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A convenient synthesis of new (1,2,4-triazolylamino)pyrimidines from cyanamide precursor

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^{1}H NMR spectra were recorded on a Bruker AM-300 spectrometer (300 MHz), ^{13}C NMR spectra were recorded on a Bruker Avance 600 spectrometer (150 MHz for ^{13}C). Residual signals of the deuterated solvent (δ 2.50 for DMSO-d_6) were used as a reference in the ^{1}H NMR spectra. Multiplet signals of the deuterated solvent (δ 39.50 for DMSO-d_6) were the reference in the ^{13}C NMR spectra. IR spectra were recorded on a Bruker Alpha spectrometer. High resolution mass spectra were recorded on a Bruker micrOTOF II instrument (ESI). Measurements were carried out in the positive ranges (capillary voltage was 4500 V). The masses were scanned in the range m/z 50-3000 Da using an external and an internal calibration (Electrospray Calibrant Solution, Fluka). An acetonitrile solution of a compound was injected by a syringe, the flow rate was 3 μm×min^{-1}, nitrogen was a sprayer gas (4 dm^3×min^{-1}), the interface temperature was 180^{o} C. The starting *N*-(4,6-dimethylpyrimidin-2-yl)cyanamide (**1**) [S1], hydrazides **2a** [S2] and **2b** [S3] were synthesized as reported. Commercially available nickel(II) acetylacetonate and anhydrous dioxane were purchased from Sigma-Aldrich and were used without additional purification.

tert-Butyl N-{[5-(4,6-dimethylpyrimidin-2-ylamino)-4H-1,2,4-triazol-3-yl]methyl}carbamate **3a.** White powder, yield 73%, mp 287 °C. IR (KBr, ν/cm^{-1}): 3451, 3308 (NH), 1696 (C=O), 1629, 1548(C=C,C=N). ^{1}H NMR, *δ*: 12.80 and 10.95 (both s, 2H, 2NH), 7.20 (s, H, CH), 4.10 (s, 2H, CH_2), 2.35 (s, 6H, 2Me), 1.40 (s, 9H, 3Me). HRMS (ESI), m/z: 320.1828 $[M+H]^+$ (calc. for $C_{14}H_{22}N_7O_2$, m/z: 320.1835).

tert-Butyl 4-{[5-(4,6-dimethylpyrimidin-2-ylamino)-4H-1,2,4-triazol-3-yl]methyl}piperazine-1-carboxylate **3b.** White powder, yield 67%, mp 325 °C. IR (KBr, ν/cm^{-1}): 3321 (NH), 1697 (C=O), 1629, 1546(C=C,C=N). ^{1}H NMR, *δ*: 12.80 and 10.85 (both s, 2H, 2NH), 6.75 (s, 1H, CH), 3.40 (s, 2H, CH_2), 3.30 (m, 4H, 2CH_2), 2.50 (m, 4H, 2CH_2), 2.35 (s, 6H, 2Me), 1.40 (s, 9H, 3Me). HRMS (ESI), m/z: 389.2407 $[M+H]^+$ (calc. for $C_{18}H_{29}N_8O_2$, m/z: 389.2413).

N-(5-Aminomethyl-4H-1,2,4-triazol-3-yl)-4,6-dimethylpyrimidin-2-amine hydrochloride **4a.** White powder, yield 67%, mp >350 °C. IR (KBr, ν/cm^{-1}): 3409 (NH, NH_2), 1625, 1536 (C=C,C=N). ^{1}H NMR, δ: 10.80-9.10 (br.s, 4H, NH, NH_2^+), 6.75 (s, 1H, CH), 3.85 (m, 2H, CH_2), 3.20 (s, 6H, 2Me), 3.05 (br. s, 2H, CH_2), 2.45 and 2.40 (both s, 6H, 2Me). ^{13}C NMR, δ: 167.8 ($C^{4'}$, and $C^{6'}$), 157.1 (C^5), 154.3(C^3), 151.3 ($C^{2'}$), 113.5 ($C^{5'}$), 53.7 (CH_2), 48.3 ($2CH_2$), 42.6 ($2CH_2$), 23.2 ($2CH_3$). Found (%): C, 42.91; H, 5.76; N, 31.34; Cl, 19.33. Calc. for $C_{13}H_{22}N_8Cl_2$ (%): C, 43.22; H, 6.14; N, 31.02; Cl, 19.62. HRMS (ESI), m/z: 289.1837 $[M+H]^+$ (calc. for $C_{13}H_{21}N_8$, m/z: 289.1844).

