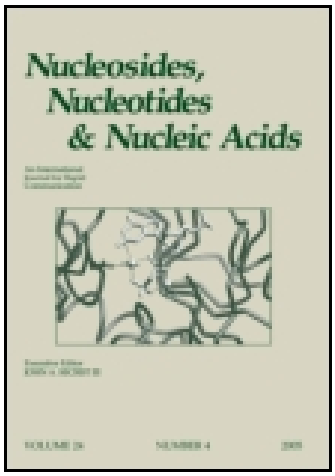

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SYNTHESIS OF HOMO-N-NUCLEOSIDE WITH 1,2,4-TRIAZOLE-3-CARBOXAMIDE

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SYNTHESIS OF HOMO-*N*-NUCLEOSIDE WITH 1,2,4-TRIAZOLE-3-CARBOXAMIDE

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▫ *On the basis of potent biological activities of ribavirin and homo-N-nucleosides, a novel homo-N-1,2,4-triazole-3-carboxamide derivative* ***1*** *was synthesized starting from 2,3,5-tri-O-benzoyl-ribofuranosyl-1-acetate as a potential antiviral agent.*

INTRODUCTION

A number of nucleoside analogues have been synthesized for the development of antiviral and anticancer agents. Among them, 2′,3′-dideoxynucleosides such as 3′-azido-2′3′-dideoxythymidine (AZT), 2′,3′-diedoxycytidine (ddC), and 2′3′-diedoxyinosine (ddI) have exhibited potent antiviral activity against HIV. However, in their antiviral chemotherapy, toxicity and emergence of drug-resistant virus strains have been major problems.[1] A number of structurally modified nucleosides have been synthesized in order to overcome these drawbacks, among which homo-*N*-nucleoside in which methylene (CH_2) is inserted between the base and the glycosyl donor, that are resistant to hydrolytic or enzymatic cleavage of glycosidic bond and are also highly conformationally flexible because they have no anomeric center,[2,3] compared to natural nucleosides. Among them, guanine and adenine derivatives have shown potent antiviral activity against herpes simplex virus.[4,5]

Ribavirin[6] is a synthetic nucleoside analogue that shows broad spectrum antiviral activity against a variety of both DNA and RNA viruses. It has been suggested that ribavirin[1] monophosphate (RMP), the active form of ribavirin inhibits IMP dehydrogenase, resulting in a decrease of the guanine nucleotide level and inhibition of viral DNA and RNA synthesis.

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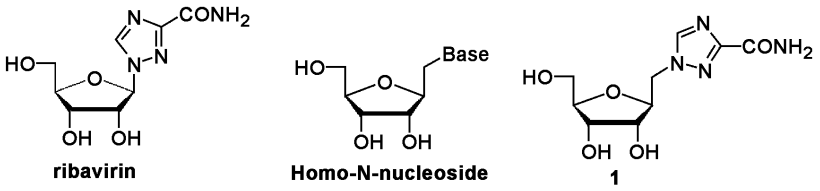
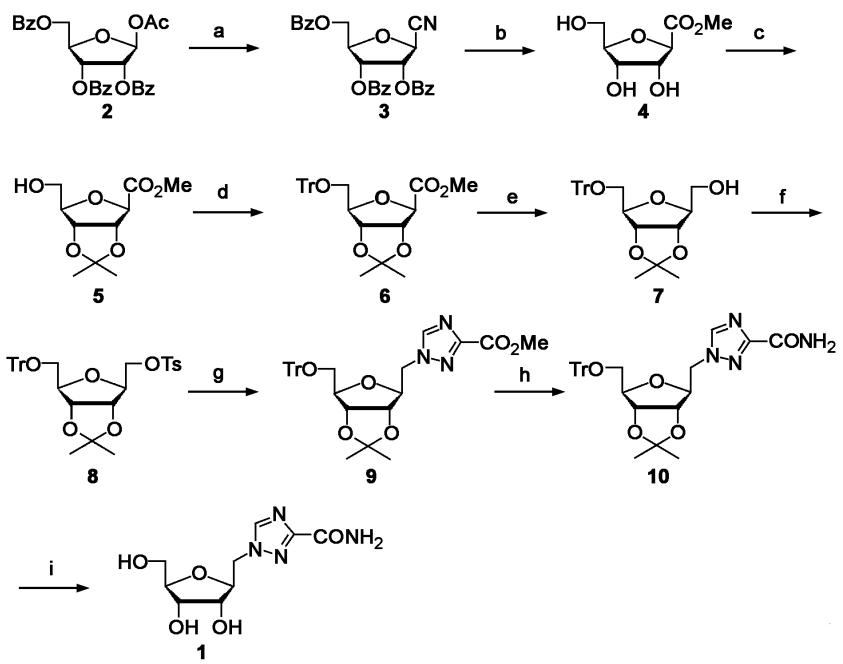


