EUROPEAN JOURNAL OF BIOMEDICAL AND PHARMACEUTICAL SCIENCES
http://www.ejbps.com

ISSN 2349-8870
Volume: 8
Issue: 9
299-308
Year: 2021

AN UPDATED CLASSIFICATION OF PRODRUGS

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Article Received on 06/07/2021 **Article Revised on 27/07/2021** **Article Accepted on 18/08/2021**

ABSTRACT
Clinical utility of many potential therapeutic agents is hampered by their undesirable organoleptic, physicochemical and biological properties. The pharmaceutical world improves therapeutic efficacy by minimizing the number and magnitude of undesirable properties while retaining the desirable ones. Since the late nineteenth century, prodrugs, bioreversible derivatives of drug molecules, have been widely used to optimize the clinical application of potential drug candidates. Prodrugs improve pharmaceutical, pharmacokinetic/pharmacodynamic properties of drug molecules via transient chemical modifications in order to develop new entities with superior efficacy. Basically prodrugs are designed to optimize "drug like" properties such as permeation across membranes, metabolic and excretory properties, low lipid or water solubility, low target selectivity, chemical instability, presystemic metabolism, toxicity, and masking of offensive taste/odor, irritation/pain at the site of injection. Conventional method of prodrug design involving non-specific chemical approach classifies prodrugs into two broad categories i.e. carrier-linked prodrugs and bioprecursors depending upon the type of derivatization and the carrier used. In this article, authors discuss basic concepts and propose an updated classification of prodrugs by citing suitable examples.

KEYWORDS: Prodrug; Bioreversible derivatives; Prodrug activation; Design of Prodrugs; Drug targeting.

INTRODUCTION

A drug can be defined as any chemical substance presented for treating, curing or preventing disease in human beings or in animals. A drug can also be used for making a medical diagnosis or for restoring, correcting, or modifying physiological functions in human beings or in animals. Generally, a drug is characterized by its physicochemical, biological and organoleptic properties, some desirable and others undesirable that may become pharmacological, pharmaceutical, or pharmacokinetic barriers in clinical drug application. Undesirable properties of potential drug candidates should be improved in order to increase their clinical usefulness. Pharmacokinetic and pharmaceutical barriers such as low oral drug absorption, short duration of action, lack of site specificity, chemical instability, toxicity, and poor patient acceptance (bad taste, odor, pain at injection site, etc.) have been reported to be main causes of high attrition in drug development. Establishing the right balance between efficacy and safety of a drug is very crucial in order to achieve a good clinical profile.[1,2] Drug efficacy can be improved by biological, physical and chemical means. The biological approach entails varying the route of drug administration which may or may not be acceptable to patient. For example injectable route of administration may be used to optimize onset of action, maximize bioavailability, and eliminate gastric irritation and acid-catalyzed drug degradation. However, versatility of biological approach is severely limited as alternative routes of administration are not frequently available, and are less convenient than oral route of administration. The physical approach offers greater degree of flexibility of altering drug efficacy by modifying design of dosage form such as controlled drug delivery system. However, the chemical approach of prodrug design offers highest degree of flexibility for enhancing drug efficacy while minimizing toxicity. The prodrug approach involves chemical modification of existing drug molecules to produce biologically reversible derivatives which revert back to the parent molecule in vivo by virtue of enzymatic and/or chemical lability. The prodrug approach has the potential to overcome these problems in a relatively short time and has been successfully used to eliminate various undesirable properties inherent in the parent drug molecule.[3-6]

The Basic Concept and History of Prodrgus

The term prodrug was first introduced by Albert in 1958 to signify pharmacologically inactive chemical

