Review Article

Promoiety: A versatile tool for improving drug acceptability

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ABSTRACT

Prodrug 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 of an obvious promoiety (bioprecursor prodrug), but instead result from a molecular modification of the active principle itself, which generates the resulting active compound on metabolism..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: Carrier-linked, molecular modification, prodrug, promoiety

Introduction

Today almost all drug candidates are associated with some undesirable physicochemical and biological properties such as poor bioavailability, incomplete absorption, adverse effects, and first-pass metabolism.[1] Their therapeutic efficacy can be improved by minimizing or eliminating these undesirable properties while retaining the desirable ones. Prodrug design is opening new doors in the challenging field of drug discovery and revolutionizing the art of drug development as they are capable to overcome these challenges.[2]

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.[3] 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.[4] 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 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 into two major classes: Carrier-linked prodrugs and bioprecursors. In the carrier-linked prodrugs, the active molecule (the drug) is temporary linked to a carrier (also known as a promoiety) through a bioreversible covalent linkage[5] such as ester, amide, carbamate, carbonate, ether, imine, phosphate, and among others.[6,7] In general, promoiety is devoid of pharmacological activity but may impart some desirable properties to the drug such as increase water or lipid solubility, and reduction of toxicity. However, mutual prodrugs are a type of carrier-linked prodrug in which two active compounds are linked each acting as the carrier to the other.

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On the other hand, bioprecursor 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 absorption, distribution, metabolism, and excretion (ADME) 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. Therefore, the prodrug approach has the ability to keep promising new drug candidates alive through the development and improving the safety and efficacy of existing drug products.[8,9] They are designed to improve the physicochemical, biopharmaceutical, and/or pharmacokinetic properties of pharmacologically potent compounds. 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.[2] However, there are several important factors that should be kept in mind while designing a prodrug structure, mainly includes:

- Parent drug: Which functional groups are amenable to chemical prodrug derivatization?
- Promoiety: This should ideally be safe and rapidly excreted from the body. The choice of promoiety should be considered with respect to the disease state, dose, and the duration of therapy.
- Parent and prodrug: The ADME and pharmacokinetic properties need to be comprehensively understood.
- Degradation by-products: These can affect chemical and physical stability and lead to the formation of new degradation products.

This article describes some common promoieties that are amenable to prodrug design and highlights applications of the various promoieties using prodrug strategy. Special emphasis is given to the role of the promoieties in the design of new drug regimens.

