Chinese Journal of Health Management
Volume 20 Issue 3, Year of Publication 2026, Page 536-552 | DoI- 10.5281/zenodo.19703983

ISSN: 1674-0815

Chinese Journal of Health Management

Chinese Medical Association

Role of Metal Complexes in Overcoming Antibiotic Resistance: A Medicinal Chemistry Perspective

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Article Information
Received: 23-12-2025
Revised: 22-01-2026
Accepted: 17-02-2026
Published: 27-03-2026

Keywords
Transition metal complexes, drug resistance, bacterial infection, antibacterial mechanism, antibacterial, antifungal, bioinorganic chemistry.

ABSTRACT:
Metal-based compounds are gaining growing attention in both science and medicine as promising antibacterial agents. This is largely because their chemical diversity offers new ways to tackle the rising challenge of antibiotic resistance. However, developing these compounds through traditional drug discovery approaches can be costly, time-intensive, and often unsuccessful. To address these challenges, researchers are exploring simpler and more efficient strategies to accelerate the development of metal-based antimicrobials. In this context, we highlight how several widely used drug discovery approaches can be adapted to these compounds to speed up their journey toward clinical use. These strategies include: (i) drug repurposing, where existing drugs are used for new antibacterial purposes; (ii) drug combination, which involves using multiple agents together to enhance effectiveness; and (iii) targeted delivery through bioconjugation, where drugs are linked to specific molecules to improve precision. Relevant examples of each approach will be discussed to demonstrate their potential in advancing metal-based antibacterial therapies more quickly and effectively.

1. INTRODUCTION:
For centuries, people have recognised the advantages of employing medications that contain metals as therapeutic agents. Metals and their compounds have been used in the treatment of several societies since ancient times. Metals have proved their worth as a strong and an encouraging agent in the field of medicine, beginning with the use of copper as a cleansing agent, to the use of zinc as an antiseptic agent. The development of the organometallic drug Salvarsan, an arsenic-based medication, used to treat syphilis in the early 20th century by Ehrlich was a breakthrough in metallodrugs. However, perhaps, the serendipitous finding of cisplatin as an anticancer drug gave rise to a lot of clinical interest in metallodrugs, which in turn resulted in the development of However, the most influential therapeutic concern regarding metallodrugs was probably awakened by the accidental finding of cisplatin as an anticancer drug that subsequently gave way to the emergence of medical inorganic chemistry. Since the discovery of cisplatin in 1965 and its use as an anticancer agent in 1978, many metallodrugs have been explored as potential anticancer agents, antibacterials, antivirals, and in many other applications. However, despite

decades of interest, metallodrugs are still understudied in preclinical screenings and, as a result, in clinical trials, indicating that a large portion of their therapeutic potential is still unknown4.

The same has been happening as multidrug-resistant bacterial diseases are increasingly becoming a larger threat to global health. The 2014 Review on Antimicrobial Resistance (AMR) suggests that 10 million deaths due to AMR may occur by 20507. More recent studies indicate that this might occur even earlier since COVID-19 patients are excessively prescribed antibiotics. This has led to the establishment of AMR as a global problem by the World Health Organization (WHO) and the European Center of Disease Prevention and Control (ECDPC) 10, 11 as an effect of this surely cementing its position as a significant health concern of the 21st century. Although this is an urgent requirement, classic organic medicinal chemistry has failed considerably to substitute the exhausting antimicrobial pipeline, providing a necessity to employ creative approaches to generate antimicrobial drugs.

Interestingly, even though the percentage of reported metal-containing compounds is low, the hit-rate of metallic compounds against Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Enterobacter (ESKAPE) and Pseudomonas aeruginosa infections is higher than only the organic substances. Other studies have also supported the efficacy of metal-based drugs by showing that metal complex agents are stronger antibiotics as compared to their purely organic counterparts. To counter the development of drug-resistant bacterial infections, metal-based compounds act as antibacterial agents have gained increased attention and seem to be a potential but largely untapped option.

Due to their various oxidation states many transition metals are able to react with a variety of metal-binding sites and participate in many redox reactions in vivo during a biological response. Moreover, the steric and electronic properties of a metal-based complex can readily be altered by substitution of substituents or ligands, which could result in tuned pharmacology. As an illustration, more lipophilicity can enhance the permeability of the complex to the blood-brain barrier or cell membrane. All put together, these properties of metal-based compounds enable them to possess numerous mechanisms of action, this is why they can potentially be used in the fight against AMR.

Thus, this review paper aims to provide a broad description of metal-based compounds with antibacterial properties and discuss their therapeutic potential, structural diversity, and mechanisms. The rising significance of such metallodrugs will be contextualized by first giving an overview of AMR. The next step will be a review of the documented metallodrugs by categories of metals they comprise, focusing on the major progress and innovations in the area. [1,2]

2. Bacterial AMR

The numerous AMR21, 22, 23, 24, 25, 26 mechanisms have been well validated in several excellent reviews. The next section therefore points out only the most relevant elements of AMR in order to provide some background information. This therefore gives the rationale of developing new materials that can bypass the different systems.

2.1. Intrinsic vs acquired resistance

Fixed mechanisms that are part of the basic genetic make-up of the bacteria are termed intrinsic antibiotic resistance. These mechanisms, containing permeability barriers, antibiotic inactivating enzymes, and non-specific efflux pumps (which are most likely an evolutionary response to environmental toxins), are generally coded in the chromosomes of the organism. Conversely, the acquired resistance mechanisms include plasmid-encoded specialised efflux pumps and enzymes that may change the antibiotic or its target, and are usually acquired by horizontal gene transfer. HGT can actually contribute greatly to AMR since it can transmit resistance to multiple medicines simultaneously. Since acquired resistance mechanisms are transmitted rapidly and may lead to the emergence of numerous drug-resistant strains of bacteria, it is considered as a more severe threat.[3]

2.2. Mechanisms of AMR

In bacteria, AMR is mediated by a number of different mechanisms, which can be broadly categorized as either having a genetic or a mechanistic basis. Evolutionarily, bacteria use two key genetic processes to adapt and survive the antibiotic: first, a mutation in genes to give a resistant strain of bacteria; and second, the foreign DNA that encodes AMR is acquired via HGT. AMR's mechanistic pathways can be divided into three primary groups: 1. These lower the intracellular levels of the antibiotic by actively pumping out the antibiotic molecule, or by

decreasing its penetration; 2. These cause a decrease in affinity towards the antibiotic molecule by changing the antibiotic target site; 3. They modify or hydrolyse the antibiotic ingredient to render it inactive. Interestingly, the bacteria that have AMR can have one or more of these mechanisms, depending on their degree of resistance.

A lot of research has also been conducted on other AMR issues that have to do with the mechanics. First, the formation of biofilms has been proposed to also promote AMR, acting as a barrier preventing the entry of antibiotic molecules into the bacteria. Second, the idea that Gram-negative bacteria are especially difficult to deal with because of their inherent characteristics that encourage resistance, like the cell wall's outer layer, which can stop antibiotic chemicals from entering or staying in the cell.

Both intrinsic and acquired AMR processes should be targeted by a potent new antibacterial drug. It may provide a workable strategy to treat illnesses brought on by bacteria resistant to traditional antibiotics by creating molecules with unique modes of action that get around current resistance mechanisms. Alternative approaches to the production of antibiotic compounds are desperately needed, given the current lack of antibacterial medicinal molecules with novel classes and mechanisms of action. In this regard, metal-based antibacterial compounds have come to play a favourable role in developing a new generation of antibiotics to cure bacterial strains that are resistant. [4,5]

3. Metal-based antibacterial complexes

Although metal-based compounds have been used long before due to their antimicrobial properties, more studies are now being conducted on metal-based compounds as anticancer agents than on their use as antibacterial agents30. The finding of penicillin and other antibiotics could have played a role in the reduction in therapeutic appeal of metal based antibacterial compounds30. However, research into metal-based antibacterial medicines has resurfaced due to the growing threat of AMR and the challenges in creating new antibiotics.

Nanoparticles of metals may be complexed with an antibiotic or with a biomolecule, or they can be used as antibacterial agents30. A metal-biomolecule complex facilitates easier entry of the metal to particular parts of the cell to execute its antibacterial activities since biomolecules are materials that are often taken up by bacterial cells31. Common structures of metal-based complexes32 are antimicrobial peptides, N-heterocyclic carbenes (NHCs), Schiff bases, photosensitivity, and aliphatic amine-based ligands.

