Different Concepts of Drug Delivery in Disease En tities

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Abstract: This is a review of classical and novel concepts of drug delivery in particular diseases such as central nervous system disease, ophthalmic disease, cardiovascular disease, cancer and others. Nowadays, scientists are trying to propose efficient and selective drugs for the site of action, with best acceptance of patients, that can be metabolized to non-toxic derivatives. Prodrugs, soft drugs, codrugs are designed to maximize the amount of active drugs that reaches the site of action, through changing the physicochemical, biopharmaceutical or pharmacokinetic properties of the parent drugs. For last years different concepts of drug delivery have been developed to achieve the best patients' tolerance of a drug that has no undesirable properties. It is established that future studies will ameliorate drug properties so as to achieve the best drug delivery system.

Key Words: Prodrugs, soft drugs, codrugs, bioavailability, drug delivery

1. INTRODUCTION

Numerous medications possess inadvisable properties that may generate pharmacological, pharmaceutical, or pharmacokinetic barriers in their clinical use. The chemical applications of reversible prodrugs, can be useful in the optimization the clinical use of a drug. By no means, it can offer the highest flexibility and improve the drug efficacy in the treatment of many diseases.

Prodrugs are the compounds with no pharmacological activity because of the transient chemical transformations of biologically active molecules, and after administration, they are metabolically changed into the effective drugs. Many prodrugs have been designed and developed to overcome pharmaceutical and pharmacokinetic barriers in clinical drug use, such as low membrane permeability or weak water-solubility, lack of site specificity, chemical instability, toxicity, and poor patient acceptance (bad taste, odor, pain at the site of application). After administration, the prodrug, due to its enhanced properties, is more available than the parent drug. The most important step to achieve an expected biological effect is the chemical or biochemical conversion of the prodrug to its active form.

The term "prodrug" or "proagent" was introduced by Albert in 1950 to describe pharmacologically inactive chemical compounds that might be used to enhance the physicochemical characteristics of drugs, so that to increase their utility or to decrease their toxicity [1]. During the next years these compounds have also been called "latentiated drugs", "bioreversible derivatives", and "congeners", but "prodrugs" is now the most commonly accepted term. Prodrugs can be considered in different aspect of target and this review article sets them into specific disease entities [2].

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2. CLASSIFICATION OF THE PRODRUGS

Central Nervous System's Prodrugs

Brain and central nervous system disorders are still the world's leader in causing the disability, and are responsible for frequent hospitalization and prolonged care. It is a well-known fact, that the major problem in drugs delivery to brain is the presence of blood-brain barrier (BBB). The basic route for chemicals to enter the brain are micro-vessels. After the lipophilic fractions passively cross the cell membrane they are subjected to degrading enzymes current in large numbers in the endothelial cells that have mitochondria densities. Finally, the BBB is supplied in P-glycoprotein (Pgp), an active protein that removes most drugs from endothelial cell cytoplasm before they cross into the brain parenchyma [3]. To be an effective and specific drug that can be used in the treatment of several neurological diseases, its prodrug must overcome most of existed barriers.

Attention deficit hyperactivity disorder (ADHD) is a neuropsychiatric and behavioral disorder characterized by inattention, distractibility, hyperactivity and impulsivity [4]. Presently, there are two classes of approved agents in the treatment of ADHD: psychostimulants (e.g., methylphenidate and *d*-amphetamine) and the non-stimulant atomexetine [5]. Psychostimulants seem to be the most potent agents, with visible enhancement presented in the majority of patients. However, the action of this class of medicines is connected with a high tendency to addiction and abuse. To reduce these side effects, a series of *d*-amphetamine prodrugs were synthesized, from which lisdexamfetamine mesilate emerged.

Lisdexamfetamine dimesylate LDX (*Vyvanse*) is an inactive prodrug, where *d*-amphetamine is covalently bonded to *l*-lysine, an essential amino acid. After oral administration the pharmacologically active component (*d*-amphetamine) is released at the same time when the covalent bond is split up during metabolism. The covalent bond linking *l*-lysine to *d*-amphetamine is an amide bond and the structure of LDX

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resembles a dipeptide. LDX is stable to hydrolysis in serum and minimal amounts of *d*-amphetamine are released when the drug is administered by parenteral routes. The active drug is non-catecholamine sympathomimetic amine with CNS stimulant activity. The prodrug is probably metabolized by enzymes of the gastrointestinal tract [6]. LDX (structural formula is shown in Fig. (**1**)) was designed to present the same efficacy and tolerability as current extended-release stimulants used in the treatment of ADHD, but with lessened potential for abuse, diversion and overdose toxicity [7]. This prodrug is also characterized by longer duration of action (12 h). LDX was approved by the FDA in 2007 in the treatment of ADHD disease in children, and currently it is being clinically examined as a prodrug for adults.

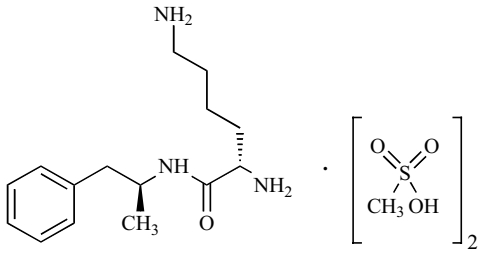

Fig. (1). Lisdexamfetamine dimesylate.

The "trojan horse" strategy for carrier proteins is the most significant solution to delivery of drugs to the brain. Designing the prodrug, which can take advantage of carrier proteins in the cell membrane, such as ones responsible for carrying amino acids into cells is often the most advisable approach [8]. Conventional Parkinson's disease (PD) treatment includes co-administration of oral levodopa (prodrug of polar dopamine) with an aromatic L-amino acid decarboxylase (AADC) inhibitor. During such treatment, catechol-*O*-methyltransferase (COMT) becomes the major enzyme responsible for the metabolism of levodopa. Despite this complex therapeutic approach, no more than 5-10% of orally administered levodopa enters the brain. Application of entacapone, together with levodopa and an AADC inhibitor, leads to improved levodopa bioavailability and to prolonged elimination of levodopa [9].

Entacapone (*Comtan, Comtess*) (structural formula is shown in Fig. (**2**)) (E)-2-cyano-N,N-diethyl-3-(3,4-dihydroxy-5-nitrophenyl)propenamide is a new 3,4-dihydroxy-5-nitro

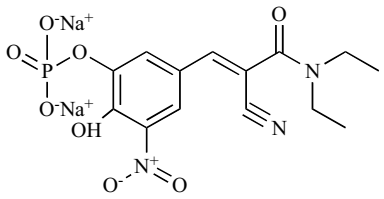

Fig. (2). Entacapone phosphate.

benzylidine derivative that plays an essential role of potent and specific inhibitor of COMT-2. Although entacapone is in clinical use as an adjunct to levodopa therapy in PD (improved total activities of daily living and motor function scores), its bioavailability is low after oral administration and characterized by large interindividual variation [10, 11]. The main reason of its low bioavailability has not been yet unidentified, but probably it is connected with poor aqueous solubility and slow dissolution rate at the pH of the stomach and the small intestine [12]. A study aimed to achieve a phosphate ester of entacapone for increasing aqueous solubility and dissolution rate has been reported [13].

Propofol (2,6-diisopropylphenol) is a widely used intravenous sedative-hypnotic anesthetic agent with a short duration of its activity, rapid formation and minimal accumulation on long-term administration [14]. Propofol's low water-solubility leads to the formulation of oil-in-water emulsion. The lipid formulations have several well-known undesirable properties [15-17]. Most of these side effects could be lightened by an aqueous formulation [18]. Designing water-soluble prodrugs is a method that was successfully applied in the past to several water-insoluble drugs (antibiotics, anesthetics, steroidal non-inflammatory drugs) [19]. The water-soluble propofol prodrug is phosphono-*O*-methyl of propofol structural formula is shown in Fig. (**3**) ((*Aquavan*) that is enzymatically changed into active compound (propofol) and nontoxic inorganic phosphate and formaldehyde [20-22].

