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ARTICLE

Influence of selected inorganic counter-ions on the structure and antimicrobial properties of silver(I) complexes with imidazole-containing ligand

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Water-soluble silver(I) complexes containing 4(5)-(hydroxymethyl)imidazole ligand of the formula $[Ag(4\text{-}CH_2OHimH)_2]X$ (where X= NO_3^-, ClO_4^-, CF_3COO^-, BF_4^- and $SO_3CH_3^-$) were synthesized. The complexes were characterized by NMR (^1H and ^{13}C) and IR spectroscopy, ESI-MS spectrometry and EA. The molecular structures of three complexes were confirmed by X-ray crystallography. The antimicrobial activity of the silver(I) complexes were evaluated against six strains of microorganism: *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Escherichia coli, Pseudomonas aeruginosa, Proteus hauseri* and *Candida albicans*. All tested silver complexes displayed excellent antibacterial properties against Gram-positive bacteria. Among them, the complex containing trifluoroacetate counter-ion exhibited the highest antibacterial activity, with MIC values 2,3-fold lower than required by silver sulfadiazine.

Introduction

In the face of increasing difficulties in the treatment of infections caused by resistant pathogenic microorganisms, new broad-spectrum antimicrobial agents are required. The medication of infectious diseases is increasingly more often associated with high levels of morbidity and fatality rates as well as increasing costs.[1,2]

Study on novel antimicrobial agents amongst silver complexes group seems to be proved as silver(I) complexes are known to possess substantial antimicrobial activity[3-5] and have been demonstrated to be less toxic to the human body than other metal complexes.[6] Silver sulfadiazine (SSD or AgSD) is the most popular topical drug used in burn infections and other serious external infections.[7,8] Unfortunately, the drug is not devoid of side effects, including a toxicity to fibroblasts and keratinocytes that delays the wound healing process as well as associated gastrointestinal reactions and blood dyscrasias.[9-12]

In addition, the silver cation is an active ingredient of healthcare products such as wound dressings, urinary tract and venous catheters and mats.[3, 13-16]

Imidazole-containing drugs (ketoconazole, clotrimazole) are commonly used to treat infections caused by a fungus or yeast. A slightly different group of imidazole-based medications is based on nitroimidazole with different side chains (metronidazole, trinidazole, ornidazole, secnidazole), these being compounds with excellent activity against anaerobic micro-organisms and protozoa.[17]

Recently, a great deal of research interest has been directed toward the discovery of new antimicrobial molecules amongst imidazole-based derivatives.[18,19]

Numerous Ag(I) complexes containing imidazole derivatives have shown significant broad spectrum antimicrobial activity.[20-27] Interestingly, although free imidazole ligands displayed no activity against pathogenic microorganisms, their activity increased when complexed with silver ions. The components of the silver(I) complexes probably act synergistically.

Lately, a silver(I) complexes containing N-heterocyclic carbenes (NHCs) have gained a special attention as potential antimicrobial agents.[28-33] The research by Wiley J. Youngs and coworkers had a high impact on the development of this group of compounds. They established a syntheses of (benz)imidazole-derived NHC–silver(I) acetates, called SCC1 and SCC10, which were highly effective against pathogens recovered from the respiratory track of patients with cystic fibrosis.[34-38] In the meantime another researchers synthetized a various Ag-NCHs complexes by a modification of substituents on the imidazolum center to improve their antimicrobial efficacy.[39-41]

Our previous article reports a study of the antimicrobial activity of a series of silver(I) complexes of metronidazole and selected counter-ions. The complex containing a

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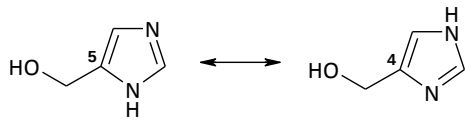


Scheme 1 Tautomeric forms of 4(5)-CH_2OHimH ligand

methanesulphonate counter-ion was found to be the most active against tested Gram-positive strains (*S. epidermidis* ATCC 12228 and *S. aureus* ATCC 6538) as well as yeast *C. albicans* ATCC 10231. However, it was not so active against tested Gram-negative strains. Nevertheless, the silver(I)-metronidazole complexes containing a perchlorate and a terafluroborate counter-ions were found to be very effective against tested Gram-negative bacteria.[42]

The aim of the present study is to determine the antimicrobial activity of a second series of novel silver(I) complexes containing 4(5)-(hydroxymethyl)imidazole [4(5)-CH_2OHimH] (Scheme 1) and selected counter-ions. It also analyses the impact of particular counter-ions (NO_3^-, ClO_4^-, CF_3COO^-, BF_4^- and $CH_3SO_3^-$) on the biological properties of tested complexes. The study describes the synthesis of five novel silver(I) complexes of 4-CH_2OHimH and selected counter-ions. The complexes are characterized by (^1H and ^{13}C) NMR and IR spectroscopy as well as ESI-MS spectrometry, three of which being described by X-ray measurements of single crystals.

Experimental

Reagents and physical measurements

4(5)-(hydroxymethyl)imidazole [4(5)-CH_2OHimH] and inorganic salts AgX (X= NO_3^-, ClO_4^-, CF_3COO^-, BF_4^- and $SO_3CH_3^-$) were purchased from Sigma-Aldrich.

Elemental analyses (C, H and N) were performed with an EuroVector 3018 analyzer. ^1H and ^{13}C NMR spectra were recorded on a Bruker Avance III 600 MHz spectrometer using D_2O as solvent. Infrared (IR) spectra were recorded in the region 4000-400 cm^{-1} on a Bruker IFS66 spectrophotometer using KBr pellets. Electrospray mass spectra (ESI-MS) were collected in positive ion mode on a Varian 500-MS LC Ion Trap using water as solvent.

Preparation and characterization of $[Ag(4\text{-}CH_2OHimH)_2]NO_3$ (1)

Silver nitrate (1 mmol, 0.170 g) was dissolved in ca. 10 ml of water and added to an aqueous solution (ca. 10 ml) of 4(5)-(hydroxymethyl)imidazole (2 mmol, 0.196 g). The reaction mixture was stirred for ca. 30 minutes at 60°C. Then the mixture was evaporated to dryness under reduced pressure (water bath: 70°C) giving a beige oil. The oil was dissolved in hot ethanol (60°C). A small amount of beige impurities was filtered and removed. The clear ethanol solution was left into refrigerator to slow evaporation. The white product which precipitated was washed with anhydrous ethyl ether and air-dried.

Yield: 0.304 g (83%); MW= 366.12. Anal. Calcd. for $C_8H_{12}N_5O_5Ag$ ($[Ag(4\text{-}CH_2OHimH)_2]NO_3$): C, 26.24; H, 3.31; N, 19.13%. Found: C, 26.25; H, 3.32; N, 19.11%. ESI-MS (H_2O) *m/z* (relative intensity): 303.1 (100) $[Ag(4\text{-}CH_2OHimH)_2]^+$, 205.0 (49) $[Ag(4\text{-}CH_2OHimH)]^+$. ^1H NMR (600 MHz, D_2O): δ 4.64 (s, 4H, 2xCH_2-O), 7.25 (s, 2H, 2xH(5)), 7.97 (s, 2H, 2xH(2)). ^{13}C NMR (151 MHz, D_2O): δ 138.0 (N=C-N), 137.1 (C5) (weak int.), 117.4 (C4), 56.3 (CH_2-O). IR (KBr) ν_{max} (cm^{-1}): (O-H, C-H) 3306(s, br), 2872(m); (C=N, C=C) 1766(w), 1654(w), 1591(m); (C-H) 1491(m); (NO_3) 1383(vs); (C-H) 1280(m), 1243(w), 1207(w); (C-O) 1106(w), 1089(m), 1027(s), 983(s); (im ring) 833(s), 749(m), 659(m), 620(s) (vs: very strong; s: strong; m: medium; w: weak, br: broad).