Silver, gallium and gold are also noted in this research as some of the most prominent examples of well-proven systems that have shown both the possibility of safe topical or systemic administration as well as the potential of good antibacterial activity. We will also discuss iridium and ruthenium compounds which have been promising and were found to have a great antibacterial activity.[6]

4. Silver

In addition to having a long history of antibacterial use, silver's antimicrobial qualities are still utilised in a variety of contemporary applications. It is frequently used as an antibacterial ingredient in consumer goods like cosmetics and in textiles and sprays to stop foul odours brought on by perspiration. Silver is also a component of silver sulfadiazine, a topical antibiotic of broad spectrum that is applied in the treatment of burn wounds. Moreover, silver has also been proposed to be used in dental and medical equipment. There has been an increasing body of research exploring the potential of silver-based compounds as a systemic antibacterial agent, although most of the current antimicrobial uses of silver are topical.

Even though the mechanism of action of the silver-based drugs remains unclear, studies show that it is related to the release of silver (I) ions, which may inactivate cysteine residues on enzymes to inhibit enzymatic activity, bind to and condense DNA to inhibit replication, and enter the cell membrane to affect its functioning. In a comparative screening study of various metal complexes as antibacterial agents, silver complexes were also found to be some of the best, which suggests their applicability in future as a novel antibacterial agent13. This implies that ligands that are able to establish strong coordination to produce complexes with silver (I) ions are necessary. The recent developments in the medical applications of silver complexes and their anticancer, antifungal, and antibacterial properties have been reviewed in detail by Liang et al.; this section will specifically look at silver complexes that have the most promising antibacterial properties. [7]

4.1. NHC-Ag(I) complexes

The use of NHCs as ligands of transition metals has proven to be extremely effective in that they are very potent nucleophiles that bind transition metals with a high affinity, which enhances the bioavailability of the metal under physiological conditions and thus makes them a good ligand to coordinate with silver (I) ions.

In 2004, Melaiye and others reported the first generation of NHC-Ag(I) complexes (1) and (2) (see Fig. 1) and found that their minimum inhibitory concentration (MIC) against Escherichia coli (E. coli), Staphylococcus aureus (S. aureus) and Pseudomonas aeruginosa (P. aerugin Research on NHC-Ag(I) complexes and analogues has increased manifold due to this breakthrough discovery. [7,8]

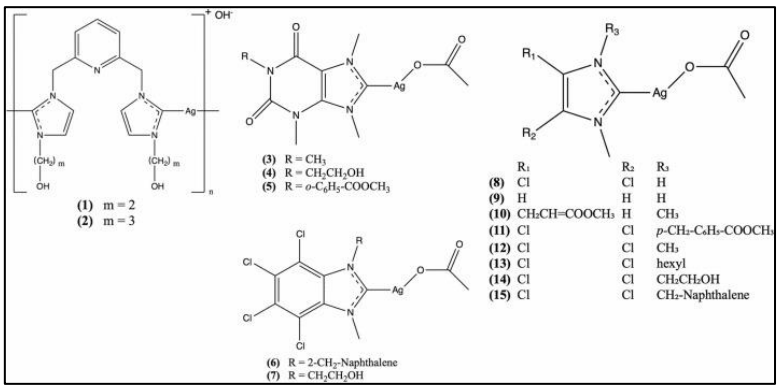
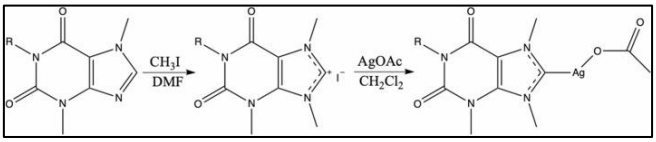


Fig. 1. Molecular structures of NHC-Ag(I) complexes (1) to (15).

Not long after, Cannon's group[41] synthesised a novel mixed NHC-Ag(I) acetate complex **(3)** (see Fig. 1) that was derived from methylated caffeine (see Scheme 1), which showed good activity against various pathogens, with MIC values ranging from 1 to 8 µg/mL, as well as low toxicity *in vivo*. In attempts to enhance the water solubility, other xanthine-silver complexes **(4)** and **(5)** (see Fig. 1) were synthesised and were found to show comparable bioactivity to complex **(3)**.[9,10]



Scheme 1. Synthetic route of complexes **(3)** to **(5)**.

A number of benzimidazole-silver and imidazolium-silver complexes were created after the xanthine-silver complexes were successful, and their bioactivities were assessed. With MIC values ranging from 0.25 to 6 µg/mL44, the results for the benzimidazole-silver complexes (6) and (7) (see Fig. 1) demonstrated antibacterial activity against highly resistant bacterial strains, such as methicillin-resistant S. aureus (MRSA). Similar to this, a number of the imidazolium-silver complexes (8) to (15) (refer to Fig. 1) showed antibacterial qualities against MRSA, with MIC values ranging from 1 to 4 µg/mL45, 46, and 47. [9,10]

4.1.1. Imidazolium-Ag(I) carbene complexes

Since its original idea, a vast array of imidazolium-silver complexes have been synthesised; the bulk of these complexes feature significant lipophilic substituents, which are intended to promote penetration through the lipid cell membrane. Other studies have synthesised imidazolium-Ag(I) halide complexes (30) to (43) (see Fig. 3) (see Scheme 3)48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65. With a discernible improvement over their NHC precursors, many of these complexes generally showed low to medium activity against both Gram-positive (E. coli) and Gram-negative (S. aureus) bacteria. It was observed that enhancement in antibacterial properties occurred in tandem with increased lipophilicity of the complex. This led to the synthesis of the lead antibacterial compound in Tacke's group, SBC3 (complex **(29)**).

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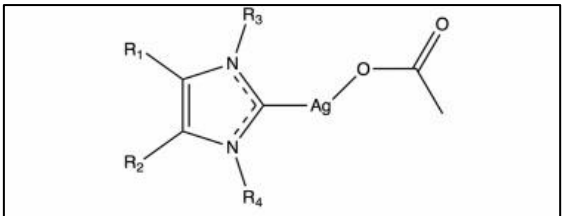
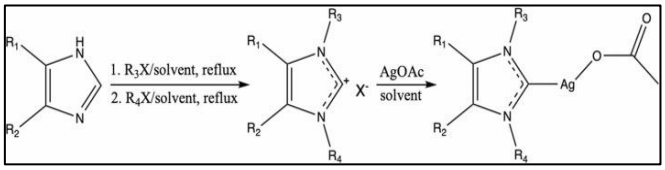
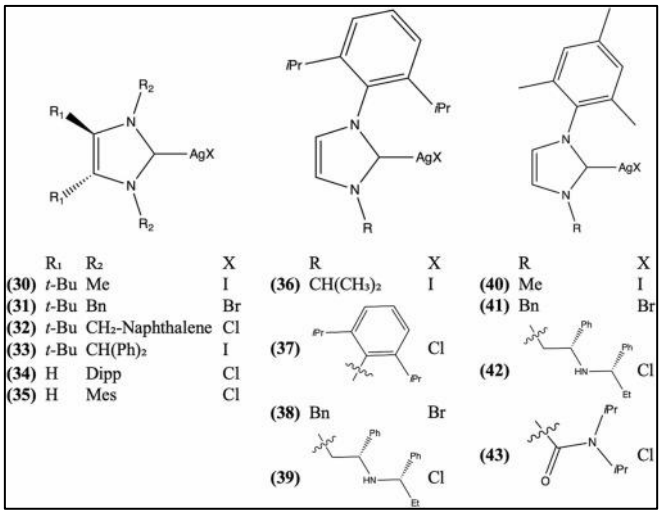


