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Antimicrobial activity and DNA/BSA binding study of new silver(I) complexes with 1,8-naphthyridine

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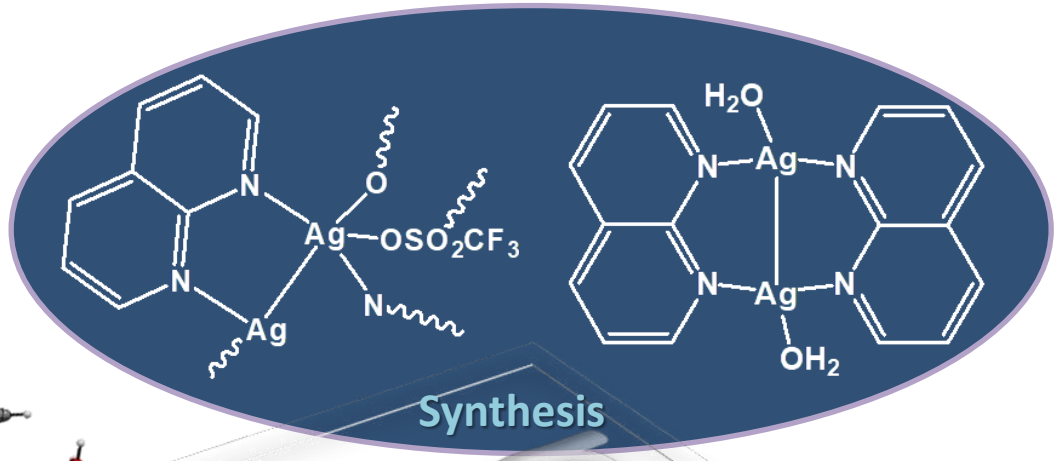


Structural characterization

DNA binding study

Antimicrobial susceptibility testing

Protein binding studies

Abstract

Among different classes of ligands used for the synthesis of biologically active silver(I) complexes, a special attention was devoted to the aromatic nitrogen-containing heterocycles. Considering this, in the present study, we have synthesized two new silver(I) complexes with 1,8-naphthyridine (1,8-naph), polynuclear $[Ag(CF_3SO_3)(1,8\text{-naph})]_n$ (**Ag1**) and dinuclear $[Ag(1,8\text{-naph})(H_2O)]_2(PF_6)_2$ (**Ag2**), and evaluated their antimicrobial activity against Gram-positive and Gram-negative bacteria, as well as *Candida* spp. The obtained results revealed that these silver(I) complexes showed significant activity toward the Gram-positive *Staphylococcus aureus* and *Candida* spp. The values of binding constants of **Ag1** and **Ag2** to BSA are high enough to indicate their interaction to this biomolecule, but not so strong to prevent their release upon arrival to the target site. The partition coefficient (log*P*) values for **Ag1** and **Ag2** are -0.14 and 0.37, respectively, what is in accordance with those for pharmacophores in the Comprehensive Medicinal Chemistry database. The investigated silver(I) complexes inside the cell could interact with DNA through the non-intercalative (electrostatic) mode.

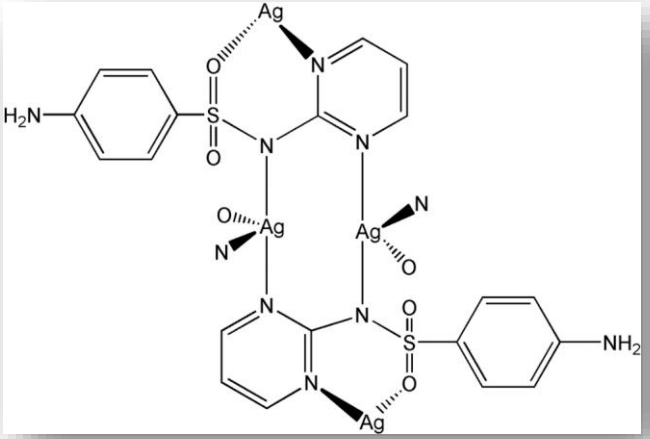
Keywords: Silver(I) complexes; 1,8-Naphthyridine; Antimicrobial activity; DNA/BSA interaction.

