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Dedicated to Full Member of the Russian Academy of Sciences O.N. Chupakhin on his 85th anniversary

Synthesis of Purine and 2-Aminopurine Conjugates with *N*-(4-Aminobenzoyl)-(*S*)-glutamic Acid

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Abstract—Purine and 2-aminopurine conjugates with *N*-(4-aminobenzoyl)-(*S*)-glutamic acid connected to C^6 of the purine system either directly or through an aminoethyl linker have been synthesized by nucleophilic substitution of chlorine in 6-chloropurine and 2-amino-6-chloropurine. 2-Aminopurine conjugate with 4-aminobenzoic acid linked through a glycine residue has also been obtained. Testing of the synthesized compounds for tuberculostatic activity *in vitro* has revealed a moderate activity of methyl 4-[2-(2-aminopurin-6-ylamino)-acetyl]amino}benzoate.

Keywords: purines, conjugates, 4-aminobenzoic acid, glutamic acid, tuberculostatic activity.

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Purine derivatives exhibit diverse biological activity and are components of a number of medicines [1–3]. We have recently found that some *N*-(purin-6-yl)glycyl and *N*-(2-aminopurin-6-yl)glycyl amino acids show pronounced antitubercular activity *in vitro* [4], which may be related to their inhibitory effect on mycobacterial glutamine synthetase [5, 6] or dihydrofolate reductase [7].

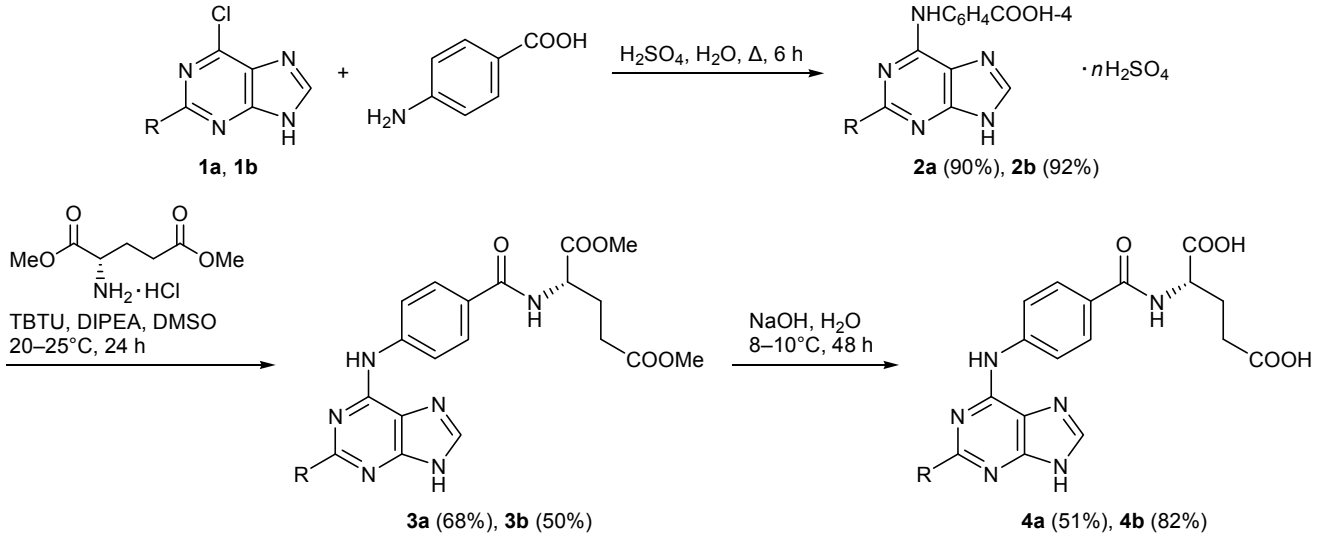
Interest in compounds containing both heterocyclic fragment and *N*-(4-aminobenzoyl)glutamic acid residue is determined by the fact that the latter is a structural unit of folic acid. Modification of the heterocyclic fragment of folic acid opens the way to new biologically active compounds [8]. Some conjugates of *N*-(4-aminobenzoyl)glutamic acid with heterocycles showed antitubercular activity [9] and inhibited aggrecanase (an enzyme promoting chondrocyte apoptosis in joint pathologies) [10] and dihydrofolate reductase [11].

The goal of the present work was to synthesize conjugates of purine and 2-aminopurine with *N*-(4-aminobenzoyl)-(*S*)-glutamic acid linked to C^6 of the purine fragment either directly or through an aminoethyl linker, as well as 2-aminopurine conjugate with 4-aminobenzoic acid linked to C^6 through a glycine residue, and study their tuberculostatic activity *in vitro*.

Purine conjugates with *N*-(4-aminobenzoyl)-(*S*)-glutamic acid were synthesized following an approach based on successive appending of required fragments to the initial purine molecule. The starting compounds were commercially available 6-chloropurine (**1a**) and 2-amino-6-chloropurine (**1b**).

