Silver coordination compounds: A new horizon in medicine

Coordination Chemistry Reviews ■■ (2016) ■■–■■

Contents lists available at ScienceDirect

Coordination Chemistry Reviews

journal homepage: www.elsevier.com/locate/ccr

Review

Silver coordination compounds: A new horizon in medicine

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Contents

ARTICLE INFO

Article history:
Received 11 March 2016
Accepted 30 May 2016
Available online

ABSTRACT

Silver coordination compounds with a number of different ligands (N-heterocyclic carbenes, phosphines, N-heterocycles and others) possess several properties, ranging from antibacterial, anti-inflammatory and antiseptic to antineoplastic activity. They also promise to be agents capable of overcoming drug resistance and beating antibiotic-resistant bacteria, fungi and parasites. In spite of the large volume of research undertaken in this area and the synthesis of several new silver complexes, most of them still remain in an academic research context and few have actually been approved for medical treatment of human diseases.

In this review we present an overview of this noble metal's active derivatives, properties, mode of action and potential uses with the aim of stimulating further evaluation of their potential clinical applications and therapeutic uses.

1. Introduction

Since the early days of the coordination chemistry era, around one century ago, silver complexes have been synthesized in a broad range of forms and compositions in order to study their structure, reactivity and applications in catalysis or as new materials. Nowadays a quick review of the literature reveals that the most common aim in making new silver complexes is to test them for biological activity. In fact, silver compounds, also in the form of nanoparticles [1,2], are very interesting in the field of medicine, since they combine the traditional use of this metal as a remedy for many diseases with the relative "novelty" of metallodrugs, which suddenly became popular with the introduction of cisplatin as a powerful chemotherapeutic agent about 40 years ago.

The use of silver, as silver nitrate, was reported in the Roman Pharmacopeia as early as 69 B.C. [3] and was a common practice against ophthalmia neonatorum under the name of Credé method until a few years ago [4]. Up to the discovery and invention of antibiotics, silver was one of the few drugs capable of healing infections, burns and wounds, and preventing contagious diseases. The introduction of antibiotics (around 1940) drastically diminished the use of silver in medicine, although it continued to be employed in the treatment of burns in the form of silver sulfadiazine or silver colloids, in dressing and ointments. Since the 1990s, it has regained credibility as a therapeutic agent, especially in its metallic form as colloidal suspensions. It has also become one of the most popular "alternative" and "cure-all" drugs, evidenced by its visibility on the internet. The "alternative" was mainly referred to antibiotics, which often turn out to be ineffective when resistant bacteria emerge, while silver was claimed not to induce resistance [5]. As a matter of fact, bacterial resistance to silver is very rare and often transitory [6,7]; there is a single report in the literature describing a silver-resistant strain of *Pseudomonas stutzeri* isolated in a silver mine [8]. Silver toxicity for bacterial cells has long been recognized and documented [9], while for humans

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http://dx.doi.org/10.1016/j.ccr.2016.05.015
0010-8545/

its toxicity seems to be quite low: this metal has no biological role but has been found in human tissues as a consequence of bioaccumulation over the lifespan, with an average concentration of a few micrograms per kilo of wet tissue [10–12], indicating that the body can tolerate the presence of silver in low doses without any toxic effects, probably through the formation of AgCl [13]. Thus, low toxicity is one of silver's greatest advantages over other medicinally relevant metals and the antimicrobial power of its ionic compounds can be exploited in medical practice with reasonable safety. On the other hand, silver complexes have also been shown to possess anticancer properties [14–19]: this is good news in the search for an alternative to cisplatin for the cure of tumors. In fact, although cisplatin and its other two derivatives, carboplatin and oxaliplatin, are the most widely used chemotherapeutic metallodrugs in medical practice, they are affected by several drawbacks, such as extended toxicity and resistance. A large volume of research has been undertaken in the effort of circumventing these disadvantages. Nevertheless, finding a substitute for cisplatin is a problematic matter, and to date only a few other complexes have entered clinical trials, in spite of the great number of coordination compounds, available among the wide range of metals, which have been synthesized for this purpose [2].

The antimicrobial and anticancer properties of silver complexes are owed to their peculiar mechanism(s) of action, different from that of other metal compounds. Indeed, although the pathways have not been completely elucidated, antimicrobial silver can exert its activity through different ways. In Fig. 1 a scheme representing the different mechanisms of action of silver as an antimicrobial agent is reported. Silver can kill bacteria by entering cells through impairment of essential enzymes that can bind Ag^+ ion on the surface of cell wall or impairment of cell wall integrity and permeability by removal of an electron from these cellular components. Inside the cells silver ions can disturb cell metabolism *via* interaction with cell enzymes, protein denaturation, inhibition of bacterial respiration and oxidation of ATP molecules, binding to subcellular components and formation of ROS, as well as inactivation and damage of DNA and RNA [7,20–22].

A recent paper [23] reported a phenomenon termed the "zombie effect" observed in silver-killed bacteria: they were able to induce death in viable bacteria they came into contact with. In this study, *Pseudomonas aeruginosa* was killed with silver nitrate, washed thoroughly, and inserted in a live culture of the same species, whereupon it showed high antibacterial activity. The reason was found in the dead bacteria which were essentially acting as a silver reservoir that was then dispatched to the live bacteria. Upon entering and killing the bacterial cells, silver ions are not deactivated and retain their lethal function: in part they are converted into silver nanoparticles through reduction by enzymes and other reducing compounds within the cellular medium; the rest is bound to proteins or other donor species *via* a chelation mechanism. In the presence of live bacteria, silver is able to diffuse or migrate toward the new target, according to Le-Chatelier's principle. This enhances its bioavailability with an improvement of its bactericidal or bacteriostatic activity.

In principle, such an effect could also hold true in the case of tumor cells. Actually, silver's anticancer action is based on different mechanisms compared to those of platinum derivatives, in terms of its DNA interaction, mitochondrial membrane targeting, and inhibition of thioredoxin reductase [24], leading to mitochondria initiated apoptosis, similarly to what has been observed with regard to gold complexes [25–27]. Silver interaction with nucleic acids seems to be preferentially directed toward the DNA bases rather than the phosphate groups, although the potentiality of this in terms of their lethal action is still uncertain [28].

The activity of silver complexes against bacteria and cancer cells is strictly connected with their water solubility and stability, lipophilicity, redox ability and rate of release of the silver ions. These properties are rigidly ruled by the choice of suitable ligands, and by slight modulations in their steric and electronic effects. Moreover, *in vivo* conditions can decrease the activity of promising silver drugs by sequestering the silver ions as AgCl or binding the whole complex to cell enzymes bearing sulfur donors. In these cases, it could be beneficial to enlist the help of biodegradable or biocompatible nanoparticles for transportation and delivery.

2. Ag(I) complexes with N-heterocyclic carbenes (NHC)

Carbenes are organic species containing a divalent carbon atom bearing two unshared electrons. They are rather unstable and

