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3’-叠氮 D-/L-核苷的合成

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摘要 本文报道了正交保护的 3’-叠氮-3’-脱氧-D-和 L-核糖关键中间产品 **32** 和 **43** 的合成，此二关键中间产品与各种嘧啶、吡啶、嘌呤相关的杂环碱基进行糖苷化，得到了相应的 3’-叠氮-3’-脱氧 D 核苷衍生物 **1**–**13** 和 **20**–**24** 以及 3’-叠氮-3’-脱氧 L 核苷衍生物 **25**–**31**。合成了药物相关的 3’-叠氮-3’-脱氧-6-氮杂尿苷、4-脱氧尿苷、2-硫代尿苷、3-去氮尿苷、硝基吡啶核苷、异胞苷衍生物 **14**–**19**。31 个最终产品中的 14 个是新化合物，其结构均得以确证。所有最终产品都是用本文描述的平行法从相应的新关键中间体合成而得。此二关键中间产品 **32** 和 **43** 可以用于合成含有任何不同碱基的新型核苷衍生物。

关键词 叠氮核苷、L-核苷、D-核苷、合成、糖苷化

Synthesis of 3’-Azido-D- and L-Nucleosides

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Abstract: The orthorganally protected 3’-azido-3’-deoxy-D- and -L-ribosides **32** and **43** were synthesized and successfully glycosylated with various pyrimidine, pyridine and purine related heterocyclic bases. 3’-Azido-3’- deoxy-D-pyrimidine nucleosides **1**–**13** and purine nucleosides **20**–**24** as well as 3’-azido-3’-deoxy-L-nucleosides **25**–**31** were synthesied. 3’-Azido-3’-deoxy-6-azauridine, 4-deoxyuridine, 2-thiouridine, 3-deazauridine, nitropyridinone, and isocytidine derivatives **14**–**19** were also synthesized as the drug analogues to explore their biological properties. 14 out of 31 final products are novel and well characterized while all of the 31 final products were synthesized by the new strategy from the corresponding novel key intermediates. The key intermediates **32** and **43** can be utilized to make all kinds of novel nucleoside derivatives by glycosylating with various heterocyclic bases.

Keywords: Azido-nucleoside; L-nucleoside; D-nucleoside; Synthesis; glycosylation

A number of nucleoside anticancer and antiviral drugs play an important role in human health [1]. Azido-modified nucleosides, such as Zidovudine, are efficient reverse transcriptase (RT) inhibitors and have been used as efficient antiviral agents [2]. A recently discovered azido-nucleoside drug, Azvudine [3], is in clinical studies for the treatment of HIV and demonstrates activity against other viruses. Therefore, more azido-modified nucleoside drugs shall be identified to address long running unmet medical needs. Due to synthetic challenges of azido-modified nucleosides, the true scope of their biological activity has not been thoroughly investigated [4]. In addition, these azido group-containing molecules and their corresponding amino group-containing derivatives can be efficiently utilized for further conjugation, and in return, the conjugated molecules [5] can be used to accelerate antisense, small RNA and genomic related technologies and further advance of modern diagnostic application.

To further expand the application of small molecule and genomic drug discovery, it’s essential to explore the

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synthesis of azido-modified nucleosides. Herein, we report the efficient synthesis of 3'-azido-modified D-nucleosides (compounds **1**–**24**; see Figure 1) and L-nucleosides (compounds **25**–**31**; see Figure 1). To avoid tedious synthesis starting from nucleosides, we utilized readily available starting materials D- and L-azido-modified ribosides **32** and **43**.

