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Supplementary Information

Synthesis and Evaluation of Phenoxymethylbenzamide Analogues as Anti-Trypanosomal Agents

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1 Experimental of Chemical Synthesis

1.1 General Materials

All reactions were conducted under an atmosphere of nitrogen unless otherwise stated. Commercially available chemicals were purified using standard procedures or used as purchased, unless otherwise noted. Coupling reagents were obtained from Novabiochem and GL Biochem. Heating of reactions was conducted with a paraffin oil or water bath; cooling of reactions was achieved using an ice (0 °C) bath. Solvents used in reactions were used directly from purchased anhydrous bottles or distilled prior to use (DCM and MeOH dried over calcium hydride, Et_2O and THF over sodium/benzophenone). Thin layer chromatography was carried out on Merck Kieselgel 60 F_{254} pre-coated aluminium sheets. Flash chromatography was performed on Davisil Grace Davison 40−63 μm (230−400 mesh) silica gel. Solvents used for chromatography were distilled prior to use. Ratios of solvent systems used for TLC and column chromatography are expressed in v/v as specified. Compounds were visualised by UV light at 254 nm or using Vanillin or 'Goofy's Dip' (cerium molybdate stain). NB: Novel final compounds are displayed in *italics* in the Experimental.

All NMR data were recorded at either 300K or 350K using either a Bruker AVANCE 200 (^{1}H at 200 MHz and ^{13}C at 50 MHz), 300 (^{1}H at 300 MHz and ^{13}C at 75 MHz), AVANCE III 400 (^{1}H at 400 MHz and ^{13}C at 100 MHz) or 500 (^{1}H at 500 MHz and ^{13}C at 125 MHz). ^{1}H NMR chemical shifts were reported in parts per million (ppm) and were referenced to solvent residual signals: $CDCl_3$ (δ 7.26), D_2O (δ 4.79), MeOD (δ 3.31), DMF-d_7 (δ 2.75), DMSO-d_6 (δ 2.50), $(CD_3)_2CO$ (δ 2.05) or Tol-d_8 (δ 2.09). ^{1}H NMR data is reported as chemical shift (δ_H), relative integral, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, ddd = doublet of doublet of doublets, dddd = doublet of doublet of doublet of doublets), coupling constant (*J* Hz) and assignment where possible. ^{13}C NMR chemical shifts are reported in parts per million and were referenced to the solvent resonance: $CDCl_3$ (δ 77.16), MeOD (δ 49.00), DMSO-d_6 (δ 39.52), $(CD_3)_2CO$ (δ 29.84), DMF-d_7 (δ 29.76) or Tol-d_8 (δ 20.40). Spectra run in D_2O were uncalibrated. ^{13}C NMR assignments were made in conjunction with DEPT experiments and 2D experiments HSQC and HMBC (C = quaternary carbon, CH = tertiary carbon, CH_2 = secondary carbon, CH_3 = primary carbon, C=O = carbonyl carbon). All 2D NMR experiments were carried out at 300K or 350 K using a Bruker AVANCE III 400 or 500.

Melting points were recorded using a Stanford Research Systems OptiMelt Automated Melting Point System. Infrared (IR) absorption spectra were recorded on *a)* a Shimadzu FTIR-8400S spectrometer as a thin film on sodium chloride plates or in liquid phase solution in $CHCl_3$ or *b)* on a Bruker Alpha Spectrometer (ALPHA-E FTIR, with a ZnSe crystal) with attenuated total reflection (ATR) capability as a thin film and were processed with OPUS 6.5 software.

Liquid-chromatography mass-spectrometry (LC-MS) was carried out using a Shimadzu LC-MS 2020 instrument consisting of a LCM20A pump, a SPD-M20A photodiode array detector coupled to a Shimadzu 2020 mass spectrometer (ESI) operating in positive mode. Separations were performed on a Waters Sunfire 5 μm,

2.1 × 150 mm column (C18) or a Waters Symmetry 300 5 μm, 2.1 x 150 mm (C4) column, operating at a flow rate of 0.2 mL min^{-1}. Separations were performed using a 30 min linear gradient between 100:0 and 0:100 v/v H_2O:MeCN, both containing 0.1% formic acid.

Low resolution electrospray ionisation mass spectra (LRMS) were measured using either *a)* a Shimadzu mass spectrometer (ESI) operating in positive mode or *b)* recorded using a Finnigan LCQ (Ion trap) mass spectrometer by the Mass Spectrometry Department at the School of Chemistry, University of Sydney. High resolution electrospray ionisation/APCI mass spectra (HRMS) were recorded on a Bruker 7T Fourier Transform Ion Cyclotron Resonance Mass Spectrometer (FTICR) by the Mass Spectrometry Department at the School of Chemistry, University of Sydney

Preparative reverse-phase HPLC was performed using a Waters 600 Multisolvent Delivery System and Waters 500 pump with 2996 photodiode array detector or Waters 490E Programmable wavelength detector operating at λ = 230 and λ = 254/280 nm. Purification was carried out using either a C-18 Waters Sunfire 5 μm preparative column operating at a flow rate of 7 mL min^{-1} using a mobile phase of 0.1% TFA or 0.1% formic acid in water (Solvent A) and 0.1% TFA or 0.1% formic acid in MeCN (Solvent B) or a C-18 Waters Sunfire 10 μm (30 × 150 mm) super-preparative column operating at a flow rate of 17 mL min^{-1} using a mobile phase of 0.1% formic acid in water (Solvent A) and 0.1% formic acid in MeCN (Solvent B). Results were analysed with Waters Empower software.

1.2 General Procedures

Procedure A: Alkylation Reaction

Methyl (4-bromomethyl) benzoate **2** (1.0 g, 4.4 mmol) was dissolved in acetone (48 mL, 11 mL/mmol), before addition of K_2CO_3 (1.2 g, 8.7 mmol). The phenol (1.1 equiv.) was added to this stirred suspension and heated at reflux for 48 h. The solvent was removed *in vacuo*, before dissolving in $CHCl_3$ (100 mL) and washing with H_2O (3 × 50 mL). The organic extracts were combined and the solvent removed *in vacuo*. The crude solid was then recrystallised from MeOH to yield the desired products.

Procedure B: Saponification of Alkyl-Esters S42-S49

The methyl ester was dissolved in THF (4 mL) before addition of 2 M aq KOH (1−2 equiv.) and H_2O was added to make the volume up to 8 mL. The mixture was left to stir for 24−48 h, before the organic solvent was removed *in vacuo*. The aqueous phase was then acidified using 1 M HCl to pH 1 to precipitate the desired product. After filtering and washing with water (50 mL) and cold Et_2O (20 mL) the desired product was isolated without further purification.

Procedure C: Amide Coupling

The acid and 1-[*bis*(dimethylamino) methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate (HATU, 1.2 equiv.) were dissolved in DMF (2 mL)

before addition of DIPEA (2.4 equiv.). The amine (2 equiv.) was then added and the mixture left to stir for 19 h, before the solvent was removed *in vacuo*. The resulting crude product was purified using one of five methods:

- **Method A:** The product was first purified by column chromatography (eluent 98:2 DCM:MeOH) to afford the desired amide product. If mixed fractions containing the reactant amine were obtained, the product was further purified by preparative HPLC (gradient: 70:30 to 0:100 H_2O:MeCN both containing 0.1% formic acid over 40 min at 7 mL/min). The HPLC fractions containing the desired product were lyophilised to afford further amide product.
- **Method B:** The solid was dissolved (4 mL, 2:1 MeCN:H_2O), filtered and then purified by preparative HPLC gradient **(i)** 100:0 to 0:100 H_2O:MeCN both containing 0.1% formic acid over 40 min at 17 mL/min or **(ii)** 70:30 to 0:100 H_2O:MeCN both containing 0.1% formic acid over 50 min at 7 mL/min. The HPLC fractions containing the desired product were lyophilised to afford the desired amide product.
- **Method C:** The solid was dissolved (4 mL, 2:1 MeCN:H_2O), filtered and then purified by preparative HPLC (gradient: 70:30 to 0:100 H_2O:MeCN both containing 0.1% formic acid over 40 min at 17 mL/min). The HPLC fractions containing the desired product were lyophilised to afford the desired amide product.
- **Method D:** The solid was dissolved (4 mL, 2:1 v/v MeCN:H_2O), filtered and then purified by preparative HPLC (gradient: 100:0 to 20:80 H_2O:MeCN both containing 0.1% formic acid over 60 min at 17 mL/min). The HPLC fractions containing the desired product were lyophilised to afford the desired amide product.

Procedure D: Benzyl Ester Formation

Benzyl chloroformate (1.1 equiv.), acid (1 equiv.) and Et_3N (1.2 equiv.) were dissolved in DCM (3.4 mL/mmol) and cooled to 0 ºC in an ice bath before addition of DMAP (0.1 equiv.). The mixture was worked up after stirring for 30 min at 0 ºC and 1 h at rt. The mixture was diluted with DCM (50 mL) before washing with a saturated aq soln of NH_4Cl (30 mL). The aqueous layer was then back extracted with DCM (40 mL) and the organic layers combined, dried (Na_2SO_4), filtered and the solvent removed *in vacuo*. The product was purified by column chromatography (eluent: 10:1 *v/v* hexane:EtOAc) to afford the corresponding benzyl ester.

Procedure E: Benzyl Ester Alkylation Product Formation

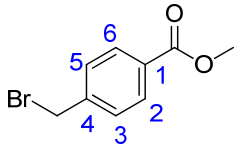
4-Ethoxyphenol (2 equiv.) and bromide (1 equiv.) were dissolved in acetone (11 mL/mmol) before K_2CO_3 (2 equiv.) and TBAI (0.2 equiv.) were added. This mixture was heated to reflux for 48 h before the solvent was removed *in vacuo*. The crude mixture was dissolved in DCM (15 mL) and washed with H_2O (6 mL). The aqueous layer was extracted with DCM (2 × 10 mL) and organic layers combined, dried (Na_2SO_4), filtered and the solvent removed *in vacuo*. The product was purified by column chromatography (eluent: 7:1 *v/v* hexane:EtOAc) to afford the corresponding alkylation product.

Procedure F: Benzyl Ester Removal

Pd/C 10% (2 equiv.) was added to a stirred soln of alkylated benzyl esters (1 equiv.) in MeOH (35 mL/mmol). The soln was saturated with H_2 (g) and the reaction stirred for 2.5 h under an H_2 atmosphere. The solvent was removed *in vacuo* and EtOAc (50 mL) was added before filtering through celite. The solvent was removed *in vacuo* to afford the desired free acids, which were used without further purification.

1.2.1 Synthesis

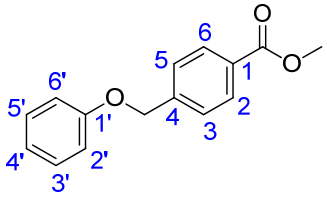
Methyl (4-bromomethyl)benzoate; 2.



Methyl 4-methyl benzoate (6.0 g, 40 mmol) and *N*-bromosuccinimide (8.5 g, 48 mmol) were dissolved in MeCN (160 mL, 4 mL/mmol) in a pyrex high pressure tube. This was sealed and the mixture stirred while irradiating with a UV lamp for 6 h. The MeCN was removed *in vacuo* before addition of hexane (50 mL). The resultant mixture was filtered and the filtrate collected. The solvent was removed *in vacuo* to reveal desired bromide **2** as an off-white solid (7.4 g, 81%).

IR ν_{max} (ATR): 3020, 2959, 1720, 1280 cm^{-1}; mp 55−57 ºC; R_f [6:2 *v/v* hexane:EtOAc] = 0.63; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.01 (2H, d, *J* 8.0 Hz, 2 × Ar-H; C_2-H, C_6-H), 7.46 (2H, d, *J* 8.0 Hz, 2 × Ar-H; C_3-H, C_5-H), 4.50 (2H, s, C_4-CH_2), 3.92 (3H, s, C_1-CO_2CH_3); These data are in agreement with those previously reported by Nishimura and co-workers.[337]

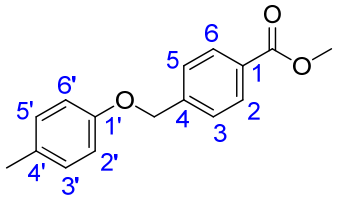
Methyl 4-(phenoxymethyl)benzoate; S42.



Phenol (0.45 g, 4.8 mmol) was reacted with **2** following Procedure A. Recrystallised product **S42** was obtained as white needles (0.74 g, 70%).

IR ν_{max} (ATR): 2919, 1721, 1282 cm^{-1}; mp 84−86 ºC; R_f [7:1 *v/v* hexane:EtOAc] = 0.50; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (2H, d, *J* 8.0 Hz, 2 × Ar-H; C_2-H, C_6-H), 7.51 (2H, d, *J* 8.0 Hz, 2 × Ar-H; C_3-H, C_5-H), 7.30 (2H, app. t, *J* 8.0 Hz, 2 × Ar-H; $C_{3'}$-H, $C_{5'}$-H), partially hidden 6.98 (1H, m, Ar-H; $C_{4'}$-H), 6.97 (2H, app. d, *J* 10.0 Hz, 2 × Ar-H; $C_{2'}$-H, $C_{6'}$-H), 5.13 (2H, s, C_4-CH_2), 3.92 (3H, s, C_1-CO_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.0 (C=O), 158.6 (C), 142.5 (C), 130.0 (2 × Ar-CH), 129.8 (C), 129.7 (2 × Ar-CH), 127.1 (2 × Ar-CH), 121.4 (Ar-CH), 115.0 (2 × Ar-CH), 69.4 (C_4-$\underline{C}H_2$), 52.3 (C_1-$CO_2\underline{C}H_3$); LRMS $[M+Na]^+$ 265.6; HRMS calcd. for $C_{15}H_{14}O_3Na$: MNa^+, 265.0841. Found: MNa^+, 265.0836.

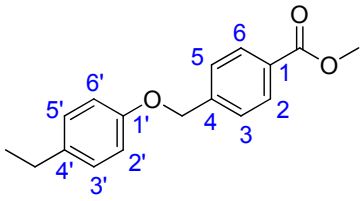
Methyl 4-((4-methylphenoxy)methyl)benzoate; S43.



p-Cresol (0.52 g, 4.8 mmol) was reacted with **2** following Procedure A. Recrystallised product **S43** was obtained as white platelets (0.69 g, 62%).

IR ν_{max} (ATR): 2940, 1723, 1282 cm^{-1}; mp 87−89 ºC; R_f [7:1 *v/v* hexane:EtOAc] = 0.56; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (2H, d, *J* 8.3 Hz, 2 × Ar-H; C_2-H, C_6-H), 7.50 (2H, d, *J* 8.3 Hz, 2 × Ar-H; C_3-H, C_5-H), 7.09 (2H, d, *J* 8.6 Hz, 2 × Ar-H; $C_{3'}$-H, $C_{5'}$-H), 6.86 (2H, d, *J* 8.6 Hz, 2 × Ar-H; $C_{2'}$-H, $C_{6'}$-H), 5.10 (2H, s, C_4-CH_2), 3.92 (3H, s, C_1-CO_2CH_3), 2.29 (3H, s, $C_{4'}$-CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.0 (C=O), 156.5 (C), 142.7 (C), 130.6 (C), 130.1 (2 × Ar-CH), 130.0 (2 × Ar-CH), 129.7 (C), 127.1 (2 × Ar-CH), 114.9 (2 × Ar-CH), 69.6 (C_4-$\underline{C}H_2$), 52.3 (C_1-$CO_2\underline{C}H_3$), 20.6 ($C_{4'}$-$\underline{C}H_3$); HRMS calcd. for $C_{16}H_{16}O_3Na$: MNa^+, 279.0997. Found: MNa^+, 279.0991.

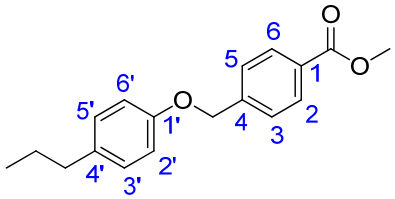
Methyl 4-((4-ethylphenoxy)methyl)benzoate; S44.



4-Ethylphenol (0.65 g, 4.8 mmol) was reacted with **2** following Procedure A. Recrystallised product **S44** was obtained as white needles (0.97 g, 82%).

IR ν_{max} (ATR): 3049, 2873, 1719, 1510, 1278 cm^{-1}; mp 77−79 ºC; R_f [7:1 *v/v* hexane:EtOAc] = 0.79; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (2H, d, *J* 8.4 Hz, 2 × Ar-H; C_2-H, C_6-H), 7.50 (2H, d, *J* 8.4 Hz, 2 × Ar-H; C_3-H, C_5-H), 7.11 (2H, d, *J* 8.6 Hz, 2 × Ar-H; $C_{3'}$-H, $C_{5'}$-H), 6.89 (2H, d, *J* 8.6 Hz, 2 × Ar-H; $C_{2'}$-H, $C_{6'}$-H), 5.11 (2H, s, C_4-CH_2), 3.92 (3H, s, C_1-CO_2CH_3), 2.50 (2H, q, *J* 8.0 Hz, $C_{4'}$-$C\underline{H}_2CH_3$), 1.21 (3H, t, *J* 8.0 Hz, $C_{4'}$-$CH_2C\underline{H}_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.0 (C=O), 156.7 (C), 142.7 (C), 135.2 (C), 130.0 (2 × Ar-CH), 129.7 (C), 129.9 (2 × Ar-CH), 127.1 (2 × Ar-CH), 114.9 (2 × Ar-CH), 69.6 (C_4-$\underline{C}H_2$), 52.2 (C_1-$CO_2\underline{C}H_3$), 28.1 ($C_{4'}$-$\underline{C}H_2CH_3$), 15.9 ($C_{4'}$-$CH_2\underline{C}H_3$); HRMS calcd. for $C_{17}H_{18}O_3Na$: MNa^+, 293.1154. Found: MNa^+, 293.1148.

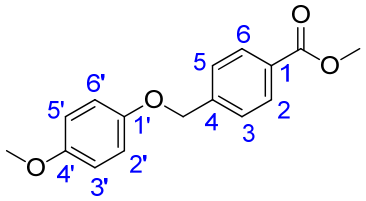
Methyl 4-((4-propylphenoxy)methyl)benzoate; S45.



4-Propylphenol (0.65 g, 4.8 mmol) was reacted with **2** following Procedure A. Recrystallised product **S45** was obtained as white needles (0.82 g, 66%).

IR ν_{max} (ATR): 2955, 1720, 1512, 1280 cm^{-1}; mp 77−79 ºC; R_f [7:1 *v/v* hexane:EtOAc] = 0.55; ^1H NMR (400 MHz, $CDCl_3$) δ 8.05 (2H, d, *J* 8.0 Hz, 2 × Ar-H; C_2-H, C_6-H), 7.50 (2H, d, *J* 8.0 Hz, 2 × Ar-H; C_3-H, C_5-H), 7.10 (2H, d, *J* 10.0 Hz, 2 × Ar-H; $C_{3'}$-H, $C_{5'}$-H), 6.88 (2H, d, *J* 10.0 Hz, 2 × Ar-H; $C_{2'}$-H, $C_{6'}$-H), 5.10 (2H, s, C_4-CH_2), 3.92 (3H, s, C_1-CO_2CH_3), 2.53 (2H, t, *J* 8.0 Hz, $C_{4'}$-$CH_2CH_2CH_3$), 1.60 (2H, m, 8.0, 6.0 Hz, $C_{4'}$-$CH_2CH_2CH_3$), 0.93 (3H, t, 6.0 Hz, $C_{4'}$-$CH_2CH_2CH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.0 (C=O), 156.7 (C), 142.7 (C), 135.6 (C), 130.0 (2 × Ar-CH), 129.7 (C), 129.6 (2 × Ar-CH), 127.1 (2 × Ar-CH), 114.8 (2 × Ar-CH), 69.6 (C_4-CH_2), 52.3 (C_1-CO_2CH_3), 37.3 ($C_{4'}$-$CH_2CH_2CH_3$), 24.9 ($C_{4'}$-$CH_2CH_2CH_3$), 13.9 ($C_{4'}$-$CH_2CH_2CH_3$); HRMS calcd. for $C_{18}H_{20}O_3Na$: MNa^+, 307.1310. Found: MNa^+, 307.1305.

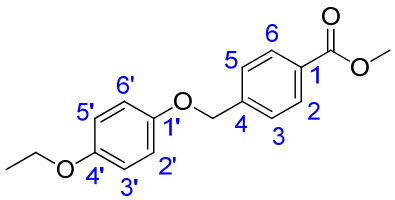
Methyl 4-((4-methoxyphenoxy)methyl)benzoate; S46.



4-Methoxyphenol (0.60 g, 4.8 mmol) was reacted with **2** following Procedure A. Recrystallised product **S46** was obtained as cream platelets (0.82 g, 69%).

IR ν_{max} (ATR): 2954, 1721, 1511, 1284 cm^{-1}; mp 118−120 ºC; R_f [7:1 *v/v* hexane:EtOAc] = 0.40; ^1H NMR (400 MHz, $CDCl_3$) δ 8.05 (2H, d, *J* 8.0 Hz, 2 × Ar-H; C_2-H, C_6-H), 7.49 (2H, d, *J* 8.0 Hz, 2 × Ar-H; C_3-H, C_5-H), 6.90 (2H, d, *J* 8.0 Hz, 2 × Ar-H; $C_{2'}$-H, $C_{6'}$-H), 6.83 (2H, d, *J* 8.0 Hz, 2 × Ar-H; $C_{3'}$-H, $C_{5'}$-H), 5.08 (2H, s, C_4-CH_2), 3.92 (3H, s, C_1-CO_2CH_3), 3.72 (3H, s, $C_{4'}$-OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.0 (C=O), 154.3 (C), 152.8 (C), 142.7 (C), 130.0 (2 × Ar-CH), 129.7 (C), 127.1 (2 × Ar-CH), 116.0 (2 × Ar-CH), 114.8 (2 × Ar-CH), 70.2 (C_4-CH_2), 55.8 ($C_{4'}$-OCH_3), 52.2 (C_1-CO_2CH_3); HRMS calcd. for $C_{16}H_{16}O_4Na$: MNa^+, 295.0946. Found: MNa^+, 295.0941.

Methyl 4-((4-ethoxyphenoxy)methyl)benzoate; S47.

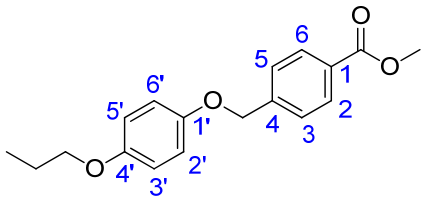


4-Ethoxyphenol (0.66 g, 4.8 mmol) was reacted with **2** following Procedure A. Recrystallised product **S47** obtained as white platelets (1.1 g, 87%).

IR ν_{max} (ATR): 2974, 1724, 1512, 1284 cm^{-1}; mp 104−106 ºC; R_f [7:1 *v/v* hexane:EtOAc] = 0.55; ^1H NMR (400 MHz, $CDCl_3$) δ 8.05 (2H, d, *J* 8.0 Hz, 2 × Ar-H; C_2-H, C_6-H), 7.49 (2H, d, *J* 8.0 Hz, 2 × Ar-H; C_3-H, C_5-H), 6.89 (2H, d, *J* 10.0 Hz, 2 × Ar-H; $C_{2'}$-H, $C_{6'}$-H), 6.83 (2H, d, *J* 10.0 Hz, 2 × Ar-H; $C_{3'}$-H, $C_{5'}$-H), 5.07 (2H, s, C_4-CH_2), 3.98 (2H, q, *J* 7.0 Hz, $C_{4'}$-OCH_2CH_3), 3.92 (3H, s, C_1-CO_2CH_3), 1.39 (3H, t, *J* 7.0 Hz, $C_{4'}$-OCH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.0 (C=O), 153.7 (C), 152.7 (C), 142.8 (C), 130.0 (2 × Ar-CH), 129.7 (C), 127.1 (2 × Ar-CH), 116.0 (2 × Ar-CH), 115.6 (2 × Ar-CH), 70.2 (C_4-CH_2), 64.1 ($C_{4'}$-OCH_2CH_3), 52.3 (C_1-CO_2CH_3),

15.1 ($C_{4'}$-$OCH_2\underline{C}H_3$); HRMS calcd. for $C_{17}H_{18}O_4Na$: MNa^+, 309.1103. Found: MNa^+, 309.1097.

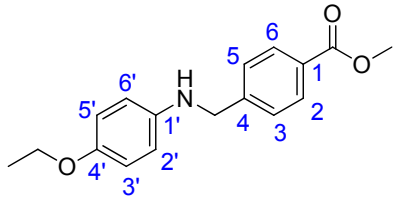
Methyl 4-((4-propoxyphenoxy)methyl)benzoate; S48.



4-propoxyphenol (0.23 g, 1.5 mmol) was reacted with **2** following a slightly altered version of Procedure A with methyl (4-bromomethyl)benzoate (0.35 g, 1.5 mmol), acetone (16 mL, 11 mL/mmol) and K_2CO_3 (0.42 g, 3.0 mmol). Recrystallised product **S48** was obtained as white platelets (0.32 g, 71%).

IR ν_{max} (ATR): 2963, 1725, 1512, 1284 cm^{-1}; mp 108−110 ºC; R_f [7:1 *v/v* hexane:EtOAc] = 0.48; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (2H, d, *J* 8.5 Hz, 2 × Ar-H; C_2-H, C_6-H), 7.49 (2H, d, *J* 8.5 Hz, 2 × Ar-H; C_3-H, C_5-H), 6.88 (2H, d, *J* 9.3 Hz, 2 × Ar-H; $C_{2'}$-H, $C_{6'}$-H), 6.82 (2H, d, *J* 9.3 Hz, 2 × Ar-H; $C_{3'}$-H, $C_{5'}$-H), 5.07 (2H, s, C_4-CH_2), 3.92 (3H, s, C_1-CO_2CH_3), 3.86 (2H, t, *J* 6.6 Hz, $C_{4'}$-$C\underline{H}_2CH_2CH_3$), 1.82-1.73 (2H, m, $C_{4'}$-$CH_2C\underline{H}_2CH_3$), 1.02 (3H, t, *J* 7.4 Hz, $C_{4'}$-$CH_2CH_2C\underline{H}_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.0 (C=O), 153.9 (C), 152.7 (C), 142.8 (C), 130.0 (2 × Ar-CH), 129.8 (C), 127.1 (2 × Ar-CH), 116.0 (2 × Ar-CH), 115.6 (2 × Ar-CH), 70.3 (C_4-$\underline{C}H_2$), 70.3 ($C_{4'}$-$\underline{C}H_2CH_2CH_3$), 52.3 (C_1-$CO_2\underline{C}H_3$), 22.8 ($C_{4'}$-$CH_2\underline{C}H_2CH_3$), 10.7 ($C_{4'}$-$CH_2CH_2\underline{C}H_3$); HRMS calcd. for $C_{18}H_{20}O_4Na$: MNa^+, 323.1259. Found: MNa^+, 323.1255.

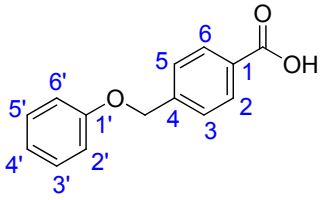
Methyl 4-(((4-ethoxyphenyl)amino)methyl)benzoate; S49.



4-Ethoxyaniline (0.62 mL, 4.8 mmol) was reacted with **2** following Procedure A. Recrystallised product **S49** was obtained as yellow platelets (0.96 g, 77%).

IR ν_{max} (ATR): 2975, 2948, 1719, 1705, 1512, 1280 cm^{-1}; mp 118−120 ºC; R_f [7:1 *v/v* hexane:EtOAc] = 0.19; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (2H, d, *J* 8.2 Hz, 2 × Ar-H; C_2-H, C_6-H), 7.43 (2H, d, *J* 8.2 Hz, 2 × Ar-H; C_3-H, C_5-H), 6.76 (2H, d, *J* 9.0 Hz, 2 × Ar-H; $C_{2'}$-H, $C_{6'}$-H), 6.56 (2H, d, *J* 9.0 Hz, 2 × Ar-H; $C_{3'}$-H, $C_{5'}$-H), 4.35 (2H, s, C_4-CH_2), 3.94 (2H, q, *J* 6.9 Hz, $C_{4'}$-$OC\underline{H}_2CH_3$), 3.91 (3H, s, C_1-CO_2CH_3), 3.67 (1H, br. s, NH), 1.36 (3H, t, *J* 6.9 Hz, $C_{4'}$-$OCH_2C\underline{H}_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.0 (C=O), 151.8 (C), 145.2 (C), 141.9 (C), 130.0 (2 × Ar-CH), 129.1 (C), 127.3 (2 × Ar-CH), 115.9 (2 × Ar-CH), 114.4 (2 × Ar-CH), 64.2 ($C_{4'}$-$O\underline{C}H_2CH_3$), 52.1 (C_1-$CO_2\underline{C}H_3$), 49.1 (C_4-$\underline{C}H_2$), 15.1 ($C_{4'}$-$OCH_2\underline{C}H_3$); HRMS calcd. for $C_{17}H_{19}NO_3Na$: MNa^+, 308.1263. Found: MNa^+, 308.1259.

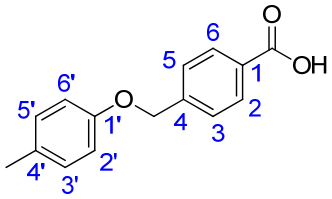
4-(Phenoxymethyl)benzoic acid; 3.



Methyl ester **227** (0.50 g, 2.1 mmol) was reacted with 2 M aq KOH (1.5 mL, 3.0 mmol) using Procedure B. Acid **3** was obtained as a white powder (0.50 g, quant.).

IR ν_{max} (ATR): 3371, 2992, 1738, 1647, 1367, 1214 cm^{-1}; decomp 282−284 ºC; ^{1}H NMR (400 MHz, 7:2 *v/v* TFA:$CDCl_3$) δ 8.17 (2H, d, *J* 8.5 Hz, 2 × Ar-H; C_2-H, C_6-H), 7.60 (2H, d, *J* 8.5 Hz, 2 × Ar-H; C_3-H, C_5-H), 7.34 (2H, app. t, *J* 8.1 Hz, 2 × Ar-H; $C_{3'}$-H, $C_{5'}$-H), partially hidden 7.11−7.07 (1H, m, Ar-H; $C_{4'}$-H), 7.06 (2H, app. t, *J* 8.1 Hz, 2 × Ar-H; $C_{2'}$-H, $C_{6'}$-H), 5.32 (2H, s, C_4-CH_2); ^{13}C NMR (100 MHz, 7:2 *v/v* TFA:$CDCl_3$) δ 173.9 (C=O), 157.7 (C), 144.1 (C), 131.5 (2 × Ar-CH), 130.4 (2 × Ar-CH), 128.3 (C), 128.3 (2 × Ar-CH), 123.5 (Ar-CH), 116.5 (2 × Ar-CH), 71.3 (C_4-$\underline{C}H_2$); LRMS $[M-H]^-$ 226.7; HRMS calcd. for $C_{14}H_{11}O_3$: $(M-H)^-$, 227.0708. Found: $(M-H)^-$, 227.0715.

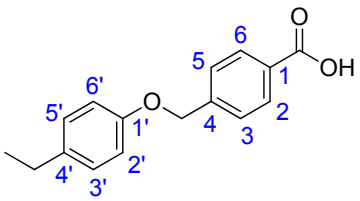
4-((4-Methylphenoxy)methyl)benzoic acid; 4.



Methyl ester **228** (0.50 g, 2.0 mmol) was reacted with 2 M aq KOH (1.5 mL, 3.0 mmol) using Procedure B with. Acid **4** was obtained as a white powder (0.49 g, quant.).

IR ν_{max} (ATR): 3061, 2972, 1739, 1648, 1369, 1214 cm^{-1}; mp 136−138 ºC; ^{1}H NMR (400 MHz, 11:1 *v/v* TFA:$CDCl_3$) δ 8.19 (2H, d, *J* 8.2 Hz, 2 × Ar-H; C_2-H, C_6-H), 7.61 (2H, d, *J* 8.2 Hz, 2 × Ar-H; C_3-H, C_5-H), 7.17 (2H, d, *J* 8.5 Hz, 2 × Ar-H; $C_{3'}$-H, $C_{5'}$-H), 6.98 (2H, d, *J* 8.5 Hz, 2 × Ar-H; $C_{2'}$-H, $C_{6'}$-H), 5.35 (2H, s, C_4-CH_2), 2.32 (3H, s, $C_{4'}$-CH_3); ^{13}C NMR (100 MHz, 11:1 *v/v* TFA:$CDCl_3$) δ 174.2 (C=O), 155.2 (C), 143.9 (C), 134.6 (C), 131.7 (2 × Ar-CH), 131.1 (2 × Ar-CH), 128.8 (2 × Ar-CH), 128.7 (C), 117.2 (2 × Ar-CH), 72.6 (C_4-$\underline{C}H_2$), 20.0 ($C_{4'}$-$\underline{C}H_3$); LRMS $[M-H]^-$ 241.5; HRMS calcd. for $C_{15}H_{14}O_3Na$: MNa^+, 265.0841. Found: MNa^+, 265.0836.

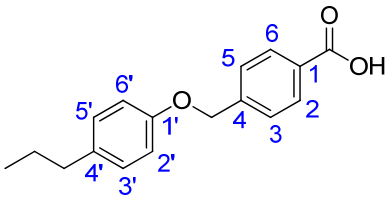
4-((4-Ethylphenoxy)methyl)benzoic acid; 5.



Methyl ester **229** (0.30 g, 1.1 mmol) was reacted with 2 M aq KOH (0.55 mL, 1.10 mmol) using Procedure B. Acid **5** was obtained as a white solid (0.24 g, 85%).

IR ν_{max} (ATR): 3288, 2970, 1739, 1679, 1368, 1214 cm^{-1}; mp 252−254 ºC; ^{1}H NMR (400 MHz, 5:1 *v/v* TFA:$CDCl_3$) δ 8.18 (2H, d, *J* 8.0 Hz, 2 × Ar-H; C_2-H, C_6-H), 7.60 (2H, d, *J* 8.0 Hz, 2 × Ar-H; C_3-H, C_5-H), 7.20 (2H, d, *J* 8.5 Hz, 2 × Ar-H; $C_{3'}$-H, $C_{5'}$-H), 7.00 (2H, d, *J* 8.5 Hz, 2 × Ar-H; $C_{2'}$-H, $C_{6'}$-H), 5.34 (2H, s, C_4-CH_2), 2.64 (2H, q, *J* 7.7 Hz, $C_{4'}$-C$\underline{H_2}$$CH_3$), 1.24 (3H, t, 7.7 Hz, $C_{4'}$-CH_2C$\underline{H_3}$); ^{13}C NMR (100 MHz, 5:1 *v/v* TFA:$CDCl_3$) δ 174.0 (C=O *via* HMBC), 155.4 (C), 144.0 (C), 140.8 (C), 131.6 (2 × Ar-CH), 129.8 (2 × Ar-CH), 128.6 (2 × Ar-CH), 128.6 (C), 116.9 (2 × Ar-CH), 72.3 (C_4-$\underline{C}H_2$), 28.5 ($C_{4'}$-$\underline{C}H_2CH_3$), 15.3 ($C_{4'}$-$CH_2\underline{C}H_3$); LRMS $[M\text{-}H]^-$ 255.3; HRMS calcd. for $C_{16}H_{16}O_3Na$: MNa^+, 279.0997. Found: MNa^+, 279.0992.

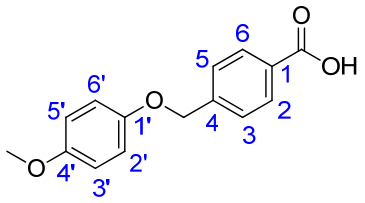
4-((4-Propylphenoxy)methyl)benzoic acid; 6.



Methyl ester **230** (0.50 g, 1.8 mmol) was reacted with 2 M aq KOH (1.3 mL, 2.6 mmol) using Procedure B. Acid **6** was obtained as a white solid (0.47 g, 98%).

IR ν_{max} (ATR): 3292, 2942, 1738, 1648, 1368, 1214 cm^{-1}; decomp 290−292 ºC; ^{1}H NMR (400 MHz, 3:1 *v/v* TFA:$CDCl_3$) δ 8.16 (2H, d, *J* 8.3 Hz, 2 × Ar-H; C_2-H, C_6-H), 7.59 (2H, d, *J* 8.3 Hz, 2 × Ar-H; C_3-H, C_5-H), 7.17 (2H, d, *J* 9.1 Hz, 2 × Ar-H; $C_{3'}$-H, $C_{5'}$-H), 6.98 (2H, d, *J* 9.1 Hz, 2 × Ar-H; $C_{2'}$-H, $C_{6'}$-H), 5.31 (2H, s, C_4-CH_2), 2.58 (2H, t, *J* 7.6 Hz, $C_{4'}$-C$\underline{H_2}$$CH_2CH_3$), 1.71−1.58 (2H, m, $C_{4'}$-CH_2C$\underline{H_2}$$CH_3$), 0.95 (3H, t, 7.6 Hz, $C_{4'}$-CH_2CH_2C$\underline{H_3}$); ^{13}C NMR (100 MHz, 3:1 *v/v* TFA:$CDCl_3$) δ 173.9 (C=O), 155.4 (C), 144.0 (C), 138.7 (C), 131.5 (2 × Ar-CH), 130.3 (2 × Ar-CH), 128.4 (2 × Ar-CH), 128.4 (C), 116.5 (2 × Ar-CH), 71.9 (C_4-$\underline{C}H_2$), 37.6 ($C_{4'}$-$\underline{C}H_2CH_2CH_3$), 25.0 ($C_{4'}$-$CH_2\underline{C}H_2CH_3$), 13.5 ($C_{4'}$-$CH_2CH_2\underline{C}H_3$); HRMS calcd. for $C_{17}H_{18}O_3Na$: MNa^+, 293.1154. Found: MNa^+, 293.1147.

