

Overview of prodrugs

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Introduction

The concept of prodrug was first introduced in medicinal chemistry by Albert [1] in 1951: “A prodrug is a molecule which does not have any intrinsic biological activity but which is capable during the different phases of its metabolism to generate a biologically active drug”. According to this definition and to that accepted by IUPAC [2], a prodrug is any compound that undergoes biotransformation before exhibiting its pharmacological effects. Prodrugs can thus be viewed as drugs that contain specialized nontoxic protective groups used in a transient manner to alter or to eliminate undesirable properties in the parent molecule.

Generally, the metabolic transformation necessary to convert the prodrug into the drug is catalyzed by specific enzymes, mainly hydrolases, and ideally this should selectively occur at the target tissue to prevent undesirable side effects. In drug research and development, the prodrug concept has found a number of useful applications since it allows several, sometimes contradictory, biological and/or physicochemical objectives to be satisfied. Some examples are shown in (Fig. 1) including cellular permeation, solubility, chemical or enzymatic stability, bioavailability, toxicity, or blood brain barrier penetration [3]. One has to bear in mind that many of these objectives are intertwined [4]. A potent suitable prodrug should overcome the crucial paradox: it has to be lipophilic enough to cross a membrane or metabolic barrier (Fig. 2) and simultaneously it should be hydrophilic enough to fulfill solubility, bioavailability and transport criteria [5,6].

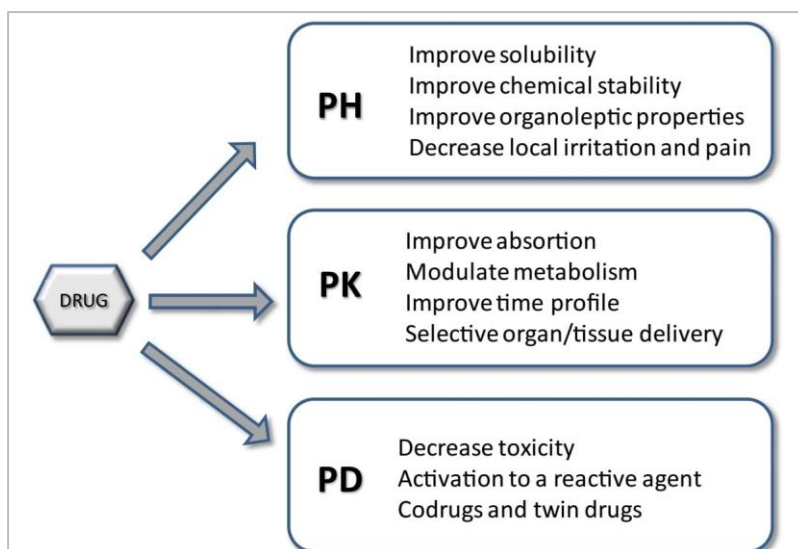


Fig. 1. A schematic classification of some objectives in prodrug research, classified by objectives related to pharmaceutical (PH), pharmacokinetic (PK) and pharmacodynamic (PD) phases

