

SYNTHESIS OF 7-SUBSTITUTED 3- β -D-RIBOFURANOSYL-3*H*-IMIDAZO[2,1-*i*]PURINES

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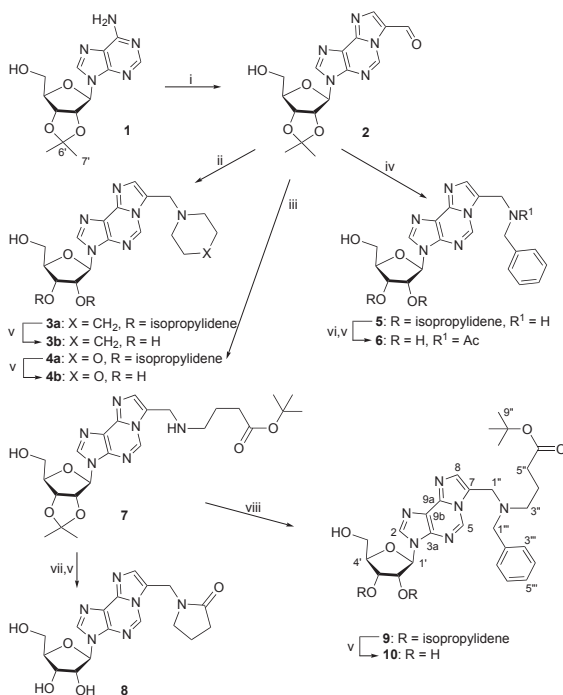
Dedicated to Professor Antonín Holý on the occasion of his 75th birthday in recognition of his outstanding contributions to the area of nucleic acid chemistry.

A method for the synthesis of 7-substituted 3- β -D-ribofuranosyl-3*H*-imidazo[2,1-*i*]purines has been devised whereby compounds were prepared in a few steps from a common intermediate, 3-(2',3'-O-isopropylidene- β -D-ribofuranosyl)-3*H*-imidazo[2,1-*i*]purine-7-carbaldehyde, obtained from the reaction of 2',3'-O-isopropylideneadenosine with bromomalonaldehyde. The formyl group of the carbaldehyde was subsequently reductively aminated and the resulting secondary amines were then further derivatized either by acylation, lactamization or reductive alkylation.

Keywords: Nucleosides; Heterocycles; Purine bases; NMR spectroscopy.

Purine nucleosides and their congeners have found applications in medicinal research as antivirals^{1,2}, antiprotozoal agents³, adenosine receptor agonists⁴⁻⁶, adenosine kinase inhibitors^{7,8} and in the treatment of lymphoid malignancies⁹⁻¹² and systemic mastocytosis¹³, just to name a few examples. Although the structural analogs of purine nucleosides have for this reason been the subject of extensive synthetic studies, there is still room for further modifications. We now report on the preparation of 7-substituted 3-(β -D-ribofuranosyl)-3*H*-imidazo[2,1-*i*]purines to expand the structural diversity of purine-derived compounds. The rationale for the preparation of these compounds is that whilst the structures closely resemble adenosine, the nitrogen atoms analogous to the N⁶ and N-1 atoms in adenosine are blocked. These moieties of adenosine are usually engaged in H-bonding with the target protein. It is hoped that this blocking will lead to improved selectivity, since it is expected that only a limited number of potential targets are able to bind these compounds efficiently as ligands.

As an extension of our previous studies on solid-supported derivatization of 3-substituted 3*H*-imidazo[2,1-*i*]purine-7-carbaldehydes^{14,15}, a solution-phase synthesis for related nucleoside analogs, 7-substituted 3-β-D-ribofuranosyl-3*H*-imidazo[2,1-*i*]purines, was developed. The compounds were prepared in a few steps from a common intermediate, 3-(2',3'-*O*-isopropylidene-β-D-ribofuranosyl)-3*H*-imidazo[2,1-*i*]purine-7-carbaldehyde (**2**), obtained by reacting 2',3'-*O*-isopropylideneadenosine (**1**) with bromomalon-aldehyde (Scheme 1). In this sequence, the formyl group was first reductively aminated with piperidine (**3a**), morpholine (**4a**), benzylamine (**5**) or *tert*-butyl 4-aminobutanoate (**7**). The resulting secondary amines (**5** and **7**) were then derivatized either by acetylation (**6**), lactamization (**8**) or reductive alkylation (**9**) after which the isopropylidene protecting group was removed.



SCHEME 1

Conditions: i) BrCH(CHO)₂, HCO₂H, 2,6-lutidine, DMF; ii) piperidine (for **3a**), morpholine (for **4a**), NaBH(OAc)₃, AcOH, DCE; iii) Cl⁻ + H₃N(CH₂)₃COO*t*-Bu, NaBH(OAc)₃, DCE; iv) BnNH₂, NaCNBH₃, AcOH, THF; v) FeCl₃·6H₂O, MeOH, DCM (for **3b**), 0.1 M HCl (aq.)/ THF (for **4b**, **6**, **8** and **10**); vi) 1. Ac₂O, Pyridine 2. NaOMe, MeOH; vii) 1. 50% TFA/DCM, 2. HBTU, DIEA, DMF; viii) PhCHO, ZnCl₂, NaCNBH₃, MeOH

RESULTS AND DISCUSSION

Formylethenoadenosine (3- β -D-ribofuranosyl-3*H*-imidazo[2,1-*i*]purine-7-carbaldehyde)¹⁶ and its 2'-deoxy analog¹⁷ have been previously synthesized by the reaction of bromomalon aldehyde with adenosine in aqueous solution and 2'-deoxyadenosine in DMF, respectively. Both methods, however, only provided low yields of their respective product carbaldehydes. By contrast, ethyl and *tert*-butyl 2-(7-formyl-3*H*-imidazo[2,1-*i*]purin-3-yl)acetates have been obtained by solution-phase synthesis in good yields¹⁵ by applying the anhydrous conditions previously¹⁴ optimized for solid-support chemistry. However, the reaction of unprotected adenosine under similar conditions produced only a thick dark product mixture that was difficult to fractionate into pure products. Protection of the 2' and 3' hydroxyl groups of the ribose moiety with an isopropylidene group to yield 2',3'-*O*-isopropylideneadenosine (**1**) markedly improved the situation. This approach thereby facilitated the production of the desired target compound, 3-(2',3'-*O*-isopropylidene- β -D-ribofuranosyl)-3*H*-imidazo[2,1-*i*]purine-7-carbaldehyde (**2**), in 81% yield after analogous reaction followed by purification using silica gel chromatography.

