An Introduction to Medicinal Chemistry

FIFTH EDITION

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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.

New to this edition

Following the success of the first four editions, as well as useful feedback from readers, there has been some reorganization and updating of chapters, especially those in Part E.

Chapters have been modified, as appropriate, to reflect contemporary topics and teaching methods. This includes:

- new coverage of 99 drugs not featured in the previous edition;
- six new boxes, covering topics such 'Cyclodextrins as drug scavengers', 'The structure-based drug design of crizotinib', and 'Designing a non-steroidal glucocorticoid agonist';
- a new case study on steroidal anti-inflammatory agents;
- over 25 new sections, providing additional depth in subject areas including 'Tethers and anchors' and 'Short-acting β-blockers';
- additional end-of-chapter questions;
- current reference lists.

We have also made significant changes to the Online Resource Centre, adding 40 molecular modelling exercises and 16 web articles.

The structure of the book

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, i.e. 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 anti-ulcer 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 anti-ulcer 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), kinase inhibitors as anticancer agents (Chapter 21), and the statins as cholesterol-lowering agents (Case study 1) are prime examples of the modern approach.

G. L. P.
November 2012

About the book

The fifth edition of *An Introduction to Medicinal Chemistry* and its accompanying companion web site contains many learning features which will help you to understand this fascinating subject. This section explains how to get the most out of these.

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.

present in the drug can be important in forming intermolecular bonds with the target binding site. If they do so, they are called **binding groups**. However, the carbon skeleton of the drug also plays an important role in binding the drug to its target through van der Waals interactions. As far as the target binding site is concerned, it too contains functional groups and carbon skeletons which can form intermolecular bonds 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 and produce a pharmacological effect is known as **pharmacodynamics**.

one or more of the following interactions, but not necessarily all of them.

1.3.1 Electrostatic or ionic bonds

An ionic or electrostatic bond is the strongest of the intermolecular bonds (20–40 kJ mol^{-1}) and takes place between groups that have opposite charges, such as a carboxylate ion and an aminium ion (Fig. 1.5). The strength of the interaction is inversely proportional to the distance between the two charged atoms and it is also dependent on the nature of the environment, being

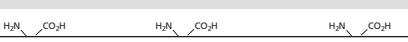
Boxes

Boxes are used to present in-depth material and to explore how the concepts of medicinal chemistry are applied in practice.

BOX 3.1 The external control of enzymes by nitric oxide

The external control of enzymes is usually initiated by external chemical messengers which do not enter the cell. However, there is an exception to this. It has been discovered that cells can generate the gas **nitric oxide** by the reaction sequence shown in Fig. 1, catalysed by the enzyme **nitric oxide synthase**.

Because nitric oxide is a gas, it can diffuse easily through cell membranes into target cells. There, it activates enzymes called **cyclases** to generate **cyclic GMP** from **GTP** (Fig. 2). Cyclic GMP then acts as a secondary messenger to influence other reactions within the cell. By this process, nitric oxide has an influence on a diverse range of physiological processes, including blood pressure, **neurotransmission**, and immunological defence mechanisms.



Key points

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

KEY POINTS

- Drugs act on molecular targets located in the cell membrane of cells or within the cells themselves.
- Drug targets are macromolecules that have a binding site into which the drug fits and binds.
- Most drugs bind to their targets by means of intermolecular bonds.
- Pharmacodynamics is the study of how drugs interact with their targets and produce a pharmacological effect.
- Electrostatic or ionic interactions occur between groups of

their pharmacological effect.

By chemical structure Many drugs which have a common skeleton are grouped together, for example penicillins, barbiturates, opiates, steroids, and catecholamines. In some cases, this is a useful classification as the biological activity and mechanism of action is the same for the structures involved, for example the antibiotic activity of penicillins. However, not all compounds with similar chemical structures have the same biological action. For example, steroids share a similar tetracyclic structure, but they have very different effects in the body. In this text, various groups of structurally-related drugs are discussed,

Questions

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

QUESTIONS

1. Enzymes can be used in organic synthesis. For example, the reduction of an aldehyde is carried out using aldehyde dehydrogenase. Unfortunately, this reaction requires the use of the cofactor NADH, which is expensive and is used up in the reaction. If ethanol is added to the reaction, only catalytic amounts of cofactor are required. Why?
2. Acetylcholine is the substrate for the enzyme acetylcholinesterase. Suggest what sort of binding

estradiol in the presence of the cofactor NADH. The initial rate data for the enzyme-catalysed reaction in the absence of an inhibitor is as follows:

Substrate concentration (10^{-2} mol dm^{-3}) 5 10 25 50 100

Initial rate (10^{-1} mol dm^{-3} s^{-1}) 28.6 51.5 111 141 145

Create a Michaelis Menton plot and a Lineweaver-Burk plot. Use both plots to calculate the values of K_M and the

Further reading

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

FURTHER READING

Broadwith, P. (2010) Enzymes do the twist. *Chemistry World*. Available at: http://www.rsc.org/chemistryworld/News/2010/January/06011001.asp (last accessed 14 June 2012).

