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REVIEW: PRODRUG CONCEPT IN DRUG DESIGN

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REVIEW: PRODRUG CONCEPT IN DRUG DESIGN

Abstract

In the world of drug discovery and development, prodrugs have become an established tool for improving physicochemical, biopharmaceutical or pharmacokinetic properties of pharmacologically active agents. Prodrugs are bio reversible derivatives of drug molecules that undergo an enzymatic and/or chemical transformation in vivo to release the active parent drug, which can then exert the desired pharmacological effect. The basic aim of prodrug design is to overcome undesirable drug properties, such as low solubility in water or lipid membranes, low target selectivity, chemical instability, undesirable taste, irritation or pain after local administration, presystolic metabolism and toxicity. In fact, about 10% of the drugs approved worldwide can be classified as prodrugs. Although the development of a prodrug can be very challenging, the prodrug approach represents a feasible way to improve the undesirable properties of investigational drugs or drugs already on the market. In this article, the concepts of prodrug and the classifications of prodrugs will be offered. Furthermore, this article describes the basic functional groups that are amenable to prodrug design and highlights the major applications of the prodrug strategy.

Key words: Prodrug, Derivatives of Drug, Drug–promoiety, Antiviral, Anticancer.

الملخص:

في عالم اكتشاف وتطوير الأدوية وأصبحت الأدوية الأولية والتي تعرف بالأدوية المساعدة أداة تستخدم لتحسين الخصائص الفيزيائية و البيولوجية والدوائية للعناصر النشطة دوائيا. الأدوية الأولية هي مشتقات قابلة للتغيير مرة أخرى إلى النموذج الكيميائية النشطة بيولوجيا من جزيئات الدواء الأصلية تحت التأثيرات الأنزيمية و / أو التحولات الكيميائية في الجسم الحي للإفراج عن دواء الأساسي النشط، والتي يمكن بعد ممارسة التأثير الدوائي المطلوب. الهدف الأساسي من تصميم دواء أولي مساعد هو التغلب على خصائص الدواء الأساسي الغير مرغوب فيها، مثل الذوبان المنخفضة في الأغشية المائية أو الدهنية، وانخفاض الانتقائية ،وعدم الاستقرار الكيميائي، وبعض الأعراض الجانبية الغير مرعوب فيها للدواء الأساسي. في الحقيقة،حوالي 10٪ من الأدوية المعتمدة في جميع أنحاء العالم يمكن أن تصنف على أنها أدوية أولية. على الرغم من أن تطوير دواء مساعد يمكن أن تكون صعبة للغاية، في هذه المقالة، سيتم تقديم مفهوم الدواء الأولي وتصنيفات الأدوية الأولية. وعلاوة على ذلك، توضح هذه المقالة المجموعات الوظيفية الأساسية التي هي قابلة لتصميم الأدوية المساعد ويسلط الضوء على التطبيقات الرئيسية لإستراتيجية الأدوية الأولية المساعدة.

1. Introduction

Early history of prodrug research:Adrien Albert has first introduced the enunciation “pro-drug” in 1958 (Albert, 1958).[1] A few decades later, he apologized for having invented such an inaccurate term, because “predrug” would have been a more descriptive term. However, by that time, the original version was used too widely to be changed.Nonetheless, the prodrug concept has been invented long before Albert’s publication.[2]The first compound considered as a prodrug was acetanilide, introduced (under the name of Antifebrin) into the medical practice byCahn and Hepp in 1867 as an antipyretic agent. In the body, acetanilide is hydroxylated (aromatic hydroxylation) to biologically active acetaminophen (paracetamol), the compound endowed with both antipyretic and analgesic activity.[3] Acetaminophen can be also formed in the process of O-DE alkylation of another analgesic drug – phenacetin (acetophenetidin), introduced into clinical use in 1887 by von Mering. Acetanilide and phenacetin were not originally designed as prodrugs, but their prodrug nature was de-termined later on. Another example of a historical prodrug is aspirin (acetylsalicylic acid), synthesized in 1897 by Felix Hoffman (Bayer, Germany), and introduced into medicine by Dreser in 1899.[4]However,the prodrug concept was intentionally used for the first time in the middle of the 20th century by the Parke-Davis company during studies on modification of chloramphenicol structure in order to improve the antibiotic’s bitter taste and poor solubility in water. [5]

