



## A review of current trends of antibacterial Schiff base complexes: Lower and higher transition metal complexes

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### ABSTRACT

The development of metal complexes has inspired researchers to progress in this domain due to their extensive applications in the biological field. Regarding the application, binuclear metal complexes are less explored than their mononuclear counterparts. Recent development in transition metal Schiff base complexes was outlined and presented in detail with their respective vast applications, especially antibacterial. The relationship of their structure, functions, properties, and key elements that affected antibacterial activities was demonstrated. This review was aimed to present the latest advancement of numerous lower and higher transition metal complexes, especially mononuclear ones. Moreover, their various properties are highlighted for future work related to binuclear Schiff base metal complexes and to persuade future research in this exciting field.

**Keywords:** Antibacterial, higher transition metals, lower transition metals, Schiff bases

### INTRODUCTION

Presently, resistance against some specific drugs has evolved into a chronic problem globally that deserves consideration to be remedied through advanced and comprehensive research for substitute antibiotics that are novel, remarkable, essential, botanical, economical and antitoxic (Abiy and Berhe, 2016). A rising medical hazard is the increasing tendency of infections resulting from penicillin-resistant *Staphylococcus aureus*.

Li and Webster (2018) recognized a broad analysis of antibiotic resistance intensity and its effects worldwide, as well as its significance, major influence and the route microorganisms use to develop antibiotic resistance. It was evidently demonstrated that *S. aureus* bacterium strain was persistently resistant to macrolide antibiotics, aminoglycoside, tetracycline, and all highly desirable antibiotics, particularly methicillin and vancomycin. In the framework of their studies, the existing disrepute lethal antibiotic-resistant bacteria, specifically *Enterococcus*

*faecium*, *S. aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa* and *Enterobacter* genus, was established as the major contributing factor of ailment and fatality around various regions globally.

Determination of novel bioactive metal complexes that play a prominent role inherently, as reflected by the enormous functional molecules, has conventionally remained a challenge in the realm of inorganic chemistry for decades. The significance of metal complexes in biological and medical sciences is mainly due to the substantial role of their inorganic elements, where the organic fragments commonly become activated or biotransferred as a consequence of metal ion metabolism (Afanas'ev *et al.*, 1989). Recognition of Schiff base complexes and several other metal complexes as bioactive compounds led to accelerated development in coordination and bioinorganic chemistry. Comprehensive research works have been instigated on the synthesis as well as practical and effective bio-utilisation of these compounds (Chohan and Jaffery, 2000; Jayabalakrishnan

and Natarajan, 2001; Yu *et al.*, 2009; Naureen *et al.*, 2021a; 2021b; Sarwar *et al.*, 2021).

Schiff bases are indispensable intermediaries in the synthesis of various bioactive compounds and are used as ligands for metal ions complexation (El-Sherif *et al.*, 2012). The vigorous attraction for Schiff bases bonding to inner or non-inner transition metal ions is vital in the synthesis of metal complexes. It is reaffirmed that certain Schiff bases exhibited amplified bioactivity when dispensed with as metal complexes (Mohamed *et al.*, 2005).

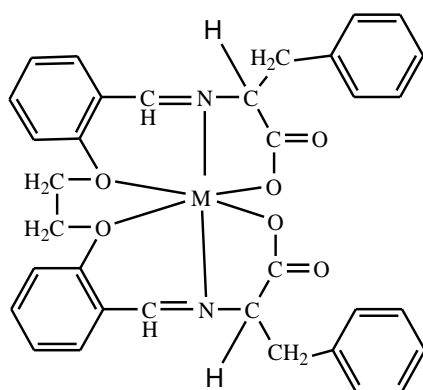
In 1964, Hugo Schiff prepared a series of bases on the reaction of primary amines with aldehydes and ketones. The prepared bases had  $\text{-HC=N-}$  (azomethine) groups in their structures. The dinitrogen dioxygen ( $\text{N}_2\text{O}_2$ ) type of ligands as obtained by the condensation reactions of a diamine with various aldehydes and ketones, could easily coordinate with one or several metal centres depending on the binding sites available for complexation. Schiff bases and their complexes have numerous applications in different fields, such as antibacterial, antiviral, anticancerous, anti-inflammatory, antioxidant, luminescent and sensor materials (Kondo *et al.*, 2007; Kumari *et al.*, 2008; Yamada *et al.*, 2015; Sarwar *et al.*, 2020; 2021; 2022a; 2022b; 2023).

Numerous tetradentate Schiff bases of each aliphatic and aromatic diamine with aldehydes and ketones were thoroughly examined and recorded as bioactive materials.

This review will open new frontiers for the synthesis as well as the antibacterial investigation of binuclear Schiff base complexes with better and enhanced bioactivity.

### Lower transition metal Schiff base complexes: Antibacterial properties

Accordingly, Aziz (2010) recorded the synthesis of sodium 2,2'-(2,2'-(ethane-1,2-diylbis(oxy))bis(2,1-phenylene))bis(methan-1-yl-1-ylidene)bis(azan-1-yl-1-ylidene)bis(3-phenyl propanoate). Schiff bases with their respective Zn(II), Co(II), Ni(II) and Cu(II) complexes are

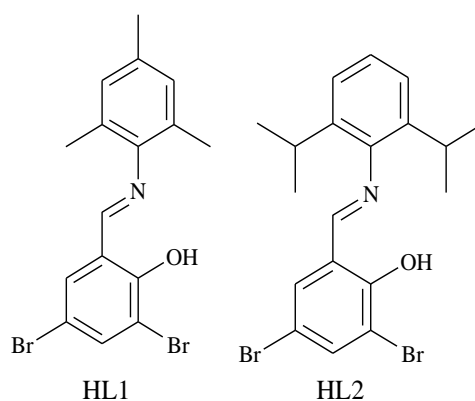


**Figure 1:** Mononuclear Zn(II), Co(II), Ni(II) and Cu(II) sodium 2,2'-(2,2'-(ethane-1,2-diylbis(oxy))bis(2,1-phenylene))bis(methan-1-yl-1-ylidene)bis(azan-1-yl-1-ylidene)bis(3-phenyl propanoate) Schiff base complexes.

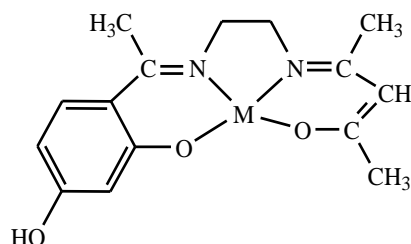
shown in Figure 1. The synthesised ligand, along with its metal complexes, was tested for antibacterial activity performed *in vitro* environment against Gram-positive bacteria, namely, *S. aureus*. The findings manifested potent inhibition detriment to bacteria strain. The inhibition zones were found for ligand = 9.0 mm, Cu(II) = 14.0 mm, Zn(II) = 15.0 mm, Ni(II) = N/A. The mechanisms that induced the results in this study were perhaps the inhibition of bacterial protein biosynthesis by binding to ribosomes stimulating bacteria death. Various other adopted mechanisms specified that several antibodies inhibited the synthesis of bacterial deoxyribonucleic acid (DNA), in essence, inhibition of DNA ligase in DNA-enzyme complexes by splitting DNA.

Feng *et al.* (2013) synthesised two metal complexes involving Schiff base ligands, namely,  $[\text{Pd}(\text{L}1)_2](1)$  and  $[\text{Zn}(\text{L}2)_2](2)$ , [HL1: 2,4-dibromo-6-((E)-(mesitylimino)methyl)phenol and HL2: 2-((E)-(2,6-diisopropylphenylimino)methyl)-4,6-dibromophenol], as shown in Figure 2. These Schiff base ligands and their metal complexes were screened for antibacterial activity against several bacteria strains, such as *S. aureus*, *Bacillus cereus*, *Rhizopus* and *Escherichia coli*, and the results were compared with the activity of penicillin. In comparison to ligands, the complexes were more active. It was possible that a metal ion might activate the ligands. The antibacterial activity tests showed that the ligands and complexes exhibited superior biological activity against *S. aureus*, *B. cereus* and *E. coli*.

Ejidike and Ajibade (2015) synthesised Zn(II), Co(II), Ni(II) and Cu(II) complexes of (4E)-4-[(2-((E)-[1-(2,4-dihydroxyphenyl)ethylidene]amino)ethyl)imino]pentan-2-one, as shown in Figure 3. Antibacterial findings against *P. aeruginosa*, *E. coli*, *Shigella flexneri* and *S. aureus* were determined. The results revealed that metal complexes were considerably more active compared to free ligands, with Cu(II) complex illustrating superior activity. The bioactivity of the compounds was found to be in the range of 10.0 mm $\leq$  in the following order: Cu(II) > Co(II) > Ni(II) > Zn(II) > L.