Knowles, J. R. (1991) Enzyme catalysis: not different, just better. *Science* 350, 121–124.

Maryanoff, B. E. and Maryanoff, C. A. (1992) Some thoughts on enzyme inhibition and the quiescent affinity label concept. *Advances in Medicinal Chemistry* 1, 235–261.

Navia, M. A. and Murcko, M. A. (1992) Use of structural information in drug design. *Current Opinion in Structural Biology* 2, 202–216.

Teague, S. J. (2003) Implications of protein flexibility for drug discovery. *Nature Reviews Drug Discovery* 2, 527–541.

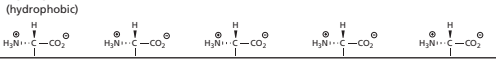
Appendix

The appendix includes an index of drug names and their corresponding trade names, and an extensive glossary.

Appendix 1

Essential amino acids

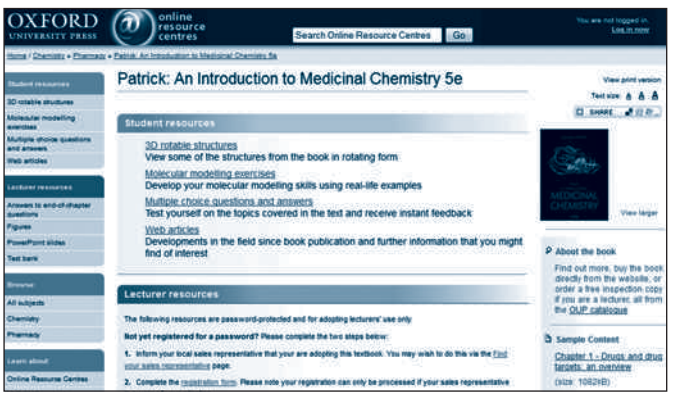
NON POLAR
(hydrophobic)



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 which are suited to electronic delivery.

You will find the material to accompany *An Introduction to Medicinal Chemistry* at:
www.oxfordtextbooks.co.uk/orc/patrick5e/



Student resources

Rotatable 3D structures
Links to where you can view the structures from the book in interactive rotating form.

Web articles
Developments in the field since the book published and further information that you may find of interest.

Molecular modelling exercises
Develop your molecular modelling skills, using Wavefunction's *Spartan*™ software to answer the set questions. To answer all the questions, you will need the full version of Spartan, which is widely distributed at colleges and universities; check with your institution for access.

You will be able to answer a selection of the questions and familiarize yourself with the basics using *Spartan Student Edition*™. Students can purchase this from store.wavefun.com/product_p/SpStudent.htm. Enter the promotional code OUPAIMC to receive 20% discount for students using *An Introduction to Medicinal Chemistry*. For questions or support for *Spartan*™, visit www.wavefun.com.

Multiple choice questions
Test yourself on the topics covered in the text and receive instant feedback.

Lecturer resources

For registered adopters of the book

All these resources can be downloaded and are fully customizable, allowing them to be incorporated into your institution's existing virtual learning environment.

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.

