THE TEXTBOOK OF

Pharmaceutical Medicine

Fifth Edition

EDITED BY

John P. Griffin & John O'Grady

BMJ Books

Blackwell Publishing

The Textbook of Pharmaceutical Medicine

Fifth edition

Edited by

John P Griffin BSc, PhD, MBBS, FRCP, FRCPath, FFPM

Director, Asklepieion Consultancy Ltd.,
Visiting Professor, University of Surrey Postgraduate Medical School
Former Director, Association of the British Pharmaceutical Industry, London
Formerly Professional Head of the Medicines Division, DHSS, London

and

John O'Grady MD, FRCP, FFPM, FBIRA, MRCPath

Visiting Professor of Clinical Pharmacology, University of London

Blackwell Publishing

BMJ Books

Blackwell Publishing, Inc., 350 Main Street, Malden, Massachusetts 02148-5020, USA
Blackwell Publishing Ltd, 9600 Garsington Road, Oxford OX4 2DQ, UK
Blackwell Publishing Asia Pty Ltd, 550 Swanston Street, Carlton, Victoria 3053, Australia

First three editions were published by The Queen's University of Belfast
First edition published in 1993
Second edition published in 1994
Third edition published in 1998
Fourth edition published in 2002
Second impression of Fourth edition published in 2002

Library of Congress Cataloging-in-Publication Data

The textbook of pharmaceutical medicine/edited by John P. Griffin and John O'Grady. – 5th ed.
p. ; cm.
Includes index.
ISBN-13: 978-0-7279-1840-6 (hardback)
ISBN-10: 0-7279-1840-0 (hardback)
1. Pharmacology, Experimental.
[DNLM: 1. Drug Approval. 2. Clinical Trials. 3. Pharmacology. QV 771 T3445 2005]
I. Griffin, J. P. (John Parry) II. O'Grady, John, Professor.

RM301.25.T49 2005
615'.1–dc22 2005015284

ISBN-13: 978-0-727918-40-6
ISBN-10: 0-727918-40-0

A catalogue record for this title is available from the British Library

Set in Chennai, India by Newgen Imaging Systems (P) Ltd
Printed and bound in Harayana, India by Replika Press PVT Ltd

Commissioning Editor: Mary Banks
Development Editor: Veronica Pock
Production Controller: Debbie Wyer

For further information on Blackwell Publishing, visit our website:
http://www.blackwellpublishing.com

The publisher's policy is to use permanent paper from mills that operate a sustainable forestry policy, and which has been manufactured from pulp processed using acid-free and elementary chlorine-free practices. Furthermore, the publisher ensures that the text paper and cover board used have met acceptable environmental accreditation standards.

Contributors

Christine H Bendall, Solicitor, Arnold & Porter, London, UK

Carole Bradley BSc(Hons) MSc, Manager, Health Economics and Reimbursement, Boehringer Ingelheim (Canada) Ltd, Burlington, Ontario, Canada

Alan G Davies MBBS MRCP(UK) MD (London), Therapeutic Director, Kendle International Inc, Crowthorne, Berkshire, UK

Anand S Dutta PhD, Department of Academic Affairs, Hope Hospital, Salford, UK

A Peter Fletcher MBBS PhD MFPM, Independent Consultant Little Maplestead, Essex formerly Senior Prinicipal Medical Officer, DOH

Andrew P Grieve, Statistical and Consulting Centre, Pfizer Global Research and Development, Sandwich, UK

Jane R Griffin BA(Hons) MSc, Head, Health Economics and Outcomes Research, Boehringer Ingelheim UK Ltd, Bracknell, UK

John P Griffin BSc PhD MBBS FRCP FRCPath FFPM, Asklepieion Consultancy Ltd, Welwyn, Hertfordshire, UK. Formarly Head of UK Regulatory Authority

