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‘On-solvent’ new domino reaction of salicylaldehyde, malononitrile and 4-hydroxy-6-methylpyridin-2(1*H*)-one: fast and efficient approach to medicinally relevant 4-pyridinyl-2-amino-4*H*-chromene scaffold

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All melting points were measured with a Gallenkamp melting point apparatus and are uncorrected. ^{1}H, ^{13}C and ^{15}N NMR spectra were recorded on a 400 MHz (400.1, 100.6 and 40.6 MHz, respectively) and 300 MHz (300.1, 75.5 and 30.4 MHz, respectively) spectrometers in DMSO-d_6 solutions containing 0.05% Me_4Si as the internal standard. Chemical shift values are given in δ scale relative to Me_4Si. Determinations of structures and stereochemistry of obtained compounds and assignments of ^{1}H, ^{13}C and ^{15}N signals were made with the aid of 2D COSY, NOESY, HSQC, HMBC, long-range HMBC, and ^{15}N-HMBC. All ^{15}N NMR spectra were acquired on natural abundance os ^{15}N-isotope using 2D pulse sequences in inverse mode. IR spectra were registered with a Bruker ALPHA-T FT-IR spectrometer in KBr pellets. Mass spectra (EI = 70 eV) were obtained directly with a Finningan MAT INCOS 50 spectrometer. HRMS (ESI) were measured on a Bruker micrOTOF II instrument; external or internal calibration was done with Electrospray Calibrant Solution (Fluka). All reagents were obtained from commercial sources and used without further purification.

General procedures

Solvent-free grinding procedure

A mixture of salicylaldehyde **1** (3 mmol), malononitrile (3 mmol, 0.198 g), 4-hydroxy-6-methylpyridin-2(1*H*)-one (3 mmol, 0.375 g) and sodium acetate (0.3 mmol, 0.025 g) was placed in a mortar and mixed thoroughly with a pestle followed by grinding for 15 min. Resulting mixture was air dried to cause crystallization of the product. The crude solid was then filtered, rinsed with water (2×2 ml) and air dried to analyze by ^{1}H-NMR spectroscopy.

‘On-solvent’ procedure

A solution of salicylaldehyde **1** (3 mmol), malononitrile (3 mmol, 0.198 g), 4-hydroxy-6-methylpyridin-2(1*H*)-one (3 mmol, 0.375 g) and sodium acetate (0.3 mmol, 0.025 g) in small amount of ethanol (3 ml) was refluxed for 5 min. The reaction mixture was kept at -10 °C for 1 h, the solid phase was filtered off, rinsed with water (2×2 ml) and air dried to isolate pure 2-amino-4*H*-chromenes **2**. In some cases, additional recrystallization from ethanol was needed.

2-Amino-4-(4-hydroxy-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)-4*H*-chromene-3-carbonitrile (**2a**)

White solid; 0.876 g (99%); mp 214-216 °C (decomp.); ν_{max} (KBr) = 3475, 3295, 3172, 2178,1640, 1575, 1475, 1267, 1046, 749 cm^{-1}; HRMS (ESI): 296.1030 $[M+H]^+$, calcd for $C_{16}H_{14}N_3O_3$: 296.1027; MS (m/z, relative intensity %): 295 $[M^+]$ (1), 171 (26), 170 (100), 143 (66), 125 (16), 115 (31), 114 (27), 88 (17), 84 (11), 62 (10), 18 (16); δ_H (300 MHz, DMSO-d_6) 2.06 (s, 3H, CH_3), 5.09 (s, 1H, CH), 5.62 (s, 1H, CH), 6.51 (s, 2H, NH_2), 6.87-7.16 (m, 4H, Ar), 10.21 (br s, 1H, OH), 10.94 (br s, 1H, NH); δ_c (75 MHz, DMSO-d_6) 18.6, 30.6, 53.7, 97.0, 98.1, 117.0, 119.6, 120.1, 123.8, 127.1, 127.8, 143.8, 149.5, 161.0, 162.9, 163.6.

