

ARTICLE

Coordination Compounds against Multi-drug Resistant Bacteria: a Critical Review

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Christian Cavalini Benedicto,^{a,b} Antonio Marçal Neto,^a Ralciane de Paula Menezes,^b Ana Carolina Gomes Jardim,^c Camilla Abbehausen,^d Fernando Rodrigues Goulart Bergamini,^{*a} Carlos Henrique Gomes Martins^b

In the effort to shed some light on the bacterial multiresistance problem and the lack of a dynamic approach able to overcome the drug innovation gap, coordination compounds arise as a very promising source of potential antibacterials. Ubiquitously active against several biomolecular components of the bacterial cell, these potential therapeutics have presented low probability of resistance development. As adjuvants those compounds were shown to reverse bacterial resistance against certain antibacterial drug. Herein the readership will find both historically relevant and current developments of coordination compounds encompassing transition and post-transition metal complexes as well as metalloid-based molecules that have shown activity against resistant strains. Seeking to further stimulate drug development, pivotal information regarding virulence and resistance factors of nosocomial pathogenic bacteria can also be found as bullet statements.

Introduction

The Antibiotic Era is on the verge of its downfall, caused by the emergence of multidrug resistant bacteria (MDRB).¹ Although a seemingly alarmist statement, since its infancy in the 20th century, the discovery and further clinical introduction of antibacterial chemotherapeutics was followed very shortly by the emergence of bacterial strains able to overcome the selective pressure caused by the (sometimes unregulated) clinical application of antibacterial compounds.^{2,3} The drug development pipeline is far behind the remarkable adaptability of these pathogenic organisms highlighting an unfortunate perspective for any prophylactic or therapeutic approach that demand antibacterial chemotherapeutics.^{1–8} Organizations such as the World Alliance against Antibiotic Resistance suggest that the currently approved drugs may lose completely their effectiveness in the next few years⁹ potentially hindering routine antibacterial treatments such as tonsil infections as well as prophylactic measures related to intricate surgical procedures as, for instance, heart transplants. Today, around 700,000 people die each year due to drug-resistant infectious diseases, and 10 million deaths per year are estimated for 2050 if no immediate action is established

globally.¹⁰ In addition, CDC calculates that, every year, more than 2.8 million bacterial resistant infections occur only in the United States, with more than 35,000 MDRB-related deaths.¹¹ Although antibiotics are not directly related to COVID-19, 15% of the hospitalized individuals can develop opportunistic bacterial types of pneumonia with the progress of the disease.¹² Such infections may delay patients recovery or even increase the number of COVID-19 related-deaths.

Therefore, there is an imperative need for a more dynamic approach able to overcome the drug innovation gap seeking to follow up the fast adaptability observed in pathogenic bacteria, in terms of emergence of resistance. In this context, coordination compounds (CCs) have gained the spotlight due to their versatility in terms of antiproliferative activities: unreachable to purely organic compounds, their differential structural and chemical features can be fine-tuned onto the generation of highly efficient drugs against infections caused by pathogens such as viruses, bacteria and protozoa.^{13–19}

A few very good reviews have covered, both historically and in perspective terms, the general topic of metal complexes as potential antibacterial agents.^{20–28} Nevertheless, in front of the diversity of such compounds one could naturally raise the question: among the plethora of these CCs reported within the years with a diversity of metal ions, oxidation numbers, ligands, and structural scaffolds, which have shown to be active against MDRB? Could they be capitalized as hits for antibacterial chemotherapeutics able to overcome multi-resistance?

Herein, the readership may find a selection of coordination compounds encompassing transition, post-transition metal ions as well as metalloids which have shown activity against MDRB. In a seek of clarity, these CCs were organized by their possible mechanisms of action. When possible, the authors will point out

^a Laboratory of Synthesis of Bioinspired Molecules, Institute of Chemistry, Federal University of Uberlândia – UFU, 38400-902, Uberlândia, MG, Brazil. E-mail: bergamini@ufu.br

^b Laboratory of Antimicrobial Testing, Institute of Biomedical Sciences, Federal University of Uberlândia – UFU, 38405-302, Uberlândia, MG, Brazil.

^c Laboratory of Virology, Institute of Biomedical Sciences, Federal University of Uberlândia – UFU, 38405-302, Uberlândia, MG, Brazil

^d Institute of Chemistry, University of Campinas – UNICAMP, 38405-302, Campinas, SP, Brazil

the similarities, in terms of chemical features, among the **CCs** which are active against a particular MDRB. In the fine line between a comprehensive and critical approach, the authors intend to highlight **CCs** that could be further explored as anti-MDRB compounds along with the challenges entailed to the development of such entities.

Finally, a brief guideline towards MDRB features such as their virulence factors and mechanisms or resistance are briefly presented aiming to inspire further development of Anti-MDRB **CCs** with differential activities. Possible complementary assays to the commonly employed disc diffuse and MIC methods are also presented to further stimulate the gap shortening between **CCs** development and application.

Coordination compounds to the rescue?

Differently to organic compounds, **CCs** may present more than one mode of action, and the potential ubiquitous and dynamic nature of such compounds may explain their activity towards MDRB with a low probability of resistance development. After a long usage of silver compounds to fight bacteria, only few reports on resistance can be found, demonstrating the potential of metal-based antibacterials.²⁹ Prone to exert their biological activities through several mechanisms, **CCs** generally possess a leading pathway in which they accomplish their antiproliferative effect. As follows, **CCs** are presented according to their proposed mechanisms.

Membrane Disruption

CCs have presented abilities to interact with membrane biomolecular constituents (*e.g.* proteoglycans) enabling higher intracellular accumulation and/or membrane disruption. These compounds have been explored as potential antiproliferative agents against several diseases such as cancer as well as those caused by *Leishmania sp.* or bacteria, with at least one **CC** (silver sulfadiazine) currently employed as an antibacterial drug. For instance, Casini and Miguel reported that the ability of cyclometallated C^N Au^{III} complexes to affect the membrane integrity of *L. amazonensis* amastigotes may be related to the their high effectivity *in vitro*.³⁰ Farrell *et al.*, on the other hand, reported that the interaction of polycationic amine-bearing trinuclear Pt^{II} complexes (TriplatinNC[®]) with heparan sulfate proteoglycans of cancer cell membranes enabled higher intracellular accumulation of these compounds when compared to neutral Pt^{II} drugs such as *cis*-diamminedichloroplatinum(II) and oxalato-(1,2-cyclohexanediamine)platinum(II) – cisplatin and oxaliplatin, respectively.^{31,32} This accumulation along with the further interaction of these compounds as phosphate clamps towards DNA and RNA were suggested to play an important role on their increased activity against human colon carcinoma (HCT116) and osteosarcoma (SAOS-2) tumor models.^{31–34} Silver(I) sulfadiazine (Figure 1, **Ag-1**) has been successfully employed as a topic antibacterial agent against Gram-positive and Gram-Negative bacteria.^{35–38} **Ag-1** is mainly employed as a prophylaxis and/or treatment agent against bacteria in burns and wounds. Mechanistic studies encompassing the **Ag-1** complexes with radioactive silver (¹¹⁰Ag) or the radioactive

ligand (³⁵S) were carried out against *Pseudomonas aeruginosa* (*P. aeruginosa*) and *Staphylococcus aureus* (*S. aureus*). These studies suggested that Ag^I, rather than the whole complex **Ag-1** is bound to the bacteria. The unbound ligand sulfadiazine plays a synergistic role on the antibacterial effect.³⁶ **Ag-1** seems to possess a ubiquitous mechanism, interacting with DNA, polysaccharides, generating of free radicals as well as affecting the integrity of the bacterial membrane.^{36,39,40,41}

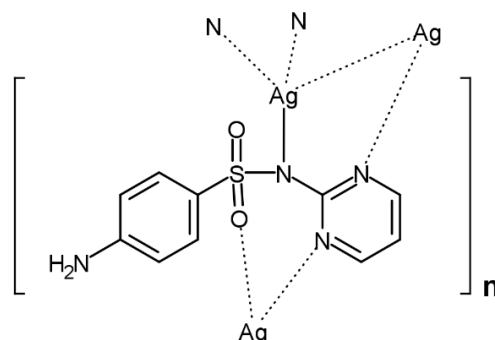


Fig. 1. Schematic representation of silver(I) sulfadiazine monomer (CCDC 1103733).³⁷

In fact, Ag^I ions from AgNO₃ have been proven to interact with *Escherichia coli* (*E. coli*) envelope proteins (OmpA, OmpC, OmpF, Oppa and MetQ) and one might suggest such mechanism of interaction could be shared by **Ag-1**.⁴² Interestingly, bacteria appears to do not develop resistance to **Ag-1** and the combined use of this **CC** to quinolones reduced the ability of *P. aeruginosa* to develop resistant strains while potentializing the quinolones activities.⁴³ Most recently the effect of **Ag-1** against Methicillin-resistant *S. aureus* (MRSA) biofilms was evaluated.⁴¹ MRSA ATCC BAA-2856 (OJ-1), a high biofilm forming strain, was employed in the assays. Differently from AgNO₃, **Ag-1** was able to eradicate mature biofilms in concentrations lower (< 4000 µg mL⁻¹) than what is found available commercially (*i.e.* in Silvadene[®] cream, 10000 µg mL⁻¹) and bactericidal activity in the same concentration.⁴¹

