약학석사학위논문

Efficient Synthesis of Homo-fluoroneplanocin A and its analogues as Potent Antiviral Agents

강력한 항바이러스제로서의 Homo-fluoroneplanocin A 유사체의 새로운 합성

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Abstract

(−)-Neplanocin A **(1)** is a representative carbocyclic nucleoside and is known to be one of the most potent inhibitors against SAH hydrolase, exhibiting potent and wide-ranging antiviral activities. However, its therapeutic utility has been limited due to its significant cytotoxicity. In search of new carbocyclic nucleosides with better therapeutic profile than (−)-neplanocin A, many modifications have been made on the carba-sugar ring and on the purine base.

Since the cytotoxicity of (−)-neplanocin A is reported to arise from 5'-phosphorylation of the corresponding nucleoside, one carbon extension of the C-5' hydroxymethyl side chain was conducted to reduce cytotoxicity. In addition, among analogues of (−)-neplanocin A, bioisosteric replacement of hydrogen with fluorine at the 6'-position was reported to increase the inhibitory activity against SAH hydrolase.

Based on these rationales, it was of great interest to synthesize homo-fluoroneplanocin A **(4)** and its analogues through a highly efficient route. Synthesized homo-fluoroneplanocin A **(4)** showed potent inhibition of SAH hydrolase (IC_{50} = 0.91 μM), high anti-Chikungunya activity (EC_{50} = 0.18 μM) and low cytotoxicity (CC_{50} > 250 μM), with selectivity index of more than 1300.

In brief, we report alternative, highly efficient synthetic route of homo-fluoroneplanocin A **(4)** and its analogues, using Michael reaction, stereoselective electrophilic fluorination and palladium-catalyzed dehydrogenation as key steps. The synthesized nucleoside showed potent activity against Chikungunya virus and low cytotoxicity.

Keywords : Antiviral, Neplanocin A, Carbocyclic nucleoside, Fluorination, Chikungunya virus

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Contents

I. Introduction

Nucleosides are fundamental elements in all living systems, as they are the building blocks of nucleic acids such as DNA and RNA. Modified nucleosides can either act as nucleic acid chain terminators, which interrupts the chain elongation of viral polymerases or as selective inhibitors of important enzymes to suppress viral survival. Through these mechanisms, many modified nucleosides have been identified and developed as antiviral agents.[1]

The carbocyclic nucleosides, in which the furanose oxygen has been replaced by methylene group, have an advantage of not being subjected to the action of nucleoside phosphorylases and hydrolases that cleave normal nucleosides.[2] This means carbocyclic nucleosides are metabolically stable under physiological conditions and are able to exert its inhibitory activity for a sufficient time to show antiviral effect.

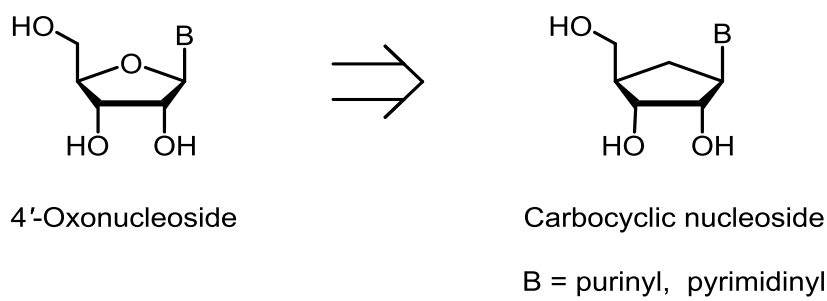
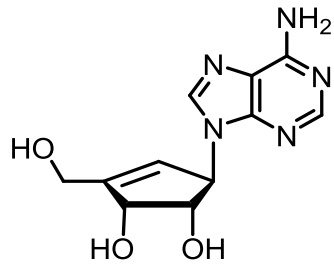


Figure 1. Gradual evolution of a nucleoside.

(−)-Neplanocin A (**1**), which is an adenosine analogue isolated from *Ampullariella regularis*, is a representative of naturally occurring carbocyclic nucleosides.[3] (−)-Neplanocin A exhibits both significant antiviral and antitumor activity, which is reported to arise from its potent inhibitory activity against *S*-adenosylhomocysteine (SAH) hydrolase.[4] *S*-adenosylhomocysteine (SAH) hydrolase is an enzyme responsible for the hydrolysis of *S*-adenosylhomocysteine (SAH) into adenosine and L-homocysteine. SAH is a strong feedback inhibitor of a methyltransferase enzyme that utilizes *S*-adenosyl-L-methionine (SAM) as the carbon source in biological methylation reactions such as methylation of an immature viral mRNA. Therefore, inhibition of SAH hydrolase hinders viral mRNA maturation and represents a rational strategy for the development of antiviral chemotherapy.[5,6]



1
(–)-Neplanocin A

Figure 2. Structure of (–)-Neplanocin A (**1**)

As a number of viruses are sensitive to SAH hydrolase inhibitors, the inhibitors show a broad and unique spectrum of antiviral activity. SAH hydrolase inhibitors were shown to be effective against poxviruses, negative stranded RNA viruses such as measles or rabies virus and double stranded RNA viruses.[7] However, members of the *Herpesviridae* and positive stranded RNA viruses other than retroviruses (HIV) are virtually resistant to SAH hydrolase inhibitors.[8]

Thus, SAH hydrolase has been recognized as a novel target for antiviral chemotherapy and several carbocyclic nucleosides including (–)-neplanocin A and (–)-aristeromycin were found to exert their antiviral action through inhibition of SAH hydrolase.

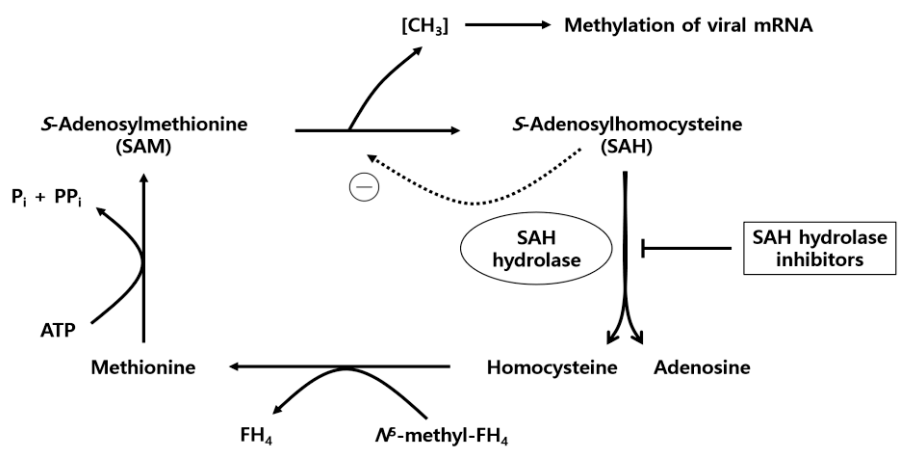


Figure 3. The mechanism of action of SAH hydrolase inhibitors.[9]

Though (–)-neplanocin A (**1**) is a potent SAH hydrolase inhibitor, its therapeutic utility has been limited due to its significant toxicity.[10] Several modifications have been made on the structure of (–)-neplanocin A to yield carbocyclic analogues, which show improved inhibitory activity toward SAH hydrolase, while being devoid of its toxicity.

Since the cytotoxicity of (–)-neplanocin A is reported to arise from 5'-phosphorylation of the corresponding nucleoside by cellular kinase[11], one carbon extension at the C-5' hydroxymethyl side chain was conducted to reduce cytotoxicity. Homologated analogues of (**1**) would not be phosphorylated because it is not a suitable substrate for the cellular kinase. In addition, among analogues of **1**, bioisosteric replacement of hydrogen with fluorine at the 6'-position was reported to increase the inhibitory activity against SAH hydrolase by novel type II mechanism based inhibition.[10] Also, increased hydrophobic interaction with the leucine residue of the binding site was confirmed by X-ray crystal structure of the 6'-fluorinated nucleosides bound to the enzyme.[12]

Based on these rationale, homo-fluoroneplanocin A and its analogues were designed and it was of great interest to synthesize the desired nucleosides through efficient synthetic route.

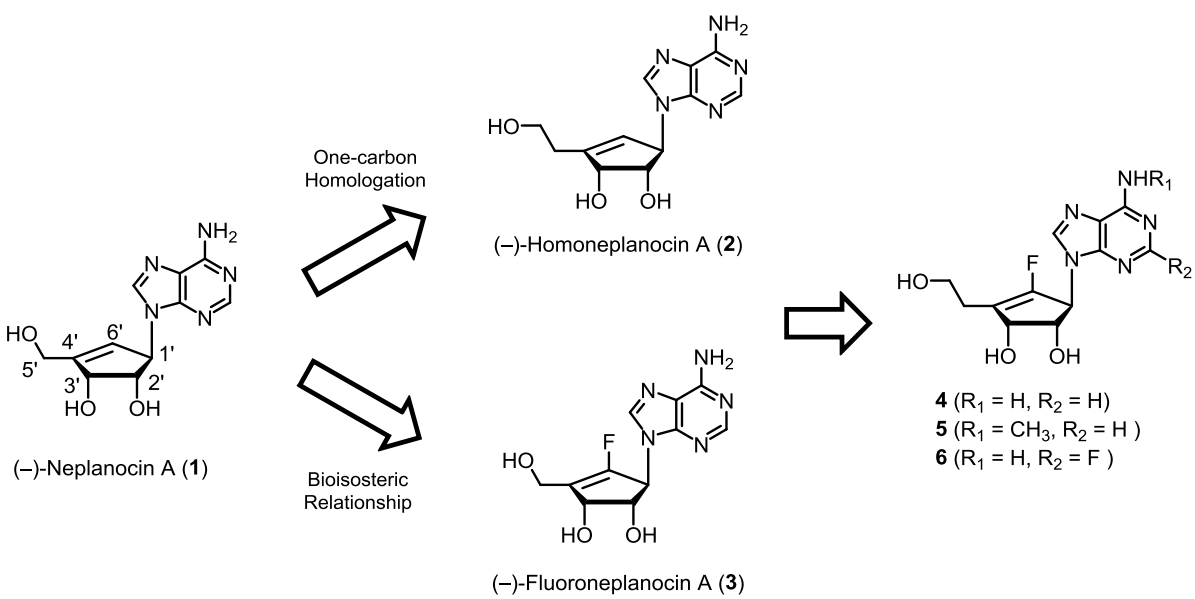


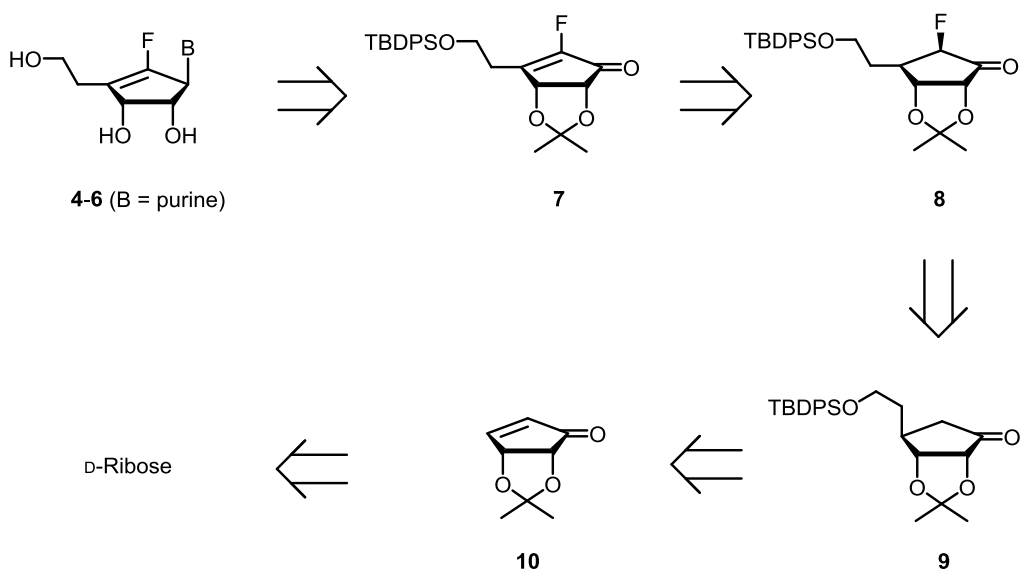
Figure 4. Rationale for the design of (–)-neplanocin analogues.