Gavin Halbert BSc PhD CChem MRSC MRPharmS, Director, Cancer Research UK Formulation Unit, Department of Pharmaceutical Sciences, University of Strathclyde, Glasgow, Scotland, UK

Dean WG Harron BSc PhD FRPharmS MPSNI, Professor, School of Pharmacy, The Queen's University of Belfast, Northern Ireland, UK

Darrall L Higson MB ChB FFPM, formerly Medical Director, Global Switch & Innovations, GlaxoSmithKline Consumer Healthcare, Uxbridge, Middlesex, UK

Janice Hirshorn BSc (Hons) PhD FAICD, Consultant, Rose Bay, NSW, Australia

Christopher JS Hodges MA (Oxon) PhD FSALS, Consultant, CMS Cameron McKenna, London, UK; Associate Fellow, University of Oxford, Oxford, UK

D Michael Humphreys MB ChB FFPM, Consulting Pharmaceutical Physician, formerly Corporate Medical Advisor, Corporate Department Medical Affairs, Boehringer Ingelheim, Ingelheim-am-Rhein, Germany

Peter Barton Hutt, Senior Counsel Covington and Burling, Washington DC USA; Lecturer in Food and Drug Law, Harvard Law School, Cambridge MASS Former Chief Counsel to the US Food and Drug Administration (FDA)

Judith K Jones MD PhD, President, The Degge Group; President, The Pharmaceutical Education and Research Institute; Adjunct Professor of Pharmacology, Georgetown University, Washington DC, USA

Yuichi Kubo, Daiichi Pharmaceutical Co Ltd, Tokyo, Japan

Valeria Molnar Clinical Pharmacology Consulting, Torquay, UK

Deborah Monk B Pharm Dip Hosp BA, Director of Scientific and Technical Affairs, Medicines Australia, Deakin, ACT, Australia

John O'Grady MD FRCP FFPM FBIRA MRCPath, Visiting Professor of Clinical Pharmacology, University of London, UK

John Posner BSc PhD MBBS FRCP FFPM, Independent Consultant in Pharmaceutical Medicine, John Posner Consulting, Beckenham, UK

Paul Rolan MBBS MD FRACP FFPM DCPSA, Professor of Clinical and Experimental Pharmacology, Medical School, University of Adelaide Adelaide SA 5005 Australia

Rashmi R Shah BSc MBBS MD FRCP FFPM, Pharmaceutical Consultant, formerly Senior Clinical Assessor, Medicines and Healthcare products Regulatory Agency (MHRA), London, UK

Susan Shaw MBBS BSc MRCPsych, Consultant Psychiatrist, Chelsea and Westminster Hospital, London, UK

Richard N Spivey Pharm D PhD, Senior Vice President, Corporate Technology Policy, Pharmacia, Peapack, New Jersey, USA

Peter D Stonier BA MB ChB Bsc PhD MRC-Psych FRCP FRCPE FFPM, Medical Director, Amdipharm plc, Basildon, UK

David J Tweats C. Biol BSc PhD FRCPath FIBiol, Professor, Centre for Molecular Genetics and Toxicology, School of Biological Sciences, University of Wales, Swansea, UK

William Vodra Senior Partner, Arnold & Porter, Washington DC, USA

William Wardell MA(Oxon), President, Wardell Associates International, Princeton, New Jersey, USA

Amanda Wearing MA (Oxon), Solicitor, Arnold and Porter, London, UK

Roger A Yates MA MB BChir MRCP(UK) FFPM DCPSA Independent Consultant in Pharmaceutical Medicinal, Ray Cander Ltd, Wilmslow, Cheshire, UK

John H Young MBBS FRCP FRCPath FFPM, Medical Director, Merck Sharp and Dohme Ltd, Hoddesdon, UK

Preface

This book has grown considerably since the first edition in 1993. The fifth edition is the most comprehensive of all editions to date and reflects the increasing complexity of the speciality. The enthusiastic uptake of this book is a tribute to The Faculty of Pharmaceutical Medicine of The Royal Colleges of Physicians of the United Kingdom who have done so much to sponsor the discipline leading to the discipline achieving the status of specialist recognition.

