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Probing the dynamic thermodynamic resolution and biological activity of Cu(II) and Pd(II) complexes with Schiff base ligand derived from proline

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ABSTRACT

Schiff base metal complexes are of great importance in pharmaceutical science owing to their unique chemical properties, which enable them to exhibit diverse biological activities such as anti-bacterial, anti-oxidant, anti-inflammatory, and anti-tumor properties. Furthermore, Schiff base metal complexes can serve as reagents and catalysts in chemical reactions. This review aims to provide an overview of our recently published studies on Cu(II) and Pd(II) complexes derived from proline Schiff base ligands. We also discuss the potential applications of these metal complexes in the fields of antibacterial and chiral resolution.

1. Introduction

Schiff bases are formed by the condensation of primary amines and aldehydes or ketones and are characterized by a carbon-nitrogen double bond (RCH = NR', where R and R' are alkyl or aryl substituents). Compared with monodentate Schiff bases, bidentate or tridentate Schiff base ligands are more efficient at coordinating with metal ions to form stable chelate metal complexes [1]. The coordination of metal ions with Schiff base nitrogen provides a ubiquitous structural motif in organic chemistry and biology, which has become the focus of many studies due to its flexibility and sensitivity to central metal atoms. Schiff base-metal complexes have numerous applications. For example, they can be used as designer materials [2] and catalysts [3–5] in organic synthesis and as antiviral, cytostatic, antibacterial, anticancer, antimalarial, antidiabetic, and antifungal agents in the pharmaceutical industry [6–12]. In particular, metal complexes of Schiff base derived from amino acids have received significant attention due to their promising applications as chemical reagents and their biological properties [13,14]. This review focuses on a sub-class of square-planar metal complexes with chiral Schiff bases derived from proline. While these complexes are well-known for their use in the asymmetric synthesis [15] of tailor-made amino acids [16], recent studies have revealed interesting data on their biological activity. This article provides an overview of the synthesis and general synthetic applications of Ni(II)-, Cu(II)-, and Pd(II)-complexes, followed by a detailed discussion of their bioactivity.

2. Pharmacological effects of Schiff base metal chelates

2.1. Antibacterial

Schiff base metal complexes have been identified as potential antibacterial and antifungal agents due to their unique chemical structure (Fig. 1).

The antibacterial and antifungal activity of Schiff bases derived from triazole Schiff bases, as well as their V(IV) metal complexes, has been investigated. The findings demonstrated that these substances had significant antibacterial effects at high concentrations on *Escherichia coli*, *Shigella flexenari*, *Pseudomonas aerugi-*

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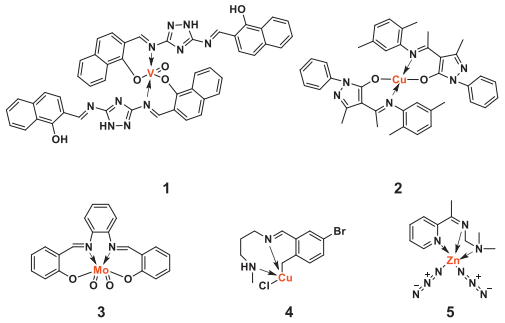


Fig. 1. Structures of Schiff base metal complexes with antibacterial activity.

nosa, *Salmonella typhi*, *Staphylococcus aureus*, and *Bacillus subtilis*. These compounds also have antifungal activity on *Trichophyton longifucus*, *Candida albicans*, *Aspergillus flavus*, *Microscopum canis*, *Fusarium solani*, and *Candida glaberata*. In addition, metal complexes exhibit higher bioactivity than single Schiff base compounds [17]. Binary tetradentate Schiff bases with Mo(VI) complexes have also been reported to inhibit some pathogenic bacteria and fungi [18]. *Staphylococcus aureus* and *Bacillus subtilis*, two Gram-positive bacteria, were significantly inhibited by a novel series of Cu(II) complexes of pyrazolone-based Schiff base ligands. Gram-negative bacteria such as *E. coli* and *Pseudomonas aeruginosa* also showed significant antibacterial activity [19]. Another study found that the bacterial strains *Staphylococcus aureus*, *Bacillus cereus*, *E. coli*, and *Klebsiella pneumoniae* were inhibited by Cu(II) and Zn(II) complexes of NNO donor tridentate Schiff base 4–bromo-2-((methylamino)propyl)imino)methyl)phenol [20]. A series of Zn(II) Schiff base azide complexes displayed potential resistance to *Staphylococcus aureus* in antibacterial assays [21]. The effect of the metal ions on normal cellular processes may be responsible for the antibacterial activity of metal chelates. The chelation theory proposed by Tweedy provides a plausible explanation for how the toxicity of these compounds increases [22]. Through sharing a portion of the positive charge of the metal ion with the donor group and potential electron delocalization within the entire chelate ring system formed during coordination, chelation can significantly reduce the polarity of the metal ion. This chelation can increase the lipophilicity of the central metal atom, increasing the hydrophobicity and liposolubility of the complex and facilitating its passage through the lipid layers of the cell membrane. This process can accelerate the rate of uptake or entry, thereby enhancing the antimicrobial activity of the test compound. Therefore, the antimicrobial activity of the complex and the ability to inactivate other essential cellular enzymes involved in various metabolic pathways of microorganisms, as well as enzymes responsible for respiratory processes, can be attributed to the increased lipophilicity of the complex. Additionally, the action mode of these compounds may involve the formation of a hydrogen bond between the azomethine nitrogen atom and the active centers of cellular constituents, thereby interfering with normal cellular processes. The variation in the effectiveness of different compounds against different organisms may depend on microbial cell ribosome variations and cell wall impermeability [23]. These complexes can also inhibit protein synthesis, interfere with cell respiration, and further limit the growth of the organism.

These findings suggest that Schiff base metal complexes exhibit the potential to serve as effective antibacterial and antifungal agents, and further research in this area is needed.

