Silver(I) complexes with 4,7-phenanthroline efficient in rescuing the zebrafish embryos of lethal *Candida albicans* infection

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Abstract

Five novel silver(I) complexes with 4,7-phenanthroline (4,7-phen), [Ag(NO₃-O)(4,7-phen-μ-N4,N7)]ₙ (1), [Ag(ClO₄-O)(4,7-phen-μ-N4,N7)]ₙ (2), [Ag(CF₃COO-O)(4,7-phen-μ-N4,N7)]ₙ (3), [Ag₂(H₂O)₀.₅₈(4,7-phen)₃](SbF₆)₂ (4) and {[Ag₂(H₂O)(4,7-phen-μ-N4,N7)₂](BF₄)₂}ₙ (5) were synthesized, structurally elucidated and biologically evaluated. These complexes showed selectivity towards Candida spp. in comparison to the tested bacteria and effectively inhibited the growth of four different Candida species, particularly of C. albicans strains, with minimal inhibitory concentrations (MICs) in the range of 2.0 – 10.0 µM. In order to evaluate the therapeutic potential of 1 – 5, in vivo toxicity studies were conducted in the zebrafish model. Based on the favorable therapeutic profiles, complexes 1, 3 and 5 were selected for the evaluation of their antifungal efficacy in vivo using the zebrafish model of lethal disseminated candidiasis. Complexes 1 and 3 efficiently controlled and prevented fungal filamentation even at sub-MIC doses, while drastically increased the survival of the infected embryos. Moreover, at the MIC doses, both complexes totally prevented C. albicans filamentation and rescued almost all infected fish of the fatal infection outcome. On the other side, complex 5, which demonstrated the highest antifungal activity in vitro, affected the neutrophils occurrence of the infected host, failed to inhibit the C. albicans cells filamentation and showed a poor potential to cure candidal infection, highlighting the importance of the in vivo activity evaluation early in the therapeutic design and development process. The mechanism of action of the investigated silver(I) complexes was related to the induction of reactive oxygen species (ROS) response in C. albicans, with DNA being one of the possible target biomolecules.

Keywords: Silver(I) complexes; Phenanthroline; DNA interaction; Candida albicans; Danio rerio; Infection model
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$^13$C NMR spectrum of 5  

Fig. S1. An extended view of the polynuclear complex 3.  
Fig. S2. Complex 4 stability over time measured by $^1$H NMR spectroscopy. $^1$H NMR spectrum was measured immediately (A) and 24 h (B) after complex dissolution in DMSO-$d_6$.  
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Fig. S6. (A) Fluorescence emission spectra of EthBr bound to DNA in the absence and presence of the silver(I) complexes in Tris buffer at 25 °C. Arrow shows the change upon increasing concentration of complex. (B) Stern-Volmer plots of relative EthBr-DNA fluorescence intensity F0/F vs [complex].

Fig. S7. Plot of log(F0 - F)/F vs log[complex].

Fig. S8. CV voltammograms of DNA after addition of complex 4 in the concentrations range from 0 to 250 ppm.

Fig. S9. Toxicity evaluation of silver(I) complexes 1, 3 and 5 in the zebrafish model. The normally developed fish are shown on the left panel of photos including the control one (DMSO-treated), while the affected (teratogenic) fish are shown on the right panel. In comparison to the untreated fish, the teratogenic fish upon complexes showed signs of weak hepatotoxicity – slightly darker liver (boxed area), weakly absorbed the yolk (asterics) and shorter body, had weak pericardial edema (arrow) and lordosys (dashed area).

Fig. S10. Eradication of C. albicans infection from the body of zebrafish larvae after the 3 days treatments with different doses (½×MIC, 1×MIC and 2×MIC) of silver(I) complexes 1, 3 and 5. In the untreated embryos at 3 dpi (120 hpf), fungal infection has mainly been localized in the head (arrow) and the intestine (dashed arrow). Complexes 1 and 3 successfully inhibited fungal filamentation by 4 dpi at any applied dose, while the treatment with 5 resulted in the filamentation increase with complex’s concentration increase.

