

ANTIBACTERIAL PROPERTIES OF METAL IONS IN METALLO-ORGANIC COMPLEX STRUCTURES: A COMPREHENSIVE REVIEW

Akhilesh Mishra¹, Gayatri Dewangan², Ajay Kodyatar³, Samprita ghosh⁴, Megh Singh Dhakad⁵, Mirza Masroor Ali Beg⁶

Address(es):

¹ Central Animal Research Facility, Department of Pharmacology, Maulana Azad Medical College and Associated Hospitals, New Delhi-110002, India.

² Department of Pharmacology, College of Veterinary Science and Animal Husbandry cum Livestock Research Institute, Indore, India.

³ Department of Pharmacology, Maulana Azad Medical College and Associated Hospitals, New Delhi-110002, India.

⁴ Department of Public Health Dentistry, Maulana Azad Institute of Dental Sciences, Delhi, India

⁵ State level Viral Research and Diagnostic Laboratory, Department of Microbiology, Maulana Azad Medical College and Associated Hospitals, New Delhi -110002, India.

⁶ Faculty of Medicine, Ala-Too International University, Bishkek, Kyrgyzstan

*Corresponding author: drgayatridewangan@gmail.com

<https://doi.org/10.55251/jmbfs.14203>

ARTICLE INFO

Received 8. 4. 2026
Revised 10. 7. 2026
Accepted 23. 7. 2026
Published 1. 8. 2026

Review



ABSTRACT

The world is facing an urgent need for new therapeutic approaches to combat the rapidly growing problem of antimicrobial resistance (AMR). The antibacterial activity exhibited by metal ions and their coordination compounds is of significant interest with multi-target mechanisms which are fundamentally different from the classic organic antibiotics and hence with less potential for resistance to develop. This review covers the historical applications of metal ions from ancient times till today in metallo-organic complex structures, the mechanism of their bactericidal/bacteriostatic activities, structural requirements for biological activity and their recent clinical and preclinical applications. Special emphasis is placed on the coordination chemistry of biologically active metals, including copper (Cu), zinc (Zn), silver (Ag), iron (Fe), gallium (Ga), ruthenium (Ru) and gold (Au) as well as the role of organic ligands in modulating pharmacological profiles. Emerging strategies such as metal-organic frameworks (MOFs), nanoparticulate systems and synergistic metal-antibiotic conjugates are discussed in the context of pipeline development. A novel comparative synthesis across key metal ion classes is provided and a systematic assessment of clinical readiness is presented to guide rational lead selection. Collectively, the evidence reviewed here positions metallo-organic complexes as highly promising candidates in the post-antibiotic era.

Keywords: Antimicrobial resistance, metal complexes, coordination compounds, antibacterial mechanisms, metal-organic frameworks, reactive oxygen species, bioinorganic chemistry

INTRODUCTION

Historical perspective on metal ions as antibacterial agents

The antimicrobial utility of metals is among the oldest empirical pharmacological observations in recorded history. Long before the germ theory of disease was formulated by Koch and Pasteur in the nineteenth century diverse civilizations had independently recognized that specific metals possessed intrinsic properties capable of inhibiting microbial spoilage, preventing wound infection and treating systemic disease (Hobman & Crossman, 2015; Lemire *et al.*, 2013). The metallic medicine tradition has a legacy of many hundreds of years that goes beyond mere anecdote; in hindsight it shows real antimicrobial activity that has been confirmed by modern microbiological techniques. Landmark discoveries outside the search window (2010-2025) that are important to the context of the field are retained for the selected foundational references.

Copper (Cu) has such an important role in this historical story. The archaeological and textual records from ancient Egypt (c. 2600-2200 BCE) show the use of copper vessels and copper-derived preparations for both the sterilisation of drinking water and the treatment of infected wounds (Grass *et al.*, 2010). The Smith Papyrus and Ebers Papyrus (c. 1550 BCE) enumerate topical applications of copper salts for ophthalmic inflammation and dermal ulceration (Metwally, 2021). Parallel traditions in ancient Indian (Vedic) and Persian medicine corroborated these observations, copper vessels incidentally suppressed enteric pathogens including *Vibrio cholerae* and *Salmonella typhi* a phenomenon now characterised as the 'oligodynamic effect'. Modern surface science studies confirm that solid copper eliminates healthcare-associated pathogens within minutes through membrane oxidation and intracellular copper-ion toxicity (Schmidt *et al.*, 2016; Warnes *et al.*, 2010).

Silver (Ag) was accorded therapeutic prominence across Greek, Roman, Byzantine and Chinese medical traditions. By the nineteenth century, silver had been formalized in mainstream Western medicine: Crede (1884) demonstrated that instillation of 1% silver nitrate into the conjunctivae of neonates effectively

prevented gonococcal ophthalmia neonatorum arguably the first evidence-based chemoprophylaxis in clinical history (Chopra, 2007). Silver sulfadiazine cream developed in 1968 remains a standard-of-care agent for burn wound infection (Klasen, 2000; Du *et al.*, 2026).

Mercury (Hg) featured in Graeco-Roman, Chinese and Ayurvedic pharmacopoeia for cutaneous infections, syphilis and parasitic diseases (Jin & Jin, 2021). Bismuth and antimony compounds formed the therapeutic backbone of antisyphilitic and antileishmanial regimens throughout the nineteenth and early twentieth centuries (Sundar & Chakravarty, 2010). The pivotal transition from empirical metal use to rational drug design was marked by Paul Ehrlich's synthesis of Salvarsan (arsphenamine, compound 606) in 1909 the first synthetic antimicrobial agent designed on pharmacological principles (Ehrlich & Hata, 1910).

The discovery of penicillin by Fleming (1928) and the subsequent development of sulfonamide and aminoglycoside antibiotic classes precipitated a dramatic decline in the clinical use of metal-based antimicrobials (Hobman & Crossman, 2015). However, the progressive erosion of antibiotic efficacy by multidrug resistant (MDR) and extensively drug resistant (XDR) bacterial pathogens has reversed this trajectory. Antimicrobial resistance (AMR) now constitutes a recognised global public health emergency. The O'Neill Commission projected that absent decisive intervention AMR could claim 10 million lives annually by 2050 and impose cumulative global economic losses exceeding USD 100 trillion (O'Neill, 2016). In 2017, the WHO set up a list of priority pathogens calling for new therapeutic agents and *Acinetobacter baumannii*, *Pseudomonas aeruginosa* and *Enterobacteriaceae* are classified as critical priority pathogens (WHO, 2017). There is a severe lack of antibiotics in the development pipeline in comparison to clinical needs (Miethke *et al.*, 2021; Theuretzbacher *et al.*, 2020). There is a significant renewed interest in the use of metal-based antibacterials. One of the main benefits of metal ions is that they can disrupt more than one essential bacterial process, namely produce reactive oxygen species (ROS) leading to oxidative damage to the bacterial lipids, proteins and nucleic acids, directly inhibit bacterial respiratory chain enzymes, mis-metallize essential metal cofactors from the active site of metalloprotein

enzymes, disrupt the cell membrane integrity, and intercalate into bacterial DNA (Lemire et al., 2013; Nies, 2016).

The result is a polypharmacology that makes evolution of resistance much more difficult. To quantify this the spontaneous mutation rate to resistance for single-target antibiotics is approximately 10^{-8} to 10^{-9} per cell per generation. Rather, multi-target agents would require independent mutations in multiple loci, which

would be approximately 10^{-16} to 10^{-24} (Nnaji et al., 2024). In practice, while silver resistance (sil operon) and copper resistance (cop/cue/cus operons) have been characterized, resistance rates in clinical isolates are low (generally below 5% when compared to other conventional antibiotics (Mijnendonckx et al., 2013, Hobman & Crossman, 2015).

Table 1 Historical milestones in the medicinal use of metals.

Period	Metal / Compound	Indication	Significance
c. 2600 BCE	Copper (Cu ²⁺)	Wound infection; water purification	Earliest documented metal antiseptics
c. 400 BCE	Silver (Ag ⁺)	Wound healing; anti-putrefaction	Hippocratic records; Roman silver vessels
1500s CE	Mercury (Hg ²⁺)	Syphilis; skin diseases	First heavy-metal pharmacotherapy
1884 CE	Silver nitrate (AgNO ₃)	Ophthalmia neonatorum prophylaxis	Credé protocol; first clinical prophylaxis
1910 CE	Salvarsan (As-organic)	Syphilis (T. pallidum)	First rationally designed synthetic antimicrobial (Ehrlich)
1968 CE	Silver sulfadiazine	Burn wound infections	Metal-antibiotic conjugate; still standard of care
1978 CE	Cisplatin (Pt complex)	Solid tumours	First approved transition-metal drug
2010s–present	Ru, Au, Ga, Cu complexes	MDR bacteria; oncology	Modern rational metallo-organic drug design

Importance of metallo-organic complexes in modern medicine

Metallo-organic complexes are a structurally and mechanistically different group of therapeutic agents that fills a distinct chemical space that is inaccessible to purely organic drugs (Gasser et al., 2010). A coordination complex is a metal ion ionically coordinated to one or more (organic or inorganic) ligands, the structure of which has properties that are a function of both the metal ion and the nature of the ligand(s), which can be rationally designed (Mjos & Orvig, 2014). The medicinal value of metallo-organic complexes was most clearly illustrated by the drug cis-platin (cis-diamminedichloroplatinum (II)) that was approved for use in 1978 for treating testicular, ovarian and bladder carcinomas (Rosenberg et al., 1965; Johnstone et al., 2016). The structural and geometric diversity of inorganic compounds is also being used in contemporary medicinal inorganic chemistry, where compounds are designed to be redox active, to undergo ligand exchange

reactions with different rates depending on the target, to be multitarget drugs, and to have an increased permeability for membranes and to show synergism with existing antibiotics (Mjos & Orvig, 2014; Frei et al., 2020). Therefore, the present review article aimed to: (i) provide a transparent account of the literature search methodology underpinning this review (ii) systematically evaluate the historical development, mechanistic basis and structural determinants of antibacterial activity of metal ions within metallo-organic complex frameworks with particular focus on Cu, Zn, Ag, Fe, Ga, Ru, and Au (iii) deliver a comparative cross-metal synthesis of antibacterial potency, resistance profiles and clinical readiness (iv) critically appraise emerging translational platforms including MOFs, nanoparticulate systems and synergistic metal-antibiotic conjugates and (v) identify priority areas for future research and clinical translation in the context of the global AMR crisis.

