

Regio- and stereoselective modification of cytosine with cyanopropargylic alcohols

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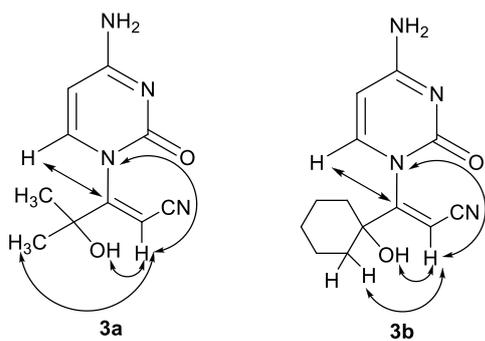
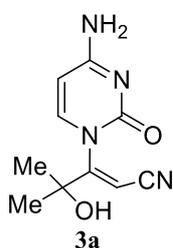


Figure S1 Cross-peaks in the 2D spectra of the adducts **3a,b**.

General methods

^1H , ^{13}C and ^{15}N NMR spectra of the studied compounds were recorded on a Bruker DPX-400 and Bruker AV-400 spectrometers (400.13, 100.62 and 40.56 MHz, respectively) in $\text{DMSO-}d_6$ at rt, 60 °C and referred to HMDSO (^1H , ^{13}C) or nitromethane (^{15}N). NMR signals were assigned using 2D NMR techniques (NOESY, HSQC, HMBC $^1\text{H-}^{13}\text{C}$ and HMBC $^1\text{H-}^{15}\text{N}$). IR spectra were measured on a Bruker Vertex-70 in KBr pellets. Elemental analyses were performed on a FLASH 2000. Melting points were taken on a Kofler micro hot stage. Cytosine is a commercial reagent (“Merck”). Cyanopropargylic alcohols **1a,b** were prepared according to a published method.¹

(Z)-3-[4-Amino-2-oxo-1(2H)-pyrimidinyl]-4-hydroxy-4-methylpent-2-enitrile (**3a**).



To a mixture of cytosine **1** (0.111 g, 1.0 mmol) and K_2CO_3 (0.04 g, 0.03 mmol) in DMF (3 mL) was added a cyanopropargylic alcohol **1a** (0.120 g, 1.1 mmol) in DMF (2 mL) dropwise over 30 min. The mixture was stirred at 20-25 °C for 3 h. The mixture was passed through Al_2O_3 (1 cm) using Schott funnel, eluents: DMF (5 mL) and Me_2CO (5 mL). The solvents were removed in vacuo. The residue was washed with small portions of the mixture of $\text{Et}_2\text{O}/\text{EtOH}$ (1:1, 5 mL) and hexane, dried *in vacuo* to afford compound **3a** (0.176 g, 80%) as a beige powder, mp 197-199 °C (decomp).

^1H NMR (400.13 MHz, $\text{DMSO-}d_6$) δ : 7.41, 7.33 (br.s, 2H, NH_2), 7.39 (d, 1H, $^3J_{\text{H}_6\text{H}_5} = 7.2$ Hz, H^6), 6.28 (s, 1H, $=\text{CHCN}$), 5.78 (d, 1H, $^3J_{\text{H}_5\text{H}_6} = 7.3$ Hz, H^5), 5.48 (s, 1H, OH), 1.30, 1.21 (s, 6H, 2 CH_3).

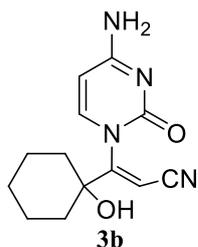
^{13}C NMR (100.62 MHz, $\text{DMSO-}d_6$) δ : 167.5 ($\text{N}\underline{\text{C}}=\text{CCN}$), 166.4 ($\text{O}=\text{C}$), 154.0 (C^4), 145.0 (C^6), 115.4 (CN), 99.9 ($=\text{CHCN}$), 93.8 (C^5), 72.4 [$(\text{CH}_3)_2\underline{\text{C}}\text{-O}$], 28.5, 28.2 (CH_3).

^{15}N NMR (40.56 MHz, $\text{DMSO-}d_6$) δ : -283.7 (NH_2), -230.2 (N^1), -168.9 (N^3), -113.3 (CN).