The chlorine atom in 6-chloropurines **1a** and **1b** was smoothly replaced by the 4-aminobenzoic acid residue on heating in boiling water in the presence of 0.9 equiv of H_2SO_4 (Scheme 1) to produce 4-(purin-6-ylamino)- and 4-(2-aminopurin-6-ylamino)benzoic acids **2a** and **2b**, respectively; acid **2b** was isolated as a salt with H_2SO_4. Similar conditions (heating in boiling water in the presence of H_2SO_4) were used previously to obtain purine and 2-aminopurine conjugates containing a heterocyclic amine residue in

Scheme 1.

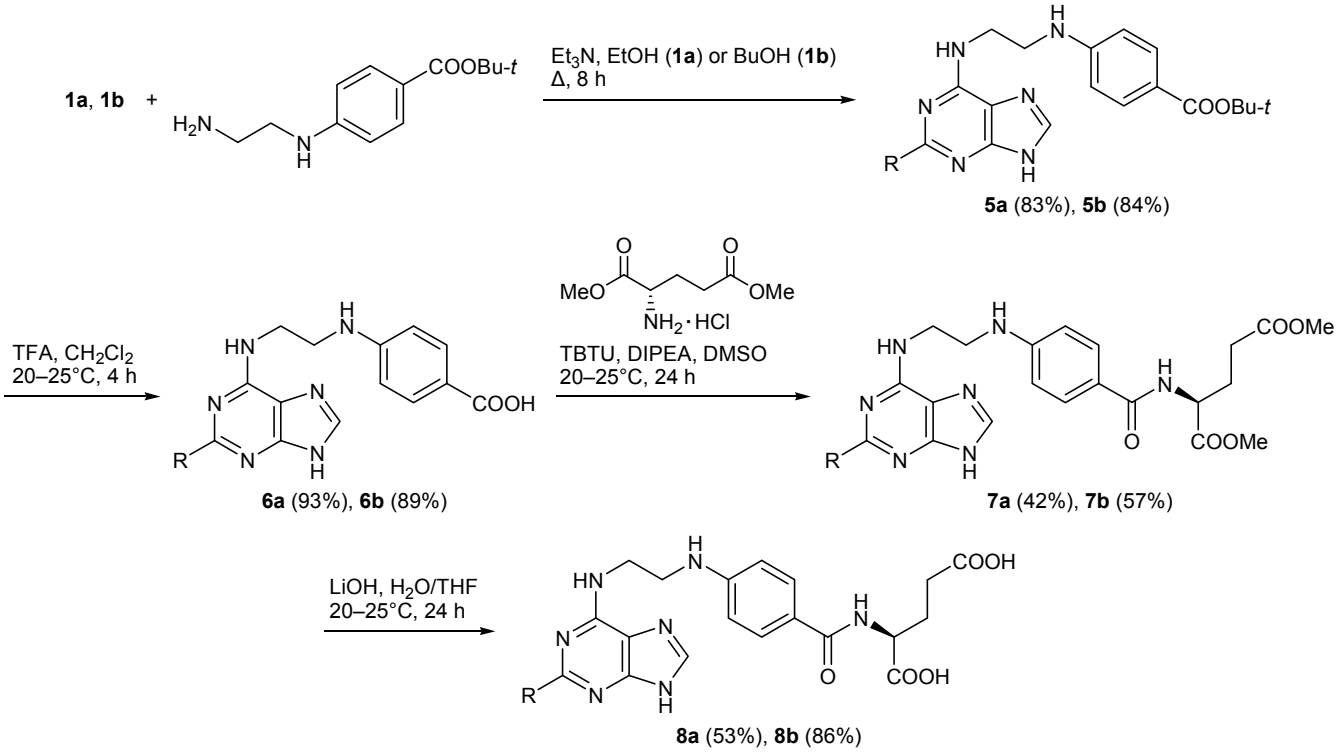


R = H (**a**), NH_2 (**b**); **2**, n = 0 (**a**), 0.6 (**b**).

position *6* [12]. The condensation of acids **2a** and **2b** with dimethyl (*S*)-glutamate in the presence of *O*-(benzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium tetrafluoroborate (TBTU) in the presence of ethyl(diisopropyl)amine (DIPEA) in DMSO gave diesters **3a** and **3b**, and alkaline hydrolysis of the latter afforded target conjugates **4a** and **4b** in which the *N*-(4-aminobenzoyl)-(*S*)-glutamic acid fragment is linked directly to C^6 of the purine moiety (Scheme 1).