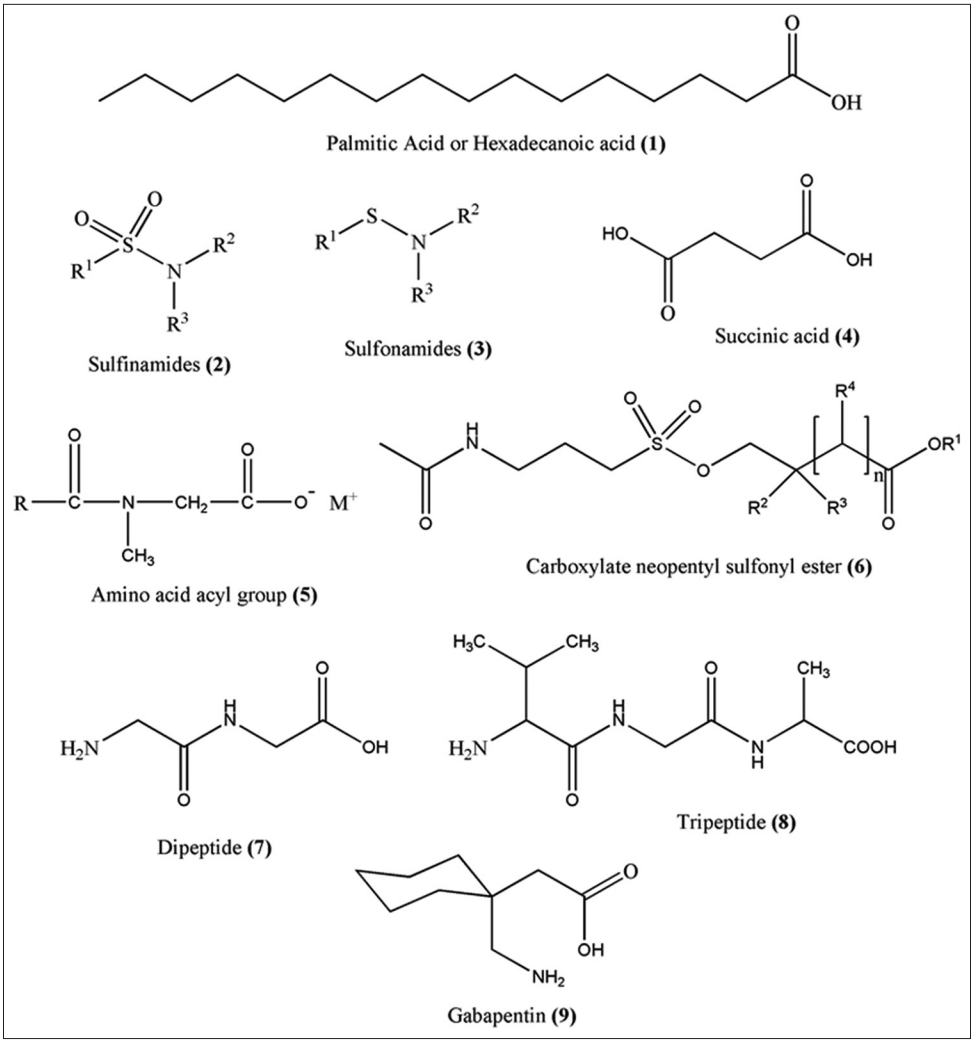

Figure 1: Structure of some common promoieties

Palmitic Acid

Palmitic acid [1; Figure 1] is the most common fatty acid found in animals, plants, and microorganisms. It is a major component of the oil from palm trees (palm oil, palm kernel oil, and coconut oil). However, it can also be found in meats, cheeses, butter, and dairy products. Palmitic acid was discovered by Edmond Fremy, in 1840, in saponified palm oil. Palmitic acid is used to produce soaps, cosmetics, and release agents. These applications utilize sodium palmitate, which is commonly obtained by saponification of palm oil. Sodium palmitate is permitted as a natural additive in organic products. According to the World Health Organization, the evidence is "convincing" that consumption of palmitic acid increases the risk of developing cardiovascular diseases.

Palmitic acid as a promoiety in NSAIDs

The class of NSAIDs represents an important group of drugs indicated for the treatment of pain and inflammation. The drugs suppress inflammation by inhibiting prostaglandins synthesis.[10]

Apart from the beneficial effect, long-term use of NSAIDs may lead to serious side effects like GI irritation due to its acidic effect. Literature survey reveals that conversion of salicylic acid (SA), anthranilic acid (AA), para amino phenol (PAP), and para-aminobenzoic acid (PABA) into palmitoyl derivatives, namely palmitoyl SA (PSA), palmitoyl AA (N-PAA), palmitoyl PAP (PPAP), and PPABA (N-PPABA) through an ester bond or amide bond to the OH or NH_2 residue of the latter may reduce their acidic nature. The selection of the fatty acid moiety is done in such a manner that the prodrugs showing lipophilic behavior with varying degree of lipophilicity are obtained. Thus, the results of this study suggest that PSA possesses promising anti-inflammatory, antipyretic, and analgesic properties compared to acetyl SA, and *N*-PAA exhibited potent pharmacological properties. Thus, the conjugation of palmitic acid to NSAID leads to new compounds that possess improved and efficient pharmacological properties. Hence, conjugation reaction products with lipids can attribute to eliminate the side effects inherent in the parent compounds. The mechanisms involved in the cell membrane penetration of these compounds are underway. Such a study may identify the interactions of modified drugs with cell receptors and their metabolic roles.[11]

Palmitic acid as a promoiety in chloramphenicol

This drug has a bitter taste, which is difficult to mask in orally administered solutions. Researchers discovered that the drug became flavorless when transformed in palmitic ester, due to the reduction of hydrosolubility. Chloramphenicol palmitate is a prodrug of chloramphenicol, obtained from the esterification reaction between the drug and palmitic acid. It is, therefore, inactive, and for it to become active, it undergoes hydrolysis of the ester bond through the action of pancreatic lipases in the duodenum. The acquired prodrug is a lipophilic compound, which means it can be marketed as an oral suspension.

