BASIC CONCEPTS IN MEDICINAL CHEMISTRY

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3rd Edition

MARC W. HARROLD, BS Pharm, PhD

Professor of Medicinal Chemistry
Duquesne University
School of Pharmacy
Pittsburgh, Pennsylvania

ROBIN M. ZAVOD, PhD, FAPhA

Editor-in-Chief, *Currents in Pharmacy Teaching and Learning*
Professor of Pharmaceutical Sciences
Midwestern University College of Pharmacy
Downers Grove, Illinois

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DEDICATION

To our students who blessed us with their joy, presented us with their challenges, and made us better educators.

To our colleagues who provided us with their encouragement and inspiration, and who have served as our role models.

TABLE OF CONTENTS

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Marc would like to thank the Duquesne University School of Pharmacy for providing the time and support required for the writing of this third edition; his colleagues who took the time to provide suggestions for various aspects of this text; his wife Barbara for her love and support and for coining the phrase "Structure Analysis Checkpoint" introduced in the second edition; and God for His countless blessings and constant guidance.

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PREFACE

Welcome to the third edition of *Basic Concepts in Medicinal Chemistry*. We are excited to be able to offer this updated version of our original text. Similar to what we experienced with our second edition, our students, readers, and peers provided us with challenges to enhance this textbook and provide additional explanations and examples. In hindsight, and with a critical review, we identified topic areas that needed additional clarification. While the basic concepts that underlie medicinal chemistry remain the same, the presentation of some of these concepts can always be improved. In this edition, we have sought to provide better examples, better explanations, additional summaries, and additional knowledge links to help those seeking to master these concepts. We are thankful for the feedback that we have received from both students and peers and have worked to address the suggestions and questions provided.

The major revisions provided in this edition include

- A revision of all of the figures and structures to allow for a more consistent "look" throughout the text
- A revision of a number of the examples throughout the text to include a wider range of drugs and drug classes
- A clarification of examples that were potentially confusing
- The creation of additional summary tables in Chapters 3 and 6 to help readers better select the proper drug binding interaction
- The addition of enhanced explanations, discussions, and examples in the following areas:
  - resonance, induction, and electron flow (Chapter 2)
  - discussion of pK_a ranges of acidic and basic functional groups with a specific emphasis on the differences seen among carboxylic acids, amines, and aromatic nitrogen atoms (Chapter 3)
  - specific links that tie together ionization states and possible binding interactions (Chapter 6)
  - the importance of properly identifying a drug binding interaction (Chapter 6)
  - certain metabolic transformations that can cause confusion (Chapter 8)
- The addition of an expanded discussion of pharmacogenomics (or pharmacogenetics) in Chapter 8, including a number of specific examples

Similar to previous editions, this text focuses on the basic, fundamental concepts governing the discipline of medicinal chemistry and emphasizes functional group analysis and the fundamentals of drug structure evaluation. Every drug that is prescribed and dispensed is a chemical structure that contains numerous functional groups oriented in a specific manner. These functional groups determine the interactions of a drug molecule with its biological target, its pharmacological action(s), the route(s) by which it is administered, the extent to which it is metabolized, and the presence or absence of specific adverse drug reactions or drug interactions. It thus seemed appropriate to begin the text with a discussion of the common characteristics and roles of functional groups. Subsequent chapters were then designed to focus upon specific aspects of these functional groups. These include the identification of acidic and basic functional groups, the use of the Henderson-Hasselbalch equation to solve quantitative and qualitative pH and pK_a problems, the formation of inorganic and organic salts of specific functional groups, the roles of water and lipid soluble functional groups and

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the need for a proper balance of solubility, the interaction of functional groups with their biological targets, the stereochemical orientations of functional groups within a drug molecule, and the routes of metabolism that are available for specific functional groups. The final two chapters serve as capstones for the text. Chapter 9 focuses upon structure activity relationships (SARs) and a brief overview of some of the common strategies employed in rational drug design, while Chapter 10 introduces the concept of Whole Molecule Drug Evaluation, an idea that we first introduced and published in our *Medicinal Chemistry Self Assessment* text in 2015.

Several aspects of this text should help students develop a strong foundation in the concepts that govern the discipline of medicinal chemistry. Chapters 2 through 9 contain specific learning objectives that coincide with the key concepts discussed in the chapters. The organization of the subject material was chosen to allow students to incrementally increase their knowledge of the functional groups that comprise drug molecules and their importance to drug therapy. Each chapter contains numerous examples to help illustrate each key concept. In choosing these examples, a conscious effort was made to try to include as many different commercially available drugs as possible. During the many years that the two of us have taught medicinal chemistry, a question that we are commonly asked is, "Why is this important to a pharmacist and the practice of pharmacy?" To address this question, each chapter includes extended discussions that link fundamental medicinal chemistry concepts to their therapeutic relevance.

We firmly belief that these concepts are difficult to learn and master without multiple forms of self-assessment. To better meet this need, we introduced Structure Analysis Checkpoint (SAC) questions in the second edition of our text. These questions "follow" two drugs, venetoclax and elamipretide, throughout the text. As new concepts and skills are introduced in each chapter, these drugs are revisited, and readers are asked to apply their newly acquired knowledge to these two drugs. By the end of the text, readers will have encountered over 30 unique questions for each of these drugs and will have ultimately completed two whole molecule drug evaluations. It is important to note that the SAC questions are based solely on two drugs, whereas the stand-alone end-of-chapter Review Questions purposely use different drugs for each question. Each set of end-of-chapter Review Questions was evaluated to determine if question format and/or question drug example should be retained or changed. Modifications to the review questions (~50%) were made in nearly all chapters. Items were added to reflect the new content, and the total number of questions in each chapter was increased. This provides instructors with an enhanced question bank for every chapter. Additionally, we introduced four additional Whole Molecule Drug Evaluations in Chapter 10, increasing the content in this chapter by 50%. Each Whole Molecule Drug Evaluation is unique and requires a specific level of evaluation. The answers for all questions are provided in an appendix; however, it is strongly suggested that readers attempt to answer the questions prior to consulting the answers.

