Synthetic Routes to a Series of Proximal and Distal 2′-Deoxy Fleximers

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Abstract: Two series of innovative 2′-deoxy nucleoside analogues have been designed where the nucleobase has been split into its imidazole and pyrimidine subunits. This structural modification serves to introduce flexibility into the nucleobase scaffold while still retaining the elements required for recognition. The synthetic efforts to realize these analogues are described within.

Key words: flexible nucleosides, fleximers, nucleobase, guanosine, adenosine, resistance

Drug resistance poses a particularly difficult problem in the development of chemotherapeutics for the treatment of bacterial, viral, or parasitic infections.[1] Consequently, there is an urgent unmet medical need for the development of drugs aimed at combating resistant mutations as well as fighting emerging new viral diseases.[2–4] Notably, it was recently shown that flexible nucleoside and nucleobase inhibitors (e.g., tenofovir and etravirine) could overcome viral HIV resistant mutations,[1,5,6] by adapting conformationally and positionally to the mutations in the HIV reverse transcriptase (RT) nucleoside and nonnucleoside binding sites, thereby retaining their activity.[1,5–7]

As an extension of those findings, and a possible answer to the on-going problem of resistance in many viral diseases, a series of flexible nucleoside analogues called ‘fleximers’ were designed. Two representative examples of the parent ribose series are shown in Figure 1 below (adenosine analogues **1** and **2**).

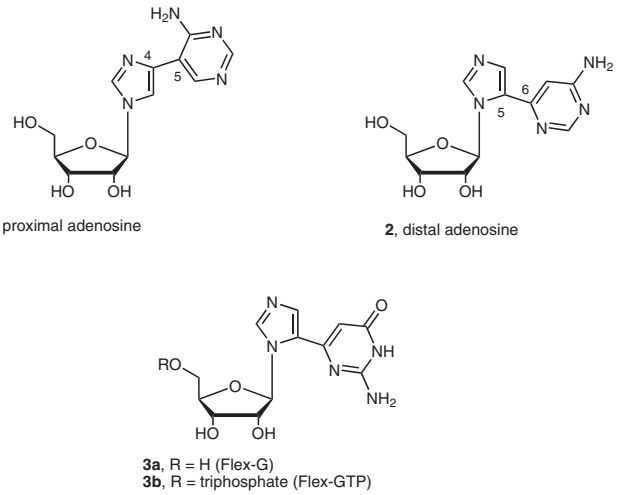

Figure 1 Fleximer numbering and nomenclature designations

This new class of modified nucleosides introduced flexibility to the heteroaromatic base by deconstructing the purine ring system into its two components, an imidazole and pyrimidine ring. This modification confers additional degrees of conformational freedom and torsional flexibility to the ligand while still retaining the molecular elements necessary for recognition.

In addition, by virtue of their inherent flexibility, these novel nucleosides should be able to sample more favorable enzyme–ligand interactions. More importantly, they should be able to overcome viral resistance mechanisms due to their ability to engage secondary amino acid residues not previously involved in an enzyme’s mechanism of action, thereby retaining their activity when confronted with a point mutation in the active site of an enzyme.

Recently, the fleximer concept was adapted by Hudson et al.[8] where they were cleverly able to construct a modified fleximer scaffold using click chemistry. Husdon’s analogues focused on a triazole ring connected by a single bond to several different aromatic ring systems. Their preparation and fluorescent and luminescent properties were reported. These analogues were proposed for use in gaining a better understanding of the interactions between oligonucleotides and various biologically significant enzymes.[8]

In our own laboratories it was observed that the distal ribofuranose guanosine fleximer, Flex-G **3a** (Figure 1) served as an inhibitor of *S*-adenosylhomocysteine hydrolase (SAHase).[9] This observation is unprecedented, since to our knowledge no other guanosine nucleoside has ever been reported to inhibit SAHase, an adenosine metabolizing enzyme. SAHase is an attractive biological target as it has been implicated in viral and parasitic replication.[9–11]

Additionally, the triphosphate of the guanosine fleximer **3b** (Figure 1) was investigated with GTP fucose pyrophosphorylase (GFPP). This enzyme catalyzes the reversible condensation of guanosine triphosphate and β-L-fucose-1-phosphate to form the nucleotide sugar GDP-β-L-fucose. This enzyme functions primarily in the mammalian liver and kidney to salvage free L-fucose during the breakdown of glycolipids and glycoproteins.[12–14] It was observed that **3b** served as a superior substrate for human GFPP, with a catalytic efficiency twice of the natural substrate, GTP.[15,16] Additionally, it was observed that despite the mutation of a critical amino acid in the active site of

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GFPP, Flex-GTP remained potent, while the natural substrate GTP was rendered completely inactive.[15,16]

This demonstrates that conformational flexibility can indeed facilitate increased affinity and allow for the engagement of secondary amino acids not previously involved in the mechanism of action. More importantly, these results confirm that flexibility facilitates retention of activity despite binding site mutations. Consequently, this provided additional motivation to pursue the synthesis of the corresponding 2′-deoxy analogues in the hopes of increasing the library of active compounds as well as to study the effects of substrate/inhibitor flexibility on DNA viruses.

The proposed 2′-deoxy targets are shown in Figures 2 and 3 for the distal and proximal fleximers, respectively.

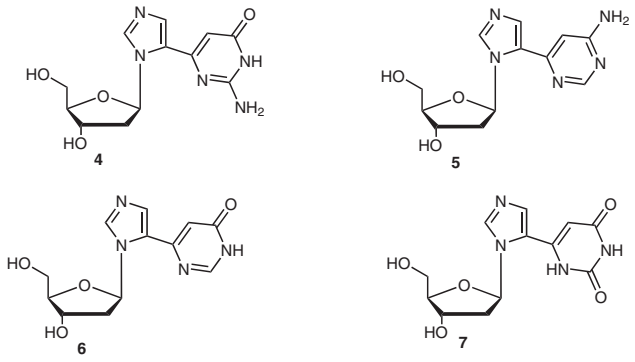


Figure 2 2′-Deoxy distal fleximer targets

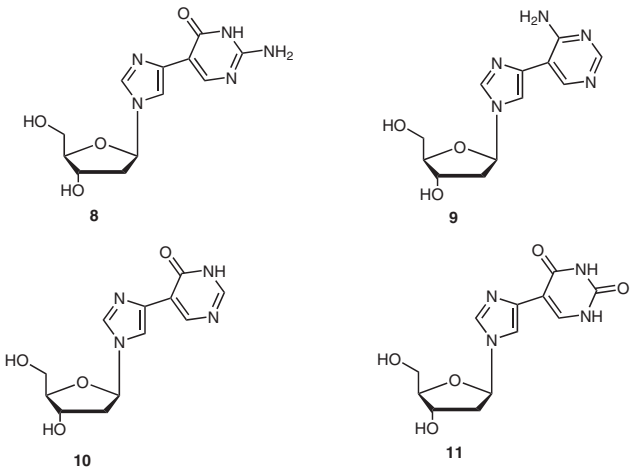
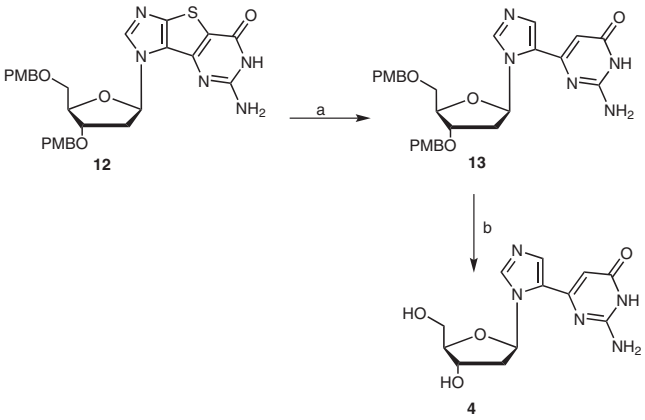


Figure 3 2′-Deoxy proximal fleximer targets

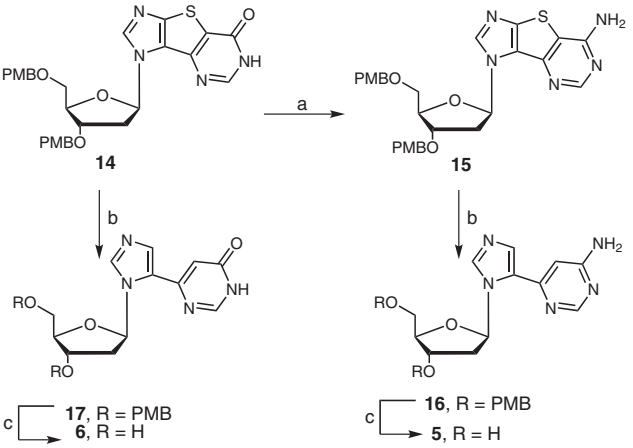
The synthetic approach to distal fleximers mirrors the route previously employed to realize the ribofuranose fleximers,[17,18] and is outlined in Scheme 1 for the guanosine analogue, **4**. It should be noted that this route was initially chosen due to the use of our previously reported tricyclic nucleosides, which could serve as facile intermediates.[18,19]

Synthesis of the tricyclic intermediate **12**[20] was pursued first and the desired fleximer **4** was subsequently obtained through desulfurization with Raney nickel as was reported with the ribose distal fleximers.[17,18] Since our initial reported approach, we have developed a shorter synthetic route[20] thereby facilitating the speed by which the 2′-deoxy distal fleximers could be obtained.



