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Synthesis of novel purin-6-yl conjugates with heterocyclic amines linked *via* 6-aminohexanoyl fragment

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Experimental

(*RS*)-7,8-Difluoro-3-methyl-3,4-dihydro-2*H*-[1,4]benzoxazine (**2**),[S1] 1,2,3,4-tetrahydroquinoline (**7**),[S2] (3*S*)-3-methyl-3,4-dihydro-2*H*-[1,4]benzoxazine ((*S*)-**1**),[S3] (3*R*)- 3-methyl-3,4-dihydro-2*H*-[1,4]benzoxazine ((*R*)-**1**),[S4] (3*S*)-7,8-difluoro-3-methyl-3,4-dihydro-2*H*-[1,4]benzoxazine ((*S*)-**2**),[S5] (3*R*)-7,8-difluoro-3-methyl-3,4-dihydro-2*H*-[1,4]benzoxazine ((*R*)-**2**),[S6] (3*S*)-3-methyl-3,4-dihydro -2*H*-[1,4]benzothiazine ((*S*)-**3**),[S7] (2*S*)-2-methyl-1,2,3,4-tetrahydroquinoline ((*S*)-**4**),[S3] (2*R*)-2-methyl-1,2,3,4-tetrahydroquinoline ((*R*)-**4**),[S4] (2*S*)-6-fluoro-2-methyl-1,2,3,4-tetrahydroquinoline ((*S*)-**5**),[S8] (2*R*,2'*S*)-6-fluoro-2-methyl-1-(*N*-tosylprolyl)-1,2,3,4-tetrahydro-quinoline,[S6] 2-acetamido-6-chloropurine (**2b**),[S9] 6-phthalimidohexanoyl chloride,[S10] and N-(6-purinyl)-aminohexanoic acid[S11] (**29**) were obtained according to literature procedures. Other reagents are commercially available.

The solvents were purified according to traditional methods and were used freshly distilled. Melting points were obtained on a SMP3 apparatus (Barloworld Scientific, UK). Optical rotations were measured on a Perkin Elmer 341 polarimeter. The ^{1}H, ^{19}F, and ^{13}C NMR spectra were recorded on Bruker DRX-400 (400, 376, and 100 MHz, respectively) or Bruker Avance 500 (500, 470, and 125 MHz, respectively) spectrometers with TMS and hexafluorobenzene as internal references. Microanalyses were performed using Perkin Elmer 2400 II analyzer. Analytical TLC was performed using Sorbfil plates (Imid, Russia). Flash-column chromatography was performed using Silica gel 40 (230–400 mesh) (Alfa Aesar, UK). Analytical HPLC of compounds (*R*)-**5**, **10-13** was performed on a Knauer Smartline-1100 instrument using a Chiralcel OD-H column (250×4.6 mm, 5 μm) (compounds **5**, **10**, **12**, **13**) or a Chiralpak AD column (250×4.6 mm, 5 μm) (compound **11**), detection at 220 nm, 1 mL/min flow rate. Analytical HPLC of compounds **9**, **14-18, 19, 21-23** was performed on an Agilent 1100 instrument with a diode array detector using a (*S*,*S*)-WHELK-O 1 column

(250×4.6 mm, 5 μm), detection at 254 nm, flow rate 0.8 mL/min. Analytical HPLC of compounds (*R*)-**20** and (*S*)-**20** was performed on an Agilent 1200 instrument using a Kromasil Cellucoat column (150×4.6 mm, 5 μm), detection at 215 nm, 0.8 mL/min flow rate. The HRMS spectra of compounds (*S*)-**9**, (*R*)-**9**, **14**, (*S*)-**16**, (*S*)-**18**, **19-21, 24-28** and **30** were registered on a Bruker maXis Impact HD instrument operating in positive ion mode with ESI probe installed at N_2 flow rate 4 L/min, nebulizer pressure 0.4 bar. The probe voltage was set to 4.5 kV. The HRMS spectra of compounds **22** and **23** were registered on a 1200 Infinity (Agilent Technologies) instrument using 6540 Accurate-Mass Q-TOF (Agilent Technologies) detector operating in positive ion mode with ESI probe installed at N_2 flow rate 10 L/min, nebulizer pressure 40 psi. The probe voltage was set to 3.5 kV.

*(2R)-6-Fluoro-2-methyl-1,2,3,4-tetrahydroquinoline [(R)-***5***]:* A solution of (2*R*,2'*S*)-6-fluoro-2-methyl-1-(*N*-tosylprolyl)-1,2,3,4-tetrahydroquinoline (2.34 g, 6.02 mmol) in a mixture of AcOH (17 mL) and concentrated HCl (17 mL) was heated at 95–100 °C for 28 h, then concentrated under reduced pressure to a half-volume and poured into water (130 mL). The solution was neutralized with Na_2CO_3 and extracted with benzene (3×20 mL). Organic layers were washed with saturated aqueous NaCl (2×20 mL), dried over $MgSO_4$, and evaporated to dryness. Purification by flash column chromatography (SiO_2, benzene as an eluent) gave amine (*R*)-**5** (0.54 g, 54%) as a yellowish solid, mp 42–43 °C. $[\alpha]_D^{20}$ +90.0 (*c* 0.9, $CHCl_3$), *ee* 99%. (Chiralcel OD-H, *n*-hexane–*i*PrOH–MeOH 100:1:1): τ 7.7 min. ^{1}H, ^{13}C and ^{19}F NMR spectra were identical to those published for racemic amine **5**.[S8] Found (%): C 72.65; H 7.27; F 11.28; N 8.56. Calc. for $C_{10}H_{12}FN$ (%): C 72.70; H 7.32; F 11.50; N 8.48.

Acylation of amines 1-6 with 6-phthalimidohexanoyl chloride. General procedure. A solution of 6-phthalimidohexanoyl chloride (1.96 g, 7.00 mmol) in CH_2Cl_2 (35 ml) was added to a solution of the corresponding amine (7.00 mmol) and *N*,*N*-diethylaniline (1.04 g, 7.00 mmol) in CH_2Cl_2 (35 ml). The reaction mixture was stirred at room temperature for 24 h, and then washed with 4N HCl (2×50 ml), saturated aqueous NaCl (4×30 ml), 5% aqueous $NaHCO_3$ (2×30 ml) and water (2×30 ml). Organic layer was dried ($MgSO_4$) and evaporated to dryness. The residue was purified by flash column chromatography.

*(3R)-3-Methyl-4-(6-phthalimidohexanoyl)-3,4-dihydro-2H-[1,4]benzoxazine [(R)-***9***]:* yield 2.44 g (89%), colorless semisolid, $[\alpha]_D^{20}$ −93.6 (*c* 1.0, $CHCl_3$), *ee* >99%, HPLC ((*S*,*S*)-WHELK-O 1, MeOH): τ 14.1 min. ^{1}H NMR (400 MHz, DMSO-d_6, 25 °C) δ: 1.08 (d, J = 5.7 Hz, 3 H, Me), 1.25–1.35 (m, 2 H, hexanoyl 2×H-4), 1.52–1.68 (m, 4 H, hexanoyl 2×H-3 and 2×H-5), 2.45 (dt, J = 15.9, 7.9 Hz, 1 H, hexanoyl H-2B), 2.65 (dt, J = 15.9, 7.5 Hz, 1 H, hexanoyl H-2A), 3.58 (t, J = 7.0 Hz, 2 H, hexanoyl 2×H-6), 4.06 (m, 1 H, H-2B), 4.19 (dd, J = 10.9, 1.1 Hz, 1 H, H-2A), 4.35–4.95 (m, 1 H, H-3), 6.82–6.90 (m, 2 H, H-7 and H-8), 6.98–

7.06 (m, 1 H, H-6), 7.20–7.80 (m, 1 H, H-5), 7.81–7.90 (m, 4 H, Phth). ^{13}C NMR (125 MHz, DMSO-d_6, 25 °C) δ: 15.19, 24.43, 25.84, 27.76, 33.43, 37.25, 44.78, 69.32, 116.30, 119.92, 122.92 (2 C), 123.75, 124.70, 124.89, 131.55 (2 C), 134.3 (2 C), 145.31, 167.88 (2 C), 170.58. HRMS, m/z: 393.1812 $[M+H]^+$, (calc. for $C_{23}H_{25}N_2O_4$, m/z: 393.1814).