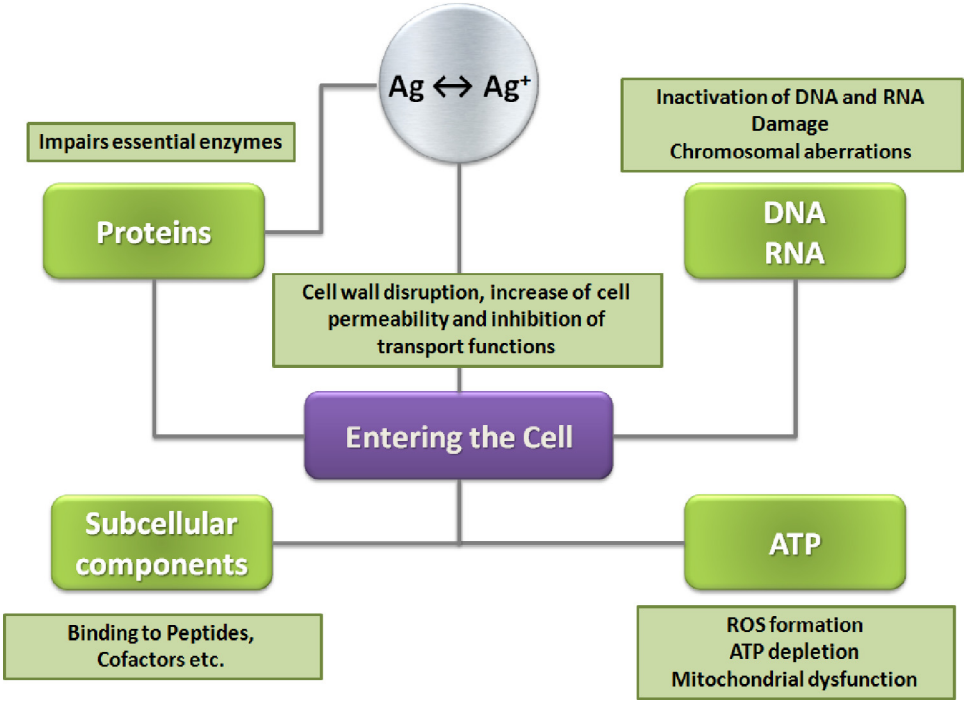

Fig. 1. Silver as an antimicrobial agent: mechanism of action.

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reactive, but can be stabilized by the presence of one or two neighboring π-donors, such as the nitrogen atom. Thus, N-heterocyclic carbenes (NHC) benefit from the donation by the p_π–p_π electrons of adjacent nitrogen(s) into the empty orbital of the carbene carbon atom. The first stable free carbene of this kind was isolated in 1991 as a crystal solid by Arduengo et al. [29], while the first NHC complexes had been prepared more than 20 years before from imidazolium salts [30,31], and "rediscovered" in 1993 with the synthesis of the first Ag(I)–NHC species [32]. Since then they have attracted an increasing interest in the field of organometallic catalysis, and lately there has been dramatic growth of attention toward their biological activity.

Three main types of NHC structures have been used as the ligands in silver complexes, and they are all imidazole-based: imidazolidin-2-ylidene, imidazole-2-ylidene and benzimidazol-2-ylidene. Naturally occurring compounds within xanthine family (i.e. theobromine, theophylline and caffeine), bearing an imidazole ring, are often employed to decrease complex toxicity.

Main types of NHC silver complexes are reported in Fig. 2.

Structural modifications are normally achieved through changes in the side chains appended to the nitrogen atoms. This accounts for a series of slight variations in both steric and electronic properties of the ligand, which in turn influence the lipophilicity, solubility and stability of the relative complexes [33]. Ag(I) complexes were prepared from corresponding ligands and silver acetate (see for instance Ref. [34] and references therein) or silver oxide [35] to yield the desired product.

In spite of the presence of an Ag–C bond, Ag–NHC compounds are easily synthesized and rather stable toward air and moisture; they are often used as synthetic intermediates to obtain carbene complexes with other transition metals which are difficult or impossible to prepare, *via* the transmetalation reaction [36]. Such a reaction can be carried out under aerobic conditions and even in the presence of moisture.

Complexes within the Ag–NHC family are the most extensively studied for their biological activity, as demonstrated by the number of reviews published in the literature [18,37–41].

Most efforts in the development of NHC silver complexes have been focused on their action as antibiotics, while gold, platinum, copper, and ruthenium carbenes are mainly screened for their anticancer activity. Nevertheless, the potential of Ag–NHCs as antitumor species is slowly emerging [42–44]. The mechanism(s) by which Ag–NHCs are effective against bacteria and cancer have not been fully elucidated, yet, but they may share the same biochemical/biological bases. In fact, most of the times the active species is the Ag^+ ion, which is able to interact with cellular (both bacterial and mitochondrial) membranes, enzymes and DNA/RNA [25–27,45–47].

The drawback of the current silver antimicrobial compounds is that they do not kill bacteria over a sustained period of time. In fact, their efficacy seems to be connected to their bioavailability and prolonged release of silver over an extended period of time to prevent reinfection. The release rate is linked to the ancillary ligands and, as NHCs are strong σ-donors, silver–NHCs can have a slow metal release rate, depending on complex degradation and/or redox processes. Under this point of view, the stability of Ag–NHCs in water medium has been increased from a couple of hours up to 17 weeks by introducing electron-withdrawing substituents such as chloride groups on the imidazole ligand [48]. Such an achievement represents a basic improvement for the efficacy of this class of complexes in preventing/counteracting bacterial infections, but also in cancer treatment [42].

The antimicrobial power of silver-based compounds is normally checked against $AgNO_3$ and/or common antibiotics as the references. Recent advances in this area include testing a broad series of mononuclear and dinuclear silver complexes with monodentate (Fig. 2, **1**) and bidentate (Fig. 2, **2**) benzimidazole-based NHCs against *Escherichia coli* and *Bacillus subtilis*, with results comparable to other silver complexes and ampicillin. The precursor benzimidazolium salts had no activity against the same strains of bacteria, even at higher concentrations compared to the relative complexes. This difference in efficacy was interpreted as being due to an increase of lipophilicity upon silver coordination [49]. The same complexes were tested for anticancer activity in HCT116 and HT29 cell lines, with the binuclear and the symmetrically substituted Ag complex recording manyfold higher activity compared with the standard.

Another Ag–NHC complex, 1,3-dibenzyl-4,5-diphenyl-imidazol-2-ylidene silver(I) acetate (SBC3) (Fig. 2, **3**), was the first used *in vivo*, on larvae of *Galleria mellonella* inoculated with *Staphylococcus aureus* or *Candida albicans* [50]. After the complex, at a concentration of 25 μg/ml, inhibited the growth of *S. aureus* by 71.2% and *C. albicans* by 86.2% *in vitro*, administration of SBC3 to inoculated larvae resulted in increased survival. The study demonstrated that the efficacy of SBC3 was not due to a raise of the insect immune response, as indicated by the lack of an increase in the density of circulating hemocytes (immune cells), suggesting a different mechanism should be sought.

Eighty-nine complexes with a broad series of NHC ligands and different metals (Au, Ag, and Cu) have been evaluated against the formation of biofilms due to pathogenic bacteria (*Listeria monocytogenes*, *P. aeruginosa*, *S. aureus* and *Staphylococcus epidermidis*, and *E. coli*) in an automated BioFilm Ring Test (conc. 1 mg/l). Complexes were both of the neutral [(NHC)MX] (M = Ag, Au, Cu) and cationic $[(NHC)_2M^+X^-]$ (M = Ag, Cu) types. Among them, the most efficient at inhibiting biofilm formation were neutral heteroleptic Ag(I) (Fig. 2, **4 a–h**) and Cu(I) compounds possessing aromatic groups on the NHC ligand, due to their higher lipophilicity [51].

A series of mono- and dinuclear silver complexes containing mono- and bis(imidazolium)-based ligands, all N-functionalized with different groups (amide, alcohol, and nitrogen containing heterocycles such as quinoline and bipyridine), were tested as antifungal (on *C. albicans* and *Candida glabrata*) and antiplasmodial (on a chloroquine-resistant strain of *Plasmodium falciparum*) agents with interesting properties, especially with regard to the dinuclear species. Unfortunately the most active complexes also manifested strong hemolytic properties on the parasite culture even at the weakest doses tested (0.5 μg/ml). For this reason, a series of changes were carried out on the functionalized arm appended to one of the imidazole nitrogens according to the principles of pharmaco-modulation, in order to increase the anti-plasmodial activity and decrease the cytotoxic effect by decreasing hemolysis. A new series of N-functionalized complexes were prepared with a lower steric hindrance on the arm, and particular attention was focused on mononuclear $Ag(NHC)_2$ species, which had a less protected environment around the metal and could result in a better delivery of the metallic cation. The new complexes had higher antimalarial activity, with a maximum efficacy recorded with dinuclear species [52].

