

Cheminformatics Analysis of Natural Products. Lessons from Nature Inspiring the Design of New Drugs

Peter Ertl

Novartis Institutes for BioMedical Research, Basel, Switzerland

Natural products (NPs) have evolved over a very long natural selection process to form optimal interactions with biological macromolecules. NPs are therefore a valuable source of inspiration for the design of new drugs. As illustrated in this study, application of cheminformatics techniques can provide useful help in this endeavor. First the physicochemical properties of NPs and their typical structural features are compared to those of bioactive molecules and average organic molecules. Then the substructure analysis of NPs is performed, with particular focus on comparing NP scaffolds with those of common synthetic molecules. The relationship between the structure of NPs scaffolds and the type of organism from which they have come is also analyzed.

To provide a guide for the design of NP-like bioactive structures a novel method to calculate natural product-likeness score is described. This score, which allows to determine how molecules are similar to the structural space covered by natural products, is shown to efficiently separate NPs from synthetic molecules in a crossvalidation experiment. Possible applications of the NP-likeness score are discussed and illustrated on several examples including prioritization of compound libraries towards NP-likeness and design of building blocks for the synthesis of NP-like libraries.

Hopefully the results of this analysis help to eliminate the old myth about NPs as being “too complex” or having “bad properties”, as well as help us to focus on these areas of NP structural space which are essential for biological activity, taking advantage of the long process of natural selection to guide us to new and as yet unexplored areas of the chemical structure universe.

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