*(3S)-3-Methyl-4-(6-phthalimidohexanoyl)-3,4-dihydro-2H-[1,4]benzoxazine [(S)-***9***]:* yield 2.30 g (84%), colorless semisolid, $[\alpha]_D^{20}$ +97.0 (*c* 1.0, $CHCl_3$), *ee* >99%, HPLC ((*S*,*S*)-WHELK-O 1, MeOH): τ 10.0 min. NMR spectra are identical to those of (*R*)-enantiomer *(R)*-**9**. Found (%): C 70.19; H 6.12; N 7.07. Calc. for $C_{23}H_{24}N_2O_4$ (%) C 70.39; H 6.16; N 7.14.

*(3R)-7,8-Difluoro-3-methyl-4-(6-phthalimidohexanoyl)-3,4-dihydro-2H-[1,4]benzoxazine [(R)-***10***]:* yield 2.31 g (77%), colorless semisolid, $[\alpha]_D^{20}$ −68.2 (*c* 1.0, $CHCl_3$), *ee* >99%, HPLC (Chiralcel OD-H, *n*-hexane–*i*PrOH 5:1): τ 22.0 min. ^{1}H NMR (400 MHz, DMSO-d_6, 100 °C) δ: 1.11 (d, *J* = 6.8 Hz, 3 H, Me), 1.30–1.38 (m, 2 H, hexanoyl 2×H-4), 1.59–1.68 (m, 4 H, hexanoyl 2×H-3 and 2×H-5), 2.42–2.50 (m, 1 H, hexanoyl H-2B, overlapped by DMSO signal), 2.55–2.63 (m, 1 H, hexanoyl H-2A), 3.58 (t, *J* = 7.0 Hz, 2 H, hexanoyl 2×H-6), 4.12 (dd, *J* = 11.0, 2.8 Hz, 1 H, H-2B), 4.31 (dd, *J* = 11.0, 1.5 Hz, 1 H, H-2A), 4.72 (qdd, *J* = 6.8, 2.8, 1.5 Hz, 1 H, H-3), 6.78-6.85 (m, 1 H, H-6), 7.53 (ddd, *J* = 9.3, 5.4, 2.5 Hz, 1 H, H-5), 7.78–7.83 (m, 4 H, Phth). ^{19}F NMR (376 MHz, DMSO-d_6, 100 °C) δ: 1.99 (ddd, *J* = 20.9, 8.2, 2.5 Hz, 1 F, F-8), 20.08 (ddd, *J* = 20.9, 10.1, 5.4 Hz, 1 F, F-7). ^{13}C NMR (125 MHz, DMSO-d_6, 100 °C) δ: 15.07, 24.20, 25.74, 27.68, 33.23, 37.22, 44.80, 69.80, 106.72 (d, *J* = 17.8 Hz), 119.20 (m), 121.74, 122.89, 131.52, 134.27, 135.65 (dd, *J* 9.8, 2.7 Hz), 138.88 (dd, *J* = 243.3, 15.4 Hz), 146.44 (dm, *J* = 241.8 Hz), 167.85, 170.82. Found (%): C 64.54; H 4.99; F 8.82; N 6.28. Calc. for $C_{23}H_{22}F_2N_2O_4$ (%) C 64.48; H 5.18; F 8.87; N 6.54.

*(3S)-7,8-Difluoro-3-methyl-4-(6-phthalimidohexanoyl)-3,4-dihydro-2H-[1,4]benzoxazine [(S)-***10***]:* yield 2.04 g (68%), colorless semisolid, $[\alpha]_D^{20}$ +67.7 (*c* 0.9, $CHCl_3$), *ee* >99%. HPLC (Chiralcel OD-H, *n*-hexane–*i*PrOH 5:1): τ 28.5 min. NMR spectra are identical to those of (*R*)-enantiomer *(R)*-**10**. Found (%): C 64.34; H 5.44; F 8.52; N 6.43. Calc. for $C_{23}H_{22}F_2N_2O_4$ (%): C 64.48; H 5.18; F 8.87; N 6.54.

*(3S)-3-Methyl-4-(6-phthalimidohexanoyl)-3,4-dihydro-2H-[1,4]benzothiazine [(S)-***11***]:* yield 2.86 g (93%), yellowish oil, $[\alpha]_D^{20}$ +104 (*c* 1.4, $CHCl_3$), *ee* 99%, HPLC (Chiralpak AD, *n*-hexane–*i*PrOH 5:1): τ (*R*)-**11** 16.8 min, τ (S)-**11** 19.5 min. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.06 (d, *J* = 6.8 Hz, 3 H, Me), 1.23–1.30 (m, 2 H, hexanoyl 2×H-4), 1.54–1.66 (m, 4 H, hexanoyl 2×H-3 and 2×H-5), 2.24 (dt, *J* = 15.0, 7.5 Hz, 1 H, hexanoyl H-2B), 2.41 (ddd, *J* = 15.0, 8.9, 6.1 Hz, 1 H, hexanoyl H-2A), 2.73 (dd, *J* = 12.2, 4.3 Hz, 1 H, H-2B), 3.37 (dd, *J* = 12.2, 6.0 Hz, 1 H, H-2A), 3.63 (t, *J* = 7.2 Hz, 2 H, hexanoyl 2×H-6), 5.38 (br. s, 1 H, H-3),

7.05–7.15 (m, 3 H, H-6, H-7 and H-8), 7.25–7.27 (m, 1 H, H-5, overlapped by $CHCl_3$ signal), 7.68–7.72 (m, 2 H, Phth), 7.81–7.85 (m, 2 H, Phth) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ = 17.67, 25.19, 26.41, 28.31, 34.33, 35.06, 37.80, 45.27, 123.12, 125.09, 126.45, 127.66, 128.16, 131.33, 132.17, 133.79, 135.35, 168.34, 172.30 ppm. $C_{23}H_{24}N_2O_3S$ (M 408.51): calcd. C 67.62, H 5.92, N 6.86, S 7.85; found: C 67.62, H 5.92, N 6.93, S 7.69.

*(2R)-2-Methyl-1-(6-phthalimidohexanoyl)-1,2,3,4-tetrahydroquinoline [(R)-***12***]:* yield 2.46 g (90%), colorless oil, $[\alpha]_D^{20}$ −192 (*c* 1.1, $CHCl_3$), *ee* 97%, HPLC (Chiralcel OD-H, *n*-hexane–*i*PrOH–MeOH 20:0.6:0.4): τ 30.6 min. ^{1}H NMR (500 MHz, DMSO-d_6, 25 °C) δ: 0.99 (d, *J* = 6.5 Hz, 3 H, Me), 1.13–1.26 (m, 3 H, H-3B and hexanoyl 2×H-4), 1.46–1.55 (m, 4 H, hexanoyl 2×H-3 and 2×H-5), 2.19–2.27 (m, 2 H, H-3A and hexanoyl H-2B), 2.35–2.50 (m, 2 H, H-4B and hexanoyl H-2A), 2.58 (ddd, *J* = 14.8, 5.0, 5.0 Hz, 1 H, H-4A), 3.51 (t, *J* = 7.0 Hz, 2 H, hexanoyl 2×H-6), 4.62 (m, 1 H, H-2), 7.09–7.12 (m, 1 H, H-6), 7.17–7.20 (m, 2 H, H-5 and H-7), 7.22–7.27 (m, 1 H, H-8), 7.82–7.87 (m, 4 H, Phth). ^{13}C NMR (125 MHz, DMSO-d_6, 100 °C) δ: 20.02, 24.66, 25.20, 25,73, 27.61, 32.01, 33.43, 37.18, 47.54, 122.88, 125.09, 125.82, 126.02, 127.30, 128.22, 131.51, 134.27, 134.72 (br. s), 137.05, 167.81, 171.04. Found (%): C 73.82; H 6.84; N 7.04. Calc. for $C_{24}H_{26}N_2O_3$ (%): C 73.82; H 6.71; N 7.17.