It is clear that the modulation of steric and electronic properties in a complex is fundamental for the regulation of its biological activity. Flexibility, nature of the NHC ligand, number of Ag centers, charge, and hydrogen-bonding capabilities of Ag–NHC complexes also play a role in controlling their anticancer potential [53,54]. The biological mechanism(s) involved are slowly being unveiled. Evidence demonstrates that benzimidazole-based complexes (Fig. 2, **5 a–d**) may accumulate in the mitochondria and depolarize their membrane. As a consequence they induce apoptosis through damage of the endoplasmatic reticulum and cytosolic translocation of the apoptotic inducing factor (AIF) from the internal part of the mitochondrial membrane, that is, a caspase-independent induction of apoptosis [55]. Similarly, another recent study carried out on Ag(I) complexes containing N-heterocyclic carbenes derived from cyclophanes (Fig. 2, **6 a and b**) mainly induced caspase- and reactive oxygen species (ROS)-independent early apoptosis [56]. A series

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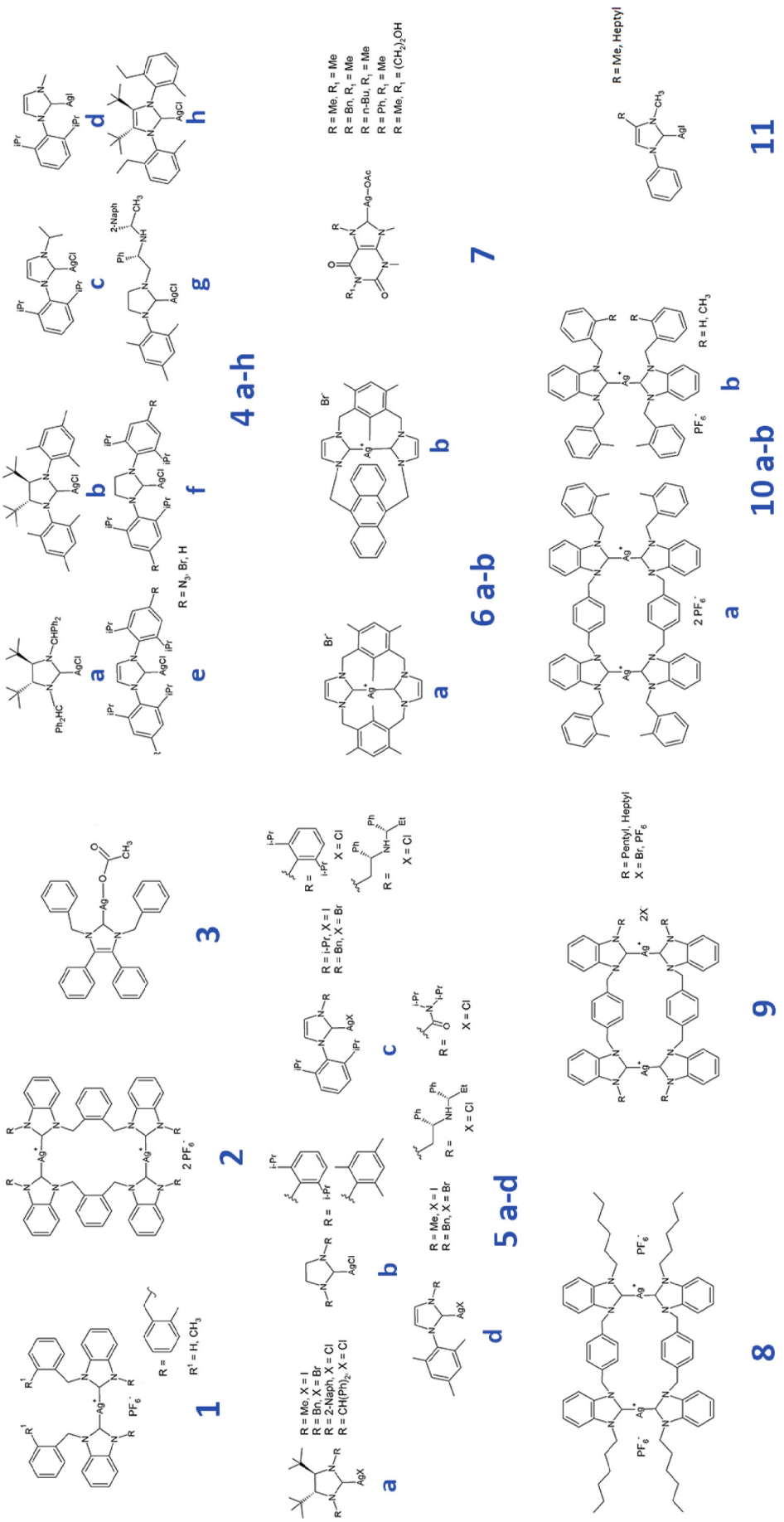

Fig. 2. Main types of NHC silver complexes.

of Ag–NHCs (Fig. 2, **7**) derived from natural xanthines (caffeine, theophylline and theobromine) gave different response profiles when compared to cisplatin in the same panel of cells, evidencing a different mechanism of action with respect to the reference compound. Furthermore, it appears that the steric effect of the ligand and the hydrophobicity of the complex both play a role in the chemosensitivity of these compounds, with greater steric bulk and greater hydrophilicity causing higher cytotoxicity [57].

There is a correlation between tumor development and a state of chronic inflammation: the two events are strictly connected. It seems clear that suppressing the inflammatory process can be beneficial for cancer treatment, therefore a series of anti-inflammatory drugs are normally used in chemotherapy. A binuclear Ag–NHC complex based on a para-xylyl linked bis-N-hexylbenzimidazole (Fig. 2, **8**) was tested for its biological activity against HCT-116 colon tumor cells, inducing caspase-3/7 most probably by tumor necrosis factor-alpha (TNF-α) independent intrinsic pathway, and significantly inhibited *in vitro* synthesis of cytokines, interleukin-1 (IL-1) and TNF-α in human macrophages (U937 cells). It also inhibited cyclooxygenase (COX) activities, with a strong and selective antiproliferative action against colorectal tumor cells which could be attributed to its pro-apoptotic and anti-inflammatory abilities [58]. Similar but less significant results were obtained in antiproliferative tests on the same colon tumor cell line with another silver binuclear complex based on an analogous para-xylyl linked bis-benzimidazole ligand (Fig. 2, **9**) [59] and with a series of benzimidazole-based Ag–NHC complexes (Fig. 2, **10 a and b**) [49].

Good results against HL60 and MOLM-13 leukemia cells were obtained with a set of 4-alkylated NHC–Ag compounds (Fig. 2, **11**). Their synthesis was carried out according to a different scheme than the one routinely employed in Ag–NHC preparation, featuring an eight/nine step procedure as reported in the literature [60]. This study evidenced that the length and the steric hindrance of the side chain on the imidazole ring are crucial for high cytotoxicity, as the imidazole complex bearing a C7 side chain at the 4-position was four- to six-fold more potent than the corresponding imidazole carrying a methyl group, stressing again the importance of the structure–activity association.

All things considered, it seems that silver carbene compounds can be eligible candidates in the search for cisplatin alternatives and strong antimicrobial agents for the control of infectious diseases. However, this might only be true for antibacterial topical applications or *in vitro* studies, because when we move toward their systemic administration a series of problems arise. In fact, the *in vivo* efficacy of Ag–NHCs may be limited by their rapid clearance, which is typical for small molecule drugs inside the body. Furthermore, the omnipresent chloride anion can abstract the silver ion from the NHC complex, impairing its activity. Finally, silver compounds can react with and be inactivated by sulfur-containing proteins present in the bloodstream. The solution to these drawbacks could be found by encapsulating the active species into proper biodegradable nanoparticles [20,61,62]. For instance, *in vitro* results have demonstrated that Ag–NHCs encapsulated into PEG–PLGA and PEG–PLA nanoparticles have efficacy against NCI-H460, an aggressive small-cell lung cancer line. Further research was planned for also testing this nanoparticle system *in vivo* [20].

