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Synthesis of spiro[chromane-2,4'-pyrimidines] by condensation of 6-styryldihydropyrimidin-2-ones with resorcinols

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1 General information

NMR spectra were recorded on Bruker DRX-400 and Bruker DRX-500 instrument in DMSO-d_6 at 30 °C. The chemical shifts are given in the δ scale relative to the residual solvent signals δ_H 2.50 (^{1}H) and δ_C 39.5 (^{13}C) and recalculated to $SiMe_4$ (ZIOC RAS, Moscow). IR spectra were collected in the reflected light mode in the 700-4000 cm^{-1} range using a PerkinElmer Spectrum Two FR-IR spectrometer. Mass spectrometry was carried out on a FINNIGAN MAT INCOS 50 GC/MS/DS system (ionization energy of 70 eV, ion source temperature of 100-220 °C) (ZIOC RAS, Moscow). Elemental analysis was carried out on a Perkin Elmer 2400 CHNS/O elemental analyzer (Laboratory of Microanalysis, INEOS RAS, Moscow). Melting points were measured on a Buchi M-560 apparatus.

Compounds **1a-d** were obtained according to Shutalev method[S1], the physicochemical characteristics of these structures are described in the work[S2].

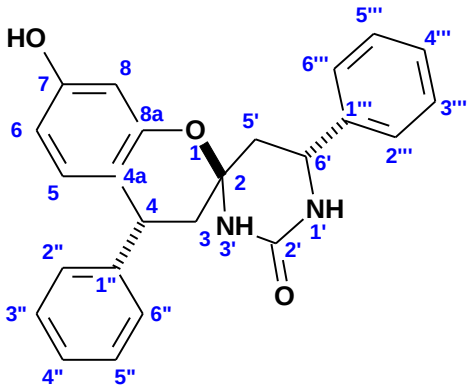
2 Crystallographic data

Single crystal X-ray diffraction experiments for compound **3b** was carried out using SMART APEX2 CCD diffractometer (λ(Mo-Kα) = 0.71073 Å, graphite monochromator, ω-scans) at 120 K. Collected data were processed by the SAINT and SADABS programs incorporated into the APEX2 program package[S3]. The structures were solved by the direct methods and refined by the full-matrix least-squares procedure against F^2 in anisotropic approximation. The refinement was carried out with the SHELXTL program[S4].

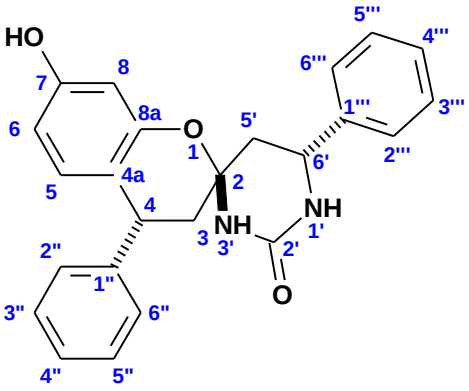
Crystallographic data for **3b**: $C_{24}H_{22}N_2O_3$ $C_3H_6O_3$ are monoclinic, space group $P2_1/n$: a = 10.0703(4)Å, b = 10.5940(4)Å, c = 22.7934(8)Å, β = 92.8542(11)°, V = 2428.7(2) Å^3, Z = 4, M = 476.51, d_{cryst} = 1.303 g·cm^{-3}. $wR2$ = 0.1092 calculated on F^2_{hkl} for all 4795 independent reflections with $2\theta < 52.2°$, (GOF = 1.067, R = 0.0399 calculated on F_{hkl} for 3717 reflections with $I > 2\sigma(I)$).

3 Synthesis of spiro[chromane-2,4'-pyrimidin]-2'(3'*H*)-one 3 and 3'

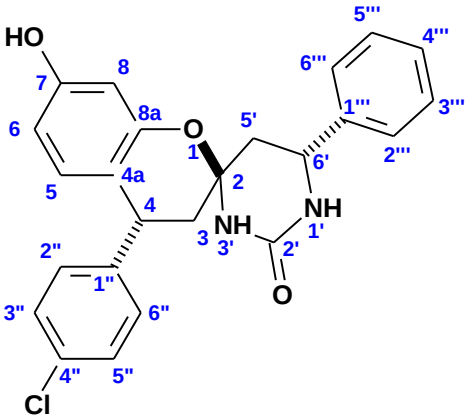
A mixture of 6-styryl-4-aryldihydropyrimidin-2-one **1a–d** (1 mmol) with 1,3-benzenediols **2a,b** (2 mmol) in $CHCl_3$ (5 ml) with the addition of H_2O (1 ml) and TsOH (52 mg, 0.3 mmol) was heated at 30-40 ºC for 1-3 h (TLC control). Then it was cooled, the precipitate formed was filtered off and washed with water. The precipitate was taken up in ethyl acetate (3-5 ml) and refluxed for 10 min. The hot solution was separated from the powder of isomer **3** remaining in the precipitate. Then this solution was cooled and the precipitated crystals of isomer **3'** were filtered off. Both powders of substances **3** and **3'** were dried in air.



(2*R,4*R**,6'*R**)-7-Hydroxy-4,6'-diphenyl-5',6'-dihydro-1'*H*-spiro[chromane-2,4'-pyrimidin]-2'(3'*H*)-one (3a)**. Yield 97 mg (25%), m.p. 265-266 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.80 (t, 1H, J = 12.6 Hz, $H_a^{5'}$), 2.09 (dd, 1H, J = 13.2, 5.7 Hz, H_a^{3}), 2.20 - 2.25 (m, 2H, $H_e^{3,5'}$), 4.11 (dd, 1H, J = 12.6, 5.7 Hz, H^4), 4.56 (dd, 1H, J = 12.2, 3.0 Hz, $H^{6'}$), 6.22 (dd, 1H, J = 8.5, 2.4 Hz, H^6), 6.30 (d, 1H, J = 2.4 Hz, H^8), 6.36 (d, 1H, J = 8.5 Hz, H^5), 6.80 (br. s., 1H, $NH^{1'}$), 7.16 (d, 2H, J = 7.6 Hz, $H^{2'',6''}$), 7.22 - 7.37 (m, 9 H, Ph, $NH^{3'}$), 9.19 (br. s., 1H, OH). ^{13}C NMR (101 MHz, DMSO-d_6): δ 37.90, 39.77, 40.42, 40.57, 50.95, 83.90, 103.07, 108.47, 114.73, 126.58 (2C), 127.54, 128.35 (2C), 128.44 (2C), 128.54 (2C), 129.70, 142.02, 144.52, 153.90, 155.23, 156.97. IR (ν/cm^{-1}): 3428 (OH), 3316, 3239 (NH), 1663 (C=O), 1616, 1508 (C=C), 1233, 1165, 1073 (C-O-C). MS (EI), m/z (%): 386 $[M]^+$ (24), 275 (22), 199 (100), 189 (9), 104 (10), 77 (8). Elemental analysis calcd (%) for $C_{24}H_{22}N_2O_3$: C, 74.59; H, 5.74; N, 7.25; found: C,74.38; H, 5.71; N, 7.21.

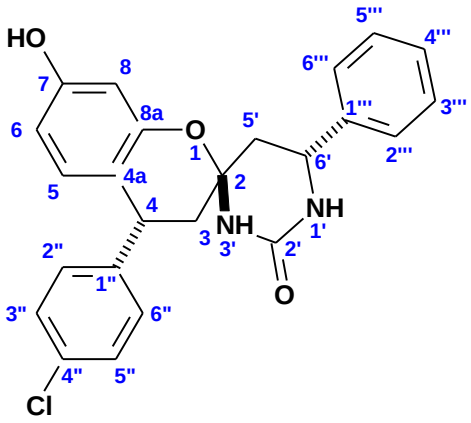


(2*S,4*R**,6'*R**)-7-Hydroxy-4,6'-diphenyl-5',6'-dihydro-1'*H*-spiro[chromane-2,4'-pyrimidin]-2'(3'*H*)-one (3'a)**. Yield 66 mg (17%), m.p. 257-258 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.79 (t, 1H, J = 12.8 Hz, $H_a^{5'}$), 2.03 - 2.09 (m, 1H, H_a^{3}), 2.13 -2.16 (m, 2H, $H_e^{3,5'}$), 4.60 (dd, 1H, J = 11.4, 5.9 Hz, H^{4}), 4.86 (dd, 1H, J = 12.2, 2.0 Hz, $H^{6'}$), 6.22 - 6.28 (m, 2H, $H^{6,8}$), 6.41 (d, 1H, J = 8.1 Hz, H^{5}), 6.92 (br. s., 1H, $NH^{1'}$), 7.17 (d, 2H, J = 7.6 Hz, $H^{2'',6''}$), 7.20 – 7.42 (m, 8H, Ph, $H^{3'',5''}$, $NH^{3'}$), 9.22 (br. s., 1 H, OH). ^{13}C NMR (101 MHz, DMSO-d_6): δ 35.53, 40.42, 40.51, 42.27, 50.57, 82.05, 103.33, 108.47, 115.90, 126.53 (2C), 127.48, 128.41 (2C), 128.47 (2C), 128.53 (2C), 129.67, 142.39, 144.91, 152.78, 154.97, 156.85.

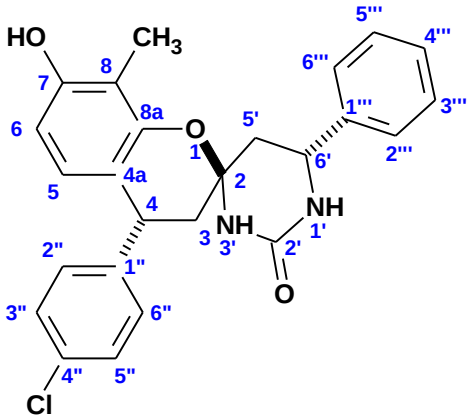


(2*R,4*R**,6'*R**)-4-(4-Chlorophenyl)-7-hydroxy-6'-phenyl-5',6'-dihydro-1'*H*-spiro[chromane-2,4'-pyrimidin]-2'(3'*H*)-one (3b)**. Yield 219 mg (52%), m.p. 278-279 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.79 (t, 1H, J = 12.5 Hz, $H_a^{5'}$), 2.05 - 2.23 (m, 3H, H_a^{3}, $H_e^{3,5'}$), 4.15 (dd, 1H, J = 12.5, 5.6 Hz, H^{4}), 4.54 (dd, 1H, J = 10.5, 3.0 Hz, $H^{6'}$), 6.23 (d, 1H, J = 7.8 Hz, H^{6}), 6.30 - 6.35 (m, 2H, $H^{5,8}$), 7.00 (s, 1H, $NH^{1'}$), 7.17 (d, 2H, J = 7.5 Hz, $H^{2'',6''}$), 7.24 - 7.36 (m, 5H, Ph), 7.38 (d, 2H, J = 7.5 Hz, $H^{3'',5''}$), 7.53 (s, 1H, $NH^{3'}$), 9.35 (br. s., 1 H, OH). ^{13}C NMR (126 MHz, DMSO-d_6): δ 37.86 (C^{3}), 38.24 (C^{4}), 40.41 ($C^{5'}$), 50.92 ($C^{6'}$), 83.87 ($C^{2/4'}$), 103.12 (C^{8}), 108.59(C^{6}), 114.26 (C^{4a}), 126.57 (2C, $C^{2'',6''}$), 127.55 ($C^{4''}$), 128.43 (2C, $C^{3'',5''}$), 128.53 (2C, $C^{3'',5''}$), 129.61(C^{5}), 130.19 (2C, $C^{2'',6''}$), 131.09 ($C^{4''}$), 141.99 ($C^{1'''}$), 143.57 ($C^{1''}$), 153.92 (C^{8a}), 155.23 ($C^{2'}$), 157.11 (C^{7}). IR (ν/cm^{-1}): 3446 (OH), 3316, 3222 (NH), 1664 (C=O), 1615, 1508 (C=C), 1228, 1165, 1084 (C-O-C). MS (EI), m/z (%): 420 $[M]^+$ (43), 360 (10), 311 (6), 298 (8),

272 (5), 233 (100), 197(21), 189 (9), 104 (7), 77 (4). Elemental analysis calcd (%) for $C_{24}H_{21}ClN_2O_3$: C, 68.49; H, 5.03; N, 6.66; found: C, 68.18; H, 5.01; N, 6.63.

