Efficient and green synthesis of purine arabinosides *via* CuO catalyzed dehydrazination in tap water

Ran Xia,*[a] and Li-Ping Sun[b]

[a] *College of Chemistry and Chemical Engineering, Xinxiang University, No 191 Jinsui Road Xinxiang City, Henan Province, P. R. China*
[b] *School of Life Science and Technology, Xinxiang University, No 191 Jinsui Road Xinxiang City, Henan Province, P. R. China*
E-mail: ranxia518@hotmail.com

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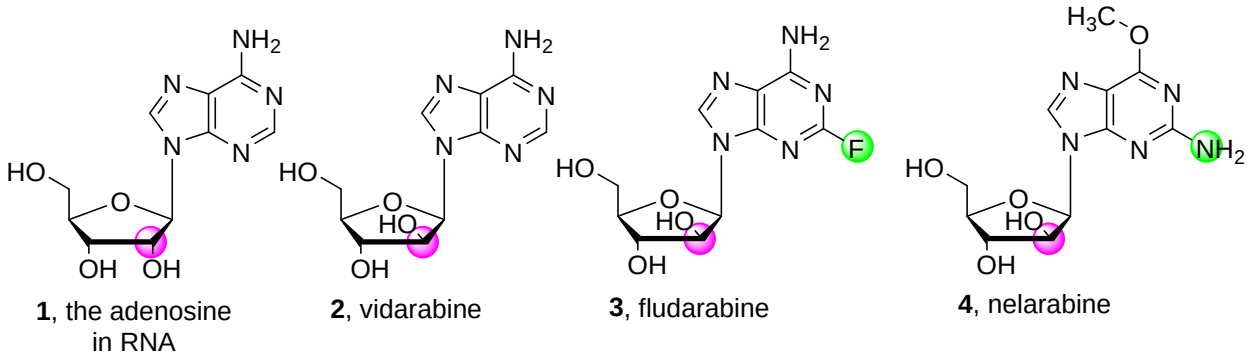
Abstract
The synthesis of purine arabinosides *via* dehydrazination catalyzed by 10 mol% CuO in water was developed for the first time. A series of purine arabinosides could be obtained in good to excellent yields. Furthermore, the drugs vidarabine and nelarabine could be obtained successfully, and even at about 50 g scales, which showed the good future of industrial application. Moreover, the tap water also worked well as the green solvent for the reaction.