A series of chiral cyclometallated C^N palladium-terpene complexes (Figure 2, **Pd-1** to **Pd-6**), inactive against Gram-negative bacteria, had their antimicrobial activity reported against MRSA. The organometallics **Pd1** - **Pd5** exhibited minimum inhibitory concentration (MIC) values in the range of 1 - 32 mg L⁻¹, with **Pd-2** presenting the lowest MIC (1 mg L⁻¹). Despite **Pd-2** cytotoxicity against human embryonic kidney cell models (HEK293 ATCC CRL-1573; CC₅₀ = 12.4 mg L⁻¹) and haemolytic activity (HC₁₀; against HRBC red blood cells) of 1.83 mg L⁻¹, this **CC** presented a promising selectivity index (SI = 12). Complex **Pd-1** was the second most active with a MIC of 4 mg L⁻¹ but with much lower SI (CC₅₀ = 3.0 mg L⁻¹, SI = 0.75 and HC₁₀ = 1.0 mg L⁻¹).⁴⁴ **Pd-6**, a coordination compound bearing a terpene derivative of ethylenediamine as ligand, presented a MIC of 8 mg L⁻¹ with low cell viability and high haemolytic activity (CC₅₀ = 0.6 mg L⁻¹, HC₁₀ = ~1 mg L⁻¹). Such toxicity towards human cells was associated with the high lipophilicity conferred by the *tert*-butyl group. Overall, the authors suggested that the **Pd-1** to **Pd-6** activities against MRSA may be associated to a non-specific

membrane disruption which leads to both antibacterial and haemolytic activities.⁴⁴

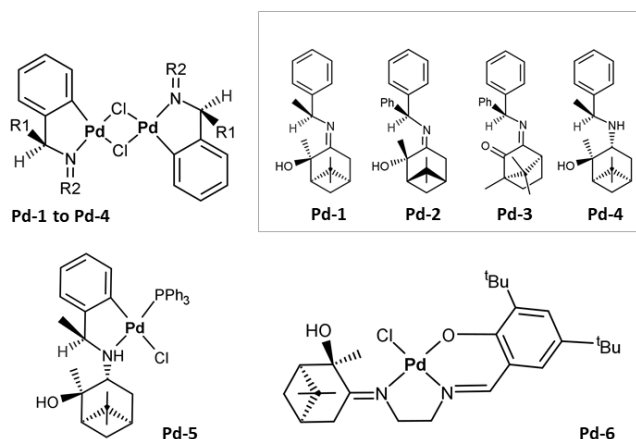


Fig. 2. Schematic representation of the coordination of complexes **Pd-1** to **Pd-4**, and structures of **Pd-5** and **Pd-6**. Ligands of **Pd-1** to **Pd-4** are presented in box.

Brahma's group synthesized and evaluated the activity of a thiosemicarbazone derived hexadentate macrocyclic Cu^{II} complex (**Cu-1**, Figure 3) against a selection of Gram-negative (*P. aeruginosa*, *Acinetobacter baumannii*, *Klebsiella pneumoniae*, and *Escherichia coli*) and Gram-positive (*Staphylococcus aureus*, *Clostridium difficile*, and *Enterococcus faecalis*) bacteria.^{45,46} The best results were obtained against two clinical isolates strains of MRSA (ATCC 33592 and ATCC 700699) and a Methicillin-sensitive *S. aureus* (MSSA) strain (ATCC 29213), in which the MIC values were of 6.25 mg L⁻¹ against ATCC 33592 and 29213, and of 12.5 mg L⁻¹ against ATCC 700699.⁴⁶ The possibility of resistance development to MRSA strains towards **Cu-1** was evaluated by adding sub-inhibitory concentrations of **Cu-1** in continuous MRSA cell passaging during 15 days. No resistance development was observed.⁴⁶ Conversely, MRSA developed resistance against ofloxacin within few days of exposure.

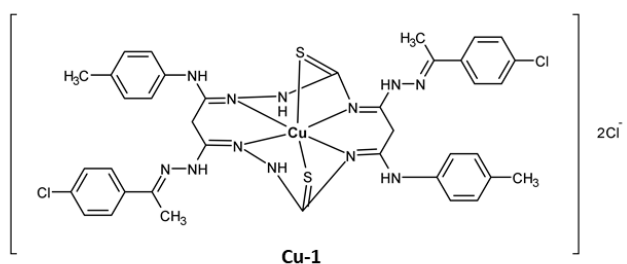


Fig. 3. Proposed coordination of the macrocyclic ring to the Cu^{II} ion in **Cu-1**.

Interestingly, **Cu-1** showed a significant anti-biofilm effect, inhibiting 50% of 24h and 72h old biofilms at 9.18 ± 0.16 mg L⁻¹ and 8.51 ± 0.68 mg L⁻¹, respectively.⁴⁶

Assays employing propidium iodide (PI) uptake using Flow cytometry in *S. aureus* cells indicated that there was an uptake of 41.7% of PI after treatment with **Cu-1**.⁴⁶ For untreated cells only a 8.3% PI uptake was observed. Additionally, Scanning Electron Microscopy (SEM) of *S. aureus* cells treated with **Cu-1** presented numerous protrusions on the cell surface along with

cell membrane damage, and lysis.⁴⁶ Moreover, studies employing RAW 264.7 cell (Murine Macrophage cells, ATCC TIB-71) infected with *S. aureus* showed that **Cu-1** has anti-*S. aureus* activity intracellularly. **Cu-1** was able to reduce 96.6% of the bacterial load at a concentration of 10 mg L⁻¹ whereas no assayed antibacterial chemotherapeutic (oxacillin, vancomycin, and linezolid) showed more than 77.3% reduction. CC₅₀ for **Cu-1** in this model was 62.99 ± 1.48 mg L⁻¹.⁴⁶

Dithiocarbamate Zn^{II} complexes (**Zn-1** and **Zn-2**, Figure 4) had their antimicrobial and antibiofilm activities screened against susceptible and MDR strains of *S. aureus* and *E. coli*.⁴⁷ Such compounds were active against the susceptible and the MRSA strains with MIC values of 4 mg L⁻¹ (susceptible strain) and 16 mg L⁻¹ (MRSA strain) for both complexes. Minimum biofilm inhibitory concentration (MBIC) values were of 1 mg L⁻¹ and 2 mg L⁻¹ against the susceptible strain, and of 8 mg L⁻¹ and 4 mg L⁻¹ against the MRSA strain for **Zn-1** and **Zn-2**, respectively. Further investigations were carried with complex **Zn-1** in which a MRSA biofilm reduction of 94.71% and 81.53% was observed at concentrations of 8 mg L⁻¹ and 4 mg L⁻¹, respectively. Fluorescence microscopy was carried out indicating that **Zn-1** induces MRSA death by damaging its membrane.⁴⁷

Mn^{I} tricarbonyl complexes bearing tripodal ligands (Figure 5, **Mn-1** to **Mn-4**) were evaluated against MDR *Acinetobacter baumannii* (*A. baumannii*) and *P. aeruginosa* strains.⁴⁸ Among the CCs, complex **Mn-4** presented the best results with MIC of 100 $\mu\text{mol L}^{-1}$ (~ 66 mg L⁻¹) to all *A. baumannii* strains and 50 $\mu\text{mol L}^{-1}$ (~ 33 mg L⁻¹) to PA 92 strain. **Mn-4** results for the other *P. aeruginosa* MDR strains ranged from 200 $\mu\text{mol L}^{-1}$ to 800 $\mu\text{mol L}^{-1}$.⁴⁸ In general, the order of activity, from the higher to the least active complexes against *A. baumannii* and *P. aeruginosa* MDR strains, was **Mn-4** > **Mn-3** > **Mn-2** > **Mn-1**. Authors correlated such order to the number of quinolinylmethyl groups and, therefore, the increased lipophilicity of the complexes from **Mn-1** to **Mn-4**.⁴⁸ Prior studies also indicated that **Mn-4** can act synergistically to the antibacterial chemotherapeutic colistin against avian MDR *Escherichia coli* (*E. coli*), which might suggest that such CC may be employed as an adjuvant.^{48,49} Monitoring the extracellular ATP levels of *A. baumannii* AB184 and *P. aeruginosa* PA1 cultures suggested that complexes **Mn-1** to **Mn-4** are able to compromise the inner bacterial membrane.⁴⁸ Nevertheless, additional intracellular interactions to bacterial supramolecular structures cannot be discarded. Further toxicity assays employing *Galleria mellonella* ("honeycomb moth") larvae as model of infection indicated no toxicity of **Mn-4** at doses up to 80 mg kg⁻¹. Post-infection treatment with **Mn-4** (5mg kg⁻¹ in PBS) against *A. Baumannii* (AB12, AB184) and *P. aeruginosa* (PA92, PA1) infected larvae indicated 80% and 50% survival rate, respectively.

