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

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Dedicated to Prof. 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; purine bases; NMR

Purine nucleosides and their congeners have found applications in medicinal research as antivirals[1,2], antiprotozoal agents[3], adenosine receptor agonists[4–6], adenosine kinase inhibitors[7,8] and in the treatment of lymphoid malignancies[9–12] and systemic mastocytosis[13], 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 N^6 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 bromomalonaldehyde (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

RESULTS AND DISCUSSION

Formylethenoadenosine (3-*β*-D-ribofuranosyl-3*H*-imidazo[2,1-*i*]purine-7-carbaldehyde)[16] and its 2'-deoxy analog[17] have been previously synthesized by the reaction of bromomalonaldehyde 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 yields[15] by applying the anhydrous conditions previously[14] 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 previously[14] 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 (ΔG = 12 kJ mol^{-1}) over the conformer with *cis* orientation (conformer B), see Fig. 1.

Figure 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 $NaBH(OAc)_3$ 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 products[19]. 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], $PdCl_2(CH_3CN)_2$[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 reflux[20] 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 $FeCl_3 \cdot 6H_2O$ in a 1:19 mixture of MeOH and DCM at elevated temperature[26]. 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, 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 elsewhere[27]. 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). ^{1}H and ^{13}C chemical shifts were referenced internally to the solvent peaks[28] (DMSO: δ_H = 2.50, δ_C = 39.52 ppm; MeOH: δ_H = 3.31, δ_C = 49.00 ppm; and HOD, δ_H = 4.79 ppm) or to TMS in the case of $CDCl_3$ solutions (δ = 0 ppm for both ^{1}H and ^{13}C). ^{15}N chemical shifts were referenced externally to 90% nitromethane in CD_3NO_2 (δ = 0 ppm). Assignment of the H-5's[29] (*proR* and *proS*) and isopropylidene methyl ^{1}H and ^{13}C nuclei[30] (*endo* and *exo*) were derived from literature. Direct observations of the ^{15}N nuclei were facilitated by the QDEPT pulse sequence adapted[31] from methodology[32,33] developed for one-bond ^{1}H–^{13}C interactions. The method of cycling the ^{1}H-selection pulse and the *J*-dependent interpulse delays, scaled accordingly to span the range 24.1–4.7 Hz, was taken from Jiang[33]. In the case of dilute samples, indirect ^{15}N observations were taken from HMBC spectra (appropriately only reported to one decimal place). ^{15}N chemical shifts were in accordance with previous examinations[27a,b,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* program[35] 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.

^{1}H NMR (500 MHz, d_6-DMSO): 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, d_6-DMSO): 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, d_6-DMSO): −204.00 (N-3), −184.15 (N-6), −145.62 (N-4), −142.61 (N-9), −137.16 (N-1). HRMS: calcd. 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 μL, 0.306 mmol) and acetic acid (31.8 μL, 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. ^{1}H 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: calcd. for [M + H^+] $C_{21}H_{29}N_6O_4^+$ 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), $FeCl_3 \cdot 6\ H_2O$ (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 $FeCl_3 \cdot 6\ H_2O$ 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 $NaHCO_3$ (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% H_2O in MeCN by suction-filtration and then further purified by HPLC (0–50% MeOH/H_2O, 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. ^{1}H NMR (500 MHz, d_6-DMSO): 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''). ^{13}C NMR (126 MHz, d_6-DMSO): 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''). ^{15}N NMR (50 MHz, d_6-DMSO):