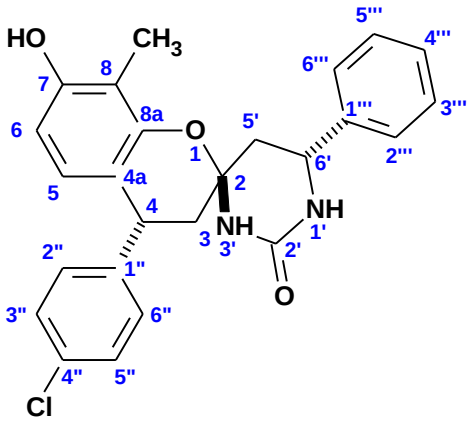


(2*S,4*R**,6'*R**)-4-(4-Chlorophenyl)-7-hydroxy-6'-phenyl-5',6'-dihydro-1'*H*-spiro[chromane-2,4'-pyrimidin]-2'(3'*H*)-one (3'b)**. Yield 76 mg (18%), m.p. 279-281 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.80 (t, 1H, J = 12.5 Hz, $H_a^{5'}$), 2.04 (t, 1H, J = 12.5 Hz, H_a^{3}), 2.11-2.18 (m, 2H, $H_e^{3,5'}$), 4.64 (dd, 1H, J = 12.5, 5.8 Hz, H_a^{4}), 4.86 (dd, 1H, J = 12.5, 3.5 Hz, $H_a^{6'}$), 6.25 - 6.29 (m, 2H, $H^{6,8}$), 6.39 (d, J = 8.8 Hz, H^5), 7.00 (br. s., 1H, $NH^{1'}$), 7.19 (d, 2H, J = 8.2 Hz, $H^{2'',6''}$), 7.29 - 7.46 (m, 8H, $H^{3'',5'',2''',3''',4''',5''',6'''}$, $NH^{3'}$), 9.29 (s, 1H, OH). ^{13}C NMR (126 MHz, DMSO-d_6): δ 34.99 (C^4), 40.26 (C^3), 42.21 ($C^{5'}$), 50.56 ($C^{6'}$), 82.03 ($C^{2/4'}$), 103.38 (C^8), 108.58 (C^6), 115.43 (C^{4a}), 126.56 (2C, $C^{3'',5''}$), 127.50 ($C^{4''}$), 128.48 (2C, $C^{3''',5'''}$), 128.54 (2C, $C^{2''',6'''}$), 129.55 (C^5), 130.26 (2C, $C^{2'',6''}$), 131.00 ($C^{4''}$), 142.37 ($C^{1'''}$), 143.91 ($C^{1''}$), 152.77 (C^{8a}), 154.91 ($C^{2'}$), 157.00 (C^7). MS (EI), m/z (%): 420 $[M]^+$ (27), 360 (5), 235 (27), 233 (100), 199 (12), 197 (38), 189 (28), 187 (20), 144 (14), 132 (28), 77 (22).

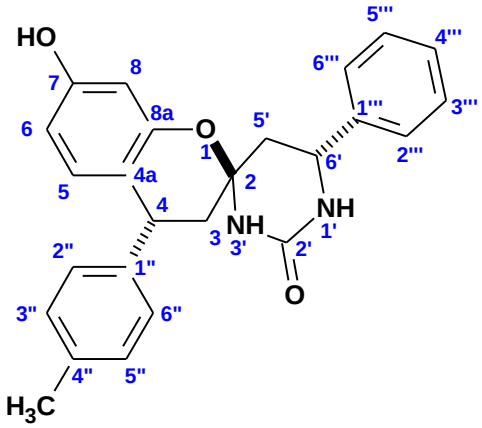


(2*R,4*R**,6'*R**)-4-(4-Chlorophenyl)-7-hydroxy-8-methyl-6'-phenyl-5',6'-dihydro-1'*H*-spiro[chromane-2,4'-pyrimidin]-2'(3'*H*)-one (3c)**. Yield 252 mg (58%), m.p. 259-260 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.79 (t, 1H, J = 12.5 Hz, $H_a^{5'}$), 2.08 (s, 3H, CH_3), 2.09 - 2.23 (m, 3H, H_a^3, $H_e^{3,5'}$), 4.15 (dd, 1H, J = 12.5, 6.7 Hz, H^4), 4.54 (dd, 1H, J = 12.2, 2.5 Hz, $H^{6'}$), 6.18 (d, 1H, J = 8.4 Hz, H^6), 6.29 (d, 1H, J = 8.4 Hz, H^5), 6.87 (br. s., 1 H, $NH^{1'}$), 7.17 (d, 2H, J = 8.1 Hz, $H^{2'',6''}$), 7.24 - 7.41 (m, 8H, Ph, $H^{3'',5''}$, $NH^{3'}$), 9.06 (br. s., 1H, OH). ^{13}C NMR (101 MHz,

DMSO-d_6): δ 7.96, 37.66, 38.46, 40.30, 50.94, 83.75, 107.69, 110.99, 114.12, 125.28, 126.03 (2C), 127.01 (4C), 127.93, 129.68 (2C), 130.71, 141.47, 143.31, 151.49, 154.25, 154.67. IR (ν/cm^{-1}): 3408 (OH), 3313, 3225 (NH), 1663 (C=O), 1607, 1493 (C=C), 1074 (C-O-C). MS (EI), m/z (%): 436 $[M]^+$ (18), 434 $[M]^+$ (50), 374 (8), 311 (6), 298 (5), 247 (100), 211 (31), 189 (24), 124 (14). Elemental analysis calcd (%) for $C_{25}H_{23}ClN_2O_3$: C, 69.04; H, 5.33; N, 6.44; found: C, 68.81; H, 5.31; N, 6.41.

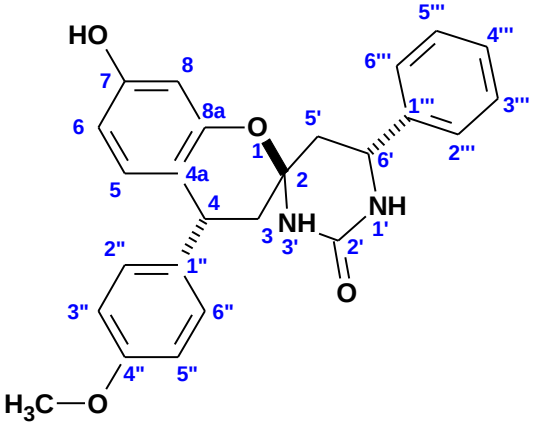


(2*S,4*R**,6'*R**)-4-(4-Chlorophenyl)-7-hydroxy-8-methyl-6'-phenyl-5',6'-dihydro-1'*H*-spiro[chromane-2,4'-pyrimidin]-2'(3'*H*)-one (3'c)**. Yield 61 mg (14%), m.p. 220-222 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.82 (t, 1H, J = 12.7 Hz, $H_a^{5'}$), 2.00 - 2.05 (m, 4H, H_a^3, CH_3), 2.12 - 2.19 (m, 2H, $H_e^{3,5'}$), 4.63 (dd, 1H, J = 12.4, 6.1 Hz, H^4), 4.93 (dd, 1H, J = 12.7, 2.2 Hz, $H^{6'}$), 6.23 (d, 1H, J = 8.5 Hz, H^6), 6.32 (d, 1H, J = 8.5 Hz, H^5), 6.97 (s, 1 H, $NH^{1'}$), 7.18 (d, 2H, J = 8.1 Hz, $H^{2'',6''}$), 7.25 (s, 1 H, $NH^{3'}$), 7.28 - 7.43 (m, 7H, Ph, $H^{3'',5''}$), 9.10 (s, 1H, OH). ^{13}C NMR (101 MHz, DMSO-d_6): δ 8.60, 35.38, 40.43, 42.66, 50.99, 81.87, 107.71, 111.14, 115.36, 125.81, 126.49 (2C), 127.50, 128.50 (4C), 130.29 (2C), 130.91, 142.33, 144.16, 150.61, 154.53, 154.94.



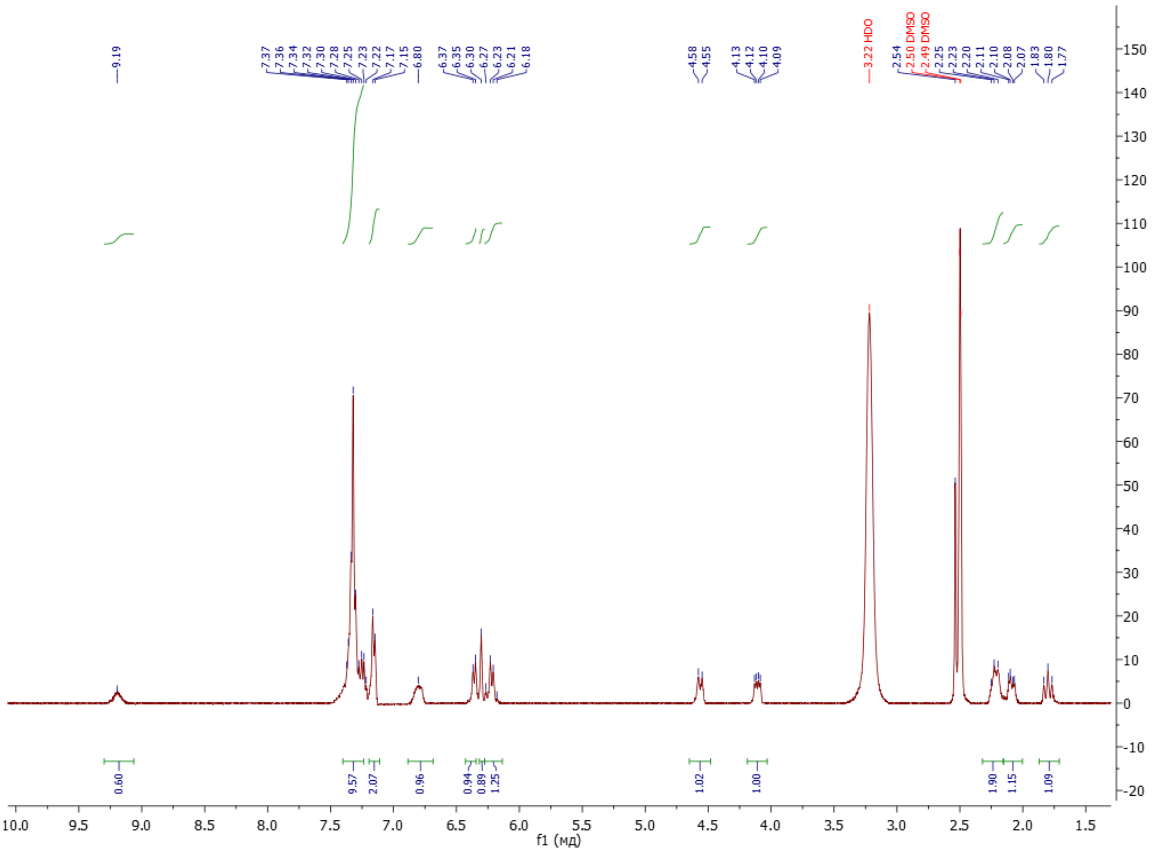
(2*R,4*R**,6'*R**)-7-Hydroxy-6'-phenyl-4-(*p*-tolyl)-5',6'-dihydro-1'*H*-spiro[chromane-2,4'-pyrimidin]-2'(3'*H*)-one (3d)**. Yield 144 mg (36%), m.p. 227-229 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.78 (t, 1H, J = 13.0 Hz, $H_a^{5'}$), 2.06 (dd, 1H, J = 12.5, 5.8 Hz, H_a^3), 2.12-2.21 (m, 2H, $H_e^{3,5'}$), 2.28 (s, 3H, CH_3), 4.05 (dd, 1H, J = 13.0, 5.8 Hz, H^4), 4.54 (d, 1H, J = 12.5 Hz, $H^{6'}$),

6.20 (dd, 1H, J = 8.5, 1.5 Hz, H^6), 6.28 (d, 1H, J = 1.5 Hz, H^8), 6.35 (d, 1H, J = 8.5 Hz, H^5), 6.89 (br. s., 1 H, $NH^{1'}$), 7.03 (d, 2H, J = 8.0 Hz, $H^{2'',6''}$), 7.12 (d, 2H, J = 8.0 Hz, $H^{3'',5''}$), 7.24 - 7.36 (m, 5 H, Ph), 7.41 (br. s., 1 H, $NH^{3'}$), 9.27 (br. s., 1 H, OH). ^{13}C NMR (101 MHz, DMSO-d_6): δ 20.61, 37.91, 38.46, 40.57, 50.94, 83.90, 103.01, 108.41, 114.90, 126.58 (2C), 127.53, 128.20 (2C), 128.42 (2C), 129.09 (2C), 129.68, 135.54, 141.39, 142.02, 153.86, 155.21, 156.91. IR (ν/cm^{-1}): 3408 (OH), 3299 (NH), 1662 (C=O), 1618, 1591, 1486 (C=C), 1150, 1072 (C-O-C). MS (EI), m/z (%): 400 $[M]^+$ (3), 213 (100), 197 (64), 189 (13), 132 (19), 115 (12), 104 (27), 77 (19). Elemental analysis calcd (%) for $C_{25}H_{24}N_2O_3$: C, 74.98; H, 6.04; N, 7.00; found: C, 74.71; H, 6.01; N, 6.97.

