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PAPER

Janus-type AT nucleosides: synthesis, solid and solution state structures†

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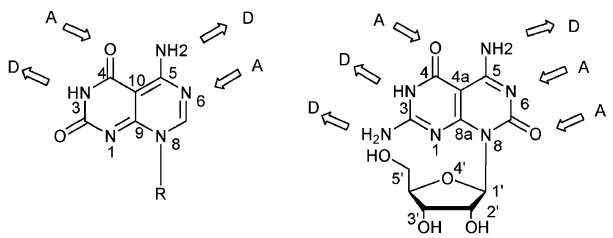
Novel Janus-type nucleoside analogues (**1a–d**) were synthesized. Their pyrimido[4,5-d]pyrimidine base moiety has one face with a bidentate Watson–Crick donor–acceptor (DA) H-bond array of adenine and the other face with an acceptor–donor (AD) H-bond array of thymine. These nucleosides may self-associate through the self-complementary base pair. Indeed, in the solid state, compound **6d** displayed a honeycomb-like supramolecular structure with tetrameric membered cavities formed through the combination of reverse Watson–Crick base pairs and aromatic stacking, in which the solvent molecules were accommodated. The result of temperature-dependent CD studies showed that the free nucleosides can form higher order chiral structures in aqueous solution.

Introduction

DNA is one of the most tailorable and versatile molecules from the "bottom-up" strategy point of view in the nanotechnology field due to its unique structural motif and self-recognition properties.[1–4] The power of DNA as a molecular tool is also enhanced by automated synthetic methods and by the PCR technique to amplify programmed DNA sequences from microscopic to macroscopic quantities. In addition, nature provides a complete toolbox of highly specific enzymes that enable the processing of the DNA material with atomic precision and accuracy. By modifying the base pairing patterns, except for the classical right-handed double-helix with Watson–Crick base pairs, polymorphic structural features[5–7] can be obtained which expands the application of DNA in the field of nanotechnology to great extent. For example, a cyclic trimeric[8] supramolecular structure based on guanosine-cytidine dinucleoside has been reported. Tetrameric[5,7,9–12] structures based on G-quartet have been used to construct nanowires,[13–15] biosensors,[16] ion pair receptors[12] and transmembrane ion transporters.[10,14,17] isoG cyclic pentamers with selective cation binding properties were also reported.[18–20]

Apart from the purine and pyrimidine derivatives, other heterocyclic systems can be employed as well to construct special supramolecular structures based on different base pair motifs. For example, Janus-type nucleobases were used as building blocks to form some unique supramolecular structures. Janus molecules (from the Roman god Janus) were first proposed to describe a new symmetrical carbocyclic system.[21] Previously, Janus-type guanosine-adenine base (J-GA) was synthesized to recognize C and U simultaneously.[22] Later, the self-complementary Janus-type ganosine-cytosine base (J-GC) deriveatives were synthesized and reported by Lehn and coworkers[23] to form a particular six-membered rosette structure. Mascal *et al.*[24] also reported a pyridopyrimidine derivative with hydrogen bonding codes of both guanine and cytosine and confirmed its rosette structure by a crystal state study. Recently, guanosine-cytosine derivatives with amino acids or the crown ethers attached to the nitrogen atom of the cytosine ring were found to form rosette helix nanotubes in solution state.[25–29] Perrin and coworkers[30] reported another self-complementary diaminopurine-thymine/uracil base (J-AT) system, which is also a tridentate system with alkyl groups attached to the nitrogen atom of the thymine ring. Through the crystal studies, they were found to form ribbon-like structures.



J-AT (1a-d) **J-GC**

Atom numbering used in AT system Systematic numbering

Scheme 1 Molecular structures and atom numbering of bidentate J-AT nucleosides and tridentate J-GC nucleoside. The arrows of A represent the hydrogen acceptors; the arrows of D represent the hydrogen donors. R = D-β-ribose (**1a**), R = L-β-ribose (**1b**), R = D-β-2′-deoxyribose (**1c**), R = D-α-2′-deoxyribose (**1d**).

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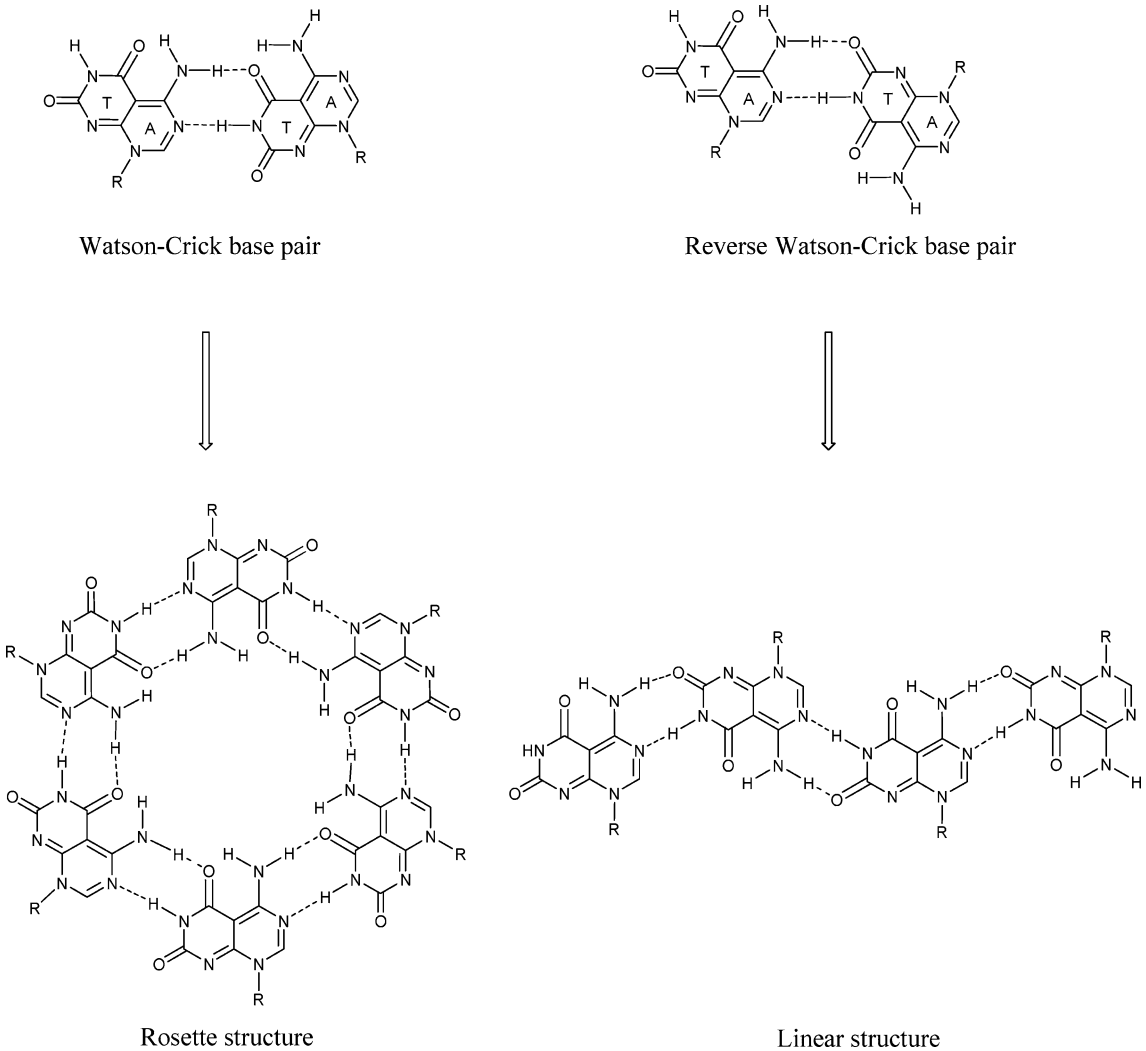
In order to employ this special base pairing of dual-hydrogen-pattern systems in the field of DNA (or RNA), the corresponding nucleosides are needed. However, there are few antecedent examples in which the Janus-type base attaching to a ribose or 2′-deoxyribose have been synthesized and investigated. Therefore, J-GC nucleoside has been synthesized in our laboratory which shows a preliminary antiviral activity.[31] Also it shows a similar nanotube-shaped structure in solution like alkylated Janus-type GC derivatives and the results will be reported elsewhere. Accordingly, we would like to expand this tridentate J-GC nucleoside system to a bidentate J-AT nucleoside system. For GC pyrimido[4,5-d]pyrimidine system, only the Watson–Crick base pair motif is feasible to maintain the tridentate H-bond array, which naturally leads to the formation of rosette structure just as reported.[23,32] Different from that, in the case of the AT system except for Watson–Crick base pairing (Scheme 2), the reverse Watson–Crick base pairing is also possible (Scheme 2). In the purine and pyrimidine system, the reverse Watson–Crick AT base pair will lead to the formation of parallel-stranded DNA which has been proven experimentally.[33–35] The energy calculation also showed a small difference between the parallel-stranded and the normal antiparallel-stranded duplex structures.[35,36] Consequently, for the AT pyrimido[4,5-d]pyrimidine system, if the Watson–Crick base pair is adopted a rosette structure will be formed; on the other hand if the reverse Watson–Crick base pair is adopted an infinite linear tape structure will be formed (Scheme 2). Therefore, it is very interesting to investigate which base pairing motif will dominate in these Janus-type AT nucleosides. For this purpose, we synthesized the Janus-type AT nucleosides **1a–d** (Scheme 1) which have never been reported before and studied their structures both in solid state and solution state.

