

Highly diastereoselective multicomponent synthesis of pyridinium-substituted piperidin-2-ones with three stereogenic centres

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1. Chemical Experimental Details

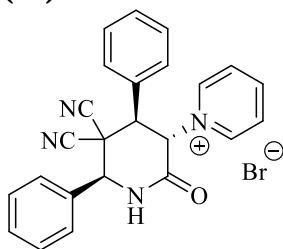
All melting points were measured with a Stuart SMP30 melting point apparatus and are uncorrected. ^1H and ^{13}C spectra were recorded with a Bruker AM300 at ambient temperature in DMSO-d_6 solution. Chemical shifts values are given in δ scale relative to Me_4Si . The J values are given in Hertz. Only discrete or characteristic signals for the ^1H NMR are reported. IR spectra were recorded with a Bruker ALPHA-T FT-IR spectrometer in KBr pellets. HR-ESI-MS was measured on a Bruker microTOF II instrument; external or internal calibration was done with electrospray calibrant solution (Fluka). All starting materials were obtained from commercial sources and used without purification.

2. Synthesis and Characterization Products

Synthesis of 4a-h:

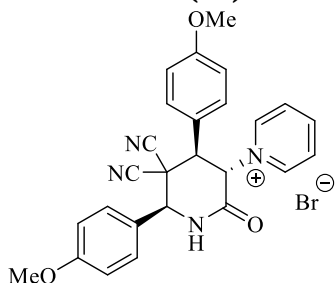
Synthesis of 4. A mixture of arylidenemalononitrile **1** (2 mmol), aldehyde **2** (2 mmol), reactant **3** (2 mmol) and ammonium acetate (4 mmol) was stirred in methanol (5 ml) under reflux for 2 hours. After the reaction completion, the mixture was maintained at $-10\text{ }^\circ\text{C}$ for 30 min for the complete precipitation of the product. The precipitate was collected by filtration and dried to give pure piperidine **4**.

1-((3*SR*,4*RS*,6*SR*)-5,5-Dicyano-2-oxo-4,6-diphenylpiperidin-3-yl)pyridin-1-ium bromide (4a) was obtained from **1a**, **2a** and **3a**.



Yield: 0.73 g (79%); white solid; m.p. $285\text{--}286\text{ }^\circ\text{C}$; ^1H -NMR (DMSO-d_6 , 300.13 MHz): δ = 9.72 (s, 1H, NH), 9.56 (d, J = 3.3 Hz, 2H, Ar), 8.67 (t, J = 7.7 Hz, 1H, Ar), 8.24 (t, J = 7.0 Hz, 2H, Ar), 7.77-7.51 (m, 7H, Ar), 7.49-7.32 (m, 3H, Ar), 6.92 (d, J = 12.9 Hz, 1H), 6.18 (s, 1H), 5.85 (d, J = 12.9 Hz, 1H); ^{13}C -NMR (CDCl_3 , 75.47 MHz): δ = 165.0, 148.6, 146.0, 133.6, 131.5, 131.0, 130.8, 130.1 (2C), 129.4 (3C), 129.1 (2C), 128.9 (2C), 128.6 (2C), 112.1, 111.7, 69.2, 60.7, 48.7, 48.0; IR (KBr): 3468, 3177, 3076, 2900, 2859, 2574, 2252, 1710, 1632, 14589, 1392, 725, 705, 680 cm^{-1} ; HRMS (ESI) m/z $[\text{M} + \text{H} - \text{Br}]^+$ calcd for $\text{C}_{24}\text{H}_{19}\text{N}_4\text{O}^+$: 379.1547 found: 379.1553.

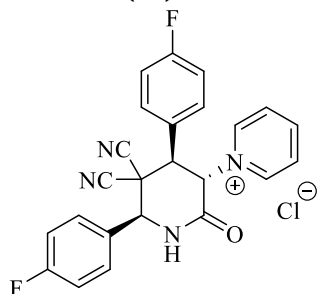
1-[(3*SR*,4*RS*,6*SR*)-5,5-Dicyano-4,6-bis(4-methoxyphenyl)-2-oxopiperidin-3-yl]pyridin-1-ium bromide (4b) was obtained from **1b**, **2b** and **3a**.



Yield: 0.90 g (87%); white solid; m.p. $239\text{--}241\text{ }^\circ\text{C}$; ^1H -NMR (DMSO-d_6 , 300.13 MHz): δ = 9.65 (s, 1H, NH), 9.53 (d, J = 3.1 Hz, 2H, Ar), 8.68 (t, J = 7.7 Hz, 1H, Ar), 8.25 (t, J = 7.1 Hz, 2H, Ar), 7.66-7.42 (m, 4H, Ar), 7.14 (d, J = 8.7 Hz, 2H, Ar), 6.97 (d, J = 8.7 Hz, 2H, Ar), 6.84 (d, J = 12.9 Hz, 1H), 6.03 (s, 1H), 5.67 (d, J = 12.9 Hz, 1H), 3.82 (s, 3H), 3.71 (s, 3H); ^{13}C -NMR (DMSO-d_6 , 75.47 MHz): δ = 165.1, 161.2, 160.7, 148.5, 145.9, 130.2 (2C), 129.9 (3C), 129.1 (2C), 125.4, 123.2, 115.3 (2C), 114.7 (2C), 112.4, 111.9, 69.4, 60.1, 55.8, 55.7, 48.8, 48.1; IR (KBr): 3483, 3047, 2942, 2568, 2252, 2105, 1689, 1517,

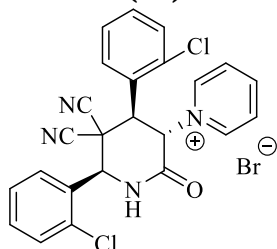
1256, 1183, 1027, 834 cm^{-1} ; HRMS (ESI) m/z $[M + H - Br]^+$ calcd for $\text{C}_{26}\text{H}_{23}\text{N}_4\text{O}_3^+$: 439.1762; found: 439.1765

1-[(3*SR*,4*RS*,6*SR*)-5,5-Dicyano-4,6-bis(4-fluorophenyl)-2-oxopiperidin-3-yl]pyridin-1-ium chloride (4c) was obtained from **1c**, **2c** and **3b**.



