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Review Article

Prodrug Approach: An Alternative to Improve Pharmacokinetic Properties

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Abstract: Prodrugs are the masked forms of active drugs that are designed to be activated once they have been administered into the body by an enzymatic or chemical means. It is a well known molecular modification strategy that aims to optimize the physicochemical and pharmacological properties of drugs to improve their undesirable pharmacokinetic properties and decrease their toxicity. In most of the cases, prodrugs design involves the introduction of carrier/promoiety by a metabolic liable linkage so that after biotransformation by one or two chemical or enzymatic steps it will lead to the active parent drug. However, some prodrugs lack an obvious promoiety but instead result from a molecular modification of the prodrug itself, which generates a new active compound. This review introduces in depth the rationale behind the use of the promoiety, and also considers the possible problems that can arise from inadequate activation of prodrugs.

Keywords: Prodrug, Molecular Modification, Promoiety, Carrier-Linked

1. Introduction

Today almost all drug candidates are associated with some undesirable physicochemical and biological properties such as poor bioavailability, incomplete absorption, adverse effects, first pass metabolism etc. [1-2]. Prodrug design is opening new doors in the challenging field of drug discovery and revolutionising the art of drug development as they are capable to overcome these challenges. Prodrugs are masked forms or bioreversible derivatives of active drug molecules that must undergo an enzymatic and/or chemical transformation *in vivo* to release the active parent drug, which can then elicit its desired pharmacological effect in the body [3].

The first compound fulfilling the classical criteria of a prodrug was acetanilide, introduced (under the name of Antifebrin®) into the medical practice by Cahn and Hepp in 1867 as an antipyretic agent. In the body, acetanilide is hydroxylated (aromatic hydroxylation) to biologically active acetaminophen (paracetamol), the compound endowed with both antipyretic and analgesic activity [4]. Another example

of a historical prodrug is aspirin (acetylsalicylic acid), synthesized in 1897 by Felix Hoffman (Bayer, Germany), and introduced into medicine by Dreser in 1899 [5]. However, the prodrug concept was intentionally used for the first time in the middle of the 20th century by the Parke-Davis company during studies on modification of chloramphenicol structure in order to improve the antibiotic's bitter taste and poor solubility in water. As a result of this work, two prodrug forms of chloramphenicol were synthesized: chloramphenicol sodium succinate with good water solubility, and chloramphenicol palmitate used in the form of a suspension in children.

Prodrugs are conventionally classified in two major classes: carrier-linked prodrugs and bioprecursors. In the carrier-linked prodrugs, the active molecule (the drug) is temporarily linked to a carrier (also known as a promoiety) through a bioreversible covalent linkage [6] such as ester, amide, carbamate, carbonate, ether, imine, phosphate, among others [7]. Generally, promoiety is devoid of pharmacological activity but may impart some desirable properties to the drug like increase water or lipid solubility, reduction of toxicity *etc*.

On the other hand, bioprecursors prodrugs lack an obvious

carrier or promoiety but instead result from a molecular modification of the prodrug itself, which generates a new active compound. The rationale behind the use of prodrugs is generally to optimize the ADME (*i.e.*, absorption, distribution, metabolism, and excretion) properties because they can cause considerable problems in subsequent drug development, if unfavorable. Although prodrug design is very challenging, it can still be more feasible and faster than searching for an entirely new therapeutically active agent with suitable ADME properties. A very good indication of the success of the prodrug approach can be obtained by examining the prevalence of prodrugs on the market. It might come as a surprise to many people that currently approximately 10% of all globally marketed medicines can be classified as prodrugs, and in 2008 alone, 33% of all approved small-molecular-weight drugs were prodrugs [8].

The most common functional groups that are amenable to prodrug design include carboxylic, hydroxyl, amine, phosphate and carbonyl groups. Prodrugs typically produced *via* the modification of these groups include esters, carbonates, carbamates, amides, phosphates and oximes. However, other uncommon functional groups have also been

investigated as potentially useful structures in prodrug design. For example, thiols react in a similar manner to alcohols and can be derivatized to thioethers [9] and thioesters [10]. Amines may be derivatized into imines [11] and N-Mannich bases [12]. The prodrug structures for the most common functionalities are illustrated in Figure 1 and discussed below.

