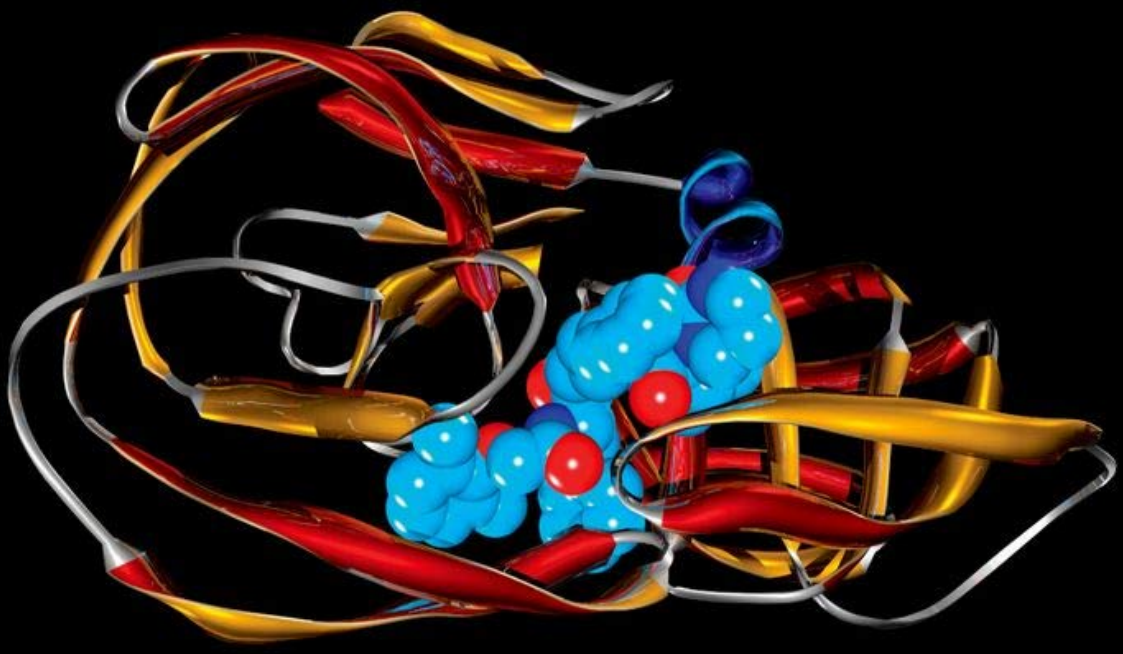
GRAHAM L. PATRICK



fifth edition

an introduction to MEDICINAL CHEMISTRY

OXFORD

An Introduction to Medicinal Chemistry

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An Introduction to Medicinal Chemistry

FIFTH EDITION

Graham L. Patrick

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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

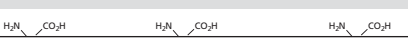
Boxes

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.

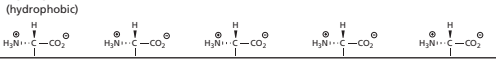
Appendix

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

Appendix 1

Essential amino acids

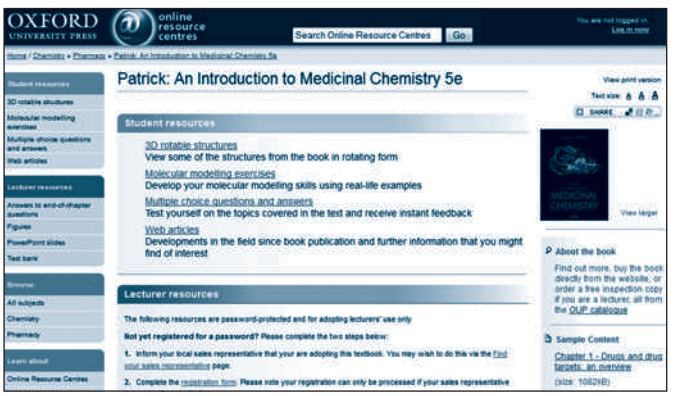
NON POLAR
(hydrophobic)



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

The author and Oxford University Press would like to thank the following people who have given advice on the various editions of this textbook:

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Brief contents

Contents

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

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1 Drugs and drug targets: an overview

1.1 What is a drug?

The medicinal chemist attempts to design and synthesize a pharmaceutical agent that has a desired biological effect on the human body or some other living system. Such a compound could also be called a 'drug', but this is a word that many scientists dislike because society views the term with suspicion. With media headlines such as 'Drugs Menace' or 'Drug Addiction Sweeps City Streets', this is hardly surprising. However, it suggests that a distinction can be drawn between drugs that are used in medicine and drugs that are abused. Is this really true? Can we draw a neat line between 'good drugs' like penicillin and 'bad drugs' like heroin? If so, how do we define what is meant by a good or a bad drug in the first place? Where would we place a so-called social drug like cannabis in this divide? What about nicotine or alcohol?

The answers we get depend on who we ask. As far as the law is concerned, the dividing line is defined in black and white. As far as the party-going teenager is concerned, the law is an ass. As far as we are concerned, the questions are irrelevant. Trying to divide drugs into two categories—safe or unsafe, good or bad—is futile and could even be dangerous.

First, let us consider the so-called 'good' drugs used in medicines. How 'good' are they? If a drug is to be truly 'good' it would have to do what it is meant to do, have no toxic or unwanted side effects, and be easy to take.

How many drugs fit these criteria?

The short answer is 'none'. There is no pharmaceutical compound on the market today that can completely satisfy all these conditions. Admittedly, some come quite close to the ideal. **Penicillin,** for example, has been one of the safest and most effective antibacterial agents ever discovered. Yet, it too has drawbacks. It cannot kill all known bacteria and, as the years have gone by, more and more bacterial strains have become resistant. Moreover, some individuals can experience severe allergic reactions to the compound.

Penicillin is a relatively safe drug, but there are some drugs that are distinctly dangerous. **Morphine** is one such example. It is an excellent analgesic, yet there are serious side effects, such as tolerance, respiratory depression, and addiction. It can even kill if taken in excess.

Barbiturates are also known to be dangerous. At Pearl Harbor, American casualties were given barbiturates as general anaesthetics before surgery. However, because of a poor understanding about how barbiturates are stored in the body, many patients received sudden and fatal overdoses. In fact, it is thought that more casualties died at the hands of the anaesthetists at Pearl Harbor than died of their wounds.

To conclude, the 'good' drugs are not as perfect as one might think.

What about the 'bad' drugs then? Is there anything good that can be said about them? Surely there is nothing we can say in defence of the highly addictive drug known as heroin?

Well, let us look at the facts about heroin. It is one of the best painkillers we know. In fact, it was named heroin at the end of the nineteenth century because it was thought to be the 'heroic' drug that would banish pain for good. Heroin went on the market in 1898, but five years later the true nature of its addictive properties became evident and the drug was speedily withdrawn from general distribution. However, heroin is still used in medicine today—under strict control, of course. The drug is called **diamorphine** and it is the drug of choice for treating patients dying of cancer. Not only does diamorphine reduce pain to acceptable levels, it also produces a euphoric effect that helps to counter the depression faced by patients close to death. Can we really condemn a drug which does that as being all 'bad'?