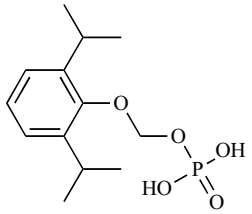

Fig. (3). Phosphono-*O*-methyl of propofol.

Gabapentin is a derivative of gamma-aminobutyric acid with therapeutic utility as an anticonvulsant drug used in epilepsy, neuropathic pain, restless legs syndrome, anxiety disorders, post-herpetic neuralgia and numerous other indications [23-26]. It suffers from some pharmacokinetic properties including low capacity, limited intestinal distribution, lack of dose proportionality [27], short half-time and variable expression of the solute transporter responsible for gabapentin absorption (high inter-patient variability) [28, 29].

XP-13512 (structural formula is shown in Fig. (**4**)) is a new oral prodrug of gabapentin synthesized to improve the pharmacokinetic restrictions of gabapentin. The prodrug is chemically stable and quickly changed into gabapentin by non-specific esterases after oral absorption in intestinal and liver tissues and blood [30]. XP-13512's p*H* dependence indicated its passive permeability across artificial membranes and it is a substrate for both monocarboxylate transporter type-1 (MCT-1) and for the sodium-dependent multivitamin transporter (SMVT) [31]. Oral bioavailability extended from 25% for gabapentin to 85% for XP-13512 in monkeys, and the saturation problem was not observed for higher prodrug doses. In the contrast to gabapentin, XP-13512 is well absorbed in the intestine track, suggesting that it could be successfully incorporated into a controlled release formulation. XP-13512 is currently in phase IIa clinical trials for post-herpetic neuralgia and restless leg syndrome on the basis of increased gabapentin exposure, reduced interpatient

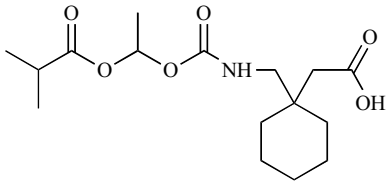

Fig. (4). XP-13512.

variability, decreased dosing frequency and reduced incidence of side effects.

Valproic acid VPA is a widely used anticonvulsant drug, however its teratogenic effects and fatal hepatic necrosis resembling Reye's Syndrome cause failure of the therapy. The unwanted side effects are the result of high concentration of the drug in the blood, however the elevated level of the drug in plasma is essential to achieve the therapeutic effect. New prodrugs of VPA were obtained by estrification with *myo*-inositol. Due to its physiological role as a second messenger, the selection of *myo*-iniositol as a carrier group can be estimated as a successful method of delivering VPA to its therapeutic site of action [32].

Carbamazepine CBZ and phenytoin are effective in the treatment of partial and generalized tonic–clonic epileptic seizures, and are less sedating and causes less cognitive impairment. Unfortunately, both of them have relatively poor aqueous solubility which impedes parenteral administration, and till now there is no commercially available injectable formulation. A new N-cysteamine CBZ (structural formula is shown in Fig. (**5**)) was designed as a water-soluble sulfenamide prodrug of CBZ to regenerate CBZ *in vivo* by cleavage of the sulfenamide bond by chemical reaction with glutathione and other endogenous sulfhydryl compounds. A successful *in vivo* result, supporting the concept of the sulfenamide prodrug strategy, could further the application of this approach to improve the physicochemical properties and/or delivery characteristics of other amido-acidic drugs, including ureas [33].

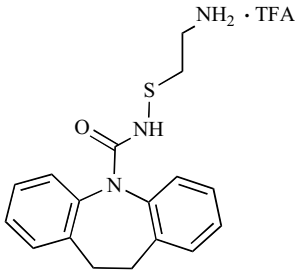

Fig. (5). N-cysteamine CBZ.

Fosphenytoin (*Cerebyx*) (structural formula is shown in Fig. (**6**)) is a water-soluble prodrug of phenytoin that provides improved efficacy and safety once given intravenously or intramuscularly. The phosphate ester after systemic administration is rapidly modified to form an unstable intermediate that breaks down to form formaldehyde and the active drug phenytoin and inorganic phosphate [34, 35].

Dexanabinol is a synthetic non-psychotropic cannabinoid with potential use as a neuroprotective agent to prevent cog-

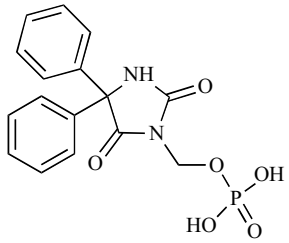

Fig. (6). Fosphenytoin.

nitive impairement with promising anti-inflammatory activity in the brain and spinal cord. The synthesis of the large number of aqueous soluble esters of dexanabinol gave result in identification of the group of derivatives of the parent drugs, that could be treated as prodrugs. Fair solubility and appropriate level of stability achieved by the esters, which are salts of the allylic N-trimethyl and triethyl amino acetates. These type of prodrugs can be used for intravenous administration of drug to achieve appropriate concentration in brain [36].

Ocular Prodrugs

The majority of ophthalmic prodrugs have been developed accidentally. They were usually adopted from parent drugs that originally were intended for other specific organs (heart, colon). By chance it turned out that these drugs perfectly suit to ophthalmic area and they are effective in specific diseases without causing systemic side effects. However, the complexity of human eye presents special challenges for drug approach. Apparently eye is well protected against absorption of drugs, first by the eyelids and tear-flow and secondly by the cornea and conjunctival epithelial barriers [37]. Ocular drug application causes an immediate tear-flow, which washes the drug from the eye and secondly, the drug is drained from precorneal area into the systemic circulation through of the nasolacrimal duct [38]. Blood-ocular barriers are significant for the removal of toxic waste products and xenobiotics. They can be divided between two barriers: the blood-vitreous barrier and the blood-retinal barriers. Because the eye is often exposed to external compounds it is not surprising that eye possesses enzymes capable of metabolizing them [39]. Therefore, ocular bioavailability through topical administration as eye drops is often very poor, usually lower than 5% [40]. Additionally, drug metabolism activities were also found in different ocular structures.

Improvement of ocular bioavailability can reduce the administration frequency or lower the drug concentration in ophthalmic preparation, with a consequent decrease in undesired side-effects, which, in turn, is good for the quality of life of patients and also greatly prolongs duration of action with high stability in eye drop formulation. The prodrug approach seems to be promising and viable idea for investigation of new active and effective ophthalmic drugs. New strategies based on metabolic activation are constructed to overcome ophthalmic drug delivery problems. The eye consists of two parts: one, lipophilic, is the main barrier for hydrophilic drugs (the cornea epithelium and endothelium) and the second one, more hydrophilic, is the main barrier for

lipophilic drugs (inner stroma) [41, 42]. Drug diffusion between these two structures may appear as a penetration-limiting factor. It is essential to achieve biphasic solubility drug that as a prodrug could be soluble in lipophilic serum and that may be transformed to more hydrophilic parent drug [43, 44].

Pilocarpine, being a mitotic agent, is always presented as the most familiar example of ophthalmic prodrug that controls intraocular pressure (IOP). Its bioavailability is very poor, about 1-3% of the topically administrated dose [45-47]. Additionally, it has a short half-life that requires frequent application of the drug. A number of lipophilic pilocarpine mono- and diesters were obtained to improve the drug delivery and bioavailability properties of parent drug [48-51]. In water solution the esters are converted by a quantitative and base-catalyzed cyclization to parental drug. The lactonization increased proportional to the concentration of the hydroxide ion and enrolled "intramolecular nucleophilic attack of alkoxide ion on the ester carbonyl moiety" [52]. Although the corneal absorption of pilocarpine was changed by the prodrug, ocular irritation appeared with the *in vivo* application of these lipophilic esters. The better lipophilicity, p*H* and concentration is, the more ocular irritation appears [53]. The ocular delivery of pilocarpine prodrugs may be increased while local irritation can be lessened by properly matching buffer, viscosity and complexation with polymer formulation strategies [54-56].

