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Synthesis of Potential Impurities of Valacyclovir Hydrochloride: An Anti-Retroviral Drug

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ABSTRACT Valacyclovir is an antiviral drug useful for the treatment of outbreaks of herpes simplex or herpes zoster (shingles). It is also useful to avoid cytomegalovirus following a kidney transplant in high-risk cases. Simple synthetic protocols toward the synthesis of two potential impurities, namely, European Pharmacopeia impurity N **(2)** and European Pharmacopeia impurity P **(3)** of valacyclovir hydrochloride **(1)** are reported from commercially accessible inexpensive raw materials. This work is predominantly useful for obtaining pure valacyclovir.

KEY WORDS Valacyclovir; EP impurity N; EP impurity P; Synthesis; Related Substances; Antiviral drug.

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INTRODUCTION

Genital herpes is one of the most unrestrained sexually transmitted diseases (STDs), and most commonly caused by infection with herpes simplex virus type 2 (HSV-2).[1] Most sexual transmission of HSV-2 occurs on days without genital abrasion in the source partner.[2] While lesion in immunocompetent patients may be benign, those in immunocompromised patients can be life threatening with high mortality and morbidity.[3] Recently, new antiviral drugs have been invented against HSV-2, and several numbers of antiviral drugs were developed. Most of the HSV-2 antiviral drugs target the thymidine kinase (TK) phosphorylation sites of herpes virus and get activated by viral TK to become inhibitors of viral DNA polymerases and block viral DNA synthesis.[4] Valacyclovir **(1)** is an antiviral drug, prodrug of acyclovir efficiently used to treat the patients with HSV-2 antiviral drugs. Valacyclovir **(1)** is sold under the brand name Valtrex.

The key role of the process chemist is to develop several synthetic routes to modern pharmaceutical active ingredients. The selection of the synthetic routes is influenced by several aspects such as product quality, availability of starting materials, yields, and safety. Many synthetic routes are to be tested especially while a generic drug product is produced by various companies. It is inherently recognized by the process and analytical scientists that the formation of impurities in pharmaceutical products varies with respect to the synthetic routes and process optimization within a synthetic route. As per the guidelines of International Conference on Harmonization (ICH), identification, synthesis, and control of impurities indeed are a major challenge for any generic pharmaceutical companies.[5] Nowadays, the regulatory agencies pay vital attention in identification, quantification of impurities of an active pharmaceutical ingredient for medical safety reasons, as well as for the drug effectiveness.[6-8] Thus, identification and characterization of unknown impurities that are present in valacyclovir (1) even at a level below 0.10% before industrial production is a challenging task.[9]

Impurity standards (**2** and **3**) are commercially available from USP/EP in very small packs and highly expensive.

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