IR (KBr, ν/cm^{-1}): 3412, 3339, 3250, 3210, 3076, 2982, 2942, 2881, 2228, 1649, 1600, 1567, 1511, 1490, 1445, 1369, 1299, 1251, 1222, 1197, 1173, 1137, 1115, 976, 948, 856, 830, 785, 708, 676, 595, 566, 532.

Found (%): C, 54.26; H, 5.63; N, 25.10. Calc. for $\text{C}_{10}\text{H}_{12}\text{N}_4\text{O}_2$ (%): C, 54.54; H, 5.49; N, 25.44.

(Z)-3-[4-Amino-2-oxo-1(2H)-pyrimidinyl]-3-(1-hydroxycyclohexyl)prop-2-enitrile (3b).



To a mixture of cytosine **1** (0.111 g, 1.0 mmol) and K_2CO_3 (0.007 g, 0.05 mmol) in DMF (3 mL) was added a cyanopropargylic alcohol **1b** (0.164 g, 1.1 mmol) in DMF (2 mL) dropwise over 30 min. The mixture was stirred at 20-25 °C for 2 h. The precipitate from the reaction mixture was filtered, washed with EtOH (5 mL) and dried *in vacuo* to afford compound **3b** (0.142 g). The DMF solution was passed through Al_2O_3 (1 cm) using Schott funnel, eluents: DMF (5 mL) and Me_2CO (5 mL). The solvents were removed *in vacuo*. The residue was washed with small portions the mixture of $Et_2O/EtOH$ (1:1, 5 mL) and hexane, dried *in vacuo* to afford compound **3b** (0.088 g). The total yield of compound **3b** was 0.230 g (88%) as a white powder, mp 209-212 °C.

1H NMR (400.13 MHz, $DMSO-d_6$) δ : 7.40, 7.33 (br. s, 2 H, NH_2), 7.38 (d, 1 H, $^3J_{H_6H_5} = 7.2$ Hz, H^6), 6.28 (s, 1 H, $=CHCN$), 5.78 (d, 1 H, $^3J_{H_5H_6} = 7.3$ Hz, H^5), 5.25 (s, 1 H, OH), 1.66-1.07 (m, 10 H, CH_2).

^{13}C NMR (100.62 MHz, $DMSO-d_6$) δ : 168.2 ($N\bar{C}=CCN$), 166.4 ($C=O$), 154.2 (C^4), 145.1 (C^6), 115.5 (CN), 100.0 ($=\bar{C}HCN$), 93.8 (C^5), 73.4 (C^1), 34.9, 34.7 (C^2), 24.8 (C^4), 21.0, 20.8 (C^3).

^{15}N NMR (40.56 MHz, $DMSO-d_6$) δ : -281.7 (NH_2), -229.2 (N^1), -170.6 (N^3), -112.3 (CN).

IR (KBr, ν/cm^{-1}): 3299, 3211, 3083, 3063, 2948, 2938, 2863, 2223, 1672, 1655, 1638, 1613, 1505, 1453, 1438, 1378, 1316, 1302, 1255, 1213, 1154, 1138, 1101, 1083, 1067, 964, 855, 820, 784, 705, 666, 594.

Found (%): C, 59.61; H, 6.36; N, 21.65. Calc. for $C_{13}H_{16}N_4O_2$ (%): C, 59.99; H, 6.20; N, 21.52.

References

- 1 S. R. Landor, B. Demetriou, R. Grzeskowiak and D. Pavey, *J. Organometal. Chem.*, 1975, **93**, 129; (b) B. A. Trofimov, L. V. Andriyankova, S. I. Shaikhudinova, T. I. Kazantseva, A. G. Mal'kina, S. A. Zhivet'ev and A. V. Afonin, *Synthesis*, 2002, 853.