Table S1

Details of the crystal structure determinations of the silver(I) complexes 1 – 5.
Supplementary Information

Table S2

Lethal and teratogenic effects observed in zebrafish (Danio rerio) embryos at different hours post fertilization (hpf).

Table S3

Selected bond distances (Å) and valence angles (°) in silver(I) complexes 1 – 5.

Table S4

Hydrogen bond parameters for silver(I) complexes 4 and 5.

Table S5

Values of binding constants of silver(I) complexes 1 – 5 with DNA.
$^1$H NMR (400 MHz, DMF-$d_7$)

\[ \text{N} \quad \text{Ag} \quad \text{ONO}_2 \]

\[ \text{[Ag(NO}_3\text{-O})(4,7\text{-phen}-\mu\text{-N}_4\text{,N}_7)]_n \quad (1) \]
$^{13}$C NMR (101 MHz, DMF-$d_7$)

[Ag(NO$_3$-$O$)(4,7-phen-$\mu$-N$_4$,N$_7$)]$_n$

(1)
$^{1}$H NMR (400 MHz, DMF-d$_7$)

\[
[\text{Ag(ClO}_4-O)(4,7\text{-phen-µ-N}_4,N_7)]_n
\]

(2)
$^{13}$C NMR (101 MHz, DMF-$d_7$)

[Ag(ClO$_4$-O)(4,7-phen-$\mu$-N$_4$,N$_7$)$_n$]$_n$ (2)

DMF
$^1$H NMR (400 MHz, DMF-$d_7$)

\[ \text{[Ag(CF}_3\text{COO-O}(4,7\text{-phen}-\mu-\text{N}_4,\text{N}_7)]_n} \]

(3)
$^{13}$C NMR (101 MHz, DMF-$d_7$)

$$[\text{Ag(CF}_3\text{COO-O})(4,7\text{-phen-}\mu-N_4,N_7)]_n$$

(3)

[Diagram of the molecule]
$^1$H NMR (400 MHz, DMF-$d_7$)

[Ag$_2$(H$_2$O)$_{0.58}$(4,7-phen)$_3$]SbF$_6$$_2$ (4)

DMF
$^{13}$C NMR (101 MHz, DMF-$d_7$)

$[\text{Ag}_2(\text{H}_2\text{O})_{0.58}(4,7\text{-phen})_3](\text{SbF}_6)_2$ (4)
$^1$H NMR (400 MHz, DMF-$d_7$)

![NMR Spectrum]

$\text{[Ag(4,7-phen)\agn(4,7-phen)(H}_2\text{O)}(\text{BF}_4]\text{)}_n}$

(5)
$^{13}$C NMR (101 MHz, DMF-$d_7$)

\[
\{[\text{Ag}(4,7\text{-phen})][\text{Ag}(4,7\text{-phen})(\text{H}_2\text{O})](\text{BF}_4)\}_n \quad (5)
\]
Fig. S1. An extended view of the polynuclear complex 3.
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**Fig. S3.** Complex 4 stability over time followed by UV-Vis spectrophotometry in DMF/RPMI medium containing 2% of glucose.
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Supplementary Information
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Table S1

Details of the crystal structure determinations of the silver(I) complexes 1 – 5.