Topical β-blockers were the first medications used as anti-glaucoma agents and they are still considered to be the first choice of drugs for initial therapy in open angle glaucoma [57]. Glaucoma is defined as a group of diseases of the eye characterized by progressive optic nerve cupping, visual field loss and characterized by high IOP [58, 59]. β-blockers administrated topically are effective in IOP - reduction through decreasing aqueous humor formation by ciliary-body processes. However, they are rapidly removed from the precorneal area because of the drainage through the nasolacrimal duct, dilution by tear turnover. Additionally, they can cause systemic side effects because of direct absorption in the tissues and the nasolacrimal system. The systemic unwanted side effects of β-blockers are mainly connected to their activation of cardiovascular system (β_1-receptor) [60], respiratory system (β_2-receptor), and central nervous systems [61]. There have been some studies about the delivery of *O*-acetyl, *O*-propionyl, *O*-butyryl, *O*-valeryl and *O*-palmitoyl ester prodrug derivatives of the β-blocker tilisolol instiled as the anti-glaucoma agents to decrease IOP [62-64]. All described prodrugs undergo quick enzymatic transformation to tilisolol in ocular tissues homogenates. It was presented that prodrug was generally absorbed by the corneal route and the transit time was increased in tissues of the eye. The potential utility of lipophilic prodrugs of tilisolol as agents used in glaucoma was proved in many scientific tests.

The study of metabolism of bimatoprost (structural formula is shown in Fig. (**7**)) (*Lumigan*) established that the ethylamide group of bimatoprost was cleaved by either human and rabbit cornea, iris and ciliary body and the sclera to achieve prostaglandin FP agonist 17-phenyl-trinor $PGF2_\alpha$ [65].

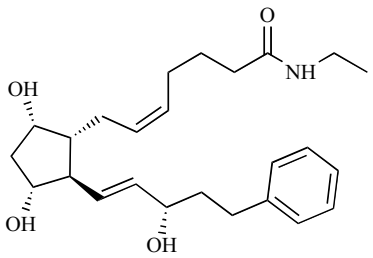

Fig. (7). Bimatoprost.

Latanoprost (*Xalatan*) (structural formula is shown in Fig. (**8**)) and travoprost (*Travatan*) (structural formula is shown in Fig. (**9**)) are prostanoid selective FP receptor agonists that are supposed to decrease IOP by extending the outflow of aqueous humor. Both are isopropyl ester prodrugs, which are absorbed through the cornea, where they are hydrolyzed by esterases to the acid form to become pharmacologically active [66-68].

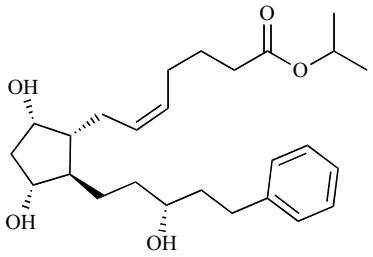

Fig. (8). Latanoprost.

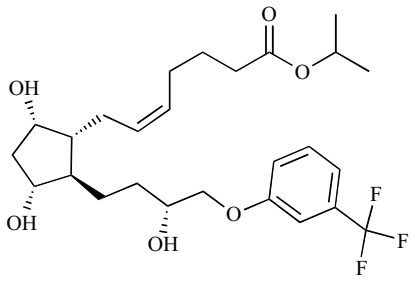

Fig. (9). Travoprost.

N-acetylcarnosine (*Can-C*™) has been discovered to be appropriate for the prevention and non-surgical treatment of cataracts connected with the age. The ophthalmic prodrug N-acetylcarnosine (NAC) was created to optimize its specific effects in producing the basic bioactivating antioxidant activity *in vivo* and minimizing unwanted effects of lipid peroxides to the crystalline lens. In the newest clinical trial it was proven to achieve an effective, safe and long-term improvement of sight. NAC, as a time-release carrier of L-carnosine, is resistant to enzymatic hydrolysis with the dipeptidase enzyme – carnosinase that transforms L-carnosine to toxic product – histamine (promotor of oxidation reactions). NAC (structural formula is shown in Fig. (**10**)) is proposed to treat ocular disorders that have an element of oxidative stress in their history (cataracts, complications of diabetes mellitus, corneal disorders, dry eye, glaucoma, ocular inflammation, retinal degeneration, systemic diseases, vitreous floaters) [69,70].

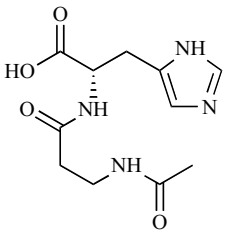

Fig. (10). N-acetylcarnosine.

The unique strategy of codrug design was also recognized as a new system of ophthalmic drug delivery. Codrugs, are also named as mutual drugs, possess a covalent linker between two or more synergestic medicines to enhance the drug delivery properties of one or both drugs [71]. The aim of the concept is to achieve better physicochemical properties of synergististic molecules compared to the physical properties of the two parent drugs separately. These improved properties result in a controlled hydrolysis of the drug in tissues [72].

Naproxen-5FU is a codrug system designed to treat experimental post-traumatic proliferative vitreoretinopathy (PVR). The results of the test suggested that the codrug successfully curbs the progression in PVR in rabbits that is closely related to PVR in humans [73].

Two β-blockers (atenolol and timolol) are covalently linked to ethacrynic acid (EAC) and as codrug systems ameliorate ocular delivery and take advantage of the apparent synergistic mechanism of EAC and β-blocking agents [74]. These two drugs are also tested as a codrug system linked to $PGF2_{\alpha}$ or $PGF2_{\alpha}$ triacetate *via* an ester part to allow hydrolytic conversion at physiological pH with enzymatic hydrolysis. The main goal of this codrug is to improve the water solubility of the parent drugs, and to intensify corneal permeability. Both codrugs PGF2α-atenolol and PGF2α-timolol effectively yielded hydrolysis *in vitro* to create PGF2α and atenolol or timolol, respectively in phosphate buffer and in human serum [75].

Eye-targeted chemical delivery system based on oxime and methoxime analogs of β-blockers is a real breakthrough in the era of ophthalmic drugs as potential antiglaucoma agents. They are enzymatically metabolized by eye's enzymes presented in the iris-ciliary body, where the high concentrations of the active β-antagonists are indicated. These derivatives, similary to prodrugs, do not present any significant systemic side effects in spite of their very high activities as decreasing IOP agents. Site-directed β_1-blocker - the oxime and methoxime derivatives of alprenolol and betaxolol were specially designed to be activated in the eye to present considerable and long-lasting reduction in the IOP at 0,25 and 0,5% concentration [76-79].

Soft drugs (SDs) represent opposite targeting concept to prodrugs [80]. They are described as active components designed to achieve targeted effects *via* a single-step inactivation, by enzymes (oxygenases) found ubiquitously in the systemic circulation to be eliminated [81, 82]. Due to the fact that the desired activity is local, the SDs are administered near or exactly at the site of action. That is why this approach is perfectly well-suited for ophthalmic application [83, 84]. The SDs are presented by the soft β-blockers (adaprolol) and corticosteroids. Adaprolol maleate (structural formula is shown in Fig. (**11**)) is an ester selected as a potential candidate for a new topical antiglaucoma agent. The lipophilicity (membrane transport) and fairly stability are important for pharmacological its activity [85-87]. The good corneal permeability is achieved and adaprolol did effective present prolonged and significant IOP-reduction, but is hydrolyzed comperatively rapidly [88, 89]. Adaprolol did not reduce the systolic blood pressure with statistical significance, whilst timolol did. Timolol also decreased the heart rate, while pulse was at the physiologically level in the adaprolol test groups. So that, adaprolol is more potent in decreasing IOP and has a better cardiovascular profile than timolol [90].

