10 Prodrugs in Drug Design and Development

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10.1 INTRODUCTION

Drug discovery is an exceedingly complex and demanding enterprise aiming to select a drug candidate that displays promising efficacy, safety, and marketing potential for clinical trials. The initial phase of the drug discovery process is devoted to increase pharmacological potency with high affinity and selective ligands at the target. This initial phase often results in lead compounds with less than optimal biopharmaceutical and pharmacokinetic properties, or properties more frequently referred to as ADME (absorption, distribution, metabolism, and excretion) properties. Designing prodrugs, when used appropriately, has the potential to enable a suitable drug candidate with the optimal ADME properties and pharmacological potency to be selected for development faster and with less overall costs. Fortunately, prodrugs are becoming an integral part of many drug discovery efforts.

10.2 PRODRUG CONCEPT

Prodrugs are derivatives of active parent drugs that require in vivo conversion, either an enzymatic and/or a chemical, to release the pharmacologically active drug. Because prodrugs are considered to be inactive or at least significantly less active than the released drugs, salt forms and drugs, whose metabolites contribute to the overall pharmacological response, are not considered as prodrugs. Typically, prodrugs are chemical derivatives consisting of a promoiety which is released in one or two chemical or enzymatic (or both) steps to release the active parent drug. Bioprecursor prodrugs