4,6-Dimethyl-N-[5-(piperazin-1-ylmethyl)-4H-1,2,4-triazol-3-yl]pyrimidin-2-amine dihydrochloride **4b.** White powder, yield 83%, mp >350 °C. IR (KBr, ν/cm^{-1}): 3361 (NH, NH_2), 1632, 1579 (C=C,C=N). ^{1}H NMR, δ: 12.80-12.10, (br.s, H, NH), 8.85 (br.s, 4H, NH, NH_2^+), 6.75 (s, 1H, CH), 4.10 (m, 2H, CH_2), 2.45 (s, 6H, 2Me). ^{13}C NMR, δ: 170.1 ($C^{4'}$, and $C^{6'}$), 152.3($C^{2'}$), 147.8, 146.3 (C^3 and C^5), 105.4 ($C^{5'}$), 33.8 (CH_2), 19.7 ($2CH_3$). Found (%): C, 42.27; H, 5.48; N, 38.36; Cl, 13.89. Calc. for $C_9H_{14}N_7Cl$ (%): C, 42.11; H, 5.76; N, 38.54; Cl, 13.63. HRMS (ESI), m/z: 220.1261 $[M+H]^+$ (calc. for $C_9H_{14}N_7$, m/z: 220.1266).

References

[S1] S. Birtwell, *J. Chem. Soc*., 1953, 1725.

[S2] S. Borg, G. Estenne-Bouhtou, K. Luthman, I. Csoeregh, W. Hesselink and U. Hacksell, *J. Org. Chem.*, 1995, **60**, 3112.

[S3] J. Jia, K. Wang, W. Shi, S. Chen, X. Li, and H. Ma, *Chem. Eur J*., 2010, **16**, 6638.

