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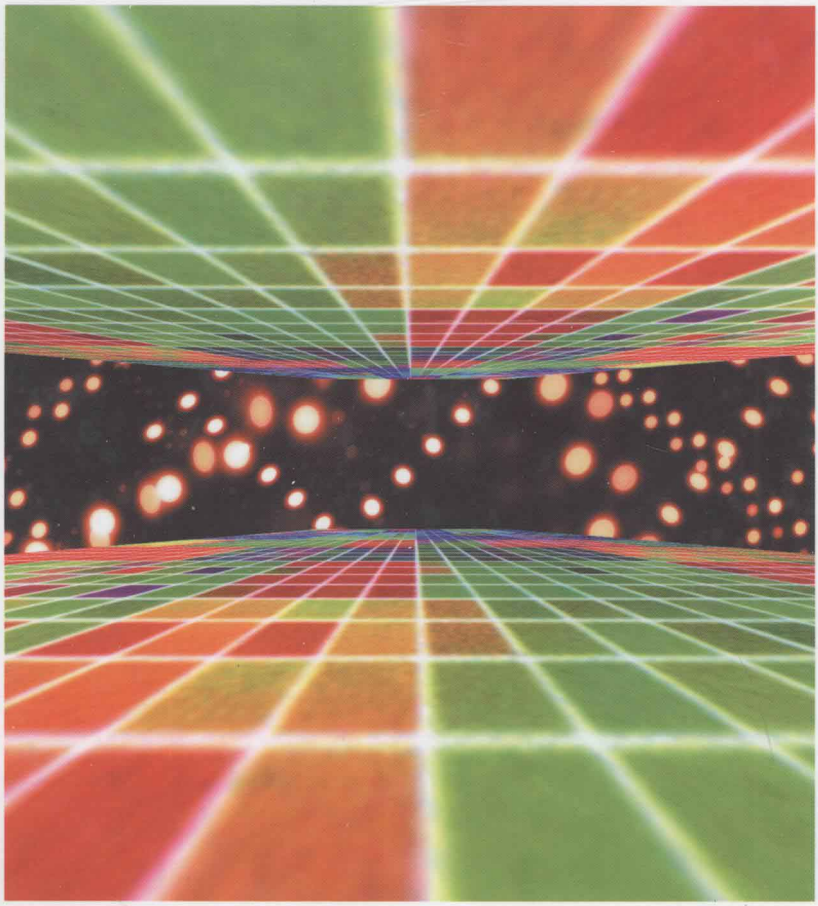
Combinatorial Chemistry

From Theory to Application

Second, Revised Edition



Volume 26

Series Editors:
R. Mannhold,
H. Kubinyi,
G. Folkers

Willi Bannwarth, Berthold Hinzen (Eds.)

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Second Revised Edition

WILEY-VCH Verlag GmbH & Co. KGaA

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Cover illustration:
Library of Congress Card No. applied for.

British Library Cataloguing-in-Publication Data: A catalogue record for this book is available from the British Library

Die Deutsche Bibliothek – CIP Cataloguing-in-Publication-Data: A catalogue record for this publication is available from Die Deutsche Bibliothek

ISBN 3-527-30693-5

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Printed on acid-free and chlorine-free paper

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Cover: Grafik-Design Schulz, Fußgönheim
Composition: Typomedia GmbH, Ostfildern
Printing: Strauss GmbH, Mörlenbach
Bookbinding: Litges & Dopf Buchbinderei GmbH, Heppenheim

Printed in the Federal Republic of Germany.

W. Bannwarth, B. Hinzen (Eds.)
Combinatorial Chemistry

Methods and Principles in Medicinal Chemistry

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Preface

Combinatorial chemistry marks the biggest revolution in synthetic organic chemistry within the past 150 years, a break with classical strategies. Around 1985, in the early beginning, the new approach was oversold, as so many drug discovery technologies are in their very beginning. The production of huge libraries of mixtures of poorly defined analogs was in the foreground. Much hope (and hype) existed at this time. It was anticipated that a vast number of new chemical compounds would more or less automatically produce an unprecedented number of new drug candidates; these early expectations failed completely, due to the lack of druglikeness of most libraries, in properties and in structures. Compounds were too lipophilic and, due to over-decoration, too large in their molecular weight.

After this failure, combinatorial chemistry matured in the mid-90's and underwent significant changes. It was the merit of Chris Lipinski at Pfizer, with his rule of five, to make the chemists of his company and the whole scientific community aware of the physicochemical properties that are typical for successful drug candidates. Nowadays, library production is not any longer driven by chemical accessibility (this, of course, still being a necessity) but by design, be it for pharma, agro, or materials. Instead of undefined mixtures, single purified compounds are produced by automated parallel synthesis, followed by solid phase extraction (SPE), high performance liquid chromatography (HPLC) or parallel column chromatography purification. The most important application of combinatorial chemistry resides in drug discovery but it is no exagggeration to say that the need for effectiveness in parallel synthesis stimulated the development of new techniques for classical synthesis. Just one example is the use of solid-phase reagents and scavengers in multi-step natural product syntheses.

