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Review: Prodrug Concept in Drug Design

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Abstract

In the world of drug discovery and development, prodrugs have become a powerful method for improving biopharmaceutical, physicochemical or pharmacokinetic properties of pharmacologically active agents. The purpose of this review is to provide some types of prodrugs which are bioreversible 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 target of prodrug design is to beat the undesirable drug properties, such as low target selectivity, low solubility in water or lipid membranes, chemical instability, irritation or pain after local administration, presystemic toxicity and metabolism. In this article, we focused on to describe the basic functional groups that are amenable to prodrug design and highlight the major applications of the prodrug strategy. Furthermore, the concepts of prodrug and the classifications of prodrugs will be offered in this article.

Keywords: *Prodrug, derivatives of drug, drug-promoiety, antiviral, anticancer*

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INTRODUCTION

Early History of Prodrug Research

Albert has first introduced the enunciation "pro-drug" in 1958 [1]. Actually, "predrug" is such an inaccurate term. However, the original version was used too widely to be changed [1]. This concept has been used before Albert's publication [2]. Acetanilide which was introduced (under the name of Antifebrin) into the medical practice by Cahn and Hepp in 1867 as an antipyretic agent was the first compound considered as a prodrug [3]. In 1887, von Mering introduced phenacetin (acetophenetidin) as analgesic drug. In 1897, Felix Hoffman designed aspirin (acetylsalicylic acid), which was introduced into medicine by Dreser, in 1899 [4]. However, the prodrug concept was used for the first time in the middle of the 20th century by the Parke-Davis company during studies [5].

PRODRUG CONCEPTS

In general, prodrugs are derivatives of active drug moieties, designed to undergo conversion in the body and to overcome undesirable drug properties. The chemical modifications of the drugs 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 (Figure 1) [6].

CLASSIFICATION OF PRODRUGS

There are many methods of classifying prodrugs:

Based on Therapeutic

Cardiovascular prodrugs, anticancer prodrugs, antiviral prodrugs, antibacterial prodrugs, nonsteroidal anti-inflammatory prodrugs, etc. are some of the examples.

Based on the Chemical Linkages

Chemical linkages or moiety/carriers that attach to the active drug are classified into two groups of prodrugs:

Fist Group: These are the carrier linked pro-drugs where the active molecule (the drug) is temporary linked to a carrier (also known as a promoiety) through a bioreversible covalent linkage. Once in the body, the carrier-linked prodrug undergoes biotransformation, releasing the parent drug and the carrier. Ideally, the carrier should be nonimmunogenic, easy to synthesize at a low cost, stable under the conditions of prodrug administration, and undergo biodegradation to nonactive metabolites [7, 8]. In the 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 sulfapyridine-5-aminosalicylic acid, indomethacin-paracetamol, L-DOPA-enthacapone, gabapentin-pregabalin, 5-fluorouracil-cytarabine, 5-fluorouracil-dexamethasone triamcinolone, ampicilin-sulbactram, and sulfamethoxazole-nalidixic acid [9]. The major groups of carrier-linked prodrugs are esters and amides; other groups include phosphates, carbamates, carbonates, oximes, imines and *N*-Mannich bases (Figure 2).

Second Groups: Bioprecursor pro-drugs that result from a molecular modification of the active compound itself and do not contain a promoiety is transformed metabolically or chemically by hydration such as oxidation (e.g., dexpanthenol), or reduction (e.g., sulindac, platinum(IV) complexes) to the active agent [8].

Based on the Site of Conversion

Based on the site of conversion into the pharmacologically active agent, these can be classified into two groups:

Type 1: Intracellularly metabolized at the cellular targets of their therapeutic actions; such as, acyclovir, cyclophosphamide, 5-fluorouracil, L-DOPA, zidovudine. The others are converted to parent drugs by metabolic tissues, namely by the liver; such as carbamazepine, captopril, molsidomine, and primidone [10].

Type 2: Metabolized extracellularly. First, prodrug that metabolized in the milieu of the gastrointestinal fluid such as loperamide oxide, sulfsalazine. Second, prodrug within the circulatory system and/or other extracellular fluid compartments such as aspirin, bambuterol, fosphenytoin. Finally, prodrug metabolized near or inside therapeutic target/cells (ADEPT, GDEPT).

