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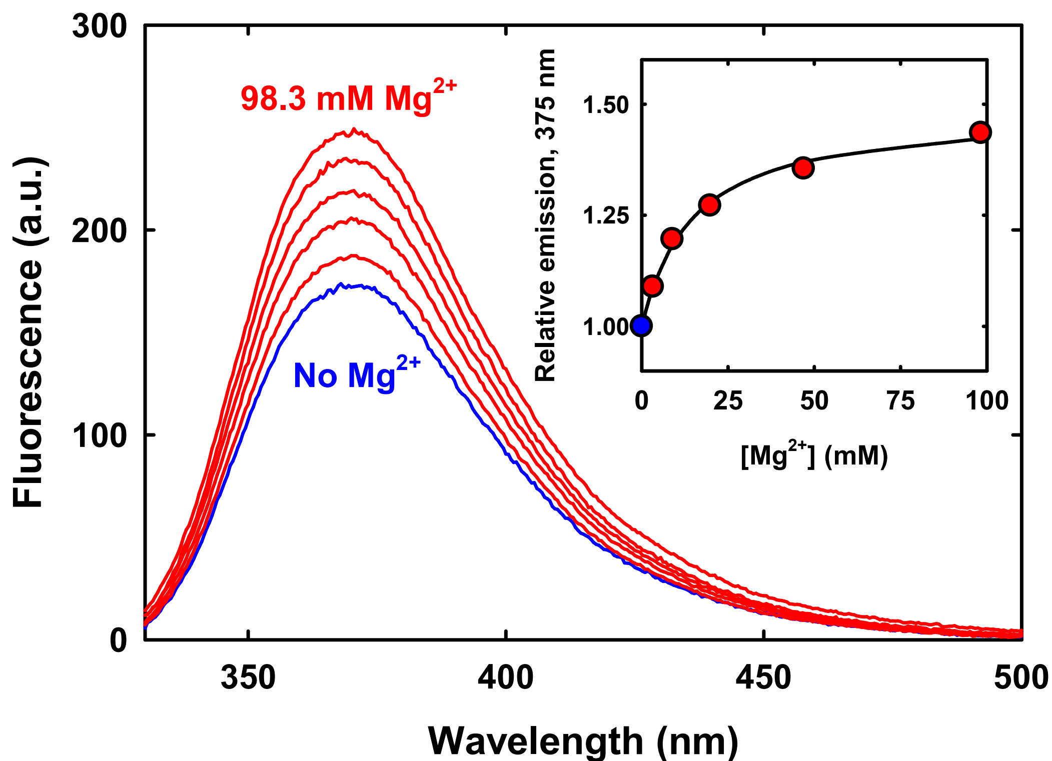
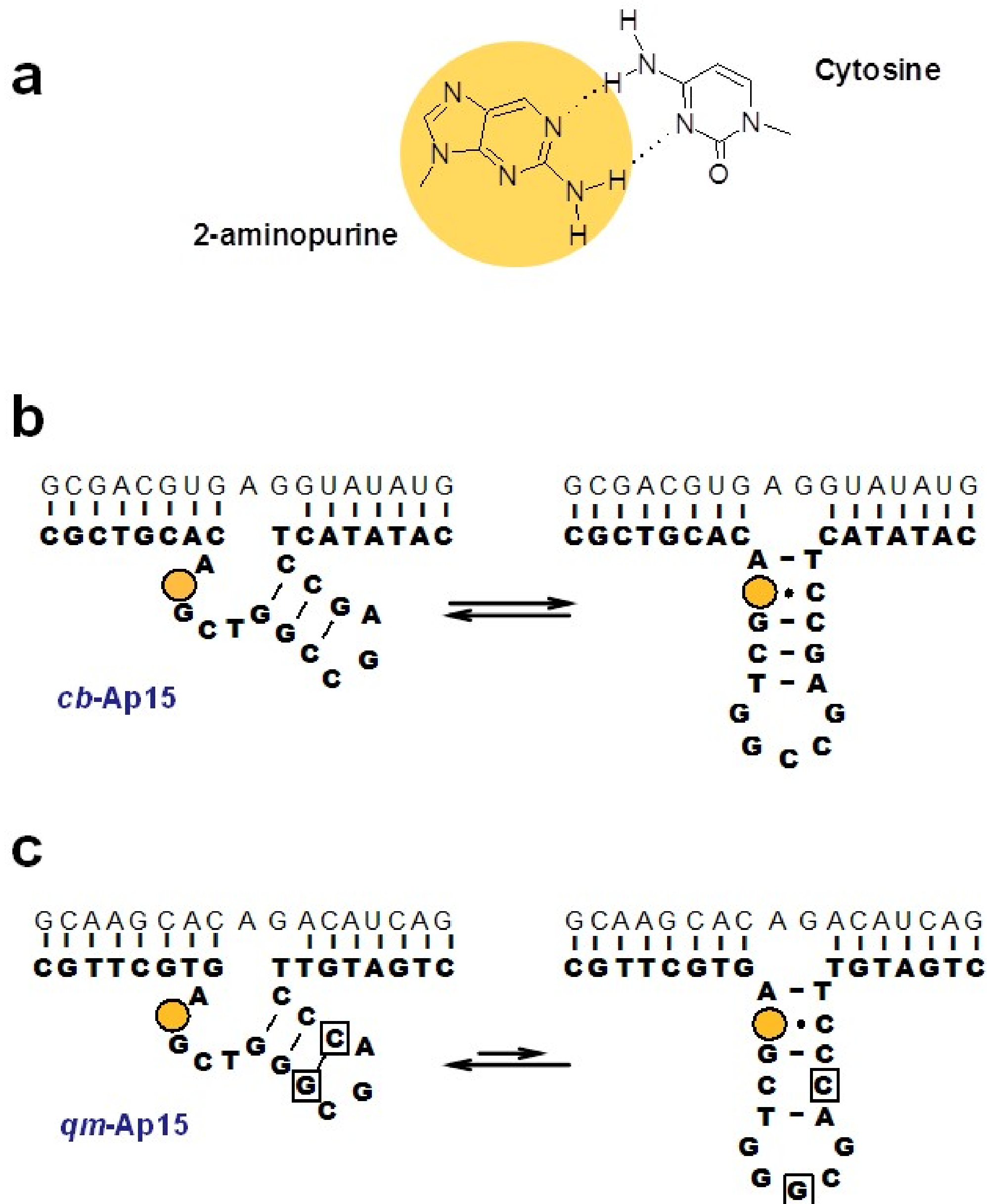
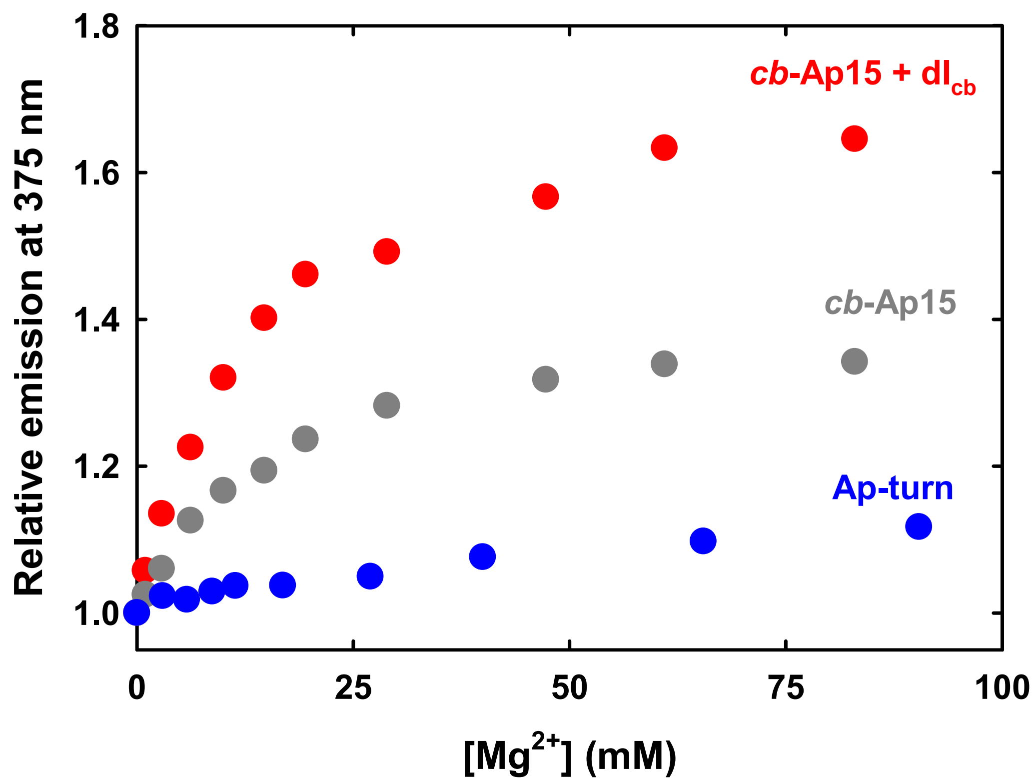


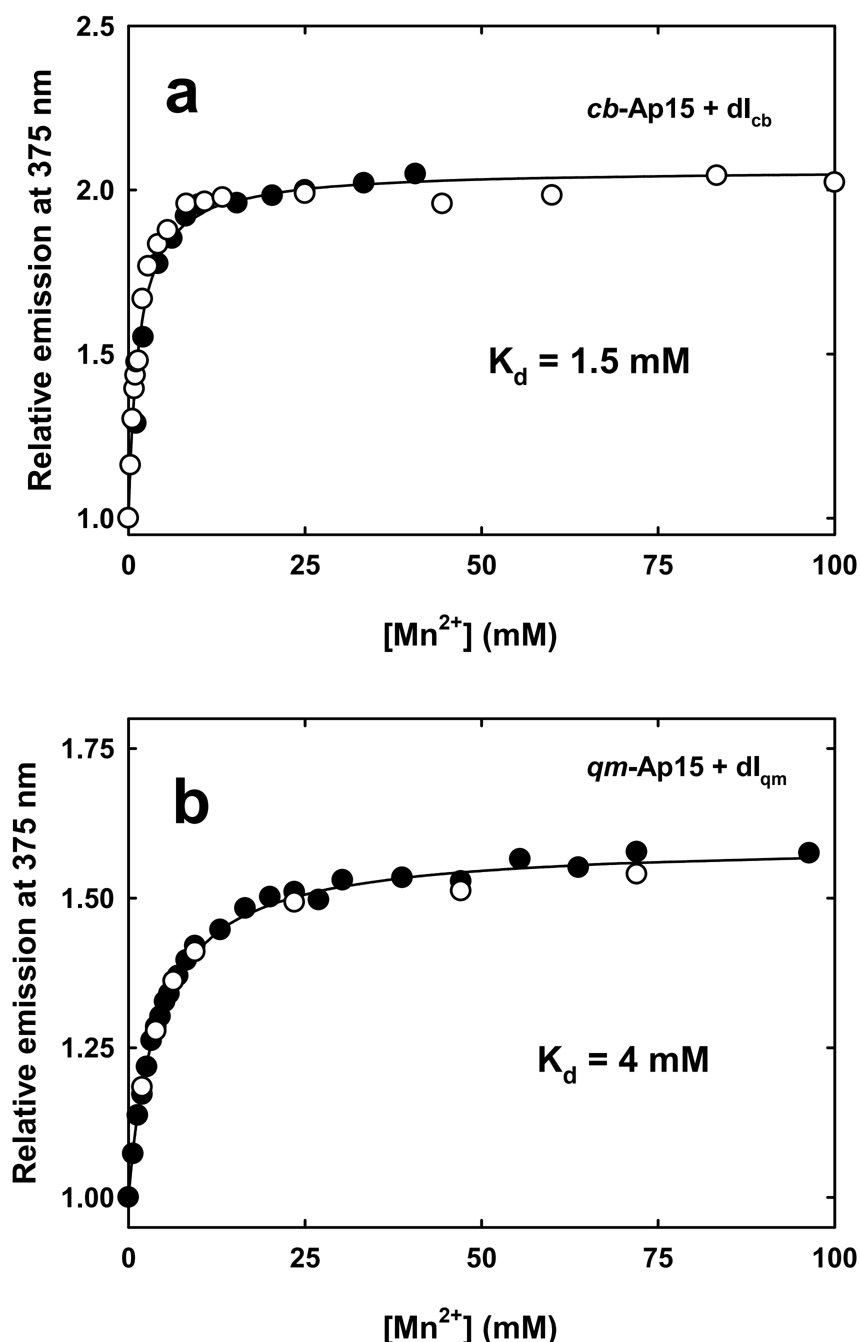
Supplementary Figure 1 – Fluorescence emission spectra of the *qm*-Ap15 construct (2 μM), complexed with an equimolar amount of the noncleavable substrate analog dI_{qm}, in the absence of divalent metal ions (blue line) and in the presence of increasing concentrations of $MgCl_2$ (red lines). PIPES-Na buffer, pH 7.4, 25°C. The inset shows the dependence of emission at 375 nm as a function of Mg^{2+} concentration.



