

Molecular field-based fragment discovery

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We have developed a fast molecular field-based superposition algorithm BRUTUS[1] for chemical similarity searching. BRUTUS uses steric, electrostatic and hydrogen-bonding fields to model the shape, charge distribution and hydrogen bonding potential of the compounds, respectively. Here we describe the application of BRUTUS to molecular field-based fragment discovery using HIV-1 Protease inhibitors as a test case. First, BRUTUS was used to superimpose some molecular fragments to evaluate its applicability to the fragment alignment procedure. Second, a large molecular database was screened towards a side chain fragment from a HIV-1 Protease inhibitor on the basis of steric and electrostatic fields. The superimposed molecular fields of the fragments were further analyzed using the three-layered self-organizing map (SOM) technique. The aim of this approach was to classify fragments based on their 3D-field similarity. In this context, single scoring functions are not as effective as the fast SOM-method, which will use all the information from 3D molecular fields.

The results clearly indicate following conclusion:

1. It is possible to use molecular fields instead of 2D-similarity to classify and compare fragments
2. Molecular fields are also usable within large databases, since the calculation time per conformation is around 0.2 second
3. Classifying fragments on the basis of their 3D molecular fields is offering a totally new type of similarity description. The overall procedure described here allows the discovery of novel fragments having similar molecular fields despite their molecular structures

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References

- [1] Tervo AJ, Rönkkö T, Nyrönen T , Poso A, submitted.