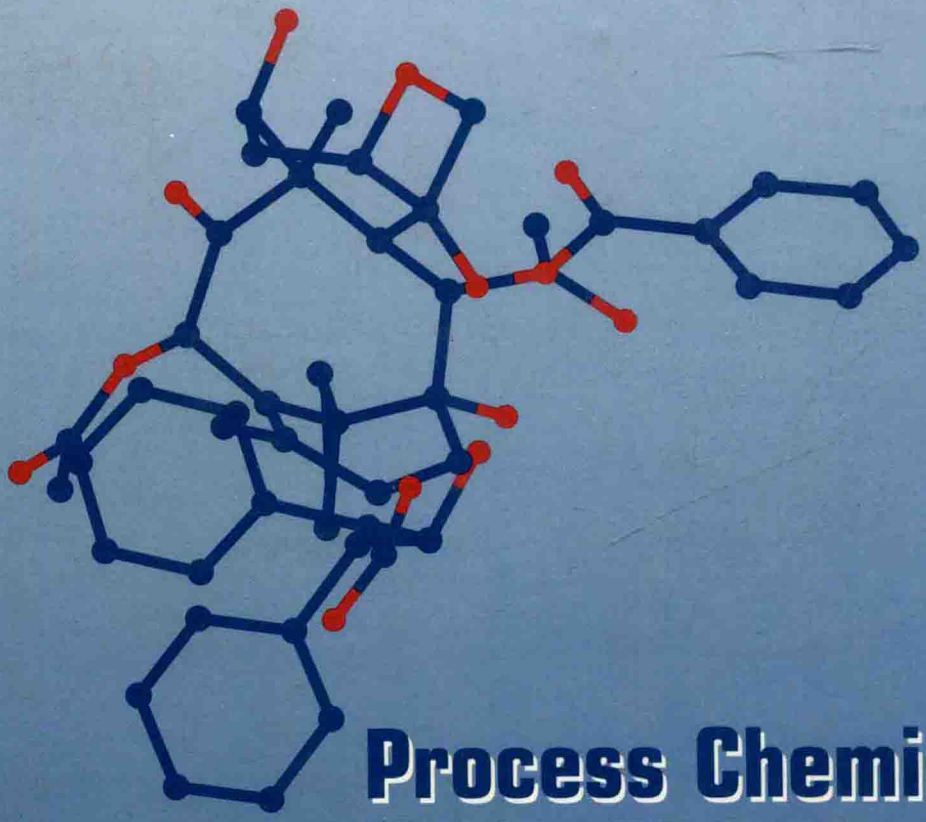

Process Chemistry in the Pharmaceutical Industry

edited by

Kumar G. Gadamasetti

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The Bristol-Myers Squibb Company
New Brunswick, New Jersey

and

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Thousand Oaks, California

MARCEL DEKKER, INC. NEW YORK · BASEL

Library of Congress Cataloging-in-Publication Data

Process chemistry in the pharmaceutical industry / edited by Kumar G. Gadamasetti.
p. cm.
Includes bibliographical references and index.
ISBN 0-8247-1981-6 (alk. paper)
1. Pharmaceutical chemistry. 2. Chemical processes. I. Gadamasetti, Kumar G.
RS403.P765 1999
615'.19--dc21 99-26854
CIP

This book is printed on acid-free paper.

Headquarters
Marcel Dekker, Inc.
270 Madison Avenue, New York, NY 10016
tel: 212-696-9000; fax: 212-685-4540

Eastern Hemisphere Distribution
Marcel Dekker AG
Hutgasse 4, Postfach 812, CH-4001 Basel, Switzerland
tel: 41-61-261-8482; fax: 41-61-261-8896

World Wide Web
http://www.dekker.com

The publisher offers discounts on this book when ordered in bulk quantities. For more information, write to Special Sales/Professional Marketing at the headquarters address above.

Current printing (last digit):
10 9 8 7 6 5 4 3 2 1

PRINTED IN THE UNITED STATES OF AMERICA

Process Chemistry in the Pharmaceutical Industry

To my brother Ram

FOREWORD 1

Chemists play major roles in the pharmaceutical industry. Some design and synthesize potential medicinal compounds and are often referred to as being in the "discovery" groups. Other chemists work in "development" groups, devising practical ways to make the compounds once their biological properties show that they have real medicinal potential. This work can lead to the synthetic schemes needed to make large amounts of a potential drug for animal and human testing, and then to the practical approach for manufacture of a compound that is approved for human or veterinary use.

