Synthesis, Characterization and X-ray Crystal Structure of 2',3'-Dideoxy-6'-fluorocarbocyclic Nucleoside Analogue

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A novel 2',3'-dideoxy-6'-fluorocarbocyclic nucleoside analogue (**1**) has been synthesized *via* the critical Mitsunobu reaction of α -fluoroalcohol (**2**) with 6-chloropurine in the presence of triphenylphosphine and diethyl azodicarboxylate. Nucleoside analogue (**1**) was fully characterized by IR, ¹H (¹⁹F, ¹³C) NMR and MS spectroscopy. In addition, the molecular structure of nucleoside analogue **1** was established by X-ray crystallography. The crystal of compound **1** crystallizes in monoclinic, space group Pna2₁ with $a = 6.2705(7)$, $b = 7.9183(8)$, $c = 24.348(2)$ Å, $V = 1204.3(2)$ Å³, $Z = 2$, $C_{26}H_{26}N_5O_2F$, $M_r = 459.52$, $D_c = 1.267$ g/cm³, $F(000) = 484$. The final $R = 0.0376$ and $wR = 0.0777$ for 6645 observed reflections with $I > 2\sigma(I)$ and $R = 0.0542$ and $wR = 0.0827$ for all data. From the analysis of the crystal structure, it was found that C(1)-F(1)···H(7B)-C(7)^{sp3} contacted in a distance of 2.655 Å in spite of the fact that the C-F was a poor hydrogen-bond acceptor. Moreover, the short contact also existed in N(2)···H(3)-C(3)^{sp2} with the length of 2.726 Å in which C(3)^{sp2}-H(3) worked as an unusual hydrogen-bond donor, which showed significant difference from the traditional N···H-X hydrogen-bond interaction.

Keywords: Fluorine, Carbocyclic nucleoside, Crystal structure, Hydrogen bond, Electrostatic interaction.

INTRODUCTION

Organofluorine compounds have found widespread applications in medicinal chemistry, bioorganic chemistry and pharmaceutical industries since the discovery of the early synthetic antineoplastic agent 5-fluorouracil¹⁻⁷. Now over 150 fluorinated drugs have come to the market and make up 20-25 % of all the drugs in the pharmaceutical pipeline². The incorporation of fluorine atom into a drug allows simultaneous modulation of metabolic stability, bioavailability and protein-ligand interactions due to its small size, high electronegativity and low polarizability^{1,3}. Despite the great progress and success in fluorine substitution for drugs hunting, the understanding of the relationship between the structures of fluorinated compounds and bioactivities is still very empirical and not clear enough⁸. In particular, how to interpret the fluorine effects on protein-ligand binding affinity and selectivity at the molecular level confronts considerable challenges⁸. It is evident that structural information is critical for elucidating the contributions of fluorine to bioactivity potency⁶⁻⁸. Considering our continuing conformational studies for potentially bioactive fluorinated nucleoside analogues⁹⁻¹⁰, herein we report the X-ray structure of a novel 2',3'-dideoxy-6'-fluorocarbocyclic

nucleoside analogue **1** and take systematic analysis of the crystal data in order to obtain a deeper understanding of the fluorine influences on the conformation of carbocyclic nucleoside.

EXPERIMENTAL

All reactions were carried out using standard Schlenk and vacuum-line techniques under N₂ atmosphere. Solvent THF was distilled from sodium and benzophenone. Triphenylphosphine (Ph₃P) and diethyl azodicarboxylate (DEAD) was commercially available and used as received. IR spectra were recorded at room temperature on a Bruker Vector 22 infrared spectrophotometer. ¹H NMR was recorded on a Bruker AM-300 spectrometer. ¹⁹F NMR was recorded on a Bruker AM-300 spectrometer (CCl₄ as outside standard and low field is positive). ¹³C NMR was recorded on a Bruker AM-400 spectrometer. Chemical shifts (δ) are reported in parts per million and coupling constants (J) are in hertz. Optical rotations were measured using a PerkinElmer 241 polarimeter. Crystallographic data were analyzed with Rigaku FCR Diffractometer. Melting points were determined on a SGW X-4 microscopic melting point apparatus and were uncorrected.