Only a few years ago, in 2000, Willi Bannwarth and Eduard Felder edited the book "Combinatorial Chemistry – A Practical Approach" (Volume 9 of "Methods and Principles in Medicinal Chemistry"), which immediately became a standard text in this area. However, a few years are almost an eternity in this discipline: new techniques, new reagents, and new, exemplary applications demanded a new edition. Because of the significant updates and additions, this edition is published as a new Volume in our series.

The updated and, in part, completely new chapters of this book cover all important aspects of combinatorial chemistry, with special emphasis on solid-phase

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ISBN: 3-527-30693-5

organic synthesis, linkers and their cleavage, C–C bond formation, syntheses of heterocycles, polymer-supported reagents, encoding strategies, purification in high-speed solution phase synthesis, automation and devices, and computer-assisted library design. An Appendix provides information on cheminformatics and Web resources for combinatorial chemistry.

We are very grateful to the Editors Willi Bannwarth and Berthold Hinzen, and all chapters authors, for having undertaken this task. Last, but no least we thank the publisher Wiley-VCH, especially Renate Dötzer and Dr. Frank Weinreich, for the ongoing support of our series "Methods and Principles in Medicinal Chemistry".

Raimund Mannhold, Düsseldorf
Hugo Kubinyi, Weisenheim am Sand
Gerd Folkers, Zurich December 2005

A Personal Forward

Willi Bannwarth and Berthold Hinzen

Within the pharmaceutical industry, one of the major aims is to increase the number of new chemical entities (NCEs) launched each year. Simultaneously, a reduction in the development time of NCEs, together with a concomitant reduction in costs, is expected. One of the key disciplines by which this goal may be achieved is that of combinatorial chemistry, the emergence of which offers unprecedented rapid synthesis of compounds that may be monitored for their biological activity by using high-throughput screening formats. This, together with efficient data management and a constant influx of new biological targets, will undoubtedly lead to an acceleration in the process of drug discovery.

Combinatorial chemistry has a major impact on lead discovery as well as on lead optimization. While in the past the initial focus in lead discovery has been on the rapid synthesis of highly complex mixtures comprising minute amounts of individual compounds, this strategy has been largely substituted by the preparation of individual compounds in amounts of 5 mg to 50 mg, by the use of parallel synthesis. This is not quite what initial hype prognosed, but it is still much more efficient than the previously performed serial synthesis of compounds. The new compounds are stored by pharmaceutical companies in their repositories, and serve as a valuable asset for lead finding. The repositories may contain a relatively large number of diverse compounds of high purity in order to produce reliable screening data, and it is in this area that computational methods for planning the diversity of the envisaged libraries will, in future, play a vital role. The data obtained in screening processes can be used in combination with structural data of target proteins, leading to rational design approaches supported by molecular modelling.

Initially, the focus in lead optimization was on improving the *in vitro* activity. Now, it has been realized that other compound properties, such as like solubility and ADME parameters, are of equal importance and should therefore be addressed as early as possible.

During the development stages of combinatorial chemistry, it was believed that efficient synthesis was only possible only by using solid-phase strategies. In part, this was influenced by the rapid and highly efficient synthesis of peptides and oligonucleotides by robots on solid support materials. One should bear in mind,

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however, that it has taken decades to develop them to the current level of performance.

The main advantage of solid-phase synthesis is that large excesses may be applied, thereby driving the reaction to completion. In this way, higher yields can be expected as compared to the same reaction performed in solution, and with equimolar amounts of reactants. Moreover, the excesses of reagents may be removed by simple filtration, thus avoiding time-consuming purifications.

The so-called "split- and- combine" procedure, which permits the synthesis of a multitude of individual compounds to be carried out on bead particles, each of which has only one defined compound attached to it, albeit in multiple copies, has had a major impact on combinatorial chemistry. This approach minimizes the synthetic effort per compound, as compounds can be screened as mixtures either while they remain attached to the solid support, or after being released from the bead into solution. The split- and- combine approach is ideal for the synthesis of minute amounts of a plethora of compounds, but it has one disadvantage in that it is boun associated with a rather time-consuming deconvolution process that involves iterative rounds of resynthesis and screening of compound subsets in order to identify the active compound. The danger exists that the originally identified activity is the sum of several moderate activities, so that invariably the original activity is lost during the deconvolution process.

As an alternative, tagging strategies have been developed, in which the active molecule can be identified by placing a tag on the same bead. These procedures are rather tedious and, with the exception of radiofrequency tagging of small polypropylene reactors, have not fulfilled expectations.

Spatially addressed synthesis is yet another alternative. This does not play an important role in general combinatorial chemistry, but has been used successfully used in biochip applications such as in DNA -probe technology.

