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G-quadruplex-based logic gates for Hg^{II} and Ag^{I} ions employing a luminescent iridium(III) complex and extension of metal-mediated base pairs by polymerase†

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We report herein the synthesis of a series of cyclometallated iridium(III) complexes as luminescent G-quadruplex-selective probes, which were used to construct AND, OR and INHIBIT logic gates for the detection of Hg^{II} and Ag^{I} ions. To our knowledge, this study is the first time that the C–Ag^{I}–T mismatched base pair has been used for the construction of luminescent assays or logic gates.

Metal-mediated base pairs, which are formed by the coordination of metal ions to natural or artificial bases, impart unique chemical and physical properties to nucleic acids, such as stability enhancement[1-11] and assemblability.[12-17] Metal-mediated base pairs have thus attracted considerable interest in the field of biosensing, such as for the construction of molecular logic gates[18-21] and luminescent detection assays.[22-42] Ono and co-workers first reported the finding of the T–Hg^{II}–T mismatch in 2004,[43-45] and other metal-mediated base pairs such as U–Hg^{II}–U, C–Ag^{I}–C and C–Ag^{I}–A have been discovered.[44, 46-54] Recently, it was reported that Ag^{I} ions could increase the thermodynamic stability of duplexes containing a C–T mismatched base pair, presumably through the formation of a C–Ag^{I}–T motif,[55, 56] which is different from previously discovered mismatched base pairs. Moreover, it has been reported a metal-mediated base pair containing an artificial base could be recognized by DNA polymerase.[57]

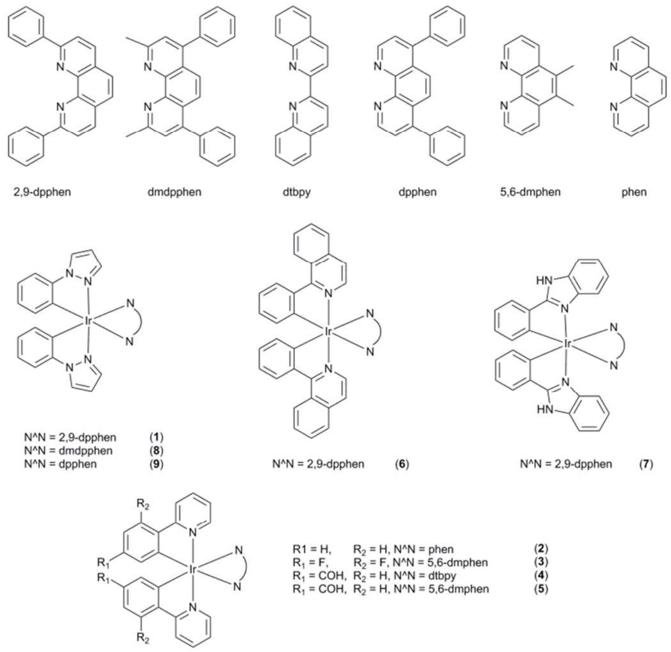
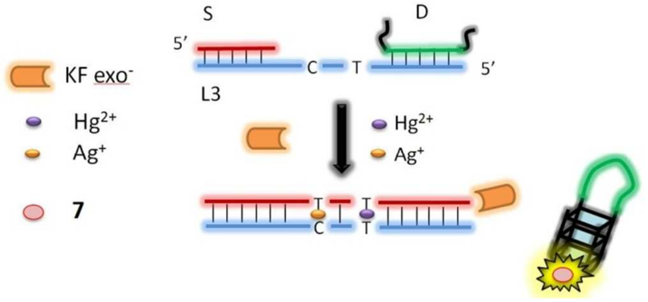


Fig. 1 Chemical structures of cyclometallated iridium(III) complexes **1**–**9**.

The G-quadruplex is a DNA secondary structure formed from guanine-rich sequences, and consists of square-planar arrangements of guanine nucleobases stabilized by Hoogsteen hydrogen bonding and monovalent cations.[58-60] The G-quadruplex motif has been widely used for the construction of analytical detection platforms due to its rich structural polymorphism.[34, 61-72] At the same time, luminescent heavy metal complexes have attracted tremendous interest in sensory applications due to their long-lived phosphorescence that can be readily distinguished from short-lived auto-fluorescence in the environment, their large Stokes shifts which prevent self-quenching, and their modular synthesis which allows their properties to be readily tuned without labor-intensive synthetic protocols.[42, 71, 73-80] To the best of our knowledge, iridium(III) complexes have not been applied to the development of logic gates in the literature.