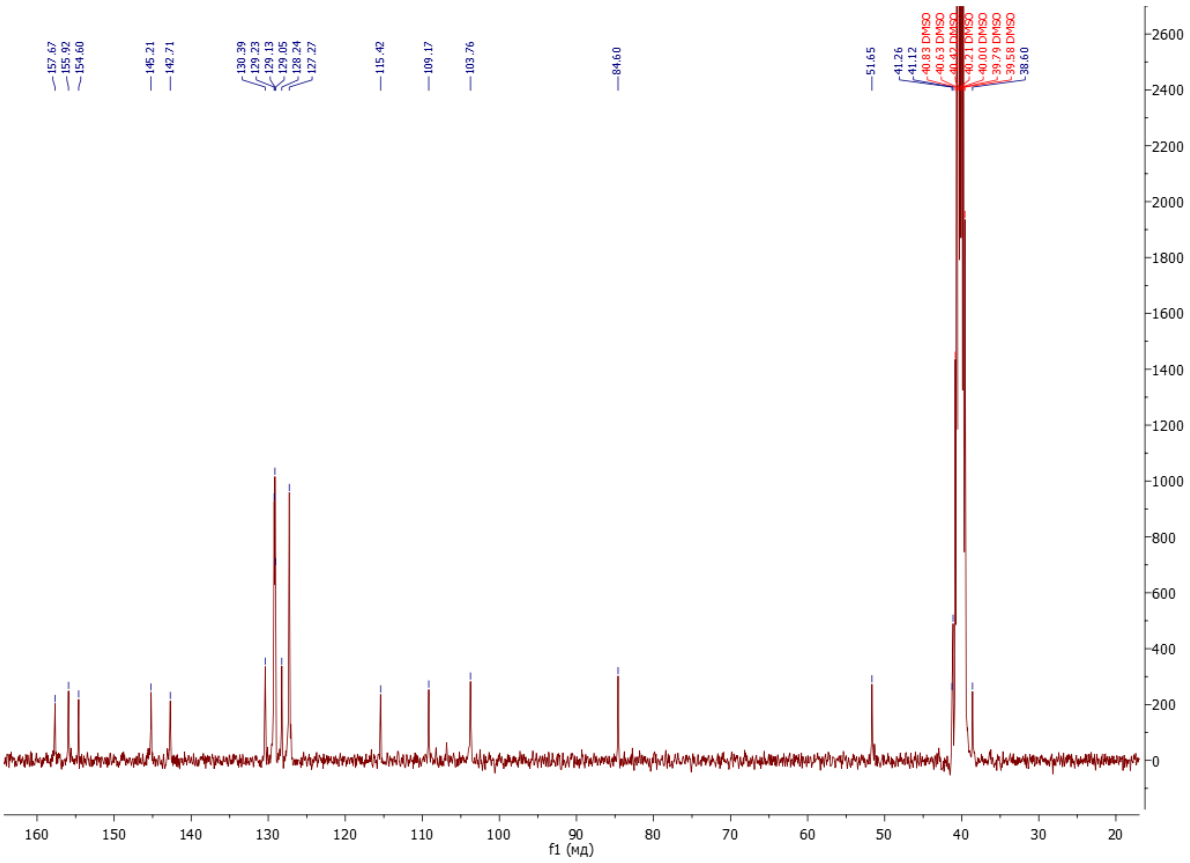


(2*R,4*R**,6'*R**)-7-Hydroxy-4-(4-methoxyphenyl)-6'-phenyl-5',6'-dihydro-1'*H*-spiro[chromane-2,4'-pyrimidin]-2'(3'*H*)-one (3e)**. Yield 74 mg (18%), m.p. 212-214 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.77 (t, 1H, J = 12.7 Hz, $H_a^{5'}$), 1.98 - 2.09 (m, 1H, H_a^3), 2.11 - 2.24 (m, 2H, $H_e^{3,5'}$), 3.73 (s, 3H, OCH_3), 4.04 (dd, 1H, J = 12.0, 5.4 Hz, H^4), 4.54 (dd, 1H, J = 12.1, 2.1 Hz, $H^{6'}$), 6.18 - 6.26 (m, 1H, H^6), 6.28 (s, 1H, H^8), 6.36 (d, 1H, J = 8.6 Hz, H^5), 6.86 - 6.92 (m, 3H, $H^{2'',6''}$, $NH^{1'}$), 7.05 (d, 2H, J = 8.1 Hz, $H^{3'',5''}$), 7.23 - 7.39 (m, 5H, Ph), 7.42 (br. s., 1H, $NH^{3'}$), 9.25 (br. s., 1H, OH). ^{13}C NMR (101 MHz, DMSO-d_6): δ 38.02, 40.42, 40.69, 50.94, 54.98, 83.92, 102.98, 108.38, 113.94 (2C), 115.11, 126.56 (2C), 127.52, 128.41 (2C), 129.26 (2C), 129.65, 136.22, 142.02, 153.82, 155.22, 156.89, 157.89. IR (ν/cm^{-1}): 3438 (OH), 3309, 3224 (NH), 1660 (C=O), 1612, 1505 (C=C), 1244, 1224 (C-O-C). MS (EI), m/z (%): 416 $[M]^+$ (11), 356 (5), 229 (100), 213 (14), 197 (49), 186 (8), 173 (6), 77 (8). Elemental analysis calcd (%) for $C_{25}H_{24}N_2O_4$: C, 72.10; H, 5.81; N, 6.73; found: C, 71.79; H, 5.79; N, 6.69.