Herein, we report design and synthesis of enantiomerically pure homo-fluoroneplanocin A and its analogues. Starting from commercially available D-ribose, the desired nucleosides were synthesized

using Michael addition, electrophilic fluorination and palladium-catalyzed dehydrogenation as key steps. Synthesized nucleosides were evaluated their SAH hydrolase inhibition and antiviral activity against several RNA viruses.

II. Results and Discussion

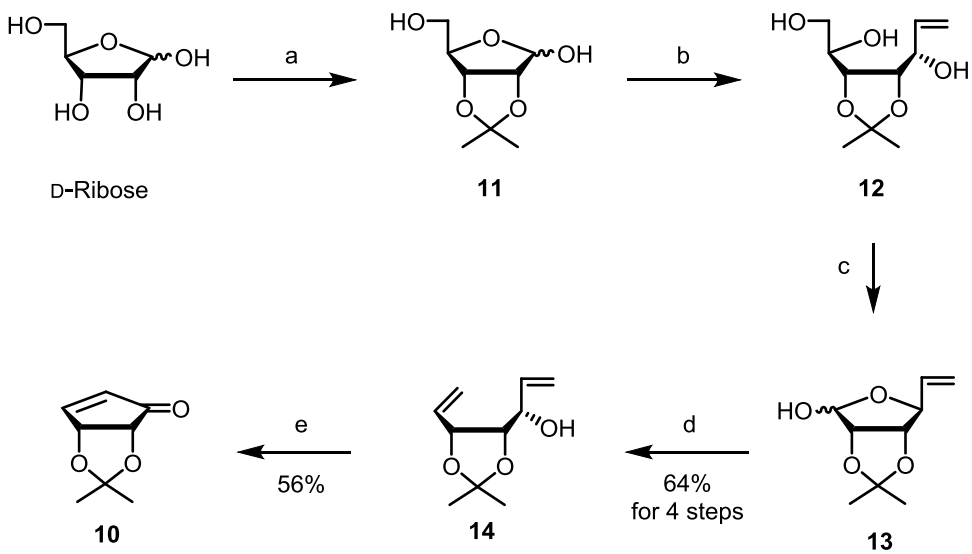
For many years of continuous research in the field of carbocyclic nucleosides, our group has gained substantial insights into the synthesis of glycosyl donors from commercially available D-ribose, which is an inexpensive and chiral starting material.[13]



Scheme 1. Retrosynthetic analysis of the homo-fluoroneplanocin A analogues.

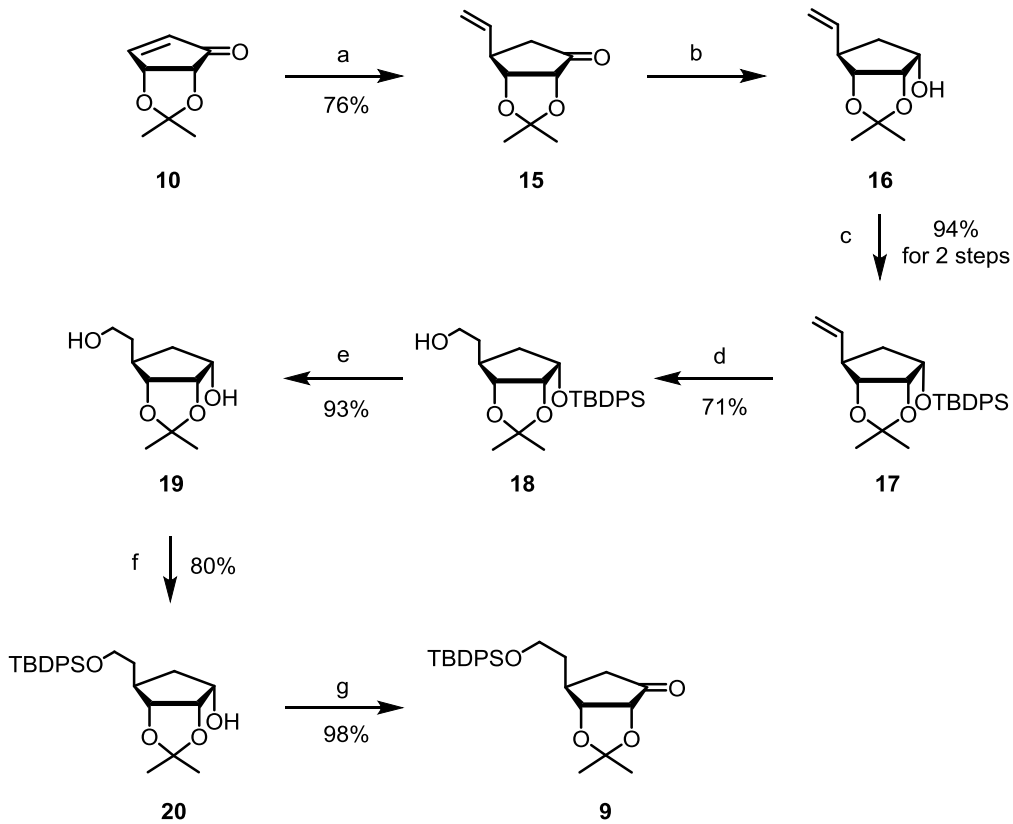
As shown in our retrosynthetic plans (Scheme 1), our strategy would utilize Mitsunobu condensation of the purine base to a fluronated glycosyl donor. It was envisaged that fluorovinyl structure of the glycosyl donor could be synthesized through Pd-catalyzed dehydrogenation of *β*-fluoroketone **8.** Compound **8** could be synthesized through stereoselective electrophilic fluorination of silyl enol ether, which could be easily accessed from compound **9**. Compound **9** could be synthesized from D-cyclopentenone **10** by Michael reaction and the intermediate **10** could be efficiently derived from D-ribose with our previously published procedure.[15]

To begin our synthesis (Scheme 2), D-ribose was converted to known **10** in five steps, according to a modified known procedure using ring-closing metathesis of **14** with Neolyst M2, followed by PDC oxidation.



Reagents and conditions: (a) acetone, *c*-H_2SO_4, rt, 3 h; (b) vinylMgBr, THF, −78 °C to 0 °C, 3 h; (c) $NaIO_4$, H_2O, 0 °C to rt, 40 min; d) NaH, DMSO, CH_3PPh_3Br, THF, 0 °C to reflux, 15 h; (e) (i) Neolyst M2, CH_2Cl_2, rt, 2 d; (ii) PDC, CH_2Cl_2, rt, 6 h.

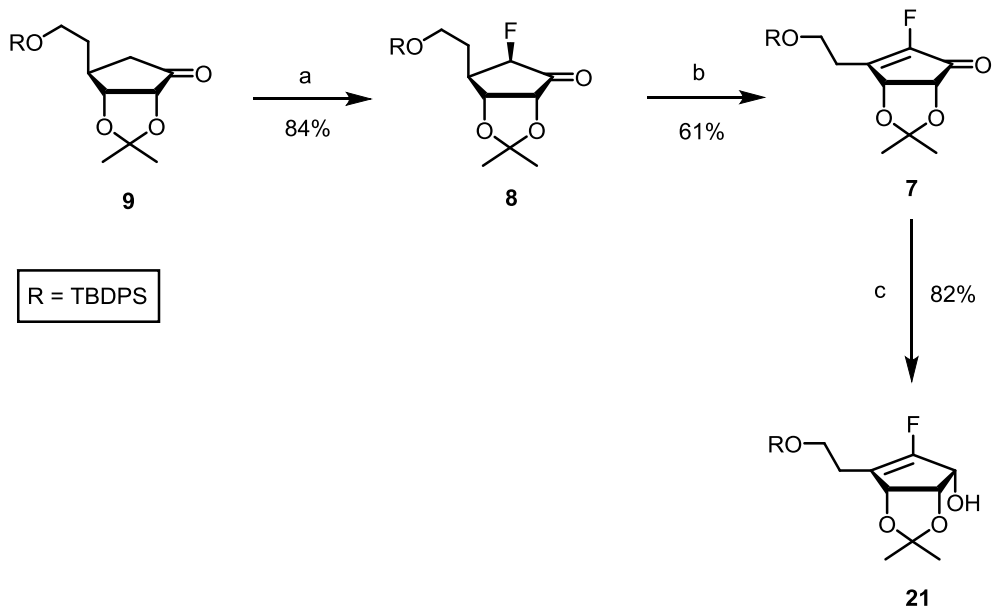
Scheme 2. Synthesis of D-cyclopentenone **10**.



Reagents and Conditions*:* (a) vinylMgBr, $CuBr{\cdot}CH_3SCH_3$, TMSCl, HMPA, THF, –78 °C, 2 h; (b) $NaBH_4$, MeOH, 0 °C, 1 h; (c) TBDPSCl, imidazole, DMF, 0 °C to rt, 3 h; (d) (i) $BH_3{\cdot}CH_3SCH_3$, THF, 0 °C to rt, 1 h; (ii) $NaBO_3{\cdot}H_2O$, H_2O, 0 °C to rt, 16 h; (e) TBAF, THF, 0 °C to rt, 16 h; (f) Et_3N, DMAP, TBDPSCl (1.2 eq.), CH_2Cl_2, 0 °C to rt, 2 h; (g) NMO, 4 Å molecular sieves, TPAP, CH_2Cl_2, rt, 1 h.

Scheme 3. Synthesis of the ketone intermediate **9**.

Michael addition of vinyl Grignard on **10** through a reported procedure afforded compound **15** in 76% yield.[14] The reduction of 1,4-addition product **15** using sodium borohydride gave the alpha alcohol **16**, since the concave region is hindered by the 2,3-isopropylidene ring group. The alcohol **16** was protected with TBDPSCl, followed by hydroboration oxidation with borane-dimethyl sulfide complex to give the hydroboration product **18**. The deprotection of TBDPS using TBAF gave the diol compound **19**, which was subjected to selective protection of primary hydroxyl group by 1.2 equivalent of TBDPSCl to afford compound **20**. The oxidation of compound **20** in the presence of tetrapropylammonium perruthenate and *N*-methylmorpholine *N*-oxide gave the ketone **9**.

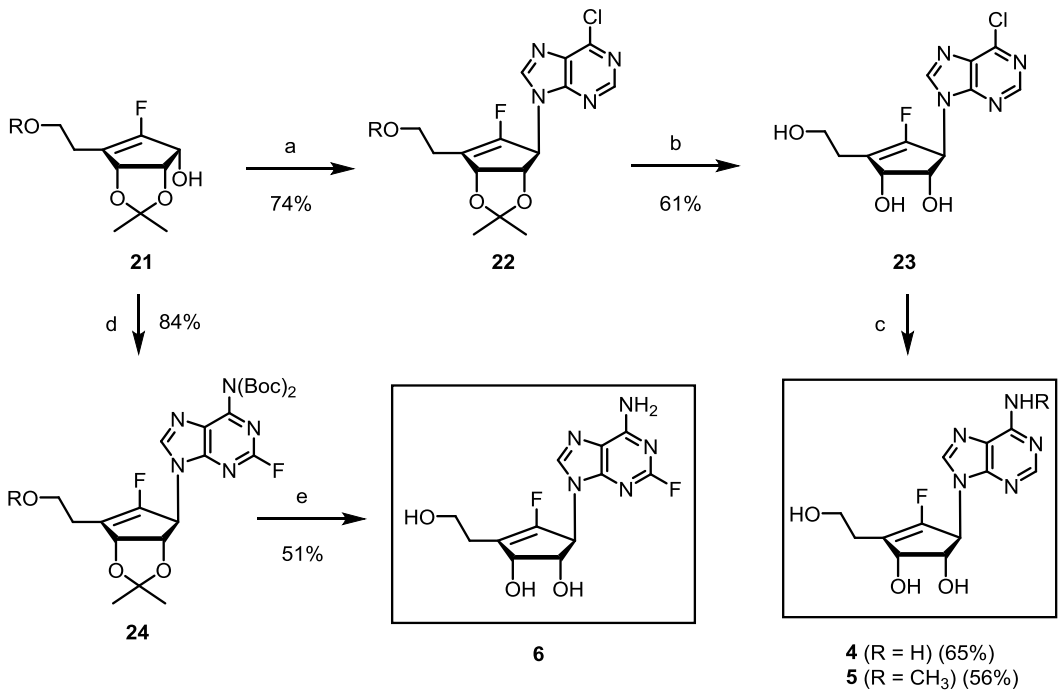


Reagents and Conditions: (a) (i) TESCl, LiHMDS, THF, −78 °C, 1 h; (ii) selectfluor, CH_3CN, 0 °C, 16 h; (b) (i) TESCl, LiHMDS, THF, −78 °C, 1 h; (ii) $Pd(OAc)_2$, CH_3CN, 60 °C, 1.5 d; (c) $NaBH_4$, $CeCl_3$-$7H_2O$, MeOH, 0 °C, 1.5 h.

