Medicinal Chemistry

Second Edition

Gareth Thomas

University of Portsmouth

John Wiley & Sons, Ltd

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Preface to the First Edition

This book is written for second, and subsequent, year undergraduates studying for degrees in medicinal chemistry, pharmaceutical chemistry, pharmacy, pharmacology and other related degrees. It assumes that the reader has a knowledge of chemistry at level one of a university life sciences degree. The text discusses the chemical principles used for drug discovery and design with relevant physiology and biology introduced as required. Readers do not need any previous knowledge of biological subjects.

Chapter 1 is intended to give an overview of the subject and also includes some topics of peripheral interest to medicinal chemists that are not discussed further in the text. Chapter 2 discusses the approaches used to discover and design drugs. The remaining chapters cover the major areas that have a direct bearing on the discovery and design of drugs. These chapters are arranged, as far as is possible, in a logical succession.

The approach to medicinal chemistry is kept as simple as possible. Each chapter has a summary of its contents in which the key words are printed in bold type. The text is also supported by a set of questions at the end of each chapter. Answers, sometimes in the form of references to sections of the book, are listed separately. A list of recommended further reading, classified according to subject, is also included.

Gareth Thomas

Preface to the Second Edition

This book is written for second and subsequent year undergraduates studying for degrees in medicinal chemistry, pharmaceutical chemistry, pharmacy, pharmacology and other related degrees. It assumes that the reader has a knowledge of chemistry at Level 1 of a university life science degree. The text discusses the chemical principles used for drug discovery and design with relevant physiology and biology introduced as required. Readers do not need any previous knowledge of biological subjects.

The second edition of *Medicinal Chemistry, an Introduction* has a new layout that I hope presents the subject in a more logical form. The main changes are that Chapter 2 has been rewritten as three separate chapters, namely, structure–activity and quantitative structure relationships, computer-aided drug design and combinatorial chemistry. Two new chapters entitled Drugs from Natural Sources and Drug Development and Production have been added. The text has been simplified and extended where appropriate with a number of case histories, new examples and topics. Among the new topics are a discussion of monoclonal antibodies and photodynamic drugs. The inclusion of the new chapters and new material has necessitated a reduction in the biological and chemical introductions to some topics and the omission of some material included in the first edition. Furthermore, the reader should be aware that there are many more drugs and targets than those discussed in this text.

Chapter 1 introduces and gives an overview of medicinal chemistry. This is followed by chapters that discuss the principal methods used in drug design and the isolation of drugs from natural sources. Chapters 7–14 are concerned with a discussion of more specialised aspects of medicinal chemistry. The final two chapters outline drug and analogue synthesis, development and production. Appropriate chapters have an outline introduction to the relevant biology. Each chapter is supported by a set of questions. Answers to these questions, sometimes in the form of references to sections and figures in the book, are listed separately. An updated list of further reading, classified according to subject, is also included.

Gareth Thomas

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Finally, I would like to thank my wife for the cover design for the first Edition and the sketches included in this text. Her support through the years has been an essential contribution to my completing the text.

Abbreviations

A	Adenine
Abe	Abequose
AC	Adenylate cyclase
ACE	Angiotensin-converting enzymes
ACh	Acetyl choline
ADAPT	Antibody-directed abzyme prodrug therapy
ADEPT	Antibody-directed enzyme prodrug therapy
ADME	Absorption, distribution, metabolism and elimination
ADR	Adverse drug reaction
AIDS	Acquired immuno deficiency syndrome
Ala	Alanine
AMP	Adenosine monophosphate
Arg	Arginine
Asp	Aspartate
ATP	Adenosine triphosphate
AUC	Area under the curve
AZT	Zidovudine
BAL	British anti-Lewisite
BESOD	Bovine erythrocyte superoxide dismutase
C	Cytosine
CaM	Calmodulin
cAMP	Cyclic adenosine monophosphate
Cbz	*N*-(Benzyloxycarbonyloxy)succinamide
Cl	Clearance
CNS	Central nervous system
CoA	Coenzyme A
CoMFA	Comparative molecular field analysis
CYP-450	Cytochrome P-450 family
Cys	Cysteine
C_x	Concentration of x
dATP	Deoxyadenosine triphosphate
d.e.	Diastereoisomeric excess
DHF	Dihydrofolic acid
DHFR	Dihydrofolate reductase
DMPK	Drug metabolism and pharmacokinetics
DNA	Deoxyribonucleic acid
dTMP	Deoxythymidylate-5′-monophosphate
dUMP	Deoxyuridylate-5′-monophosphate
EC	Enzyme Commission
EDRF	Endothelium-derived relaxing factor