2.2. Anticancer

Schiff base metal complexes have been widely used in cancer treatment due to their ability to target intracellular regulatory enzymes and nuclear DNA, resulting in cancer cell death *via* apoptosis without affecting normal cell growth (Fig. 2). Various human tumor cell lines, including the breast cancer MCF-7, the liver cancer HepG2, the lung cancer (A549), and the colorectal cancer (HCT116), were used to test the anticancer activity of Schiff base complexes containing thiazole groups. The complexes showed significant inhibition rates in the range from 61% to 80% when compared to untreated cells [24]. The cytotoxicity of complexes of a tridentate Schiff base ligand with Mn(II), Co(II), Ni(II), and Cu(II) on human colon cancer (HCT-116) and breast cancer cell lines (MCF-7) has been reported. The most potent inhibitory activity against both cell lines was demonstrated by Cu(II) complexes, with half maximal inhibitory concentration (IC_{50}) values for HCT-116 and MCF-7 of 52.7 and 61.1 g/mL, respectively [25]. Additionally, a number of Ag(I), Cr(III), Fe(III), Co(II), Cu(II), and Cd(II) complexes of furfural-type Schiff base complexes were reported, and their cytotoxicity on HepG2 cell lines was evaluated. With an IC_{50} value of 1.95 g/mL, the Cd(II) complex demonstrated strong cytotoxic activity, outperforming the well-known anticancer drug vinblastine ($IC_{50} = 2.93$ g/mL) [26].

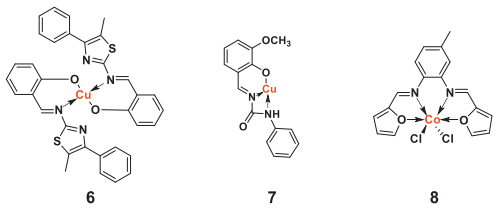


Fig. 2. Structures of Schiff base metal complexes with anticancer activity.

The cytotoxicity of the complexes is considerably higher than that of the free ligand. The observed increase clearly shows that the antiproliferative activity is significantly influenced by the presence of a metal center in the ligand moiety. The increased biological activity of these complexes can be attributed to the coordination between the ligand and the metal ion, which results in a decrease in their polarity *via* charge equilibration. This modification encourages the complexes to pass through the lipid bilayer of the cell membrane, ultimately leading to increased cytotoxicity. The cytotoxic activity of the complexes can also be explained by the chelation theory of Tweedy, which states that the focused metal atom plays a significant role in their biological activity [22]. Consequently, it is evident that changes in the complexation and metal ions have a profound effect on the biological activity of the compound.

2.3. Others

Metal complexes with Schiff base structures have emerged as a versatile class of compounds that exhibit a wide range of biological activities and applications (Fig. 3). A series of Cu(II) complexes with tridentate Schiff base ligands have been reported to exhibit potent antioxidant properties and remarkable free radical scavenging activities [27]. A novel series of Schiff base ligands containing imidazole moieties, along with their Ni(II) and Zn(II) complexes,

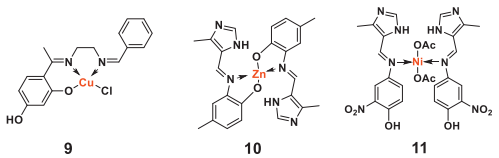


Fig. 3. Structures of Schiff base metal complexes with antioxidant and anti-inflammatory activity.

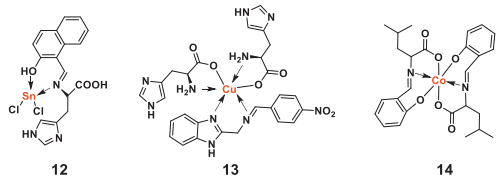


Fig. 4. Structures of amino acid derived Schiff bases and their metal complexes.

showed the antioxidant activity of these compounds, which was assessed through the 1,1-diphenyl-2-trinitrohydrazine (DPPH) technique, revealing comparable antioxidant activity of the Schiff base ligand and some of its metal complexes with the standard product, ascorbic acid. Furthermore, the Zn(II) complex was evaluated for its anti-inflammatory activity using the *in vitro* human red blood cell (HRBC) membrane stabilization method, which demonstrated superior activity in comparison with the positive control drug, diclofenac [28].

3. Antibacterial pharmacological activities of amino acid derived Schiff bases and their metal complexes

Schiff base metal complexes are known for their biological activity, as well as their stability and electron donor ability, which may result from the chelation of Schiff bases and metal ions. Amino acids, with coordination functional groups (-NH_2 and -COOH), can participate in various biological processes and form Schiff bases by condensing with aldehydes or ketones [29]. These Schiff bases can easily coordinate with metal ions, leading to the formation of metal complexes with different pharmacological activities (Table 1).

Amino acid-derived Schiff base metal complexes have significant potential in the field of antibacterial activity (Fig. 4). For instance, Sn(II) complexes of 2–hydroxy-1-naphththaldehyde Schiff base derivatives with L-histidine and sulfamethazine (HNSM) were prepared, and their antibacterial and antifungal efficacy was tested against a variety of bacterial and fungal strains. Two Gram-negative (*Klebsiella pneumoniae* and *E. coli*) and three Gram-positive (*Staphylococcus aureus*, *Staphylococcus epidermidis*, and *Bacillus subtilis*) bacterial strains were used to evaluate the antibacterial activity using the agar-well diffusion method. Using the agar tube dilution method, the antifungal activity was assessed against three fungal strains (*Aspergillus niger*, *Aspergillus flavus*, and *Alternaria solani*). The DPPH-free radical was used to assess the antioxidant activity of the ligands and their complexes. Ligand HNSM displayed exceptional performance in terms of antibacterial activity (22 mm), antifungal activity (55%), and antioxidant activity (119 ppm) [30]. Schiff base complexes of benzimidazoles and L-histidine could exhibit cytotoxic effects on cancer cell lines and are nontoxic to normal lymphocytes [31].

