

Nucleosides, Nucleotides and Nucleic Acids

Publication details, including instructions for authors and subscription information:

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STRUCTURE-ACTIVITY RELATIONSHIP OF 5'-SUBSTITUTED FLUORO-NEPLANOCIN A ANALOGUES AS POTENT INHIBITORS OF S-ADENOSYLHOMOCYSTEINE HYDROLASE

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Published online: 28 Jul 2006.

To cite this article: Hyung Ryong Moon, Kang Man Lee, Hyun Joo Lee, Sang Kook Lee, Seung Bin Park, Moon Woo Chun & Lak Shin Jeong (2005) STRUCTURE-ACTIVITY RELATIONSHIP OF 5'-SUBSTITUTED FLUORO-NEPLANOCIN A ANALOGUES AS POTENT INHIBITORS OF S-ADENOSYLHOMOCYSTEINE HYDROLASE, *Nucleosides, Nucleotides and Nucleic Acids*, 24:5-7, 707-708, DOI: [10.1081/NCN-200060286](https://doi.org/10.1081/NCN-200060286)

To link to this article: <http://dx.doi.org/10.1081/NCN-200060286>

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STRUCTURE-ACTIVITY RELATIONSHIP OF 5'-SUBSTITUTED FLUORO-NEPLANOCIN A ANALOGUES AS POTENT INHIBITORS OF S-ADENOSYLHOMOCYSTEINE HYDROLASE

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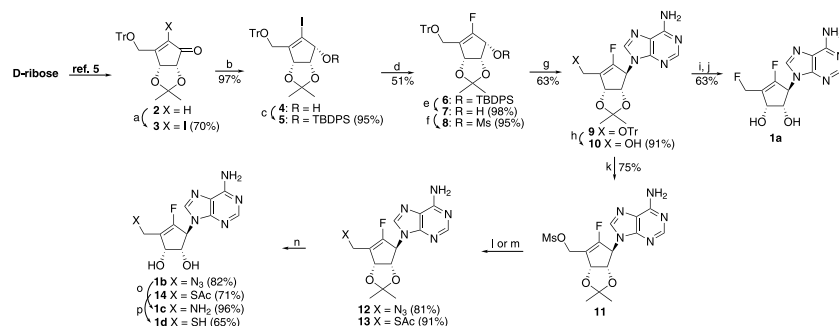
□ *Four 5'-substituted fluoro-neplanocin A analogues **1a–d** were designed and synthesized, and the inhibitory activity against SAH was in the following order: $NH_2 > SH > F, N_3$, indicating a hydrogen bonding donor is essential for inhibitory activity.*

INTRODUCTION

A number of adenosine analogues, which were known to inhibit S-adenosylhomocysteine hydrolase (SAH) have shown antiviral activity against DNA and RNA viruses by interfering with formation of cap structure of viral mRNA.^[1] However, they were not developed as antiviral agents due to their cellular cytotoxicity.^[2] Fluoro-neplanocin A^[3] developed in our laboratory exhibited potent inhibitory activity against SAH and significant antiviral activity with cytotoxicity. Herein, we wish to report the structure-SAHI inhibitory activity and cytotoxicity relationships study of 5'-substituted fluoro-neplanocin A analogues **1a–d**. All desired products **1a–d** were synthesized via cyclopentenone **2**^[4] as a key intermediate, as shown in Scheme 1. Introduction of fluorine substituent at vinyl position was accomplished by electrophilic fluorination. Coupling of mesylate

This work was supported by the grant from the Korea Health R&D Project, Ministry of Health & Welfare, Korea (HMP-02-PJ2-PG10-21503-0004).

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SCHEME 1 Reagents and conditions: (a) I_2 , pyridine, CCl_4 , rt, 12 h; (b) $NaBH_4$, $CeCl_3$, MeOH, $0^\circ C$, 30 min; (c) TBDPSCl, imidazole, DMF, $40^\circ C$, overnight; (d) *N*-fluorobenzene sulfonimide, *n*-BuLi, THF, $-78^\circ C$, 1 h; (e) *n*-Bu₄NF, THF, rt, 2 h; (f) methanesulfonyl chloride, Et₃N, CH₂Cl₂, $0^\circ C$, 30 min; (g) adenine, K₂CO₃, 18-Crown-6, DMF, $80^\circ C$, overnight; (h) *p*-toluenesulfonic acid, MeOH, rt, 18 h; (i) DAST, CH₂Cl₂, $0^\circ C$, 30 min; (j) 33% aqueous CF₃CO₂H, THF, rt, 3 d; (k) methanesulfonyl chloride, Et₃N, CH₂Cl₂, $-5^\circ C$, 20 min; (l) NaN₃, DMF, $60^\circ C$, 1 h for **12**; (m) KSac, DMF, rt, 1 h for **13**; (n) 33% aqueous CF₃CO₂H, THF, rt, 3–4 d; (o) Lindlar's catalyst, MeOH, rt, 30 min; (p) 28% NH₄OH, MeOH, rt, 20 min.

8 with adenine base in the presence of K₂CO₃ gave the protected nucleoside **9**. Introduction of fluorine substituent at 5'-position successfully proceeded employing DAST. 5'-Azido- and 5'-amino-substituted analogues, **1b** and **1c** were synthesized from treatment of mesylate **11** with sodium azide followed by chemoselective reduction of azido group. 5'-Sulhydryl-substituted fluoro-neplanocin A derivative **1d** was synthesized by reaction of mesylate **11** with KSac and then deprotection of *S*-acetyl group using 28% NH₄OH. The inhibitory activity for the final compounds **1a–d** was assayed against SAH. 5'-Azido- and 5'-fluoro-substituted derivatives did not exhibit inhibitory activity up to 100 μM and compound **1d** with 5'-thiol group showed very weak enzyme inhibition ($IC_{50} = 97.27 \mu M$), while conversion into 5'-amino-substituted analogue restored inhibitory activity ($IC_{50} = 12.68 \mu M$). This trend explained that the ability as hydrogen bonding donor at 5'-position was essential for inhibitory activity. As expected, cytotoxicity of the synthesized compounds **1a–d** decreased, probably due to the lack of ability of phosphorylation at 5'-position.

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