In consulting with various pharmaceutical companies for almost 40 years, I have been impressed by the difference in chemical approach needed in these two areas. For drug discovery, a procedure is needed to produce the desired target compound rapidly, essentially without regard to cost or manufacturing practicality. A synthesis will be preferred if it proceeds through an intermediate that can branch to generate an entire family of potential drugs, in order to permit their evaluation. Normally, no time would be spent optimizing a reaction or inventing new reactions to achieve the goal. That time would have been wasted if the target compound turned out to be biologically uninteresting.

In development research, the target compound is known to be of significant biological interest, a potential product. Thus time must be spent to optimize the synthetic scheme, so it can be used to make large quantities of the target. Even early in the development stage the chemists are already considering whether the synthetic scheme—normally different from the one first used during the discovery phase—might be used for manufacturing if the candidate compound did survive further testing. The cost of reagents, and the cost of handling waste products, are kept very much in mind.

In both activities (drug discovery and development research), a firm grounding in synthetic organic chemistry is essential. In discovery research this should be supplemented by some knowledge of pharmacology and increasingly by some familiarity with computer design of molecules. Discovery chemists work at the chemistry/biology interface.

Chemists doing process research in the development groups must also have a good grounding in physical organic chemistry, as well as synthetic organic chemistry. They will be called on to change reactions so as to improve them, even to invent new reactions based on fundamental reasoning. They are working at the forefront of chemistry.

In the best companies, discovery and development are both very strong. The discoverers might have the excitement of actually inventing a drug; however, some beautiful chemistry can lead to a medicinal failure. Many thousands of compounds are made for every one that succeeds

as a useful medicine, so there is a good chance that someone could spend an entire career in discovery without coming up with a commercial product. The developers work on projects with a much higher likelihood that their efforts will contribute to an actual medicinal product. Also, they can afford to be truly inventive in their chemistry.

Both activities are enjoyable and challenging, and both are necessary parts of the great contribution that chemistry makes to health. This contribution needs to be better appreciated. I am glad to see that Dr. Gadamasetti has organized and contributed to this book that illustrates so well the world of process chemistry in the pharmaceutical industry. It is important reading for all those who want to understand how the miracle of modern medicinal chemistry is performed, especially for those considering a career in the pharmaceutical industry.

Ronald Breslow
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FOREWORD 2

When historians record the key scientific achievements of the twentieth century, they surely will note the role of pharmaceuticals in extending life expectancy and improving our quality of life. They undoubtedly will highlight the pharmaceutical industry's brilliant discoveries and the creative chemical and biological insights that led to them. An interesting question is whether or not historians will recognize the critical role that process chemistry has played in bringing these discoveries to the patient. This part of the "new drug" story often is less visible than the discovery part. Yet present in every drug discovery achievement is an exciting story of chemical process development. The successful launch of a new therapeutic agent requires the timely development of an economically feasible chemical process. The problems that must be solved to achieve this end are intellectually challenging and usually require creative chemistry. In the era of "green chemistry" and sustainability, the importance and value of world-class process chemistry can only rise in the pharmaceutical industry. *Process Chemistry in the Pharmaceutical Industry* tells a series of compelling stories that should help everyone to appreciate the importance of process chemistry in drug discovery and development.

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THE CHALLENGES OF PROCESS R&D

The translation of a laboratory method for making an organic chemical on a milligram scale to a production process on a kilogram to tonne scale while maintaining high quality, reproducibility, and minimum cost, is an extremely challenging task. Most organic chemists working in this field of process R&D find it intellectually stimulating, as well as very satisfying, when the process is eventually successfully operated on a large scale. As we move toward the end of the century, however, the challenges of process R&D are even greater, particularly in the pharmaceutical industry, for the following reasons.

The molecules are becoming more complex.

New drugs seem to have higher molecular weights, a wider variety of heterocyclic functionality, more chiral centers, and more complex structural features than drugs developed in the 1970s and 1980s. These drugs can only be made selectively by using the armory of new methodologies initially devised in academic laboratories but adapted for industrial processes on a larger scale.

The specifications and analytical chemistry requirements for new chemical entities are becoming increasingly narrow.