Preparation and characterization of complexes 2-4

4(5)-(Hydroxymethyl)imidazole [4(5)-CH_2OHimH] (2 mmol, 0.196g) was dissolved in ca. 10 ml of ethanol at room temperature. An ethanol solution (ca. 10 ml) of AgX (1 mmol) (X= ClO_4^- (0.207 g), CF_3COO^- (0.221 g), BF_4^- (0.195 g)) was add to the solution of 4(5)-CH_2OHimH and stirred for 10 minutes at 60°C. The reaction mixture was evaporated under reduced pressure (water bath: 60°C) to half the initial volume. A small amount of beige impurities was filtered and removed. The ethanol solution was left in the refrigerator to crystalize. After a few days colourless crystals suitable for X-ray determination were collected and washed with anhydrous diethyl ether.

$[Ag(4\text{-}CH_2OHimH)_2]ClO_4$ (2). MW= 403.56. Yield: 0.339 g (84%); ESI-MS (H_2O) *m/z* (relative intensity): 303.1 (100) $[Ag(4\text{-}CH_2OHimH)_2]^+$, 205.0 (7) $[Ag(4\text{-}CH_2OHimH)]^+$. Anal. Calcd. for $C_8H_{12}N_4O_6ClAg$ ($[Ag(4\text{-}CH_2OHimH)_2]ClO_4$): C, 23.81; H, 3.00; N, 13.89%. Found: C, 23.94; H, 3.01; N, 13.88%. ^1H NMR (600 MHz, D_2O): δ 4.66 (s, 4H, 2xCH_2-O), 7.28 (s, 2H, 2xH(5)), 7.96 (s, 2H, 2xH(2)). ^{13}C NMR (151 MHz, D_2O): δ 138.1 (N=C-N), 137.1 (C5) (weak int.), 117.6 (C4), 56.4 (CH_2-O). IR (KBr) ν_{max} (cm^{-1}): (O-H, C-H) 3270(s, br), 2876(m); (C=N, C=C) 1631(w), 1590(m); (C-H) 1492(m), 1448(m); (C-H) 1281(m), 1242(w); (ClO_4, C-O) 1146(vs), 1111(vs), 1089(vs), 1022(m), 982(s); (im ring) 835(m), 749(m), 660(m), 636(vs) (vs: very strong; s: strong; m: medium; w: weak, br: broad).

$[Ag(4\text{-}CH_2OHimH)_2]CF_3COO$ (3). MW= 417.13. Yield: 0.321 g (77%); ESI-MS (H_2O) *m/z* (relative intensity): 303.1 (78) $[Ag(4\text{-}CH_2OHimH)_2]^+$, 205.0 (100) $[Ag(4\text{-}CH_2OHimH)]^+$. Anal. Calcd. for $C_{10}H_{12}N_4O_4F_3Ag$ ($[Ag(4\text{-}CH_2OHimH)_2]CF_3COO$): C, 28.79; H, 2.91; N, 13.43%. Found: C, 29.00; H, 2.81; N, 13.40%. ^1H NMR (600 MHz, D_2O): δ 4.65 (s, 4H, 2xCH_2-O), 7.27 (s, 2H, 2xH(5)), 7.96 (s, 2H, 2xH(2)). ^{13}C NMR (151 MHz, D_2O): δ 162.9 ($\underline{C}F_3COO$) (weak int.), 138.1 (N=C-N), 137.1 (C5) (weak int.), 117.5 (C4), 115.5 ($CF_3\underline{C}OO$) (weak int.), 56.3 (CH_2-O). IR (KBr) ν_{max} (cm^{-1}): (O-H, C-H) 3386(s, br), 2932(w), 2869(w); (C=O) 1682 (vs) (C=N, C=C) 1632(w), 1595(w); (C-H) 1499(m), 1434(w), 1354(m), 1283(m); (CF_3COO) 1207(vs), 1137(s); (C-O) 1088(m), 1021(s), 981(s); (im ring) 840(s), 803(s), 750(w), 724(s), 627(s) (vs: very strong; s: strong; m: medium; w: weak, br: broad).

[Ag(4-CH_2OHimH)$_2$]BF_4 (4). MW= 390.92. Yield: 0.289 g (74%); ESI-MS (H_2O) *m/z* (relative intensity): 303.1 (100) [Ag(4-CH_2OHimH)$_2$]$^+$, 205.0 (66) [Ag(4-CH_2OHimH)]$^+$. Anal. Calcd. for $C_8H_{12}N_4O_2BF_4Ag$ ([Ag(4-CH_2OHimH)$_2$]BF_4): C, 24.58; H, 3.10; N, 14.34%. Found: C, 24.68; H, 2.82; N, 14.52%. ^{1}H NMR (600 MHz, D_2O): δ 4.65 (s, 4H, 2xCH_2-O), 7.26 (s, 2H, 2xH(5)), 7.93 (s, 2H, 2xH(2)). ^{13}C NMR (151 MHz, D_2O): δ 138.2 (N=C-N), 137.2 (C5) (weak int.), 117.7 (C4) (weak), 56.4 (CH_2-O). IR (KBr) ν_{max} (cm^{-1}): (O-H, C-H) 3117(s), 2870(s), 2794(s), 2613(m); (C=N, C=C) 1656(w), 1631(m,) 1572(m); (C-H) 1499(s), 1462(s), 1450(m), 1358(s), 1284(s), 1238(w); (BF_4, C-O) 1198(m), 1086(vs), 1021(s), 981(s), 953(s); (im ring) 848(s), 805(m), 751(m), 665(w), 627(s) (vs: very strong; s: strong; m: medium; w: weak).

Preparation and characterization of [Ag(4-CH_2OHimH)$_2$]SO_3CH_3 (5)

$AgSO_3CH_3$ (1 mmol, 0,203 g) was dissolved in ca. 20 ml of ethanol at 70°C. A solution of 4(5)-CH_2OHimH (2 mmol, 0.196g) in hot ethanol (ca. 10 ml) was added to the previous solution. The resulting mixture was stirred for 15 minutes at 70°C. A small amount of a beige solid was filtered off and the solution was evaporated to one-third of the initial volume and left to crystalize. The white solid precipitated the following day was washed with anhydrous diethyl ether.

Yield: 0.252 g. MW= 399.22. Anal. Calcd. for $C_9H_{15}N_4O_5SAg$ ([Ag(4-CH_2OHimH)$_2$]SO_3CH_3): C, 27.08; H, 3.79; N, 14.04%. Found: C, 27.01; H, 3.80; N, 13.98%. ESI-MS (H_2O) *m/z* (relative intensity): 303.1 (100) [Ag(4-CH_2OHimH)$_2$]$^+$, 205.0 (19) [Ag(4-CH_2OHimH)]$^+$. ^{1}H NMR (600 MHz, D_2O): δ 2.80 (s, 3H, CH_3), 4.63 (s, 4H, 2xCH_2-O), 7.24 (s, 2H, 2xH(5)), 7.92 (s, 2H, 2xH(2)). ^{13}C NMR (151 MHz, D_2O): δ 138.1 (N=C-N), 137.1 (weak int.) (C5), 117.4 (C4) (weak), 56.3 (CH_2-O), 38.6 (CH_3). IR (KBr) ν_{max} (cm^{-1}): (O-H, C-H) 3118(s), 2932(s), 2870(m), 2794(m); (C=N, C=C) 1631(m), 1572(m); (C-H) 1499(m), 1450 (m), 1357(s), 1284(s), 1239(w); (SO_3) 1195(vs) (C-O) 1088(m), 1058(vs), 1021(s), 981(s); (im ring) 847(m), 785(s), 665(w), 627(s) (vs: very strong; s: strong; m: medium; w: weak).

