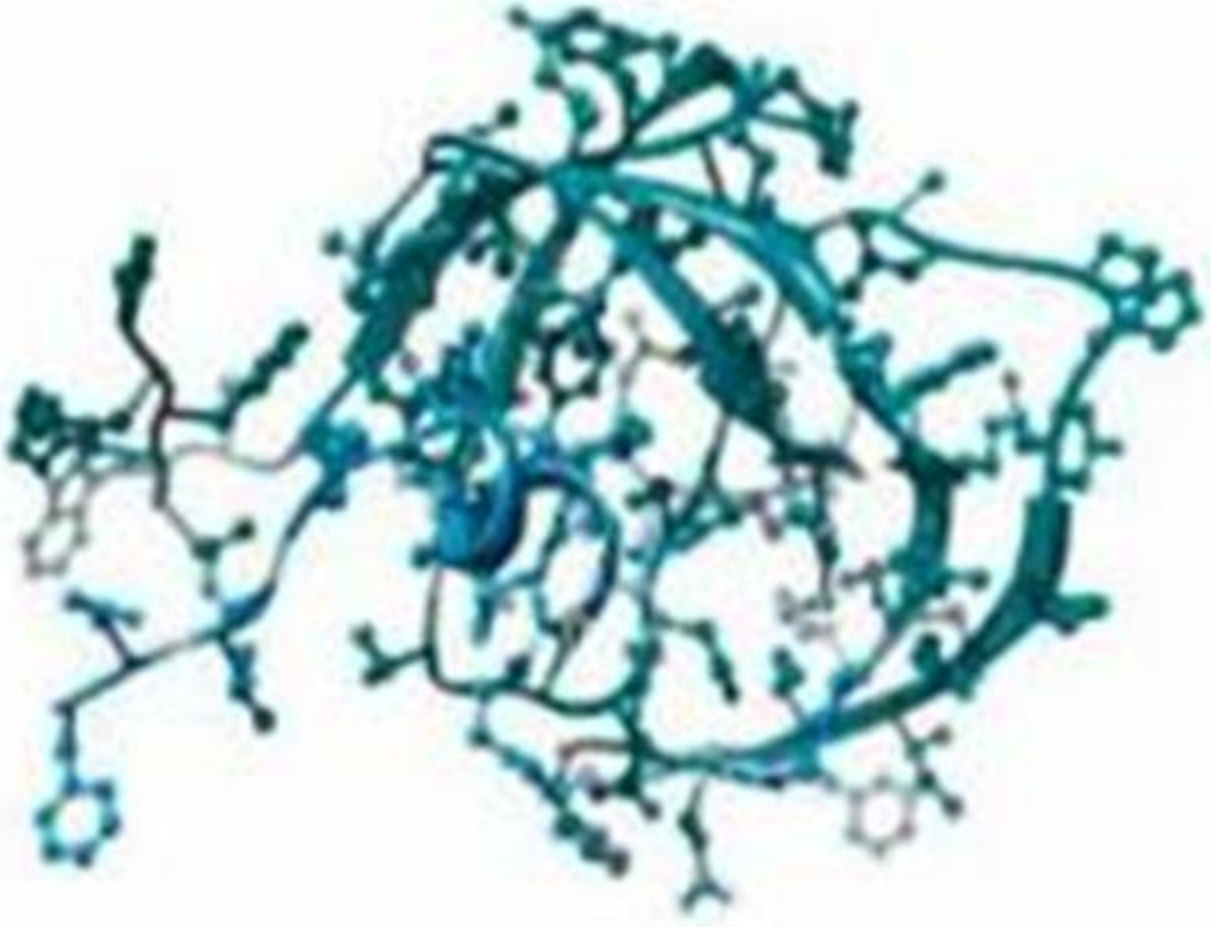
OXFORD

An Introduction to Medicinal Chemistry

FOURTH EDITION



Graham L. Patrick

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Medicinal Chemistry

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With a chapter on COMBINATORIAL AND PARALLEL SYNTHESIS
co-authored by **John Spencer**

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1 3 5 7 9 10 8 6 4 2

Preface

This text is aimed at undergraduates and postgraduates who have a basic grounding in chemistry and are studying a module or degree in medicinal chemistry. It attempts to convey, in a readable and interesting style, an understanding about drug design and the molecular mechanisms by which drugs act in the body. In so doing, it highlights the importance of medicinal chemistry in all our lives and the fascination of working in a field which overlaps the disciplines of chemistry, biochemistry, physiology, microbiology, cell biology, and pharmacology. Consequently, the book is of particular interest to students who might be considering a future career in the pharmaceutical industry.

