

[P13] Similarity Analysis on Fatty Acid Synthase Inhibitors Based on Three-Dimensional Electronic Descriptors

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The concept of molecular similarity plays an important role in drug discovery since similarity to a known active ligand can be a good measure to make a transition to another scaffold of molecules. In this presentation, we report our computational method to evaluate three-dimensional electronic-structure similarity (3D-ESS) of molecules, which is the one evaluated by electronic-structure calculations. Plausible descriptors for 3D-ESS would be e.g. molecular orbitals and electron density distribution. In this work, we focus on 3D-ESS of electrostatic potential (ESP) since it is expected to be one of the dominant factors in ligand-receptor docking.

In this study, geometry optimization of a molecule is performed by using the DFT(M06-2X)/6-31G** method. The ESP and electron density are calculated for each lattice point defined around the optimized molecule. The lattice points whose electron density value is 0.0004 and more are chosen to define candidates of the sampling points. Then surficial points are extracted from the candidates as the sampling points for evaluating ESP similarity. The similarity is numerically evaluated by a scoring algorithm based on minimization of RMSD of the overlap between ESPs of the reference and target molecules. The minimization was performed by using the simulated-annealing method.

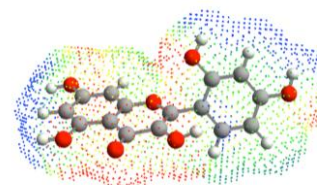


Figure 1. ESP of morin

As an application, we analyzed 33 fatty acid synthase (FAS) inhibitors [1-3]. Since the FAS proteins synthesize fatty acids which contribute the growth of cancer cells, the inhibitors can be classified as one of the anti-cancer drugs. In the present 3D-ESS analysis, we took morin (Figure 1) as a reference since its IC_{50} was the lowest among the 33 compounds. The correlation coefficient between the ESP similarity score and IC_{50} was reasonably good as shown in Figure 2.

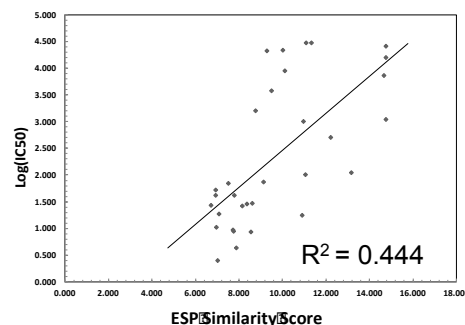


Figure 2. The correlation between the ESP similarity score and IC_{50} .

Bibliography:

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