2-Amino-4-(4-hydroxy-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)-8-methoxy-4*H*-chromene-3-carbonitrile (2b)

White solid; 0.878 g (90%); mp 239-241 °C; ν_{max} (KBr) = 3468, 3328, 2832, 2176, 1612, 1576, 1268, 1088, 836, 740 cm^{-1}; HRMS (ESI): 326.1136 $[M+H]^+$, calcd for $C_{17}H_{16}N_3O_4$: 326.1135; MS (m/z, relative intensity %): 325 $[M^+]$ (1), 200 (52), 129 (30), 125 (167), 102 (62), 97 (25), 84 (100), 76 (34), 75 (35), 42 (66); δ_H (300 MHz, DMSO-d_6) 2.07 (s, 3H, CH_3), 3.80 (s, 3H, OCH_3), 5.09 (s, 1H, CH), 5.61 (s, 1H, CH), 6.49-6.53 (s, 3H, Ar + NH_2), 6.82-6.93 (m, 2H, Ar), 10.18 (br s, 1H, OH), 10.94 (br s, 1H, NH); δ_c (75 MHz, DMSO-d_6) 18.6, 29.1, 55.5, 55.7, 98.2, 106.6, 110.4, 119.2, 121.3, 123.4, 124.4, 143.8, 145.3, 146.5, 161.0, 163.0, 163.8.

2-Amino-8-ethoxy-4-(4-hydroxy-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)-4*H*-chromene-3-carbonitrile (2c)

White solid; 0.926 g (91%); mp 230-232 °C; ν_{max} (KBr) = 3397, 3326, 3081, 2180, 1610, 1572, 1411, 1280, 1216, 833 cm^{-1}; HRMS (ESI): 340.1295 $[M+H]^+$, calcd for $C_{18}H_{18}N_3O_4$: 340.1292; MS (m/z, relative intensity %): 339$[M^+]$ (1), 310 (3), 294 (1), 427 (3), 236 (4), 186 (13), 158 (12), 125 (31), 84 (59), 75 (28), 29 (100); δ_H (300 MHz, DMSO-d_6) 1.36 (t, *J* = 6.9 *Hz*, 3H, CH_3), 2.08 (s, 3H, CH_3), 4.07 (q, *J* = 6.9 *Hz*, 2H, OCH_2), 5.08 (s, 1H, CH), 5.62 (s, 1H, CH), 6.46-6.52 (s, 3H, Ar + NH_2), 6.80-6.90 (m, 2H, Ar), 10.21 (br s, 1H, OH), 11.00 (br s, 1H, NH); δ_c (75 MHz, DMSO-d_6) 14.7, 18.3, 29.0, 53.8, 64.0, 98.3, 106.6, 111.5, 119.2, 121.3, 123.3, 124.5, 144.3, 145.3, 145.6, 160.9, 162.9, 163.8.

2-Amino-7-diethylamino-4-(4-hydroxy-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)-4*H*-chromene-3-carbonitrile (2d)

White solid; 0.900 g (82%); mp > 300 °C; ν_{max} (KBr) = 3464, 3388, 3108, 2976, 2892, 2200, 1636,1560, 1252, 796 cm^{-1}; HRMS (ESI): 367.1768 $[M+H]^+$, calcd for $C_{20}H_{23}N_4O_3$: 367.1765; MS (m/z, relative intensity %): 366 $[M^+]$ (1), 125 (36), 97 (20), 96 (16), 84 (100), 69 (16), 55

(11), 54 (5), 42 (16), 29 (13), 27 (6); δ_H (300 MHz, DMSO-d_6) 1.04 (t, *J* = 9.6 *Hz*, 6H, CH_3), 2.03 (s, 3H, CH_3), 3.31 (q, *J* = 9.6 *Hz*, 4H, NCH_2), 5.13 (s, 1H, CH), 5.49 (s, 1H, CH), 6.12 (s, 2H, NH_2), 6.26 (d, *J* = 7.6 *Hz*, 1H, Ar), 6.46 (s, 1H, Ar), 6.65 (d, *J* = 7.6 *Hz* , 1H, Ar),10.16 (br s, 1H, OH), 11.39 (br s, 1H, NH); δ_c (75 MHz, DMSO-d_6) 12.4(2C), 18.2, 27.4, 47.3(2C), 70.0, 90.1, 97.6, 99.6, 107.4, 110.2, 111.9, 128.6, 146.9, 152.3, 156.8, 158.9, 159.5, 164.7.