Scheme 1 *Reagents and conditions:* (a) Raney Ni, MeOH, 65%; (b) Pd/C, ammonium formate, EtOH, 80%.

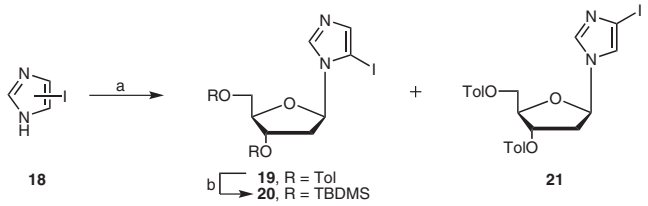
It should be noted that the removal of the sulfur made deprotection of the 4-methoxybenzyl (PMB) groups facile utilizing standard hydrogenation conditions of palladium-on-carbon and ammonium formate to give the distal guanosine **4** in good yield (Scheme 1).



Scheme 2 *Reagents and conditions:* (a) (i) 2,4,6-*i*-$Pr_3C_6H_2SO_2Cl$, DMAP, Et_3N, MeCN, 3 h; (ii) NH_3, r.t., 18 h; (b) Raney Ni, EtOH, 60% (**16**), 70% (**17**); (c) Pd/C, ammonium formate, EtOH, 50% (**5**), 75% (**6**).

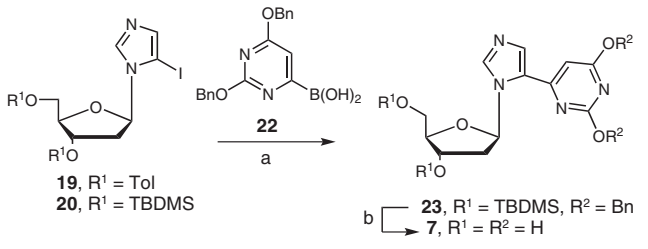
The distal adenosine and inosine targets were obtained in a similar fashion (Scheme 2). Once the previously reported inosine tricycle **14**[20] was in hand, analogous to the guanosine intermediate, standard desulfurization followed by deprotection afforded the inosine target **6** (Scheme 2). The adenosine tricycle was obtained by converting the carbonyl of **14**[20] into the relatively labile 2,4,6-triisopropylphenylsulfonyl group followed by displacement with ammonia to provide **15**.[20] Standard deblocking protocols were then used in order to obtain the adenosine fleximer target **5**.

Next, attention turned to the synthesis of the 2′-deoxyxanthosine fleximer. Surprisingly, the xanthosine tricycle resisted all attempts at desulfurization under several different sets of conditions, including increasing reaction times and temperatures. As a result, a new route was considered. The shortest approach appeared to be via cross-coupling methodology (e.g., the Suzuki coupling) to connect the imidazole and pyrimidine subunits.



Scheme 3 *Reagents and conditions:* (a) (i) NaH, MeCN; (ii) 2-deoxy-3,5-di-*O*-toluoyl-β-D-ribofuranosyl chloride; (b) (i) NaOMe, MeOH; (ii) TBDMSCl, imidazole, DMF, 86% (2 steps).

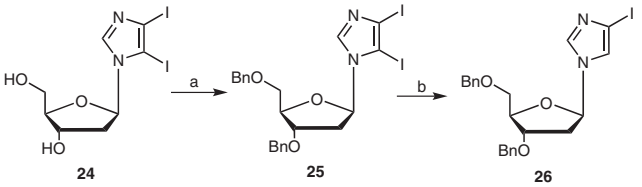
Starting with a standard literature procedure, 4,5-diiodo-1*H*-imidazole was reduced with sodium sulfite to give **18** (Scheme 3).[21] Reaction of the sodium salt of **18** with the 2′-deoxy chlorosugar gave a mixture of isomeric compounds **19** and **21**. Using NOE NMR techniques, the desired isomer **19** was delineated from **21** by irradiation of the 1′-proton, which showed no correlation with any of the aromatic hydrogens in the imidazole ring. The opposite was shown for isomer **21**, where a clear correlation was observed between the anomeric proton and the H5 of the imidazole ring. Intermediate **19** was then deprotected under basic conditions and then protected with the common *tert*-butyldimethylsilyl protecting group with a yield of 86% for the two steps. It should be noted that *tert*-butyldimethylsilyl was chosen to facilitate ease of removal at the end of the scheme. The pyrimidine subunit, **22** was made as previously reported.[22,23]



Scheme 4 *Reagents and conditions:* (a) (i) $Pd(PPh_3)_4$, DME (ii) **22**, $NaHCO_3$, 75%; (b) (i) Pd/C, ammonium formate, EtOH; (ii) TBAF, THF, 53% (2 steps).

Initially, the toluoyl-protected imidazole synthon **19** was used in the Suzuki coupling reaction in the hopes that the reaction was basic enough to simultaneously deprotect the ester groups during the formation of the coupled product. However, the coupling reaction did not proceed with **19** so the protecting group was exchanged to employ the *tert*-butyldimethylsilyl group instead (Scheme 4). Coupling of **20** with boronic acid **22** proved successful and gave **23** in 75% yield. Stepwise deprotection of the benzyl and *tert*-butyldimethylsilyl protecting groups of **23** was conducted to give the xanthosine target **7** in 53% for the two deblocking steps.

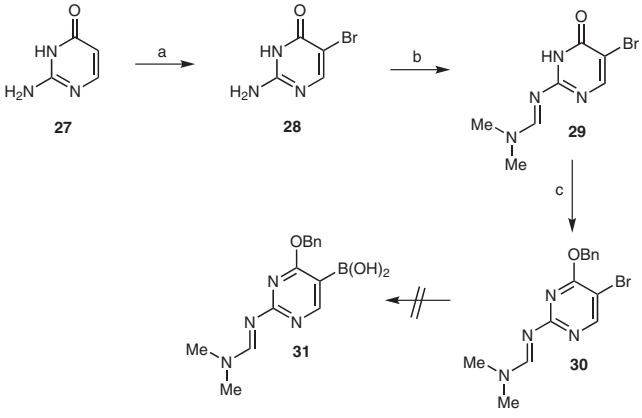
The approach to realize the 2′-deoxy proximal targets did not involve the expanded purine tricyclic nucleosides. Since the Suzuki reaction had previously been successful in making the ribose derivatives,[17,24,25] efforts turned to synthesizing the requisite coupling partners. As shown in Scheme 5, the synthesis of the imidazole synthon was analogous to that utilized for the ribose series.[24,25]



Scheme 5 *Reagents and conditions:* (a) (i) NaH, THF; (ii) TBAI, BnBr, 85%; (b) (i) EtMgBr, THF, 0 °C; (ii) EtOH, 80%.

The hydroxy groups of **24**[20] were protected with the robust benzyl groups using standard benzylation conditions of sodium hydride, followed by the in situ generation of benzyl iodide from benzyl bromide and tetrabutylammonium iodide to provide **25** in good yield (Scheme 5).[25] The protected 4-iodoimidazole synthon **26** was then achieved by treating **25** with ethylmagnesium bromide followed by quenching with ethanol.[24,25]

Next, synthesis of the pyrimidine partner was undertaken. Beginning with the proximal 2′-deoxy guanosine target **8**, the pyrimidine subunit was planned as shown in Scheme 6.

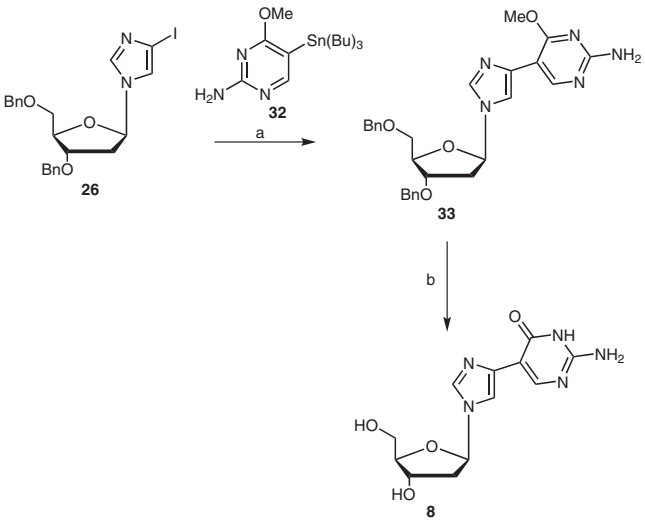


Scheme 6 *Reagents and conditions:* (a) Br_2, H_2O, 75%; (b) DMF-DMA, DMF, 60%; (c) DIAD, Ph_3P, BnOH, DMF, 80%; (d) (i) $B(O\textit{i}\text{-}Pr)_3$, THF, toluene, –78 °C, (ii) BuLi, (iii) aq HCl.