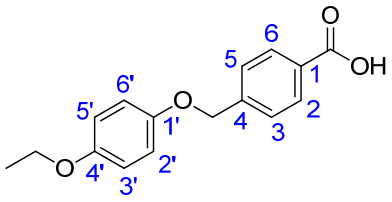
4-((4-Methoxyphenoxy)methyl)benzoic acid; 7.



Methyl ester **231** (0.50 g, 1.8 mmol) was reacted with 2 M aq KOH (1.4 mL, 2.8 mmol) using Procedure B. Acid **7** was obtained as an off- white solid (0.46 g, 97%).

IR ν_{max} (ATR): 3026, 2998, 1739, 1367, 1214 cm^{-1}; decomp 236−238 ºC; ^{1}H NMR (400 MHz, 5:1 *v/v* TFA:$CDCl_3$) δ 8.18 (2H, d, *J* 8.5 Hz, 2 × Ar-H; C_2-H, C_6-H), 7.60 (2H, d, *J* 8.5 Hz, 2 × Ar-H; C_3-H, C_5-H), 7.06 (2H, d, *J* 9.2 Hz, 2 × Ar-H; $C_{2'}$-H, $C_{6'}$-H), 7.03 (2H, d, *J* 9.2 Hz, 2 × Ar-H; $C_{3'}$-H, $C_{5'}$-H), 5.29 (2H, s, C_4-CH_2), 3.98 (3H, s, $C_{4'}$-OCH_3); ^{13}C NMR (100 MHz, 5:1 *v/v* TFA:$CDCl_3$) δ 174.0 (C=O), 153.9 (C), 153.5 (C), 143.9 (C), 131.6 (2 × Ar-CH), 128.6 (C), 128.5 (2 × Ar-CH), 118.3 (2 × Ar-CH), 117.0 (2 × Ar-CH), 72.5 (C_4-$\underline{C}H_2$), 57.5 ($C_{4'}$-O$\underline{C}H_3$); HRMS calcd. for $C_{15}H_{14}O_4Na$: MNa^+, 281.0790. Found: MNa^+, 281.0784.

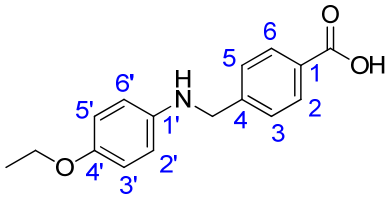
4-((4-Ethoxyphenoxy)methyl)benzoic acid; 8.



Methyl ester **232** (1.5 g, 5.2 mmol) was reacted with 2 M aq KOH (5.2 mL, 10.4 mmol) using Procedure B. Acid **8** was obtained as a white solid (1.5 g, 99%).

IR ν_{max} (ATR): 3315, 2973, 1739, 1678, 1367, 1215 cm^{-1}; decomp 289−291 ºC; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.84 (2H, d, *J* 8.0 Hz, 2 × Ar-H; C_2-H, C_6-H), 7.33 (2H, d, *J* 8.0 Hz, 2 × Ar-H; C_3-H, C_5-H), 6.91 (2H, d, *J* 9.1 Hz, 2 × Ar-H; $C_{2'}$-H, $C_{6'}$-H), 6.83 (2H, d, *J* 9.1 Hz, 2 × Ar-H; $C_{3'}$-H, $C_{5'}$-H), 5.02 (2H, s, C_4-CH_2), 3.94 (2H, q, *J* 7.0 Hz, $C_{4'}$-O$\underline{CH_2}$$CH_3$), 1.28 (3H, t, *J* 7.0 Hz, $C_{4'}$-$OCH_2C\underline{H_3}$); ^{13}C NMR (100 MHz, DMSO-d_6) δ 169.9 (C=O), 155.8 (C), 154.9 (C), 144.5 (C), 143.7 (C), 129.0 (2 × Ar-CH), 126.4 (2 × Ar-CH), 115.7 (2 × Ar-CH), 115.2 (2 × Ar-CH), 69.6 (C_4-$\underline{C}H_2$), 63.3 ($C_{4'}$-O$\underline{C}H_2CH_3$), 14.7 ($C_{4'}$-$OCH_2\underline{C}H_3$); LRMS $[M-H]^-$ 271.0; HRMS calcd. for $C_{16}H_{16}O_4K$: MK^+, 311.0686. Found: MK^+, 311.0680.

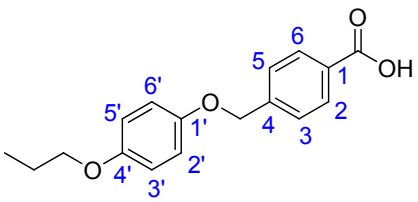
4-(((4-Ethoxyphenyl)amino)methyl)benzoic acid; 10.



Methyl ester **234** (0.50 g, 1.8 mmol) was reacted with 2 M aq KOH (0.88 mL, 1.8 mmol) using Procedure B. Acid **10** was obtained as a yellow solid (0.37 g, 78%).

IR ν_{max} (ATR): 2975, 2964, 1680, 1514, 1242 cm^{-1}; mp 251−253 ºC; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.87 (2H, d, *J* 8.2 Hz, 2 × Ar-H; C_2-H, C_6-H), 7.42 (2H, d, *J* 8.2 Hz, 2 × Ar-H; C_3-H, C_5-H), 6.66 (2H, d, *J* 8.9 Hz, 2 × Ar-H; $C_{2'}$-H, $C_{6'}$-H), 6.49 (2H, d, *J* 8.9 Hz, 2 × Ar-H; $C_{3'}$-H, $C_{5'}$-H), 5.90 (1H, br. s, NH), 4.26 (2H, s, C_4-CH_2), 3.84 (2H, q, *J* 7.0 Hz, $C_{4'}$-O$\underline{CH_2}$$CH_3$), 1.24 (3H, t, *J* 7.0 Hz, $C_{4'}$-$OCH_2C\underline{H_3}$); ^{13}C NMR (100 MHz, DMSO-d_6) δ 167.6 (C=O), 149.9 (C), 145.1 (C), 142.7 (C), 131.1 (C), 129.2 (2 × Ar-CH), 126.9 (2 × Ar-CH), 115.3 (2 × Ar-CH), 113.3 (2 × Ar-CH), 63.3 ($C_{4'}$-O$\underline{C}H_2CH_3$), 47.1 (C_4-$\underline{C}H_2$), 14.9 ($C_{4'}$-$OCH_2\underline{C}H_3$); LRMS $[M-H]^-$ 270.1; HRMS calcd. for $C_{16}H_{18}NO_3$: MH^+, 272.1287. Found: MH^+, 272.1281.

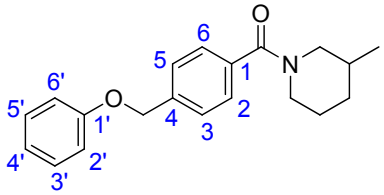
4-((4-Propoxyphenoxy)methyl)benzoic acid; 9.



Methyl ester **233** (0.22 g, 0.74 mmol) was reacted with 2 M aq KOH (0.74 mL, 1.5 mmol) using Procedure B. Acid **9** was obtained as a white solid (0.22 g, quant.).

IR ν_{max} (ATR): 3040, 2937, 1690, 1509, 1228 cm^{-1}; mp 285−287 ºC; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.83 (2H, d, *J* 8.0 Hz, 2 × Ar-H; C_2-H, C_6-H), 7.32 (2H, d, *J* 8.0 Hz, 2 × Ar-H; C_3-H, C_5-H), 6.92 (2H, d, *J* 9.2 Hz, 2 × Ar-H; $C_{2'}$-H, $C_{6'}$-H), 6.84 (2H, d, *J* 9.2 Hz, 2 × Ar-H; $C_{3'}$-H, $C_{5'}$-H), 5.02 (2H, s, C_4-CH_2), 3.85 (2H, q, *J* 6.5 Hz, $C_{4'}$-O$\underline{C}H_2CH_2CH_3$), 1.69 (3H, m, $C_{4'}$-OCH$_2$C$\underline{H}_2$CH$_3$); 0.96 (3H, t, *J* 7.3 Hz, $C_{4'}$-OCH$_2$CH$_2$C$\underline{H}_3$); ^{13}C NMR (100 MHz, DMSO-d_6) δ 168.8 (C=O), 153.5 (C), 152.7 (C), 139.9 (C), 137.9 (C), 128.3 (2 × Ar-CH), 126.0 (2 × Ar-CH), 115.3 (2 × Ar-CH), 115.0 (2 × Ar-CH), 69.2 (C_4-$\underline{C}H_2$), 68.6 ($C_{4'}$-O$\underline{C}H_2CH_2CH_3$), 21.6 ($C_{4'}$-OCH$_2\underline{C}H_2$CH$_3$), 10.1 ($C_{4'}$-OCH$_2$CH$_2\underline{C}H_3$); LRMS [M-H]$^-$ 285.1; HRMS calcd. for $C_{17}H_{18}O_4K$: MK^+, 325.0842. Found: MK^+, 325.0837.

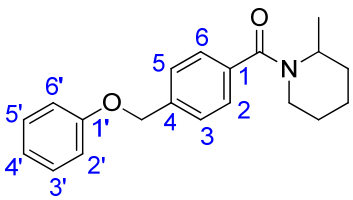
(3-Methylpiperidin-1-yl)(4-(phenoxymethyl)phenyl)methanone; S50.



Phenoxy acid **3** (50 mg, 0.22 mmol) was reacted with HATU (100 mg, 0.26 mmol), DIPEA (92 µL, 0.53 mmol) and 3-methylpiperidine (51 µL, 0.44 mmol) using Procedure C. The product was purified by Method C to afford the desired *amide* **S50** as a white solid (34 mg, 50%).

HPLC Retention time: 27.95 min; IR ν_{max} (ATR): 2938, 1738, 1629, 1435, 1377, 1238 cm^{-1}; mp 54−56 ºC; R_f [98:2 *v/v* DCM:MeOH] = 0.38; ^{1}H NMR (400 MHz, Tol-d_8, 350 K) δ 7.31 (2H, d, *J* 8.0 Hz, 2 × Ar-H; C_2-H, C_6-H), 7.18 (2H, d, *J* 8.0 Hz, 2 × Ar-H; C_3-H, C_5-H), partially hidden 7.09 (2H, app. t, *J* 8.0 Hz, 2 × Ar-H; $C_{3'}$-H, $C_{5'}$-H), 6.81 (2H, d, *J* 8.0 Hz, 2 × Ar-H; $C_{2'}$-H, $C_{6'}$-H), partially hidden 6.80 (1H, app. t, *J* 8.0 Hz, Ar-H; $C_{4'}$-H), 4.71 (2H, s, C_4-CH_2), 3.96 (2H, br. d, 2 × pip NCH$\underline{H}$H), 2.60 (1H, td, *J* 7.0, 3.6 Hz, pip NCH$\underline{H}$), 2.30 (1H, dd, *J* 12.4, 10.4 Hz, pip NCH$\underline{H}$), 1.54−1.45 (1H, m, pip CH), 1.44−1.16 (3H, m, pip C$\underline{H}$CH$_3$ and pip CH_2), 0.82 (1H, ddd, *J* 24.0, 11.0, 4.0 Hz, pip CH), 0.63 (3H, d, *J* 6.5 Hz, pip CHC$\underline{H}_3$); ^{13}C NMR (100 MHz, Tol-d_8, 350 K) δ 169.5 (C=O), 159.7 (C), 139.1 (C), 137.4 (C), 129.8 (2 × Ar-CH), 127.8 (2 × Ar-CH), 127.3 (2 × Ar-CH), 121.5 (Ar-CH), 115.6 (2 × Ar-CH), 70.0 (C_4-$\underline{C}H_2$), 52.4 (pip N$\underline{C}H_2$, br.), 45.7 (pip NCH$_2$, br.), 33.6 (pip CH_2), 31.6 (pip CH), 25.7 (pip CH_2), 18.8 (pip CH$\underline{C}$H$_3$); LRMS [M+H]$^+$ 310.2; HRMS calcd. for $C_{20}H_{23}NO_2Na$: MNa^+, 332.1626. Found: MNa^+, 332.1623.

(2-Methylpiperidin-1-yl)(4-(phenoxymethyl)phenyl)methanone; S51.

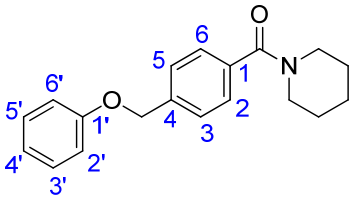


Phenol acid **3** (50 mg, 0.22 mmol) was reacted with HATU (100 mg, 0.26 mmol), DIPEA (92 µL, 0.53 mmol) and 2-methylpiperidine (51 µL, 0.44 mmol)

using Procedure C. The product was purified by Method C to afford the desired *amide* **S51** as a white solid (46 mg, 68%).

HPLC Retention time: 27.20 min; IR ν_{max} (ATR): 2940, 1737, 1365, 1211 cm^{-1}; mp 63−65 ºC; R_f [98:2 *v/v* DCM:MeOH] = 0.25; ^{1}H NMR (400 MHz, Tol-d_8, 350 K) δ 7.29 (2H, d, *J* 7.6 Hz, 2 × Ar-H; C_2-H, C_6-H), 7.19 (2H, d, *J* 7.6 Hz, 2 × Ar-H; C_3-H, C_5-H), partially hidden 7.09 (2H, app. t, *J* 8.1, 7.3 Hz, 2 × Ar-H; $C_{3'}$-H, $C_{5'}$-H), 6.83 (2H, d, *J* 8.1 Hz, 2 × Ar-H; $C_{2'}$-H, $C_{6'}$-H), partially hidden 6.79 (1H, app. t, *J* 7.3 Hz, Ar-H; $C_{4'}$-H), 4.72 (2H, s, C_4-CH_2), 4.55−4.44 (1H, br. m, pip C<u>H</u>CH_3), 3.93 (1H, br. d, pip NC<u>H</u>H), 2.68 (1H, td, *J* 7.2, 4.4 Hz, pip NCH<u>H</u>), 1.54−1.09 (6H, m, 3 × pip CH_2), 0.99 (3H, d, *J* 6.9 Hz, pip CHC<u>H</u>$_3$); ^{13}C NMR (100 MHz, Tol-d_8, 350 K) δ 169.9 (C=O), 159.7 (C), 138.9 (C), 137.9 (C), 129.8 (2 × Ar-CH), 127.5 (2 × Ar-CH), 127.4 (2 × Ar-CH), 121.5 (Ar-CH) 115.6 (2 × Ar-CH), 70.0 (C_4-<u>C</u>H_2), 47.3 (pip C<u>H</u>CH_3), 40.2 (pip CH_2), 30.7 (pip CH_2), 26.4 (pip CH_2), 19.5 (pip CH_2), 16.0 (pip CH<u>C</u>H_3); LRMS $[M+H]^+$ 310.2; HRMS calcd. for $C_{20}H_{23}NO_2Na$: MNa^+, 332.1626. Found: MNa^+, 332.1622.

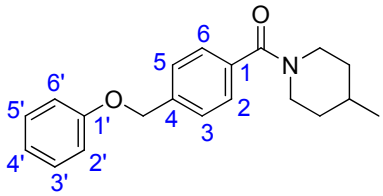
(4-(Phenoxymethyl)phenyl)(piperidin-1-yl)methanone; S52.



Phenol acid **3** (50 mg, 0.22 mmol) was reacted with HATU (100 mg, 0.26 mmol), DIPEA (92 µL, 0.53 mmol) and piperidine (43 µL, 0.44 mmol) using Procedure C. The product was purified by Method C to afford the desired *amide* **S52** as a white solid (40 mg, 62%).

HPLC Retention time: 25.15 min; IR ν_{max} (ATR): 2939, 1675, 1630, 1441, 1240 cm^{-1}; mp 94−96 ºC; R_f [98:2 *v/v* DCM:MeOH] = 0.22; ^{1}H NMR (400 MHz, Tol-d_8, 350 K) δ 7.30 (2H, d, *J* 7.9 Hz, 2 × Ar-H; C_2-H, C_6-H), 7.18 (2H, d, *J* 7.9 Hz, 2 × Ar-H; C_3-H, C_5-H), partially hidden 7.09 (2H, app. t, *J* 8.6, 7.5 Hz, 2 × Ar-H; $C_{3'}$-H, $C_{5'}$-H), 6.83 (2H, d, *J* 8.6 Hz, 2 × Ar-H; $C_{2'}$-H, $C_{6'}$-H), partially hidden 6.79 (1H, app. t, *J* 7.5 Hz, Ar-H; $C_{4'}$-H), 4.71 (2H, s, C_4-CH_2), 3.29 (4H, br. s, 2 × pip NCH_2), 1.34−1.27 (2H, m, pip CH_2), 1.27−1.18 (4H, m, 2 × pip CH_2); ^{13}C NMR (100 MHz, Tol-d_8, 350 K) δ 169.6 (C=O), 159.7 (C), 139.0 (C), 137.4 (C), 129.8 (2 × Ar-CH), 127.8 (2 × Ar-CH), 127.3 (2 × Ar-CH), 121.5 (Ar-CH), 115.6 (2 × Ar-CH), 70.0 (C_4-<u>C</u>H_2), 46.1 (2 × pip NCH_2, br.), 26.4 (2 × pip CH_2), 25.1 (pip CH_2); LRMS $[M+H]^+$ 296.2; HRMS calcd. for $C_{19}H_{21}NO_2Na$: MNa^+, 318.1470. Found: MNa^+, 318.1465.

(4-Methylpiperidin-1-yl)(4-(phenoxymethyl)phenyl)methanone; S53.

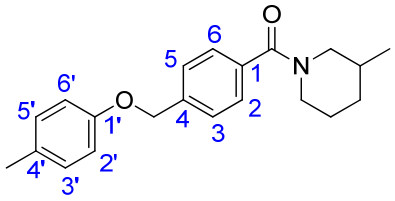


Phenol acid **3** (50 mg, 0.22 mmol) was reacted with HATU (100 mg, 0.26 mmol), DIPEA (92 µL, 0.53 mmol) and 4-methylpiperidine (52 µL, 0.44 mmol)

using Procedure C. The product was purified by Method C to afford the desired *amide* **S53** as a white solid (45 mg, 66%).

HPLC Retention time: 28.55 min; IR ν_{max} (ATR): 2920, 1739, 1630, 1444, 1373, 1234 cm^{-1}; mp 64−66 ºC; R_f [98:2 *v/v* DCM:MeOH] = 0.32; ^{1}H NMR (400 MHz, Tol-d_8, 350 K) δ 7.31 (2H, d, *J* 7.7 Hz, 2 × Ar-H; C_2-H, C_6-H), 7.19 (2H, d, *J* 7.7 Hz, 2 × Ar-H; C_3-H, C_5-H), 7.10 (2H, app. t, *J* 8.0 Hz, 2 × Ar-H; $C_{3'}$-H, $C_{5'}$-H), 6.84 (2H, d, *J* 8.0 Hz, 2 × Ar-H; $C_{2'}$-H, $C_{6'}$-H), partially hidden 6.80 (1H, app. t, *J* 8.0 Hz, Ar-H; $C_{4'}$-H), 4.72 (2H, s, C_4-CH_2), 4.07 (2H, br. s, 2 × pip NC<u>H</u>H), 2.55 (2H, app. t, *J* 12.6 Hz, 2 × pip NCH<u>H</u>), 1.40−1.11 (3H, m, 3 × pip CH), 0.98−0.83 (2H, m, 2 × pip CH), 0.73 (3H, d, *J* 5.9 Hz, pip CHC<u>H</u>$_3$); ^{13}C NMR (100 MHz, Tol-d_8, 350 K) δ 169.7 (C=O), 159.7 (C), 139.2 (C), 137.1 (C), 129.8 (2 × Ar-CH), 127.8 (2 × Ar-CH), 127.4 (2 × Ar-CH), 121.5 (Ar-CH), 115.6 (2 × Ar-CH), 70.0 (C_4-<u>C</u>H_2), 45.4 (2 × pip NCH_2, br.), 34.7 (2 × pip CH_2), 31.5 (pip CH_2), 21.7 (pip CH<u>C</u>H_3); LRMS $[M+H]^+$ 310.2; HRMS calcd. for $C_{20}H_{23}NO_2Na$: MNa^+, 332.1626. Found: MNa^+, 332.1622.

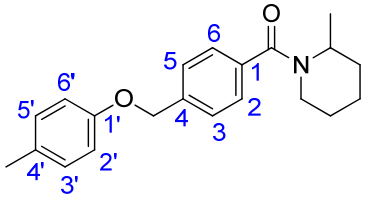
(3-Methylpiperidin-1-yl)(4-((*p*-tolyloxy)methyl)phenyl)methanone; S54.



Cresol acid **236** (50 mg, 0.21 mmol) was reacted with HATU (94 mg, 0.25 mmol), DIPEA (86 µL, 0.49 mmol) and 3-methylpiperidine (48 µL, 0.41 mmol) using Procedure C. The product was purified by Method A to afford the desired *amide* **S54** as a white solid (42 mg, 62%).

HPLC Retention time: 33.44 min; IR ν_{max} (ATR): 2939, 1739, 1631, 1511, 1436, 1375, 1232 cm^{-1}; mp 84−86 ºC; R_f [98:2 *v/v* DCM:MeOH] = 0.41; ^{1}H NMR (400 MHz, Tol-d_8, 350 K) δ 7.31 (2H, d, *J* 8.1 Hz, 2 × Ar-H; C_2-H, C_6-H), 7.20 (2H, d, *J* 8.1 Hz, 2 × Ar-H; C_3-H, C_5-H), 6.90 (2H, d, *J* 8.4 Hz, 2 × Ar-H; $C_{3'}$-H, $C_{5'}$-H), 6.77 (2H, d, *J* 8.4 Hz, 2 × Ar-H; $C_{2'}$-H, $C_{6'}$-H), 4.73 (2H, s, C_4-CH_2), 3.95 (2H, br. d, 2 × pip NC<u>H</u>H), 2.60 (1H, ddd, *J* 11.0, 4.0 Hz, pip NCH<u>H</u>), 2.30 (1H, dd, *J* 13.0, 11.0 Hz, pip NCH<u>H</u>), 2.11 (3H, s, $C_{4'}$-CH_3), 1.54−1.44 (1H, m, pip CH), 1.43−1.14 (3H, m, 3 × pip CH), 0.88−0.75 (1H, m, pip CH), 0.62 (3H, d, *J* 6.6 Hz, pip CHC<u>H</u>$_3$); ^{13}C NMR (100 MHz, Tol-d_8, 350 K) δ 169.7 (C=O), 157.7 (C), 139.4 (C), 137.1 (C), 130.5 (C), 130.3 (2 × Ar-CH), 127.8 (2 × Ar-CH), 127.3 (2 × Ar-CH), 115.5 (2 × Ar-CH), 70.2 (C_4-<u>C</u>H_2), 52.2 (pip NCH_2, br.), 45.8 (pip NCH_2, br.), 33.6 (pip CH_2), 31.6 (pip CH), 25.7 (pip CH_2), 20.5 ($C_{4'}$-<u>C</u>H_3), 18.8 (pip CH<u>C</u>H_3); LRMS $[M+H]^+$ 324.3; HRMS calcd. for $C_{21}H_{26}NO_2Na$: MH^+, 324.1964. Found: MH^+, 324.1959.

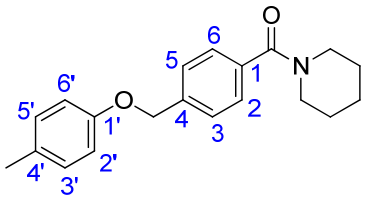
(2-Methylpiperidin-1-yl)(4-((*p*-tolyloxy)methyl)phenyl)methanone; 14.



Cresol acid **236** (50 mg, 0.21 mmol) was reacted with HATU (94 mg, 0.25 mmol), DIPEA (86 µL, 0.49 mmol) and 2-methylpiperidine (48 µL, 0.41 mmol) using Procedure C. The product was purified by Method A to afford the desired *amide* **14** as a white solid (45 mg, 68%).

HPLC Retention time: 32.32 min; IR ν_{max} (ATR): 2942, 1737, 1625, 1510, 1428, 1239 cm^{-1}; mp 86−87 ºC; R_f [98:2 *v/v* DCM:MeOH] = 0.44; ^{1}H NMR (400 MHz, Tol-d_8, 350 K) δ 7.29 (2H, d, *J* 8.1 Hz, 2 × Ar-H; C_2-H, C_6-H), 7.20 (2H, d, *J* 8.1 Hz, 2 × Ar-H; C_3-H, C_5-H), 6.90 (2H, d, *J* 8.5 Hz, 2 × Ar-H; $C_{3'}$-H, $C_{5'}$-H), 6.77 (2H, d, *J* 8.5 Hz, 2 × Ar-H; $C_{2'}$-H, $C_{6'}$-H), 4.73 (2H, s, C_4-CH_2), 4.73 (1H, br. t, *J* 6.4 Hz, pip C<u>H</u>CH_3), 3.93 (1H, br. d, *J* 12.5 Hz, pip NC<u>H</u>H), 2.74−2.62 (1H, m, pip NCH<u>H</u>), 2.11 (3H, s, $C_{4'}$-CH_3), 1.52−1.10 (6H, m, 3 × pip CH_2), 0.99 (3H, d, *J* 6.9 Hz, pip CHC<u>H</u>$_3$); ^{13}C NMR (100 MHz, Tol-d_8, 350 K) δ 169.9 (C=O), 157.7 (C), 139.1 (C), 137.8 (C), 130.4 (C), 130.3 (2 × Ar-CH), 127.4 (2 × Ar-CH), 127.4 (2 × Ar-CH), 115.5 (2 × Ar-CH), 70.2 (C_4-<u>C</u>H_2), 47.2 (pip C<u>H</u>CH_3, br.), 40.2 (pip CH_2, br.), 30.7 (pip CH_2), 26.4 (pip CH_2), 20.5 ($C_{4'}$-<u>C</u>H_3), 19.5 (pip CH_2), 16.0 (pip CH<u>C</u>H_3); LRMS $[M+H]^+$ 324.3; HRMS calcd. for $C_{21}H_{25}NO_2Na$: MNa^+, 346.1783. Found: MNa^+, 346.1779.

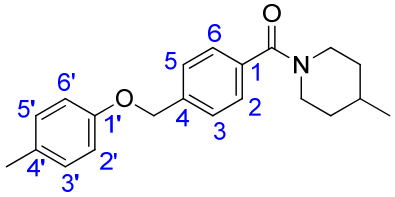
Piperidin-1-yl(4-((*p*-tolyloxy)methyl)phenyl)methanone; S55.



Cresol acid **236** (50 mg, 0.21 mmol) was reacted with HATU (94 mg, 0.25 mmol), DIPEA (86 µL, 0.49 mmol) and piperidine (41 µL, 0.41 mmol) using Procedure C. The product was purified by modified Method A without HPLC purification, to afford the desired *amide* **S55** as a white solid (39 mg, 61%).

IR ν_{max} (ATR): 2920, 1739, 1632, 1510, 1436, 1368, 1229 cm^{-1}; mp 99−100 ºC; R_f [98:2 *v/v* DCM:MeOH] = 0.32; ^{1}H NMR (400 MHz, Tol-d_8, 350 K) δ 7.30 (2H, d, *J* 8.0 Hz, 2 × Ar-H; C_2-H, C_6-H), 7.20 (2H, d, *J* 8.0 Hz, 2 × Ar-H; C_3-H, C_5-H), 6.90 (2H, d, *J* 8.7 Hz, 2 × Ar-H; $C_{3'}$-H, $C_{5'}$-H), 6.77 (2H, d, *J* 8.7 Hz, 2 × Ar-H; $C_{2'}$-H, $C_{6'}$-H), 4.74 (2H, s, C_4-CH_2), 3.29 (4H, br. s, 2 × pip NCH_2), 2.11 (3H, s, $C_{4'}$-CH_3), 1.36−1.28 (2H, m, pip CH_2), 1.27−1.19 (4H, m, 2 × pip CH_2); ^{13}C NMR (100 MHz, Tol-d_8, 350 K) δ 169.6 (C=O), 157.7 (C), 139.3 (C), 137.3 (C), 130.5 (C), 130.3 (2 × Ar-CH), 127.8 (2 × Ar-CH), 127.3 (2 × Ar-CH), 115.5 (2 × Ar-CH), 70.2 (C_4-<u>C</u>H_2), 46.0 (2 × pip NCH_2, br.), 26.4 (2 × pip CH_2), 25.1 (pip CH_2), 20.4 ($C_{4'}$-CH_3); LRMS $[M+H]^+$ 310.2; HRMS calcd. for $C_{20}H_{23}NO_2Na$: MNa^+, 332.1626. Found: MNa^+, 332.1622.

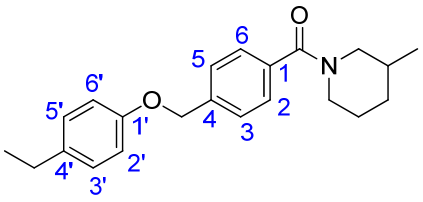
(4-Methylpiperidin-1-yl)(4-((*p*-tolyloxy)methyl)phenyl)methanone; 19.



Cresol acid **4** (50 mg, 0.21 mmol) was reacted with HATU (94 mg, 0.25 mmol), DIPEA (86 µL, 0.49 mmol) and 4-methylpiperidine (49 µL, 0.41 mmol) using Procedure C. The product was purified by Method A to afford the desired *amide* **19** as a white solid (42 mg, 63%).

HPLC Retention time: 33.69 min; IR ν_{max} (ATR): 2921, 1739, 1631, 1511, 1439, 1374, 1234 cm^{-1}; mp 100−101 ºC; R_f [98:2 *v/v* DCM:MeOH] = 0.43; ^1H NMR (400 MHz, Tol-d_8, 350 K) δ 7.32 (2H, d, *J* 8.0 Hz, 2 × Ar-H; C_2-H, C_6-H), 7.20 (2H, d, *J* 8.0 Hz, 2 × Ar-H; C_3-H, C_5-H), 6.90 (2H, d, *J* 8.4 Hz, 2 × Ar-H; $C_{3'}$-H, $C_{5'}$-H), 6.77 (2H, d, *J* 8.4 Hz, 2 × Ar-H; $C_{2'}$-H, $C_{6'}$-H), 4.74 (2H, s, C_4-CH_2), 4.10 (2H, br. s, 2 × pip NCHH), 2.54 (2H, td, *J* 12.9, 3.2 Hz, 2 × pip NCHH), 2.11 (3H, s, $C_{4'}$-CH_3), 1.41−1.15 (3H, m, 3 × pip CH), 0.91 (2H, ddd, *J* 24.0, 12.6, 4.6 Hz, 2 × pip CH), 0.74 (3H, d, *J* 6.3 Hz, pip CHCH_3); ^{13}C NMR (100 MHz, Tol-d_8, 350 K) δ 169.5 (C=O), 157.7 (C), 139.3 (C), 137.3 (C), 130.5 (C), 130.3 (2 × Ar-CH), 127.8 (2 × Ar-CH), 127.3 (2 × Ar-CH), 115.5 (2 × Ar-CH), 70.2 (C_4-CH_2), 45.4 (2 × pip NCH_2, br.), 34.7 (2 × pip CH_2), 31.5 (pip $CHCH_3$), 21.7 (pip $CHCH_3$), 20.4 ($C_{4'}$-CH_3, *via* HSQC); LRMS $[M+H]^+$ 324.3; HRMS calcd. for $C_{21}H_{25}NO_2Na$: MNa^+, 346.1783. Found: MNa^+, 346.1779.

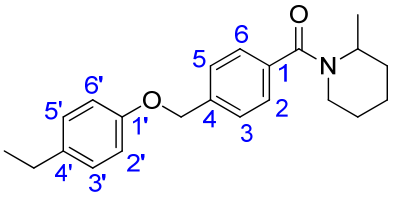
(4-((4-Ethylphenoxy)methyl)phenyl)(3-methylpiperidin-1-yl)methanone; S56.



4-Ethylphenol acid **5** (50 mg, 0.20 mmol) was reacted with HATU (89 mg, 0.23 mmol), DIPEA (82 µL, 0.47 mmol) and 3-methylpiperidine (46 µL, 0.39 mmol) using Procedure C. The product was purified by Method A to afford the desired *amide* **S56** as a white solid (39 mg, 59%).

HPLC Retention time: 36.35 min; IR ν_{max} (ATR): 2939, 1739, 1634, 1510, 1436, 1366, 1214 cm^{-1}; mp 70−71 ºC; R_f [98:2 *v/v* DCM:MeOH] = 0.34; ^1H NMR (400 MHz, Tol-d_8, 350 K) δ 7.31 (2H, d, *J* 7.0 Hz, 2 × Ar-H; C_2-H, C_6-H), 7.21 (2H, d, *J* 7.0 Hz, 2 × Ar-H; C_3-H, C_5-H), 6.95 (2H, d, *J* 8.0 Hz, 2 × Ar-H; $C_{3'}$-H, $C_{5'}$-H), 6.80 (2H, d, *J* 8.0 Hz, 2 × Ar-H; $C_{2'}$-H, $C_{6'}$-H), 4.74 (2H, s, C_4-CH_2), 3.95 (2H, br. d, 2 × pip NCHH), 2.60 (1H, app. t, *J* 11.5 Hz, pip NCHH), 2.45 (2H, q, *J* 7.6 Hz, $C_{4'}$-CH_2CH_3), 2.30 (1H, app. t, *J* 11.5 Hz, pip NCHH), 1.50 (1H, br. d, *J* 13.0 Hz, pip $CHCH_3$), 1.45−1.16 (4H, m, 2 × pip CH_2), 1.10 (3H, t, *J* 7.6 Hz, $C_{4'}$-CH_2CH_3), 0.97−0.75 (2H, m, pip CH_2), 0.62 (3H, d, *J* 5.7 Hz, pip CHCH_3); ^{13}C NMR (100 MHz, Tol-d_8, 350 K) δ 169.6 (C=O), 157.8 (C), 139.3 (C), 137.2 (C), 137.1 (C), 129.1 (2 × Ar-CH), 127.8 (2 × Ar-CH), 127.3 (2 × Ar-CH), 115.6 (2 × Ar-CH), 70.2 (C_4-CH_2), 52.5 (pip NCH_2, br.), 45.7 (pip NCH_2, br.), 33.6 (pip CH_2), 31.6 (pip CH), 28.4 ($C_{4'}$-CH_2CH_3), 25.7 (pip CH_2), 18.8 (pip $CHCH_3$), 15.8 ($C_{4'}$-CH_2CH_3); LRMS $[M+H]^+$ 338.3; HRMS calcd. for $C_{22}H_{27}NO_2Na$: MNa^+, 360.1939. Found: MNa^+, 360.1934.

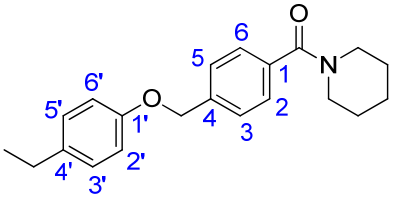
(4-((4-Ethylphenoxy)methyl)phenyl)(2-methylpiperidin-1-yl)methanone; S57.



4-Ethylphenol acid **5** (50 mg, 0.20 mmol) was reacted with HATU (89 mg, 0.23 mmol), DIPEA (82 µL, 0.47 mmol) and 2-methylpiperidine (46 µL, 0.39 mmol) using Procedure C. The product was purified by Method A to afford the desired *amide* **S57** as a white solid (31 mg, 47%).