By now it should be evident that the division between good drugs and bad drugs is a woolly one and is not really relevant to our discussion of medicinal chemistry. All drugs have their good and bad points. Some have more good points than bad and vice versa, but, like people, they all have their own individual characteristics. So how are we to define a drug in general?

One definition could be to classify drugs as 'compounds which interact with a biological system to produce a biological response'. This definition covers all the drugs we have discussed so far, but it goes further. There are chemicals that we take every day and which have a biological effect on us. What are these everyday drugs?

One is contained in all the cups of tea, coffee, and cocoa that we consume. All of these beverages contain the stimulant **caffeine.** Whenever you take a cup of coffee, you are a drug user. We could go further. Whenever you crave a cup of coffee, you are a drug addict. Even children are not immune. They get their caffeine 'shot' from Coke or Pepsi. Whether you like it or not, caffeine is a drug. When you take it, you experience a change of mood or feeling.

So too, if you are a worshipper of the 'nicotine stick'. The biological effect is different. In this case you crave sedation or a calming influence, and it is the **nicotine** in the cigarette smoke which induces that effect.

There can be little doubt that **alcohol** is a drug and, as such, causes society more problems than all other drugs put together. One only has to study road accident statistics to appreciate that fact. If alcohol was discovered today, it would probably be restricted in exactly the same way as **cocaine.** Considered in a purely scientific way, alcohol is a most unsatisfactory drug. As many will testify, it is notoriously difficult to judge the correct dose required to gain the beneficial effect of 'happiness' without drifting into the higher dose levels that produce unwanted side effects, such as staggering down the street. Alcohol is also unpredictable in its biological effects. Either happiness or depression may result, depending on the user's state of mind. On a more serious note, **addiction** and **tolerance** in certain individuals have ruined the lives of addicts and relatives alike.

Our definition of a drug can also be used to include other compounds which may not be obvious as drugs, for example poisons and toxins. They too interact with a biological system and produce a biological response—a bit extreme, perhaps, but a response all the same. The idea of poisons acting as drugs may not appear so strange if we consider penicillin. We have no problem in thinking of penicillin as a drug, but if we were to look closely at how penicillin works, then it is really a poison. It interacts with bacteria (the biological system) and kills them (the biological response). Fortunately for us, penicillin has no such effect on human cells.

Even those drugs which do not act as poisons have the potential to become poisons—usually if they are taken in excess. We have already seen this with morphine. At low doses it is a painkiller; at high doses, it is a poison which kills by the suppression of breathing. Therefore, it is important that we treat all medicines as potential poisons and treat them with respect.

There is a term used in medicinal chemistry known as the **therapeutic index**, which indicates how safe a particular drug is. The therapeutic index is a measure of the drug's beneficial effects at a low dose versus its harmful effects at a high dose. To be more precise, the therapeutic index compares the dose level required to produce toxic effects in 50% of patients with the dose level required to produce the maximum therapeutic effects in 50% of patients. A high therapeutic index means that there is a large safety margin between beneficial and toxic doses. The values for cannabis and alcohol are 1000 and 10, respectively, which might imply that cannabis is safer and more predictable than alcohol. Indeed, a cannabis preparation **(nabiximols)** has now been approved to relieve the symptoms of multiple sclerosis. However, this does not suddenly make cannabis safe. For example, the favourable therapeutic index of cannabis does not indicate its potential toxicity if it is taken over a long period of time (chronic use). For example, the various side effects of cannabis include panic attacks, paranoid delusions, and hallucinations. Clearly, the safety of drugs is a complex matter and it is not helped by media sensationalism.

If useful drugs can be poisons at high doses or over long periods of use, does the opposite hold true? Can a poison be a medicine at low doses? In certain cases, this is found to be so.

Arsenic is well known as a poison, but arsenic-derived compounds are used as antiprotozoal and anticancer agents. **Curare** is a deadly poison which was used by the native people of South America to tip their arrows such that a minor arrow wound would be fatal, yet compounds based on the **tubocurarine** structure (the active principle of curare) are used in surgical operations to relax muscles. Under proper control and in the correct dosage, a lethal poison may well have an important medical role. Alternatively, lethal poisons can be the starting point for the development of useful drugs. For example, **ACE inhibitors** are important cardiovascular drugs that were developed, in part, from the structure of a snake venom.

As our definition covers any chemical that interacts with any biological system, we could include all pesticides and herbicides as drugs. They interact with bacteria, fungi, and insects, kill them, and thus protect plants.

Even food can act like a drug. Junk foods and fizzy drinks have been blamed for causing hyperactivity in children. It is believed that junk foods have high concentrations of certain amino acids which can be converted in the body to neurotransmitters. These are chemicals that pass messages between nerves. If an excess of these chemical messengers should accumulate, then too many messages are transmitted in the brain, leading to the disruptive behaviour observed in susceptible individuals. Allergies due to food additives and preservatives are also well recorded.

Some foods even contain toxic chemicals. Broccoli, cabbage, and cauliflower all contain high levels of a chemical that can cause reproductive abnormalities in rats. Peanuts and maize sometimes contain fungal toxins, and it is thought that fungal toxins in food were responsible for the biblical plagues. Basil contains over 50 compounds that are potentially carcinogenic, and other herbs contain some of the most potent carcinogens known. Carcinogenic compounds have also been identified in radishes, brown mustard, apricots, cherries, and plums. Such unpalatable facts might put you off your dinner, but take comfort—these chemicals are present in such small quantities that the risk is insignificant. Therein lies a great truth, which was recognized as long ago as the fifteenth century when it was stated that 'Everything is a poison, nothing is a poison. It is the dose that makes the poison'.

Almost anything taken in excess will be toxic. You can make yourself seriously ill by taking 100 aspirin tablets or a bottle of whisky or 9 kg of spinach. The choice is yours!

To conclude, drugs can be viewed as actual or potential poisons. An important principle is that of **selective toxicity**. Many drugs are effective because they are toxic to 'problem cells', but not normal cells. For example, antibacterial, antifungal, and antiprotozoal drugs are useful in medicine when they show a selective toxicity to microbial cells, rather than mammalian cells. Clinically effective anticancer agents show a selective toxicity for cancer cells over normal cells. Similarly, effective antiviral agents are toxic to viruses rather than normal cells.

Having discussed what drugs are, we shall now consider why, where, and how they act.

KEY POINTS

- Drugs are compounds that interact with a biological system to produce a biological response.
- No drug is totally safe. Drugs vary in the side effects they might have.
- The dose level of a compound determines whether it will act as a medicine or as a poison.
- The therapeutic index is a measure of a drug's beneficial effect at a low dose versus its harmful effects at higher dose. A high therapeutic index indicates a large safety margin between beneficial and toxic doses.
- The principle of selective toxicity means that useful drugs show toxicity against foreign or abnormal cells but not against normal host cells.

1.2 Drug targets

Why should chemicals, some of which have remarkably simple structures, have such an important effect on such a complicated and large structure as a human being? The answer lies in the way that the human body operates. If we could see inside our bodies to the molecular level, we would see a magnificent array of chemical reactions taking place, keeping the body healthy and functioning.

Drugs may be mere chemicals, but they are entering a world of chemical reactions with which they interact. Therefore, there should be nothing odd in the fact that they can have an effect. The surprising thing might be that they can have such *specific* effects. This is more a result of *where* they act in the body—the drug targets.