Keywords: Dehydrazination, vidarabine, fludarabine, nelarabine, green synthesis

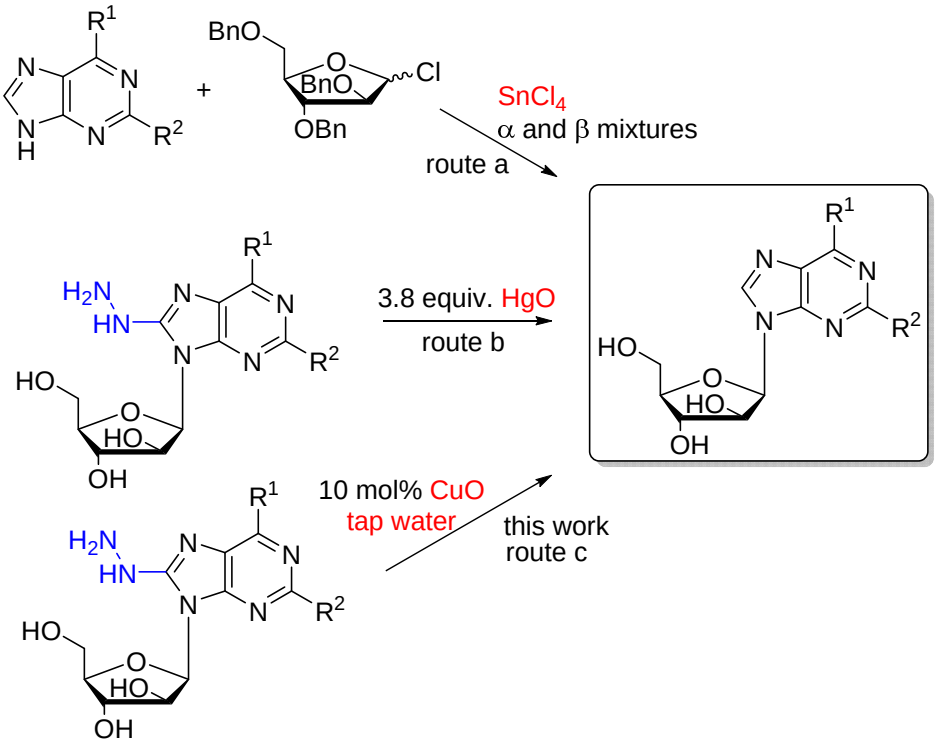
Introduction

Purine arabinoside is the analogue of naturally occurring riboside in RNA. The main difference between arabinoside and riboside is the absolute configuration of 2′ hydroxy group in the sugar cycle. Purine arabinosides are currently used as antiviral drugs with a broad spectrum of activities. For instance, vidarabine (**2**) is an antiviral drug which is active against herpes simplex and varicella zoster viruses.[1] Fludarabine (**3**) is the active pharmaceutical ingredient in the commercial drug Fludara, which is used to treat chronic lymphocytic leukemia (CLL).[2] Nelarabine (**4**) is the clinical drug approved by the US Food and Drug Administration (FDA) in 2005 for the treatment of T-cell acute lymphoblastic leukemia (T-ALL) and T-cell lymphoblastic lymphoma (T-LBL).[3] Thus great endeavor has been devoted to the synthesis of purine arabinosides.



Scheme 1. The adenosine and selected purine arabinoside drugs.

However, only a few synthetic routes are available for purine arabinosides so far. The process of these reported methods mainly relied on the coupling of purine bases with benzyl protected arabinose (route a, Scheme 2).[4-5] The shortcoming was that the benzyl protected arabinose usually needed to be prepared by lengthy or difficult processes. Furthermore, the toxic catalysts in the coupling and deprotection steps presented a health risk to workers and could cause serious environmental pollution. Meanwhile, the coupling method always gave α and β mixtures which needed lengthy processes to separate.



Scheme 2. Different routes to purine arabinosides.

The dehydrazination of 8-hydrazino-9-β-D-arabinofuranosyladenine (**4**) was used to synthesize vidarabine starting from the cheap adenosine.[6] However, the excess amount of catalyst HgO limited the application of this method (route b, Scheme 2). This method has not ever been used in the synthesis of other arabinosides to date. Although other methods including multistep synthesis from purine xyloside,[7] oxazolidine arabinoside,[8] oxidation/reduction of 2′ hydroxy group or trans- glycosidation[9-10] were reported, to date, no better alternative suitable for industrial application has been developed. Therefore, an efficient and green method with a broad substrate scope is highly desirable.

In the context of ongoing projects on the synthesis of purine nucleosides,[11-15] herein, we realized the efficient synthesis of a series of arabinosides *via* dehydrazination reaction at a catalytic amount of CuO (route c, Scheme 2). In addition, tap water was suitable for this reaction as an environmentally benign solvent.