Meanwhile, molecular logic gates have arisen as a fascinating combination of computational concepts with molecular structures.[81-87] Luminescence and other detections have been widely used for the development of sensors and logic gates due to its simplicity and sensitivity.[88-103] Taking advantage of the newly discovered C–Ag^{I}–T mismatch motif, we report herein the construction of G-quadruplex-based luminescent logic gates using Hg^{II} (Hg^{2+}) and Ag^{I} (Ag^{+}) ions as inputs due to their toxicity to the environment and living organisms.[104-107] To our knowledge, the C–Ag^{I}–T mismatched base pair has not been previously used for the construction of luminescent assays or logic gates.

The mechanism of the proposed G-quadruplex-based assay is depicted in Scheme 1. Initially, a long oligonucleotide sequence (**L3**, blue line) is partially hybridised to a G-quadruplex-forming sequence (**D**, black and green line) and another short complementary sequence (**S**, red line). In the presence of Hg^{2+} and/or Ag^{+} ions, Klenow fragment (KF exo^{-}), which retains polymerase activity but



Scheme 1 Schematic representation of the G-quadruplex-based luminescence sensing logic gate for Hg^{II} and Ag^{I} ions detection.

lacks 5′ → 3′ exonuclease activity, catalyzes the extension of **S** in the 5′ to 3′ direction to form a duplex product. This process involves the incorporation of mismatched 2’-deoxythymidine 5’-triphosphate (dTTP) opposite T and C residues in the long oligonucleotide **L3**, which is aided by the formation of T–Hg^{II}–T and/or C–Ag^{I}–T base pairs. The extension of **S** displaces **D** into solution, and the formation of the nascent G-quadruplex structure is detected by the G-quadruplex-selective iridium(III) complex with a luminescent response.

Firstly, five iridium(III) complexes (**1**–**5**, Fig. 1) were screened for their ability to selectively distinguish Pu27 G-quadruplex DNA from double-stranded DNA (ds17) and single-stranded DNA (ssDNA) by testing their luminescence responses towards various forms of DNA. The cyclometallated iridium(III) complex **1** which contains the 1-phenyl-1H-pyrazole (ppyz) C^N ligand and the 2,9-diphenyl-1,10-phenanthroline (2,9-dpphen) N^N ligand emerged as the top candidate, as it possessed the highest $I_{\mathrm{Pu27}}/I_{\mathrm{ds17}}$ and $I_{\mathrm{Pu27}}/I_{\mathrm{ssDNA}}$ ratios (3.66 and 3.37) out of the five complexes tested (Fig. S1a). Based on the structure of **1**, a focused library of four other cyclometallated iridium(III) complexes (**6**–**9**, Fig. 1) was designed and synthesised. This library was enriched in the favorable sub-structures of complex **1** that were identified in the first round of screening. Complexes **8**, **9** contain the same ppyz C^N ligand as complex **1**, but vary in their nature of the phenanthroline-based N^N ligand. Conversely, complexes **6** and **7** possess the same 2,9-dpphen N^N ligand as **1**, but differ in their C^N ligand. In the second round of screening, the novel iridium(III) complex **7** (Fig. 2a) which contains the 2-phenyl-1H-benzo[d]imidazole (pbi) C^N ligand and the 2,9-dpphen N^N ligand, exhibited the greatest $I_{\mathrm{Pu27}}/I_{\mathrm{ds26}}$ and $I_{\mathrm{Pu27}}/I_{\mathrm{ssDNA}}$ ratios (Fig. S1b).

Based on the analysis of these results, a brief structure-activity relationship can be concluded. As complexes **1**, **6** and **7** all possess the same 2,9-dpphen N^N ligand, the superior $I_{\mathrm{Pu27}}/I_{\mathrm{ds17}}$ and $I_{\mathrm{Pu27}}/I_{\mathrm{ssDNA}}$ values of **7** could be attributed to its pbi C^N ligands. This suggests that the pbi ligand, which is not carried by any other complex in this library, is highly important for G-quadruplex-binding selectivity. Additionally, complexes **8** and **9** all showed lower $I_{\mathrm{Pu27}}/I_{\mathrm{ds17}}$ and $I_{\mathrm{Pu27}}/I_{\mathrm{ssDNA}}$ values compared to the parent complex **1**, indicating the 2,9-dpphen N^N is also an important determinant for G-quadruplex selectivity. Interestingly, the dpphen ligand of **9** is simply a regioisomer of the 2,9-dpphen ligand of **1**, showing that the position of the pendant phenyl groups on the phenanthroline motif has a large effect on G-quadruplex affinity.

