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Regioselective synthesis of 2-(1*H*-benzimidazol-1-yl)-5-nitro- and 2-(5-nitro-1*H*-benzimidazol-1-yl)anilines

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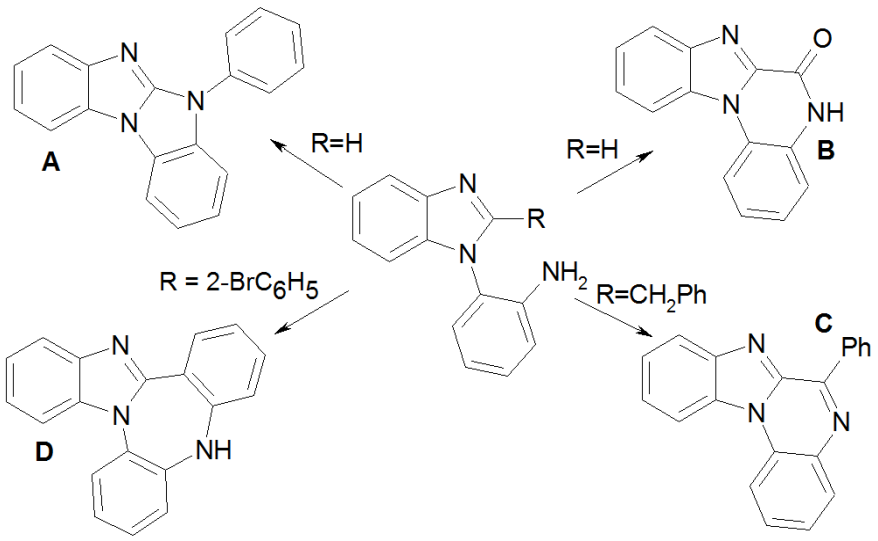


Scheme S1

1. Experimental Procedures and Analytical Data

The melting points were determined with a Poly Therm A instrument with a heating rate of 3 °C and were not corrected. NMR spectra were recorded at the N.D. Zelinsky Institute of Organic Chemistry of the Russian Academy of Sciences. ^{1}H NMR spectra were recorded on a Bruker DRX500 instrument at a frequency of 500 MHz ^{13}C NMR spectra were recorded at a frequency of 125 MHz using DMSO-d_6 as the solvent and internal standard. High-resolution mass spectra were recorded on a Bruker micrOTOF II instrument (Bruker Daltonics) with the electrospray ionization method (ESI) and MeCN as the solvent.

Method for the synthesis of *N*-(2-chloro-5-nitrophenyl)propanamide (4a) and *N*-(4-chloro-3-nitrophenyl)propanamide (4b). A solution of nitroaniline **3a** or **3b** (5 g, 29 mmol) in DMF (20 ml) and propionic anhydride (5.6 g, 43 mmol) was heated at 90 °C for 1 h. After cooling, the reaction mixture was poured into water. The precipitate was filtered out and recrystallized from Pr^{i}OH.

***N*-(2-Chloro-5-nitrophenyl)propanamide** (**4a**). Yield 6.43 g (97%), mp 120-122 °C. ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 1.11 t (3H, CH_3, J = 7.5 Hz,), 2.37 q (2H, CH_2, J = 7.5 Hz), 7.78 d (1H, H^3, J = 8.8 Hz), 7.98 dd (1H, H^4, J_1 = 8.9 Hz, J_2 = 2.7 Hz), 8.75 d (1H, H^6, J = 2.7 Hz), 9.75 (s, 1H, NH). ESI-HRMS: *m/z* calcd for $C_9H_{10}ClN_2O_3$ $[M+H]^+$ 229.6324, found 229.6327

***N*-(4-Chloro-3-nitrophenyl)propanamide** (**4b**). Yield 6.5 g (98%), mp 97-100 °C. ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 1.09 t (3H, CH_3, J = 7.5 Hz), 2.37 q (2H, CH_2, J = 7.5 Hz), 7.68 d (1H, H^5, J = 8.9 Hz), 7.77 dd (1H, H^6, J_1 = 8.9 Hz, J_2 = 2.5 Hz), 8.42 d (1H, H^2, J = 2.5 Hz), 10.40 s (1H, NH). ESI-HRMS: *m/z* calcd for $C_9H_{10}ClN_2O_3$ $[M+H]^+$ 229.6324, found 229.6329

Method for the synthesis of *N*-[2-(1*H*-benzimidazol-1-yl)-5-nitrophenyl]propanamide (5a) and *N*-[4-(1*H*-benzimidazol-1-yl)-3-nitrophenyl]propanamide (5b). Amide **4a** or **4b** (6 g, 26.2 mmol), K_2CO_3 (5.43 g, 39.4 mmol) and benzimidazole (3.25 g, 27.5 mmol) was heated for 8.5 h in DMF (70 ml) at 120 °C. After cooling, the reaction mixture was poured into water. The precipitate was filtered off and recrystallized from Pr^{i}OH.

***N*-[2-(1*H*-Benzimidazol-1-yl)-5-nitrophenyl]propanamide** (**5a**). Yield 4.63 g (57%), mp 222-226 °C. ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 0.88 t (3H, CH_3, J = 7.5 Hz), 2.09 q (2H, CH_2, J = 7.5 Hz), 7.13 m (1H, H^7), 7.30 m (2H, $H^{4',5'}$), 7.80 dd (2$H^{3,6'}$, J_1 = 9.0 Hz, J_2 = 2.4 Hz), 8.18 dd (1H, H^6, J_1 = 8.8, J_2 = 2.5 Hz), 8.46 (s, 1H, $H^{2'}$), 8.76 d (1H, H^2, J = 2.5 Hz), 9.79 s (1H, NH). ^{13}C NMR (DMSO-d_6, 125 MHz) δ: 9.98, 29.47, 111.41, 120.59, 120.76, 121.28, 123.24, 124.17, 129.41, 133.64, 134.21, 134.89, 144.22, 144.47, 147.91, 173.29. ESI-HRMS: *m/z* calcd for $C_{16}H_{15}N_4O_3$ $[M+H]^+$ 311.3074, found 311.3071

***N*-[4-(1*H*-Benzimidazol-1-yl)-3-nitrophenyl]propanamide (5b)**. Yield 5.12 g (63%), mp 187-191 °C. ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 1.13 t (3H, CH_3, J = 7.5 Hz), 2.43 q (2H, CH_2, J = 7.5 Hz), 7.20 m (1H, $H^{5'}$), 7.25-7.32 m (2H, $H^{4',6'}$), 7.77 dd (2H, $H^{5,7'}$, J_1 = 8.9 Hz, J_2 = 1.4 Hz), 8.03 dd (1H, H^6, J_1 = 8.7 Hz, J_2 = 2.4 Hz), 8.43 s (1H, $H^{2'}$), 8.66 d (1H, H^2, J = 2.4 Hz), 10.60 (s, 1H, NH). ^{13}C NMR (DMSO-d_6, 125 MHz) δ: 9.96, 30.22, 110.48, 115.86, 120.51, 123.19, 123.91, 124.54, 124.79, 131.52, 135.27, 141.46, 143.69, 144.72, 145.77, 173.76. ESI-HRMS: *m/z* calcd for $C_{16}H_{15}N_4O_3$ $[M+H]^+$ 311.3074, found 311.3076

Method for the synthesis of 2-(1*H*-benzimidazol-1-yl)-5-nitroaniline (**1a**) **and 4-(1*H*-benzimidazol-1-yl)-3-nitroaniline** (**1b**). Amide **5a** or **5b** (4 g, 12.9 mmol) was heated for 1.5 h in 50% H_2SO_4 (50 ml) at 40 °C. The reaction mass was poured into ice and treated with NH_4OH to pH = 7-8. The precipitate was filtered of and recrystallized from $CHCl_3$.

2-(1*H*-Benzimidazol-1-yl)-5-nitroaniline (**1a**). Yield 3.02 g (92%), mp 231-236 °C. ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 5.76 s (2H, NH_2), 7.20 m (1H, $H^{6'}$), 7.29 m (2H, $H^{4',5'}$), 7.41 d (1H, H^3, J = 8.6 Hz), 7.48 dd (1H, H^4, J_1 = 8.7 Hz, J_2 = 2.5 Hz), 7.79 m (2H, $H^{6,7'}$), 8.34 d (1H, $H^{2'}$, J = 2.1 Hz). ^{13}C NMR (DMSO-d_6, 125 MHz) δ: 110.7, 110.9, 111.6, 120.5, 122.9, 123.9, 125.8, 129.9, 134.2, 144.1, 144.3, 146.3, 148.9. ESI-HRMS: *m/z* calcd for $C_{13}H_{11}N_4O_2$ $[M+H]^+$ 255.2441, found 255.2438

4-(1*H*-Benzimidazol-1-yl)-3-nitroaniline (**1b**). Yield 3.09 g (94%), mp 159-163 °C. ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 6.21 s (2H, NH_2), 7.02 dd (1H, H^6, J_1 = 8.6, J_2 = 2.6 Hz), 7.09-7.16 m (1H, $H^{6'}$), 7.26 m (2H, $H^{4',5'}$), 7.33-7.42 m (2H, $H^{2,5}$), 7.67-7.79 m (1H, $H^{7'}$), 8.30 d (1H, $H^{2'}$, J = 1.5 Hz). ^{13}C NMR (DMSO-d_6, 125 MHz) δ: 109.3, 110.5, 115.9, 118.9, 120.4, 122.8, 124.0, 131.7, 135.7, 143.6, 145.1, 146.9, 151.4. ESI-HRMS: *m/z* calcd for $C_{13}H_{11}N_4O_2$ $[M+H]^+$ 255.2441, found 255.2439

Method for the synthesis of 1-(2,4-dinitrophenyl)-1*H*-benzimidazole (7). 2,4-Dinitrochlorobenzene **6** (10 g, 49.4 mmol), K_2CO_3 (10.22 g, 74.0 mmol) and benzimidazole (5.83 g, 49.4 mmol) were heated for 1 h in DMF (100 ml) at 100 °C. After cooling, the reaction mixture was poured into water. The precipitate was filtered of and recrystallized from Pr^iOH. Yield 13.6 g (97%), mp 171-174 °C. ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 7.38 – 7.30 m (3H, $H^{5,6,7}$), 7.82 m (1H, H^4), 8.21 d (1H, $H^{6'}$, J = 8.7 Hz), 8.57 s (1H, H^2), 8.78 dd (1H, $H^{5'}$, J_1 = 8.7 Hz, J_2 = 2.6 Hz,), 9.05 d (1H, $H^{3'}$, J = 2.6 Hz). ^{13}C NMR (DMSO-d_6, 125 MHz) δ: 110.5, 120.9, 122.5, 123.9, 124.8, 130.0, 132.1, 134.2, 134.5, 143.9, 144.1, 145.2, 147.6. ESI-HRMS: *m/z* calcd for $C_{13}H_9N_4O_4$ $[M+H]^+$ 285.2270, found 285.2267

Method for the synthesis of 2-(1*H*-benzimidazol-1-yl)-*N*-hydroxy-5-nitroaniline (8).

