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# Investigation of a Series of Silver–N-Heterocyclic Carbenes as Antibacterial Agents: Activity, Synergistic Effects, and Cytotoxicity

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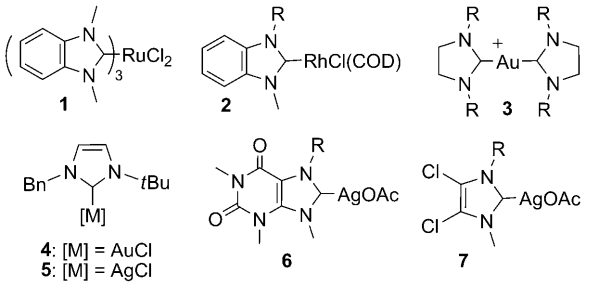
An impressive amount of research has been dedicated to the preparation of metal N-heterocyclic carbene (NHC) complexes and to the development of catalytic applications.[1] By comparison, biological applications of metal–NHCs have been much less explored. Various studies focusing on the antimicrobial or anticancer activity have highlighted their promising potential as novel therapeutic agents.[2] Metal–NHCs (metal = Ru, Rh, Au, or Ag) have been investigated for their antimicrobial activity against a number of bacterial and fungal strains.[3] Some of these complexes, such as **1**–**7** (Scheme 1), showed significant activities against Gram-negative and/or Gram-positive bacteria with minimum inhibitory concentrations (MICs) below 10 $\mu g\,mL^{-1}$,[2a,4] which is a minimal value generally recognized in the pharmaceutical industry for a valuable hit to be further developed as a potential drug. In recent decades, with the growing appearance of multidrug-resistant (MDR) bacterial strains,[5] silver has reemerged as a viable and useful antibacterial agent. At present, silver-based compounds are commonly used in the topical chemotherapy of infections encountered in burns, open wounds, and chronic ulcers.[6] Silver, as silver salt ($AgNO_3$), nanocrystalline silver (silver-coated dressings), or in combination with antibiotics (silver sulfadiazine), has been incorporated into several commercial products. However, the development of new and more efficient silver-based antibacterial drugs is still of interest. One of the main challenges is to improve the ability to provide sustained bactericidal action while lowering the toxicity.[6,7] In this context, stable silver–NHCs have given promising results.[3d–l] Some of these, such as **6** and **7** (Scheme 1), have been found to exhibit high in vitro antimicrobial efficacy against a broad spectrum of highly resistant respiratory pathogens and against *E. coli* with MIC values as low as 1 $\mu g\,mL^{-1}$.[3g–i] Silver–NHCs have also been shown to be active against *S. aureus*.[3d,f,i] However, the potential against resistant strains of *S. aureus*, which cause major problems to public health due to MDR strains in hospitals and community infections,[5] has only been scarcely investigated. A few complexes, including **6**, have been reported to be effective against methicillin-resistant *S. aureus* (MRSA).[3i]




Scheme 1. Examples of metal–NHCs that have been investigated for antimicrobial activity. COD = 1,5-cyclooctadiene.

The implications of in vitro cytotoxicity of silver for clinical wound care has been well studied.[7] Currently, little information is available on the cytotoxic effects of silver–NHCs tested as antimicrobial agents. One noteworthy ex-