Results and Discussion

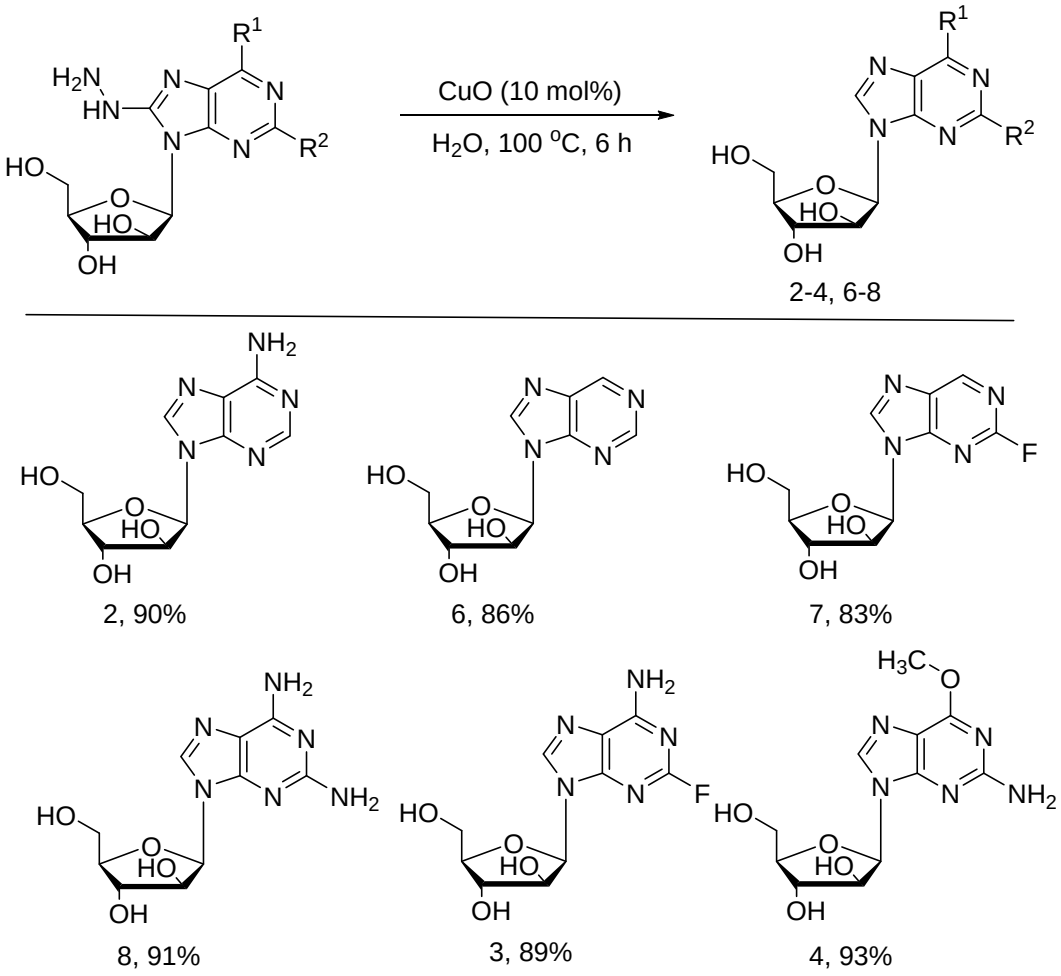
Initially, we started our study by using 8-hydrazino-9-β-D-arabinofuranosyladenine (**5**) as a model substrate to optimize the reaction conditions (Table 1). When 20 mol% Ag_2O or MnO_2 were used as catalyst, only a trace amount of product **2** was observed (entries 1 and 2). Fe_3O_4 and ZnO could afford **2** in 62% and 21% yield respectively (entries 3 and 4). Other metal oxides such as MgO or Al_2O_3 was not effective for the dehydrazination reaction (entries 5 and 6). We were happy to observe that a 84% yield was obtained when CuO was used as a catalyst (entry 7). The temperature was beneficial to the yield as the yield was improved to 91% at 100 ^oC (entry 8). Remarkably, the catalytic efficiency was also satisfactory with a lower catalyst loading of 10 mol% (entry 9). When the catalyst loading was further lowered to 5 mol%, **2** could still be obtained in a slightly decreased yield (entry 10). The reaction time could be shortened to 6 h and the yield was maintained (entry 11). Other copper salts including $CuSO_4$, $CuCl_2$ and Cu_2O were also tested, but decreased yields were observed (entries 12-14). More importantly, when the solvent changed to tap water, the cheaper and more environmentally benign solvent, the yield also was maintained which showed the good future of industrial application (entry 15). Besides, the blank experiment without metal salt showed that the catalyst was essential for the reaction to happen (entry 16). Meanwhile, N_2 atmosphere led to trace amount of dehydrazination product and the color of catalyst was not changed. The same reaction conditions under air or oxygen could give the product in 90% yield and N_2 released from the reaction mixture (entry 17). Therefore, it should also be noted that the gas atmosphere was crucial for the dehydrazination reaction to happen. The optimal reaction condition is 10 mol% CuO in water under air at 100 ^oC for 6 h.