Sulfenamide

Sulfenamides (also spelled sulfenamides) are a class of organosulfur compounds with characteristic C-S, S-N bonds, and the general formula RSNHR', where R and R' are H, alkyl, or aryl.[12] They are closely related to their oxygenated cousins sulfonamides ($R^1SO_2NR^2R^3$) [2; Figure 1] and sulfonamids ($R^1SNR^2R^3$) [3; Figure 1].

The gastric H, K-ATPase is the primary target for the treatment of acid-related diseases. Proton pump inhibitors (PPIs) are weak bases composed of two moieties, a substituted pyridine with a primary pKa of about 4.0, which allows selective accumulation in the secretory canaliculus of the parietal cell and a benzimidazole with a second pKa of about 1.0. PPIs are acid-activated prodrugs that convert to sulfenic acids or sulfenamides that react covalently with one or more cysteines accessible from the luminal surface of the ATPase. Due to covalent binding, their inhibitory effects last much longer than their plasma half-life. However, the short half-life of the drug in the blood and the requirement for acid activation impairs their efficacy in acid suppression, particularly at night. PPIs with longer half-life promise to improve acid suppression. All PPIs give excellent healing of peptic ulcers and produce good results in reflux esophagitis.[13]

However, sulfenic acids or sulfenamides when added to acid transporting vehicles, inhibition of H+K+ATPase take considerable time, approximately related to the rate of activation of different drugs. The sulfonamide formed in the bulk solution does not react with the pump, at least not in case of pantoprazole. The rate of formation of sulfenamide within the extracytoplasmic domain determines the cysteines that react. Lansoprazole react with the cysteines initially available, namely, Cys321, 813, 892, and perhaps in this compound, the sulfenamide being formed in free solution is responsible for inhibition. Omeprazole which converts somewhat more slowly to the sulfonamide reacts with Cys813 and 892. Pantoprazole which converts even more slowly has time to penetrate the vestibule of the enzyme and react therefore with both the cysteines in the loop M5/loop/M6 sector, but not the more superficial cysteines at position 321 and 892.

Succinic Acid

Succinic acid [4; Figure 1] is a dicarboxylic acid with the chemical formula $(CH_2)_2(CO_2H)_2$. Succinate is generated in mitochondria through the tricarboxylic acid cycle, an ancient energy-yielding process shared by all organisms. Succinate can exit the mitochondrial matrix and function in the cytoplasm as well as the extracellular space, changing gene expression patterns, modulating epigenetic landscape, or demonstrating hormone-like signaling.[14] Prednisolone 21-hemisuccinate/beta-cyclodextrin (beta-CyD) amide conjugate was prepared by binding prednisolone 21-hemisuccinate covalently to the amino group of mono(6-deoxy-6-amino)-beta-CyD through an amide linkage. Prednisolone 21-hemisuccinate was intramolecularly transformed to prednisolone 17-hemisuccinate, and the parent drug, prednisolone, was slowly released from the 21-hemisuccinate with a half-life of 69 h in pH 7.0 at 37°C; the drug release at 25°C was <10% for 48 h. In sharp contrast, the hydrolysis of prednisolone 21-hemisuccinate/beta-CyD amide conjugate was significantly faster (half-life of 6.50 min at 25°C) and gave prednisolone and mono(6-deoxy-6-succimino)-beta-CyD as products. The hydrolysis of the beta-CyD amide conjugate was subject to specific-base catalysis

in the alkaline region. The rapid hydrolysis of the conjugate can be ascribed to the involvement of intramolecular nucleophilic catalysis of the amide group in the reaction. The succinic acid, bound to a drug through an ester linkage at one carboxylic group and bound to a promoiety through amide linkage at another carboxylic group, may be useful as a spacer for construction of the immediate release type prodrugs of CyDs.[15]

