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REVIEW

REVISITING THERAPEUTIC SULFONAMIDES IN THE ATTEMPT TO IMPROVE THE ANTIMICROBIAL PROPERTIES THROUGH METAL-ION COORDINATION

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Abstract

The serious health issues raised by microbial resistance to first-line and last-resort antibiotics have triggered the search for efficient strategies to prevent and treat infections. Metal coordination of structures with antibacterial properties represents a promising approach in improving and refining the biological activity of both antibiotics and metal ions as it provides the opportunity to design compounds with unique and tunable features. Sulfonamides in particular are an interesting choice since they combine the structural characteristics required for both antibacterial activity and metal coordination. The present paper reviews the reports on the antimicrobial properties of complexes of metal ions coordinating sulfonamides widely used in the therapy of infections over the past decades.

Rezumat

Identificarea unor soluţii fezabile care să rezolve problema rezistenţei la antibiotice rămâne o provocare continuă pentru cercetători, determinând de-a lungul timpului dezvoltarea unor strategii eficiente de prevenţie şi tratare a infecţiilor bacteriene. Obţinerea unor compuşi prin coordinarea ionilor metalici cu liganzi ce prezintă activitate antibacteriană consacrată reprezintă o abordare promiţătoare privind proiectarea de noi compuşi mai eficienţi din punct de vedere al acţiunii antimicrobiene. În acest sens, sulfonamidele reprezintă o alegere interesantă deoarece combină caracteristicile structurale necesare atât pentru activitatea antibacteriană cât şi pentru funcţionarea lor ca liganzi în chimia coordinativă. Lucrarea de faţă aduce informaţii actuale privind proprietăţile antimicrobiene ale complecşilor metalici ai unor sulfonamide utilizate pe scară largă în ultimele decenii în tratarea infecţiilor bacteriene.

Keywords: sulfonamides, metal complexes, antibacterial activity

Introduction

The discovery of antimicrobial compounds is a turning point in modern medicine. The introduction in therapy in the 1930s of the first sulfonamide (prontosil, a prodrug sulfanilamide), followed shortly by the introduction of penicillin, resulted in a drastic decrease of the morbidity and mortality caused by bacterial infections. Currently however, the misuse and overuse of antibiotics, the use of invasive medical procedures and extensive surgery, and the increase of immune-compromised patients are listed among the main causes of microbial resistance to first-line and last-resort antibiotics [26]. The 2018 World Health Organization's report on antibiotic resistance reveals high levels of resistance to a number of serious bacterial infections caused by *Escherichia coli* (*E. coli*), *Klebsiella pneumoniae* (*K. pneumoniae*), *Staphylococcus aureus* (*S. aureus*), *Streptococcus pneumoniae* (*S. pneumoniae*), *Salmonella spp*. and *Mycobacterium tuberculosis* (*M. tuberculosis*). Moreover, biofilm production characteristic for pathogens such as *S. aureus* and *Pseudomonas aeruginosa* (*P. aeruginosa*) plays a crucial role in the virulence of the bacteria and in the persistence of chronic infections. Within this ecosystem with particular features such as primitive homeostasis, a primitive circulatory system, and metabolic cooperativity [18], bacteria survive exposure to concentrations of antibiotics up to 1000-fold greater than those lethal for free bacterial cells [48]. It is wide world accepted that the ability to treat infections relies nowadays on efficient strategies to prevent infections, to limit drug and multi drug resistance and to develop new effective antibiotics. One valid strategy could be the metal ion coordination of structures with known and well characterized anti-bacterial activity. The present paper aims to support a proof of concept, which is the possibility to improve and refine the antibacterial activity of therapeutical sulfonamides upon coordination with diverse metal ions.

Historically, the first agents with antibacterial properties were metal compounds; their wide use dates back hundreds of years and gradually decreased, only when organic antibiotics came into play in the 20th century. The renewed interest in metal-based antimicrobials reflects the hopes that less microbial resistance will develop [31, 53].

Domagk's report (1932) on the protective effects of prontosil against murine streptococcal infections triggered the rapid development of numerous sulfonamides widely used in therapy: sulfapyrine against pneumonia, sulfacetamide against urinary infections, succinoylsulfathiazole against gastrointestinal infections, sulfathiazole to treat wound infections [41, 42]. Nowadays, sulfonamides are seldom used as monotherapy because of their limited spectrum and fast developing drug-resistance.