2. Esters as Prodrugs of Carboxyl, Hydroxyl and Thiol Functionalities

Esters are estimated approximately 49% of all marketed prodrugs are activated by enzymatic hydrolysis [13]. Ester prodrugs are most often used to enhance the lipophilicity, and thus the passive membrane permeability, of water-soluble drugs by masking charged groups such as carboxylic acids and phosphates [14]. Once in the body, the ester bond is readily hydrolysed by ubiquitous esterases found in the blood, liver and other organs and tissues [15], including carboxylesterases, acetylcholinesterases, butyrylcholinesterases, paraoxonases, and arylesterases.
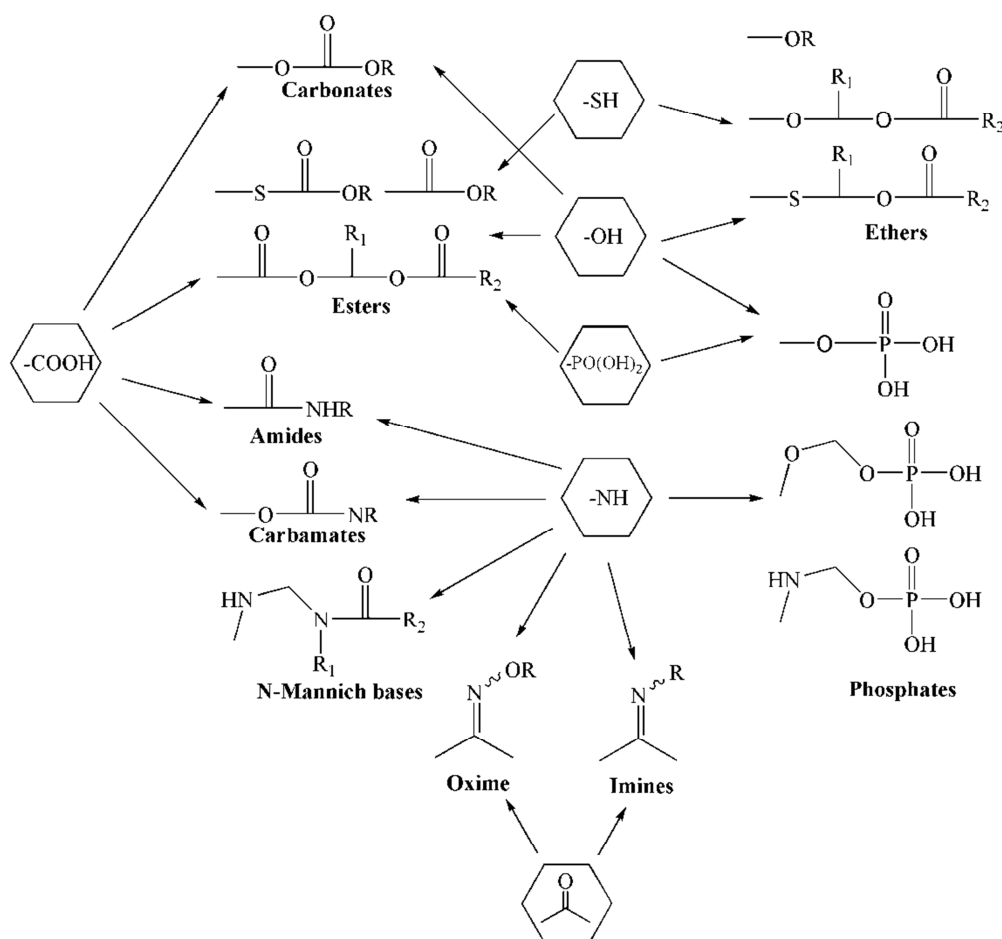

Figure 1. Common functional group on parent drugs that are amenable to prodrug design.

However, one significant challenge with ester prodrugs is the accurate prediction of pharmacokinetic disposition in humans, owing to significant differences in specific carboxylesterase activities in preclinical species [16]. Several alkyl and aryl ester prodrugs are in clinical use as depicted in Table 1.

