Electronic supplementary materials *Mendeleev Commun.*, 2022, **32**, 265–267

New type of recyclization in 3,4-dihydroisoquinolines in the synthesis of β-(*o*-indazolylaryl)ethylamines and their 7-azaindazolyl analogues

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1. General Information

NMR spectra were recorded on a spectrometer Bruker Avance 600 (600 MHz) or Varian XL 300 (300 MHz) (compound **2b**) in DMSO-d_6. Chemical shifts of nuclei ^1H and ^{13}C were measured relatively the residual signals of deuterated solvent (see δ values in ref. [S1]). Coupling constants (*J*) are reported in Hz. Melting points were determined by using Fisher-Johns Melting Point Apparatus (Fisher Scientific) and are uncorrected. Elemental analysis was performed by the classical method of microanalysis. The reaction and purity of the obtained compounds were monitored by TLC (plates with Al_2O_3 III activity grade, eluent $CHCl_3$, development of TLC plates by exposition to iodine vapors in iodine chamber).

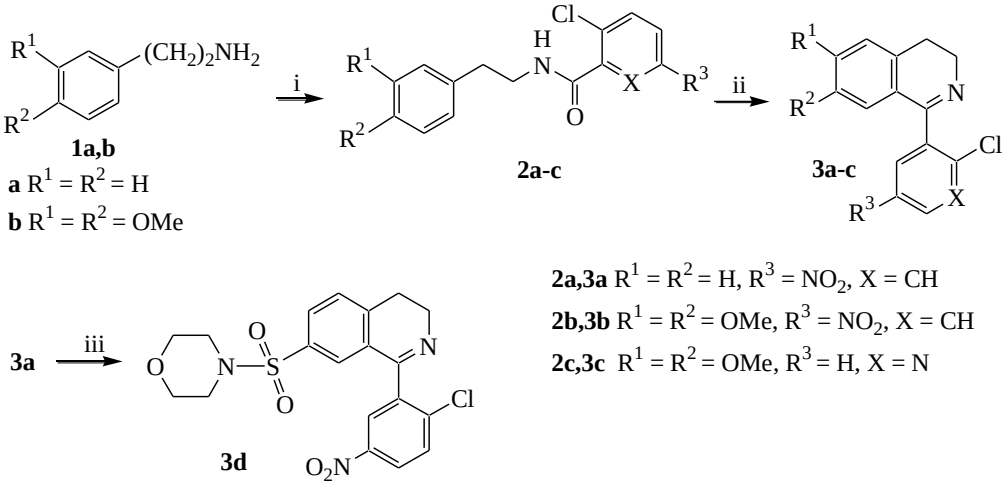
The crystallographic data for structure **5c**·$HClO_4$ were obtained on an Agilent SuperNova diffractometer by using a microfocus X-ray source with copper anode and an Atlas S2 two-dimensional CCD detector. The reflections were collected, unit cell parameters determined and refined by using the specialized CrysAlisPro 1.171.38.41 software suite (Rigaku Oxford Diffraction, 2015) [S2]. The structures were solved by using the ShelXT program (Sheldrick, 2015) [S3] and refined with the ShelXL program (Sheldrick, 2015) [S4].

Molecular graphics for structure **6c** were performed with the Olex^2 software suite (ver 1.2.7) [S5]. CCDC 2047116 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via http://www.ccdc.cam.ac.uk.

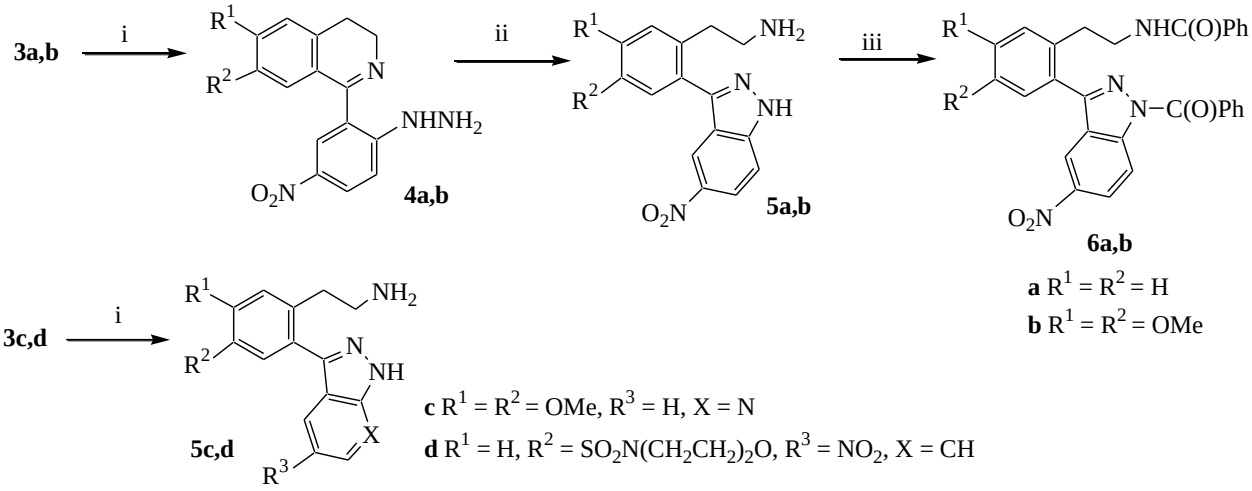
Quantum-chemical calculations were performed using quantum chemical program package Firefly 8.0 [S6], which is partially based on the GAMESS (US) [S7] source code.

The solvents were purified according to standard procedures. Starting and intermediate compounds **2a**, **2c** [S8]**, 3a** [S9] and **3c** [S8] were synthesized as described previously.

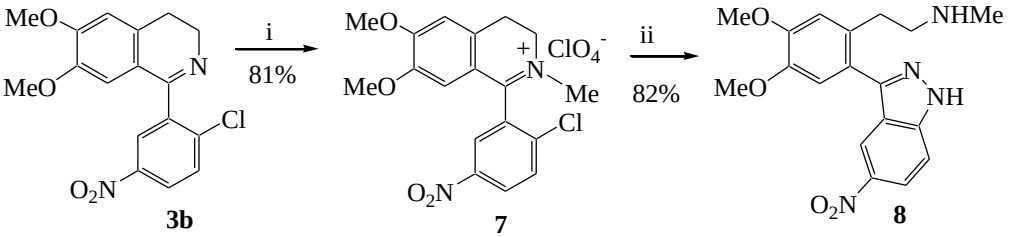
2. Synthesis and characterization of compounds 1-8.



Scheme S1 *Reagents and conditions*: i, 2-Cl-5-$O_2NC_6H_3COCl$ (for **2a,b**) or 2-chloronicotinoyl chloride (for **2c**), K_2CO_3, H_2O, 0-5 °C; ii, $POCl_3$, 105–110 °C; iii, $ClSO_3H$, 130-135°C, then morpholine, DMF, 20-25°C.

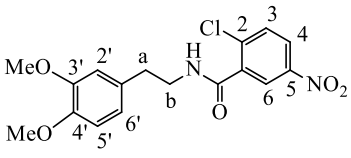


Scheme S2 *Reagents and conditions*: i, $NH_2NH_2 \cdot H_2O$, $MeO(CH_2)_2OH$, reflux, 0.5-1 h (for **3a,b**) or 4-5 h (for **3c,d**); ii, NH_2NH_2, $MeO(CH_2)_2OH$, HCl, reflux, 8-20 h; iii, PhCOCl, pyridine, 20-25°C.



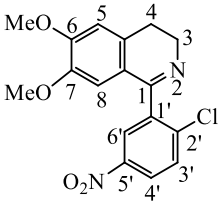
Scheme S3 *Reagents and conditions*: i, Me_2SO_4, 125 °C, EtOH, then 60% $HClO_4$; ii, $NH_2NH_2 \cdot H_2O$, $MeO(CH_2)_2OH$, reflux.

2-Chloro-N-(3,4-dimethoxyphenethyl)-5-nitrobenzamide **2b**.



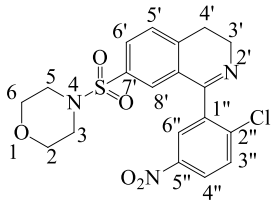
A mixture of 2-chloro-5-nitrobenzoic acid (20.16 g, 0.1 mol), $CHCl_3$ (30 mL), DMF (2 mL), thionyl chloride (8.7 mL, 14.28 g, 0.12 mol) was boiled for 2.5 h. The resulting solution was added at 0-5°C to a vigorous stirred mixture of 2-(3,4-dimethoxyphenyl)ethan-1-amine **1b** (18.1 g, 0.1 mol), saturated K_2CO_3 (50 mL) and $CHCl_3$ (40 mL). Then H_2O (250 mL) and petroleum ether (100 mL) was added, the precipitate was filtered off, washed with water (3×100 mL) and petroleum ether (100 mL). Yield **2b** was 28.4 g (78%). Colorless crystals, m.p. 144-146 °C. ^{1}H NMR (300 MHz), DMSO-d_6, δ, ppm: 2.77 (t, *J* 7.2, 2H, H-α), 3.44-3.50 (m, 2H, H-β), 3.71 (s, 3H, OMe), 3.74 (s, 3H, OMe), 6.76 (dd, *J* 1.8, 8.1, 1H, H-6'), 6.86-6.88 (m, 2H, H-2', H-5'), 7.79 (d, *J* 8.7, 1H, H-3), 8.11 (d, *J* 2.7, 1H, H-6), 8.25 (dd, *J* 8.8, 2.8 H-4), 8.73 (t, *J* 5.5,1H, NH). Found (%): C, 55.74; H, 4.48; Cl, 9.54; N, 7.52. Calc. for $C_{17}H_{17}ClN_2O_5$ (%): C, 55.97; H, 4.70; Cl, 9.72; N, 7.68.

1-(2-Chloro-5-nitrophenyl)-6,7-dimethoxy-3,4-dihydroisoquinoline **3b**.



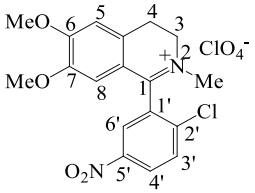
A solution of amide **2b** (14.58 g, 0.04 mol), $POCl_3$ (29.52 g, 18 mL, 0.19 mol) was kept 3 h at 105 °C, then it was cooled, poured into water (300 mL). After 1 h, conc. NH_4OH (150 mL) was added, and in 8 h the precipitate was filtered off and washed with water (3×500 mL). Yield **3b** was 28.4 g (76%). Colorless crystals, m.p. 130-131 °C (EtOH). ^{1}H NMR (600 MHz), DMSO-d_6, δ, ppm: 2.76 (t, *J* 7.7, 2H, H-4), 3.54 (s, 3H, OMe), 3.84 (br. s, 5H, OMe, H-3), 6.35 (s, 1H, H-8), 7.00 (s, 1H, H-5), 7.85 (d, *J* 8.8, 1H, H-3'), 8.23 (d, *J* 2.8, 1H, H-6'), 8.32 (dd, *J* 8.8, 2.8, 1H, H-4'). ^{13}C NMR (150 MHz), DMSO-d_6, δ, ppm: 24.73, 47.30, 55.64, 55.87, 110.20, 111.14, 120.42, 124.86, 125.38, 130.95, 130.96, 138.38, 139.31, 146.48, 147.21, 151.40, 162.86. Found (%): C, 58.56; H, 4.15; Cl, 9.94; N, 8.32. Calc. for $C_{17}H_{15}ClN_2O_4$ (%): C, 58.88; H, 4.36; Cl, 10.22; N, 8.08.

4-{[1-(2-Chloro-5-nitrophenyl)-3,4-dihydroisoquinolin-7-yl]sulfonyl}morpholine **3d**.



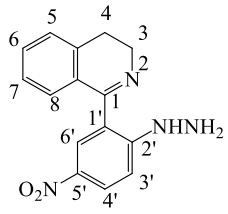
A mixture of 1-(2-chloro-5-nitrophenyl)-3,4-dihydroisoquinoline **3a** (0.87 g, 0.003 mol) and chlorosulfonic acid (2 mL) was heated 1 h at 130-135°C, cooled and poured onto ice (100 g), the precipitate was filtered off and washed with water (3×5 mL). The wet precipitate was dissolved in DMF (5 mL), morpholine (5 mL) was added, and the mixture was stirred for 3 h. After keeping at room temperature for 8 h, water (20 mL) was added, the reaction product was filtered off and washed with water (3×500 mL). The yield of **3d** was 45%. Colorless crystals, m.p. 159-161 °C (EtOH). The product was introduced, without additional purification, into the reaction with hydrazine hydrate. ^{1}H NMR (600 MHz), DMSO-d_6, δ, ppm: 2.77-2.78 (m, 4H, H-3, H-5), 2.96 (br. s, 2H, H-4'), 3.56-3.58 (m, 4H, H-2, H-6), 3.77 (br.s, 1H, H-3'), 4.07 (br. s, 1H, H-3'), 7.05 (d, *J* 1.8, 1H, H-8'), 7.68 (d, *J* 8.0, 1H, H-5'), 7.81 (dd, *J* 7.9, 1.9, 1H, H-4''), 7.89 (d, *J* 8.8, 1H, H-6'), 8.35 (dd, *J* 8.8, 2.8, 1H, H-6'), 8.39 (d, *J* 2.8, 1H, H-6''). ^{13}C NMR (150 MHz), DMSO-d_6, δ, ppm: 24.88, 45.64, 46.85, 65.20, 124.36, 125.56, 125.93, 128.13, 129.22, 130.09, 131.14, 133.42, 138.14, 142.87, 146.72, 162.04. Found (%): C, 52.14; H, 4.00; Cl, 8.44; N, 4.52; S, 7.42. Calc. for $C_{19}H_{18}ClN_3O_5S$ (%): C, 52.35; H, 4.16; Cl, 8.13; N, 9.64; S, 7.36.

1-(2-Chloro-5-nitrophenyl)-6,7-dimethoxy-2-methyl-3,4-dihydroisoquinolin-2-ium perchlorate **7**.



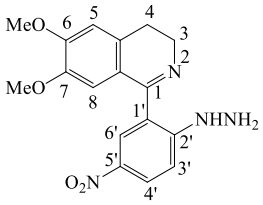
A mixture of 1-(2-chloro-5-nitrophenyl)-6,7-dimethoxy-3,4-dihydroisoquinoline **3b** (0.74 g, 0.003 mol) and Me_2SO_4 (0.44 g, 0.33 mL, 0.0035 mol) was heated at 125 °C for 30 min. The mixture was cooled, EtOH (15 mL) and 60% $HClO_4$ (0.5 mL) were added, the precipitate was filtered off, washed with EtOH (3×5 mL). Yield of compound **7** was 1.12 g (81%). Colorless crystals, m.p. 233-234 °C (EtOH). ^{1}H NMR (600 MHz), DMSO-d_6, δ, ppm: 3.27-3.34 (m, 3H, 2H-4, overlapped with signal of water), 3.46 (s, 3H, OMe), 3.53 (s, 3H, OMe), 3.95 (s, 3H, NMe), 4.25-4.28 (m, 2H, 2H-3), 6.35 (s, 1H, H-5), 7.29 (s, 1H, H-8), 8.10 (d, *J* 8.9, 1H, H-3'), 8.56 (dd, *J* 8.9, 2.8, 1H, H-4'), 8.76 (d, *J* 2.8, 1H, H-6'). ^{13}C NMR (150 MHz), DMSO-d_6, δ, ppm: 24.50, 45.03, 56.13, 56.61, 111.76, 113.78, 117.95, 125.52, 128.03, 129.57, 131.97, 134.27, 137.22, 146.96, 148.08, 157.03, 167.82. Found (%): C, 46.44; H, 3.62; Cl, 15.04; N, 5.82. Calc. for $C_{18}H_{18}Cl_2N_2O_8$ (%): C, 46.87; H, 3.93; Cl, 15.37; N, 6.07.

1-(2-Hydrazinyl-5-nitrophenyl)-3,4-dihydroisoquinoline **4a**.



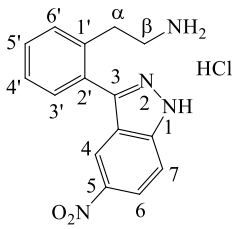
A mixture of 1-(2-chloro-5-nitrophenyl)-3,4-dihydroisoquinoline **3a** (0.87 g, 0.003 mol), hydrazine hydrate (0.4 mL) in 2-methoxyethanol (5 mL) was refluxed for 30 min and cooled; after that H_2O (20 mL) and saturated solution $NaHCO_3$ (5 mL) were added, and reaction product was extracted with $CHCl_3$ (5×5 mL). The extract was dried (Na_2SO_4), and the volatiles were distilled off in vacuum. Yield of product **4a** was 0.30 g (35%). Colorless crystals, m.p. 184-185 °C (EtOH). ^{1}H NMR (600 MHz), DMSO-d_6, δ, ppm: 2.69-2.72 (m, 2H, 2H-4), 2.80-2.83 (m, 2H, 2H-3), 4.99 (br. s, 3H, NH, NH_2), 7.39-7.47 (m, 3H, H-5 - H-7), 7.52 (dd, *J* 7.3, 1.4, 1H, H-4'), 7.77 (d, *J* 9.2, 1H, H-3'), 8.18-8.21 (m, 1H, H-8), 8.46 (d, *J* 2.1, 1H, H-6'). ^{13}C NMR (150 MHz), DMSO-d_6, δ, ppm: 36.82, 43.11, 111.83, 118.01, 120.54, 121.02, 126.23, 128.53, 130.31, 130.46, 130.98, 139.19, 141.52, 143.47, 146.94. Found (%): C, 63.59; H, 4.80; N, 19.52. Calc. for $C_{15}H_{14}N_4O_2$ (%): C, 63.82; H, 5.00; N, 19.85. H-8.

1-(2-Hydrazinyl-5-nitrophenyl)-6,7-dimethoxy-3,4-dihydroisoquinoline **4b**.



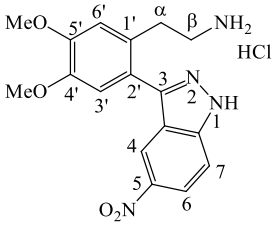
Compound **4b** was synthesized from 1-(2-chloro-5-nitrophenyl)-6,7-dimethoxy-3,4-dihydroisoquinoline **3b** (0.074 g, 0.003 mol) and hydrazine analogously to **4a** (reaction time 1 h) in yield of 0.51 g (50%). Colorless crystals, m.p. 187-188 °C (EtOH). ^{1}H NMR (600 MHz), DMSO-d_6, δ, ppm: 2.74 (s, 4H, 2H-3, 2H-4), 3.79 (s, 3H, OMe), 3.86 (s, 3H, OMe), 6.48 (br. s, 3H, NH, NH_2), 7.05 (s, 2H, H-5, H-8), 7.77 (d, *J* 9.2, 1H, H-3'), 8.21 (d, *J* 9.2, 1H, H-4'), 8.49 (d, *J* 2.1, 1H, H-6'). ^{13}C NMR (150 MHz), DMSO-d_6, δ, ppm: 35.37, 42.70, 55.55, 55.75, 111.66, 113.93, 118.25, 120.68, 121.11, 122.83, 131.32, 141.56, 142.76, 143.17, 146.96, 147.04, 148.99. Found (%): C, 59.41; H, 5.00; N, 16.34. Calc. for $C_{17}H_{18}N_4O_4$ (%): C, 59.64; H, 5.30; N, 16.37.