Following the success of the first three editions, as well as useful feedback from readers, there has been some reorganization and updating of chapters. Some case studies that were embedded in chapters now stand alone, and a couple of new case studies have been introduced that cover the statins and the antimalarial agent artemisinin.

Following the introductory chapter, the book is divided into five parts:

- Part A contains six chapters that cover the structure and function of important drug targets such as receptors, enzymes, and nucleic acids. Students with a strong background in biochemistry will already know this material, but may find these chapters a useful revision of the essential points.
- Part B covers pharmacodynamics in chapters 7–10, and pharmacokinetics in chapter 11. Pharmacodynamics is the study of how drugs interact with their molecular targets, and the consequences of those interactions. Pharmacokinetics relates to the issues involved in a drug reaching its target in the first place.
- Part C covers the general principles and strategies involved in discovering and designing new drugs and developing them for the marketplace.
- Part D looks at particular 'tools of the trade', which are invaluable in drug design—QSAR, combinatorial synthesis, and computer aided design.
- Part E covers a selection of specific topics within medicinal chemistry—antibacterial, antiviral and anticancer agents, cholinergics and anticholinesterases, adrenergics, opioid analgesics, and antiulcer agents. To some extent, those chapters reflect the changing emphasis in medicinal chemistry research. Antibacterial agents, cholinergics, adrenergics, and opioids have long histories, and much of the early development of these drugs relied heavily on random variations of lead compounds on a trial and error basis. This approach was wasteful but it led to the recognition of various design strategies which could be used in a more rational approach to drug design. The development of the antiulcer drug cimetidine (chapter 25) represents one of the early examples of the rational approach to medicinal chemistry. However, the real revolution in drug design resulted from giant advances made in molecular biology and genetics, which have provided a detailed understanding of drug targets and how they function at the molecular level. This, allied to the use of molecular modelling and X-ray crystallography, has revolutionized drug design. The development of protease inhibitors as antiviral agents (chapter 20) is a prime example of the modern approach.

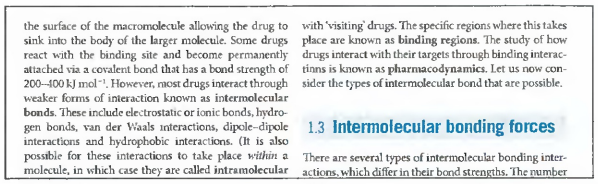
G. L. P.
Dec 2008

About the book

The fourth edition of *An Introduction to Medicinal Chemistry* and its accompanying Online Resource Centre contains many learning features. This section illustrates each of these learning features and explains how they will help you to understand this fascinating subject.

Emboldened key words

Terminology is emboldened and defined in a glossary at the end of the book, helping you to become familiar with the language of medicinal chemistry.

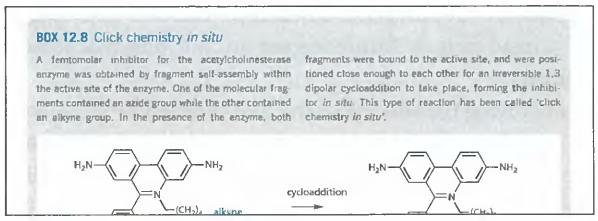

the surface of the macromolecule allowing the drug to sink into the body of the larger molecule. Some drugs react with the binding site and become permanently attached via a covalent bond that has a bond strength of 200–400 kJ mol^{-1}. However, most drugs interact through weaker forms of interaction known as **intermolecular bonds**. These include electrostatic or ionic bonds, hydrogen bonds, van der Waals interactions, dipole–dipole interactions and hydrophobic interactions. (It is also possible for these interactions to take place *within* a molecule, in which case they are called **intramolecular** with 'visiting' drugs. The specific regions where this takes place are known as **binding regions**. The study of how drugs interact with their targets through binding interactions is known as **pharmacodynamics**. Let us now consider the types of intermolecular bond that are possible.

1.3 Intermolecular bonding forces

There are several types of intermolecular bonding interactions, which differ in their bond strengths. The number

Boxes

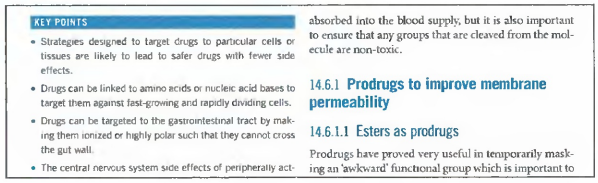
Boxes are used to present in-depth material and to explore how the concepts of medicinal chemistry are applied in practice. Boxes are grouped into three themes, General Interest, Synthesis, and Clinical Correlation. See page xix for a full list.