**Figure 2:** Antibacterial  $[\text{Pd}(\text{L}1)_2](1)$  and  $[\text{Zn}(\text{L}2)_2](2)$ , [HL1: 2,4-dibromo-6-((E)-(mesitylimino)methyl)phenol and HL2: 2-((E)-(2,6-diisopropylphenylimino)methyl)-4,6-dibromophenol] Schiff base complexes.

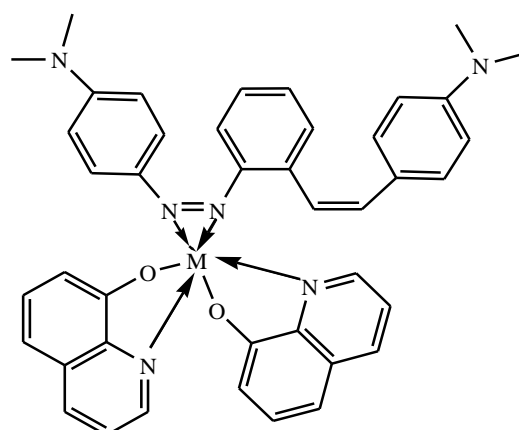


**Figure 3:** Mononuclear Zn(II), Co(II), Ni(II) and Cu(II) complexes of (4E)-4-[(2-(E)-[1-(2,4-dihydroxyphenyl)ethylidene]amino)ethyl]imino]pentan-2-one Schiff base.

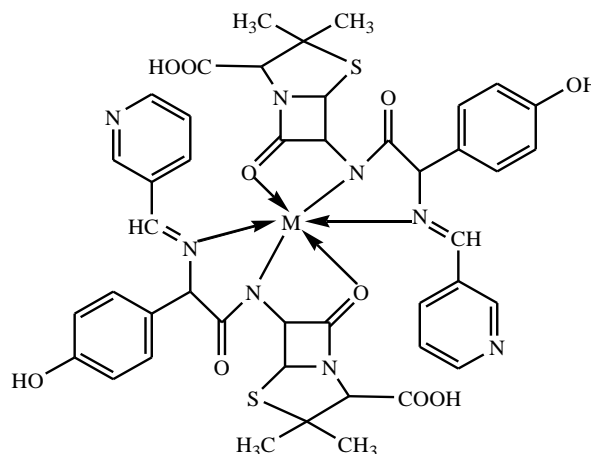
Packianathan *et al.* (2017) presented a detailed exploratory analysis of DNA binding/cleavage and antibacterial proficiency of  $N_4O_2$  type mixed ligands and their respective complexes (Figure 4). Various mechanisms were adopted to investigate DNA binding properties that implied the potential of complexes to interface with DNA by intercalative mode. The complexes showed higher activity than the parent ligand in the given order: ligand = 9.0 mm, Cu(II) = 20 mm, Ni(II) = 17 mm, Co(II) = 19 mm, Zn(II) = 16 mm. Amongst all, Cu(II) complex manifested a maximal antibacterial activity in relation to a ligand and the respective complexes against *Escherichia coli* with a 20.0 mm inhibition zone.

Chaudhary and Mishra (2017) also synthesised a novel Schiff base ligand using the condensation procedure of amoxicillin trihydrate and nicotinaldehyde (Figure 5). The prepared ligand, along with the corresponding Co(II), Ni(II), Cu(II) and Zn(II) complexes, were examined *in vitro* environment for antibacterial activity in relation to *E. coli* and *S. aureus* at two completely separate concentrations. Comparatively, a stronger activity was exhibited by the complexes to the parent ligand and control drugs. Importantly, all the complexes with the exception of Cu(II) were vibrantly active towards two bacterial pathogens at stronger concentrations over their parent ligand and control drugs. This superior activity might be attributed to azomethine linkage and heteroatoms in these compounds.

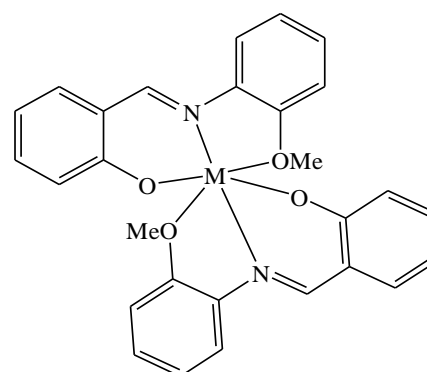
Galini *et al.* (2017) synthesised four transition-metal complexes [Co<sup>II</sup>(L)<sub>2</sub>] (1), [Zn<sup>II</sup>(L)<sub>2</sub>] (2), [Ni<sup>II</sup>(L)<sub>2</sub>] (3) and [Cu<sup>II</sup>(L)<sub>2</sub>] (4) from tridentate Schiff base ligand (HL = 2-((E)-(2-methoxyphenylimino)methyl)-4-bromophenol) (Figure 6). The *in vitro* antibacterial activity of the complexes against *Bacillus subtilis*, *S. aureus*, *Enterobacter cloacae* and *E. coli* was found to be higher than the free ligand. Chloramphenicol and kanamycin were used as standard drugs. Superior antimicrobial activity was exhibited by [Cu<sup>II</sup>(L)<sub>2</sub>] (4) complex in relation to the rest of the complexes concerning each specific class of organisms. Although notably, [Co<sup>II</sup>(L)<sub>2</sub>] (1) complex displayed inferior activity with respect to the other complexes. The tendency of antibacterial activity that was noted on complexes 1-4, 4>2>3>1 could be interpreted in terms of steric and electronic effects, complex size, and geometrical framework, besides stability constants of the complexes. Moreover, the



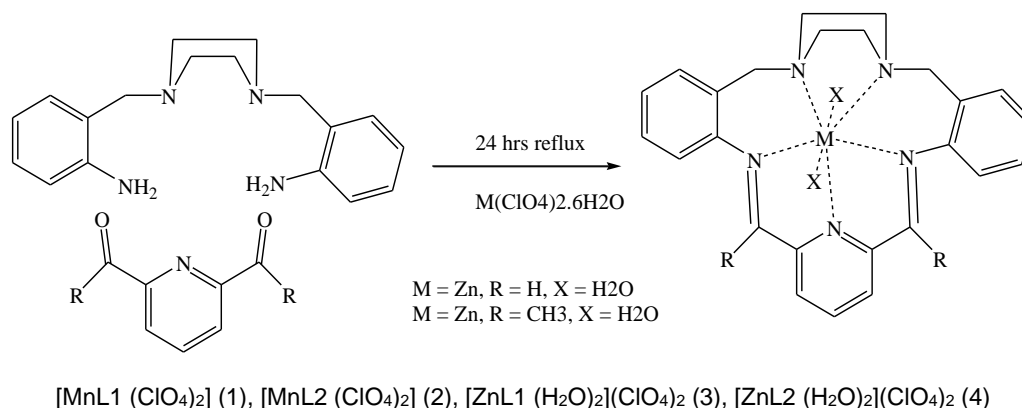
**Figure 4:** Mononuclear Cu(II), Ni(II), Co(II), Zn(II) complexes of Schiff base derived from benzene-1,2-diamine as primary ligand and 8-hydroxyquinoline as co-ligand.



**Figure 5:** Mononuclear Co(II), Ni(II), Cu(II) and Zn(II) Schiff base complexes derived from amoxicillin trihydrate and nicotinaldehyde.



**Figure 6:** [Co<sup>II</sup>(L)<sub>2</sub>] (1), [Zn<sup>II</sup>(L)<sub>2</sub>] (2), [Ni<sup>II</sup>(L)<sub>2</sub>] (3) and [Cu<sup>II</sup>(L)<sub>2</sub>] (4) with 2-((E)-(2-methoxyphenylimino)methyl)-4-bromophenol) Schiff base complexes.



