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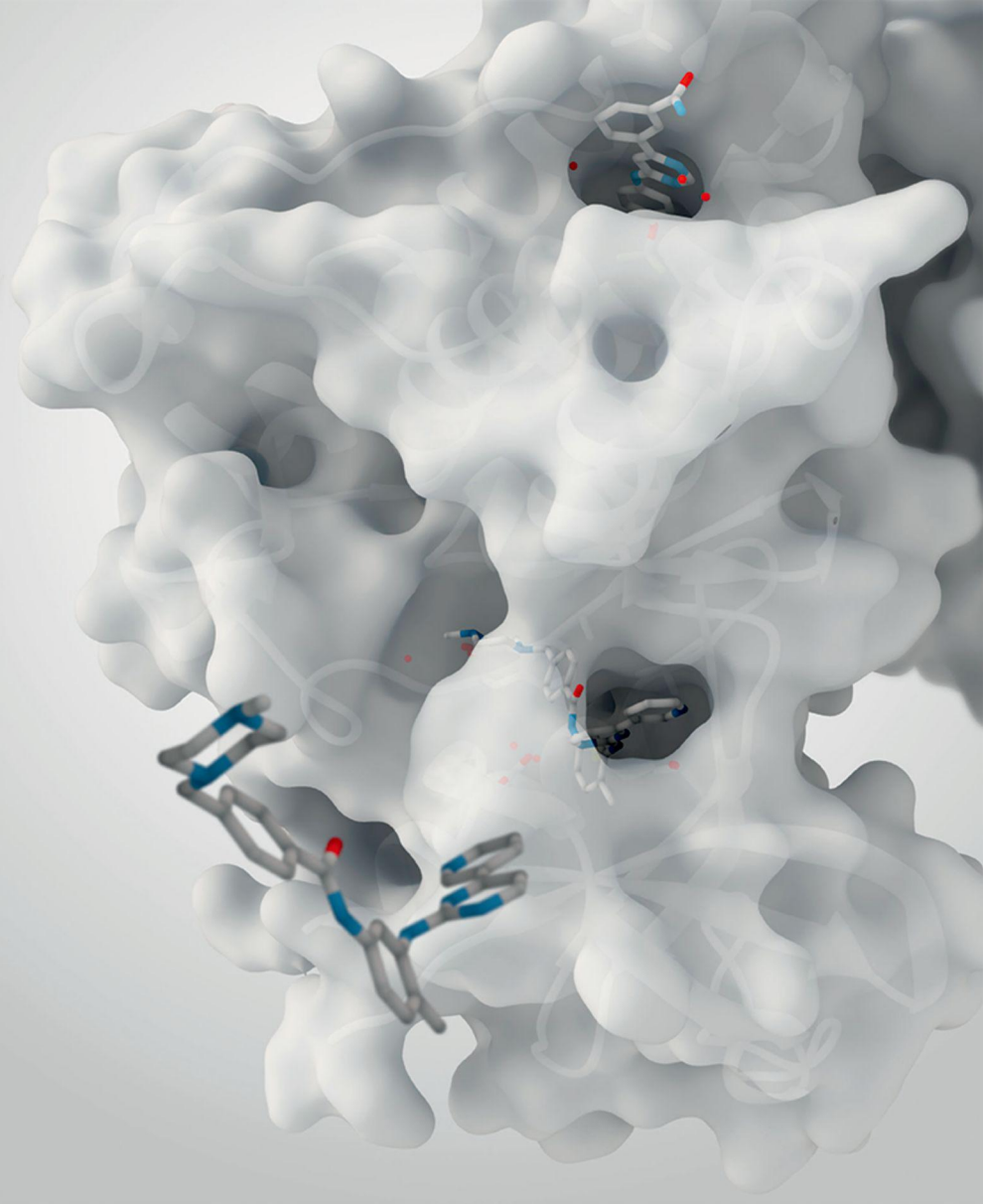

an introduction to

MEDICINAL CHEMISTRY

GRAHAM L. PATRICK

sixth edition

An Introduction to Medicinal Chemistry

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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.

Following the success of the first five editions, as well as useful feedback from readers, there has been some reorganization and updating of chapters, especially those in section E. A chapter on cardiovascular agents has also been added.

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

- Part A contains five 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, anti-ulcer agents, and cardiovascular 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.

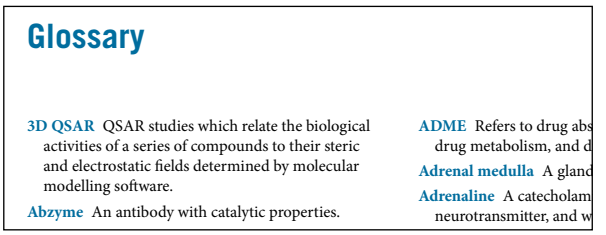
G. L. P.
December 2016

About the book

The sixth edition of *An Introduction to Medicinal Chemistry* and its accompanying companion website contains many learning features. This section illustrates each of these learning features and explains how they will help you to gain a deeper understanding of this fascinating subject.

Emboldened keywords

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



Glossary

3D QSAR QSAR studies which relate the biological activities of a series of compounds to their steric and electrostatic fields determined by molecular modelling software.

Abzyme An antibody with catalytic properties.

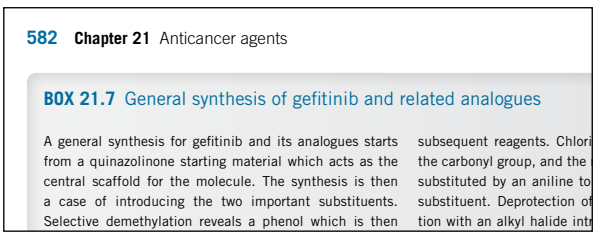
ADME Refers to drug abs
drug metabolism, and d

Adrenal medulla A gland

Adrenaline A catecholam
neurotransmitter, and w

Boxes

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



582 **Chapter 21** Anticancer agents

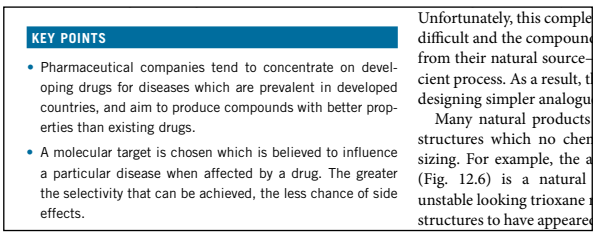
BOX 21.7 General synthesis of gefitinib and related analogues

A general synthesis for gefitinib and its analogues starts from a quinazolinone starting material which acts as the central scaffold for the molecule. The synthesis is then a case of introducing the two important substituents. Selective demethylation reveals a phenol which is then

subsequent reagents. Chlori
the carbonyl group, and the
substituted by an aniline to
substituent. Deprotection of
tion with an alkyl halide intr

Key points

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



KEY POINTS

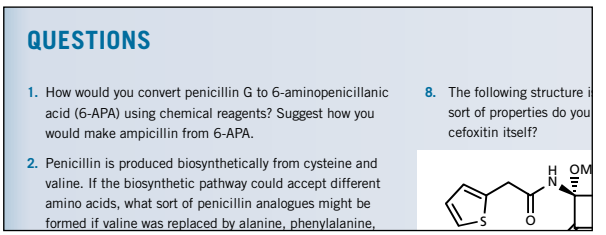
- Pharmaceutical companies tend to concentrate on developing drugs for diseases which are prevalent in developed countries, and aim to produce compounds with better properties than existing drugs.
- A molecular target is chosen which is believed to influence a particular disease when affected by a drug. The greater the selectivity that can be achieved, the less chance of side effects.

Unfortunately, this comple
difficult and the compoun
from their natural source–
cient process. As a result, t
designing simpler analogu

Many natural products
structures which no cher
sizing. For example, the a
(Fig. 12.6) is a natural
unstable looking trioxane r
structures to have appeare

Questions

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



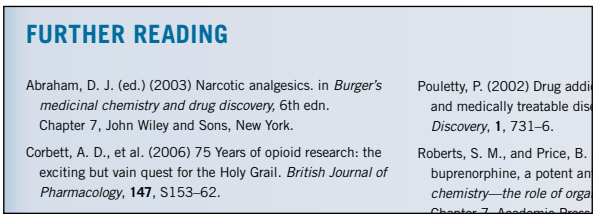
QUESTIONS

1. How would you convert penicillin G to 6-aminopenicillanic acid (6-APA) using chemical reagents? Suggest how you would make ampicillin from 6-APA.
2. Penicillin is produced biosynthetically from cysteine and valine. If the biosynthetic pathway could accept different amino acids, what sort of penicillin analogues might be formed if valine was replaced by alanine, phenylalanine,

8. The following structure i
sort of properties do you
cefoxitin itself?

Further reading

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



FURTHER READING

Abraham, D. J. (ed.) (2003) Narcotic analgesics. in *Burger's medicinal chemistry and drug discovery*, 6th edn. Chapter 7, John Wiley and Sons, New York.