Table 1. The optimization of the reaction conditions of vidarabine [a]

Entry	Cat. (mol%)	Temp./°C	Time/h	Yield/% [b]
1	Ag_2O (20)	80	10	trace
2	MnO_2 (20)	80	10	trace
3	Fe_3O_4 (20)	80	10	62
4	ZnO	80	10	21
5	MgO (20)	80	10	0
6	Al_2O_3 (20)	80	10	0
7	CuO (20)	80	10	84
8	CuO (20)	100	10	91
9	CuO (10)	100	10	90
10	CuO (5)	100	10	85
11	CuO (10)	100	6	90
12	$CuSO_4$ (10)	100	6	64
13	$CuCl_2$ (10)	100	6	53
14	Cu_2O	100	6	42
15 [c]	**CuO (10)**	**100**	**6**	**90**
16	0	100	6	0
17 [d]	CuO (10)	100	6	0

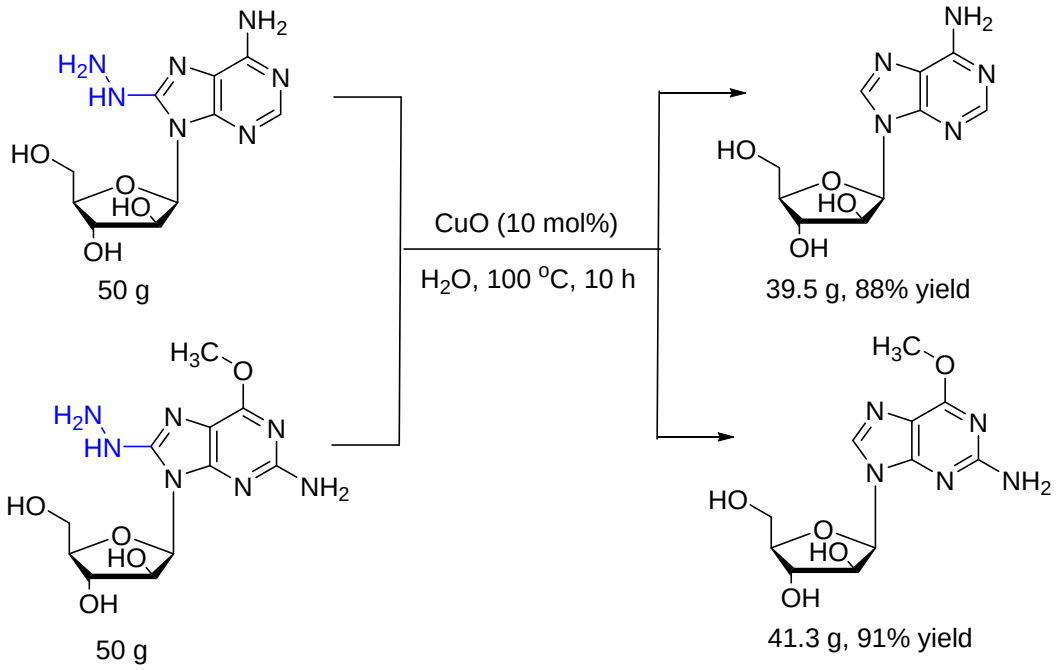
[a] Reaction conditions: **5** (0.297 g, 1 mmol), H_2O (10 mL); [b] Isolated yields; [c] Tap water was used as solvent; [d] under N_2.