*(2S)-2-Methyl-1-(6-phthalimidohexanoyl)-1,2,3,4-tetrahydroquinoline [(S)-***12***]:* yield 2.19 g (80%), colorless oil, $[\alpha]_D^{20}$ +201 (*c* 1.3, $CHCl_3$), *ee* >99%, HPLC (Chiralcel OD-H, *n*-hexane–*i*PrOH–MeOH 20:0.6:0.4): τ 28.2 min. NMR spectra are identical to those of (*R*)-enantiomer (*R*)-**12**. Found (%): C 73.73; H 6.58; N 6.81. Calc. for $C_{24}H_{26}N_2O_3$ (%): C 73.82; H 6.71; N 7.17.

*(2R)-6-Fluoro-2-methyl-1-(6-phthalimidohexanoyl)-1,2,3,4-tetrahydroquinoline [(R)-***13***]:* yield 2.55 g (89%), colorless oil, $[\alpha]_D^{20}$ −172 (*c* 0.8, $CHCl_3$), *ee* 99%, HPLC (Chiralcel OD-H, *n*-hexane–*i*PrOH–MeOH 10:0.8:0.2): τ 21.8 min. ^{1}H NMR (500 MHz, DMSO-d_6, 25 °C) δ: 0.98 (d, *J* = 6.5 Hz, 3 H, Me), 1.13–1.22 (m, 3 H, H-3B and hexanoyl 2×H-4), 1.45–1.54 (m, 4 H, hexanoyl 2×H-3 and 2×H-5), 2.15–2.27 (m, 2 H, H-3A and hexanoyl H-2B), 2.35–2.50 (m, 2 H, H-4B and hexanoyl H-2A), 2.56–2.63 (m, 1 H, H-4A), 3.51 (t, *J* = 7.0 Hz, 2 H, hexanoyl 2×H-6), 4.61 (m, 1 H, H-2), 7.00 (m, 1 H, H-7), 7.07 (m, 1 H, H-5), 7.30 (br. s, 1 H, H-8), 7.85 (m, 4 H, Phth). ^{19}F NMR (376 MHz, DMSO-d_6, 25 °C) δ: 45.43 (br. s, F-6). ^{13}C NMR (125 MHz, DMSO-d_6, 100 °C) δ: 19.88, 24.56, 25.23, 25.72, 27.62, 31.52, 33.31, 37.17, 47.48, 95.34, 112.60 (d, *J* = 22.2 Hz), 113.88 (d, *J* = 22.4 Hz), 122.88, 127.56 (d, *J* = 8.5 Hz), 131.51, 133.23, 134.26, 159.18 (d, *J* = 243.0 Hz), 167.80, 170.99. Found (%): C 70.40; H 6.13; F 4.28; N 6.61. Calc. for $C_{24}H_{25}FN_2O_3$ (%): C 70.57; H 6.17; F 4.65; N 6.86.

*(2S)-6-Fluoro-2-methyl-1-(6-phthalimidohexanoyl)-1,2,3,4-tetrahydroquinoline [(S)-***13***]:* yield 2.20 g (77%), colorless oil, $[\alpha]_D^{20}$ +171 (*c* 1.0, $CHCl_3$), *ee* >99%, HPLC (Chiralcel OD-H, *n*-hexane–*i*PrOH–MeOH 10:0.8:0.2): τ 19.6 min. NMR spectra are identical to those of (*R*)-enantiomer (*R*)-**13**. Found (%): C 70.45; H 6.25; F 4.55; N 6.84. Calc. for $C_{24}H_{25}FN_2O_3$ (%): C 70.57; H 6.17; F 4.65; N 6.86.

*(RS)-2-Methyl-1-(6-phthalimidohexanoyl)indoline (***24***):* yield 2.29 g (87%), brown oil. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 1.17 (d, *J* = 5.5 Hz, 3 H, Me), 1.32-1.38 (m, 2 H, hexanoyl 2×H-4), 1.61-1.67 (m, 4 H, hexanoyl 2×H-3 and 2×H-5), 2.38-2.43 (m, 1 H, hexanoyl H-2A), 2.55-2.64 (m, 2 H, hexanoyl H-2B and H-3A), 3.31-3.36 (m, 1 H, H-3B, overlapped by H_2O signal), 3.59 (t, *J* = 7.1 Hz, 2 H, hexanoyl 2×H-6,), 4.60 (br. s, 1 H, H-2), 6.99 (ddd, *J* = 7.5, 7.5, 0.6 Hz, 1 H, H-5), 7.14 (dd, *J* = 7.5, 7.5 Hz, 1 H, H-6), 7.24 (d, *J* = 7.2 Hz, 1 H, H-4), 7.82-7.88 (m, 4 H, Phth), 8.00 (br. d, *J* = 6.5 Hz, 1 H, H-7). ^{13}C NMR (125 MHz, DMSO-d_6) δ: 21.48, 24.15, 25.89, 27.82, 33.74, 35.76, 37.29, 54.79, 116.85, 122.94 (2 C), 123.25, 125.07, 126.86, 130.66 (2 C), 131.57, 134.31 (2 C), 141.53, 167.91 (2 C), 170.30. HRMS, m/z: 377.1864 $[M+H]^+$, (calc. for $C_{23}H_{25}N_2O_3$, m/z: 377.1865).

*1-(6-Phthalimidohexanoyl)-1,2,3,4-tetrahydroquinoline (***25***):* yield 1.87 g (71%), yellow solid, mp 99 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.23 (br. s, 2 H, hexanoyl 2×H-4), 1.50-1.58 (m, 4 H, hexanoyl 2×H-3 and 2×H-5), 1.79-1.86 (m, 2 H H-3), 2.43-2.47 (m, 2 H, hexanoyl H-2), 2.66 (dd, *J* = 6.6, 6.5, 2 H, H-4), 3.52-3.55 (m, 2 H, hexanoyl 2×H-6,), 3.64 (dd, *J* = 6.4, 6.3 Hz, 1 H, H-2), 7.04-7.08 (m, 1 H, H-6), 7.12-7.17 (m, 2 H, H-5 and H-7), 7.38 (br. s, 1 H, H-8), 7.82-7.88 (m, 4 H, Phth). HRMS, m/z: 377.1860 $[M+H]^+$, (calc. for $C_{23}H_{25}N_2O_3$, m/z: 377.1865).

Synthesis of 6-(2-acetamidopurin-6-ylamino)hexanoyl amines 14-18. General procedure. Aqueous N_2H_4 (64%, 0.44 ml, 9.00 mmol) was added to a solution of the corresponding amide **9–13** (5.00 mmol) in EtOH (30 ml). The mixture was refluxed for 80 min, and then evaporated to dryness. 2 N HCl (30 ml) was added to the residue, the precipitate was filtered off; the filtrate was alkalized with NaOH to pH 12 and extracted with diethyl ether (3×30 ml). Organic layers were dried (NaOH) and evaporated to dryness. The residue was re-dissolved in DMA (4.8 ml). 2-Acetamido-6-chloropurine (0.402 g, 1.9 mmol) and TEA (0.53 ml, 3.8 mmol) were added to the resulting solution. The reaction mixture was heated at 100 °C for 20 h, poured into water (50 ml), and kept at +5 °C for 16 h; the precipitate was separated by centrifuging, dried under reduced pressure and recrystallized from EtOH. The additional amount of the product was isolated from the mother liquor by flash column chromatography.

