Supporting Information

Synthesis and Antiplasmodial Activity of Purine Based C-Nucleoside Analogues

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1. Experimental Section

1.1. Chemistry

Commercially available reagent grade chemicals used as received. All reactions were monitored by TLC on E. Merck Kieselgel 60 F254, with detection by UV light, spraying 20% aq. KMnO₄ solution or spraying 4% ethanolic H₂SO₄. Column chromatography performed on Silica Gel (60-120 mesh, E. Merck). IR spectra were recorded as thin films or in KBr solution with a Perkin-Elmer Spectrum RX-1 (4000-450 cm⁻¹) spectrophotometer. ¹H NMR spectra were recorded on 400 and 300 MHz Bruker NMR spectrometers in CDCl₃ or DMSO-d6. Chemical shift values reported in δ ppm relative to the residual signals of TMS in CDCl₃ or deuterated solvent DMSO d_6 . 13C NMR spectra were recorded on 125, 100 and 75 MHz Bruker NMR spectrometers. Unless otherwise stated; s (singlet), d (doublet), t (triplet), dd (double doublet), m (multiplet); J in Hertz. ESI mass spectra were recorded using a Quattro II (Micromass) instrument. HRMS spectra were recorded using a mass spectrometer Q-TOF. The purity of all tested compounds characterized by HPLC analysis (Discovery HS C-18 HPLC) system. The HPLC system consisted of a pump (LC-10AT VP with FCV-10AL VP), degasser (DGU-14A) and auto-injector (SIL-HTc, fixed with a 100 µl loop) (Shimadzu, Japan). Eluents monitored at 260 nm with a UV-Vis multiple wavelength detector and chromatograms were integrated using Class-VP (version 6.12 SP5) software (Shimadzu, Japan). Individual compounds with a purity of >95% used for subsequent experiments.

1.1.1. General procedure for the synthesis of compounds 20-23

Purine derivatives (1 mmol), synthesized glycosyl esters (1 mmol) and DBU (1 mmol) refluxed in ethanol/ methanol for 12-16h. After completion of reaction (TLC), the reaction solvent was removed by evaporation under reduced pressure to give a crude mixture. The mixture extracted with DCM and water. The organic layer dried (anhd. Na₂SO₄) and evaporated under reduced pressure to give crude mass. The latter was purified by silica gel (230-400 mesh, Merck) column chromatography using chloroform: methanol (98:2) as eluent to give diastereomeric compounds in 55:45 ratio of respective esters of *C*-nucleoside analogs.

1.1.1.1. Methyl-[3-*O*-benzyl-5,6-dideoxy-5-(6-amino-9H-purin-9-yl)-1,2-*O*isopropylidene]-β-L-ido and α-D-glucoheptofuranuronates (20). It was obtained by the reaction of (1R, 2R, 3S, 4R)-ethyl-(3-O-benzyl-1,2-isopropylidene-1,4pentofuranose-4-yl)-hept-5-enoate **15** (1 g, 2.87 mmol) and adenine **17** (0.39 g, 2.87 mmol) in presence of DBU (0.44 ml, 2.87 mmol) refluxed in methanol (30 ml) as describe above give the mixture diastereomeric compounds.

Major Isomer (20a): White solid (42 % yield); m.p. 88-90 °C. ¹H NMR (400 MHz, CDCl₃): δ 8.28 (s, 1H, Ar-H), 7.67 (s, 1H, Ar-H), 7.35-7.31 (m, 3H, Ar-H), 7.24 (m, 2H, Ar-H), 5.98 (d, *J* = 3.00 Hz, 1H, CH), 5.83 (s, 2H, NH₂), 5.19 (dd, *J*₁ = 7.88 Hz, *J*₂ = 2.56 Hz, 1H, CH), 5.13 (td, *J*₁ = 8.44 Hz, *J*₂ = 2.20 Hz, 1H, CH), 4.58 (d, *J* = 3.00 Hz, 1H, CH), 4.47 (d, *J* = 8.96 Hz, 1H, CH), 4.11 (d, *J* = 8.92 Hz, 1H, CH), 3.55 (m, 1H, CH), 3.53 (s, 3H, CH₃), 3.48 (d, *J* = 2.56 Hz, 1H, CH), 3.16 (dd, *J*₁ = 13.96 Hz, *J*₂ = 2.16 Hz, 1H, CH), 1.53 (s, 3H, CH₃), 1.30 (s, 3H, CH₃); ¹³C NMR (100 MHz, CDCl₃) δ 171.5, 155.7, 152.8, 150.0, 142.4, 136.8, 128.8, 128.4, 128.1, 120.2, 112.5, 105.5, 82.0, 81.5, 78.6, 72.3, 52.5, 51.1, 35.2, 27.1, 26.6; HRMS: Calcd. Accurate mass for (C₂₃H₂₈N₅O₆): 470.2034. Found 470.2061 [M+H]⁺.

