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Acid-catalysed rearrangement of acyl groups: synthesis of β -D-glucosaminocyclopentitols and carbanucleoside derivatives

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N-Benzyl-1,2,3-tri-*O*-benzyl- β -D-glucosaminocyclopentitol (**8**) displays anticancer activity, whereas β -D-glucosaminocyclopentitol (**9**) and its *N*-benzyl analogue (**10**) are potent glycosidase inhibitors. Acid-catalysed 1,2-acetonide deprotection of a D-glucose derived precursor featuring a vinyl functionality at C-4 and *O*-acyl group at C-3 produced latent aldehydes with the ester group moving between the C-2 and C-4 hydroxyl groups. Subsequent stereoselective intramolecular nitrone cycloaddition (INC) reactions yielded various desired cyclopentano-isoxazolidines, which, upon heterocyclic ring or N–O bond cleavage as the key step formed **9** and partially *O*-acetylated/benzoylated derivatives of **9** and **10**, respectively. During the process, formal syntheses of **8** and **10** were also completed. Compound **9** and its dideoxy derivative **32**, obtained through the Barton–McCombie deoxygenation reaction of the appropriate isoxazolidine, were elaborated to carbanucleoside derivatives having 6-chloropurine, hypoxanthine, and adenine as nucleoside bases.

Introduction

Various natural and synthetic aminocyclopentitols display a wide array of biological activities.¹ The most important members of this family are natural allosamidin (**1**),² mannostatins (**2–3**),³ and trehazolin (**4**)⁴ (Fig. 1), which are well-known glycosidase inhibitors, while pactamycin⁵ has antibacterial, antitumor, antiviral, and antiprotozoal activities. The carbanucleoside analogues of aminocyclopentitols show potent anticancer and antiviral efficacy,⁶ and have enhanced metabolic

stability against hydrolase and phosphorylase enzymes due to the absence of the furanose moiety.⁷ Natural aristeromycin (**5**)⁸ is an antibiotic and potent *S*-adenosylhomocysteine hydrolase inhibitor, while neoplanocin A (**6**)⁹ has both antitumor and antiviral activities. Among the synthetic analogues of aminocyclopentitols, 4-hydroxy cispentacin (**7**)¹⁰ exhibits antifungal activity. Entecavir¹¹ and peramivir^{11a-c,12} are used as antiviral drugs, while MLN4924,¹³ RX-3117,^{13a,b,14} and *N*-benzyl-1,2,3-tri-*O*-benzyl- β -D-glucosaminocyclopentitol (**8**)¹⁵ display anticancer activity. Both β -D-glucosaminocyclopentitol (**9**)¹⁶ and *N*-benzyl- β -D-glucosaminocyclopentitol (**10**)^{15,16a} are potent glycosidase inhibitors.

Moreover, isoxazolidine,¹⁷ a privileged scaffold of various natural products and biomolecules, has various biological properties, including antiviral,¹⁸ antifungal,¹⁹ and anti-inflammatory activities,²⁰ as well as cytotoxicity.²¹ Natural pyrinodemins A–D (**11–14**) (Fig. 2), which show attractive cytotoxicity,^{21a,b} have inspired chemists to synthesise cyclopentane-fused isoxazolidine derivatives.

Additionally, many of the natural and synthetic bioactive molecules are found in a partially *O*-acylated form, and it is

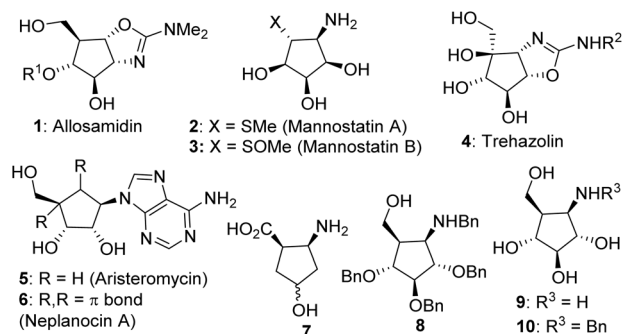


Fig. 1 Bioactive natural (**1–6**) and synthetic (**7–10**) aminocyclopentitols.

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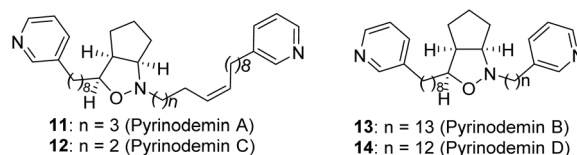


Fig. 2 Bioactive natural cyclopentane-fused isoxazolidine derivatives (**11–14**).



believed that the partial acyl group has a crucial role in their bioactivities.²² Naturally occurring partially *O*-acetylated variants of *N*-acetylneuraminic acid (Neu5Ac),^{22a,b} anisomycin,^{22c} and taxol^{22d,e} are important examples. Thus, efforts have been made to obtain such products through site-selective^{22b,23} or enzymatic²⁴ esterification reactions.

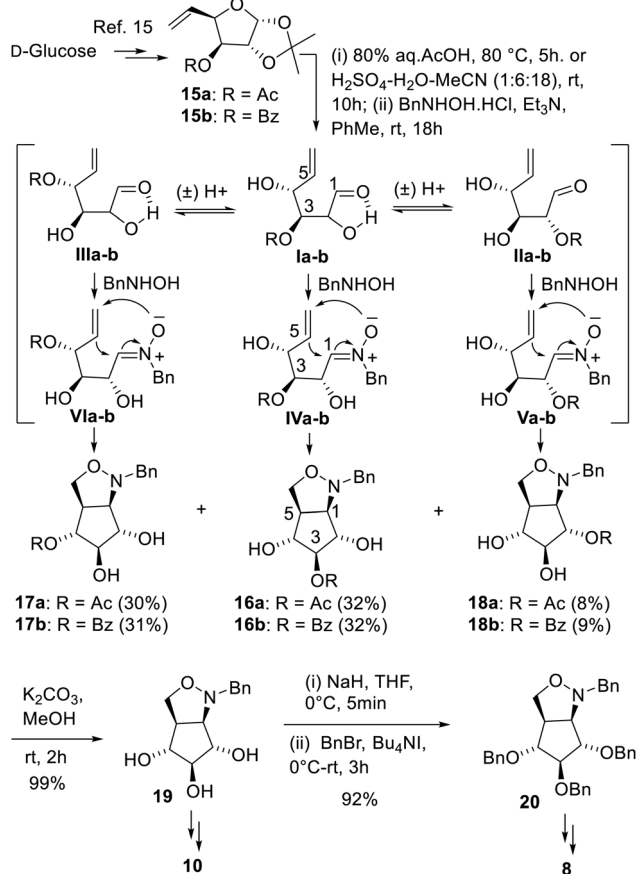
Based on this observation, and as a part of our previous discovery of **8**,¹⁵ it was proposed that the advances of partially *O*-acylated derivatives of **9–10**, their fused isoxazolidines, and various carbanucleoside analogues of **9** would be a desirable strategy to meet the demand for chiral intermediates for the synthesis of biologically active molecules like **8–10** and other analogues. Towards this goal, we envisioned the production of partially *O*-acylated 5,6-dideoxy-5-eno-*D*-xylo-hexose intermediates (**Ia–b** to **IIIa–b**) (Scheme 1) using a *D*-glucose-derived substrate (**15a,b**) through acid-catalysed 1,2-acetonide deprotection and subsequent ester group rearrangement²⁵ reaction between the available hydroxyl groups. The latent aldehydes could be exploited to prepare partially-*O*-acylated analogues of **9–10** through fused isoxazolidine derivatives using a stereo-controlled INC reaction^{15,26,27} followed by isoxazolidine ring/N–O bond cleavage. Aminocyclopentitol (**9**) and its dideoxy analogue (**32**) could be generated through judicious functional group manipulation of the appropriate isoxazolidine derivatives

and potentially be used to generate various carbanucleoside analogues *via* the purine ring construction strategy.²⁶ Herein, along with the preparation of **9**, we also report formal syntheses of **8** and **10**.¹⁵

Results and discussion

Synthesis of partially *O*-acylated cyclopentano-isoxazolidine derivatives (**16a,b–18a,b**) and formal syntheses of **8** and **10**