Table 1. *Esters as prodrugs of carboxyl, hydroxyl and thiol functionalities.*

S/N	Prodrug Name & Category	Functional group	Structure	Prodrug strategy
1	Enalapril (ACE inhibitor)	Monoethyl ester of enalapril		Improved lipophilicity or permeability
2	Pivampicillin (β-lactam antibiotic)	Pivaloylmethyl ester of Ampicillin		Improved lipophilicity or permeability
3	Oseltamivir (anti-influenza)	Ethyl ester of oseltamivir Carboxylate		Improved lipophilicity or permeability
4	Adefovir dipivoxil (antiviral)	Bis-(pivaloyloxy methyl) ester of adefovir		Improved lipophilicity or permeability
5	Tenofovir disoproxil (antiviral)	Bis-(isopropyloxy carbonyloxy methyl) ester of tenofovir		Improved lipophilicity or permeability
6	Famciclovir (antiviral)	Dimethyl ester of Penciclovir		Improved lipophilicity or permeability
7	Ximelagatran (anticoagulant)	Hydroxyamidine and ethyl ester of melagatran		Improved lipophilicity or permeability
8	Valacyclovir (antiviral)	l-Valyl ester of acyclovir		Improved carrier-mediated absorption
9	Valganciclovir (antiviral)	l-Valyl ester of ganciclovir		Improved carrier-mediated absorption
10	Dipivefrin (glaucoma)	Dipivalic acid diester of adrenaline		Improved ophthalmic and dermal delivery

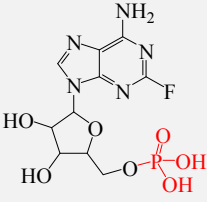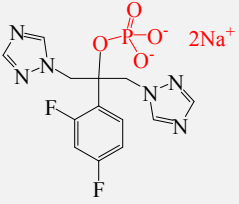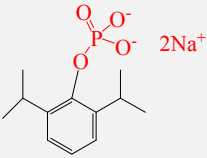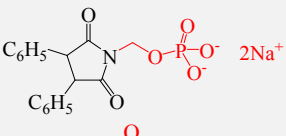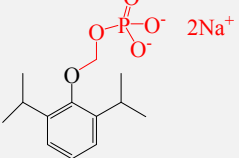| S/N	Prodrug Name & Category	Functional group	Structure	Prodrug strategy
11	Latanoprost (glaucoma)	Isopropyl ester of latanoprost acid		Improved ophthalmic and dermal delivery
12	Tazarotene (topical skin disorders, psoriasis, acne)	Ethyl ester of tazarotenic acid		Improved ophthalmic and dermal delivery

3. Phosphate Esters as Prodrugs of Hydroxyl or Amine Functionalities

Phosphate ester prodrugs are typically designed for hydroxyl and amine functionalities of poorly water-soluble drugs with an aim to enhance their aqueous solubility to allow a more favorable oral or parenteral administration (see examples in Table 2). The synthesis of phosphate prodrugs is fairly straightforward, and the presence of the dianionic phosphate promoiety usually raises the aqueous solubility [17]. Unlike carboxylic acid esters, phosphate esters are typically hydrolysed at similar rates in different preclinical species by alkaline phosphatases [18]. A highly ionic phosphate Prodrug may, for example, exhibit suboptimal enzymatic bioconversion by phosphatases (usually the aqueous solubility of the phosphate prodrug is enhanced to such an extent that passive diffusion through the intestinal membrane is prevented); lead to precipitation of the parent drug following cleavage in the intestinal lumen — this eventually leads to poor absorption or drug flux of the parent drug, as the parent drug is not in a soluble form [17].

Table 2. Phosphate esters as prodrugs of hydroxyl or amine functionalities.