2-Amino-4-(4-hydroxy-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)-6-methoxy-4*H*-chromene-3-carbonitrile (2e)

White solid; 0.956 g (98%); mp 210-212 °C; ν_{max} (KBr) = 3408, 3300, 3120, 2172, 1588, 1412, 1264, 1036, 776, 636 cm^{-1}; HRMS (ESI): 326.1137 $[M+H]^+$, calcd for $C_{17}H_{16}N_3O_4$: 326.1135; MS (m/z, relative intensity %): 325 $[M^+]$ (1), 200 (100), 158 (41), 125 (80), 102 (62), 84 (95), 76 (45), 42 (52), 31 (76), 27 (38); δ_H (300 MHz, DMSO-d_6) 2.03 (s, 3H, CH_3), 3.59 (s, 3H, OCH_3), 5.02 (s, 1H, CH), 5.58 (s, 1H, CH), 6.39 (s, 3H, Ar+NH_2), 6.65-6.81 (m, 2H, Ar), 10.15 (br s, 1H, OH), 10.91 (br s, 1H, NH); δ_c (75 MHz, DMSO-d_6) 18.2, 29.3,55.2, 56.1, 98.1, 110.9, 112.2, 122.4, 115.8, 121.3, 124.6, 143.6, 143.8, 155.3, 161.3, 163.7, 163.9.

2-Amino-6-chloro-4-(4-hydroxy-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)-4*H*-chromene-3-carbonitrile (2f)

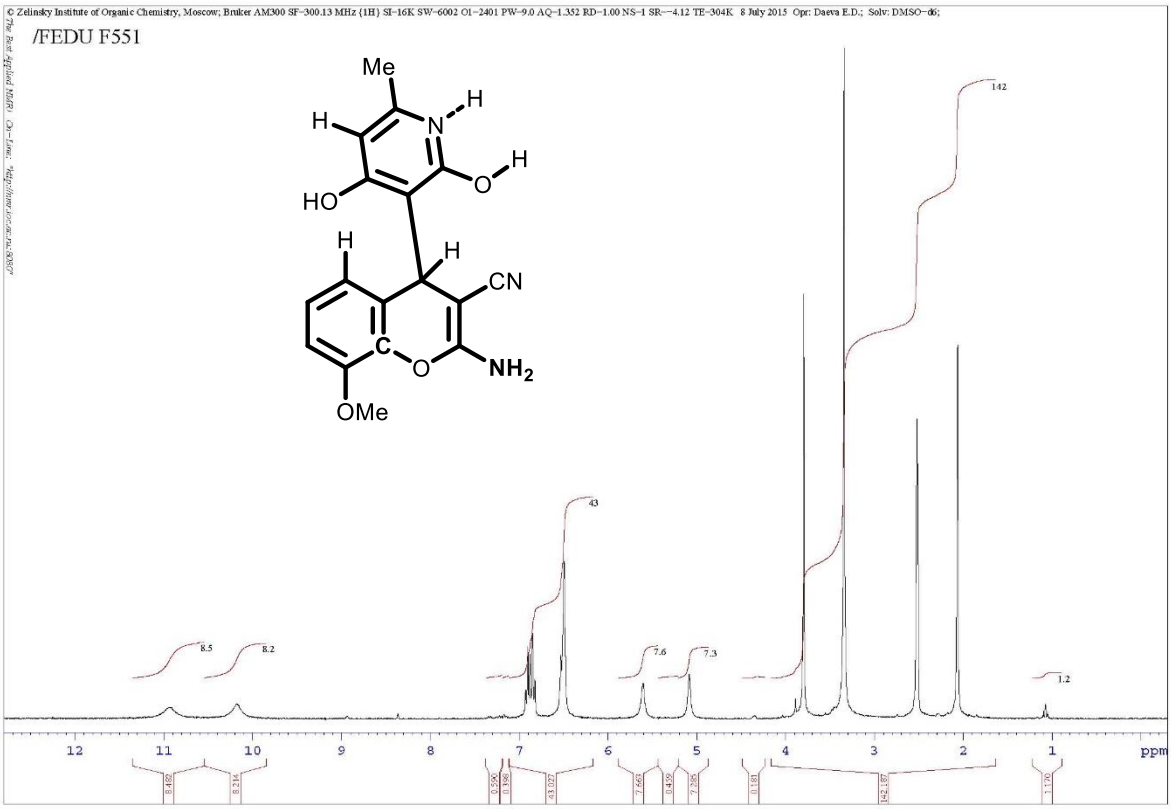
White solid; 0.879 g (89%); mp 270-272 °C (decomp.); ν_{max} (KBr) = 3340, 3312, 3144, 2648, 2184, 1160, 1604, 1264, 820, 776 cm^{-1}; HRMS (ESI): 330.0643 $[M+H]^+$, calcd for $C_{16}H_{13}ClN_3O_3$: 330.0640; MS (m/z, relative intensity %): 331 $[M^+]$ (1), 329 $[M^+]$ (1), 285 (1), 204 (52), 177 (67), 149 (12), 125 (82), 84 (100), 45 (33), 42 (64); δ_H (300 MHz, DMSO-d_6) 2.08 (s, 3H, CH_3), 5.02 (s, 1H, CH), 5.59 (s, 1H, CH), 6.57 (s, 2H, NH_2), 6.83 (s, 1H, Ar), 6.88 (d, *J* = 8.6 *Hz*, 1H, Ar), 7.14 (d, *J* = 8.6 *Hz*, 1H, Ar), 10.29 (br s, 1H, OH), 10.95 (br s, 1H, NH); δ_c (75 MHz, DMSO-d_6) 18.3, 29.0, 54.4, 56.0, 110.4, 117.0, 120.8, 126.9, 127.0, 127.2, 132.9, 144.2, 148.3, 162.5, 163.5, 163.6.

