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Chirality in metal-based antimicrobial agents: a growing frontier in biomedical research

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Chirality is increasingly being recognised as a valuable tool in the design of novel metal complexes aimed at combating antimicrobial resistance. Chiral metal complexes possess unique spatial configurations that enable selective interactions with biological targets, providing innovative solutions for treating diseases such as cancer and antimicrobial-resistant infections. Although the relationship between the chirality of metal complexes and their antimicrobial activity was initially highlighted by Dwyer and collaborators in a seminal mid-20th-century study, subsequent research exploring this intriguing relationship has been limited. The few documented cases of enantiomer-dependent biocidal activity are mainly limited to a series of chiral silver complexes recently investigated by our group and the Nomiya research team, which demonstrate enhanced antimicrobial efficacy of specific enantiomers.

Introduction

Antimicrobial resistance (AMR) is a global health crisis, often referred to as a "silent pandemic".[1–3] AMR occurs when microorganisms, including bacteria,[4] viruses, fungi,[5] and parasites, evolve to resist the effects of antimicrobial drugs, making treatments ineffective. Several factors have contributed to the rapid development and spread of antimicrobial resistance, including (i) a lack of public awareness about antibiotics, resulting in overuse or misuse of antibiotics, (ii) the misuse of antibiotics to improve production in the livestock sector, (iii) the natural process of evolution of bacterial resistance to antibiotics, and (iv) the low interest in antibiotic development within the pharmaceutical industry. Therefore, a major current challenge for public health is the development and implementation of new effective strategies to reduce the emergence and spread of antimicrobial resistance. In this sense, inorganic medicinal chemistry can offer an alternative approach to current treatments based on conventional organic drugs through the design of therapies with the ability to target different biochemical pathways. Metal-based agents, particularly in the fields of antimicrobial and anticancer research, represent a rapidly growing area of study with immense potential to address some of the most pressing challenges in modern medicine. These compounds leverage the unique spatial arrangements of their ligands or metal centres to selectively interact with biological targets, offering innovative solutions for combating diseases such as cancer and antimicrobial-resistant infections.[6]

Although the mechanisms of action of conventional organic antibiotics are very varied,[7] it is important to highlight that there are a significant number of them that require metal ions for their correct biological activity, such as bleomycin, which operates through an Fe(II)-dependent DNA cleavage mechanism, or bacitracin, which acts by disrupting cell wall synthesis *via* Zn(II) coordination.[8] The term "metalloantibiotic" has been coined to describe these metal ion-dependent antibiotics, whose bioactivity is carried out through interactions with a variety of biomolecules, including DNA, RNA, proteins, lipids and receptors. The meaning of the term "metalloantibiotic" has recently expanded to include, more generally, all metal complexes that exhibit antibacterial ability. Additionally, the incorporation of chirality into these metalloantibiotics could further enhance their potential, as chiral compounds can exhibit enantiomer-specific interactions with biological targets, potentially overcoming resistance mechanisms.

Chirality, the geometric property of molecules that are non-superimposable on their mirror images, is a fundamental concept in chemistry and biology. Chirality is also an important tool in modern drug development, since molecular recognition of chiral biological targets can provide insight into the design of new active drugs. Thus, drugs derived from natural sources, either directly or after laboratory modification, are usually found only as a single enantiomer rather than as a racemate. In contrast, synthetic chiral drugs are typically produced in their racemic form, which involves chemical waste generation due to synthesising and administering an enantiomer (distomer) that does not fulfill its intended purpose, and sometimes the presence of the distomer in a racemic mixture

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impairs the body's ability to properly utilise the eutomer or even has undesirable pharmacological effects. A notable example is thalidomide, a sedative drug that was released in Europe in 1956 but withdrawn from the market in the 1960s due to the teratogenic effects of the distomeric isomer.[9]

In the context of metal-based drugs, chirality has emerged as a critical factor influencing their biological activity, selectivity, and therapeutic efficacy. Chiral metal-based agents, particularly in the fields of antimicrobial and anticancer research, represent a rapidly growing area of study with immense potential to address some of the most pressing challenges in modern medicine. Chiral configurations can influence the pharmacodynamic, pharmacokinetic, and toxicological properties of drugs, often leading to enantiomer-dependent biological behaviour.