3. Ag(I) complexes with phosphines

Phosphines, or phosphanes according to IUPAC, are one of the classes of ligands most widely employed in the preparation of metal complexes, especially for their use in catalysis. The electronic and steric properties of the complexes can be influenced by the proper choice of their substituents. Phosphines are both σ-donors and π-acceptors; hence the important role played by different groups on the phosphorus atom in regulating the electronic properties of the ligand. The Tolman cone angle [63], on the other hand, is determined by the bulkiness of the substituents, and it is strategic in modulating the activity of the complex because the size of the ligand is crucial in regulating the reactivity of the attached metal center. Complexes with phosphine ligands tend to have lipophilic properties and are compatible with metals in multiple oxidation states. Their versatility has been exploited for many purposes, including studies on the biological activities of the relevant metal complexes. Silver compounds are not an exception.

The nature of the co-ligand is also very important for the efficacy of the phosphine complexes. Recently, a series of interesting mixed ligand species have appeared in the literature.

Examples of phosphine silver complexes are reported in Fig. 3.

Different heterocyclic thioamides of the 2-mercaptothiazole family have been used in association with triphenylphosphine to prepare tetrahedral mononuclear silver species that are able to strongly bind DNA through intercalation or electrostatic interaction [64]. The DNA affinity depends on the associated thioamide ligand.

In another study, a series of mixed silver saccharinate complexes was prepared in order to check the effects on their biological activity following an increase in the spacer length of bidentate diphenylphosphines with a general formula $Ph_2P(CH_2)_nPPh_2$ (n = 1–4) [65]. X-ray analysis evidenced that the diphosphines can act both as bridging ligands to yield a dinuclear complex in the case of dppm (n = 1), or as one-dimensional coordination polymers (dppe, n = 2, dppb, n = 4), whereas the saccharinate can behave both as an N/O bridging ligand or an N-coordinating donor. These complexes have been tested for their binding to fish sperm DNA, giving DNA-intercalation with high binding affinity. Moreover, they possess very high antibacterial activity against *E. coli*, *Salmonella typhimurium*, and *S. aureus*, much higher than that of the common antibacterial reference agents, namely $AgNO_3$, silver sulfadiazine, ciprofloxacin, and gentamicin. Some of the complexes were also highly cytotoxic against A549 and MCF-7 cancer cell lines, compared with $AgNO_3$ and cisplatin. The study proposes that the mechanism behind this high bacterial and cell growth inhibitions by the Ag(I) complexes might be closely related to their DNA binding affinities.

The same group of researchers also tested a series of tertiary monophosphines where three aromatic rings had been gradually replaced by saturated aliphatic rings (PPh_3, PPh_2Cy, $PPhCy_2$, PCy_3) and had been flanked by a saccharinate ligand in the formation of silver complexes. The choice of saccharinate as the co-ligand followed the observation that silver(I) species bearing N,O-donors seem to target bacterial proteins containing thiol groups in their active sites. The soft character of sulfur-containing groups makes them apt to coordinate the equally soft silver(I) centers, so that the more labile N,O-donors are easily replaced by the thiol groups [6,66–68]. It was also noticed that the easier the ligand is replaced, the wider the spectrum of antimicrobial activity [69]. Therefore, not only is saccharinate a ligand with the right lability capable of forming a variety of metal complexes from mononuclear species to coordination polymers [70], but it is also a non-toxic compound that may help minimize the drawbacks of metallodrugs. All of the silver complexes formed with the monophosphines are dimeric species except one, containing the PCy_3 ligand, which is polymeric, and the saccharinate moieties behave as the bridging ligands. DNA binding studies revealed that the four complexes had high affinity for the double strand, higher than silver sulfadiazine and $AgNO_3$, decreasing in the order $PPh_3 > PPh_2Cy > PPhCy_2 > PCy_3$. The proposed DNA interaction is of the intercalative type. The same order was found in the activity against *E. coli*, methicillin resistant *S. aureus*, and *S. typhimurium*. *In vitro* cytotoxicities of the complexes against two human cancer cell lines (A549 and MCF-7) afforded better results than $AgNO_3$ and cisplatin.

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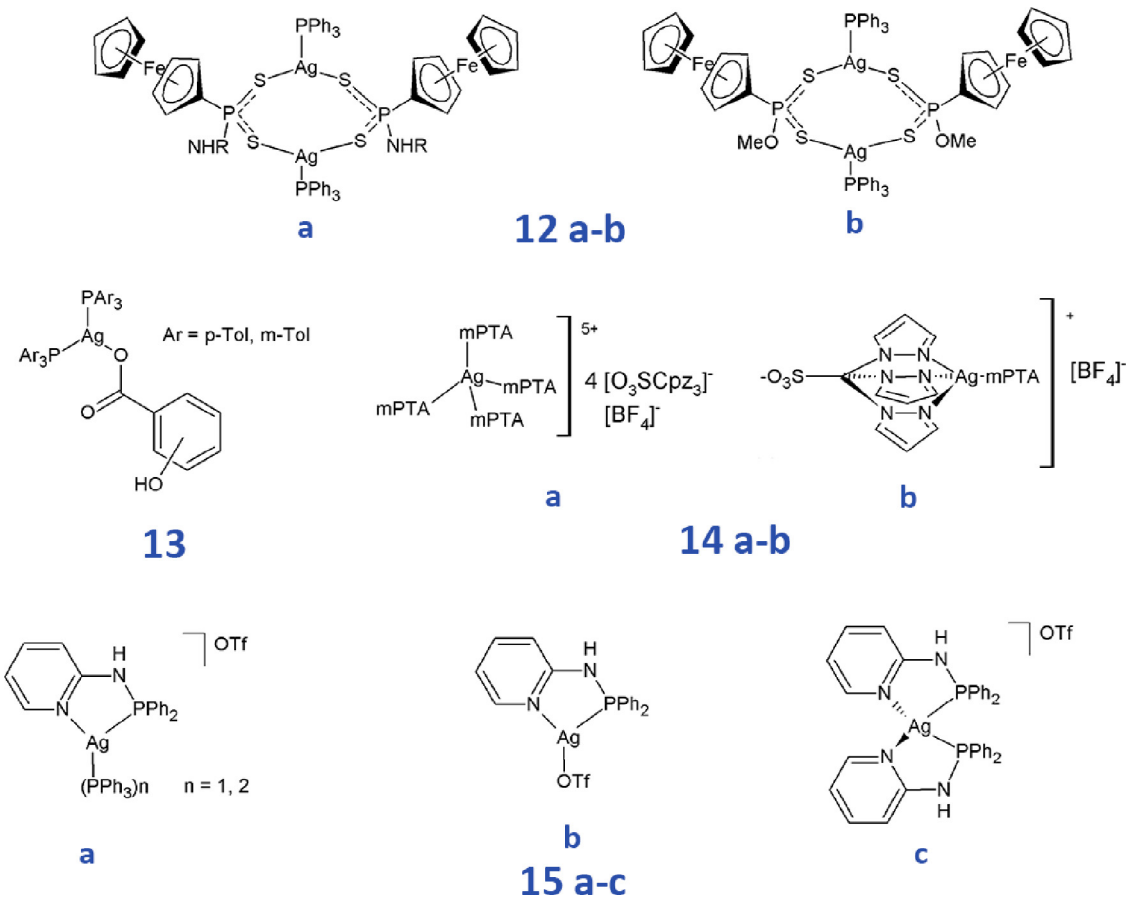

Fig. 3. Examples of silver complexes with phosphines.

Another example of Ag–phosphine complexes with mixed ligands includes triphenylphosphine with amido and O-ferrocenyldithiophosphonates, $[Ag_2\{FcP(OMe)S_2\}_2(PPh_3)_2]$ (Fig. 3, **12 a and b**), which were inserted into electrospun nanofibers in order to check their antibacterial properties. *Micrococcus luteus* and *E. coli* were tested against these materials, and moderate levels of antimicrobial activity were detected [71].