derivatives that could be used to optimize the physicochemical properties of drugs, in a temporary manner, in order to increase their usefulness and/or to decrease associated toxicity.[7] International Union of pure and applied chemistry (IUPAC) defines prodrug as any compound that undergoes biotransformation before exhibiting its pharmacological effects.[8] The basic concept of prodrug design has been illustrated in Figure 1. Basically, the term prodrug implies a covalent link between a drug and a chemical moiety (termed as promoiety), in order to form a new compound (termed as prodrug) with favourable desirable properties. Ideally, prodrugs are designed to undergo biotransformation rapidly via chemical or enzymatic process to its active form and a non-toxic moiety within the body, followed by the subsequent rapid elimination of the released derivatizing group. The classical/ traditional non-specific prodrug approach aims to alter the physiochemical properties, such as hydrophilicity/lipophilicity by covalently modifying the drug either to increase its aqueous solubility by attaching it to hydrophilic functionalities or to increase its passive permeability by attaching lipophilic moieties. These prodrugs are nonspecifically activated at sites other than the active site, resulting in related toxicities and low bioavailability.[9,10] Whereas, the modern prodrug approach targets specific enzymes or carriers by considering enzyme-substrate specificity or carrier-substrate specificity in order to overcome various undesirable drug properties.[11-13] In this way, modern prodrug approach overcomes toxic issues associated with the classical prodrugs approach. Prodrugs have little or no pharmacological activity of their own; but have a built-in structural liability that permits bioconversion to active drug in vivo. The ultimate goal of prodrug design is to improve physicochemical properties of drugs in order to make them useful in clinical practice. Development of a prodrug of an existing drug with improved properties may also represent life-cycle management opportunity.[14,15]

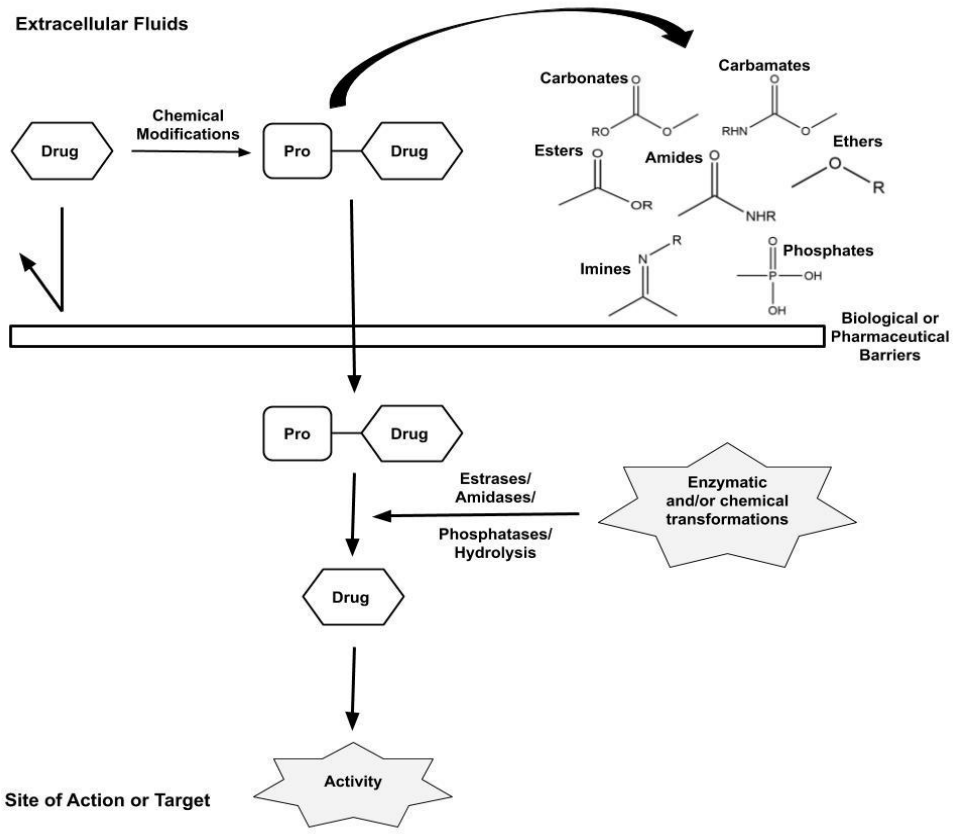


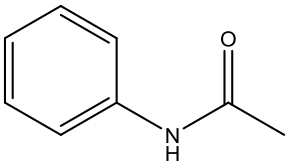
Figure 1: An illustration of the prodrug concept: the drug is released after chemical or enzymatic activation eliciting the pharmacological effect near to the site of action.

Although Albert formally recognized prodrug concept in 1958, but few drugs namely acetanilide, phenacetin, methenamine and prontosil introduced into medical practice before then are regarded as prodrugs.

