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Synthesis of C-Nucleosidic ATP Mimics as Potential FGFR3 Inhibitors

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Receptor tyrosine kinases (RTKs) play an important role in signal transduction pathways, and in particular, FGFR3 is one of the four RTKs related to the fibroblast growth factor family. This paper describes the synthesis of C-nucleosidic ATP mimics, as potential FGFR3 inhibitors, by nucleophilic epoxide ring-opening followed by in situ *O*-heterocyclization of 1,2:5,6-dianhydro-3,4-di-*O*-benzyl-D-mannitol or L-iditol. Cesium carbonate [Cs_2CO_3] was found to be the best catalyst for the reaction of purine derivatives with these bis-epoxides.

Introduction

FGFRs consist of four (FGFR1–4) related receptor tyrosine kinases (RTKs) coupled with the fibroblast growth factor family. These receptors are involved in biological events that include mitogenic and angiogenic activity with a consequent and crucial role in cell differentiation and/or proliferation.[1] Among them, FGFR3 has been identified to be particularly implicated in different malignant tumours, benign tumours[2] and genetic diseases[3] through its constitutive activation. Within the large number of different structural classes of RTK inhibitors reported, small molecules competing with ATP are considered to be of great interest.[4]

In this context, we became interested in the synthesis of ATP mimics as potential FGFR3 inhibitors. We have previously reported the synthesis of enantiopure polyhydroxylated tetrahydrofuran skeletons **A** bearing an aromatic moiety in the pseudo-anomeric position.[5] The general strategy (Figure 1, path *a*) relies on a one-pot tandem alkylation-*O*-cyclization of enantiopure C_2-symmetrical bis-epoxide **1** derived from D-mannitol by action of aromatic carbon nucleophiles followed by hydrogenolysis.

We have previously shown[5] that the intermediate allowed the reaction to proceed through either the expected *5-exo-tet* (path *a*) pathway or the 6-*endo-tet* *O*-cyclization (path *b*), or by double nucleophilic attack on the primary carbon atoms.

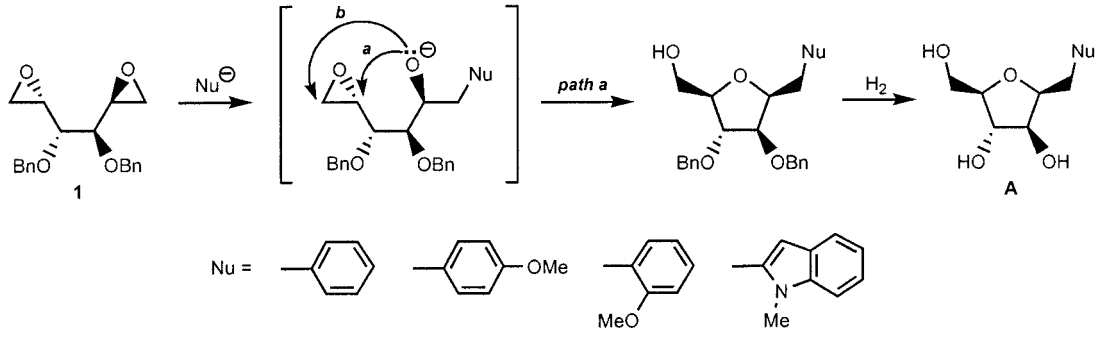

Figure 1. General strategy for the synthesis of C-glycosides.

As a continuation of our ongoing program, we wished to broaden the scope of our methodology to aromatic nitrogen nucleophiles such as purine derivatives in order to synthesize adenosine-like C-nucleosides **B** (Figure 2). These compounds could be used to interfere with cell signalling derived from TK activation.

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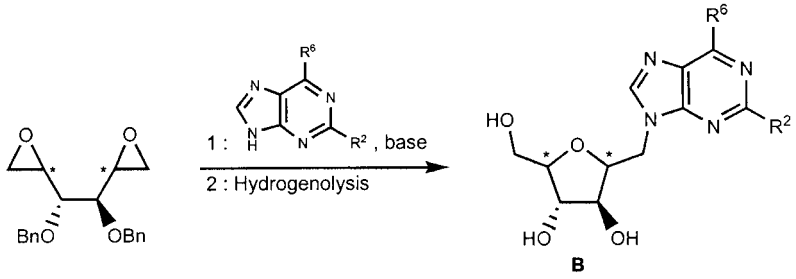


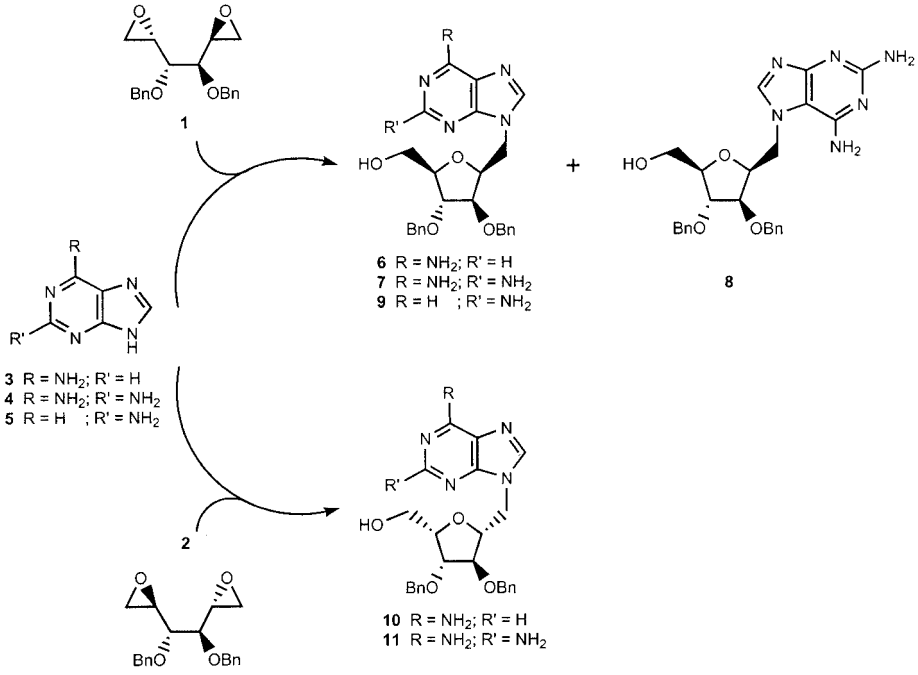
Figure 2. Synthesis of adenosine-like C-nucleosides.