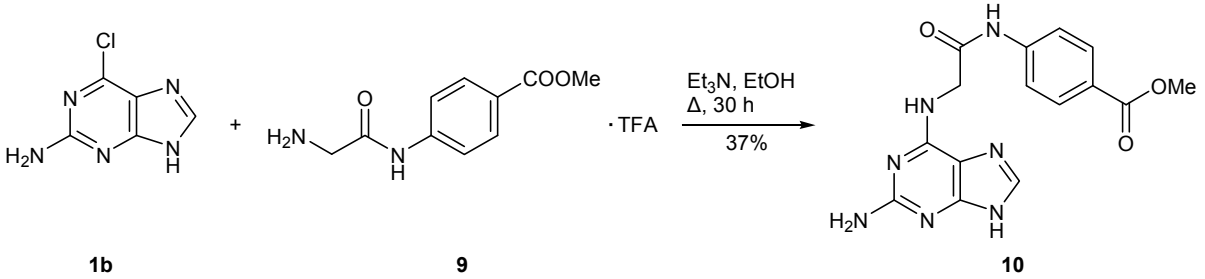
Purine and 2-aminopurine conjugates with *N*-(4-aminobenzoyl)-(*S*)-glutamic acid linked to C^6 through an aminoethyl linker were obtained by heating

Scheme 2.



R = H (**a**), NH_2 (**b**).

Scheme 3.



1b **9** **10**

6-chloropurines **1a** and **1b** with *tert*-butyl *N*-(2-aminoethyl)-4-aminobenzoate in ethanol or butan-1-ol in the presence of triethylamine, followed by hydrolysis of the ester group in **5a** and **5b** by the action of trifluoroacetic acid, condensation of acids **6a** and **6b** with dimethyl (*S*)-glutamate, and alkaline hydrolysis of the ester groups in dimethyl esters **7a** and **7b**. We thus isolated conjugates **8a** and **8b** (Scheme 2).

We also tried to synthesize a conjugate of 2-aminopurine with *N*-(4-aminobenzoyl)-(*S*)-glutamic acid linked to C^6 of the purine moiety through a glycine residue. As shown previously, compounds containing a [(2-aminopurin-6-yl)amino]glycine fragment exhibit pronounced antitubercular activity *in vitro* [4]. The reaction of 2-amino-6-chloropurine (**1b**) with methyl 4-[(2-amino-1-oxoethyl)amino]benzoate (trifluoroacetic acid salt) (**9**) gave methyl 4-{[2-(2-aminopurin-6-ylamino)acetyl]amino}benzoate (**10**) in a moderate yield (Scheme 3). However, attempted hydrolysis of the ester group in **10** resulted in cleavage of the amide bond between the glycine and 4-aminobenzoic acid fragments with the formation of *N*-(2-aminopurin-6-yl)glycine. It should be noted that the hydrolysis of ethyl 4-{[2-(6-bromo-1*H*-indazol-4-ylamino)acetyl]-amino}benzoate under similar conditions was reported [13] to produce the target carboxylic acid in a moderate yield (42%).

The *in vitro* tuberculostatic activity of the synthesized compounds against *Mycobacterium tuberculosis* H37Rv was studied at the Ural Research Institute of Phthisiopulmonology (National Medical Research Center, Ministry of Healthcare of the Russian Federation, Yekaterinburg) by the vertical diffusion method on a *Novaya* solid nutrient medium according to the procedure described in [14]. The minimum inhibitory concentration (MIC) of compounds **2a**, **2b**, **3a**, **4a**, **4b**, **7a**, **7b**, **8a**, **8b**, and **11** was higher than 12.5 μg/mL; i.e., these compounds turned out to be inactive. The MIC value for compound **10** was 1.5 μg/mL, which indicated a moderate tuberculostatic activity.

Thus, we have synthesized conjugates of purine and 2-aminopurine with *N*-(4-aminobenzoyl)-(*S*)-glutamic acid linked to C^6 of the purine moiety both directly and through an aminoethyl linker, as well as a 2-aminopurine conjugate with methyl 4-aminobenzoate linked through a glycine residue. The latter conjugate showed a moderate tuberculostatic activity *in vitro*.

EXPERIMENTAL

6-Chloropurine (**1a**) and 2-amino-6-chloropurine (**1b**) were commercial products. *tert*-Butyl 4-(2-aminoethyl)aminobenzoate was synthesized from 4-fluorobenzoic acid according to the procedures described in [15, 16]. *N*-(2-Aminopurin-6-yl)glycine necessary for the identification of alkaline hydrolysis products of **10** was prepared as reported in [17].

The ^{1}H NMR spectra were recorded at 25°C on Bruker DRX-400 (400 MHz) and Bruker Avance 500 (500 MHz) spectrometers relative to tetramethylsilane as internal standard. The ^{13}C and ^{19}F NMR spectra were measured at 25°C on a Bruker Avance 500 instrument (126 and 470 MHz, respectively). The melting points were determined with a Stuart SMP3 melting point apparatus (Barloworld Scientific, UK). The optical rotations were measured on a Perkin-Elmer M341 polarimeter (USA). The elemental analyses were obtained on a Perkin Elmer 2400 Series II automated CHNS-O analyzer. The high-resolution mass spectra were recorded on a Bruker maXis Impact HD mass spectrometer under atmospheric pressure chemical ionization or electrospray ionization (nebulizer gas nitrogen, flow rate 4 L/min; nebulizer pressure 0.4 bar; capillary voltage 4.5 kV). Thin-layer chromatography was performed on Sorbfil plates (*Imid* Ltd., Russia); spots were visualized under UV light (λ 254 nm).