A series of Schiff base derivatives of amino acids were synthesized and coordinated with Co, Mn, Cu, and Cd metals to obtain the corresponding complexes. Using the disk diffusion method, the synthesized ligands and metal complexes were assessed for their antibacterial and antifungal activities against three bacterial strains (*B. sabtilus*, *S. aureus*, and *E. coli*) and three fungal strains (*A. flavus*, *A. alternate*, and *A. niger*), respectively. The findings showed that metal complexes had improved antibacterial and antifungal activities compared to synthesized ligands. The Co(VI) complex demonstrated a maximum antibacterial activity of 11.47 ± 0.8 mm against *B. sabtilus*, while the Co(VI) complex also exhibited the maximum antifungal activity of 14.25 ± 0.96 mm against *A. flavus*. The observed results were compared with the standard drugs rifamipicin and fluconazole, which showed maximum activity at 20 ± 0.2 and 21.7 ± 1.2 mm, respectively [32].

A Schiff base prepared by the condensation of 2-acetylferrocene and L-histidine with Cr(III), Mn(II), Fe(III), Co(II), Ni(II), Cu(II), Zn(II), and Cd(II) was reported to exhibit good inhibitory activity against both Gram-positive and Gram-negative bacteria. The Gram-negative bacterium *S. typhimurium* was tested for antimicrobial activity, and the Co(II) and Zn(II) complexes showed noticeable activity. Meanwhile, the Cd(II) complex exhibited remarkable cellular inhibitory activities with an IC_{50} value of 3.5 μg/mL in the MCF-7 cell line, while exhibiting the highest surviving fraction in the normal cell line [33].

Table 1
Biological activity associated with the reported Schiff base ligands.

No.	Complexes involved in ligand synthesis		Biological activity	Ref.
	(I) Carbonyl group	(II) Amino group		
1	2-Hydroxy-1-naphthaldehyde	3,5-Diamino-1,2,4-triazole	Antibacterial, antifungal and cytotoxic	[17]
2	2-Hydroxyketone	Mono 5-bromosalicylaldehyde-orthophenylenediamine	Antimicrobial	[18]
3	Pyrazolonone	2,5-Dimethylaniline	Antibacterial against *P. aeruginosa*, *S. aureus* and *B. subtilis*	[19]
4	5-Bromosalicylaldehyde	*N*-Methyl-1,3-diaminopropane	Antibacterial against *Bacillus cereus*, *Staphylococcus aureus*, *Klebsiella pneumonia*, *E. coli* and cytotoxic	[20]
5	2-Acetylpyridine	*N*,*N*-Diethylethane-1,2-diamine	Antiproliferative against breast cancer cell MCF-7 and antibacterial	[21]
6	Salicyladehyde	2-Amino-4-phenyl-5-methyl thiazole	Anticancer against HepG2 and MCF-7 cells	[24]
7	*O*-Vanillin	Phenyl urea	Antibacterial and anticancer against human colon carcinoma (HCT-116) and breast carcinoma cells (MCF-7)	[25]
8	2-Furaldehyde	4-Methyl-*o*-phenylenediamine	Antibacterial against *C. albicans*	[26]
9	2′,4′-Dihydroxyacetophenone and benzaldehyde	Ethylenediamine	Antibacterial against *S. aureus*	[27]
10	5-Methyl-imidazole-4-carboxaldehyde	Aromatic amines	Antioxidant, anti-inflammatory and anti-inflammatory	[28]
11	2-Hydroxy-1-naphthaldehyde	L-Histidine	Antimicrobial and antioxidant	[30]
12	Benzimidazole	L-Histidine	Antibacterial, antifungal and cytotoxicity	[31]
13	Salicyldehyde	Leucine	Antibacterial against *B. sabtilus*, *S. aureus* and *E. coli* and antifungal against *A. flavus*	[32]
14	2-Acetylferrocene	L-Histidine	Antimicrobial against *S. typhimurium* and anticancer against MCF7 cell line	[33]

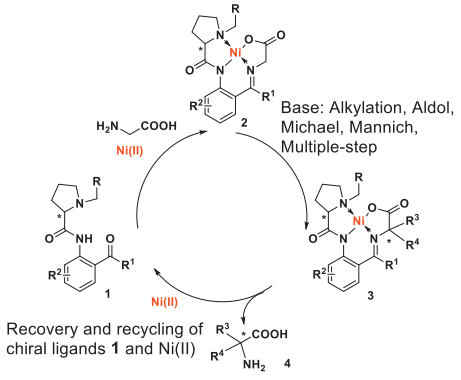
4. Chemical properties, synthesis, and derivatization of Schiff base and Schiff base metal complexes

For most applications, tridentate ligands (*S*)- or (*R*)–**1** are first converted to nucleophilic glycine equivalents **2** (Scheme 1). Both **1** and **2** can be prepared on a kilogram scale under convenient conditions [34,35]. Elaboration of the glycine moiety in **2** can be prepared using such generalized reaction types such as alkyl halide alkylations [36,37], aldol [38], Mannich [39] and Michael [40,41] additions. Furthermore, multiple-step reaction sequences allow for the preparation of several types of more complex cyclic amino acids (AAs) [42,43]. Ni(II) complexes **3** can disassemble under mild acidic conditions, followed by the release of target AAs **4** along with the near-complete recovery of chiral ligands **1** and Ni(II) ions, allowing a new catalytic cycle to proceed [44].

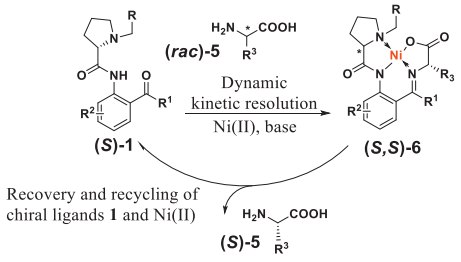
Ligands **1** can also be used for direct reactions with unprotected AAs **5** (Scheme 2) to afford Ni(II) complexes **6**. This approach was shown to be quite efficient for performing deracemization, dynamic kinetic resolution (DKR), or (*S*)/(*R*) interconversion of unprotected tailor-made AAs [45–50].

Reactions of ligands **1** with AAs **5** are conducted under mild basic conditions to afford intermediate Ni(II) complexes **6** with high yields and high diastereoselectivity. As in the case of Scheme 1, compound **6** easily disassembled under acidic conditions to afford highly enantiomerical AAs **5** together with the recovery of chiral ligands **1** and Ni(II). Compared to the literature examples of chemical and even enzymatic DKR of AAs [51–57], the approach of Scheme 2, in which Ni(II) complexes intermediate was formed has numerous advantages, including low cost, operational convenience, and an overall stereochemical outcome.