- Acetanilide **1,** an antipyretic agent, introduced into the medical practice in 1867, has been reported to be the first compound that fulfills the classical criteria of prodrug. Acetanilide exhibits its antipyretic activity after being metabolized within the body. It undergoes metabolism (aromatic hydroxylation) by cytochrome P450 enzymes in vivo to yield parent active compound paracetamol **2** (acetaminophen), the metabolite responsible for its biological effects. Another analgesic prodrug –phenacetin **3**, introduced into the clinical practice in 1887, also undergoes metabolic activation (O-dealkylation) in

vivo to yield parent active compound paracetamol.[16,17]

- Methenamine **4** was discovered in 1899 as an inactive prodrug that delivers its parent antibacterial agent formaldehyde. Formaldehyde, a pungent odor disinfectant gas, is too toxic to be given directly. It is corrosive to the gastrointestinal tract and causes inflammation and ulceration of the mouth, esophagus, and stomach. Structurally, methenamine is a low molecular weight solid stable polymer of ammonia and formaldehyde which gets decomposed in aqueous acid. So the prodrug circulates unchanged in the body at normal pH of blood which is slightly alkaline in nature in order to prevent systemic toxicity of formaldehyde. Further, methenamine is administered in enteric-coated form in order to prevent its premature hydrolysis in the highly acidic environment of the stomach. However, in the acidic environment (P^H 4.8) of the urine due to bacterial infection, it gets hydrolyzed back to formaldehyde. Therefore, methenamine also serves as an example of site-specific targeted delivery as it delivers therapeutic agent at the specific site by exploiing pH differences between the urine (acidic pH) and other body tissues (physiological pH of 7.4).[18,19] Since, methenamine was discovered accidentally, it is also termed as fortuitous prodrug.
- Many decades later, in 1935 - still before the conceptual introduction of prodrugs – another fortuitous prodrug- prontosil **5** was introduced into the medical practice. Prontosil was found to be effective against microorganisms only in vivo, and not in vitro. Later on it was established that prontosil is a prodrug that undergoes biotranaformation by azo reductases in the gut to yield parent active compound sulfanilamide **6,** the first sulfonamide to be discovered.[20]



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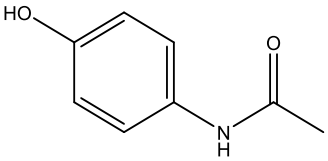

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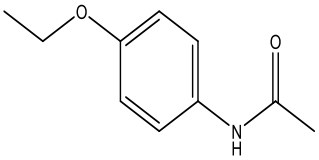

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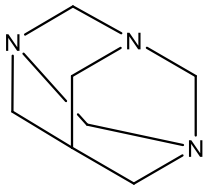

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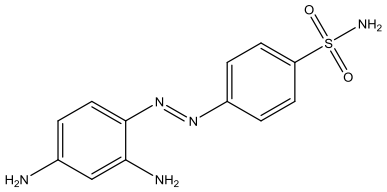

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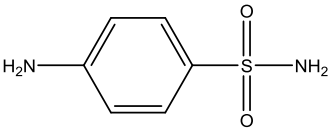

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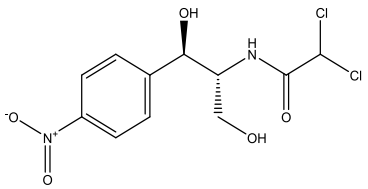
- The prodrug concept was intentionally utilized in the mid of 20th century for the first time by Parke-Davis company for modification of broad-spectrum antibiotic chloramphenicol structure **7** in order to improve its bitter taste and poor solubility in water. Two prodrug forms of chloramphenicol were synthesized: chloramphenicol sodium succinate with a good water solubility for IV, IM, and ophthalmic use; and chloramphenicol palmitate to mask its bitter taste used in the form of suspension for children. Chloramphenicol produces a bitter taste upon oral administration. The undesirable taste arises due to adequate solubility and interaction of drug with taste receptors. This limitation has been overcome by lowering the solubility of drug in saliva by developing its hydrophobic ester prodrug chloramphenicol palmitate **8.** Due to its low aqueous solubility, chloramphenicol palmitate is practically tasteless, and is hydrolysed back to active chloramphenicol by the action of pancreatic lipase. In order to make chloramphenicol (slightly soluble in water) suitable for parenteral and ophthalmic use, a higher water soluble derivative, chloramphenicol sodium succinate **9** (freely soluble in water), was designed. Chloramphenicol sodium succinate has no antibacterial activity of its own but is hydrolysed to free chloramphenicol by esterases in vivo.[21]