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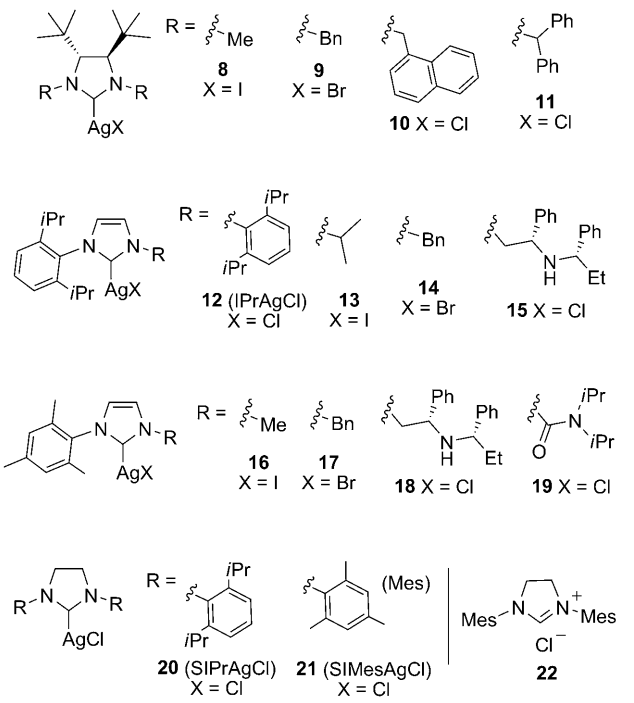
ception deals with complex **6** for which in vitro cytotoxicity was reported to be negligible on mouse tracheal epithelial cells at bactericidal concentrations.[3k] To the best of our knowledge, the cytotoxicity of silver–NHCs on normal human cells was not examined, whereas several studies on the anticancer properties revealed high toxicity towards some cancer cell lines.[2a,b] A great library of silver–NHCs, mainly used as carbene transfer agents, have been prepared for catalytic applications.[8] Few of these compounds have been tested as antibacterial agents. This prompted us to investigate the antibacterial activity of a series of silver–NHCs that we have prepared over the past decade.[9] Their activity against susceptible and resistant strains of *S. aureus* as well as *E. coli* was evaluated. The combination of silver–NHCs with antibiotics, such as ciprofloxacin (CIP), was also studied as well as the cytotoxicity on several cell lines, including normal human cells. Our results for a set of 14 complexes are reported herein.

Silver–NHCs **8–21** (Scheme 2) were readily synthesized from the corresponding imidazoli(ni)um salts in the presence of $Ag_2O$.[9,10] The synthesized compounds can be classified into three basic families based on the fundamental structure of the heterocyclic backbone (unsaturated, saturated, or disubstituted by *tert*-butyl groups). Within each family the complexes differ by the nature of the substituents on the nitrogen atoms (alkyl, aryl, or functionalized groups). The NHC ligands of complexes **12**, **20**, and **21** commonly called IPr, SIPr and SIMes, respectively, are well known for applications in catalysis.[1]




Scheme 2. $Ag^I$–NHC complexes **8–21** and imidazolinium salt **22** tested in this study. Bn = benzyl, Mes = 2,4,6-trimethylphenyl.

The antibacterial activity of **8–21** against the two susceptible bacterial strains, *E. coli* ATCC25922 (Gram-negative) and *S. aureus* ATCC25923 (Gram-positive), was first evaluated (Table 1). For comparison, the activity of $AgNO_3$ and that of **22** was also examined. Ten of these complexes (**8–10** and **13–19**) were found to display significant activity against *E. coli* with MICs ranging from 4 to 16 $\mu g\,mL^{-1}$. Complexes **8** and **13** gave the best values with MICs (4 $\mu g\,mL^{-1}$) in the same range as those previously reported for complexes **6** and **7**.[3h,j] In contrast, compounds **12** and **20** (MIC > 128 $\mu g\,mL^{-1}$), and to a lesser extend **11** and **21** (MIC 64 $\mu g\,mL^{-1}$), showed no significant antibacterial activity against this strain. This lack of activity against *E. coli* was already observed with complex **5**.[3l] Most of the complexes exhibiting significant activity against *E. coli* (**9**, **10**, and **13–19**) were also found to be active against the Gram-positive susceptible strain of *S. aureus* with MICs in the same range (16–8 $\mu g\,mL^{-1}$), with the exception of complex **8** for which the MIC is eightfold higher against *S. aureus* (32 $\mu g\,mL^{-1}$) than against *E. Coli* (4 $\mu g\,mL^{-1}$). In contrast, four of the complexes (**11**, **12**, **20**, and **21**) showed much higher activities against *S. aureus* than against *E. coli*. Among these, compounds **11** and **21** (SIMesAgCl) exhibited the best activities among the whole set of silver–NHCs tested, with a MIC of 1 $\mu g\,mL^{-1}$.