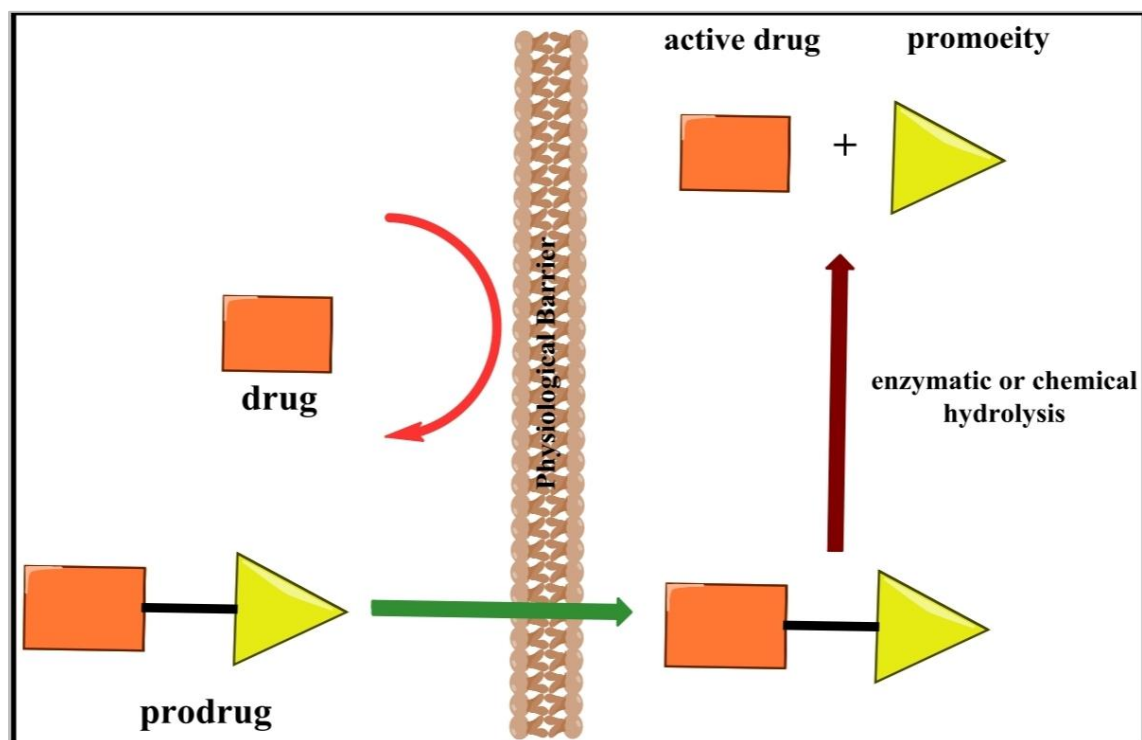


Fig. 2. Schematic representation of a prodrug [7].

PRODRUGS CLASSIFICATION

The conventional method used to classify prodrugs is based on derivatization and the type of carriers attached to the drug. This method classifies prodrugs into two sub-major classes:

1. Carrier-linked prodrugs, in which the promoiety is covalently linked to the active drug but it can be easily cleaved by enzymes (such as an ester or labile amide) or non-enzymatically to provide the parent drug. Ideally, the group removed is pharmacologically inactive, nontoxic, and non-immunogenic, while the promoiety must be labile for in vivo efficient activation [8, 9].

Carrier-linked prodrugs can be further subdivided into: (a) bipartite which is composed of one carrier (promoiety) attached directly to the drug, (b) tripartite which utilizing a spacer or connect a group between the drug and a promoiety. In some cases bipartite prodrug may be unstable due to inherent nature of the drug-promoiety linkage. This can be solved by designing a tripartite prodrug and (c) mutual prodrugs, which are consisting of two drugs linked together.

2. Bioprecursors result from a molecular modification of the active principle. The modification generates a new compound that is capable of being a substrate of the metabolic enzymes, with the metabolite being the expected active compound [3,10,11]. For example, if the drug contains a carboxylic acid group, the bioprecursor may be an alcohol that is metabolized by oxidation to the aldehyde and then to the carboxylic acid drug. Although pharmacologically active metabolites are generally formed by phase I reactions (oxidation, reduction or phosphorylation),

phase II conjugation reactions can also produce biologically active compounds (Fig. 3).