Results and Discussion

Adenosine mimics are generally prepared by alkylation of adenine either with activated polyhydroxy derivatives[6] or through nucleophilic opening of the polyhydroxylated epoxide,[7] or they can be obtained from methylaminopentofuranose with subsequent construction of the nucleobase.[8]

Usually, nucleophilic opening of the epoxide by adenine or purinyl derivatives is carried out by heating under basic conditions with sodium hydride or cesium carbonate.[7] The latter condition was more efficient since the use of NaH led to complex mixtures. Thus, ring opening of L-*ido* bis-epoxide **1**[9] by commercially available adenine (**3**), 2,6-diaminopurine (**4**) and 2-aminopurine (**5**) as nucleophiles (Scheme 1) afforded the desired D-*gluco*-homonucleosides **6**, **7** and **9**, respectively, with an average yield of 55%. It is well known that N9- and N7-alkylated compounds are both products of the purine alkylation process; their ratio usually depends on the nature and the position of the substituents of the purine moiety.[10] In our case, excellent regioselectivity was observed in favour of the N9-alkylated derivative, as the N7 regioisomer **8** was isolated as a byproduct only when the reaction was scaled up to 1.5 mmol. The chemical shift patterns of the N9 (compound **7**) and N7 (compound **8**) regioisomers were consistent in both ^{1}H- and ^{13}C NMR spectra with those observed for related compounds.[11] Starting from the diastereoisomeric bis-epoxide **2**[9] of D-*manno* configuration, the above-mentioned conditions led to the adenosine analogs **10** and **11** in the L-*gulo* configuration with no significant variation of yields. In both series, these conditions allowed the reaction to proceed only through the expected *5-exo-tet* pathway (Figure 1, path *a*).

Subsequent hydrogenolysis of the benzyl protecting groups has been achieved in standard conditions (Pd black in acetic acid) for adenine and guanine derivatives,[12] or by catalytic transfer hydrogenation (HCO_2NH_4, Pd/C 10%). The latter conditions were always more efficient and furnished the debenzylated products in better yields (86% yield for **12**, for example). Nevertheless, with these conditions, the reaction required a longer time (up to four days in re-



Scheme 1. Reagents, conditions and yields: purine **3**, **4** or **5** (1 equiv.), Cs_2CO_3 (3 equiv.), DMF, 2 h, 20 °C, then bis-epoxide **1** or **2** (1 equiv.), DMF, 15–20 h, 110 °C, **6**: 49%, **7**: 49%, **8**: 3%, **9**: 66%, **10**: 45%, **11**: 56%.

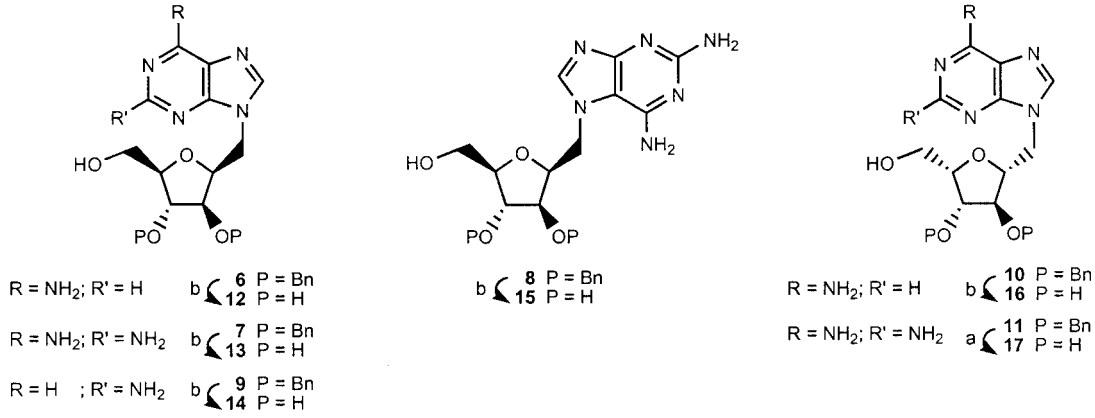
fluxing methanol) and additional catalyst (up to 200 wt.-%) to reach completion (Scheme 2).

In order to confirm both cyclization mode and regioselectivity, an X-ray analysis of compound **13** was made. The resulting structure depicted in Figure 3 is consistent with an N9–C linkage, in a *cis* relationship for the 1′ and 4′ substituents of the furanose-type heterocycle.

In the course of our study, Hanessian and coworkers[14] reported the synthesis of **10** and **16** following an analogous strategy, but the epoxide opening was carried out by trimethylsilylated adenine under Lewis acid catalysis [$Mg(ClO_4)_2$]. However, the ^1H- and ^{13}C NMR spectroscopic data of compounds **10** and **16** were not in agreement with those reported herein.[15]

Finally, we applied the same strategy for the synthesis of 2,6-disubstituted analogs (Scheme 3) which could be interesting from a biological point of view, for example for the investigation of the hydrophobic pocket of the binding site of ATP in kinases.[4] Starting from 2,6-dichloropurine (**18**), aniline was introduced in position 6 under standard S_{NAr} conditions.[16] Either an aliphatic side chain known to improve solubility or benzylamine was introduced through a second S_{NAr} reaction.

The resulting 2,6-disubstituted purines **20** and **21** were used to open bis-epoxide **1** by applying the above-mentioned conditions. In this series, the amount of N7 regioisomers was found to be more important (up to 15%), slightly lowering the overall yields of **22** and **23**. Hydrogenolysis



Scheme 2. Reagents, conditions and yields: (a) H_2, Pd/C, AcOH; (b) $NH_4{\cdot}HCO_2$, Pd/C 10%, MeOH, 1–4 d, reflux, **12**: 86%, **13**: 70%, **14**: 50%, **15**: 53%, **16**: 77%, **17**: 60%.