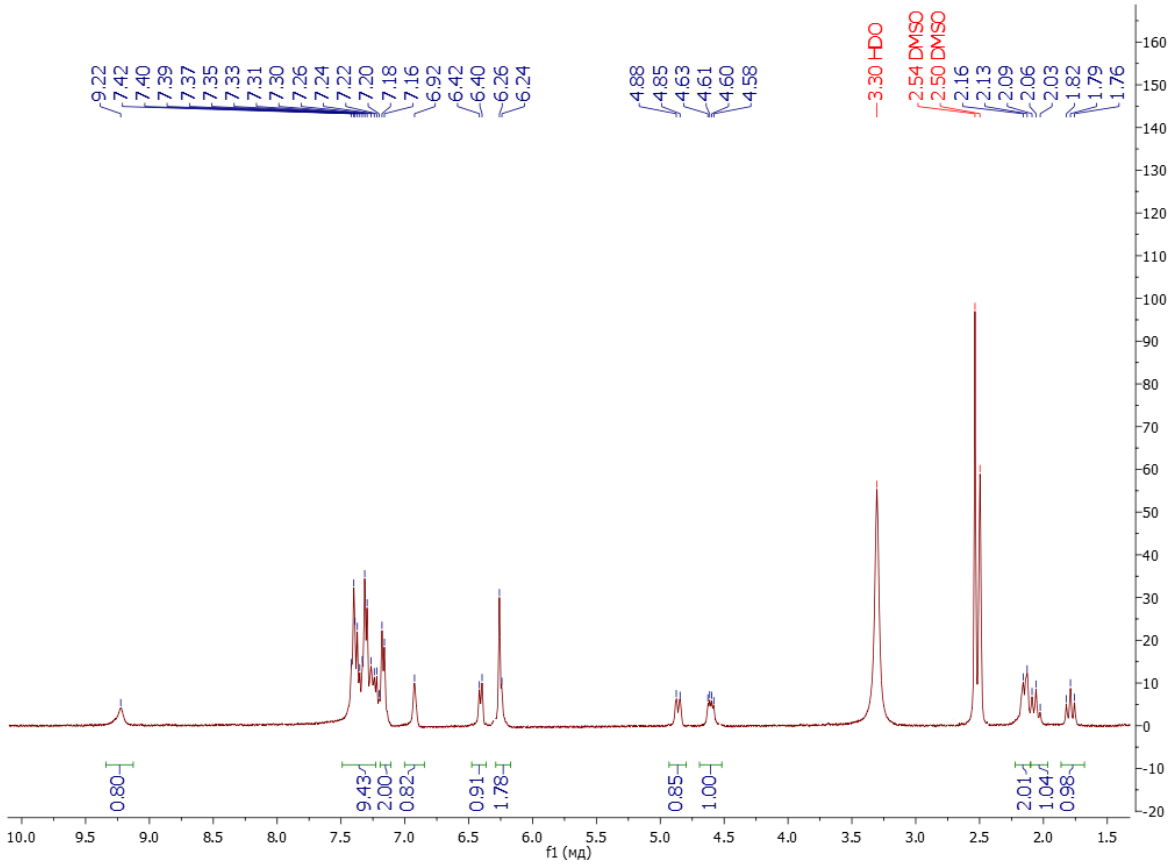
4 NMR Spectra



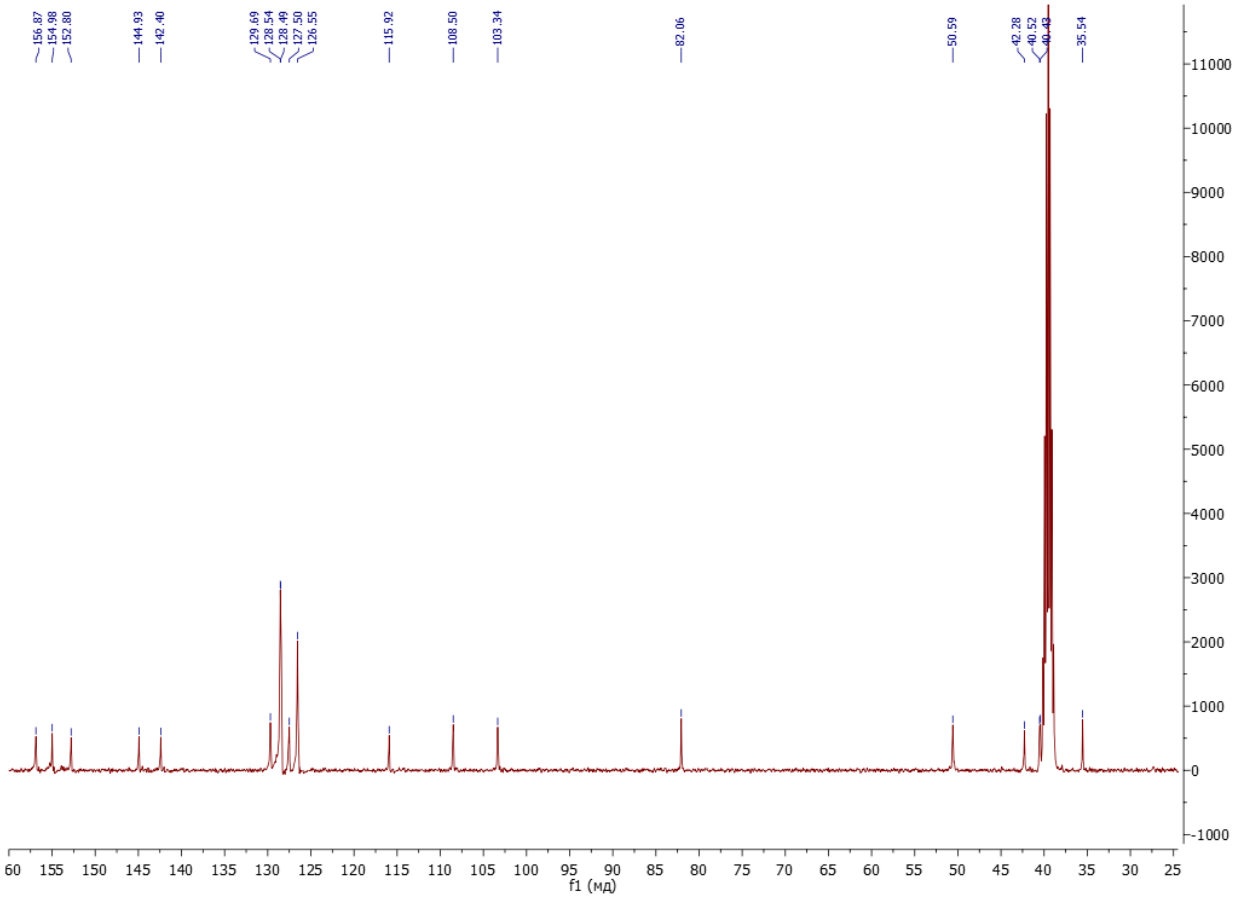
^{1}H NMR spectrum of compound **3a**



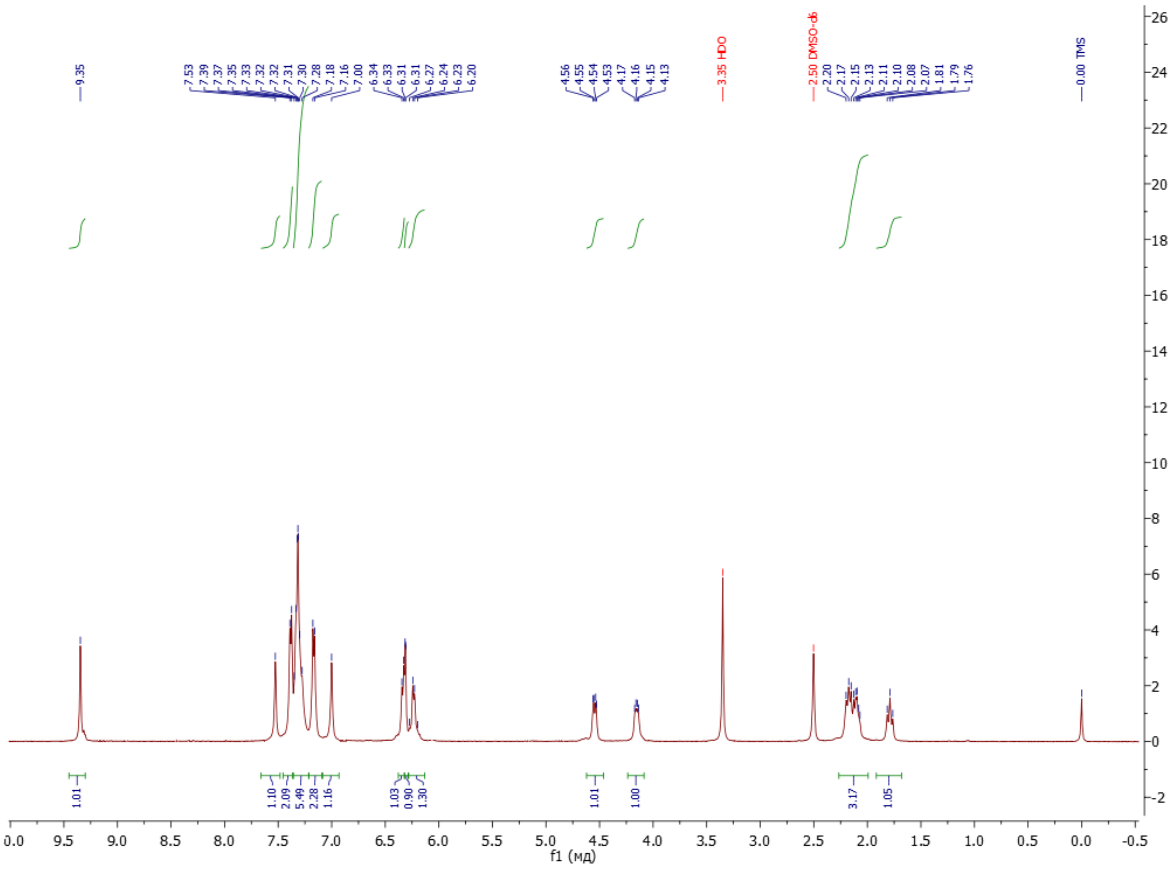
^{13}C NMR spectrum of compound **3a**



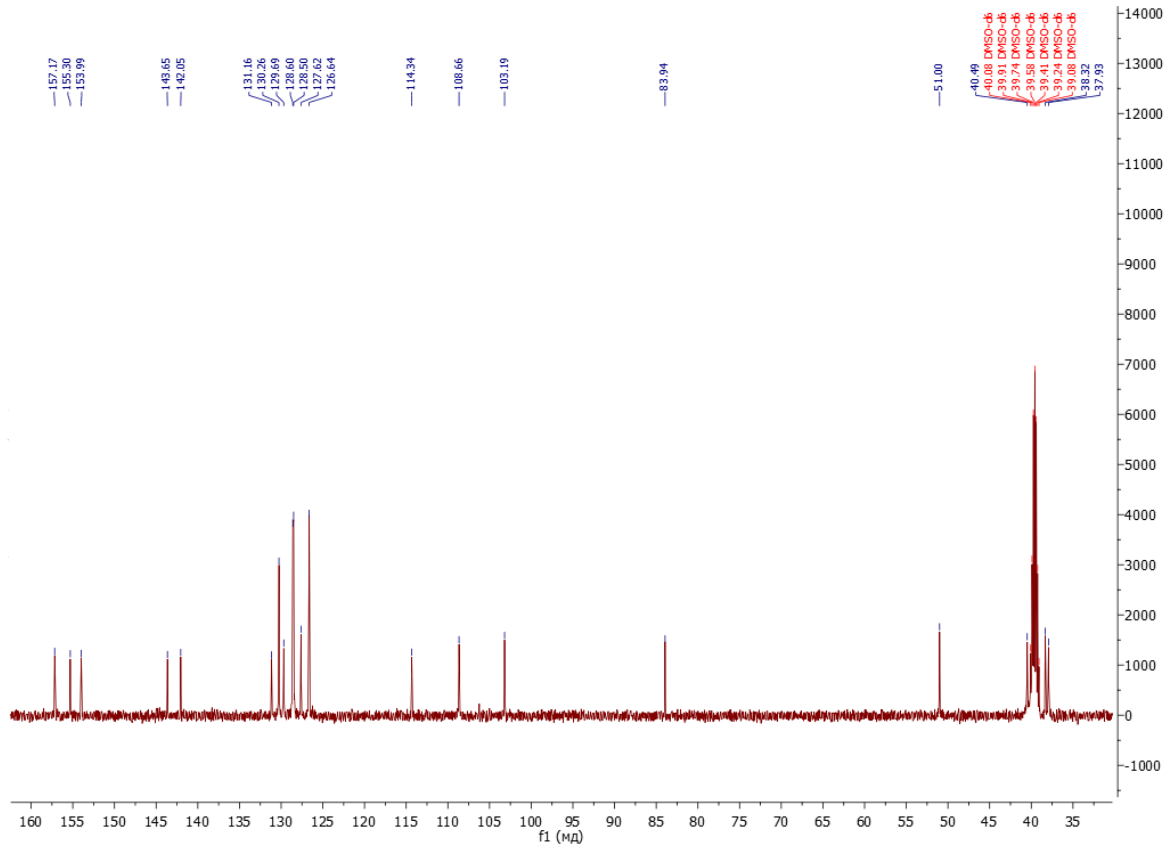
^{1}H NMR spectrum of compound **3'a**



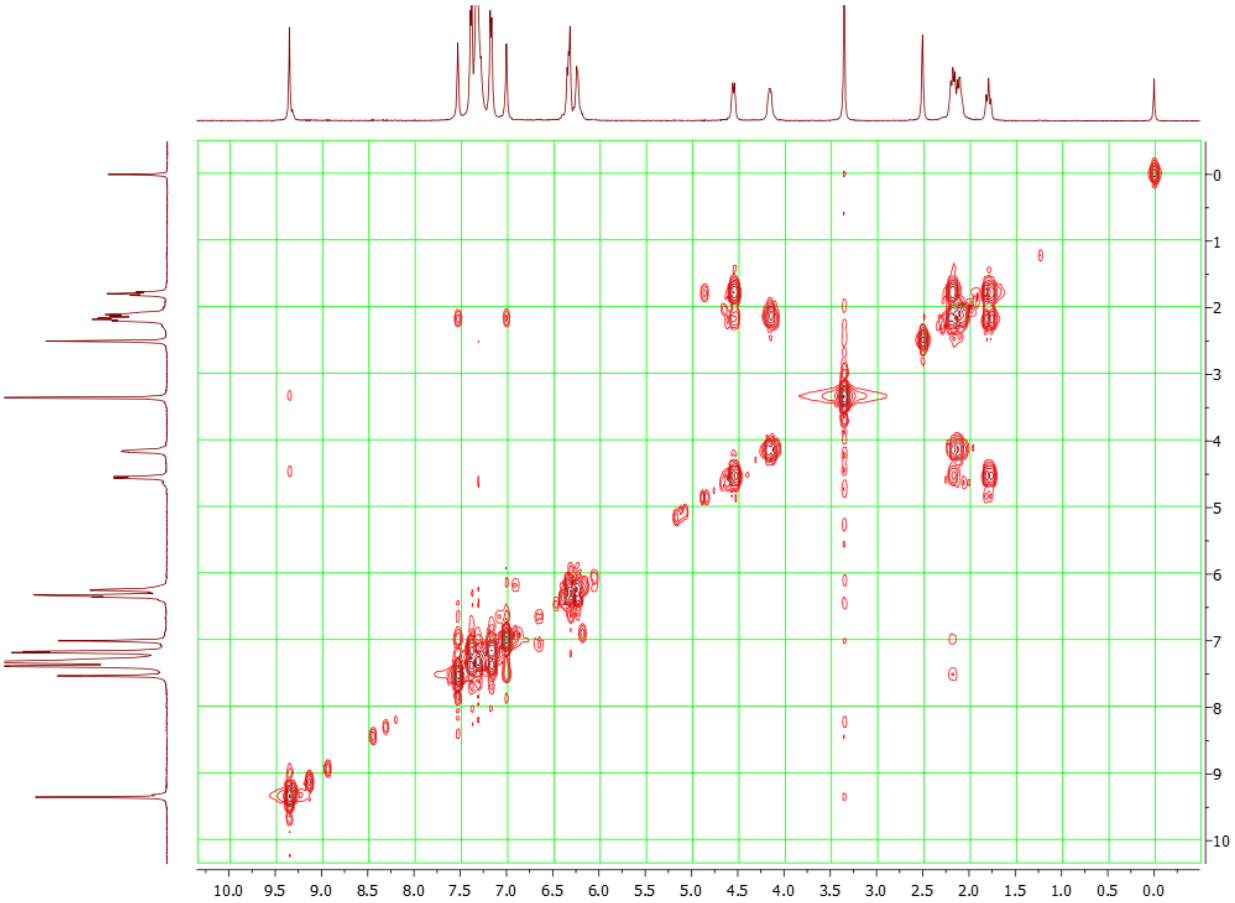
^{13}C NMR spectrum of compound **3'a**



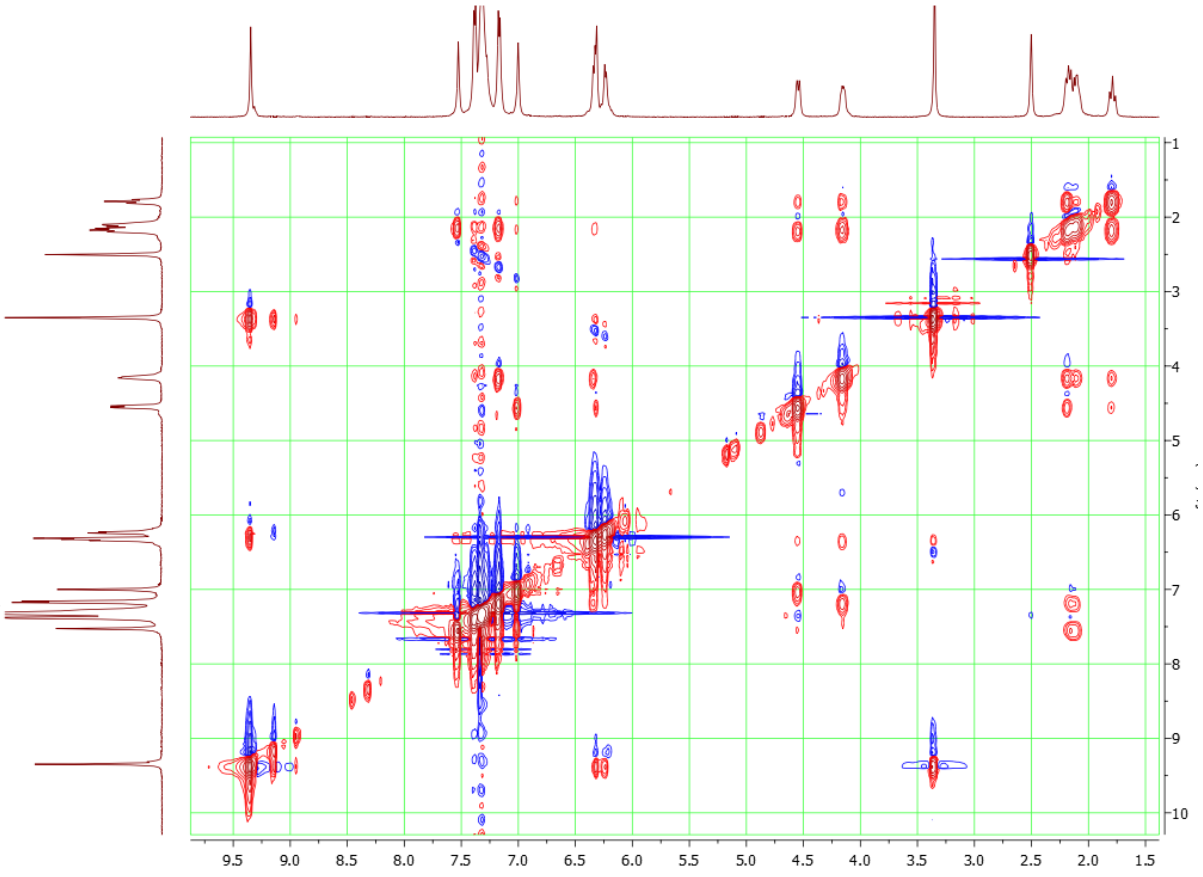
