**ΔS (CDK9 - CDK2)** ΔΔG Selectivity (CDK9 - CDK2) CDK9 CDK2 MUE:  $0.88_{0.54}^{1.29}$ MUE: 1.71<sub>1.10</sub><sup>2.34</sup> MUE: 1.17<sup>1.53</sup><sub>0.82</sub> RMSE: 1.15<sup>1.59</sup><sub>0.67</sub> RMSE: 2.10<sup>2.65</sup><sub>1.47</sub> RMSE: 1.37<sup>1.66</sup><sub>1.04</sub> Predicted  $\Delta\Delta G$  (kcal/mol) ∆∆G (kcal/mol) (kcal/mol) Predicted AS Predicted -4-2 -2 -6 Experimental  $\Delta S$  (kcal/mol) Experimental ΔΔG (kcal/mol) Experimental ΔΔG (kcal/mol) **ΔS (ERK2 - CDK2)**  $\Delta\Delta G$ CDK2 ERK2 Selectivity (ERK2 - CDK2) MUE:  $0.76^{1.04}_{0.52}$ MUE: 0.83<sup>1.07</sup><sub>0.59</sub> MUE: 1.22<sup>1.55</sup><sub>0.91</sub> RMSE: 0.95<sup>1.25</sup><sub>0.63</sub> RMSE: 1.41<sup>1.75</sup><sub>1.07</sub> RMSE: 0.97<sup>1.22</sup><sub>0.70</sub> cal/mol) cal/mol) :al/mol) 8 Predicted AAG (k  $\Delta\Delta G$ Predicted AS Predicted -2 -4

-6

-2

Experimental ΔΔG (kcal/mol)

-2

Experimental ΔS (kcal/mol)

-6

−6 <del>/</del> −6

-2

Experimental ΔΔG (kcal/mol)