Scheme 4. Synthesis of the glycosyl donor **21**.

The ketone **9** was then treated with chlorotriethylsilane and lithium bis(trimethylsilyl)amide to give silyl enol ether. The silyl enol ether was treated with selectfluor (1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane ditetrafluoroborate) which is as a conventional source of electrophilic fluorine to give the desired β-fluoro-cyclopentanone **8**. The carbanion formed at C6 attacks electrophilic fluorine, which results in the formation of the desired β-fluorinated compound **8**, because of the steric hindrance by the 2,3-isopropylidene ring.

Fluorinated sugar **8** was subjected to dehydrogenation, using stoichiometric amount of $Pd(OAc)_2$ in acetonitrile to synthesize intermediate **7** with the fluorovinyl structure, which was reduced under luche reduction condition to yield glycosyl donor **21**.



Reagents and Conditions: (a) 6-chloropurine, PPh_3, DIAD, THF, rt, 15 h.; (b) 50% aq. TFA, rt, 8 h; (c) NH_3/*t*-BuOH, 120 °C, 15 h (for **4**) or 40% aq. $MeNH_2$, 80 °C, 15 h (for **5**) (d) N^6-bisboc-2-fluoroadenine, PPh_3, DIAD, THF, rt, 15 h; (e) 50% aq. TFA, rt, 8 h. .

Scheme 5. Synthesis of the homo-fluoroneplanocin A analogues.

The glycosyl donor **21** was coupled with 6-chloropurine and N^6-bisboc-2-fluoroadenine under conventional mitsunobu condition to yield compound **22** and **24,** respectively. Removal of the 2,3-isopropylidene ring, TBDPS and boc protecting groups of the intermediate **24** by 50% aqueous trifluoroacetic acid gave the nucleoside **6**. Similarly, protecting groups of the intermediate **22** were removed under same acidic condition to give nucleoside **23**. For the synthesis of the adenine nucleoside **4**, saturated *tert*-butanolic ammonia was added to the 6-chloropurine nucleoside **23** in steel bomb. Moreover, 40 wt. % aqueous methylamine was used in steel bomb for synthesis of the *N*-methyl adenine nucleoside **5**.

compound	SAH Hydrolase IC_{50} (μM)	Chikungunya virus		Semliki forest virus	
		EC_{50} (μM)	CC_{50} (μM)	EC_{50} (μM)	CC_{50} (μM)
4	**0.91**	**0.18**	>250	5.15	>250

Table 1. Results for the antiviral activity observed for compound **4**.

Synthesized homo-fluoroneplanocin A (**4**) was tested for its inhibitory activity on SAH hydrolase and antiviral activities against several RNA viruses. Biological evaluation of other synthesized compounds will be performed in the near future. As shown in table 1, homo-fluoroneplanocin A showed inhibition of SAH hydrolase and potent antiviral activity against Chikungunya virus and Semliki forest virus without cytotoxicity up to 250 μM. In particular, homo-fluoroneplanocin A was able to suppress viral replication of Chikungunya virus at a concentration of 0.18 μM. This is a greater inhibitory activity compared to several commercially available antiviral agents such as chloroquine or arbidol, which are reported to be active against the virus.[16]

ADME studies of homo-fluoroneplanocin A (**4**) were conducted to evaluate and predict pharmacokinetic properties of the compound. As shown in table 2, homo-fluoroneplanocin A showed high liver microsomal phase I stability in all three tested models.

Compound	Mouse	Rat	Human
4	83.7 ± 0.850	85.7 ± 4.00	93.3 ± 3.03
Reference (Buspirone)	0.036 ± 0.012	0.122 ± 0.016	3.22 ± 0.653

Table 2. Liver microsomal phase I stability of compound **4**. (% remaining after 30 min)
(mean $\pm$ SD, n=3)

Also, CYP inhibition assay demonstrated that homo-fluoroneplanocin A (**4**) does not inhibit human CYP isozymes, which are enzymes responsible for majority of drug metabolism (Table 3). This is an important aspect of a lead compound in that it is directly related to drug-drug interactions.

Compound	**1A2**	**2C9**	**2C19**	**2D6**	**3A4**
4 (10 μM)	3.29	20.4	9.08	3.45	5.08
Inhibitor*	99.0	95.2	94.4	97.8	97.8

Table 3. % inhibition of human CYP isozymes
*1A2 : α-naphthoflavone (10 μM), 2C9 : sulfaphenazole (10 μM), 2C19 : amitriptyline (100 μM), 2D6: quinidine (10 μM), 3A4 : ketoconazole (10 μM)

hERG ligand binding assay of **4** was performed to predict cardiotoxicity of the compound. It is one of the crucial safety-related studies which has to be conducted in the early development stage.[17] As shown in table 4, compound **4** exhibited low hERG inhibition of 5.28 %, indicating that it is not likely to cause cardiotoxic side effects such as arrhythmia or long-QT syndrome.

Treatment		Concentration (μM)	% inhibition
Positive control	E-4031	10	93.2 ± 11.9
Test compound	**4**	10	5.28 ± 3.95

Table 4. Result of hERG ligand binding assay (mean $\pm$ SD, n=3)

Inhibition of SAH hydrolase, potent antiviral activity and promising ADME studies demonstrate that homo-fluoroneplanocin A (**4**) may be a potential candidate for the development of a novel anti-Chikungunya agent.

III. Conclusion

Based on the structure of (–)-neplanocin A, homo-fluoroneplanocin A and its analogues were designed and synthesized from D-ribose. Michael addition, stereoselective electrophilic fluorination and palladium catalyzed dehydrogenation were used in the synthesis as key steps. Homo-fluoroneplanocin A (**4**) showed potent anti-Chikungunya (EC_{50} = 0.18 μM) without cytotoxicity up to 250 μM, showing high selectivity index (CC_{50}/EC_{50} > 1300). Antiviral activity of compound **4** seems to be in correlation with its potent inhibitory activity against SAH hydrolase (IC_{50} = 0.91 μM). Low cytotoxicity of **4**

compared with (-)-neplanocin A can be attributed to one carbon homologation at the 5′ position, which is assumed to prevent phosphorylation by cellular kinase. ADME studies of **4** revealed some promising pharmacokinetic properties of the compound, including high metabolic stability and low risk of cardiotoxicity.

In brief, homo-fluoroneplanocin A (**4)** is a potential candidate for the development of novel anti-chikungunya agents. Also, the chemistry used in this study is believed to contribute greatly to the research field of carbocyclic nucleosides.

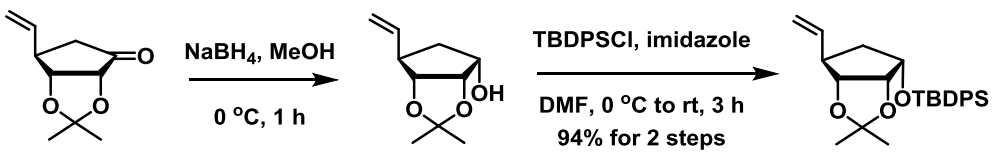
IV. Experimental Section

1. General Procedure

Proton (^{1}H) and carbon (^{13}C) NMR spectra were recorded on a Jeol JNMLA300 (300/75 MHz), Bruker AV 400 (400/100 MHz), Bruker AMX 500 (500/125 MHz), Jeol JNM-ECA600 (600/150 MHz), or Bruker AVANCE III 800 (800/200 MHz) spectrometer. Chemical shifts are reported in ppm units with Me_4Si or NMR solvent as the internal standard. All reactions were routinely carried out under an inert atmosphere of dry nitrogen. Reactions were checked by thin layer chromatography (Kieselgel 60 F254, Merck). Spots were detected by viewing under a UV light, and by colorizing with charring after dipping in a *p*-anisaldehyde solution or phosphomolybdic acid solution. In aqueous work-up, all organic solutions were dried over anhydrous magnesium sulfate and filtered prior to rotary evaporation at water pump pressure. The crude compounds were purified by column chromatography on a silica gel (Kieselgel 60, 70-230 mesh, Merck). Unless otherwise noted, materials were obtained from commercial suppliers and were used without purification. All solvents were purified and dried by standard techniques just before use. THF and Et_2O were freshly distilled from sodium and benzophenone. Methylene chloride, toluene, and benzene were purified by refluxing with CaH_2. Hexanes and ethyl acetate were purified by simple distillation.

2. Experimental Procedures

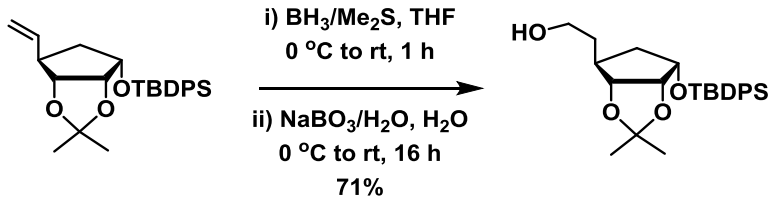
Preparation of 17



15 16 17

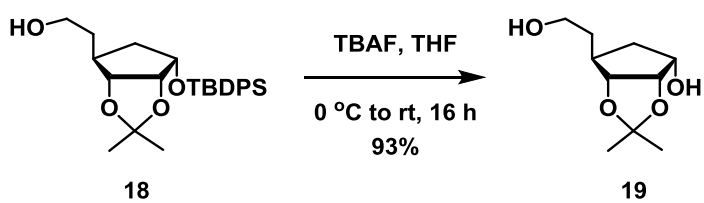
***tert*-Butyl(((3a*R*,4*S*,6*R*,6a*R*)-2,2-dimethyl-6-vinyltetrahydro-4*H*-cyclopenta[d][1,3]dioxol-4-yl)oxy)diphenylsilane (17).** To a stirred solution of **15** (8.2 g, 45.0 mmol) in methanol (500 mL) was added sodium borohydride (2.2 g, 58.5 mmol) at 0 °C and the reaction mixture was stirred at the same temperature for 1 h. The mixture was quenched with water (20 mL) and concentrated *in vacuo*. The residue was diluted with brine and extracted with ethyl acetate (3 × 300 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure to give the crude alcohol, which was used for the next reaction without further purification. To a stirred solution of crude alcohol **16** and imidazole (15.3 g, 224.5 mmol) in *N,N*-dimethylformamide (240 mL) was added TBDPSCl (18.7 mL, 71.85 mmol) at 0 °C, under nitrogen atmosphere. The reaction mixture was stirred at room temperature for 3 h, quenched with water (150 mL) and extracted with diethyl ether (2 × 300 mL). The combined organic layers were washed with water (5 × 200 mL), dried using anhydrous $MgSO_4$ and concentrated *in vacuo*. The residue was purified by silica gel chromatography (hexanes:ethyl acetate = 99:1) to obtain **17** as colorless syrup (18.7 g, 99%): $[\alpha]_D^{25}$ –59.2 (*c* 0.125, CH_3OH); ^1H NMR (400 MHz, $CDCl_3$) δ 7.76 (m, 4H), 7.40 (m, 6H), 5.55 (ddd, *J* = 6.0, 10.4, 17.2 Hz, 1H), 4.85 (dt, *J* = 1.2, 9.2 Hz, 1H), 4.76 (dt, *J* = 2.0, 17.6 Hz, 1H), 4.26 (m, 1H), 4.03 (m, 1H) 2.60 (m, 2H), 2.06 (m, 1H), 1.61 (m, 1H), 1.57 (s, 3H), 1.32 (s, 3H), 1.09 (s, 9H); ^{13}C NMR (100 MHz $CDCl_3$) δ 138.6, 136.0, 129.7, 127.7, 114.7, 84.3, 79.8, 73.4, 44.1, 34.7, 27.1, 26.5, 24.8, 19.4; HRMS (FAB) found 445.2165 [calcd for $C_{26}H_{34}NaO_3Si^+$ $(M + Na)^+$ 445.2169].