Introduction

- Silver(I) compounds are well known for their pharmacological applications as antibiotics and have been also evaluated as potential anticancer agents

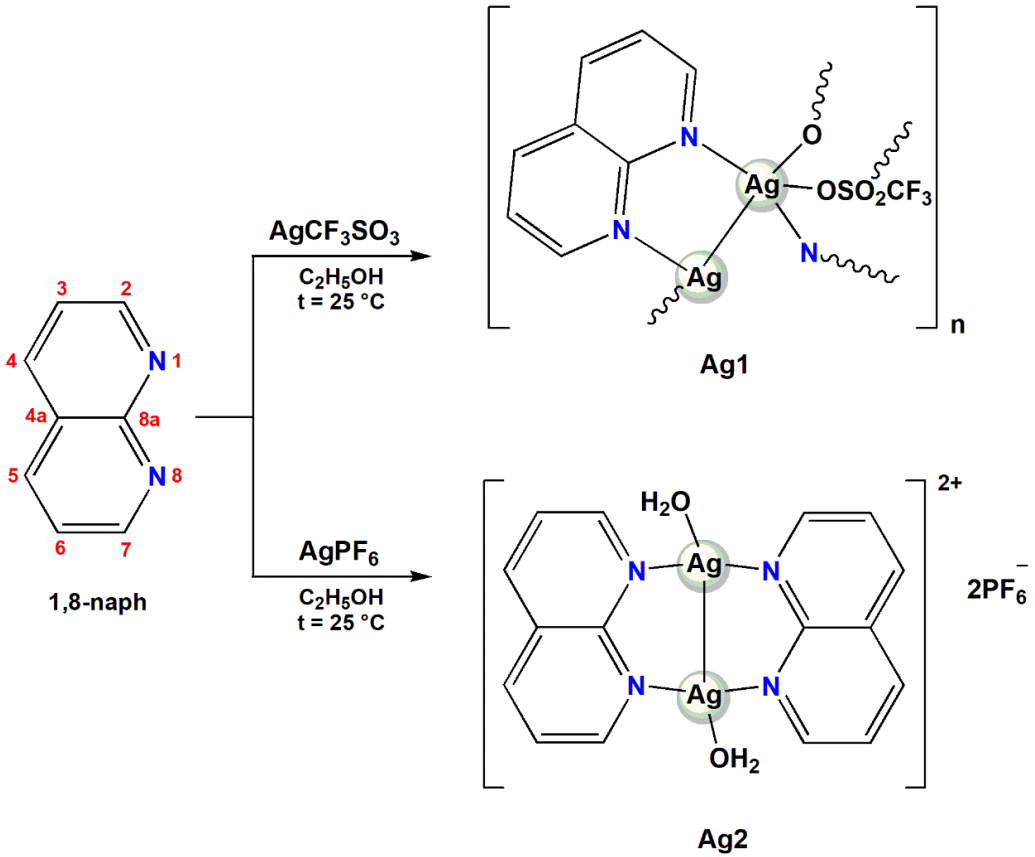
- The use of simple silver(I) salts, such as $AgNO_3$, as an antimicrobial agent, has been limited due to the formation of AgCl precipitate under the physiological conditions, preventing a major part of Ag(I) ions to reach the infected site

- On the other hand, a slow and maintainable release of Ag(I) ion into the infected cell or tissue could be achieved by its administration in the form of complexes (such as silver(I) sulfadiazine)