Purpose of design prodrugs: prodrug therapy provides an alternative approach to design less reactive and less cytotoxic form of a marketable drug.[6] Conventional prodrug design aims to overcome undesirable drug molecules properties : (i) pharmaceutical problems such as poor solubility, insufficient chemical stability, unacceptable taste or odor, and irritation or pain; (ii) pharmacokinetic problems such as insufficient oral absorption, inadequate blood-brain barrier permeability, marked presystemic metabolism, and toxicity; and (iii) pharmacodynamics problems such as low therapeutic index and lack of selectivity at the site of action. Therefore, the major objective of prodrug design is to temporarily alter the physicochemical properties of drugs to accomplish modification of drug pharmacokinetics, prolongation of action, reduce toxicities and side effects, increased selectivity, and resolve formulation challenges.[7]

2. Prodrug concepts

The term of “pro-drug”or "proagent" was first introduced in 1958 by Adrien Albert.[1]In general, prodrugs are convinced forms of active drugs that are designed to be activated to produce the active parent drug after an enzymatic or chemical reaction once they have been administered into the body (Fig.1).[2] In simplified terms, the drug–promoiety is the prodrug that is typically pharmacologically inactive.[8]In most cases, prodrugs are simple chemical derivatives that require only one to two chemical or enzymatic transformation steps to yield the active parent drug. In broad terms, prodrugs are derivatives of active drug moieties, designed to undergo conversion in the body and to overcome undesirable drug properties, such as low solubility in water or lipid membranes, low target selectivity, chemical instability, undesirable taste, irritation or pain after local administration, systemic metabolism and toxicity, thereby releasing the active parent drug.[9]In fact, ~10% of the globally marketed medications are prodrugs, 20% of all small molecular medicines approved between 2000 and 2008 were prodrugs, and when focusing on 2008. Nowadays, it emerges that over 30% of drugs approved were prodrugs.[8,10]The concept of prodrugs in the late 1950s, such compounds have also been called latentiated drugs, is a commonly employed technique for new drug development that often results in an enhancement of the therapeutic utility of a drug,

"bioreversible derivatives," and "congeners," but "prodrug" is now the most commonly accepted term. [11]

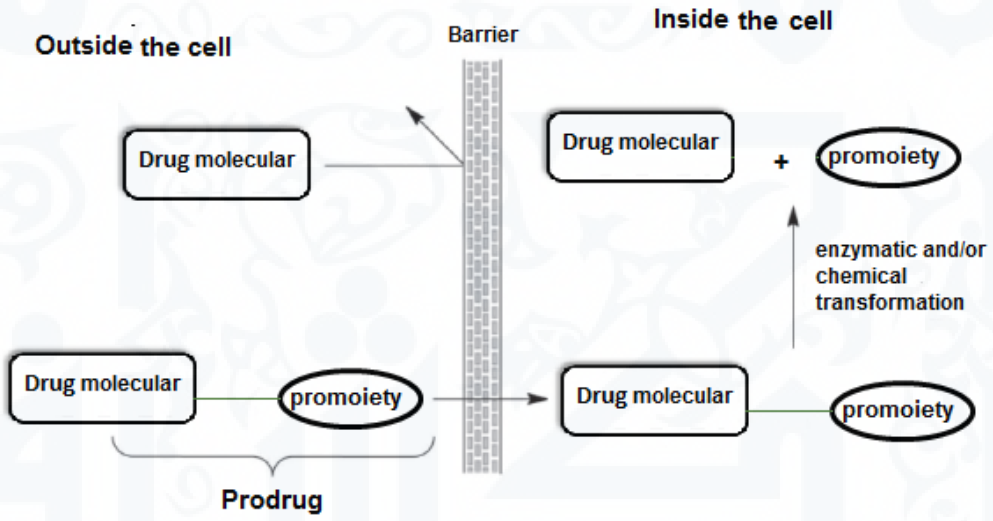

Figure 1: A simplified illustration of prodrug concept.