Acknowledgements

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List of boxes

General interest

Synthesis

Clinical correlation

Acronyms and abbreviations

Note: Abbreviations for amino acids are given in Appendix 1

5-HT	5-hydroxytryptamine (serotonin)
7-ACA	7-aminocephalosporinic acid
6-APA	6-aminopenicillanic acid
ACE	angiotensin-converting enzyme
ACh	acetylcholine
AChE	acetylcholinesterase
ACT	artemisinin combination therapy
ADAPT	antibody-directed abzyme prodrug therapy
ADEPT	antibody-directed enzyme prodrug therapy
ADH	alcohol dehydrogenase
ADME	absorption, distribution, metabolism, excretion
ADP	adenosine diphosphate
AIC	5-aminoimidazole-4-carboxamide
AIDS	acquired immune deficiency syndrome
AML	acute myeloid leukaemia
AMP	adenosine 5′-monophosphate
AT	angiotensin
ATP	adenosine 5′-triphosphate
AUC	area under the curve
cAMP	cyclic AMP
BuChE	butylcholinesterase
CCK	cholecystokinin
CDKs	cyclin-dependent kinases
CETP	cholesteryl ester transfer protein
cGMP	cyclic GMP
CHO cells	Chinese hamster ovarian cells
CKIs	cyclin-dependent kinase inhibitors
CLogP	calculated logarithm of the partition coefficient
CML	chronic myeloid leukaemia
CMV	cytomegalovirus
CNS	central nervous system
CoA	coenzyme A
CoMFA	comparative molecular field analysis
COMT	catechol *O*-methyltransferase
COX	cyclooxygenase
CSD	Cambridge Structural Database
CYP	enzymes that constitute the cytochrome P450 family
D-Receptor	dopamine receptor
dATP	deoxyadenosine triphosphate
DCC	dicyclohexylcarbodiimide
dCTP	Deoxycytosine triphosphate
DG	diacylglycerol
dGTP	deoxyguanosine triphosphate
DHFR	dihydrofolate reductase
DMAP	dimethylaminopyridine
DNA	deoxyribonucleic acid
DOR	delta opioid receptor
dsDNA	double-stranded DNA
dsRNA	double-stranded RNA
dTMP	deoxythymidylate monophosphate
dTTP	deoxythymidylate triphosphate
dUMP	deoxyuridylate monophosphate
EC_{50}	concentration of drug required to produce 50% of the maximum possible effect
E_s	Taft's steric factor
EGF	epidermal growth factor
EGF-R	epidermal growth factor receptor
EMEA	European Agency for the Evaluation of Medicinal Products
EPC	European Patent Convention
EPO	European Patent Office
FDA	US Food and Drug Administration
FdUMP	fluorodeoxyuracil monophosphate
FGF	fibroblast growth factor
FGF-R	fibroblast growth factor receptor
FH_4	tetrahydrofolate
F	oral bioavailability
F	inductive effect of an aromatic substituent in QSAR
F-SPE	fluorous solid phase extraction
FLOG	flexible ligands orientated on grid
FPGS	folylpolyglutamate synthetase
FPP	farnesyl diphosphate
FT	farnesyl transferase
FTI	farnesyl transferase inhibitor
G-Protein	guanine nucleotide binding protein
GABA	γ-aminobutyric acid
GAP	GTPase activating protein
GCP	Good Clinical Practice

GDEPT	gene-directed enzyme prodrug therapy
GDP	guanosine diphosphate
GEF	guanine nucleotide exchange factors
GGTase	geranylgeranyltransferase
GH	growth hormone
GIT	gastrointestinal tract
GLP	Good Laboratory Practice
GMC	General Medical Council
GMP	Good Manufacturing Practice
GMP	guanosine monophosphate
GnRH	gonadotrophin-releasing hormone
gp	glycoprotein
GTP	guanosine triphosphate
h-PEPT	human intestinal proton-dependent oligopeptide transporter
H-receptor	histamine receptor
HA	hemagglutinin
HAART	highly active antiretroviral therapy
HAMA	human anti-mouse antibodies
HBA	hydrogen bond acceptor
HBD	hydrogen bond donor
HCV	hepatitis C virus
HDL	high density lipoprotein
HERG	human ether-a-go-go related gene
HIF	hypoxia-inducible factor
HIV	human immunodeficiency virus
HMG-SCoA	3-hydroxy-3-methylglutaryl-coenzyme A
HMGR	3-hydroxy-3-methylglutaryl-coenzyme A reductase
HOMO	highest occupied molecular orbital
HPLC	high-performance liquid chromatography
HPMA	*N*-(2-hydroxypropyl)methacrylamide
HPT	human intestinal di-/tripeptide transporter
HRV	human rhinoviruses
HSV	herpes simplex virus
HTS	high-throughput screening
IC_{50}	concentration of drug required to inhibit a target by 50%
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
ITC	isothermal titration calorimetry
IUPAC	International Union of Pure and Applied Chemistry
IV	intravenous
K_D	dissociation binding constant
K_i	inhibition constant
K_M	Michaelis constant
KOR	kappa opioid receptor
LAAM	L-α-acetylmethadol
LD_{50}	lethal dose required to kill 50% of a test sample of animals
LDH	lactate dehydrogenase
LH	luteinizing hormone
LHRH	luteinizing hormone-releasing hormones
LipE	lipophilic efficiency
Log*P*	logarithm of the partition coefficient
LDL	low density lipoprotein
LUMO	lowest unoccupied molecular orbital
M-receptor	muscarinic receptor
MAA	Marketing Authorization Application
MAB	monoclonal antibody
MAO	monoamine oxidase
MAOI	monoamine oxidase inhibitor
MAOS	microwave assisted organic synthesis
MAP	mitogen-activated protein
MAPK	mitogen-activated protein kinases
MCH-R	melanin-concentrating hormone receptor
MDR	multidrug resistance
MDRTB	multidrug-resistant tuberculosis
MEP	molecular electrostatic potential
miRNA	micro RNA
miRNP	micro RNA protein
MMP	matrix metalloproteinase
MMPI	matrix metalloproteinase inhibitor
MOR	mu opioid receptor
MR	molar refractivity
mRNA	messenger RNA
MRSA	methicillin-resistant *Staphylococcus aureus*
MTDD	multi-target drug discovery
mTRKI	multi-tyrosine receptor kinase inhibitor
MWt	molecular weight
N-receptor	nicotinic receptor
NA	neuraminidase or noradrenaline
NAD^+/NADH	nicotinamide adenine dinucleotide
$NADP^+$/NADPH	nicotinamide adenine dinucleotide phosphate
NAG	*N*-acetylglucosamine
NAM	*N*-acetylmuramic acid

