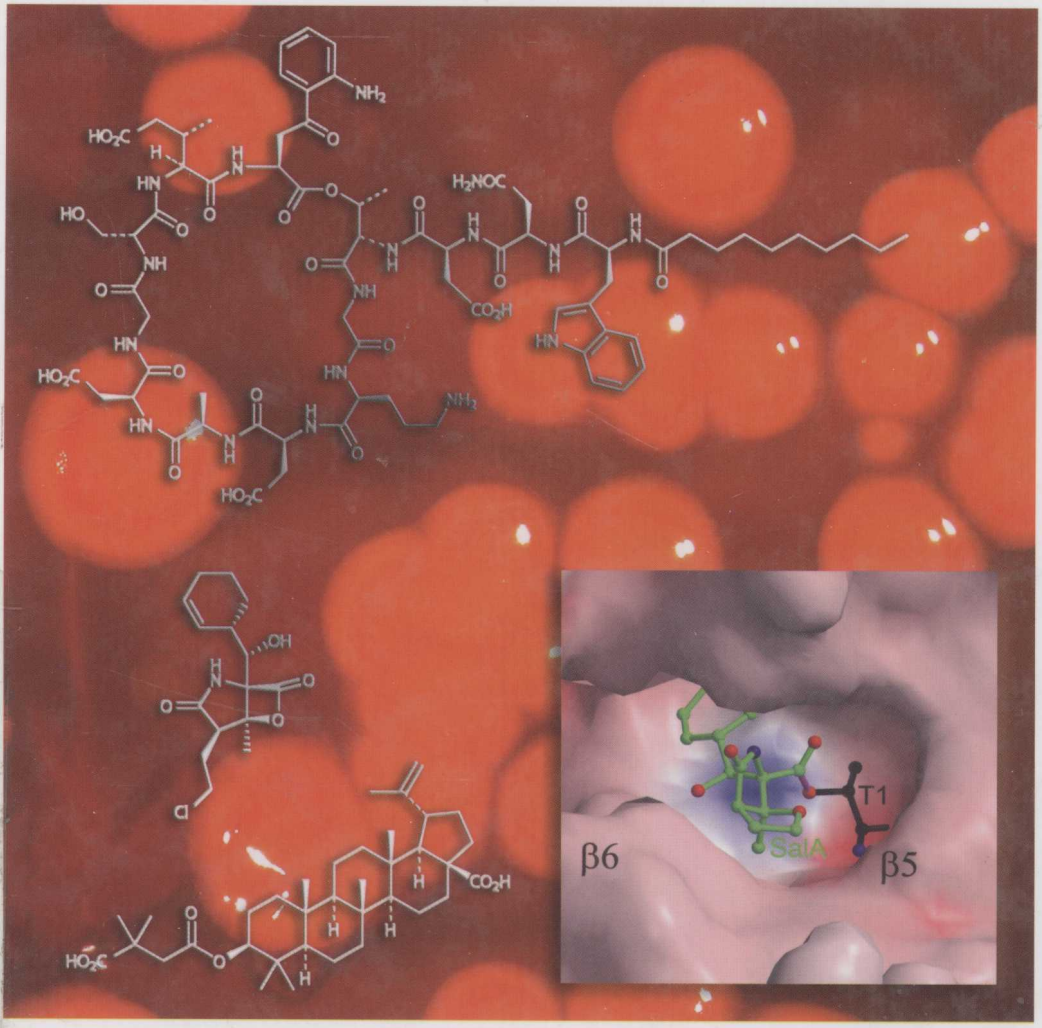
RSC Biomolecular Sciences

Edited by Antony D Buss and Mark S Butler

Natural Product Chemistry for Drug Discovery



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Preface

Natural products hold a special place in drug discovery having provided and inspired numerous life saving medicines and medical breakthroughs, particularly in the treatment of infectious diseases, cancer, hypercholesterolemia and immunological disorders. Twenty one drugs approved for marketing between 2003 and 2008 owe their existence to natural product leads discovered from mainly actinomycete, bacteria and fungal sources.[1] It has been our intention with this book to not only provide insights into the likely sources and methodologies that may be used to discover new natural product based drugs in the future, but also to stress the utility and importance of this approach to drug discovery in terms of new clinical candidates and recent commercial successes.

The final section of this book provides fascinating accounts of the twists, turns and pitfalls, as well as the role serendipity played, in the successful development and commercialisation of daptomycin and micafungin. Accounts of natural product derived drug candidates which are currently being evaluated in clinical trials may be found in Chapters 11–13, with salinosporamide A and bevirimat described in detail. The pipeline of 36 drug candidates which are in late stage clinical development may imply a continuing role for natural products in drug discovery, but we will return to this issue towards the end of this preface. Before then, let us look at the earlier chapters which follow in this book.