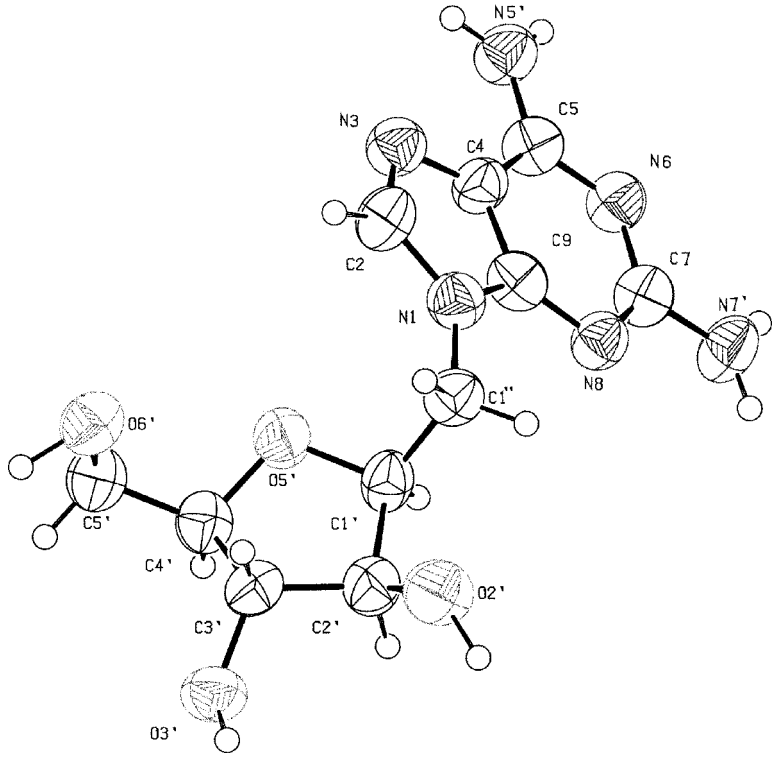
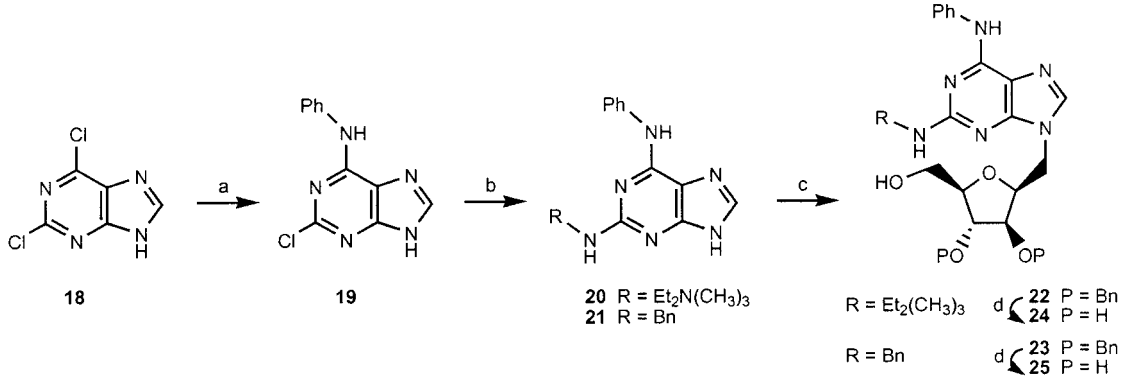


Figure 3. X-ray structure of compound **13** solved with SHELXS and anisotropically refined with SHELXL.[13]



Scheme 3. Reagents, conditions and yields: (a) Ph–NH_2 (5 equiv.), Et_3N (5 equiv.), *n*BuOH, 3 h, 80 °C, 95%; (b) $Et_2N(CH_2)_3NH_2$ or $BnNH_2$ neat, 20 h, 110 °C, **20**: 97%, **21**: 50%; (c) purine (1 equiv.), Cs_2CO_3 (3 equiv.), DMF, 2 h, 20 °C, then bis-epoxide **1** (1 equiv.), DMF, 15–20 h, 110 °C, **22**: 55%, **23**: 34%; (d) H_2, Pd/C, AcOH **24**: 38%, **25**: 35%.

was performed under the previously mentioned conditions, leading to **24** and **25**.

Conclusion

The synthesis of 1′-homo-N-nucleosidic ATP analogs was efficiently achieved by nucleophilic epoxide ring-opening followed by in situ *O*-heterocyclization of 1,2:5,6-dianhydro-3,4-di-*O*-benzyl-D-*manno* or L-*ido* bis-epoxides. This flexible strategy combines a ribose mimic bearing aminopurines with various substituents in order to explore possible interactions with the different regions of the ATP binding sites. These structures should be promising leads in the development of FGFR3 inhibitors. Exploration of their inhibitory activity is currently in progress and will be presented in due course.

Experimental Section

Methods: ^{1}H- and ^{13}C NMR were recorded with a Bruker AM250 spectrometer at 250 and 63 MHz respectively. Compound **13** was only obtained as microcrystals (max size 20 microns); X-ray diffraction data were recorded at the ESRF synchrotron facility (Grenoble) on the BM14 beam-line, at a wavelength of 0.972 Å, by using a MAR CCD detector. The sample was kept at 100 K with an Oxford Cryosystem nitrogen gas cooler. Optical rotations were measured with a Perkin-Elmer 241C polarimeter with a sodium (589 nm) lamp at 20 °C. Melting points were determined with a Büchi 530 apparatus and are uncorrected. High resolution mass spectra (HRMS) were recorded by the service de spectrometrie de masse, Ecole Normale Supérieure, Paris. All reactions were carried out under an argon atmosphere (except for hydrogenolysis), and monitored by thin-layer chromatography with Merck 60 F_{254} precoated silica on aluminium sheets. The visualisation of spots was carried out by staining TLC with an ethanolic phosphomolybdic acid solution followed by heating. Flash chromatography was performed with Merck Kieselgel 60 (0.2–0.5 mm).

Typical Procedure for Nucleophilic Opening: A suspension of purine (1 equiv.) and cesium carbonate (3 equiv.) in dry DMF (5 mL/mmol purine) was stirred at room temperature for 2 h. A solution of bis-epoxide (1 equiv.) in dry DMF (5 mL/mmol epoxide) was added, and the mixture was stirred at 110 °C overnight. TLC monitoring was carried out in cyclohexane/EtOAc = 1:1. After hydrolysis, the crude mixture was extracted twice with ethyl acetate, and the combined organic layers were washed with brine, dried ($MgSO_4$), filtered and concentrated in vacuo. The residue afforded by flash chromatography the protected C-nucleosides with 53% average yield.