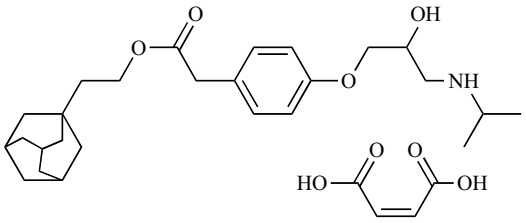

Fig. (11). Adaprolol maleate.

Soft anti-inflammatory corticosteroids establish very significant and most successful improvement of topical corticosteroids used in the treatment of ocular inflammations (injury, surgery, infection) and allergies**.** Traditional corticosteroids cause many systemic side effects but also can trigger some ocular complications (IOP-elevation, resultant steroid-induced glaucoma, cataract formation) [91-93]. Loteprednol etabonate (structural formula is shown in Fig. (**12**)) LE (*Lotemax*) belongs to first-generation cortienic acid-based steroids that comes from cortienic acid, which makes the starting point. The pharmacokinetic profile of LE indicates that, when absorbed systemically, it is rapidly transformed to the inactive 17 β -carboxylic acid metabolite and eliminated from the body mainly through the bile and urine.

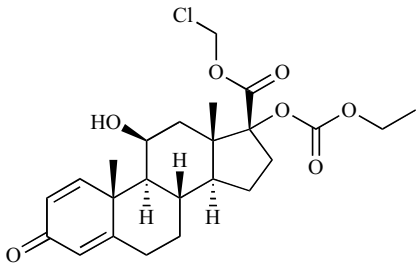

Fig. (12). Loteprednol etabonate.

The main factors that decrease the ocular bioavailability of drugs are P-glycoproteins present in the cornea that remove the topically applied drugs from the cornea [94]. Quinidine prodrugs such as L-valine and L-valine-valine esters can change P-gp-mediated efflux and strongly encourage its permeability, what gives us hope to create a viable strategy for overcoming P-gp-mediated efflux. Utility of antiviral prodrugs has been known for long time. First two substances were valacyclovir (VACV) as the L-valine ester of acyclovir and gly-val-acyclovir (GVACV) as a L-glicine-valine ester of acyclovir [95, 96]. Furthermore, series of dipeptide mono-

ester ganciclovir (GCV) prodrugs: Val-Val-GCV, Tyr-Val-GCV, Gly-Val-GCV and monopeptide ester of ganciclovir Val-GCV were synthetized. The Val-Val-GCV presents excellent *in vivo* antiviral activity against HSV-1 and improved properties such as: corneal permeability, chemical stability, water solubility [97].

Cardiovascular Prodrugs

In cardiovascular therapy, the ester prodrugs of some angiotensin converting enzyme inhibitors (ACEI), such as ramipril, zofenopril and enalaprilat, being substrate of the small intestinal dipeptide transporter, are designed to surmount the erratic problem and low absorption [98]. The deestrifications take place in the liver to release the active parent compounds. They are good examples of an approach designed to achieve better absorption.

The prodrug CGP 22979 (structural formula is shown in Fig. (**13**)) is the N-acetyl-γ-L-glutamyl derivative of the hydralazine-like vasodilator CPG 18126. It was designed to achieve high concentration of the active compound in the place of its action (kidney) and to decrease undesirable properties.

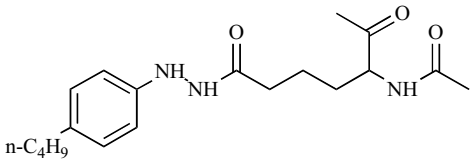

Fig. (13). CGP 22979.

The main target of the prodrug, using in the cardiovascular diseases, was to achieve selective renal vasodilation [99]. Dopaminergic activity some dopamine prodrugs like TA-870 (structural formula is shown in Fig. **(14))** [100, 101] and ibopamine (structural formula is shown in Fig. **(15))** [102, 103] present. The renal selective DA prodrugs – gludopa (structural formula is shown in Fig. **(16))** and SIM 2055 (structural formula is shown in Fig. **(17))** are potentially ideal therapeutic agents for the treatment of disease states such as essential hypertension and renal failure, respectively [104].

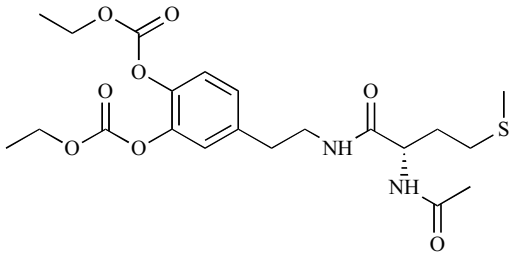

Fig. (14). TA-870.

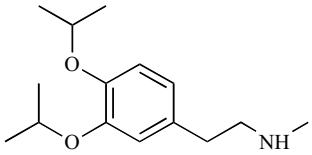

Fig. (15). Ibopamine.

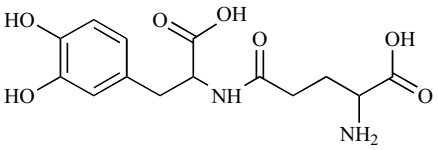

Fig. (16). Gludopa.

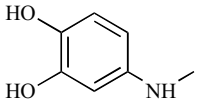

Fig. (17). SIM 2055.

Clopidogrel (structural formula is shown in Fig. (**18**)) and ticlopidine (structural formula is shown in Fig. (**19**)) are prodrugs, of proven benefits, that need to be administered several hours before their reactivity. They must undergo metabolic change in the liver and plasma levels to the active metabolite that can vary between subjects [105, 106].

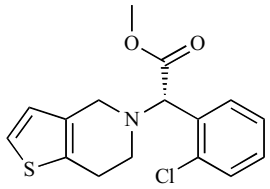

Fig. (18). Clopidogrel.

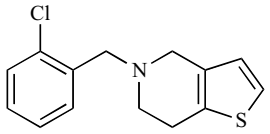

Fig. (19). Ticlopidine.

An Irish pharmaceutical development company holds patents on two new prodrugs, esters of established cardiovascular drugs in combination with aspirin: ACEI aspirin prodrugs and nitrate (isosorbide 5-mononitrate) aspirin prodrugs. These new compounds create an opportunity for administering these drugs not only by the oral route but also *via* a transdermal delivery route. This property of delivering two drugs *via* a new route of administration will improve patient compliance. Early development of both isosorbide 5-mononitrate (ISMN) and aspirin absorption has been carried out. There is evidence that the platelet aggregation was reduced in all 6 volunteers suitable for assessment what indicates clearly that aspirin was absorbed in clinically effective amounts.

d-γ-tocopherol (γ-Toc) is one of the major natural forms of tocopherols, which is known as vitamin E. For many years this form γ of vitamin E has been ignored in favour of form α, because of its poor bioactivity defined by the rat fetal resorption assay. Everybody thought that form α was the best one [107]. However, several independent studies have demonstrated beneficial effects of *d*-γ-tocopherol connected with coronary heart disease [108-110]. *d*-γ-tocopherol has better properties than α-tocopherol in its ability to latch reactive nitrogen species, mutagenic electrophiles generated during inflammation [111, 112]. In addition, γ-Toc and *S*-γ-CEHC

(its metabolite) curbed the generation of prostaglandin E2 (PGE2), a significant mediator synthesized *via* the cyclooxygenase-2 (COX-2) - catalyzed oxidation of arachidonic acid during inflammation [113]. Due to these facts, it was certain that γ-Toc and *S*-γ-CEHC acquire important pharmacological activities as drugs. Unfortunately, so as to achieve highly available drug with no limits to its therapeutic applications it was obvious to eliminate the poor water-solubility and instability to oxygen. Besides, the bioavailability of *S*-γ-CEHC is very low because of its quick elimination rate [114, 115]. To improve above mentioned physicochemical properties of γ-Toc the phenolic group should be freely esterified. γ-TDMG (structural formula is shown in Fig. (**20**)) (hydrochloride salt of the *N*, *N*-dimethylglycinate of γ-Toc) is a desirable prodrug, which displays an adequate solubility profile in water, and high susceptibility to the enzymatic hydrolysis by rat and human liver enzymes [116].