FIGURE 1 The rationale for the design of the target nucleosides.

Based on these findings, it was great interesting to synthesize 1′-home-*N*-nucleoside with 1,2,4-triazole base moiety (**1**) for the development of novel antiviral agents (Figure 1).

RESULTS AND DISCUSSION

Our synthetic strategy to the target homo-*N*-nucleoside **1** is to synthesize 1-*C*-hydroxymethyl-ribofuranoside **7** as a key intermediate from 2,3,5-tri-*O*-benzoyl-ribofuranosyl-1-acetate (**2**) and then to treat with methyl-1,2,4-triazole-3-carboxylate, as shown in Scheme 1.



SCHEME 1 *Reagents and conditions*: (a) TMSCN, $SnCl_4$, CH_2Cl_2, reflux, 3 h, 79%; (b) NaOMe/MeOH, Dowex $50H^+$, MeOH, H_2O, rt, 5 h, 75%; (c) DMP, p-TsOH, acetone, rt, overnight, 65%; (d) TrCl, pyridine, rt, 2 d, 62%; (e) 1 M LAH in THF, THF, 0°C, 2 h, 96%; (f) TsCl, DMAP, CH_2Cl_2, rt, overnight, 77%; (g) methyl-1,2,4-triazole-3-carboxylate, DBU, CH_3CN, reflux, 56%; (h) NH_3/MeOH, rt, 24 h, 96%; (i) TFA, THF, H_2O, rt, 1 h, 67%.

Commercially available starting material 2 was treated with trimethylsilyl cyanide in dichloromethane in the presence of stannic chloride as a Lewis acid catalyst to give the ribouranosyl cyanide 3. Compound **3**[7] was converted to 1-*C*-methoxycarbonyl ribose **4** by treating with sodium methoxide followed by treating with Dowex 50 H^+ resin in $MeOH/H_2O$. Treatment of **4** with 2,2-dimethoxypropane in acetone gave its 2,3-O-acetonide derivative **5**, in which primary hydroxyl group was protected with trityl chloride to afford **6**. Reduction of **6** with lithium aluminum hydride (LAH) in THF yielded 1-*C*-hydroxymethyl derivative **7** as a key intermediate.

Treatment of compound **7** with p-toluenesulfonyl chloride gave the tosylate **8**. Direct nucleophilic displacement of **8** with a triazole anion derived from deprotonation of methyl-1,2,4-triazole-3-carboxylate with DBU in acetonitrile provided the desired triazole-homonucleside **9**. Compound **9** was treated with methanolic ammonia to give the amide **10**, which was deprotected with trifluoroacetic acid to yield the desired home-*N*-1,2,4-triazole-3-carboxamide derivative **1**.

In summary, we have completed the stereoselective, synthesis of novel homo-*N*-nucleoside, starting from commercially available intermediate **2** via β-selective anomeric cyanation as a key step. Biological evaluation of homo-*N*-nucleoside derivative (**1**) is in progress and will be reported in due course.

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