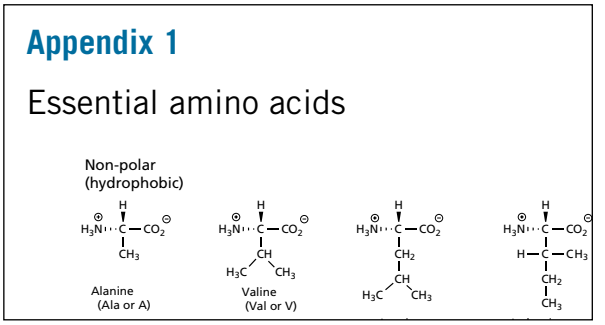
Corbett, A. D., et al. (2006) 75 Years of opioid research: the exciting but vain quest for the Holy Grail. *British Journal of Pharmacology*, **147**, S153–62.

Pouletty, P. (2002) Drug addi
and medically treatable dis
Discovery, **1**, 731–6.

Roberts, S. M., and Price, B.
buprenorphine, a potent an
chemistry—the role of orga

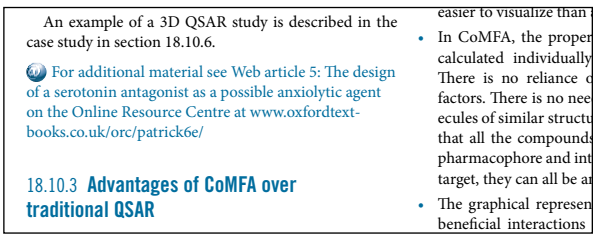
Appendices

There are several appendices provided at the end of the book, providing further information which you may find useful. Appendix 1 shows the structures of common amino acids, with the standard genetic code given in Appendix 2. Statistical data for QSAR is provided in Appendix 3, while further information relating to the action of nerves, and microorganisms, are given in Appendices 4 and 5, respectively. Appendix 6 lists trade names and the drug(s) to which they correspond, while trade names corresponding to specific drugs in the main index are shown in brackets. Appendix 7 shows the likely hydrogen bonding interactions for different functional groups. Related appendices on the website give information on properties such as molecular weight, log *P*, the number of hydrogen bonding groups and rotatable bonds, molecular weight, and polar surface area for several clinically important drugs.



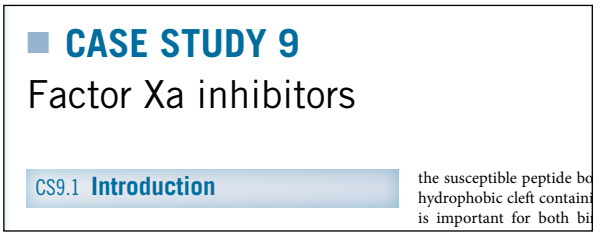
Links

Links have been added to the text which alert the reader to relevant articles and molecular modelling exercises on the accompanying website for the textbook. These exercises involve the use of Spartan and/or ChemBio3D molecular modelling software, as well as Excel.



Case Studies

Case Studies help you to link the underlying theory to its pharmaceutical applications and appreciate the real-world applications of the science.



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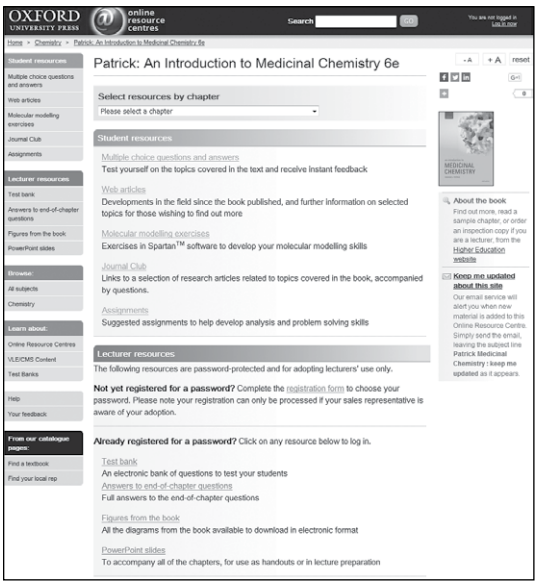
Online Resource Centres provide students and lecturers with ready-to-use teaching and learning resources. They are free-of-charge, and designed to complement the textbook.
You will find the Online Resource Centre at:
www.oxfordtextbooks.co.uk/orc/patrick6e/



Student resources

Multiple-choice questions
Self-test multiple-choice questions are available for each chapter allowing you to test your knowledge and understanding of key concepts as you progress through the book.

Web articles
A series of articles have been placed on the web to enable you to read further into selected topics. These articles describe recent developments in the field and give further information on some of the topics covered in the book. Cross-references to these articles are provided at relevant points in the text.

Molecular modelling exercises
A series of molecular modelling exercises have been added to the website aimed at students using Spartan or ChemBio3D molecular modelling software. Alerts are provided in the book to molecular modelling exercises related to specific topic areas.

Journal Club
Suggested papers are provided along with questions and answer guidance, to help you to critically analyse the research literature.

Assignments
Suggested assignments are provided to help you develop your analysis and problem-solving skills.

Lecturer resources

For registered adopters of the book

Test Bank
A bank of multiple-choice questions, with links to relevant sections in the book, which can be downloaded and customized for your teaching.

Answers
Answers to end-of-chapter questions in the book.

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 accompany selected topics from the book.

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Brief contents

Detailed contents

PART C Drug discovery, design, and development

List of boxes

General interest

Synthesis

Clinical correlation

Acronyms and abbreviations

Note: Abbreviations for amino acids are given in Appendix 1

5-HT5	hydroxytryptamine (serotonin)
7-ACA7	aminocephalosporinic acid
6-APA6	aminopenicillanic acid
ACE	angiotensin-converting enzyme
ACh	acetylcholine
AChE	acetylcholinesterase
ACP	acyl carrier protein
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 5′-diphosphate
AGO	argonaute protein
AIC	5-aminoimidazole-4-carboxamide
AIDS	acquired immune deficiency syndrome
Akt	protein kinase B
ALK	anaplastic lymphoma kinase
AME	aminoglycoside modifying enzyme
AML	acute myeloid leukaemia
AMP	adenosine 5′-monophosphate
AT	angiotensin
ATP	adenosine 5′-triphosphate
AUC	area under the curve
BiTE	bi-specific T-cell engager
BuChE	butyrlcholinesterase
BTK	Bruton's tyrosine kinase
cAMP	cyclic AMP
β-CCE	carboline-3-carboxylate
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
c-KIT	mast/stem cell growth factor receptor
Clog *P*	calculated logarithm of the partition coefficient
c-MET receptor	hepatocyte growth factor receptor
CML	chronic myeloid leukaemia
CMV	cytomegalovirus
CNS	central nervous system
CoA	coenzyme A
CoMFA	comparative molecular field analysis
COMT	catechol *O*-methyltransferase
COPD	chronic obstructive pulmonary disease
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
Dhh	desert hedgehog
DMAP	dimethlaminopyridine
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
EGFR	epidermal growth factor receptor
EMEA	European Agency for the Evaluation of Medicinal Products
EPC	European Patent Convention
EPO	European Patent Office
EPO	erythropoietin
ErbB	epidermal growth factor receptor
ERK	see MAPK
ET	endothelin
FDA	US Food and Drug Administration
FdUMP	fluorodeoxyuracil monophosphate
FGF	fibroblast growth factor
FGFR	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
GRB2 growth factor receptor bound protein 2
gt genotype
GTP guanosine triphosphate
h-PEPT human intestinal proton-dependent oligopeptide transporter
H-receptor histamine receptor
HA haemagglutinin
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
HER human epidermal growth factor receptor
HGFR hepatocyte growth factor receptor
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%
ICMT1 isoprenylcysteine carboxylmethyltransferase
If funny ion channels
IGF-1R insulin growth factor 1 receptor
Ihh Indian hedgehog
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
JAK Janus kinase
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
LDL low density lipoprotein
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
MCHR melanin-concentrating hormone receptor
MDR multidrug resistance
MDRTB multidrug-resistant tuberculosis
MEP molecular electrostatic potential
miRNA micro RNA
miRNP micro RNA protein
MMAE monomethyl auristatin E (vedotin)
MMP matrix metalloproteinase
MMPI matrix metalloproteinase inhibitor
MOR mu opioid receptor
MR molar refractivity
mRNA messenger RNA
MRSA methicillin-resistant *Staphylococcus aureus*
mRTKI multi-receptor tyrosine kinase inhibitors
MTP microsomal triglyceride transfer protein
MTDD multi-target drug discovery
mTOR mechanistic or mammalian target of rapamycin
mTORC mechanistic or mammalian target of rapamycin complex
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
NEP neutral endopeptidase
NHS National Health Service
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
NS non-structural
NSAID non-steroidal anti-inflammatory drug
NSCLC non-small-cell lung carcinoma
NVOC nitroveratryloxycarbonyl
ORL1 opioid receptor-like receptor
P partition coefficient
P_2Y receptor purinergic G-protein-coupled receptor
PABA *p*-aminobenzoic acid
PAR protease activated receptor
PARP poly ADP ribose polymerase
PBP penicillin binding protein
PCP phencyclidine, otherwise known as 'angel dust'
PCT patent cooperation treaty
PD-1 receptor programmed cell death 1 receptor
PDB protein data bank
PDE phosphodiesterase
PDGF platelet-derived growth factor
PDGFR platelet-derived growth factor receptor
PDK1 phosphoinositide dependent kinase 1
PDT photodynamic therapy
PEG polyethylene glycol
PGE prostaglandin E
PGF prostaglandin F
PGI_2 prostacyclin
PH Pleckstrin homology
PI3K phosphoinositide 3-kinases
PIP_2 phosphatidylinositol diphosphate
PIP_3 phosphatidylinositol (3,4,5)-triphosphate
PI protease inhibitor
piRNA piwi-interacting RNA
PKA protein kinase A
PKB protein kinase B
PKC protein kinase C
PLC phospholipase C
PLS partial least squares
PPAR peroxisome proliferator-activated receptor
PPBI protein–protein binding inhibitor
PPI proton pump inhibitor