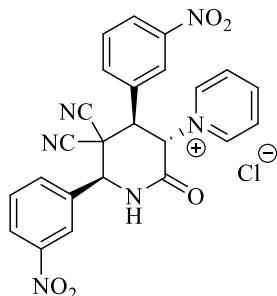
Yield: 0.54 g (60%); white solid; m.p. 275–277 $^{\circ}\text{C}$; ^1H -NMR (DMSO- d_6 , 300.13 MHz): δ = 9.73 (s, 3H, NH, Ar), 8.67 (t, J = 7.7 Hz, 1H, Ar), 8.24 (t, J = 7.1 Hz, 2H, Ar), 7.80-7.69 (m, 2H, Ar), 7.69-7.60 (m, 2H, Ar), 7.45 (t, J = 8.7 Hz, 2H, Ar), 7.30 (t, J = 8.7 Hz, 2H, Ar), 6.91 (d, J = 12.8 Hz, 1H), 6.34 (s, 1H), 6.24 (d, J = 12.9 Hz, 1H); ^{13}C -NMR (DMSO- d_6 , 75.47 MHz): δ = 165.0, 163.6 (d, $J^1_{\text{C-F}}$ = 247.3 Hz), 163.3 (d, $J^1_{\text{C-F}}$ = 248.0 Hz), 148.5, 146.1, 131.3 (d, $J^3_{\text{C-F}}$ = 6.8 Hz, 2C), 130.92 (d, $J^3_{\text{C-F}}$ = 8.8 Hz, 2C), 129.9 (d, $J^4_{\text{C-F}}$ = 2.9 Hz), 129.1 (3C), 128.0 (d, $J^4_{\text{C-F}}$ = 3.0 Hz), 117.2 (d, $J^2_{\text{C-F}}$ = 21.9 Hz, 2C), 116.42 (d, $J^2_{\text{C-F}}$ = 22.0 Hz, 2C), 112.1, 111.6, 69.2, 59.8, 48.1, 47.8; IR (KBr): 3635, 3390, 3069, 2913, 2868, 2726, 2594, 2256, 1712, 1515, 1231, 845, 529 cm^{-1} ; HRMS (ESI) m/z $[M + H - Br]^+$ calcd for $\text{C}_{24}\text{H}_{17}\text{F}_2\text{N}_4\text{O}^+$: 415.1371; found: 415.1365.

1-[(3*SR*,4*SR*,6*RS*)-4,6-Bis(2-chlorophenyl)-5,5-dicyano-2-oxopiperidin-3-yl]pyridin-1-ium bromide (4d) was obtained from **1d**, **2d** and **3a**.



Yield: 0.68 g (64%); white solid; m.p. 232–235 $^{\circ}\text{C}$; ^1H -NMR (DMSO- d_6 , 300.13 MHz): δ = 9.67 (s, 1H, NH), 9.52 (s, 2H, Ar), 8.70 (t, J = 7.6 Hz, 1H, Ar), 8.38-8.23 (m, 2H, Ar), 8.19 (d, J = 7.7 Hz, 1H, Ar), 7.82 (d, J = 7.4 Hz, 1H, Ar), 7.75-7.34 (m, 6H, Ar), 6.95 (d, J = 12.7 Hz, 1H), 6.66 (s, 1H), 5.89 (d, J = 12.7 Hz, 1H); ^{13}C -NMR (DMSO- d_6 , 75.47 MHz): δ = 165.0, 148.9, 146.0, 135.0, 133.9, 132.7 (2C), 131.2, 131.0, 130.7, 130.3, 129.2 (3C), 129.1, 128.8, 128.6, 128.5, 111.5, 111.0, 69.0, 56.4, 45.9, 45.4; IR (KBr): 3380, 3246, 3025, 2944, 2726, 2581, 2335, 2253, 1711, 1629, 1483, 1444, 755, 679 cm^{-1} ; HRMS (ESI) m/z $[M + H - Br]^+$ (for ^{35}Cl) 447.0763 calcd for $\text{C}_{24}\text{H}_{17}\text{Cl}_2\text{N}_4\text{O}^+$: 447.0774.

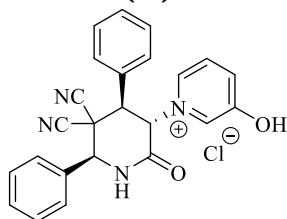
1-[(3*SR*,4*RS*,6*SR*)-5,5-Dicyano-4,6-bis(3-nitrophenyl)-2-oxopiperidin-3-yl]pyridin-1-ium chloride (4e) was obtained from **1e**, **2e** and **3b**.



Yield: 0.65 g (65%); white solid; m.p. 271–274 $^{\circ}\text{C}$; ^1H -NMR (DMSO- d_6 , 300.13 MHz): δ = 9.94 (s, 1H, NH), 9.60 (s, 2H, Ar), 8.68 (t, J = 8.0 Hz, 1H, Ar), 8.60 (s, 1H), 8.53-8.41 (m, 2H, Ar), 8.39-8.17 (m, 3H, Ar), 8.16-8.03 (m, 2H, Ar), 7.95 (t, J = 8.3 Hz, 1H, Ar), 7.80 (t, J = 8.2 Hz, 1H, Ar), 7.11 (d, J = 12.7 Hz, 1H), 6.47 (s, 1H), 6.30 (d, J = 12.6 Hz, 1H); ^{13}C -NMR (DMSO- d_6 , 75.47 MHz): δ = 164.8, 148.8, 148.7,

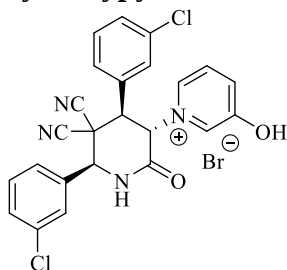
148.2, 146.0, 135.2 (2C), 135.3, 133.2, 132.0, 131.4, 129.4 (4C), 126.1, 126.0, 123.3, 111.6, 111.0, 68.5, 59.7, 47.9, 47.5; IR (KBr): 3468, 3071 2954, 2877, 2729, 2598, 2252, 1715, 1531, 1351, 726, 684 cm^{-1} ; HRMS (ESI) m/z $[\text{M} + \text{H} - \text{Br}]^+$ calcd for $\text{C}_{24}\text{H}_{17}\text{N}_6\text{O}_5^+$: 469.1256; found: 469.1255.

1-((3*SR*,4*RS*,6*SR*)-5,5-Dicyano-2-oxo-4,6-diphenylpiperidin-3-yl)-3-hydroxypyridin-1-ium chloride (4f) was obtained from **1a**, **2a** and **3c**.



