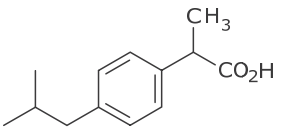
1 INTRODUCTION

LEARNING OBJECTIVES

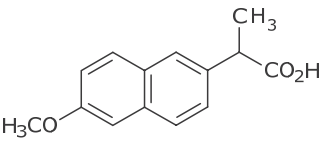
After completing this chapter, students will be able to:

- Identify the following acidic functional groups: carboxylic acids, β-dicarbonyls, imides, sulfonamides, sulfonylureas, tetrazoles, phenols, thiols, phosphates, phosphonates, and sulfates.
- Identify the following basic functional groups: aliphatic amines, alicyclic amines (aka saturated heterocycles), aromatic amines, imines, hydrazines, amidines, guanidines, and nitrogen containing aromatic heterocycles.
- Classify a drug molecule as one of the following: acidic, basic, amphoteric, an electrolyte, or a nonelectrolyte.

This text focuses on the fundamental concepts that govern the discipline of medicinal chemistry, as well as how and why these concepts are essential in therapeutic decision making. In very simplistic terms, *medicinal chemistry* can be defined as the chemistry of how drugs work. In other words, it is the discipline that seeks to identify the specific atoms or functional groups that are responsible for specific biological/biochemical actions. To illustrate this point, let's compare the structures and dosing of two commonly used drugs, ibuprofen, and naproxen.



Ibuprofen



Naproxen

Both of these drugs are available without a prescription (i.e., over-the-counter [OTC]) and produce anti-inflammatory, analgesic, and antipyretic actions. Ibuprofen is a shorter acting drug and must be administered every 4–6 hours, whereas naproxen is a longer acting drug that can be dosed every 12 hours. In evaluating

these chemical structures, it is found that there are both similarities (i.e., carboxylic acid and adjacent methyl group) and differences (i.e., bicyclic ring with a methoxy group versus monocyclic ring with an alkyl chain). The discipline of medicinal chemistry seeks to explain how these structural (i.e., chemical) differences result in different durations of action. Once this relationship is established, this information can be used to predict the relative durations of action of other agents within this chemical/pharmacological class.

The primary goal of this text is to help the reader develop a solid foundation in medicinal chemistry. Once this foundation has been established, the reader should be able to analyze drug structures and understand how their composite pieces can contribute to the overall properties and/or activity of the drug molecules. Every drug that is prescribed and dispensed is a chemical structure with a specific composition. The atoms and functional groups that comprise these chemical structures dictate the route of administration, the duration of action, the pharmacological actions, and the presence or absence of specific adverse drug reactions or drug interactions.

The organization of topics within this text has been carefully selected to allow the reader to progressively gain knowledge about the chemistry of drug molecules. Each chapter builds on one another and, when applicable, relevant examples are cross-referenced. The authors of this text assume that the reader has a basic understanding of inorganic chemistry, organic chemistry, and biochemistry. When applicable, key concepts from these disciplines will be reviewed as they apply to medicinal chemistry.

Because every atom within the drug structure is part of a specific functional group, we chose functional group identification and evaluation as the starting point to begin our discussion. In Chapter 2, we focus on the chemical characteristics of functional groups and the roles they can play in drug action. From there, Chapter 3 examines those functional groups that can be classified as either acidic or basic. We also explore the reasons why it is important to know the acid/base character of a drug molecule. In Chapter 4, we continue our examination of acidic and basic functional groups via introduction of the Henderson-Hasselbalch equation and review of several strategies for solving quantitative and qualitative pH and pK_a problems. Numerous examples are provided throughout this chapter to help the reader become more proficient in solving these types of problems. Similar to Chapter 3, we devote the end of this chapter to selected examples designed to help the reader understand the importance of pH, pK_a, and ionization in drug therapy. In Chapter 5, we discuss how acidic and basic functional groups can form inorganic and organic salts. Additionally, we discuss how these salts influence the water/lipid solubility of a drug molecule and how this relates to various routes of administration. An emphasis is also placed on the need for a balance between water