2-[2-(5-Nitro-1H-indazol-3-yl)phenyl]ethanamine hydrochloride **5a**·HCl.



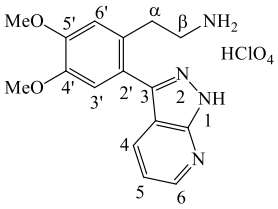
A mixture of 1-(2-hydrazinyl-5-nitrophenyl)-3,4-dihydroisoquinoline **4a** (0.85 g, 0.003 mol), 2-methoxyethanol (4 mL) and conc. HCl (0.2 mL) was refluxed 8 h. The solvent was distilled off in vacuum, and the residue was treated with EtOH and a solution of hydrogen chloride in Pr^{i}OH. Yield of **5a**·HCl was 0.59 g (62%). Colorless crystals with mp 225-227 °C (EtOH). ^{1}H NMR (600 MHz), DMSO-d_6, δ, ppm: 2.93-2.96 (m, 2H, 2H-α), 2.98-3.01 (m, 2H, 2H–β), 7.44-7.50 (m, 3H, H-4' – H-6'), 7.57 (d, *J* 7.1, 1H, H-3'), 7.80 (d, *J* 9.1, 1H, H-7), 7.85-8.15 (m, 3H, $^{+}NH_3$), 8.19-8.25 (m, 1H, H-6), 8.46 (d, *J* 2.1, 1H, H-4), 14.15 (s, 1H, NH). ^{13}C NMR (150 MHz), DMSO-d_6, δ, ppm: 30.97, 39.98, 111.79, 118.00, 120.80, 121.44, 123.63, 125.23, 132.00, 132.61, 142.38, 142.77, 144.42, 144.54, 146.66. Found (%): C, 56.19; H, 4.49; Cl, 11.00; N, 17.39. Calc. for $C_{15}H_{15}ClN_4O_2$ (%): C, 56.52; H, 4.74; Cl, 11.12; N, 17.58.

2-[4,5-Dimethoxy-2-(5-nitro-1H-indazol-3-yl)phenyl]ethanamine hydrochloride **5b**·HCl.



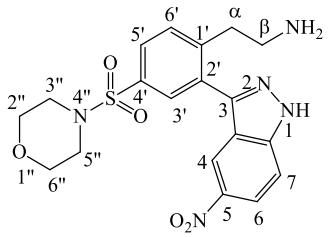
A mixture of 1-(2-hydrazinyl-5-nitrophenyl)-6,7-dimethoxy-3,4-dihydroisoquinoline **4b** (0.68 g, 0.002 mol), 2-methoxyethanol (4 mL) and conc. HCl (0.2 mL) was refluxed for 20 h. The mixture was cooled, treated with H_2O (10 mL) and saturated solution $NaHCO_3$ (5 mL). The base **5b** was filtered off and washed with H_2O (3×3 mL). Yield was 0.65 g (95%). Hydrochloride **5b**·HCl was obtained by the action of HCl/Pr^{i}OH solution on the free base **5b** in EtOH, m.p. 290-292 °C (EtOH). ^{1}H NMR (600 MHz), DMSO-d_6, δ, ppm: 2.95 (s, 4H, 2H-α, 2H–β), 3.80 (s, 3H, OMe), 3.88 (s, 3H, OMe), 7.11 (s, 1H, H-6'), 7.16 (s, 1H, H-3'), 7.82 (d, *J* 9.2, 1H, H-7), 8.15 (br. s, 3H, $^{+}NH_3$), 8.24 (dd, *J* 9.2, 2.1, 1H, H-6), 8.52 (d, *J* 2.1, 1H, H-4), 14.18 (s, 1H, NH). ^{13}C NMR (150 MHz), DMSO-d_6, δ, ppm: 30.45, 40.09, 55.66, 55.80, 111.39, 114.00, 114.19, 118.25, 121.00, 123.00, 128.98, 141.75, 142.63, 146.58, 147.50, 149.11. Found (%): C, 53.64; H, 4.91; Cl, 9.08; N, 14.46. Calc. for $C_{17}H_{19}ClN_4O_4$ (%): C, 53.90; H, 5.06; Cl, 9.36; N, 14.79.

2-[4,5-Dimethoxy-2-(1H-pyrazolo[3,4-b]pyridin-3-yl)phenyl]ethanamine hydroperchlorate **5c**·$HClO_4$.



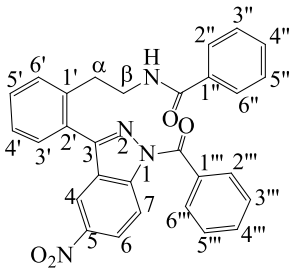
A mixture of 1-(2-chloropyridin-3-yl)-6,7-dimethoxy-3,4-dihydroisoquinoline **3c** (0.91 g, 0.003 mol), hydrazine hydrate (0.6 mL) in 2-methoxyethanol (4 mL) was refluxed 4 h. Then $NaHCO_3$ (0.3 g) was added, and the mixture was refluxed for 15 min, the solvent was distilled off in vacuum. The residue was dissolved in EtOH (10 mL), and 60% $HClO_4$ (0.2 mL) was added. Hydroperchlorate **5c**·$HClO_4$ was filtered off and washed with EtOH (3×5 mL). Yield of salt **5c** was 0.92 g (77%), m.p. 269-271°C (EtOH). ^{1}H NMR (600 MHz), DMSO-d_6, δ, ppm: 2.88-2.99 (m, 4H, 2H-α, 2H–β), 3.76 (s, 3H, OMe), 3.82 (s, 3H, OMe), 7.03 (s, 1H, H-6'), 7.08 (s, 1H, H-3'), 7.22-7.24 (m, 1H, H-5), 8.11 (br. s, 3H, $^+NH_3$), 8.20 (dd, *J* 8.0, 1.5, 1H, H-6), 8.55-8.56 (m, 1H, H-4).^{13}C NMR (150 MHz), DMSO-d_6, δ, ppm: 30.56, 40.28, 55.68, 55.70, 113.84, 114.05, 114.21, 117.08, 123.71, 128.71, 131.02, 143.15, 147.50, 148.31, 148.89, 151.51. Found (%): C, 48.00; H, 4.62; Cl, 8.56; N, 13.69. Calc. for $C_{16}H_{19}ClN_4O_6$ (%): C, 48.19; H, 4.80; Cl, 8.89; N, 14.05.

2-[4-Morpholinosulfonyl-2-(5-nitro-1H-indazol-3-yl)phenyl]ethan-1-amine **5d**



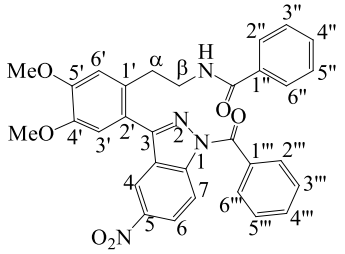
A mixture of compound **3d** (0.44 g, 0.001 mol), hydrazine hydrate (0.1 mL) in 2-methoxyethanol (4 mL) was refluxed for 4 h. The mixture was cooled, H_2O (10 mL) and saturated solution $NaHCO_3$ (5 mL) was added. The precipitate was filtered off and washed with H_2O (3×3 mL) and EtOH (3×3 mL). Yield of product **5d** was 0.18 g (42%), beige crystals, m.p. 233-235 °C (EtOH). ^{1}H NMR (600 MHz), DMSO-d_6, δ, ppm: 2.77 (t, *J* 7.1, 2H, 2H-α), 2.92-2.99 (m, 6H, 2H-β, 2H-3", 2H-5"), 3.64-3.66 (m, 4H, 2H-2", 2H-6"), 5.06 (br. s, 2H, NH_2), 7.74-7.81 (m, 4H, H-7, H-3', H-5', H-6'), 8.18 (dd, *J* 9.2, 2.1, 1H, H-6), 8.52 (d, *J* 2.1, 1H, H-4). ^{13}C NMR (150 MHz), DMSO-d_6, δ, ppm: 36.44, 42.44, 45.92, 65.27, 112.21, 117.74, 120.49, 120.95, 127.37, 129.13, 131.73, 132.37, 141.69, 143.89, 145.02, 143.33. Found (%): C, 52.69; H, 4.64; N, 16.00; S, 7.11. Calc. for $C_{19}H_{21}N_5O_5S$ (%): C, 52.89; H, 4.91; N, 16.23; S, 7.43.

N-[2-(1-Benzoyl-5-nitro-1H-indazol-3-yl)phenethyl]benzamide **6a**.



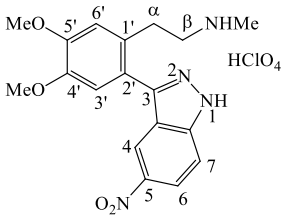
A mixture of 2-[2-(5-nitro-1*H*-indazol-3-yl)phenyl]ethanamine hydrochloride **5a**·HCl (0.32 g, 0.001 mol), benzoyl chloride (0.35 g, 0.29 mL, 0.0025 mol) in pyridine (10 mL) was stirred at room temperature for 1 h. Diethyl ether (5 mL) was added; the precipitate was filtered off and washed with diethyl ether (2×5 mL) and water (2×10 mL). Yield of compound **6a** was 0.35 g (72%). Colorless crystals, mp 209-211°C (EtOH). ^{1}H NMR (600 MHz), DMSO-d_6, δ, ppm: 3.16 (t, *J* 6.7, 2H, 2H-α), 3.33-3.36 (m, 2H, 2H-β), 7.20-7.23 (m, 2H, H-4', H-6'), 7.33-7.37 (m, 1H, H-5'), 7.44-7.46 (m, 3H, H-3''- H-5''), 7.52-7.57 (m, 4H, H-3', H-3'''- H-5'''), 7.59 (d, *J* 7.5, 1H, H-6''), 7.63-7.67 (m, 1H, H-2''), 8.08-8.10 (m, 2H, H-2''', H-6'''), 8.18-8.20 (m, 1H, NH), 8.36 (d, *J* 2.2, 1H, H-4), 8.41 (dd, *J* 9.1, 2.1, H-6), 8.53 (d, *J* 9.1, 1H, H-7). ^{13}C NMR (150 MHz), DMSO-d_6, δ, ppm: 31.81, 41.19, 115.93, 117.91, 124.47, 125.40, 126.58, 126.69, 127.79, 127.94, 128.92, 129.92, 130.30, 130.64, 130.66, 131.13, 132.39, 132.60, 133.75, 139.34, 142.55, 144.43, 150.92, 165.56, 167.95. Found (%): C, 71.23; H, 4.76; N, 11.16. Calc. for $C_{29}H_{22}N_4O_4$ (%): C, 71.01; H, 4.52; N, 11.42.

N-[2-(1-Benzoyl-5-nitro-1H-indazol-3-yl)-4,5-dimethoxyphenethyl]benzamide **6b**.



Compound **6b** was synthesized from 2-[4,5-dimethoxy-2-(5-nitro-1*H*-indazol-3-yl)phenyl]ethanamine hydrochloride **5b**·HCl (0.38 g, 0.001 mol) analogously to benzamide **6a.** Yield was 0.36g (66%). Colorless crystals with mp 158-161 °C (EtOH). ^{1}H NMR (600 MHz), DMSO-d_6, δ, ppm: 3.07 (t, *J* 6.5, 2H, 2H-α), 3.32-3.36 (m, 5H, 2H-β, overlapped with signal of water), 3.75 (s, 3H, OMe), 3.80 (s, 3H, OMe), 7.07-7.10 (m, 2H, H-3', 6'), 7.20-7.23 (m, 2H, H-3'', H-5''), 7.33-7.35 (m, 1H, H-4''), 7.44-7.46 (m, 2H, H-3'''-5'''), 7.53-7.56 (m, 2H, H-2''', H-6'''), 7.64-7.65 (m, 1H, H-4'''), 8.07-8.09 (m, 2H, H-2'', H-6''), 8.18 (t, *J* 5.6, 1H, NH), 8.37-8.39 (m, 2H, H-6, H-7), 8.49-8.51 (m, 1H, H-4). ^{13}C NMR (150 MHz), DMSO-d_6, δ, ppm: 31.37, 41.32, 55.48, 55.85, 113.59, 114.33, 115.83, 118.16, 120.70, 124.39, 125.66, 126.59, 127.79, 127.79, 127.95, 130.66, 132.22, 132.42, 132.60, 133.83, 142.51, 144.42, 147.23, 149.80, 151.05, 165.57, 167.90. Found (%): C, 67.29; H, 4.50; N, 10.00. Calc. for $C_{31}H_{26}N_4O_4$ (%): C, 67.63; H, 4.76; N, 10.18.

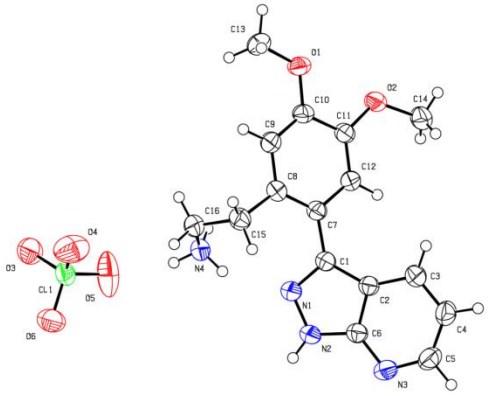
2-(4,5-Dimethoxy-2-(5-nitro-1H-indazol-3-yl)phenyl)-N-methylethanamine hydroperchlorate **8**·$HClO_4$.



A mixture of 1-(2-chloro-5-nitrophenyl)-6,7-dimethoxy-2-methyl-3,4-dihydroisoquinolin-2-ium perchlorate **7** (0.92 g, 0.002 mol), hydrazine hydrate (0.3 mL) in 2-methoxyethanol (4 mL) was refluxed for 4 h. The mixture was cooled, H_2O (10 mL) was added followed by saturated solution $NaHCO_3$ (5 mL), and extracted with $CHCl_3$ (3×5 mL). The extract was dried with K_2CO_3, and the volatiles were distilled off in vacuum. Yield of free base **8** was 0.58 g (82%). This was dissolved in Pr^nOH (10 mL), and 60% $HClO_4$ was added. The precipitate was filtered off and washed with EtOH (3×5 mL) and H_2O (2×5 mL). Colorless crystals **8**·$HClO_4$, mp 163-165 °C (EtOH). ^{1}H NMR (600 MHz), DMSO-d_6, δ, ppm: 2.50 (s, 4H, NMe, H_2O), 2.92-2.95 (m, 2H, 2H-α), 3.06-3.11 (m, 2H, 2H-β), 3.79 (s, 3H, OMe), 3.87 (s, 3H, OMe), 7.08 (s, 1H, H-6'), 7.12 (s, 1H, H-3'), 7.79-7.81 (m, 1H, H-6), 8.23-8.26 (m, 2H, H-7, NH_2^+), 8.52 (d, J 2.2, 1H, H-4), 13.83 (s, 1H, NH). ^{13}C NMR (150 MHz), DMSO-d_6, δ, ppm: 28.92. 32.53, 49.49, 55.67, 55.85, 111.38, 113.99, 114.04, 118.33, 121.12, 121.19, 123.01, 128.32, 141.90, 142.71, 146.65, 147.69, 149.24. Found (%): C, 47.06; H, 4.22; Cl,7.39; N, 12.00; S, 7.11. Calc. for $C_{18}H_{21}ClN_4O_8$ (%): C, 47.32; H, 4.63; Cl, 7.76; N, 12.26.

3. Structure and crystal data for compound 5c·$HClO_4$.

Table S1. Structure and crystal data for compound 5c.



CCDC Number	2047116
Empirical formula	$C_{16}H_{19}ClN_4O_6$
Formula weight	398.80
Temperature/K	293.0
Crystal system	triclinic
Space group	P-1
a/Å	9.5028(3)
b/Å	9.8960(3)
c/Å	10.6677(4)
α/°	82.837(3)
β/°	63.674(3)
γ/°	89.785(3)
Volume/$Å^3$	890.63(6)
Z	2
$\rho_{calc}g/cm^3$	1.487
μ/mm^{-1}	2.292
F(000)	416.0
Crystal size/mm^3	0.333 × 0.177 × 0.131
Radiation	CuKα (λ = 1.54184)
2Θ range for data collection/°	9.022 to 152.478
Index ranges	$-11 \leq h \leq 8$, $-11 \leq k \leq 12$, $-13 \leq l \leq 12$
Reflections collected	9923
Independent reflections	3612 [R_{int} = 0.0157, R_{sigma} = 0.0159]
Data/restraints/parameters	3612/0/320
Goodness-of-fit on F^2	1.066
Final R indexes [I>=2σ (I)]	R_1 = 0.0366, wR_2 = 0.1011
Final R indexes [all data]	R_1 = 0.0389, wR_2 = 0.1036
Largest diff. peak/hole / e $Å^{-3}$	0.28/-0.40

Table S2 Bond Lengths for 5c·HClO4.

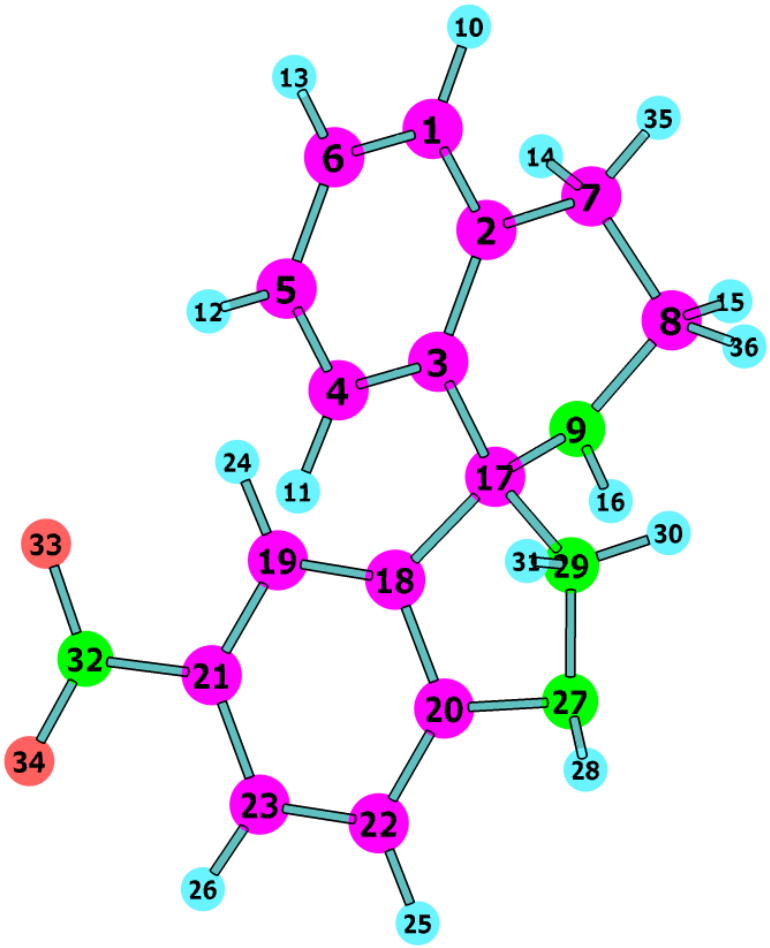
Atom	Atom	Length/Å	Atom	Atom	Length/Å
Cl1	O3	1.4325(14)	C1	C2	1.425(2)
Cl1	O6	1.4250(14)	C1	C7	1.474(2)
Cl1	O4	1.4231(15)	C2	C6	1.408(2)
Cl1	O5	1.4130(15)	C2	C3	1.395(2)
O2	C11	1.3629(17)	C7	C12	1.410(2)
O2	C14	1.425(2)	C7	C8	1.399(2)
O1	C10	1.3715(18)	C12	C11	1.375(2)
O1	C13	1.4263(19)	C11	C10	1.409(2)
N4	C16	1.491(2)	C8	C9	1.400(2)
N1	N2	1.3570(19)	C8	C15	1.520(2)
N1	C1	1.3285(19)	C10	C9	1.377(2)
N2	C6	1.353(2)	C3	C4	1.373(2)
N3	C6	1.338(2)	C15	C16	1.519(2)
N3	C5	1.330(2)	C4	C5	1.394(3)

Table S3 Bond Angles for 5c·HClO4.

