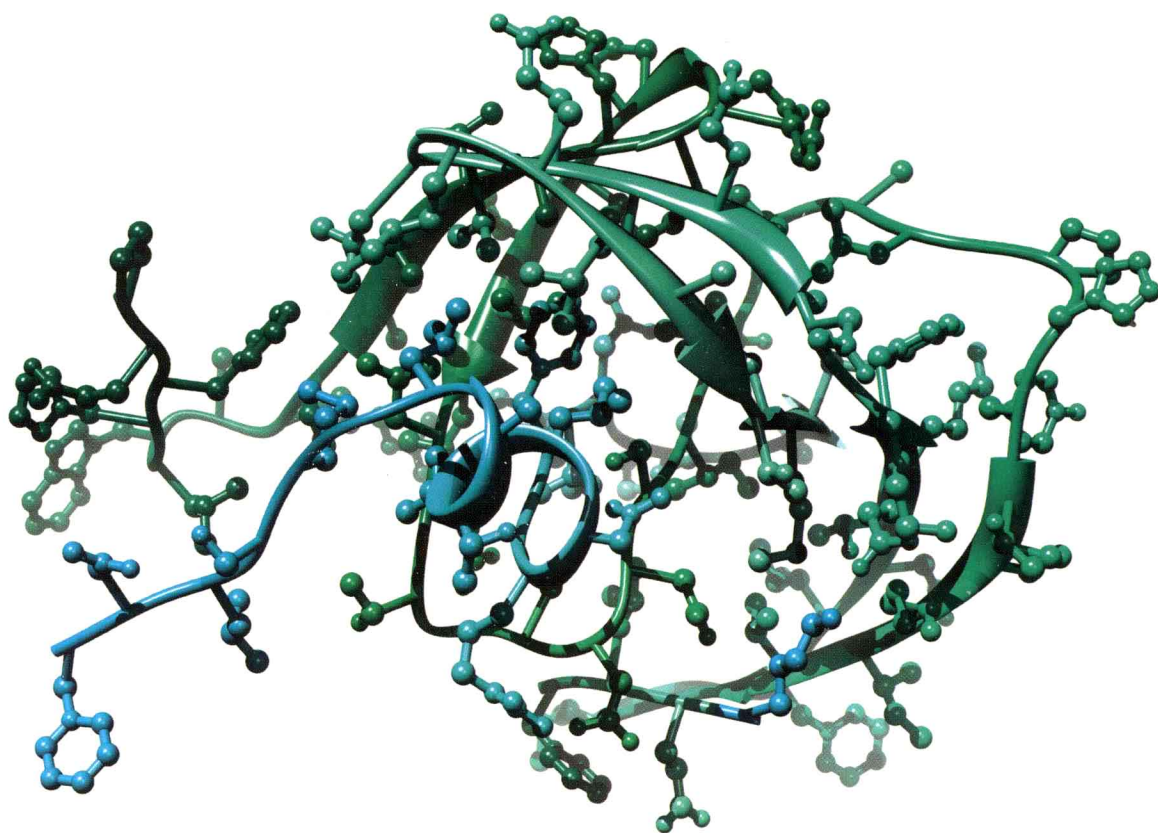


OXFORD

An Introduction to

Medicinal Chemistry

FOURTH EDITION



Graham L. Patrick

An Introduction to

Medicinal Chemistry

FOURTH EDITION

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



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

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

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

G. L. P.
Dec 2008

About the book

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

Emboldened key words

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

Boxes

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

Key points

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

Questions

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

Further reading

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

Appendices

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

the surface of the macromolecule allowing the drug to sink into the body of the larger molecule. Some drugs react with the binding site and become permanently attached via a covalent bond that has a bond strength of 200–400 kJ mol⁻¹. However, most drugs interact through weaker forms of interaction known as **intermolecular bonds**. These include electrostatic or ionic bonds, hydrogen bonds, van der Waals interactions, dipole-dipole interactions and hydrophobic interactions. (It is also possible for these interactions to take place *within* a molecule, in which case they are called **intramolecular**

with 'visiting' drugs. The specific regions where this takes place are known as **binding regions**. The study of how drugs interact with their targets through binding interactions is known as **pharmacodynamics**. Let us now consider the types of intermolecular bond that are possible.

