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Supporting Information

for

Ultrasonic-assisted unusual four-component synthesis of 7-azolylamino-4,5,6,7-tetrahydroazolo[1,5-*a*]pyrimidines

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Experimental and analytical data as well as X-ray crystallographic information

General

All solvents were obtained from standard commercial vendors and used without additional purification. Starting 5-aminopyrazoles **1a**/**b** and (*p*-methoxybenzylidene)pyruvic acid (**8**) were synthesized according to described procedures [1,2]. 3-Amino-1,2,4-triazole (**1c**), pyruvic acid (**3a**), and ethyl 2-oxopropanoate (**3b**) are commercially available.

Ultrasonication was carried out with the help of a standard US bath (SELDI, Ukraine), producing irradiation at 44.2 kHz in a round-bottom flask equipped with a condenser. Melting points of all the compounds synthesized were determined with a Kofler melting point apparatus and are uncorrected. The ^{1}H, ^{13}C, and 2D NMR experiments were performed in DMSO-d_6 at 400 MHz (100 MHz for ^{13}C) with a Varian MR-400 spectrometer, at 300 MHz (75 MHz for ^{13}C) with a Bruker Advance 300 spectrometer, and at 600 MHz (150 MHz for ^{13}C) with a Bruker Advance DRX600 spectrometer. The mass spectra were measured on a GS-MS Varian 1200L (direct input of the sample, ionizing voltage 70 eV) instrument and on a LCQ Advantage system for LC–MS. Elemental analysis was performed on a Euro Vector EA-3000 and Heraeus (CHN-O-RAPID) CHN analyzer. Samples for elemental analysis and for measuring the melting temperature were prepared separately.

Chemistry

3-Cyano-7-((4-cyano-1H-pyrazol-5-yl)amino)-5-phenyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrimidine-7-carboxylic acid (**4a**). 5-Amino-1*H*-pyrazole-4-carbonitrile (**1a**, 0.92 mmol) was dissolved in 1.5 mL of acetic acid, followed by benzaldehyde (**2a**, 0.46 mmol) and pyruvic acid (**3a**, 0.46 mmol). The mixture was ultrasonicated for 90 min and allowed to stand until a precipitate formed. The precipitate was filtered off and dried in vacuum.

White solid (0.13 g, 76%); [Found: C, 57.52; H, 3.81; N, 29.99. $C_{18}H_{14}N_8O_2$ requires C, 57.57; H, 3.77; N, 29.93%]; The ^{1}H NMR, δ_H, (400 MHz, DMSO-*d6*) (two stereoisomers): **A** stereoisomer (70% mol.): 2.33-2.40 (m, 1H, CH), 3.16-3.25 (m, 1H, CH), 4.69-4.78 (m, 1H, CH), 6.71 (br s, 1H, NH), 7.29-7.47 (m, 5H, Ar), 7.55 (s, 1H, CH), 7.99 (s, 1H, NH), 8.19 (s, 1H, CH), 12.76 (br s, 1H, NH); **B** stereoisomer (30% mol.): 2.40-2.49 (m, 1H, CH), 3.03-3.11 (m, 1H, CH), 4.69-4.78 (m, 1H, CH), 6.96 (br s, 1H, NH), 7.29-7.47 (m, 5H, Ar), 7.69 (s, 1H, CH), 7.99 (s, 1H, NH), 8.34 (s, 1H, CH), 12.76 (br s, 1H, NH); The ^{13}C NMR, δ_C (100 MHz, DMSO-*d6*) **A** stereoisomer: 170.3, 153.3, 152.1, 141.3, 141.2, 135.4, 129.0, 128.4, 127.2, 115.2, 114.5, 79.0, 73.4, 73.0, 53.4, 37.8; **B** stereoisomer: 169.2, 152.9, 151.5, 142.0, 141.0, 135.2, 129.0, 128.4, 127.3, 115.0, 114.8, 78.9, 71.6, 71.2, 51.3, 38.8. ESI MS, m/z (%): negative mode: 373 (100) $[M-H]^-$.

The compounds **4b**/**c** were obtained according to the procedure for **4a**:

3-Cyano-7-((4-cyano-1H-pyrazol-5-yl)amino)-5-(4-methoxyphenyl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrimidine-7-carboxylic acid (**4b**). White solid (0.16 g, 86%); [Found: C, 56.37; H, 4.11; N, 27.76. $C_{19}H_{16}N_8O_3$ requires C, 56.43; H, 3.99; N, 27.71%]; The ^{1}H NMR, δ_H, (400 MHz, DMSO-*d6*) (two stereoisomers): **A** stereoisomer (70% mol.): 2.27-2.34 (m, 1H, CH), 3.12-3.23 (m, 1H, CH), 3.75 (s, 3H, OCH_3), 4.61-4.74 (m, 1H, CH), 6.69 (br s, 1H, NH), 6.90-7.38 (m, 4H, Ar), 7.54 (s, 1H, CH), 7.91 (s, 1H, NH), 8.19 (s, 1H, CH), 12.76 (br s, 1H, NH); **B** stereoisomer (30% mol.): 2.41-2.47 (m, 1H, CH), 2.96-3.06 (m, 1H, CH), 3.86 (s, 3H, OCH_3), 4.61-4.74 (m, 1H, CH), 6.90-7.38 (m, 4H, Ar), 7.68 (s, 1H, CH), 7.91 (s, 1H, NH), 8.26 (s, 1H, CH), 12.77 (br s, 1H, NH); The ^{13}C NMR, δ_C (100 MHz, DMSO-*d6*) **A** stereoisomer: 169.5, 158.8, 152.5, 141.3, 140.6, 135.6, 134.4, 132.4, 127.8, 127.7, 113.7, 81.6, 72.8, 72.4, 55.0, 52.2, 37.2; **B** stereoisomer: 169.2, 158.7, 152.5, 151.5, 150.9, 141.3, 140.8, 135.5, 132.1, 127.9, 127.7, 114.3, 72.4, 71.0, 55.0, 50.0, 38.4. ESI MS, m/z (%): negative mode: 403 (100) $[M-H]^-$.