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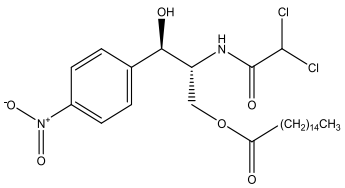

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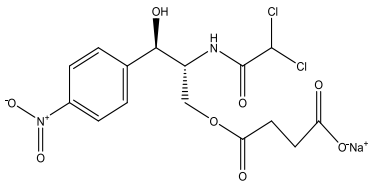

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CLASSIFICATION OF PRODRUGS

Depending upon three different criteria prodrugs can be classified as per Table 1:

Table 1: classification of prodrugs.

Criteria for classification	Class	Criteria for sub-classification	Sub-class	Example
1. Depending upon the nature of modification	Carrier linked	Nature of linkage	Bipartite prodrugs	Prednisolone sodium phosphate **10**
			Tripartite prodrugs	Bacampicillin **11**
		Nature of carrier	Double prodrugs	Cefpodoxime proxetil **12**
			Bifunctional prodrugs	Dabigatran etexilate **13**
			Macromolecule prodrugs	Naproxen-2-glyceride **14**
			Site specific prodrugs	Methenamine **4**
			Mutual prodrugs	Estramustine **15**
	Bioprecursor prodrugs	----------	----------	Simvastatin **16**
2. Depending upon the metabolic fate	Type 1 (metabolized intracellularly)	Metabolized at target tissues/cells	1A	Zidovudine **20**
		Metabolized by metabolic tissues like liver	1B	Captopril **21**
	Type II (metabolized extrcellularly)	Metabolized in the milieu of the gastrointestinal fluid	1IA	Loperamide oxide **22**
		Metabolized within circulatory system	1IB	Chloramphenicol **9**
		Metabolized near or inside therapeutic target tissue/cells	1IC	ADEPTs
	Hard drug (highly resistant to metabolism)	----------	-------- ---------	Chlorpropamide **24**
	Soft drug (highly susceptible to metabolism)	----------	----------	Clevidipine butyrate **25**
3. Depending upon the nature of linkage	Ester and phosphate prodrugs	----------	----------	Chloramphenicol palmitate **9** and Fosaprepitant **26**
	Amide prodrugs			
	carbonate, carbamate prodrugs			Rolitetracyclin **27** Candesartan cilexetil 28, Doxorubicin galactoside **29**
	oxime prodrugs			Ximelagatran **30**

1. **Depending upon the nature of modification, prodrugs have been further classified as carrier linked prodrugs and bioprecursor prodrugs.[22]**

1.1 Carrier linked prodrugs

A carrier-linked prodrug is a prodrug in which active drug molecule is covalently linked to a transient carrier molecule (also known as a promoiety) through a metabolically labile linkage. The promoiety is not necessary for activity but imparts some desirable property to the drug such as increased lipid or water solubility or site-directed delivery. Ideally, the carrier should be safe, non-immunogenic, easily synthesizable at a low cost, stable under the conditions of prodrug administration, and undergo biodegradation to nontoxic metabolite. Correct choice of a carrier is of utmost importance for a successful prodrug design and depends upon what properties are sought for the agent. If it is desirable to increase water solubility, then an ionizable/polar promoiety is used. If it is desirable to increase lipid solubility or decrease water solubility, then a non-polar promoiety is chosen. Therefore, choice of a carrier is dictated by several factors such as purpose of prodrug design, available functional groups, safety, disease state, dose, and the duration of therapy. The unique feature of this approach is that the physicochemical properties can be tailored by selecting a suitable carrier.

Based upon the nature of linkage, carrier linked prodrugs are further sub-classified as bipartite & tripartite prodrugs.