Table 2 Selected metallo-organic complexes under clinical or advanced preclinical investigation as antibacterials, with evidence quality ratings.

Complex	Metal	Key Ligand	Bacterial Target(s)	Stage	Evidence Quality	Reference
BOLD-100 (IT-139)	Ru(II)	Pyridine carboxylate	Ribosomes; GRP78	Phase Ib/II	Moderate (early clinical)	D'Amato et al., 2023
Auranofin (repurposed)	Au(I)	Phosphine; thiosugar	Thioredoxin reductase (TrxR)	Phase I/II trials	High (mechanistically validated)	Harbut et al., 2011
Cu-Schiff base complexes	Cu(II)	Schiff base	DNA; membrane; ROS	Preclinical	Moderate (in vitro + limited in vivo)	Jayamani et al., 2014
Gallium nitrate (Nuvelo)	Ga(III)	Inorganic nitrate	Iron metabolism; RNR	Phase II (CF lung)	High (RCT-level evidence)	Kaneko et al., 2007
Zn-Schiff base complexes	Zn(II)	Schiff base	Enzyme inhibition	Preclinical	Low (limited in vitro data)	Kalaivani et al., 2014
Ag-NHC complexes	Ag(I)	N-heterocyclic carbene	Membrane; thiol enzymes	Preclinical	Moderate (in vitro)	Garrison et al., 2020

It presents selected metallo-organic complexes under clinical or advanced preclinical investigation as antibacterial with evidence quality ratings assigned according to the following criteria: High = RCT or multiple independent clinical/in vivo studies; Moderate = mechanistically validated in vitro with limited in vivo confirmation; Low = in vitro only or single study.

METHODS

Literature Search Strategy and Scope

The present comprehensive review was conducted following a literature search of PubMed/MEDLINE, Scopus, Web of Science and Google Scholar databases, covering publications. Selected landmark historical references predating this window are retained where essential to contextualize foundational discoveries. Search terms included combinations of: metal complexes antibacterial, coordination compounds antimicrobial, metallo-organic antibacterial, copper, zinc, silver, gallium, ruthenium gold antibacterial, metal-organic frameworks drug delivery antibacterial, nanoparticles antibacterial and antimicrobial resistance metal ions. Inclusion criteria comprised peer-reviewed original research articles, systematic reviews, meta-analyses and clinical trial reports in English that reported mechanistic, in vitro, in vivo, or clinical antibacterial data for metal-containing agents. Grey literature, conference abstracts and unpublished data were excluded. Additional references were identified through citation tracking. Studies were omitted if they were purely organic, lacked clear coordination complexes, reported only non-bacterial activity, or were case reports, or editorials articles. The authors

acknowledge that this approach cannot guarantee exhaustive coverage of a rapidly growing field however, every effort was made to represent the major mechanistic paradigms, clinically advanced candidates and points of genuine scientific controversy.

Metal Ions in Metallo-Organic Complex Structures

Overview of Common Biologically Active Metal Ions

The selection of the metal centre is the primary determinant of a coordination complex's biological activity, toxicity and mechanism of action. Metal ions are broadly classified as essential (required for normal cellular function) or non-essential/pharmacological (no endogenous metabolic role but exhibiting selective toxicity towards pathogens). The interplay between the metal's intrinsic properties ionic radius, electron configuration, redox potential, coordination number preference and its ligand environment govern every aspect of its pharmacological behaviour (Bertini et al., 2007; Mjos & Orvig, 2014) (Figure 1). Table 3 summarizes the key biologically active metal ions discussed below, with evidence levels assigned.

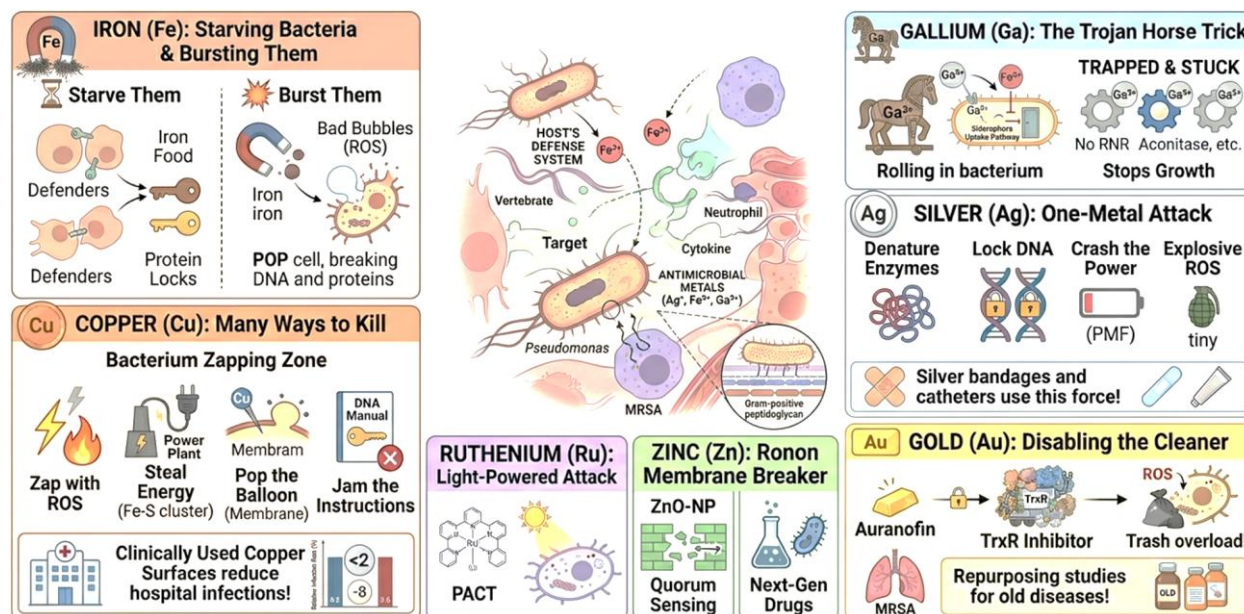


Figure 1 Demonstration of metals based mechanism for in bacterial cells killing in different way

Iron (Fe): The Double-Edged Sword

The most biologically essential transition metal is iron, which is a cofactor for hemoglobin, cytochromes, ferredoxins and oxidoreductases. Iron homeostasis is an important area of host-pathogen interaction, as iron is a critical component for the function of ribonucleotide reductase (RNR), which is essential for de novo deoxyribonucleotide synthesis in bacteria (Cassat & Skaar, 2013; Drakesmith & Prentice, 2012). Nutritional immunity in vertebrates involves sequestration of iron from invading pathogens by the deployment of transferrin, lactoferrin and ferritin to limit free iron below the level needed for bacterial growth. Bacteria have developed iron acquisition systems based on siderophores, which have been used in the synthesis of siderophore-antibiotics like the FDA approved 2019 compound cefiderocol (Ito et al., 2017; Page, 2019). Iron-containing complexes can also produce ROS through a Fenton type reaction ($\text{Fe}^{2+} + \text{H}_2\text{O}_2 \rightarrow \text{Fe}^{3+} + \cdot\text{OH} + \text{OH}^-$) which causes catastrophic non-reversible damage to bacterial DNA, lipids and proteins (Lemire et al., 2013).

Copper (Cu): Biocidal Mechanisms and Clinical Applications

Copper is the one of the most abundant transition metal in the human body and an important cofactor in cytochrome c oxidase, Cu/Zn-superoxide dismutase, and ceruloplasmin. Paradoxically, excess copper is profoundly toxic to bacteria. Bactericidal mechanisms include: (i) ROS generation via Fenton/Haber-Weiss chemistry (ii) disruption of Fe-S cluster assembly by copper-mediated iron displacement (iii) oxidative damage to the cytoplasmic membrane and (iv) direct DNA interaction (Grass et al., 2010; Lemire et al., 2013). Metallic copper surfaces have been demonstrated in randomised controlled trials to reduce healthcare-associated infections (HAIs) by 40–58% compared with standard materials among the strongest clinical evidence for any metal-based antimicrobial surface (Salgado et al., 2013; Salgado et al., 2013). Copper(II) coordination complexes incorporating Schiff base, thiosemicarbazone, and phenanthroline ligands exhibit MIC values of 0.5–8 $\mu\text{g}/\text{mL}$ against MDR clinical isolates in vitro. For context the clinical MIC breakpoints for vancomycin against MRSA are $\leq 2 \mu\text{g}/\text{mL}$ (susceptible), suggesting that optimised copper complexes approach clinically relevant potency. However, direct contrasts are confounded by assay inconsistency (up to 2-fold dilution inter-laboratory variation) and the absence of standardized challenging protocols for metal complexes (Jayamani et al., 2014; Endale & Desalegn, 2018).

