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New Synthetic Technologies in Medicinal Chemistry

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Foreword

I think everyone recognises the pharmaceutical industry has undergone, and is still undergoing, massive changes in the way drugs are discovered, synthesised and manufactured. The medicinal chemist plays a vital role in coordinating the wide-ranging scientific disciplines and driving technological innovations in the quest for these new medicines. This enormously complex task must also be responsive to the demands of our modern society, be they for economical reasons, having enhanced safety profiles or leading to environmental issues. Similarly, time-lines and the global nature of this highly competitive business add additional burdens to the discovery process.

For these many reasons the molecular architects who design these exquisite structures and the synthesisers who transform simple building blocks to functional systems are forced to be increasingly creative and innovative by taking their craft to a higher art form. The rapid evolution and incorporation of new tools and novel technologies together with advances that arise by challenging the chemical reactivity dogmas of the past provides the engine to drive future successes.

This book refreshingly brings together diverse concepts, techniques and processes, all of which enhance our ability to assemble functional molecules and provides the reader with a modern skill set and an appreciation of the dynamic character of medicinal chemistry today. Indeed, many of the authors remove the constraints and blinkers associated with the traditional labour-intensive practices of the past and provide a glimpse of the future. The chapters reflect modern thinking in terms of automation and parallel methods of synthesis, particularly focussing on design by making what *should* be made as opposed to what *can* be made.

There is an emphasis on work-up tools using solid-supported reagents and scavengers to eliminate many of the time-consuming unit operations necessary to obtain pure materials during unoptimised synthesis sequences. These

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concepts lead on naturally to methods of fast serial processing whereby microwave methods of heating are now commonplace in medicinal chemistry laboratories. Furthermore, opportunities arise by moving from conventional batch-mode synthesis to dynamic continuous or segmental flow-chemistry methods. This concept requires new thinking and apparatus but opens up exciting ways to conduct chemistry either in microfluidic channels or in larger systems which incorporate packed scavenger tubes to facilitate work-up using a machine assisted approach.

A further chapter focuses on high throughput reaction screening including biological methods. No longer is it acceptable to use expensive and talented operators to perform routine tasks; rather these should be relegated to more automated environments. Likewise, the use of software packages for reaction optimisation such as ''design of experiment'' and ''principal component'' analysis are now widely adopted and proving their worth in synthesis programming. The final visionary chapter on emerging technologies paints a seductive picture of the future. In particular, it features the importance of knowledge capture and its use in a closed loop, integrated and interactive fashion by bringing together wide-ranging techniques and devices.

The future is indeed a bright one and will continue to develop based upon the collective genius of its practitioners.

Steven V. Ley
Cambridge

Preface

It is fair to say that, for a synthetic chemist working in drug discovery, the last 15 years have seen sometimes uncomfortable levels of change in the tools and methods applied to the task of designing and synthesising new potential drug molecules. The experiments of the late 1990's with high throughput, almost industrialised, approaches to lead-molecule generation and testing failed to result in an associated increase of new drugs on the market. The ethos behind this movement was a response to the promise of advances in genomic technology to provide an enormous wealth of drugable targets for the industry to exploit, all needing tool molecules and lead material to start the process towards a drug. Over recent years, estimates of the number of genes that can be considered disease-modifying targets have been refined, resulting in the late Sir James Black's observation:[†]

> *"The techniques have galloped ahead of the concepts. We have moved away from studying the complexity of the organism; from processes and organisation to composition."*

Despite the fact that, with a few exceptions, the enormous libraries of closely related structures of the 1990's are now no longer being made, the technological ingenuity of this period has had a lasting impact on synthetic chemistry. Many of the techniques developed during this time are now being used routinely in medicinal chemistry labs the world over to increase productivity and access new chemical space; this is the true legacy of the "combichem revolution".

It is hoped that this book provides a useful background and context for scientists already engaged in drug discovery or entering this fascinating and

[†] *The Financial Times*, February 1st 2009, interview by Andrew Jack.

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New Synthetic Technologies in Medicinal Chemistry
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worthwhile profession, as well as demonstrating the undoubted benefits of the judicious use of synthetic technologies in drug discovery.

I would like to thank the chaptor authors, all of whom are experts and pioneers in these fields, for their high quality and timely contributions. In addition I acknowledge the particular contribution of Dr David Fox at Pfizer Sandwich and Gwen Jones at RSC Publishing for their "gentle" persistence in helping me get this project to completion. Special thanks also go to Rachel Osborne who was heroic in her efforts to write the chapter on microwave assisted chemistry in an incredibly short time-frame and late in the evolution of this book.