Preparation of 18



2-((3a*R*,4*S*,6*S*,6a*R*)-6-((tert-Butyldiphenylsilyl)oxy)-2,2-dimethyltetrahydro-4*H*-cyclopenta[d][1,3]dioxol-4-yl)ethan-1-ol (18). To a stirred solution of **17** (1.72 g, 4.07 mmol) in anhydrous tetrahydrofuran (35 mL) was carefully added borane-dimethyl sulfide complex (1.0 M solution in tetrahydrofuran, 8.95 mL, 8.95 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 1 h and cooled to 0 °C, before sodium perborate (1.34 g, 13.43 mmol) and water (40 mL) were carefully added. The mixture was stirred at room temperature for 16 h, diluted with brine (10 mL) extracted with ethyl acetate (2 × 50 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexanes:ethyl acetate = 4:1) to obtain **18** as colorless syrup (1.22 g, 71%): $[\alpha]_D^{25}$ – 40.1 (*c* 0.187, CH_3OH); ^1H NMR (400 MHz, $CDCl_3$) δ 7.74 (m, 4H), 7.40 (m, 6H), 4.26 (m, 2H), 4.18 (m, 1H), 4.05 (m, 1H), 3.53 (m, 1H), 1.99 (m, 1H) 1.55 (s, 3H), 1.35 (s, 3H), 1.35 (m, 1 H), 1.32 (s, 3H), 1.26 (m, 1H), 1.09 (s, 9H); ^{13}C NMR (100 MHz $CDCl_3$) δ 136.0, 134.4, 129.7, 127.7, 117.7, 84.8, 80.1, 78.2, 61.5, 38.3, 36.6, 35.5, 27.1, 26.5, 24.8, 19.4; HRMS (FAB) found 463.2281 [calcd for $C_{26}H_{36}NaO_4Si^+$ $(M + H)^+$ 463.2275].

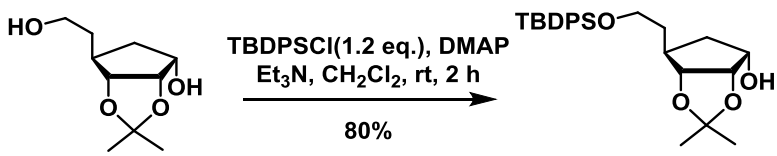
Preparation of 19



(3a*S*,4*S*,6*S*,6a*R*)-6-(2-Hydroxyethyl)-2,2-dimethyltetrahydro-4*H*-cyclopenta[d][1,3]dioxol-4-ol (19). To a stirred solution of **18** (7.5 g, 17.0 mmol) in anhydrous tetrahydrofuran (200 mL) was added

tetra-*n*-butylammonium fluoride (1.0 M solution in tetrahydrofuran, 51.0 mL, 51.0 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 16 h. The solvent was removed under reduced pressure and the residue was purified by column chromatography (methylene chloride:methanol = 9:1) to obtain **19** as colorless syrup (3.3 g, 93%): $[\alpha]_D^{25}$ –8.26 (*c* 0.121, CH_3OH); ^1H NMR (400 MHz, $CDCl_3$) δ 4.50 (t, *J* = 5.9 Hz, 1H), 4.36 (dd, *J* = 5.9, 2.4 Hz, 1H), 4.07 (m, 1H), 3.69 (t, *J* = 6.1 Hz, 2H), 2.56 (br, 1H), 2.19 (m, 2H), 2.05 (br, 1H), 1.94 (dt, *J* = 13.2, 6.5 Hz, 1H), 1.62 (dt, *J* = 13.2, 6.1 Hz , 1H), 1.55 (m, 2H), 1.51 (m, 3H), 1.35 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 112.4, 85.1, 79.5, 70.6, 61.4, 38.8, 37.5, 35.2, 26.1, 24.1; HRMS (FAB) found 203.1274 [calcd for $C_{10}H_{19}O_4^+$ $(M + H)^+$ 203.1278].

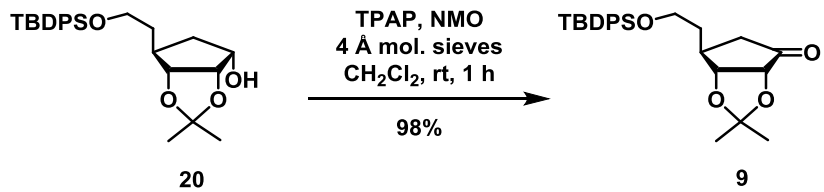
Preparation of 20



19 20

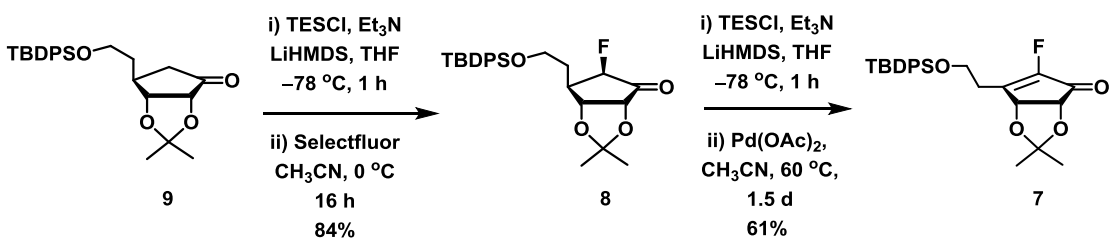
(3a*S*,4*S*,6*S*,6a*R*)-6-(2-((*tert*-Butyldiphenylsilyl)oxy)ethyl)-2,2-dimethyltetrahydro-4H-cyclopenta[d][1,3]dioxol-4-ol (20). To a stirred solution of **19** (3.3 g, 16.3 mmol), triethylamine (6.8 mL, 48.9 mmol) and 4-*N,N*-dimethylaminopyridine (0.2 g, 1.6 mmol) in methylene chloride (40 mL) was added TBDPSCl (4.9 g, 17.9 mmol) at 0 °C, under nitrogen atmosphere. The reaction mixture was stirred for 2 h at room temperature, quenched with water (5 mL) and extracted with methylene chloride (2 × 40 mL). The organic portion was dried using anhydrous $MgSO_4$ and concentrated *in vacuo*. The residue was purified by silica gel chromatography (hexanes:ethyl acetate = 4:1) to obtain **20** as colorless oil (5.7 g, 80%): $[\alpha]_D^{25}$ –20.4 (*c* 0.093, CH_3OH); ^1H NMR (400 MHz, $CDCl_3$) δ 7.69 (m, 4H), 7.42 (m, 6H), 4.43 (t, *J* = 5.6 Hz, 1H), 4.34 (dd, *J* = 1.2, 6 Hz, 1H), 4.02 (m, 1H), 3.72 (m, 2H), 2.47 (d, *J* = 7.6 Hz, 1H), 2.19 (m, 1H), 1.87 (m, 1 H), 1.68 (m, 1 H), 1.56 (m, 1 H), 1.51 (s, 3H), 1.46 (m, 1H), 1.34 (s, 3H), 1.08 (s, 9H); ^{13}C NMR (100MHz, $CDCl_3$) δ 135.7, 133.8, 129.7, 111.5, 85.1, 79.1, 71.3, 62.5; HRMS (FAB) found 441.2458 [calcd for $C_{26}H_{36}NaO_4Si^+$ $(M + H)^+$ 441.2456].

Preparation of 9



(3a*R*,6*S*,6a*R*)-6-(2-((*tert*-Butyldiphenylsilyl)oxy)ethyl)-2,2-dimethyltetrahydro-4*H*-cyclopenta[d][1,3]dioxol-4-one (9). To a stirred solution of **20** (1.04 g, 2.36 mmol) in methylene chloride (50 mL) were added 4 Å molecular sieves (1.04 g), 4-*N*-methylmorpholine-*N*-oxide (0.55 g, 4.72 mmol) and tetra-*n*-propylammonium perruthenate (TPAP) (33 mg, 0.094 mmol) at room temperature. The reaction mixture was stirred at room temperature for 1 h and filtered through a pad of Celite and silica. The filtrates was concentrated to give a residue, which was purified by silica gel column chromatography (hexanes:ethyl acetate = 2.3:1) to obtain **9** as a colorless syrup (1.13 g, 99%): $[\alpha]_D^{25}$ –84.1 (*c* 0.12, CH_3OH); ^1H NMR (400 MHz, $CDCl_3$) δ 7.64 (m, 4H), 7.41 (m, 6H), 4.57 (d, *J* = 5.6 Hz, 1H), 4.17 (m, 1H), 3.72 (m, 3H), 2.73 (dd, *J* = 8.8, 18.4 Hz, 1H), 2.61 (m, 1H), 2.03 (dt, *J* = 1.6, 17.6 Hz, 1H), 1.68 (m, 1H), 1.43 (s, 3H), 1.33 (s, 3H), 1.05 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 214.4, 135.7, 133.5, 130.0, 127.9, 112.3, 82.2, 78.3, 61.7, 40.1, 36.2, 34.0, 27.0, 25.1, 19.3; HRMS (FAB) found 456.2572 [calcd for $C_{26}H_{38}NO_4Si^+$ $(M + NH_4)^+$ 456.2565].

Preparation of 7



(3aR,6aR)-6-(2-((tert-butyldiphenylsilyl)oxy)ethyl)-5-fluoro-2,2-dimethyl-3a,6a-dihydro-4H-cyclopenta[d][1,3]dioxol-4-one (7). To a stirred solution of **9** (6.4 g, 14.5 mmol) in anhydrous tetrahydrofuran (105 mL) at –78 °C, under nitrogen atmosphere were added chlorotrietylsilane (9.73

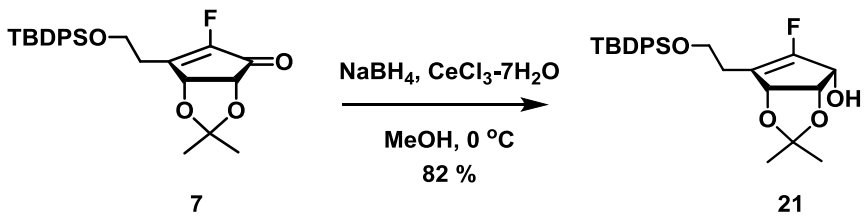
mL, 58.0 mmol) and lithium *bis* (trimethylsilyl)amide (1.0 M solution in tetrahydrofuran, 29.0 mL, 29.0 mmol). The reaction mixture was stirred at –78 °C for 1 h, warmed to 0 °C and quenched using saturated aqueous NH_4Cl (30 mL). The solution was extracted with ethyl acetate (2 × 100 mL). The combined organic layers were dried using anhydrous $MgSO_4$ and concentrated *in vacuo* to get the crude silyl enol ether, which was used immediately for the next step without further purification.

To a stirred solution of the crude silyl enol ether in anhydrous acetonitrile (120 mL) was added Selectfluor® (7.7 g, 21.8 mmol) at 0 °C. The reaction mixture was stirred for 16 h at 0 °C, diluted with brine (50 mL) and extracted with ethyl acetate (2 × 100) . The organic layers were dried using anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexanes:ethyl acetate = 5.6:1) to obtain an inseparable mixture of the mono fluoroketone **8** and the mono fluoro geminal diol (3.7 g, 84%).

To a stirred solution of **8** (3.12 g, 6.83 mmol) in anhydrous tetrahydrofuran (35 mL) at –78 °C, under nitrogen atmosphere were added chlorotrietylsilane (4.6 mL, 27.32 mmol) and lithium *bis* (trimethylsilyl)amide (1.0 M solution in tetrahydrofuran, 13.66 mL, 13.66 mmol). The reaction mixture was stirred at –78 °C for 1 h, warmed to 0 °C and quenched using saturated aqueous NH_4Cl (30 mL). The solution was extracted with ethyl acetate (2 × 100 mL). The combined organic layers were dried using anhydrous $MgSO_4$ and concentrated *in vacuo* to get the crude silyl enol ether, which was used immediately for the next step without further purification.

To a stirred solution of the crude silyl enol ether in anhydrous acetonitrile (120 mL) was added $Pd(OAc)_2$ (4.47 g, 19.9 mmol) at room temperature. The reaction mixture was stirred for 1.5 d at 60 °C, diluted with ethyl acetate (50 mL) and filtered through a pad of celite. The organic layers were washed with brine, dried using anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexanes:ethyl acetate = 19:1) to obtain **7** as a colorless liquid (1.82 g, 61%); $[\alpha]_D^{25}$ +2.76 (*c* 0.5, CH_3OH): ^1H NMR (500 MHz, $CDCl_3$) δ 7.68-7.63 (m, 4H), 7.47-7.36 (m, 6H), 4.99 (merged dd, $J_1 = J_2 = 6.08$ Hz, 1H), 4.38 (dd, $J_1 = J_2 = 2.13$ Hz, 1H), 3.97 (t, J = 6.1 Hz 2H), 2.87-2.81 (m, 1H), 2.64-2.58 (m, 1H), 1.37 (s, 6H), 1.05 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 191.8 (J = 17.3 Hz), 154.8 (J = 286 Hz), 148.0, 135.4, 133.1, 129.8, 127.7, 115.1, 75.0 (J = 7.5 Hz), 74.7 (J = 6.6 Hz), 60.3, 29.2, 27.4, 26.7, 25.9, 19.0; ^{19}F NMR (376 MHz, $CDCl_3$) δ –140.7; HRMS (ESI) found 477.1868 [calcd for $C_{26}H_{31}FNaO_4Si^+$ $(M + Na)^+$ 477.1868].