A solution of $SnCl_2 \cdot H_2O$ (2.4 g, 10.5 mmol) in HCl (4% aq., 100 ml) was added to the solution of dinitro compound **7** (1 g, 3.5 mmol) in Pr^iOH (50 ml) at 50 °C. After 20 min, the reaction mixture was cooled and neutralized with NH_4OH to pH 7-8 and extracted with several portions of hot chloroform (Σ = 80 ml). After distilling about 70 ml of chloroform, compound **8** was obtained. Yield 0.83 g (88 %), mp 193-197 °C. ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 7.22-7.31 m (3H, $H^{5',6',7'}$), 7.56 d (1H, H^3, J = 8.5 Hz,), 7.73-7.79 m (2H, $H^{4,4'}$), 8.06 d (1H, H^6, J = 2.6 Hz), 8.36 s (1H, $H^{2'}$), 8.83 s (1H, NH), 8.97 s (1H, OH). ^{13}C NMR (DMSO-d_6, 125 MHz) δ: 108.7,

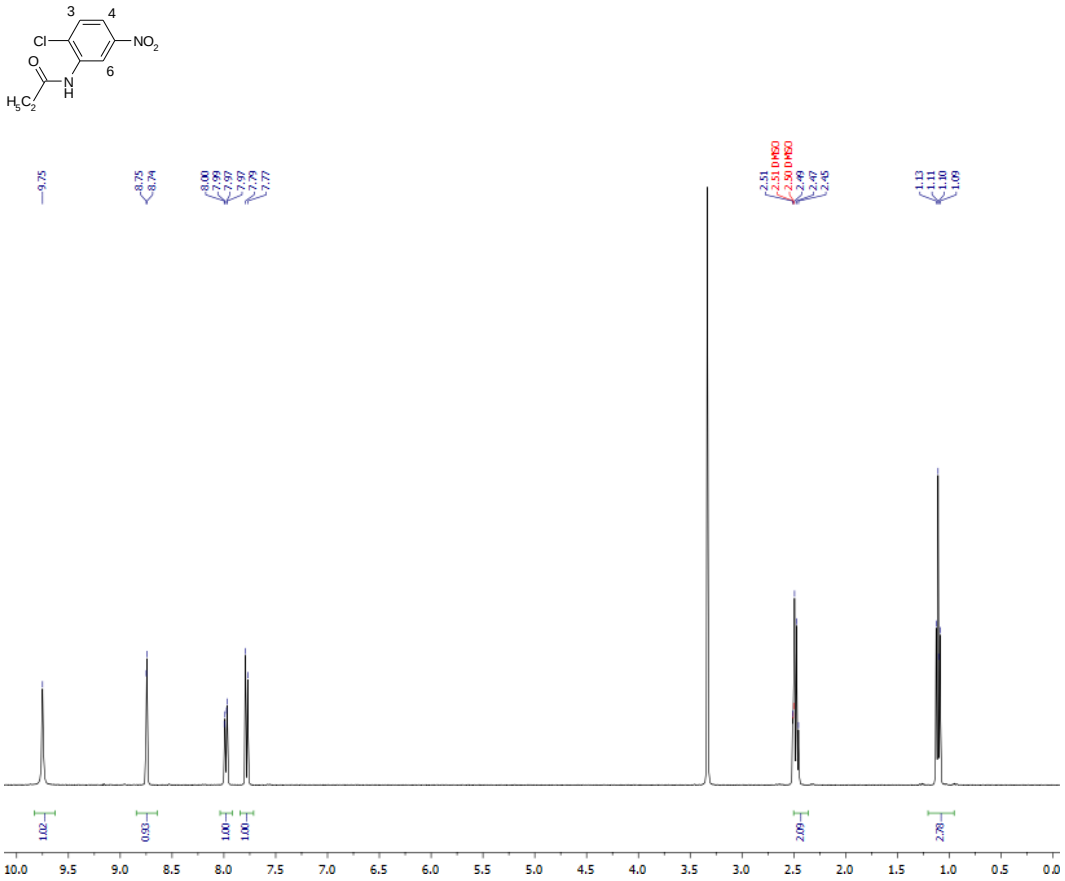
111.9, 114.4, 120.5, 123.0, 123.8, 126.3, 129.1, 134.1, 144.1, 144.2, 148.8, 148.9. ESI-HRMS: *m/z* calcd for $C_{13}H_{11}N_4O_3$ $[M+H]^+$ 271.2435, found 271.2431

Method for the synthesis of 4-(1*H*-benzimidazol-1-yl)benzene-1,3-diamine (9). Titanium trichloride **(**15% solution in 10% HCl, 7 g, 40 ml, 45.6 mmol) was added to a solution of dinitro compound **7** (1 g, 3.5 mmol) in 36% HCl (50 ml) at 50 °C. After 10 min, the mixture was cooled and neutralized with NH_4OH to pH 7-8 and extracted with several portions of hot chloroform (Σ = 80 ml). After distillation of chloroform, compound **9** was obtained. The product was purified by recrystallization in a mixture of hexane - Pr^iOH. Yield 0.74 g (94%), mp 115-118 °C. ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 3.51 s (2H, NH_2), 3.66 s (2H, NH_2), 6.09-6.19 m (2H, $H^{2,6}$), 6.91 d (1H, H^5, J = 8.6 Hz), 7.18-7.34 m (3H, $H^{4',5',6'}$), 7.84 d (1H, $H^{7'}$, J = 7.1 Hz), 7.92 (c, 1H, $H^{2'}$). ^{13}C NMR (DMSO-d_6, 125 MHz) δ: 101.9, 106.0, 111.0, 112.8, 120.6, 122.7, 123.6, 129.5, 134.8, 143.7, 144.0, 144.2, 148.6. ESI-HRMS: *m/z* calcd for $C_{13}H_{13}N_4$ $[M+H]^+$ 225.2612, found 225.2608

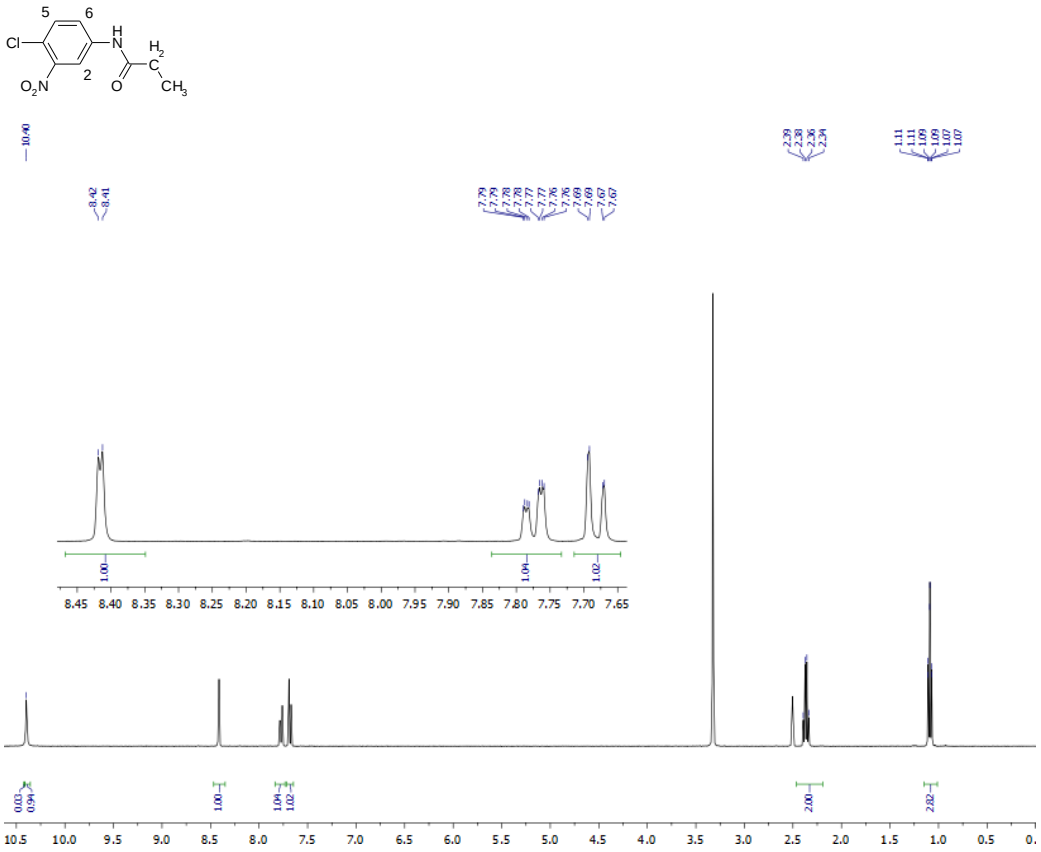
Method for the synthesis of 2-(1*H*-benzimidazol-1-yl)-5-nitroaniline (1a) in the reaction of *orto*-reduction. A solution of $TiCl_3$ (3.3 g, 21.4 mmol) in HCl was added to a solution of dinitro compound 7 (1 g, 3.5 mmol) in 36% HCl (50 ml) at 30 °C for 5 min, which was prepared by mixing 15% $TiCl_3$ solution in 10% HCl (18.5 ml) and 36% HCl (31.5 ml). The reaction mixture was cooled and neutralized with NH_4OH to pH 7-8 and extracted with several portions of hot chloroform (Σ = 80 ml). After distilling 70 ml of chloroform, compound **1a** was obtained. Yield 0.83g (93 %).

Method for the synthesis of 2-(5-nitro-1*H*-benzimidazol-1-yl)aniline (2). A solution of $TiCl_3$ (3.3 g, 21.4 mmol) in HCl was added to a solution of dinitro compound 7 (1 g, 3.5 mmol) in 36% HCl (50 ml) at 30 °C for 5 min, which was prepared by mixing 15% $TiCl_3$ solution in 10% HCl (18.5 ml) and 36% HCl (31.5 ml). Then 70% aqueous PrOH (100 ml) was introduced, and this was stirred at 80 °C for 4 h. After cooling, the mixture was neutralized with NH_4OH to pH 7-8 and extracted with several portions of hot chloroform (Σ = 80 ml). After distillation of chloroform, compound **2** was obtained. The product was purified by recrystallization in a mixture of $CHCl_3$ - Pr^iOH. Yield 0.76 g (86%), mp 203-205°C. ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 5.22 s (2H, NH_2), 6.71 t (1H, H^4, J = 8.8 Hz), 6.94 dd (1H, H^6, J_1 = 8.6, J_2 = 1.8 Hz) 7.17 dd (1H, H^3, J_1 = 8.4, J_2 = 2.0 Hz), 7.27 t (1H, H^5, J = 8.9 Hz), 7.32 d (1H, $H^{7'}$, J = 8.6 Hz), 8.17 dd (1H, $H^{6'}$, J_1 = 8.7 Hz, J_2 = 2.2 Hz), 8.61 s (1H, $H^{2'}$), 8.63 d (1H, $H^{4'}$, J = 2.2 Hz). ^{13}C NMR (DMSO-d_6, 125 MHz) δ: 112.3, 116.4, 116.7, 116.9, 119.3, 119.8, 128.7, 131.1, 139.3, 143.4, 143.7, 145.4, 149.3. ESI-HRMS: *m/z* calcd for $C_{13}H_{11}N_4O_2$ $[M+H]^+$ 255.2441, found 255.2437

2. NMR Spectral Data



^{1}H NMR spectrum of *N*-(2-chloro-5-nitrophenyl)propanamide (**4a**) (DMSO-d_6)