The ^1H and ^{13}C spectra of the synthesized products 3a,b

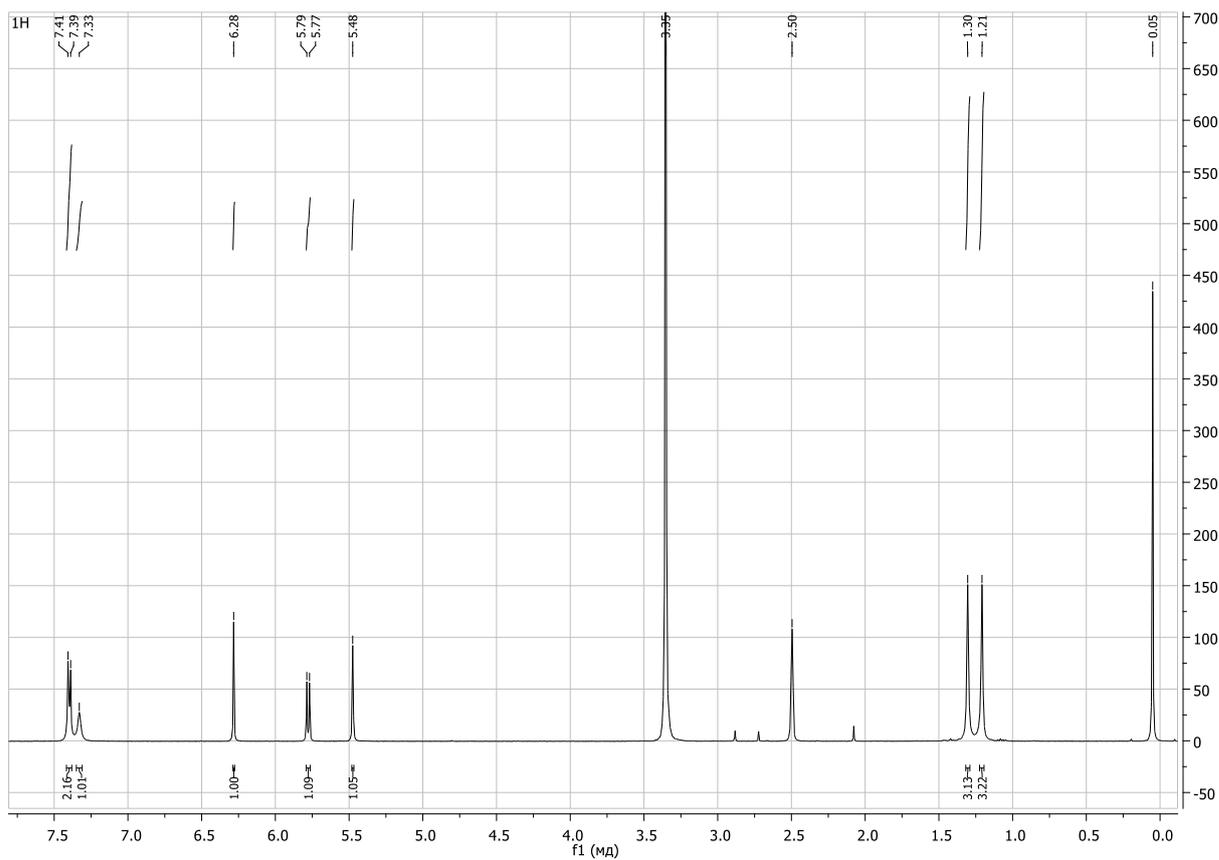


Figure S2 The ^1H NMR spectrum of the compound 3a in $\text{DMSO-}d_6$ (25 °C).