The conditions applied previously¹⁴ for the reductive amination of a formyl group on a solid support were found to be too harsh to be used in solution-phase synthesis. For example, treatment with sodium cyanoborohydride in THF containing 1% formic acid was found to give a product mixture where the reduced starting material was the main component (data not presented). The replacement of formic acid with acetic acid reduced the amount of this side product but still did not lead to a generally satisfactory result. Only when using benzylamine as the nucleophile was the obtained yield of the amination product **5** sufficiently acceptable. Sodium triacetoxyborohydride in DCE was found to produce less byproducts and thus it was used for the amination of **2** with piperidine, morpholine and *tert*-butyl 4-aminobutanoate to obtain, respectively, compounds **3a**, **4a** and **7**. Of the secondary amines, **5** was subjected to acetylation and **7** to lactamization and alkylation. Although the treatment of **5** with acetic anhydride esterified the 5'-hydroxyl group in addition to the secondary nitrogen atom, the 5'-*O*-acetyl group could be selectively removed by the application of sodium hydride in methanol. Finally, acidolytic removal of the isopropylidene protection then yielded the desired nucleoside **6**.

NMR spectroscopic examination of **6** revealed that it existed as two interconverting conformations in solution as evidenced by the cross-signals present in an EXSY spectrum between corresponding protons in the major

and minor species. Compound **6** contains an acetamide moiety and thus it is expected to have restricted rotation about the amide bond. The structural assignment of these conformers was based on quantum mechanical (QM)-calculated energies and QM-predicted ^{13}C NMR chemical shifts, both of which indicated that the conformer having the carbonyl oxygen *trans* to the benzyl group (conformer A, the major species) was preferred ($\Delta G = 12 \text{ kJ mol}^{-1}$) over the conformer with *cis* orientation (conformer B), see Fig. 1.

Compound **7** was first converted to a carboxylic acid by TFA promoted removal of the *tert*-butyl group under anhydrous conditions and the exposed γ -aminobutyric acid moiety was then lactamized in dilute solution using 2-(1*H*-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HBTU) as an activator and *N,N*-diisopropylethylamine as the base. Finally, the isopropylidene protecting group was also removed to obtain **8**. Alternatively, compound **7** was also subjected to reductive benzylation with benzaldehyde in DCE using zinc-modified NaCNBH_3 ¹⁸ as the reducing agent. Of note, the reaction was found to be very slow using either $\text{NaBH}(\text{OAc})_3$ or NaCNBH_3 without zinc chloride addition and, furthermore, the addition of acetic or formic acid instead brought about the formation of acylated and lactamized side products¹⁹. The product (**9**) was acidolytically deprotected to yield compound **10**.

All the synthetic processes described above involved the removal of the 2',3'-*O*-isopropylidene protection as the last step. Of note, this step, somewhat unexpectedly, was found to be a rather difficult one. Of the numerous methods attempted, including 80% aqueous AcOH at 25 °C ²⁰, I_2/MeOH ²¹,

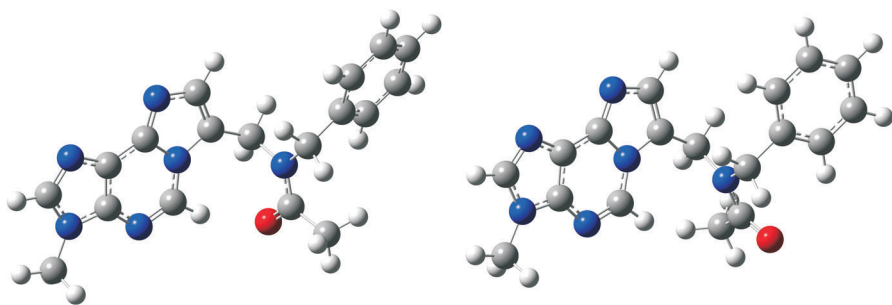


FIG. 1

The *trans* (conformer A, left) and *cis* (conformer B, right) structures of compound **6** calculated at the B3LYP/6-31G(d,p) level of theory. N.b. the ribose moiety was substituted by methyl to expedite the modeling calculations

$\text{PdCl}_2(\text{CH}_3\text{CN})_2$ ²², CAN ²³, CAN-SiO_2 ²⁴, and hydrolysis at pH 2, many were found to be too inefficient whilst harsher treatments such as 80% aqueous AcOH at reflux²⁰ or a 1:1 mixture of 1 M HCl (aq.) and THF ²⁵, resulted in side reactions such as depurination or even pyrimidine ring opening. The best results were obtained using a 1:1 mixture of 0.1 M HCl (aq.) and THF at 55 °C or $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ in a 1:19 mixture of MeOH and DCM at elevated temperature²⁶. The Brønsted acid-catalyzed reaction, however, was still accompanied by some depurination whilst the Lewis acid-catalyzed reaction, though cleaner, was hampered by a more laborious work up that resulted ultimately in reduced yields. The former method was therefore mainly used since it was more convenient, faster and approximately equally yielding as the latter.