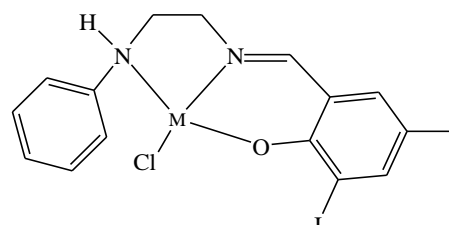
**Figure 7:** Mn(II) and Zn(II) macrocyclic Schiff-base from 2,2'-(piperazine-1,4-diylbis(methylene)).

antibacterial activity of the complexes was further governed by the number and essence of donor atoms and intrinsic properties of metal ions in the corresponding metal complexes. The greatest activity of Cu(II) complex can be explained given that in tetracoordinated Cu(II) complex possessing square planar geometry, free sites are available on or around metal ions centre to coordinate with cellular constituents active centres causing proteins synthesis termination; and thus limits subsequent growth of organisms.

Keypour *et al.* (2017) synthesised Mn(II) and Zn(II) macrocyclic Schiff base complexes from 2,2'-(piperazine-1,4-diylbis(methylene)), as presented in Figure 7. The synthesised four complexes were thoroughly analysed in vitro environment for antibacterial activity with respect to *Bacillus subtilis*, *Bacillus thuringiensis*, *Staphylococcus saprophyticus*, *Pectobacterium* sp. and *P. fluorescens*. The consequential analysis signified that complexes 1 [MnL1 (ClO<sub>4</sub>)<sub>2</sub>] and 2 [MnL2 (ClO<sub>4</sub>)<sub>2</sub>] against *B. thuringiensis*, *S. saprophyticus* and *Pectobacterium* sp. 1 [MnL1(ClO<sub>4</sub>)<sub>2</sub>] manifested a stronger activity in relation to the standard tobramycin and tetracycline. All complexes hampered the growth of bacterial strains with an inhibition zone of 7.0-32.0 mm. Besides inhibition zone size, the minimal inhibitory concentration (MIC) values of the compounds were also determined. Consequently, these complexes manifested amplified activity against several bacterial strains compared to the standard antibiotics.

Sakhti and Ramu (2017) prepared 2,4-diiodo-6-((2-phenylaminoethylimino)methyl)phenol Schiff base (L) and its transition metal complexes Cu(II) (1), Ni(II) (2), Co(II) (3), Mn(II) (4) and Zn(II) (5), as shown in Figure 8. The ligand and all the complexes were tested for their antibacterial activities against *S. aureus*, vancomycin-resistant *E. coli* and *P. aeruginosa*. All complexes and ligands showed moderate antibacterial activity compared to the standard drug tetracycline.

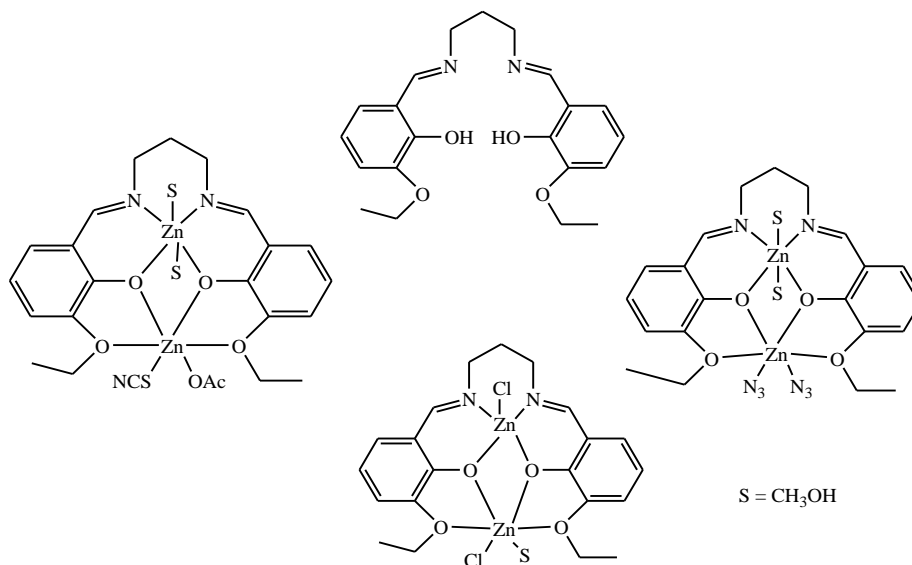
A series of binuclear Zn(II) complexes were synthesised by Majumdar *et al.* (2018), namely [Zn<sub>2</sub>(L<sup>1</sup>)(CH<sub>3</sub>OH)<sub>2</sub>(SCN)(OAc)] (1), [Zn<sub>2</sub>(L<sup>1</sup>)(CH<sub>3</sub>OH)<sub>2</sub>(N<sub>3</sub>)<sub>2</sub>] (2) and [Zn<sub>2</sub>(L<sup>1</sup>)(Cl)<sub>2</sub>(CH<sub>3</sub>OH)].CH<sub>3</sub>OH (3) accompanied by [N,N'-Bis(3-ethoxysalicylideneimino)-1,3-diaminopropane], as shown in Figure 9. The preferred complexes were



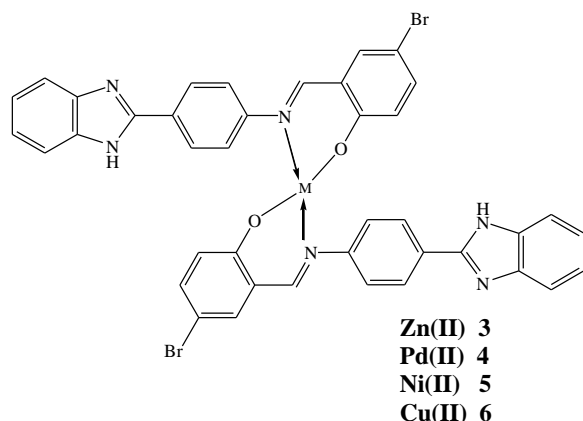
**Figure 8:** Cu(II) (1), Ni(II) (2), Co(II) (3), Mn(II) (4) and Zn(II) (5) metal complexes with 2,4-diiodo-6-((2-phenylaminoethylimino)methyl)phenol Schiff base ligand.

screened against *Staphylococcus haemolyticus*, *E. gallinarum*, *Proteus vulgaris* and *Salmonella enterica* ser. *Typhi* strains. Complexes 1-3 exhibited stronger antimicrobial proficiency than the standard antibiotic ampicillin used in this study against *S. haemolyticus*, *E. gallinarum* and *P. vulgaris*. In contrast, against *S. enterica* ser. *Typhi*, synthesised complexes manifested an inferior antimicrobial activity than the reference drug.

Synthesis of Schiff base ligand (E)-2-((4-(1H-benzo[d]imidazole-2-yl)phenylimino)methyl)-4-bromophenol and its corresponding Zn(II) (3), Pd(II) (4), Ni(II) (5), Cu(II) (6) complexes was carried out by Mahmood *et al.* (2019), as shown in Figure 10. The selected compounds were screened against *E. coli*, *Enterobacter aerogenes* and *Micrococcus luteus*. All compounds exhibited antibacterial activity against both Gram-positive and Gram-negative bacteria, except Pd(II) (4) and Cu(II) (6), which remained inactive against *E. coli* and *E. aerogenes*. Fundamentally, metal complexes were comparatively more active than the parent ligand except positive control kanamycin, whereby less activity was observed. The obtained MIC values of Ni(II) and Zn(II) complexes against *E. coli* and *E. aerogenes* showed better activity pattern, though Cu(II) complex manifested lesser activity for *E. coli* and remained inactive for *E. aerogenes*. Furthermore, the acquired results against *M. luteus* illustrated that Ni(II) (5) and Cu(II) (6) exhibited superior activity than Zn(II) complex. Consequently, Ni(II) complex proved promising with distinctive results against all bacteria strains; apparently, biological activity was



**Figure 9:** Antibacterial  $[Zn_2(L^1)(CH_3OH)_2(SCN)(OAc)](1)$ ,  $[Zn_2(L^1)(CH_3OH)_2(N_3)_2](2)$  and  $[Zn_2(L^1)(Cl)_2(CH_3OH)] \cdot CH_3OH(3)$  accompanying  $[N,N'$ -Bis(3-ethoxysalicylideneimino)-1,3-diaminopropane] Schiff base complexes.



**Figure 10:** Zn(II) (3), Pd(II) (4) Ni(II) (5), Cu(II) (6) metal complexes with (E)-2-((4-(1H-benzo[d]imidazole-2-yl)phenylimino)methyl)-4-bromo phenol.