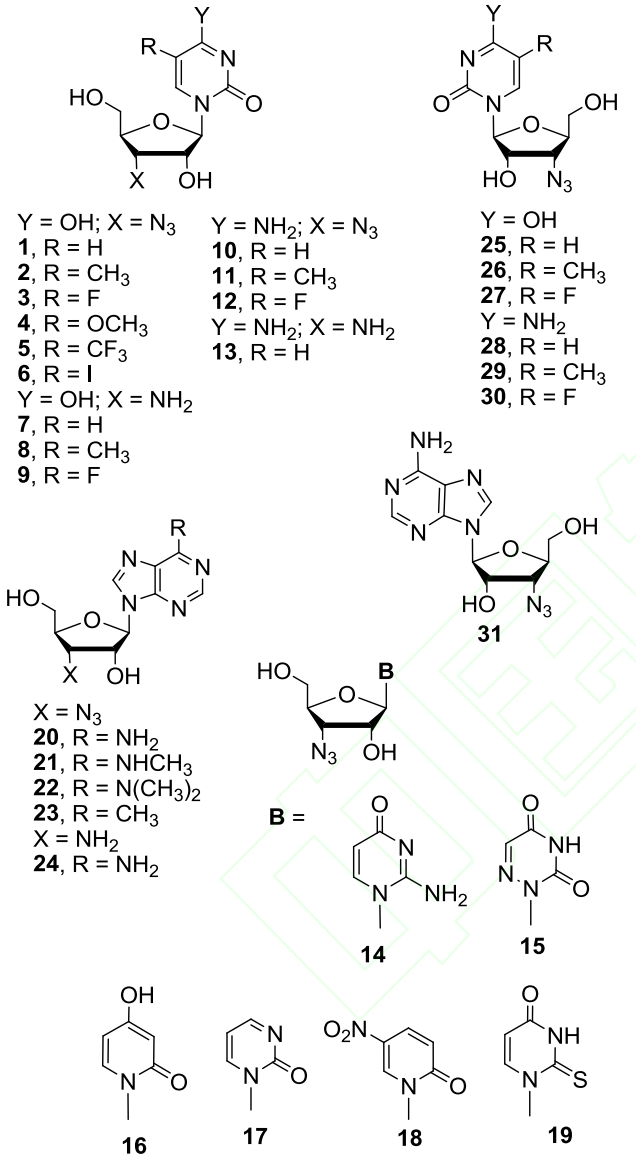


Figure 1. 3'-Azido-3'-deoxy-D- and L-nucleosides

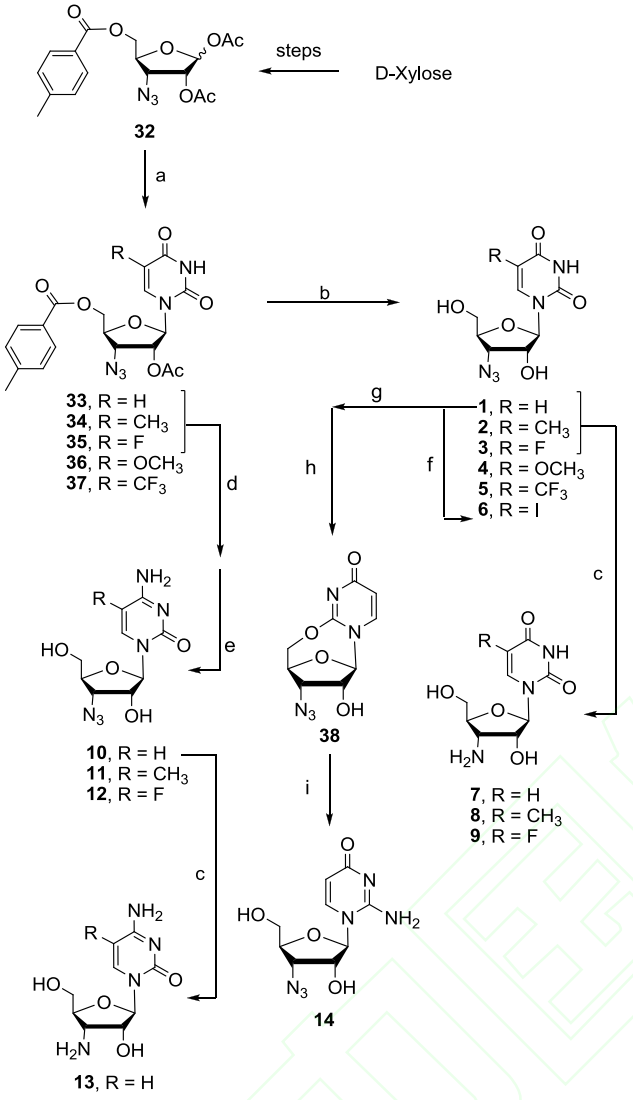
1 Results and Discussion

Some 3-azido- and amino-nucleosides were synthesized by traditional methods starting from nucleosides [6]. The methods do not allow the late-stage functionalization for the synthesis of a structurally diverse nucleoside library. Therefore, we decided to utilize a well-protected 3'-azido-3'-deoxyriboside which can be glycosylated with any heterocyclic base, enabling the synthesis of all possible azido-nucleoside derivatives. The reported literature for the synthesis of benzoyl and acetyl protected 3'-azido-3'-deoxyriboside suffer from the formation of the elimination side product in over 40% in the azido nucleophilic substitution step [6,7]. We constructed 1,2-di-*O*-acetyl-5-*O*-(4-methylbenzoyl)-D-riboside **32** (Scheme I) in large scale from D-(+)-xylose with less than 20% eliminated side product in the key step. The developed process for the synthesis of fully-protected 3'-azido-riboside **32** was also adopted for the synthesis of new 1,2-di-*O*-acetyl-5-*O*-(4-methylbenzoyl)-L-riboside **43** (Scheme IV). With these two orthogonally protected ribosides in hands, we were able to synthesize various new azido-modified nucleosides.

The orthogonally protected 3'-azido-3'-deoxyriboside **32** was glycosylated with uracil, 5-methyluracil, 4-fluorouracil, 5-methoxyuracil, and 5-trifluoromethyl uracil under TMS-Tf conditions to provide the corresponding protected nucleosides **33**–**37**. They were deprotected under saturated ammonia solution in methanol to give the desired uridine and 5-substituted uridine derivatives **1**–**5**. 3'-Azido-3'-deoxyuridine (**1**) was iodinated, resulting in the formation of 5-iodouridine derivative **6**. Compounds **1**–**3** were hydrogenated with Pd/C as the catalyst to generate desired 3'-amino-3'-deoxyuridine derivatives **7**–**9**. The protected key intermediates **33**–**35** (R = H, CH_3 and F) were converted to the corresponding cytidine derivatives **10**–**12** utilizing $POCl_3$/triazole method [8]. The 3'-azido-3'-deoxycytidine (**10**) was hydrogenated to 3'-amino-3'-deoxycytidine (**13**). 3'-Azido-3'-deoxyuridine (**1**) reacted with *p*-methylphenylsulfonyl chloride to generate the 5'-tosylate, which was cyclized with the oxygen atom at the 2-position on the uracil ring to form 2,5'-anhydro-uridine **38**. Uridine **38** was then treated with ammonium hydroxide to complete the synthesis of 3'-azido-3'-deoxy-isocytidine (**14**).

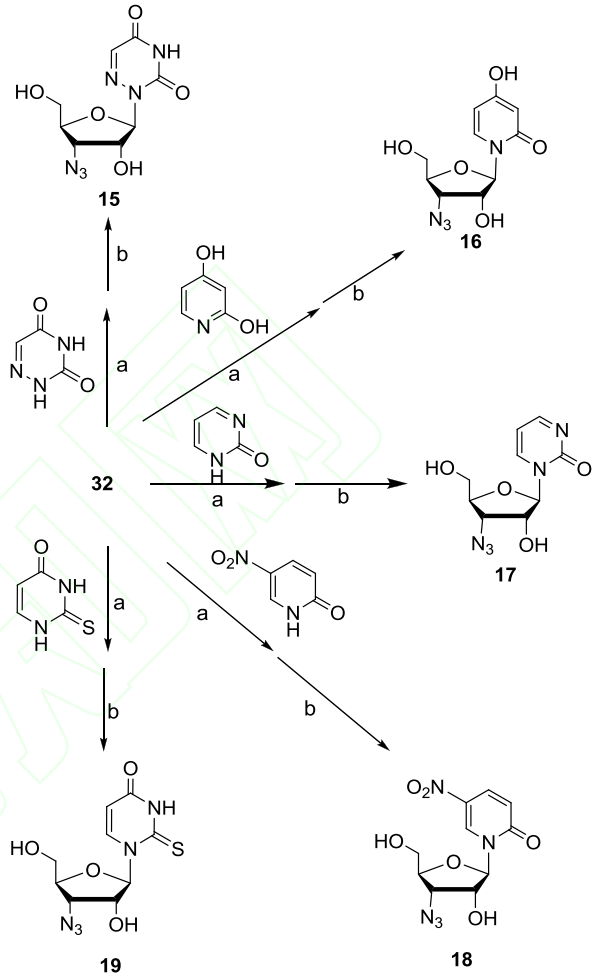
6-Azauridine and 2',3',5'-tri-*O*-acetyl-6-azauridine, azaribine, are all antimetabolic antineoplastic agents [9]. The synthase inhibitor 3-deazauridine [10] and the DNA methylation inhibitor 4-deoxyuridine [11] have been used as anticancer drugs. 2-Thiouridine and 5-nitropyridone ribofuranosyl nucleosides are also biologically relevant

molecules. In order to explore the biological properties of these drugs with substitution at the 3'-position with an azide, we synthesized the 3'-azido-3'-deoxy derivatives of these drugs. The orthogonally protected azido-riboside **32** was glycosylated with 6-azauracil, and the resulting compound was deprotected with saturated ammonia in methanol to furnish 3'-azido-modified 6-azauridine analogue **15**. Riboside **32** was glycosylated with 2,6-dihydroxypyridine and 2-hydroxypyrimidine. The resulting protected nucleoside intermediates were deprotected to produce 3'-azido-3'-deoxy-3-deazauridine (**16**) and 3'-azido-3'-deoxy-4-deoxyuridine (**17**), which are the 3'-azido-modified derivatives of 3-dezazurine and 4-deoxyuridine drugs. The same glycosylation and deprotection strategy were used for the synthesis of compounds **18** and **19** where riboside **32** was glycosylated with 5-nitro-pyridin-2-one and 2-thiouracil.



Conditions: (a) Bases, BSA, CH_3CN, rt; TMSOTf, rt; (b) NH_3/MeOH, rt; (c) Pd/C, H_2; (d) $POCl_3$, 1,2,4-triazole, Et_3N, rt; (e)NH_3/MeOH, rt; (f) ICl, NaN_3, CH_3CN; (g) TsCl, pyridine; (h) DBU, CH_3CN, reflux; (i) NH_4OH, rt

Scheme I. Synthesis of 3'-azido-3'-deoxy D-pyrimidine nucleosides 1–14

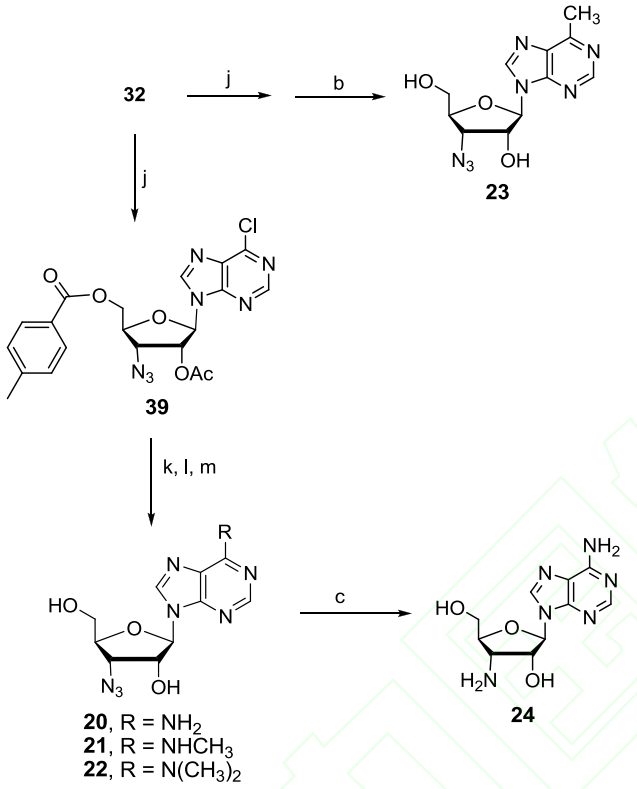


Conditions: (a) Bases, BSA, CH_3CN, rt; TMSOTf, rt; (b) NH_3/MeOH, rt;