<table>
<thead>
<tr>
<th></th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
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<tbody>
<tr>
<td><strong>Empirical formula</strong></td>
<td>C₁₂H₈AgN₃O₃</td>
<td>C₁₂H₈AgClN₂O₄</td>
<td>C₁₄H₈AgF₃N₂O₃</td>
<td>C₃₆H₂₅.₁₅Ag₂F₁₂N₆O₀.₅₈Sb₂</td>
<td>C₂₈H₁₉Ag₂B₂F₃N₆O</td>
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<td><strong>CCDC number</strong></td>
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<td>1879002</td>
<td>1879003</td>
<td>1879004</td>
<td>1880758</td>
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<td><strong>Formula weight (g/mol)</strong></td>
<td>350.08</td>
<td>387.52</td>
<td>401.09</td>
<td>1238.21</td>
<td>767.78</td>
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<td><strong>Crystal system, space group</strong></td>
<td>monoclinic, P2₁/c</td>
<td>monoclinic, P2₁/c</td>
<td>monoclinic, P2₁/c</td>
<td>triclinic, PⅠ</td>
<td>triclinic, PⅠ</td>
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<td><strong>a (Å)</strong></td>
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<td>10.2659(6)</td>
<td>11.7244(14)</td>
<td>10.7878(8)</td>
<td>7.1974(4)</td>
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<td><strong>b (Å)</strong></td>
<td>14.485(2)</td>
<td>14.6602(11)</td>
<td>14.7916(16)</td>
<td>12.1188(8)</td>
<td>11.8682(6)</td>
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<td><strong>c (Å)</strong></td>
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<td>7.9925(7)</td>
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<td>14.5250(10)</td>
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<td><strong>α (°)</strong></td>
<td>82.918(5)</td>
<td>79.146(4)</td>
<td>85.176(6)</td>
<td>88.316(6)</td>
<td>76.397(4)</td>
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<td><strong>β (°)</strong></td>
<td>100.585(17)</td>
<td>97.922(6)</td>
<td>95.644(10)</td>
<td>83.316(6)</td>
<td>82.976(4)</td>
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<td><strong>γ (°)</strong></td>
<td>1123.5(4)</td>
<td>1191.39(15)</td>
<td>1286.5(3)</td>
<td>1877.4(2)</td>
<td>1224.75(12)</td>
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<td><strong>V (Å³)</strong></td>
<td>688</td>
<td>760</td>
<td>784</td>
<td>1184</td>
<td>748</td>
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<td><strong>Z</strong></td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>2</td>
<td>2</td>
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<tr>
<td><strong>X-radiation, λ /Å</strong></td>
<td>Mo-Kα 0.71073</td>
<td>Mo-Kα 0.71073</td>
<td>Mo-Kα 0.71073</td>
<td>Mo-Kα 0.71073</td>
<td>Mo-Kα 0.71073</td>
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<td><strong>data collect. temperat. /K</strong></td>
<td>298(2)</td>
<td>250(2)</td>
<td>298(2)</td>
<td>250(2)</td>
<td>200(2)</td>
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<td><strong>Calculated density (Mg/m³)</strong></td>
<td>2.070</td>
<td>2.160</td>
<td>2.071</td>
<td>2.190</td>
<td>2.082</td>
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<td><strong>Absorption coefficient (mm⁻¹)</strong></td>
<td>1.801</td>
<td>1.931</td>
<td>1.612</td>
<td>2.551</td>
<td>1.689</td>
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<tr>
<td><strong>Crystal size (mm³)</strong></td>
<td>0.64 x 0.26 x 0.02</td>
<td>0.38 x 0.167 x 0.04</td>
<td>0.39 x 0.17 x 0.05</td>
<td>0.37 x 0.183 x 0.07</td>
<td>0.30 x 0.15 x 0.06</td>
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<tr>
<td><strong>2θ range (°)</strong></td>
<td>3.8 to 50.5</td>
<td>4.0 to 50.5</td>
<td>3.4 to 50.6</td>
<td>2.8 to 50.5</td>
<td>3.5 to 50.2</td>
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<tr>
<td><strong>index ranges h, k, l</strong></td>
<td>-12 ... 12, -17 ... 17, -8 ... 8</td>
<td>-12 ... 12, -17 ... 17, -9 ... 9</td>
<td>-14 ... 13, -17 ... 17, -8 ... 8</td>
<td>-12 ... 12, -14 ... 14, -17 ... 17</td>
<td>-8 ... 8, -14 ... 14, -17 ... 17</td>
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<tr>
<td><strong>No. of collected and independent reflections</strong></td>
<td>12782, 2013</td>
<td>12271, 2126</td>
<td>16077, 2296</td>
<td>6286, 6286</td>
<td>13046, 4351</td>
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<td><strong>Rint</strong></td>
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<td>0.0371</td>
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<td>0.0929</td>
<td>0.2586</td>
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<tr>
<td><strong>Data / restraints / parameters</strong></td>
<td>2013 / 0 / 172</td>
<td>2126 / 0 / 181</td>
<td>2296 / 0 / 199</td>
<td>6286 / 57 / 408</td>
<td>4351 / 3 / 376</td>
</tr>
<tr>
<td><strong>Goodness-on-fit on F²</strong></td>
<td>1.040</td>
<td>1.034</td>
<td>1.055</td>
<td>1.041</td>
<td>1.045</td>
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<tr>
<td><strong>Final R indices</strong></td>
<td>0.0362, 0.0727</td>
<td>0.0232, 0.0546</td>
<td>0.0346, 0.0800</td>
<td>0.0929, 0.2586</td>
<td>0.0237, 0.0628</td>
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<tr>
<td><strong>[I ≥ 2σ(I)]</strong></td>
<td>0.0543, 0.0779</td>
<td>0.0348, 0.0579</td>
<td>0.0497, 0.0888</td>
<td>0.1125, 0.2837</td>
<td>0.0268, 0.0645</td>
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<td><strong>Difference density: max, min (e/Å³)</strong></td>
<td>0.75, -0.34</td>
<td>0.32, -0.34</td>
<td>0.70, -0.61</td>
<td>2.01, -2.11</td>
<td>0.56, -0.46</td>
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Table S2

