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Poster presentation

Virtual chemical reactions for drug design

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Two methods for the fast, fragment-based combinatorial molecule assembly were developed. The software COLIBREE® (Combinatorial Library Breeding) generates candidate structures from scratch, based on stochastic optimization [1]. Result structures of a COLIBREE design run are based on a fixed scaffold and variable linkers and side-chains. Linkers representing virtual chemical reactions and side-chain building blocks obtained from *pseudo*-retrosynthetic dissection of large compound databases are exchanged during optimization. The process of molecule design employs a discrete version of Particle Swarm Optimization (PSO) [2]. Assembled compounds are scored according to their similarity to known reference ligands. Distance to reference molecules is computed in the space of the topological pharmacophore descriptor CATS [3].

In a case study, the approach was applied to the *de novo* design of potential peroxisome proliferator-activated receptor (PPAR gamma) selective agonists. In a second approach, we developed the formal grammar Reaction-MQL [4] for the *in silico* representation and application of chemical reactions. Chemical transformation schemes are defined by functional groups participating in known organic reactions. The substructures are specified by the linear *Molecular Query Language* (MQL) [5]. The developed software package contains a parser for Reaction-MQL-expressions and enables users to design, test and virtually apply chemical reactions. The program has already been used to create combinatorial libraries for virtual screening studies. It was also applied in fragmentation studies with different sets of retrosynthetic reactions and various compound libraries.

References

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