A Systematic Search for Scaffold Hops in PubChem

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Scaffold hopping is the bioisosteric replacement of structural elements of a molecule and plays an important role in lead optimization. The focus of this study was the replacement process in which only the central core of a compound is substituted.1,2 There are several computational ligand-based methods that propose these scaffold replacements for a given query using different theoretical backgrounds. Surprisingly, retrospective examples to validate the output of these programs are rare.

A systematic search for scaffold replacements was developed to extend the number of known retrospective examples of scaffold hops. It was performed in datasets of active compounds of 71 selected PubChem bioassays. The method searches for molecule pairs with common but disconnected substructures because these are candidates for scaffold hopping. A set of selected scaffold hop candidates was aligned with the programs FieldAlign3 and ParaFit4 to explore the agreement in interaction potential of the according scaffold pairs. As both programs use a combination of electronic features and shape information for the alignment, a scaffold hop is supposed to show a high score for the alignment that conserves the orientation of the common substituents.

The search identified several scaffold replacements in the PubChem experimental data that also possess bioisosteric similarity and that therefore represent retrospective examples of successful scaffold hops.

[4] ParaFit’08, Cepos InSilico Ltd., UK