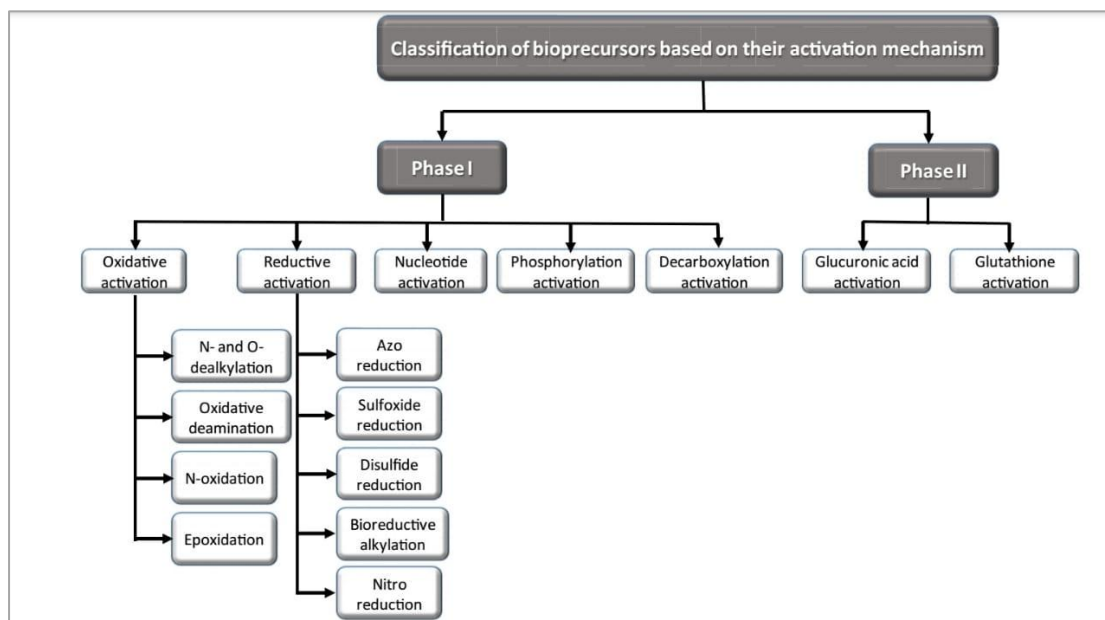


Fig. 3. Classification of bioprecursor prodrugs based on their activation mechanisms (adapted from Ref. [11]).

APPLICATIONS OF PRODRUGS

The principal objectives of the prodrug approach can be summarized as follows: (1) improving drug water-solubility, (2) improving absorption and membrane permeability, (3) targeted release, and (4) reducing metabolism and side effects.

1. Improving drug water-solubility

An inadequate water-solubility affects, amongst other factors, the via of drug administration and the pharmaceutical form. A general strategy involves the introduction into this poorly watersoluble drug of

some ionizable groups, such as phosphate, hemisuccinate or amino acid esters, or a link to neutral macromolecules such as polyethylene glycol.

2. Improving absorption and membrane permeability

The ability of a drug to cross cell membranes is frequently related to the lipophilicity of that drug. However, many polar groups are important to receptor binding but hinder the drug from crossing membranes. This is the case, for example, of carboxylic acid groups. In these cases, one solution is to protect the acid group in the form of a less polar ester. The ester could cross fatty membranes and once it is in the bloodstream it is hydrolyzed back to the parent acid drug. The variety of ester prodrugs in the literature is immense and has served to mask carboxylate, phosphate and tetrazole groups, as well as alcoholic or phenolic functions. An example of this approach is RO-64-0802 [\[12\]](#), a neuraminidase inhibitor of therapeutic value against type A and B influenza in humans.

3. Targeted release

method that unifies the prodrug approach with target specificity, where the drug is inactive during transport and is activated only when released to specific target tissue without any toxic effects, would be very effective in the field of drug delivery. This concept comes from the scientist Paul Ehrlich's principle known as the “magic bullet”: he considered the chemical as a bullet that could search out and destroy the invading microorganism without adversely affecting the host. Several strategies have been pursued in an effort to improve the selectivity of low molecular weight drugs and thus to increase the concentration of the active agent in the desired tissue, while its concentration is reduced in

healthy tissues in order to reduce side effects. Some examples of this strategy are :

5-Aminosalicylic acid (5-ASA **18**, Fig. 4) is a drug used to attenuate the inflammatory response in idiopathic inflammatory bowel diseases, such as ulcerative colitis, although its mechanism of action is not fully understood. However, 5-ASA usually fails to reach the colon and this leads to significant adverse effects, such as ulcerogenic potential. Therefore, a prodrug approach for colon delivery of 5-ASA has become a rational system of drug delivery for the topical treatment of such diseases. Balsalazide (**19**, Fig. 4), a prodrug in which 5-ASA is linked to the carrier 4-aminobenzoyl balanine by an azo bond, is specifically converted to 5-ASA by azoreducing bacteria present in the colon [13]. Thus, the prodrugs based on non-sulfapyridine azo-conjugates of 5-ASA, such as Balsalazide **19**, protect against proximal absorption and have the potential to separate dose-ranging benefits from side effects related to the presence of the sulfapyridine moiety.