Scheme II. Synthesis of 3'-azido-3'-deoxy-D-nucleosides 15–19 with special heterocyclic bases

3'-Azido-3'-deoxyadenosine (**20**) and 3'-amino-3'-deoxyadenosines (**24**) were previously synthesized from adenosine or xylo-adenosine [4] using a long synthetic route that required functional groups manipulation and hydroxyl group alpha-/beta-conversion. In addition, this strategy does not enable late-stage functionalization to install various heterocycles. Robins and co-workers also converted 3'-azidoadenosine to 6-dialkylsubstituted derivatives by the triazole strategy [12] which could be much easier if chloro- is at the 6-position of such adenosine analogue, such as intermediate **39** (Scheme III). We glycosyl-

ated riboside **32** with 6-methylpurine, and the resulted compound was deprotected with saturated ammonia in methanol resulting in the desired 3'-aziso-3'-deoxy-6-methylpurine nucleoside **23** which is the derivative of natural product 6-methylpurine riboside. Riboside **32** was also glycosylated with 6-chloroadenine resulting a versatile intermediate **39**, which can be utilized to make all kinds of 6-modified purine nucleoside derivatives.

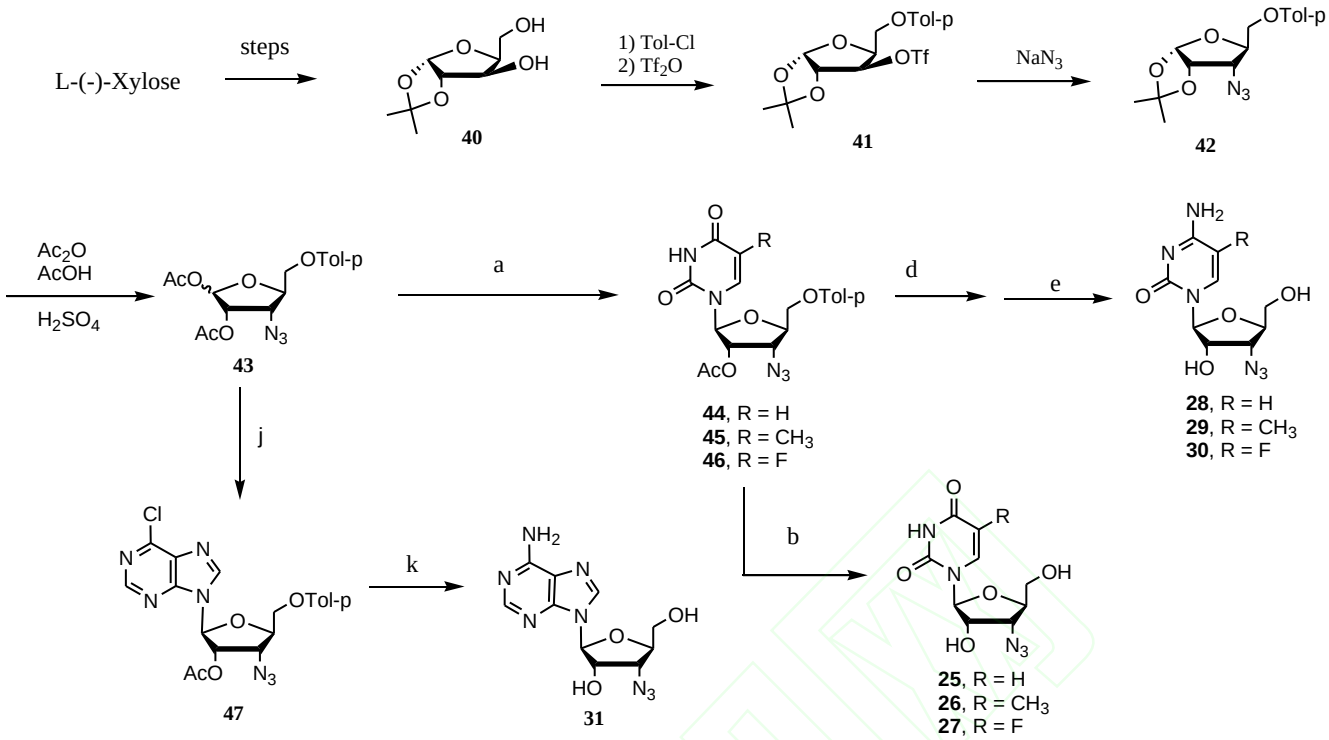


Scheme III. Synthesis of 3'-azido-3'-deoxy-D-purine nucleosides 20–24

The key intermediate **39** was synthesized and treated with ammonia resulting in desired compound **20**. Compound **39** was also treated with methylamine and *N*,*N*-dimethylamine. The chloro- at position 6 was replaced and the protecting groups were removed at the same time to furnish the synthesis of N^6-methylated compounds **21** and **22**. Hydrogenation of compound **20** gave 3'-amino-3'-deoxyadenosine **24**. Compounds **20** and **24** was synthesized by Kim and co-workers [13] with long route and OH conversion starting from adenosine which can only be used for the synthesis of this compound. Therefore, the key intermediate **39** can be used as a versatile scaffold to make all kinds of 6-*N*-substituted and *C*-substituted adenosine derivatives by nucleophilic substitution and various C-C bond formation reactions. In addition, the amino and azido groups on the derivatives can be used for various conjugation.

L-Nucleosides demonstrated special biological property and have different application compared to the normal D-nucleosides [14]. With the developed protocol for the synthesis of the protected 3'-azido-3'-deoxyriboside **32** (Scheme I) ready at Granlen, we transferred the strategy to the synthesis of new 1,2-di-*O*-acetyl-5-*O*-(4-methylbenzoyl)-L-riboside **43** (Scheme I). 1,2-*O*-Isopropylidene-α-L-xylofuranose **40** was synthesized from L-(-)-xylose according to the reported protocol [15]. Compound **40** was selectively protected and then activated with Tf_2O giving the active triflate intermediate **41**. Further nucleophilic substituted with sodium azide resulting in the 3'-azido-L-riboside **42**. Further treatment with acetic anhydride under acidic condition by our routine protocol furnished the synthesis of 3'-azido-3'-deoxy- L-riboside **43**.

The key intermediate 3'-azido-3'-deoxy-L-riboside **43** was glycosylated with uracil, 5-methyluracil and 5-fluorouracil. The resulting intermediates **44**–**46** were deprotected with ammonia to give the desired 3'-azido-3'-deoxy-L-uridine derivatives **25**–**27**. The key intermediates **44**–**46** were reacted with $POCl_3$/triazole, followed by the treatment with ammonia, giving the desired 3'-azido-3'-deoxy-L-cytidine derivatives **28**–**30**, respectively. L-Riboside **43** was glycosylated with 6-chloropurine, and the key intermediate **47** was obtained. It was further treated with ammonia giving the desired 3'-aziso-3'-deoxy-L-adenosine (**31**). Therefore, our parallel-last strategy just stated starting from the versatile D- and L-ribosides **32** and **43** can be utilized broadly to make a variety of L-nucleosides with all kinds of heterocyclic bases, and more derivatives can be made from the key intermediates.



Conditions: (a) Bases, BSA, CH_3CN, rt; TMSOTf, rt; (b) NH_3/MeOH, rt; (d) $POCl_3$, 1,2,4-triazole, Et_3N, rt; (e)NH_3/MeOH, rt; (j) Bases, DBU, TMSOTf, rt→60℃; (k) NH_3/MeOH, 80℃.