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Contents

Chapter 1 Introduction **1**
Elizabeth Farrant

1.1 Introduction 1
1.2 The Legacy of Combinatorial Chemistry 1
1.3 Case Study: Sorafenib 3
1.4 Conclusion 4
References 5

Chapter 2 High Throughput Chemistry in Drug Discovery **6**
Andy Merritt

2.1 Introduction 6
2.2 The Potential of High Throughput Chemistry in Drug Discovery 7
2.3 The Start of Combichem in Drug Discovery 8
2.4 From Peptides to Small Molecules 11
2.5 My Library's Bigger Than Your Library: The 'Universal' Library 13
2.6 From Combichem to High Throughput Chemistry: Remembering It's All About Drugs 14
2.7 Technology to Make It Happen 17
2.8 Illustrative Approaches in Drug Discovery 21
2.8.1 SAR Development using Parallel Chemistry 22
2.8.2 Lead Discovery: Split and Mix Examples 26
2.8.3 Dynamic Combinatorial Chemistry: From Fragments to Libraries 29

RSC Drug Discovery Series No. 11
New Synthetic Technologies in Medicinal Chemistry
Edited by Elizabeth Farrant

Published by the Royal Society of Chemistry, www.rsc.org

2.8.4 Other Approaches and Uses of Combinatorial Chemistry in Drug Discovery 31
2.9 Conclusion 34
References 35

Chapter 3 High Throughput Reaction Screening 42
Andrew I. Morrell

3.1 Introduction 42
3.2 High Throughput Reaction Screening 44
3.2.1 Statistical Design of Experiments in Reaction Screening 46
3.2.2 Suzuki–Miyaura Reaction Catalyst Screening 48
3.2.3 Heck Reaction Catalyst Screening 51
3.2.4 Hydrogenation Catalyst Screening 52
3.2.5 Biotransformation Reaction Screening 54
3.2.6 Reaction Screening Using Continuous Processes 56
3.3 High Throughput Salt Screening 57
3.4 High Throughput Solubility Screening 58
3.5 Equipment and Automation Used in High Throughput Reaction Screening 59
3.6 Analytical Techniques Used in High Throughput Reaction Screening 60
3.7 Conclusion 61
References 61

Chapter 4 Microwave Assisted Chemistry 63
Rachel Osborne

4.1 Introduction 63
4.2 An Overview of Microwave Theory 64
4.2.1 How Do Microwaves Enhance Chemical Reactions? 64
4.2.2 Microwave Heating 65
4.3 An Overview of Commercial Microwave Reactors 67
4.4 Current Applications of Microwave Assisted Synthesis 70
4.4.1 Metal-catalysed Reactions 71
4.4.2 S_NAr reactions: Rate and Purity Enhancements 74
4.4.3 Reactions Utilising a Gaseous Reagent 75
4.4.4 Transfer Hydrogenations 77
4.4.5 Synthesis of Aromatic Heterocycles 78
4.4.6 Synthesis of Saturated Heterocycles 80

4.4.7 "Click Chemistry" 81
4.4.8 Reactions Utilising Solid-supported Reagents 83
4.4.9 Parallel Synthesis 83
4.4.10 Multi-gram Scale Reactions 85
4.5 Conclusion 87
References 87

Chapter 5 Continuous Flow Chemistry in Medicinal Chemistry 90
Martyn Deal

5.1 Introduction 90
5.2 Benefits of Flow Chemistry 91
5.2.1 Thermal Control 91
5.2.2 Mixing 92
5.2.3 Stoichiometric Control and Selectivity 94
5.2.4 Safety 94
5.2.5 Enhanced Process Parameters 95
5.2.6 Hazardous Reactions 97
5.2.7 Multistep Processes 97
5.3 Limitations and Technology Hurdles 99
5.3.1 Solubility of Reagents 99
5.3.2 Solubility of Products 99
5.3.3 Scale 100
5.3.4 Other Issues 102
5.4 Flow Dynamics: Some Basic Theory 102
5.4.1 Reynolds Number 102
5.4.2 Laminar Flow 103
5.4.3 Turbulent Flow 103
5.4.4 Parabolic and Plug Flow 104
5.4.5 Residence Time Distribution 105
5.4.6 Electroosmotic Flow 105
5.5 Experimental Set-up 106
5.5.1 Pumps 106
5.5.2 Mixing 107
5.5.3 The Reactor 108
5.5.4 Sample Collection 109
5.6 Converting a Process from Batch to Flow 110
5.7 Packed Bed Reactors 111
5.8 Published Chemistry Examples 113
5.8.1 Hazardous Reagents 113
5.8.2 Exothermic Reactions 113
5.8.3 Unstable Intermediates 115
5.8.4 Selectivity 116
5.8.5 Multistep Processes 117