S/N	Prodrug Name & Category	Functional group	Structure	Prodrug strategy
1	Miproxifene phosphate (anticancer)	Phosphate ester of Miproxifene		Improved aqueous solubility
2	Fosamprenavir (antiviral)	Phosphate ester of Amprenavir		Improved aqueous solubility
3	Estramustine phosphate (anticancer)	Phosphate ester of Estramustine		Improved aqueous solubility
4	Prednisolone phosphate (glucocorticoid)	Phosphate ester of Prednisolone		Improved aqueous solubility

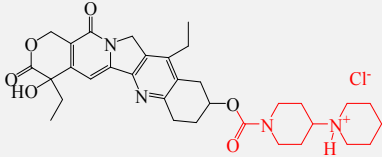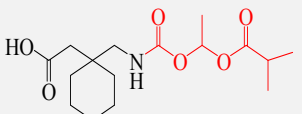| S/N	Prodrug Name & Category	Functional group	Structure	Prodrug strategy
5	Fludarabine phosphate (antiviral)	Phosphate ester of Fludarabine		Improved aqueous solubility
6	Fosfluconazole (antifungal)	Phosphate ester of Fluconazole		Improved parenteral administration
7	Propofol phosphate (anaesthetic)	Phosphate ester of Propofol		Improved parenteral administration
8	Fosphenytoin (anticonvulsant)	Phosphonooxymethyl amine of phenytoin		Improved parenteral administration
9	Phosphonooxymethylpropofol (anaesthetic)	Phosphonooxymethyl ether of propofol		Improved parenteral administration

4. Carbonates and Carbamates as Prodrugs of Carboxyl, Hydroxyl or Amine Functionalities

Carbonates and carbamates are often enzymatically more stable than the corresponding esters but are more susceptible to hydrolysis than amides. Carbonates are derivatives of carboxylic acids and alcohols, and carbamates are carboxylic acid and amine derivatives. The bioconversion of many carbonates and carbamate prodrugs requires esterases for the formation of the parent drug [19] (Table 3).

5. Amides as Prodrugs of Carboxylic Acids and Amines

In prodrug design, amides have been used only to a limited extent owing to their relatively high enzymatic stability *in vivo*. An amide bond is usually hydrolysed by ubiquitous carboxylesterases [19], peptidases or proteases [20]. Amides are often designed for enhanced oral absorption by synthesizing substrates of specific intestinal uptake transporters [20] (Table 3).

Table 3. Carbonates/carbamates or amide as prodrugs of carboxyl, hydroxyl or amine functionalities.

S/N	Prodrug Name & Category	Functional group	Structure	Prodrug strategy
1	Irinotecan (anticancer)	Dipiperidino carbamate of camptothecin		Improved parenteral administration
2	XP13512 (restless leg syndrome, neuropathic pain)	Isobutanoyl oxyethoxy carbamate of gabapentin		Improved carrier-mediated absorption

S/N	Prodrug Name & Category	Functional group	Structure	Prodrug strategy
3	Bambuterol (asthma)	Bisdimethyl carbamate of Terbutaline		Prolongs duration of drug action
4	Midodrine (vasopressor)	Glycyl amide of desglymidodrine		Improved carrier-mediated absorption

6. Oximes as Derivatives of Ketones, Amidines and Guanidines

Oximes (for example, ketoximes, amidoximes, and guanidoximes) are derivatives of ketones, amidines and guanidines, thus providing an opportunity to modify molecules that lack hydroxyl, amine or carboxyl functionalities. Oximes, especially strongly basic amidines and guanidoximes, can be used to enhance the membrane permeability and absorption of a parent drug [21] (see an example in Table 1).

However, the prodrug strategy has been successfully applied to a wide range of drug molecules using the functional groups described above. The major promoieties used for the development of prodrugs are includes Palmitic acid (1; Figure 2) [22], Sulfenamides (2; Figure 2) and sulfonamids (3; Figure 2) [23], Succinic acid (4; Figure 2) [24], Amino Acid ester (5; Figure 2) [25], Dipeptides (7; Figure 2) and Tripeptides (8; Figure 2) [26], Carboxylate neopentyl sulfonyl ester (6; Figure 2), Gabapentin (9; Figure 2), Phosphodiester [27].