Scheme IV. Synthesis of 3'-azido-3'-deoxy-L-riboside 43 and nucleosides 25–31

2 Conclusion

In conclusion, we have developed the protocol and synthesized the fully-protected 3'-azido-3'-deoxy-D-riboside **32** in large scale, and synthesized new protected 3'-azido-3'-deoxy-L-riboside **43**. These D- and L-riboside key intermediates were successfully glycosylated with various substituted uracil, adenine, 6-azauracil, 2-thiouracil, pyrimidone, and pyridinone related heterocyclic bases in a parallel fashion for the synthesis of the diversified nucleoside derivatives after deprotection and simple functional group manipulation. 3'-Azido-3'-deoxy-D-nucleoside derivatives **1–6, 10–12** and **14–23** and L-nucleoside derivatives **25–31** were obtained and ready for further biological and genomic studies. The key riboside intermediates **32** and **43** reported here can be utilized further for the synthesis of various novel nucleoside derivatives with other heterocyclic bases to expand further research in the related fields.

3 Experiment Section

3.1 Instrument and reagent:

Starting materials and reagents were obtained from commercial suppliers and were used without further purification unless otherwise stated. ^{1}H NMR spectra were obtained with a Bruker Avance 400 spectrometer using DMSO-d_6 (ppm) downfield with respect to an internal δ as solvents. Chemical shifts are reported as standard of tetramethylsilane (TMS). Product purity was tested by an Agilent 1260 analytical HPLC system. LC–MS spectra were measured on an Agilent 6120 LC–MS spectrometer. TLC was performed on silica gel GF254. Flash chromatography was performed on silica gel 200–300 mesh (Yantai Silica Gel Co. LTD). 1,2-Di-*O*-acetyl-5-*O*-(4-methylbenzoyl)-D-riboside **32** was prepared from D-xylose by adopting literature strategy with modification and different protecting scheme [7]. 6-methylpurine was prepared from 6-chloropurine according to procedures described in the literature [16].

3.2 Experimental procedures

General procedure for the glycosylation of uracil, 5-methyluracil, 4-fluorouracil, 5-methoxyuracil, and 5-trifluoromethyluracil with 1,2-di-*O*-acetyl-5-*O*-(4-methylbenzoyl)riboside (32) (Scheme I) (Method 1): To a suspension of uracil, 5-methyluracil, 4-fluorouracil, 5-methoxyuracil, or 5-trifluoromethyluracil (9.6 mmoL, 1.2 eq) in anhydrous acetonitrile (100 mL) was added *N*,*O*-bis(trimethylsilyl)acetamide (7.8 mL, 31.8 mmol, 4.0 eq) dropwise with stirring. The mixture was stirred for 1 h at room temperature. Then 1,2-di-*O*-acetyl-5-*O*- (4-methyl benzoyl)riboside **32** (3.0 g, 7.95 mmol, 1.0 eq) was added, and the reaction mixture was cooled to 0 ℃ followed by addition of trimethylsilyl triflate (4.30 mL, 23.85 mmol, 3.0 eq). The mixture was stirred overnight at room temperature. Upon completion of the reaction as monitored by TLC, the reaction mixture was poured into ice water and then treated with a mixture of saturated sodium bicarbonate and ethyl acetate. The organic phase was separated, and the aqueous phase was extracted with ethyl acetate. The combined organic phases were dried over anhydrous sodium sulfate. The drying agent was filtered off, and the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography on a silica gel column using petroleum ether–ethyl acetate as eluents providing products **33–37** as white solids in 82–93% yields.

General procedure for the conversion of compounds 33–37 to compounds 1–5 (Scheme I) (Method 2): The obtained compounds **33–37** was dissolved in NH_3–MeOH, and the reaction mixture was allowed to stir at room temperature overnight. Upon completion of the reaction as monitored by TLC, the solution was concentrated in vacuum under reduced pressure, and the residue was purified on a silica gel column resulting in compounds **1–5** in 78–95% yields as white solids.

Experimental details for 3'-azido-3'-deoxyuridine (1) (Scheme I): gray solid, 76% yield in two steps with an HPLC purity of 98.7%. R_f = 0.4 (dichloromethane –methanol = 10:1). m.p. decomposed at 130–135 ℃. ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 3.48～3.70 (m, 2H, CH_2), 3.80～4.10 (m, 2H, 2',3'-H), 4.42 (m, 1H, 4'-H), 5.28 (br, 1H, 5'-OH), 5.66 (d, 1H, J=8.0 Hz, ArH), 5.76 (d, 1H, J =5.2 Hz, 2'-OH), 6.17 (s, 1H, 1'-H), 7.87 (d, 1H, J=8.4 Hz, ArH), 11.29 (s, 1H, NH); ESI-MS *m*/*z*: 269.9 $[M + H]^+$, 291.9 $[M + Na]^+$.

Experimental details for 3'-azido-3'-deoxy-5-methyl uridine (2) (Scheme I): light yellow foam, 77% yield in two steps with an HPLC purity of 99.8%. R_f = 0.6 (dichloromethane–methanol = 10:1). ESI-MS *m*/*z*: 284.0 $[M + H]^+$, 305.9 $[M + Na]^+$ [17].

Experimental details for 3'-azido-3'-deoxy-5-fluorouridine (3) (Scheme I): light yellow foam, 73% yield in two steps with an HPLC purity of 97.7%. R_f = 0.2 (petroleum ether–ethyl acetate = 1:1). ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 3.55～3.75 (m, 2H, CH_2), 3.91～4.07 (m, 2H, 3,4'-H), 4.37～4.45 (m, 1H, 2'-H), 5.42 (br, 1H, 5'-OH), 5.70～5.75 (m, 1H, 2'-OH), 6.18 (d, 1H, J=5.2 Hz, 1'-H), 8.27 (d, 1H, J=7.2 Hz, ArH), 11.62 (s, 1H, NH); ESI-MS *m*/*z*: 287.8 $[M + H]^+$.

Experimental details for 3'-azido-3'-deoxy-5-methoxy uridine (4) (Scheme I): light yellow solid, 72% yield over two steps with an HPLC purity of 95.7%. R_f = 0.7 (dichloromethane–methanol = 10:1). m.p. decomposed at 150–155 ℃. ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 3.56～3.64 (m, 4H, CH_3, CH), 3.66～3.78 (m, 1H, CH), 3.90～3.98 (m, 1H, 4'-H), 4.08 (t, 1H, J=5.2 Hz, 3'-H), 4.42～4.52 (m, 1H, 2'-H), 5.42 (t, 1H, J=4.4 Hz, 5'-OH), 5.79 (d, 1H, J=4.8 Hz, 2'-OH), 6.14 (d, 1H, J=5.6 Hz, 1'-H), 7.61 (s, 1H, ArH), 11.48 (s, 1H, NH); ESI-MS *m*/*z*: 299.8 $[M + H]^+$, 322.7 $[M + Na]^+$. HRMS calcd for $C_{10}H_{13}N_5NaO_6$ $[M + Na]^+$ 322.0764, found 322.0761.

Experimental details for 3'-azido-3'-deoxy-5-trifluoro methyluridine (5) (Scheme I): yellow foam, 65% yield over two steps with an HPLC purity of 95.8%. R_f = 0.4 (dichloromethane–methanol = 15:1). ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 3.50～3.85 (m, 2H, CH_2), 3.90～4.10 (m, 2H, 4'-H, 3'-H), 4.40～4.50 (m, 1H, 2'-H), 5.53 (t, 1H, J =4.4 Hz, 5'-OH), 5.69 (d, 1H, J=2.4 Hz, 2'-OH), 6.28 (d, 1H, J=4.8 Hz, 1'-H), 8.83 (s, 1H, ArH), 11.41 (s, 1H, NH); ESI-MS *m*/*z*: 359.7 $[M + Na]^+$.