5-(4-Chlorophenyl)-3-cyano-7-((4-cyano-1H-pyrazol-5-yl)amino)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrimidine-7-carboxylic acid (**4c**). White solid (0.14 g, 75%); [Found: C, 52.78; H, 3.27; N, 27.50. $C_{18}H_{13}ClN_8O_2$ requires C, 52.89; H, 3.21; N, 27.41%]; The ^{1}H NMR, δ_H, (400 MHz, DMSO-*d6*) (two stereoisomers): **A** stereoisomer (75% mol.): 2.33-2.42 (m, 1H, CH), 3.12-3.23 (m, 1H, CH), 4.69-4.83 (m, 1H, CH), 6.69 (br s, 1H, NH), 7.35-7.53 (m, 4H, Ar), 7.56 (s, 1H, CH), 7.99 (s, 1H, NH), 8.19 (s, 1H, CH), 12.75 (br s, 1H, NH); **B** stereoisomer (25% mol.): 2.42-2.48 (m, 1H, CH), 3.03-3.11 (m, 1H, CH), 4.69-4.83 (m, 1H, CH), 6.92 (br s, 1H, NH), 7.35-7.53 (m, 4H, Ar), 7.69 (s, 1H, CH), 7.99 (s, 1H, NH), 8.33 (s, 1H, CH), 12.75 (br s, 1H, NH); The ^{13}C NMR, δ_C (100 MHz, DMSO-*d6*) **A** stereoisomer: 169.6, 151.5, 140.7, 139.7, 134.9, 134.6, 132.3, 128.6, 128.3, 114.5, 113.9, 81.6, 72.7, 72.4, 52.2, 36.9; **B** stereoisomer: 168.6, 152.7, 141.4, 139.5, 134.8, 134.7, 132.1, 128.8, 128.7, 114.3, 114.1, 78.5, 71.1, 71.0, 50.2, 38.1. ESI MS, m/z (%): negative mode: 407 (100) $[M-H]^-$.

Ethyl 3-cyano-7-((4-cyano-1H-pyrazol-5-yl)amino)-5-phenyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrimidine-7-carboxylate (**4d**). 5-Amino-1*H*-pyrazole-4-carbonitrile (**1a**, 0.92 mmol) was dissolved in 1.5 mL of acetic acid, followed by benzaldehyde (**2a**, 0.46 mmol) and ethyl pyruvate (**3b**, 0.46 mmol). The mixture was ultrasonicated for 2 hours and allowed to stand until a precipitate formed. The precipitate was filtered off and dried in vacuum.

White solid (0.11 g, 60%), m.p. 198-200 °C; [Found: C, 59.60; H, 4.55; N, 27.91. $C_{20}H_{18}N_8O_2$ requires C, 59.69; H, 4.51; N, 27.85%]; The ^{1}H NMR, δ_H, (400 MHz, DMSO-*d6*): 1.25 (t, *J* 7.3 Hz, 3H, $OCH_2C\underline{H}_3$), 2.38-2.48 (m, 1H, CH), 3.11-3.25 (m, 1H, CH), 4.29 (q, *J* 7.3 Hz, 2H, $C\underline{H}_2CH_3$), 4.55-4.63 (m, 1H, CH), 7.14 (br s, 1H, NH), 7.28-7.50 (m, 5H, Ar), 7.59 (s, 1H, CH), 8.06 (s, 1H, NH), 8.21 (s, 1H, CH) 12.35 (br s, 1H,

NH); The ^{13}C NMR, δ_C (150 MHz, DMSO-*d6*): 168.7, 153.8, 151.8, 141.3, 141.0, 135.3, 129.1, 128.5, 127.2, 115.3, 114.7, 78.9, 74.1, 71.5, 63.1, 53.2, 38.7, 14.3. MS, m/z (%): negative mode: 401 (100) $[M-H]^-$.