1.2.1 Cell structure

As life is made up of cells, then quite clearly drugs must act on cells. The structure of a typical mammalian cell is shown in Fig. 1.1. All cells in the human body contain a boundary wall called the **cell membrane** which encloses the contents of the cell—the **cytoplasm**. The cell membrane seen under the electron microscope consists of two identifiable layers, each of which is made up of an ordered row of phosphoglyceride molecules, such as **phosphatidylcholine** (**lecithin**) (Fig. 1.2). The outer layer of the membrane is made up of phosphatidylcholine, whereas the inner layer is made up of phosphatidylethanolamine, phosphatidylserine, and phosphatidylinositol. Each phosphoglyceride molecule consists of a small polar head-group and two long, hydrophobic (water-hating) chains.

In the cell membrane, the two layers of phospholipids are arranged such that the hydrophobic tails point towards each other and form a fatty, hydrophobic centre, while the ionic head-groups are placed at the inner and outer surfaces of the cell membrane (Fig. 1.3). This is a stable structure because the ionic, hydrophilic head-groups

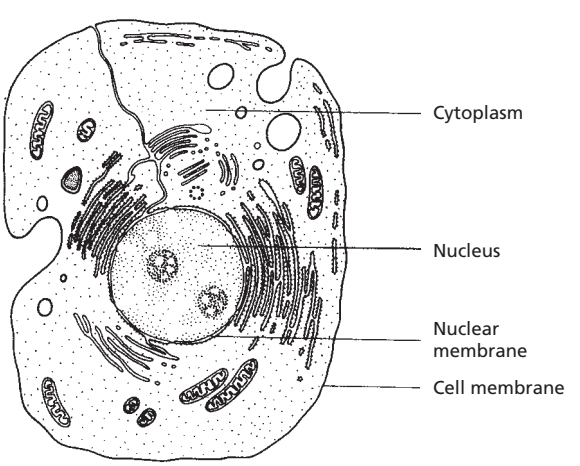


FIGURE 1.1 A typical mammalian cell. Taken from Mann, J. (1992) *Murder, Magic, and Medicine*. Oxford University Press, with permission.

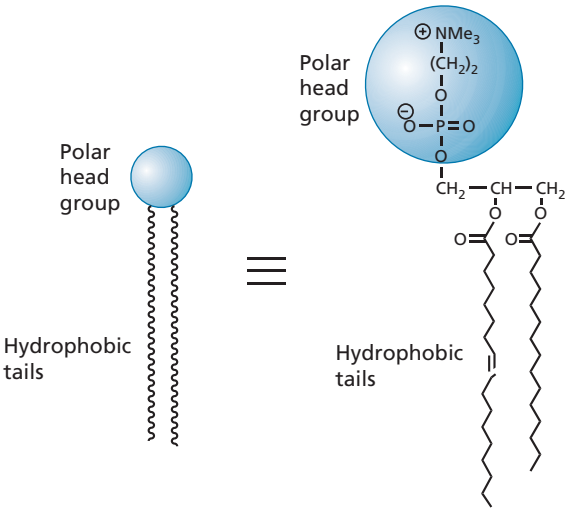


FIGURE 1.2 Phosphoglyceride structure.

interact with the aqueous media inside and outside the cell, whereas the hydrophobic tails maximize hydrophobic interactions with each other and are kept away from the aqueous environments. The overall result of this structure is to construct a fatty barrier between the cell's interior and its surroundings.

The membrane is not just made up of phospholipids, however. There are a large variety of proteins situated in the cell membrane (Fig. 1.3). Some proteins lie attached to the inner or the outer surface of the membrane. Others are embedded in the membrane with part of their structure exposed to one surface or both. The extent to which these proteins are embedded within the cell membrane structure depends on the types of amino acid present. Portions of protein that are embedded in the cell membrane have a large number of hydrophobic amino acids, whereas those portions that stick out from the surface have a large number of hydrophilic amino acids. Many surface proteins also have short chains of carbohydrates attached to them and are thus classed as **glycoproteins**.

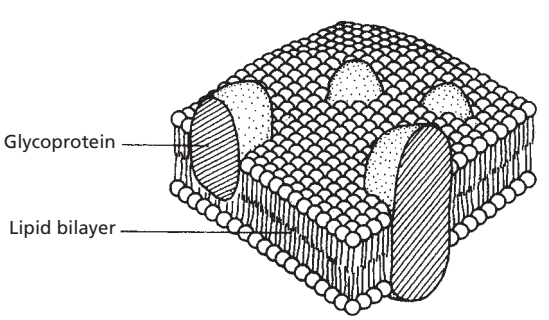


FIGURE 1.3 Cell membrane. Taken from Mann, J. (1992) *Murder, Magic, and Medicine*. Oxford University Press, with permission.

These carbohydrate segments are important in cell–cell recognition (section 10.7).

Within the cytoplasm there are several structures, one of which is the **nucleus**. This acts as the 'control centre' for the cell. The nucleus contains the genetic code—the DNA—which acts as the blueprint for the construction of all the cell's proteins. There are many other structures within a cell, such as the mitochondria, the Golgi apparatus, and the endoplasmic reticulum, but it is not the purpose of this book to look at the structure and function of these organelles. Suffice it to say that different drugs act on molecular targets at different locations in the cell.

1.2.2 Drug targets at the molecular level

We shall now move to the molecular level, because it is here that we can truly appreciate how drugs work. The main molecular targets for drugs are proteins (mainly enzymes, receptors, and transport proteins) and nucleic acids (DNA and RNA). These are large molecules (**macromolecules**) that have molecular weights measured in the order of several thousand atomic mass units. They are much bigger than the typical drug, which has a molecular weight in the order of a few hundred atomic mass units.

The interaction of a drug with a macromolecular target involves a process known as binding. There is usually a specific area of the macromolecule where this takes place, known as the **binding site** (Fig. 1.4). Typically, this takes the form of a hollow or canyon on 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 bonds**; see for example protein structure, sections 2.2 and 2.3.) None of these bonds is as strong as the covalent bonds that make up the skeleton of a molecule, and so they can be formed and then broken again. This means that an equilibrium takes place between the drug being bound and unbound to its target. The binding forces are strong enough to hold the drug for a certain period of time to let it have an effect on the target, but weak enough to allow the drug to depart once it has done its job. The length of time the drug remains at its target will then depend on the number of intermolecular bonds involved in holding it there. Drugs that have a large number of interactions are likely