A phosphine silver(I) thiocyanate series bearing a variation of 4-substituted triphenylphosphines, namely $[AgSCN(PPh_3)_2]_2$, $[AgSCN\{P(4\text{-}MeC_6H_4)_3\}_2]_2$, $[AgSCN\{P(4\text{-}ClC_6H_4)_3\}_2]_2$, $[AgSCN\{P(4\text{-}FC_6H_4)_3\}_2]_2$, was studied in order to clarify the mechanism(s) behind their toxicity against SNO-esophageal cancer cells [72]. Flow cytometry revealed that morphological changes, including blebbing and apoptotic body formation, could be observed in the cancer cells upon contact with these complexes, indicating that apoptosis was significantly induced by the silver(I) phosphine treatment. Compared to cisplatin, which was able to induce the same effect but only at 10 times higher concentrations, these complexes are promising as potential anticancer agents. However their exact targeting mechanism should be studied and clarified.

The same research group also reported of a nearly identical set of phosphine–Ag(I) thiocyanate adducts, where only the fluoride phosphine derivative had been changed with a methoxo analogous, $[AgSCN\{P(4\text{-}MeOC_6H_4)_3\}_2]_2$, which had been tested against MCF-7 breast cancer cells. All four complexes possessed cytotoxic activity against this tumor cell line, inducing apoptotic cell death, while the ligands on their own were not toxic. Furthermore, this antiproliferative action seemed to be selective toward the MCF-7 line, since the complexes were not toxic to nonmalignant fibroblast cells at the IC50 concentrations [73].

One of the consequences of the inclusion of phosphines into a metal complex (Fig. 3, **13**) is the subsequent increase in lipophilicity, which can enhance their anticancer activity [74,75] but it makes the complex less water-soluble and limits the applications of these compounds to ointments and cream formulations for topical use. Water soluble 1,3,5-triaza-7-phosphaadamantane (PTA) or its highly hydrophilic derivative mPTA salt (N-methyl-1,3,5-triaza-7-phosphaadamantane) have been used to increase the hydrophilicity of phosphine–Ag complexes with remarkable success. PTA was employed in the synthesis of Ag-complexes with polypyridines (bipyridines and 1,10-phenanthrolines), to give both coordination polymers ($[Ag(N\text{–}N)(\mu\text{-}PTA)]_n(X)_n$) and discrete monomers ($[Ag(N\text{–}N)(PTA)_2](X)$) [76]. These compounds were tested against a vast range of malignant bacteria and the corresponding results were very interesting: the most active complexes had an efficacy twice as high as $AgNO_3$'s. When tested against human malignant melanoma cells, the same complexes evaluated by the MTT assay for their cell growth proliferation activity recorded significantly lower IC50 values than that of $AgNO_3$. The spectrophotometric methods used to clarify their mechanism of interaction with DNA suggest that all derivatives can intercalate into the base group pairs and possess a strong binding affinity toward DNA, causing DNA damage in cancer cells and inhibiting their division and proliferation. Moreover, two mPTA complexes, $[Ag(mPTA)_4](Tpms)_4(BF_4)$ (Fig. 3, **14 a**) and $[Ag(Tpms)(mPTA)](BF_4)$ (Fig. 3, **14 b**), where Tpms is the scorpionate tris(1-pyrazolyl)methanesulfonate anion, were synthesized and tested for their activity against different bacterial strains. $[Ag(mPTA)_4]^{5+}$ has an activity comparable to that of $AgNO_3$, while $[Ag(Tpms)(mPTA)]^+$ is a little less efficient. Both species are able to interact with calf thymus DNA, probably through a strong

electrostatic attraction instead of an intercalation mode. They also displayed a good binding ability toward the BSA protein [77].

Mixed ligand complexes with acetylsalicylic acid ($salH_2$) or p-hydroxy-benzoic acid (p-$HbzaH_2$) along with two aromatic monophosphines, tri(p-tolyl)phosphine (tptp) or tri(m-tolyl)phosphine (tmtp), were used to prepare a series of complexes: $[Ag(tptp)_2(salH)]$, $[Ag(tptp)_2(p\text{-}Hbza)]$, $[Ag(tmtp)_2(salH)]$, and $\{[Ag(tptp)_4]^+[(salH)^-]\cdot[(CH_3)_2NCHO]\cdot(H_2O)\}$, in an effort to increase these compounds lipophilicity through the insertion of the phosphine ligands (also increasing their solubility in organic media) though still maintaining their water solubility thanks to the carboxylic acid moieties. Their effect on the viability of MCF-7 (breast) and HeLa (cervix) adenocarcinoma cells was evaluated by trypan blue assay, evidencing that all the complexes were highly cytotoxic against these cellular lines. DNA binding tests indicated all the silver compounds had the ability to modify the activity of cells, while changes in fluorescent emission light of ethidium bromide (EB) in the presence of DNA revealed that intercalations or electrostatic interactions into DNA were the most probable mechanisms behind DNA interaction. This was also confirmed by docking studies, which indicated that the silver complexes preferred binding to the minor groove of B-DNA. A study of the peroxidation of linoleic acid by the enzyme lipoxygenase (LOX) in the presence of the complexes was also carried out, since LOX inhibition is known to induce apoptosis: a negligible inhibitory activity toward LOX was evidenced for the three silver compounds [78].

The same group of researchers used a similar approach for the preparation and the study of a new silver iodide triphenylphosphine (TPP) derivative with 2-mercapto-benzothiazole (MBZT), [AgI(TPP)2(MBZT)] [26]. This complex represents the first example in the literature of a mixed ligand complex of Ag(I) iodide with thiones and phosphines exhibiting significant biological effects, also considering that such compounds have rarely been reported thus far. Its cytotoxic activity was evaluated *in vitro* with SRB assay for cell viability both under UV light and without irradiation, against a wide series of human cancer cell lines: MCF-7 (breast, ER positive), MDA-MB-231 (breast, ER negative), Caki-1 (renal), A549 (lung), OAW-42 (ovarian), HeLa (cervical) and, in addition, against the normal human lung cell line MRC-5 (normal human fetal lung fibroblast cells) and MTSV17 (normal immortalized human mammary gland epithelial cells). It was found that the silver complex mediated a strong cytotoxic response in both normal and cancer cell lines, with an equivalent effect against MDA-MB-231 cells, where estrogen receptors (ERs) are devoid, and against MCF-7 cells, where ERs are present.

Studies focusing on molecular docking have demonstrated that the mixed Ag(I) iodide complex is docked in a pocket different than that of the ER receptors [26]. In order to better understand the mechanism of its cytostasis, research has been undertaken with the aim of studying the binding affinity of the complex toward DNA and lipoxygenase (LOX). The results suggest that both intercalation and electrostatic interactions of the complex with DNA occur. Furthermore, the complex activity on the catalytic peroxidation by LOX of linoleic acid to hydroperoxylinoleic acid has been assayed both kinetically and theoretically. Moreover, since cisplatin deactivation caused by glutathione seems to be relevant in determining the cytotoxic activity, the interaction of the silver complex with glutathione has also been examined by using UV spectroscopy [26].

If polar ligands have been used in order to increase water solubility of lipophilic silver–phosphine complexes, on the other hand aminophosphines, have been introduced in coordination compounds because of the versatility of the amino group, which is easily functionalized by introduction of biologically significant moieties. Four different Ag compounds containing 2-(diphenylphosphinoamino)pyridine (Ph_2PNHpy) have been prepared: $[Ag(PPh_3)(PPh_2NHpy)](OTf)$, $[Ag(PPh_3)_2(PPh_2NHpy)](OTf)$, $[Ag(PPh_2NHpy)(OTf)]$ and $[Ag(PPh_2NHpy)_2](OTf)$. Another series included silver compound containing 3-(diphenylphosphinoamino)-1,2,4-triazole (Htrz): $[Ag\{PPh_2NH(Htrz)\}](OTf)$ and $[Ag\{PPh_2NH(Htrz)\}_2](OTf)$ (Fig. 3, **15 a–c**). These complexes have been tested in bactericidal assays and were effective on Gram-negative and Gram-positive bacteria, with a moderate antimicrobial activity for all the silver(I) derivatives except those bearing PPh_3 groups. Their effectiveness is comparable to the reference antibiotics. The authors suggested that, due to the specific selectivity to Gram-positive versus Gram-negative bacteria of these complexes, the mechanism for their antibacterial action might be related to the inhibition of peptidoglycan synthesis in the cell wall [79].