To realise our objectives, we started our exploration by synthesising partially *O*-acylated cyclopentane-fused isoxazolidine derivatives *via* the intramolecular nitron cycloaddition reaction (INC) on *D*-glucose derived substrates. Toward this end, individual acetonide deprotection of **15a,b**,¹⁵ using 80% aqueous AcOH at 80 °C, followed by reaction with *N*-benzyl hydroxylamine hydrochloride and triethylamine in toluene, produced a mixture of three isomeric products (**16a–18a** and **16b–18b**, respectively; Scheme 1) in each case (8–32%). The products remained the same even when the acetonide group was removed using 4% H₂SO₄ in aqueous MeCN (72%) at room temperature. All six products contain the same nucleus, as each of them produced **19** (99%) upon deacylation with K₂CO₃ in MeOH,¹⁵ which, upon the benzylation reaction with benzyl bromide and NaH in THF, smoothly produced **20** (92%).¹⁵ The conversion of **19** and **20** to the bioactive molecules **10** and **8**, respectively, has been reported previously, thereby completing the formal syntheses of **8** and **10**.¹⁵ Regarding the possible mechanism of the movement of the acyl group after acid treatment, the ester group of the hydroxy aldehyde intermediates (**Ia,b**) rearrange reversibly between **Ia,b** and **IIIa,b**, and an equilibrium is reached between the intermediates. DFT calculations of the representative intermediates **Ib–IIIb** (SI, Fig. S1–S3) revealed that **Iib** is less stable in energy than **Ib** and **IIIb** by 5.20 kJ mol^{−1} and 15.53 kJ mol^{−1}, respectively. These results indicated that **Ia,b** and **IIIa,b** form a stable 5-membered ring through a hydrogen bond with a C-1 aldehyde group, which makes the C-2 hydroxyl group electronically different and less available for participation in the rearrangement reaction compared to the C-3 and C-4 hydroxyl groups. Thus, the concentration of **Ia,b** becomes lower than those of the other aldehydes in the mixture, which was reflected in the yield of the final products **18a,b**. The success of the INC reactions was evident from the absence of olefinic proton signals and the occurrence of five aromatic proton signals in **16a–18a** and ten aromatic proton signals in **16b–18b** in the ¹H NMR spectra. As expected, the similar ester-bearing carbon of the compounds shows an almost identical chemical shift. For example, among the pairs, the carbon signals of C-3 of **16a,b**, C-4 of **17a,b**, and C-2 of **18a,b** appeared at δ (86.16–86.36), (82.69–82.80), and (82.21–83.26), respectively, in the ¹³C NMR spectra. Further structural confirmation of **17a,b** and **18a,b** was obtained from a single crystal X-ray crystallographic study of representative molecules **17a** (Fig. 3) and **18b** (Fig. 4), which also indicates the position of the acetyl and benzoyl groups at C-3 for **16a,b**. Finally, the ¹H and ¹³C NMR data of **19** and **20** were in agreement with those reported in the literature.¹⁵



Scheme 1 Synthesis of partially *O*-acetylated (**16a–18a**), *O*-benzoylated (**16b–18b**) cyclopentano-isoxazolidine derivatives, and formal syntheses of **8** and **10**.

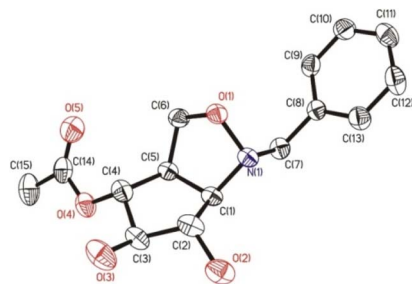


Fig. 3 X-ray crystal structure of 17a.

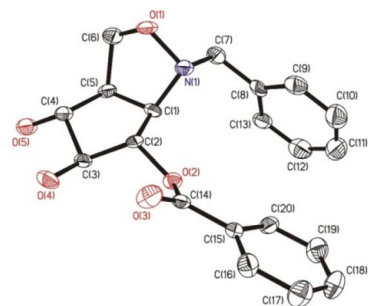


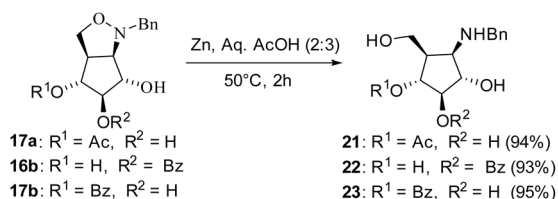
Fig. 4 X-ray crystal structure of 18b.

Synthesis of partially *O*-acylated *N*-benzyl- β -D-glucosaminocyclopentitols (21–23)

Accordingly, to demonstrate the feasibility of converting the isoxazolidine-fused cyclopentane derivatives to the corresponding partially *O*-acylated analogues of *N*-benzyl- β -D-glucosaminocyclopentitol (10), we chose 17a, 16b and 17b; selective N–O bond cleavage¹⁵ of these compounds with Zn in aqueous AcOH (2 : 3, v/v) produced partially *O*-acetylated (21) (94%) and *O*-benzoylated (22–23) (93–95%) aminocyclopentitol derivatives, respectively (Scheme 2). In the ¹H NMR spectra, the signals of the cyclopentyl protons attached to the hydroxymethyl group of the products were observed between δ 2.25–2.48 (m), while in the ¹³C NMR spectra, the signals appeared at δ 43.77–45.49; these values are quite similar to those in the literature.¹⁵

Synthesis of partially *O*-acylated β -D-glucosaminocyclopentitols

Here, we concentrated on the synthesis of partially *O*-acylated derivatives of β -D-glucosaminocyclopentitol (9). Cleavage of the isoxazolidine rings of 16a–17a and 16b–18b through hydrogenation reactions over Pd/C (Scheme 3) afforded the desired *O*-

Scheme 2 Synthesis of partially *O*-acetylated (21) and *O*-benzoylated (22–23) derivatives of *N*-benzyl- β -D-glucosaminocyclopentitol.

acetylated (24–25) (90–92%) and *O*-benzoylated (26–28) (87–93%) aminocyclopentitol derivatives, respectively.

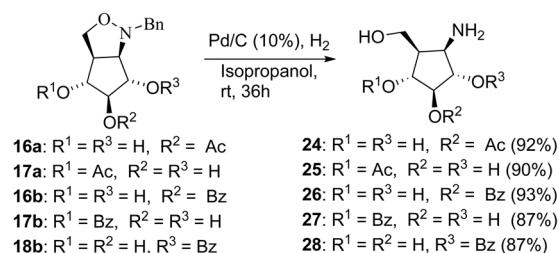
The disappearance of the benzylic proton signals in the ¹H NMR spectra of the products confirmed the success of the reaction.

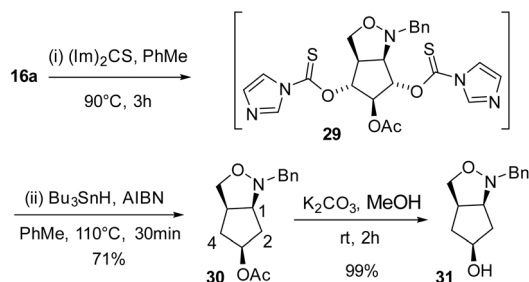
Barton–McCombie deoxygenation reaction and synthesis of a mono-hydroxy cyclopentano-isoxazolidine derivative (31)

Taking advantage of the position of the hydroxyl groups on 16a, we focused on cyclopentane ring modification to obtain the 3-acetoxycyclopenteno-isoxazolidine derivative. Thus, for the C-2 and C-4 deoxygenation reaction, 16a was treated with 1,1'-(thiocarbonyl) diimidazole and *in situ* generated imidazo-thiocarbonyl diester (29), and upon reduction under the Barton–McCombie conditions^{15,28} produced orthogonally protected 5-acetoxy cyclopentano-isoxazolidine 30 (71%) (Scheme 4), which upon deacetylation smoothly furnished 31 with 99% yield. The two methylene (–CH₂–) units of 30 were deduced from the usual ¹H NMR spectral evidence. The signals of the C-2 protons of 30 were observed at δ 2.08–2.13 (m, 1H) 2.19–2.25 (m, 1H), along with the C-4 proton signals at δ 1.67–1.78 (m, 2H), while the ¹³C NMR spectra contained signals at δ 45.55 and δ 36.87 corresponding to the C-2 and C-4 carbons, respectively.