HPLC Retention time: 35.46 min; IR ν_{max} (ATR): 2937, 1738, 1628, 1511, 1427, 1370, 1235 cm^{-1}; mp 75−76 ºC; R_f [98:2 *v/v* DCM:MeOH] = 0.38; ^{1}H NMR (400 MHz, Tol-d_8, 350 K) δ 7.29 (2H, d, *J* 8.3 Hz, 2 × Ar-H; C_2-H, C_6-H), 7.20 (2H, d, *J* 8.3 Hz, 2 × Ar-H; C_3-H, C_5-H), partially hidden 6.94 (2H, d, *J* 8.5 Hz, 2 × Ar-H; $C_{3'}$-H, $C_{5'}$-H), 6.80 (2H, d, *J* 8.5 Hz, 2 × Ar-H; $C_{2'}$-H, $C_{6'}$-H), 4.74 (2H, s, C_4-CH_2), 4.54−4.44 (1H, m, pip C<u>H</u>CH_3), 3.94 (1H, br. d, pip NC<u>H</u>H), 2.72−2.63 (1H, m, pip NCH<u>H</u>), 2.45 (2H, q,*J* 7.6 Hz, $C_{4'}$-C<u>H_2</u>CH_3), 1.52−1.13 (6H, m, 3 × pip CH_2), 1.11 (3H, t, *J* 7.6 Hz, $C_{4'}$-CH_2C<u>H_3</u>), 0.99 (3H, d, *J* 6.7 Hz, pip CHC<u>H_3</u>); ^{13}C NMR (100 MHz, Tol-d_8, 350 K) δ 169.9 (C=O), 157.8 (C), 153.9 (C), 139.1 (C), 137.1 (C), 129.1 (2 × Ar-CH), 127.5 (2 × Ar-CH), 127.4 (2 × Ar-CH), 115.6 (2 × Ar-CH), 70.2 (C_4-<u>CH_2</u>), 47.2 (pip C<u>H</u>CH_3, br.), 40.2 (pip CH_2, br.), 30.7 (pip CH_2), 28.4 ($C_{4'}$-<u>CH_2</u>CH_3), 26.4 (pip CH_2), 19.5 (pip CH_2), 16.0 (pip CH<u>CH_3</u>), 15.8 ($C_{4'}$-CH_2<u>CH_3</u>); LRMS $[M+H]^+$ 338.3; HRMS calcd. for $C_{22}H_{27}NO_2Na$: MNa^+, 360.1939. Found: MNa^+, 360.1935.

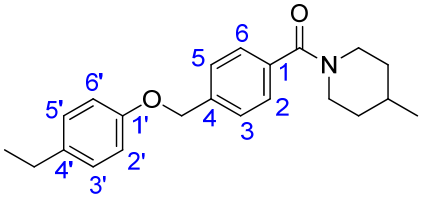
(4-((4-Ethylphenoxy)methyl)phenyl)(piperidin-1-yl)methanone; S58.



4-Ethylphenol acid **5** (21 mg, 0.08 mmol) was reacted with HATU (37 mg, 0.10 mmol), DIPEA (34 µL, 0.20 mmol) and piperidine (16 µL, 0.16 mmol) using Procedure C. The product was purified by Method A to afford the desired *amide* **S58** as a white solid (15.3 mg, 58%).

HPLC Retention time: 31.32 min; IR ν_{max} (ATR): 2938, 1737, 1631, 1441, 1374, 1232 cm^{-1}; mp 57−58 ºC; R_f [98:2 *v/v* DCM:MeOH] = 0.35; ^{1}H NMR (400 MHz, Tol-d_8, 350 K) δ 7.30 (2H, d, *J* 8.1 Hz, 2 × Ar-H; C_2-H, C_6-H), 7.20 (2H, d, *J* 8.2 Hz, 2 × Ar-H; C_3-H, C_5-H), 6.95 (2H, partially hidden d, *J* 8.6 Hz, 2 × Ar-H; $C_{3'}$-H, $C_{5'}$-H), 6.80 (2H, d, *J* 8.6 Hz, 2 × Ar-H; $C_{2'}$-H, $C_{6'}$-H), 4.74 (2H, s, C_4-CH_2), 3.29 (4H, br. s, 2 × pip NCH_2), 2.45 (2H, q, *J* 7.7 Hz, $C_{4'}$-C<u>H_2</u>CH_3), 1.34−1.27 (2H, m, pip CH_2), 1.27−1.19 (4H, m, 2 × pip CH_2), 2.45 (3H, t, *J* 7.7 Hz, $C_{4'}$-CH_2C<u>H_3</u>); ^{13}C NMR (100 MHz, Tol-d_8, 350 K) δ 169.6 (C=O), 157.9 (C), 139.3 (C), 137.3 (C), 137.2 (C), 129.1 (2 × Ar-CH), 127.8 (2 × Ar-CH), 127.3 (2 × Ar-CH), 115.6 (2 × Ar-CH), 70.2 (C_4-<u>CH_2</u>), 46.1 (2 × pip NCH_2, br.), 28.5 ($C_{4'}$-<u>CH_2</u>CH_3), 26.5 (2 × pip CH_2), 25.1 (pip CH_2), 15.9 ($C_{4'}$-CH_2<u>CH_3</u>); LRMS $[M+H]^+$ 324.0; HRMS calcd. for $C_{21}H_{25}O_2Na$: MNa^+, 346.1783. Found: MNa^+, 346.1777.

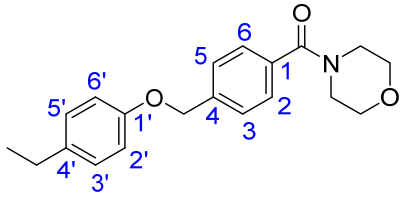
(4-((4-Ethylphenoxy)methyl)phenyl)(4-methylpiperidin-1-yl)methanone; 20.



4-Ethylphenol acid **5** (50 mg, 0.20 mmol) was reacted with HATU (89 mg, 0.23 mmol), DIPEA (82 µL, 0.47 mmol) and 4-methylpiperidine (46 µL, 0.39 mmol) using Procedure C. The product was purified by Method A to afford the desired *amide* **20** as a white solid (31 mg, 46%).

HPLC Retention time: 36.24 min; IR ν_{max} (ATR): 2971, 1738, 1633, 1510, 1442, 1372, 1229 cm^{-1}; mp 75−76 ºC; R_f [98:2 *v/v* DCM:MeOH] = 0.32; ^{1}H NMR (400 MHz, Tol-d_8, 350 K) δ 7.29 (2H, d, *J* 8.1 Hz, 2 × Ar-H; C_2-H, C_6-H), 7.20 (2H, d, *J* 8.1 Hz, 2 × Ar-H; C_3-H, C_5-H), 6.95 (2H, d, *J* 8.5 Hz, 2 × Ar-H; $C_{3'}$-H, $C_{5'}$-H), 6.80 (2H, d, *J* 8.5 Hz, 2 × Ar-H; $C_{2'}$-H, $C_{6'}$-H), 4.74 (2H, s, C_4-CH_2), 4.49 (1H, br. t, *J* 6.1 Hz, pip C<u>H</u>CH_3), 3.94 (1H, br. d, *J* 4.2 Hz, pip NC<u>H</u>H), 2.71-2.64 (1H, m, pip NC<u>H</u>H), 2.45 (2H, q, *J* 7.6 Hz, $C_{4'}$-C<u>H_2</u>CH_3), 1.49−1.14 (6H, m, 6 × pip CH), 1.11 (3H, t, *J* 7.6 Hz, $C_{4'}$-C<u>H_2</u>CH_3), 0.99 (3H, d, *J* 7.0 Hz, pip CHC<u>H_3</u>); ^{13}C NMR (100 MHz, Tol-d_8, 350 K) δ 169.9 (C=O), 157.8 (C), 139.1 (C), 137.8 (C), 137.1 (C), 129.1 (2 × Ar-CH), 127.5 (2 × Ar-CH), 127.4 (2 × Ar-CH), 115.6 (2 × Ar-CH), 70.2 (C_4-<u>C</u>H_2), 47.2 (pip NCH_2), 40.2 (pip NCH_2), 30.7 (pip <u>C</u>HCH_3), 28.4 ($C_{4'}$-<u>C</u>H_2CH_3), 26.4 (pip CH_2), 19.5 (pip CH_2), 16.0 ($C_{4'}$-CH_2<u>C</u>H_3), 15.8 (pip CH<u>C</u>H_3); LRMS $[M+H]^+$ 338.3; HRMS calcd. for $C_{22}H_{27}NO_2Na$: MNa^+, 360.1939. Found: MNa^+, 360.1935.

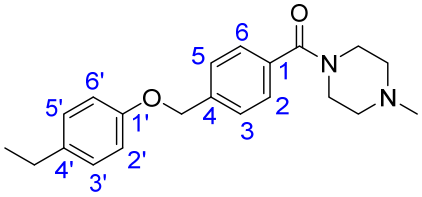
(4-((4-Ethylphenoxy)methyl)phenyl)(morpholino)methanone, 25.



4-Ethylphenol acid **5** (50 mg, 0.20 mmol) was reacted with HATU (89 mg, 0.23 mmol), DIPEA (82 µL, 0.47 mmol) and morpholine (34 µL, 0.39 mmol), stirring for 2 h using Procedure C. The product was purified *via* column chromatography (eluent: 95:5 v/v DCM:MeOH) followed by Method B (i) to afford the desired *amide* **25** as a white solid (29 mg, 46%).

HPLC Retention time: 32.27 min; IR ν_{max} (ATR): 2907, 1634, 1512, 1116 cm^{-1}; mp 96−98 ºC; ^{1}H NMR (400 MHz, Tol-d_8, 350 K) δ 7.25 (2H, d, *J* 8.0 Hz, 2 × Ar-H; C_2-H, C_6-H), 7.19 (2H, d, *J* 8.0 Hz, 2 × Ar-H; C_3-H, C_5-H), 6.95 (2H, d, *J* 8.8 Hz, 2 × Ar-H; $C_{3'}$-H, $C_{5'}$-H), 6.81 (2H, d, *J* 8.8 Hz, 2 × Ar-H; $C_{2'}$-H, $C_{6'}$-H), 4.74 (2H, s, C_4-CH_2), 3.26 (8H, br. s, 4 × morph CH_2), 2.45 (2H, q, *J* 7.6 Hz, $C_{4'}$-C<u>H_2</u>CH_3), 1.11 (3H, t, *J* 7.6 Hz, $C_{4'}$-CH_2C<u>H_3</u>); ^{13}C NMR (100 MHz, Tol-d_8, 350 K) δ 169.6 (C=O), 157.8 (C), 139.8 (C), 137.3 (C), 136.2 (C), 129.1 (2 × Ar-CH), 128.0 (2 × Ar-CH), 127.4 (2 × Ar-CH), 115.6 (2 × Ar-CH), 70.1 (C_4-<u>C</u>H_2), 67.0 (2 × morph NCH_2), 45.8 (2 × morph NCH_2, br.), 28.4 ($C_{4'}$-<u>C</u>H_2CH_3), 15.8 ($C_{4'}$-CH_2<u>C</u>H_3); LRMS $[M+H]^+$ 326.3; HRMS calcd for $C_{20}H_{23}NO_3Na$: *M*Na^+, 348.1576. Found: *M*Na^+, 348.1567.

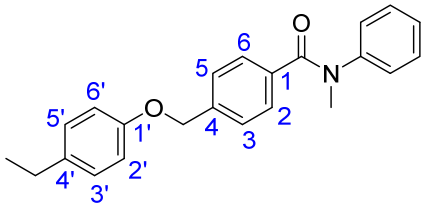
(4-((4-Ethylphenoxy)methyl)phenyl)(4-methylpiperazin-1-yl)methanone, 29.



4-Ethylphenol acid **5** (50 mg, 0.20 mmol) was reacted with HATU (89 mg, 0.23 mmol), DIPEA (82 µL, 0.47 mmol) and 1-methylpiperazine (43 µL, 0.39 mmol), stirring for 2 h using Procedure C. The product was purified *via* column chromatography (eluent: 93:5:2 v/v DCM:MeOH:Et_3N) followed by Method B (i) to afford the desired *amide* **29** as a white solid (35 mg, 53%).

HPLC Retention time: 7.37 min; IR ν_{max} (ATR): 2950, 2857, 1633, 1510, 1236 cm^{-1}; mp 75−77 ºC; ^{1}H NMR (400 MHz, Tol-d_8, 350 K) δ 7.29 (2H, d, *J* 7.8 Hz, 2 × Ar-H; C_2-H, C_6-H), 7.20 (2H, d, *J* 7.8 Hz, 2 × Ar-H; C_3-H, C_5-H), partially hidden 6.95 (2H, d, *J* 8.4 Hz, 2 × Ar-H; $C_{3'}$-H, $C_{5'}$-H), 6.81 (2H, d, *J* 8.4 Hz, 2 × Ar-H; $C_{2'}$-H, $C_{6'}$-H), 4.74 (2H, s, C_4-CH_2), 3.40 (4H, br. s, 2 × piperaz NCH_2), 2.45 (2H, q, *J* 7.6 Hz, $C_{4'}$-C$\underline{H_2}$$CH_3$), 2.02 (4H, app. t, *J* 5.0 Hz, 2 × piperaz NCH_2), 1.97 (3H, s, piperaz NCH_3), 1.11 (3H, t, *J* 7.6 Hz, $C_{4'}$-CH_2C$\underline{H_3}$); ^{13}C NMR (100 MHz, Tol-d_8, 350 K) δ 169.6 (C=O), 157.8 (C), 139.6 (C), 137.2 (C), 136.7 (C), 129.1 (2 × Ar-CH), 128.0 (2 × Ar-CH), 127.4 (2 × Ar-CH), 115.6 (2 × Ar-CH), 70.2 (C_4-$\underline{C}H_2$), 55.4 (2 × piperaz NCH_2), 45.8 (piperaz NCH_3), 45.2 (2 × piperaz NCH_2, br.), 28.4 ($C_{4'}$-$\underline{C}H_2CH_3$), 15.8 ($C_{4'}$-$CH_2\underline{C}H_3$); LRMS $[M+H]^+$ 339.2; HRMS calcd for $C_{21}H_{26}N_2O_2Na$: *M*Na^+, 361.1892. Found: *M*Na^+, 361.1886.

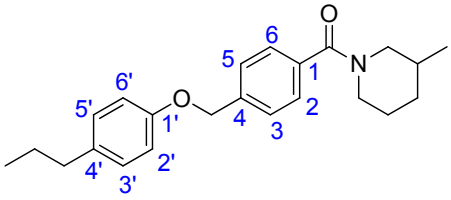
4-((4-Ethylphenoxy)methyl)-*N*-methyl-*N*-phenylbenzamide; 32.



4-Ethylphenol acid **5** (50 mg, 0.20 mmol) was used in a modification to Procedure C with HATU (89 mg, 0.23 mmol), DIPEA (82 µL, 0.47 mmol) and *N*-methylaniline (42 µL, 0.39 mmol), stirring for 12 h. The product was purified by Method B (i) to afford the desired *amide* **32** as a white solid (47 mg, 70%).

HPLC Retention time: 32.55 min; IR ν_{max} (ATR): 3836, 2926, 1653, 1512, 1241 cm^{-1}; mp 108−110 ºC; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 (2H, d, *J* 8.1 Hz, 2 × Ar-H; C_2-H, C_6-H), partially hidden 7.24 (2H, d, 2 × Ar-H), 7.22 (2H, d, *J* 8.1 Hz, 2 × Ar-H; C_3-H, C_5-H), 7.16-7.13 (1H, m, Ar-H), 7.08 (2H, d, *J* 8.6 Hz, 2 × Ar-H; $C_{2'}$-H, $C_{6'}$-H), 7.04 (2H, d, *J* 7.7 Hz, 2 × Ar-H), 6.82 (2H, d, *J* 8.6 Hz, 2 × Ar-H; $C_{3'}$-H, $C_{5'}$-H), 4.96 (2H, s, C_4-CH_2), 3.50 (3H, s, NCH_3), 2.58 (2H, q, *J* 7.6 Hz, $C_{4'}$-C$\underline{H_2}$$CH_3$), 1.20 (3H, t, *J* 7.6 Hz, $C_{4'}$-CH_2C$\underline{H_3}$); ^{13}C NMR (100 MHz, Tol-d_8, 350 K) δ 169.6 (C=O), 157.8 (C), 146.3 (C), 139.6 (C), 137.1 (C), 136.6 (C), 129.6 (2 × Ar-CH), 129.3 (2 × Ar-CH), 127.2 (2 × Ar-CH), 126.6 (2 × Ar-CH), 126.2 (Ar-CH), 115.6 (2 × Ar-CH), 70.1 (C_4-$\underline{C}H_2$), 38.2 (NCH_3), 28.4 ($C_{4'}$-$\underline{C}H_2CH_3$), 15.8 ($C_{4'}$-$CH_2\underline{C}H_3$), 1 hidden (2 × Ar-CH); LRMS $[M+H]^+$ 346.3; HRMS calcd for $C_{23}H_{23}NO_2Na$: *M*Na^+, 368.1626. Found: *M*Na^+, 368.1619.

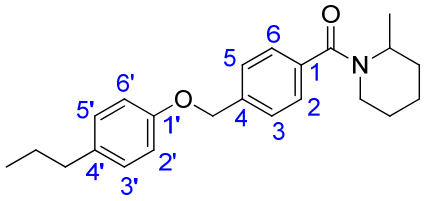
(3-Methylpiperidin-1-yl)(4-((4-propylphenoxy)methyl)phenyl)methanone; 12.



4-Propylphenol acid **6** (50 mg, 0.19 mmol) was reacted with HATU (84 mg, 0.22 mmol), DIPEA (77 µL, 0.44 mmol) and 3-methylpiperidine (43 µL, 0.37 mmol) using Procedure C. The product was purified by Method A to afford the desired *amide* **12** as a white solid (49 mg, 75%).

HPLC Retention time: 38.66 min; IR ν_{max} (ATR): 2939, 1738, 1634, 1511, 1435, 1375, 1232 cm^{-1}; mp 80−82 ºC; R_f [98:2 *v/v* DCM:MeOH] = 0.47; ^{1}H NMR (400 MHz, Tol-d_8, 350 K) δ 7.32 (2H, d, *J* 8.0 Hz, 2 × Ar-H; C_2-H, C_6-H), 7.21 (2H, d, *J* 8.0 Hz, 2 × Ar-H; C_3-H, C_5-H), 6.94 (2H, d, *J* 8.5 Hz, 2 × Ar-H; $C_{3'}$-H, $C_{5'}$-H), 6.80 (2H, d, *J* 8.5 Hz, 2 × Ar-H; $C_{2'}$-H, $C_{6'}$-H), 4.74 (2H, s, C_4-CH_2), 3.96 (2H, br. d, 2 × pip NCHH), 2.60 (1H, ddd, *J* 11.0, 4.8 Hz, pip NCHH), 2.42 (2H, t, *J* 7.4 Hz, $C_{4'}$-$CH_2CH_2CH_3$), 2.30 (1H, dd, *J* 13.0, 10.0 Hz, pip NCHH), 1.52 (2H, sex, *J* 7.4 Hz, $C_{4'}$-$CH_2CH_2CH_3$), 1.51−1.16 (4H, m, 4 × pip CH), 0.84 (3H, t, *J* 7.4 Hz, $C_{4'}$-$CH_2CH_2CH_3$), 0.87−0.76 (1H, m, pip CH), 0.63 (3H, d, *J* 6.6 Hz, pip $CHCH_3$); ^{13}C NMR (100 MHz, Tol-d_8, 350 K) δ 169.5 (C=O), 157.9 (C), 139.3 (C), 137.3 (C), 137.5 (C), 129.7 (2 × Ar-CH), 127.8 (2 × Ar-CH), 127.3 (2 × Ar-CH), 115.5 (2 × Ar-CH), 70.2 (C_4-CH_2), 52.4 (pip NCH_2, br.), 45.7 (pip NCH_2, br.), 37.7 ($C_{4'}$-$CH_2CH_2CH_3$), 33.6 (pip CH_2), 31.6 (pip CH), 25.7 (pip CH_2), 24.9 ($C_{4'}$-$CH_2CH_2CH_3$), 18.8 (pip $CHCH_3$), 13.8 ($C_{4'}$-$CH_2CH_2CH_3$); LRMS $[M+H]^+$ 323.6; HRMS calcd. for $C_{23}H_{29}NO_2Na$: MNa^+, 346.1783. Found: MNa^+, 346.1778.

(2-Methylpiperidin-1-yl)(4-((4-propylphenoxy)methyl)phenyl)methanone; 15.

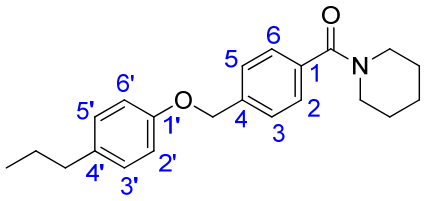


4-Propylphenol acid **6** (50 mg, 0.19 mmol) was reacted with HATU (84 mg, 0.22 mmol), DIPEA (77 µL, 0.44 mmol) and 2-methylpiperidine (43 µL, 0.37 mmol) using Procedure C. The product was purified by Method A to afford the desired *amide* **15** as a white solid (45 mg, 69%).

HPLC Retention time: 38.36 min; IR ν_{max} (ATR): 2973, 1738, 1630, 1511, 1428, 1369, 1230, 1215 cm^{-1}; mp 46−48 ºC; R_f [98:2 *v/v* DCM:MeOH] = 0.38; ^{1}H NMR (400 MHz, Tol-d_8, 350 K) δ 7.30 (2H, d, *J* 8.1 Hz, 2 × Ar-H; C_2-H, C_6-H), 7.21 (2H, d, *J* 8.0 Hz, 2 × Ar-H; C_3-H, C_5-H), 6.94 (2H, d, *J* 8.5 Hz, 2 × Ar-H; $C_{3'}$-H, $C_{5'}$-H), 6.81 (2H, d, *J* 8.5 Hz, 2 × Ar-H; $C_{2'}$-H, $C_{6'}$-H), 4.75 (2H, s, C_4-CH_2), 4.50 (1H, br. t, *J* 5.6 Hz, pip $CHCH_3$), 3.94 (1H, br. d, *J* 13.7 Hz, pip NCHH), 2.72−2.63 (1H, m, pip NCHH), 2.42 (2H, t, *J* 7.5 Hz, $C_{4'}$-$CH_2CH_2CH_3$), 1.61−1.50 (2H, m, $C_{4'}$-$CH_2CH_2CH_3$), 1.49−1.11 (6H, m, 3 × pip CH_2), 0.99 (3H, d, *J* 7.0 Hz, pip $CHCH_3$), 0.86 (3H, t, *J* 7.3 Hz, $C_{4'}$-$CH_2CH_2CH_3$); ^{13}C NMR (100 MHz, Tol-d_8, 350 K) δ 169.8 (C=O), 157.9 (C), 139.1 (C), 137.8 (C), 135.5 (C), 129.7 (2 × Ar-CH), 127.5 (2 × Ar-CH), 127.4 (2 × Ar-CH), 115.5 (2 × Ar-CH), 70.2 (C_4-CH_2), 47.2 (pip $CHCH_3$), 40.2

(pip CH_2), 37.7 ($C_{4'}$-$\underline{C}H_2CH_2CH_3$), 30.7 (pip CH_2), 26.4 (pip CH_2), 24.9 ($C_{4'}$-$CH_2\underline{C}H_2CH_3$), 19.5 (pip CH_2), 16.0 (pip $CH\underline{C}H_3$), 13.8 ($C_{4'}$-$CH_2CH_2\underline{C}H_3$); LRMS $[M+H]^+$ 352.3; HRMS calcd. for $C_{23}H_{29}NO_2Na$: MNa^+, 374.2096. Found: MNa^+, 374.2088.

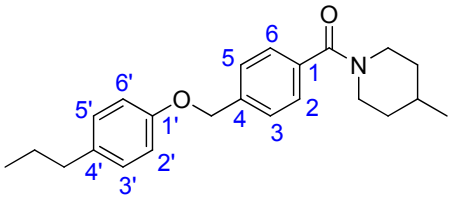
Piperidin-1-yl(4-((4-propylphenoxy)methyl)phenyl)methanone; S59.



4-Propylphenol acid **6** (50 mg, 0.19 mmol) was reacted with HATU (84 mg, 0.22 mmol), DIPEA (77 µL, 0.44 mmol) and piperidine (37 µL, 0.37 mmol) using Procedure C. The product was purified by Method A to afford the desired *amide* **S59** as a white solid (43 mg, 70%).

HPLC Retention time: 36.63 min; IR ν_{max} (ATR): 2940, 1738, 1625, 1507, 1428, 1230 cm^{-1}; mp 67−68 ºC; R_f [98:2 *v/v* DCM:MeOH] = 0.38; ^1H NMR (400 MHz, Tol-d_8, 350 K) δ 7.30 (2H, d, *J* 8.1 Hz, 2 × Ar-H; C_2-H, C_6-H), 7.20 (2H, d, *J* 8.1 Hz, 2 × Ar-H; C_3-H, C_5-H), 6.94 (2H, d, *J* 8.6 Hz, 2 × Ar-H; $C_{3'}$-H, $C_{5'}$-H), 6.80 (2H, d, *J* 8.6 Hz, 2 × Ar-H; $C_{2'}$-H, $C_{6'}$-H), 4.74 (2H, s, C_4-CH_2), 3.29 (4H, br. s, 2 × pip NCH_2), 2.42 (2H, t, *J* 7.5 Hz, $C_{4'}$-$C\underline{H}_2CH_2CH_3$), 1.60−1.46 (2H, m, $C_{4'}$-$CH_2C\underline{H}_2CH_3$), 1.35−1.27 (2H, m, pip CH_2), 1.26−1.19 (4H, m, 2 × pip CH_2), 0.86 (3H, t, *J* 7.3 Hz, $C_{4'}$-$CH_2CH_2C\underline{H}_3$); ^{13}C NMR (100 MHz, Tol-d_8, 350 K) δ 169.6 (C=O), 157.9 (C), 139.3 (C), 137.3 (C), 135.5 (C), 129.7 (2 × Ar-CH), 127.8 (2 × Ar-CH), 127.3 (2 × Ar-CH), 115.5 (2 × Ar-CH), 70.2 (C_4-$\underline{C}H_2$), 46.1 (2 × pip NCH_2, br.), 37.7 ($C_{4'}$-$\underline{C}H_2CH_2CH_3$), 26.5 (2 × pip CH_2), 25.1 (pip CH_2), 24.9 ($C_{4'}$-$CH_2\underline{C}H_2CH_3$), 13.8 ($C_{4'}$-$CH_2CH_2\underline{C}H_3$); LRMS $[M+H]^+$ 338.2; HRMS calcd. for $C_{22}H_{27}NO_2Na$: MNa^+, 360.1939. Found: MNa^+, 360.1932.

(4-Methylpiperidin-1-yl)(4-((4-propylphenoxy)methyl)phenyl)methanone; S60.

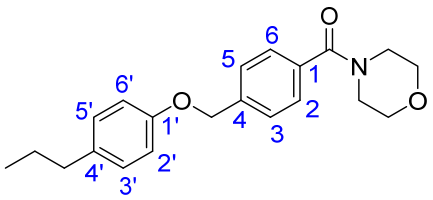


4-Propylphenol acid **6** (50 mg, 0.19 mmol) was reacted with HATU (84 mg, 0.22 mmol), DIPEA (77 µL, 0.44 mmol) and 4-methylpiperidine (44 µL, 0.37 mmol) using Procedure C. The product was purified by Method A to afford the desired *amide* **S60** as a white solid (44 mg, 68%).

HPLC Retention time: 38.98 min; IR ν_{max} (ATR): 2919, 1738, 1633, 1512, 1443, 1373, 1214 cm^{-1}; mp 63−65 ºC; R_f [98:2 *v/v* DCM:MeOH] = 0.46; ^1H NMR (400 MHz, Tol-d_8, 350 K) δ 7.31 (2H, d, *J* 8.0 Hz, 2 × Ar-H; C_2-H, C_6-H), 7.21 (2H, d, *J* 8.0 Hz, 2 × Ar-H; C_3-H, C_5-H), 6.95 (2H, d, *J* 8.6 Hz, 2 × Ar-H; $C_{3'}$-H, $C_{5'}$-H), 6.81 (2H, d, *J* 8.6 Hz, 2 × Ar-H; $C_{2'}$-H, $C_{6'}$-H), 4.75 (2H, s, C_4-CH_2), 4.08 (2H, br. s, 2 × pip NC$\underline{H}$H), 2.56 (1H, dd, *J* 12.0, 2.5 Hz, pip NCH$\underline{H}$), 2.53 (1H, dd, *J* 12.0, 2.7 Hz, pip NCH$\underline{H}$), 2.42 (2H, t, *J* 7.4 Hz, $C_{4'}$-$C\underline{H}_2CH_2CH_3$), 1.53 (2H, sex, *J* 7.4 Hz, $C_{4'}$-$CH_2C\underline{H}_2CH_3$), 1.31−1.15 (3H, m, pip $C\underline{H}CH_3$ and 2 × pip CH), 0.98−0.88 (2H, m, 2 ×

pip CH), 0.86 (3H, t, *J* 7.4 Hz, $C_{4'}$-$CH_2CH_2C\underline{H_3}$), 0.74 (3H, d, *J* 6.3 Hz, pip $CHC\underline{H_3}$); ^{13}C NMR (100 MHz, Tol-d_8, 350 K) δ 169.6 (C=O), 157.9 (C), 139.4 (C), 137.3 (C), 135.5 (C), 129.8 (2 × Ar-CH), 127.9 (2 × Ar-CH), 127.4 (2 × Ar-CH), 115.5 (2 × Ar-CH), 70.2 (C_4-$\underline{C}H_2$), 45.4 (2 × NCH_2), 37.7 ($C_{4'}$-$\underline{C}H_2CH_2CH_3$), 34.7 (2 × pip CH_2), 31.5 (pip $\underline{C}HCH_3$), 25.0 ($C_{4'}$-$CH_2\underline{C}H_2CH_3$), 21.7 (pip $CH\underline{C}H_3$), 13.8 ($C_{4'}$-$CH_2CH_2\underline{C}H_3$); LRMS $[M+H]^+$ 352.3; HRMS calcd. for $C_{23}H_{29}NO_2Na$: MNa^+, 374.2096. Found: MNa^+, 374.2088.

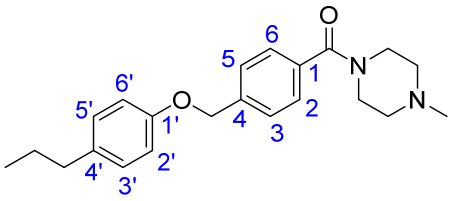
Morpholino(4-((4-propylphenoxy)methyl)phenyl)methanone, 26.



4-Propylphenol acid **6** (50 mg, 0.19 mmol) was used in a modification to Procedure C with HATU (84 mg, 0.22 mmol), DIPEA (77 µL, 0.44 mmol) and morpholine (32 µL, 0.37 mmol), stirring for 2 h. The product was purified *via* column chromatography (eluent: 95:5 v/v DCM:MeOH) followed by Method B (i) to afford the desired *amide* **26** as a white solid (32 mg, 51%).

HPLC Retention time: 34.73 min; IR ν_{max} (ATR): 3674, 2970, 2857, 1635, 1511, 1427, 1242, 1116 cm^{-1}; mp 88−90 ºC; ^{1}H NMR (400 MHz, Tol-d_8, 350 K) δ 7.24 (2H, d, *J* 8.0 Hz, 2 × Ar-H; C_2-H, C_6-H), 7.19 (2H, d, *J* 8.0 Hz, 2 × Ar-H; C_3-H, C_5-H), 6.95 (2H, d, *J* 8.8 Hz, 2 × Ar-H; $C_{3'}$-H, $C_{5'}$-H), 6.81 (2H, d, *J* 8.8 Hz, 2 × Ar-H; $C_{2'}$-H, $C_{6'}$-H), 4.74 (2H, s, C_4-CH_2), 3.26 (8H, br. s, 4 × morph CH_2), 2.42 (2H, t, *J* 7.4 Hz, $C_{4'}$-$C\underline{H_2}CH_2CH_3$), 1.53 (2H, sex, *J* 7.4 Hz, $C_{4'}$-$CH_2C\underline{H_2}CH_3$), 0.86 (3H, t, *J* 7.4 Hz, $C_{4'}$-$CH_2CH_2C\underline{H_3}$); ^{13}C NMR (100 MHz, Tol-d_8, 350 K) δ 169.6 (C=O), 157.8 (C), 139.8 (C), 136.2 (C), 135.6 (C), 129.8 (2 × Ar-CH), 127.4 (2 × Ar-CH), 115.5 (2 × Ar-CH), 70.1 (C_4-$\underline{C}H_2$), 67.0 (2 × morph NCH_2), 45.8 (2 × morph NCH_2, br.), 37.7 ($C_{4'}$-$\underline{C}H_2CH_2CH_3$), 24.9 ($C_{4'}$-$CH_2\underline{C}H_2CH_3$), 13.8 ($C_{4'}$-$CH_2CH_2\underline{C}H_3$), one peak hidden; LRMS $[M+H]^+$ 340.2; HRMS calcd for $C_{21}H_{25}NO_3Na$: *M*Na^+, 362.1732. Found: *M*Na^+, 362.1724.

(4-Methylpiperazin-1-yl)(4-((4-propylphenoxy)methyl)phenyl)methanone, S61.

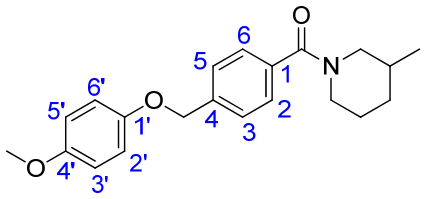


4-Propylphenol acid **6** (50 mg, 0.19 mmol) was used in a modification to Procedure C with HATU (84 mg, 0.22 mmol), DIPEA (77 µL, 0.44 mmol) and 1-methylpiperazine (41 µL, 0.37 mmol), stirring for 2 h. The product was purified *via* column chromatography (eluent: 93:5:2 v/v DCM:MeOH:Et_3N) followed by Method B (i) to afford the desired *amide* **S61** as a white solid (40 mg, 61%).

HPLC Retention time: 19.85 min; IR ν_{max} (ATR): 3759, 2952, 2858, 1630, 1512, 1242 cm^{-1}; mp 46−47 ºC; ^{1}H NMR (400 MHz, Tol-d_8, 350 K) δ 7.29 (2H, d, *J* 8.2 Hz, 2 × Ar-H; C_2-H, C_6-H), 7.20 (2H, d, *J* 8.2 Hz, 2 × Ar-H; C_3-H, C_5-H), 6.95 (2H, d, *J* 8.8 Hz, 2 × Ar-H; $C_{3'}$-H, $C_{5'}$-H), 6.81 (2H, d, *J* 8.8 Hz, 2 × Ar-H; $C_{2'}$-H, $C_{6'}$-

H), 4.74 (2H, s, C_4-CH_2), 3.40 (4H, br. s, 2 × piperaz NCH_2), 2.42 (2H, t, *J* 7.4 Hz, $C_{4'}$-$C\underline{H}_2CH_2CH_3$), 2.01 (4H, app. t, *J* 5.0 Hz, 2 × piperaz NCH_2), 1.97 (3H, s, piperaz NCH_3), 1.53 (2H, sex, *J* 7.4 Hz, $C_{4'}$-$CH_2C\underline{H}_2CH_3$), 0.86 (3H, t, *J* 7.4 Hz, $C_{4'}$-$CH_2CH_2C\underline{H}_3$); ^{13}C NMR (100 MHz, Tol-d_8, 350 K) δ 169.6 (C=O), 157.8 (C), 139.6 (C), 136.6 (C), 135.6 (C), 129.7 (2 × Ar-CH), 128.0 (2 × Ar-CH), 127.4 (2 × Ar-CH), 115.5 (2 × Ar-CH), 70.2 (C_4-$\underline{C}H_2$), 55.3 (2 × piperaz NCH_2), 45.7 (piperaz NCH_3), 45.1 (2 × piperaz NCH_2, br.), 37.7 ($C_{4'}$-$\underline{C}H_2CH_2CH_3$), 24.9 ($C_{4'}$-$CH_2\underline{C}H_2CH_3$), 13.8 ($C_{4'}$-$CH_2CH_2\underline{C}H_3$); LRMS $[M+H]^+$ 353.3; HRMS calcd for $C_{22}H_{28}N_2O_2Na$: *M*Na^+, 375.2048. Found: *M*Na^+, 375.2041.

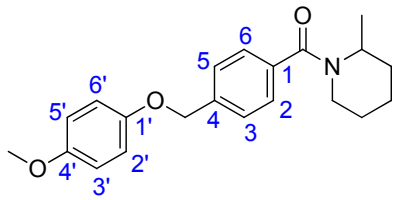
(4-((4-Methoxyphenoxy)methyl)phenyl)(3-methylpiperidin-1-yl)methanone; 11.



4-Methoxyphenol acid **7** (50 mg, 0.19 mmol) was reacted with HATU (88 mg, 0.23 mmol), DIPEA (81 µL, 0.47 mmol) and 3-methylpiperidine (46 µL, 0.39 mmol) using Procedure C. The product was purified by Method A to afford the desired *amide* **11** as a white solid (57 mg, 87%).