Synthetic procedure

Step-1: To a mixture of α -fluoroalcohol (**2**)¹⁰ (0.069 g, 0.204 mmol), 6-chloropurine (0.064 g, 0.416 mmol) and PPh₃ (0.142 g, 0.541 mmol) in dry THF (2 mL) was added diethyl azodicarboxylate (0.095 g, 0.546 mmol) slowly at 0 °C. Then the reaction mixture was warmed to room temperature and stirred overnight. The solvent was removed *in vacuo* and the residue was purified by flash chromatography (petroleum ether/ethyl acetate = 3:1) on silica gel to give compound **3** as a pale yellow oil (0.047 g, 48 % yield). $[\alpha]_D^{25} = -42.4^\circ$ (c 0.75, CHCl₃); IR (KBr, $\nu_{\max}$, cm⁻¹): 3064, 2864, 1776, 1699, 1591, 1561, 1402, 1336, 1200, 1102; ¹H NMR (300 MHz, CDCl₃, TMS) δ ppm: 8.79 (s, 1H), 8.05 (d, $J = 2.4$ Hz, 1H), 7.40-7.31 (m, 10H), 6.22 (d, $J = 5.7$ Hz, 1H), 6.02 (d, $J = 17.7$ Hz, 1H), 5.95 (d, $J = 5.7$ Hz, 1H), 5.07 (dd, $J = 52.8$ Hz, 5.4 Hz, 1H), 4.78-4.54 (m, 4H), 3.91 (dd, $J = 9.6$ Hz, 4.5 Hz, 1H), 3.69-3.58 (m, 2H), 3.40 (d, $J = 27.3$ Hz, 1H); ¹³C NMR (100.7 MHz, CDCl₃) δ ppm: 152.1, 151.9, 150.9, 144.9, 137.7, 137.6, 135.2, 131.5, 128.7, 128.6, 128.3, 128.2, 128.0, 127.8, 93.3 (d, $J = 190.5$ Hz), 73.7, 72.4, 70.2, 60.8 (d, $J = 16.9$ Hz), 54.6 (d, $J = 21.9$ Hz); ¹⁹F NMR (282 MHz, CDCl₃) δ ppm: -188.3 (ddd, $J = 44.0$ Hz, 25.4 Hz, 18.0 Hz, 1F); MS (ESI) m/z 479 (M + H)⁺, 501 (M + Na)⁺; HRMS Calcd for C₂₆H₂₅N₄O₂Cl: 479.1650; Found: 479.1645.

Step-2: Compound **3** (0.050 g, 0.105 mmol) was dissolved in NH₃/MeOH (2 mL) in a sealed tube. The mixture was heated to 80 °C and stirred for 12 h. The solvent was then removed *in vacuo* and the residue was purified by flash chromatography (CH₂Cl₂/MeOH = 20:1) on silica gel to give compound **1** as a white solid (0.041 g, 86 % yield). m.p.: 193 °C; $[\alpha]_D^{25} = -25.5^\circ$ (c 1.60, CHCl₃); IR (KBr, $\nu_{\max}$, cm⁻¹): 3311, 2922, 2851, 1647, 1597, 1473, 1096, 698; ¹H NMR (300 MHz, CDCl₃, TMS) δ ppm: 8.39 (s, 1H), 7.74 (s, 1H), 7.39-7.35 (m, 10H), 6.19 (d, $J = 5.1$ Hz, 1H), 5.97-5.92 (m, 2H), 5.78 (s, 2H), 5.07 (dd, $J = 54.0$ Hz, 5.7 Hz, 1H), 4.76-4.52 (m, 4H), 3.85 (dd, $J = 10.2$ Hz, 5.1 Hz, 1H), 3.67-3.59 (m, 2H), 3.36 (d, $J = 24.0$ Hz, 1H); ¹³C NMR (100.7 MHz, CDCl₃) δ ppm: 155.4, 153.0, 140.2 (d, $J = 5.8$ Hz), 137.7, 137.7, 134.7, 128.7, 128.6, 128.5, 128.3, 128.0, 127.9, 127.8, 93.2 (d, $J = 190.2$ Hz), 73.6, 72.5, 70.4, 60.0 (d, $J = 15.8$ Hz), 54.4 (d, $J = 22.4$ Hz), 41.0; ¹⁹F NMR (282 MHz, CDCl₃) δ ppm: -190.0 (ddd, $J = 44.0$ Hz, 25.4 Hz, 18.0 Hz, 1F); MS (ESI) m/z 460 (M + H)⁺, 482 (M + Na)⁺; HRMS Calcd for C₂₆H₂₇N₅O₂F: 460.2149; Found: 460.2143.