However, we have been aware that the book has appealed to a much wider audience than those for whom it was initially written, namely those studying for the Diploma of Pharmaceutical Medicine. It is now the standard text used by courses in pharmaceutical medicine in both Europe and the Unites States.

Widening the scope of the textbook to cover all aspects of the speciality's Higher Medical Training (HMT) programme has also increased the usefulness of the book to those working in National Drug Regulatory Authorities, as well as those involved in the economics of healthcare, pharmaceutical marketing and NHS purchasing of medical products.

Acknowledgements

We would like to thank all those who have contributed in any way to this book, either to the current fifth edition or previous editions. We owe the success of this book to every one of its contributors, who have produced work of the highest quality promptly from edition to edition.

We would particularly like to pay tribute to those contributors who are no longer with us: Dr John Domenet, Professor Ken McRea, Professor PF D'Arcy and Professor Lou Lasagna – whose expertise will be greatly missed.

We would also like to record our great appreciation to Mary Banks who steered this book through its fourth and fifth editions, and to her colleague at Blackwell Publishing, Veronica Pock.

Finally, we would like to thank the World Medical Association, The European Medicines Evaluation Agency and the Association of the British Pharmaceutical Industry for permission to reproduce their various documents as appendices to this book. All others who allowed us to quote or use their material are acknowledged in the text, however, a general thanks is appropriate at this point.

John P Griffin
John O'Grady

The Editors

Professor John P Griffin BSc PhD MBBS FRCP MRCS FRCPath FFPM graduated in medicine at the Royal London Hospital, where he was also in clinical practice. He was a lecturer in Physiology at King's College, London and held the post of Head of Clinical Research at Riker Laboratories from 1967 to 1971. Professor Griffin joined the then Medicines Division of the Department of Health, now Medicines Healthcare Agency (MHRA) London, as a Senior Medical Officer, in 1971, and was subsequently appointed Medical Assessor to the Committee on Safety of Medicines. From 1977 to 1984, Professor Griffin was Senior Principal Medical Officer and Professional Head of Medicines Division in addition to being Medical Assessor to the Medicines Commission. As the Professional Head of Medicines Division he also attended the Scientific Sub-Committee of the Veterinary Products Committee of the Ministry of Agriculture, Food and Fisheries. During this time he was a member of the EC committee on Proprietary Medicinal Products and Chairman of the CPMP's Working Party on Safety Requirements.

From 1976 to 1984 John Griffin served on the Joint Formulary Committee of the British National Formulary, during which period the first eight issues of the current format were produced.

John Griffin was the director of the Association of the British Pharmaceutical Industry from 1984 to 1994. During this time he was a member of the Executive Board of the European Federation of the Pharmaceutical Industries' Associations and IFPMA. He chaired the ICH Safety Working Group from 1988 to 1994 and presented papers at ICH1 and ICH2 in the plenary sessions.

Since June 1994, John Griffin has run his own independent consultancy company, which has provided independent and impartial advice to governments on the development of a pharmaceutical policy, and to national trade associations and individual companies. John Griffin is Visiting Professor in Pharmaceutical Medicine at the University of Surrey, and is also Honorary Consultant Clinical Pharmacologist at the Lister Hospital in Hertfordshire, UK.

Professor Griffin is on the Board of the Faculty of Pharmaceutical Medicine, was Chairman of the Board of Examiners of the Faculty of Pharmaceutical Medicine of the Royal College of Physicians for 7 years, and is currently Academic Registrar and serves on the Task Force on Specialist Medical Training in Pharmaceutical Medicine. He has served on a number of Royal College of Physicians, London Working Parties including that on the 'Development of Clinical Pharmacology and Therapeutics in a Changing World'.