Lethal and teratogenic effects observed in zebrafish (*Danio rerio*) embryos at different hours post fertilization (hpf).

<table>
<thead>
<tr>
<th>Category</th>
<th>Developmental endpoints</th>
<th>Exposure time (hpf)</th>
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<tr>
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<td>48</td>
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<tr>
<td>Lethal effect</td>
<td>Coagulated eggs</td>
<td>●</td>
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<tr>
<td></td>
<td>Lack of the heart beating</td>
<td>●</td>
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<tr>
<td>Teratogenic effect</td>
<td>Malformation of head</td>
<td>●</td>
</tr>
<tr>
<td></td>
<td>Malformation of eyes</td>
<td>●</td>
</tr>
<tr>
<td></td>
<td>Malformation of sacculi/otothils</td>
<td>●</td>
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<tr>
<td></td>
<td>Malformation of chorda</td>
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<td></td>
<td>Malformation of tail</td>
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<tr>
<td></td>
<td>Scoliosis</td>
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<tr>
<td></td>
<td>Yolk edema</td>
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<tr>
<td></td>
<td>Yolk deformation</td>
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<tr>
<td></td>
<td>Growth retardation</td>
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<td></td>
<td>Hatching</td>
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<tr>
<td>Cardiotoxicity</td>
<td>Pericardial edema</td>
<td>●</td>
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<tr>
<td></td>
<td>Heart morphology</td>
<td>●</td>
</tr>
<tr>
<td></td>
<td>Heart beating rate (beat/min)</td>
<td></td>
</tr>
</tbody>
</table>

aNo clear organs structure is recognized.
bMalformation of eyes was recorded for the retardation in eye development and abnormality in shape and size.
cPresence of none, one or more than two otoliths per sacculus, as well as reduction and enlargement of otoliths and/or sacculi (otic vesicles).
dTail malformation was recorded when the tail was bent, twisted or shorter than to control embryos as assessed by optical comparation.
eGrowth retardation was recorded by comparing with the control embryos in a body length (after hatching, at and onwards 72 hpf) using by optical comparation using an inverted microscope (CKX41; Olympus, Tokyo, Japan).
### Table S3

Selected bond distances (Å) and valence angles (°) in silver(I) complexes 1 – 5.