Consistent with our longstanding general interest in AAs, including the self-disproportionation of enantiomers (SDE) properties [58,59] and synthesis of various types of tailor-made AAs, in particular, sterically constrained [60,61], fluorine- [62,63] and phosphorus-containing [64,65] derivatives, we are actively exploring DKR of AAs *via* Ni(II) complexes [45-50,66-68] as a potentially scalable method for the preparation of tailor-made AAs of pharmaceutical interest. Over the years, several chiral ligands **7**–**13** (Fig. 5) have been introduced to be used for the general applications (Scheme 1) as well as the DKR (Scheme 2) of AAs.



Scheme 1. General application of ligands of type **1** for asymmetric synthesis of tailor-made amino acids™ *via* Ni(II)-complex methodology.



Scheme 2. DKR of amino acids using ligands of type **1**.

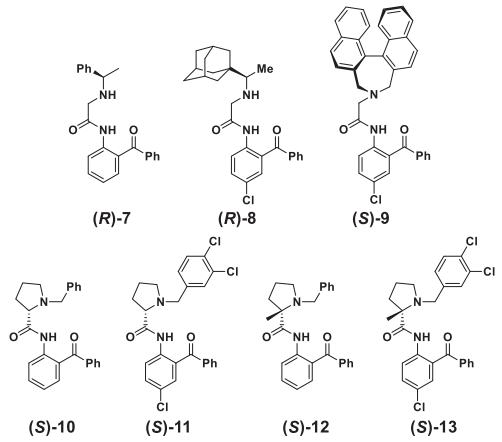


Fig. 5. Chiral ligands used in the literature for the DKR of AAs (ligands **7**–**13** are available in both (*S*) and (*R*) configurations).

All these chiral Schiff base ligands form stable complexes with Ni(II), Cu(II) and Pd(II), providing a wealth of structural variety for future synthetic and biological applications. So far, only complexes derived from ligand **11** have been reported with biological data, which will be discussed in detail in the following sections.

5. Pharmacological activities of Cu(II) and Pd(II) proline Schiff base chelates in antibacterial activities

Bacterial infections remain a major public health concern and pose a serious threat to human health. Bacterial infections primarily arise from the invasion and proliferation of pathogenic bacteria within the human body. These bacteria induce diseases by attaching to host cell surfaces, releasing toxins, inducing inflammatory responses, and impairing the host's immune system. The treatment of bacterial infections often involves a combination of drug therapy and supportive measures. Pharmacotherapy, which encompasses the use of antibiotics, antimicrobials, and other anti-infective agents, serves as the primary treatment modality. Antibiotics, in particular, are widely employed medications that impede the biological functions of bacteria, inhibiting their growth and reproduction. However, the abuse of antibiotics has led to the emergence and spread of multidrug resistance, which severely threatens public health and has resulted in a sharp increase in the global incidence rate and mortality [69–71]. Given the current clinical demand for new antibacterial agents, there is an urgent need to develop alternative treatment approaches, such as metal drugs [72–74]. Metal complexes can reduce the polarity of metal ions during the chelation process, which increases the lipophilicity of the complex by improving electron delocalization on the chelating ring. Unlike most antibacterial drugs that exert their effects through a single mechanism, metal complexes exhibit antibacterial effects through multiple pathways, such as penetration of bacterial cell membranes, causing enzyme inhibition and active oxygen generation, inducing cell cycle arrest, and intracellular biomolecular interactions [75].

Cu(II) increases intracellular reactive oxygen species (ROS) production by catalytically forming hydroxyl radicals in the body or through thiol-mediated reduction of Cu(II) *via* intermediate S radical chemistry [76–78]. The combination of Cu(II) and quaternary ammonium cations has synergistic bactericidal and antifungal activity against *Pseudomonas aeruginosa* [79]. In this study, the au-

Table 2
Biological activity associated with the reported Schiff base ligands.

Compd.	MIC (μg/mL)[a]	Compd.	MIC (μg/mL)[a]
(*S*,*S*)–**3a**	2	(*S*,*S*)–**3l**	>128
(*S*,*S*)–**3b**	16	(*S*,*S*)–**3m**	32
(*S*,*S*)–**3c**	>128	(*S*,*S*)–**3n**	>128
(*S*,*S*)–**3d**	>128	(*S*,*S*)–**3o**	8
(*S*,*S*)–**3e**	>128	(*S*,*S*)–**3p**	>128
(*S*,*S*)–**3f**	32	(*S*,*S*)–**3q**	>128
(*S*,*S*)–**3g**	4	(*S*,*S*)–**3r**	>128
(*S*,*S*)–**3h**	>128	(*S*,*S*)–**3s**	>128
(*S*,*S*)–**3i**	16	Ligand (*S*)–**1**	>128
(*S*,*S*)–**3j**	>128	$CuSO_4$	>128
(*S*,*S*)–**3k**	32	Vancomycin	4

[a] MIC values of the compounds were the lowest concentration to inhibit *Staphylococcus aureus* Mu50 growth completely.

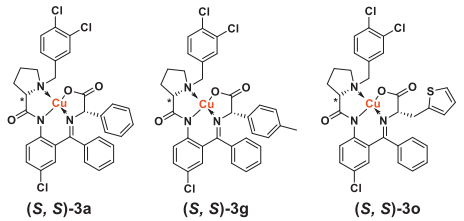


Fig. 6. Antibacterial active compounds (*S*,*S*)–**3a**, (*S*,*S*)–**3g**, and (*S*,*S*)–**3o**.

thors investigated the biological activities of transition metal complexes with proline-derived Schiff base ligands, including novel Cu(II) complexes [80].