Zinc (Zn): Structural and Enzymatic Roles

Zinc is the second most prevalent trace mineral in the human body and the only one in all six classes of enzymes. In contrast to iron and copper, Zn^{2+} is redox-inert in physiological conditions, and does not present the risk of the formation of radicals by the Fenton-type mechanism. Zinc functions antibacterially by, (i) competitively displacing other metal cofactors from bacterial metalloenzymes (ii) inhibiting biofilm formation through interference with quorum sensing and (iii) direct membrane disruption at supratherapeutic concentrations (Jin & Jin, 2021). Zinc oxide nanoparticles (ZnO-NPs) demonstrate broad-spectrum antibacterial activity against MRSA and carbapenem-resistant *K. pneumoniae* primarily through ROS generation and membrane disruption (Siddiqi et al., 2018; Sirelkhatim et al., 2015).

Silver (Ag): Mechanisms of Antibacterial Action

Silver holds a distinguished position in the history of antiseptics and exhibits some of the broadest-spectrum and most potent antibacterial activity of any metal (Franci et al., 2015). The bactericidal mechanisms of Ag^+ include: (i) high-affinity binding to thiol (-SH) groups in bacterial enzymes causing irreversible denaturation (ii) intercalation with bacterial DNA, cross-linking the double helix and preventing replication (iii) disruption of the proton-motive force (PMF) across the cytoplasmic membrane collapsing energy metabolism and (iv) catalytic ROS generation (Dakal et al., 2016; Lara et al., 2010). Silver nanoparticles (AgNPs) of 1–10 nm exhibit the highest specific surface area, maximal Ag^+ release and deepest membrane penetration. Although silver resistance mechanisms have been described (notably sil operon-encoded efflux pumps in Enterobacteriaceae) these remain considerably less prevalent than conventional antibiotic resistance determinants occurring in fewer than 5% of clinical isolates (Mijnendonckx et al., 2013). Silver sulfadiazine, silver-impregnated catheters and nanocrystalline silver dressings are in widespread clinical use (Du et al., 2026).

Gallium (Ga): Iron Mimicry as a Therapeutic Approach

Gallium (Ga^{3+}) is a 'Trojan horse' metal, chemically similar in terms of ionic radius (0.62 Å vs. 0.64 Å) of Ga^{3+} and Fe^{3+} , which can substitute for Fe^{3+} in bacterial iron-uptake pathways (Bernstein, 1998; Kaneko et al., 2007). However, Ga^{3+} , unlike Fe^{3+} , cannot be reduced to Ga^{2+} under physiological conditions and hence the iron-dependent enzyme functions, such as RNR, aconitase and catalase, are blocked (Bonchi et al., 2014; Li et al., 2022). A feasibility study showed the efficacy of gallium nitrate, when administered intravenously, to improve FEV and reduce the density of *P. aeruginosa* in sputum samples from CF patients (Kaneko et al., 2007).

Ruthenium (Ru): Next-Generation Metallo-Organic Drugs

Ruthenium complexes focus on the tunability of their ligand environment, variable oxidation states (Ru^{2+} and Ru^{3+}) and low systemic toxicity (Süss-Fink, 2010). Ru(II) complexes can perform three types of antibacterial mechanisms: (i) intercalation and groove binding of the bacterial DNA that inhibits gyrase and topoisomerase IV, (ii) photodynamic activation that produces singlet oxygen ($^1\text{O}_2$) upon visible-light irradiation, which enables photodynamic antimicrobial chemotherapy (PACT), and (iii) direct membrane disruption for cationic polypyridyl complexes (Li et al., 2015; Ng et al., 2024). The Ru(II) polypyridyl complexes have MIC of 1–4 $\mu\text{g}/\text{mL}$ against MRSA and *A. baumannii*, including CPE and colistin resistant strains (Li et al., 2015; D'Amato et al., 2023).

Gold (Au): From Antirheumatic to Antibacterial Applications

Gold compounds have been used in medicine at nanomolar concentrations. Auranofin, a gold(I) complex of triethyl phosphine thio-sugar, inhibits thioredoxin reductase (TrxR), a flavoenzyme that plays a key role in the maintenance of redox homeostasis in bacteria, leading to impairment of their antioxidant activity and making them vulnerable to ROS-mediated killing (Harbut et al., 2015; May et al., 2018). Gold N-heterocyclic carbene (Au-NHC) complexes are highly active against *Staphylococcus aureus* (Ceramella et al., 2025), which forms biofilms.

Studies of auranofin have been started to repurpose for MRSA, M. tuberculosis and Clostridioides difficile (May et al., 2018; She et al., 2020).

Table 3 Biologically dynamic metal ions in metallo-organic complexes: properties, mechanisms and evidence levels.

Metal Ion	Ox. State(s)	Coord. No.	Primary Mechanism(s)	Key Clinical Applications	Evidence Level
Fe	+2, +3	4, 6	ROS (Fenton); iron starvation; siderophore mimicry	Siderophore-antibiotic conjugates; cefiderocol	High
Cu	+1, +2	4, 6	ROS; Fe-S cluster disruption; membrane damage; DNA binding	Hospital copper surfaces (RCT-validated); wound dressings	High
Zn	+2	4, 6	Enzyme inhibition; biofilm disruption; membrane damage	ZnO-NPs; Zn wound creams	Moderate
Ag	+1	2, 4	Thiol binding; DNA intercalation; PMF collapse; ROS	Silver sulfadiazine; AgNPs; catheters	High (clinical use)
Ga	+3	4, 6	Iron mimicry (Fe ³⁺ substitute); RNR inhibition	CF lung (P. aeruginosa); Phase II trial	Moderate (Phase II)
Ru	+2, +3	6	DNA intercalation; PACT (singlet oxygen); membrane disruption	Preclinical; MDR pathogens; PACT	Low-Moderate (preclinical)
Au	+1, +3	2, 4	TrxR inhibition; thiol binding; ROS	MRSA; M. tuberculosis (repurposing)	Moderate (early clinical)
Pt	+2, +4	4, 6	DNA intrastrand cross-linking	Anticancer (cisplatin); limited antibacterial	High (oncology)
Bi	+3	6, 8	Urease inhibition; Fe/Ni metabolism disruption	H. pylori eradication (WHO-endorsed)	High (approved)

Comparative Synthesis Across Key Metal Classes

A detailed side-by-side comparison of the pharmacology of the main antibacterial metal ions summarizes the similarities and differences in properties essential in rational lead choice (Table 5). At the mechanistic level, the gold, silver, and gallium compound each target at least one target that is absent in Western medicine, or is targeted inadequately; silver and gold metals are unique in their inhibition of thiol-dependent enzymes like TrxR, gallium appears to mimic the iron-dependence of respiratory metabolism, and copper and iron generate bactericidal ROS by Fenton chemistry. These mechanisms have no equivalent in the targets of lactams (cell wall), fluoroquinolones (DNA gyrase) and the 30S ribosomes of the aminoglycosides, so cross-resistance seems unlikely. Silver consistently demonstrates the lowest minimum inhibitory concentrations (MICs) for a range of multidrug-resistant (MDR) pathogens (0.1–10 µg/mL for silver nanoparticles (AgNPs) against MRSA). Gold (with auranofin having an MIC of <2 µg/mL for MRSA) comes next, followed by the ruthenium polypyridyl (1–4 µg/mL) and copper metallated compounds (0.5–8 µg/mL). Care must be taken when comparing studies in terms of direct MICs since variability between

laboratories exceeds 2-fold dilution and ac617metallated complex MICs cannot yet be determined by standardized test methods. The absolute potency of gallium (8–64 µg/mL) is lower than that of silver, gold or ruthenium or copper, however the exquisite selectivity of gallium relative to Pseudomonas aeruginosa biofilm infections and its proven clinical activity in Phase II clinical studies (Kaneko et al., 2007) compensate for this. The potential for resistance development is also a distinguishing factor, since there is a very low probability of gallium, ruthenium and gold resistance due to the lack of known specific resistance genes, compared to silver (sil operon) and copper (cop/cue/cus operons) where resistance has been described, and where there is a clinical prevalence of resistance of less than 5% (Mijnendonckx et al., 2013; Hobman & Crossman, 2015). Of those metals tested, biofilm activity, which plays an important role in chronic infection management, is found to be greatest for the respective silver, gold-NHC, and gallium compounds and is therefore a significant advantage of these against traditional antibiotics, which typically show an increase in MICs of 100- to 1,000-fold when comparing biofilm to planktonic forms of bacteria.

Table 4 Comparative summary of key antibacterial metal ions: mechanism, potency, resistance, and clinical status.