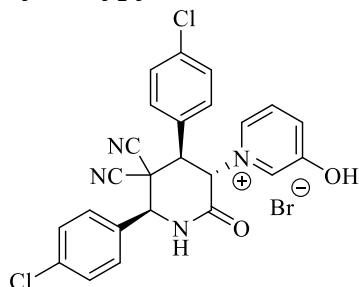
Yield: 0.65 g (75%); white solid; m.p. 202–204 °C; ^1H -NMR (DMSO- d_6 , 300.13 MHz): δ = 9.30-7.95 (1H, OH), 7.76 (s, 1H, NH), 7.70-7.49 (m, 9H, Ar), 7.48-7.28 (m, 3H, Ar), 7.21 – 7.14 (m, 1H, Ar), 6.90-6.77 (m, 1H, Ar), 6.20 (d, J = 12.7 Hz, 1H), 5.87 (s, 1H), 5.17 (d, J = 12.6 Hz, 1H); ^{13}C -NMR (DMSO- d_6 , 75.47 MHz): δ = 168.5, 165.5, 133.4, 132.3, 130.9, 130.4, 129.7 (3C), 129.3 (3C), 129.0 (2C), 128.6 (3C), 127.0, 112.5, 111.8, 67.9, 60.7, 49.5, 48.0; IR (KBr): 3658, 3159, 3064, 3022, 2899, 2603, 2530, 1700, 1566, 1502, 1367, 724, 702 cm^{-1} ; HRMS (ESI) m/z $[\text{M} + \text{H} - \text{Br}]^+$ calcd for $\text{C}_{24}\text{H}_{19}\text{N}_4\text{O}_2^+$: 395.1512; found: 395.1503.

1-[(3*SR*,4*RS*,6*SR*)-4,6-Bis(3-chlorophenyl)-5,5-dicyano-2-oxopiperidin-3-yl]-3-hydroxypyridin-1-ium bromide (4g) was obtained from **1f**, **2f** and **3d**.



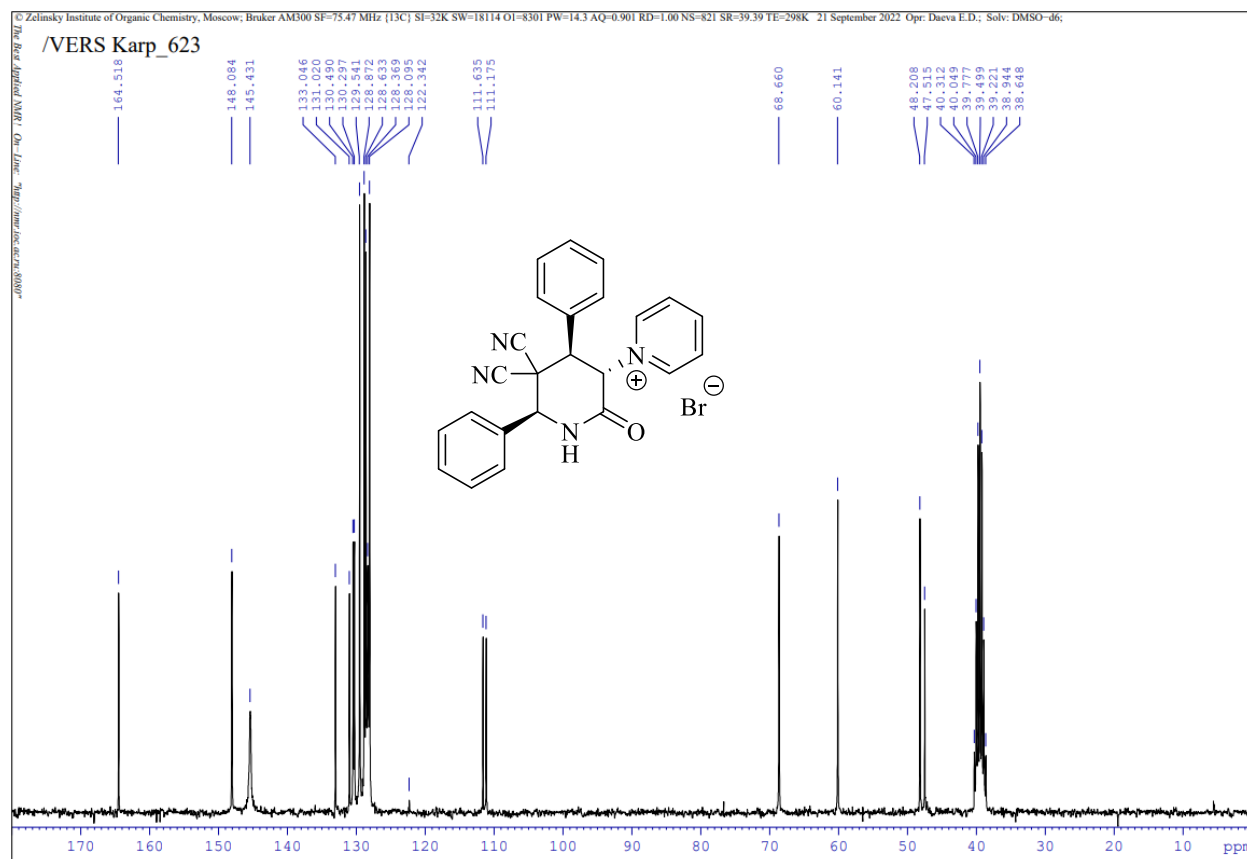
Yield: 0.88 g (81%); white solid; m.p. 195–197 °C; ^1H -NMR (DMSO- d_6 , 300.13 MHz): δ = 9.51-8.40 (1H, OH), 7.82-7.71 (m, 2H), 7.70 – 7.40 (m, 9H, Ar), 7.32 – 7.14 (m, 1H), 6.90 (dd, J = 8.9, 2.2 Hz, 1H, Ar), 6.26 (d, J = 12.6 Hz, 1H), 5.88 (s, 1H), 5.24 (d, J = 12.7 Hz, 1H); ^{13}C -NMR (DMSO- d_6 , 75.47 MHz): δ = 168.4, 165.1, 135.9 (2C), 134.6, 134.4 (2C), 134.3, 133.9, 131.7, 131.4, 131.0, 130.7, 128.6, 128.3, 127.9, 127.5, 127.2, 112.1, 111.4, 67.4, 59.9, 48.6, 47.6; IR (KBr): 3517, 3067, 3013, 2931, 2669, 2389, 2229, 2105, 1705, 1691, 1572, 1508, 1357, 1026, 796, 686 cm^{-1} ; HRMS (ESI) m/z $[\text{M} + \text{H} - \text{Br}]^+$ (for ^{35}Cl) 463.0713 calcd for $\text{C}_{24}\text{H}_{17}\text{Cl}_2\text{N}_4\text{O}_2^+$: 463.0723.

1-[(3*SR*,4*RS*,6*SR*)-4,6-Bis(4-chlorophenyl)-5,5-dicyano-2-oxopiperidin-3-yl]-3-hydroxypyridin-1-ium bromide (4h) was obtained from **1g**, **2g** and **3d**.