PPts pyridinium 4-toluenesulphonate
PTase palmitoyl transferase
PTCH patched receptor
QSAR quantitative structure–activity relationships
r regression or correlation coefficient
R resonance effect of an aromatic substituent in QSAR
RAAS renin–angiotensin–aldosterone system
RANK receptor activator of nuclear factor-kappa B
RCE1 ras converting enzyme 1
RES reticuloendothelial system
RET rearranged during transcription
RFC reduced folate carrier
RISC RNA induced silencing complex
RMSD root mean square distance
rRNA ribosomal RNA
RNA ribonucleic acid
RNAi RNA interference
s standard error of estimate or standard deviation
SAR structure–activity relationships
SCAL safety-catch acid-labile linker
SCF stem cell factor
SCFR mast/stem cell growth factor receptor
SCID severe combined immunodeficiency disease
sGC soluble guanylate cyclase
SH src homology
Shh sonic hedgehog
siRNA small interfering RNA
SKF Smith-Kline and French
Smo Smoothened receptor
SNRI selective noradrenaline reuptake inhibitors
siRNA Small inhibitory RNA
snRNA Small nuclear RNA
SOP standard operating procedure
SOS son of sevenless protein
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
STAT signal transducer and activator of transcription
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
TNFR tumour necrosis factor receptor
TNT trinitrotoluene
TRAIL TNF-related apoptosis-inducing ligand
TRIPS trade related aspects of intellectual property rights
tRNA transfer RNA
T-VEC talimogene laherparepvec
UTI urinary tract infection
vdW van der Waals
VEGF vascular endothelial growth factor
VEGFR 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

1 Drugs and drug targets: an overview

1.1 What is a drug?

Medicinal chemistry involves the design and synthesis of 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 of the way it is viewed by society. 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. But 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 treat all known bacterial infections, 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 it suffers from 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, a poor understanding of how barbiturates are stored in the body led to many patients receiving a fatal overdose. 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 **heroin**?

Well, let us look at the facts about heroin. It is one of the best painkillers known to medicine. 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 had to be withdrawn from general distribution 5 years later when its addictive properties became evident. 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 such a drug as being all 'bad'?

By now, it should be evident that the division between 'good' 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 which we take every day and which have a biological effect on us. What are these everyday drugs?

One is contained in 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. **Alcohol** is another example of a 'social' 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 less obvious compounds; 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 acts as 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 suppressing 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 to 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.

Since our definition covers any chemical that interacts with any biological system, we can include all the pesticides used in agriculture as drugs. They interact with the biological systems of harmful bacteria, fungi, and insects to produce a toxic effect that protects 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—chemicals that pass messages between nerves. In excess, these chemical messengers overstimulate the nervous system, 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 one of 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 a 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

Since 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

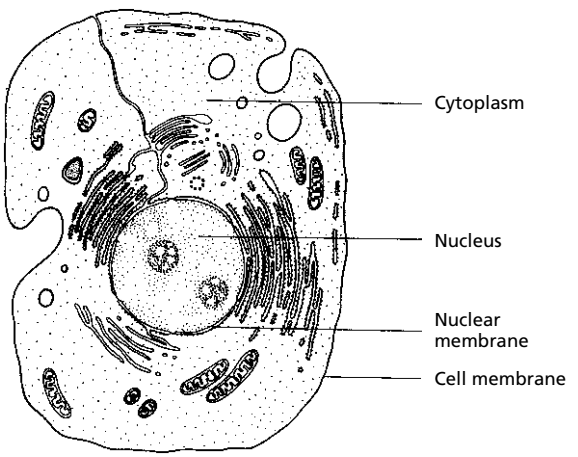


FIGURE 1.1 A typical mammalian cell. Taken from J. Mann, *Murder, magic, and medicine*, Oxford University Press (1992), with permission.

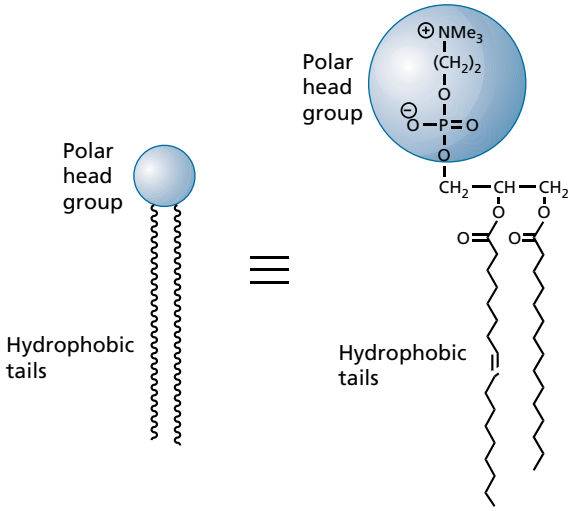


FIGURE 1.2 Phosphoglyceride structure.

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**.

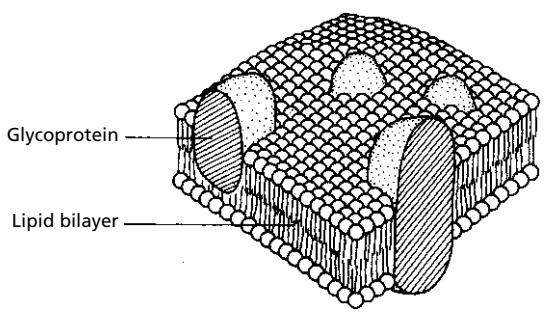


FIGURE 1.3 Cell membrane. Taken from J. Mann, *Murder, magic, and medicine*, Oxford University Press (1992), with permission.

These carbohydrate segments are important to 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 (enzymes, receptors, and transport proteins), and nucleic acids (DNA and RNA). These are large molecules (**macromolecules**) having molecular weights measured in the order of several thousand atomic mass units. They are much bigger than a 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, and this is 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, 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 it to depart once it has done its job. The length of time the drug remains at its target will depend on the number of intermolecular bonds involved in holding it there. Drugs having a large number of interactions are likely to remain bound longer than those that have only a few. The relative strength of the different intermolecular binding forces

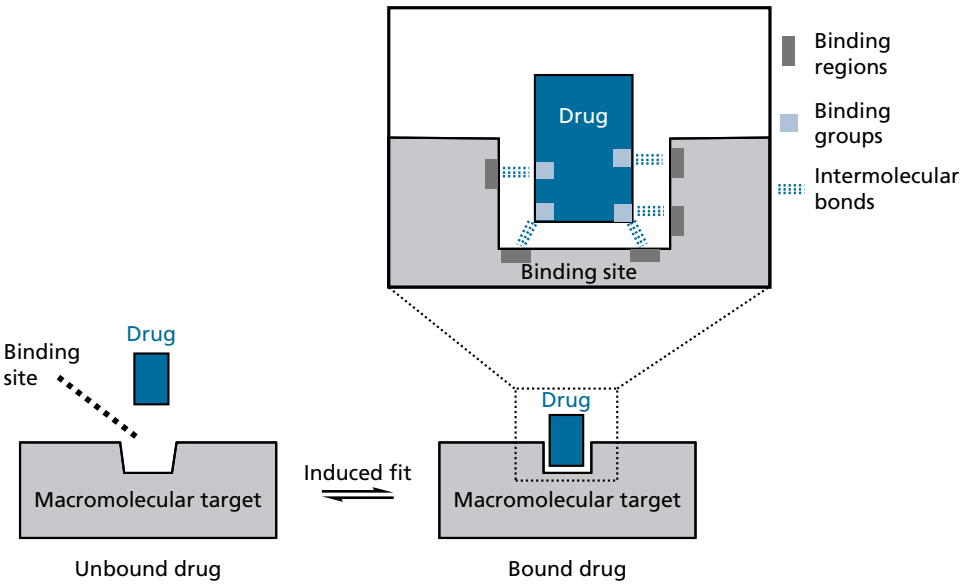


FIGURE 1.4 The equilibrium of a drug being bound and unbound to its target.

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 having 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.