4. Ag(I) complexes with N-heterocycles

N-heterocyclic ligands, especially polypyridines, have been extensively screened in association with a wide range of metals in the search of promising anticancer agents [2], but are not commonly studied in combination with silver (Fig. 4). Such complexes normally exert their antiproliferative action through intercalation with DNA. Among the limited cases of silver complexes used for this purpose, we can point out some compounds containing 1,10-phenanthroline (phen), such as $[Ag(hnc)(phen)_2]$ (Hnc = 4-oxy-3-nitro-coumarin) [80], which was more active than cisplatin toward hepatic cancer cells, or complex $[Ag_2(phen)_3(mal)]\cdot 2H_2O$ (mal = malonate) stronger than cisplatin against human kidney carcinoma cells [81].

More recently, Ag(I) compounds bearing N-heterocyclic ligands have been reported in the case of 2,6-bis(substituted)pyridine ligands, such as pyridine-2,6-bis(3-oxopropanenitrile), pyridine-2,6-bis(2-cyano-N-phenyl-3-oxopropanethioamide), and pyridine-2,6-bis((E)-2-(2-phenylhydrazono)-3-oxopropanenitrile) (Fig. 4, **16 a–c**), whose complexes have been tested against hepatocellular carcinoma (HePG2), lung adenocarcinoma (A549), colon carcinoma (HT29), and breast adenocarcinoma (MCF7), using doxorubicin as the reference drug. Most of the silver complexes in this series exhibited higher cytotoxic activity against tested cancer cell lines than doxorubicin, but their mechanism of action was not elucidated [82].

New fluorescent silver(I) helicates containing 6,6″-dimethyl-2,2′:6′,2″-terpyridine have *in vitro* antiproliferative activity against three human cancer cell lines: human breast cancer (T47D), human cervical carcinoma (HeLa) and human lung cancer (A-549) [83]. As expected, DNA binding tests showed that these complexes specifically interact with DNA *via* an intercalation mechanism. Confocal microscopy indicated that they also specifically bind to the cellular nuclei, so that the anticancer activity seems to be exerted through selective nucleoli targeting. These helical systems also present promising antibacterial activity against both Gram-negative (*E. coli*) and Gram-positive (*S. aureus*) strains.

In addition, silver(I)-pyridinedicarboxylate compounds bearing pyridine derivatives such as pyridine-2,3-dicarboxylic (quinolinic), pyridine-2,4-dicarboxylic (lutidinic) and pyridine-2,5-dicarboxylic (isocinchomeronic) acids (Fig. 4, **17 a–c**), were checked as antimicrobial agents against *E. coli*, *L. monocytogenes*, *S. typhi* and *S. aureus*. All three complexes exhibited remarkable antibacterial behavior, but the quinolinic derivative was more active than the others. In order to understand the antimicrobial mechanism, the bacterial cells exposed to silver compounds were studied by optical microscopy; disruption of cell morphology was demonstrated, evidencing a bacteriolytic mechanism for both Gram-positive and Gram-negative strains [84].

Quinoline derivatives were employed in a study where the relative silver complexes (Fig. 4, **18 a and b**) were screened against 15 different multidrug-resistant strains of bacteria isolated from diabetic foot ulcers and compared to the antimicrobial activities of the reference drug, silver sulfadiazine. $[Ag(8\text{-nitroquinoline})_2]NO_3\cdot H_2O$

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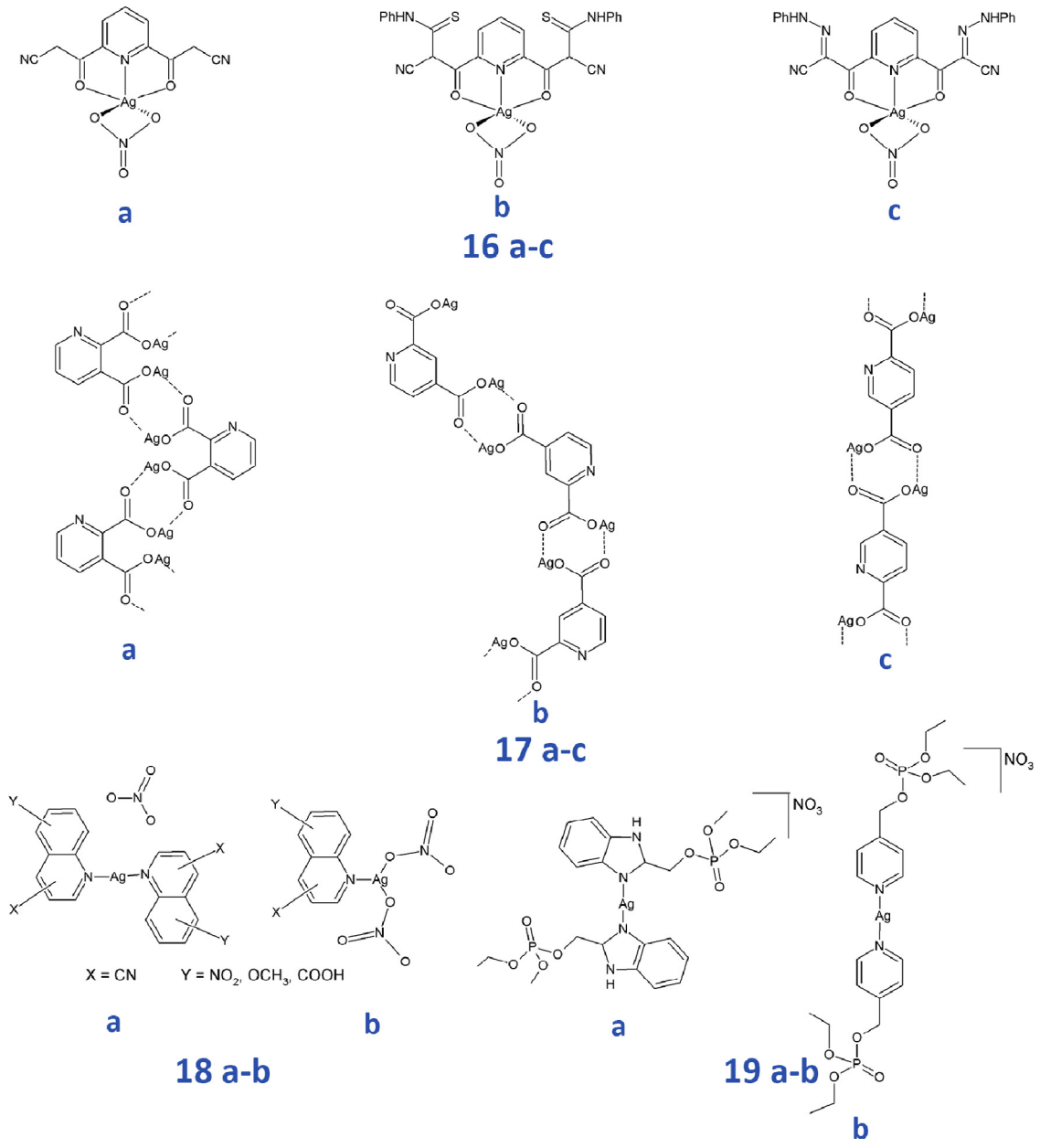

Fig. 4. Examples of silver complexes with N-heterocycles.

was the most active compounds in this series, and was slightly more effective than silver sulfadiazine against all the bacterial strains tested. $[Ag(5\text{-nitroquinoline})_2]NO_3$, on the other hand, was better than $AgNO_3$ against the standard nonresistant bacterial strains of *S. aureus*, *P. aeruginosa*, *Proteus mirabilis*, and *Streptococcus pyogenes* [85].

