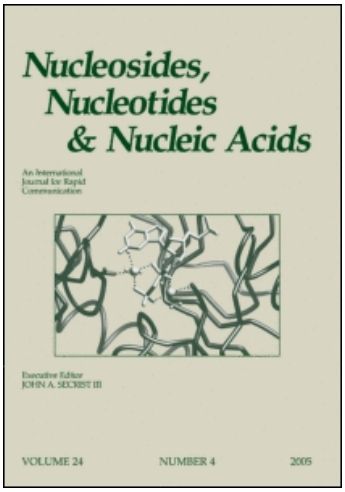

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Monoval-LdC: Efficient Prodrug of 2′-Deoxy-β-L-cytidine (L-dC), A Potent and Selective Anti-HBV Agent†

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ABSTRACT

In order to improve the oral bioavailability of LdC, valinyl esters were prepared as prodrugs. We report here the syntheses of the 3′-mono-, 5′-mono, and 3′,5′-di-*O*-valinyl esters of LdC. The comparison of their ease of synthesis, their physicochemical properties, as well as their pharmacokinetic parameters in cynomologus monkeys has revealed 3′-mono-*O*-valinyl derivative as the most promising of the studied prodrugs. This compound is being developed as a new anti-HBV agent.

Key Words: Nucleoside analogs; Prodrugs; LdC; Oral bioavailability; Anti-HBV agent.

†Dedicated to the memory of Martin Bryant, deceased on March 4, 2002.

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INTRODUCTION

Hepatitis B virus (HBV) is a leading cause of chronic hepatitis, liver cirrhosis and hepatocellular carcinoma. As part of our anti-HBV program, we have shown that LdC was a potent, selective and specific anti-HBV agent, both in vitro and in vivo,[1] despite relatively low oral bioavailability (16% in cynomologus monkeys). Our efforts have recently been devoted to the discovery of LdC prodrugs in order to improve the oral bioavailability of LdC. In this regard, we have synthesized and studied various derivatives of LdC,[2–4] among which the valinyl esters seemed the most promising. We report here the syntheses of the 3′-mono-, 5′-mono, and 3′,5′-di-*O*-valinyl esters of LdC (Sch. 1). Their physicochemical properties, as well as their pharmacokinetic parameters in cynomologus monkeys are compared, in order to select the ideal candidate as an anti-HBV drug.

CHEMISTRY

We developed a multi-step sequence involving dimethylaminomethylene protection of the exocyclic amino function of L-dC,[5] silylation of the 5′-hydroxyl group, condensation with *N*-tert-butyloxycarbonyl (Boc) L-valine,[6] and total deprotection to obtain the hydrochloric form of the 3′-monovaline derivative with an overall yield of 60%. Similar approach was used for the synthesis of 3′,5′-di-*O*-L-valinyl ester of LdC which was obtained with an overall yield of 52% by selective protection of the exocyclic amino function[5] followed by condensation with Boc- valine,[6] and total deprotection. The synthesis of 5′-monovaline ester of LdC involved a selective silylation of the 5′-hydroxyl group of LdC, followed by monomethoxytritylation of both the exocyclic amino function and the 3′-hydroxyl group. After removal of the silyl blocking group, the nucleoside was condensed with Boc-valine,[6] and totally deprotected. The hydrochloric form of 5′-monovaline derivative was obtained with an overall yield of 36%.

PHYSICOCHEMICAL AND PHARMACOKINETIC PROPERTIES

All the L-valine derivatives of L-dC presented good physicochemical profiles (good stability at pH 1.2, better water solubility than the parent nucleoside, log P values similar or higher than for L-dC). However, unlike 3′- and 5′-monovaline esters, 3′,5′-divaline derivative proved to be very hygroscopic. Finally, the pharmacokinetic profile of 3′-monovaline in the monkey was excellent and its oral bioavailability was 84.6%, significantly greater than for LdC, and higher than for the other two prodrugs.

CONCLUSION

Based on the ease of synthesis, on the physico-chemical studies and on the pharmacokinetic profile in the monkey, the 3′-monoval L-dC emerged as the most

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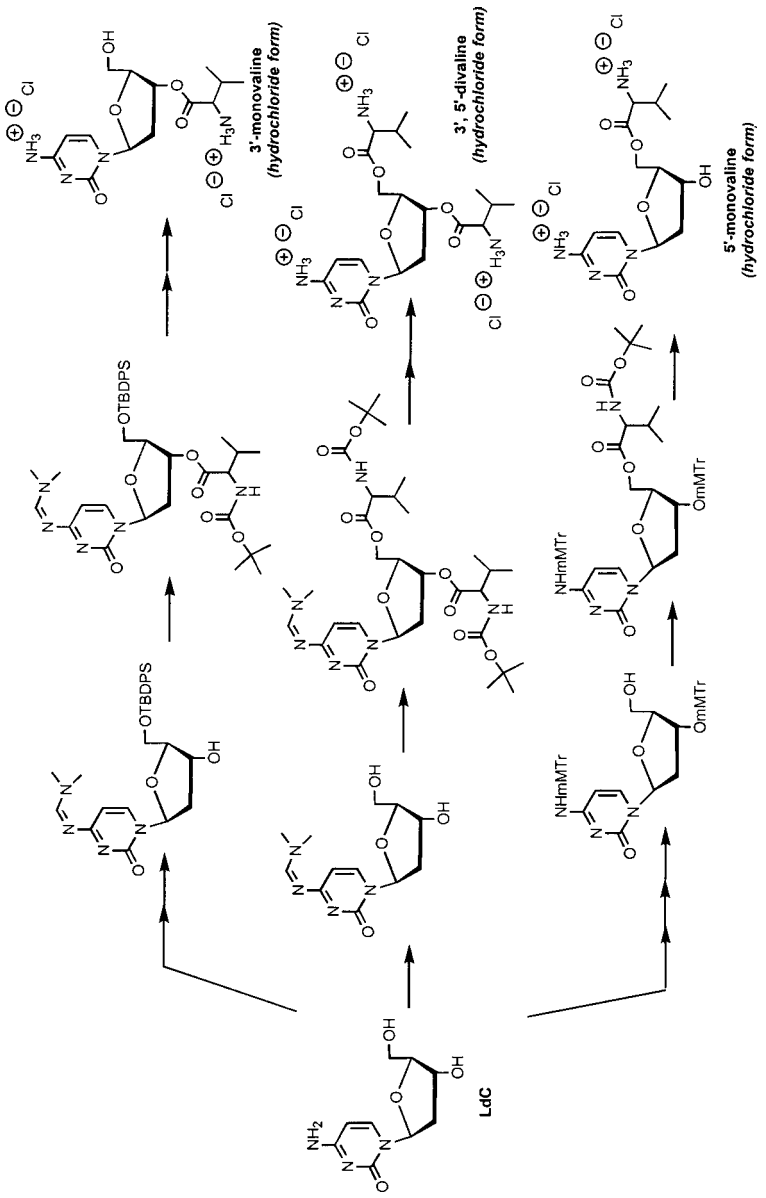

Scheme 1.

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attractive studied LdC prodrugs, and is currently being developed as a new anti-HBV agent.

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