Minor Isomer (20b): White solid (34 % yield); m.p. 124-126 °C. ¹H NMR (400 MHz, CDCl3): δ 8.23 (s, 1H, Ar-H), 7.53 (s, 1H, Ar-H), 7.35-7.32 (m, 3H, Ar-H), 7.30 (m, 2H, Ar-H), 5.86 (d, J = 2.92 Hz, 1H, CH), 5.69 (s, 2H, NH₂), 5.14 (dd, $J_I = 7.52$ Hz, $J_2 = 2.48$ Hz, 1H, CH), 5.08 (td, $J_I = 8.20$ Hz, $J_2 = 2.16$ Hz, 1H, CH), 4.73 (d, J = 9.44 Hz, 1H, CH), 4.68 (d, J = 2.96 Hz, 1H, CH), 4.43 (d, J = 9.44 Hz, 1H, CH), 4.02 (d, J = 2.44 Hz, 1H, CH), 3.53 (s, 3H, CH₃), 3.39 ($J_I = 13.48$ Hz, $J_2 = 8.40$ Hz, 1H, CH 1H, CH), 2.36 (dd, $J_I = 13.48$ Hz, $J_2 = 2.24$ Hz, 1H, CH), 1.42 (s, 3H, CH₃), 1.28 (s, 3H, CH₃); ¹³C NMR (100 MHz, CDCl₃) δ 170.5, 155.6, 152.4, 150.1, 142.3, 136.7, 128.9, 128.6, 128.4, 120.6, 112.6, 105.1, 82.1, 80.8, 78.5, 71.9, 53.7, 52.1, 34.1, 27.1, 26.7; HRMS: Calcd. Accurate mass for (C₂₃H₂₈N₅O₆): 470.2034. Found 470.2061 [M+H]⁺.

4.1.1.2. Ethyl-[3-*O*-(2-nitrophenyl)-5,6-dideoxy-5-(6-amino-9H-purin-9-yl)-1,2-*O*isopropylidene]- β -L-ido and α -D-glucoheptofuranuronates (21). It was obtained by the reaction of (1R, 2R, 3S, 4R)-ethyl-(3-O-(2-nitrophenyl)-1,2-isopropylidene-1,4pentofuranose-4-yl)-hept-5-enoate **16** (1 g, 2.64 mmol) and adenine **17** (0.36 g, 2.64 mmol) in presence of DBU (0.40 ml, 2.64 mmol) refluxed in ethanol (30 ml) as describe above give the mixture of diastereomeric compounds.

Major Isomer (21a): White solid (38 % yield); m.p. 116-118 °C. ¹H NMR (400 MHz, CDCl3): δ 8.26 (s, 1H, Ar-H), 7.92 (s, 1H, Ar-H), 7.88 (dd, $J_1 = 6.48$ Hz, $J_2 = 0.96$ Hz, 1H, Ar-H), 7.45 (m, 1H, Ar-H), 7.08 (t, J = 6.2 Hz, 1H, Ar-H), 6.80 (d, J = 6.72 Hz, 1H, Ar-H), 6.02 (d, J = 3.04 Hz, 1H, CH), 5.72 (s, 2H, NH₂), 5.50 (dd, $J_1 = 8.04$ Hz, $J_2 = 2.32$ Hz, 1H, CH), 5.42 (td, $J_1 = 8.68$ Hz, $J_2 = 2.04$ Hz, 1H, CH), 4.54 (d, J = 3.08

Hz, 1H, CH), 4.30, (d, J = 2.32 Hz, 1H, CH), 4.04 (m, 2H, CH), 3.61 (dd, $J_1 = 13.76$ Hz, $J_2 = 8.84$ Hz, 1H, CH), 3.23 (dd, $J_1 = 13.76$ Hz, $J_2 = 2.04$ Hz, 1H, CH), 1.57 (s, 3H, CH₃), 1.30 (s, 3H, CH₃), 1.16 (t, J = 5.68 Hz, 3H, CH₃); ¹³C NMR (100 MHz, CDCl₃) δ 170.4, 155.6, 152.8, 150.0, 149.4, 142.6, 140.5, 134.6, 126.6, 122.0, 120.3, 114.6, 113.0, 105.5, 82.0, 80.5, 77.9, 61.1, 52.6, 35.5, 26.9, 26.6, 14.2; HRMS: Calcd. Accurate mass for (C₂₃H₂₇N₆O₈): 515.1885. Found 515.1877 [M+H]⁺.

Minor Isomer (21b): White solid (28 % yield), m.p. 112-114 °C. ¹H NMR (400 MHz, CDCl3): δ 8.26 (s, 1H, Ar-H), 7.92 (s, 1H, Ar-H), 7.88 (dd, $J_I = 6.48$ Hz, $J_2 = 0.84$ Hz, 1H, Ar-H), 7.62 (m, 1H, Ar-H), 7.24 (d, J = 6.72 Hz, 1H, Ar-H), 7.16 (t, J = 6.16 Hz, 1H, Ar-H), 5.92 (d, J = 2.96 Hz, 1H, CH), 5.81 (s, 2H, NH₂), 5.47 (dd, $J_I = 7.44$ Hz, $J_2 = 2.44$ Hz, 1H, CH), 5.28 (td, $J_I = 8.16$ Hz, $J_2 = 2.56$ Hz, 1H, CH), 4.92 (d, J = 2.44 Hz, 1H, CH), 4.66, (d, J = 3.00 Hz, 1H, CH), 3.98 (m, 2H, CH), 3.60 (dd, $J_I = 13.24$ Hz, $J_2 = 8.44$ Hz, 1H, CH), 2.76 (dd, $J_I = 13.20$ Hz, $J_2 = 2.60$ Hz, 1H, CH), 1.49 (s, 3H, CH₃), 1.28 (s, 3H, CH₃), 1.09 (t, J = 5.68 Hz, 3H, CH₃); ¹³C NMR (100 MHz, CDCl₃) δ 169.4, 155.7, 152.4, 150.0, 149.6, 142.6, 140.6, 134.6, 126.6, 122.3, 120.6, 114.9, 113.1, 105.0, 82.4, 81.3, 78.2, 61.3, 54.0, 34.7, 27.0, 26.7, 14.1; HRMS: Calcd. Accurate mass for (C₂₃H₂₇N₆O₈): 515.1885. Found 515.1876 [M+H]⁺.