Professor Griffin is the author and co-author of over 250 publications on adverse drug reactions and iatrogenic disease, aspects of neurophysiology and clinical pharmacology and toxicology and drug regulation. Notable among his publications are the following four standard texts:

- *Iatrogenic Diseases* Oxford University Press, 1st edn 1972, 3rd edn 1986; jointly with Prof PF D'Arcy.
- *A Manual of Adverse Drug Interactions* John Wright Bristol, 1st edn 1975; Elsevier Press Amsterdam, 5th edn 1997; jointly with Prof PF D'Arcy.
- *The Textbook of Pharmaceutical Medicine* The Queen's University of Belfast Press, 1st edn 1993, 2nd edn 1994, 3rd edn 1998, 4th edn 2002 published by the *BMJ* Publishing Group in 2002.

• *Medicines, Research, Regulation and Risk* The Queen's University of Belfast Press, 1st edn 1989, 2nd edn 1992.

From 1991 to 2003 he served as Editor in Chief of *Adverse Drug Reactions and Toxicological Reviews*, a peer-reviewed journal produced quarterly by Oxford University Press.

Professor John O'Grady MD FRCP FFPM FBIRA

MRCPath, after graduating in medicine, trained in general medicine and also in clinical pharmacology and therapeutics to achieve specialist registrations. He held medical appointments at the Radcliffe Infirmary in Oxford, Royal Postgraduate Medical School, Hammersmith Hospital, Hospital for Nervous Diseases Queen's Square, London and St Bartholomew's Hospital, London.

Formerly Head of Clinical Pharmacology at Wellcome Research Laboratories, then Medical Director Rhone-Poulenc and Visiting Professor at the University of Cape Town, South Africa. He was later a Director of Imperial Cancer Research Technology Ltd, Visiting Professor of Clinical Pharmacology and Therapeutics at the University of Vienna, Austria, the University of Cape Town, South Africa and a member of the British Pharmacopoeia Commission.

Professor O'Grady is Examiner of the Royal College of Physicians, Faculty of Pharmaceutical Medicine. He is a Fellow of the Royal Statistical Society and Visiting Professor of Clinical Pharmacology, University of London.

He has published widely in the field of medicine, in clinical pharmacology and therapeutics and in pharmaceutical medicine. He is editor of several books dealing with drug effects in man and with medicines and the law.

