Arylsulfonamides as Inhibitors for Carbonic Anhydrase : Prediction & Validation

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Arylsulfonamide derivs. are widely studied high affinity inhibitors of the isoenzyme human carbonic anhydrase II (hCA II).ă From mol. dynamics simulations and MM-GBSA calcns., reliable (R = 0.89) relative binding free energies are detd. for 17 previously exptl. characterized protein-ligand complexes.ă Decompn. of these energies led to the identification of crit. amino acid residues with a significant contribution to the affinity towards the ligands.ă In particular, Leu198 was predicted as a key residue and was subjected to computational mutagenesis.ă This prediction was verified exptl. by producing hCA II mutants L198A, L198F and L198Q and detg. the resulting affinities towards inhibitor 1.ă The computed vs. exptl. energies are in good agreement thus suggesting that the force field parameters reported herein are useful for the in silico design of a wider range of carbonic anhydrase inhibitors.
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