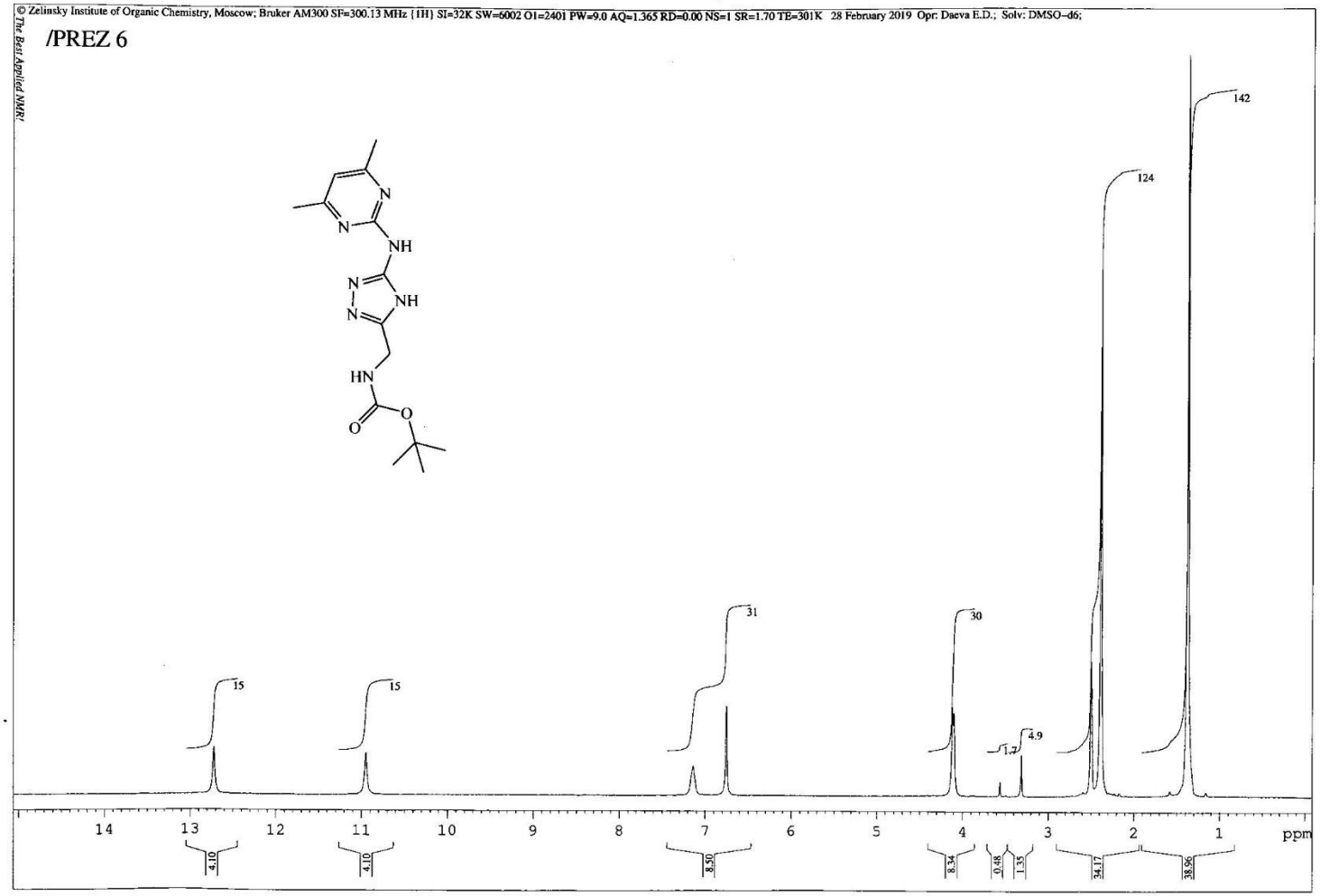

Figure S1. ^{1}H NMR spectrum of *tert*-butyl({5-[(4,6-dimethylpyrimidin-2-yl)amino]-4*H*-1,2,4-triazol-3-yl}methyl) carbamate **3a.**