Chirality in metal coordination complexes can manifest in three main ways: (1) chiral-at-metal complexes through an asymmetric arrangement of ligands around the metal center, which is commonly observed in octahedral and tetrahedral complexes,[10–12] (2) the common metal-plus-chiral-ligand approach in which the presence of a chiral ligand transfers the chirality to the complex,[13] and more recently (3) by the existence of atropisomerism due to hindered rotation around a linear L–M–L bond.[14]

In the field of cancer research, chirality has proven to be a decisive factor in determining the efficacy of metal-based drugs.[15–21] This can be exemplified by oxaliplatin,[19] a platinum-based anticancer drug containing the chiral ligand (*R*,*R*)-cyclohexane-1,2-diamine. Oxaliplatin exhibits significantly higher biological activity than its enantiomer with the (*S*,*S*)-configuration, underscoring the importance of chirality in drug design. In contrast, the potential of enantiomerically pure metal complexes as antimicrobial agents has hardly been explored, despite early work in the middle of the last century by Dwyer *et al.*, in which a chirality–biocidal activity relationship was demonstrated.[22]

To the best of our knowledge, there are few examples reported in the literature in which the chirality–bactericidal activity relationship of chiral metalloantibiotics is studied. Examples are limited to some Ru,[23,24] Cu,[25] Au[26] and, most frequently, Ag complexes, among which are our recent studies, which will be described in more detail below.

Antimicrobial properties of chiral silver complexes

In recent years, we have been interested in the use of ionic liquids, based on the imidazolium moiety, as solvents in homogeneous catalysis.[27–29] For this reason, the report of amino acid-based ionic liquids, wherein those derived from the D-enantiomeric amino acid exhibited superior antibacterial properties in comparison with their L-enantiomer counterpart, garnered our interest.[30] Subsequently, we became interested in the use of chiral amino acid-derived imidazolium carboxylate ligands as chiral inductors in molybdenum asymmetric catalysis[31,32] or, alternatively, as ligands in coordination polymers of zinc, copper and silver.[33,34] The extension of this research to silver metal prompted us to explore the antimicrobial behaviour of these complexes and to analyse whether the chirality of the complex influences its biocidal behaviour, as was previously described for amino acid-based ionic liquids and poly(ionic liquid) membranes.[30] The complexes $[Ag(L^R)]_n$ (L^R = 2,2′-(imidazolium-1,3-diyl)di(2-*alkyl*acetate), Scheme 1) were prepared by reacting compounds HL^R

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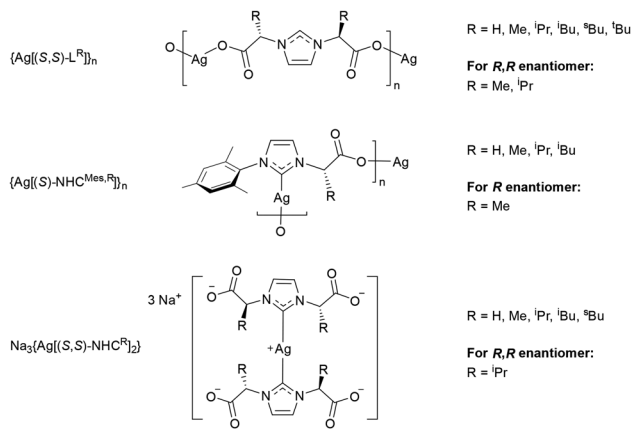

Scheme 1 Silver complexes with antimicrobial activity investigated by our group.[35,47,48]

with Ag_2O and they were characterized, in the solid state, as novel one-dimensional or two-dimensional coordination polymers.[35] The antimicrobial behaviour of these silver complexes was investigated *versus* Gram-negative and Gram-positive bacteria. However, no activity was observed against strains *S. aureus* and *S. pseudintermedius* (Gram-positive). In contrast, activity against *E. coli* and *P. aeruginosa* (Gram-negative) was observed and was found to be similar to that of related silver carboxylate derivatives (see selected examples in Table 1).

