

Prodrugs from Serendipity to Design by Computational Chemistry Methods

EDITORIAL

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Imagination is more important than knowledge when knowledge is limited and can not solve important questions. Inventiveness in the drug design has been clumsiness in quality and quantity. This may be due to the ineptness and incapability of medicinal chemists to comprehend biochemistry and biology issues. On the other hand, biochemists, biologists, and pharmaceutical chemists do not possess the expertise to make complex organic entities. Hence, a team comprising of all expertise is a must to invoke a novel drug.

Drug discovery and development is expensive and time-consuming since it consists of many steps that start with target and lead discovery and end with human clinical trials. The estimation is that about 10-15 years are needed to present a new drug to the market with a cost of 1-1.5 billion dollars (Figure 1), (Karaman 2014 a,b). During the recent few decades, considerable attention has been focused on improving the pharmacokinetics of existing marketed drugs, thus providing new organic entities capable of providing more efficiency with fewer drawbacks than their corresponding parent drugs. Among the approaches that can fulfill the requirements for invoking therapeutics with optimum absorption, distribution, metabolism, and excretion (ADME) properties is the prodrug approach.

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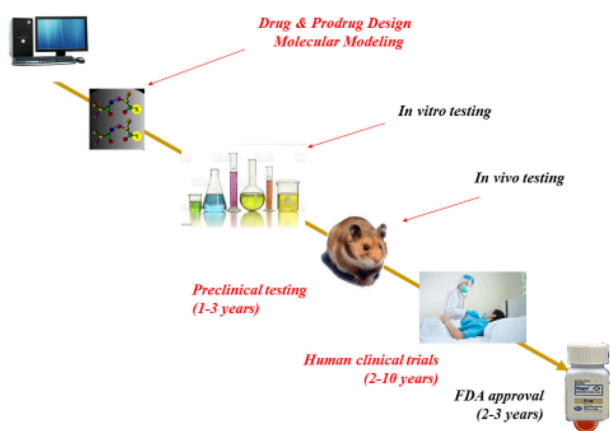


Figure 1. A diagram illustrating the different stages in drug and prodrug development.

This approach is considered a well-established strategy with a high potential of success in obtaining organic moieties having a vast efficacy and negligible toxicity.

It is about a tenth of all worldwide marketed drugs are listed as prodrugs, and in the recent ten years their percentage was significantly increased and their share of all approved small molecular weight medicines reached 30%, and this high percentage signifies the great success of this approach. A prodrug is a chemically modified inactive agent consisting of a non-toxic promoiety and pharmacologically active moiety which upon exposure to a physiologic environment liberates the pharmacologically active parent drug to elicit its therapeutic benefits (Figure 2). Prodrugs are designed to undergo interconversion in physiologic environments via enzyme catalysis

or chemical reactions. In both cases, the prodrug interconversion rate is not controlled by the designer chemist but by the abundance of certain enzymes in the route of administration. Generally, the yield of interconversion by enzymes is less than 50% and could be varied among persons with different ethnicity

Among the great number of prodrugs exist in the market are the ant rheumatic agent oxindole succinate, the anti-inflammatory drugs valdecoxib, prednisolone, and fluocinolone acetonide, the anti-glaucoma agent dipivefrin, the anti-convulsant agent progabide, the antiviral agent valacyclovir, the analgesic buprenorphine decanoate, fluphenazine decanoate to treat chronic schizophrenia, naltrexone ester prodrugs for narcotic dependence, nalbuphine ester as analgesic, and mestranol for birth control.

The classical prodrug approach by which the interconversion of the prodrug is achieved via enzyme catalysis has scored a significant success in reducing toxicity and increasing the bioavailability of many drugs. On the other hand, prodrugs designed to release the parent active drug through inter or intramolecular reaction without enzyme catalysis is a more advantageous approach since it lacks the intra-individual variability caused by the metabolic enzymes.

In this editorial, we discuss a modern approach that implies the design of prodrugs that interconvert to their corresponding parent drugs through an intramolecular process. In this approach, molecular orbital and molecular mechanics methods are used to estimate reaction rates which then are correlated with experimental rate values. In this approach, there is no need for an enzyme to catalyze the process, and the cleavage rate of the prodrug to its parent drug is solely determined on the rate-limiting step of the process which is entirely dependent on the nature of the prodrug's promoiety.