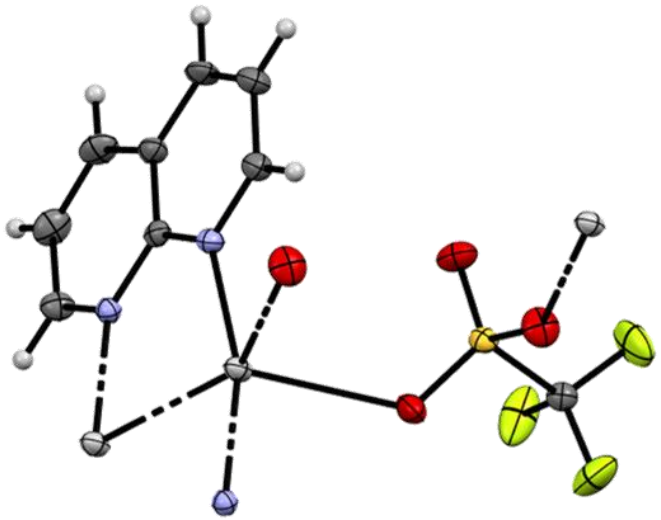
Results and discussion

- ✓ Silver(I) complexes were synthesized according to the presented procedure

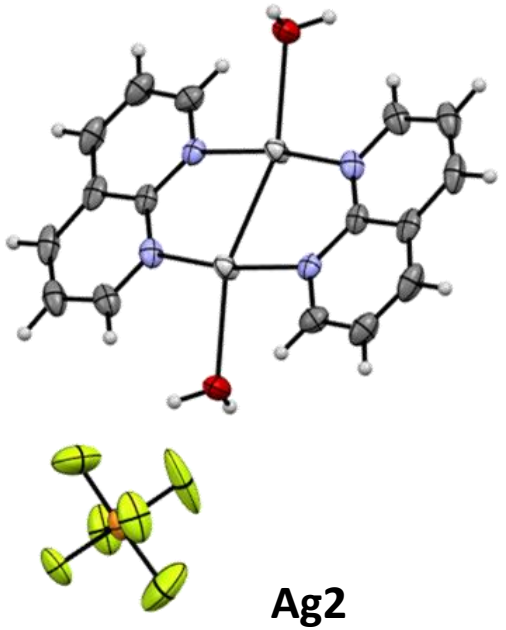


Structural characterization

- ✓ The synthesized complexes were characterized by elemental analysis, UV-Vis, IR, ^{1}H and ^{13}C NMR spectroscopy, mass spectrometry and cyclic voltammetry, while their structure was determined by a single-crystal X-ray diffraction analysis



Ag1



Ag2

Antimicrobial susceptibility testing

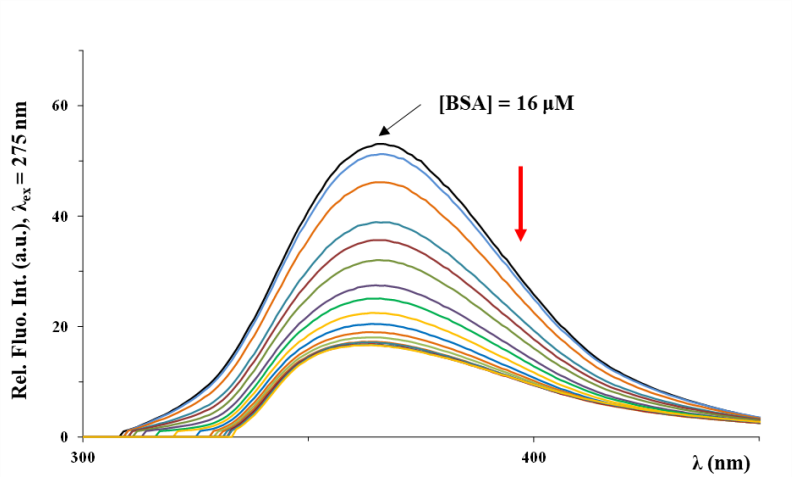
Antimicrobial activity of silver(I) complexes and the corresponding 1,8-naphthyridine ligand expressed as MIC (μg/mL) in comparison to their cytotoxicity against healthy human fibroblasts MRC-5 (IC_{50}, μg/mL)

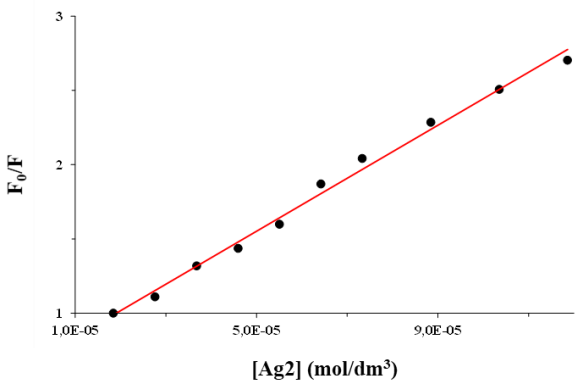
Test organism / Compounds	*Candida albicans* ATCC 10231	*Candida parapsilosis* ATCC 22019	*Staphylococcus aureus* ATCC 25923	*Listeria monocytogenes* NCTC 11994	*Escherichia coli* NCTC 9001	MRC-5
Ag1	3.91	3.91	7.81	15.62	31.25	3.65
Ag2	3.91	7.81	7.81	125	15.62	3.75
1,8-naph	> 200	> 200	> 250	> 250	> 250	> 100