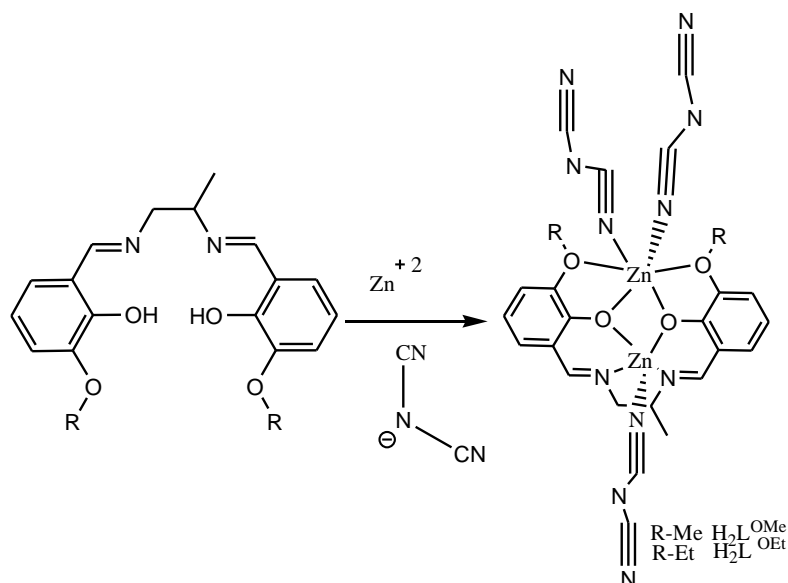
based on the bacteria utilised. Amongst all compounds, Ni(II) complex showed promising results with the exception of Pd(II) and Cu(II) complexes (4 and 6), even though they were less active than the standard kanamycin.

Synthesis of two novel dicyanamide-interlaced tetranuclear Zn(II) Schiff base complexes was reported by Majumdar *et al.* (2019),  $[Zn_2(LOMe)(\mu-dca-\kappa N^1 \kappa N^5)(\mu-dca-\kappa N^1)]_2(1)$  and  $[Zn_2(LOEt)(\mu-dca-\kappa N^1 \kappa N^5)(\mu-dca-\kappa N^1)]_2(2)$  using salicylaldehyde type Schiff bases (H2LOMe) and (H2LOEt), as shown in Figure 11. Both the synthesised complexes and corresponding Schiff base ligands displayed antibacterial activity against *E. gallinarum*, *S. haemolyticus*, *E. aerogenes* and *P. vulgaris*. Both Zn(II) complexes showed significant antibacterial activity that were apparent from their MIC values and inhibition zone

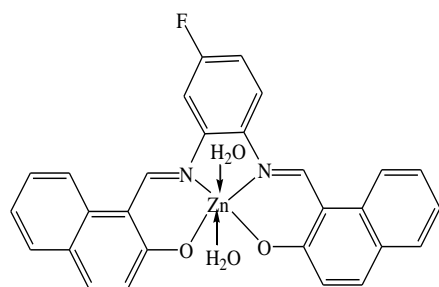
growth, possessing lower MIC (200-300  $\mu\text{g/mL}$ ) values with respect to their parent ligands, MIC values (300-550  $\mu\text{g/mL}$ ). Remarkably, the complexes were more efficient against *P. vulgaris*. Contrarily, they exhibited minimal potency against *E. gallinarum*.

Synthesis of four mononuclear metal chelated complexes,  $[Co(L)](1)$ ,  $[Ni(L)](2)$ ,  $[Cu(L)](3)$  and  $[Zn(L)](4)$  from Salen-type Schiff base ligand (H2L) obtained from 2-hydroxy naphthaldehyde and 4-fluoro-1,2-phenylenediamine was reported by Ramesh *et al.* (2020), as displayed in Figure 12. All synthesised compounds were screened *in vitro* environment for antibacterial efficiency against *Bacillus amyloliquefaciens*, *S. aureus*, *P. aeruginosa* and *Escherichia coli*, while streptomycin and mancozeb were utilised as standard drugs in this study. All the metal complexes exhibited superior antibacterial activity compared to the free ligand, evident from the wider inhibition zones. The structural changes, type of chelations, solubility nature, dipole moment, size and permeability nature were perhaps the basis for better antimicrobial potency of the metal complexes. It was apparent from the studies that Cu(II) complex exhibited considerable activity compared to all complexes. Smaller atomic size and higher electro negativity of Cu(II) ion might possibly be the reason for higher antimicrobial activity. It was found in the following ranges: ligand = 8-11 mm, A = Co(II) (1) 19-22 mm, B = Ni(II) (2) 22-25 mm, C = Cu(II) (3) 25-28 mm, D = Zn(II) (4) 14-17 mm.

Synthesis of three Cu(II) and Zn(II) complexes, namely  $[Cu(HL1)(CH_3CH_2OH)] \cdot (CH_3COO)(1)$ ,  $[Zn_3(HL1)_2(CH_3COO)_4](2)$  and  $[Zn_2(L2)] \cdot (CH_3COO)(3)$  from  $[H_2L1 = N,N'$ -bis(salicylidene)diethylenetriamine and  $H_3L2 = 2,2'-(1E,1'E)-(2,2'-(2-hydroxyphenyl)imidazolidine-1,3-diyl)bis(ethane-2,1-diyl)bis(azan-1-yl-1-ylidene)bis(methan-1-yl-1-ylidene)diphenol]$  Schiff base ligands was performed by



**Figure 11:** Dicyanamide interlaced tetranuclear Zn(II) Schiff base complexes  $[Zn_2(LOMe)(\mu\text{-dca-}\kappa N^1\kappa N^5)(\mu\text{-dca-}\kappa N^1)]_2$  (1) and  $[Zn_2(LOEt)(\mu\text{-dca-}\kappa N^1\kappa N^5)(\mu\text{-dca-}\kappa N^1)]_2$  (2).



A = Co(II), B = Ni(II), C = Cu(II), D = Zn(II)

**Figure 12:** Mononuclear Co(II), Ni(II), Cu(II), Zn(II) derived from 2-hydroxy naphthaldehyde and 4-fluoro-1,2-phenylenediamine Salen-type ligand.

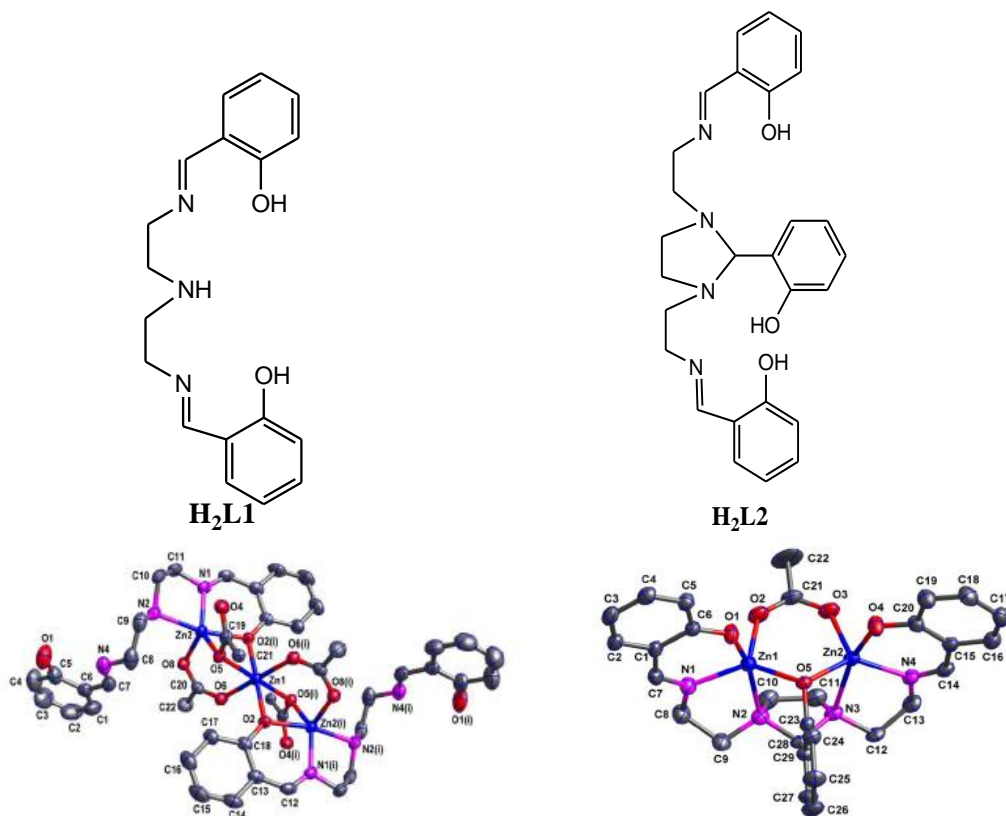
Liu *et al.* (2020), as shown in Figure 13. All the synthesised compounds were screened against *Escherichia coli*, *K. pneumoniae*, *P. aeruginosa*, *Bacillus subtilis*, *S. aureus* and *Corynebacterium xerosis*. The complexes exhibited considerably bigger inhibition zones than their respective ligands. Complex 1  $[Cu(HL1)(CH_3CH_2OH)] \cdot (CH_3COO)_2$  manifested higher antibacterial activity against *S. aureus* that possessed an inhibition zone of 14 mm compared to the other five bacteria, which had an inhibition zone ranging from 11-13 mm. While, complex 2  $[Zn_3(HL1)_2(CH_3COO)_4]$  showed excellent activity against *K. pneumoniae* with an inhibition zone diameter of 17 mm, complex 3  $[Zn_2(L2)] \cdot (CH_3COO)_2$  exhibited strong activity against *S. aureus* and *C. xerosis* that possessed an inhibition zone of 14 mm. For MIC values, ciprofloxacin and gentamicin were utilised as positive control standard drugs. MIC values for all three complexes were between 16  $\mu\text{g/mL}$  and 128  $\mu\text{g/mL}$ ,