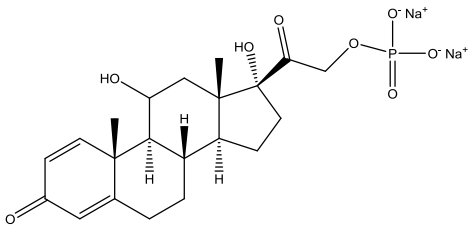
1.1.1 Bipartite prodrugs

Bipartite prodrugs consist of a direct linkage between the parent drug molecule and the promoiety. The covalent linkage between the drug molecule and promoiety is liable to be cleaved chemically or enzymatically to release the parent drug in vivo. The example is prednisolone sodium phosphate **10**. Most carrier-linked prodrugs are bipartite in nature.

1.1.2 *Tripartite Prodrugs*

Tripartite prodrugs consist of an active drug molecule and the promoiety linked through a molecule. This type

of prodrug is produced when the linkage between the drug and promoiety is unstable or covalent bond cannot be formed between them. These are mainly used to overcome the instability problems. The mechanism of activation involves chemical/enzymatic cleavage of the carrier first, followed by spontaneous cleavage of the linker to release the active parent drug. Therefore, drug-linker connection must be designed so that it cleaves spontaneously (i.e. is self-immolative) after the carrier has been detached. This strategy has been employed to design prodrugs of ampicillin, a β-lactam antibiotic that is poorly absorbed (40%) when administered orally. For example bacampicillin **11** is tripartite prodrug of ampicillin that utilizes acetaldehyde as a linker. Unlike ampicillin, bacampicillin is absorbed to the extent of 98–99%, and ampicillin is released into the bloodstream within 15 minutes.



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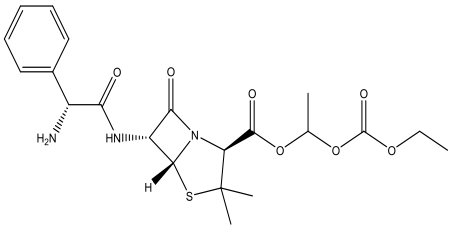

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Depending upon the nature of carrier, carrier linked prodrugs are further sub-classified into following five categories:

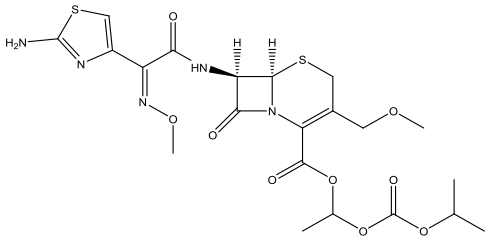
- Double prodrugs
- Bifunctional prodrugs
- Macromolecule prodrugs
- Site specific prodrugs
- Mutual prodrugs

1.2.1. Double prodrugs

Double prodrugs (or pro-prodrugs) are biologically inactive compounds which are biotransformed in two steps (enzymatically and/or chemically) to release their active species. These have been designed to overcome various draw backs of usual prodrugs.[23] They have been used for targeted drug delivery by attaching a suitable second promoiety to the first promoiety. These promoieties are generally different from each other, and, are derived in such a manner that they initially undergo enzymatic hydrolysis, followed by spontaneous chemical reaction to release the active drugs. To some extent, double-prodrugs have also been employed to solve instability problems of ester-prodrugs. This approach has been used to develop oral β-lactam antibiotics e.g. cefpodoxime proxetil **12** in which carbonate function has been used as a second promoiety.

1.2.2. Bifunctional prodrugs

Prodrugs obtained by modifying two functional groups of drug molecules are termed as bifunctional prodrugs. Bifunctional prodrugs should not be confused with double prodrugs which are biotransformed in two steps. Dabigatran etexilate **13,** a direct thrombin inhibitor used for stroke prevention, is an example of bifunctional prodrug. Dabigatran etexilate has been obtained by masking its two polar groups i.e. amidinium moiety and carboxylate as carbamic acid ester and carboxylic acid ester groups, respectively.[24]



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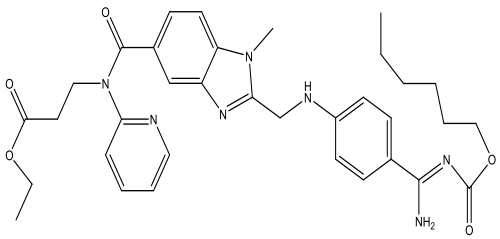

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1.2.3. Macromolecule prodrugs

Macromolecular prodrugs also known as polymeric prodrugs use large molecular weight compounds such as polysaccharides, proteins, dextrans, cyclodextrins, and peptides as carriers.[25] The example is non-steroidal anti-inflammatory drug naproxen-2-glyceride **14**.