The compounds **4e**–**o** were obtained similarly to the **4d**:

Ethyl 3-cyano-7-((4-cyano-1H-pyrazol-5-yl)amino)-5-(4-methoxyphenyl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrimidine-7-carboxylate (**4e**). White solid (0.15 g, 73%), m.p. 144-146 °C; [Found: C, 58.29; H, 4.72; N, 25.98. $C_{21}H_{20}N_8O_3$ requires C, 58.33; H, 4.66; N, 25.91%]; The ^{1}H NMR, δ_H, (400 MHz, DMSO-*d6*): 1.23 (t, *J* 7.3 Hz, 3H, $OCH_2C\underline{H}_3$), 2.39 (dd, ^2J 2.2 Hz, ^3J 12.2 Hz, 1H, CH), 3.11-3.21 (m, 1H, CH), 3.77 (s, 3H, OCH_3), 4.21-4.23 (m, 2H, $C\underline{H}_2CH_3$), 4.52 (dd, ^3J 2.2 Hz, ^3J 12.2 Hz, 1H, CH), 6.92-7.38 (m, 4H, Ar), 7.13 (br s, 1H, NH), 7.57 (s, 1H, CH), 7.97 (s, 1H, NH), 8.20 (s, 1H, CH) 12.71 (br s, 1H, NH); The ^{13}C NMR, δ_C (150 MHz, DMSO-*d6*): 168.7, 159.6, 151.7, 141.3, 141.2, 135.3, 132.8, 128.4, 115.3, 114.7, 114.4, 78.9, 74.1, 71.3, 63.0, 55.7, 52.6, 38.7, 14.3. MS, m/z (%): negative mode: 431 (100) $[M-H]^-$.

Ethyl 5-(4-chlorophenyl)-3-cyano-7-((4-cyano-1H-pyrazol-5-yl)amino)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrimidine-7-carboxylate (**4f**). White solid (0.11 g, 55%), m.p. 146-148 °C; [Found: C, 54.91; H, 3.95; N, 25.72. $C_{20}H_{17}ClN_8O_2$ requires C, 54.99; H, 3.92; N, 25.65%]; The ^{1}H NMR, δ_H, (400 MHz, DMSO-*d6*): 1.24 (t, *J* 7.1 Hz, 3H, $OCH_2C\underline{H}_3$), 2.37-2.48 (m, 1H, CH), 3.09-3.24 (m, 1H, CH), 4.22-4.34 (m, 2H, $C\underline{H}_2CH_3$), 4.55-4.66 (m, 1H, CH), 7.14 (br s, 1H, NH), 7.40-7.53 (m, 4H, Ar), 7.59 (s, 1H, CH), 8.06 (s, 1H, NH), 8.20 (s, 1H, CH) 12.73 (br s, 1H, NH); The ^{13}C NMR, δ_C (150 MHz, DMSO-*d6*): 168.6, 153.7, 151.6, 141.3, 140.0, 135.5, 132.9, 129.1, 129.0, 115.2, 114.7, 78.9, 73.9, 71.5, 63.1, 52.5, 38.3, 14.3. MS, m/z (%):negative mode: 435 (100) $[M-H]^-$.

Ethyl 5-(4-bromophenyl)-3-cyano-7-((4-cyano-1H-pyrazol-5-yl)amino)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrimidine-7-carboxylate (**4g**). White solid (0.18 g, 80%), m.p. 152-154 °C; [Found: C, 49.82; H, 3.62; N, 23.33. $C_{20}H_{17}BrN_8O_2$ requires C, 49.91; H, 3.56; N, 23.28%]; The ^{1}H NMR, δ_H, (400 MHz, DMSO-*d6*): 1.24 (t, *J* 7.1 Hz, 3H, $OCH_2C\underline{H}_3$), 2.38-2.48 (m, 1H, CH), 3.11-3.23 (m, 1H, CH), 4.19-4.36 (m, 2H, $C\underline{H}_2CH_3$), 4.55-4.64 (m, 1H, CH), 7.14 (br s, 1H, NH), 7.32-7.61 (m, 4H, Ar), 7.62 (s, 1H, CH), 8.06 (s, 1H, NH), 8.19 (s, 1H, CH) 12.71 (br s, 1H, NH); The ^{13}C NMR, δ_C (150 MHz, DMSO-*d6*): 168.6, 153.7, 151.6, 141.3, 140.0, 135.5, 131.9, 129.1, 129.5, 121.4, 115.2, 114.7, 78.9, 73.9, 71.5, 63.1, 52.5, 38.2, 14.3. MS, m/z (%): 479 (100) $[M-H]^-$.

Ethyl 3-cyano-7-((4-cyano-1H-pyrazol-5-yl)amino)-5-(4-(methoxycarbonyl)phenyl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrimidine-7-carboxylate (**4h**). White solid (0.135 g, 64%), m.p. 205-207 °C; [Found: C, 57.30; H, 4.46; N, 24.39. $C_{22}H_{20}N_8O_4$ requires C, 57.39; H, 4.38; N, 24.34%]; The ^{1}H NMR, δ_H, (400 MHz, DMSO-*d6*): 1.24 (t, *J* 7.3 Hz, 3H, $OCH_2C\underline{H}_3$), 2.38 (dd, ^3J 2.2 Hz, ^2J 12.2 Hz, 1H, CH), 3.07-3.25 (m, 1H, CH), 3.77 (s, 3H, OCH_3), 4.18-4.36 (m, 2H, $C\underline{H}_2CH_3$), 4.52 (dd, ^3J 2.2 Hz, ^3J 12.2 Hz, 1H, CH), 6.92-7.41 (m, 4H, Ar), 7.12 (br s, 1H, NH), 7.56 (s, 1H, CH), 7.97 (s, 1H, NH), 8.21 (s, 1H, CH) 12.72 (br s, 1H, NH); The ^{13}C NMR, δ_C (150 MHz, DMSO-*d6*): 172.5, 168.7, 159.5, 153.8, 151.7, 141.2, 135.3, 132.8, 128.4, 115.3, 114.7, 114.4, 78.9, 74.1, 71.3, 63.0, 55.7, 52.6, 38.7, 14.3. ESI MS, m/z (%): negative mode: 431 (100) $[M-C_2H_5]^-$.