With optimal reaction conditions in hand, we next evaluated the scope of substrates. A series of 8-hydrazinopurine derivatives with arabinosyl group at N9 were subjected to the dehydrazination reaction conditions (Scheme 3). The key intermediate 8-hydrazino-9-β-D-arabinofuranosyladenine was obtained *via* bromination, tosylation, cyclization and hydrazination[6]. These steps were investigated in detail and could be carried out in scalable production. As shown in Scheme 3, the corresponding arabinosides were obtained in good to excellent yields. The purine rings bearing different functional groups at C2 or C6 such as hydrogen, fluoro, amino, carbonyl and methoxy groups all furnished the target arabinosides in good yields. In general, the electron-donating groups such as amino group and methoxy group gave higher yields compared to the substrates with electron-withdrawing groups. When H atom was substituted with an amino group in the purine cycles, the yields of purine arabinosides were enhanced (**6** vs. **2**, **2** vs. **8**, **3** vs. **7**). When H atom at C2 in the purine cycle was substituted with fluro group, a slightly reduced yield could be observed (**2** vs. **3**). The methoxy group gave a little better result compared to amino group (**8** vs. **4**). These results indicated that the catalytic system could tolerate different functional groups successfully. Among the products, the drugs vidarabine, fludarabine and nelarabine were synthesized efficiently in good to excellent yields (**2-4**). The 2,6-diaminopurine arabinoside was synthesized chemically for the first time (**8**).



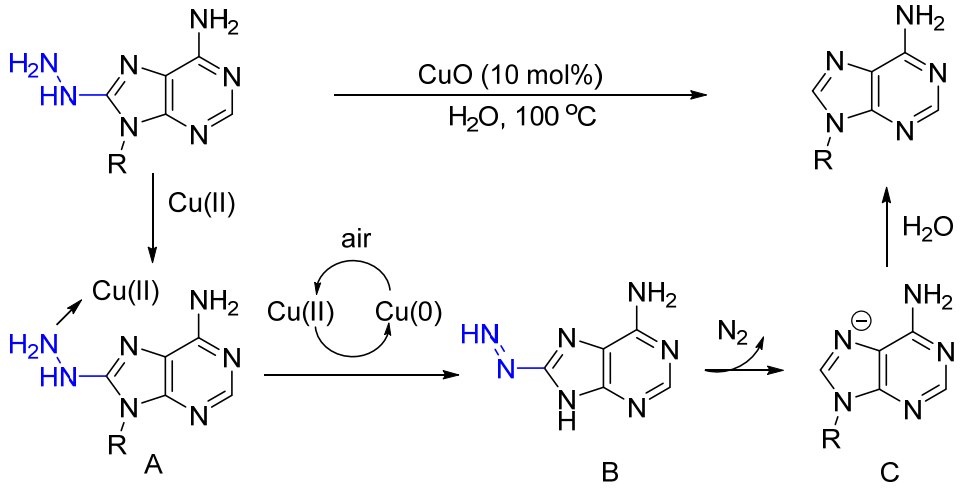
Scheme 3. The synthesis of purine arabinosides *via* CuO catalyzed dehydrazination.

To further demonstrate the reproducibility and the stability of the reaction, we presented the synthesis of drugs vidarabine and nelarabine on lager scales (50 g). In order to obtain good yields, the air was bubbled to the reaction mixture and the reaction time was lengthened to 10 h. Tens of grams of vidarabine and nelarabine were obtained in 88% and 91% yields after routine work-up process in laboratory (Scheme 4). More importantly, the product could be purified through crystallization from water avoiding of chromatography.



Scheme 4. The scalable synthesis of drugs vidarabine and nelarabine.

Based on the above results and our reported findings,[11] a preliminary mechanism for the dehydrazination reaction is proposed in Scheme 5. Firstly, the hydrazine group is coordinated by the Cu(II) salt (Scheme 5, A) and oxidized to the diazene intermediate B. Indeed, the hydrazine group is not activated without catalyst (Table 1, entry 16). Cu(II) is regenerated in the presence of air. It is the reason that the reaction was shut off when conducted under N_2. The anion intermediate C is then generated from diazene with the release of N_2. Finally, the C8–H bond is formed between the anion intermediate C and H_2O to give the product **2**.



