# Analysis of Biologically Relevant Chemical Space using the Scaffold Tree – Towards Automated Strategies for Ligand Design and Scaffold Hopping

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## Introduction

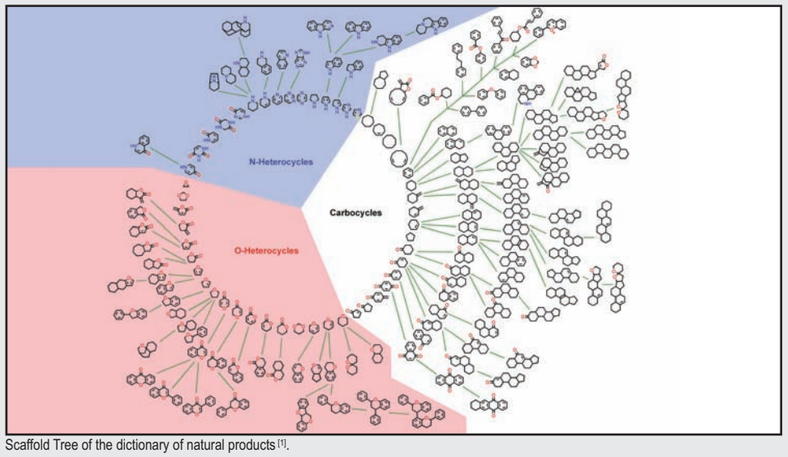
Charting biologically relevant chemical space using a scaffold tree has been introduced recently as a successful strategy to structure the incredibly large number of molecules offered by nature in a chemically intuitive way. [1,2] The tree-like organization of scaffolds provides a means to identify essential core scaffolds for the development of combinatorial libraries and for lead optimization. A first reported successful application was the design of a library based on a natural product core fragment that identified potent and selective inhibitors for structurally related enzymes. [1]

Here we address two questions related to the scaffold tree and the potential application of the method for drug discovery projects:

**1)** Is the pruning of active scaffolds a valid approach and is the current pruning strategy done in a biology relevant manner? For this question pairs of childs and parents from the WOMBAT database [3] were extracted, that corresponded to real existing molecules. These pairs were compared with virtually generated parent-child pairs. Using a biology relevant pruning strategy has a prospect to be used for brachiation in the tree as a ligand design strategy.

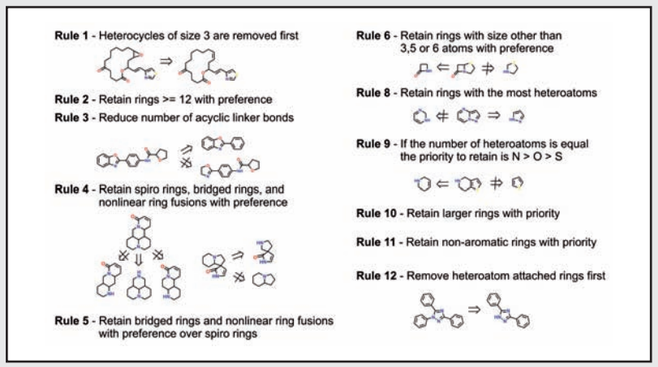
**2)** Is the concept of the scaffold relevant with respect to biology? To answer this question a recently reported validation of different computational methods for the clustering of molecules with similar biological profile [4] was extended to clustering molecules using only scaffold information, or the frequencies of substructures observed within all molecules of a particular scaffold. These results evaluate the prospect of the scaffolds tree to be used for "scaffold hopping". [5-7]