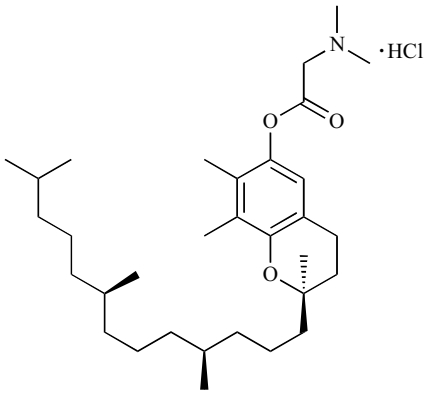

Fig. (20). γ-TDMG.

Ximelagatran (structural formula is shown in Fig. (**21**)) is a double prodrug of melagatran, that was identified as a prospective direct inhibitor of thrombin and platelet aggregation. The parent drug's oral bioavailability was only about 5% and was strongly reduced in the presence of food and there was need to improve these pharmacological properties [117]. The prodrug is more lipophilic and penetrable than the parent drug, leading to increase bioavailability of about 20% for the active melagatran [118].

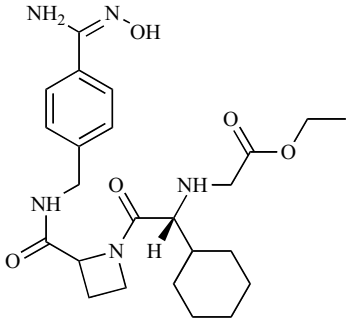

Fig. (21). Ximelagatran.

Anti-Inflammatory Prodrugs

Prodrugs that hide the acidic group of non-steroidal anti-inflammatory drugs NSAIDs have been reported to alleviate gastrointestinal toxicity due to local action [119]. The improved safety profile of COX-2 inhibitors may permit the utility of these new prodrugs for long-term prophylactic use in people with a known genetic susceptibility to certain chronic diseases [120-122]. Based on the data obtained from various animal models of acute and chronic inflammation, it was proved that pharmacokinetic profile of celecoxib was significantly improved by creating DRF 4367 (structural formula is shown in Fig. (**22**)). The derivative of celecoxib presented the proof-of-concept that an *N*-acylated sulfonamide could be metabolized to $-SO_2NH_2$ in rat tissue preparations as well as in whole animals after oral application [123]. Sodium salt of 2-hydroxymethyl-4-[5-(4-methoxyphenyl)-3-trifluoromethyl pyrazol-1-yl]-N-propionylbenzenesulfonamide exhibited better *in vivo* efficacy, pharmacokinetic properties, and high water solubility [124-126].

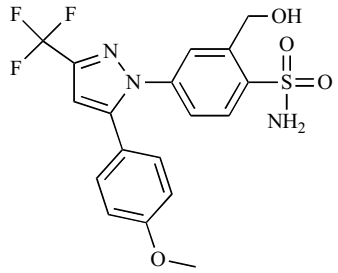

Fig. (22). DRF 4367.

As an example of decreasing gastrointestinal irritation parecoxib sodium (structural formula is shown in Fig. (**23**)) is introduced as a prodrug of valdecoxib for parenteral administration for acute pain management, particularly post-surgical pain. It is a hydrophilic prodrug that was identified as a highly potent and selective inhibitor PGs synthesis by COX-2 [127].

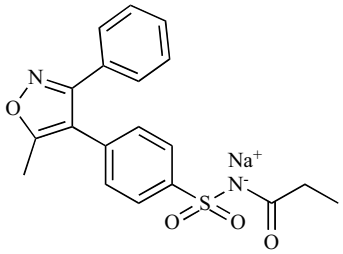

Fig. (23). Parecoxib sodium.

There was also a study whose aim was to synthesize several ester derivatives of mefenamic acid to reduce gastric toxicity. To design these prodrugs a computational method was effectively used so as to eliminate the efflux process by P-gp [128, 129]. The prodrugs were tested for their stability profile in the enzymatic environment, bidirectional permeability through Caco-2 monolayer, and their potential as transporter modulators. Bidirectional permeability tests proved that two prodrugs (2-morpholin-4-ylethyl2-[(2,3-dimethylphenyl) amino]benzoate and 2-pyrrolidin-1-ylethyl-2-[(2,3-dimethylphenyl)amino]benzoate) were substrates of active efflux transporters. These prodrugs increased the cellular calcein accumulation, indicating that they can work as P-gp and/or MRP inhibitors. These compounds may be useful as leaders for designing new inhibitors of efflux transporters [130].

To overcome the worst side effects of non-selective anti-inflammatory drugs, which are gastric irritation, serious gastrointestinal bleeding, perforation and ulceration, was developed – ampiroxicam (structural formula is shown in Fig. (**24**)) [131].

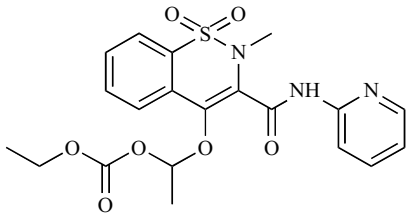

Fig. (24). Ampiroxicam.

To avoid the gastric ulcerogenic side effects diacyl glyseryl esters of naproxen were synthesized and their dermal application *in vitro,* as an NSAID used in the treatment of arthritis, was investigated [132].

Antiviral Prodrugs

Stachyflin is a drug active against influenza A (H1N1 and H2N2) viruses *in vitro* [133]. It presents different mode of action than ramantadine and amantadine. Its antiviral activity *in vitro* is very high, unfortunately it decreases when stachyfilin is administered orally [134-138]. The reason of the low bioavailability was thought to be poor water-solubility of the drug. There was large number of studies which aimed to improve stachyflin properties by: reducing of size [139], adding of surfactans [140], formulating of solid dispersions [141], complexing with solubilizing agents and chemical modification [142]. Stachyflin, its derivative and its phosphate ester prodrug (structural formula is shown in Fig. (**25**)) were achieved to improve oral absorption and *in vivo* anti-influenza virus activity [143].

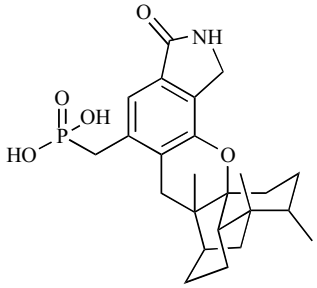

Fig. (25). Stachyflin phosphate.

To improve the low hydrophilic profile of inhibitors of the type 1 human immunodeficiency virus (HIV-1) protease, the efficient approach is to change the lipophilic parent drugs into water-soluble prodrugs. The parent drugs were covalently bonded to the solubilizing agents such as phosphates [144, 145], sugars [146, 147] and amines [148, 149]. They can be hydrolized enzymatically or chemically under physiological conditions to release the parent drug. The prodrugs' activity related to the O→N intramolecular acyl migration reaction such as potent tripeptide-type HIV-1 PR inhibitors, KNI-272 and K-279 and dipeptide-type inhibitor, KNI-727 were designed and their ability as the water-soluble agents was evaluated [150-152]. These prodrugs were created to make possible a chemical regeneration of the parent drug adjusting a special p*H* sensitive self-cleavable linker [153].