Scheme 5. Preliminary proposal for the mechanism.

Conclusions

We realized the synthesis of a series of arabinosides *via* dehydrazination catalyzed by 10 mol% CuO in tap water for the first time. A series of arabinoside drugs such as vidarabine, fludarabine and nelarabine also proceeded well in good yields. More importantly, the drug vidarabine and nelarabine could be obtained successfully at about 40 g scales, which showed the good future of industrial application. This environmentally friendly method represents a promising green synthesis of arabinosides. Further studies into the mechanism are currently underway.

Experimental Section

General. Melting points were recorded with a micro melting point apparatus and uncorrected. NMR spectra were recorded with a 400 MHz spectrometer for ^{1}H NMR, 100 MHz for ^{13}C NMR. Chemical shifts δ are given in ppm relative to tetramethylsilane as internal standard, residual DMSO-d_6 for ^{1}H or DMSO-d_6 in ^{13}C NMR spectroscopy. Multiplicities are reported as follows: singlet (s), doublet (d), doublet of doublets (dd), triplet (t), quartet (q), multiplet (m). High resolution mass spectra were taken with a 3000 mass spectrometer, using Waters Q-TofMS/MS system. For column chromatography silica gel (200-300 mesh) was used as the stationary phase. All reactions were monitored by thin layer chromatography (TLC). All reagents and solvents were purchased from commercial sources and purified commonly before used.

Procedures for preparation of vidarabine (1). 8-Hydrazino-9-β-D-arabinofuranosyladenine 1 g (**2**, 3.4 mmol) and CuO 0.26 g (10 mol %) was dissolved in H_2O (20 mL). The mixture was stirred at 100 ^{o}C for 6 h and monitored by TLC (thin layer chromatography). Upon completion, the resulting mixture was concentrated under reduced pressure and purified by silica gel chromatography with ethyl acetate/methanol (8:2) as eluent to give vidarabine **1** in 90% yield.
8-hydrazino-9-β-D-arabinofuranosyladenine 50 g (**2**, 170 mmol) and CuO 6.5 g (5 mol%) was dissolved in H_2O (1.0 L). The air was bubbled to the mixture. The mixture was stirred at 100 ^{o}C for 10 h and monitored by TLC (thin layer chromatography). Upon completion, the resulting mixture was de-colored by activated carbon and filtrated. The filtrate was evaporated and cooled. The product precipitated slowly affording vidarabine **1** in 91% yield. White solid. mp 264-266 ^{o}C. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.19 (s, 1H), 8.14 (s, 1H), 7.22 (brs, 2H), 6.27 (d, *J* 3.6 Hz, 1H), 5.62 (d, *J* 4.4 Hz, 1H), 5.52 (d, *J* 3.6 Hz, 1H), 5.10 (t, *J* 5.6 Hz, 1H), 4.15 (brs, 2H) , 3.80 (d, *J* 3.6 Hz, 1H) , 3.72-3.61 (m, 2H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 156.0, 152.5, 149.6, 140.4, 118.4, 84.3, 83.8, 75.8, 75.3, 61.1; HRMS calcd for $C_{10}H_{13}N_5NaO_4$ [M+Na^{+}] 290.0860, found 290.0857.
The other products were synthesized according to the similar procedure of vidarabine.
(2*R*,3*S*,4*S*,5*R*)-2-(Hydroxymethyl)-5-(9*H*-purin-9-yl)tetrahydrofuran-3,4-diol (6). White solid. mp 264-266 ^{o}C. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.13 (s, 1H), 8.99 (s, 1H), 8.18 (s, 1H),

6.25 (d, *J* 4.4 Hz, 1H), 5.64 (d, *J* 4.4 Hz, 1H), 5.56 (d, *J* 4.4 Hz, 1H), 5.13 (t, *J* 4.4 Hz, 1H), 4.13 (brs, 2H) , 3.79-3.6 (m, 1H) , 3.69-3.43 (m, 2H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 152.6, 151.4, 148.7, 145.9, 134.6, 88.1, 86.2, 74.3, 70.7, 61.7; HRMS calcd for $C_{10}H_{13}N_4O_4$ [M+H$^+$] 253.0931, found 253.0933.