Mixed-Type Prodrugs

The prodrugs that are called mixed-type 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 [11, 12].

SOME EXAMPLES OF PRODRUGS

Fosamprenavir (Telzir®) (Figure 3)

Functional group is phosphate ester bioconverted by alkaline phosphatases to amprenavir, a HIV protease inhibitor (Antiviral, HIV infections) [2, 10, 13].

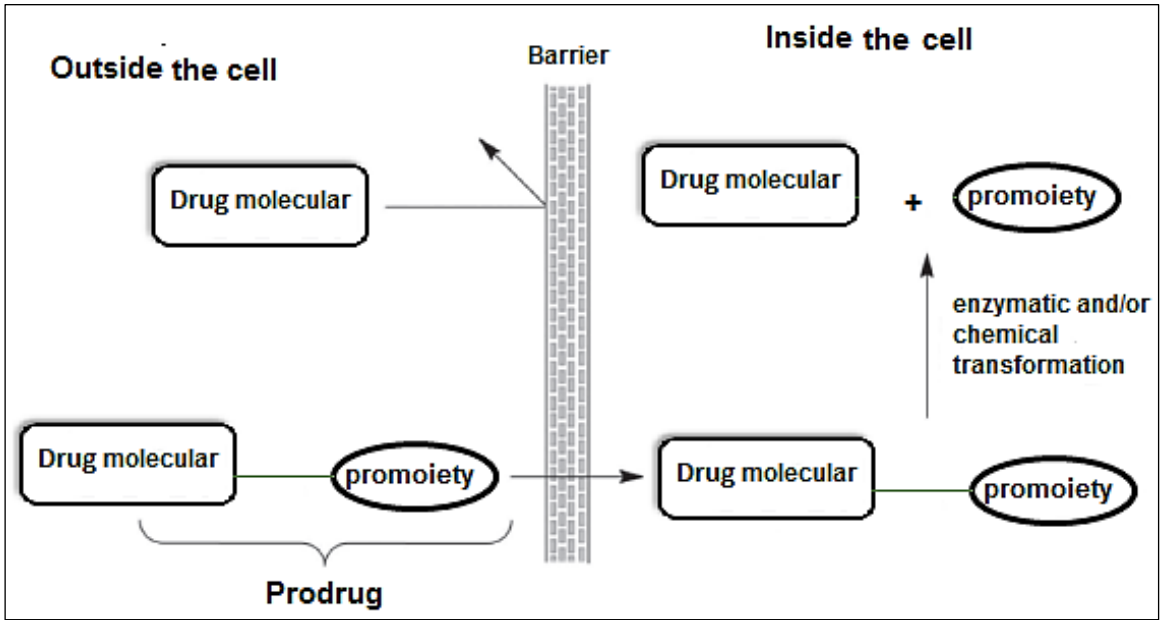


Fig. 1: *A Simplified Illustration of Prodrug Concept.*

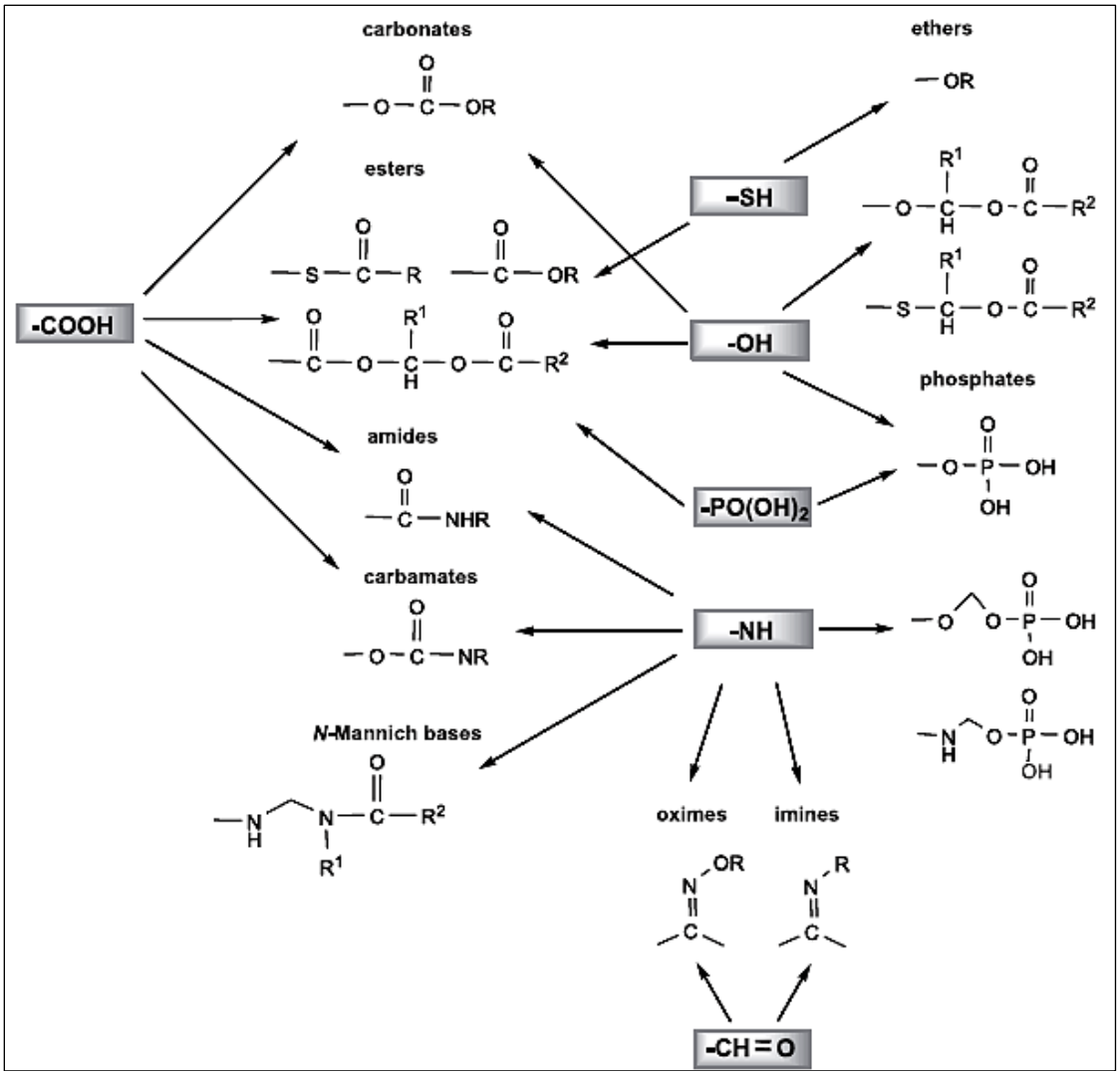


Fig. 2: *Functional Groups Utilized in Prodrug Design.*

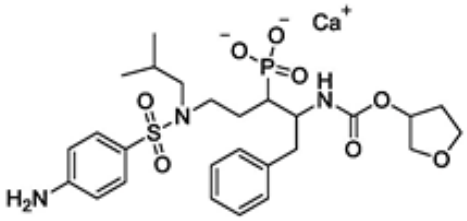


Fig. 3: *Structure of Fosamprenavir.*

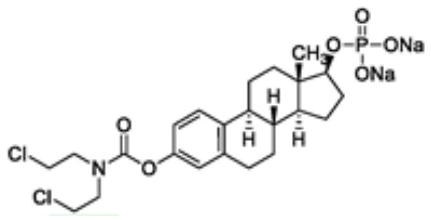


Fig. 4: *Structure of Estramustine.*

Estramustine Phosphate (Emcyt®) (Figure 4)

Functional group is phosphate ester of estramustine. Bioconverted by alkaline phosphatases to estramustine, which is further transformed into estromustine (Antimitotic) [10, 13].

Fludarabine Phosphate (Fludara®) (Figure 5)

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) [10, 13].

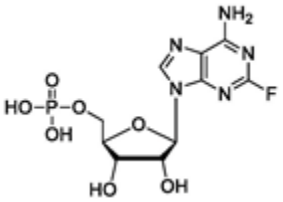


Fig. 5: *Structure of Fludarabine Phosphate.*

Prednisolone Phosphate

Functional group is phosphate ester of prednisolone (Inflamase®, Orapred ODT®) (Figure 6). Bioconverted by alkaline phosphatases to prednisolone (Anti-inflammatory, antiallergic) (Figure 7) [10, 13].