1-(6-Amino-9*H*-purin-9-yl)-2,5-anhydro-3,4-di-*O*-benzyl-1-deoxy-D-glucitol (6): R_f = 0.66 (CH_2Cl_2/MeOH, 10:1), 49% yield (303 mg) from **1** (437 mg); yellowish solid. $[\alpha]_D$ = +5.0 (*c* = 0.9, CH_2Cl_2); m.p. 118 °C. ^{1}H NMR ($CDCl_3$): δ = 3.62 (dd, *J* = 2.8, 12.6 Hz, 1 H, 6a-H), 3.79 (dd, *J* = 2.6, 12.6 Hz, 1 H, 6b-H), 3.90–3.99 (m, 1 H, 5-H), 4.17–4.29 (m, 3 H, 1a-H, 2-H, 3-H), 4.30–4.43 (m, 2 H, 1b-H, 4-H), 4.48 (AB, *J* = 11.7 Hz, 1 H, C*H*Ph), 4.54–4.69 (m, 2 H, CH_2Ph), 4.73 (AB, *J* = 11.7 Hz, 1 H, C*H*Ph), 6.04 (br. s, 2 H, NH_2), 7.27–7.41 (m, 10 H, 2 Ph), 7.59 (s, 1 H, 8′-H-Ade), 8.29 (s, 1 H, 2′-H-Ade) ppm. ^{13}C NMR ($CDCl_3$): δ = 44.8 (C-1), 61.5 (C-6), 72.5, 72.7 (*C*H_2Ph), 78.6, 81.2, 83.6, 83.7 (C-2, C-3, C-4, C-5), 119.4 (Cq), 127.6, 127.9, 128.2, 128.3, 128.5, 128.7 (CH-Ar), 137.3, 137.9 (Cq), 140.7 (C-8′), 150.1 (Cq), 152.6 (C-2′), 155.7 (Cq) ppm. MS (ESI): *m*/*z* = 462 $[M + H]^+$.

2,5-Anhydro-1-(2,6-diamino-9*H*-purin-9-yl)-3,4-di-*O*-benzyl-1-deoxy-D-glucitol (7): R_f = 0.44 (EtOAc/MeOH/NH_4OH, 5:1:0.1), 49% yield (2.259 g) from **1** (3.15 g); white solid. $[\alpha]_D$ = –3.8 (*c* = 0.5, CH_2Cl_2); m.p. 165 °C. ^{1}H NMR ($CDCl_3$): δ = 3.59 (dd, *J* = 2.4, 1 H, 12.8 Hz, 6a-H), 3.82 (dd, *J* = 2.8, 12.8 Hz, 1 H, 6b-H), 3.90–3.99 (m, 2 H, 1a-H, 5-H), 4.15–4.22 (m, 2 H, 1b-H, 2-H), 4.28 (t, *J* = 5.9 Hz, 1 H, 3-H), 4.47 (t, *J* = 5.9 Hz, 1 H, 4-H), 4.55–4.68 (AB, *J* = 12.0 Hz, 2 H, CH_2Ph), 4.48–4.78 (AB, *J* = 11.8 Hz, 2 H, CH_2Ph), 4.83 (s, 2 H, NH_2), 5.57 (s, 2 H, NH_2), 7.24–7.38 (m, 11 H, 2 Ph, 8′-H-Ade) ppm. ^{13}C NMR ($CDCl_3$): δ = 44.8 (C-1), 61.1 (C-6), 72.7, 73.0 (*C*H_2Ph), 78.5, 80.6, 83.0, 83.9 (C-2, C-3, C-4, C-5), 114.6 (Cq), 127.6, 127.9, 128.2, 128.5, 128.7 (CH-Ar), 137.5 (Cq) 137.9 (Cq, C-8′), 152.6, 156.1, 159.6 (Cq) ppm. HRMS (ESI): calcd. for $C_{25}H_{29}N_6O_4$ $[M + H]^+$ 477.2257; found 477.2245.

2,5-Anhydro-1-(2,6-diamino-7*H*-purin-9-yl)-3,4-di-*O*-benzyl-1-deoxy-D-glucitol (8): R_f = 0.35 (EtOAc/MeOH/NH_4OH, 5:1:0.1), 3% yield (138 mg) from **1** (3.15 g); orange foam. $[\alpha]_D$ = +13.5 (*c* = 1.1, CH_2Cl_2); m.p. 109 °C. ^{1}H NMR ($CDCl_3$): δ = 3.47 (s, 1 H, 5-H), 3.64 (s, 1 H, 2-H), 3.80–3.85 (m, 3 H, 6-H, 3-H), 4.01–4.12 (m, 3 H, 1-H, 4-H), 4.34–4.68 (m, 5 H, 2 CH_2Ph, OH), 5.17 (s, 2 H, NH_2), 6.19 (s, 2 H, NH_2), 7.29 (m, 10 H, 2 Ph), 7.45 (s, 1 H, 8′-H-Ade) ppm. ^{13}C NMR ($CDCl_3$): δ = 44.4 (C-1), 66.6 (C-2), 68.9 (C-6), 71.1 (C-3), 72.1, 72.5 (CH_2Ph), 73.4, 74.5 (C-4, C-5), 113.8 (Cq), 127.7, 128.0, 128.4, 128.5, 128.7 (CH-Ar), 136.7, 137.5 (Cq),

138.9 (C-8′), 156.8, 156.1, 160.0 (Cq) ppm. MS (ESI): *m*/*z* = 477 $[M + H]^+$.

1-(2-Amino-9*H*-purin-9-yl)-2,5-anhydro-3,4-di-*O*-benzyl-1-deoxy-D-glucitol (9): R_f = 0.14 (CH_2Cl_2/MeOH, 9:5), 66% yield (102 mg) from **1** (109 mg); yellowish solid. $[\alpha]_D$ = +41.0 (*c* = 2.0, CH_2Cl_2); m.p. 68 °C. ^{1}H NMR ($CDCl_3$): δ = 3.62 (dd, *J* = 2.2, 12.5 Hz, 1 H, 6a-H), 3.77 (dd, *J* = 2.2, 12.5 Hz, 1 H, 6b-H), 3.90–3.98 (m, 1 H, 5-H), 4.08 (d, *J* = 11.6 Hz, 1 H, 1a-H), 4.14–4.31 (m, 3 H, 1b-H, 2-H, 3-H), 4.37 (t, *J* = 4.4 Hz, 1 H, 4-H), 4.47 (AB, *J* = 11.7 Hz, 1 H, C*H*Ph), 4.56–4.70 (m, 2 H, CH_2Ph), 4.73 (AB, *J* = 11.7 Hz, 1 H, C*H*Ph), 4.85–5.10 (br. s, 1 H, OH), 5.15 (br. s, 2 H, NH_2), 7.27–7.42 (m, 10 H, 2 Ph), 7.51 (s, 1 H, 8′-H-Ade), 8.64 (s, 1 H, 6′-H-Ade) ppm. ^{13}C NMR ($CDCl_3$): δ = 44.2 (C-1), 61.4 (C-6), 72.6, 72.8 (*C*H_2Ph), 78.3, 80.9, 83.3, 83.6 (C-2, C-3, C-4, C-5), 127.6, 127.9, 128.2, 128.4, 128.5, 128.7 (Cq, CH-Ar), 137.3, 137.7 (Cq), 142.5 (C-8′), 150.2 (C-6′), 153.3, 159.5 (Cq) ppm. MS (ESI): *m*/*z* = 462 $[M + H]^+$.