Determination of crystal structure: A white single crystal of 2',3'-dideoxy-6'-fluorocarbocyclic nucleoside (**1**) for X-ray diffraction analysis was grown by the slow evaporation of methanol solutions at room temperature. The crystal of compound **1** with dimensions of 0.369 × 0.311 × 0.079 mm was mounted on a Rigaku RAXIS-RAPID diffractometer equipped with a graphite-monochromated MoK α radiation

($\lambda = 0.71073$ Å) by using an ω scan mode at 293(2) K in the range of $1.68^\circ = \theta = 26^\circ$. The crystal belongs to monoclinic system with space group P21/n and crystal parameters of $a = 6.2705(7)$, $b = 7.9183(8)$, $c = 24.348(2)$ Å, $\alpha = 90$, $\beta = 95.013(2)$, $\gamma = 90^\circ$, $V = 1204.3(2)$ Å³, $D_c = 1.267$ g/cm³. The absorption coefficient $\mu = 0.088$ mm⁻¹ and $Z = 2$. Absorption correction was performed by the CRYSTALCLEAR program¹¹. The structure was solved by direct methods using the SHELXS-97 program¹² and refined by full-matrix least-squares techniques on F² data using SHELXL-97¹³. The empirical absorption corrections were applied to all intensity data. All the hydrogen atoms were located by using the geometric method, with $d(C-H) = 0.95$ - 0.98 Å and $U_{iso}(H) = 1.2$ Ueq(C) or 1.5 Ueq (Cmethyl). The final $R = 0.0376$ and $wR = 0.0777$ for 6645 observed reflections with $I > 2\sigma(I)$ and $R = 0.0542$ and $wR = 0.0827$ for all data.

RESULTS AND DISCUSSION

The 2',3'-dideoxy-6'-fluorocarbocyclic nucleoside **1** could be prepared by two steps from α -fluoroalcohol (**2**)¹⁰. The Mitsunobu reaction of α -fluoroalcohol (**2**) with 6-chloropurine was chosen for introducing the base to the carbocyclic sugar ring¹⁴. The coupling of alcohol **2** with 6-chloropurine (2 equiv) in the presence of PPh₃ (2.6 equiv) and diethyl azodicarboxylate (2.6 equiv) afforded compound **3** with the inversion of C(2) configuration in the moderate yield of 48 % (**Scheme-I**). Following by the replacement of 6-chlorine atom by amino group under NH₃/MeOH condition, the target nucleoside **1** was obtained in two successive manipulations in the overall yield of 41 %.

Compound **1** was an air-stable white solid and characterized by IR, ¹H NMR, ¹³C NMR, MS spectroscopies. IR spectra of **1** displayed absorptions at 3311 ν (N-H), 2922 ν_{as} (C-H), 2851 ν_s (C-H), 1647 ν (C=C), 1597 ν (C=N), 1473 ν (C=N'), 1096 ν (C-O, C-N) cm⁻¹. The ¹H NMR spectra of compound **1** exhibited a strong spin-spin coupling between H(1) and F(1) with the J^2 coupling constant of 54 Hz. The above coupling of H(1) and F(1) was confirmed again in the ¹⁹F NMR. From the analysis of the ¹³C NMR spectra, the spin-spin coupling between F(1) and C(1) also be detected in which the coupling constant reached the value of 190.2 Hz.