In conclusion, a method to produce 7-substituted 3*H*-imidazo[2,1-*i*]-purines on solid support was successfully adapted to solution chemistry to produce 7-substituted 3-β-D-ribofuranosyl-3*H*-imidazo[2,1-*i*]purines. Because of the different nature of the reaction media, several modifications to the reaction conditions were necessitated. In addition, the use of a protecting group for the ribose ring of the starting material was required. Unfortunately, the isopropylidene protection was more stable than expected which reduced the yields of the acid labile end products. For further developments, it could be worthwhile to thus evaluate other protection strategies.

EXPERIMENTAL

Solvents and reagents were dried or tested for dryness before use when appropriate. The purified products existed as transparent glassy solids after rotary evaporation except compound **2** which was a white solid.

NMR spectra (δ , ppm; J , Hz), at 298.1 K (uncorrected) unless otherwise indicated, were recorded on Bruker Avance spectrometers with field strengths of 14.1, 10.75 and 9.4 T. General NMR experimental details (e.g. standard gradient-selected COSY, HMBC and HSQC) have been described elsewhere²⁷. NMR samples in solvents as indicated consisted of dilute samples (~5 mg in ca. 0.6 ml) up to concentrated samples (~50 mg in ca. 0.6 ml). ¹H and ¹³C chemical shifts were referenced internally to the solvent peaks²⁸ (DMSO : δ_{H} 2.50, δ_{C} 39.52; MeOH : δ_{H} 3.31, δ_{C} 49.00 and HOD : δ_{H} 4.79) or to TMS in the case of CDCl_3 solutions (δ 0 for both ¹H and ¹³C). ¹⁵N chemical shifts were referenced externally to 90% nitromethane in CD_3NO_2 (δ 0). Assignment of the H-5's²⁹ (*proR* and *proS*) and isopropylidene methyl ¹H and ¹³C nuclei³⁰ (*endo* and *exo*) were derived from literature. Direct observations of the ¹⁵N nuclei were facilitated by the QDEPT pulse sequence adapted³¹ from methodology^{32,33} developed for one-bond ¹H-¹³C interactions. The method of cycling the ¹H-selection pulse and the J -dependent interpulse delays, scaled accordingly to span the range 24.1–4.7 Hz, was taken from Jiang³³. In the case of dilute samples, indirect ¹⁵N observations were taken from HMBC spectra (appropriately only reported to one decimal place). ¹⁵N chemical shifts were in accordance with previous examinations^{27a,27b,34} with shielded

resonances for sp^3 -type nitrogens (N-3, N-6) and deshielded resonances for sp^2 -type nitrogens (N-1, N-4, N-9).

Geometry optimizations, frequency calculations and chemical shielding calculations using GIAO were performed using the Gaussian09W program³⁵ at the restricted B3LYP/6-31G(d,p) level of theory for all calculations with inclusion of methanol as the solvent using the IEF-PCM model.

A Bruker ESI-QTOF mass spectrometer was used for the measurement of high resolution mass spectra.

3-(2,3-O-Isopropylidene- β -D-ribofuranosyl)-3*H*-imidazo[2,1-*i*]purine-7-carbaldehyde (**2**)

2',3'-O-Isopropylideneadenosine (**1**; 0.50 g, 1.63 mmol) and bromomalonaldehyde (0.37 g, 2.44 mmol) were dissolved in a mixture of formic acid (0.19 ml, 5.01 mmol), 2,6-lutidine (0.53 ml, 4.57 mmol) and dry DMF (9.3 ml). The reaction mixture was agitated in a stoppered bottle at 60 °C for 6 h during which time the color of the mixture turned a dark orange. The reaction was monitored by TLC (10% MeOH/ CH_2Cl_2) and upon completion, the volatiles were removed by a rotary evaporator and the residue taken up in DCM followed by extraction with saturated $NaHCO_3$. The organic phase was dried over Na_2SO_4 and then evaporated to dryness after filtration. The crude material was purified by silica gel column chromatography (5% MeOH in DCM) yielding 0.47 g (81%) of **2**. Some batches contained minor amounts of a fluorescent intensely orange-colored byproduct. The impurity was not characterized. 1H NMR (500 MHz, $DMSO-d_6$): 10.00 s, 1 H (H-1''); 9.91 s, 1 H (H-5); 8.74 s, 1 H (H-2); 8.58 s, 1 H (H-8); 6.33 d, 1 H, $J = 2.6$ (H-1'); 5.40 dd, 1 H, $J = 6.2, 2.6$ (H-2'); 5.12 br, 1 H (OH); 5.03 dd, 1 H, $J = 6.2, 2.6$ (H-3'); 4.29 dt, 1 H, $J = 4.9, 2.6$ (H-4'); 3.59 dd, 1 H, $J = -11.8, 4.9$ (H-5' $_{proS}$); 3.55 dd, 1 H, $J = -11.8, 4.9$ (H-5' $_{proR}$); 1.56 s, 3 H (H-7' $_{endo}$); 1.34 s, 3 H (H-7' $_{exo}$). ^{13}C NMR (126 MHz, $DMSO-d_6$): 179.17 (C-1''), 147.83 (C-8), 144.71 (C-9a), 142.22 (C-2), 140.96 (C-3a), 136.76 (C-5), 124.72 (C-7), 122.99 (C-9b), 113.13 (C-6'), 90.12 (C-1'), 87.23 (C-4'), 84.07 (C-2'), 81.36 (C-3'), 61.44 (C-5'), 26.99 (C-7' $_{endo}$), 25.15 (C-7' $_{exo}$). ^{15}N NMR (50 MHz, $DMSO-d_6$): -204.00 (N-3), -184.15 (N-6), -145.62 (N-4), -142.61 (N-9), -137.16 (N-1). HRMS: calculated for $[M + H]^+$ $C_{16}H_{18}N_5O_5^+$ 360.1302 amu; found 360.1303 amu.