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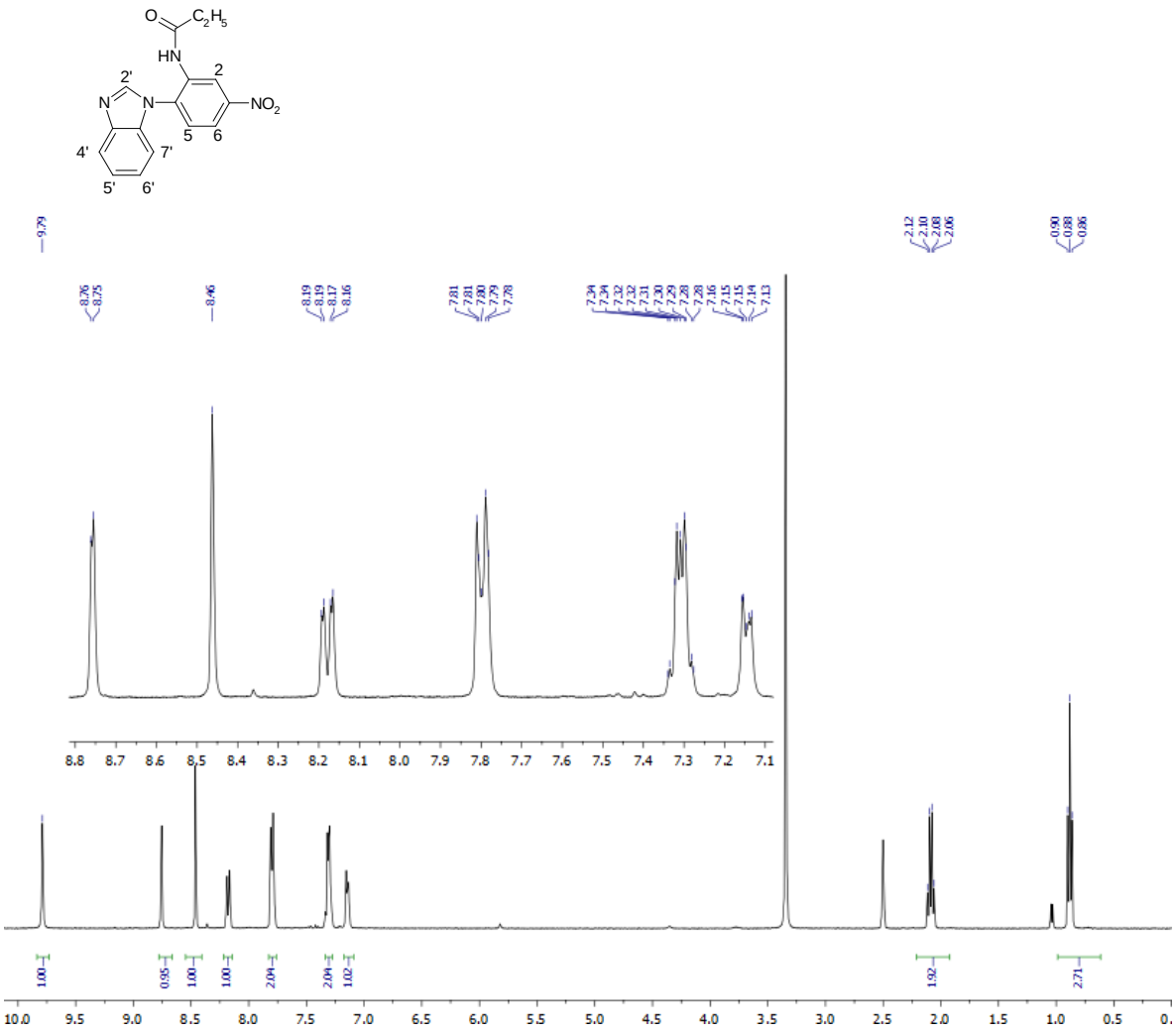
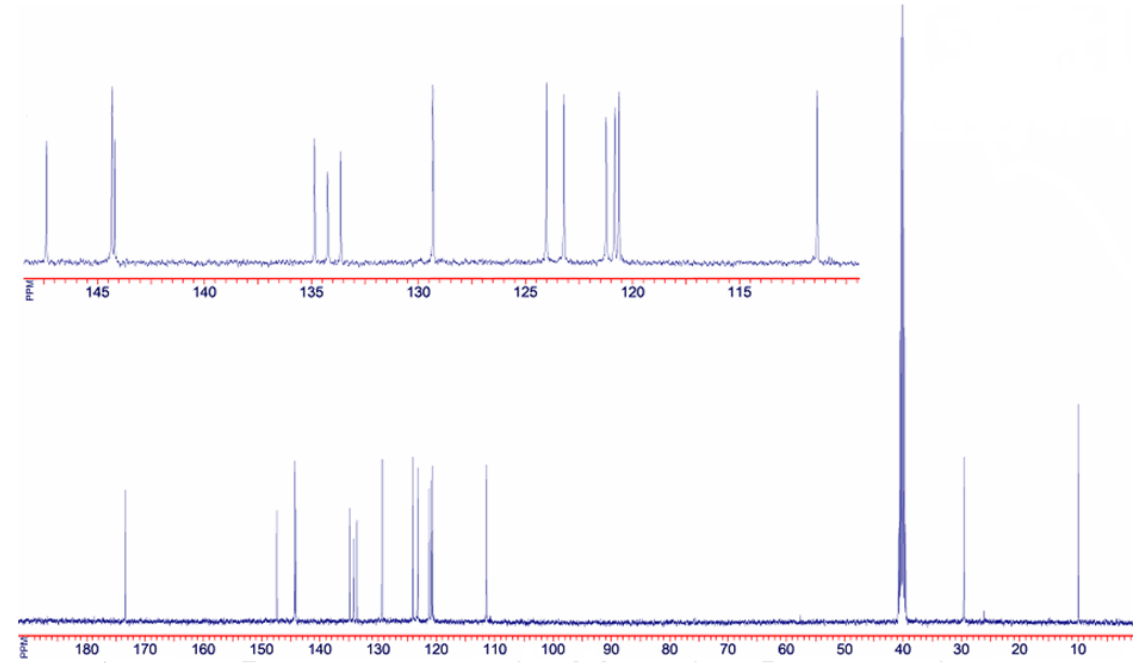


^{1}H NMR spectrum of *N*-[2-(1*H*-benzimidazol-1-yl)-5-nitrophenyl]propanamide (**5a**) (DMSO-d_6)



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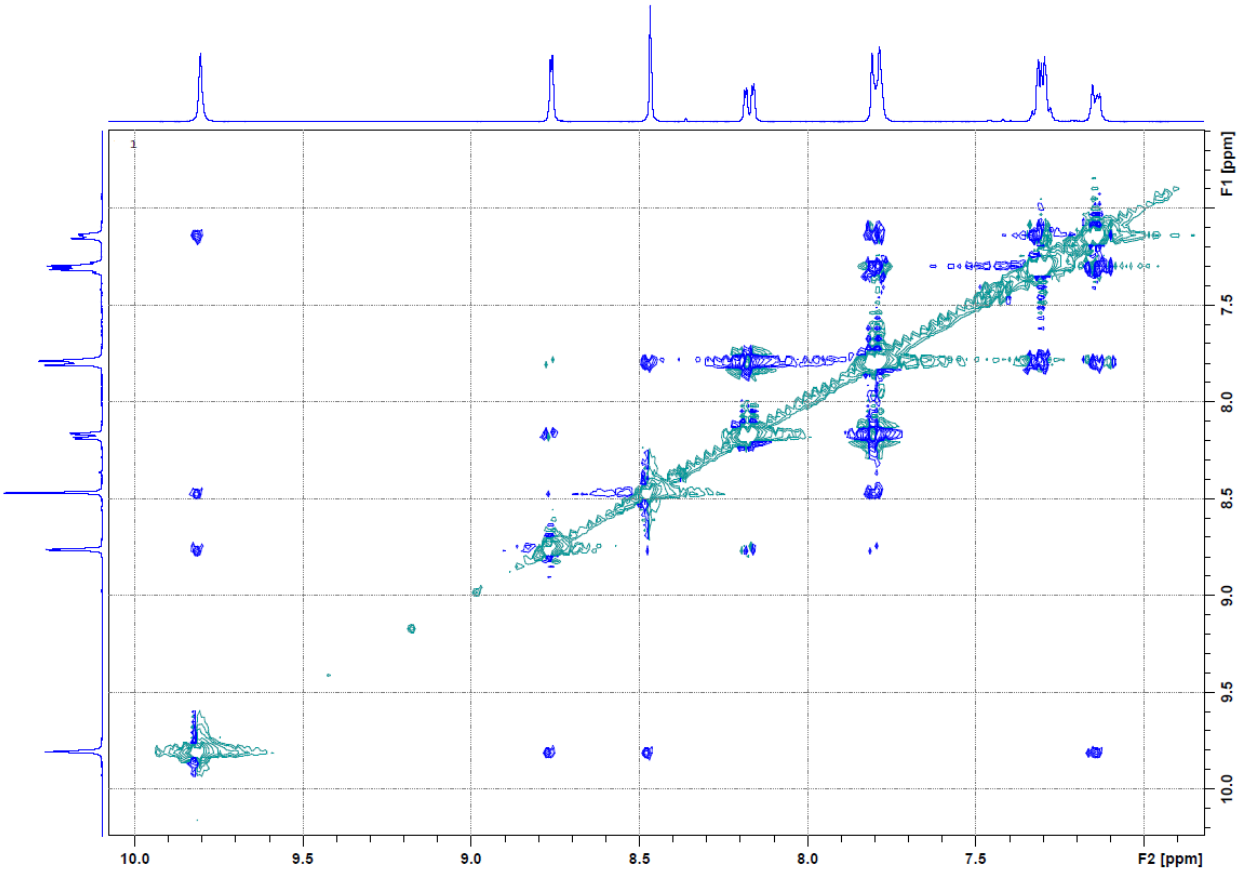
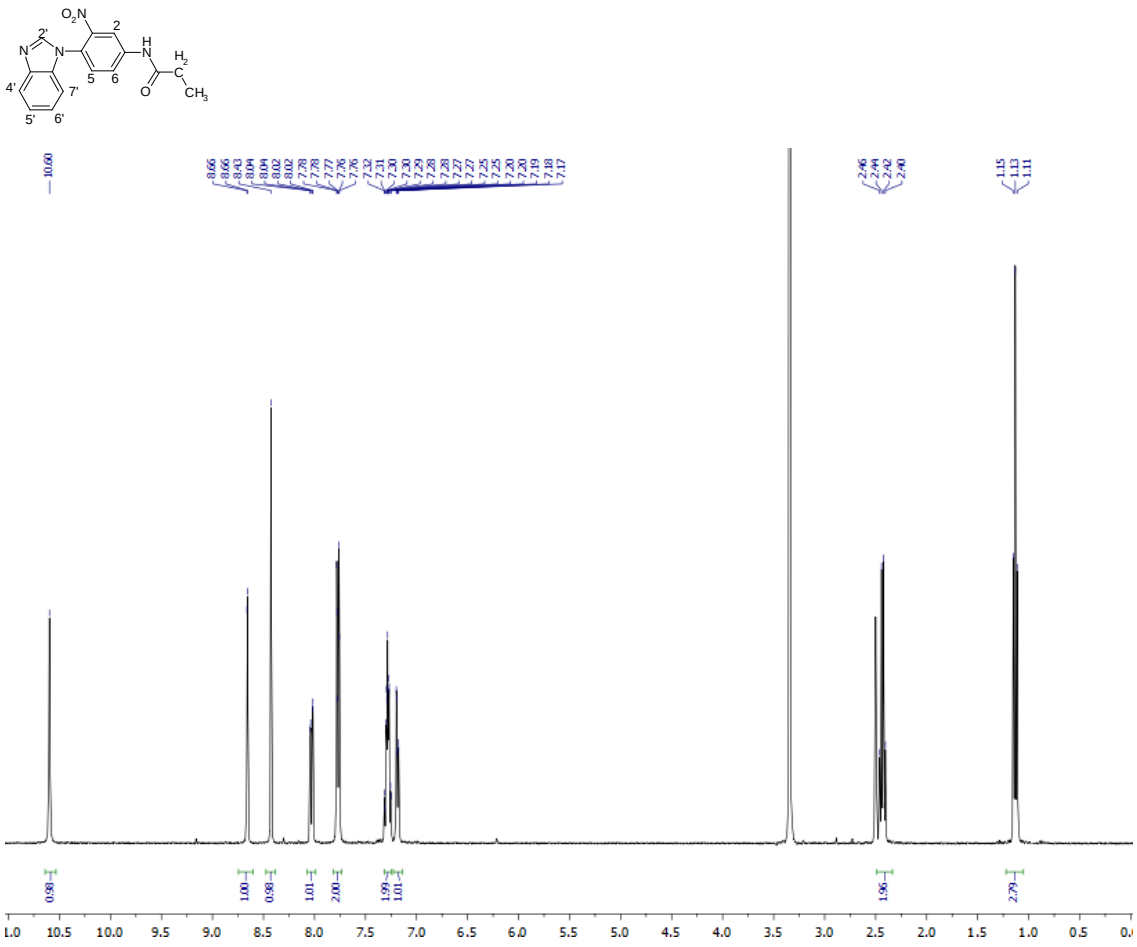
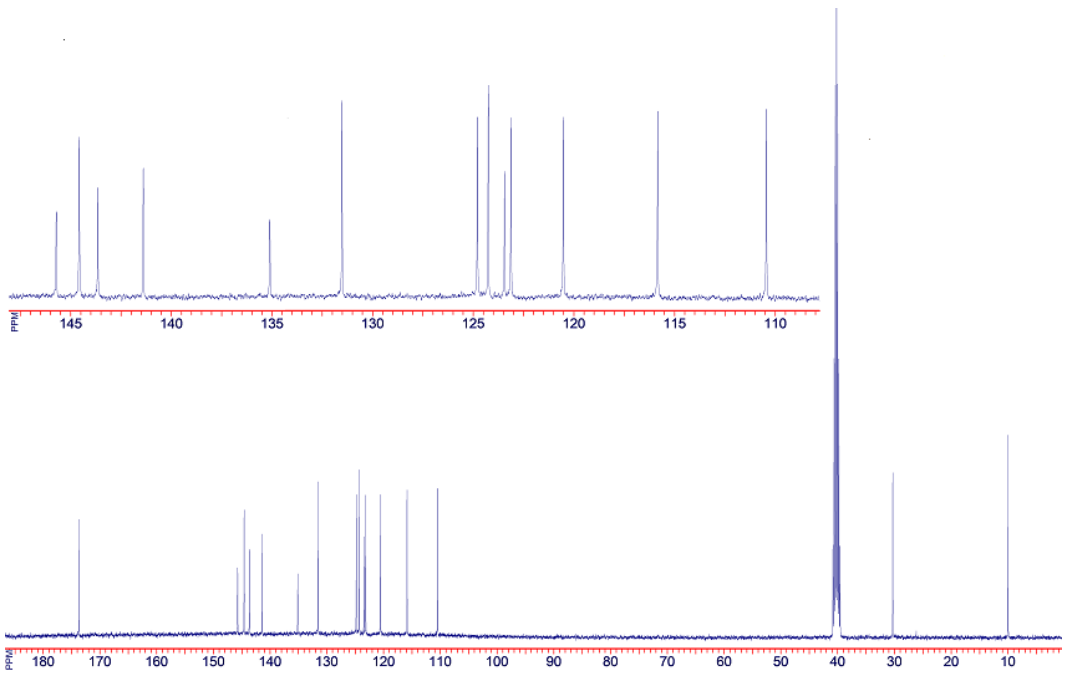