(3R)-4-[6-(2-Acetamidopurin-6-ylamino)hexanoyl]-3-methyl-3,4-dihydro-2H-

*[1,4]benzoxazine [(R)-***14***]:* yield 0.415 g (50%), colorless solid, mp 203–205 °C, $[\alpha]_D^{20}$ −55.1 (*c* 1.0, DMF), *ee* >99%, HPLC ((*S*,*S*)-WHELK-O 1, MeOH–H_2O 80:20): τ 20.7 min. ^{1}H NMR (400 MHz, DMSO-d_6, 100 °C) δ: 1.08 (d, *J* = 6.8 Hz, 3 H, Me), 1.35–1.45 (m, 2 H, hexanoyl 2×H-4), 1.59–1.72 (m, 4 H, hexanoyl 2×H-3 and 2×H-5), 2.26 (s, 3 H, Ac), 2.48 (m, 1 H, hexanoyl H-2B, overlapped by DMSO signal), 2.62 (dt, *J* = 15.5, 7.3 Hz, 1 H, hexanoyl H-2A), 3.45–3.65 (m, 2 H, hexanoyl 2×H-6), 4.05 (dd, *J* = 10.9, 2.7 Hz, 1 H, H-2B), 4.15 (dd, *J* = 10.9, 1.1 Hz, 1 H, H-2A), 4.70 (m, 1 H, H-3), 6.80–6.90 (m, 2 H, H-7 and H-8), 7.00 (m, 1 H, H-6), 7.05 (br. s, 1 H, hexanoyl NH-6), 7.63 (m, 1 H, H-5), 7.85 (s, 1 H, purine H-8), 9.05 (s, 1 H, NH-Ac), 12.35 (br. s, 1H, purine NH-9). ^{13}C NMR (125 MHz, DMSO-d_6, 25 °C) δ: 15.18, 24.54, 24.62, 26.01, 28.88, 33.56, 39.5 (overlapped by DMSO signal), 44.46, 69.35, 116.30, 119.90, 123.78, 124.72, 124.95, 138.25, 145.34, 150.61, 152.52, 154.08, 169.45, 170.71. Found (%): C 60.38; H 6.19; N 22.31. Calc. for $C_{22}H_{27}N_7O_3$ (%): C 60.40; H 6.22; N 22.41.

*(3S)-4-[6-(2-Acetamidopurin-6-ylamino)hexanoyl]-3-methyl-3,4-dihydro-2H-[1,4]benzoxazine [(S)-***14***]:* yield 0.423 g (51%), colorless solid, mp 203–205 °C, $[\alpha]_D^{20}$ +54.6 (*c* 1.0, DMF), *ee* >99%, HPLC ((*S*,*S*)-WHELK-O 1, MeOH–H_2O 80:20): τ 13.8 min. NMR spectra are identical to those of (*R*)-enantiomer (*R*)-**14**. HRMS, m/z: 438.2249 $[M+H]^+$, (calc. for $C_{22}H_{28}N_7O_3$, m/z: 438.2254).

*(3R)-4-[6-(2-Acetamidopurin-6-ylamino)hexanoyl]-7,8-difluoro-3-methyl-3,4-dihydro-2H-[1,4]benzoxazine [(R)-***15***]:* yield 0.612 g (68%), colorless solid, mp 195–196 °C, $[\alpha]_D^{20}$ −41.7 (*c* 1.0, DMF), *ee* >99%, HPLC ((*S*,*S*)-WHELK-O 1, MeOH–H_2O 80:20): τ 21.8 min. ^{1}H NMR (400 MHz, DMSO-d_6, 100 °C) δ: 1.10 (d, *J* = 6.9 Hz, 3 H, Me), 1.35–1.45 (m, 2 H, hexanoyl 2×H-4), 1.59–1.72 (m, 4 H, hexanoyl 2×H-3 and 2×H-5), 2.26 (s, 3 H, Ac), 2.46 (m, 1 H, hexanoyl H-2B, overlapped by DMSO signal), 2.60 (dt, *J* = 15.3, 7.5 Hz, 1 H, hexanoyl H-2A), 3.55 (m, 2 H, hexanoyl 2×H-6), 4.12 (dd, *J* = 10.9, 2.8 Hz, 1 H, H-2B), 4.32 (dd, *J* = 10.9, 1.3 Hz, 1 H, H-2A), 4.71 (qdd, *J* = 6.8, 2.8, 1.5 Hz, 1 H, H-3), 6.82 (dd, *J* = 9.7, 9.7, 8.4 Hz, 1 H, H-6), 7.04 (s, 1 H, hexanoyl NH-6), 7.56 (ddd, *J* = 9.5, 5.4, 2.5 Hz, 1 H, H-5), 7.83 (s, 1 H, purine H-8), 9.05 (s, 1 H, NH-Ac), 12.37 (br. s, 1H, purine NH-9). ^{19}F NMR (470 MHz, DMSO-d_6, 100 °C) δ: 1.99 (ddd, *J* = 21.0, 8.2, 2.4 Hz, 1 F, F-8), 20.09 (ddd, *J* = 20.7, 10.3, 5.4 Hz, 1 F, F-7). ^{13}C NMR (125 MHz, DMSO-d_6, 100 °C) δ: 14.61, 23.74, 23.97, 25.50, 28.54, 33.03, 39.5 (overlapped by DMSO signal), 44.43, 69.64, 106.20 (d, *J* = 18.0 Hz), 115.34, 118.73 (m), 121.67, 135.57 (d, *J* = 8.9 Hz), 137.18, 138.64 (dd, *J* = 244.2, 15.2 Hz), 146.26 (dd, *J* = 241.9, 9.7 Hz), 150.28, 152.30, 154.28, 168.84, 170.58. Found (%): C 56.06; H 5.28; F 8.14; N 20.43. Calc. for $C_{22}H_{25}F_2N_7O_3$ (%): C 55.81; H 5.32; F 8.02; N

20.71.

*(3S)-4-[6-(2-Acetamidopurin-6-ylamino)hexanoyl]-7,8-difluoro-3-methyl-3,4-dihydro-2H-[1,4]benzoxazine [(S)-***15***]:* yield 0.558 g (62%), colorless solid, mp 186–188 °C, $[\alpha]_D^{20}$ +42.8 (*c* 1.0, DMF), *ee* >99%, HPLC ((*S*,*S*)-WHELK-O 1, MeOH–H_2O 80:20): τ 16.2 min. NMR spectra are identical to those of (*R*)-enantiomer (*R*)-**15**. Found (%): C 55.62; H 5.37; F 7.86; N 20.67. Calc. for $C_{22}H_{25}F_2N_7O_3$ (%): C 55.81; H 5.32; F 8.02; N 20.71.

*(3S)-4-[6-(2-Acetamidopurin-6-ylamino)hexanoyl]-3-methyl-3,4-dihydro-2H-[1,4]benzothiazine [(S)-***16***]:* yield 0.595 g (69%), colorless solid, mp 132–135 °C, $[\alpha]_D^{20}$ +87.0 (*c* 1.0, DMF), *ee* >99%, HPLC ((*S*,*S*)-WHELK-O 1, MeOH–H_2O 80:20): τ 14.7 min. ^{1}H NMR (400 MHz, DMSO-d_6, 100 °C) δ: 1.00 (d, *J* = 6.7 Hz, 3 H, Me), 1.26–1.35 (m, 2 H, hexanoyl 2×H-4), 1.48–1.60 (m, 4 H, hexanoyl 2×H-3 and 2×H-5), 2.21 (dt, *J* = 22.7, 7.5 Hz, 1 H, hexanoyl H-2B), 2.26 (s, 3 H, Ac), 2.37–2.45 (m, 1 H, hexanoyl H-2A), 2.76 (dd, *J* = 12.3, 4.6 Hz, 1 H, H-2B), 3.33 (dd, *J* = 12.3, 6.0 Hz, 1 H, H-2A), 3.40–4.20 (m, 1 H, hexanoyl NH-6), 3.60 (m, 2 H, hexanoyl 2×H-6, overlapped by hexanoyl NH-6 signal), 5.16 (qdd, *J* = 6.7, 6.0, 4.6 Hz, 1 H, H-3), 7.11–7.15 (m, 2 H, H-7 and H-8), 7.21–7.21 (m, 2 H, H-5 and H-6), 8.15 (s, 1 H, purine H-8), 8.68 (br. s, 1 H, NH-Ac), 10.66 (br. s, 1H, purine NH-9). HRMS, m/z: 454.2020 $[M+H]^+$, (calc. for $C_{22}H_{28}N_7O_3S$, m/z: 454.2025).