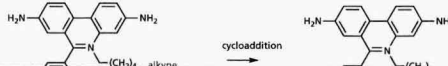
1.3 Intermolecular bonding forces

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

BOX 12.8 Click chemistry *in situ*

A femtomolar inhibitor for the acetylcholinesterase enzyme was obtained by fragment self-assembly within the active site of the enzyme. One of the molecular fragments contained an azide group while the other contained an alkyne group. In the presence of the enzyme, both

fragments were bound to the active site, and were positioned close enough to each other for an irreversible 1,3 dipolar cycloaddition to take place, forming the inhibitor *in situ*. This type of reaction has been called 'click chemistry *in situ*'.



KEY POINTS

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

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

14.6.1 Prodrugs to improve membrane permeability

14.6.1.1 Esters as prodrugs

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

QUESTIONS

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



Proflavine

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

4. The genetic code involves three nucleic acid bases coding

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Appendix 3

Statistical data for QSAR

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

and the calculated activity is $Y_{\text{calc}} = Y_{\text{obs}} + Y_{\text{res}}$ (Fig. A3.1). This is then squared and the values are added together to give the sum of the squares (SS_{res}).

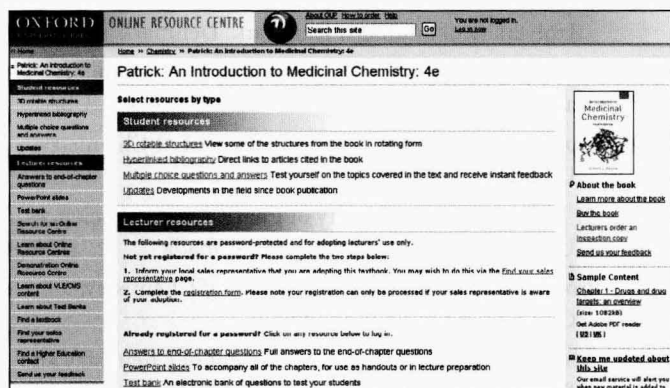
SS_{res} is a measure of how much the experimental activity varies from the mean of all the experimental activities and

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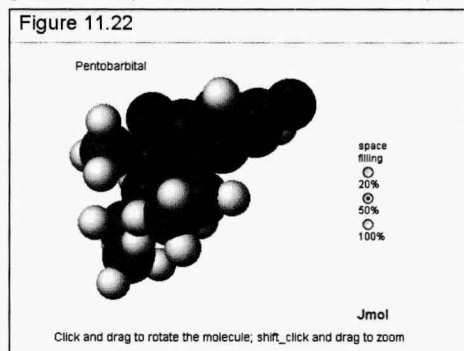


Student resources

Rotatable 3D structures

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

Figure 11.22



Online quiz

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

Hyperlinked bibliography

Direct links to online articles cited in the book.*

Updates

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

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Answers to end-of-chapter questions.

