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Review

Recent Studies on the Antimicrobial Activity of Transition Metal Complexes of Groups 6–12

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Abstract: Antimicrobial resistance is an increasingly serious threat to global public health that requires innovative solutions to counteract new resistance mechanisms emerging and spreading globally in infectious pathogens. Classic organic antibiotics are rapidly exhausting the structural variations available for an effective antimicrobial drug and new compounds emerging from the industrial pharmaceutical pipeline will likely have a short-term and limited impact before the pathogens can adapt. Inorganic and organometallic complexes offer the opportunity to discover and develop new active antimicrobial agents by exploiting their wide range of three-dimensional geometries and virtually infinite design possibilities that can affect their substitution kinetics, charge, lipophilicity, biological targets and modes of action. This review describes recent studies on the antimicrobial activity of transition metal complexes of groups 6–12. It focuses on the effectiveness of the metal complexes in relation to the rich structural chemical variations of the same. The aim is to provide a short *vade mecum* for the readers interested in the subject that can complement other reviews.

Keywords: antimicrobial; transition metals; complex; organometallic; drug-resistant

1. Introduction

Antimicrobial resistance has become a global concern ultimately affecting humans' ability to prevent and treat an increasing number of infections caused by bacteria, parasites, viruses and fungi and the success of surgery and cancer chemotherapy. It occurs naturally over time, usually through genetic changes of the pathogens when exposed to antimicrobial drugs. One of the causes for the emergence of the problem is the overuse and misuse of existing antibiotics, which fueled the evolution of pathogens resistant to the current library of antimicrobial agents [1,2]. As a result, available medicines become ineffective, infections persist in the body, increasing the risk to patients' health, spreading and health care costs. Multidrug resistant bacteria, such as *Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acetinobacter baumanii*, *Pseudomonas aeruginosa*, and *Enterobacteriaceae* ("ESKAPE") species, are a major concern of the World Health Organization (WHO) and health authorities. These pathogens cause a large number of victims worldwide [3–5]. As an example, methicillin-resistant *Staphylococcus aureus* (MRSA) is one of the most critical causes of healthcare-related or community-related infections, because of the multiple resistances to antibiotics and the toxins produced [6]. It is, therefore, evident that there is an urgent need for the development of new antimicrobial agents with more effective mechanisms of action [7].

While the problem is escalating, major pharmaceutical companies have interrupted their antibiotic drug discovery programs, leaving academia at the forefront of the discovery of new classes of active compounds, especially for Gram-negative bacteria [8,9]. The classical approach of medicinal chemists based exclusively on organic molecules is poised to have a short-term limited impact because pathogens will adapt and develop resistance to new drugs. Furthermore, as recently pointed out by Frei [10],

only ~25% of the compounds currently in clinical development represent entirely new structural classes, with the remaining 75% of drugs being merely derivatives and modifications of already approved antibiotics. Thus, there is not just an urgent need for new antibiotics, but also a need for entirely new classes of molecules for the purpose. Transition metal complexes offer this possibility. They possess a wide range of three-dimensional geometries, virtually infinite possibilities to design their coordination sphere in order to affect their substitution kinetics, charge, lipophilicity biological targets and modes of action. Such complexes, however, are still (prejudicially) ignored by pharmaceutical companies despite the fact that several of them are used in hospitals worldwide. For example, arsphenamine, also known as Salvarsan or compound 606, is an effective drug for the treatment for syphilis; cisplatin is a chemotherapeutic agent, administered intravenously, and used to treat a number of cancers (e.g., testicular, ovarian, cervical, breast, bladder, head and neck, esophageal cancer); auranofin is a gold salt approved by the WHO as an antirheumatic agent; technetium sestamibi (trade name *Cardiolite*) is a pharmaceutical agent used in nuclear medicine imaging to visualize the myocardium.

In the last ten years, inorganic and organometallic transition metal medicinal chemists have begun to develop new antimicrobial agents with great promise and remarkable success. Complexes of virtually all ions of the transition periods have been tested. In this article, we present an overview of antimicrobial transition metal (groups 6–12) complexes published in the scientific literature in the last five years. We only describe inorganic and organometallic complexes of group 6–12 with a few exceptions. Thus, e.g., silver and iron complexes are not included. Antimicrobial iron and silver complexes and (nano)materials have been recently reviewed elsewhere [11–25]. Due to the growing interest in the field, recent reviews and prospective on the antibacterial applications of transition metal complexes have appeared [10,26–29]. This work aims at being complementary to those, including some important common seminal examples but mostly species not included by the other authors.

2. Group 6

2.1. Chromium Complexes

Schiff base complexes of chromium are most commonly studied for their antimicrobial efficacy, but the species have seldom shown high potency. Kumar et al. synthesized a new class of tetradentate Schiff bases as ligands and their corresponding chromium(III) complexes (**1**, Figure 1) by using $CrCl_3$ as the metal ion source [30]. The antimicrobial activities of the chromium(III) complexes were tested against *S. aureus* (Gram-positive), *E. coli* and *P. aeruginosa* (Gram-negative) bacterial strains, but their efficacies were lower than the standard drug, i.e., ampicillin. Rathi et al. reported the preparation of thiophene based macrocyclic Schiff base complexes from the reaction of succinohydrazide and thiophene-2,5-dicarbaldehyde in the presence of chromium(III) and iron(III) salts of chloride, nitrate and acetate (**2**, Figure 1) [31]. The antimicrobial activities of all synthesized complexes were tested against bacterial strains, such as *B. subtilis* and *E. coli*, and fungal strains, such as *S. cerevisiae* and *C. albicans*. The data showed good activity of compounds against all tested microbial strains with the MIC values in the range of 8–128 μg/mL. In 2017, Shaabani et al. prepared bridged chromium(III) complexes, of hydrazine Schiff bases tridentate ligands and azide (**3**, Figure 1) [32]. The complexes, however, were not particularly effective against tested pathogens with MIC values (~1250 μg/mL) higher than standard drugs (MIC = 8–28 μg/mL). Kafi-Ahmadi and coworkers synthesized thiourea derivatives as Schiff base ligands (**4**, Figure 1) and their chromium(III) complexes [33]. The complexes were tested for their antibacterial activities against clinically important bacteria, such as *E. coli*, *S. aureus*, and *B. subtilis*, and they showed good activities against all strains, comparable to that of streptomycin as the standard. The mechanism of action of these complexes is unknown. The authors suggested that chelation theory might help explain the biological activities of the metal chelates. This phenomenon relates to a decrease in the polarity of the metal ion due to overlap metal and ligand orbitals, resulting in partial sharing of the positive charge of the metal ion with donor groups and possibly electron delocalization over the whole molecule [33–36].

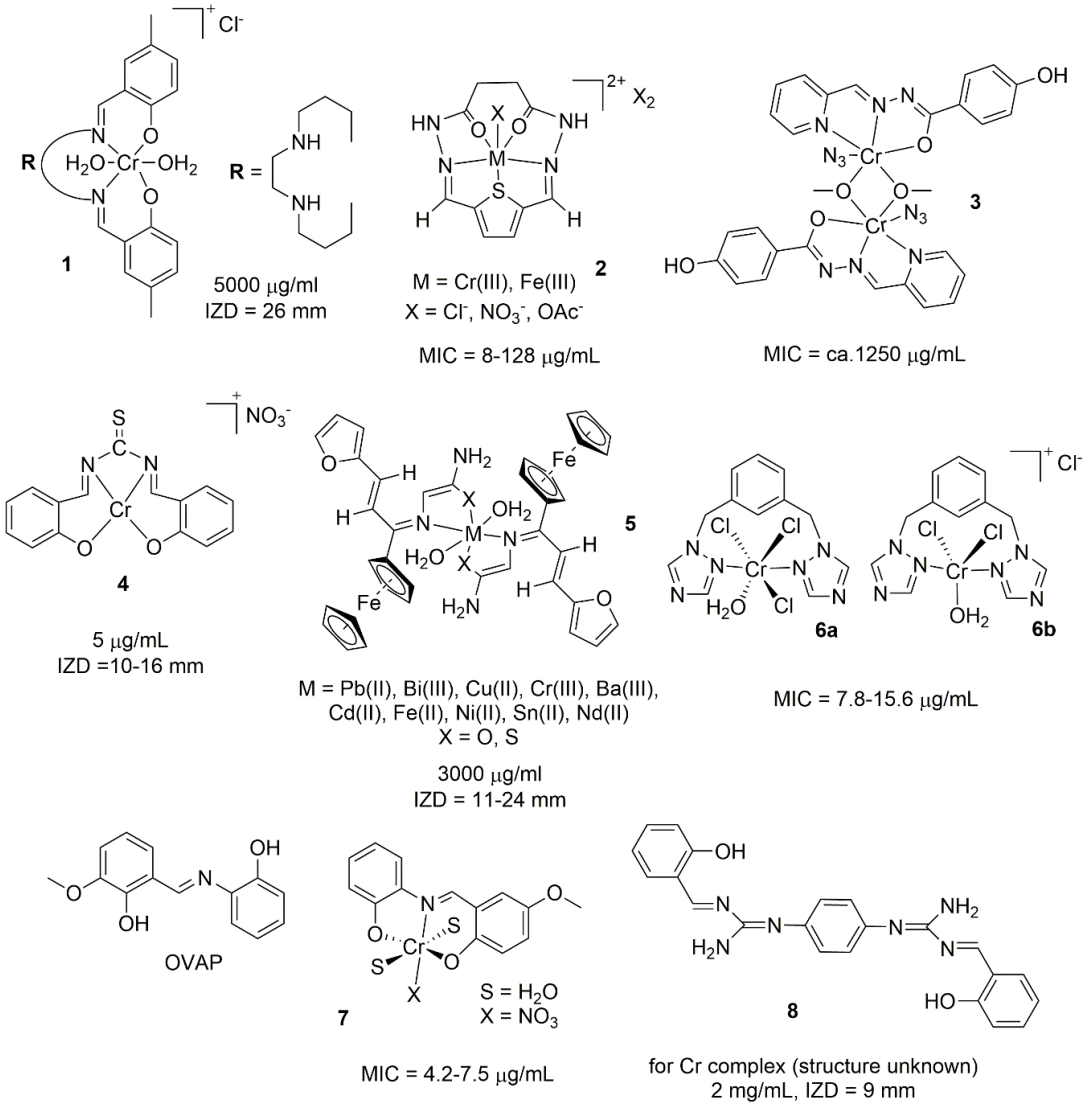

Figure 1. Structural formula of selected antimicrobial chromium(III) complexes and corresponding ligands. MIC = minimal inhibitory concentration; IZD = inhibition zone diameter at given concentration.

In 2018, Liu et al. introduced a Schiff base ligand, 1-ferrocenyl-3-(2-furyl) propenone diamino (thio) urea, and coordinated it to a range of metal ions (e.g., Pb(II), Bi(III), Cu(II), Cr(III), Ba(III), Cd(II), Fe(II), Ni(II), Sn(II) and Nd(II), **5**, Figure 1) [37]. All compounds were screened for their antimicrobial activities against bacteria, such as *E. coli*, *S. aureus* and MRSA, also fungi, such as *C. albicans* and *A. flavus*. The complexes were not particularly effective. The zones of inhibition (mm) were found in a range between 11 and 24 mm (3 mg/mL concentrations) with the chromium(III) complex being amongst the least effective compounds. In 2018, tridentate triazole based ligands of chromium(III) complexes were reported by Murcia et al. (**6a** and **6b**, Figure 1) [38]. The antimicrobial activities of both ligands and complexes were tested against a wide range of bacterial and fungal strains of clinical relevance. The results indicated that the chromium(III) complexes were more potent than free ligands and more effective against fungi than bacteria. The complexes **6a** and **6b** showed MIC values in the range of 7.8 to 15.6 μg/mL. A study on azomethine chelates of Cu(II), Pd(II), Zn(II) and Cr(III) with tridentate dianionic azomethine OVAP ligand (where OVAP = 2-[(2-hydroxyphenylimino)methyl]-6-methoxyphenol), was carried out by Abu-Dief et al. (**7**, Figure 1) [39]. All OVAP metal complexes were screened against a broad-spectrum of antimicrobial strains (bacterial strains: *M. luteus*, *E. coli* and *S. marcescence*; fungal strains: *A. flavus*, *G. candidum* and *F. oxysporum*) and showed MIC values between 4.25 and 7.50 μg/mL.

The investigated azomethine metal chelates revealed significantly enhanced antimicrobial activities in comparison to the free ligand (MIC = 9.0–10.75 μg/mL) and showed comparable activities to ofloxacin and fluconazol. Very recently, copper(II), nickel(II), cobalt(II), manganese(II), iron(III), chromium(III), bismuth(III), and zinc(II) complexes of the guanidine Schiff bases **8** (Figure 1) were reported [40]. Compounds were screened against *S. aureus* (Gram-positive), *P. aeruginosa* (Gram-negative) and the fungi strains, such as *C. albicans* and *A. niger*. In general, metal complexes were found to be more toxic than ligand **8** and showed greater activity than neomycin and the naturally occurring fungicide cycloheximide. Several other chromium metal complexes have been recently tested for their antimicrobial efficacy but were not found to be active [41–45].