Table 1 Antimicrobial activities of enantiomeric pairs of silver(I) complexes evaluated using minimum inhibitory concentration (MIC; μg mL^{-1})[a]

Complex	*E. coli*	*S. aureus*	*P. Aeruginosa*	Ref.
$\{Ag[(S,S)\text{-}L^{Me}]\}_n$	32	Not active	16	35
$\{Ag[(R,R)\text{-}L^{Me}]\}_n$	32	Not active	4	35
$\{Ag[(S,S)\text{-}L^{iPr}]\}_n$	64	Not active	32	35
$\{Ag[(R,R)\text{-}L^{iPr}]\}_n$	32	Not active	16	35
$\{Ag[(S)\text{-}NHC^{Mes,Me}]\}_n$	57	Not active	57	47
$\{Ag[(R)\text{-}NHC^{Mes,Me}]\}_n$	28	Not active	14	47
$Na_3[Ag((S,S)\text{-}NHC^{iPr})_2]$	189.3	165.2	189.3	48
$Na_3[Ag((R,R)\text{-}NHC^{iPr})_2]$	141.8	141.8	141.8	48
$[Ag(R\text{-othf})]_2$	7.9	62.5	15.7	36
$[Ag(S\text{-othf})]_2$	15.7	31.3	15.7	36
$\{[Ag(R\text{-Hpyrrld})]_2\}_n$	15.7	31.3	15.7	37
$\{[Ag(S\text{-Hpyrrld})]_2\}_n$	7.9	15.7	7.9	37
$\{[Ag_2(R\text{-ca})_2]\}_n$	62.5	125	62.5	38
$\{[Ag_2(S\text{-ca})_2]\}_n$	31.3	250	31.3	38
$\{[Ag(R\text{-his})]_2\}_n$	62.5	15.7	15.7	39
$\{[Ag(S\text{-his})]_2\}_n$	15.7	62.5	15.7	39
[(*R*)-AgL1]	25	75	—	26
[(*S*)-AgL1]	75	50	—	26
[(*R*)-AgL2]	50	75	—	26
[(*S*)-AgL2]	75	75	—	26

[a] Ligand abbreviations: L^R = 2,2′-(imidazolium-1,3-diyl)di(2-*alkyl*acetate); $NHC^{Mes,Me}$ = carbene of 2-methyl(3-mesityl-1*H*-imidazol-3-ium-1-yl)acetate; NHC^{iPr} = carbene of 2,2′-(imidazolium-1,3-diyl)di(2-isopropylacetate); Hothf = 5-oxo-2-tetrahydrofurancarboxylic acid; H_2pyrrld = 2-pyrrolidone-5-carboxylic acid; *R*- and *S*-Hca = (1*R*,4*S*)- and (1*S*,4*R*)-4,7,7-trimethyl-3-oxo-2-oxabicyclo[2.2.1]heptane-1-carboxylic acid; Hhis = histidine; L1 = *N*-methyl, *N*′-(2-hydroxy-2-phenylethyl)-imidazol-3-ium-2-yl; L2 = 4,5-dichloro *N*-methyl, *N*′-(2-hydroxy-2-phenylethyl)-imidazol-3-ium-2-yl.

From the observed minimal inhibitory concentration (MIC) and minimal bactericidal concentration (MBC) values, the complexes $\{Ag[(R,R)\text{-}L^R]\}_n$ (R = Me, ^{i}Pr) showed better antimicrobial properties for both bacteria than their (*S*,*S*)-enantiomers. These eutomers were prepared with precursor ligands obtained from the non-proteinaceous amino acids D-alanine and D-valine, respectively. This fact confirmed the relationship between chirality and antimicrobial behaviour that we had hypothesised. Furthermore, the behaviour of $\{Ag[(R,R)\text{-}L^{iPr}]\}_n$ as a eutomer was supported by its impact on the formation of biofilms, a significant virulence factor in bacteria that must be considered. This complex was capable of inhibiting biofilm formation at a concentration that was lower than the MIC in *E. coli* assays, while for *P. aeruginosa*, it was necessary to reach the MIC to achieve this inhibition. The efficacy of the complex in inhibiting bacterial growth and biofilm formation was further substantiated by scanning electron microscopy (SEM). At the MIC value, significant deformation and damage to the bacterial walls were observed, indicating the potent inhibitory effect of the complex. Before our study, Nomiya's research group carried out a systematic study of silver complexes with amino acids and carboxylates as ligands.[36–43] Concerning chiral derivatives, the researchers examined the behaviour of several pairs of enantiomers, as detailed in Table 1. It should be noted that although disparities in the antimicrobial activities of the two enantiomers were discerned, this observation was not explicitly accentuated in any of the studies.