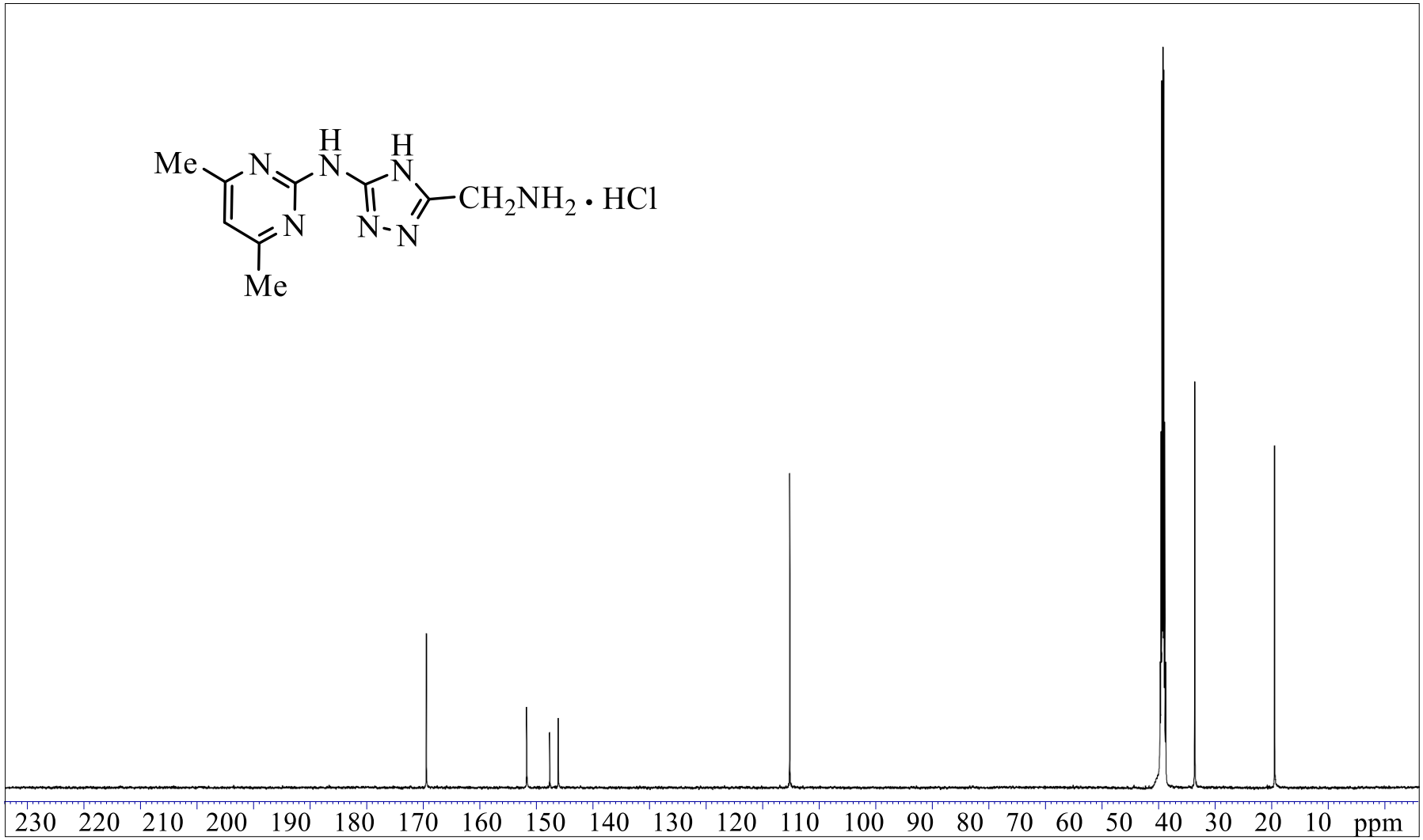

Figure S2. ^{13}C NMR spectrum of *N*-(5-(aminomethyl)-4*H*-1,2,4-triazol-3-yl)-4,6-dimethylpyrimidin-2-amine hydrochloride **4a.**