Well known for their thorough analyses of the sources of new and approved drugs, Newman and Cragg set the scene in Chapter 1 with a discussion on the historical influence natural products have had on the drug discovery process, with particular emphasis on antibacterial, antifungal and anticancer agents. The reason for the success of natural product chemistry in drug discovery is multifactorial, but certainly includes the unique "chemical space" that is occupied by such molecules. A particularly elegant account of how this applies to the required physicochemical property space for antibacterial compounds

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has been made recently by O'Shea and Moser.[2] In Chapter 2, Singh and Culberson expand on this theme with a comparison of the diversity of natural products with various synthetic compound libraries and their impact as drug leads in general.

La Clair, in Chapter 3, adopts a cinematic approach whilst delving into the mechanistic modes of action and the complex roles that natural products play. Included in this account are descriptions of how natural products have led to a better understanding of the regulation of tubulin and actin assembly in tumour cells and to the identification of an array of new, putative anticancer drug targets.

In Chapter 4, Cordell thoroughly evaluates the impact of the Convention on Biological Diversity (CBD) and other related agreements on academic and industrial natural product research. While the CBD has resulted in the development of laws and practices that have protected the sovereign rights of countries over their genetic resources, it has also led to natural product research programmes being compromised in scope and has perhaps contributed, at least in part, to many pharmaceutical companies terminating their natural product research activities.

Plants, microorganisms and, to a lesser extent, macromarines have been the main sources of natural product based drugs (produced as secondary metabolites). Reviews of these traditional sources of naturally occurring chemical compounds are found in Chapters 5–7, together with hints and suggestions as to how these sources may be better utilised to continue supplying new drug leads in the future.

Advances in high throughput screening technology, particularly with regard to detection methods and readouts, are reviewed in Chapter 8. These advances in biological screening, coupled with improvements in chromatographic and analytical techniques (highlighted in Chapter 9), have led to a significant reduction in the time required to purify active compounds from complex mixtures and to determine their chemical structures. In addition to conventional natural product discovery approaches, new versions of two major classes of natural products, the non-ribosomal peptides and polyketides, can now be engineered and produced using genetic manipulation techniques because of the ability to correlate gene sequence with amino acid sequence and thus, the chemical structure of the biosynthetic product. In Chapter 10, Udwary reviews the advances made in this field of combinatorial biosynthesis over the last 15 years, together with an account of some of the significant technical limitations that still need to be overcome before the rational engineering of biosynthetic pathways can be more readily harnessed for drug discovery.

We promised to return to the earlier statement that a healthy development pipeline of natural product derived candidates implies that natural products will still have a role to play in modern day drug discovery. In fact, this is far from reality. Firstly, these late-stage clinical candidates reflect the output from research activities undertaken at least 10 years ago and certainly not the current situation. Secondly, there is a lack of truly novel chemical templates in the pipeline and thirdly, it is clear that very few pharmaceutical companies remain engaged, at least internally, in natural product drug discovery activities.

In 2007, the US Food and Drug Administration approved only 16 new molecular entities, the lowest in a single year since 1983.[3] Despite a slight improvement in 2008, there remains a disturbing overall decline in pharmaceutical R&D productivity that is exacerbated by exponential rises in R&D costs, erosion of sales as many key products face patent expiration and increasing regulatory hurdles. With a burgeoning and aging population, the need for innovative new medicines throughout the world will not diminish. So is there a place for natural product based drug discovery in the future and, if so, where will new biologically active natural products come from?

In this book many of the significant technical advances which have accelerated the screening, purification and structural identification of bioactive natural products have been highlighted. As Bugni *et al.* remind us in Chapter 9, many of the previous bottlenecks that made natural products discovery a slow, laborious process have indeed been removed. However, for natural product based drug discovery to become cost effective and remain competitive, a number of key problems must be addressed, including the continual discovery of known compounds from existing natural product extract collections, the scarcity of novel bioactive chemical templates and the challenge of structurally modifying sometimes complex, often oxygen-rich, chiral natural product lead structures.

With the concept that secondary metabolites have evolved to specifically interact with protein targets and that these are not so different from human proteins, the construction of synthetic compound libraries inspired or based on natural product templates will continue to gain popularity and general acceptance as a valid drug discovery approach. Given that access to biologically relevant, drug-like chemical space is central to the drug discovery process and that natural products often occupy very different areas of this "space" compared to synthetic compounds,[4] then we believe that the search for drug leads from natural products offers a complimentary and much needed approach to other drug discovery strategies.

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