In addition to carboxylates as ligands, one of the most studied families of silver complexes with respect to their biocidal activity has been that of N-heterocyclic carbene (NHC) ligands.[44–46] For this reason, our research was extended to the preparation of silver complexes of this nature obtained from chiral amino acids. The aim was to obtain further confirmation of the improved activity against bacteria that one of the enantiomers might exhibit. Complexes $\{Ag[NHC^{Mes,R}]\}_n$ were prepared by the reaction of the specific imidazolium precursor compound with Ag_2O.[47] These compounds were characterised, in the solid state, as one-dimensional coordination polymers, in which the silver ion is bonded to the carbon atom of the NHC ligand and to the carboxylate group of a symmetry-related carbene ligand (Scheme 1). The antimicrobial properties of these complexes were evaluated *versus* Gram-negative bacteria, *E. coli* and *P. aeruginosa*. However, the complexes did not demonstrate significant biocidal activity against Gram-positive strains *S. aureus* and *S. pseudintermedius*. From the observed MIC and MBC values, it was found that the complex $\{Ag[(R)\text{-}NHC^{Mes,Me}]\}_n$ exhibited the most effective antimicrobial properties compared to the complexes with other alkyl groups. Moreover, this complex was the eutomer for both bacteria, which was prepared with the precursor ligand obtained from the non-proteinaceous α-amino acid D-alanine. The MIC and MBC values were significantly superior to those of its (*S*)-enantiomeric pair (Table 1), confirming the chirality–activity relationship. An additional structure–antimicrobial effect relationship was revealed by analysing the MIC and MBC values of $\{Ag[NHC^{Mes,R}]\}_n$ complexes. Specifically, the study

Table 2 Antimicrobial activities of enantiomeric pairs of metal complexes evaluated using minimum inhibitory concentration (MIC; μg mL^{-1})[a]

Complex	*E. coli*	*S. aureus*	*P. aeruginosa*	Other bacteria	Ref.
{Ru[(*S*,*S*)-Salen']$(dmso)_2$}	Not active	12.5	—	12.5[b]	52
{Ru[(*R*,*R*)-Salen']$(dmso)_2$}	Not active	12.5	—	25[b]	52
ΛΛ-[{Ru$(phen)_2$}$_2${μ-bb$_2$}]Cl_4	64	>128	>128	—	24
ΔΔ-[{Ru$(phen)_2$}$_2${μ-bb$_2$}]Cl_4	>128	>128	>128	—	24
ΛΛ-[{Ru$(phen)_2$}$_2${μ-bb$_5$}]Cl_4	64	128	128	—	24
ΔΔ-[{Ru$(phen)_2$}$_2${μ-bb$_5$}]Cl_4	128	128	>128	—	24
ΛΛ-[{Ru$(phen)_2$}$_2${μ-bb$_7$}]Cl_4	16	64	64	—	24
ΔΔ-[{Ru$(phen)_2$}$_2${μ-bb$_7$}]Cl_4	16	16	128	—	24
ΛΛ-[{Ru$(phen)_2$}$_2${μ-bb$_{10}$}]Cl_4	4	8	32	—	24
ΔΔ-[{Ru$(phen)_2$}$_2${μ-bb$_{10}$}]Cl_4	4	4	64	—	24
ΛΛ-[{Ru$(phen)_2$}$_2${μ-bb$_{12}$}]Cl_4	2	2	16	—	24
ΔΔ-[{Ru$(phen)_2$}$_2${μ-bb$_{12}$}]Cl_4	2	1	16	—	24
ΛΛ-[{Ru$(phen)_2$}$_2${μ-bb$_{14}$}]Cl_4	2	1	8	—	24
ΔΔ-[{Ru$(phen)_2$}$_2${μ-bb$_{14}$}]Cl_4	4	1	8	—	24
ΛΛ-[{Ru$(phen)_2$}$_2${μ-bb$_{16}$}]Cl_4	4	1	8	—	24
ΔΔ-[{Ru$(phen)_2$}$_2${μ-bb$_{16}$}]Cl_4	4	1	8	—	24
Δ-[Ru$(phen)_2$(dppz)]Cl_2	32	—	—	8[c]	23
Λ-[Ru$(phen)_2$(dppz)]Cl_2	128	—	—	16[c]	23
[(*R*)-AuL1]	75	25	—	—	26
[(*S*)-AuL1]	75	75	—	—	26
[(*R*)-AuL2]	75	75	—	—	26
[(*S*)-AuL2]	100	75	—	—	26