BOX 12.8 Click chemistry *in situ*

A femtomolar inhibitor for the acetylcholinesterase enzyme was obtained by fragment self-assembly within the active site of the enzyme. One of the molecular fragments contained an azide group while the other contained an alkyne group. In the presence of the enzyme, both fragments were bound to the active site, and were positioned close enough to each other for an irreversible 1,3 dipolar cycloaddition to take place, forming the inhibitor *in situ*. This type of reaction has been called 'click chemistry *in situ*'.

Key points

Summaries at the end of major sections within chapters highlight and summarize key concepts and provide a basis for revision.


KEY POINTS

- Strategies designed to target drugs to particular cells or tissues are likely to lead to safer drugs with fewer side effects.
- Drugs can be linked to amino acids or nucleic acid bases to target them against fast-growing and rapidly dividing cells.
- Drugs can be targeted to the gastrointestinal tract by making them ionized or highly polar such that they cannot cross the gut wall.
- The central nervous system side effects of peripherally act-

absorbed into the blood supply, but it is also important to ensure that any groups that are cleaved from the molecule are non-toxic.

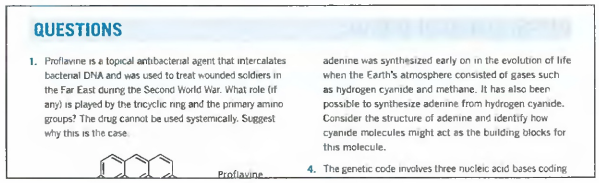
14.6.1 Prodrugs to improve membrane permeability

14.6.1.1 Esters as prodrugs

Prodrugs have proved very useful in temporarily masking an 'awkward' functional group which is important to

Questions

End-of-chapter questions allow you to test your understanding and apply concepts presented in the chapter.


QUESTIONS

1. Proflavine is a topical antibacterial agent that intercalates bacterial DNA and was used to treat wounded soldiers in the Far East during the Second World War. What role (if any) is played by the tricyclic ring and the primary amino groups? The drug cannot be used systemically. Suggest why this is the case.

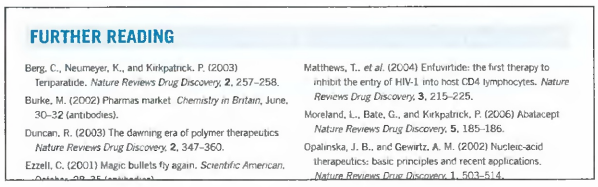
Proflavine

adenine was synthesized early on in the evolution of life when the Earth's atmosphere consisted of gases such as hydrogen cyanide and methane. It has also been possible to synthesize adenine from hydrogen cyanide. Consider the structure of adenine and identify how cyanide molecules might act as the building blocks for this molecule.

4. The genetic code involves three nucleic acid bases coding

Further reading

Selected references allow you easily to research those topics that are of particular interest to you.


FURTHER READING

Berg, C., Neumeyer, K., and Kirkpatrick, P. (2003) Teriparatide. *Nature Reviews Drug Discovery*, **2**, 257–258.

Burke, M. (2002) Pharmas market. *Chemistry in Britain*, June, 30–32 (antibodies).

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Ezzell, C. (2001) Magic bullets fly again. *Scientific American*,

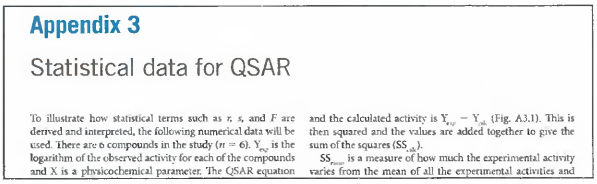
Matthews, T., *et al.* (2004) Enfuvirtide: the first therapy to inhibit the entry of HIV-1 into host CD4 lymphocytes. *Nature Reviews Drug Discovery*, **3**, 215–225.

Moreland, L., Bate, G., and Kirkpatrick, P. (2006) Abatacept. *Nature Reviews Drug Discovery*, **5**, 185–186.

Opalinska, J. B., and Gewirtz, A. M. (2002) Nucleic-acid therapeutics: basic principles and recent applications. *Nature Reviews Drug Discovery*, **1**, 503–514.