1.1.1.3. Ethyl-[3-*O*-benzyl-5,6-dideoxy-5-(6-benzylamino-9H-purin-9-yl)-1,2-*O*-isopropylidene]- β -L-ido and α -D-glucoheptofuranuronates (22). It's obtain by the reaction of (1R, 2R, 3S, 4R)-ethyl-(3-O-benzyl-1,2-isopropylidene-1,4-pentofuranose-4-yl)-hept-5-enoate **15** (1 g, 2.87 mmol) and 6-benzylaminopurine **18** (0.65 g, 2.87 mmol) in presence of DBU (0.44 ml, 2.87 mmol) refluxed in ethanol (30 ml) as describe above give the mixture of diastereomeric compounds.

Major Isomer (22a): White solid (40 % yield); m.p. 136-138 °C. ¹H NMR (400 MHz, CDCl3): δ 8.35 (s, 1H, Ar-H), 7.60 (s, 1H, Ar-H), 7.40 (m, 2H, Ar-H), 7.36-7.29 (m, 6H, Ar-H), 7.23 (m, 2H, Ar-H), 6.17 (s, 1H, NH), 5.97 (d, *J* = 3.72 Hz, 1H, CH), 5.17 (td, *J*₁ = 9.72 Hz, *J*₂ = 3.04 Hz, 1H, CH), 5.14 (dd, *J*₁ = 9.84 Hz, *J*₂ = 2.56 Hz, 1H, CH), 4.86 (s, 2H, CH₂), 4.58, (d, *J* = 3.72 Hz, 1H, CH), 4.47, (d, *J* = 11.20 Hz, 1H, CH), 4.12 (d, *J* = 11.16 Hz, 1H, CH), 1.53 (s, 3H, CH₂), 3.57-3.45 (m, 2H, CH), 3.15 (*J*₁ = 17.36 Hz, *J*₂ = 2.76 Hz, 1H, CH), 1.53 (s, 3H, CH₃), 1.30 (s, 3H, CH₃), 1.09 (t, *J* = 7.16 Hz 3H); ¹³C NMR (100 MHz, CDCl₃) δ 170.8, 154.6, 152.8, 141.5, 138.5, 136.6, 128.7, 128.6, 128.2, 127.8, 127.5, 120.1, 112.3, 105.3, 81.9, 81.3, 78.5, 72.1, 60.7, 52.3, 35.4, 26.9, 26.4, 14.0; HRMS: Calcd. Accurate mass for (C₃₁H₃₆N₅O₆): 574.2660. Found 574.2645 [M+H]⁺.

Minor Isomer (22b): White solid (32 % yield); m.p. 70-72 °C. ¹H NMR (400 MHz, CDCl3): δ 8.30 (s, 1H, Ar-H), 7.76 (s, 1H, Ar-H), 7.39-7.28 (m, 10H, Ar-H), 6.15 (s, 1H, NH), 5.86 (d, J = 3.68 Hz, 1H, CH), 5.15 (dd, $J_I = 9.44$ Hz, $J_2 = 3.16$ Hz, 1H, CH), 5.07 (td, $J_I = 10.36$ Hz, $J_2 = 3.04$ Hz, 1H, CH), 4.83 (s, 2H, CH₂), 4.74, (d, J = 11.80 Hz, 1H, CH), 4.68, (d, J = 3.72 Hz, 1H, CH), 4.44 (d, J = 11.76 Hz, 1H, CH), 4.02 (m, 1H,), 4.01-3.91 (m, 2H,), 3.48 (q, J = ,7.00Hz 1H), 3.37 (dd, $J_I = 16.68$ Hz, $J_2 = 10.52$ Hz, 1H, CH), 2.38 (dd, $J_I = 16.64$ Hz, $J_2 = 2.84$ Hz, 1H, CH), 1.43 (s, 3H, CH₃), 1.29 (s, 3H, CH₃), 1.10 (t, J = 7.12 Hz 3H); ¹³C NMR (100 MHz, CDCl₃) δ 169.8, 154.6, 152.4, 141.4, 138.5, 136.5, 128.7, 128.4, 128.2, 127.8, 127.4, 120.4, 112.4, 104.9, 81.9, 80.6, 78.5, 71.7, 65.8, 60.9, 53.5, 34.3, 26.9, 26.5, 15.3, 14.0; HRMS: Calcd. Accurate mass for (C₃₁H₃₆N₅O₆): 574.2660. Found 574.2642 [M+H]⁺.

1.1.1.4. Ethyl-[3-*O*-benzyl-5,6-dideoxy-5-(6-dodecylamino-9H-purin-9-yl)-1,2-*O*-isopropylidene]- β -L-ido and α -D-glucoheptofuranuronates (23). It's obtain by the reaction of (1R, 2R, 3S, 4R)-ethyl-(3-O-benzyl-1,2-isopropylidene-1,4-pentofuranose-4-yl)-hept-5-enoate **15** (1 g, 2.87 mmol) and 6-dodecylaminopurine **19** (0.87 g, 2.87 mmol) in presence of DBU (0.44 ml, 2.87 mmol) refluxed in ethanol (30 ml) as describe above give the mixture of diastereomeric compounds.