Results and discussion

Chemical synthesis

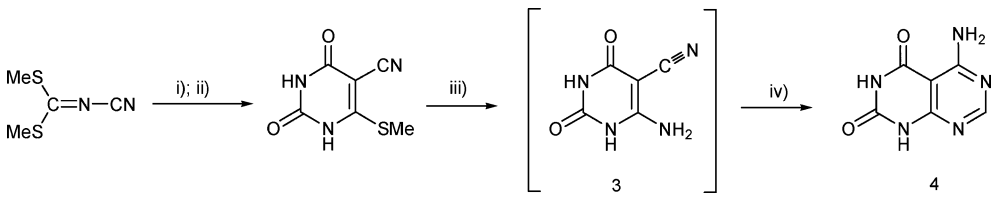
There are two major approaches for the synthesis of nucleosides. The first approach employs the corresponding base derivatives reacting with an appropriate sugar component (convergent glycosylation reaction). The second one involves the construction of a purine or pyrimidine system from a simple N-glycosylated precursor (linear method). We intended to adopt the direct



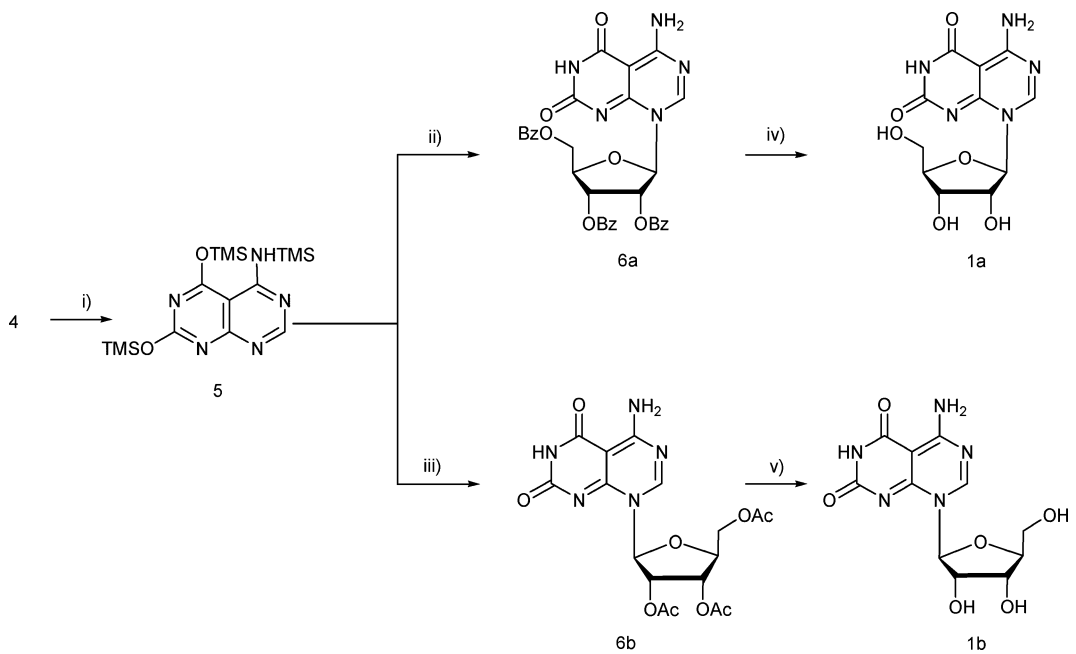
Scheme 2 Base pair motifs (R represents sugar moieties).

glycosylation reaction through Vorbrueggen method[37] using corresponding silylated Janus-type AT base moiety. To prepare the nucleobase **4**, we adopted the reported procedure employing *N*-bis(methylthio)methylenecyanamide as starting material.[38] However, during the synthesis we could not obtain the base **4** in larger scale as stated in the reference. The initial precipitate obtained in the reaction was not the final product we desired and probably with the structure of **3** according to its molecular weight of 152.03 from the mass spectra. So, after washing it with methanol, this intermediate was treated further with formamide, then pure compound **4** was obtained as yellowish powder precipitated from methanol (Scheme 3). Next, for silylation, base **4** and HMDS were refluxed with catalytic amount of TMSCl. The completion of the silylation of **4** was indicated by clarification of the reaction mixture and the excess of HMDS was removed by evaporation. The silylated base moiety **5** was used immediately in the glycosylation step due to its sensitivity to moisture. The glycosylation was accomplished by treating the compound **5** with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose at the presence of Lewis acid catalyst $SnCl_4$. The reaction leads to the formation of main product **6a** (Scheme 4). Its structure was studied with X-ray analysis (Fig. 1a) in which we found the sugar moiety attached to the N8 atom of adenine ring. The reason of regioselectivity in coupling of heterocyclic base and sugar may be due to steric hindrance of the thymine carbonyl group. To remove the protecting group, compound **6a** was treated with 0.5 M sodium methoxide. The structure of obtained compound **1a** was confirmed with 1H and 13 C HMQC and HMBC NMR spectroscopy. A similar procedure was used for synthesis of J-AT L-ribonucleoside (Scheme 4). The silylated base **5** was treated with 1,2,3,5-*O*-tetra-acetyl-β-L-ribofuranose employing catalyst $SnCl_4$ followed by deprotection, the corresponding L-nucleoside **1b** was afforded. In the case of L-nucleoside **1b**, the same structure determination procedure using NMR techniques was employed as in the case of D-ribonucleoside **1a**. Compound **1b** was assigned to be the L-β-nucleoside which indicated that the sugar ring was connected to the adenine ring.