2.2. Molybdenum Complexes

In comparison to chromium complexes, only a few studies on the antimicrobial potential of molybdenum metal complexes have appeared over the last decade in the literature, while we are not aware of tungsten species having been reported lately. A series of *cis*-dichloro/dibromodioxidobis (2-amino-6-substitutedbenzothiazole) molybdenum(VI) complexes (**9**, Figure 2) were reported by Saraswat et al. in 2013 [46]. The complexes of dihalodioxidomolybdenum(VI) have played a special role in the higher valent molybdenum enzymes such as sulfite oxidase, nitrate reductase, xanthine oxidase and xanthine dehydrogenase during biological processes [47,48]. The authors reported the antibacterial activities of the species against *P. aeruginosa*, *S aureus* and *K. pneumoniae* and antifungal activities against *A. flavus* and *A. niger*. The results showed that derivatives of **9** were generally as active as ampicillin against bacteria strains, and most effective against *P. aeruginosa* and *K. pneumonia*, while their antifungal MIC values were in the range of 10–20 μg/mL.

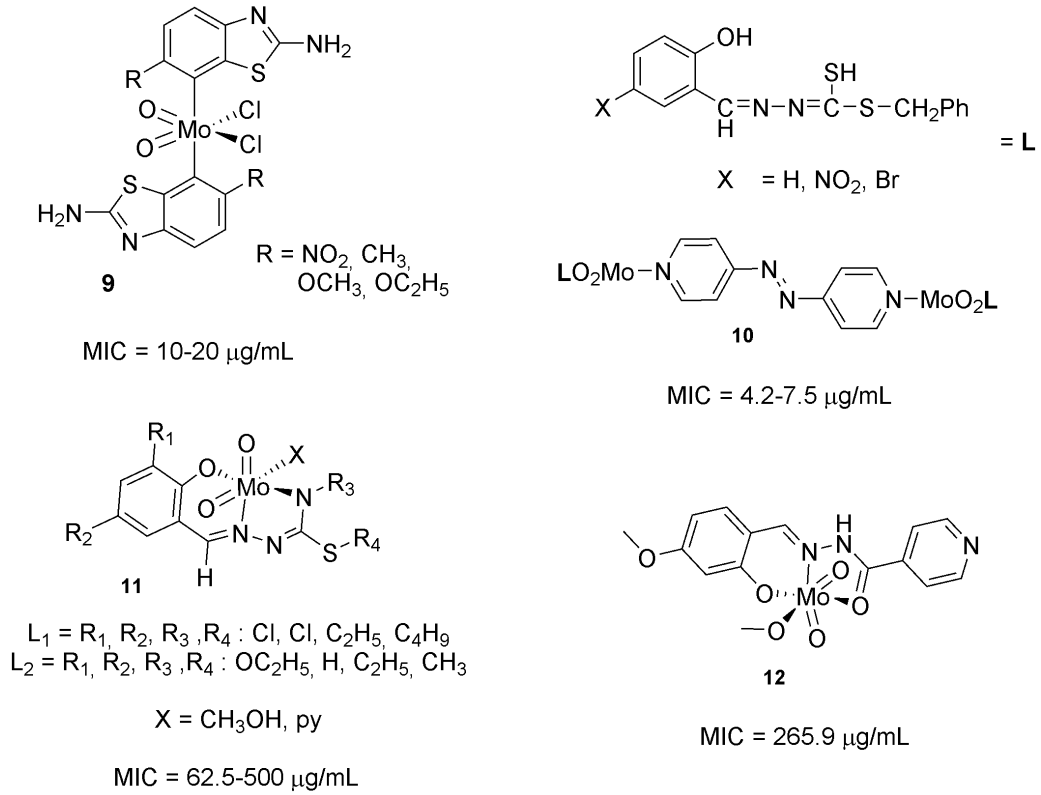

Figure 2. Structural formula of selected antimicrobial molybdenum(VI) complexes and corresponding ligands.

In 2015, Biswal et al. reported isostructural 4,4′-azopyridine (4,4′-azpy) pillared binuclear dioxomolybdenum(VI) complexes of formula $[(MoO_2L_1)_2(4,4'\text{-azpy})]$, $[(MoO_2L_2)_2(4,4'\text{-azpy})]$ and

$[(MoO_2L_3)_2(4,4'\text{-azpy})]$ (where $L_{\#}$ = Schiff base ligand, **10**, Figure 2) [49]. The ligands and molybdenum(VI) complexes were tested against *B. cerus* and *L. monocytogenes* (Gram-positive), *E. coli* and *S. aureus* (Gram-negative) bacteria by the disc diffusion method. The compounds exhibited different degrees of antimicrobial activities at a concentration of 10 μg per disc against the pathogens with antimicrobial activities comparable with those of common antibiotics ampicillin and tetracycline (as standard drugs). Schiff base ligands also showed moderate to good antimicrobial activities against all test microorganisms and were more active than their corresponding complexes. In 2019, Çelen et al. synthesized a group of thiosemicarbazonato-based ligands (2-hydroxy-3-methoxy/3,5-dibromo benzaldehyde 4-phenyl/ethyl-*S*-methyl/butyl thiosemicarbazones), and then coordinated the ligands through the ONN set to the molybdenum(VI) ion center to prepare *cis*-dioxomolybdenum(VI) complexes (**11**, Figure 2) [50]. All ligands and the complexes were tested (10 mg/mL) against *C. albicans*, *E. coli*, *P. aeruginosa* and *S. aureus*. The results confirmed the antimicrobial activities of all thiosemicarbazones and their dioxomolybdenum(VI) complexes and MIC values were in the range of 62.5–500 μg/mL. In 2020, Sang et al. reported the synthesis and the antimicrobial properties of a dioxidomolybdenum(VI) complex of *N*′-(2-hydroxy-4-methoxybenzylidene)isonicotinohydrazide (**12**, Figure 2) [51]. The free ligand showed modest antibacterial activity against *S. aureus* and *E. coli* (MIC = ~5 mmol/L), however, the molybdenum complex showed higher antibacterial activity against *E. coli* with MIC value of 0.62 ± 0.04 mmol/L. Finally, a report on two cationic cluster complexes based on the $\{Mo_6I_8\}^{4+}$ core with (4-carboxybutyl)triphenylphosphonium and 4-carboxy-1-methylpyridinium as apical ligands, indicated no antimicrobial activities of the species [52].

3. Group 7

3.1. Manganese Complexes

Several manganese complexes have been reported in the field, including photoactivatable CO-releasing molecules, which are described separately in the following section. In 2013, Zampakou et al. prepared $[KMn(oxo)_3(MeOH)_3]$ and $[Mn(erx)_2(phen)]$ complexes by reacting $MnCl_2$ with the quinolone antibacterial drug oxolinic acid (Hoxo), enrofloxacin (Herx) and the *N*,*N*′-donor heterocyclic ligand 1,10-phenanthroline (phen), respectively (**13**, Figure 3) [53]. Complexes were found significantly active against three Gram-positive (*B. subtilis*, *B. cereus* and *S. aureus*) and two Gram-negative (*X. campestris* and *E. coli*) bacterial strains with half-minimum inhibitory concentration (MIC) between 1.2 and 44 μg/mL. In 2018, Barmpa et al. reported similar types of manganese(II) complexes by using the quinolone antimicrobial agent sparfloxacin (Hsf) and flumequine (Hflmq) with or without nitrogen-donor heterocyclic ligands 1,10–phenanthroline (phen), 2,2′–bipyridine (bipy), 2,2′–bipyridylamine (bipyam) or pyridine (py) (**14**, Figure 3) [54]. The in vitro antimicrobial tests gave MIC values for the complexes in the range of, or slightly better than free Hsf. Against bacterial strains, such as *E. coli*, *B. subtilis*, and *S. aureus*, MICs were significantly low ranging from 0.0625–1.000 and 0.5–19 μg/mL. In 2015, P. Arthi and coworkers reported a series of pendant-armed Schiff base hexaaza macrocycles manganese(II) complexes by the condensation of equimolar amounts of terephthalaldehyde and *N*,*N*-bis(2-aminoethyl)benzamide derivatives in the presence of $Mn(ClO_4)_2{\cdot}6H_2O$ as a templating agent (**15**, Figure 3) [55]. In comparison to the standard drug, ciprofloxacin, the complexes showed good activities against both Gram-negative (*K. pneumoniae*, *P. aeruginosa*, *V. alginolyticus*, *V. cholerae* and *V. harveyi*) and Gram-positive (*S. aureus* and *S. mutans*) bacterial strains. The mean zone of inhibition values of the complexes and the standard were in the range of 4–21 and 20–25 mm (100 μg/mL), respectively. Also in 2015, Simpson et al. described the antibacterial and antiparasitic activities of manganese(I) tricarbonyl complexes with ketoconazole, miconazole, and clotrimazole ligands [56]. The molecules were tested against eight different bacterial strains: Gram-positive, such as *S. aureus*, *S. epidermidis*, *E. faekalis*, and *E. faecium*, and Gram-negative, such as *E. coli*, *P. aeruginosa*, *Y. pseudotuberculosa*, and *Y. pestis*. Only the miconazole complex (MIC values of 10−20 μM on *E. coli*, *Y. pseudotuberculosa*, and *Y. pestis*) was active against Gram-negative bacteria

and showed higher activity than miconazole alone. Conversely, all species were active against Gram-positive bacteria at submicromolar concentrations (MIC = 0.625 to 2.5 μM), particularly against *staphylococci*. The complexation of luteolin to manganese(II) was carried out to prepare manganese(IV) complex **16**, (Figure 3) [57]. The ligand and complex were screened against different microbial strains (e.g., *E. coli*, *S. aureus*, *L. monocytogenes* and *P. aeruginosa*) and **16** was found ~x1.5 more active than the ligand alone. A study on a series of manganese(I) tricarbonyl complexes bearing bis(2-pyridinylmethyl)(2-quinolinylmethyl)amine, bis(2-quinolinylmethyl)(2-pyridinylmethyl)amine, tris(2-quinolinylmethyl)amine, and tris(2-pyridinylmethyl)amine ligands (**17**, Figure 3), was reported recently by Güntzel and coworkers [58]. The compounds were examined against 14 different multidrug-resistant clinical isolates of *A. baumannii* and *P. aeruginosa* showing MIC values in the range of 0.2–0.8 mM. Finally, Kottelat et al. described a series of carbonyl complexes of manganese bearing isocyanide ligands of formula *fac*-$[Mn(CO)_3(CNR)_2Br]$ and found that for CNR = (1-isocyanoethyl)benzene, the complex showed a MIC of 128 μg/mL against *E. coli* [59]. Several other manganese metal complexes have been recently tested for their antimicrobial efficacy but were not found to be active [60–63].

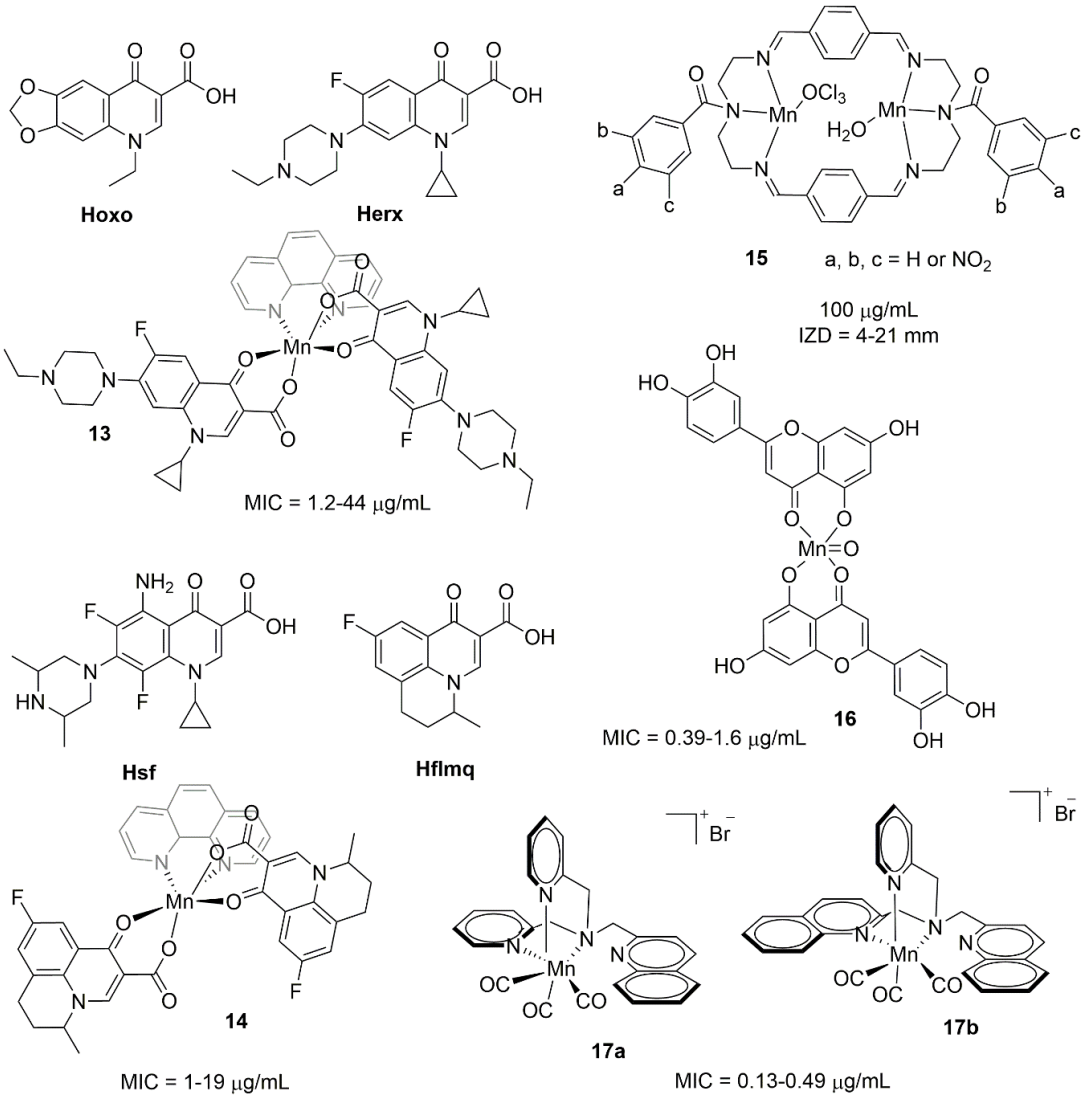

Figure 3. Structural formula of selected manganese(I), (II) and (IV) complexes and antibacterial drugs oxalinic acid (Hoxo), enrofloxacin (Herox), sparfloxacin (Hsf) and flumequine (Hflmq).