Synthesis of 3'-azido-3'-deoxy-5-iodouridine (6) (Scheme I): Iodine monochloride (2.4 g, 14.8 mmol, 2.0

eq) was added to a suspension of sodium azide (1.4 g, 22.2 mmol, 3.0 eq) in acetonitrile (50 mL) at ice-bath temperature with stirring. This mixture was stirred for another 5 min, and a solution of 3'-azido-3'-deoxyuridine **1** (2.0 g, 7.4 mmol) in acetonitrile (60 mL) was then added. The resulting reaction mixture was warmed to 25 ℃ and stirred for 24 h. Upon completion of the reaction as monitored by TLC, solvent was evaporated and the crude product was purified by flash chromatography on a silica gel column using dichloromethane–methanol as eluent to afford 1.5 g compound **6** as a white solid in 70% yield with an HPLC purity of 97.2%. R_f = 0.4 (dichloromethane–methanol = 10:1). m.p. decomposed at 170–175 ℃. UV-vis (MeOH) λ_{max}: 285 nm; ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 3.55～3.75 (m, 2H, CH_2), 3.92～3.97 (m, 1H, 4'-H), 4.03 (t, 1H, J=5.2 Hz, 3'-H), 4.41～4.46 (m, 1H, 2'-H), 5.43 (t, 1H, J =4.8 Hz, 5'-OH), 5.70 (d, 1H, J=4.4 Hz, 2'-OH), 6.17 (d, 1H, J=5.2 Hz, 1'-H), 8.45 (s, 1H, ArH), 11.72 (s, 1H, NH); ESI-MS *m*/*z*: 395.7 $[M + H]^+$, 418.6 $[M + Na]^+$. HRMS calcd for $C_9H_{10}IN_5NaO_5$ $[M + Na]^+$ 417.9624, found 417.9627.

General procedure for the synthesis of compounds 7–9 (Scheme I) (Method 3): Compound **1** or **2** or **3** was dissolved in anhydrous methanol and triethylamine (1.0 eq). Catalyst 10% Pd/C (50% w/w) was added, and the mixture was stirred for 5 h under H_2 (50 Psi) atmosphere. Upon completion of the reaction as monitored by TLC, the catalyst was filtered off through Celite. The solvent was evaporated and the crude product was purified by flash chromatography on a silica gel column using dichloromethane–methanol as eluent giving compounds **7–9**, respectively, in 80–86% yields as white solids.

Experimental details for 3'-amino-3'-deoxyuridine (7) (Scheme I): white foam, 86% yield with an HPLC purity of 96.0%. R_f = 0.30 (dichloromethane–methanol = 5:1). ESI-MS *m*/*z*: 244.0 $[M + H]^+$; UV-vis (MeOH) λ_{max}: 265 nm [18].

Experimental details for 3'-amino-3'-deoxy-5-methyl uridine (8) (Scheme I): white foam, 83% yield with an HPLC purity of 96.6%. R_f = 0.40 (dichloromethane –methanol = 5:1). ESI-MS *m*/*z*: 258.0 $[M + H]^+$; UV-vis (MeOH) λ_{max}: 268 nm [17].

Experimental details for 3'-amino-3'-deoxy-5-fluoro uridine (9) (Scheme I): white solid, 80% yield with an HPLC purity of 95.0%. R_f = 0.45 (dichloromethane –methanol = 5:1). ESI-MS *m*/*z*: 261.9 $[M + H]^+$; UV-vis (MeOH) λ_{max}: 270 nm [19].

General procedure for the synthesis of 3'-azido-3'-deoxycytidine derivatives (10–12) (Method 4) (Scheme I): To a solution of 1,2,4-triazole (5 eq) in dry dichloromethane was added phosphorus oxychloride (3.0 eq) followed by triethylamine (3.0 eq) at 0 ℃ and the reaction mixture was stirred for 30 minutes at 0 ℃. A solution of compound **33** or **34** or **35** (1.0 eq) in dry dichloromethane was then added dropwise. The mixture was moved to room temperature and was stirred for 1 h. Upon completion of the reaction as monitored by TLC, the reaction mixture was poured into ice water and was treated with saturated sodium bicarbonate and ethyl acetate. The organic phase was separated, and the aqueous phase was extracted with ethyl acetate. The combined organic phases were dried over anhydrous sodium sulfate. The drying agent was filtered off, and the filtrate was concentrated under reduced pressure. The residue was dissolved in NH_3–MeOH, and the reaction mixture was allowed to stir at room temperature overnight. Upon completion of the reaction as monitored by TLC, the solution was concentrated in vacuum under reduced pressure, and the residue was purified on a silica gel column resulting in compounds **10–12**, respectively, in 76–85% yields as white solids.

Experimental details for 3'-azido-3'-deoxycytidine (10) (Scheme I): light yellow solid, 85% yield with an HPLC purity of 98.2%. R_f = 0.2 (dichloromethane–methanol = 5:1). ESI-MS *m*/*z*: 268.8 $[M + H]^+$; UV-vis (MeOH) λ_{max}: 270 nm [20].

Experimental details for 3'-azido-3'-deoxy-5-methyl cytidine (11) (Scheme I): white foam, 76% yield in two steps with an HPLC purity of 98.3%. R_f = 0.45 (dichloromethane–methanol = 5:1). UV-vis (MeOH) λ_{max}: 280 nm; ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 1.82 (s, 3H, CH_3), 3.50～3.72 (m, 2H, CH_2), 3.84～3.92 (m, 1H, 4'-H), 3.97 (t, 1H, J=5.2 Hz, 3'-H), 4.32～4.40 (m, 1H, 2'-H), 5.25 (t, 1H, J=5.2 Hz, 5'-OH), 5.77 (d, 1H, J=4.8 Hz, 2'-OH),

6.07 (d, 1H, J=5.2 Hz, 1'-H), 6.84 (s, 1H, NH), 7.33 (s, 1H, NH), 7.64 (s, 1H, ArH); ESI-MS m/z: 383.3 $[M + H]^+$, 565.5 $[2M + H]^+$.

Experimental details for 3'-azido-3'-deoxy-5-fluoro cytidine (12) (Scheme I): white solid, 79% yield in two steps with an HPLC purity of 99.0%. R_f = 0.45 (dichloromethane–methanol = 5:1). m.p. decomposed at 165–170 ℃. UV-vis (MeOH) λ_{max}: 239, 280 nm; ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 3.54～3.61 (m, 1H, CH), 3.69～3.76 (m, 1H, CH), 3.90～3.98 (m, 2H, 3'-H, 4'-H), 4.30～4.36 (m, 1H, 2'-H), 5.37 (t, 1H, J=5.2 Hz, 5'-OH), 5.70～5.74 (m, 1H, 2'-OH), 6.15 (d, 1H, J=5.2 Hz, 1'-H), 7.54 (s, 1H, NH), 7.78 (s, 1H, NH), 8.16 (d, 1H, J=7.2 Hz, ArH); ESI-MS m/z: 287.1 $[M + H]^+$, 309.1 $[M + Na]^+$, 325.0 $[M + K]^+$. HRMS calcd for $C_9H_{11}FN_6NaO_4$ $[M + Na]^+$ 309.0724, found 309.0725.

Synthesis of 3'-amino-3'-deoxycytidine (13) (Scheme I): This compound was synthesized by **Method 3** as described above from compound **10** (2.0 g, 7.5 mmoL). 1.4 g of compound **13** was obtained as a white foam in 75% yield with an HPLC purity of 97.3%; R_f = 0.30 (dichloromethane–methanol = 2:1). UV-vis (MeOH) λ_{max}: 270 nm; ESI-MS m/z: 243.0 $[M + H]^+$ [19].