NCE	new chemical entity
NDA	New Drug Application
NICE	National Institute for Health and Clinical Excellence
NMDA	*N*-methyl-D-aspartate
NME	new molecular entity
NMR	nuclear magnetic resonance
NNRTI	non-nucleoside reverse transcriptase inhibitor
NO	nitric oxide
NOR	nociceptin opioid receptor
NOS	nitric oxide synthase
NRTI	nucleoside reverse transcriptase inhibitor
NSAID	non-steroidal anti-inflammatory drug
NVOC	nitroveratryloxycarbonyl
ORL1	opioid receptor-like receptor
P	partition coefficient
PABA	*p*-aminobenzoic acid
PBP	penicillin binding protein
PCP	phencyclidine, otherwise known as 'angel dust'
PCT	patent cooperation treaty
PDB	protein data bank
PDE	phosphodiesterase
PDGF	platelet-derived growth factor
PDGF-R	platelet-derived growth factor receptor
PDT	photodynamic therapy
PEG	polyethylene glycol
PGE	prostaglandin E
PGF	prostaglandin F
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
PPBI	protein–protein binding inhibitor
PPI	proton pump inhibitor
PPts	pyridinium 4-toluenesulfonate
QSAR	quantitative structure–activity relationships
r	regression or correlation coefficient
R	resonance effect of an aromatic substituent in QSAR
RES	reticuloendothelial system
RFC	reduced folate carrier
RISC	RNA induced silencing complex
RMSD	root mean square distance
rRNA	ribosomal RNA
RNA	ribonucleic acid
s	standard error of estimate or standard deviation
SAR	structure–activity relationships
SCAL	safety-catch acid-labile linker
SCF	stem cell factor
SCID	severe combined immunodeficiency disease
SKF	Smith-Kline and French
SNRI	selective noradrenaline reuptake inhibitors
siRNA	small inhibitory RNA
snRNA	small nuclear RNA
SOP	standard operating procedure
SPA	scintillation proximity assay
SPE	solid phase extraction
SPOS	solution phase organic synthesis
SPR	surface plasmon resonance
ssDNA	single-stranded DNA
SSRI	selective serotonin reuptake inhibitor
ssRNA	single-stranded RNA
TB	tuberculosis
TCA	tricyclic antidepressants
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
TRIPS	trade related aspects of intellectual property rights
tRNA	transfer RNA
UTI	urinary tract infection
vdW	van der Waals
VEGF	vascular endothelial growth factor
VEGF-R	vascular endothelial growth factor receptor
VIP	vasoactive intestinal peptide
VOC–Cl	vinyloxycarbonyl chloride
VRE	vancomycin-resistant enterococci
VRSA	vancomycin-resistant *Staphylococci aureus*
VZV	varicella-zoster viruses
WHO	World Health Organization
WTO	World Trade Organization