The bacteriostatic properties of sulfonamides derive from their structural analogy and their competitive interference with the para-aminobenzoic acid in the synthesis of tetrahydrofolic acid (an essential growth factor for bacteria) by the dihydropteroate synthase [41, 49, 50]. The ionic species formed as a result of the deprotonation of the sulfonamide moiety is, in fact, the bioactive compound, but its limited lipid solubility prevents efficient penetration across the bacterial membrane. It has been suggested that it is the unionized form of the sulfonamide that actually penetrates the cellular membrane and that ionization occurs within the bacterial cell [24, 27].

Metal-ion coordination

Coordination to metal ions has been proven to be a valid and promising strategy to improve and enhance the antimicrobial activity of both organic drugs and metal ions. Coordination compounds take advantage of the complementarities between the properties of the metal ion and of the ligand. They provide the opportunity to exploit the unique properties of metal centres, such as: multiple oxidation states, redox properties, a wide variety of coordination numbers, symmetries and structural patterns, which offer highly adaptable platforms for drug design [20, 58]; at the same time, the ligands may be pharmacologically active, or they may play a key role in transport, target recognition or interaction. Moreover, as it is the case of many metallodrugs within biological media, the complex may undergo ligand substitution and/or redox reactions with beneficial effects on the antibacterial activity [47].

Thus, aiming to develop complexes with antimicrobial properties researchers have revisited old antibiotic molecules or synthesized analogues, derivatives or completely new molecules that can coordinate metal ions [9, 42, 54, 59]. Some authors argue however that the relationship between chelation and bacterial toxicity is very complex and, as it is expected to be a function of steric, electronic and pharmacokinetic factors, the antibacterial activity may actually be hindered upon metal coordination [3, 32, 46]. It is the case for instance of the reported Cu(II) ternary complexes with sulfathiazole and cephalosporin ligands [3], or the case of the Ru(III) and Pt(II) complexes of sulfamethazine [32].

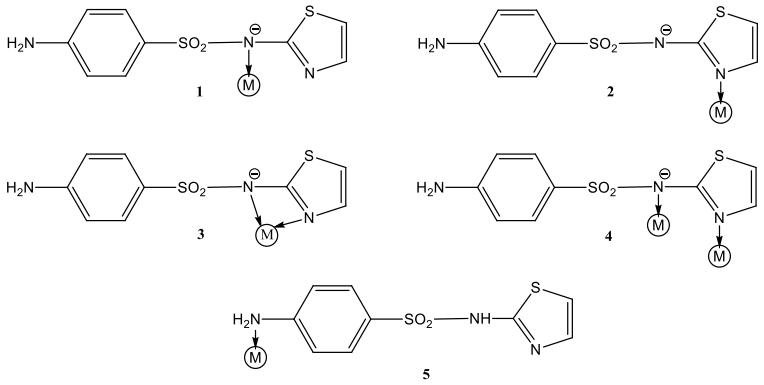


Figure 1.
Coordination modes of sulfonamides exemplified for sulfathiazole

In this context, sulfonamides have attracted increasing attention since they combine the features required for both antibacterial activity and metal ion coordination. It has been observed that sulfonamides can coordinate metal ions in several different ways [4, 6, 9, 52], in most cases as a consequence of the deprotonation of the N-sulfonamidic atom. The most frequent coordination modes are exemplified for sulfathiazole, 4-amino-*N*-(2-thiazolyl)benzenesulfonamide, and shown in Figure 1. Sulfonamides can act as monodentate ligands, coordinating the metal ion through the N-sulfonamidic atom or a donor atom belonging to the N-sulfonamidic substituent [28, 29] (coordination modes 1 and 2). More frequently, sulfonamides are reported as polydentate ligands, involving the N-sulfonamidic and its heterocyclic substituent (mode 3) [12,

40], but they can also appear as bridging two metal ions (mode 4) [12, 15]. The amino group in the para position (mode 5) may be also involved in metal-ion coordination [11, 13, 14]. Since the amino group is essential for the antimicrobial activity of the sulfonamide, it is however desired to remain non-coordinated.

