When a compound made up of non-polar molecules is mixed with an aqueous solvent such as water, the molecules cluster together into a ball while water tends to form a ring around them. They do so because they are hydrophobic (. Wikibooks 2015).

When more of this solute is added, the water ring is disturbed as more of the hydrophobic molecules join the non-polar core and the displaced water molecules are freed to move around. This causes high disorder in the solution environment referred to as high entropy.
According to the 2nd Law of Thermodynamics, “The total entropy of the system plus its surrounding must always be increasing”(Wikibooks 2015). In this case the release of the water molecules from the cage around nonpolar surfaces is favourable and responsible for phenomenon called the hydrophobic effect.

The degree of freedom i.e. the free movement of drugs in solution or receptor proteins also favours entropy optimization and the binding phenomenon reduces this freedom as well as the binding affinity. Creation of more rigid drug molecules with less interference on the protein degree of freedom results in compensated enthalpy/entropy environments that favour binding affinity.

1. The binding affinity of drug molecules to protein receptor sites is a function of the solubility of the drug molecule and the part of the protein bound to the drug. The less soluble the drug molecule is, the more hydrophobic it is and therefore the higher the entropy as explained in the background above which creates a favourable environment for entropic optimization. Solvation of the protein (hydrophobicity) that is buried during binding will increase binding affinity if it is more hydrophobic. Binding Affinity (Ka) is a function of Gibbs Energy which is a difference between enthalpy and entropy. A more negative enthalpy and more positive entropy are more favourable for binding affinity (Freire 2005).

2. The limitations of this approach to affinity optimization include the following:

2.1. The resulting drug molecules are insoluble in water due to their hydrophobicity

2.2. Drug resistance may result from mutations of the binding site.

3. Enthalpy/Entropy compensation is any gain in enthalpy contributions to binding is opposed by an accompanying loss in entropic contributions. Afﬁnity optimization is accomplished by selecting chemical modiﬁcations that carry a low enthalpy/entropy compensation ((Lumry and Rajender, 1970; Eftink et al., 1983). Examples of the practical application of the entropy/enthalpy compensation principle including conformational constraints are all 1st generation HIV Protease Inhibitors Nelfinavir, Saquinavir and Ritonavir (Velasquez et.al 2003)