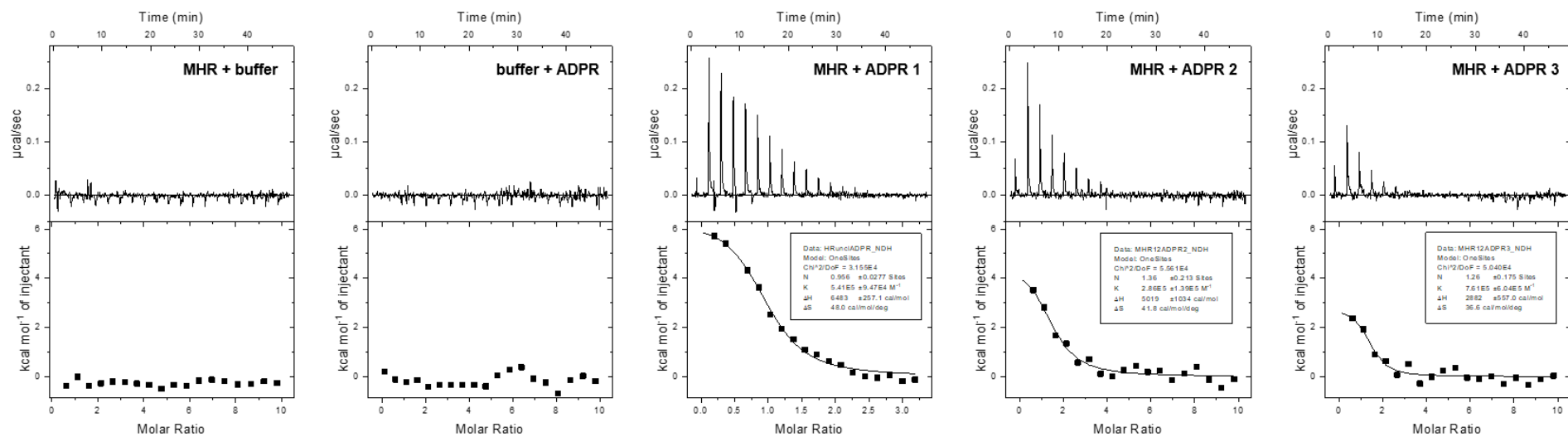
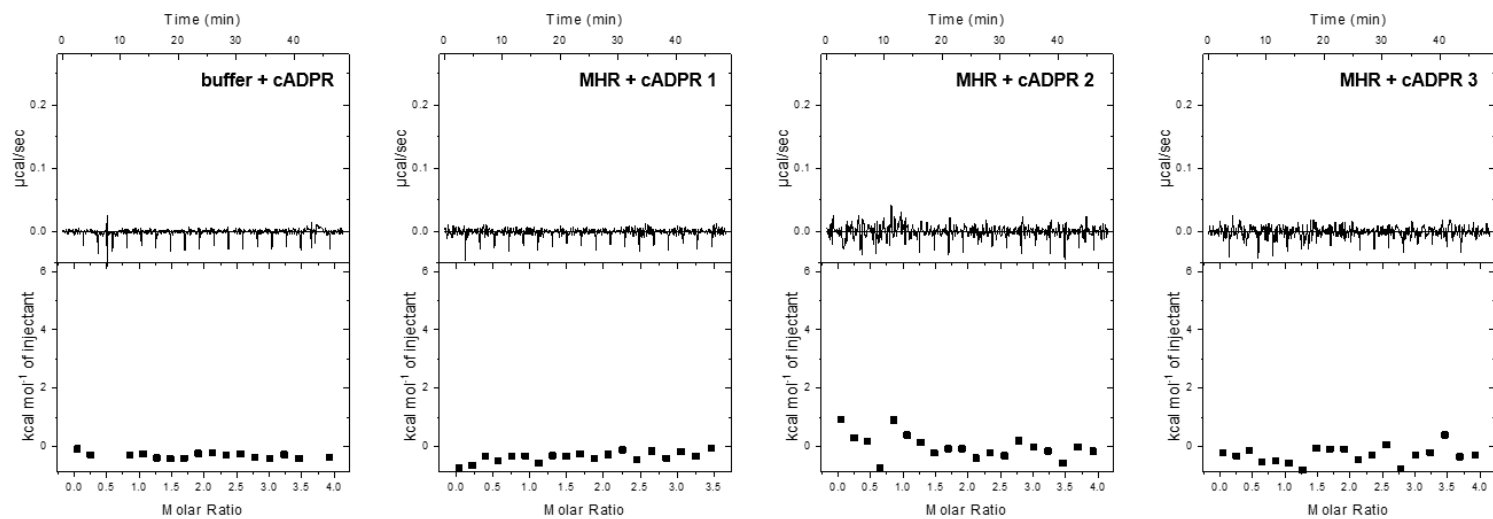


**Supplementary Figure S1: Exemplary whole cell patch clamp experiments** (a and b) Whole cell patch clamp experiments were performed with the patch pipette containing buffer alone, or buffer containing 250  $\mu$ M ADPR or 125  $\mu$ M cADPR. A total of 90 voltage ramps from -85 mV and +20 mV (over 140ms) were applied every 5 seconds. (a) The current-volt-relationship obtained from representative ramps displaying maximal current at +15 mV within their measurement. (b) Time course of the maximum current at +15 mV from representative recordings. (c) Schematic representation of the voltage ramps applied during the recordings.