For several decades, the extraordinary efficiency of enzymes has been modeled by several well-known chemists and biochemists. Menger, Bruice, Kirby, Bender, and Jencks have assembled enzyme model devices that are capable

of obtaining rates similar to that observed with enzyme-catalyzed reactions. Striking examples of such devices are those invoked by Menger, Kirby, and Bruice in which the extraordinary rate acceleration is due to covalently enforced proximity. For more than six decades, computational methods have been utilized by inorganic, organic, organometallic, and pharmaceutical chemists alike for predicting the physical, chemical, and molecular properties of compounds. Molecular orbital methods such as DFT, a semi-empirical and ab initio, and molecular mechanics methods have proven to be successful tools for the prediction of thermodynamic and kinetic parameters for biological moieties that have pharmaceutical / medicinal interest; drugs and prodrugs (Karaman 2011).

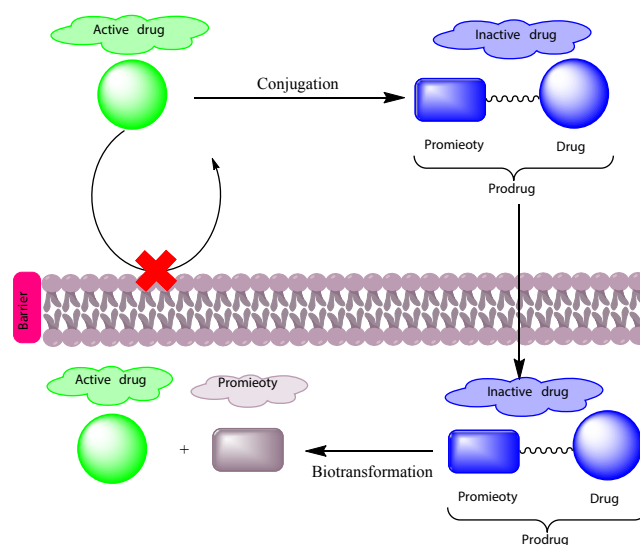


Figure 2: A diagram showing the prodrug concept.

Aiming to design novel prodrugs for commonly used drugs that suffer from reduced bioavailability or/ and bitter sensation we have used DFT and molecular mechanics methods to invoke the mechanisms and assign the factors determining the reaction rates in several intramolecular processes. Among these intramolecular reactions are: (1) cyclization reactions of di-carboxylic semi-esters by Bruice and Pandit, (2) lactonization of hydroxy-acids by Cohen and

Milstein and Menger, (3) proton transfer between two oxygen's in Kirby's acetals and proton transfer between nitrogen and oxygen in Kirby's carboxylic amines, (4) proton transfer between two oxygens in rigid carboxylic amides by Menger et al. (5) proton transfer between two oxygens in N- alkylmaleamic acids by Kirby. The information gained from these studies was utilized to design an efficient chemical entity to be exploited as a prodrug promoiety having the potential to release the parent drug in a programmable manner. For instance, unraveling the proton transfer mechanism of Kirby's acetals has resulted in the design of azanucleosides' prodrugs for the treatment of myelodysplastic syndromes, where the prodrug promoiety is linked to the hydroxyl group of the nucleoside.

Furthermore, paracetamol prodrugs lacking the bitter sensation of the parent drug, paracetamol, have been through linking the hydroxyl phenolic group to a linker, thus inhibiting any binding with the bitter taste receptors. A variety of different linkers were also studied for the design of several prodrugs including the anticonvulsant agent gabapentin, the antihypertensive agent, atenolol, the anti-Parkinson's agent dopamine, the anti-viral agent acyclovir, and the anti-malarial agent, atovaquone, the anti-bleeding agent, tranexamic acid, and the antibacterial agents, amoxicillin, and cephalexin.

This novel approach which is relatively fast and with minimum cost can provide new prodrugs with increased bioavailability, reduced bitter sensation, and enhanced dissolution and membrane penetration (Haddad et al. 2018, Karaman 2014 c).

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