



Figure 1 | ITC data plotted onto an enthalpy–entropy diagram. The diagram is split by the thick dashed diagonal line (main diagonal) into areas where enthalpy (ΔH ; green) or entropy ($-T\Delta S$; red) dominate the Gibbs free energy of binding (ΔG). The scatter in ΔG , from about -15 kJ per mol to the more favourable -60 kJ per mol, corresponds to the range that is accessible to medicinal chemistry. The perpendicular scatter shows enthalpy and entropy with opposing contributions to ΔG . It spreads across a very large range, thus depicting the inherent enthalpy–entropy compensation. Data are classified according to whether they originate from medicinal chemistry optimization (blue triangles) or as biomolecules from natural sources (brown circles). The optimization that results from medicinal chemistry programmes (large bold arrow) improves ΔG typically via entropically driven means. Reprinted from *J. Mol. Biol.* **384**, Olsson, T. S. G., Williams, M. A., Pitt, W. R. & Ladbury, J. E., The thermodynamics of protein–ligand interactions and solvation: insights for ligand design. 1002–1017 Copyright (2008), with permission from Elsevier. ITC, isothermal titration calorimetry.