−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: calcd. for [M + H^+] $C_{18}H_{25}N_6O_4^+$ 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 $NaHCO_3$ prior to evaporation. The crude material was purified by silica gel column chromatography (10% MeOH/CH_2Cl_2) yielding 0.116 g (97%) of **4a**. ^{1}H NMR (600 MHz, $CDCl_3$): 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'$_{exo}$). ^{13}C NMR (151 MHz, $CDCl_3$): 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'$_{exo}$). ^{15}N NMR (50 MHz, d_6-DMSO): −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: calcd. for [M + H^+] $C_{20}H_{27}N_6O_5^+$ 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 stirred on an oil bath at 50 °C for 4½ h and monitored by TLC (20% H_2O in MeCN). Upon completion, the solution was cooled to room temperature, the pH adjusted to 8 with saturated $NaHCO_3$ followed by evaporation to dryness. The crude material was purified by silica gel column chromatography (10–12.5% H_2O in MeCN) yielding 17 mg (80%) of **4b**. ^{1}H NMR (400 MHz, D_2O): 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''). ^{13}C NMR (101 MHz, D_2O): 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''). ^{15}N NMR (50 MHz, d_6-DMSO): −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: calcd. for [M + H^+] $C_{17}H_{23}N_6O_5^+$ 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), $NaCNBH_3$ (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 $NaHCO_3$. The organic phase was dried over Na_2SO_4 and again evaporated to dryness after filtration. The crude material was purified by silica gel column chromatography (10% MeOH/CH_2Cl_2) yielding 0.11 g (81%) of **5**. ^{1}H NMR (500 MHz, $CDCl_3$): 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'$_{exo}$). ^{13}C NMR (101 MHz, $CDCl_3$): 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: calcd. for [M + H$^+$] $C_{23}H_{27}N_6O_4^+$ 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 μmol), 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 $NaHCO_3$. The organic phase was dried over Na_2SO_4 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 μmol). When deacetylation of the hydroxyl groups was complete, the mixture was diluted with DCM and extracted with 3% aq. KH_2PO_4. The organic phase was dried over Na_2SO_4 and the solvent removed after filtration. The product was purified by silica gel column chromatography (5% MeOH DCM) yielding 16.5 mg (74%) of **6**. The isopropylidene protection was removed as described for **4b** and the deprotected material purified by silica gel column chromatography (10% H_2O/MeCN) yielding 11 mg (53% from **5**) of **6**. Conformers A and B denoted by demarkations A and B, respectively. ^{1}H NMR (500 MHz, CD_3OD): 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). ^{13}C NMR (126 MHz, CD_3OD): 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: calcd. for [M + H$^+$] $C_{22}H_{25}N_6O_5^+$ 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% H_2O/MeCN) yielding 0.224 g (53%) of **7**. ^{1}H NMR (500 MHz, CD_3OD): 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, H 1, *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"). ^{13}C NMR (126 MHz, CD_3OD): 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: calcd. for [M + H^+] $C_{24}H_{35}N_6O_6^+$ 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 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% H_2O/MeCN) yielding 7.7 mg (43% from **7**) of **8**. ^{1}H NMR (500 MHz, CD_3OD): 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''). ^{13}C NMR (126 MHz, CD_3OD): 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''). ^{15}N NMR (50 MHz, d_6-DMSO): −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: calcd. for [M + H^+] $C_{17}H_{21}N_6O_5^+$ 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 $ZnCl_2$ (9.5 mg, 70.0 μmol) and $NaCNBH_3$

(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% H_2O/MeCN) and by ESI-MS analysis. Upon completion of the reaction, saturated aq. $NaHCO_3$ (0.20 mL) and water (0.3 mL) were added and the mixture extracted with DCM, after which the water phase was concentrated to near dryness and some MeCN added. The volatiles were removed and the product purified by silica gel column chromatography (2.5% H_2O/MeCN) yielding 37.4 mg (90%) of **9**. ^{1}H NMR (400 MHz, $CDCl_3$): 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''). ^{13}C NMR (101 MHz, $CDCl_3$): 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: calcd. for [M + H^+] $C_{31}H_{41}N_6O_6^+$ 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 purified by silica gel column chromatography (10% MeOH/CH_2Cl_2) yielding 12.6 mg (51%) of **10**. ^{1}H NMR (500 MHz, 2:5 $CD_3OD/CDCl_3$): 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'$_{proS}$); 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''). ^{13}C NMR (126 MHz, 2/5 $CD_3OD/CDCl_3$): 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, d_6-DMSO): −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: calcd. for [M + H^+] $C_{28}H_{37}N_6O_6^+$ 553.2769 amu; found 553.2762 amu.