4(5)-CH_2OHimH (given for comparative purposes). MW= 98.12. ^{1}H NMR (600 MHz, D_2O): δ 4.59 (s, 2H, CH_2-O), 7.13 (s, 1H, H(4(5)), 7.73 (s, 1H, H(2)). ^{13}C NMR (151 MHz, D_2O): δ 136.9 (C4(5)) (weak int.), 136.3 (N=C-N), 117.3 (C5(4)), 56.1 (CH_2-O).

Light stability of the complexes 1-5 and salts S1-S5

A cotton pads were impregnated with 0,025 mol/l aqueous solutions of the complexes **1**-**5** and their appropriate silver salts **S1**-**S5** and then exposed to indirect light in air atmosphere at room temperature. The stability was monitored visually within 120 hours (5 days). The photos of the samples were placed in Electronic Supplementary Information (Fig. S1†).

X-ray crystal structure determination

X-ray data for compounds **2**-**4** were measured from single crystals using an Agilent SuperNova diffractometer with an Atlas detector at T=100(2)K with monochromatic MoKα radiation (λ=0.71073 Å). Multi-scan absorption correction was applied for all data.[43] All structures were solved by direct methods using SHELX and further refined on F^2 using SHELXL-2014/7.[44] All non-hydrogen atoms were refined anisotropically.

The fluorine atoms (F1, F2, F3) in CF_3COO^- anion in structure **3** were found to be disordered and as a consequence refined over two position with ratio 0.56(2): 0.42(2). To the disordered components appropriate restraints of geometry and displacement parameters using SADI and EADP commands were applied.

In structure **4** the hydroxymethyl group is disordered over two position with ratio 0.731(4): 0.269(4).

In all structures heteoaromatic NH and hydroxyl OH atoms were located on the Fourier difference map and refined with isotropic thermal parameters.

The position of remaining hydrogen atoms were calculated from known geometry (C-H bond lengths at 0.95, 0.99 Å for aromatic CH and methylene CH_2 atoms, respectively) and treated as riding, where the isotropic thermal parameters of these hydrogen atoms were fixed as U_{iso}(H)=1.2U_{eq}(C) for H atoms. However, atomic coordinates for H4A1, H4A2, H4B1, H4B2 in disordered hydroxymethyl group of structure **4** and hydroxyl H1A and H1B atoms were refined with C-H and O-H distances restrained to 0.99 and 0.84 Å, respectively. Basic experimental details and crystallographic data are presented in Table 1.

Further crystallographic details for the structure reported in this paper may be obtained from the Cambridge Crystallographic Data Center, on quoting the depository numbers: CCDC-1411662 (**2**), CCDC-1411663 (**3**) and CCDC-1411664 (**4**).

Antimicrobial activity determination

The antibacterial and antifungal properties of synthesized complexes, free ligand and silver sulfadiazine were evaluated against two Gram-positive strains: *Staphylococcus aureus* ATCC 6538 and *Staphylococcus epidermidis* ATCC 12228, three Gram-negative bacteria: *Pseudomonas aeruginosa* ATCC 15442, *Escherichia coli* ATCC 25922, *Proteus hauseri* ATCC 13315 and yeast *Candida albicans* ATCC 10231. The Minimum Inhibitory Concentration (MIC) and Minimum Bactericidal Concentration (MBC)/Minimum Fungicidal Concentration (MFC) were determined by a modified broth microdilution method according to the recommendation of Clinical & Laboratory Standards Institute(M07-A8) for bacteria and Standards of European Committee on Antimicrobial Susceptibility Testing (EDef7.1.) for fermentative yeasts with modifications. The MIC and MBC values were expressed in μmol L^{-1}.

Results and discussion

Synthesis and structural characterization

The silver(I) complexes **1**-**5** containing 4-(hydroxymethyl)-imidazole ligands were obtained by a stirring and heating the

Table 1 Crystallographic data for **2**-**4**

	2	3	**4**
Empirical formula	$C_{32}H_{48}N_{16}O_{24}Cl_4Ag_4$	$C_{20}H_{24}N_8O_8F_6Ag_2$	$C_{16}H_{24}N_8O_4B_2F_8Ag_2$
Formula weight	1614.14	834.21	781.79
Crystal system	Triclinic	Monoclinic	Triclinic
Space group	$P\bar{1}$	$P2_1/c$	$P\bar{1}$
a (Å)	10.6600(2)	7.7766(2)	7.9688(3)
b (Å)	10.7580(2)	15.2479(3)	9.2044(2)
c (Å)	13.6855(3)	11.6266(2)	9.3306(3)
α (°)	106.201(2)	90.000	73.719(3)
β (°)	95.799(2)	97.599(2)	76.471(3)
γ (°)	119.067(2)	90.000	74.445(2)
V (Å^3)	1263.90(6)	1366.54(5)	623.48(4)
Z	1	2	1
T (K)	100(2)	100(2)	100(2)
F(000)	800	824	384
D_x (g cm^{-3})	2.121	2.027	2.082
μ (mm^{-1})	1.84	1.53	1.67
Scan method	ω scan	ω scan	ω scan
θ range (°)	2.2-30.0	2.2-27.0	2.3-30.0
Measured reflections	16910	15057	6974
Unique reflections	7321	2983	3626
Observed reflections [$I>2\sigma(I)$]	7007	2950	3532
Completeness to θ_{max} (%)	99.4	100	99.7
No. of parameters/restraints	394/0	219/16	211/18
R [$I>2\sigma(I)$]	0.017	0.029	0.021
wR (all data)	0.046	0.067	0.050
S	1.10	1.14	1.05
Largest diff. peak (e Å^{-3})	0.61	1.97	0.69
Largest diff. hole (e Å^{-3})	-0.51	-0.36	-0.94

ligand (2 moles) with the appropriate silver salts AgX (X= NO_3^-, ClO_4^-, CF_3COO^-, BF_4^- and $SO_3CH_3^-$) (1 mol) in ethanol or water solution for a short time.

Colourless products were isolated in ca. 70-80% yields. All products were soluble in water, methanol and hot ethanol. The novel complexes were characterized using spectroscopic methods including (^{1}H and ^{13}C) NMR and IR spectroscopy, ESI-MS spectrometry as well as X-ray diffraction analysis.