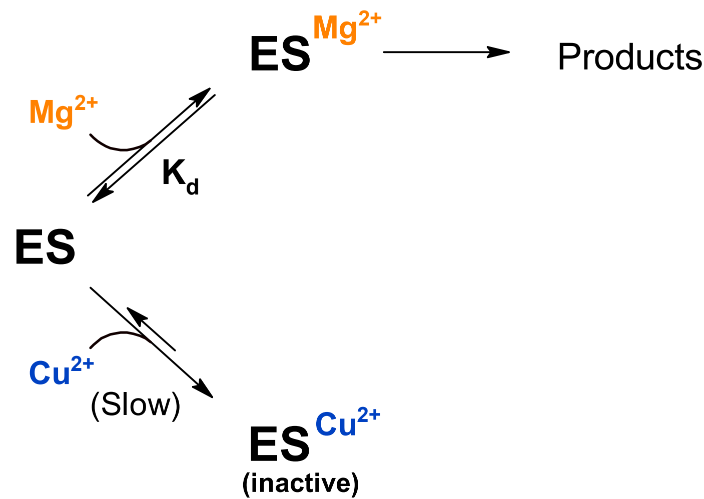
Supplementary Figure 2 – Base-pairing abilities of 2-Ap and potential secondary structures accessible to the *cb*-Ap15 and *qm*-Ap15 constructs. (a) In addition to forming a standard base pair with thymine, 2-Ap can form a wobble pair with cytosine[1-3], the stability of which depends on the context[1, 4]. (b) In the *cb*-Ap15 core, pairing between 2-Ap (shown as an orange circle) and cytosine could favor the alternative secondary structure on the right. This is analogous to the structure stabilized by introduction of a G residue in position 15 [5]. If the stability of this alternative structure (in which 2-Ap is stacked and hence quenched) were similar to that of the 'standard' core structure (on the left), then the effect of activating metals on *cb*-Ap15 fluorescence could simply mirror a leftward shift of the equilibrium. (c) The *qm*-Ap15 core contains a double mutation (boxed letters) that destabilizes by an estimated 300-fold the alternative secondary structure [5].



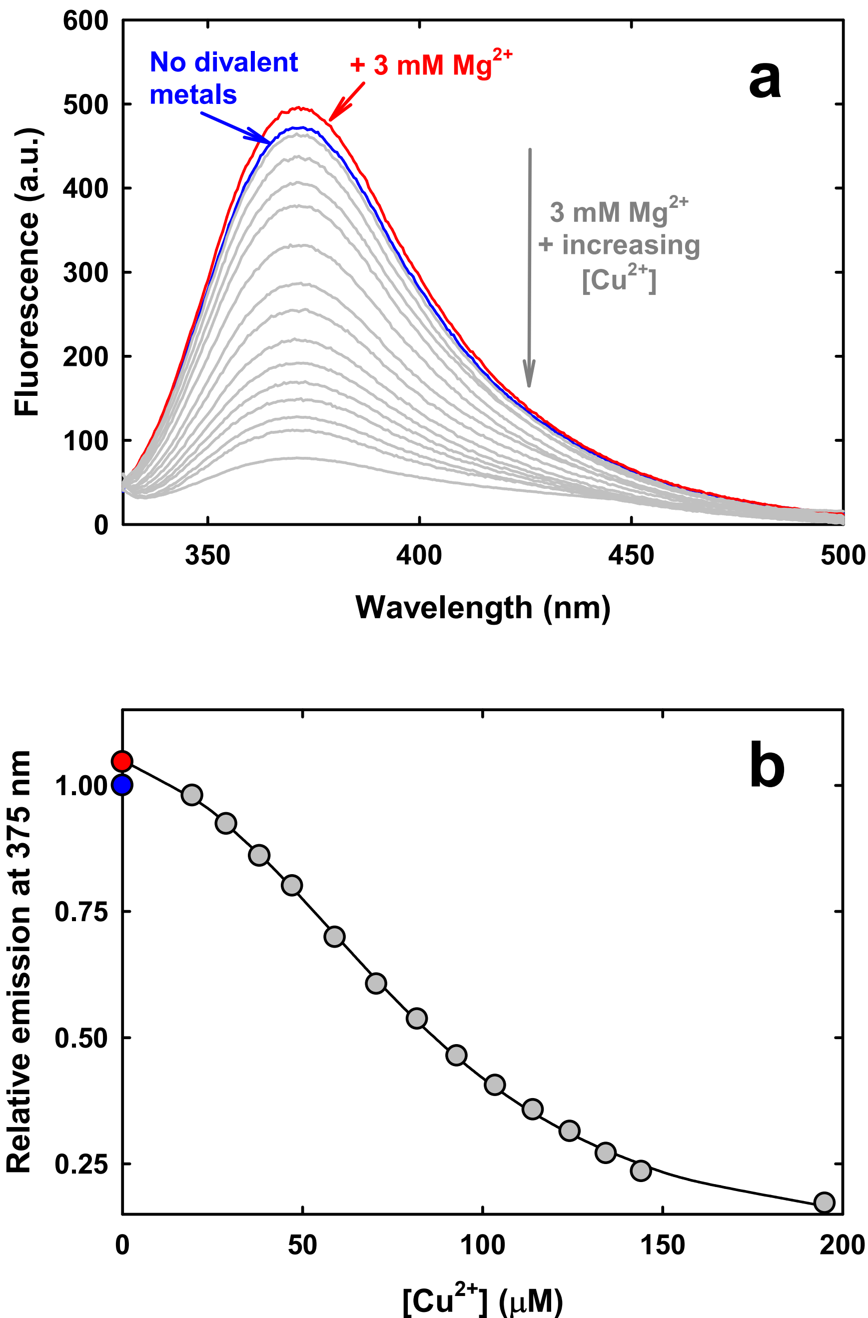
Supplementary Figure 3 – Changes in the fluorescence emission of *cb*-Ap15 alone (gray circles) or complexed with its substrate analog dI$_{cb}$ (red circles) or of the Ap-turn hexanucleotide (blue circles) as a function of added $MgCl_2$. Experiments were conducted (in different days) in PIPES-Na buffer, pH 7.4, 25°C. Concentration of oligonucleotides was ~2 μM in all cases. In each experiment, the reported fluorescence is normalized with respect to the initial emission measured in the absence of Mg^{2+} (which by definition is equal to 1).



Supplementary Figure 4 – (a) Effect of Mn^{2+} concentration on the emission of *cb*-Ap15 (2 μM) complexed with an equimolar amount its all-DNA substrate analog dI_{cb}. PIPES-NaOH, pH 7.4 (25 °C). Open and closed symbols correspond to independent experiments. The solid line through the data points represent the best fitting of