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THE SYNTHESIS OF ACV

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Abstract. *Acyclovir is effective against herpes simplex virus (HSV) type 1 and type 2, varicella zoster virus (VZV) and Epstein-Barr virus (EBV). Acyclovir is taken up by the virus infected cell, converted to acyclovir triphosphate (by viral thymidine kinase) and this inhibits viral DNA synthesis by inhibiting viral DNA polyme rases and causing DNA chain termination. Like acyclovir, valaciclovir, ganciclovir, valganciclovir, famciclovir, penciclovir and idoxuridine get converted to their respective monophosphate, diphosphate and then triphosphate derivatives which are the active metabolites. The active metabolite inhibits viral DNA/RNA polymerases and interferes with viral replication [1].*

Keywords: *synthesis of acyclovir, 5-Aminoimidazole-4-carboxamide, purine derivatives.*

Introduction

Acylovir differs from previous nucleoside analogues in that it contains only a partial nucleoside structure: the sugar ring is replaced by an open-chain structure. It is selectively converted into acyclo-guanosine monophosphate (acyclo-GMP) by viral thymidine kinase, which is far more effective (3000 times) in phosphorylation than cellular thymidine kinase.

Subsequently, the *monophosphate* form is further phosphorylated into the active *triphosphate* form, acyclo-guanosine triphosphate (acyclo-GTP), by cellular kinases. Acyclo-GTP is a very potent inhibitor of viral DNA polymerase; it has approximately 100 times greater affinity for viral than cellular polymerase. As a substrate, acyclo-GMP is incorporated into viral DNA, resulting in chain termination. It has also been shown that viral enzymes cannot remove acyclo-GMP from the chain, which results in inhibition of further activity of DNA polymerase.

Acyclo-GTP is fairly rapidly metabolised within the cell, possibly by cellular phosphatases [3]. In sum, aciclovir can be considered a prodrug: it is administered in an inactive (or less active form) and is metabolised into a more active species after administration.

Synthesis from the 5-Aminoimidazole-4-carboxamide

5-Aminoimidazole-4-carboxamide ribonucleotide (**AICAR**) is an intermediate in the generation of inosine monophosphate. AICAR is an analog of adenosine monophosphate (AMP) that is capable of stimulating AMP-dependent protein kinase (AMPK) activity. The drug has also been shown as a potential treatment for diabetes by increasing the metabolic activity of tissues by changing the physical composition of muscle [2].

The synthesis of ACV starting with 5-aminoimidazole-4-carboxamide is displayed in below scheme. Briefly, 5-aminoimidazole-4-carboxamide undergoes alkylations with 3-oxy-4-chlorobutanol acetate ($ClCH_2OCH_2CH_2OAc$), after which the product is condensed with benzoyl othiocyanate (PhCONCS) by heating reflux, in acetone (CH_3COCH_3). Finally, ACV is obtained by cyclodesulfurization hydrolysis under alkaline aqueous solution, containing a suspension of a slight excess of the metal salt (Cu^{2+}, Ag^{+}, or Hg_2). This scheme cleverly adopts the method of cyclodesulfurization by using heavy metal salts to make it possible for the synthesis of ACV from 5-aminoimidazole-4-carboxamide. Although the strategy has the advantages of mild reaction conditions and simple operation, the raw material is not very easy to obtain, so it would potentially take a long time to carry out the work. More importantly, it is not environmentally friendly to add the heavy salts during the production process [4].

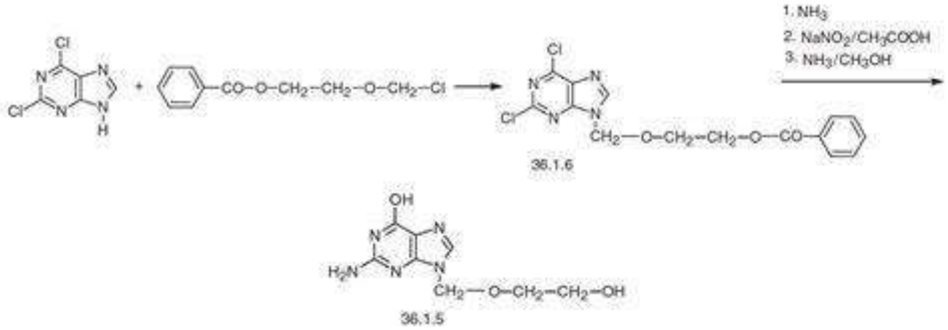
Synthesis from Guanine and Its Derivatives

As biochemical reagents, guanosine and guanine, which have extensive application, are relatively easy to obtain. In the pharmaceutical industry, they are often used for the synthesis of pharmaceutical products. In 1992, Wang et al. reported a synthesis method of ACV from guanosine by three steps. This synthesis route is displayed in below scheme. First, guanosine was acylated by acetic anhydride to become *N, N'*-diacetylguanine. After that, the condensation of *N, N'*-diacetylguanine and 2-oxy-1, 4-butanediol diacetate ($AcOCH_2CH_2OCH_2OAc$) was done in the presence of *p*-totuenesulfonic acid in organic solvents. Finally, ACV was produced by aminolysis in the presence of methylamine. It is recommended as an ideal route for designing experiments, due to the accessible raw materials, simple industrial conditions and high yield.