Major Isomer (23a): Colure less oil (48 % yield). ¹H NMR (400 MHz, CDCl3): δ 8.31 (s, 1H, Ar-H), 7.60 (s, 1H, Ar-H), 7.37-7.31 (m, 3H, Ar-H), 7.25-7.23 (m, 2H, Ar-H), 5.97 (d, J = 3.76 Hz, 1H, CH), 5.93 (s, 1H, NH), 5.17 (dd, $J_I = 8.12$ Hz, $J_2 = 3.08$ Hz, 1H, CH), 5.12 (td, $J_I = 10.16$ Hz, $J_2 = 2.60$ Hz, 1H, CH), 4.57 (d, J = 3.76 Hz, 1H, CH), 4.46 (d, J = 11.16 Hz, 1H, CH), 4.12 (d, J = 11.16 Hz, 1H, CH), 4.05-3.90 (m, 2H, CH), 3.62 (s, 2H, CH₂), 3.53 (m, 1H, CH), 3.49 (m, 1H, CH), 3.14 (dd, $J_I = 17.40$ Hz, $J_2 = 2.80$ Hz, 1H, CH), 1.72-1.65 (m, 2H, CH₂), 1.52 (s, 3H, CH₃), 1.46-1.39 (m, 2H), 1.36-1.23 (m, 19H), 1.09 (t, J = 7.16 Hz 3H), 0.87 (t, J = 6.68 Hz 3H); 1³C NMR (100 MHz, CDCl₃) δ 170.8, 154.9, 152.8, 141.2, 136.6, 128.6, 128.2, 127.8, 112.2, 105.3, 81.9, 81.3, 78.5, 72.1, 60.7, 52.2, 35.4, 31.9, 30.9, 29.6, 29.6, 29.6, 29.4, 29.3, 27.0, 26.9, 26.4, 22.7, 14.1, 14.0; HRMS: Calcd. Accurate mass for (C₃₆H₅₄N₅O₆): 652.4069. Found 652.4053 [M+H]⁺.

Minor Isomer (23b): Colure less oil (38 % yield). ¹H NMR (400 MHz, CDCl3): δ 8.28 (s, 1H, Ar-H), 7.77 (s, 1H, Ar-H), 7.37-7.34 (m, 3H, Ar-H), 7.32-7.30 (m, 2H, Ar-H), 5.89 (s, 1H, NH), 5.87 (d, J = 3.68 Hz, 1H, CH), 5.15 (dd, $J_1 = 9.40$ Hz, $J_2 = 3.12$ Hz, 1H, CH), 5.12 (td, $J_1 = 10.36$ Hz, $J_2 = 2.80$ Hz, 1H, CH), 4.75 (d, J = 11.76 Hz, 1H, CH), 4.69 (d, J = 3.75 Hz, 1H, CH), 4.45 (d, J = 11.80 Hz, 1H, CH), 4.05-

4.00 (m, 2H, CH), 4.00-3.94 (m, 1H, CH), 3.61 (s, 2H), 3.50 (s, 1H), 3.38 (dd, $J_I = 16.68$ Hz, $J_2 = 10.52$ Hz, 1H, CH), 2.40 (dd, $J_I = 16.68$ Hz, $J_2 = 2.88$ Hz, 1H, CH), 1.68 (m, 2H), 1.44 (s, 3H, CH₃), 1.30-1.27 (m, 21H), 1.12 (t, J = 7.16 Hz 3H), 0.89 (t, J = 6.68 Hz 3H); ¹³C NMR (100 MHz, CDCl₃) δ 169.8, 154.9, 141.1, 136.5, 128.6, 128.4, 128.2, 112.4, 104.8, 81.9, 80.6, 78.5, 71.7, 60.9, 53.5, 34.3, 31.9, 30.9, 29.6, 29.6, 29.6, 29.4, 29.3, 27.0, 26.9, 26.5, 22.7, 14.1, 14.0; HRMS: Calcd. Accurate mass for (C₃₆H₅₄N₅O₆): 652.4069. Found 652.4051 [M+H]⁺.

1.1.2. General procedure for the synthesis of compounds 24-29

To a magnetically stirred slurry of LiAlH₄ (0.012 g, 0.30 mmol) in anhydrous THF (5.0 ml), a solution of esters of nucleoside analogues (0.1 g, 0.30 mmol) in anhydrous THF (5.0 ml) was added drop-wise at 0 °C under inert atmosphere and stirring continued for 30 min at 0 °C. The reaction mixture was further stirred for about.2.5-3 h at ambient temperature. Excess LiAlH₄ was quenched by adding saturated aqueous sodium sulfate solution and the reaction mixture was filtered. The solid cake was washed with THF and the filtrate concentrated under reduced pressure. The later was extracted with chloroform and water, organic layer was dried (Na₂SO₄) and concentrated under reduced pressure to give a crude mass, which was chromatographed over SiO₂ column using chloroform/ methanol (98:2) as eluent to give the respective hydroxy derivative of nucleoside analogues.