Atom	Atom	Atom	Angle/°	Atom	Atom	Atom	Angle/°
O6	Cl1	O3	109.30(9)	C11	C12	C7	121.72(14)
O4	Cl1	O3	109.27(10)	O2	C11	C12	125.70(13)
O4	Cl1	O6	109.17(11)	O2	C11	C10	115.34(13)
O5	Cl1	O3	109.97(11)	C12	C11	C10	118.94(13)
O5	Cl1	O6	109.73(12)	C7	C8	C9	118.69(13)
O5	Cl1	O4	109.37(12)	C7	C8	C15	123.84(14)
C11	O2	C14	117.48(13)	C9	C8	C15	117.44(13)
C10	O1	C13	117.44(13)	N2	C6	C2	106.81(13)
C1	N1	N2	107.11(13)	N3	C6	N2	125.67(15)
C6	N2	N1	111.42(13)	N3	C6	C2	127.50(15)
C5	N3	C6	112.88(14)	O1	C10	C11	114.98(13)
N1	C1	C2	110.04(13)	O1	C10	C9	125.37(13)
N1	C1	C7	120.92(13)	C9	C10	C11	119.65(14)
C2	C1	C7	128.98(13)	C10	C9	C8	121.81(14)
C6	C2	C1	104.61(13)	C4	C3	C2	116.89(15)
C3	C2	C1	138.42(14)	C16	C15	C8	115.43(13)
C3	C2	C6	116.94(14)	N4	C16	C15	112.61(13)
C12	C7	C1	116.81(13)	C3	C4	C5	120.64(16)
C8	C7	C1	124.12(13)	N3	C5	C4	125.14(15)
C8	C7	C12	119.05(13)				

4. Quantum chemical data

Spirostructure **B** with frozen chemical bond C(17)—N(29)



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C	1.824035409800	0.290047450300	0.250831964200
C	1.579520727700	1.051383132900	1.406332135400
C	2.430319451100	2.093257402400	1.761091807400
C	3.533626710300	2.382853320100	0.954641926600
C	3.199249043400	-0.209282566200	-1.831421291000
C	2.524631380300	-1.576493034000	-1.791127473700
N	1.131187197500	-1.392777413600	-1.382386403000
H	4.633440738800	1.863589014100	-0.816988249600
H	0.697219715800	0.857662405400	2.013267265600
H	2.227054614300	2.682588919800	2.648798826700
H	4.203041867300	3.194647341300	1.219864347000
H	2.807392165900	0.350977131300	-2.689467430900
H	2.525600466200	-2.044061209500	-2.777562192900
H	0.482325570900	-2.113127657700	-1.674618615100
C	0.884788637000	-0.870951115700	-0.084656201400
C	-0.608993892100	-0.629163188900	0.104419310200

C	-1.407044685100	0.395379792200	-0.378486515800
C	-1.165969749700	-1.705858756800	0.791421649000
C	-2.773744095400	0.298249495900	-0.121186184800
C	-2.531149230600	-1.808654390000	1.040305093400
C	-3.340777324200	-0.773507747000	0.571304137200
H	-1.011832889700	1.243271714400	-0.924139527100
H	-2.958471319400	-2.652328162800	1.570945034700
H	-4.411322845700	-0.781828242900	0.735153748700
N	-0.152736738500	-2.661107567700	1.105544742300
H	-0.204690693400	-3.090301277000	2.027702228400
N	1.084422855400	-1.897042985400	0.975159233400
H	1.848424305200	-2.532911893300	0.718881375200
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O	-4.856312985200	1.272424849000	-0.368712313300
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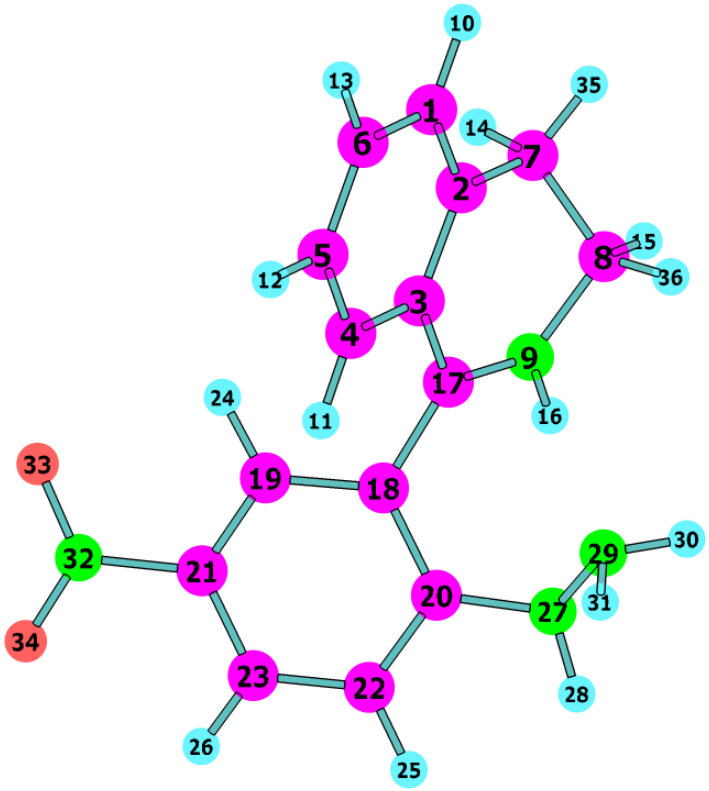
Spirostructure **B** full optimization:



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C	-1.413684322000	1.269107523600	-1.198315524600

C	-2.249208046800	2.304457007600	-1.595431884200
C	-3.418193008800	2.565178562200	-0.874536634000
C	-3.264748342800	-0.115109285500	1.848409008700
C	-2.746365331300	-1.534964047900	1.647447635200
N	-1.339877789700	-1.483595668900	1.216095565300
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C	-0.878800029800	-0.600976277400	0.354909991600
C	0.544252887800	-0.693376819400	-0.032225660300
C	1.348661100900	0.430517323500	0.203101347700
C	1.144786573400	-1.899892143700	-0.487907564300
C	2.723075673300	0.343904235900	0.045190063600
C	2.543469139200	-1.948498234500	-0.630598421700
C	3.334673917800	-0.843889129600	-0.354901878800
H	0.921909240300	1.364530083100	0.546976852800
H	3.008161714700	-2.863239865700	-0.986796856500
H	4.411227934000	-0.875765525200	-0.471079480900
N	0.392683862600	-3.036701050300	-0.777442510200
H	0.952792347000	-3.789955979900	-1.168350234300
N	-0.861417922400	-2.824674316600	-1.409255215900
H	-1.476989156100	-3.594437435800	-1.160997472500
H	-0.753330116800	-2.824225271600	-2.424446100100
N	3.545458605200	1.533965114200	0.310759414100
O	2.956614894900	2.560663552000	0.644625219300
O	4.759770357200	1.416229538900	0.178399217900
H	-4.342441878800	-0.144861532100	2.028408093500
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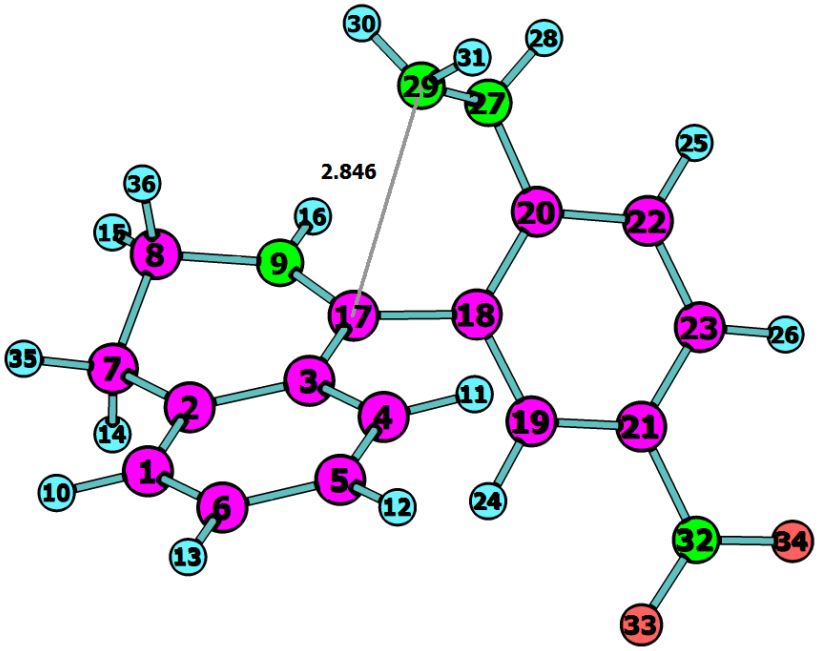
Protonated hydrazine **4a**:



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36
symmetry c1

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C	1.751581763	-0.441156499	-0.163196995
C	1.388171543	-1.215944953	-1.284054080
C	2.227418873	-2.226365455	-1.734194355
C	3.430286263	-2.475153183	-1.066870459
C	3.336725187	0.155031883	1.707061985
C	2.785112551	1.567763895	1.549303402
N	1.362772899	1.495856028	1.176836511
H	4.743836506	-1.908563488	0.544904837
H	0.460443489	-1.008392035	-1.804224712
H	1.949688978	-2.817561786	-2.599788341
H	4.086611667	-3.266907760	-1.414032268
H	2.920524918	-0.306322493	2.612930519
H	2.859155232	2.137694223	2.476635110
H	0.743580219	2.237994759	1.484700795
C	0.881148810	0.615797552	0.324258374
C	-0.559430811	0.683066064	0.003158500
C	-1.325560076	-0.466270384	0.244396875
C	-1.209486218	1.886008989	-0.390440367
C	-2.707543589	-0.409722771	0.152797934
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H	-0.861499723	-1.397959708	0.543233083
H	-3.116356979	2.815301989	-0.775927458
H	-4.446425211	0.780619306	-0.251140949

N	-0.499449691	3.049701079	-0.680882960
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H	1.333471651	3.665995593	-1.144009975
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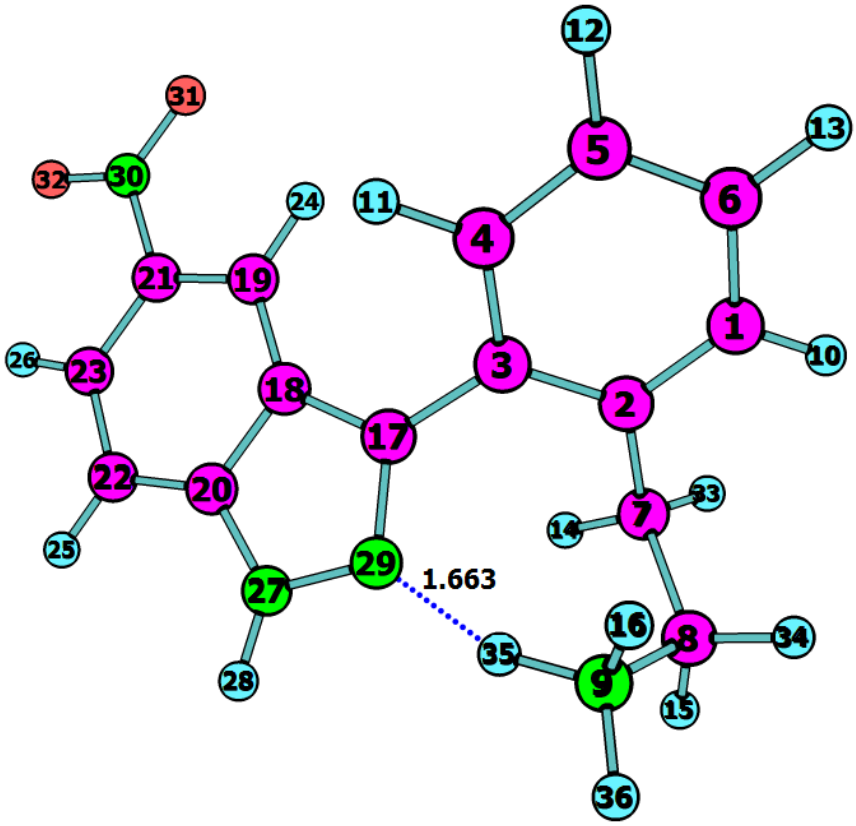
Protonated indazolylphenylethylamine **5a**:



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36

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C	-1.323315484	-1.670440853	0.938432298
C	-2.203973279	-2.747794766	0.932187684
C	-3.363137815	-2.688683651	0.158355257
C	-3.094015028	0.741135874	-1.485120079
C	-4.072738836	1.730085937	-0.830735147
N	-3.612876519	2.083128367	0.568004245

H	-4.516508106	-1.522727187	-1.226367735
H	-0.430027495	-1.712424909	1.552885147
H	-1.984396778	-3.628172357	1.526993823
H	-4.052158138	-3.526636680	0.136786397
H	-2.187956168	1.276013295	-1.777852310
H	-4.128865555	2.663007349	-1.395306004
H	-3.803656888	1.304072319	1.204474301
C	-0.581218346	0.577284007	0.240232990
C	0.847297229	0.469094892	0.164680796
C	1.750086631	-0.587128821	-0.042664529
C	1.331687370	1.793507136	0.312396903
C	3.091370556	-0.263371124	-0.067184335
C	2.703116242	2.105198511	0.284163717
C	3.577951914	1.053986183	0.095503934
H	1.437104289	-1.613507042	-0.184916288
H	3.063862298	3.120919954	0.401001755
H	4.648401984	1.213054010	0.062257907
N	0.230266028	2.583221874	0.455265196
H	0.189420149	3.579560033	0.603310883
N	-0.919690305	1.855502090	0.416013721
N	4.069558882	-1.349359800	-0.279431240
O	3.626484256	-2.487578331	-0.414587363
O	5.257145187	-1.039818602	-0.304959105
H	-3.571023070	0.398419539	-2.408602636
H	-5.078419776	1.313554134	-0.742878492
H	-2.536910420	2.208951654	0.573657299
H	-4.086951547	2.912335437	0.931343813

5. References

[S1] http://chem.ch.huji.ac.il/nmr/software/solvent.html.

[S2] *CrysAlisPro, version 1.171.38.41, Rigaku Oxford Diffraction*, Oxford, 2015.

[S3] G. M. Sheldrick, *Acta Crystallogr., Sect. A: Found. Adv.*, 2015, **71**, 3.

[S4] G. M. Sheldrick, *Acta Crystallogr., Sect. C: Struct. Chem.*, 2015, **71**, 3.

[S5] O. V. Dolomanov, L. J. Bourhis,; R. J. Gildea, J. A. K. Howard and H. J. Puschmann, *Appl. Crystallogr.*, 2009, **42**, 339.

[S6] A. A. Granovsky, *Firefly version 8*, http://classic.chem.msu.su/gran/firefly/index.html

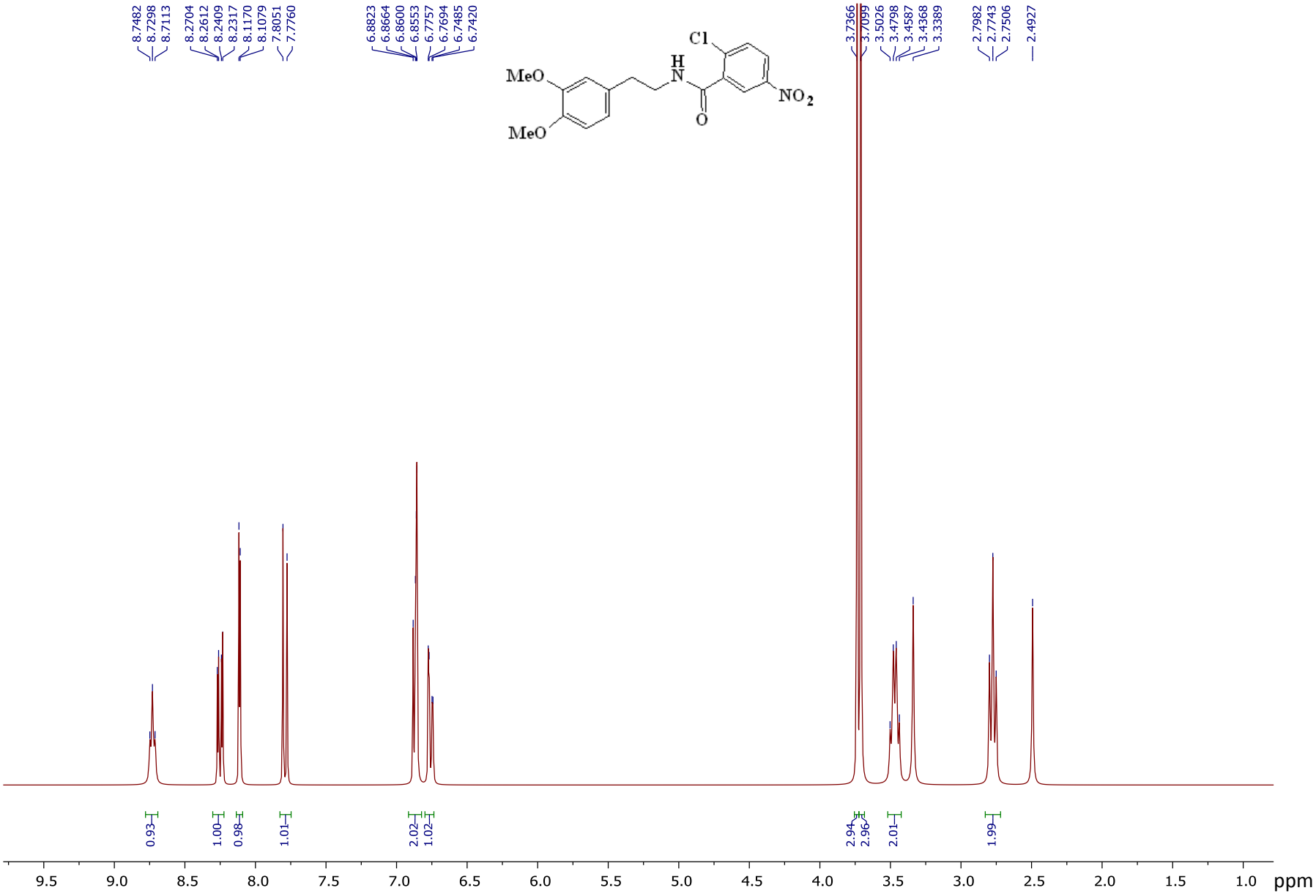
[S7] M. W. Schmidt, K. K. Baldridge, J. A. Boatz, S. T. Elbert, M. S. Gordon, J. H. Jensen, S. Koseki, N. Matsunaga, K. A. Nguyen, S. Su, T. L. Windus, M. Dupuis and J. A. Montgomery, *J. Comput. Chem.*, 1993, **14**, 1347.