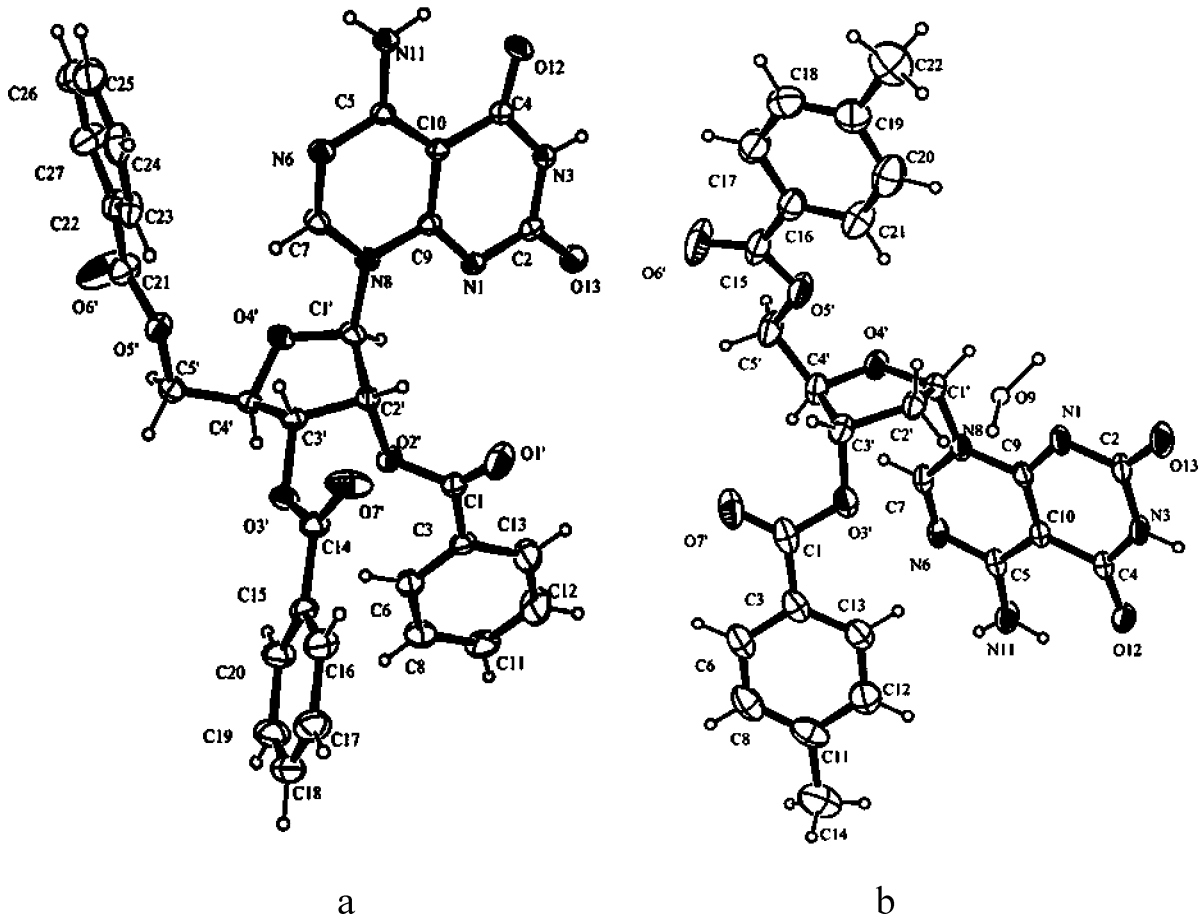
For the synthesis of 2′-deoxyribonucleosides, the same silylated base **5** was used as the acceptor and 1-α-chloro-3,5-di-*O*-toluoyl-2-deoxy-D-ribofuranose was used as donor. In the case of riboside, because of the steric hinderance of the 2′-acyloxy group, only β anomer nucleoside was formed. However, in the case of deoxyribonucleoside, without the neighboring-group participation, usually 1 : 1 mixtures of α : β anomers will be formed when employing the Vorbrueggen's glycolsylation conditions.[37] It was reported that CuI in $CHCl_3$ can facilitate the β-configuration selectivity with a electrical push-pull process for the normal purine and pyrimidine system.[39] However, this method did not give satisfactory result in this pyrimido[4,5-d]pyrimidine system. We had tried the reaction



Scheme 3 Synthesis of J-AT nucleobase: (i) DMSO, methyl cyanoacetate, K_2CO_3, 4 h, 10% HCl, 95%. (ii) 10% NaOH, r.t., 2 h, 70 °C, 10 min, 93%. (iii) Formamide, 180 °C, 4 h, 80%. (iv) Formamide, 180 °C, 4 h, 80%.



Scheme 4 Synthesis of J-AT D- and L-ribonucleosides: (i) HMDS, TMSCl, reflux. (ii) Dry acetonitrile, $SnCl_4$, 45%. (iii) Dry acetonitrile, $SnCl_4$ 50%. (iv) 0.5 M MeONa, reflux, 80%. (v) 0.1 M MeONa, reflux, 93%.



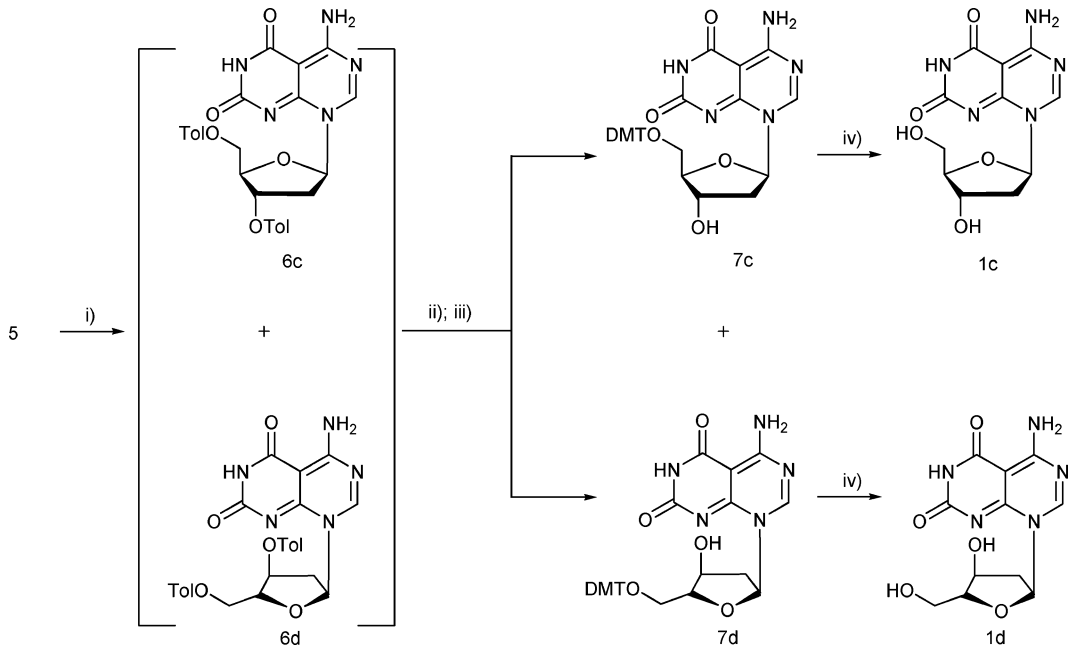
a b

Fig. 1 A perspective view of compounds **6a** (a) and **6d** (b) showing the atom-numbering and N8 atom on the adenine ring is connected to C1′-atom of sugar residues.

of silylated base **5** by treating with 1-α-chloro-3,5-di-*O*-toluoyl-2-deoxy-D-ribofuranose and with CuI as catalyst, however both anomeric isomers **6c** and **6d** were obtained in equal amounts and the total yield was poor. Later on, when using $SnCl_4$ as catalyst, the yield of the products was poor as well. Therefore, we finally chose Lewis acid trimethylsilyl triflate as catalyst which provided better total yield than either CuI or $SnCl_4$. However, due to the similar polarity of compound **6c** and **6d**, we failed to separate them by flash column chromatograph using different eluent systems. Even the protecting groups on sugars were removed, it was also not feasible to separate α and β isomers of the free nucleosides. The separation of them was achieved by introducing DMT group to 5′-OH group of the nucleosides later on. The compounds **7c** and **7d** with DMT attached can be separated by column chromatography. Subsequently, the DMT group was removed by treating **7c** and **7d** with 2.5% DCA methylene chloride solution (2.5 mL DCA was added in 10 mL methylene chloride), and the free nucleosides **1c** and **1d** were obtained as white powders (Scheme 5). Considering the laborious process of such operations, we tried to find another convenient method. After numerous attempts with different solvents, finally we found **6c** can precipitate as a white powder from ethyl acetate while **6d** will be remained in solution. Subsequently, **1c** and **1d** were obtained by removing the toluoyl group accordingly. The regioselectivity and anomeric configuration of **6d** were proven by X-ray analysis (Fig. 1b). It was identified as the D-α-deoxyribonucleoside and the sugar moiety was also attached to the N8 atom of the adenine ring (Fig. 1b). For compound **6c**, we failed to obtain a good quality single crystal for X-ray diffraction studies. Therefore, we employed the ^{1}H-^{13}C HMQC and ^{1}H-^{13}C HMBC NMR spectroscopy to determine the configuration of compound **1c** to be D-β-2′-deoxyribonucleoside.

