Design and Synthesis of 5"'-Iodoneplanocin A and Its Analogues as Potential S-Adenosylhomocysteine Hydrolase Inhibitor

Ah-Young Park, Kyung Ran Kim, Hyung-Rock Lee, Jin-Ah Kang, Won Hee Kim, Pusoon Chun, Pervez Ahmad, Lak Shin Jeong, and Hyung Ryong Moon

Laboratory of Medicinal Chemistry, College of Pharmacy and Research Institute for Drug Development, Pusan National University, Busan 609-735, Korea. E-mail: mhr108@pusan.ac.kr

†Laboratory of Medicinal Chemistry, College of Pharmacy, Ewha Womans University, Seoul 120-750, Korea

Received November 17, 2008

5"'-Iodoneplanocin A (1) and its analogues 2 and 3 were designed and synthesized as potential SAHH inhibitor via iodocyclopentenol 6, which was prepared using a Michael addition-iodination-elimination process. All final compounds did not show antiviral activity, maybe due to a steric hindrance induced by 5"'-iodo substituent.

Key Words: 5"'-Iodoneplanocin A, S-Adenosylhomocysteine hydrolase, Steric hindrance, Michael addition-iodination-elimination, Michael addition-elimination reaction

Introduction

Neplanocin A (1) (Figure 1), a naturally occurring carbo cyclic nucleoside has been found to exhibit potent antitumor and antiviral activities by inhibiting polymerases and/or S-adenosylhomocysteine hydrolase (SAHH), which catalyzes hydrolysis of S-adenosylhomocysteine (SAH) to adenosine and homocysteine. It is well known that the hydrolysis is the only catabolic pathway of SAH in eukaryotes. Inhibition of SAHH causes an accumulation of SAH in cells, which in turn induces an inhibition of methyltransferases by a negative feedback inhibition mechanism. Methyltransferases are related to formation of 5'-cap structure, which is responsible for the stability of m-RNA against phosphatases and ribonucleases, and a normal splicing. Therefore, the inhibition of SAHH might show potent antiviral and antitumor activities by interfering with formation of 5'-cap structure of viral and cellular m-RNA.

Recently, fluoroneplanocin A, synthesized by Jeong and coworkers has been reported to exhibit better and irreversible SAHH inhibition and more potent antitumor activity than neplanocin A. According to their results, after conversion of 3'-hydroxy group to a keto group by NAD the fluorine atom acts as a leaving group during a Michael addition-elimination reaction induced by a nucleophile present in SAHH, as shown in Scheme 1. Generally, an iodide is much better leaving group than a fluoride. Therefore, it was of great interest to synthesize 5"'-iodoneplanocin A (1), an isostere of fluoroneplanocin A, and its analogs, 2 and 3 having different purine nucleobases and to evaluate their antiviral activity and cytotoxicity.

Results and Discussion

As shown in Scheme 2, D-ribose was used as starting material for the synthesis of glycosyl donor 6. It was envisioned that cyclopentenone 4 would be an appropriate intermediate for the synthesis of the glycosyl donor 6. Compound 4 was prepared in the same manner as our previous report, including a stereoselective Grignard reaction, ring closing metathesis (RCM) and an oxidative rearrangement of tert-allylic alcohol by PDC. Iodination at α-position of

![Scheme 1](image)

**Scheme 1.** A plausible inhibitory mechanism of SAHH by fluoroneplanocin A via a Michael addition-elimination process (SAHH: S-adenosylhomocysteine hydrolase, Ade: adenine).
Scheme 2. (a) h, pyridine, CCl₄, rt, 12 h; (b) NaBH₄, CeCl₃-7H₂O, MeOH, 0 °C, 30 min.

Scheme 3. (a) 6-chloropurine, PPh₃, DEAD, THF, rt, 12 h; (b) NaBH₄, CeCl₃-7H₂O, MeOH, 0 °C, 30 min.

α,β-unsaturated ketone 4 was achieved using I₂ and pyridine, probably via an addition of pyridine to β-position, iodonation of the enolate generated temporarily and elimination of β-pyridinium ion by abstracting α-hydrogen. Conversion of cyclopentenone 5 to glycosyl donor, α-cyclopentenol 6 was accomplished by NaBH₄ in the presence of CeCl₃. 40

The reduction gave α-stereoisomer 6 as a sole product. The Ce(III) metal ion might assist stereo- and regioselectivity in the reduction of enone 5 by chelating the oxygen of carbonyl and the proximal oxygen of the acetonide at the more encumbered concave face.

Synthesis of purine nucleosides 1-3 is described in Scheme 3. 6-Chloropurine was coupled with glycosyl donor 6 under Mitsunobu conditions 11 using DEAD and triphenylphosphine to give nucleoside 7. Chloro substituent at 6-position was converted to amino and N-methylamino groups by treatment with methanolic ammonia and methylamine to afford adenine and N-methyladenine nucleosides, 8 and 9, respectively. Finally, removal of the protecting groups, triyl and acetonide at the more proximal oxygen of the acetonide at the more encumbered concave face. 24

The reduction gave 8, α-cyclopentenol 6 was achieved under acidic conditions (2 N HCl, 1,4-dioxane, rt) to give 5''-iodoneplanocin A (1) and its N-methyl analogue 2, respectively. Hypoxanthine analogue 3 was directly synthesized from 6-chloropurine nucleoside 7 by treating with 1 N HCl at reflux.