Synthesis of 3'-deoxy-3'-azido-isocytidine (14) (Scheme I): To a solution of 3'-azido-3'-deoxyuridine (**1**) (5.0 g, 18.6 mmol) in dry pyridine (70 mL) at 0 ℃ with stirring was added *p*-toluenesulfonyl chloride (4.3 g, 22.32 mmol, 1.2 eq). The reaction mixture was stirred overnight at room temperature. Upon completion of the reaction as monitored by TLC, the reaction mixture was poured into ice water and was treated with saturated sodium bicarbonate and ethyl acetate. The organic phase was separated, and the aqueous phase was extracted with ethyl acetate. The combined organic phases were dried over anhydrous sodium sulfate. The drying agent was filtered off, and the filtrate was concentrated under reduced pressure. The residue was then dissolved in acetonitrile (100 mL), and 1,8-diazabicyclo [5.4.0]undec-7-ene (5.6 mL, 37.2 mmol, 2.0 eq) was added to the solution. The reaction mixture was heated to reflux for 1 h. Upon completion of the reaction as monitored by TLC, the hot solution was immediately filtered through a Celite pad, and the filtrate was evaporated to dryness. The residue was purified on a silica gel column to provide 3.0 g of product **38**. The obtained compound **38** was dissolved in 30 mL MeOH, and 30 mL ammonium hydroxide was added. The reaction mixture was allowed to stir at room temperature overnight. Upon completion of the reaction as monitored by TLC, the solution was concentrated in vacuum under reduced pressure, and the residue was purified on a silica gel column resulting in 2.6 g of compound **14** as a white solid in 52% yield for three steps with an HPLC purity of 95.8%. R_f = 0.2 (dichloromethane–methanol = 5:1). m.p. decomposed at 164–169 ℃. ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 3.62～3.70 (m, 3H, 4'-H, CH_2), 4.02 (t, 1H, J=2.8 Hz, 3'-H), 4.30～4.45 (m, 1H, 2'-H), 5.35 (t, 1H, J=4.8 Hz, 5'-OH), 5.54 (d, 1H, J=7.6 Hz, ArH), 5.76 (d, 1H, J=6.0 Hz, 2'-OH), 6.17 (d, 1H, J=4.8 Hz, 1'-H), 6.84 (s, 2H, NH_2), 7.61 (d, 1H, J=8.0 Hz, ArH); ESI-MS m/z: 269.1 $[M + H]^+$. HRMS calcd for $C_9H_{12}N_6NaO_4$ $[M + Na]^+$ 291.0818, found 291.0815.

Synthesis of 3'-azido-3'-deoxy-D-nucleosides 15–19 (Scheme II): These compounds were synthesized by **Method 1** as described above by the glycosylation of 6-azauracil, 2,6-dihydroxypyridine, 2-hydroxypyrimidine, 5-nitro-pyridin-2-one and 2-thiouracil with **32**. The resulted compounds were further deprotected by **Method 2** resulted in final products **15–19**.

Experimental details for 3'-azido-3'-deoxy-6-azauridine (15) (Scheme II): yellow foam, 71% yield in two steps with an HPLC purity of 98.3%. R_f = 0.5 (dichloromethane–methanol = 10:1). UV-vis (MeOH) λ_{max}: 262 nm; ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 3.40～3.60 (m, 3H, CH_2, 4'-H), 3.88～4.00 (m, 2H, 2', 3'-H), 4.54～4.58 (m, 1H, 5'-OH), 4.85 (br, 1H, 2'-OH), 5.91 (d, 1H, J=3.6 Hz, 1'-H), 6.10 (br, 1H, NH), 7.53 (s, 1H, ArH); ESI-MS m/z: 271.1 $[M + H]^+$, 293.0 $[M + Na]^+$.

Experimental details for 3'-azido-3'-deoxy-3-deaza uridine (16) (Scheme II): white foam, 68% yield over two steps with an HPLC purity of 98.0%. R_f = 0.1 (petroleum ether–ethyl acetate = 1:1). ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 3.53～3.69 (m, 2H, CH_2), 3.87～3.92 (m, 1H, 4'-H), 4.05 (t, 1H, J=4.8 Hz, 3'-H), 4.40～4.45 (m, 1H, 2'-H), 5.26 (t, 1H, J=4.8 Hz, 5'-OH), 5.65 (d, 1H, J=8.0 Hz, 2'-OH), 5.76 (d, 1H, J=5.6 Hz, 1'-H), 6.15 (d, 1H, J=5.2

Hz, ArH), 7.86 (d, 1H, J=8.0 Hz, ArH), 11.34 (s, 1H, ArH); ESI-MS m/z: 269.8 $[M + H]^+$, 291.9 $[M + Na]^+$.

Experimental details for 3'-azido-3'-deoxy-4-deoxy uridine (17) (Scheme II): light yellow foam, 78% yield over two steps with an HPLC purity of 95.2%. R_f = 0.6 (dichloromethane–methanol = 10:1). ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 3.59～3.66 (m, 1H, CH), 3.80～3.92 (m, 2H, CH, 4'-H), 4.08～4.13 (m, 1H, 3'-H), 4.38～4.43 (m, 1H, 2'-H), 5.39 (t, 1H, J=0.8 Hz, 5'-OH), 5.75 (d, 1H, J=2.4 Hz, 2'-OH), 6.36 (d, 1H, J=5.2 Hz, 1'-H), 6.48～6.52 (m, 1H, ArH), 8.52～8.58 (m, 1H, ArH); ESI-MS m/z: 254.0 $[M + H]^+$, 275.9 $[M + Na]^+$.

Experimental details for 1-(3-azido-3-deoxy-β-D-ribo furanosyl)-5-nitropyridine-2(1H)-one (18) (Scheme II): white solid, 65% yield over two steps with an HPLC purity of 95.7%. R_f = 0.5 (dichloromethane–methanol = 10:1). m.p. decomposed at 150–155 ℃. ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 3.62～3.70 (m, 1H, CH), 3.87～4.00 (m, 2H, CH, 4'-H), 4.14～4.21 (m, 1H, 3'-H), 4.37～4.43 (m, 1H, 2'-H), 5.61 (t, 1H, J=4.4 Hz, 5'-OH), 5.90 (d, 1H, J=1.6 Hz, 2'-OH), 6.43 (d, 1H, J=5.2 Hz, 1'-H), 6.51 (d, 1H, J =10.0 Hz, ArH), 8.15 (dd, 1H, J_1=2.8 Hz, J_2=10.2 Hz, ArH), 9.63 (d, 1H, J=2.8 Hz, ArH); ESI-MS m/z: 319.9 $[M + Na]^+$. HRMS calcd for $C_{10}H_{11}N_5NaO_6$ $[M + Na]^+$ 320.0607, found 320.0605.

Experimental details for 3'-azido-3'-deoxy-2-thiouridine (19) (Scheme II): white solid, 72% yield over two steps with an HPLC purity of 98.4%. R_f = 0.4 (dichloromethane–methanol = 10:1). m.p. decomposed at 155–160 ℃. UV-vis (MeOH) λ_{max}: 273 nm; ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 3.50～3.70 (m, 2H, CH_2), 3.73～3.80 (m, 2H, 4', 3'-H), 4.45～4.48 (m, 1H, 2'-H), 5.44 (t, 1H, J=5.2 Hz, 5'-OH), 5.99 (d, 1H, J=8.4 Hz, ArH), 6.23 (d, 1H, J=5.6 Hz, 2'-OH), 6.54 (d, 1H, J=3.2 Hz, 1'-H), 8.15 (d, 1H, J=8.2 Hz, ArH), 12.65 (s, 1H, NH); ESI-MS m/z: 285.8 $[M]^+$. HRMS calcd for $C_9H_{11}N_5NaO_4S$ $[M + Na]^+$ 308.0429, found 308.0429.

Synthesis of 6-chloro-9-(2-*O*-acetyl-5-*O*-*p*-toluoyl-3-azido-3-deoxy-beta-D-ribofuranosyl)-9H-purine (39) (Scheme III) (Method 5): To a precooled (0 ℃) mixture of 1,2-di-*O*-acetyl-5-*O*-(4-methylbenzoyl)riboside (**32**) (7.5 g, 19.9 mmol, 1.0 eq) and 6-chloropurine (3.38 g, 21.9 mmol, 1.1 equiv) in anhydrous acetonitrile (100 mL) was added dropwise a solution of 1,8-diazabicyclo [5.4.0] undec-7-ene (DBU) (9.0 mL, 9.13 g, 60.0 mmol, 3.0 equiv) in anhydrous acetonitrile (30 mL), followed by addition of trimethylsilyl triflate (14.5 mL, 17.8 g, 80.0 mmol, 4.0 equiv). The reaction mixture was then stirred at 60 ℃ for 4 h. Upon completion of the reaction as monitored by TLC, the reaction mixture was poured into ice water and was treated with saturated sodium bicarbonate and ethyl acetate. The organic phase was separated, and the aqueous phase was extracted with ethyl acetate. The combined organic phases were dried over anhydrous sodium sulfate. The drying agent was filtered off, and the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography on a silica gel column using petroleum ether–ethyl acetate (5:1 to 3:1) as eluents providing product **39** (8.4 g, 89%) as a white solid. ESI-MS m/z: 272.1 $[M]^+$.