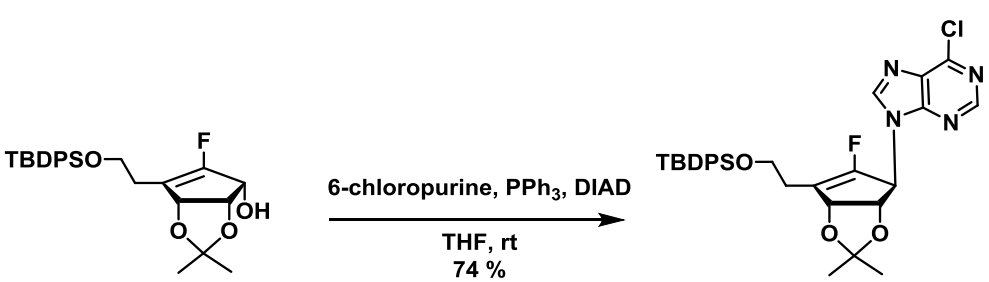
Preparation of 21



7 21

(3aS,4R,6aR)-6-(2-((tert-butyldiphenylsilyl)oxy)ethyl)-5-fluoro-2,2-dimethyl-3a,6a-dihydro-4H-cyclopenta[d][1,3]dioxol-4-ol (21). To a stirred solution of **7** (1.2 g, 2.64 mmol) in methanol (15 mL) at 0 °C, was added cesiumchloride heptahydrate (1.2 g, 3.17 mmol) and the reaction mixture was stirred at 0 °C for 5 min. After 5 min, Sodium borohydride (76 mg, 2 mmol) was added to the mixture and stirred for 1 h at 0 °C. After completion of the reaction, H_2O was added and the solvent was concentrated *in vacuo*. Aqueous layer was extracted with ethyl acetate and the organics were washed with brine, dried using anhydrous $MgSO_4$ and concentrated *in vacuo* to get the alcohol, which was purified by silica gel column chromatography (hexanes:ethyl acetate = 9:1) to obtain **21** as a colorless syrup (0.99 g, 82%): $[\alpha]_D^{25}$ +3.29 (*c* 0.1, CH_3OH); ^1H NMR (500 MHz, $CDCl_3$) δ 7.68-7.62 (m, 4H), 7.45-7.34 (m, 6H), 4.73 (merged dd, $J_1 = J_2 = 6.7$ Hz, 1 H), 4.58 (m, 1H), 4.39 (brs, 1H), 3.82 (t, 2H), 2.77 (d, $J = 8.1$ Hz, 1H), 2.58-2.50 (m, 1H), 2.35-2.26 (m, 1H), 1.39 (s, 3H), 1.36 (s, 3H), 1.04 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.2 ($J = 284$ Hz), 135.5, 133.7, 129.6, 127.6, 115.5, 112.1, 79.8 ($J = 10.3$ Hz), 73.8 ($J = 7.75$ Hz), 68.8 ($J = 21.1$ Hz), 61.1, 27.5, 26.8, 26.4, 19.1; ^{19}F NMR (376 MHz, $CDCl_3$) δ –133.10, -135.65; HRMS (ESI) found 479.203 [calcd for $C_{26}H_{33}FNaO_4Si^+$ $(M + Na)^+$ 479.2024].

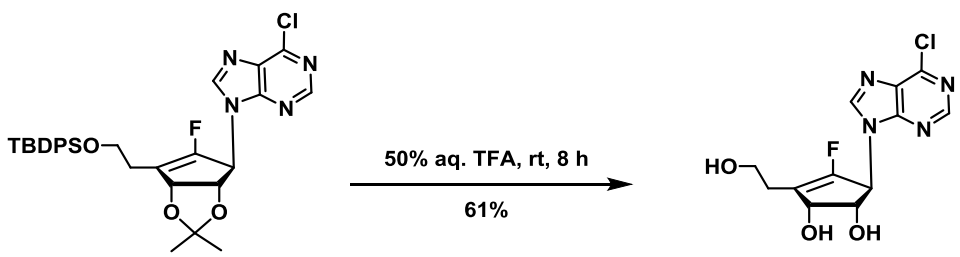
Preparation of 22



21 22

9-((3aS,4S,6aR)-6-(2-((tert-butyldiphenylsilyl)oxy)ethyl)-5-fluoro-2,2-dimethyl-3a,6a-dihydro-4H-cyclopenta[d][1,3]dioxol-4-yl)-6-chloro-9H-purine (22). To a stirred suspension of **21** (185 mg, 0.41 mmol), triphenylphosphine (323 mg, 1.23 mmol) and 6-chloropurine (190 mg, 1.23 mmol) in anhydrous THF (15 mL), was added diisopropylazodicarboxylate (0.13 mL, 0.66 mmol) at 0 °C. The reaction mixture was stirred at room temperature overnight. After completion of the reaction, the reaction mixture was concentrated *in vacuo* and the residue was purified by silica gel column chromatography (hexanes:ethyl acetate = 3:1) to obtain **22** as a colorless syrup (0.18 g, 74%). $[\alpha]_D^{25}$ –12.1 (*c* 0.12, CH_3OH); UV (CH_3OH) λ_{max} 265 nm; ^1H NMR (400 MHz, $CDCl_3$) δ 8.67 (s, 1H), 8.03 (s, 1H), 7.67–7.62 (m, 4H), 7.46–7.32 (m, 6H), 5.55 (s, 1H), 5.37 (merged dd, $J_1 = J_2 = 5.2$ Hz, 1H), 4.73 (merged dd, $J_1 = J_2 = 5.2$ Hz, 1H), 3.96-3.83 (m, 2H), 2.69-2.60 (m, 1H), 2.49–2.39 (m, 1H), 1.47 (s, 3H), 1.33 (s, 3H), 1.01 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.2, 151.3 (J = 3.63 Hz), 150.1 (J = 281 Hz), 143.6, 135.5, 133.4, 132.1, 129.7 (J = 1.38 Hz), 127.7 (J = 1.88 Hz), 122.5 (J = 5.5 Hz), 112.5, 81.2 (J = 9.88 Hz), 80.5 (J = 6.13 Hz), 62.9 (J = 20.9 Hz), 60.8, 27.5, 27.3, 26.7, 25.7, 19.1; ^{19}F NMR (376 MHz, $CDCl_3$) δ –131.2; HRMS (ESI) found 615.1972 [calcd for $C_{31}H_{34}ClFN_4NaO_3Si^+$ $(M + Na)^+$ 615.1965].

Preparation of 23

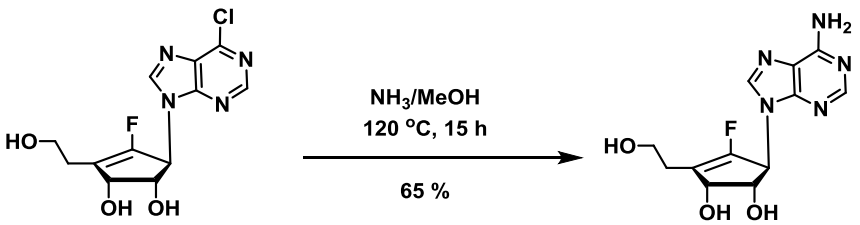


22 23

(1S,2R,5S)-5-(6-chloro-9H-purin-9-yl)-4-fluoro-3-(2-hydroxyethyl) cyclopent-3-ene-1,2-diol (23). A solution of **22** (0.28 g, 0.47 mmol) in 50% aqueous trifluoroacetic acid solution (12 mL) was stirred at 0 °C to room temperature for 8 h. The mixture was concentrated *in vacuo* and the residue was purified by silica gel column chromatography (methylene chloride:methanol = 9:1) to obtain **23**, which was crystallized from diethyl ether/methanol: white solid (0.09 g, 61 %): mp 220-225 °C; $[\alpha]_D^{25}$ +3.36 (*c* 0.10, CH_3OH); UV (CH_3OH) λ_{max} 265 nm; ^1H NMR (400 MHz, CD_3OD) δ 8.72 (s, 1H), 8.64 (s, 1H), 5.75-5.68 (m, 1H), 4.73-4.68 (m, 1H), 4.61-4.55 (m, 1H), 3.84-3.70 (m, 2H), 2.50

(t, 6.8 Hz, 2H); ^{13}C NMR (125 MHz, CD_3OD) δ 156.2, 153.9, 153.3 (221 Hz), 148.1, 133.6, 122.6, 122.5, 76.2 (5.13 Hz), 73.8 (9.25 Hz), 64.9 (18.5 Hz), 61.1, 29.4; ^{19}F NMR (376 MHz, CD_3OD) δ –134.8; HRMS (ESI) found 316.0679 [calcd for $C_{12}H_{13}ClFN_4O_3^+$ $(M + H)^+$ 316.0682].

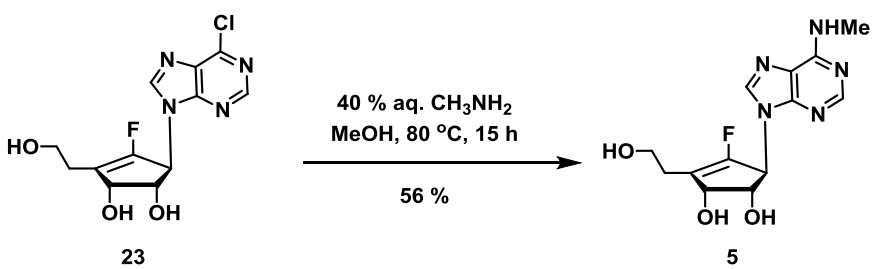
Preparation of 4



23 4

(1S,2R,5S)-5-(6-amino-9H-purin-9-yl)-4-fluoro-3-(2-hydroxyethyl)cyclopent-3-ene-1,2-diol (4). A steel pressure vessel containing a solution of **23** (90 mg, 0.29 mmol) in saturated methanolic ammonia (20 mL) was heated at 120 °C overnight. After cooling the reactor to room temperature, the solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography (methylene chloride:methanol = 4:1) to obtain **4**, which was crystallized from diethyl ether/methanol: yellowish solid (0.055 g, 65%); mp 125–126 °C; $[\alpha]_D^{25}$ –124.9 (*c* 5.5, CH_3OH); UV (CH_3OH) λ_{max} 259.9 nm; ^{1}H NMR (500 MHz, CD_3OD) δ 8.18 (s, 2H), 5.57 (s, 1H), 4.65-4.75 (m, 1H), 4.51-4.55 (m, 1H), 3.84-3.72 (m, 1H), 2.51 (m, 2H); ^{13}C NMR (150 MHz, CD_3OD) δ 158.2, 155.7 (*J* = 280 Hz), 154.6, 151.7, 142.5, 122.0 (*J* = 3.60 Hz), 121.3, 76.4 (*J* = 5.75 Hz), 73.8 (*J* = 9.33 Hz), 64.3 (*J* = 18.7 Hz), 61.2, 29.4; ^{19}F NMR (376 MHz, CD_3OD) δ –134.52; HRMS (ESI) found 297.1183 [calcd for $C_{12}H_{15}FN_5O_3^+$ $(M + H)^+$ 297.118].