3-(2,3-O-Isopropylidene- β -D-ribofuranosyl)-7-(piperidin-1-ylmethyl)-3*H*-imidazo[2,1-*i*]purine (**3a**)

Compound **2** (0.100 g, 0.278 mmol) was suspended in DCE (1 ml) to which piperidine (30.2 μ l, 0.306 mmol) and acetic acid (31.8 μ l, 0.556 mmol) were added under magnetic stirring. $NaBH(OAc)_3$ (0.295 g, 1.39 mmol) in DCE (1 ml) was added to the reaction mixture in three aliquots with reaction monitoring by TLC (10% H_2O /MeCN). After ca. 24 h, the reaction mixture was taken to dryness and the residue taken up twice with water and once with MeOH with solvent removal effecting the co-evaporation of any residual acetic acid. The crude material was purified by silica gel column chromatography (10% H_2O in MeCN) yielding 0.083 g (61%) of **3a** as an acetate salt. 1H NMR (500 MHz, $CDCl_3$): 9.25 s, 1 H (H-5); 8.48 s, 1 H (H-2); 7.47 s, 1 H (H-8); 6.33 d, 1 H, $J = 2.9$ (H-1'); 5.37 dd, 1 H, $J = 6.2, 2.9$ (H-2'); 5.08 dd, 1 H, $J = 6.2, 2.8$ (H-3'); 4.41–4.35 m, 1 H (H-4'); 3.99 s, 2 H (H-1''); 3.79 dd, 1 H, $J = -11.9, 4.1$ (H-5' $_{proS}$); 3.73 dd, 1 H, $J = -11.9, 4.7$ (H-5' $_{proR}$); 2.55 s, 4 H (H-3''); 1.94 s, 3 H (AcO^-); 1.63 s, 3 H (H-7' $_{endo}$); 1.62–1.54 m, 4 H (H-4''); 1.54–1.42 m, 2 H (H-5''); 1.40 s, 3 H (H-7' $_{exo}$). ^{13}C NMR (126 MHz, $CDCl_3$): 178.96 (AcO^-), 143.06 (C-9a), 141.93 (C-2), 139.83 (C-3a), 137.51 (C-5), 133.71 (C-8), 124.21 (C-9b), 122.18 (C-7), 115.33 (C-6'), 92.58

(C-1'), 88.62 (C-4'), 86.03 (C-2'), 82.95 (C-3'), 63.34 (C-5'), 55.13 (C-3''), 52.63 (C-1''), 27.58 (C-7'_{endo}), 26.66 (C-4''), 25.55 (C-7'_{exo}), 25.07 (C-5''), 22.79 (AcO⁻). HRMS: calculated for [M + H⁺] C₂₁H₂₉N₆O₄⁺ 429.2245 amu; found 429.2248 amu.

7-(Piperidin-1-ylmethyl)-3-β-D-ribofuranosyl-3*H*-imidazo[2,1-*i*]purine (**3b**)

Compound **3a** (34.2 mg, 70.0 μmol), FeCl₃·6H₂O (37.8 mg, 0.140 mmol) and MeOH (50 μl) in DCM (950 μl) were refluxed first for 7 h and then allowed to stand at room temperature overnight. One eq. of FeCl₃·6H₂O was then added and refluxing was continued for a few hours until the reaction was complete as indicated by TLC (10% MeOH in DCM). Aqueous NaHCO₃ (1 ml, half-saturated solution) was then added under stirring followed by evaporation to dryness. The residue containing the deprotected product **3b** and ferric hydroxide was suspended in aqueous MeOH and mixed with silica gel followed by evaporation of the solvent. The product **3b** was eluted from the silica gel with 20% H₂O in MeCN by suction-filtration and then further purified by HPLC (0–50% MeOH/H₂O, 0.1 TFA, 250 × 21.2 mm, 5 μm Hypersil ODS2, UV detection at λ = 220 nm). Yield 23 mg (65%) of **3b** as a TFA salt. ¹H NMR (500 MHz, DMSO-*d*₆): 9.21 s, 1 H (H-5); 8.57 s, 1 H (H-2); 7.44 s, 1 H (H-8); 6.05 d, 1 H, *J* = 5.7 (H-1'); 5.60 br, 1 H (OH); 5.33 br, 1 H (OH); 5.12 br, 1 H (OH); 4.60–4.62 m, 1 H (H-2'); 4.18–4.22 m, 1 H (H-3'); 3.98–4.00 m, 1 H (H-4'); 3.87 s, 2 H (H-1''); 3.69–3.72 m, 1 H (H-5'_{proS}); 3.57–3.60 m, 1 H (H-5'_{proR}); 2.37 br, 4 H (H-3''); 1.43–1.49 m, 4 H (H-4''); 1.33–1.41 m, 2 H (H-5''). ¹³C NMR (126 MHz, DMSO-*d*₆): 141.23 (C-9a), 140.10 (C-2), 138.32 (C-3a), 136.22 (C-5), 132.52 (C-8), 123.09 (C-9b), 121.00 (C-7), 87.95 (C-1'), 85.63 (C-4'), 74.14 (C-2'), 70.33 (C-3'), 61.34 (C-5'), 53.55 (C-3''), 51.45 (C-1''), 25.56 (C-4''), 23.98 (C-5''). ¹⁵N NMR (50 MHz, DMSO-*d*₆): –206.90 (N-3), –179.15 (N-6), –152.42 (N-4), –150.82 (N-9), –137.77 (N-1), N-1'' not observed. HRMS: calculated for [M + H⁺] C₁₈H₂₅N₆O₄⁺ 389.1932 amu; found 389.1924 amu.