Generally, prodrug approach has been used to overcome the limitations arising due to various undesirable drug properties to optimize drug properties such as absorption, distribution, metabolism, and excretion (ADME), because these properties can cause considerable problems in subsequent drug development.[2] Moreover, the prodrug strategy has been used to increase the selectivity of drugs for their intended target.[12]the major applications of the prodrug strategy, including the ability to improve oral absorption and aqueous solubility, increase lipophilicity, enhance active transport, as well as achieve site-selective delivery. Special emphasis is given to the role of the prodrug concept in the design of new anticancer therapies, including antibody-directed enzyme prodrug therapy and gene-directed enzyme prodrug therapy.[13]

3. Classification of prodrugs

There are potentially many methods of classifying prodrugs. These could include those:

1. Based on therapeutic categories; for example, anticancer prodrugs, antiviral prodrugs, antibacterial prodrugs, no steroidal anti-inflammatory prodrugs, cardiovascular prodrugs, etc.2.Based on the categories of chemical linkages or moiety/carriers that attach to the active drug classified into two groups of prodrugs . **Fist group**, carrier linked pro-drugs where the active molecule (the drug) is temporary linked to a carrier (also known asa promoiety) through a bio reversible covalent linkage. Once in the body, the carrier-linked prodrug undergoes biotransformation, releasing the parent drug and the carrier. Ideally, the carrier should be no immunogenic, easy to synthesize at a low cost, stable under the conditions of prodrug administration, and undergo biodegradation to nonnative metabolites.[10,14] In so-called co-drugs (mutual prodrugs, multiple prodrugs), a prodrug is formed from two pharmacologically active agents coupled together into a single molecule, and act as promoieties of each other. Examples of co-drugs include sulfa pyridine – 5-aminosalicylic acid, indomethacin – paracetamol, L-DOPA– enthacapone, gabapentin – pregabalin, 5-

fluorouracil – cytarabine, 5-fluorouracil – dexamethasone triamcinolone, ampicillin – sulbactram, sulfamethoxazole – nalidixic acid.[15] The major groups of carrier-linked prodrugs are esters and amides; other groups include phosphates, carbamates, carbonates, oximes, imines and *N*-Mannich bases (Fig.2).

2. Second groups, Bioprecursor pro-drugs, that do not contain a promoiety but result from a molecular modification of the active compound itself, is transformed metabolically or chemically by hydration (e.g., lactones such as some statins), oxidation (e.g., dexpanthenol, nabumetone) or reduction (e.g., sulindac, platinum(IV) complexes) to the active agent.[14]

3. Based on the site of conversion into the pharmacologically active agent, the prodrugs can be additionally classified into two groups: Type **I** – metabolized intracellularly. Type IA prodrugs (e.g., acyclovir, cyclophosphamide, 5-fluorouracil, L-DOPA, zidovudine) are metabolized at the cellular targets of their therapeutic actions. Type IB prodrugs (e.g., carbamazepine, captopril, molsidomine, primidone) are converted to parent drugs by metabolic tissues, namely by the liver.[13]

Type **II** – metabolized extracellularly. Type IIA – in the milieu of the gastrointestinal fluid (e.g., loperamide oxide, sulfsalazine). Type IIB – within the circulatory system and/or other extracellular fluid compartments (e.g., aspirin, bambuterol, fosphenytoin). Type IIC – near or inside therapeutic target/cells (ADEPT, GDEPT).