Table 1. Antibacterial activity of compounds **8–22** and $AgNO_3$. Minimum inhibitory concentrations [$\mu g\,mL^{-1}$] and minimum bactericidal concentrations [$\mu g\,mL^{-1}$] (indicated in brackets). The experiments were performed as duplicates.

| | *E. coli* | *S. aureus* | *S. aureus* MsrA | *S. aureus* NorA | *S. aureus* NorA + CIP[a] |
|---|---|---|---|---|---|
| **8** | 4 | 32 | 8 | 32 | 32 |
| **9** | 16 | 16 | 8 | 16 | 16 |
| **10** | 16 | 8 | 8 | 16 | 4 |
| **11** | 64 | 1 | 1 | 4 | 2 |
| **12** | >128 | 16 | 16[b] | 32 | 16(16) |
| **13** | 4 | 8 | 2 | 2 | 8 |
| **14** | 16 | 8 | 4 | 4 | 4 |
| **15** | 16 | 16 | 8 | 8 | 8 |
| **16** | 16 | 16 | 8 | 16 | 8 |
| **17** | 8 | 16 | 32 | 16 | 32 |
| **18** | 16 | 16 | 4 | 16 | 8 |
| **19** | 8(8) | 16 | 8 | 4 | 16 |
| **20** | >128 | 16 | 64 | 64 | 8(>16) |
| **21** | 64 | 1 | 1[b] | 2 | 0.5(0.5) |
| **22** | >128 | 64 | 128 | 128 | 32 |
| CIP | | 0.5 | | 16 | |
| ERY | | 0.5 | 128 | | |
| $AgNO_3$ | 4(4) | 16 | >128 | 16 | 16(16) |

[a] *S. aureus* NorA + CIP 2 $\mu g\,mL^{-1}$. [b] The same value was obtained in the presence of erythromycin (ERY) at a subinhibitory concentration (16 $\mu g\,mL^{-1}$).

The antimicrobial potential of **8–21** was further investigated against the two following resistant strains: *S. aureus* 1199B (*S. aureus* NorA), a ciprofloxacin (CIP)-resistant strain that constitutively overexpresses the multidrug efflux pump NorA,[11] and *S. aureus* RN4220/pUL5054 (*S. aureus*

MsrA), which contains the multicopy plasmid pUL5054 with constitutive resistance to ERY.[12] Except **20**, all silver–NHCs were found to have significant activities against these two resistant strains with MICs of 1–32 $\mu g mL^{-1}$ (Table 1). Complexes **11** and **21** (SIMesAgCl) are the most active with MIC values of 1–4 $\mu g mL^{-1}$, which is similar to the values obtained against the susceptible strain. These two complexes are therefore able to inhibit both sensitive and resistant strains of *S. aureus* at clinically achievable concentrations. The MICs of **11** and **21** against the susceptible *S. aureus* strain (1 $\mu g mL^{-1}$) are very close to those of CIP and ERY (0.5 $\mu g mL^{-1}$),[13] which are widely used antibiotics to cure *S. aureus* infections. More interestingly, compounds **11** and **21** have MICs that are 128-fold lower than that of ERY against the resistant strain *S. aureus* MsrA (128 $\mu g mL^{-1}$) and 4- to 8-fold lower than that of CIP against *S. aureus* NorA (16 $\mu g mL^{-1}$).[13] Complex **13**, which is active both against *E. Coli* and *S. aureus* with MICs of 2–8 $\mu g mL^{-1}$, is also interesting for its broad spectrum of activity. Several complexes are significantly more efficient than $AgNO_3$ against the susceptible strain of *S. aureus* and the resistant strain *S. aureus* NorA. In addition, $AgNO_3$ is inactive against resistant *S. aureus* MsrA, whereas MIC values reaching 1–4 $\mu g mL^{-1}$ have been obtained with silver–NHCs. The lower activity observed for the imidazolinium salt **22** by comparison with the corresponding silver complex **21** demonstrates the major role of silver in antibacterial activity.[14]

