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Development and Validation of Methodology for Designing and Analysis of Virtual Combinatorial Libraries Based on Defined Reaction Pathways.

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New synthetic methods in combinatorial chemistry, such as parallel solid-phase synthesis, enable preparation of large number of compounds for drug development screening campaigns in a very fast and efficient way. Large libraries of compounds are usually synthesized as combinations of different building blocks (BB's) [1,2]. However, the number of compounds that can be synthesized using elaborated synthesis protocol, and tested for biological activity (even in HTS) is often limited by the project's budget. In that case, methodology enabling prioritization and helping in decision making of which compound, from the available synthetic space, should be obtained first, would be very useful.
Herein we present a new approach to generating and ranking of the virtual combinatorial library based on defined chemical reactions [3]. For searching a specified type of substrates, the biggest 26 vendors building blocks databases were used. All the possible combinations of the selected building blocks with core substructures resulted in approx. 15×106 synthetically available compounds. By applying a modified protocol of multistep Virtual Screening the ranking list of the best derivatives was obtained.
In collaboration with medicinal chemists, several compounds were selected, synthesized and biologically evaluated in order to verify the effectiveness of the methodology applied.

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