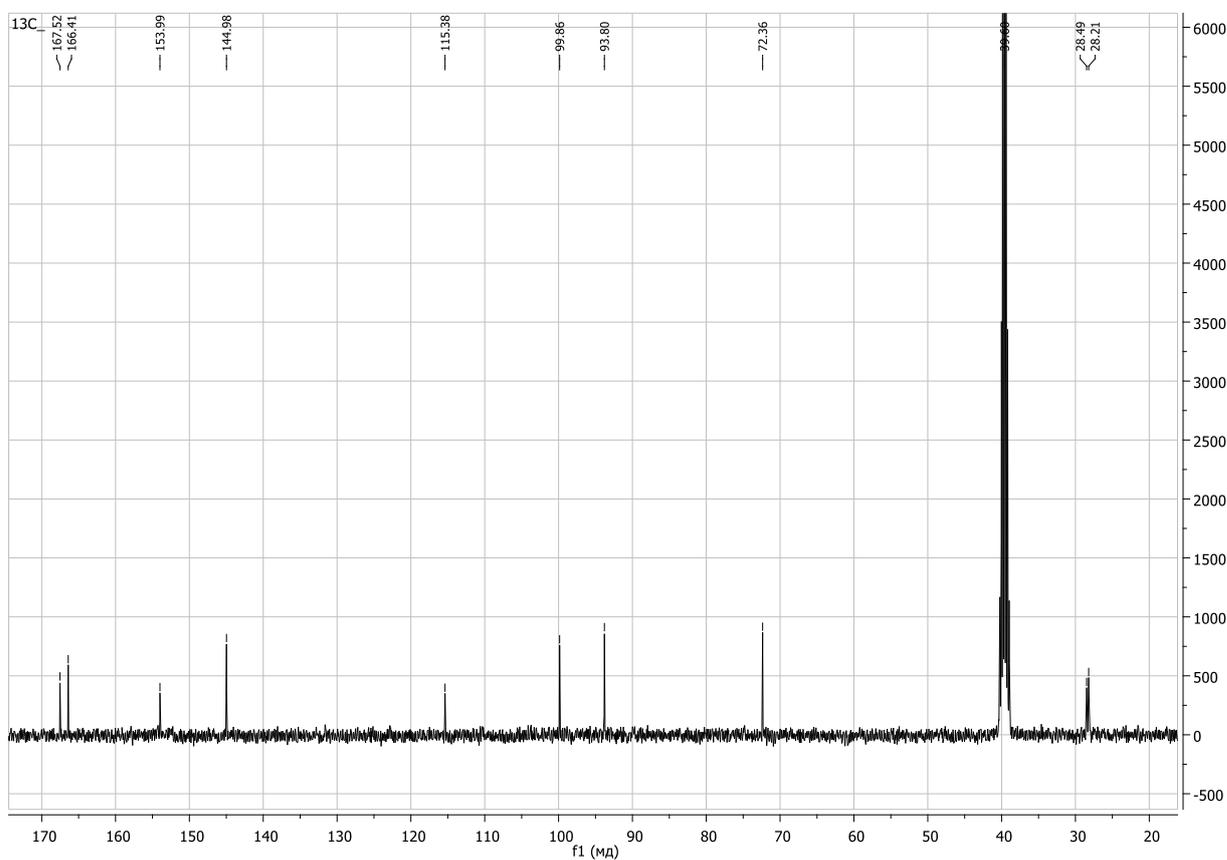


Figure S3 The ^{13}C NMR spectrum of the compound 3a in $\text{DMSO-}d_6$.

