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SYNTHESIS OF PURINE MODIFIED 2′,3′-DIDEOXY-2′,3′-DIFLUORO-D-ARABINOFURANOSYL NUCLEOSIDES FROM THE UNIVERSAL CARBOHYDRATE PRECURSOR

(Communicated by Corresponding Member I. A. Mikhailopulo)

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Based on advances in the medicinal chemistry of nucleosides over the past years, synthetic nucleoside analogues have provided key medicines for treatment of different viral infections. Introduction of a fluorine atom into nucleosides may lead to a change in biological activity, lipophilicity or bioavailability [1; 2]. Unique properties of the fluorine substituent, such as small size and strong electronegativity, which can mimic either a hydrogen or a hydroxyl, may critically influence both the pharmacokinetic properties or toxicity of a drug. It has been established that fluorination of a nucleoside in the sugar moiety or heterocyclic base may alter binding of the nucleoside with enzymes involved in its metabolism and may exert influence on the stereochemistry of the pentofuranose ring of the nucleoside molecule in solution [3; 4].

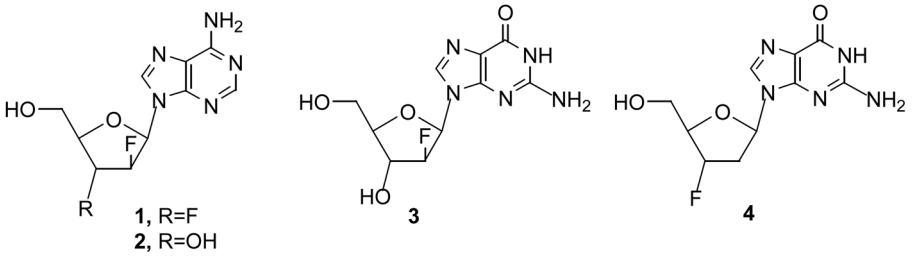
Nucleosides fluorinated at the 2′-position exhibit interesting biological properties [1; 5]. Among the series, purine nucleosides with 2′-ara-fluorine substitution are of special interest because the location of the fluorine atom in the β-orientation of the carbohydrate moiety affects phoshorylation of these analogues, provides metabolic and acidic stabilities of the glycosidic bond and therefore has an impact on the antiviral and anticancer activities of fluorinated nucleoside analogues.

In our previous investigations, we have found that 9-(2,3-dideoxy-2,3-difluoro-β-D-arabinofuranosyl) adenine (**1**) possesses potent antiviral activity against HIV-1 *in vitro* [6]. A number of purine nucleosides with 2′-fluoro-β-D-arabinofuranosyl moiety were synthesized and tested for their biological activity. Thus, 9-(2-deoxy-2-fluoro-β-D-arabinofuranosyl)adenine (**2**) have been shown to display potent anti-protosoal activity against *T. vaginalis in vitro* [7] and its guanine analogue **3** demonstrated anticancer activity against humane leukemic T-cell lines (figure) [8]. Besides, 3′-α-fluoro-2′,3′-dideoxyguanosine (**4**) showed high anti-HIV activity in MT-4 cells and at present time its valyloxy-propionyl ester prodrug is being developed for antiviral therapy of patients infected by HIV as well as hepatitis B virus [9].

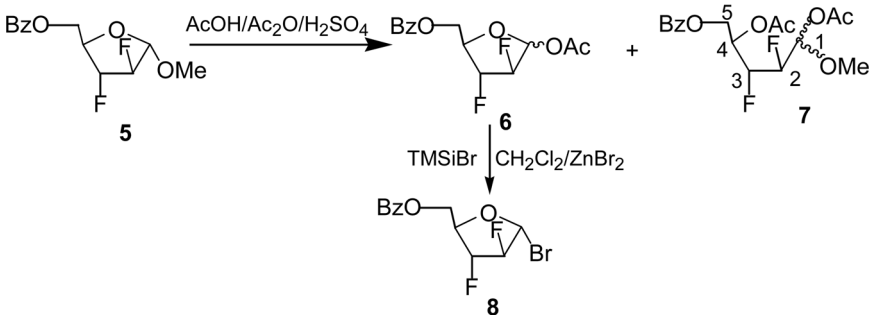
Our preceding studies on the convergent approach to the purine 2′,3′-dideoxy-2′,3′-difluoro arabinonucleosides and their anti-HIV-1 activities *in vitro* revealed that this class of nucleosides is of interest for the further elaboration and evaluation as potential antiviral agents [6]. The investigated synthetic routes to purine 2′,3′-dideoxy-2′,3′-difluoro arabinonucleosides proceed *via* the key intermediate difluoride **5**, for which different approaches were taken starting from D-xylose [6; 10]. According to these communications, 2′,3′-difluoro-β-arabinonucleosides adenine and 2-chloroadenine were obtained in low yields as a result of the glycosylation of N^6-benzoyladenine by α-methyl glycoside **5** under Vorbrüggen conditions in the presence of Lewis catalyst or anionic glycosylation of sodium salts of heterocyclic bases with bromosugar.