Interaction with DNA

DNA and RNA are among the most common CC targets. These complexes may be directly coordinated to DNA (e.g. nucleobases) or interact non-covalently through electrostatic (e.g. phosphate clamps)³² and π -stacking interactions. For instance, the anticancer mechanism of Pt^{II} drugs such as cispla-

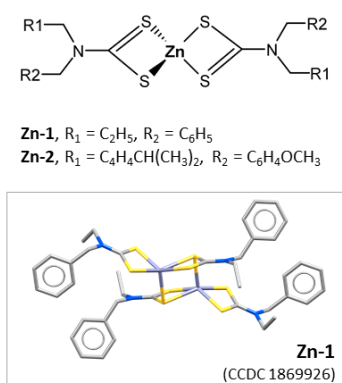


Fig. 4. Schematic structure of Zn^{II} dithiocarbamate complexes **Zn-1** and **Zn-2**. Crystal structure of **Zn-1** inbox.

tin, carboplatin and oxaliplatin entails majorly the coordination of DNA guanine residues to Pt^{II} in an intra-strand 1,2-GpG fashion, ultimately leading to cancer death.^{50–53}

Additionally, as previously mentioned, **Ag-1** antibacterial action also encompasses the coordination by the bacterial DNA to Ag^I .³⁶ Other examples involve the study of complexes as intercalators, able to interact with bacterial DNA through non-covalent interactions (π -stacking).⁵⁴ Some of these complexes were active against MDRB.⁵⁴

Curcumin-based Ru^{II} complexes (**Ru-1** and **Ru-2**, Figure 6) had their antibacterial activities assayed against ESKAPE pathogens, including clinically isolated MRSA and Vacomycin Resistant *Staphylococcus aureus* (VRSA) with an equipotent MIC of 1 – 2 $mg\ L^{-1}$.⁵⁵ Despite the activity of **Ru-2** against *A. baumannii* BAA-1705 (MIC 8–16 $mg\ L^{-1}$), the other pathogens were not affected by the compounds.⁵⁵ These **CCs** were viable to Vero cell models (ATCC CCL-81) with a SI > 80 towards bacterial cells. Biophysical assays employing ethidium bromide displacement of DNA resulted in apparent binding constants (K_{app}) on the order of $10^6\ L\ mol^{-1}$, suggesting a stronger binding affinity with groove binding as the most probable mode of interaction.⁵⁵

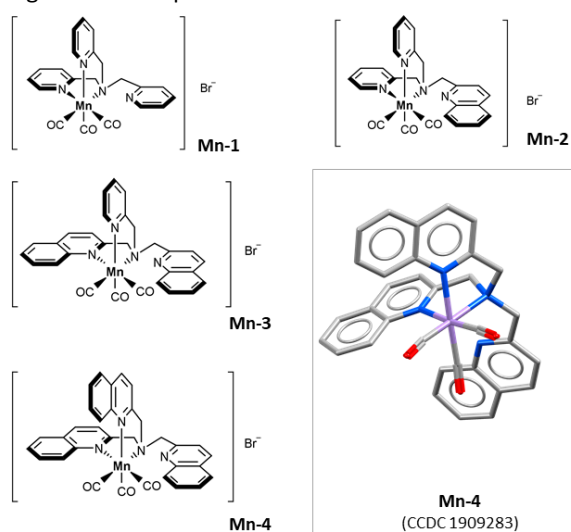


Fig. 5. Tricarbonyl Mn^{II} complexes with tripodal ligands. Inbox shows crystallographic structure of **Mn-4**.

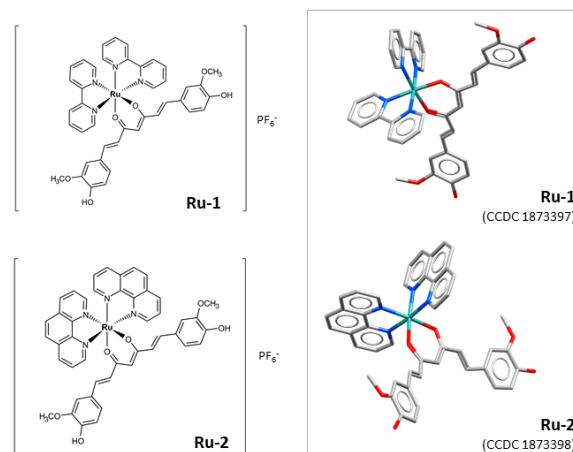


Fig. 6. Schematic structure of **Ru-1** and **Ru-2**. Crystal structures are represented inbox.

Stern-Volmer quenching constants and binding constants of the interaction between the Ru^{II} complexes and HSA are on the order $10^5\ L\ mol^{-1}$ and $10^6\ L\ mol^{-1}$, respectively.⁵⁵

Such values indicate strong binding affinity of the complexes. Since HSA is a carrier protein for many compounds and metal ions in the bloodstream, this interaction might enhance **CCs** biodistribution if eventually applied *in vivo*.⁵⁵

Bolhuis and co-workers evaluated the antibacterial activities of three Ru^{II} polypyridyl complexes (**Ru-3** to **Ru-5**, Figure 7).⁵⁴ The **CCs** showed no effect against Gram-negative bacteria but promising results MIC and minimum bactericidal concentration (MBC) against MRSA strains. The order of activities was **Ru-5** > **Ru-4** > **Ru-3**. The best activity of **Ru-5** was observed against MRSA252 (MIC = 2 $mg\ L^{-1}$; MBC = 8 $mg\ L^{-1}$). Time-kill assays were also performed employing **Ru-5** against MRSA252 indicating a concentration-activity dependence onto bactericidal activity.⁵⁴ **Ru-5** was also screened using *S. aureus*-infected *Caenorhabditis elegans* (*C. elegans*) *in vivo* models. *C. elegans* were infected with *S. aureus* 1h prior to **Ru-5** treatment. At concentrations of 8 or 32 $mg\ L^{-1}$ of **Ru-5**, a 80% nematodes survival was observed after 6 days. Untreated *S. aureus*-infected *C. elegans* died within 6 days. Although *C. elegans* may be considered a good model in the evaluation of toxicity of a certain compound in higher eukaryotes, no mammalian cell cultures were assayed in this study.⁵⁴ Authors suggested that the DNA-binding affinity order of the ligands (dppz, of **Ru-5** > dppQ, of **Ru-4** > dppQ, of **Ru-3**) may be related to the observed antibacterial activities.^{54,56}

Li and co-workers reported the strong activity of complexes **Ru-6** to **Ru-10** (Figure 7) against MSSA, MRSA, *E. coli* (ATCC 25922) and *P. aeruginosa* (ATCC 27853).⁵⁷ The activity of the compounds was slightly higher over the MSSA and MRSA strains when compared to *E. coli*, and even more when compared to *P. aeruginosa*. Among these complexes **Ru-8** was the most active against MRSA (1 $mg\ L^{-1}$ of MIC and MBC), followed by **Ru-7** (1 and 2 $mg\ L^{-1}$) and **Ru-9** (4 and 8 $mg\ L^{-1}$).

Time-kill curve indicated that **Ru-7** and **Ru-8** are bactericidal at 2x MIC, killing 99% of the bacterial population within 2 – 6 h, with **Ru-8** presenting a faster effect when compared to **Ru-7**.⁵⁷

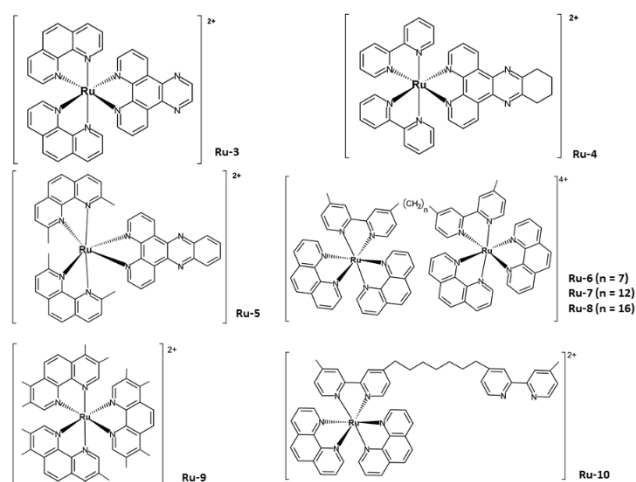


Fig. 7. Schematic structures of Ru^{II} polypyridyl complexes **Ru-3** to **Ru-10**

Ru-7 showed the highest cellular uptake in the MRSA strain, explaining the highest MIC.⁵⁷

It is puzzling, however, that the effect of light-driven oxidative damage on MRSA was not explored in **Ru-3** to **Ru-10** complexes, especially considering that all three Ru^{II} complexes present chromophores and might act as photosensitizers.^{58,59} For instance, Glazer and co-workers investigated similar polypyridyl compounds that were able to produce DNA photocleavage and/or DNA photobinding.⁵⁹ In absence of light no activity is observed.⁵⁹

Efflux pump

The expression of efflux pumps, biofilm formation and bacterial quorum sensing (QS) controls are related to bacterial resistance.