EDTA	Ethylenediaminotetraacetic acid
e.e.	Enantiomeric excess
ELF	Effluent load factor
EMEA	European Medicines Evaluation Agency
EPC	European Patent Convention
EPO	European Patent Office
E_s	Taft steric parameter
F	Bioavailability
FAD	Flavin adenine dinucleotide
FDA	Food and Drug Administration (USA)
FdUMP	5-Fluoro-2′-deoxyuridyline monophosphate
FGI	Functional group interconversion
FH_4	Tetrahydrofolate
FMO	Flavin monooxygenases
Fmoc	9-Fluorenylmethoxychloroformyl group
FUdRP	5-Fluoro-2′-deoxyuridylic acid
G	Guanine
GABA	γ-Aminobutyric acid
GC	Guanylyl cyclase
GDEPT	Gene-directed enzyme prodrug therapy
GDP	Guanosine diphosphate
GI	Gastrointestinal
Gln	Glutamine
Glu	Glutamatic acid
Gly	Glycine
5′-GMP	Guanosine 5′-monophosphate
GSH	Glutathione
GTP	Guanosine triphosphate
HAMA	Human anti-mouse antibodies
Hb	Haemoglobin
HbS	Sickle cell haemoglobin
His	Histidine
HIV	Human immunodeficiency disease
hnRNA	Heterogeneous nuclear RNA
HTS	High-throughput screening
IDDM	Insulin-dependent diabetes mellitus
Ig	Immunoglobins
Ile	Isoleucine
IP_3	Inositol-1,4,5-triphosphate
IV	Intravenous
IM	Intramuscular
KDO	2-Keto-3-deoxyoctanoate
k_x	Reaction rate constant for reaction x
LDA	Lithium diisopropylamide

LDH	Lactose dehydrogenase
Leu	Leucine
Lys	Lysine
MA(A)	Marketing authorisation (application)
Mab	Monoclonal antibody
mACh	Muscarinic cholinergic receptor
MAO	Monoamine oxidase
MCA	Medicines Control Agency
MESNA	2-Mercaptoethanesulphonate
Met	Methionine
MO	Molecular orbital
Moz	4-Methoxybenzyloxychloroformyl group
MR	Molar refractivity
mRNA	Messenger RNA
nACh	Nicotinic cholinergic receptor
NAD^+	Nicotinamide adenine dinucleotide (oxidised form)
NADH	Nicotinamide adenine dinucleotide (reduced form)
$NADP^+$	Nicotinamide dinucleotide phosphate (oxidised form)
NADPH	Nicotinamide dinucleotide phosphate (reduced form)
NAG	β-*N*-Acetylglucosamine
NAM	β-*N*-Acetylmuramic acid
NCI	National Cancer Institute (USA)
NOS	Nitric oxide synthase
P-450	Cytochrome P-450 oxidase
PABA	*p*-Aminobenzoic acid
PCT	Patent Cooperation Treaty
PDT	Photodynamic therapy
PEG	Polyethyene glycol
PG	Prostaglandin
Phe	Phenylalanine
PO	Per os (by mouth)
pre-mRNA	Premessenger RNA
Pro	Proline
ptRNA	Primary transcript RNA
QSAR	Quantitative structure–activity relationship
Q_x	Rate of blood flow for x
RMM	Relative molecular mass
RNA	Ribonucleic acid
S	Svedberg units
SAM	*S*-Adenosylmethionine
SAR	Structure–activity relationship
Ser	Serine
SIN-1	3-Morpholino-sydnomine
T	Thymine

