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Review

Prodrugs available on the Brazilian pharmaceutical market and their corresponding bioactivation pathways

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The aim of this paper was to emphasize the importance of prodrug design to therapy, by examining examples available on the Brazilian pharmaceutical market. The principles of prodrug design are briefly discussed herein. Examples of prodrugs from many important therapeutic classes are shown and their advantages relative to the drugs they are derived from are also discussed. Considering the importance of these therapeutic classes, from both therapy and economic standpoints, prodrug design is a very valuable aspect in the research of new drugs and for the pharmaceutical industry as a whole.

Uniterms: Prodrug design. Molecular modification. Drug development.

O objetivo do trabalho foi ressaltar a importância do planejamento de pró-fármacos para a terapia, por meio de exemplos disponíveis no mercado farmacêutico brasileiro. Os princípios da latenciação são sucintamente discutidos. Apresentam-se exemplos de pró-fármacos de muitas classes terapêuticas importantes e as vantagens relativas aos fármacos dos quais derivam são, também, discutidas. Considerando-se a importância dessas classes terapêuticas, tanto do aspecto terapêutico quanto do econômico, o planejamento de pró-fármacos representa aspecto de grande valor na busca de novos fármacos e na indústria farmacêutica como um todo.

Uniterms: Pró-fármacos/planejamento Fármacos/latenciação. Modificação molecular. Fármacos/desenvolvimento.

INTRODUCTION

Currently, several tools are available for researching chemical entities aimed at introducing new pharmaceuticals for use in therapy. Among the different strategies employed, molecular modification deserves special mention. This approach entails the structural alteration of a known and previously characterized lead compound. The starting molecule is called a prototype, whilst the derivatives obtained from the prototype are classified as either analogues or prodrugs, depending on the type of molecular modification executed. Molecular modification can have different aims with the main objectives being: the acquisition of substances with superior pharmaceutical properties compared to those of the prototype, the discovery of a **pharmacophoric** group, or the study of the relationship between a chemical structure of a compound and its biological activity (Korolkovas, Burckhalter, 1988; Patani, Lavoie, 1996; Wermuth, 2006).

The molecular modification strategy is widely employed in the research and development of new drugs. Considering that this strategy involves use of a compound with previously known biological activity, the biological experiments to be executed with the new derivatives consist of routine, and hence less complex, studies. Molecular modification enables the optimization of compounds that have previously been marketed and have presented pharmacokinetic or toxicity issues. Furthermore, it is important to mention that the rate of success in the acquisition of a new chemical entity is greater when the structure of a pro-

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totype with a proven biological property is used (Ettmayer *et al.*, 2004; Barreiro, Fraga, 2008).

As mentioned previously, molecular modification may give rise to compounds called prodrugs. This process is known as drug latentiation (Figure 1).

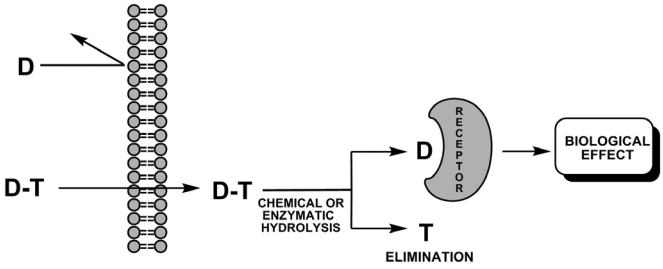

FIGURE 1 - Diagram of the latentiation process. (D: drug, T: transporter group, D-T: prodrug) Adapted from Friis and Bundgaard(1996).

Latentiation may be defined as the chemical union between a drug and a "transporter group", normally by means of a covalent labile bond, giving rise to the classical concept of a prodrug. It is a temporarily inactive compound that, once inside the organism, needs to be metabolized to attain its active form (Bundgaard, 1985; Bundgaard, 1991; Chung *et al.*, 2005; Liederer, Borchardt, 2006; Parise-Filho *et al*., 2007; Rautio *et al.,* 2008; Silva *et al*., 2005; Stella, 2004; Wermuth, 2006).

The term latentiation was first used to describe inactive compounds that required biotransformation before they could carry out their biological function (Albert, 1958; Harper, 1959). The compounds covered by this designation, known as prodrugs, are inactive by nature, and as such are not designed to function (Stella *et al*., 1985). Some long-known compounds provide examples of prodrugs, notwithstanding the fact that they were discovered before the concept of latentiation. One such example is codeine (Figure 2), isolated in the 19th Century. It was observed that this compound was converted into morphine when administered *in vivo* (Ettmayer *et al*., 2004; Santos, 2008).

In 1897, Felix Hoffmann employed the latentiation principal when he modified the structure of salicylic

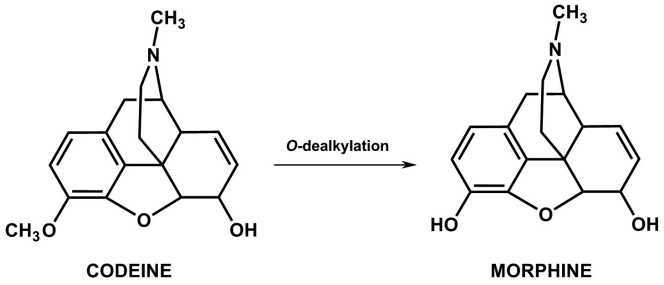

FIGURE 2 - Biotransformation of codeine, with the consequent release of morphine *in vivo*.

acid and obtained acetylsalicylic acid (Figure 3), with the aim of reducing its irritating effects on the stomach (Chung, Ferreira, 1998). However, it is known that acetylsalicylic acid acts *per se,* on cyclooxygenases 1 and 2 by means of acylation, as well as being active after the release of salicylic acid, whose properties are analogous to its derivative. It could therefore be considered a hybrid analogue-prodrug structure, like some other examples used in therapy.

It was only from the 1970s onwards that the concept emerged of designing prodrugs to modify the non-ideal physical-chemical properties of certain compounds, thus making them more efficient (Stella, Nti-Addae, 2007). Accordingly, the latentiation method has since been employed by pharmaceutical chemists in the development of pharmaceuticals because it enables the improvement of several undesirable properties of a prototype without however, altering its biological effectiveness (Han, Amidon, 2000; Wermuth, 2006).

Because it causes changes in physical-chemical properties, the latentiation method is usually employed to resolve issues pertaining to the transport of drugs within the organism, whether by increasing their rate of absorption through cellular barriers, regulating their retention time within the organism (Han, Amidon, 2000; Shan *et al.*, 1997; Wermuth, 1984) or even by directing the drug to a specific location, a situation in which they are classified as *directed drugs*. These are highly selective latent types,

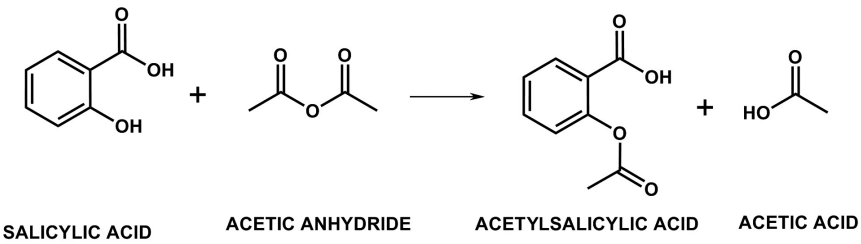

FIGURE 3 - Reaction of salicylic acid with acetic anhydride for the acquisition of acetylsalicylic acid and the release of acetic acid (the principal of latentiation).

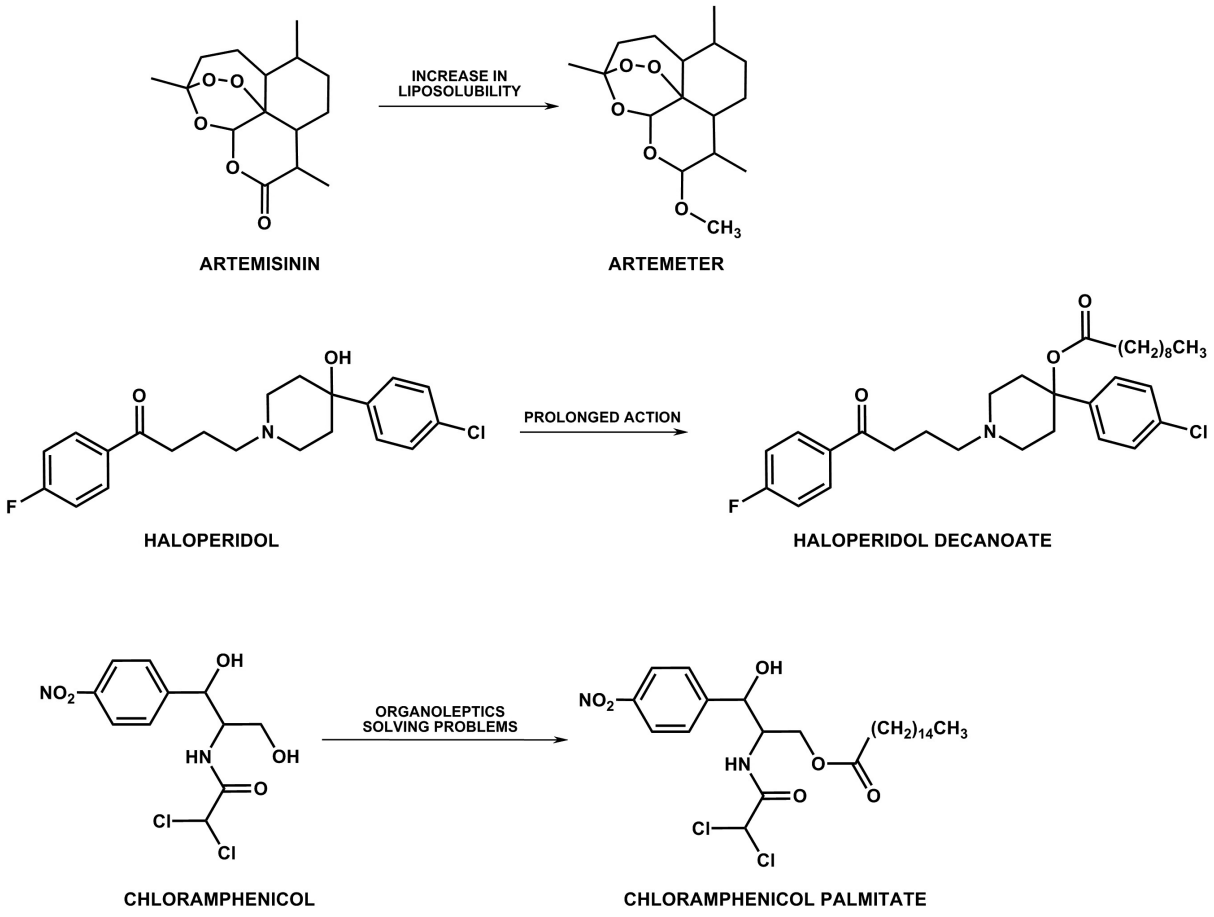

FIGURE 4 - Examples of prodrugs and their respective purposes.

and form the basis of advanced forms of drug transporters (Chung *et al.*, 2005; Silva *et al.*, 2005). Based on these facts, the first step in latentiation comprises establishing the nature of the problem the drug presents. Such problems include: (1) instability or inadequate solubility in the formulation or when in contact with gastrointestinal fluids; (2) undesirable organoleptic characteristics; (3) inadequate hydrolipophilic equilibrium to pass through biological membranes, thus leading to a reduction in the rate of absorption; (4) drug toxicity; (5) high rate of biotransformation or pre-systemic elimination; (6) low functional specificity (Blau *et al.*, 2006; Chung *et al.*, 2005; Silva *et al.*, 2005; Taylor, 1996). Consequently, the purpose of designing a prodrug is to provide solutions to all the above-mentioned problems.

The examples in Figure 4 illustrate cases in which it was possible to design prodrugs to resolve inherent issues in some drugs.

The first example shows an increase in the liposolubility of an antimalarial drug by replacing the carbonyl group with the methoxy group. In this case, the increase in liposolubility facilitates the passage of the drug through the blood-brain barrier, thus making it useful in the treatment of cerebral malaria. The next drug, haloperidol, had its hydroxyl masked by the formation of an ester bond with decanoic acid, giving a consequential increase in liposolubility. This alteration in solubility led to the acquisition of a longer-acting, intra-muscularly applied, haloperidol derivative that releases the drug gradually into the organism. In the next example, chloranfenicol was esterified, by means of its primary hydroxyl group, upon reaction with palmitic acid, also resulting in increased liposolubility. Thus, the alteration in solubility of chloramphenicol reduced the dissolution of the drug in patients' mouths, hence masking its bitter flavor (Chung *et al.*, 2005).

Latentiation as a method of developing new drugs has been attracting increasing interest (Testa, 2004). In 1985, Stella *et al*., questioned whether prodrugs presented any advantages in clinical practice. Six years later, in 1991, Hiller answered this question: 20% to 30% of drugs introduced into therapy between 1986 and 1991 were developed with the latentiation method. More recent data indicates that approximately 15% of new drugs approved during the 2001-02 period comprised prodrugs (Rautio *et al.*, 2008).

Considering the importance of molecular modification of drugs as a source for the acquisition of new compounds and given that the latentiation of drugs is an important tool for this modification, this study aimed to prove, by means of the prodrugs available for use in therapy in Brazil, the real value of this process in the introduction of new drugs into clinical medicine. This review is based on the classification proposed by Wermuth (1984), which proposes the classification of latent forms into prodrugs and directed drugs. Wermuth classified the former into the following categories: classic, bioprecursors, reciprocal and mixed. The prodrugs, in their different categories, are the main focus of this study.