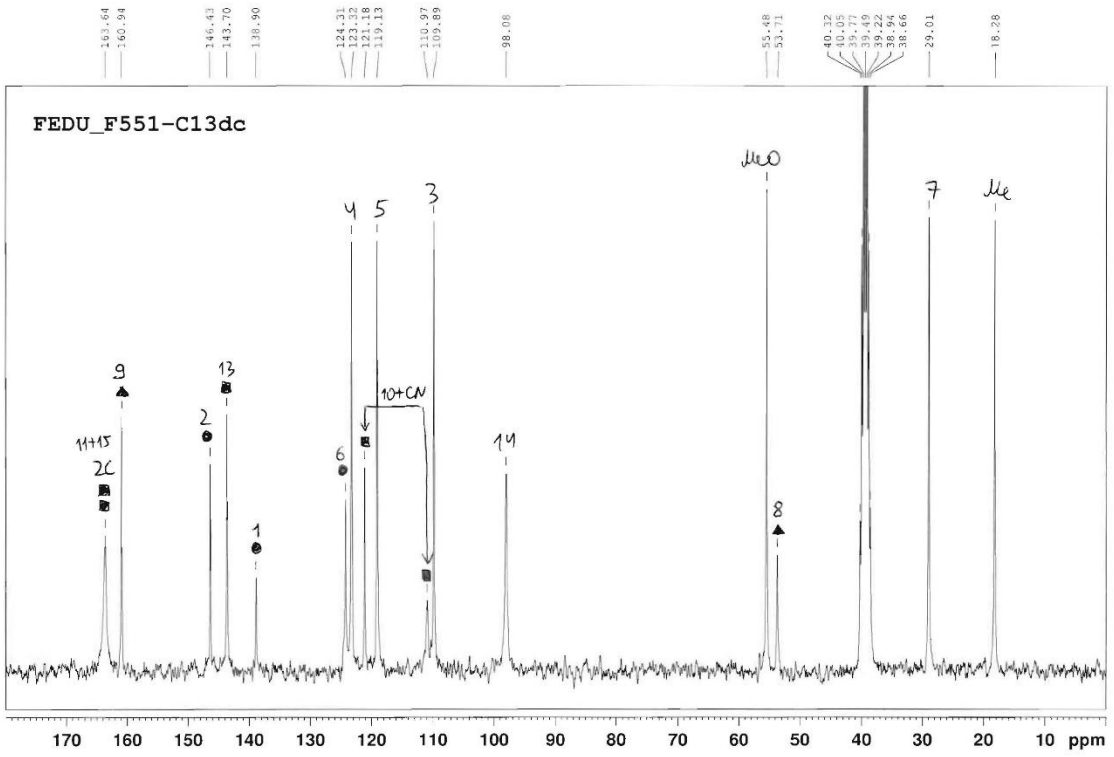
2-Amino-6-bromo-4-(4-hydroxy-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)-4*H*-chromene-3-carbonitrile (2g)

