

Recore: Instant 3D Scaffold Hopping using Replacement Fragments

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Recore is a 3D ligand scaffold replacement tool [1] which allows the user to generate new ligand cores within a few seconds. The method is an ideal solution for deriving new lead structures from existing ones, which may be patent protected or otherwise unusable.

Given a user-defined central part of a molecule (the 'core'), Recore identifies the geometrically best possible replacement from a 3D fragment database containing millions of moieties. This is achieved within seconds using an ultra-fast indexing mechanism, based on the exit vectors which connect the core with the side-chains.

We used Recore to define multiple 3D fragment sets based on either 3D crystal structures or generated conformers of drug-like molecules. In this step Recore identifies suitable fragments by shredding according to RECAP-type rules [2] for high likelihood of synthetic accessibility. We then applied the search engine on a number of pharmaceutically relevant targets using the bioactive conformations of known binders.

We present results showing that Recore is able to replace a central unit such as to jump from one chemical series to another, while preserving the position of the side-chains. In the hit-lists of Recore we identified other known actives in their bioactive conformation. We show that the use of additional pharmacophore-constraints help further guide the search towards relevant solution sets.

1. Maass, P.; Schulz-Gasch, T.; Stahl, M.; Rarey, M. Recore: A Fast and Versatile Method for Scaffold Hopping Based on Small Molecule Crystal Structure Conformations. *J. Chem. Inf. Model.* **2007**, 47(2), 390-399.
2. Lewell, X. Q.; Judd, D. B.; Watson, S. P.; Hann, M. M. RECAP—retrosynthetic combinatorial analysis procedure: a powerful new technique for identifying privileged molecular fragments with useful applications in combinatorial chemistry. *J. Chem. Inf. Model.* **1998**, 38(3), 511-522.