Protein binding studies

✓ The affinity of silver(I) complexes to BSA was studied using florescence spectroscopy

[Ag2] = 0 - 120 µM, Phosphate buffer saline (pH = 7.4)



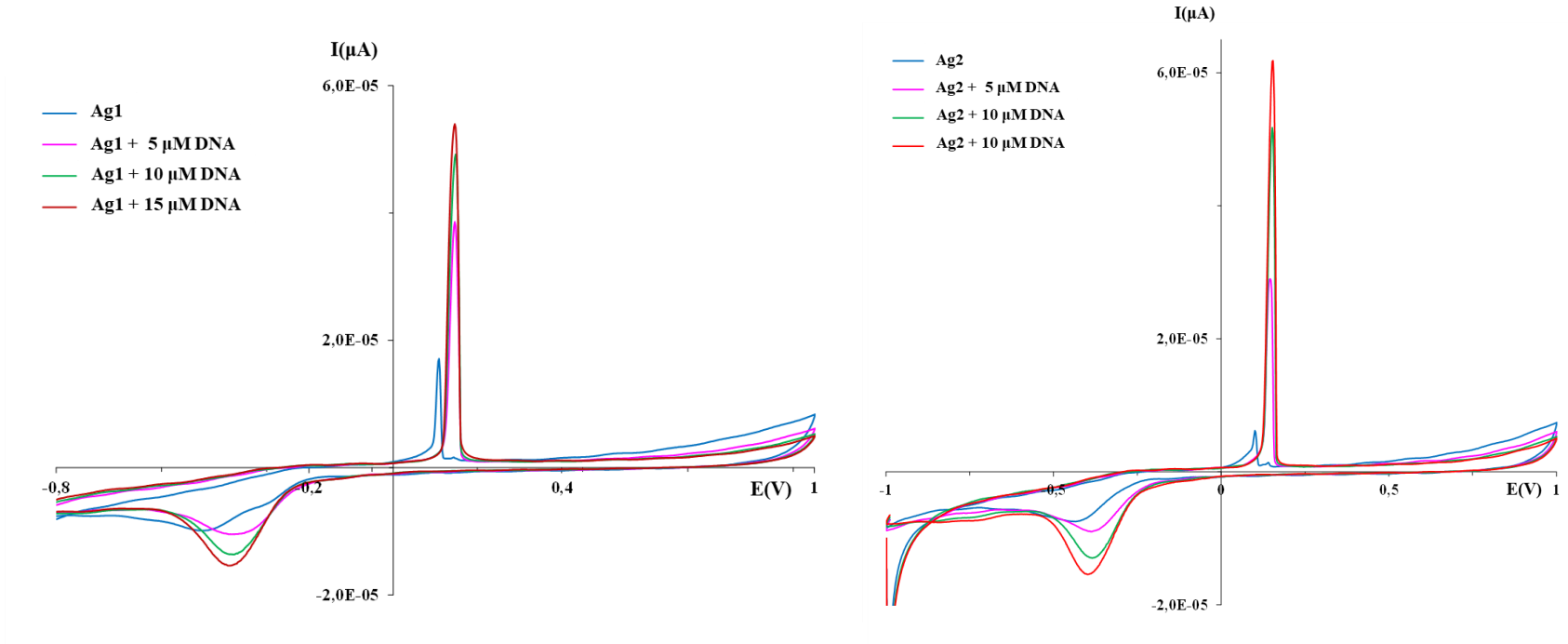


Complex	K_{SV} (M^{-1})	Hypochromism (%)	K_q ($M^{-1}s^{-1}$)	K_A (M^{-1})	n
Ag1	$(1.21 \pm 0.02)\cdot10^4$	71.92	$1.21\cdot10^{12}$	$7.42\cdot10^4$	1.22
Ag2	$(2.70 \pm 0.05)\cdot10^4$	68.70	$2.70\cdot10^{12}$	$6.08\cdot10^5$	1.37