PRODRUGS IN THERAPY

Bioprecursors

Bioprecursors are latent forms that require biotransformation, generally by means of oxy-reduction mechanisms, with the aim of producing an active metabolite. These are compounds without a transporter group and several examples of prodrugs available for use in therapy in Brazil are classified as bioprecursors (Ettmayer *et al.*, 2004).

Antivirals

Acyclovir, marketed under several pharmaceutical brandnames (Carneiro França, 2008), is a nucleoside analogue with an inhibiting function against the human herpes virus, including *Herpes simplex* (VHs) virus, types 1 and 2, Varicella *zoster* (VVZ) virus, *Epstein Barr* (VEB) virus and cytomegalovirus (CMV). It was discovered by triage and introduced onto the market in 1981. It represents an evolution in the treatment of herpes, as it was the first relatively safe and non-toxic drug to be used systemically (Ettmayer *et al.*, 2004; Patrick, 2005). In infected cells, the agent undergoes phosphorylation in three stages, thus generating an active triphosphate compound. Because it requires oxidative bioactivation, acyclovir is considered a bioprecursor prodrug. Figure 5 illustrates the mono-, bi- and triphosphorylation stages of acyclovir.

It is important to emphasize that acyclovir only undergoes triphosphorylation in infected cells. It more readily undergoes first step phosphorylation with viral *thymidine kinase* (100 x) than by the same enzyme in non-infected cells. Therefore, in normal cells, acyclovir is a poor substrate for cellular *thymidine kinase*, as it does not become active for these cells. This, together with the fact that selective capturing of acyclovir by infected cells occurs, explains its excellent effectiveness and low toxicity (Patrick, 2005; Steingrimsdottir *et al.*, 2000).

It should be noted that all antiviral drug nucleoside analogues, such as **gancyclovir** and **pencyclovir,** that present an open *saccharide* portion, require triphosphorylation in order to execute their antiviral function and thus are analog bioprecursors. In the same context, several antiretroviral drugs (Figure 6) such as **zidovudine, estavudine, didanosine, lamivudine, zalcitabine** (Carneiro França, 2008) and **entricitabine**, not yet available on the Brazilian market, that present a similar bioactivation mechanism,

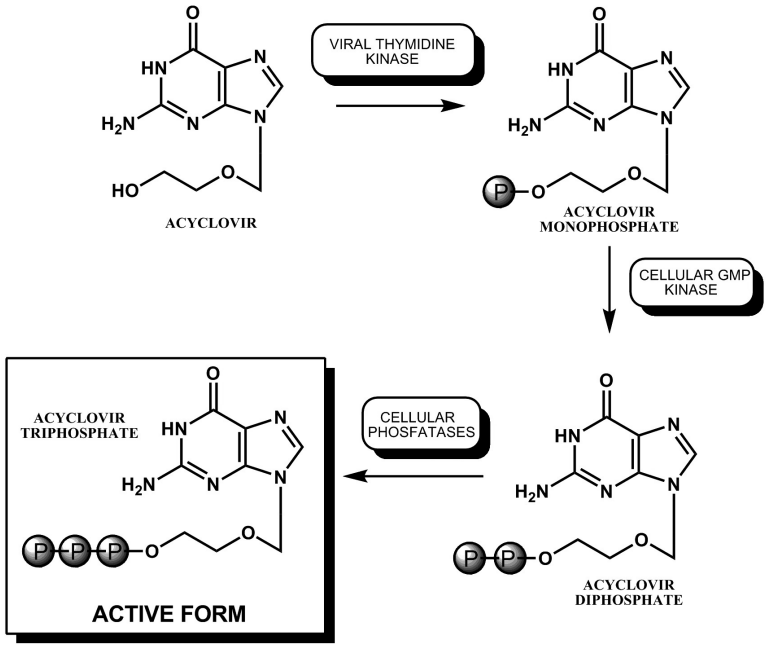

FIGURE 5 - Diagram of acyclovir bioactivation into acyclovir trisphosphate. GMP-guanosine monophosphate.

are considered bioprecursor prodrugs (De Clercq, 2002, 2004; Otto, 2004).

Antilipemic Agents

Currently, high levels of cholesterol associated with other risk factors have led to serious repercussions in the quality of life of the world's population. Thus, imminent risks regarding the development of cardiovascular diseases have aroused great interest on the part of the pharmaceutical industries, resulting in the search for new therapeutically useful agents.

Statins (Carneiro França, 2008) are hypocholesterolemic drugs discovered in the 1970s that are currently the blockbusters of the pharmaceutical industry, topping one billion dollars in sales. Statins are capable of inhibiting 3-hydroxy-3-methylglutaryl-CoA reductase (HMGCo-A reductase - HMGR), a fundamental enzyme in the cholesterol biosynthetic pathway (Figure 7). This enzyme

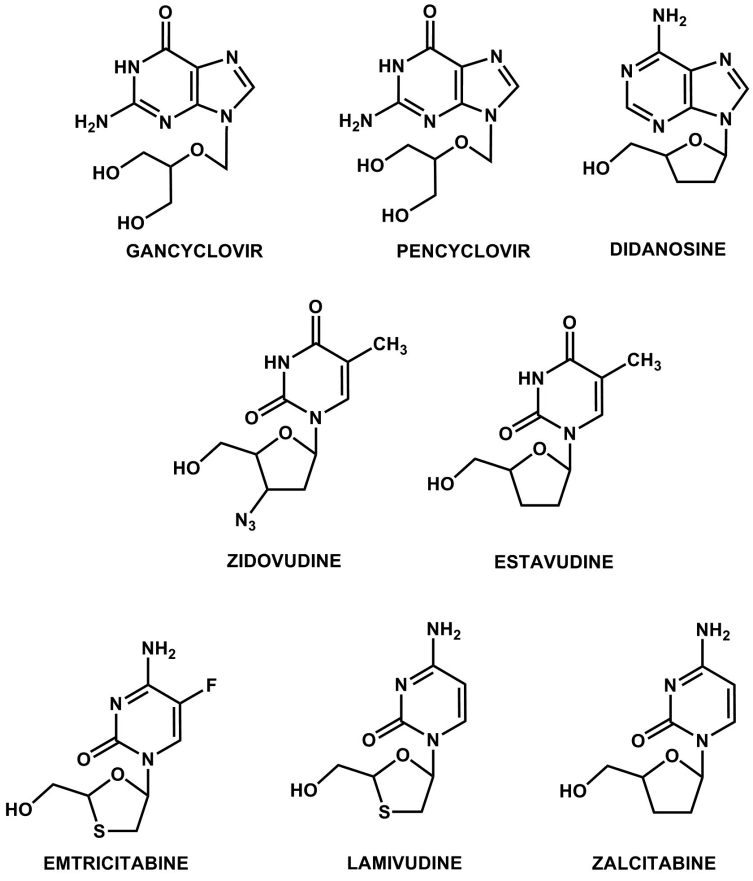

FIGURE 6 - Structures of bioprecursor-type antiviral prodrugs (ganciclovir and penciclovir) and antiretrovirals (zidovudine, estavudine, didanosine, emtricitabine, lamivudine, zalcitibine).

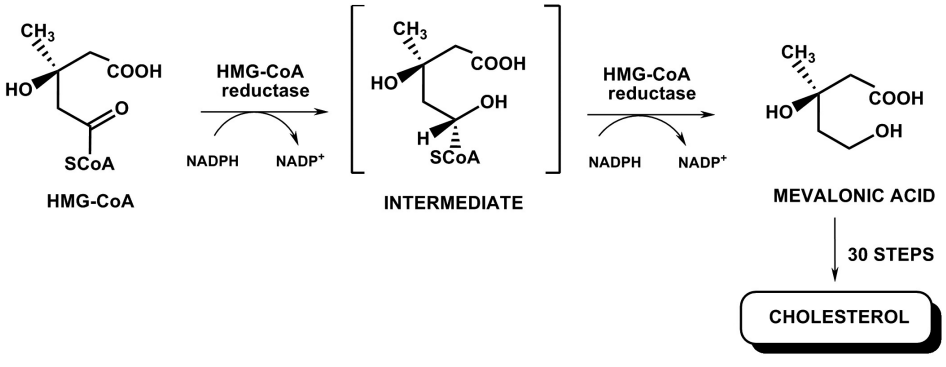

FIGURE 7 - The cholesterol biosynthetic pathway of HMGCo-A (hydroxy-methylglutaryl-Coenzyme A).

presents hydroxy-methylglutaryl-Coenzyme A (HMGCo-A) as a natural substrate. Upon acting on this substrate, HMGCo-A reductase converts it into mevalonic acid, one of the precursors of cholesterol synthesis (Mauro, 1993; Viegas-Junior *et al.*, 2006).

The first statin to be isolated was mevastatin (Figure 8), a substance extracted from the fungus *Penicillium sp*. Researchers in Sankyo (Japan) noted the similarity of the active metabolite of mevastatin to the natural substrate of the cholesterol biosynthetic pathway. The effectiveness of this metabolite can be explained by the structural similarity to the precursor of cholesterol, as indicated in Figure 8.

Accordingly, mevastatin needs to be biotransformed into its active form (acyclic derivative) to become active. Consequently, this compound is a bioprecursor, since lactone hydrolysis is required (function γ-lactone-β-hydroxylate) for its hypocholesterolemic function. The statins on the market, for example lovastatin and sinvastatin (Figure 9), which present the γ-lactone-β-hydroxylate function, are also bioprecursors. After being absorbed by

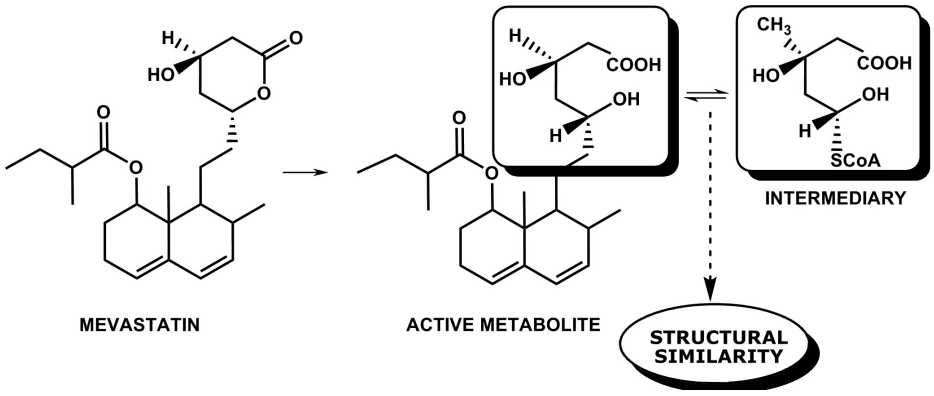

FIGURE 8 - The structure of mevastatin, of its active metabolite and the similarity to the HMG-CoA reductase substrate (intermediary).

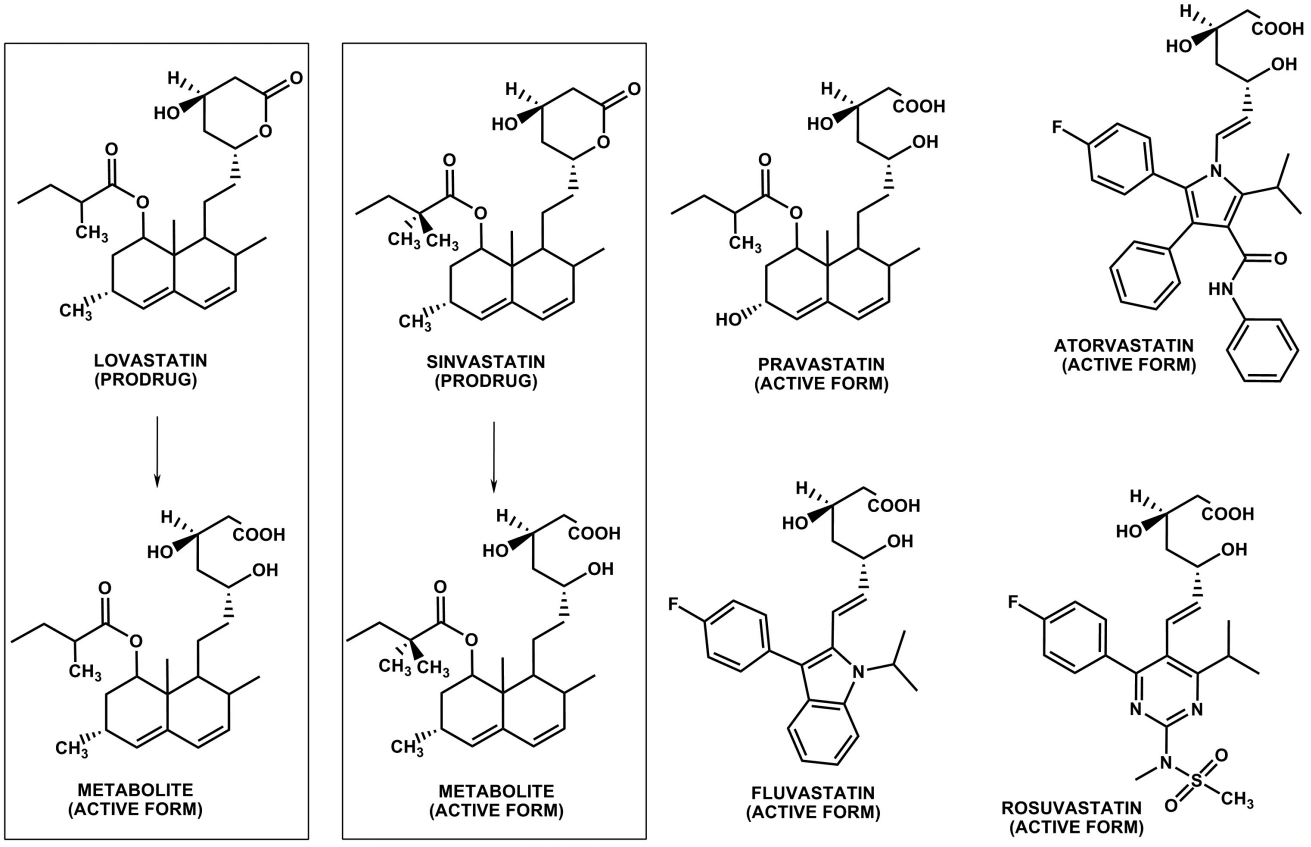

FIGURE 9 - Statins used in therapeutics.

the intestine, lovastatin and sinvastatin are hydrolized and quickly converted into open hydroxy acids, which in turn correspond to the active metabolite (Roche, 2005).