Commercially available isocytosine **27** was brominated under standard conditions of bromine and water to give **28**.[26] Once **28** was in hand, the exocyclic amine was protected with *N*,*N*-dimethylformamide dimethyl acetal (DMF-DMA) to give **29**. To reduce the risk of any acidic

protons possibly interfering with the Suzuki coupling, **29** was converted into **30** using standard Mitsunobu conditions in 80% yield.[27] These reactions were also conducted with a C5 iodo group instead of the bromine with similar reactivity and yields. It was important that the amino group be protected before the Mitsunobu reaction, as amino groups are known to react under these conditions. Disappointingly, **30** (either with the 5-Br or 5-I) could not be converted into the boronic acid even under many different reaction conditions.

Searching for a new approach, examination of other work done in our laboratories for another project,[24,25] as well as the literature from others revealed an article by Matsuda et al.[28] where they had successfully used an organotin pyrimidine moiety in a Stille coupling reaction. As shown in Scheme 7, the protected guanosine analogue **8** was successfully achieved via Stille coupling of the protected imidazole synthon **26** with **32**[28] in moderate yield.

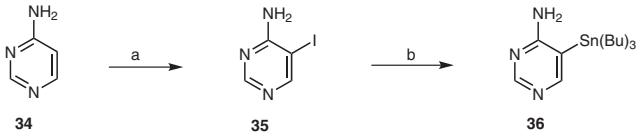


Scheme 7 *Reagents and conditions:* (a) $Pd_2dba_3{\cdot}CHCl_3$, DMF, 100 °C, 65%; (b) Pd/C, ammonium formate, EtOH, reflux, 80%.

Additionally, this route did not require the protection of the exocyclic amino group as had been necessary in the other attempted approaches. Moreover, the overall route proved to be relatively short and the yields reasonable enough to allow for scaleup. The 2′-deoxyguanosine target, **8** was then achieved following hydrogenation (Scheme 7) in 80% yield.

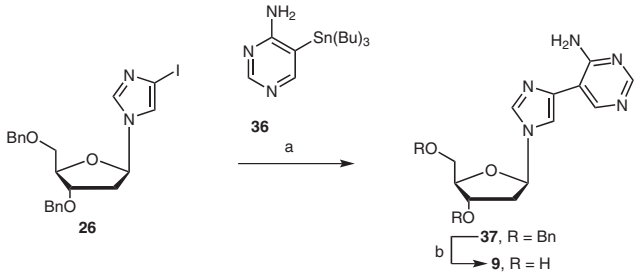
Once the guanosine analogue **8** was achieved, the adenosine target **9** was pursued. Since it was observed that the Stille coupling could be performed without protection of amine groups, the approach to realize the adenosine fleximer was much more straightforward.

Iodination of commercially available 4-aminopyrimidine **34** using *N*-iodosuccinimide in acetic acid gave **35** (Scheme 8). As was utilized for the guanosine analogue, **35** was converted into the 5-tributylstannyl intermediate **36** under palladium-catalyzed conditions. Stille coupling under the identical conditions for the protected guanosine



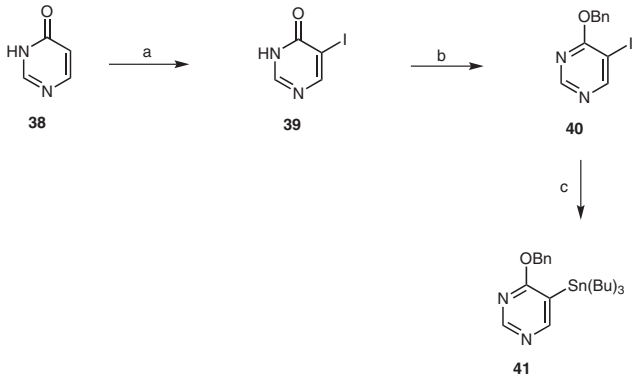
Scheme 8 *Reagents and conditions:* (a) NIS, AcOH, 79%; (b) $(Bu_3Sn)_2$, $Pd_2dba_3{\cdot}CHCl_3$, DMF, 65%.

analogue **33** gave the analogous adenosine intermediate **37** (Scheme 9). Typical deprotection protocols then gave the target **9** in 70% yield.



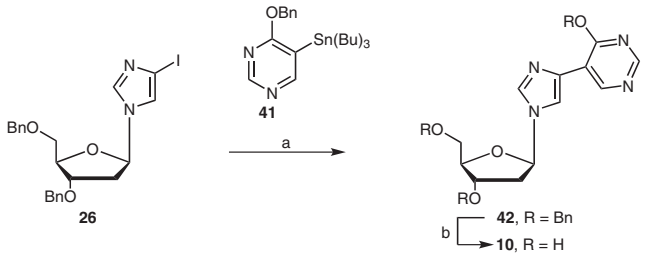
Scheme 9 *Reagents and conditions:* (a) $Pd_2dba_3{\cdot}CHCl_3$, DMF, 100 °C, 65%; (b) Pd/C, ammonium formate, EtOH, reflux, 70%.

After successfully making the guanosine and adenosine targets, attention then turned towards the 2′-deoxy proximal inosine target **10**. Since the Stille coupling had been proven to work for the guanosine and adenosine analogues, there was motivation to attempt to make the 5-(tributylstannyl)pyrimidine intermediate and then subject it to Stille coupling with the imidazole synthon. Iodination[29] of commercially available **38** followed by protection utilizing Mitsunobu conditions[27] was then conducted. Utilizing standard literature procedures **41** was obtained (Scheme 10). The transformation to the 5-tributylstannyl intermediate **41** was also done in an analogous manner to the other previously employed tin compounds, with the exception that tetrakis(triphenylphosphine)palladium(0) was used as the catalyst instead of tris(dibenzylideneacetone)dipalladium–chloroform as the former resulted in a higher yield.[30]



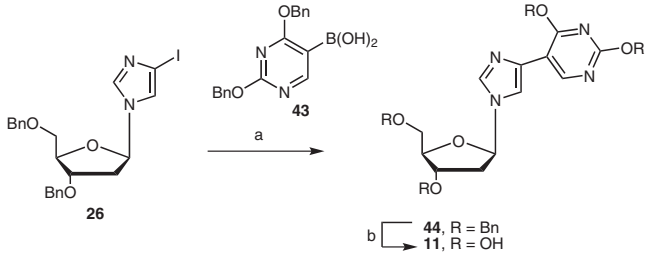
Scheme 10 *Reagent and conditions:* (a) NaOH, I_2, 70%; (b) DIAD, Ph_3P, BnOH, DMF, 77%; (c) $(Bu_3Sn)_2$, $Pd(PPh_3)_4$, toluene, 60%.

The Stille coupling was then performed as before with the guanosine and adenosine analogues as summarized in Scheme 11. Finally, the inosine target, **10** was obtained from deprotection of **42** in 60% yield.



Scheme 11 *Reagents and conditions*:(a) $Pd_2dba_3{\cdot}CHCl_3$, DMF, 100 °C, 60%; (b) Pd/C, ammonium formate, EtOH, reflux, 60%.

The final proximal 2′-deoxy target was the xanthosine fleximer **11**. This target initially appeared straightforward since there were no sensitive groups on the pyrimidine subunit to consider during the synthesis. The requisite pyrimidine coupling partner **43**[25] was synthesized using previously reported procedures.[25] Coupling was then successfully carried out with tetrakis(triphenylphosphine)palladium(0) in refluxing 1,2-dimethoxyethane and saturated aqueous sodium hydrogen carbonate to give **44** (64%) (Scheme 12).[24,25] Removal of all five of the benzyl groups with palladium-on-carbon and ammonium formate in ethanol was accomplished in 52% yield to give the 2′-deoxy proximal xanthosine fleximer **11** directly (Scheme 12).



Scheme 12 *Reagents and conditions:* (a) $Pd(PPh_3)_4$, $NaHCO_3$, DME, reflux, 4 h, 64%; (b) Pd/C, ammonium formate, EtOH, reflux, 52%.

In summary, two series of 2′-deoxy fleximers were synthesized using optimized procedures and in some cases, new coupling approaches. Biological testing is currently underway for the newly synthesized 2′-deoxy fleximers, including against resistant strains. These results will be evaluated as they become available, and it is our hope that they will provide additional insight toward increasing our understanding of enzyme/ligand structure and function, and as such, may serve as the foundation for the design of a new generation of chemotherapeutic agents.