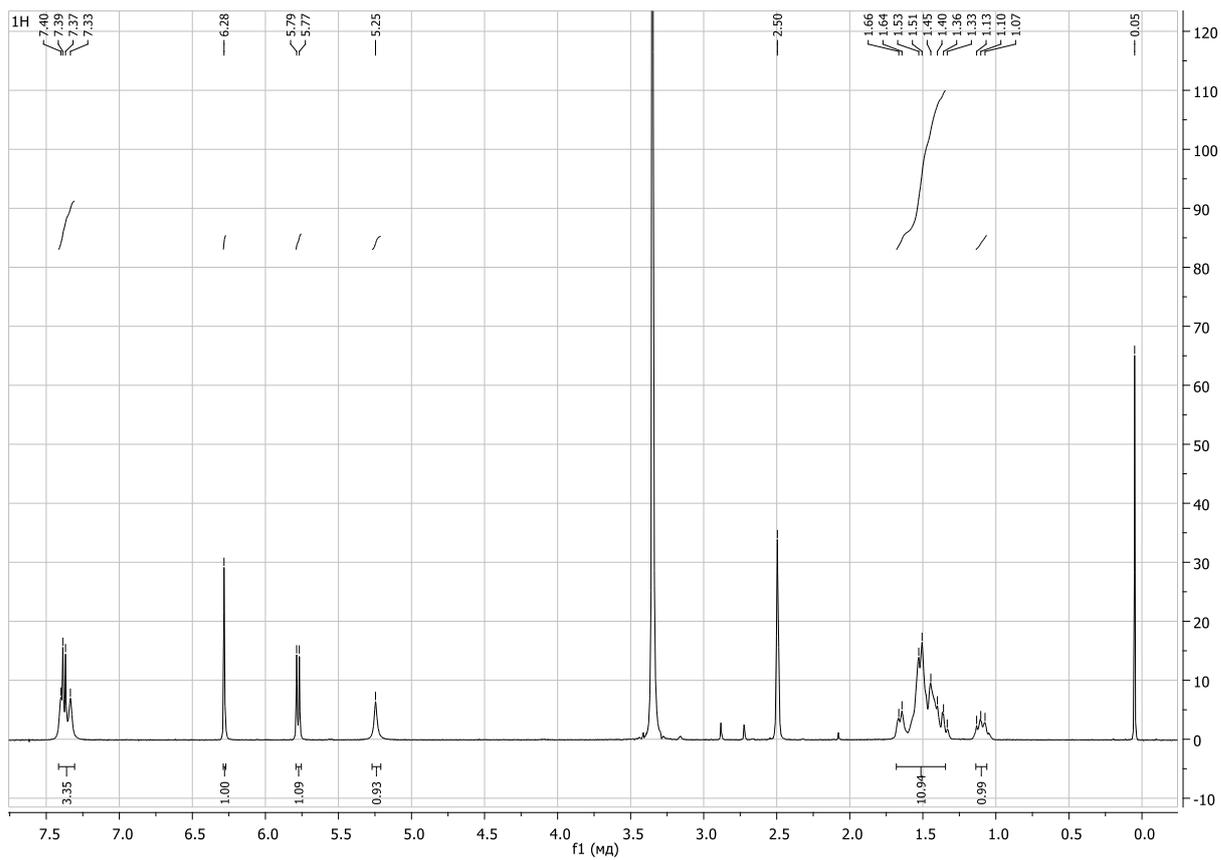


Figure S4 The ¹H NMR spectrum of the compound **3b** in DMSO-*d*₆ (25 °C).

