

A Concise Route to Valacyclovir Hydrochloride

by **Prasada Raju V. N. K. V. Vetukuri***, **Ravindra Vedantham**, **Vijayavithal Thippannachar Mathad**,
Pratap Reddy Padi, and **Vijaya Anand Ramasamy**

Research & Development, Integrated Product Development, Innovation Plaza, *Dr. Reddy's Laboratories Ltd.*, Bachupally, Ranga Reddy District, Andhra Pradesh-500072, India

(phone: + 91-4044346412; mobile: + 91-9989997170; fax: + 91-4044346840;

e-mail: prasadvnkv@drreddys.com)

An efficient and concise synthesis of valacyclovir hydrochloride (**4**), which is a prodrug of acyclovir (**3**) is described. The synthesis was accomplished in two stages by coupling acyclovir with (2*S*)-2-azido-3-methylbutanoic acid followed by reduction (*Scheme 2*).

Introduction. – Genital herpes is one of the most unbridled sexually transmitted diseases (STD), 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 immuno-competent patients may be benign, those in immuno-compromised patients can be life threatening with high mortality and morbidity [3]. In the past two decades, the invention of new antiviral drugs against HSV-2 has been emerging, and a number of antiviral drugs were developed in recent years. 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]. The currently available and efficient HSV-2 antiviral drugs are penciclovir (**1**), famciclovir (**2**), acyclovir (= 2-amino-1,9-dihydro-9-[(2-hydroxyethoxy)methyl-6*H*-purin-6-one; **3**), and its prodrug valacyclovir hydrochloride (**4**) (*Fig. 1*).

Valacyclovir hydrochloride (**4**), the L-valine ester of acyclovir (**3**), was designed to enhance bioavailability of the parent compound. Recent investigations established that the spectrum of bioavailability of **4** is three times more than that of **3** [5]. Therefore, an efficient synthetic route to **4** is highly enviable. In this communication, we would like to divulge our efforts towards the synthesis of **4**.

Since **4** is an L-valine ester of **3**, most of the hitherto known syntheses involve coupling of **3** with a protected form of L-valine followed by deprotection (*Scheme 1*). *Beauchamp et al.* reported the synthesis of valacyclovir by condensing acyclovir (**3**) with *N*-[(benzyloxy)carbonyl]-L-valine in the presence of dicyclohexylcarbodiimide (DCC) followed by removal of the protecting group by hydrogenolysis [6]. Similarly, **4** was prepared from *N*-[(*tert*-butoxy)carbonyl]-L-valine or *N*-formyl-L-valine [7]. Another approach involved condensation of the tosylate of acyclovir with an enamine derived from L-valine and methyl acetoacetate [8]. Reaction of **3** with the NCA of L-valine (= *N*-carboxy-L-valine anhydride = (4*S*)-4-(1-methylethyloxazolidine-2,5-dione) was also reported to give **4** in a single step [9] (NCA = *N*-carboxyanhydride).

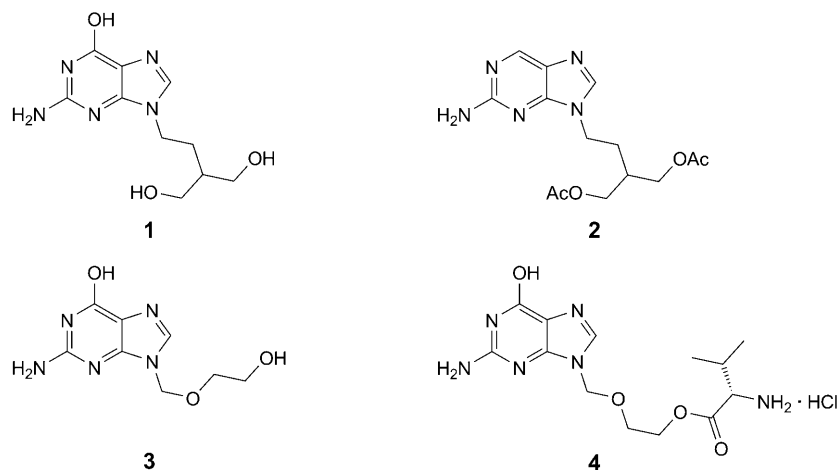
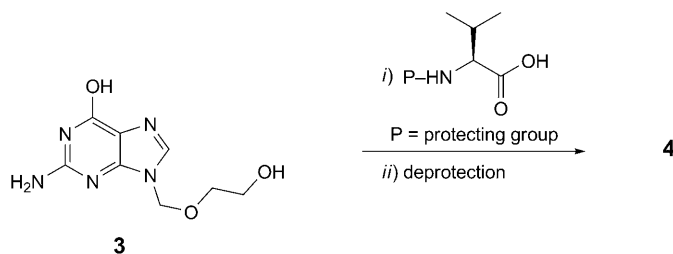


