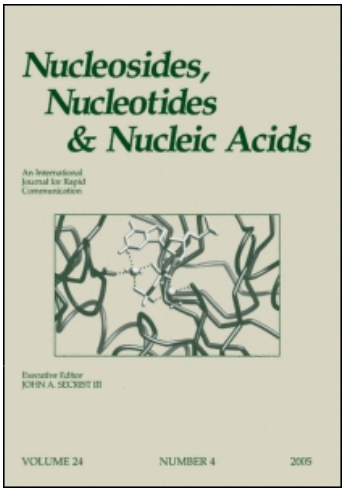

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SYNTHESIS AND ANTIVIRAL EVALUATION OF C-4-HYDRAZIDE DERIVATIVES OF 2′,3′-DIDEOXYCYTIDINE

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ABSTRACT

Syntheses of three hitherto unknown derivatives of 2′,3′-dideoxycytidine, namely *C*-4-(salicylic hydrazide)-ddC, *C*-4-(*N*-butyloxycarbonyl-isoleucine hydrazide)-ddC and its *N*-unprotected chlorhydrate salt have been carried out. These compounds do not induce inhibition of HIV-1 replication in cell culture experiments. Nevertheless, the modifications on the base moiety increased in all cases the lipophilicity of the parent molecule with an acceptable water solubility compared to ddC.

INTRODUCTION

During the last decade, significant progress has been accomplished in the discovery of new antiviral agents and in the therapeutic approaches against human immunodeficiency virus (HIV) infection (1). To date, six nucleoside analogues have been approved by the Food and Drug Administration for the treatment of AIDS. However, these compounds suffer from several drawbacks such as low oral bioavailability, chemical or enzymatic instability or non appropriate biodistribution (2,3).

Within the framework of our research program on the improvement of pharmacological and pharmacokinetic properties of nucleoside analogues with antiviral

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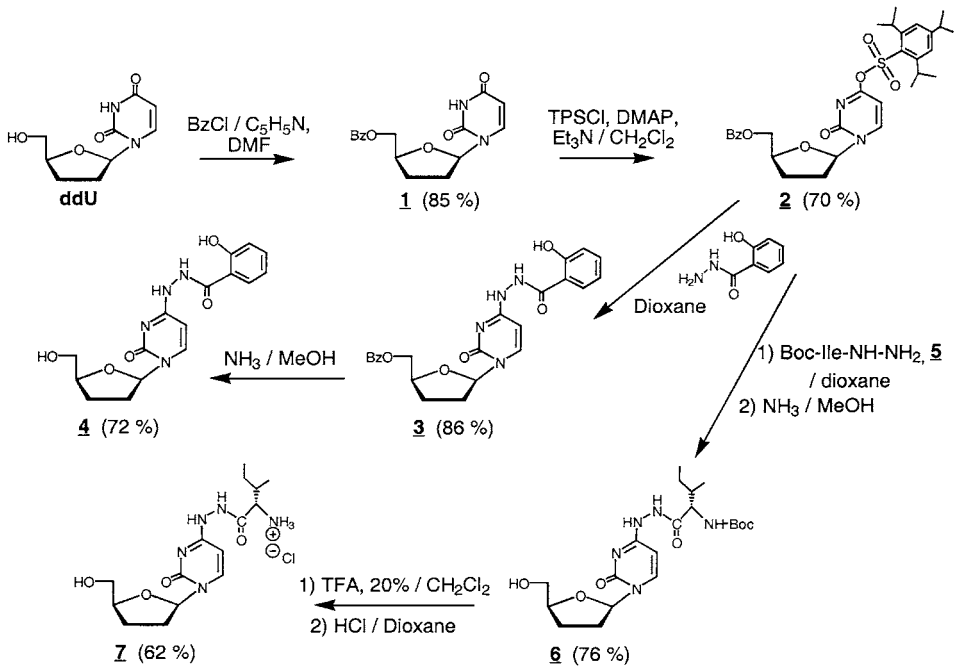
properties, we have designed hitherto unknown derivatives of 2′,3′-dideoxycytidine (ddC). Here, we report the preparation and the studies of *C*-4-(salicylic hydrazide)-ddC, (**4**) *C*-4-(*N*-butyloxycarbonyl-isoleucine hydrazide)-ddC (**6**) and its *N*-unprotected chlorhydrate salt (**7**).

SYNTHESES

From a synthetic viewpoint, the target compounds (**4**, **6** and **7**) were prepared from commercially available 2′,3′-dideoxyuridine (ddU).

Firstly, the 5′-hydroxyl function of ddU was suitably protected with a benzoyl group to afford compound (**1**). Then, the *C*-4 position of the base was activated *via* triisopropylbenzene-sulfonyl chloride treatment to give (**2**), as a key intermediate.

Reaction of **2** with commercially available salicylic hydrazide provided compound (**3**), which upon treatment with methanolic ammonia gave the first desired molecule (**4**) in 70% yield. Isoleucine hydrazide, (**5**) prepared by action of hydrazine on *N*-Boc-isoleucine in the presence of BOP and triethylamine in dichloromethane) was reacted with intermediate (**2**) to give a fully protected derivative which upon treatment with methanolic ammonia afforded *C*-4-(*N*-butyloxycarbonyl-isoleucine hydrazide)-ddC (**6**). Finally, removal of the Boc protecting group from **6** afforded the last desired compound (**7**).



Scheme.

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Table.

	Partition Coefficient		Solubility
	P	Log P	g/l
ddC	0.04	−1.36	63
4	1.19	0.07	15
6	8.19	0.91	4
7	0.077	−1.06	55

Structural assignments for compounds **4**, **6** and **7** were based on elemental analysis and physicochemical properties.

LIPOPHILICITY AND SOLUBILITY STUDIES

The lipophilicity of the new compounds (**4**, **6** and **7**) was determined measuring their partition coefficient between octanol and water. All of them show a higher lipophilicity than the reference molecule ddC, with an acceptable water solubility.

ANTIVIRAL EVALUATION

Compounds **4**, **6** and **7** were tested for their *in vitro* inhibitory effects on the replication of HIV-1 in CEM-SS and MT-4 cell systems. None of these compounds showed significant antiviral activity nor cytotoxicity at the highest concentration tested (100 μM). In the same assays, ddC had EC_{50} of 0.023 μM in CEM-SS and $\geq$1 μM in MT-4 cells.

CONCLUSION

From the present work, it appears that the *C*-4 hydrazide derivatives of ddC do not induce inhibition of HIV-1 replication in cell culture experiments. Among the several hypotheses than can explain this lack of activity, the inability of these compounds to release appropriately (intra or extra-cellularly) the parent ddC nucleoside, as well as their chemical or enzymatic instability (with cleavage of the glycosidic bond), can be proposed. Nevertheless, the modifications on the base moiety increased in all cases the lipophilicity of the parent molecule with an acceptable water solubility compared to ddC. Synthesis and antiviral evaluation of other ddC derivatives bearing various groups on the base moiety with different linkers are currently in progress in our laboratory.

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