Structural Modifications of Drug Candidates: How Useful Are They in Improving Metabolic Stability of New Drugs? Part I: Enhancing Metabolic Stability

ALA F. NASSAR

The rule of three, which attempts to define the activity–exposure–toxicity triangle, presents the single most difficult challenge in the design and advancement of drug candidates to the development stage. Absorption, distribution, metabolism, and excretion (ADME) studies are widely used in drug discovery to optimize this balance of properties necessary to convert lead compounds into drugs that are both safe and yet effective for human patients. Metabolite characterization has become one of the main drivers of the drug discovery process, helping to optimize ADME properties and increase the success rate for drugs. The study of structural modifications produces valuable information which, throughout the process of drug discovery, keeps on giving direction and focus in the effort to improve and balance the relationships between activity, exposure, and toxicity for drug candidates. In this chapter, the strategies for the decision-making process in structural modification of drug candidates are addressed to improve metabolic stability. Several examples are included to show how metabolic stability has influenced and guided drug design.

1 BACKGROUND

During the process of metabolism, the molecular structure of a drug is changed from one that is absorbed (lipophilic, or capable of crossing the membrane lipid core of membranes) to one that can be readily eliminated from the body (incapable of crossing

Pharmaceutical Sciences Encyclopedia: Drug Discovery, Development, and Manufacturing
Edited by Shayne C. Gad
Copyright © 2010 John Wiley & Sons, Inc.