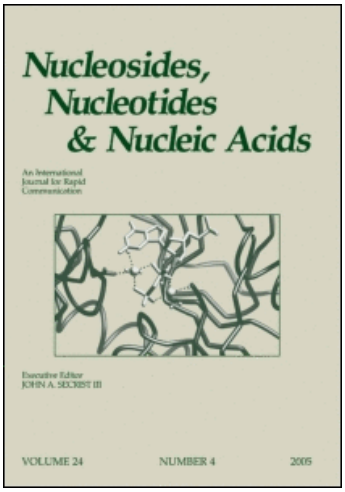


Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

Synthesis of 5-Azacytidine Nucleosides with Rigid Sugar Moiety as Potential Antitumor Agents

Moon Woo Chun[ab]; Myong Jung Kim[a]; Hea Ok Kim[c]; Hee-Doo Kim[d]; Joong Hyup Kim[e]; Hyung Ryong Moon[f]; Lak Shin Jeong[f]
[a] College of Pharmacy, Seoul National University, Seoul, Korea [b] Seoul National University, Seoul, Korea [c] Division of Chemistry and Molecular Engineering, Seoul National University, Seoul, Korea [d] College of Pharmacy, Sookmyung Women's University, Seoul, Korea [e] Korea Institute of Science and Technology, Seoul, Korea [f] College of Pharmacy, Ewha Womans University, Seoul, Korea

Online publication date: 09 August 2003

To cite this Article Chun, Moon Woo , Kim, Myong Jung , Kim, Hea Ok , Kim, Hee-Doo , Kim, Joong Hyup , Moon, Hyung Ryong and Jeong, Lak Shin(2003) 'Synthesis of 5-Azacytidine Nucleosides with Rigid Sugar Moiety as Potential Antitumor Agents', Nucleosides, Nucleotides and Nucleic Acids, 22: 5, 915 — 917
To link to this Article: DOI: 10.1081/NCN-120022685
URL: http://dx.doi.org/10.1081/NCN-120022685

NUCLEOSIDES, NUCLEOTIDES & NUCLEIC ACIDS
Vol. 22, Nos. 5–8, pp. 915–917, 2003

Synthesis of 5-Azacytidine Nucleosides with Rigid Sugar Moiety as Potential Antitumor Agents

Moon Woo Chun,[1,*] Myong Jung Kim,[1] Hea Ok Kim,[2] Hee-Doo Kim,[3] Joong Hyup Kim,[4] Hyung Ryong Moon,[5] and Lak Shin Jeong[5]

[1]College of Pharmacy and
[2]Division of Chemistry and Molecular Engineering,
Seoul National University, Seoul, Korea
[3]College of Pharmacy, Sookmyung Women's University, Seoul, Korea
[4]Korea Institute of Science and Technology, Seoul, Korea
[5]College of Pharmacy, Ewha Womans University, Seoul, Korea

ABSTRACT

The bicyclic 3′-*O*,5′-*C*-methylene-linked and 2′-*O*,5′-*C*-methylene-linked 5-azacytidine derivatives were readily synthesized from 1,2;5,6-di-*O*-isopropylidene-D-glucose and evaluated against several cancer cell lines.

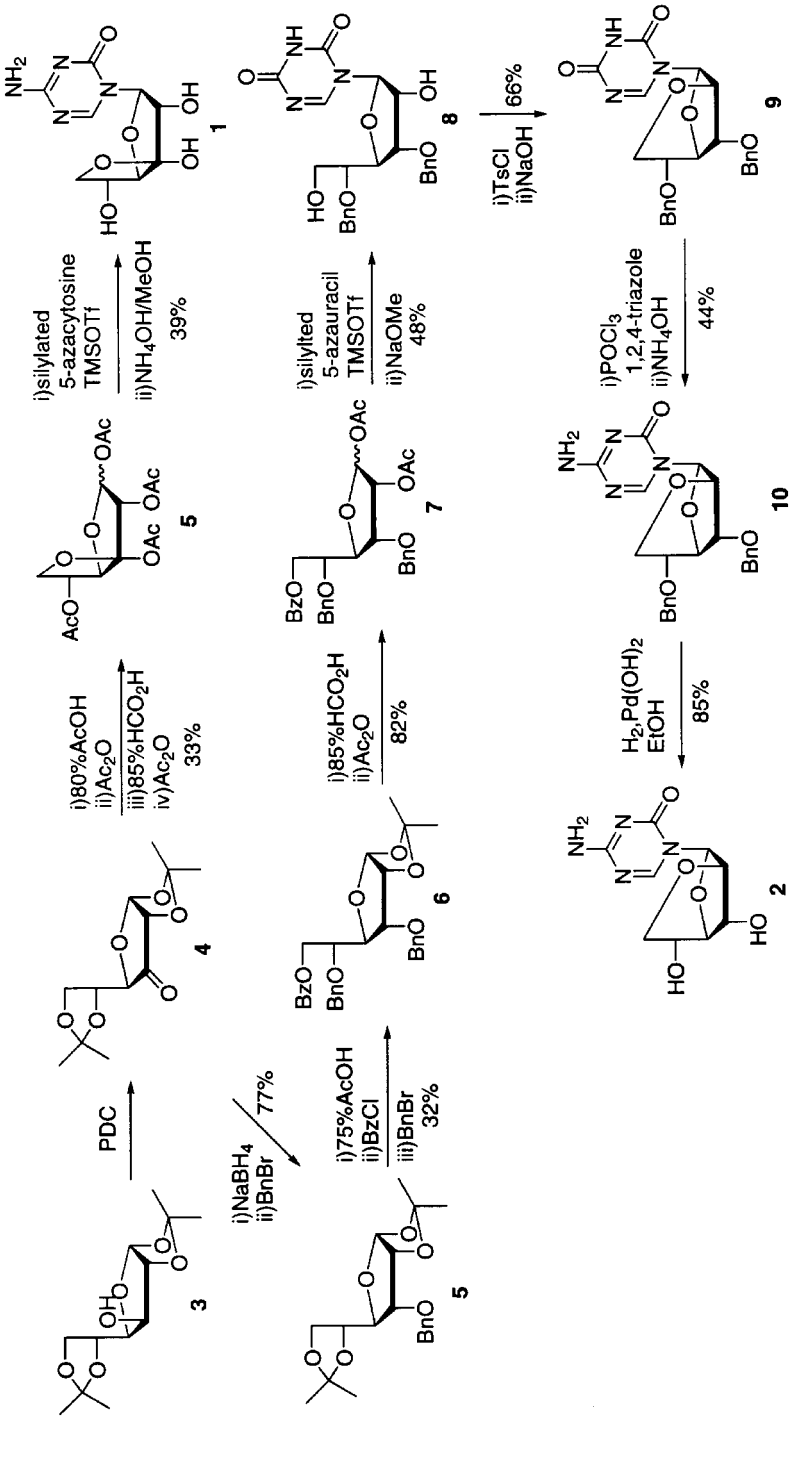
Key Words: 5-Azacytidine; Conformationally locked nucleosides.