Solid state structure

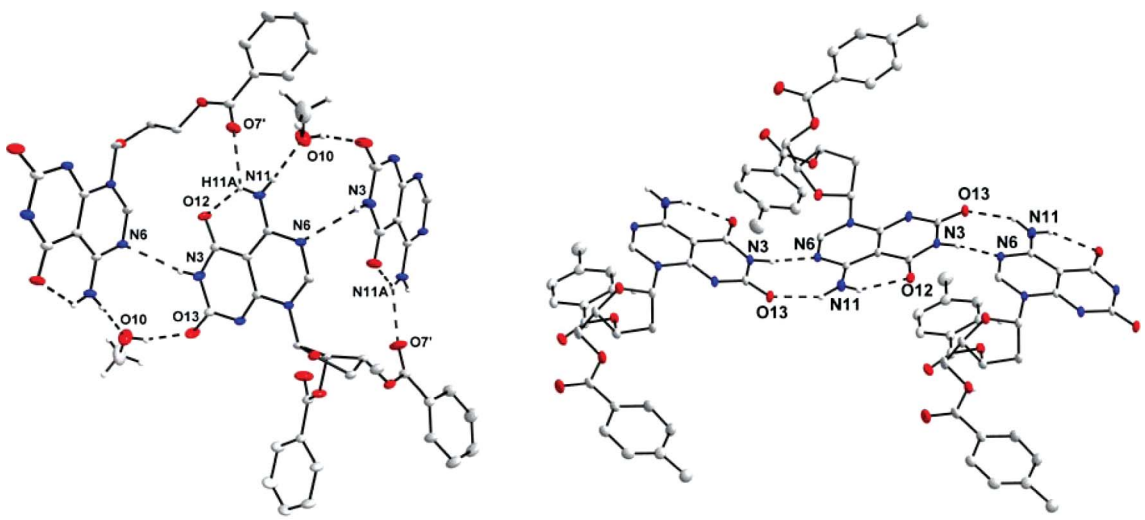
The single crystals of compounds **6a** and **6d** were obtained and some interesting structural differences in their solid state can be seen from the X-ray diffraction studies. The structure and atom numbering are shown in Fig. 1. Compound **6a** crystallized slowly from methanol while compound **6d** crystallized from methylene chloride/ethanol solution after the failure of crystallization from methanol. The detailed structural parameters of **6a** have been published elsewhere.[40] The nucleobase ring of **6d** is nearly planar just as **6a**. The deviations of ring atoms are less than 0.02 Å for each pyrimidine ring and the dihedral angle between the two rings is 2.03(8)°. The biggest deviation of exocyclic groups from the rings is –0.084(6) Å (O12). The orientation of the nucleobase relative to the sugar ring (*anti*/*syn* conformation) in normal N9-glycosylated purine nucleoside system is defined by the torsion angle χ (O4′–C1′–N9–C4).[41] When the pyrimidine ring of the purine is located outside the sugar plane, the conformation is defined as *anti*; on



Scheme 5 Synthesis of J-AT 2′-deoxy-ribonucleosides: (i) Dry 1,2-dichloroethane, trimethylsilyl triflate, 34%. (ii) 0.2 M MeONa, reflux, 80%. (iii) Dry pyridine, DMT-Cl, triethylamine, DMAP, overnight at r.t., 81%. (iv) 2.5% of DCA in CH_2Cl_2 r.t., 50%.

the other hand, when it is located above the sugar plane, the conformation is defined as *syn*. In the case of **6d**, the *anti*/*syn* conformation is also defined by the torsion angle χ (O4′–C1′–N8–C9) and the value is 173.6 (3)°, with the thymine ring located outside the sugar ring. Therefore, **6d** adopts an *anti* conformation which is consistent with that of **6a**. However, there is a difference in the sugar puckering mode between **6a** and **6d**. **6a** adopts an N-type (3′-*endo*) conformation with a twist of C3-*endo* ($^3T_4$) $P = 24.5\ (2)°$, $\tau_m = 38.3\ (2)°$, a typical sugar puckering mode for ribonuleosides. **6d** adopts an N-type (2′-*endo*) conformation, with an asymmetrical twist of ($^2T_1$), $P = 159.1\ (2)°$, $\tau_m = 30.9\ (2)°$ which is a typical sugar puckering mode for 2′-deoxynucleosides.

The most striking difference between the two compounds was displayed in their hydrogen bond patterns. For compound **6a**, each nucleoside molecule contains an intramolecular H-bond formed between the bifurcated H11A atom and O12 atom and six intermolecular hydrogen bonds (Fig. 2a). The intermolecular hydrogen bonds N3–H3···N6 (formed directly between the thymine and adenine faces), N11–H11A···O7′ together with the bridged methanol act as the repeated units connecting adjacent nucleosides head to head in an anti-parallel way to form an infinite one dimension tape with a nearly perpendicular dihedral angle between the adjacent nucleobase planes. For compound **6d**, each nucleoside molecule contains an intramolecular hydrogen bond



(**a**) (**b**)

Fig. 2 A detailed view of the H-bonds on compounds **6a** (a) and **6d** (b). H-bonds are shown in dashed lines. Atoms are coded as follows: red, oxygen; blue, nitrogen; gray, carbon. H atoms and some groups which are not involved in H-bonds have been omitted for clarity.

which is the same as in **6a** and five intermolecular hydrogen bonds. The intermolecular hydrogen bonds are formed between the faces of adenine (A) and thymine (T): (A) N11–H11A···O13 (T) and (A) N3–H3···N6 (T). They connected adjacent nucleoside molecules to form an infinite wavy tape in typical reverse Watson–Crick base pair pattern. The distance between the hydrogen bond of A (H11B) and T (O13) is 0.211 nm and the distance between another hydrogen bond of A (N6) and T (H3) is 0.194 nm, which were just located in the reported hydrogen bonds range of 0.19–0.22 nm for the reverse Watson–Crick AT base pairs.[34]

The supramolecular structure for **6a** and **6d** was also different. In case of **6a**, the one dimensional tapes were arranged in parallel to form an infinite two-dimensional pleated sheet structure through the aromatic stacking between the nucleobase plane and the benzene ring of the benzoyl protecting group on furanoribose 5′-OH with a distance of 0.35 nm (Fig. 3a1). Comparing to the pleated sheet structure of **6a**, a quite different structure was formed by **6d**. The neighboring two tapes were associated together through two types of aromatic stacking (Fig. 3b1 and 3b2). One such stacking mode is a sandwich shape with the 3′-benzoyl groups located at the bottom, the nucleobase plane of the reverse Watson–Crick base pair from the same tape inserted into the middle and the 5′-benzoyl groups from adjacent tape located on the top of the base pair (Fig. 3b1). The other stacking is also in a sandwich shape but with the base pair on the top, 3′-benzoyl groups in the middle, and the 5′-benzoyl groups of next nucleoside from adjacent tape located below the 3′-benzoyl group (Fig. 3b2). The distance of the aromatic stacking is 0.34 nm, exactly the same as the base pair stack distance in the DNA duplexes. As a whole, both aromatic stacking and the reverse Watson–Crick base pair tethered four **6d** molecules together to form a rectangular cavity with two water molecules and two ethanol molecules located inside. This cavity was repeated to form an infinite honeycomb-like network structure.

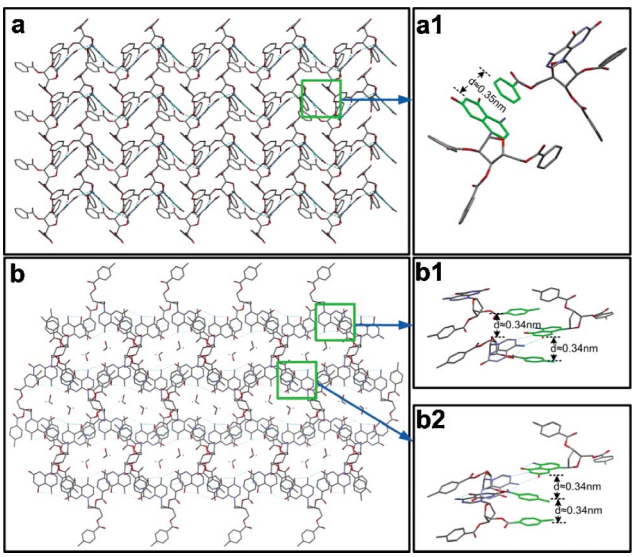


Fig. 3 The pleated supramolecular structure formed by one dimensional tapes in compounds **6a** (a) and the honeycomb-like structure formed by one dimensional tapes in compound **6d** (b). The aromatic stacking interaction between the tapes in **6a** (a1). Two types of π-stacking interactions between the tapes in **6d** (b1), (b2). With the exception of the green π-stacking planes, all atoms are coded as follows: red, oxygen; blue, nitrogen; gray, carbon. The H atoms were omitted for clarity.