Ethyl 3-cyano-7-((4-cyano-1H-pyrazol-5-yl)amino)-5-(4-cyanophenyl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrimidine-7-carboxylate (**4i**). White solid (0.1 g, 53%), m.p. 159-161 °C; [Found: C, 58.96; H, 4.11; N, 29.53. $C_{21}H_{17}N_9O_2$ requires C, 59.01; H, 4.01; N, 29.49%]; The ^{1}H NMR, δ_H, (400 MHz, DMSO-*d6*): 1.23 (t, *J* 7.1 Hz, 3H, $OCH_2C\underline{H}_3$), 2.45-2.48 (m, 1H, CH), 3.13-3.25 (m, 1H, CH), 4.20-4.34 (m, 2H, $C\underline{H}_2CH_3$), 4.64-4.76 (m,

1H, CH), 7.12 (br s, 1H, NH), 7.61 (s, 1H, CH), 7.62-7.91 (m, 4H, Ar), 8.15 (s, 1H, NH), 8.19 (s, 1H, CH) 12.71 (br s, 1H, NH); The ^{13}C NMR, δ_C (150 MHz, DMSO-*d6*): 168.4, 153.6, 151.5, 146.7, 141.3, 135.3, 133.0, 128.3, 119.1, 115.1, 114.6, 111.2, 78.9, 73.8, 71.7, 63.1, 52.7, 37.7, 14.3. MS (EI, 70 eV), m/z (%): 222 (85), 246 (54), 427 (5) $[M]^+$.

Ethyl 3-cyano-7-((4-cyano-3-methyl-1H-pyrazol-5-yl)amino)-2-methyl-5-phenyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrimidine-7-carboxylate (**4j**). White solid (0.08 g, 45%); [Found: C, 61.22; H, 5.25; N, 26.05. $C_{22}H_{22}N_8O_2$ requires C, 61.38; H, 5.15; N, 26.03%]; The ^{1}H NMR, δ_H, (400 MHz, DMSO-*d6*) (two stereoisomers): **A** stereoisomer (80% mol.): 1.07 (t, *J* 7.1 Hz, 3H, $OCH_2C\underline{H}_3$), 2.12 (s, 1H, CH_3), 2.27 (s, 1H, CH_3), 2.41-2.47 (m, 1H, CH), 3.22-3.29 (m, 1H, CH), 4.04 (q, *J* 7.1 Hz, 2H, $C\underline{H}_2CH_3$), 4.61-4.68 (m, 1H, CH), 7.04 (br s, 1H, NH), 7.29-7.45 (m, 5H, Ar), 8.25 (s, 1H, NH), 12.40 (br s, 1H, NH); **B** stereoisomer (20% mol.): 1.24 (t, *J* 6.9 Hz, 3H, $OCH_2C\underline{H}_3$), 2.06 (s, 1H, CH_3), 2.23 (s, 1H, CH_3), 2.32-2.39 (m, 1H, CH), 3.14-3.20 (m, 1H, CH), 4.22-4.30 (m, 2H, $C\underline{H}_2CH_3$), 4.55-4.61 (m, 1H, CH), 6.89 (br s, 1H, NH), 7.29-7.45 (m, 5H, Ar), 7.95 (s, 1H, NH), 12.46 (br s, 1H, NH); The ^{13}C NMR, δ_C (150 MHz, DMSO-*d6*) **A** stereoisomer: 167.6, 153.7, 151.5, 150.2, 145.9, 141.1, 129.0, 128.3, 127.3, 115.3, 115.1, 79.1, 73.4, 71.5, 62.2, 50.9, 37.2, 14.2, 13.2, 10.5. MS, m/z (%): negative mode 429 (100) $[M-H]^-$.

Ethyl 3-cyano-7-((4-cyano-3-methyl-1H-pyrazol-5-yl)amino)-5-(4-methoxyphenyl)-2-methyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrimidine-7-carboxylate (**4k**). White solid (0.13 g, 68%); [Found: C, 59.82; H, 5.37; N, 24.23. $C_{23}H_{24}N_8O_3$ requires C, 59.99; H, 5.25; N, 24.33%]; The ^{1}H NMR, δ_H, (400 MHz, DMSO-*d6*) (two stereoisomers): **A** stereoisomer (65% mol.): 1.07 (t, *J* 7.3 Hz, 3H, $OCH_2C\underline{H}_3$), 2.12 (s, 1H, CH_3), 2.26 (s, 1H, CH_3), 2.43 (dd, ^2J 13.2 Hz, ^3J 2.6 Hz, 1H, CH), 3.15 (dd, ^2J 13.2 Hz, ^3J 11.4 Hz, 1H, CH), 3.75 (s, 3H, OCH_3), 4.07 (q, *J* 7.3 Hz, 2H, $C\underline{H}_2CH_3$), 4.59 (dd, ^3J 2.6 Hz, ^3J 11.4 Hz, 1H, CH),