Sulfonamide-containing metal complexes with antibacterial properties

For numerous reported metal complexes, the antibacterial activity is higher than that of the free parent sulfonamide but there are scarce data regarding mechanistic studies, or the detailed structure of the complexes that could lead to pertinent conclusions regarding a structure-activity relationship. The following section focuses on those studies that conclude on mechanistic aspects such as identification of the bioactive entity, evaluation of lipophilicity or synergistic action of metal ions and free ligands and does not aim to be an exhausting inventory of metal-based antimicrobials. The table lists those complexes with antibacterial activity superior to that of the free parent compound and/or to the activity of a relevant standard.
Early studies brought evidence of the higher antimicrobial activity of the coordinated species with respect to the free sulfonamides for complexes such as Ag(I)-sulfadiazine, Cu(II)-sulfacetamide or Cu(II)-sulfamethoxazole complex [5, 30]. In some cases the biological activity of the sulfonamide based metal complexes differs completely from that of the free ligand. It is the case of the non-steroidal anti-inflammatory drug nimesulid, a structure bearing a sulfonamide moiety without antibacterial properties. Cu(II) or Ag(I) complexes of nimesulid (i.e. $[Cu(NMS)_2(bipy)]$ and [Ag(NMS)], respectively) were reported to exert antibacterial activity against both Gram-positive (*S. aureus*) and Gram-negative (*E. coli*, *P. aeruginosa*) bacteria. For [Ag(NMS)] the antibacterial activity was similar to that of $AgNO_3$ and gentamicin against the tested strains [7, 19].
The Ag(I)-sulfadiazine complex (Silvazine™, Flamazine™, Acticoat™) is probably the best-known example of the success of the metal-ion coordination strategy (as depicted in Figure 2). This complex has been proven to be an effective topical antimicrobial agent employed in burn therapy, effective on Gram-positive and Gram-negative bacteria including *P. aeruginosa*, one of the bacteria most often incriminated in recurrent wound infections. It is worth mentioning however that the antibacterial activity of the majority of the Ag(I) complexes with sulfonamides, including Ag(I)-sulfadiazine, appears to be actually linked to the presence of the Ag(I) ions that are slowly released from the complex, whereas the ligand's role is mainly that of a carrier. The ligand's presence also prevents Ag(I) precipitation with chlorides and the subsequent hypochloraemia in burns [23]. The fast release of Ag(I) ions from the inorganic salt limits the use of $AgNO_3$ in therapy, since Ag(I) concentrations higher than 1% exhibit tisular toxicity [17, 23, 25].

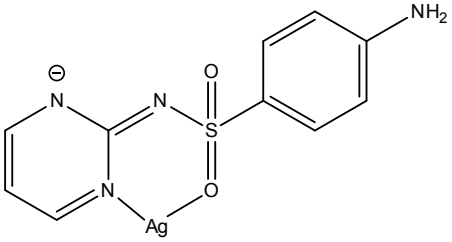


Figure 2.
Structure of Ag(I)-sulfadiazine complex

Several other Ag(I) complexes with sulfonamides (sulfamethizole, sulfisoxazole, sulfadimethoxine, sulfamethoxydiazine, sulfachloropyridazine) exhibit minimum inhibitory concentrations (MIC) similar or higher than those observed for $AgNO_3$, and they have interesting features that allow for the slow release of the bioactive Ag(I) ions [22, 37, 38, 57]. On the other hand, the results reported by Velluti *et al*. for the Ag(I) complexes of sulfamoxole showed that the antibacterial activity of the coordinated compounds against *P. aeruginosa* is not due to the synergism of the free components, but rather to new active species resulting from the coordination process. Moreover, the authors suggest that despite the low solubility and suboptimal lipophilicity, the observed microbiological activity on Gram-negative and Gram-positive bacteria and fungi (Table I) relies on the nanometric size of the complexes [55].
Several studies concluded that the chelation process translates into an increase of the hydrophobicity and lipophilicity and therefore favours the penetration of the metal complexes through the lipid layer of the cell membrane [2, 16, 30]. Upon chelation, the ligand's polarity will be reduced due to the overlap of the ligands' orbitals and the metal-ligand charge transfer. Furthermore, the chelation process increases the delocalization of the π electrons over the whole chelate ring and this translates into an increase in the lipophilicity of the metal complex [45]. The comparative study reported by Kremer *et al*. [30] on the lipophilicity and antimicrobial activity of a series of Cu(II) complexes with sulfisoxazole, sulfamethoxazole, sulfamethizole, sulfadiazine, sulfamerazine, sulfapyridine, sulfachloropyridazine, sulfamethoxypyridazine concluded that lipophilicity generally increased upon Cu(II) coordination. All complexes were active against *S. aureus* and *E. coli* but, interestingly, the complexes with sulfonamides bearing five-membered heterocycles as N-substituents (i.e. isoxazole, diazomethizole) were more efficient than the free parent compounds, whereas the complexes with six-membered rings substituents (i.e. heteropyrimidine, pyridine, pyridazine) were less efficient