HPLC Retention time: 29.87 min; IR ν_{max} (ATR): 2921, 1629, 1508, 1438, 1273, 1232 cm^{-1}; mp 70−71 ºC; R_f [98:2 *v/v* DCM:MeOH] = 0.38; ^{1}H NMR (400 MHz, Tol-d_8, 350 K) δ 7.33 (2H, d, *J* 8.2. Hz, 2 × Ar-H; C_2-H, C_6-H), 7.22 (2H, d, *J* 8.2 Hz, 2 × Ar-H; C_3-H, C_5-H), 6.78 (2H, d, *J* 8.8 Hz, 2 × Ar-H; $C_{2'}$-H, $C_{6'}$-H), 6.69 (2H, d, *J* 8.8 Hz, 2 × Ar-H; $C_{3'}$-H, $C_{5'}$-H), 4.72 (2H, s, C_4-CH_2), 4.10−3.83 (2H, br. m, 2 × pip NC$\underline{H}$H), 3.40 (3H, s, $C_{4'}$-OCH_3), 2.60 (1H, td, *J* 12.0, 3.4 Hz, pip NCH$\underline{H}$), 2.31 (1H, dd, *J* 11.6, 10.3 Hz, pip NCH$\underline{H}$), 1.55−1.45 (1H, m, pip CH), 1.45−1.17 (3H, m, pip C$\underline{H}CH_3$ and pip CH_2), 0.90−0.76 (1H, m, pip CH), 0.63 (3H, d, *J* 6.9 Hz, pip CHC$\underline{H}_3$); ^{13}C NMR (100 MHz, Tol-d_8, 350 K) δ 169.5 (C=O), 155.2 (C), 153.8 (C), 139.4 (C), 137.3 (C), 127.8 (2 × Ar-CH), 127.3 (2 × Ar-CH), 116.6 (2 × Ar-CH), 115.4 (2 × Ar-CH), 70.9 (C_4-$\underline{C}H_2$), 55.5 ($C_{4'}$-$O\underline{C}H_3$), 52.5 (pip NCH_2, br.), 45.8 (pip NCH_2, br.), 33.6 (pip CH_2), 31.6 (pip CH), 25.7 (pip CH_2), 18.8 (pip CH$\underline{C}H_3$); LRMS $[M+H]^+$ 340.3; HRMS calcd. for $C_{21}H_{25}NO_3Na$: MNa^+, 362.1732. Found: MNa^+, 362.1728.

(4-((4-Methoxyphenoxy)methyl)phenyl)(2-methylpiperidin-1-yl)methanone; 16.

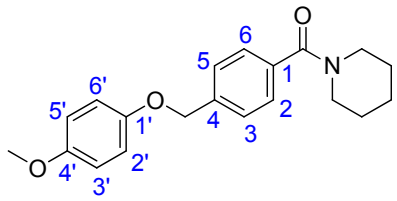


4-Methoxyphenol acid **7** (50 mg, 0.19 mmol) was reacted with HATU (88 mg, 0.23 mmol), DIPEA (81 µL, 0.47 mmol) and 2-methylpiperidine (46 µL, 0.39 mmol) using Procedure C. The product was purified by Method A to afford the desired *amide* **16** as a white solid (55 mg, 84%).

HPLC Retention time: 27.63 min; IR ν_{max} (ATR): 2930, 2872, 1626, 1508, 1428, 1232 cm^{-1}; mp 74−76 ºC; R_f [98:2 *v/v* DCM:MeOH] = 0.37; ^{1}H NMR (400

MHz, Tol-d_8, 350 K) δ 7.29 (2H, d, *J* 8.0 Hz, 2 × Ar-H; C_2-H, C_6-H), 7.21 (2H, d, *J* 8.0 Hz, 2 × Ar-H; C_3-H, C_5-H), 6.77 (2H, d, *J* 9.0 Hz, 2 × Ar-H; $C_{2'}$-H, $C_{6'}$-H), 6.69 (2H, d, *J* 9.0 Hz, 2 × Ar-H; $C_{3'}$-H, $C_{5'}$-H), 4.72 (2H, s, C_4-CH_2), 4.48 (1H, br. t, *J* 6.1 Hz, pip C<u>H</u>CH_3), 3.92 (1H, br. d, *J* 13.2 Hz, pip NC<u>H</u>H), 3.40 (3H, s, $C_{4'}$-CH_3), 2.74−2.61 (1H, m, pip NCH<u>H</u>), 1.53−1.12 (6H, m, 3 × pip CH_2), 0.99 (3H, d, *J* 6.8 Hz, pip CHC<u>H</u>$_3$); ^{13}C NMR (100 MHz, Tol-d_8, 350 K) δ 170.2 (C=O), 155.3 (C), 139.9 (C), 139.4 (C), 137.6 (C), 127.5 (2 × Ar-CH), 127.4 (2 × Ar-CH), 116.6 (2 × Ar-CH), 115.5 (2 × Ar-CH), 70.9 (C_4-<u>C</u>H_2), 55.6 ($C_{4'}$-O<u>C</u>H_3), 47.4 (pip C<u>H</u>CH_3), 40.3 (pip CH_2), 30.7 (pip CH_2), 26.4 (pip CH_2), 19.5 (pip CH_2), 16.1 (pip CH<u>C</u>H_3); LRMS $[M+H]^+$ 340.2; HRMS calcd. for $C_{21}H_{25}NO_3Na$: MNa^+, 362.1732. Found: MNa^+, 362.1727.

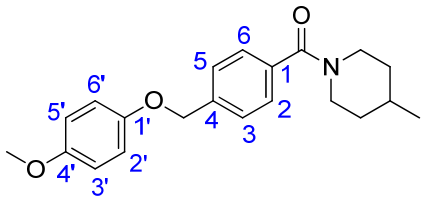
(4-((4-Methoxyphenoxy)methyl)phenyl)(piperidin-1-yl)methanone; S62.



4-Methoxyphenol acid **7** (50 mg, 0.19 mmol) was reacted with HATU (88 mg, 0.23 mmol), DIPEA (81 µL, 0.47 mmol) and piperidine (38 µL, 0.39 mmol) using Procedure C. The product was purified by Method A to afford the desired *amide* **S62** as a white solid (54 mg, 86%).

HPLC Retention time: 26.12 min; IR ν_{max} (ATR): 2940, 1740, 1632, 1509, 1445, 1367, 1215 cm^{-1}; mp 79−81 ºC; R_f [98:2 *v/v* DCM:MeOH] = 0.27; ^{1}H NMR (400 MHz, Tol-d_8, 350 K) δ 7.31 (2H, d, *J* 7.8 Hz, 2 × Ar-H; C_2-H, C_6-H), 7.21 (2H, d, *J* 7.8 Hz, 2 × Ar-H; C_3-H, C_5-H), 6.78 (2H, d, *J* 9.0 Hz, 2 × Ar-H; $C_{2'}$-H, $C_{6'}$-H), 6.69 (2H, d, *J* 9.0 Hz, 2 × Ar-H; $C_{3'}$-H, $C_{5'}$-H), 4.73 (2H, s, C_4-CH_2), 3.41 (3H, s, $C_{4'}$-OCH_3), 3.30 (4H, br. s, 2 × pip NCH_2), 1.36−1.28 (2H, m, pip CH_2), 1.27−1.17 (4H, m, 2 × pip CH_2); ^{13}C NMR (100 MHz, Tol-d_8, 350 K) δ 169.6 (C=O), 155.2 (C), 153.8 (C), 139.4 (C), 137.2 (C), 127.8 (2 × Ar-CH), 127.4 (2 × Ar-CH), 116.6 (2 × Ar-CH), 115.4 (2 × Ar-CH), 70.9 (C_4-<u>C</u>H_2), 55.5 ($C_{4'}$-O<u>C</u>H_3), 46.1 (2 × pip NCH_2, br.), 26.4 (2 × pip CH_2), 25.1 (pip CH_2); LRMS $[M+H]^+$ 326.2; HRMS calcd. for $C_{20}H_{23}NO_3Na$: MNa^+, 348.1576. Found: MNa^+, 348.1568.

(4-((4-Methoxyphenoxy)methyl)phenyl)(4-methylpiperidin-1-yl)methanone; 21.

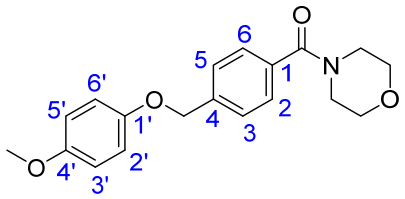


4-Methoxyphenol acid **7** (50 mg, 0.19 mmol) was reacted with HATU (88 mg, 0.23 mmol), DIPEA (81 µL, 0.47 mmol) and 4-methylpiperidine (46 µL, 0.39 mmol) using Procedure C. The product was purified by Method A to afford the desired *amide* **21** as a white solid (46 mg, 75%).

HPLC Retention time: 29.74 min; IR ν_{max} (ATR): 2955, 1738, 1631, 1508, 1444, 1374, 1232 cm^{-1}; mp 112−113 ºC; R_f [98:2 *v/v* DCM:MeOH] = 0.25; ^{1}H NMR (400 MHz, Tol-d_8, 350 K) δ 7.32 (2H, d, *J* 8.1 Hz, 2 × Ar-H; C_2-H, C_6-H), 7.21 (2H, d,

J 8.1 Hz, 2 × Ar-H; C_3-H, C_5-H), 6.78 (2H, d, *J* 9.3 Hz, 2 × Ar-H; $C_{2'}$-H, $C_{6'}$-H), 6.69 (2H, d, *J* 9.3 Hz, 2 × Ar-H; $C_{3'}$-H, $C_{5'}$-H), 4.73 (2H, s, C_4-CH_2), 4.09 (2H, br. s, 2 × pip NC<u>H</u>H), 3.40 (3H, s, $C_{4'}$-OC<u>H</u>$_3$), 2.31 (2H, td, *J* 13.8, 4.0 Hz, 2 × pip NCH<u>H</u>), 1.27 (2H, br. d, *J* 12.5 Hz, 2 × pip CH_2C<u>H</u>H), 1.24−1.16 (1H, m, pip C<u>H</u>CH_3), 0.92 (2H, ddd, *J* 24.4, 12.5, 4.4 Hz, 2 × pip CH<u>H</u>CH), 0.74 (3H, d, *J* 6.5 Hz, pip CHC<u>H</u>$_3$); ^{13}C NMR (100 MHz, Tol-d_8, 350 K) δ 169.6 (C=O), 155.3 (C), 153.9 (C), 139.4 (C), 137.3 (C), 127.8 (2 × Ar-CH *via* HSQC), 127.3 (2 × Ar-CH), 116.6 (2 × Ar-CH), 115.4 (2 × Ar-CH), 70.9 (C_4-<u>C</u>H_2), 55.5 ($C_{4'}$-O<u>C</u>H_3), 45.4 (2 × pip NCH_2, br.), 34.7 (2 × pip CH_2), 31.5 (pip <u>C</u>HCH_3), 21.7 (pip CH<u>C</u>H_3); LRMS $[M+H]^+$ 340.2; HRMS calcd. for $C_{21}H_{25}NO_3Na$: MNa^+, 362.1732. Found: MNa^+, 362.1726.

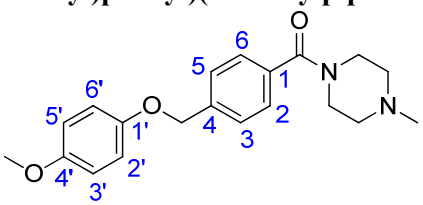
(4-((4-Methoxyphenoxy)methyl)phenyl)(morpholino)methanone; S63.



4-Methoxyphenol acid **7** (50 mg, 0.19 mmol) was reacted with HATU (88 mg, 0.23 mmol), DIPEA (81 µL, 0.47 mmol) and morpholine (34 µL, 0.39 mmol) using Procedure C. The product was purified by Method A to afford the desired *amide* **S63** as a white solid (40 mg, 63%).

HPLC Retention time: 27.3 min; IR ν_{max} (ATR): 2942, 1634, 1508, 1232, 1114 cm^{-1}; mp 105−106 ºC; ^{1}H NMR (400 MHz, Tol-d_8, 350 K) δ 7.26 (2H, d, *J* 8.2 Hz, 2 × Ar-H; C_2-H, C_6-H), 7.20 (2H, d, *J* 8.2 Hz, 2 × Ar-H; C_3-H, C_5-H), 6.78 (2H, d, *J* 9.0 Hz, 2 × Ar-H; $C_{3'}$-H, $C_{5'}$-H), 6.69 (2H, d, *J* 9.0 Hz, 2 × Ar-H; $C_{2'}$-H, $C_{6'}$-H), 4.72 (2H, s, C_4-CH_2), 3.40 (3H, s, $C_{4'}$-OC<u>H</u>$_3$), 3.27 (8H, br. s, 4 × morph CH_2); ^{13}C NMR (100 MHz, Tol-d_8, 350 K) δ 169.6 (C=O), 155.3 (C), 153.8 (C), 139.9 (C), 136.2 (C), 128.0 (2 × Ar-CH), 127.5 (2 × Ar-CH), 116.6 (2 × Ar-CH), 115.5 (2 × Ar-CH), 70.8 (C_4-<u>C</u>H_2), 67.0 (2 × morph NCH_2), 55.5 ($C_{4'}$-O<u>C</u>H_3), 45.8 (2 × morph NCH_2, br.); LRMS $[M+H]^+$ 328.3; HRMS calcd. for $C_{19}H_{21}NO_4Na$: MNa^+, 350.1368. Found: MNa^+, 350.1361.

(4-((4-Methoxyphenoxy)methyl)phenyl)(4-methylpiperazin-1-yl)methanone; 30.

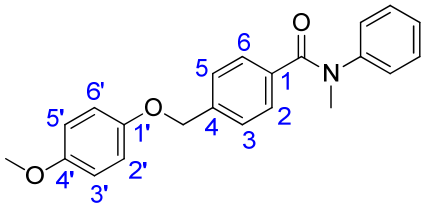


4-Methoxyphenol acid **7** (50 mg, 0.19 mmol) was reacted with HATU (88 mg, 0.23 mmol), DIPEA (81 µL, 0.47 mmol) and 1-methylpiperizine (43 µL, 0.39 mmol) using Procedure C. The product was purified by Method A to afford the desired *amide* **30** as a white solid (36 mg, 55%).

HPLC Retention time: 6.23 min; IR ν_{max} (ATR): 3555, 2951, 1630, 1508, 1323 cm^{-1}; mp 118−120 ºC; ^{1}H NMR (400 MHz, Tol-d_8, 350 K) δ 7.29 (2H, d, *J* 8.0 Hz, 2 × Ar-H; C_2-H, C_6-H), 7.21 (2H, d, *J* 8.0 Hz, 2 × Ar-H; C_3-H, C_5-H), 6.78 (2H, d, *J* 9.2 Hz, 2 × Ar-H; $C_{3'}$-H, $C_{5'}$-H), 6.69 (2H, d, *J* 9.2 Hz, 2 × Ar-H; $C_{2'}$-H, $C_{6'}$-H), 4.73 (2H, s, C_4-CH_2), 3.40 (7H, br. s, 2 × piperaz NCH_2 and $C_{4'}$-OC<u>H</u>$_3$), 2.02 (4H, app. t, *J* 5.0

Hz, 2 × piperaz NCH_2), 1.95 (3H, s, piperaz NCH_3); ^{13}C NMR (100 MHz, Tol-d_8, 350 K) δ 169.6 (C=O), 155.3 (C), 153.8 (C), 139.8 (C), 136.4 (C), 128.0 (2 × Ar-CH), 127.4 (2 × Ar-CH), 116.6 (2 × Ar-CH), 115.5 (2 × Ar-CH), 70.8 (C_4-$\underline{C}H_2$), 55.5 ($C_{4'}$-O$\underline{C}H_3$), 55.0 (2 × piperaz NCH_2), 45.4 (piperaz NCH_3), 44.7 (2 × piperaz N$\underline{C}H_2$, br.); LRMS $[M+H]^+$ 341.2; HRMS calcd. for $C_{20}H_{24}N_2O_3Na$: MNa^+, 363.1685. Found: MNa^+, 363.1679.

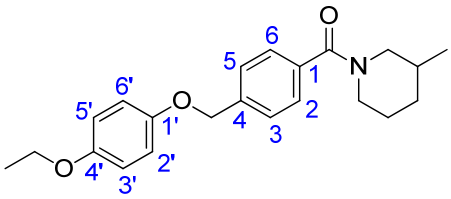
4-((4-Methoxyphenoxy)methyl)-*N*-methyl-*N*-phenylbenzamide; 30.



4-Methoxyphenol acid **7** (50 mg, 0.19 mmol) was reacted with HATU (88 mg, 0.23 mmol), DIPEA (81 µL, 0.47 mmol) and *N*-methylaniline (42 µL, 0.39 mmol) using Procedure C. The product was purified by Method A to afford the desired *amide* **30** as a white solid (19 mg, 28%).

HPLC Retention time: 33.25 min; IR ν_{max} (ATR): 3759, 2949, 1640, 1508, 1231 cm^{-1}; mp 115−117 ºC; ^1H NMR (400 MHz, $CDCl_3$) δ 7.31 (2H, d, *J* 8.0 Hz, 2 × Ar-H; C_2-H, C_6-H), 7.27−7.19 (2H, m, 2 × Ar-H), 7.21 (2H, d, *J* 8.0 Hz, 2 × Ar-H; C_3-H, C_5-H), partially hidden 7.15 (1H, t, *J* 7.2 Hz, Ar-H), 7.05 (2H, app. d, *J* 8.0 Hz, 2 × Ar-H), 6.82 (2H, d, *J* 8.0 Hz, 2 × Ar-H; $C_{2'}$-H, $C_{6'}$-H), 6.79 (2H, d, *J* 8.0 Hz, 2 × Ar-H; $C_{3'}$-H, $C_{5'}$-H), 4.92 (2H, s, C_4-CH_2), 3.75 (3H, s, $C_{4'}$-OCH_3), 3.50 (3H, s, NCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5 (C=O), 154.2 (C), 152.8 (C), 145.0 (C), 139.1 (C), 135.4 (C), 129.3 (2 × Ar-CH), 129.1 (2 × Ar-CH), 127.0 (2 × Ar-CH), 126.7 (Ar-CH), 126.6 (2 × Ar-CH), 116.1 (2 × Ar-CH), 114.8 (2 × Ar-CH), 70.3 (C_4-$\underline{C}H_2$), 55.8 (d, *J* = 1.7 Hz, $C_{4'}$-OCH_3), 38.6 (NCH_3); LRMS $[M+H]^+$ 348.2; HRMS calcd. for $C_{22}H_{21}NO_3Na$: MNa^+, 370.1419. Found: MNa^+, 370.1415.

(4-((4-Ethoxyphenoxy)methyl)phenyl)(3-methylpiperidin-1-yl)methanone; 1.

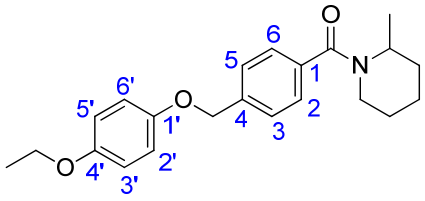


4-Ethoxyphenol acid **8** (50 mg, 0.18 mmol) was reacted with HATU (84 mg, 0.22 mmol), DIPEA (77 µL, 0.44 mmol) and 3-methylpiperidine (43 µL, 0.37 mmol) using Procedure C. The product was purified by Method A to afford the desired amide **1** as a white solid (36 mg, 56%).

HPLC Retention time: 31.45 min; IR ν_{max} (ATR): 2938, 1739, 1631, 1508, 1437, 1366, 1229 cm^{-1}; mp 81−83 ºC; R_f [98:2 *v/v* DCM:MeOH] = 0.34; ^1H NMR (400 MHz, Tol-d_8, 350 K) δ 7.33 (2H, d, *J* 7.9 Hz, 2 × Ar-H; C_2-H, C_6-H), 7.21 (2H, d, *J* 7.9 Hz, 2 × Ar-H; C_3-H, C_5-H), 6.78 (2H, d, *J* 9.1 Hz, 2 × Ar-H; $C_{2'}$-H, $C_{6'}$-H), 6.71 (2H, d, *J* 9.1 Hz, 2 × Ar-H; $C_{3'}$-H, $C_{5'}$-H), 4.71 (2H, s, C_4-CH_2), 3.97 (2H, br. s, 2 × pip NC$\underline{H}$H), 3.67 (2H, q, *J* 7.0 Hz, $C_{4'}$-O$\underline{C}H_2CH_3$), 2.60 (1H, td, *J* 11.6, 3.8 Hz, pip NCH$\underline{H}$), 2.30 (1H, dd, *J* 12.7, 10.7 Hz, pip NCH$\underline{H}$), 1.56−1.45 (1H, m, pip CH), 1.44−1.19 (3H, m, pip C$\underline{H}CH_3$ and pip CH_2), 1.16 (3H, t, *J* 7.0 Hz, $C_{4'}$-$OCH_2C\underline{H}_3$),

0.89−0.75 (1H, m, pip CH), 0.63 (3H, d, *J* 6.6 Hz, pip CHC<u>H</u>$_3$); ^{13}C NMR (100 MHz, Tol-d$_8$, 350 K) δ 169.6 (C=O), 154.5 (C), 153.8 (C), 139.4 (C), 137.3 (C), 127.8 (2 × Ar-CH), 127.3 (2 × Ar-CH), 116.6 (2 × Ar-CH), 116.2 (2 × Ar-CH), 70.9 (C$_4$-C<u>H</u>$_2$), 64.2 (C$_{4'}$-OC<u>H</u>$_2$CH$_3$), 52.5 (pip NCH$_2$, br.), 45.9 (pip NCH$_2$, br.), 33.6 (pip CH$_2$), 31.6 (pip CH), 25.7 (pip CH$_2$), 18.8 (pip CHC<u>H</u>$_3$), 15.0 (C$_{4'}$-OCH$_2$C<u>H</u>$_3$); LRMS [M+H]$^+$ 354.3; HRMS calcd. for $C_{22}H_{27}NO_3Na$: MNa$^+$, 376.1889. Found: MNa$^+$, 376.1883.

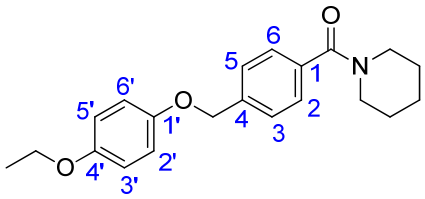
(4-((4-Ethoxyphenoxy)methyl)phenyl)(2-methylpiperidin-1-yl)methanone; 17.



4-Ethoxyphenol acid **8** (50 mg, 0.18 mmol) was reacted with HATU (84 mg, 0.22 mmol), DIPEA (77 µL, 0.44 mmol) and 2-methylpiperidine (43 µL, 0.37 mmol) using Procedure C. The product was purified by Method A to afford the desired *amide* **17** as a white solid (40 mg, 61%).

HPLC Retention time: 28.73 min; IR ν$_{max}$ (ATR): 2940, 1738, 1629, 1508, 1430, 1367, 1230 cm^{-1}; mp 76−77 ºC; R$_f$ [98:2 *v/v* DCM:MeOH] = 0.35; ^{1}H NMR (400 MHz, Tol-d$_8$, 350 K) δ 7.30 (2H, d, *J* 7.8 Hz, 2 × Ar-H; C$_2$-H, C$_6$-H), 7.21 (2H, d, *J* 7.8 Hz, 2 × Ar-H; C$_3$-H, C$_5$-H), 6.78 (2H, d, *J* 8.8 Hz, 2 × Ar-H; C$_{2'}$-H, C$_{6'}$-H), 6.71 (2H, d, *J* 8.8 Hz, 2 × Ar-H; C$_{3'}$-H, C$_{5'}$-H), 4.73 (2H, s, C$_4$-CH$_2$), 4.50 (1H, br. t, *J* 6.0 Hz, pip C<u>H</u>CH$_3$), 3.94 (1H, br. d, *J* 13.3 Hz, pip NC<u>H</u>H), 3.68 (2H, q, *J* 7.0 Hz, C$_{4'}$-OC<u>H</u>$_2$CH$_3$), 2.75−2.62 (1H, m, pip NCH<u>H</u>), 1.53−1.19 (6H, m, 3 × pip CH$_2$), 1.16 (3H, t, *J* 7.0 Hz, C$_{4'}$-OCH$_2$C<u>H</u>$_3$), 0.99 (3H, d, *J* 6.8 Hz, pip CHC<u>H</u>$_3$); ^{13}C NMR (100 MHz, Tol-d$_8$, 350 K) δ 169.8 (C=O), 154.5 (C), 153.8 (C), 139.2 (C), 137.8 (C), 127.4 (2 × Ar-CH), 127.4 (2 × Ar-CH), 116.6 (2 × Ar-CH), 116.2 (2 × Ar-CH), 70.9 (C$_4$-C<u>H</u>$_2$), 64.2 (C$_{4'}$-OC<u>H</u>$_2$CH$_3$), 47.2 (pip C<u>H</u>CH$_3$), 40.2 (pip CH$_2$), 30.7 (pip CH$_2$), 26.4 (pip CH$_2$), 19.5 (pip CH$_2$), 16.0 (pip CHC<u>H</u>$_3$), 15.0 (C$_{4'}$-OCH$_2$C<u>H</u>$_3$); LRMS [M+H]$^+$ 354.3; HRMS calcd. for $C_{22}H_{27}NO_3Na$: MNa$^+$, 376.1889. Found: MNa$^+$, 376.1885.

(4-((4-Ethoxyphenoxy)methyl)phenyl)(piperidin-1-yl)methanone; 23.

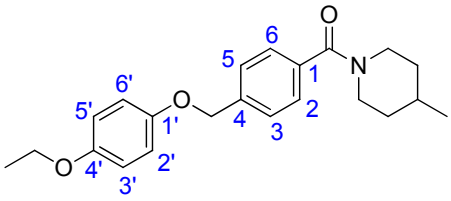


4-Ethoxyphenol acid **8** (50 mg, 0.18 mmol) was reacted with HATU (84 mg, 0.22 mmol), DIPEA (77 µL, 0.44 mmol) and piperidine (36 µL, 0.37 mmol) using Procedure C. The product was purified by Method A to afford the desired *amide* **23** as a white solid (42 mg, 68%).

HPLC Retention time: 26.65 min; IR ν$_{max}$ (ATR): 2930, 2913, 1628, 1507, 1429, 1229 cm^{-1}; mp 97−98 ºC; R$_f$ [98:2 *v/v* DCM:MeOH] = 0.22; ^{1}H NMR (400 MHz, Tol-d$_8$, 350 K) δ 7.31 (2H, d, *J* 8.0 Hz, 2 × Ar-H; C$_2$-H, C$_6$-H), 7.21 (2H, d, *J* 8.0 Hz, 2 × Ar-H; C$_3$-H, C$_5$-H), 6.78 (2H, d, *J* 9.2 Hz, 2 × Ar-H; C$_{2'}$-H, C$_{6'}$-H), 6.71 (2H, d, *J* 9.2 Hz, 2 × Ar-H; C$_{3'}$-H, C$_{5'}$-H), 4.73 (2H, s, C$_4$-CH$_2$), 3.68 (2H, q, *J* 6.9 Hz, C$_{4'}$-OC<u>H</u>$_2$CH$_3$), 3.30 (4H, br. s, 2 × pip NCH$_2$), 1.36−1.28 (2H, m, pip CH$_2$),

1.27−1.19 (4H, m, 2 × pip CH_2), 1.16 (3H, t, *J* 6.9 Hz, $C_{4'}$-$OCH_2\underline{C}H_3$); ^{13}C NMR (100 MHz, Tol-d_8, 350 K) δ 169.6 (C=O), 154.5 (C), 153.8 (C), 139.4 (C), 137.3 (C), 127.8 (2 × Ar-CH), 127.4 (2 × Ar-CH), 116.6 (2 × Ar-CH), 116.2 (2 × Ar-CH), 70.9 (C_4-$\underline{C}H_2$), 64.2 ($C_{4'}$-$O\underline{C}H_2CH_3$), 46.1 (2 × pip NCH_2, br.), 26.5 (2 × pip CH_2), 25.1 (pip CH_2), 15.1 ($C_{4'}$-$OCH_2\underline{C}H_3$); LRMS $[M+H]^+$ 340.2; HRMS calcd. for $C_{21}H_{25}NO_3Na$: MNa^+, 362.1732. Found: MNa^+, 362.1727.

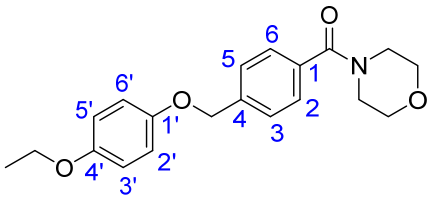
(4-((4-Ethoxyphenoxy)methyl)phenyl)(4-methylpiperidin-1-yl)methanone; 22.



4-Ethoxyphenol acid **8** (50 mg, 0.18 mmol) was reacted with HATU (84 mg, 0.22 mmol), DIPEA (77 µL, 0.44 mmol) and 4-methylpiperidine (44 µL, 0.37 mmol) using Procedure C. The product was purified by Method A to afford the desired *amide* **22** as a white solid (43 mg, 66%).

HPLC Retention time: 29.80 min; IR ν_{max} (ATR): 2922, 1739, 1630, 1507, 1441, 1375, 1229 cm^{-1}; mp 85−87 ºC; R_f [98:2 *v/v* DCM:MeOH] = 0.34; ; ^{1}H NMR (400 MHz, Tol-d_8, 350 K) δ 7.32 (2H, d, *J* 7.8 Hz, 2 × Ar-H; C_2-H, C_6-H), 7.22 (2H, d, *J* 7.8 Hz, 2 × Ar-H; C_3-H, C_5-H), 6.78 (2H, d, *J* 8.9 Hz, 2 × Ar-H; $C_{2'}$-H, $C_{6'}$-H), 6.71 (2H, d, *J* 8.9 Hz, 2 × Ar-H; $C_{3'}$-H, $C_{5'}$-H), 4.73 (2H, s, C_4-CH_2), 4.09 (2H, br. s, 2 × pip NC<u>H</u>H), 3.68 (2H, q, *J* 6.9 Hz, $C_{4'}$-$OC\underline{H}_2CH_3$), 2.55 (2H, app. t, *J* 12.5 Hz, 2 × pip NCH<u>H</u>), 1.40−1.19 (3H, m, 3 × pip CH), 1.16 (3H, t, *J* 6.9 Hz, $C_{4'}$-$OCH_2\underline{C}H_3$), 1.01−0.82 (2H, m, 2 × pip CH), 0.74 (3H, d, *J* 6.2 Hz, pip $CHC\underline{H}_3$); ^{13}C NMR (100 MHz, Tol-d_8, 350 K) δ 169.6 (C=O), 154.5 (C), 153.8 (C), 139.5 (C), 137.3 (C), 127.8 (2 × Ar-CH), 127.4 (2 × Ar-CH), 116.6 (2 × Ar-CH), 116.2 (2 × Ar-CH), 70.9 (C_4-$\underline{C}H_2$), 64.2 ($C_{4'}$-$O\underline{C}H_2CH_3$), 45.4 (2 × pip NCH_2, br.), 34.7 (2 × pip CH_2), 31.5 (pip $\underline{C}HCH_3$), 21.7 (pip $CH\underline{C}H_3$), 15.1 ($C_{4'}$-$OCH_2\underline{C}H_3$); LRMS $[M+H]^+$ 354.3; HRMS calcd. for $C_{22}H_{27}NO_3Na$: MNa^+, 376.1889. Found: MNa^+, 376.1884.

(4-((4-Ethoxyphenoxy)methyl)phenyl)(morpholino)methanone, 27.

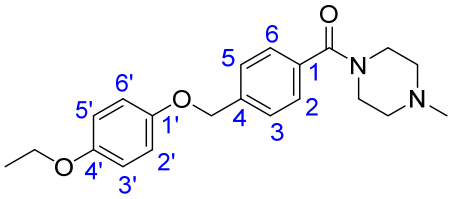


4-Ethoxyphenol acid **8** (50 mg, 0.18 mmol) was used in a modification to Procedure C with HATU (84 mg, 0.22 mmol), DIPEA (77 µL, 0.44 mmol) and morpholine (32 µL, 0.37 mmol), stirring for 2 h. The product was purified *via* column chromatography (eluent: 95:5 v/v DCM:MeOH) followed by Method B (i) to afford the desired *amide* **27** as a white solid (31 mg, 49%).

HPLC Retention time: 29.45 min; IR ν_{max} (ATR): 3727, 3302, 1625, 1508, 1239, 1117, 878 cm^{-1}; mp 124-126 ºC; ^{1}H NMR (400 MHz, Tol-d_8, 350 K) δ 7.25 (2H, d, *J* 8.2 Hz, 2 × Ar-H; C_2-H, C_6-H), 7.20 (2H, d, *J* 8.2 Hz, 2 × Ar-H; C_3-H, C_5-H), 6.78 (2H, d, *J* 9.0 Hz, 2 × Ar-H; $C_{3'}$-H, $C_{5'}$-H), 6.71 (2H, d, *J* 9.0 Hz, 2 × Ar-H; $C_{2'}$-H, $C_{6'}$-H), 4.72 (2H, s, C_4-CH_2), 3.68 (2H, q, *J* 6.9 Hz, $C_{4'}$-$OC\underline{H}_2CH_3$), 3.27 (8H, br. s, 4

× morph CH_2), 1.16 (3H, t, *J* 6.9 Hz, $C_{4'}$-$OCH_2C\underline{H}_3$); ^{13}C NMR (100 MHz, Tol-d_8, 350 K) δ 169.6 (C=O), 154.6 (C), 153.8 (C), 139.9 (C), 136.2 (C), 128.0 (2 × Ar-CH), 127.5 (2 × Ar-CH), 116.6 (2 × Ar-CH), 116.3 (2 × Ar-CH), 70.8 (C_4-$\underline{C}H_2$), 67.0 (2 × morph NCH_2), 64.2 ($C_{4'}$-$O\underline{C}H_2CH_3$), 45.9 (2 × morph NCH_2, br.), 15.9 ($C_{4'}$-$OCH_2\underline{C}H_3$); LRMS $[M+H]^+$ 342.2; HRMS calcd for $C_{20}H_{23}NO_4Na$: *M*Na^+, 364.1525. Found: *M*Na^+, 364.1520.

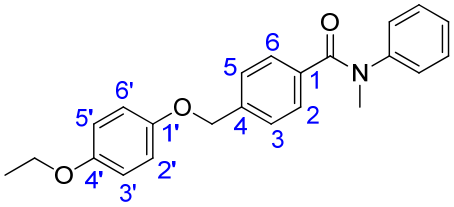
(4-((4-Ethoxyphenoxy)methyl)phenyl)(4-methylpiperazin-1-yl)methanone, 31.



4-Ethoxyphenol acid **8** (50 mg, 0.18 mmol) was used in a modification to Procedure C with HATU (84 mg, 0.22 mmol), DIPEA (77 µL, 0.44 mmol) and 1-methylpiperazine (41 µL, 0.37 mmol), stirring for 2 h. The product was purified *via* column chromatography (eluent: 93:5:2 v/v DCM:MeOH:Et_3N) followed by Method B (i) to afford the desired *amide* **31** as a white solid (35 mg, 54%).

HPLC Retention time: 16.15 min; IR ν_{max} (ATR): 3893, 3665, 2837, 1630, 1508, 1230, 1051 cm^{-1}; mp 79−80 ºC; ^{1}H NMR (400 MHz, Tol-d_8, 350 K) δ 7.30 (2H, d, *J* 8.0 Hz, 2 × Ar-H; C_2-H, C_6-H), 7.21 (2H, d, *J* 8.0 Hz, 2 × Ar-H; C_3-H, C_5-H), 6.78 (2H, d, *J* 9.0 Hz, 2 × Ar-H; $C_{3'}$-H, $C_{5'}$-H), 6.71 (2H, d, *J* 9.0 Hz, 2 × Ar-H; $C_{2'}$-H, $C_{6'}$-H), 4.72 (2H, s, C_4-CH_2), 3.68 (2H, q, *J* 7.0 Hz, $C_{4'}$-$OC\underline{H}_2CH_3$), 3.41 (4H, br. s, 2 × piperaz NCH_2), 2.01 (4H, app. t, *J* 5.0 Hz, 2 × piperaz NCH_2), 1.96 (3H, s, piperaz NCH_3), 1.16 (3H, t, *J* 7.0 Hz, $C_{4'}$-$OCH_2C\underline{H}_3$); ^{13}C NMR (100 MHz, Tol-d_8, 350 K) δ 169.5 (C=O), 154.5 (C), 153.8 (C), 139.8 (C), 136.6 (C), 128.0 (2 × Ar-CH), 128.4 (2 × Ar-CH), 116.6 (2 × Ar-CH), 116.2 (2 × Ar-CH), 70.8 (C_4-$\underline{C}H_2$), 64.2 ($C_{4'}$-$O\underline{C}H_2CH_3$), 55.3 (2 × piperaz NCH_2), 45.7 (piperaz NCH_3), 45.0 (2 × piperaz NCH_2, br.), 15.0 ($C_{4'}$-$OCH_2\underline{C}H_3$); LRMS $[M+H]^+$ 355.3; HRMS calcd for $C_{21}H_{26}N_2O_3Na$: *M*Na^+, 377.1841. Found: *M*Na^+, 377.1837.

4-((4-Ethoxyphenoxy)methyl)-*N*-methyl-*N*-phenylbenzamide; 34.