6.91-7.30 (m, 4H, Ar), 7.06 (br s, 1H, NH), 8.20 (s, 1H, NH), 12.35 (br s, 1H, NH); **B** stereoisomer (35% mol.): 1.23 (t, *J* 7.3 Hz, 3H, $OCH_2C\underline{H}_3$), 2.06 (s, 1H, CH_3), 2.23 (s, 1H, CH_3), 2.34 (dd, ^2J 12.9 Hz, ^3J 2.9 Hz, 1H, CH), 3.15 (dd, ^2J 12.9 Hz, ^3J 12.4 Hz, 1H, CH), 3.76 (s, 3H, OCH_3), 4.23-4.28 (m, 2H, $C\underline{H}_2CH_3$), 4.53 (dd, ^3J 2.9 Hz, ^3J 12.4 Hz, 1H, CH), 6.91 (br s, 1H, NH), 6.95-7.33 (m, 4H, Ar), 7.87 (s, 1H, NH), 12.35 (br s, 1H, NH); The ^{13}C NMR, δ_C (150 MHz, DMSO-*d6*) **A** stereoisomer: 167.7, 159.4, 153.4, 151.5, 150.3, 146.2, 132.8, 128.5, 115.3, 115.1, 114.3, 79.0, 73.5, 71.4, 62.3, 55.6, 50.3, 37.3, 14.2, 13.2, 10.6; **B** stereoisomer: 168.8, 159.5, 153.4, 152.2, 150.4, 145.8, 133.0, 128.4, 115.5, 114.9, 114.4, 78.9, 73.5, 71.8, 63.0, 54.7, 52.5, 38.4, 14.3, 13.3, 10.8. MS, m/z (%): negative mode 459 (100) $[M-H]^-$.

Ethyl 5-(4-chlorophenyl)-3-cyano-7-((4-cyano-3-methyl-1H-pyrazol-5-yl)amino)-2-methyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrimidine-7-carboxylate (**4l**). White solid (0.105 g, 55%), m.p. 151-153 °C; [Found: C, 56.75; H, 4.62; N, 24.18. $C_{22}H_{21}ClN_8O_2$ requires C, 56.84; H, 4.55; N, 24.10%]; The ^{1}H NMR, δ_H, (400 MHz, DMSO-*d6*): 1.23 (t, *J* 7.1 Hz, 3H, $OCH_2C\underline{H}_3$), 2.07 (s, 1H, CH_3), 2.23 (s, 1H, CH_3), 2.39 (dd, ^3J 2.7 Hz, ^2J 12.2 Hz, 1H, CH), 3.09-3.22 (m, 1H, CH), 4.26 (q, *J* 7.1 Hz, 2H, $C\underline{H}_2CH_3$), 4.61 (dd, ^3J 2.7 Hz, ^3J 12.2 Hz, 1H, CH), 6.90 (br s, 1H, NH), 7.38-7.50 (m, 4H, Ar), 7.96 (s, 1H, NH), 12.44 (br s, 1H, NH); The ^{13}C NMR, δ_C (150 MHz, DMSO-*d6*): 168.7, 153.3, 152.1, 149.7, 145.7, 140.1, 132.9, 129.1, 129.0, 115.4, 114.8, 79.1, 73.3, 72.0, 63.1, 52.4, 37.9, 14.3, 13.3, 10.6. MS, m/z (%): negative mode 463 (100) $[M-H]^-$.

Ethyl 5-(4-bromophenyl)-3-cyano-7-((4-cyano-3-methyl-1H-pyrazol-5-yl)amino)-2-methyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrimidine-7-carboxylate (**4m**). White solid (0.13 g, 63%), m.p. 162-164 °C; [Found: C, 51.81; H, 4.12; N, 22.11. $C_{22}H_{21}BrN_8O_2$ requires C, 51.88; H, 4.16; N, 22.0%]; The ^{1}H NMR, δ_H, (400 MHz, DMSO-*d6*): 1.23 (t, *J* 7.1 Hz, 3H,

$OCH_2C\underline{H}_3$), 2.07 (s, 1H, CH_3), 2.23 (s, 1H, CH_3), 2.41 (dd, ^3J 2.7 Hz, ^2J 11.7 Hz, 1H, CH), 3.10-3.21 (m, 1H, CH), 4.26 (q, J 7.1 Hz, 2H, $C\underline{H}_2CH_3$), 4.59 (dd, ^3J 2.7 Hz, ^3J 11.7 Hz, 1H, CH), 6.88 (br s, 1H, NH), 7.33-7.63 (m, 4H, Ar), 7.96 (s, 1H, NH), 12.45 (br s, 1H, NH); The ^{13}C NMR, δ_C (150 MHz, DMSO-*d6*): 168.7, 153.4, 152.1, 149.6, 145.7, 140.6, 131.9, 129.4, 121.4, 115.4, 114.8, 79.1, 73.3, 72.0, 63.1, 52.4, 37.8, 14.3, 13.3, 10.5. MS, m/z (%): 509 (100) $[M+H]^+$.