As shown in Scheme 1, the ligand 4(5)-CH_2OHimH exists in two tautomeric forms. The form containing the hydroxymethyl group in position 4 is preferable in the complexes **2**-**4**, as was unambiguously confirmed by X-ray determination. Although the ligand is able to form five-membered chelate rings with metal ions,[45,46] it acts as a monodentate ligand coordinated through the nitrogen atom (N^3) in the complexes **2**-**4**. The same way of coordination was observed in isostructural Cd(II)[47] and Zn(II)[48] complexes of 4-CH_2OHimH and tri-tert-butoxysilanethiolate, in which the oxygen atom of the hydroxymethyl group also does not act as an electron donor, the hydroxyl group of the 4(5)-CH_2OHimH forms an intramolecular hydrogen bond with sulfur O-H···S. The coordination mode of a very similar ligand, 4(5)-CH_2OH-5(4)-CH_3imH, in the Co(II), Cu(II) and Ni(II) complexes, where the ligands present a dualistic nature, appears somewhat different. Two of the ligands act as monodentate (N^3) and two other as bidentate (O,N^3).[49,50]

The ^{1}H NMR spectra of complexes **1**-**5** and free ligand were submitted in ESI as Fig. S2†. The spectra are virtually identical as they differ from each other only by the counter-ions. In the spectrum of free ligand 4(5)-CH_2OHimH, three singlets at 7.73 ppm, 7.13 ppm and 4.59 ppm are observed and can be attributed to the respective proton signals H(2), H(4(5)) and CH_2O. Although the ligand exists in tautomeric forms (Scheme 1), the presence of these two forms are not visible in the ^{1}H NMR spectrum of the D_2O solvent. The NH proton of the imidazole ring is not observed in the spectrum because it is

exchanged for deuterium, the same as the hydroxyl proton. Accordingly, it is impossible to state which tautomeric form (4 or 5) exists in the complexes. Finally, the X-ray crystal structures of complexes **2-4** and a literature review[47,48] indicates that the tautomeric form 4 is also preferable in the complexes **1** and **5**. A comparison of the spectra of **1**-**5** with the spectrum of free ligand revealed slight shifts of the signals to a higher field, ca. 0.24 ppm, 0.16 ppm and 0.08 ppm. The greatest shift was observed for the signal of H(2) proton located in the neighborhood of the coordination site (*N3*). Weak displacement of the signals of the Ag(I) complexes with respect to free ligands seemed to be specific to silver complexes in solution.[51-53]

The ^{13}C NMR spectra of **1-5** and the free ligand are very similar. The signals of the carbons C(2) of **1-5** are shifted at ca. 1.7 ppm compared to the ligand. The signals of further carbon atoms are nearly unaffected, ca. 0.1-0.3 ppm. The spectrum of **5** contains an additional peak at 38.6 ppm attributed to $CH_3SO_3^-$ group, and the spectrum of **3** contains two weak peaks at 162.9 ppm and 115.5 ppm assigned to the CF_3COO^- counter-ion.

Light stability study

As the silver complexes **1**-**5** are potential antimicrobial agents for external application on infected skin in form of creams, gels or impregnated wound dressings, the stability of complexes **1**-**5** when exposed to indirect light at room temperature was tested. Cotton pads were impregnated with 0,025 mol/l aqueous solutions of **1**-**5** and their appropriate silver salts **S1**-**S5** for comparison purposes. The stability of the samples was monitored visually within 120 hours (Fig. S1†).

The treatment of infections with silver nitrate salt has a negative side, namely its solutions make the skin and dressings darken. The light stability test on cotton pads will show whether solutions of **1-5** cause the cotton pads to blacken.

The results were generally positive, as complexes **1-5** had clearly better light stability than their appropriate silver salts **S1-S5**. Cotton pads treated with complexes **1**-**5** started to become gently beige only after 44 hours. The referenced silver salts **S1-S5** caused the pads to become dark brown after that period. Salts **S1-S5** induced greater darkening of the pads after 4 h of exposure than complexes **1-5** did after 44 h. All the cotton pads impregnated by **1-5** appeared similar and were coloured grey-beige after 5 days of light exposure.

Crystal and molecular structures 2-4

X-ray single-crystal structure of 2. The molecular structure of complex **2** is shown in Figure 1*a*, and selected bond lengths and angles around Ag atoms are listed in Table 2.

The crystal structure of complex **2** crystalizes in $P\bar{1}$ space group with a monomer, half of a centrosymmetric dimer and two ClO_4^- ions in the asymmetric unit. In the monomer, the Ag2 atom is coordinated approximately linearly by two nitrogen atoms (N5, N7) from imidazole rings with the N5-Ag2-N7 angle equal to 172.87(4)°. However, the coordination sphere is complemented by the short interaction between the Ag2 and O11^{ii} atoms (symmetry code (ii) 2-*x*,1-*y*,-*z*) (Figure 2a and Table 2). In the crystal lattice two Ag2 ions only weakly interact, the distance separating them being 3.4282(3) Å, which is on the border of sum of the van der Waals' radius for silver(I).

The centrosymmetric dimer includes two $[Ag(L)_2]^+$ (L= 4(5)-CH_2OHimH) units with an Ag1-Ag1^i short length of 3.2205(2) Å (symmetry code (i) 1-*x*, -*y*, 1-*z*). This is in agreement with other Ag-Ag lengths observed for silver complexes.[24,42,54,55] Each Ag1 atom is coordinated by two imidazole nitrogens, N1 and N3, with N1-Ag1-N3 of 166.21(3)° angle, which is smaller than in the monomer. The environment of the central ion is completed by a short Ag1···O2^i (symmetry code (i) 1-*x*, -*y*, 1-*z*) (Figure 2*a* and Table 2).

In the crystal packing of complex **2**, oxygens from hydroxymethyl groups act as donors in several O-H···O hydrogen bonds and together with N-H···O hydrogen bonds (Table 3) form a 3-D network. Additionally, it is stabilized by π···π interactions between particular imidazole rings with the centroid separation distances ranging from 3.529(1) to 3.904(1) Å (Table 4). Interestingly, when looking down the *a*-axis, it can be observed a form of layered structure in the crystal packing. Between layers created by π···π stacking interactions, ClO_4^- anions are located with short O6···O6 (2-*x*, 2-*y*, 1-*z*) and O12···O12 (1-*x*, -*y*, -*z*) interactions with corresponding distances: 2.841(2) and 2.897(2) Å (Figure 2*b*).

X-ray single-crystal structure of 3. The silver complex **3** crystalizes in the monoclinic group $P2_1/c$. Crystal structure analysis (Figure 1*b*. and Table 2) showed complex **3** to be centrosymmetric dimer, containing two $[Ag(L)_2]^+$ units. The two metal ions are two-coordinated by N1 and N3 imidazole nitrogens with nearly linear coordination for each monomeric complex. The N1-Ag1-N3 angle is 166.46(9)°, while the N1-Ag1-Ag1^i and N3-Ag1-Ag1^i angles are 114.09(6)° and 73.21(6)°. These values clearly indicate the distortion of the linear geometry around every separate Ag atom. The Ag1-Ag1^i bond length is 3.2044(4) Å. Two imidazole rings are not coplanar, the dihedral angle between rings is 8.2(1)°. The silver bond lengths are essentially similar to those in **2**. The coordination of the Ag metal center is additionally completed by two weak Ag1···O2 and Ag1···O3^i interactions (symmetry code (i) 1-x, 1-y, 1-z) (see Fig. 2 and Table 2). Further the crystal packing of complex **3** is enhanced by a combination of a net of O-H···O and N-H···O hydrogen bonds forming 2-D layers perpendicular to the *a*-axis. These 2-D sheets of molecules create double ribbons propagating along the *b*-axis which are strengthened by π···π stacking interactions between centrosymmetrically related imidazole rings. The Cg1···Cg2^i distance is 3.666(2) Å and Cg1···Cg2^{iv} distance is 4.153(2) Å (symmetry codes (i) 1-*x*, 1-*y*, 1-*z*; (iv) 2-*x*, 1-*y*, 1-*z*). Part of the crystal packing of complex **3** with Ag···O and other intermolecular hydrogen interactions is presented in Fig. 2 and appropriate geometric parameters are in Table 3 and 4.