Figure. HSV-2 Antiviral drugs

Scheme 1. Previous Synthesis of Valacyclovir Hydrochloride (**4**)

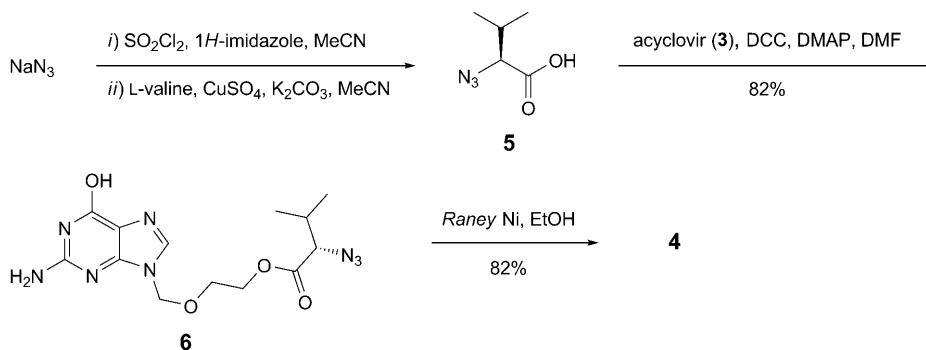
From the literature, it is evident that protection of the amino group of L-valine has been the nub of almost all the synthetic routes reported (*Scheme 1*). The bulky protecting groups used may cause steric hindrance, which may affect the formation of the L-valine ester. The protection–deprotection steps further increase the risk of racemization.

Results and Discussion. – The use of a small-size versatile synthetic precursor of the amino group such as an azide group holds great promise to circumvent the problem of steric hindrance and racemization in the synthesis of the L-valine ester **4**. The azido group being an excellent masked amino equivalent is relatively stable and can be readily reduced to the desired amino function when required. The protocol, being highly effective, inspired us to incorporate it in the synthesis of **4** from **3**.

The strategy adopted by us was to prepare the α -azido ester **6** of acyclovir followed by reduction to give the desired α -amino ester. The required starting α -azido acid, (2*S*)-2-azido-3-methylbutanoic acid (**5**), was prepared by following a literature procedure [10]. Sodium azide was treated with sulfuryl chloride (SO₂Cl₂) followed by 1*H*-imidazole to provide 1*H*-imidazole-1-sulfonyl azide, which on diazo-transfer reaction with L-valine in the presence of CuSO₄ as a catalyst gave the (2*S*)-2-azido-3-

methylbutanoic acid (**5**) (*Scheme 2*). DCC-Mediated coupling of acyclovir (**3**) with **5** provided the α -azido ester **6** in good yield and purity. Then, **6** was reduced to valacyclovir hydrochloride (**4**) under catalytic-hydrogenation conditions with *Raney* nickel as a catalyst as described in the *Exper. Part*.

Scheme 2. The Azide Route to Valacyclovir Hydrochloride (4)



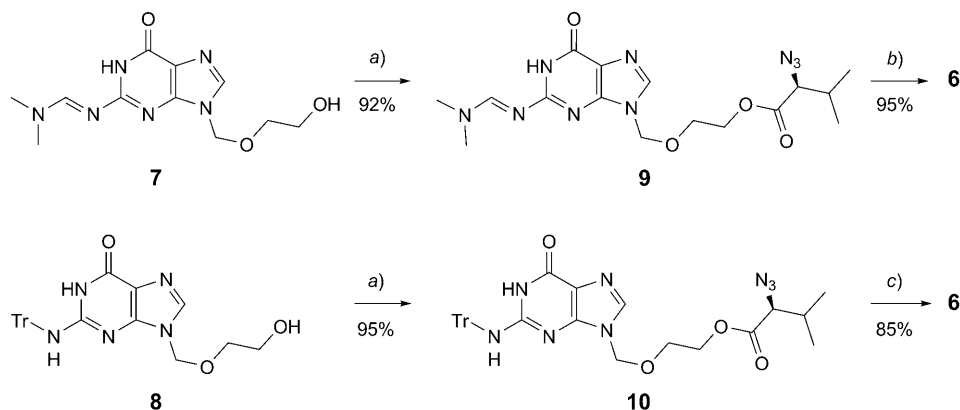
It was envisaged that N^2 -substituted acyclovir would give better results in the DCC condensation step due to enhanced solubility as compared to acyclovir (**3**). In this context, two different N^2 -substituted acyclovirs, namely, N^2 -[(dimethylamino)methylene] and N^2 -trityl derivatives **7** and **8** (trityl = triphenylmethyl) were prepared. The above choices were made to account for different types of N^2 -substituents, *i.e.*, of the imine and alkyl type. N^2 -[(Dimethylamino)methylene]acyclovir (**7**) was prepared by modifying the literature procedure [11], and N^2 -tritylacyclovir (**8**) by tritylation of **3**.