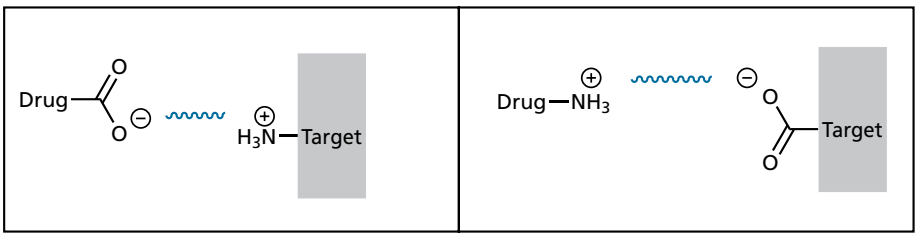


FIGURE 1.5 Electrostatic (ionic) interactions between a drug and the binding site.

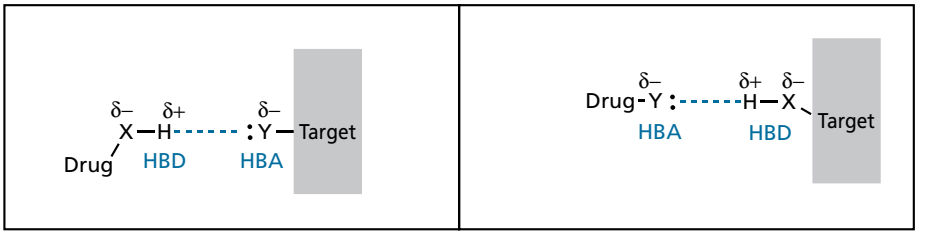


FIGURE 1.6 Hydrogen bonding shown by a dashed line between a drug and a binding site (X, Y = oxygen or nitrogen; HBD = hydrogen bond donor, HBA = hydrogen bond acceptor).

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 a slight positive charge. Such a hydrogen atom can act as a **hydrogen bond donor (HBD)**. The electron-rich heteroatom that receives the hydrogen bond is known as the **hydrogen bond acceptor (HBA)**. Some functional groups can provide both 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, and 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 the strengths of the hydrogen bond acceptor and the hydrogen bond donor. 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, which are larger and more diffuse than second-shell orbitals. This means that

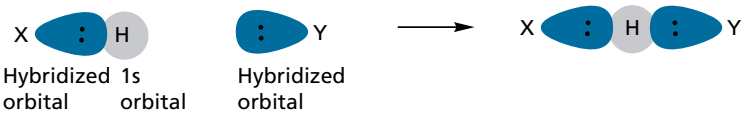


FIGURE 1.7 Orbital overlap in a hydrogen bond.

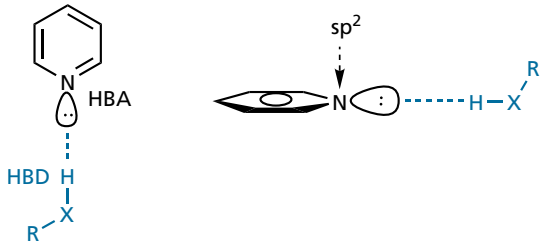


FIGURE 1.8 Directional influence of hybridization on hydrogen bonding.

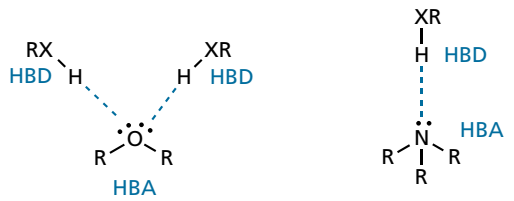


FIGURE 1.9 Oxygen and nitrogen acting as hydrogen bond acceptors (HBD = hydrogen bond donor, HBA = hydrogen bond acceptor).

the orbitals concerned interact less efficiently with the small 1s orbital of a hydrogen atom.

Fluorine, which is present in several drugs, is more electronegative than either oxygen or nitrogen. It also has three lone pairs of electrons, and this might suggest that it would make a good hydrogen bond acceptor. In fact, it is rather 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 a fluoride ion which is a very strong hydrogen bond acceptor.

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 functional groups,

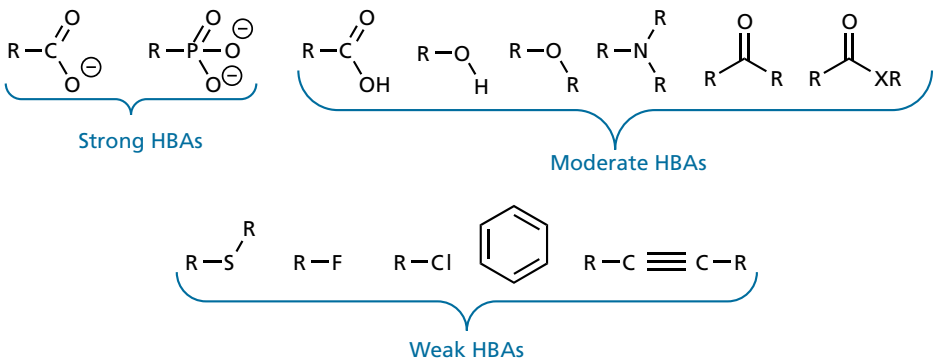


FIGURE 1.10 Relative strengths of hydrogen bond acceptors (HBAs).

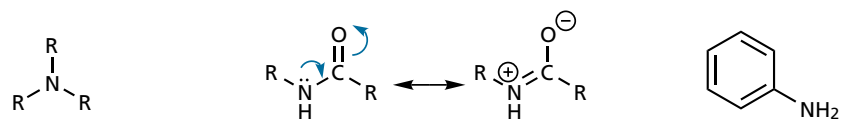


FIGURE 1.11 Comparison of different nitrogen-containing functional groups as hydrogen bond acceptors (HBAs).

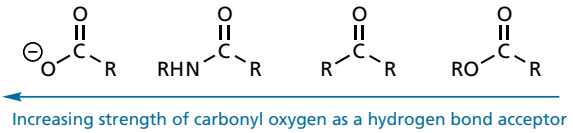


FIGURE 1.12 Comparison of carbonyl oxygens as hydrogen bond acceptors.

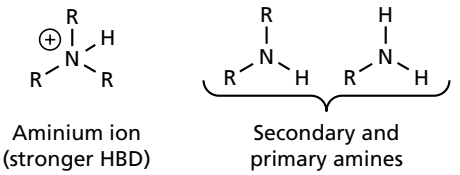


FIGURE 1.13 Comparison of hydrogen bond donors (HBDs).

the lone pair of the nitrogen can interact with neighbouring pi 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 positively 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 the drug and the binding site, then 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 anti-ulcer drugs (section 25.2.8.3).

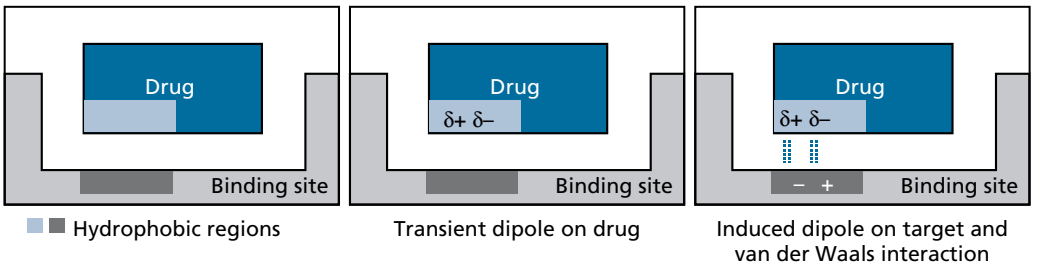


FIGURE 1.14 Van der Waals interactions between hydrophobic regions of a drug and a binding site.

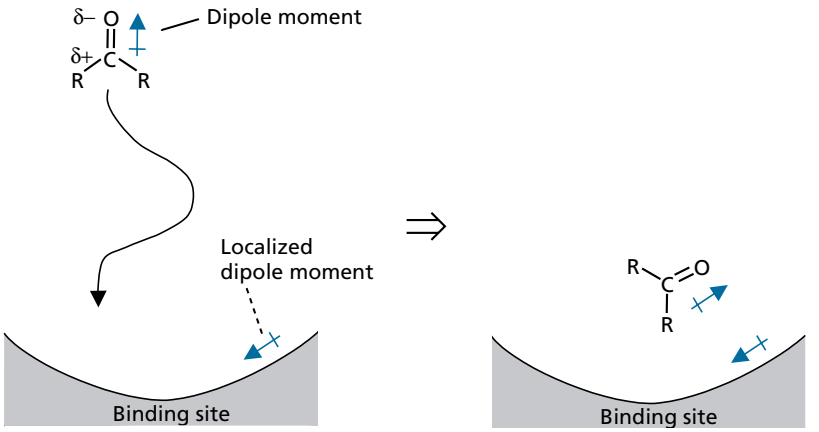


FIGURE 1.15 Dipole–dipole interactions between a drug and a binding site.