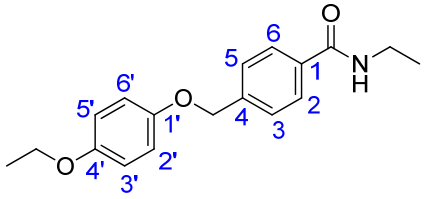


4-Ethoxyphenol acid **8** (50 mg, 0.18 mmol) was reacted with HATU (84 mg, 0.22 mmol), DIPEA (77 µL, 0.44 mmol) and *N*-methylaniline (40 µL, 0.37 mmol) using Procedure C. The product was purified by modified Method B (i) (60 min gradient) to afford the desired *amide* **34** as a white solid (51 mg, 76%).

HPLC Retention time: 46.79 min; IR ν_{max} (ATR): 2929, 2849, 1644, 1507, 1413, 123 cm^{-1}; mp 118−120 ºC; ^{1}H NMR (400 MHz, DMF-d_7, 350 K) δ 7.35 (2H, d, *J* 7.8 Hz, 2 × Ar-H; C_2-H, C_6-H), 7.33−7.25 (2H, m, 4 × Ar-H), 7.31 (2H, d, *J* 7.8 Hz, 2 × Ar-H; C_3-H, C_5-H), 7.21 (2H, app. d, *J* 9.0 Hz, 2 × Ar-H), partially hidden 7.17 (1H, t, *J* 7.6 Hz, Ar-H), 6.91 (2H, d, *J* 8.0 Hz, 2 × Ar-H; $C_{2'}$-H, $C_{6'}$-H), 6.85 (2H, d, *J*

8.0 Hz, 2 × Ar-H; $C_{3'}$-H, $C_{5'}$-H), 5.00 (2H, s, C_4-CH_2), 4.00 (2H, q, *J* 7.0 Hz, $C_{4'}$-O<u>C</u>$H_2$$CH_3$), 3.43 (3H, s, NCH_3), 1.31 (3H, t, *J* 7.0 Hz, $C_{4'}$-OCH_2<u>C</u>H_3); ^{13}C NMR (100 MHz, DMF-d_7, 350 K) δ 169.8 (C=O), 153.8 (C), 153.1 (C), 145.4 (C), 139.4 (C), 136.5 (C), 129.2 (2 × Ar-CH), 128.7 (2 × Ar-CH), 127.3 (2 × Ar-CH), 126.8 (2 × Ar-CH), 126.5 (Ar-CH), 116.4 (2 × Ar-CH), 115.9 (2 × Ar-CH), 70.3 (C_4-<u>C</u>H_2), 64.1 ($C_{4'}$-O<u>C</u>H_2CH_3), 37.9 (NCH_3), 14.5 ($C_{4'}$-OCH_2<u>C</u>H_3); LRMS $[M+H]^+$ 362.2; HRMS calcd. for $C_{23}H_{23}NO_3Na$: MNa^+, 384.1576. Found: MNa^+, 384.1568.

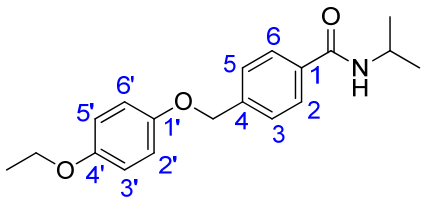
4-((4-Ethoxyphenoxy)methyl)-*N*-ethylbenzamide; S64.



4-Ethoxyphenol acid **8** (50 mg, 0.18 mmol) was reacted with HATU (84 mg, 0.22 mmol), DIPEA (77 µL, 0.44 mmol) and ethylamine (184 µL of 2.0M sol. in THF, 0.37 mmol) using Procedure C. The product was purified by Method C to afford the desired *amide* **S64** as a white solid (42 mg, 76%).

HPLC Retention time: 21.20 min; IR ν_{max} (ATR): 3316, 2978, 2928, 1635, 1544, 1509, 1235 cm^{-1}; mp 165−167 ºC; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76 (2H, d, *J* 8.0 Hz, 2 × Ar-H; C_2-H, C_6-H), 7.46 (2H, d, *J* 8.0 Hz, 2 × Ar-H; C_3-H, C_5-H), 6.87 (2H, d, *J* 8.8 Hz, 2 × Ar-H; $C_{2'}$-H, $C_{6'}$-H), 6.81 (2H, d, *J* 8.8 Hz, 2 × Ar-H; $C_{3'}$-H, $C_{5'}$-H), 6.24 (1H, br. s, NH), 5.04 (2H, s, C_4-CH_2), 3.97 (2H, q, *J* 7.0 Hz, $C_{4'}$-O<u>C</u>H_2CH_3), 3.49 (2H, app. quin, *J* 7.0 Hz, NH<u>C</u>H_2CH_3), 1.38 (3H, t, *J* 7.0 Hz, $C_{4'}$-OCH_2<u>C</u>H_3), 1.24 (3H, t, *J* 6.8 Hz, $NHCH_2$<u>C</u>H_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.3 (C=O), 153.6 (C), 152.7 (C), 141.0 (C), 134.3 (C), 127.4 (2 × Ar-CH), 127.2 (2 × Ar-CH), 116.0 (2 × Ar-CH), 115.5 (2 × Ar-CH), 70.2 (C_4-<u>C</u>H_2), 64.1 ($C_{4'}$-O<u>C</u>H_2CH_3), 35.1 (NH<u>C</u>H_2CH_3), 15.0 ($NHCH_2$<u>C</u>H_3), 15.0 ($C_{4'}$-OCH_2<u>C</u>H_3); LRMS $[M+H]^+$ 299.9; HRMS calcd. for $C_{18}H_{21}NO_3Na$: MNa^+, 322.1419. Found: MNa^+, 322.1413.

4-((4-Ethoxyphenoxy)methyl)-*N*-isopropylbenzamide; 36.

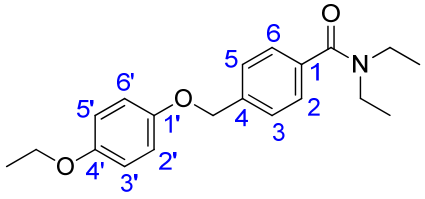


4-Ethoxyphenol acid **8** (50 mg, 0.18 mmol) was reacted with HATU (84 mg, 0.22 mmol), DIPEA (77 µL, 0.44 mmol) and isopropylamine (32 µL, 0.37 mmol) using Procedure C. The product was purified by Method B (i) to afford the desired *amide* **36** as a white solid (25 mg, 43%).

HPLC Retention time: 30.55 min; IR ν_{max} (ATR): 3317, 2975, 2903, 1632, 1538, 1510, 1235 cm^{-1}; mp 172−174 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (2H, d, *J* 8.2 Hz, 2 × Ar-H; C_2-H, C_6-H), 7.46 (2H, d, *J* 8.2 Hz, 2 × Ar-H; C_3-H, C_5-H), 6.87 (2H, d, *J* 9.6 Hz, 2 × Ar-H; $C_{2'}$-H, $C_{6'}$-H), 6.81 (2H, d, *J* 9.6 Hz, 2 × Ar-H; $C_{3'}$-H, $C_{5'}$-H), 5.93 (1H, d, *J* 6.8 Hz, NH), 5.05 (2H, s, C_4-CH_2), 4.33−4.24 (1H, m, NHC<u>H</u>$(CH_3)_2$), 3.97 (2H, q, *J* 7.0 Hz, $C_{4'}$-O<u>C</u>H_2CH_3), 1.38 (3H, t, *J* 7.0 Hz, $C_{4'}$-OCH_2<u>C</u>H_3), 1.26 (6H, d, *J* 6.8 Hz, NHCH(C<u>H</u>$_3$)$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ

166.5 (C=O), 153.6 (C), 152.7 (C), 141.0 (C), 134.5 (C), 127.4 (2 × Ar-CH), 127.2 (2 × Ar-CH), 116.0 (2 × Ar-CH), 115.5 (2 × Ar-CH), 70.2 (C_4-$\underline{C}H_2$), 64.1 ($C_{4'}$-O$\underline{C}H_2CH_3$), 42.1 (NH$\underline{C}H(CH_3)_2$), 23.0 (NHCH($\underline{C}H_3)_2$), 15.0 ($C_{4'}$-OCH$_2\underline{C}H_3$); LRMS $[M+H]^+$ 314.3; HRMS calcd. for $C_{19}H_{23}NO_3Na$: MNa^+, 336.1576. Found: MNa^+, 336.1571.

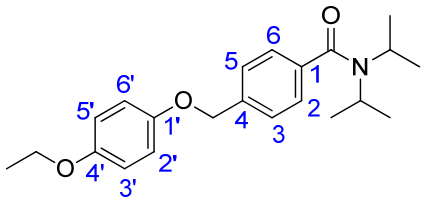
4-((4-Ethoxyphenoxy)methyl)-*N*,*N*-diethylbenzamide; S65.



4-Ethoxyphenol acid **8** (50 mg, 0.18 mmol) was reacted with HATU (84 mg, 0.22 mmol), DIPEA (77 µL, 0.44 mmol) and diethylamine (38 µL, 0.37 mmol) using Procedure C. The product was purified by Method B (i) to afford the desired *amide* **S65** as a white solid (48 mg, 80%).

HPLC Retention time: 33.55 min; IR ν_{max} (ATR): 2976, 2937, 1630, 1507, 1229 cm^{-1}; mp 86−88 ºC; ^{1}H NMR (400 MHz, Tol-d_8, 350 K) δ 7.26 (2H, d, *J* 8.2 Hz, 2 × Ar-H; C_2-H, C_6-H), 7.19 (2H, d, *J* 8.2 Hz, 2 × Ar-H; C_3-H, C_5-H), 6.78 (2H, d, *J* 9.2 Hz, 2 × Ar-H; $C_{2'}$-H, $C_{6'}$-H), 6.71 (2H, d, *J* 9.2 Hz, 2 × Ar-H; $C_{3'}$-H, $C_{5'}$-H), 4.72 (2H, s, C_4-CH_2), 3.68 (2H, q, *J* 7.0 Hz, $C_{4'}$-OC$\underline{H}_2$CH$_3$), 3.16 (4H, q, *J* 7.0 Hz, 2 × NC$\underline{H}_2$CH$_3$), 1.16 (3H, t, *J* 7.0 Hz, $C_{4'}$-OCH$_2$C$\underline{H}_3$), 0.93 (6H, t, *J* 7.0 Hz, 2 × NCH$_2$C$\underline{H}_3$); ^{13}C NMR (100 MHz, Tol-d_8, 350 K) δ 170.5 (C=O), 154.5 (C), 153.9 (C), 139.2 (C), 138.1 (C), 127.4 (2 × Ar-CH), 127.3 (2 × Ar-CH), 116.6 (2 × Ar-CH), 116.3 (2 × Ar-CH), 70.9 (C_4-$\underline{C}H_2$), 64.3 ($C_{4'}$-O$\underline{C}H_2CH_3$), 41.6 (2 × N$\underline{C}H_2CH_3$), 15.0 ($C_{4'}$-OCH$_2\underline{C}H_3$), 13.8 (2 × NCH$_2\underline{C}H_3$); LRMS $[M+H]^+$ 328.3; HRMS calcd. for $C_{20}H_{25}NO_3Na$: MNa^+, 350.1732. Found: MNa^+, 350.1726.

4-((4-Ethoxyphenoxy)methyl)-*N*,*N*-diisopropylbenzamide; 37.

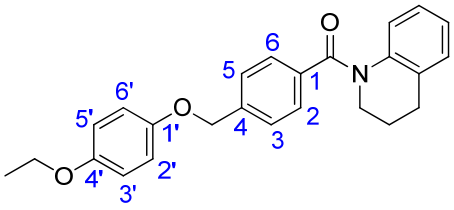


4-Ethoxyphenol acid **8** (50 mg, 0.18 mmol) was reacted with HATU (84 mg, 0.22 mmol), DIPEA (77 µL, 0.44 mmol) and diisopropylamine (52 µL, 0.37 mmol) using Procedure C. The product was purified by Method B (i) to afford the desired *amide* **37** as a white solid (54 mg, 82%).

HPLC Retention time: 37.30 min; IR ν_{max} (ATR): 2981, 1631, 1508, 1341, 1230 cm^{-1}; mp 98−100 ºC; ^{1}H NMR (400 MHz, Tol-d_8, 350 K) δ 7.22 (2H, d, *J* 8.6 Hz, 2 × Ar-H; C_2-H, C_6-H), 7.20 (2H, d, *J* 8.6 Hz, 2 × Ar-H; C_3-H, C_5-H), 6.77 (2H, d, *J* 9.2 Hz, 2 × Ar-H; $C_{2'}$-H, $C_{6'}$-H), 6.70 (2H, d, *J* 9.2 Hz, 2 × Ar-H; $C_{3'}$-H, $C_{5'}$-H), 4.72 (2H, s, C_4-CH_2), 3.67 (2H, q, *J* 7.0 Hz, $C_{4'}$-OC$\underline{H}_2$CH$_3$), 3.49 (2H, sep, *J* 6.8 Hz, 2 × NC$\underline{H}$(CH$_3$)$_2$), 1.19 (12H, d, 2 × NCH(C$\underline{H}_3$)$_2$), 1.15 (3H, t, *J* 7.0 Hz, $C_{4'}$-OCH$_2$C$\underline{H}_3$); ^{13}C NMR (100 MHz, Tol-d_8, 350 K) δ 170.3 (C=O), 154.5 (C), 153.9 (C), 139.7 (C), 138.7 (C), 127.5 (2 × Ar-CH), 126.5 (2 × Ar-CH), 116.6 (2 × Ar-CH), 116.3 (2 × Ar-CH), 71.0 (C_4-$\underline{C}H_2$), 64.2 ($C_{4'}$-O$\underline{C}H_2CH_3$), 48.4 (2 × NCH($\underline{C}H_3)_2$), 21.0

(2 × NCH(CH$_3$)$_2$), 15.0 (C$_{4'}$-OCH$_2$CH$_3$); LRMS [M+H]$^+$ 356.3; HRMS calcd. for C$_{22}$H$_{29}$NO$_3$Na: MNa$^+$, 378.2045. Found: MNa$^+$, 378.2040.

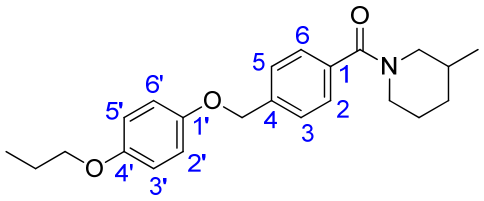
(3,4-Dihydroquinolin-1(2*H*)-yl)(4-((4-ethoxyphenoxy)methyl)phenyl)methanone; S66.



4-Ethoxyphenol acid **8** (50 mg, 0.18 mmol) was reacted with HATU (84 mg, 0.22 mmol), DIPEA (77 µL, 0.44 mmol) and 1,2,3,4-tetrahydroquinoline (46 µL, 0.37 mmol) using Procedure C. The product was purified by Method B (i) to afford the desired *amide* **S66** as a white solid (41 mg, 57%).

HPLC Retention time: 38.38 min; IR ν_{max} (ATR): 2939, 1739, 1641, 1506, 1375, 1228 cm^{-1}; mp 110−111 ºC; R_f [98:2 *v/v* DCM:MeOH] = 0.64; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.37 (2H, d, *J* 8.4 Hz, 2 × Ar-H; C$_2$-H, C$_6$-H), 7.32 (2H, d, *J* 8.4 Hz, 2 × Ar-H; C$_3$-H, C$_5$-H), 7.15 (1H, br. d, *J* 7.5 Hz, Ar-H), 7.00 (1H, dt, *J* 7.5, 1.5 Hz, Ar-H), 6.90−6.86 (1H, m, Ar-H), 6.86 (2H, d, *J* 9.4 Hz, 2 × Ar-H; C$_{2'}$-H, C$_{6'}$-H), 6.81 (2H, d, *J* 9.4 Hz, 2 × Ar-H; C$_{3'}$-H, C$_{5'}$-H), 6.72 (1H, br. d, *J* 7.7 Hz, Ar-H), 5.00 (2H, s, C$_4$-CH$_2$), 3.98 (2H, q, *J* 7.0 Hz, C$_{4'}$-OCH$_2$CH$_3$), 3.91 (2H, t, *J* 6.5 Hz, pip CH$_2$), 2.84 (2H, t, *J* 6.7 Hz, pip CH$_2$), 2.05 (2H, dt, *J* 6.7, 6.5 Hz, pip CH$_2$), 1.39 (3H, t, *J* 7.0 Hz, C$_{4'}$-OCH$_2$CH$_3$); ^{13}C NMR (100 MHz, DMF-d$_7$, 350 K) δ 169.6 (C=O), 153.8 (C), 153.1 (C), 140.1 (C), 139.8 (C), 136.7 (C), 131.7 (C), 128.7 (Ar-CH), 128.4 (2 × Ar-CH), 127.2 (2 × Ar-CH), 125.6 (Ar-CH), 125.1 (Ar-CH), 124.4 (Ar-CH), 116.4 (2 × Ar-CH), 115.9 (2 × Ar-CH), 70.3 (C$_4$-CH$_2$), 64.1 (C$_{4'}$-OCH$_2$CH$_3$), 45.0 (pip CH$_2$), 26.7 (pip CH$_2$), 24.0 (pip CH$_2$), 14.5 (C$_{4'}$-OCH$_2$CH$_3$); LRMS [M+H]$^+$ 388.3; HRMS calcd. for C$_{25}$H$_{25}$NO$_3$Na: MNa$^+$, 410.1732. Found: MNa$^+$, 410.1726.

(3-Methylpiperidin-1-yl)(4-((4-propoxyphenoxy)methyl)phenyl)methanone; S67.

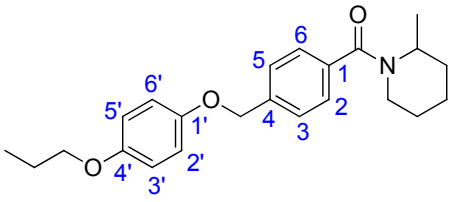


4-Propoxyphenol acid **9** (30 mg, 0.11 mmol) was reacted with HATU (48 mg, 0.13 mmol), DIPEA (44 µL, 0.25 mmol) and 3-methylpiperidine (25 µL, 0.21 mmol) using Procedure C. The product was purified by Method C to afford the desired *amide* **S67** as a white solid (30 mg, 77%).

HPLC Retention time: 33.27; IR ν_{max} (ATR): 2961, 2881, 1631, 1507, 1434, 1229 cm^{-1}; mp 62−64 ºC; R_f [98:2 *v/v* DCM:MeOH] = 0.67; ^{1}H NMR (400 MHz, Tol-d$_8$, 350 K) δ 7.33 (2H, d, *J* 7.4 Hz, 2 × Ar-H; C$_2$-H, C$_6$-H), 7.22 (2H, d, *J* 7.4 Hz, 2 × Ar-H; C$_3$-H, C$_5$-H), 6.78 (2H, d, *J* 8.5 Hz, 2 × Ar-H; C$_{2'}$-H, C$_{6'}$-H), 6.73 (2H, d, *J* 8.5 Hz, 2 × Ar-H; C$_{3'}$-H, C$_{5'}$-H), 4.73 (2H, s, C$_4$-CH$_2$), 4.06−3.85 (2H, br. m, 2 × pip NCHH), 3.62 (2H, t, *J* 6.3 Hz, C$_{4'}$-OCH$_2$CH$_2$CH$_3$), 2.61 (1H, t, *J* 6.3 Hz, pip NCHH), 2.31 (1H, t, *J* 6.3 Hz, pip NCHH), 1.66−1.55 (2H, m, C$_{4'}$-OCH$_2$CH$_2$CH$_3$), 1.54−1.17

(4H, m, 2 × pip CH_2), 0.89 (3H, t, *J* 7.3 Hz, $C_{4'}$-$OCH_2CH_2C\underline{H}_3$), 0.87−0.76 (1H, m, pip $C\underline{H}CH_3$), 0.63 (3H, d, *J* 6.3 Hz, pip $CHC\underline{H}_3$); ^{13}C NMR (100 MHz, Tol-d_8, 350 K) δ 169.6 (C=O), 154.7 (C), 153.9 (C), 139.5 (C), 137.3 (C), 127.8 (2 × Ar-CH *via* HSQC), 127.4 (2 × Ar-CH), 116.6 (2 × Ar-CH), 116.3 (2 × Ar-CH), 70.9 (C_4-$\underline{C}H_2$), 70.6 ($C_{4'}$-$O\underline{C}H_2CH_2CH_3$), 52.5 (pip CH_2 *via* HSQC), 45.7 (pip CH_2 *via* HSQC), 33.7 (pip CH_2), 31.6 (pip CH), 25.7 (pip CH_2), 23.2 ($C_{4'}$-$OCH_2\underline{C}H_2CH_3$), 18.8 (pip $CH\underline{C}H_3$), 10.6 ($C_{4'}$-$OCH_2CH_2\underline{C}H_3$); LRMS $[M+H]^+$ 368.0; HRMS calcd. for $C_{23}H_{29}NO_3Na$: MNa^+, 390.2045. Found: MNa^+, 390.2041.

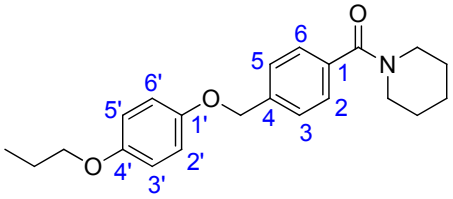
(2-Methylpiperidin-1-yl)(4-((4-propoxyphenoxy)methyl)phenyl)methanone; S68.



4-Propoxyphenol acid **9** (30 mg, 0.11 mmol) was reacted with HATU (48 mg, 0.13 mmol), DIPEA (44 µL, 0.25 mmol) and 2-methylpiperidine (25 µL, 0.21 mmol) using Procedure C. The product was purified by Method C to afford the desired *amide* **S68** as a white solid (29 mg, 76%).

HPLC Retention time: 32.69 min; IR ν_{max} (ATR): 2962, 2873, 1627, 1507, 1426, 1229 cm^{-1}; mp 73−74 ºC; R_f [98:2 *v/v* DCM:MeOH] = 0.83; ^{1}H NMR (400 MHz, Tol-d_8, 350 K) δ 7.30 (2H, d, *J* 7.9 Hz, 2 × Ar-H; C_2-H, C_6-H), 7.21 (2H, d, *J* 7.9 Hz, 2 × Ar-H; C_3-H, C_5-H), 6.79 (2H, d, *J* 9.0 Hz, 2 × Ar-H; $C_{2'}$-H, $C_{6'}$-H), 6.72 (2H, d, *J* 9.0 Hz, 2 × Ar-H; $C_{3'}$-H, $C_{5'}$-H), 4.74 (2H, s, C_4-CH_2), 4.54−4.45 (1H, m, pip $C\underline{H}CH_3$), 3.93 (1H, app. d, pip NC$\underline{H}$H), 3.63 (2H, t, *J* 6.4 Hz, $C_{4'}$-$OCH_2CH_2CH_3$), 2.74−2.63 (1H, m, pip NCH$\underline{H}$), 1.66−1.55 (2H, m, $C_{4'}$-$OCH_2C\underline{H}_2CH_3$), 1.54−1.12 (6H, m, 3 × pip CH_2), 1.00 (3H, d, *J* 7.2 Hz, pip $CHC\underline{H}_3$), 0.89 (3H, t, *J* 7.4 Hz, $C_{4'}$-$OCH_2CH_2C\underline{H}_3$); ^{13}C NMR (100 MHz, Tol-d_8, 350 K) δ 169.9 (C=O), 154.8 (C), 153.9 (C), 139.3 (C), 137.9 (C), 127.5 (2 × Ar-CH), 127.4 (2 × Ar-CH), 116.7 (2 × Ar-CH), 116.3 (2 × Ar-CH), 71.0 (C_4-$\underline{C}H_2$), 70.6 ($C_{4'}$-$O\underline{C}H_2CH_2CH_3$), 47.3 (pip $C\underline{H}CH_3$), 40.3 (pip CH_2), 30.7 (pip CH_2), 26.4 (pip CH_2), 23.3 ($C_{4'}$-$OCH_2\underline{C}H_2CH_3$), 19.5 (pip CH_2), 16.1 (pip $CH\underline{C}H_3$), 10.6 ($C_{4'}$-$OCH_2CH_2\underline{C}H_3$); LRMS $[M+H]^+$ 368.0; HRMS calcd. for $C_{23}H_{29}NO_3Na$: MNa^+, 390.2045. Found: MNa^+, 390.2040.

Piperidin-1-yl(4-((4-propoxyphenoxy)methyl)phenyl)methanone; S69.

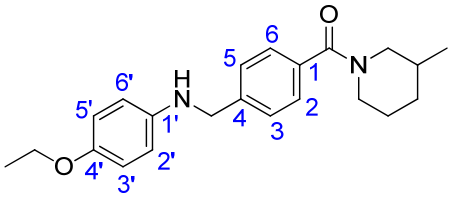


4-Propoxyphenol acid **9** (30 mg, 0.11 mmol) was reacted with HATU (48 mg, 0.13 mmol), DIPEA (44 µL, 0.25 mmol) and piperidine (21 µL, 0.21 mmol) using Procedure C. The product was purified by Method C to afford the desired amide **S69** as a white solid (30 mg, 82%).

HPLC Retention time: 30.81 min; IR ν_{max} (ATR): 2964, 2857, 1631, 1507, 1433, 1230 cm^{-1}; mp 91−93 ºC; R_f [98:2 *v/v* DCM:MeOH] = 0.70; ^{1}H NMR (400 MHz, Tol-d_8, 350 K) δ 7.31 (2H, d, *J* 8.3 Hz, 2 × Ar-H; C_2-H, C_6-H), 7.21 (2H, d, *J*

8.3 Hz, 2 × Ar-H; C_3-H, C_5-H), 6.79 (2H, d, *J* 9.2 Hz, 2 × Ar-H; $C_{2'}$-H, $C_{6'}$-H), 6.72 (2H, d, *J* 9.2 Hz, 2 × Ar-H; $C_{3'}$-H, $C_{5'}$-H), 4.74 (2H, s, C_4-CH_2), 3.63 (2H, t, *J* 6.4 Hz, $C_{4'}$-O$\underline{CH_2}CH_2CH_3$), 3.34−3.25 (4H, m, 2 × pip NCH_2), 1.66−1.55 (2H, m, $C_{4'}$-$OCH_2\underline{CH_2}CH_3$), 1.35−1.28 (2H, m, pip CH_2), 1.28−1.21 (4H, m, 2 × pip CH_2), 0.89 (3H, t, *J* 7.4 Hz, $C_{4'}$-$OCH_2CH_2\underline{CH_3}$); ^{13}C NMR (100 MHz, Tol-d_8, 350 K) δ 169.9 (C=O), 155.1 (C), 154.2 (C), 139.8 (C), 137.6 (C), 127.5 (2 × Ar-CH *via* HSQC), 127.7 (2 × Ar-CH), 117.0 (2 × Ar-CH), 116.6 (2 × Ar-CH), 71.3 (C_4-CH_2), 70.9 ($C_{4'}$-O$\underline{CH_2}CH_2CH_3$), 46.4 (2 × pip NCH_2), 26.8 (2 × pip CH_2), 25.4 (pip CH_2), 23.5 ($C_{4'}$-$OCH_2\underline{CH_2}CH_3$), 10.9 ($C_{4'}$-$OCH_2CH_2\underline{CH_3}$); LRMS $[M+H]^+$ 354.0; HRMS calcd. for $C_{22}H_{27}NO_3Na$: MNa^+, 376.1889. Found: MNa^+, 376.1882.

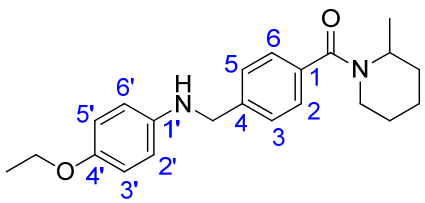
(4-(((4-Ethoxyphenyl)amino)methyl)phenyl)(3-methylpiperidin-1-yl)methanone; 13.



4-Ethoxyaniline acid **10** (50 mg, 0.18 mmol) was reacted with HATU (84 mg, 0.22 mmol), DIPEA (77 µL, 0.44 mmol) and 3-methylpiperidine (43 µL, 0.37 mmol) using Procedure C. The product was purified by modified Method D (20 to 100 MeCN gradient) to afford the desired *amide* **13** as a light pink amorphous solid (32 mg, 49%).

HPLC Retention time: 24.42−26.01 min; IR ν_{max} (ATR): 2981, 2871, 1624, 1512, 1443, 1274, 1237 cm^{-1}; mp 84−86 ºC; ^{1}H NMR (400 MHz, Tol-d_8, 350 K) δ 7.31 (2H, d, *J* 7.9 Hz, 2 × Ar-H; C_2-H, C_6-H), 7.14 (2H, d, *J* 7.9 Hz, 2 × Ar-H; C_3-H, C_5-H), 6.70 (2H, d, *J* 8.8 Hz, 2 × Ar-H; $C_{2'}$-H, $C_{6'}$-H), 6.45 (2H, d, *J* 8.8 Hz, 2 × Ar-H; $C_{3'}$-H, $C_{5'}$-H), 3.98 (2H, br. s, 2 × pip NC$\underline{H}$H), 3.95 (2H, s, C_4-CH_2), 3.70 (2H, q, *J* 6.9 Hz, $C_{4'}$-O$\underline{CH_2}CH_3$), 2.61 (1H, td, *J* 11.0, 3.8 Hz, pip NCH$\underline{H}$), 2.32 (1H, dd, *J* 13.0, 10.5 Hz, pip NCH$\underline{H}$), 1.55−1.45 (1H, m, pip CH), 1.44−1.20 (3H, m, pip C$\underline{H}CH_3$ and pip CH_2), 1.16 (3H, t, *J* 6.9 Hz, $C_{4'}$-$OCH_2\underline{CH_3}$), 0.89−0.75 (1H, m, pip CH), 0.63 (3H, d, *J* 6.6 Hz, pip CHC$\underline{H_3}$); ^{13}C NMR (100 MHz, Tol-d_8, 350 K) δ 169.6 (C=O), 151.9 (C), 140.8 (C), 140.4 (C), 136.8 (C), 127.9 (2 × Ar-CH), 127.9 (2 × Ar-CH), 116.5 (2 × Ar-CH), 116.0 (2 × Ar-CH), 64.2 ($C_{4'}$-O$\underline{CH_2}CH_3$), 52.5 (pip NCH_2, br.), 50.3 (C_4-$\underline{CH_2}$), 45.9 (pip NCH_2, br.), 33.6 (pip CH_2), 31.6 (pip CH), 25.7 (pip CH_2), 18.8 (pip CH$\underline{CH_3}$), 15.1 ($C_{4'}$-O$\underline{CH_2}\underline{CH_3}$); LRMS $[M+H]^+$ 353.3; HRMS calcd. for $C_{22}H_{29}N_2O_2$: MH^+, 353.2229. Found: MH^+, 375.2222.

(4-(((4-Ethoxyphenyl)amino)methyl)phenyl)(2-methylpiperidin-1-yl)methanone; 18.

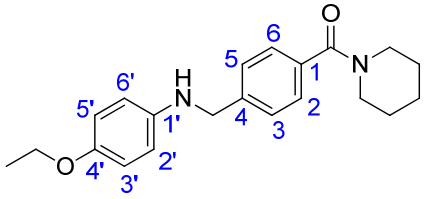


4-Ethoxyaniline acid **10** (50 mg, 0.18 mmol) was reacted with HATU (84 mg, 0.22 mmol), DIPEA (77 µL, 0.44 mmol) and 2-methylpiperidine (43 µL,

0.37 mmol) using Procedure C. The product was purified by Method D to afford the desired *amide* **18** as a tan amorphous solid (31 mg, 47%).

HPLC Retention time: 39.32−41.06 min; IR ν_{max} (ATR): 3364, 2977, 2909, 1618, 1512, 1429, 1233 cm^{-1}; mp 89−91 ºC; ^1H NMR (400 MHz, Tol-d_8, 350 K) δ 7.28 (2H, d, *J* 7.9 Hz, 2 × Ar-H; C_2-H, C_6-H), 7.13 (2H, d, *J* 7.9 Hz, 2 × Ar-H; C_3-H, C_5-H), 6.70 (2H, d, *J* 8.8 Hz, 2 × Ar-H; $C_{2'}$-H, $C_{6'}$-H), 6.39 (2H, d, *J* 8.8 Hz, 2 × Ar-H; $C_{3'}$-H, $C_{5'}$-H), 4.53 (1H, br. t, *J* 7.9 Hz, pip C<u>H</u>CH_3), 3.97 (2H, s, C_4-CH_2), partially hidden 3.96 (1H, br. d, pip NC<u>H</u>H), 3.70 (2H, q, *J* 6.9 Hz, $C_{4'}$-OC<u>H_2</u>CH_3), 2.79 (1H, br. s, NH), 2.74−2.61 (1H, m, pip NCH<u>H</u>), 1.54−1.17 (6H, m, 3 × pip CH_2), 1.17 (3H, t, *J* 6.9 Hz, $C_{4'}$-OCH_2C<u>H_3</u>), 1.00 (3H, d, *J* 6.9 Hz, pip CHC<u>H_3</u>); ^{13}C NMR (100 MHz, Tol-d_8, 350 K) δ 170.1 (C=O), 152.7 (C), 143.1 (C), 141.8 (C), 137.2 (C), 127.6 (2 × Ar-CH), 127.6 (2 × Ar-CH), 116.6 (2 × Ar-CH), 114.8 (2 × Ar-CH), 64.3 ($C_{4'}$-O<u>C</u>H_2CH_3), 49.4 (C_4-<u>C</u>H_2), 47.3 (pip C<u>H</u>CH_3), 40.3 (pip CH_2), 30.7 (pip CH_2), 26.4 (pip CH_2), 19.5 (pip CH_2), 16.1 (pip CH<u>C</u>H_3), 15.2 ($C_{4'}$-OCH_2<u>C</u>H_3); LRMS $[M+H]^+$ 353.3; HRMS calcd. for $C_{22}H_{28}N_2O_2Na$: MNa^+, 375.2048. Found: MNa^+, 375.2043.

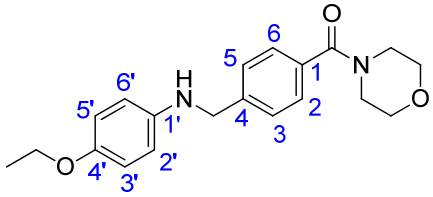
(4-(((4-Ethoxyphenyl)amino)methyl)phenyl)(piperidin-1-yl)methanone; 24.



4-Ethoxyaniline acid **10** (50 mg, 0.18 mmol) was reacted with HATU (84 mg, 0.22 mmol), DIPEA (77 µL, 0.44 mmol) and piperidine (36 µL, 0.37 mmol) using Procedure C. The product was purified by Method D to afford the desired *amide* **24** as a light tan solid (33 mg, 53%).

HPLC Retention time: 34.96−36.70 min; IR ν_{max} (ATR): 3354, 2941, 2855, 1614, 1512, 1443, 1232 cm^{-1}; mp 97−99 ºC; ^1H NMR (400 MHz, Tol-d_8, 350 K) δ 7.29 (2H, d, *J* 8.3 Hz, 2 × Ar-H; C_2-H, C_6-H), 7.12 (2H, d, *J* 8.3 Hz, 2 × Ar-H; C_3-H, C_5-H), 6.70 (2H, d, *J* 8.9 Hz, 2 × Ar-H; $C_{2'}$-H, $C_{6'}$-H), 6.38 (2H, d, *J* 8.9 Hz, 2 × Ar-H; $C_{3'}$-H, $C_{5'}$-H), 3.96 (2H, s, C_4-CH_2), 3.71 (2H, q, *J* 7.1 Hz, $C_{4'}$-OC<u>H_2</u>CH_3), 3.31 (4H, br. s, 2 × pip NCH_2), 2.78 (1H, br. s, NH), 1.36−1.20 (6H, m, 3 × pip CH_2), 1.17 (3H, t, *J* 7.1 Hz, $C_{4'}$-OCH_2C<u>H_3</u>); ^{13}C NMR (100 MHz, Tol-d_8, 350 K) δ 169.7 (C=O), 152.7 (C), 143.0 (C), 141.9 (C), 136.6 (C), 127.9 (2 × Ar-CH), 127.5 (2 × Ar-CH), 116.6 (2 × Ar-CH), 114.8 (2 × Ar-CH), 64.3 ($C_{4'}$-O<u>C</u>H_2CH_3), 49.4 (C_4-<u>C</u>H_2), 46.1 (2 × pip NCH_2, br.), 26.5 (2 × pip CH_2), 25.1 (pip CH_2), 15.2 ($C_{4'}$-OCH_2<u>C</u>H_3); LRMS $[M+H]^+$ 339.3; HRMS calcd. for $C_{21}H_{26}N_2O_2Na$: MNa^+, 361.1892. Found: MNa^+, 361.1885.

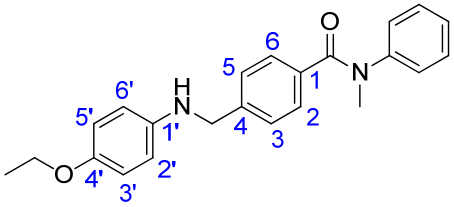
(4-(((4-Ethoxyphenyl)amino)methyl)phenyl)(morpholino)methanone; 28.