^{1}H NMR spectrum of compound **3b**



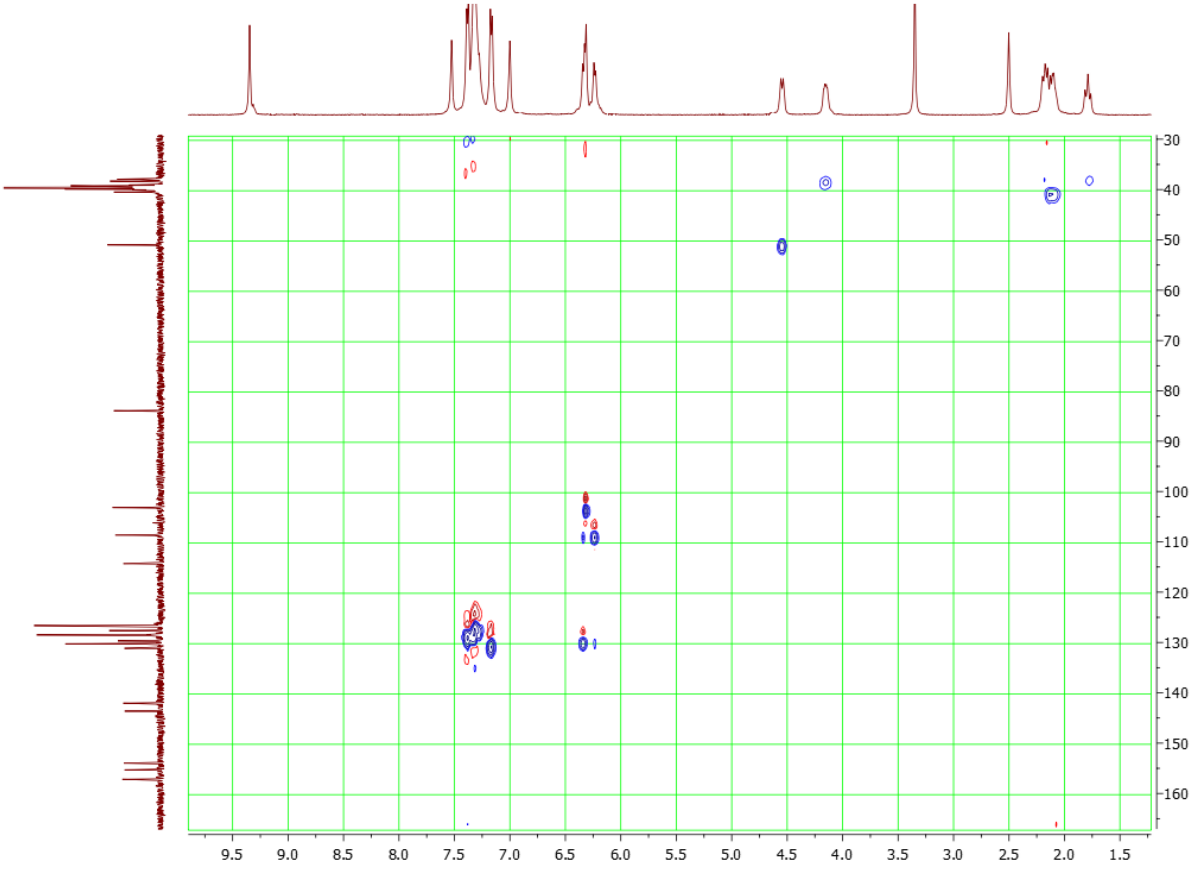
^{13}C NMR spectrum of compound **3b**



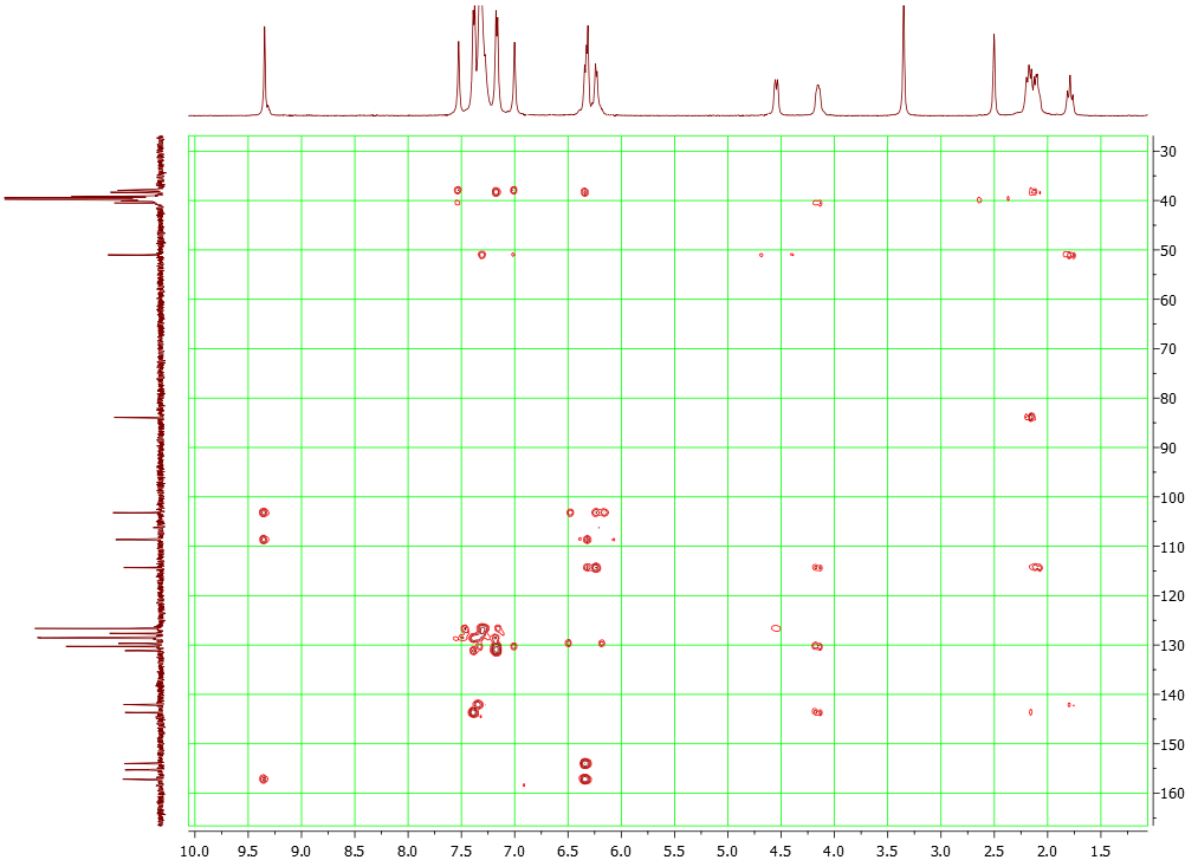
^{1}H-^{1}H COSY spectrum of compound **3b**



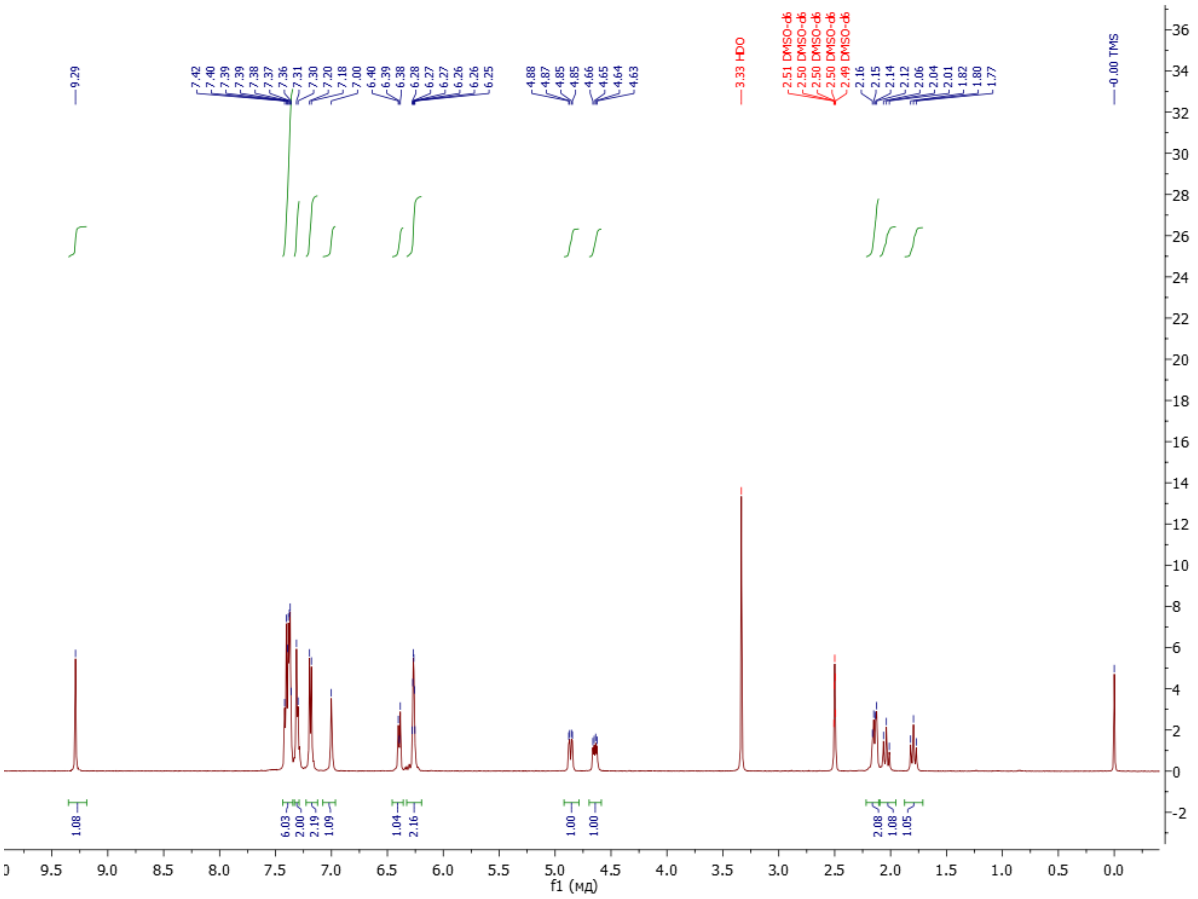
^{1}H-^{1}H NOESY spectrum of compound **3b**



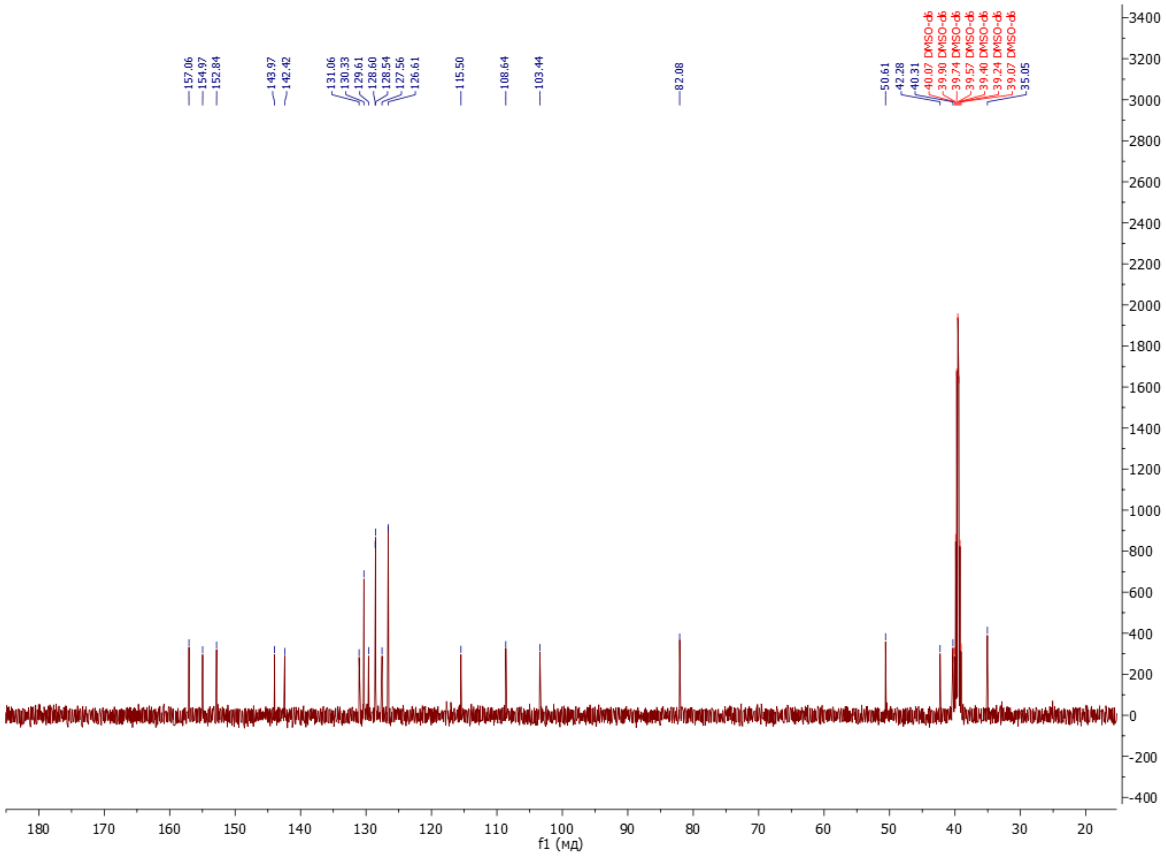
^{1}H-^{13}C HSQC spectrum of compound **3b**



