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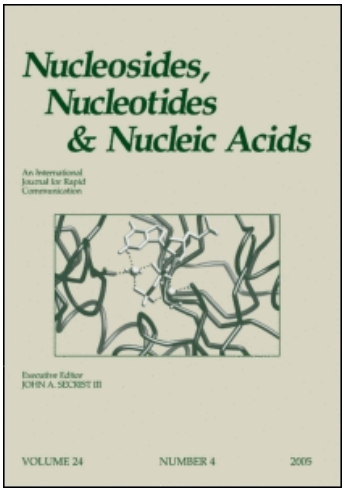

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Synthesis and Antiviral Activity Assay of Novel (*E*)-3′,5′-Diamino-5-(2-bromovinyl)-2′,3′,5′-trideoxyuridine

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ABSTRACT

(*E*)-3′,5′-diamino-5-(2-bromovinyl)-2′,3′,5′-trideoxyuridine (**5**), the diamino analogue of BVDU (**1**), was synthesized from BVDU. In contrast with BVDU, compound **5** did not show activity against herpes simplex virus or varicella-zoster virus.

INTRODUCTION

Nucleoside analogues have figured prominently in the search for effective antiviral agents despite concerns over the toxicity generally associated with this class of compounds. This has resulted in an explosion of synthetic activity in the field of nucleosides and in the discovery of a number of derivatives with potent antitumor

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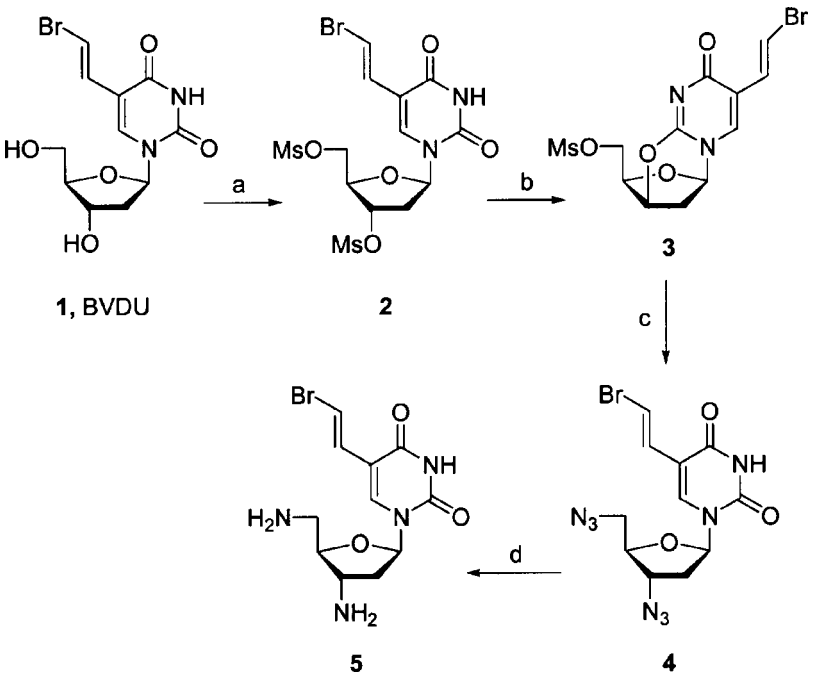

Scheme 1. *Reagents and conditions:* (a) MsCl, Py, 0°C, 37 h (99%); (b) Et_3N, EtOH, 80°C, 18 h (84%); (c) NaN_3, *p*-$O_2NC_6H_4OH$, DMF, 110°C, 4 h (67%); (d) PPh_3, THF-H_2O, 30 h, rt (71%).

and antiviral activities.[1] Nucleoside derivatives are present in most of the treatment protocols for human viral infections. Thus, 3′-azido-3′-deoxythymidine (AZT, Zidovudine)[2] was the first anti-HIV nucleoside analogue approved by the FDA to treat AIDS patients.

A variety of 5-substituted-2′-deoxyuridine derivatives have showed interesting biological properties.[3] Among them (*E*)-5-(2-Bromovinyl)-2′-deoxyuridine (BVDU, Brivudin®) (**1**, Sch. 1) has emerged as a potent and selective inhibitor of herpes simplex virus type 1 (HSV-1) and varicella-zoster virus (VZV).[4] Its mechanism of action[5] is based on the intracellular phosphorylation to its 5′-diphosphate derivative by HSV-1 and VZV-encoded thymidine kinases (TK), further conversion to the triphosphate derivative by cellular enzymes, and incorporation into viral DNA. Owing to its lower affinity for other cellular and viral TKs, BVDU exhibits low cytotoxicity and poor inhibitory activity against viral infections caused by HSV-2 or HSV-1 strains lacking TK.

Recently, we have accomplished a short and convenient synthesis of pyrimidine 3′,5′-diaminonucleosides from the parent natural nucleosides.[6] As an extension of this work, here we describe the preparation, for the first time, of (*E*)-3′,5′-diamino-5-(2-bromovinyl)-2′,3′,5′-trideoxyuridine (**5**) from BVDU. Examples of amino sugar nucleosides are known to possess anticancer, antibacterial, and antimetabolic activities.[7] In addition, in vitro antiviral activity of this novel derivative was also carried out.

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RESULTS AND DISCUSSION

For the synthesis of (*E*)-3′,5′-diamino-5-(2-bromovinyl)-2′,3′,5′-trideoxyuridine (**5**), BVDU (**1**) was first converted into its 3′,5′-di-*O*-mesyl derivative **2** by treatment with methanesulfonyl chloride in pyridine at 0°C (Sch. 1). When this dimesyl derivative was heated under reflux with an excess of Et_3N in EtOH solution, anhydronucleoside **3** was isolated in 84% yield. Conversion of **3** into the diazide **4** was attempted by treatment with sodium azide in the presence of *p*-nitrophenyl alcohol affording **4** in 67% yield after flash chromatography column.

Subsequent reduction of diazide **4** by PPh_3 gave the diamino nucleoside **5** in 71% yield, since reduction by catalytic hydrogenation afforded side reactions at the exocyclic double bond.

The synthesized nucleoside **5** was tested for its cytotoxicity and antiviral activity in HeLa, Vero, and HEL cells using BVDU, (*S*)-DHPA, ribavirin, acyclovir, ganciclovir, and ciclofovir as reference compounds. In general, the cytotoxicity of 3′,5′-diamino-BVDU was similar to that of BVDU. In contrast to BVDU, **5** was inactive against VZV and HSV-1. Compound **5** also did not exhibit any appreciable activity against any of the other viruses tested (vesicular stomatitis virus, coxsackie B4 virus, respiratory syncytial virus, parainfluenza-3 virus, reovirus 1, sindbis, punta toro, vaccinia virus, and cytomegalovirus).

In summary, we have synthesized (*E*)-3′,5′-diamino-5-(2-bromovinyl)-2′,3′,5′-trideoxyuridine (**5**) from BVDU. The synthesized compound was tested as an antiviral agent against several viruses; however, no appreciable antiviral activity was found. Further biological evaluation is needed to assess the biological significance, if any, of this novel derivative.

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