The aim of present work was to examine new aspects of synthetic methodology for improved construction of these nucleosides [6], synthesize novel purine 2′,3′-dideoxy-2′,3′-difluoro-arabinonucleosides analogs of known biologically active adenine and guanine fluorodeoxynucleosides **1**–**4** (figure) for evaluation of their antiviral activity and cytotoxicity. Herein, this report describes the further development of convergent approach for novel purine purine modified 2′,3′-dideoxy-2′,3′-difluoronucleosides with β-D-*arabino*-configuration by: i) optimization of reaction conditions for chemical conversions of methyl arabinoside **5** *via* acetate **6** into α-bromide **8** as the universal glycosylating agent for coupling reactions

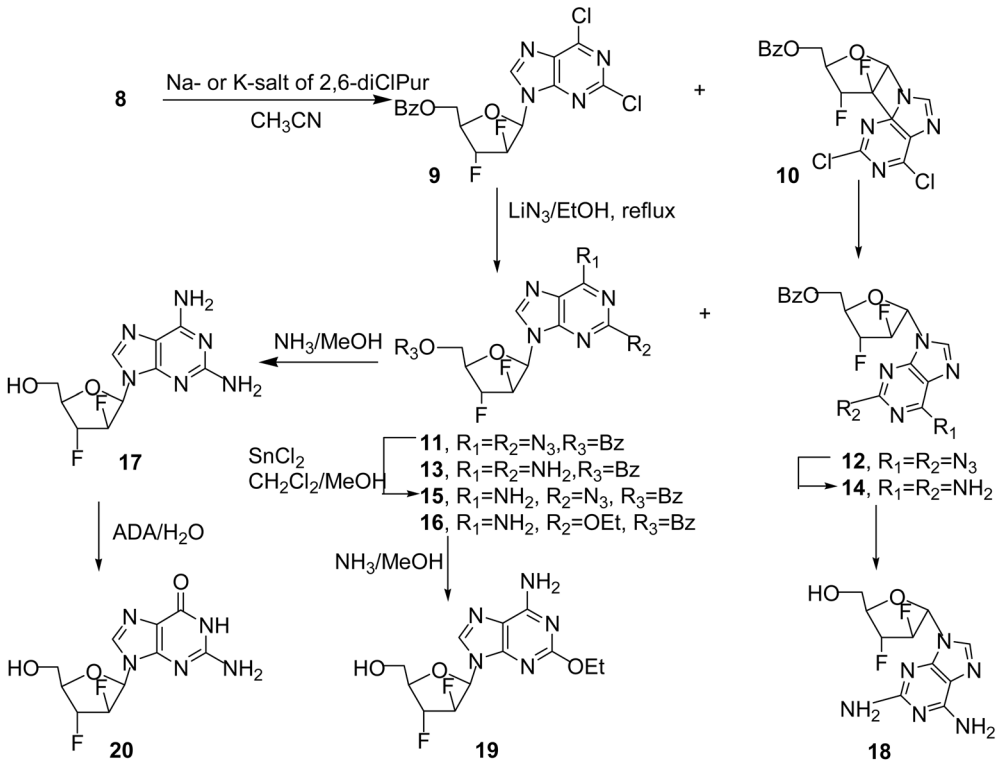
with different purine and pyrimidine bases, and ii) efficient synthesis of N^9-β-arabinosides of 2,6-dichloropurine and 2-amino-6-chloropurine as key intermediates for preparing 2,6-disubstituted and natural purine nucleosides of this library by chemical transformations of the heterocyclic base.