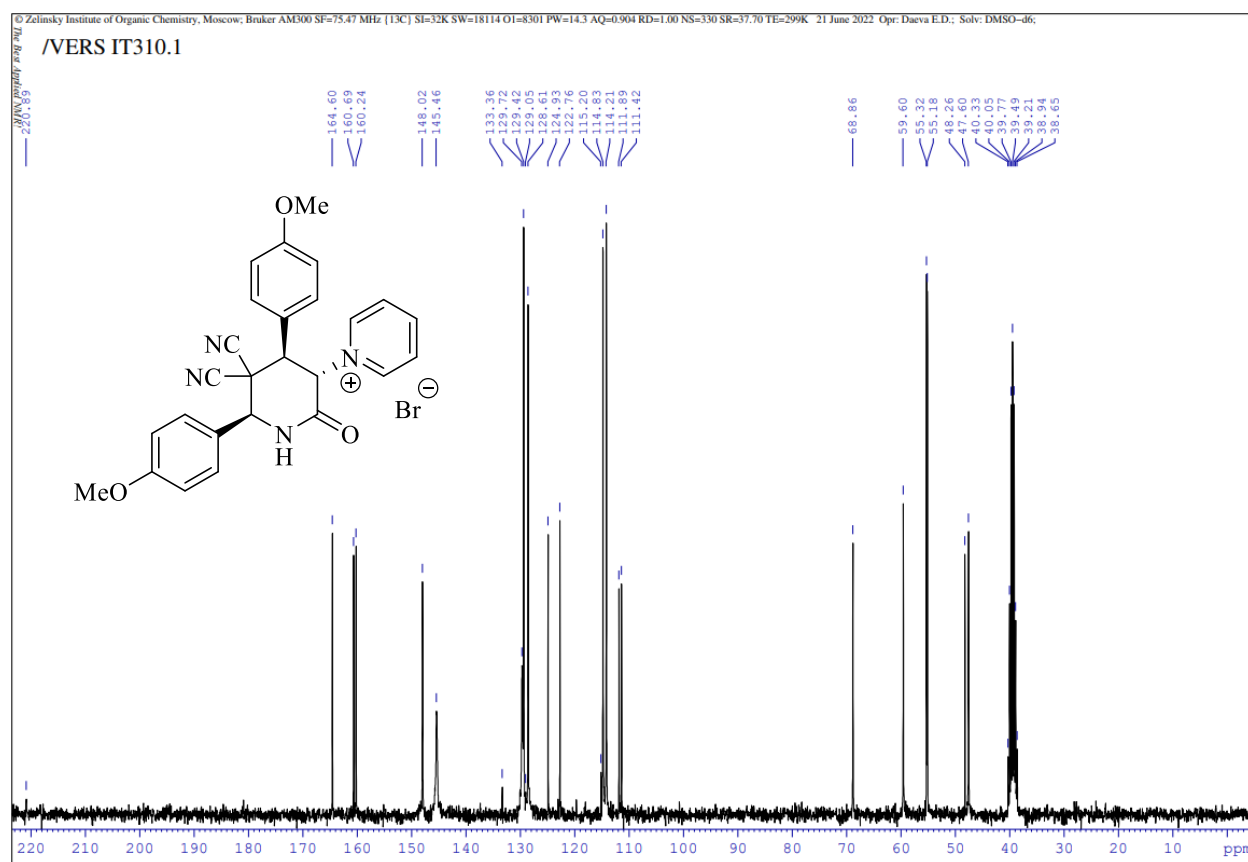
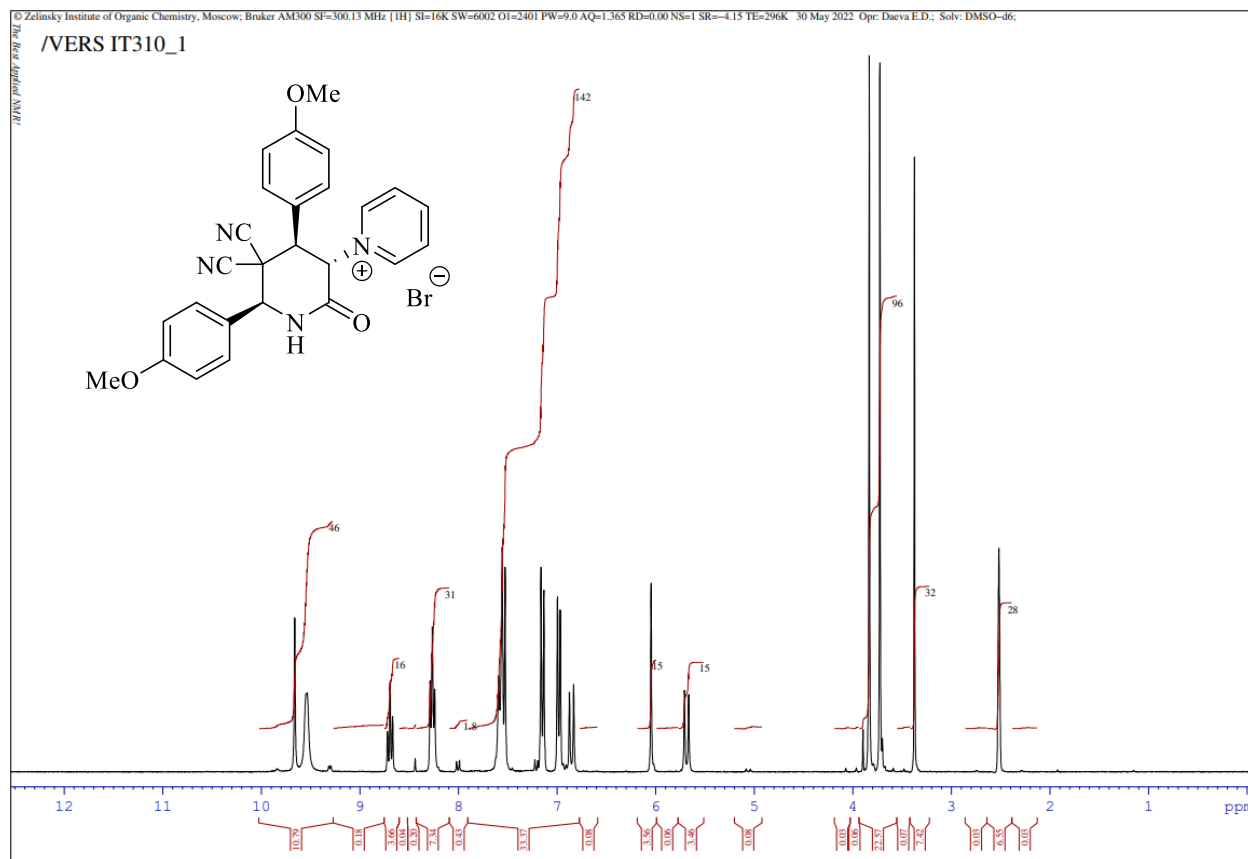