*(2R)-1-[6-(2-Acetamidopurin-6-ylamino)hexanoyl]-2-methyl-1,2,3,4-tetrahydroquinoline [(R)-***17***]:* yield 0.588 g (71%), colorless solid, mp 216–217 °C, $[\alpha]_D^{20}$ −167 (*c* 1.0, DMF), *ee* >99%, HPLC ((*S*,*S*)-WHELK-O 1, MeOH–H_2O 80:20): τ 20.9 min. ^{1}H NMR (500 MHz, DMSO-d_6, 100 °C) δ: 1.00 (d, *J* = 6.5 Hz, 3 H, Me), 1.26–1.33 (m, 3 H, H-3B, hexanoyl 2×H-4), 1.49–1.62 (m, 4 H, hexanoyl 2×H-3 and 2×H-5), 2.22 (dt, *J* = 7.5, 5.7 Hz, 1 H, H-3A/hexanoyl H-2B), 2.27 (s, 3 H, Ac), 2.30 (dt, *J* = 15.1, 7.5 Hz, 1 H, hexanoyl H-2B/H-3A), 2.39–2.46 (m, 2 H, H-4B and hexanoyl H-2A), 2.58 (dt, *J* = 15.1, 5.5 Hz, 1 H, H-4A), 3.49 (m, 2 H, hexanoyl 2×H-6), 4.68 (td, *J* = 6.7, 6.7 Hz, 1 H, H-2), 7.03 (br. s, 1 H, hexanoyl NH-6), 7.08 (m, 1 H, H-6), 7.15 (m, 2 H, H-5 and H-7), 7.22 (m, 1 H, H-8), 7.84 (s, 1 H, purine H-8), 9.08 (s, 1H, NH-Ac), 12.38 (br. s, 1 H, purine H-9). ^{13}C NMR (125 MHz, DMSO-d_6, 100 °C) δ: 19.35, 23.77, 24.39, 24.57, 25.53, 28.53, 31.36, 33.25, 39.5 (overlapped by DMSO signal), 46.97, 115.36, 124.49, 125.33, 125.40, 126.85, 133.99, 136.90, 137.23, 137.34, 152.29, 154.20, 168.86, 170.80. Found (%): C 63.30; H 6.64; N 22.44. Calc. for $C_{23}H_{29}N_7O_2$ (%): C 63.43; H 6.71; N 22.51.

*(2S)-1-[6-(2-Acetamidopurin-6-ylamino)hexanoyl]-2-methyl-1,2,3,4-tetrahydroquinoline [(S)-***17***]:* yield 0.703 g (85%), colorless solid, mp 216–217 °C, $[\alpha]_D^{20}$ +167 (*c* 1.0, DMF), *ee* >99%, HPLC ((*S*,*S*)-WHELK-O 1, MeOH–H_2O 80:20): τ 15.9 min. NMR spectra are

identical to those of (*R*)-enantiomer (*R*)-**17**. Found (%): C 63.28; H 6.85; N 22.48. Calc. for $C_{23}H_{29}N_7O_2$ (%): C 63.43; H 6.71; N 22.51.

*(2R)-1-[6-(2-Acetamidopurin-6-ylamino)hexanoyl]-6-fluoro-2-methyl-1,2,3,4-tetrahydroquinoline [(R)-***18***]:* yield 0.638 g (74%), colorless solid, mp 200–202 °C, $[\alpha]_D^{20}$ −137 (*c* 1.0, DMF), *ee* >99%, HPLC ((*S*,*S*)-WHELK-O 1, MeOH–H_2O 80:20): τ 20.4 min. ^{1}H NMR (400 MHz, DMSO-d_6, 100 °C) δ: 0.99 (d, *J* = 6.5 Hz, 3 H, Me), 1.27–1.34 (m, 3 H, H-3B and hexanoyl 2×H-4), 1.51–1.60 (m, 4 H, hexanoyl 2×H-3 and 2×H-5), 2.26 (s, 3 H, Ac), 2.19–2.31 (m, 2 H, H-3A and hexanoyl H-2B), 2.39–2.49 (m, 2 H, H-4B and hexanoyl H-2A), 2.61 (ddd, *J* = 15.3, 5.6, 5.6 Hz, 1 H, H-4A), 3.50 (m, 2 H, hexanoyl 2×H-6), 4.67 (dt, *J* = 6.6, 6.6 Hz, 1 H, H-2), 6.92–7.05 (m, 3 H, hexanoyl NH-6, H-5 and H-8), 7.26 (dd, *J* = 8.7, 5.2 Hz, 1 H, H-7), 7.82 (s, 1 H, purine H-8), 9.05 (s, 1 H, NH-Ac), 12.32 (br. s, 1 H, purine H-9). ^{19}F NMR (376 MHz, DMSO-d_6, 100 °C) δ: 45.06 (ddd, *J* = 8.2, 5.9, 5.9, F-6). ^{13}C NMR (125 MHz, DMSO-d_6, 100 °C) δ: 19.19, 23.75, 24.30, 24.59, 25.52, 28.52, 30.88, 33.12, 39.5 (overlapped by DMSO signal), 46.95, 111.89, 111.98 (d, *J* = 22.6 Hz), 113.35 (d, *J* = 22.4 Hz), 127.01 (d, *J* = 8.4 Hz), 133.05, 136.29 (d, *J* = 7.2 Hz), 137.13, 137.37, 152.28, 154.09, 158.84 (d, *J* = 242.4 Hz), 168.83, 170.75. Found (%): C 60.93; H 6.32; F 3.97; N 21.79. Calc. for $C_{23}H_{28}FN_7O_2$ (%): C 60.91; H 6.22; F 4.19; N 21.62.

*(2S)-1-[6-(2-Acetamidopurin-6-ylamino)hexanoyl]-6-fluoro-2-methyl-1,2,3,4-tetrahydroquinoline [(S)-***18***]:* yield 0.741 g (86%), colorless solid, mp 198–201 °C, $[\alpha]_{546}^{20}$ +137 (*c* 1.0, DMF), *ee* >99%, HPLC ((*S*,*S*)-WHELK-O 1, MeOH–H_2O 80:20): τ 16.0 min. NMR spectra are identical to those of enantiomer (*R*)-**18**. HRMS, *m/z*: 454.2363 $[M+H]^+$ (calc. for $C_{23}H_{28}FN_7O_2$, *m/z*: 454.2361).

Alkaline hydrolysis of acetamides 14–18. General procedure. A mixture of the corresponding acetamide (0.90 mmol) and 1 N NaOH (5.6 ml) was stirred at room temperature for 48 h, then neutralized with 1 N HCl to pH 5–6 and evaporated to dryness. The residue was purified by flash column chromatography.

*(3R)-4-[6-(2-Aminopurin-6-ylamino)hexanoyl]-3-methyl-3,4-dihydro-2H-[1,4]benzoxazine [(R)-***19***]:* yield 0.242 g (68%), colorless solid, mp 90–93 °C, $[\alpha]_D^{20}$ −57.0 (*c* 1.0, DMF), *ee* >99%, HPLC ((*S*,*S*)-WHELK-O 1, MeOH– H_2O 80:20): τ 16.2 min. ^{1}H NMR (400 MHz, DMSO-d_6, 100 °C): δ = 1.09 (d, *J* = 6.8 Hz, 3 H, Me), 1.33–1.43 (m, 2 H, hexanoyl 2×H-4), 1.55–1.70 (m, 4 H, hexanoyl 2×H-3 and 2×H-5), 2.44–2.52 (m, 1 H, hexanoyl H-2B, overlapped by DMSO signal), 2.57–2.66 (m, 1 H, hexanoyl H-2A), 3.45–3.53 (m, 2 H, hexanoyl 2×H-6), 4.05 (dd, *J* = 10.9, 2.7 Hz, 1 H, H-2B), 4.15 (dd, *J* = 10.9, 1.5 Hz, 1 H, H-2A), 4.67–4.74 (m, 1 H, H-3), 5.28 (br. s, 2 H, NH_2), 6.52 (br. s, 1 H, hexanoyl

NH-6), 6.81–6.87 (m, 2 H, H-5 and H-6), 7.00 (ddd, *J* = 7.7, 7.7, 1.4 Hz, 1 H, H-7), 7.56 (s, 1 H, purine H-8), 7.62–7.67 (m, 1 H, H-8), 10.00–13.00 (br. s, 1 H, purine H-9) ppm. HRMS, m/z: 396.2140 $[M+H]^+$, (calc. for $C_{20}H_{26}N_7O_2$, m/z: 396.2148).