4-(Purin-6-ylamino)benzoic acid (2a). Concentrated sulfuric acid, 0.102 mL (1.8 mmol), was added to a suspension of 0.309 g (2.0 mmol) of 6-chloro-

purine (**1a**) and 0.329 g (2.4 mmol) of 4-aminobenzoic acid in 26 mL of water, and the mixture was refluxed for 6 h. The precipitate was filtered off and washed with water. Yield 0.457 g (90%), light yellow crystals, mp >360°C. ^{1}H NMR spectrum (500 MHz, DMSO-d_6), δ, ppm: 7.90 d (2H, H_{arom}, J = 8.6 Hz), 8.15 d (2H, H_{arom}, J = 8.6 Hz), 8.34 s (1H, 8-H), 8.46 s (1H, 2-H), 10.17 s (1H, 6-NH), 12.58 br.s (1H, COOH), 13.28 br.s (1H, 9-H). Mass spectrum (ESI): m/z 254.0682 $[M - H]^-$. Found, %: C 56.16; H 3.82; N 27.16. $C_{12}H_9N_5O_2$. Calculated, %: C 56.47; H 3.55; N 27.44. M – H 254.0683. The ^{1}H NMR and mass spectra of 4-(purin-6-ylamino)benzoic acid hydrochloride were given in [18].

4-(2-Aminopurin-6-ylamino)benzoic acid (2b, sulfuric acid salt) was synthesized as described above for compound **2a** from 2-amino-6-chloropurine (**1b**). Yield 92%, white crystals, mp 350–360°C (decomp.). ^{1}H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm: 6.91 br.s (2H, NH_2), 7.91 d (2H, H_{arom}, J = 8.8 Hz), 8.10 s (1H, 8-H), 8.11 d (2H, H_{arom}, J = 8.8 Hz), 10.14 s (1H, 6-NH), 12.35 br.s (2H, 9-H, COOH). Found, %: C 43.78; H 3.59; N 25.12. $C_{12}H_{10}N_6O_2 \cdot 0.6H_2SO_4$. Calculated, %: C 43.80; H 3.43; N 25.54.

Dimethyl (2*S*)-2-{[4-(purin-6-ylamino)benzoyl]amino}pentanedioate (3a). Triethylamine, 3.7 mL (26.5 mmol), was added to a suspension of 0.564 g (2.2 mmol) of acid **2a** in 10 mL of anhydrous DMSO. The mixture was stirred for 30 min, 0.935 g (4.4 mmol) of dimethyl (*S*)-glutamate hydrochloride and 1.42 g (4.42 mmol) of TBTU were added, and the mixture was stirred for 24 h. The mixture was then poured into 200 mL of water and kept in a refrigerator, and the precipitate was filtered off and washed with water. Yield 0.622 g (68%), white crystals, mp 160–162°C, $[\alpha]_D^{22}$ = +3.0° (c = 0.6, AcOH). ^{1}H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm: 2.02 d.d.d.d (1H, C**H**$_2$CH, J = 13.8, 9.2, 7.1, 7.1 Hz), 2.13 d.d.d.d (1H, C**H**$_2$CH, J = 13.8, 7.7, 7.7, 5.4 Hz), 2.47 m (2H, CH_2CO), 3.59 s (3H, OMe), 3.65 s (3H, OMe), 4.46 d.d.d (1H, CHCO, J = 9.3, 7.3, 5.5 Hz), 7.86 d (2H, H_{arom}, J = 8.8 Hz), 8.12 d (2H, H_{arom}, J = 8.8 Hz), 8.33 s (1H, 8-H), 8.45 s (1H, 2-H), 8.60 d (1H, CONH, J = 7.4 Hz), 10.09 s (1H, 6-NH), 13.26 br.s (1H, 9-H). Mass spectrum (APCI): m/z 413.1565 $[M + H]^+$. Found, %: C 55.28; H 4.80; N 20.48. $C_{19}H_{20}N_6O_5$. Calculated, %: C 55.33; H 4.89; N 20.38. M + H 413.1568.

Dimethyl (2*S*)-2-{[4-(2-aminopurin-6-ylamino)benzoyl]amino}pentanedioate (3b) was synthesized as described above for **3a**. Yield 50%, white crystals, mp 128–132°C (decomp.). ^{1}H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm: 2.03 m and 2.12 m (1H each, C**H**$_2$CH), 2.47 m (2H, CH_2CO), 3.59 s (3H, OMe), 3.65 s (3H, OMe), 4.46 d.d.d (1H, C**H**NH, J = 9.4, 7.4, 5.4 Hz), 6.67 br.s (2H, NH_2), 7.86 d (2H, H_{arom}, J = 8.6 Hz), 8.04 br.s (1H, 8-H), 8.10 d (2H, H_{arom}, J = 8.6 Hz), 8.65 d (1H, CONH, J = 7.4 Hz), 10.03 br.s (1H, 6-NH), 12.4 br.s (1H, 9-H). Mass spectrum (ESI): m/z 428.1672 $[M + H]^+$. Found, %: C 53.28; H 4.82; N 22.59. $C_{19}H_{21}N_7O_5$. Calculated, %: C 53.39; H 4.95; N 22.94. M + H 428.1677.