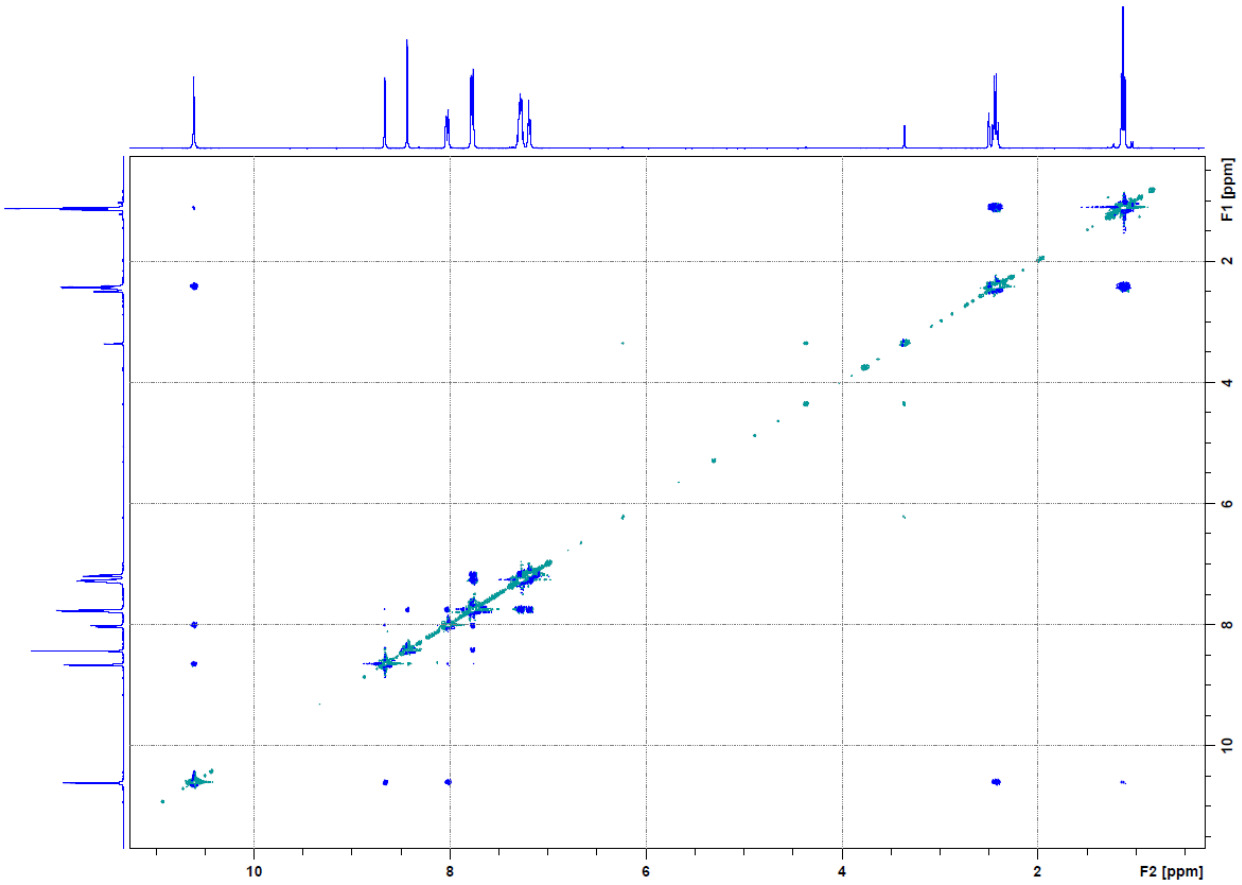
Fragment of ^{1}H-^{1}H NOESY spectrum of *N*-[2-(1*H*-benzimidazol-1-yl)-5-nitrophenyl]propanamide (**5a**) (DMSO-d_6)



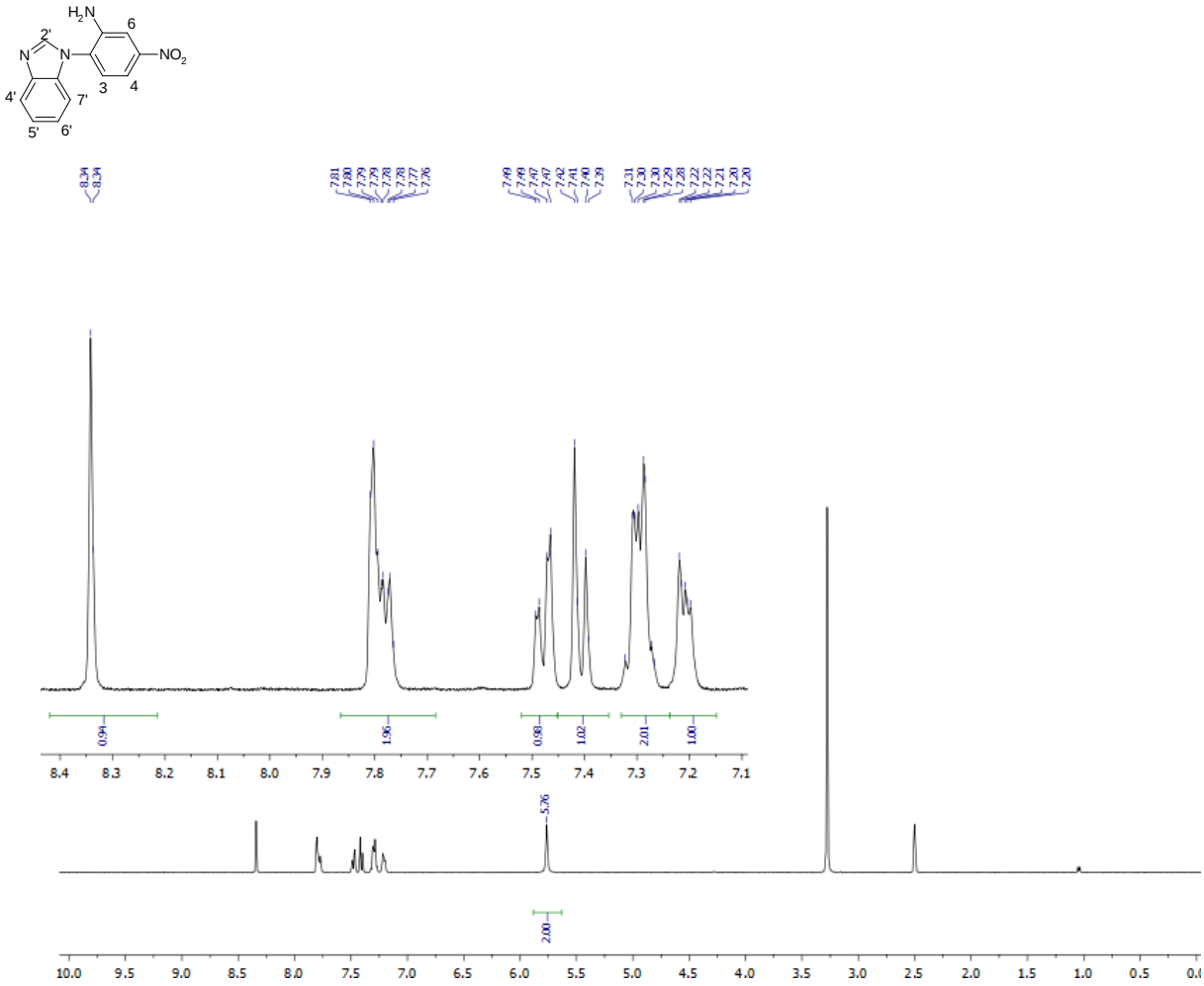
^{1}H NMR spectrum of *N*-[4-(1*H*-benzimidazol-1-yl)-3-nitrophenyl]propanamide (**5b**) (DMSO-d_6)



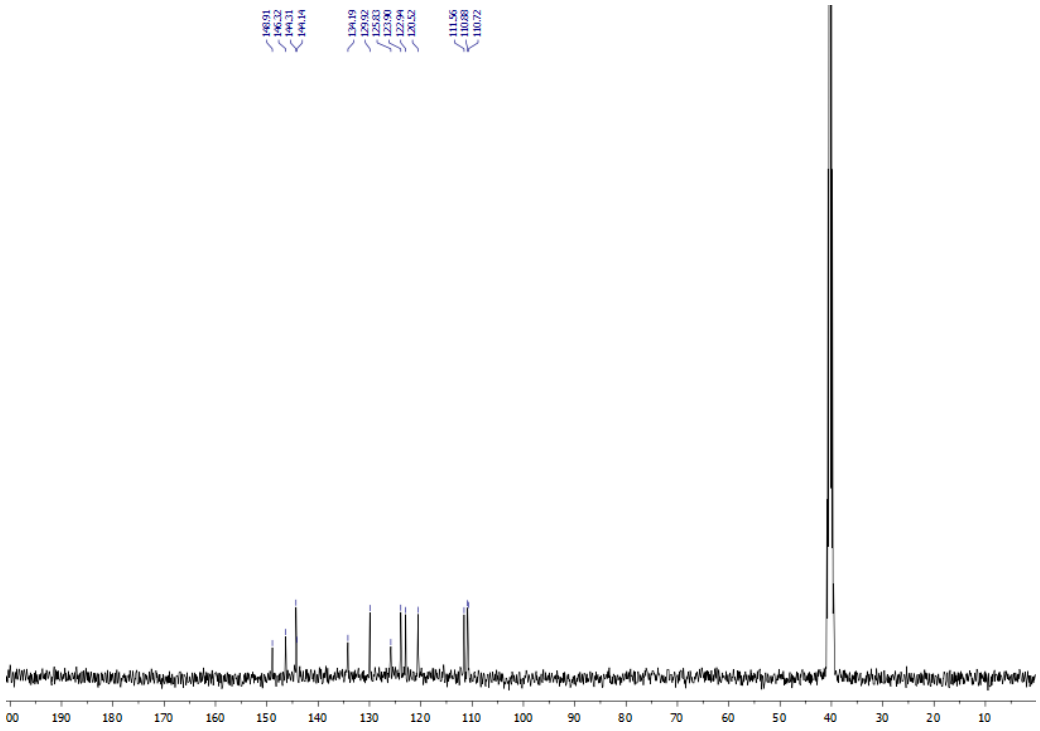
^{13}C NMR spectrum of *N*-[4-(1*H*-benzimidazol-1-yl)-3-nitrophenyl]propanamide (**5b**) (DMSO-d_6)