3.2. Manganese Photoactivatable CO-Releasing Molecules (PhotoCORMs)

PhotoCORMs are a special class of manganese-based antimicrobial complexes (Figure 4). The molecules are able to release carbon monoxide when activated with light. Carbon monoxide then acts in concert with the metal fragment to impart antimicrobial efficacy to the species. The $[Mn(CO)_3(tpa\text{-}k^3N)]Br$ complex (**18**, Figure 4) was the first one reported in the literature and it remains the most extensively studied [64–67]. It was active against several *E. coli* strains (K12 derivative MG1655, EC958, APEC), if photo-activated and perturbs the growth of multidrug-resistant isolates of Avian Pathogenic *E. coli* (APEC) (both in vitro and in vivo) without the need of light activation. In vivo (*G. mellonella* wax moth model), **18** showed no toxicity at double the concentration required in the treatment assay. The complex **19** (known as Trypto-CORM), was described in 2014 by Ward et al. [68,69]. The compound was not toxic to eukaryotic RAW264.7 cells but showed a strong antibacterial effect against *E. coli* strain W3110, *N. gonorrhoeae* and *S. aureus*. It completely inhibited *E. coli* growth following irradiation, leading to a loss of >99.9% of cell viability. Trypto-CORM was similarly toxic to *N. gonorrhoeae*, in the dark resulting in a loss of >99% cellular viability (half maximal inhibitory concentration (IC_{50}) value of 22 μM). Furthermore, complex **19** exhibited a cytostatic effect in the dark and cytotoxic effect if exposed to light against *S. aureus*. Mann et al. introduced molecule **20** and studied the broad-spectrum antimicrobial potential of the molecules [70,71]. The complex **20** inhibited growth of *E. coli* and several antibiotic resistant clinical isolates of pathogenic bacteria in a concentration-dependent manner. It extensively concentrated in *E. coli* cells, reaching concentrations of ~3.5 mM after 80 min of incubation. Significantly, **20** was effective against several pathogens isolated from clinical infections and causes in vitro a complete growth arrest of the multidrug-resistant *E. coli* EC958 clinical pathogen, *K. pneumoniae*, *S. flexneri*, *S. kedougou* and *E. hormaechei*, but it was ineffective against growth of *P. aeruginosa*, *C. koseri*, and *A. baumannii*.

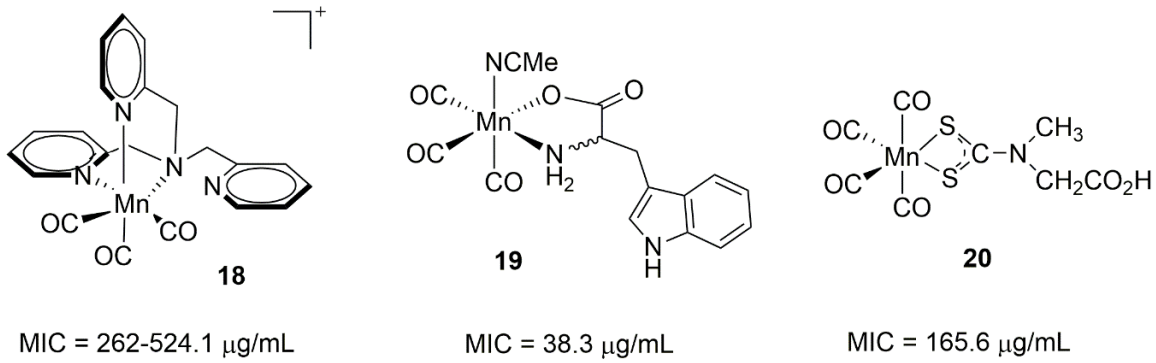

Figure 4. Structural formula of selected antimicrobial manganese(I) photoactivatable CO-releasing molecules.

3.3. Rhenium Complexes

In 2014, Noor et al. described a family of bioconjugated tridentate pyridyl-1,2,3-triazole macrocycles and the corresponding rhenium(I) complexes (**21**, Figure 5), which were screened for antimicrobial activities in vitro against both Gram-positive (*S. aureus*) and Gram-negative (*E. coli*) bacterial strains [72]. The minimum inhibitory concentrations for the compounds, however, showed values >256 μg/mL. At the same time Partra and coworkers introduced an interesting trimetallic complex (**22**, Figure 5) containing a ferrocenyl (Fc), a cymantrene and a $[(dpa)Re(CO)_s]$ residue (dpa = *N*,*N*-bis(pyridine-2-ylmethyl)prop-2-yn-1-amine) as the main biological active moiety of the construct [73]. A systematic structure–activity relationship (SAR) study against various Gram-positive pathogenic bacteria, including methicillin-resistant *S. aureus* (MRSA) strains proved that $[(dpa)Re(CO)_3]$ moiety was the essential part for the antibacterial activity of the trimetallic complex. The other two metallic units (Fc and cymantrene) could be replaced by organic compounds without affecting the

antibacterial activities of the construct. The MIC values of the compounds against Gram-positive bacterial strains, such as *B. subtilis*, *S. aureus* DSM 20231 and *S. aureus* ATCC43300 (MRSA) were found in the range of 1.4–21 μM. In 2016, Kumar et al. [74] reported a group of mono- and bis-*fac*-rhenium tricarbonyl 2-pyridyl-1,2,3-triazole complexes with different aliphatic and aromatic substituents (**23**, Figure 5) which were tested for antimicrobial activities in vitro against both Gram-positive (*S. aureus*) and Gram-negative (*E. coli*) bacterial strains. The MICs for all the complexes were measured between 16 and 1024 μg/mL. In 2017, a family of *N*-heterocyclic carbene (NHC) *fac*-[Re(I)(CO)$_3$] complexes containing unsubstituted benzimidazol-2-ylidene and bisimine ligands (N^N) ligands (**24**, Figure 5), were reported by Siegmund et al. [75]. The antimicrobial tests gave MIC values of the complexes between 0.7–2 μg/mL against Gram-positive strains, such as *B. subtilits* and *S. aureus*. However, the same complexes were inactive against Gram-negative strains, such as *E. coli*, *A. baumannii* and *P. aeruginosa*. Recently, Frei et al. reported the synthesis and antibacterial profiling of three rhenium bisquinoline complexes (**25**, Figure 5) [76]. The complexes displayed light-induced activities against drug-resistant *S. aureus* and *E. coli* showed MICs under photo-irradiation between 4- to 16-fold lower than in the dark. Other rhenium metal complexes have been tested for their antimicrobial efficacy but were inactive [77–80].

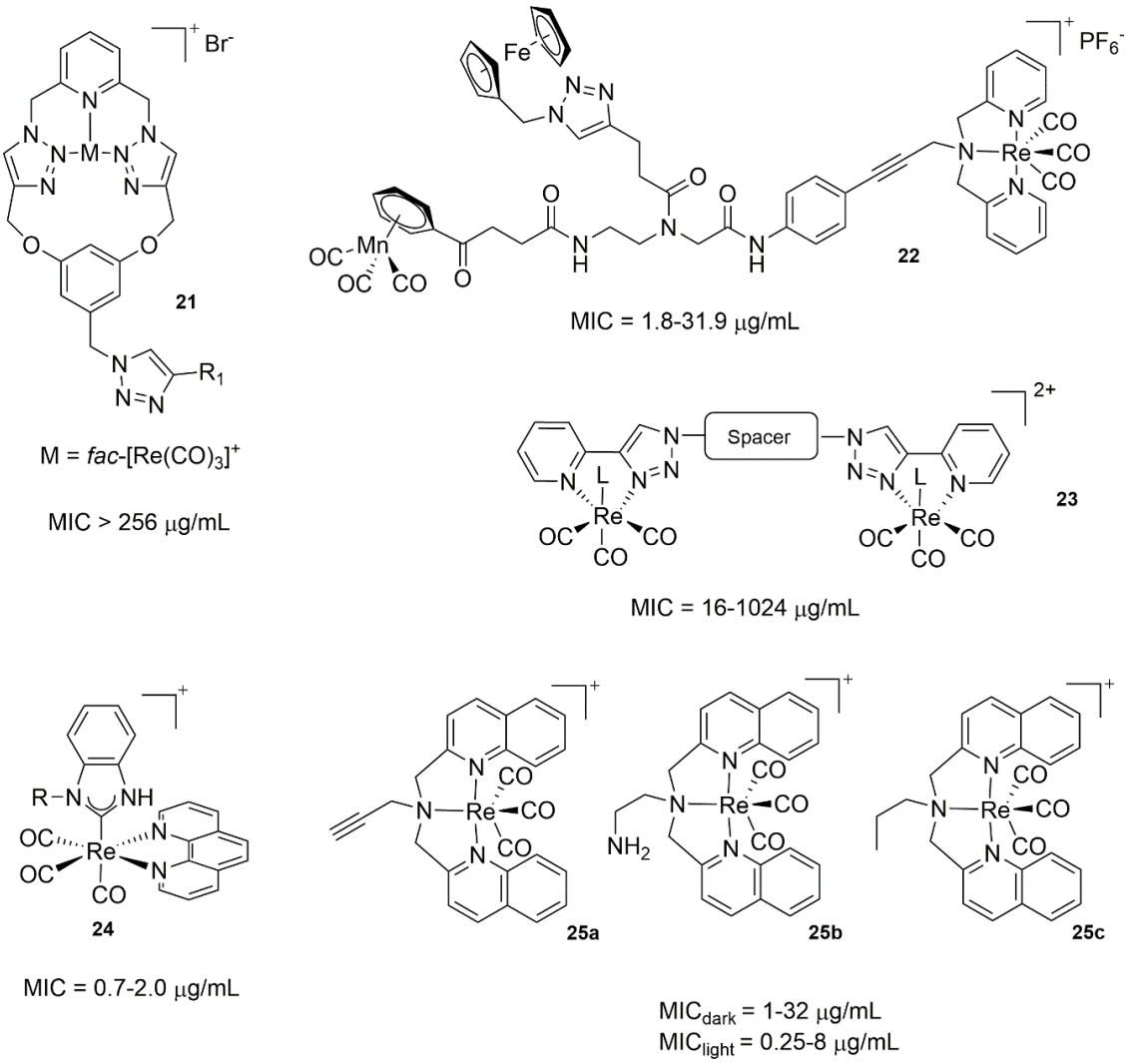

Figure 5. Structural formula of selected antimicrobial rhenium(I) complexes.

4. Group 8

4.1. Ruthenium Complexes

As stated in the introduction, iron complexes are not treated in this review; however, before discussing Ru species, the helicates-chiral assemblies reported by Howson et al. in 2012 deserves a special mention for their unique structure [81]. The species (**26**, Figure 6) were prepared by alkylation of 2 equiv. of (*R*)-2-phenylglycinol with 1 equiv. of α,α′-dibromo-p-xylene followed by reaction with 2-pyridinecarboxaldehyde and $Fe(ClO_4)_2 \cdot 6H_2O$ in the proportions 3:6:2. Single bimetallic diastereomerically pure flexicates Δ_{Fe},R_C-$[Fe_2L_3][ClO_4]_4$ were isolated following heating of the mixture at 85 °C for 24 h. These flexicates showed good antibacterial activities against MRSA and *E. coli* with MIC values in the 4–8 μg/mL range.

Ruthenium, as the second member of group 8 transition metals, has appeared in many reports as the central metal ion of new potential antimicrobial agents [82–93]. Here we describe the latest examples, but a recent perspective offers more details on the subject [10]. In 2016, Kumar and coworkers reported a series of tris(homoleptic) ruthenium(II) complexes with 2-(1-*R*-1*H*-1,2,3-triazol-4-yl)pyridine ligands (R-pytri) containing different aliphatic and aromatic substituents (**27**, Figure 7) [94]. The in vitro antimicrobial activities of R-pytri ligands and their *mer*- and *fac*-$[Ru(R\text{-pytri})_3]^{2+}$ complexes were screened against both Gram-positive (*S. aureus*, *S. pyogenes* and MRSA) and Gram-negative (*A. calcoaceticus*) bacterial strains. The experiments resulted in the good activity of two $[Ru(R\text{-pytri})_3]^{2+}$ complexes (where R = hexyl or octyl) against Gram-positive bacteria with MIC values between 1 and 8 μg/mL (depending on the strain), but lower activity was seen against Gram-negative *A. calcoaceticus* (MIC = 16–128 μg/mL). More importantly, both complexes showed stronger antibacterial effects (MIC = 4–8 μg/mL) than gentamicin as the control (MIC = 16 μg/mL) against two strains of MRSA (MR 4393 and MR 4549). Liao et al. have reported a study involving octahedral ruthenium(II) complexes as antimicrobial agents against the mycobacterium *M. smegmatis* [95]. The complex **28** (Figure 7) selectively inhibited *M. smegmatis* growth with MIC of 2 μg/mL comparable to those of norfloxacin and rifampicin (MIC of 2 and 1 μg/mL, respectively). All complexes, however, were found to be inactive against *S. aureus* (MSSA), *P. aeruginosa*, *E. coli*, *C. albicans* and *C. neoformans*.