The strength of dipole–dipole interactions reduces with the 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. Otherwise, there would be nothing to stop molecules

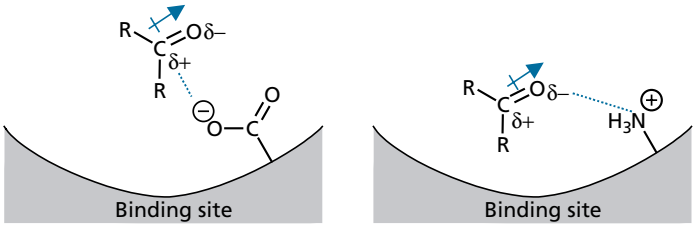


FIGURE 1.16 Ion–dipole interactions between a drug and a binding site.

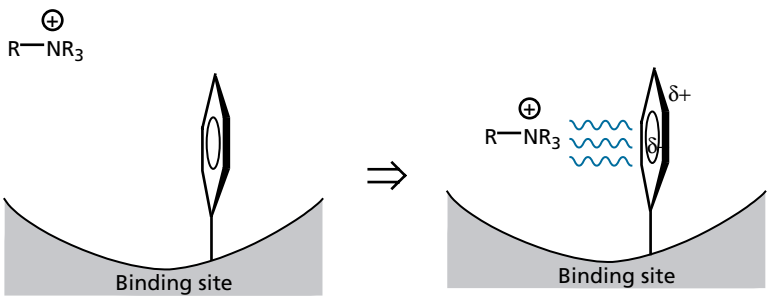


FIGURE 1.17 Induced dipole interaction between an alkylammonium ion and an aromatic ring.

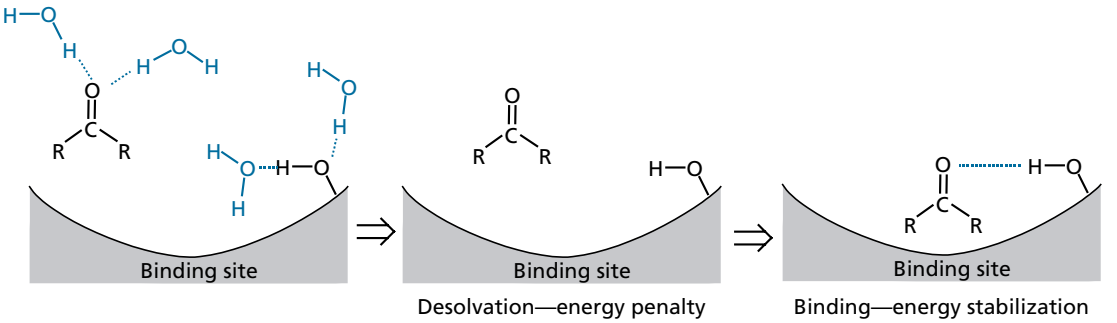


FIGURE 1.18 Desolvation of a drug and its target binding site prior to binding.

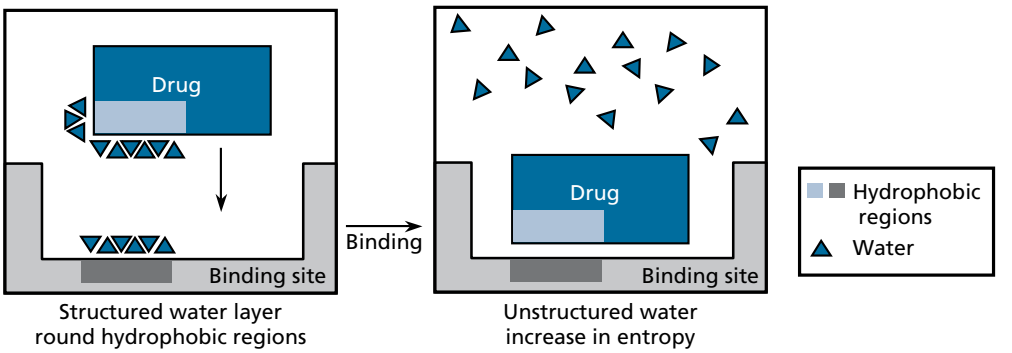


FIGURE 1.19 Hydrophobic interactions.

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, a polar binding group was removed 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. Examples of this can be seen in sections 21.6.2.1, 26.9.1.2, 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 an 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.[1] The interactions involved are small, at 0.1–0.2 kJ mol^{-1} for each square angstrom of hydrophobic surface, but overall they can be substantial. Sometimes, a hydrophobic region in the drug may not be sufficiently close to a

[1]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 the value of ΔG, the more likely binding will take place.

hydrophobic 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, 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. On the other hand, 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 methods by which a drug is formulated and administered are just as important. Medicines are not just composed of the active pharmaceutical agent. For example, a pill contains a whole range of chemicals which 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 hydrogen involved in a hydrogen bond is called the hydrogen bond donor. The electronegative atom 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, anti-ulcer, and cardiovascular drugs (Chapters 19, 20, 21, 25, and 26) 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 since 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 structure 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 19.4–19.5, 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 due to 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 since 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 forward to pre-clinical trials then clinical studies, by which time they are often 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 Britain, such drugs were given a **British Approved Name** (BAN), but these have now been modified to fall in line with rINNs. rINNs generally have a suffix which indicates the therapeutic area for the named drug. For example, saquinavir, ritonavir, and indinavir all end with the suffix -vir indicating that they are antiviral agents.

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

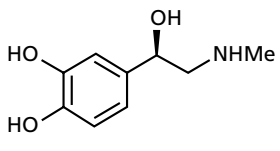
Throughout this text, the names of the active constituents are used rather than the trade names, although the trade name may be indicated if it is particularly well known. For example, it is indicated that **sildenafil** is **Viagra®** and that **paclitaxel** is **Taxol®**. If you wish to find out the trade name for a particular drug, these are listed in the index. If you wish to 'go the other way', Appendix 6 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

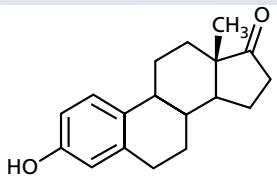
- Drugs can be classified by their pharmacological effect, their chemical structure, their effect on a target system, or their effect on a target structure.
- Clinically useful drugs have a trade (or brand) name, as well as a recommended international non-proprietary name.
- Most structures produced 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?



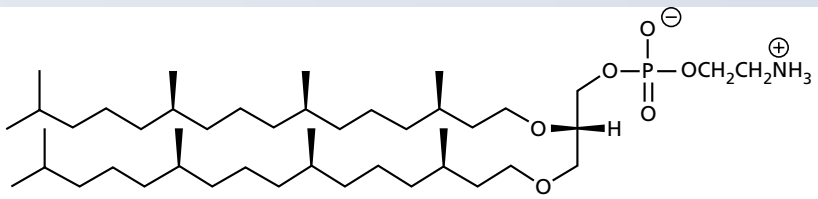
Adrenaline



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

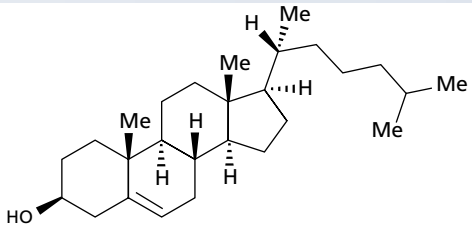


Structure I

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 8 (on the website), identify the structures and trade names for the following drugs—amoxicillin, ranitidine, gefitinib, atracurium.

Multiple-choice questions are available on the Online Resource Centre at www.oxfordtextbooks.co.uk/orc/patrick6e/

FURTHER READING

Kubinyi, H. (2001) Hydrogen bonding: The last mystery in drug design? in Testa, B., van de Waterbeemd, H., Folkers, G., and Guy, R. (eds), *Pharmacokinetic optimization in drug research*. Wiley-VCH, Weinheim.

Mann, J. (1992) *Murder, magic, and medicine*, Chapter 1. Oxford University Press, Oxford.

Page, C., Curtis, M., Sutter, M., Walker, M., and Hoffman, B. (2002) Drug names and drug classification systems. in *Integrated pharmacology 2nd edn*, Chapter 2. Mosby, Elsevier, Maryland Heights, MO.

Sneader, W. (2005) *Drug discovery: a history*. John Wiley and Sons, Chichester.

WEBSITES

International non-proprietary names, World Health Organization. www.who.int/medicines/services/inn/en/

Brand names of some commonly used drugs. www.mwrckmanuals.com/professional/appendices/brand-names-of-some-commonly-used-drugs?starting with=a

Titles for general further reading are listed on p.845.

PART A

Drug targets

Medicinal chemistry is the study of how novel drugs can be designed and developed. This process is helped immeasurably by a detailed understanding of the structure and function of the molecular targets that are present in the body.

The major drug targets are normally large molecules (macromolecules), such as proteins and nucleic acids. Knowing the structures, properties, and functions of these macromolecules is crucial if we are to design new drugs. There are a variety of reasons for this.

Firstly, it is important to know what functions different macromolecules have in the body and whether targeting them is likely to have a beneficial effect in treating a particular disease. There is no point designing a drug to inhibit a digestive enzyme if one is looking for a new analgesic.