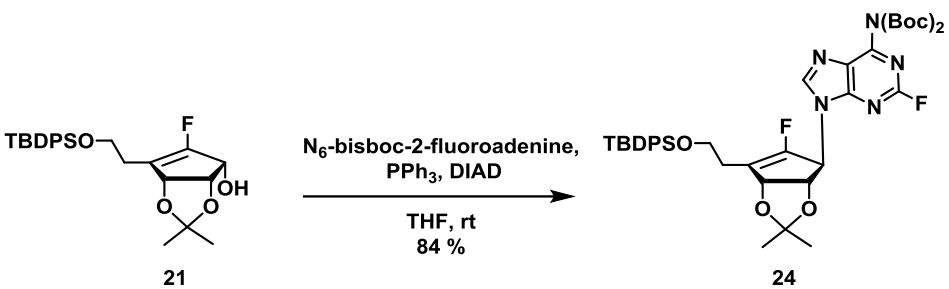
Preparation of 5



23 5

(1S,2R,5S)-4-fluoro-3-(2-hydroxyethyl)-5-(6-(methylamino)-9H-purin-9-yl)cyclopent-3-ene-1,2-diol (5). A steel pressure vessel containing a solution of **23** (9 mg, 0.03 mmol) in methanol (3 mL) was added 40 % methylamine aqueous solution (0.5 mL, 4.9 mmol). The reaction mixture was heated at 80 °C for 15 h. After cooling the reactor to room temperature, the solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography (methylene chloride:methanol = 7:1) to obtain **4**, which was crystallized from diethyl ether/methanol: yellowish solid (5 mg, 56 %); mp 120–125 °C; $[\alpha]_D^{25}$ –449.7 (*c* 0.01, CH_3OH); UV (CH_3OH) λ_{max} 267.8 nm; ^1H NMR (500 MHz, CD_3OD) δ 8.21 (s, 1H), 8.10 (s, 1H), 5.53 (s, 1H), 4.67 (merged dd, $J_1 = J_2 = 5.2$ Hz, 1H), 4.50 (merged dd, $J_1 = J_2 = 4.8$ Hz, 1H), 3.83-3.70 (m, 1H), 3.08 (s, 3H), 2.55-2.42 (m, 2H); ^{13}C NMR (100 MHz, CD_3OD) δ 156.9, 155.1 (*J* = 281 Hz), 154.0, 149.8, 141.3, 121.3, 121.2, 75.8 (*J* = 5.80 Hz), 73.1 (*J* = 9.5 Hz), 63.5 (*J* = 18.2 Hz), 60.5, 28.7, 27.8; ^{19}F NMR (376 MHz, CD_3OD) δ –134.38; HRMS (ESI) found 310.1313 [calcd for $C_{13}H_{17}FN_5O_3^+$ $(M + H)^+$ 310.131].

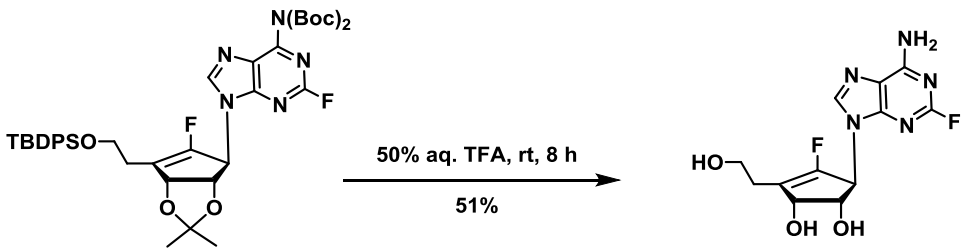
Preparation of 24



9-((3aS,4S,6aR)-6-(2-((tert-butyldiphenylsilyl)oxy)ethyl)-5-fluoro-2,2-dimethyl-3a,6a-dihydro-4H-cyclopenta[d][1,3]dioxol-4-yl)-6-chloro-9H-purine (24). To a stirred suspension of **21** (100 mg, 0.22 mmol), triphenylphosphine (173 mg, 0.66 mmol) and N^6-bisboc-2-fluoroadenine (86 mg, 0.24 mmol) in anhydrous THF (11 mL), was added diisopropylazodicarboxylate (0.13 mL, 0.66 mmol) at 0 °C. The reaction mixture was stirred at room temperature overnight. After completion of the reaction, the reaction mixture was concentrated *in vacuo* and the residue was purified by silica gel column chromatography (hexanes:ethyl acetate = 3:1) to obtain **24** as a colorless syrup (146 mg, 84%). $[\alpha]_D^{25}$ +27.5 (*c* 0.10, CH_3OH); UV (CH_3OH) λ_{max} 274.5 nm; ^1H NMR (400 MHz, $CDCl_3$) δ 7.92 (s, 1H), 7.7-7.63 (m, 4H), 7.45–7.34 (m, 6H), 5.48 (s, 1H), 5.33 (merged dd, $J_1 = J_2 = 5.4$ Hz, 1H), 4.67 (merged dd, $J_1 = J_2 = 5.0$ Hz, 1H), 3.96-3.83 (m, 2H), 2.68-2.57 (m, 1H), 2.49–2.39 (m, 1H), 1.46 (s, 18H), 1.45 (s,

3H) 1.33 (s, 3H), 1.03 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.8 (J = 216 Hz), 154.5 (J = 16.9 Hz), 152.3 (J = 16.9 Hz), 150.1 (J = 281 Hz), 149.9, 143.2, 135.5, 133.4, 129.7, 127.7, 127.1, 122.5, 112.5 84.3, 81.2 (J = 9.88 Hz), 80.5 (J = 6.13 Hz), 62.5 (J = 20.9 Hz), 60.9, 27.7, 27.6, 27.4, 26.8, 25.8, 19.1; ^{19}F NMR (376 MHz, $CDCl_3$) δ –49.54, –131.23; HRMS (ESI) found 792.3597 [calcd for $C_{41}H_{52}F_2N_5O_7Si^+$ $(M + H)^+$ 792.3599].

Preparation of 6



24 6

(1S,2R,5S)-5-(6-amino-2-fluoro-9H-purin-9-yl)-4-fluoro-3-(2-hydroxyethyl)cyclopent-3-ene-1,2-diol (6). A solution of **24** (80 mg, 0.1 mmol) in 50% aqueous trifluoroacetic acid solution (20 mL) was stirred at 0 °C to room temperature for 8 h. The mixture was concentrated *in vacuo* and the residue was purified by silica gel column chromatography (methylene chloride:methanol = 6:1) to obtain **6**, which was crystallized from diethyl ether/methanol: white solid (16 mg, 51 %): mp 220-225 °C; $[\alpha]_D^{25}$-100.9 (*c* 0.10, CH_3OH); UV (CH_3OH) λ_{max} 262.3 nm; ^{1}H NMR (400 MHz, CD_3OD) δ 8.08 (s, 1H), 5.45-5.41 (m, 1H), 4.68-4.63 (m, 1H), 4.49-4.44 (m, 1H), 3.8-3.70 (m, 2H), 2.55-2.41 (m, 2H); ^{13}C NMR (100 MHz, CD_3OD) δ 160.8 (207 Hz), 159.2 (20 Hz), 154.8 (280 Hz), 152.6 (19.1 Hz), 141.9, 121.3 (3.9 Hz), 118.8, 75.6 (5.8 Hz), 73.0 (9.6 Hz), 63.6 (18.2 Hz), 60.5, 28.7; ^{19}F NMR (376 MHz, CD_3OD) δ –134.77, –53.23; HRMS (ESI) found 314.1063 [calcd for $C_{12}H_{14}F_2N_5O_3^+$ $(M + H)^+$ 314.1059].

V. References

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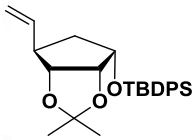
VI. ^{1}H and ^{13}C NMR Copies



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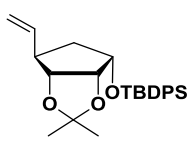
^{1}H NMR of 17



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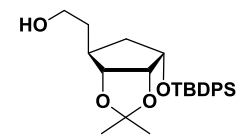

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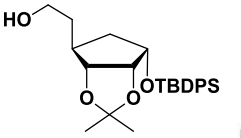

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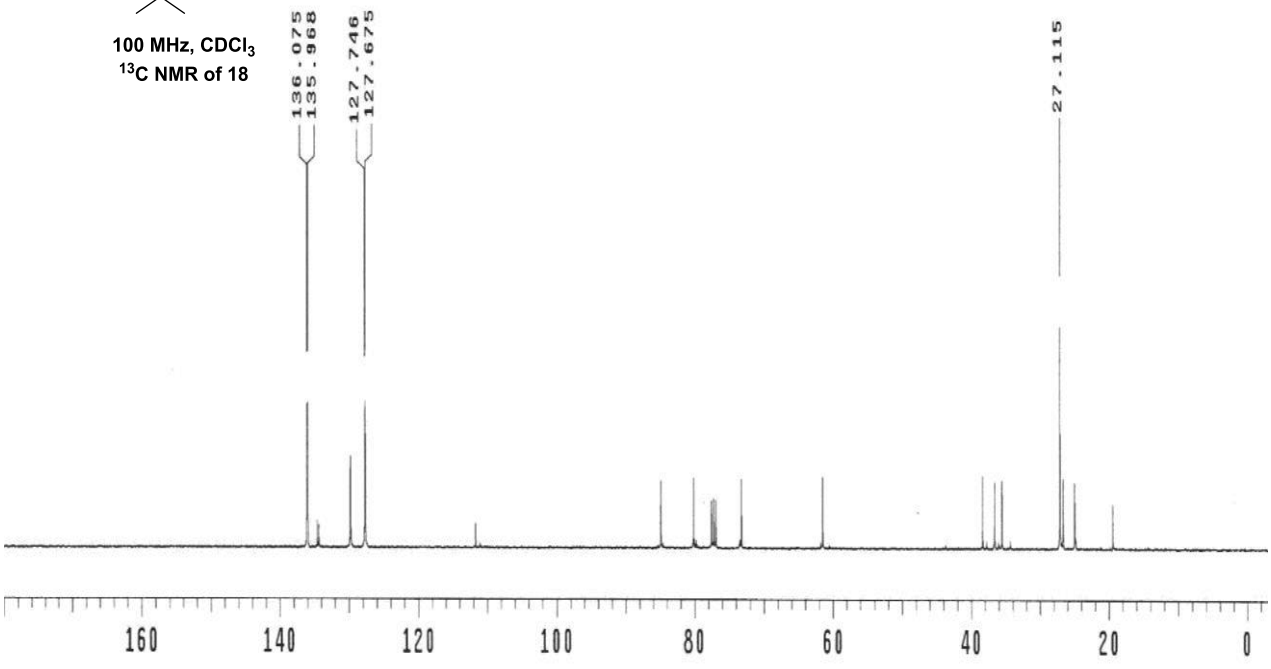

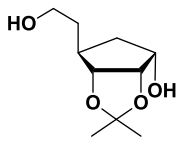

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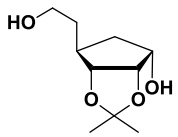

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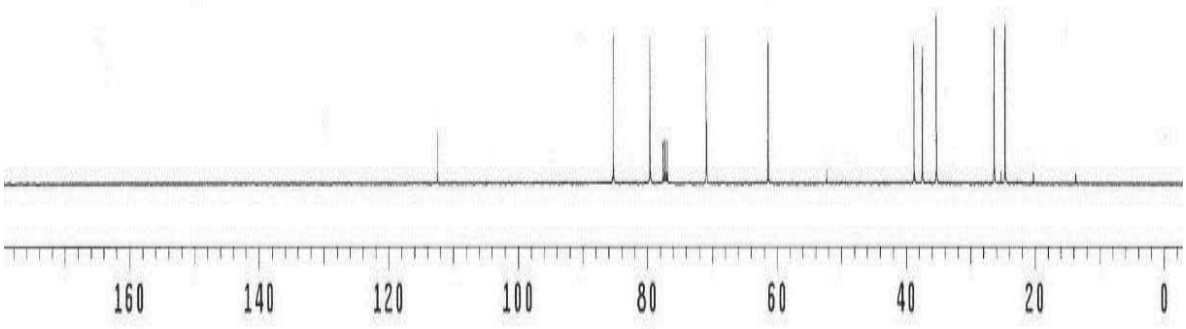

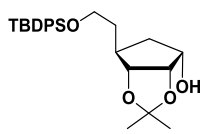

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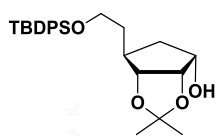

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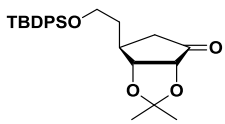

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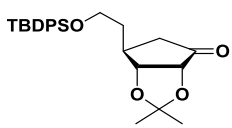