Kincses and co-workers evaluated the antibacterial and anti-biofilm activities of a series of 2-trifluoroacetylbenzoxazole derivatives and their **CCs** encompassing a variety of metal ions (Fe^{II}, Mn^{II}, Zn^{II}, Cu^{II}, Ag^I and Pd^{II}) against *S. aureus* ATCC 25923, MRSA 272123, *E. coli* AG100, *Chromobacterium violaceum* 026, and *Enterobacter cloacae* 3198 strains.⁶⁰ The potential inhibition of efflux pumps and QS was also assessed. Among the results of antibacterial activity, the best MIC values observed were of 3.125 $\mu\text{mol L}^{-1}$, 6.25 $\mu\text{mol L}^{-1}$ and 12.5 $\mu\text{mol L}^{-1}$, for **L-2**, **Zn-3** and **Cu-2** (Figure 8), respectively, against the MRSA strain. Resistance modulation effects of the ligands and complexes at 0.25 MIC was evaluated in the presence of antibacterial chemotherapeutics ciprofloxacin (CIP) and tetracycline (TET). Especially, a synergistic activity was observed between CIP and **L-3**, **Zn-3** and **Cu-2**, in which CIP MIC was reduced from 12.5 $\mu\text{mol L}^{-1}$ to 6.25 $\mu\text{mol L}^{-1}$.⁶⁰ Efflux-pump (EP) inhibition was assessed through on real-time automated ethidium bromide intracellular accumulation.⁶⁰ Although only **L-3** was able to successfully inhibit the EP in MRSA, complexes **Zn-3** and **Ag-2** presented remarkable inhibition of AcrAB-TolC in non-resistant *E. coli* AG100.⁶⁰ Authors suggested that the observed differences between EP inhibition profiles in MRSA and *E. coli* are related to

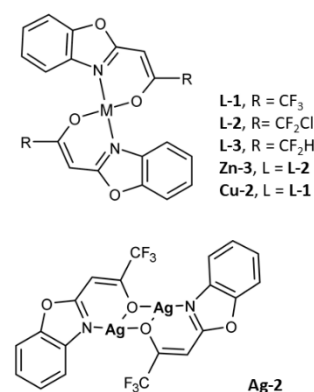


Fig. 8. Ligands (**L-1** to **L-3**) and highlighted benzoxazole-based complexes.

cell wall composition and the thick peptidoglycan layer of Gram-positive MRSA may present different essential membrane protein distribution when compared to *E. coli* (Gram-negative).⁶⁰ Quorum-sensing inhibition using *Chromobacterium violaceum* 026 sensor strain and *Enterobacter cloacae* 3198 (AHL producer) was observed for **L-3** as well as highlighted complexes **Zn-3** and **Ag-2**.⁶⁰ No highlighted complex presented anti-biofilm activity against *S. aureus* ATCC 25923 (non-resistant) model.⁶⁰ Another interesting work reports the evaluation of Cu^{II} and Co^{II} complexes (**Cu-3** and **Co-1**, Figure 9) with the ligand pyrophosphate against a series of bacterial strains, including a multidrug resistant tuberculosis (MDR-TB).⁶¹ **Cu-3** and **Co-1** presented specificity over *Mycobacteria*, notably against the MDR-TB, with MIC of 2.8 $\mu\text{mol L}^{-1}$ (1.95 mg L^{-1}) and 2.41 $\mu\text{mol L}^{-1}$ (2.44 mg L^{-1}), respectively. Authors suggested that, for **Cu-3**, the mechanism entail copper overload. The active uptake through the transmembrane channel protein Rv1698 leads to copper intoxication. In a similar mechanism, the *M. tb* CorA protein responsible for transporting Mg²⁺ to the cell may also transports Co^{II}, potentially increasing intracellular Co^{II} concentration upon **Co-1** administration.⁶¹ Continuous treatment with sub-MIC concentrations of **Co-1** did not generate resistant strains. Multiple interactions with *M. tuberculosis* biomolecular machinery might explain the lack of resistance towards **Co-1**.⁶¹

Redox homeostasis

CCs can both trigger the generation ROS through light and non-light activated mechanisms. For the first case, the non-light activated ROS generation may occur through two distinct pathways: redox reaction of the CC with inert oxygen species generating ROS as byproducts, and/or inhibition of redox enzymes, further leading to imbalance on the intracellular redox homeostasis.

For instance, diphosphine Au^I compounds have shown to interact majorly with mitochondrial thioredoxin/thioredoxin reductase (Trx/TrxR) system of cancer cells, causing imbalance to tumors redox homeostasis thus triggering apoptosis by a apoptosis stimulating kinase 1 (APK1) mechanism.⁶² Trypanothione/Trypanothione reductase inhibition by Au^I/Au^{III} **CCs** have been observed in trypanosomatids.^{62,63} Bacterial Trx/TrxR along with NADPH exert a critical role on DNA

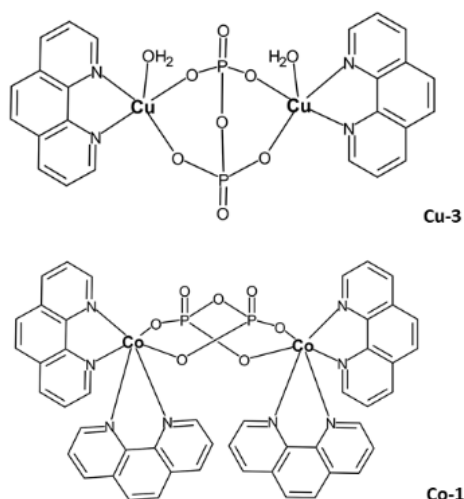


Fig. 9. Pyrophosphate complexes **Cu-3** and **Co-1**.

synthesis.⁶⁴ As for the case of human Trx/TrxR system, it is responsible for redox homeostasis in bacterial cells with almost low homology between human and bacterial TrxR.⁶⁴ Such system can thus be explored as an antibacterial target for both metal and metalloid-based compounds.

Metalloid-based competitive inhibitors of TrxR such as ebselen (**Se-1**, (2-phenyl-1,2 benziselenazol-3(2H-one), Figure 10) have shown bactericidal activities against macrolide resistant *Helicobacter pylori* (*H. pylori* MR162 and MRG193) and multidrug-resistant *Mycobacterium tuberculosis* (*M. tuberculosis* panel 3:24 and BTB 98-310) strains with MICs of 12.5 and 20 mg L⁻¹, respectively.⁶⁴

Ag^I ions, on the other hand, were reported to be coordinated by antioxidant proteins superoxide dismutase A (SodA), DNA-protection during starvation protein (Dps) and glutaredoxin (GrxB), thus inducing oxidative stress in *E. coli* by ROS generation.⁶⁵ One might suggest that such mechanism can also be shared by Ag^I CCs, especially those in which the ligand is a carrier for Ag^I ions such as **Ag-1**.

Copper(II)-bis(thiosemicarbazone) complexes **Cu-4** and **Cu-5** (Figure 11) have been reported to inhibit respiratory electron transfer processes in *Neisseria gonorrhoeae* (*N. gonorrhoeae*) strains via succinate and NADH dehydrogenases.⁶⁶ Complexes **Cu-4** and **Cu-5** were evaluated against *N. gonorrhoeae* MDRB strain.⁶⁷ **Cu-5** presented higher activity with MIC of 0.1 μmol L⁻¹ for all MDRB strains. **Cu-4**, on the other hand presented MIC in the range of 0.7 to 3.0 μmol L⁻¹ for the resistant *N. gonorrhoeae* strains.⁶⁷ The ligands themselves would act as carriers for Cu^{II}

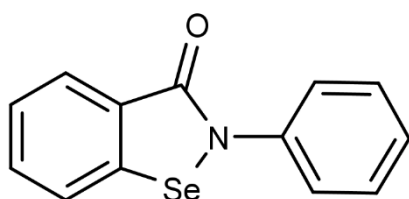


Fig. 10. Metalloid-based compound Ebselen®, **Se-1**.

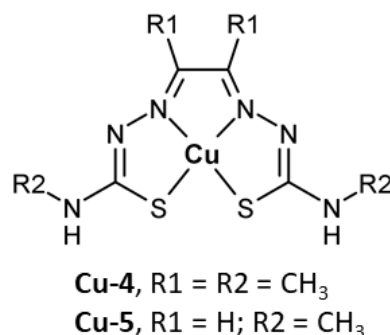


Fig. 11. Schematic structures of complexes **Cu-4** and **Cu-5**.

ions, enabling copper-poisoning. Differences among the activities of **Cu-4** and **Cu-5** were assigned to different efflux profiles caused MtrCDE efflux pump inhibition. Inactivation of mtrD gene, responsible for MtrCDE expression, generated higher MIC values for **Cu-4** whereas for **Cu-5** no difference was observed. Authors suggested that **Cu-4** is effluxed by MtrCDE while **Cu-5** is not.⁶⁷

Auranofin (**Au-1**, Figure 12) is a Au^I complex employed as an antiarthritic drug which has been explored as an antimicrobial agent against pathogens such as viruses and bacteria.¹³ **Au-1** displays antibacterial activity especially against Gram-positive bacteria and *M. tuberculosis* due to the inhibition of TrxRs enzymes.