3-(2,3-*O*-Isopropylidene-β-D-ribofuranosyl)-7-(morpholinomethyl)-3*H*-imidazo[2,1-*i*]purine (**4a**)

The synthesis was performed as described for **3a** except that morpholine (48.4 μl, 0.556 mmol) was substituted for piperidine. The reaction was monitored by TLC (10% MeOH in DCM) and upon completion, the reaction mixture was stirred with aqueous NaHCO₃ prior to evaporation. The crude material was purified by silica gel column chromatography (10% MeOH/CH₂Cl₂) yielding 0.116 g (97%) of **4a**. ¹H NMR (600 MHz, CDCl₃): 9.16 s, 1 H (H-5); 8.18 s, 1 H (H-2); 7.50 s, 1 H (H-8); 6.07 d, 1 H, *J* = 4.5 (H-1'); 5.24 dd, 1 H, *J* = 5.9, 4.5 (H-2'); 5.16 dd, 1 H, *J* = 6.0, 1.6 (H-3'); 4.60–4.56 m, 1 H, *J* = 1.9 (H-4'); 4.05 dd, *J* = –12.4, 2.1 (H-5'_{proS}); 3.89 dd, 1 H, *J* = –12.4, 2.0 (H-5'_{proR}); 3.88 d, 1 H, *J* = 14.1 (H-1''); 3.84 d, 1 H, *J* = 14.1 (H-1'); 3.68 t, 4 H, *J* = 4.3 (H-4''); 2.49–2.42 m, 4 H (H-3''); 1.68 s, 3 H (H-7'_{endo}); 1.40 s, 3 H (H-7'_{exo}). ¹³C NMR (151 MHz, CDCl₃): 142.23 (C-9a), 140.45 (C-2), 137.62 (C-3a), 135.71 (C-5), 133.99 (C-8), 125.31 (C-9b), 119.88 (C-7), 114.35 (C-6'), 93.71 (C-1'), 86.15 (C-4'), 83.95 (C-2'), 81.66 (C-3'), 66.84 (C-4''), 63.20 (C-5'), 53.40 (C-3''), 52.60 (C-1''), 27.60 (C-7'_{endo}), 25.34 (C-7'_{exo}). ¹⁵N NMR (50 MHz, DMSO-*d*₆): –206.05 (N-3), –179.18 (N-6), –152.39 (N-4), –150.7 (N-9), –137.86 (N-1), N-1'' not observed. HRMS: calculated for [M + H⁺] C₂₀H₂₇N₆O₅⁺ 431.2037 amu; found 431.2033 amu.

7-(Morpholinomethyl)-3- β -D-ribofuranosyl-3*H*-imidazo[2,1-*i*]purine (**4b**)

Compound **4a** (23.8 mg, 55.2 μ mol) was dissolved in 0.1 M HCl in aqueous (53%) THF (2 ml) and the reaction mixture was stirred on an oil bath at 50 °C for 4.5 h and monitored by TLC (20% H₂O in MeCN). Upon completion, the solution was cooled to room temperature, the pH adjusted to 8 with saturated NaHCO₃ followed by evaporation to dryness. The crude material was purified by silica gel column chromatography (10–12.5% H₂O in MeCN) yielding 17 mg (80%) of **4b**. ¹H NMR (400 MHz, D₂O): 9.03 s, 1 H (H-5); 8.41 s, 1 H (H-2); 7.45 s, 1 H (H-8); 6.15 d, 1 H, *J* = 5.6 (H-1'); 4.84 t, 1 H, *J* = 5.4 (H-2'); 4.49 dd, 1 H, *J* = 5.2, 4.0 (H-3'); 4.30 q, 1 H, *J* = 3.8 (H-4'); 3.96 dd, 1 H, *J* = -12.8, 3.2 (H-5'_{proS}); 3.94 s, 2 H (H-1''); 3.89 dd, 1 H, *J* = -12.8, 4.2 (H-5'_{proR}); 3.73 t, 4 H, *J* = 4.6 (H-4''); 2.69–2.52 m, 4 H (H-3''). ¹³C NMR (101 MHz, D₂O): 142.40 (C-9a), 142.08 (C-2), 139.61 (C-3a), 137.45 (C-5), 134.33 (C-8), 123.65 (C-9b), 121.55 (C-7), 90.14 (C-1'), 86.96 (C-4'), 75.50 (C-2'), 71.90 (C-3'), 67.56 (C-4''), 62.88 (C-5'), 53.81 (C-3''), 51.49 (C-1''). ¹⁵N NMR (50 MHz, DMSO-*d*₆): -206.90 (N-3), -179.31 (N-6), -152.27 (N-4), -150.88 (N-9), -137.77 (N-1), N-1'' not observed. HRMS: calculated for [M + H⁺] C₁₇H₂₃N₆O₅⁺ 391.1724 amu; found 391.1728 amu.