Unmodified nucleosides exist in either the S-type or N-type conformation. However, due to the low energy barrier between these two dominating conformers, a fast equilibrium between them exists in solution state.[1] Therefore, many approaches to lock the puckering of the furanose ring into N-type or S-type have been made since it is known that HIV-1 reverse transcriptase is able to discriminate between two

*Correspondence: Moon Woo Chun, Seoul National University, 56-1 Shinrim-dong San, Kwanak-gu, 151-742 Seoul, Korea; Fax: +82 2 888 0649; E-mail: mwchun@snu.ac.kr.

DOI: 10.1081/NCN-120022685
1525-7770 (Print); 1532-2335 (Online)

MARCEL DEKKER, INC.
270 Madison Avenue, New York, New York 10016



Scheme 1.

Marcel Dekker, Inc.
270 Madison Avenue, New York, New York 10016

conformationally locked carbocyclic AZT triphosphate analogues.[2] Therefore, as we have found antitumor activity of 3′,4′-tetrahydrofuran fused pyrimidine nucleosides locked in the C1′-exo conformation, it became interesting to study the antitumor activity of analogues locked into the S-type or the N-type conformation.

For this purpose, we report the synthesis of 5-azacytidine nucleoside analogues locked into the S-type or the N-type conformation as potential antitumor agents because 5-azacytidine derivatives like D-5-azacytidine and 2′-deoxy-D-5-azacytidine exhibit very potent anti-leukemic activity.[3]

1,2;5,6-Di-*O*-isopropylidene-D-glucose (**3**) was oxidized with PDC to give ketone **4** (Sch. 1). Selective removal of 5,6-*O*-isopropylidene of **4** using 80% acetic acid followed by acetylation afforded the tricyclic diacetate which was hydrolyzed and acetylated to give **5**. Condensation of **5** with silylated 5-azacytosine and deacetylation of the resulting nucleoside using NH_4OH/MeOH afforded the final nucleoside **1**.

Ketone **4** was stereoselectively reduced using $NaBH_4$ to give diacetone D-allofuranose which was benzylated to afford **5**. 5,6-*O*-Isopropylidene of **6** was selectively removed using 75% acetic acid to give diol **11** of which primary and secondary hydroxyl groups were selectively protected as a benzoate and a benzyl ether, respectively, to give **6**. Hydrolysis of **6** and acetylation afforded diacetate **7**. Condensation of diacetate **7** with silylated 5-azauracil gave the protected nucleoside which underwent deacetylation and debenzoylation to give **8**. Selective tosylation of primary hydroxyl group of **8** followed by treatment with aqueous sodium hydroxide furnished cyclized derivative **9**. Treatment of **9** with $POCl_3$ and 1,2,4-triazole yielded triazole derivative which was hydrolyzed with aqueous NH_4OH to afford 5-azacytosine derivative **10**. Debenzylation of **10** using hydrogenolysis yielded the final nucleoside **2**.

The final nucleosides **1** and **2** were evaluated against several cancer cell lines, but they did not show significant antitumor activities.

REFERENCES

1. a) Altona, C.; Sunderalingam, M. J. Am. Chem. Soc. **1972**, *94*, 8205; b) Altona, C.; Sunderalingam, M. J. Am. Chem. Soc. **1973**, *95*, 2333.
2. Marquez, V.E.; Ezzitouni, A.; Russ, P.; Siddiqui, M.A.; Ford, H., Jr.; Feldman, R.J.; Mitsuya, H.; George, C.; Barchi, J.J., Jr. J. Am. Chem. Soc. **1998**, *120*, 2780.
3. a) Sorm, F.; Vesely, J. Neoplasma **1968**, *15*, 339; b) Momparler, R.L.; Momparler, L.F.; Samson, J. Leuk. Res. **1984**, *8* 1043.

MARCEL DEKKER, INC.
270 Madison Avenue, New York, New York 10016

MARCEL DEKKER, INC.
270 Madison Avenue, New York, New York 10016