All chemicals were obtained from commercial sources and used without further purification unless otherwise noted. Anhyd DMF, MeOH, DMSO, and toluene were purchased or obtained using a solvent purification system (mBraun Labmaster 130). Melting points are uncorrected. All ^1H and ^{13}C NMR spectra were referenced to internal TMS (δ = 0.0 ppm); primed assignments refer to furanose positions, H_{im} to imidazole protons, and H_{pyr} to pyrimidine protons. Reactions were monitored by TLC. Column chromatography was performed using commercial silica gel and eluted with the indicated solvent system. Yields refer to chromatographically and spectroscopically (^1H and ^{13}C NMR) homogeneous materials.

2-Amino-6-{1-[2-deoxy-3,5-di-*O*-(4-methoxybenzyl)-β-D-ribofuranosyl]-1*H*-imidazol-5-yl}pyrimidin-4(3*H*)-one (13); Typical Procedure

To a soln of **12** (300 mg, 0.532 mmol) in anhyd MeOH (25 mL) was added washed Raney Ni. The mixture was heated under reflux for 18 h. The mixture was then filtered through Celite and the Celite pad was washed several times with hot EtOH. The EtOH washings were combined and the solvent was removed under reduced pressure to give **13** (184 mg, 0.344 mmol, 65%) as a colorless syrup, which was used in the next step without purification.

^1H NMR (400 MHz, DMSO-d_6): δ = 2.34 (m, 2 H, H2′), 3.56 (m, 1 H, H3′), 3.63 (m, 1 H, H5′), 3.70–3.71 (s, 6 H, 2 OCH_3), 4.12 (m, 1 H, H5′), 4.23 (m, 1 H, H4′), 4.38 (m, 2 H, PMB-CH_2), 4.45 (s, 2 H, PMB-CH_2), 5.67 (br s, 2 H, NH_2), 6.04 (s, 1 H, H1′), 6.85 (s, 1 H, $H4_{im}$), 6.82–6.89 (m, 4 H, H_{PMB}), 7.15 (m, 2 H, H_{PMB}), 7.22 (m, 2 H, H_{PMB}), 7.51 (s, 1 H, $H5_{pyr}$), 8.24 (s, 1 H, $H2_{im}$).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 68.3, 71.6, 74.8, 84.6, 87.0, 99.2, 113.8, 114.2, 114.5, 128.4, 128.5, 128.7, 129.4, 129.6, 129.8, 130.2, 139.9, 141.2, 142.3, 146.2, 150.1, 159.6, 159.8.

HRMS (FAB): *m*/*z* [M + H] calcd for $C_{28}H_{32}N_5O_6$: 534.2353; found: 534.2354.

2-Amino-6-[1-(2-deoxy-β-D-ribofuranosyl)-1*H*-imidazol-5-yl]pyrimidin-4(3*H*)-one (4); Typical Procedure

A mixture of **13** (0.20 g, 0.37 mmol), 10% Pd/C (0.20 g), and ammonium formate (0.20 g, 3.2 mmol) in EtOH (50 mL) was heated under reflux for 18 h. The mixture was filtered through Celite and the Celite pad was washed several times with hot EtOH. The combined filtrate was evaporated under reduced pressure. The residue was purified by column chromatography (EtOAc–EtOH–acetone–H_2O, 4:1:1:1) to give **4** (87 mg, 0.297 mmol, 80%) as hygroscopic white needles.

^1H NMR (400 MHz, D_2O): δ = 3.70 (dd, *J* = 2.4, 10.5 Hz, 2 H, H2′), 3.87 (dd, *J* = 1.8, 10.5 Hz, 1 H, H3′), 4.07– 4.16 (m, 2 H, H5′), 4.29 (dd, 1 H, H4′), 6.11 (s, 1 H, H1′), 6.38 (d, *J* = 1.2 Hz, 1 H, $H4_{im}$), 7.84 (s, 1 H, $H2_{im}$), 9.14 (s, 1 H, $H6_{pyr}$).

^{13}C NMR (100 MHz, D_2O): δ = 10.1, 32.3, 41.2, 60.1, 70.4, 75.6, 85.4, 92.3, 102.8, 122.5, 130.0, 135.8, 145.3, 154.0, 163.4.

HRMS (FAB): *m*/*z* [M + H] calcd for $C_{12}H_{16}N_5O_4$: 294.1202; found: 294.1204.

6-{1-[2-Deoxy-3,5-di-*O*-(4-methoxybenzyl)-β-D-ribofuranosyl]-1*H*-imidazol-5-yl}pyrimidin-4-amine (16)

Following the typical procedure for **13** using **15** (400 mg, 0.730 mmol), anhyd EtOH (25 mL) and Raney Ni gave **16** (227 mg, 0.439 mmol, 60%) as a colorless syrup, which was used in the next step without purification.

^1H NMR (400 MHz, DMSO-d_6): δ = 2.34 (m, 2 H, H2′), 3.56 (d, *J* = 2.4 Hz, 1 H, H3′), 3.63 (d, *J* = 2.4 Hz, 1 H, H5′), 3.70–3.71 (s, 6 H, 2 OCH_3), 4.12 (m, 1 H, H5′), 4.23 (m, 1 H, H4′), 4.38 (m, 2 H, PMB-CH_2), 4.45 (s, 2 H, PMB-CH_2), 5.67 (br s, 2 H, NH_2), 6.04 (t, *J* = 4.5 Hz, 1 H, H1′), 6.95 (s, 1 H, $H4_{im}$), 6.82–6.89 (m, 4 H, H_{PMB}), 7.15 (m, 2 H, H_{PMB}), 7.22 (m, 2 H, H_{PMB}), 7.45 (s, 1 H, $H5_{pyr}$), 8.26 (s, 1 H, $H2_{im}$), 8.28 (s, 1 H, $H2_{pyr}$).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 32.8, 42.6, 43.6, 60.1, 68.9, 75.9, 85.4, 91.6, 104.9, 105.0, 122.5, 126.6, 126.7, 127.2, 129.6, 130.1, 130.5, 135.8, 145.3, 145.4, 153.9, 163.4.

HRMS (FAB): *m/z* [M + H] calcd for $C_{28}H_{32}N_5O_5$: 518.2403; found: 518.2406.

6-[1-(2-Deoxy-β-D-ribofuranosyl)-1*H*-imidazol-5-yl]pyrimidin-4-amine (5)

Following the typical procedure for **4** using **16** (95 mg, 1.205 mmol), 10% Pd/C (100 mg), ammonium formate (115 mg, 1.83 mmol), and anhyd EtOH; during the standard work up the Celite pad was washed repeatedly with hot EtOH. Column chromatography (EtOAc–acetone–EtOH–H_2, 6:1:1:1) gave **5** (25 mg, 0.090 mmol, 50%) as a white powder; mp 195–196 °C.

^{1}H NMR (400 MHz, D_2O): δ = 3.65 (dd, *J* = 2.4, 10.5 Hz, 2 H, H2′), 3.97 (m, 1 H, H3′), 4.07–4.16 (m, 2 H, H5′), 4.29 (m, 1 H, H4′), 6.11 (t, *J* = 4.5 Hz, 1 H, H1′), 6.38 (s, 1 H, $H4_{pyr}$), 7.25 (s, 1 H, $H2_{pyr}$), 8.21 (s, 1 H, $H2_{im}$), 8.24 (s, 1 H, $H6_{im}$).

^{13}C NMR (100 MHz, D_2O): δ = 60.7, 66.1, 73.4, 74.5, 75.6, 84.9, 90.5, 110.4, 124.9, 127.7, 136.5, 150.2, 157.9, 162.8.

HRMS (FAB): *m/z* [M + H] calcd for $C_{12}H_{16}N_5O_3$: 278.1253; found: 278.1255.

6-{1-[2-Deoxy-3,5-di-*O*-(4-methoxybenzyl)-β-D-ribofuranosyl]-1*H*-imidazol-5-yl}pyrimidin-4(3*H*)-one (17)

Following the typical procedure for **13** using **14** (300 mg, 0.547 mmol), anhyd EtOH (25 mL), and Raney nickel gave **17** (198 mg, 0.382 mmol, 70%) as a colorless syrup, which was used in the next step without purification.

^{1}H NMR (400 MHz, DMSO): δ = 2.37 (m, 2 H, H2′), 3.48 (m, 1 H, H3′), 3.65 (m, 2 H, H5′), 3.70–3.71 (m, 6 H, 2 OCH_3), 4.36 (m, 1 H, H4′), 4.39 (s, 2 H, PMB-CH_2), 4.49 (s, 2 H, PMB-CH_2), 6.48 (t, *J* = 4.5 Hz, 1 H, H1′), 6.82–6.89 (m, 4 H, H_{PMB}), 7.25 (m, 2 H, H_{PMB}), 7.29 (m, 2 H, H_{PMB}), 7.44 (s, 1 H, $H4_{im}$), 8.35 (s, 1 H, $H2_{pyr}$), 8.42, (s, 1 H, $H2_{im}$), 9.46 (s, 1 H, $H5_{pyr}$).