Subsequently, a white single crystal of 2',3'-dideoxy-6'-fluorocarbocyclic nucleoside **1** was grown by the slow evaporation of methanol solutions at room temperature and the molecular structure of compound **1** was determined by X-ray diffraction analysis. ORTEP and crystal packing diagram of **1** are shown in Figs. 1 and 2, respectively and crystallographic and refinement parameters of the title compound **1** are listed in Table-1. The selected bond lengths and angles are given in Tables 2 and 3. From ORTEP view of compound **1** (Fig. 1), we could figure out that the Mitsunobu coupling for base

Scheme-I: Preparation of 2',3'-dideoxy-6'-fluorocarbocyclic nucleoside analogue (**1**)

introduction takes place selectively at the C(2) and N(1) sites with the configuration inversion of C(2). The bond length of C(1)-F(1) is 1.401(3) Å which is in accordance with the normal C-F bond length (1.39-1.43 Å)¹⁵. However, the C(1)-H(1) and C(2)-H(2) bond lengths are 0.9800 Å which is far less than the bond length of common C^{sp3}-H bonds (1.09-1.10 Å). This sharp shortening of bond lengths can be rationally explained by Bent's rule¹⁶-Atomic *p*-character concentrates in the orbitals directed toward electronegative substituents. As C(1)^{sp3}-F(1) and C(2)^{sp3}-N(1) pull the *p*-orbital electrons from the sp³ carbon to electronegative atoms (F and N), the bonding orbitals of C(1) and C(2) become more s-character and more close to carbon nuclei. As a result, the C(1)-H(1) and C(2)-H(2) bond lengths shorten significantly in contrast with common C^{sp3}-H bonds.

Fig. 1. ORTEP view of compound **1** with 30 % probability level ellipsoids

Fig. 2. Crystal packing diagram of compound **1**

TABLE-1
CRYSTAL DATA AND STRUCTURAL
REFINEMENT FOR COMPOUND **1**

Properties	Data
Empirical formula	C ₂₆ H ₂₆ N ₅ O ₂ F
Formula weight	459.52
Crystal system	Monoclinic
Unit cell dimensions	
a (Å)	6.2705(7)
b (Å)	7.9183(8)
c (Å)	24.348(2)
Unit cell angles (°)	
α	90.00
β	95.013(2)
γ	90.00
Volume (Å ³)	1204.3(2)
Z	2
Temperature (K)	293(2)
Space group	P 21/n
Wavelength (Å)	0.71073
Calculated density (g cm ⁻³)	1.267
Absorption coefficient μ (mm ⁻¹)	0.088
F(000)	484
Crystal size (mm ³)	0.369 x 0.311 x 0.079
θ range for data collection (°)	1.68 – 26.00
Limiting indices	-7 < h < 6, -9 < k < 9, -26 < l < 30
Reflection collected	6645
Independent reflection	2544 (R _{int} = 0.0397)
Completeness to θ _{max} (%)	99.7
Data/restraints/parameters	2544/1/307
Goodness-of-fit on F ²	0.891
Final R indices [I > 2σ(I)]	R ₁ = 0.0376, wR ₂ = 0.0777
R indices (all data)	R ₁ = 0.0542, wR ₂ = 0.0827
Largest diff. peak and hole (eÅ ⁻³)	0.134 and -0.112

TABLE-2
SELECTED BOND LENGTHS (Å) FOR COMPOUND **1**

Bond	Bond length (Å)
F(1)-C(1)	1.401(3)
N(1)-C(2)	1.451(3)
C(5)-C(6)	1.523(3)
C(1)-H(1)	0.9800
C(2)-H(2)	0.9800
C(1)-C(2)	1.545(3)
C(1)-C(5)	1.530(3)
C(2)-C(3)	1.485(4)
C(4)-C(5)	1.500(4)
C(3)=C(4)	1.304(3)
C(7)-H(7A)	0.9700
C(7)-H(7B)	0.9700
C(3)-H(3)	0.9300
N(5)-H(5A)	0.8600
N(5)-H(5B)	0.8600

With the preliminary view of molecular architecture in hand, we then turn our attention to analyze the intermolecular interactions in this nucleoside analogue crystal. It is well known that the hydrogen-bonding properties of the organic compounds directly correlate to molecular recognition and pharmacological activities¹⁷. In the crystal structure of nucleoside analogue **1**, the hydrogen-bonds N(5)-H(5B)⋯N(4)#1 and N(5)-H(5A)⋯N(2)#2 are formed in networks which make