Amino Acid Ester

Prodrug approaches with amino acid modification have been widely employed to improve intestinal absorption of poorly permanent drugs. The antiviral drug valacyclovir is an example of a successful amino acid ester prodrug strategy which contains amino acid acyl group [5; Figure 1] as promoiety. The improved oral bioavailability of valacyclovir has been attributed to the enhanced transport by intestinal oligopeptide transporters. Dipeptide and tripeptide compounds, along with mono amino acid derivatives, have been investigated for their suitability as substrates for the oligopeptide transporter. Mono amino acid ester prodrugs of antiviral and anticancer drugs such as gemcitabine, acyclovir, and 2-bromo-5,6-dichloro-1-(β-D-ribofuranosyl)benzimidazole have been synthesized and evaluated for their suitability as transporter substrates.[16]

Moreover, certain acyclic nucleoside phosphonates (ANPs) such as (S)-HPMPC (cidofovir, Vistide®) and (S)-HPMPA have been shown to be active against a broad spectrum of DNA and retroviruses. However, their poor absorption, as well as their toxicity, limit the utilization of these therapeutics in the clinic. Nucleoside phosphonates are poorly absorbed primarily due to the presence of the phosphonic acid group, which ionizes at physiological pH. When dosed intravenously they display dose-limiting nephrotoxicity due to their accumulation in the kidney as a result of their poor absorption. To overcome these limitations, nucleoside phosphonate prodrug strategies have taken center stage in the development pathway, and a number of different approaches are at various stages of development. Our efforts have focused on the development of ANP prodrugs in which a benign amino acid promoiety masks a phosphonate P-OH through a hydroxyl side chain. The design of these prodrugs incorporates multiple chemical groups (the P−X−C linkage, the amino acid stereochemistry, and the C-terminal and N-terminal functional groups) that can be been tuned to modify absorption, pharmacokinetic, and efficacy properties with the goal of improving overall prodrug performance.[17]

Dipeptides [7; Figure 1] and Tripeptides [8; Figure 1]

The mammalian proton-coupled peptide transporter 1 (PepT1), which is predominantly located principally on the luminal cell membrane of the intestine, plays an important role in the absorption of di- and tripeptides from the digestion of ingested protein. A lot of poorly absorbed drugs (β-lactam antibiotics such as cephalosporins and penicillins, angiotensin-converting enzyme inhibitors such as zofenopril, trandolapril, quinaprilat and perindopril, selected rennin inhibitors, and antitumor agents such as bestatin and dopamine receptor antagonists such as sulpiride) have been modified into peptidomimetic prodrugs with affinity for PepT1 to improve permeability across intestinal membrane, and eventually enhance oral bioavailability of the drugs. Due to the broad substrate specificity of the transporter this strategy has become a hot topic of research on targeted prodrug. This review addressed the progress of functional properties of PepT1, expression and transporter structure of PepT1, and structural features of PepT1 substrates. In addition, PepT1-targeted prodrugs with various structures (amide, ester, and other types) and different functions, such as improvement of oral bioavailability, circumvention of drug efflux transporter, increase of ocular bioavailability, and improvement of tumor targetability and efficiency, have also been summarized. With the recognition of crystal structural model of PepT1 just provided in 2011, rational design of peptidomimetic drugs/prodrugs utilizing the transport activity of PepT1 is expected.