4. Some of the prodrugs, called mixed-type[17] or co-drugs prodrugs, consist of two pharmacologically active drugs that are coupled together in a single molecule so that each drug acts as a promoiety for the other.[18]

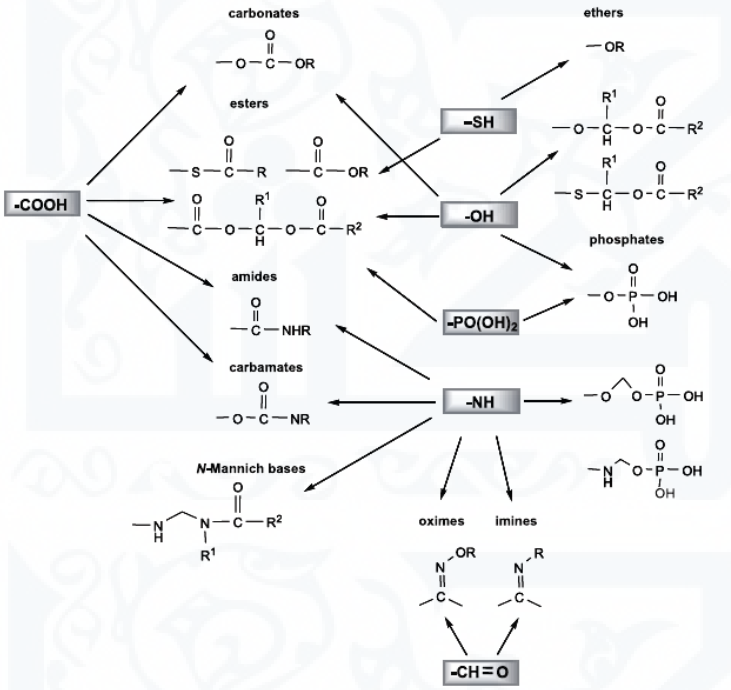

Figure2: functional groups utilized in prodrug design.

4. Some Examples of Prodrugs:

1. Fosamprenavir (Telzir®); functional group is phosphate ester Bioconverted by alkaline phosphatases to amprenavir, a HIV protease inhibitor (Antiviral, HIV infections).[2,8,13]

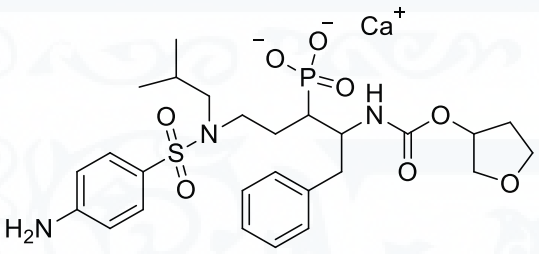

Figure 3: Structure of Fosamprenavir.

2. Estramustine phosphate (Emcyt®); functional group is phosphateester of estramustine. Bioconverted by alkaline phosphatasesto estramustine, which is further transformedinto estromustine (Antimitotic).[8,13]

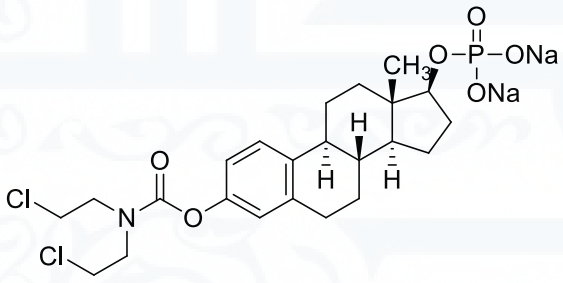

Figure 4: Structure of Estramustine.

3. Fludarabine phosphate (Fludara®); functional group is phosphate ester of fludarabine. Bioconverted by alkaline phosphatases to fludarabine. Fludarabine undergoes transformation to 2-fluoro-9-β-D-arabinofuranosyladenine, which after uptake into cells is converted to active 2-fluoro-9-β-D-arabinofuranosyladenine 5'-triphosphate (Antiviral).[8,13]

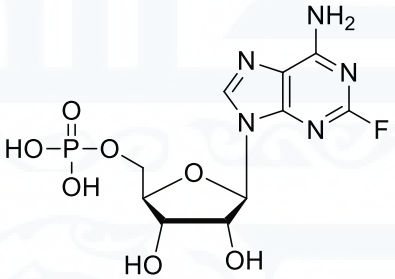

Figure 5: Structure of Fludarabine phosphate.