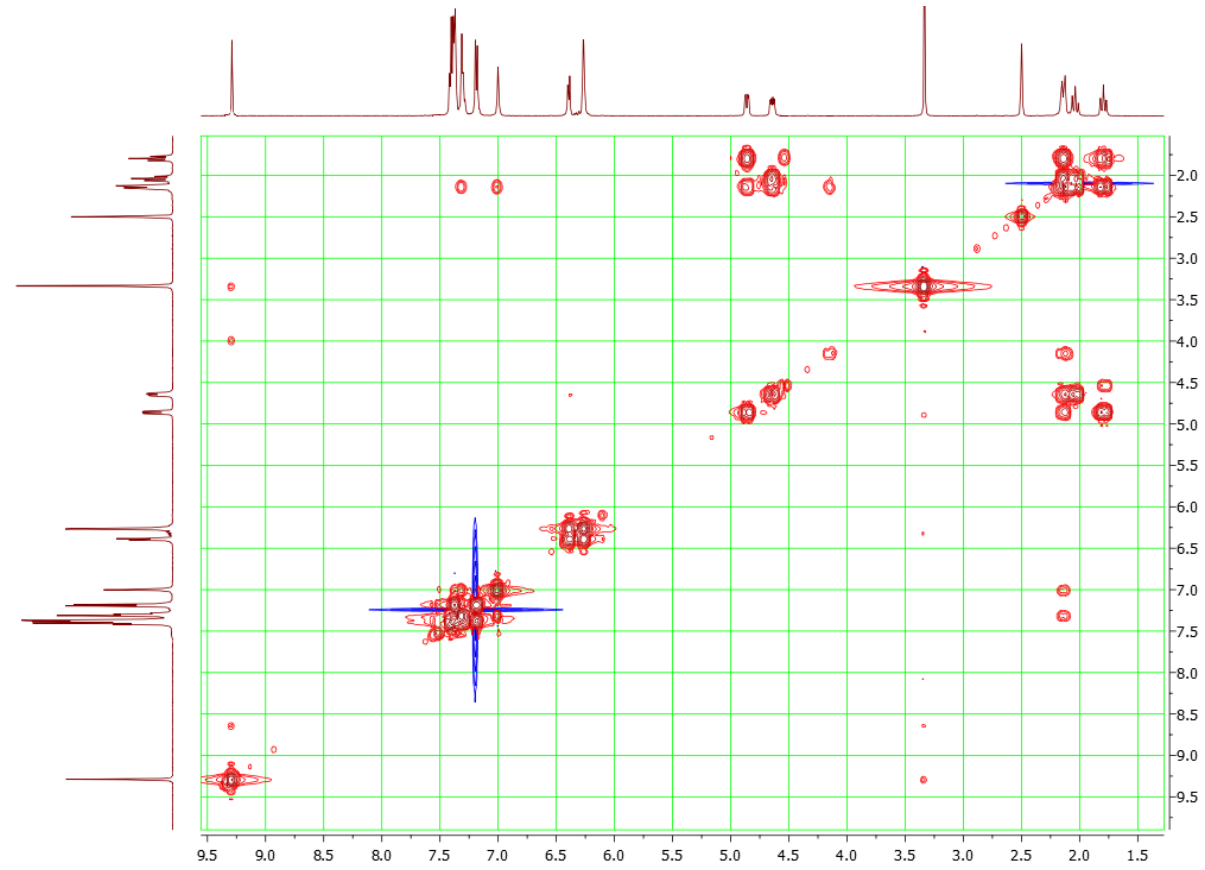
^{1}H-^{13}C HMBC spectrum of compound **3b**



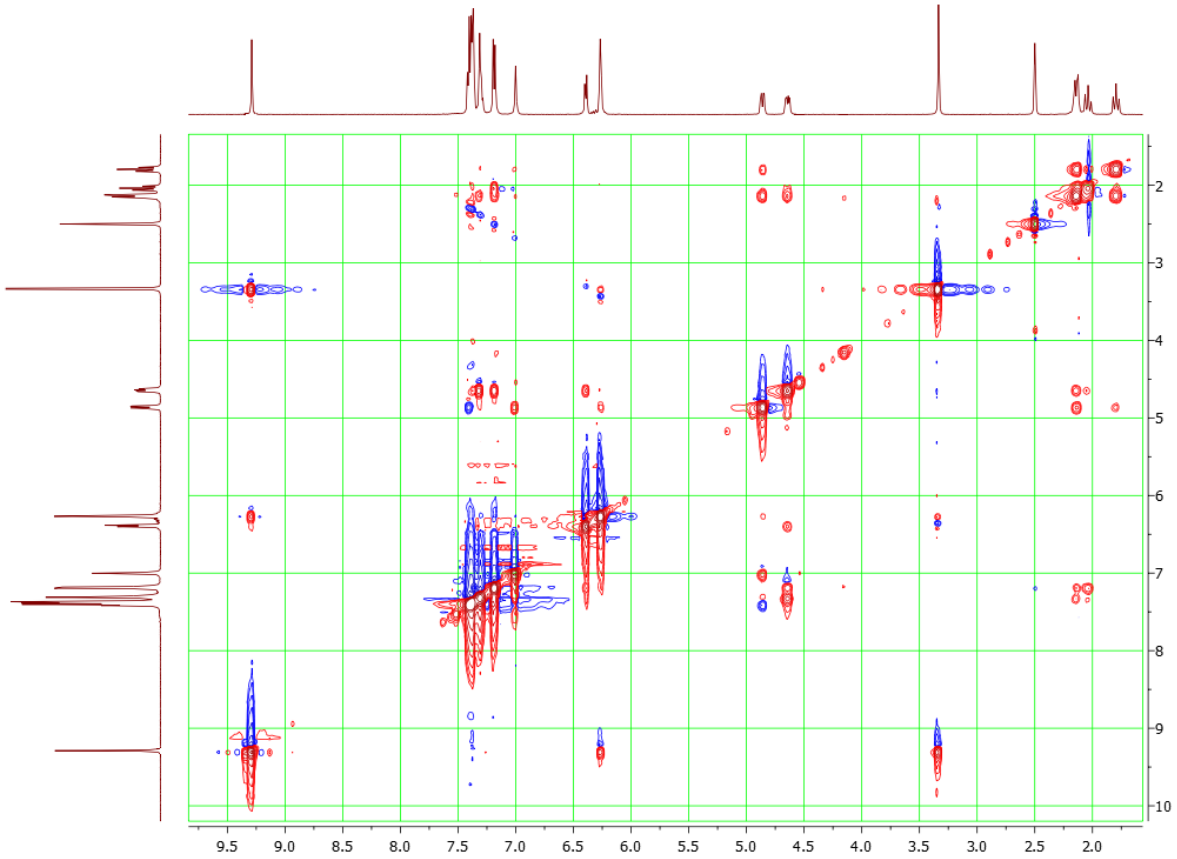
^{1}H NMR spectrum of compound **3'b**



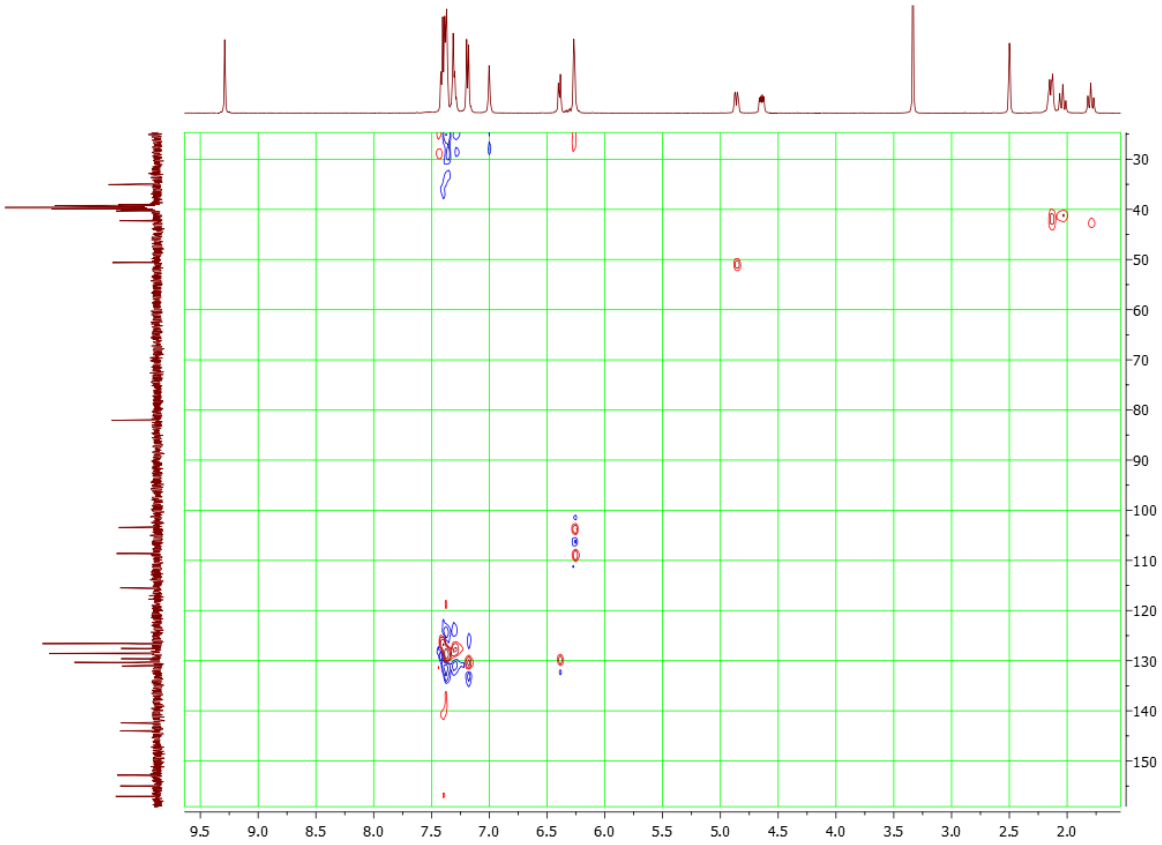
^{13}C NMR spectrum of compound **3'b**



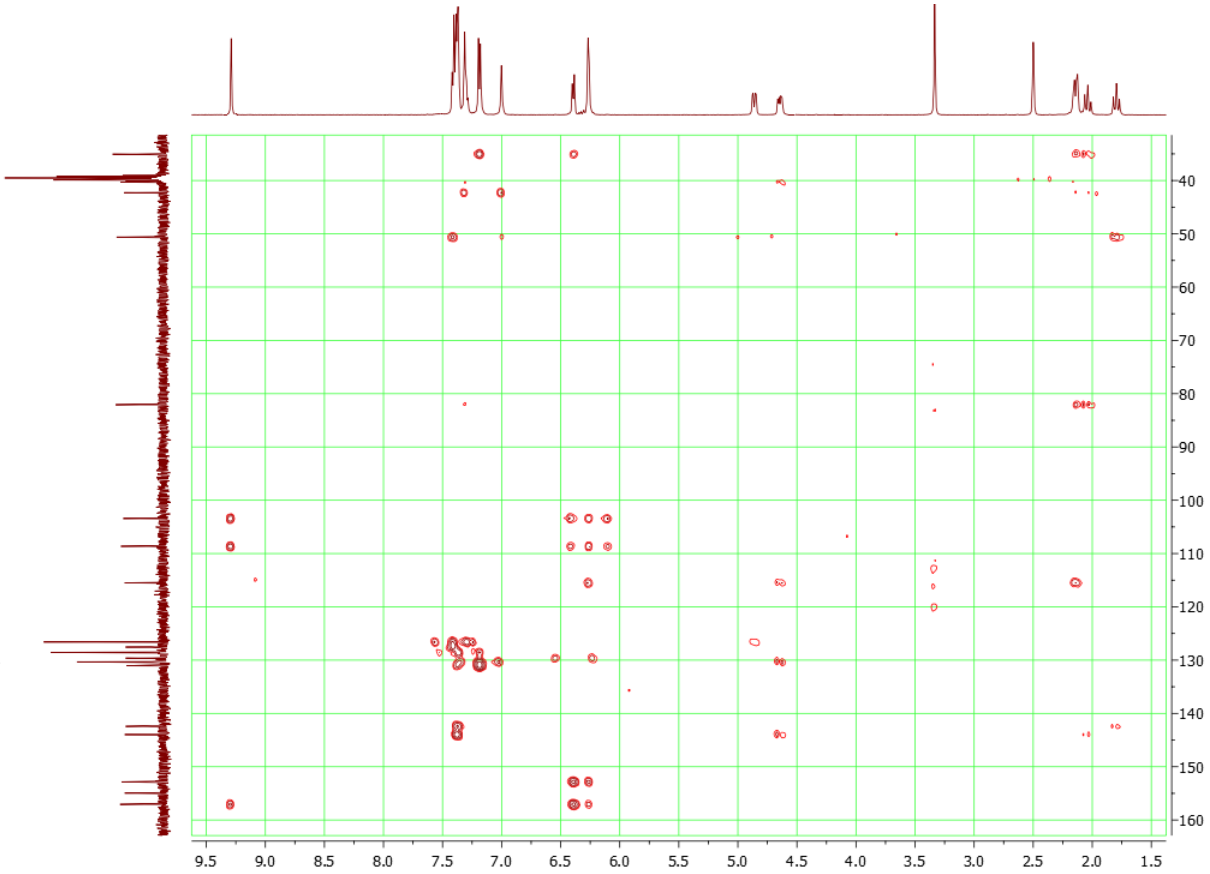
^{1}H-^{1}H COSY spectrum of compound **3'b**