[a] Ligand abbreviations: H_2Salen' = *N*,*N*′-bis[3-(piperidinomethyl)-5-(*tert*-butyl) salicylidene]cyclohexane-1,2-diamine. bb$_n$ = bis[4(4′-methyl-2,2′-bipyridyl)]-1,*n*-alkane, with *n* = 2, 5, 7, 10, 12, 14, 16. dppz = dipyrido[3,2-*a*:2′,3′-*c*]phenazine. L1 = *N*-methyl, *N*′-(2-hydroxy-2-phenylethyl)-imidazol-3-ium-2-yl; L2 = 4,5-dichloro *N*-methyl, *N*′-(2-hydroxy-2-phenylethyl)-imidazol-3-ium-2-yl. [b] Bacteria: *B. subtilis*, *B. megaterium* and *B. cereus*. [c] Bacteria: *B. subtilis*.

found that the antimicrobial activity decreased in proportion to the increase in the steric properties of the alkyl group R in the complex.

Last year, we described the antimicrobial properties of a series of anionic bis(carbene) silver complexes Na_3[Ag$(NHC^R)_2$], where NHC^R is a 2,2′-(imidazol-2-ylidene) dicarboxylate-type N-heterocyclic carbene (Scheme 1). Complexes were synthesised by the interaction of imidazolium dicarboxylate compounds with Ag_2O in the presence of aqueous sodium hydroxide.[48] Although they exhibit somewhat diminished antibacterial activity compared to analogous derivatives (Table 1), these complexes demonstrate a notable distinction from other results we analysed. Specifically, these complexes exhibit activity against a Gram-positive strain, *S. aureus*, in addition to the usual activity observed against Gram-negative bacteria, *E. coli* and *P. aeruginosa*. Interestingly, the comparison of MIC and MBC values for all strains of the enantiomeric complexes Na_3[Ag((*S*,*S*)-NHC^{iPr})$_2$] and Na_3[Ag((*R*,*R*)-NHC^{iPr})$_2$] confirmed the relationship between chirality and antimicrobial activity, as observed in related silver systems. The eutomer for all strains was the (*R*,*R*)-enantiomer, which was derived from D-valine and showed biocidal activity better than its (*S*,*S*)-pair, derived from L-valine. This result confirmed the connection between chirality and biocidal activity, suggesting a possible generalisation of the chirality–antimicrobial activity trend. This relationship was also highlighted in the simultaneous report of NHC silver complexes with a chiral 2-hydroxy-2-phenylethyl substituent in the imidazolium ring ([AgL1] and [AgL2] in Table 1).[26]

Table 1 provides a summary of the chiral silver complexes for which the chirality–activity relationship has been investigated. In all cases, the chirality is found to reside on an asymmetric carbon atom of the coordinated ligand. Although examples of silver complexes exhibiting axial chirality have been documented,[49] and the first case of chirality at the metal (atropisomerism) has recently been described,[14] studies examining the correlation between these forms of chirality and antibacterial activity remain absent. Further studies are required to understand the mechanisms of action of silver complexes and to determine whether chirality influences their four known interactions with bacteria, which lead to cell death: disruption of cell walls and membranes, interaction with DNA, interaction with or inhibition of proteins and enzymes, and generation of reactive oxygen species (ROS).[50]

Antimicrobial properties of chiral complexes of other transition metals

While silver complexes are well-documented examples of complexes with antibacterial activity, there are other transition metals that have the potential to serve as a valuable source of new antibiotics.[2,3] For example, Frei *et al.* highlighted 30 complexes with activity against Gram-positive and/or Gram-negative bacteria containing Mn, Co, Zn, Ru, Ag, Eu, Ir and Pt metals from 906 metal-containing compounds that were screened for antimicrobial activity by the Community for Open Antimicrobial Drug Discovery (CO-ADD†).[3] In this section, we

† https://db.co-add.org/

will provide a concise overview of chiral complexes where the biocidal activity of the pair of enantiomeric species was investigated. As previously mentioned, the seminal study by Dwyer *et al.* was the first to examine the relationship between chirality and biocidal activity for multiple metals, including Ru, Co, Fe, Ni, and Os.[22]