1.1.2.1. 5-(6-Amino-9H-purin-9-yl)-5,6-dideoxy-6-hydroxymethyl-1,2-*O***isopropylidene-3-***O***-benzyl-β-L-idofuranose (24). It was obtain by the reduction of 20a** (0.10 g, 0.30 mmol) with LiAlH₄ (0.012 g, 0.30 mmol) as describe above and give product as white solid in 94% yield. m.p. 80-82 °C. ¹H NMR (400 MHz, CDCl3): δ 8.28 (s, 1H, Ar-H), 7.74 (s, 1H, Ar-H), 7.28-7.26 (m, 3H, Ar-H), 7.12 (m, 2H, Ar-H), 6.01 (d, J = 3.76 Hz, 1H, CH), 5.88 (s, 2H, NH₂), 5.04 (m, 1H, CH), 4.96 (dd, $J_1 =$ 8.64 Hz, $J_2 = 3.20$ Hz, 1H, CH), 4.60 (d, J = 3.76, 1H, CH), 4.45 (d, J = 11.36 Hz, 1H, CH), 4.08 (d, J = 11.36 Hz, 1H, CH), 3.66-3.61 (m, 2H), 3.17 (td, $J_1 = 11.32$ Hz, $J_2 =$ 3.28 Hz, 1H, CH), 2.53-2.45 (m, 1H, CH), 2.24-2.17 (m, 1H, CH), 1.53 (s, 3H, CH₃), 1.32 (s, 3H, CH₃); ¹³C NMR (100 MHz, CDCl₃); 155.5, 152.9, 150.1, 140.3, 136.4, 128.5, 128.2, 128.0, 119.3, 112.1, 105.3, 81.7, 81.4, 80.1, 72.0, 58.1, 51.6, 34.7, 26.9, 26.3; HRMS: Calcd. Accurate mass for (C₂₂H₂₈N₅O₅): 442.2085. Found 442.2074 [M+H]⁺. **1.1.2.2. 5-(6-Amino-9H-purin-9-yl)-5,6-dideoxy-6-hydroxymethyl-1,2-***O***isopropylidene-3-***O***-(2-nitrophenyl)-β-L-idofuranose (25). It was obtain by the reduction of 21a** (0.15 g, 0.30 mmol) with LiAlH₄ (0.012 g, 0.30 mmol) as describe above and give product as white solid in 90% yield. m.p. 116-118 °C. ¹H NMR (400 MHz, CDCl3): δ 8.25 (s, 1H, Ar-H), 7.90 (s, 1H, Ar-H), 7.87 (d, J = 8.12 Hz, 1H, 7.44 (m, 1H, Ar-H), 7.07 (m, 1H, Ar-H), 6.79 (d, J = 8.40 Hz, 1H, Ar-H), 6.04 (d, J = 3.76Hz, 1H, CH), 5.78 (s, 2H, NH₂), 5.44 (dd, $J_1 = 9.40$ Hz, $J_2 = 2.88$ Hz, 1H, CH), 5.20 (td, $J_1 = 9.68$ Hz, $J_2 = 4.28$ Hz, 1H, CH), 4.54 (d, J = 3.84 Hz, 1H, CH), 4.34 (d, J =2.84 Hz, 1H, CH), 3.68 (m, 1H, CH), 3.32 (m, 1H, CH), 2.59-2.45 (m, 2H, CH), 1.58 (s, 3H, CH₃), 1.30 (s, 3H, CH₃); ¹³C NMR (100 MHz, CDCl₃) δ 155.5, 152.7, 149.9, 149.3, 141.7, 140.2, 134.4, 126.4, 121.7, 114.3, 112.6, 105.3, 81.7, 80.7, 78.9, 58.4, 52.8, 33.5, 26.7, 26.4; HRMS: Calcd. Accurate mass for (C₂₁H₂₅N₆O₇): 473.1779. Found 473.1768 [M+H]⁺.

1.1.2.3. 5-(6-benzylamino-9H-purin-9-yl)-5,6-dideoxy-6-hydroxymethyl-1,2-*O***isopropylidene-3-***O***-benzyl-β-L-idofuranose (26). It was obtain by the reduction of 22a** (0.16 g, 0.30 mmol) with LiAlH₄ (0.012 g, 0.30 mmol) as describe above and give product as white solid in 92% yield. m.p. 80-82 °C. ¹H NMR (400 MHz, CDCl3): δ 8.38 (s, 1H, Ar-H), 7.69 (s, 1H, Ar-H), 7.43 (m, 2H, Ar-H), 7.37 (m, 3H, Ar-H), 7.32 (m, 1H, Ar-H), 7.26 (m, 2H, Ar-H), 7.14 (m, 2H, Ar-H), 6.32 (s, 1H, NH), 6.03 (d, J =3.24 Hz, 1H, CH), 5.17 (m, 1H, CH), 5.14 (m, 1H, CH), 4.90 (s, 2H, CH₂), 4.62 (d, J =3.32 Hz, 1H, CH), 4.46 (d, J = 11.36 Hz, 1H, CH), 4.10 (d, J = 11.32 Hz, 1H, CH), 3.67-3.63 (m, 2H, CH₂), 3.17 (m, 1H, CH), 2.51 (m, 1H, CH), 2.17 (m, 1H, CH), 1.55 (s, 3H, CH₃), 1.34 (s, 3H, CH₃); ¹³C NMR (100 MHz, CDCl₃) δ 154.7, 153.0, 139.4, 138.4, 136.4, 128.7, 128.5, 128.1, 128.0, 127.9, 127.6, 112.1, 105.3, 81.7, 81.5, 80.2, 72.0, 58.1, 51.3, 34.9, 26.9, 26.3; HRMS: Calcd. Accurate mass for (C₂₉H₃₄N₅O₅): 532.2554. Found 532.2546 [M+H]⁺.

1.1.2.4. 5-(6-Amino-9H-purin-9-yl)-5,6-dideoxy-1,2-*O***-isopropylidene-3-***O***-benzyl-***a***-D-glucoheptofuranose (27).** It was obtain by the reduction of **20b** (0.10 g, 0.30 mmol) with LiAlH₄ (0.012 g, 0.30 mmol) as describe above and give product as white solid in 92% yield. m.p. 82-84 °C. ¹H NMR (400 MHz, CDCl3): δ 8.24 (s, 1H, Ar-H), 7.87 (s, 1H, Ar-H), 7.35-7.29 (m, 3H, Ar-H), 7.25 (m, 2H, Ar-H), 5.90 (s, 2H, NH₂), 5.88 (d, *J* = 3.72 Hz, 1H, CH), 5.05 (m, 1H, CH), 4.90 (dd, *J*₁ = 7.52 Hz, *J*₂ = 2.48 Hz, 1H, CH), 4.65 (m, 2H, CH), 4.43 (d, *J* = 11.52 Hz, 1H, CH), 4.08 (d, *J* = 3.16 Hz, 1H, CH), 3.55-3.50 (m, 2H, CH), 3.12 (td, *J*₁ = 11.04 Hz, *J*₂ = 3.32 Hz, 1H, CH), 2.14 (m,

1H, CH), 1.93-1.85 (m, 1H, CH), 1.48 (s, 3H, CH₃), 1.31 (s, 3H, CH₃); ¹³C NMR (100 MHz, CDCl₃); 155.5, 152.5, 150.3, 140.8, 136.5, 128.5, 128.3, 128.2, 119.4, 112.1, 104.8, 81.8, 81.5, 79.8, 72.0, 57.5, 52.1, 34.0, 26.9, 26.3; HRMS: Calcd. Accurate mass for ($C_{22}H_{28}N_5O_5$): 442.2085. Found 442.2070 [M+H]⁺.