	R_1	R_2	R_3	R_4
(16)	H	H	CH_3	*p*-CH_2-C_6H_5-$COOCH_3$
(17)	Cl	Cl	CH_3	*p*-CH_2-C_6H_5-$COOCH_3$
(18)	H	H	*p*-CH_2-C_6H_5-$COOCH_3$	*p*-CH_2-C_6H_5-$COOCH_3$
(19)	H	H	CH_2-C_6H_5	CH_2-C_6H_5
(20)	benzo	benzo	CH_3	*p*-CH_2-C_6H_5-$COOCH_3$
(21)	Cl	Cl	*p*-CH_2-C_6H_5-OCH_3	*p*-CH_2-C_6H_5-OCH_3
(22)	Cl	Cl	CH_2-C_6H_5	CH_2-C_6H_5
(23)	*p*-CH_3-C_6H_5	*p*-CH_3-C_6H_5	*p*-CH_2-C_6H_5-CH_3	*p*-CH_2-C_6H_5-CH_3
(24)	*p*-$CH(CH_3)_2$-C_6H_5	*p*-$CH(CH_3)_2$-C_6H_5	CH_2-C_6H_5	CH_2-C_6H_5
(25)	*p*-$CH(CH_3)_2$-C_6H_5	*p*-$CH(CH_3)_2$-C_6H_5	*p*-CH_2-C_6H_5-CH_3	*p*-CH_2-C_6H_5-CH_3
(26)	Cl	Cl	CH_3	*p*-CH_2-C_6H_5-CN
(27)	benzo	benzo	CH_2-C_6H_5-CN	CH_2-C_6H_5-CN
(28)	benzo	benzo	CH_3	CH_2-C_6H_5
(29)	benzo	benzo	CH_2-C_6H_5	CH_2-C_6H_5

Fig. 2. Molecular structures of imidazolium-Ag(I) complexes (16) to (29). (29) SBC3.



Scheme 2. Synthetic route of complexes **(8)** to **(29)**.

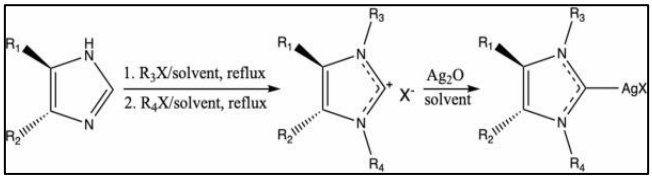


	R_1	R_2	X
(30)	*t*-Bu	Me	I
(31)	*t*-Bu	Bn	Br
(32)	*t*-Bu	CH_2-Naphthalene	Cl
(33)	*t*-Bu	$CH(Ph)_2$	I
(34)	H	Dipp	Cl
(35)	H	Mes	Cl

	R	X
(36)	$CH(CH_3)_2$	I
(37)		Cl
(38)	Bn	Br
(39)		Cl

	R	X
(40)	Me	I
(41)	Bn	Br
(42)		Cl
(43)		Cl

Fig. 3. Molecular structures of imidazolium-Ag(I) halide complexes (30) to (43).



Scheme 3. Synthetic route of complexes **(30)** to **(43)**.

The MIC values of SBC3 versus MRSA, Salmonella, E. coli, and P. aeruginosa57 were between 3.13 and 20 µg/mL. Additionally, in vivo research on Galleria mellonella (G. mellonella) larvae showed that giving SBC3 at a dose of 25 µg/mL reduced S. aureus growth by 71.2% and improved survival rates compared to the untreated group58. In these studies, G. mellonella is often employed as an infection model due to the remarkable structural and functional resemblances between the insect and the mammalian innate immune system66, 67. Also, the in

vivo experiments showed that the injection of SBC3 in G. mellonella larvae failed to increase the number of immune cells in the insect meaning that SBC3 did not promote the immune system of the insect58. This information indicates that G. mellonella larvae survived because of a direct antibacterial effect of SBC3 but not because of an immunological response that was not specific but caused by the substance. Due to the good results of the in vivo and in vitro studies, SBC3 has portrayed a tremendous amount of potential as an antibacterial agent. It is even under consideration as a starting point of new injectable emergency medicines against the resistant bacteria53. To completely assess its safety for systemic or even topical administration in humans, more research is necessary.

Complexes of imidazolium-Ag(I) with Ag(I) that showed significant antibacterial properties also included complexes of imidazolium-Ag(I) acetate that had values of MIC between 4 and 32 mcg/mL against E. coli and S. aureus59. Complex was found to be the most active (see Fig. 3), and this may be a potential choice to develop a new topical antibacterial drug.

NHC-Ag(I) complexes have shown excellent antibacterial effects in Gram-positive and Gram-negative bacterial strains and NHC ligands have been shown to be an effective method of delivering silver(I) ions when required. Also, in vivo experiments have shown that complexes like SBC3 enhance the survival of infected G. mellonella. To completely understand the mechanism of action of NHC-Ag(I) complexes, more research is necessary. However, the bioavailability of silver (I) ions according to the current studies has a considerable influence on their activity68. Successful efforts to increase the bioavailability of silver(I) ions usually required increasing the lipophilicity of the silver(I) complex. The higher the lipophilicity, the better the complex should enter the cell to then execute its antibacterial properties since the bacterial cell wall is coated with a lipid barrier that allows the passage of lipid-soluble molecules. This was evidenced by observations of the increase in the biological activity of chemicals with longer aliphatic chains.

4.2. Novel Ag(I) complexes

Tacke's group70 synthesised eight new silver(I) complexes, four triphenylphosphino (Ph3P)-Ag(I) benzoate complexes (44) to (47) (see Fig. 4) (see Scheme 4) and four NHC*-Ag(I) benzoate complexes (48) to (51) (see Fig. 4), and evaluated their antibacterial efficacy against MRSA and E. coli. Besides NHCs, phosphines have been shown to enhance the bioavailability of silver under physiologic conditions71, 72. The compounds were tested with the Kirby-Bauer disc diffusion method to determine their antibacterial activity and compare it to SBC3.

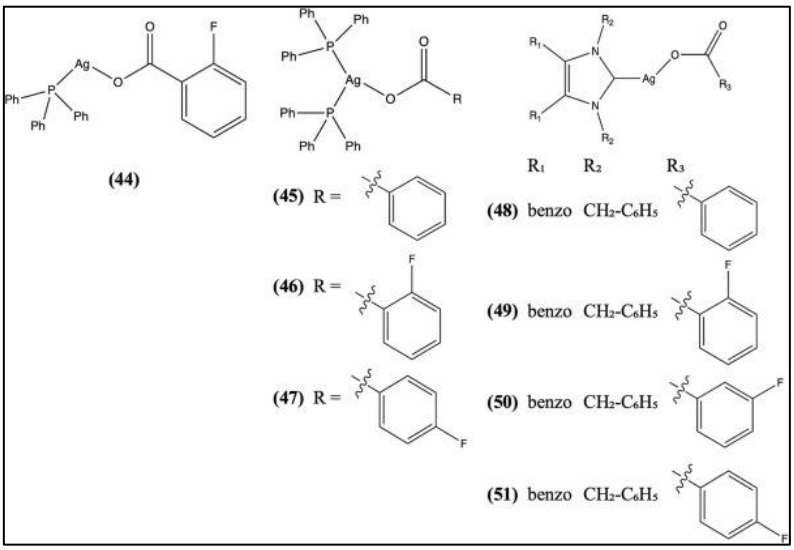


Fig. 4. Molecular structures of novel silver-based antibacterial complexes (44) to (47) (Ph_3P)-Ag(I) benzoate complexes. (48) to (51) NHC*-Ag(I) benzoate complexes.

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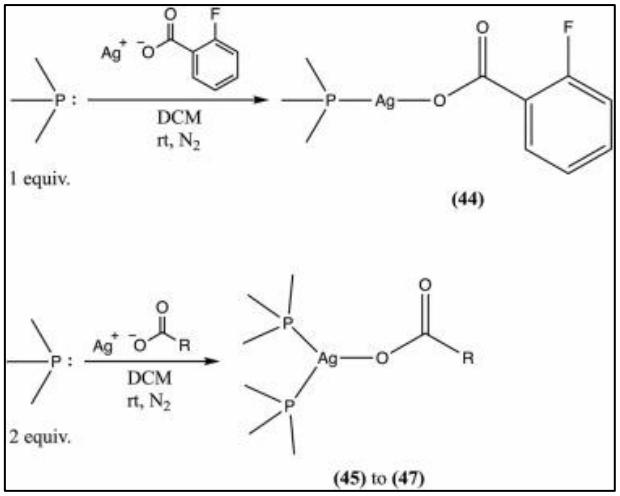


Scheme 4. Synthetic route of complexes **(44)** to **(47)**.