On the other hand, pravastatin was the first statin to present an open lactone function and therefore it is not classified as a bioprecursor. For the same reason, fluvastatin, atorvastatin and rosuvastatin are also not considered bioprecursors (Campo, Carvalho, 2007; Viegas-Junior *et al.*, 2006).

Lovastatin was approved for clinical use in 1987 and after its introduction, other statins were launched on the market and since then these compounds have also been ranked as "*blockbuster*" drugs. Currently, it is estimated that the world pharmaceutical market generates about 700 billion dollars a year, with the statin trade alone accounting for more than 15 billion dollars of this total (IMS, 2009; Viegas-Junior *et al.*, 2006). This observation is an indication of the importance of latentiation of drugs in the world pharmaceutical market.

Antiparkinsonian Agents

A classic example of a bioprecursor prodrug is **levodopa**. This drug corresponds to the immediate dopamine precursor, although contrary to the latter, it is able to cross the blood-brain barrier. Levodopa has been used to treat Parkinson's disease, a condition caused by deficiency in dopamine, which cannot be employed due to insufficient lipophilicity to cross the blood-brain barrier. However, levodopa is an even more polar structure compared to dopamine. Its amino acid characteristic enables it to use transporters of neutral amino acids (LAT1) present in the blood-brain barrier and accordingly, it can cross the cellular membrane. Subsequently, it undergoes decarboxylation through the action of the aromatic L-amino acid decarboxylase, thus releasing dopamine (Figure 10) (Stefano *et al.*, 2008; Bravo, Nassif, 2006).

Antiulcerous agents

The gastric H^+/K^+ ATPase pump inhibitors, also called proton pump inhibitors, consist of a group of drugs widely employed in the treatment of gastric ulcers. The enzyme is responsible for the production of acid in the stomach and is located in the apical membranes of the parietal cells. Over the last decade, these drugs have largely replaced H_2 antihistamines, such as cimetidine, ranitidine and famotidine. The lowering of enzymatic activity leads to a reduction in the concentration of hydrogen ions (H^+) in the stomach, thus increasing the stomach´s pH (Lindberg *et al.*, 1986; Roche, 2006).

The main inhibitors used in therapy in Brazil are omeprazole and its pure enantiomer, **esomeprazole (*S*-omeprazole)**, along with **lansoprazole, pantoprazole** and **rabeprazole** (Figure 11) (Carneiro França, 2008; Robinson, 2004).

All of these drugs are administered in their inactive form, becoming active under acidic conditions of the canaliculi of the gastric mucosa, as shown in Figure 12 (Lindeberg *et al.*, 1986). All members of this class are therefore considered to be bioprecursors (Barradell *et al.,* 1992; Shin *et al.*, 2004).

Antineoplasic Agents

Cyclophosphamide is a synthetic bioprecursor antineoplasic drug, belonging to the alkylating agents class of the nitrogen mustard group, that bonds covalently to DNA. This drug is inactive when tested *in vitro* on human lymphocyte cultures or on human neoplastic cells. However, *in vivo*, when converted to its active form by microsomal cells in the liver, it interferes with the growth of susceptible neoplastic tumors.

The biological function of cyclophosphamide, as well as the other members of the nitrogen mustard group, is based on the presence of the *bis*-(2-chloroethyl) group. Cyclophosphamide is hydroxylated in the liver by $CYP450_{2B}$, and converted into 4-hydroxy-cyclophosphamide (Figure 13). This dependency on bioactivation by the CYP450 system is an advantage over other compounds of the nitrogen mustard group (Cohen, Jao, 1970). These are chemically unstable to varying degrees, with some reacting almost totally in the organism a few minutes after being administered, which can lead to high rates of toxicity (Griskevicius *et al.*, 2003).

The 4-hydroxy-cyclophosphamide is found in dynamic equilibrium with its acyclic tautomer, aldofosfamide. It can undergo two pathways of biotransformation, one *enzymatic* and the other *non-enzymatic*. Through the *enzymatic* pathway, it can be oxidized to aldehyde in the liver

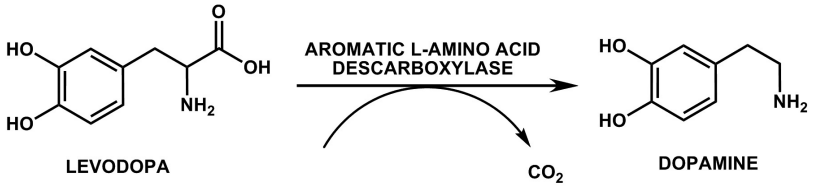

FIGURE 10 - Metabolic pathway for dopamine formation.

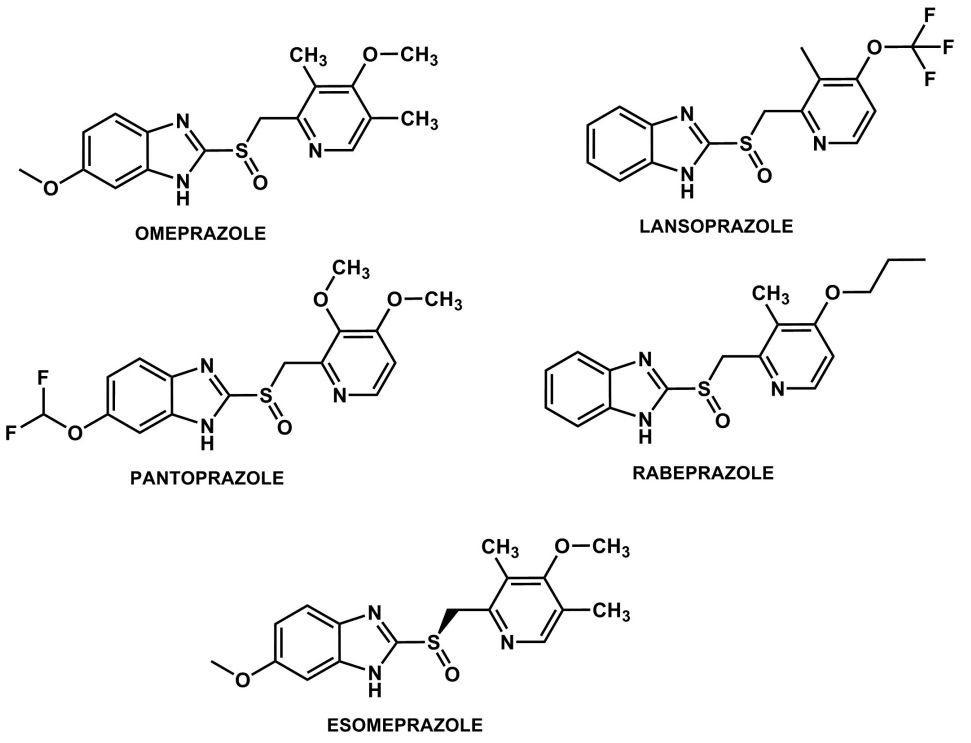

FIGURE 11 - The main gastric H^+/K^+ ATPase inhibitors.

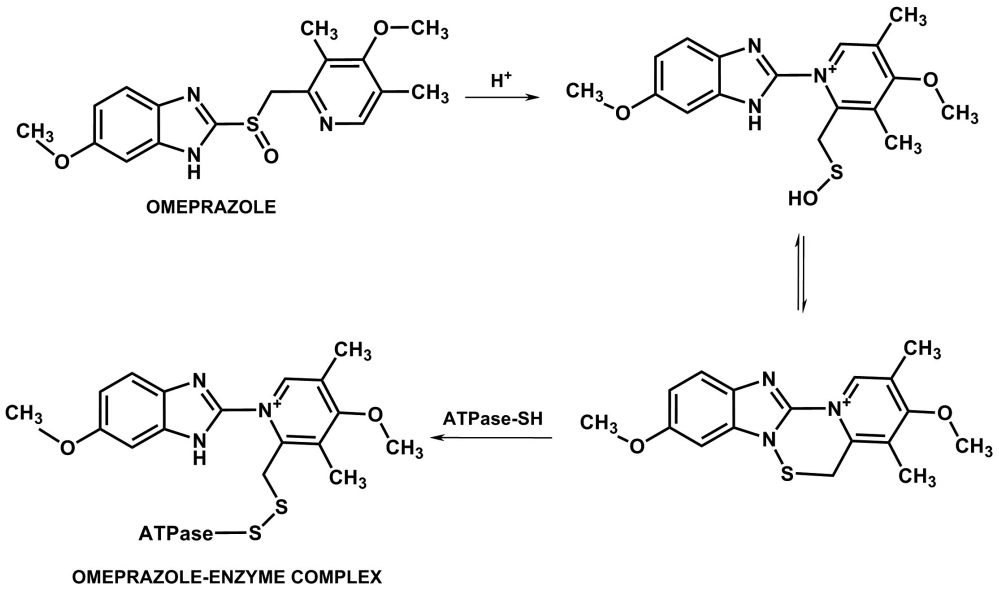

FIGURE 12 - Omeprazole activation mechanism and sequential inhibition of gastric H^+/K^+ ATPase.

or in the tumor and, perhaps by other enzymes, producing carboxy-phosphamide and 4-ceto-cyclophosphamide that have no significant biological activity. Through the *non-enzymatic* pathway, aldofosfamide undergoes spontaneous cleavage, producing fosforamide mustard and acrolein, the former being responsible for antitumoral effects, and the latter for haemorrhagic cystitis observed after using cyclophosphamide. The fosforamide mustard engages DNA in the tumor cells, resulting in the cross-bonding of the nucleic acid chains or binding to a nucleic acid or a protein. Such alterations severely damage the DNA molecule, leading to the demise of the cell (Lemke, Williams, 2008; Rooney *et al.,* 2004; Santos *et al.,* 2007).Currently, besides cyclophosphamide, a derivative of this drug, **ifosfamide,**

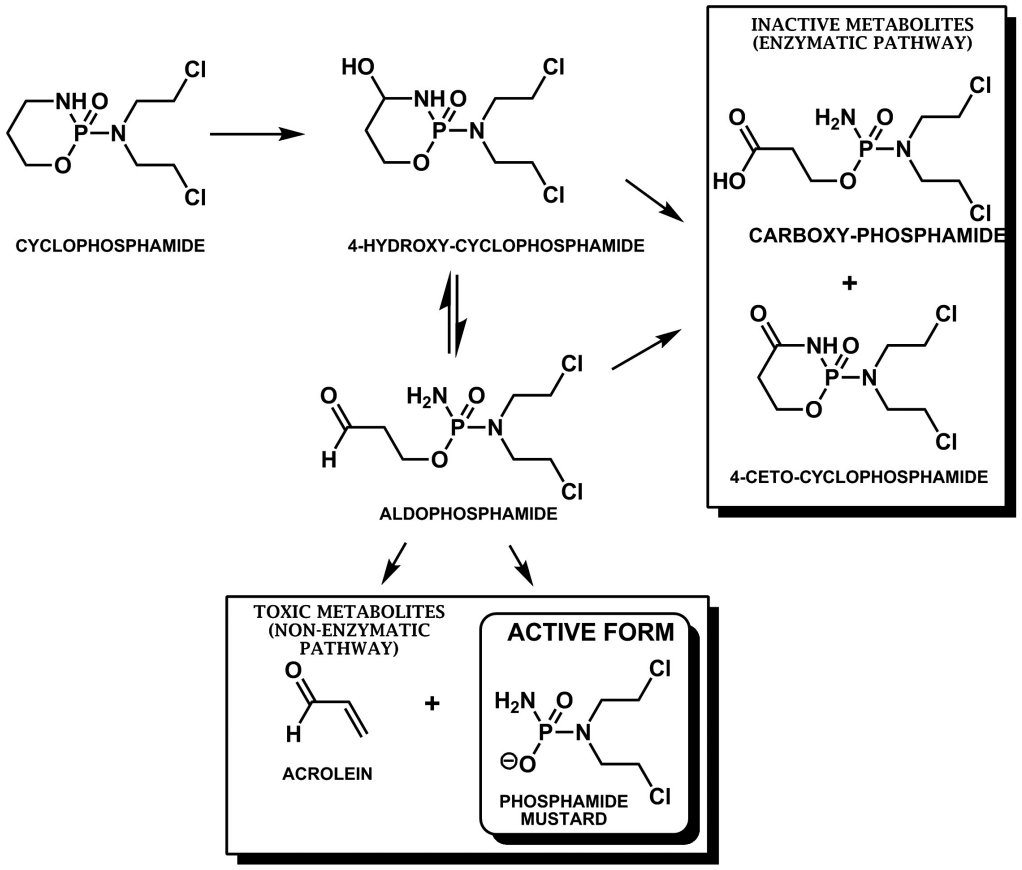

FIGURE 13 - Diagram of cyclophosphamide bioactivation**.**

is employed in anticancer chemotherapy treatment. This drug also requires bioactivation, and is thus another example of a bioprecursor prodrug (Lemke, Williams, 2008).

