Study of Enzymatic Hydrolysis, Diastereomer Phosphoramidate Prodrug of Acyclovir

Thitiphong Khamkhenshorngphanuch,[a] Pitchayathida Mee-udorn,[b] Sewan Theeramunkong* and Nitipol Srimongkolpithak*[b]

[a] Thammasat University Research Unit in Drug, Health Product Development and Application (DHP-DA), Department of Pharmaceutical Sciences, Faculty of Pharmacy, Thammasat University, Pathum Thani, 12120, Thailand. [b] Medical Molecular Biology Research Unit, National Center for Genetic Engineering and Biotechnology (BIOTEC), 113 Thailand Science Park, Phahonyothin Road, Khlong Luang Pathum Thani 12120 Thailand.

E-mail: thitiphong.kha@dome.tu.ac.th, sewan@tu.ac.th* and nitipol.sri@biotec.or.th*

Acyclovir (ACV) is currently used as a treatment for herpes simplex virus types 1 and 2 (HSV-1 and HSV-2). However, it still faces the challenge of poor bioavailability[1] and resistance[2,3]. Reported mutant strains of HSV-1 have been discovered that affect the TK enzyme, which is involved in the phosphorylation of the drug[4]. As a result, ACV is unable to be converted into its phosphorylated active metabolite. The Product nucleotid (ProTide) technology is a technique used to deliver antiviral drugs, specifically nucleoside analogues, into infected cells through monophosphate and monophosphonate mechanisms. In this work, the synthesis of a series of ACV-ProTide, and the separation of its two diastereomers with phosphorus chiral centers were carried out. To order to investigated the effect of phosphorus chirality, a subsequent metabolic study of the isomers using carboxypeptidase Y revealed that the hydrolysis of the *R*p isomer of ester derivatives was more preferred than *S*p isomer. In addition, a confirmation of metabolic preference of isomer was done by molecular docking using MOE. Therefore, the synthesis of a single isomer for ACV-ProTide through a diastereoselective approach and the variation of ester are important factor for bio-activation. Furthermore, biological investigations has been carried out and the results will be further discussed.

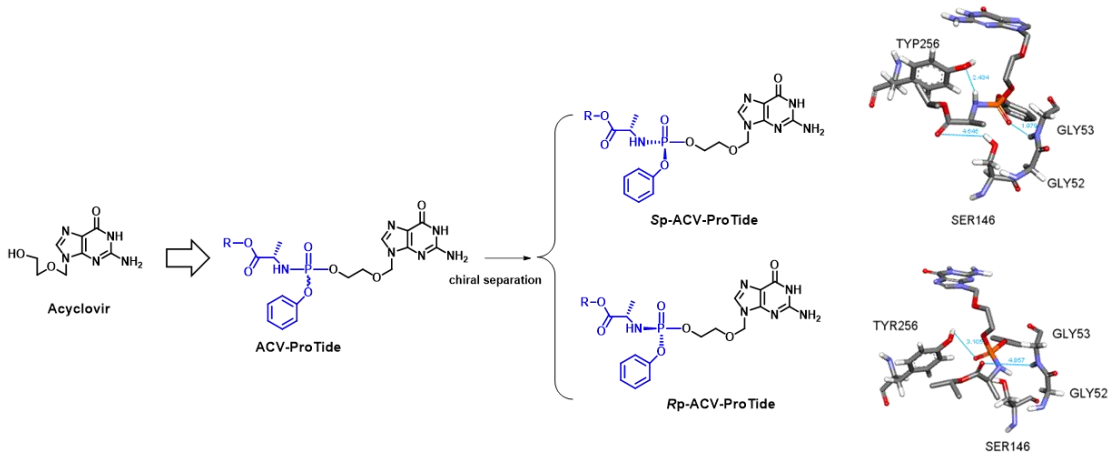

Figure 1. Synthesis, separation of P chiral center and hydrolysis of ACV-ProTide

References

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