Using vancomycin as a positive control, the authors examined the antibacterial efficacy activity of Cu(II) complexes against the multidrug-resistant *Staphylococcus aureus* Mu50. The findings revealed that the unmodified benzene ring exhibited superior antibacterial efficacy, while the incorporation of electron donor and acceptor moieties onto the ring resulted in a reduction of the chelate's antibacterial activity. Furthermore, the presence of the thiophene ring also exhibited favorable retention of antibacterial properties. Notably, when the substituent comprised an aliphatic chain, a substantial decline in antibacterial activity was observed. Compounds (*S*,*S*)–**3a**, (*S*,*S*)–**3g**, and (*S*,*S*)–**3o** showed excellent antibacterial potential, with minimum inhibitory concentrations (MIC) values of 2–8 μg/mL. Compound (*S*,*S*)–**3a** had a 2-fold greater inhibitory effect on *Staphylococcus aureus* Mu50 growth when compared to vancomycin, and compound (*S*,*S*)–**3g** had comparable antibacterial activity. However, *Staphylococcus aureus* Mu50 was not significantly inhibited by the ligands (*S*)–**1** or $CuSO_4$ alone (Table 2).

Subsequently, the antimicrobial spectrum of the Cu(II) complexes (*S*,*S*)–**3a**, (*S*,*S*)–**3g**, and (*S*,*S*)–**3o** (Fig. 6) exhibiting potent inhibitory activity against *Staphylococcus aureus* Mu50 was screened against several bacterial strains, including Gram-positive bacteria such as *S. aureus* Newman, *Streptococcus pyogenes* ATCC 12344, *E. coli Efm*-HS-0649, and *Bacillus subtilis* CMCC 63501, as well as Gram-negative bacteria such as *Burkholderia cepacian* and *E. coli* AB1157. The Cu(II) complexes displayed significant antibacterial activity against most Gram-positive bacteria, except for *E. coli Efm*-HS-0649, while exhibiting negligible inhibitory effects against the Gram-negative bacteria *Burkholderia cepacia* and *E. coli* AB1157 (Table 3). The results indicated that the antimicrobial activity of the compounds is related to the cell wall structure of the bacteria. Specifically, Gram-positive bacteria are more vulnerable to antibiotics that prevent the synthesis of peptidoglycan due to their thick cell wall, which is made up of multiple layers of teichoic acids and peptidoglycan. On the other hand, the cell wall of gram-negative bacteria is comparatively thin and consists of just a few layers of peptidoglycan that are encircled by a second lipid membrane that contains lipoproteins and lipopolysaccharides. Due to these structural variations in the cell wall, some antibiotics are only effective against Gram-positive bacteria, which can affect their susceptibility to infection. Solubility, the presence of larger organic moieties, conductivity, and the length of the bond between the metal and the ligand are additional elements that can affect activity. The effective positive charge on the metal complex is said to be reduced by the higher electronegativity and larger atomic radius, increasing the antimicrobial activity [81]. Based on the initial assessment of biological activity, these Cu(II) complexes can serve as promising lead compounds for the development of antibacterial Cu(II) complexes.

Pd(II) complexes, as transition metal complexes, have received significant attention due to their considerable biological activity, lower side effects, and higher lipophilicity or solubility compared to their homologous element, Pt(II) [82,83]. Owing to its unique property as soft Lewis acids, Pd(II) tends to form bonds of enhanced strength with soft bases, particularly nitrogen or sulfur donors, as opposed to hard bases such as oxygen donors. The Pd(II)-putrescine complex has been demonstrated as a prospective agent for anticancer therapy [84]. It is reported that the Pd(II) complex with benzyl bis(thiosemicarbazone) exhibited antibacterial activity against a wide range of microorganisms, including *E. coli*, *Klebsiella pneumoniae*, *Proteus mirabilis*, *Pseudomonas aeruginosa*, *S. typhimurium*, *Shigella flexneri*, *Staphylococcus aureus*, *Staphylococcus epidermidis*, and *Candida albicans* [85]. These findings suggest that the potential of Pd(II)-based compounds as therapeutic agents is highly dependent on the nature of the ligands employed and their mode of interaction with the target cells. Further investigations are warranted to elucidate the mechanism of the observed activities and to optimize the design of Pd(II)-based complexes for enhanced therapeutic efficacy. Therefore, the investigation of the biological evaluation of Pd(II) complexes has attracted increasing attention [86–89].

The authors have reported the development of a chiral proline derivative ligand coordinated with Pd(II) to synthesize Pd(II) complexes, and evaluated their antibacterial activity against *Staphylo-*

Table 3
Antibacterial activities of the representative Cu(II) complexes against different Gram-positive and Gram-negative bacterial strains.

Bacterial strains	MIC (μg/mL)				
	(*S*,*S*)–**3a**	(*S*,*S*)–**3g**	(*S*,*S*)–**3o**	$CuSO_4$	Vancomycin
S. aureus Newman[a]	8	8	16	>128	2
Streptococcus pyogenes ATCC 12344[a]	2	0.5	8	>128	0.5
E. faecium Efm-HS-0649[a]	>128	>128	>128	>128	>128
Bacillus subtilis CMCC 63501[a]	8	8	16	>128	0.25
Burkholderia cepacia[b]	>128	>128	>128	>128	>128
E. coli AB1157[b]	>128	>128	>128	>128	>128

[a] Gram-positive bacterium.
[b] Gram-negative bacterium.

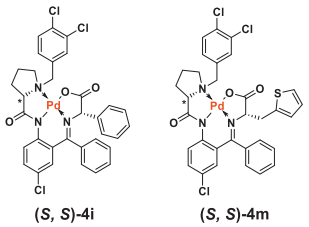


Fig. 7. Antibacterial active compounds (*S*,*S*)–**4i** and (*S*,*S*)–**4m**.

Table 4
In vitro antibacterial activities against *S. aureus* Mu50 of the Pd(II) complexes.