Contents

PART I

Research and development

CHAPTER 1

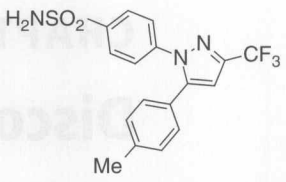
1 Discovery of new medicines

Anand S Dutta

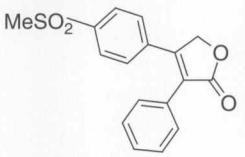
1.1 Introduction

Ancient civilisations, like modern society, had a keen interest in the health of man and other animals. Continuation of this interest over a period of time led to the discovery of a large number of therapeutic agents primarily from the natural sources; many of the natural sources are still being used as lead structures for the discovery of new drugs.[1] In more recent times (~50 years), with the involvement of a large number of pharmaceutical companies and many academic institutions, progress in the understanding of disease processes and mechanisms to control or eliminate the disease has accelerated. Similarly, despite the advances and achievements of the last 50 years, the need to discover treatments for existing and evolving diseases has also increased. This is primarily due to the inadequacies of the current medicines. In many cases the treatment only leads to symptom relief, and in various other cases, the cure is associated with undesirable side effects. In some cases (e.g. infectious diseases such as tuberculosis, malaria and HIV), resistance/tolerance to the existing treatments may develop, thus making them ineffective against the infecting bacteria, parasite or the virus.[2] New infectious agents such as SARS, hepatitis C, human herpes virus-6, -7 and -8 are also appearing.[3] In addition, with the changing environmental factors, lifestyle and increasing life span, more and more pathological abnormalities that require new treatments are being identified. For example, obesity and a number of cardiovascular diseases may have their origins in altered (more prosperous?) lifestyle habits including environmental and psychosocial factors and diet.[4–6] Changing social attitudes are also creating markets for the so-called lifestyle drugs. Although the term 'lifestyle drug' is applied currently to drugs such as sildenafil for erectile dysfunction and minoxidil or finasteride for baldness, the precise definition of lifestyle drugs is a subject of debate.[7] Increasing knowledge about the underlying causes of diseases is enabling the discovery of more selective and less toxic drugs. Progress in molecular biology (e.g. sequencing of human genome, proteomics, pharmacogenomics and protein engineering) is creating new avenues for the understanding of precise disease mechanisms (biochemical pathways) and discovery of new targets based on new disease pathways. Advances in this field are expected to lead to highly selective and efficacious medicines. Recombinant technologies are enabling the synthesis of larger biologically active proteins in sufficient quantities. Proteins and monoclonal antibodies are therefore becoming more important and common as therapeutic agents. Equally important is the progress being made in the fields of combinatorial chemistry, enabling the synthesis of millions of compounds, high-throughput screening technologies and other automation techniques facilitating more rapid drug discovery. In the longer run, a combination of all the new developments is likely to generate safer and more effective medicines not only for the existing diseases but also for the diseases of the future which may become more important as a consequence of changes in lifestyle, and increasing age.

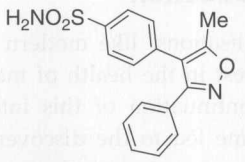
Malaria (caused in humans by single-celled *Plasmodium* protozoa parasites), tuberculosis (caused by *Mycobacterium tuberculosis*) and leprosy (caused by *Mycobacterium leprae*) can be considered examples of 'older' diseases still in need of more effective and cheaper treatments.[8–14] Each year, 300–500 million people contract malaria and about 2–3 million die. A number of medicines, including chloroquine, 4-aminoquinolines, atovaquone, malarone, halofantrine, mefloquine, proguanil and artemisinin derivatives are available. Three main types of vaccines, based on the three major phases of the parasite's life cycle, are being developed: anti-sporozoite vaccines designed to prevent infection (pre-erythrocytic vaccines), anti-asexual blood stage vaccines (anti-invasion and anti-complication) designed to reduce severe and complicated manifestations of the disease and transmission-blocking vaccines aimed at arresting the development of the parasite in the mosquito itself. A number of vaccines are in phase I and phase II clinical trials. Monoclonal antibodies against specific malarial antigens are being explored for diagnostic and potential therapeutic purposes. In addition, efforts are also being made to shed light on the origin of the development of resistance in specific cases. Discovery of complete genome sequences of the human malarial parasite *Plasmodium falciparum* and the malaria-transmitting mosquito *Anopheles gambiae* is likely to enhance the discovery of antimalarial drug candidates. Like malaria, tuberculosis and leprosy are more common in less-developed countries. Tuberculosis is the second leading cause of death worldwide, killing nearly 2 million people each year. Multidrug-resistant tuberculosis continues to be a serious problem, particularly among some countries of Eastern Europe, China and Iran.[15] Currently available drugs for tuberculosis include isoniazid, rifampicin, pyrazinamide and ethambutol. The first-line drugs against leprosy are rifampicin, clofazimine and dapsone. Other drugs like minocycline, the macrolide clarithromycin and the fluoroquinolones pefloxacin and ofloxacin are all highly active against *M. leprae* but are rarely used in field programmes because of their cost.