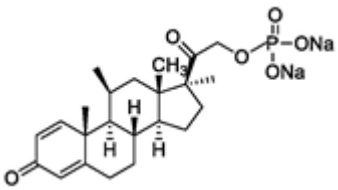


Fig. 6: *Structure of Prednisolone Phosphate.*

Enalapril (Innovace®, Vasotec®, Renitc®) (Figure 7)

Functional group is monoethylester of enalaprilat. In the liver it is bioconverted by esterases to enalaprilat, an angiotensin-converting enzyme inhibitor. Used in the treatment of hypertension, ischemic heart disease [13].

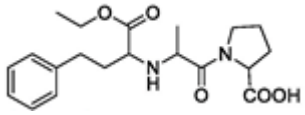


Fig. 7: *Structure of Enalapril.*

Adefovir dipivoxil (Viread®) (Figure 8)

Functional group is bis-(pivaloyloxymethyl) ester of adenofovir, bioconverted by esterases and phosphodiesterases to tenofovir. In lymphocytes, tenofovir in converted to active metabolite, tenofovir diphosphate, an inhibitor of HIV virus reverse transcriptase (Anti-HIV) [10, 13].

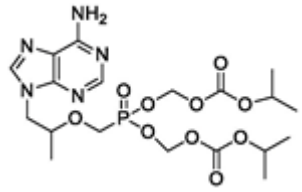
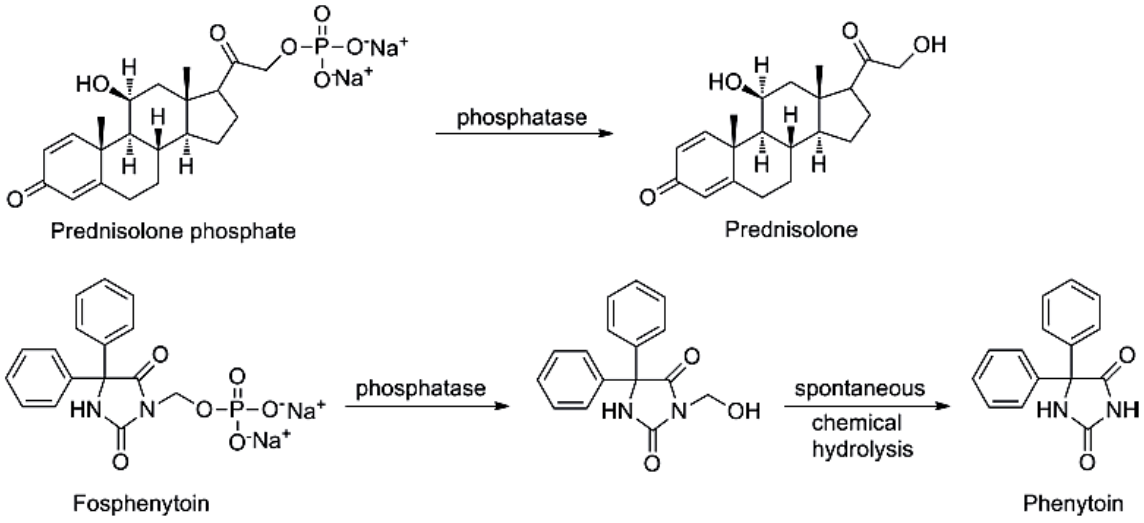


Fig. 8: *Structure of Adefovir Dipivoxil.*

Famciclovir (Famvir®) (Figure 9)

Functional group is dimethyl ester of penciclovir, bioconverted by esterases and aldehyde oxidase to penciclovir used as inhibitor of *Herpes* DNA synthesis (Antiviral) [10, 13].



Scheme 1: *Bioactivation of Phosphate Prodrugs of Prednisolone and Phenytoin.*

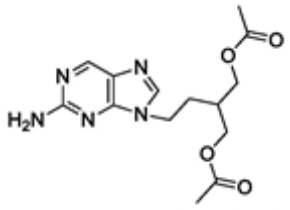


Fig. 9: *Structure of Famciclovir.*

Oseltamivir (Tamiflu®) (Figure 10)
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) [10, 13].