New drugs of the 1990s may be extremely pure (>99.9%) or their impurities have to be characterized when present in levels of 0.1% and below. These specifications place stricter requirements on intermediate, starting material, reagent and solvent quality such that analytical chemistry is a more important part of process R&D than in the past.

The time scale for developing new routes and new processes is much more compressed.

Since drug companies have compressed the time to market from a typical 8–10 years in the 1980s down to 4–6 years in the 1990s, the pressure on process R&D is now intense. Process research is often the rate-limiting step in moving a drug forward into trials—the need to generate kilograms of complex drug substance within months of the project being started means that organic process chemists must be even more innovative. The pressure to retain the chemistry devised by discovery chemists and simply scale it up is always present but, in my view, should be resisted. Time spent on developing a robust synthetic route suitable for large scale operation will pay for itself in the longer term, even if the effort encounters initial delays.

The legislative requirements of processes impose additional tasks on process R&D.

The Food and Drug Administration and other regulatory bodies have imposed (quite correctly, in my view) the concept of validation of processes on the pharmaceutical industry. The process R&D chemist is faced with extra tasks which require a more detailed understanding of each chemical reaction in the sequence, but this has the result that this understanding leads to better,

more reproducible processes. However, additional requirements regarding safety in scale-up and environmental issues all impact on the process research.

These challenges are being met by process chemists all over the world. In this book, case studies from process R&D in the pharmaceutical industry will show how these challenges have been addressed. Each company will approach the challenges in a slightly different way, and each new molecule brings its own problems, which require innovative and creative solutions.

The reader of this book will, I am sure, be stimulated by the chapters describing successful strategies for making these complex molecules efficiently, and in many cases on a tonne scale. Dr. Gadamasetti is to be congratulated on persuading so many industrial chemists to find the time to write up their work and that of their colleagues (after all, process R&D is very much a team effort) for the benefit of readers, both from industry and academia. This book will provide valuable teaching material for universities and will help students to understand the fascination of organic process R&D, hopefully persuading the best chemists to enter this most rewarding profession.

Trevor Laird
Scientific Update, UK
(Editor, *Organic Process Research & Development*)

PREFACE

On our return flight from the conference on Chiral Discrimination (1993) in Montreal, Canada, Conrad Kowalski (SmithKline Beecham Pharmaceuticals) and I were engaged in sharing some general views about process development in the pharmaceutical industry. We reached a consensus that chemical development, unlike the rest of the sciences, is not taught in academic institutions. Hence, the fresh graduates looking to pursue careers would less likely consider process research and development. This prompted me to organize a volume on process chemistry in the pharmaceutical industry. The conception came to reality due to the encouragement and support of my mentor, Chris Cimarusti, from Bristol-Myers Squibb Co.

The chapters in this volume have stemmed from in-depth discussions with several experts in the pharmaceutical industry and in academia. The principles and the practices related to process research and development are spread throughout the chapters in the volume. Each chapter has been contributed by experts in the specialized field. No attempt has been made to discuss the principles and the definitions of process research and development in a separate chapter. A conscious effort was made to choose the topics of the chapters and the division of the chapters so as to bring to the reader a complete picture of the chemical process development in the global pharmaceutical industry. Hopefully, the reader will have an opportunity to understand and apply the basic principles involved in the development of the active pharmaceutical ingredient of potential drugs to improve the quality of human life.

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ACKNOWLEDGMENTS

I wish to acknowledge Chris Cimarusti, Jerry Moniot, and Neal Anderson from Bristol-Myers Squibb Co. for their encouragement and continuous support throughout this project. I would also like to thank Ronald Breslow from Columbia University, Martin Kuehne from the University of Vermont, Tim Osslund from Amgen, Burt Chritensen (formerly from Merck Research Laboratories), Seemon Pines (formerly from Merck Research Laboratories), Paul Anderson (DuPont Pharmaceuticals) and Trevor Laird (Scientific Update) for their valuable ideas and suggestions. My special thanks to all my friends in the pharmaceutical industry for their input and support throughout the evolution, progress and completion of this volume. The main credit goes to all the contributors for their dedication and effort. I am indebted to all the reviewers for their time, constructive criticism and input. Finally, I would like to thank my wife, Vidya, who gave tremendous moral support during the preparation of this volume.

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