Antiviral activities of the synthesized purine compounds 1-3 were evaluated against HIV-1 and 2, influenza viruses (Seoul, Taiwan and Panama), EMCV, Cox. B3, VSV, and HSV-1 and 2. All of them showed neither antiviral activity nor cytotoxicity up to 100 μg/mL. Considering that there have been many reports on the very close relationship between the inhibition of SAHH and antiviral activities, SAHH can not accommodate the final compounds properly at its active site, probably resulting from steric hindrance of the bulky iodo group upon the interaction with them. And also, considering no cytotoxicity, they might not be phosphorylated by kinases or their triphosphates might not be perceived by cellular polymerases, probably due to the same reason as the above. These facts provide very useful information for designing and developing SAHH inhibitors for medicinal chemists.

In conclusion, in order to find more potent antiviral and antitumor agents we have synthesized 5''-iodoneplanocin A (1) and its analogs 2 and 3 as potential SAHH inhibitor, on the basis that the fluorine atom in fluoroneplanocin A plays a role as a leaving group and that an iodide is much better leaving group than a fluoride. Introduction of an iodine substituent into the vinyl position was accomplished by a Michael addition-iodination-elimination process. All of the synthesized compounds did not exhibit antiviral activity and cytotoxicity. Maybe they might undergo a difficulty of phosphorylation upon the interaction with kinases, due to a steric hindrance induced by the introduction of the bulky iodo group into the 5''-vinyl position. And also, they might not be a competitive inhibitor for SAHH due to the same steric hindrance derived from the iodine substituent. Synthesis of 5-chloroneplanocin A and 5-bromoneplanocin A are in progress in our laboratory and a series of halogen-containing structure-activity relationship will be reported in due course in close future.

Experiments

Melting points are uncorrected. 1H and 13C NMR spectra were recorded on Varian Unity INOVA 400 and Varian Unity AS 500 instruments. Chemical shifts are reported with reference to the respective residual solvent or deuteriated solvent (δH 3.30 and δC 77.0 for CDCl₃). Coupling constants are reported in hertz. The abbreviations used are as follows: s (singlet), d (doublet), m (multiplet), t (triplet), dd (doublet of doublet), br s (broad singlet). All the reactions described below were performed under argon or nitrogen atmosphere and monitored by TLC. All anhydrous solvents were distilled over CaH₂ or Na'
methyl-6-(trityloxymethyl)-4,6a-dihydro-3aH-purin-6-amine (8) and 9-((3aS)-5'-iodo-2,2-di-methyl-6-(trityloxymethyl)-4,6a-dihydro-3aH-purin-6-amine (9): 1H NMR (500 MHz, CDCl3) δ 8.37 (s, 1H, H-8), 7.78 (brs, 1H, H-2), 7.55-7.25 (m, 15H, 3a,4R), 6.48 (brs, 1H, NH2), 5.80 (dd, 1H, J = 5.5, 6a-H), 5.48 (s, 1H, 4-H), 4.98 (dd, 1H, J = 6.0 Hz, 3a-H), 3.97 (dd, 1H, J = 1.5, 13.0 Hz, TrOCH3), 3.93 (dd, 1H, J = 12.5 Hz, TrOCH3), 1.47 (s, 3H, CH3), 1.45 (s, 3H, CH3); HRMS (FAB+) m/z 672 (M+H)+; HRMS (FAB+) m/z C21H16NO4 (M+H)+ cated 672.1427, obsd 672.1485; methoxy analog: 1H NMR (500 MHz, CDCl3) δ 8.57 (s, 1H, H-8), 7.78 (brs, 1H, H-2), 7.55-7.25 (m, 15H, 3a, 4R), 5.78 (s, 1H, J = 5.5 Hz, 6a-H), 5.51 (s, 1H, 4-H), 4.95 (dd, 1H, J = 6.0 Hz, 3a-H), 4.23 (s, 3H, OCH3), 3.98 (dd, 1H, J = 2.0, 12.0 Hz, TrOCH3), 3.93 (dd, 1H, J = 12.0 Hz, TrOCH3), 1.47 (s, 3H, CH3), 1.44 (s, 3H, CH3); LRMS (FAB+) m/z 687 (M+H)+; HRMS (FAB+) m/z C23H22NO4 (M+H)+ cated 687.1468, obsd 687.1461.
reaction mixture was stirred at the same temperature overnight. After evaporation, the residue was purified by silica gel column chromatography using CHCl₃ and MeOH (7:1) as the eluent to give the final adenine nucleoside 1 (86 mg, 88%) as a white solid: mp 168.2-172.5 °C; [α]D²⁵ = -100.6° (c 0.83, MeOH); UV (MeOH) λ max 260.0 nm; ¹H NMR (500 MHz, CD₃OD) δ 8.42 (s, 1H, H-8), 8.41 (s, 1H, H-2), 5.67 (d, 1H, J = 5.0 Hz, 2-H), 4.85 (d, 1H, J = 6.0 Hz, 5-H), 4.96 (t, 1H, J = 6.0 Hz, 1-H), 4.34 (brd, 1H, J = 13.0 Hz, HOCH₂H), 4.29 (d, 1H, J = 5.5 Hz, 1-H), 4.33 (dd, 1H, J = 2.5, 13.5 Hz, HOCH₂H); ¹³C NMR (125 MHz, CD₃OD) δ 157.8, 154.4, 150.9, 147.9, 141.4, 123.7, 98.2, 76.9, 73.7, 73.6, 62.3; LRMS (FAB+) m/z 390 (M+H)⁺, 413 (M+Na)⁺.

Acknowledgments. This work was supported by the Korea Research Foundation Grant funded by the Korean Government (KRF-2007-521-E00188).

References