Complex **7** generated the highest luminescence response towards G-quadruplex DNA. A *ca.* 7-fold enhancement was observed in the luminescence signal of complex **7** at 5 μM of Pu27 G-quadruplex DNA (Fig. 2b). On the other hand, the addition of ssDNA or dsDNA (ds17) did not induce significant changes in the luminescence intensity of **7**.

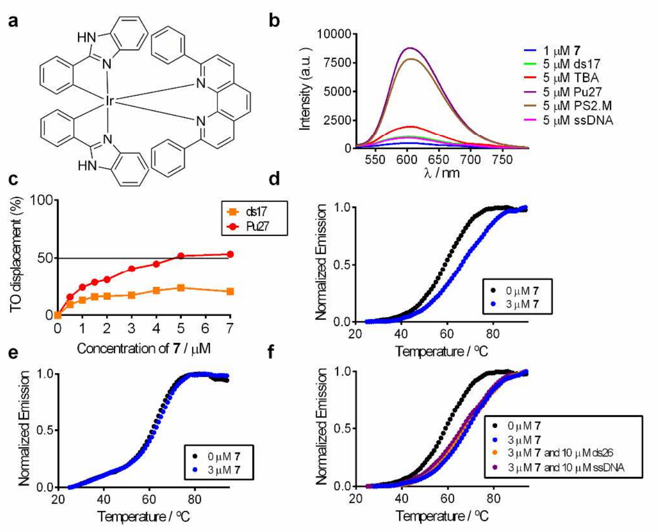
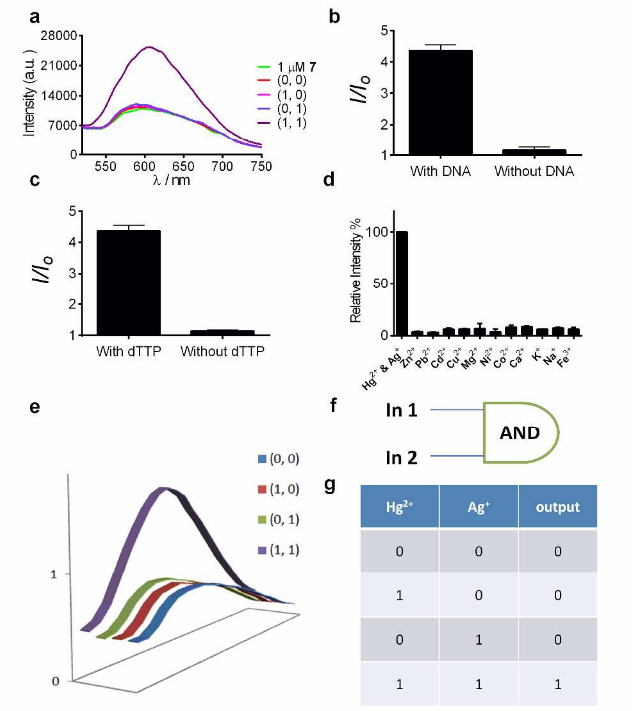


Fig. 2 (a) Chemical structure of complex **7**. (b) Emission spectrum of complex **7** (1 μM) in the presence of 5 μM of ssDNA, ds17 or various G-quadruplexes. (c) G4-FID titration curves of complex **7** with duplex (ds17) or G-quadruplex (Pu27) DNA. (d) Melting profile of F21T G-quadruplex DNA (0.2 μM) in the absence and presence of **7** (3 μM). (e) Melting profile of F10T dsDNA (0.2 μM) in the absence and presence of **7** (3 μM). (f) Melting profile of F21T G-quadruplex DNA (0.2 μM) in the absence and presence of **7** (3 μM) and ds26 (10 μM) or ssDNA (10 μM).

Fluorescence resonance energy transfer (FRET) melting assays and G-quadruplex fluorescent intercalator displacement (G4-FID) assays were employed to further validate the suitability of complex **7** as a G-quadruplex-selective probe. Although the emission region of thiazole orange (TO) (510−750 nm) and complex **7** (500−750 nm) overlap, complex **7** is not expected to interfere in the G4-FID assay due to its very low absorbance at the excitation wavelength of TO (501 nm). The results of the G4-FID assay indicated that complex **7** could displace TO from G-quadruplex structures with ${}^{G4}DC_{50}$ values (half-maximal concentration of compound required to displace 50% TO from DNA) of 4.9 μM, while the displacement of TO from dsDNA was below 25% even at the 7 μM of **7** tested (Fig. 2c). The selectivity of complex **7** towards G-quadruplex DNA was further investigated by FRET-melting assays. The melting temperature (ΔT_m) of the F21T G-quadruplex was increased by about 7.5 °C upon the addition of 3 μM of complex **7** (Fig. 2d). By comparison, only a 1 °C increase in the melting temperature of F10T dsDNA was observed under the same conditions (Fig. 2e). Furthermore, the addition of a 50-fold higher concentration of unlabeled competitor dsDNA (ds26) or ssDNA almost did not perturb the stabilizing effect of complex **7** towards the F21T G-quadruplex (Fig. 2f). Taken together, these results indicate that complex **7** binds selectively to G-quadruplex DNA over dsDNA or ssDNA.