Yield: 0.75 g (69%); white solid; m.p. 212–214 °C; ^1H -NMR (DMSO- d_6 , 300.13 MHz): δ = 9.62-9.42 (1H, OH), 7.78 – 7.43 (m, 11H), 7.28-7.17 (m, 1H, Ar), 6.89 (d, J = 9.0 Hz, 1H, Ar), 6.20 (d, J = 12.7 Hz, 1H), 5.82 (s, 1H), 5.15 (d, J = 12.5 Hz, 1H); ^{13}C -NMR (DMSO- d_6 , 75.47 MHz): δ = 168.5, 165.2, 135.7, 135.4, 134.6, 132.6, 131.1, 130.8, 130.4 (3C), 129.9 (3C), 129.5 (3C), 127.1, 112.2, 111.5, 67.6, 60.1, 48.8, 47.6; IR (KBr): 3655, 3468, 3048, 2850, 2531, 2256, 2106, 1718, 1563, 1509, 1388, 1093, 512 cm^{-1} ; HRMS (ESI) m/z $[\text{M} + \text{H} - \text{Br}]^+$ (for ^{35}Cl) 463.0713 calcd for $\text{C}_{24}\text{H}_{17}\text{Cl}_2\text{N}_4\text{O}_2^+$: 463.0723.

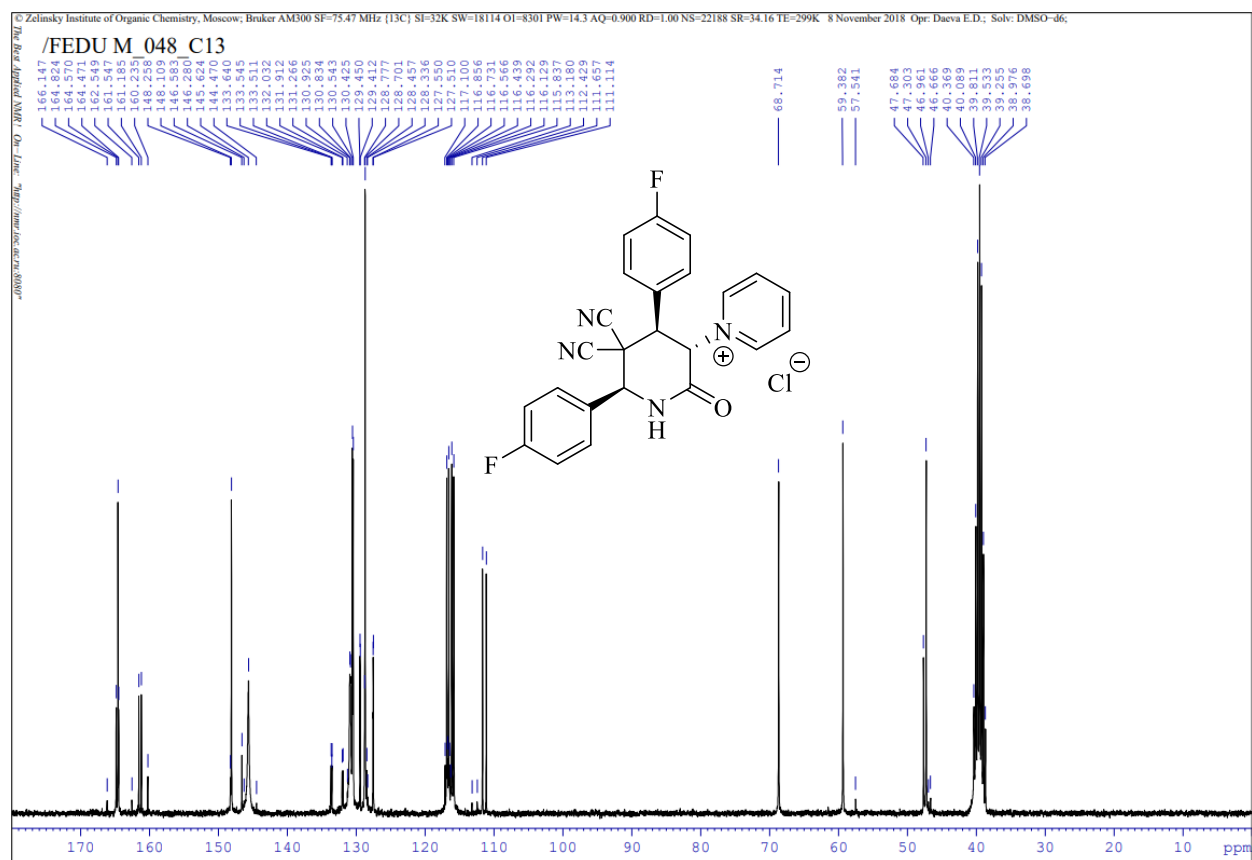
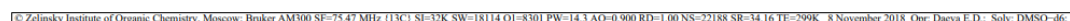
4a