Classic prodrugs

Classic prodrugs are obtained from the binding of a matrix drug and an adequate transporter group through a covalent hydrolysable bond. The purpose of these prodrugs is to improve physical-chemical properties and consequently, overall therapeutic effectiveness, with a reduction in toxicity, prolonged action and an increase in bioavailability or selectivity. They are normally inactive and need to undergo chemical or enzymatic hydrolysis, thus releasing the active portion. Therefore, they abide by the classical definition of latentiation (Beaumont *et al.,* 2003; Chung *et al.*, 2005).

The main classic prodrugs available on the Brazilian market are listed below, divided according to the different therapeutic categories.

Antivirals

Valacyclovir (Carneiro França, 2008) is a classic prodrug of acyclovir (Figure 14) and is therefore active against the *Herpes simplex* (VHs) virus, types 1 and 2, and *Varicella zoster* (VVZ), Epstein Barr (VEB) virus and cytomegalovirus (CMV). This prodrug was obtained from the esterification reaction between acyclovir and the valine amino acid.

Valacyclovir was designed to increase the bioavailability of acyclovir. Peptide transporters represent attractive groups for the development of prodrugs. Prodrugs that have amino acids as transport groups present three- to ten-fold greater passage through the membrane than the original drug. Thus, the greater absorption of valacyclovir compared to acyclovir is due to the presence of the amino acid (valine) (Ettmayer *et al.,* 2004; Thomsen *et al.*, 2003; Thomsen *et al.,* 2004; Vabeno *et al.*, 2004). The presence of valine enables the passage of the drug through membranes by means of specific amino acid transporters (hPEPT 1 and 2) (Andersen *et al.*, 2006; Steingrimsdottir *et al.,* 2000; Steffansen *et al.,* 2004; Sugawara *et al.*, 2000). Upon absorption, orally ingested valacyclovir is converted into acyclovir by the action of esterases. The acyclovir, in turn, is affected by viral *thymidine kinase*, thus transforming into its active form, acyclovir monophosphate, and then

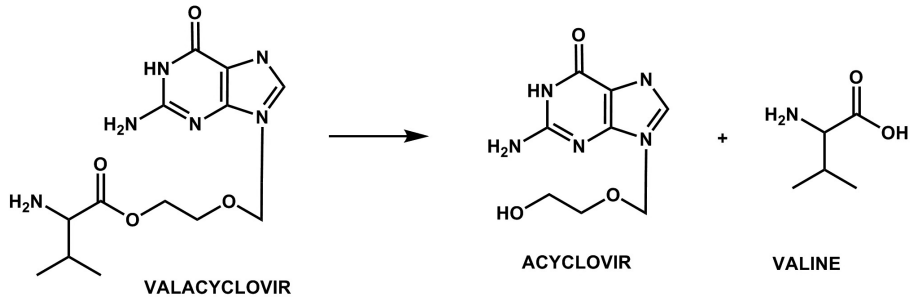

FIGURE 14 - Reaction illustrating the release of acyclovir from its prodrug.

di and triphosphate, with 54% absolute bioavailability, compared to the 12-20% of acyclovir. The fact that the bioavailability of oral valacyclovir is considerably greater than that obtained from oral acyclovir results in the need for smaller daily doses (Guo *et al.,* 1999; Han, Amidon, 2000).

Fancyclovir (Carneiro França, 2008), the **diacetate of pencyclovir,** is classified as a classic prodrug (Figure 15), whose purpose is to increase bioavailability. Fancyclovir was acquired after the acetylation of the hydroxyl groups present in the "open sugar" of pencyclovir. This compound was developed to adjust the pharmacokinetic properties of pencyclovir, which has limited oral absorption (4% oral bioavailability) which is increased to 75% with fancyclovir (Barreiro, Fraga, 2008; Simpson, Lyseng-Williamson, 2006). After absorption, fancyclovir is biotransformed by esterases, and pencyclovir is released which is subsequently affected by viral *thymidine kinase,* and is hence transformed into its active form, pencyclovir triphosphate.

Fosamprenavir is an antiretroviral drug belonging to the class of protease inhibitors. It inhibits this enzyme, preventing the breakdown of a polyprotein precursor into functional and structural proteins of HIV (Stella *et al.*, 2007). Fosamprenavir is a prodrug of amprenavir (Figure 16).

Fosamprenavir is a calcium phosphate ester of amprenavir. This prodrug was designed to optimize the use of amprenavir by reducing the heavy dosage regimen, which in turn significantly reduces the quantity of pills to be taken compared to amprenavir, and accordingly, minimizing collateral effects. Therapy with amprenavir requires the ingestion of eight capsules daily to reach the total dosage of 1200mg. In contrast, the use of its prodrug requires the administration of only two pills per day, containing a total of 1400mg. Fosamprenavir is a more hydrosoluble derivative (10 times more soluble in water), compared to amprenavir, facilitating its formulation and absorption. Upon oral administration, fosamprenavir is quick and almost completely hydrolyzed in amprenavir and inorganic phosphate. The conversion of fosamprenavir into amprenavir, as well as its absorption, takes place in the intestinal epithelium. Fosamprenavir was licensed for the treatment of AIDS in 2004 (Chapman *et al.*, 2004; Wire *et al.,* 2006).

Tenofovir disoproxil is a prodrug derived from tenofovir, an analog of monophosphorylated nucleoside, which acts by inhibiting reverse transcriptase, an important HIV enzyme capable of promoting the transcription of viral RNA into viral DNA (Chapman *et al.*, 2003; Gallant, Deresinski, 2003). The prodrug tenofovir disoproxil fumarate was designed as a solution to overcome the limited oral bioavailability of tenofovir. It is transformed into tenofovir upon absorption (Figure 17). The hydrolysis

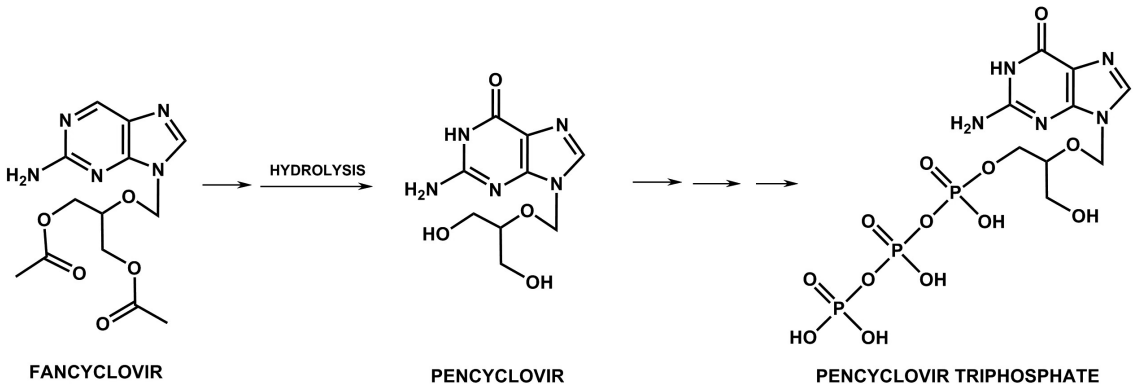

FIGURE 15 - The bioactivation pathway of fancyclovir.

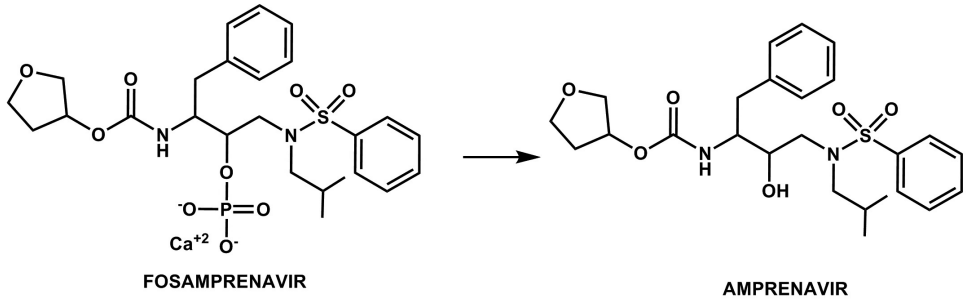

FIGURE 16 - Fosamprenavir structure (prodrug) and its conversion into amprenavir**.**

of tenofovir disoproxil fumarate, promoted by esterases, stechiometrically generates four types of molecules: isopropanol, carbon dioxide, formaldehyde and tenofovir (Larsen *et al.*, 2004).

Oseltamivir is an orally administered prodrug of proven efficacy in the treatment of infections caused by the Influenza A and B viruses. This prodrug is converted into carboxylate of oseltamivir (GS4071), its active form, by hepatic esterases (Figure 18). The active metabolite is a powerful and selective inhibitor of the neuraminidase enzyme, a glycoprotein present on the surface of the virus, essential for the release of viral particles recently formed from infected cells and for the later expansion of the infecting virus in the organism. The prodrug was designed to improve the bioavailability of its precursor, GS4071. Considering that carboxylate is a very hydrosoluble chemical entity, the masking of this group was promoted by the formation of an ethyl ester. Accordingly, oseltamivir presents greater lipophilicity and, consequently, greater bioavailability (Fatima *et al.,* 2005; Finley *et al.*, 1999; Hayden *et al.,* 1999; He *et al.*, 1999).

Cardiovascular agents

The angiotensin-converting enzyme inhibitors represent a fairly significant class of cardiovascular drugs. The introduction of this family of antihypertensive agents arose from the experimental work carried out by Sérgio Ferreira involving venom from the *Bothrops jararaca* snake (Ferreira, 1965). A peptide was identified in this venom that, when administered intravenously, was capable of preventing the conversion of angiotensin I into angiotensin II, through the inhibition of the angiotensin-converting en-

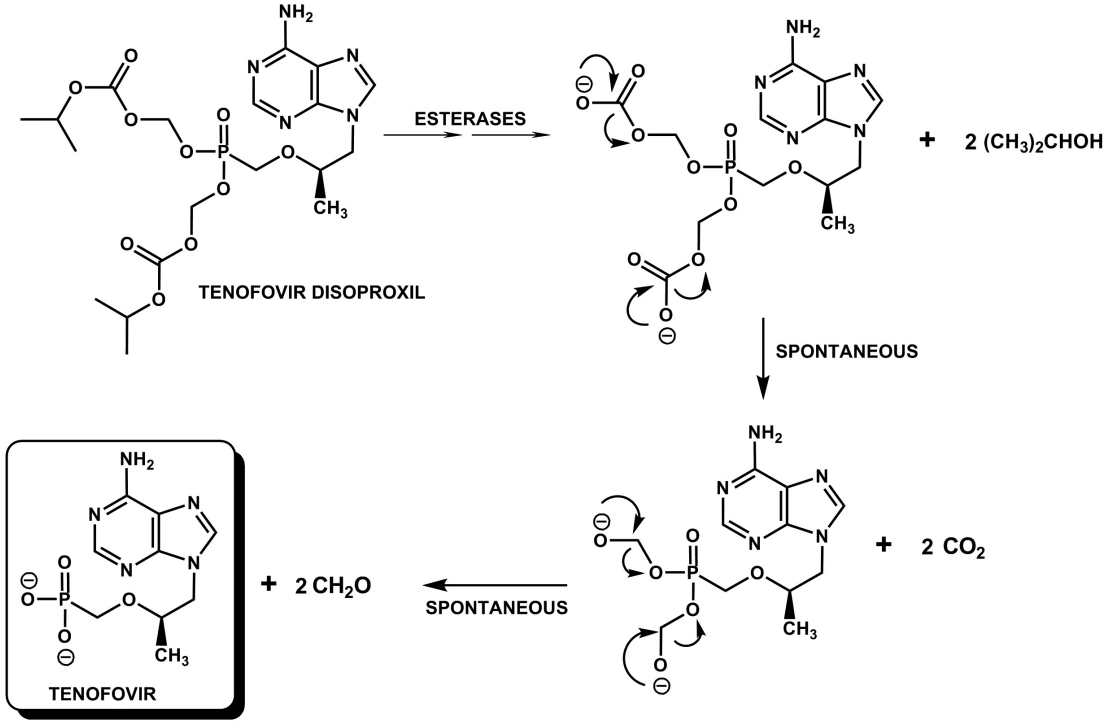

FIGURE 17 - Chemical and enzymatic hydrolysis of tenofovir disoproxil fumarate into its active component, tenofovir.