[S8] A. Hannu, N. Hannu, PCT/FI87/00032, 1988, WO 88/07041; https://patentscope.wipo.int/search/en/detail.jsf?docId=WO1988007041

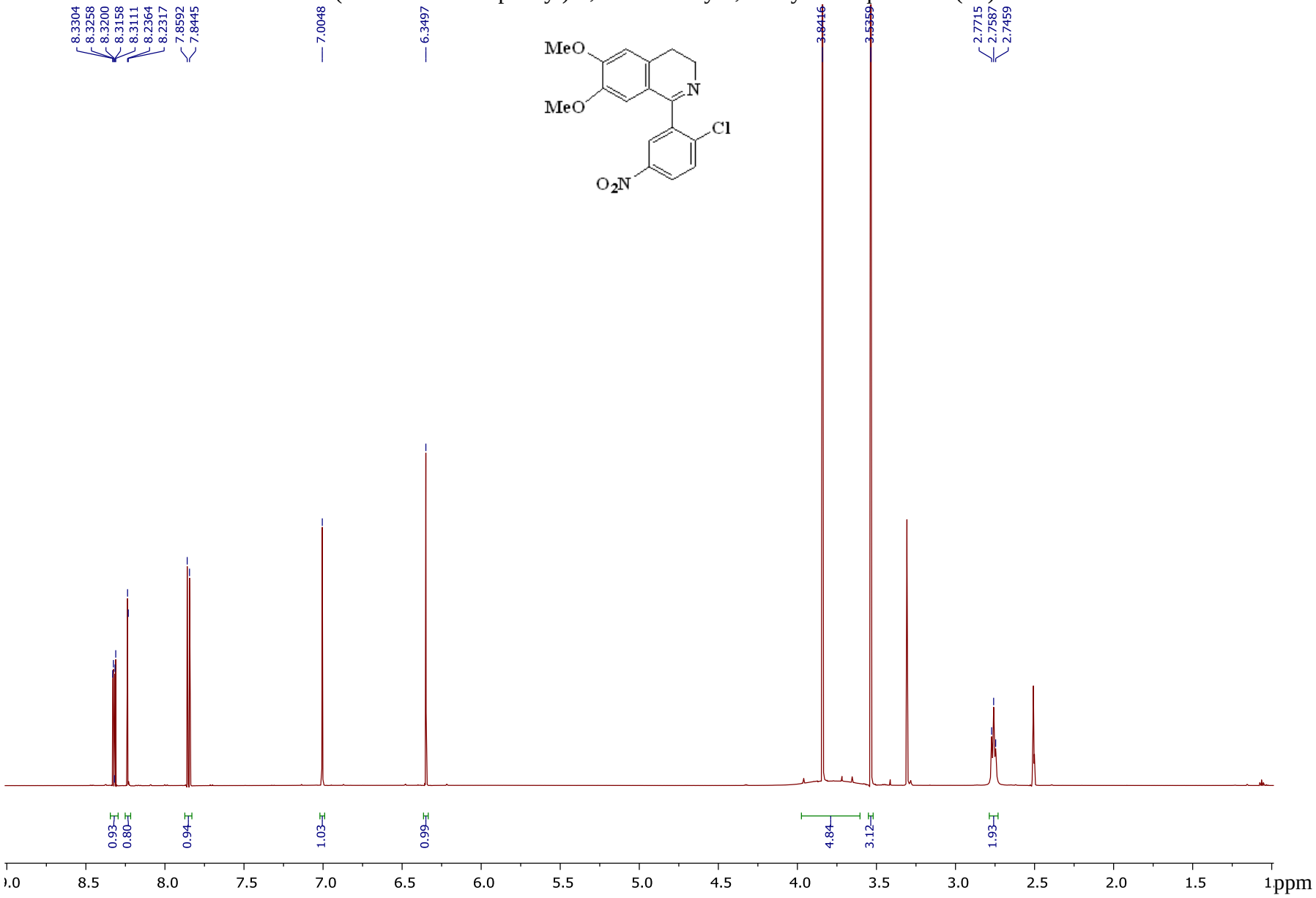
[S9] E. Suna, P. Trapencieris, *Chem. Heterocycl. Comp.*, 2000, **36**, 287.

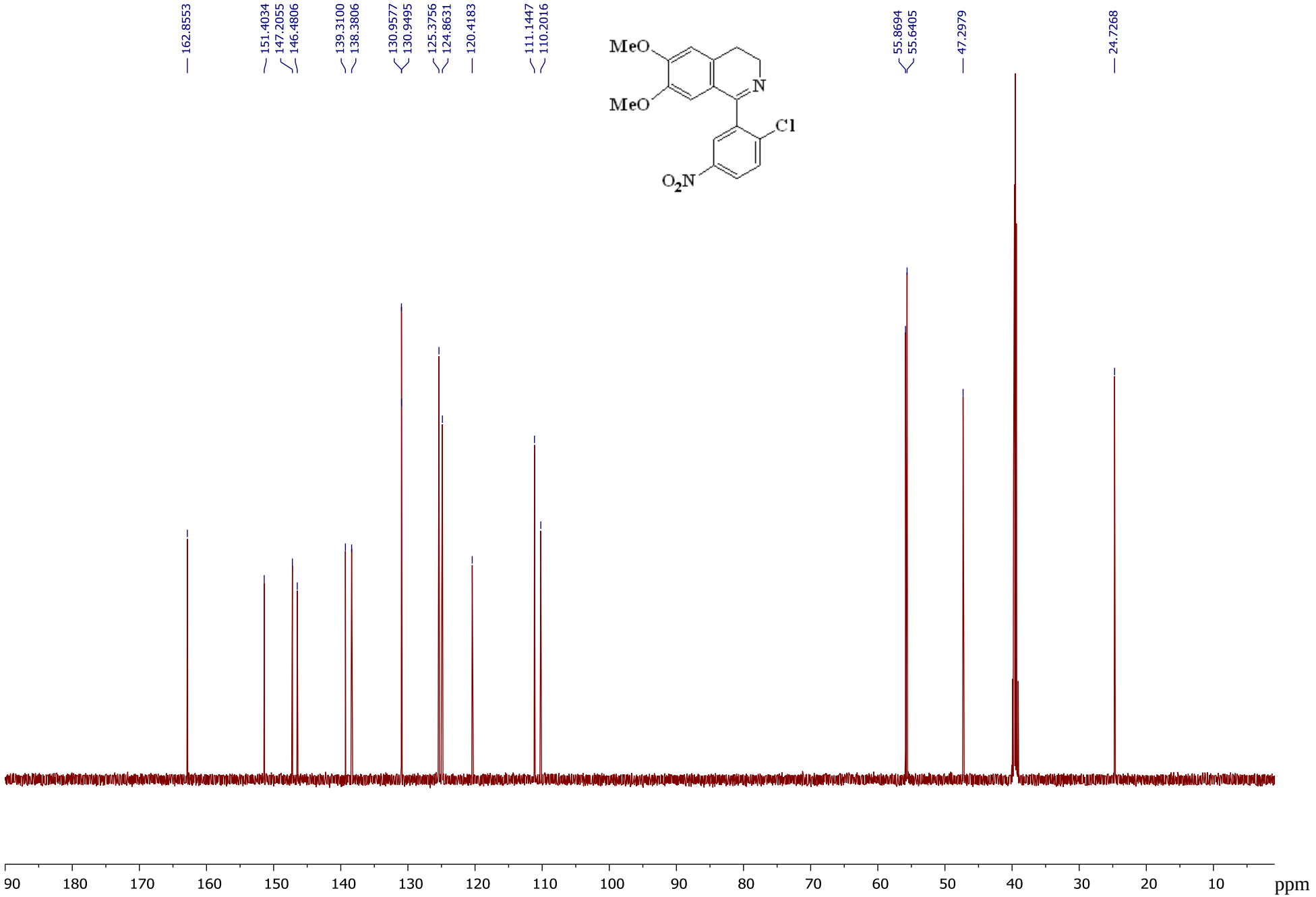
6. NMR Spectra of compounds 1-8.

2-Chloro-N-(3,4-dimethoxyphenethyl)-5-nitrobenzamide (**2b**).

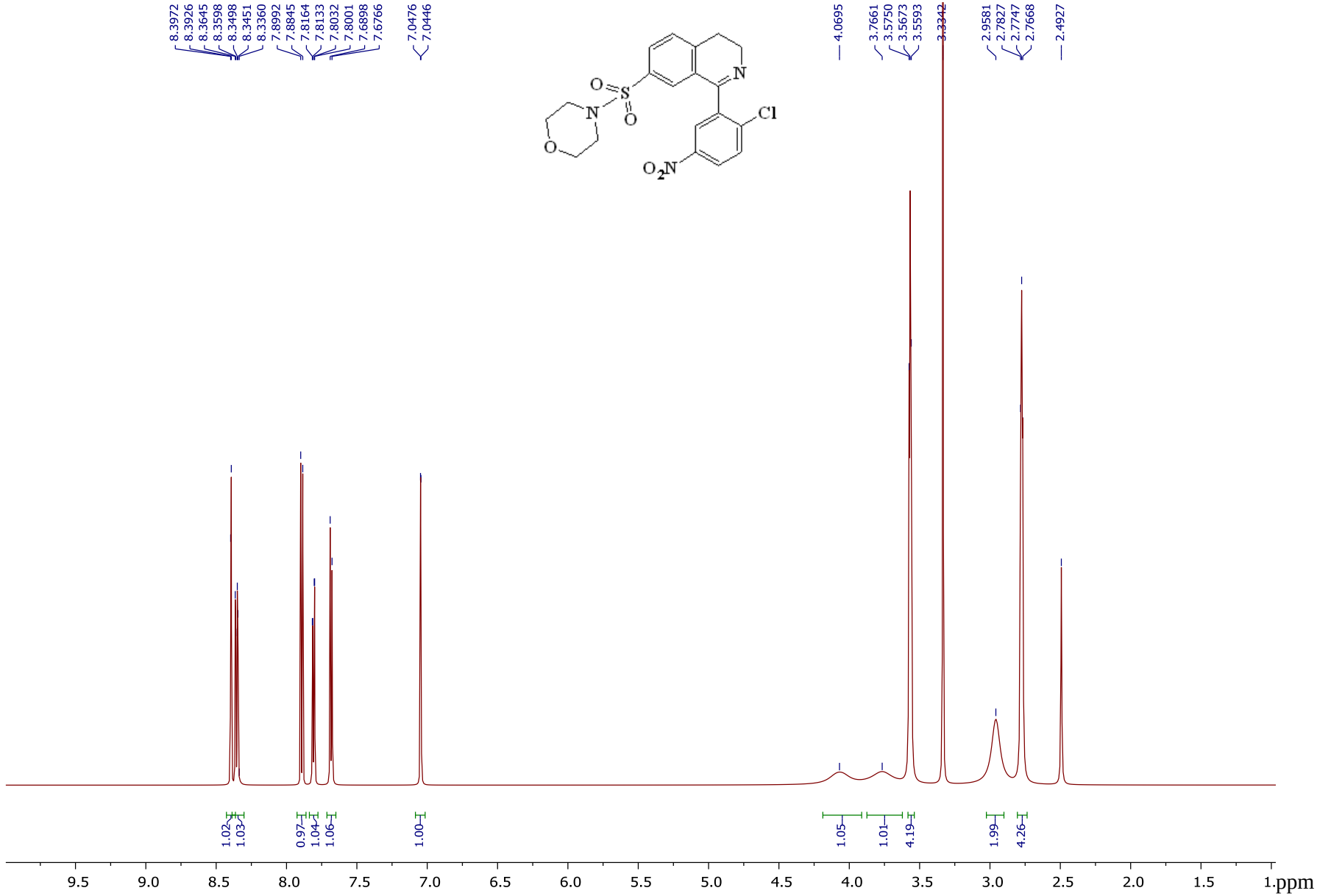


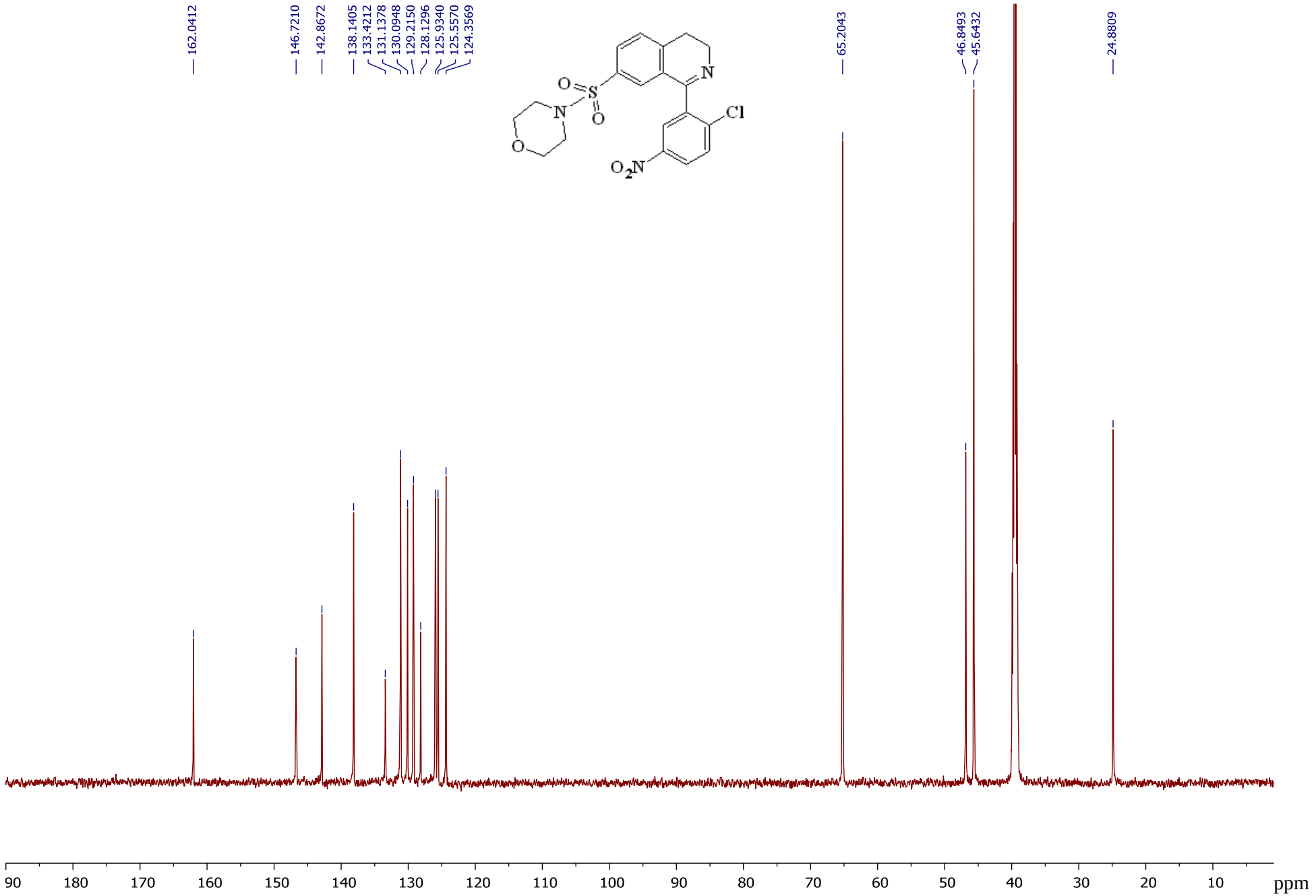
1-(2-Chloro-5-nitrophenyl)-6,7-dimethoxy-3,4-dihydroisoquinoline (**3b**).



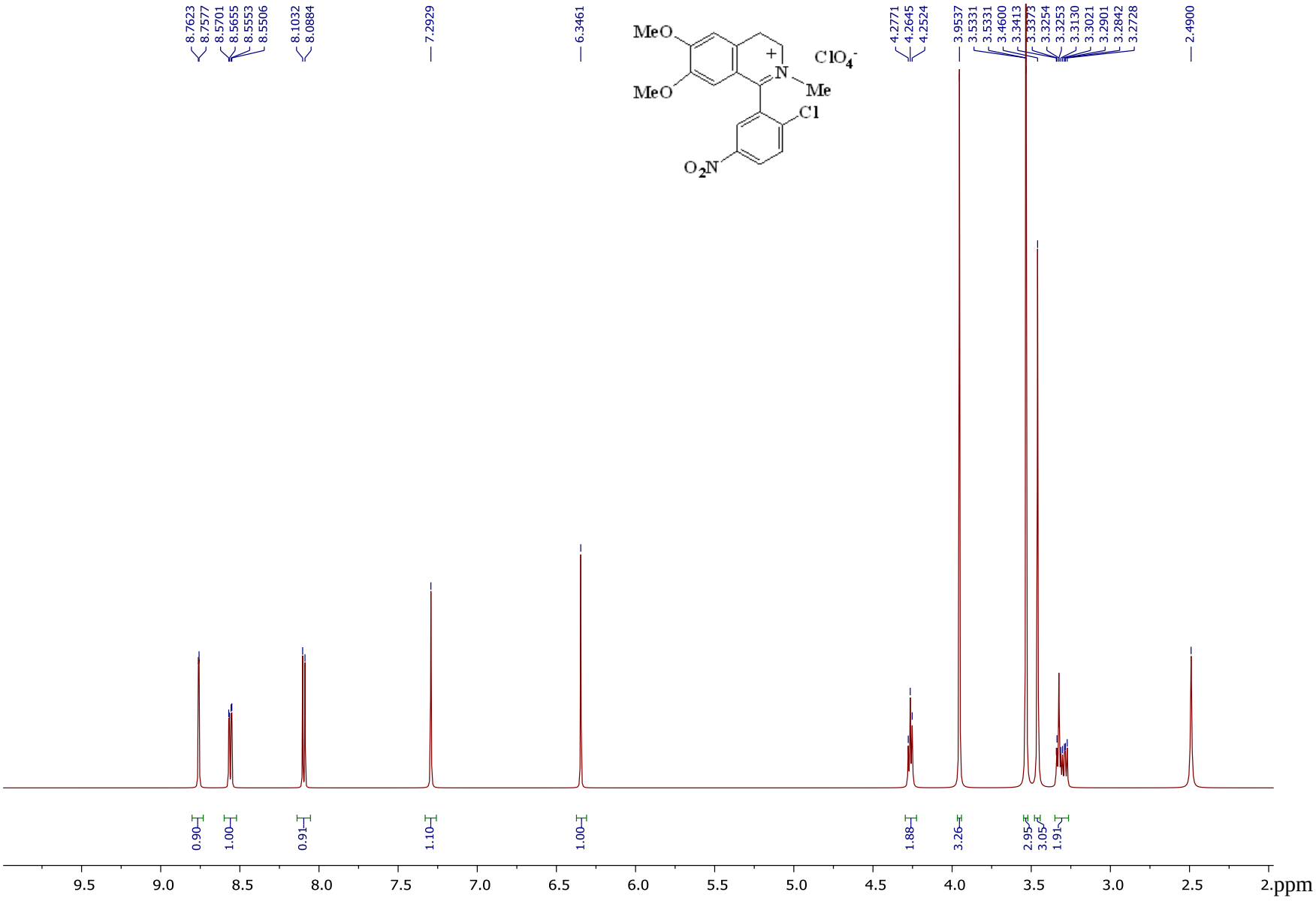

162.8553
151.4034
147.2055
146.4806
139.3100
138.3806
130.9577
130.9495
125.3756
124.8631
120.4183
111.1447
110.2016
55.8694
55.6405
47.2979
24.7268
MeO
MeO
N
Cl
O2N
90
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

