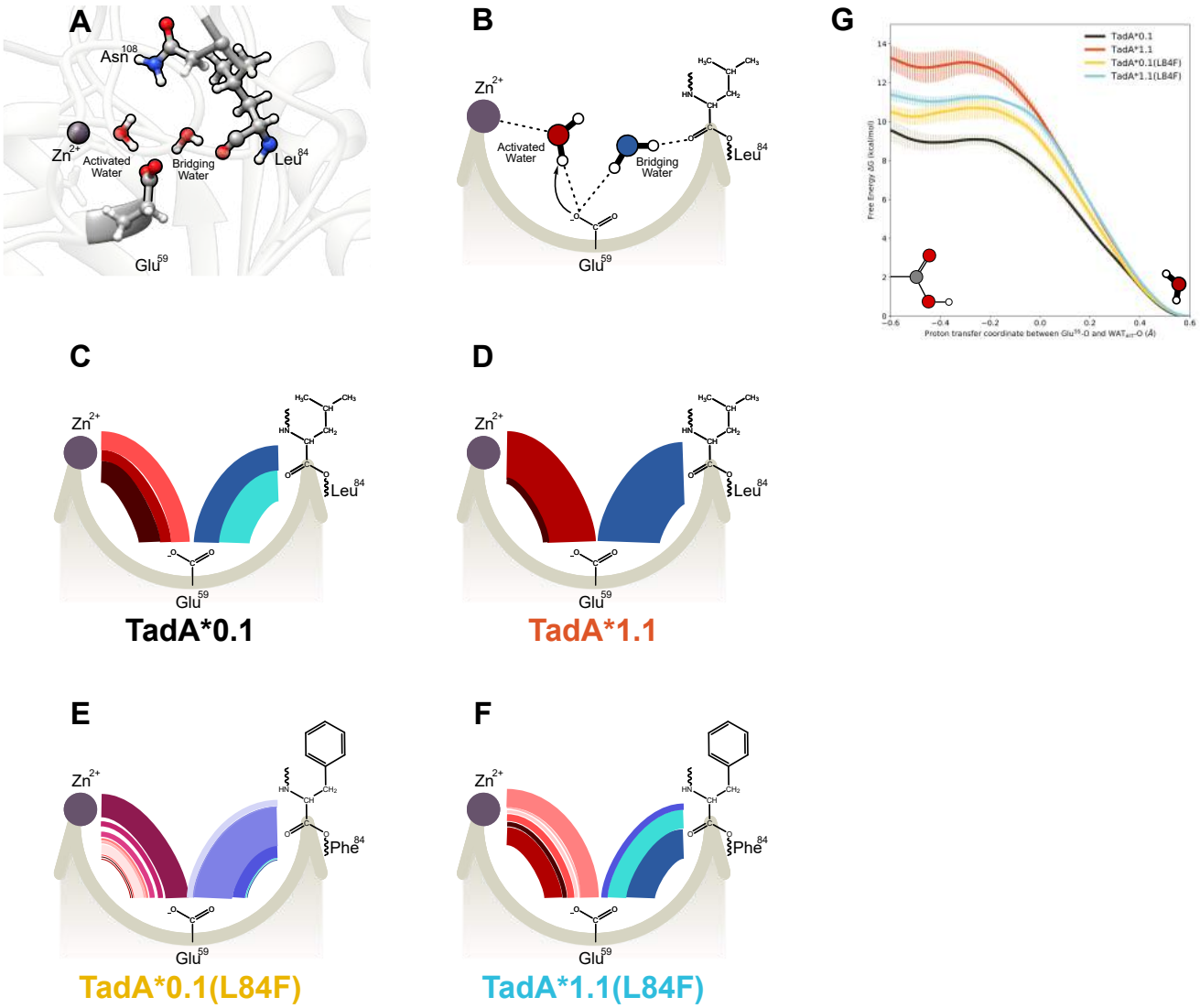

Figure S12: (A) Side view of the of the apo-TadA* models highlighting the location of the catalytically relevant residues. The Zn^{+2}ion is coordinated by His^{57},Cys^{87}, and Cys^{90} (not shown here for clarity) and a water molecule. This water molecule is activated by Glu^{59},which is also connected to another water molecule. This second water acts as a bridge between the Glu^{59} and the carbonyl backbone of residue 84. The target adenine is deep within the active site and residue 108 is farther away from the active site waters. (B) Simplified flat lay representation to highlight the interactions of active site waters. Modified chord diagrams to demonstrate the persistence of the active site waters for (C) TadA*0.1, (D) TadA*1.1, (E) TadA*0.1(L84F), and (F) TadA*1.1(L84F). The red chords connecting Glu^{59} with Zn^{+2} depict the stability of the activated water molecule. Similarly the blue chords connecting Glu^{59} with residue 84 depict the stability of the bridging water molecule. Different colors signify unique water molecules, with the thickness of individual chords being directly proportional to the total time these water molecules interact with the active site of TadA*–RNA during the simulation. (G) Reaction profile for the deprotonation of the activated water molecule the various TadA*-RNA systems.