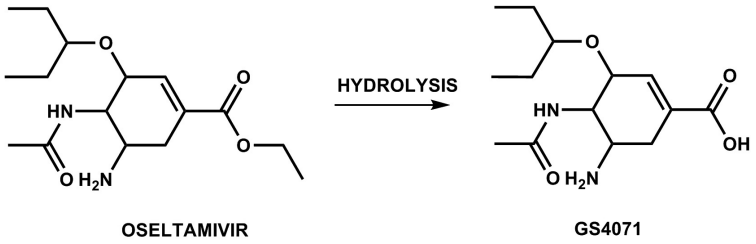

FIGURE 18 - The activation of olsetamivir into the active metabolite GS4071.

zyme (ACE). Based on the recognition that ACE inhibition results in hypotensive activity, a series of powerful ACE inhibitors was developed, which are active upon oral administration (Wermuth, 2006). Captopril, marketed under several pharmaceutical brandnames (Carneiro França, 2008) (Figure 19), was the first ACE inhibiting antihypertensive agent and is an example of a drug developed from rational drug design, supported by contributions from Brazilian researchers. Captopril presents satisfactory bioavailability, when administered orally. However, it is one of the ACE inhibiting drugs with the lowest half-lives, compared to others from the same class, for example, **enalapril**, **benazepril**, **quinapril**, **ramipril** and **fosinopril** (Friedman, Amidon, 1989; Dhareshwar *et al.*, 2007), all classified as prodrugs with greater advantages in terms of half-life and improved bioavailability (Figure 19).

Esterification of the ester group or etherification of the phosphate group leads not only to an increase in liposolubility, but also minimizes the biotransformation that rapidly takes place in the carboxylic-free group (Beaumont *et al.*, 2003). Thus, as intended, the bioavailability and the half-life of the prototype drugs are altered.

Antibiotics

The antibiotics class includes a very wide range of prodrugs available for use in therapy, whether to increase bioavailability, reduce toxicity or even to solve organoleptic and pharma-technical issues (Chung, Ferreira, 1998).

Ampicillin is currently a fairly widely used antibiotic due to its broad spectrum bactericidal activity and reduced toxicity. However, its bioavailability, when ingested orally, is only 30% to 50%, due to its low absorption (Carneiro França, 2008). Thus, there is an interest in ampicillin prodrugs with more lipophilic transporters, and a subsequent increase in lipophilicity. **Bacampicillin** (Figure 20) is an example of a classic ampicillin prodrug, with greater bioavailability than the penicillin it is derived from. With bioavailability greater than 95%, bacampicillin is administered in an average oral dose of 400mg and thus attains high plasmatic levels, 7 μg/ml, which is equivalent to 1000 mg of ampicillin. This pharmacokinetic characteristic provides rapid and elevated plasmatic concentrations, two or three times greater than those attained from the same doses of ampicillin. Its plasmatic half-life is approximately 60 minutes in individuals with normal renal function. Furthermore, its binding with plasmatic proteins is very low (18%), maintaining a high concentration of free and therapeutically active ampicillin (Bergan, 1978; Bodin *et al.*, 1975; Sjövall *et al.*, 1978).

It is important to observe that the transporter bonded to position 2 of the thiazolidine ring is a double ester. This characteristic means greater access of the enzyme to the ester further away from the ring, thus preventing any steric hindrance that could interfere with the release of the drug. The esterases cleave the ester bond and a spontaneous rearrangement releases ampicillin and aldehyde, as illustrated in Figure 20.

The cephalosporin class of antibiotics also includes several prodrugs. Those of third and fourth generations, in particular, are fairly hydrophilic drugs that include aminotiazol and methoxamine groups in their structure, which are responsible for their broad spectrum bactericidal activity and resistance to beta-lactamases, respectively. Despite these characteristics, the high hydrosolubility of these more recent generation of cephalosporins impairs gastro-intestinal absorption, making oral administration unfeasible (Patrick, 2005). This difficulty led to the design of new chemical entities with, simultaneously, oral absorption, broad spectrum bactericidal activity and resistance to beta-lactamases. Accordingly, new orally administered cephalosporin prodrugs have arisen based on dual-esters, such as **cefuroxime axetil**, **cefpodoxime proxetil** and **cefetamet pivoxil** (Fuchs, 2007; Stella *et al.*, 2007). As with bacampicillin, these prodrugs, being more lipophilic, are administered orally and feature greater bioavailability. After absorption, they initially undergo enzymatic hydrolysis, followed by a chemical rearrangement due to the electronic characteristics of the intermediary formed, thus releasing cephalosporin (Figures 21 and 22) (Ehrnebo *et al.*, 1979; Perry, Brogden, 1996).

Chloramphenicol is an antibiotic that was isolated by Burkholde for the first time in 1947 from *Streptomyces*

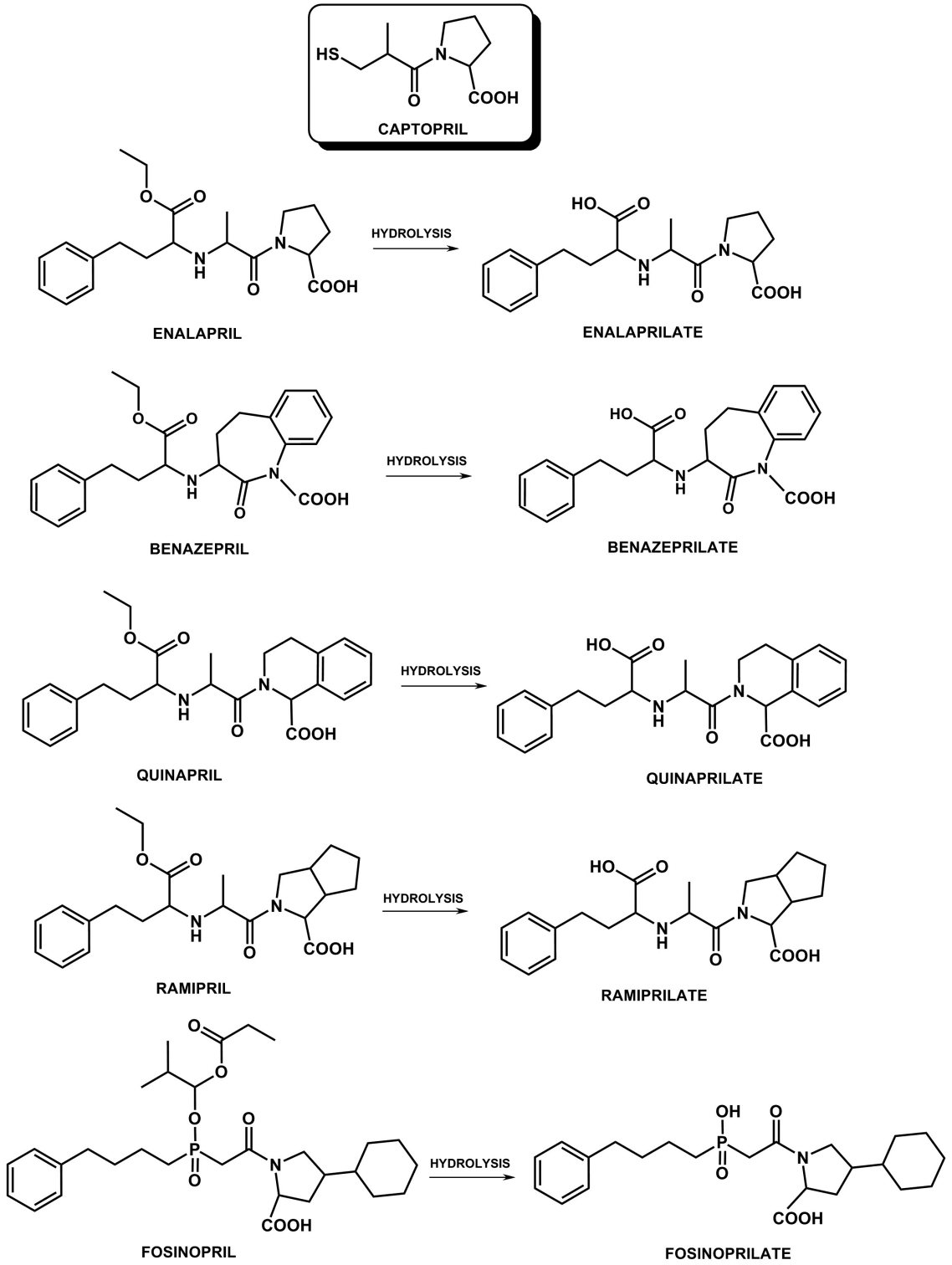

FIGURE 19 - Angiotensin-converting enzyme (ACE) inhibiting prodrugs and their respective hydrolyses to their active forms

venezuelae. This compound was the first antibiotic effective against a wide variety of microorganisms to be used particularly in the treatment of serious infections such as typhoid fever and other forms of salmonellosis, *Haemophilus Influenza* infections, especially of the meninges, as well as other infections of the nervous system and respiratory tract (Carneiro França, 2008). However, it is associated with severe toxic side effects such as bone marrow depression, especially fatal aplastic anemia (Powell, Nahata, 1982).

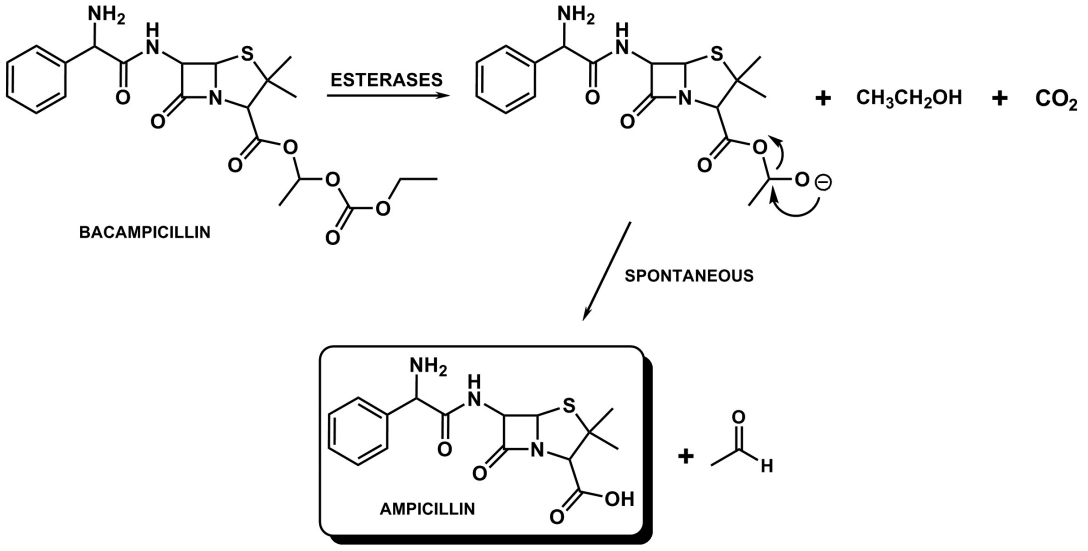

FIGURE 20 - Bacampicillin structure and its conversion into ampicillin.

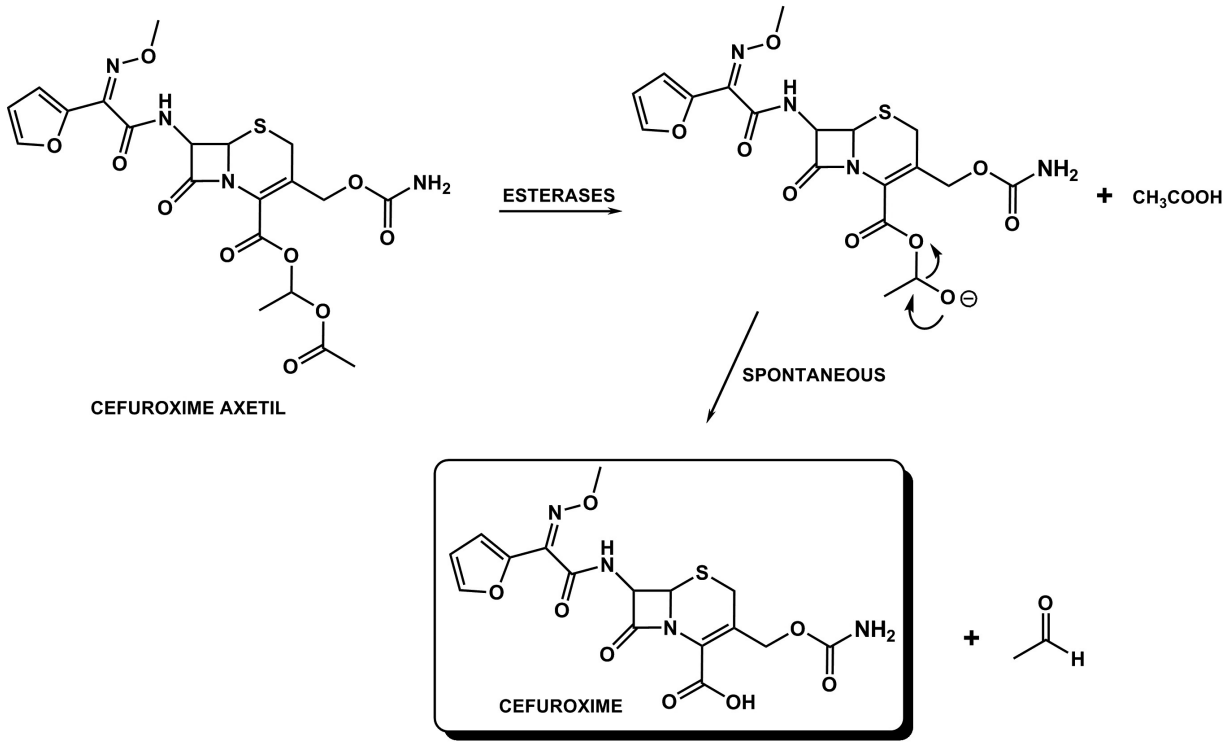

FIGURE 21 - Cefuroxime axetil structure and its conversion into cefuroxime.