^{13}C NMR (100 MHz, DMSO): δ = 55.6, 68.1, 71.4, 74.7, 75.6, 77.4, 78.9, 84.8, 87.0, 99.2, 113.8, 114.5, 114.3, 127.4, 127.5, 127.6, 128.0, 129.6, 129.8, 129.9, 131.2, 139.4, 146.5, 150.3, 159.6, 159.8.

HRMS (FAB): *m/z* [M + H] calcd for $C_{28}H_{31}N_4O_6$: 519.2244; found: 519.2243.

6-[1-(2-Deoxy-β-D-ribofuranosyl)-1*H*-imidazol-5-yl]pyrimidin-4(3*H*)-one (6)

Following the typical procedure for **4** using **17** (0.250 g, 0.482 mmol), Pd/C (662 mg), ammonium formate (300 mg, 4.82 mmol) in anhyd EtOH (50 mL); during the standard workup the Celite pad was washed repeatedly with hot EtOH. Column chromatography (EtOAc–acetone–EtOH–H_2, 8:1:1:0.5) gave **6** (100 mg, 0.360 mmol, 75%) as a white powder; mp 135–137 °C.

^{1}H NMR (400 MHz, D_2O): δ = 3.67 (dd, *J* = 2.4, 10.5 Hz, 2 H, H2′), 3.94 (m, 1 H, H3′), 4.06–4.16 (m, 2 H, H5′), 4.26 (m, 1 H, H4′), 6.11 (t, *J* = 4.5 Hz, 1 H, H1′), 6.83 (s, 1 H, $H4_{im}$), 7.25 (s, 1 H, $H2_{pyr}$), 8.22 (s, 1 H, $H2_{im}$), 8.25 (s, 1 H, $H5_{pyr}$).

^{13}C NMR (100 MHz, D_2O): δ = 60.7, 66.1, 73.4, 74.5, 75.6, 84.9, 90.5, 110.4, 124.9, 127.7, 136.5, 150.2, 157.9, 162.8.

HRMS (FAB): *m/z* [M + H] calcd for $C_{12}H_{15}N_4O_4$: 279.1093; found: 279.1095.

1-(2-Deoxy-3,5-di-*O*-toluoyl-β-D-ribofuranosyl)-5-iodo-1*H*-imidazole (19)

Monoiodoimidazole **18** (2.29 g, 11.78 mmol) was added to anhyd MeCN (25 mL) under N_2. The mixture was allowed to stir at 0 °C for 15 min. NaH (60%, 283 mg, 11.78 mmol) was added portionwise over 5 min and the resulting mixture was stirred at 0 °C under N_2 for 30 min. Then 2-deoxy-3,5-di-*O*-toluoyl-β-D-ribofuranosyl chloride (5.04 g, 12.96 mmol) was added in portions (2 × 30 min intervals) to the mixture. The mixture was then stirred under N_2 for 18 h at r.t.. TLC analysis (hexane–EtOAc, 1:1) indicated the presence of two strongly fluorescent spots. The spots were isolated by chromatography using the same TLC system as above to give the isomers as a yellow foam and a yellow oil. NMR analysis, both 1D and 2D (COSY, NOESY), was used to identify the products following separation by chromatography.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.40 (s, 6 H, 2 $C_6H_4CH_3$), 2.61–2.67 (m, 2 H, H2′), 4.59–4.60 (m, 1 H, H3′), 4.60–4.61 (m, 2 H, H5′), 5.61–5.63 (m, 1 H, H4′), 6.07 (t, *J* = 4.5 Hz, 1 H, H1′), 7.12 (s, 1 H, H4), 7.24–7.25 (m, 4 H, H_{Ph}), 7.54 (s, 1 H, H2), 7.85–7.92 (m, 4 H, H_{Ph}).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.8, 21.9, 29.8, 39.5, 39.6, 63.9, 74.9, 83.0, 86.4, 122.1, 126.4, 129.4, 129.6, 129.7, 129.9, 137.4, 144.4, 144.7, 165.9, 166.2.

HRMS (ESI): *m/z* [M + H] calcd for $C_{24}H_{24}IN_2O_5$: 547.0730; found: 547.0726.

1-[3,5-Di-*O*-(*tert*-butyldimethylsilyl)-2-deoxy-β-D-ribofuranosyl]-5-iodo-1*H*-imidazole (20)

To a soln **19** (368 mg, 0.674 mmol) in anhyd MeOH (20 mL) was added NaOMe (75 mg, 1.347 mmol) was added and the resulting soln was stirred for 4 h at r.t. Then the solvent was evaporated and purified by flash chromatography (silica gel, EtOAc–MeOH, 4:1) to give the deprotected product (0.188 g, 90%) as colorless solid. The deprotected product (188 mg, 0.606 mmol) and imidazole (272 mg, 4.00 mmol) were then dissolved in the minimum amount of DMF and the soln was cooled and stirred at 0 °C. TBDMSCl (301 mg, 2 mmol) was added portionwise at 0 °C. The mixture was allowed to warm up to r.t. and stirred overnight. H_2O was added and the organic layer was extracted with hexanes (4 × 10 mL). The combined organic layers were dried ($MgSO_4$) and filtered and the solvent removed to give **20** (310 mg, 0.576 mmol, 95%) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.08–0.09 (m, 12 H, 4 $SiCH_3$), 0.89–0.91 [m, 18 H, 2 $SiC(CH_3)_3$], 2.26–2.29 (m, 2 H, H2′), 2.88 (s, 1 H, H3′), 3.72–3.76 (m, 2 H, H5′), 4.48–4.49 (m, 1 H, H4′), 5.93–5.96 (t, *J* = 4.5 Hz, 1 H, H1′), 7.25 (s, 1 H, H4), 7.55 (s, 1 H, H2).

^{13}C NMR (100 MHz, $CDCl_3$): δ = –4.7, 25.8, 26.1, 42.8, 63.4, 72.2, 86.5, 78.8, 122.3, 137.3, 137.4.

HRMS (FAB): *m/z* [M + H] calcd for $C_{20}H_{40}IN_2O_3Si_2$: 539.1622; found: 539.1623.

2,4-Bis(benzyloxy)-6-{1-[3,5-di-*O*-(4-*tert*-butyldimethylsilyl)-2-deoxy-β-D-ribofuranosyl]-1*H*-imidazol-5-yl}pyrimidine (23)

A mixture of **20** (310 mg, 0.576 mmol) and $Pd(PPh_3)_4$ (67 mg, 0.0576 mmol) in DME (20 mL) was stirred at r.t. under argon for 10 min. To this mixture was added 2,6-bis(benzyloxy)pyrimidin-4-ylboronic acid (**22**, 1.39 mmol) in DME (20 mL). Sat. aq $NaHCO_3$ (15 mL) was added and the mixture refluxed under argon for 4 h. The soln was cooled to r.t. and the DME layer separated and set aside. The aqueous layer was then extracted with EtOAc (3 × 50 mL), and the organic extracts were combined with the DME layer, washed with brine (100 mL), and dried ($MgSO_4$). The solvent was removed to give a pale brown syrup. Column chromatography (2% EtOH–CH_2Cl_2) gave **23** (290 mg, 0.413 mmol, 75%) as a yellow syrup.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.08–0.09 (m, 12 H, 2 $SiCH_3$), 0.89–0.91 [m, 18 H, $SiC(CH_3)_3$], 1.59 (s, 1 H), 2.26–2.29 (m, 2 H, H2′), 3.72–3.76 (m, 2 H, H5′), 3.95–3.97 (m, 1 H, H3′), 4.48–4.49 (m, 1 H, H4′), 5.39–5.42 (m, 4 H, 2 $PhCH_2$), 5.93–5.96 (t, *J* = 4.5 Hz, 1 H, H1′), 6.43 (s, 1 H, H4), 7.36 (s, 1 H, H5), 7.37–7.38 (m, 10 H, H_{Ph}), 8.34 (s, 1 H, H2).

^{13}C NMR (100 MHz, $CDCl_3$): δ = –4.7, 25.8, 25.9, 26.0, 26.1, 42.7, 67.4, 68.3, 69.2, 72.2, 86.7, 102.6, 121.2, 128.2, 128.3, 128.5, 136.1, 136.7, 158.8, 170.9.

HRMS (FAB): *m/z* [M + H] calcd for $C_{38}H_{55}N_4O_5Si_2$: 703.3711; found: 703.3713.