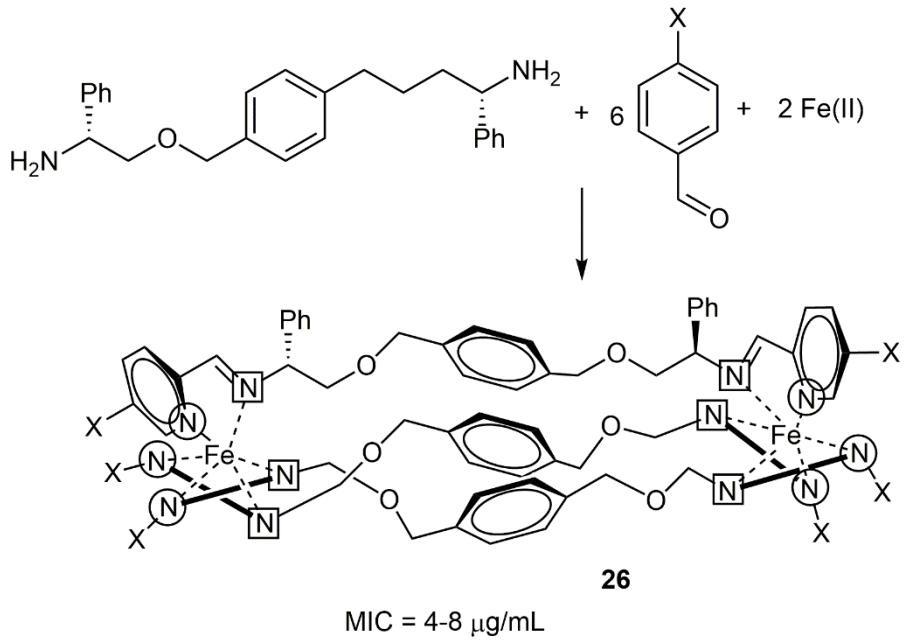

Figure 6. Structural formula of antimicrobial iron(II) flexicates.

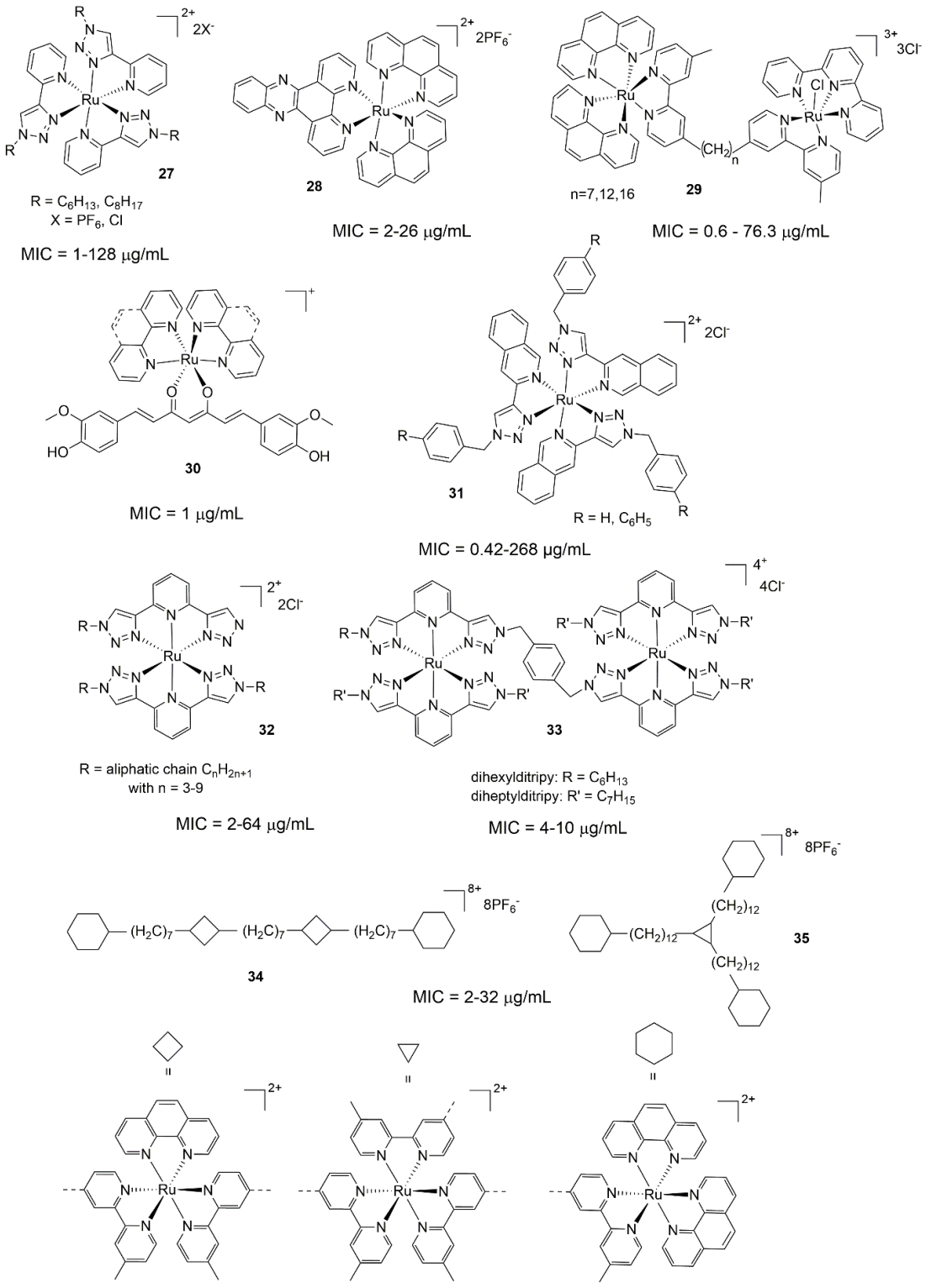

Figure 7. Structural formula of selected antimicrobial ruthenium(II) complexes.

In a study published in 2016 [96], Li et al. introduced a series of non-symmetric dinuclear polypyridylruthenium(II) complexes (**29**, Figure 7), and tested the same as antimicrobial agents. These complexes contained one inert metal center and one coordinatively-labile metal center, linked via the bis[4(4′-methyl-2,2′-bipyridyl)]-1,n-alkane ligand. The ruthenium(II) complexes were tested against four strains of bacteria, *S. aureus* and MRSA (Gram-positive), and *E. coli* and *P. aeruginosa*

(Gram-negative). In most cases, the compounds showed good MIC values (0.6–0.7 μM, comparable to gentamicin) against MRSA, they were less effective against *E. coli* and nearly inactive against *P. aeruginosa*. More recently, Srivastava et al. reported ruthenium(II) polypyridyl complexes [97] coordinated to curcumin, $[Ru(NN)_2(cur)](PF_6)$ [NN = bpy, phen], (**30**, Figure 7) and tested them against a panel of ESKAPE pathogens, including the drug resistant *S. aureus* ATCC. The results revealed a good inhibitory effect of the complexes against the latter pathogen and a remarkably high selectivity index (MIC = 1 μg/mL vs 0.25 for levofloxacin, SI = 80). Also in 2019, ruthenium(II) complexes of bidentate chelators 1-(1-benzyl-1,2,3-triazol-4-yl)isoquinoline and 3-(1-benzyl-1,2,3-triazol-4-yl)isoquinoline (**31**, Figure 7) were reported by Kreofsky et al. [98]. The complexes were screened against Gram-positive bacteria (e.g., *B. subtilis* and *S. epidermidis*), and revealed a very low MIC value of 0.4 μM. In the same year, van Hilst et al. described mono and dinuclear ruthenium(II) complexes of 2,6-bis(1-*R*-1,2,3-triazol-4-yl)pyridine ligands (**32** and **33**, Figure 7), bearing aliphatic substituents [99]. The antibacterial activities of the complexes were evaluated by in vitro tests against *S. aureus*, and *E. coli* strains. The MIC values for the most active mononuclear complex, $[Ru(hexyltripy)(heptyltripy)]^{2+}$ (i.e., **33** with n = 7 in Figure 7), were 2 μg/mL and 8 μg/mL, against *S. aureus* and *E. coli*, respectively. $[Ru(hexyltripy)(heptyltripy)]^{2+}$ and $[Ru_2(dihexylditripy)(hexyltripy)_2]^{4+}$ also showed good activities against the Gram positive and Gram negative methicillin resistant *S. aureus* strains (MICs = 4–8 μg/mL and 8–16 μg/mL, respectively). Finally, linear (**34**) and non-linear (**35**) tetranuclear ruthenium(II) complexes were reported by Sun and coworkers [100], as having MIC values against six strains of bacteria (Gram-positive *S. aureus* and MRSA; Gram-negative, *E. coli* strains MG1655, APEC, UPEC and *P. aeruginosa*) in the range between 2 and 32 μg/mL.

4.2. Osmium Complexes

There are only a few reports that have appeared lately detailing antimicrobial studies of osmium complexes. In 2015, a series of enantiopure (*S*,*S*)-iPr-pybox and {(*S*,*S*)-iPr-pybox = 2,6-bis[4(*S*)-isopropyloxazolin-2-yl]pyridine} osmium(II) complexes (**36**, Figure 8), were prepared by Menéndez-Pedregal and coworkers [101]. The complexes were screened against *M. luteus*, *B. subtilis*, *E. coli*, *S. coelicolor*, *S. antibioticus*, and *P. aeruginosa* bacteria. The results showed inhibition halos (mm) of the complexes in the range of 6–20 mm at concentrations between 99 and 500 μg/mL. Gichumbi and coworkers reported a class of osmium(II)-arene complexes with bidentate *N*,*N*′-ligands (**37**, Figure 8) [102]. A panel of antimicrobial-susceptible and -resistant Gram-negative (*E. coli*, *K. pneumonia* and *P. aeruginosa*) and Gram-positive (*B. subtilis*, *E. faecalis*, *S. aureus*, *S. aureus*, *S. saprophyticus* and *M. smegmatis*) bacterial strains were used to examine the antimicrobial activities of the synthesized complexes. The results showed promising anti-mycobacterial activity against *M. smegmatis*, and bactericidal activity against drug-resistant *E. faecalis* and methicillin-resistant *S. aureus* ATCC 43300.

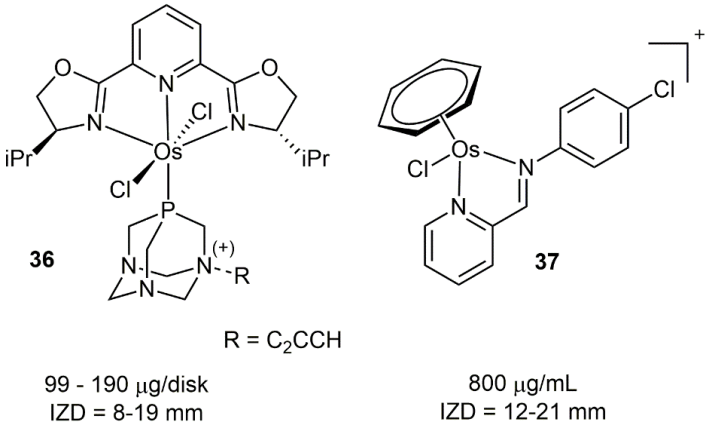

Figure 8. Structural formula of selected antimicrobial osmium(II) complexes.

5. Group 9

5.1. Cobalt Complexes

In 2010, Zhu et al. reported azide bridged Schiff bases 5-methoxy-2-[(2-morpholin-4-ylethylimino) methyl]phenol and 2-ethoxy-6-[(2-isopropylaminoethylimino)methyl]phenol cobalt(III) complexes (**38** and **39**, Figure 9) [103], and tested them against a panel of pathogens. The complexes **38** and **39** were active against *B. subtilis*, *E. coli* and *S. aureus* with the MIC values in the range of 4–18.5 μg/mL, but less active against *P. fluorescens* with MIC values of 21.7 and 37.3 μg/mL, respectively. The authors explained the bactericidal mechanism of action of the metal complexes by Overtone's concept [104] and Tweedy's chelation theory [105]. Coordination to the metal ion of the chelating Schiff bases results in the overlap of the ligand orbital and partial sharing of the positive charge of the ion with donor groups, which gives rise to a decrease in the polarity of the metal ion. As a result, the delocalization of π-electrons over the whole chelate ring increases and, consequently, enhances the lipophilicity of the complex. The main effect of increased lipophilicity is that of improving complexes penetration through lipid membranes, and finally, deactivation of the binding sites on enzymes of microorganisms.