With the appearance of safer agents, chloramphenicol is frequently considered to be an antibiotic of purely historical interest. However, it is still useful in some situations, such as in seriously ill individuals for whom safer alternatives are less effective, or when such alternatives are not available. This drug has a bitter taste, which is difficult to mask in orally administered solutions. Researchers discovered that the drug became flavorless when transformed in palmitic ester, due to the reduction of hydrosolubility (Figure 23). Chloramphenicol palmitate is a prodrug of cloramphenicol, obtained from the sterification reaction between the drug and palmitic acid. It is therefore inactive, and for it to become active, it undergoes hydrolysis of the ester bond through the action of pancreatic lipases in the duodenum[54]. The acquired prodrug is a lipophilic compound, which means it can be marketed as an oral suspension (Bechelli, 2003; Carneiro França, 2008).

With the aim of acquiring a hydrosoluble pharma-

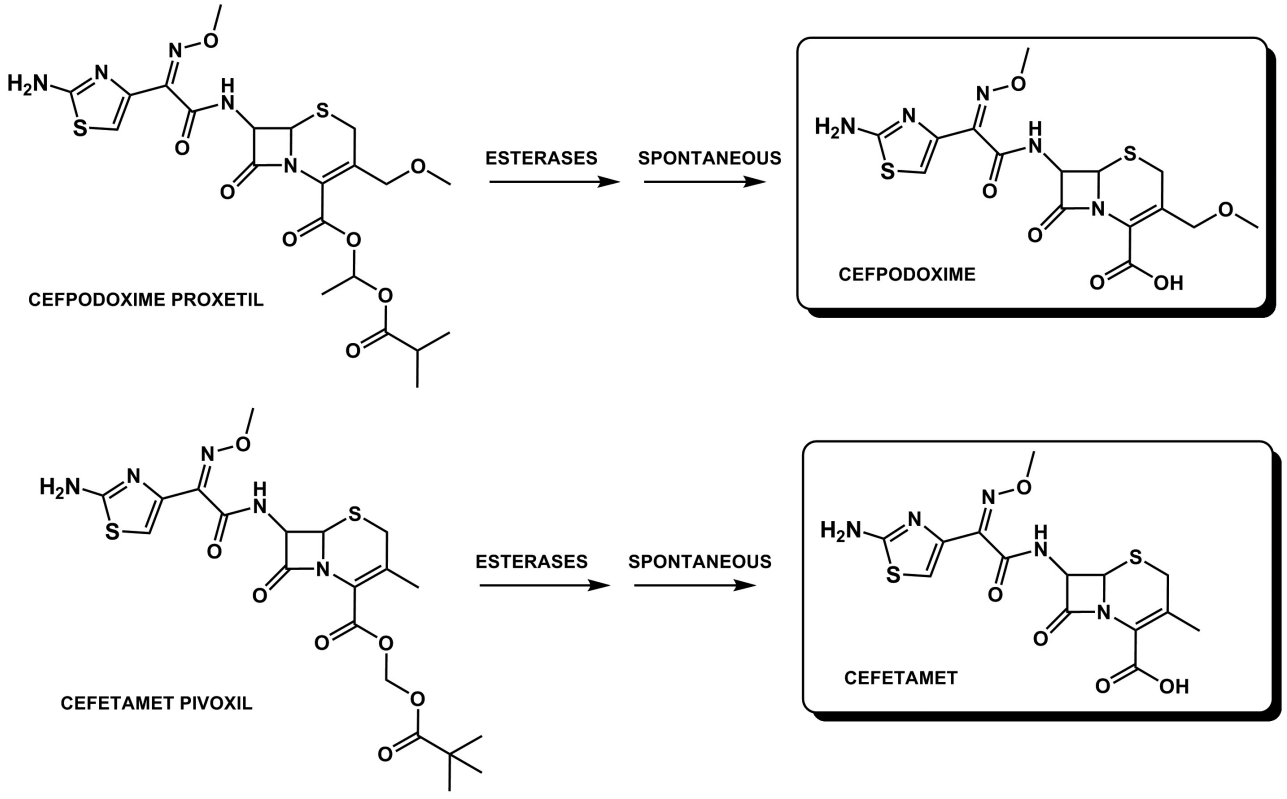

FIGURE 22 - Cefpodoxime proxetil and cefetamet pivoxil structures being bioactivated into cefpodoxime and cefetamet, respectively.

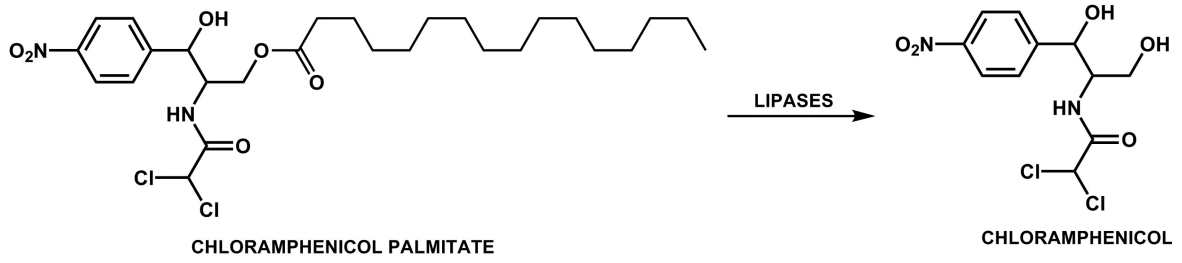

FIGURE 23 - Enzymatic conversion of the chloramphenicol palmitate into chloramphenicol, its active form.

ceutical form for ophthalmic application, chloramphenicol has also been transformed into succinic hemiester (Figure 24), which, through hydrolysis, releases the antibiotic locally (Carneiro França, 2008).

Erythromycin (Figure 25) is a macrolide antibiotic, structurally characterized by the presence of a 14-atom lactone, to which two sugars are bonded. One of these sugars features an amino group, giving the drug the characteristic of a weak base that enables the formation of salts with organic acids (Lemke, Williams, 2008). It is a drug that is effective against a wide variety of microorganisms. However, its bitter taste and instability in an acidic medium prevented its therapeutic use. In an attempt to solve these limitations, its derivatives, erythromycin stearate and erythromycin estolate, are used for therapy in Brazil (Carneiro França, 2008; Tavares, 2001). **Erythromycin stearate** is a salt capable of reducing the bitterness and, especially, increasing stability in an acidic medium. The lauryl sulfate salt of propionyl erythromycin ester, more commonly known as **erythromycin estolate,** is the prodrug available in Brazil (Carneiro França, 2008; Tavares, 2001). This prodrug is obtained from the sterification reaction between the hydroxyl group of amino sugar present in erythromycin and propionic acid carboxyl group, which acts as a transporter group. Sterification reduces the bitterness of erythromycin and increases its oral absorption, releasing free erythromycin into the bloodstream or muscle tissue after the action of esterases. Data from literature indicates that erythromycin estolate is

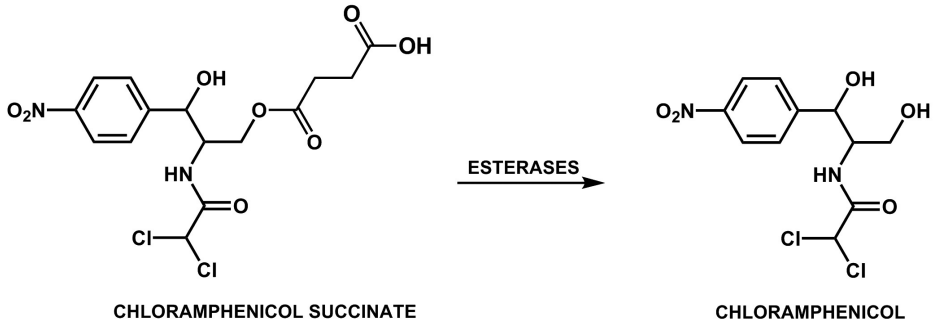

FIGURE 24 - Bioactivation of chloramphenicol succinate.

capable of producing more elevated and prolonged serum levels than other salts due to the greater absorption rate of esters (Lemke, Williams, 2008; Tavares, 2001). Figure 25 illustrates the structures of erythromycin, erythromycin stearate and erythromycin estolate.

Antipsychotics

Antipsychotics are drugs used for the treatment of schizophrenia. In some circumstances, orally administered medicine regimens are not suitable for schizophrenic patients and the administration of long-acting prodrugs by intramuscular injection is recommended. This is the safest means of maintaining clinical stability and preventing relapses. In Table 1, several long-acting antipsychotics are listed. For instance, fluphenazine enanthate, haloperidol decanoate, zuclopenthixol decanoate and pipothiazine palmitate are available on the Brazilian market (Carneiro França, 2008). All are administered by intramuscular injection and obtained through sterification reaction between the drugs and long-chain carboxylic acids, which confer a high rate of liposolubility on the resulting derivatives (Bechelli, 2003).

Fluphenazine decanoate (piperazine phenothiazine) and haloperidol decanoate (butyrophenone) are prodrugs administered in an oil-based depot injection, where the agent is stored in the adipose tissue and then gradually released into the organism over a long period of time. After deep intramuscular injection, fluphenazine decanoate and haloperidol decanoate spread slowly and are hydrolyzed into their active forms fluphenazine and haloperidol, respectively, which then cross the blood-brain barrier (Figure 26). It is possible to obtain a stable serum concentration from the drugs for nearly four weeks after an initial peak, and half-life is in the range of 2.5 to 16 weeks (Beresford, Ward, 1987; Jann *et al.,* 1985).

Steroid hormones

One of the strategies for extending the period of action is to design prodrugs with increased lipophilicity, thus obtaining depot forms whose drugs are gradually release into the organism (Batres *et al.,* 1956). This strategy can be observed in the development of sexual hormones with long-acting release during contraceptive therapy, hormonal replacement therapy or pregnancy (Petrow, 1970; Ghiselli, Jardim, 2007). The use of prodrug steroid hormones in therapy may also be applied to compounds that can be administered orally, thus increasing the absorption of the hormones. This design involves the binding of the hormone to a transporter group, generally masking a hydrophilic functional group, through an ester bond which increases lipophilicity and leads to derivatives for oral or parenteral administration. The extension of the period of action of these steroid hormones derived from parenterally

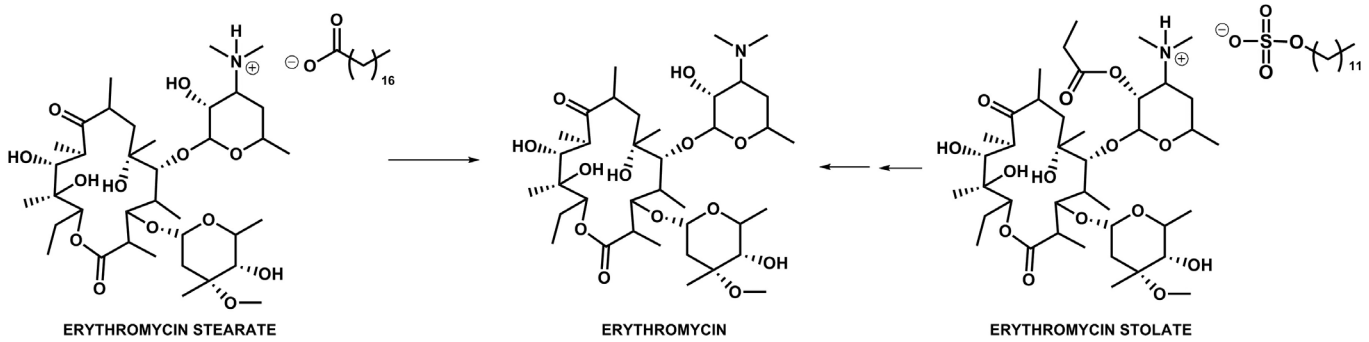

FIGURE 25 - Conversion of erythromycin stearate and erythromycin estolate into erythromycin.

TABLE I - Long-acting antipsychotics

PRODRUGS	ADMINISTRATION INTERVAL (WEEKS)
BROMPERIDOL (DECANOATE)	4
CLOPENTIXOL (DECANOATE)	3 to 4
FLUPHENAZINE (DECANOATE)	2 to 3
FLUPHENAZINE (ENANTHATE)	2
HALOPERIDOL (DECANOATE)	4
PERPHENAZINE (DECANOATE)	3 to 4
PERPHENAZINE (ENANTHATE)	2
PIPOTHIAZINE (PALMITATE)	2
PIPOTHIAZINE (UNDECYLENATE)	4
ZUCLOPENTIXOL (DECANOATE)	2 to 4

administered esters can be explained by the slow absorption from the site of administration or by the resistance to biotransformation (Biagi *et al.*, 1975).

A practical and long-acting form of contraception is the use of injectable progesterone prodrugs, providing 2-4 months of contraception. There are also monthly injections, which are combinations of estrogen and progesterone prodrugs, administered in intramuscular injections once a month (Araújo-Junior, Athanazio, 2007). The structures of steroid hormone prodrugs, as well as their release to active form, are illustrated in Figure 27. The main compounds include (Carneiro França, 2008): **medroxyprogesterone acetate**, **hydroxyprogesterone caproate**, **algestone acetophenide** (long-acting progestogens), **estradiol valerate** and **estradiol enanthate** (estrogenic prodrugs) (Aguilar *et al.*, 1997; Mishell, 1996; Pasqualini, 1996).