If the solid-phase synthesis of peptides and nucleotides is to be extended to general organic synthesis, a few stumbling blocks become apparent. Most notably, there is a the need for suitable linker entities whic that allow the for attachment of all kinds of starting materials and whic that should also guarantee an efficient release of the product after synthesis.

In peptide or nucleotide chemistry, the biopolymer sequence is assembled by repetitive cycles of identical chemical steps. In contrast, the synthesis of an organic compound usually involves different synthetic steps, each to being performed under specific conditions. The linker entity, which represents the adapter between the solid support and starting material, intermediate or final product, must withstand all these conditions and yet allow for the efficient and specific release of the desired compound, without side -reactions. Thus, it becomes clear that general organic synthesis on solid supports requires the development of a huge array of different linker molecule units that are suitable for the attachment of all types of functional groups, and thus permit the application of all types of chemistries. to be applied. In order to avoid the laborious development of linkers, alternative strategies have rbeen implemented, which were mainly based on a release of the desired compounds by a cyclization process.

Another problem when embarking on synthesis on solid supports is the difficulty in analyzing compounds attached to the at support. Methods arex available for analyzing compounds on individual beads, such as magic-angle spinning NMR or FT-infrared spectroscopy, but these are too demanding to be carried out on a routine basis on a multitude of beads.

A further limitation of general organic synthesis on solid supports arises from the limited types of support materials that are available. These also restrict the use of different types of solvents, as only those solvents can be employed whic that lead to a sufficient swelling of the polymer and hence to an acceptable reaction rate. As a result of the aforementioned restrictions, it became clear that synthesis on solid supports requires a somewhat careful and time-consuming optimization of the reaction conditions. However, once properly developed – and with the scope of the pertinent reactions carefully evaluated – solid-support-based synthesis offers high-speed preparations of compound libraries whic that can also be carried out also by automated synthesizers.

Due to the sabovementioned difficulties, however, a number of solution chemistry approaches have emerged as alternatives.

Multicomponent reactions offer a high degree of atom economy, but most of their productse rea typically tons require subsequent purification in order to obtain reliable screening data. Furthermore, the number of multicomponent reactions is rather limited, which, in turn, leads to a limitation co inc terms of ning structural variety. ies. For these reasons, we have omitted in this edition, the chapter on multicomponent reactions from this edition.

The development of methods employing biphasic systems in combination with suitable tag entities on the compound that affect their physical properties ihas offered an alternative to solid- phase chemistry since it allows the replacement of time-consuming chromatographic separation procedures by simple extraction steps, which can be performed in parallel. As an For example, pH-switchable tags have been applied successfully applied in these organic/aqueous systems. The most prominent biphasic systems are composed of ionic liquids and organic solvents. These systems are especially well suited for catalytic processes, and often there is no need cessity to incorporate special tags on the catalyst to mediate ing its solubility in the ionic liquid. Another class of biphasic systems is composed of fluorous solvents in combination with organic solvents. Such is systems require the application of perfluorinated tags.

Of great help in solution chemistry is are presented by solid-phase- bound reagents, which can be removed after reaction by a simple filtration process. The great potential of this approach has recently been demonstrated in a total synthesis of epothilones applying only solid- phase-bound reagents.

In contrast to the aforementioned elegant strategies to simplify work- up and purification stategi steps, large companies are focussing more and more on non-optimized solution chemistry followed by preparative HPLC with mass spectrometric detection. This is costly with respect to consumables but less labor- intensive.

Microwave-supportenhanced synthesis has become a valuable tool for reducing up reaction times and has meanwhile found widespread acceptance in the combinatorial chemistry community.

The decision as to whether solution chemistry or chemistry on a solid support should be applied to the preparation of a compound library also depends also on whether the generated compounds produced are to be screened either for lead finding or for lead optimization. In the latter case, an evaluation must be made as to whether analogues of the desired structure are best prepared in solution or by solid-phase approaches. On occasion, combinations of between the two strategies can be effective. It must be emphasized that lead optimization based solely on a by combinatorial approach es is often not possible, and in these cases a combination of traditional medicinal chemistry and a combinatorial approach es is the method of choice. However, as the more reactions are developed for combinatorial chemistry, the greater will be their impact in lead optimization.

This clearly requires the biological evaluation in appropriate screening systems. Since chemists are not always familiar with modern assay methods, we have added a chapter describing the general principles of assays suitable for high- throughput screening (HTS).

Finally, it should be emphasized that the influence of combinatorial methods will not only be apparent only in medicinal chemistry. Were the entire periodic system is to be exploited, then of all the molecules that are theoretically possible, only a very small fraction has vhitherto been synthesized and their properties explored. to date. Thus, a vast array of as yet unknown properties can be expected to be found through via combinatorial chemistry. This will have a particular impact in material sciences, and perhaps most notably in the search for new catalysts.

Freiburg und Wuppertal
December 2005

Willi Bannwarth and
Berthold Hinzen

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ISBN: 3-527-30693-5

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