Marzo's group evaluated the effect of **Au-1** and Au^I and Ag^I complexes (**Au-2** to **Au-6** and **Ag-3** to **Ag-6**, Figure 12) against Gram-positive and Gram-negative MDRB.⁶⁸ **Au-2** to **Au-5** exhibited antibacterial activity comparable to or slightly lower than **Au-1** against the Gram-positive MDR strains, with MICs ≤ 0.062 mg L⁻¹, while **Au-6** presented to be less active, with MIC ranging between 0.5 to 8 mg L⁻¹. When it comes to the Gram-negative MDR strains, **Au-1** activity is reportedly to be scarce¹⁹⁷, however, **Au-2** to **Au-5** presented slightly greater activity than **Au-1** but in lower effect than against the Gram-positive, with MIC in the range between 4 and >32 mg L⁻¹. Again, **Au-6** were the less active, with MIC of 16 mg L⁻¹ against all Gram-negative strains. The compounds were also assessed in combination with the permeabilizing agent polymyxin B nanopeptide (PMBN), and results displayed an increase of the antibacterial activity for **Au-1** and **Au-2** to **Au-5** (MIC = 0,125 to 2 mg L⁻¹). **Au-6** presented no significant increase of the antibacterial effects even in the presence of PMBN, nevertheless, specifically against *P. aeruginosa* Vr143/97, the MIC of all Au^I compounds, including **Au-6**, decreased noticeably, and this effect may be related to the already observed higher susceptibility of this stain to PMBN.^{68,198}

Au-2-Au-4 are **Au-1** analogues where the thiosugar ligand is replaced by a halide ligand. Considering that the results obtained for these compounds are similar to one another, and

also comparable or slightly lower than **Au-1**, the authors implies that the thiosugar is not essential for the antimicrobial activity

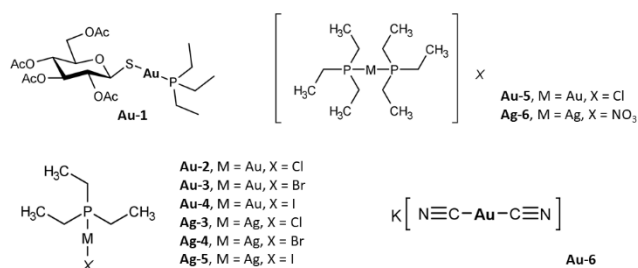


Fig. 12. Schematic structures of complexes **Au-1** to **Au-6**, and **Ag-3** to **Ag-6**.

of the latter, neither is the halide ligand for **Au-2** - **Au-4**. Actually, the antimicrobial activity may be related to the $[\text{Au}(\text{PET}_3)]^+$ moiety. For the case of **Au-6**, the lack of activity may be related to the stronger coordination of the cyanide ligand to Au^{I} in comparison to other ligands impairing cyanide dissociation and subsequent binding of Au^{I} to bacterial targets.⁶⁸ Despite the known antimicrobial properties of silver compounds (e.g. **Ag-1**), replacement of Au^{I} with Ag^{I} resulted in decrease of the antibacterial potency of the compounds against both Gram-positive and Gram-negative MDR strains even in the presence of PMBN. According to NMR experiments, this decrease may be related to the lower stability of the silver complexes in the biological medium.⁶⁸

In a recent study, Wu and collaborators synthesized 40 **Au-1** analogues and evaluated their activity against ESKAPE pathogens.⁶⁹ Different phosphine and thiol ligands were utilized in the analogues synthesis to effectively modulate the anti-GNB activity of **Au-1**.⁶⁹

Generally, the best compound against all four MDR Gram-negative strains was **Au-7** (Figure 13), with MIC in the range of 2.9 to 23 $\mu\text{mol L}^{-1}$ and MBC in the range of 2.9 to 91 $\mu\text{mol L}^{-1}$. The lowest MIC and MBC (2.9 $\mu\text{mol L}^{-1}$) was obtained against *E. cloacae*, 65-fold more active than **Au-1**.⁶⁹ Specifically against *A. baumannii*, **Au-7** and **Au-8** (Figure 13) exhibited the best activity with MICs of 5.7 and 13 $\mu\text{mol L}^{-1}$, respectively. In the case of *P. aeruginosa*, the best analogue was **Au-9** (Figure 13) presenting MIC and MBC of 41 $\mu\text{mol L}^{-1}$, 9 times better than **Au-1**. **Au-7** was also the best complex against *K. pneumoniae* with MIC of 11 mg L^{-1} , which is 34-fold better than **Au-1**. Furthermore, a cytotoxicity assay utilizing A549 cells (ATCC CCL-185) demonstrated that **Au-7**, **Au-8** and **Au-9** present similar or lower mammalian cell toxicities compared to **Au-1**.⁶⁹

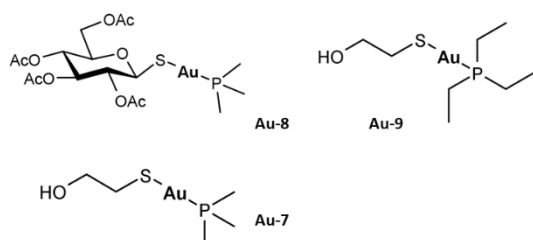


Fig. 13. Schematic structures of **Au-7** to **Au-9**.

Although these complexes were not assayed as for the redox imbalance, the well reported interaction of Au^{I} and Ag^{I} complexes onto the interaction with redox proteins leads to the suggestion that these complexes present antibacterial activities through similar pathways.

ROS Generation by Photosensitizers:

Light-activated ROS generation by CCs have been covered by several current and historically relevant reviews.²¹⁷⁰⁷¹ Metal-based aggregation-induced emission luminogens are also broadly discussed elsewhere.⁷² Herein, a very strict selection of CCs photosensitizers which were assayed against MDRB is presented. In 2020, Pierce's group synthesized **Ru-12** (Figure 14) conjugated with the peptide buforin II, characterized by targeting DNA. **Ru-12** was analysed as an antimicrobial photodynamic therapy (APDT) agent against MDR *A. baumannii* Naval-17 in the dark and under irradiation conditions of 470 nm light over 12 h (12 mW/cm^2).⁷³ The results obtained were of MIC 4 $\mu\text{mol L}^{-1}$ in the dark and 0.5 $\mu\text{mol L}^{-1}$ under irradiation. Furthermore, electrophoresis assay utilizing the plasmid pUC19 demonstrated that **Ru-12** might damage DNA model under irradiation by generation of ROS. The authors suggest that **Ru-12** is addressed to the DNA by influence of the peptide.⁷³

Heme analogs and Iron uptake transporters

Hijazi's group evaluated three Ga^{III} compounds (Figure 15) in three different media with diverse iron concentration against several microorganisms, including MRSA strains. **Ga-1**, **Ga-2** and **Ga-3** had its effects evaluated.⁷⁴

Ga-3 demonstrated MIC in the range of 0.06 to 0.12 $\mu\text{mol L}^{-1}$ against *S. aureus* ATCC 43300, *S. aureus* Sau117 and *S. aureus* UD95 and of 16 to 32 $\mu\text{mol L}^{-1}$ against *A. baumannii* AYE, *A. baumannii* ACICU and *A. baumannii* C13-373. Considering that Ga^{III} act as a metabolic competitor of Fe^{III} , it was expected that the scarcity of iron in the utilized medium would influence the antibacterial activity of the compound, enhancing it. Highlighting the concentration of iron in both media that showed the lowest MIC values, the obtained results suggests that **Ga-3** does not depends on a mechanism of action responsive to this metal.⁷⁴

The reason why all *S. aureus* strains presented resistance against **Ga-3** (MIC > 128 $\mu\text{mol L}^{-1}$) was attributed to the presence of human serum albumin (HSA) in media which might reduce **Ga-3** bioavailability, since this protein might bind to the compound due to its chemical similarities with heme, impairing its translocation across the cell membrane through heme-uptake systems. Similarly, low MIC against *A. baumannii* ACICU

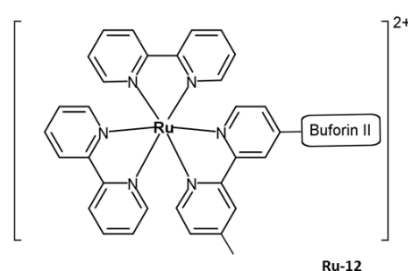


Fig. 14. Schematic structure of **Ru-12**.