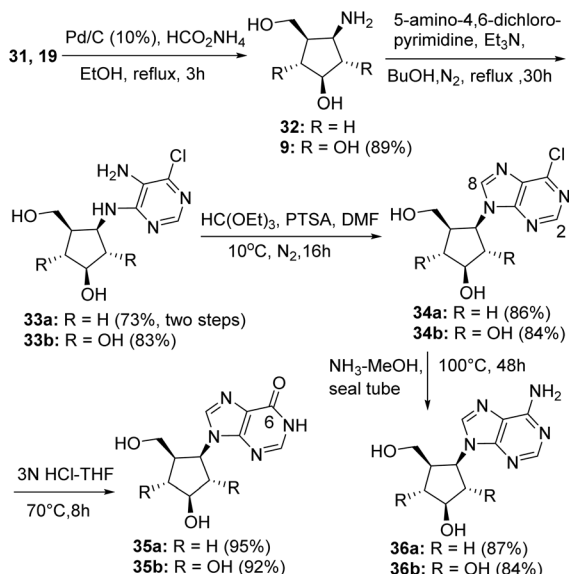
Synthesis of 9, its dideoxy derivative (32), and their conversion to carbanucleoside analogues (34a–36a and 34b–36b)

Finally, we focused on the conversion of aminocyclopentitols to the corresponding purine carbanucleoside analogues as presented in Scheme 5. Towards this, 31 and 19 were converted to aminocyclopentitols 32 and 9 (89%), respectively, by treatment with HCO₂NH₄ and Pd–C in MeOH. 32 was used for the next step without purification. The coupling reaction of 32 and 9 with 5-amino-4,6-dichloropyrimidine in *n*-butanol and Et₃N under reflux conditions produced the corresponding pyrimidine carbocycles 33a,b, respectively, with good yields. The pyrimidine rings of 33a,b were transformed into purine rings by treatment with triethyl orthoformate in a catalytic acidic medium to achieve the chloropurine carbanucleosides 34a,b (86–84%), which upon heating with 3 N HCl in THF produced the hypoxanthine carbanucleoside derivatives 35a,b (95–92%). Alternatively, ammonolysis of 34a,b in a sealed tube using a saturated solution of ammonia in methanol furnished the adenine carbanucleoside derivatives 36a,b in 87–84% yield. Regarding the structure of the products, the signals of the C-2

Scheme 3 Synthesis of partially *O*-acetylated (24–25) and *O*-benzoylated (26–28) analogues of β -D-glucosaminocyclopentitol.



Scheme 4 Barton–McCombie deoxygenation reaction for the synthesis of **30–31**.



Scheme 5 Conversion of **19** and **31** to its 6-chloropurine (**34a–b**), hypo-xanthine (**35a–b**) and adenine (**36a–b**) carbanucleoside analogues.

and C-8 aromatic protons of the purine ring in **34a,b** were observed at δ (8.85–8.76) and δ (8.77–8.72), respectively, while the NH proton signal of **35b** appeared at δ 12.24, and the NH₂ proton signal of **36a,b** appeared at δ 7.22–7.14 in the ¹H NMR spectra. In the ¹³C NMR spectra, the carbon signals of C-6 of **35a,b** appeared at δ 157.68–157.17.

Conclusion

In conclusion, the aldehydes generated after acid-catalysed acetone deprotection of D-glucose derived 3-O-acetyl-5,6-di-deoxy-1,2-O-isopropylidene- α -D-xyllo-hexo-5-enofuranose, were utilised to prepare various cyclopentano-isoxazolidines *via* the INC reaction. Appropriate deprotection and isoxazolidine ring cleavage produced aminocyclopentitol **9** and the analogues of **9** and **10**. The compound **9** and its dideoxy analogue **32** obtained through the Barton McCombie deoxygenation reaction were converted into six corresponding novel carbanucleosides. During the process, formal syntheses of **8** and **10** were achieved. Considering the advantages of the strategy and related

approaches, attempts could be initiated to conveniently synthesise various functionalised carbocyclic *cis*- β -amino acids, including the natural antifungal antibiotic cispentacin, 4-hydroxy cispentacin, icofungipen, and related analogues.²⁹ A few of these works are ongoing in our laboratory.

Experimental

General methods

For TLC analysis, pre-coated plates (0.25 mm, Silica Gel 60 F254) were used and visualised by UV light (254 nm). Melting points were determined in open capillaries and are uncorrected. Specific rotations were measured with an Anton Paar Modular Circular Polarimeter (MCP) 200 and Rudolph Autopol-I using a sodium lamp source (589 nm) and are reported as: $[\alpha]_D^{25}$ (c = g/100 mL, solvent). ¹H and ¹³C NMR spectra were recorded using 400 MHz and 500 MHz NMR spectrometers. For reference, residual solvent signals or internal standards were used. NMR spectra are reported as chemical shift (δ) in parts per million (ppm), and to indicate their multiplicities, the following abbreviations have been used: s = singlet, br-s = broad singlet, d = doublet, dd = doublet of doublets, t = triplet, dt = doublet of triplets, tt = triplet of triplets and m = multiplet. Coupling constants (*J*) are reported in Hz. ESI-HRMS mass spectra analysis was recorded using the LCQORBITRAP-XL instrument. X-ray diffraction data of compounds **17a** and **18b** were collected using a Bruker SMART APEX2 area detector. Details of single crystal preparation are given in the characterisation data section of each compound. CCDC 2440708 and 2440709 contain the crystallographic data (CIF files) of the compounds and can be obtained at <https://summary.ccdc.cam.ac.uk/structure-summary>.

Density functional theory (DFT) calculations of **Ib–IIIb**

All DFT calculations were performed with the ORCA program package. All calculations were performed using the hybrid PBE0 DFT method. The gas-phase geometries of **Ib–IIIb** were optimised with the singlet spin state. For all calculations, the all-electron valence double-zeta, def2-SVP basis set with the new polarisation function developed by the Karlsruhe group was used for the O, C, and H atoms. The resolution of identity RUCOSX approximation with the def2/J auxiliary basis set for Coulomb and HF exchange integral for HF and hybrid DFT methods were employed for self-consistent field (SCF) gradient calculations. The geometry optimisations were carried out in redundant internal coordinates without imposing symmetry constraints. The SCF calculations were converged tightly (1×10^{-8} E_h in energy, 1×10^{-7} E_h in the density change and 1×10^{-7} in the maximum element of the DIIS error vector).

General procedure (G.P-1) for synthesis of **16a–18a** and **16b–18b**

A solution of the appropriate compound (**15a,b**) (24 mmol) in 80% aqueous acetic acid (100 mL) was heated at 80 °C for 5 h. It was then concentrated under reduced pressure, and trace amounts of water and acid were removed by co-evaporation



using toluene (3 × 30 mL). The gummy semi-solid aldehyde intermediate was dried over P₂O₅ and subjected to the next step without further purification. To the solution of the aldehyde intermediate in dry toluene (60 mL) was added triethylamine (60 mmol, 2.5 eq.), and the solution was stirred for 5 minutes at room temperature. *N*-Benzylhydroxylamine hydrochloride (48 mmol, 2.0 eq.) was added in portions and stirred at room temperature for 18 h. The mixture was filtered to remove salt, and the residue was washed with toluene (30 mL). The combined filtrate was concentrated under reduced pressure and the crude mass was purified by silica gel (100–200 mesh) column chromatography using petroleum ether–ethyl acetate as an eluent to obtain **16a–18a** or **16b–18b** as applicable.

[For 1,2-acetonide deprotection of **15a,b**, we also used 4% H₂SO₄ in aqueous MeCN (72%) and carried out the reaction at room temperature for 12 h.^{26,27} The solution was neutralised by portion-wise addition of solid CaCO₃. The precipitate was filtered off and the filtrate was concentrated under vacuum to give a gummy semi-solid, which was dried (P₂O₅) under vacuum and subjected to the next step as stated above, but provided the same products in similar yields.]

General procedure (G.P-2) for the preparation of **19** and **31**

To a solution of suitable starting material (**16a–18a**, **16b–18b** and **30**) in methanol (5 mL for 200 mg compounds) was added K₂CO₃ (1.5 eq.), and the solution was stirred at room temperature for 2 h. The mixture was filtered and the filtrate was concentrated. The crude mass was purified using silica gel (100–200 mesh) column chromatography to obtain the desired products **19** and **31** as applicable.

General procedure (G.P-3) for the synthesis of **21–23** through selective N–O bond cleavage reaction

To a solution of the appropriate compound (**17a**, **16b–17b**) (6 mmol) in acetic acid–H₂O (3 : 2, v/v) (3 mL) was added zinc dust (60 mmol) and the mixture was heated at 50 °C for 2 h. It was cooled to room temperature, the excess zinc dust was filtered off, and the filtrate was concentrated. Trace amounts of acid were removed by co-evaporation with toluene (2 × 20 mL). The residue was dissolved using a methanol–ethyl acetate solution (1 : 4) (30 mL), and a pinch of solid NaHCO₃ was added to this solution, which was then stirred and filtered. The filtrate was concentrated and the crude mass was purified *via* silica gel (100–200 mesh) column chromatography to furnish the desired product **21–23** as applicable.