Biologically active fluoro-containing purine nucleosides

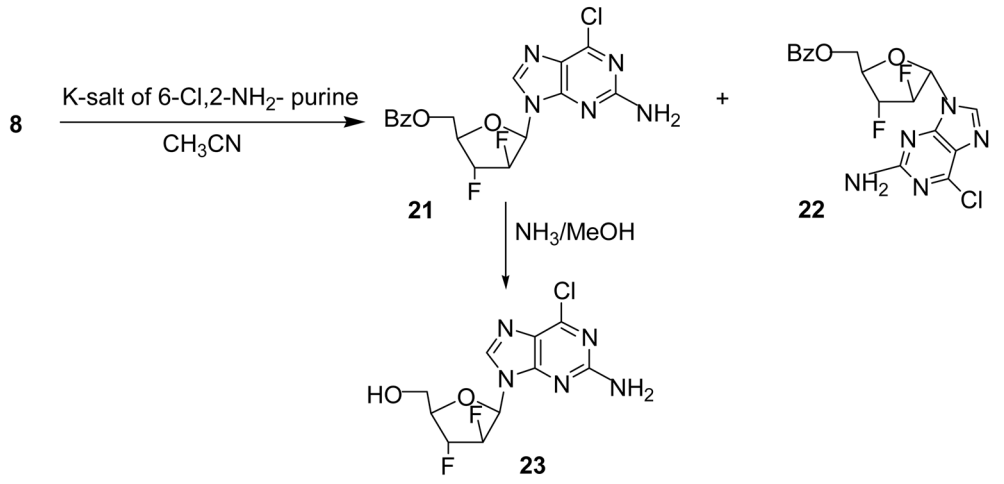


Recently, we reported that conventional acetolysis of **5** in mixture of acetic acid/acetic anhydride/H_2SO_4 gave acetates **6** (77 %) after work-up and chromatography [6] Further analysis of the mixture of products prepared under these conditions of acetolysis reaction of **5** over several experiments has enabled to identify compound **7** as a side product that was isolated by chromatography on silica gel as a mixture of 1-*R* and 1-*S* isomers according to NMR spectral data in 10–12 % yield. Such formation of acyclic byproducts of similar to compound **7**, along with common 1-O-acetyl derivatives, have previously been reported from 5-O-benzoyl derivative of β-methyl 2,3-difluororibofuranoside under acetolysis [11]. The optimized acetolysis conditions of **5** were determined by variation of the reaction temperature and time. Acetates **6** (α/β ratio ca. 3:1) were prepared in 87 % yield under conducting acetolysis at temperature range 0 °C→rt and shortening the reaction time, and only traces of **7** were detected by ^{1}H NMR analysis of the reaction products after the conventional work-up of the reaction mixture. Bromination of the acetate **6** with conventional conditions (TMSBr/$CDCl_3$) generated crude glycosyl bromide **8** (in an approximate 50 % yield) [6], which was used in a subsequent anionic *N*-glycosylation of purine bases without isolation. Herein, we describe a procedure with improved efficiency for preparation of the 1-α-bromide **8**, using TMSBr in CH_2Cl_2 in the presence of the inexpensive and easily available catalyst $ZnBr_2$ [12]. Addition of the catalyst allowed to prepare the bromide **8** from the acetate **6** under mild conditions within high yield (95 %) and employ it on next step without an additional purification. The assignment of the α-anomeric configuration of halosugar **8** was based on its ^{1}H NMR data as in the case of 1-α-bromo anomer of 3,5-di-O-benzoyl-2-deoxy-2-fluoro-D-arabinofuranose [13]. Next, the sodium salt of 2,6-dichloropurine [14] was used in the stereoselective nucleobase-anion glycosylation reaction with pure 5-O-benzoyl-2,3-dideoxy-2,3-difluoro-α-D-arabinofuranosyl bromide (**8**) and resulted in protected nucleosides **9** and **10** which were separated by silica gel column chromatography in 55 % and 13 % yields, respectively. In an effort to improve the anomer ratio of protected nucleosides in the glycosylation reaction (a ratio of β/α ~ 4 : 1), we employed potassium t-butoxide as base [15] for preparation of potassium salt of 2,6-dichloropurine and used the latter in acetonitrile in glycosylation with the bromide **8** which resulted in the formation of N^9-β-D-nucleoside **9** (73 %) along with -α-D-protected nucleoside **10** (8 %). Thus, the stereoselective glycosylation, utilizing the potassium salt, provided a higher yield of the desired β-D-nucleoside **9** along with better β/α-selectivity for the coupling reaction of 2,6-dichloropurine with the glycosylating agent **8** *versus* results obtained with the sodium salt.



Reaction of individual β- and α-protected nucleosides of 2,6-dichloropurine **9** and **10** with LiN_3 in EtOH [16] under reflux afforded 2,6-diazido derivatives **11** and **12** in 97 % yield. The reduction of azido groups in nucleosides **11** and **12** with $SnCl_2$ in a mixture of dichloromethane-methanol [16] resulted in 5′-O-benzoyl derivatives of N^9-β- and N^9-α-arabinosides **13** (87 %) and **14** (91 %). It should be noted that individual blocked β-nucleosides **15** and **16** were also isolated in 4 % yields as byproducts containing 2-azido- or 2-ethoxy group at the heterocyclic base, respectively, after nucleophilic displacement of the chlorine atoms of **9** by the azide ion in ethanol followed by reduction of 6-azido groups of intermediate N^9-β-arabinoside(s) with stannous chloride and column chromatography.

Standard debenzoylation of individual nucleosides **13** and **14** with saturated methanolic ammonia then gave pure 2′,3′-dideoxy-2′,3′-difluoronucleosides of 2,6-diaminopurine **17** and **18** in 72 % and 79 % yield, respectively. Debenzoylation of 2,6-disubstituted purine β-nucleoside **16** under the same reaction conditions gave rise to 2-amino-6-ethoxy purine analogue **19** in 73 % yield. Next, guanine 2′,3′-difluoro-β-arabinonucleoside **20** was prepared by enzymatic deamination of N^9-β-nucleoside **18** in water with calf intestine adenosine deaminase in 85 % yield after silica gel column chromatography. The α-arabinoside of 2,6-diaminopurine **19** was resistant to deamination using a similar procedure.



Finally, synthetic method for the preparation of a series of novel purine modified nucleosides **21**–**23** was investigated from difluoride **8**. The coupling of potassium salt of 2-amino-6-chloropurine with the bromo sugar **8** in acetonitrile under room temperature gave a mixture of protected N^9-β- and N^9-α-nucleosides **21** and **22** which were separated into individual compounds by column chromatography in 47 % and 4 % yields, respectively. Debenzoylation of protected β-nucleoside **21** with saturated methanolic ammonia under room temperature gave rise to 2-amino-6-chloropurine purine analogue **23** in 77 % yield. Thus, efficient synthesis of N^9-β-arabinoside of 2-amino-6-chloropurine **21** was developed as the other key intermediate to prepare 2,6-disubstituted purine nucleosides *via* stereoselective anionic glycosylation reaction of salt of purine base by the α-bromide **8** with high β/α-selectivity.

The structure of nucleosides **9**–**23** was confirmed by ^{1}H, ^{19}F and ^{13}C NMR, UV and mass spectroscopy. The assignments of the configurations of synthesized nucleosides at the anomeric centers were based upon ^{1}H and ^{13}C NMR data [6; 16; 17]. The diagnostic for the β-anomeric configuration of purine difluoro-nucleosides **9**, **11**, **13**, **15**–**16**, **17**, **19** and **20**–**21** is the long-range coupling of 1.9-3.2 Hz between the H-8 proton of heterobase to 2′-β fluorine atom *via* five bonds. The absence of such long-range couplings is characteristic of proton spectra of α-anomers **10**, **12**, **14** and **18** and the H-8 proton appeared as a singlet.

