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EDITORIAL

Natural Products in Drug Discovery

Natural products are an important source of new structures leading to drugs in all major disease areas. This issue of CHIMIA illustrates current activities and trends in natural products research and drug discovery.

Finding new habitats of fungi, bacteria or plants and identifying new living organisms has been a continuous challenge. Mark Hamann *et al.* explore marine organisms for new secondary metabolites. Kurt Hostettmann and Andrew Marston identify new biologically active natural products in plants and plant material used in traditional medicine.
Testing and identifying biologically active natural products from microbial or plant extracts in today's high-throughput screening (HTS) environment poses a challenge to sample preparation and single component identification. The three articles by Mark Butler and coworkers, Thomas Henkel's group and Dietmar Wolf and Karsten Siems explain different approaches in library production and sample characterization from extracts. Harald Schröder and coworkers give an overview on single compound structure elucidation as an efficient and timely process integrating and combining IR-, MS- and NMR-spectroscopic methods.
In silico characterization of natural products and pharmacophore modeling is challenging, particularly for complex and conformationally flexible molecules such as macrolactones or peptides. Herbert Waldmann and coworkers review cheminformatic characterizations of natural products and the new concept of the structural characterization of natural products, termed SCONP. Thierry Langer *et al.* apply pharmacophore-based virtual screening to identify bioactive natural products against valuable drug targets.
Medicinal chemistry is the cornerstone for successful hit to lead exploration and further lead optimization. Serine protease inhibitors derived from oscillarin with activities against thrombin and factor XIa are described by Stephen Hanessian *et al.* Karl-Heinz Altmann and coworkers provide a comparative analysis of tubulin polymerization inhibitors from plants.
Finally, Karl Gademann elucidates the antifouling and other manifold biological activities of nostocarboline, a metabolite isolated from cyanobacteria.

Most recently, Newman and Cragg[1] reviewed the drugs introduced on the market over the last 25 years with emphasis on contributions by natural products. An increase in productivity in the drug discovery process has been achieved with the implementation of library chemistry and HTS technologies. Despite these efforts the number of new chemical entities reaching the market has not increased. Only one drug originated from a *de novo* combinatorial chemistry approach. However, the natural products remain an important source of structures contributing to mostly semi-synthetic or synthetic drugs in all disease areas.
Lipinski's 'Rule of Five' (RO5)[2] has been one of the most effective guiding principles in the selection of hits and leads over the last decade. Potentially successful drug substances need to comply with those physicochemical parameters. As a consequence of the rigorous application of this rule natural products were de-prioritized or even eliminated from the drug discovery process. At some point it was proposed to exempt natural products from RO5; some do not comply to the rule but prove to be excellent drugs.[3]

Natural products have been optimized over long time periods against their gene product. Therefore, therapeutic effects of natural product-derived drugs are predominantly achieved in antibiotic therapies, oncology and immunoregulation. It is less likely to identify potent natural products against molecular targets of human diseases in indications such as the nervous or cardiovascular systems. Those targets are generally not related to the biological environment of the producing organism. Nonetheless, higher hit rates are generally obtained for natural product libraries in HTS campaigns compared to medchem or combichem libraries. Natural products are a valuable source of unsurpassed structural diversity and functional density to identify screening hits.
Given that only a tiny fraction of the microbial world has been explored and new synthetic methodologies are only gradually applied in natural product small library synthesis, one can expect many more molecules derived from nature with surprising biological activities. After being neglected for years natural products drug discovery has reclaimed attention and is on the verge of a comeback.

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[1] D. J. Newman, G. M. Cragg, *J. Nat. Prod.* **2007**, *70*, 461.
[2] C. A. Lipinsky, F. Lombardo, B. W. Dominy, P. J. Feeney, *Adv. Drug Del. Rev.* **1997**, 3; RO5: not more than 5 H-bond donors, not more than 10 H-bond acceptors, MW <500 g/mol, logP <5.
[3] J. Owens, *Drug Disc. Today* **2003**, *8*, 12.

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