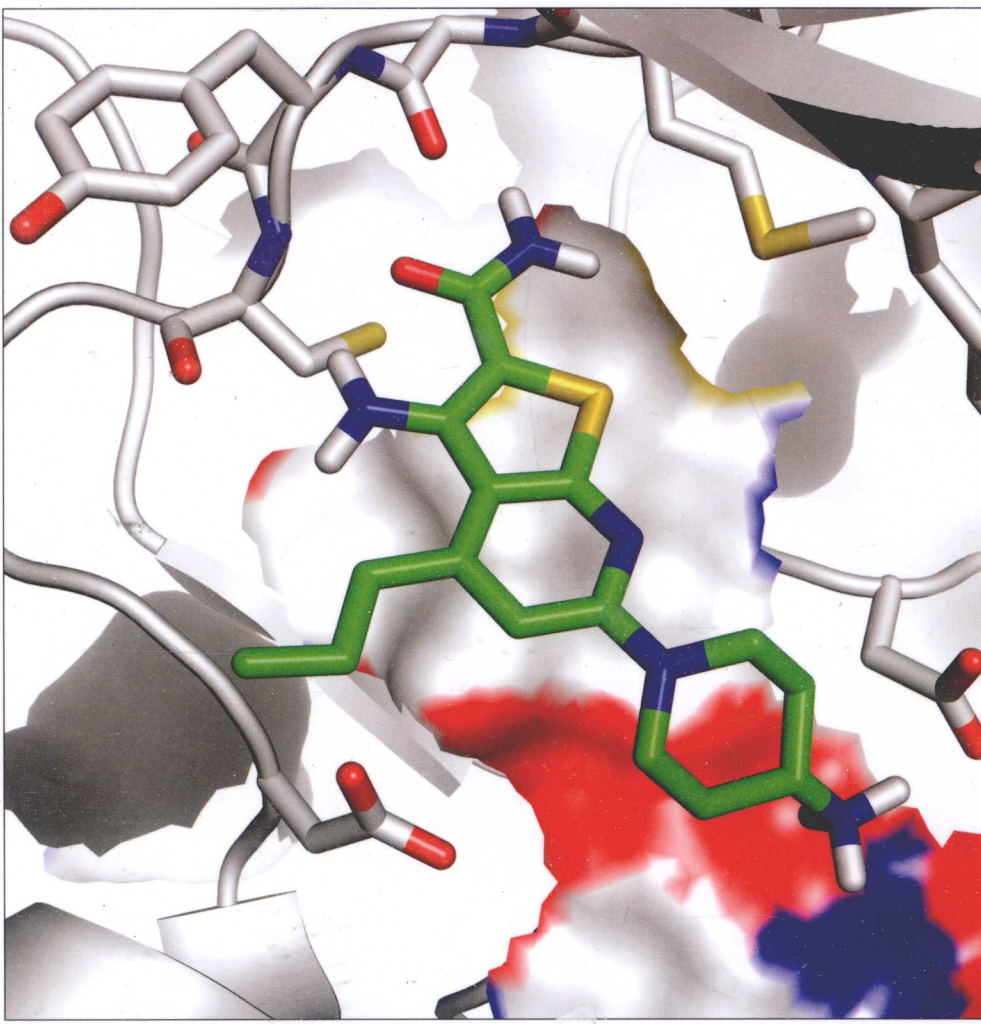
RSC Drug Discovery

Edited by Jeremy I Levin and Stefan Laufer

Anti-Inflammatory Drug Discovery



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Preface

Driven by the need for new orally active anti-inflammatory medicines, intensive research is ongoing in both industry and academia on a diverse set of biological pathways and targets with the goal of delivering therapeutics to improve the lives of patients with conditions such as asthma, rheumatoid arthritis, atherosclerosis, inflammatory bowel disease, psoriasis, allergic diseases, and pain. It was the goal of this volume to bring together respected scientists who have been directly involved in these drug discovery efforts to present the rationale for prosecuting specific targets, a current review of the medicinal chemistry strategies that have been used, and the outcome of those efforts. For some of these targets drugs with exciting potential have been delivered to clinical trials, while others have encountered unexpected roadblocks, and both of those outcomes provide important lessons for today's drug hunters. It is our hope that the stories presented herein will serve as a valuable resource for anyone interested in the discovery of new anti-inflammatory drugs.

In addition, we would like to express our great appreciation to all of the chapter authors for delivering clear, comprehensive reviews that will inform and enlighten readers on the state of the art in their respective areas of research. We would also like to express our appreciation to Professor David Rotella (Montclair State University), and Gwen Jones and Amaya Camara at RSC Publishing for their help, support and patience in the course of putting together this book.