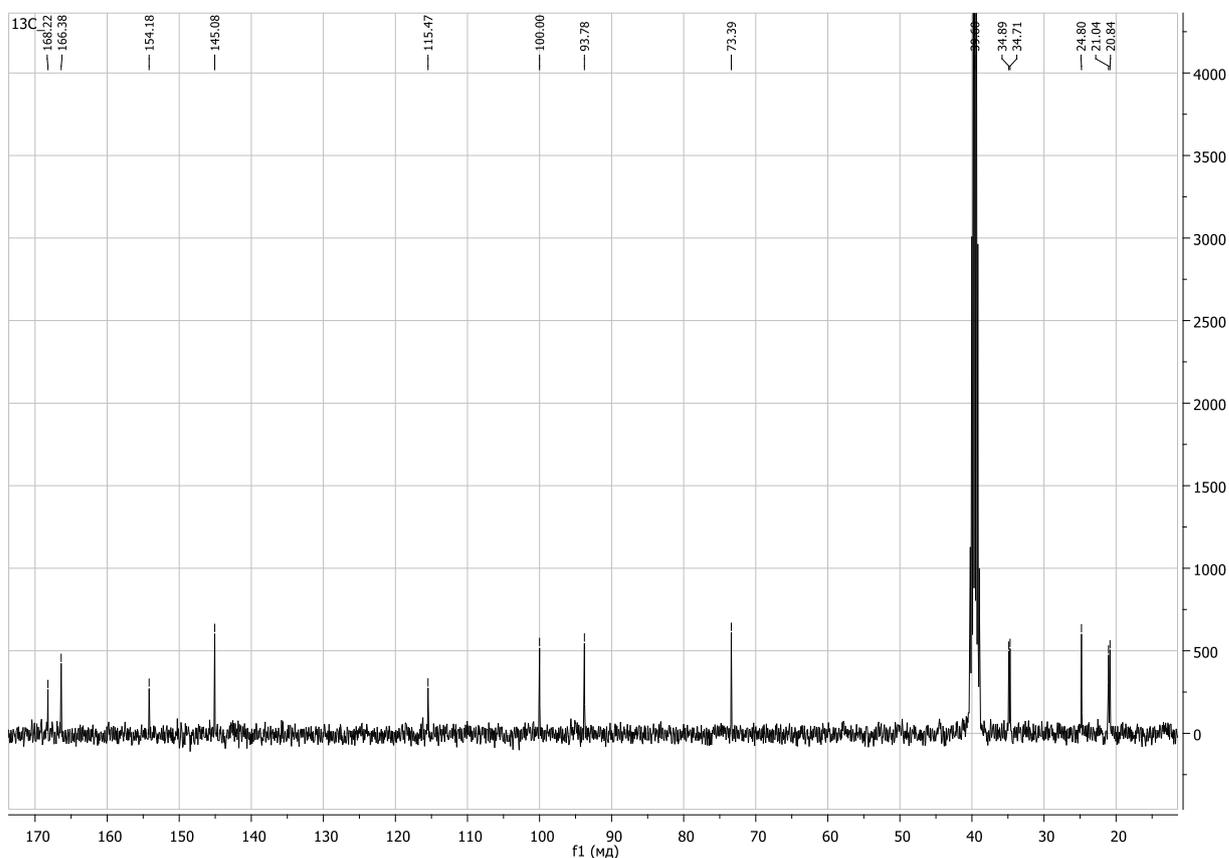


Figure S5 The ¹³C NMR spectrum of the compound **3b** in DMSO-*d*₆.

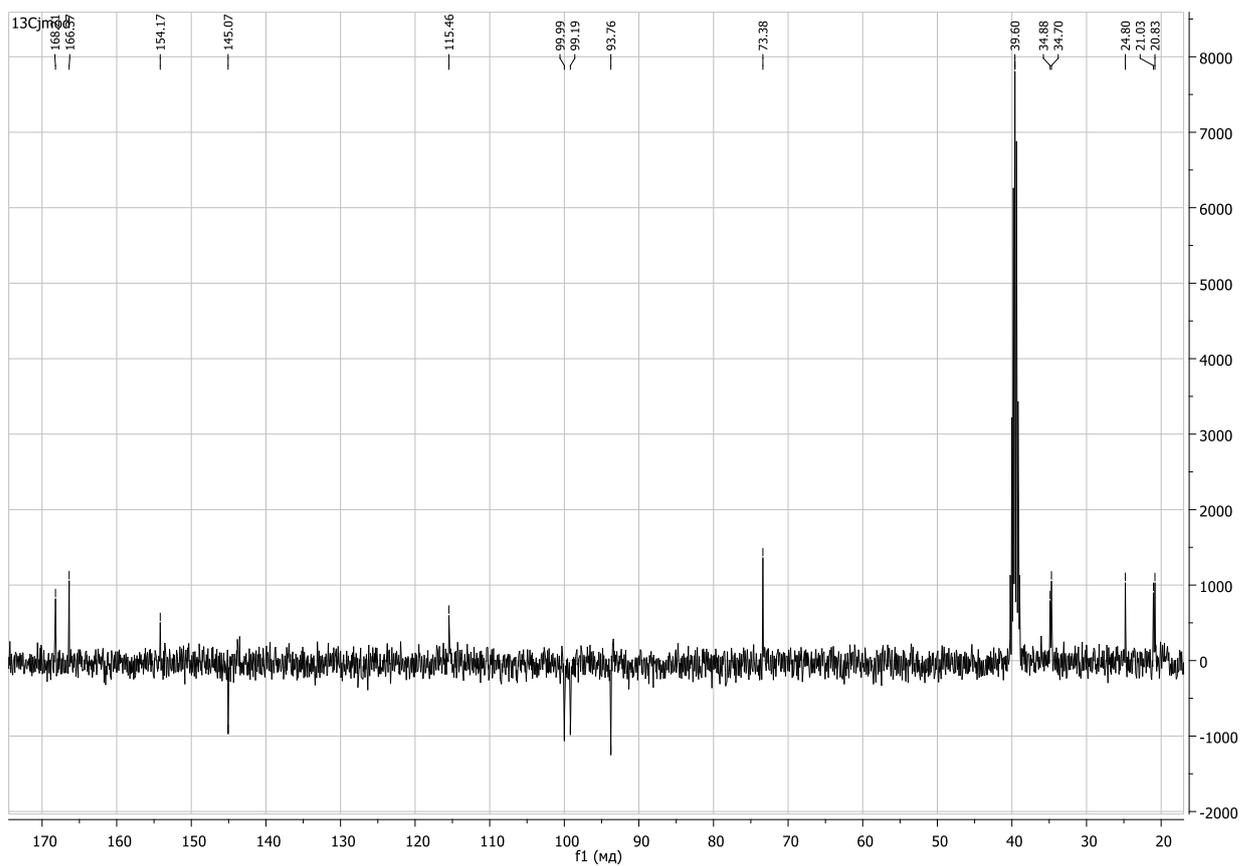


Figure S6 The ^{13}C jmod NMR spectrum of the compound **3b** in $\text{DMSO-}d_6$.