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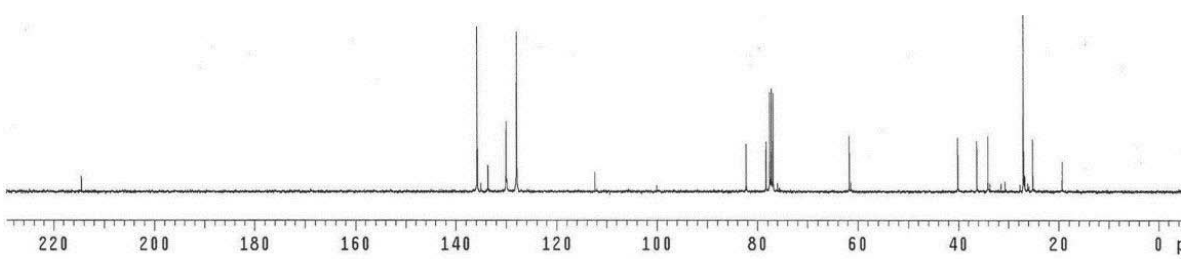

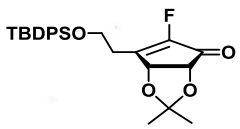

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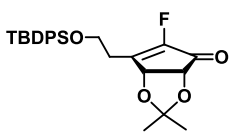

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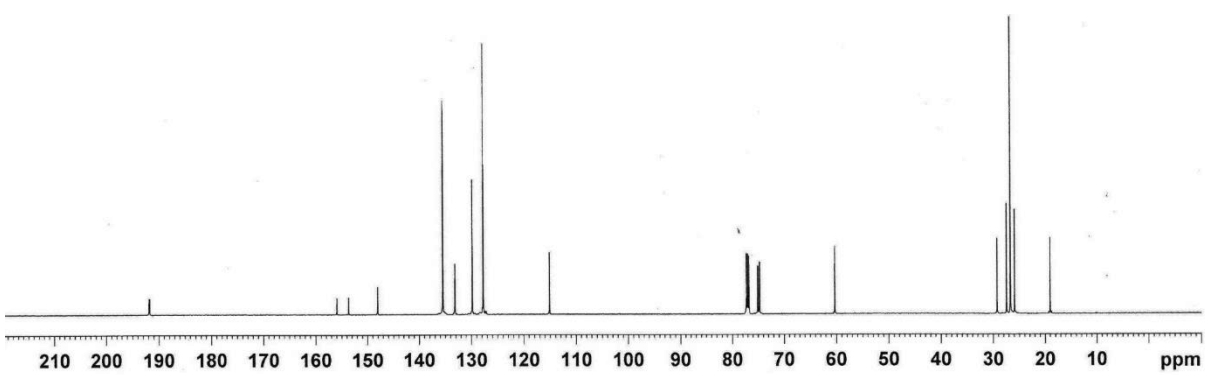

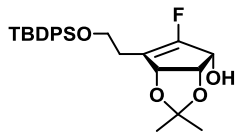

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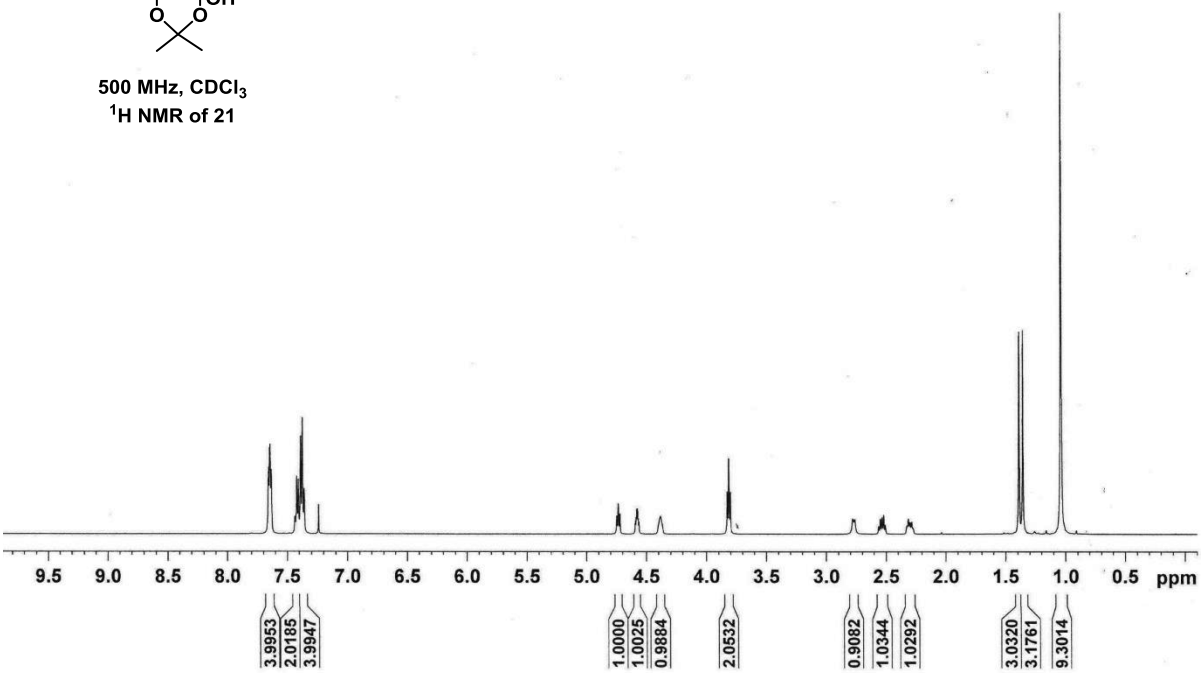

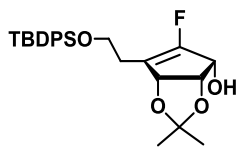

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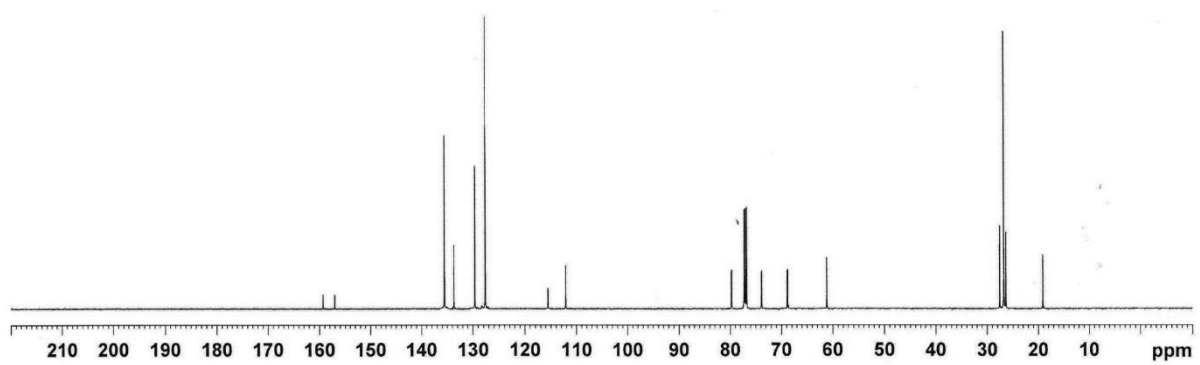

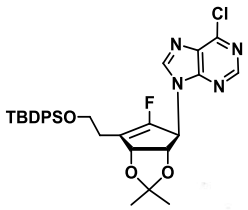

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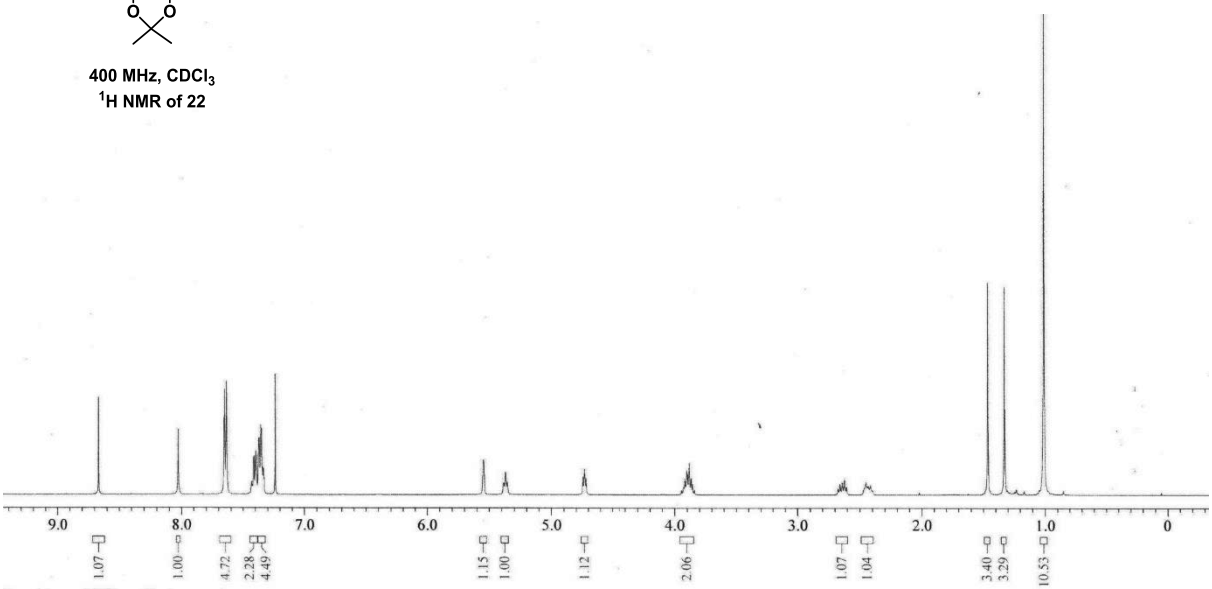

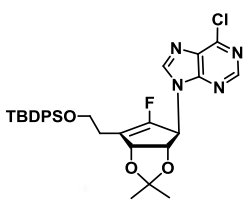

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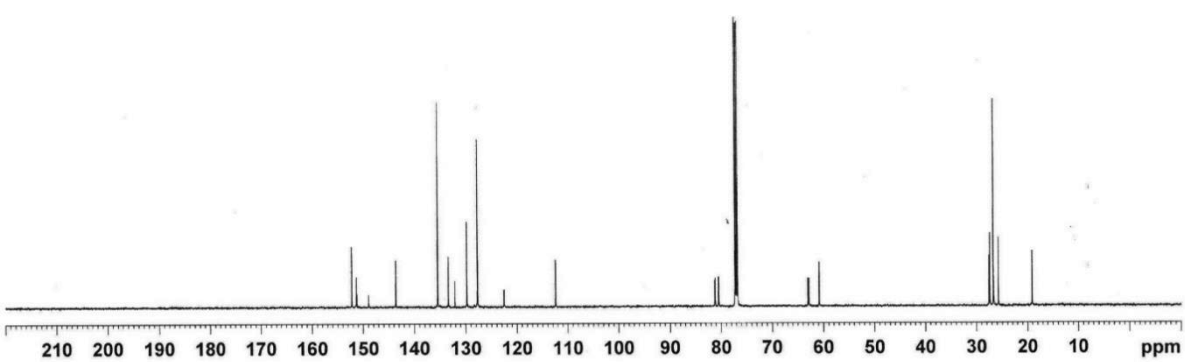

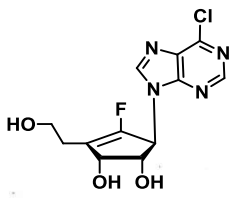

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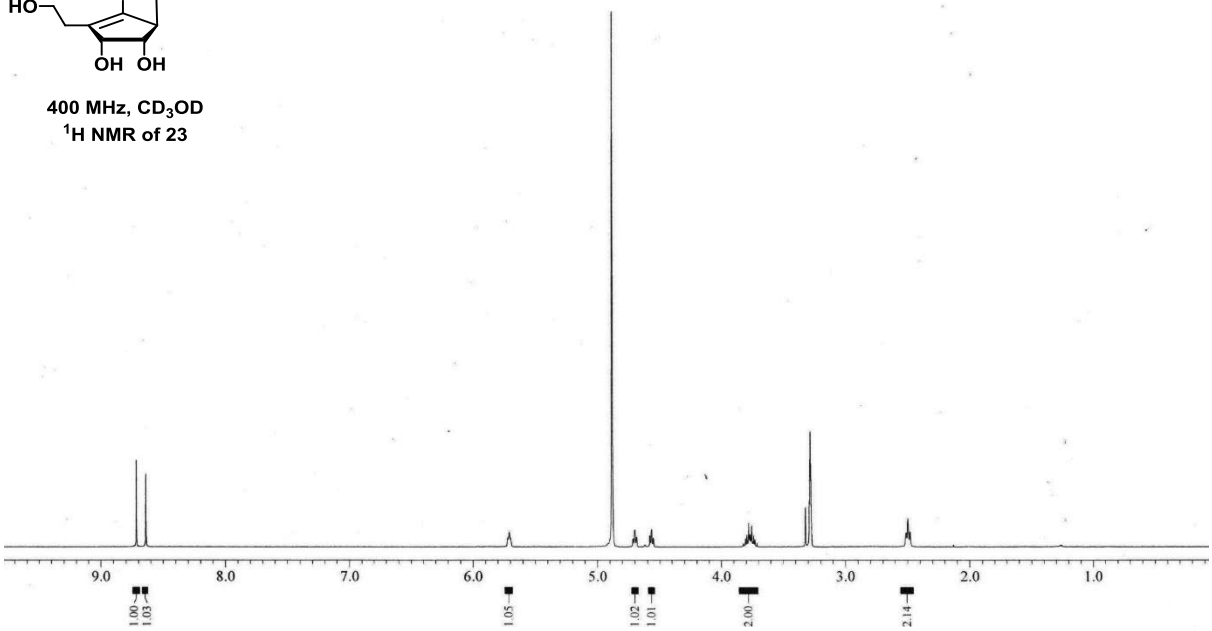