The resonance signal of the purine H-8 proton for the nucleoside of 2,6-diaminopurine **17** is observed as a doublet in its ^{1}H NMR spectrum and the magnitude of the $^5J_{H,F}$ coupling was 2.4 Hz. It should be stressed that two $^4J_{H,F}$ the long-range coupling constants of 2.0 Hz and 1.0 Hz between sugar H-1′ and H-5′ protons, and F-3′ substituent, respectively, were exhibited also in the spectrum of difluoride **17** due to the W-arrangements between these protons and fluorine atom at C-3′. The magnitudes of $J_{C\text{-}1',F\text{-}2'}$ coupling constants for β- and α-anomers of difluoronucleosides **9** and **10** in their ^{13}C NMR spectra is also diagnostic for the stereochemistry of purine analogues at the anomeric centre as in the case of purine 2′-deoxy-2′-fluoro-β-D-arabinofuranosyl nucleosides [17].

^{19}F NMR data of nucleosides **9**–**23** is indicative of the assigned structures of synthesized compounds, the fluorine resonances of sugars and nucleosides with two fluorine atoms are found as complex multiplets in their ^{19} F NMR spectra.

In summary, an efficient approach to novel purine 2′,3′-difluoro arabinonucleosides was developed *via* 1-α-bromosugar, the universal sugar precursor for the glycosylation reaction of different heterocyclic bases, and N^9-β-D-protected arabinosides of 2,6-dichloropurine or 2-amino-6-chloropurine, key intermediates for the synthesis of 2,6-disubstituted purine nucleosides with 2′,3′-difluoro-β-D-arabinofuranosyl moiety. The elaborated method has enabled us to enhance a small library of this interesting class of nucleoside analogs for biological assays.

The UV spectra were recorded on Specord Cary 100 (Varian). ^{1}H, ^{13}C and ^{19}F NMR Spectra were recorded in $CDCl_3$, CD_3OD and (D_6)-DMSO with Bruker Avance-500-DRX spectrometer at 500.13, 126.76 and 470.593 MHz, respectively. NMR (δ values) are in ppm downfield from internal $SiMe_4$ (^{1}H, ^{13}C) or external $CFCl_3$ (^{19}F). *J* values are reported in Hz. Mass spectra were recorded on a chromatomass spectrometer with HPLC-Accela and LCQ Fleet mass detector (Thermo electron corporation, USA). Selected spectral data of prepared sugars and nucleosides are presented below.

A mixture of acyclic compounds 7a and 7b. ^{1}H NMR ($CDCl_3$): (ratio of compounds **7a** and **7b** ca. 1.0 : 0.43), 7.45–8.05 (m, ArH), 6.06 (dd, 1H, H-1a, $J_{1,F\text{-}2}$ = 5.2, $J_{1,2}$ = 7.37), 5.99 (t, 0.43H, H-1b, $J_{1,F\text{-}2}$ = 6.4, $J_{1,2}$ = 6.4), 5.48 (m, H-4a and H-4b), 5.21 (dm, H-2b), 4.97 (ddd, H-3a), 4.80–4.86 (m, H-5a and H-5b), 4.65 (dm, H-3b), 4.50 (ddd, H-2a), 4.44–4.48 (m, H-5′a and H-5′b), 3.58 (s, OCH_3 b), 3.54 (s, OCH_3 a), 2.17 (s, OAc a), 2.15 (s, OAc b), 2.11 (s, OAc b), 2.10 (s, OAc a).

C^{13} ($CDCl_3$): 170.73, 169.89, 169.4, 166.18 (4s, 2C=O, Ac and 2C=O, Bz), 133.4, 129.9, 129.8, 128.8, 129.7, 128.6 (s, $2C_6H_5CO$-), 94.4 (dd, $J_{C\text{-}1,F\text{-}2}$ = 30.1, $J_{C\text{-}1,F\text{-}3}$ = 6.3, C-1b), 94.3 (dd, $J_{C\text{-}1,F\text{-}2}$ = 29.2, $J_{C\text{-}1,F\text{-}3}$ = 6.9, C-1a), 88.74 (dd, $J_{C\text{-}2,F\text{-}2}$ = 185.5, $J_{C\text{-}2,F\text{-}3}$ = 16.9, C-2b), 88.33 (dd, $J_{C\text{-}2,F\text{-}2}$ = 183.5, $J_{C\text{-}2,F\text{-}3}$ = 16.0, C-2a), 87.5 (dd, $J_{C\text{-}3,F\text{-}3}$ = 181.5, $J_{C\text{-}3,F\text{-}2}$ = 17.9, C-3a and C-3b), 68.1 (dd, C-4b), 67.9 (dd, C-4a), 62.0 (s, C-5a and C-5b), 58.63 (s, OCH_3 b), 58.0 (s, OCH_3 a), 21.06 (s, CH_3CO), 21.02 (s, CH_3CO), 20.9 (s, CH_3CO). HPLC/ESI-MS, m/z 396 $[M\text{-}H + Na]^+$, 354 $[M\text{-}HF]^+$. ^{19}F NMR ($CDCl_3$): –214.07 (F-2, dddd), –214.4 (F-3, m), (F-3, m, $J_{F\text{-}2,F\text{-}3}$ = 9.3) (compound **7a**), –212.74 (F-2, dddd), –213.29 (F-3, m, $J_{F\text{-}2,F\text{-}3}$ = 6.4) (compound **7b**).