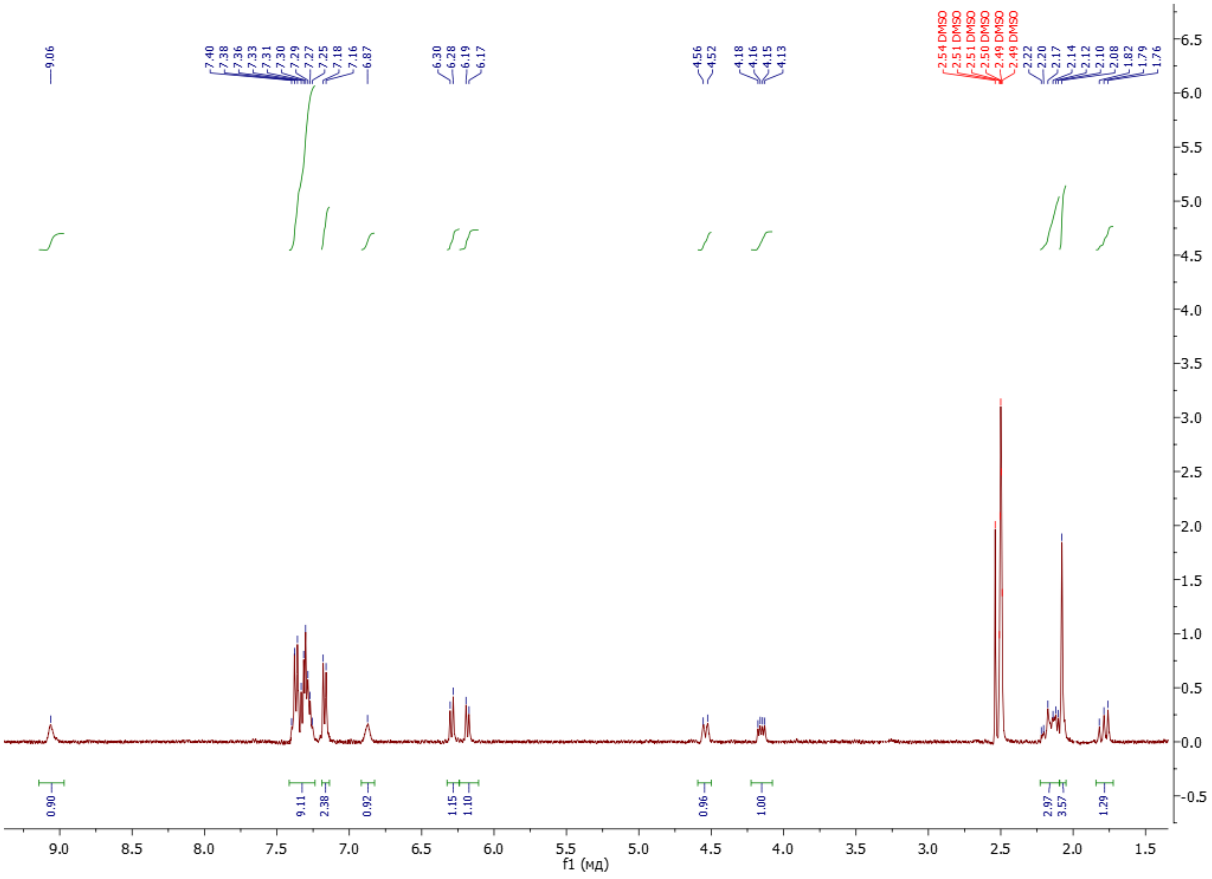
^{1}H-^{1}H NOESY spectrum compound **3'b**



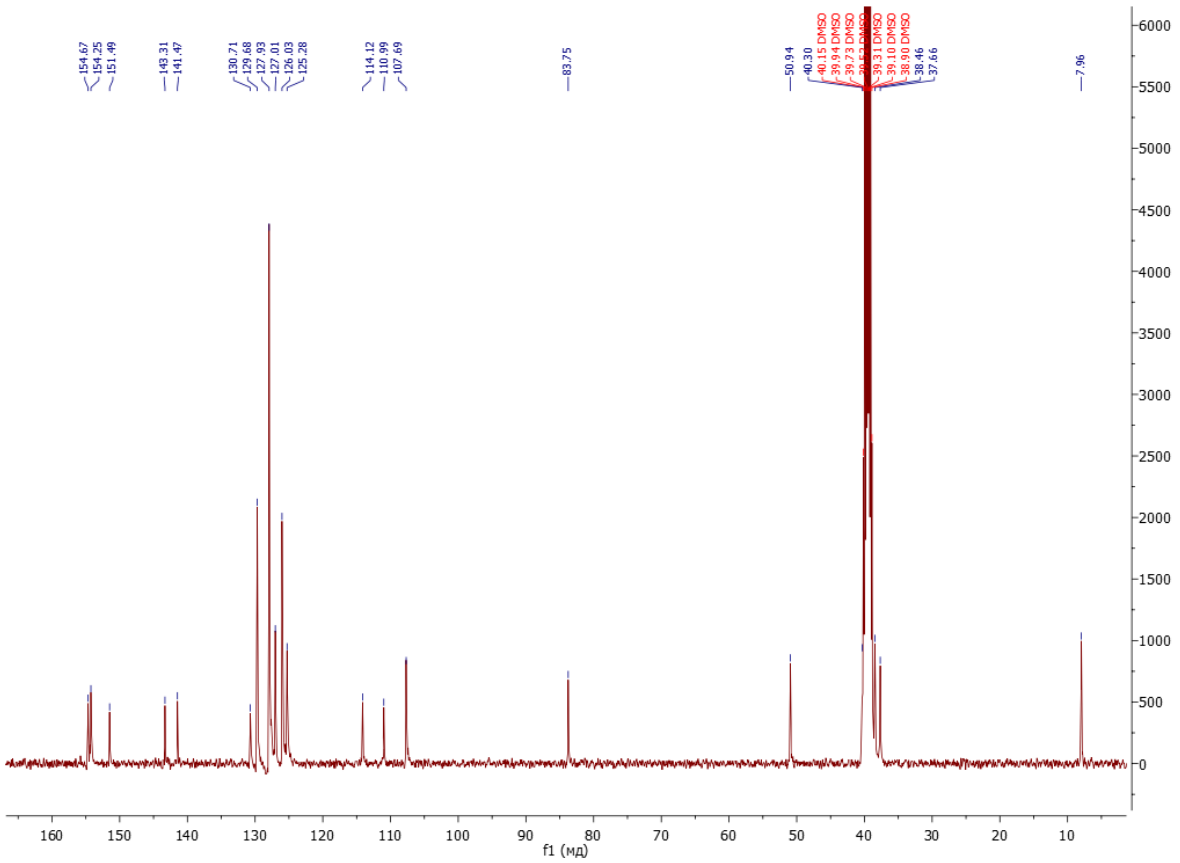
^{1}H-^{13}C HSQC spectrum of compound **3'b**



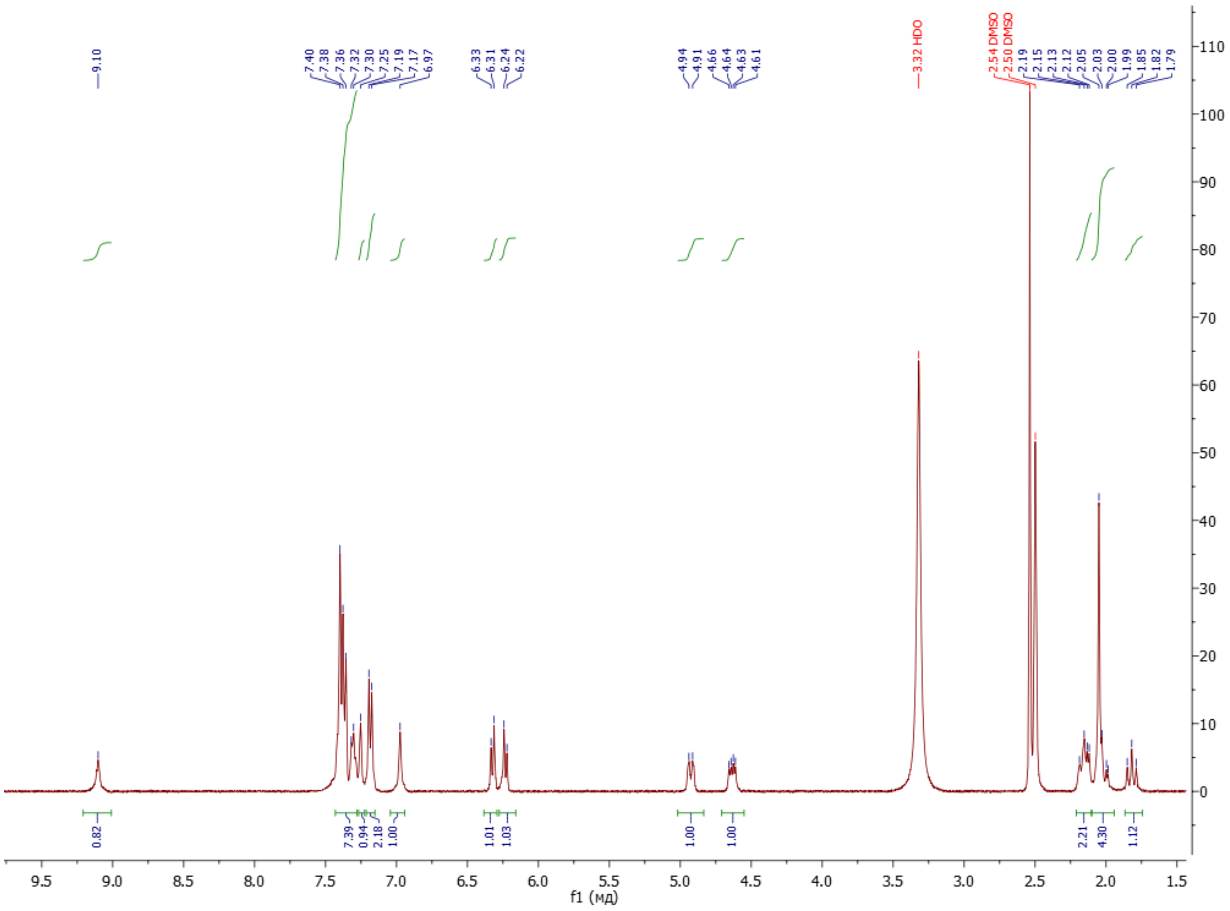
^{1}H-^{13}C HMBC spectrum of compound **3'b**