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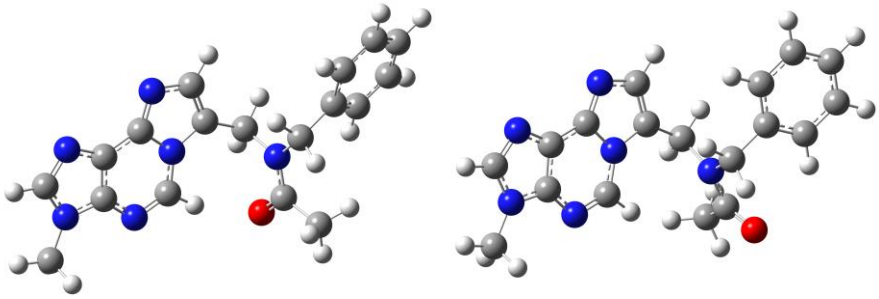
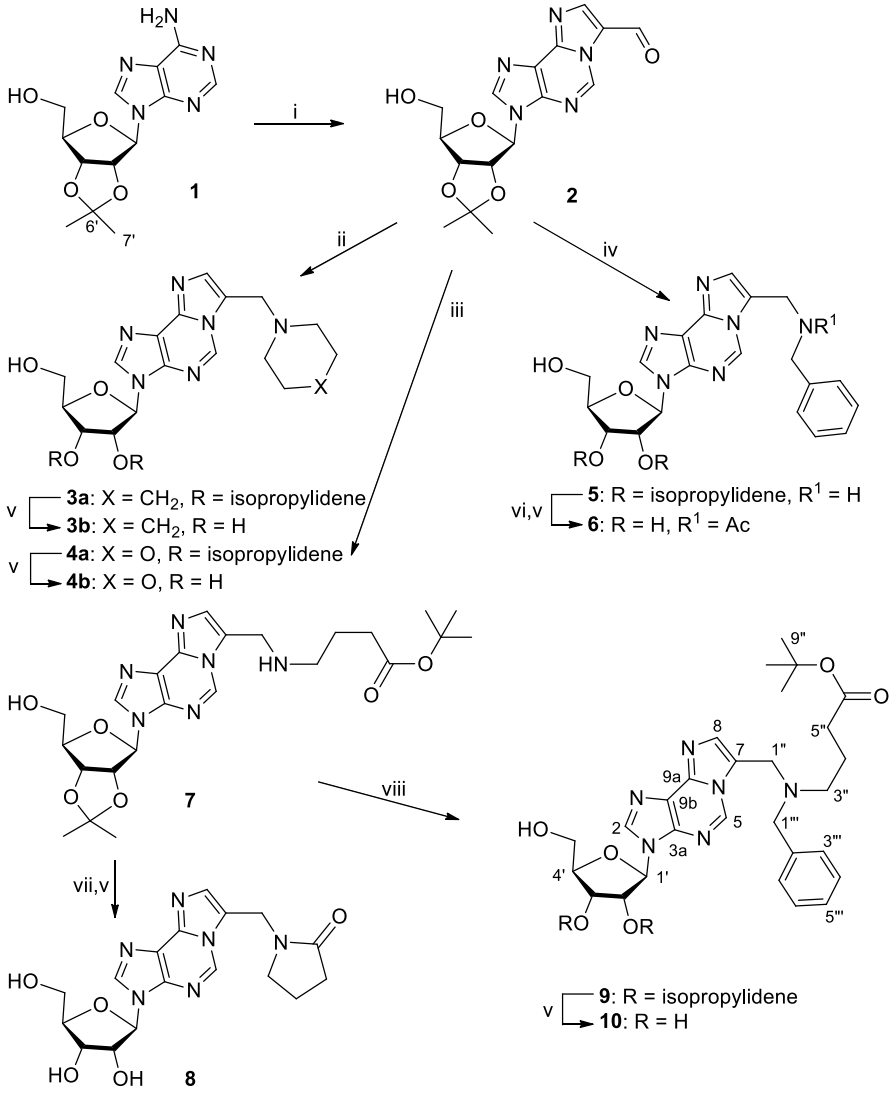


Fig. 1.

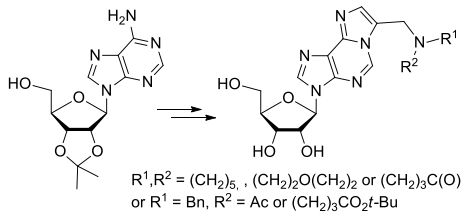
The *trans* (conformer A, left) and *cis* (conformer B, right) structures of compound **6** calculated at the B3LYP/6-31G(d,p) level of theory. N.b. the ribose moiety was substituted by methyl to expedite the modeling calculations.



Scheme 1

Conditions: i) $BrCH(CHO)_2$, HCO_2H, 2,6-lutidine, DMF, ii) piperidine (for **3a**), morpholine (for **4a**), $NaBH(OAc)_3$, AcOH, DCE, iii) $Cl^-\ {}^+H_3N(CH_2)_3COOtBu$, $NaBH(OAc)_3$, DCE, iv) $BnNH_2$, $NaCNBH_3$, AcOH, THF, v) $FeCl_3{\cdot}6\ H_2O$, MeOH, DCM (for **3b**), 0.1 M HCl (aq.)/THF (for **4b**, **6**, **8** and **10**), vi) 1. Ac_2O, Pyridine 2. NaOMe, MeOH, vii) 1. 50% TFA/ DCM, 2. HBTU, DIEA, DMF, viii) PhCHO, $ZnCl_2$, $NaCNBH_3$, MeOH.

Graphic Abstract



R^1,R^2 = $(CH_2)_5$, , $(CH_2)_2O(CH_2)_2$ or $(CH_2)_3C(O)$
or R^1 = Bn, R^2 = Ac or $(CH_2)_3CO_2t$-Bu