Ethyl 3-cyano-7-((4-cyano-3-methyl-1H-pyrazol-5-yl)amino)-5-(4-(methoxycarbonyl)phenyl)-2-methyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrimidine-7-carboxylate (**4n**). White solid (0.11 g, 55%), m.p. 160-162 °C; [Found: C, 58.92; H, 5.11; N, 23.07. $C_{24}H_{24}N_8O_4$ requires C, 59.01; H, 4.95; N, 22.94%]; The ^{1}H NMR, δ_H, (400 MHz, DMSO-*d6*): 1.24 (t, J 7.1 Hz, 3H, $OCH_2C\underline{H}_3$), 2.07 (s, 1H, CH_3), 2.22 (s, 1H, CH_3), 2.40-2.48 (m, 1H, CH), 3.12-3.24 (m, 1H, CH), 3.87 (s, 3H, OCH_3), 4.27 (q, J 7.1 Hz, 2H, $C\underline{H}_2CH_3$), 4.65-4.73 (m, 1H, CH), 6.91 (br s, 1H, NH), 7.52-8.02 (m, 4H, Ar), 8.04 (s, 1H, NH),12.42 (br s, 1H, NH); The ^{13}C NMR, δ_C (150 MHz, DMSO-*d6*): 168.6, 166.4, 153.3, 152.1, 149.7, 146.6, 145.8, 129.9, 129.7, 127.5, 115.4, 114.8, 79.1, 73.3, 72.1, 63.1, 52.8, 52.6, 37.8, 14.3, 13.3, 10.5. ESI MS, m/z (%): 318 (100), 489 (69) $[M+H]^+$.

Ethyl 3-cyano-7-((4-cyano-3-methyl-1H-pyrazol-5-yl)amino)-5-(4-cyanophenyl)-2-methyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrimidine-7-carboxylate (**4o**). White solid (0.09 g, 47%); [Found: C, 60.58; H, 4.57; N, 27.73. $C_{23}H_{21}N_9O_2$ requires C, 60.65; H, 4.65; N, 27.68%]; The ^{1}H NMR, δ_H, (400 MHz, DMSO-*d6*) (two stereoisomers): **A** stereoisomer (70% mol.): 1.05 (t, J 7.1 Hz, 3H, $OCH_2C\underline{H}_3$), 2.13 (s, 1H, CH_3), 2.26 (s, 1H, CH_3), 2.46 (dd, ^3J 2.3 Hz, ^2J 10.2 Hz, 1H, CH), 3.23-3.31 (m, 1H, CH), 3.99 (q, J 7.1 Hz, 2H, $C\underline{H}_2CH_3$), 4.78 (dd, ^3J 2.3 Hz, ^3J 10.1 Hz, 1H, CH), 7.16 (br s, 1H, NH), 7.51-7.90 (m, 4H, Ar), 8.34 (s, 1H, NH), 12.26 (br s, 1H, NH); **B** stereoisomer (30% mol.): 1.24 (t, J 7.0 Hz, 3H,

$OCH_2C\underline{H}_3$), 2.08 (s, 1H, CH_3), 2.22 (s, 1H, CH_3), 2.47 (dd, ^3J 2.5 Hz, ^2J 11.5 Hz, 1H, CH), 3.15-3.24 (m, 1H, CH), 4.26 (q, J 7.0 Hz, 2H, $C\underline{H}_2CH_3$), 4.72 (dd, ^3J 2.5 Hz, ^3J 11.5 Hz, 1H, CH), 6.90 (br s, 1H, NH), 7.51-7.90 (m, 4H, Ar), 8.06 (s, 1H, NH), 12.26 (br s, 1H, NH); The ^{13}C NMR, δ_C (150 MHz, DMSO-*d6*) **A** stereoisomer: 167.4, 153.4, 151.2, 150.2, 146.8, 146.4, 132.9, 128.4, 119.1, 115.2, 115.0, 111.0, 78.9, 73.2, 71.7, 62.4, 50.7, 36.8, 14.1, 13.2, 10.6; **B** stereoisomer: 168.5, 153.2, 151.9, 149.7, 147.6, 145.1, 132.9, 128.2, 119.1, 115.3, 114.7, 112.6, 79.0, 72.6, 72.1, 63.1, 52.6, 37.2, 14.3, 12.5, 10.5. MS, m/z (%): negative mode: 454 (100) $[M-H]^-$.

7-(1H-1,2,4-Triazol-5-ylamino)-5-(4-methoxyphenyl)-4,5,6,7-tetrahydro-[1,2,4]triazolo[1,5-a]pyrimidine-7-carboxylic acid (**4p**). 3-Amino-1,2,4-triazole (**1c**, 2 mmol) was dissolved in 2.5 mL of acetic acid, followed by 4-methoxybenzaldehyde (**2b**, 1 mmol) and pyruvic acid (**3a**, 1 mmol). The mixture was ultrasonicated for 2 hours. The solvent was evaporated and 6 mL of acetone were added to the crude product. The formed precipitate has to be quickly filtered off using pleated paper filter avoiding water and then dried under vacuum.