5.9 Integrating Continuous Flow with Other Technologies 118
5.9.1 Microwaves 118
5.9.2 Other Technologies 119
5.10 Beyond Synthesis 119
5.10.1 Liquid–Liquid Extraction 119
5.10.2 Purification 120
5.10.3 Continuous Flow Crystallisation 121
5.11 Conclusion 121
References 122

Chapter 6 Emerging Synthetic Technologies 126
Brian H. Warrington

6.1 Introduction 126
6.2 Template Guided Systems 127
6.2.1 Overview 127
6.2.2 Dynamic Combinatorial Chemistry 128
6.2.3 Click Chemistry 131
6.2.4 siRNA Approaches 133
6.3 Knowledge-based Iterative Systems 136
6.3.1 Overview 136
6.3.2 New Tools for Iterative Working 137
6.3.3 Fast and Efficient Realisation of Novel Leads: Rescaling the Process 138
6.3.4 Prediction of Unforeseen Structures 141
6.3.5 Challenges for High Speed Iterative Chemistry 144
6.3.6 Directed Assembly using DNA 145
6.4 Conclusion 148
References 149

Subject Index 154

CHAPTER 1

Introduction

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1.1 Introduction

When I was training as a synthetic chemist just under 15 years ago, the range of technologies we were expected to become familiar with as postdoctoral chemists was very limited: we were expected to pack a perfect flash column, be adept with an inert gas/vacuum line and to be able to shim a 250 MHz NMR instrument. In some special cases we might have been required to use a HPLC. Now, a standard industrial lab is likely to be equipped with automated HPLC, flash chromatography, microwave reactors, maybe a flow reactor and parallel synthesis is expected as routine to maintain productivity. Analytically, the chemist has routine access to LC-MS, automated NMR instruments running complex experiments and open-access accurate mass determination. The synthetic chemistry laboratory has become a highly technology-enabled environment.

1.2 The Legacy of Combinatorial Chemistry

Many of the technologies now routinely used in synthesis have their roots in the combinatorial chemistry paradigm of the late 1990's. As the possibilities in drug discovery resulting from the sequencing of the human genome culminated in a rough draft announced by the Sanger Institute in 2001, the need to discover ligands for these estimate 3 000 to 10 000 potential disease genes[1] led to the implementation of bead-based combinatorial mixture libraries. Using this

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technique, libraries of compounds of immense theoretical size could be manufactured but very soon it became clear that their utility was severely hampered by the deconvolution of any active products, the range of chemistry suitable for use with solid support and the close structural similarity of all the molecules generated.

The field evolved gradually into what is now practiced as high throughput medicinal chemistry, focusing on the synthesis of pure single compounds through solution-phase methods using diverse and imaginative chemistries with short cycle times from array design to biological test.

Many of the analytical and purification technologies developed during this time, including high throughput open-access LC-MS with UV and evaporative light scattering detection, mass-directed high throughput purification, automated medium-pressure liquid chromatography and high throughput flow NMR are now in routine use in standard synthetic chemistry labs.

In addition, the methods developed to carry out high throughput plate-based chemistry have evolved as an approach to generating rich data sets to guide the optimisation of chemical reactions where there is an array of reactant, solvent and condition combinations. This has also been extended to applications as diverse as biotransformation screening and de-racemisation *via* chiral salt formation. The power of this approach to find optimal reaction conditions for key reactions as well as to discover and enable new synthetic transformations has only begun to be exploited.

A recent addition to the synthetic chemist's tool box has been the use of microwave energy to heat reactions. In many cases this more efficient heating method has been shown to dramatically shorten reaction times and also improve impurity profiles.

Another key innovation of the last 15 years has been the application of microfluidics, an approach that was initiated in the analytical community, to synthetic chemistry. In its true microfluidic format this technology is being explored as a methodology for combining the efficiency of combinatorial chemistry with the fast biological feedback needed to reduce the time to go from a hit molecule to a lead.[2] In addition, conducting chemistry in larger (mesofluidic) tube reactors has also grown in popularity due to the ability to improve reproducibility of heating and mixing over the standard round-bottomed flask. One interesting and fruitful application has been to use this approach to help control reactions using unstable intermediates and as a scale-up route for reactions that progress well due to the efficient heating observed in a microwave reactor.