The NHC*-Ag(I) benzoate complexes (49) and (51) with the most active activity in MRSA (zone of clearance radii of 4.2 and 5 mm, respectively) were found to be more active than The results of the study not only proved the potential of the NHC*-Ag(I) benzoate complexes in the role of antibacterial agents, but also suggest that the antibacterial activity of the complexes is superior to silver-based complexes with phosphine ligands. Everything said and done, this could present valuable clues to the future development of silver-based antibacterial compounds.

However NHC-silver complexes and their derivatives remain the most actively studied and synthesised type of silver complexes. A recent study by Contini et al. as an example developed and tested silver(I) salicylate-metronidazole complexes as novel antibacterial agents. Metronidazole (MET) is the first-line therapy in the bacterial and anaerobic protozoan infections even now, 50 years after its introduction in the 1960s74. The development of resistance in several infections has raised questions on the long-term effectiveness of MET, however, and efforts are underway to change it to suit contemporary medical issues. In order to create metal-MET complexes with improved antimicrobial activity, for example, Contini et al.73 investigated the use of salicylate as a co-ligand to boost the complex's effectiveness as an antibacterial agent77.

The novel [Ag(Sal)(MET)] complex (52) (see Fig. 5) (see Scheme 5) was tested against two Gram-positive (Streptococcus epidermidis and S. aureus) and two Gram-negative (E. coli and P. aeruginosa) pathogens. Moreover, the antibacterial activity was compared with the original reagent [Ag(Sal)]. The antibacterial efficacy was evaluated by the conventional method of broth dilution and the minimum bactericidal concentration (MBC) and minimum inhibitory concentration (MIC) were obtained. The [Ag(Sal)(MET) complex was observed to have the lowest MIC and MBC values of all bacterial strains tested, which are much better than those of starting material. This means that this complex can possibly combat diseases that are resistant to a large number of drugs.

Biofilm inhibition was also tested and the [Ag(Sal(MET)] complex proved to be an effective biofilm inhibitor as compared to the other complexes studied. Considering that biofilms have already shown a great resistance to antimicrobial drugs, this is another way through which the complex can fight AMR.

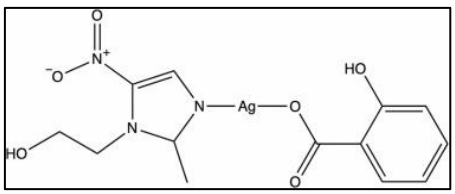
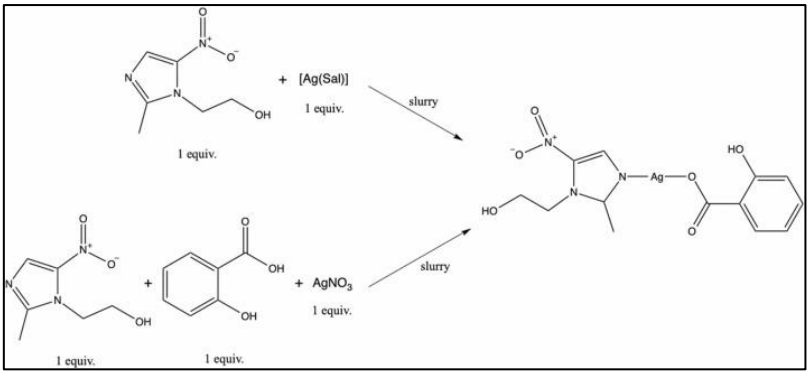


Fig. 5. Molecular structure of silver complex (52) [Ag(Sal)(MET)].



Scheme 5. Synthetic route of complex **(52)**.

5. Gallium

Gallium, though known to possess antimicrobial activity in the past, has been negatived due to the discovery and use of traditional antibiotics and its potential use as an antibacterial agent. Rather, the anticancer properties of gallium were explored, and now is the second most frequently used metal in cancer therapy, following platinum. The anticancer activity of gallium is believed to come about by its capacity to bind to transferrin, the iron carrying protein in the blood and hence reduce the amount of iron available to cancer cells80, 80. There has been an increasing interest in the antibacterial properties of gallium due to the essential nature of iron in the operation of bacteria.

The gallium(III) ion is an effective substitute of the iron(III) ion due to the resemblance in charge and size of the two ions. Gallium (III) ions can compete with ferric ions for absorption into the bacteria through the same processes since the bacterial iron uptake systems are unable to distinguish between iron (III) and gallium (III) ions. Ferric reductases in bacteria usually reduce ferric ions to the more soluble ferrous ions to be incorporated into the iron-dependent enzymes. But under normal physiological conditions, gallium(III) ions cannot be changed to gallium(II) ions, and thus, block iron-dependent enzymes, disturbing key metabolic processes and reducing the chance of infection dramatically. Thus, the possibilities of gallium-based compounds to demonstrate new and promising antibacterial activity can be explained by the fact that it can disrupt the iron metabolism in bacteria.

5.1. Gallium nitrate

Ganite, or gallium nitrate, [Ga(NO3)3] (see Fig. 6), is an FDA-approved anti-hypercalcemic used to treat cancer patients. It has recently shown promising activity against bacterial strains such as P. aeruginosa and Acinetobacter baumannii (A. baumannii)88 and is currently in clinical trials to establish its effectiveness as an antibacterial agent. Although A. baumannii is often considered as one of the most resistant pathogens of non-fermenting Gram-negative bacteria88, P. aeruginosa is an important cause of severe hospital infection and it is highly intrinsically resistant to antibiotics87. Thus, new antibiotics to fight these diseases are in extreme demand and Ganite might prove to be a good solution or at least a good point to begin with.

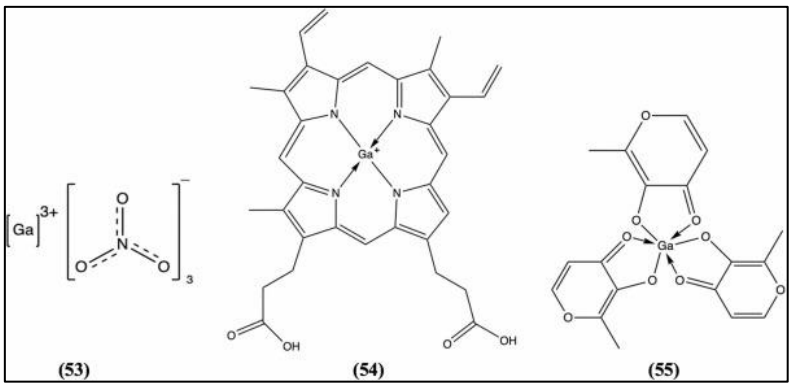


Fig. 6. Molecular structures of gallium-based antibacterial complexes. (53) Gallium nitrate (Ganite). (54) Gallium protoporphyrin. (55) Gallium maltolate.

Ganite has demonstrated a bactericidal effect to lower lung injury and bacterial load in a murine model of acute and chronic lung infections. Research has demonstrated that Ganite is effective at inhibiting the growth of clinical P. aeruginosa strains, including multidrug-resistant and cystic fibrosis (CF) isolates. When Ganite was given to G. mellonella in in vivo trials, A. baumannii pathogenicity was effectively suppressed, and G. mellonella survival rates were at least 75%.

According to preliminary in vivo research by Goss et al., systemic gallium nitrate can improve lung function in CF patients with persistent P. aeruginosa infections and increase survival in mice lung infection models. Additionally, the study discovered that P. aeruginosa developed resistance to gallium nitrate at rates comparable to those of the traditional anti-pseudomonal drugs ciprofloxacin, tobramycin, and colistin. This suggests that gallium nitrate may be especially useful against bacteria that are extremely resistant, such as P. aeruginosa.

Additionally, research has demonstrated that a sub-micromolar concentration of gallium nitrate (0.5 µM) significantly reduced the formation of P. aeruginosa biofilms, although larger doses (100 µM) killed P. aeruginosa cells that were deeply embedded in the biofilm matrix, where the majority of antibiotic action is often lost87. Given that P. aeruginosa bacterial infections in cystic fibrosis (CF) frequently result in biofilms, which subsequently foster antibiotic resistance, a medication that can successfully target P. aeruginosa biofilm development would be extremely beneficial for CF patients. The promise of gallium(III) compounds as an antibacterial agent is further supported by the fact that, in addition to gallium nitrate, additional gallium(III) compounds including gallium trichloride and gallium(III)-citrate have demonstrated efficacy against P. aeruginosa biofilm formation in the micromolar range.