Irgi et al. reported in 2015 a study of the antimicrobial potential of cobalt(II) complexes featuring coordination to the quinolone oxolinic acid drug (Hoxo), and 2,2′-bipyridine (bipy), 2,2′-bipyridylamine (bipyam), 1,10-phenanthroline (phen), pyridine (py) or 4-benzylpyridine (4bzpy) ligands (**40**, Figure 9) [106]. The antimicrobial activities of Hoxo and its complexes were screened against Gram-negative (*E. coli* NCTC 29212 and *X. campestris* ATCC 1395), and Gram-positive (*S. aureus* ATCC 6538 and *B. subtilis* ATCC 6633) bacterial species. Oxolinic acid and its cobalt(II) complexes showed inhibitory action against all the microorganisms tested, with MIC values in the 1–2 μg/mL range for most of the complexes. Similar cobalt(II) complexes, based on a series of coordinated quinolone sparfloxacin and nitrogen-donor heterocyclic ligands bipy, phen or 2,2′-bipyridylamine (bipyam) (**41**, Figure 9), were introduced in 2016 by Kouris et al. [107]. The ligand and complexes showed remarkable antimicrobial activities against bacteria strains, such as *X. campestris*, *S. aureus*, *B. subtilis* and *E. coli* with MICs of 0.031–0.500 μg/mL. The authors suggested that the chelate effect and the presence of sparfloxacinato and *N*-donor ligands, as well as the generation of the quinolone ligand, could be the prevailing factors contributing to the antimicrobial activities of the complexes.

A class of $[CoCl_2(dap)_2]Cl$ (dap = 1,3-diaminopropane) and $[CoCl_2(en)_2]Cl$ (en = ethylenediamine) were recently reported by Turecka et al. [108], and tested against a broad spectrum of reference and clinical fungal strains of *Candida.* The complexes showed MICs of ~16 μg/mL on the selected species (e.g., *C. glabrata* ATCC 2001) but were not as effective as amphotericin B and ketoconazole. A series of zinc(II), copper(II) and cobalt(II) metallophthalocyanine (Pc) compounds derivatized with four 2-methoxy-4-{(*Z*)-[(4-morpholin-4-ylphenyl)imino]methyl}phenol at the peripheral positions (**42**, Figure 9) were reported by Unluer et al. [109]. According to the in vitro studies, cobalt(II)Pc and copper(II)Pc complexes, in particular, showed antibacterial activities against *S. typhimurium* and *E. coli*. Recently, a series of 2-formylpyridine 4-allyl-*S*-methylisothiosemicarbazone of zinc(II), copper(II), nickel(II) and cobalt(III) complexes were reported [110]. The in vitro tests showed that cobalt(III) complexes (**43**, Figure 9) were more active against Gram-positive bacteria (e.g., *S. aureus*) and fungal strains (*C. albicans*) with MIC values of 0.7–3 and 7–250 μg/mL, respectively, and less active against Gram-negative strains, such as *E. coli* and *K. pneumoniae*. Several other types of cobalt metal complexes have been tested for their antimicrobial efficacy, however, their activities were not found remarkably high [111–121].

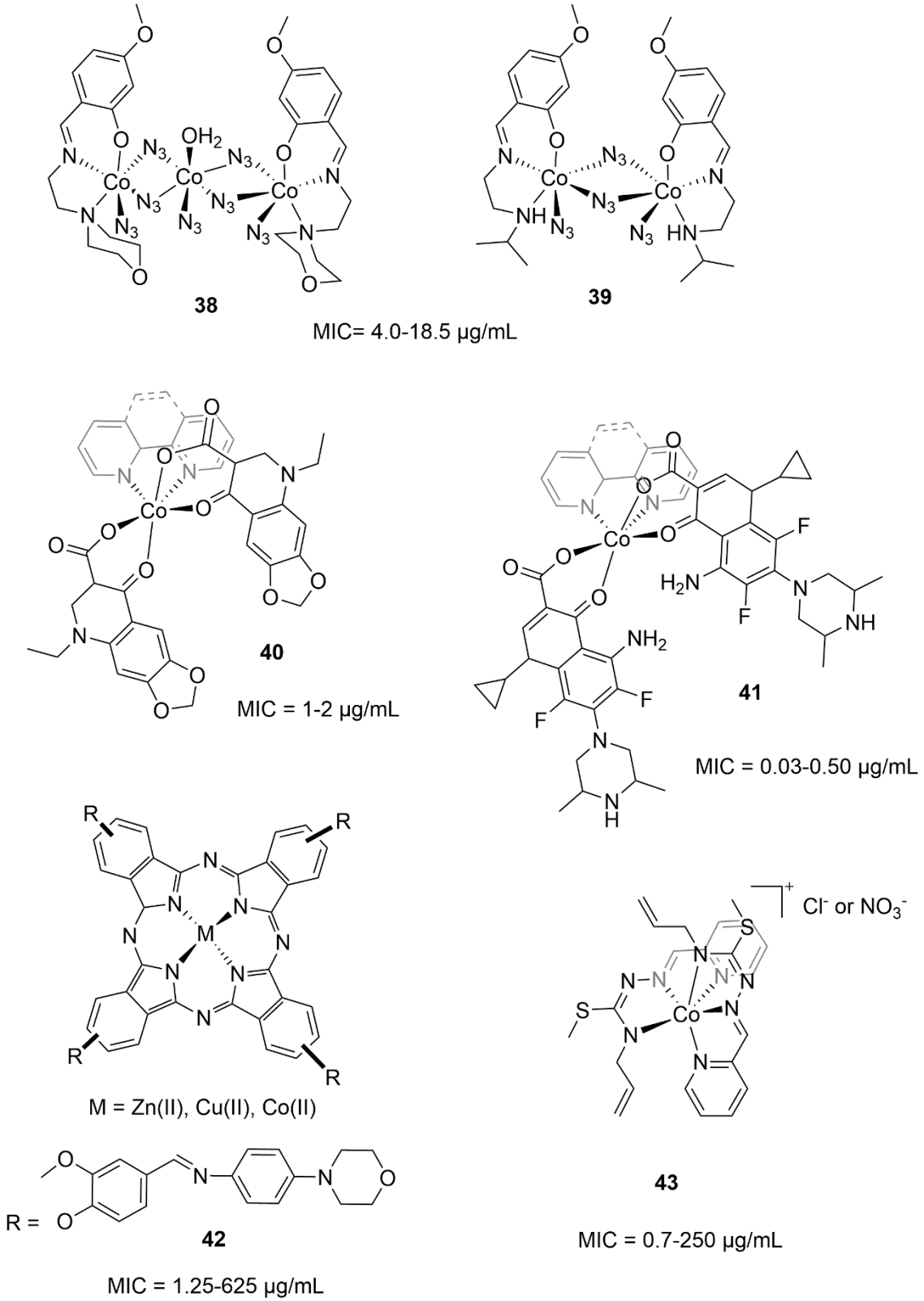

Figure 9. Structural formula of selected antimicrobial cobalt(II) and cobalt(III) complexes and corresponding ligands.

5.2. Rhodium and Iridium Complexes

Rhodium and iridium complexes hold great potential as metal-based antimicrobial agents. In 2015, Lu et al. tested a series of cyclometallated rhodium(III) and iridium(III) complexes for their antimicrobial activities [122]. The in vitro tests revealed that complex **44** (Figure 10) had a selective inhibitory effect against *S. aureus* growth with MIC and MBC values of 3.60 and 7.19 μM, respectively. The complex was the first example of a substitutionally-inert, group 9 organometallic compound utilized as a direct inhibitor of *S. aureus*. In 2017, Fiorini et al. [123] reported methylation of iridium(III) tetrazolato complexes as an effective route to modulate the emission outputs and to switch the antimicrobial properties of the species. Transformation of neutral iridium(III) tetrazolato complexes **45** to the equivalent methylated cations **46** (Figure 10), was accompanied by a remarkable change in the antimicrobial activities of the complexes. Compounds of general structure **45** were inactive against Gram-negative (*E. coli*) and Gram-positive (*D. radiodurans*) microorganisms. However, by converting them to methylated cationic derivatives **46**, the MIC values of the latter dropped to 1–4 μg/mL against the *D. radiodurans* bacterial strain. The same year, Kumar et al. prepared an iridium(III) complex of formula $[Ir(cod)(dmtu)_2]Cl$ (where cod = 1,5-cyclooctadiene and dmtu = *N*,*N*′-dimethylthiourea, **47** in Figure 10), from the reaction of dmtu with the $[Ir(cod)(Cl)]_2$ dimer [124]. The antimicrobial activity of the complex was investigated against *E. coli*, *S. aureus* and *P. aeruginosa*, and it showed good activity against the two latter strains. In 2018, DuChane and coworkers reported a series of ~40 rhodium(III) and iridium(III) half-sandwich complexes of formula [(η^5-Cp*R)M(β-diketonato)Cl] (M = Rh(III), Ir(III), **48** in Figure 10) [125] and tested them against *M. smegmatis*. The rhodium(III) complexes were found consistently more active than the iridium analogs with MIC values in the range of 2–16 μM and 15–69 μM for the two ions, respectively. The most active rhodium(III) complex was the one bearing pentamethylcyclopentadiene (η^5-Cp*R where R = $-CH_3$) and dipivaloylmethane as the β-diketonato chelate.

Recently, Lapasam and coworkers have reported a family of mononuclear metal complexes containing hydrazone ligands (L) of the type $[(arene)MLCl]^+$ (M = Ru(II), Rh(III) and Ir(III), **49** in Figure 10) [126]. The antibacterial efficacies of the complexes were evaluated against four pathogenic bacteria, such as *S. aureus*, *E. coli*, *B. thuringiensis* and *P. aeruginosa*. All the complexes behaved selectively against *P. aeruginosa* and *B. thuringiensis* with comparable activities to gentamycin but were inactive against *E. coli* and *S. aureus*. In a report in 2019, the same author described related ruthenium(II), rhodium(III) and iridium(III) arene complexes bearing pyridyl azine Schiff base ligands (**50** and **51**, Figure 10) showing potent antibacterial activities against *S. aureus*, *E. coli* and *K. pneumonia* with the zone of inhibition (at conc. 2.0 mg/mL) greater than that of ciprofloxacin [127]. A class of neutral heteroleptic cyclometalated iridium(III) complexes linked to boron dipyrromethene (BODIPY) substituted *N*-heterocyclic carbene (NHC) ligands was characterized by Liu et al. in 2019 [128]. The antimicrobial photo-biological properties of **52** and **53** (Figure 10) were evaluated against *S. aureus* bacteria growing as planktonic cultures. The results revealed good activity of **53** against the pathogen upon visible light activation, with a phototherapeutic index >15 and the half-maximal effective concentration (EC_{50}) value of 6.67 μM.

In 2018, a series of organoiridium(III) antimicrobial complexes containing biguanides derivatives as chelated ligands were reported by Chen et al. (**54**, Figure 10) [129]. The compounds have remarkable activities against both Gram-negative and Gram-positive bacteria, including MRSA with MICs as low as 0.125 μg/mL. The complexes also exhibited a high fungicidal effect toward *C. albicans* and *C. neoformans* with MIC values of 0.25 μg/mL (0.34 μM), and generally, low cytotoxicity toward mammalian cells. In 2019, DuChane et al. evaluated a series of piano-stool iridium complexes with 1,2-diaminoethane ligands against bacterial strains of *S. aureus*, including various isolates of methicillin-resistant strains (MRSA) [130]. The in vitro tests indicated an interesting difference between stereoisomers of the species with complex **55** (*cis* isomer, Figure 10) being the most effective compound with MIC values of 5 and 7.5 μg/mL against *S. aureus* and MRSA, respectively. Recently, Lapasam et al. introduced a series of ruthenium(II), rhodium(III) and iridium(III) complexes with 4-phenyl-1-(pyridin-4yl)methylene

thiosemicarbazide and 4-phenyl-1-(pyridin-4yl)ethylidene thiosemicarbazide ligands (**56**, Figure 10) with comparable antibacterial properties to that of ciprofloxacin [131]. The MIC values of the complexes were as low as 0.015 mg/mL (MIC of ciprofloxacin = 0.031–0.062 mg/mL) against *S. aureus*, *E. Coli* and *K. pneumonia*.