1 Celecoxib



2 Rofecoxib



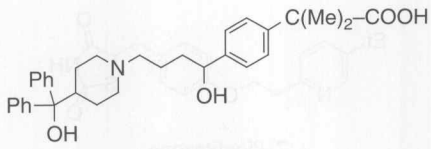
3 Valdecoxib

Bone disorders like arthritis and osteoporosis are examples of diseases that are becoming increasingly important with the ageing population.[16–18] Anti-inflammatory glucocorticoids like prednisolone and methylprednisolone and immunosuppressants such as cyclosporin-A and dexamethasone are used for the treatment. Although the treatment options have increased recently, most of these therapies focus on addressing the symptoms rather than the underlying causes of the disease. For example, cyclooxygenase-2 (COX-2) inhibitors such as celecoxib (**1**), rofecoxib (**2**, recently withdrawn from the market), etoricoxib,[19] valdecoxib[20] (**3**) and parecoxib (prodrug of valdecoxib) are being marketed as safer non-steroidal anti-inflammatory drugs (NSAIDs).[21–23] Although the older NSAIDs are highly effective as analgesic, antipyretic and anti-inflammatory agents, long-term ingestion causes gastric lesions. The discovery that the COX enzyme, which catalyses the conversion of arachidonic acid to prostaglandin H_2 (common biosynthetic precursor to prostaglandins and thromboxane – mediators of physiological and pathological processes, including pain, fever,

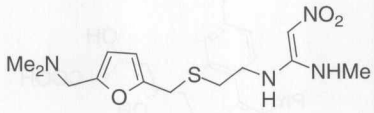
inflammation),[24] exists in two isoforms, with COX-2 being the primary isoform at sites of inflammation, led to a suggestion that inhibition of this isoform accounts for the therapeutic benefit of NSAIDs whereas inhibition of COX-1 results in adverse effects. The newer COX-2 selective agents appear to have a superior gastrointestinal (GI) safety profile. COX-2 inhibitors are also being investigated for the prevention and treatment of colorectal cancer.[25] In addition to COX-2 inhibitors, inhibitors of matrix metalloproteinases (MMPs) are emerging for the treatment of many diseases including arthritis. Enzymes that degrade the extracellular matrix are normally controlled by a set of tissue inhibitors that, if disrupted, will allow the enzymes to work unchecked, degrading the matrix and promoting not only arthritis but also tumour growth and metastasis. Another treatment option is the inhibition of tumour necrosis factor-α (TNF-α), an inflammation-promoting cytokine associated with multiple inflammatory events, including arthritis. Anti-TNF-α therapies are already in the market. Finally, a variety of genes that code for antiarthritic proteins are under investigation.

Recently, the process of drug discovery has been expanded to cover a range of molecular biology, biotechnology and medicinal chemistry (including combinatorial chemistry) techniques. The newer disciplines like genome analysis, proteomics and bioinformatics are likely to lead to many new targets (receptors, enzymes, etc.) and therapeutically important proteins. Techniques like combinatorial chemistry and high-throughput screening are expected to identify hits/leads against various therapeutically important receptors and enzymes. Depending upon the knowledge available on the receptor or the enzyme of interest, the hits/leads can then be modified in a random, semi-rational or rational manner to generate the drug candidates.

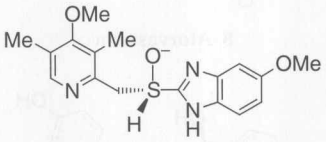
Like the chapter in the fourth edition of this book,[26] this chapter includes a short account of the historical aspects[27] and a short introduction to some of the newer disciplines. The main theme/objective of this chapter is to give an idea about the changing disease patterns, which may be reflected in the discovery process,



4 Fexofenadine



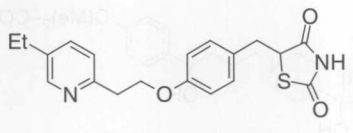
5 Ranitidine



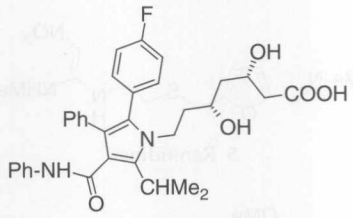
6 Esomeprazole

examples of receptor agonists and antagonists, enzyme inhibitors, including signal transduction inhibitors and inhibitors of protein–protein interaction that have been discovered by random and 'semi-rational/rational' approaches, antibody and protein therapeutics and currently available drugs for more widespread diseases. This enables one to understand actual drug discovery procedures and the science that has led to many drugs currently in the market. Examples include