## The Scaffold Tree



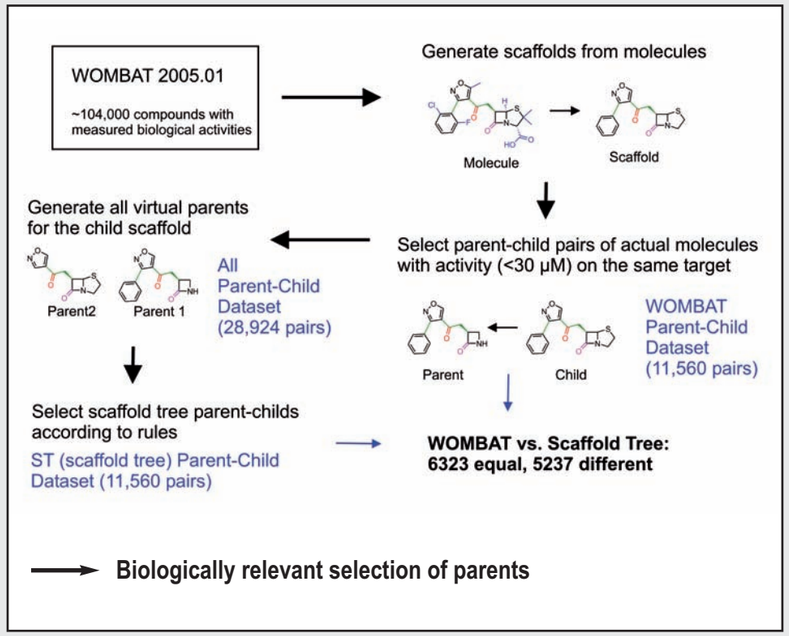

Scaffold Tree of the dictionary of natural products [1].

## Hierarchical Set of Ring Pruning Rules



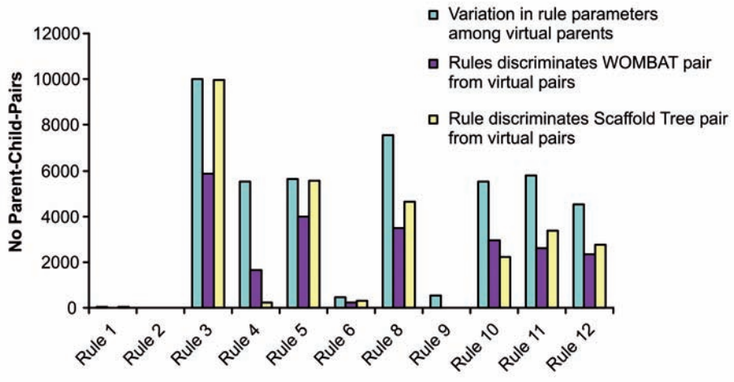

## Biological Relevance of the Pruning Rules

### Data Set Generation




→ **Biologically relevant selection of parents**

### Rule Analysis

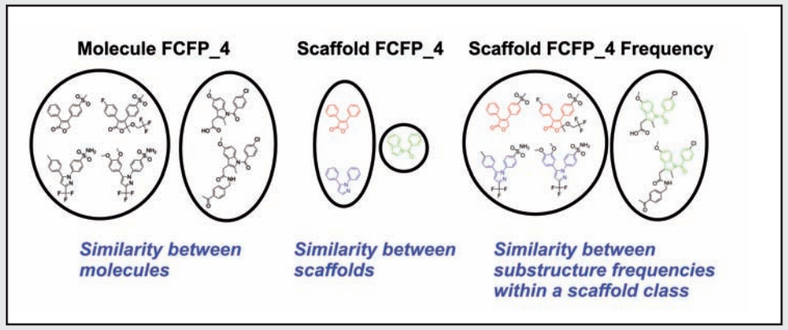



→ **Scaffold Tree rule frequencies similar to the ones observed in WOMBAT parent-childs!**

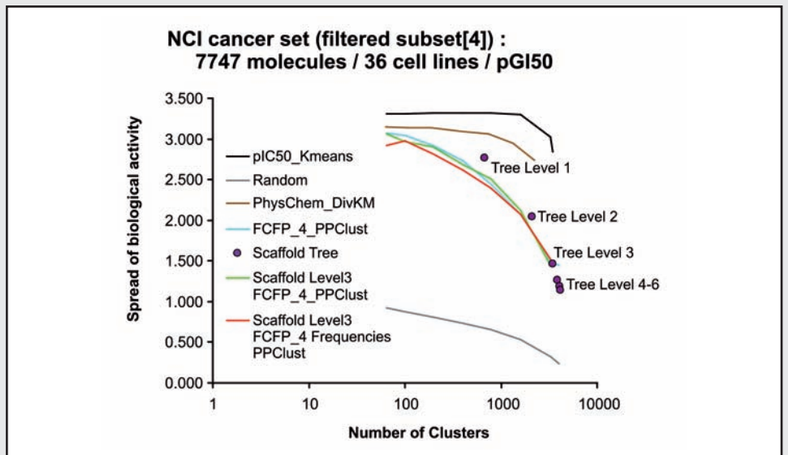
**Brachiation strategy valid ligand design strategy!**

## Biological Relevance of the Scaffold Concept

### Clustering Approaches




### Cluster Analysis




→ **Scaffolds as efficient as full molecules for biology relevant clustering!**

**Prospect for scaffold hopping!**

## References

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