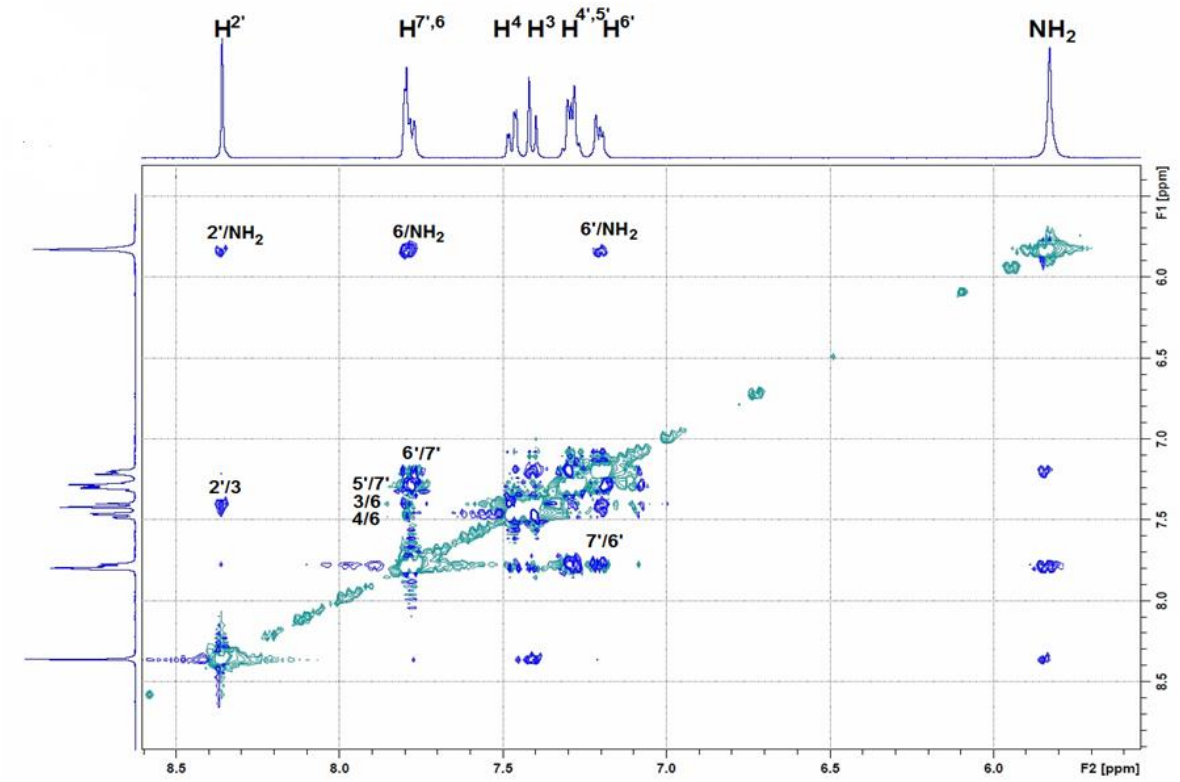
^{1}H-^{1}H NOESY spectrum of *N*-[4-(1*H*-benzimidazol-1-yl)-3-nitrophenyl]propanamide (**5b**) (DMSO-d_6)



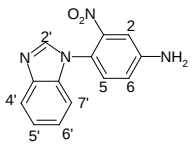
^{1}H NMR spectrum of 2-(1*H*-benzimidazol-1-yl)-5-nitroaniline **(1a)** (DMSO-d_6)

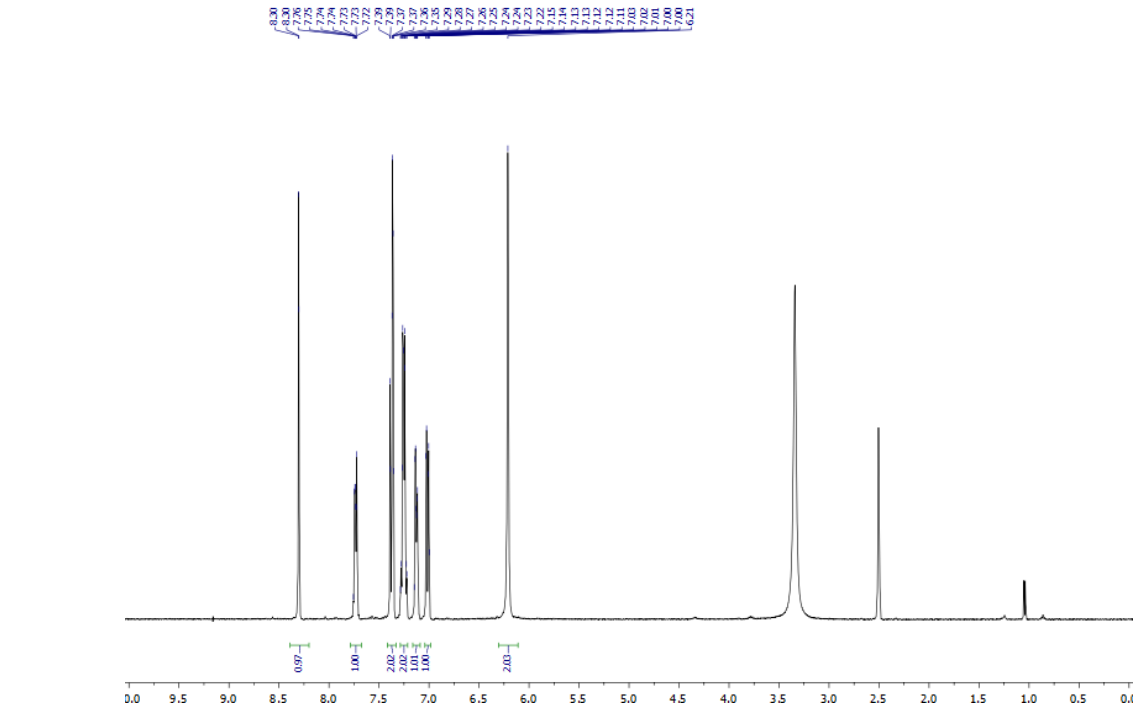


^{13}C NMR spectrum of 2-(1*H*-benzimidazol-1-yl)-5-nitroaniline (**1a**) (DMSO-d_6)

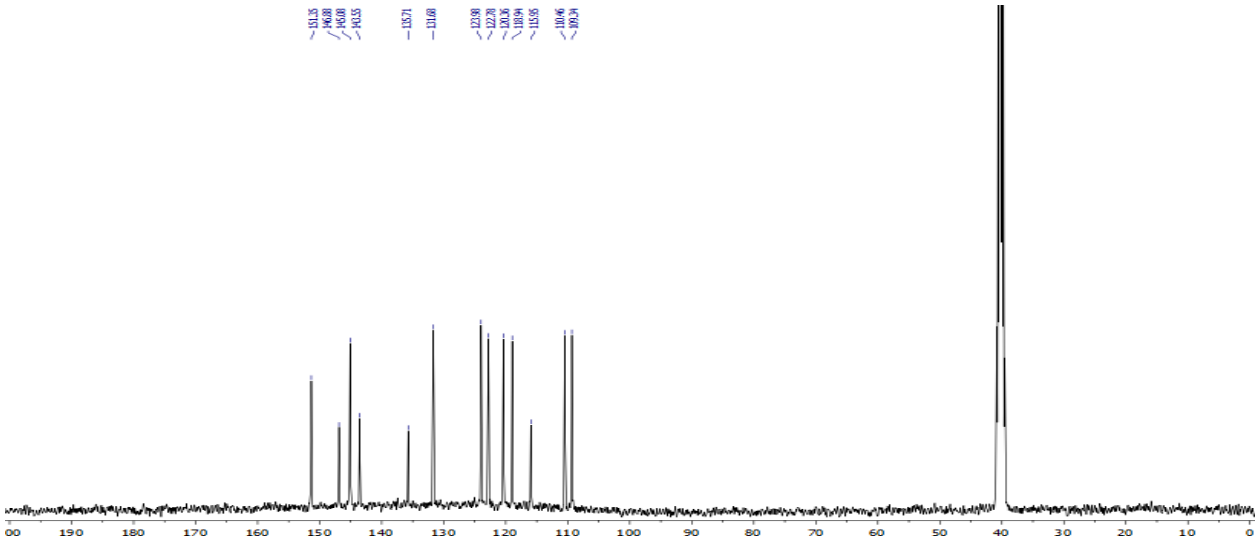


Fragment of ^{1}H-^{1}H NOESY spectrum of 2-(1*H*-benzimidazol-1-yl)-5-nitroaniline (**1a**) (DMSO-d_6)