Regarding the ruthenium metal, there are several complexes with biological activity,[51] but the number of studies about the biocidal activity of enantiomeric pairs is low. For example, the antimicrobial behaviour of ruthenium(II) complexes with a chiral salen ligand was effective against the growth of Gram-positive bacteria but not against Gram-negative. The enantiomer {Ru[(*S*,*S*)-Salen']$(dmso)_2$} inhibited the growth of organisms to a greater extent than the (*R*,*R*)-enantiomer for three bacteria (Table 2).[52] Dinuclear ruthenium(II) complexes with chirality at the metal, namely, ΔΔ/ΛΛ-[{Ru$(phen)_2$}$_2${μ-bb_n}]$^{4+}$ (see Table 2, where the bridging bb_n is a bis[4(4′-methyl-2,2′-bipyridyl)]-1,*n*-alkane ligand), were highly active in cases where the length of the hydrocarbon chain of the bridging ligand was longer.[24] Complexes with a short link chain or a rigid polycyclic aromatic link ligand showed very little or no activity against any of the bacterial strains. Only slight differences in activity were observed between some examples of the ΔΔ and ΛΛ enantiomers (Table 2), suggesting that chiral receptors may not be the intracellular target for these metal complexes.[24] A second example of chirality at the metal was the report of the antimicrobial activity of enantiopure [Ru$(phen)_2$dppz]$^{2+}$ complexes (dppz = dipyrido[3,2-*a*:2′,3′-*c*]phenazine, Table 2) on Gram-negative *E. coli* and Gram-positive *B. subtilis* as bacterial models. The Δ-enantiomer showed a 2-fold higher bactericidal effect than the Λ-enantiomer.[23]

The antibacterial activity of (*S*) and (*R*) tetranuclear complexes $[Cu_4(vanPheol)_2(HvanPheol)_2(CH_3OH)_2](NO_3)_2$, where vanPheol is a Schiff base ligand, was evaluated in batch cultures of Gram-positive *B. subtilis* and Gram-negative *E. coli*. Both enantiomers possess comparable growth inhibitory effects on the Gram-positive strain, but they have no bactericidal activity against *E. coli*.[25]

The antibacterial activities of the gold enantiopure complexes [AuL1] and [AuL2] were also studied, which have the same formula as the silver derivatives shown in Table 1. The most active compound against *S. aureus* was the complex [(*R*)-AuL1], which exhibited a higher MIC value than its (*S*)-enantiomer and the silver derivatives (Table 2).[26]

Conclusions and future prospects

The growing issue of AMR represents a formidable challenge to global health and requires innovative approaches to develop effective treatments. The exploration of metal-based agents, particularly those that incorporate chirality, offers a promising chance for addressing this crisis. Chiral metal complexes, with their unique spatial configurations, have demonstrated the potential to selectively interact with biological targets, thereby enhancing their antimicrobial efficacy. The relationship between chirality and antimicrobial activity, although recognised in early studies, remains underexplored, highlighting a significant opportunity for future research.

Recent studies on chiral silver complexes have provided compelling evidence for the enhanced antimicrobial properties of specific enantiomers. These findings underscore the importance of chirality in the design of new antimicrobial agents and suggest that further investigation of other metal-based chiral complexes could yield valuable insights. The development of chiral metalloantibiotics, taking advantage of the principles of inorganic medicinal chemistry, could lead to novel therapies capable of overcoming current resistance mechanisms.

Future research should focus on expanding the library of chiral metal complexes and systematically studying their antimicrobial properties. This includes exploring different metals, ligands, and chiral configurations to identify the most effective combinations. Additionally, understanding the mechanisms by which chirality influences antimicrobial activity will be crucial in optimising these compounds for clinical use. Integrating advanced techniques such as high-throughput screening, computational modelling, and structural biology will be critical for accelerating the discovery and development of new chiral metalloantibiotics. Collaboration between chemists, microbiologists, and pharmacologists will be essential for translating these findings into practical treatments.

In conclusion, the strategic incorporation of chirality into metal-based antimicrobial agents represents a promising frontier in the fight against AMR. By continuing to explore and understand the complex interplay between chirality and biological activity, we can develop innovative solutions to one of the most pressing challenges in modern medicine.

Author contributions

The authors contributed equally to the investigation, data curation, and writing – original draft preparation, review and editing.

Data availability

No new data were generated as part of this article.

Conflicts of interest

There are no conflicts to declare.

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