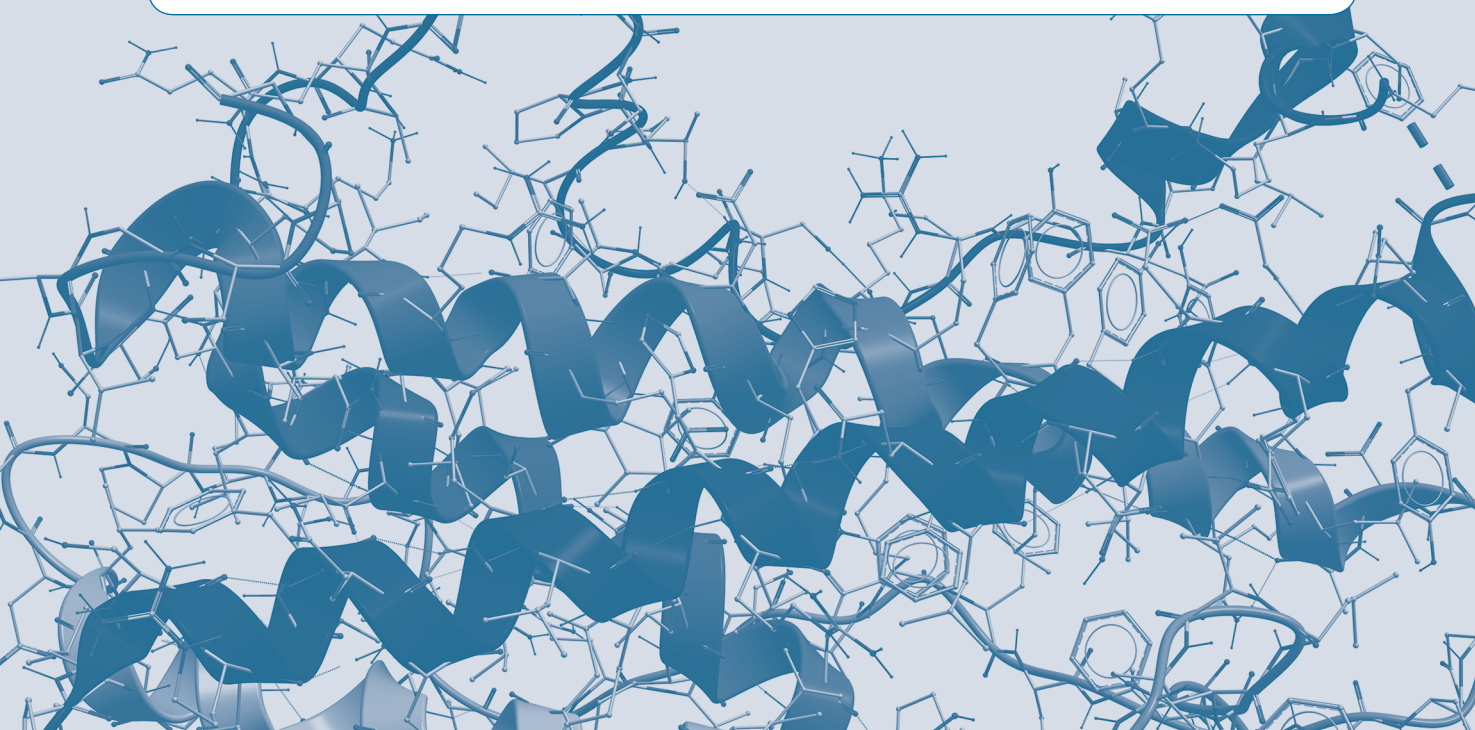
Secondly, a knowledge of macromolecular structure is crucial if one is to design a drug that will bind effectively to the target. Knowing the target structure and its functional groups will allow the medicinal chemist to design a drug that contains complementary functional groups that will bind the drug to the target.

Thirdly, a drug must not only bind to the target, it must bind to the correct region of the target. Proteins and nucleic acids are extremely large molecules in comparison to a drug and if the drug binds to the wrong part of the macromolecule, it may not have any effect. An appreciation of the target's structure and function will guide the medicinal chemist in this respect.

Finally, an understanding of how a macromolecule operates is crucial if one is going to design an effective drug that will interfere with that process. For example, understanding the mechanism of how enzymes catalyse reactions has been extremely important in the design of many important drugs, for example the protease inhibitors used in HIV therapy (section 20.7).

Proteins are the most important drug targets used in medicinal chemistry and so it should be no surprise that the major focus in Part A (Chapters 2–5) is devoted to them. However, there are some important drugs which interact with nucleic acids. The structure and function of these macromolecules are covered in Chapter 6.

If you have a background in biochemistry, much of the material in this section may already be familiar to you, and you may wish to move directly to Part B. Alternatively, you may find the material in Part A useful revision.



2 Protein structure and function

The vast majority of drugs used in medicine are targeted on proteins such as receptors, enzymes, and transport proteins. Therefore, it is important to understand protein structure in order to understand drug action on proteins. Proteins have four levels of structure—primary, secondary, tertiary, and quaternary.

2.1 The primary structure of proteins

The primary structure is the order in which the individual amino acids making up the protein are linked together through peptide bonds (Fig. 2.1). The 20 common amino acids found in humans are listed in Table 2.1, with the three-letter and one-letter codes often used to represent

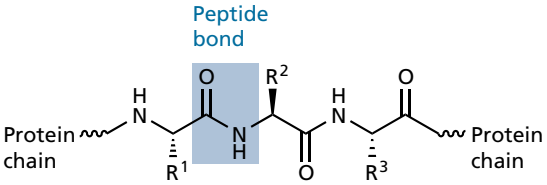


FIGURE 2.1 Primary structure of proteins (R^1, R^2, and R^3 = amino acid side chains).

them. The structures of the amino acids are shown in Appendix 1. The primary structure of **Met-enkephalin** (one of the body's own painkillers) is shown in Fig. 2.2.

The peptide bond in proteins is planar in nature as a result of the resonance structure shown in Fig. 2.3. This gives the peptide bond a significant double bond character which prevents rotation. As a result, bond rotation in the protein backbone is only possible for the bonds on

TABLE 2.1 The 20 common amino acids found in humans.

Synthesized in the human body			Essential to the diet		
Amino acid	Codes		Amino acid	Codes	
	3-letter	1-letter		3-letter	1-letter
Alanine	Ala	A	Histidine	His	H
Arginine	Arg	R	Isoleucine	Ile	I
Asparagine	Asn	N	Leucine	Leu	L
Aspartic acid	Asp	D	Lysine	Lys	K
Cysteine	Cys	C	Methionine	Met	M
Glutamic acid	Glu	E	Phenylalanine	Phe	F
Glutamine	Gln	Q	Threonine	Thr	T
Glycine	Gly	G	Tryptophan	Trp	W
Proline	Pro	P	Valine	Val	V
Serine	Ser	S			
Tyrosine	Tyr	Y			

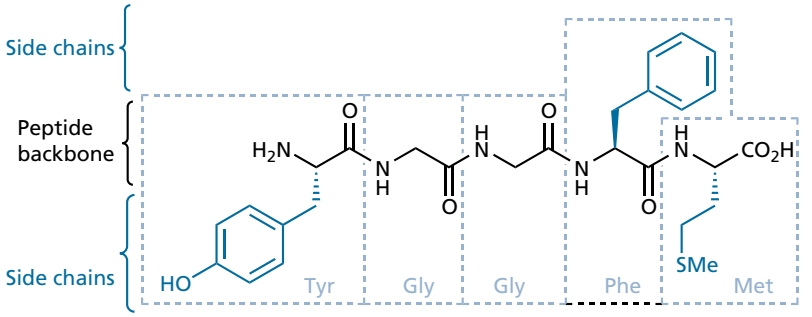


FIGURE 2.2 Met-enkephalin. The short hand notation for this peptide is H-Tyr-Gly-Gly-Phe-Met-OH or YGGFM.

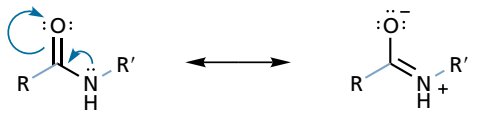


FIGURE 2.3 The planar peptide bond (free bond rotation allowed for coloured bonds only).

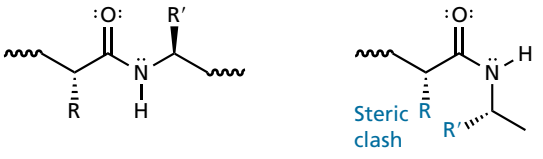


FIGURE 2.4 *Trans* and *cis* conformations of the peptide bond.

either side of each peptide bond. This has an important consequence for protein tertiary structure (section 2.3.6).

There are two possible conformations for the peptide bond (Fig. 2.4). The *trans* conformation is the one that is normally present in proteins, because the *cis* conformation leads to a steric clash between the residues. However, the *cis* conformation is possible for peptide bonds next to a proline residue.

2.2 The secondary structure of proteins

The secondary structure of proteins consists of regions of ordered structure adopted by the protein chain. In structural proteins such as wool and silk, secondary structures are extensive and determine the overall shape and properties of such proteins. However, there are also regions of secondary structure in most other proteins. There are three main secondary structures—the α-helix, β-pleated sheet, and β-turn.