Fluorescence emission spectra of BSA in the presence of an increasing concentration of **Ag2** complex alongside with the values of the binding constants for both complexes. Arrow shows the intensity changes upon increased amount of the complex.
Inserted graph: Stern-Volmer plots of F_0/F *vs* [complex]

DNA binding study

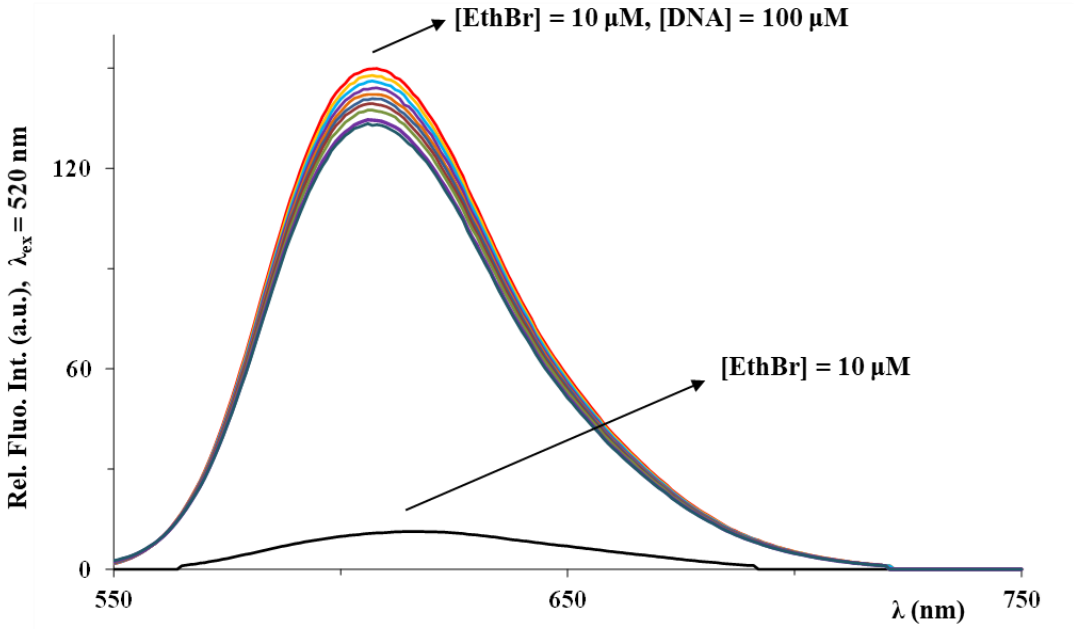
✓ DNA interaction of Ag1 and Ag2 was studied by cyclic voltammetry and florescence spectroscopy

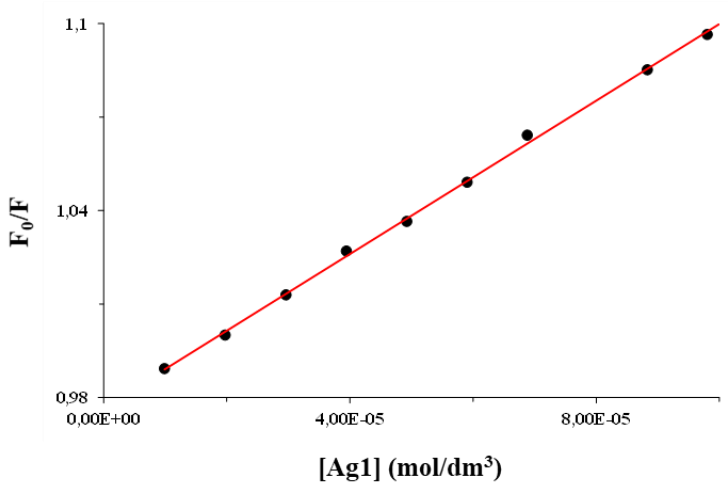


Cyclic voltammograms of the silver(I) complexes **Ag1** and **Ag2** in the absence and presence of DNA at GC electrode in DMSO/PBS with a scan rate of 50 mV/s