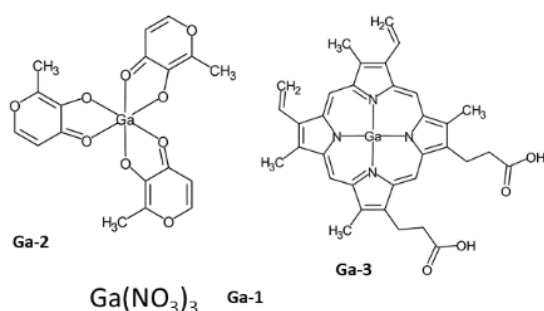


Fig. 15. Schematic structures of **Ga-1** to **Ga-3**.

(1 $\mu\text{mol L}^{-1}$) and *A. baumannii* C13-373 (0.25 $\mu\text{mol L}^{-1}$) might be related to the expression of *hemT* and *hemO* heme-uptake clusters, increasing **Ga-3** intracellular availability. **Ga-1** and **Ga-2** displayed MIC in the range of 0.5 to 16 $\mu\text{mol L}^{-1}$ against *K. pneumoniae*, *A. baumannii* and *P. aeruginosa* MDR strains.⁷⁴ **Ga-3** was previously assayed in 2015 against multiple strains of *A. baumannii* with different profile of resistance. However, the rich media utilized in the study might have not mimic the real condition encountered *in vivo*.⁷⁵

Pyridine-2-thiol 1-oxide (Hmpo) metal complexes (Figure 16) with Bi^{III} (**Bi-1**), Fe^{III} (**Fe-1**), and Ga^{III} (**Ga-4**) were evaluated against MDR *M. tuberculosis* strains.⁷⁶ **Ga-4** and **Fe-1** presented MIC in the range of 0.94 to 2.03 $\mu\text{mol L}^{-1}$ and 0.80 to 2.46 $\mu\text{mol L}^{-1}$, respectively, both more active than the free ligand assessed alone. Additionally, toxicity assays were realized on VERO cells (ATCC CCL-81) to determine IC_{50} and SI. Results obtained were of IC_{50} of 10.04 $\mu\text{mol L}^{-1}$ for **Ga-4** and 4.61 $\mu\text{mol L}^{-1}$ for **Fe-1**, and SI of 9.37 for **Ga-4** and 3.03 for **Fe-1**, indicating that **Ga-4** is a promising candidate for drug development.⁷⁶

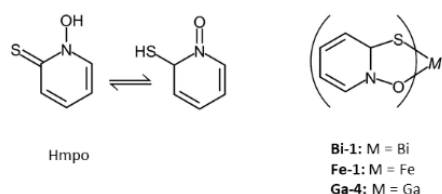


Fig. 16. Schematic structure of **Bi-1**, **Fe-1**, **Ga-4** e mpo.

More recently, Campos et al synthesized and investigated the same Fe^{III} complex **Fe-1** against two MDR and one XDR *M. tuberculosis* strains by determination of MIC, time-kill curve, IC in eukaryotic cells (MRC-5—ATCC CCL-171), and SI.⁷⁷ Against the MDR strains, MIC obtained for **Fe-1** were 2.25 ± 0.7 and 0.30 ± 0.1 $\mu\text{mol L}^{-1}$, and 2.25 ± 0.7 $\mu\text{mol L}^{-1}$ against the XDR strain. In the time-kill curve assay, utilizing the MIC concentration, **Fe-1** sterilized one of the MDR strains in 11 days *in vitro*, demonstrating a remarkable potential in the treatment of TB. The salt alone presents a sterilizing effect in 7 days at MIC of 6.52 ± 4.0 $\mu\text{mol L}^{-1}$. According to the authors, **Fe-1** takes longer to exert its effect due to Fe^{III} uptake by bacterial siderophores releasing the mpo molecules that posteriorly display its activity. **Fe-1** IC_{50} and SI over MRC-5 were of 5.26 $\mu\text{mol L}^{-1}$ and 4.9,

respectively, while the ligand appears to be less toxic with IC_{50} of 88.7 $\mu\text{mol L}^{-1}$ and SI of 12.3, requiring some modifications to improve **Fe-1** toxicity profile.⁷⁷

Metal ions coordinated by antibacterial chemotherapeutics: CCs with Synergistic Effect

As previously mentioned, the combination of **Ag-1** with quinolones (e.g. norfloxacin, perfloxacin, and enoxacin) had increased the activity of these drugs against bacterial commonly found in burns (i.e. *P. aeruginosa*).⁴³ Especially, this association also seemed to decrease the ability of *P. aeruginosa* strains to develop resistance towards the quinolones.⁴³

One complementary strategy to the combinatory treatment rely on the direct coordination of antibacterial drugs to the metal ions, also seeking synergistic effects.

For this reason, Kanwar et al. synthesized an isonicotinoyldithiocarbamic acid (IN-DtczH) ligand derived from Isoniazid (INH), one of the recommended first-line drugs for the treatment of TB, and developed **Ni-1**, **Co-2**, **Zn-4** and **Cu-6** (Figure 17) to evaluate their activity against mycobacteria, including the MDR-TB strain BC-750.⁷⁸ From the complexes, **Ni-1** expressed the highest activity against the MDR-TB strain, with MIC of 10 mg L^{-1} , followed by **Zn-4**, with MIC of 50 mg L^{-1} . Furthermore, **Ni-1** and **Zn-4** were very well tolerated on rhabdomyosarcoma cells without compromising cell survival even at the highest tested concentration of 75 mg L^{-1} .⁷⁸

Likewise, INH-like Ru^{II} complexes were synthesized and tested *in vitro* against *M. tuberculosis* susceptible and resistant strains.⁷⁹ **Ru-13** (Figure 18), however, was the only that presented activity against the resistant strains, with MIC of 22.55 and 24.26 mg L^{-1} . **Ru-13** IC_{50} was 250 mg L^{-1} and its SI = 416.66, exhibiting no toxicity in VERO epithelial cells and low cytotoxicity against J774A.1 macrophage cells. The authors considered these result promising, as INH did not show any inhibition even in the concentration of 25.00 mg L^{-1} .⁷⁹

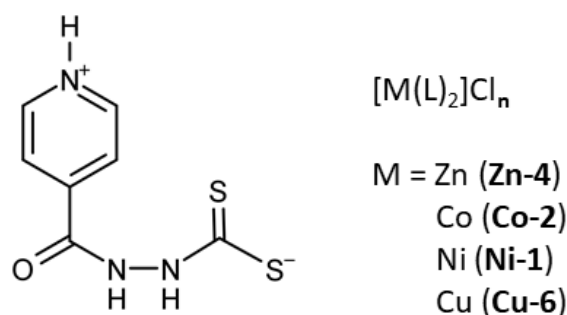


Fig. 17. Schematic structure of ligand IN-DtczH and molecular formula for its metal complexes. For all complexes $n=2$.

Inorganic Compounds as Adjuvants

Antibacterial adjuvants constitute an alternative and complementary strategy of drug development.^{80,81} Adjuvants are small molecules that do not kill bacteria directly. However, they can potentialize or even restore the previously lost antibacterial activities of current chemotherapeutics, thus surpassing the multi-drug resistance threshold. In order to accomplish the reactivation of the antibacterial activity, these compounds target mostly the bacterial resistance mechanisms.

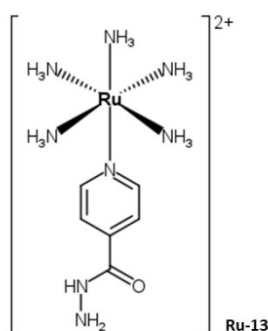


Fig. 18. Schematic structure of Ru-13.

In 2016, **Cu-7**, **Cu-8** and **Cu-9** (Figure 19) were synthesized with Casiopeínas® and assayed against *M. tuberculosis* strains, including MDR-TB, individually and combined with the antibiotics INH, rifampicin (RIF), or ethambutol (EMB), to evaluate if any antituberculosis activity was expressed.⁸² Individually, MIC were obtained in the range of 0.78 to 12.50. Fractional inhibitory concentration index (FICI) was calculated to evaluate the expression of synergistic effects and only values ≤ 0.5 were considered as an indication of synergy.⁸² Under this criterion the following combinations presented synergy: INH/Cu-8, RIF/Cu-7, RIF/Cu-9, EMB/Cu-7, EMB/Cu-8, and EMB/Cu-9, in which the compounds with EMB displayed better results. Supposedly, the polymerization of cell wall arabinan of arabinogalactam by EMB improves the compounds uptake, which in turn presents various levels of hydrophobicity.⁸²

Protein inhibition

Silver(I) ions have shown to be able to interact with bacterial envelope proteins (see section Membrane Disruption) also displaying capacity to interact with *E. coli* 30S ribosomal subunits (S6, IbpA and IbpB).⁴² Such proteins possess chaperone function against stress induced protein denaturation.⁴²

Sun and co-workers efforts towards the mechanism of activity of Ag^I ions indicated that such ions are able to target primarily enzymes in related to glycolysis and the oxidative branch of Citric Acid Cycle (CAC).^{65,83} Gel-electrophoresis coupled with ICP-MS showed that three *E. coli* enzymes involved in glycolysis, glyceraldehyde-3-phosphate dehydrogenase (GAPDH), phosphoglycerate kinase (Pgk) and dihydrolipoil dehydrogenase (LpdA) were found to be coordinated to Ag^I.⁶⁵ Further studies encompassing continuous-flow gel electrophoresis coupled with ICP-OES and single-crystal X-Ray crystallography showed that the inhibition GAPDH occurs through coordination of Cys149 and His176 catalytic site to Ag^I.

