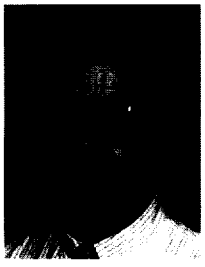
Combinatorial chemistry – the way forward



The author considers the role of this 'all-pervasive' branch of chemistry and how *Drug Discovery Today* will keep readers informed of future developments

Combinatorial chemistry was thrust upon an initially sceptical scientific community in 1991, following seminal papers from Hruby and Houghten that described the rapid synthesis of peptide libraries[1,2]. However, since then we have seen a phenomenal explosion in interest and involvement in this area of chemistry, and have now reached a position where combinatorial chemistry is almost universally accepted as a routine tool for all practising chemists.

So all-pervasive has combinatorial chemistry become, that it is being recommended in academic centres that a basic understanding of the principles and techniques be engendered through inclusion of relevant lectures in all undergraduate chemistry courses. All research chemists may have need of such high-speed techniques at some time, whether it be for reaction optimization, catalyst design, lead discovery or drug optimization.

Initially, exponents of combinatorial chemistry investigated and promoted the use of a wide range of different techniques. The opinions of the key research groups were highly diverse; eminent chemists advocated every variation of technique, including the synthesis of single compounds or mixtures, the use of solid-phase or solution techniques, or use of thorough structural analysis or, essentially, none.

However, in the last few years we have seen two consolidating features in this branch of chemistry. First, this wide range of techniques is shaking down to a smaller number of tried and trusted approaches, which have each been successfully employed by many research groups worldwide. Second, there is a wider acceptance of some need for a diversity of techniques. Many different tools come under the broad umbrella of combinatorial chemistry, and exponents accept that each and every one of these may have a relevant application to some stage of the drug discovery process. No longer do we see combinatorial chemists in dispute over the best way to use the technology.

Drug discovery, in particular, has benefited from the applications of these new techniques[3]. Frequently, failure to discover lead compounds has been due to insufficient availability of compounds for screening programmes, both in terms of number and structural diversity. Consequently, combinatorial chemistry has been whole-heartedly embraced.

Because of the impact of combinatorial chemistry on the many stages of the drug discovery process, it is appropriate that *Drug Discovery Today* covers the important advances in this fast-moving branch of chemistry. This issue of *Drug Discovery Today* focuses on topical issues in combinatorial chemistry – scientists from CombiChem report on the recent *Molecular Diversity* and *Solid-phase Synthesis* meetings, held in San Diego (p. 132), and there is an excellent overview of the contribution of solid-phase combinatorial chemistry to drug discovery from Affymax (p. 134). Starting with the May issue of *Drug Discovery Today*, the latest developments and key issues in combinatorial chemistry will feature in a dedicated column in the *Monitor* section of each issue. Additionally, to meet the demands of researchers in all areas of combinatorial chemistry, the journals *Bioorganic and Medicinal Chemistry* and *Bioorganic and Medicinal Chemistry Letters* especially welcome submissions of papers describing new techniques and applications in this field. There will also be a special page in *Tetrahedron Alert* featuring current papers from the *Tetrahedron* journals that cover all aspects of combinatorial chemistry, including solid-phase chemistry, library design, synthesis and applications.

Where will this technology take us in the future? Most chemists are agreed that this is a methodology that is so valuable to drug discovery, that it is with us to stay. Only the details will change, as chemists attempt to make the techniques more reliable, predictable and accessible.

The techniques of combinatorial chemistry were developed primarily for generating increasingly large numbers of compounds. However, making large numbers is not the only objective; after all, it takes only one compound to make a drug. The most promising developments in the future therefore will be those that exploit the potential of combinatorial chemistry in smarter and more creative ways. Quality rather than quantity will become the new goal. In coming months, we will report within *Drug Discovery Today* on all the significant advances in the application of combinatorial chemistry.

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REFERENCES

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