4. Prednisolone phosphate; functional group is phosphate ester ofprednisolone (Inflamase®, Orapred ODT®). Bioconverted by alkaline phosphatasesto prednisolone (Anti-inflammatory, antiallergic).[8,13]

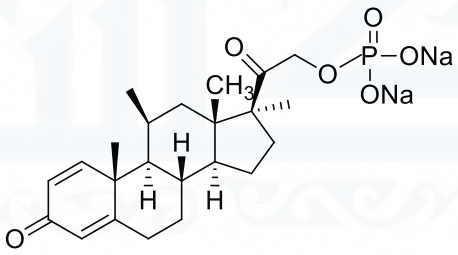

Figure 5: Structure of Prednisolone phosphate.

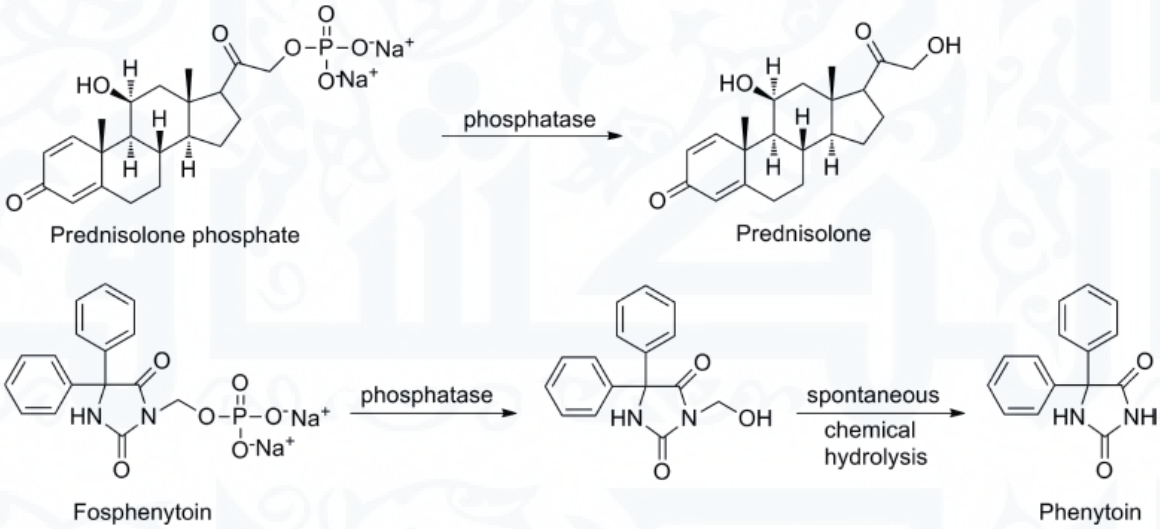

Figure 6 : Bioactivation of phosphate prodrugs of prednisolone and phenytoin.

5. Enalapril (Innovace®, Vasotec®, Renitc®), functional group is monoethylester of enalaprilat. In the liver bioconverted by esterases to enalaprilat, an angiotensin-converting enzymeinhibitor. Used in the treatment of hypertension, ischemic heart disease.[8]

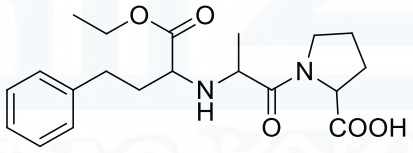

Figure 7 : Structure of Enalapril.