X-ray single-crystal structure of 4. The triclinic (space group $P\bar{1}$) crystal structure of complex **4** consists of discrete centrosymmetric dimeric cation $[Ag_2(L)_4]^{2+}$ consisting of two

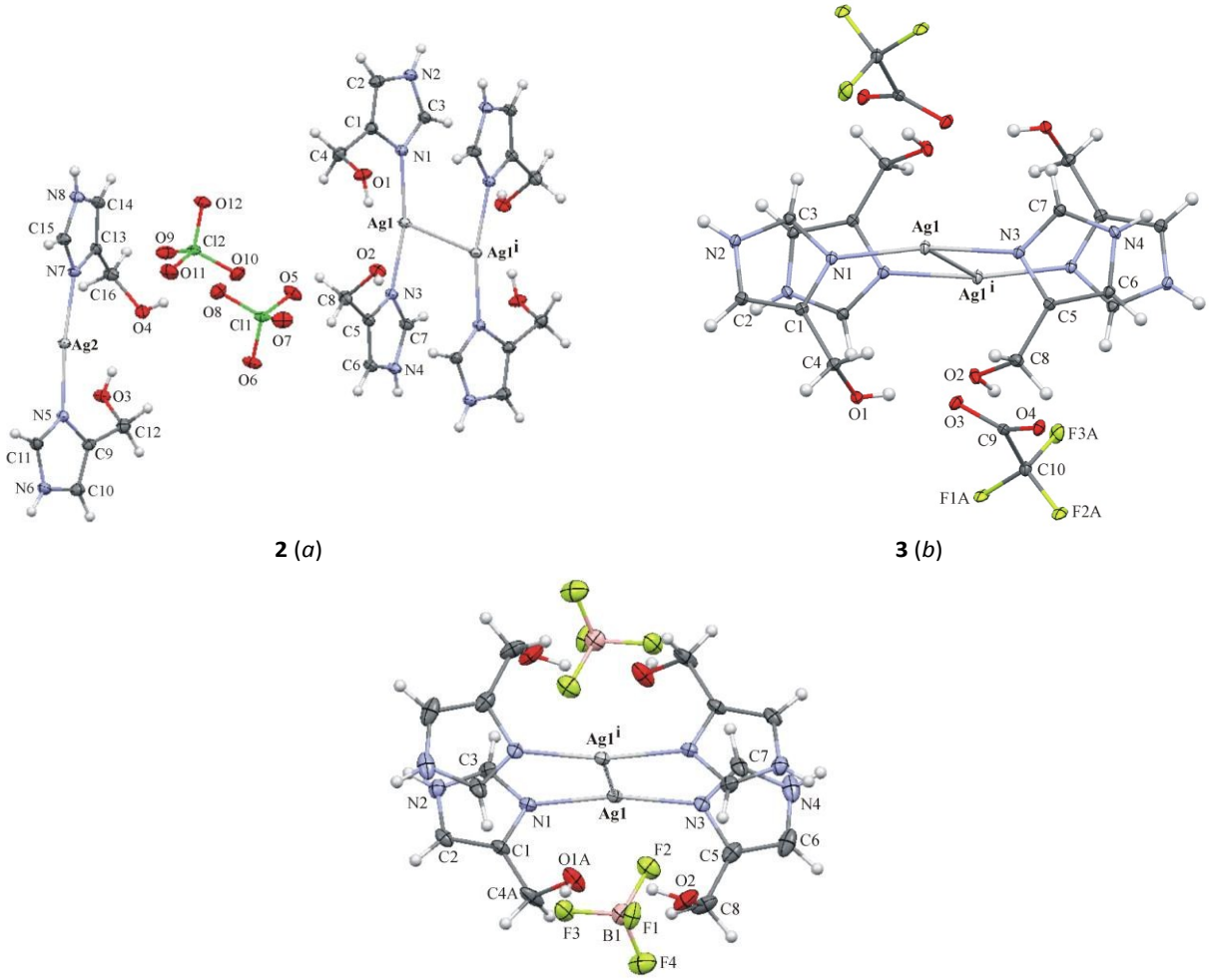
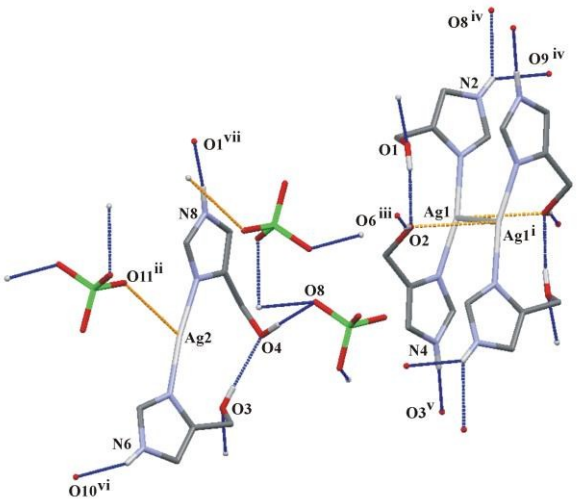


Fig. 1 Crystal structure of Ag complexes with different counter-ions : ClO_4^- (**2**) (a), CF_3COO^- (**3**) (b), BF_4^- (**4**) (c) with displacement ellipsoids at the 30% probability level. For clarity the major parts of disordered atoms (A) are only drawn: F1A, F2A, F3A atoms in CF_3COO^- (**3**) ion and C4A, O1A, H1A atoms in hydroxymethyl group (**4**).
Symmetry codes: (**2**) (i) 1-*x*, -*y*, 1-*z* ; (**3**) (i) 1-*x*, 1-*y*, 1- *z*; (**4**) (i) 1-*x*, 1-*y*, 1-*z*.

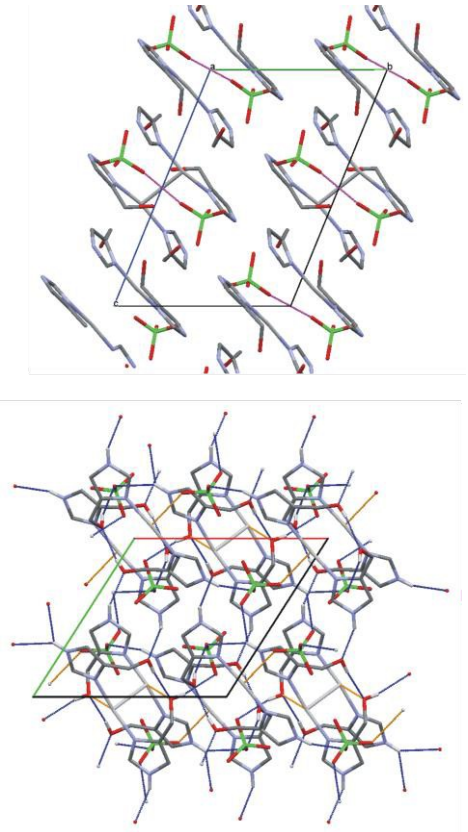
Table 2. Selected geometrical parameters (Å,°) for **2–4**

2				**3**		**4**	
Bond lengths							
Ag1-N1	2.1024(11)	Ag2-N5	2.0959(10)	Ag1-N1	2.106(2)	Ag1-N1	2.0900(15)
Ag1-N3	2.0963(10)	Ag2-N7	2.0919(10)	Ag1-N3	2.108(2)	Ag1-N3	2.0938(16)
Ag1···O2^{i}	2.9091(11)	Ag2···O11^{ii}	3.0123(13)	Ag1···O2	3.089(2)	Ag1···O1A^{i}	3.079(3)
Ag1-Ag1^{i}	3.2205(2)	Ag2···Ag2^{viii}	3.4282(3)	Ag1···O3^{i}	2.875(2)	Ag1···Ag1^{i}	3.2967(3)
				Ag1-Ag1^{i}	3.2044(4)		
Bond angles							
N1-Ag1-N3	166.21(4)	N5-Ag2-N7	172.87(4)	N1-Ag1-N3	166.46(9)	N1-Ag1-N3	169.28(6)
Ag1^{i}-Ag1-N1	101.29(3)			Ag1^{i}-Ag1-N1	114.09(6)	Ag1^{i}-Ag1-N1	80.69(4)
Ag1^{i}-Ag1-N3	83.52(3)			Ag1^{i}-Ag1-N3	73.21(6)	Ag1^{i}-Ag1-N3	103.53(4)