1.1.2.5. 5-(6-Amino-9H-purin-9-yl)-5,6-dideoxy-6-hydroxymethyl-1,2-*O***isopropylidene-3-***O***-(2-nitrophenyl)-\alpha-D-glucofuranose (28). It was obtain by the reduction of 21b** (0.15 g, 0.30 mmol) with LiAlH₄ (0.012 g, 0.30 mmol) as describe above and give product as white solid in 88% yield. m.p. 134-136 °C. ¹H NMR (400 MHz, CDCl3): δ 8.25 (s, 1H, Ar-H), 7.90-7.87 (m, 2H, Ar-H), 7.60 (m, 1H, Ar-H), 7.23 (d, *J* = 8.36 Hz, 1H, Ar-H), 7.16 (t, *J* = 7.72 Hz, 1H, Ar-H), 5.93 (d, *J* = 3.76 Hz, 1H, CH), 5.78 (s, 2H, NH₂), 5.40 (dd, *J*₁ = 8.92 Hz, *J*₂ = 2.92 Hz, 1H, CH), 5.28 (td, *J*₁ = 10.40 Hz, *J*₂ = 3.48 Hz, 1H, CH), 4.96 (d, *J* = 3.00 Hz, 1H, CH), 4.66 (d, *J* = 3.80 Hz, 1H, CH), 3.56 (m, 1H, CH), 3.27 (m, 1H, CH), 2.50 (m, 1H, CH), 2.03-1.95 (m, 1H, CH), 1.52 (s, 3H, CH₃), 1.43 (s, 3H, CH₃); ¹³C NMR (100 MHz, CDCl₃) δ 155.5, 152.4, 149.7, 141.8, 140.2, 134.4, 126.4, 125.5, 121.9, 114.5, 112.7, 104.8, 82.1, 81.2, 78.8, 57.9, 53.8, 33.0, 30.3, 29.7, 26.8, 26.5; HRMS: Calcd. Accurate mass for (C₂₁H₂₅N₆O₇): 473.1779. Found 473.1767 [M+H]⁺.

1.1.2.6. 5-(6-benzylamino-9H-purin-9-yl)-5,6-dideoxy-6-hydroxymethyl-1,2-*O***-isopropylidene-3***-O***-benzyl-***a***-D-glucofuranose (29).** It was obtain by the reduction of **22b** (0.16 g, 0.30 mmol) with LiAlH₄ (0.012 g, 0.30 mmol) as describe above and give product as white solid in 92% yield. m.p. 88-90 °C. ¹H NMR (400 MHz, CDCl3): δ 8.34 (s, 1H, Ar-H), 7.80 (s, 1H, Ar-H), 7.41-7.27 (m, 10H, Ar-H), 6.44 (s, 1H, NH), 5.90 (d, *J* = 3.48 Hz, 1H, CH), 5.07 (m, 1H, CH), 4.91 (dd, *J*₁ = 8.26 Hz, *J*₂ = 2.84 Hz, 1H, CH), 4.86 (s, 2H, CH₂), 4.67 (m, 2H, CH), 4.45 (d, *J* = 11.52 Hz, 1H, CH), 4.09 (d, *J* = 2.80 Hz, 1H, CH), 3.67 (m, 1H, CH), 3.54 (m, 1H, CH), 3.12 (m, 1H, CH), 2.10 (m, 1H, CH), 1.90 (m, 1H, CH), 1.51 (s, 3H, CH₃), 1.33 (s, 3H, CH₃); ¹³C NMR (100 MHz, CDCl₃) δ 154.7, 152.7, 140.0, 138.5, 136.6, 128.7, 128.5, 128.2, 128.2, 128.0, 127.7, 127.4, 119.5, 112.1, 104.8, 81.8, 81.5, 79.8, 72.0, 57.5, 51.9, 44.6, 34.3, 26.9, 26.4; HRMS: Calcd. Accurate mass for (C₂₉H₃₄N₅O₅): 532.2554. Found 532.2546 [M+H]⁺.

1.1.3. Ethyl-[3-O-(2-aminophenyl)-5,6-dideoxy-5-(6-amino-9H-purin-9-yl)-1,2-O-isopropylidene]-β-L-idoheptofuranuronates (30). To a methanolic solution (15 mL) of ethyl-[3-O-(2-nitrophenyl)-5,6-dideoxy-5-(6-amino-9H-purin-9-yl)-1,2-O-isopropylidene]-β-L-idoheptofurannuronates (21a) (0.10 g, 0.20 mmol), 10% Pd in