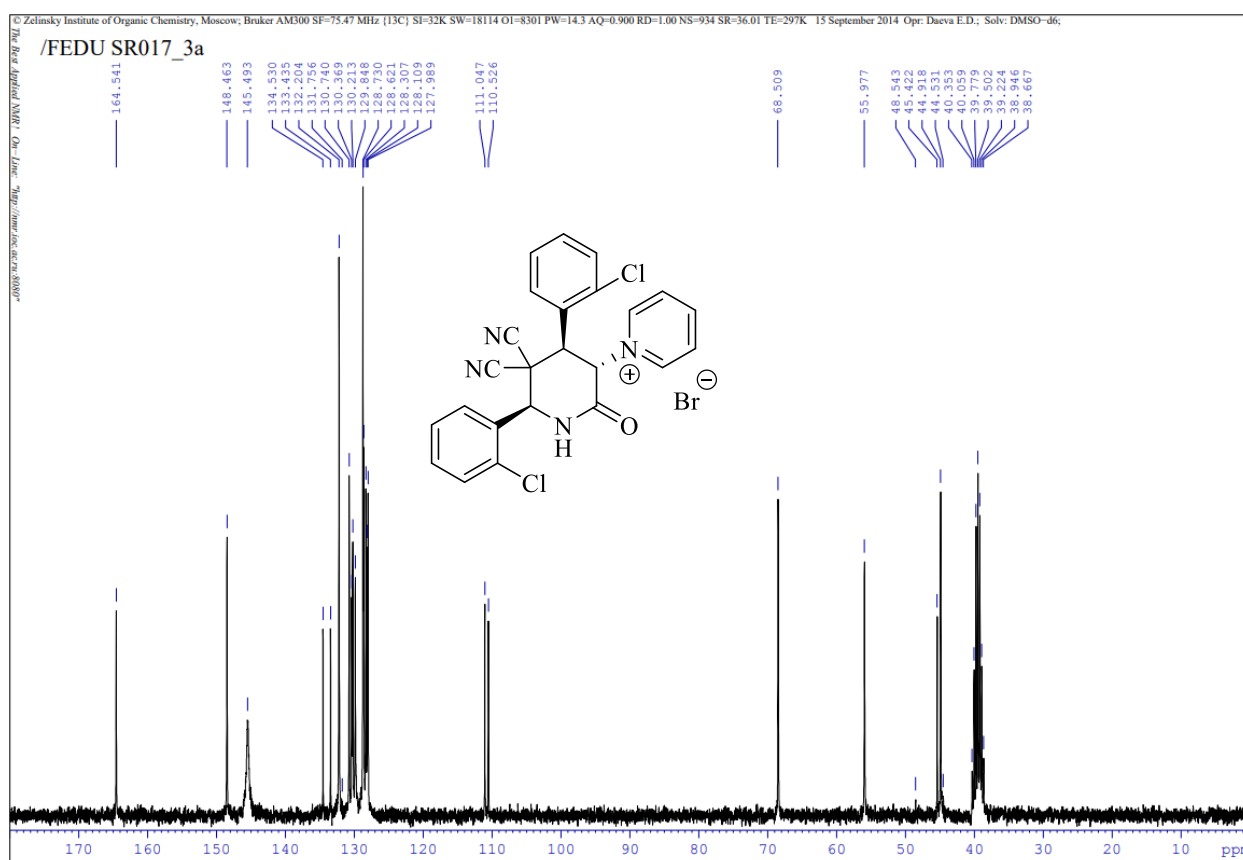
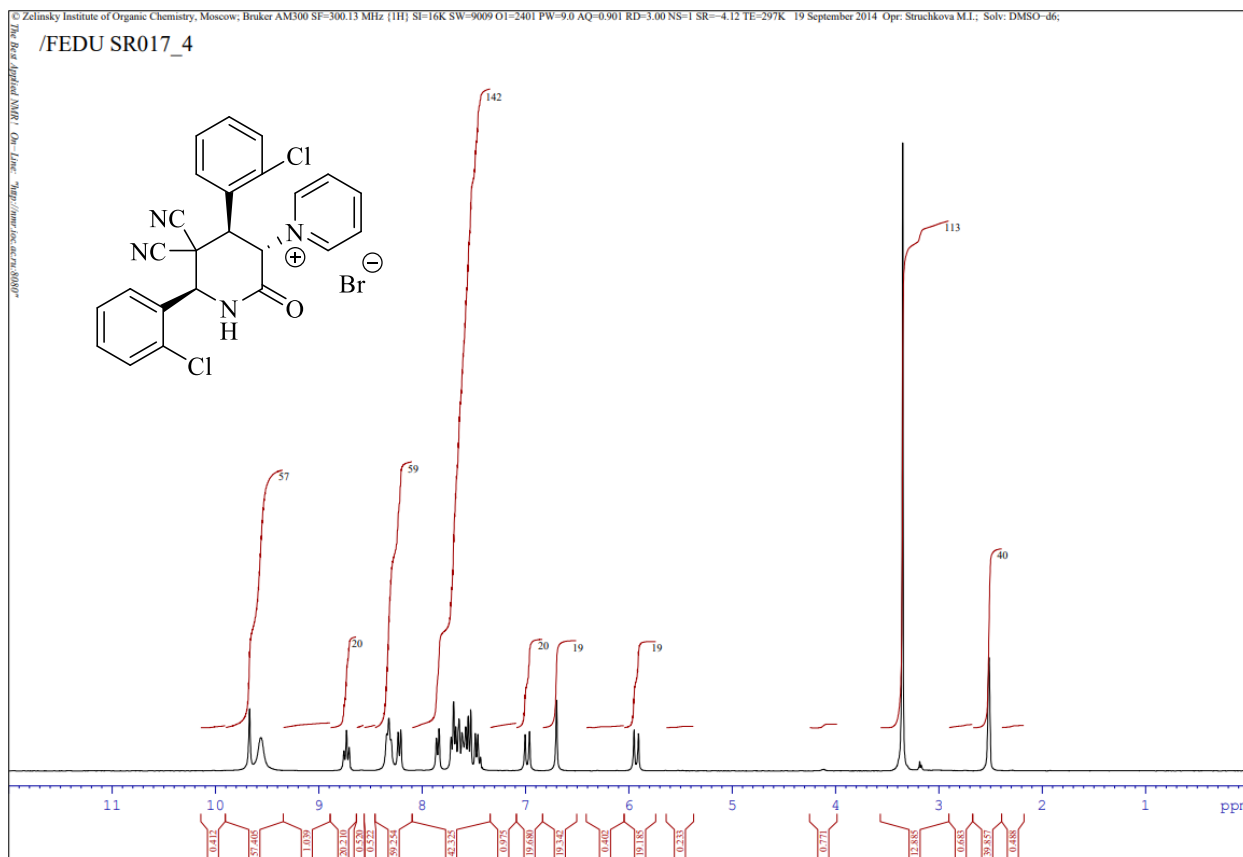
4b