Feature	Copper (Cu)	Silver (Ag)	Gallium (Ga)	Ruthenium (Ru)	Gold (Au)
Primary mechanism	ROS; Fe-S disruption	Thiol binding; PMF collapse	Iron mimicry (Fe ³⁺ substitute)	DNA intercalation; PACT	TrxR inhibition; thiol binding
Typical MIC vs. MDR (µg/mL)	0.5–8	0.1–10 (AgNPs)	8–64	1–4	<2 (auranofin; nM range)
MIC vs. vancomycin (MRSA)	Broadly comparable (2–4 µg/mL)	Superior (<1 µg/mL AgNPs)	Inferior (requires higher dose)	Comparable (1–4 µg/mL)	Superior (sub-µg/mL)
Resistance frequency (clinical)	Low (<5%; cop/cue operons)	Low (<5%; sil operon)	Very low (no characterised genes)	Very low (no known resistance genes)	Very low
Clinical status	Approved (surfaces, dressings; RCT)	Approved (dressings, catheters)	Phase II (cystic fibrosis)	Preclinical only	Phase I/II (repurposing trials)
Biofilm activity	Moderate	High	High (vs. P. aeruginosa)	Moderate	High (Au-NHC)
Main toxicity concern	Redox-mediated host cell ROS	Low at therapeutic doses	Low (selective for bacteria)	Low (being evaluated)	Low (auranofin FDA-approved for RA)

Ligand Design and Its Role in Modulating Antibacterial Activity

The metal complex shows how it works in medicine, its solubility, stability, and bioavailability, whether it will cross the cell membrane (cell membrane permeability), and how specific the drug will be toward the target (target selectivity) (Bertini et al., 2007; Mjos & Orvig, 2014). A good design of the ligand framework can significantly increase the antibacterial activity of the metal, while decreasing the toxicity to the host that receives the drug and increasing the length of time that the drug is active (pharmacokinetic half-life). Schiff base ligands provide excellent design versatility for synthesis. The imine nitrogen (C=N) and other donor atoms like O, S, N provide a chelating system that affords strong binding to Cu(II), Zn(II), Ni(II), and Co(II) metal ions. Many Schiff base complexes of Cu(II) and Zn(II) have been shown to have minimal inhibitory concentrations (MICs) of 2–16 µg/mL against MRSA and many other gram-negative bacteria that are multi-drug resistant (MDR), primarily through the disruption of the DNA and inhibition of enzymes (Jayamani et al., 2014; Endale & Desalegn, 2018; Trishna et al., 2026). The addition of fluorinated, brominated or hydroxy-substituted ligands increases the lipophilicity, as well as the antibacterial potency of the Schiff base complex (Moreno-Narváez et al., 2025). Thiosemicarbazone (TSC) ligands are bioactive in their metal-free form and are

able to inhibit Ribonucleotide Reductase (RNR) by chelating with the iron central atom of the enzyme (Yu et al., 2009; Jyothi, 2026). When Cu(II) metal is complexed with TSC, both the metal and TSC acquire additional reduction/oxidation properties as well as permeability of the cellular membranes allowing for synergistic antibacterial effects that exceed either the metal or the ligand in isolation. One important feature was that NHC ligands can form very stable metal-carbene bonds under physiological conditions, resulting in Au(I)-NHC, Ag(I)-NHC, and Cu(I)-NHC systems that can inhibit MRSA bacteria, including those that have formed a biofilm (Ceramella et al., 2025; Jalal et al., 2020; Wenzel et al., 2013). The ability of phenanthroline and bipyridyl ligands to intercalate within DNA allows these ruthenium (II) and iridium (III) complexes to produce both singlet oxygen and superoxide upon being irradiated to generate PACT (Ng et al., 2024; Li et al., 2015).

Antibiotic-appended ligands represent an emerging strategy in which known antibacterial pharmacophores (quinolone, β-lactam, sulphonamide) are incorporated directly into the ligand framework creating dual-action complexes with both metal-mediated and antibiotic-mediated killing mechanisms (Torres et al., 2019; Gatti et al., 2022).

Antibacterial Mechanisms: A Unified Framework

The bactericidal and bacteriostatic mechanisms of metallo-organic complexes are organised into four principal target categories, acknowledging that most complexes act simultaneously through several of these pathways (Figure 2; Table 4):

(i) Reactive Oxygen Species (ROS) Generation

Redox-active metal centres (Cu, Fe, Mn) catalyse the Fenton/Haber-Weiss reactions converting superoxide and hydrogen peroxide into the hydroxyl radical ($\cdot\text{OH}$) the most reactive oxidant in biological chemistry (Lemire et al., 2013). The hydroxyl radical inflicts non-repairable single- and double-strand breaks in DNA, peroxidises membrane fatty acids, and oxidises critical amino acid residues in proteins. ROS-mediated killing is amplified in bacteria because unlike mammalian cells they lack mitochondrial compartmentalization of redox processes.

(ii) Enzyme and Protein Inhibition

Metal ions possess intrinsic affinity for sulphur- and nitrogen-containing amino acid residues (cysteine, histidine, methionine) enabling them to bind to the active sites of critical bacterial enzymes. Ag^+ and Au^+ preferentially bind thiol groups (at femtomolar to picomolar affinity for TrxR inhibition), while Cu^{2+} and Zn^{2+} inhibit enzymes through Lewis acid coordination or displacement of Mg^{2+} or Fe^{2+} cofactors (Harbut et al., 2015; Lemire et al., 2013). Resulting enzyme dysfunction impairs the TCA cycle, respiratory chain and nucleotide biosynthesis.

(iii) Cell Membrane Disruption

The amphiphilic nature of various metallo-organic complexes, which is due to the lipophilic organic ligands attached to a charged metal core, allows these complexes to partition into the bacterial phospholipid bilayer and disrupt its structural integrity. Because of this, there will be a loss of the PMF (proton motive force), an outflow of intracellular material (K^+ , ATP, and or protein), and resultant cell lysis (Li et al., 2015; Ceramella et al., 2025). Specifically, cationic Ru(II) polypyridyl and Ag-NHC complexes are to be noted as very efficacious membrane-active agents.

(iv) DNA Binding and Replication Inhibition

Cisplatin creates DNA damage and stops DNA replication and transcription by creating 1,2-intrastrand cross-links between adjacent guanine residues, which are not reversible. (Rosenberg et al., 1965; Johnstone et al., 2016). Ru (II) and Ir (III) with ligands that are planar and aromatic can intercalate into the spaces between base pairs of DNA and stop topoisomerase from relaxing the DNA strands by inhibiting the topoisomerase-mediated strand relaxation. (Li et al., 2015; Kalaivani et al., 2014). Cu (II) can cleave the DNA strands in an oxidative manner, resulting in creating breaks in the DNA, as a result overwhelms the bacterial SOS repair system (Jayamani et al., 2014).

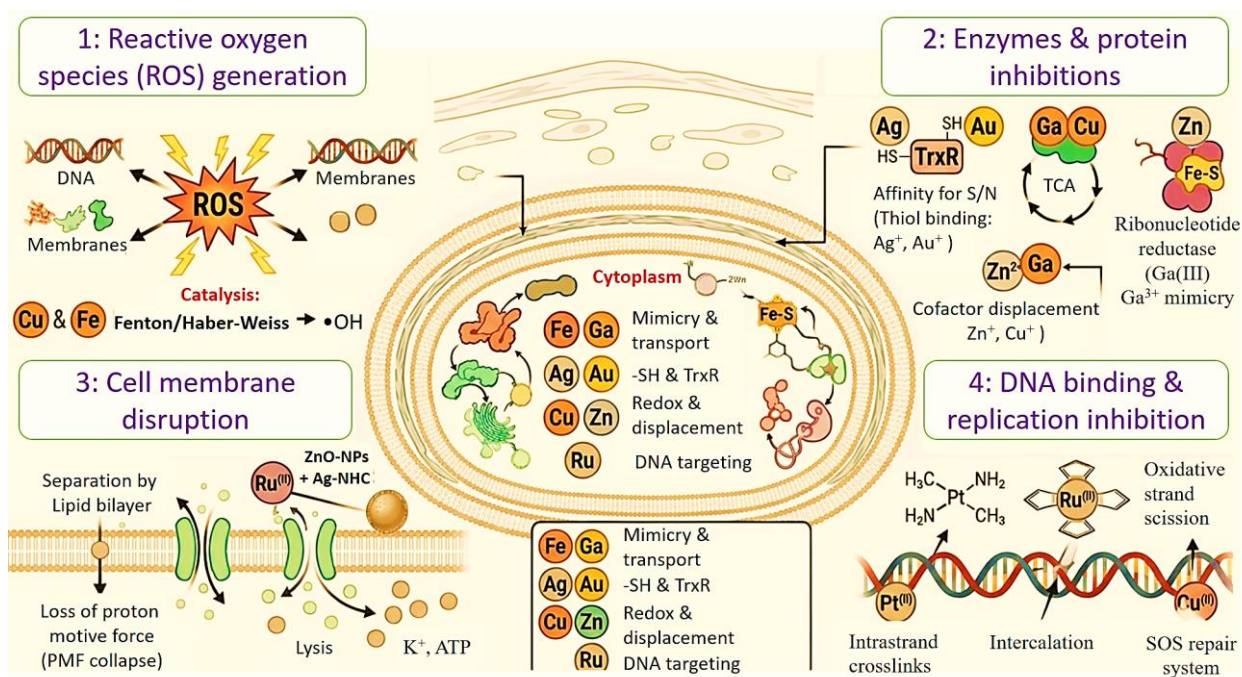


Figure 2 Antibacterial action of metallo-organic complexes with a mechanistic target to compromise the bacterial cells.

Table 5 Summary of antibacterial mechanisms of metallo-organic complexes with evidence quality assessment.