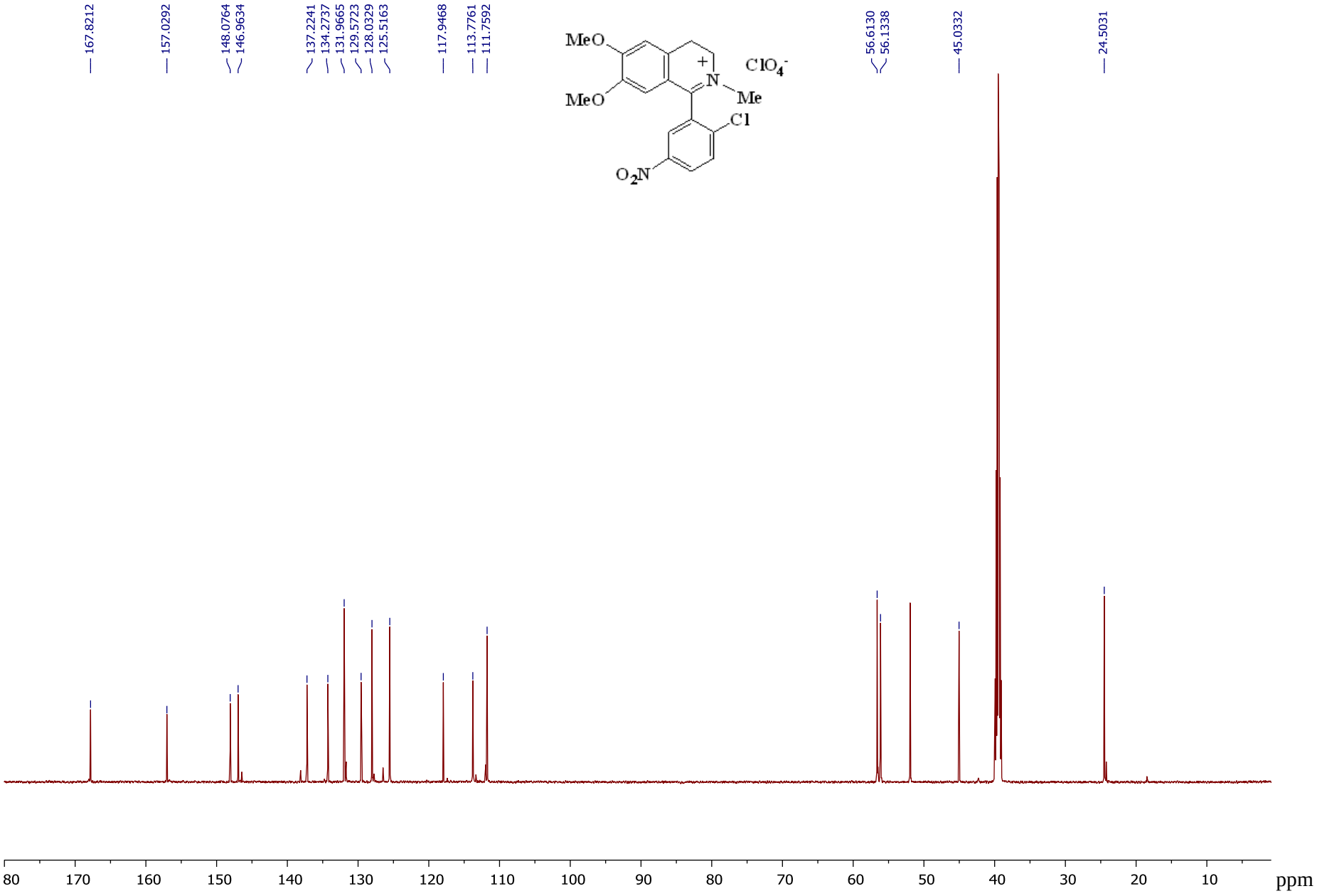
4-{[1-(2-Chloro-5-nitrophenyl)-3,4-dihydroisoquinolin-7-yl]sulfonyl}morpholine (**3d**).



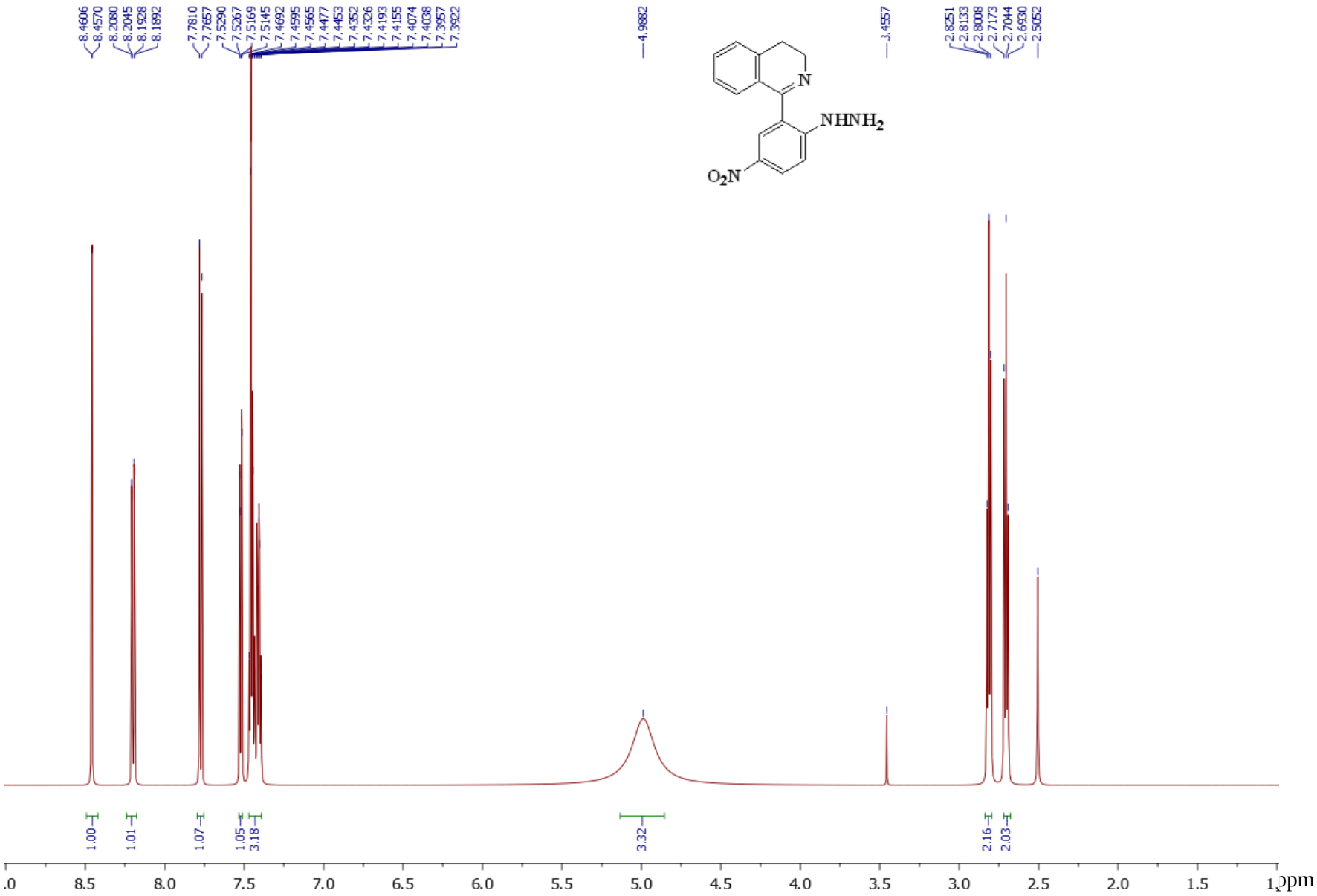

162.0412
146.7210
142.8672
138.1405
133.4212
131.1378
130.0948
129.2150
128.1296
125.9340
125.5570
124.3569
65.2043
46.8493
45.6432
24.8809
O
S
O
N
O
N
Cl
O2N
90
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

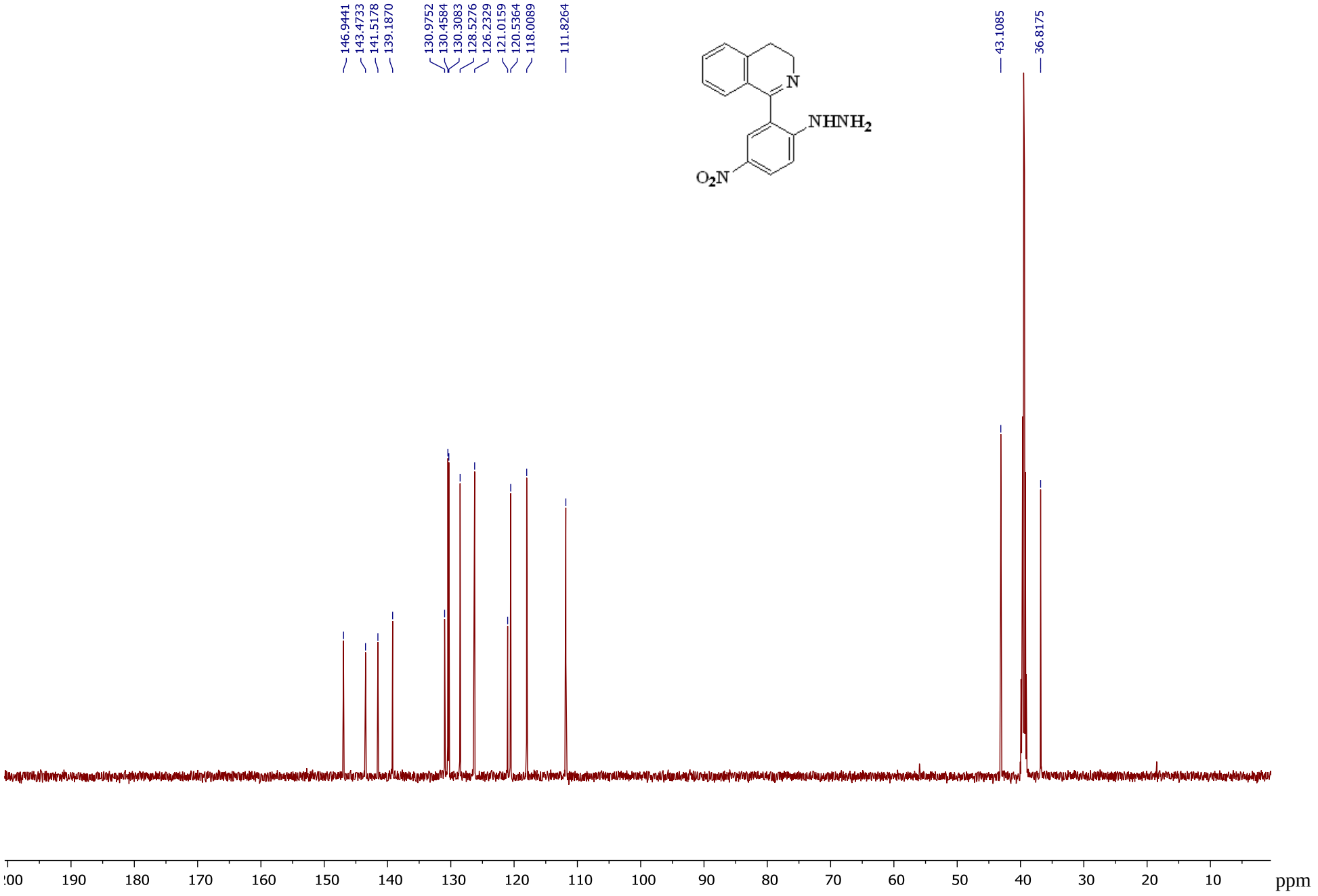
1-(2-Chloro-5-nitrophenyl)-6,7-dimethoxy-2-methyl-3,4-dihydroisoquinoline perchlorate (**7**).



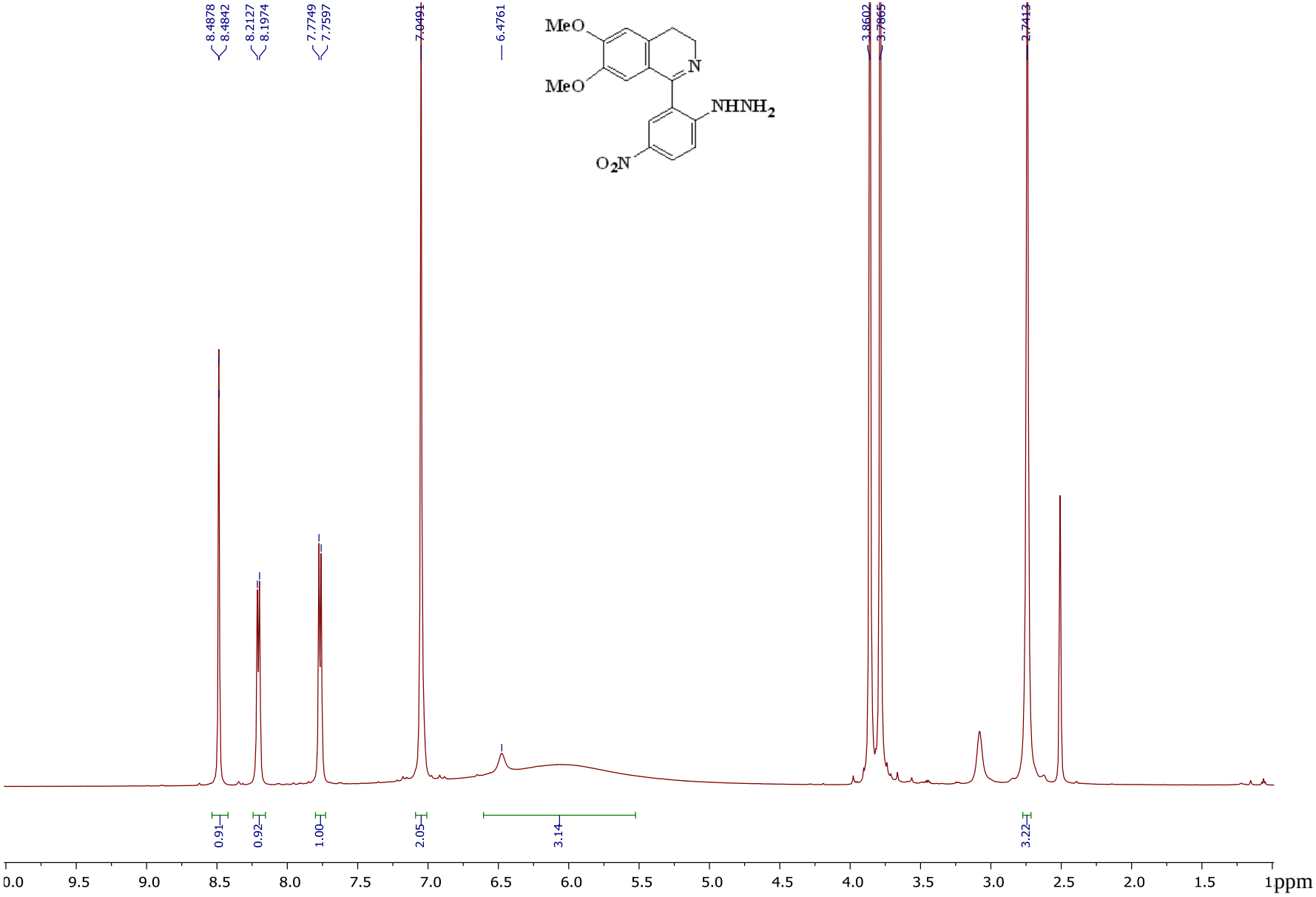

167.8212
157.0292
148.0764
146.9634
137.2241
134.2737
131.9665
129.5723
128.0329
125.5163
117.9468
113.7761
111.7592
56.6130
56.1338
45.0332
24.5031
MeO
MeO
N
Me
Cl
ClO_4^-
O_2N
80
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

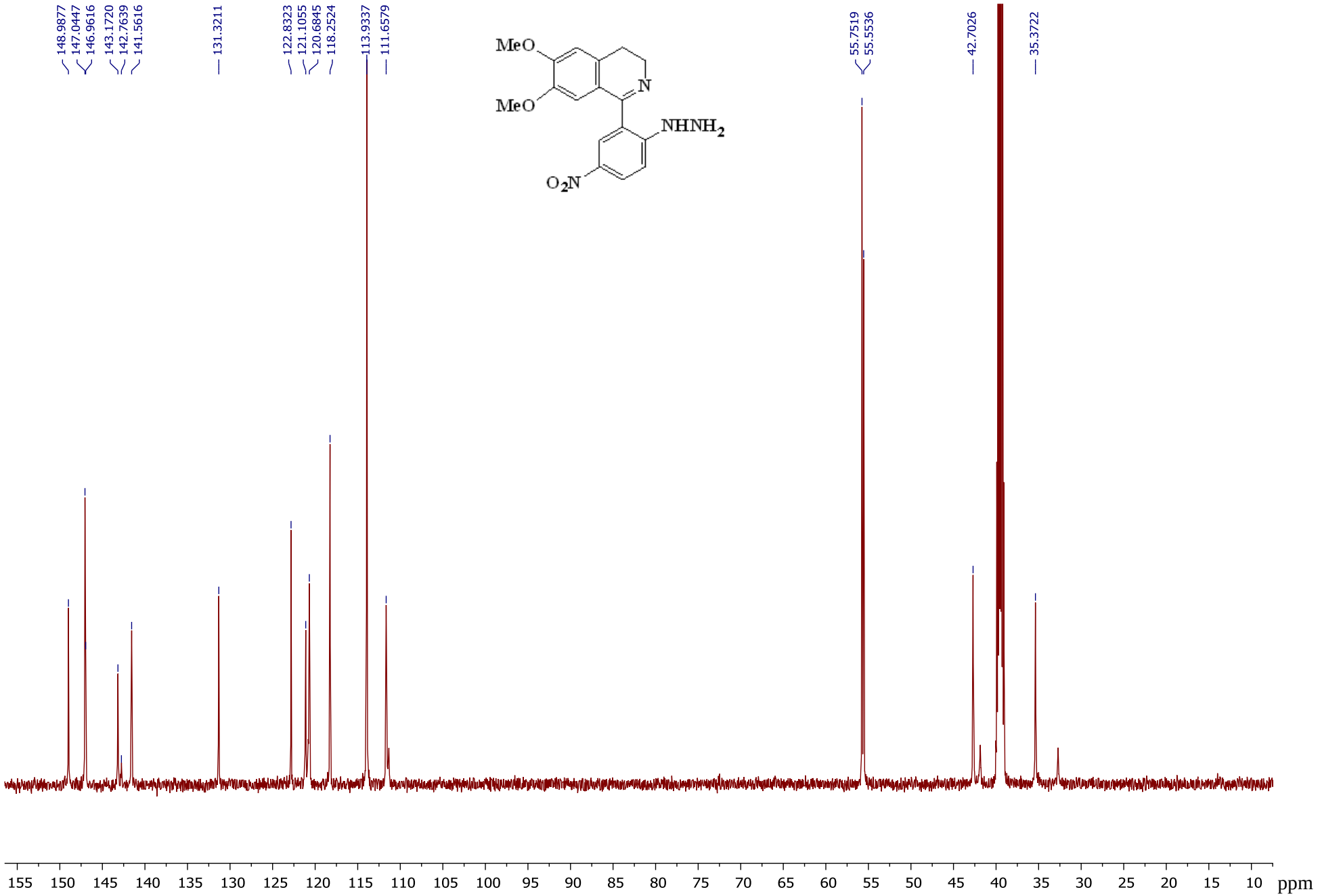
1-(2-Hydrazinyl-5-nitrophenyl)-3,4-dihydroisoquinoline (**4a**).