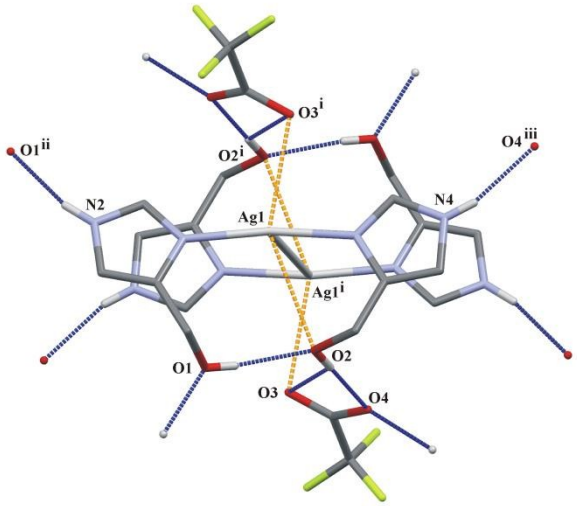
Symmetry codes: (**2**) (i) 1-*x*, -*y*, 1-*z*; (ii) 2-*x*,1-*y*,-*z*; (viii) 2-x, 2-y, -z; (**3**) (i) 1-*x*, 1-*y*, 1-*z*; (**4**) (i) 1-*x*, 1-*y*, 1-*z*;



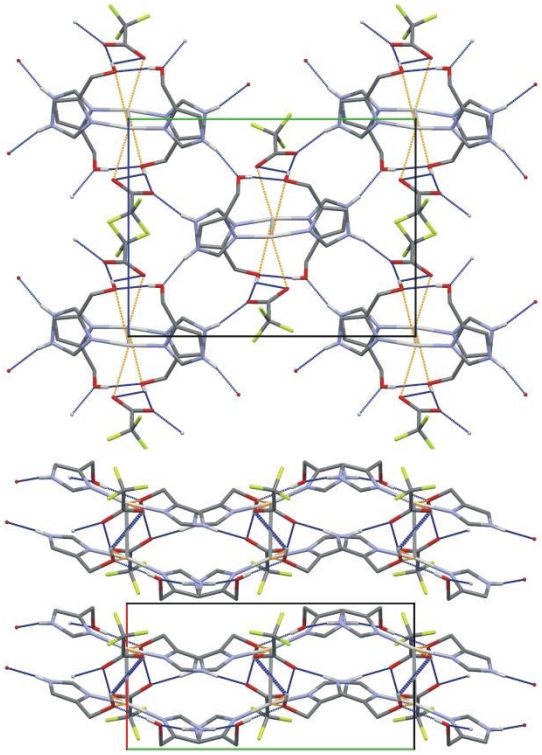
2 (*a*)



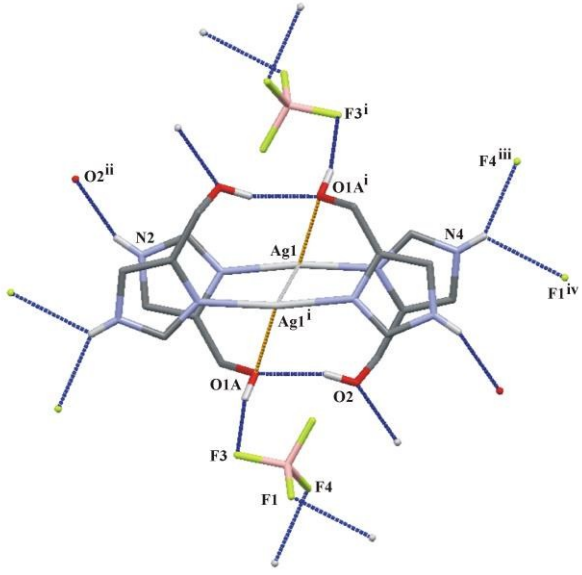
2 (*b*)



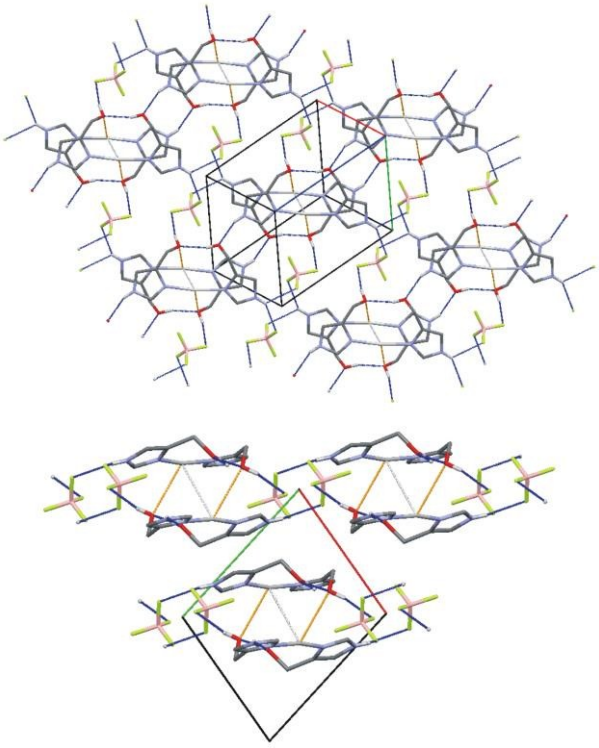
3 (*c*)



3 (*d*)



4 (*e*)



4 (*f*)

Fig. 2 A part of crystal structures (**2**-**4**) (a, c, e) showing weak interactions to Ag(I) (yellow dotted), Ag···Ag contact (grey dotted lines) and hydrogen bonds (blue dotted lines). On the right the crystal packing diagrams for complexes **2**-**4** are presented: (b): upper figure - layered molecular packing with O···O interactions (magenta lines); lower figure presents 3-D molecular network (along *c*) of complex **2** and solvent, (d) 2-D supramolecular network of sheets in complex **3** (upper figure – along *a* axis and lower figure- along *c* axis); (f) formation of 3-D molecular network in complex **4** (upper figure) and 2-D layers perpendicular to [110] direction (lower figure). Hydrogen atoms not involved in hydrogen bonds are omitted for clarity.
Symmetry codes:
(**2**) (i) 1-*x*, -*y*, 1-*z*; (ii) 2-*x*,1-*y*,-*z*, (iii) *x*, *y*-1, *z*; (iv) *x*-1, *y*-1, *z*; (v) 2-*x*, 2-*y*, 1-*z*; (vi) 1+*x*, 1+*y*, *z*; (vii) 1-*x*, -*y*, -*z*;
(**3**) (i) 1-*x*, 1-*y*, 1-*z*, (ii) *x*, 3/2-*y*, *z*-½; (iii) *x*, ½-*y*, *z*-½;
(**4**) (i) 1-*x*, 1-*y*, 1-*z*; (ii) *x*, *y*, 1+*z*; (iii) *x*-1, 1+*y*, *z*; (iv) 1-*x*, 1-*y*, -*z*;