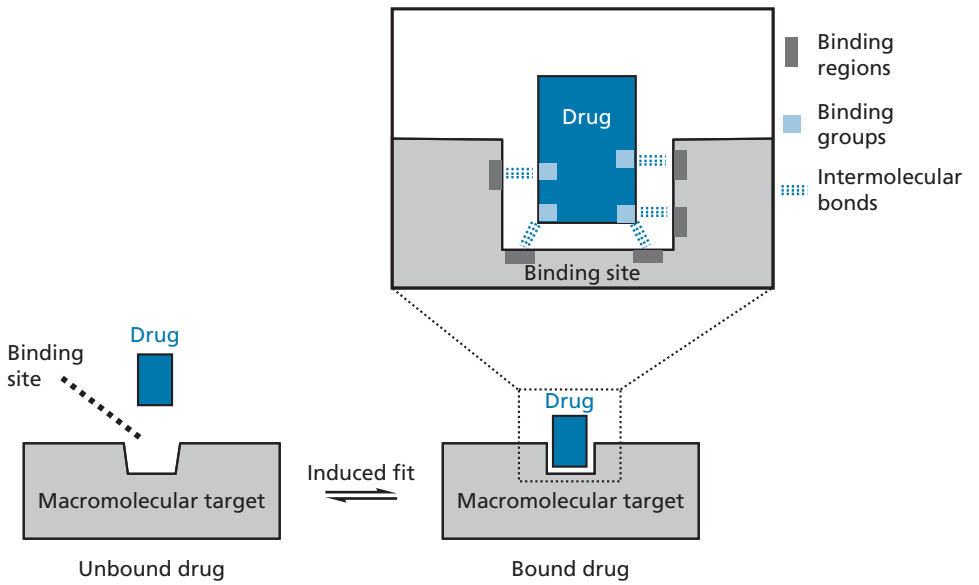


FIGURE 1.4 The equilibrium of a drug being bound and unbound to its target.

to remain bound longer than those that have only a few. The relative strength of the different intermolecular binding forces is also an important factor. Functional groups 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**. 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 and types of these interactions depend on the structure of the drug and the functional groups that are present (section 13.1 and Appendix 7). Thus, each drug may use 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 stronger in hydrophobic environments than in polar environments. Usually, the binding sites of macromolecules are more hydrophobic in nature than the surface and so this enhances the effect of an ionic interaction. The drop-off in ionic bonding strength with separation is less than in other intermolecular interactions, so if an ionic interaction is possible, it is likely to be the most important initial interaction as the drug enters the binding site.

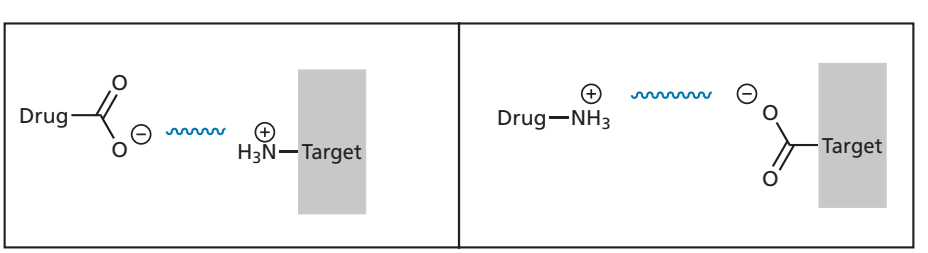


FIGURE 1.5 Electrostatic (ionic) interactions between a drug and the binding site.

FIGURE 1.6 Hydrogen bonding shown by a dashed line between a drug and a binding site (X, Y = oxygen or nitrogen; HBD = hydrogen bond donor, HBA = hydrogen bond acceptor).

1.3.2 Hydrogen bonds

A **hydrogen bond** can vary substantially in strength and normally takes place between an electron-rich heteroatom and an electron-deficient hydrogen (Fig. 1.6). The electron-rich heteroatom has to have a lone pair of electrons and is usually oxygen or nitrogen.

The electron-deficient hydrogen is usually linked by a covalent bond to an electronegative atom, such as oxygen or nitrogen. As the electronegative atom (X) has a greater attraction for electrons, the electron distribution in the covalent bond (X–H) is weighted towards the more electronegative atom and so the hydrogen gains its slight positive charge. The functional group containing this feature is known as a **hydrogen bond donor (HBD)** because it provides the hydrogen for the hydrogen bond. The functional group that provides the electron-rich atom to receive the hydrogen bond is known as the **hydrogen bond acceptor (HBA)**. Some functional groups can act both as hydrogen bond donors and hydrogen bond acceptors (e.g. OH, NH_2). When such a group is present in a binding site, it is possible that it might bind to one ligand as a hydrogen bond donor and to another as a hydrogen bond acceptor. This characteristic is given the term **hydrogen bond flip-flop**.

Hydrogen bonds have been viewed as a weak form of electrostatic interaction because the heteroatom is slightly negative and the hydrogen is slightly positive. However, there is more to hydrogen bonding than an attraction between partial charges. Unlike other intermolecular interactions, an interaction of orbitals takes place between the two molecules (Fig. 1.7). The orbital containing the lone pair of electrons on heteroatom (Y) interacts with the atomic orbitals normally involved in the covalent bond between X and H. This results in a weak form of sigma (σ) bonding and has an important directional consequence that is not evident in electrostatic bonds. The optimum orientation is where the X–H bond points directly to the lone pair on Y such that the angle formed between X, H, and Y is 180°. This is observed in very strong hydrogen bonds. However, the angle can vary between 130° and 180° for moderately strong hydrogen bonds, and can be as low as 90° for weak hydrogen bonds. The lone pair orbital of Y also has a directional property depending on its hybridization. For example, the nitrogen of a pyridine ring is sp^2 hybridized and so the lone pair points directly away from the ring and in the same plane (Fig. 1.8). The best location for a hydrogen bond donor would be the region of space indicated in the figure.

The strength of a hydrogen bond can vary widely, but most hydrogen bonds in drug–target interactions are moderate in strength, varying from 16 to 60 kJ mol^{-1}—approximately 10 times less than a covalent bond. The bond distance reflects this; hydrogen bonds are typically 1.5–2.2 Å compared with 1.0–1.5 Å for a covalent bond. The strength of a hydrogen bond depends on how strong the hydrogen bond acceptor and the hydrogen bond donor are. A good hydrogen bond acceptor has to be electronegative and have a lone pair of electrons. Nitrogen and oxygen are the most common atoms involved as hydrogen bond acceptors in biological systems. Nitrogen has one lone pair of electrons and can act as an acceptor for one hydrogen bond; oxygen has two lone pairs of electrons and can act as an acceptor for two hydrogen bonds (Fig. 1.9).

Several drugs and macromolecular targets contain a sulphur atom, which is also electronegative. However, sulphur is a weak hydrogen bond acceptor because its lone pairs are in third-shell orbitals that are larger and more

FIGURE 1.7 Orbital overlap in a hydrogen bond.

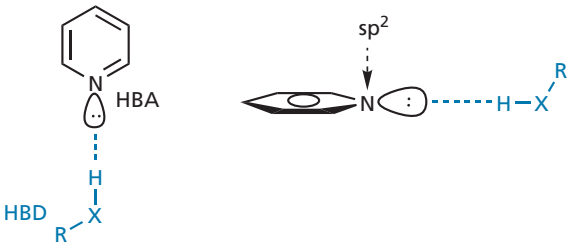


FIGURE 1.8 Directional influence of hybridization on hydrogen bonding.

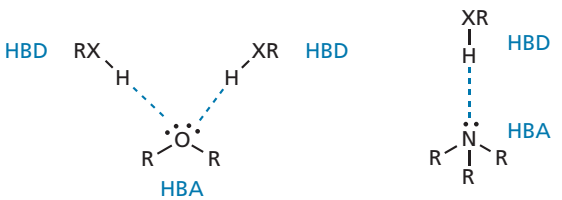


FIGURE 1.9 Oxygen and nitrogen acting as hydrogen bond acceptors (HBD = hydrogen bond donor, HBA = hydrogen bond acceptor).

diffuse. This means that the orbitals concerned interact less efficiently with the small 1s orbitals of hydrogen atoms.