Encouraged by the selective luminescence response of **7** to G-quadruplex DNA, we sought to employ **7** as a luminescent G-quadruplex probe for the construction of an AND logic gate responding to Hg^{2+} and Ag^{+} ions using the mechanism depicted in Scheme 1. In the absence of Hg^{2+} and Ag^{+} ions, complex **7** was only slightly emissive as the G-quadruplex-forming sequence **D** remained hybridized to the long oligonucleotide (**L3**). Encouragingly, however, the luminescence signal of **7** was enhanced by *ca.* 4-fold in the presence of Hg^{2+} and Ag^{+} ions (Fig. 3a), presumably due to the formation of T-Hg^{2+}-T and C-Ag^{+}-T mismatches in the DNA sequence that allowed

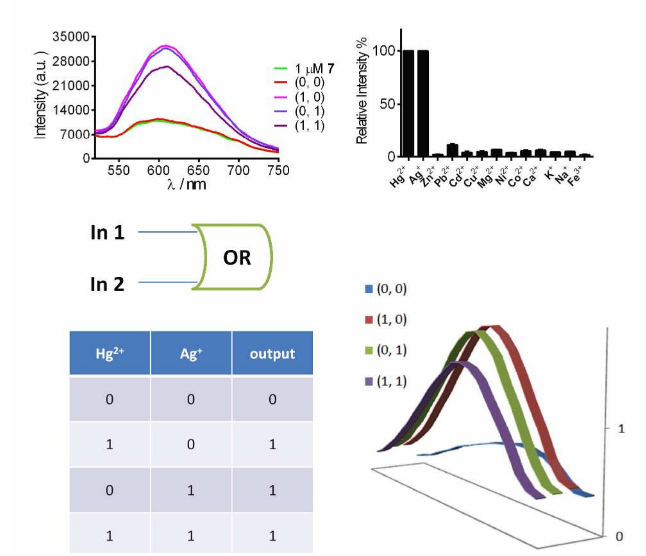


Hg^{2+}	Ag^{+}	output
0	0	0
1	0	0
0	1	0
1	1	1

Fig. 3 (a) Emission spectrum of complex **7** (1 μM) for the Boolean logic functions based on four combinations of two inputs: In1 = 25 nM Hg^{2+}, In2 = 25 nM Ag^{+} (AND logic gate, A AND B). (b) Luminescence of the system in the presence or absence of G-quadruplex-forming DNA **D** (2 μM). (c) Luminescence enhancement of the system in response to Hg^{2+} and Ag^{+} ions (25 nM) in the presence or absence of dTTP (2 μM). (d) Relative luminescence intensity of the system ([**7**] = 1 μM, [DNA] = 2 μM) in the presence of 100 nM Hg^{2+} and Ag^{+} ions or 5-fold excess of other metal ions. (e) Output values for the Boolean logic functions based on four combinations of two inputs: In1 = Hg^{2+}, In2 = Ag^{+} (A AND B). (f) Logic circuitry for the integrated AND logic system. (g) Truth table for the integrated AND logic system. Unless otherwise stated, the concentration of complex **7** was 1 μM and the concentration of DNA was 2 μM.

extension of **S** by KF exo^{-}, leading to the subsequent release of the G-quadruplex-forming sequence **D** that interacted strongly with **7**. In contrast, the luminescence intensity of **7** was not significantly enhanced in response to Hg^{2+} and Ag^{+} ions in the absence of the G-quadruplex sequence **D** (Fig. 3b), eliminating the possibility that complex **7** interacted directly with the metal ions and indicating the importance of G-quadruplex formation in the mechanism of the system. While no luminescence enhancement was observed in response to Hg^{2+} and Ag^{+} ions when dTTP was absent, indicating the extension of **S** plays an important role in the system (Fig. 3c). The selectivity of the AND gate system for Hg^{2+} and Ag^{+} over 11 other metal ions (K^{+}, Na^{+}, Zn^{2+}, Pb^{2+}, Cd^{2+}, Cu^{2+}, Mg^{2+}, Ni^{2+}, Co^{2+}, Ca^{2+} and Fe^{3+}) was also evaluated. The results showed that the luminescence response of the system for Hg^{2+} and Ag^{+} ions was significantly stronger than that for five-fold excess concentrations of the other metal ions (Fig. 3d).