White solid; 1.112 g (99%); mp: 250-252 °C (decomp.); ν_{max} (KBr) = 3471, 3398, 3308, 3156, 2176, 1639, 1569, 1403, 1285, 821 cm^{-1}; HRMS (ESI): 374.0139 $[M+H]^+$, calcd for $C_{16}H_{13}BrN_3O_3$: 374.0135; MS (m/z, relative intensity %): 375 $[M^+]$ (1), 373 $[M^+]$ (1), 248 (1), 221 (1), 171 (1), 141 (1), 114 (10), 84 (100), 84 (26), 42 (100); δ_H (300 MHz, DMSO-d_6) 2.08 (s, 3H, CH_3), 5.08 (s, 1H, CH), 5.66 (s, 1H, CH), 6.61 (s, 2H, NH_2), 6.88 (d, *J* = 8.7 *Hz*, 1H, Ar), 7.02 (s, 1H, Ar), 7.30 (d, *J* = 8.7 *Hz*, 1H, Ar), 10.36 (br s, 1H, OH), 11.02 (br s, 1H, NH); δ_c (75

MHz, DMSO-d_6) 18.4, 28.9, 56.0, 96.7, 105.4, 115.1, 117.5, 120.8, 126.4, 129.8, 129.9, 144.3, 154.5, 160.8, 162.5, 163.5.

NMR spectra for 2-amino-4-(4-hydroxy-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)-8-methoxy-4*H*-chromene-3-carbonitrile 2b (F551)

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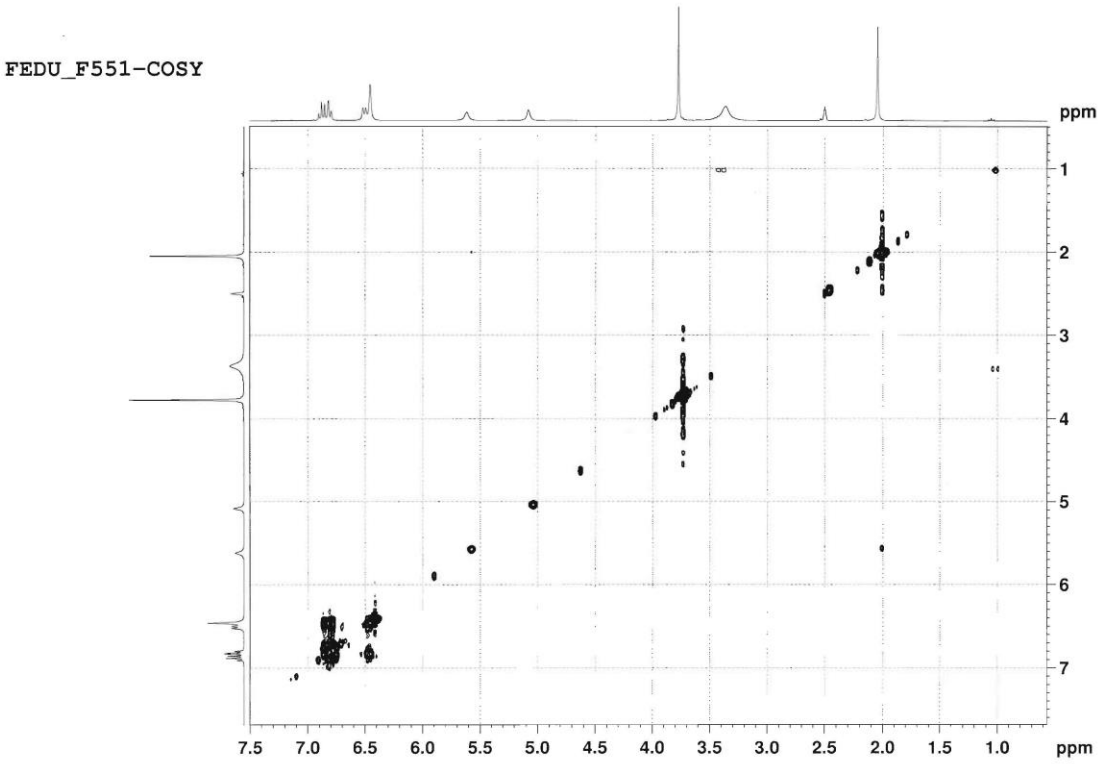
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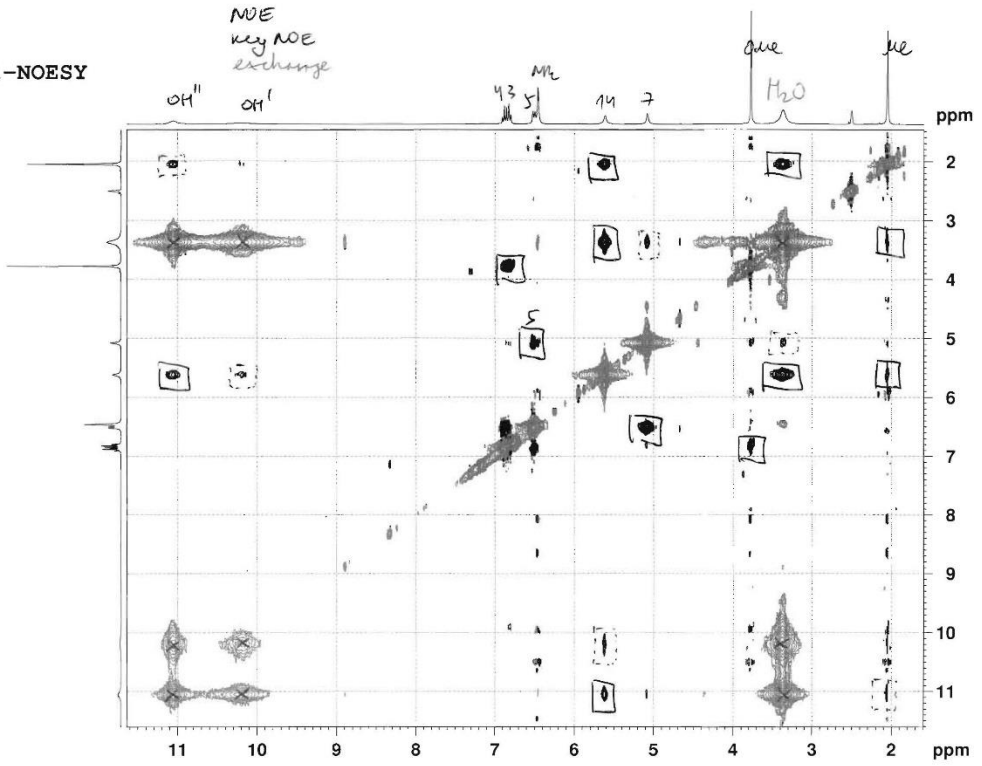

