



## EDITORIAL

### Combinatorial Chemistry and Natural Product: Recycling the Past in the Present

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Historically, natural products from microbial, marine, plant and animal sources have provided a useful starting point for the development of important drugs. For example, the antimalarial - quinine and artemisinins, the opioid analgesics - morphine, the antineoplastic - paclitaxel, the antibacterial – penicillins, the anticancer and antiviral – cytarabine, just to mention a few, are derived from natural products. Despite these many successes, the discovery of drugs from natural products is a time- and resource-intensive endeavour. Therefore, scientists have devised several other approaches for the discovery of therapeutically useful molecules.

One of such approaches is combinatorial chemistry which was developed to support high-throughput screening (HTS) campaigns. It allows the simultaneous/parallel synthesis of a large number (hundreds to thousands or even millions) of the possible compounds that could be formed from a number of building blocks. The products of such a process are known as combinatorial libraries. Libraries may be a collection of individual compounds or mixtures of compounds. Screening the components of a library for activity using HTS techniques enables the selection of suitable compounds for more detailed investigations.

The development of combinatorial synthesis and high-throughput screening has allowed scientists to generate a range of new molecular structures and observe how they interact with biological targets. Over the last few decades, Combinatorial chemistry has made tremendous strides in organic synthesis and has already become a standard part of the repertoire used in drug discovery.

Conventionally, combinatorial chemistry technologies have been focused on solid-phase synthesis which is particularly suited for very large libraries, especially those featuring the repetition of a few reliable carbon-heteroatom bond-forming reactions such as peptides. Solution-phase library synthesis is increasingly becoming popular. Here, a plethora of organic reactions are available, but high-throughput workup does require more creative solutions than simple filtration as in solid-phase synthesis. Over the years, combinatorial technologies have continued to evolve. Dynamic combinatorial chemistry, a technique that makes use of equilibrium processes in libraries is now being employed to identify enzyme inhibitors and novel receptors. Deconvolution methods have been used as a technique to identify active compounds in libraries. Microwave heating has been used to reduce reaction times and reagent requirements in combinatorial syntheses. Polymer-supported reagents and scavengers

are also of growing interest as possible solution to some of the challenges associated with conventional solid-phase synthetic techniques.

The fields of natural products and combinatorial chemistry have major differences as well as much in common. Unique to combinatorial chemistry is the need to devise rapid and efficient methods for parallel synthesis and purification, while an area of overlap is the targeting of natural product scaffolds for combinatorial libraries.

An important question in this rapidly evolving field is how does one select a scaffold around which to build a library for drug discovery? One answer to this is to choose a biologically active natural product, whose structure is already the result of combinatorial experimentation by nature.

This approach involves combining the power of natural products and organic chemistry, ranging from the total synthesis of natural products, the combinatorial construction of libraries around the natural product core structures to the exploration of natural product scaffolds and the design of completely unnatural molecules that resemble natural products in their molecular characteristics.<sup>1</sup>

#### Natural product-like libraries

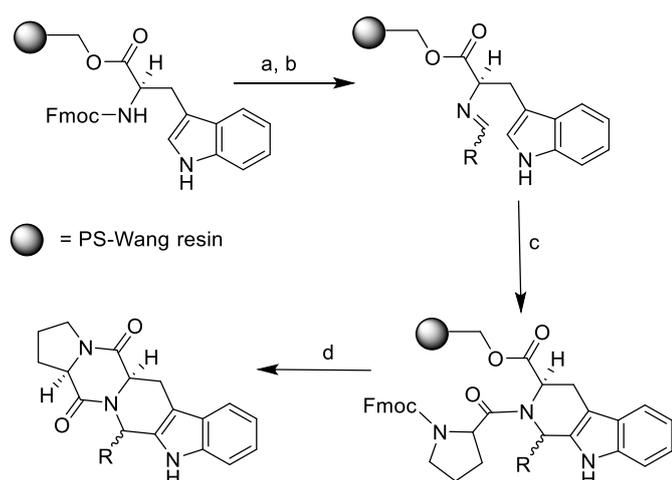
Until recently, the field of diversity and library design has not paid attention to natural products as sources of compounds. The neglect of natural products in this regard is due to the fact that the early days of combinatorial library design was focused on reaction-based approach and the view that natural products are often complex and not amenable to synthetic manipulations. To fully harness the potential of natural products, it is necessary to be able to synthesize analogues and discover structure-activity relationship (SAR) in a rapid, precise and efficient manner. Combinatorial chemistry has risen to this challenge. It is now possible to target natural products for combinatorial synthesis. Research efforts in this field, although still in their infancy, have employed natural products from the peptide, polyketide, alkaloid, terpenoid, flavonoid and steroid classes in combinatorial chemistry approach for the production of medicinally useful compounds.<sup>2,3</sup>

Several scientists are leading the way for the construction of natural product-like libraries. Some important successes in the integration of natural products and combinatorial chemistry are;

- Synthesis of a natural-product-based library starting from the labdane diterpenoid - andrographolide. The use of andrographolide in parallel solution-phase synthesis resulted in a 360-membered library.<sup>4</sup>

- Synthesis of two resin supported teicoplanin aglycone moieties via iminodiacetate based spacers.<sup>5</sup>
- Combinatorial synthesis of the indole alkaloid demethoxyfomitremorgin C using Wang resin in both solution- and solid-phase.<sup>6</sup>
- Synthesis of a family of the quinazoline derivative - fumiquinazoline G on solid-phase.<sup>7</sup>
- Synthetic transformation of gibberellic acid, adrenosterone and quinine has led to the construction of >160 complex and diverse compounds.<sup>8</sup>
- Synthesis of an oxepane library inspired by the core structure of oxepane natural products resulted in 115 oxepanes.<sup>9</sup>

This approach of transforming natural products via combinatorial synthesis has provided a number of interesting and biologically useful scaffolds. However, the selection of the synthesized compounds is based on the assessment of its members with respect to physicochemical parameters, thus ensuring pharmacological relevance of the compounds.



**Figure 1:** Solid phase synthesis of demethoxyfomitremorgin C and its analogues, R = alkyl or aryl group. (a) 20% piperidine, CH<sub>2</sub>Cl<sub>2</sub> (b) R<sub>1</sub>-CHO, HC(OMe)<sub>3</sub>, CH<sub>2</sub>Cl<sub>2</sub> (c) Fmoc-L-ProCl, pyridine, CH<sub>2</sub>Cl<sub>2</sub> (d) 20% piperidine, CH<sub>2</sub>Cl<sub>2</sub>.<sup>6</sup>

## Conclusion

In recent times, combinatorial chemistry has become an important catalyst in fueling major improvements in organic synthesis. The scope and limitations of several venerable reactions is now much better understood with their incorporation into combinatorial sequences for the generation of compound libraries. Combinatorial chemistry also has a growing impact on natural product total synthesis. Drawing attention to the interplay of drug discovery, natural products, and Combinatorial Synthesis of Natural Product-Based Libraries contains the most recent and significant methods used to search and assess new compounds for their ability to mitigate biological processes that may lead to improved treatments for various diseases.

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