SOLID-PHASE SYNTHESIS AND COMBINATORIAL TECHNOLOGIES

SOLID-PHASE SYNTHESIS AND COMBINATORIAL TECHNOLOGIES

Pierfausto Seneci
GlaxoWellcome Medicines Research Centre

WILEY-INTERSCIENCE
A JOHN WILEY & SONS, INC., PUBLICATION
New York • Chichester • Weinheim • Brisbane • Singapore • Toronto

This book is printed on acid-free paper. ♾

Published simultaneously in Canada.

Library of Congress Cataloging-in-Publication Data:

Seneci, Pierfausto, 1960–
Solid-phase synthesis and combinatorial technologies / by Pierfausto Secenci
p. cm.
Includes index.
ISBN 0-471-33195-3 (cloth: alk. paper)
1. Solid-phase synthesis. 2. Combinatorial chemistry. I. Title
QD262.S465 2000
547'.2—dc21 99-086954

Printed in the United States of America.

10 9 8 7 6 5 4 3 2 1

To Dora and Lorenzo, for their continuous support and for their indefatigable patience, which allows my being a father, a husband, and a writer.

CONTENTS

PREFACE

During the last decade, the emergence of the so-called high-throughput screening (HTS) technique in pharmaceutical research has allowed biologists to design and set up assays, aimed toward the identification of active compounds, that can test large numbers of compounds in a short time period. Great advances in automation, information science, data management, and related disciplines have contributed to create a typical environment where every biological laboratory requires tens of thousands of compounds to be tested on several assays in a week.

The challenge represented by this phenomenon for the medicinal chemists immediately appeared too demanding if only classical organic synthesis was to be used to provide biologists with the large number of compounds they needed. The assembly of large chemical collections derived from either commercial sources or from the proprietary chemical stores of major pharmaceutical companies was used to partially fulfil these needs; however, the limitations of these collections in terms of chemical diversity and as sources of positives on different biological targets were immediately apparent.

A new discipline capable of significantly increasing the throughput of chemical synthesis in terms of diversity and numbers of biologically relevant compounds has emerged to fulfill the HTS needs. This discipline, called combinatorial chemistry, officially dates to a few key papers that appeared in the mid-1980s and since then has experienced an enormous growth and has steadily attracted the interest of many researchers, at first only in pharmaceutical research but more recently in many other disciplines.

Since the beginning, combinatorial chemistry has strongly depended on the techniques of solid-phase synthesis (SPS). For this reason a detailed presentation of solid-phase (SP) chemistry in which the differences compared to classical organic chemistry in solution are highlighted appears at the beginning of this book.

The strong involvement of many other disciplines together with chemistry in the combinatorial arena prompts the more correct definition of combinatorial technologies, in which organic, inorganic, and analytical chemistry meet automation, statistical sciences, science information, data management, and various biological disciplines with the aim of producing and testing large number of high-quality compounds for one or more specific activity. The result is the extreme acceleration of the process of discovery of active entities, and examples of the use of combinatorial technologies in various applications will be presented. The main goal of this book is to provide the reader with the general concepts related to the core aspects of combinatorial technologies, and just to mention less well established approaches that have yet to prove their worth. An integrated description of related combinatorial disciplines will provide the reader with a general multidisciplinary overview of combinatorial technologies and

will hopefully be of help in understanding their enormous and still partially unexploited potential. The strengths and weaknesses of each significant approach that has appeared in the literature will be analyzed and critically discussed. Significant new trends will be presented and their possible future impact on combinatorial technologies will be analyzed.

Combinatorial technologies have been historically associated with pharmaceutical applications, and several chapters of this book are centered around this application. Several other emerging applications, though are exhaustively treated: entire chapters are dedicated to combinatorial libraries from biological sources and to inorganic or polymeric combinatorial libraries, and several sections illustrate the use of synthetic organic libraries in catalysis research, in molecular recognition, and in agricultural research among others.

This book is aimed at three main groups of readers. First, experienced combinatorial chemists and scientists will find coverage of the most recent combinatorial approaches and a detailed multidisciplinary bibliography, including more than 1700 relevant papers, reviews, books, abstracts, and patents, as well as coverage of every relevant aspect of combinatorial technologies. Second, experienced chemists who are approaching SPS and combinatorial technologies for the first time and who wish to enhance their knowledge of the area will discover the basic concepts of SPS and combinatorial chemistry and a critical evaluation of their applications to specific strategies and disciplines. This book, though, is mainly aimed at chemistry students at both graduate and postgraduate advanced course level who will find the concepts of SPS, combinatorial chemistry, and related combinatorial technologies presented in a clear and exhaustive format. The first five chapters are conceived to provide the material for a basic course on solid-phase synthesis and combinatorial technologies, with focus both on explaining the theoretical fundamentals of these disciplines and making them more obvious through many examples; appropriate citations allow the expansion of any subject according to the reader's interests. The following six chapters are dedicated to an expert treatment of combinatorial technologies which hopefully covers most, if not all of the combinatorial hot topics; each of these chapters, either alone or together with several others, can represent the material for advanced, postgraduate courses. A large number of relevant examples will be thoroughly described in Chapters 6 to 11 to clarify each of the theoretical sections. The accessibility of the original papers will allow both the students to follow up an intriguing subject and their professors to expand a specific subject and to make it even more suitable for an advanced, postgraduate course.

The goal to reach such a wide and diverse audience may be overambitious, but a good blend of basic principles and detailed information about combinatorial technologies should really be useful for many workers, or future workers, in the field. The homogeneous organization of the book should also be instrumental for the reader and for the student to receive a balanced but complete overview of this new and exciting discipline and hopefully attract the attention of new talented scientists, or soon-to-be scientists, who will eventually contribute to the future development of combinatorial technologies.

PIERFAUSTO SENECI
Verona, Italy