1-(6-Amino-9*H*-purin-9-yl)-2,5-anhydro-3,4-di-*O*-benzyl-1-deoxy-L-gulitol (10): R_f = 0.35 (CH_2Cl_2/MeOH, 9:1), 45% yield (177 mg) from **2** (278 mg); colourless oil. $[\alpha]_D$ = +43.0 (*c* = 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ = 3.74–4.46 (m, 10 H, 1-H, 2-H, 3-H, 4-H, 5-H, 6-H, CH_2Ph), 4.51 (s, 2 H, CH_2Ph), 5.95 (br. s, 2 H, NH_2), 7.10–7.31 (m, 10 H, 2 Ph), 7.59 (s, 1 H, 8′-H-Ade), 8.28 (s, 1 H, 2′-H-Ade) ppm. ^{13}C NMR ($CDCl_3$): δ = 45.5 (C-1), 61.2 (C-6), 71.8, 72.1 (*C*H_2Ph), 81.4, 82.0, 83.3, 83.6 (C-2, C-3, C-4, C-5), 119.0 (Cq), 127.7, 127.8, 128.1, 128.6 (CH-Ar), 137.0, 137.2 (Cq), 141.8 (C-8′), 150.2 (Cq), 152.9 (C-2′), 155.4 (Cq) ppm. HRMS (ESI): calcd. for $C_{25}H_{28}N_5O_4$ $[M + H]^+$ 462.2136; found 462.2147.

2,5-Anhydro-1-(2,6-diamino-9*H*-purin-9-yl)-3,4-di-*O*-benzyl-1-deoxy-L-gulitol (11): R_f = 0.6 (EtOAc/MeOH, 5:1), 56% yield (230 mg) from **2** (280 mg); white solid. $[\alpha]_D$ = +15.5 (*c* = 2.0, DMSO); m.p. 165 °C. ^{1}H NMR ([D$_6$]DMSO): δ = 3.55–3.70 (m, 2 H, 6-H), 3.90–4.00 (m, 3 H, 3-H, 4-H, 5-H), 4.12 (m, 3 H, 1-H, 2-H), 4.37 (s, 2 H, CH_2Ph), 4.50 (AB, *J* = 12.0 Hz, 2 H, CH_2Ph), 4.70 (t, *J* = 5.2 Hz, 1 H, OH), 5.69 (br. s, 2 H, NH_2), 6.62 (br. s, 2 H, NH_2), 7.26 (m, 10 H, 2 Ph), 7.63 (s, 1 H, 8′-H-Ade) ppm. ^{13}C NMR ([D$_6$]DMSO): δ = 45.0 (C-1), 59.2 (C-6), 70.7, 70.8 (*C*H_2Ph), 81.2, 81.9, 82.2, 89.9 (C-2, C-3, C-4, C-5), 113.0 (Cq), 127.5, 127.6, 128.2, 128.3 (CH-Ar), 137.7, 137.8 (Cq), 138.2 (C-8′), 151.7, 156.1, 160.2 (Cq) ppm. MS (ESI): *m*/*z* = 477 $[M + H]^+$.

2-Chloro-6-phenylamino-purine (19): To a solution of 2,6-dichloropurine (500 mg, 2.65 mmol, 1 equiv.) in butanol (45 mL) were added triethylamine (1.8 mL, 13.23 mmol, 5 equiv.) and aniline (1.21 mL, 13.23 mmol, 5 equiv.). After stirring for 3 h at 80 °C, the mixture was concentrated. To the residue was added H_2O (50 mL), the precipitate was then filtered and washed with H_2O, affording **19** in 95% yield (617 mg) as a white solid; m.p. 298 °C. ^{1}H NMR ([D$_6$]DMSO): δ = 7.07 (t, *J* = 7.3 Hz, 1 H, H-Ar), 7.35 (t, *J* = 7.6 Hz, 2 H, H-Ar), 7.83 (d, *J* = 7.8 Hz, 2 H, H-Ar), 8.29 (s, 1 H, 8-H), 10.15 (m, 1 H, N*H*Ph) ppm. MS (ESI): *m*/*z* = 244 $[M - H]^+$.

2-(*N*,*N*-Diethylamino-3-propylamino)-6-phenylamino-purine (20): A solution of **19** (170 mg, 0.69 mmol, 1 equiv.) in diethylaminopropylamine (5 mL) was stirred at 110 °C for 17 h and then concentrated in vacuo. The residue was taken up in EtOAc (10 mL) and washed with H_2O (10 mL) and brine (10 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated in vacuo to yield **20** in 97% yield (228 mg) as an orange solid; R_f = 0.20 (EtOAc/MeOH/NEt_3, 85:15:1); m.p. 140 °C. ^{1}H NMR ($CDCl_3$): δ = 1.02 (t, *J* = 6.9 Hz, 6 H, 2 CH_3ε), 1.82 (quint, *J* = 6.5 Hz, 2 H, CH_2β), 2.58 (m, 6 H, CH_2γ, 2 CH_2δ), 3.46 (br. s, 2 H, CH_2α), 6.25 (br. s, 1 H, NH), 7.01 (t, *J* = 7.2 Hz, 1 H, H-Ar), 7.29 (t, *J* = 7.7 Hz, 2 H, H-Ar), 7.64 (s, 1 H, 8-H), 7.81 (d, *J* = 7.9 Hz, 2 H, H-Ar), 8.49 (br. s, 1 H, NH) ppm. ^{13}C NMR ($CDCl_3$): δ = 11.0 (Cε), 26.3 (Cβ), 41.1 (Cα), 46.5 (Cδ), 51.1 (Cγ), 113.7 (Cq), 119.9, 122.7, 128.8 (CH-Ar), 135.8 (C-8), 139.7, 152.0, 152.3, 159.7 (Cq) ppm. MS (ESI): *m*/*z* = 338 $[M - H]^+$.