7-[(Benzylamino)methyl]-3-(2,3-*O*-isopropylidene- β -D-ribofuranosyl)-3*H*-imidazo[2,1-*i*]purine (**5**)

Compound **2** (0.108 g, 0.300 mmol), benzylamine (32.8 μ l, 0.300 mmol), NaCNBH₃ (85%, 23.0 mg, 0.311 mmol) and acetic acid (34.4 μ l, 0.601 mmol) were stirred in dry THF (2.0 ml) for 24 h. The reaction mixture was evaporated to dryness and the residue taken up in DCM and extracted with saturated NaHCO₃. The organic phase was dried over Na₂SO₄ and again evaporated to dryness after filtration. The crude material was purified by silica gel column chromatography (10% MeOH/CH₂Cl₂) yielding 0.11 g (81%) of **5**. ¹H NMR (500 MHz, CDCl₃): 9.18 s, 1 H (H-5); 8.16 s, 1 H (H-2); 7.44 s, 1 H (H-8); 7.34–7.22 m, 5 H (Ph); 6.07 d, 1 H, *J* = 4.3 (H-1'); 5.43 br, 1 H (OH); 5.24 dd, 1 H, *J* = 6.0, 4.3 (H-2'); 5.16 dd, 1 H, *J* = 6.0, 1.7 (H-3'); 4.56–5.54 m, 1 H (H-4'); 4.15 s, 2 H (H-1''); 4.03 dd, 1 H, *J* = -12.4, 2.1 (H-5'_{proS}); 3.88 dd, 1 H, *J* = -12.4, 1.6 (H-5'_{proR}); 3.80 s, 2 H (H-1'''); 1.67 s, 3 H (H-7'_{endo}); 1.40 s, 3 H (H-7'_{exo}). ¹³C NMR (101 MHz, CDCl₃): 141.99 (C-9a), 140.35 (C-2), 139.47 (C-2''), 137.61 (C-3a), 135.99 (C-5), 132.84 (C-8), 128.66 (C-4'''), 128.32 (C-3'''), 127.38 (C-5'''), 125.17 (C-9b), 122.13 (C-7), 114.32 (C-6'), 93.57 (C-1'), 86.30 (C-4'), 84.03 (C-2'), 81.69 (C-3'), 63.20 (C-5'), 53.17 (C-1'''), 42.60 (C-1''), 27.64 (C-7'_{endo}), 25.40 (C-7'_{exo}). HRMS: calculated for [M + H⁺] C₂₃H₂₇N₆O₄⁺ 451.2088 amu; found 451.2087 amu.

7-[(*N*-Acetyl-*N*-benzyl)aminomethyl]-3- β -D-ribofuranosyl-3*H*-imidazo[2,1-*i*]purine (**6**)

Compound **5** (20.5 mg, 45.5 μ mol), acetic anhydride (0.500 ml, 5.29 mmol) and pyridine (0.200 ml, 2.48 mmol) were stirred in DCM (4.5 ml) until all of the starting material had been consumed according to TLC monitoring (10% MeOH in DCM). The reaction mixture was then evaporated to dryness and the residue taken up in DCM and extracted with saturated NaHCO₃. The organic phase was dried over Na₂SO₄ and again evaporated to dryness after filtration. The remaining mixture of acetylated products was dissolved in dry MeOH (1.0 ml) containing sodium hydride (60% dispersion in mineral oil, 3.0 mg, 75 μ mol). When deacetylation of the hydroxyl groups was complete, the mixture was diluted with DCM and extracted with 3% aq. KH₂PO₄. The organic phase was dried over Na₂SO₄ and the solvent was removed after filtration. The product was purified by silica gel column chromatography

(5% MeOH in DCM) yielding 16.5 mg (74%) of **6**. The isopropylidene protection was removed as described for **4b** and the deprotected material was purified by silica gel column chromatography (10% H₂O/MeCN) yielding 11 mg (53% from **5**) of **6**. Conformers A and B denoted by demarkations A and B, respectively. ¹H NMR (500 MHz, CD₃OD): 9.48 s, 0.9 H (H-5A); 8.98 s, 0.1 H (H-5B); 8.85 s, 0.9 H (H-2A); 8.81 s, 0.1 H (H-2B); 7.84 s, 0.1 H (H-8B); 7.81 s, 0.9 H (H-8A); 7.32–7.24 m, 1.8 H (H-4''A); 7.23–7.16 m, 2.7 H (H-3''A, H-5''A); 7.11–7.03 m, 1.8 H (H-4''B); 7.01–6.94 m, 2.7 H (H-3''B, H-5''B); 6.26 d, 0.9 H, *J* = 5.1 (H-1'A); 6.23 d, 0.1 H, *J* = 5.0 (H-1'B); 5.15 s, 2 H (1''); 4.72 s, 2 H (H-1'''); 4.70–4.68 m, 1 H (H-2'); 4.40–4.38 m, 1 H (H-3'); 4.20–4.18 m, 1 H (H-4'); 3.92 dd, 1 H, *J* = –12.2, 3.2 (H-5'_{proS}); 3.82 dd, 1 H, *J* = –12.2, 3.5 (H-5'_{proR}); 2.40 s, 0.3 H (H-4''B); 2.28 s, 2.7 H (H-4''A). ¹³C NMR (126 MHz, CD₃OD): 174.44 (C-3''A), 174.08 (C-3''B), 143.20 (C-9a), 142.03 (C-2A), 141.81 (C-2B), 140.20 (C-3a), 137.49 (C-2''), 137.30 (C-5A), 135.96 (C-5B), 134.41 (C-8A), 133.38 (C-8B), 129.92 (C-4''A), 129.24 (C-4''B), 128.66 (C-5''A), 128.37 (C-3''B), 127.91 (C-5''B), 127.47 (C-3''A), 124.25 (C-9b), 121.94 (C-7), 90.78 (C-1'A), 90.87 (C-1'B), 87.30 (C-4'), 76.20 (C-2'), 72.03 (C-3'), 62.94 (C-5'), 52.15 (C-1''A), 49.73 (C-1''B), 43.86 (C-1'B), 39.00 (C-1'A), 21.88 (C-4'B), 21.81 (C-4'A). HRMS: calculated for [M + H⁺] C₂₂H₂₅N₆O₅⁺ 453.2881 amu; found 453.2883 amu.

