# Essentials of Pharmaceutical Chemistry

Third edition

**Donald Cairns** 



## **Essentials of Pharmaceutical Chemistry**

## Essentials of Pharmaceutical Chemistry

Third edition

### **Donald Cairns**

BSc, PhD, CSci, CChem, MRPharmS, MRSC

Associate Head of School of Pharmacy The Robert Gordon University Aberdeen, UK



#### Published by the Pharmaceutical Press

An imprint of RPS Publishing

1 Lambeth High Street, London SE1 7JN, UK 100 South Atkinson Road, Suite 200, Grayslake, IL 60030-7820, USA

© Pharmaceutical Press 2008



(**PP**) is a trade mark of Pharmaceutical Press

First edition published 2000 Second edition published 2003 Third edition published 2008

Typeset by J&L Composition, Filey, North Yorkshire Printed in Great Britain by TJ International, Padstow, Cornwall

ISBN 978 0 85369 745 9

All rights reserved. No part of this publication may be reproduced, stored in a retrieval system, or transmitted in any form or by any means, without the prior written permission of the copyright holder.

The publisher makes no representation, express or implied, with regard to the accuracy of the information contained in this book and cannot accept any legal responsibility or liability for any errors or omissions that may be made.

The right of Donald Cairns to be identified as the author of this work has been asserted by him in accordance with the Coypright, Designs and Patents Act, 1988.

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

## For Elaine, Andrew and Mairi

## Contents

Preface to the third edition xi Acknowledgements xiii About the author xv	
Chemistry of acids and bases Dissociation of weak acids and bases 3 Hydrolysis of salts 9 Amphiprotic salts 11 Buffer solutions 11 Buffer capacity 14 Biological buffers 16	1
Ionisation of drugs 19 $pK_a$ values of drug molecules 20 $pH$ indicators 20 $Tutorial$ examples 23 $Problems$ 28	
Partition coefficient and biopharmacy Experimental measurement of partition coefficient 33 Drug absorption, distribution and bioavailability 36 Passive diffusion 39 The pH partition hypothesis 40 Active transport mechanisms 44 The action of local anaesthetics 45 Excretion and reabsorption of drugs 48 Food and drink 50 Tutorial examples 51 Problems 56	29

3	Physicochemical properties of drugs Carboxylic acids 59 Phenols 63 Warfarin 64 Phenylbutazone 67 Indometacin 67 Barbiturates 67 Phenytoin 69 Sulfonamides 69 Basic drugs 71 Basicity of heterocyclic compounds 73 Separation of mixtures 73 Tutorial examples 75 Problems 79	59
4	Stereochemistry Polarimetry 84 Biological systems 88 Fischer projections 89 Stereochemistry case study: thalidomide 97 Geometrical isomerism 99 Tutorial examples 101 Problems 103	83
5	Drug metabolism  Metabolic pathways 106 Cytochromes P450 107 Enzyme induction and inhibition 111 Drug conjugation reactions (Phase 2) 112 Stereochemistry 119 Metabolic pathways for common drugs 120 Tutorial example 128 Problems 130	105
6	Volumetric analysis of drugs Volumetric flask 134 Pipette 134 Burettes 135 Units of concentration 135	133

Concentration of active ingredients 138  Design of an assay 138  Practical points 141  Back and blank titrations 144  Assay of unit-dose medicines 147  Non-aqueous titrations 149  REDOX titrations 150  Compleximetric titrations 152  Argentimetric titrations 154  Limit tests 154  Problems 155	
Analytical spectroscopy  Effect of pH on spectra 164 Instrumentation 168  Experimental measurement of absorbance 170  Dilutions 171  Quantitative aspects of spectroscopy 172  Beer's and Lambert's laws 173  Methods of drug assay 175  Derivative spectroscopy 177  Infrared spectroscopy 179  Fluorimetry 182  Structure elucidation 183  Tutorial examples 193  Problems 201	159
Stability of drugs and medicines  Oxidation 205  Stability of free radicals 207  Prevention of oxidative deterioration 211  Autoxidation of fats and oils 215  Ageing 216  Hydrolysis 217  Examples of drugs susceptible to hydrolysis 220  Other mechanisms of degradation 222  Prodrugs 223  Tutorial examples 225  Problems 226	205