White solid (60%); [Found: C, 49.31; H, 4.69; N, 30.67. $C_{15}H_{16}N_8O_3 \cdot 0.5H_2O$ requires: C, 50.02; H, 4.87; N, 30.95 %]; The ^{1}H NMR, δ_H, (300 MHz, DMSO-*d6*): 2.22-2.43, 3.01-3.24 (m, 2H, CH_2), 3.73 (s, 3H, $C\underline{H}_3O$), 4.69-4.80 (m, 1H, CH), 6.90-7.30 (m, 4H, ArH), 7.35 (s, 1H, NH), 7.51-7.82 (s, 1H, NH; s, 1H, CH; s, 1H, CH); The ^{13}C NMR, δ_c, (75MHz, DMSO-*d6*): 170.2, 169.3, 158.8, 155.3, 154.9, 148.2, 133.2, 127.7, 113.9, 72.0, 55.1, 52.4, 50.7. LC/MS (ESI): 357 $[M+H]^+$.

The compounds **4q**–**u** were obtained similarly to **4p**:

7-(1H-1,2,4-Triazol-5-ylamino)-5-(3-methoxyphenyl)-4,5,6,7-tetrahydro-[1,2,4]triazolo[1,5-a]pyrimidine-7-carboxylic acid (**4q**). White solid (65%); [Found.: C,

45.92; H, 5.14; N, 28.56. $C_{15}H_{16}N_8O_3 \cdot 2H_2O$ requires C, 47.13; H, 4.65; N, 28.68 %]; The ^{1}H NMR, δ_H, (300 MHz, DMSO-*d6*): 3.07-3.27, 2.26-2.45 (m, 2H, CH_2), 3.75 (s, 3H, C<u>H$_3$</u>O), 4.74-4.86 (m, 1H, CH), 6.85-7.32 (m, 4H, ArH), 7.35(s, 1H, NH), 7.51-7.91(s, 1H, NH; c, 1H, CH; c, 1H, CH), 12.67 (s, 1H, NH); The ^{13}C NMR, δ_c, (75MHz, DMSO-*d6*): 170.2, 169.2, 159.3, 155.2, 148.1, 142.9, 129.6, 118.7, 113.3, 113.1, 112.2, 111.9, 72.0, 55.0, 52.9, 51.2, 40.0. LC/MS (ESI): 357 $[M+H]^+$.

7-(1H-1,2,4-Triazol-5-ylamino)-5-(2-methoxyphenyl)-4,5,6,7-tetrahydro-[1,2,4]triazolo[1,5-a]pyrimidine-7-carboxylic acid (**4r**). White solid (70%); [Found: C, 48.13; H, 4.85; N, 29.93. $C_{15}H_{16}N_8O_3 \cdot H_2O$ requires C, 48.21; H, 4.74; N, 26.95 %]; The ^{1}H NMR, δ_H, (300 MHz, DMSO-*d6*): 2.97-3.25, 2.17-2.38 (m, 2H, CH_2), 3.77 (s, 3H, C<u>H$_3$</u>O), 5.05-5.13 (m, 1H, CH), 6.93-7.49 (m, 4H, ArH), 7.33 (s, 1H, NH), 7.36-7.74 (s, 1H, CH; s, 1H, NH; c, 1H, CH); The ^{13}C NMR, δ_c, (150MHz, DMSO-*d6*): 172.5, 170.8, 156.6, 156.5, 156.1, 148.6, 129.4, 129.1, 126.8, 121.1, 111.4, 72.8, 56.1, 46.9, 37.4. LC/MS (ESI): 357 $[M+H]^+$.

7-(1H-1,2,4-Triazol-5-ylamino)-5-(4-hydroxyphenyl)-4,5,6,7-tetrahydro-[1,2,4]triazolo[1,5-a]pyrimidine-7-carboxylic acid (**4s**). White solid (76%); [Found: C, 42.42; H, 5.09; N, 28.27. $C_{14}H_{14}N_8O_3 \cdot 3H_2O$ requires C, 40.98; H, 4.92; N, 26.87 %]; The ^{1}H NMR, δ_H, (300 MHz, DMSO-*d6*): 3.01-3.23, 2.22-2.43 (s, 2H, CH_2), 4.64-4.75 (m, 1H, CH), 6.74-7.22 (m, 4H, ArH), 7.34 (s, 1H, NH), 7.45-7.77 (s, 1H, NH; s, 1H, CH; s, 1H, CH), 9.43 (s, 1H, OH), 12.97 (s, 1H, NH); The ^{13}C NMR, δ_c, (150MHz, DMSO-*d6*): 170.7, 169.8, 157.5, 155.7, 155.4, 148.4, 131.8, 128.2, 115.7, 72.6, 53.0, 51.3. LC/MS (ESI): 343 $[M+H]^+$.

7-(1H-1,2,4-Ttriazol-5-ylamino)-5-(3-hydroxyphenyl)-4,5,6,7-tetrahydro-[1,2,4]triazolo[1,5-a]pyrimidine-7-carboxylic acid (**4t**). White solid (34%); [Found: C, 47.15; H, 4.37; N, 31.81. $C_{14}H_{14}N_8O_3 \cdot H_2O$ requires C, 46.67; H, 4.48; N, 31.10 %]; The ^{1}H NMR, δ_H, (300 MHz, DMSO-*d6*): 2.99-3.24, 2.14-2.39 (m, 2H, CH_2), 4.67-4.78 (m, 1H, CH), 6.65-7.19 (m, 4H, ArH), 7.31 (s, 1H, NH), 7.48-7.81 (s, 1H, NH; s, 1H, CH; s, 1H, CH), 9.45 (s, 1H, OH); LC/MS (ESI): 343 $[M+H]^+$.

