

Prodrug Design vs. Drug Design

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Introduction

A drug is defined as a substance which is used in the cure, relief, diagnosis, treatment, or prevention of disease. The development of any potential drug commences with the study of the biochemistry and physiology behind a disease for which pharmaceutical intervention is feasible [1]. Prodrug is a term that was first introduced by Albert to signify a pharmacologically inactive chemical moiety that can be used to temporarily alter the physicochemical properties of a drug to increase its usefulness and decrease its associated toxicity [2]. The use of the term usually implies a covalent link between a drug and a chemical promoiety. Prodrugs can be enzymatically or chemically converted in vivo to provide the parent active drug which exerts a therapeutic effect. Ideally, the prodrug should be converted to the parent drug once its goal is achieved, followed by rapid elimination of the released promoiety group [3-6].

Drug discovery is a lengthy interdisciplinary endeavor. It is a consecutive process that commences with target and lead discovery, followed by lead optimization and pre-clinical in vitro and in vivo studies to evaluate if a compound satisfies a number of pre-set criteria to start clinical development [7-8]. The number of years it takes to introduce a drug to the pharmaceutical market is about 10 years with a cost of up to \$1 billion dollars. Traditionally, drugs were discovered by a time-consuming multi-step synthetic process which was followed by in vivo biological screening and further investigation for the promising compounds in terms of their Absorption, Distribution, Metabolism, Excretion (ADME) properties, and potential toxicity. Such drug development processes have resulted in high attrition rates with failures attributed to poor pharmacokinetic properties, lack of efficacy, toxicity, side effects in humans, and various commercial factors [7-8].

Nowadays, the process of drug discovery has been revolutionized with the advent of genomics, proteomics, bioinformatics, and efficient technologies including combinatorial chemistry, High Throughput Screening (HTS), virtual screening, de novo design, in vitro, in silico ADME screening, and structure-based drug design [9-11]. Structure-based drug design is widely considered one of the most innovative and powerful approaches in drug design. It is an approach that requires a 3D structure of the target protein with or without a hosted ligand, where binding mode, affinity, and confirmation of ligand binding can be discerned. Various computational methods are used to design a high-affinity inhibitor either via virtual computer screening of large compound libraries or through design and synthesis of novel ligands. These methods can also be utilized to analyze the target structures for possible binding/active sites, generate candidate structures, check for their drug-likeness, dock structures with the target, rank according to their binding affinities, and optimize the molecules to improve binding properties.

As structures of more protein targets become available via crystallography, NMR and bioinformatics methods have provided the opportunity for computational methods to use the structure of the protein target as a tool to develop novel lead compounds. The computational methods include: (i) De novo design, (ii) Virtual

screening, and (iii) Fragment based discovery. (i) De novo design attempts to use the structure of the protein without a ligand to generate a novel chemical structure that can bind. There are varying algorithms, most of which depend on identifying initial sites of interaction that develop into complete ligands. (ii) Virtual screening refers to the computational screening of large libraries of chemicals for structures that complement targets of known compounds that can be tested experimentally. Since virtual screening takes place in the 3D active site of the target, it is also called a structure-based virtual screening. (iii) Fragment based discovery is based on the premise that most ligands that bind strongly to a protein active site can be considered as a number of smaller fragments or functionalities. Fragments are identified by screening a relatively small number of molecules (400-20,000) by X-ray crystallography and NMR spectroscopy. The molecules of the fragment binding to the protein can be used to design new ligands by adding functionality to the fragments or by incorporating features of the fragment into existing ligands [12-20].

Studies have indicated that poor pharmacokinetics and toxicity are the most important causes of high attrition-rates in the drug development process, and it has been widely accepted that these areas should be considered as early as possible in drug discovery to improve the efficiency and cost-effectiveness of the industry. Resolving the pharmacokinetic and toxicological properties of drug candidates remains a key challenge for drug developers [21]. The most efficient approach for overcoming these negative drug characteristics is the prodrug approach. The rationale behind the use of prodrugs is to optimize the ADME properties and to increase the selectivity of drugs for their intended target. Development of a prodrug with improved properties may also represent a life-cycle management opportunity. Unfortunately, prodrugs have often been considered only when obstacles are encountered with the parent drug. However, it has become increasingly important to consider the design of an appropriate prodrug in the early stages of preclinical development and not as a last resort [22].

Modifying the ADME properties of an active drug requires a complete understanding of the physicochemical and biological behavior of the drug candidate [23-26]. This includes comprehensive evaluation of drug-likeness involving prediction of ADME properties. These predictions can be attempted at several levels: (1) in vitro-in vivo using data obtained from tissue or recombinant material from human and pre-clinical species, and (2) in silico or computational

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predictions projecting in vitro or in vivo data involving the evaluation of various ADME properties using computational approaches such as Quantitative Structure Activity Relationship (QSAR) or molecular modeling [22-26].