Palmitic Acid or Hexadecanoic acid (1)

Sulfinamides (2)

Sulfonamides (3)

Succinic acid (4)

Amino acid acyl group (5)

Carboxylate neopentyl sulfonyl ester (6)

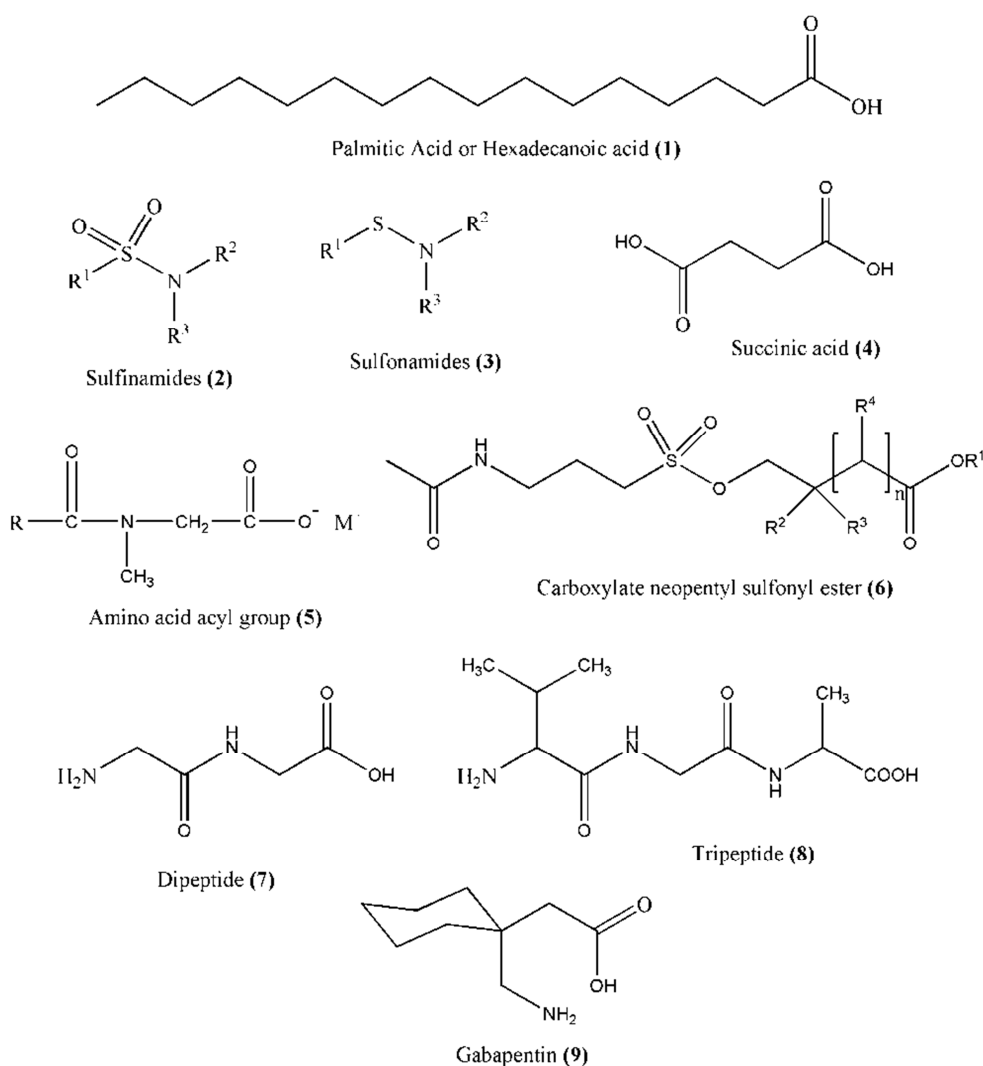Dipeptide (7)

Tripeptide (8)

Gabapentin (9)

***Figure 2.** Structure of some common promoieties.*

7. Conclusion

Prodrugs can offer an attractive alternative to improve undesirable ADMET properties of a wide variety of drugs without losing the benefits of the drug molecule. Because of its versatility, the Prodrug approach has enhanced the clinical usefulness of many pharmacological agents in the past, and as many as 10% of all approved small molecular drugs on the market today can be classified as prodrugs. However, the design of prodrugs should be considered at very early stages of the drug research and development process, because changing the ADMET properties may expose other undesired properties of the drug candidates. Perhaps, promoeities are the most vulnerable link in the chain, because many undesirable factors can be overcome by utilizing these with bioactive compounds. Nonetheless, developing a prodrug can still be more feasible and faster strategy than searching for an entirely new therapeutically active agent with suitable ADMET properties.

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