(2*S*)-2-{[4-(Purin-6-ylamino)benzoyl]amino}pentanedioic acid (4a). A solution of 0.937 g (2.27 mmol) of dimethyl ester **3a** in 13.6 mL (13.6 mmol) of 1 M aqueous sodium hydroxide was kept for 4 days at 10°C. The mixture was filtered, the filtrate was acidified to pH 5 with 1 M aqueous HCl, and the jelly-like precipitate was separated by centrifugation and washed twice with water. Yield 0.443 g (51%), white crystals, mp 260–270°C (decomp.), $[\alpha]_D^{25}$ = +19.7° (c = 0.3, 1 M NaOH). ^{1}H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm: 1.97 m and 2.11 m (1H each, C**H**$_2$CH), 2.37 t (2H, CH_2CO, J = 7.4 Hz), 4.40 m (1H, CHCO), 7.87 d (2H, H_{arom}, J = 8.5 Hz), 8.12 d (2H, H_{arom}, J = 8.5 Hz), 8.34 s (1H, 8-H), 8.41 d (1H, CONH, J = 7.9 Hz), 8.46 s (1H, 2-H), 10.11 br.s (1H, 6-NH), 12.53 br.s (2H, COOH), 13.26 br.s (1H, 9-H). ^{13}C NMR spectrum (126 MHz, DMSO-d_6), δ_C, ppm: 26.36 (**C**H$_2$CH), 30.56 (**C**H$_2$CO), 52.14 (**C**HCO), 119.13 (C^m), 123.93 (C^5), 127.29 (C^i), 127.92 (C^o), 130.06, 141.04, 142.95 (C^p), 150.71, 151.61, 165.94 (CONH), 173.93 (CO_2H), 174.03 (CO_2H). Found, %: C 53.29; H 4.18; N 21.83. $C_{17}H_{16}N_6O_5$. Calculated, %: C 53.13; H 4.20; N 21.86.

(2*S*)-2-{[4-(2-Aminopurin-6-ylamino)benzoyl]amino}pentanedioic acid (4b). A solution of 0.23 g (0.54 mmol) of dimethyl ester **3b** in 3.22 mL (3.22 mmol) of 1 M aqueous sodium hydroxide was kept for 4 days at 10°C. The mixture was filtered, the filtrate was acidified to pH with concentrated aqueous HCl, and the precipitate was filtered off, washed with water, dried under reduced pressure, and treated with 2.1 mL of boiling methanol. After cooling to room temperature, the undissolved material was filtered off. Yield 0.176 g (82%), white crystals, mp 263–265°C (decomp.), $[\alpha]_D^{25}$ = +21.6° (c = 0.5, 1 M NaOH). ^{1}H NMR spectrum (500 MHz, DMSO-d_6), δ, ppm: 1.97 m and 2.10 m (1H each, C**H**$_2$CH), 2.37 t (2H, CH_2CO, J = 7.4 Hz), 4.40 d.d.d (1H, CHCO, J = 9.3,

7.6, 5.0 Hz), 6.12 br.s (2H, NH_2), 7.83 d (2H, H_{arom}, J = 8.6 Hz), 7.86 br.s (1H, 8-H), 8.15 d (2H, H_{arom}, J = 8.6 Hz), 8.44 d (1H, CONH, J = 7.6 Hz), 9.60 s (1H, 6-NH), 12.37 br.s (3H, 9-H, COOH). ^{13}C NMR spectrum (126 MHz, DMSO-d_6), δ_C, ppm: 25.98 (**C**H_2CH), 30.42 (**C**H_2CO), 51.86 (**C**HCO), 113.58 (C^5), 118.72 (C^m), 126.42 (C^i), 127.90 (C^o), 136.65 (C^8), 143.51 (C^p), 151.59, 153.03, 159.73, 166.19 (CONH), 173.58 (CO_2H), 173.89 (CO_2H). Mass spectrum (ESI): m/z 400.1360 $[M + H]^+$. Found, %: C 50.78; H 4.38; N 24.32. $C_{17}H_{17}N_7O_5$. Calculated, %: C 51.13; H 4.29; N 24.55. M + H 400.1364.