Anti-asthmatic agents

Bambuterol is a prodrug of long-acting terbutaline, with an effective duration of 24 hours, thus able to be administered once a day. Bambuterol features catecholic hydroxyls (susceptible to pre-systemic metabolism). The fact that this type of bond is relatively resistant to hydrolysis explains the longer action of bambuterol. Terbutaline is an adrenergic agonist, which predominantly stimulates the beta-2 receptors, thus producing relaxation of the smooth muscle of the bronchus. After being absorbed, bambuterol undergoes a slow biotransformation, as indicated in

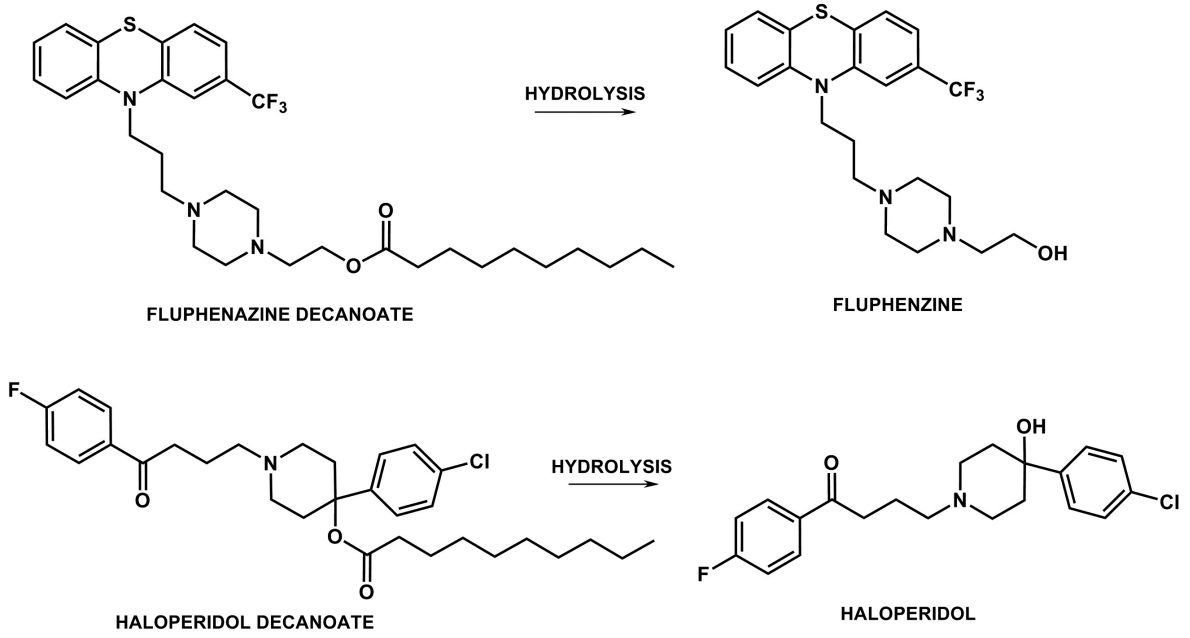

FIGURE 26 - Release of haloperidol and fluphenazine from their respective prodrugs.

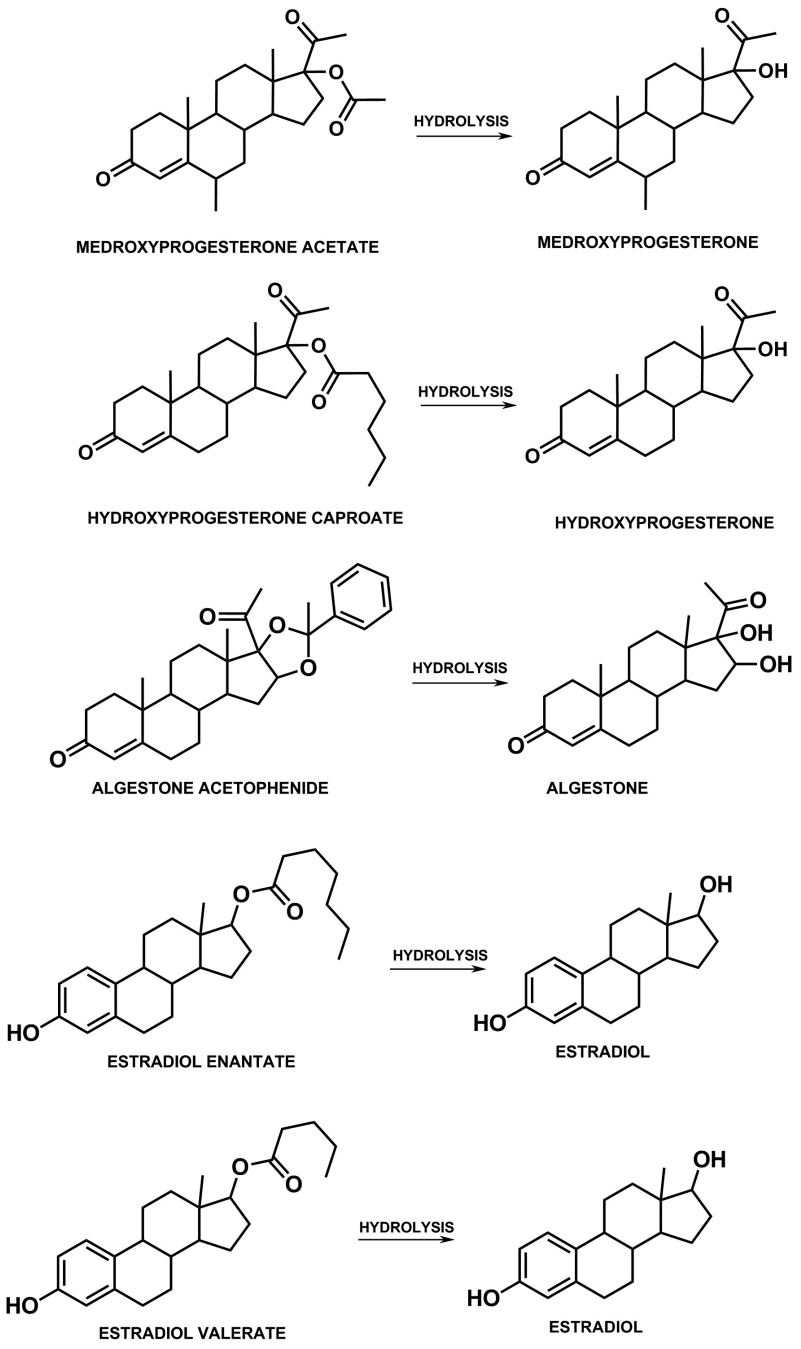

FIGURE 27 - The main sexual hormones available on the market and their bioactivation.

Figure 28, through hydrolytic and oxidation metabolic conversion, in order to form terbutaline. The maximum plasmatic concentration (C_{max}) of the active metabolite (terbutaline) is reached in approximately 2-6 hours and it lasts at least 24 hours (Rautio *et al.*, 2008; Rosenborg *et al.*, 2001; Testa, 2004; Tunek, Svensson, 1988).

Antiglaucoma agents

Dipivefrin, derived from epinephrin is recommended for the treatment of ocular hypertension in open-angle chronic glaucoma, and it functions by reducing the production of aqueous humor (Carneiro França, 2008). Dipivefrin is a prodrug of epinephrin obtained from the sterification of the catecholic hydroxyl groups present in epinephrin with pivalic acid. This sterification leads to an increase in lipophilicity and as a consequence, this prodrug is capable of permeating the corneal extract 17 times faster than epinephrin. After absorption, hydrolysis of the esters

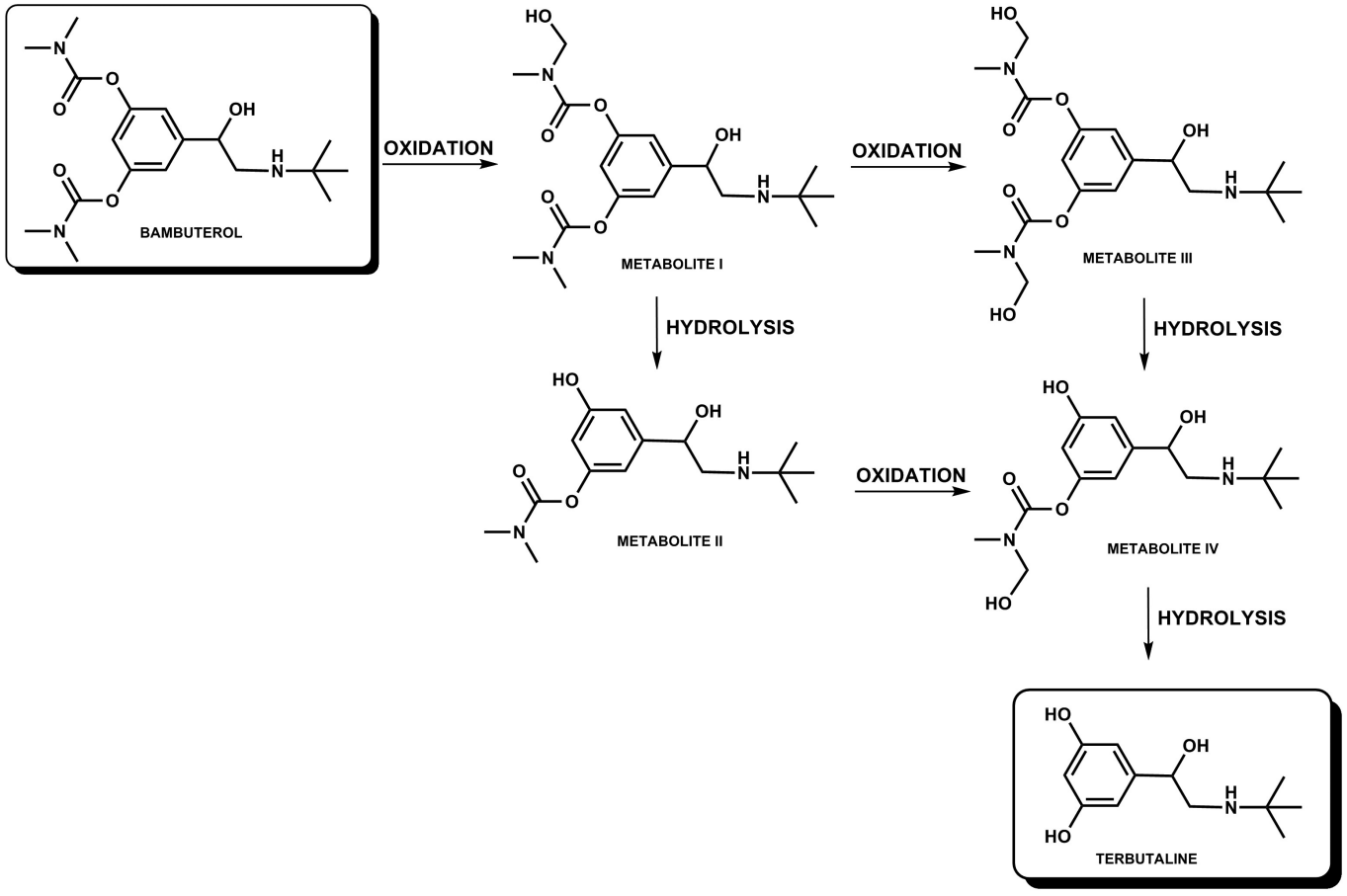

FIGURE 28 - Hydrolytic and oxidation metabolic conversion of bambuterol into terbutaline.

takes place, releasing the epinephrin (Figure 29) (Rautio *et al.*, 2008; Mandell *et al.*, 1978; Wei *et al.,* 1978).

Mixed prodrugs used in therapy

Mixed prodrugs are latent forms with the simultaneous characteristics of bioprecursors and classic prodrugs. In other words, they present as biologically inactive molecules that need to undergo several chemical reactions (hydrolytic and/or oxyreductive) in order to be converted into their active forms (Bodor, Abdelalim, 1985; Chung *et al.,* 2005;).

Antineoplasic agents

Capecitabine is a carbamoyl fluoropyrimidine with an antineoplasic function, which features reduced gastrointestinal toxicity and high tumor selectivity. It is a prodrug that, after three stages of biotransformation (Figure 30), creates fluorouracil, a compound with an antineoplasic function. It is quickly absorbed by the gastrointestinal system, initially undergoing hepatic bioactivation by carboxylic esterase, thus forming 5'-deoxy-5-fluorocytidine. Cytidine deaminase, an enzyme found in several types of tissue, including tumors, subsequently converts 5'-deoxy-5-fluorocytidine into 5'-deoxy-5-fluorouridine. The enzyme thymidine phosphorylase then converts 5'-deoxy-5-fluorouridine into the active drug fluorouracil. Many tissues throughout the organism contain thymidine phosphorylase. Some human carcinomas have high concentrations of this enzyme, a fact that favors the high rate of specificity of this drug (Miwa, 1998; Quinney *et al.*, 2005; Schuller *et al.*, 2000; Tabata *et al.*, 2004).