6-[1-(2-Deoxy-1-β-D-ribofuranosyl)-1*H*-imidazol-5-yl]uracil (7)
Following the typical procedure for **4** using **23** (400 mg, 0.569 mmol), 10% Pd/C (400 mg), ammonium formate (359 mg, 5.69 mmol), in anhyd EtOH (30 mL) gave the debenzylated product (208 mg, 70%). The product used in the next reaction without further purification, as it was quite pure.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 0.01–0.06 (m, 12 H), 0.81–0.87 (m, 18 H), 2.45–2.46 (m, 1 H), 2.47–2.48 (m, 1 H), 3.61–3.62 (m, 2 H), 3.78–3.79 (m, 1 H), 4.41–4.43 (m, 1 H), 6.01 (t, 1 H), 7.61 (s, 1 H), 7.76 (s, 1 H), 7.78 (s, 1 H), 10.9 (s, 1 H), 11.2 (s, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 17.4, 18.6, 19.3, 25.9, 26.4, 61.5, 71.3, 75.4, 85.4, 89.3, 106.3, 113.5, 133.7, 135.7, 136.8, 150.5, 162.4.

HRMS (FAB): *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{43}N_4O_5Si_2$: 523.2772; found: 523.2772.

To a soln of the debenzylated product (200 mg, 0.383 mmol) in anhyd THF (25 mL) was added 1 M TBAF in THF (0.8 mL, 0.765 mmol). The mixture was stirred at r.t. for 4 h and the solvent was removed under reduced pressure. The product was purified by column chromatography (EtOAc–acetone–EtOH–H_2O) to give **7** (84 mg, 0.286 mmol, 75%) as a white solid; mp 251–252 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 3.46–3.49 (m, 2 H, H2′, OH), 3.74–3.75 (m, 1 H, H2′), 4.08–4.19 (m, 2 H, H5′), 4.37 (br s, 1 H, OH), 4.90 (s, 1 H, H3′), 5.23–5.24 (m, 1 H, H4′), 6.04 (t, *J* = 4.5 Hz, 1 H), 7.66 (s, 1 H, $H4_{im}$), 7.87 (s, 1 H, $H5_{pyr}$), 7.93 (s, 1 H, H2), 11.06 (s, 1 H, NH), 11.24 (s, 1 H, NH).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 7.7, 32.5, 42.2, 60.5, 69.3, 75.0, 86.9, 113.3, 126.7, 151.7, 157.6.

HRMS (FAB): *m*/*z* [M + H] calcd for $C_{12}H_{15}N_4O_5$: 295.1042; found: 295.1043.

1-[3,5-Di-*O*-benzyl-2-deoxy-β-D-ribofuranosyl]-4-iodo-1*H*-imidazole (26)
To a soln of **25** (1.295 g, 2.642 mmol) in anhyd THF (20 mL) was added 3 M EtMgBr (1.06 mL, 3.17 mmol) dropwise. The mixture was stirred at r.t. for 3 h and then quenched with EtOH (5 mL). The solvent was removed under vacuum. Sat. NH_4Cl (20 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 25 mL). The organic layers were combined, washed with brine, and dried ($MgBr_2$) to give **26** (1.0 g, 2.04 mmol, 80%) as a colorless syrup.

^{1}H NMR (400 MHz, acetone-d_6): δ = 2.50–2.55 (m, 2 H, H2′), 3.65–3.67 (m, 1 H, H3′), 4.26–4.27 (m, 2 H, H5′), 4.36–4.37 (m, 1 H, H4′), 4.56 (s, 2 H, PhCH_2), 4.59 (s, 2 H, PhCH_2), 6.09 (t, *J* = 4.5 Hz, 1 H, H1′), 7.34–7.41 (m, 10 H, H_{Ph}), 7.41 (s, 1 H, H2), 7.69 (s, 1 H, H5).

^{13}C NMR (100 MHz, acetone-d_6): δ = 60.3, 72.4, 72.7, 73.7, 76.7, 77.4, 77.7, 81.7, 82.8, 127.9, 128.1, 128.2, 128.6, 137.5, 137.8, 171.0.

HRMS (FAB): *m*/*z* [M + H] calcd for $C_{22}H_{24}IN_2O_3$: 491.0832; found: 491.0833.

5-Bromoisocytosine (28)
Isocytosine (650 mg, 5.85 mmol) was suspended in H_2O (10 mL) and Br_2 (0.93 g, 5.85 mmol) was added. The mixture was stirred at r.t. for 2 h and refrigerated overnight. NH_4OH (5 mL) was added and the mixture was concentrated to give **28** (0.780 g, 4.13 mmol, 75%) as a white solid; mp 235–237 °C (dec.).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 6.70 (br s, 2 H, NH_2), 7.93 (s, 1 H, H6), 11.26 (br s, 1 H, NH).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 71.3, 156.8, 160.0, 161.4.

HRMS (FAB): *m*/*z* [M + H] calcd for $C_4H_5BrN_3O$: 189.9616; found: 189.9617.

5-Bromo-N^2-[(dimethylamino)methylene]isocytosine (29)
To a soln of 5-bromoisocytosine (1.5 g, 7.89 mmol) in anhyd DMF (25 mL) was added DMF-DMA (1.3 mL, 9.47 mmol). The mixture was stirred at r.t. for 18 h. The solvent was removed under reduced pressure and the product was purified by column chromatography (EtOAc–MeOH (10:1) to give **29** (1.16 g, 4.75 mmol, 60%) as a white solid; mp 110–112 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 3.06 (s, 3 H, CH_3), 3.10 (s, 3 H, CH_3), 7.85 (s, 1 H, N=CH–NMe_2), 7.93 (s, 1 H, H6), 11.26 (br s, 1 H, NH).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 35.1, 41.3, 71.5, 156.7, 157.5, 160.2, 161.1.

HRMS (FAB): *m*/*z* [M + H] calcd for $C_7H_{10}BrN_4O$: 245.0038; found: 245.0039.

4-(Benzyloxy)-5-bromo-N^2-[(dimethylamino)methylene]isocytosine (30)
A mixture of 5-bromo-N^2-[(dimethylamino)methylene]isocytosine (1.16 g, 4.73 mmol) and Ph_3P (1.5 g, 5.68 mmol) was dissolved in anhyd DMF. DIAD (1.2 mL, 5.68 mmol) was added dropwise followed by the addition of BnOH (0.6 mL, 5.68 mmol) at 0 °C. The mixture was then allowed to warm up to r.t. and stirred for 1.5 h. The solvent was removed under vacuum and the product was purified by column chromatography (EtOAc–hexanes, 1:3) to give **30** (1.26 g, 3.77 mmol, 80%) as a colorless syrup.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 3.08 (s, 3 H, CH_3), 3.14 (s, 3 H, CH_3), 5.15 (s, 2 H, PhCH_2), 7.33–7.38 (m, 5 H, H_{Ph}), 7.87 (s, 1 H, CH), 7.96 (s, 1 H, H6).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 35.3, 41.5, 71.6, 128.0, 128.1, 128.2, 128.5, 128.6, 156.6, 157.4, 160.6, 161.1.

HRMS (FAB): *m*/*z* [M + H] calcd for $C_{14}H_{16}BrN_4O$: 335.0508; found: 335.0505.

5-{1-[3,5-Di-*O*-benzyl-2-deoxy-β-D-ribofuranosyl]-1*H*-imidazol-4-yl}-4-methoxypyrimidin-2-amine (33)
A mixture of **26** (1.08 g, 2.21 mmol), **32** (1.37 g, 3.31 mmol) and Pd_2dba_3·$CHCl_3$ (274 mg, 0.26 mmol) in anhyd DMF (20 mL) was heated at 100 °C for 11 h. The mixture was filtered through Celite, diluted with EtOAc (30 mL), washed with brine, and dried ($MgSO_4$). The organic solvents were removed and the product was purified by column chromatography (CH_2Cl_2–MeOH, 3:1) to give **33** (183 mg, 0.376 mmol, 65%) as a yellow oil.

^{1}H NMR (400 MHz, acetone-d_6): δ = 3.62 (m, 2 H, H2′), 3.75 (m, 1 H, H3′), 3.84 (s, 3 H, CH_3), 4.29 (br s, 2 H, H5′), 4.33–4.36 (m, 1 H, H4′), 4.49–4.69 (m, 4 H, PhCH_2), 6.68 (s, 1 H), 6.87 (t, *J* = 4.5 Hz, 1 H, H1′), 6.95 (br s, 2 H, NH_2), 7.19–7.33 (m, 10 H, H_{Ph}), 7.43 (s, 1 H, $H5_{im}$), 8.23 (s, 1 H, $H2_{im}$), 8.62 (s, 1 H, $H6_{pyr}$).

^{13}C NMR (100 MHz, acetone-d_6): δ = 67.4, 72.4, 72.6, 73.5, 75.5, 82.9, 103.6, 127.7, 128.1, 128.4, 128.3, 128.6, 137.8, 137.9, 138.4, 158.3, 166.5.