Fluorine, which is present in several drugs, is more electronegative than either oxygen or nitrogen. It also has three lone pairs of electrons, which might suggest that it would make a good hydrogen bond acceptor. In fact, it is a weak hydrogen bond acceptor. It has been suggested that fluorine is so electronegative that it clings on tightly to its lone pairs of electrons, making them incapable of hydrogen bond interactions. This is in contrast to fluoride ions which are very strong hydrogen bond acceptors.

Any feature that affects the electron density of the hydrogen bond acceptor is likely to affect its ability to act as a hydrogen bond acceptor; the greater the electron density of the heteroatom, the greater its strength as a hydrogen bond acceptor. For example, the oxygen of a negatively charged carboxylate ion is a stronger hydrogen bond acceptor than the oxygen of the uncharged carboxylic acid (Fig. 1.10). Phosphate ions can also act as good hydrogen bond acceptors. Most hydrogen bond acceptors present in drugs and binding sites are neutral functional groups, such as ethers, alcohols, phenols, amides, amines, and ketones. These groups will form moderately strong hydrogen bonds.

It has been proposed that the pi (π) systems present in alkynes and aromatic rings are regions of high electron density and can act as hydrogen bond acceptors. However, the electron density in these systems is diffuse and so the hydrogen bonding interaction is much weaker than those involving oxygen or nitrogen. As a result, aromatic rings and alkynes are only likely to be significant hydrogen bond acceptors if they interact with a strong hydrogen bond donor, such as an alkylammonium ion (NHR_3^+).

More subtle effects can influence whether an atom is a good hydrogen bond acceptor or not. For example, the nitrogen atom of an aliphatic tertiary amine is a better hydrogen bond acceptor than the nitrogen of an amide or an aniline (Fig. 1.11). In the latter cases, the lone pair

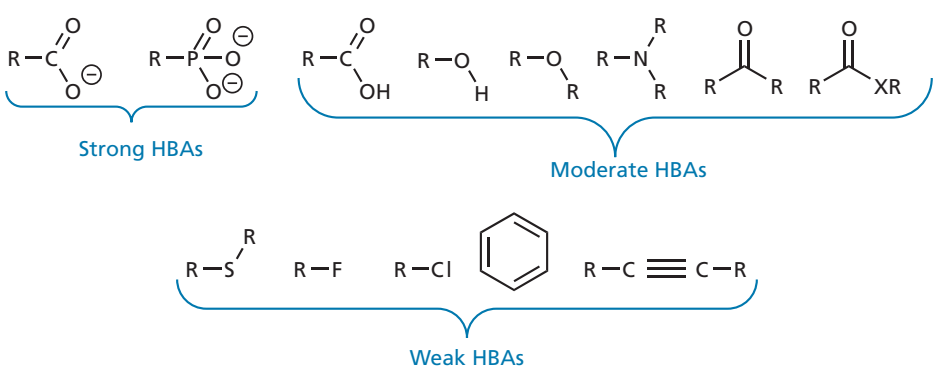


FIGURE 1.10 Relative strengths of hydrogen bond acceptors (HBAs).

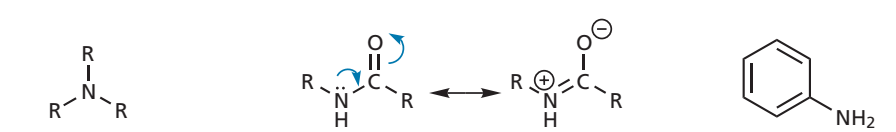


FIGURE 1.11 Comparison of different nitrogen containing functional groups as hydrogen bond acceptors (HBAs).

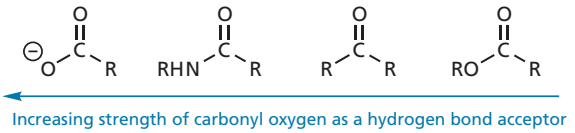


FIGURE 1.12 Comparison of carbonyl oxygens as hydrogen bond acceptors.

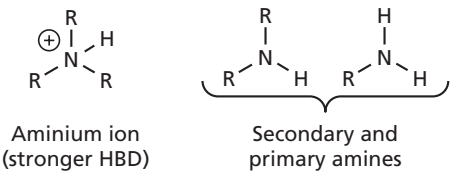


FIGURE 1.13 Comparison of hydrogen bond donors (HBDs).

of the nitrogen can interact with neighbouring π systems to form various resonance structures. As a result, it is less likely to take part in a hydrogen bond.

Similarly, the ability of a carbonyl group to act as a hydrogen bond acceptor varies depending on the functional group involved (Fig. 1.12).

It has also been observed that an sp^3 hybridized oxygen atom linked to an sp^2 carbon atom rarely acts as an HBA. This includes the alkoxy oxygen of esters and the oxygen atom present in aromatic ethers or furans.

Good hydrogen bond donors contain an electron-deficient proton linked to oxygen or nitrogen. The more electron-deficient the proton, the better it will act as a hydrogen bond donor. For example, a proton attached to a positively charged nitrogen atom acts as a stronger hydrogen bond donor than the proton of a primary or secondary amine (Fig. 1.13). Because the nitrogen is charged, it has a greater pull on the electrons surrounding it, making attached protons even more electron-deficient.

1.3.3 Van der Waals interactions

Van der Waals interactions are very weak interactions that are typically 2–4 kJ mol^{-1} in strength. They involve interactions between hydrophobic regions of different molecules, such as aliphatic substituents or the overall carbon skeleton. The electronic distribution in neutral, non-polar regions is never totally even or symmetrical, and there are always transient areas of high and low electron densities leading to temporary dipoles. The dipoles in one molecule can induce dipoles in a neighbouring molecule, leading to weak interactions between the two molecules (Fig. 1.14). Thus, an area of high electron density on one molecule can have an attraction for an area of low electron density on another molecule. The strength of these interactions falls off rapidly the further the two molecules are apart, decreasing to the seventh power of the separation. Therefore, the drug has to be close to the target binding site before the interactions become important. Van der Waals interactions are also referred to as **London forces**. Although the interactions are individually weak, there may be many such interactions between a drug and its target, and so the overall contribution of van der Waals interactions is often crucial to binding. Hydrophobic forces are also important when the non-polar regions of molecules interact (section 1.3.6).