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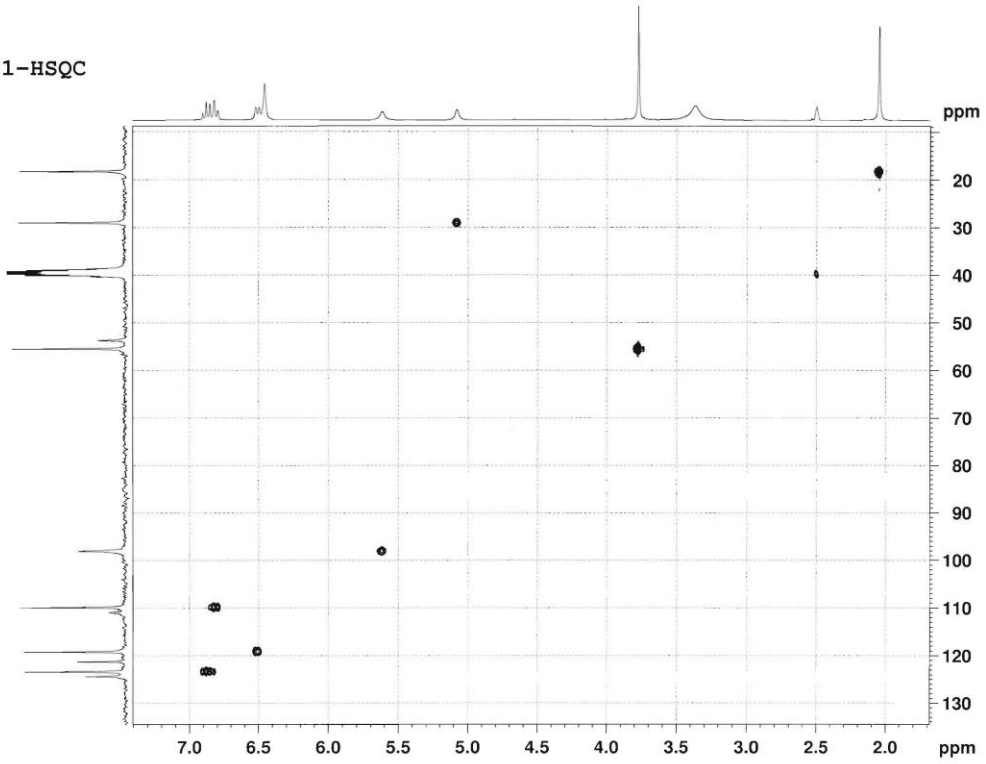