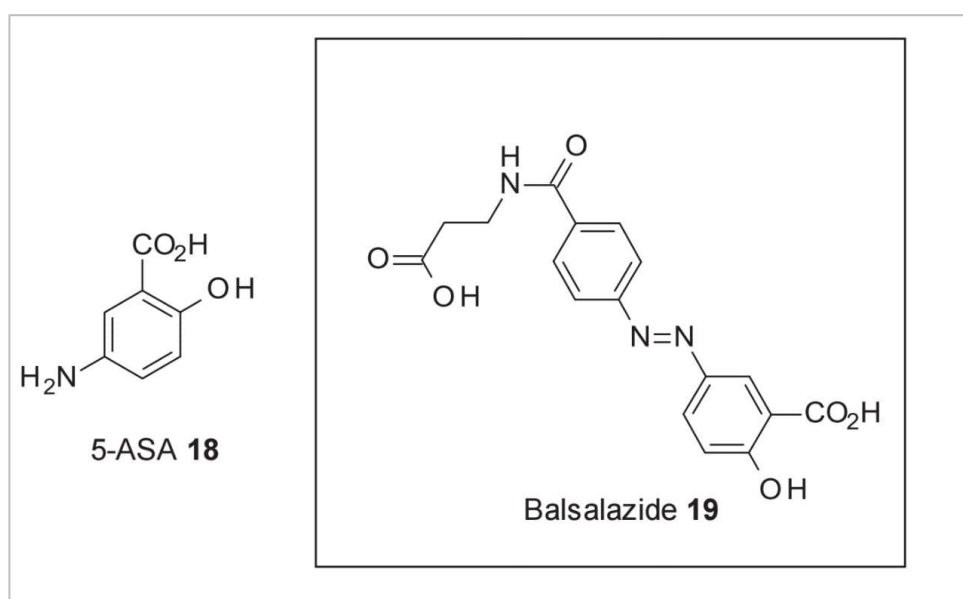


Fig. 4. Molecular structures of 5-ASA **18** and Balsalazide **19**.

4. Reducing metabolism and side effects

Many drugs suffer from extensive metabolism leading to drug inactivation, frequently due to the presence of metabolically labile chemical groups. In some cases drugs undergo metabolic activation into toxic chemical species and sometimes toxicity is associated with high initial plasma levels. In all cases, these drugs are attractive targets for a prodrug strategy. Curcumin 46 [14] (Fig. 5) is a polyphenolic compound. It is the main bioactive ingredient of turmeric extract and has been widely investigated as an antioxidant, anti-inflammatory and antimicrobial agent. The most attractive feature of curcuminoids is the lack of significant toxicity, as shown in animal and human studies. The major obstacle in clinical trials has been the low bioavailability of Curcumin 46 due to its instability in a biological environment, inadequate absorption and fast metabolism resulting in rapid systemic elimination. Phenolic groups and double bonds are the main sites of in vitro and in vivo degradation by pathways that include conjugations and reduction process. Numerous strategies have been used to enhance the bioavailability of Curcumin and these include the conjugation of small endogenous molecules such as amino acids and glucose at the phenolic groups [15].

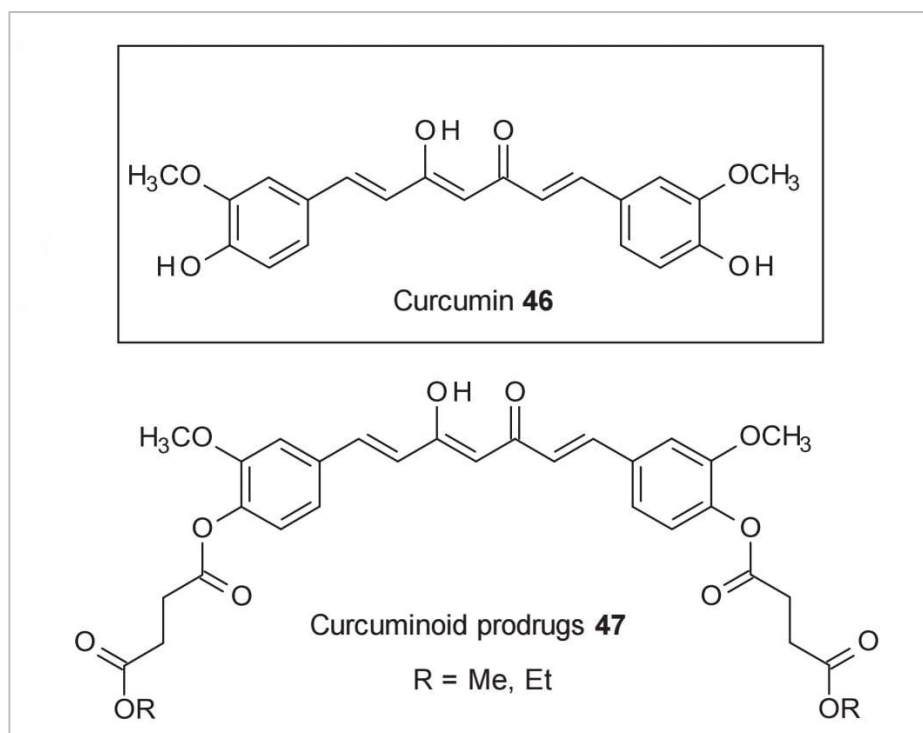


Fig. 5. Structure of Curcumin 46 and its succinate prodrugs 47.

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