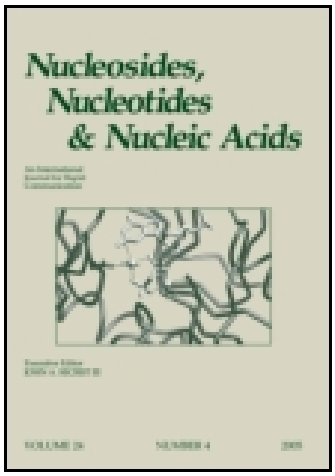

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STRUCTURE-ACTIVITY RELATIONSHIP OF 5′-SUBSTITUTED FLUORO-NEPLANOCIN A ANALOGUES AS POTENT INHIBITORS OF S-ADENOSYLHOMOCYSTEINE HYDROLASE

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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-SAH 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

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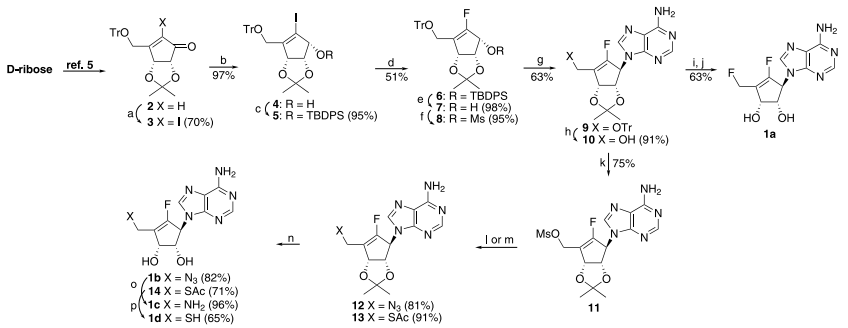

SCHEME 1 Reagents and conditions: (a) I_2, pyridine, CCl_4, rt, 12 h; (b) $NaBH_4$, $CeCl_3$, MeOH, 0°C, 30 min; (c) TBDPSCI, imidazole, DMF, 40°C, overnight; (d) *N*-fluorobenzene sulfonimide, *n*-BuLi, THF, −78°C, 1 h; (e) *n*-Bu_4NF, THF, rt, 2 h; (f) methanesulfonyl chloride, Et_3N, CH_2Cl_2, 0°C, 30 min; (g) adenine, K_2CO_3, 18-Crown-6, DMF, 80°C, overnight; (h) *p*-toluenesulfonic acid, MeOH, rt, 18 h; (i) DAST, CH_2Cl_2, 0°C, 30 min; (j) 33% aqueous CF_3CO_2H, THF, rt, 3 d; (k) methanesulfonyl chloride, Et_3N, CH_2Cl_2, −5°C, 20 min; (l) NaN_3, DMF, 60°C, 1 h for **12**; (m) KSAc, DMF, rt, 1 h for **13**; (n) 33% aqueous CF_3CO_2H, THF, rt, 3–4 d; (o) Lindtar's catalyst, MeOH, rt, 30 min; (p) 28% NH_4OH, MeOH, rt, 20 min.

8 with adenine base in the presence of K_2CO_3 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′-Sulfhydryl-substituted fluoro-neplanocin A derivative **1d** was synthesized by reaction of mesylate **11** with KSAc and then deprotection of *S*-acetyl group using 28% NH_4OH. 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 μM), while conversion into 5′-amino-substituted analogue restored inhibitory activity (IC_{50} = 12.68 μM). 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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