Figures from the book

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PowerPoint slides

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

*Institutional subscription required for full text access

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Acronyms and abbreviations

| | | | |
|------------------|--|-----------------|---|
| ACE | angiotensin-converting enzyme | GABA | γ -aminobutyric acid |
| ADAPT | antibody-directed abzyme prodrug therapy | GAP | GTPase activating protein |
| ADEPT | antibody-directed enzyme prodrug therapy | GCP | Good Clinical Practice |
| ADH | alcohol dehydrogenase | GDEPT | gene-directed enzyme prodrug therapy |
| AIC | 5-aminoimidazole-4-carboxamide | GEF | guanine nucleotide exchange factors |
| AIDS | acquired immune deficiency syndrome | GGTase | geranylgeranyltransferase |
| AML | acute myeloid leukaemia | GH | growth hormone |
| AMP | adenosine 5'-monophosphate | GIT | gastrointestinal tract |
| ATP | adenosine 5'-triphosphate | GLP | Good Laboratory Practice |
| AUC | area under the curve | GMP | Good Manufacturing Practice |
| CCK | cholecystokinin | GnRH | gonadotrophin-releasing hormone |
| CDKs | cyclin-dependent kinases | HA | haemagglutinin |
| cGMP | cyclic GMP | HAART | highly active antiretroviral therapy |
| CKIs | cyclin-dependent kinase inhibitors | HAMA | human anti-mouse antibodies |
| CML | chronic myeloid leukaemia | HIV | human immunodeficiency virus |
| CMV | cytomegalovirus | HOMO | highest occupied molecular orbital |
| CNS | central nervous system | HPLC | high-performance liquid chromatography |
| COMT | catechol <i>O</i> -methyltransferase | HPMA | <i>N</i> -(2-hydroxypropyl)methacrylamide |
| COX | cyclooxygenase | HRV | human rhinoviruses |
| CSD | Cambridge Structural Database | HTS | high-throughput screening |
| CYP | enzymes that constitute the cytochrome P450 family | IGF-1R | insulin growth factor 1 receptor |
| DG | diacylglycerol | IND | Investigational Exemption to a New Drug Application |
| DHFR | dihydrofolate reductase | IP ₃ | inositol triphosphate |
| DNA | deoxyribonucleic acid | IPER | International Preliminary Examination Report |
| dTMP | deoxythymidine monophosphate | IRB | Institutional Review Board |
| dUMP | deoxyuridine monophosphate | ISR | International Search Report |
| EC ₅₀ | concentration of drug required to produce 50% of the maximum possible effect | K _M | Michaelis constant |
| EGF | epidermal growth factor | LH | luteinizing hormone |
| EMA | European Agency for the Evaluation of Medicinal Products | LHRH | luteinizing hormone-releasing hormones |
| EPC | European Patent Convention | LUMO | lowest unoccupied molecular orbital |
| EPO | European Patent Office | MAA | Marketing Authorization Application |
| FDA | US Food and Drug Administration | MAB | monoclonal antibody |
| FGF | fibroblast growth factor | MAO | monoamine oxidase |
| FGF-R | fibroblast growth factor receptor | MAOI | monoamine oxidase inhibitor |
| FH ₄ | tetrahydrofolate | MAP | mitogen-activated protein |
| FPGS | folylpolyglutamate synthetase | MAPK | mitogen-activated protein kinases |
| FPP | farnesyl diphosphate | MDR | multidrug resistance |
| FT | farnesyl transferase | MEP | molecular electrostatic potential |
| FTI | farnesyl transferase inhibitor | MMP | matrix metalloproteinase |
| | | MMPI | matrix metalloproteinase inhibitor |

xxii Acronyms and abbreviations

| | | | |
|------------------------|---|---------------|--|
| NA | neuraminidase or noradrenaline | PLS | partial least squares |
| NAD ⁺ /NADH | nicotinamide adenine dinucleotide | PPI | proton pump inhibitor |
| NAG | <i>N</i> -acetylglucosamine | PPTs | pyridinium 4-toluenesulfonate |
| NAM | <i>N</i> -acetylmuramic acid | QSAR | quantitative structure–activity relationship |
| NCE | new chemical entity | RES | reticuloendothelial system |
| NDA | New Drug Application | RFC | reduced folate carrier |
| NMDA | <i>N</i> -methyl-D-aspartate | RMSD | root mean square distance |
| NME | new molecular entity | RNA | ribonucleic acid |
| NMR | nuclear magnetic resonance | SAR | structure–activity relationships |
| NNRTIs | non-nucleoside reverse transcriptase inhibitors | SCAL | safety-catch acid-labile linker |
| NO | nitric oxide | SCF | stem cell factor |
| NRTI | nucleoside reverse transcriptase inhibitor | SCID | severe combined immunodeficiency disease |
| NSAID | non-steroidal anti-inflammatory drug | SOP | standard operating procedure |
| NVOC | nitroveratryloxycarbonyl | SPA | scintillation proximity assay |
| PABA | <i>p</i> -aminobenzoic acid | SPR | surface plasmon resonance |
| PBP | penicillin binding protein | TB | tuberculosis |
| PCP | phencyclidine, otherwise known as ‘angel dust’ | TFA | trifluoroacetic acid |
| PCT | Patent Cooperation Treaty | TGF- α | transforming growth factor α |
| PDB | Protein Data Bank | TGF- β | transforming growth factor β |
| PDGF | platelet-derived growth factor | THF | tetrahydrofuran |
| PDGF-R | platelet-derived growth factor receptor | TM | transmembrane |
| PDT | photodynamic therapy | TNF | tumour necrosis factor |
| PEG | polyethylene glycol | TNF-R | tumour necrosis factor receptor |
| PIP ₂ | phosphatidylinositol diphosphate | TNT | trinitrotoluene |
| PI | protease inhibitor | TRAIL | TNF-related apoptosis-inducing ligand |
| PKA | protein kinase A | VEGF | vascular endothelial growth factor |
| PKB | protein kinase B | VEGF-R | vascular endothelial growth factor receptor |
| PKC | protein kinase C | VIP | vasoactive intestinal peptide |
| PLC | phospholipase C | VOC-Cl | vinylloxycarbonyl chloride |
| | | VRE | vancomycin-resistant enterococci |
| | | VZV | varicella-zoster viruses |

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