(2*R*,3*S*,4*S*,5*R*)-2-(2-Fluoro-9*H*-purin-9-yl)-5-(hydroxymethyl)tetrahydrofuran-3,4-diol (7). White solid. mp 264-266 °C. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.74 (s, 1H), 8.16 (s, 1H), 6.10 (d, *J* 4.8 Hz, 1H), 5.64 (d, *J* 5.2 Hz, 1H), 5.56 (d, *J* 5.2 Hz, 1H), 5.10 (t, *J* 5.2 Hz, 1H), 4.15-4.09 (m, 2H) , 3.76 (t, *J* 5.2 Hz, 1H) , 3.67-3.47 (m, 2H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 159.9 ($J_{C\text{-}F}$ 220 Hz), 156.3 ($J_{C\text{-}F}$ 20 Hz), 151.2 ($J_{C\text{-}F}$ 20 Hz), 144.9 ($J_{C\text{-}F}$ 2.8 Hz), 132.5 ($J_{C\text{-}F}$ 4.2 Hz), 83.1, 80.3, 75.7, 74.7, 62.7; HRMS calcd for $C_{10}H_{11}FN_4NaO_4$ [M+Na$^+$] 293.0657, found 293.0655.

(2*R*,3*S*,4*S*,5*R*)-2-(2,6-Diamino-9*H*-purin-9-yl)-5-(hydroxymethyl)tetrahydrofuran-3,4-diol (8). White solid. mp 264-266 °C. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.77 (s, 1H), 6.64 (brs, 2H), 6.05 (d, *J* 4.4 Hz, 1H), 5.75 (brs, 2H), 5.62 (d, *J* 5.2 Hz, 1H), 5.50 (d, *J* 4.4 Hz, 1H), 5.11 (t, *J* 5.2 Hz, 1H), 4.07-4.01 (m, 2H) , 3.74 (d, *J* 4.4 Hz, 1H) , 3.45-3.06 (m, 2H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 160.6, 156.4, 152.0, 137.6, 112.9, 84.5, 83.7, 76.0, 61.6; HRMS calcd for $C_{10}H_{15}N_6O_4$ [M+H$^+$] 283.1149, found 283.1151.

Fludarabine (3). White solid. mp 264-266 °C. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.16 (s, 1H), 7.33 (brs, 2H), 6.10 (d, *J* 5.2 Hz, 1H), 5.64 (d, *J* 5.6 Hz, 1H), 5.56 (d, *J* 4.4 Hz, 1H), 5.09 (t, *J* 5.2 Hz, 1H), 4.15-4.09 (m, 2H) , 3.77 (t, *J* 5.2 Hz, 1H) , 3.47-3.15 (m, 2H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 160.0 ($J_{C\text{-}F}$ 200 Hz), 158.0 ($J_{C\text{-}F}$ 21.2 Hz), 151.2 ($J_{C\text{-}F}$ 20.1 Hz), 144.1, 117.1 ($J_{C\text{-}F}$ 4 Hz), 84.5, 84.2, 76.0, 75.2, 61.2; HRMS calcd for $C_{10}H_{12}FN_5NaO_4$ [M+Na$^+$] 308.0766, found 308.0762.

Nelarabine (4). White solid. mp 264-266 °C. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.92 (s, 1H), 6.46 (brs, 2H), 6.12 (d, *J* 4.0 Hz, 1H), 5.64 (d, *J* 5.2 Hz, 1H), 5.56 (s, 1H), 5.08 (s, 1H), 4.07 (s, 2H), 3.96 (s, 3H) , 3.75 (d, *J* 4.4 Hz, 1H), 3.63 (d, *J* 4.0 Hz, 2H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 161.0, 160.2, 154.4, 139.5, 113.6, 84.6, 83.8, 75.9, 75.7, 61.4, 53.6; HRMS calcd for $C_{11}H_{15}N_5NaO_5$ [M+Na$^+$] 320.0965, found 320.0967.