To compare the reactivity of the N^2 -substituted acyclovir derivatives **7** and **8** with that of acyclovir, the former were coupled with **5** under standard DCC conditions (*Scheme 3*). As expected, both **7** and **8** gave better results in terms of yield within 1 h (92% of **9** and 95% of **10**, resp.). This outcome clearly endorses the enhanced solubility of **7** and **8** in DMF under normal reaction conditions¹). The N^2 -[(dimethylamino)methylene] group in **9** was deprotected with aqueous HCl solution at 50° to provide **6** in 95% yield. Similarly, the trityl deprotection of **10** was carried out with AcOH at 50° to give **6** in 85% yield.

Conclusion. – We have developed a succinct synthesis of valacyclovir hydrochloride (**4**) by coupling of acyclovir (**3**) with azido acid **5** derived from L-valine, followed by reduction with *Raney* nickel.

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¹) N^2 -[(Dimethylamino)methylene]acyclovir (**7**) is *ca.* two times more soluble than acyclovir (**3**), and N^2 -tritylacyclovir (**8**) is highly soluble in DMF.

Scheme 3. Coupling of **7** and **8** with Azido Acid **5**

a) **5**, DCC, Et₃N, DMF, 15°, 1 h. b) HCl, 50°. c) AcOH, 50°.

Experimental Part

General. Solvents and reagents were used without further purification. Solvent removal was accomplished by a Büchi rotary evaporator at 30–40 Torr. IR Spectra: Perkin-Elmer-1650 FT-IR spectrometer; in KBr dispersion; $\tilde{\nu}$ in cm⁻¹. ¹H-NMR Spectra: Mercury-Plus/Varian Gemini-2000 FT-NMR spectrometer; in (D₆)DMSO and CDCl₃ at 200 or 400 MHz; δ in ppm rel. to Me₄Si as internal standard, *J* in Hz. MS: HP-5989A LC/MS spectrometer at 70 eV; in *m/z* (rel. %). HR-MS: Micromass-LCT-Premier-XE mass spectrometer equipped with an ESI lack spray source for accurate mass values (Water Corporation, Milford, MA, USA); in *m/z*.

(2*S*)-2-Azido-3-methylbutanoic Acid 2-[(2-Amino-1,6-dihydro-6-oxo-9*H*-purin-9-yl)methoxy]ethyl Ester (**6**). (2*S*)-2-Azido-3-methylbutanoic acid (**5**; 90% in AcOEt; 21.3 g, 0.13 mol) was taken in DMF (400 ml) under N₂ and cooled to 10–15°. DCC (27.5 g, 0.13 mol) was charged to it, and the mixture was agitated for 30 min. Acyclovir (**3**; 20 g, 0.089 mol) was added to the reaction mass at 10–15° followed by *N,N*-dimethylpyridin-4-amine (DMAP; 1.62 g, 0.013 mol), and the resulting mixture was stirred for 45 min at 10–15°. The separated solid was filtered, and the filtrate was cooled to 0–5°. H₂O (1.35 l) was added to the filtrate in a dropwise manner to precipitate the solid. Filtration of the solid followed by drying at 60° gave the desired **6** (25.5 g, 82%). White solid. IR: 3470, 3293, 3191, 2931, 2099, 1732, 1655, 1629, 1104. ¹H-NMR (400 MHz, (D₆)DMSO): 10.65 (*s*, 1 H); 7.81 (*s*, 1 H); 6.50 (*s*, 2 H); 5.36 (*s*, 2 H); 4.28–4.34 (*m*, 1 H); 4.18–4.23 (*m*, 1 H); 4.10 (*d*, *J* = 5.6, 1 H); 3.67–3.74 (*m*, 1 H); 1.96–2.05 (*m*, 1 H); 0.89 (*d*, *J* = 6.8, 3 H); 0.80 (*d*, *J* = 6.8, 3 H). HR-MS: 351.1537 ([*M* + H]⁺, C₁₃H₁₉N₈O₄⁺; calc. 351.1529).