the data to a binding hyperbola, yielding an apparent K_d of 1.5 ± 0.4 mM. (b) Effect of Mn^{2+} on the emission of *qm*-Ap15 (2 μM) complexed with its substrate analog dI_{qm}. Other conditions as in panel A. The solid line represents a binding hyperbola with an apparent K_d of 4 ± 1 mM.



Supplementary Figure 5 – A kinetic scheme tentatively explaining the inhibitory effect of Cu^{2+} on the activity of 8-17. ES represents the deoxyribozyme complexed with its substrate. The experimental data (e.g., Fig. 3a in the main text) indicate that this complex can bind, with modest affinity, an activating Mg^{2+} ion and undergo cleavage. Alternatively, however, it is postulated here that the ES complex can bind *with high affinity* one or more Cu^{2+} ions and become trapped in an inactive state. The rate of this 'trapping' process will depend on the concentration of Cu^{2+}. At high [Cu^{2+}], all ES will be trapped before it can react, essentially preventing cleavage. At low [Cu^{2+}], however, the rate of trapping will be comparable to the rate of cleavage, so that a fraction of the ES complexes will react before being trapped. This will result in reduced reaction endpoints. The model does not posit whether the binding sites of Mg^{2+} and Cu^{2+} overlap.



Supplementary Figure 6 – Interaction of Cu^{2+} with the *qm*-Ap15 construct. (a) Emission spectra of *qm*-Ap15 (2 μM), complexed with an equimolar amount of dI_{qm} substrate analog, in the absence of divalent metal ions (blue line), upon the addition of 3 mM $MgCl_2$ (red line) and upon the further addition of increasing concentrations of $CuCl_2$ (gray lines). Titration was conducted as in Fig. 4c of the main text, (b) Relative fluorescence emission as a function of Cu^{2+} concentration. Data are taken from the experiment in panel a. The solid line does not represent a fitting of the data to a theoretical model.

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