General procedure (G.P-4) for the synthesis of **24–28** through hydrogenation reaction using Pd–C

To a solution of the appropriate substrate (**16a–17a**, **16b–18b**) (0.38 mmol) in dry isopropanol (5 mL) was added 10% Pd/C (97 mg, 0.091 mmol). The mixture was stirred at room temperature for 48 h under a high-pressure hydrogen atmosphere. The catalyst was filtered off, and the filtrate was concentrated under reduced pressure to obtain the desired product **24–28** as applicable.

General procedure (G.P-5) for the synthesis of pyrimidine carbanucleosides **33a–b**

To a solution of the appropriate starting material (**32** or **9**) (1.23 mmol) in *n*-BuOH (25 mL) were added 5-amino-4,6-dichloropyrimidine (300 mg, 1.84 mmol) and Et₃N (5.0 mL, 35.87 mmol), and the mixture was heated at reflux for 30 hours under an N₂ atmosphere. For compound **33a**, the reaction mixture was concentrated and subjected to purification *via* silica gel (100–200 mesh) column chromatography to obtain the desired product. For **33b**, the reaction mixture was concentrated and the residue was dissolved in H₂O (10 mL). The aqueous solution was washed with CHCl₃ (2 × 15 mL) to remove free pyrimidine base and evaporated to give the crude mass, which was purified *via* silica gel (100–200 mesh) column chromatography to obtain the desired product **33a,b** as applicable.

General procedure (G.P-6) for the synthesis of chloropurine carbanucleosides **34a–b**

To a solution of the appropriate starting material (**33a,b**) (0.58 mmol) in anhydrous DMF (10 mL) were added HC(OEt)₃ (7.3 mL, 43.88 mmol) and PTSA (83 mg, 0.58 mmol), and the mixture was stirred at 10 °C for 16 hours under an N₂ atmosphere. The solvent was evaporated under vacuum, and the gummy residue was purified *via* silica–gel (100–200 mesh) flash column chromatography to furnish the desired product **34a,b** as applicable.

General procedure (G.P-7) for the synthesis of hypoxanthine carbanucleosides **35a,b**

A solution of the appropriate substrate (**34a,b**) (0.1 mmol) in aqueous HCl (3N)–THF (1 : 1) (3 mL) was heated at 70 °C for 8 hours. It was then cooled and neutralised with solid sodium bicarbonate, the solvent was evaporated under vacuum, and the crude product was purified by reverse phase (LiChroprep RP-18, particle size 25–40 µm) flash column chromatography using MeOH as an eluent to furnish the desired product **35a,b** as applicable.

General procedure (G.P-8) for the synthesis of adenine carbanucleosides **36a,b**

A solution of the appropriate starting material (**34a,b**) (0.24 mmol) in saturated ammonia in methanol (100 mL) was heated at 100 °C for 48 hours in a sealed tube. The solvent was evaporated to dryness, and the crude residue was purified to obtain the desired product **36a,b** as applicable.

(*3aR,4R,5S,6S,6aR*)-1-Benzyl-4,6-dihydroxyhexahydro-1*H*-cyclopenta[*c*]isoxazol-5-yl acetate (**16a**), (*3aR,4R,5R,6S,6aR*)-1-benzyl-5,6-dihydroxyhexahydro-1*H*-cyclopenta[*c*]isoxazol-4-ylacetate (**17a**), (*3aR,4R,5S,6S,6aR*)-1-benzyl-4,5-dihydroxyhexahydro-1*H*-cyclopenta[*c*]isoxazol-6-yl acetate (**18a**)

Compounds **16a–18a** were prepared from **15a** according to G.P-1. Elution with petroleum ether–ethyl acetate in (1 : 1), (2 : 3) and (3 : 7) ratios furnished **16a** (32%) as a white solid, **17a** (30%)



as a crystalline white solid and **18a** (8%) as a white solid respectively.

Compound **16a**. M.p. 137 °C; $[\alpha]_D^{25} = +8.342$ (c 0.251, MeOH); $^1\text{H-NMR}$ (400 MHz, CDCl_3): δ 2.13 (s, 3H), 2.93 (d, $J = 0.8$ Hz, 1H), 3.03–3.09 (m, 1H), 3.52 (dd, $J = 6.4, 9.2$ Hz, 1H), 3.64 (s, 1H), 3.75 (d, $J = 12.8$ Hz, 1H), 3.81 (dd, $J = 2.8, 9.2$ Hz, 1H), 3.93 (t, $J = 6.8$ Hz, 1H), 3.99–4.02 (m, 2H), 4.17 (t, $J = 8.4$ Hz, 1H), 4.65 (dd, $J = 7.6, 8.8$ Hz, 1H) 7.27–7.38 (m, 5H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ 21.1, 50.5, 59.9, 70.4, 72.4, 76.9, 78.4, 86.2, 127.9, 128.7 (2C), 129.2 (2C), 136.6, 173.7; HRMS (ESI, m/z) calcd for $\text{C}_{15}\text{H}_{20}\text{NO}_5$ $[\text{M} + \text{H}]^+$ 294.1341, found 294.1349.

Compound **17a**. M.p. 139 °C; $[\alpha]_D^{25} = +7.200$ (c 0.500, MeOH); $^1\text{H-NMR}$ (400 MHz, CDCl_3): δ 2.10 (s, 3H), 2.90–2.96 (m, 1H), 3.23 (br-s, 1H), 3.43–3.48 (m, 1H), 3.53 (br-s, 1H), 3.72 (d, $J = 12.4$ Hz, 1H), 3.81–3.85 (m, 1H), 3.89–3.93 (m, 1H), 3.99 (d, $J = 12.8$ Hz, 1H), 4.04 (dd, $J = 3.6, 9.6$ Hz, 1H), 4.19 (t, $J = 8.8$ Hz, 1H), 4.63 (dd, $J = 5.6, 8.0$ Hz, 1H), 7.28–7.37 (m, 5H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ 21.1, 48.9, 59.9, 70.8, 72.4, 77.0, 78.9, 82.7, 127.9, 128.7 (2C), 129.3 (2C), 136.4, 171.7; HRMS (ESI, m/z) calcd for $\text{C}_{15}\text{H}_{20}\text{NO}_5$ $[\text{M} + \text{H}]^+$ 294.1341, found 294.1331.

Compound **18a**. M.p. 139 °C; $[\alpha]_D^{25} = +22.314$ (c 0.210, MeOH); $^1\text{H-NMR}$ (400 MHz, CDCl_3): δ 1.74 (s, 2H), 1.99 (s, 3H), 2.99–3.05 (m, 1H), 3.50 (dd, $J = 5.2, 9.6$ Hz, 1H), 3.78–3.84 (m, 2H), 3.88–3.94 (m, 2H), 4.03 (d, $J = 13.2$ Hz, 1H), 4.13 (dd, $J = 6.8, 8.8$ Hz, 1H), 4.82 (dd, $J = 5.2, 8.0$ Hz, 1H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ 21.1, 50.8, 60.0, 69.9, 77.06 (merged with solvent peak), 79.9, 81.1, 82.2, 127.8, 128.5 (2C), 129.2 (2C), 136.4, 172.4; HRMS (ESI, m/z) calcd for $\text{C}_{15}\text{H}_{20}\text{NO}_5$ $[\text{M} + \text{H}]^+$ 294.1341, found 294.1349.

(*3aR,4R,5S,6S,6aR*)-1-Benzyl-4,6-dihydroxyhexahydro-1H-cyclopenta[c]isoxazol-5-yl benzoate (**16b**), (*3aR,4R,5R,6S,6aR*)-1-benzyl-5,6-dihydroxyhexahydro-1H-cyclopenta[c]isoxazol-4-yl benzoate (**17b**), (*3aR,4R,5S,6S,6aR*)-1-benzyl-4,5-dihydroxyhexahydro-1H-cyclopenta[c]isoxazol-6-yl benzoate (**18b**)

Compounds **16b–18b** were prepared from **15b** according to G.P-1. Elution with petroleum ether–ethyl acetate in (3 : 2), (2 : 3) and (3 : 7) ratios furnished **16b** (32%) and **17b** (31%) as white solids and **18b** (9%) as a crystalline white solid, respectively.

