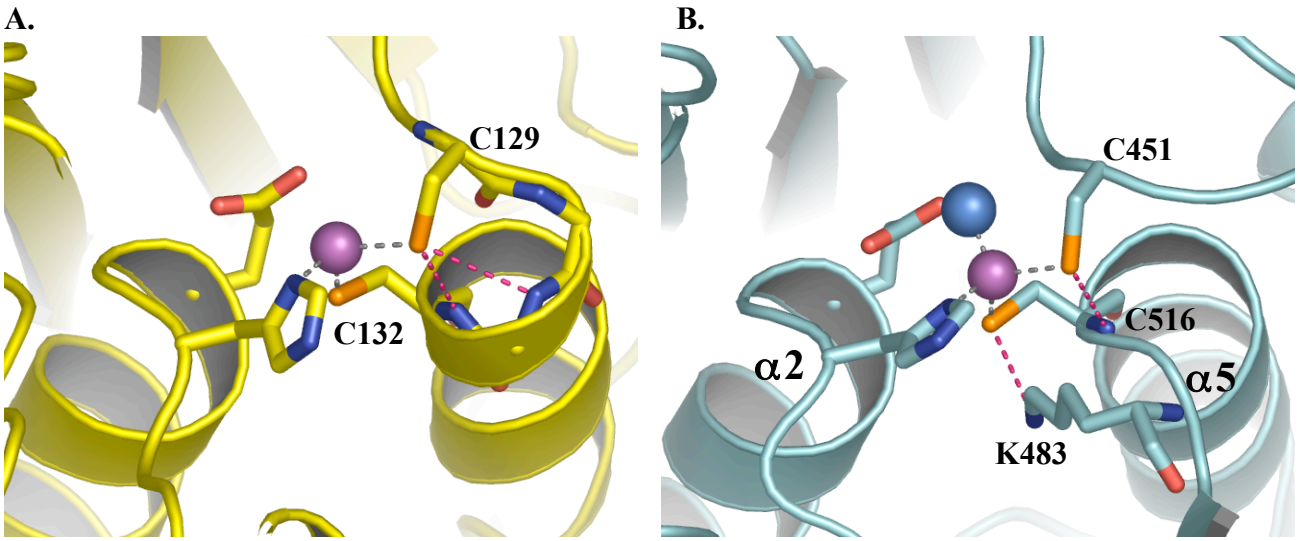

Figure S5. **(A)** The zinc coordinating environment of cytidine deaminase (*S15*). Zinc ion (magenta sphere), nucleophilic water (blue sphere), zinc coordinating bonds (grey dashed lines), hydrogen bonds (pink dashed lines). The thiolate of C129 forms hydrogen bonds with the backbone NH groups of residues H131 and C132 located at the N-terminus of the helix. These interactions are expected to reduce the negative character of the C129 thiolate, and thus increase the positive potential of the zinc ion. This may modulate catalysis by lowering the pKa of the coordinated water molecule that attacks the substrate C4 center of cytidine (*S16*). C132 is not within hydrogen bonding distance to any other residues. (**B)** The zinc-coordinating environment of hADAR2. A 64-residue loop separates C451 from C516, and the N-terminus of helix α5 is therefore less extended than in cytidine deaminase. The thiolate of C451 only forms one hydrogen bond with an amide NH (of C516). A consequent increase in water molecule pKa may be offset by a hydrogen-bonding interaction seen between the thiolate of C516 and the side chain of K483. The equivalent C132 of cytidine deaminase does not participate in hydrogen bonding interactions, whereas K483 is invariant in ADARs.