Appendices

The appendices include an index of drug names and their corresponding trade names, and an extensive glossary.


Appendix 3

Statistical data for QSAR

To illustrate how statistical terms such as r, s, and F are derived and interpreted, the following numerical data will be used. There are 6 compounds in the study ($n = 6$). Y_{exp} is the logarithm of the observed activity for each of the compounds and X is a physicochemical parameter. The QSAR equation

and the calculated activity is $Y_{exp} - Y_{calc}$ (Fig. A3.1). This is then squared and the values are added together to give the sum of the squares (SS_{calc}).

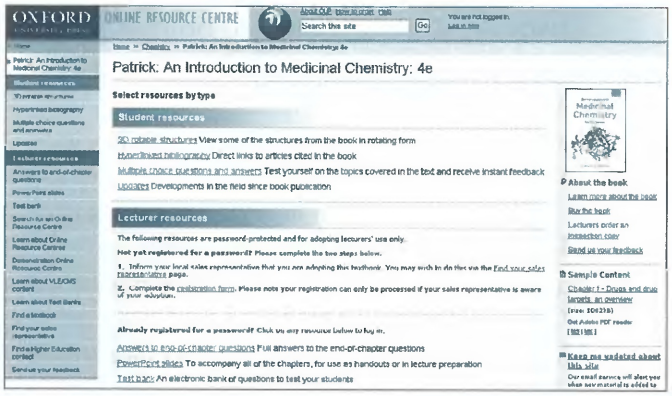
SS_{exp} is a measure of how much the experimental activity varies from the mean of all the experimental activities and

About the Online Resource Centre

Online Resource Centres provide students and lecturers with ready-to-use teaching and learning resources. They are free-of-charge, designed to complement the textbook, and offer additional materials that are suited to electronic delivery.

Many of these resources can be downloaded and can be fully customized, allowing them to be incorporated into your institution's existing virtual learning environment.

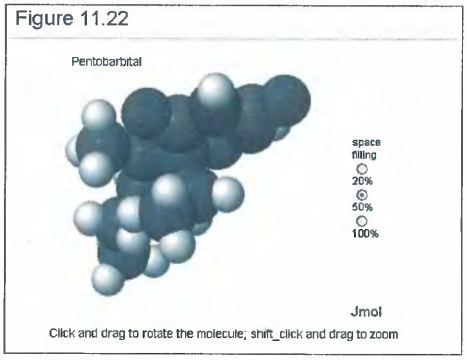
You will find this material at: **www.oxfordtextbooks.co.uk/orc/patrick4e/**



Student resources

Rotatable 3D structures

Fully interactive 3D models of selected molecules in the book help you to visualize them. All models kindly generated by Dr James Keeler, University of Cambridge.



Online quiz

A range of multiple-choice questions for each chapter, to check your understanding, or for use as a revision tool.

Hyperlinked bibliography

Direct links to online articles cited in the book.*

Updates

Six-monthly updates to the content in the fourth edition, focusing on fast-moving research areas.

Lecturer resources

Test Bank

A bank of multiple choice questions, which can be downloaded and customized for your teaching.

Answers

Answers to end-of-chapter questions.

Figures from the book

All of the figures from the textbook are available to download electronically for use in lectures and handouts.

PowerPoint slides

PowerPoint slides are provided to help teach selected topics from the book.