3-(2,3-O-Isopropylidene-β-D-ribofuranosyl)-7-[N-(4-*tert*-butoxy-4-oxobutyl)aminomethyl]-3*H*-imidazo[2,1-*i*]purine (**7**)

Compound **2** (0.300 g, 0.835 mmol) and *tert*-butyl 4-aminobutanoate hydrochloride (0.196 g, 1.00 mmol) were suspended in DCE (6 ml) to which NaBH(OAc)₃ (0.505 g, 2.38 mmol) was added in three batches. The reaction mixture was stirred at room temperature for 24 h followed by refrigeration over a weekend and then evaporation to dryness. To remove any residual acetic acid, the residue was taken up twice with water (2 × 10 ml) to effect co-removal via solvent evaporation. The crude material was purified by silica gel column chromatography (10–15% H₂O/MeCN) yielding 0.224 g (53%) of **7**. ¹H NMR (500 MHz, CD₃OD): 9.18 s, 1 H (H-5); 8.44 s, 1 H (H-2); 7.53 s, 1 H (H-8); 6.25 d, 1 H, *J* = 2.9 (H-1'); 5.29 dd, 1 H, *J* = 6.1, 2.9 (H-2'); 5.01 dd, 1 H, *J* = 6.1, 2.7 (H-3'); 4.46 s, 2 H (H-1''); 4.37–4.30 m, 1 H (H-4'); 3.74 dd, 1 H, *J* = –11.9, 4.0 (H-5'_{proS}); 3.69 dd, 1 H, *J* = –12.0, 4.7 (H-5'_{proR}); 2.96–2.88 m, 2 H (H-3''); 2.31 t, 2 H, *J* = 7.2 (H-5''); 1.85 p, 2 H, *J* = 7.2 (H-4''); 1.58 s, 3 H (H-7'_{endo}); 1.35 s, 12 H (H-7'_{exo}, H-9''). ¹³C NMR (126 MHz, CD₃OD): 173.21 (C-6''), 142.20 (C-9a), 141.26 (C-2), 139.04 (C-3a), 136.17 (C-5), 133.68 (C-8), 123.06 (C-9b), 119.99 (C-7), 114.45 (C-6'), 91.66 (C-1'), 87.76 (C-4'), 85.15 (C-2'), 82.07 (C-3'), 80.90 (C-8''), 62.48 (C-5'), 47.67 (C-3''), 41.11 (C-1''), 32.68 (C-5''), 27.43 (C-9''), 26.73 (C-7'_{endo}), 24.72 (C-7'_{exo}), 23.56 (C-4''). HRMS: calculated for [M + H⁺] C₂₄H₃₅N₆O₆⁺ 503.2613 amu; found 503.2611 amu.

7-[(2-Oxopyrrolidin-1-yl)methyl]-3-β-D-ribofuranosyl-3*H*-imidazo[2,1-*i*]purine (**8**)

Compound **7** (23.0 mg, 45.8 μmol) was stirred for 1 h in a 1:1 mixture of TFA and DCM after which the volatiles were removed under vacuum. To the residue, HBTU (19.1 mg, 50.3 μmol) and DIEA (8.9 μl, 50.3 μmol) dissolved in dry DMF (3.0 ml) were added. After two days, an additional one-half equivalent of HBTU was added to the incomplete reaction and stirring was continued for an additional day. After completion of the reaction, the DMF was evaporated off and the isopropylidene protection removed as described for **4b**. The deprotected material was purified by silica gel column chromatography (10–12.5%

H₂O/MeCN) yielding 7.7 mg (43% from 7) of 8. ¹H NMR (500 MHz, CD₃OD): 9.15 s, 1 H (H-5); 8.53 s, 1 H (H-2); 7.58 s, 1 H (H-8); 6.16 d, 1 H, *J* = 5.3 (H-1'); 4.93 s, 1 H (H-1''); 4.71 t, 1 H, *J* = 5.2 (H-2'); 4.38 t, 1 H, *J* = 4.6 (H-3'); 4.16 q, 1 H, *J* = 3.5 (H-4'); 3.90 dd, 1 H, *J* = -12.2, 3.1 (H-5'_{pros}); 3.79 dd, 1 H, *J* = -12.2, 3.6 (H-5'_{proR}); 3.39 t, 2 H, *J* = 7.1 (H-5''); 2.43 t, 2 H, *J* = 8.1 (H-3''); 2.05–1.95 m, 2 H, *J* = 8.1, 7.1 (H-4''). ¹³C NMR (126 MHz, CD₃OD): 178.03 (C-3''), 143.19 (C-9a), 142.01 (C-2), 140.27 (C-3a), 136.88 (C-5), 133.98 (C-8), 124.32 (C-9b), 121.28 (C-7), 90.75 (C-1'), 87.23 (C-4'), 76.19 (C-2'), 71.97 (C-3'), 62.87 (C-5'), 47.90 (C-4''), 36.56 (C-1''), 31.77 (C-6''), 18.49 (C-5'). ¹⁵N NMR (50 MHz, DMSO-*d*₆): -206.70 (N-3), -180.00 (N-6), -151.62 (N-4), -150.36 (N-9), -137.7 (N-1), N-1'' not observed. HRMS: calculated for [M + H⁺] C₁₇H₂₁N₆O₅⁺ 389.1568 amu; found 389.1564 amu.