Another two Ag^I ions are seen coordinated by Cys288 and Glu286 non-catalytic site being further stabilized by argentophilic interactions.⁸³ The authors suggested stated that such inhibition may affect *E. coli* glucose consumption.⁶⁵ Additionally, an 80% and 50% inhibition of the CAC proteins isocitrate dehydrogenase (Icd) and malate dehydrogenase (Mdh) was observed, respectively.⁶⁵ These data together with the observed depletion of CAC substrates citrate, 2-oxoglutarate and isocitrate indicates that Ag^I ions affect CAC oxidative branch.⁶⁵

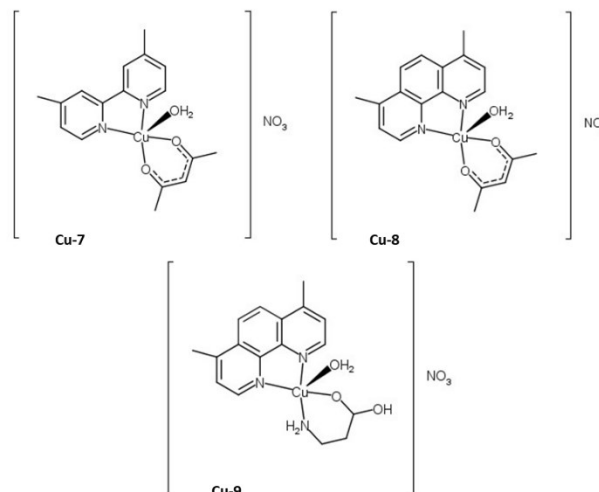


Fig. 19. Schematic structures of Cu-7 to Cu-9.

Other possible effects

Zombies effect is a term related to bacteria which were killed by a metal ion.^{38,84} Such bacteria function as a reservoir of these metal ions and, as a delivery system, is able to induce death to live strains. Such effect was firstly reported by Wakshlak and co-workers for Ag^I-killed bacteria.^{38,84}

MDRB Virulence and Mechanisms of Resistance

ESKAPE pathogens are the bacteria mainly involved in the resistance process. Such acronym is composed by the first letters of the bacteria *Enterococcus faecium* (*E. faecium*), *S. aureus*, *K. pneumoniae*, *A. baumannii*, *P. aeruginosa*, and *Enterobacteriaceae*.⁸⁵ In a seek to provide additional data that could further help on the development of effective antibacterial CCs, the readership will find as follows some bullet information regarding ESKAPE and non-ESKAPE multi-drug resistant pathogens. Additionally, from a microbiology point-of-view, some antimicrobial assays are herein highlighted. Most of these assays were employed in the works discussed in this manuscript.

According to Diard and Hardt, virulence is the capacity of a microorganism to cause damage to the host.¹⁹⁹ The concept of virulence factors covers a variety of molecules produced by microorganisms that enhance their ability to evade the defense mechanisms of the host and cause diseases. Products such as toxins, enzymes, cell surface structures, and the regulation of

genes involved in the expression of these molecules can be considered virulence factors.²⁰⁰

Enterococcus faecium is commonly found in the gut, oral cavity and female genital tract. Several strains of these bacteria are responsible for intra-abdominal, urinary tract and bloodstream infections.⁸⁶ *E. faecium* may present several virulence factors in which one could highlight the SagA protein (75kDa) that binds to human extracellular matrix and is essential for bacterial growth and biofilm formation.⁸⁷ The first VRE strains were reported in 1986.^{88,89} In this bacteria, mobile gene clusters confer resistance to glycopeptide antibiotics such as vancomycin and teicoplanin, by the vanA and vanB genotypes.⁹⁰ Likewise, the acquisition of mobile genetics elements also confer resistance to β -lactams, aminoglycosides and fluoroquinolones.⁸⁷

Staphylococcus aureus are bacteria that infect the blood stream causing endocarditis, pneumonia as well as bone and joint infections, which ultimately leads to sepsis.⁸⁶ Several factors contribute to its virulence such as the production of exotoxins, tissue invasion enzymes as well as the expression of immune-evasive surface factors.⁹¹ Many of these factors are acquired by mutations in the core genome or, majorly, through horizontal transference of mobile genetic elements (MGE) between different bacterial strains.⁹² These MGEs are known to provide resistance to β -lactam antibiotics, trimethoprim, erythromycin, clindamycin and tetracyclines and vancomycin.^{91–96}

Enterobacter aerogenes strains are facultative anaerobic Gram-negative and non-spore-forming bacilli commonly associated with respiratory, bloodstream, skin and soft tissue as well as urinary tract infections.^{97,98} Its most common virulence factors are adherence to mucosal and epithelial surfaces, expression of enterobactin and salmochelin siderophores, regulation of mucoid phenotype A and production of toxins, such as enterotoxin, microcin and colibactin.⁹⁹ *E. aerogenes* strains have a considerable ability to generate resistance factors to antimicrobials, such as the superexpression of efflux pumps.⁹⁸ Broad-spectrum β -lactamase expression associated with aminoglycoside enzymatic resistance also corroborates the resistance profile of these bacteria to β -lactam chemotherapeutics.^{98,100}

K. pneumoniae is a fermenting Gram-Negative bacteria natural to human gut and known to become an opportunistic pathogen.¹⁰¹ Despite living the human gastrointestinal tract asymptotically, it may cause pneumonia as well as urinary tract and bloodstream infections, mostly in immunocompromised individuals.^{102–104} It is a nosocomial problem usually triggering infections on surgical sites which can eventually escalate to sepsis.^{104,105} Four virulent factors play the major roles in *K. pneumoniae*: pili, capsule, liposaccharides (LPS), and iron carriers.¹⁰⁶ The pili promotes adhesion to immune and epithelial cells, as well as to abiotic surfaces. Its capsule, confers protection against immune response and it is associated with the high-mucus phenotype of hypervirulent *K. pneumoniae*.¹⁰⁷ LPS modifications may occur in order “camouflage” the bacteria, thus inhibiting the inflammatory response and reducing its clearance from the organism.^{108,109}

The expression of iron carriers, in their turn, play major roles in the growth and replication of bacterial cells.¹⁰⁶

As for the case of resistance, *K. pneumoniae* generally develops resistance horizontally through plasmids encoding antibiotic resistance genes (ARGs).¹¹⁰ For example, it was reported that genes from *aac*, *ant* and *aph* families confers resistance against aminoglycosides¹¹¹ whereas the *qnr* gene encodes proteins responsible for the protection of DNA gyrase and topoisomerase IV from quinolones¹¹², and *ramA* is responsible for efflux pump activation, increasing acquired β -lactamase-mediated β -lactam resistance.¹¹³ As a result of the acquired resistance, carbapenem-resistant *K. pneumoniae* for instance, possess high mortality rates (up to 48%) when compared to susceptible strains (17%).¹¹⁴

Acinetobacter baumannii is a non-fermenting Gram-negative in which the mortality rates may reach up to 54%.¹¹⁵ In most cases, *A. baumannii* causes ventilator-associated pneumonia and bloodstream infections, but it is also responsible for infections in the skin, soft tissues, urinary tract, and central nervous system.¹¹⁶ These bacterial strains possess remarkable survivability in a variety of environments, thus facilitating its dissemination as a nosocomial pathogen.¹¹⁷

A. baumannii virulence factors are related to outer membrane proteins (Omp) such as OmpA, Omp 33-36, and CarO which have important roles in biofilm formation, dissemination into the bloodstream, cell invasion and death.^{118–122} Other virulence factors are liposaccharides and capsule, which confers resistance and protection against the immune system^{116,123–125} as well as the expression of several enzymes able to promote its survivability and dissemination as, for instance, phospholipases and the enzyme CpaA.^{126,127} The formation of biofilm mediated by Quorum Sensing (QS) is another important virulence factor that confers resistance against external stress (e.g. antibiotics, immune system clearance, and desiccation) and allows bacterial interaction with the host, by cell attachment.^{128,129}

A. baumannii resistance is a major concern since its resistance profile is converting from MDRB to pan-drug resistant bacteria.^{130–132} This resistance is expressed depending on the antibacterial chemotherapeutic: enzymes and nonenzymatic mechanisms; energy-dependent efflux pumps and proteins that shield bacterial ribosomes; mutations on DNA gyrase and DNA topoisomerase IV; AbeS small multidrug resistance pumps; MacA-MacB-TolC tripartite complex transmembrane machine; mechanisms involving synthesis and composition of lipid A of the outer membrane as well as deficient expression of cell wall polysaccharide (LPS) synthesis cofactors are the main examples.^{116,133–138}