Mechanism	Key Metals	Molecular Targets	Bactericidal Outcome	Evidence Strength
ROS generation (Fenton/Haber-Weiss)	Fe^{2+} , Cu^{2+} , Mn^{2+}	DNA; membrane lipids; Fe-S proteins	Oxidative strand breaks; peroxidation; enzyme inactivation	Strong (multiple independent studies)
Enzyme/protein inhibition	Ag^+ , Au^+ , Cu^{2+} , Ga^{3+} , Zn^{2+}	TrxR; RNR; aconitase; Fe-S cluster enzymes	Metabolic collapse; disrupted redox homeostasis	Strong (biochemical mechanistic data)
Membrane disruption	Ag^+ , Ru^{2+} , Cu^{2+} , Au(I)-NHC	Phospholipid bilayer; PMF; membrane proteins	PMF collapse; ion leakage; lysis	Strong (TEM and electrophysiology data)
DNA interaction	Pt^{2+} , Ru^{2+} , Cu^{2+} , Ir^{3+}	DNA helix; topoisomerases; gyrase	Replication arrest; transcription block; SOS induction	Strong (crystallographic + gel assay data)
Iron metabolism disruption	Ga^{3+} ; Fe chelators	Siderophore uptake; RNR; catalase	Iron starvation; RNR inhibition; growth arrest	Moderate (Phase II clinical data for Ga)
Biofilm disruption	Ag^+ , Zn^{2+} , Ga^{3+}	Quorum sensing; EPS matrix; adhesins	Biofilm dispersal; antibiotic re-sensitisation	Moderate (in vitro + limited in vivo)

Advanced Platforms: MOFs, Nanoparticles, and Combination Strategies

Metal-Organic Frameworks (MOFs) as Drug Delivery Vehicles

Metal-organic frameworks (MOFs) are porous crystalline materials with extraordinarily high surface areas (500–7,000 m^2/g), tunable pore sizes, and readily functionalised surfaces (Furukawa et al., 2013; Horcajada et al., 2012). MOF design combines the intrinsic antibacterial properties of metal nodes with the

ability to load, protect and release antibacterial cargo in a site-specific, stimulus-responsive manner (Horcajada et al., 2010; Wyszogrodzka et al., 2016). Zeolitic imidazolate frameworks (ZIF-8) can encapsulate ciprofloxacin with loading efficiencies exceeding 20% w/w, releasing antibiotic in response to the acidic pH of infected tissue a stimulus-responsive property unachievable with conventional formulations (Zheng et al., 2016; Liang et al., 2021). Gallium-based MOFs loaded with tobramycin demonstrated superior efficacy against *P. aeruginosa* biofilms compared to tobramycin alone in a murine pulmonary

infection model, with the dual mechanism (Ga^{3+} iron mimicry + antibiotic delivery) being a key advantage (Qiao *et al.*, 2022). Nonetheless, there are significant constraints that should be noted. Most investigations into the antibacterial properties of MOFs are still conducted in vitro with limited in vivo results. Physiological stability over time (at pH 7.4, in the presence of serum proteins, and at physiological ionic strength) is not widely determined and varies. The synthesis of clinical-grade MOFs on a commercial scale is complicated and costs more to produce than other chemical substances. The cytotoxic effects associated with metabolite products derived from MOFs (i.e., metal salts and organic linkers) require careful consideration of their toxicological profiles. Despite these significant disadvantages, the unique drug-release characteristics that can be attained from the MOF class offer many advantages compared to traditional formulations, especially when it comes to the treatment of biofilms and potentially limiting the amount of antibiotic delivered systemically (Liang *et al.*, 2021; Hubab & Al-Ghouti, 2024).

Metal Nanoparticles and Nanocomposites

Metal nanoparticles (1 to 100 nm) have a very high ratio of surface area to volume compared to the bulk material from which they originate, thereby increasing the maximum possible rate of release of ions from a metal and providing a higher contact surface area for both bacteria and metal. Silver nanoparticles, for example, have broad-spectrum antibacterial properties in concentrations much lower than required for silver salts with MIC of 0.1-10 $\mu\text{g/ml}$ against MRSA, *P. aeruginosa*, and *E. coli*. CuO-NPs and ZnO-NPs have been shown to have clinically relevant activity against biofilm-associated pathogens and are included in antimicrobial textiles, wound dressings and hospital surface coatings. While these novel constructs offer great promise, many key barriers exist regarding the translation of nanoparticle platforms into clinical applications. Regulatory agencies (FDA, EMA) require specific characterization of nanoparticles (size, shape, surface charge, aggregation state), additional toxicological assessment of nanoparticles, and biodistribution and elimination studies of nanoparticles. Manufacturing reproducibility is more difficult for AgNPs because AgNP activity is more highly dependent on shape (triangle > sphere > rod) than it is on chemical composition alone. Hybrid nanocomposites (e.g. AgNPs + ampicillin; ZnO-NPs + colistin) have restored susceptibility to antimicrobial agents on multidrug-resistant bacteria in vitro but there is little in vivo verification of this.

Synergistic Metal-Antibiotic Strategies

Advocating for the combining of metal ions with traditional/standard antibiotics has the potential to create a clinically feasible solution over the short term in combatting AMR by using currently available antibiotic infrastructures to restore/enhance efficacy (Gatti *et al.*, 2022; Jayamani *et al.*, 2014). There have been several different noted types of mechanisms of synergism.

- Outer membrane permeabilisation: Metal ions (Ga^{3+} , Ag^{+} , Cu^{2+}) destabilise the LPS layer of gram-negative outer membranes by displacing divalent Mg^{2+} and Ca^{2+} , enhancing penetration of hydrophilic antibiotics that are normally excluded (Bonchi *et al.*, 2014)

- Efflux pump inhibition: Sub-inhibitory concentrations of Ag^{+} , Cu^{2+} , and Ga^{3+} inhibit RND-family efflux pumps (MexAB-OprM, AcrAB-TolC), reducing efflux of fluoroquinolones and β -lactams (Bonchi *et al.*, 2014; Lara *et al.*, 2010)
- Biofilm eradication: Metal ions disrupt biofilm formation by interfering with quorum-sensing signals and degrading the EPS matrix, re-sensitizing sessile bacteria to antibiotics whose MICs increase 100- to 1,000-fold in biofilm vs. planktonic bacteria (Jin & Jin, 2021; Ceramella *et al.*, 2025)
- Siderophore-antibiotic conjugates: Antibiotics conjugated to siderophore moieties exploit TonB-dependent iron-uptake machinery for active intracellular delivery, thereby circumventing outer-membrane permeability barriers and efflux pumps. The cephalosporin-catechol siderophore conjugate, FDA-approved in 2019, is the foremost clinical example (Ito *et al.*, 2017).

Clinical Perspectives and Future Directions

The incremental translation of metal-based antibacterial agents into clinical use is indicative of challenges that are typically associated with developing any type of antimicrobial compound. These include stringent regulatory requirements, preclinical attrition rates that are very high, requirements for iv formulations, selective toxicity issues and various other commercial limitations (Theuretzbacher *et al.*, 2020; Miethke *et al.*, 2021). For a comprehensive overview of clinical readiness and the major barriers to development, refer to Table 6.

Silver-based agents represent the most clinically established class, with silver sulfadiazine, nanocrystalline silver dressings and silver-impregnated catheters endorsed in national guidelines for burn wound care and catheter-associated infection prevention (Du *et al.*, 2026). Bismuth-containing quadruple regimens for *Helicobacter pylori* eradication are WHO-recommended first-line therapy in high-clarithromycin-resistance settings (Malfertheiner *et al.*, 2017). Gallium nitrate demonstrated encouraging Phase II results in cystic fibrosis (Kaneko *et al.*, 2007), while auranofin is under active repurposing investigation for MRSA and *M. tuberculosis* (May *et al.*, 2018; Harbut *et al.*, 2015).

Key translational barriers include: (i) selective toxicity distinguishing antibacterial potency from host-cell cytotoxicity is particularly challenging for redox-active metals (Cu, Fe); (ii) resistance development the sil and cop/cue/cus resistance operons are disseminated on mobile genetic elements, raising surveillance concerns and (iii) absence of a validated regulatory pathway specific to metallic antimicrobials, requiring navigation of the conventional antibiotic development framework with all its associated costs (Gasser *et al.*, 2010; Miethke *et al.*, 2021). The path forward requires convergence across synthetic chemistry, pharmacology, microbiology, and clinical medicine. Systematic QSAR modelling, genomic resistance surveillance, nanotechnology-based formulations, and rigorous RCTs in well-defined clinical populations are all essential. Machine learning and AI-assisted virtual screening of metal-ligand combinatorial libraries against bacterial target structures is accelerating lead identification (Atz *et al.*, 2021; Schneider *et al.*, 2020).

Table 6 Systematic assessment of clinical readiness and key translational barriers for selected metal-based antibacterials.

Agent	Clinical Stage	Key Barriers	Readiness (1-5)*	Priority Next Step
Silver sulfadiazine / AgNPs	Approved (burns, wound care)	Argyria risk; emerging sil resistance	5	Post-market surveillance; resistance monitoring
Bismuth quadruple therapy	Approved (<i>H. pylori</i>)	Patient compliance; neurotoxicity at high dose	5 (<i>H. pylori</i> indication)	Expanded indications (other GI pathogens)
Gallium nitrate	Phase II (CF-associated <i>P. aeruginosa</i>)	IV formulation only; selectivity concerns	3	Phase III RCT (CF); oral formulation development
Auranofin (repurposed)	Phase I/II (MRSA, TB, <i>C. difficile</i>)	Toxicity profile; antibiotic-specific trial design	3	Dedicated Phase II antibacterial RCT
BOLD-100 (Ru complex)	Phase Ib/II (oncology)	No dedicated antibacterial trials yet	2	Antibacterial-specific Phase II design
Cu-Schiff base complexes	Preclinical (in vitro)	Systemic toxicity; formulation; no in vivo data	1	Systematic in vivo profiling; toxicology
Ag-NHC complexes	Preclinical (in vitro)	Stability in serum; selectivity data absent	1	Serum stability + animal infection model studies

*Readiness Score: 1 = early preclinical only, 5 = approved for clinical use in an antibacterial indication. Criteria: in vitro efficacy, in vivo efficacy, toxicity profile, formulation readiness, clinical trial data.