Amprenavir APV (*Agenerase*) is one of seven HIV-1 protease inhibitors in common use [154, 155]. Several favorable clinical attributes such as simple regimen of drug administration connected with its relatively long half-time [156], highly effective and an unique resistance pathway, that may preserve future protease inhibitor treatment options, make the APV-based therapy very accessible by patients [157-159]. However, there are difficulties in gastrointestinal tract solubility and ultimately absorption because of the low water solubility of APV and a high ratio of excipients in drug. Several studies have registered that a high pill burden is the result of its low aqueous solubility, that diminishes antiretroviral adherence and finally, virologic control [160, 161]. It was proposed that changes in therapy that bring about improvements in patient compliance and will improve the overall success rate of these therapies. A phosphate ester prodrug of amprenavir - fosamprenavir GW433908 (structural formula is shown in Fig. (**26**)), with improved water-solubility has been developed with a view to providing more flexible dosing schedule and reducing the pill burden of current a highly active antiretroviral therapy HAART regimens [162, 163].

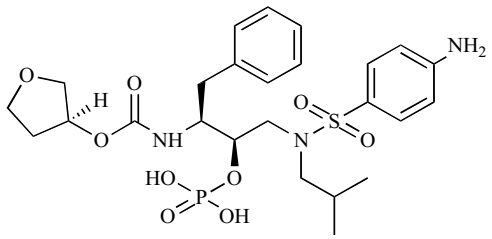

Fig. (26). Fosamprenavir.

There were two studies, first one investigated the pharmacokinetics properties of calcium and sodium salts of the prodrugs (GW433908G and GW433908A) to identify the most effective prodrug salt. Moreover, the effect of food on GW433908G absorption, as well as its safety and tolerability, were investigated [164]. The fosamprenavir calcium was chosen because of its high aqueous solubility, solution and solid-state stability and rapid transforamtion to the parent drug at the place of action. The second study investigated the pharmacokinetics profile of amprenavir while it is used as GW433908G tablets, before and after a meal, that was compared to GW433908G suspension and amprenavir capsules [165]. The results of the study indicated that the prodrug can release from a solid dosage form with a lower pill burden and two tablets can replace eight amprenavir soft-gels. In 2003 fosamprenavir calcium was approved by FDA for the treatment of HIV infections in adults.

Adefovir dipivoxil (structural formula is shown in Fig. (**27**)), an esterase-activated prodrug of adefovir (PMEA) is effective in the treatment of lamivudine-resistant chronic hepatitis B (HBV) [166-168].

Remofovir mesylate (structural formula is shown in Fig. (**28**)) is a CYP3A4-activated prodrug of 9-(2-phosphonylmethoxyethyl) adenine. This prodrug of PMEA possesses

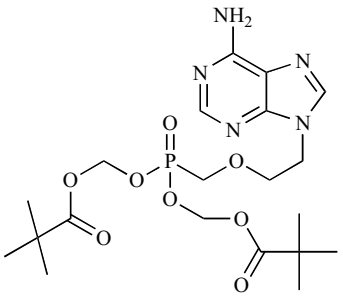

Fig. (27). Adefovir dipivoxil.

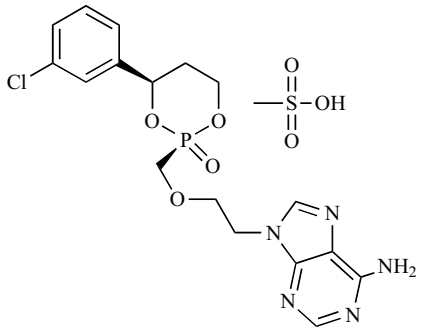

Fig. (28). Remofovir mesylate.

excellent absorbation and rapid liver-target qualities in rats and is safer than adeofovir dipivoxil in one-month monkey toxicity study. That is the reason why remofovir can improve its clinical effectiveness with lower nephrotoxicity potential than adefovir dipivoxil. The prodrug is in Phase II clinical development for *hepatitis B* and is designed to transport appropriate concentrations of adefovir to the liver, while limiting the amount of adefovir generated outside the liver to considerably reduce dose-related toxicities [169].

Tenofovir disoproxil fumarate (structural formula is shown in Fig. (**29**)) is a following example of bioavailable prodrug with better permeability than a parent drug. It is a

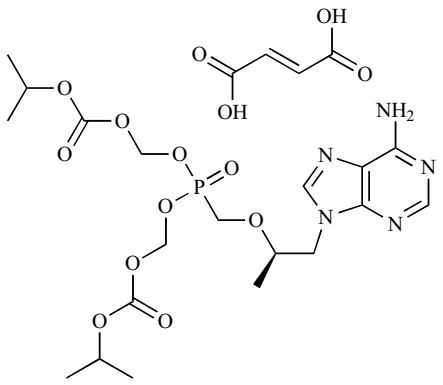

Fig. (29). Tenofovir disoproxil fumarate.

potent nucleotide analogue reverse-transcriptase inhibitor with activity against HIV and *hepatitis B* virus. It is the most stable of several evaluated phosphonate prodrugs that is quickly converted to the parent tenofovir with high oral bioavailability and well-tolerance. It is connected with its better lipophilicity profile than stavudine (a well-known nucleoside analog reverse transcriptase inhibitor active against HIV) possesses and has not been connected with the mitochondrial toxicity ascribed to other nucleoside analogues. [170].

Antibacterial Prodrugs

Interest in the development of new antibacterial agents remains high, about 80 years after the clinical introduction of the first antibiotic - penicillin [171]. The aim of these researches is to achieve a broader spectrum of antibacterial activities, to discover new modes of action, to which existing bacteria are not resistant and finally, to decrease the toxicity. As a part of *Ozaki's et al.* continuing program to develop effective derivatives of fluoroquinolones it was prepared the NM 441, which is the lipophilic prodrug of its active form – NM 394 {6-fluoro-1-methyl-4-oxo-7-(1-piperazinyl)-4-H-[1,3]thiazeto[3,2-a]-quinoline-3-carboxylic acid}, a novel fluoroquinolone antibacterial agent with a sulfur atom at the C-2 position (structural formula is shown in Fig. (**30**)). The prodrug showed in the antibacterial studies greater activity than ofloxacin and ciprofloxacin, including activity against Gram-positive patogenes [172].

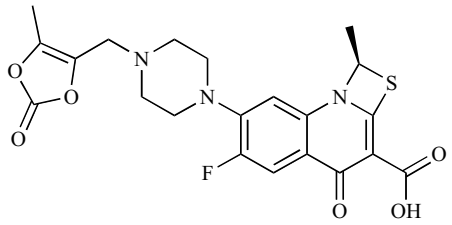

Fig. (30). NM 441.

PA 2808 prodrug (structural formula is shown in Fig. (**31**)) containing a phosphate group would be suitable for aerosol delivery in respiratory-compromised cystic fibrosis (CF) patients [173]. Although the parent drug – PA 2789 demonstrated excellent activity against both, Gram-positive

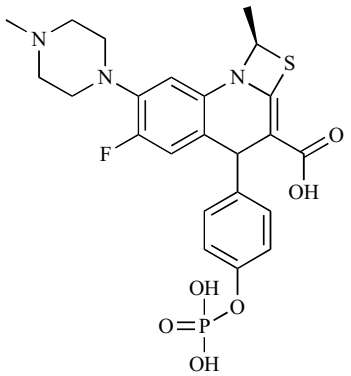

Fig. (31). PA 2808 (parent: PA 2789).

and Gram-negative organisms, it had poor oral bioavailability [174]. Due to the ability of the phosphate group to increase water solubility as well as to be cleaved by ubiquitous alkaline phosphatase, the active molecule (PA 2789) is easily released at the site of infection. The use of a phosphate group

was also important in light of literature reports showing that cystic fibrosis sufferers have elevated alkaline phosphatase levels in their lung tissues [175, 176].

