

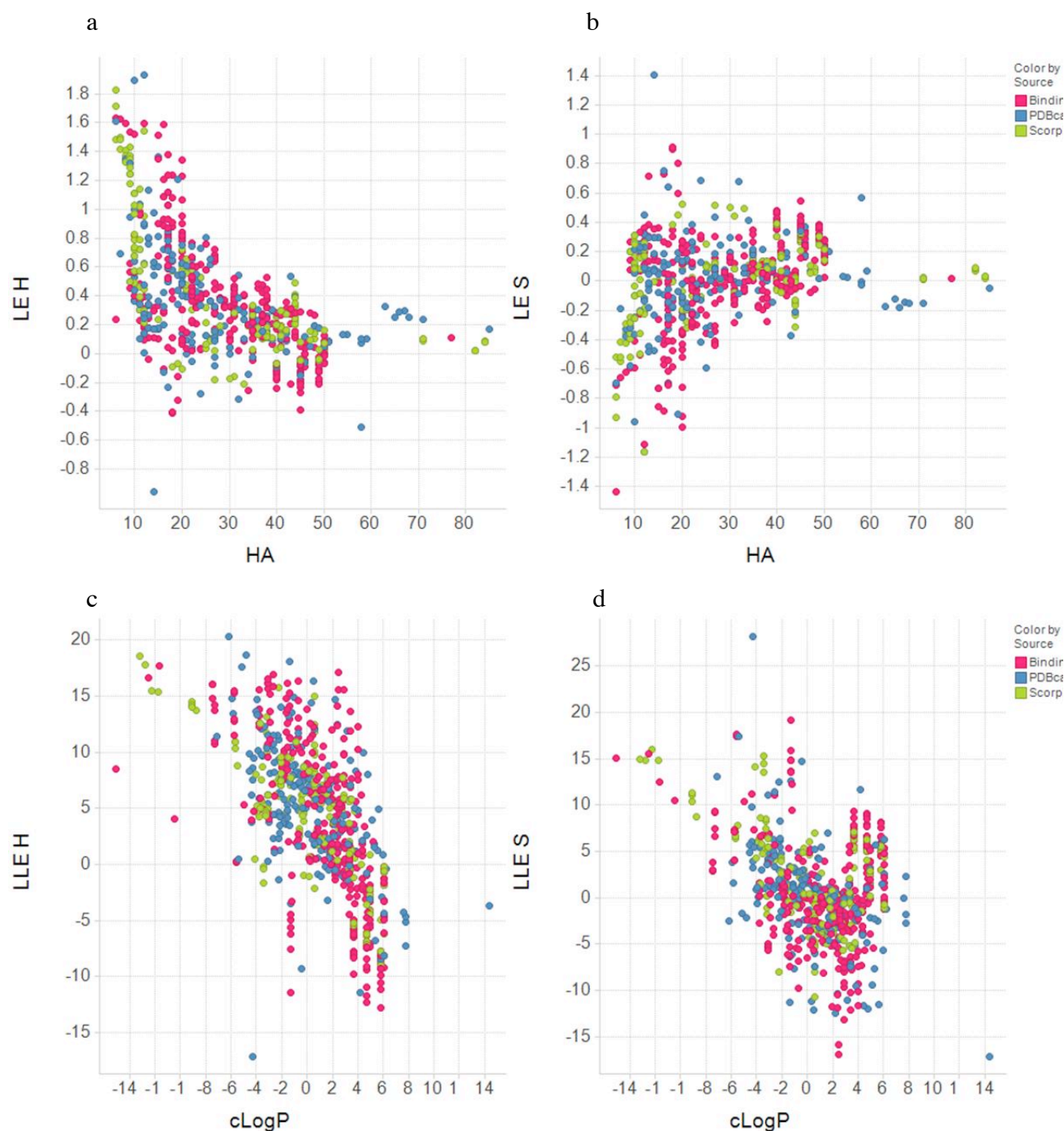


Figure S2 | **Enthalpy and entropy ligand efficiencies versus properties.** a) Enthalpy efficiency ($LE_H = pK_H \cdot 1.37 / \text{number of heavy atoms}$), and b) entropy efficiency ($LE_S = pK_S \cdot 1.37 / \text{number of heavy atoms}$) versus number of heavy atoms. c) Lipophilic enthalpy efficiency ($LLE_H = pK_H - cLogP$) versus cLogP and d) lipophilic entropy efficiency ($LLE_S = pK_S - cLogP$) versus cLogP. pK_H and pK_S are measures of the enthalpic and entropic components of binding calculated by the

formulas of $\frac{H}{2.303 \cdot R \cdot T} = pK_d^{enthalpy} = pK_H$ and $\frac{S}{2.303 \cdot R} = pK_d^{entropy} = pK_S$, respectively.

Binding affinity, $pK_d = pK_H + pK_S$. Data (n=754) are from ref 36 (Ferenczy, G. G., Keserű, G. M. Enthalpic efficiency of ligand binding. *J. Chem. Inf. Mod.* **50**, 1536-1541 (2010)); points are coloured by data sources.