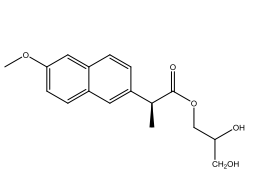
1.2.4. Site-specific prodrugs

Site-specific prodrugs represent a new strategy for directed and efficient drug delivery. They deliver therapeutic agents to specific tissues in a pursuit to maximize drug action and minimize side effects by ensuring local activation of the drug at the site of action.[26] The basic goal of these prodrugs is to protect the drug from the nonspecific biological environment and to protect the nonspecific biological environment from the drug. Methenamine **4** is a venerable example of site-specific prodrug for disinfection of acidic urine.

1.2.5. Mutual Prodrugs

Mutual prodrugs combine two pharmacologically active agents, usually synergistic, to form a single molecule so

that each acts as carrier for the other one.[27] Mutual prodrugs may be of bipartite or tripartite nature. The carrier in mutual prodrug may have the same therapeutic action as that of the parent drug in order to give synergistic action, or may have different pharmacological activity whose action is needed together. Mutual prodrugs have been developed to avoid the practice of clinically co-administering two drugs simultaneously. Simultaneous administration of two drugs separately does not guarantee equivalent absorption or transportation at the site of action. Hence, mutual prodrugs are beneficial when two synergistic drugs need to be administered at the same site at the same time. An example of this approach is antineoplastic agent estramustine **15**, used for the treatment of prostate cancer. Estramustine is composed of 17α-estradiol having anti-androgenic effect linked to an alkylating agent normustard through a carbamate linkage.[28]



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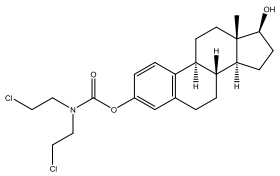

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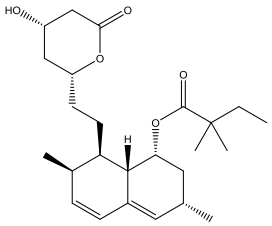

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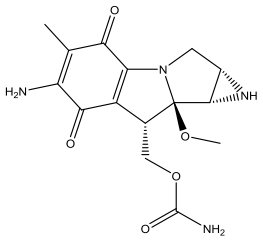
1.2. Bioprecursor prodrugs

Bioprecursor prodrugs are biologically inactive compounds that contain no promoiety but are obtained by a molecular modification of active drug itself. This modification generates a new compound which undergoes transformation in vivo to yield the parent active drug. The prodrug is generally metabolized by the action of phase I metabolizing enzymes (normally redox reactions). Various metabolic pathways may include hydration (e.g., antihyerlipidemic agent simvastatin **16**), reduction (e.g., antineoplastic agent mitomycin C **17**), or oxidation (e.g., nonsteroidal anti-inflammatory drug nabumetone **18**), or phosphorylation (e.g., antiviral agent iodoxuridine **19**).



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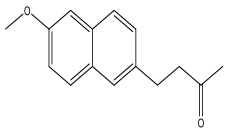

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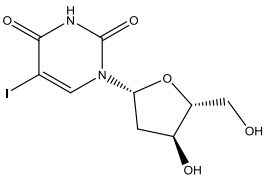

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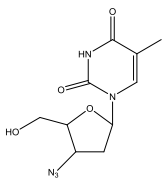
2. Depending upon the metabolic fate, prodrugs can be classified as Type I prodrugs, Type II prodrugs,[29] hard drugs and soft drugs.[30,31]

2.1. Type I

Prodrugs that are metabolized intracellularly are classified as type I. These prodrugs are further sub-classified as Type IA and Type IB. Type IA prodrugs are metabolized at target tissues/cells. These include various antimicrobial and chemotherapeutic agents; for example zidovudine **20**. Type IB prodrugs are metabolized by metabolic tissues like liver, for example angiotensin-converting enzyme inhibitor captopril **21**.