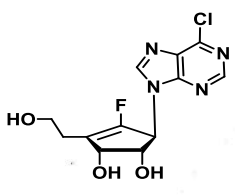

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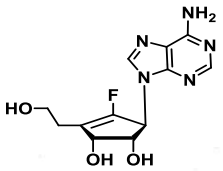

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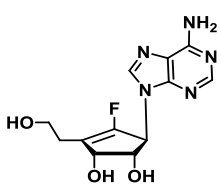

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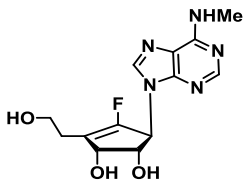

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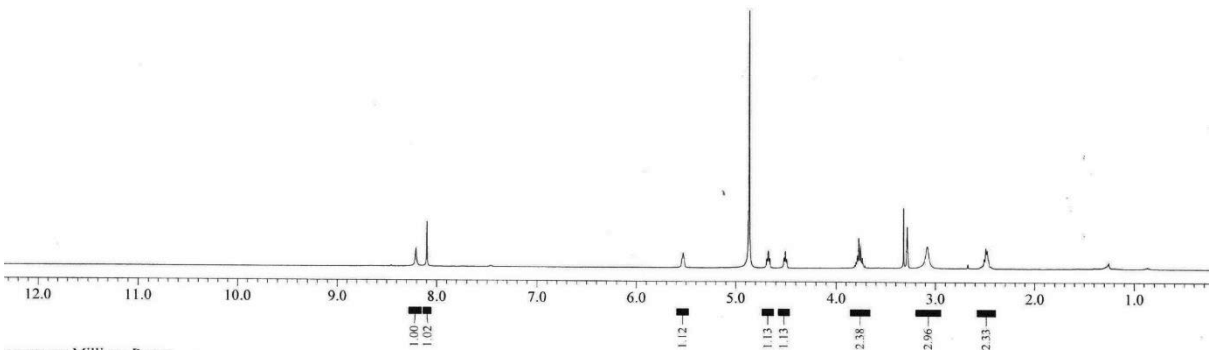

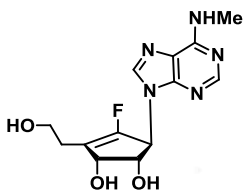

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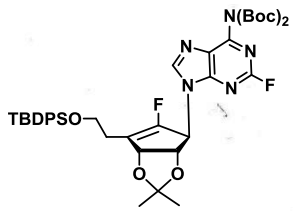

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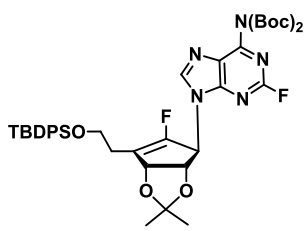
^1H NMR of 24



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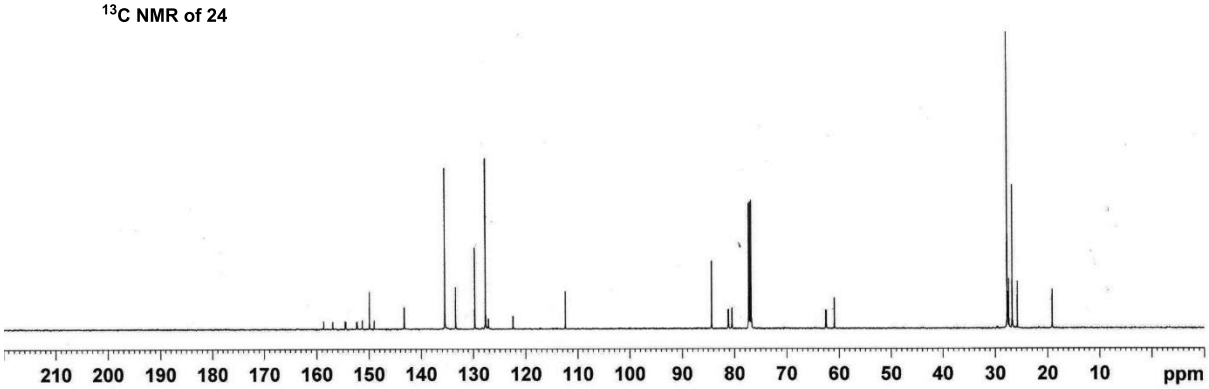

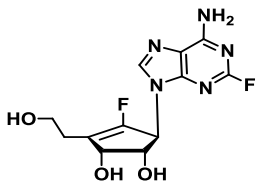

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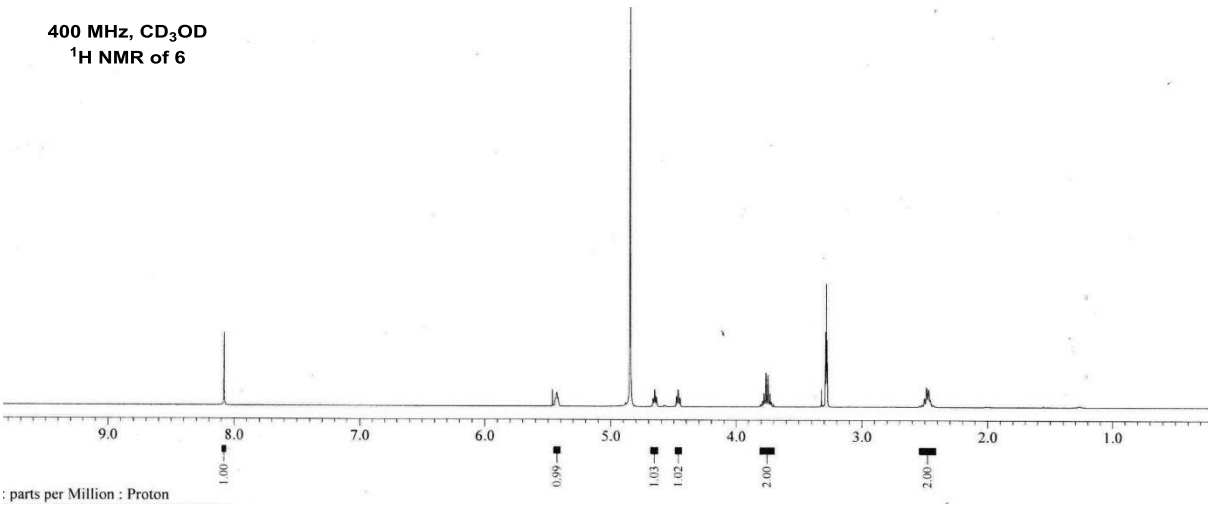

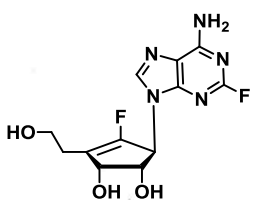

100 MHz, CD_3OD
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국문 초록

박테리아에서 유래한 천연물 neplanocin A (1)은 탄소 골격을 갖는 변형핵산으로, *S*-adenosylhomocysteine (SAH) hydrolase를 저해하여 항바이러스 효과를 보인다. 하지만 이 물질은 adenosine kinase에 의해 5 번 위치의 알코올기가 인산화 되면서 세포 독성을 나타내기 때문에 의약품으로써의 사용에 한계가 있었다.

본 연구의 목적은 neplanocin A의 독성은 줄이고 활성을 증가시킨 새로운 변형핵산 유도체의 도출 및 합성이다. 이를 위해, 5 번 위치에 탄소 원자를 추가하여 인산화를 피하고자 하였으며 6 번 위치의 수소 원자를 생물학적 동등기인 불소 원자로 치환하여 활성을 높이고자 하였다. 또한, 팔라듐 촉매 이성질화 반응을 사용하는 새로운 합성 경로를 통해 효과적인 합성이 가능하였다.

최종 물질들은 팔라듐 촉매 이성질화 반응, 입체 선택적 불소화 반응을 주요 반응으로 합성했다. 합성한 물질들을 SAH hydrolase와 치쿤구니야 바이러스를 포함한 다양한 RNA 바이러스에 대해 생물학적 활성을 측정한 결과, homo-fluoroneplanocin A (4)이 강력하게 SAH hydrolase를 저해(IC_{50} = 0.91 μM)하였으며, 우수한 치군구니야 바이러스 억제 활성과(EC_{50} = 0.18 μM) 낮은 세포독성(CC50 > 250 μM)을 보였다. Selectivity index는 1300이상으로 높은 선택성을 나타냈으며 다양한 초기 약물성 실험 결과 우수한 약물성을 확인하였다.

결론적으로, 본 연구를 통해 도출된 homo-fluoroneplanocin A (4)은 치쿤구니아 바이러스에 높은 활성과 낮은 독성을 보일 뿐만 아니라 우수한 약물성을 갖는 물질로써 새로운 항바이러스 치료제로 개발될 전도유망한 물질이다.

주요어 : 항바이러스, 네플라노신, 변형핵산, 플루오르화 반응, 팔라듐 촉매, 치쿤구니야 바이러스

학번 : 2017 – 22729

감사의 글

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규동 박ㅅ..아니 교수님, 새로운 시작을 진심으로 축하드리고 항상 저희 학생들이 보고 배울 수 있는 좋은 귀감이 되어주셔서 감사드립니다. 제 이웃 후드에서 따듯한 분위기 만들어주시는 진하 박사님, 몸 조리 잘하시고 앞으로 좋은 소식이 반드시 많을 걸 알기에 편한 마음으로 멀리서 응원하도록 하겠습니다. 지성이형, 그 동안 고생 많으셨고, 어디에서든 더 밝은 세상을 경험하실 수 있길 바래요. 제 롤 모델 홍래형, 형을 만난 건 정말 저한테 큰 행운이었던 거 같아요. 항상 감사드리고 앞으로도 오래오래 보면서 롤 모델 역할 좀 계속 부탁드리겠습니다. 새로운 권력 영음이형, 멋진 방장이 되실 거 같아요. 기수 금방 돌아올거라 믿는다. 학교를 잘 부탁할께. 혜진, 지원 누나도 하는 일 다 잘 되길 빌어요. 항상 단호하게 나를 거절하는 기배, 실험실의 궂은 일 다 맡아서 해주시는 세환이형, 돈까스 좋아하는 홍석이 소리질러, 실험실 소란과 웃음의 중심 민재까지, 좋은 후배들 덕분에 소중하게 간직하는 추억이 많은 점 정말 감사하고 있습니다. 앞으로 들어올 후배들에게도 멋진 선배의 모습 보여줘서 좋은 분위기 이어 나갔으면 좋겠습니다. Dr. dnyandev, it was a great pleasure working with you. I was grateful to have such a friend and a teacher who knows me so well and comforts me everytime I'm in need. You are a great researcher and you have my respect. My good friend Karishma, now that I'm leaving, our lab needs someone else to lead the fashion trends among the members and I think it should be you. Please remember the momentary moment and that karma has its way. Dr. Pramod, thanks for every advice you have given. It helped me a lot in many ways and I believe it will also do so in the future. Good luck with the company work. 마지막으로, 학교 생활을 하는 동안 불안하고 지칠 때마다 따듯하고 소중한 버팀목이 되어준 소라에게 고마운 마음을 전하며 글을 마무리 합니다. 너무 늦기 전에 다시 뵙도록 하겠습니다. 감사합니다.