***tert*-Butyl 4-{[2-(purin-6-ylamino)ethyl]amino}-benzoate (5a).** A mixture of 0.785 g (5.08 mmol) of chloropurine **1a**, 1.20 g (5.08 mmol) of *tert*-butyl 4-[(2-aminoethyl)amino]benzoate, and 0.71 mL (5.08 mmol) of triethylamine in 20 mL of ethanol was refluxed for 8 h. The mixture was cooled and dilute with 60 mL of water, and the precipitate was filtered off. Yield 1.50 g (83%), white crystals, mp 231–233°C. ^1H NMR spectrum (500 MHz, DMSO-d_6), δ, ppm: 1.50 s (9H, *t*-Bu), 3.33 m (2H, CH_2CH_2, overlapped by the signal of H_2O), 3.66 m (2H, CH_2CH_2), 6.58–6.68 m (3H, H_{arom}, NH), 7.63 m (2H, H_{arom}), 7.74 s (1H, NH), 8.11 s (1H, 8-H), 8.23 s (1H, 2-H), 12.94 s (1H, 9-H). Mass spectrum (ESI): m/z 377.1700 $[M + Na]^+$. Found, %: C 60.86; H 6.33; N 23.75. $C_{18}H_{22}N_6O_2$. Calculated, %: C 61.00; H 6.26; N 23.71. M + Na 377.1696.

***tert*-Butyl 4-{[2-(2-aminopurin-6-ylamino)ethyl]-amino}benzoate (5b).** A mixture of 0.764 g (4.5 mmol) of chloropurine **1b**, 1.07 g (4.5 mmol) of *tert*-butyl 4-(2-aminoethylamino)benzoate, and 0.63 mL (4.5 mmol) of triethylamine in 60 mL of butan-1-ol was refluxed for 8 h. The mixture was evaporated to dryness, and the residue was recrystallized from 150 mL of ethanol–water (1:2). Yield 1.40 g (84%), off-white crystals, mp 162–165°C. ^1H NMR spectrum (500 MHz, DMSO-d_6), δ, ppm: 1.49 s (9H, *t*-Bu), 3.22–3.30 m and 3.60 m (2H each, CH_2CH_2), 5.73 br.s (2H, NH_2), 6.58–6.68 m (3H, H_{arom}, NH), 7.26 s (1H, NH), 7.58–7.70 m (3H, H_{arom}, 8-H), 12.09 s (1H, 9-H). Mass spectrum (ESI): m/z 370.1989 $[M + H]^+$. $C_{18}H_{24}N_7O_2$. Calculated: M + H 370.1986.

4-{[2-(Purin-6-ylamino)ethyl]amino}benzoic acid (6a). A solution of 1.50 g (4.23 mmol) of ester **5a** in a mixture of 35 mL of trifluoroacetic acid and 35 mL of methylene chloride was stirred for 4 h at room temperature. The mixture was evaporated to dryness, the residue was treated with diethyl ether, the mixture was stirred, and the precipitate was filtered off and dried under reduced pressure. The product was dispersed in 50 mL of water, 0.8 mL (5 mmol) of *N*,*N*-diethylaniline was added with stirring, and the precipitate was filtered off. Yield 1.17 g (93%), white crystals, mp 233–235°C. ^1H NMR spectrum (500 MHz, DMSO-d_6), δ, ppm: 3.34 m (2H, CH_2CH_2, overlapped by the signal of water), 3.67 m (2H, CH_2CH_2), 6.58–6.68 m (3H, H_{arom}, NH), 7.68 m (2H, H_{arom}), 7.75 s (1H, NH), 8.11 s (1H, 8-H), 8.24 s (1H, 2-H), 12.01 s (1H, COOH), 12.94 s (1H, 9-H). Mass spectrum (ESI): m/z 299.1266 $[M + H]^+$. $C_{14}H_{15}N_6O_2$. Calculated: M + H 299.1251.

4-{[2-(2-Aminopurin-6-ylamino)ethyl]amino}-benzoic acid (6b). A solution of 0.94 g (2.53 mmol) of ester **5b** in a mixture of 23 mL of trifluoroacetic acid and 23 mL of methylene chloride was stirred for 4 h at room temperature. The mixture was evaporated to dryness, the residue was treated with diethyl ether, the mixture was stirred, and the precipitate was filtered off and dried under reduced pressure. The product was dissolved in 50 mL of aqueous methanol (1:1), 0.48 mL (3 mmol) of *N*,*N*-diethylaniline was added, and the precipitate was filtered off. Yield 0.70 g (89%), white crystals, mp 283–285°C. ^1H NMR spectrum (500 MHz, DMSO-d_6), δ, ppm: 3.34 m (2H, CH_2CH_2, overlapped by the signal of water), 3.65 m (2H, CH_2CH_2), 5.90–7.00 br.s (2H, NH_2), 6.58–6.68 m (3H, H_{arom}, NH), 7.69 m (2H, H_{arom}), 7.75–8.30 m (2H, NH, 8-H), 11.80–12.80 m (2H, 9-H, COOH). Mass spectrum (ESI): m/z 314.1354 $[M + H]^+$. $C_{14}H_{16}N_7O_2$. Calculated: M + H 314.1360.

