Prodrug Design

Introduction to Prodrug Design

- A **prodrug** is an inactive or less active precursor that is converted in the body into the active drug responsible for the intended effect.
- The precursor may contain a removable chemical group or may require a metabolic transformation to create the active structure.
- The purpose is usually to improve delivery or another property that limits the use of the active molecule.
- The administered prodrug and the active species have different chemical structures, so delivery and target recognition can be improved at different stages.
- The benefit depends on reliable conversion to the active form and on the properties of every fragment released during activation.

Why an Active Drug May Need Modification

Problems Before the Drug Reaches Its Target

- Poor solubility can prevent an acceptable formulation or slow dissolution.
- Poor membrane permeability can reduce absorption.
- Unpleasant taste, local irritation, rapid elimination or poor distribution can also limit usefulness.

First Hope

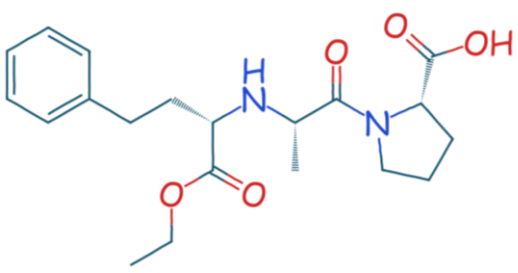
The Design Principle

- Modify the molecule to improve the limiting property, while preserving a reliable route back to the active drug.
- The modification should be stable enough during manufacture and administration but convertible at a useful rate in the body.

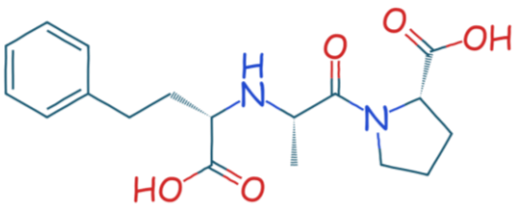
Example: Enalapril and Enalaprilat

- **Enalapril** masks one carboxyl group of **enalaprilat** as an ethyl ester.

Ester masking in an oral prodrug



Enalapril: ester prodrug



Enalaprilat: active diacid

Hydrolysis of the ethyl ester restores the additional carboxyl group

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- The ester improves oral delivery and is hydrolysed after absorption to release the more active ACE inhibitor enalaprilat.

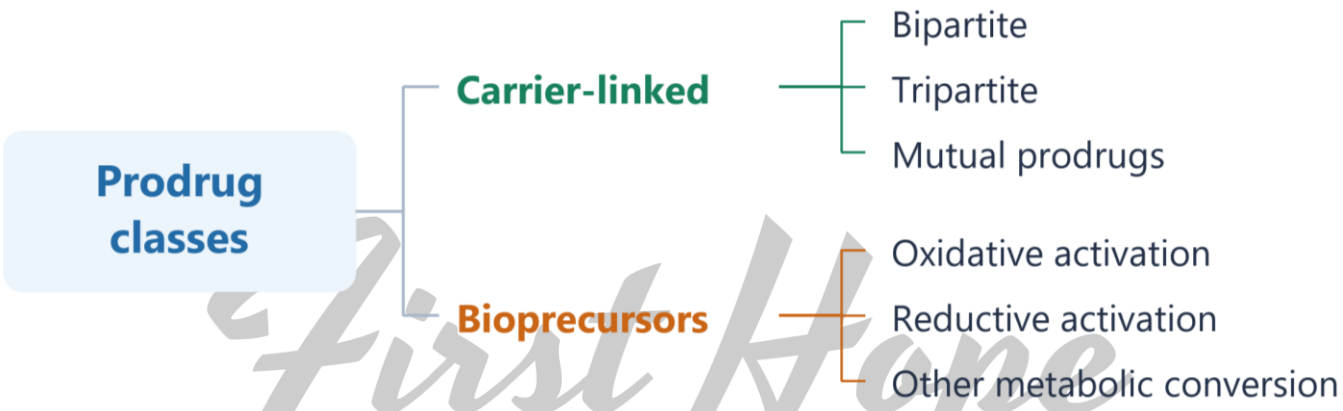
Prodrugs and Formulations

- A prodrug changes the covalent chemical structure.
- A salt, coating or ordinary controlled-release tablet can change delivery without necessarily creating a new prodrug.

Basic Concept of Prodrug Design

- Prodrug design separates the properties needed for delivery from the properties needed for binding to the target.

Classification of Prodrugs



- The two broad classes are **carrier-linked prodrugs** and **bioprecursors**.
- Carrier-linked designs release the drug by removing a temporary attached group, whereas bioprecursors create the active structure through a biochemical transformation.

Components of the Design

1. Active Drug

- The active drug contains the structure that produces the intended pharmacological effect.

2. Temporary Chemical Modification

- A carrier-linked prodrug contains a removable group, often called a promoiety, attached through a suitable bond.
- A bioprecursor prodrug is activated by a transformation of the molecule itself rather than simple removal of an attached carrier.

3. Activation Process

- Activation may involve hydrolysis, oxidation, reduction or another biotransformation.
  - The responsible process must occur in the relevant biological setting at a useful rate.