*Institutional subscription required for full text access

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Brief contents

Detailed contents

List of boxes

General interest

Synthesis

Clinical correlation

Acronyms and abbreviations

ACE	angiotensin-converting enzyme
ADAPT	antibody-directed abzyme prodrug therapy
ADEPT	antibody-directed enzyme prodrug therapy
ADH	alcohol dehydrogenase
AIC	5-aminoimidazole-4-carboxamide
AIDS	acquired immune deficiency syndrome
AML	acute myeloid leukaemia
AMP	adenosine 5′-monophosphate
ATP	adenosine 5′-triphosphate
AUC	area under the curve
CCK	cholecystokinin
CDKs	cyclin-dependent kinases
cGMP	cyclic GMP
CKIs	cyclin-dependent kinase inhibitors
CML	chronic myeloid leukaemia
CMV	cytomegalovirus
CNS	central nervous system
COMT	catechol *O*-methyltransferase
COX	cyclooxygenase
CSD	Cambridge Structural Database
CYP	enzymes that constitute the cytochrome P450 family
DG	diacylglycerol
DHFR	dihydrofolate reductase
DNA	deoxyribonucleic acid
dTMP	deoxythymidine monophosphate
dUMP	deoxyuridine monophosphate
EC_{50}	concentration of drug required to produce 50% of the maximum possible effect
EGF	epidermal growth factor
EMEA	European Agency for the Evaluation of Medicinal Products
EPC	European Patent Convention
EPO	European Patent Office
FDA	US Food and Drug Administration
FGF	fibroblast growth factor
FGF-R	fibroblast growth factor receptor
FH_4	tetrahydrofolate
FPGS	folylpolyglutamate synthetase
FPP	farnesyl diphosphate
FT	farnesyl transferase
FTI	farnesyl transferase inhibitor
GABA	γ-aminobutyric acid
GAP	GTPase activating protein
GCP	Good Clinical Practice
GDEPT	gene-directed enzyme prodrug therapy
GEF	guanine nucleotide exchange factors
GGTase	geranylgeranyltransferase
GH	growth hormone
GIT	gastrointestinal tract
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
GnRH	gonadotrophin-releasing hormone
HA	haemagglutinin
HAART	highly active antiretroviral therapy
HAMA	human anti-mouse antibodies
HIV	human immunodeficiency virus
HOMO	highest occupied molecular orbital
HPLC	high-performance liquid chromatography
HPMA	*N*-(2-hydroxypropyl)methacrylamide
HRV	human rhinoviruses
HTS	high-throughput screening
IGF-1R	insulin growth factor 1 receptor
IND	Investigational Exemption to a New Drug Application
IP_3	inositol triphosphate
IPER	International Preliminary Examination Report
IRB	Institutional Review Board
ISR	International Search Report
K_M	Michaelis constant
LH	luteinizing hormone
LHRH	luteinizing hormone-releasing hormones
LUMO	lowest unoccupied molecular orbital
MAA	Marketing Authorization Application
MAB	monoclonal antibody
MAO	monoamine oxidase
MAOI	monoamine oxidase inhibitor
MAP	mitogen-activated protein
MAPK	mitogen-activated protein kinases
MDR	multidrug resistance
MEP	molecular electrostatic potential
MMP	matrix metalloproteinase
MMPI	matrix metalloproteinase inhibitor

NA	neuraminidase or noradrenaline
NAD^+/NADH	nicotinamide adenine dinucleotide
NAG	*N*-acetylglucosamine
NAM	*N*-acetylmuramic acid
NCE	new chemical entity
NDA	New Drug Application
NMDA	*N*-methyl-D-aspartate
NME	new molecular entity
NMR	nuclear magnetic resonance
NNRTIs	non-nucleoside reverse transcriptase inhibitors
NO	nitric oxide
NRTI	nucleoside reverse transcriptase inhibitor
NSAID	non-steroidal anti-inflammatory drug
NVOC	nitroveratryloxycarbonyl
PABA	*p*-aminobenzoic acid
PBP	penicillin binding protein
PCP	phencyclidine, otherwise known as 'angel dust'
PCT	Patent Cooperation Treaty
PDB	Protein Data Bank
PDGF	platelet-derived growth factor
PDGF-R	platelet-derived growth factor receptor
PDT	photodynamic therapy
PEG	polyethylene glycol
PIP_2	phosphatidylinositol diphosphate
PI	protease inhibitor
PKA	protein kinase A
PKB	protein kinase B
PKC	protein kinase C
PLC	phospholipase C
PLS	partial least squares
PPI	proton pump inhibitor
PPts	pyridinium 4-toluenesulfonate
QSAR	quantitative structure–activity relationship
RES	reticuloendothelial system
RFC	reduced folate carrier
RMSD	root mean square distance
RNA	ribonucleic acid
SAR	structure–activity relationships
SCAL	safety-catch acid-labile linker
SCF	stem cell factor
SCID	severe combined immunodeficiency disease
SOP	standard operating procedure
SPA	scintillation proximity assay
SPR	surface plasmon resonance
TB	tuberculosis
TFA	trifluoroacetic acid
TGF-α	transforming growth factor α
TGF-β	transforming growth factor β
THF	tetrahydrofuran
TM	transmembrane
TNF	tumour necrosis factor
TNF-R	tumour necrosis factor receptor
TNT	trinitrotoluene
TRAIL	TNF-related apoptosis-inducing ligand
VEGF	vascular endothelial growth factor
VEGF-R	vascular endothelial growth factor receptor
VIP	vasoactive intestinal peptide
VOC–Cl	vinyloxycarbonyl chloride
VRE	vancomycin-resistant enterococci
VZV	varicella-zoster viruses