than the uncoordinated antibiotic. In the group of ligands with a five-membered heterocycle substituent, all sulfonamides coordinate through the heterocyclic N atom, whereas in case of the ligands with a six-membered heterocycle the coordination is suggested to occur through a different donor moiety (e.g. the phenylamino group) which is required to remain free for the antimicrobial activity [56]. Moreover, coordination through the heterocyclic N atom decreases the electron density on the sulfonamide N atom favouring the bioactive anionic form of the sulfonamide [30]. Another study on a Ni(II) complex with sulfisoxazole supported the results obtained in case of the Cu(II) analogue and pointed out the role of the metal ion for the antibacterial activity. $[Ni(sulfisoxazole)_2(H_2O)_4]\cdot 2H_2O$ and the free sulfisoxazole presented equal MIC, while the isostructural $[Cu(sulfisoxazole)_2(H_2O)_4]\cdot 2H_2O$ was four-fold more active than the free sulfonamide. It was suggested that coordination to Cu(II) favours the penetration into the cell where the complex releases the anionic active form of the sulfonamide presumably due to the Cu(II) reduction [44]. In case of the Ni(II) complex either the transport of the complex through the membrane or the liberation of the sulfonamide species inside the cell is not achieved [36, 51].

Boughougal *et al*. [10] recently reported a Zn(II) ternary mononuclear complex that associates in two antibiotics the coordination environment, enrofloxacin and sulfadiazine, $[Zn(LH)(Erx)(ErxH)]ClO_4$ (Table I). The antibacterial efficiency of the complex was tested against *E. coli*, *S. aureus* and *E. faecalis* and compared to that of the Zn(II), Co(II), Cu(II) and Ni(II) binary complexes of enrofloxacin or sulfadiazine. The results are noteworthy since the antibacterial efficiency was found to be between 2 and 20 times higher than the efficiency of both the free antibiotics and of the metal complexes bearing only one of the two antibiotics as ligands. Although the mechanism and the role of the metal centre are not clear, it appears that the synergetic effect of entities within the complex (two different antibiotics and the metal centre with antiseptic properties) drastically increases the antibacterial activity of the ternary complex. Moreover, it was suggested that the interaction and transfer through the lipoidal membrane are favoured by the positive charge of the cationic complex. In contrast, the ternary Cu(II) complexes associating sulfathiazole and a series of cephalosporins (cefazolin, cefalotin, cefotaxime and ceftriaxone) reported by Anacona *et al*. did not prove to be characterized by the same synergetic effect; their antibacterial activity was comparable to that of the free cephalosporin [3].