$[Ag(L)_2]^+$ units, where Ag1…Ag1^i (symmetry code (i) 1-*x*, 1-*y*, 1-*z*) interaction is formed with a distance of 3.2967(3) Å and two BF_4^- anions. The environment around every silver atom is defined by two nitrogen atoms (N1 and N3) of imidazole ligands with nearly linear coordination. The N1-Ag1-N3 angle is 169.28(6)^o being between analogous angles in **2** and **3**. The silver donor bond lengths are similar to those in **2** and slightly shorter than corresponding bonds in **3**. The coordination sphere around the silver atom is completed by the oxygen atom O1A^i (symmetry code (i) 1-*x*, 1-*y*, 1-*z*) from the hydroxymethyl group.
In case of the crystal packing of **4**, the molecules are linked by a combination of N-H···O/F and Ag···O interactions (Figure 2*f* and Table 3). The formation of the molecular framework can be described as 2-D sheets perpendicular to [110] direction, consisting of double ribbons which are formed by N2-H20…O2^{ii} (symmetry code (ii) *x*, *y*, 1+*z*) hydrogen bonds and Ag1···O1A^i (symmetry code (i) 1-*x*, 1-*y*, 1-*z*) interaction (lower Figure 2*f*). Neighboring ribbons are linked by π···π interactions with separation distance between centroids 3.540(1) and 4.234(1) Å, respectively for Cg1···Cg2 (1-*x*, 1-*y*, 1-*z*) and Cg2···Cg2 (-*x*, 1-*y*, 1-*z*;). In the crystal packing further O2-H2A···O1A intramolecular interaction as well as other O1A-H1A···F3, N4-H40···F4^{iii} (symmetry code (iii) *x*-1, 1+*y*, *z*) and N4-H40···F1^{iv} (symmetry code (iv) 1-*x*, 1-*y*, -*z*) intermolecular interactions are observed.

Antimicrobial activity

Newly synthesized silver(I) complexes with 4-(hydroxymethyl)-imidazole **1-5** were assessed for antimicrobial activity against six strains of microorganisms: *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Escherichia coli, Pseudomonas aeruginosa, Proteus hauseri* and *Candida albicans*. Their antimicrobial properties were compared with the biological activity of free ligand 4(5)-(hydroxymethyl)imidazole and silver sulfadiazine (AgSD), the most widely used silver drug. The studies revealed that the tested imidazole ligand lack antibacterial and antifungal activity in concentrations up to 500 mg L^{-1}. The obtained MIC (Minimum Inhibitory Concentration) (Figure 3) and MBC (Minimum Bactericidal Concentration) (Table 5) values indicated that complexes **1-5** exhibit excellent activity against tested Gram-positive bacteria

Table 3. Hydrogen bonding geometry (Å,°) for **2** – **4**.

H-bond	D-H	H···A	D···A	∠D-H···A
2				
O1-H1A···O2	0.82(2)	2.01(2)	2.823(1)	173(2)
O2-H2A···O6^{iii}	0.79(2)	2.10(2)	2.870(1)	168(2)
N2-H20···O8^{iv}	0.87(2)	2.47(2)	2.179(2)	140(2)
N2-H20···O9^{iv}	0.87(2)	2.31(2)	2.921(2)	128(2)
N4-H40···O3^{v}	0.85(2)	2.02(2)	2.794(1)	151(2)
O3-H3A···O4	0.76(3)	2.00(3)	2.755(1)	169(3)
O4-H4A···O8	0.79(2)	2.25(2)	3.014(2)	165(2)
N6-H60···O10^{vi}	0.83(2)	2.15(2)	2.935(1)	157(2)
N8-H80···O1^{vii}	0.88(2)	1.97(2)	2.777(2)	153(2)
3				
O1-H1A···O2	0.72(4)	1.97(5)	2.690(3)	172(5)
O2-H2A···O3	0.81(4)	2.67(4)	3.222(3)	127(4)
O2-H2A···O4	0.81(4)	1.90(4)	2.709(3)	177(4)
N2-H20···O1^{ii}	0.84(2)	1.91(3)	2.733(3)	166(4)
N4-H40···O4^{iii}	0.80(4)	2.01(4)	2.787(3)	164(4)
4				
O2-H2A···O1A	0.84	1.92	2.741(3)	164
O1A-H1A···F3	0.84	2.01	2.832(3)	165
N2-H20···O2^{ii}	0.80(3)	2.05(3)	2.776(3)	152(3)
N4-H40···F4^{iii}	0.82(4)	2.23(4)	2.936(3)	143(3)
N4-H40···F1^{iv}	0.82(4)	2.45(4)	2.994(2)	124(3)

Symmetry codes: (**2**) (iii) *x*, *y*-1, *z*; (iv) *x*-1, *y*-1, *z*; (v) 2-*x*, 2-*y*, 1-*z*; (vi) 1+*x*, 1+*y*, *z*; (vii) 1-*x*, -*y*, -*z*; (**3**) (ii) *x*, 3/2-*y*, *z*-½; (iii) *x*, ½-*y*, *z*-½;(**4**) (ii) *x*, *y*, 1+*z*; (iii) *x*-1, 1+*y*, *z*; (iv) 1-*x*, 1-*y*, -*z*;

Table 4. Parameters describing aromatic π···π stacking interactions for **2** – **4**:
Cg···*Cg* – distance between ring centroids (Å), *Cg*I_(J)/*Cg*J_(I) – perpendicular distance of *Cg*(I) on ring J [and *Cg*(J) on ring I, respectively] (Å), ∠ α - dihedral angle between planes I and J (°).

Cg(I)···*Cg*(J)	*Cg*I···*Cg*J	*Cg*I_(J)	*Cg*J_(I)	∠ α
2				
*Cg*1···*Cg*2^{i}	3.529(1)	-3.476(1)	-3.379(1)	15.3(1)
*Cg*1···*Cg*3^{iv}	3.904(1)	-3.222(1)	3.283(1)	2.1(1)
*Cg*3···*Cg*4^{viii}	3.584(1)	3.485(1)	3.470(1)	17.6(1)
3				
*Cg*1···*Cg*2^{i}	3.666(2)	-3.460(1)	-3.255(1)	8.2(2)
*Cg*1···*Cg*2^{iv}	4.153(2)	3.635(1)	3.313(1)	8.2(1)
4				
*Cg*1···*Cg*2^{i}	3.540(1)	3.402(1)	3.481(1)	14.2(1)
*Cg*2···*Cg*2^{v}	4.234(1)	-3.283(1)	-3.283(1)	0.0(1)

Symmetry codes:
(**2**) (i) 1-*x*, -*y*, 1-*z*; (iv) *x*-1, *y*-1, *z*; (viii) 2-*x*, 2-*y*, -*z*;
(**3**) (i) 1-*x*, 1-*y*, 1-*z*; (iv) 2-*x*, 1-*y*, 1-*z*;
(**4**) (i) 1-*x*, 1-*y*, 1-*z*; (v) -*x*, 1-*y*, 1-*z*;

(*S. aureus* and *S. epidermidis*). All the complexes inhibited the growth of Gram-positive bacteria at concentrations much lower than those required by silver sulfadiazine (AgSD). Among them, the highest antibacterial properties were expressed by complex **3**, containing trifluoroacetate as a counter-ion: The complex inhibited the growth of *S. aureus* and *S. epidermidis* at a concentration 2,3-fold lower than that established for AgSD. Moreover, all the tested silver compounds showed better bactericidal activity (Table 5) against Gram-positive strains than referenced silver sulfadiazine. In case of *S. aureus,* the MBC values of complex **3** and AgSD were 71 µM and 252 µM, respectively.

The antimicrobial properties of the complexes **1-5** towards Gram-negative bacteria and yeasts are insignificant. Their activity are about two times lower than commercially available AgSD**.**

The obtained results are in agreement with our previous studies[42], which indicated that silver(I) complexes of metronidazole displayed better antibacterial activity against Gram-positive bacteria than Gram-negative strains and yeasts.