1.3.4 Dipole–dipole and ion–dipole interactions

Many molecules have a permanent dipole moment resulting from the different electronegativities of the atoms and functional groups present. For example, a ketone has a dipole moment due to the different electronegativities of the carbon and oxygen making up the carbonyl bond. The binding site also contains functional groups, so it is inevitable that it too will have various local dipole moments. It is possible for the dipole moments of the drug and the binding site to interact as a drug approaches, aligning the drug such that the dipole moments are parallel and in opposite directions (Fig. 1.15). If this positions the drug such that other intermolecular interactions can take place between it and the target, the alignment is beneficial to both binding and activity. If not, then binding and activity may be weakened. An example of such an effect can be found in antiulcer drugs (section 25.2.8.3). The strength of dipole–dipole interactions reduces with the

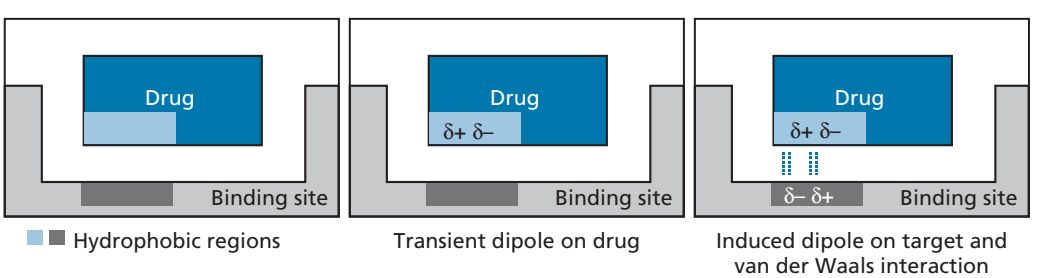


FIGURE 1.14 Van der Waals interactions between hydrophobic regions of a drug and a binding site.

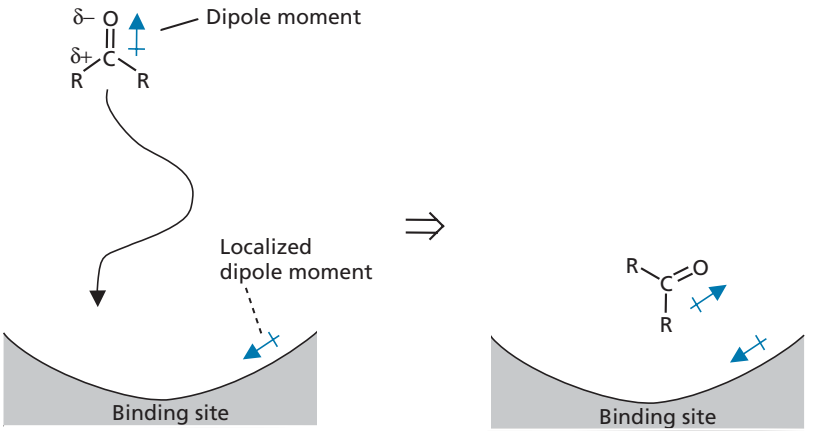


FIGURE 1.15 Dipole–dipole interactions between a drug and a binding site.

cube of the distance between the two dipoles. This means that dipole–dipole interactions fall away more quickly with distance than electrostatic interactions, but less quickly than van der Waals interactions.

An ion–dipole interaction is where a charged or ionic group in one molecule interacts with a dipole in a second molecule (Fig. 1.16). This is stronger than a dipole–dipole interaction and falls off less rapidly with separation (decreasing relative to the square of the separation).

Interactions involving an induced dipole moment have been proposed. There is evidence that an aromatic ring can interact with an ionic group such as a quaternary ammonium ion. Such an interaction is feasible if the positive charge of the quaternary ammonium group distorts the π electron cloud of the aromatic ring to produce a dipole moment where the face of the aromatic ring is electron-rich and the edges are electron-deficient (Fig. 1.17). This is also called a **cation-pi interaction**. An important neurotransmitter called **acetylcholine** forms this type of interaction with its binding site (section 22.5).

1.3.5 Repulsive interactions

So far we have concentrated on attractive forces, which increase in strength the closer the molecules approach each other. Repulsive interactions are also important.

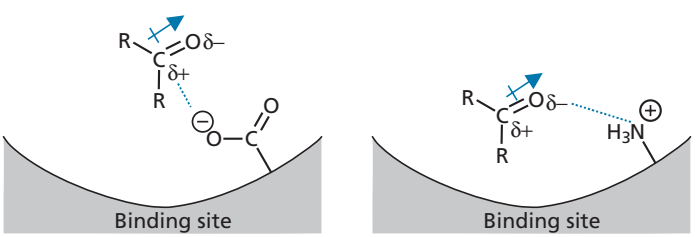


FIGURE 1.16 Ion–dipole interactions between a drug and a binding site.

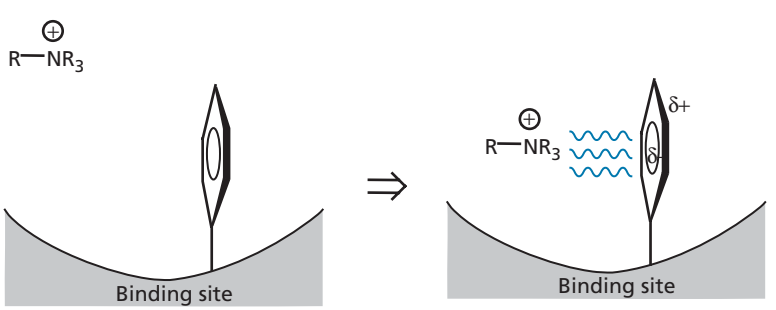


FIGURE 1.17 Induced dipole interaction between an alkylammonium ion and an aromatic ring.

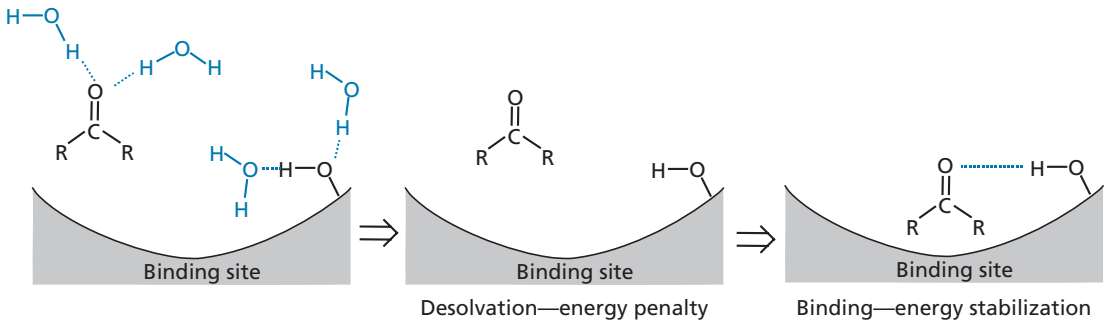


FIGURE 1.18 Desolvation of a drug and its target binding site prior to binding.

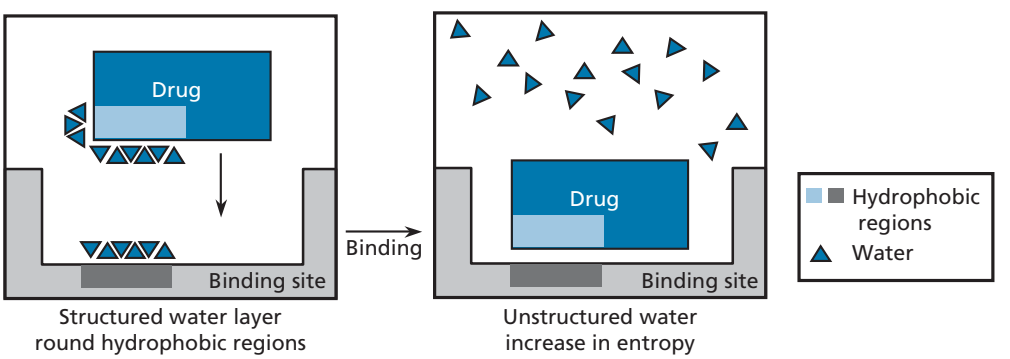


FIGURE 1.19 Hydrophobic interactions.