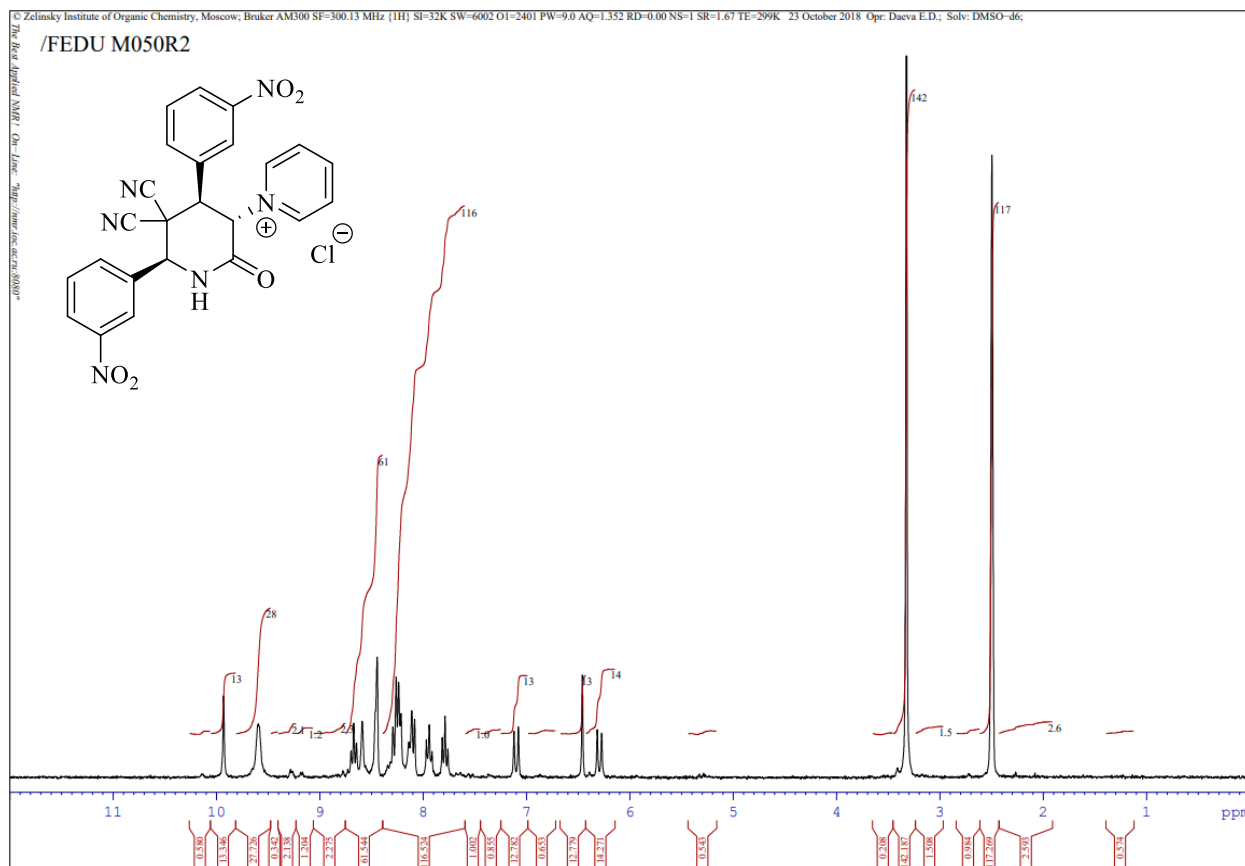
© Zelinsky Institute of Organic Chemistry, Moscow; Bruker AM300 SF=300.13 MHz [1H] SI=32K SW=6002 O1=2401 PW=9.0 AQ=1.352 RD=1.00 NS=1 SR=1.67 TE=299K 23 October 2018 Opr: Daeva E.D.; Solv: DMSO-d6