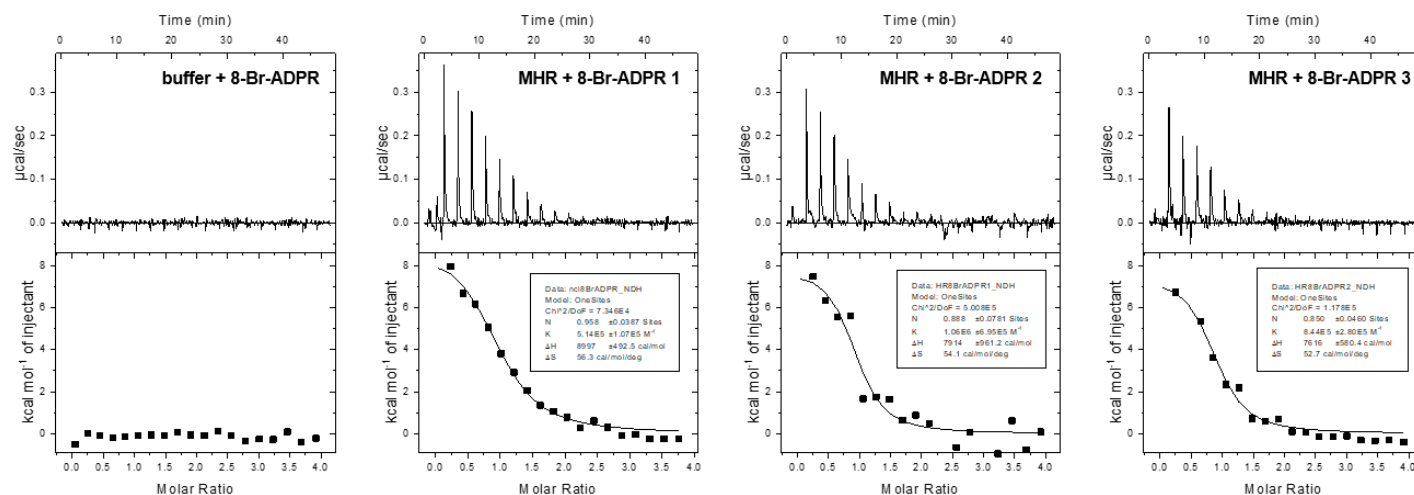
(a)



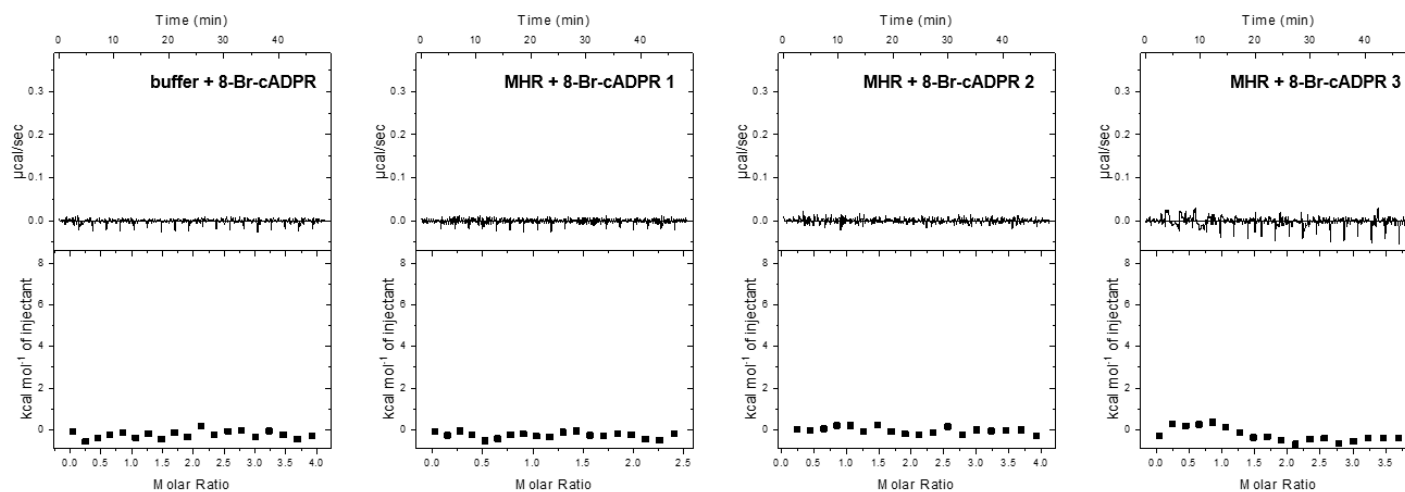
(b)



(c)



(d)



**Supplementary Figure S2: Individual ITC Experiments.** Binding of (a) ADPR, (b) cADPR, (c) 8-Br-ADPR and (d) 8-Br-cADPR to the isolated MHR1/2 domain of drTRPM2 was determined by isothermal titration calorimetry. Negative controls by titration of buffer to the MHR1/2 domain as well as titration of the ADPR analogues to the buffer are included.