ELSEVIER

Combinatorial chemistry

Editorial Overview

Prabhat Arya and Hans-Jörg Roth

Current Opinion in Chemical Biology 2005, **9**:229–231

Available online 5th May 2005

1367-5931/$ – see front matter

DOI 10.1016/j.cbpa.2005.04.009

Prabhat Arya

Steacie Institute for Molecular Sciences, National Research Council of Canada, 100 Sussex Drive, Ottawa, ON, K1A 0R6, Canada
e-mail: Prabhat.Arya@nrc-cnrc.gc.ca

PA is a Senior Research Officer at the Steacie Institute for Molecular Sciences, National Research Council of Canada, and an Adjunct Professor at the Ottawa-Carleton Chemistry Institute, University of Ottawa and the Department of Biochemistry, McGill University. He obtained a PhD from Delhi University (1985) and worked as a post-doctoral fellow with Professors Robert Corriu (France), Ian Paterson (UK) and Bill Chan (Canada). His research group is developing combinatorial chemistry methods leading to the library generation of natural product-like, small molecules in search for the chemical dissectors of bio-macromolecular interactions and protein networking-based signaling pathways.

Hans-Jörg Roth

Novartis Institutes for BioMedical Research, Lead Synthesis & Chemogenetics, CH-4002 Basel, Switzerland
e-mail: hansjoerg.roth@novartis.com

H-JR is group leader in the Novartis Institute for Biomedical Research. He gained his PhD in synthetic organic chemistry at the ETH in Zürich with Professor Albert Eschenmoser. In 1991 he joined Novartis (former Sandoz) as a medicinal chemist, and in 1994 he joined the newly formed group for combinatorial chemistry. Since then, he has been involved in the development and the application of combinatorial methods for high-throughput synthesis in solution. Since 2001, his group has been responsible for a program that applies the method of focused and discovery library synthesis to enrich the Novartis compound archive for lead finding.

Combinatorial chemistry has been with us for a long time, such that it has brought several new ways of undertaking medicinal chemistry research projects. Some undertakings include (i) the utilization of solid-phase organic synthesis, (ii) the ability to carry out organic reactions in a parallel manner, and (iii) the use of solid-supported reagents and catalysts. Over the years, combinatorial chemistry has had a remarkable influence on developing new technical directions too (i.e. advanced instrumentation) in the area of high-throughput analytical chemistry. In medicinal chemistry, however, efforts are more geared towards speeding up the generation of small molecules and subsequently bringing useful small molecules into the medical arena.

As a combinatorial chemistry community, we have accomplished the production of simple organic compounds in a high-throughput manner. In most cases, these efforts have led to simple compounds, lacking the general features that natural products offers. Due to the simple structures, combinatorial chemistry has certainly lacked broad interest and, thus, has not been very successful in attracting global attention from the organic synthetic community. Why this has been the case is a question we need to address!

In the past few decades, the field of organic synthesis has been a powerhouse for generating new and smart methodologies leading to the efficient synthesis of highly complex natural products. Progress in the area of stereoselective and enantioselective organic synthesis has been phenomenal, and this knowledge has benefited the medicinal community tremendously. It is crucial that the combinatorial chemistry community starts to benefit from the advancements made in the past few decades in the area of advanced organic synthesis. As a result, insight gained from organic transformations is going to lead to the development of combinatorial synthetic projects to obtain a rapid access to biologically relevant chemical probes.

Since nature has been very successful in providing bioactive small-molecule chemical probes (for example, alkaloids, flavonoids, terpenes and polyether antibiotics) to the biological and medical community, these compounds provide a stimulating direction to chemists interested in developing small-molecule probes for dissecting cellular pathways. In most cases, these compounds are rich in stereochemistry, rich in chiral functional groups and possess three-dimensional architectures. These features appear to be highly important in exhibiting selectivity to protein binding and in differentiating closely related proteins. Several examples of natural products have been used to dissect bio-macromolecular interactions (protein–protein, protein–DNA/RNA) in a highly organized manner.

Therefore, the inherent three-dimensional complex nature of natural products is an intriguing property that remains to be captured by the combinatorial community.

From a historical perspective, the research efforts made in classical combinatorial chemistry can be briefly outlined in three phases:

1. In the early 1990s, the initial efforts in the combinatorial chemistry arena were driven by the improvements made in high-throughput screening (HTS) technologies. This led to a demand for access to a large set of compounds for biological screening. To keep up with this growing demand, chemists were under constant pressure to produce compounds in vast numbers for screening purposes. For practical reasons, the molecules in the first phase were simple peptides (or peptide-like) and lacked the structural complexity commonly found in modern organic synthesis literature.
2. The second phase started in the late 1990s, when chemists became aware that it is not just about numbers; but something was missing in compounds produced in a combinatorial fashion. Emphasis was thus shifted towards quality rather than quantity.
3. Like the first phase, the third phase had its origin in progress made by the biomedical community. As the scientific community moved into the post-genomic chemical biology age, there was a growing demand in understanding the role of newly discovered proteins and their interactions with other bio-macromolecules (i.e. other proteins and DNA or RNA). For example, the early goals of the biomedical research community were centered on the identification of small-molecule ligands for biological targets, such as G-protein-coupled receptors (GPCRs) and enzymes. However, the current challenges are moving in the direction of understanding bio-macromolecular (i.e. protein–protein, protein–DNA/RNA) interactions and how small molecules could be utilized as useful chemical probes in systematic dissection of these interactions. By no means will this be a trivial undertaking! The development of biological assays towards understanding biomacromolecular interactions is equally challenging as the need for having access to useful small molecule chemical probes.