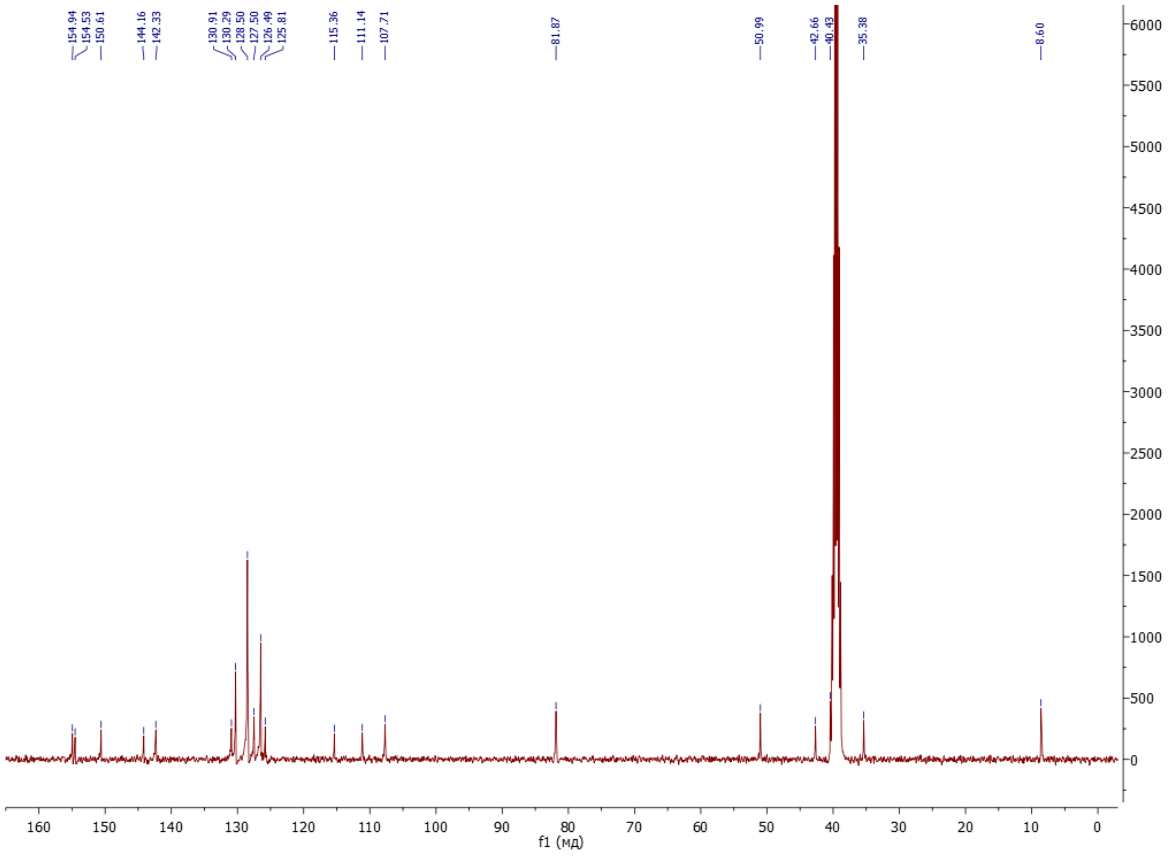
^{1}H NMR spectrum of compound **3c**



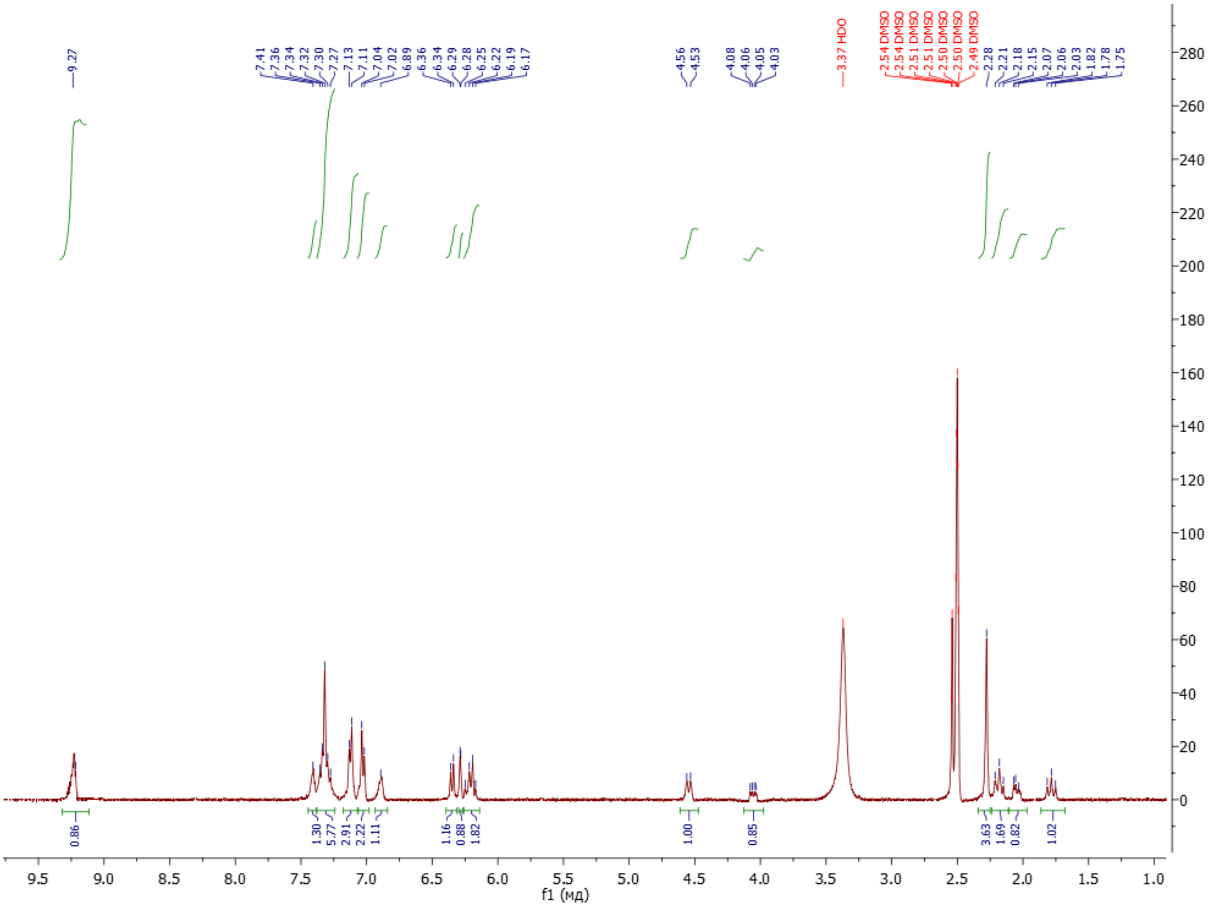
^{13}C NMR spectrum of compound **3c**



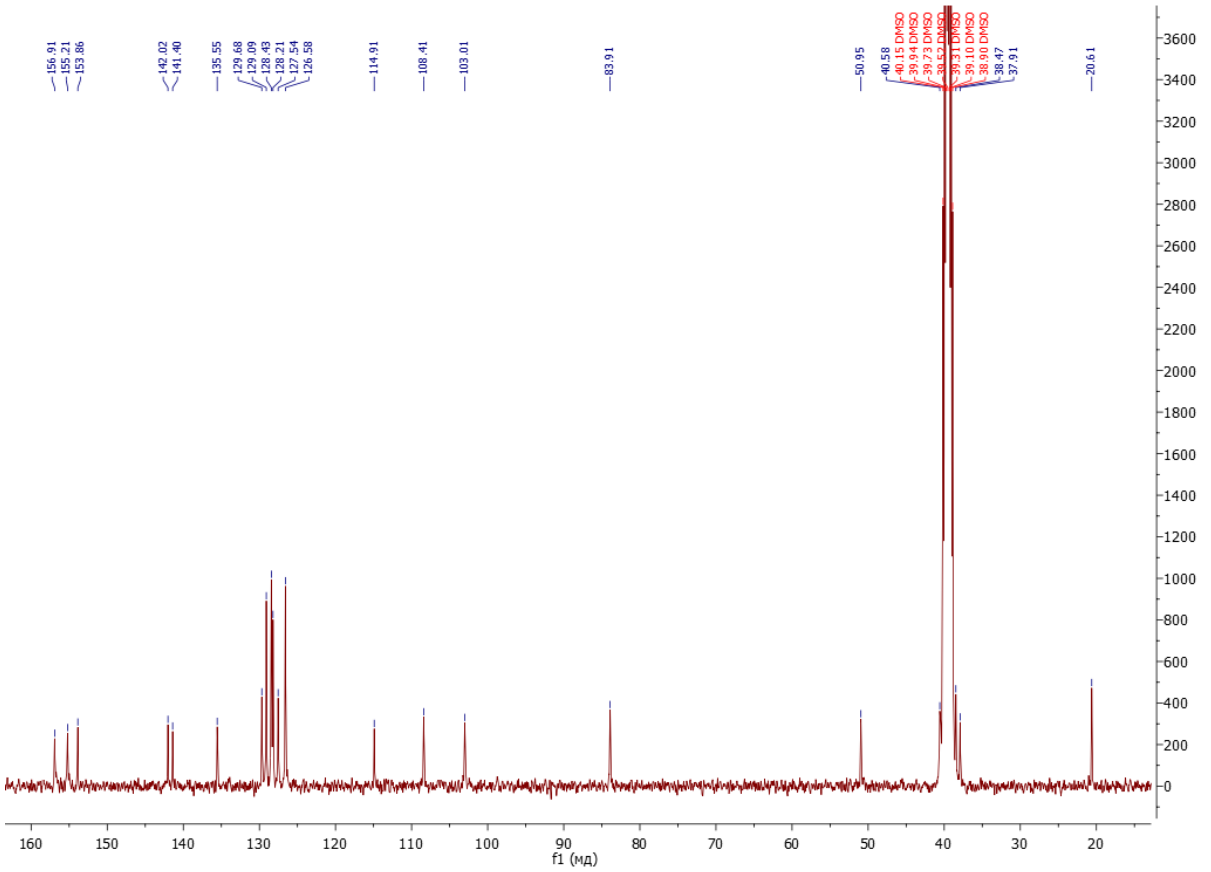
^{1}H NMR spectrum of compound **3'c**



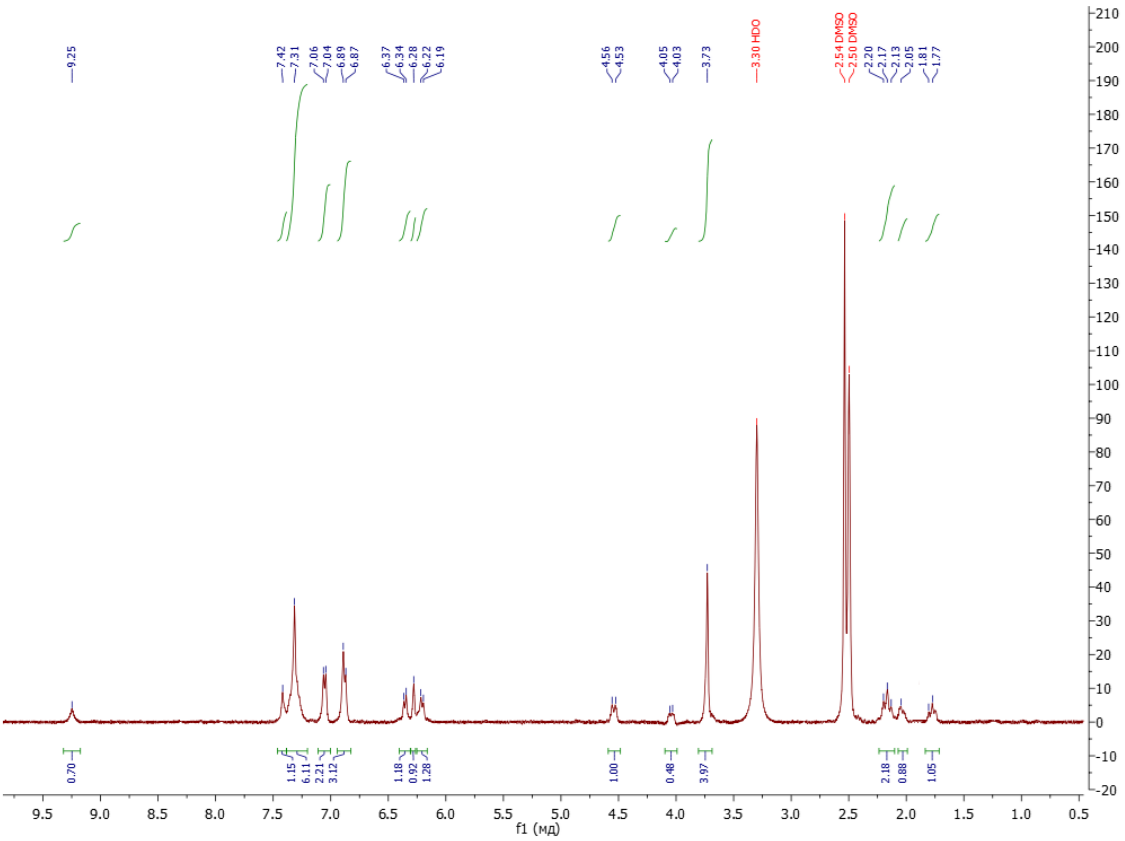
^{13}C NMR spectrum of compound **3'c**



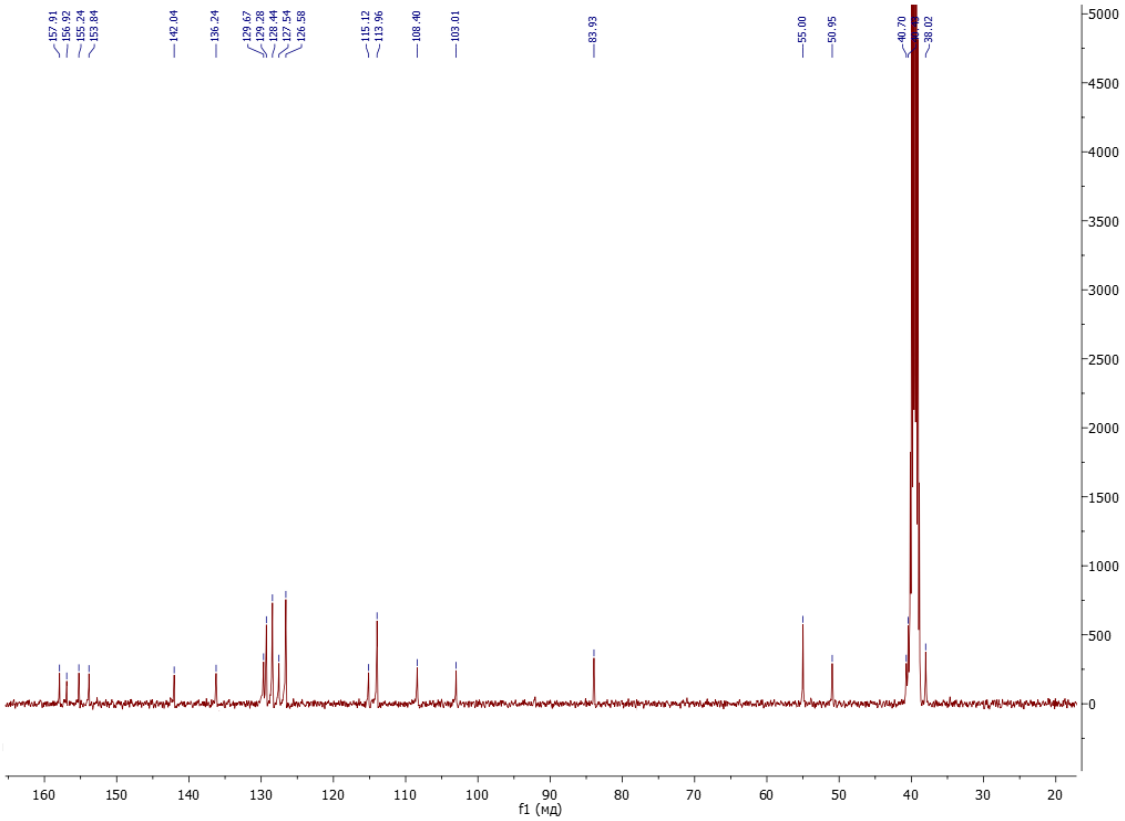
^{1}H NMR spectrum of compound **3d**



^{13}C NMR spectrum of compound **3d**



^{1}H NMR spectrum of compound **3e**



^{13}C NMR spectrum of compound **3e**

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