TdRP	Deoxythymidylic acid
THF	Tetrahydrofolic acid
Thr	Threonine
tRNA	Transfer RNA
Tyr	Tyrosine
U	Uracil
UDP	Uridine diphosphate
UDPGA	Uridine diphosphate glucuronic acid
UdRP	Deoxyuridylic acid
Val	Valine
V_{d}	Volume of distribution
WHO	World Health Organization

1

An introduction to drugs, their action and discovery

1.1 Introduction

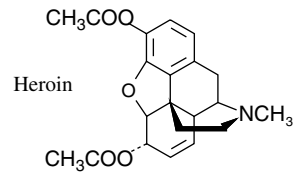
The primary objective of medicinal chemistry is the design and discovery of new compounds that are suitable for use as drugs. This process involves a *team of workers* from a wide range of disciplines such as chemistry, biology, biochemistry, pharmacology, mathematics, medicine and computing, amongst others.

The discovery or design of a new drug not only requires a discovery or design process but also the synthesis of the drug, a method of administration, the development of tests and procedures to establish how it operates in the body and a safety assessment. Drug discovery may also require fundamental research into the biological and chemical nature of the diseased state. These and other aspects of drug design and discovery require input from specialists in many other fields and so medicinal chemists need to have an outline knowledge of the relevant aspects of these fields.

1.2 What are drugs and why do we need new ones?

Drugs are strictly defined as chemical substances that are used to prevent or cure diseases in humans, animals and plants. The *activity* of a drug is its pharmaceutical effect on the subject, for example, analgesic or β-blocker, whereas its *potency* is the quantitative nature of that effect. Unfortunately the term drug is also used by the media and the general public to describe the substances taken for their psychotic rather than medicinal effects. However, this does not mean that these substances cannot be used as drugs. Heroin, for example, is a very effective painkiller and is used as such in the form of diamorphine in terminal cancer cases.

Medicinal Chemistry, Second Edition Gareth Thomas



Drugs act by interfering with biological processes, so no drug is completely safe. *All* drugs, including those non-prescription drugs such as aspirin and paracetamol (Fig. 1.1) that are commonly available over the counter, act as poisons if taken in excess. For example, overdoses of paracetamol can causes coma and death. Furthermore, in addition to their beneficial effects most drugs have non-beneficial biological effects. Aspirin, which is commonly used to alleviate headaches, can also cause gastric irritation and occult bleeding in some people The non-beneficial effects of some drugs, such as cocaine and heroin, are so undesirable that the use of these drugs has to be strictly controlled by legislation. These unwanted effects are commonly referred to as *side effects.* However, side effects are not always non-beneficial; the term also includes biological effects that are beneficial to the patient. For example, the antihistamine promethazine is licenced for the treatment of hayfever but also induces drowsiness, which may aid sleep.

Figure 1.1 Aspirin and paracetamol

Drug resistance or tolerance (*tachyphylaxis*) occurs when a drug is no longer effective in controlling a medical condition. It arises in people for a variety of reasons. For example, the effectiveness of barbiturates often decreases with repeated use because the body develops mixed function oxidases in the liver that metabolise the drug, which reduces its effectiveness. The development of an enzyme that metabolises the drug is a relatively common reason for drug resistance. Another general reason for drug resistance is the *downregulation* of receptors (see section 8.6.1). Downregulation occurs when repeated stimulation of areceptor results in the receptor being broken down. This results in the drug being less effective because there are fewer receptors available for it to act on. However, downregulating has been utilised therapeutically in a number of cases. The continuous use

of gonadotrophin releasing factor, for example, causes gonadotrophin receptors that control the menstrual cycle to be downregulated. This is why gonadotrophin-like drugs are used as contraceptives. Drug resistance may also be due to the appearance of a significantly high proportion of drug-resistant strains of microorganisms. These strains arise naturally and can rapidly multiply and become the currently predominant strain of that microorganism. Antimalarial drugs are proving less effective because of an increase in the proportion of drug-resistant strains of the malaria parasite.

New drugs are constantly required to combat drug resistance even though it can be minimised by the correct use of medicines by patients. They are also required for improving the treatment of existing diseases, the treatment of newly identified diseases and the production of safer drugs by the reduction or removal of adverse side effects.