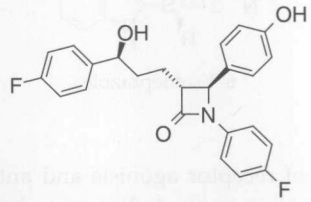
- COX inhibitors (**1–3**)
- angiotensin-converting enzyme (ACE) inhibitors (antihypertensives such as captopril and lisinopril)
- histamine H_1 receptor antagonists (anti-allergic compounds such as fexofenadine (**4**))
- histamine H_2 receptor antagonists (acid secretion inhibitors such as cimetidine and ranitidine (**5**))
- proton pump inhibitors (acid secretion inhibitors such as omeprazole and esomeprazole (**6**))[28,29]
- nuclear peroxisome proliferator activated receptor-γ activators such as pioglitazone (**7**)[30] and troglitazone (type 2 diabetes mellitus treatments)



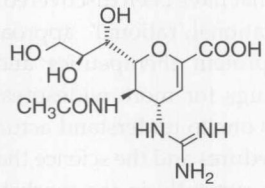
7 Pioglitazone



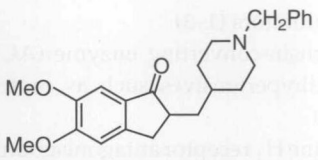
8 Atorvastatin



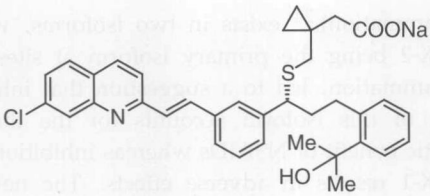
9 Ezetimibe



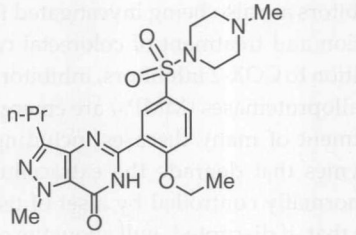
10 Zanamivir



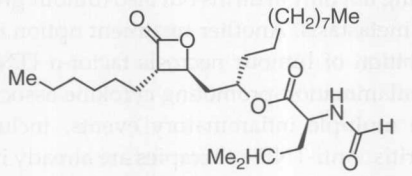
11 Donepezil



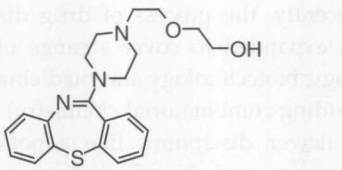
12 Montelukast



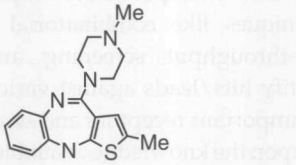
13 Sildenafil



14 Orlistat



15 Quetiapine



16 Olanzapine

- lipid lowering agents such as atorvastatin (**8**) and rosuvastatin and cholesterol absorption inhibitor ezetimibe (**9**)[31]
- anti-influenza treatments like zanamivir (**10**)[32]
- acetylcholinesterase inhibitors such as donepezil (**11**) for the treatment of Alzheimer's disease
- selective and competitive inhibitor of the cysteinyl leukotrienes (LTC_4, LTD_4 and LTE_4) such as zafirlukast and montelukast (**12**) for the treatment of asthma
- sildenafil (**13**; an inhibitor of phosphodiesterase type 5 used for erectile dysfunction)[33]
- antiobesity compound orlistat (**14**)
- atypical antipsychotic agents such as quetiapine (**15**) and olanzapine (**16**).