Compound **16b**. M.p. 95 °C; $[\alpha]_D^{25} = +36.595$ (c 0.470, MeOH); $^1\text{H-NMR}$ (400 MHz, CDCl_3): δ 2.85 (s, 1H), 3.12–3.17 (m, 1H), 3.59 (t, $J = 8.8$ Hz, 1H), 3.67 (s, 1H), 3.79 (d, $J = 13.2$ Hz, 1H), 3.85 (dd, $J = 2.4, 9.2$ Hz, 1H), 3.98 (d, $J = 13.6$ Hz, 1H), 4.02–4.13 (m, 1H), 4.19–4.22 (m, 2H), 4.89 (t, $J = 8.0$ Hz, 1H), 7.28 (d, $J = 6.8$ Hz, 1H), 7.32–7.39 (m, 4H), 7.44 (t, $J = 7.6$ Hz, 2H), 7.59 (t, $J = 7.2$ Hz, 1H), 8.03 (d, $J = 7.6$ Hz, 2H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ 50.6, 59.9, 70.7, 72.8, 78.3, 78.5, 86.4, 127.9, 128.7 (2C), 128.7 (2C), 129.1, 129.3 (2C), 130.1 (2C), 133.8, 136.2, 168.7; HRMS (ESI, m/z) calcd for $\text{C}_{20}\text{H}_{22}\text{NO}_5$ $[\text{M} + \text{H}]^+$ 356.1498, found 356.1500.

Compound **17b**. M.p. 184 °C; $[\alpha]_D^{25} = +9.074$ (c 0.540, MeOH); $^1\text{H-NMR}$ (400 MHz, DMSO-d_6): δ 2.95–3.02 (m, 1H), 3.40–3.42 (m, 1H), 3.53–3.58 (m, 1H), 3.74 (d, $J = 14.0$ Hz, 1H), 3.81–3.87 (m, 2H), 3.92 (dd, $J = 2.8, 9.2$ Hz, 1H), 4.09 (s, 1H), 4.66 (dd, $J = 6.0, 8.4$ Hz, 1H), 5.35 (d, $J = 6.0$ Hz, 1H), 5.45 (d, $J = 6.0$ Hz, 1H),

7.23–7.26 (m, 1H), 7.26–7.37 (m, 4H), 7.53–7.57 (m, 2H), 7.66–7.70 (m, 1H), 8.00–8.03 (m, 2H); $^{13}\text{C NMR}$ (100 MHz, DMSO-d_6): δ 47.6, 58.5, 69.6, 72.2, 76.5, 77.8, 82.8, 126.9, 128.0 (2C), 128.8 (2C), 128.9 (2C), 129.3 (2C), 129.6, 133.5, 137.8, 166.2; HRMS (ESI, m/z) calcd for $\text{C}_{20}\text{H}_{22}\text{NO}_5$ $[\text{M} + \text{H}]^+$ 356.1498, found 356.1494.

Compound **18b**. M.p. 62 °C; $[\alpha]_D^{25} = +0.220$ (c 0.455, MeOH); $^1\text{H-NMR}$ (400 MHz, CDCl_3): δ 2.68 (br-s, 2H), 3.06–3.12 (m, 1H), 3.70–3.74 (m, 1H), 3.87 (d, $J = 12.4$ Hz, 1H), 3.94 (t, $J = 8.0$ Hz, 1H), 3.98–4.04 (m, 2H), 4.11 (d, $J = 12.8$ Hz, 1H), 4.18 (t, $J = 7.6$ Hz, 1H), 5.01 (t, $J = 6.8$ Hz, 1H), 7.27–7.30 (m, 3H), 7.35–7.40 (m, 4H), 7.55–7.59 (m, 1H), 7.75 (dd, $J = 1.6, 9.2$ Hz, 2H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ 50.5, 60.0, 69.4, 70.5, 79.9, 81.0, 83.3, 127.8, 128.5 (2C), 128.7 (2C), 129.1, 129.5 (2C), 130.1 (2C), 133.7, 136.0, 167.9; HRMS (ESI, m/z) calcd for $\text{C}_{20}\text{H}_{21}\text{NNaO}_5$ $[\text{M} + \text{Na}]^+$ 378.1317, found 378.1338.

(*3aR,4R,5S,6S,6aR*)-1-Benzylhexahydro-1H-cyclopenta[c]isoxazole-4,5,6-triol (**19**)

Compound **19** was prepared from **16a–18a** and **16b–18b** according to G.P-2. Elution with MeOH–EtOAc (1 : 19) furnished the same product **19** (99% from each of the reactions) as a white solid. M.p. 70 °C; $[\alpha]_D^{25} = +50.638$ (c 0.280 MeOH); (ref. 15 $[\alpha]_D^{25} = +51.339$ (c 0.485, MeOH)); $^1\text{H-NMR}$ (400 MHz, DMSO-d_6): δ 2.71 (d, $J = 6.8$ Hz, 1H), 3.18 (s, 1H), 3.54–3.56 (m, 1H), 3.69 (d, $J = 14.0$ Hz, 1H), 3.81 (d, $J = 14.0$ Hz, 1H), 3.97 (s, 1H), 4.95 (d, $J = 4.0$ Hz, 1H), 5.02 (d, $J = 4.8$ Hz, 2H), 7.20–7.33 (m, 5H); both the $^1\text{H NMR}$ and melting point data were consistent with literature values.¹⁵

(*3aR,4R,5S,6S,6aR*)-1-Benzyl-4,5,6-tris(benzyloxy)hexahydro-1H-cyclopenta[c]isoxazole (**20**)

To a solution of **19** (950 mg, 3.78 mmol) in THF (20 mL) was added NaH (1.090 g, 45.42 mmol) in portions at 0 °C, and the mixture was stirred for 5 min. Benzyl bromide (2.0 mL, 16.83 mmol) and NaI (170 mg, 1.135 mmol) were added to the reaction mixture, followed by stirring at room temperature for 3 h. Excess NaH was destroyed by adding aq. NH_4Cl (5 mL) under ice-cooled conditions. The mixture was concentrated under reduced pressure, and the residue was extracted with dichloromethane (2 × 30 mL). The organic layer was washed with water (2 × 25 mL), dried (Na_2SO_4) and concentrated to a crude mass, which was purified by *via* silica gel (100–200 mesh) column chromatography using petroleum ether : ethyl acetate (9 : 1) as an eluent to furnish **20** (1.815 g, 92%) as a colourless solid. M.p. 60 °C; $^1\text{H-NMR}$ (500 MHz, CDCl_3): δ 3.02–3.06 (m, 1H), 3.58–3.61 (m, 1H), 3.65–3.69 (m, 2H), 3.76 (t, $J = 7.0$ Hz, 1H), 3.85–3.93 (m, 2H), 3.98 (d, $J = 12.5$ Hz, 1H), 4.06–4.09 (m, 1H), 4.40 (d, $J = 11.5$ Hz, 1H), 4.51 (d, $J = 12.0$ Hz, 1H), 4.59 (d, $J = 12.0$ Hz, 1H), 4.67 (d, $J = 11.5$ Hz, 1H), 4.75 (d, $J = 11.5$ Hz, 1H), 4.81 (d, $J = 11.5$ Hz, 1H), 7.17–7.18 (m, 2H), 7.24–7.40 (m, 18H); $^{13}\text{C NMR}$ (125 MHz, CDCl_3): δ 48.9, 60.1, 70.4, 71.1, 72.3, 72.4, 72.8, 85.8, 86.7. One aliphatic carbon is not discernible, 127.6–129.6 (20C), 136.7, 138.2, 138.5, 138.8. The M.p. and NMR spectra were consistent with the literature.¹⁵



(1R,2R,3R,4S,5R)-3-(Benzylamino)-4,5-dihydroxy-2-(hydroxymethyl)cyclopentyl acetate (21)

Compound **21** was prepared from **17a** according to G.P-3 as a white semisolid (94%). $[\alpha]_{\text{D}}^{25} = -6.043$ (*c* 0.417, MeOH); $^1\text{H-NMR}$ (500 MHz, CDCl_3): δ 2.06 (s, 3H), 2.25–2.29 (m, 1H), 3.27 (t, *J* = 8.5 Hz, 1H), 3.89–3.95 (m, 8H), 3.99–4.02 (m, 1H), 4.06 (t, *J* = 8.5 Hz, 1H), 4.84 (t, *J* = 5.5 Hz, 1H), 7.31–7.34 (m, 5H); $^1\text{H-NMR}$ (400 MHz, $\text{CDCl}_3 + \text{D}_2\text{O}$): δ 2.10 (s, 3H), 2.33–2.39 (m, 1H), 3.28 (t, *J* = 8.4 Hz, 1H), 3.84–3.88 (m, 4H), 4.40 (dd, *J* = 6.0, 11.6 Hz, 1H), 4.70 (t, *J* = 4.8 Hz, 1H), 4.81 (t, *J* = 5.6 Hz, 1H), 7.32–7.33 (m, 5H); $^{13}\text{C NMR}$ (125 MHz, CD_3Cl): δ 21.2, 43.4, 52.4, 60.6, 61.5, 78.0, 79.5, 79.9, 128.4, 128.9 (2C), 129.2 (2C), 135.6, 170.0; HRMS (ESI, *m/z*) calcd for $\text{C}_{15}\text{H}_{22}\text{NO}_5$ [$\text{M} + \text{H}$] $^+$ 296.1498, found 296.1487.

