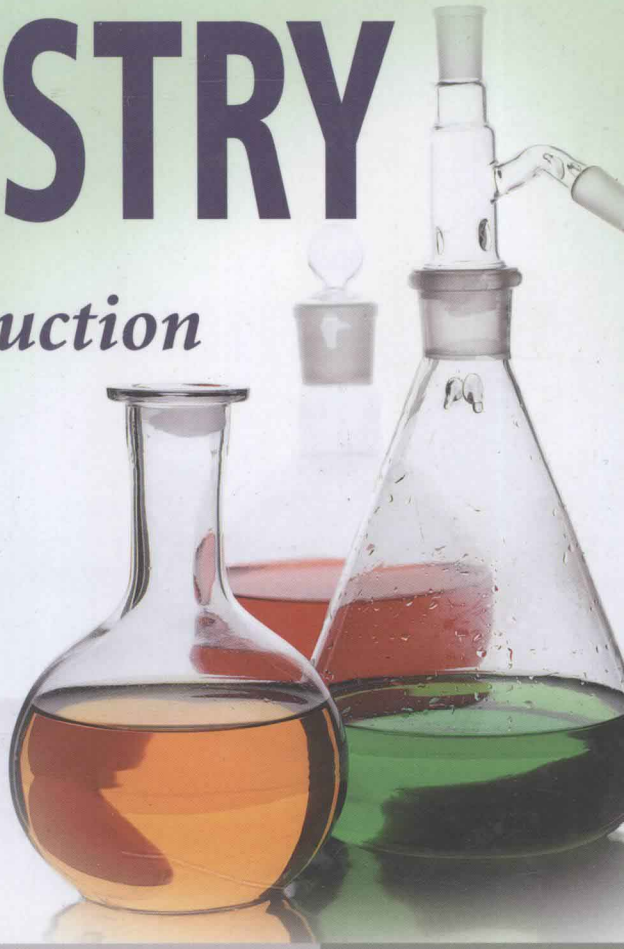
GARETH THOMAS

MEDICINAL CHEMISTRY

An Introduction



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Medicinal Chemistry

Second Edition

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Medicinal Chemistry

Second Edition

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

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