3-(2,3-*O*-Isopropylidene-β-D-ribofuranosyl)-7-[[*N*-(4-*tert*-butoxy-4-oxobutyl)-*N*-benzyl]aminomethyl]-3*H*-imidazo[2,1-*i*]purine (9)

Compound 7 (35.2 mg, 70.0 μmol) and benzaldehyde (14.3 μl, 0.140 mmol) were dissolved in dry MeOH (0.40 ml) to which ZnCl₂ (9.5 mg, 70.0 μmol) and NaCNBH₃ (85%, 10.4 mg, 0.140 mmol) in dry MeOH (0.20 ml) were added followed by stirring for 28 h. The reaction was monitored by TLC (10% H₂O/MeCN) and by ESI-MS analysis. Upon completion of the reaction, saturated aq. NaHCO₃ (0.20 ml) and water (0.3 ml) were added and the mixture was extracted with DCM, after which the water phase was concentrated to near dryness and some MeCN was added. The volatiles were removed and the product was purified by silica gel column chromatography (2.5% H₂O/MeCN) yielding 37.4 mg (90%) of 9. ¹H NMR (400 MHz, CDCl₃): 8.87 s, 1 H (H-5); 8.26 s, 1 H (H-2); 7.48 s, 1 H (H-8); 7.36–7.29 m, 2 H (H-4'''); 7.29–7.19 m, 3 H (H-2'', H-3'''); 6.12 d, 1 H, *J* = 4.1 (H-1'); 5.24 dd, 1 H, *J* = 6.0, 4.1 (H-2'); 5.17 dd, 1 H, *J* = 6.0, 1.5 (H-3'); 4.58–4.55 m, 1 H, *J* = 2.1 (H-4'); 4.05 dd, 1 H, *J* = -12.3, 2.2 (H-5'_{pros}); 3.91 dd, 1 H, *J* = -12.3, 2.5 (H-5'_{proR}); 3.90 d, 1 H, *J* = 14.3 (H-1''); 3.86 d, 1 H, *J* = 14.3 (H-1''); 3.63 d, 1 H, *J* = 13.3 (H-1'''); 3.58 d, 1 H, *J* = 13.3 (H-1'''); 2.54–2.42 m, 2 H (H-3''); 2.16–2.06 m, 2 H (H-5''); 1.87–1.75 m, 2 H (H-4''); 1.68 s, 3 H (H-7'_{endo}); 1.41 s, 3 H (H-7'_{exo}); 1.36 s, 9 H (H-9''). ¹³C NMR (101 MHz, CDCl₃): 172.61 (C-6'), 141.95 (C-9a), 140.36 (C-2), 138.25 (C-2''), 137.78 (C-3a), 135.71 (C-5), 133.66 (C-8), 129.23 (C-3'''), 128.60 (C-4'''), 127.49 (C-5'''), 124.76 (C-9b), 121.18 (C-7), 114.21 (C-6'), 93.27 (C-1'), 86.48 (C-4'), 84.27 (C-2'), 81.79 (C-3'), 80.42 (C-8''), 63.09 (C-5'), 58.43 (C-1'''), 53.01 (C-3''), 48.06 (C-1''), 33.17 (C-5''), 28.10 (C-9'), 27.60 (C-7'_{endo}), 25.40 (C-7'_{exo}), 22.13 (C-4''). HRMS: calculated for [M + H⁺] C₃₁H₄₁N₆O₆⁺ 593.3082 amu; found 593.3071 amu.

3-(β-D-Ribofuranosyl)-7-[[*N*-(4-*tert*-butoxy-4-oxobutyl)-*N*-benzyl]aminomethyl]-3*H*-imidazo[2,1-*i*]purine (10)

Compound 9 (26.5 mg, 44.7 μmol) was deprotected as described for 4b and the product was purified by silica gel column chromatography (10% MeOH/CH₂Cl₂) yielding 12.6 mg (51%) of 10. ¹H NMR (500 MHz, 2:5 CD₃OD/CDCl₃): 8.87 s, 1 H (H-5); 8.33 s, 1 H (H-2); 7.44 s, 1 H (H-8); 7.36–7.30 m, 2 H (H-4'''); 7.30–7.26 m, 2 H (H-3'''); 7.26–7.21 m, 1 H (H-5'''); 6.10 d, 1 H, *J* = 6.1 (H-1'); 4.73 dd, 1 H, *J* = 6.1, 5.1 (H-2'); 4.44 dd, 1 H, *J* = 5.1, 2.9 (H-3'); 4.29 ddd, 1 H, *J* = 2.9, 2.4 (H-4'); 3.99 dd, 1 H, *J* = -12.6, 2.4 (H-5'_{pros}); 3.92 s, 2 H (H-1''); 3.84 dd, 1 H, *J* = -12.6, 2.4 (H-5'_{proR}); 3.63 s, 2 H (H-1'''); 2.57–2.46 m, 2 H (H-3''); 2.15 t, 2 H, *J* = 7.3 (H-5''); 1.83 p, 2 H, *J* = 7.3 (H-4''); 1.36 s, 9 H (C-9''). ¹³C NMR (126 MHz, 2:5 CD₃OD/CDCl₃): 173.41 (C-6''), 141.91 (C-9a), 140.90 (C-2), 138.48 (C-2''), 138.43 (C-3a), 135.90 (C-5), 132.93 (C-8), 129.40 (C-3'''), 128.77 (C-4'''), 127.70 (C-5'''), 124.12 (C-9b),

121.84 (C-7), 90.45 (C-1'), 86.76 (C-4'), 81.01 (C-8''), 75.05 (C-2'), 71.33 (C-3'), 62.51 (C-5'), 58.64 (C-1''), 53.22 (C-3''), 48.09 (C-1''), 33.35 (C-5''), 28.04 (C-9''), 22.34 (C-4''). ^{15}N NMR (50 MHz, $\text{DMSO}-d_6$): -206.79 (N-3), -179.50 (N-6), -152.49 (N-4), -150.64 (N-9), -137.58 (N-1), N-1'' not observed. HRMS: calculated for $[\text{M} + \text{H}^+]$ $\text{C}_{28}\text{H}_{37}\text{N}_6\text{O}_6^+$ 553.2769 amu; found 553.2762 amu.

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