(1S,2S,3R,4R,5R)-3-(Benzylamino)-2,5-dihydroxy-4-(hydroxymethyl)cyclopentyl benzoate (22)

Compound **22** was prepared from **16b** according to G.P-3 as a white semisolid (93%). $[\alpha]_{\text{D}}^{25} = -2.938$ (*c* 1.135, MeOH); $^1\text{H-NMR}$ (400 MHz, CDCl_3): δ 2.33–2.39 (m, 1H), 3.48 (t, *J* = 8.4 Hz, 1H), 3.79–3.89 (m, 2H), 3.98 (s, 2H), 4.16 (t, *J* = 5.6, 1H), 4.31 (t, *J* = 7.6 Hz, 1H), 4.78 (s, 4H), 4.87–4.90 (m, 1H), 7.27–7.35 (m, 5H), 7.38–7.41 (m, 2H), 7.52–7.56 (m, 1H), 8.01 (dd, *J* = 1.6, 8.8 Hz, 2H); $^{13}\text{C NMR}$ (100 MHz, CD_3Cl): δ 45.5, 52.6, 61.0, 62.5, 74.7, 77.4, 87.1, 128.2, 128.6 (2C), 128.91 (2C), 128.94 (2C), 129.2, 130.0 (2C), 133.8, 136.4, 168.5; HRMS (ESI, *m/z*) calcd for $\text{C}_{20}\text{H}_{24}\text{NO}_5$ [$\text{M} + \text{H}$] $^+$ 358.1654, found 358.1637.

(1R,2R,3R,4S,5R)-3-(Benzylamino)-4,5-dihydroxy-2-(hydroxymethyl)cyclopentyl benzoate (23)

Compound **23** was prepared from **17b** according to G.P-3 as a white semisolid (95%). $[\alpha]_{\text{D}}^{25} = -3.162$ (*c* 0.732, MeOH); $^1\text{H-NMR}$ (500 MHz, CDCl_3): δ 2.46 (dd, *J* = 4.5, 9.0 Hz, 1H), 3.38 (t, *J* = 9.0 Hz, 1H), 3.88–3.99 (m, 8H), 4.06–4.13 (m, 2H), 5.17 (t, *J* = 5.5 Hz, 1H), 7.31–7.38 (m, 5H), 7.45 (t, *J* = 7.5 Hz, 2H), 7.59 (t, *J* = 7.5 Hz, 1H), 8.03 (d, *J* = 8.5 Hz, 2H); $^{13}\text{C NMR}$ (100 MHz, CD_3Cl): δ 44.1, 53.3, 61.4, 62.1, 79.3, 80.7, 81.3, 127.6, 128.5 (2C), 128.6 (2C), 128.8 (2C), 129.6, 129.9 (2C), 133.5, 138.7, 167.8; HRMS (ESI, *m/z*) calcd for $\text{C}_{20}\text{H}_{24}\text{NO}_5$ [$\text{M} + \text{H}$] $^+$ 358.1654, found 358.1637.

(1S,2S,3R,4R,5R)-3-Amino-2,5-dihydroxy-4-(hydroxymethyl)cyclopentyl acetate (24)

Compound **24** was prepared from **16a** according to G.P-4 as a white semisolid (92%). $[\alpha]_{\text{D}}^{25} = -7.813$ (*c* 0.511, MeOH); $^1\text{H-NMR}$ (400 MHz, CD_3OD): δ 2.07–2.17 (m, 4H), 3.43 (s-like, 1H, partially merged with solvent peak), 3.72–3.83 (m, 3H), 3.93–3.98 (m, 1H), 4.93–4.97 (m, 1H); $^1\text{H NMR}$ (400 MHz, $\text{DMSO}-d_6$): δ 1.86–1.87 (m, 1H), 2.01 (s, 3H), 3.07 (dd, *J* = 0, 8.8 Hz, 1H), 3.40 (t, *J* = 7.0 Hz, 1H), 3.51–3.59 (m, 2H), 3.73 (m, 1H), 4.79 (t, *J* = 7.3 Hz, 1H), 4.87 (s, 1H), 4.99 (s, 1H), Signals for 3H were not discernible; $^{13}\text{C NMR}$ (100 MHz, $\text{DMSO}-d_6$): δ 21.0, 47.3, 56.6, 58.9, 72.7, 79.5, 83.6, 169.9; HRMS (ESI, *m/z*) calcd for $\text{C}_8\text{H}_{16}\text{NO}_5$ [$\text{M} + \text{H}$] $^+$ 206.1028, found 206.1021.

(1R,2R,3R,4S,5R)-3-Amino-4,5-dihydroxy-2-(hydroxymethyl)cyclopentyl acetate (25)

Compound **25** was prepared from **17a** according to G.P-4 as a white semisolid (90%). $[\alpha]_{\text{D}}^{25} = -16.516$ (*c* 0.508, MeOH); $^1\text{H-NMR}$ (400 MHz, CD_3OD): δ 2.06 (s, 3H), 2.10–2.16 (m, 1H), 3.19–3.24 (m, 1H), 3.65 (t, *J* = 8.0 Hz, 1H), 3.78–3.85 (m, 3H), 4.96 (t, *J* = 6.0, 1H); $^{13}\text{C NMR}$ (100 MHz, CD_3OD): δ 20.9, 46.6, 57.1, 60.5, 80.2, 80.5, 81.9, 172.9; HRMS (ESI, *m/z*) calcd for $\text{C}_8\text{H}_{16}\text{NO}_5$ [$\text{M} + \text{H}$] $^+$ 206.1028, found 206.1023.

(1S,2S,3R,4R,5R)-3-Amino-2,5-dihydroxy-4-(hydroxymethyl)cyclopentyl benzoate (26)

Compound **26** was prepared from **16b** according to G.P-4 as a white semisolid (93%). $[\alpha]_{\text{D}}^{25} = +6.953$ (*c* 0.503, MeOH); $^1\text{H-NMR}$ (400 MHz, CD_3OD): δ 2.17–2.24 (m, 1H), 3.38 (dd, *J* = 7.6, 9.6 Hz, 1H), 3.78–3.90 (m, 3H), 4.14 (t, *J* = 7.2, 1H), 5.18 (t, *J* = 7.2, 1H), 7.49 (t, *J* = 7.6 Hz, 2H), 7.60–7.64 (m, 1H), 8.08–8.10 (m, 2H); $^{13}\text{C NMR}$ (100 MHz, CD_3OD): δ 44.4, 56.9, 60.3, 74.8, 80.6, 85.7, 129.5 (2×C), 130.7 (2C), 131.4, 134.3, 168.1; HRMS (ESI, *m/z*) calcd for $\text{C}_{13}\text{H}_{18}\text{NO}_5$ [$\text{M} + \text{H}$] $^+$ 268.1185, found 268.1175.

(1R,2R,3R,4S,5R)-3-Amino-4,5-dihydroxy-2-(hydroxymethyl)cyclopentyl benzoate (27)

Compound **27** was prepared from **17b** according to G.P-4 as a white semisolid (87%). $[\alpha]_{\text{D}}^{25} = -6.800$ (*c* 0.500, MeOH); $^1\text{H-NMR}$ (400 MHz, CD_3OD): δ 2.22–2.32 (m, 1H), 3.34 (s, 1H, partially merged with solvent peak), 3.74–3.77 (m, 1H), 3.82–3.86 (m, 1H), 3.91–3.95 (m, 1H), 3.99 (t, *J* = 7.2 Hz, 1H), 5.22 (t, *J* = 6.0 Hz, 1H), 7.49 (t, *J* = 7.6 Hz, 2H), 7.62 (t, *J* = 7.2 Hz, 1H), 8.04–8.06 (m, 2H); $^{13}\text{C NMR}$ (100 MHz, CD_3OD): δ 46.7, 57.2, 60.6, 80.6, 80.9, 81.8, 129.6 (2C), 130.6 (2C), 131.3, 134.4, 168.1; HRMS (ESI, *m/z*) calcd for $\text{C}_{13}\text{H}_{18}\text{NO}_5$ [$\text{M} + \text{H}$] $^+$ 268.1185, found 268.1196.