charcoal (15 mg) was stirred under a hydrogen atmosphere at room temperature for 2 h. The reaction mixture was filtered through a pad of celite. The pad was washed with CH₂Cl₂ (20 mL). After evaporating the solvent, a white solid was obtained as the product in 98% of yield. m.p. 112-114 °C. ¹H NMR (400 MHz, CDCl3): δ 8.30 (s, 1H, Ar-H), 7.84 (s, 1H, Ar-H), 6.84 (m, 1H, Ar-H), 6.76 (dd, $J_1 = 7.80$ Hz, $J_2 = 1.56$ Hz, 1H, Ar-H), 6.62 (m, 1H, Ar-H), 6.50 (dd, $J_1 = 8.12$ Hz, $J_2 = 0.92$ Hz, 1H, Ar-H), 6.03 (d, J = 3.80 Hz, 1H, CH), 5.71 (s, 2H, NH₂), 5.40-5.32 (m, 2H, CH), 4.58 (d, J = 3.84 Hz, 1H, CH), 4.18 (d, J = 2.32 Hz, 1H, CH), 4.09-3.97 (m, 2H, CH), 3.68 (m, 1H, CH), 3.25 (m, 1H, CH), 1.57 (s, 3H, CH₃), 1.30 (s, 3H, CH₃), 1.13 (t, J = 7.16 Hz, 3H, CH₃); ¹³C NMR (100 MHz, CDCl₃) δ 170.8, 155.4, 152.6, 149.8, 143.5, 142.1, 137.0, 123.0, 120.0, 118.8, 116.1, 113.4, 112.5, 105.4, 82.0, 79.9, 78.2, 60.9, 52.3, 35.3, 26.7, 26.3, 14.0; HRMS: Calcd. Accurate mass for (C₂₃H₂₉N₆O₆): 485.2143. Found 485.2167 [M+H]⁺.

1.1.4. 5-(6-amino-9H-purin-9-yl)-5,6-dideoxy-1,2-O-isopropylidene-3-O-(2aminophenyl)-β-L-idoheptofuranuronic acid (31). To the magnetically stirred solution of the ethyl-[3-O-(2-aminophenyl)-5,6-dideoxy-5-(6-amino-9H-purin-9-yl)-1,2-O-isopropylidene]- β -L-idoheptofuranuronates (30) (0.10 g, 0.20 mmol) in aq. EtOH (50%, 15 ml), Et₃N (0.60 ml) was added and the reaction were stirred for 36 h. Solvent evaporated under reduced pressure with an azeotrop of EtOH and C₆H₅CH₃ to give a residual mass which was subjected to column chromatography over SiO₂ using CHCl₃/ MeOH (9:1) as eluent to give title compound (43) as white solid in 88% yield. m.p. 110-112 °C. ¹H NMR (400 MHz, DMSO) δ 8.10 (s, 1H, Ar-H), 7.94 (s, 1H, Ar-H), 7.17 (s, 2H, NH₂), 6.69 (m, 2H, Ar-H), 6.64 (m, 2H, Ar-H), 6.06 (d, J = 3.84 Hz, 1H, Ar-H), 5.39 (td, $J_1 = 10.56$ Hz, $J_2 = 3.28$ Hz, 1H, CH), 5.11 (dd, $J_1 = 10.04$ Hz, J_2 = 3.08 Hz, 1H, CH), 4.55 (d, J = 3.88 Hz, 1H, CH), 4.18 (d, J = 3.24 Hz, 1H, CH), 3.47 (dd, $J_1 = 16.48$ Hz, $J_2 = 11.04$ Hz, 1H, CH), 3.01 (dd, $J_1 = 16.48$ Hz, $J_2 = 3.12$ Hz, 1H, CH), 1.47 (s, 3H, CH₃), 1.25 (s, 3H, CH₃); 13 C NMR (100 MHz, DMSO) δ 171.8, 156.5, 152.7, 149.7, 143.6, 141.6, 138.9, 122.5, 119.4, 116.8, 115.5, 112.9, 111.9, 105.3, 82.1, 79.6, 78.9, 51.5, 36.2, 27.1, 26.5; HRMS: Calcd. Accurate mass for $(C_{21}H_{25}N_6O_6)$: 457.1830. Found 457.1826 $[M+H]^+$.

1.1.5. 1-(4-(6-amino-9H-purin-9-yl)phenyl)ethan-1-one (33). It was obtained by the reaction of 4-fluoro acetophenone 32 (0.5 ml, 3.04 mmol) with adenine (3.04 mmol.) by K_2CO_3 (1 gm, 7.23 mmol) in DMSO at 120-140 °C temperature. The resulted mixture was stirred with heat till the completion of reaction (TLC). After the

completion of reaction, the workup was done with ethyl acetate and water and then the organic layer was separated, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure The latter was purified by silica gel (60-120 mesh) column chromatography using ethyl acetate: hexane (1:1) as eluent give the product in 62% yield as white solid. m.p. 288-290 °C. ¹H NMR (400 MHz, CDCl3): δ 8.74 (s, 1H, Ar-H), 8.25 (s, 1H, Ar-H), 8.16 (s, 4H, Ar-H), 7.45 (s, 2H, NH₂), 2.64 (s, 3H, CH₃); ¹³C NMR (100 MHz, CDCl₃) δ 197.6, 156.9, 153.8, 149.6, 139.8, 139.4, 135.6, 130.1, 122.6, 119.9, 27.3; HRMS: Calcd. Accurate mass for (C₁₃H₁₂N₅O): 254.1036. Found 254.1044 [M+H]⁺.

1.1.6. 1-(4-(6-amino-9H-purin-9-yl)phenyl)ethan-1-ol (34). It was obtained by the reduction of keto product **33** (100 mg, 0.039 mmol) by NaBH₄ (47 mg, 0.12 mmol) in methanol at room temperature. The resulted mixture was stirred till the completion of reaction (TLC). After the completion of reaction, the workup was done with ethyl acetate and water then the organic layer was separated, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to give product 46 as a creamy solid in 100% yield, mp 258-260 °C; IR (v_{max}, cm⁻¹): 3583, 3019, 1543, 1518, 1407, 1353, 1215, 1064, 823, 755; ¹H NMR (400 MHz, CDCl3): δ 8.55 (s, 1H, Ar-H), 8.20 (s, 1H, Ar-H), 7.81 (d, *J* = 8.32 Hz, 2H, Ar-H), 7.54 (d, *J* = 8.32 Hz, 2H, Ar-H), 7.37 (s, 2H, NH₂), 5.29 (d, *J* = 4.12 Hz, 1H, O-H), 4.81 (m, 1H, CH), 1.37 (d, *J* = 6.40 Hz, 3H, CH₃); ¹³C NMR (100 MHz, CDCl₃) δ 156.8, 153.6, 149.7, 147.2, 140.1, 134.0, 126.7, 123.2, 119.7, 68.1, 26.4; HRMS: Calcd. Accurate mass for (C₁₃H₁₄N₅O): 256.1193. Found 256.1199 [M+H]⁺.

