Identifying Medicinal Chemistry Relevant Scaffolds for Scaffold Hopping

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We have developed and applied a scaffold hopping protocol based on Scaffold Trees. This protocol includes a similarity search performed between a query scaffold and compound library represented as Level 1 scaffolds from the Scaffold Tree. A prospective validation of this protocol identifies active compounds that are more structurally differentiated from the query.

We have identified some limitations of the application of Level 1 scaffolds in our scaffold hopping protocol and therefore require a scaffold representation better suited to our requirements. We have developed a new scaffold representation for use in our scaffold hopping protocol that uses simple scores to retain ring systems that make up the most medicinal chemistry relevant scaffold.

We have applied our scaffold representation to 20 medicinal chemistry series extracted from the ChEMBL database. We show that in 17 of the 20 series, our scaffold representation performs better at identifying the common key chemotype of the series than the Level 1 scaffold and the Murcko framework.