In Silico Design of Monomolecular Drug Carriers based on Calix- and Thiacalix[*n*]arene Host Molecules using DFT and Molecular Dynamics Methods

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Intermolecular interaction energies (E_{int}) in host-guest complexes were calculated for 72 systems where the hosts were functionalized calix- and thia-calix[*n*]arenes and the guest is the tyrosine kinase inhibitor drug, Imatinib, in order to rationally design a drug delivery agent that reduces the excretion rate of the drug as well as its bioaccumulation in its active form. These E_{int} values were assessed with the use of *ab initio* and Density Functional Theory (DFT) methods under the NBODel methodology. Three structural variables for the host molecules were considered: R = {SO_3H (**1**), t-Bu (**2**), i-Pr (**3**), COOH (**4**), $(CH_2)_2OH$ (**5**), $(CH_2)_2NH_2$ (**6**)}; b = {CH_2, S}; *n* = {5, 6, 8}, and two possible orientations for the insertion of Imatinib within the macrocycle cavity: Pyridine moiety pointing inwards (*N1*); and Piperazine pointing inwards (*N2*). Initial Molecular Mechanics geometry optimizations with the UFF potential were undertaken for every host-guest complex, with further optimization at the B3LYP/6-31G(*d,p*). All free hosts were originally optimized at the HF/6-311G(*d,p*) level. Using the same optimized structures, Molecular Dynamics (MD) simulations were carried out on all 72 assemblies using the General Amber Force Field and the AMBER 12 MD package. Electronic parameters where fitted using the RESP method and the complexes where run for 100ns. Potential of mean force was obtained for the most stable systems using umbrella sampling and the Weighted Histogram Analysis Method. Calixarenes families (**1**) and (**2**) (R = SO_3H and t-Bu, respectively) constitute the most promising candidates to become drug carriers within our parameter space due to their more negative E_{int} values and increased flexibility to allow the inclusion of the drug.