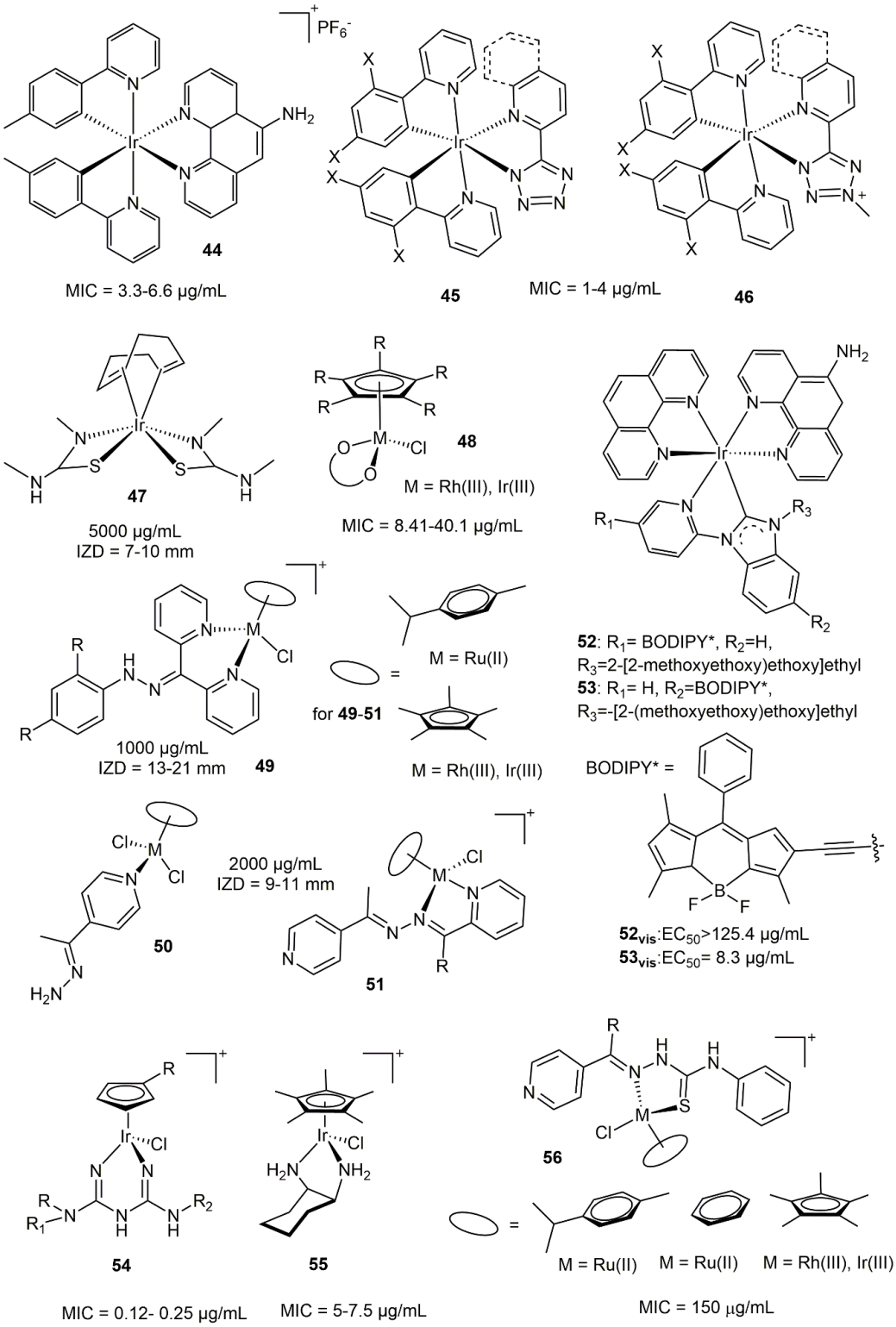

Figure 10. Structural formula of selected antimicrobial rhodium(III) and iridium(III) complexes. EC_{50} = half-maximal effective concentration.

6. Group 10

6.1. Nickel Complexes

Group 10 antimicrobial complexes are not as active as metal complexes of other groups and generally show relatively high MICs when compared to other transition metal species. Nickel is no exception. Therefore, only two selected cases will be given in the current section. In 2017, Raj et al. described Schiff base (**57**, Figure 11) nickel(II) complexes with MIC values against *S. aureus* (15–30 μg/mL) comparable to the standard drug, ciprofloxacin [132]. The complexes, whose structures remained undefined, also showed good MICs against methicillin resistant *S. aureus* (MRSA, 20–50 μg/mL), but were inactive against other tested pathogens (e.g., *S. flexneri* MTCC-1457, *P. aeruginosa* MTCC-741, and *E. coli* MTCC-119) and several fungal strains. The complexes exert their antimicrobial action by disintegrating the bacterial cell membrane. Recently, Ibrahim et al. [133] presented nickel(II) complexes of NNS tridentate thiosemicarbazone based ligands (**58**, Figure 11) and evaluated them against several bacterial (e.g., *E. coli*, *P. aeruginosa*, *B. cereus*, *S. aureus*, *M. luteus* and *S. marcescens*) and fungal (e.g., *F. oxysporum*, *C. albicans*, *G. candidum*, *A. flavus*, *S. brevicaulis* and *T. rubrum*) strains. The complexes all showed similar and comparable effects as the standard antibacterial chloramphenicol drug. The results varied in terms of the antifungal potency of complexes **58**, but the active ones showed greater inhibition than clotrimazole (the standard drug).

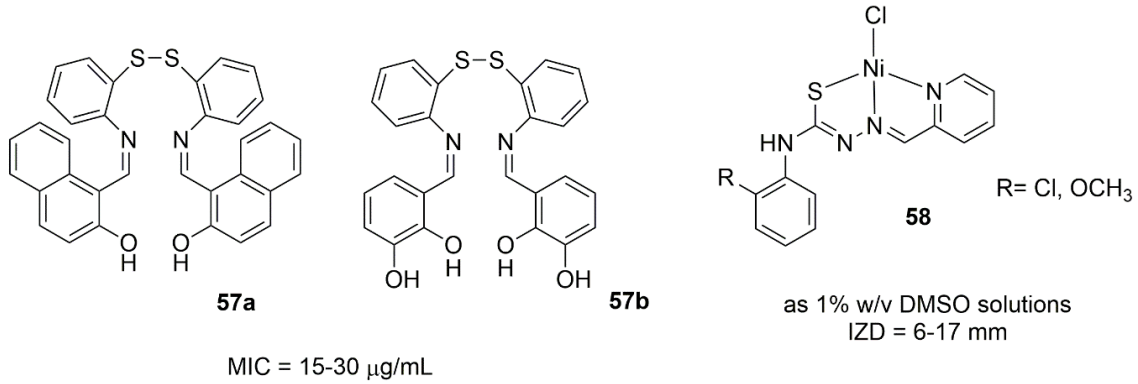

Figure 11. Structural formula of Schiff base ligands **57a** and **57b** and nickel(II) antimicrobial complex **58**.

6.2. Palladium and Platinum Complexes

Several palladium and platinum complexes have been tested for their antimicrobial potencies and a few species showed significant effects. In general, the reported complexes of the two metal ions were not as effective as those of other metals and palladium compounds were more active than the platinum ones. It is, however, instructive to also overview some of the latest reported examples not showing antimicrobial potential. By varying reaction conditions and stoichiometry of reagents, Juribašić et al. [134] prepared a series of quinolinylaminophosphonate palladium(II) halide complexes (**59**–**61**, Figure 12) and tested them on a wide spectrum of bacterial and fungal strains. None of the species was active. Similarly, the methylpyrazole-4-carboxaldehyde thiosemicarbazone and the 2-((6-allylidene-2-hydroxycyclohexa-1,3-dienylmethylene)amino)benzoic acid complexes (**62** and **63**, Figure 12) were inactive [135]. Radić et al. introduced *S*-alkyl thiosalicylic acid derivatives of palladium(II) (**64**, Figure 12) and investigated the antimicrobial potential of the ligands and complexes on a wide panel of 26 microorganism species [136]. The palladium(II) complexes were inactive against nearly all pathogens with the exception of fungal strains (e.g., *A. fumigatus* and *A. flavus*) with MICs <7.8 μg/mL.

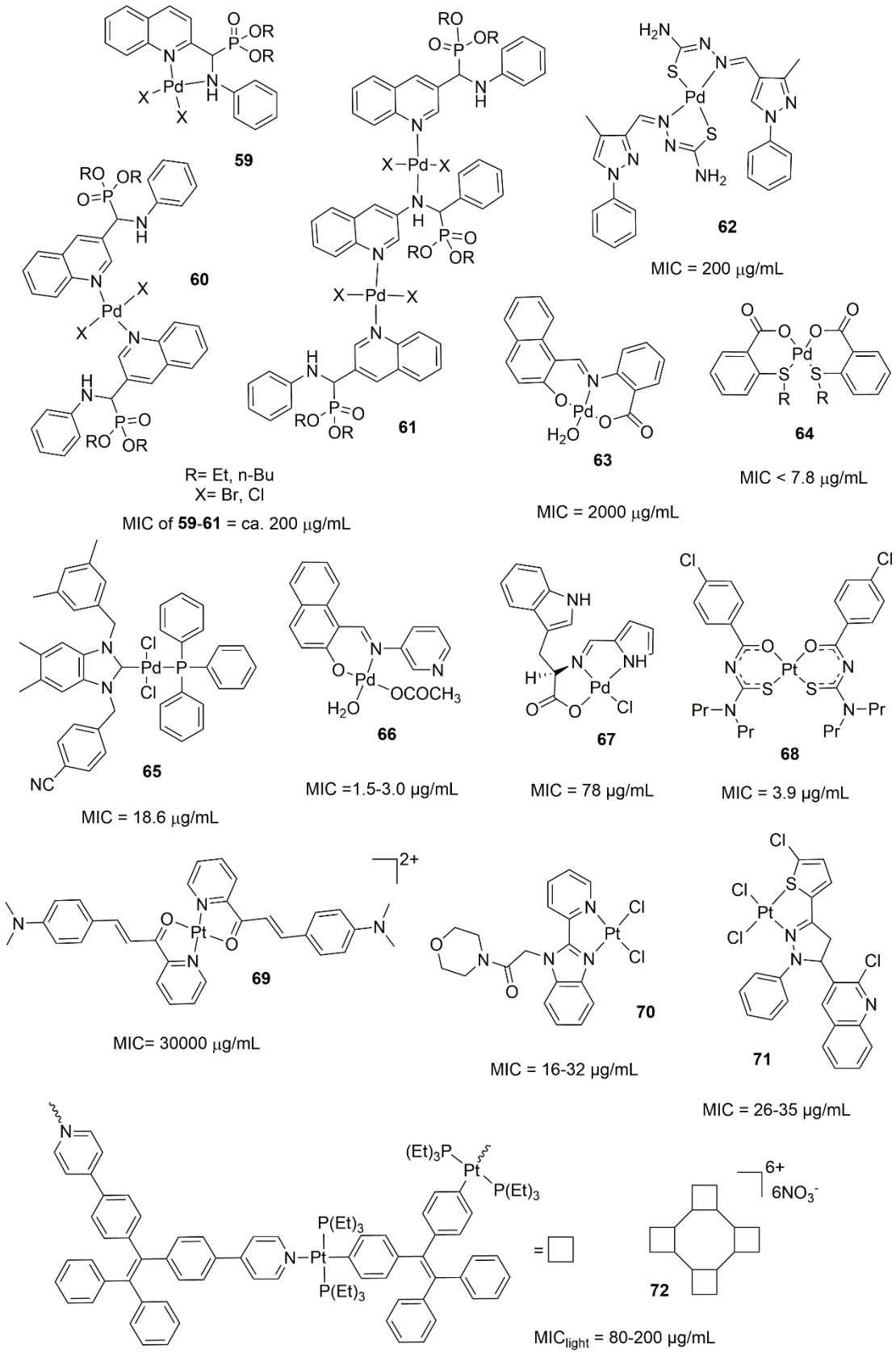

Figure 12. Structural formula of selected antimicrobial palladium(II) and platinum(II) complexes.

In 2018, Boubakri et al., reported the synthesis and antibacterial properties of triphenylphosphine (PPh_3) *N*-heterocycle carbene (NHC) complexes of palladium(II) (**65**, Figure 12) [137]. The complexes were prepared by combining the NHC benzimidazolium salts with, $PdCl_2$, K_2CO_3 in pyridine at 80 °C, followed by reaction with triphenylphosphine. The in vitro tests of palladium(II)-NHC-PPh_3 complexes against Gram-positive (*M. luteus* LB 14110, *S. aureus* ATCC 6538 and *L. monocytogenes* ATCC 19117) and Gram-negative (*S. typhimurium* ATCC14028 and *P. aeruginosa* ATCC 49189) pathogens showed moderate to significant activities of the complexes against the different bacterial strains. The MIC values against *M. luteus*, *L. monocytogenes* and *S. typhimurium* were in the range of 0.0197–0.625, 0.078–1.25, and 1.25–5 mg/mL, respectively. A remarkable example of active palladium(II) complexes was obtained by Abu-Dief et al. [138]. The authors prepared a series of metal complexes bearing the 1-(pyridin-3-yliminomethyl)-naphthalen-2-ol ligand and tested the silver(I), palladium(II) and vanadium(II) oxide derivatives against different strains of bacteria and fungi (*S. Marcescens*, *E. coli*, *M. Luteus F. oxysporum*, *G. candidum* and *A. flavus*). The palladium(II) complex (**66**, Figure 12) showed MIC values against all tested strains between 1.50 and 3.00 μg/mL, close to the standard drugs (ofloxacin and fluconazole). Recently, Nyawade et al. reported new 2-pyrral amino acid Schiff base palladium(II) complexes [139] and investigated their antibacterial effects against six species (Gram-positive, such as *S. aureus*, MRSA, *S. epidermidis*, *S. pyogenes*, and Gram-negative, such as *P. aeruginosa* and *K. pneumonia*). Of the series of compounds, complex **67** (Figure 12) was the most active showing comparable antimicrobial potency to ampicillin against MRSA, *S. epidermidis* and *S. pyogenes*.