*(3S)-4-[6-(2-Aminopurin-6-ylamino)hexanoyl]-3-methyl-3,4-dihydro-2H-[1,4]benzoxazine [(S)-***19***]:* yield 0.266 g (75%), colorless solid, mp 90–93 °C, $[\alpha]_D^{20}$ +55.6 (*c* 1.0, DMF), *ee* >99%, HPLC ((*S*,*S*)-WHELK-O 1, MeOH– H_2O 80:20): τ 11.9 min. NMR spectra are identical to those of enantiomer (*R*)-**19**. HRMS, m/z: 396.2145 $[M+H]^+$, (calc. for $C_{20}H_{26}N_7O_2$, m/z: 396.2148).

*(3R)-4-[6-(2-Aminopurin-6-ylamino)hexanoyl]-7,8-difluoro-3-methyl-3,4-dihydro-2H-[1,4]benzoxazine [(R)-***20***]:* yield 0.214 g (55%), colorless solid, mp 110–114 °C, $[\alpha]_D^{20}$ −42.6 (*c* 0.7, DMF), *ee* 99.2%, HPLC (Kromasil Cellucoat, MeCN–H_2O 25:75): τ 23.8 min. ^{1}H NMR (500 MHz, DMSO-d_6, 100 °C) δ: 1.12 (d, *J* = 6.9 Hz, 3 H, Me), 1.37–1.42 (m, 2 H, hexanoyl 2×H-4), 1.58–1.68 (m, 4 H, hexanoyl 2×H-3 and 2×H-5), 2.45–2.51 (m, 1 H, hexanoyl H-2B, overlapped by DMSO signal), 2.58–2.64 (m, 1 H, hexanoyl H-2A), 3.48–3.52 (m, 2 H, hexanoyl 2×H-6), 4.13 (dd, *J* = 11.0, 2.8 Hz, 1 H, H-2B), 4.32 (dd, *J* = 11.0, 1.4 Hz, 1 H, H-2A), 4.70–4.76 (m, 1 H, H-3), 5.25 (br. s, 2 H, NH_2), 6.50 (br. s, 1 H, hexanoyl NH-6), 6.84 (ddd, *J* = 9.8, 9.8, 8.3 Hz, 1 H, H-6), 7.54–7.58 (m, 2 H, H-5 and purine H-8), 11.62 (br. s, 1 H, purine H-9). ^{19}F NMR (470 MHz, DMSO-d_6, 100 °C) δ: 1.98 (ddd, *J* = 21.0, 8.2, 2.2 Hz, 1 F, F-8), 20.05–20.12 (m, 1 F, F-7). ^{13}C NMR (125 MHz, DMSO-d_6, 100 °C) δ: 14.63, 23.99, 25.51, 28.73, 33.06, 39.5 (overlapped by DMSO signal), 44.45, 69.52, 106.22 (d, *J* = 18.1 Hz), 112.30, 118.75 (dd, *J* = 7.8, 4.2 Hz), 121.67, 134.79 (m), 135.57 (dd, *J* = 10.1, 3.1 Hz), 138.64 (dd, *J* = 243.9, 15.4 Hz), 146.26 (dd, *J* = 242.1, 10.1 Hz), 152.08, 154.34, 159.49, 170.61. HRMS, *m/z*: 432.1953 $[M+H]^+$, (calc. for $C_{20}H_{24}F_2N_7O_2$, *m/z*: 432.1954).

*(3S)-4-[6-(2-Aminopurin-6-ylamino)hexanoyl]-7,8-difluoro-3-methyl-3,4-dihydro-2H-[1,4]benzoxazine [(S)-***20***]:* yield 0.291 g (75%), colorless solid, mp 109–113 °C, $[\alpha]_D^{20}$ +43.8 (*c* 0.3, DMF), *ee* >99.5%, HPLC (Kromasil Cellucoat, MeCN–H_2O 25:75): τ 26.9 min. NMR spectra were identical to those of (*R*)-enantiomer **(*R*)-20**. HRMS, *m/z*: 432.1956 $[M+H]^+$, (calc. for $C_{20}H_{24}F_2N_7O_2$, *m/z*: 432.1954).

*(3S)-4-[6-(2-Aminopurin-6-ylamino)hexanoyl]-3-methyl-3,4-dihydro-2H-[1,4]benzothiazine [(S)-***21***]:* yield 0.303 g (82%), yellowish foam, $[\alpha]_D^{20}$ = +105 (*c* 0.85, DMF), *ee* >99%, HPLC ((*S*,*S*)-Whelk-O 1, MeOH–0.25% aq. AcOH 63:37, 0.8 mL/min): τ (*S*)-**22** 9.0 min, τ (*R*)-**22** 11.6 min. ^{1}H NMR (500 MHz, DMSO-d_6, 100 °C): δ = 1.00 (d, *J* = 6.7 Hz, 3 H, Me), 1.23–1.29 (m, 2 H, hexanoyl 2×H-4), 1.45–1.57 (m, 4 H, hexanoyl 2×H-3

and 2×H-5), 2.22 (dt, *J* = 14.9, 7.5 Hz, 1 H, hexanoyl H-2B), 2.39 (ddd, *J* = 14.9, 8.2, 6.4 Hz, 1 H, hexanoyl H-2A), 2.77 (dd, *J* = 12.3, 4.6 Hz, 1 H, H-2B), 3.34 (dd, *J* = 12.3, 6.0 Hz, 1 H, H-2A), 3.43 (dt, *J* = 6.3, 6.2 Hz, 2 H, hexanoyl 2×H-6), 5.17 (qdd, *J* = 6.7, 6.0, 4.6 Hz, 1 H, H-3), 5.23 (br. s, 2 H, NH_2), 6.44 (br. s, 1 H, hexanoyl NH-6), 7.12–7.15 (m, 2 H, H-6 and H-8), 7.22–7.27 (m, 2 H, H-5 and H-7), 7.55 (s, 1 H, purine H-8), 11.66 (br. s, 1 H, purine H-9) ppm. ^{13}C NMR (125 MHz, DMSO-d_6, 23 °C): δ = 17.31, 24.69, 25.88, 29.03, 33.70, 34.26, 39.5 (overlapped by DMSO signal), 44.76, 112.61, 124.99, 126.15, 127.05, 128.41, 129.98, 134.92, 135.11, 151.73, 154.55, 159.96, 171.31 ppm. HRMS (ESI): calcd. for $C_{20}H_{26}N_7OS$ $[M+H]^+$ 412.1914; found 412.1910.

*(2R)-1-[6-(2-Aminopurin-6-ylamino)hexanoyl]-2-methyl-1,2,3,4-tetrahydroquinoline [(R)-***22***]:* yield 0.244 g (69%), colorless solid, mp 100–102 °C, $[\alpha]_D^{20}$ −170 (*c* 0.7, DMF), *ee* >99%, HPLC ((*S*,*S*)-WHELK-O 1, MeOH–H_2O 75:25): τ 25.5 min. ^{1}H NMR (500 MHz, DMSO-d_6, 100 °C) δ: 1.00 (d, *J* = 6.5 Hz, 3 H, Me), 1.25–1.34 (m, 3 H, H-3B, hexanoyl 2×H-4), 1.48–1.60 (m, 4 H, hexanoyl 2×H-3 and 2×H-5), 2.22–2.33 (m, 2 H, H-3A and hexanoyl H-2B), 2.40–2.47 (m, 2 H, H-4B and hexanoyl H-2A), 2.60 (ddd, *J* = 15.1, 5.5, 5.5 Hz, 1 H, H-4A), 3.42–3.47 (m, 2 H, hexanoyl 2×H-6), 4.69 (ddq, *J* = 6.8, 6.7, 6.5 Hz, 1 H, H-2), 5.31 (br. s, 2 H, NH_2), 6.45 (br. s, 1 H, hexanoyl NH-6), 7.09 (ddd, *J* = 7.8, 7.3, 1.3 Hz, 1 H, H-6), 7.14–7.17 (m, 2 H, H-5 and H-7), 7.22 (dd, *J* = 8.1, 1.3 Hz, 1 H, H-8), 7.57 (s, 1 H, purine H-8), 11.72 (br. s, 1 H, purine H-9). ^{13}C NMR (125 MHz, DMSO-d_6, 100 °C) δ: 19.15, 24.26, 24.39, 25.42, 28.55, 31.17, 33.16, 39.5 (overlapped by DMSO signal), 46.84, 111.98, 124.32, 125.20, 125.24, 126.73, 133.79, 135.02, 136.88, 151.89, 154.13, 159.07, 170.73. HRMS, *m/z*: 394.2354 $[M+H]^+$, (calc. for $C_{21}H_{28}N_7O$, *m/z*: 394.2350).