Synthesis of 3'-azido-3'-deoxyadenosine 20 (Scheme III) (Method 6): 6-Chloro-9-(2-*O*-acetyl-5-*O*-*p*-toluoyl-3-azido-3-deoxy-beta-D-ribofuranosyl)-9H-purine (**39**) (3.0 g, 6.4 mmol) was dissolved in methanol (30 mL) and the solution was saturated with dry ammonia gas at 0 ℃. The reaction mixture was stirred for overnight at 80 ℃, and was concentrated under reduced pressure. The resulting residue was purified by flash chromatography on a silica gel column to afford 1.3 g of compound **20** as a white solid in 70% yield with an HPLC purity of 96.7%. R_f = 0.20 (dichloromethane–methanol = 10:1). m.p. decomposed at 200–205 ℃ (Lit. m.p. 208–212 ℃ [21]). UV-vis (MeOH) λ_{max}: 260 nm; ESI-MS m/z: 292.9 $[M + H]^+$.

Synthesis of 3'-azido-3'-deoxy-N^6-methyladenosine 21 (Scheme III): 6-Chloro-9-(2-*O*-acetyl-5-*O*-*p*-toluoyl-3-azido-3-deoxy-beta-D-ribofuranosyl)-9H-purine (**39**) (4.6 g, 9.7 mmol) was dissolved in methylamine (60 mL) solution in methanol. The reaction mixture was stirred at 80 ℃ overnight. Upon completion of the reaction as monitored by TLC, the reaction solvent was evaporated under reduced pressure. The resulting residue was purified by flash chromatography on a silica gel column to afford 2.4 g of compound **21** as a white solid in 82% yield with an HPLC purity of 98.5%. R_f = 0.6 (dichloromethane –methanol = 10:1). m.p. decomposed at 165–170 ℃. UV-vis (MeOH)

λ_{max}: 261 nm; ESI-MS *m*/*z*: 307.1 $[M + H]^+$, 329.1 $[M + Na]^+$ [22].

Synthesis of 3'-Azido-3'-deoxy-N^6,N^6-dimethyl adenosine 22 (Scheme III): 6-Chloro-9-(2-*O*-acetyl-5-*O*-*p*-toluoyl-3-azido-3-deoxy-beta-D-ribofuranosyl)-9H-purine (**39**) (4.2 g, 8.9 mmol) was dissolved in dimethylamine (20 mL) solution in methanol. The reaction mixture was heated at 100 ℃ overnight. Upon completion of the reaction as monitored by TLC, the reaction solvent was evaporated under reduced pressure. The resulting residue was purified by flash chromatography on a silica gel column to afford 2.4 g of compound **22** as a white solid in 86% yield with an HPLC purity of 98.5%. R_f = 0.7 (dichloromethane–methanol = 10:1). m.p. decomposed at 185–190 ℃ (Lit. m.p. 199–201 ℃ [12]).

Synthesis of 6-methylpurine-β-D-(3-azido-3-deoxy) riboside 23 (Scheme III): This compound was synthesized by **Method 5** as described above from the glycosylation of 6-methylpurine (1.4 g, 8.8 mmoL, 1.1 eq) with **32** (3.0 g, 8.0 mmoL) and the resulted compound was further deprotected by **Method 2** resulted in 1.6 g of final product **23** as a white solid in 72% total yield with an HPLC purity of 99.2%. R_f = 0.6 (dichloromethane–methanol = 10:1). m.p. decomposed at 170–173 ℃. ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 2.73 (s, 3H, CH_3), 3.56～3.65 (m, 1H, CH), 3.69～3.76 (m, 1H, CH), 4.00～4.05 (m, 1H, 4'-H), 4.31～4.36 (m, 1H, 3'-H), 4.99～5.05 (m, 1H, 2'-H), 5.27 (t, 1H, J=5.2 Hz, 5'-OH), 6.03 (d, 1H, J=5.6 Hz, 2'-OH), 6.29 (d, 1H, J=5.6 Hz, 1'-H), 8.75 (s, 1H, ArH), 8.80 (s, 1H, ArH); ESI-MS *m*/*z*: 292.1 $[M + H]^+$, 314.1 $[M + Na]^+$. HRMS calcd for $C_{11}H_{13}N_7NaO_3$ $[M + Na]^+$ 314.0978, found 314.0979.

Synthesis of 3'-amino-3'-deoxyadenosine 24 (Scheme III): This compound was synthesized by **Method 3** as described above from compound **20** (2.0 g, 6.8 moL) resulting in 1.6 g of compound **24** as a gray solid in 87% yield with an HPLC purity of 96.6%. R_f = 0.60 (dichloromethane–methanol = 2:1). m.p. decomposed at 230–235 ℃ (Lit. >230 ℃ [21]). UV-vis (MeOH) λ_{max}: 258 nm; ESI-MS *m*/*z*: 267.1 $[M + H]^+$, 329.1 $[M + Na]^+$.

Synthesis of 1,2-di-*O*-acetyl-5-*O*-(4-methyl benzoyl)-L-riboside (43) (Scheme IV): 1,2-*O*-Isopropylidene-α-L-xylofuranose (**40**) was synthesized from L-(-)-xylose by two steps in 98% total yield according to procedures described in the literature [15]. This material (100 g, 0.53 mol) was dissolved in 800 mL of dry pyridine and the mixture was cooled to 0 ℃. Then 4-methylbenzoyl chloride (76.3 mL, 0.58 mol, 1.1 eq) was added dropwise with stirring. The reaction mixture was stirred for 2 h. Upon completion of the reaction as monitored by TLC, the reaction mixture was poured into ice water and was treated with ethyl acetate. The organic phase was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by flash chromatography on a silica gel column to provide product 1,2-*O*-isopropylidene-5-*O*-(4-methylbenzoyl)-α-L-xylofuranose as a colorless oil. It was then dissolved in 200 mL dry pyridine and 600 mL dichloromethane. The mixture was cooled to -20 ℃. Then trifluoromethanesulfonic anhydride (96.5 mL, 0.58 mol, 1.1 eq) was added dropwise with stirring. The reaction mixture was stirred for 2 h at -20 ℃. Upon completion of the reaction as monitored by TLC, the reaction mixture was poured into saturated sodium bicarbonate and was treated with ethyl acetate. The organic phase was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by flash chromatography on a silica gel column to provide 178 g of product 1,2-*O*-isopropylidene-5-*O*-(4-methyl benzoyl)-3-*O*-trifluoromethanesulfonyl-α-L-xylofuranose (**41**) in 76.5% yield in two steps as a white solid. This material was dissolved in 1500 mL dry DMF, and sodium azide (52.0 g, 0.81 moL, 2.0 eq) was added. The reaction mixture was stirred for 72 h at room temperature. The reaction mixture was poured into water and was treated with ethyl acetate. The organic phase was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by flash chromatography on a silica gel column to provide 74.0 g of product 3-azido-1,2-*O*-isopropylidene-5-*O*-(4-methylbenzoyl)-3-deoxy-α-L-xylofuranose (**42**) in 55% yield as a colorless oil. This material was dissolved in 200 mL of acetic acid and 100 mL of acetic anhydride, and 3.0 mL of concentrated sulfuric acid was added under stirring. The reaction mixture was stirred at room temperature overnight, and treated with 200 mL water. It was neutralized with sodium bicarbonate carefully and extracted with dichloromethane.

The organic phase was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by flash chromatography on a silica gel column using petroleum ether–ethyl acetate as an eluent to give 63.0 g white sticky product **43** in 75% yield.

Synthesis of 3'-azido-3'-deoxy-L-nucleoside derivatives 44–46 and deprotected compounds 25–27 (Scheme IV): These compounds were synthesized by **Method 1** as described above by the glycosylation of uracil, 5-methyl uracil and 4-fluorouracil with **43**, respectively, resulting in compounds **44–46**. Further deprotection by **Method 2** resulted in final products **25–27** as white solids in 65–72% overall yield.