A series of Ag(I) complexes with phosphate derivatives of pyridine and benzimidazole (Fig. 4, **19 a and b**) were active as antifungal agents against *C. albicans* strains. Among these, $[Ag(2\text{-bimOpe})_2]NO_3$ (2-bimOpe = 1H-benzimidazol-2-ylmethyldiethylphosphate) was highly effective against *P. aeruginosa* and methicillin-resistant *S. epidermidis*, whereas the free ligands had no activity [86].

Finally, Ag(I) complexes of the type $[Ag(L)(PR_3)]^+$, L = valine-N-(4-pyridylcarbonyl)methyl-ester, $PR_3 = PPh_3$, PPh_2Py, where nitrogen atom from pyridine coordinates metal fragments, have been tested in different tumor cell lines for their anti proliferation activity. The complexes induced cell death mainly by an apoptotic mechanism [87].

5. Ag(I) complexes with a variety of pharmaceutical agents

A typical approach in the search of biologically active metal compounds is to prepare complexes of drugs that are already in use or have previously demonstrated to be effective on their own. In fact, many medicinal drugs show modified pharmacological and toxicological potential if administered in the form of metal-based compounds. In this way, an enhancement of their efficacy could be expected, although this might not always hold true.

Sulfachloropyridazine (SCP, 4-amino-N-(6-chloro-3-pyridazinyl)-benzenesulfonamide) is a sulfonamide antimicrobial compound that could be a good candidate for the preparation of effective silver derivatives, especially after the introduction in 1960s of silver sulfadiazine (Fig. 5, **20**) (Silverex, Silvazine, Silvadene) or cerium nitrate-silver sulfadiazine (Flammacerium) since 1976, as a topical treatment for burns and wounds [88,89]. Two of its complexes, heteroleptic Ag(SCP)(SCN) (SCN = thiocyanate anion) and homoleptic

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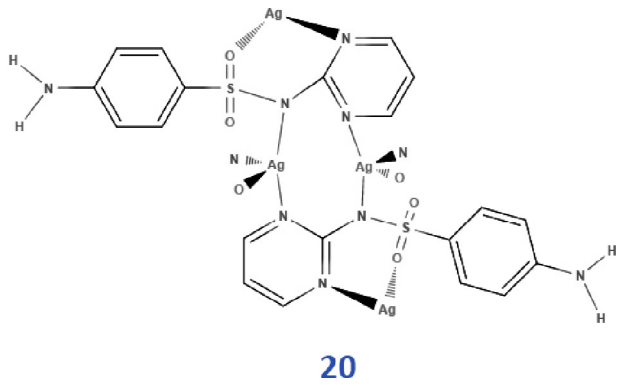

Fig. 5. Structure of silver sulfadiazine.

$[Ag_2(SCP)]_n$, have been tested for their activity against a series of bacterial strains. With *E. coli* and *P. aeruginosa* they both performed better than SCP alone, with an activity comparable or even superior to that of other silver complexes [90]. In the case of *P. aeruginosa* both complexes gave a MIC lower than other tested compounds, even lower than the reference antibiotic cefotaxime. The same two compounds had moderate antimycotic activity against different fungi and yeasts, such as *Cryptococcus neoformans*, probably through the inhibition of phosphomannose isomerase, a key enzyme in the biosynthesis of yeast cell walls. In all the cases, SCP alone was ineffective. A test of phytotoxicity carried out on common onion plants evidenced that both Ag(SCP)(SCN) and $[Ag_2(SCP)]_n$ had no phytotoxic effects in the concentration range, which demonstrated that antibacterial and antifungal activities occurred. At the same time no chromosomal aberrations were observed.

The same group reported of an analogous study performed on sulfamoxole (SMX, 4-amino-N-(4,5-dimethyl-1,3-oxazol-2-yl)benzenesulfonamide) with similar complexes, homoleptic $[Ag_2(SMX)_2]\cdot H_2O$ (Fig. 6, **21**) and heteroleptic $[Ag_4(SCN)_3(SMX)]\cdot H_2O$. In this case, MICs were lower than that of SMX alone for *S. aureus*, *E. coli*, and *P. aeruginosa*. The complexes were more effective than $AgNO_3$ against *E. coli* and *P. aeruginosa*, while against *S. aureus* they were less active. They also possessed antifungal activity, especially against yeasts. Moreover, they caused no cytotoxic effects on onions in the tested concentration range; no chromosome aberrations were also observed [91].

Metronidazole (MTZ, 2-(2-methyl-5-nitro-1H-imidazol-1-yl)ethanol) is an antibiotic and antiprotozoal drug, widely used in the medicinal treatment of (anaerobic) bacterial and parasitic infections. Metronidazole needs to be combined with another antibiotic agent to cover mixed infections with aerobic bacteria, and silver could be the right partner for it. A series of water-soluble silver complexes with metronidazole have thus been synthesized and tested in the treatment of Gram-positive (*S. aureus, S. epidermidis)* and Gram-negative strains *(P. aeruginosa, E. coli, Proteus hauseri*), as well as yeast *C. albicans* [92]. These novel silver(I) coordination compounds of metronidazole have been synthesized in the form of monomers, $[Ag(MTZ)_2X]$ ($X = NO_3^-$, ClO_4^-, CF_3COO^-) (Fig. 6, **22 a**), or dimers, $[Ag_2(MTZ)_4]Y_2$ ($Y = BF_4^-$ and $CH_3SO_3^-$) (Fig. 6, **22 b**). They all exhibited significant antibacterial activity against Gram-positive bacteria, higher than silver sulfadiazine, the reference drug. The importance of the counter-ion was also evaluated in the antimicrobial tests. The best active silver(I)-metronidazole complex was the one containing a methanesulfonate counter-ion, which also inhibited the growth of yeast *C. albicans* at a concentration 3-fold lower than that required for silver sulfadiazine. In addition, the complexes containing a tetrafluoroborate and a perchlorate as the counter-ions were also characterized as effective antibacterial agents against the tested Gram-negative bacteria.

Carbocysteine (Ccy, (R)-2-Amino-3-(carboxymethylsulfanyl) propanoic acid) is a mucolytic drug that reduces the viscosity of sputum, so it can be used to help relieve the symptoms of chronic obstructive pulmonary disorder (COPD) and similar problems. COPD is characterized by chronic inflammation and premature lung aging, and is mainly caused by prolonged cigarette smoke exposure, which can determine oxidative stress, a critical event in the COPD pathogenesis, and induce cell senescence. In a recent study a new silver(I)-Ccy complex, $[Ag_2(Ccy)_2(H_2O)_2]$, has been prepared and assessed in the treatment of COPD and bronchial asthma, in an effort to diminish the side effects of cigarette smoking. Administration of $[Ag_2(Ccy)_2(H_2O)_2]$ to rats in two doses, either 125 mg/kg or 250 mg/kg, improved their immunity and ameliorated the antioxidant capacities, so that the silver compound was more efficient in reducing smoke side effects than the carbocysteine drug alone [93].

Coumarin (2H-1-benzopyran-2-one, or 2H-chromen-2-one) is a natural substance found in many plants; it belongs to the benzopyrone chemical class, whose derivatives possess potential antimicrobial [94,95] and antifungal activities [96]. Moreover, there are a number of commercially available coumarin-based antibiotics (novobiocin, clorobiocin and coumermycin A1), and anticoagulants (warfarin, dicoumarol). Different antimicrobically active silver(I)–coumarin complexes have also been prepared [94,97] that are able to disrupt microbial respiration and also block the synthesis of cytochromes [96]. Silver(I) complexes of coumarin-based ligands (hydroxyl ortho-substituted-nitro-2H-chromen-2-one derivatives) and one of their phenanthroline (phen) adducts have been prepared and tested for their cytotoxicity against human-derived hepatic carcinoma cells (Hep-G2) and a renal cancer cell line (A498). These compounds were more cytotoxic than the clinically used chemotherapeutic mitoxantrone, taken as the reference. They also had little interaction with DNA and no nuclease activity, but demonstrated excellent superoxide dismutase activity, indicating that their mechanism of action is probably rather different from the majority of other metal-based therapeutics [98].