Multidrug combinations are increasingly important in stamping out the spread of antibiotic resistance in bacterial pathogens.[15] Enhanced antimicrobial activities have been reported by combining antibiotics with silver-based compounds, such as silver nanoparticles.[16] This led us to investigate the activity of **8**–**21** against resistant *S. aureus* NorA in the presence of CIP at subinhibitory concentration (MIC/8, i.e., 2 $\mu g mL^{-1}$). In several cases, an increased antibacterial effect was observed (Table 1, right column). The most significant results were obtained with **10**, **20**, and **21**, which gave MICs that are four- to eightfold lower than those of the silver complexes alone. A MIC as low as 0.5 $\mu g mL^{-1}$ was obtained with **21** under these conditions. Interestingly, the presence of CIP at a subinhibitory concentration also potentiates the antibacterial activity of salt **22** against *S. aureus* NorA, whereas no enhanced activity was detected for $AgNO_3$. MIC determination in the presence of varying subinhibitory concentrations of CIP and silver complex was then undertaken for **20** and **21** to state more precisely the effect of combining the two drugs. Complex **12** was also studied for structural similarities to **20**. An important synergistic effect between CIP and **20** (SIPrAgCl) was evidenced and clearly demonstrated by the isobole obtained (Figure 1). As described by the Loewe theory, synergistic drug pairs have a stronger than additive effect corresponding to an isobole below the additive straight line.[17] This synergy allows **20** to be almost as efficient (MIC 2 $\mu g mL^{-1}$) as **21** (MIC 0.5 $\mu g mL^{-1}$) in the presence of 4 $\mu g mL^{-1}$ of CIP, whereas the MICs without CIP are 64 and 2 $\mu g mL^{-1}$, respectively. By comparison, synergistic effects between **12**, **21**, and CIP

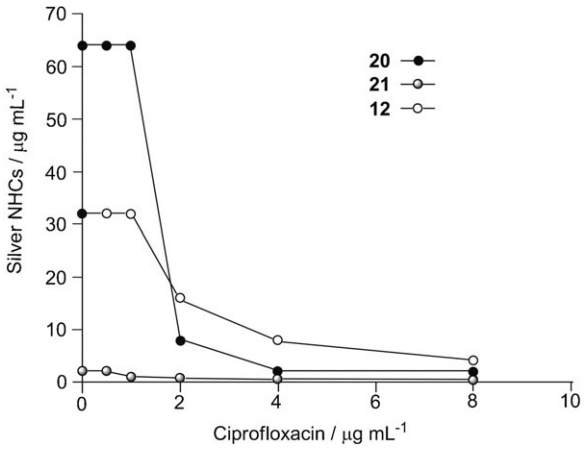



Figure 1. Combination of silver–NHCs **12**, **20**, and **21** with CIP at varying subinhibitory concentrations. MICs [$\mu g mL^{-1}$] determined against *S. aureus* NorA. The lines indicate the drug pair concentrations required to stop bacterial growth. Growth responses to one single compound alone lie along each axis.

are less marked. Similar experiments carried out with complexes **12**, **21**, and ERY showed no synergistic effect against the resistant strain *S. aureus* MsrA, thus suggesting a specific effect on *S. aureus* NorA. This could be ascribed to a specific inhibition of the NorA overexpressed efflux pump by silver–NHCs, which thereby restore the antimicrobial activity of CIP. The development of efflux pump inhibitors (EPIs) is an important strategy in combating MDR in *S. aureus*.[18] However, the high intrinsic antimicrobial activity of **21** does not allow any conclusions to be drawn on the possible mechanism of action as an EPI. This could be more accurately proposed for **20** for which the activity against *S. aureus* NorA in the absence of CIP is very low.

Previous in vitro studies carried out with commonly used silver-based topical antimicrobial agents showed that keratinocytes and fibroblasts are susceptible to lethal damage when exposed to concentrations of silver that are lethal for bacteria.[7] To evaluate the in vitro cytotoxicity of silver–NHCs **8**–**21**, we determined the inhibition percentage of MRC5 (human noncancerous cells in rapid proliferation) cell proliferation at concentrations of 50 and 10 $\mu g mL^{-1}$. For comparison, the activity of **22** was also examined. As shown in Figure 2, silver–NHCs **8**–**21** as well as **22** inhibit more than 90–95 % of the cell growth at the highest concentration. A high toxicity was also observed at 10 $\mu g mL^{-1}$, except for complex **9** and imidazolinium **22** (70 and 65 % inhibition, respectively). This cytotoxicity is comparable to that reported for $AgNO_3$ on human fibroplasts at similar concentrations.[19,7b]