Solution state structure

For free nucleosides **1a–d**, without aromatic stacking of the protecting groups, in principle only the base pairs can be used for self-assembly. In order to explore if they can, in fact, form the regular structures like the tridentate-hydrogen-bonds J-GC system, we investigated their self-assemble property in solution state. Earlier, the variable temperature ^{1}HNMR (VT NMR) spectrometry has been used to investigate the self-assembly of the J-GC base derivatives in toluene.[23] Therefore, we employed this VT NMR technique to study the hydrogen bonds formation of compounds **1a** and **1d** in DMSO. As can be seen from Fig. 4, for compound **1a**, the chemical shift of the hydrogen atom of imino group on the thymine ring (N3H) moves from δ 10.80 (293 K) to δ 10.57 ppm (333 K) with $\Delta\delta = 0.23$ ppm; and the chemical shift for N11H atom of the amino group on the adenine ring moving from δ 8.94 (293 K) to δ 8.75 ppm (333 K) with $\Delta\delta = 0.19$ ppm. These results indicate that these hydrogen atoms participating in the intermolecular hydrogen bonds formation. Another hydrogen atom from the amino group on the adenine ring at δ 8.96 ppm was assigned to be the intramolecular hydrogen bond since its chemical shift remains unchanged. For compound **1d**, similar chemical shift changes were observed, with $\Delta\delta = 0.24$ ppm (from 293 K to 333 K) for N3H and $\Delta\delta = 0.20$ ppm (from 293 K to

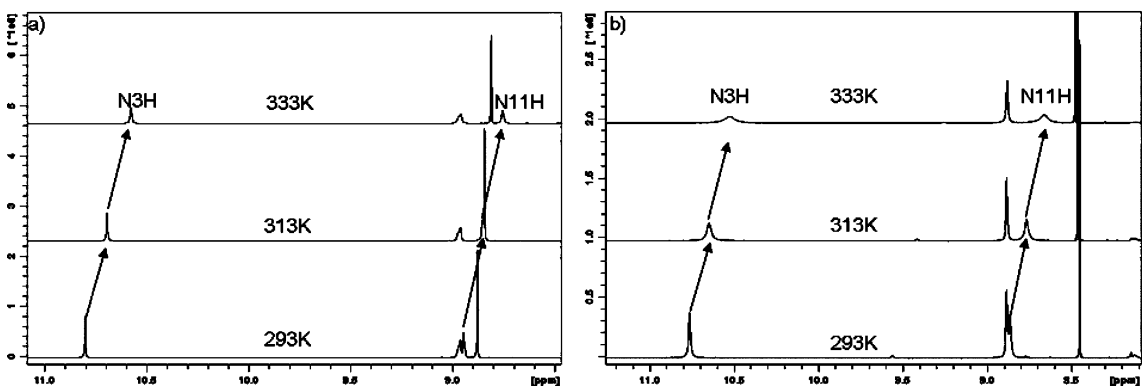
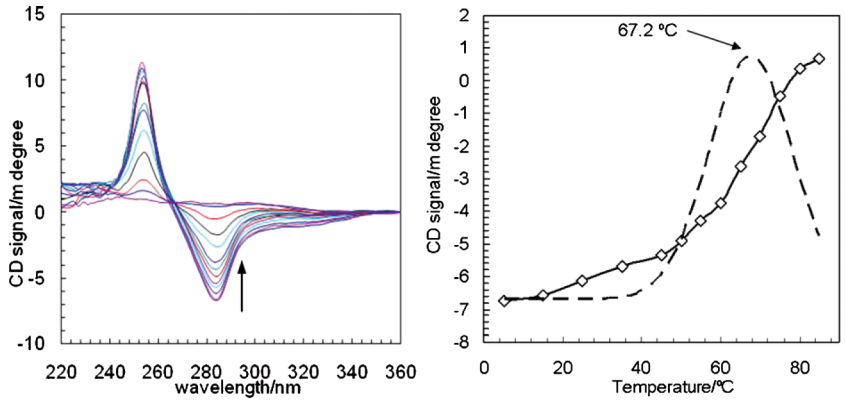


Fig. 4 The variable temperature ^{1}HNMR spectra of compounds **1a** (a) and **1d** (b).



(a) (b)

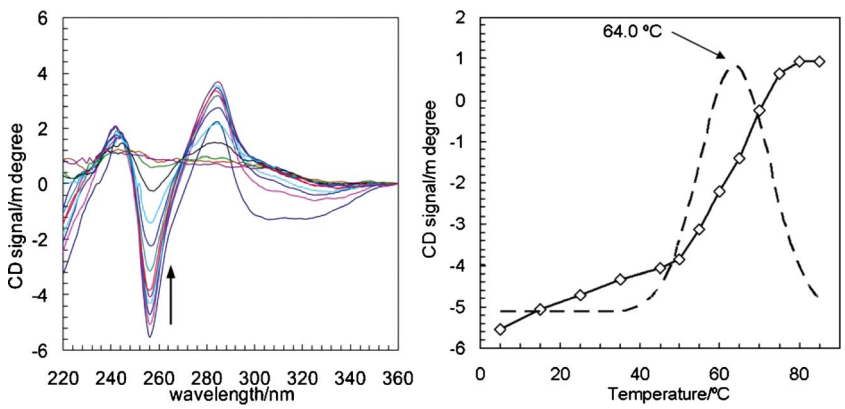
Fig. 5 (a) Temperature-dependent CD spectra of unbuffered aqueous solution for compound **1d** (3.69×10^{-4} mol L^{-1}). The arrow indicates the trend of temperature increasing: 5.0 °C, 15.0 °C, 25.0 °C, 35.0 °C, 45.0 °C, 50.0 °C, 55.0 °C, 60.0 °C, 65.0 °C, 70.0 °C, 75.0 °C, 80.0 °C, 85.0 °C; temp. ramp: 1 °C min^{-1}. Wavelength start: 360 nm, wavelength end: 220 nm, wavelength step: 1 nm. (b) Temperature dependence of **1d** at 284 nm. T_m: 67.2 °C.

333 K) for N11H. Another N11H atom (δ 8.88 ppm) in amino group on the adenine ring participating in the intramolecular hydrogen bond remained unchanged upon the increasing of the temperature. Therefore, the VT NMR studies indicated the self-assembly structure of compounds **1a** and **1d** in DMSO were formed through hydrogen bonds. Next, in order to study whether some higher order structures will be formed by compounds **1a–d** in aqueous solution like the J-GC derivatives, the temperature-dependent CD spectra were performed.

In the case of 2′-deoxyribonucleosides **1c**, **1d**, CD spectra displayed the positive and negative Cotton effect. With the temperature changes, a temperature dependent melting phenomenon was observed. The maximum (253 nm) and minimum (284 nm) of CD spectra for compound **1d** (Fig. 5) disappeared completely upon the temperature rising to 85 °C. By plotting the CD signal at 284 nm against the temperature, a sigmoid melting curve was obtained with the T_m value to be 67.2 °C. For compound **1c**, a similar phenomenon was observed which gave a T_m value of 64 °C (Fig. 6). The phenomenon in CD spectra is similar to that of the J-GC derivatives indicating a higher order chiral structure was also formed by the bidentate J-AT deoxyribonuleosides in solution state. In the case of J-AT ribonucleosides, their CD spectra also displayed positive and negative Cotton effects and the D-isomer (**1a**) and L-isomer (**1b**) gave a spatial mirror image (Fig. 7) due to their enantiomeric character of the sugar residues. On the contrary, their CD peaks of maximum and minimum were not vanished as the temperature increasing from 5 °C to 85 °C. This phenomenon indicates that the structures of **1a** and **1b** formed in aqueous solution may be more stable than that of compounds **1c** and **1d**, the T_m values are higher than 85 °C; or the structure of ribonucleosides **1a** and **1b** formed in water is very different to that of the deoxyribonucleosides **1c** and **1d**. To solve this problem other techniques are needed, the suitable conditions for further X-ray structure determination are under investigations.

Conclusion

We synthesized a series of novel Janus-type AT ribonucleosides and 2′-deoxyribonucleosides by Vorbrueggen glycosylation



(a) (b)

Fig. 6 (a) Temperature-dependent CD spectra of unbuffered aqueous solution for compound **1c** (3.39×10^{-4} mol L^{-1}), The arrow indicates the trend of temperature increasing: 5.0 °C, 15.0 °C, 25.0 °C, 35.0 °C, 45.0 °C, 50.0 °C, 55.0 °C, 60.0 °C, 65.0 °C, 70.0 °C, 75.0 °C, 80.0 °C, 85.0 °C; temp. ramp: 1 °C min^{-1}. Wavelength start: 360 nm, wavelength end: 220 nm, wavelength step: 1 nm. (b) Temperature dependence of **1c** at 256 nm. T_m: 64 °C.