Capecitabine (Xeloda) (Figure 11)
Functional group is carbamates, bioconverted by carboxylesterase -1 and 2 to 5-fluorouracil (5-FU), a relatively selective activation in and delivery to tumors in the body (anticancer) [14–16].

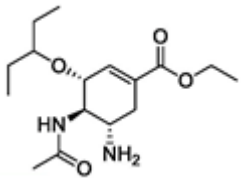


Fig. 10: *Structure of Famciclovir.*

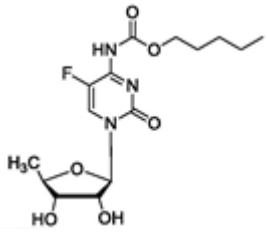
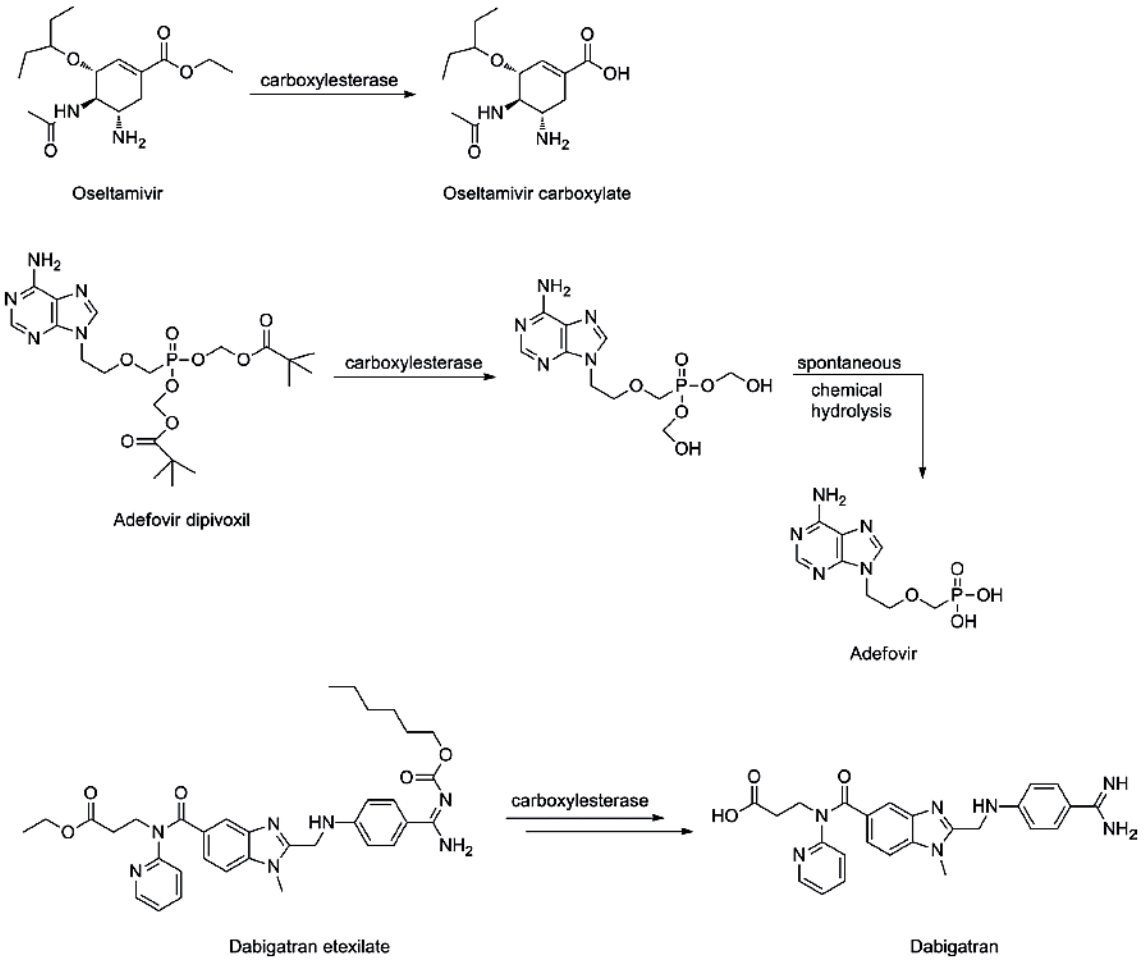
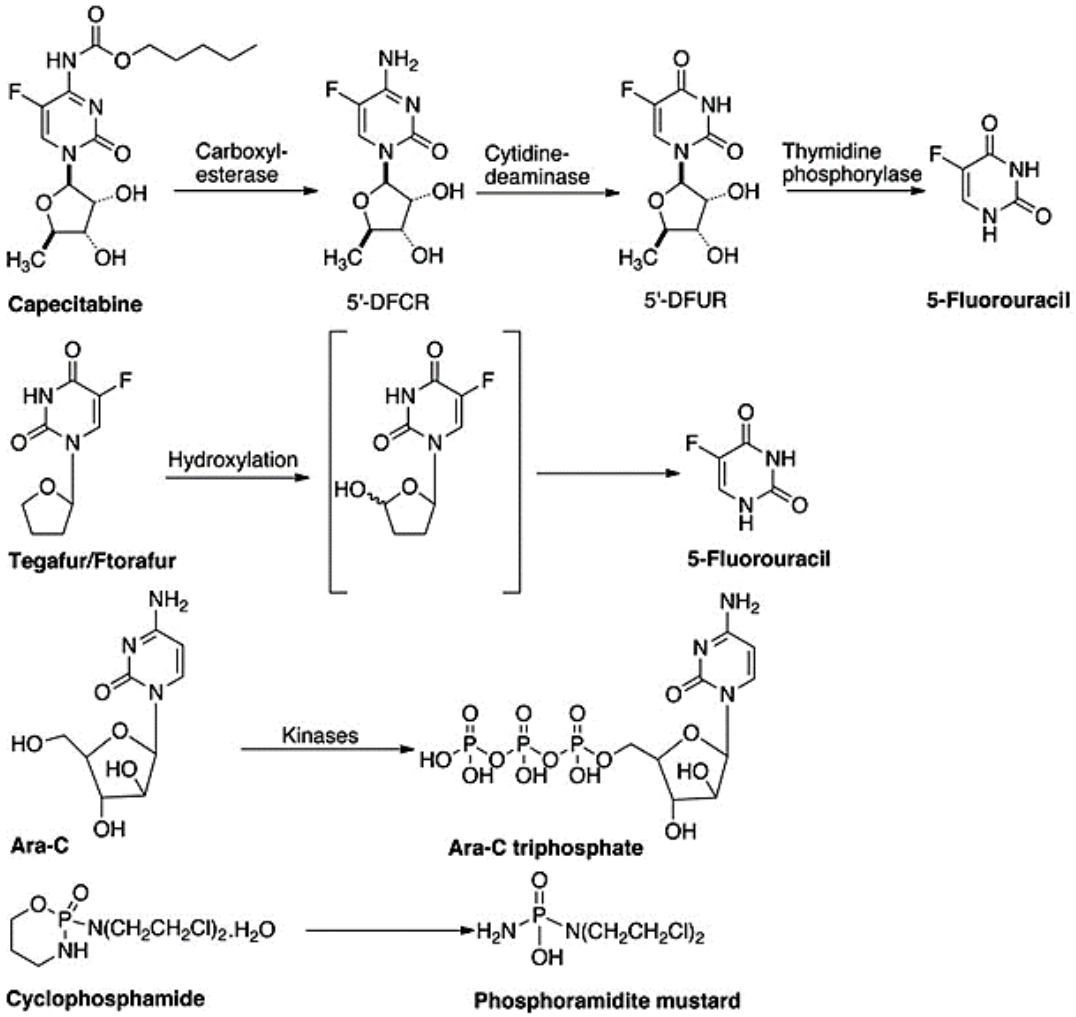


Fig. 11: *Structure of Capecitabine.*



Scheme 2: *Bioactivation of Ester Prodrugs Oseltamivir, Adefovir Dipivoxil, and Dabigatran Etexilate.*



Scheme 3: *Bioactivation of Carbamates Prodrugs Oseltamivir Capecitabine.*

CONCLUSION

In this review, we introduced a brief history of prodrug research and the purpose of designing prodrugs. Moreover, we explained the concept of prodrugs, the classification of prodrugs and the functional groups and the bioconverted of some prodrugs. Nowadays, the prodrug approach has been widely utilized to overcome the undesirable pharmacokinetic properties and to optimize therapeutic efficacy without losing the benefits of the drug molecule.

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