5.2. Gallium protoporphyrin

The original goal of the compound gallium protoporphyrin (GaPP) (see Fig. 6) was to restrict iron metabolism by focusing on heme absorption. Its strong structural resemblance to heme, with gallium in place of the core iron atom, is what gives it its activity. GaPP has demonstrated strong antibacterial action against both Gram-negative (P. aeruginosa and A. baumannii, MICs = 4–16 µg/mL) and Gram-positive (methicillin-sensitive S. aureus (MSSA) and MRSA strains, MICs = 0.031–0.062 µg/mL). A GaPP-based topical therapy decreased bacterial biomass in S. aureus biofilms in a sheep sinusitis model, according to recent research. Studies have shown that GaPP binds to serum albumin, the most prevalent plasma protein, despite its great antibacterial efficacy from in vitro screening.This could result in a reduction in the amount of free GaPP to interact with bacteria, therefore leading to a significant decline in its activity *in vivo*.

Studies looked into using medication combination therapy to get around this problem. GaPP, Ganite, and colistin were combined by Choi et al. to produce a synergistic antibacterial activity against MRSA, A. baumannii, and Klebsiella pneumoniae (K. pneumoniae). GaPP is thought to maximise the benefits of combining two forms of gallium by targeting the heme absorption pathway, while the free gallium from gallium nitrate is absorbed by siderophore-mediated and/or free iron uptake pathways.

5.3. Gallium maltolate

A gallium-based substance with promising antibacterial efficacy is gallium maltolate (GaM) (see Fig. 6), particularly against very clinically significant antibiotic-resistant bacteria such staphylococci. Because GaM is a water-soluble compound, it can circulate under physiological conditions. Additionally, the three maltolate ligands that chelate the core gallium atom give GaM considerable lipophilicity, which makes it easier for bacterial cells to absorb it. Research has demonstrated that GaM exhibits antibacterial activity in vitro against a range of bacterial species, such as Mycobacterium avis, Salmonella Newport, P. aeruginosa, Rhodococcus equi101, and 102. According to a study by Arnold et al., GaM suppressed bacterial growth in vitro between 8 and 36 hours after inoculation when given to S. aureus and MRSA at concentrations of 50–200 µM.

Because GaM has shown activity against bacterial strains that are usually antibiotic-resistant and linked to significant morbidity and mortality, it shows great promise as a treatment option for bacterial infections where there is a critical need for novel antibiotics. Overall, the mimic gallium(III)-based compounds are probably able to act against several target locations because iron(III) ions are involved in a variety of bacterial activities. Gallium-based compounds may be one of the most promising options for new antibacterial medicines in this post-antibiotic era since multitarget compounds often show lower rates of drug resistance than traditional single-target antibiotics.

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6. Gold

Gold has been utilised medicinally since the 19th century, when sodium tetrachloroaurate [Na(AuCl4)] was used to treat syphilis, a bacterial infection brought on by Treponema pallidum (T. Pallidum). Potassium dicyanidooaurate (I) (K[Au(CN)2]), a gold-based chemical, is thought to have shown antibacterial activity against Mycobacterium tuberculosis (M. tuberculosis) in 1890, sparking interest in gold's antimicrobial qualities.

The qualities of gold (I) and gold (III) are principally responsible for the biological and medical uses of gold. While gold (III) is isoelectronic with platinum (II) in cisplatin and is therefore thought to have similar capabilities, gold (I) has been found to selectively target enzymes containing sulfhydryl or selenol groups. Although these characteristics of gold (I) and gold (III) have mostly been used for their anticancer effects, there is growing interest in their antibacterial qualities.

The mitochondrial oxidative phosphorylation pathways are important intracellular targets of both gold(I) and gold(III), according to numerous studies. Additionally, research indicates that the inhibition of thioredoxin reductase (TrxR) appears to be a common mechanistic characteristic of gold(I) and gold(III) action. Together with NADPH, thioredoxin helps cells produce reduced disulphide bonds and carries out other vital tasks like DNA replication and protecting some bacteria from oxidative stress. Therefore, it is hypothesised that severe TrxR inhibition may cause the bacterial cell to undergo apoptosis.

6.1. Auranofin

Currently licensed as an antirheumatic medication, auranofin is a phosphine-Au(I) derivative (see Fig. 7) that has demonstrated encouraging antibacterial action by targeting TrxR. According to studies, auranofin has little to no activity against Gram-negative bacteria like A. baumannii and P. aeruginosa121, but it is effective against drug-resistant Gram-positive bacteria like S. aureus, MRSA, Enterococcus faecium (E. faecium), Enterococcus faecalis (E. faecalis), and M. tuberculosis (MIC = 0.5 µg/mL). The glutathione system found in Gram-negative bacteria is thought to make up for the loss of TrxR function, which lowers auranofin's effectiveness. However, auranofin's capacity to specifically target and eradicate the Gram-positive bacteria in the ESKAPE pathogen class is a potentially useful feature.

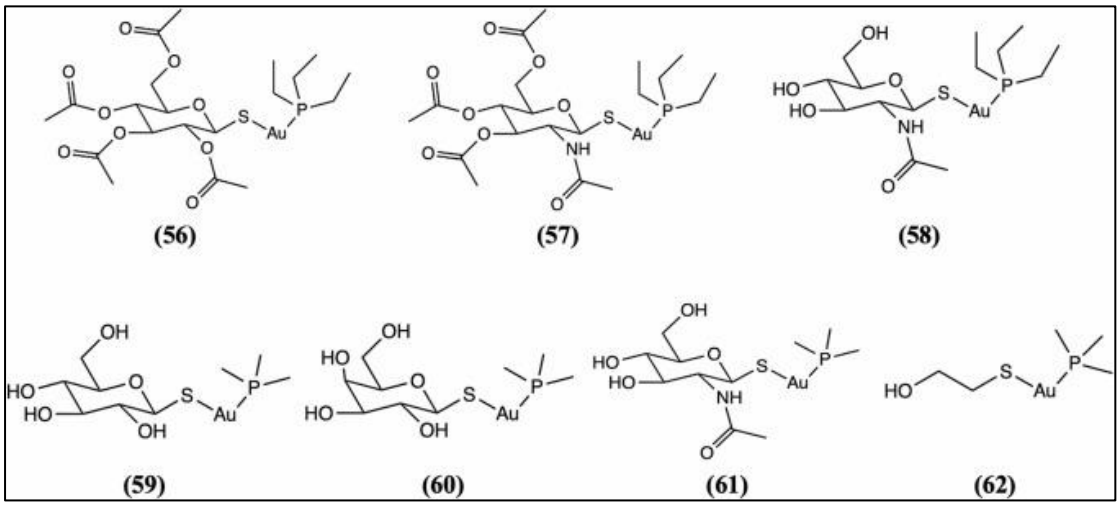

Fig. 7. Molecular structures of gold(I)-based antibacterial compounds. (56) Auranofin (57) to (62) Analogues.

In addition to in vitro experiments, a murine systemic MRSA infection mode demonstrated auranofin's in vivo antibacterial efficacy. Compared to the vehicle control group, oral treatment of 0.25 mg/kg one hour after infection produced an 80% survival rate over five days123. These results demonstrate auranofin's potential as a powerful antibacterial agent against human Gram-positive MRSA, which is an important factor to take into account when assessing novel antibacterial candidates given the growing threat of AMR worldwide. Notably, a study by Tharmalingam et al.124 found that a S. aureus strain exposed to auranofin continuously for 25 days showed no discernible resistance.

Furthermore, auranofin has exhibited synergistic antibacterial activities with Fosfomycin, linezolid, and chloramphenicol in both in vitro and in vivo screens, as well as excellent anti-biofilm activity against E. faecalis and S. aureus biofilms125. A lower chance of bacterial resistance to auranofin is suggested by the combination of strong anti-biofilm activity, low demonstrated resistance potential, and synergistic antibacterial impact with current antibiotics.

Wu et al.126 synthesised and tested 40 auranofin analogues against both Gram-positive and Gram-negative bacterial strains in an effort to increase the drug's effectiveness and therapeutic index. Among the several analogues, compounds (57) to (62) (Fig. 7) showed favourable MIC and MBC up to 65 times higher than auranofin. Additionally, compounds (59) through (62) had a comparatively wider range of antibacterial activity, exhibiting bactericidal activities against both Gram-positive and Gram-negative bacteria, such as S. aureus, A. baumannii, Enterobacter cloacae (E. cloacae), E. faecium, and E. coli.