#### **x** Contents

9	Kinetics of drug stability Rate, order and molecularity 229 Rate equations and first-order reactions 230 Half-life 233 Shelf-life 233 Second-order reactions 234 Zero-order reactions 236 Reaction rates and temperature 236 Tutorial example 238 Problems 238	229
10	Licensing of drugs and the British Pharmacopoeia  Structure of the MHRA 242  European licensing procedures 242  Applications for Marketing Authorisations 244  British Pharmacopoeia Commission 245  The British Pharmacopoeia 246	241
11	Answers to problems  Selected bibliography 267  Index 269	251

### Preface to the third edition

The last few years have seen many changes to the science and practice of pharmacy. The number of UK Schools of Pharmacy is set to double, independent pharmacist prescribing is a reality, and the Royal Pharmaceutical Society is set to split with the creation of a regulatory body and a Royal College. This third edition of *Essentials of Pharmaceutical Chemistry* has been written against this backdrop of major change. A new chapter on regulation and licensing of drugs and medicines has been included and every other chapter has been reviewed and updated, particularly the chapter on analytical spectroscopy which now includes a section on structure elucidation. In response to requests from a number of readers, a short bibliography of books which I find useful has been included.

As ever, I am grateful for the help, advice and comments of colleagues, readers and most of all, the many undergraduate students of pharmacy and pharmaceutical science who have to use this book as part of their studies. The inspiration to write the first edition came from the comments of a pharmacy student and the only reason the book exists at all is to help students understand the importance of pharmaceutical chemistry to their course and subsequent careers.

Donald Cairns December, 2007

## **Acknowledgements**

This book could not have been completed without the help of a great many people. I am very grateful to my colleagues, past and present, for their advice and encouragement and, particularly, for allowing me to assimilate their good practice (with or without their knowledge!). This book would be poorer without their efforts. Special thanks must go to Paul Hambleton who read and commented on my first drafts and who not only allowed me to use a great many of his examination questions but also provided most of the answers!

I am grateful to Paul Weller, Christina De Bono, Linda Paulus and all the staff at the Pharmaceutical Press for keeping me on track when diversions threatened and giving helpful advice about indexes, content pages, etc.

Finally, I must thank my wife, Elaine, who looked after the weans while I bashed the keyboard upstairs.

### About the author

Donald Cairns obtained a Bachelor of Science degree in pharmacy from the University of Strathclyde in 1980 and after a pre-registration year spent in hospital pharmacy, he returned to Strathclyde to undertake a PhD on the synthesis and properties of benzylimidazolines. Following a year as a post-doctoral research fellow in the department of pharmacy at Sunderland Polytechnic (now the University of Sunderland), Dr Cairns moved to Leicester Polytechnic (now De Montfort University) where he held a five-year lectureship in Pharmacy. In 1992 Dr Cairns was appointed senior lecturer in medicinal chemistry in Sunderland School of Pharmacy and in 2003 moved to his present post of Associate Head of the School of Pharmacy at The Robert Gordon University in Aberdeen. In 2006, he was promoted to Professor of Pharmaceutical and Medicinal Chemistry at RGU.

Professor Cairns has been external examiner at Strathclyde, Liverpool and Aberdeen Schools of Pharmacy and has authored over 50 peer reviewed research papers.

His research interests include the design and synthesis of selective anticancer agents, the molecular modelling of drug-DNA interactions and the design of prodrugs for the treatment of nephropathic cystinosis.

Donald Cairns is a member of the Royal Pharmaceutical Society of Great Britain (RPSGB), the Royal Society of Chemistry and the Association of Pharmaceutical Scientists. In 2006 he was appointed to the British Pharmacopoeia Commission and serves on an Expert Advisory Group of the Commission on Human Medicines.

To travel hopefully is a better thing than to arrive, and the true success is to labour.

Robert Louis Stevenson, 1850–1894