Structural Modifications of Drug Candidates: How Useful Are They in Improving PK Parameters of New Drugs? Part II: Drug Design Strategies

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1 INTRODUCTION

One key to successful drug design and development is the process of finding the right combination of diverse properties such as activity, toxicity, exposure, and so on. It is very important to first determine, and then optimize, the exposure–activity–toxicity relationships for drug candidates, and thus their suitability for advancement to development. Therefore, the concern of the drug metabolism scientist is to optimize plasma half-life, drug/metabolic clearance, metabolic stability, and the ratio of metabolic to renal clearance. The effort to achieve these positives must be balanced by the need to minimize or eliminate potential difficulties or dangers such as gut/hepatic-first-pass metabolism, inhibition/induction of drug-metabolizing enzymes by metabolites, biologically active metabolites, metabolism by polymorphically expressed drug-metabolizing enzymes, and formation of reactive metabolites. The optimal result will be a safer drug that undergoes predictable metabolic inactivation or even undergoes no metabolism. Among the approaches available to the drug design team, as they seek to meet these goals, are active metabolites, prodrugs, and hard and soft drugs; these will be discussed with some examples from recent case studies.

2 ACTIVE METABOLITES

Some drugs produce metabolites that are pharmacologically active; in some cases, these metabolites surpass their parent drugs as candidates for development. Active metabolites are often indicated by an elevated level of pharmacological effect, which is revealed through pharmacokinetic tests on the parent drug candidate. These metabolites often are subject to phase II metabolism and thus have better safety profiles. Table 1 contains

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