TABLE-3
SELECTED BOND ANGLES (°) FOR COMPOUND 1

Bond	Bond angles (°)
F(1)-C(1)-H(1)	111.8
F(1)-C(1)-C(5)	107.3(2)
F(1)-C(1)-C(2)	107.88(19)
N(1)-C(2)-H(2)	108.6
C(6)-C(5)-H(5)	108.0
C(5)-C(1)-C(2)	105.8(2)
C(3)-C(2)-C(1)	102.7(2)
C(4)-C(5)-C(1)	102.5(2)
C(3)-C(4)-C(5)	112.8(2)
C(4)-C(3)-C(2)	112.4(2)
O(2)-C(7)-C(6)	108.7(2)
H(7A)-C(7)-H(7B)	108.3
H(5A)-N(5)-H(5B)	120.0
C(4)-C(3)-H(3)	123.8
C(3)-C(4)-H(4)	123.6

important contributions to the topologic structure (Figs. 3 and 4). The bond length values and geometries of these hydrogen-bonds are summarized in Table-4. Both the short distance of $d(D\cdots A)$ and nearly collinear arrangement of $D-H\cdots A$ indicate that $N(5)-H(5B)\cdots N(4)\#1$ and $N(5)-H(5A)\cdots N(2)\#2$ are genuine moderate hydrogen-bonds (Table-2). Additionally, it is interesting to find out that $C(1)-F(1)\cdots H(7B)-C(7)^{sp^3}$ contacted in a distance of 2.655 Å which is within the sum of van der Waals radii of hydrogen and fluorine (2.670 Å) (Fig. 5). In view of the slightly shortening effect of contact distance *versus* van der Waals radii, $C(1)-F(1)\cdots H(7B)-C(7)^{sp^3}$ can be considered as a "weak" hydrogen bond rather than a "genuine" hydrogen bond¹⁸ which arises from the electrostatic attraction of positive charge on H(7B) and negative charge on F(1) like the reported $C-F\cdots H-C_\alpha$ (C_α carbon of carbonyl compounds or amino acids)

Fig. 3. Hydrogen-bonds in the single crystal for compound 1

Fig. 4. Hydrogen-bonding networks in crystal 1

Fig. 5. Electrostatic interactions of $C(1)-F(1)\cdots H(7B)-C(7)^{sp^3}$ and $N(2)\cdots H(3)-C(3)^{sp^2}$

interactions in Cambridge Structural Database (CSD)¹⁹⁻²⁰. Moreover, the short contact also exists in $N(2)\cdots H(3)-C(3)^{sp^2}$ with the length of 2.726 Å which also stem from the electrostatic attraction between the positive charge on H(3) and negative charge on N(2) (Fig. 5). It is evident that this $N(2)\cdots H(3)-C(3)^{sp^2}$ contact is significantly distinguished from the conventional $N\cdots H-X$ hydrogen-bonds²⁰.

Conclusion

In conclusion, we described herein the synthesis, characterization and X-ray crystal structure of 2',3'-dideoxy-6'-fluorocarbocyclic nucleoside analogue **1**. The X-ray crystal structure shows that the hydrogen-bonds $N(5)-H(5B)\cdots N(4)\#1$ and $N(5)-H(5A)\cdots N(2)\#2$ are important binding forces for the topologic structure. Two uncommon "weak" hydrogen-bonds $C(1)-F(1)\cdots H(7B)-C(7)^{sp^3}$ and $N(2)\cdots H(3)-C(3)^{sp^2}$ are also unveiled which could be interpreted as the electrostatic attraction. Further investigations of the relationship between the structural characteristics of nucleoside analogue **1** and its bioactivity are underway and the results will be reported in due course.

TABLE-4
BOND LENGTHS AND GEOMETRIES OF HYDROGEN-BONDS FOR COMPOUND 1

D-H $\cdots$ A	d(D-H) (Å)	d(H $\cdots$ A) (Å)	d(D $\cdots$ A) (Å)	$\angle DHA$
$N(5)-H(5B)\cdots N(4)\#1$	0.86	2.18	3.003(3)	158.9°
$N(5)-H(5A)\cdots N(2)\#2$	0.86	2.17	3.025(3)	170.5°

Supplementary data L: CCDC-805686 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via <http://www.ccdc.cam.ac.uk/conts/retrieving.html>, or from the Cambridge Crystallographic Data Centre, 12 Union Road Cambridge CB2 1EZ, UK (Fax: +44-1223-336033; or E-mail: deposit@ccdc.cam.ac.uk).

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