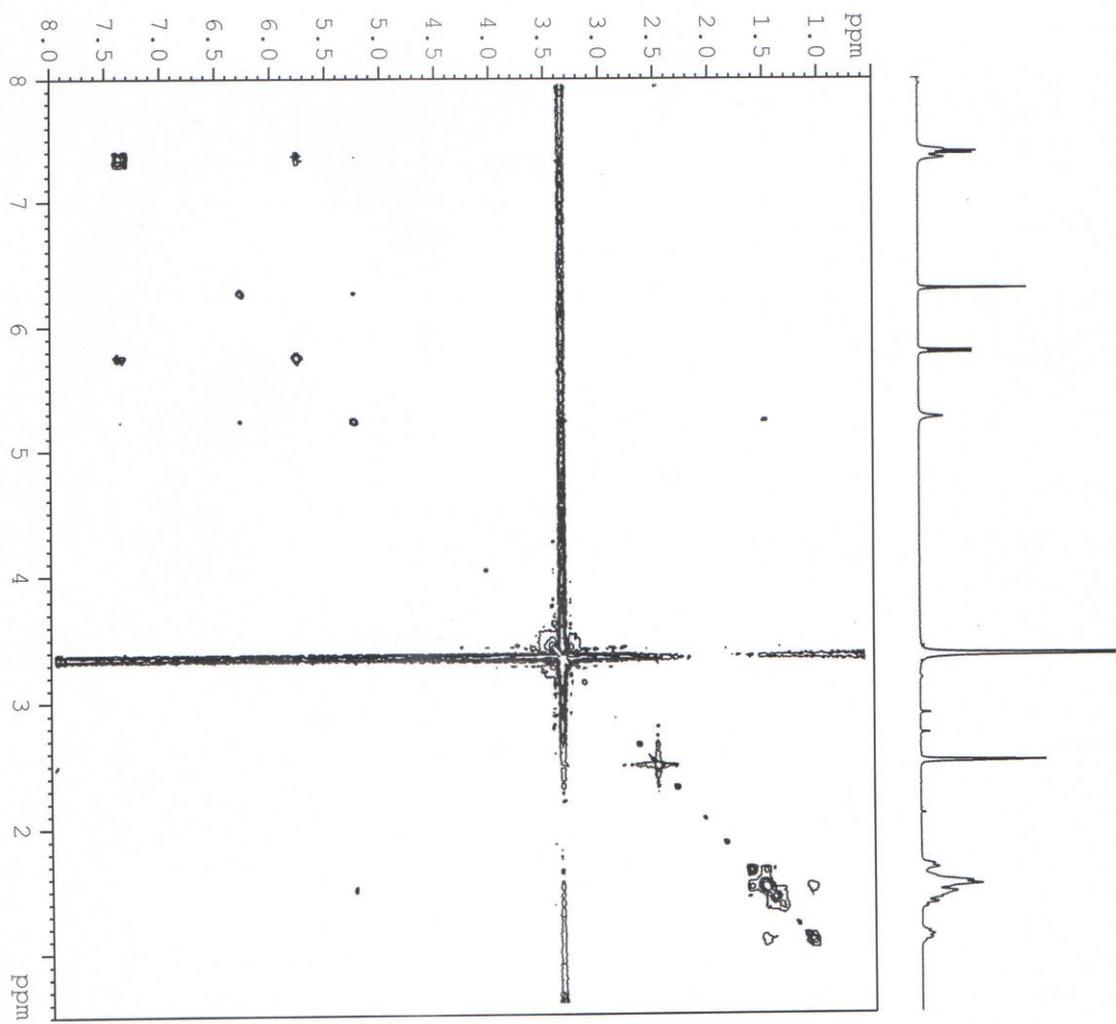


Figure S7 The 2D NOESY (^1H - ^1H) NMR of the compound **3b** in $\text{DMSO-}d_6$.