whereas the ligands values were over 128  $\mu\text{g/mL}$ , verifying ligands deficient activity. Out of all the compounds, complex 2 exhibited proficient antibacterial activity.

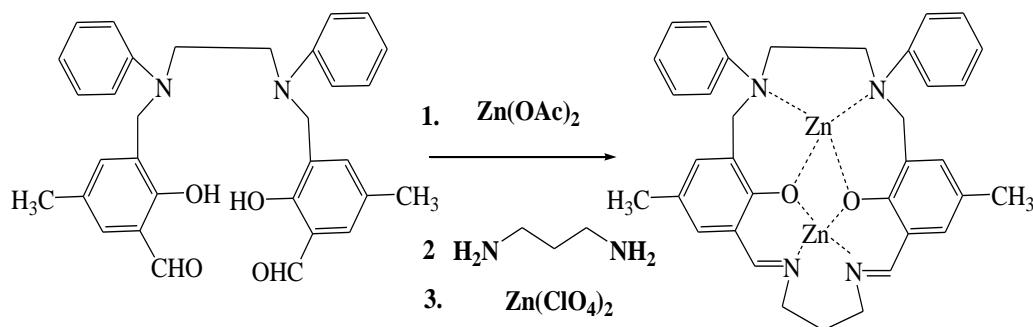
Synthesis of a novel macrocyclic binuclear Zn(II) complex was reported by Kou *et al.* (2020) using condensation between 3,3'-(ethane-1,2-diylbis(benzylazanediyl))bis(methylene)bis(2-hydroxy-5-methylbenzaldehyde) and 1,3-diaminopropane, and subsequently with zinc salts (Figure 14). The synthesised binuclear Zn(II) compound was screened for antibacterial activity against *Escherichia coli* bacteria. The activity improved with the increasing concentration of the complex; however, it held lower than penicillin that was used as a standard drug, considering *E. coli*'s thick wall membrane against the reagent endosmosis. Significantly, the complex inhibition zone was larger than the ligand. The complex inhibition zone diameter was over 7 mm.

#### Higher transition metal Schiff base complexes: Antibacterial properties

Over the past decades specific consideration was given to the synthesis and characterisation of metal ions binuclear compounds that led to significant advances, especially such transition metal elements had divergent coordination ligands (Vigato and Tamburini, 2004; Jain and Jain, 2005; Lozan *et al.*, 2009; Maggini, 2009; Singh *et al.*, 2009; Wang and Zhang, 2014; Ait-Ramdane-Terbouche *et al.*, 2018). Prospective utilisation in particular photoluminescence (Li *et al.*, 2014; Zhao *et al.*, 2017), catalysis (van den Beuken and Feringa, 1998; Hollingsworth *et al.*, 2017), materials (Balzani *et al.*, 2007; Li *et al.*, 2011), pharmaceuticals (Geeta *et al.*, 2010) and sensors (Ait-Ramdane-Terbouche *et al.*, 2018)



**Figure 13:** [Cu(HL1)(CH<sub>3</sub>CH<sub>2</sub>OH)]·(CH<sub>3</sub>COO) (1) (Mononuclear), [Zn<sub>3</sub>(HL1)<sub>2</sub>(CH<sub>3</sub>COO)<sub>4</sub>] (2) (Trinuclear), [Zn<sub>2</sub>(HL2)]·(CH<sub>3</sub>COO) (3) (Binuclear) Schiff base complexes (Source: Liu *et al.*, 2020).

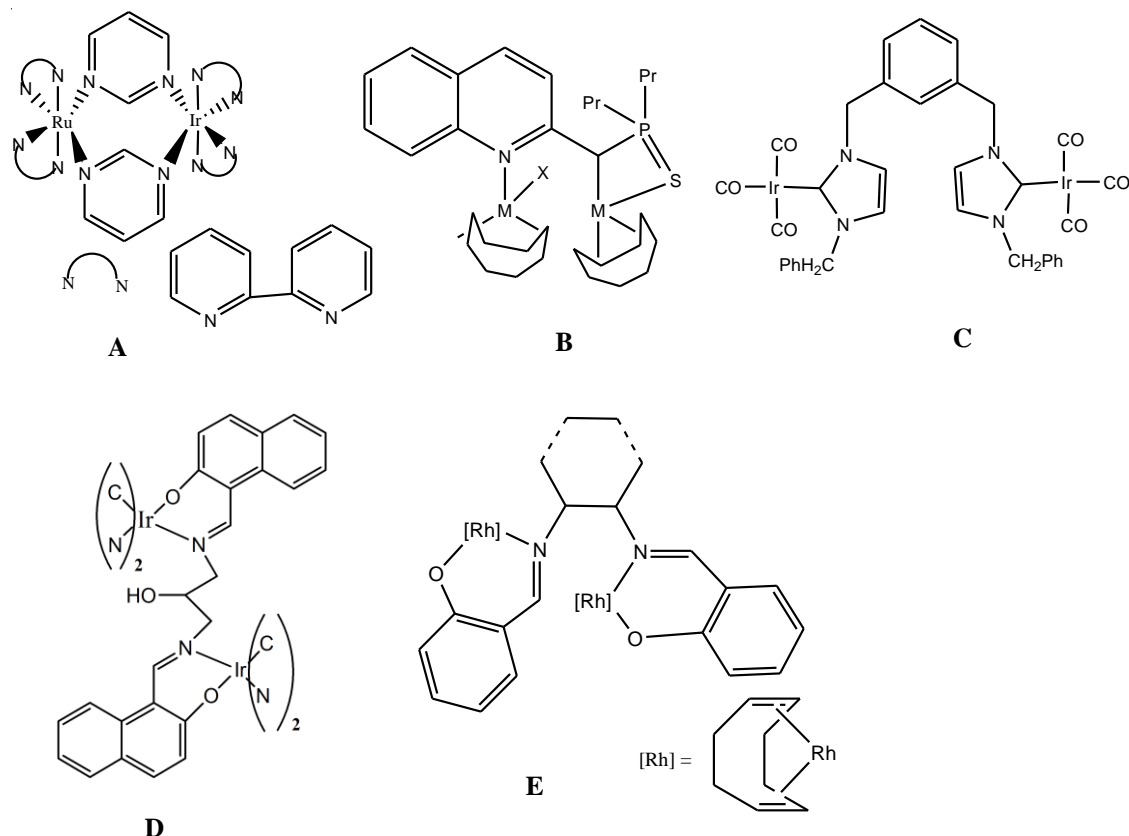


**Figure 14:** Macrocyclic binuclear Schiff Base Zn(II) complex.

acknowledged these to be the most thriving classes of materials. Furthermore, Scheme 1 displays several iridium homo and hetero-bimetallic complexes that employed separate ligands (Janiak *et al.*, 2009; Kuo *et al.*, 2012; Leung *et al.*, 2016; Sun *et al.*, 2017). The bimetallic iridium complexes synthesis and characterisation were recently described, emphasising on systematic hydroalkynylation catalysis of imines by Ir(III)-based system (Nguyen *et al.*, 2013). However, Jainak *et al.* (2009) adopted a unique synthesis and characterisation method using XRD polymorphs binuclear

complexes of rhodium bridge-over by the Salen and Salphen ligands.