All of these technology solutions have contributed to the chemist's toolbox, supplementing traditional approaches and equipment, and have revolutionised the way synthetic chemists design and carry out their syntheses. The impact they have had has not been the explosion in hits and lead molecules (and drug molecules) promised by the early vision of the combinatorial chemistry—that is still an underlying problem the industry is attempting to address on many fronts. However, it has been an enabling of the creativity of the synthetic chemist to build molecules and enter novel chemical space.

The case study of sorafenib illustrates beautifully the impact these technologies have been having in a drug discovery programme which used the true power of combinatorial chemistry to solve a problem that would have blocked progress to the discovery of an important cancer therapy.

1.3 Case Study: Sorafenib

The time scale for drug discovery programmes is frustratingly slow and attrition is high; however, the mid-2000's have seen drugs entering the market whose discovery has relied heavily on the application of these novel technologies. One example is the Bayer molecule sorafenib (Nexavar®) (Figure 1.1).

Sorafenib was the first oral multikinase inhibitor on the market and was designed to target Raf which is important in tumor signaling and vasculature. It was first approved for the treatment of advanced renal cell carcinoma in 2005. Despite extensive traditional analoguing and structure–activity relationship (SAR) generation around the 17 μM high throughput screening hit **1** (Figure 1.2), the chemists were unable to improve the IC_{50} beyond 10-fold from this hit.

A high throughput chemistry programme was initiated in parallel with the later stages of this work and among the 1000 compounds efficiently generated in this manner, chemists identified compound **4** (Figure 1.3) which had an IC_{50} of 0.54 μM. Crucially, during traditional analoguing, compounds **2** and **3** had been synthesised and proved essentially inactive. These data would normally significantly deprioritise the synthesis of **4** when made by resource intensive single compound synthesis as they indicate that compound **4**, a combination of the ringed groups, would lie outside the established SAR. In this case the chemists asserted that they would not have synthesised this compound in the normal course of the drug discovery programme.[3]

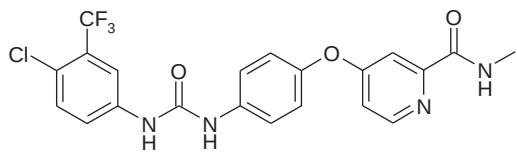


Figure 1.1 Sorafenib (Nexavar®).

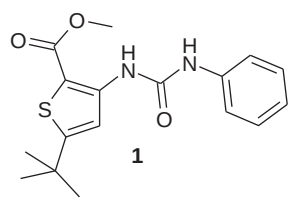
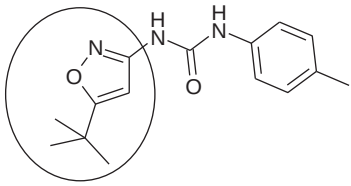
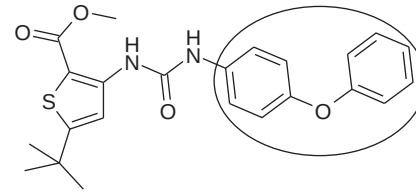


Figure 1.2 17 μM high-throughput screening hit.



2: 34% inhibition of Raf kinase at 25uM



3: 34% inhibition of Raf kinase at 25uM

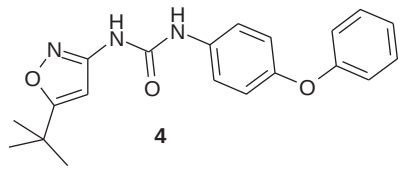


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Figure 1.3 Key structures in the discovery of sorafenib.

Further traditional medicinal chemistry then led to the discovery of sorafenib. The researchers observed that this discovery programme shows the power of high throughput chemistry to explore efficiently the additive effects of medicinal chemistry modifications outside the normal SAR; in this case they postulate that compound **4** may adopt a binding conformation different from that of compounds **2** and **3**, explaining the divergence from the initially proposed SAR.

1.4 Conclusion

In many ways the flowering of technology development in the 1990's was largely about a wish to increase productivity in response to the increases in capacity in genomics and the promise of thousands of new drug discovery targets. In practice, however, as has often been observed, this resulted early on in an increase in the size of the drug discovery haystack rather than a rise in the number of needles found. As the following chapters of this book will demonstrate, the true result has been routine use in the synthesis lab of a range of new tools. These are used to their greatest effect when it is not merely to increase productivity by a numerical measure but to expand the access of the synthetic chemist to new chemical space which would not have been accessible by traditional approaches. The sorafenib story illustrates this in a programme that resulted in a marketed drug but the ensuing chapters will also show the many examples where wise use of technology has contributed to drug discovery, be it in target validation, medicinal chemistry design or the provision of a compound for drug discovery programmes.

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