However, there are numerous methods to synthesize ACV by using guanines as the starting material, which use fewer steps, or just one reaction step. Typically, it can be prepared by acylation of guanines followed by condensation and ammonolysis. In 1988, Matsumoto et al. proposed a convenient and economical synthesis of ACV from guanine. Guanine can be acylated to N, N'-diacetylguanine by Ac_2O. Subsequently, N^2, *O*-diacetylacyclovir is prepared by the condensation of *N, N'*-diacetylguanine and $AcOCH_2CH_2OCH_2OAc$ in the presence of *p*-toluenesulfonic acid (*p*-TsOH) in dimethyl sulfoxide (DMSO). Finally, ACV is successfully synthesized by using ammonia–methanol (NH_3–CH_3HO) as an organic solvent. Considering the need to be environmentally friendly and the production yield of ACV, Chen and Wang consulted and modified Matsumoto's synthesis route to improve the ACV production yield to 52%. They used (the cheaper) toluene instead of using DMSO as the solvent for the condensation reaction, which greatly reduced the amount of reprocessing work. Meanwhile, a methylamine solution (CH_3NH_2–H_2O) was employed instead of NH_3–CH_3OH in ammonolysis, which mitigated the application of a large number of organic media. Interestingly, differing from Matsumoto and Chen, Luo prepared the ACV by the silanization of hexamethyldisiline (HMDS), then by condensation with 3-oxy-4-bromobutanol acetate ($BrCH_2OCH_2CH_2OAc$), and finally by alkaline hydrolysis. The silanization route does not easily form 7-by-product of guanine, due to the large steric hindrance, and condensation is carried out by $Hg(CN)_2$ as a catalyst, which is able to eliminate 7-by-product, thus greatly improving the purity of the product. This synthetic route has a potential industrial value, as it increases the total yield to 72.3%.

The aforementioned methods of preparing ACV from guanine involve a three-step reaction but reducing and simplifying the reaction steps is also important for the synthesis process.

Hakimelahi and Khalafi-Nezhad took a different approach. They developed a general and rapid procedure for the preparation of ACV, which was produced by the condensation of guanine with 3-oxy-4-chloro-butanol benzoate ($ClCH_2OCH_2CH_2OCOPh$) or chloromethylchloroethyl ether ($ClCH_2OCH_2CH_2Cl$) in the presence of tetrabutylammonium fluoride (Bu_4NF) in one step, achieving the condensation and deprotection of the acyl protecting group and nucleophilic displacement of the halogen atoms.



Synthesis from Other Purine Derivatives

It is commonly seen that purine derivatives as starting material provide promising options for the preparation of ACV. For example, Kelley and Schaeffe adopted 2, 6-dichloropurine as the raw material. After carrying out the condensation with 3-oxy-4-chloro-butanol benzoate, methylamine ammoniation and hydrolysis, ACV was finally obtained. Similarly, when 2-chloro-6-iodopurine was used as raw material, it needed to undergo condensation with $Me_3SiOCH_2CH_2OCH_2I$, ammoniation and hydrolysis to obtain ACV. Moreover, Han et al. invented a method involving an efficient and selective process for the production of 9-(2-hydroxyethoxymethyl)-guanine (ACV). With the presence of benzyl triethyl ammonium chloride, 3-oxy-4-chlorobutanol trifluoroacetate alkylated the 6-iodopurine. After that, it was chlorinated with phosphorus oxychloride and iodized with potassium iodide. Finally, it underwent alkaline hydrolysis by potassium bicarbonate to successfully produce the ACV. In addition, a synthesis method starting with 2-amino-6-chloropurine. After silanization with hexamethyldisilane, condensation with 3-oxy-4-bromobutanol acetate and hydrolysis, ACV was finally produced.

Conclusion. Acyclovir is one of the most common and broad-spectrum antiviral drugs. It is widely and extensively used against herpes simplex virus (HSV), herpes simplex, and varicella-zoster virus. This article reviews the synthesis, modification, and detection methods of ACV. Although synthetic methods of ACV are relatively mature for now, with the development of drug analysis theory and application technology, new methods have emerged. At present, there are a variety of methods for determining ACV, such as spectrophotometry, chromatography, and MIPs.

In recent years, electrochemical analysis methods based on modified working electrodes have attracted widespread attention in the field of pharmaceutical analysis, due to their simple operation, rapid response, and high sensitivity as well as selectivity, low cost and good reproducibility.

Finally, in response to the future challenge of reducing, refining and replacing the use of animal models, it is concluded that machine learning approaches, especially deep learning models, have made significant contribution to the efforts to find new biological functions of ACV.

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