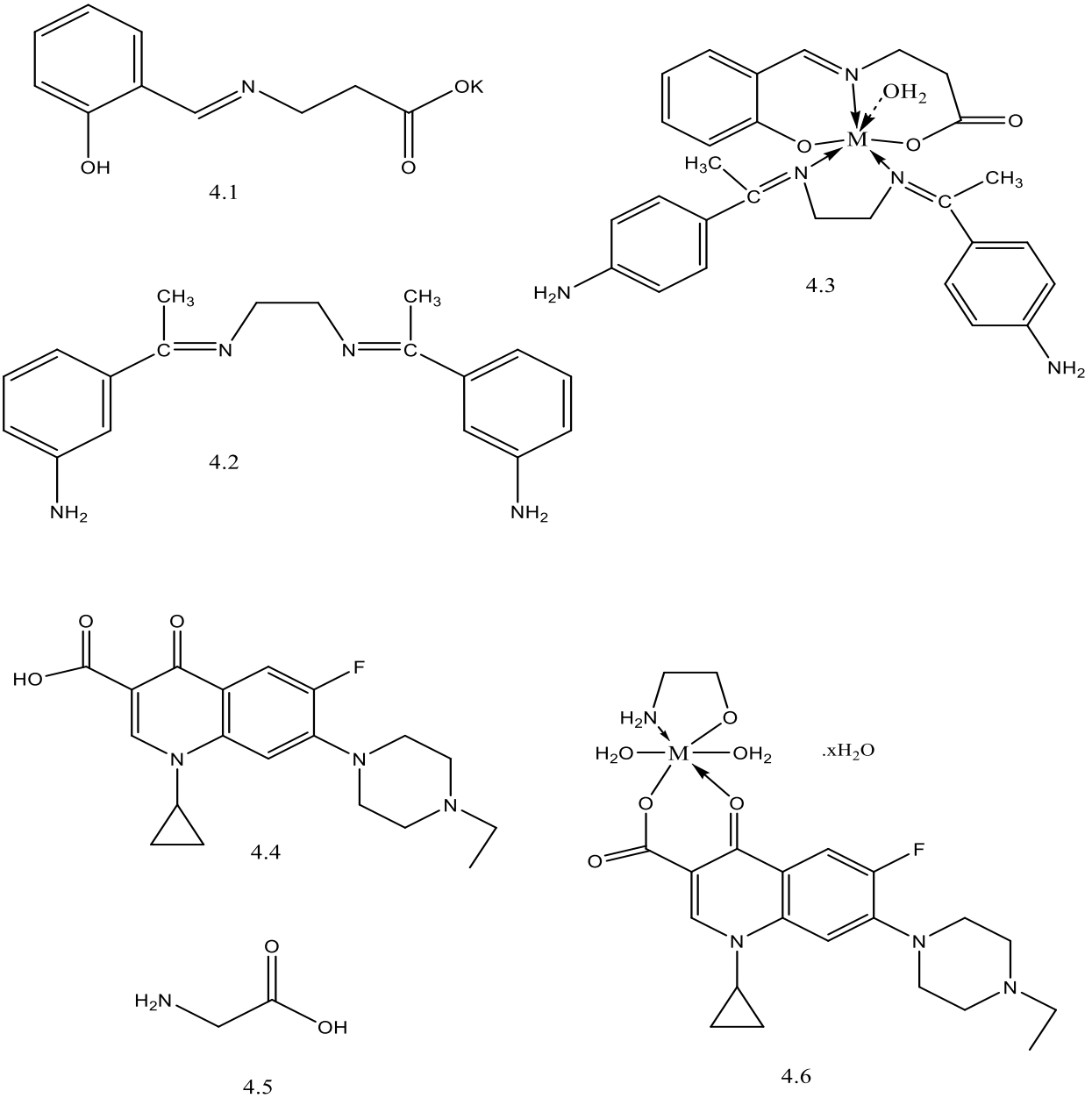

Fig 4: Antifungal activities of mixed ligands and its metal complexes.

2. CONCLUSION

The escalating challenge of antimicrobial resistance demands exploration of novel therapeutic agents beyond

conventional antibiotics. This review emphasizes the broad spectrum of antimicrobial strategies, including natural products, synthetic compounds, nanomaterials, and bioengineered solutions. Among these, mixed ligand metal complexes have emerged as particularly promising candidates due to their ability to enhance biological activity through synergistic interactions between ligands and metal centers. Such complexes often demonstrate improved stability, selectivity, and potency against resistant strains, making them valuable in the search for next-generation antimicrobials. Future research should focus on optimizing ligand design, understanding structure–activity relationships, and evaluating biocompatibility to translate these findings into clinical applications. Ultimately, integrating mixed ligand complexes with other innovative approaches could provide a sustainable path forward in overcoming microbial resistance and safeguarding global health.

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