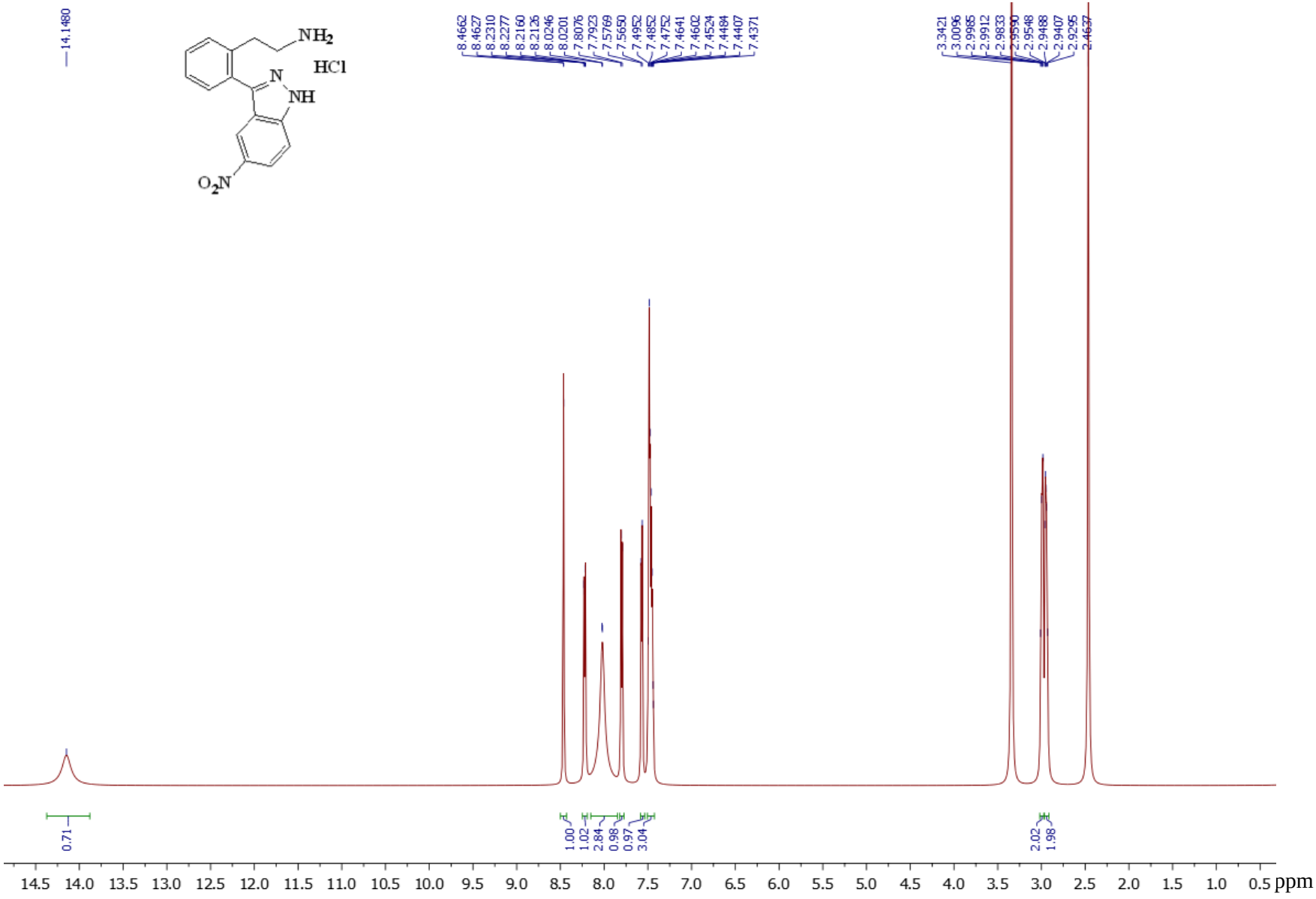

146.9441
143.4733
141.5178
139.1870
130.9752
130.4584
130.3083
128.5276
126.2329
121.0159
120.5364
118.0089
111.8264
43.1085
36.8175
N
NHNH2
O2N
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

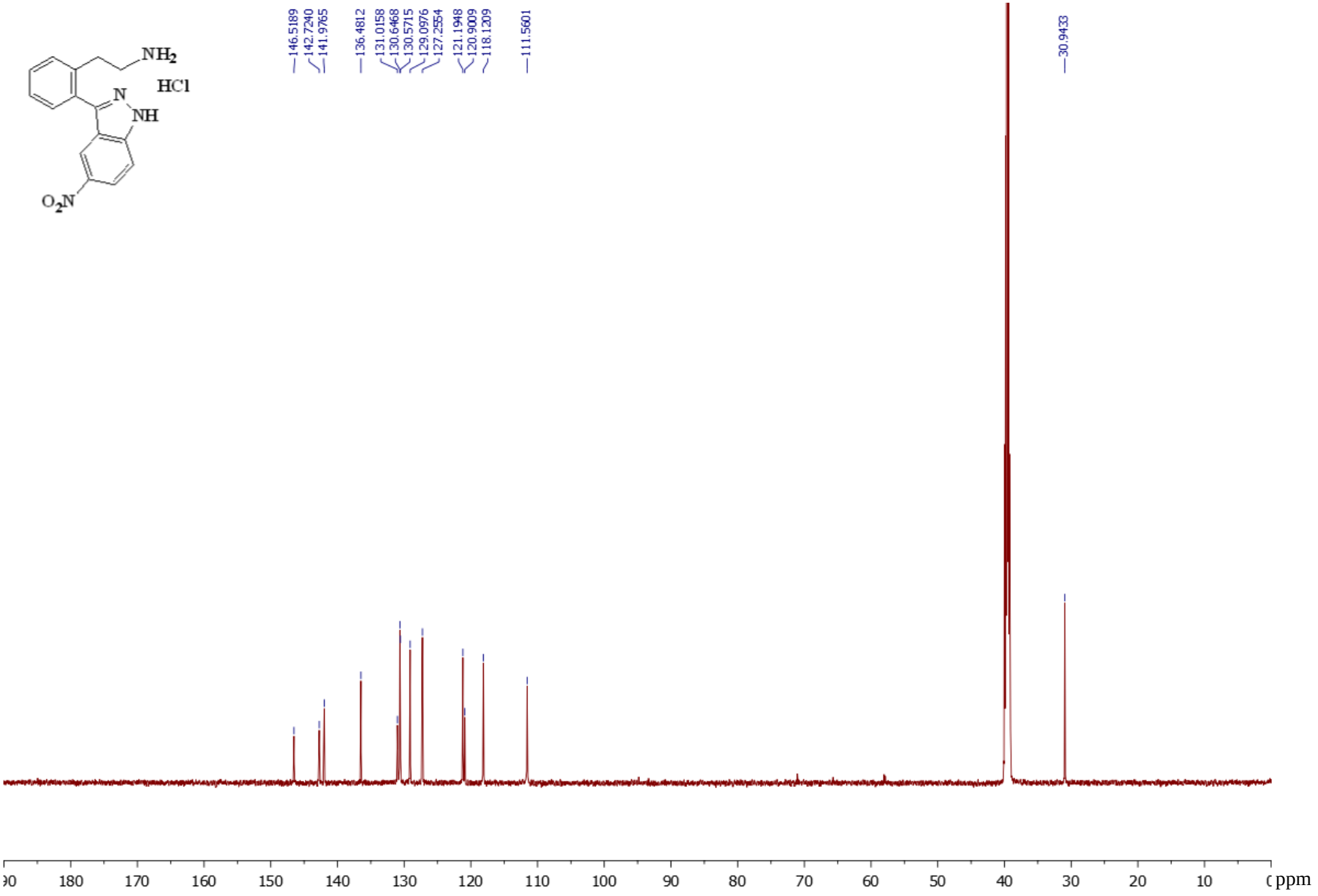
1-(2-Hydrazinyl-5-nitrophenyl)-6,7-dimethoxy-3,4-dihydroisoquinoline (**4b**).



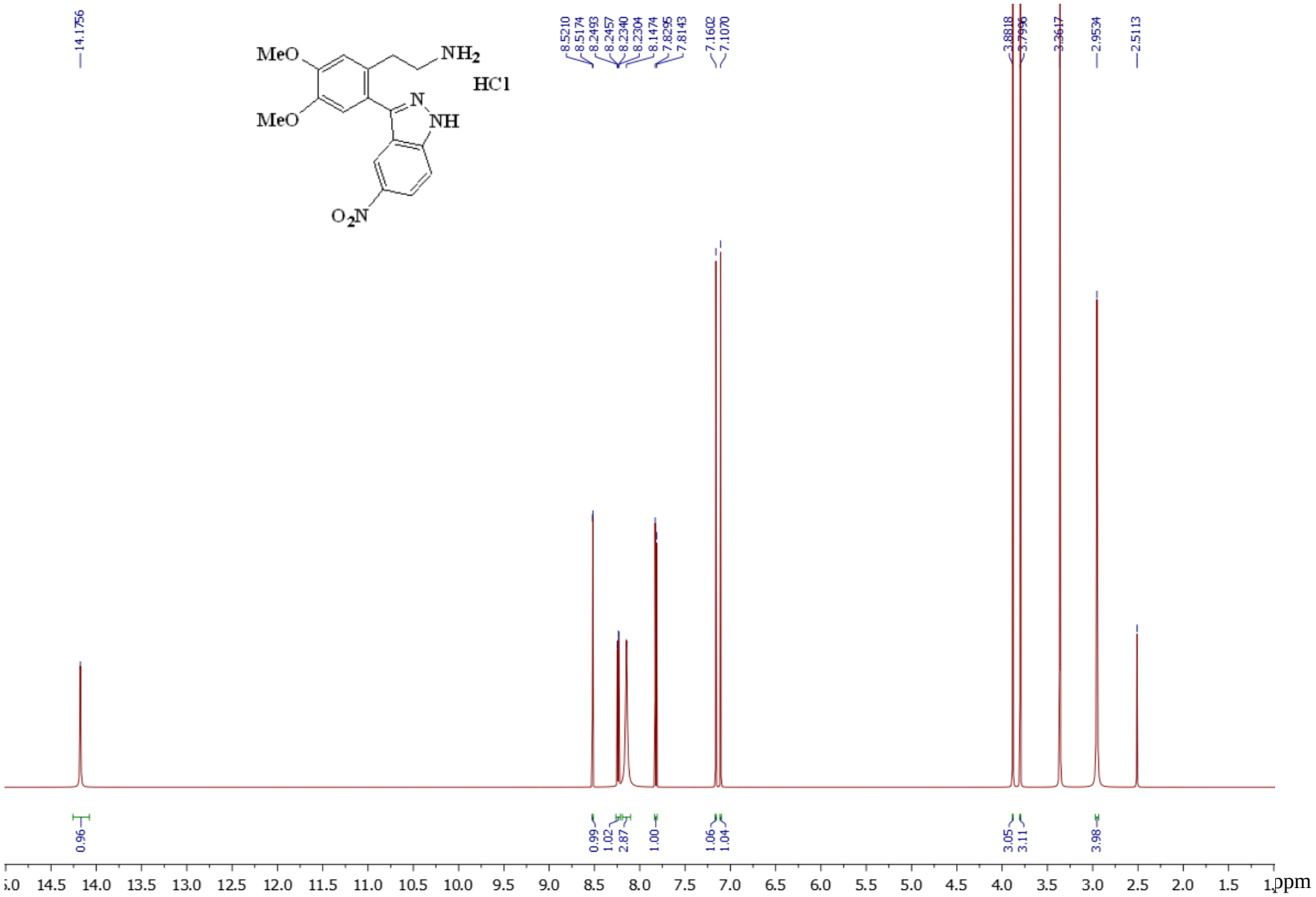

148.9877
147.0447
146.9616
143.1720
142.7639
141.5616
131.3211
122.8323
121.1055
120.6845
118.2524
113.9337
111.6579
55.7519
55.5536
42.7026
35.3722
MeO
MeO
N
NHNH2
O2N
155 150 145 140 135 130 125 120 115 110 105 100 95 90 85 80 75 70 65 60 55 50 45 40 35 30 25 20 15 10 ppm

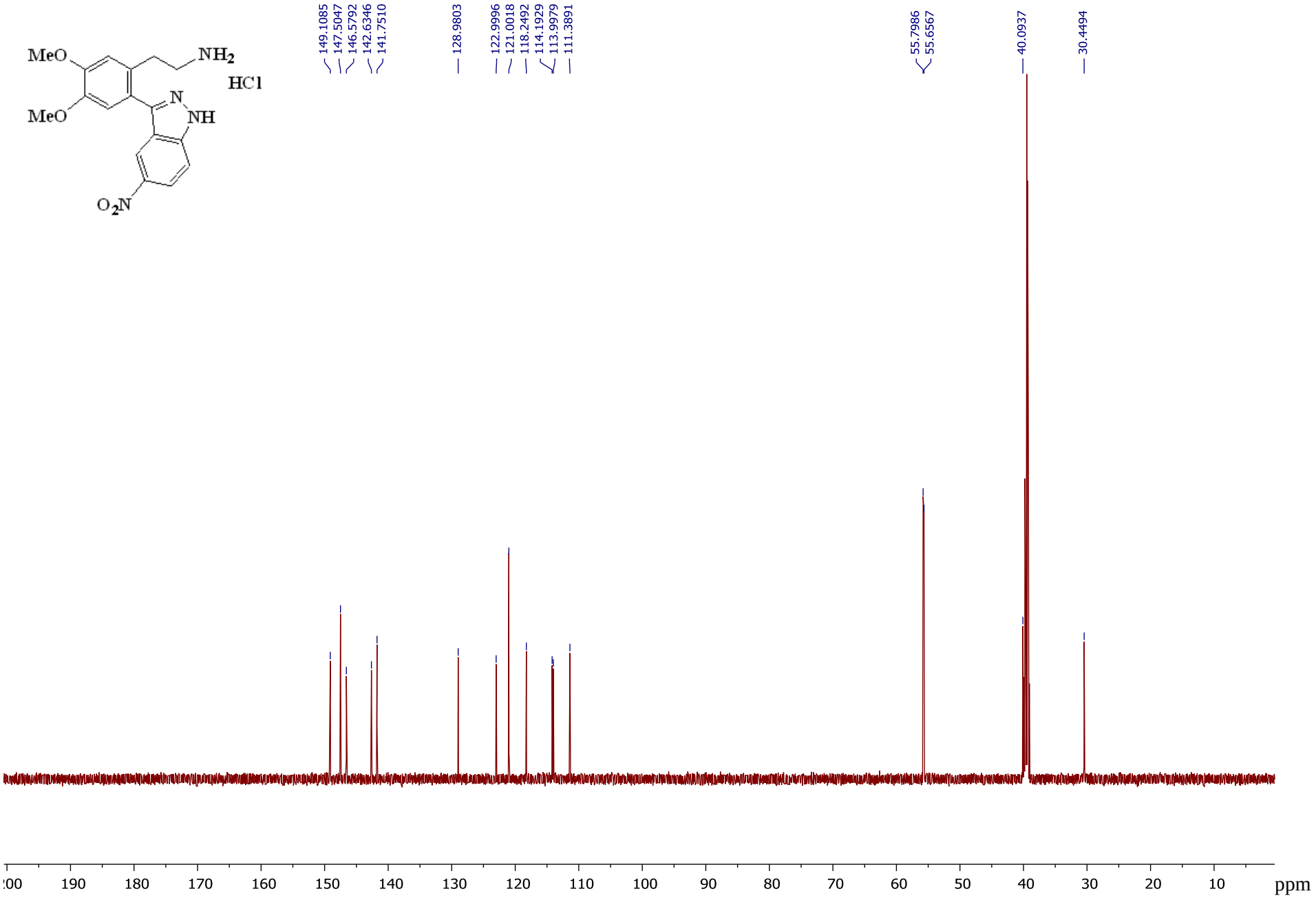
2-[2-(5-Nitro-1*H*-indazol-3-yl)phenyl]ethanamine hydrochloride (**5a**).