The antimicrobial drug metronidazole has been used for topical application in the treatment of acne rosacea and acne vulgaris. This compound is very hydrophilic, what reduces its dermal absorption. Application of this drug in more lipophilic form would be advantageous to release the significant amount of drug within the skin. Some aliphatic esters of metronidazole with the aliphatic side chains containing 1 to 17 carbon atoms were achieved [177].

Chemotherapy for leishmaniasis is currently not sufficient, so there is a real need for improved drugs and formulations treating this disease. Pentavalent antimony compounds have been used as the primary therapy for leishmaniasis over the past 50 years. These drugs are highly toxic and they need to be administered parenterally at high dosages and for long durations of therapy [178]. In order to minimize toxicity and optimize physicochemical properties of these antimony compounds, the novel drug - buparvaquone was synthetized. Since improvement of its properties was not satisfactory enough, further modifications were introduced to its structure and, as a result, the 3-phosphate and 3-phosphonooxymethyl were created. These compounds significantly increased the water solubility of the parent drug. In addition, the prodrugs quickly released buparvaquone in alkaline phosphatase environment. On the other hand, chemical stability in aqueous solution over a p*H* range of 3.0–7.4 was only reserved, which limits their clinical utility [179]. New hydrophilic phosphate prodrugs of buparvaquone-oxime and buparvaquone-*O*-methyloxime were achieved. The most potential prodrug, phosphonooxymethyl-buparvaquoneoxime, had high aqueous solubility and chemical stability over a p*H* range of 3.0–7.4, and it rapidly liberated the parent buparvaquoneoxime *via* enzymatic bioconversion. After alkaline hydrolysis of the prodrug, the active compounds is supposed to effectively permeate through the intestinal wall as a lipophilic agent, and further oxidation to buparvaquone takes place in the body after absorption. These improved properties prompt the new prodrug hopeful for oral drug administration in the treatment of visceral leishmaniasis [180].

Antifungal Prodrugs

Fosfluconazole (structural formula is shown in Fig. (**32**)) as a prodrug of fluconazole allowed for bolus administration, reducing fluid and sodium load, and it facilitated access to a small-volume high-dose formulation of active drug [181]. A smaller, concentrated product would therefore offer advantages to the patient, as well as being more convenient for storage and in clinical use [182]. Fluconazole is removed especially by renal excretion, where almost 80% of the administered drug appearing in the urine as unchanged form [183, 184].

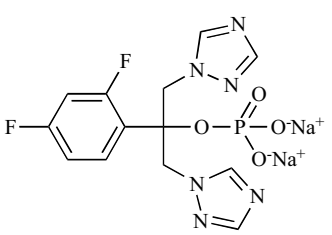

Fig. (32). Fosfluconazole.

Phosphate ester of the parent drug is readily ionizable and, in a salt form, it significantly increases water solubility. The prodrug is also sufficiently stable in the solid state and in water solution which facilitates its intravenous administration [185, 186]. Furthermore, it is readily metabolized *in vivo* by nonselective alkaline phosphatases, thus releasing the parent drug. As well as fluconazole, the poor aqueous solubility of ravuconazole (0.6 mg/mL) rules its development for intravenous administration out [187]. There was the research of synthesis the prodrugs of ravuconazole – BMS 379224 and BMS 315801. The phosphonooxymethyl ether analogue (BMS 379224) and N-phosphonooxymethyl triazolium salt (BMS 315801) were both highly soluble in water and modified to the parent in alkaline phosphatase, and also *in vivo* (rat). However, BMS 315801 was examinated to be less stable than BMS 379224 in aqueous environment at physiological p*H*. The results from preclinical tests, including animal safety evidence, suggest that the prodrug BMS 379224 (structural formula is shown in Fig. (**33**)) (phosphonooxymethyl ether derivative) is one of the most promising prodrugs of ravuconazole that has been tested [188].

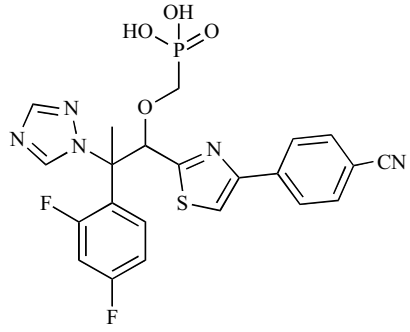

Fig. (33). BMS 379224.

Anticancer Prodrugs

Anticancer prodrugs strategy supposes that prodrugs are inactive until they are activated in the place of action, where they should fight only against tumours. It can be said that there are two main strategies for "switching on" prodrugs when they reach tumour cells. The first one is based on the hypoxic or oxygen deficient nature of tumours which distinguishes them from most of the normal tissues. The second one introduced as gene-directed enzyme prodrug therapy (GDEPT), utilizes gene therapy to internalize non-human enzymes into the tumour to activate the prodrug. To eliminate poor pharmacokinetic properties such as low solubility of parent drug, there were developed phosphate anticancer prodrug to use them as an injectable dosage forms. Following parenteral application, the prodrugs are enzymatically cleaved by endogenous alkaline phosphatases yielding the parent drug [189]. When we want to use phosphate prodrugs for oral administration, the permeability of the parent drugs could be significantly limited by the absorptive flux. On the other hand, there are few examples of oral phosphate pro-

drugs being successful in this field, as they often possess lower absorption rate compared to their parent drugs.

Estramustine phosphate EMP (structural formula is shown in Fig. (**34**)), which is used in both intravenous and oral formulations, has been on the market in Europe and the United States for the treatment of prostate cancer [190].

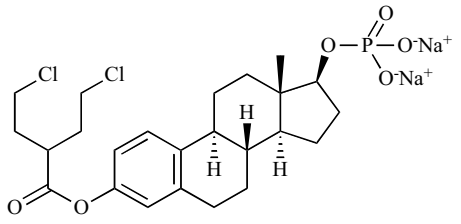

Fig. (34). Estramustine phosphate.

Etoposide disodium phosphate (structural formula is shown in Fig. (**35**)) (Etopophos) is used for the treatment of lung cancer [191].

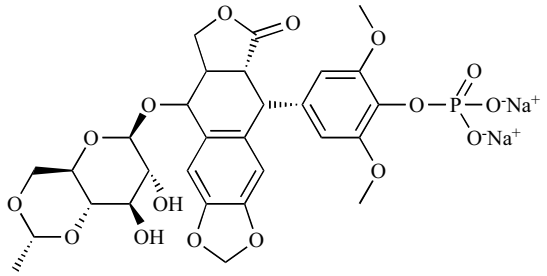

Fig. (35). Etoposide disodium phosphate.

TAT-59 (Miproxifene phosphate) (structural formula is shown in Fig. (**36**)) is an extraordinary lipophilic, zwitterionic, phosphate prodrug of the insoluble DP-TAT-59 [192].

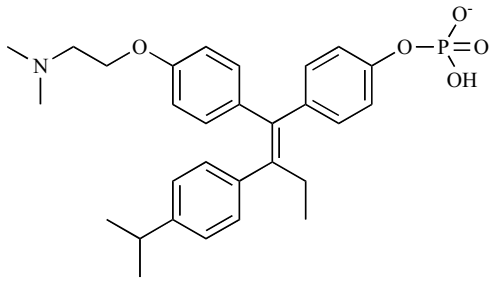

Fig. (36). Miproxifene phosphate.