6.2. NHC-Au(I) complexes

In the medical applications of gold, phosphine-gold complexes like auranofin are the most researched, but in recent years, NHC has gained attention as an alternative ligand. In contrast to phosphine ligands, NHCs form thermodynamically stronger coordination to the metal and have more stable and versatile steric, electronic, and physical properties. All of these factors contributed to the growing interest in NHCs in medicinal chemistry, including antibacterial medicines based on gold.

TrxR enzymes, G-quadruplexes, the zinc-finger enzyme PARP-1, and mitochondrial respiration are among the proteins, enzymes, and metabolic processes that have been found to be antibacterial targets of NHC-Au(I). The nature of the coordinated NHC ligand and the type of complex determine the specific targets. For instance, gold(III) complexes are reduced by cellular sulfides, but gold(I) complexes usually show stronger mitochondrial effects. As a result, it is thought that NHC-gold complexes and other gold-based complexes have comparable antibacterial processes, with minor variations in targets based on the oxidation state of gold and the kind of NHC ligand.

A. baumannii, E. coli, P. aeruginosa, E. faecium, and S. aureus were among the Gram-positive and Gram-negative bacterial strains against which the activity of NHC-Au(I) complexes (63) to (70) (see Fig. 8) was assessed and compared with that of auranofin137. With MIC values ranging from 0.64 to 12.51 µM and IC50 values ranging from 0.1 to 0.5 µM, all complexes were very effective against Gram-positive bacteria and inhibited bacterial TrxR. These results demonstrate and bolster NHC-gold complexes' potential as effective antibacterial agents, especially against Gram-positive bacteria.

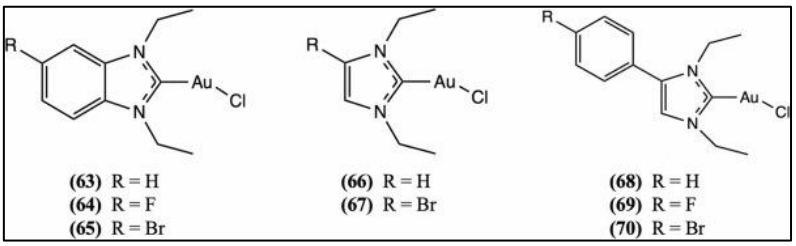

Fig. 8. Molecular structures of NHC-Au(I) complexes (63) to (70).

6.3. Gold (III) complexes

The emergence of multidrug-resistant bacteria has encouraged the examination of gold(III) complexes as possible antibacterial agents in addition to their well-established anticancer role, despite the fact that publications on their antibacterial activity are scarcer than those on gold(I) complexes. Stability problems are a major reason for the paucity of research on the antibacterial characteristics of gold(III) complexes. The biological activity of gold(III) complexes depends on stabilising the +3 oxidation state of gold, but this is difficult to do because gold(III) readily reduces to gold(I). The different gold(III) complexes and their antibacterial qualities have been compiled in a thorough review by Ratia et al. Thus, only a few cases will be the subject of this paper.

The equivalent gold(III) analogues of NHC-Au(I) complexes were also synthesised and assessed as antibacterial agents due to their biological significance. In line with findings for analogous NHC-Au(I) complexes, the NHC-Au(III) complexes (71) to (73) (see Fig. 9) showed more activity against Gram-positive bacterial strains (MRSA

and E. faecium) than Gram-negative bacterial strains (A. baumannii, E. coli, and P. aeruginosa). Furthermore, all of the NHC-Au(III) complexes successfully inhibited bacterial TrxR, suggesting a potential link between the enzyme's inhibition and the NHC-Au(III) complexes' antibacterial action mechanism.

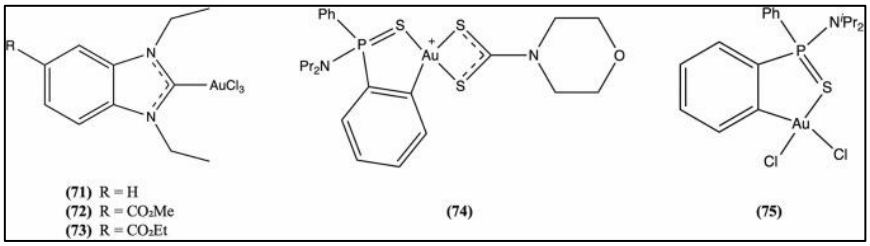

Fig. 9. Molecular structures of gold(III)-based antibacterial complexes. (71) to (73) NHC-Au(III) complexes. (74) to (75) (S^C)-cyclometalated Au(III) complex.

The impact of several dithiocarbamate ligands on the therapeutic index of dithiophenylphosphine-Au(III) complexes has been thoroughly investigated, building on earlier research142. Complex (74) (see Fig. 9) demonstrated significant in vitro antibacterial activity against multidrug-resistant strains, specifically S. aureus (MIC = 0.04–0.37 µg/mL) and P. aeruginosa (MIC = 11.8 µg/mL), while exhibiting low cytotoxicity among a series of (S^C)-cyclometalated gold(III) complexes developed and tested against a variety of Gram-positive and Gram-negative bacterial strains. Additionally, complex (74) prevented the formation of biofilms in S. aureus, P. aeruginosa, and A. baumannii, with minimum biofilm inhibitory concentration (MBIC) values that were about twice as high as their corresponding MICs. Additionally, complex (74) showed strong stability under physiological settings, suggesting that it will probably continue to have antibacterial activity in vivo.

More recently, Ratia et al. reported a novel (S^C)-cyclometalated gold(III) complex (75) (see Fig. 9) with a diphenylphosphinothioic amide moiety that exhibited significant antibacterial activities against multidrug-resistant Gram-positive (MIC = 4–8 µg/mL) and Gram-negative (MIC = 16–32 µg/mL) bacteria. Interestingly, this study confirms the function of the outer membrane as a permeability barrier and describes for the first time a synergistic interaction between a gold(III) complex and colistin, generating fast bactericidal activity in less than two hours. Furthermore, complex (75) did not cause resistance mutants to evolve throughout a 30-day period, in contrast to the study's control antibiotics. Together, these results highlight this compound's membership in a recently developed class of antibacterial drugs based on gold.

7. Promising metals

7.1. Iridium

Amongst metal complexes, iridium was found to be one of the most common element found in bioactive compounds, and also shows one of the highest overall success rates in terms of complexes showing bioactivity. Within the vast library of iridium complexes, cyclometalated iridium(III) complexes are an emerging group of antibacterial agents that act as photosensitisers, absorbing light of a specific wavelength to generate reactive oxygen species (ROS). This approach is known as antibacterial photodynamic therapy (aPDT), where ROS has the ability to damage enzymes, proteins, DNA and/or RNA, and is particularly promising for localised infections. An extensive range of cyclometalated iridium(III) complexes has been synthesised to date, many of which display promising antibacterial properties. For example, complex **(76)** (see Fig. 10) showed positive antibacterial activity against *E. coli* (MIC = 4 µg/mL), and complex **(77)** (see Fig. 10) was shown to effectively kill *P. aeruginosa* (MIC = 4 µg/mL), a Gram-negative bacterial strain that has proven to be significantly difficult to kill. According to a different study, two new cyclometalated iridium(III) complexes (78) and (79) (see Fig. 10) have quantum yields of 0.16 and 0.30, respectively, and function as photoactivated antibacterial agents by producing singlet oxygen. Mature S. aureus biofilms were partially disrupted by both complexes' antibacterial efficacy against E. coli and S. aureus. Interestingly, these compounds need to be exposed to radiation around 370 nm, which makes direct skin application difficult. However, the results continue to validate the complexes as good beginning points for additional improvement and modification. Cyclometalated iridium(III) complexes' antibacterial mechanism usually entails rupturing the bacterial membrane's integrity and/or causing the formation of ROS. Furthermore, a number of these complexes have demonstrated effectiveness in both targeting cells beneath the biofilm and inhibiting and eliminating biofilms.