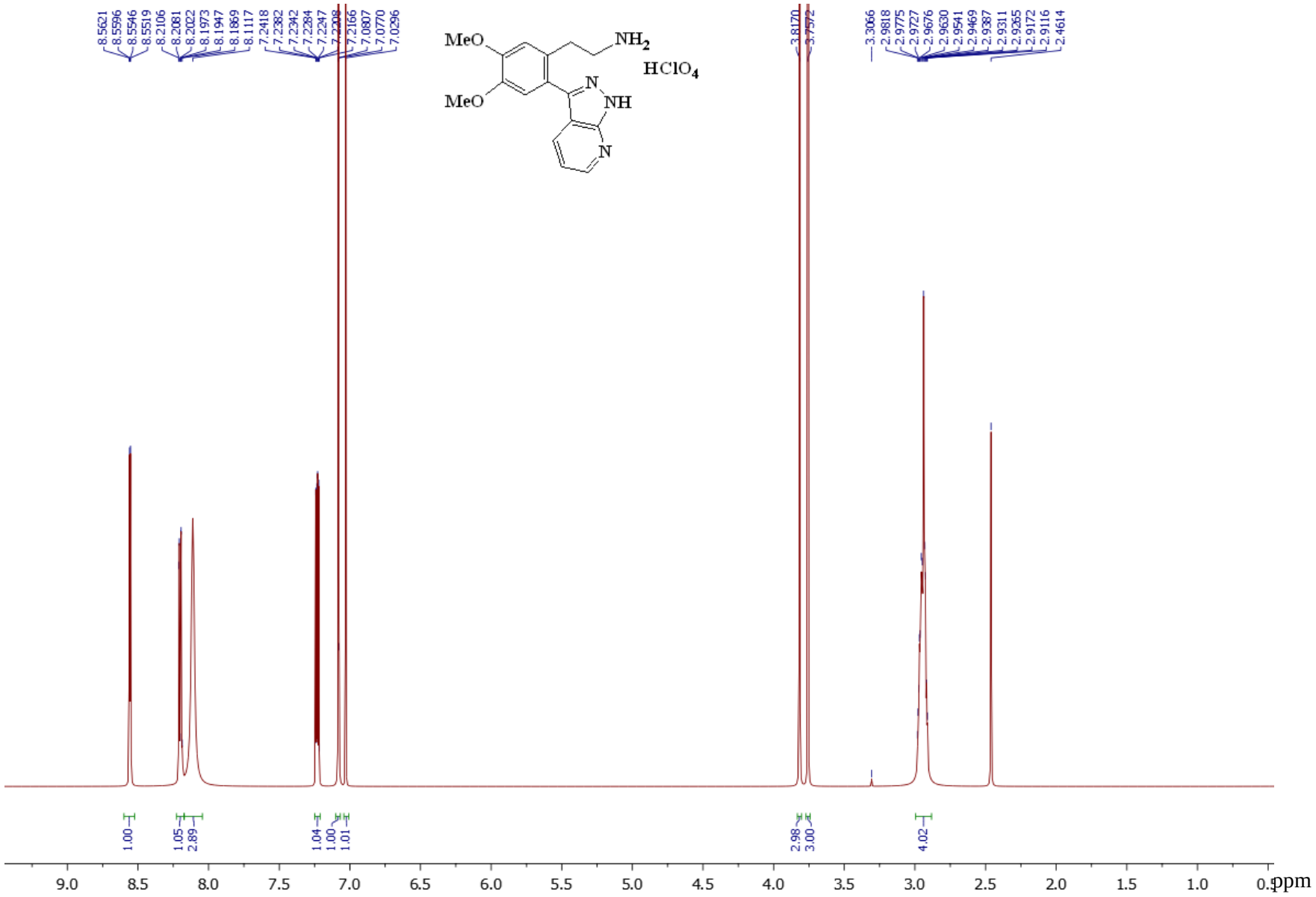

NH2
HCl
N
NH
O2N
146.5189
142.7240
141.9765
136.4812
131.0158
130.6468
130.5715
129.0976
127.2554
121.1948
120.9009
118.1209
111.5601
30.9433
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

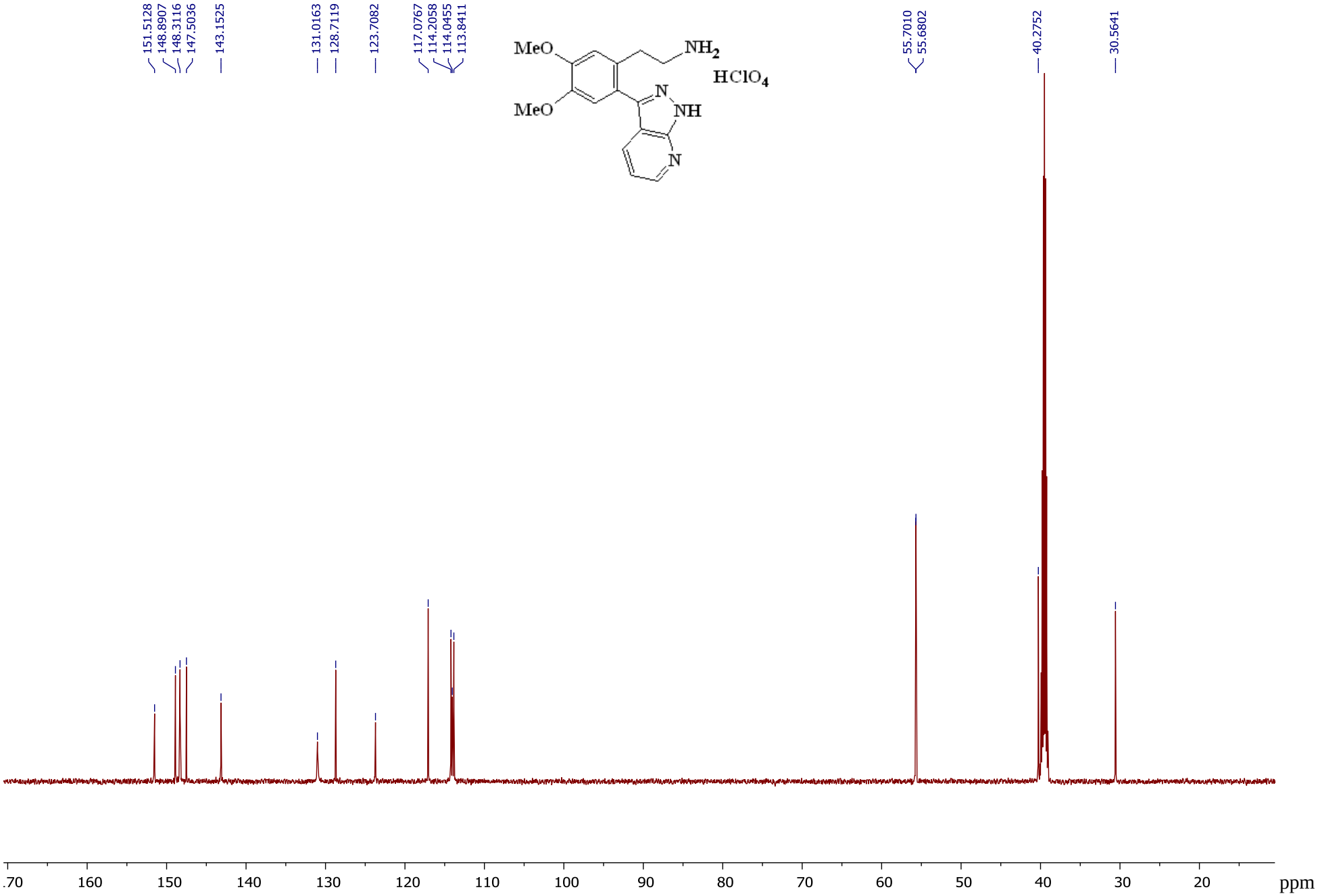
2-[4,5-Dimethoxy-2-(5-nitro-1*H*-indazol-3-yl)phenyl]ethanamine hydrochloride (**5b**).



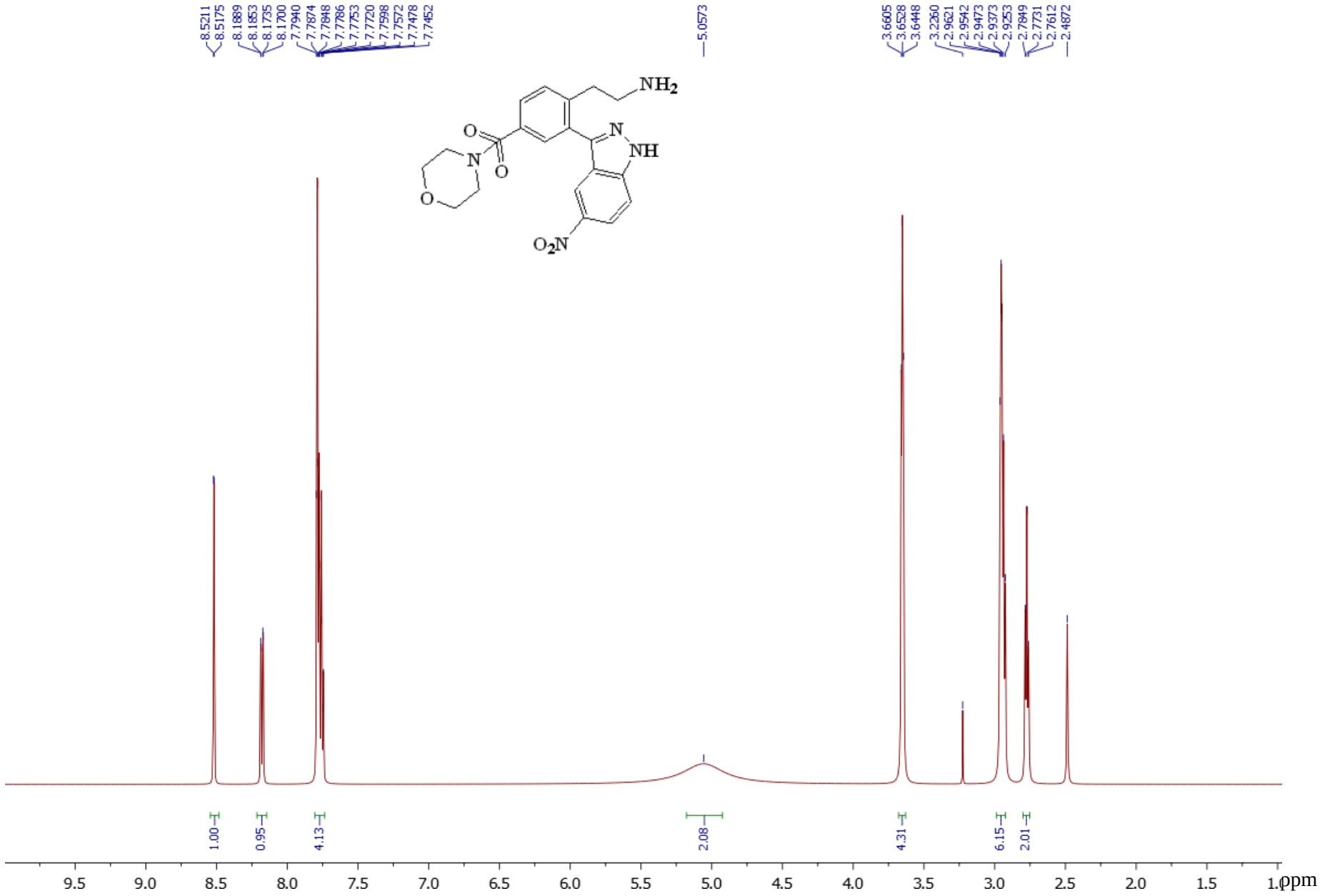

MeO
MeO
NH2
HCl
N
NH
O2N
149.1085
147.5047
146.5792
142.6346
141.7510
128.9803
122.9996
121.0018
118.2492
114.1929
113.9979
111.3891
55.7986
55.6567
40.0937
30.4494
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

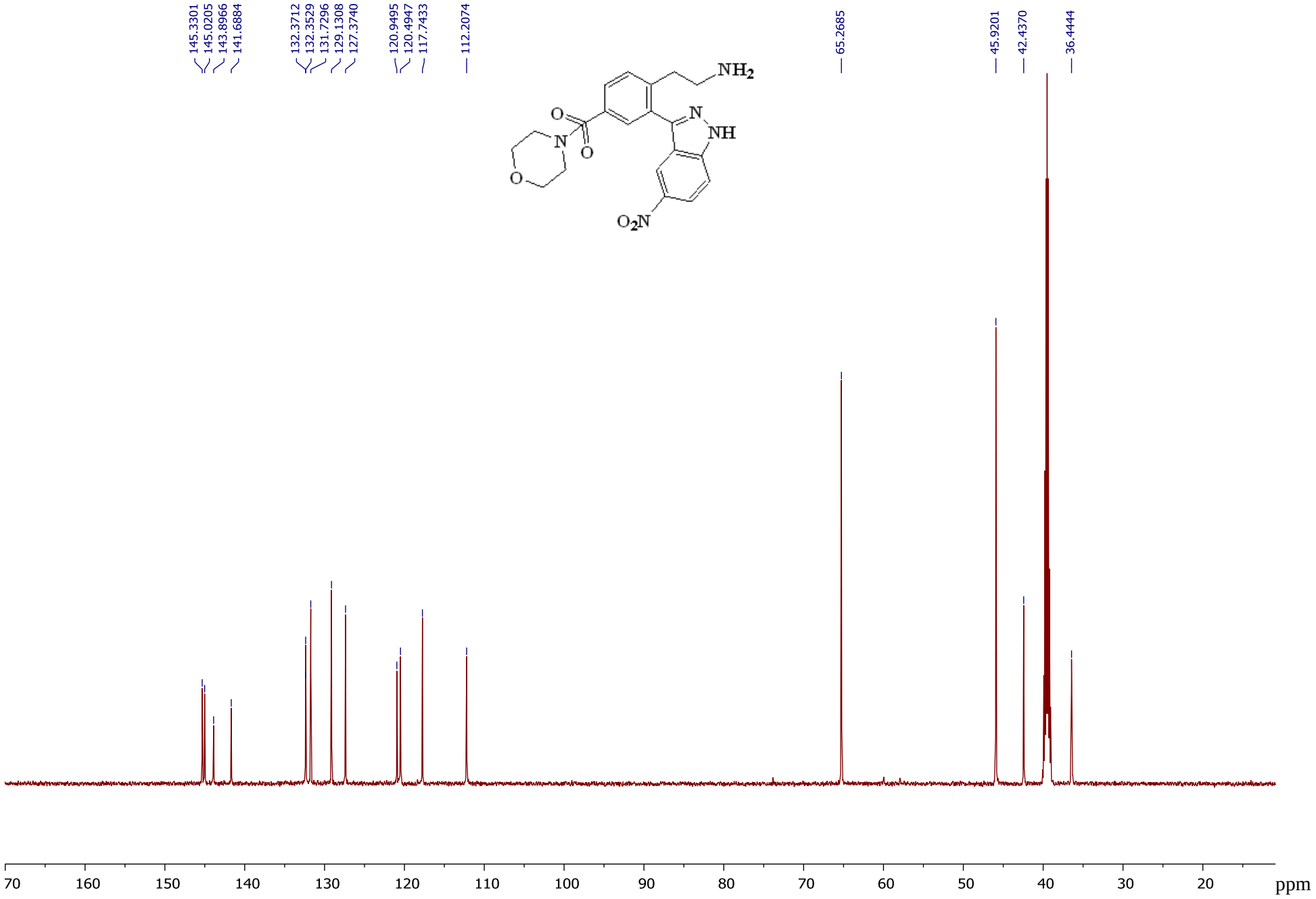
2-[4,5-Dimethoxy-2-(1*H*-pyrazolo[3,4-*b*]pyridin-3-yl)phenyl]ethanamine perchlorate (**5c**)



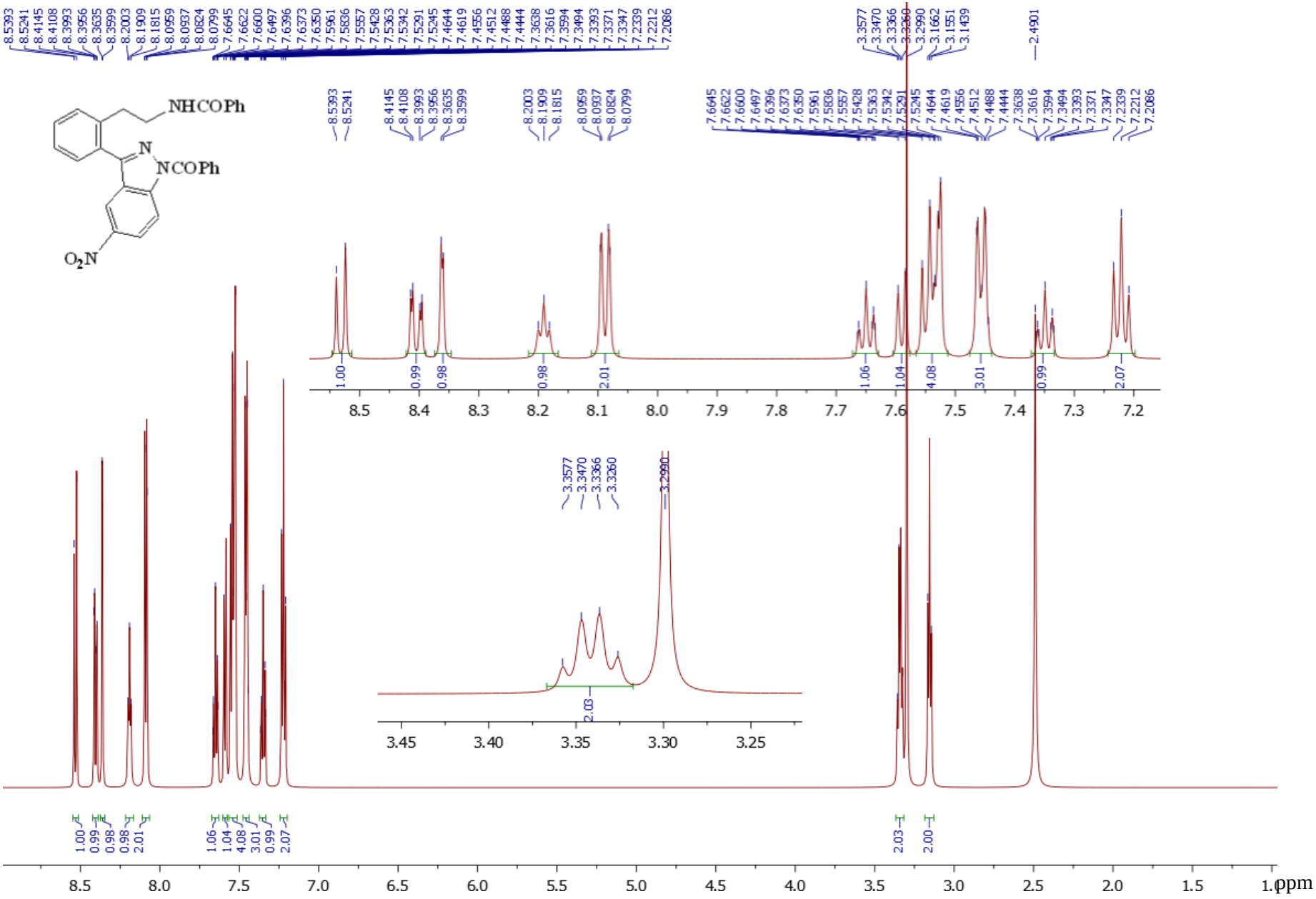

151.5128
148.8907
148.3116
147.5036
143.1525
131.0163
128.7119
123.7082
117.0767
114.2058
114.0455
113.8411
55.7010
55.6802
40.2752
30.5641
MeO
MeO
NH2
HClO4
N
NH
N
.70
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm

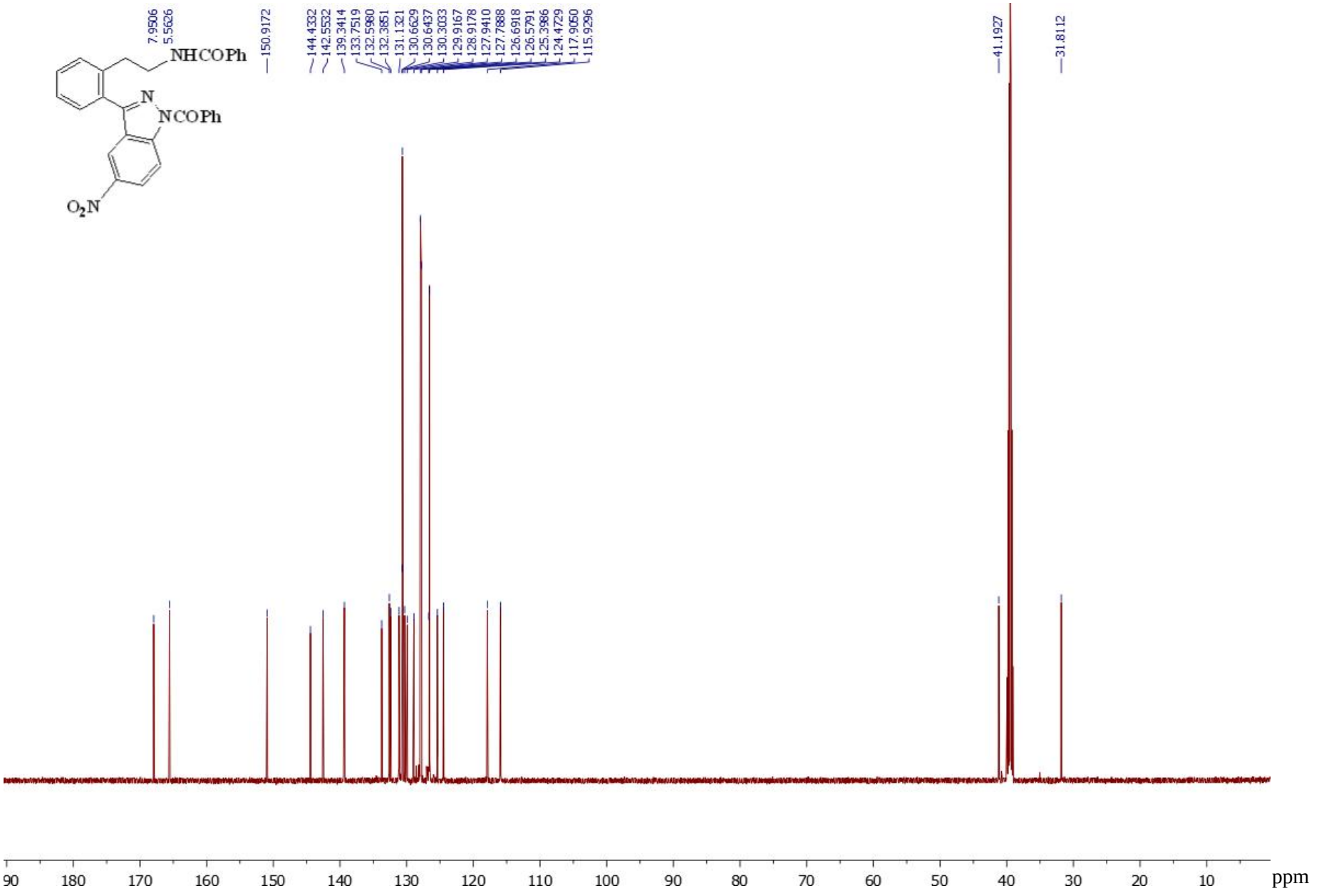
2-[4-(Morpholinosulfonyl)-2-(5-nitro-1*H*-indazol-3-yl)phenyl]ethan-1-amine (**5d**)



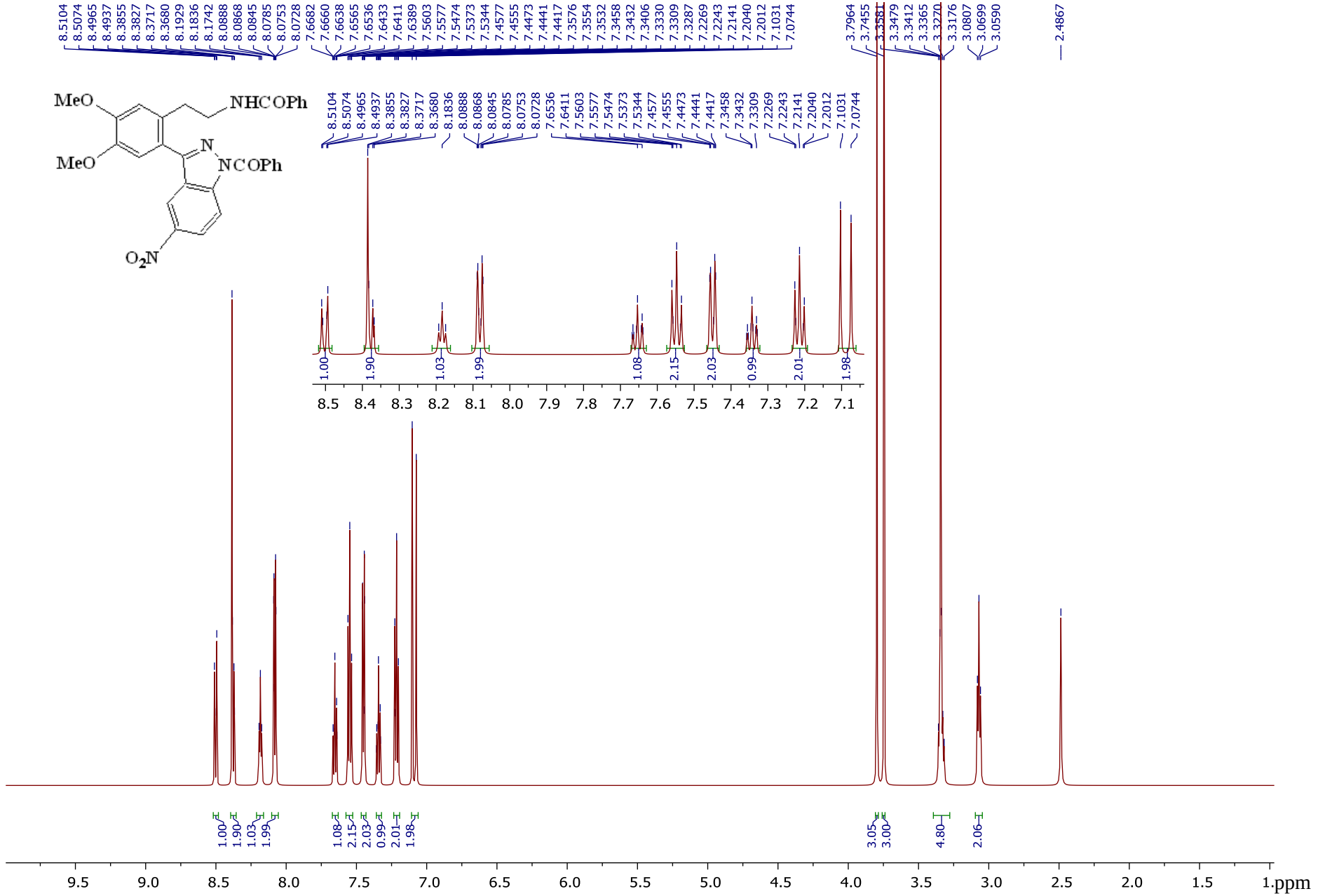

145.3301
145.0205
143.8966
141.6884
132.3712
132.3529
131.7296
129.1308
127.3740
120.9495
120.4947
117.7433
112.2074
65.2685
45.9201
42.4370
36.4444
NH2
O
N
O
N
NH
O
O2N
70
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm

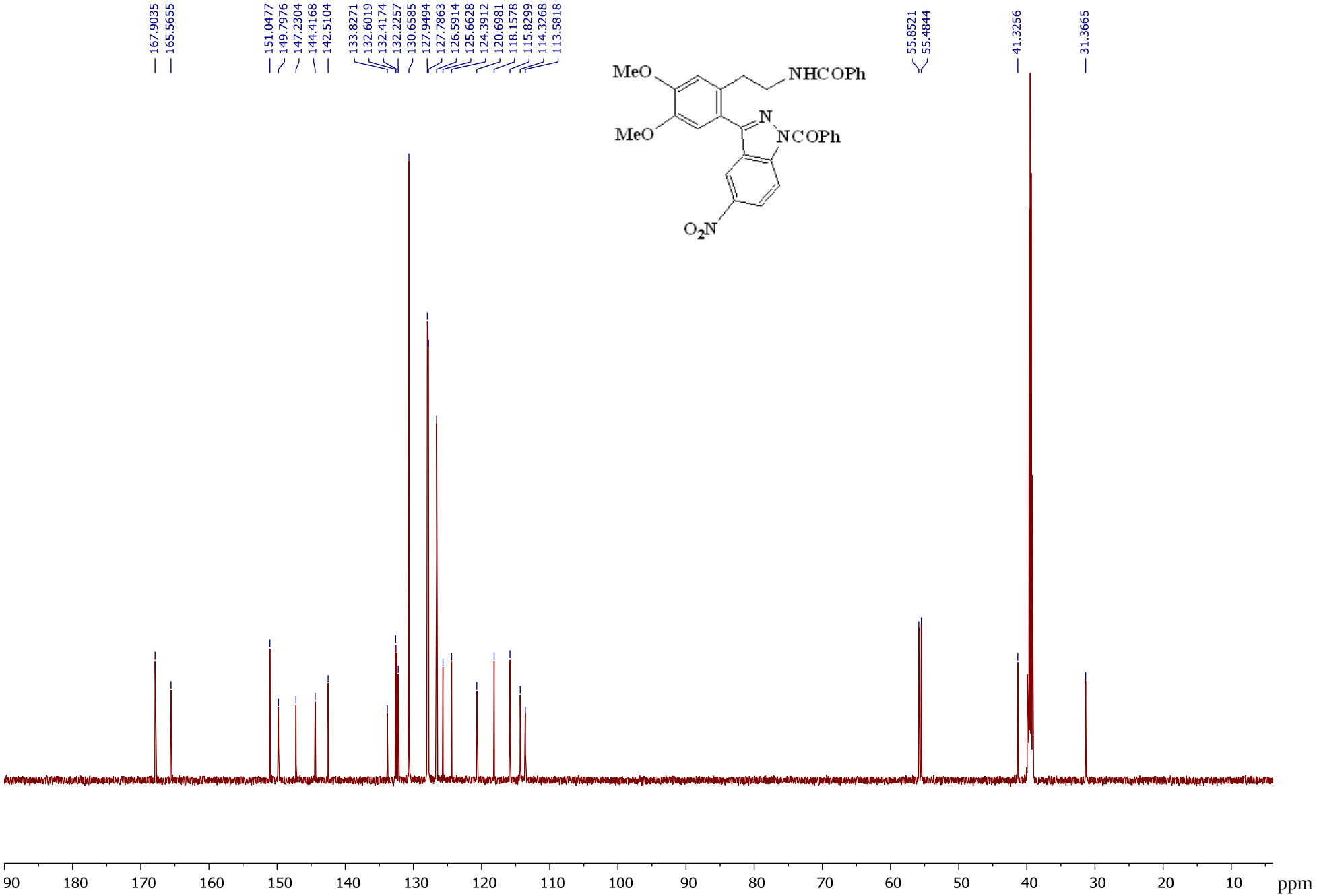
N-[2-(1-Benzoyl-5-nitro-1*H*-indazol-3-yl)phenethyl]benzamide (**6a**).



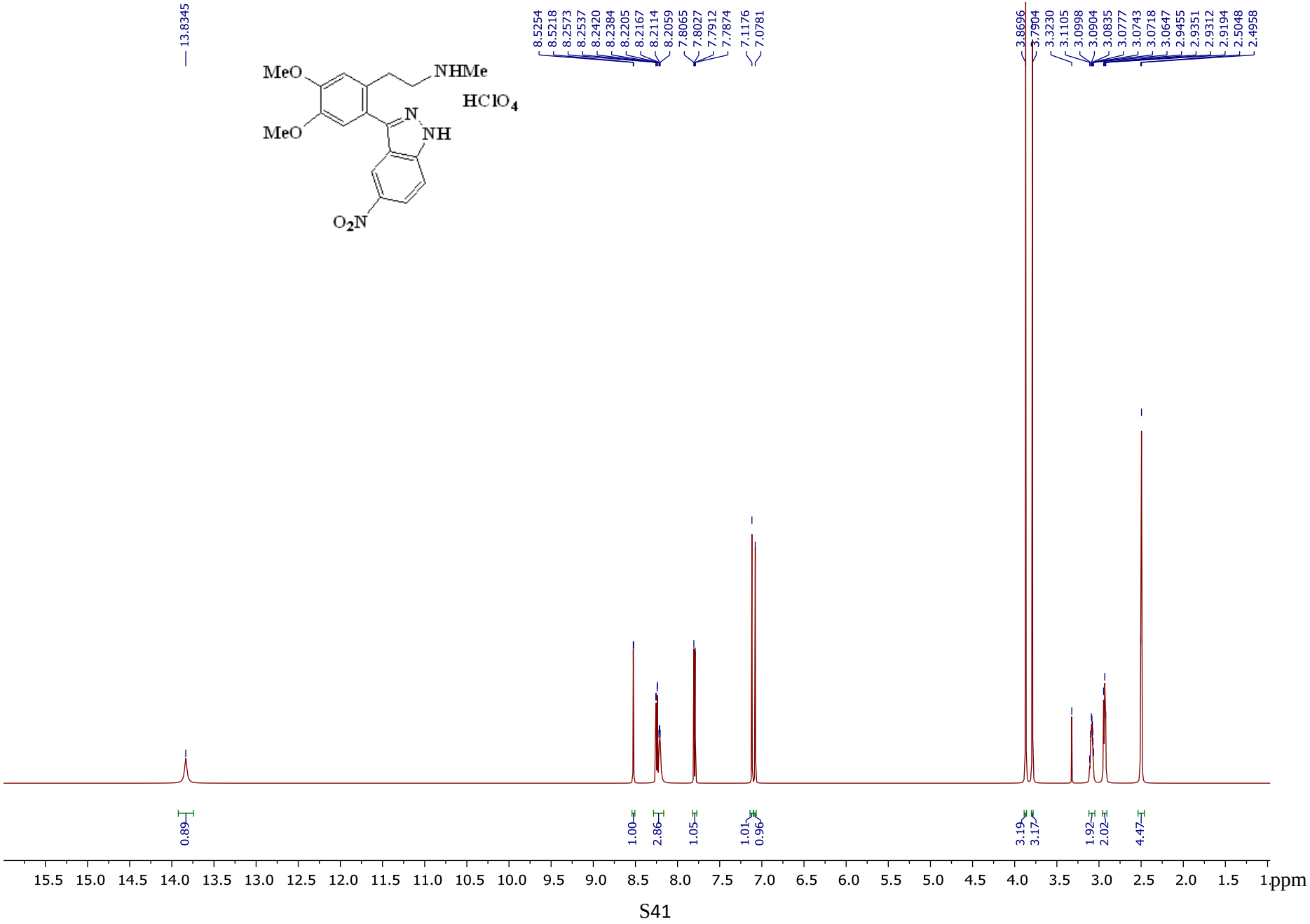

7.9506
5.5626
NHCOPh
N
NCOPh
O2N
150.9172
144.4332
142.5532
139.3414
133.7519
132.5980
132.3851
131.1321
130.6629
130.6437
130.3033
129.9167
128.9178
127.9410
127.7888
126.6918
126.5791
125.3986
124.4729
117.9050
115.9296
41.1927
31.8112
90
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

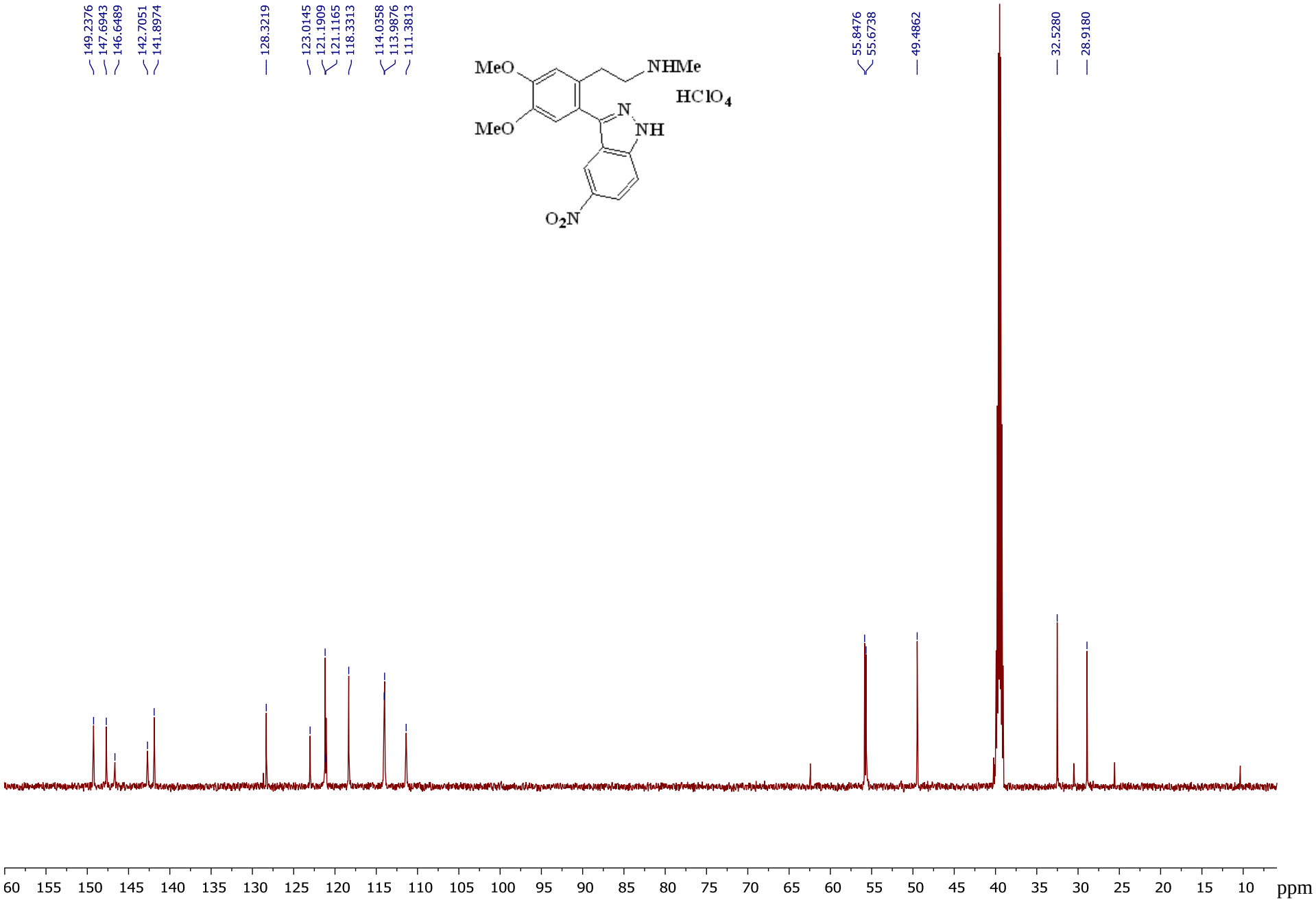
N-[2-(1-Benzoyl-5-nitro-1*H*-indazol-3-yl)-4,5-dimethoxyphenethyl]benzamide (**6b**).




167.9035
165.5655
151.0477
149.7976
147.2304
144.4168
142.5104
133.8271
132.6019
132.4174
132.2257
130.6585
127.9494
127.7863
126.5914
125.6628
124.3912
120.6981
118.1578
115.8299
114.3268
113.5818
55.8521
55.4844
41.3256
31.3665
MeO
MeO
NHCOPh
N
NCOPh
O2N
90
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

2-(4,5-Dimethoxy-2-(5-nitro-1*H*-indazol-3-yl)phenyl)-N-methylethanamine (**8a**).




149.2376
147.6943
146.6489
142.7051
141.8974
128.3219
123.0145
121.1909
121.1165
118.3313
114.0358
113.9876
111.3813
55.8476
55.6738
49.4862
32.5280
28.9180
MeO
MeO
NHMe
HClO4
N
NH
O2N
60 155 150 145 140 135 130 125 120 115 110 105 100 95 90 85 80 75 70 65 60 55 50 45 40 35 30 25 20 15 10 ppm