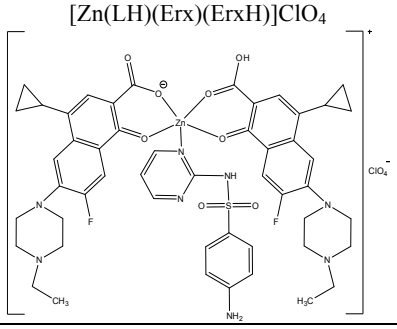
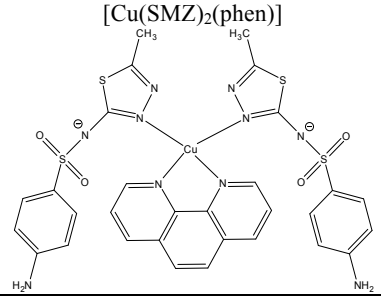
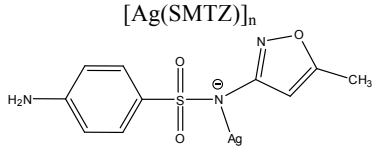
The antibacterial activity of ternary complexes of Ag(I) and Au(I) with sulfonamides and phosphine derivatives, respectively (Table I), was reported with interesting results [1, 2, 33-35]. The study of the Au(I) monomer complex and Ag(I) polymeric complex with sulfamethoxazole reported by Marques *et al.* concluded that these complexes exhibited significant antibacterial properties against *E. coli*, *S. aureus* and *P. aeruginosa*. $[Ph_3PAu(SMTZ)]$ was 256 times more active than a 5:1 mixture of sulfamethoxazole and trimethoprim against *S. aureus,* and 64 times more active than the free sulfamethoxazole against *E. coli.* $[Ag(SMTZ)]_n$ was 32 times more active than the uncoordinated sulfonamide on *P. aeruginosa* [33]. The Au(I) complex of sulfathiazole and triphenylphosphine and its analogue bearing sulfamethoxazole and triphenylphosphine as ligands showed *in vitro* activity against *M. tuberculosis* and their effects were potentiated by the combination with trimethoprim (Table I) [2]. More recently, the same research group extended the study and tested the Ag(I) and Au(I) binary and ternary complexes against rapidly growing mycobacteria, *M. fortuitum*, *M. abscessus*, *M. massiliense* (Table I). The results showed that several complexes of sulfadiazine and sulfamethoxazole (Table I) were significantly more active than the free sulfamethoxazole, one of the antimicrobial agents of choice for the treatment of mycobacteriosis. The metal complexes showed bactericidal activity and synergistic effect when combined to trimethoprim against *M. abscessus* and, in addition, acted faster than the free sulfamethoxazole [1]. The study reported by Mizdal *et al*. confirmed that sulfadiazine Au-PPh_3, sulfamethoxazole Au-PPh_3, sulfadiazine Ph_2P-Au-Au-PPh_2, and sulfamethoxazole Ph_2P-Au-Au-PPh_2, were more active against *S. aureus* and *P. aeruginosa* that the free sulfamethoxazole, and, in addition, induced a reduction in the metabolic activity and biofilm formation for the tested strains [34, 35].

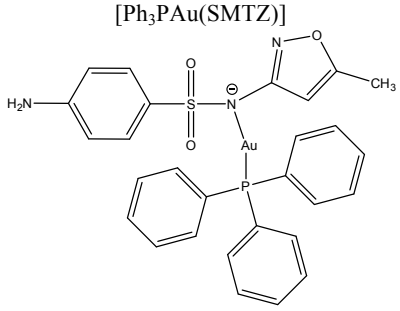
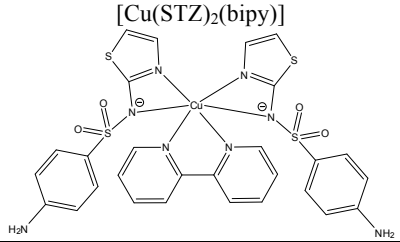
The Cu(II) complex of sulfathiazole and diethylenetriamine, $[Cu(stz)_2(dien)]\cdot 3H_2O$ was found to exhibit a very effective antimicrobial activity, especially against Gram-negative bacteria and fungi (MIC values in the range 1 - 4 μg/mL); for instance, the antimicrobial activity of the complex against *P. aeruginosa*, *E. coli* and *A. niger* increased at least 256-fold in comparison with the activity of the free sulfathiazole [39], as presented in Table I.