CONCLUSIONS

The antibacterial action of metal ions found in metal-organic complex entities provides a scientific wealth, historical foundation and clinical urgency to the future of anti-infective therapeutic development. The first example of clearly defined and valid (meaning scientifically validated) antibacterial candidates is silver and gold as the two most effective agents, both in total antibacterial power and particularly as they both inhibit TrxR in the case of gold's specific mechanism and multi-target,

thiol binding and PMF interruption for silver; silver-based therapeutic agents also have the greatest clinical validated value. The second example is gallium, which represents a rational 'metal' based antibacterial strategy as it takes advantage of an essential bacterial metabolic vulnerability (i.e., dependence upon iron) that has validated Phase II data and a unique low risk of developing resistance. The third example of copper-based surfaces and dressings has extensive clinical evidence of use for prevention of infection (RCT approved with reductions in HAI of 40-58%); the challenge to translate copper coordination complexes into systemic therapeutic

agents is their potential for toxicity and formulation difficulties. Finally, ruthenium and iridium PACT complexes will represent a truly novel, photoactivated mechanism of action with absolutely no antibiotics, however, they will require considerably more preclinical development before being considered clinically ready to use. Several key translational obstacles must be addressed: selective toxicity, regulatory pathway definition, resistance monitoring, and formulation development through coordinated, multidisciplinary programs. Emerging platforms, including MOFs, nanoparticulate systems, and siderophore-antibiotic conjugates, extend the translational potential of this field, though rigorous in vivo validation remains the critical unmet need. With the global AMR crisis deepening and the conventional antibiotic pipeline inadequate to meet clinical need, metallo-organic complexes constitute a compelling, mechanistically distinct, and increasingly well-validated class of next-generation antibacterial therapeutics.

Conflict of interest: None

Data availability: No data was generated for the research described in the article.

Funding statement: None

REFERENCES

- Atz, K., Grisoni, F., & Schneider, G. (2021). Geometric deep learning on molecular representations. *Nature Machine Intelligence*, 3(12), 1023–1032.
- Barry, N. P., & Sadler, P. J. (2013). Exploration of the medical periodic table: towards new targets. *Chemical communications (Cambridge, England)*, 49(45), 5106–5131. <https://doi.org/10.1039/c3cc41143e>
- Bergamo, A., Gaiddon, C., Schellens, J. H., Beijnen, J. H., & Sava, G. (2012). Approaching tumour therapy beyond platinum drugs: status of the art and perspectives of ruthenium drug candidates. *Journal of inorganic biochemistry*, 106(1), 90–99. <https://doi.org/10.1016/j.jinorgbio.2011.09.030>
- Bernstein L. R. (1998). Mechanisms of therapeutic activity for gallium. *Pharmacological reviews*, 50(4), 665–682.
- Beyth, N., Hourri-Haddad, Y., Domb, A., Khan, W., & Hazan, R. (2015). Alternative antimicrobial approach: nano-antimicrobial materials. *Evidence-based complementary and alternative medicine : eCAM*, 2015, 246012. <https://doi.org/10.1155/2015/246012>
- Bonchi, C., Imperi, F., Minandri, F., Visca, P., & Frangipani, E. (2014). Repurposing of gallium-based drugs for antibacterial therapy. *BioFactors (Oxford, England)*, 40(3), 303–312. <https://doi.org/10.1002/biof.1159>
- Cassat, J. E., & Skaar, E. P. (2013). Iron in infection and immunity. *Cell host & microbe*, 13(5), 509–519. <https://doi.org/10.1016/j.chom.2013.04.010>
- Ceramella, J., Catalano, A., Mariconda, A., D'Amato, A., Aquila, S., Saturnino, C., Rosano, C., Sinicropi, M. S., & Longo, P. (2024). Silver N-Heterocyclic Carbene (NHC) Complexes as Antimicrobial and/or Anticancer Agents. *Pharmaceuticals (Basel, Switzerland)*, 18(1), 9. <https://doi.org/10.3390/ph18010009>
- Chopra I. (2007). The increasing use of silver-based products as antimicrobial agents: a useful development or a cause for concern?. *The Journal of antimicrobial chemotherapy*, 59(4), 587–590. <https://doi.org/10.1093/jac/dkm006>
- Dakal, T. C., Kumar, A., Majumdar, R. S., & Yadav, V. (2016). Mechanistic Basis of Antimicrobial Actions of Silver Nanoparticles. *Frontiers in microbiology*, 7, 1831. <https://doi.org/10.3389/fmicb.2016.01831>
- D'Amato, A., Mariconda, A., Iacopetta, D., Ceramella, J., Catalano, A., Sinicropi, M. S., & Longo, P. (2023). Complexes of Ruthenium(II) as Promising Dual-Active Agents against Cancer and Viral Infections. *Pharmaceuticals (Basel, Switzerland)*, 16(12), 1729. <https://doi.org/10.3390/ph16121729>
- Drakesmith, H., & Prentice, A. M. (2012). Hepcidin and the iron-infection axis. *Science (New York, N.Y.)*, 338(6108), 768–772. <https://doi.org/10.1126/science.1224577>
- Du, Y., Lu, J., Guo, X., Xia, Z., & Ji, S. (2026). The Role of Silver and Silver-Based Products in Wound Management: A Review of Advances and Current Landscape. *Journal of functional biomaterials*, 17(1), 27. <https://doi.org/10.3390/jfb17010027>
- Ehrlich, P., & Hata, S. (1910). Die experimentelle Chemotherapie der Spirillosen (Syphilis, Rückfallfieber, Hühnerspirillose, Frambösie). <https://doi.org/10.1007/978-3-642-64926-4>
- Endale, A. T. M., & Desalegn, T. (2018). Synthesis, characterization and antibacterial activity of copper (II) and cobalt (II) vanillin-aniline schiff base complexes. *Synthesis*, 10(2).
- Franci, G., Falanga, A., Galdiero, S., Palomba, L., Rai, M., Morelli, G., & Galdiero, M. (2015). Silver nanoparticles as potential antibacterial agents. *Molecules (Basel, Switzerland)*, 20(5), 8856–8874. <https://doi.org/10.3390/molecules20058856>
- Frei, A., Zuegg, J., Elliott, A. G., Baker, M., Braese, S., Brown, C., Chen, F., G Dowson, C., Dujardin, G., Jung, N., King, A. P., Mansour, A. M., Massi, M., Moat, J., Mohamed, H. A., Renfrew, A. K., Rutledge, P. J., Sadler, P. J., Todd, M. H., Willans, C. E., ... Blaskovich, M. A. T. (2020). Metal complexes as a promising source for new antibiotics. *Chemical science*, 11(10), 2627–2639. <https://doi.org/10.1039/c9sc06460e>
- Furukawa, H., Cordova, K. E., O'Keeffe, M., & Yaghi, O. M. (2013). The chemistry and applications of metal-organic frameworks. *Science (New York, N.Y.)*, 341(6149), 1230444. <https://doi.org/10.1126/science.1230444>
- Gasser, G., Ott, I., & Metzler-Nolte, N. (2011). Organometallic anticancer compounds. *Journal of medicinal chemistry*, 54(1), 3–25. <https://doi.org/10.1021/jm100020w>
- Gatti, M., Cojutti, P. G., Bartoletti, M., Tonetti, T., Bianchini, A., Ramirez, S., Pizzilli, G., Ambretti, S., Giannella, M., Mancini, R., Siniscalchi, A., Viale, P., & Pea, F. (2022). Expert clinical pharmacological advice may make an antimicrobial TDM program for emerging candidates more clinically useful in tailoring therapy of critically ill patients. *Critical care (London, England)*, 26(1), 178. <https://doi.org/10.1186/s13054-022-04050-9>
- Giedraitienė, A., Vitkauskienė, A., Naginienė, R., & Pavilonis, A. (2011). Antibiotic resistance mechanisms of clinically important bacteria. *Medicina (Kaunas, Lithuania)*, 47(3), 137–146.
- Grass, G., Rensing, C., & Solioz, M. (2011). Metallic copper as an antimicrobial surface. *Applied and environmental microbiology*, 77(5), 1541–1547. <https://doi.org/10.1128/AEM.02766-10>
- Harbut, M. B., Vilchère, C., Luo, X., Hensler, M. E., Guo, H., Yang, B., Chatterjee, A. K., Nizet, V., Jacobs, W. R., Jr, Schultz, P. G., & Wang, F. (2015). Auranofofin exerts broad-spectrum bactericidal activities by targeting thiol-redox homeostasis. *Proceedings of the National Academy of Sciences of the United States of America*, 112(14), 4453–4458. <https://doi.org/10.1073/pnas.1504022112>
- Hobman, J. L., & Crossman, L. C. (2015). Bacterial antimicrobial metal ion resistance. *Journal of medical microbiology*, 64(Pt 5), 471–497. <https://doi.org/10.1099/jmm.0.023036-0>
- Horcajada, P., Chalati, T., Serre, C., Gillet, B., Sebrie, C., Baati, T., Eubank, J. F., Heurtaux, D., Clayette, P., Kreuz, C., Chang, J. S., Hwang, Y. K., Marsaud, V., Bories, P. N., Cynober, L., Gil, S., Férey, G., Couvreur, P., & Gref, R. (2010). Porous metal-organic-framework nanoscale carriers as a potential platform for drug delivery and imaging. *Nature materials*, 9(2), 172–178. <https://doi.org/10.1038/nmat2608>
- Horcajada, P., Gref, R., Baati, T., Allan, P. K., Maurin, G., Couvreur, P., Férey, G., Morris, R. E., & Serre, C. (2012). Metal-organic frameworks in biomedicine. *Chemical reviews*, 112(2), 1232–1268. <https://doi.org/10.1021/cr200256v>
- Hubab, M., & Al-Ghouti, M. A. (2024). Recent advances and potential applications for metal-organic framework (MOFs) and MOFs-derived materials: Characterizations and antimicrobial activities. *Biotechnology reports (Amsterdam, Netherlands)*, 42, e00837. <https://doi.org/10.1016/j.btre.2024.e00837>
- Ito, A., Sato, T., Ota, M., Takemura, M., Nishikawa, T., Toba, S., Kohira, N., Miyagawa, S., Ishibashi, N., Matsumoto, S., Nakamura, R., Tsuji, M., & Yamano, Y. (2017). In Vitro Antibacterial Properties of Cefiderocol, a Novel Siderophore Cephalosporin, against Gram-Negative Bacteria. *Antimicrobial agents and chemotherapy*, 62(1), e01454-17. <https://doi.org/10.1128/AAC.01454-17>
- Jalal, M., Hammouti, B., Touzani, R., Aouniti, A., & Ozdemir, I. (2020). Metal-NHC heterocycle complexes in catalysis and biological applications: Systematic review. *Materials today. Proceedings*, 31, S122–S129. <https://doi.org/10.1016/j.matpr.2020.06.398>
- Jayamani, A., Thamilarasan, V., Sengottuvelan, N., Manisankar, P., Kang, S. K., Kim, Y. I., & Ganesan, V. (2014). Synthesis of mononuclear copper(II) complexes of acyclic Schiff's base ligands: spectral, structural, electrochemical, antibacterial, DNA binding and cleavage activity. *Spectrochimica acta. Part A, Molecular and biomolecular spectroscopy*, 122, 365–374. <https://doi.org/10.1016/j.saa.2013.11.079>
- Jin, S. E., & Jin, H. E. (2021). Antimicrobial Activity of Zinc Oxide Nano/Microparticles and Their Combinations against Pathogenic Microorganisms for Biomedical Applications: From Physicochemical Characteristics to Pharmacological Aspects. *Nanomaterials (Basel, Switzerland)*, 11(2), 263. <https://doi.org/10.3390/nano11020263>
- Johnstone, T. C., Suntharalingam, K., & Lippard, S. J. (2016). The Next Generation of Platinum Drugs: Targeted Pt(II) Agents, Nanoparticle Delivery, and Pt(IV) Prodrugs. *Chemical reviews*, 116(5), 3436–3486. <https://doi.org/10.1021/acs.chemrev.5b00597>
- Jyothi, P. (2026). Recent advances in thiosemicarbazone metal complexes: structure-activity relationship and therapeutic prospects. *Discover Chemistry*, 3(1), 73.
- Kalaivani, P., Saranya, S., Poornima, P., Prabhakaran, R., Dallemer, F., Vijaya Padma, V., & Natarajan, K. (2014). Biological evaluation of new nickel(II) metallates: Synthesis, DNA/protein binding and mitochondrial mediated apoptosis in human lung cancer cells (A549) via ROS hypergeneration and depletion of cellular antioxidant pool. *European journal of medicinal chemistry*, 82, 584–599. <https://doi.org/10.1016/j.ejmech.2014.05.075>
- Kaneko, Y., Thoendel, M., Olakanmi, O., Britigan, B. E., & Singh, P. K. (2007). The transition metal gallium disrupts *Pseudomonas aeruginosa* iron metabolism and has antimicrobial and antibiofilm activity. *The Journal of clinical investigation*, 117(4), 877–888. <https://doi.org/10.1172/JCI30783>
- Klasen H. J. (2000). Historical review of the use of silver in the treatment of burns. I. Early uses. *Burns : journal of the International Society for Burn Injuries*, 26(2), 117–130. [https://doi.org/10.1016/s0305-4179\(99\)00108-4](https://doi.org/10.1016/s0305-4179(99)00108-4)
- Kohanski, M. A., Dwyer, D. J., & Collins, J. J. (2010). How antibiotics kill bacteria: from targets to networks. *Nature reviews. Microbiology*, 8(6), 423–435. <https://doi.org/10.1038/nrmicro2333>