Dimethyl (2*S*)-2-[({4-[2-(purin-6-ylamino)ethyl]-amino}benzoyl)amino]pentanedioate (7a). Acid **6a**, 1.17 g (3.92 mmol), was dissolved in 15 mL of DMSO, 1.52 g (11.75 mmol) of DIPEA, 1.26 g (3.92 mmol) of TBTU, and 0.83 g (3.92 mmol) of dimethyl (*S*)-glutamate hydrochloride were added. The mixture was stirred for 24 h at room temperature, poured into 250 mL of water, neutralized to pH 7 with 6 M aqueous HCl, and extracted with butan-1-ol (3×50 mL). The combined extracts were dried over $MgSO_4$ and evaporated to dryness, and the product was isolated from the residue by flash chromatography using chloroform–methanol–aqueous ammonia as eluent. Yield 0.75 g (42%), light yellow crystals, mp 96–98°C, $[\alpha]_D^{25} = -2.65°$ (c = 1.0, DMF). ^1H NMR spectrum (500 MHz, DMSO-d_6), δ, ppm: 1.92–2.03 m and 2.05–2.13 m (1H each, C**H**$_2$CH), 2.43 t (2H,

CH_2CO, J = 7.5 Hz), 3.34 m (2H, CH_2CH_2, overlapped by the signal of water), 3.58 s (3H, OMe), 3.62 s (3H, OMe), 3.66 m (2H, CH_2CH_2), 4.40 d.d.d (1H, CHCO, J = 9.6, 7.4, 5.3 Hz), 6.43 t (1H, N**H**CH_2, J = 5.7 Hz), 6.65 m (2H, H_{arom}), 7.67 m (2H_{arom}), 7.74 s (1H, NH), 8.10 s (1H, 8-H), 8.22 s (1H, 2-H), 8.27 d (1H, CHN**H**, J = 7.4 Hz), 12.93 s (1H, 9-H). Mass spectrum (ESI): m/z 462.2070 $[M + Li]^+$. $C_{21}H_{25}LiN_7O_5$. Calculated: M + Li 462.2072.

Dimethyl (2*S*)-2-[({4-[2-(2-aminopurin-6-ylamino)ethyl]amino}benzoyl)amino]pentanedioate (7b) was synthesized as described above for **7a**. Yield 57%, off-white crystals, mp 148–150°C. $[\alpha]_D^{25} = -2.25°$ (c = 1.0, DMF). ^{1}H NMR spectrum (500 MHz, DMSO-d_6), δ, ppm: 1.92–2.03 m and 2.05–2.13 m (1H each, C**H**$_2$CH), 2.43 t (2H, CH_2CO, J = 7.5 Hz), 3.27 m (2H, CH_2CH_2), 3.34 s (3H, OMe), 3.50–3.70 m (2H, CH_2CH_2, overlapped by the OMe signal), 3.58 s (3H, OMe), 4.40 d.d.d (1H,CHCO, J = 9.6, 7.4, 5.4 Hz), 5.73 s (2H, NH_2), 6.44 t (1H, N**H**CH_2, J = 5.2 Hz), 6.63 m (2H, H_{arom}), 7.27 s (1H, NH), 7.58–7.74 m (3H, H_{arom}, 8-H), 8.27 d (1H, CHN**H**, J = 7.4 Hz), 12.09 s (1H, 9-H). Mass spectrum (ESI): m/z 477.2174 $[M + Li]^+$. $C_{21}H_{26}LiN_8O_5$. Calculated: M + Li 477.2181.

(2*S*)-2-[({4-[2-(Purin-6-ylamino)ethyl]amino}benzoyl)amino]pentanedioic acid (8a). A solution of 0.33 g (0.72 mmol) of dimethyl ester **7a** in 18 mL of THF was cooled to –5°C, 18 mL of a 0.2 M solution of lithium hydroxide (3.6 mmol) was added, and the mixture was stirred for 24 h at room temperature. The mixture was filtered, the filtrate was washed with 10 mL of chloroform, the aqueous phase was acidified to pH 2 with 6 M aqueous HCl, and the precipitate was filtered off and recrystallized from ethanol. Yield 0.165 g (53%), white crystals, mp 228–230°C (decomp.). $[\alpha]_D^{25} = +4.67°$ (c = 1.0, DMF). ^{1}H NMR spectrum (500 MHz, DMSO-d_6), δ, ppm: 1.84–2.00 m and 2.01–2.11 m (1H each, C**H**$_2$CH), 2.33 t (2H, CH_2CO, J = 7.5 Hz), 3.36 m (2H, CH_2CH_2, overlapped by the signal of water), 3.67 m (2H, CH_2CH_2), 4.35 d.d.d (1H, CHCO, J = 9.7, 7.9, 5.1 Hz), 6.41 m (1H, N**H**CH_2), 6.66 m (2H, H_{arom}), 7.68 m (2H, H_{arom}), 7.74 s (1H, NH), 8.00–8.17 m (2H, 8-H, N**H**CH), 8.24 s (1H, 2-H), 12.32 br.s (2H, COOH), 12.93 s (1H, 9-H). Mass spectrum (ESI): m/z 434.1765 $[M + Li]^+$. $C_{19}H_{21}LiN_7O_5$. Calculated: M + Li 434.1759.