Distinctive characteristics were previously reported concerning metal precursors of iridium, ruthenium and rhodium attributed to their various applications, namely catalytic, photochemical, and biological potencies (Hirayama *et al.*, 2014; Kollipara *et al.*, 2020). Considering that the composition of metal complexes involving Salen-type ligands, coupled with a diamine bridge, the components on the ligand framework and the metal ions were conveniently adapted. This rendered the



**Scheme 1:** Examples of binuclear complexes.

compounds exceptionally beneficial for the analysis of stereochemistry and reactivity of a broad range of reactions following a wide range of applications.

The Ir(III) Schiff base complexes with potent antibacterial properties were reported as follows:

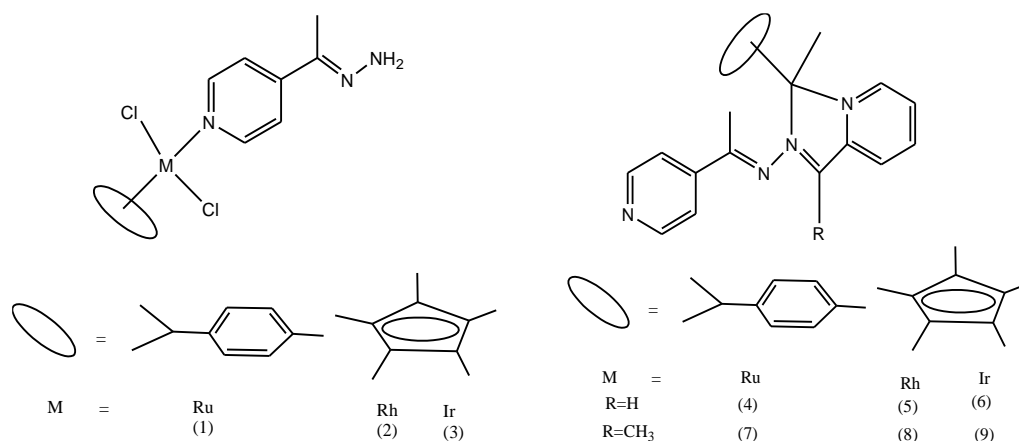
Synthesis and characterisation of rhodium, iridium and ruthenium metal complexes involving pyridyl azine Schiff base ligands were carried out by Lapasam *et al.* (2019a), as shown in Figure 15. The analysed results demonstrated that ligand L1 acted as a neutral monodentate N donor; however, ligand L2 and L3 formed bidentate NNO cationic complexes. On the other hand, the complexes were investigated for antibacterial activity against Gram-positive and Gram-negative bacteria, namely *S. aureus*, *E. coli* and *K. pneumoniae*. Complexes 2-4 remained inactive, while complexes 1, 5-9 displayed modest activity exceeding free ligands. Complex 5 and complex 6 exhibited favourable activity in relation to all; perhaps this was attributed to coordination that tended to compel complexes to function as potential antimicrobial agents inhibiting microorganism growth.

Synthesis of a series of novel hydrazone mononuclear complexes type [(arene) MLCI]PF<sub>6</sub> (M=Ru, Rh, Ir) was performed (Lapasam *et al.*, 2019a), as depicted in Figure 16. Complexes (1-3) with corresponding ligand coordinated to metal utilising two pyridine nitrogen atoms constituted six numbered metallocycle, while complexes

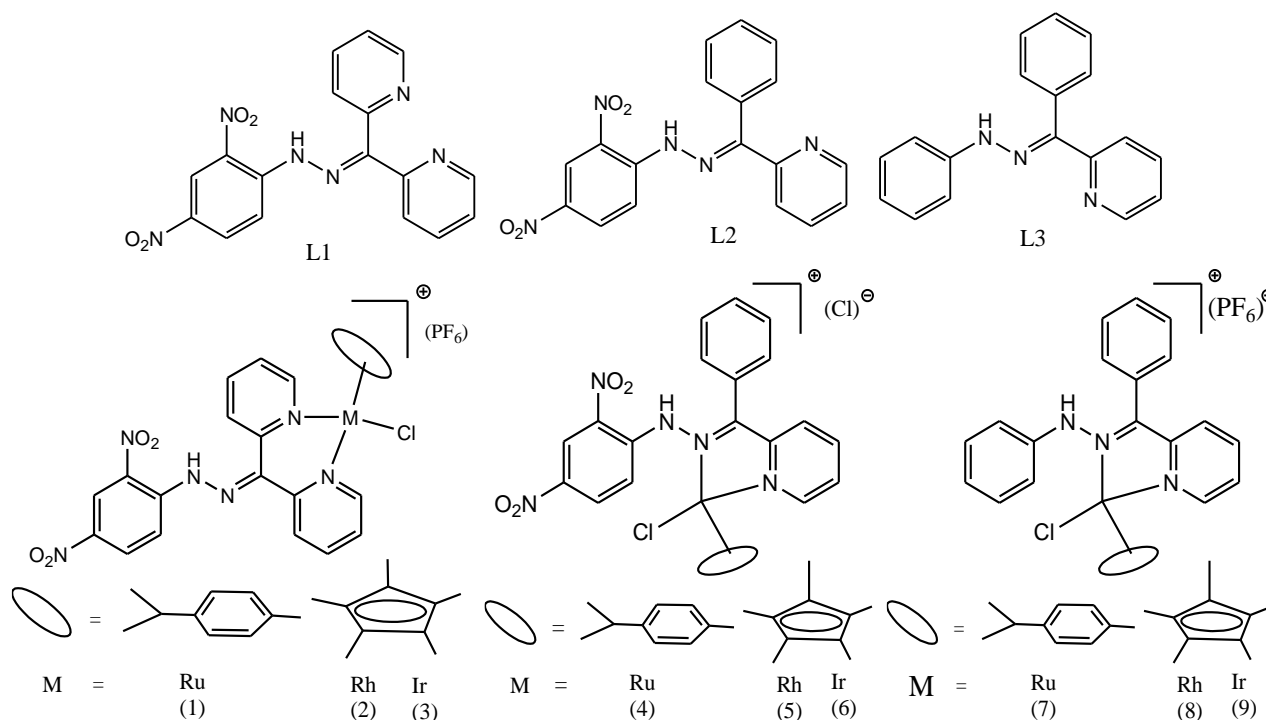
(4-9) utilising a single hydrazone nitrogen atom and a single pyridine nitrogen atom formed five numbered metallocycles. Antibacterial activity of the complexes was assessed against two Gram-positive bacteria (*S. aureus* and *Bacillus thuringiensis*) and two Gram-negative bacteria (*Escherichia coli* and *P. aeruginosa*). It was determined that high activity was exhibited by the complexes against *P. aeruginosa*. Whereas insignificant activity was depicted against *E. coli*. Comparably, the complexes exhibited notable antibacterial activity against *B. thuringiensis*, while they remained inactive against *S. aureus*.

Synthesis and characterisation of 9-fluorenone Schiff base derivatives L1, L2 and L3 with their corresponding mononuclear rhodium, ruthenium and iridium complexes were performed by Kollipara *et al.* (2020), displaying potent antibacterial activity and DNA-binding (Figure 17). Analysis for antibacterial activity was conducted against *S. aureus*, *E. coli* and *K. pneumoniae* organisms. Potential activity was demonstrated by all the complexes, with complexes 4, 7 and 9 being the best. Complex 7 (23 ± 1.16 mm) and complex 9 (21 ± 1.02 mm) displayed activity against Gram-positive (*S. aureus*). Complex 7 (24 ± 1.25 mm) and complex 4 (23 ± 1.19 mm) also showed the highest activity against Gram-negative (*E. coli*), while complex 7 (25 ± 1.36 mm) and complex 9 (22 ± 1.06 mm) showed more activity against Gram-negative (*K.*





**Figure 15:** Structures of rhodium, iridium and ruthenium metal complexes (1-9) involving pyridyl azine Schiff base ligands.