We also noticed that in the presence of only one of the two metal ions, the luminescence signal of the system was relatively lower (*ca.* 1.1-fold) (Fig. 3e) compared to when both ions were present (*ca.* 3.6-fold). Hence, after transforming the luminescence intensity into binary code, the output values for the Boolean logic functions based on the four combinations of two inputs (In1 = Hg^{2+}, In2 = Ag^{+}) could be read out directly and easily from the three dimensional model of luminescence spectra (Fig. 3e). The truth table and logic circuitry for this integrated logic system (Fig. 3f and 3g) indicates that the system behaves as an AND logic gate.



Hg^{2+}	Ag^{+}	output
0	0	0
1	0	1
0	1	1
1	1	1

Fig. 4 (a) Emission spectrum of complex **7** (1 μM) for the Boolean logic functions based on four combinations of two inputs: In1 = 25 nM Hg^{2+}, In2 = 25 nM Ag^{+} (OR logic gate, A OR B). (b) Relative luminescence intensity of the system ([**7**] = 1 μM, [DNA] = 2 μM) in the presence of 100 nM Hg^{2+} and 100 nM Ag^{+} ions or 5-fold excess of other metal ions. (c) Logic circuitry for the integrated OR logic system. (d) Truth table for the integrated OR logic system. (e) Output values for the Boolean logic functions based on four combinations of two inputs: In1 = Hg^{2+}, In2 = Ag^{+} (A OR B). Unless otherwise stated, the concentration of complex **7** was 1 μM and the concentration of DNA was 2 μM.

We also constructed an OR logic gate for Hg^{2+} and Ag^{+} ions, in which **L1** and **L2** were used together (Scheme S1). **L1** and **L2** are long oligonucleotides that can potentially form T–Hg^{II}–T and C–Ag^{I}–T mismatches, respectively. The luminescence signal of **7** was enhanced by *ca.* 4.5, 4.2 and 3.7 fold in the presence of Hg^{2+}, Ag^{+}, and both ions, respectively (Fig. 4a). The assay still showed good selectivity towards Hg^{2+} or Ag^{+} ions (Fig. 4b). The truth table and logic circuitry for this integrated logic system (Fig. 4c, 4d and 4e) indicates that the system behaves as an OR logic gate. Encouraged by the successful construction of both AND and OR gate systems utilizing the iridium(III) complex **7**, we anticipated that the system could be extended into more complicated systems uzinv multiple inputs. As glutathione (GSH) or cysteine (Cys) strongly binds to Hg^{2+} or Ag^{+} ions and disrupts the structure of Hg^{2+}/Ag^{+} ion-mismatched pairs,[108, 109] two INHIBIT gates were developed by introducing GSH as the third input. In the presence of GSH, no luminescence enhancement was observed in both AND and OR gate system with different kinds of input (Fig. S3 and S4), which led to the construction of two different INHIBIT gates. The results demonstrate the potential ability of the system to integrate higher level logic gates involving multiple inputs.

To further investigate the potential amenability of these logic gates to other applications, a microfluidic chip was employed to detect the formation of G-quadruplex **D** in response to various inputs (Fig. S5a). Using the AND logic gate as an example, we observed a similar luminescence signal enhancement using the microfluidic chip compared to detection in a quartz cell (Fig. S5b), while the sample and buffer input volumes were greatly reduced. These data suggest that our logic gates may be readily adapted to a microfluidics platform for the detection of various analytes on a miniature scale.

In conclusion, we have synthesised a series of cyclometallated iridium(III) complexes as G-quadruplex-selective probes to construct luminescent logic gates for the detection of Hg^{2+} and Ag^{+} ions. This kind of construction is simple and convenient to use and can be a flexible linker between luminescent signal and binary computer language, which might have the potential application of the assay in the field of bioanalytical chemistry, luminescent sensing and DNA biotechnology especially when complicated systems are to be dealt with.

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Notes and references

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G-quadruplex-based logic gates for Hg^{II} and Ag^{I} ions employing a luminescent iridium(III) complex and extension of metal-mediated base pairs by polymerase

Abstract

We report herein the synthesis of a series of cyclometallated iridium(III) complexes as luminescent G-quadruplex-selective probes, which were used to construct AND, OR and INHIBIT logic gates for the detection of Hg^{II} and Ag^{I} ions. To our knowledge, this study is the first time that the C–Ag^{I}–T mismatched base pair has been used for the construction of luminescent assays or logic gates.