5-O-Benzoyl-2,3-dideoxy-2,3-difluoro-α-D-arabinofuranosyl bromide (8). ^{1}H NMR ($CDCl_3$): 7.46-8.04 (m, 5H, Ar-H), 6.55 (d, 1H, $J_{1,2}$ < 1.0, $J_{1,F\text{-}2}$ = 12.64, H-1), 5.57 (dd, 1H, $J_{2,3}$ < 1.0, $J_{2,F\text{-}2}$ = 49.65,

$J_{2,F-3}$ = 10.68, H-2), 5.21 (ddd, 1H, $J_{3,4}$ = 3.7, $J_{3,F-2}$ = 19.1, $J_{3,F}$ = 51.4, H-3), 4.85 (ddt, 1H, $J_{4,F}$ = 20.2, H-4), 4.67 (dd, 1H, $J_{5,4}$ = 3.8, $J_{5,5'}$ = 12.8, H-5), 4.62 (dd, 1H, $J_{5,4}$ = 4.4, H-5′). ^{19}F NMR ($CDCl_3$): –170.98 (dm, F-2, $J_{F-2,F-3}$ = 8.5), –188.31 (dt, F-3).

2,6-Dichloro-9-(5-O-benzoyl-2,3-dideoxy-2,3-difluoro-β-D-arabinofuranosyl)purine (9) and its α-anomer (10). Compound **9**. ^{1}H NMR ($CDCl_3$): 8.32 (d, 1H, $J_{H-8,F-2'}$ = 2.6, H-8), 7.46-8.07 (3m, 5H, Bz), 6.60 (dt, 1H, $J_{1',2'}$ = 2.56, $J_{1',F-2'}$ = 21.8, $J_{1',F-3'}$ = 2.56, H-1′), 5.46 (br. dd, 1H, $J_{2',3'}$ < 1.0, $J_{2',F-2'}$ = 50.03, $J_{2',F-3'}$ = 11.94, H-2′), 5.35 (ddd, 1H, $J_{3',4'}$ = 2.38, $J_{3',F-2'}$ = 9.2, $J_{3',F'}$ = 49.51, H-3′), 4.74 (dm, 1H, H-4′), 4.65–4.71 (m, 2H, H-5′and H-5″). C^{13} NMR ($CDCl_3$): 166.17 (s, C=O, Bz), 128.81–133.85 (C_6H_5CO- and C-5), 153.27, 152,56, 152.35 (C-6, C-2, C-4), 144.88 (d, $J_{C-8,F-2'}$ = 5.6, C-8), 129.18 (C-5), 93.64 (dd, $J_{C-2',F-2'}$ = 184.4, $J_{C-2',F-3'}$ = 30.2, C-2′), 91.57 (dd, $J_{C-3',F-2'}$ = 30.7, $J_{C-3',F-3'}$ = 192.3, C-3′), 83.42 (d, $J_{C-4',F-3'}$ = 27.3, C-4′), 80.8 (d, $J_{C-1',F-2'}$ = 16.71, C-1′), 62.46 (d,$J_{C-5',F-3'}$ = 8.71, C-5′). UV (EtOH) λ_{max}, nm (ε): 231 (7300), 274 (5660). ^{19}F NMR ($CDCl_3$): –188.77 (dm, F-2′ or F-3′), –203.62 (m, F-3′ or F-2′). HPLC/APCI-MS: m/z 429 and 431, C^{35}/C^{37} ratio ~ 3 : 1, $[M]^+$, 430 and 432 $[M+1]^+$.

Compound **10**. ^{1}H NMR ($CDCl_3$): 8.24 (s, 1H, H-8), 7.47–8.08 (3m, 5H, Bz), 6.55 (d, 1H, $J_{1',2'}$ < 1.0, $J_{1',F-2'}$ = 15.0, H-1′), 5.84 (dd, 1H, $J_{2',3'}$ = 1.8, $J_{2',F-2'}$ = 48.14, $J_{2',F-3'}$ = 11.22, H-2′), 5.47 (ddt, 1H, $J_{3',4'}$ = 1.7, $J_{3',F-2'}$ = 12.6, $J_{3',F'}$ = 50.12, H-3′), 4.47 (dt, 1H, H-4′), 4.64 (dd, 1H, H-5′), 4.57 (dd, 1H, H-5″). C^{13} NMR ($CDCl_3$): 166.1 (s, C=O, Bz), 128.13–133.78 (C_6H_5CO- and C-5), 153.71, 152,58, 152.29 (C-6, C-2, C-4), 143.35 (d, $J_{C-8,F-2'}$ = 3.8, C-8), 96.09 (dd, $J_{C-2',F-2'}$ = 188.9, $J_{C-2',F-3'}$ = 30.92, C-2′), 94.64 (dd, $J_{C-3',F-2'}$ = 29.39, $J_{C-3',F-3'}$ = 183.9, C-3′), 84.23 (d, $J_{C-4',F-3'}$ = 26.0, C-4′), 88.92 (d, $J_{C-1',F-2'}$ = 36.25, C-1′), 62.4 (d, $J_{C-5',F-3'}$ = 7.65, C-5′). UV (EtOH): λ_{max}, nm (ε): 231 (7350), 274 (5680). ^{19}F NMR ($CDCl_3$): –190.48 (m, F-3′), –191.43 (m, F-2). HPLC/APCI-MS: m/z 429 and 431, C^{35}/C^{37} ratio ~ 3 : 1, $[M]^+$.