Compd.	MIC (μg/mL)[a]	Compd.	MIC (μg/mL)[a]
(*S*,*S*)–**4a**	>256	(*S*,*S*)–**4o**	>256
(*S*,*S*)–**4b**	>256	(*S*,*S*)–**4p**	16
(*S*,*S*)–**4c**	>256	(*S*,*S*)–**4q**	>256
(*S*,*S*)–**4d**	>256	(*R*,*R*)–**4a**	>256
(*S*,*S*)–**4e**	>256	(*R*,*R*)–**4e**	>256
(*S*,*S*)–**4f**	>256	(*R*,*R*)–**4g**	>256
(*S*,*S*)–**4g**	16	(*R*,*R*)–**4m**	>256
(*S*,*S*)–**4h**	>256	(*R*,*R*)–**4n**	16
(S,S)–**4i**	8	(*R*,*R*)–**4r**	16
(*S*,*S*)–**4j**	>256	(*R*,*R*)–**4s**	256
(*S*,*S*)–**4k**	>256	Ligand (*S*)–**1**	>256
(*S*,*S*)–**4l**	>256	$Pd(OAc)_2$	>256
(*S*,*S*)–**4m**	8	Vancomycin·HCl	8
(*S*,*S*)–**4n**	16		

[a] MIC values of these compounds were the lowest concentration to inhibit *S. aureus* Mu50 growth completely.

Table 5
In vitro activities of Pd(II) complexes (*S*,*S*)–**4i** and (*S*,*S*)–**4m** against different bacterial strains.

Bacterial strain	MIC (μg/mL)		
	(*S*,*S*)–**4i**	(*S*,*S*)–**4m**	Vancomycin·HCl
Newman[a]	32	32	2
USA300[b]	4	8	1
NRS271[c]	16	16	1

[a] A strain of vancomycin-susceptible methicillin-sensitive *S. aureus* (MSSA).
[b] A strain of community-associated methicillin-resistant *S. aureus* (MRSA).
[c] A strain of methicillin- and linezolid-resistant *S. aureus* (MRSA/LRSA).

coccus aureus Mu50, using vancomycin as the positive control [90]. The assessment of the antibacterial potential of Pd(II) complexes revealed an association between their inhibitory efficacy and the structural attributes of the Pd(II) complexes. Specifically, the presence of electron-donating benzene rings, thiophene rings, and specific aliphatic chains such as methyl or allyl displayed prominent antibacterial activity. Notably, Pd(II) complexes (*S*,*S*)–**4i** and (*S*,*S*)–**4m** (Fig. 7) demonstrated the strongest inhibitory activity against Staphylococcus aureus Mu50, with a MIC value of 8 μg/mL, equivalent to vancomycin. Moreover, Pd(II) complexes (*S*,*S*)–**4g**, (*S*,*S*)–**4n**, (*S*,*S*)–**4p**, (*R*,*R*)–**4n**, and (*R*,*R*)–**4r** also exhibited significant antibacterial activity, with a MIC value of 16 μg/mL. The configuration of the compound was found not to be a determinant of antibacterial activity, as demonstrated by the antibacterial activity of complexes (*S*,*S*)–**4g**, (*R*,*R*)–**4g**, (*S*,*S*)–**4n**, and (*R*,*R*)–**4n** (Table 4). Further evaluation of Pd(II) complexes (*S*,*S*)–**4i** and (*S*,*S*)–**4m** against three sensitive and resistant *Staphylococcus aureus* strains (Newman, USA271, and NRS4) revealed a broad antibacterial spectrum, with MIC values ranging from 4 μg/mL to 32 μg/mL (Table 5). The antibacterial activity of the Pd(II) complexes could be attributed to metal chelation, which reduces the polarity of metal ions, and π electron delocalization throughout the chelating ring system formed during coordination. Chelation also enhances the lipophilicity of the central metal atom, thereby increasing the hydrophobicity and lipophilicity of the complex, facilitating its penetration to the lipid layer of the cell membrane, improving the absorption rate of the compound, and enhancing its antibacterial activity. These findings demonstrate the potential of Pd(II) complexes as antibacterial agents, particularly in vancomycin-resistant superbacteria. Further research is warranted to fully characterize the activity and mechanism of action of Pd(II) complexes.

6. Conclusion and outlook

Schiff base metal complexes have attracted significant attention in the field of antibacterial research due to their potential in the fight against antibiotic-resistant bacterial infections. These complexes are formed by the reaction of a Schiff base ligand with a metal ion, resulting in a stable coordination compound that exhibits unique chemical and biological properties. Numerous studies have investigated the antibacterial activity of Schiff base metal complexes, with promising results. *In vitro* studies have demonstrated that these complexes possess potent antibacterial activity against a range of pathogenic bacteria, including Gram-positive and Gram-negative strains. The Schiff base metal complexes are thought to be capable of rupturing bacterial cell membranes and inhibiting enzymatic activity, which would result in cell death. In the corresponding study, the authors present a novel series of Cu(II) and Pd(II) complexes derived from proline Schiff base ligands that have demonstrated high efficacy in α-dynamic thermodynamic resolution of amino acids with excellent yield and enantioselectivity. Additionally, the potential antibacterial ability of these metal complexes was evaluated on bacterial strains, including *Staphylococcus aureus*. The findings reveal the remarkable inhibitory activity of the synthesized compounds against *S. aureus*, highlighting the potential of these complexes as effective antibacterial agents. To enhance the antibacterial efficacy of Schiff base metal complexes, a promising strategy is to investigate drug combinations of these complexes with established antibacterial agents. This approach may enable more effective combat against bacterial infections by utilizing different mechanisms of action, thereby addressing the challenge of antibiotic resistance while enhancing overall antibacterial activity.

In conclusion, Schiff base metal complexes possess significant antibacterial activity and offer exciting prospects for the development of novel antibacterial agents. Considering the increasing prevalence of antibiotic-resistant bacterial infections, it is urgent to develop novel antibacterial agents, and Schiff base metal complexes may become a promising strategy in the future.

Declaration of competing interest

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

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References

[1] P.A. Vigato, S. Tamburini, Coord. Chem. Rev. 248 (2004) 1717–2128.
[2] F.A. Almashal, M.Q. Mohammed, Q.M.A. Hassan, et al., Opt. Mater. 100 (2020) 109703.