- Lambert J. R. (1991). Pharmacology of bismuth-containing compounds. *Reviews of infectious diseases*, 13 Suppl 8, S691–S695. https://doi.org/10.1093/clindis/13.supplement_8.s691
- Lara, H. H., Ayala-Núñez, N. V., Ixtepan-Turrent, L., & Rodríguez-Padilla, C. (2010). Mode of antiviral action of silver nanoparticles against HIV-1. *Journal of nanobiotechnology*, 8, 1. <https://doi.org/10.1186/1477-3155-8-1>
- Lemire, J. A., Harrison, J. J., & Turner, R. J. (2013). Antimicrobial activity of metals: mechanisms, molecular targets and applications. *Nature reviews. Microbiology*, 11(6), 371–384. <https://doi.org/10.1038/nrmicro3028>
- Li, C. X., Shi, M., Tian, J. H., Lin, X. D., Kang, Y. J., Chen, L. J., Qin, X. C., Xu, J., Holmes, E. C., & Zhang, Y. Z. (2015). Unprecedented genomic diversity of RNA viruses in arthropods reveals the ancestry of negative-sense RNA viruses. *eLife*, 4, e05378. <https://doi.org/10.7554/eLife.05378>
- Li, F., Collins, J. G., & Keene, F. R. (2015). Ruthenium complexes as antimicrobial agents. *Chemical Society reviews*, 44(8), 2529–2542. <https://doi.org/10.1039/c4cs00343h>
- Li, F., Liu, F., Huang, K., & Yang, S. (2022). Advancement of Gallium and Gallium-Based Compounds as Antimicrobial Agents. *Frontiers in bioengineering and biotechnology*, 10, 827960. <https://doi.org/10.3389/fbioe.2022.827960>
- Liang, W., Wied, P., Carraro, F., Sumbly, C. J., Nidetzky, B., Tsung, C. K., Falcaro, P., & Doonan, C. J. (2021). Metal-Organic Framework-Based Enzyme Biocomposites. *Chemical reviews*, 121(3), 1077–1129. <https://doi.org/10.1021/acs.chemrev.0c01029>
- Malfertheiner, P., Megraud, F., O'Morain, C. A., Gisbert, J. P., Kuipers, E. J., Axon, A. T., Bazzoli, F., Gasbarrini, A., Atherton, J., Graham, D. Y., Hunt, R., Moayyedi, P., Rokkas, T., Rugge, M., Selgrad, M., Suerbaum, S., Sugano, K., El-Omar, E. M., & European Helicobacter and Microbiota Study Group and Consensus panel (2017). Management of Helicobacter pylori infection—the Maastricht V/Florence Consensus Report. *Gut*, 66(1), 6–30. <https://doi.org/10.1136/gutjnl-2016-312288>
- May, H. C., Yu, J. J., Guentzel, M. N., Chambers, J. P., Cap, A. P., & Arulanandam, B. P. (2018). Repurposing Auranofin, Ebselen, and PX-12 as Antimicrobial Agents Targeting the Thioredoxin System. *Frontiers in microbiology*, 9, 336. <https://doi.org/10.3389/fmicb.2018.00336>
- Metwaly, A. M., Ghoneim, M. M., Eissa, I. H., Elsehemy, I. A., Mostafa, A. E., Hegazy, M. M., Afifi, W. M., & Dou, D. (2021). Traditional ancient Egyptian medicine: A review. *Saudi journal of biological sciences*, 28(10), 5823–5832. <https://doi.org/10.1016/j.sjbs.2021.06.044>
- Miethke, M., Pieroni, M., Weber, T., Brönstrup, M., Hammann, P., Halby, L., ... & Müller, R. (2021). Towards the sustainable discovery and development of new antibiotics. *Nature Reviews Chemistry*, 5(10), 726–749.
- Mijnendonckx, K., Leys, N., Mahillon, J., Silver, S., & Van Houdt, R. (2013). Antimicrobial silver: uses, toxicity and potential for resistance. *Biometals : an international journal on the role of metal ions in biology, biochemistry, and medicine*, 26(4), 609–621. <https://doi.org/10.1007/s10534-013-9645-z>
- Mjos, K. D., & Orvig, C. (2014). Metallodrugs in medicinal inorganic chemistry. *Chemical reviews*, 114(8), 4540–4563. <https://doi.org/10.1021/cr400460s>
- Moreno-Narváez, M. E., González-Sebastián, L., Colorado-Peralta, R., Reyes-Márquez, V., Franco-Sandoval, L. O., Romo-Pérez, A., ... & Morales-Morales, D. (2025). Anticancer and antimicrobial activity of copper (II) complexes with fluorine-functionalized Schiff bases: a mini-review. *Inorganics*, 13(2), 38.
- Ng, X. Y., Fong, K. W., Kiew, L. V., Chung, P. Y., Liew, Y. K., Delsuc, N., Zulkefli, M., & Low, M. L. (2024). Ruthenium(II) polypyridyl complexes as emerging photosensitisers for antibacterial photodynamic therapy. *Journal of inorganic biochemistry*, 250, 112425. <https://doi.org/10.1016/j.jinorgbio.2023.112425>
- Nies D. H. (2016). The biological chemistry of the transition metal "transportome" of Cupriavidus metallidurans. *Metallomics : integrated biometal science*, 8(5), 481–507. <https://doi.org/10.1039/c5mt00320b>
- Nnaji, N. D., Anyanwu, C. U., Miri, T., & Onyeaka, H. (2024). Mechanisms of heavy metal tolerance in bacteria: A review. *Sustainability*, 16(24), 11124.
- O'Neill, J. (2016). Tackling drug-resistant infections globally: final report and recommendations.
- Page M. G. P. (2019). The Role of Iron and Siderophores in Infection, and the Development of Siderophore Antibiotics. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America*, 69(Suppl 7), S529–S537. <https://doi.org/10.1093/cid/ciz825>
- Qiao, Y., Li, Y., Ye, Y., Yu, Y., Wang, W., Yao, K., & Zhou, M. (2022). Gallium-Based Nanopatform for Combating Multidrug-Resistant *Pseudomonas aeruginosa* and Postoperative Inflammation in Endophthalmitis Secondary to Cataract Surgery. *ACS applied materials & interfaces*, 14(46), 51763–51775. <https://doi.org/10.1021/acsami.2c15834>
- Rai, M. K., Deshmukh, S. D., Ingle, A. P., & Gade, A. K. (2012). Silver nanoparticles: the powerful nanoweapon against multidrug-resistant bacteria. *Journal of applied microbiology*, 112(5), 841–852. <https://doi.org/10.1111/j.1365-2672.2012.05253.x>
- Rosenberg, B., Vancamp, L., & Krigas, T. (1965). Inhibition Of Cell Division In Escherichia Coli By Electrolysis Products From A Platinum Electrode. *Nature*, 205, 698–699. <https://doi.org/10.1038/205698a0>
- Salgado, C. D., Sepkowitz, K. A., John, J. F., Cantey, J. R., Attaway, H. H., Freeman, K. D., Sharpe, P. A., Michels, H. T., & Schmidt, M. G. (2013). Copper surfaces reduce the rate of healthcare-acquired infections in the intensive care unit. *Infection control and hospital epidemiology*, 34(5), 479–486. <https://doi.org/10.1086/670207>