2.2. Type II

Prodrugs that are metabolized extracellularly are classified as type II. These prodrugs are further sub-classified as Type IIA, Type IIB and Type IIC. Type IIA prodrugs are metabolized in the milieu of the gastrointestinal fluid, example is loperamide oxide **22**. Type IIB are metabolized within circulatory system and/or other extracellular fluid compartments, example is chloramphenicol **9**. Type IIC are metabolized near or inside therapeutic target tissue/cells (ADEPTs, GDEPTs).



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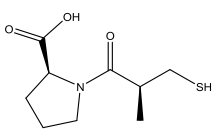

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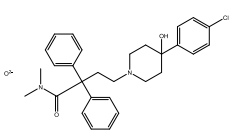

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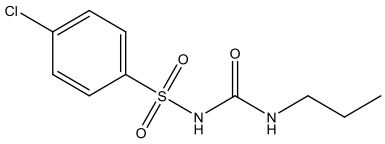
Additionally, In 1980s, two new terms i.e. hard drugs and soft drugs were coined to describe altogether different purposes of prodrug design.

2.3. Hard drugs

Hard drugs can be defined as compounds that contain structural features necessary for pharmacological activity but in a form not susceptible to metabolic or chemical transformation in vivo. In this way, the production of any toxic intermediates is avoided and there is an increased efficiency of action. As a result of this, hard drugs remain unchanged in the body, and therefore may lead to potential risk of drug accumulation in the body on long term therapy. Hard drugs are designed by masking/replacing metabolically labile functional groups. For example, chlorpropamide **23,** a hard prodrug of hypoglycemic agent tolbutamide **24,** has been designed by replacing metabolically labile benzylic methyl group in tolbutamide with metabolically stable chloro group. Due to higher metabolic stability, chlorpropamide exhibits longer duration of action of 33 hrs as compared to only 6 hrs of tolbutamide.[32]

2.4. Soft drugs

Soft drugs are biologically active compounds that, after exerting their desired therapeutic effect, are designed to undergo predictable metabolic degradation to give a non-toxic product. Soft drugs have very short duration of action as they are deactivated and detoxified shortly after exerting their biological effect. By definition, prodrugs must be activated to produce active parent compound. Therefore, soft drugs are considered to be opposite of prodrugs. Clevidipine butyrate **25,** an ultrashort-acting calcium- channel blocker, is an example of soft drug with a half-life of ~1 minute. It is rapidly hydrolysed to its inactive form after intravenous administration and is used for the treatment of hypertension intravenously.[33]



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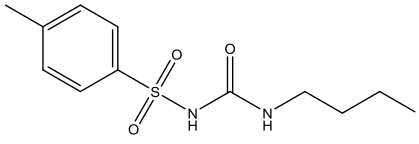

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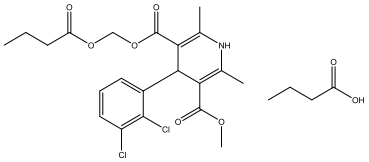

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3. Depending upon the nature of linkage between the parent drug and promoiety, the prodrugs can be classified as under:

- Ester and phosphate prodrugs
- Amide prodrugs
- carbonate, carbamate prodrugs
- Oxime prodrugs

3.1. Ester and phosphate prodrugs

Esters prodrugs have been most commonly designed prodrugs to enhance lipophilicity of water soluble drugs as well as to enhance solubility of highly lipophilic drugs in water. Drugs having carboxyl or alcoholic functionalities have been widely modified as ester prodrugs in order to improve their bioavailability. Ester prodrugs are most commonly designed because of the ease by which they can be synthesized, and their acceptable in vitro chemical stability that reduces formulation problems. An additional factor that has contributed to the popularity of ester prodrugs is their facile chemical or enzymatic hydrolysis in vivo to release the parent drug. Another favourable feature of ester prodrugs is that by choosing a suitable carboxylic or alcohol promoiety, a wide range of hydrophilic or lipophilic properties can be imparted to a drug molecule depending upon what is required. Chloramphenicol palmitate **8** is an example of ester prodrug of historical importance. Phosphate esters prodrugs are generally employed for circumventing the poor aqueous solubility of parent drugs. They are relatively stable upon formulation but undergo biotransformation in vivo via alkaline phosphatases to liberate the active parent compound.[34,35] Fosaprepitant **26**, phosphate ester prodrug of anti-emetic drug aprepitant, is an important example to cite here. Fosaprepitant has been obtained by directly attaching phosphate moiety is to an amide group of aprepitant in order to enhance its aqueous solubility for parenteral use.[36]