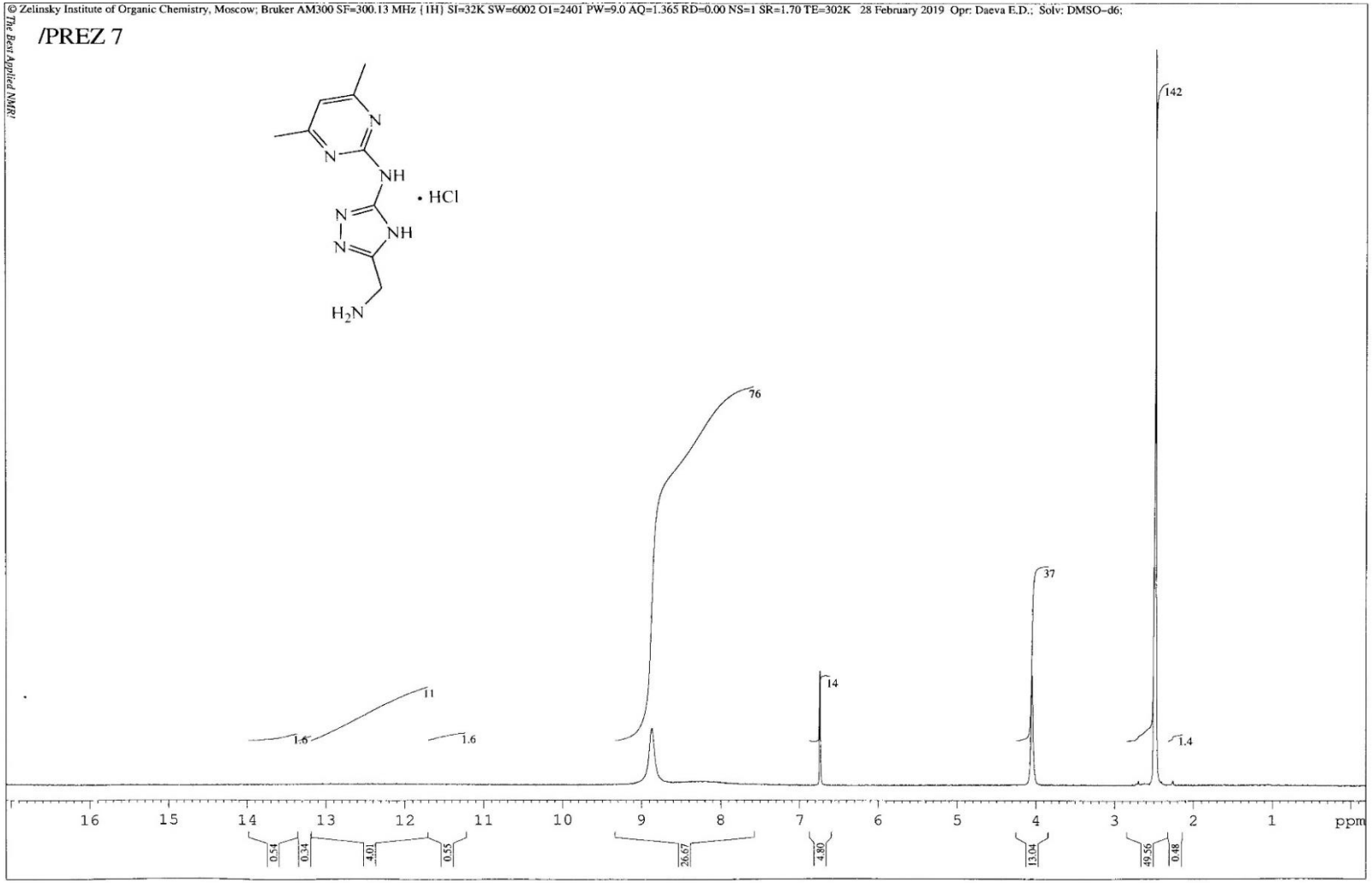

Figure S3. ^{1}H NMR spectrum of *N*-(5-(aminomethyl)-4*H*-1,2,4-triazol-3-yl)-4,6-dimethylpyrimidin-2-amine hydrochloride **4a.**