2,6-Diazido-9-(5-O-benzoyl-2,3-dideoxy-2,3-difluoro-β-D-arabinofuranosyl)purine (11) and its α-anomer (12). Compound **11**. ^{1}H NMR ($CDCl_3$): 8.10 (d, 1H, $J_{H-8,F-2'}$ = 1.93, H-8), 7.44–8.06 (3m, 5H, Bz), 6.53 (dt, 1H, $J_{1',2'}$ = 2.56, $J_{1',F-2'}$ = 22.1, $J_{1',F-3'}$ = 2.56, H-1′), 5.44 (dd, 1H, $J_{3',4'}$ < 1.0, $J_{3',F-2'}$ = 12.42, $J_{3',F'}$ = 50.44, H-3′), 5.31 (ddd, 1H, $J_{2',3'}$ < 1.0, $J_{2',F-2'}$ = 49.51, $J_{2',F-3'}$ = 9.46, H-2′), 4.62 (dm, 1H, H-4′), 4.69 (dd, 1H, H-5′), 4.65 (dd, 1H, H-5″). UV (EtOH) λ_{max}, nm (ε): 232 (7300), 270 (2240), 297 (1120). ^{19}F NMR ($CDCl_3$): –188.90 (m, F-2), –203.74 (m, F-3). HPLC/APCI-MS: m/z 443 $[M+H]^+$.

Compound **12**. ^{1}H NMR ($CDCl_3$): 8.07 (s, 1H, H-8), 7.46–8.12 (3m, 5H, Bz), 6.44 (br.d, 1H, $J_{1',2'}$ < 1.0, $J_{1',F-2'}$ = 15.71, H-1′), 5.88 (dd, 1H, $J_{2',F-2'}$ = 48.41, $J_{2',F-3'}$ = 12.3, H-2′), 5.43 (ddt, 1H, $J_{3',4'}$ = 2.9, $J_{3',F-2'}$ = 13.4, $J_{3',F-3'}$ = 50.0, H-3′), 4.62 (dm, 1H, H-4′), 4.61 (dd, 1H, H-5′), 4.57 (dd, 1H, H-5″). UV (EtOH) λ_{max}, nm (ε): 228 (7300), 271 (2250), 298 (1130). ^{19}F NMR ($CDCl_3$): –191.47 (dm, F-2), –191.85 (m, F-3). HPLC/APCI-MS: m/z 443 $[M+H]^+$.

2,6-Diamino-9-(5-O-benzoyl-2,3-dideoxy-2,3-difluoro-β-D-arabinofuranosyl)purine (13) and its α-anomer (14). Compound **13.** ^{1}H NMR ($CDCl_3$): 7.73 (d, 1H, $J_{H-8,F-2'}$ = 3.2, H-8), 7.46–8.05 (3m, 5H, Bz), 6.37 (dt, 1H, $J_{1',2'}$ = $J_{1',F-3'}$ = 3.2, $J_{1',F-2'}$ = 23.02, H-1′), 5.67 (br.s, 2H, NH_2), 5.41 (ddd, 1H, $J_{3',4'}$ = 1.3, $J_{3',F-2'}$ = 12.9, $J_{3',F'}$ = 49.95, H-3′), 5.26 (ddd, 1H, $J_{2',3'}$ < 1.0, $J_{2',F-2'}$ = 49.46, $J_{2',F-3'}$ = 9.71, H-2′), 4.85 (br.s, 2H, NH_2), 4.66 (dd, 1H, H-5′), 4.62 (dd, 1H, H-5″), 4.56 (ddt, 1H, H-4′). UV (EtOH) λ_{max}, nm (ε): 235 (7350), 256 (6690), 277 (6180). ^{19}F NMR ($CDCl_3$): –188.85 (m, F-2′ or F-3′), –203.75 (m, F-3′ or F-2′). HPLC/APCI-MS: m/z 391 $[M+H]^+$.

Compound **14**. ^{1}H NMR ($CDCl_3$): 7.63 (s, 1H, H-8), 7.42–8.07 (3m, 5H, Bz), 6.26 (dd, 1H, $J_{1',2'}$ < 1.0, $J_{1',F-2'}$ = 16.5, $J_{1',F-3'}$ = 1.56, H-1′), 6.01 (ddt, 1H, $J_{2',3'}$ = 1.9, $J_{2',F-2'}$ = 49.7, $J_{2',F-3'}$ = 13.1, H-2′), 5.44 (br.s, 2H, NH_2), 5.38 (ddd, 1H, $J_{3',4'}$ = 1.3, $J_{3',F-2'}$ = 16.0, $J_{3',F'}$ n.d., H-3′), 5.01 (dq, 1H, H-4′), 4.77 (br.s, 2H, NH_2), 4.60 (dd, 1H, H-5′), 4.57 (dd, 1H, H-5″). UV (EtOH) λ_{max}, nm (ε): 235 (7350), 256 (6600), 277 (6150). ^{19}F NMR ($CDCl_3$): –191.72 (m, F-2′ or F-3′), –194.23 (m, F-3′ or F-2′). HPLC/APCI-MS: m/z 391 $[M+H]^+$.