L-Valine 2-[(2-Amino-1,6-dihydro-6-oxo-9*H*-purin-9-yl)methoxy]ethyl Ester Hydrochloride (1:1) (**4**). Raney nickel (4.0 g) was added to a soln. of **6** (20 g, 0.057 mol) in EtOH (300 ml), and the resulting suspension was vigorously stirred at 50–60°. After completion of the reaction, the mixture was cooled to r.t., and the unwanted solid was separated by filtration. The pH of the filtrate was adjusted to 2.5–3.0 with 10% aq. HCl soln. (35 ml). The resulting homogeneous mass was treated with charcoal at 50–60°. The mixture was filtered, and the filtrate was concentrated at 50°. The residue was washed with acetone (100 ml), and the product was separated by filtration and finally dried at 50°: **4** (16.9 g, 82%). IR: 3472, 3327, 3110, 2925, 1732, 1631, 1607, 1100. ¹H-NMR (400 MHz, (D₆)DMSO): 10.81 (*s*, 1 H); 8.46 (*s*, 2 H); 7.84 (*s*, 1 H); 6.66 (*s*, 2 H); 5.37 (*s*, 2 H); 4.35–4.41 (*m*, 1 H); 4.18–4.23 (*m*, 1 H); 3.83 (*d*, *J* = 4.0, 1 H); 3.71–3.74 (*m*, 2 H); 2.07–2.12 (*m*, 1 H); 0.90 (*d*, *J* = 7.2, 3 H); 0.87 (*d*, *J* = 6.8, 3 H); 0.80 (*d*, *J* = 6.8, 3 H).

REFERENCES

- [1] J. S. Smith, N. J. Robinson, *J. Infect. Dis.* **2002**, *186*, 3; L. Corey, H. H. Handsfield, *J. Am. Med. Assoc.* **2000**, *283*, 791; F. Xu, M. R. Sternberg, B. J. Kottiri, *J. Am. Med. Assoc.* **2006**, *8*, 964.
- [2] G. J. Mertz, O. Schmidt, J. L. Jourden, *Sex. Transm. Dis.* **1985**, *12*, 33; A. Langenberg, L. Corey, R. Ashley, W. Leong, S. A. Straus, *N. Eng. J. Med.* **1999**, *341*, 1432.
- [3] M. Vajpayee, N. Malhotra, *Indian J. Pharmacol.* **2000**, *32*, 330.
- [4] S. K. Tyring, D. Baker, W. Snowden, *J. Infect. Dis.* **2002**, *186*, 40.
- [5] R. Gupta, A. Wald, E. Krantz, S. Selke, T. Warren, M. Vargas-Cortes, G. Miller, L. Corey, *J. Infect. Dis.* **2004**, *190*, 1374; L. M. Beauchamp, T. A. Krenitsky, *Drugs Future* **1993**, *18*, 619.
- [6] L. M. Beauchamp, G. F. Orr, P. DeMiranda, T. Burnette, T. A. Krenitsky, *Antiviral Chem. Chemother.* **1992**, *3*, 157.
- [7] M. Y. Etinger, L. M. Yudovich, M. Yuzefovich, G. A. Nisnevich, B. Z. Dolitzki, B. Pertsikov, B. Tishin, D. Blasberger, PCT Int. Appl. 041647, 2003.
- [8] M. Montoro, S. Pirovano, PCT Int. Appl. 003553, 1998.
- [9] W. P. Jackson, PCT Int. Appl. 029311, 1994.
- [10] E. D. Goddard-Borger, R. V. Stick, *Org. Lett.* **2007**, *9*, 3797.
- [11] C. McGuigan, M. Derudas, J. J. Bugert, G. Anderi, R. Snoeck, J. Balzarini, *Bioorg. Med. Chem. Lett.* **2008**, *18*, 4364.

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