(2*S*)-2-[({4-[2-(2-Aminopurin-6-ylamino)ethyl]amino}benzoyl)amino]pentanedioic acid (8b) was synthesized as described above for **8a**. Yield 86%, white crystals, mp 213–216°C (decomp.), $[\alpha]_D^{25}$ = +5.41° (c = 0.6, DMF). ^{1}H NMR spectrum (500 MHz, DMSO-d_6), δ, ppm: 1.87–1.98 m and 1.98–2.08 m (1H each, CH_2CH), 2.32 m (2H, CH_2CO), 3.37 m and 3.60 m (2H each, CH_2CH_2), 4.34 m (1H, CHCO), 5.74 s (2H, NH_2), 6.41 m (1H, N**H**CH_2), 6.63 m (2H, H_{arom}), 7.29 s (1H, NH), 7.67 m (3H, H_{arom}, 8-H), 8.06 d (1H, N**H**CH, J = 7.1 Hz), 11.20–13.15 br.s (3H, COOH, 9-H). Mass spectrum (ESI): m/z 449.1876 $[M + Li]^+$. $C_{19}H_{22}LiN_8O_5$. Calculated: M + Li 449.1868.

Methyl 4-[(aminoacetyl)amino]benzoate trifluoroacetic acid salt (9). A solution of 1 mL of trifluoroacetic acid in 4 mL of methylene chloride was added to 0.50 g (1.62 mmol) of methyl 4-{[(*tert*-butoxycarbonylamino)acetyl]amino}benzoate prepared as described in [19]. The resulting solution was kept for 2 h at 20°C and evaporated to dryness, and the residue was recrystallized from ethyl acetate. Yield 0.367 g (71%), white crystals, mp 194–195°C. ^{1}H NMR spectrum (500 MHz, DMSO-d_6), δ, ppm: 3.83 s (3H, OMe), 3.84 s (2H, CH_2CO), 7.73 d (2H, H_{arom}, J = 8.8 Hz), 7.97 d (2H, H_{arom}, J = 8.8 Hz), 8.18 br.s (3H, NH_3^+), 10.82 s (1H, NH). ^{19}F NMR spectrum (470 MHz, DMSO-d_6): δ_F 89.03 ppm, s (CF_3). ^{13}C NMR spectrum (126 MHz, DMSO-d_6), δ_C, ppm: 41.19 (**C**H_2CO), 51.95 (OCH_3), 117.26 q (CF_3, $^1J_{CF}$ = 300 Hz), 118.60 (C^m), 124.60 (C^i), 130.49 (C^o), 142.49 (C^p), 158.05 q (CO_2^-, $^2J_{CF}$ = 30.6 Hz), 165.45 (CO), 165.68 (CO). Found, %: C 44.54; H 4.00; F 17.42; N 8.51. $C_{10}H_{12}N_2O_3 \cdot CF_3CO_2H$. Calculated, %: C 44.73; H 4.07; F 17.69; N 8.69.

Methyl 4-{[(2-aminopurin-6-ylamino)acetyl]amino}benzoate hemihydrate (10). A suspension of 0.111 g (0.66 mmol) of chloropurine **1b**, 0.315 g (0.98 mmol) of compound **9**, and 0.25 mL (1.79 mmol) of triethylamine in 5 mL of ethanol was refluxed for 30 h. The mixture was cooled to room temperature, and the precipitate was filtered off and recrystallized from 40 mL of methanol. Yield 0.085 g (37%), white crystals, mp 243–245°C (decomp.). ^{1}H NMR spectrum (500 MHz, DMSO-d_6), δ, ppm: 3.82 s (3H, OMe), 4.27 m (2H, CH_2CO), 5.79 br.s (2H, NH_2), 7.31 br.s (1H, N**H**CH_2), 7.72 s (1H, 8-H), 7.75 d (2H, H_{arom}, J = 8.6 Hz), 7.92 d (2H, H_{arom}, J = 8.6 Hz), 10.41 s (1H, CONH), 12.18 br.s (1H, 9-H). ^{13}C NMR spectrum (126 MHz, DMSO-d_6), δ_C, ppm: 43.99 (**C**H_2CO), 51.78 (OCH_3), 112.86 (C^5), 118.43 (C^m), 123.82 (C^i), 130.22 (C^o), 135.85 (C^8), 143.33 (C^p), 152.35, 154.43, 159.80, 165.75 (CONH), 169.18 (**C**O_2CH_3). Mass

spectrum (ESI): *m*/z 340.1167 $[M - H]^-$. Found, %: C 51.65; H 4.48; N 28.04. $C_{15}H_{15}N_7O_3 \cdot 0.5H_2O$. Calculated, %: C 51.42; H 4.57; N 28.00.

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CONFLICT OF INTERESTS

The authors declare the absence of conflict of interests.

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