- Salgado, C. D., Sepkowitz, K. A., John, J. F., Cantey, J. R., Attaway, H. H., Freeman, K. D., Sharpe, P. A., Michels, H. T., & Schmidt, M. G. (2013). Copper surfaces reduce the rate of healthcare-acquired infections in the intensive care unit. *Infection control and hospital epidemiology*, 34(5), 479–486. <https://doi.org/10.1086/670207>
- Schalk, I. J., & Guillon, L. (2013). Fate of ferrisiderophores after import across bacterial outer membranes: different iron release strategies are observed in the cytoplasm or periplasm depending on the siderophore pathways. *Amino acids*, 44(5), 1267–1277. <https://doi.org/10.1007/s00726-013-1468-2>
- Schmidt, M. G., von Dessauer, B., Benavente, C., Benadof, D., Cifuentes, P., Elgueta, A., Duran, C., & Navarrete, M. S. (2016). Copper surfaces are associated with significantly lower concentrations of bacteria on selected surfaces within a pediatric intensive care unit. *American journal of infection control*, 44(2), 203–209. <https://doi.org/10.1016/j.ajic.2015.09.008>
- Schneider, P., Walters, W. P., Plowright, A. T., Sieroka, N., Listgarten, J., Goodnow, R. A., Jr, Fisher, J., Jansen, J. M., Duca, J. S., Rush, T. S., Zentgraf, M., Hill, J. E., Krutchohlow, E., Kohler, M., Blaney, J., Funatsu, K., Luebckemann, C., & Schneider, G. (2020). Rethinking drug design in the artificial intelligence era. *Nature reviews. Drug discovery*, 19(5), 353–364. <https://doi.org/10.1038/s41573-019-0050-3>
- Shankar, P. R., & Balasubramaniam, R. (2014). Antimicrobial resistance: global report on surveillance 2014. *Australasian Medical Journal (Online)*, 7(5), 237.
- She, P., Liu, Y., Wang, Y., Tan, F., Luo, Z., & Wu, Y. (2020). Antibiofilm efficacy of the gold compound auranofin on dual species biofilms of *Staphylococcus aureus* and *Candida* sp. *Journal of applied microbiology*, 128(1), 88–101. <https://doi.org/10.1111/jam.14443>
- Shrivastava, S. R., Shrivastava, P. S., & Ramasamy, J. (2018). World health organization releases global priority list of antibiotic-resistant bacteria to guide research, discovery, and development of new antibiotics. *Journal of Medical Society*, 32(1), 76–77.
- Siddiqi, K. S., Ur Rahman, A., Tajuddin, & Husen, A. (2018). Properties of Zinc Oxide Nanoparticles and Their Activity Against Microbes. *Nanoscale research letters*, 13(1), 141. <https://doi.org/10.1186/s11671-018-2532-3>
- Singh, A., Patel, R., Bharty, M. K., Singh, A. K., & Prasad, L. B. (2026). Anti-MRSA and antibiofilm activity of a dinuclear zinc (II) Dithiocarbamate complex with multimodal antibacterial effects. *Inorganic Chemistry Communications*, 116674.
- Sirelkhatim, A., Mahmud, S., Seeni, A., Kaus, N. H. M., Ann, L. C., Bakhori, S. K. M., Hasan, H., & Mohamad, D. (2015). Review on Zinc Oxide Nanoparticles: Antibacterial Activity and Toxicity Mechanism. *Nano-micro letters*, 7(3), 219–242. <https://doi.org/10.1007/s40820-015-0040-x>
- Stillman, M. (2007). Biological Inorganic Chemistry. Structure and Reactivity. Edited by Ivano Bertini, Harry B. Gray, Edward I. Stiefel and Joan S. Valentine. *Angewandte Chemie International Edition*, 46(46), 8741–8742.
- Sundar, S., & Chakravarty, J. (2010). Antimony toxicity. *International journal of environmental research and public health*, 7(12), 4267–4277.
- Süss-Fink G. (2010). Arene ruthenium complexes as anticancer agents. *Dalton transactions (Cambridge, England : 2003)*, 39(7), 1673–1688. <https://doi.org/10.1039/b916860p>
- Theuretzbacher, U., Outtersson, K., Engel, A., & Karlén, A. (2020). The global preclinical antibacterial pipeline. *Nature reviews. Microbiology*, 18(5), 275–285. <https://doi.org/10.1038/s41579-019-0288-0>
- Tiwari, M., Narayanan, K., Thakar, M. B., Jagani, H. V., & Venkata Rao, J. (2014). Biosynthesis and wound healing activity of copper nanoparticles. *IET nanobiotechnology*, 8(4), 230–237. <https://doi.org/10.1049/iet-nbt.2013.0052>
- Torres, M. D. T., Sothiselvam, S., Lu, T. K., & de la Fuente-Nunez, C. (2019). Peptide Design Principles for Antimicrobial Applications. *Journal of molecular biology*, 431(18), 3547–3567. <https://doi.org/10.1016/j.jmb.2018.12.015>
- Warnes, S. L., Green, S. M., Michels, H. T., & Keevil, C. W. (2010). Biocidal efficacy of copper alloys against pathogenic enterococci involves degradation of genomic and plasmid DNAs. *Applied and environmental microbiology*, 76(16), 5390–5401. <https://doi.org/10.1128/AEM.03050-09>
- Wenzel, M., Patra, M., Senges, C. H., Ott, I., Stepanek, J. J., Pinto, A., Prochnow, P., Vuong, C., Langklotz, S., Metzler-Nolte, N., & Bandow, J. E. (2013). Analysis of the mechanism of action of potent antibacterial hetero-tri-organometallic compounds: a structurally new class of antibiotics. *ACS chemical biology*, 8(7), 1442–1450. <https://doi.org/10.1021/cb4000844>
- Wyszogrodzka, G., Marszałek, B., Gil, B., & Dorożyński, P. (2016). Metal-organic frameworks: mechanisms of antibacterial action and potential applications. *Drug discovery today*, 21(6), 1009–1018. <https://doi.org/10.1016/j.drudis.2016.04.009>

- Yu, Y., Kalinowski, D. S., Kovacevic, Z., Siafakas, A. R., Jansson, P. J., Stefani, C., Lovejoy, D. B., Sharpe, P. C., Bernhardt, P. V., & Richardson, D. R. (2009). Thiosemicarbazones from the old to new: iron chelators that are more than just ribonucleotide reductase inhibitors. *Journal of medicinal chemistry*, 52(17), 5271–5294. <https://doi.org/10.1021/jm900552r>
- Zhao, M., Li, Y., & Wang, Z. (2022). Mercury and Mercury-Containing Preparations: History of Use, Clinical Applications, Pharmacology, Toxicology, and Pharmacokinetics in Traditional Chinese Medicine. *Frontiers in pharmacology*, 13, 807807. <https://doi.org/10.3389/fphar.2022.807807>
- Zheng, H., Zhang, Y., Liu, L., Wan, W., Guo, P., Nyström, A. M., & Zou, X. (2016). One-pot Synthesis of Metal-Organic Frameworks with Encapsulated Target Molecules and Their Applications for Controlled Drug Delivery. *Journal of the American Chemical Society*, 138(3), 962–968. <https://doi.org/10.1021/jacs.5b11720>