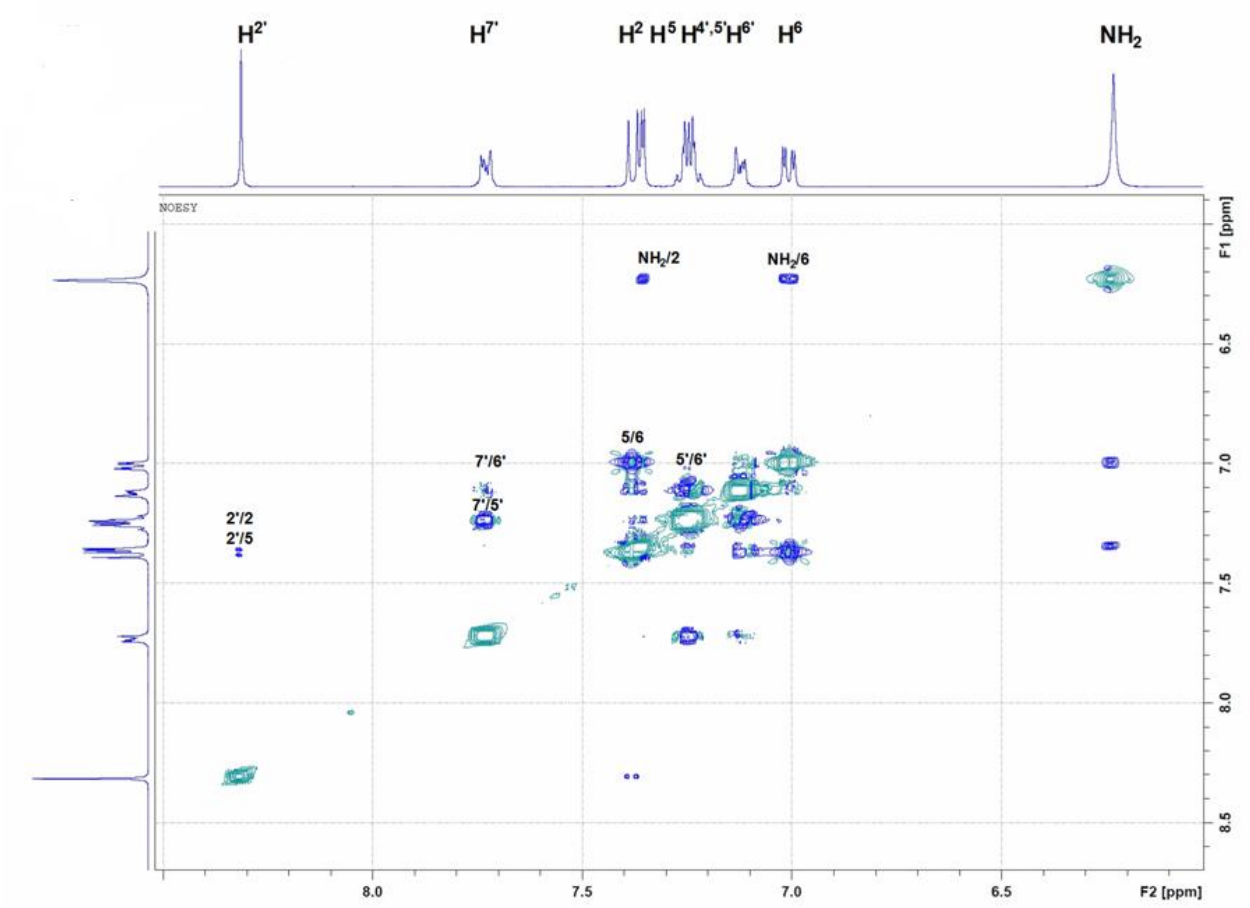




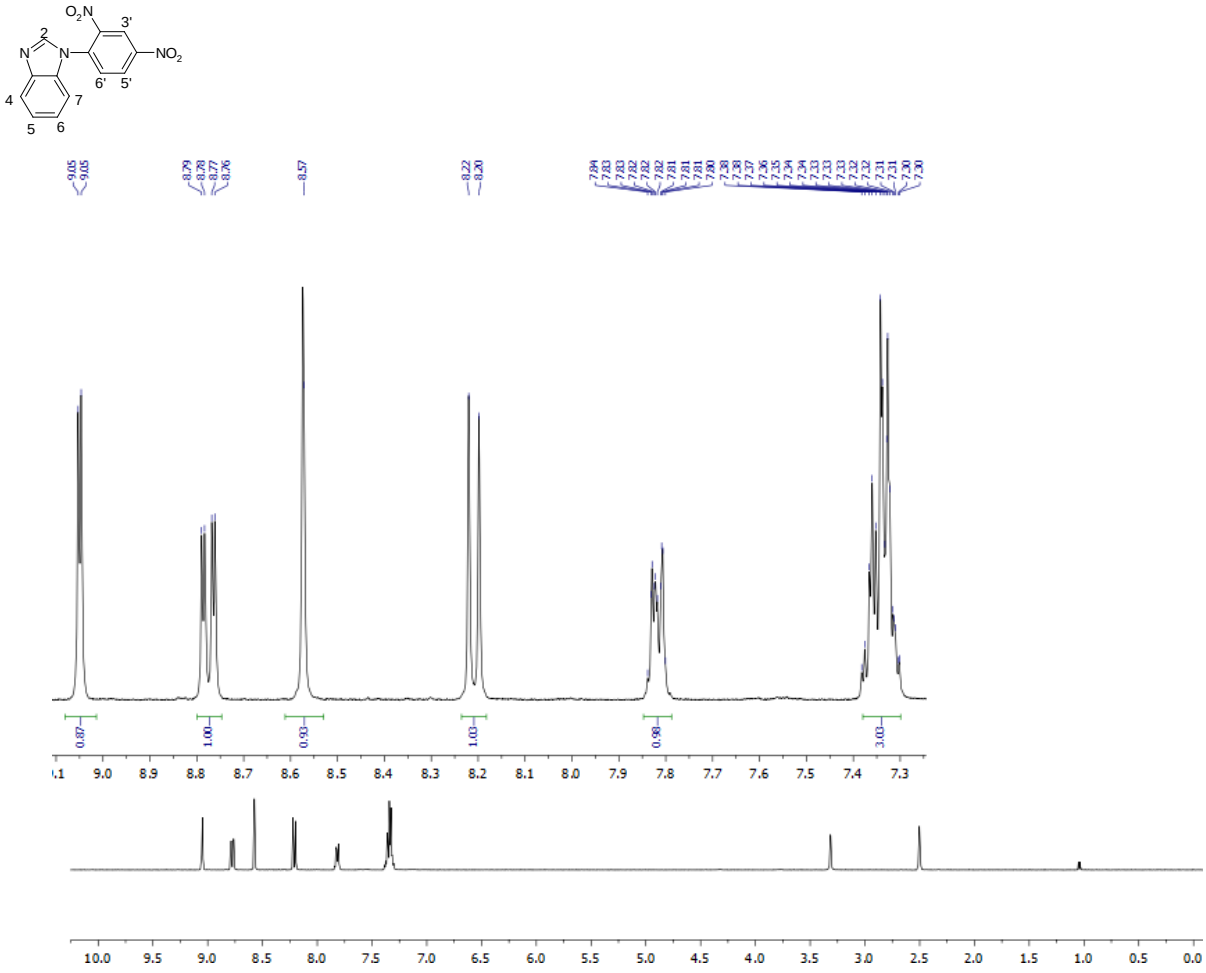
^{1}H NMR spectrum of 4-(1*H*-benzimidazol-1-yl)-3-nitroaniline (**1b**) (DMSO-d_6)



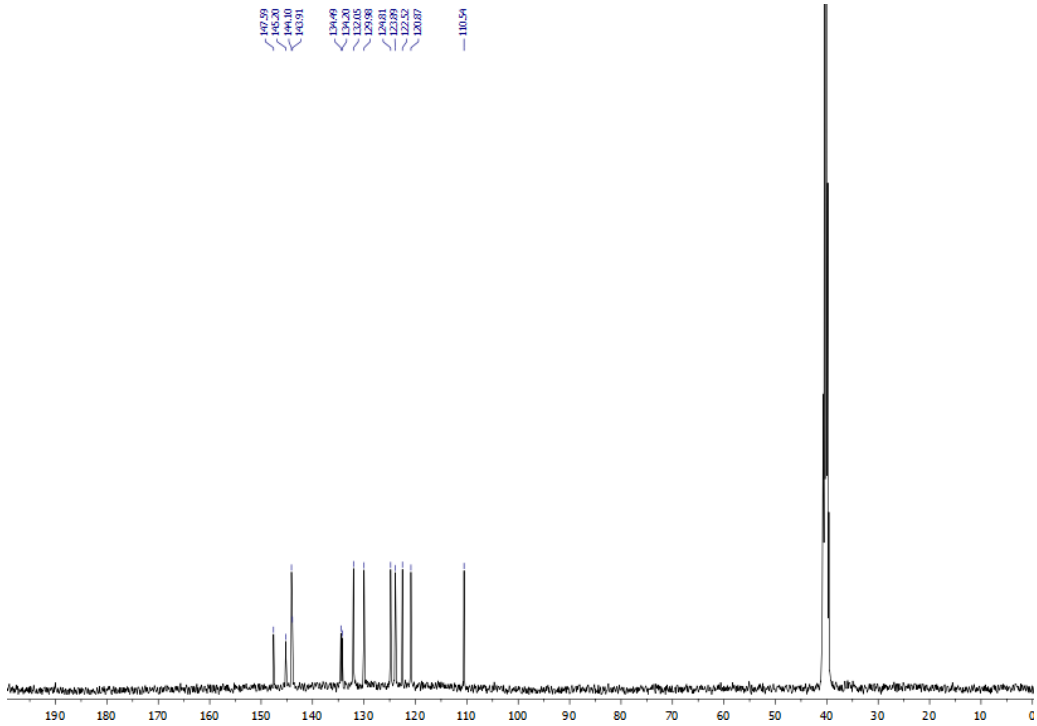
^{13}C NMR spectrum of 4-(1*H*-benzimidazol-1-yl)-3-nitroaniline (**1b**) (DMSO-d_6)



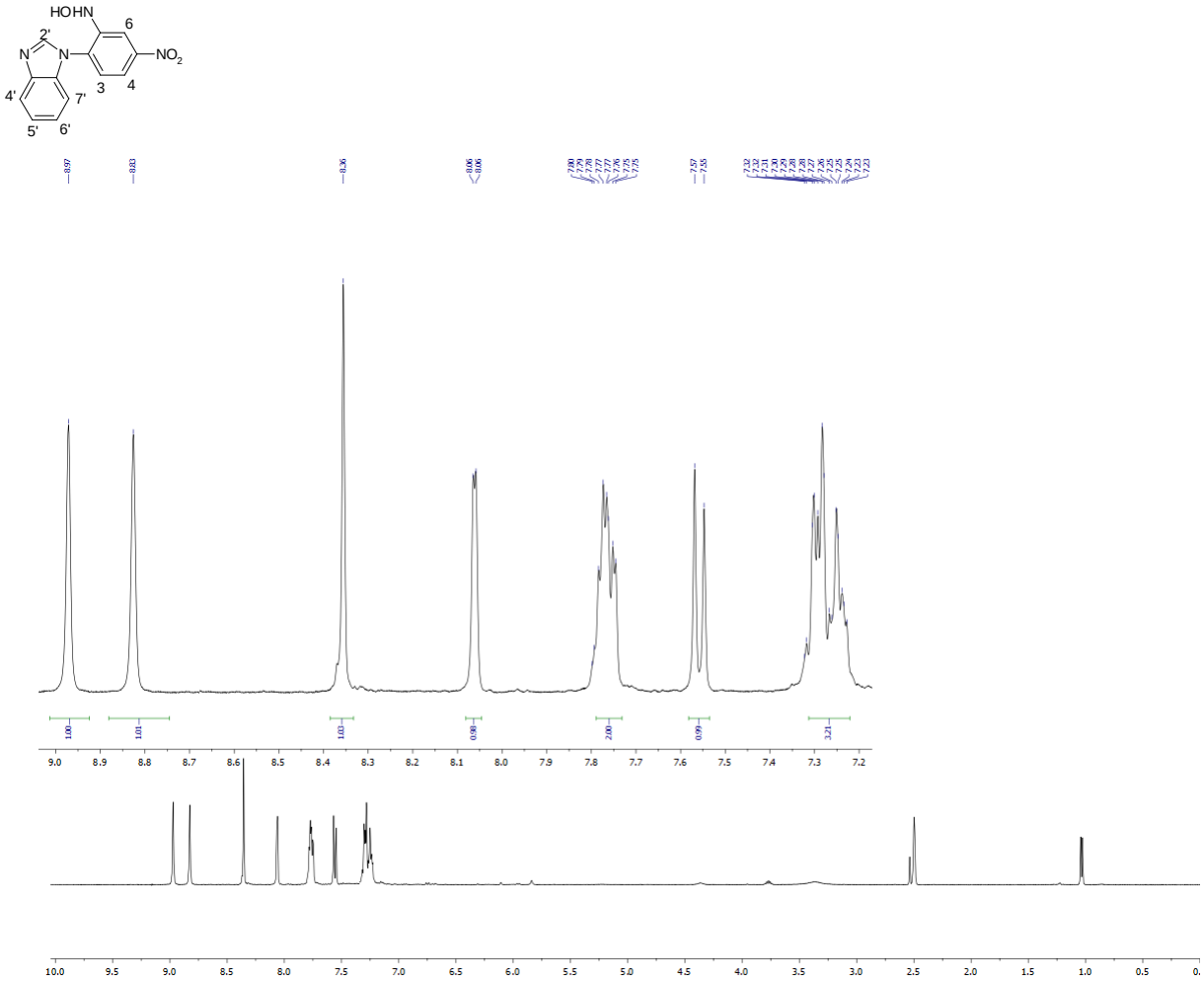
Fragment of ^{1}H-^{1}H NOESY spectrum of 4-(1*H*-benzimidazol-1-yl)-3-nitroaniline (**1b**) (DMSO-d_6)