*(2S)-1-[6-(2-Aminopurin-6-ylamino)hexanoyl]-2-methyl-1,2,3,4-tetrahydroquinoline [(S)-***22***]:* yield 0.340 g (96%), colorless solid, mp 101–103 °C, $[\alpha]_D^{20}$ +165 (*c* 0.7, DMF), *ee* >99%, HPLC ((*S*,*S*)-WHELK-O 1, MeOH–H_2O 75:25): τ 19.0 min. NMR spectra were identical to those of (*R*)-enantiomer **(*R*)-22**. HRMS, *m/z*: 394.2351 $[M+H]^+$, (calc. for $C_{21}H_{28}N_7O$, *m/z*: 394.2350).

*(2R)-1-[6-(2-Aminopurin-6-ylamino)hexanoyl]-6-fluoro-2-methyl-1,2,3,4-tetrahydroquinoline [(R)-***23***]:* yield 0.363 g (98%), colorless solid, mp 95–100 °C, $[\alpha]_D^{20}$ −132 (*c* 0.8, DMF), *ee* >99%, HPLC ((*S*,*S*)-WHELK-O 1, MeOH–H_2O 75:25): τ 27.2 min. ^{1}H NMR (500 MHz, DMSO-d_6, 100 °C) δ: 1.00 (d, *J* = 6.5 Hz, 3 H, Me), 1.27–1.36 (m, 3 H, H-3B and hexanoyl 2×H-4), 1.51–1.60 (m, 4 H, hexanoyl 2×H-3 and 2×H-5), 2.20–2.32 (m, 2 H, H-3A and hexanoyl H-2B), 2.40–2.47 (m, 2 H, H-4B and hexanoyl H-2A), 2.62 (ddd, *J* = 15.4, 5.6, 5.6 Hz, 1 H, H-4A), 3.47 (m, 2 H, hexanoyl 2×H-6), 4.68 (ddq, *J* = 6.7, 6.6, 6.5 Hz,

1 H, H-2), 5.44 (br. s, 2 H, NH_2), 6.69 (br. s, 1 H, hexanoyl NH-6), 6.92–7.00 (m, 2 H, H-5 and H-7), 7.28 (dd, *J* = 8.7, 5.2 Hz, 1 H, H-8), 7.61 (s, 1 H, purine H-8), 11.3–12.0 (br. s, 1 H, hexanoyl H-9). ^{19}F NMR (470 MHz, DMSO-d_6, 100 °C) δ: 45.02–45.08 (m, F-6). ^{13}C NMR (125 MHz, DMSO-d_6, 100 °C) δ: 19.21, 24.33, 24.62, 25.54, 28.65, 30.90, 33.15, 39.5 (overlapped by DMSO signal), 46.98, 111.77, 112.01 (d, *J* = 22.6 Hz), 113.37 (d, *J* = 22.6 Hz), 127.04 (d, *J* = 8.8 Hz), 133.08 (d, *J* = 2.5 Hz), 135.33, 136.31 (d, *J* = 7.5 Hz), 151.77, 154.12, 158.86 (d, *J* = 242.7 Hz), 159.04, 170.81. HRMS, *m/z*: 412.2261 $[M+H]^+$ (calc. for $C_{21}H_{27}FN_7O$, *m/z*: 412.2256).

*(2S)-1-[6-(2-Aminopurin-6-ylamino)hexanoyl]-6-fluoro-2-methyl-1,2,3,4-tetrahydroquinoline [(S)-***23***]:* yield 0.259 g (70%), colorless solid, mp 94–98 °C, $[\alpha]_D^{20}$ +140 (*c* 0.7, DMF), *ee* >99%, HPLC ((*S,S*)-WHELK-O 1, MeOH–H_2O 75:25): τ 21.7 min. NMR spectra are identical to those of (*R*)-enantiomer **(*R*)-23**. HRMS, *m/z*: 412.2258 $[M+H]^+$, (calc. for $C_{21}H_{27}FN_7O$, *m/z*: 412.2256).

Synthesis of 6-(purin-6-ylamino)hexanoyl amines 26-28. General procedure. Removal of *N*-phthaloyl protection in compounds **10, 24, 25** by hydrazinolysis was carried out as described above for preparation of compounds **14-18**. The residue was re-dissolved in *n*-BuOH (1 mL); 6-chloropurine (0.11 g, 0.68 mmol) and TEA (0.16 mL, 1.15 mmol) were added to the resulting solution. The reaction mixture was heated at 85–90 °C for 12 h, cooled to room temperature, washed subsequently with 1 N HCl (4×2 mL), saturated aqueous NaCl (5×5 mL). Organic layer was dried ($MgSO_4$) and evaporated to dryness under reduced pressure. The residue was purified by flash column chromatography.

*(RS)-4-[6-(Purin-6-ylamino)hexanoyl]-7,8-difluoro-3-methyl-3,4-dihydro-2H-[1,4]benzoxazine (***26***):* yield 0.10 g (50%), yellow solid, mp 96.5 °C (decomp.). ^{1}H NMR (500 MHz, DMSO-d_6, 80 °C) δ: 1.11 (d, *J* = 6.9 Hz, 3 H, Me), 1.36-1.40 (m, 2 H, hexanoyl 2×H-4), 1.58-1.66 (m, 4 H, hexanoyl 2×H-3 and 2×H-5), 2.48-2.52 (m, 1 H, hexanoyl H-2A, overlapped by DMSO signal), 2.59-2.65 (m, 1 H, hexanoyl H-2B), 3.56 (br. s, 2 H, hexanoyl 2×H-6,), 4.13 (dd, *J* = 11.0, 2.6 Hz, 1 H, H-2A), 4.33 (dd, *J* = 11.0, 1.2 Hz, 1 H, H-2B), 4.70-4.74 (m, 1 H, H-3), 6.86 (ddd, *J* = 9.8, 9.8, 8.5 Hz, 1 H, H-6), 7.21 (br. s, 1 H, hexanoyl NH-6), 7.58 (br. s, 1 H, H-5), 7.97 (s, 1 H, purine H-8), 8.13 (s, 1 H, purine H-2), 12.63 (br. s, 1 H, purine NH-9). ^{19}F NMR (470 MHz, DMSO-d_6, 80 °C) δ: 1.91-1.97 (m, 1 F, F-8), 20.05 (m, 1 F, F-7). ^{13}C NMR (125 MHz, DMSO-d_6) δ: 15.08, 24.42, 25.93, 28.93, 33.39, 44.99, 69.83, 79.10, 107.39 (d, *J* = 17.9 Hz), 119.40, 119.97, 122.52, 136.49 (d, *J* = 7.5 Hz), 139.23, 139.75 (dd, *J* = 243.3, 15.4 Hz), 147.49 (dd, *J* = 244.1, 9.5 Hz), 150.22, 152.31, 154.45, 170.95. HRMS, *m/z*: 417.1844 $[M+H]^+$ (calc. for $C_{20}H_{23}F_2N_6O_2$, *m/z*: 417.1850).