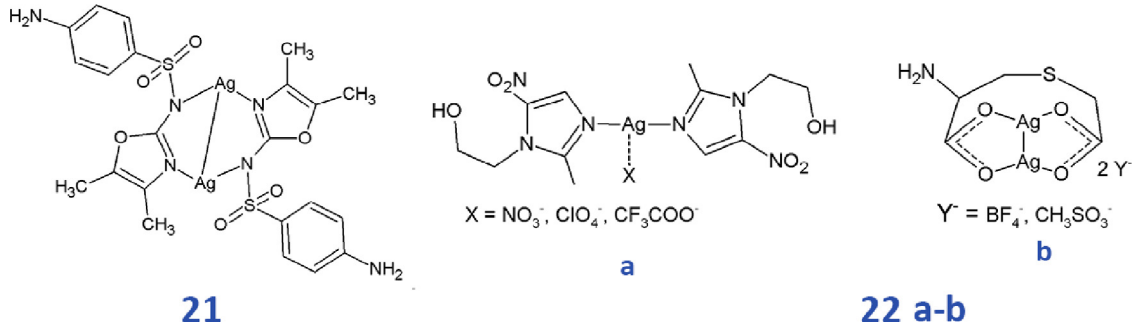

Fig. 6. Silver complexes with a variety of pharmaceutical agents.

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6. Comparison between the properties of silver and platinum and gold based-drugs

In Table 1 a summary concerning the peculiar activity exerted by Ag(I), Au(I) and Pt(II) complexes as antimicrobial or anticancer agents has been reported.

Although there are no determinant or fixed parameters to discriminate between the antimicrobial and anticancer activity, from the comparison of the effects determined respectively on different microorganisms or cell lines it is possible to infer that, while to beat platinum supremacy in the field of chemotherapy is a very hard task, nevertheless the low toxicity of silver for humans makes it a good candidate in the search of new silver drugs, both as anticancer and antibacterial agents. Many silver and gold based-drugs, albeit being successful in *in vitro* experimentation, have never been tested on animal models or humans. Clinical trials are in fact very expensive and mostly afforded only by the pharmaceutical companies. So a new compound must be exceptionally active and promising to raise the interest of the pharmaceutical industry.

As reported in Table 1, what we have learnt so far [2] is that platinum-based drugs are highly effective in killing cancer cells, but in the same way they do kill also the healthy ones: they lack selectivity. Platinum drugs employed to date are also affected by a series of drawbacks, from systemic toxicity to resistance induction in many cancer cells. Their activity is restricted to a limited spectrum of tumors, and high doses should be administered to the patients, since only 1% of the drug reaches the DNA.

Platinum compounds have been tested against bacteria and fungi with remarkable results *in vitro*, but cytotoxicity considered, it would be interesting to understand whether they could have *in vivo* applications. Claims have been made for instance that a Pt–vancomycin complex, 720 times more potent than vancomycin itself, was not cytotoxic to mammalian cells [99], but we were not able to find further studies in the literature about this issue.

Gold is in the same group (IB) as silver, and its properties in medicine have been extensively evaluated, both as Au(I) and Au(III) compounds. Auranofin, is an Au(I) thiolate–triethylphosphine complex, admitted in the clinical use in 1985 to treat rheumatoid arthritis. Since then, no other gold compounds have been introduced as a medical treatment, for arthritis or any other disease. Although auranofin possesses a certain degree of toxicity, nevertheless it exhibited an *in vitro* anticancer activity similar to that of cisplatin. Analogous compounds were highly effective against cancer but some of them exhibited a series of drawbacks, such as high cardiotoxicity or poor stability. Au(III) derivatives, on the other hand, were effective but often limited by high toxicity, induced drug resistance, poor cancer-cell specificity and scarce bioavailability.

Both Au(I) and Au(III) complexes seem to be effective in the treatment of leishmaniasis, malaria, tuberculosis, and were also tested against HIV infection with good results.

Silver compounds have a remarkable potential as anticancer agents *in vitro*, but there is an anomalous lack of information about their *in vivo* activity, together with any problem or drawback that could emerge following human administration. Silver on its own is considered to be non-toxic for humans and other mammalians, although the scientific community is still debating on this point, especially regarding silver nanoparticles after they have been massively introduced as antibacterial agents under a vast variety of uses. Anyway, low toxicity is one of silver's greatest advantages over other medicinally relevant metals together with its ability to overcome drug resistance and beat antibiotic-resistant bacteria, fungi and parasites. In comparison to platinum and gold, silver bioavailability, though related to its efficacy, could also be a problem, since Ag(I) ions are rapidly precipitated as AgCl or are sequestered as Ag–protein complexes, although this could be overcome by encapsulation into biodegradable polymers.

Table 1
Properties of Ag(I), Au(I) and Pt(II) complexes as antimicrobial or anticancer agents.

	Pt(II)	Au(I)	Ag(I)
Anticancer drugs [2]			
Efficacy	High	High (*in vitro*)	High (*in vitro*)
Cytotoxicity	High	High (*in vitro*)	Low (*in vitro*)
Drawbacks	Many	Many	Not known
Resistance	Yes	Yes	Not known
Bioavailability	Scarce	Scarce	Low
Antibacterial drugs [2]			
Efficacy	High (*in vitro*)	High (*in vitro*)	High
Human toxicity	Under assessment	Not reported	No
Resistance	Not known	Not known	No

7. Conclusions

Silver complexes have shown interesting properties and applications, ranging from antibacterial and anti-inflammatory to antineoplastic activities. In particular, they exhibited very good results against bacteria and especially against antibiotic-resistant bacteria, fungi and parasites.

Actually, although silver ions and silver compounds can be toxic to some bacteria, viruses, algae and fungi, they nevertheless usually present low toxicity against mammalian cells. This feature is fundamental in the selection of new metallodrugs and their applications as antibiotic, antiviral and antimycotic agents that should clearly have very little or no toxicity for humans. Silver complexes have also demonstrated their efficacy against different cancer cell lines, holding promise for successful treatment of tumors and other malignancies. The spherically symmetric configuration of the Ag(I) ion allows the coordination number to vary from 2 to 6, hosting a wide variety of ligands that influence both the electronic and steric properties of the relative complexes, which in turn modulate the rate of silver release. All these factors are fundamental for maintaining their bioavailability over an extended period of time and preventing reinfection or resistance. A wide variety of ligands can be bound to the silver center in order to regulate the complex hydrophilicity or lipophilicity, as well as the stability and redox ability of the active silver complexes. This impressive versatility accounts for the huge interest of current medicinal inorganic chemistry toward silver coordination compounds, and the number of papers published during the past decade on this topic confirms it. The massive contribution to the literature of studies focused upon metallodrugs, especially in the past few years, demonstrates how intense the ongoing research is on this stimulating area.

In spite of the large volume of research undertaken and the synthesis of several new silver complexes, most of them still remain in an academic research context and actually only a few have been approved for medical treatment of human diseases.

In fact, apart from some exceptions, such as for example silver sulfadiazine complex which is used as a cream formulation to treat burn-derived infections, not many other silver complexes are currently used in therapy, though *in vitro* studies have demonstrated activity for many of them.

In this review we have presented an overview of this noble metal's active derivatives, properties, mode of action and potential uses with the aim of stimulating further study for their clinical applications and highlighting some of the novel silver complexes as promising candidates for clinical trials and subsequent therapeutic use.

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Please cite this article in press as: Serenella Medici, et al., Silver coordination compounds: A new horizon in medicine, Coordination Chemistry Reviews (2016), doi: 10.1016/j.ccr.2016.05.015