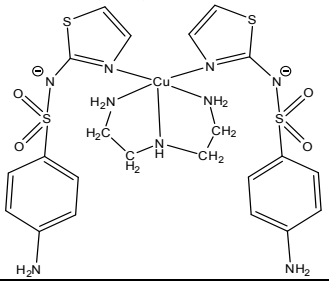
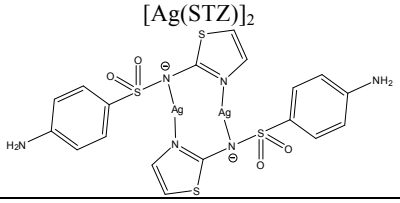
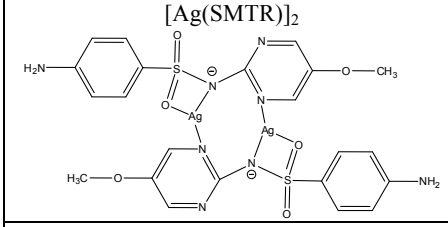
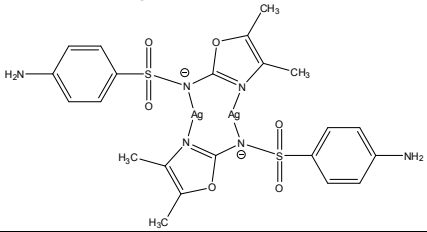
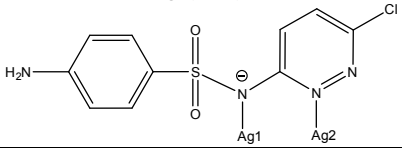
The results obtained by A. Di Santo *et al*. on a Mn(II) complex of sulfamethoxazole, $[Mn(H_2O)_6]_{0.5}[Mn(SMX)_3]$, suggest an effect of the complex on the mechanism involved in biofilm formation, i.e. quorum sensing, more than antibiotic properties. It was suggested that the anti-biofilm properties of the complex could be explained in terms of the positive charge of Mn(II) aquacation that might increase its sorption to typically negatively charged biofilms [21].

Table I

Sulfonamide-containing metal complexes with antibacterial properties

Compound	MIC for complex (MIC for free sulfonamide or MIC for chosen standard)	Remarks	Reference
Sulfadiazine complexes			
$[Zn(LH)(Erx)(ErxH)]ClO_4$ 	*E. coli*: < 0.5 mg/L (128 mg/L), *S. aureus*: < 0.5 mg/L (8 mg/L), *E. faecalis*: < 0.5 mg/L (> 256 mg/L)	Complex more active than the Zn(II), Co(II), Ni(II) or Cu(II) binary complexes with Erx or sulfadiazine.	[10]
Sulfadiazine Au-PPh_3 *Note: detailed structure not available*	*M. fortuitum*: 19.53 μg/mL, MRSA: 2 μg/mL	Synergism when associated with trimethoprim against *M. abscessus*. Antibiofilm properties against MRSA. No data available for free sulfadiazine; complex more active than the reference sulfamethoxazole - *M. fortuitum*: 32 mg/L, MRSA: 256 mg/L	[1, 34]
Sulfadiazine Ph_2P-Au-Au-PPh_2 *Note: detailed structure not available*	*M. fortuitum*: 19.53 μg/mL, *M. massiliense*: 9.76 μg/mL, MRSA: 8 μg/mL	No data available for free sulfadiazine; complex more active than the reference sulfamethoxazole - *M. fortuitum*: 32 mg/L, *M. massiliense*: 64 mg/L, MRSA: 256 mg/L. Synergism when associated with trimethoprim against *M. abscessus;* Anti-biofilm properties against MRSA.	[1, 34]
Sulfamethizole complexes			
$[Cu(SMZ)_2(phen)]$ 	*S. aureus*: 3.20 mmol/L (9.25 mmol/L), *E. coli*: 3.20 mmol/L (9.25 mmol/L), *P. aeruginosa*: 1.60 mmol/L (9.25 mmol/L)		[57]
[Ag(SMZ)] *Note: detailed structure not available*	*S. aureus*: 3.31 mmol/L, *E. coli*: 0.83 mmol/L, *P. aeruginosa*: 0.41 mmol/L	[Ag(SMZ)] is less active than $AgNO_3$. The free sulfonamide does not present inhibitory activity under the tested concentrations and conditions.	[57]
Sulfamethoxazole complexes			
$[Ag(SMTZ)]_n$ 	*E. coli*: 64 μg/mL (512 μg/mL), *S. aureus*: 64 μg/mL (> 512 μg/mL), *P. aeruginosa*: 16 μg/mL (512 μg/mL),		[33]
	M. smegmatis: 0.305 μg/mL	No data available for free sulfamethoxazole; complex more active than the reference trimethoprim - *M. smegmatis:* 4.88 μg/mL	[2]
	M. massiliense: 9.76 μg/mL (64 μg/mL)	Synergism when associated with trimethoprim against *M. abscessus.*	[1]