*(RS)-1-[6-(Purin-6-ylamino)hexanoyl]-2-methylindoline (***27***):* yield 0.17 g (68%), slightly colored solid, mp 88 °C (decomp.). ^{1}H NMR (500 MHz, DMSO-d_6, 60 °C) δ: 1.18 (d, J = 6.4 Hz, 3 H, Me), 1.40-1.46 (m, 2 H, hexanoyl 2×H-4), 1.63-1.70 (m, 4 H, hexanoyl 2×H-3 and 2×H-5), 2.40-2.46 (m, 1 H, hexanoyl H-2A), 2.56-2.62 (m, 1 H, hexanoyl H-2B), 2.61 (d, J = 15.7 Hz, 1 H, H-3A), 3.33 (dd, J = 15.7, 8.8 Hz, 1 H, H-3B), 3.50-3.65 (m, 2 H, hexanoyl 2×H-6,), 4.61 (m, 1 H, H-2), 6.98 (ddd, J = 7.4, 7.4, 0.8 Hz, 1 H, H-6), 7.14 (dd, J = 7.8, 7.6 Hz, 1 H, H-5), 7.23 (d, J = 7.4 Hz, 1 H, H-4), 7.31 (br. s, 1 H, hexanoyl NH-7), 7.91 (br. s, 1 H, H-7), 7.99 (s, 1 H, purine H-8), 8.14 (s, 1 H, purine H-2), 12.68 (br. s, 1 H, purine NH-9). ^{13}C NMR (125 MHz, DMSO-d_6) δ: 21.45, 24.35, 26.06 (2 C), 29.03, 33.89, 35.74, 54.79, 116.83, 118.72, 123.20, 125.06, 126.84, 130.64, 138.40, 141.53, 149.27, 152.31, 154.46, 170.36. HRMS, *m/z*: 365.2085 $[M+H]^+$, (calc. for $C_{20}H_{25}N_6O$, *m/z*: 365.2090).

*1-[6-(Purin-6-ylamino)hexanoyl]-1,2,3,4-tetrahydroquinoline (***28***):* yield 0.10 g (40%), yellow solid, mp 61 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.28 (br. s, 2 H, hexanoyl 2×H-4), 1.56 (br. s, 4 H, hexanoyl 2×H-3 and 2×H-5), 1.83 (br. s, 2 H 2×H-3), 2.65 (br. s, 2 H, hexanoyl 2×H-2), 3.34-3.43 (m, 4 H, 2×H-2 and 2×H-4), 3.66 (br. s, 2 H, hexanoyl 2×H-6), 7.08-7.15 (m, 3 H, H-5, H-6 and H-7), 7.39 (br. s, 1 H, hexanoyl NH-6), 7.61 (br. s, 1 H, H-8), 8.08 (br. s, 1 H, purine H-8), 8.25 (m, 1 H, purine H-2), 12.88 (br. s, 1 H, purine NH-9). HRMS, *m/z*: 365.2087 $[M+H]^+$, (calc. for $C_{20}H_{25}N_6O$, *m/z*: 365.2090).

Synthesis of 6-(purin-6-ylamino)hexanoyl amines 27, 28, 30. General procedure. The corresponding amine (0.80 mmol), DIEA (0.43 mL, 2.47 mmol), and TBTU (0.28 g, 0.88 mmol) were added to a cold (0 °C) solution of acid **29** (0.20 g, 0,80 mmol) in a 4:1 mixture of DMSO/DMF (5 mL) at continuous stirring. The reaction mixture was stirred at 0 °C for 40 min, at room temperature for 48 h, and then poured into cold water (25 mL). The precipitate (in the case of compound **28**) was filtered off, washed with cold water (2×5 mL), and recrystallized from EtOH. In other cases, the reaction mixture was acidified to pH 3-5 with 1 N HCl and extracted with EtOAc (3×5 mL). Organic layers were dried ($MgSO_4$) and evaporated to dryness under reduced pressure. The residue was purified by flash column chromatography.

*(RS)-1-[6-(Purin-6-ylamino)hexanoyl]-2-methylindoline (***27***):* yield 0.08 g (28%). All characteristics are identical to those described above.

*1-[6-(Purin-6-ylamino)hexanoyl]-1,2,3,4-tetrahydro-quinoline (***28***):* yield 7%. All characteristics are identical to those described above.

*1-[6-(Purin-6-ylamino)hexanoyl]indoline (***30***):* yield 0.17 g (60%), slightly colored solid, mp 206 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 1.36-1.42 (m, 2 H, hexanoyl 2×H-4), 1.59-1.66 (m, 4 H, hexanoyl 2×H-3 and 2×H-5), 2.44 (dd, J = 7.2, 7.1 Hz, 2 H, hexanoyl 2×H-2),

3.12 (dd J = 8.5, 8.3 Hz, 2 H, H-3), 3.42-3.47 (m, 2 H, hexanoyl 2×H-6), 4.06 (t, J = 8.6 Hz, 2 H, H-2), 6.96 (dd, J = 7.7, 7.0 Hz, 1 H, H-5), 7.13 (dd, J = 7.7, 7.5 Hz, 1 H, H-6), 7.21 (d, J = 7.3 Hz, 1 H, H-4), 7.64 (br. s, 1 H, hexanoyl NH-6), 8.06 (s, 1 H, H-7), 8.07 (d, J = 8.0 Hz, 1 H, purine H-8), 8.17 (s, 1 H, purine H-2), 12.86 (br. s, 1 H, purine NH-9). ^{13}C NMR (125 MHz, DMSO-d_6) δ: 23.77, 26.05, 27.31, 29.00, 34.79, 47.28, 115.80, 118.67, 122.87, 124.64, 126.80, 131.56, 138.39, 143.00, 149.31, 152.33, 154.46, 170.84. Found (%): C 65.20; H 6.51; N 23.68. Calc. for $C_{19}H_{22}N_6O$: C 65.12; H 6.33; N 23.98.

References for Supplementary Materials

S1 V. N. Charushin, E. B. Gorbunov, G. L. Rusinov, V. A. Likholobov and V. A. Rodionov, *RF Patent* 2434005, C07D, 2011 (*Chem. Abstr*., 2011, **155**, 683753).

S2 W. Oldham and I. B. Johns, *J. Am. Chem. Soc.*, 1939, **61**, 3289.

S3 D. A. Gruzdev, G. L. Levit and V. P. Krasnov, *Tetrahedron: Asymmetry*, 2012, **23**, 1640.

S4 V. P. Krasnov, G. L. Levit, I. M. Bukrina, I. N. Andreeva, L. Sh. Sadretdinova, M. A. Korolyova, M. I. Kodess, V. N. Charushin and O. N. Chupakhin, *Tetrahedron: Asymmetry*, 2003, **14**, 1985.

S5 V. N. Charushin, V. P. Krasnov, G. L. Levit, M. A. Korolyova, M. I. Kodess, O. N. Chupakhin, M. H. Kim, H. S. Lee, Y. J. Park and K.-C. Kim, *Tetrahedron: Asymmetry*, 1999, **10**, 2691.

S6 D. A. Gruzdev, S. A. Vakarov, G. L. Levit and V. P. Krasnov, *Chem. Heterocycl. Compd. (Engl. Transl.)*, 2014, **49**, 1795 (*Khim. Geterotsikl. Soedin*., 2014, **49**, 1936).

S7 D. A. Gruzdev, E. N. Chulakov, L. Sh. Sadretdinova, M. I. Kodess, G. L. Levit and V. P. Krasnov, *Tetrahedron: Asymmetry*, 2015, **26**, 186.

S8 D. A. Gruzdev, E. N. Chulakov, G. L. Levit, M. A. Ezhikova, M. I. Kodess and V. P. Krasnov, *Tetrahedron: Asymmetry*, 2013, **24**, 1240.

S9 W. A. Bowles, F. H. Schneider, L. R. Lewis and R. K. Robins, *J. Med. Chem.*, 1963, **6**, 471.

S10 E. Guénin, M. Monteil, N. Bouchemal, T. Prangé and M. Lecouvey, *Eur. J. Org. Chem.*, 2007, 3380.

S11 F. Hausch and A. Jäschke, *Tetrahedron*, 2001, **57**, 1261.