1.3 Drug discovery and design: a historical outline

Since ancient times the peoples of the world have had a wide range of natural products that they use for medicinal purposes. These products, obtained from animal, vegetable and mineral sources, were sometimes very effective. However, many of the products were very toxic and it is interesting to note that the Greeks used the same word *pharmakon* for both poisons and medicinal products. Information about these ancient remedies was not readily available to users until the invention of the printing press in the fifteenth century. This led to the widespread publication and circulation of Herbals and Pharmacopoeias, which resulted in a rapid increase in the use, and misuse, of herbal and other remedies. Misuse of tartar emetic (antimony potassium tartrate) was the reason for its use being banned by the Paris parliament in 1566, probably the first recorded ban of its type. The usage of such remedies reached its height in the seventeenth century. However, improved communications between practitioners in the eighteenth and nineteenth centuries resulted in the progressive removal of preparations that were either ineffective or too toxic from Herbals and Pharmacopoeias. It also led to a more rational development of new drugs.

The early nineteenth century saw the extraction of pure substances from plant material. These substances were of consistent quality but only a few of the compounds isolated proved to be satisfactory as therapeutic agents. The majority were found to be too toxic although many, such as morphine and cocaine for example, were extensively prescribed by physicians.

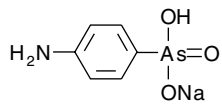
The search to find less toxic medicines than those based on natural sources resulted in the introduction of synthetic substances as drugs in the late nineteenth century and their widespread use in the twentieth century. This development was based on the structures of known pharmacologically active compounds, now referred to as *leads*. The approach adopted by most nineteenth century workers was to synthesise structures related to that of the lead and test these compounds for the required activity. These lead-related compounds are now referred to as *analogues*.

The first rational development of synthetic drugs was carried out by Paul Ehrlich and Sacachiro Hata who produced arsphenamine in 1910 by combining synthesis with reliable

biological screening and evaluation procedures. Ehrlich, at the beginning of the nineteenth century, had recognised that both the beneficial and toxic properties of a drug were important to its evaluation. He realised that the more effective drugs showed a greater selectivity for the target microorganism than its host. Consequently, to compare the effectiveness of different compounds, he expressed a drug's selectivity and hence its effectiveness in terms of its chemotherapeutic index, which he defined as:

$$\text{Chemotherapeutic index} = \frac{\text{Minimum curative dose}}{\text{Maximum tolerated dose}} \tag{1.1}$$

At the start of the nineteenth century Ehrlich was looking for a safer antiprotozoal agent with which to treat syphilis than the then currently used atoxyl. He and Hata tested and catalogued in terms of his therapeutic index over 600 structurally related arsenic compounds. This led to their discovery in 1909 that arsphenamine (Salvarsan) could cure mice infected with syphilis. This drug was found to be effective in humans but had to be used with extreme care as it was very toxic. However, it was used up to the mid- 1940s when it was replaced by penicillin.



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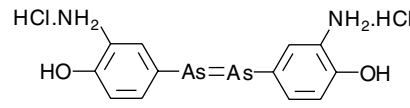

Arsphenamine (Salvarsan)

Ehrlich's method of approach is still one of the basic techniques used to design and evaluate new drugs in medicinal chemistry. However, his chemotherapeutic index has been updated to take into account the variability of individuals and is now defined as its reciprocal, the therapeutic index or ratio:

$$\text{Therapeutic index} = \frac{LD_{50}}{ED_{50}} \tag{1.2}$$

where LD_{50} is the lethal dose required to kill 50 per cent of the test animals and ED_{50} is the dose producing an effective therapeutic response in 50 per cent of the test animals. In theory, the larger a drug's therapeutic index, the greater is its margin of safety. However, because of the nature of the data used in their derivation, therapeutic index values can only be used as a limited guide to the relative usefulness of different compounds.

The term *structure–activity relationship* (*SAR*) is now used to describe Ehrlich's approach to drug discovery, which consisted of synthesising and testing a series of structurally related compounds (see Chapter 3). Although attempts to quantitatively relate chemical structure to biological action were first initiated in the nineteenth century, it was not until the 1960s that Hansch and Fujita devised a method that successfully incorporated quantitative measurements into structure–activity relationship determinations (see section 3.4.4). The technique is referred to as *QSAR* (*quantitative structure–activity relationship*).