1.1.7. Ethyl-3-(6-amino-9H-purin-9-yl)propanoate (36). It was obtained by the refluxing adenine (1 equiv.) and ethylacrylate (3 equiv.) with sodium ethoxide (1 equiv.) in absolute ethanol (10 ml) for 12h, resulting solution was cooled afford white solid. The solid reslurried in cold ethanol (5 ml), filtered and dried to afford pure solid in 98% of yield. m.p. 178-180 °C. ¹H NMR (400 MHz, CDCl3): δ 8.14 (s, 1H, Ar-H), 8.10 (s, 1H, Ar-H), 7.20 (s, 2H, NH₂), 4.38 (t, *J* = 6.80 Hz, 2H, CH₂), 4.03 (q, *J* = 7.12 Hz, 2H, CH₂), 2.94 (t, *J* = 6.80 Hz, 2H, CH₂); 1.12 (t, *J* = 7.12 Hz, 3H, CH₃); ¹³C NMR (100 MHz, CDCl₃) δ 171.0, 156.4, 152.9, 149.9, 141.4, 119.2, 60.7, 39.5, 34.1, 14.4; HRMS: Calcd. Accurate mass for (C₁₀H₁₄N₅O₂): 236.1142. Found 236.1140 [M+H]⁺.

1.2. Biology

1.2.1. In Vitro Cultivation of P. falciparum and screening

The CQ sensitive (3D7) and resistant (K1) strains of P. falciparum were cultured in vitro as per Trager and Jensen (1976) method with some modifications.⁵² Cultures were maintained in fresh human erythrocytes at 5% hematocrit in complete medium. RPMI-1640 (HEPES modified) medium (Sigma) supplemented with 0.5% AlbuMaxII, 0.2% glucose, 0.2% sodium bicarbonate and 15 µM hypoxanthine and incubated at 37 °C in CO₂ incubator. Parasite growth rate and stage was determined by the test of Giemsa's stained thin smears of the RBCs. All the above mentioned final compounds were tested over a concentration range of 5 µM to 78 nM. P. falciparum drug susceptibility test was carried out by determining fifty percent inhibitory concentration (IC₅₀) according to the method of Johnson *et al.* (2007) with some modifications.⁵³ Briefly, two fold serial dilutions of compounds and chloroquine were prepared in 96 well plates and then 50 µL asynchronous cultures of infected erythrocytes with 0.8-1% parasitaemia and 1% haematocrit was added to each well (100 µL-final volume). Eight wells were treated as positive control (without drug) and 4 wells as negative control (without parasite and drug). These plates were incubated in CO₂ incubator maintained at 37 °C for 72 h. Then 100 µL lytic buffer containing SYBR Green 1x final concentration was added to each well and incubated in 37 °C CO₂ incubator for 2 h. Plates were read under fluorescence reader at Ex. 485 nm, Em. 535 nm. Fifty percent inhibitory concentration (IC₅₀) was determined by quantifying DNA in treated and control cultures of parasites in human erythrocytes according to the SYBR Green I (Invitrogen) fluorescence based method.

1.2.2. Cytotoxicity Assay

Cytotoxicity of compounds was determined according to O'Brien *et. al.* (2000) method with few modifications.⁵⁴ The monkey kidney cell line (VERO) was maintained *in vitro* in MEM medium (Sigma) supplied with 15% fetal bovine serum (FBS) and 5% CO₂ at 37 °C. An appropriate serial drug dilution was prepared in culture plates and the cells were exposed to the concentrations of particular compounds for three days, 10% resazurin, a cell viability marker, was added and read under fluorescent reader at excitation of 530 \pm 25 nm and emission of 590 \pm 25 nm wavelength for calculation of the median cytotoxic concentration (CC₅₀).

2. Scan NMR Spectra of Selected Compounds

¹H NMR of compound 20a



¹³C NMR of compound 20a



COSY spectrum of compound 20a



NOESY spectrum of compound 20a



HSQC spectrum of compound 20a







HRMS spectrum of compound 20a



¹H NMR of compound 20b



¹³C NMR of compound 20b



COSY spectrum of compound 20b



NOESY spectrum of compound 20b



HSQC spectrum of compound 20b



HMBC spectrum of compound 20b



HRMS spectrum of compound 20b





¹³C NMR of compound 21a



HRMS of compound 21a



¹H NMR of compound 21b



¹³C NMR of compound 21b



HRMS of compound 21b



¹H NMR of compound 22a



¹³C NMR of compound 22a



HRMS of compound 22a



¹H NMR of compound 22b



¹³C NMR of compound 22b



HRMS of compound 22b





¹³C NMR of compound 23a



HRMS of compound 23a



¹H NMR of compound 23b



¹³C NMR of compound 23b



HRMS of compound 23b



¹H NMR of compound 24



¹³C NMR of compound 24



HRMS of compound 24



¹H NMR of compound 25



¹³C NMR of compound 25







¹³C NMR of compound 26



HRMS of compound 26



¹H NMR of compound 27









¹³C NMR of compound 28



HRMS of compound 28



¹HNMR of compound 29







¹H NMR of compound 30



¹³C NMR of compound 30



HRMS of compound 30



¹H NMR of compound 31



¹³C NMR of compound 31

















¹H NMR of compound 36



¹³C NMR of compound 36