We are thankful for the opportunity to provide you with what we believe is an updated and improved version of our initial text, for the invaluable contributions provided by our students and peers, and for those who have chosen to use this text to further their knowledge in the area of medicinal chemistry.

Marc W. Harrold
Robin M. Zavod

ABBREVIATIONS USED IN THIS TEXT

Many of these are defined in the chapters in which they appear, but a comprehensive list of all abbreviations used in the text is provided here for your convenience.

ACE	Angiotensin converting enzyme
ADH	Alcohol dehydrogenase
ADME	Absorption, distribution, metabolism, excretion
ADP	Adenosine diphosphate
ALDH	Aldehyde dehydrogenase
ALL	Acute lymphoblastic leukemia
AMP	Adenosine monophosphate
ARB	Angiotensin II receptor blocker (aka angiotensin II receptor antagonist)
ATP	Adenosine triphosphate
APS	Adenosine-5′-phosphosulfate
BID	*bis in die* (Latin for twice daily)
BPH	Benign prostatic hyperplasia
CIP	Cahn-Ingold-Prelog
cLog P	Calculated log P
CoA	Coenzyme A
CNS	Central nervous system
COMT	Catechol-*O*-methyltransferase
COPD	Chronic obstructive pulmonary disease
COX	Cyclooxygenase
CYP450	Cytochrome P450
1,4-DHP	1,4-Dihydropyridine
DNA	Deoxyribonucleic acid
E (isomer)	*Entgegen* (German for opposite)
EDTA	Ethylenediaminetetraacetic acid
FAD	Flavin adenine dinucleotide
FDA	Food and Drug Administration
FMO	Flavin monooxygenase
GERD	Gastroesophageal reflux disease
GI	Gastrointestinal
GMP	Guanosine monophosphate
GTP	Guanosine triphosphate
GSH	Glutathione
HDL	High density lipoprotein
HIV	Human immunodeficiency virus
HIV-1	Human immunodeficiency virus type 1
HMG-CoA	3-Hydroxy-3-methylglutaryl coenzyme A

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IM	Intramuscular
IMP	Inosine monophosphate
IR	Infrared
IUP	Intrauterine device
IV	Intravenous
LDL	Low density lipoprotein
Log D	Logarithmic expression of the distribution coefficient
Log P	Logarithmic expression of the partition coefficient
LTC_4	Leukotriene C_4
LTD_4	Leukotriene D_4
LTE_4	Leukotriene E_4
MMAE	Monomethylauristatin E
MTT	Methyl-tetrazole-thiomethyl
NADH	Nicotinamide adenine dinucleotide (reduced form)
NAD^+	Nicotinamide adenine dinucleotide (oxidized form)
NAPDH	Nicotinamide adenine dinucleotide phosphate (reduced form)
$NADP^+$	Nicotinamide adenine dinucleotide phosphate (oxidized form)
NAT	*N*-Acetyltransferase
NMR	Nuclear magnetic resonance
NPH insulin	Neutral protamine Hagedorn insulin (aka isophane insulin)
NSAID	Nonsteroidal anti-inflammatory drug
OTC	Over-the-counter
P_i	Phosphate (inorganic)
PABA	*para*-Aminobenzoic acid
PAH	Pulmonary arterial hypertension
2-PAM	Pralidoxime chloride (aka 2-Pyridine aldoxime methyl chloride)
PAP	3′-Phosphoadenosine-5′-phosphate
PAPS	3′-Phosphoadenosine-5′-phosphosulfate
PAR-1	Protease-activated receptor-1
PEG	Polyethylene glycol
Pen VK	Potassium penicillin V
PGE_2	Prostaglandin E_2
PGI_2	Prostaglandin I_2 (aka prostacyclin)
pH	Negative log of the hydrogen ion concentration in a solution
pK_a	Negative log of the K_a, the dissociation constant for an acid in an aqueous environment
PO	*per os* (Latin for once daily)
POMT	Phenol-*O*-methyltransferase
PPARα	Peroxisome proliferator-activated receptor
PP_i	Pyrophosphate (inorganic)
PRPP	5-Phosphoribosyl 1-pyrophosphate
QID	*quater in die* (Latin for four times daily)

R (isomer)	*Rectus* (Latin for right)
RNA	Ribonucleic acid
S (isomer)	*Sinister* (Latin for left)
SAM	*S*-Adenosylmethionine
SAR	Structure activity relationship
SC	Subcutaneous
SULT	Sulfotransferase
T_3	Liothyronine (aka triiodothyronine)
T_4	Levothyroxine
TID	*ter in die* (Latin for three times daily)
T-IMP	Thioinosine monophosphate
tRNA	Transfer ribonucleic acid
TXA_2	Thromboxane A_2
UDP	Uridine diphosphate
UDPGA	UDP-glucuronic acid
UGT	UDP-glucuronyltransferase
VEGF-2	Vascular endothelin growth factor 2
Z (isomer)	*Zusammen* (German for together)