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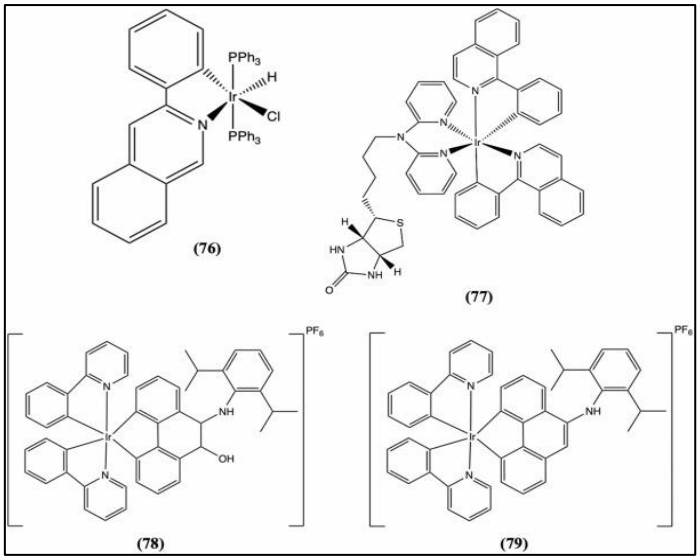

Fig. 10. Molecular structures of cyclometalated Ir(III) complexes (76) to (79).

A recent work by Lin et al.150 introduced three cyclometalated iridium(III) complexes (80) to (82) (see Fig. 11) with comparatively improved antibacterial activity, building upon previous generations of these complexes. With MICs ranging from 1.9 to 7.9 μg/mL, all three reported complexes demonstrated potent antibacterial activity against S. aureus in this latest study. Interestingly, the most active combination (82) showed notable antibacterial effectiveness against clinically isolated drug-resistant bacteria and relative stability in mammalian fluids. Complex (82) demonstrates a multi-target mode of action on S. aureus, compromising bacterial membrane integrity and boosting intracellular ROS generation, according to additional research on its mechanism. When combined, this multi-target advantage enables complex (82) to fight both the bacterial biofilm and AMR. Additionally, an *in vivo* assessment of complex **(82)** using *G. mellonella* and mouse infection models displayed low toxicity and robust anti-infective efficacy, further supporting the potential of complex **(82)** as a promising new antibacterial agent.[11]

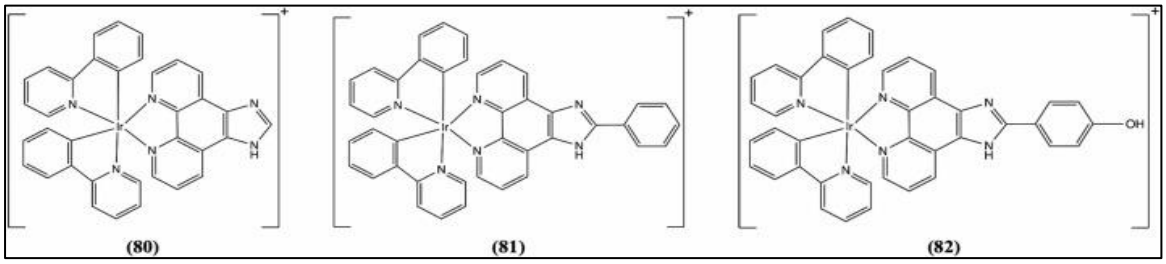

Fig. 11. Molecular structures of cyclometalated Ir(III) complexes (80) to (82).

Other kinds of iridium-based compounds have also been synthesised and assessed, in addition to cyclometalated iridium(III) complexes. For example, 14 organoiridium(III) complexes were synthesised by Chen et al.151, many of which showed encouraging action against a variety of Gram-positive and Gram-negative bacteria. Among the 14 complexes, complex (83) (see Fig. 12) had the strongest antibacterial activity against K. pneumoniae, E. coli, A. baumannii, and MRSA151. Three tetrazolium iridium(III) complexes (84) to (86) were synthesised and their antibacterial effectiveness assessed in a recently published study by Lu et al.152 (see Fig. 12). These compounds' potential as antibacterial agents was highlighted by their encouraging antibacterial activity against P. aeruginosa. [12,13]

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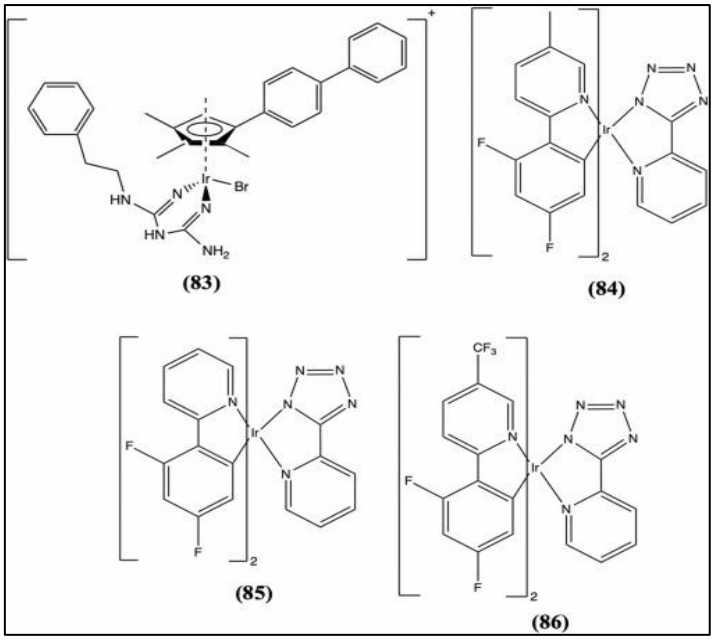

Fig.12. Molecular structures of iridium-based antibacterial complexes (83) Organoiridium (III) complex. (84) to (86) Tetrazolium-Ir(III) complexes.

It is thought that iridium (III) complexes could successfully prevent the development of AMR because of the multi-target mechanism. Iridium is not expected to be a commercially viable antibiotic, though, because it is more expensive than other metals. However, having a powerful and highly effective iridium-based antibiotic is preferable than having none at all. [13,14]

7.2. Ruthenium

The biological activity of ruthenium compounds, particularly their anticancer effects, has been extensively studied. The potential of ruthenium complexes as antibacterial agents has been shown in an increasing number of research in recent years. Strong binding of proteins and nucleic acids, similar ligand exchange mechanisms to platinum complexes, the presence of two primary oxidation states (II and III), and the imitation of iron when bound to biological molecules are all factors contributing to their antibacterial. Furthermore, certain complexes have produced ROS119 by acting as photosensitisers. The majority of the many ruthenium complexes that have been synthesised and tested for their antibacterial qualities show good action against Gram-positive bacteria. In this review, the focus will be on a complex that has demonstrated notable efficacy against Gram-negative bacterial strains.

In this regard, the antibacterial activity of a dinuclear ruthenium complex (87) was reported by Smitten et al. (see Fig. 13). With MIC values ranging from 0.5 to 1.6 µM, this compound demonstrated encouraging antibacterial activity against pathogenic, multidrug-resistant Gram-negative bacterial strains like E. coli and E. faecalis. Furthermore, there was no discernible cytotoxicity of the compound against eukaryotic cells (IC50 = 135 µM, HEK293). In line with findings previously documented for polynuclear ruthenium complexes, the complex seemed to localise near the cell poles. In the same study, the effectiveness of complex (87) was assessed against different strains of S. aureus. The complex's overall effectiveness against S. aureus was limited, and its potency was diminished in clinical isolates of MRSA and AMR.

Resistance via mprF-mediated membrane modification further decreased susceptibility to the complex, and the reduced effectiveness against mutant S. aureus strains indicated that binding of the complex to teichoic acids hinders penetration. Given that Gram-negative bacterial strains usually have higher intrinsic resistance to antimicrobial drugs, it is interesting to note that complex (87) was more efficient against Gram-negative bacteria than Gram-positive bacteria. This implies that the complex would be especially promising as an illustration of a metal complex that is effective against infections that are Gram-negative. [14,15,21]

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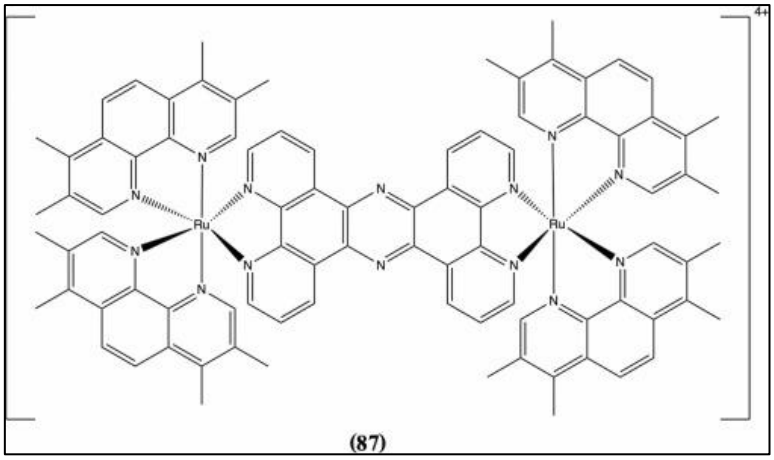

Fig. 13. Molecular structure of dinuclear ruthenium complex (87).