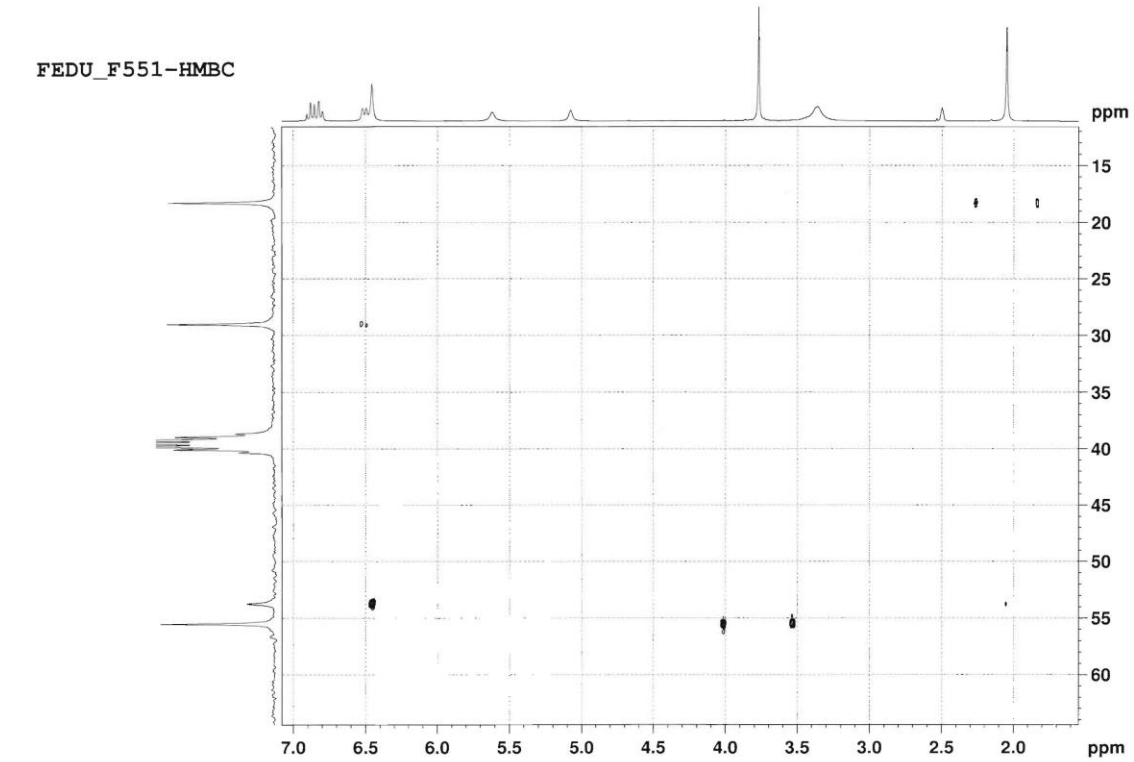
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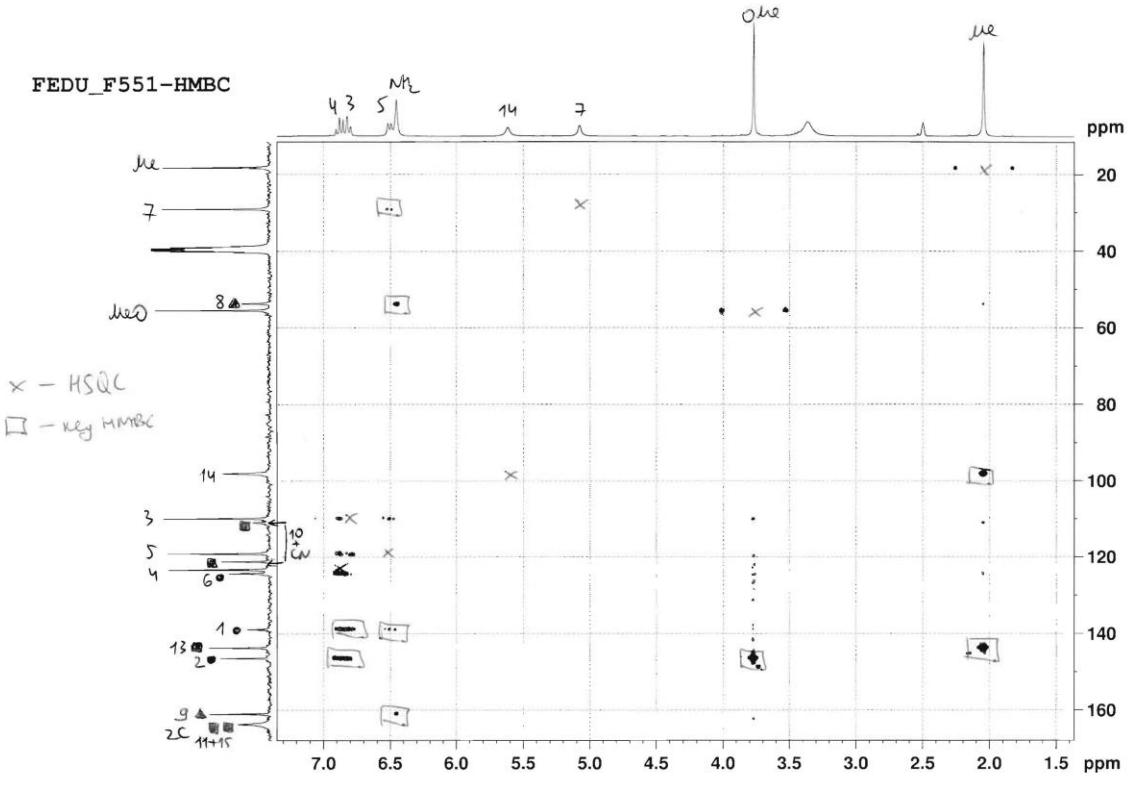