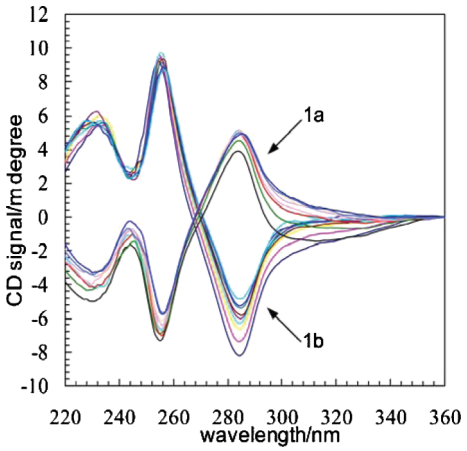


Fig. 7 CD spectra of unbuffered aqueous solution for compound **1a** (3.37×10^{-4} mol L^{-1}) and compound **1b** (3.47×10^{-4} mol L^{-1}). Temp. start: 5 °C, end: 85 °C, temp. step: 10 °C, temp. ramp: 1 °C min^{-1}; wavelength start: 360 nm, wavelength end: 220 nm, wavelength step: 1 nm.

reaction using silylated AT pyrimido[4,5-d]pyrimidine base moieties and the corresponding sugar donors. In the solid state, depending on the variation of sugar residues and solvent environment different supramolecular structures will be formed. Especially, with the combination of reverse Watson–Crick base pairs and the aromatic stacking from sugar hydroxyl protecting groups, compound **6d** can form a honeycomb-like supramolecular network structure with rectangle cavities containing two water molecules and two ethanol molecules inside. From the NMR studies, the hydrogen bonds were maintained in DMSO for both free ribonuleosides and 2′-deoxyribonuleosides. According to the CD spectra, the nucleoside monomers can form a higher order chiral suprastructure in aqueous solution. If these nucleoside monomers are incorporated into the oligonucleotides, with the help of phosphodiester and sugar backbone and the base pair stacking, whether some interesting structures will be formed at the DNA/RNA level is a very interesting topic to be explored. The relevant work is under investigation and will be reported in due time.

Experimental

General

All chemicals were bought from Sigma–Aldrich. The solvent and reagent are analytic pure. Solvents 1,2-dichloroethane and acetonitrile have been purified by distilling from phosphorus pentoxide. Pyridine is treated with calcium hydride in a similar way. Thin-layer chromatography (TLC) is performed on aluminium sheet covered with silica gel 60 F254 (0.2 mm, Merck, Germany). Flash column chromatography (FC): silica gel 60 (Haiyang chemical company, P. R. China) at 0.4 bar. The new compounds were characterized by NMR, high-resolution ESI Mass spectra and UV-spectra. NMR spectra were recorded on a *AV II* (Bruker, Germany) spectrometer at 400 MHz and 600 MHz. ESI mass spectra were performed on a mass spectrometer (Q-TOF-premier, Waters company, US), the UV/vis absorption spectra were collected on a DU-800 spectrophotometer (Beckman, US) using 1 cm path length quartz cuvettes, λ_{max} in nm, ε in dm^3 mol^{-1} cm^{-1}. CD spectra were recorded on circular dichroism spectrometer (Aviv Biomedical, Inc.). Proper size single crystals of **6a** and **6d** were stabilized into a tiny glass tube including mother liquor with epoxy resin to minimize solvent loss. Crystal Data were collected on CAD4SDP-44 M/H instrument (Xcalibur, Eos, Oxford Diffraction Ltd.).

5-Amino-8-(2,3,5-tri-*O*-benzoyl-β-D-furanosyl) pyrimido[4,5-d]pyrimidine-2,4(3H,8H)-dione (6a)

Compound **4** (600 mg, 3.3 mmol) was suspended in Hexamethyldisilazane (HMDS) (30 mL) and stirred at 140 °C for about 3 min, then trimethylsiyl chloride (TMSCl) (600 µL, 4.7 mmol) was added, the reaction was stirred at reflux for 18 h until the mixture was clear, then the solution was evaporated to remove HMDS, the silylated base **5** was obtained which was immediately used in next step without further purification. Dry 1,2-dichloroethane (20 mL) was added in the pot containing silylated base **5** and stirred. 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose (630 mg, 1.6 mmol) dissolved in dry acetonitrile (20 mL) was added in this solution above. $SnCl_4$ (550 µL, 4.2 mmol) was added as catalyst at 0 °C. After the mist vanished, the reaction stirred at room temperature. 0.5 h later, saturated $NaHCO_3$ aqueous solution (40 mL) was added at 0 °C to quench the reaction; CH_2Cl_2 (3 × 40 mL) was used to extract the organic phase, after dried with anhydrous Na_2SO_4, the organic phase was evaporated. The residue was applied to F.C. (silica gel, column 4 × 8 cm, elution with CH_2Cl_2 to CH_2Cl_2 : methanol 98 : 2) and afforded **6a** (940 mg, 45%): UV (MeOH): 225 (95658), 251 (27263), 273 (15395), 278 (14355); δ_H (600 MHz; d_6-DMSO): 4.73–4.75 (2H, t, $J = 6$ Hz, 5′-H_2), 4.82–4.84 (1H, t, $J = 6$ Hz, 4′-H), 6.12–6.13 (1H, d, $J = 6$ Hz, 3′-H), 6.17–6.20 (1H, t, $J_1 = 12$ Hz, $J_2 = 6$ Hz, 2′-H), 6.51 (1H, s, 1′-H), 7.40–7.99 (15H, m, H-arom), 8.66 (1H, s, CH), 9.07 (1H, s, NH_α) 9.14 (1H, s, NH_β), 10.87 (1H, s, NH). δ_C (600 MHz; d_6-DMSO): 64.41, 71.12, 74.68, 80.25, 87.59, 129.00, 129.05, 129.13, 129.20, 129.62, 129.73, 129.78, 129.89, 133.98, 134.27, 134.37, 153.06, 156.72, 157.70, 162.03, 164.99, 165.13, 165.31. HRMS (ESI+) *m/z*: Calc. for $C_{32}H_{25}N_5O_9$: 646.1550 $[M+Na]^+$. Found 646.1549 $[M+Na]^+$.

5-Amino-8-(β-D-furanosyl) pyrimido[4,5-d]pyrimidine-2,4(3H,8H)-dione (1a)

Compound **6a** (80 mg, 0.13 mmol) was suspended in solution of 0.5 M NaOMe/MeOH (10 mL), the reaction continued at reflux for 20 min, the mixture solution turned to be gel attached to the wall of the glass pot. After cooling to room temperature, the gel was neutralized with diluted acetic acid to about pH 6.5 and filtered; the precipitate obtained was washed with methanol (2 × 10 mL) and water (1 × 10 mL). After vacuum drying, **1a** was obtained (32 mg, 80%): UV (MeOH): 251 (25943), 277 (5681); δ_H (600 MHz; d_6-DMSO): 3.60–3.80 (2H, m, 5′-H_2), 3.94–3.97 (1H, m, 4′-H), 4.08–4.17 (2H, m, 3′-H, 2′-H), 5.08–5.10 (1H, d, J = 12 Hz, 5′-OH), 5.27–5.29 (1H, t, $J = 6$ Hz, 3′-OH), 5.55–5.56 (1H, d, $J = 6$ Hz, 2′-OH), 6.17–6.18 (1H, d, $J = 6$ Hz, 1′-H), 8.88 (1H, s, CH), 8.92 (1H, s, NH_α), 8.98 (1H, s, NH_β), 10.77 (1H, s, NH). δ_C (600 MHz; d_6-DMSO): 60.04, 69.04, 74.98, 85.06, 87.44, 90.26, 151.88, 157.00, 158.18, 162.00, 165.44. HR-MS (ESI–) *m/z*: Calc. for $C_{11}H_{13}N_5O_6$: 310.0788 $[M - H]^-$. Found 310.0787 $[M - H]^-$.