4-Ethoxyaniline acid **10** (50 mg, 0.18 mmol) was reacted with HATU (84 mg, 0.22 mmol), DIPEA (77 µL, 0.44 mmol) and morpholine (32 µL, 0.37 mmol) using Procedure C. The product was purified by Method D to afford the desired *amide* **28** as a light pink solid (16 mg, 25%).

HPLC Retention time: 25.74−27.44 min; IR ν_{max} (ATR): 3357, 2923, 2858, 1626, 1613, 1513, 1432, 1232 cm^{-1}; mp 121−122 ºC; ^{1}H NMR (400 MHz, MeOD) δ 7.47 (2H, d, *J* 8.1 Hz, 2 × Ar-H; C_2-H, C_6-H), 7.37 (2H, d, *J* 8.1 Hz, 2 × Ar-H; C_3-H, C_5-H), 6.69 (2H, d, *J* 8.9 Hz, 2 × Ar-H; $C_{2'}$-H, $C_{6'}$-H), 6.58 (2H, d, *J* 8.9 Hz, 2 × Ar-H; $C_{3'}$-H, $C_{5'}$-H), 4.31 (2H, s, C_4-CH_2), 3.90 (2H, q, *J* 7.1 Hz, $C_{4'}$-O$\underline{CH_2}CH_3$), 3.81−3.54 (6H, m, 6 × morph CH), 3.54−3.37 (2H, m, 2 × morph CH), 1.31 (3H, t, *J* 7.1 Hz, $C_{4'}$-$OCH_2\underline{CH_3}$), NB: 8 × morph CH coalesce to form one peak in Tol-d_8 at 350 K; ^{13}C NMR (100 MHz, Tol-d_8, 350 K) δ 169.8 (C=O), 152.8 (C), 142.9 (C), 142.5 (C), 135.6 (C), 128.2 (2 × Ar-CH), 127.6 (2 × Ar-CH), 116.6 (2 × Ar-CH), 114.8 (2 × Ar-CH), 67.0 (2 × morph CH_2), 64.3 ($C_{4'}$-O$\underline{CH_2}CH_3$), 49.4 (C_4-$\underline{CH_2}$), 45.9 (2 × morph CH_2, br.), 15.2 ($C_{4'}$-$OCH_2\underline{CH_3}$); LRMS $[M+H]^+$ 341.3; HRMS calcd. for $C_{20}H_{25}N_2O_3$: MH^+, 341.1865. Found: MH^+, 341.1858.

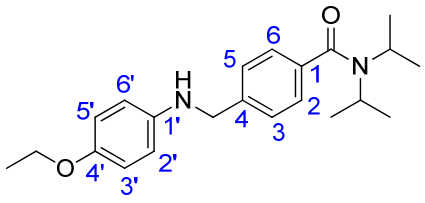
4-(((4-Ethoxyphenyl)amino)methyl)-*N*-methyl-*N*-phenylbenzamide; 35.



4-Ethoxyaniline acid **10** (50 mg, 0.18 mmol) was reacted with HATU (84 mg, 0.22 mmol), DIPEA (77 µL, 0.44 mmol) and *N*-methylaniline (40 µL, 0.37 mmol) using Procedure C. The product was purified by Method D to afford the desired *amide* **35** as a yellow amorphous solid (39 mg, 58%).

HPLC Retention time: 38.59−40.87 min; IR ν_{max} (ATR): 2980, 2874, 1642, 1594, 1497, 1370, 1246 cm^{-1}; mp 103−104 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25−7.19 (2H, m, 2 × Ar-H), 7.22 (2H, d, *J* 7.9 Hz, 2 × Ar-H; C_2-H, C_6-H), partially hidden 7.16 (1H, t, *J* 7.2 Hz, Ar-H), 7.13 (2H, d, *J* 7.9 Hz, 2 × Ar-H; C_3-H, C_5-H), 7.04 (2H, d, *J* 7.8 Hz, 2 × Ar-H), 6.75 (2H, d, *J* 8.9 Hz, 2 × Ar-H; $C_{2'}$-H, $C_{6'}$-H), 6.63 (2H, d, *J* 8.9 Hz, 2 × Ar-H; $C_{3'}$-H, $C_{5'}$-H), 4.19 (2H, s, C_4-CH_2), 3.95 (2H, q, *J* 7.0 Hz, $C_{4'}$-O$\underline{CH_2}CH_3$), 3.25 (3H, br. s, NCH_3), 1.37 (3H, t, *J* 7.0 Hz, $C_{4'}$-$OCH_2\underline{CH_3}$); ^{13}C NMR (100 MHz, DMF-d_7, 350 K) δ 170.0 (C=O), 157.3 (C), 151.3 (C), 145.5 (C), 142.5 (C), 135.5 (C), 129.2 (2 × Ar-CH), 128.6 (2 × Ar-CH), 127.2 (2 × Ar-CH), 126.4 (2 × Ar-CH), 122.6 (Ar-CH), 116.0 (2 × Ar-CH), 114.2 (2 × Ar-CH), 64.2 (C_4-$\underline{CH_2}$), 48.2 ($C_{4'}$-O$\underline{CH_2}CH_3$), 37.9 (NCH_3), 14.5 ($C_{4'}$-$OCH_2\underline{CH_3}$); LRMS $[M+H]^+$ 361.2; HRMS calcd. for $C_{23}H_{24}N_2O_2Na$: MNa^+, 383.1735. Found: MNa^+, 383.1728.

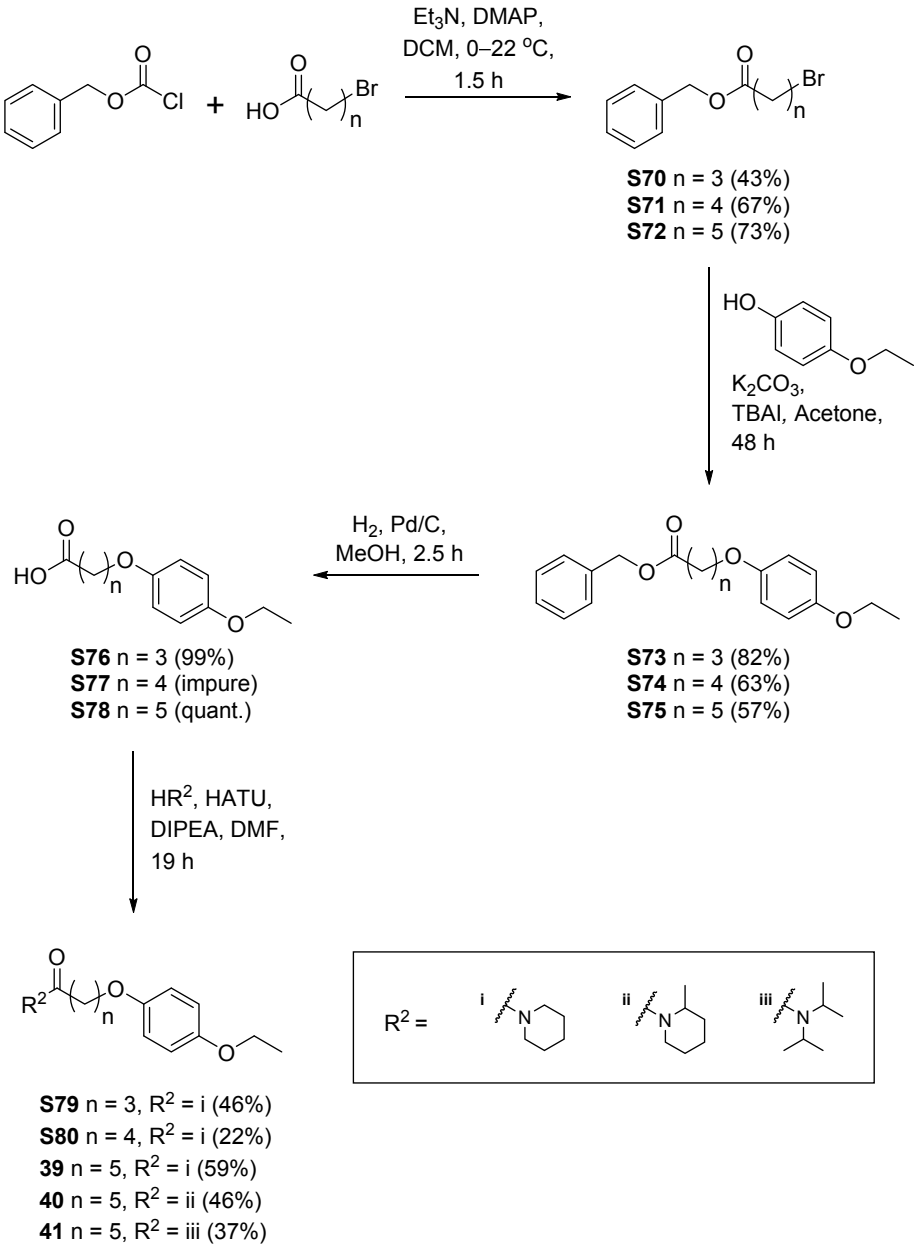
4-(((4-Ethoxyphenyl)amino)methyl)-*N*,*N*-diisopropylbenzamide; 38.



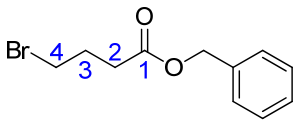
4-Ethoxyaniline acid **10** (50 mg, 0.18 mmol) was reacted with HATU (84 mg, 0.22 mmol), DIPEA (77 μL, 0.44 mmol) and diisopropylamine (52 μL, 0.37 mmol) using Procedure C. The product was purified by Method D to afford the desired *amide* **38** as a cream solid (42 mg, 64%).

HPLC Retention time: 42.15−43.56 min; IR ν_{max} (ATR): 2981, 2890, 1625, 1593, 1510, 1343, 1246 cm^{-1}; mp 103−105 ºC; ^{1}H NMR (400 MHz, Tol-d_8, 350 K) δ 7.19 (2H, d, *J* 7.9 Hz, 2 × Ar-H; C_2-H, C_6-H), 7.12 (2H, d, *J* 7.9 Hz, 2 × Ar-H; C_3-H, C_5-H), 6.69 (2H, d, *J* 8.8 Hz, 2 × Ar-H; $C_{2'}$-H, $C_{6'}$-H), 6.81 (2H, d, *J* 8.8 Hz, 2 × Ar-H; $C_{3'}$-H, $C_{5'}$-H), 3.95 (2H, s, C_4-CH_2), 3.70 (2H, q, *J* 7.0 Hz, $C_{4'}$-O<u>C</u>$H_2$$CH_3$), 3.51 (2H, sep, *J* 6.6 Hz, 2 × N<u>C</u>H$(CH_3)_2$), 1.19 (12H, d, *J* 6.6 Hz, 2 × NCH(CH_3)$_2$), partially hidden 1.16 (3H, t, *J* 7.0 Hz, $C_{4'}$-OCH$_2$CH_3); ^{13}C NMR (100 MHz, Tol-d_8, 350 K) δ 170.5 (C=O), 152.7 (C), 142.9 (C), 141.0 (C), 139.0 (C), 127.7 (2 × Ar-CH), 126.6 (2 × Ar-CH), 116.5 (2 × Ar-CH), 114.8 (2 × Ar-CH), 64.3 ($C_{4'}$-O<u>C</u>$H_2$$CH_3$), 49.5 ($C_4$-<u>C</u>$H_2$), 48.4 (2 × N<u>C</u>H$(CH_3)_2$), 21.0 (2 × NCH(<u>C</u>H_3)$_2$), 15.2 ($C_{4'}$-OCH$_2$<u>C</u>H_3); LRMS $[M+H]^+$ 355.3; HRMS calcd. for $C_{22}H_{31}N_2O_2$: MH^+, 355.2386. Found: MH^+, 355.2379.

1.2.2 Synthesis of Alkyl-linked analogues



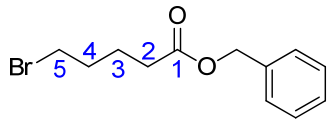
Benzyl 4-bromobutanoate; S70.



4-Bromobutyric acid **294** (0.20 g, 1.2 mmol) was reacted with benzyl chloroformate (0.19 mL, 1.3 mmol), Et_3N (0.20 mL, 1.4 mmol) and DMAP (15 mg, 0.12 mmol) using Procedure D. Benzyl ester **S70** was obtained as a yellow liquid (0.13 g, 43%).

IR ν_{max} (ATR): 2981, 1735, 1248, 1167 cm^{-1}; R_f [10:1 *v/v* hexane:EtOAc] = 0.35; ^1H NMR (400 MHz, $CDCl_3$) δ 7.39−7.33 (5H, m, 5 × Ar-H), 5.13 (2H, s, C_1-O_2CH_2), 3.46 (2H, t, *J* 6.5 Hz, C_4-H_2), 2.56 (2H, t, *J* 7.2 Hz, C_2-CH_2), 2.23−2.16 (2H, m, C_3-H_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.5 (C=O), 135.9 (C), 128.7 (2 × Ar-CH), 128.4 (Ar-CH), 128.3 (2 × Ar-CH), 66.4 (C_1-$O_2\underline{C}H_2$), 32.7 (C_4; CH_2), 32.6 (C_2; CH_2), 27.9 (C_3; CH_2); HRMS calcd. for $C_{11}H_{13}O_2BrNa$: MNa^+, 278.9997/280.9976. Found: MNa^+, 278.9992/280.9971.

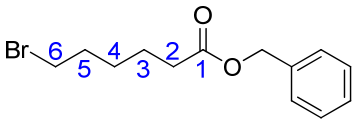
Benzyl 5-bromopentanoate; S71.



5-Bromovaleric acid **295** (0.15 g, 0.83 mmol) was reacted with benzyl chloroformate (0.13 mL, 0.91 mmol), Et_3N (0.14 mL, 0.99 mmol) and DMAP (10 mg, 0.08 mmol) using Procedure D. Benzyl ester **S71** was obtained as a colourless liquid (0.15 g, 67%).

IR ν_{max} (ATR): 2955, 1733, 1255, 1165 cm^{-1}; R_f [10:1 *v/v* hexane:EtOAc] = 0.48; ^1H NMR (400 MHz, $CDCl_3$) δ 7.39−7.31 (5H, m, 5 × Ar-H), 5.12 (2H, s, C_1-O_2CH_2), 3.40 (2H, t, *J* 6.6 Hz, C_5-H_2), 2.40 (2H, t, *J* 7.3 Hz, C_2-H_2), 1.93−1.86 (2H, m, C_4-H_2), 1.84−1.78 (2H, m, C_3-H_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.2 (C=O), 136.2 (C), 128.8 (2 × Ar-CH), 128.5 (Ar-CH), 128.5 (2 × Ar-CH), 66.5 (C_1-$O_2\underline{C}H_2$), 33.5 (C_2; CH_2), 33.2 (C_5; CH_2), 32.2 (C_4; CH_2), 23.7 (C_3; CH_2); LRMS $[M+H]^+$ 271.0; HRMS calcd. for $C_{12}H_{15}O_2BrNa$: MNa^+, 293.0153/295.0133. Found: MNa^+, 293.0148/295.0128.

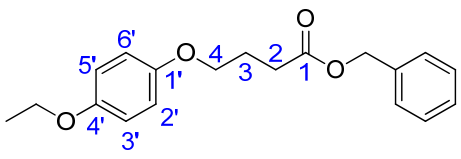
Benzyl 6-bromohexanoate; S72.



6-Bromohexanoic acid **296** (0.20 g, 1.0 mmol) was reacted with benzyl chloroformate (0.16 mL, 1.1 mmol), Et_3N (0.17 mL, 1.2 mmol) and DMAP (13 mg, 0.10 mmol) using Procedure D. Benzyl ester **S72** was obtained as a yellow liquid (0.21 g, 73%).

IR ν_{max} (ATR): 2933, 1735, 1256, 1170 cm^{-1}; R_f [10:1 *v/v* hexane:EtOAc] = 0.38; ^1H NMR (400 MHz, $CDCl_3$) δ 7.38−7.32 (5H, m, 5 × Ar-H), 5.12 (2H, s, C_1-O_2CH_2), 3.39 (2H, t, *J* 6.8 Hz, C_6-H_2), 2.38 (2H, t, *J* 7.5 Hz, C_2-H_2), 1.90−1.83 (2H, m, C_5-H_2), 1.72−1.64 (2H, m, C_3-H_2), 1.51−1.45 (2H, m, C_4-H_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.4 (C=O), 136.2 (C), 128.7 (2 × Ar-CH), 128.4 (3 × Ar-CH), 66.3 (C_1-$O_2\underline{C}H_2$), 34.2 (C_2; CH_2), 33.6 (C_6; CH_2), 32.5 (C_5; CH_2), 27.8 (C_4; CH_2), 24.2 (C_3; CH_2); HRMS calcd. for $C_{13}H_{17}O_2BrNa$: MNa^+, 307.0310/309.0289. Found: MNa^+, 307.0305/309.0285.

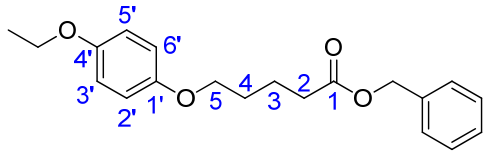
Benzyl 4-(4-ethoxyphenoxy)butanoate; S73.



Benzyl 4-bromobutanoate **S70** (93 mg, 0.36 mmol) was reacted with 4-ethoxyphenol (99 mg, 0.72 mmol), K_2CO_3 (99 mg, 0.72 mmol) and TBAI (27 mg, 0.07 mmol) using Procedure E. Alkylated benzyl ester **S73** was obtained as a yellow oil (93 mg, 82%).

IR ν_{max} (ATR): 2977, 2857, 1736, 1508, 1229, 1165 cm^{-1}; mp 39−41 ºC; R_f [7:1 *v/v* hexane:EtOAc] = 0.50; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38−7.32 (5H, m, 5 × Ar-H), 6.81 (4H, s, 4 × Ar-H), 5.15 (2H, s, C_1-O_2CH_2), 3.98 (2H, q, *J* 7.0 Hz, $C_{4'}$-OCH_2CH_3), 3.95 (2H, t, *J* 6.2 Hz, C_4-H_2), 2.58 (2H, t, *J* 7.4 Hz, C_2-H_2), 2.15−2.08 (2H, m, C_3-H_2), 1.40 (3H, t, *J* 7.0 Hz, $C_{4'}$-OCH_2CH_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.2 (C=O), 153.3 (C), 153.0 (C), 136.1 (C), 128.7 (2 × Ar-CH), 128.3 (3 × Ar-CH), 115.5 (4 × Ar-CH), 67.4 (C_4; CH_2), 66.4 (C_1-O_2CH_2), 64.1 ($C_{4'}$-OCH_2CH_3), 31.0 (C_2; CH_2), 24.9 (C_3; CH_2), 15.1 ($C_{4'}$-OCH_2CH_3); LRMS $[M+H]^+$ 314.7; HRMS calcd. for $C_{19}H_{22}O_4Na$: MNa^+, 337.1416. Found: MNa^+, 337.1411.

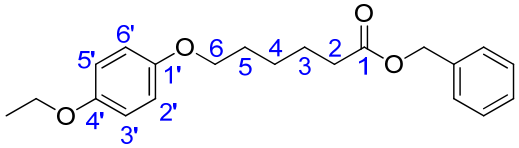
Benzyl 5-(4-ethoxyphenoxy)pentanoate; S74.



Benzyl 5-bromopentanoate **S71** (140 mg, 0.52 mmol) was reacted with 4-ethoxyphenol (140 mg, 1.0 mmol), K_2CO_3 (140 mg, 1.0 mmol) and TBAI (38 mg, 0.10 mmol) using Procedure E. Alkylated benzyl ester **S74** was obtained as a colourless liquid (110 mg, 63%).

IR ν_{max} (ATR): 2977, 2870, 1733, 1507, 1227, 1158 cm^{-1}; R_f [7:1 *v/v* hexane:EtOAc] = 0.38; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37−7.32 (5H, m, 5 × Ar-H), 6.81 (2H, s, 2 × Ar-H), 6.80 (2H, s, 2 × Ar-H), 5.12 (2H, s, C_1-O_2CH_2), 3.98 (2H, q, *J* 6.9 Hz, $C_{4'}$-OCH_2CH_3), 3.91 (2H, t, *J* 6.0 Hz, C_5-H_2), 2.44 (2H, t, *J* 7.2 Hz, C_2-H_2), 1.86−1.75 (4H, m, C_4-H_2 and C_3-H_2), 1.38 (3H, t, *J* 6.9 Hz, $C_{4'}$-OCH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.4 (C=O), 153.2 (C), 153.2 (C), 136.2 (C), 128.7 (2 × Ar-CH), 128.3 (3 × Ar-CH), 115.6 (2 × Ar-CH), 115.5 (2 × Ar-CH), 68.1 (C_5; CH_2), 66.3 (C_1-O_2CH_2), 64.2 ($C_{4'}$-OCH_2CH_3), 34.1 (C_2; CH_2), 28.9 (C_4; CH_2), 21.8 (C_3; CH_2), 15.1 ($C_{4'}$-OCH_2CH_3); HRMS calcd. for $C_{20}H_{24}O_4Na$: MNa^+, 351.1572. Found: MNa^+, 351.1567.

Benzyl 6-(4-ethoxyphenoxy)hexanoate; S75.

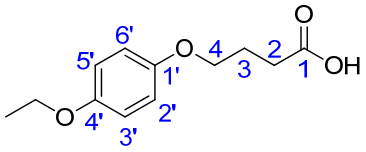


Benzyl 6-bromohexanoate **S72** (120 mg, 0.40 mmol) was reacted with 4-ethoxyphenol (110 mg, 0.80 mmol), K_2CO_3 (110 mg, 0.80 mmol) and TBAI (30 mg, 0.08 mmol) using Procedure E. Alkylated benzyl ester **S75** was obtained as a colourless oil (79 mg, 57%).

IR ν_{max} (ATR): 2922, 2852, 1734, 1507, 1228, 1157 cm^{-1}; R_f [7:1 *v/v* hexane:EtOAc] = 0.52; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38−7.30 (5H, m, 5 × Ar-H), 6.82 (2H, s, 2 × Ar-H), 6.82 (2H, s, 2 × Ar-H), 5.13 (2H, s, C_1-O_2CH_2), 3.98 (2H, q, *J* 7.0 Hz, $C_{4'}$-OCH_2CH_3), 3.89 (2H, t, *J* 6.5 Hz, C_6-H_2), 2.40 (2H, t, *J* 7.5 Hz, C_2-H_2), 1.81−1.68 (4H, m, C_5-H_2 and C_3-H_2), 1.54−1.46 (2H, m, C_4-H_2), 1.39 (3H, t, *J* 7.0 Hz,

$C_{4'}$-$OCH_2\underline{C}H_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.5 (C=O), 153.2 (C), 153.2 (C), 136.2 (C), 128.7 (2 × Ar-CH), 128.3 (3 × Ar-CH), 115.5 (4 × Ar-CH), 68.4 (C_6; CH_2), 66.2 (C_1-$O_2\underline{C}H_2$), 64.1 ($C_{4'}$-$O\underline{C}H_2CH_3$), 34.3 (C_2; CH_2), 29.2 (C_5; CH_2), 25.8 (C_4; CH_2), 24.8 (C_3; CH_2), 15.1 ($C_{4'}$-$OCH_2\underline{C}H_3$); LRMS $[M+H]^+$ 342.7; HRMS calcd. for $C_{21}H_{26}O_4Na$: MNa^+, 365.1729. Found: MNa^+, 365.1723.

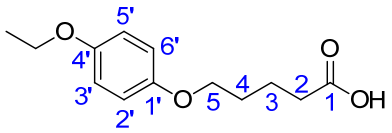
4-(4-Ethoxyphenoxy)butanoic acid; S76.



Benzyl 4-(4-ethoxyphenoxy)butanoate **S73** (27 mg, 0.09 mmol) was reacted with Pd/C (19 mg, 0.18 mmol) and H_2 (g) using Procedure F. The desired acid **S76** was obtained as a white solid (19 mg, 99%).

IR ν_{max} (ATR): 2975, 1729, 1511, 1233 cm^{-1}; mp 72−74 ºC; ^1H NMR (400 MHz, 3:1 *v/v* $CDCl_3$:MeOD) δ 6.74 (4H, s, 4 × Ar-H), 3.90 (2H, q, *J* 7.0 Hz, $C_{4'}$-$OC\underline{H}_2CH_3$), 3.87 (2H, t, *J* 6.2 Hz, C_4-H_2), 2.45 (2H, t, *J* 7.2 Hz, C_2-H_2), 2.02−1.97 (2H, m, C_3-H_2), 1.30 (3H, t, *J* 7.0 Hz, $C_{4'}$-$OCH_2C\underline{H}_3$); ^{13}C NMR (100 MHz, 3:1 *v/v* $CDCl_3$:MeOD) δ 174.3 (C=O), 153.1 (C), 153.1 (C), 115.5 (4 × Ar-CH), 67.4 (C_4; CH_2), 64.2 ($C_{4'}$-$O\underline{C}H_2CH_3$), 30.7 (C_2; CH_2), 24.7 (C_3; CH_2), 14.8 ($C_{4'}$-$OCH_2\underline{C}H_3$); LRMS $[M-H]^-$ 223.0; HRMS calcd. for $C_{12}H_{16}O_4Na$: MNa^+, 247.0946. Found: MNa^+, 247.0941.

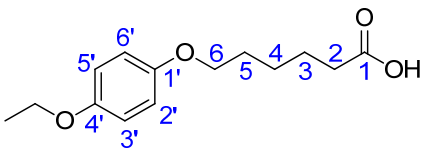
5-(4-Ethoxyphenoxy)pentanoic acid; S77.



Benzyl 5-(4-ethoxyphenoxy)pentanoate **S74** (50 mg, 0.15 mmol) was reacted with Pd/C (33 mg, 0.31 mmol) and H_2 (g) using Procedure F. The desired acid **S77** was obtained as a mixture with the lactonised form (1:1), carried through to next reaction.

IR ν_{max} (ATR): 2979, 2872, 1736, 1506, 1224, 1165 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.81 (2H, s, 2 × Ar-H), 6.80 (2H, s, 2 × Ar-H), 3.97 (2H, q, *J* 7.0 Hz, $C_{4'}$-$OC\underline{H}_2CH_3$), 3.91 (2H, t, *J* 5.8 Hz, C_5-H_2), 2.44 (2H, t, *J* 7.1 Hz, C_2-H_2), 1.87−1.77 (4H, m, C_4-H_2 and C_3-H_2), 1.38 (3H, t, *J* 7.0 Hz, $C_{4'}$-$OCH_2C\underline{H}_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.1 (C=O), 153.2 (C), 153.2 (C), 115.5 (2 × Ar-CH), 115.5 (2 × Ar-CH), 68.1 (C_5; CH_2), 64.1 ($C_{4'}$-$O\underline{C}H_2CH_3$), 33.8 (C_2; CH_2), 28.9 (C_4; CH_2), 21.8 (C_3; CH_2), 15.1 ($C_{4'}$-$OCH_2\underline{C}H_3$); LRMS $[M-H]^-$ 236.9; HRMS calcd. for $C_{13}H_{18}O_4Na$: MNa^+, 261.1103. Found: MNa^+, 261.1098.

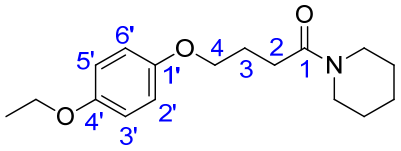
6-(4-Ethoxyphenoxy)hexanoic acid; S78.



Benzyl 6-(4-ethoxyphenoxy)hexanoate **S75** (31 mg, 0.09 mmol) was reacted with Pd/C (20 mg, 0.19 mmol) and H_2 (g) using Procedure F. The desired acid **S78** was obtained as a white solid (23 mg, quant.).

IR ν_{max} (ATR): 2976, 2870, 1708, 1509, 1252, 1224 cm^{-1}; mp 79−81 ºC; ^{1}H NMR (500 MHz, 3:1 *v/v* $CDCl_3$:MeOD) δ 6.77 (2H, s, 2 × Ar-H), 6.76 (2H, s, 2 × Ar-H), 3.93 (2H, q, *J* 6.9 Hz, $C_{4'}$-OC<u>H</u>$_2$CH$_3$), 3.86 (2H, t, *J* 6.5 Hz, C_6-H$_2$), 2.27 (2H, t, *J* 7.2 Hz, C_2-H$_2$), 1.76−1.68 (2H, m, C_5-H$_2$), 1.67−1.59 (2H, m, C_3-H$_2$), 1.51−1.40 (2H, m, C_4-H$_2$), 1.32 (3H, t, *J* 6.9 Hz, $C_{4'}$-OCH$_2$C<u>H</u>$_3$); ^{13}C NMR (126 MHz, 3:1 *v/v* $CDCl_3$:MeOD) δ 176.8 (C=O), 153.1 (C), 152.9 (C), 115.4 (2 × Ar-CH), 115.4 (2 × Ar-CH), 68.4 (C_6; CH_2), 64.1 ($C_{4'}$-O<u>C</u>H$_2$CH$_3$), 34.3 (C_2; CH_2), 29.0 (C_5; CH_2), 25.6 (C_4; CH_2), 24.7 (C_3; CH_2), 14.7 ($C_{4'}$-OCH$_2$<u>C</u>H$_3$); LRMS $[M-H]^-$ 251.1; HRMS calcd. for $C_{14}H_{20}O_4Na$: MNa^+, 275.1259. Found: MNa^+, 275.1254.

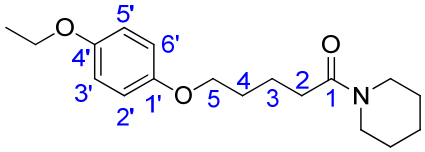
4-(4-Ethoxyphenoxy)-1-(piperidin-1-yl)butan-1-one; S79.



4-(4-Ethoxyphenoxy)butanoic acid **S76** (19 mg, 0.08 mmol) was reacted with HATU (39 mg, 0.10 mmol), DIPEA (35 µL, 0.20 mmol) and piperidine (17 µL, 0.17 mmol) using Procedure C. The product was purified by Method B (ii) to afford the desired *amide* **S79** as a white solid (11 mg, 46%).

HPLC Retention time: 28.39 min; IR ν_{max} (ATR): 2974, 2857, 1639, 1507, 1440, 1226, 1049 cm^{-1}; mp 54−56 ºC; R_f [98:2 *v/v* DCM:MeOH] = 0.54; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.81 (4H, s, 4 × Ar-H), 3.97 (2H, q, *J* 7.0 Hz, $C_{4'}$-OC<u>H</u>$_2$CH$_3$), 3.97 (2H, t, *J* 5.9 Hz, C_4-H$_2$), 3.56 (2H, br. t, *J* 5.6 Hz, pip NCH_2), 3.41 (2H, br. t, *J* 5.4 Hz, pip NCH_2), 2.52 (2H, t, *J* 7.3 Hz, C_2-H$_2$), 2.13−2.06 (2H, m, C_3-H$_2$), 1.66−1.58 (2H, m, pip CH_2), 1.58−1.49 (4H, m, 2 × pip CH_2), 1.30 (3H, t, *J* 7.0 Hz, $C_{4'}$-OCH$_2$C<u>H</u>$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.0 (C=O), 153.2 (C), 153.1 (C), 115.6 (2 × Ar-CH), 115.5 (2 × Ar-CH), 67.8 (C_4; CH_2), 64.2 ($C_{4'}$-O<u>C</u>H$_2$CH$_3$), 46.8 (pip CH_2), 42.9 (pip CH_2), 29.6 (C_2; CH_2), 26.6 (pip CH_2), 25.7 (pip CH_2), 25.3 (pip CH_2), 24.6 (C_3; CH_2), 15.1 ($C_{4'}$-OCH$_2$<u>C</u>H$_3$); LRMS $[M+H]^+$ 291.9; HRMS calcd. for $C_{17}H_{25}NO_3Na$: MNa^+, 314.1732. Found: MNa^+, 314.1728.

5-(4-Ethoxyphenoxy)-1-(piperidin-1-yl)pentan-1-one; S80.

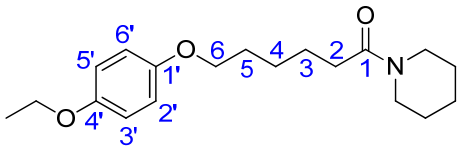


The prior mixture containing 5-(4-Ethoxyphenoxy)pentanoic acid **S77** (19 mg) was reacted with HATU (26 mg, 0.07 mmol), DIPEA (23 µL, 0.13 mmol) and piperidine (11 µL, 0.11 mmol) using Procedure C. The product was purified by Method C to afford the desired *amide* **S80** as a white solid (5.4 mg, 22% over 2 steps).

HPLC Retention time: 24.52 min; IR ν_{max} (ATR): 2937, 2863, 1639, 1508, 1442, 1229 cm^{-1}; mp 48−50 ºC; R_f [98:2 *v/v* DCM:MeOH] = 0.41; ^{1}H NMR (400 MHz, Tol-d_8, 350 K) δ 6.75 (2H, d, *J* 9.5 Hz, 2 × Ar-H), 6.72 (2H, d, *J* 9.5 Hz, 2 × Ar-H), 3.74 (2H, t, *J* 6.2 Hz, C_5-H$_2$), 3.70 (2H, q, *J* 7.0 Hz, $C_{4'}$-OC<u>H</u>$_2$CH$_3$), 3.19 (4H, br. s, 2 × pip NCH_2), partially hidden 2.08 (2H, t, C_2-H$_2$), 1.83−1.74 (2H, m, C_4-H$_2$), 1.74−1.66 (2H, m, C_3-H$_2$), 1.32−1.24 (2H, m, pip CH_2), 1.24−1.18 (4H, m, 4 × pip CH_2), 1.16 (3H, t, *J* 7.0 Hz, $C_{4'}$-OCH$_2$C<u>H</u>$_3$); ^{1}H NMR (400 MHz, Tol-d_8, 350 K) δ 170.1 (C=O), 154.3 (C), 154.1 (C), 116.3 (2 × Ar-CH), 116.3 (2 × Ar-CH), 69.0 (C_5;

CH_2), 64.3 ($C_{4'}$-O<u>C</u>H_2CH_3), 44.4 (2 × pip N<u>C</u>H_2, br.), 33.0 (C_2; CH_2), 29.8 (C_4; CH_2), 26.4 (2 × pip CH_2, br.), 25.1 (pip CH_2), 22.5 (C_3; CH_2), 15.1 ($C_{4'}$-OCH$_2$<u>C</u>H_3); LRMS $[M+H]^+$ 306.0; HRMS calcd. for $C_{18}H_{27}NO_3Na$: MNa^+, 328.1889. Found: MNa^+, 328.1883.

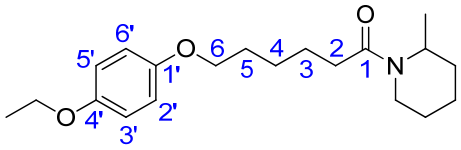
6-(4-Ethoxyphenoxy)-1-(piperidin-1-yl)hexan-1-one; 39.



6-(4-Ethoxyphenoxy)hexanoic acid **S78** (24 mg, 0.10 mmol) was reacted with HATU (44 mg, 0.11 mmol), DIPEA (40 µL, 0.23 mmol) and piperidine (19 µL, 0.19 mmol) using Procedure C. The product was purified by Method B (ii) to afford the desired *amide* **39** as a white solid (18 mg, 59%).

HPLC Retention time: 33.29 min; IR ν_{max} (ATR): 2937, 2858, 1640, 1508, 1440, 1228 cm^{-1}; mp 44−46 ºC; R_f [98:2 *v/v* DCM:MeOH] = 0.51; ^{1}H NMR (400 MHz, Tol-d_8, 350 K) δ 6.75 (2H, d, *J* 9.2 Hz, 2 × Ar-H), 6.72 (2H, d, *J* 9.2 Hz, 2 × Ar-H), 3.72 (2H, q, *J* 6.9 Hz, $C_{4'}$-OC<u>H$_2$</u>CH_3), 3.69 (2H, t, *J* 7.1 Hz, C_6-H_2), 3.20 (4H, br. s, 2 × pip NCH_2), 2.07 (2H, t, *J* 7.3 Hz, C_2-H_2), 1.72−1.62 (4H, m, C_5-H_2 and C_3-H_2), 1.48−1.38 (2H, m, C_4-H_2), 1.33−1.25 (2H, m, pip CH_2), 1.25−1.18 (4H, m, 2 × pip CH_2), 1.16 (3H, t, *J* 6.9 Hz, $C_{4'}$-OCH$_2$C<u>H$_3$</u>); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.6 (C=O), 153.3 (C), 153.1 (C), 115.5 (2 × Ar-CH), 115.5 (2 × Ar-CH), 68.5 (C_6; CH_2), 64.1 ($C_{4'}$-O<u>C</u>H_2CH_3), 46.4 (pip CH_2 *via* HSQC), 42.9 (pip CH_2 *via* HSQC), 33.3 (C_2; CH_2), 29.3 (C_5; CH_2), 26.1 (C_4; CH_2), 26.1−25.5 (3 × pip CH_2, br.), 24.6 (C_3; CH_2), 15.0 ($C_{4'}$-OCH$_2$<u>C</u>H_3); LRMS $[M+H]^+$ 320.0; HRMS calcd. for $C_{19}H_{29}NO_3Na$: MNa^+, 342.2045. Found: MNa^+, 342.2040.