Solmaz and coworkers synthesized *N*,*N*-Di-(*R*)-*N*′-(4-chlorobenzoyl)thiourea platinum(II) complexes (**68**, Figure 12) and carried out antimicrobial tests against *S. aureus*, *S. pneumonia*, *E. coli*, *P. aeruginosa*, *A. baumannii*, *C. albicans* and *C. glabrata* [140]. The compounds were particularly effective against *S. pneumonia*, *P. aeruginosa*, and *A. baumannii* (MIC value of 3.90 μg/mL) and moderately active against *S. aureus*, *E. coli* and *C. albicans* (MIC value of 15.62 μg/mL). More recently, Gaber et al. reported palladium(II) and platinum(II) chalcone complexes of the bidentate ligand, (*E*)-3-(4-(dimethylamino)phenyl)-1-(pyridin-2-yl)prop-2-en-1-one (**69**, Figure 12) [141]. The platinum(II) complex showed low IC_{50} values but virtually no antimicrobial potency (MIC value of ~30 mg/mL) against *C. albicans*, *A. flavus*, *E. coli* or *S. aureus*. Palladium(II) and platinum(II) complexes with good antifungal activities against *C. albicans* and *C. neoformans* (MIC values of 32 and 16 μg/mL, respectively for the two species) were those bearing a derivatized *N*,*N*-bidentate pyridyl benzimidazole ligand (**70**, Figure 12) reported by Mansour et al. [142]. In 2018, Lunagariya et al. tested square planar mononuclear platinum(II) complexes bearing 5-quinoline 1,3,5-tri-substituted pyrazole scaffolds against *S. Aureus*, *B. subtilis*, *S. marcescens*, *P. aeruginosa* and *E. coli* [143]. Within the series, compound **71** (Figure 12) showed good activity against the pathogens with MIC values between 25 and 35 μg/mL. Finally, in 2019, Gao and coworkers published a bacterial membrane intercalation-enhanced photodynamic inactivation (PDI) system, of discrete organoplatinum(II) metallacycles (**72**, Figure 12) [144]. The compound acted as a photosensitizer with aggregation-induced emission. It self-assembled with a transacting activator of the transduction (TAT) peptide-decorated virus coat protein. The resulting aggregate intercalated in the bacterial cell membrane and decreased the survival rate of Gram-negative *E. coli* to nearly zero and that of Gram-positive *S. aureus* to ~30% upon light irradiation. Several other complexes of these ions have been tested for their antimicrobial efficacy, however, their activities were not found remarkably high [145–169].

7. Group 11

7.1. Copper Complexes

In the last five years, hundreds of scientific publications have reported antimicrobial properties of copper complexes. As for iron and the other members of this group, the complexes of the metal ion would be best reviewed alone, but for completeness, a few recent selected examples will be mentioned in this section. In 2019, Kaushal et al. described the synthesis and characterization of

several 2-acetylpyridine-*N*-substituted thiosemicarbazonates of copper(II) species (**73**, Figure 13) with remarkable antimicrobial activities against methicillin resistant *S. aureus* (MRSA), *K. pneumoniae* and *C. albicans* [170]. The complexes showed MICs values between 0.5 and 5 μg/mL and often equated the potency of amphotericin and gentamicin. The authors attempted a structure–activity relationship of the variation of antimicrobial bioactivity with variations of R substituents and halogens (X).

In general, for all pathogens, the halogens did not provide any preferential trend but variations occurred due to the substituents R, with ethyl/methyl substituents showing high activity. Oladipo et al. reported a synthetic and structural study of copper(II) *N*,*N*′-diarylformamidine dithiocarbamate complexes (**74**, Figure 13), showing excellent antibacterial activities against Gram-negative, *S. typhimurium*, *P. aeruginosa*, *E. coli* and *K. pneumoniae* and Gram-positive, *S. aureus* bacteria, including MRSA [171]. The MIC values of complexes were in the order of 6.25 ng /mL to 0.8 μg/mL, surpassing in many cases the potency of ciprofloxacin. Krishnegowda and coworkers prepared 1-phenyl-1,3-butanedione copper(II) complexes (**75**, Figure 13), showing activity against *B. cereus*, *Bacillus substilis*, methicillin-resistant *S. aureus*, *E. coli*, *P. aerogenes* and *K. pneumonia* (MICs in the range of 10.4–16.5 μg/mL) similar to ampicillin [172].

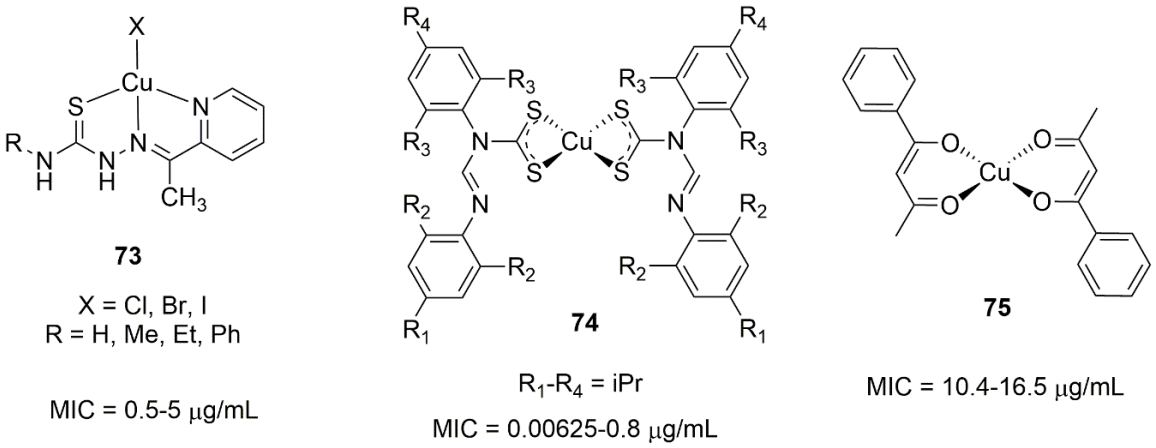

Figure 13. Structural formula of selected antimicrobial copper(II) complexes.

7.2. Gold Complexes

Gold complexes have been investigated in a wide range of therapeutic applications (e.g., as antiarthritic agents for the treatment of rheumatoid arthritis and a variety of rheumatic diseases, including psoriatic arthritis, juvenile arthritis, palindromic rheumatism and discoid lupus erythematosus [173]), and continue to attract the attention of many organometallic chemists [174]. They also have great potential as antimicrobial agents. In this section, we have selected only a few examples, but a recent perspective offers more details on the subject [10].

In 2016, Savić et al. reported a series of aromatic nitrogen-containing heterocycles gold(III) species (**76**, Figure 14) in a comparative antimicrobial and toxicological study of gold and silver complexes of the same [175]. All square-planar gold complexes were evaluated in vitro against *P. aeruginosa*, *E. coli*, *S. aureus*, *L. monocytogenes* and *C. albicans*. They revealed good antibacterial activity with the MIC values in the 2.5 to 100 μg/mL range but were not as effective as the silver analogues. Hikisz et al. studied the antibacterial activities of the gold(I) alkynyl chromone complexes (**77**, Figure 14) against *E. coli* and Gram-positive methicillin-sensitive (MSSA) and methicillin-resistant (MRSA) *S. aureus* including clinical isolates [176]. In vitro tests of the complexes showed high activities against *S. aureus* pathogens with MICs between 2 and 32 μg/mL, but they were not active against *E. coli*. Glišić et al. prepared dinuclear gold(III) complexes with bridging aromatic nitrogen-containing heterocyclic ligands (**78**, Figure 14) and studied their antimicrobial activities in relation to the complex nuclearity [174]. In most cases, complexes showed higher antibacterial activity than $K[AuCl_4]$ with MICs in the range of 3.9–62.5 μg/mL. The complexes **78** were particularly effective against *M. luteus*

being ~3x more potent than kanamycin. In 2017, Schmidt and co-workers evaluated a series of gold(I) bis-*N*-heterocyclic carbene complexes (**79**, Figure 14) [177] for their effects against pathogenic bacteria *E. faecium*, *E. coli*, *P. aeruginosa*, *A. baumannii*, *K. pneumonia* and methicillin-resistant *S. aureus* strains (MRSA). The complexes showed good activity against MRSA (for R = Phe, MIC = 1.7–2.3 μM) but were not as effective as auranofin or standard antibiotics. These biscarbene gold complexes act by inhibiting bacterial thioredoxin reductase (TrxRs) with moderate potency. Finally, Pöthig et al. recently described structurally interesting gold pillarplexes [178]. The compounds (**80**, Figure 14), however, showed little or no activity against *B. subtilis*, *S. aureus*, *E. coli*, *P. aeruginosa* or *C. albicans*.

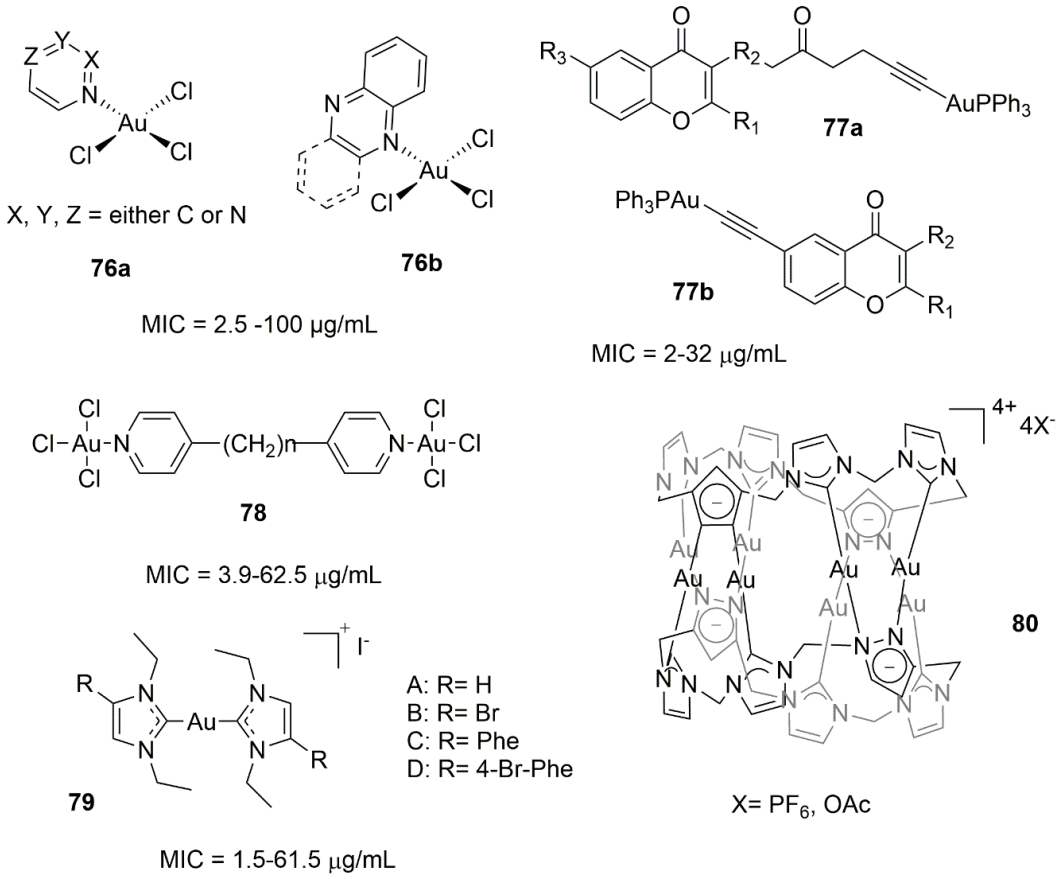

Figure 14. Structural formula of selected antimicrobial gold(I) and gold(III) complexes.

8. Group 12

8.1. Zinc Complexes

Zinc, the first element in group 12, is the only metal that appears in all enzyme classes [179–182]. Complexes of the element have been the topic of many studies, including antibacterial and antiviral activities [183]. In the last five years, more than 100 scientific publications on the antimicrobial properties of zinc complexes have been reported. As mentioned in Section 7, it is beyond the scope of this short review to detail all these studies. We have selected, therefore, only a few cases as interesting examples from the structural and chemical point of view.

In 2015, Zaltariov et al. reported zinc(II) complexes of trimethylsilyl-propyl-p-aminobenzoate (**81**, Figure 15) with remarkable antimicrobial properties [184]. The compounds showed the MIC values as low as 16 ng/mL against *A. fumigatus*, *P. chrysogenum* and *Fusarium*, and 0.38 μg/mL against *Bacillus* sp. and *Pseudomonas* sp., being more active than the standards, i.e., caspofungin and kanamycin. Abu Ali et al. investigated ibuprofen zinc(II) complexes in combination with mono and bidentate ligands such as 2-aminopyridine, 2-aminomethylpyridine and 2,2′-bipyridine (**82** and **83**,

Figure 15) [185]. Compounds were screened against three Gram-positive (*M. luteus*, *S. aureus* and *B. subtilis*) and three Gram-negative (*E. coli*, *K. pneumonia* and *P. mirabilis*) bacterial strains. The complex containing ibuprofen and 2,2′-bipy (**83**, Figure 15) was the most potent compound against all bacteria with MICs of ~1.5–3 mg/mL. In 2018, Boughougal et al. reported a series of zinc(II) complexes coordinated to sulfadiazine and enrofloxacin (**84**, Figure 15) [186].