Determination of $IC_{50}$ values on MRC5 and EPC cell lines for **11**–**13**, **20**, and **21** corroborated these preliminary results (Table 2). These values are superior on the EPC quiescent cell line than on MRC5, suggesting a higher cytotoxicity on cells in rapid proliferation. Values in the same range were previously reported for **12**, **20**, and **21** against several cancer cell lines.[2b] Compound **21** (SIMesAgCl) is the least

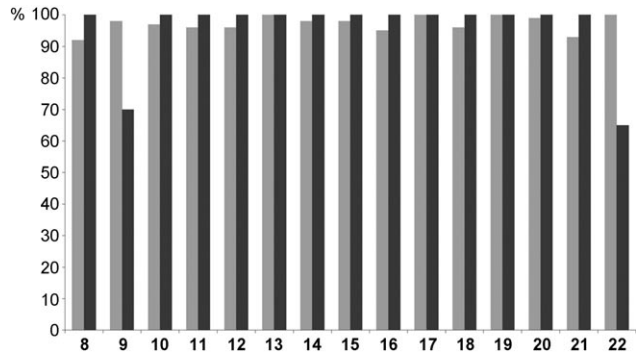



Figure 2. Inhibition percentages of MRC5 cell proliferation exerted by compounds **8**–**22** in DMSO at 50 (gray) and 10 $\mu g\,mL^{-1}$ (black). The data are the average of three experiments.

Table 2. $IC_{50}$ [$\mu g\,mL^{-1}$] of complexes **11**, **12**, **13**, **20**, and **21**. The values shown are the averages of two experiments.

| Cell line | **11** | **12** | **13** | **20** | **21** |
|---|---|---|---|---|---|
| MRC5 | 0.04 | 0.053 | 0.019 | 0.051 | 0.17 |
| EPC[a] | 0.28 | 0.56 | 0.2 | 0.1 | 1.5 |

[a] Quiescent cell line (Epithelioma Papulosum Cyprini (EPC)).

cytotoxic with an $IC_{50}$ value of 1.5 $\mu g\,mL^{-1}$ on the EPC line; this is only threefold higher than the lowest MIC measured for the same compound in combination with CIP (0.5 $\mu g\,mL^{-1}$). This slight difference observed in vitro between antibacterial and antiproliferative activities suggests that these silver–NHCs cannot selectively discriminate between healthy human cells and pathogenic bacteria. As for other silver-based antimicrobials, this may limit the application to the topical treatment of infections.[20]

In conclusion, we showed that silver–NHCs, previously used in catalysis and not specifically designed for biological applications, can exhibit significant antibacterial activity. Slight differences in the NHC ligand structure induce dramatic changes in the activity. Two of the complexes, including SIMesAgCl, were found to inhibit both susceptible and resistant strains of *S. aureus* at low and clinically achievable concentrations. Synergistic effects have been evidenced by combining silver–NHCs with CIP. These effects allow restoring the activity of CIP against resistant *S. aureus* NorA at very low silver concentrations. This could open new perspectives in the treatment of infections caused by resistant *S. aureus* and must be further explored. Similarly to various silver-based antibacterial drugs, these complexes are also cytotoxic in vitro on normal human cells at bactericidal concentrations. The most active complex with the lowest cytotoxicity on the EPC cell line is SIMesAgCl, which could be a potential candidate for the development of new topical antibacterial drugs. Studies are underway to further investigate the influence of the NHC structure on antibacterial activity and cytotoxicity and to explore the potential of these silver–NHCs as anticancer agents.

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**Keywords:** antibiotics · carbene ligands · cytotoxicity · silver · synergy

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[20] In vitro cytotoxicity, which measures nonspecific and late occurring cytotoxic events, is not comparable to in vivo toxicity. However, it is commonly recognized that $IC_{50}$ on human cells has to be at least two orders of magnitude higher than the MIC against bacteria for a compound to be further developed as a potential oral antibiotic.

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