2-Azido-6-amino-9-(5-O-benzoyl-2,3-dideoxy-2,3-difluoro-β-D-arabinofuranosyl) purine (15). ^{1}H NMR ($CDCl_3$): 7.92 (d, 1H, $J_{H-8,F-2'}$ = 3.1, H-8), 7.46–8.08 (3m, 5H, Bz), 6.48 (dt, 1H, $J_{1',2'}$ = $J_{1',F-3'}$ = 2.56, $J_{1',F-2'}$ = 22.7, H-1′), 5.73 (br.s, 2H, NH_2), 5.44 (dd, 1H, $J_{3',4'}$ ~ 1.6, $J_{3',F-2'}$ = 12.6, $J_{3',F'}$ = 49.7, H-3′), 5.26 (ddd, 1H, $J_{2',3'}$ < 1.0, $J_{2',F-2'}$ = 49.37, $J_{2',F-3'}$ = 9.3, H-2′), 4.69 (dd, 1H, H-5′), 4.56–4.66 (m, 2H, H-5″ and H-4′). ^{19}F NMR ($CDCl_3$): –188.88 (m, F-2′ or F-3′), –203.85 (m, F-3′ or F-2′). IR (film) 2120 cm^{-1} (N_3). UV (EtOH) λ_{max}, nm (ε): 270 (16530). HPLC/APCI-MS: m/z 417 $[M+H]^+$.

2-Ethoxy-6-amino-9-(5-O-benzoyl-2,3-dideoxy-2,3-difluoro-β-D-arabinofuranosyl) purine (16). ^{1}H NMR (CD_3OD): 7.93 (d, 1H, $J_{H-8,F-2'}$ = 2.53, H-8), 7.46–8.05 (3m, 5H, Bz), 6.44 (dm, 1H, $J_{1',2'}$ =

3.2, $J_{1',F-3'}$ = 1.9, $J_{1',F-2'}$ = 19.2, H-1′), 5.64 (ddm, 1H, $J_{3',F-2'}$ = 14.1, $J_{2',F-2'}$ = 50.32, H-2′), 5.53 (ddm, 1H, $J_{2',F-3'}$ = 11.2, $J_{3',F-3'}$ = 50.0, H-3′), 4.69 (d, 2H, H-5′and H-5″), 4.61 (dm, 1H, H-4′), 4.36 (dq, 2H, OCH_2CH_3), 1.36 (t, 3H, OCH_2CH_3). UV (EtOH) λ_{max}, nm (ε): 235 (7390), 266 (6700). HPLC/APCI-MS: m/z 420 $[M+H]^+$.

2,6-Diamino-9-(2,3-dideoxy-2,3-difluoro-β-D-arabinofuranosyl)purine (17) and its α-anomer (18). Compound **17**. ^{1}H NMR (CD_3OD): 7.91 (d, 1H, $J_{H-8,\ F-2'}$ = 2.42, H-8), 6.32 (ddd, 1H, $J_{1',2'}$ = 3.87, $J_{1',F-3'}$ = 2.0, $J_{1',F-2'}$ = 18.37, H-1′), 5.44 (dddd, 1H, $J_{2',3'}$ = 2.0, $J_{2',F-2'}$ = 51.3, $J_{2',F-3'}$ = 14.69, H-2′), 5.40 (dddd, 1H, $J_{3',4'}$ = 3.85, $J_{3',F-2'}$ = 12.2, $J_{3',\ F-3'}$ = 50.65, H-3′), 4.22 (dm, 1H, H-4′), 3.84 (ddd, 1H, $J_{5',F-3'}$ = 1.0, H-5′), 3.82 (dd, 1H, H-5″). UV (EtOH) λ_{max}, nm (ε): 215 (18450), 256 (7020), 277 (7280). ^{19}F NMR (CD_3OD): –195.19 (m, F-2′ or F-3′), –204.95 (m, F-3′ or F-2′). HPLC/APCI-MS: m/z 287 $[M+H]^+$.

Compound **18**. ^{1}H NMR (CD_3OD): 7.84 (s, 1H, H-8), 6.22 (dd, 1H, $J_{1',2'}$ = 2.56, $J_{1',F-2'}$ = 15.4, H-1′), 5.99 (ddt, 1H, $J_{2',3'}$ = 2.88, $J_{2',F-2'}$ = 50.3, $J_{2',F-3'}$ = 14.42, H-2′), 5.36 (dddd, 1H, $J_{3',4'}$ = 4.2, $J_{3',F-2'}$ = 16.35, $J_{3',F'}$ = 52.2, H-3′), 4.69 (ddt, 1H, H-4′), 3.75 (dd, 1H, H-5′), 3.72 (dd, 1H, H-5″). UV (EtOH) λ_{max}, nm (ε): 215 (18400), 256 (7000), 277 (7240). ^{19}F NMR ($CDCl_3$): –196.56 (m, F-2′ or F-3′), –197.764 (m, F-3′ or F-2′). HPLC/APCI-MS: m/z 287 $[M+H]^+$.

2-Ethoxy-6-amino-9-(2,3-dideoxy-2,3-difluoro-β-D-arabinofuranosyl) purine (19). ^{1}H NMR (CD_3OD): 8.07 (d, 1H, $J_{H-8,\ F-2'}$ = 2.4, H-8), 6.39 (ddd, 1H, $J_{1',2'}$ = 3.8, $J_{1',F-3'}$ = 1.7, $J_{1',F-2'}$ = 17.9, H-1′), 5.36–5.53 (dm, 2H, H-2′ and H-3′), 3.84 (dd, 1H, H-5′), 3.81 (dd, 1H, H-5″), 4.23 (dm, 1H, H-4′), 4.36 (q, 2H, OCH_2CH_3), 1.36 (t, 3H, OCH_2CH_3).UV (EtOH) λ_{max}, nm (ε): 266 (8300). ^{19}F NMR (CD_3OD): –195.93 (m, F-2′ or F-3′), –204.67 (m, F-3′ or F-2′). HPLC/APCI-MS: m/z 316 $[M+H]^+$.