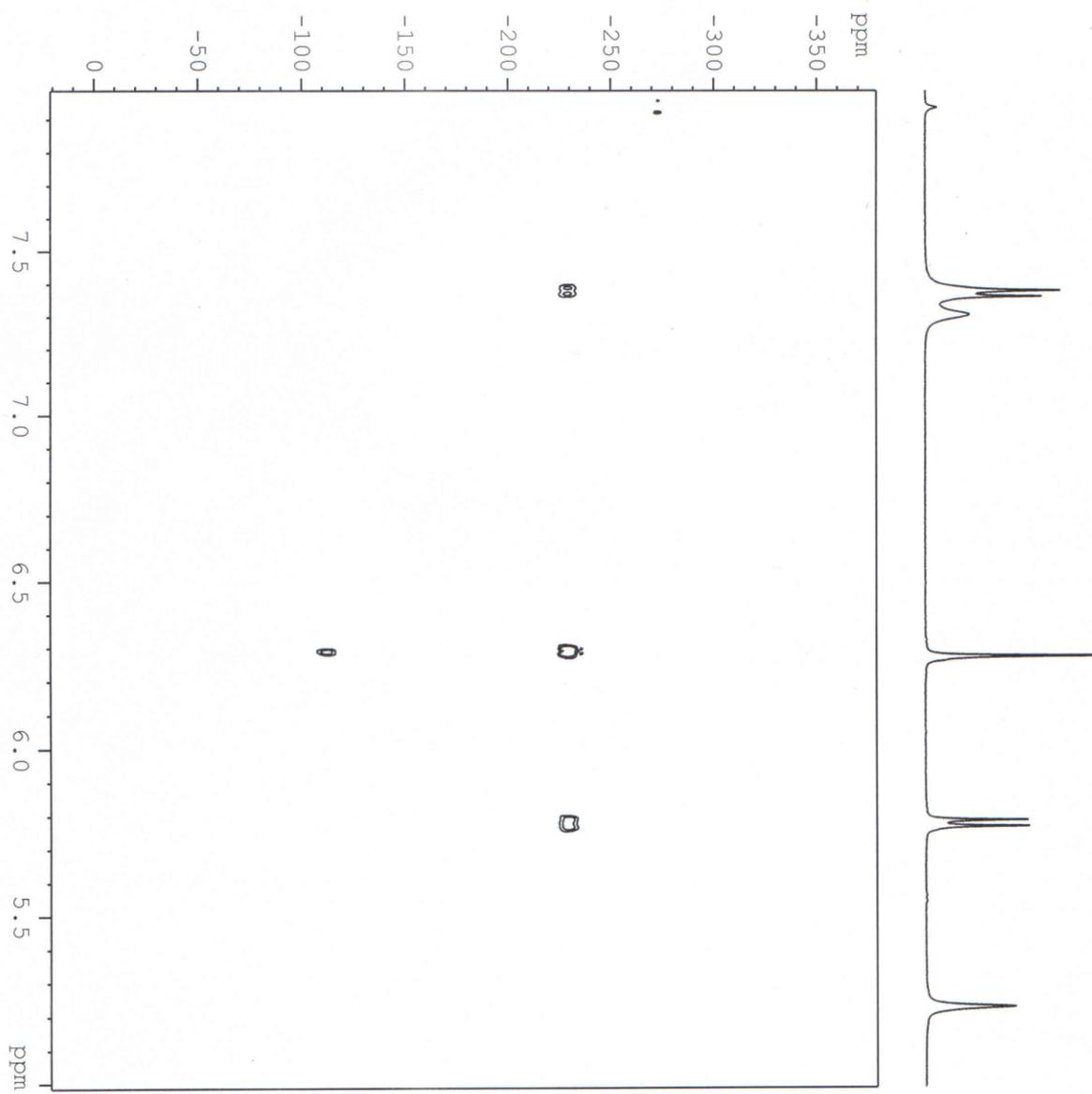


Figure S8 The 2D HMBC (¹H-¹⁵N) NMR of the compound **3b** in DMSO-*d*₆.