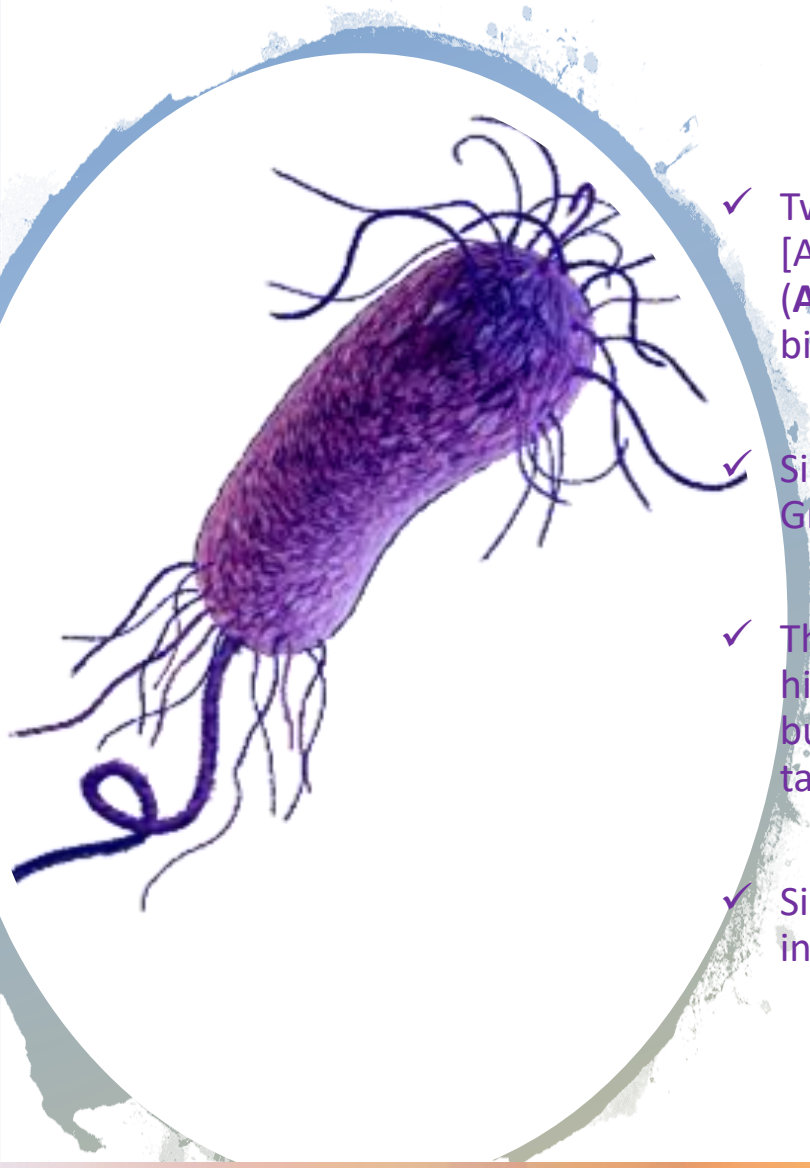
DNA binding study

[complex Ag1] = 0 – 100 µM, Phosphate buffer saline (pH = 7.4)





Fluorescence emission spectra of DNA-EthBr system in the presence of an increasing concentration of **Ag1** complex. Inserted graph: Stern-Volmer plots of F_0/F *vs* [complex]



Conclusions

- ✓ Two silver(I) complexes with 1,8-naphthyridine (1,8-naph), $[Ag(CF_3SO_3)(1,8\text{-naph})]_n$ (**Ag1**) and $[Ag(1,8\text{-naph})(H_2O)]_2(PF_6)_2$ (**Ag2**) were synthesized, structurally characterized and biologically evaluated
- ✓ Silver(I) complexes showed significant activity toward the Gram-positive *Staphylococcus aureus* and *Candida* spp.
- ✓ The values of binding constants of **Ag1** and **Ag2** to BSA are high enough to indicate their interaction to this biomolecule, but not so strong to prevent their release upon arrival to the target site
- ✓ Silver(I) complexes interact with DNA through the non-intercalative (electrostatic) mode

Acknowledgments

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