HRMS (FAB): *m*/*z* [M + H] calcd for $C_{27}H_{30}N_5O_4$: 488.2298; found: 488.2300.

5-[1-(2-Deoxy-β-D-ribofuranosyl)-1*H*-imidazol-4-yl]-4-methoxypyrimidin-2-amine (8)
Following the typical procedure for **4** using **33** (0.21 g, 0.41 mmol), 10% Pd/C (0.21 g), and ammonium formate (0.20 g, 3.2 mmol) in MeOH (50 mL). Purification by column chromatography (EtOAc–EtOH–acetone–H_2, 4:1:1:1) gave **8** (96 mg, 0.328 mmol, 80%) as hygroscopic white needles.

1H NMR (400 MHz, D_2O): δ = 3.73 (dd, *J* = 2.4, 10.5 Hz, 2 H, H2′), 3.85 (dd, *J* = 1.8, 10.5 Hz, 1 H, H3′), 4.07– 4.16 (m, 2 H, H5′), 4.26 (m, 1 H, H4′), 6.13 (t, *J* = 4.5 Hz, 1 H, H1′), 7.35 (s, 1 H, $H5_{im}$), 8.10 (s, 1 H, $H2_{im}$), 9.16 (s, 1 H, $H6_{pyr}$).

^{13}C NMR (100 MHz, D_2O): δ = 7.74, 32.5, 42.3, 60.5, 69.3, 75.0, 91.0, 113.4, 151.7, 157.6.

HRMS (FAB): *m*/*z* [M + H] calcd for $C_{12}H_{16}N_5O_4$: 294.1202; found: 294.1203.

4-Amino-5-iodopyrimidine (35)
To a soln of 4-aminopyrimidine (**34**; 147 mg, 1.55 mmol) in AcOH (10 mL) was added NIS (417 mg, 1.85 mmol). The mixture was then heated at 80 °C for 2.5 h. The solvent was removed under vacuum and the residue was partitioned between $CHCl_3$ and 5% aq $Na_2S_2O_3$ (10 mL total volume). The organic layers were washed with brine, dried, and filtered, and the solvent was removed to give **35** (273 mg, 1.236 mmol, 79%) as a light yellow oil.

^{1}H NMR (400 MHz, acetone-d_6): δ = 5.65 (br s, 2 H, NH_2), 8.18 (s, 1 H, H6), 8.35 (s, 1 H, H2).

^{13}C NMR (100 MHz, acetone-d_6): δ = 113.5, 164.5, 162.5, 167.8.

HRMS (FAB): *m*/*z* [M + H] calcd for $C_4H_5IN_3$: 221.9528; found: 221.9529.

4-Amino-5-(tributylstannyl)pyrimidine (36)
To a mixture of 4-amino-5-iodopyrimidine (138 mg, 0.625 mmol) and $(Bu_3Sn)_2$ (0.376 mL, 0.750 mmol) in anhyd DMF (5 mL) was added $Pd_2dba_3{\cdot}CHCl_3$ (194 mg, 0.19 mmol) and the mixture was heated at 65 °C. The mixture was filtered through Celite and diluted with EtOAc (5 mL), washed with brine, and dried ($MgSO_4$). The organic solvents were removed and the product was purified by column chromatography (hexanes–EtOAc (3:1) to give **36** (156 mg, 0.405 mmol, 65%) as a yellow oil.

^{1}H NMR (400 MHz, acetone-d_6): δ = 0.86–0.88 (m, 9 H, Bu), 1.12–1.22 (m, 6 H, Bu), 1.31–1.38 (m, 6 H, Bu), 1.54–1.59 (m, 6 H, Bu), 5.72 (br s, 2 H, NH_2), 8.08 (s, 1 H, H6), 8.33 (s, 1 H, H2).

^{13}C NMR (100 MHz, acetone-d_6): δ = 7.2, 8.9, 10.7, 13.1, 28.7, 28.8, 29.4, 113.5, 158.6, 161.9, 162.4, 162.5, 167.8.

HRMS (FAB): *m*/*z* [M + H] calcd for $C_{16}H_{32}N_3Sn$: 386.1618; found: 386.1619.

5-[1-(3,5-Di-*O*-benzyl-2-deoxy-β-D-ribofuranosyl)-1*H*-imidazol-4-yl]pyrimidin-4-amine (37)
A mixture of **26** (302 mg, 0.616 mmol), **36** (355 mg, 0.924 mmol), and $Pd_2dba_3{\cdot}CHCl_3$ (51 mg, 0.05 mmol) in anhyd DMF (10 mL) was heated at 100 °C for 11 h. The mixture was filtered through Celite and diluted with EtOAc (5 mL), washed with brine, and dried ($MgSO_4$). The organic solvents were removed and the product was purified by column chromatography (CH_2Cl_2–MeOH, 3:1) to give **37** (183 mg, 0.400 mmol, 65%) as a yellow oil.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 3.61 (dd, *J* = 4.1, 10.1 Hz, 2 H, H2′), 3.73 (dd, *J* = 1.9, 10.7 Hz, 1 H, H3′), 4.19 (br s, 2 H, H5′), 4.33–4.36 (m, 1 H, H4′), 4.49–4.69 (m, 4 H, PhCH_2), 6.87 (t, *J* = 4.5 Hz, 1 H, H1′), 6.95 (br s, 2 H, NH_2), 7.19–7.33 (m, 10 H, H_{Ph}), 7.43 (s, 1 H, $H5_{im}$), 8.21 (s, 1 H, $H2_{im}$), 8.39 (s, 1 H, $H6_{pyr}$), 9.16 (s, 1 H, $H2_{pyr}$).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 67.4, 72.5, 72.8, 73.2, 75.5, 81.7, 101.6, 127.7, 128.1, 128.2, 128.3, 128.6, 137.8, 137.9, 138.4, 158.3, 164.5.

HRMS (FAB): *m*/*z* [M + H] calcd for $C_{26}H_{28}N_5O_3$: 458.2192; found: 458.2195.

5-[1-(2-Deoxy-β-D-ribofuranosyl)-1*H*-imidazol-4-yl]pyrimidin-4-amine (9)
Following the typical procedure for **4** using **37** (0.320 g, 0.699 mmol), 10% Pd/C (0.320 g), and ammonium formate (0.44 g, 6.99 mmol) in EtOH (50 mL). Purification by column chromatography (EtOAc–EtOH–acetone–H_2, 4:1:1:1) gave **9** (136 mg, 0.491 mmol, 70%) as hygroscopic white needles.

^{1}H NMR (400 MHz, D_2O): δ = 3.69 (m, 2 H, H2′), 3.84 (m, 1 H, H3′), 4.00–4.13 (m, 2 H, H5′), 4.32 (m, 1 H, H4′), 6.40 (t, *J* = 4.5 Hz, 1 H, H1′), 7.22 (s, 1 H, $H5_{im}$), 8.05 (s, 1 H, $H2_{im}$), 8.48 (s, 1 H, $H2_{pyr}$), 9.46 (s, 1 H, $H6_{pyr}$).

^{13}C NMR (400 MHz, D_2O): δ = 62.1, 70.7, 74.8, 86.6, 89.5, 127.9, 145.4, 149.3, 155.1, 158.9.

HRMS (FAB): *m*/*z* [M + H] calcd for $C_{12}H_{16}N_5O_3$: 278.1253; found: 278.1255.

5-Iodopyrimidin-3(4*H*)-one (39)[29]
A mixture of pyrimidin-3(4*H*)-one (1.44 g, 15 mmol), I_2 (3.81 g, 15 mmol), and NaOH (800 mg, 20 mmol) was heated at 80 °C for 18 h. After neutralization with AcOH, the precipitate was recrystallized (EtOH) to give 39 (2.3 g, 10.4 mmol, 70%) as a white solid. Spectral data were in agreement with literature values.[29]

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.15 (s, 1 H, H6), 8.37 (s, 1 H, H2), 11.25 (s, 1 H, NH).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 81.4, 150.3, 151.5, 162.3.

4-(Benzyloxy)-5-iodopyrimidine (40)
Pyrimidine **39** (1.67 g, 7.52 mmol) and Ph_3P (2.37 g, 9.03 mmol) were dissolved in DMF (20 mL) while stirring at 0 °C. DIAD (1.79 mL, 9.03 mmol) was added dropwise, followed by the addition of BnOH (0.94 mL, 9.03 mmol) at 0 °C. The mixture was stirred at r.t. and monitored. After the reaction was complete, the solvents were removed under vacuum. Column chromatography (80% EtOAc–hexanes) gave **40** (1.81 g, 5.80 mmol, 77%) as a yellow oil.

^{1}H NMR (400 MHz, acetone-d_6): δ = 5.21 (s, 2 H, PhCH_2), 7.35–7.40 (m, 5 H, H_{Ph}), 8.39 (s, 1 H, H6), 8.52 (s, 1 H, H2).