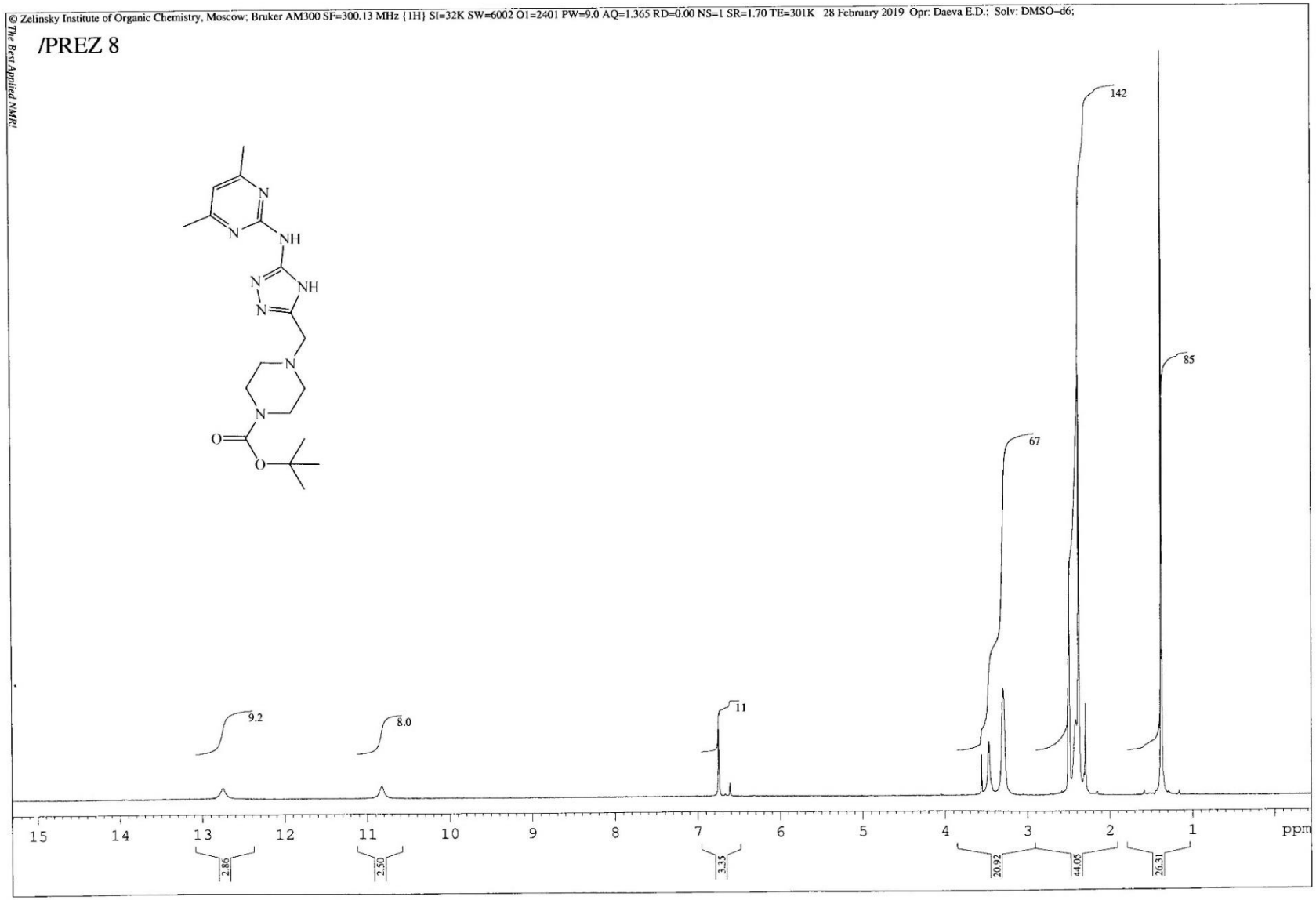

Figure S4. ^{1}H NMR spectrum of *tert*-butyl 4-((5-((4,6-dimethylpyrimidin-2-yl)amino)-4*H*-1,2,4-triazol-3-yl)methyl)piperazine-1-carboxylate **3b.**