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Introduction

The discovery of new and novel anti-inflammatory drugs is an area of intense interest within both the pharmaceutical industry and academic laboratories. Significant advances have been made in the treatment of inflammatory diseases such as rheumatoid arthritis (RA) and multiple sclerosis, but most dramatically with new biologic agents. Perhaps due in part to the mixed experiences with COX-2 inhibitors, very few small molecule anti-inflammatory drugs with novel modes of action have made it to the market in the last decade. Therefore, there remains an enormous unmet medical need for new, effective and safe small molecule disease-modifying therapies to expand treatment options for these and other indications, including asthma and chronic obstructive pulmonary disease (COPD), allergic diseases, atherosclerosis, psoriasis, inflammatory bowel disease and pain.

Inflammatory diseases are characterized by numerous symptoms and, on a mechanistic basis, multiple pathways are involved. This multi-factorial nature of inflammation is both an opportunity and a challenge for drug discovery. The aim of this book is to review recent noteworthy medicinal chemistry approaches to a variety of important therapeutic targets and so provide a key reference for those interested in the prosecution of modern drug-discovery programs directed at anti-inflammatory mechanisms of action. The biology, pharmacology and medicinal chemistry literature of a collection of topics ranging from components of the arachidonic acid cascade, to kinases, GPCRs, sphingolipids and steroid hormone receptors have been summarized by highly respected scientists from academia and industry offering new insights on major advances and issues related to bringing new anti-inflammatory therapies to market.

In the first section of this text, drug targets in the arachidonic acid (AA) cascade are described. This pathway, although it is the molecular target of very old drugs like aspirin, is still not fully understood. For example, COX-1b ("COX-3") might be the molecular target for paracetamol (acetaminophen) in

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dogs, but not in man. Taking into account the lessons of COX-2 drug development, an important downstream target is the microsomal prostaglandin E2 synthase-1 (mPGES1), and inhibition of this mechanism has the potential to yield a third generation of non-steroidal anti-inflammatory drugs (NSAIDs).

The opposite approach, going upstream, leads to cytosolic phospholipase A_2 alpha (cPLA$_2\alpha$) as a target for therapeutic intervention. The rate-limiting step in the generation of prostaglandins, leukotrienes and platelet activating factor (PAF), all highly active substances with diverse biological actions in inflammation, is the cleavage of the *sn*-2-ester of membrane phospholipids by a phospholipase A_2 (PLA_2). Among the superfamily of PLA_2 enzymes, cPLA$_2\alpha$ is thought to play the primary role in this biochemical reaction. Therefore, the inhibition of cPLA$_2\alpha$ activity is an attractive approach for the control of inflammatory disorders. Furthermore, on the leukotriene branch of the arachidonic acid cascade is the cytosolic enzyme leukotriene A_4 hydrolase (LTA_4H), which catalyzes the formation of the pro-inflammatory mediator LTB_4. The inhibition of LTA_4H offers an alternative to blocking the targets 5-lipoxygenase (5-LO) and 5-lipoxygenase activating protein (FLAP) for modulating LTB_4 levels and has potential utility for treating a variety of inflammatory disorders including coronary artery disease, though this awaits clinical validation.

The AA cascade section concludes with CRTH2, the chemoattractant receptor homologous molecule expressed on T helper type 2 cells, though this target could have also been placed in Section 3 since it is a G-protein coupled receptor (GPCR). Small-molecule antagonists of CRTH2, the receptor for prostaglandin D_2 (PGD_2), have been the subject of extensive research in the pharmaceutical industry and more than ten of these have been advanced to clinical trials for indications ranging from seasonal allergic rhinitis to asthma and atopic dermatitis, making it a very promising therapeutic target.

The second section of this volume focuses on protein kinase inhibitors as anti-inflammatory agents, although this field still suffers from important unanswered questions. From 518 protein kinases in our genome, about 250 are disease related. However, the fundamental role of kinases in signal transduction raises questions about how safe and free of side-effects kinase inhibitors can be. Another important question concerns selectivity within the human kinome. Thus, how selective is selective enough, and is the dogma "one mechanism, one target, one disease" still valid? The inhibition of multiple kinases might be beneficial in cancer, but it remains to be demonstrated that similarly promiscuous inhibitors provide the necessary safety margin for utility in treating inflammation. Despite excellent pre-clinical evidence, many kinase targets still suffer from a lack of clinically proven target validation.

Nevertheless, there has been an explosion of academic and industrial research in this field, fuelled by the groundbreaking success of anti-TNF biologicals for the treatment of rheumatoid arthritis. In the search for small-molecule drugs that impact the biosynthesis and/or release of pro-inflammatory cytokines, prominent targets include the kinases p38, MK2, Syk, JAK, IKKβ and Btk. Many p38 MAP kinase inhibitors have entered clinical trials but,