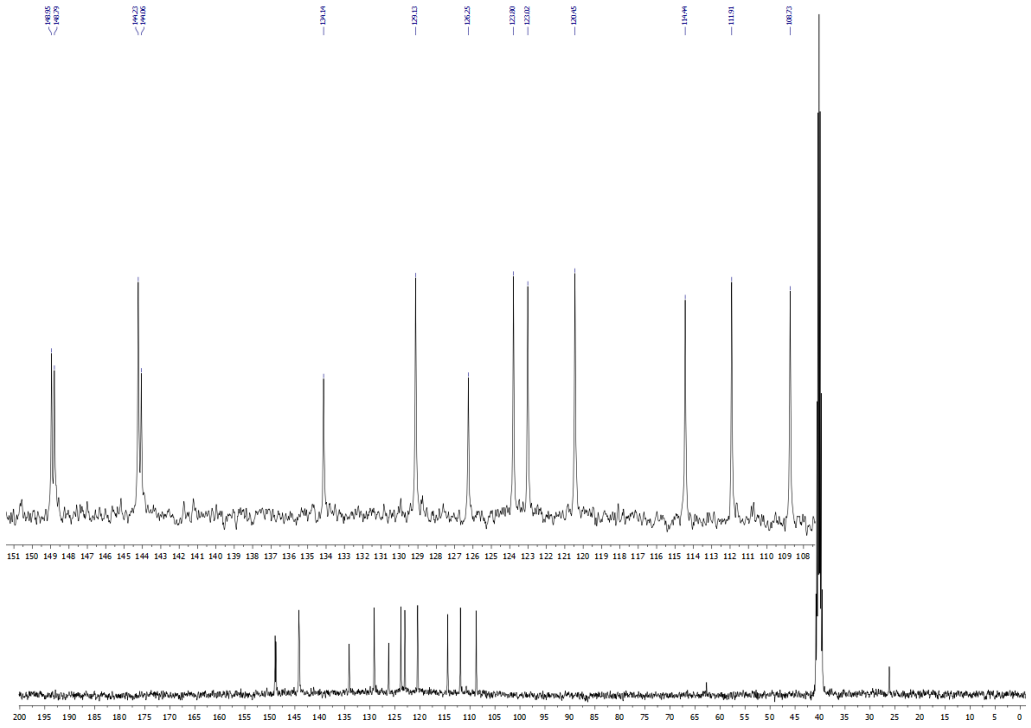
^{1}H NMR spectrum of 1-(2,4-dinitrophenyl)-1*H*-benzimidazole (**7**) (DMSO-d_6)



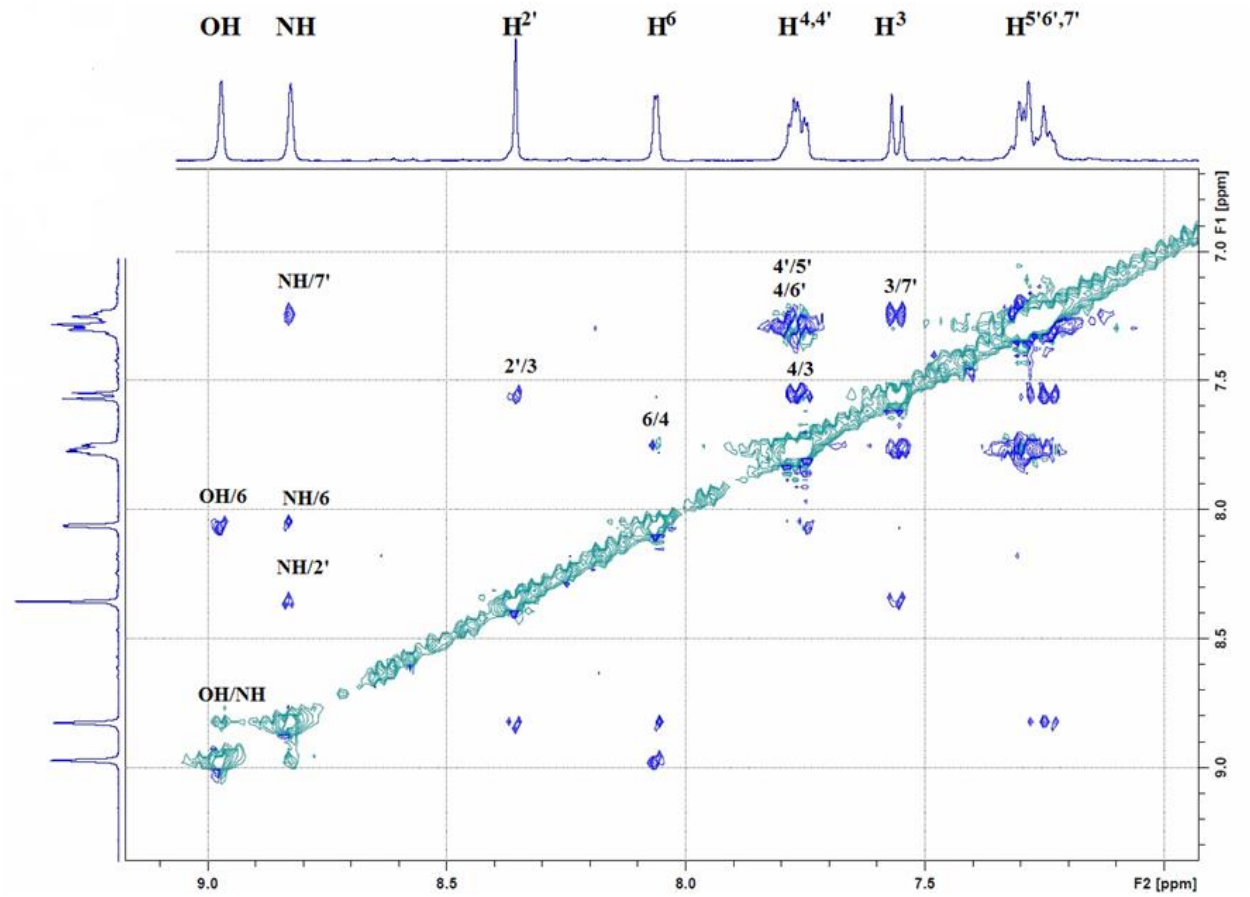
^{13}C NMR spectrum of 1-(2,4-dinitrophenyl)-1*H*-benzimidazole (**7**) (DMSO-d_6)



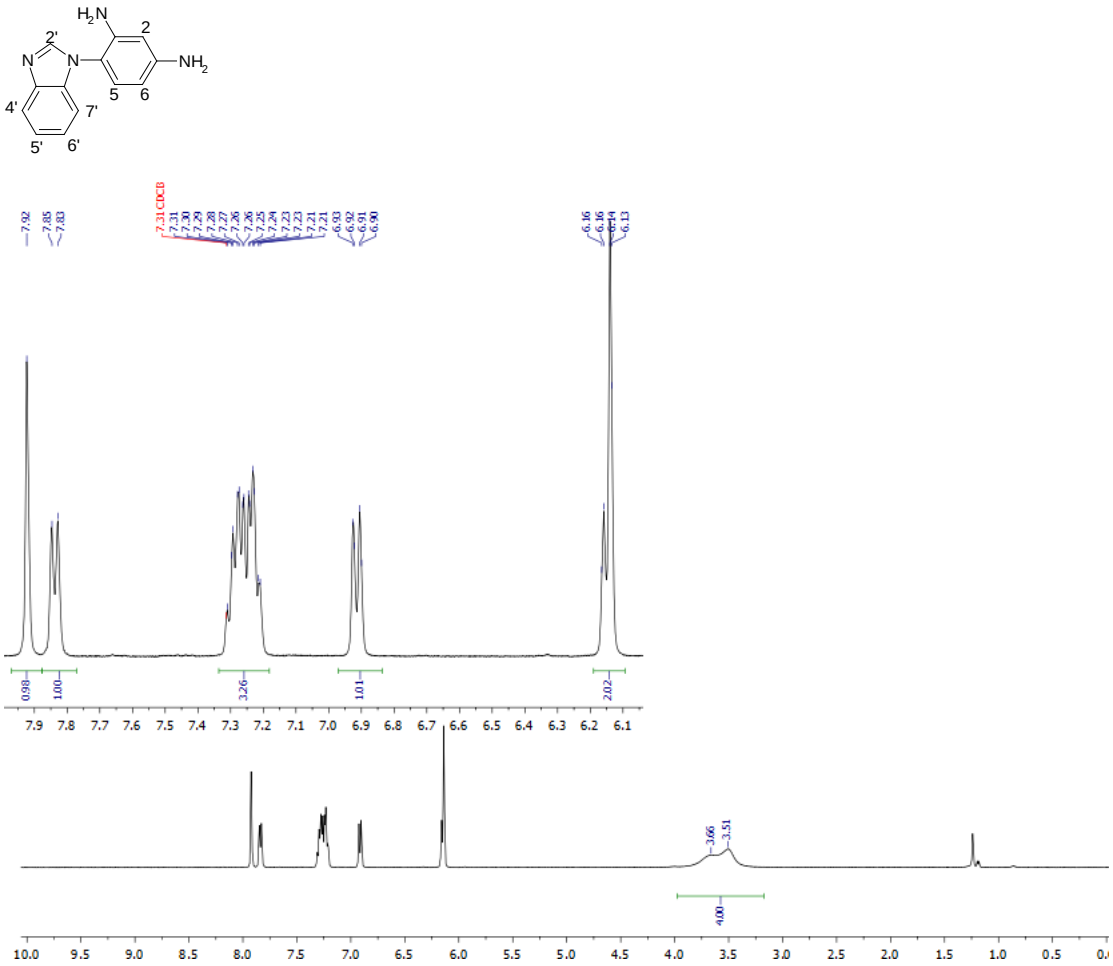
^{1}H NMR spectrum of 2-(1*H*-benzimidazol-1-yl)-*N*-hydroxy-5-nitroaniline (**8**) (DMSO-d_6)



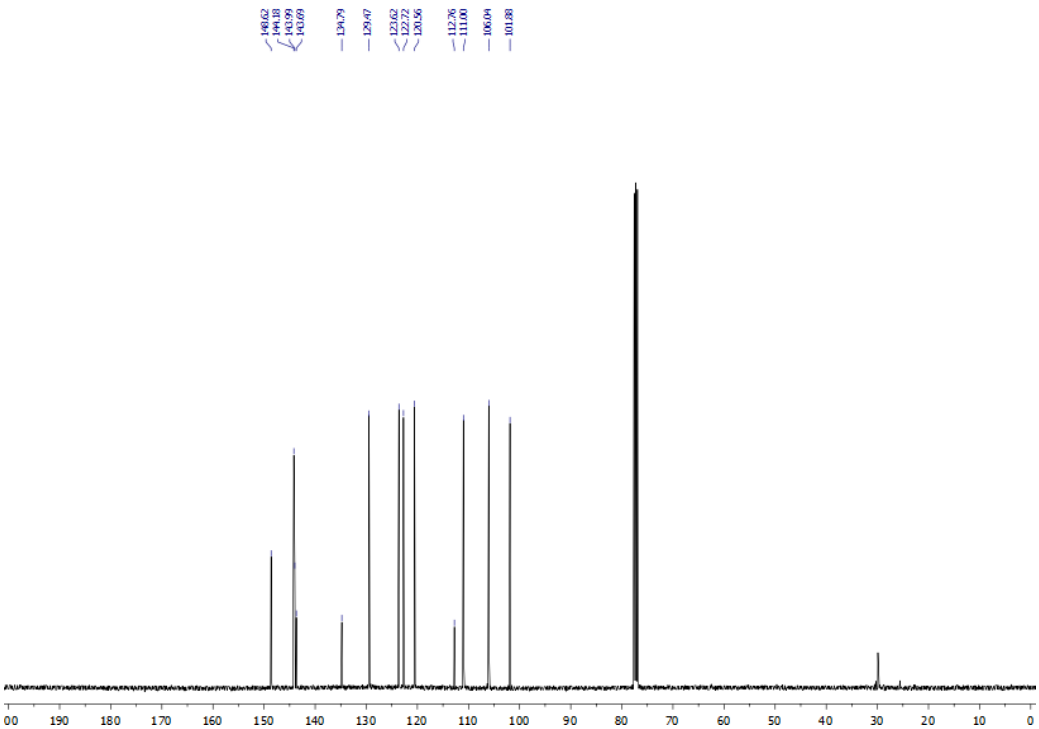
^{13}C NMR spectrum of 2-(1*H*-benzimidazol-1-yl)-*N*-hydroxy-5-nitroaniline (**8**) (DMSO-d_6)