Reciprocal prodrugs

Despite the fact that the classic concept of latentiation refers to compounds containing pharmacologically inactive transporter groups, this cannot be extended to what is termed the reciprocal prodrug. In this type of derivative the transporter also has a therapeutic function, as it is constituted from the chemical association between two drugs, in such a manner that one acts as the transporter for the other, thus improving the effect of both. From their development, it is possible to obtain prodrugs with different or similar

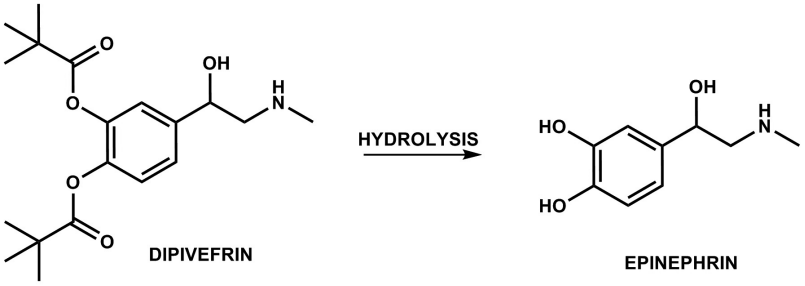

FIGURE 29 - Enzymatic conversion of dipivefrin into its active metabolite, epinephrin

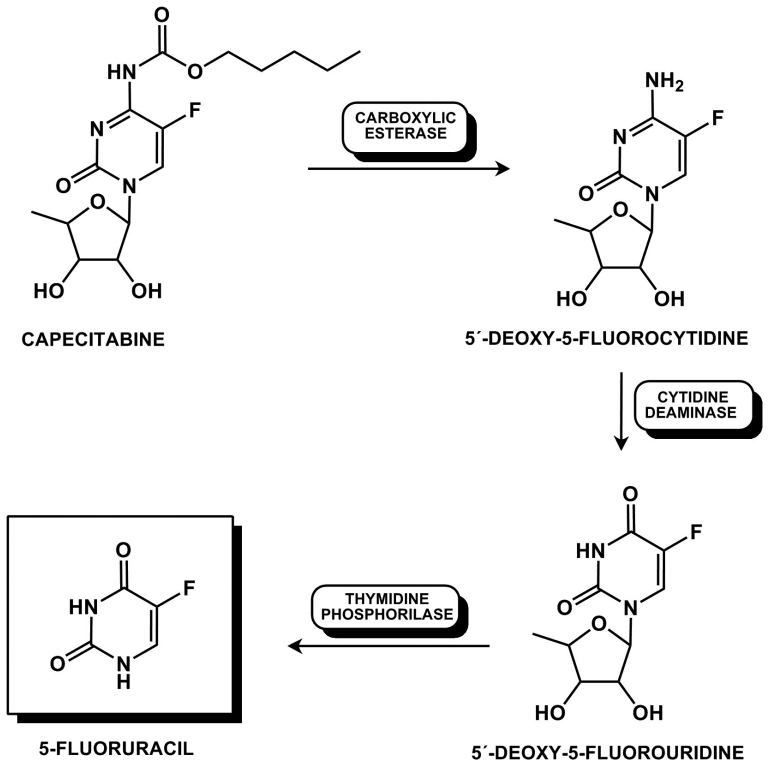

FIGURE 30 - Diagram of the metabolic bioactivation of capecitabine.

therapeutic functions, acting through distinctive or equal mechanisms of action (Chung *et al.,* 2005; Chung, Ferreira, 1998; Silva *et al.,* 2005; Singh, Sharma, 1994).

Reciprocal prodrugs differ from molecular hybrids (Barreiro, Fraga, 2008) because the former must be released through bond cleavage to perform its therapeutic effect.

Antibacterial agents

Sulfasalazine, introduced in 1942, is a highly useful prodrug, and one of the few available for the treatment of several types of chronic inflammatory intestinal diseases and rheumatoid arthritis. Through the action of intestinal azoreductases, this prodrug (Figure 31) releases, *in vivo*, two pharmacologically active substances, sulfapyridine and 5-aminosalicylic acid (5-ASA) (Chung *et al.*, 2005;

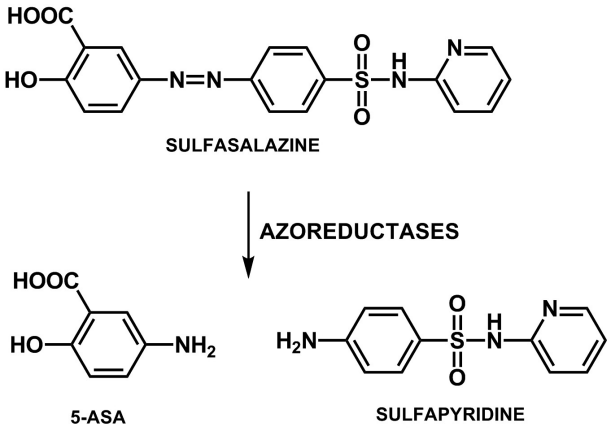

FIGURE 31 - Diagram of the bioactivation of sulfasalazine through the action of azoreductases.

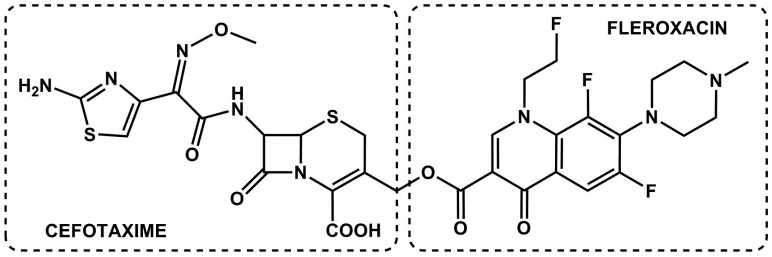

FIGURE 32 - Example of a reciprocal prodrug between fleroxacin and cefotaxine.

Freire *et al.*, 2006; Singh, Sharma, 1994). 5-ASA is the effective component in diseases of the colon, however, after oral administration it undergoes intense absorption in the upper parts of the gastrointestinal tract, and is not locally effective on the colon (Dash, Brittain, 1998). In fact, when administered in sulfasalazine form, at least 85% of an oral dose passes intact through the stomach and small intestine (Watts, Illum, 1997).

In 1960, the idea of synthesizing antibacterial drugs with dual-function arose, by employing the reciprocal prodrug concept. One of the first attempts at producing dual-function antibacterial drugs involved binding of the central nucleus of penicillin (6-APA) with norfloxacin, with the aim of providing more powerful antibacterial agents and two mechanisms with several functions. Later, prodrugs from cephalosporins with wide-ranging fluoroquinolones were obtained. The most efficient bifunctional derivative obtained consisted of the union between fleroxacin and cefotaxine (Figure 32). This compound, called Ro-239424, featured a broad range of effectiveness and a dual-function mechanism, i.e., it possessed effectiveness against transpeptidase and bacterial DNA gyrase, due to the beta-lactams and the fluroquinolonic portions of the molecule, respectively. This compound, however, is not yet available for use in therapy (Bhanot *et al.*, 2001).

Sultamiciline is an example of a reciprocal prodrug used in therapy. It consists of a dual ester obtained from the bond between ampicillin and sulbactam, a non-classic beta-lactams antibiotic. Besides masking the free carboxylic acid present in the structure of these compounds, thus facilitating absorption, this union is an advantage, because ampicillin is active in oral administration but inactive with beta-lactamases, while the latter is just a beta-lactamase inhibitor. After the absorption of the sultamicilin, hydrolysis of the esters takes place (Figure 33) which releases ampicillin with antibacterial function and sulbactam, capable of binding to beta-lactamase enzymes. This protects classic penicillin from beta-lactamase action. Sultamiciline is recommended for infections caused by microorganisms sensitive to the combination of ampicillin and sulbactam (Carneiro França, 2008). Typical recommendations are: infections of the upper and lower respiratory tracts, including sinusitis, otitis media and epiglotitis; bacterial pneumonia; infections of the urinary tract and pyelonephritis; intra-abdominal infections, including peritonitis, cholecystitis, endometritis and pelvic cellulitis; bacterial sepsis; skin, soft tissue, bone and joint infections, as well as gonococcal infections (Friedel *et al.,* 1989; Lopez, Rivas, 1998).

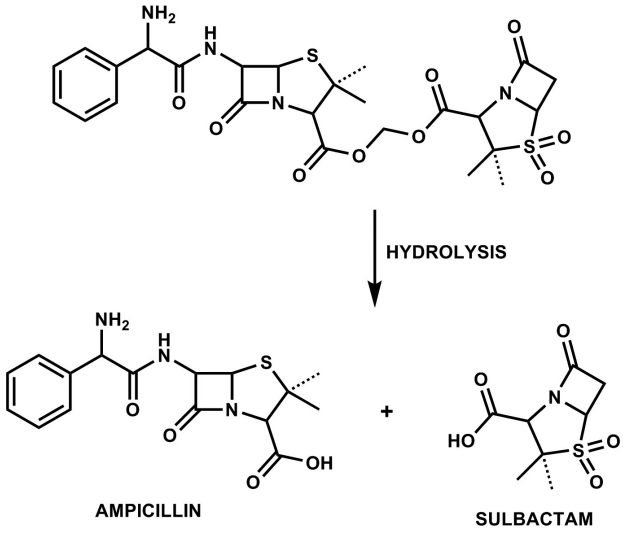

FIGURE 33 - Diagram of bioactivation of the sultamiciline prodrug.

CONCLUSION

Latentiation can be considered a tool of Pharmaceutical Chemistry that enables, in a simple fashion, improvement of the physical-chemical properties of drugs, adapting their pharmaceutical and/or pharmacokinetic characteristics, thus allowing the introduction, re-introduction or simple optimization of drugs used in therapy.

Through data found in literature, we observed that most prodrugs available for use in therapy are classic prodrugs, making up 53% of the total analyzed, followed by bioprecursors, with 42% market share. Regarding classic

prodrugs, despite the possibility of designing different types of hydrolysable bonds between the drug and the transporter group, it was observed that most of the agents available for use in therapy are of an ester-type bond, which is easily hydrolyzed within the organism. The main purpose of these ester derivatives is to increase bioavailability and to extend the period of effectiveness. Despite the first reciprocal prodrug compound (sulfasalazine) having been introduced into therapy in 1942, not many examples of this type of prodrug are found in clinics. On the other hand, proposals for several reciprocal prodrugs were observed in different lines of research.

From the results obtained, it was evident that the number of prodrugs introduced onto the market has increased. For example, of all the medicine approved in 2001-02, prodrugs accounted for 15% (Stella, 2004). On the other hand, it is important to emphasize the importance of the therapeutic significance of existing prodrugs. Several classes of drugs considered to be "blockbusters", that is top-selling drugs, such as statins, antiulcerous agents, anti-hypertensive agents and antivirals feature some examples that are prodrugs, for example, sinvastatin (a hypocholesterolemic agent), omeprazol (an antiulcerous agent), enalapril (an anti-hypertensive ECA inhibitor) and acyclovir (an antiviral), respectively.

It has been further observed that antineoplasic prodrugs on the market are classified as either bioprecursors or mixed prodrugs. Despite featuring a lower level of toxicity compared to other antineoplasic agents of the same class, latentiation of drugs should be examined further for the acquisition of antineoplasic agents with greater selectivity and lower toxicity. In addition, it is important to emphasize that there is some research directed towards the acquisition of antineoplasic prodrugs using, for example, peptides as transporters or more advanced techniques, known as ADEPT *(Antibody-Directed Enzyme Prodrug Therapy)* or GDEPT/VDEPT *(GeneVirus-Directed Enzyme Prodrug Therapy)* (Chung *et al.,* 2005), for which, derivatives have not yet been used in therapy.

Although several types of prodrugs from very distinctive classes are available for use in therapy, it can be noted that none of those mentioned are used for the treatment of neglected illnesses. However, latentiation should be explored when designing chemical entities for tropical endemic diseases, since it is not a costly method and has the potential of giving rise to therapeutically useful compounds.

Several prodrugs for the therapeutic treatment of these diseases have already been proposed and synthesized (Chung *et al.,* 2005). In most cases, such compounds aim to increase selectivity. In 1996, for example, Chung, 1996, synthesized reciprocal prodrugs from primaquine and nitrofural (Chung *et al.,* 2000),using dipeptidyl spacers with a scission selected by cruzipain (the exclusive enzyme of *T. Cruzi*), the purpose being to obtain potential drugs to combat American trypanosomiasis. The derivative hydroxymethylnitrofural has proven to be more active and less toxic than its prototype (Chung *et al.*, 2003) and despite the mechanism still not having been fully understood, several aspects of it are being studied (Barbosa *et al.*, 2007; Doriguetto *et al.*, 2005; Guido *et al.*, 2001a; Guido *et al.*, 2001b; Grillo *et al.*, 2007; Grillo *et al.*, 2008a; Grillo *et al.*, 2008b; Melo *et al.*, 2007; Trossini, 2008). On the other hand, Parise-Filho *et al*. (2004, 2007) and Parise-Filho and Silveira (2001) proposed polymeric prodrugs from oxamniquine with the aim of extending its period of effectiveness and reducing the toxicity of this schistosomal agent.

Many studies and research projects are being carried out in an effort to design new prodrugs which open up new perspectives for the treatment of several diseases. However, the aim of the present study was only to present existing prodrugs used in therapy, confirming the importance of this method not only as a research tool. It was ascertained that, although current research on the latentiation of drugs explores more advanced technologies, the prodrugs available for therapy to date have mostly been based on simpler design strategies.

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