Experimental details for 3'-azido-3'-deoxy-β-L-uridine (25) (Scheme IV): white solid, 73% yield in two steps with an HPLC purity of 96.8%. R_f = 0.5 (dichloromethane –methanol = 10:1). m.p. 135–138 ℃. UV-vis (MeOH) λ_{max}: 259 nm; ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 3.49～3.54 (m, 2H, CH_2), 3.80～4.05 (m, 2H, 4',3'-H), 4.35～4.50 (m, 1H, 2'-H), 5.29 (t, 1H, J=5.2 Hz, 5'-OH), 5.66 (d, 1H, J=8.0 Hz, ArH), 5.76 (d, 1H, J=5.2 Hz, 2'-OH), 6.17 (d, 1H, J=5.2 Hz, 1'-H), 7.88 (d, 1H, J=8.0 Hz, ArH), 11.48 (s, 1H, NH); ESI-MS m/z: 270.2 $[M + H]^+$, 291.9 $[M + Na]^+$.

Experimental details for 3'-azido-3'-deoxy-5-methyl-β-L-uridine (26) (Scheme IV): white foam, 77% yield in two steps with an HPLC purity of 98.9%. R_f = 0.6 (dichloromethane–methanol = 10:1). UV-vis (MeOH) λ_{max}: 260 nm; ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 1.77 (s, 3H, CH_3), 3.53～3.71 (m, 2H, CH_2), 3.85～3.89 (m, 1H, 4'-H), 4.07 (t, 1H, J=5.2 Hz, 3'-H), 4.40～4.45 (m, 1H, 2'-H), 5.26 (t, 1H, J=5.2 Hz, 5'-OH), 5.76 (d, 1H, J=5.6 Hz, 2'-OH), 6.11 (d, 1H, J=5.6 Hz, 1'-H), 7.71 (s, 1H, ArH), 11.34 (s, 1H, NH); ESI-MS m/z: 284.1 $[M + H]^+$, 306.1 $[M + Na]^+$.

Experimental details for 3'-azido-3'-deoxy-5-fluoro-β-L-uridine (27) (Scheme IV): white solid, 70% yield in two steps with an HPLC purity of 97.5%. R_f = 0.6 (dichloromethane–methanol = 10:1). m.p. 160–163 ℃. UV-vis (MeOH) λ_{max}: 261 nm; ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 3.55～3.64 (m, 1H, CH), 3.68～3.76 (m, 1H, CH), 3.90～3.98 (m, 1H, 4'-H), 4.03 (t, 1H, J=5.2 Hz, 3'-H), 4.37～4.52 (m, 1H, 2'-H), 5.44 (t, 1H, J=4.8 Hz, 5'-OH), 5.69～5.73 (m, 1H, 2'-OH), 6.19 (d, 1H, J=5.6 Hz, 1'-H), 8.27 (d, 1H, J=7.2 Hz, ArH), 11.89 (s, 1H, NH); ESI-MS m/z: 288.2 $[M + H]^+$, 310.1 $[M + Na]^+$. HRMS calcd for $C_9H_{10}fN_5NaO_5$ $[M + Na]^+$ 310.0564, found 310.0563.

General procedure for the synthesis of 3'-azido-3'-deoxy-L-cytidine derivatives 28–30 (Scheme IV): Compound **28–30** were synthesized by **Method 4** as described above from compound **44–46**, respectively.

Experimental details for 3'-azido-3'-deoxy-beta-L- cytidine (28) (Scheme IV): white solid, 78% yield in two steps with an HPLC purity of 98.4%. R_f = 0.3 (dichloromethane–methanol = 5:1). m.p. decomposed at 140–143 ℃. UV-vis (MeOH) λ_{max}: 265 nm; ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 3.53～3.60 (m, 1H, CH), 3.65～3.71 (m, 1H, CH), 3.88～3.97 (m, 2H, 3'-H, 4'-H), 4.33～4.39 (m, 1H, 2'-H), 5.21 (t, 1H, J=5.2 Hz, 5'-OH), 5.70～5.77 (m, 2H, 2'-OH, ArH), 6.10 (d, 1H, J=5.2 Hz, 1'-H), 7.20 (s, 1H, NH), 7.30 (s, 1H, NH), 7.82 (d, 1H, J=7.6 Hz, ArH); ESI-MS m/z: 269.1 $[M + H]^+$.

Experimental details for 3'-azido-3'-deoxy-5-methyl-beta-L-cytidine (29) (Scheme IV): light yellow solid, 74% yield in two steps with an HPLC purity of 95.3%. R_f = 0.45 (dichloromethane–methanol = 5:1). m.p. 105–107 ℃. UV-vis (MeOH) λ_{max}: 275 nm; ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 1.87 (s, 3H, CH_3), 3.54～3.62 (m, 1H, CH), 3.68～3.77 (m, 1H, CH), 3.90～4.00 (m, 2H, 4', 3'-H), 4.37～4.40 (m, 1H, 2'-H), 5.31 (t, 1H, J=5.2 Hz, 5'-OH), 5.75 (d, 1H, J=4.4 Hz, 2'-OH), 6.14 (d, 1H, J=5.2 Hz, 1'-H), 7.72 (s, 1H, NH), 7.81 (s, 1H, NH), 7.84 (s, 1H, ArH); ESI-MS m/z: 283.1 $[M + H]^+$.

Experimental details for 3'-azido-3'-deoxy-5-fluoro-beta-L-cytidine (30) (Scheme IV): white foam, 74% yield in two steps with an HPLC purity of 97.3%. R_f = 0.5 (dichloromethane–methanol = 5:1). UV-vis (MeOH) λ_{max}: 239, 280 nm; ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 3.54～3.62 (m, 1H, CH), 3.70～3.76 (m, 1H, CH), 3.90～3.98 (m, 2H, 3'-H, 4'-H), 4.31～4.37 (m, 1H, 2'-H), 5.38 (br, 1H, 5'-OH), 5.70～5.74 (m, 1H, 2'-OH), 6.15 (br, 1H,

1'-H), 7.61 (s, 1H, NH), 7.81 (s, 1H, NH), 8.17 (d, 1H, J= 7.2 Hz, ArH); ESI-MS m/z: 287.1 $[M + H]^+$, 573.2 $[2M + H]^+$.

Synthesis of 6-Chloro-9-[2-*O*-acetyl-5-*O*-(*p*-toluoyl)-3-azido-3-deoxy-beta-L-ribofuranosyl]-9H-purine (47) and 3'-Azido-3'- deoxy-beta-L-adenosine (31) (Scheme IV): Compound **47** was synthesized by Method **5** as described above from 6-chloropurine (1.80 g, 11.7 mmoL, 1.1 eq) and **43** (4.0 g, 10.6 mmoL, 1.0 eq). Further deprotection by **Method 6** resulted in 2.2 g of final product **31** as a white solid in 70% over yield with an HPLC purity of 97.0%. R_f = 0.4 (dichloromethane–methanol = 10:1). m.p. decomposed at 191–195 ℃ [21]. UV-vis (MeOH) λ_{max}: 259 nm; ESI-MS m/z: 293.1 $[M + H]^+$, 315.2 $[M + H]^+$.

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Supporting Information: ^{1}H NMR, MS and HRMS spectral data. This material is available free of charge via Internet at http://sioc-journal.cn.

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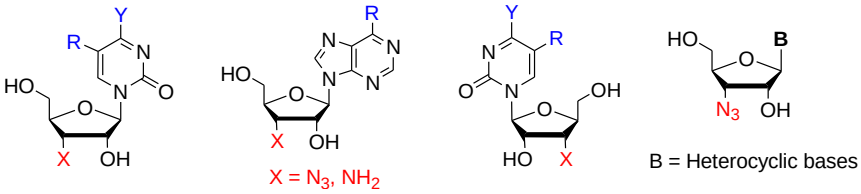
Synthesis of 3'-Azido-L- and D-Nucleosides



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3'-Azido-3'-deoxy-D-pyrimidine nucleosides **1**–**13**, purine nucleosides **20**–**24** and drug derivatives **14**–**19** as well as 3'-azido-3'-deoxy-L-nucleosides **25**–**31** were synthesied in parallel starting from the well protected key riboside intermediates **32** and **43**.

