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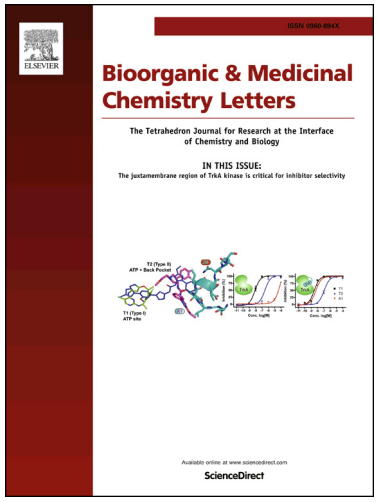

Digest

Recent progress in prodrug design strategies based on generally applicable modifications

Yoshio Hamada

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BMCL Digest

Recent progress in prodrug design strategies based on generally applicable modifications

Yoshio Hamada[a,b,*]

[a]*Faculty of Frontiers of Innovative Research in Science and Technology, Konan University, Minatojima-minamimachi, Chuo, Kobe 650-0043, Japan*
[b]*Fuculty of Pharmaceutical Sciences, Kobe Pharmaceutical University, Motoyamakita, Higashinada, Kobe 658-8558, Japan*

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ABSTRACT

The development of prodrugs has progressed with the aim of improving drug bioavailability by overcoming various barriers that reduce drug benefits in clinical use, such as stability, duration, water solubility, side effect profile, and taste. Many conventional drugs act as the precursors of an active agent *in vivo*; for example, the anti-HIV agent azidothymidine (AZT) is converted into its corresponding active triphosphate ester in the body, meaning that AZT is a prodrug in the broadest sense. However prodrug design is generally difficult owing to the lack of general versatility. Thus, these podrugs, broadly defined, are often discovered by chance or trial-and-error. Recently, many prodrugs that could release the corresponding parent drugs with or without enzymatic action under physiological conditions have been reported. These prodrugs can be easily designed and synthesized because of their generally applicable modifications. This digest paper provides an overview of recent development in prodrug strategies for drugs with a carboxylic acid or hydroxyl/amino group on the basis of a generally applicable modification strategy, such as esterification, amidation, or benzylation.

The prodrug strategy is a practical approach to improving drug bioavailability. Prodrugs often overcome various barriers that reduce drug benefits, such as stability, duration, water-solubility, side effect profile, and taste. Many approaches to their design have been outlined.[1-5] In fact, many conventional drugs known to be activated after metabolic modification, such as L-3,4-dihydroxyphenylalanine (levodopa), the precursor of the neurotransmitters dopamine, norepinephrine, and epinephrine, could be considered a type of prodrug.[6] Anti-viral nucleoside analogue reverse transcriptase inhibitors, such as azidothymidine (AZT),[7] are known to act as corresponding active triphosphate esters, and can also be thought of as prodrugs in the broadest sense. Although the anti-viral agent tenofovir (TFV) also acts as an active triphosphate ester in the body, some prodrugs of tenofovir were developed to improve its bioavailability. One of the TFV prodrugs, tenoforvir alafenamide (TAF), which is a phosphoramide of tenofovir and alanine isopropylester, is stable in human plasma and can release TFV in target cells such as CD4 lymphocytes.[8] TAF is the prodrug of prodrug (TFV), namely a pèro-prodrug. However, the design of prodrugs is generally difficult owing to the lack of general versatility; therefore, most prodrugs, broadly defined, have been discovered by chance or trial-and-error.[9] This digest paper describes recent developments in prodrug design strategies that are generally based on applicable modifications such as esterification, amidation, or

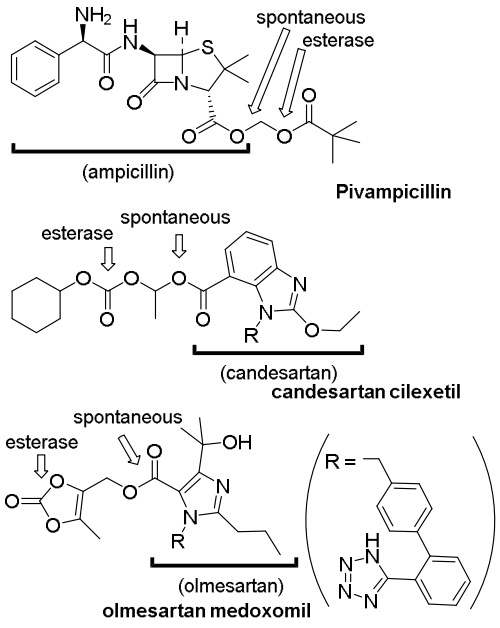

Figure 1. Enzyme-triggered prodrugs of carboxylic acids.

* Corresponding author. Tel.: +81-78-303-1418; e-mail: pynden@gmail.com