Otherwise, there would be nothing to stop molecules trying to merge with each other! If molecules come too close, their molecular orbitals start to overlap and this results in repulsion. Other forms of repulsion are related to the types of groups present in both molecules. For example, two charged groups of identical charge are repelled.

1.3.6 The role of water and hydrophobic interactions

A crucial feature that is often overlooked when considering the interaction of a drug with its target is the role of water. The macromolecular targets in the body exist in an aqueous environment and the drug has to travel through that environment in order to reach its target; therefore, both the drug and the macromolecule are solvated with water molecules before they meet each other. The water molecules surrounding the drug and the target binding site have to be stripped away before the interactions described above can take place (Fig. 1.18). This requires energy and if the energy required to desolvate both the drug and the binding site is greater than the stabilization energy gained by the binding interactions, then the drug may be ineffective. In certain cases, it has even proved beneficial to remove a polar binding group from a drug in order to lower its energy of desolvation. For example, this was carried out during the development of the antiviral drug **ritonavir** (section 20.7.4.4).

Sometimes polar groups are added to a drug to increase its water solubility. If this is the case, it is important that such groups are positioned in such a way that they protrude from the binding site when the drug binds; in other words, they are solvent-accessible or solvent-exposed. In this way, the water that solvates this highly polar group does not have to be stripped away and there is no energy penalty when the drug binds to its target (see section 21.6.2.1 and Case study 5).

It is not possible for water to solvate the non-polar or hydrophobic regions of a drug or its target binding site. Instead, the surrounding water molecules form stronger-than-usual interactions with each other, resulting in a more ordered layer of water next to the non-polar surface. This represents a negative entropy due to the increase in order. When the hydrophobic region of a drug interacts with a hydrophobic region of a binding site, these water molecules are freed and become less ordered (Fig. 1.19). This leads to an increase in entropy and a gain in binding energy.* The interactions involved are small at 0.1–0.2 kJ mol^{-1} for each $Å^2$ of hydrophobic surface, but overall they can be substantial. Sometimes, a hydrophobic region in the drug may not be sufficiently close to a hydrophobic

* The free energy gained by binding (ΔG) is related to the change in entropy (ΔS) by the equation $\Delta G = \Delta H - T\Delta S$. If entropy increases, ΔS is positive, which makes ΔG more negative. The more negative ΔG is, the more likely binding will take place.

region in the binding site and water may be trapped between the two surfaces. The entropy increase is not so substantial in that case and there is a benefit in designing a better drug that fits more snugly.

1.4 Pharmacokinetic issues and medicines

Pharmacodynamics is the study of how a drug binds to its target binding site and produces a pharmacological effect. However, a drug capable of binding to a particular target is not necessarily going to be useful as a clinical agent or medicine. For that to be the case, the drug not only has to bind to its target, it has to reach it in the first place. For an orally administered drug, that involves a long journey with many hazards to be overcome. The drug has to survive stomach acids then digestive enzymes in the intestine. It has to be absorbed from the gut into the blood supply and then it has to survive the liver where enzymes try to destroy it (drug metabolism). It has to be distributed round the body and not get mopped up by fat tissue. It should not be excreted too rapidly or else frequent doses will be required to maintain activity. However, it should not be excreted too slowly or its effects could linger on longer than required. The study of how a drug is absorbed, distributed, metabolized, and excreted (known as ADME in the pharmaceutical industry) is called **pharmacokinetics**. Pharmacokinetics has sometimes been described as 'what the body does to the drug' as opposed to pharmacodynamics—'what the drug does to the body'.

There are many ways in which medicinal chemists can design a drug to improve its pharmacokinetic properties, but the method by which the drug is formulated and administered is just as important. Medicines are not just composed of the active pharmaceutical agent. For example, a pill contains a whole range of chemicals that are present to give structure and stability to the pill, and also to aid the delivery and breakdown of the pill at the desired part of the gastrointestinal tract.

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 opposite charge.
- Hydrogen bonds occur between an electron-rich heteroatom and an electron-deficient hydrogen.
- The functional group providing the hydrogen for a hydrogen bond is called the hydrogen bond donor. The functional group that interacts with the hydrogen in a hydrogen bond is called the hydrogen bond acceptor.
- Van der Waals interactions take place between non-polar regions of molecules and are caused by transient dipole–dipole interactions.
- Ion–dipole and dipole–dipole interactions are a weak form of electrostatic interaction.
- Hydrophobic interactions involve the displacement of ordered layers of water molecules which surround hydrophobic regions of molecules. The resulting increase in entropy contributes to the overall binding energy.
- Polar groups have to be desolvated before intermolecular interactions take place. This results in an energy penalty.
- The pharmacokinetics of a drug relate to its absorption, distribution, metabolism, and excretion in the body.

1.5 Classification of drugs

There are four main ways in which drugs might be classified or grouped.

By pharmacological effect Drugs can be classified depending on the biological or pharmacological effect that they have, for example analgesics, antipsychotics, antihypertensives, anti-asthmatics, and antibiotics. This is useful if one wishes to know the full scope of drugs available for a certain ailment, but it means that the drugs included are numerous and highly varied in structure. This is because there are a large variety of targets at which drugs could act in order to produce the desired effect. It is therefore not possible to compare different painkillers and expect them to look alike or to have some common mechanism of action.

The chapters on antibacterial, antiviral, anticancer, and anti-ulcer drugs (Chapters 19–21 and 25) illustrate the variety of drug structures and mechanisms of action that are possible when drugs are classified according to 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, for example penicillins, cephalosporins, sulphonamides, opioids, and glucocorticoids (sections 19.4 and 19.5, Chapter 24 and Case study 6). These are examples of compounds with a similar structure and similar mechanism of action. However, there are exceptions. Most sulphonamides are used as antibacterial agents, but there are a few which have totally different medical applications.

By target system Drugs can be classified according to whether they affect a certain target system in the body. An example of a target system is where a neurotransmitter is synthesized, released from its neuron, interacts with a protein target, and is either metabolized or reabsorbed into the neuron. This classification is a bit more specific than classifying drugs by their overall pharmacological effect. However, there are still several different targets with which drugs could interact in order to interfere with the system and so the drugs included in this category are likely to be quite varied in structure because of the different mechanisms of action that are involved. In Chapters 22 and 23 we look at drugs that act on target systems—the cholinergic and the adrenergic system respectively.

By target molecule Some drugs are classified according to the molecular target with which they interact. For example, anticholinesterases (sections 22.12–22.15) are drugs which act by inhibiting the enzyme **acetylcholinesterase**. This is a more specific classification as we have now identified the precise target at which the drugs act. In this situation we might expect some structural similarity between the agents involved and a common mechanism of action, although this is not an inviolable assumption. However, it is easy to lose the wood for the trees and to lose sight of why it is useful to have drugs which switch off a particular enzyme or receptor. For example, it is not intuitively obvious why an anticholinesterase agent could be useful in treating Alzheimer's disease or glaucoma.