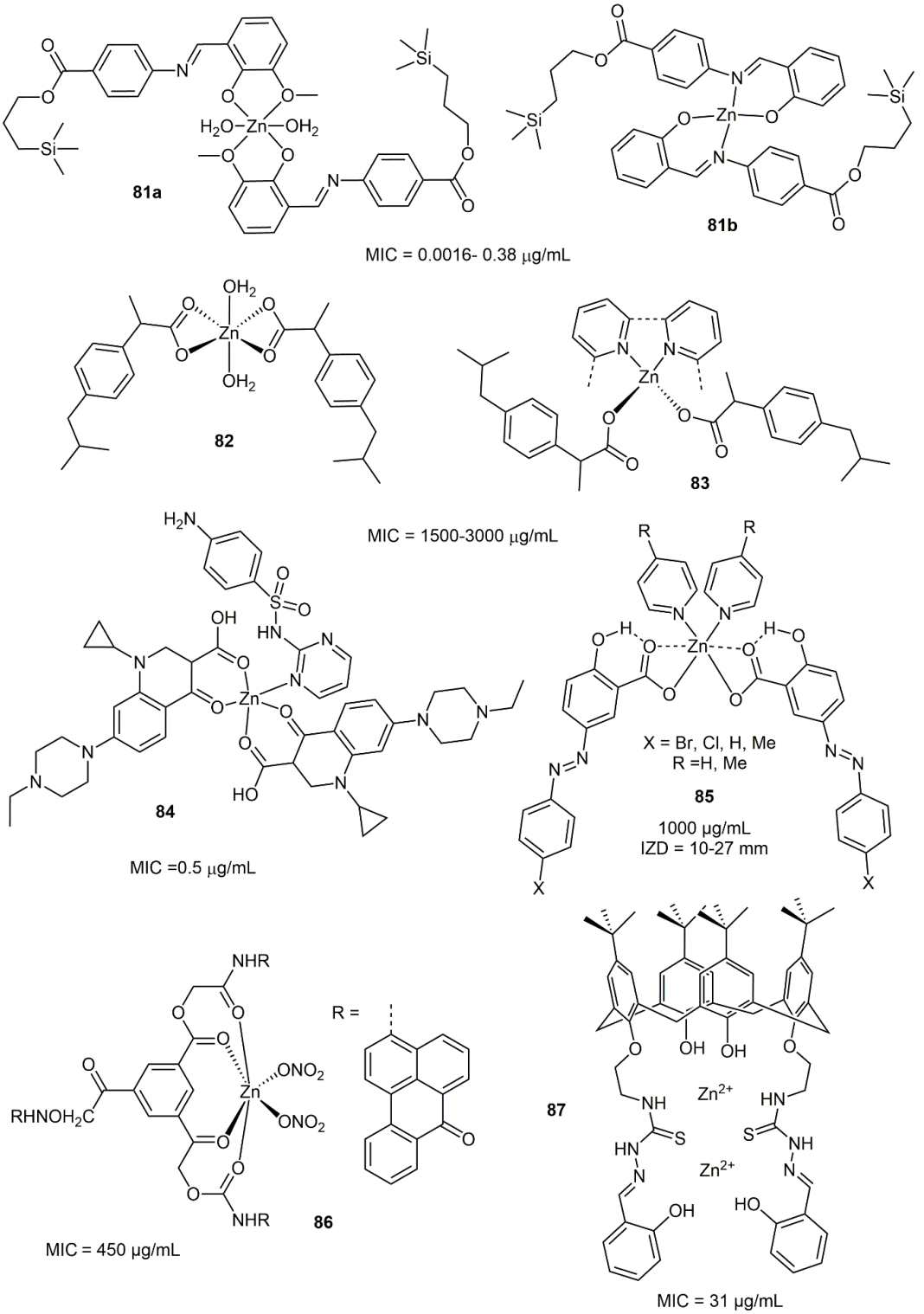

Figure 15. Structural formula of selected antimicrobial zinc(II) complexes.

In all complexes, enrofloxacin acted as a bidentate ligand via the pyridinone and carboxylate oxygens. Free ligands and complexes showed good antibacterial activity against *E. Coli*, *S. Aureus* and *E. Faecalis* with MICs lower than 0.5 mg/L. A series of zinc(II) compounds of aryl-substituted diazosalicylato- and pyridine ligands, was recently described by Basu Baul et al. (**85**, Figure 15) and tested along with copper and cadmium analogs against *B. subtilis*, *S. aureus* and *K. pneumonia* and *C. albicans* [187]. The zinc(II) complexes showed comparable activity to the standard chloramphenicol and fluconazole antimicrobial drugs. In 2019, Stataneva et al. described a new bioactive zinc(II) complex with a fluorescent symmetrical benzanthrone tripod for applications in antibacterial textiles (**86**, Figure 15) [188]. Tested against different pathogens, the complex showed the highest activity against *B. cereus* with a MIC of 450 µg/mL. Recently, Noruzi et al. reported the biological activities of metal complexes of a multidentate calix[4]arene ligand doubly functionalized by 2-hydroxybenzeledene-thiosemicarbazone (**87**, Figure 15) [189]. Both the calix[4]arene ligand and its zinc(II) complex showed activity against *B. subtilis*, *E. coli* and *P. aeruginosa* with MICs of 31 µg/mL.

8.2. Cadmium and Mercury Complexes

Several studies have described the antimicrobial properties of cadmium and mercury complexes since 2015. Despite the harmful nature of the metal ions and their complexes, they can still be remarkably useful for antimicrobial applications and they should not be neglected. However, given the inherent high toxicity associated with the metal ions, we decided to select only studies of complexes showing MICs in the low µg/mL/µM range and (where possible) with activities comparable to tested standard drugs. These stringent requirements considerably reduced the number of studies that we could consider here. Montazerozohori et al. have reported cadmium(II) and mercury(II) complexes of the bidentate Schiff base ligand 4-(3-(2-(4-(dimethyl aminophenyl alylidene aminopropylimino)prop-1-ethyl)-*N*,*N*-dimethyl benzene (**88**, Figure 16) and tested the molecules against two Gram-positive (*B. substilis* and *S. aureus*), and two Gram-negative (*P. aeruginosa* and *E. coli*) bacterial strains [190]. Mercury complexes with X = I and SCN showed minimum bactericidal concentration (MBC) of 3.7 and 7.5 µg/mL, respectively, against *S. aureus* and *P. aeruginosa* (SCN complex only). The cadmium complexes were less toxic, with the most active species (X = SCN) showing a MIC of 25 µg/mL against *P. aeruginosa*. In 2016, Agertt et al. evaluated sulfonamide metal complexes of Au, Ag, Cd, Cu and Hg for their antimycobacterial activities against *M. abscessus*, *M. fortuitum* and *M. massiliense* [191]. Cadmium and mercury complexes showed MICs of 4.9 µg/mL against *M. fortuitum* and *M. massiliense* and of 19.5 and 9.8 µg/mL, respectively, against *M. abscessus*. It should be noted that the study did not report a full characterization of cadmium(II) and mercury(II) complexes and their structures are unknown. In a study published in 2019, Matiadis et al. investigated the antimicrobial properties of cadmium(II) metal complexes of the *N*-acetyl-3-acetyl-5-benzylidenetetramic acid (**89**, Figure 16) [192]. The in vitro tests against five key "ESKAPE" pathogens (*E. coli*, *MRSA*, *K. pneumoniae*, *A. baumannii* and *P. aeruginosa*) and two fungi (*C. neoformans* and *C. albicans*) revealed that **89** was active only against *C. neoformans* (MIC = 8 µg/mL).

In 2017 and 2018, Mandal et al. reported the synthesis, characterization and antimicrobial activities of cadmium(II) and mercury(II) complexes of 5-methyl pyrazole-3yl-*N*-(2′-methylthiophenyl) methyleneimine [193] and pyrazol-3-yl-*N*-(2-methoxyphenyl) methanimine [194] (**90**–**93**, Figure 16) against a panel of pathogens. In comparison to amoxicillin, cadmium(II) and mercury(II) complexes **90** and **92** showed very good antimicrobial activity against *P. vulgaris* and *S. aureus* with MICs of 35 and 25 µg/mL and 5 and 2 µg/mL, respectively (MICs of amoxicillin = 129 and 85 µg/mL, respectively). Furthermore, **92** was 8-fold more effective than amoxicillin against *E. aerogenes* (MIC of **92** = 35 µg/mL) [193]. The complex **91** was inactive while **93** showed a MIC value of 10 µg/mL against different *V. cholerae* strains, *P. aeruginosa* and *M. luteus* [194]. Lam et al. have reported a series of bis-(alkynyl)mercury(II) complexes with oligothiophene and bithiazole linking units (**94** and **95**, Figure 16) with remarkable antimicrobial activity against MRSA and *C. albicans* [195]. Complex **94** showed the strongest bactericidal activity against MRSA with MIC and MBC values 0.2 µg/mL, and fungicidal effect against *C. albicans* with MIC and MBC values 0.4 µg/mL. Finally, Weng et al.

reported cadmium(II) supramolecular Kandinsky circles (**96**, Figure 16) with high antibacterial activity against Gram-positive methicillin-resistant *S. aureus* (MRSA) [196]. The MIC values of the different supramolecular were between 0.5 and 3 μg/mL. The compounds **96a–96c** were not active against *E. coli* and showed negligible toxicity to eukaryotic cells.

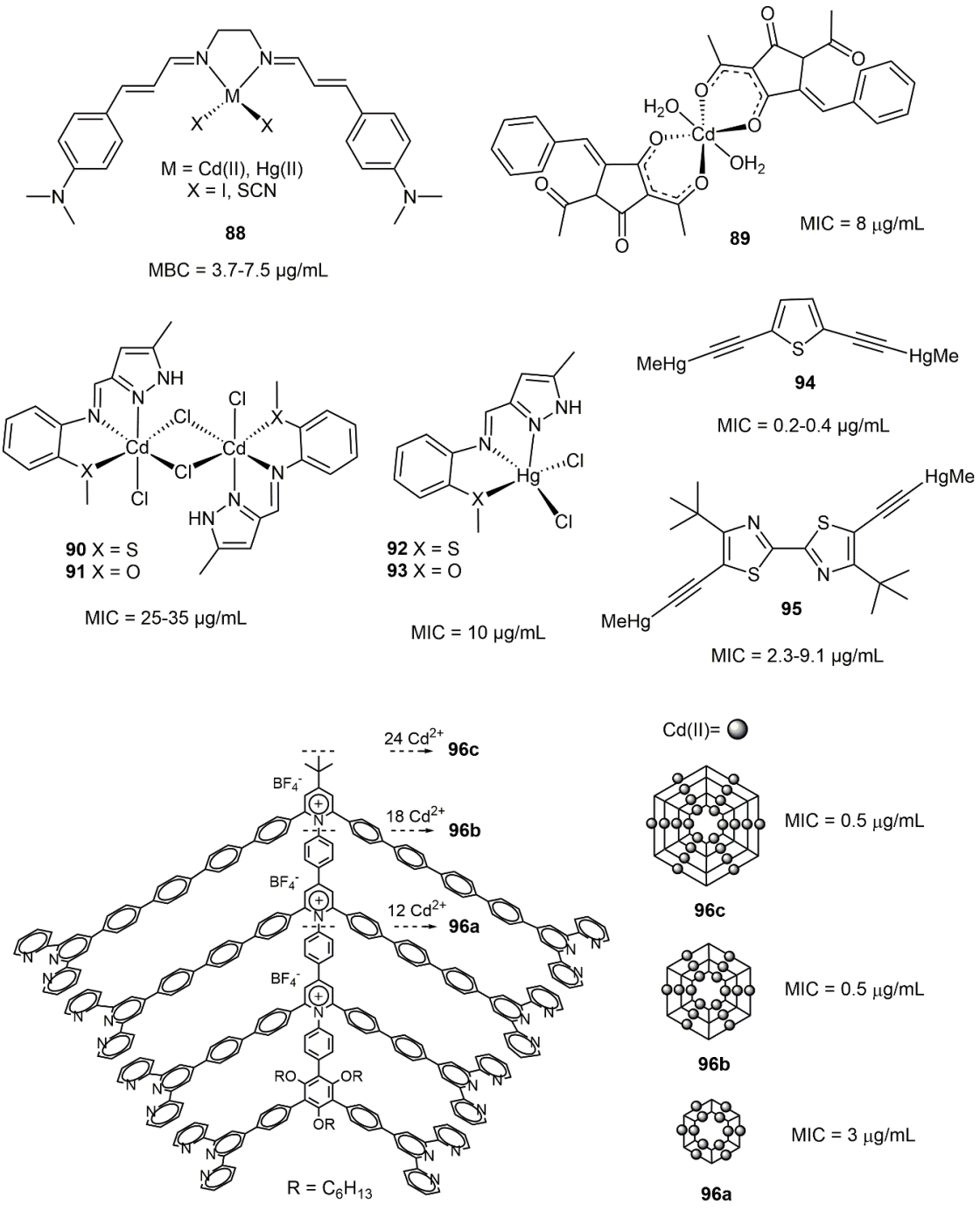

Figure 16. Structural formula of selected antimicrobial cadmium(II) and mercury(II) complexes.

9. Conclusions

In the last ten years, inorganic and organometallic transition metal medicinal chemists have begun to develop new antimicrobial agents with great promise and noteworthy success. Complexes of virtually all ions of the transition periods have been tested. In this review, we have detailed in particular recent studies on the antimicrobial activities and potential of transition metal complexes

of groups 6–12. Several species show remarkable prospective as candidates for the development of new classes of highly active antimicrobial agents. The majority of compounds still need validation in vivo but the unique properties of the complexes offer the possibility of fine-tuning in the future their properties, reactivity and toxicological profiles. Metal complexes operate via specific modes of actions unknown to carbon-based drugs and yet unexperienced by infectious pathogens. This will likely translate into long-term new strategies in this urgent global fight.

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