(1S,2R,3R,4R,5S)-2-Amino-4,5-dihydroxy-3-(hydroxymethyl)cyclopentyl benzoate (28)

Compound **28** was prepared from **18b** according to G.P-4 as a white semisolid (87%). $[\alpha]_{\text{D}}^{25} = +6.460$ (*c* 0.510, MeOH); $^1\text{H-NMR}$ (400 MHz, CD_3OD): δ 2.16–2.23 (m, 1H), 3.55 (dd, *J* = 5.6, 9.6 Hz, 1H), 3.81–3.88 (m, 2H), 3.90–3.94 (m, 1H), 4.01 (t, *J* = 7.2 Hz, 1H), 4.95 (t, *J* = 6.8 Hz, 1H), 7.50 (t, *J* = 7.6 Hz, 2H), 7.63 (t, *J* = 7.2 Hz, 1H), 8.09 (d, *J* = 7.6 Hz, 1H); $^{13}\text{C NMR}$ (100 MHz, CD_3OD): δ 44.3, 55.3, 60.1, 76.2, 81.1, 85.7, 129.6 (2C), 130.8 (2C), 131.2, 134.5, 168.5; HRMS (ESI, *m/z*) calcd for $\text{C}_{13}\text{H}_{18}\text{NO}_5$ [$\text{M} + \text{H}$] $^+$ 268.1185, found 268.1175.

(3aR,5S,6aS)-1-Benzylhexahydro-1H-cyclopenta[c]isoxazol-5-yl acetate (30)

A solution of **16a** (560 mg, 1.91 mmol) and 1,1-thiocarbonyldimidazole (870 mg, 4.88 mmol) in dry toluene (7 mL) was heated at 100 °C for 3 h. A mixture of tributyltinhydride (1.5 mL, 5.66 mmol) and azobisisobutyronitrile (315 mg, 1.91 mmol) in toluene (15 mL) was added dropwise to the reaction mixture under reflux conditions. The mixture was further heated at



reflux for 30 minutes, cooled to room temperature and concentrated under reduced pressure. The crude product was purified *via* silica gel (100–200 mesh) column chromatography using petroleum ether–ethyl acetate (9 : 1) as the eluent to obtain **30** (71%) as a white solid. M.p. 57 °C; $[\alpha]_{\text{D}}^{25} = +29.999$ (*c* 0.180, MeOH); ^1H NMR (400 MHz, CDCl_3): δ 1.67–1.78 (m, 2H), 2.03 (s, 3H), 2.08–2.13 (m, 1H), 2.19–2.25 (m, 1H), 3.02–3.09 (m, 1H), 3.43–3.49 (m, 1H), 3.69 (dd, *J* = 4.8, 8.8 Hz, 1H), 3.79–3.83 (m, 1H), 3.97–4.00 (m, 1H), 4.15 (t, *J* = 8.4 Hz, 1H), 4.96–5.02 (m, 1H), 7.27–7.38 (m, 5H); ^{13}C NMR (100 MHz, CDCl_3): δ 21.4, 36.9, 45.6, 60.4, 69.2, 72.4, 75.7, 77.9, 127.5, 128.5 (2C), 129.1 (2C), 137.4, 171.1; HRMS (ESI, *m/z*) calcd for $\text{C}_{15}\text{H}_{20}\text{NO}_3$ [*M* + *H*] $^+$ 262.1443, found 262.1445.

(3*aR*,5*S*,6*aS*)-1-Benzylhexahydro-1*H*-cyclopenta[*c*]isoxazol-5-ol (31)

Compound **31** was prepared from **30** according to G.P-2 as a colourless liquid (99%). $[\alpha]_{\text{D}}^{25} = +71.056$ (*c* 1.040, MeOH); ^1H NMR (400 MHz, CDCl_3): δ 1.69–1.75 (m, 1H), 1.86–1.95 (m, 3H), 3.11–3.17 (m, 1H), 3.45 (t, *J* = 6.4 Hz, 1H), 3.73 (dd, *J* = 6.3, 8.3 Hz, 1H), 3.90 (d, *J* = 13.6 Hz, 1H), 4.06 (d, *J* = 13.6 Hz, 1H), 4.25 (t, *J* = 8.8 Hz, 2H), 7.27–7.36 (m, 5H), 1H not discernible; ^{13}C NMR (100 MHz, CDCl_3): δ 38.9, 40.7, 46.7, 60.5, 72.8, 74.4, 74.9, 127.7, 128.6 (2C), 128.9 (2C), 136.8; HRMS (ESI, *m/z*) calcd for $\text{C}_{13}\text{H}_{18}\text{NO}_2$ [*M* + *H*] $^+$ 220.1338, found 220.1342.

(1*R*,2*S*,3*S*,4*R*,5*R*)-4-Amino-5-(hydroxymethyl)cyclopentane-1,2,3-triol (9)

To a solution of **19** (950 mg, 3.78 mmol) in methanol (15 mL) was added HCO_2NH_4 (2.863 g, 45.42 mmol) and heated at reflux for 5 h, and the solution was then cooled. It was filtered through Celite to obtain **9** (89%) as a white gummy mass. $[\alpha]_{\text{D}}^{25} = +11.819$ (*c* 0.516, MeOH); (ref. 16a $[\alpha]_{\text{D}}^{25} = +8$) (*c* 0.61, MeOH) ^1H -NMR (400 MHz, CD_3OD): δ 2.02–2.09 (m, 1H), 3.23–3.27 (m, 1H), 3.55 (t, *J* = 8.0 Hz, 1H), 3.59 (t, *J* = 7.6 Hz, 1H), 3.73–3.77 (m, 2H), 3.79–3.83 (m, 1H); HRMS (ESI, *m/z*) calcd for $\text{C}_6\text{H}_{14}\text{NO}_4$ [*M* + *H*] $^+$ 164.0923, found 164.0925. ^1H NMR was consistent with ref. 16a.

(1*S*,3*S*,4*R*)-3-((5-Amino-6-chloropyrimidin-4-yl)amino)-4-(hydroxymethyl)cyclopentanol (33a)

Compound **32** was prepared from **31** (400 mg, 1.82 mmol) according to the procedure adopted for the preparation of **9** from **19**, and it was used in the next step without further purification. Compound **33a** was prepared from **32** according to G.P-5. The crude product was purified using methanol : ethyl acetate (1 : 49) as the eluent to obtain **33a** (344 mg, 73%, two steps) as a white liquid. $[\alpha]_{\text{D}}^{25} = -13.965$ (*c* 0.580, MeOH); ^1H -NMR (400 MHz, $\text{DMSO}-d_6$): δ 1.52–1.54 (m, 1H), 1.57–1.64 (m, 1H), 1.94–2.01 (m, 1H), 2.14–2.23 (m, 2H), 3.17 (d, *J* = 5.2 Hz, 1H), 4.06–4.11 (m, 2H), 4.33 (t, *J* = 5.1 Hz, 1H), 4.42 (t, *J* = 7.6 Hz, 1H), 4.76 (d, *J* = 4.3 Hz, 1H), 5.06 (s, 2H), 6.52 (d, *J* = 7.5 Hz, 1H), 7.71 (s, 1H); ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$): δ 37.3, 41.0, 42.1, 51.4, 61.2, 69.2, 123.4, 136.8, 145.6, 151.9; HRMS (ESI, *m/z*) calcd for $\text{C}_{10}\text{H}_{16}\text{ClN}_4\text{O}_2$ [*M* + *H*] $^+$ 259.0962, found 259.0936.

(1*R*,2*S*,3*S*,4*R*,5*R*)-4-((5-Amino-6-chloropyrimidin-4-yl)amino)-5-(hydroxymethyl)cyclopentane-1,2,3-triol (33b)

Compound **33b** was prepared from **9** according to G.P-5. The crude product was purified using methanol–ethyl acetate (3 : 17) as the eluent to obtain **33b** (83%) as a white solid. M.p. 68 °C; $[\alpha]_{\text{D}}^{25} = -56.070$ (*c* 0.280, MeOH); ^1H -NMR (400 MHz, $\text{DMSO}-d_6$): δ 2.04–2.11 (m, 1H), 3.21–3.27 (m, 1H), 3.37 (d, *J* = 4.0 Hz, 1H, partially merged with solvent peak), 3.47–3.52 (m, 1H), 3.64–3.70 (m, 2H), 4.24 (t, *J* = 5.2 Hz, 1H), 4.23–4.34 (m, 1H), 4.72 (d, *J* = 5.6 Hz, 1H), 4.90 (d, *J* = 5.6 Hz, 1H), 4.99 (d, *J* = 4.8 Hz, 1H), 5.08 (s, 2H), 6.55 (d, *J* = 7.2 Hz, 1H), 7.70 (s, 1H); ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$): δ 46.8, 55.5, 59.2, 75.4, 78.3, 81.7, 123.4, 136.9, 145.9, 152.5; HRMS (ESI, *m/z*) calcd for $\text{C}_{10}\text{H}_{16}\text{ClN}_4\text{O}_4$ [*M* + *H*] $^+$ 291.0860, found 291.0874.