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The Required Balance

- If conversion is too rapid before absorption, the modification may fail to improve delivery.
- If conversion is too slow after the prodrug reaches the body, insufficient active drug may be released.
- The active drug, the remaining fragments and any intermediates all contribute to the overall benefit–risk profile.

Criteria for a Successful Prodrug

- A successful prodrug improves a specific limitation while providing predictable exposure to the active species.

Carrier-Linked Prodrugs

- A **carrier-linked prodrug** contains an active drug attached to a temporary carrier through a bond that can be cleaved in the body.



Structural Components

- The drug supplies the pharmacologically useful part of the structure.
- The carrier changes a property such as solubility, permeability, taste or distribution.
- The linkage determines how and where the active drug can be released.

Structural Types of Carrier-Linked Prodrugs

Bipartite and Tripartite Architecture

A. Bipartite Prodrugs

- The drug is attached directly to the promoiety through a cleavable bond.
- **Enalapril** illustrates direct masking of a carboxyl group as an ester.

B. Tripartite Prodrugs

- A spacer is placed between the drug and the carrier or trigger group.
- Activation removes or changes the trigger, and the remaining spacer subsequently releases the drug.
- This arrangement can be useful when a direct drug–carrier bond does not provide the required stability or release behaviour.

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Mutual Prodrugs

- Two therapeutically useful components are joined so that cleavage releases both of them.
- **Example: Sultamicillin** is a mutual prodrug of **ampicillin** and the beta-lactamase inhibitor **sulbactam**.
- The term mutual describes the roles of the released components; bipartite and tripartite describe the linkage architecture, so the classifications can overlap.

Common Linkages

- Esters are widely used because esterases or chemical hydrolysis can regenerate an alcohol or carboxylic acid.
- Phosphate esters can increase aqueous solubility when the phosphate group is ionised.
- Carbamates, carbonates and other linkages provide different activation and stability profiles.

Examples

1. Enalapril

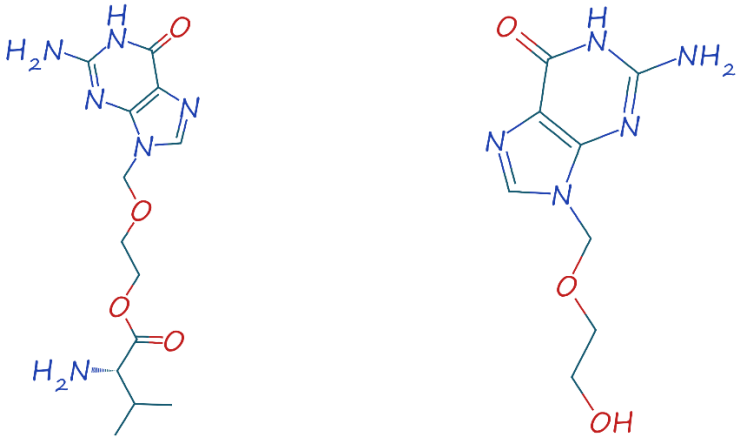
- An ethyl ester masks a carboxyl group of **enalaprilat** and is removed by hydrolysis.

2. Valacyclovir

- An L-valyl ester is attached to **acyclovir** and improves oral delivery before conversion to **acyclovir** and **L-valine**.

First Hope

An amino-acid ester prodrug



Valacyclovir
L-Valyl ester: (2S)

Acyclovir
Parent active drug

- In the illustrated pair, the **L-valyl group** is attached to the terminal hydroxyl group of **acyclovir** through an ester bond.
- Cleavage of this ester regenerates **acyclovir** and releases **L-valine**; the guanine-containing part of the drug is retained.

3. Fosphenytoin

- A phosphate-containing modification makes a soluble precursor of phenytoin suitable for an aqueous parenteral formulation.

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Advantages of Carrier-Linked Prodrugs

- The approach permits systematic changes to the carrier and linkage while retaining the active-drug framework.

Limitations of Carrier-Linked Prodrugs

- The carrier must be adequately tolerated, and cleavage must not depend on an unreliable biological process.

Bioprecursor Prodrugs

- A **bioprecursor prodrug** is converted into an active drug by a metabolic transformation that changes its functional groups or oxidation state.

How It Differs from a Carrier-Linked Prodrug

- Activation does not mainly consist of removing a separate, detachable carrier from an already complete active drug.
- Instead, the chemical transformation creates an active functional group or molecular form.

Types of Activation

1. Oxidative Activation

- Oxidation can create a reactive or target-binding metabolite.
  - **Example: Clopidogrel** requires metabolic activation to a thiol-containing species that inhibits platelet aggregation.

2. Reductive Activation

- Reduction can convert a functional group into a form that produces the intended biological activity.
- The local biological environment and available enzymes influence whether activation occurs.
- **Example: Metronidazole** undergoes reduction of its nitro group in susceptible organisms, producing short-lived reactive species that damage cellular targets.

3. Other Biochemical Conversions

- **Levodopa** is converted to **dopamine** by decarboxylation.
  - Its use illustrates delivery of a precursor that can reach a relevant compartment more effectively than the active transmitter itself.

Design Considerations

- The activation pathway must be sufficiently efficient and reproducible.
- Genetic variation, interacting medicines and disease can change the amount of active metabolite produced.

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