Moreover, five dipeptidomimetic-based model prodrugs containing ketomethylene amide bond replacements were synthesized from readily available α, β-unsaturated, and γ-ketoesters. The model drug (BnOH) was attached to the C-terminus or one of the side chain positions of the dipeptidomimetic. The stability, the affinity for the di-/tripeptide transporter hPEPT1 and the transepithelial transport properties of the model prodrugs were investigated. ValΨ[$COCH_2$]Asp(OBn) was the compound with the highest chemical stability in buffers at pH 6.0 and 7.4, with half-lives of 190 and 43 h, respectively. All five compounds showed high affinity for hPEPT1 (Ki values <1 mM), and PheΨ[$COCH_2$]Asp(OBn) and ValΨ[$COCH_2$]Asp(OBn) had the highest affinities with Ki values of 68 and 19 μM, respectively. An hPEPT1-mediated transport component was demonstrated for the transepithelial transport of three compounds, a finding that was corroborated by hPEPT1-mediated intracellular uptake. The results indicate that the stabilized Phe-Asp and Val-Asp derivatives are promising promoieties in a prodrug approach targeting hPEPT1.[18]

Carboxylate Neopentyl Sulfonyl Ester [6; Figure 1]

Acamprosate is a polar molecule that lacks the requisite physicochemical characteristics for effective passive permeability across cellular membranes. Intestinal absorption of acamprosate is mainly by passive diffusion and to a lesser extent by an active transport mechanism such as through an amino acid transporter. As a consequence, the oral bioavailability of acamprosate in humans is only about 11%. The mean elimination half-life of acamprosate following intravenous infusion (15 min) is 3.2 ± 0.2 h. Efforts to enhance the gastrointestinal absorption and oral bioavailability of acamprosate includes coadministrating the drug with polyglycolysed glycerides. Acamprosate prodrugs exhibiting enhanced absorption from the lower gastrointestinal tract have the potential to increase the oral bioavailability of the drug and to facilitate administration of acamprosate using sustained release oral dosage forms. Thus, there is a need for new prodrugs of acamprosate with demonstrated enhanced oral bioavailability. In particular, masked carboxylate neopentyl sulfonyl ester prodrugs of acamprosate that exhibits enhanced absorption throughout the gastrointestinal tract and

especially in the large intestine/colon and hence that is suitable for sustained release oral formulations can enhance the convenience (by reducing the dose and dosing frequency), efficacy, and side effect profile of acamprosate.

Gabapentin as Prodrug

Gabapentin or 2-(1-(aminomethyl)cyclohexyl)acetic acid [9; Figure 1] is believed to be actively transported across the gut wall by a carrier transporter localized in the human small intestine. The gabapentin transporter is easily saturated which means that the amount of gabapentin absorbed into the blood is not proportional to the amount of gabapentin that is administered orally, since once the transport mechanism is saturated, further absorption of gabapentin does not occur to any significant degree. In comparison to gabapentin, the compound disclosed herein is absorbed across the gut wall along a greater portion of the gastrointestinal tract, including the colon.

Since the compound disclosed herein can be formulated in sustained release formulations which provide for sustained release over a period of hours into the gastrointestinal tract and particularly, release within the colon, 1-{[(α-isobutanoyloxyethoxy)carbonyl] aminomethyl}-1-cyclohexane acetic acid (gabapentin enacarbil) may also be more efficacious than gabapentin in treating or preventing epilepsy, pain (especially, neuropathic pain, and muscular and skeletal pain), post-herpetic neuralgia, depression, anxiety, psychosis, faintness attacks, hypokinesia, cranial disorders, neurodegenerative disorders, panic, inflammatory disease (i.e., arthritis), insomnia, gastrointestinal disorders, hot flashes, restless legs syndrome, urinary incontinence, or ethanol withdrawal syndrome. The ability of the compound disclosed herein to be used in sustained release oral dosage forms reduces the dosing frequency necessary for the maintenance of a therapeutically effective drug concentration in the blood.

Phosphodiester as the Promoiety

Oral administration of chemotherapeutic agents is the mainstay for the treatment of disease. Aqueous solubility is likewise a critical attribute for an orally available drug. Accordingly, the bioavailability and consequent efficacy of many compounds rely on enhancing their aqueous solubility.[19] The formation of a phosphomonoester or diester can improve the oral bioavailability of poorly water-soluble chemotherapeutic agents. These are the promising promoieties for the timed release of orally available drugs. The promoiety enhances the aqueous solubility of a model drug, metronidazole, and masks its activity until release by a human pancreatic ribonuclease. The rate of drug release can be tuned by changing the nucleobase.[20]

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. Due to 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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