(1*S*,3*S*,4*R*)-3-(6-Chloro-9*H*-purin-9-yl)-4-(hydroxymethyl)cyclopentanol (34a)

Compound **34a** was prepared from **33a** according to G.P-6. The crude product was purified using ethyl acetate as the eluent to obtain **34a** (86%) as a white foamy solid. M.p. 132 °C; $[\alpha]_{\text{D}}^{25} = -9.506$ (*c* 0.431, MeOH); ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 1.54–1.61 (m, 1H), 2.11–2.25 (m, 2H), 2.41–2.48 (m, 2H), 3.05–3.08 (m, 2H), 4.17–4.19 (m, 1H), 4.27–4.35 (m, 1H), 5.12–5.17 (m, 2H), 8.77 (s, 1H), 8.85 (s, 1H); ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$): δ 37.0, 40.6, 43.1, 55.1, 60.7, 69.1, 130.7, 147.3, 148.8, 151.2, 152.6; HRMS (ESI, *m/z*) calcd for $\text{C}_{11}\text{H}_{14}\text{ClN}_4\text{O}_2$ [*M* + *H*] $^+$ 269.0805, found 269.0800.

(1*R*,2*S*,3*S*,4*R*,5*R*)-4-(6-Chloro-9*H*-purin-9-yl)-5-(hydroxymethyl)cyclopentane-1,2,3-triol (34b)

Compound **34b** was prepared from **33b** according to G.P-6. The crude product was purified using methanol–ethyl acetate (7 : 93) as the eluent to furnish **34b** (84%) as a white foamy solid. M.p. 93 °C; $[\alpha]_{\text{D}}^{25} = -33.749$ (*c* 0.240, MeOH); ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 2.23–2.30 (m, 1H), 3.18 (dd, *J* = 4.0, 5.6 Hz, 2H), 3.60–3.65 (m, 1H), 3.73–3.78 (m, 1H), 4.27 (t, *J* = 4.0 Hz, 1H), 4.42–4.48 (m, 1H), 4.86–4.91 (m, 1H), 5.09 (d, *J* = 6.0 Hz, 1H), 5.32 (d, *J* = 5.2 Hz, 1H), 5.39 (d, *J* = 6.0 Hz, 1H), 8.72 (s, 1H), 8.76 (s, 1H); ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$): δ 46.6, 59.0, 59.4, 74.4, 75.6, 80.5, 131.1, 147.7, 149.0, 151.5, 153.1; HRMS (ESI, *m/z*) calcd for $\text{C}_{11}\text{H}_{14}\text{ClN}_4\text{NaO}_4$ [*M* + *Na*] $^+$ 323.0523, found 323.0553.

9-((1*S*,2*R*,4*S*)-4-Hydroxy-2-(hydroxymethyl)cyclopentyl)-1*H*-purin-6(9*H*)-one (35a)

Compound **35a** was prepared from **34a** according to G.P-7. Yield: 95%, as a white solid. M.p. 177 °C; $[\alpha]_{\text{D}}^{25} = -28.576$ (*c* 0.731, MeOH); ^1H -NMR (400 MHz, $\text{DMSO}-d_6$): δ 1.48–1.56 (m, 1H), 1.69 (s, 1H), 2.04–2.17 (m, 2H), 2.29–2.39 (m, 1H), 2.93–3.04 (m, 3H), 4.25–4.33 (m, 2H), 4.92 (dd, *J* = 7.6, 15.2 Hz, 1H), 8.02 (s, 1H), 8.22 (s, 1H), the NH proton was not discernible; ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$): δ 37.3, 40.3, 43.9, 54.6, 60.8, 69.2, 123.7, 139.8, 145.9, 148.9, 157.7; HRMS (ESI, *m/z*) calcd for $\text{C}_{11}\text{H}_{15}\text{N}_4\text{O}_3$ [*M* + *H*] $^+$ 251.1144, found 251.1140.

9-((1*R*,2*S*,3*S*,4*R*,5*R*)-2,3,4-Trihydroxy-5-(hydroxymethyl)cyclopentyl)-1*H*-purin-6(9*H*)-on (35b)

Compound **35b** was prepared from **34b** according to G.P-7. Yield: 92% as a white solid. M.p. 267 °C. $[\alpha]_D^{25} = -30.692$ (c 0.185, MeOH); $^1\text{H-NMR}$ (400 MHz, DMSO- d_6): δ 2.14–2.21 (m, 1H), 3.11–3.19 (m, 3H), 3.45 (s, 1H, merged with solvent peak), 3.59 (t, $J = 7.6$ Hz, 1H), 3.77 (t, $J = 6.8$ Hz, 1H), 4.31 (t, $J = 8.8$ Hz, 1H), 4.70 (t, $J = 10.0$ Hz, 1H), 5.03–5.31 (m, 2H), 8.01 (d, $J = 3.6$ Hz, 1H), 8.05 (s, 1H), 12.24 (s, 1H); $^{13}\text{C NMR}$ (100 MHz, DMSO- d_6): δ 47.0, 58.9, 59.0, 74.8, 76.2, 81.1, 124.1, 140.9, 145.5, 149.7, 157.2; HRMS (ESI, m/z) calcd for $\text{C}_{11}\text{H}_{15}\text{N}_4\text{O}_4$ $[\text{M} + \text{H}]^+$ 283.1042, found 283.1048.

(1*S*,3*S*,4*R*)-3-(6-Amino-9*H*-purin-9-yl)-4-(hydroxymethyl)cyclopentan-1-ol (36a)

Compound **36a** was prepared from **34a** according to G.P-8. The crude residue was purified *via* neutral alumina column chromatography using methanol–ethyl acetate (2 : 98) as the eluent to furnish **36a** (87%) as a white solid. M.p. 205 °C; $[\alpha]_D^{25} = -47.199$ (c 0.250, MeOH); $^1\text{H NMR}$ (400 MHz, DMSO- d_6): δ 1.46–1.54 (m, 1H), 2.09–2.18 (m, 2H), 2.30–2.40 (m, 1H), 2.52–2.55 (m, 1H), 2.95–2.98 (m, 2H), 4.29–4.36 (m, 1H), 4.44 (t, $J = 5.2$ Hz, 1H), 4.94 (dd, $J = 7.2$, 13.2 Hz, 1H), 5.23 (d, $J = 4.4$ Hz, 1H), 7.22 (s, 2H), 8.13 (s, 1H), 8.29 (s, 1H); $^{13}\text{C NMR}$ (100 MHz, DMSO- d_6): δ 37.2, 40.2, 44.2, 54.4, 60.8, 69.2, 118.5, 140.7, 149.9, 152.2, 156.1; HRMS (ESI, m/z) calcd for $\text{C}_{11}\text{H}_{16}\text{N}_5\text{O}_2$ $[\text{M} + \text{H}]^+$ 250.1304, found 250.1309.

(1*R*,2*S*,3*S*,4*R*,5*R*)-4-(6-Amino-9*H*-purin-9-yl)-5-(hydroxymethyl)cyclopentane-1,2,3-triol (36b)

Compound **36b** was prepared from **34b** according to G.P-8. The crude product was purified by reverse phase (LiChroprep RP-18, particle size 25–40 μm) flash column chromatography using water as an eluent to furnish **36b** (84%) as a foamy solid. M.p. 288 °C; $[\alpha]_D^{25} = -17.111$ (c 0.514, MeOH); $^1\text{H NMR}$ (400 MHz, DMSO- d_6): δ 2.17–2.24 (m, 1H), 3.10–3.14 (m, 2H), 3.50 (s, 1H, merged with solvent peak), 3.61 (t, $J = 7.6$ Hz, 1H), 3.83 (t, $J = 6.8$ Hz, 1H), 4.38 (t, $J = 8.4$ Hz, 2H), 4.70 (t, $J = 9.6$ Hz, 1H), 5.15–5.47 (m, 2H), 7.13 (s, 2H), 8.07 (s, 1H), 8.11 (s, 1H); $^{13}\text{C NMR}$ (100 MHz, DMSO- d_6): δ 47.1, 58.5, 58.8, 74.8, 76.0, 81.4, 118.7, 140.9, 150.3, 152.1, 155.9; HRMS (ESI, m/z) calcd for $\text{C}_{11}\text{H}_{16}\text{N}_5\text{O}_4$ $[\text{M} + \text{H}]^+$ 282.1202, found 282.1210.

Conflicts of interest

There are no conflicts to declare.

Data availability

CCDC 2440708 (**17a**) and 2440709 (**18b**) contain the supplementary crystallographic data for this paper.^{30a,b}

The data supporting this article have been included as part of the supplementary information (SI). Supplementary information is available. See DOI: <https://doi.org/10.1039/d5ra05811b>.

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