2-Benzylamino-6-phenylamino-purine (21): A solution of **19** (170 mg, 0.60 mmol, 1 equiv.) in benzylamine (5 mL) was stirred at 110 °C for 17 h and concentrated in vacuo. The residue was taken up in EtOAc (10 mL) and washed with H_2O (20 mL) and brine (20 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated in vacuo. Purification by flash chromatography (EtOAc then EtOAc/MeOH, 9:1) afforded **21** in 50% yield (109 mg) as a pinkish solid. R_f = 0.17 (EtOAc); m.p. 287 °C. ^{1}H NMR ([D$_6$]DMSO): δ = 4.50 (s, 2 H, CH_2), 4.51 (s, 1 H, NH), 6.92 (t, *J* = 7.1 Hz, 1 H, H-Ar), 7.10–7.20 (m, 2 H, H-Ar), 7.30 (m, 5 H, H-Ar), 7.77 (s, 1 H, 8-H), 7.90 (m, 2 H, H-Ar), 9.26 (s, 1 H, NHPh), 12.33 (s, 1 H, NH) ppm. ^{13}C NMR ([D$_6$]DMSO): δ = 44.7 (*C*H_2Ph), 113.7 (Cq), 120.0, 121.8, 126.4, 126.9, 128.1, 128.4 (CH-Ar), 136.3 (C-8), 140.4, 141.3, 152.0, 152.6, 159.7 (Cq) ppm. MS (ESI): *m*/*z* = 315 $[M - H]^+$.

2,5-Anhydro-3,4-di-*O*-benzyl-1-[2-(*N*,*N*-diethylamino-3-propylamino)-6-phenylamino-9*H*-purin-9-yl]-1-deoxy-D-glucitol (22): R_f = 0.22 (EtOAc/MeOH/NEt_3, 2:1:0.1), 55% yield (189 mg) from **1** (180 mg); orange foam. $[\alpha]_D$ = –22.5 (*c* = 1.0, CH_2Cl_2). ^{1}H NMR ($CDCl_3$): δ = 1.04 (t, *J* = 7.0 Hz, 6 H, 2 CH_3ε), 1.79 (m, 2 H, CH_2β), 2.56 (m, 6 H, CH_2γ, 2 CH_2δ), 3.50 (m, 2 H, CH_2α), 3.64 (dd, *J* = 2.4, 12.0 Hz, 1 H, 6a-H), 3.80 (dd, *J* = 2.8, 12.0 Hz, 1 H, 6b-H), 3.97 (m, 1 H, 4-H), 4.09 (m, 2 H, CH_2Ph), 4.23 (m, 2 H, CH_2Ph), 4.41 (m, 2 H, 3-H, 5-H), 4.48 (m, 1 H, 1a-H), 4.65 (m, 1 H, 2-H), 4,71 (m, 1 H, 1b-H), 5.66 (m, 1 H, NH), 7.02 (t, *J* = 7.3 Hz, 1 H, H-Ar), 7.29 (m, 10 H, 2 Ph), 7.80 (d, *J* = 7.9 Hz, 2 H, H-Ar), 7.97 (s, 1 H, 8′-H-Ade) ppm. ^{13}C NMR ($CDCl_3$): δ = 11.4 (Cε), 26.6 (Cβ), 41.1 (Cα), 44.2 (C-1), 46.7 (Cδ), 51.0 (Cγ), 61.3 (C-6), 72.4, 72.6 (*C*H_2Ph), 78.5, 81.1, 83.3, 83.6 (C-2, C-3, C-4, C-5), 114.0 (Cq), 119.7, 122.5, 127.5, 127.7, 128.0, 128.1, 128.3, 128.5 (CH-Ar), 137.4, 137.5 (Cq), 137.8 (C-8′), 139.4, 151.7, 152.2, 159.4 (Cq) ppm. MS (ESI): *m*/*z* = 666 $[M + H]^+$.

2,5-Anhydro-3,4-di-*O*-benzyl-1-(2-benzylamino-6-phenylamino-9*H*-purin-9-yl)-1-deoxy-D-glucitol (23): R_f = 0.50 (EtOAc), 34% yield (165 mg) from **1** (250 mg); yellowish oil. $[\alpha]_D$ = +16.5 (*c* = 1.0, CH_2Cl_2). ^{1}H NMR ($CDCl_3$): δ = 3.62 (dd, *J* = 2.5, 12.7 Hz, 1 H, 6a-H), 3.80 (dd, *J* = 2.3, 12.7 Hz, 1 H, 6b-H), 3.94–4.77 (m, 12 H, 1-H, 2-H, 3-H, 4-H, 5-H, 3 CH_2Ph), 5.48 (br. s, 1 H, OH), 7.01 (t, *J* = 7.3 Hz, 1 H, H-Ar), 7.22–7.36 (m, 17 H, H-Ar), 7.63 (d, *J* = 7.3 Hz, 2 H, H-Ar), 7.70 (s, 1 H, 8′-H-Ade) ppm. ^{13}C NMR ($CDCl_3$): δ = 44.5, 46.0 (C-1, N*C*H_2Ph), 61.4 (C-6), 72.6, 72.8 (*C*H_2Ph), 78.5, 80.9, 83.2, 83.7 (C-2, C-3, C-4, C-5), 114.3 (Cq), 119.9, 126.9, 127.2, 127.6, 127.8, 127.9, 128.1, 128.5, 128.7 (CH-Ar), 137.4 (Cq), 137.7 (C-8′), 139.0, 139.8, 151.5, 152.3, 159.1 (Cq) ppm. MS (ESI): *m*/*z* = 644 $[M + H]^+$.

Typical Procedure for Hydrogenolysis

Method A: A mixture of benzylated C-nucleoside and palladium black (100 wt.-%) in AcOH (10 mL/mmol) was stirred under a hydrogen atmosphere. After completion of the reaction monitored by TLC, the crude mixture was filtered through Celite before concentration under reduced pressure. Purification by flash chromatography afforded the corresponding C-nucleoside.