Although silver(I) complexes with N-heterocyclic carbenes, described in the introduction part,[28-41] have completely different mode of coordination than the complexes **1-5**, both the groups show moderate to excellent antimicrobial activity.

MIC values of the Ag-NHCs range from 0,25 to 6 µg mL^{-1} for the best ones,[56] but usually from 25 to 200 µg mL^{1}, depending on the tested strains. The activity of the complexes **1-5** is similar and amounts to ca. 30-40, when expressed in µg mL^{-1}. Overall, the Ag-NHCs are effective against highly resistant bacteria strains, such as MRSA, *P. aeruginosa, E. coli* or *B. subtilis.*

Silver(I) complexes with imidazole or benzimidazole moieties are known to be effective antimicrobial drugs.[57,58] Silver(I) complexes of 2-hydroxymethyl-*N*-alkylimidazoles displayed meaningful antimicrobial activity against *E. coli* and *B. spizizenii* depending on the alkyl chain length.[24] Further study found that the incorporation of the above mentioned ligands and their Ag(I) complexes into electrospun nylon 6 nanofibers produces attractive antimicrobial materials.[25]

Rowan et al.[20] investigated the growth of inhibitory effects of silver(I) complexes containing imidazole derivatives against the pathogenic bacteria MRSA and *E. coli* and the fungal pathogen

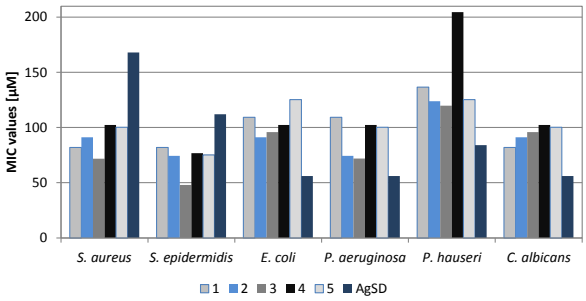


Fig. 3 Antibacterial activity of silver(I) complexes containing 4(5)-(hydroxymethyl)imidazole, given as MIC (Minimum Inhibitory Concentration). MIC values of the free ligand are >500 mg L^{-1}.

Table 5. MBC (Minimum Bactericidal Concentration) values of the tested compounds.

Tested compound	MBC [μM]					
	S. aureus ATCC 6538	*S. epidermidis* ATCC 12228	*E. coli* ATCC 25922	*P. aeruginosa* ATCC 15442	*P. hauseri* ATCC 13315	*C. albicans* ATCC 10231
1	109	109	164	137	219	>273
2	91	124	91	124	173	>248
3	71	96	120	72	144	>240
4	153	153	179	102	230	>256
5	200	150	175	125	175	>250
AgSD	252	224	84	56	84	56

C. albicans. Amongst five investigated Ag(I)-imidazole (imH) complexes, two of them, i.e. $[Ag_2(imH)_4](salH)_2$ ($salH_2$= salicylic acid) and $[Ag(MeNO_2imH)_2]ClO_4$, exhibited significant bacterial effects which were better or comparable of those of AgSD. All of them also showed excellent activity against *C. albicans*, especially the complex $[Ag_2(imH)_4](salH)_2$, which was 47 times more active than ketoconazole.

Similarly, silver(I) complexes of 9-anthracenecarboxilic acid and *N*-substituted imidazoles demonstrated very high antifungal activity about 10 times better than the activity of ketoconazole, against *C. albicans*. These compounds possess also meaningful antibacterial activity toward *E. coli* and MRSA.[21]

Other Ag(I) complexes containing substituted imidazole ligands, i.e. bis(imidazole-2-yl)methane and its derivatives[22] and (imidazol-1-yl)-2-phenylpropenenitrile[23], displayed only moderate activity against *C. albicans*.[22]

The antimicrobial activity of Ag(I) histidines (proteinogenic amino acids containing an imidazole functional group) against selected bacteria, yeasts and molds was compared of that of $AgNO_3$, which was effective only against two Gram-negative bacteria. Most of the tested silver(I)-histidines showed a wider spectrum of activity than $AgNO_3$.[26,27] Significantly, all of the mentioned metal-free imidazole ligands were found to be inactive against the considered pathogens.

Conclusions

Silver(I) complexes containing 4(5)-(hydroxymethyl)imidazole ligand (L) and various counter-ions were successfully synthesized and characterized by elemental, ESI-MS, NMR and IR analysis. X-ray crystal structures of complexes **2**-**4** were also determined. Complex **2** consists of a monomeric unit $[Ag(L)_2]ClO_4$ and dimeric unit $[Ag_2(L)_4](ClO_4)_2$, while complexes **3** and **4** consist only of dimeric units $[Ag_2(L)_4](CF_3COO)_2$ (**3**) and $[Ag_2(L)_4](BF_4)_2$ (**4**). The crystal packing of **2** is dominated by a 3-D network of hydrogen bonds. Characteristic feature of molecular arrangement of **3** and **4** is 2-D sheets forming by hydrogen bonds and Ag···O interactions.

The study on the antimicrobial activity of a series of novel silver(I) complexes of 4(5)-CH_2OHimH and selected counter-ions, i.e. NO_3^-, ClO_4^-, CF_3COO^-, BF_4^- and $CH_3SO_3^-$, was done. We evaluated the impact of particular counter-ions on the biological properties of the tested complexes. The results suggested that the variation of the counter-ions of the complexes affected their antimicrobial activity. The complex containing CF_3COO^- as a counter-ion had the highest activity against Gram-positive bacteria. It differs from our previous research[42] in which we studied silver complexes metronidazole (MTZ) and various counter-ions. Those data showed that $CH_3SO_3^-$ counter-ion contributed to the highest antimicrobial activity against Gram-positive bacteria and yeasts. However, both series of the silver complexes, viz. containing 4(5)-CH_2OHimH and MTZ ligands, displayed better activity against Gram-positive bacteria than Gram-negative strains and yeasts. It is probably associated with the differences in the structure of cell wall and membrane of particular microorganisms.

Newly synthesized silver complexes exhibit significant antibacterial properties against Gram-positive bacteria, better than commercially available silver sulfadiazine. In future they may represent an attractive alternative for existing drugs. In addition, all complexes are water soluble which is desirable feature of potential antimicrobial drugs.

Acknowledgements

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Notes and references

‡ Footnotes relating to the main text should appear here. These might include comments relevant to but not central to the matter under discussion, limited experimental and spectral data, and crystallographic data.

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etc.

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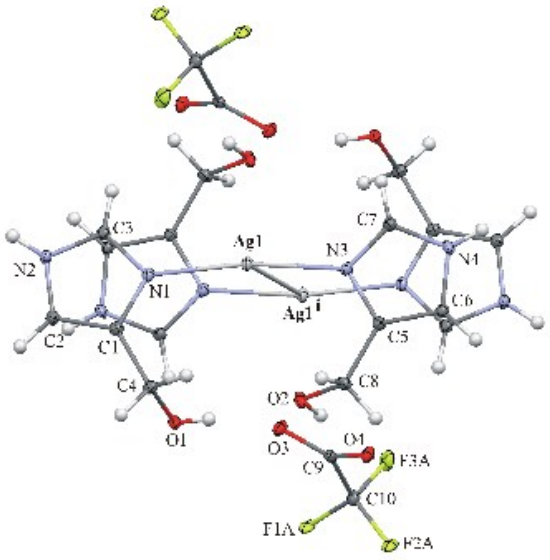
Newly synthetized silver(I) complexes with 4(5)-(hydroxymethyl)imidazole and selected counter-ions show significant activity against Gram-positive bacteria, especially this containing trifluoroacetate counter-ion.



$[Ag(4\text{-}CH_2OHimiH)_2]CF_3COO$