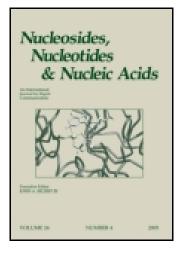
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## SYNTHESIS OF HOMO-N-NUCLEOSIDE WITH 1,2,4-TRIAZOLE-3-CARBOXAMIDE

Moon Woo Chun<sup>a</sup>, Jin Hee Kim<sup>a</sup>, Myong Jung Kim<sup>a</sup>, Bo Ram Kim<sup>a</sup> & Lak Shin Jeong<sup>b</sup> <sup>a</sup> Research Institute of Pharmaceutical Sciences, College of Pharmacy, Seoul National University, Seoul, Korea

<sup>b</sup> College of Pharmacy, Ewha Womans University, Seoul, Korea Published online: 15 Nov 2011.

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

**Moon Woo Chun, Jin Hee Kim, Myong Jung Kim, and Bo Ram Kim** Research Institute of Pharmaceutical Sciences, College of Pharmacy, Seoul National University, Seoul, Korea

Lak Shin Jeong • College of Pharmacy, Ewha Womans University, Seoul, Korea

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.<sup>[1]</sup> A number of structurally modified nucleosides have been synthesized in order to overcome these drawbacks, among which homo-*N*nucleoside in which methylene (CH<sub>2</sub>) 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,<sup>[2,3]</sup> compared to natural nucleosides. Among them, guanine and adenine derivatives have shown potent antiviral activity against herpes simplex virus.<sup>[4,5]</sup>

Ribavirin<sup>[6]</sup> 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<sup>[1]</sup> 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.

Address correspondence to Moon Woo Chun, Research Institute of Pharmaceutical Sciences, College of Pharmacy, Seoul National University, Seoul 151-742, Korea.

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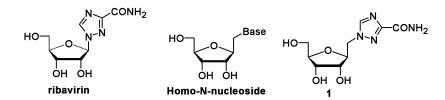
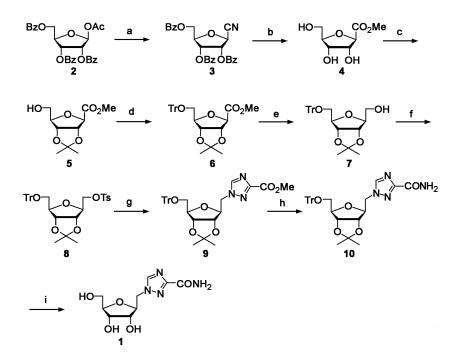


FIGURE 1 The rationale for the design of the target nucleosides.

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<sub>2</sub>O, 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<sub>2</sub>Cl<sub>2</sub>, rt, overnight, 77%; (g) methyl-1,2,4-triazole-3-carboxylate, DBU, CH<sub>3</sub>CN, reflux, 56%; (h) NH<sub>3</sub>/MeOH, rt, 24 h, 96%; (i) TFA, THF, H<sub>2</sub>O, 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  $\mathbf{3}^{[7]}$  was converted to 1-*C*-methoxycarbonyl ribose **4** by treating with sodium methoxide followed by treating with Dowex 50 H<sup>+</sup> resin in MeOH/H<sub>2</sub>O. Treatment of **4** with 2,2-dimethoxy-propane 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  $\beta$ -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.

#### REFERENCES

- De Clercq, E. Non-nucleoside reverse transcriptase inhibitors (NNRTIs) for the treatment of human immunodeficiency virus type 1 (HIV-1) infections: strategies to overcome drug resistance development. Med. Res. Rev. 1996, 16, 125.
- Hossain, N.; Blaton, N.; Peeters, O.; Rozenski, J.; Herdewijn, P.A. Synthesis of homo-N-nucleosides, a series of Cl' branched-chain nucleosides. Tetrahedron 1996, 52, 5563.
- Lamberth, C. Nucleosides with a carbon bridge between sugar and nucleobase: the chemistry of 1'homonucleosides and reversed nucleosides. A review. Org. Prep. Proced. Int. 2002, 34, 149.
- De Clercq, E.; Descamps, J.; Verhelst, G.; Walker, R.T.; Jones, A.S.; Torrence, P.F.; Shugar, D. Comparative efficacy of antiherpes drugs against different strains of herpes simplex virus. J. Infect. Dis. 1980, 141, 563.
- De Clercq, E.; Holy, A.; Rosemberg, I.; Sakuma, T.; Balzarini, J.; Maudgal, P.C.A. A novel selective broadspectrum anti-DNA virus agent. Nature 1986, 323, 464.
- Wray, S.K.; Gilbert, B.E.; Noall, M.W.; Knight, V. Mode of action of ribavirin: effect of nucleotide pool alterations on influenza virus ribonucleoprotein synthesis. Antivir. Res. 1985, 5, 29.
- Montgomery, J.A.; Hewson, K. 1-(Adenin-9-yl)-2,5-anhydro-1-deoxy-D-allitol, a homolog of adenosine. J. Heterocycl. Chem. 1970, 7, 443.