A major barrier in the successful treatment of the ovarian cancer is the development of drug resistance of platinum-based therapy. It was previously proven that increased expression of a serine/threonine kinase, DNA-PK, is associated with resistance to cisplatin and adriamycin in various ovarian cancer cell lines [193]. Describing the cellular flexibility leading to resistance lets a more rational approach to the design of new drug therapies**.** The most of prodrug strategies included synthesizing hydrophilic prodrugs by introducing functional groups, that ionized at physiological p*H*. The enhanced solubility of the prodrug and high membrane permeability of the parent compound provided the driving force for increased flux of the drug, with the reconversion reaction maintaining sink condition at the membrane.

TLK 286 is a new glutathione *S*-transferase π- activated (GST- π) prodrug [194]. A favourable therapeutic index for TLK 286 was expected on the base of activation through a β-elimination reaction that changes the drug into a phosphorodiamidate and a glutathione analogue. Due to the fact that many solid tumors and a number of drug resistant cell lines express high levels of GST- π, selectivity should be achieved. In Phase I study of TLK 286, the drug was well tolerated, without bone marrow toxicity, that is characteristics of other clinically used nitrogen mustards. The promising results of the phase I studies with TLK 286 initiated Phase II trials, which include ovarian cancer patients [195].

Bisantrene is a synthetic antitumor agent that is clinically active against breast cancer, leukemias and lymphomas. There were several tests, which aimed to obtain a more easily administered, but slowly hydrolyzed prodrug. The selective phosphorylation of bisantrene supplies bis(phosphonoguanidinic acid), a prodrug with improved water solubility at physiological p*H*. It also appeared to have a greatly reduced potential for phlebitis, but its gradual hydrolysis to bisantrene could also reduce other toxicities. Additionally, preliminary animal test data suggested increased antitumor activities, further tests might also show a broader spectrum of antitumor efficacies due to the reverse polarity and enhanced pharmacodynamic properties of this prodrug [196].

FK 228 (FR 901228) is a natural prodrug, generated by *Chromobacterium violaceum* and demonstrates potent *in vivo* anticancer activity against human tumor xenografts and also murine tumors [197]. Additionally, FK 228 is a novel and potentially effective agent for patients with T-cell lymphoma [198]. FK 228 is metabolized to the active reduced form (redFK) by cellular reducing activity. The active form strongly inhibits HDAC, a specific enzyme family that is thought to be linked to tumorigenesis. The reduced form redFK has a active sulfhydryl group responsible for reacting with the zinc in the active-site pocket of the enzymes**.** It is suggested to utilize the more stable form FK 228 as a natural prodrug which can be activated to redFK form after incorporation into the cells [199].

Antiangiogenic therapies against the VEGF-VEGFR kinases axes through a variety of tests have been a hopeful and well-validated approach under evaluation for multiple solid tumors [200]. CEP-7055 is a synthetic prodrug of CEP-5214, an orally active blocker of all VEGFR kinase receptor subtypes (VEGFR1/FLT-1, VEGFR2/KDR IC50, VEGFR3/FLT-4). The parent drug presents potent antiangiogenic efficiency, and shows oral anticancer activity against different rodent and human tumor xenograft [201]. The ester derivative, CEP-7055, was synthesized to improve water solubility and to enhance oral delivery [202]. CEP-7055 is currently in Phase I trials in patients with variety of solid tumors. CEP-7055 was estimated together with temozolomide in a human orthotopic glioblastoma multiforme model in nude mice, which gave the significant efficacy and tolerability. Temozolomide (structural formula is shown in Fig. (**37**)) is a imidazotetrazinone prodrug, that shows hoping, but also limited,

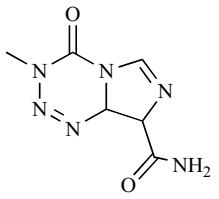

Fig. (37). Temozolomide.

positive responses in clinical tests in patients with high-grade malignant gliomas [203]. Temozolomide application has presented the improvement of patients' quality-of-life, it also revealed reduced objective response rates and lack of important survival benefit using monotherapy [204].

Camptothecin CPT is a antitumor alkaloid with potent antineoplastic activity. Therapeutic application of unmodified CPT is limited by very poor solubility in aqueous media, high toxicity, and rapid inactivation through lactone ring hydrolysis *in vivo* [205]. Several hydrophilic derivatives of CPT with enhanced lactone ring stability have been achieved [206-208]. All of them require endoplasmic activation, mainly in liver, for conversion to the active form. Two of these derivatives (irinotecan CPT-11 and topotecan) have recently been approved for clinical use and several other derivatives are now in pre-clinical and clinical development (GG-211, CDK-602). These compounds possess basic amines, and they are loaded into the core of pre-made small unilamellar vesicles by well estimated chemical gradient methods [209].

Irinotecan CPT-11 (structural formula is shown in Fig. (**38**)) has performed engaging antitumor activity against a broad spectrum of tumor types in early clinical trials, but hematopoietic and gastrointestinal toxicities reduce its application. Currently, there was the study to describe the molecular modeling of the structure of rCE-activated camptothecin with its biological activation. This specific activation by CEs may improve the therapeutic index of CPT-11 and to discover other prodrug analogues for enzyme/prodrug gene therapy applications [210].

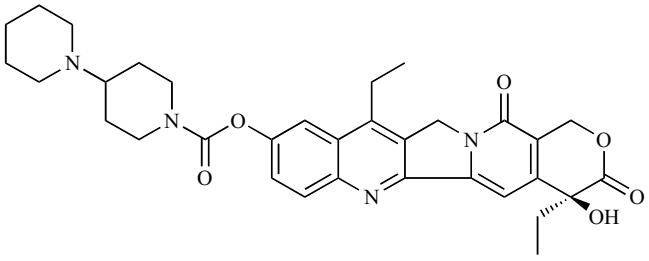

Fig. (38). Irinotecan CPT-11.

9-Aminocamptothecin glucuronide (9ACG) is a novel water-soluble prodrug of 9-aminocamptothecin (9AC) [211]. 9ACG lactone was designed as a prodrug for use in ADEPT therapy**.** It is a substrate for β-glucuronidase presents at tumors and because of the enzymatic transformation at the site of action 9AC lactone can be used in selective tumor therapy [212].

Uncontrolled proliferation is a special attribute of cancer cells, and CDKs are overexpressed with high frequency in many popular solid tumors [213]. These evidences have led to a strenuou search for compound inhibitors targeted for CDK family as an approach for cancer chemotherapy. JNJ-7706621 shows antiproliferative activity against various human tumor cells, however it has low oral bioavailabilities in rodents [214]. Developing aqueous-soluble prodrugs for JNJ-7706621 seems to be an alternative approach. Most of the prodrugs presented appropriate water solubility and could be formulated as clear solutions for clinical intravenous injection. The N-acyl groups on the sulfonamide substituent were split up to release the active drug in rat studies. The *in vivo* efficacy of these prodrugs will be estimated in the nearest future [215, 216].

CONCLUSION

This review article presents the most novel and significant scientific information connected with drug delivery, especially prodrugs as solution of poor pharmacokinetics properties of the parent drugs. Although many of recently discovered new drugs possess widespread activity it is essential to improve their permeability after administration. In addition, creating prodrugs extends the range of drugs' application. Here we found many examples of both the classic and the newest prodrugs that are divided into groups connected with the disease entities. Prodrug discovery and development seem to be complementary for the generation of target specific medicines now and in the future. Design of prodrugs creates new opportunities in application of classic drugs with poor pharmacokinetics properties.

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