6. Adefovir dipivoxil (Viread®), functional group isbis-(pivaloyloxymethyl) ester of adenofovir. Bioconverted by esterases and phosphodiesterases to tenofovir. In lymphocytes T tenofovir in converted to activemetabolite, tenofovir diphosphate, an inhibitorof HIV virus reverse transcriptase (Anti-HIV).[8,13]

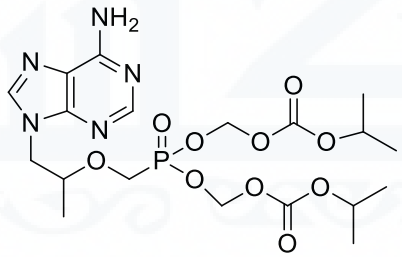

Figure 8 : Structure of Adefovir dipivoxil.

7. Famciclovir (Famvir®), functional group is dimethyl ester of penciclovir. Bioconverted by esterases and aldehydeoxidase to penciclovir used as inhibitor of *Herpes* DNA synthesis (Antiviral).[8,13]

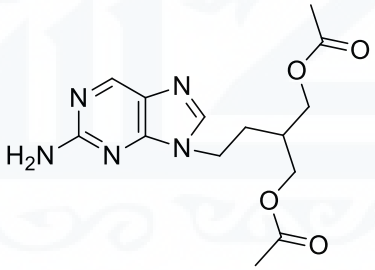

Figure 9 : Structure of Famciclovir.

8. Oseltamivir (Tamiflu®), functional group is ethyl ester of oseltamivir carboxylate. Bioconverted by carboxylesterase-1 to oseltamivir carboxylate – selective inhibitor of viral neuroamidase glycoprotein type A and B. Antiviral (anti-influenza).[8,13]

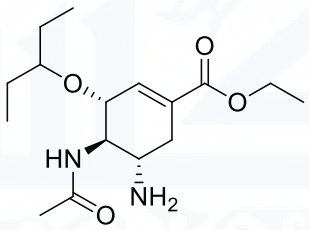

Figure 9 : Structure of Famciclovir.