2.2.1 The α-helix

The α-helix results from coiling of the protein chain such that the peptide bonds making up the backbone are able to form hydrogen bonds between each other. These hydrogen bonds are directed along the axis of the helix, as shown in Fig. 2.5. The side chains of the component amino acids stick out at right angles from the helix, thus minimizing steric interactions and further stabilizing the structure. Other less common types of helices can occur in proteins, such as the 3(10)-helix which is more stretched than the ideal α-helix, and the π-helix which is more compact and extremely rare.

Test your understanding and practise your molecular modelling with Exercise 2.1 on the Online Resource Centre: at www.oxfordtextbooks.co.uk/orc/patrick6e/

2.2.2 The β-pleated sheet

The β-pleated sheet is a layering of protein chains one on top of another, as shown in Fig. 2.6. Here too, the structure is held together by hydrogen bonds between the peptide chains. The side chains are situated at right angles to the sheets, once again to reduce steric interactions. The chains in β-sheets can run in opposite directions (antiparallel) or in the same direction (parallel) (Fig. 2.7).

2.2.3 The β-turn

A β-turn allows the polypeptide chain to turn abruptly and go in the opposite direction. This is important in allowing the protein to adopt a more globular compact shape. A hydrogen bonding interaction between the first and third peptide bond of the turn is important in stabilizing the turn (Fig. 2.8). Less abrupt changes in the direction of the polypeptide chain can also take place through longer loops, which are less regular in their structure, but are often rigid and well defined.

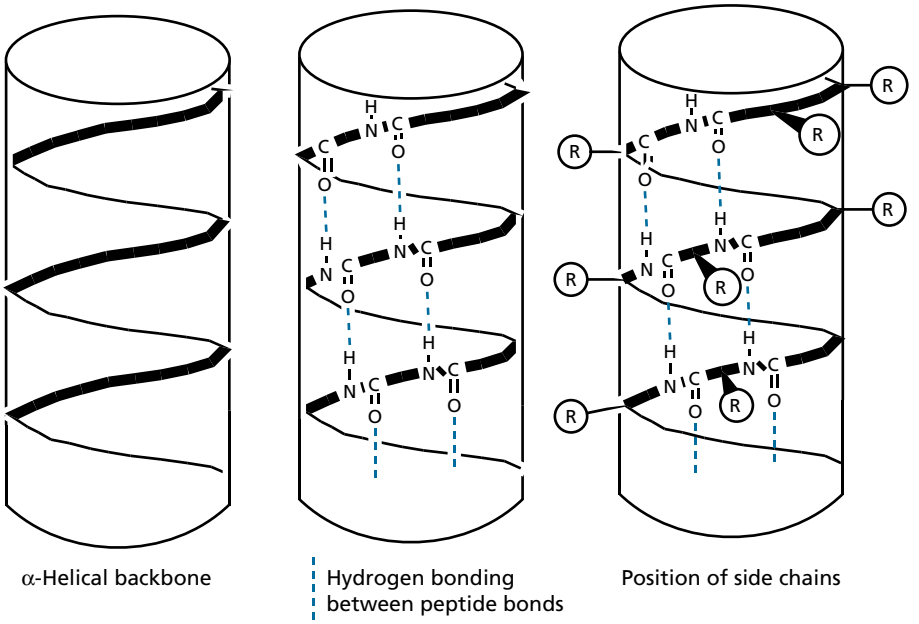


FIGURE 2.5 The α-helix for proteins showing intramolecular hydrogen bonds and the position of side chains.

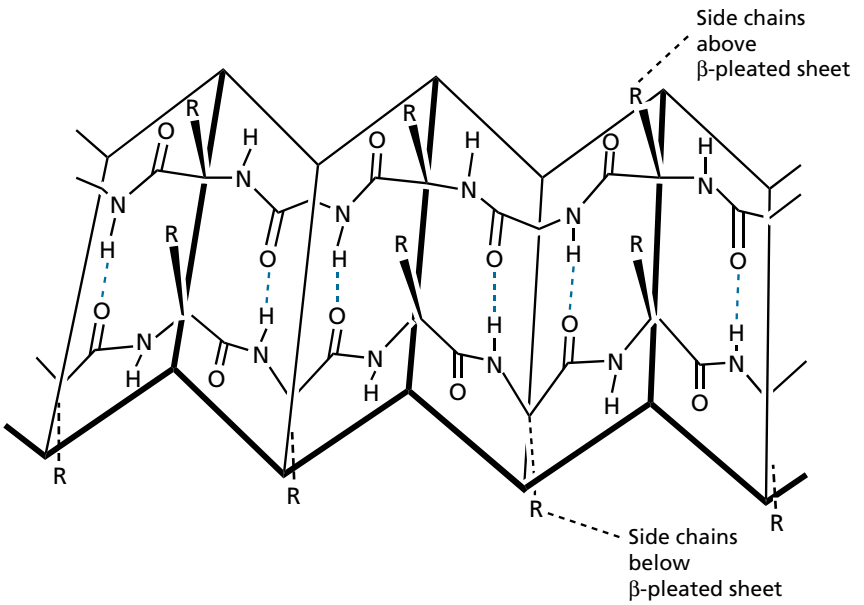


FIGURE 2.6 The β-pleated sheet (antiparallel arrangement).

2.3 The tertiary structure of proteins

The tertiary structure is the overall three-dimensional shape of a protein. Structural proteins are quite ordered in shape, whereas globular proteins, such as enzymes and receptors (Chapters 3 and 4), fold up to form more complex structures. The tertiary structure of enzymes and receptors is crucial to their function and also to their interaction with drugs; therefore it is important to appreciate the forces that control tertiary structure.

Globular proteins often contain regions of ordered secondary structure, the extent of which varies from protein to protein. For example, **cyclin-dependent kinase 2** (a protein that catalyses phosphorylation reactions) has several regions of α-helices and β-pleated sheets (Fig. 2.9), whereas the digestive enzyme **chymotrypsin**

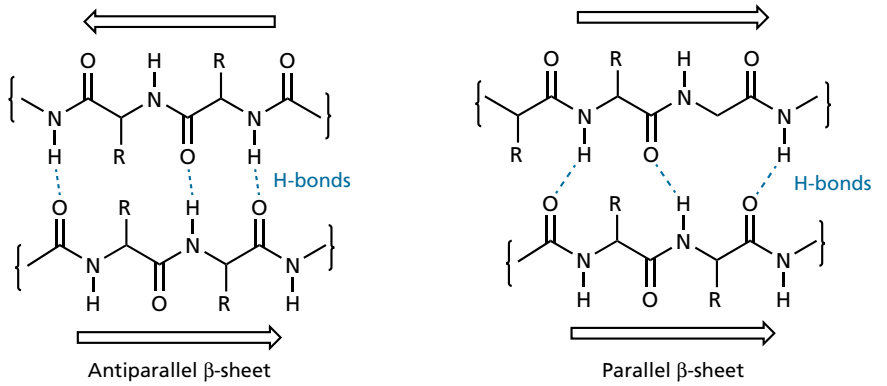


FIGURE 2.7 Hydrogen bonding in antiparallel and parallel β-sheets (the arrows are pointing to the *C*-terminal end of the chain).

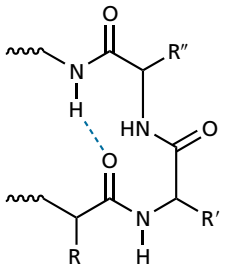


FIGURE 2.8 The β-turn showing hydrogen bonding between the first and third peptide bond.

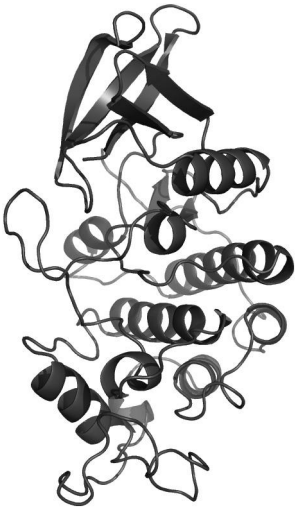


FIGURE 2.9 The pdb file (1hcl) for human cyclin-dependent kinase 2 (CDK2) where cylinders represent α-helices and arrows represent β-sheets. A pdb file contains the 3D structural information for a protein and can be downloaded from the Brookhaven protein data bank. Each protein structure file is given a code, for example, 1hcl.

has very little secondary structure. Nevertheless, the protein chains in both cyclin-dependent kinase 2 and chymotrypsin fold up to form a complex, but distinctive, globular shape. How does this come about?

At first sight, the three-dimensional structure of cyclin-dependent kinase 2 looks like a ball of string after the cat has been at it. In fact, the structure shown is a very precise shape which is taken up by every molecule of this protein, and which is determined by the protein's primary structure[1]. Indeed, in the laboratory, it is possible to synthesize proteins which automatically adopt the same three-dimensional structure and function as the naturally occurring protein. The HIV-1 protease enzyme is an example (section 20.7.4.1).

This poses a problem. Why should a chain of amino acids take up such a precise three-dimensional shape? At first sight, it does not make sense. If we place a length of string on the table, it does not fold itself up into a precise complex shape. So why should a chain of amino acids do such a thing?