Pseudomonas aeruginosa, also a non-fermenting Gram-negative bacteria, is an opportunistic pathogen that takes advantage of immunocompromised and/or critically ill patients.^{139–142} It is related to ventilator-associated pneumonia, can cause urinary tract infections, external otitis as well as infect burns, wounds, bone and joints.^{143,144} If not treated correctly those infections can escalate to bacteremia.^{145–147}

Since the introduction of carbapenems, carbapenem-resistant *P. aeruginosa* (CRPA) strains have been described.^{148,149} Several factors are determinant in expression of resistance by *P.*

aeruginosa, as the emergence of sequential chromosomal mutations that alters the cell permeability over these substances and hyperexpresses MDR efflux (MEX) pumps, as MexAB-OprM and MexEF-OprN.^{150–152} An important characteristic of these MEX pumps is that they lack specificity, affecting different classes of antibacterial chemotherapeutics.¹⁴⁵ Additionally, the acquirement of β -lactamases like MBLs and OXA-type carbapenemases has increased spreading of resistant strains.^{145,150,153}

As *A. baumannii*, *P. aeruginosa* also relies on QS for the production of biofilm and regulation of gene expression, thus it is closely related to virulence. In *P. aeruginosa*, QS is responsible for the upregulation of key virulence factors.^{154–157} For example, pyocyanin, a phenazine cytotoxic to host cells, tissues, and immune system cells, that induces apoptosis and causes oxidative stress.^{158–160}

Additionally, QS regulates the production of Lectin A, an important protein for cell attachment, cell-cell interaction, and biofilm formation, which also influences intestinal epithelium permeability to ExoA.^{161–163} ExoA, considered one of the most toxic virulence factors in *P. aeruginosa*, is exotoxin regulated by QS which inhibits protein synthesis by the host cell causing cell death, tissue damage, bacterial invasion, and immunosuppression.^{164–166}

A. baumannii, *P. aeruginosa*, and *K. pneumoniae*, considering that these pathogens are among major causes of high-mortality HAIs¹⁶⁷ and are responsible for up to 40% of ICU infections.¹⁶⁸

Other non-ESKAPE MDRB

Staphylococcus epidermidis also express antibiotic resistance, including against methicillin and even in higher rates than *S. aureus*.¹⁶⁹ This resistance comes from the same MGE present in MRSA, namely the SCCmec containing *mecA*.¹⁷⁰ Additionally, *S. epidermidis* have acquired resistance to rifamycin, fluoroquinolones, gentamicin, tetracycline, chloramphenicol, erythromycin, clindamycin, sulfonamides and, in some cases, vancomycin.^{171,172}

Corynebacterium are Gram-positive, pleomorphic and non-sporulating bacilli that are usually part of the skin and the upper respiratory tract microbiota.¹⁷³ *Corynebacterium striatum* MDRB may cause respiratory and urinary tract infections. It may also be responsible for skin and eye wounds, endocarditis, meningitis, osteomyelitis, septic arthritis and bacteremia.^{173–175} *Corynebacterium* spp. virulence relies mainly on biofilm formation and adherence to human epithelial cells, which is mediated by cell surface pili.¹⁷⁶ These structures are also implicated in the colonization of host cells and evasion of the immunity.^{173,177} Resistance is mediated by the expression of resistance genes leading to the resistance to a variety of chemotherapeutics such as macrolides, lincosamides, streptogramins B, clindamycin and aminoglycosides.^{178–182} Additionally, mutations on *gyrA* gene was described to confer resistance to ciprofloxacin and moxifloxacin.¹⁸⁰

Mycobacterium tuberculosis is a bacillus that, different from the other bacteria herein presented, is a Gram-variable microorganism.¹⁸³ The distinct coating complex on its cell surface that precludes Gram staining and is described as “a waxy mycolic acid lipid complex” by Talip et al in 2013,

composed by a soluble outer compartment containing lipid-linked polysaccharides, and by an insoluble inner compartment of peptidoglycan, arabinogalactan, and mycolic acid.^{184–186}

M. tuberculosis is the causative agent of tuberculosis, one of the major causes of death worldwide, and the leading cause of death from a single disease.¹⁸⁷ About 206 030 people around the globe were notified with multidrug-resistant *M. tuberculosis* in 2019, a 10% increase from 2018. MDR-TB are those strains which are resistant to at least isoniazid and rifampicin, and its infections require longer (6 – 20 months) and expensive treatments that with low success rate (57%).¹⁸⁷ *M. tuberculosis* aerosolization implicates in air-born infections. Entering the lungs and triggering symptoms of prolonged coughing, chest pain, dyspnea, low-grade fever, night sweats and severe weight-loss.¹⁸³ Aggravatingly, it can also infect other organs displaying symptoms as meningitis, synovitis, pericarditis, cervical lymphadenitis, pleuritis, and infections of the skin, joints, bones and internal organs.^{188,189}

Antimicrobial Assays

Commonly *in vitro* employed assays to determine a microorganism susceptibility towards a certain compound encompasses the disk diffusion method and micro-dilution in broth (MIC determination).¹⁹⁰ Nevertheless, from these assays no information is gathered in terms of a bactericidal or bacteriostatic mode of action.¹⁹⁰ Among *in vitro* and post-MIC determination, one should highlight the death kinetics assays, the evaluation of synergism with commercial antimicrobials, along with the determination of post-treatment membrane integrity through ATP bioluminescence.¹⁹¹ Virulence factors inhibition entails the evaluation of biofilm eradication, exotoxin and quorum sensor synthesis inhibition.^{192,193} The ADMeTox assessment of a compound is then performed by *in vivo* assays, which include larvae (e.g. *Galleria mellonella*; *Caenorhabditis elegans*), Zebrafish as well as small mammals such as mice.¹⁹³

Conclusions and Perspectives

Infectious diseases caused by MDRB are far from being a manageable problem and a health crisis is a probable upcoming reality.¹⁹⁴ Medium-term economic and social welfare aside, the less profitable revenue expected on the development and commercialization of antibacterial agents seems to be the main cause of pharmaceuticals low interest on this class of drug.¹⁹⁴ Although some companies such as Paratek Pharmaceuticals have been swimming against the tide with the development and test of new antibacterial chemotherapeutics (e.g. omadacycline, Nuzyra), the low approval of antibiotics in Phase I clinical trials (~ 14%) along with the aforementioned less profitable commercial niche are a good ally to the end of the Antibiotic Era.¹² Could COVID-19 pandemic be a wake-up call to prevent the next crisis?¹² And how could CCs be capitalized in this context?

Able to impair cell metabolic pathways through coordination with the biomolecular machinery, to catalytically generate cytotoxic compounds including reactive oxygen species, to deplete substrates that are essential to bacterial multiplication, CCs may be the (possibly underrated) required arsenal against

pathogenic bacteria.^{195,196} With differential ligand arrangements around the metal center depending on the ligand themselves, the metal nature and its nox such compounds can easily form three-dimensional structures able to access underexplored sites in biomolecules.^{195,196} Moreover, such structures can become even more intricate when less planar ligands are considered, allowing the fine-tune between the three-dimensional structures and their biomolecule recognition sites.^{195,196} In between the possibility of specific bimolecular interaction and a ubiquitous antibacterial activity, **CCs** may provide long-term choices of antibacterial drugs, with less probability of resistance development thus, fulfilling the innovation gap currently observed. Although such compounds would have to be submitted to the same hurdles faced by any other potential antibacterial drug (especially those financially-related) **CCs** development could provide a more assured approach to overcome the limited lifespan observed of such class of compounds, guaranteeing the long-term profit desired by pharmaceutical companies.¹² Finally, from the results herein presented, it is clear that *in vitro* assays are generally the only assessment such compounds are submitted to. There is a clear lack of information both from *in vitro* and *in vivo* tests regarding the toxicity of such compounds, their ADMeTox profiles as well as first passage effects, which are mandatory if one is willing to give the next steps towards a possible clinical trial. Furthermore, although the ubiquitous nature of activity of such compounds is a promise towards overcoming (multi)drug resistance, the possibility of interactions with the host biomolecular machinery is a reality that cannot be discarded. Biorthogonal interactions with pathogenic bacteria biomolecular targets are thus somewhat envisaged in order to induce reduced adverse effects.

Author Contributions

Christian C. Benedicto: survey, writing, review; Antônio Marçal Neto: survey, writing, review; Ralciane P. Menezes: survey, review; Ana Carolina G. Jardim: conceptualization, review; Camilla Abbehausen: discussion, review; Carlos H.G. Martins: conceptualization, review; Fernando R.G. Bergamini: conceptualization, writing, discussion, review and editing.

Conflicts of interest

There are no conflicts to declare.

Dedicatory

CCB dedicates this manuscript to the memory of his grandfather, Mauro Benedicto, who passed away during this year.

FRGB dedicates this manuscript to the memory of his former professors of IQ-UNICAMP, Dr. Ronei J. Poppi and Dr. Oswaldo L. Alves and to his colleagues of IQ-UFU, Dr. Maria Stela C. Gomdin and Mr. Aníbal A. Ladir who passed away during the last year.

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