7-(1H-1,2,4-Triazol-5-ylamino)-5-(2-hydroxyphenyl)-4,5,6,7-tetrahydro-[1,2,4]triazolo[1,5-a]pyrimidine-7-carboxylic acid (**4u**). White solid (49%); [Found: C, 45.85; H, 4.76; N, 29.89. $C_{14}H_{14}N_8O_3 \cdot H_2O$ requires C, 46.67; H, 4.48; N, 31.10 %]; The ^{1}H NMR, δ_H, (300 MHz, DMSO-*d6*): 2.93-3.10, 2.33-2.39 (m, 2H, CH_2), 5.09-5.17 (m, 1H, CH), 6.75-7.41 (m, 4H, ArH), 7.30 (s, 1H, NH), 7.45-7.74 (s, 1H, CH; s, 1H, NH; s, 1H, CH), 9.62 (s, 1H, OH); LC/MS (ESI): 343 $[M+H]^+$.

3-Cyano-7-(4-methoxyphenyl)-4,7-dihydropyrazolo[1,5-a]pyrimidine-5-carboxylic acid (**7**):

Reaction of **1a** and **8**: A mixture of 5-aminopyrazole-4-carbonitrile (**1a**, 0.1 g, 0.95 mmol) and ethyl (*E*)-4-(4-methoxyphenyl)-2-oxobut-3-enoate (**8**, 0.2 g, 0.95 mmol) in 2 mL of acetic acid was heated at reflux for 10 min. After cooling, the precipitate formed was filtered off and dried in vacuum.

Reaction of **1a**, **2b**, and **3a**: A mixture of 5-aminopyrazole-4-carbonitrile (**1a**, 0.1 g, 0.95 mmol), 4-methoxybenzaldehyde (**2b**, 0.13 g, 0.95 mmol), and pyruvic acid (**3a**, 0.08 g, 0.95 mmol) was refluxed in 2 mL of acetic acid for 4 h. The mixture was allowed to stand until a precipitate formed. The precipitate formed was filtered off and dried in vacuum.

Synthesis of **7** from tetrahydro derivative **4b**: Compound **4b** (40 mg) was refluxed for 2 h in 2 mL of acetic acid. After cooling, the precipitate was filtered off and dried in vacuum.

Yellow solid (0.08 g, 28% - from reaction of **1a**+**8**; 0.18 g, 66% - from reaction of **1a**, **2b**, and **3a**; 0.01 g, 35% - from tetrahydro derivative **4b**), m.p. 247-249 °C. [Found: C, 60.77; H, 4.15; N, 18.98. $C_{15}H_{12}N_4O_3$ requires C, 60.81; H, 4.08; N, 18.91%]; The ^{1}H NMR, δ_H, (400 MHz, DMSO-*d6*): 3.70 (s, 1H, OCH_3), 5.82 (dd, ^3J 4.3 Hz, ^4J 1.5 Hz, 1H, CH), 6.14 (d, ^3J 4.3 Hz, 1H, CH), 6.84-7.14 (m, 4H, Ar), 7.76 (s, 1H, CH), 10.14 (d, ^4J 1.5 Hz, 1H, NH), 12.42 (br s, 1H, COOH); The ^{13}C NMR, δ_C (100 MHz, DMSO-*d6*): 163.2, 159.7, 150.4, 143.4, 142.7, 133.3, 128.6, 126.9, 114.6, 107.9, 74.1, 59.4, 55.7. ESI MS, m/z (%): negative mode 295 (100) $[M-H]^-$.

X-ray analysis

The colorless crystals of **4g** ($C_{22}H_{20}N_9O_2Br$) are triclinic. At 293 K a = 8.6432(6), b = 10.8530(8), c = 14.1860(9) Å, α = 96.470(6)°, β = 107.447(6)°, γ = 107.557(7)°, V = 1179.78(15) Å^3, M_r = 522.38, Z = 2, space group $P\bar{1}$, d_{calc} = 1.471 g/cm^3, μ(Mo K_α) = 1.781 mm^{-1}, F(000) = 532. Intensities of 24215 reflections (4649 independent, R_{int} = 0.078) were measured on the Xcalibur-3 diffractometer (graphite monochromated Mo K_α radiation, CCD detector, ω-scaning, $2\Theta_{max}$ = 52°). The structure was solved by direct method using SHELXTL package [3]. The absorption was taken into account using an analytical approach (T_{min} = 0.740, T_{max} = 0.871). The positions of the hydrogen atoms were located from electron density difference maps and refined by a riding model with $U_{iso} = n \cdot U_{eq}$ (n = 1.5 for methyl groups and n = 1.2 for other hydrogen atoms) of the carrier atom. Full-matrix least-squares refinement against F^2 in anisotropic approximation for nonhydrogen atoms using 4649 reflections was converged to wR_2 = 0.208 (R_1 = 0.083 for 2628 reflections, with F > 4σ(F), S = 0.988). The final atomic coordinates and crystallographic data for molecule **4g** have been deposited with the Cambridge Crystallographic Data Centre, 12 Union Road, CB2 1EZ, UK (fax: +44-1223-336033;

email: deposit@ccdc.cam.ac.uk), and are available on request quoting the deposition numbers CCDC 1970864).

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