The answer lies in the fact that a protein is not just a bland piece of string. That is because it contains a large number of different chemical functional groups, which include the peptide bonds of the polypeptide backbone, as well as a variety of functional groups in the amino acid side chains. These can interact with each other, such that there is either an attractive or a repulsive interaction. Thus, the protein will twist and turn to minimize the unfavourable interactions and maximize the favourable ones until the most stable shape or conformation is found—the tertiary structure (Fig. 2.10).

With the exception of disulphide bonds, the attractive interactions involved in tertiary structure are the same as the **intermolecular bonds** described in section 1.3. The latter occur between different molecules, whereas the bonds controlling protein tertiary structure occur within

[1] Some proteins contain species known as **cofactors** (e.g. metal ions or small organic molecules) which also have an effect on tertiary structure.

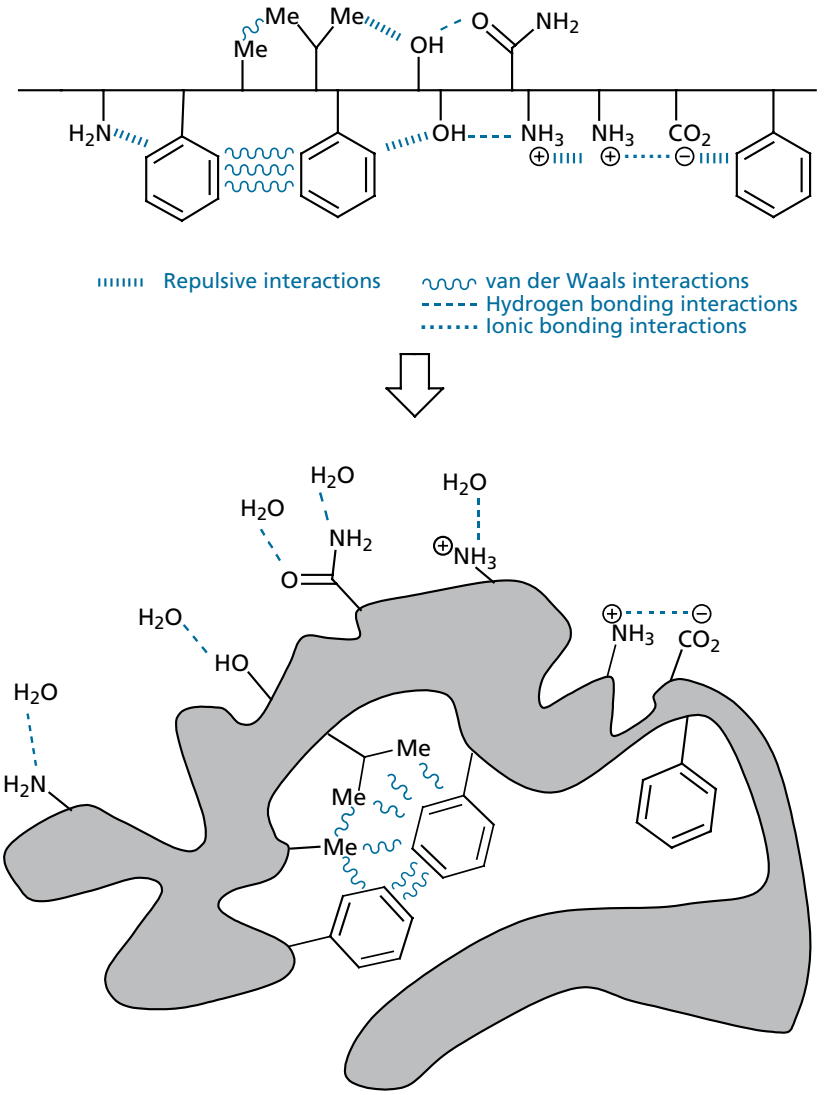


FIGURE 2.10 Tertiary structure formation as a result of intramolecular interactions.

the same molecule, and so they are called **intramolecular bonds**. Nevertheless, the principles described in section 1.3 are the same.

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2.3.1 Covalent bonds: disulphide links

Cysteine has a residue containing a thiol group capable of forming a covalent bond in protein tertiary structure. When two such residues are close together, a covalent disulphide bond can be formed as a result of oxidation. A covalent bridge is thus formed between two different parts of the protein chain (Fig. 2.11). It should be noted that the two cysteine residues involved in this bond formation may be far apart from each other in the primary structure of the protein, but are brought close together as a result of protein folding.

2.3.2 Ionic or electrostatic bonds

An ionic bond or salt bridge can be formed between the carboxylate ion of an acidic residue such as aspartic acid or glutamic acid, and the aminium ion of a basic residue such as lysine, arginine, or histidine (Fig. 2.12). This is the strongest of the intramolecular bonds.

2.3.3 Hydrogen bonds

Hydrogen bonds can be viewed as a weak form of ionic interaction as they involve interactions between atoms having partial charges. They can be formed between

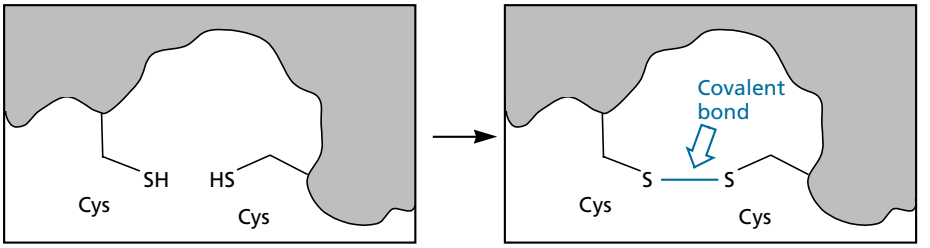

FIGURE 2.11 The formation of a disulphide covalent bond between two cysteine side chains.

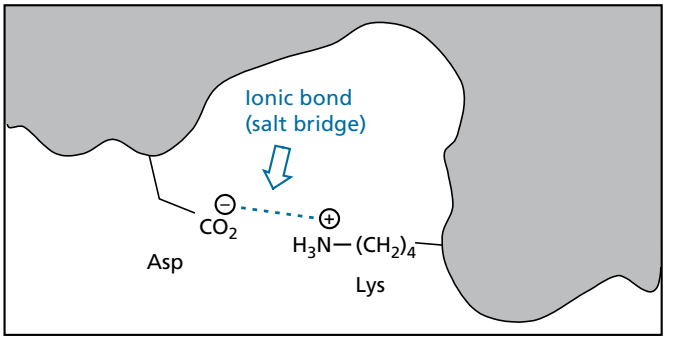

FIGURE 2.12 Ionic bonding between an aspartate side chain and a lysine side chain.

a large number of amino acid residues such as serine, threonine, aspartic acid, glutamic acid, glutamine, lysine, arginine, histidine, tryptophan, tyrosine, and asparagine. Two examples are shown in Fig. 2.13.

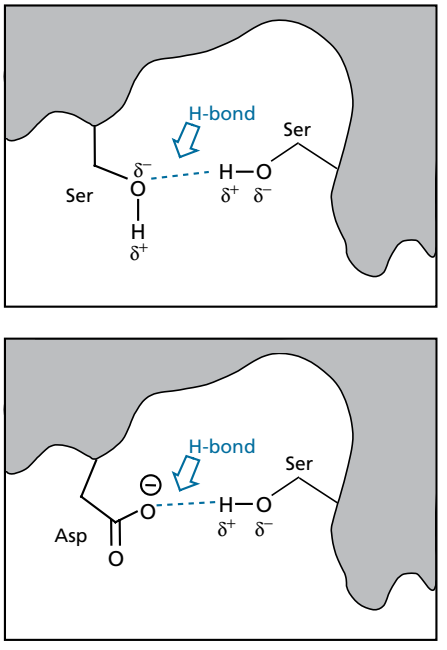

FIGURE 2.13 Hydrogen bonding between amino acid side chains.

2.3.4 Van der Waals and hydrophobic interactions

Van der Waals interactions are weaker interactions than hydrogen bonds, and can take place between two hydrophobic regions of the protein. For example, they can take place between two alkyl groups (Fig. 2.14). The amino acids alanine, valine, leucine, isoleucine, phenylalanine, and proline all have hydrophobic side chains capable of interacting with each other by van der Waals interactions. The side chains of other amino acids such as methionine, tryptophan, threonine, and tyrosine contain polar functional groups, but the side chains also have a substantial

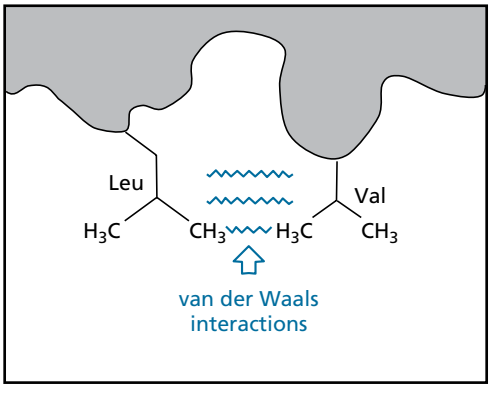

FIGURE 2.14 Van der Waals interactions between amino acid side chains.