1.6 Naming of drugs and medicines

The vast majority of chemicals that are synthesized in medicinal chemistry research never make it to the market place and it would be impractical to name them all. Instead, research groups label them with a code which usually consists of letters and numbers. The letters are specific to the research group undertaking the work and the number is specific for the compound. Thus, Ro31-8959, ABT-538, and MK-639 were compounds prepared by Roche, Abbott, and Merck pharmaceuticals respectively. If the compounds concerned show promise as therapeutic drugs they are taken into development and named. For example, the above compounds showed promise as anti-HIV drugs and were named **saquinavir, ritonavir**, and **indinavir** respectively. Finally, if the drugs prove successful and are marketed as medicines, they are given a proprietary, brand, or trade name, which only the company can use. For example, the above compounds were marketed as **Fortovase®, Norvir®** and **Crixivan®** respectively (note that brand names always start with a capital letter and have the symbol R or TM to indicate that they are registered brand names). The proprietary names are also specific for the preparation or formulation of the drug. For example, Fortovase® (or Fortovase™) is a preparation containing 200 mg of saquinavir in a gel-filled, beige-coloured capsule. If the formulation is changed, then a different name is used. For example, Roche sell a different preparation of saquinavir called **Invirase®** which consists of a brown/green capsule containing 200 mg of saquinavir as the mesylate salt. When a drug's patent has expired, it is possible for any pharmaceutical company to produce and sell that drug as a generic medicine. However, they are not allowed to use the trade name used by the company that originally invented it. European law requires that generic medicines are given a **recommended International Non-proprietary Name** (rINN), which is usually identical to the name of the drug. In the UK, such drugs were given a **British Approved Name** (BAN), but these have now been modified to fall in line with rINNs.

As the naming of drugs is progressive, early research articles in the literature may only use the original letter/number code as the name of the drug had not been allocated at the time of publication.

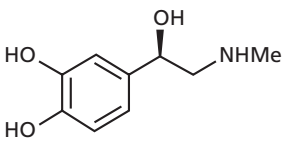
Throughout this text, the names of the active constituents are used rather than the trade names, although the trade name may be indicated if it is particularly well known. For example, it is indicated that **sildenafil** is **Viagra®** and that **paclitaxel** is **Taxol®**. If you wish to find out the trade name for a particular drug, these are listed in Appendix 6. If you wish to 'go the other way', Appendix 7 contains trade names and directs you to the relevant compound name. Only those drugs covered in the text are included and if you cannot find the drug you are looking for, you should refer to other textbooks or formularies such as the British National Formulary (see 'General further reading').

KEY POINTS

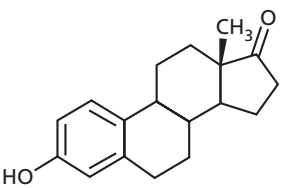
- Drugs can be classified by their pharmacological effect, their chemical structure, their effect on a target system, or their effect on a target structure.
- Clinically useful drugs have a trade (or brand) name, as well as a recommended international non-proprietary name.
- Most structures produced during the development of a new drug are not considered for the clinic. They are identified by simple codes that are specific to each research group.

QUESTIONS

1. The hormone adrenaline interacts with proteins located on the surface of cells and does not cross the cell membrane. However, larger steroid molecules, such as estrone, cross cell membranes and interact with proteins located in the cell nucleus. Why is a large steroid molecule able to cross the cell membrane when a smaller molecule such as adrenaline cannot?



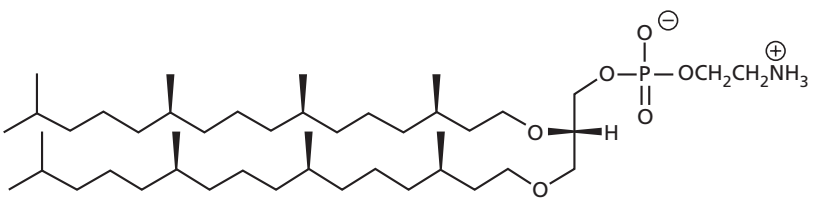
Adrenaline



Estrone

2. Valinomycin is an antibiotic which is able to transport ions across cell membranes and disrupt the ionic balance of the cell. Find out the structure of valinomycin and explain why it is able to carry out this task.

3. Archaea are microorganisms that can survive in extreme environments, such as high temperature, low pH, or high salt concentrations. It is observed that the cell membrane phospholipids in these organisms (see Structure I below) are markedly different from those in eukaryotic cell membranes. What differences are present and what function might they serve?

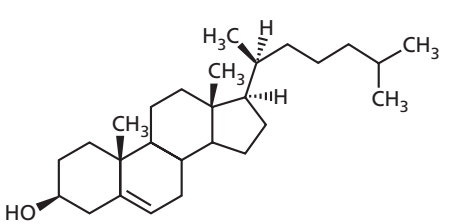


Structure I

4. Teicoplanin is an antibiotic which 'caps' the building blocks used in the construction of the bacterial cell wall such that they cannot be linked up. The cell wall is a barrier surrounding the bacterial cell membrane and the building blocks are anchored to the outside of this cell membrane prior to their incorporation into the cell wall. Teicoplanin contains a very long alkyl substituent which plays no role in the capping mechanism. However, if this substituent is absent, activity drops. What role do you think this alkyl substituent might serve?

5. The Ras protein is an important protein in signalling processes within the cell. It exists freely in the cell cytoplasm, but must become anchored to the inner surface of the cell membrane in order to carry out its function. What kind of modification to the protein might take place to allow this to happen?

6. Cholesterol is an important constituent of eukaryotic cell membranes and affects the fluidity of the membrane. Consider the structure of cholesterol (shown below) and suggest how it might be orientated in the membrane.



Cholesterol

7. Most unsaturated alkyl chains in phospholipids are *cis* rather than *trans*. Consider the *cis*-unsaturated alkyl chain in the phospholipid shown in Fig. 1.2. Redraw this chain to give a better representation of its shape and compare it with the shape of its *trans*-isomer. What conclusions can you make regarding the packing of such chains in the cell membrane and the effect on membrane fluidity?

8. The relative strength of carbonyl oxygens as hydrogen bond acceptors is shown in Fig. 1.12. Suggest why the order is as shown.

9. Consider the structures of adrenaline, estrone, and cholesterol and suggest what kind of intermolecular interactions are possible for these molecules and where they occur.

10. Using the index and Appendix 6, identify the structures and trade names for the following drugs—amoxicillin, ranitidine, gefitinib, and atracurium.

FURTHER READING

Hansch, C., Sammes, P. G., and Taylor, J. B. (eds) (1990) Classification of drugs. *Comprehensive Medicinal Chemistry*, Vol. 1, Chapter 3.1. Pergamon Press, ISBN 0-08-037057-8.

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Kubinyi, H. (2001) Hydrogen bonding: The last mystery in drug design? In: Testa, B. (ed.) *Pharmacokinetic Optimisation in Drug Research*. Wiley, 513–24.

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Page, C., Curtis, M., Sutter, M., Walker, M., and Hoffman, B. (2002) Drug names and drug classification systems. *Integrated Pharmacology*, 2nd edn, Chapter 2. Mosby, St Louis, MO.

Titles for general further reading are listed on p.763.