Prodrug design can be utilized in the following: (1) improving active drug solubility and consequently bioavailability; dissolution of the drug molecule from the dosage form may be a rate-limiting step to absorption, (2) increasing permeability and absorption; membrane permeability has a significant effect on drug efficacy, and (3) modifying the distribution profile; before the drug reaches its physiological target and exerts the desired effect [22-26]. In this editorial, prodrug design based on a computational approach consisting of calculations using Molecular Orbital (MO) and Molecular Mechanics (MM) methods and correlations between experimental and calculated values of intramolecular processes is used. In this prodrug approach, no enzyme is needed for the catalysis of the intraconversion of a prodrug to its parent drug. The interconversion of the prodrug is solely dependent on the rate-limiting step for the intramolecular reaction.

Thermodynamic and kinetic energy-based calculations for biological systems that have pharmaceutical and medicinal interests are a great challenge to the health community. Nowadays, quantum mechanics (QM) such as ab initio, a semi-empirical and Density Functional Theory (DFT), and molecular mechanics (MM) are increasingly being utilized and widely recommended as tools for providing structure-energy calculations for potential drugs and prodrugs alike [27]. Ab initio quantum methods are computational chemistry methods based on quantum chemistry. The ab initio molecular orbital methods (quantum mechanics) such as HF, G1, G2, G2MP2, MP2 and MP3 are based on rigorous use of the Schrodinger equation with a number of approximations. The disadvantage of ab initio methods is their computational cost. They often take a lot of computer time, memory, and disk space [28-30].

Semi-empirical quantum chemistry methods are based on the Hartree-Fock formalism with many approximations and some parameters from empirical data. Among the semi-empirical methods commonly used are MINDO, MNDO, MINDO/3, AM1, PM3 and SAM1. The semi-empirical methods have provided rich information for practical application [31-34]. Calculations of molecules exceeding 60 atoms can be completed using such methods. Density Functional Theory (DFT) is a quantum mechanical method used to investigate the electronic structure (principally the ground state) of many-body systems, particularly atoms, molecules, and the condensed phases. With this theory, the properties of many electron systems can be determined by using functional, i.e. functions of another function, which in this case is the spatially dependent electron density. DFT is among the most popular and versatile methods available in condensed-matter physics, computational physics, and computational chemistry. The DFT method is used to calculate structures and energies for medium-sized systems (30-60 atoms) of biological and pharmaceutical interest and is not restricted to the second row of the periodic table [35].

On the other hand, molecular mechanics is a mathematical approach used for the computation of structures, energy, dipole moment, and other physical properties. It is widely used in calculating many diverse biological and chemical systems such as proteins, large crystal structures, and relatively large solvated systems. However, this method is limited by the determination of parameters such as the large number of unique torsion angles present in structurally diverse molecules [36]. Ab initio is an important tool to investigate functional

mechanisms of biological macromolecules based on their 3D and electronic structures. The system size which ab initio calculations can handle is relatively small despite the large sizes of bio macromolecules surrounding solvent water molecules. Accordingly, isolated models of areas of proteins such as active sites have been studied in ab initio calculations. However, the disregarded proteins and solvent surrounding the catalytic centers have also been shown to contribute to the regulation of electronic structures and geometries of the regions of interest.

To overcome these discrepancies, Quantum Mechanics/Molecular Mechanics (QM/MM) calculations are utilized, in which the system is divided into QM and MM regions where QM regions correspond to active sites to be investigated and are described quantum mechanically. MM regions correspond to the remainder of the system and are described molecular mechanically. The pioneer work of the QM/MM method was accomplished by Warshel and Levitt [37], and since then, there has been much progress on the development of a QM/MM algorithm and applications to biological systems [38, 39].

Recently, we have been investigating the mechanisms of some intramolecular processes that have been used to gain a better understanding of enzyme catalysis and the design of novel prodrug linkers [40-58]. Using molecular mechanics, DFT, and ab initio methods, we studied various intramolecular processes in order to assign factors affecting the rate-determining step. Among the processes studied are: (1) proton transfer between two oxygens in Kirby's acetals [59] and proton transfer between nitrogen and oxygen in Kirby's enzyme models [59]; (2) intramolecular acid-catalyzed hydrolysis in Kirby's maleamic acid amide derivatives [59]; (3) proton transfer between two oxygens in rigid systems in Menger's enzyme model [60-63].

The information from our studies on enzyme models was used to design an efficient chemical moiety to be utilized as a prodrug linker with the potential to release the parent drug in a slow or fast manner. Unraveling the mechanisms of the enzyme models mentioned above has led to the design of several prodrugs for the treatment of various diseases such as myelodysplastic syndromes, Parkinson's, malaria, hypertension, psoriasis, and osteoporosis. Successful synthesis of most of the prodrugs for the treatment of these diseases was achieved and in vitro kinetic results at a wide pH range have shown promising results for obtaining novel prodrugs that might have enhanced dissolution, membrane penetration, and thus better bioavailability than their corresponding drugs [64-77]. The modern computational approach has the capability to provide a design for both drugs and prodrugs. Drug design involves multi-step procedures to resolve obstacles stemming from pharmacodynamic and pharmacokinetic characteristics, whereas prodrug design is limited to resolving only pharmacokinetic issues related to a drug candidate.

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