6-(4-Ethoxyphenoxy)-1-(2-methylpiperidin-1-yl)hexan-1-one; 40.

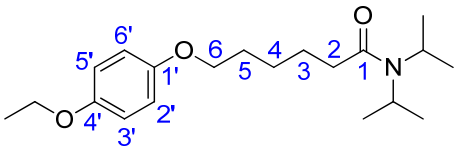


6-(4-Ethoxyphenoxy)hexanoic acid **S78** (16 mg, 0.06 mmol) was reacted with HATU (29 mg, 0.08 mmol), DIPEA (28 µL, 0.16 mmol) and 2-methylpiperidine (15 µL, 0.13 mmol) using Procedure C. The product was purified by Method B (ii) to afford the desired *amide* **40** as a white solid (9.9 mg, 46%).

HPLC Retention time: 34.34 min; IR ν_{max} (ATR): 3205, 2958, 1623, 1507, 1441, 1231 cm^{-1}; mp 62-63 ºC; R_f [98:2 *v/v* DCM:MeOH] = 0.51; ^{1}H NMR (400 MHz, Tol-d_8, 350 K) δ 6.76 (2H, d, *J* 9.0 Hz, 2 × Ar-H), 6.72 (2H, d, *J* 9.0 Hz, 2 × Ar-H), 4.45 (1H, br. s, pip NC<u>H</u>H), 3.83 (1H, br. s, pip NCH<u>H</u>), 3.72 (2H, q, *J* 6.9 Hz, $C_{4'}$-OC<u>H$_2$</u>CH_3), partially hidden 3.68 (2H, t, *J* 6.7 Hz, C_6-H_2), 2.57 (1H, br. t, pip C<u>H</u>CH_3), 2.10 (2H, hudden t *via* HSQC, C_2-H_2), 1.76−1.59 (4H, m, C_5-H_2 and C_3-H_2), 1.58−1.06 (8H, m, C_4-H_2 and 3 × pip CH_2), 1.16 (3H, t, *J* 6.9 Hz, $C_{4'}$-OCH$_2$C<u>H$_3$</u>), 0.92 (3H, d, *J* 6.9 Hz, pip CHC<u>H$_3$</u>); ^{13}C NMR (100 MHz, Tol-d_8, 350 K) δ 170.6 (C=O), 154.3 (C), 154.1 (C), 116.2 (2 × Ar-CH), 116.2 (2 × Ar-CH), 69.0 (C_6; CH_2), 64.2 ($C_{4'}$-O<u>C</u>H_2CH_3), 45.7 (pip C<u>H</u>CH_3 *via* HSQC), 38.2 (pip CH_2 *via* HSQC), 33.4 (C_2; CH_2), 30.7 (pip CH_2), 29.9 (C_5; CH_2), 26.6 (C_4; CH_2), 26.4 (pip CH_2), 25.7 (C_3; CH_2),

19.3 (pip CH_2), 16.0 (pip $CH\underline{C}H_3$), 15.1 ($C_{4'}$-$OCH_2\underline{C}H_3$); LRMS $[M+H]^+$ 333.9; HRMS calcd. for $C_{20}H_{31}NO_3Na$: MNa^+, 356.2202. Found: MNa^+, 356.2196.

6-(4-Ethoxyphenoxy)-*N*,*N*-diisopropylhexanamide; 41.



6-(4-Ethoxyphenoxy)hexanoic acid **S78** (15 mg, 0.06 mmol) was reacted with HATU (27 mg, 0.07 mmol), DIPEA (26 µL, 0.15 mmol) and diisopropylamine (17 µL, 0.12 mmol) using Procedure C. The product was purified by Method B (ii) to afford the desired *amide* **41** as a white solid (7.4 mg, 37%).

HPLC Retention time: 36.82 min; IR ν_{max} (ATR): 2963, 2907, 1642, 1508, 1229 cm^{-1}; mp 66−67 ºC; R_f [98:2 *v/v* DCM:MeOH] = 0.48; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.81 (4H, s, 4 × Ar-H), 3.97 (2H, q, *J* 7.0 Hz, $C_{4'}$-$OC\underline{H}_2CH_3$), 3.97 (1H, br. s *via* HSQC, $NC\underline{H}(CH_3)_2$), 3.91 (2H, t, *J* 7.1 Hz, C_6-H_2), 3.49 (1H, br. s, $NC\underline{H}(CH_3)_2$), 2.33 (2H, t, *J* 7.7 Hz, C_2-H_2), 1.79 (2H, app. quin, C_5-H_2), 1.68 (2H, app. quin, C_3-H_2), 1.57−1.44 (2H, m, C_4-H_2), partially hidden 1.38 (3H, t, *J* 7.0 Hz, $C_{4'}$-$OCH_2C\underline{H}_3$), 1.37 (6H, d, $NCH(C\underline{H}_3)_2$), 1.20 (6H, d, $NCH(C\underline{H}_3)_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 1721.3 (C=O), 153.3 (C), 153.2 (C), 115.6 (2 × Ar-CH), 115.5 (2 × Ar-CH), 68.5 (C_6; CH_2), 64.2 ($C_{4'}$-$O\underline{C}H_2CH_3$), 48.7 ($N\underline{C}H(CH_3)_2$, br.), 45.9 ($N\underline{C}H(CH_3)_2$, br.), 35.2 (C_2; CH_2), 29.4 (C_5; CH_2), 26.1 (C_4; CH_2), 25.1 (C_3; CH_2), 21.1 ($NCH(\underline{C}H_3)_2$), 20.8 ($NCH(\underline{C}H_3)_2$), 15.1 ($C_{4'}$-$OCH_2\underline{C}H_3$); LRMS $[M+H]^+$ 336.0; HRMS calcd. for $C_{20}H_{33}NO_3Na$: MNa^+, 358.2358. Found: MNa^+, 358.2352.

2 Biological Experimental

2.1 *T.b. brucei* and HEK293 Assay Conditions: Initial Screen

The compounds were dissolved in 100% DMSO to give a stock solution of 21 mM. The stock solutions were subsequently diluted in 100% DMSO to give concentrations of 5.25 mM, 2.62 mM and 0.262 mM (final assay concentrations of 20.83 μM, 10.42 μM and 1.04 μM respectively). The compounds were screened at each concentration against *T.b. brucei*. Insoluble compounds were not screened. The percentage activity of each compound against *T.b. brucei* at 20.83 μM, 10.42 μM and 1.04 μM was calculated. Compounds with >50% activity at 10.42 μM were classed as active and rescreened in dose response against *T.b. brucei* and HEK293 in order for their IC_{50} value and SI to be determined.

2.1.1 IC_{50} and SI Determination

The compounds classed as active in the initial screen against *T.b. brucei* were screened against both *T.b. brucei* and HEK293 using the methodology previous described by Sykes and Avery.[1] Two previously screened parent compounds are included as controls for each screen. The compounds were screened in triplicate, against two different *T.b. brucei* and HEK293 cultures, designated cultures A and B. The 21 mM compound stock solution was serially diluted in 100% DMSO to give 14 concentrations: 83.3 μM, 41.7 μM, 20.8 μM, 10.4 μM, 5.2 μM, 4.1 μM, 2.1 μM, 1.0 μM, 0.52 μM, 0.42 μM, 0.21 μM, 0.10 μM, 0.05 μM and 0.04 μM. The final DMSO concentration in the assay was 0.42%. In order to allow the SI of the compounds to be estimated only the highest concentration of 83.3 μM was used in the HEK293 assay.

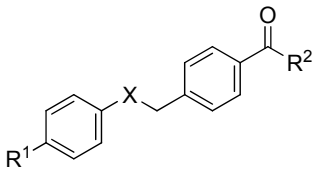
IC_{50} values were determined by exporting the compound activity data into GraphPad Prism. The SI of the compounds was determined where possible by directly comparing the IC_{50} values from the *T.b. brucei* and HEK293 assay. If this was not possible, an estimated IC_{50} value was calculated by comparing the dose at which the compound was active >50% in the *T.b. brucei* assay and the highest dose at which there was no activity (<50%) in the HEK293 assay.

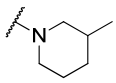
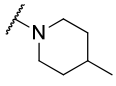
2.1.2 Assay Controls

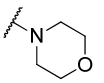
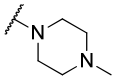
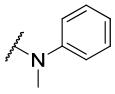
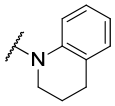
As a measure of the sensitivity of the assay and to ensure that each compound plate was stamped correctly into the assay plates, the reference compounds pentamidine, diminazene aceturate and puromycin were included on the compound plates with the test compounds. In the *T. b. brucei* assay the average IC_{50} of pentamidine was 1.98 ± 0.5 nM. Diminazene aceturate and puromycin gave IC_{50} values of 21.03 ± 6.1 nM and 40.44 ± 10.73 nM respectively. In the HEK293 assay puromycin gave an IC_{50} value of 475.59 ± 128.54 nM. Pentamidine and diminazene aceturate had no activity in the HEK293 assay.

2.1.3 Full Results Table

Table S1. Preliminary screen of compound library against *T.b. brucei in vitro*, with selectivity compared against HEK293.



Entry	Compound	R^1	X	R^2	*T.b. brucei* IC_{50} [μM]	Selectivity Index (SI)†
1	**8**	OEt	O		>50	-
2	**S50**	H	O		<41.67‡	-
3	**S54**	Me	O		<41.67‡	-
4	**S56**	Et	O		<41.67‡	-
5	**12**	*n*Pr	O		>50	-
6	**11**	OMe	O		4.60	> 18.0
7	**1**	OEt	O		1.15	36.3
8	**S67**	O*n*Pr	O		<41.67‡	-
9	**13**	OEt	NH		3.13	26.6
10	**S51**	H	O		<41.67‡	-
11	**14**	Me	O		9.20	> 9.0
12	**S57**	Et	O		<41.67‡	-
13	**15**	*n*Pr	O		10.00	> 8.0
14	**16**	OMe	O		3.75	22.3
15	**17**	OEt	O		0.49	84.3
16	**S68**	O*n*Pr	O		<41.67‡	-
17	**18**	OEt	NH		1.93	43.2
18	**S52**	H	O		>50	
19	**S55**	Me	O		<41.67‡	-
20	**S58**	Et	O		insoluble	-
21	**S59**	*n*Pr	O		insoluble	-
22	**S62**	OMe	O		<41.67‡	-
23	**23**	OEt	O		2.70	>31.0
24	**S69**	O*n*Pr	O		<41.67‡	-
25	**24**	OEt	NH		2.90	28.7
26	**S53**	H	O		>50	-
27	**19**	Me	O		>50	-
28	**20**	Et	O		>50	-
29	**S60**	*n*Pr	O		<41.67‡	-
30	**21**	OMe	O		>50	-
31	**22**	OEt	O		>50	-

32	**25**	Et	O		14.77	> 5.6
33	**26**	*n*Pr	O		4.17	20.0
34	**S63**	OMe	O		20.36	4.1
35	**27**	OEt	O		4.20	19.8
36	**28**	OEt	NH		20.56	4.1
37	**29**	Et	O		>50	-
38	**S61**	*n*Pr	O		11.00	7.6
39	**30**	OMe	O		>50	-
40	**31**	OEt	O		>50	-
41	**32**	Et	O		4.84	17.3
42	**33**	OMe	O		17.95	> 4.6
43	**34**	OEt	O		2.88	28.9
44	**35**	OEt	NH		4.64	18.0
45	**S64**	OEt	O		<41.67‡	-
46	**36**	OEt	O		>50	-
47	**S65**	OEt	O		<41.67‡	-
48	**37**	OEt	O		1.73	> 48.2
49	**38**	OEt	NH		3.51	23.7
50	**S66**	OEt	O		>50	-

† SI = (HEK293 IC_{50})/(*T.b. brucei* IC_{50}); ‡ These compounds inhibit the growth of *T.b. brucei* more than 50% at 41.67 μM, but precipitate at lower concentrations, meaning IC_{50} values could not be calculated.

2.2 Virulent Protozoan Assay Conditions and Results

2.2.1 Activity against *T.b. rhodesiense* STIB900

This stock was isolated in 1982 from a human patient in Tanzania and after several mouse passages cloned and adapted to axenic culture conditions,[2] a Minimum Essential Medium (50 μL) supplemented with 25 mM HEPES, 1 g/L additional glucose, 1% MEM non-essential amino acids (100×), 0.2 mM 2-mercaptoethanol, 1 mM Na-pyruvate and 15% heat inactivated horse serum was added to each well of a 96-well microtiter plate. Serial drug dilutions of eleven 3-fold dilution steps covering a range from 100 to 0.002 μg/mL were prepared. Then 4×10^3 bloodstream forms of *T. b. rhodesiense* STIB 900 in 50 μL was added to each well and the plate incubated at 37 °C under a 5% CO_2 atmosphere for 70 h. 10 μL of a resazurin solution (125 ng/mL of double-distilled water) was then added to each well and incubation continued for a further 2–4 h.[3] Then the plates were read with a Spectramax Gemini XS microplate fluorometer (Molecular Devices Cooperation, Sunnyvale, CA, USA) using an excitation wavelength of 536 nm and an emission wave length of 588 nm. The IC_{50} values were calculated by linear regression[4] from the sigmoidal dose inhibition curves using SoftmaxPro software (Molecular Devices Cooperation, Sunnyvale, CA, USA). Melarsoprol is used as a control.

2.2.2 Activity against *T. cruzi*

Rat skeletal myoblasts (L6 cells) were seeded in 96-well microtitre plates at 2000 cells/well in 100 μL RPMI 1640 medium with 10% FBS and 2 mM L-glutamine. After 24 h the medium was removed and replaced by 100 μL per well containing 5000 trypomastigote forms of *T. cruzi* Tulahuen strain C2C4 containing the β-galactosidase (Lac Z) gene.[5] After 48 h the medium was removed from the wells and replaced by 100 μL fresh medium with or without a serial drug dilution of eleven 3-fold dilution steps covering a range from 100 to 0.002 μg/mL. After 96 h of incubation the plates were inspected under an inverted microscope to assure growth of the controls and sterility. Then the substrate CPRG/Nonidet (50 μL) was added to all wells. A color reaction developed within 2–6 h and could be read photometrically at 540 nm. Data were analysed with the graphic programme Softmax Pro (Molecular Devices), which calculated IC_{50} values by linear regression[4] from the sigmoidal dose inhibition curves. Benznidazole is used as a control.

2.2.3 Activity Against *L. donovani* Axenic Amastigotes

Amastigotes of *L. donovani* strain MHOM/ET/67/L82 were grown in axenic culture at 37 °C in SM medium[6] at pH 5.4 supplemented with 10% heat-inactivated fetal bovine serum under an atmosphere of 5% CO_2 in air. 100 μL of culture medium with 10^5 amastigotes from axenic culture with or without a serial drug dilution were seeded in 96-well microtitre plates. Serial drug dilutions of eleven 3-fold dilution steps covering a range from 100 to 0.002 μg/mL were prepared. After 70 h of incubation the plates were inspected under an inverted microscope to assure growth of the controls and sterile conditions. 10 μL of a resazurin solution (125 ng/mL of distilled water),[7] was then added to each well and the plates incubated for another 2 h. Then the plates were read with a Spectramax Gemini XS microplate fluorometer (Molecular Devices Cooperation, Sunnyvale, CA, USA) using an excitation wave length of 536 nm and an emission wave length of 588 nm. Data were analysed using the software Softmax Pro (Molecular Devices Cooperation, Sunnyvale, CA, USA). Decrease of fluorescence

(= inhibition) was expressed as percentage of the fluorescence of control cultures and plotted against the drug concentrations. From the sigmoidal inhibition curves the IC_{50} values were calculated by linear regression.[6] Miltefosine is used as a control.

2.2.4 Activity Against *P. falciparum*

Activity against erythrocytic stages of *P. falciparum* was determined using a ^{3}H-hypoxanthine incorporation assay,[8, 9] using the drug sensitive NF54 strain (Schipol Airport, The Netherlands[10]) and the standard drug chloroquine (Sigma C6628). Compounds were dissolved in DMSO at 10 mg/mL and added to parasite cultures incubated in RPMI 1640 medium without hypoxanthine, supplemented with HEPES (5.94 g/L), $NaHCO_3$ (2.1 g/L), neomycin (100 U/mL), Albumax® (5 g/L) and washed human red cells A^+ at 2.5% haematocrit (0.3% parasitaemia). Serial drug dilutions of eleven 3-fold dilution steps covering a range from 100 to 0.002 µg/mL were prepared. The 96-well plates were incubated in a humidified atmosphere at 37 °C; 4% CO_2, 3% O_2, 93% N_2. After 48 h 50 µL of ^{3}H-hypoxanthine (= 0.5 µCi) was added to each well of the plate. The plates were incubated for a further 24 h under the same conditions. The plates were then harvested with a Betaplate™ cell harvester (Wallac, Zurich, Switzerland), and the red blood cells transferred onto a glass fibre filter then washed with distilled water. The dried filters were inserted into a plastic foil with 10 mL of scintillation fluid, and counted in a Betaplate™ liquid scintillation counter (Wallac, Zurich, Switzerland). IC_{50} values were calculated from sigmoidal inhibition curves by linear regression[4] using Microsoft Excel. Chloroquine was used as a control.

2.2.5 *In vitro* Cytotoxicity with L6 Cells.

Assays were performed in 96-well microtiter plates, each well containing 100 µL of RPMI 1640 medium supplemented with 1% L-glutamine (200mM) and 10% fetal bovine serum, and 4000 L6 cells (a primary cell line derived from rat skeletal myoblasts).[11, 12] Serial drug dilutions of eleven 3-fold dilution steps covering a range from 100 to 0.002 µg/mL were prepared. After 70 hours of incubation the plates were inspected under an inverted microscope to assure growth of the controls and sterile conditions. 10 µL of a resazurin solution, (125 ng/mL of distilled water) was then added to each well and the plates incubated for another 2 h. Then the plates were read with a Spectramax Gemini XS microplate fluorometer (Molecular Devices Cooperation, Sunnyvale, CA, USA) using an excitation wavelength of 536 nm and an emission wavelength of 588 nm. The IC_{50} values were calculated by linear regression[4] from the sigmoidal dose inhibition curves using SoftmaxPro software (Molecular Devices Cooperation, Sunnyvale, CA, USA). Podophyllotoxin is used as a control.

2.2.6 Results

Results of these assays against selected compounds are provided in Table S2 and Table S3. IC_{50} values for positive control compounds are as follows:

IC_{50} (Melarsoprol) = 0.010 µM (*T.b. rhodesiense*);

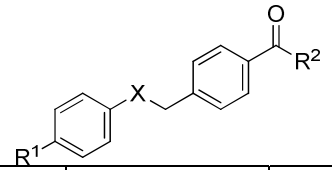
IC_{50} (Benznidazole) = 2.325 µM (*T. cruzi*);

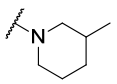
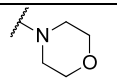
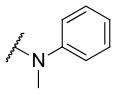
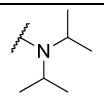
IC_{50} (Miltefosine) = 0.572 µM (*L. donovani*);

IC_{50} (Chloroquine) = 0.013 µM (*P. falciparum*);

IC_{50} (Podophylotoxin) = 0.022 µM (L6 cells).

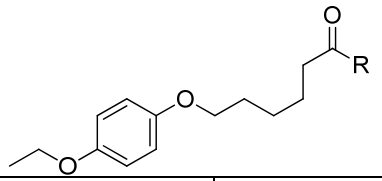
Table S2. Results of *T.b. rhodesiense* screening of the 13 most active first generation compounds from initial *T.b. brucei* testing (these results are repeated in the last column).

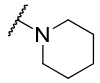
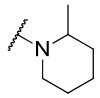
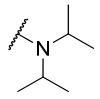


Entry	Comp	R^1	X	R^2	*T.b. rhodesiense* IC_{50} [µM]	*T. cruzi* IC_{50} [µM]	*L. donovani* IC_{50} [µM]	*P. falciparum* IC_{50} [µM]	Cytotoxicity L6 IC_{50}	*T.b. brucei* IC_{50} [µM] (SI)†
1	**11**	OMe	O		2.64 ± 0.243	65.4 ± 22.7	35.1 ± 4.27	35.9 ± 2.27	79.3 ± 44.6	4.6 (18)
2	**1**	Oet	O		0.985 ± 0.076	107 ± 34.5	35.7 ± 6.22	22.3 ± 1.06	186 ± 94.2	1.2 (36)
3	**13**	OEt	NH		4.94 ± 1.96	15.3 ± 6.73	37.8 ± 2.70	24.9 ± 1.04	26.9 ± 1.24	3.1 (27)
4	**16**	OMe	O		1.82 ±0.022	59.8 ± 21.1	39.2 ± 3.98	25.7 ± 5.45	85.7 ± 35.8	3.8 (22)
5	**17**	OEt	O		0.365 ± 0.059	50.1 ± 23.5	28.9 ± 1.02	17.6 ± 3.43	116 ± 6.93	0.49 (84)
6	**18**	OEt	NH		1.88 ± 0.122	60.8 ± 19.6	45.4 ± 1.42	20.3 ± 1.72	71.6 ± 36.8	1.9 (43)
7	**23**	OEt	O		1.74 ± 0.230	172 ± 49.5	94.0 ± 40.1	48.3 ± 11.3	263 ± 31.71	2.7 (31)
8	**26**	*n*Pr	O		9.73 ± 1.28	32.1 ± 11.5	40.4 ± 11.6	19.1 ± 5.13	106 ± 14.2	4.2 (20)
9	**32**	Et	O		7.16 ± 3.17	168 ± 37.1	64.0 ± 23.2	113 ± 31.4	>275	4.8 (17)
10	**34**	OEt	O		3.38 ± 1.58	135 ± 71.2	136.5 ± 87.5	117 ± 38.3	>275	2.9 (29)
11	**35**	OEt	NH		5.28 ± 0.472	16.2 ± 5.38	38.6 ± 4.30	15.4± 0.222	75.0 ± 23.3	4.6 (18)
12	**37**	OEt	O		0.464 ± 0.162	229 ± 26.3	>275	88.3 ± 41.4	>275	1.7 (48)
13	**38**	OEt	NH		3.61 ± 1.12	50.5 ± 15.1	44.9 ± 0.423	12.3 ± 1.21	83.6 ± 24.4	3.5 (24)

† SI = (HEK293 IC_{50})/(*T.b. brucei* IC_{50})

Table S3 Results of *T.b. rhodesiense* screening of the three most active second generation alkyl linked compounds **39**, **40** and **41** from initial *T.b. brucei* testing (these results are repeated in the last column).



Entry	Comp	R	*T.b. rhodesiense* IC_{50} [µM]	*T. cruzi* IC_{50} [µM]	*L. donovani* IC_{50} [µM]	*P. falciparum* IC_{50} [µM]	Cytotoxicity L6 IC_{50}	*T.b. brucei* IC_{50} [µM] (SI)[†]
1	**39**		7.89 ± 1.46	45.4 ± 1.10	70.4 ± 12. 4	25.0 ± 3.96	102 ± 41.8	7.4 (24)
2	**40**		4.71 ± 2.25	36.9 ± 5.70	47.7 ± 3.60	19.4 ± 3.15	97.8 ± 44.1	1.7 (50)
3	**41**		4.68 ± 1.95	64.4 ± 21.0	38.8 ± 3.88	7.99 ± 0.952	89.7 ± 27.0	2.0 (41)

[†] SI = (HEK293 IC_{50})/(*T.b. brucei* IC_{50})

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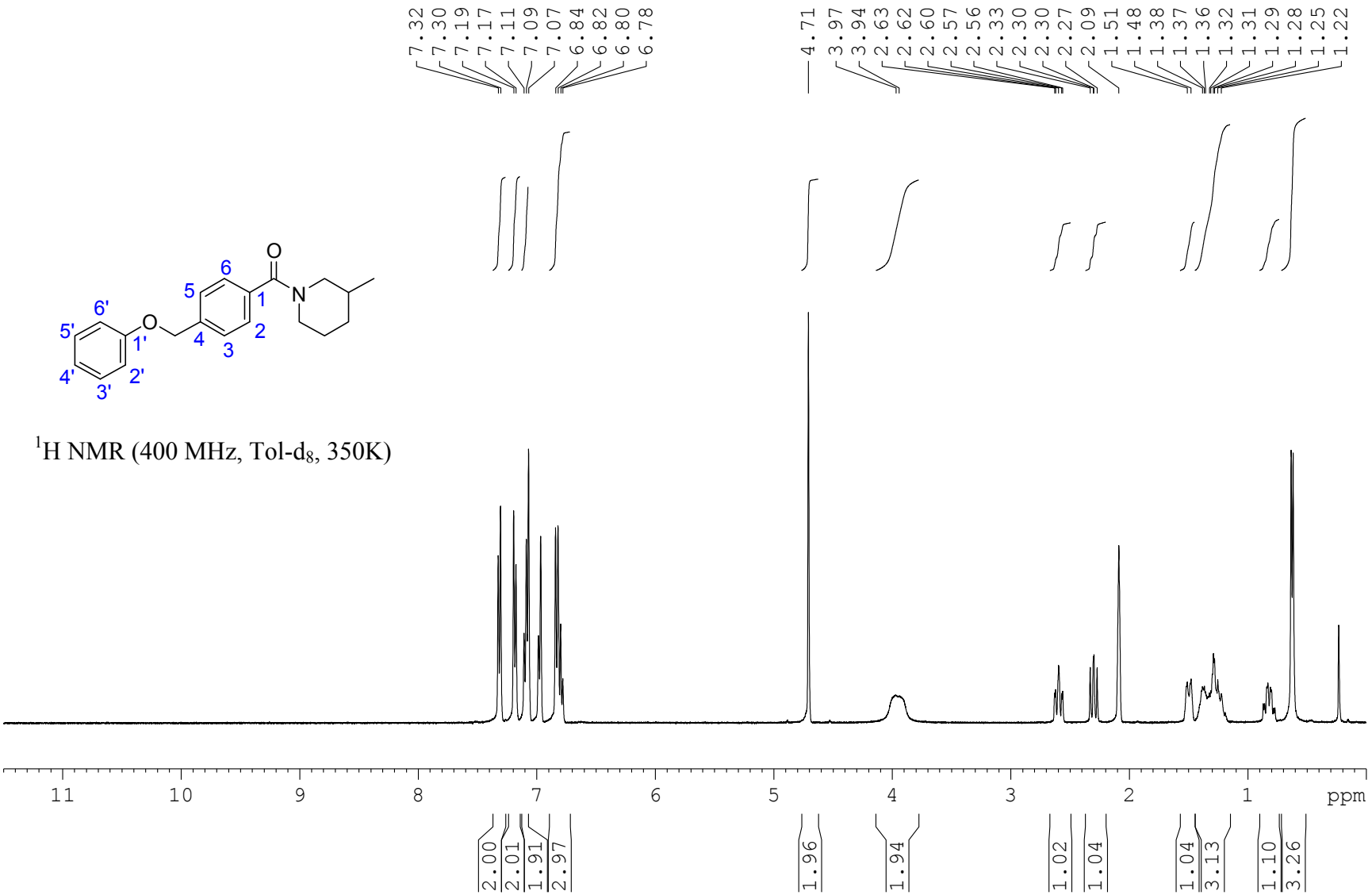
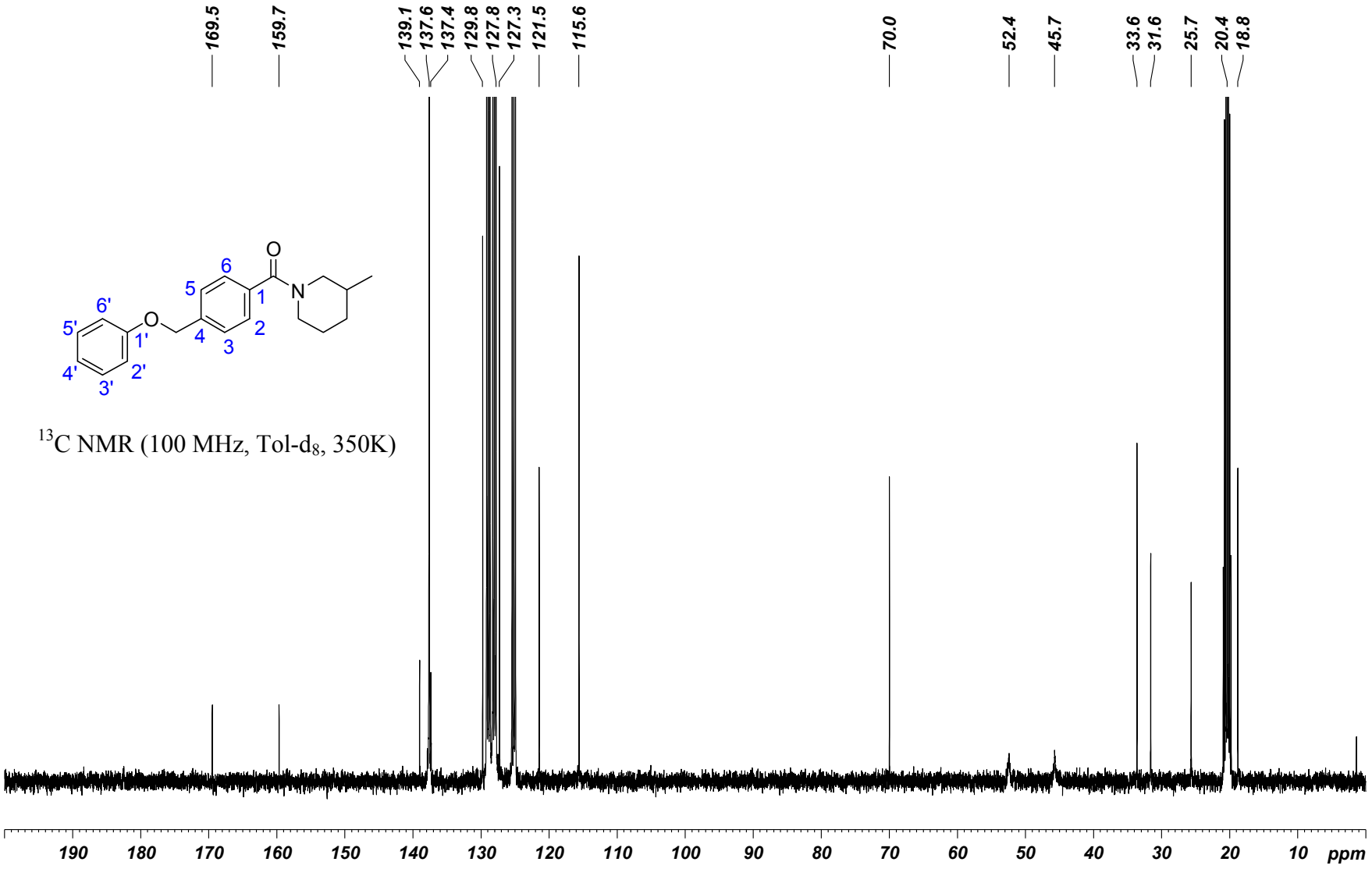
(3-Methylpiperidin-1-yl)(4-(phenoxymethyl)phenyl)methanone; S50.

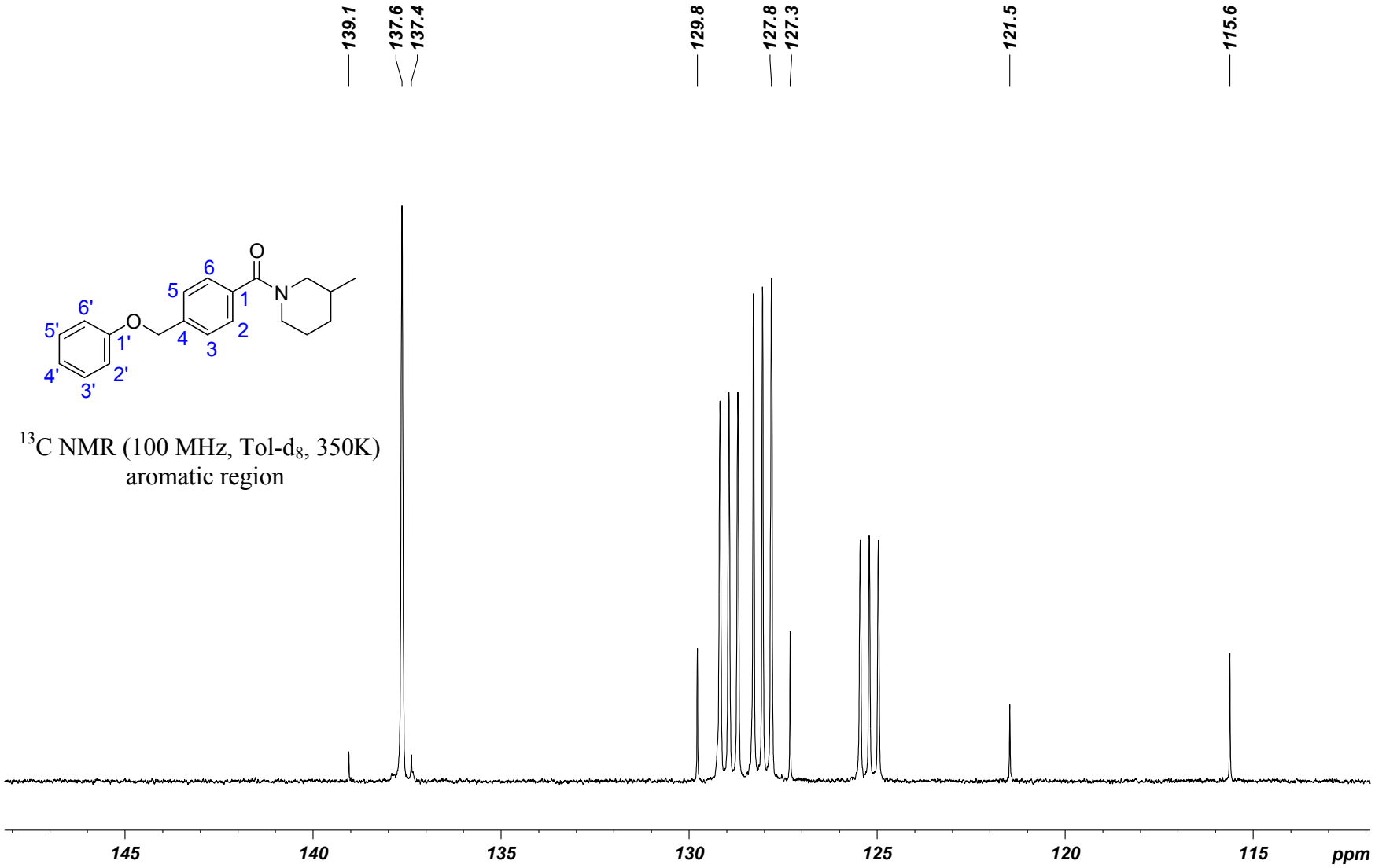


(3-Methylpiperidin-1-yl)(4-(phenoxymethyl)phenyl)methanone; S50.