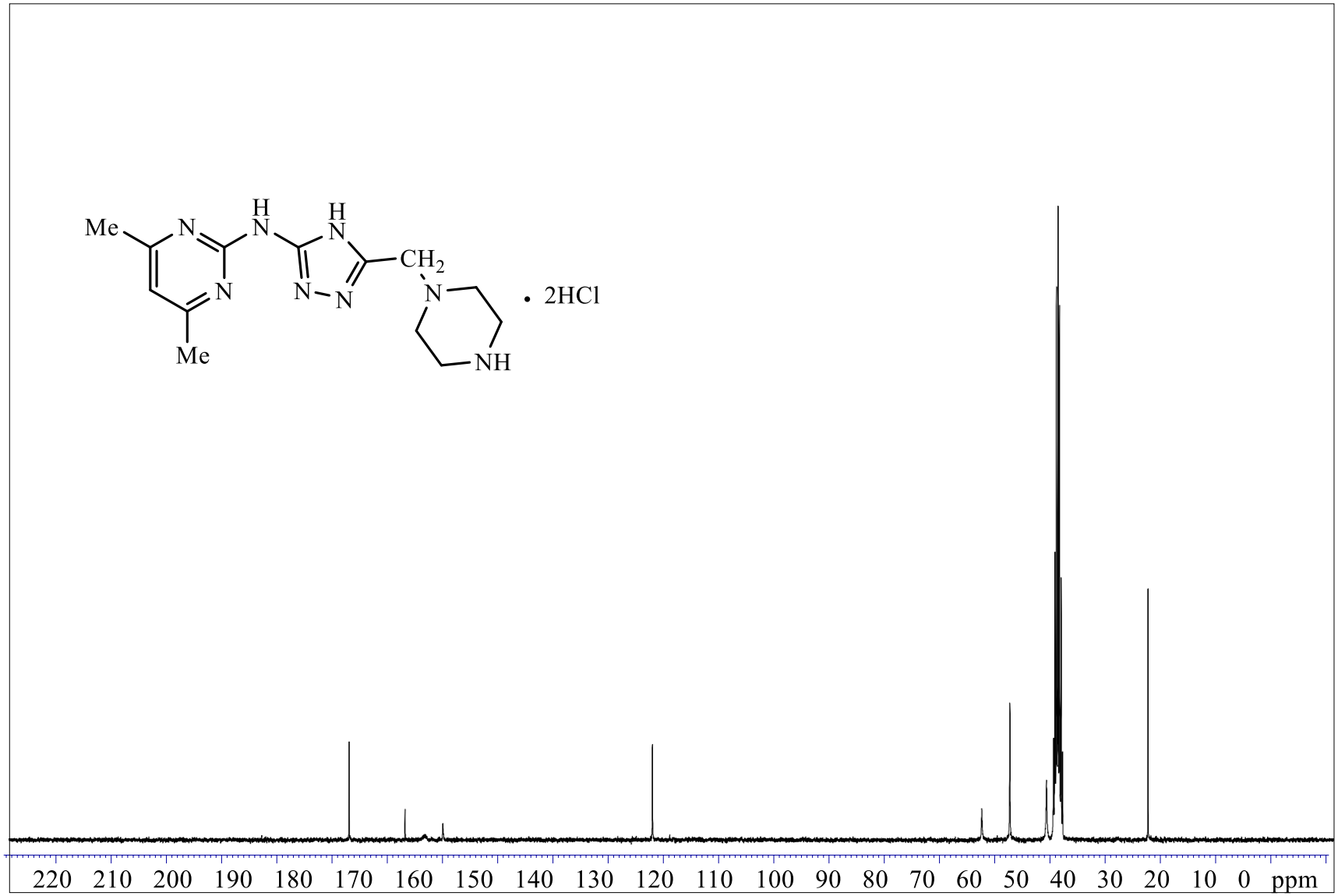

Figure S5. ^{13}C NMR spectrum of 4,6-dimethyl-*N*-[5-(piperazin-1-ylmethyl)-4*H*-1,2,4-triazol-3-yl]pyrimidin-2-amine dihydrochloride **4b.**