^{13}C NMR (100 MHz acetone-d_6): δ = 176.1, 162.4, 156.3, 141.8, 128.0, 128.1, 128.2, 128.5, 128.6, 127.4, 110.2.

HRMS (FAB): *m*/*z* [M + H] calcd for $C_{11}H_{10}IN_2O$: 312.9838; found: 312.9840.

4-(Benzyloxy)-5-(tributylstannyl)pyrimidine (41)
To a mixture of **40** (200 mg, 0.641 mmol) and $(Bu_3Sn)_2$ (0.41 mL, 0.769 mmol) in anhyd DMF (10 mL) was added $Pd(PPh_3)_4$ (220 mg, 0.192 mmol). The mixture was heated at 65 °C. The mixture was filtered through Celite and diluted with EtOAc (5 mL), washed with brine, and dried ($MgSO_4$). The organic solvents were removed and the product was purified by column chromatography (hexanes–EtOAc, 3:1) to give **41** (183 mg, 0.384 mmol, 60%) as a yellow oil.

^{1}H NMR (400 MHz, acetone-d_6): δ = 0.83–0.86 (m, 9 H, Bu), 1.05–1.07 (m, 6 H, Bu), 1.09–1.28 (m, 6 H, Bu), 1.29–1.31 (m, 6 H, Bu), 5.13 (s, 2 H, PhCH_2), 7.32–7.36 (m, 5 H, H_{Ph}), 7.78 (s, 1 H, H6), 8.39 (s, 1 H, H2).

^{13}C NMR (100 MHz, acetone-d_6): δ = 7.2, 8.9, 10.7, 13.1, 28.7, 28.8, 29.4, 113.5, 127.6, 128.1, 128.5, 128.6, 128.8, 128.9.

HRMS (FAB): *m*/*z* [M + H] calcd for $C_{23}H_{37}SnN_2O$: 477.1928; found: 477.1929.

4-(Benzyloxy)-5-[1-(3,5-di-*O*-benzyl-2-deoxy-β-D-ribofuranosyl)-1*H*-imidazol-4-yl]pyrimidine (42)
A mixture of **26** (85 mg, 0.173 mmol), **41** (123 mg, 0.259 mmol) and $Pd_2dba_3{\cdot}CHCl_3$ (14 mg, 0.0137 mmol) in anhyd DMF (5 mL) was heated at 100 °C for 11 h. The mixture was filtered through Celite and diluted with EtOAc, washed with brine, and dried ($MgSO_4$). The organic solvents were removed and the product was purified by column chromatography (hexanes–EtOAc (3:1) to give **42** (56 mg, 0.102 mmol, 60%) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.54 (m, 2 H, H2′), 3.85 (m, 1 H, H3′), 4.18–4.25 (m, 2 H, H5′), 4.36–4.39 (m, 1 H, H4′), 4.45–4.67 (m, 4 H, 2 PhCH_2), 5.21–5.22 (m, 2 H, PhCH_2), 6.76 (t, *J* = 4.5 Hz, 1 H, H1′), 7.33–7.34 (m, 10 H, H_{Ph}), 7.38–7.42 (m, 5 H, H_{Ph}), 7.94 (s, 1 H, $H5_{im}$), 8.55 (s, 1 H, $H2_{im}$), 8.64 (s, 1 H, $H2_{pyr}$), 9.16 (s, 1 H, $H6_{pyr}$).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.3, 21.2, 31.6, 36.6, 60.5, 68.5, 72.8, 72.4, 73.4, 75.7, 81.2, 81.5, 88.9, 110.5, 127.8, 127.7, 127.8, 127.9, 128.1, 133.3, 136.9, 137.6, 139.5, 148.6, 155.1, 163.6, 173.7.

HRMS (FAB): *m/z* [M + H] calcd for $C_{33}H_{33}N_4O_4$: 549.2502; found: 549.2503.

5-[1-(2-Deoxy-β-D-ribofuranosyl)-1*H*-imidazol-4-yl]pyrimidin-4-ol (10)

Following the typical procedure for **4** using **42** (0.662 g, 1.205 mmol), Pd/C (662 mg), ammonium formate (760 mg, 12.05 mmol), and anhyd EtOH (20 mL); during the standard work up the Celite pad was washed repeatedly with hot EtOH. Purification by column chromatography (EtOAc–acetone–EtOH–H_2, 8:1:1:0.5) gave **10** (200 mg, 0.719 mmol, 60%) as a white powder; mp >215 °C.

^{1}H NMR (400 MHz, CD_3OD): δ = 3.65 (m, 2 H, H2′), 3.78 (m, 1 H, H3′), 4.09–4.15 (m, 2 H, H5′), 4.32 (m, 1 H, H4′), 5.64 (t, *J* = 4.5 Hz, 1 H, H1′), 7.83 (s, 1 H, $H5_{im}$), 7.92 (s, 1 H, $H2_{im}$), 8.52 (br s, 1 H, $H6_{pyr}$), 9.16 (s, 1 H, $H6_{pyr}$).

^{13}C NMR (100 MHz, CD_3OD): δ = 61.2, 70.2, 76.1, 86.7, 89.5, 108.8, 131.6, 150.4, 151.7, 160.4.

HRMS (FAB): *m/z* [M + H] calcd for $C_{12}H_{15}N_4O_4$: 279.1093; found: 279.1094.

2,4-Bis(benzyloxy)-5-1-[(3,5-di-*O*-benzyl-2-deoxy-β-D-ribofuranosyl)-1*H*-imidazol-4-yl]pyrimidine (44)

A mixture of **26** (200 mg, 0.408 mmol) and $Pd(PPh_3)_4$ (47 mg, 0.0406 mmol) in DME (5 mL) was stirred at r.t. under argon for 10 min. To this mixture was added **43** (0.449 mmol) in DME (5 mL). Sat. aq $NaHCO_3$ (30 mL) was added and the mixture refluxed under argon for 4 h. The soln was cooled to r.t. and the DME layer separated and set aside. The aqueous layer was then extracted with EtOAc (3 × 50 mL), and the organic extracts were combined with the DME layer, washed with brine (100 mL), and dried ($MgSO_4$). The solvent was removed to give a pale brown syrup. Column chromatography (2% EtOH–CH_2Cl_2) gave **44** (170 mg, 0.260 mmol, 64%) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.33–2.35 (m, 2 H, H2′), 2.42–2.45 (m, 1 H, H3′), 3.49 (m, 2 H, H5′), 4.40–4.49 (m, 1 H, H4′), 5.44–5.37 (m, 4 H, PhCH_2), 4.56 (s, 2 H, PhCH_2), 4.59 (s, 2 H, PhCH_2), 5.96 (t, *J* = 4.5 Hz, 1 H, H1′), 6.97 (s, 1 H, $H5_{im}$), 7.34–7.67 (m, 20 H, H_{Ph}), 7.67 (s, 1 H, $H2_{im}$), 9.13 (s, 1 H, $H6_{pyr}$).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.4, 22.9, 39.7, 53.3, 68.5, 68.7, 69.4, 72.4, 72.5, 73.3, 76.5, 81.5, 82.5, 88.7, 109.5, 115.7, 127.5, 127.6, 127.8, 127.9, 128.3, 134.0, 135.6, 136.1, 136.5, 136.8, 137.2, 137.3, 141.5.

HRMS (FAB): *m/z* [M + H] calcd for $C_{40}H_{39}N_4O_5$: 655.2921; found: 655.2922.

5-[1-(2-Deoxy-β-D-ribofuranosyl)-1*H*-imidazol-4-yl]uracil (11)

Following the typical procedure for **4** using **44** (479 mg, 0.73 mmol), 10% Pd/C (730 mg), and ammonium formate (461 mg, 7.30 mmol) in EtOH (20 mL). Purification by column chromatography (EtOAc–acetone–EtOH–H_2, 7:1:1:0.5) afforded **11** (200 mg, 0.680 mmol, 52%) as a white crystalline product; mp 245–247 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 3.44–3.47 (m, 2 H, H2′), 3.74–3.75 (m, 1 H, H3′), 4.25–4.28 (m, 2 H, H5′), 5.23–5.24 (m, 1 H, H4′), 5.98 (t, *J* = 4.5 Hz, 1 H, H1′), 7.62 (s, 1 H, $H5_{pyr}$), 7.77 (s, 1 H, $H5_{im}$), 7.83 (s, 1 H, $H2_{im}$), 10.9 (s, 1 H, NH), 11.2 (s, 1 H, NH).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 61.5, 71.3, 75.4, 85.4, 89.3, 106.3, 113.5, 133.7, 135.7, 136.8, 150.5, 162.4.

HRMS (FAB): *m/z* [M + H] calcd for $C_{12}H_{15}N_4O_5$: 295.1042; found: 295.1040.

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