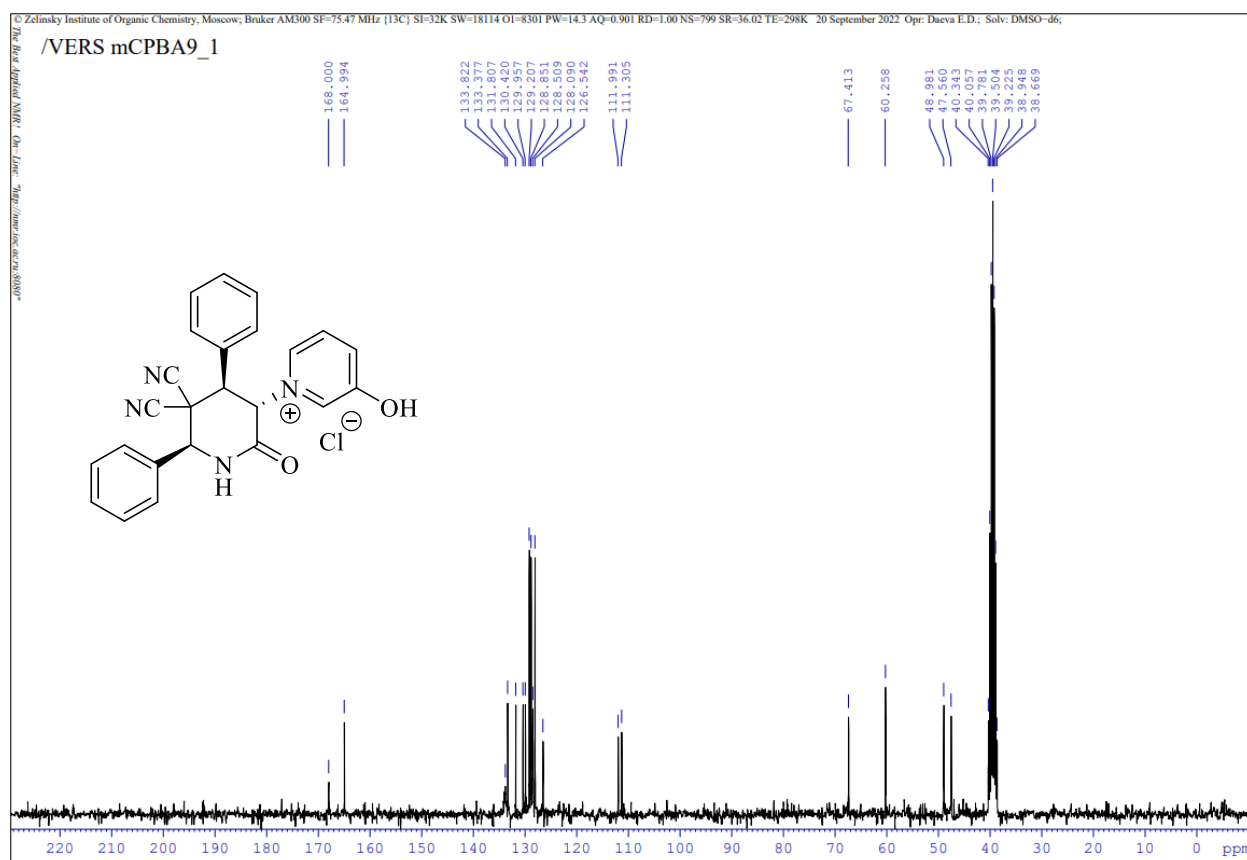
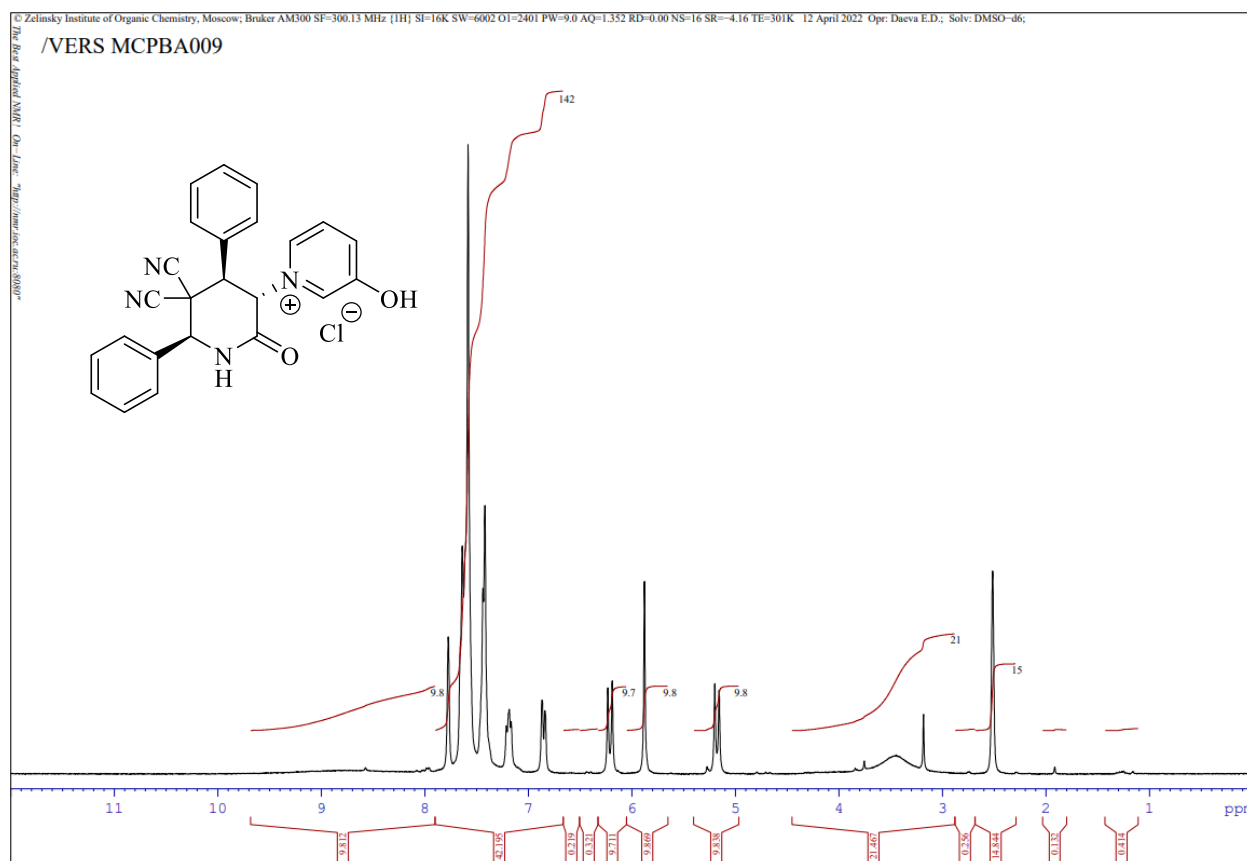
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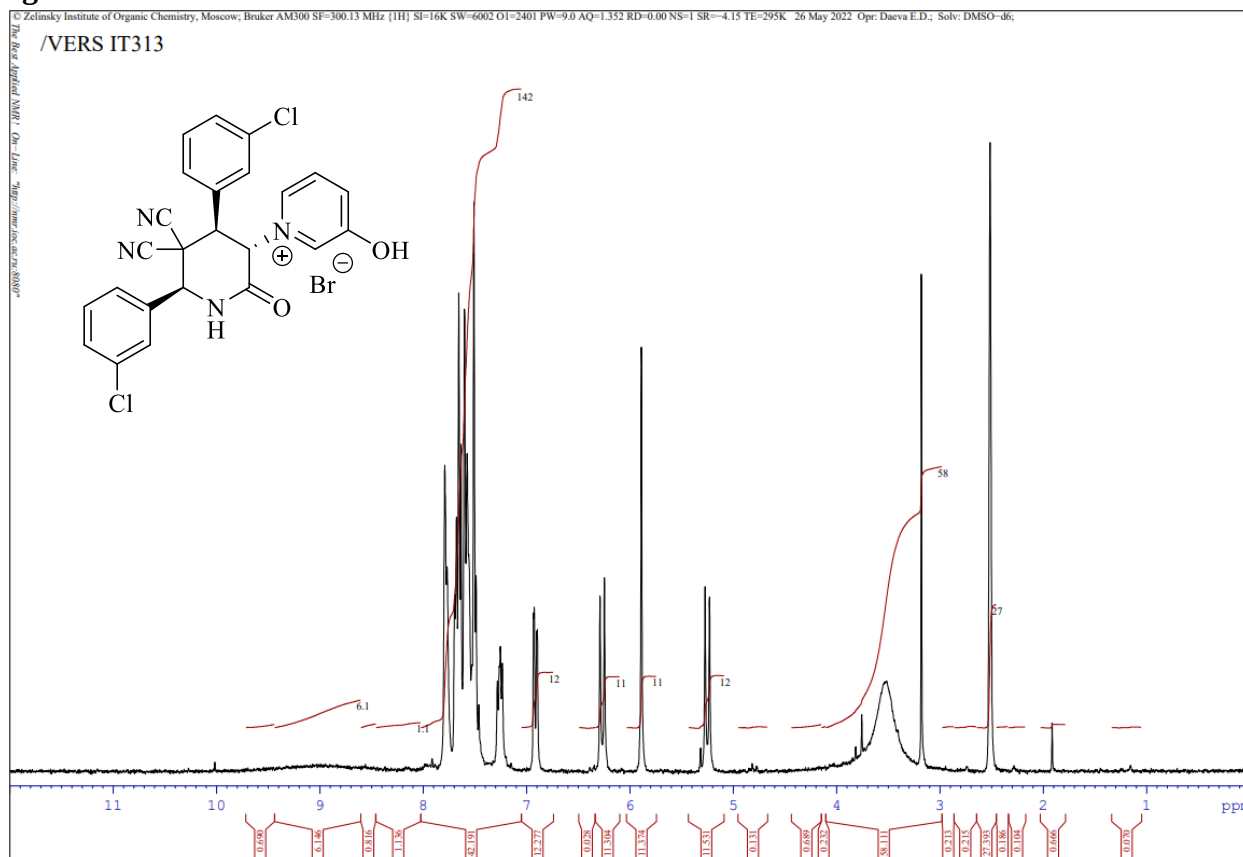
4e



4f



4g



4h