<table>
<thead>
<tr>
<th></th>
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<tr>
<td>Ag—N1</td>
<td>2.274(3)</td>
<td>Ag—N1</td>
<td>2.196(2)</td>
<td>Ag—N1</td>
<td>2.239(3)</td>
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<td>Ag—N2</td>
<td>2.268(3)</td>
<td>Ag—N2</td>
<td>2.193(2)</td>
<td>Ag—N2</td>
<td>2.254(3)</td>
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<td>Ag—O3</td>
<td>2.544(4)</td>
<td>Ag—O1</td>
<td>2.571(2)</td>
<td>Ag—O1</td>
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<td>Ag—O1</td>
<td>3.495(5)</td>
<td>Ag—O2</td>
<td>2.635(4)</td>
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<td>Ag—O3’</td>
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<table>
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<th>110.70(9)</th>
<th>112.42(12)</th>
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<td>N1—Ag1—N2</td>
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<td>N2—Ag1—O1</td>
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<td>167.7(5)</td>
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<td>C1—N1—Ag1</td>
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<td>C1—N1—Ag1</td>
<td>84.49(11)</td>
<td>N5—Ag2—O1</td>
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<td>C5—N1—Ag1</td>
<td>120.44(18)</td>
<td>C2—N1—Ag1</td>
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<td>C13—N3—Ag1</td>
<td>121.0(10)</td>
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<td>C12—N2—Ag1</td>
<td>120.3(2)</td>
<td>C12—N2—Ag1</td>
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<td>C17—N3—Ag1</td>
<td>122.1(12)</td>
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<td>C8—N2—Ag1</td>
<td>121.67(19)</td>
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<td>121.2(2)</td>
<td>C8—N2—Ag1</td>
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<td>N3—O3—Ag1</td>
<td>123.2(3)</td>
<td>C1—O1—Ag1</td>
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<td>C5—N1—Ag1</td>
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<td>C25—O2—Ag1</td>
<td>123.1(10)</td>
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</tbody>
</table>

<table>
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<tr>
<th></th>
<th>BVS&lt;sub&gt;Ag1&lt;/sub&gt;</th>
<th></th>
<th>BVS&lt;sub&gt;Ag1&lt;/sub&gt;</th>
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<th>BVS&lt;sub&gt;Ag1&lt;/sub&gt;</th>
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<tr>
<td></td>
<td>0.97</td>
<td>1.32</td>
<td>1.01</td>
<td>0.97</td>
<td>0.84</td>
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| Symmetry code(s): (i) -x+1, y+1/2, -z+3/2; (ii) -x+1, y-1/2, -z+3/2; (iii) x, -y+1/2, z+1/2; (iv) x-1, y, z+1; (v) x+1, y, z-1
Table S4

Hydrogen bond parameters for silver(I) complexes 4 and 5.

<table>
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<tr>
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<tr>
<td>4</td>
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<tr>
<td>O1–H1A⋯N1</td>
<td>0.87(2)</td>
<td>2.66(3)</td>
<td>1.944(17)</td>
<td>139.4(18)</td>
<td>+x, +y, -1+z</td>
</tr>
<tr>
<td>O1–H1B⋯N1</td>
<td>0.91(2)</td>
<td>3.16(3)</td>
<td>2.360(19)</td>
<td>147.1(19)</td>
<td>1-x, 2-y, 2-z</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>O1–H1B⋯F7</td>
<td>0.832(18)</td>
<td>2.897(3)</td>
<td>2.12(2)</td>
<td>155(3)</td>
<td>2-x, 1-y, 1-z</td>
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<tr>
<td>O1–H1B⋯F5</td>
<td>0.832(18)</td>
<td>3.054(3)</td>
<td>2.34(3)</td>
<td>144(3)</td>
<td>x+1, y, z-1</td>
</tr>
<tr>
<td>O1–H1A⋯F3</td>
<td>0.826(18)</td>
<td>2.753(3)</td>
<td>1.928(19)</td>
<td>176(4)</td>
<td>-x+2, -y+1, -z+1</td>
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Table S5

Values of binding constants of silver(I) complexes 1 – 5 with DNA.

<table>
<thead>
<tr>
<th>Complex</th>
<th>UV-Vis titration</th>
<th>Fluorescent titration</th>
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<tbody>
<tr>
<td></td>
<td>$K_b$ (M$^{-1}$)</td>
<td>$\Delta G^*$ (kcal/mol)</td>
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<tr>
<td>1</td>
<td>1.03 x 10$^4$</td>
<td>-5.5</td>
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<tr>
<td>2</td>
<td>1.22 x 10$^3$</td>
<td>-4.2</td>
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<tr>
<td>3</td>
<td>7.00 x 10$^3$</td>
<td>-5.2</td>
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<tr>
<td>4</td>
<td>3.74 x 10$^3$</td>
<td>-4.9</td>
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<tr>
<td>5</td>
<td>1.20 x 10$^4$</td>
<td>-5.5</td>
</tr>
</tbody>
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