Method B: A mixture of benzylated C-nucleoside, ammonium formate (16 equiv.) and Pd/C (100 wt.-%) in MeOH was heated at reflux for two days. The reaction was monitored by TLC. If necessary, more ammonium formate (16 equiv.) and Pd/C (100 wt.-%) were added, and the mixture was heated at reflux again for two

days. After completion, methanol was added, and the crude mixture was sonicated for 30 min, filtered through Celite and concentrated under reduced pressure. Purification by flash chromatography afforded the corresponding C-nucleoside.

1-(6-Amino-9*H*-purin-9-yl)-2,5-anhydro-1-deoxy-D-glucitol (12): Method B, R_f = 0.31 (CH_2Cl_2/MeOH, 7:3), 86% yield (146 mg) from **6** (278 mg); yellowish solid. $[\alpha]_D$ = –1.5 (*c* = 0.5, H_2O); m.p. 185 °C. ^{1}H NMR (D_2O): δ = 3.69–3.81 (m, 2 H, 6-H), 3.82–3.92 (m, 1 H, 5-H), 4.17 (t, *J* = 4.0 Hz, 1 H, 4-H), 4.24–4.56 (m, 4 H, 1-H, 2-H, 3-H), 8.15 (s, 2 H, 2′-H-Ade, 8′-H-Ade) ppm. ^{13}C NMR (D_2O): δ = 46.8 (C-1), 64.2 (C-6), 79.4, 80.4, 81.8, 87.5 (C-2, C-3, C-4, C-5), 120.9 (Cq), 145.5 (C-8′), 151.6 (Cq), 154.7 (C-2′), 157.8 (Cq) ppm. HRMS (ESI): calcd. for $C_{11}H_{16}N_5O_4$ $[M + H]^+$ 282.1197; found 282.1203.

2,5-Anhydro-1-deoxy-1-(2,6-diamino-9*H*-purin-9-yl)-D-glucitol (13): Method B, R_f = 0.36 (CH_2Cl_2/MeOH/NH_4OH, 9:1:0.1), 70% yield (130 mg) from **7** (418 mg); white solid. $[\alpha]_D$ = –14.0 (*c* = 2.0, DMSO); m.p. 206 °C. ^{1}H NMR ([D_6]DMSO): δ = 3.48 (m, 2 H, 6-H), 3.59 (m, 1 H, 5-H), 3.75 (m, 1 H, 3-H), 3.88 (s, 1 H, 4-H), 4.03–4.15 (m, 3 H, 1-H, 2-H), 4.98 (t, *J* = 7.5 Hz, 1 H, 6-OH), 5.13 (d, *J* = 4.0 Hz, 1 H, 4-OH), 5.58 (d, *J* = 4.9 Hz, 1 H, 3-OH), 5.80 (s, 2 H, NH_2), 6.68 (s, 2 H, NH_2), 7.67 (s, 1 H, 8′-H-Ade) ppm. ^{13}C NMR ([D_6]DMSO): δ = 42.4 (C-1), 61.8 (C-6), 76.4 (C-3), 77.7 (C-4), 78.8 (C-2), 86.1 (C-5), 113.0 (Cq), 138.1 (C-8′), 151.6, 156.2, 160.1 (Cq) ppm. HRMS (DCI): calcd. for $C_{11}H_{17}N_6O_4$ 297.1311 $[M + H]^+$; found 297.1318. X-ray diffraction data: Space group $P2_12_12_1$ (*Z* = 4) with cell parameters *a* = 5.095(1), *b* = 10.363(1) and *c* = 25.535(2) Å. Final *R* factor = 6.25% (880 observed *F*) and *R* = 6.5% (958 *F*, all data). CCDC-293495 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

1-(2-Amino-9*H*-purin-9-yl)-2,5-anhydro-1-deoxy-D-glucitol (14): Method B, R_f = 0.24 (CH_2Cl_2/MeOH/NH_4OH, 7:3:0.1), 50% yield (17 mg) from **9** (56 mg); yellow solid. $[\alpha]_D$ = +13.5 (*c* = 1.4, MeOH); m.p. 172 °C. ^{1}H NMR (D_2O): δ = 3.70–3.81 (m, 2 H, 6-H), 3.83–3.92 (m, 1 H, 5-H), 4.10–4.20 (m, 1 H, 4-H), 4.24–4.33 (m, 2 H, 1a-H, 3-H), 4.38–4.51 (m, 2 H, 1b-H, 2-H), 8.14 (s, 1 H, 8′-H-Ade), 8.54 (s, 1 H, 6′-H-Ade) ppm. ^{13}C NMR (D_2O): δ = 45.9 (C-1), 64.2 (C-6), 79.4, 80.2, 81.4, 87.7 (C-2, C-3, C-4, C-5), 129.5 (Cq), 147.8 (C-8′), 151.7 (Cq), 151.8 (C-6′), 162.4 (Cq) ppm. MS (ESI): *m*/*z* = 282 $[M + H]^+$.

2,5-Anhydro-1-(2,6-diamino-7*H*-purin-9-yl)-1-deoxy-D-glucitol (15): Method B, R_f = 0.20 (CH_2Cl_2/MeOH, 7:3), 53% yield (52 mg) from **8** (158 mg); white powder. $[\alpha]_D$ = –40.0 (*c* = 1.0, MeOH); m.p. 232 °C. ^{1}H NMR ([D_6]DMSO): δ = 3.4–3.8 (m, 5 H, 3-H, 4-H, 5-H, 6-H), 3.91 (m, 1 H, 2-H), 4.01 (dd, *J* = 4.8, 14.0 Hz, 1 H, 1a-H), 4.14 (dd, *J* = 8.8, 14.0 Hz, 1 H, 1b-H), 4.96 (d, *J* = 7.5 Hz, 1 H, OH), 5.06 (br. s, 1 H, OH), 5.25 (br. s, 1 H, OH), 5.79 (br. s, 2 H, NH_2), 6.61 (br. s, 2 H, NH_2), 7.60 (s, 1 H, 8′-H-Ade) ppm. ^{13}C NMR ([D_6]DMSO): δ = 43.5 (C-1), 67.4 (C-6), 68.2, 68.8, 69.1 (C-3, C-4, C-5), 72.9 (C-2), 113.2 (Cq), 138.5 (C-8′), 152.1, 156.3, 160.5 (Cq) ppm. MS (ESI): *m*/*z* = 297 $[M + H]^+$.