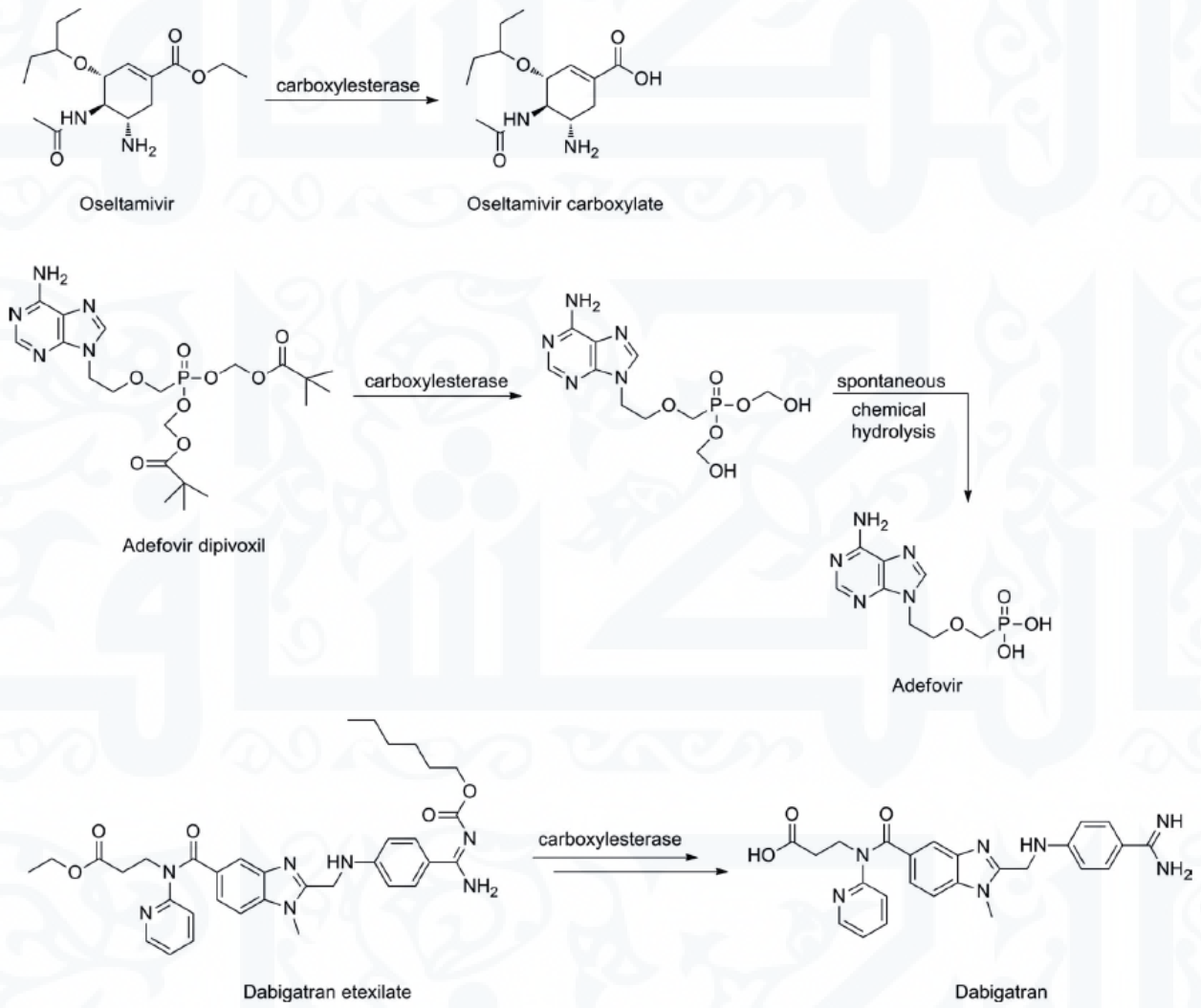

Figure 10: Bioactivation of ester prodrugs oseltamivir, adefovir dipivoxil, and dabigatran etexilate.

9. Capecitabine (Xeloda), functional group is Carbamates. Bio converted by carboxyl esterase – 1 and 2to 5-fluorouracil (5-FU) a relatively selective activation in and delivery to tumors in the body (anticancer).[7,19,20]

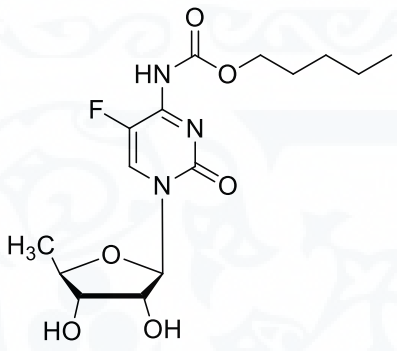

Figure 11 : Structure of Capecitabine.