3.2. Amide prodrugs

Drugs having carboxylic acid or amine functionalities can be modified as amide prodrugs. Amides have not been used widely as prodrugs due to high chemical stability of the amide linkage and the lack of amidase enzymes necessary for hydrolysis. However, amines have been occasionally incorporated into peptide linkages to render them as substrates of specific intestinal uptake transporters in order to increase oral absorption.[37] Altenatively Mannich bases of amines have been designed as prodrugs in order to improve both aqueous soloubility and lipophilicity for oral, topical and parenteral administration. Rolitetracyclin **27** is *N*-Mannich base prodrug of antibiotic tetracycline that is formed by a Mannich condensation of formaldehyde and pyrrolidine with tetracycline.[38,39]

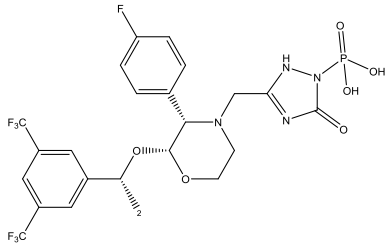
3.3. Carbonate and carbamate prodrugs

Carbonates are derivatives of carboxylic acids and alcohols; whereas carbamates are derivatives of carboxylic acid and amines. Carbonates and carbamates differ from esters by the presence of an oxygen or nitrogen on both sides of the carbonyl carbon. They are enzymatically more stable than their ester counterparts but are less stable than their corresponding amides. Since, no specific enzymes are available for the biotranaformtion of carbamates and carbonates; they are degraded by esterases only to release the parent active compound in vivo. Candesartan cilexetil **28** is an example of carbonate prodrug of candesartan, a selective angiotensin II subtype 1 receptor antagonist used orally

for the treatment of high blood pressure.[39] Doxorubicin galactoside **29** is an example of carbamate ester prodrug of anthracycline antibiotic doxorubicin. Carbamate prodrugs are generally considered as double prodrugs, in which ester bond is cleaved first enzymatically, followed by a spontaneous decomposition of the resulting carbamic acid.[40,41]

3.4. Oxime prodrugs

Oximes i.e. ketoximes, amidoximes and guanidoximes are derivatives of ketones, amidines and guanidines respectively. These are used to modify drug molecules that lack hydroxyl, amine or carboxyl functionalities. They are metabolised back to parent drugs by microsomal cytochrome P450 (CYP450) enzymes. Oximes, especially strongly basic amidines and guanidoximes, have been employed to increase membrane permeability and absorption of drugs. Anticoagulant ximelagatran **30** is an example of doule prodrug of hydroxyamidine and ethyl ester prodrug of melagatran.[42]



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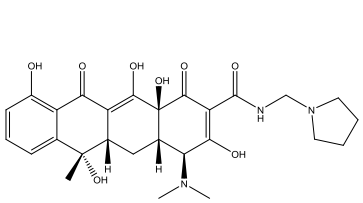

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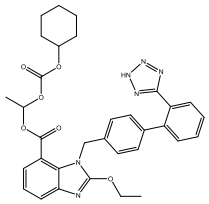

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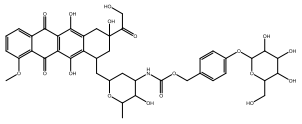

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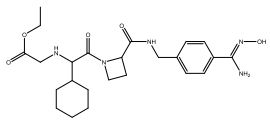

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CONCLUSION

The prodrug approach has been used wdely to alter the physicochemical, pharmacokinetic and biopharmaceutical properties of drugs in order to optimize their clinical outcome. Prodrugs offer a handle to further fine tune physicochemical properties for enhancement of therapeutic efficacy and/or to reduce adverse effects of the pharmacologically active agents via different mechanisms. It is an adaptable method that can be applicable for series of parent drug molecules. Moreover, synthesis of new compounds is a time consuming and too costly process, designing derivatives of existing/investigational drugs is definitely an interesting and promising area of research. Therefore, it could be easily argued that the design of prodrugs may serve as a resourceful chemical/biochemical approach to overcome limitations associated with the parent drugs.

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