[3] M.W. Khan, B. Patel, K. Channani, S. Patel, R. Mishra, Int. J. Eng. Sci. 9 (2021) 56–63.
[4] Z.R. Dai, C.F. Yin, C. Wang, J.C. Wu, Chin. Chem. Lett. 27 (2016) 1649–1654.
[5] S. Peng, X. Ouyang, Y. Wang, et al., Chin. Chem. Lett. 34 (2023) 108044.
[6] S.H. Sumrra, M. Ibrahim, S. Ambreen, et al., J. Drug Des. Med. Chem. 2 (2016) 26–34.
[7] V. Ambike, S. Adsule, F. Ahmed, et al., J. Inorg. Biochem. 101 (2007) 1517–1524.
[8] B.S. Sathe, E. Jaychandran, V.A. Jagtap, G.M. Sreenivasa, Int. J. Pharm. 3 (2011) 164–169.
[9] D. Mahendiran, R.S. Kumar, V. Viswanathan, D. Velmurugan, A.K. Rahiman, Dalton Trans. 45 (2016) 7794–7814.
[10] M. Azarkish, T. Sedaghat, Chin. Chem. Lett. 23 (2012) 1063–1066.
[11] T. Sedaghat, R. Habibi, H. Motamedi, H.R. Khavasi, Chin. Chem. Lett. 23 (2012) 1355–1358.
[12] J.W. Zheng, L. Ma, Chin. Chem. Lett. 27 (2016) 283–286.
[13] O.Z. Ozdemir, P. Gurkan, B. Ozcelik, O. Oyard, J. Mol. Struct. 1106 (2016) 181–191.
[14] P.A. Reddy, M. Nethaji, A.R. Chakravarty, Eur. J. Inorg. Chem. 2004 (2004) 1440–1446.
[15] Y. Wang, X. Song, J. Wang, et al., Amino Acids 49 (2017) 1487–1520.
[16] V.A. Soloshonok, C. Cai, V.J. Hruby, L.V. Meervelt, Tetrahedron 55 (1999) 12045–12058.
[17] Z.H. Chohan, S.H. Sumrra, M.H. Youssoufi, T.B. Hadda, Eur. J. Med. Chem. 45 (2010) 2739–2747.
[18] M.N. Uddin, D.A. Chowdhury, N. Mase, et al., J. Coord. Chem. 71 (2018) 3874–3892.
[19] E.B. Poormohammadi, M. Behzad, Z. Abbasi, S.D.A. Astaneh, J. Mol. Struct. 1205 (2020) 127603.
[20] M. Jayendran, P.S. Begum, M.P. Kurup, J. Mol. Struct. 1206 (2020) 127682.
[21] M. Das, A. Biswas, B.K. Kundu, et al., Chem. Eng. J. 357 (2019) 447–457.
[22] B.G. Tweedy, Phytopathology 55 (1964) 910–914.
[23] A.A. El-Sherif, M.M. Shoukry, M.M. Abd-Elgawad, Spectrochim. Acta A: Mol. Biomol. Spectrosc. 98 (2012) 307–321.
[24] M.M. Abd-Elzaher, A.A. Labib, H.A. Mousa, et al., Beni-Suef Univ. J. Basic Appl. Sci. 5 (2016) 85–96.
[25] A.M. Hassan, A. Osman, B.H. Heakal, et al., Adv. J. Chem. Sect. A 3 (2020) 621–638.
[26] B.A. Ismail, D.A. Nassar, Z.H. Abd El-Wahab, O.A. Ali, J. Mol. Struct. 1227 (2021) 129393.
[27] I.P. Ejidike, Molecules 23 (2018) 1581.
[28] G.A. Krishna, T.M. Dhanya, A.A. Shanty, K.G. Raghu, P.V. Mohanan, J. Mol. Struct. 1274 (2023) 134384.
[29] T. Ma, J. Xu, Y. Wang, et al., J. Inorg. Biochem. 144 (2015) 38–46.
[30] N. Neelofar, N. Ali, A. Khan, et al., Bull. Chem. Soc. Ethiop. 31 (2017) 445–456.
[31] G. Kumaravel, P.P. Utthra, N. Raman, Bioorg. Chem. 77 (2018) 269–279.
[32] M. Pervaiz, I. Ahmad, M. Yousaf, et al., Spectrochim. Acta A Mol. Biomol. Spectrosc. 206 (2019) 642–649.
[33] W.H. Mahmoud, M.M. Omar, F.N. Sayed, G.G. Mohamed, Appl. Organomet. Chem. 32 (2018) e4386.
[34] T.K. Ellis, H. Ueki, T. Yamada, Y. Ohfune, V.A. Soloshonok, J. Org. Chem. 71 (2006) 8572–8578.
[35] V.A. Soloshonok, H. Ueki, T.K. Ellis, T. Yamada, Y. Ohfune, Tetrahedron Lett. 46 (2005) 1107–1110.
[36] V.A. Soloshonok, X. Tang, V.J. Hruby, L.V. Meervelt, Org. Lett. 3 (2001) 341–343.
[37] X. Tang, V.A. Soloshonok, V.J. Hruby, Tetrahedron Asymmetry 11 (2000) 2917–2925.
[38] V.A. Soloshonok, D.V. Avilov, V.P. Kukhar, et al., Tetrahedron Asymmetry 6 (1995) 1741–1756.
[39] V.A. Soloshonok, D.V. Avilov, V.P. Kukhar, L.V. Meervelt, N. Mischenko, Tetrahedron Asymmetry 38 (1997) 4671–4674.
[40] C. Cai, V.A. Soloshonok, V.J. Hruby, J. Org. Chem. 66 (2001) 1339–1350.
[41] V.A. Soloshonok, C. Cai, V.J. Hruby, Tetrahedron Asymmetry 10 (1999) 4265–4269.
[42] T. Yamada, T. Okada, K. Sakaguchi, et al., Org. Lett. 8 (2006) 5625–5628.
[43] V.A. Soloshonok, A.E. Sorochinsky, Synthesis 14 (2010) 2319–2344.
[44] V.A. Soloshonok, H. Ueki, R. Tiwari, C. Cai, V.J. Hruby, J. Org. Chem. 69 (2004) 4984–4990.
[45] V.A. Soloshonok, T.K. Ellis, H. Ueki, T. Ono, J. Am. Chem. Soc. 131 (2009) 7208–7209.
[46] R. Takeda, A. Kawamura, A. Kawashima, et al., Angew. Chem. Int. Ed. 53 (2014) 12214–12217.