After working in the area of combinatorial chemistry for some time, as a community, we asked ourselves how society has benefited from embracing this field. We also wanted to convey to the scientific community that complexity in small molecules (serving as chemical probes) will impact our understanding of the biological pathways found in cellular systems such as the signaling pathways. This special issue addresses these concerns in four different sections.

Section 1: Combinatorial chemistry approaches to obtaining natural product analogs

The article by **Waldmann and co-workers** strongly advocates the need for staying close to natural products when it comes to designing small-molecule chemical probes. The rationale behind this philosophy is that natural products have gone through the evolutionary process, and thus serve as a useful guiding principle for developing combinatorial chemistry programs.

Section 2: Diversity-oriented synthesis approaches to obtaining natural product-like compounds

Several leading research labs have contributed their views and outlined their perspectives to this relatively new and growing area within combinatorial chemistry. As mentioned earlier, the goal here is to develop combinatorial chemistry programs that provide small-molecule chemical probes that are (i) rich in three-dimentional architectures, (ii) rich in stereochemistry, and (iii) are either natural product-directed or natural product-like. This section begins with a contribution from **Reayi and Arya** that clearly describes the challenges, advantages and biological results in developing natural product-like small molecule probes to be used as systematic chemical dissectors of biomacromolecular interactions. By citing a few examples from the literature on the use of natural products, the article also emphasizes the need for charting the chemical space that is currently occupied by natural products. A similar voice is also echoed by articles from **Shang and Tan** and by **Messer, Fuhrer and Häner**, who are advocates of using diversity-oriented synthesis to obtain natural product-like compounds. Several examples discussed in these two articles further validate the need for developing such chemical probes in a high-throughput manner.

In the next category, an article by **Ulaczyk-Lesanko and Hall** nicely presents the growing use of multicomponent reactions in producing libraries of complex natural derivatives. The development of stereoselective, multicomponent-based methods are in demand and we are going to see a rise in this demand in coming years. On the other hand, **Beeler, Schaus and Porco Jr** advocate the convergent approaches to producing chemical libraries of hybrid natural products. Several examples that utilize different ligation-based strategies clearly testify the power of this approach in rapidly generating complex small molecules. Finally in this section, an article by **Seitz and Reiser** focuses on developing diversity-oriented synthesis approaches that are targeted to mapping the chemical space around γ-butyrolactones.

Section 3: Chemical vs biological space

An article from **Roth** has a different perspective on the notion of diversity. Diversity is an element of function-

ality where the response of diversity is measured by the application of external criteria such as a biological assay. The author asserts that a relevant diversity of chemical structures, *per se*, does not exist.

An article from **Haggarty** nicely describes the need for developing tools for better understanding the complementarity between chemical and biological spaces. With a few examples of the recent work from the Broad Institute, the use of several descriptors to understanding the chemical space and its relevance to the biological world is outlined. The author also describes how this knowledge could assist in developing chemical genomics program for systematic understanding of the interactions of small molecules with biological systems.

Spring and co-workers give an overview on the assessment of structural diversity in combinatorial synthesis. Finally, **Selzer, Roth, Ertl and Schuffenhauer** report their results in finding a descriptor that describes the type of complexity of chemical structures which is able to differentiate between biological active and inactive compounds.

Section 4: The emerging biological challenges; protein–protein interactions and protein networking-based cell signaling pathways

This section is aimed at outlining a few emerging biological challenges and the desperate need for developing biologically relevant small molecule probes that could help in understanding (and dissecting) complex interactions. The editors of this issue are of the opinion that the field of combinatorial chemistry has the potential to impact this area of research and hope that the articles covered in the section will serve as a stimulating biological direction for the newer generation of combinatorial chemists. For example, the article by **Arkin** clearly outlines the need for developing small molecules as modulators (inhibitor or promoter) of protein–protein interactions. Protein–protein interactions are central to protein networking-based cell-signaling events and their modulation by small molecules provides a highly useful starting point in understanding their roles in complex cellular protein networking pathways. Because of the dynamic and multiple roles of protein interactions in networking pathways, the use of chemical tools (by chemical genetic approaches) to modulate these interactions in a systematic and reversible manner is very much required. On the same level, an excellent overview by **Johnson and co-workers** describes protein networking machinery in MAPK kinases. These authors also discuss the role of protein networking machinery in organizing cellular signals and protein trafficking events. The systematic chemical dissection of protein networking pathways is likely to provide a better understanding into its precise roles. At the same time, it offers a challenging task for the combinatorial community to develop small molecule-based programs that could assist in dissecting such interactions in a highly organized manner!