Compound	MIC for complex (MIC for free sulfonamide or MIC for chosen standard)	Remarks	Reference
[Ph_3PAu(SMTZ)] 	*E. coli*: 8 µg/mL (512 µg/mL), *S. aureus*: 2 µg/mL (> 512 µg/mL), *P. aeruginosa*: 256 µg/mL (512 µg/mL),		[33]
	MRSA: 2 µg/mL (256 µg/mL)	Anti-biofilm properties against MRSA.	[34]
	M. massiliense: 19.53 µg/mL (64 µg/mL).		[1]
	M. smegmatis: 2.44 µg/mL	No data available for free sulfamethoxazole; complex more active than the reference trimethoprim - *M. smegmatis*: 4.88 µg/mL. Additive effect when associated with trimethoprim against *M. smegmatis* and synergy when associated with trimethoprim against *M. abscessus*.	[2]
Sulfamethoxazole Ph_2P-Au-Au-PPh_2 *Note: detailed structure not available*	*M. massiliense*: 19.53 µg/mL (64 µg/mL), MRSA: 8 µg/mL (256 µg/mL)	Synergy when associated with trimethoprim against *M. abscessus;* Anti-biofilm properties against MRSA.	[1, 34]
Sulfamethoxazole Au *Note: detailed structure not available*	*M. fortuitum*: 19.53 µg/mL (32 µg/mL), *M. abscessus*: 4.88 µg/mL (8 µg/mL), *M. massiliense*: 9.76 µg/mL (64 µg/mL)	Synergism when associated with trimethoprim against *M. abscessus.*	[1]
[$Cu(SMTZ)_2(H_2O)_4]\cdot 3H_2O$ *Note: detailed structure not available*	*S. aureus*: 4 µg/mL (16 µg/mL), *E. coli*: 4 µg/mL (128 µg/mL)		[30]
Sulfamethoxazole Cu *Note: detailed structure not available*	*M. fortuitum*: 9.76 µg/mL (32 µg/mL), *M. massiliense*: 19.53 µg/mL (64 µg/mL)	Synergy when associated with trimethoprim against *M. abscessus.*	[1]
Sulfamethoxazole Cd *Note: detailed structure not available*	*M. fortuitum*: 19.53 µg/mL (32 µg/mL), *M. abscessus*: 4.88 µg/mL (8 µg/mL), *M. massiliense:* 4.88 µg/mL (64 µg/mL)	Synergy when associated with trimethoprim against *M. abscessus.*	[1]
Sulfamethoxazole Hg *Note: detailed structure not available*	*M. fortuitum:* 9.76 µg/mL (32 µg/mL), *M. abscessus*: 4.88 µg/mL (8 µg/mL), *M. massiliense*: 4.88 µg/mL (64 µg/mL)	Synergy when associated with trimethoprim against *M. abscessus.*	[1]
Sulfathiazole complexes			
[Au(STZ)(PPh_3)] *Note: detailed structure not available*	*M. smegmatis*: 4.88 µg/mL (4.88 µg/mL)	Synergism when associated with trimethoprim against *M. smegmatis.*	[2]
[$Cu(STZ)_2$(bipy)] 	*E. coli*: 0.84 mmol/L, *P. aeruginosa*: 0.10 mmol/L	Complex inactive against Gram positive bacteria. The free sulfonamide does not present inhibitory activity under the tested concentrations and conditions.	[7]