1-(6-Amino-9*H*-purin-9-yl)-2,5-anhydro-1-deoxy-L-gulitol (16): Method B, R_f = 0.30 (CH_2Cl_2/MeOH, 8:2), 77% yield (70 mg) from **10** (150 mg); white solid. $[\alpha]_D$ = +69.0 (*c* = 2.0, DMSO); m.p. 240 °C. ^{1}H NMR ([D_6]DMSO): δ = 3.40–3.70 (m, 2 H, 6-H), 3.75–4.0 (m, 4 H, 2-H, 3-H, 4-H, 5-H), 4.21 (dd, *J* = 8.0, 13.8 Hz, 1 H, 1a-H), 4.32 (dd, *J* = 4.5, 13.8 Hz, 1 H, 1b-H), 4.60 (t, *J* = 4.9 Hz, 1 H, 6-OH), 5.13 (br. s, 1 H, OH), 5.29 (d, *J* = 3.6 Hz, 1 H, OH), 7.15 (s, 2 H, NH_2), 8.04 (s, 1 H, 8′-H-Ade), 8.12 (s, 2 H, 2′-H-Ade) ppm. ^{13}C NMR ([D_6]DMSO): δ = 46.0 (C-1), 60.0 (C-6), 76.8, 79.1, 82.3, 82.9 (C-2, C-3, C-4, C-5), 118.7 (Cq), 141.5 (C-8′), 149.7 (Cq), 152.5 (C-6′), 156.1 (Cq) ppm. HRMS (DCI): calcd. for $C_{11}H_{16}N_5O_4$ 282.1203; found 282.1198.

2,5-Anhydro-1-deoxy-1-(2,6-diamino-9*H*-purin-9-yl)-L-gulitol (17): Method A, R_f = 0.30 (CH_2Cl_2/MeOH/NH_4OH, 7:3:0.1), 60% yield (56 mg) from **11** (150 mg); yellow powder. $[\alpha]_D$ = +25.0 (*c* = 0.5, H_2O); m.p. 250 °C (dec.). ^{1}H NMR (D_2O): δ = 3.73 (dd, *J* = 6.5, 12.1 Hz, 1 H, 6a-H), 3.84 (dd, *J* = 4.2, 12.1 Hz, 1 H, 6b-H), 4.08 (dd, *J* = 2.6, 3.8 Hz, 1 H, 3-H), 4.18 (m, 2 H, 2-H, 5-H), 4.25 (dd, *J* = 2.6, 4.4 Hz, 1 H, 4-H), 4.35 (d, *J* = 5.1 Hz, 2 H, 1-H), 7.87 (s, 1 H, 8′-H-Ade) ppm. ^{13}C NMR (D_2O): δ = 47.9 (C-1), 63.0 (C-6), 79.7, 81.5, 84.0, 85.2 (C-2, C-3, C-4, C-5), 115.5 (Cq), 143.5 (C-8′), 154.0, 158.9, 162.8 (Cq) ppm. MS (ESI): *m*/*z* = 297 $[M + H]^+$.

2,5-Anhydro-1-[2-(*N*,*N*-diethylamino-3-propylamino)-6-phenylamino-9*H*-purin-9-yl]-1-deoxy-D-glucitol (24): Method A, R_f = 0.20 (CH_2Cl_2/MeOH/NEt_3, 9:1:0.1), 38% yield (50 mg) from **22** (179 mg); orange solid. $[\alpha]_D$ = –31.0 (*c* = 0.6, CH_2Cl_2); m.p. 99 °C. ^{1}H NMR ($CDCl_3$): δ = 0.98 (t, *J* = 6.5 Hz, 6 H, $CH_3\varepsilon$), 1.74 (m, 2 H, $CH_2\beta$), 2.56 (m, 6 H, $CH_2\gamma$, 2 $CH_2\delta$), 3.34 (m, 2 H, $CH_2\alpha$), 3.69 (m, 2 H, 6-H), 3.89 (m, 1 H, 4-H), 4.00–4.10 (m, 2 H, 3-H, 5-H), 4.21 (m, 3 H, 1-H, 5-H), 5.95 (m, 1 H, NH_2), 6.97 (t, *J* = 7.0 Hz, 1 H, H-Ar), 7.20 (m, 10 H, 2 Ph), 7.47 (s, 1 H, 8′-H-Ade), 7.73 (d, *J* = 7.4 Hz, 2 H, H-Ar), 8.11 (s, 1 H, NH) ppm. ^{13}C NMR ($CDCl_3$): δ = 10.4 (Cε), 25.7 (Cβ), 40.6 (Cα), 42.7 (C-1), 46.3 (Cδ), 50.6 (Cγ), 61.9 (C-6), 76.6, 77.5, 79.7, 85.7 (C-2, C-3, C-4, C-5), 113.7 (Cq), 119.9, 122.6, 128.6 (CH-Ar), 138.1 (C-8′), 139.2, 151.1, 152.3, 159.2 (Cq) ppm. MS (ESI, MeOH): *m*/*z* = 486 $[M + H]^+$.

1-(2-Amino-6-phenylamino-9*H*-purin-9-yl)-2,5-anhydro-1-deoxy-D-glucitol (25): Method A, R_f = 0.10 (CH_2Cl_2/MeOH, 8:2), 35% yield (42 mg) from **23** (200 mg); yellowish foam. $[\alpha]_D$ = –31.0 (*c* = 1.6, MeOH). ^{1}H NMR (CD_3OD): δ = 3.71 (t, *J* = 4.0 Hz, 1 H, 6-H), 3.81 (t, *J* = 3.6 Hz, 1 H, 5-H), 4.01 (t, *J* = 3.3 Hz, 1 H, 3-H), 4.10 (t, *J* = 3.3 Hz, 1 H, 4-H), 4.23–4.39 (m, 3 H, 1-H, 2-H), 7.04 (t, *J* = 7.4 Hz, 1 H, H-Ar), 7.33 (t, *J* = 7.5 Hz, 1 H, H-Ar), 7.81 (d, *J* = 7.6 Hz, 2 H, H-Ar), 7.85 (s, 1 H, 8′-H-Ade) ppm. ^{13}C NMR (CD_3OD): δ = 44.4 (C-1), 63.1 (C-6), 78.2, 79.2, 80.8, 87.3 (C-2, C-3, C-4, C-5), 114.8 (Cq), 121.4, 124.0, 129.7 (CH-Ar), 140.3 (C-8′), 140.8, 152.5, 154.0, 161.7 (Cq) ppm. MS (ESI): *m*/*z* = 373 $[M + H]^+$.

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