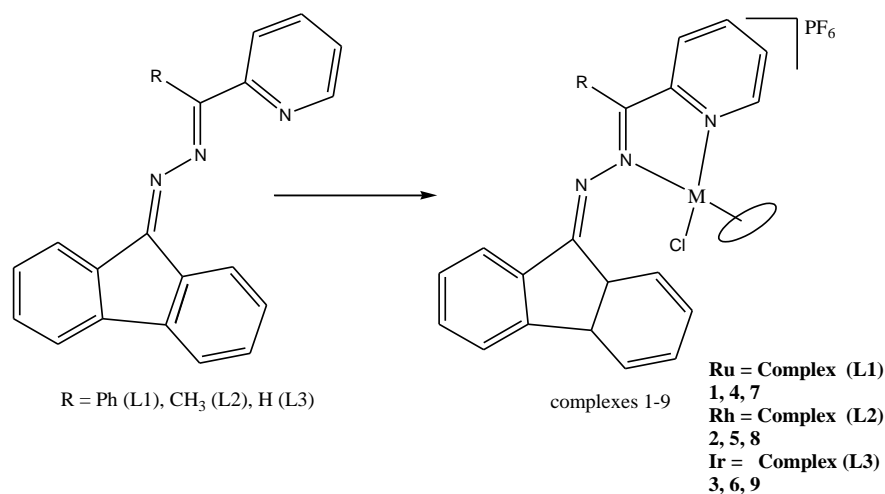
**Figure 16:** Structure of hydrazone mononuclear complexes type [(arene) MCl]PF<sub>6</sub> (M=Ru, Rh, Ir).

*pneumoniae*). The results revealed that the compounds conceivably were antibacterial agents. While DNA-binding studies showed that complex 4 and complex 5 exhibited remarkable mutations in their spectral properties with the inclusion of SM-DNA, specifying complexes to be bound to DNA with substantial affinity.

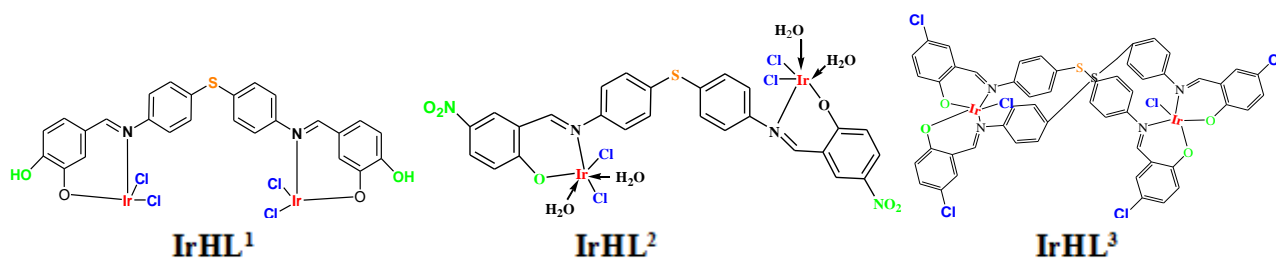
Sarwar *et al.* (2021) synthesised binuclear Ir(III) azomethine complexes derived from 4,4'-diaminodiphenyl sulphide spacer and aldehydes bearing a variety of functional groups (OH, NO<sub>2</sub>, Cl) (Figure 18). The compounds were screened against Gram-negative and Gram-positive bacteria, namely *E. coli*, *Salmonella typhi*,

*P. aeruginosa*, *E. faecalis*, *Streptococcus mutant* and *S. aureus* for their bactericidal activities, which possessed mild to moderate antibacterial properties. The IrHL<sup>2</sup> complex with *p*-nitro substituent showed the highest activity against *S. mutant*, *S. aureus* and *P. aeruginosa*, succeeded by the IrHL<sup>3</sup> complex with *p*-Cl substituent for *S. mutant*.

To the best of the authors' knowledge, limited published works on the synthesis and biological activities are available on binuclear Ir, Rh and Ru complexes consisting of azomethine-type tetradentate Schiff base ligands.



**Figure 17:** Structures of 9-fluorenone Schiff base derivatives L1, L2 and L3 with their corresponding mononuclear rhodium, ruthenium and iridium complexes (1-9).



**Figure 18:** Antibacterial binuclear Ir(III) azomethine complexes (Sarwar *et al.*, 2021).

It was shown that the complexation of Schiff bases with different metal ions showed enhanced bioactivity and all of the synthesized complexes showed higher antibacterial activity against the initial Schiff-based ligands. The enhanced antibacterial activity was explained by the implications of the idea of cell permeability. The lipo solubility of the substance was an aspect that regulated the antibacterial activity since only lipophilic substances could permeate the lipid membrane of a bacterial cell wall (Anjaneyulu and Rao, 1986). It is generally recognised that chelation tends to make the ligand act as a vigorous and effective bacterial agent through the presence of metal ions. Surrounded by organic ligands, the metal is able to enter the bacteria cell membrane and cellular disorder functions.

Additionally, such improved activity of the complexes was explained by Tweedy's chelation theory. For chelation, the polarity of metal ions reduced significantly due to the overlap of the ligand orbital and partial sharing of the positive charge of the metal ion with donor atoms of azomethine ligands (Král'ová *et al.*, 2004; Parekh *et al.*, 2005). Moreover, it strengthened the delocalisation of  $\pi$ -electrons over the whole chelate ring; thus, it improved the complex lipophilicity, increasing the ability to penetrate a lipid membrane. The metal complexes disrupted the cell processes, thereby blocking protein synthesis. Therefore, bacterial cell wall genesis was

nonviable, resulting in eventual cell death (Yamgar *et al.*, 2014).

It could also be explained that complexes suppressed the DNA gyrase enzyme responsible for DNA multiplication phases, terminating the multiplication of bacterial cells (Elsome *et al.*, 1996; Alvarez *et al.*, 1997; Galm *et al.*, 2004).

Furthermore, it was noted that the efficiency of different complexes varied against different bacterial strains depending on the differences in the permeability of the microbial cells or the difference of ribosomes of the microbial cells (Lapasam *et al.*, 2019b).

Compared to Co (II), Ni (II) and Zn (II), the Cu (II) complexes exhibited higher antibacterial activity. According to reports, enhanced antibacterial activity of metal complexes is attributed to the size, permeability nature, solubility type, dipole moment, structure modifications and type of chelations. Smaller atomic size and higher electro negativity of Cu(II) ion might possibly be the reason for higher antimicrobial activity (Aziz, 2010; Ejidike and Ajibade, 2015; Galini *et al.*, 2017; Packianathan *et al.*, 2017; Ramesh *et al.*, 2020).

Additionally, greater nuclearity imparts increased density of bioactive sites; and thus, enhanced antibacterial activity. A trinuclear complex in a series of complexes showed greater potency compared to the ligands and their mono and binuclear counterparts as well