5-Amino-8-(2,3,5-tri-*O*-benzoyl-β-L-furanosyl)pyrimido[4,5-d]pyrimidine-2,4(3H,8H)-dione (6b)

Compound **4** (4.2 g, 23.4 mmol) was suspended in HMDS (300 mL) and stirred at 140 °C for about 3 min, TMSCl (4 mL, 31.6 mmol) was added as catalyst, and the reaction was refluxed with exclusion of humidity for 7 days until it became clear. Then, the solution was evaporated to remove HMDS. Compound **5** was afforded, which was used for the next step immediately without further purification. The silylated base **5** was dissolved in dry 1, 2-dichloroethane (200 mL) and stirred at room temperature. To which 1,2,3,4-tetra-*O*-acetyl-β-L-ribofuranose (3.8 g 12 mmol) suspended in dry acetonitrile (200 mL) was added. $SnCl_4$ (4 mL, 30.3 mmol) was added as catalyst at 0 °C. After the mist vanished, the reaction mixture was stirred at room temperature for 1.5 h. Then the acetonitrile was removed by evaporating, the reaction mixture was diluted with (3 × 200 mL) CH_2Cl_2 to extract the organic phase, and then cold saturated $NaHCO_3$ aqueous solution (200 mL) was added to wash the organic phase. The combined organic phase was dried with anhydrous Na_2SO_4 and evaporated, the residue was applied to FC (silica gel, column 5 × 10 cm, elution with CH_2Cl_2 to CH_2Cl_2 : methanol 98 : 2), furnishing compound **6b** (5.8 g, 50%): UV (MeOH): 251 (16690), 231 (11163), 278 (4319). δ_H (600 MHz; d_6-DMSO): 2.05–2.08 (9H, t, 3OAc), 4.32–4.40 (3H, m, 4′-H, 5′-H_2), 5.53–5.56 (1H, t, J_1 = 8 Hz, J_2 = 4 Hz, 3′-H), 5.64–5.67 (1H, q, J = 4 Hz, 2′-H), 6.27–6.28 (1H, d, J = 4 Hz, 1′-H), 8.56 (s, 1H, CH), 9.06–9.07 (1H, d, J = 4 Hz, NH_α), 9.15–9.16 (1H, d, J = 4 Hz, NH_β), 10.85 (s, 1H, NH). δ_C (600 MHz; d_6-DMSO): 20.74, 20.77, 20.98, 63.42, 70.15, 73.39, 80.36, 87.41, 89.88, 152.58, 156.70, 157.69, 161.93, 165.28, 169.74, 169.86, 170.51. MS (ESI–) m/z: Calc. for $C_{17}H_{19}N_5O_9$: 436.1104 $[M - H]^-$. Found: 436.1102 $[M - H]^-$.

5-Amino-8-(β-L-furanosyl)pyrimido[4,5-d]pyrimidine-2,4(3H,8H)-dione (1b)

Compound **6b** (2 g, 4.5 mmol) was suspended in 0.2 M NaOMe/MeOH (50 mL), the mixture reaction was stirred at room temperature until the compound **6b** disappeared monitored by TLC. Then the reaction solution was neutralized with diluted acetic acid, filtered and the precipitate was washed with methanol (3 × 50 mL), after the vacuum drying, giving compound **1b** (1.3 g, 93%): UV (MeOH) 226 (47903), 251 (22074), 272 (9568). δ_H (600 MHz; d_6-DMSO): 3.60–3.63 (1H, m, 5′-Hα), 3.76–3.79 (1H, m, 5′-H_β), 3.94–3.96 (1H, m, 4′-H), 4.08–4.09 (1H, d, J = 6 Hz, 3′-H), 4.14–4.15 (1H, d, J = 6 Hz, 2′-H), 5.10–5.11 (1H, d, J = 6 Hz, 5′-OH), 5.28–5.30 (t, J = 6 Hz, 1H, 3′-OH), 5.57–5.58 (1H, d, J = 6 Hz, 2′-OH), 6.15–6.16 (1H, d, J = 2 Hz, 1′-H), 8.87 (1H, s, CH), 8.92 (1H, s, NH_α), 8.97 (1H, s, NH_β), 10.79 (s, 1H, NH). δ_C (600 MHz; d_6-DMSO): 59.98, 68.97, 74.96, 85.01, 87.45, 90.27, 151.86, 157.06, 158.16, 161.98, 165.43. MS (ESI–) m/z: Calc. for $C_{11}H_{13}N_5O_6$: 310.0787 $[M - H]^-$. Found: 310.0793 $[M - H]^-$.

5-Amino-8-[2-deoxy-3,5-di-*O*-(*p*-toluoyl)-β-D-*erythro*-pentofuranosyl]pyrimido[4,5-d]pyrimidine-2,4(3*H*,8H)-dione (6c); 5-amino-8-[2-deoxy-3,5-di-*O*-(*p*-toluoyl)-α-D-*erythro*-pentofuranosyl]pyrimido[4,5-d]pyrimidine-2,4(3H, 8H)-dione (6d)

Compound **4** (2 g, 11.2 mmol) was suspended in HMDS (150 mL) and the mixture was stirred at 140 °C for about 3 min. TMSCl (2 mL, 15.8 mmol) was added as catalyst, the reaction was stirred at reflux until the mixture solution became clear, and then evaporated to remove HMDS, the silylated base was obtained which was used for next step without further purification. The silylated base **5** was dissolved in dry 1,2-dichloroethane (60 mL), to which 1-α-chloro-3,5-di-*O*-toluoyl-2-deoxy-D-ribofuranose (3 g 7.7 mmol) dissolved in dry acetonitrile (60 mL) was added, trimethylsilyl triflate (TMSOTf) (1 mL, 5.6 mmol) was added at 0 °C, the reaction continued at room temperature for about 1.5 h. Saturated $NaHCO_3$ aqueous solution (120 mL) was added to quench the reaction at 0 °C, CH_2Cl_2 (3 × 120 mL) was used to extracted organic phase. The organic phase was combined and dried with anhydrous Na_2SO_4, then evaporated; the residues were applied to FC (silica gel, column 4 × 10 cm, elution with CH_2Cl_2 to CH_2Cl_2 : methanol 99 : 1 to 98 : 2), afforded a mixture of **6c** and **6d** as light yellow powder (2 g, 34%), and the mixture powder was dissolved in ethyl acetate, **6c** was separated as a precipitate, the supernate was evaporated to furnish the compound **6d** (at a ratio of **6c**:**6d** ≈ 2 : 1).

Compound **6c**: UV (MeOH) 247.0 (25867), 274.0 (4481). δ_H (600 MHz; d_6-DMSO): 2.37, 2.40 (6H, 2 s, $2CH_3$), 2.72–2.74 (1H, t, J = 6 Hz, 2′-H_α), 2.816–2.827 (1H, t, J = 4.2 Hz; 2′-H_β), 4.66–4.70 (3H, m, 4′-H, 5′-H_2), 5.62–5.64 (1H, t, J = 6 Hz, 3′-H), 6.53–6.55 (1H, t, J = 6 Hz; 1′-H), 7.30–7.94 (8H, m, H-arom), 8.57 (1H, s, CH), 8.970–8.974 (1H, d, J = 2.4 Hz, NH_α), 9.01 (1H, s, NH_β), 10.83 (1H, s, NH); δ_C (600 MHz; d_6-DMSO): 21.65, 21.69, 38.62, 64.69, 75.21, 83.07, 87.36, 87.48, 126.89, 129.72, 129.82, 129.93, 144.41, 144.57, 151.02, 156.96, 157.73, 162.01, 165.34, 165.75, 165.93. HR-MS (ESI+): Calc. for $[C_{27}H_{25}N_5O_7]$: 553.1573 $[M+Na]^+$; Found 554.1623 $[M+Na]^+$.

Compound **6d**: UV (MeOH) 226.0 (139822), 203.0 (135088), 272.0 (22378), 278.0 (20111), δ_H (600 MHz; d_6-DMSO): 2.36, 2.40 (6H, 2 s, $2CH_3$), 2.60–2.63 (1H, d, J = 18 Hz, 2′-H_α), 2.97–3.00 (1H, q, J = 6 Hz, 2′-H_β), 4.50–4.51 (2H, d, J = 6 Hz, 5′-H_2), 5.28–5.30 (1H, t, J = 6 Hz, 4′-H), 5.57–5.58 (1H, d, J = 6 Hz, 3′-H), 6.47–6.48 (1H, d, J = 6 Hz, 1′-H), 7.25–7.94 (8H, m, arom-H), 8.65 (1H, s, CH), 8.89–8.90 (1H, d, J = 6 Hz, NH_α), 8.947–8.953 (1H, d, J = 3.6 Hz, NH_β), 10.78 (1H, s, NH); δ_C (600 MHz; d_6-DMSO): 21.63, 21.67, 64.37, 75.18, 85.48, 87.66, 89.63, 126.79, 127.00, 129.62, 129.77, 129.82, 129.92, 144.39, 144.47, 150.98, 156.98, 157.84, 162.24, 165.37, 165.92. HR-MS (ESI+): Calc. for $[C_{27}H_{25}N_5O_7]$: 553.1573 $[M+Na]^+$; Found 554.1623 $[M+Na]^+$.