References

1. Priest, C.; Prives, C.; Poyurovsky, M. V. *Nucl. Acids Res.* **2010**, *38* (21), 7587-7598. http://dx.doi.org/10.1093/nar/gkq669
2. Liu, C.-C.; Tseng, Y.-T.; Li, W.-Y.; Wu, C.-Y.; Mayzus, I.; Rzhetsky, A.; Sun, F.-Z.; Waterman, M.; Chen, J. W.; Chaudhary, P. M.; Loscalzo, J.; Crandall, E.; Zhou, X.-H. *Nucl. Acids Res.* **2014**, *42*, W137-W146. http://dx.doi.org/10.1093/nar/gku412
3. Varsha, G.; William, P. *Curr. Opin. Oncol*. **2006**, *18* (6), 584-590. http://dx.doi.org/10.1097/01.cco.0000245326.65152.af

4. Herbal, K.; Kitteringham, J.; Voyle, M.; Whitehead, A. J. *Tetrahedron Lett*. **2005**, *46* (17), 2961-2964.
http://dx.doi.org/10.1016/j.tetlet.2005.03.039
5. Reist, E. J.; Bartuska, V. J.; Goodman, L. *J. Org. Chem*. **1964**, *29*, 3725-3726.
http://dx.doi.org/10.1021/jo01035a525
6. Chattopadhyaya, J. B.; Reese, C. B. *Synthesis* **1978**, *12*, 908-910.
http://dx.doi.org/10.1055/s-1978-25391
7. Reist, E. J.; Benitez, A.; Goodman, L.; Baker, B. R.; Lee, W. W. *J. Org. Chem*. **1962**, *27*, 3274-3279.
http://dx.doi.org/10.1021/jo01056a071
8. Ranganathan, R. *Tetrahedron Lett*. **1975**, *16*, 1185-1188.
http://dx.doi.org/10.1016/S0040-4039(00)72090-9
9. Sakairi, N.; Hirao, I.; Zama, Y.; Ishido, Y. *Nucleos. Nucleot. Nucl*. **1983**, *2* (3), 221-229.
http://dx.doi.org/10.1080/07328318308078856
10. Hansske, F.; Madej, D.; Robins, M. J. *Tetrahedron* **1984**, *40*, 125-135.
http://dx.doi.org/10.1016/0040-4020(84)85111-X
11. Xia, R.; Xie, Ming-Sheng; Niu, H.-Y.; Qu, G.-R.; Guo, H.-M. *Green Chem*. **2014**, *16*, 1077-1081.
http://dx.doi.org/10.1039/C3GC41658E
12. Xia, R.; Niu, H.-Y.; Qu; G.-R.; Guo, H.-M. *Org. Lett*. **2012**, *14*, 5546-5549.
http://dx.doi.org/10.1021/ol302640e
13. Xia, R.; Xie, M.-S.; Niu, H.-Y.; Qu, G.-R.; Guo, H.-M. *Org. Lett*. **2014**, *16*, 444-447.
http://dx.doi.org/10.1021/ol4033336
14. Qu, G.-R.; Xia, R.; Yang, X.-N.; Li, J.-G.; Wang, D.-C.; Guo, H.-M. *J. Org. Chem*. **2008**, *73*, 2416-2419.
http://dx.doi.org/10.1021/jo702680p
15. Xia, R.; Guo, Z.; Qin, B.-W.; Ji, Z.-Y.; Xie, M.-S.; Qu, G.-R.; Guo, H.-M. *Chin. J. Org. Chem*. **2014**, *34*, 1154-1160.
http://dx.doi.org/10.6023/cjoc201401024