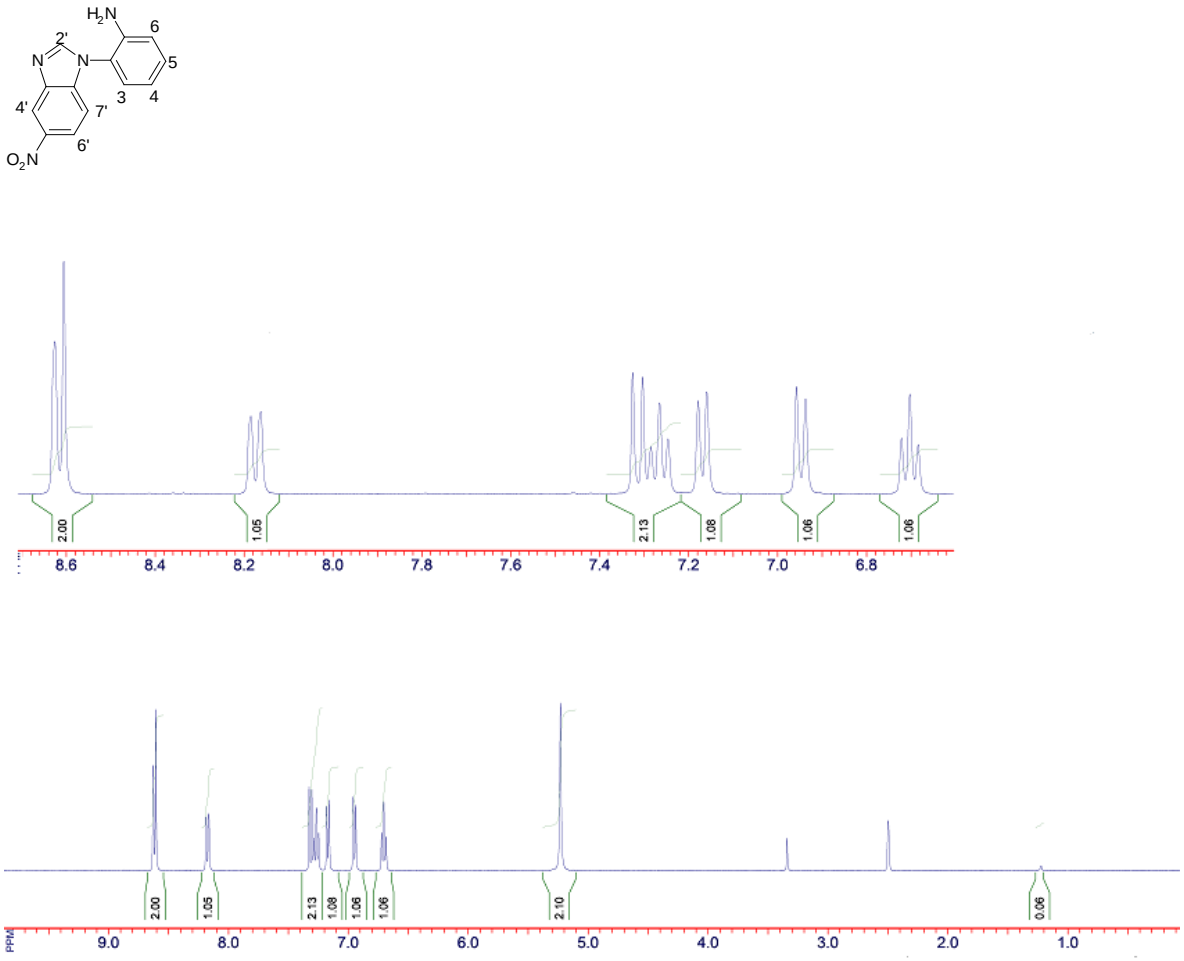
Fragment of ^{1}H-^{1}H NOESY spectrum of 2-(1*H*-benzimidazol-1-yl)-*N*-hydroxy-5-nitroaniline (**8**) (DMSO-d_6)



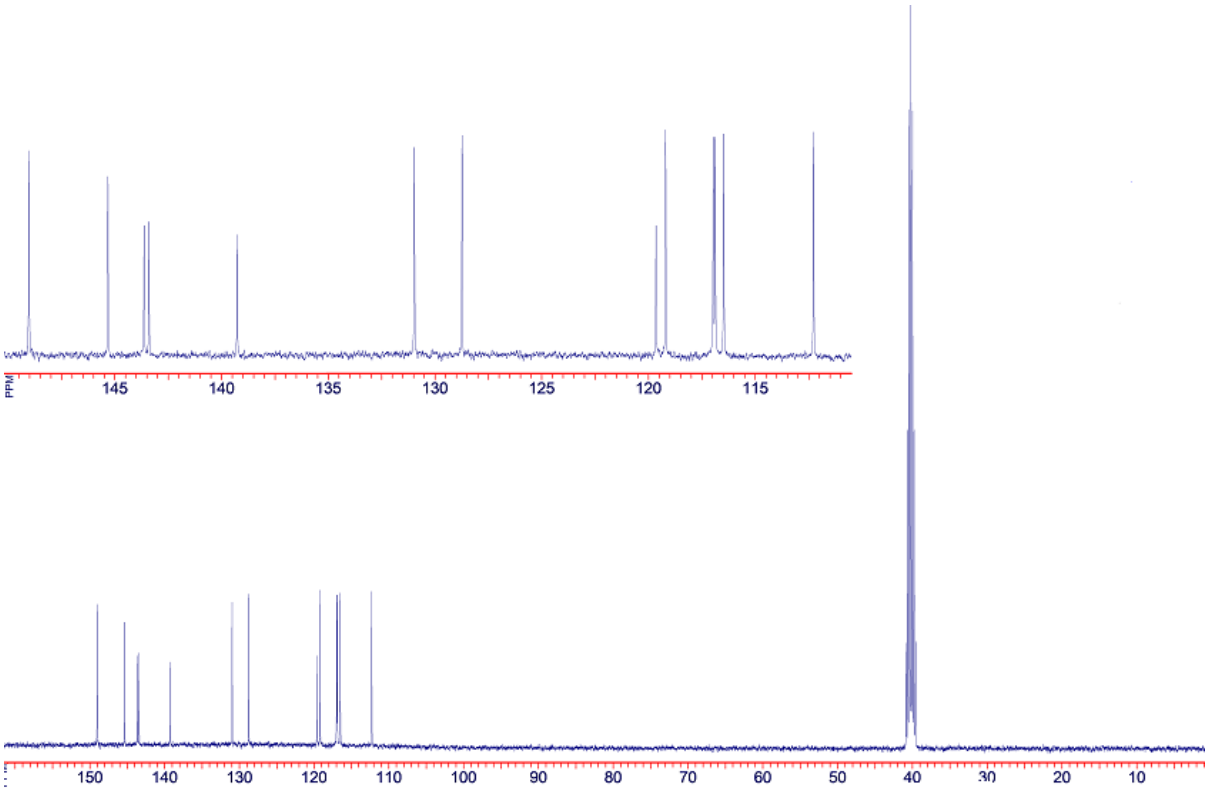
^{1}H NMR spectrum of 4-(1*H*-benzimidazol-1-yl)benzene-1,3-diamine (**9**) (DMSO-d_6)



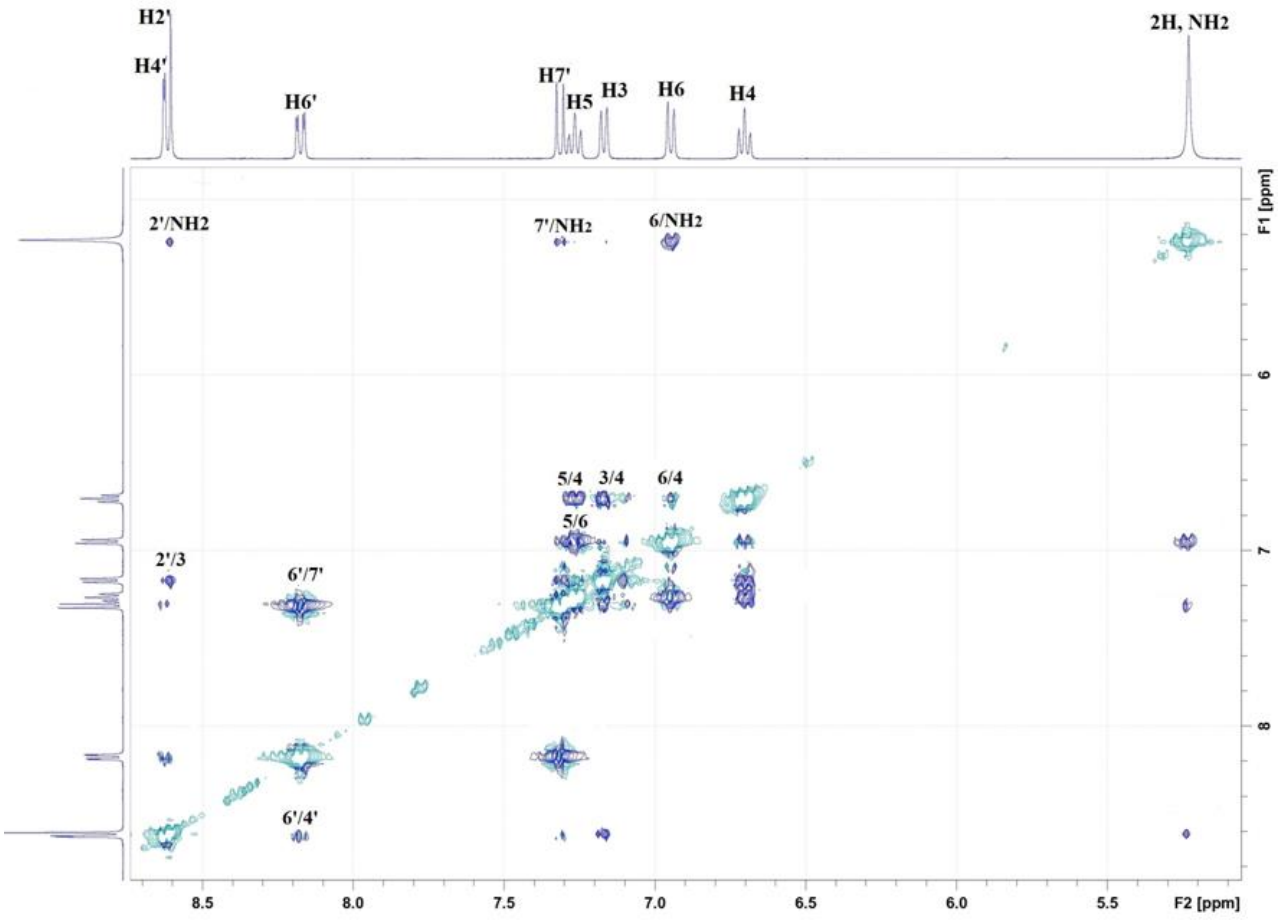
^{13}C NMR spectrum of -(1*H*-benzimidazol-1-yl)benzene-1,3-diamine (**9**) (DMSO-d_6).



^{1}H NMR spectrum of 2-(5-nitro-1*H*-benzimidazol-1-yl)aniline (**2**) (DMSO-d_6)



^{13}C NMR spectrum of 2-(5-nitro-1*H*-benzimidazol-1-yl)aniline (**2**) (DMSO-d_6)



Fragment of ^{1}H-^{1}H NOESY spectrum of 2-(5-nitro-1*H*-benzimidazol-1-yl)aniline (**2**) (DMSO-d_6)