Compound	MIC for complex (MIC for free sulfonamide or MIC for chosen standard)	Remarks	Reference
$[Cu(STZ)_2dien]\cdot 3H_2O$ 	*B. subtilis*: 2 µg/mL (8 µg/mL), *S. aureus*: 2 µg/mL (16 µg/mL), *P. aeruginosa*: 1 µg/mL (256 µg/mL), *E. coli*: 2 µg/mL (> 512 µg/mL), *E. faecalis*: 4 µg/mL (> 512 µg/mL)	Complex presents antifungal activity - *C. albicans*: 4 µg/mL (> 512 µg/mL), *A. niger*: 2 µg/mL (> 512 µg/mL).	[39]
$[Ag(STZ)]_2$ 	S. *aureus*: 6.90 mmol/L, *P. aeruginosa*: 3.45 mmol/L, *S. enterica*: 3.45 mmol/L	The free sulfonamide does not present inhibitory activity under the tested concentrations and conditions.	[8]
$[Co(STZ)_2OH(H_2O)_3]$ *Note: detailed structure not available*	*P. aeruginosa*: 30 µg/mL (> 30 µg/mL)	Complex less active than the free sulfonamide against *E. coli*; Complex has antifungal activity - *A. flavus*: *100* µg/mL (> 250 µg/mL).	[43]
Sulfamethoxydiazine (sulfameter)			
$[Ag(SMTR)]_2$ 	*S. aureus*: 320 µmol/L, *E. coli*: 40.9 µmol/L, *P. aeruginosa*: 40.9 µmol/L	The free sulfonamide does not present inhibitory activity under the tested concentrations and conditions. Complex less active than $AgNO_3$.	[38]
Sulfamoxole complexes			
$[Ag_2(SMX)_2]\cdot DMSO$ 	*S. aureus*: 7.8 µg/mL (> 49 µg/mL), *E. coli*: < 4.0 µg/mL (> 49 µg/mL), *P. aeruginosa*: 7.8 µg/mL (> 49 µg/mL)		[55]
$[Ag_4(SCN)_3(SMX)]\cdot H_2O$ *Note: detailed structure not available*	*S. aureus*: 7.9 µg/mL (> 49 µg/mL), *E. coli*: 7.8 µg/mL (> 49 µg/mL), *P. aeruginosa*: 7.8 µg/mL (> 49 µg/mL)	Complex less active than $AgNO_3$ against *S. aureus*, but more active than $AgNO_3$ against *E. coli* and *P. aeruginosa*. No synergism between components (i.e. Ag(I) and SMX).	[55]
Sulfachloropyridazine complexes			
$[Ag_2(SCP)]_n$ 	*E. coli*: 10 µg/mL (> 23.5 µg/mL), *P. aeruginosa:* 5.20 µg/mL (> 8.3 µg/mL)	Complex less active than $AgNO_3$ against *S. aureus* and *E. coli*, but more active than $AgNO_3$ against *P. aeruginosa*. Complex more active than the reference antibiotic cefatoxime against *P. aeruginosa*.	[37]

*MIC - minimum inhibitory concentration

*All chemical names and abbreviations for complexes and units for MIC are in accordance with the corresponding references

LH – sulfadiazine; Erx – enrofloxacin; PPh_3 – triphenylphosphine; MRSA – methicillin resistant *S. aureus*; PPh_2 – diphenylphosphine; SMZ – sulfamethizole; phen – 1,10-phenantroline; SMTZ – sulfamethoxazole; STZ – sulfathiazole; bipy – 2,2'-bipyridine; dien – diethylenetriamine; SMTR – sulfamethoxydiazine (sulfameter); SMX – sulfamoxole; DMSO – dimethyl sulfoxide; SCN^- – thiocyanate; SCP – sulfachloropyridazine

Conclusions

Metal-ion coordination is a promising tool in the development of diverse new antimicrobial agents. Numerous reported metal complexes of sulfonamides exhibit an antibacterial activity higher than that of the free parent sulfonamide which turns them into good candidates for future pharmaceutical research. The antibacterial activity of distinct reported metal complexes of therapeutic sulfonamides is presumably due to one of the following: (i) *the metal ion* that is slowly released from its complex with the sulfonamide, (ii) *the sulfonamide* that overcomes cell penetration problems when coordinated with a metal ion, (iii) a *synergism* of action between the sulfonamide and the metal ion, or (iv) the *new active species* resulting from the coordination process.

The data currently available in the literature concerning the metal complexes of sulfonamides with known therapeutic value represent however only the proof of concept on the improvement of the antibacterial activity upon metal ion coordination. Detailed mechanistic studies are scarce and further research is required to shed light on aspects such as identification of the bioactive entity, synergistic action of metal ions and free ligands, and a reliable structure-activity relationship. Moreover, literature lacks in well documented studies on the type of mechanism of action that results in an antibacterial effect, e.g. enzyme-like activity (nuclease or superoxide dismutase - like activity), or enzymatic inhibition (inhibition of proteases or carbonic anhydrases). Further studies are therefore required for the design of complexes characterized by selectivity of action, ability to interact with specific targets within the bacterial cell and to disrupt the biochemical pathways involved in drug-resistance, and optimal pharmacokinetic profile.

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