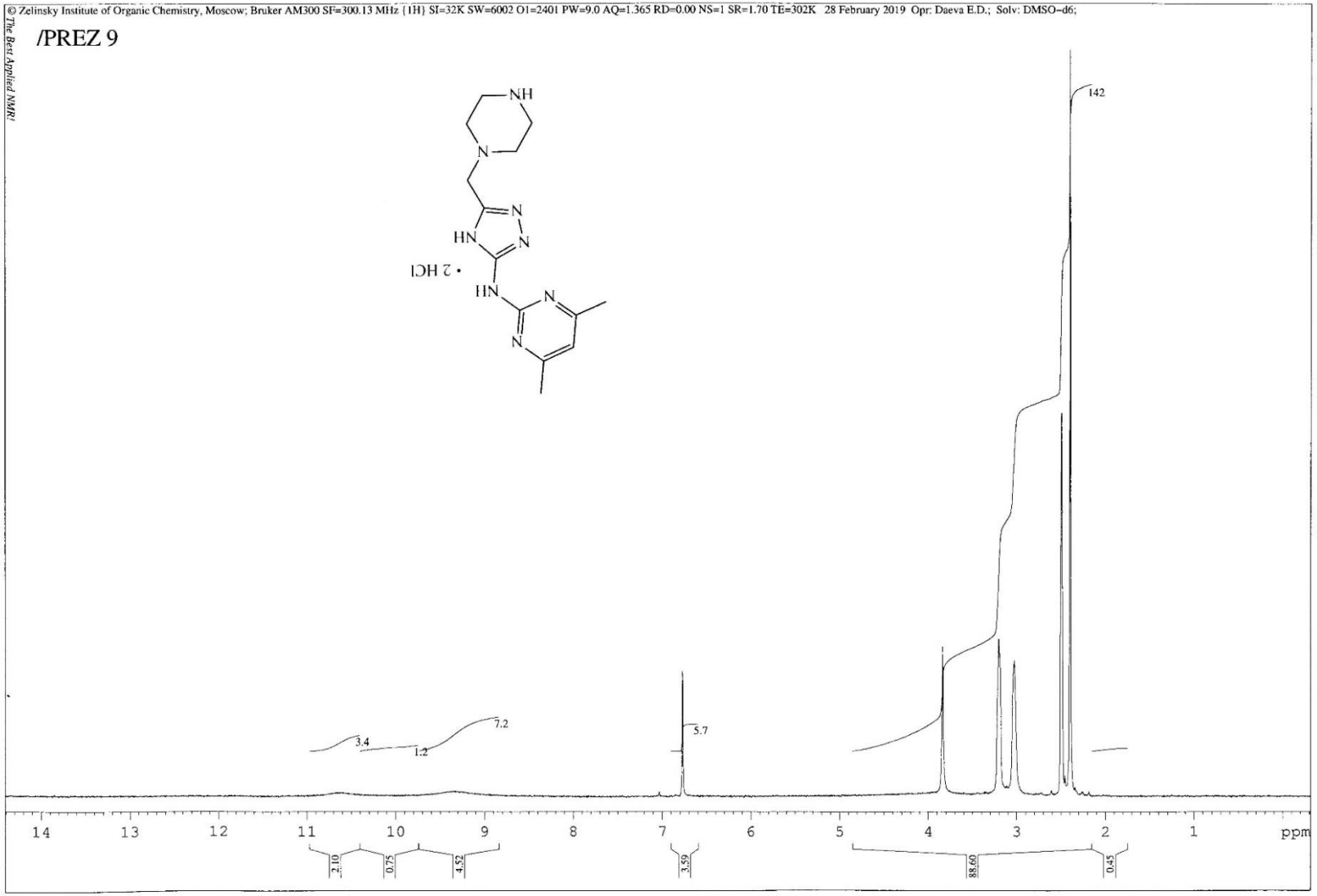

Figure S6. [1]H NMR spectrum of 4,6-dimethyl-*N*-[5-(piperazin-1-ylmethyl)-4*H*-1,2,4-triazol-3-yl]pyrimidin-2-amine dihydrochloride **4b.**