5-Amino-8-(2-deoxy-β-D-*erythro*-pentofuranosyl)pyrimido[4,5-d]pyrimidine-2,4(3H,8H)-dione (1c)

Method 1: compound **6c** (820 mg, 1.5 mmol) was suspended in 0.2 M NaOMe/MeOH (40 mL), the reaction was stirred at reflux until **6c** had disappeared (monitored by TLC, CH_2Cl_2 : MeOH 95 : 5), and then the reaction mixture was neutralized with diluted acetic acid to about pH 6.5, filtered and the precipitate was washed with methanol (3 × 40 mL), and water (1 × 40 mL), after vacuum drying, afforded **1c** (410 mg, 93%). Method 2: A solution of **7c** (200 mg, 0.3 mmol) in CH_2Cl_2 (6 mL) was treated with 2.5% DCA in CH_2Cl_2 (4 ml). The reaction was stirred at room temperature for 5min. When compound **7c** disappeared (monitored by TLC, CH_2Cl_2 : MeOH, 12 : 1), triethylamine was added to neutralize the reaction mixture. Then the reaction mixture was filtered and the precipitate was washed with CH_2Cl_2 (3 × 10 mL) and acetone

(3 × 10 mL). After vacuum drying, **1c** was given 48 mg (50%): UV (MeOH) 251(28571), 277(6158). δ_H (600 MHz; d_6-DMSO): 2.18–2.22 (1H, m, 2′-H_α), 2.35–2.39 (1H, m, 2′-H_β), 3.59–3.61 (1H, d, J = 12 Hz, 5′-H_α), 3.67–3.69 (1H, d, J = 12 Hz, 5′-H_β), 3.89–3.91 (1H, t, J = 6 Hz, 4′-H), 4.27 (1H, s, 3′-H), 5.20 (1H, s, 5′-OH), 5.34 (1H, s, 3′-OH), 6.41–6.43 (1H, t, J = 6 Hz, 1′-H), 8.77 (1H, s, CH), 8.89–8.93 (2H, 2 s, NH_2), 10.76 (1H, s, NH). δ_C (600 MHz; d_6-DMSO): 41.60, 60.95, 69.99, 86.75, 87.46, 88.59, 151.39, 157.11, 157.78, 162.07, 165.43. HR-MS (ESI–): Calc. for $[C_{27}H_{25}N_5O_4]$: 294.0838 $[M - H]^-$, Found 294.0838 $[M - H]^-$.

5-Amino-8-(2-deoxy-α-D-*erythro*-pentofuranosyl)pyrimido[4,5-d]pyrimidine-2,4(3H,8H)-dione (1d)

Compound **6d** (170 mg, 0.3 mmol) was suspended in 0.2 M NaOMe/MeOH (10 mL), the reaction was stirred at reflux until **6d** had disappeared (monitored by TLC, CH_2Cl_2 : MeOH 95 : 5), and then the reaction solution was neutralized with diluted acetic acid to about pH 6.5, filtered and washed with methanol (3 × 10 mL) and water (1 × 10 mL). After vacuum drying, **1d** was afforded (80 mg, 90%): UV (MeOH) 225 (49672), 272 (66694), 279.0 (60606), 295 (20771), 323 (16281). δ_H (600 MHz; d_6-DMSO): 2.08–2.11 (1H, d, J = 18 Hz, 2′-H_α), 2.56–2.60 (1H, m, 2′-H_β), 3.42–3.45 (2H, dd, J = 6 Hz 5′-H_2), 4.25–4.26 (1H, d, J = 6 Hz, 4′-H), 4.39–4.41 (1H, t, J = 6 Hz, 3′-H), 4.96 (1H, s, 5′-OH), 5.23 (1H, s, 3′-OH), 6.34–6.35 (1H, d, J = 6 Hz, 1′-H), 8.45 (1H, s, CH), 8.87–8.89 (2H, 2 s, NH_2), 10.76 (1H, s, NH). δ_C (600 MHz; d_6-DMSO): 41.23, 62.12, 71.09, 87.49, 89.06, 91.35, 151.66, 157.04, 157.81, 162.25, 165.40. HR-MS (ESI–): Calc. for $[C_{27}H_{25}N_5O_4]$: 294.0838 $[M - H]^-$, Found 294.0838 $[M - H]^-$.

5-Amino-8-[2-deoxy-5-*O*-(4,4′-dimethoxytrityl)-β-D-*erythro*-pentofuranosyl]pyrimido[4,5-d]pyrimidine-2,4(3*H*,8H)-dione (7c); 5-amino-8-[2-deoxy-5-*O*-(4,4′-dimethoxytrityl)-α-D-*erythro*-pentofuranosyl]pyrimido[4,5-d]pyrimidine-2,4(3H, 8H)-dione (7d)

The mixture of compounds **1c** and **1d** (400 mg, 1.4 mmol) was dried by repeated coevaporation with pyridine (3 × 5 mL) dried and then suspended in dry pyridine (10 mL). 4,4-Dimethoxytrityl chloride (934 mg, 2.8 mmol) was added, and triethylamine (390 mg, 2.8 mmol) was added. 4-Dimethylaminopyridine (9 mg, 0.4 mmol) was added as catalyst. The reaction was stirred at room temperature and overnight. 5% $NaHCO_3$ aqueous solution (10 ml) was added to quench the reaction at 0 °C. The mixture of reaction was extracted with ethyl acetate (3 × 30 mL). Combined the organic phase and evaporated. The residue was applied to FC (silica gel, column 2 × 8 cm, elution with CH_2Cl_2 : MeOH 99 : 1 to 98 : 2), and afforded **7c** 460 mg and **7d** 220 mg (total yield: 81%).

Compound **7c**: UV (MeOH) 251.0 (29301), 234.0 (28453), 275.0 (8239). δ_H (600 MHz; d_6-DMSO): 2.31–2.45 (2H, m, 2′-H_2), 3.21–3.28 (2H, m, 5′-H_2), 3.73 (6H, s, 2OCH_3), 4.01–4.03 (1H, m, 4′-H), 4.29–4.31 (1H, t, J = 6 Hz, 3′-H), 5.40–5.41 (1H, d, J = 6 Hz, 3′-OH) 6.42–6.44 (1H, t, J = 6 Hz; 1′-H), 6.88–7.39 (13H, m, H-arom), 8.53 (1H, s, CH), 8.96 (2H, s, NH_2), 10.79 (1H, s, NH). δ_C (600 MHz; d_6-DMSO): 41.40, 46.09, 55.50, 63.71, 70.26, 86.34, 86.73, 86.78, 87.53, 113.71, 127.20, 128.09, 128.38, 130.16, 135.79, 135.88, 145.15, 150.94, 157.05, 157.76, 158.55, 162.09, 165.43. HR-MS (ESI–): calc. for $[C_{32}H_{31}N_5O_7]$ 597.2223, found $[M - H]^-$ 596.2150.

Compound **7d**: UV (MeOH) 230.0 (45654), 250.0 (36857), 273.0 (11634). δ_H (600 MHz; d_6-DMSO): 2.17–2.19 (1H, d, J = 12 Hz, 2′-H_α), 2.61–2.65 (1H, m, 2′-H_β), 3.02–3.14 (2H, m, 5′-H_2), 3.74 (6H, s, 2OCH_3), 4.23 (1H, s, 4′-H), 4.56–4.57 (1H, t, J = 6 Hz, 3′-H), 5.289–5.293 (1H, d, J = 2.4 Hz; 3′-OH), 6.45–6.46 (1H, d, J = 6 Hz; 1′-H), 6.92–7.40 (13H, m, H-arom), 8.47 (1H, s, CH), 8.875–8.881 (1H, d, J = 3.6 Hz; NH_α), 8.90–8.91 (1H, d, J = 6 Hz; NH_β), 10.78 (1H, s, NH). δ_C (600 MHz; d_6-DMSO): 40.96, 55.01, 63.77, 70.80, 85.69, 87.00, 88.67, 89.07, 113.26, 126.73, 127.64, 127.91, 129.62, 129.66, 135.31, 135.44, 144.67, 151.14, 156.58, 157.32, 158.09, 161.75, 164.91. HR-MS (ESI–): Calc. for $[C_{32}H_{31}N_5O_7]$ 597.2223, Found $[M - H]^-$ 596.2150.

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