**Table 1:** A review of potent antibacterial lower and higher transition metal Schiff base complexes.

Metals used	Types of complexes/ Types of bacteria	Antibacterial activity	Reference
Cu(II) Zn(II) Ni(II)	Mononuclear ( <i>S. aureus</i> )	The results revealed an inhibition zone of ligand = 9.0 mm; Cu(II) = 14.0 mm; Zn(II) = 15.0 mm; Ni (II) = N/A.	(Aziz, 2010)
Zn(II) Pd(II)	Mononuclear ( <i>S. aureus</i> , <i>B. cereus</i> , <i>Rhizopus</i> , <i>E. coli</i> )	As a comparison to ligands, the complexes were more active.	(Feng <i>et al.</i> , 2013)
Cu(II) Co(II) Ni(II) Zn(II)	Mononuclear ( <i>P. aeruginosa</i> , <i>E. coli</i> , <i>S. flexneri</i> , <i>S. aureus</i> )	The compounds bioactivity was found to be in the range of 10.0 mm≤ in the following order: Cu(II)>Co(II)>Ni(II)>Zn(II)>L	(Ejidike and Ajibade, 2015)
Cu(II) Ni(II) Co(II) Zn(II)	Mononuclear ( <i>E. coli</i> )	The complexes showed higher activity than the parent ligand. Ligand = 9.0 mm; Cu(II) = 20 mm; Ni(II) = 17 mm; Co(II) = 19 mm; Zn(II) = 16 mm.	(Packianathan <i>et al.</i> , 2017)
Co(II) Ni(II) Cu(II) Zn(II)	Mononuclear ( <i>E. coli</i> , <i>S. aureus</i> )	The complexes showed greater potency against all the bacterial strains at higher concentrations, except copper complexes, which was due to azomethine linkage and heteroatoms.	(Chaudhary and Mishra, 2017)
Co(II) Zn(II) Ni(II) Cu(II)	Mononuclear ( <i>B. subtilis</i> , <i>S. aureus</i> , <i>E. cloacae</i> , <i>E. coli</i> )	Antibacterial activity of the complexes against the bacterial strains was found to be higher than the free ligand in the given order: Cu(II)>Zn(II)>Ni(II)>Co(II).	(Galini <i>et al.</i> , 2017)
Mn(II) Zn(II)	Mononuclear ( <i>B. thuringiensis</i> , <i>S. saprophyticus</i> , <i>B. subtilis</i> , <i>P. fluorescens</i> , <i>Pectobacterium</i> sp.)	The complexes exhibited higher activity than the parent ligands with zone of inhibition in the range of 7.0-32.0 mm.	(Keypour <i>et al.</i> , 2017)
Cu(II) Ni(II) Mn(II) Co(II) Zn(II)	Mononuclear ( <i>S. aureus</i> , <i>E. coli</i> , <i>P. auregenosa</i> )	The complexes and ligand showed moderate antibacterial activity in comparison to the standard drug tetracycline.	(Sakthi and Ramu, 2017)
[Zn <sub>2</sub> (L <sup>1</sup> )(CH <sub>3</sub> OH) <sub>2</sub> (SCN)(OAc)](1) [Zn <sub>2</sub> (L <sup>1</sup> )(CH <sub>3</sub> OH) <sub>2</sub> (N <sub>3</sub> ) <sub>2</sub> ](2) [Zn <sub>2</sub> (L <sup>1</sup> )(Cl) <sub>2</sub> (CH <sub>3</sub> OH)].CH <sub>3</sub> OH (3)	Binuclear ( <i>S. haemolyticus</i> , <i>E. gallinarum</i> , <i>P. vulgaris</i> , <i>S. enterica</i> ser. <i>Typhi</i> )	The bacterial growth inhibition pattern for the complexes was 3>2>1.	(Majumdar <i>et al.</i> , 2018)
Zn(II) (3) Pd(II) (4) Ni(II) (5) Cu(II) (6)	Mononuclear ( <i>Micrococcus luteus</i> , <i>E. coli</i> , <i>E. aerogenes</i> )	Amongst all compounds, Ni(II) complex showed promising results with the exception of Pd(II) and Cu(II) complexes (4 and 6).	(Mahmood <i>et al.</i> , 2019)
Zn(II)	Tetranuclear ( <i>S. haemolyticus</i> , <i>E. gallinarum</i> , <i>P. vulgaris</i> , <i>E. aerogenes</i> )	The complexes exhibited greater activity than the parent ligand. MIC and inhibition zone of ligands = 300-550 µg/mL; 4.13-8.29 mm. MIC and zone of inhibition of complexes = 200-300 µg/mL; 7.20-14.4 mm.	(Majumdar <i>et al.</i> , 2019)
Co(II) Ni(II) Cu(II) Zn(II)	Mononuclear ( <i>B. amyloliquefaciens</i> , <i>S. aureus</i> , <i>P. aeruginosa</i> , <i>E. coli</i> )	The complexes exhibited greater activity than the parent ligand. Ligand = 8-11 mm; A = Co(II) (1) 19-22 mm; B = Ni(II) (2) 22-25 mm; C = Cu(II) (3) 25-28 mm; D = Zn(II) (4) 14-17 mm.	(Ramesh <i>et al.</i> , 2020)

Metals used	Types of complexes/ Types of bacteria	Antibacterial activity	Reference
Cu(II) Zn(II) [Cu(HL1)(CH <sub>3</sub> CH <sub>2</sub> OH)]-( CH <sub>3</sub> COO)(1), Zn <sub>3</sub> (HL1) <sub>2</sub> (CH <sub>3</sub> COO) <sub>4</sub> (2) and [Zn <sub>2</sub> (L2)]-(CH <sub>3</sub> COO) (3)	Mononuclear, binuclear and trinuclear ( <i>E. coli</i> , <i>K. pneumoniae</i> , <i>P. aeruginosa</i> , <i>B.</i> <i>subtilis</i> , <i>S. aureus</i> , <i>C.</i> <i>xerosis</i> )	The complexes exhibited MIC = 16- 128 µg/mL. Ligands with more than 128 µg/mL. Trinuclear complex 2 showed greater potency compared to the two ligands and other two complexes.	(Liu <i>et al.</i> , 2020)
Zn(II)	Binuclear ( <i>E. coli</i> )	The complex was found to be more potent than the ligand with an inhibition zone of over 7 mm.	(Kou <i>et al.</i> , 2020)
Ru(III) (1) (4) (7) Rh(III) (2) (5) (8) Ir(III) (3) (6) (9)	Mononuclear ( <i>S. aureus</i> , <i>E. coli</i> and <i>K. pneumoniae</i> )	Complex 5 and complex 6 with L2 and L3 bidentate NNO cationic ligands, respectively, exhibited superior activity.	(Lapasam <i>et al.</i> , 2019a)
Ir(III) Ru(III) Rh(III)	Mononuclear ( <i>S. aureus</i> , <i>B.</i> <i>thuringiensis</i> , <i>E. coli</i> , <i>P.</i> <i>aeruginosa</i> )	The activity exhibited by the complexes against bacterial strains was high for <i>P. aeruginosa</i> and insignificant against <i>E. coli</i> . Whereas, a notable antibacterial activity was noted for <i>B. thuringiensis</i> , though remained inactive against <i>S. aureus</i> .	(Lapasam <i>et al.</i> , 2019b)
Ir(III) Ru(III) Rh(III) Ru = Complex (L1) 1, 4, 7 Rh = Complex (L2) 2, 5, 8 Ir = Complex (L3) 3, 6, 9	Mononuclear ( <i>S. aureus</i> , <i>E. coli</i> , <i>K.</i> <i>pneumoniae</i> )	Complex 7 (23 ± 1.16 mm), Complex 9 (21 ± 1.02 mm) for <i>S. aureus</i> . Complex 7 (24 ± 1.25 mm), Complex 4 (23 ± 1.19 mm) against <i>E. coli</i> . Complex 7 (25 ± 1.36 mm), Complex 9 (22 ± 1.06 mm) against <i>K.</i> <i>pneumoniae</i> .	(Kollipara <i>et al.</i> , 2020)
IrHL <sup>1</sup> IrHL <sup>2</sup> IrHL <sup>3</sup>	Binuclear ( <i>E. coli</i> , <i>S. typhi</i> , <i>P.</i> <i>aeruginosa</i> , <i>E. faecalis</i> , <i>S. mutant</i> , <i>S. aureus</i> )	IrHL <sup>2</sup> complex with <i>p</i> -nitro substituent showed the best activity against <i>S.</i> <i>mutant</i> , <i>S. aureus</i> and <i>P. aeruginosa</i> . IrHL <sup>3</sup> complex with <i>p</i> -Cl substituent was more potent for <i>S. mutant</i> . IrHL <sup>1</sup> antibacterial was lower than the parent Schiff base ligand.	(Sarwar <i>et al.</i> , 2021)

as in a set of tetranuclear complexes (Majumdar *et al.*, 2019; Liu *et al.*, 2020).

The structure of the ligands and coordination sites also play significant roles in antimicrobial activities, where similar metal ions with different ligands bearing different coordination sites had displayed different bioactivities in various Ru(III), Rh(III) and Ir(III) complexes (Lapasam *et al.*, 2019a; 2019b; Kollipara *et al.*, 2020).

## CONCLUSION

The study analysis revealed that numerous research was conducted on mononuclear antibacterial Schiff base metal complexes. In comparison to the thorough progress of mononuclear metal complexes, their binuclear counterparts were underexamined and slightly explored. Binuclear complexes, whereby the ligand allows for two metal centres to be attached in the same molecule, constitute a vital criterion in transition metal system analysis compared with mononuclear species as a consequence of tuning the bridging ligands or the two metal centres. In addition, binuclear-azomethine

complexes with two metal centres held in close proximity might allow significant metal-metal interaction that could give rise to unusual spectroscopic properties, which heightened bioactivity unattainable by their mononuclear analogues.

Complexes with higher nuclearity impart increased density of bioactive sites; and thus, enhanced antibacterial activity. The medical fraternity's ongoing struggle concerning increased bacterial resistance to contemporary antibiotics may perhaps be addressed by adopting the strategy of adding metal nuclei in the complexes. The consequent increase of resistant microbes due to misapplication and overutilisation of these medications have jeopardised the efficacy of existing antibiotics, urgently raising need of development of new drugs. This review provided some insights which could be useful.

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## DECLARATION OF INTERESTS

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the paper.

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