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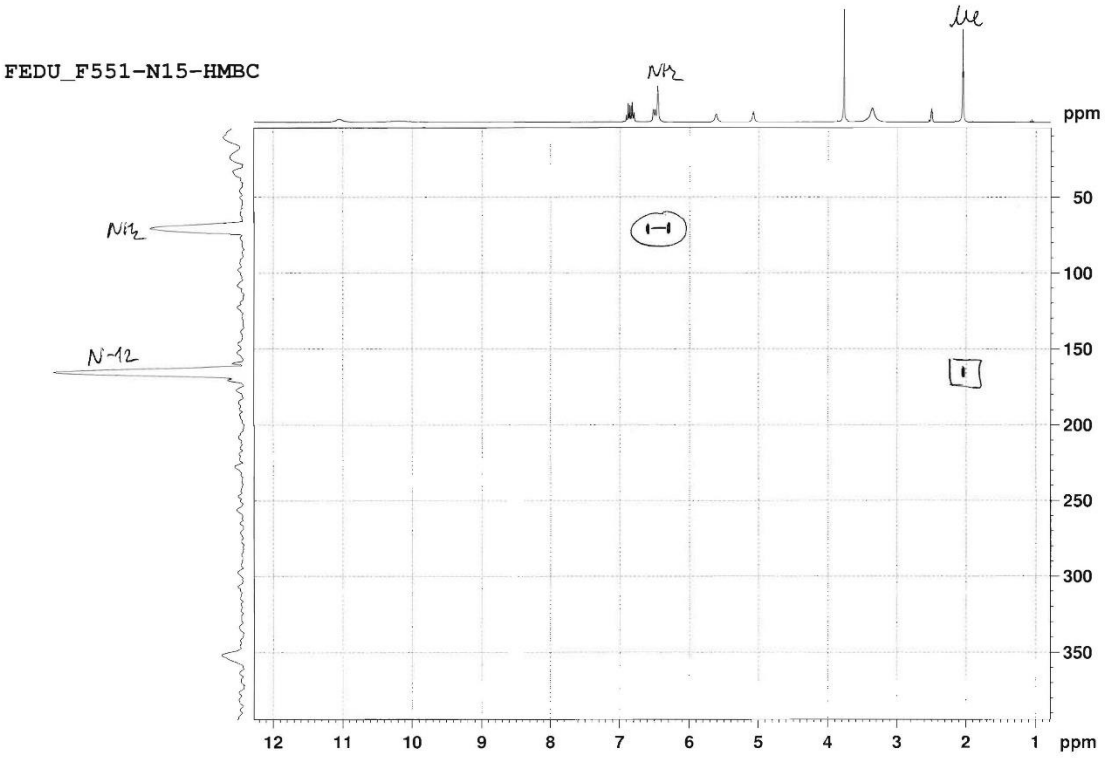
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