[47] Y. Nian, J. Wang, S. Zhou, et al., Angew. Chem. Int. Ed. 54 (2015) 12918–12922.
[48] S. Zhou, J. Wang, X. Chen, et al., Angew. Chem. Int. Ed. 53 (2014) 7883–7886.
[49] A.E. Sorochinsky, H. Ueki, J.L. Acena, et al., Org. Biomol. Chem. 11 (2013) 4503–4507.
[50] A.E. Sorochinsky, J.L. Acena, H. Moriwaki, T. Sato, V.A. Soloshonok, Amino Acids 45 (2013) 1017–1033.
[51] S.M. So, H. Kim, L. Mui, J. Chin, Eur. J. Org. Chem. 45 (2012) 229–241.
[52] P. D'Arrigo, L. Cerioli, S. Servi, F. Viani, D. Tessaro, Catal. Sci. Technol. 2 (2012) 1606–1616.
[53] P.D. Arrigo, L. Cerioli, A. Fiorati, et al., Tetrahedron Asymmetry 23 (2012) 938–944.
[54] M.M. Musa, Chirality 32 (2020) 147–157.
[55] V. Bhat, E.R. Welin, X. Guo, B.M. Stoltz, Chem. Rev. 117 (2017) 4528–4561.
[56] J. Chin, S.S. Lee, K.J. Lee, S. Park, D.H. Kim, Nature 401 (1999) 254–257.
[57] S.M. So, K. Moozeh, A.J. Lough, J. Chin, Angew. Chem. Int. Ed. 53 (2014) 829–832.
[58] A.E. Sorochinsky, T. Katagiri, T. Ono, et al., Chirality 25 (2013) 365–368.
[59] J. Han, O. Kitagawa, A. Wzorek, K.D. Klika, V.A. Soloshonok, Chem. Sci. 9 (2018) 1718–1739.
[60] W. Qiu, X. Gu, V.A. Soloshonok, M.D. Carducci, V.J. Hruby, Tetrahedron Lett. 42 (2001) 145–148.
[61] P. Bravo, S. Capelli, S.V. Meille, et al., Tetrahedron Asymmetry 5 (1994) 2009–2018.
[62] P. Bravo, A. Farina, V.P. Kukhar, et al., J. Org. Chem. 62 (1997) 3424–3425.
[63] V.A. Soloshonok, T. Hayashi, Tetrahedron Asymmetry 5 (1994) 1091–1094.
[64] G. Roschenthaler, V.P. Kukhar, I.B. Kulik, et al., Tetrahedron Lett. 53 (2012) 539–542.
[65] K.V. Turcheniuk, K.O. Poliashko, V.P. Kukhar, et al., Chem. Commun. 48 (2012) 11519–11521.
[66] S. Wang, S. Zhou, J. Wang, et al., J. Org. Chem. 80 (2015) 9817–9830.
[67] Y. Nian, J. Wang, S. Zhou, et al., J. Org. Chem. 81 (2016) 3501–3508.
[68] S. Zhou, S. Wang, J. Wang, et al., Eur. J. Org. Chem. 2018 (2018) 1821–1832.
[69] T.M. Rawson, R.C. Wilson, D. Ohare, et al., Nat. Rev. Microbiol. 19 (2021) 747–758.
[70] B.M. Kuehn, JAMA Netw. Open 324 (2020) 223-223.
[71] C. Nathan, Nat. Rev. Microbiol. 18 (2020) 259–260.
[72] K.D. Mjos, C. Orvig, Chem. Rev. 114 (2014) 4540–4563.
[73] A.T. Fiori-Duarte, R.E.F. de Paiva, C.M. Manzano, W.R. Lustri, P.P. Corbi, J. Mol. Struct. 1214 (2020) 128158.
[74] D.H. Nakahata, R.E. de Paiva, W.R. Lustri, P.P. Corbi, New J. Chem. 44 (2020) 17236–17244.
[75] K.K.W. Lo, Inorganic and Organometallic Transition Metal Complexes With Biological Molecules and Living Cells, Academic Press, Hong Kong, 2017.
[76] L. Macomber, C. Rensing, J.A. Imlay, J. Bacteriol. 189 (2007) 1616–1626.
[77] M. Valko, C. Rhodes, J. Moncol, M.M. Izakovic, M. Mazur, Chem. Biol. Interact. 160 (2006) 1–40.
[78] J.A. Lemire, J.J. Harrison, R.J. Turner, Nat. Rev. Microbiol. 11 (2013) 371–384.
[79] J.J. Harrison, R.J. Turner, D.A. Joo, et al., Antimicrob. Agents Chemother. 52 (2008) 2870–2881.
[80] H. Zhu, J. Wang, Y. Lu, et al., J. Org. Chem. 87 (2022) 12900–12908.
[81] T. Rosu, E. Pahontu, C. Maxim, et al., Polyhedron 29 (2010) 757–766.
[82] E. Gao, C. Liu, M. Zhu, et al., Anti-Cancer Agents Med. Chem. 9 (2009) 356–368.
[83] K.S. Prasad, L.S. Kumar, S. Chandan, R.N. Kumar, H.D. Revanasiddappa, Spectrochim. Acta A Mol. Biomol. Spectrosc. 107 (2013) 108–116.
[84] C. Navarro-Ranninger, F. Zamora, J.R. Masaguer, et al., J. Inorg. Biochem. 52 (1993) 37–49.
[85] I. Kizilcikli, Y.D. Kurt, B. Akkurt, et al., Folia Microbiol. 52 (2007) 15–25.
[86] A. Garoufis, S.K. Hadjikakou, N. Hadjiliadis, Coord. Chem. Rev. 253 (2009) 1384–1397.
[87] S. Ray, R. Mohan, J.K. Singh, et al., J. Am. Chem. Soc. 129 (2007) 15042–15053.
[88] M. Azam, I. Warad, S.I. Al-Resayes, et al., J. Mol. Struct. 1047 (2013) 48–54.
[89] A.M. Mansour, O.R. Shehab, Dalton Trans. 47 (2018) 3459–3468.
[90] H. Zhu, J. Wang, Y. Lu, et al., J. Org. Chem. 88 (2023) 3808–3821.