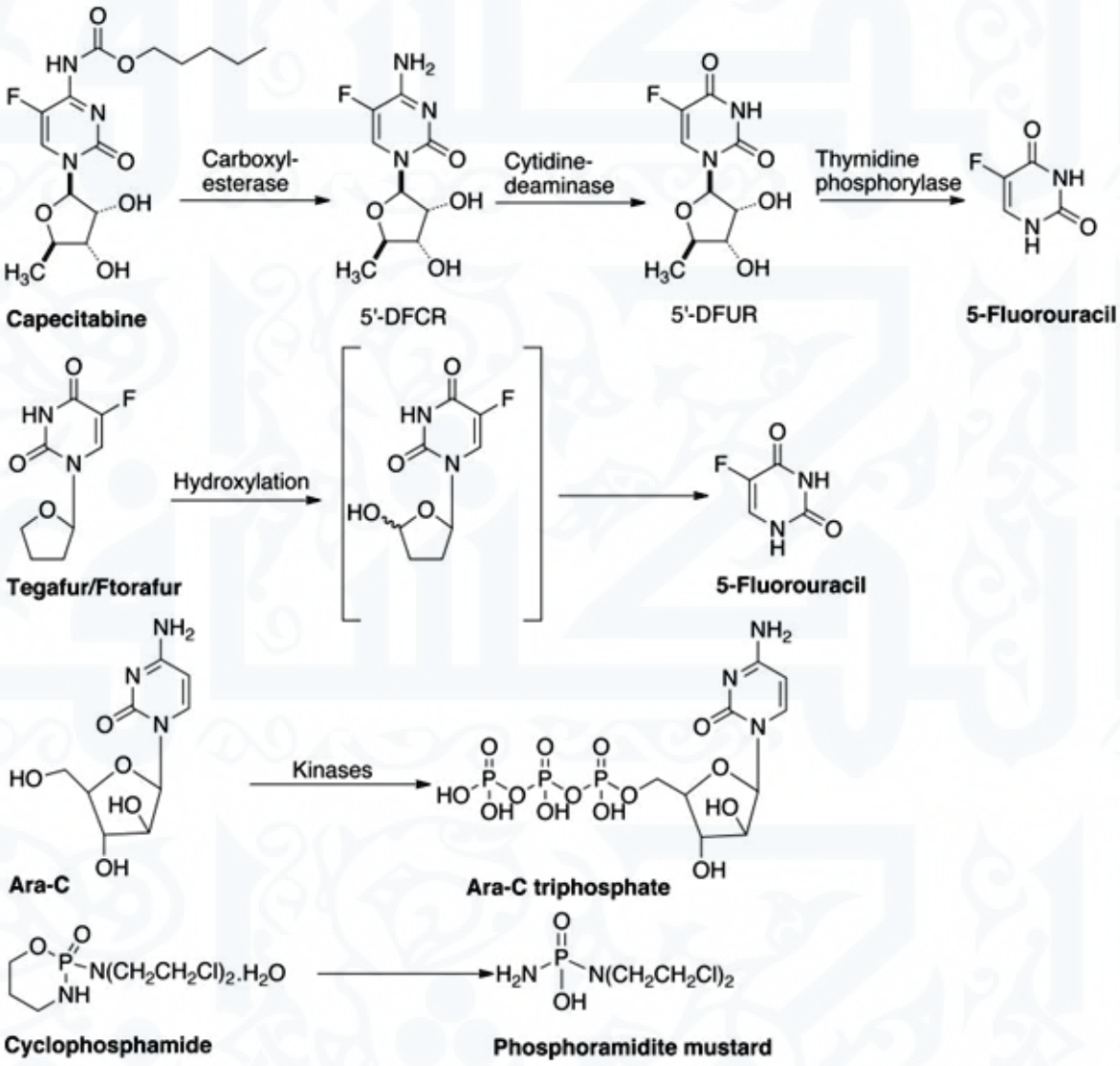

Figure 12: Bioactivation of Carbamates prodrugs oseltamivir Capecitabine.

5. Conclusion

In this review, we introduced the early history of prodrug research and the purpose of design prodrugs. Furthermore, we explained the prodrug concept, the classification of prodrugs and the functional groups and the bio converted of some prodrugs. Nowadays, the prodrug approach has been widely utilized to overcome the undesirable pharmacokinetic properties and to optimize therapeutic efficacy. The prodrug strategy has been used to increase the selectivity of drugs for their intended target. The major applications of the prodrug strategy, including the ability to improve oral absorption and aqueous solubility, increase lipophilicity, enhance active transport, as well as achieve site-selective delivery. The prodrug approach has been used to overcome the limitations arising due to various undesirable drug properties to optimize clinical drug applications. The prodrug strategy has been used to enhance the therapeutic efficacy and/or reduce the adverse effects of the pharmacologically active agents via different mechanisms, including increased solubility, stability, improved permeability and

bioavailability, prolonged biological half-life time, and tissue-targeted delivery also it used to increase the selectivity of drugs for their intended target. As we noted previously, the major applications of the prodrug strategy, including the ability to improve oral absorption and aqueous solubility, increase lipophilicity, enhance active transport, as well as achieve site-selective delivery. Collectively, the emphasis is given to the role of the prodrug concept in the design of new drugs such as antiviral and anticancer therapies.

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