9-(2,3-Dideoxy-2,3-difluoro-β-D-arabinofuranosyl)guanine (20). ^{1}H NMR (DMSO-d_6): 10.66 (br.s, 1H, NH), 7.74 (d, 1H, $J_{H-8,F-2'}$ = 2.9, H-8), 6.15 (dd, 1H, $J_{1',2'}$ = 4.2, $J_{1',F-2'}$ = 16.34, H-1′), 6.51 (br.s, 2H, NH_2), 5.60 (dddd, 1H, $J_{2',3'}$ = 3.2, $J_{2',F-2'}$ = 50.64, $J_{2',F-3'}$ = 14.42, H-2′), 5.56 (dddd, 1H, $J_{3',4'}$ = 3.21, $J_{3',F-2'}$ = 16.3, $J_{3',\ F-3'}$ = 51.6, H-3′), 5.17 (t, 1H, J = 5.64, 5′-OH), 4.10 (dm, 1H, H-4′), 3.65 (br.m, 1H, H-5′), 3.61 (br.m, 1H, H-5″), UV (H_2O) λ_{max}, nm (ε): 251 (14200), 270 sh. ^{19}F NMR (DMSO-d_6): –191.72 (m, F-2′ or F-3′), –194.23 (m, F-3′ or F-2′). HPLC/APCI-MS: m/z 288 $[M+H]^+$.

2-Amino-6-chloro-9-(5-O-benzoyl-2,3-dideoxy-2,3-difluoro-β-D-arabinofuranosyl)-purine (21) and its α-anomer (22). Compound **21**. ^{1}H NMR ($CDCl_3$): 7.97 (d, 1H, $J_{H-8,\ F-2'}$ = 2.8, H-8), 7.45–8.05 (3m, 5H, Bz), 6.41 (dt, 1H, $J_{1',2'}$ = 2.5, $J_{1',F-2'}$ = 19.8, H-1′), 5.46 (dd, 1H, $J_{2',3'}$ < 1.0, $J_{2',F-2'}$ = 49.9, $J_{2',F-3'}$ = 12.78, H-2′), 5.29 (ddd, 1H, $J_{3',4'}$ = 2.46, $J_{3',F-2'}$ = 25.0, $J_{3',F'}$ = 49.95, H-3′), 5.29 (br.s, 2H, NH_2), 4.67 (d, 2H, H-5′and H-5″), 4.58 (ddt, 1H, H-4′). ^{19}F NMR ($CDCl_3$): –188.82 (m, F-2′ or F-3′), –203.76 (m, F-3′ or F-2′). UV (MeOH) λ_{max}, nm (ε): 232 (16350), 308 (6600). HPLC/APCI-MS: m/z 410 $[M]^+$.

Compound **22**. ^{1}H NMR ($CDCl_3$): 7.88 (s, 1H, H-8), 7.46–8.08 (3m, 5H, Bz), 6.34 (d, 1H, $J_{1',F-2'}$ = 15.8, H-1′), 5.90 (dd, 1H, $J_{2',3'}$ < 1.0, $J_{2',F-2'}$ = 48.6, $J_{2',F-3'}$ = 12.49, H-2′), 5.42 (ddd, 1H, $J_{3',4'}$ = 2.46, $J_{3',F-2'}$ = 25.0, $J_{3',F'}$ = 49.95, H-3′), 5.16 (br.s, 2H, NH_2), 5.02 (dm, 1H, H-4′), 4.61 (dd, 1H, H-5′), 4.58 (dd, 1H, H-5″). ^{19}F NMR ($CDCl_3$): –191.63 (m, F-2′ or F-3′), –192.6 (m, F-3′ or F-2′). UV (MeOH) λ_{max}, nm (ε): 222 (16450), 308 (6700). HPLC/APCI-MS: m/z 410 $[M]^+$.

2-Amino-6-chloro-9-(2,3-dideoxy-2,3-difluoro-β-D-arabinofuranosyl)-purine (23). ^{1}H NMR (CD_3OD): 8.21 (d, 1H, $J_{H-8,\ F-2'}$ = 2.4, H-8), 6.43 (ddd, 1H, $J_{1',2'}$ = 3.8, $J_{1',F-3'}$ = 1.9, $J_{1',F-2'}$ = 17.3, H-1′), 5.48 (dm, 1H, H-2′), 5.45 (dm, 1H, H-3′), 4.25 (dm, 1H, H-4′), 3.85 (dd, 1H, H-5′), 3.83 (dd, 1H, H-5″).^{19}F NMR (CD_3OD): –195.72 (m, F-2′ or F-3′), –204.7 (m, F-3′ or F-2′). HPLC/APCI-MS: m/z 306 $[M]^+$.

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SYNTHESIS OF PURINE MODIFIED 2′,3′-DIDEOXY-2′,3′-DIFLUORO-D-ARABINOFURANOSYL NUCLEOSIDES FROM THE UNIVERSAL CARBOHYDRATE PRECURSOR

Summary

A series of purine modified nucleosides with 2′,3′-difluoro-β-D-arabinofuranosyl moiety have been synthesized starting from derivative of 2′,3′-dideoxy-2′,3′-difluoro-D-arabinofuranose *via* anionic glycosylation reaction of salts of purine heterocyclic bases by α-bromide as the universal sugar precursor. 2,6-Disubstituted purine 2′,3′-difluoro-D-arabinofuranosyl nucleosides and guanine nucleoside analogue were prepared by chemical transformations of protected arabinosides of 2,6-dichloropurine or 2-amino-6-chloropurine as key intermediates for constructing diverse nucleoside analogues of this class.