Linking Molecular Simulations and Classical QSAR Analysis of Protein-ligand Complexes

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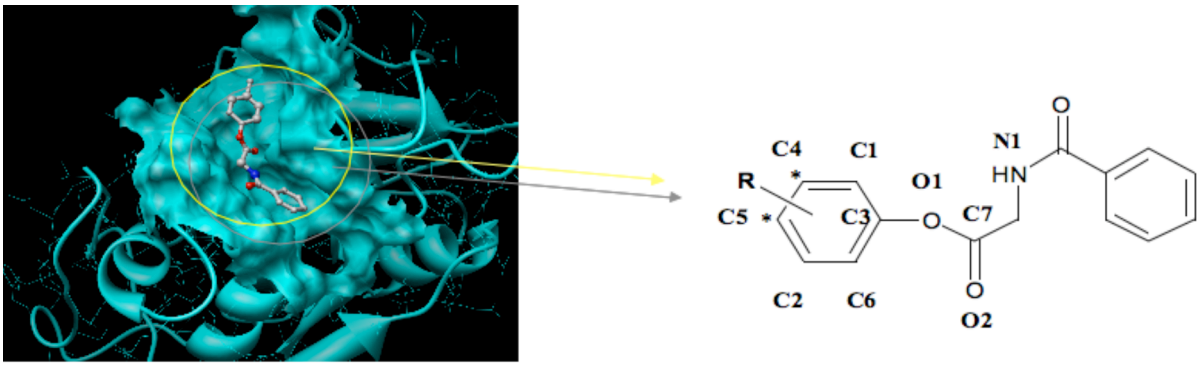
Molecular dynamics and full structure Local SCF semiempirical quantum mechanics calculations of receptor-ligand complexes were carried out to investigate structure activity relationship for the papain hydrolysis of a series of N-benzoylglicine esters and re-implement classical QSAR descriptors using detailed structural information.



Methods

Protein-ligand complexes were generated by docking the ligand into the active site by the FlexX module of Sybyl 6.91. Nanosecond length molecular dynamics calculations using Amber 7 were applied to obtain optimal conformations for complexes and statistical ensemble for structure-activity relationship analyses. Semiempirical quantum mechanics calculations were performed on the full complexes by the LocalSCF method and LocalSCF2003 program to determine electronic properties.

Results

Structure-activity reletionship studies were carried out using the most important parameters governing the complex formation. These effects were the charge distribution on the ligands, and the solvation effects.

The charge redistribution after complex formation was studied. The alteration of electronic properties on both the ligand and protein was determined. Principal component analyses were performed to compare the correlations among atoms of ligands. It was shown that the tendency of charge distribution on the ester group is different for para- and meta- substituted compounds if charges of complex ligands are analyzed, but no such difference can be observed in the case of free ligands..

The effects of complexation on the electronic properties of protein were also shown.

Ref.: Connecting Traditional QSAR and Molecular Simulations of Papain Hydrolysis - Importance of Charge Transfer. Z. Lepp, H.Chuman. Bioorganic and Medicinal Chemistry Bioorganic & Medicinal Chemistry. 2005, 13, 3093-3105