8. Metal-based antibacterials vs. conventional antibiotics

While several compounds with strong antibacterial activity have been identified as a result of the increased interest in metal-based complexes, it is still unclear if metal-based complexes actually offer appreciable advantages over conventional antibiotics or simply organic drugs. When assessing their relative merits, a number of aspects might be taken into account. First of all, metal complexes can interact with nucleic acids119, produce reactive oxygen species (ROS), release bioactive chemicals, or engage in ligand exchange processes. On the other hand, traditional antibiotics typically target a singular cellular pathway. Table 1 provides a brief summary of the modes of action for each metal covered in this review.

Since the bacteria must develop numerous mechanisms of resistance against the metal complex, this multi-target action is especially helpful in the fight against AMR and multidrug-resistant bacteria. Furthermore, the development of resistance is made even more challenging by relatively non-specific antibacterial activity, such as the production of ROS. According to some research, resistance to metal complexes develops at a rate comparable to that of traditional antibiotics86, while other findings reveal no discernible resistance even after several treatment cycles. Although further research is required to precisely determine how frequently bacteria become resistant to particular metal-based complexes, the available data clearly indicates that these complexes may be less likely to cause AMR. [16,17,22]

Table 1. Summary of possible mode(s) of action of selected metal-based antibacterial agents.

Metal Complex	Possible Mode(s) of Action
Silver (Ag)	Release of Ag(I) ions disrupt bacterial cell membrane; inhibit enzyme activity; disrupt DNA replication
Gallium (Ga)	Ga(III) acts as an iron mimetic to inhibit activity of iron-dependent enzymes; inhibit biofilm formation
Gold (Au)	Inhibit sulfhydryl/selenol enzymes (e.g. TrxR)
Iridium (Ir)	Generate ROS (often via aPDT); damages enzymes, proteins, DNA and RNA
Ruthenium (Ru)	Bind nucleic acids and proteins; similar ligand exchange mechanism as Pt; iron mimetic when bound to biomolecule; generate ROS (often via aPDT)

Second, metal complexes' adaptability—which includes the ability to change the metal, ligand, and oxidation state—allows for precise control over antibacterial potency and selectivity—a quality that is more difficult to get with conventional antibiotics. Additionally, coordination complexes have access to a wide variety of 3D geometries, which has been linked in certain studies to improved clinical outcomes. Another study discovered that because Metallo fragments have a greater degree of available three-dimensional chemical space, they exhibit excellent promise for fragment-based drug development approaches.

Metal complexes provide benefits, but it's important to recognise their drawbacks as well. While the pharmacological and metabolic characteristics of organic compounds as antibiotics have been thoroughly studied over many years, research devoted to comprehending metal complexes as antibacterial agents is still scarce. As a result, the organic compound synthesis toolset is extremely advanced and even scalable for industrial production. This is still mostly unknown for metal complexes, and it will take years of extensive and expensive experimentation to fully understand. As previously mentioned, the development process may be hampered by the expense of certain metals, especially in the field of antibiotics, where dosages are often greater and margins are

narrow. However, if such metal complexes show notable antibacterial activity, they are still worth investigating. However, complexes based on less expensive metals will be less likely to encounter this obstacle.

The in vivo toxicity of metal complexes should also be taken into account, particularly as mammalian cells share some targets with bacterial cells. Since some metals are not found in the human body naturally, it is plausible to speculate that introducing these foreign elements could cause the immune system to respond negatively.

To address this issue, Frei et al. analysed the antibacterial profile of 906 metal complexes and reported that their toxicity rates were comparable to those of various purely organic compounds, with similar levels of cytotoxicity against HEK293 cells and haemolytic effects against human red blood cells (64.5 % vs. 64.2 %). While this study is limited in scope and further research is needed to fully characterise the cytotoxicity of metal complexes, the findings are encouraging and indicate that metal complexes may not be inherently more toxic than conventional antibiotics. [6,17,22]

9. Challenges in Developing antimicrobial metal-based drugs

Obstacles in the creation of medications based on antibacterial metals Having said all of this, the scientific community is well aware that the creation of antimicrobial drugs—and not just metal-based drugs—faces a number of difficulties, despite the fact that these compounds have significant promise due to the special characteristics of metal centers. Here, we'll go over some of the main problems that chemists could run into when creating new metal antimicrobials. A wide range of metal ions are harmful to human cells. The creation of highly selective chemicals that guarantee selective targeting of microbial cells is significantly hampered by this. Coordination with organic ligands is one tactic that could be used to improve specificity and lessen off-target effects.

Metal lophores, which are low molecular weight organic ligands that typically supply an organism with metal ion nutrition, are an excellent illustration of this.33 Under physiological conditions, metal-based compounds often show unstable behaviour in solution, which can result in early breakdown, low absorption, and difficulties maintaining therapeutic levels in vivo. In this case, the utilisation of delivery methods or stabilising ligands could be helpful. Microbial resistance to metal ions is another issue that may arise, albeit usually more slowly than with organic antibiotics. The effectiveness of metal-based antimicrobials may be significantly diminished by bacterial defence mechanisms including efflux pumps or metal ion sequestration. Designing chemicals that act through several routes is crucial to overcoming this phenomenon and making it more difficult for bacteria to build resistance.

Furthermore, as previously mentioned, combination therapy that mix metals with other medications (such as adjuvants or antibiotics) might stop or lessen the development of resistance. Optimising the antimicrobial activity of metal ions can be difficult due to their complex and multifactorial mechanisms, which involve interactions with proteins, lipids, and nucleic acids. Understanding how these metals impact microbial cells and how they could be adjusted for specificity and efficacy can be improved by in-depth mechanistic investigations that make use of methods like proteomics, genomes, and metabolomics. [18,19,23]

10. CONCLUSION:

In the hunt for new antibacterial drugs, metal-based complexes have shown promise because they have a variety of mechanisms of action that set them apart from traditional antibiotics. While emerging candidates like iridium and ruthenium demonstrate the wide range of mechanisms of action that have not yet been investigated, metals like silver, gold, and gallium have demonstrated their therapeutic promises. But there are still many obstacles to overcome. In vivo efficacy data for metal complexes are typically quite few, and there are still many knowledge gaps that prevent the development of potentially beneficial drugs. Therefore, it is undeniable that further research is required before metal complexes may be employed safely and effectively. For example, tests to evaluate the stability of metal complexes in water, biological media, and human blood should be part of metal complex studies. Gathering more comprehensive information regarding the processes and stability of metal complexes is crucial. The most recent example of how cutting-edge technologies like Metallo proteomics can be used to reveal the intricate mechanisms behind the activity of metal-based complexes is the work of Sun et al.167. Building on these technologies, future studies can adopt a more forward-thinking strategy by using these developments to direct the logical design of metal complexes with enhanced bioavailability, target selectivity, and reduced cytotoxicity. Predictive computational models and high-throughput screening may be more effectively incorporated into

research as artificial intelligence (AI) continues to progress, which would speed up the identification of complexes appropriate for in vivo applications. This may help close the gap between promising in vitro activity and clinical use. However, there is little doubt that metal-based antibacterial agents have a promising future. The millions of organic molecules that have been investigated still far outweigh the vast library of metal complexes that have been created and assessed thus far. However, there are still a lot of undiscovered metals. When combined, these point to a substantial knowledge gap that can serve as a basis for further study. More intriguing ways to investigate and improve the therapeutic potential of metal complexes are provided by developments in ligand design, targeted delivery strategies, and even combinatorial approaches with traditional antibiotics. Metal-based antibacterial drugs may provide a workable approach in our global fight against AMR in bacteria with more thorough research.

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