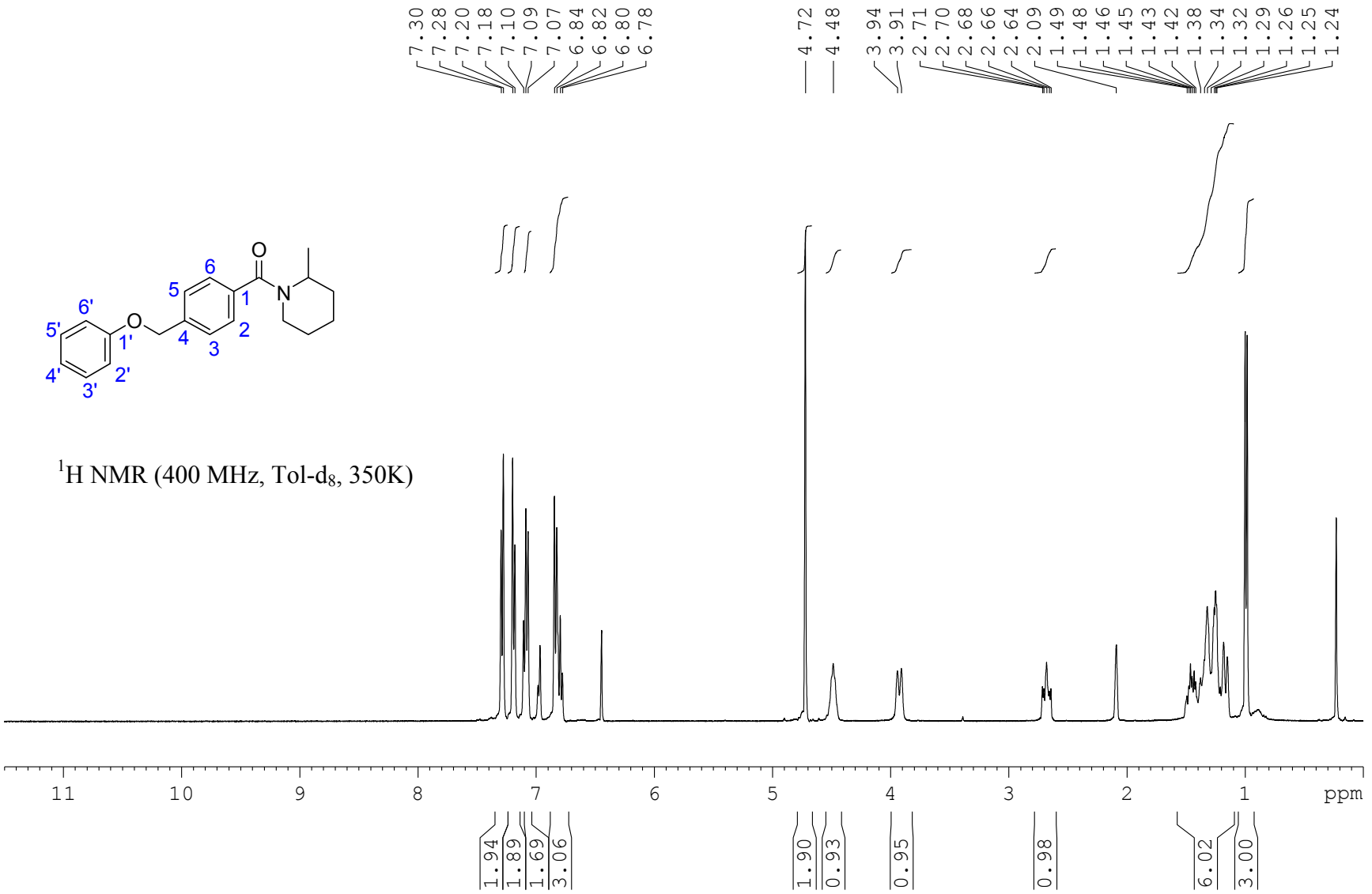
^{13}C NMR (100 MHz, Tol-d_8, 350K)

(3-Methylpiperidin-1-yl)(4-(phenoxymethyl)phenyl)methanone; S50.

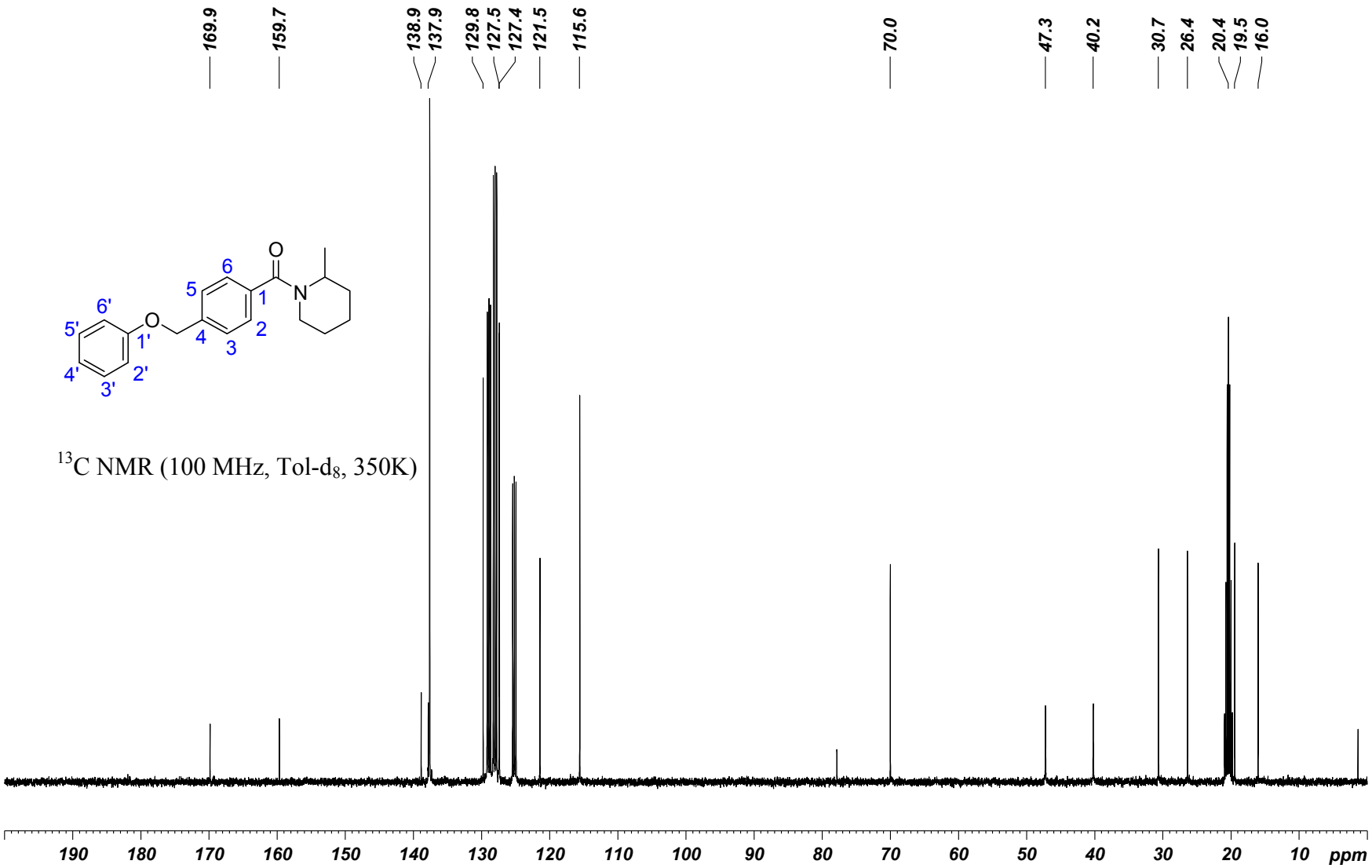


^{13}C NMR (100 MHz, Tol-d$_8$, 350K)
aromatic region

(2-Methylpiperidin-1-yl)(4-(phenoxymethyl)phenyl)methanone; S51.

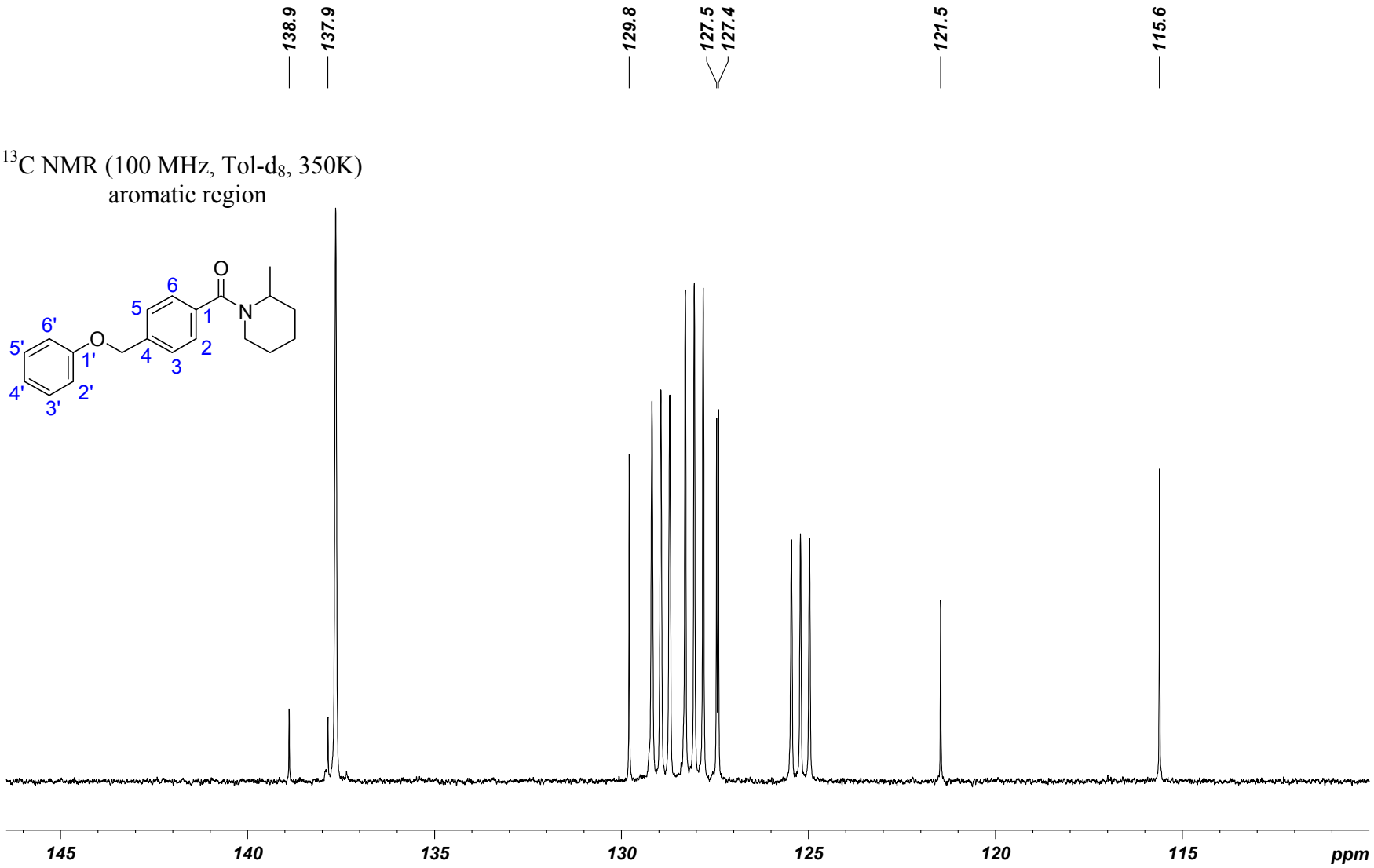


(2-Methylpiperidin-1-yl)(4-(phenoxymethyl)phenyl)methanone; S51.

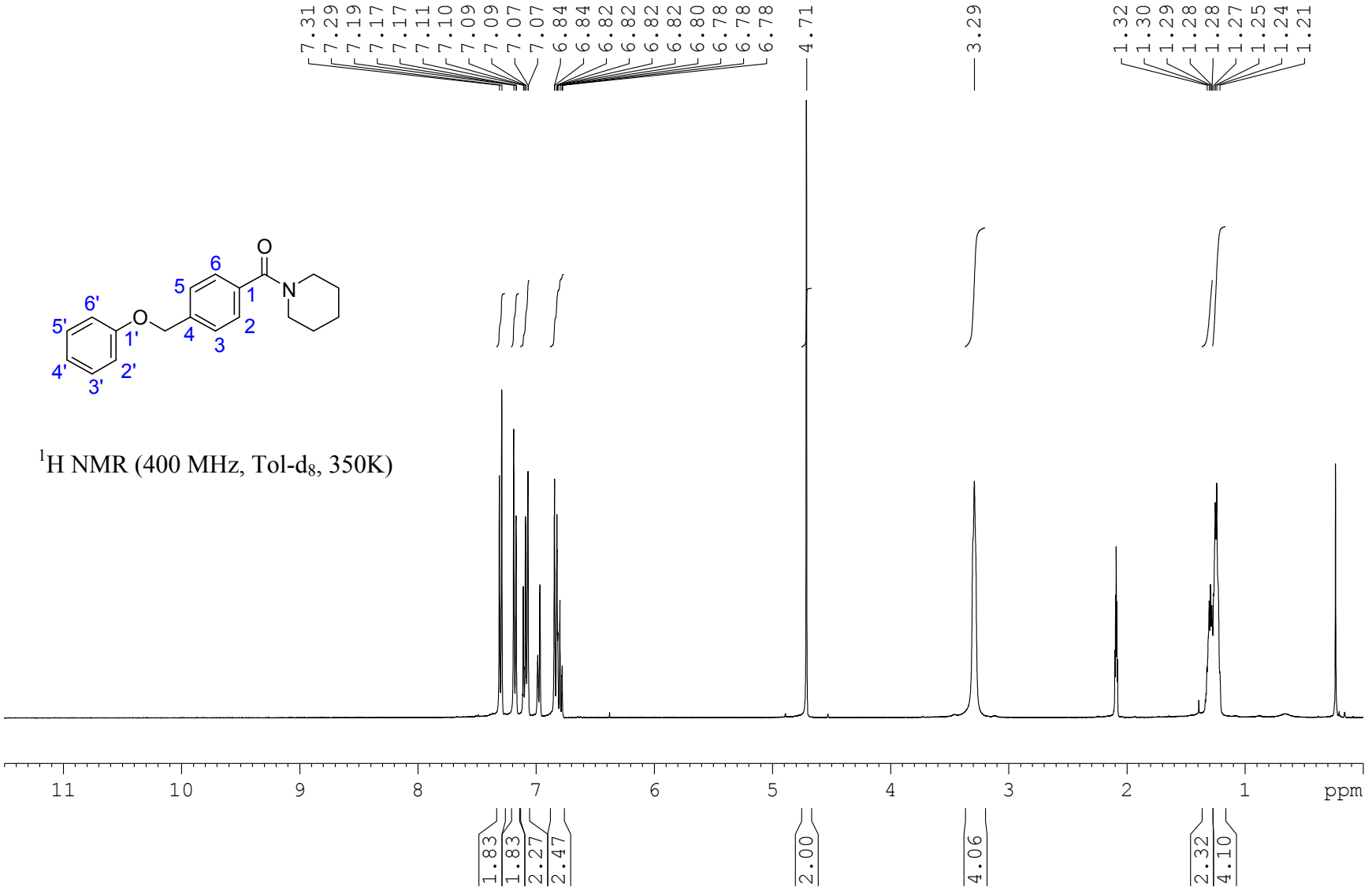


^{13}C NMR (100 MHz, Tol-d_8, 350K)

(2-Methylpiperidin-1-yl)(4-(phenoxymethyl)phenyl)methanone; S51.

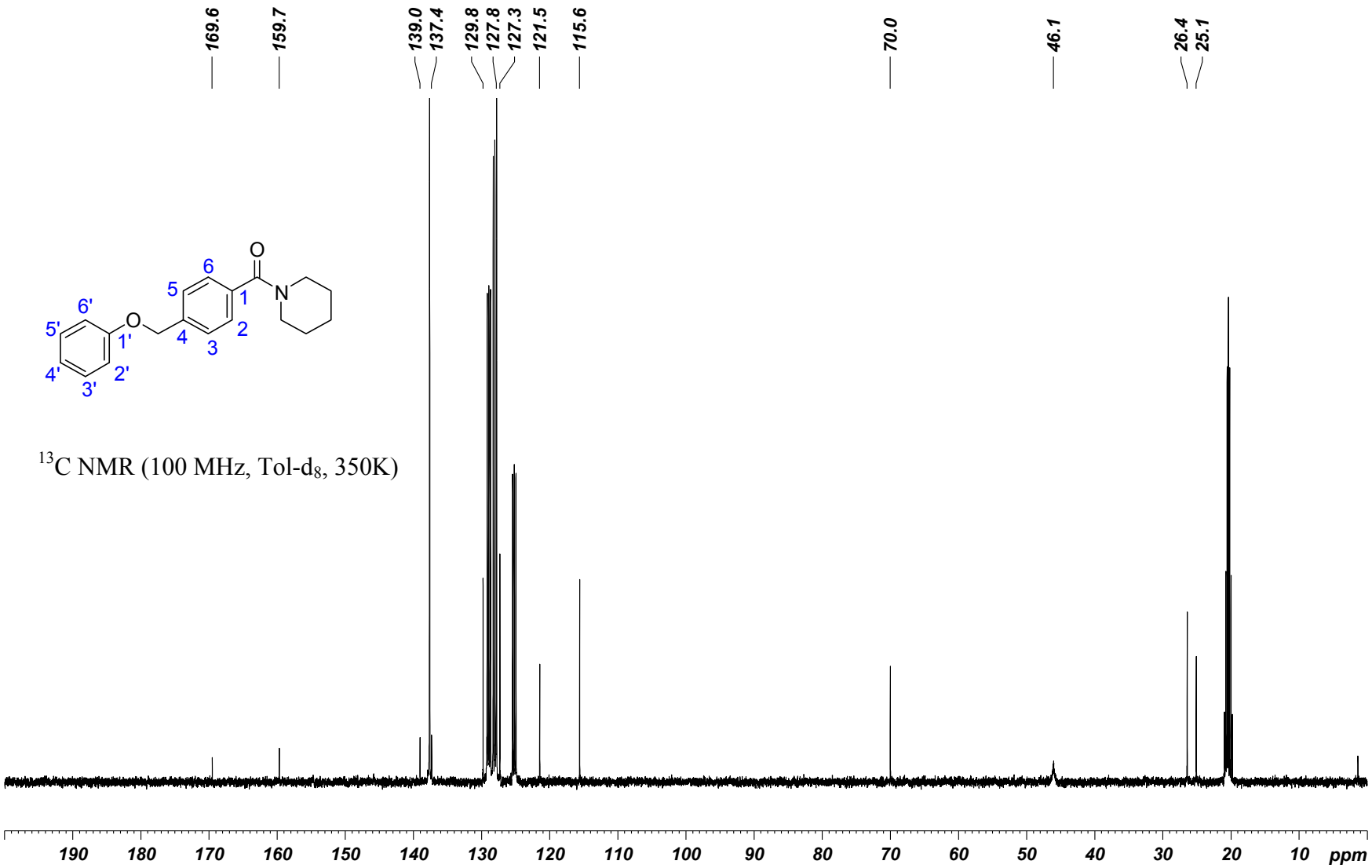


(4-(Phenoxymethyl)phenyl)(piperidin-1-yl)methanone; S52.



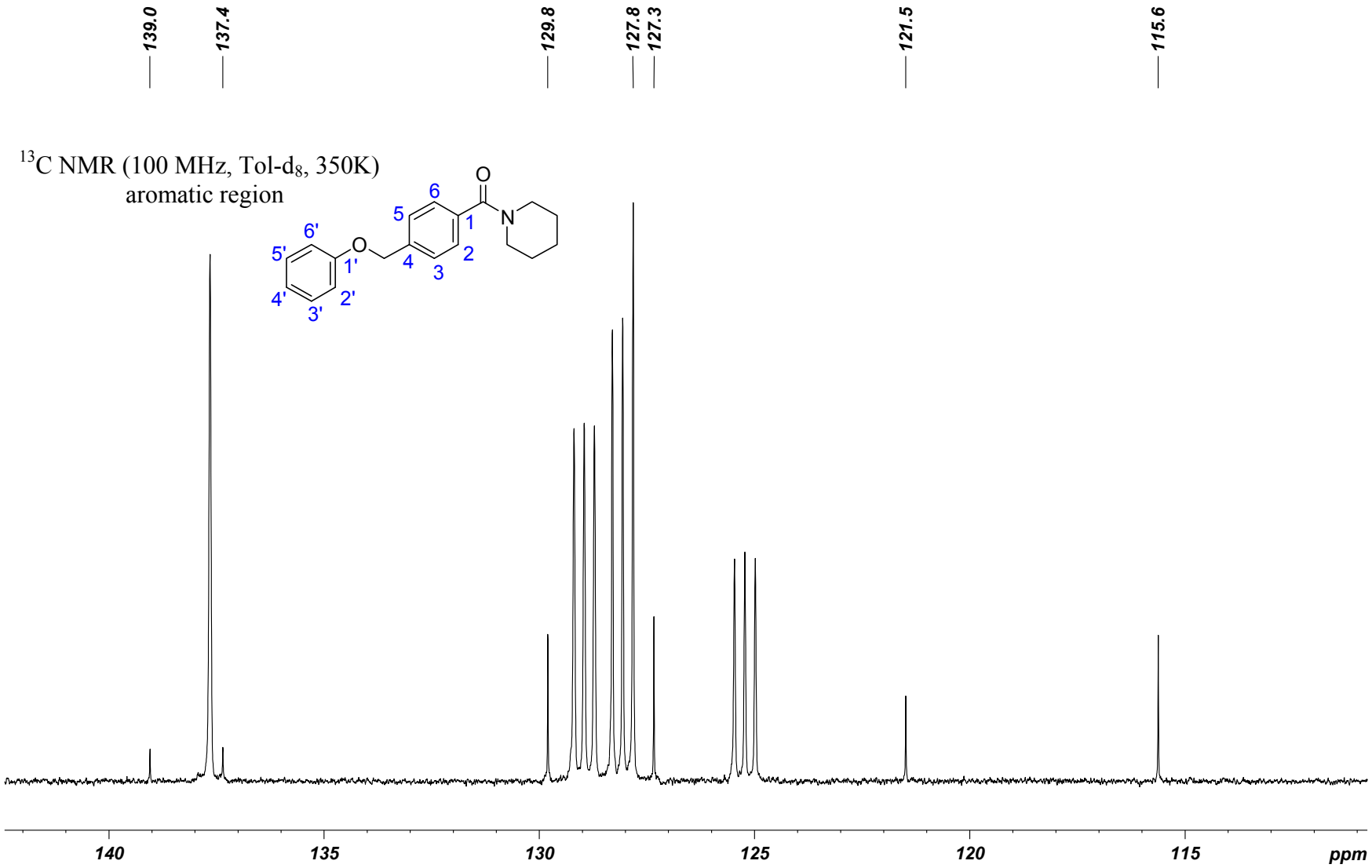
^{1}H NMR (400 MHz, Tol-d_8, 350K)

(4-(Phenoxymethyl)phenyl)(piperidin-1-yl)methanone; S52.

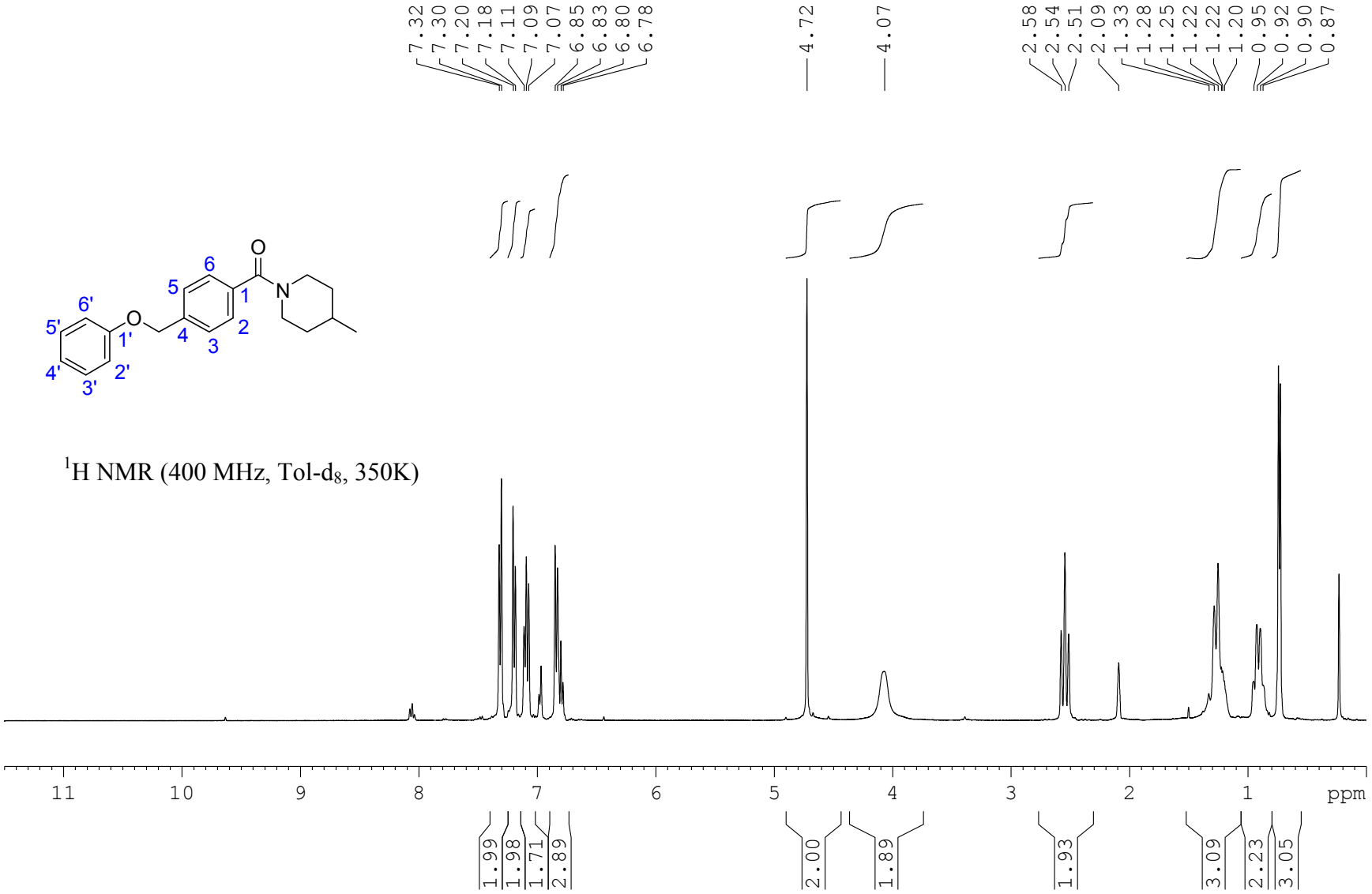


^{13}C NMR (100 MHz, Tol-d_8, 350K)

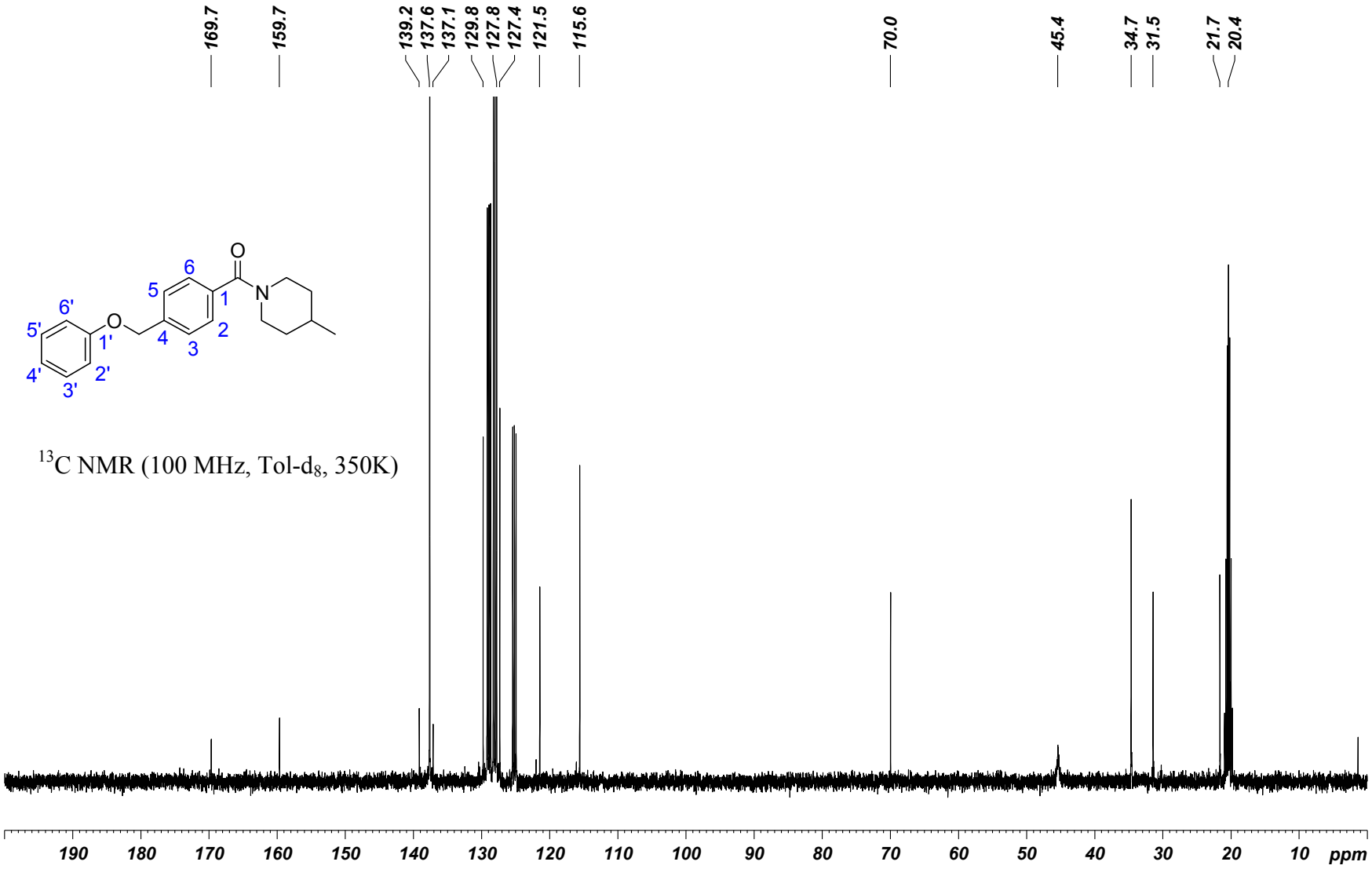
(4-(Phenoxymethyl)phenyl)(piperidin-1-yl)methanone; S52.



(4-Methylpiperidin-1-yl)(4-(phenoxymethyl)phenyl)methanone; S53.

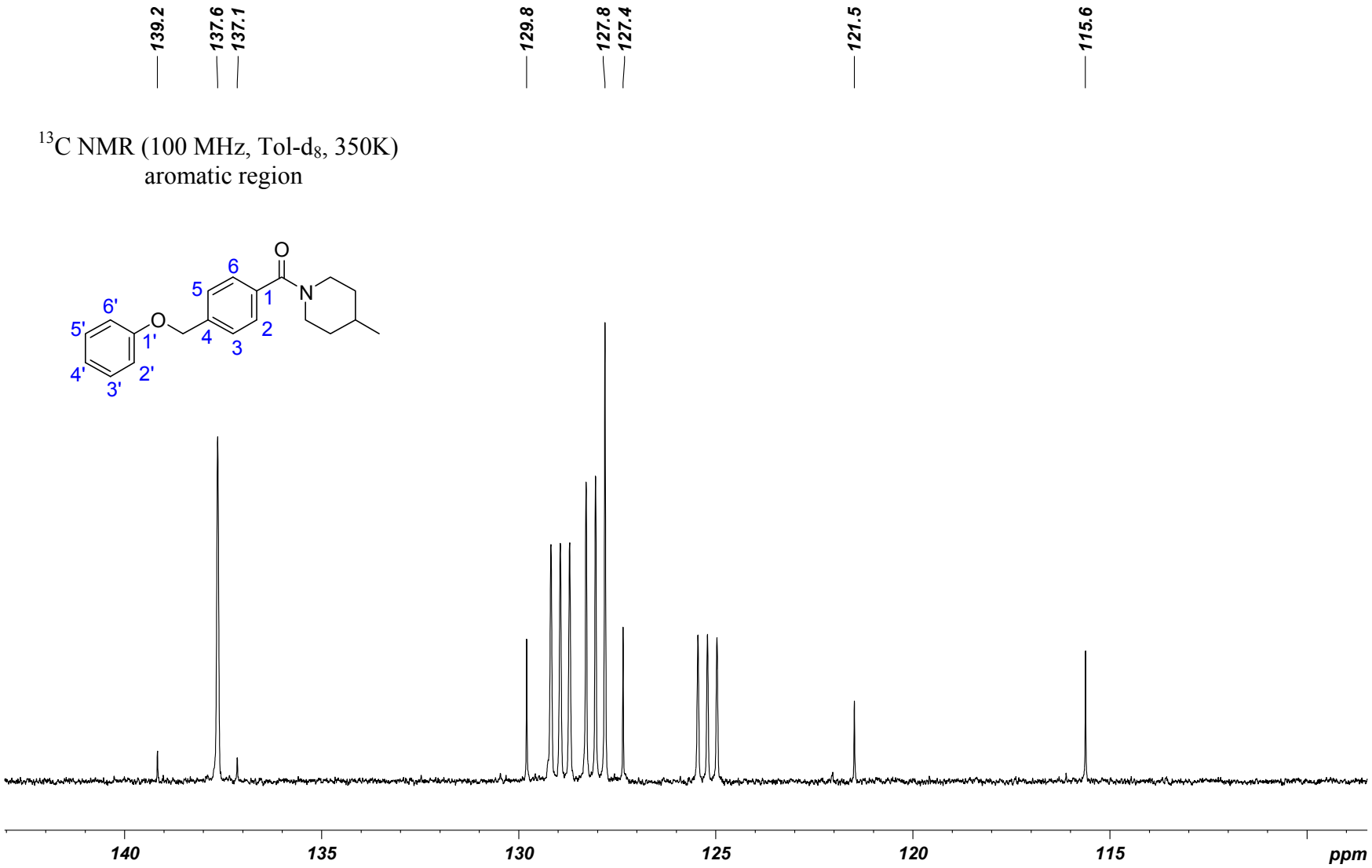


(4-Methylpiperidin-1-yl)(4-(phenoxymethyl)phenyl)methanone; S53.

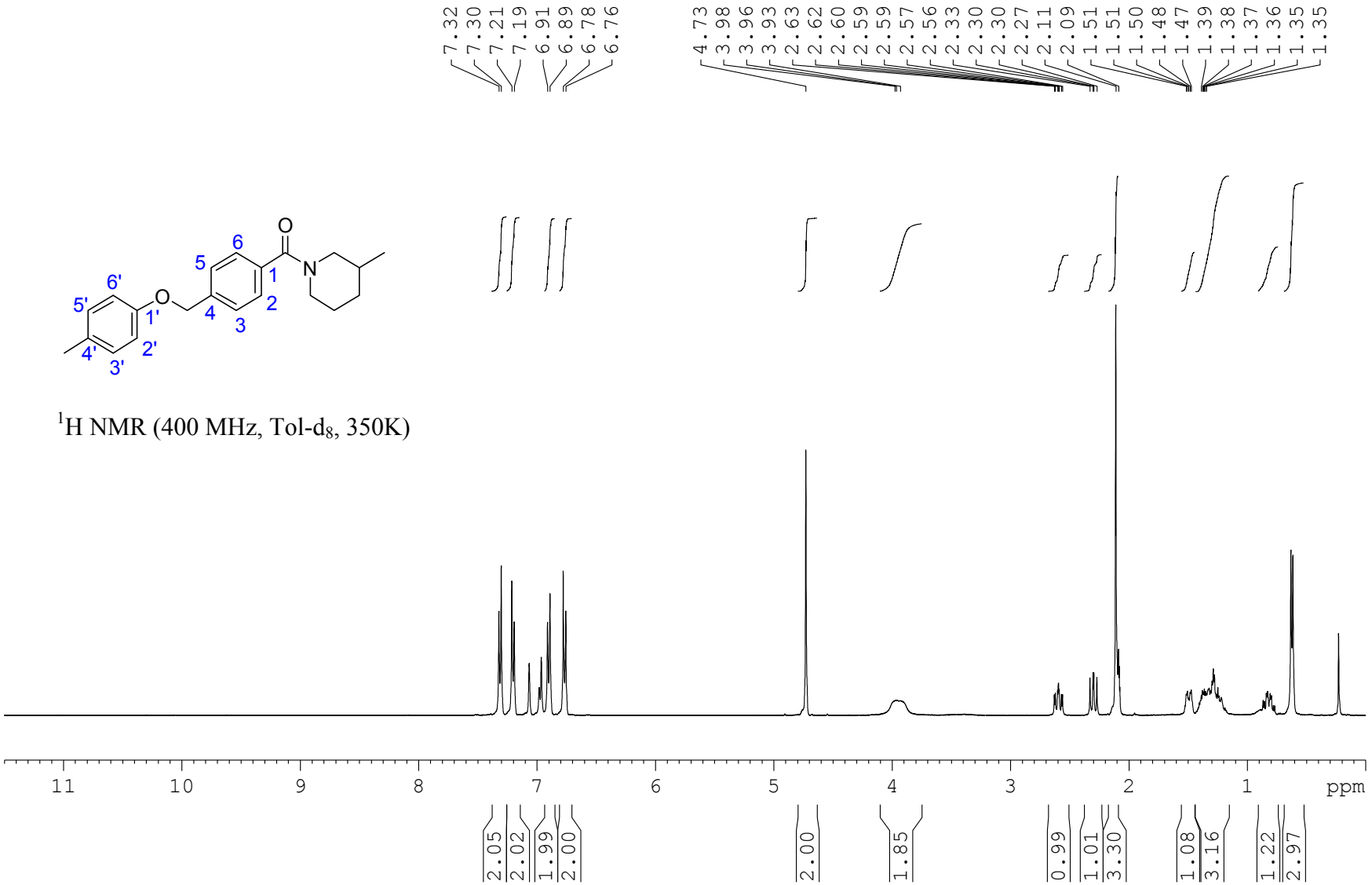


^{13}C NMR (100 MHz, Tol-d_8, 350K)

(4-Methylpiperidin-1-yl)(4-(phenoxymethyl)phenyl)methanone; S53.

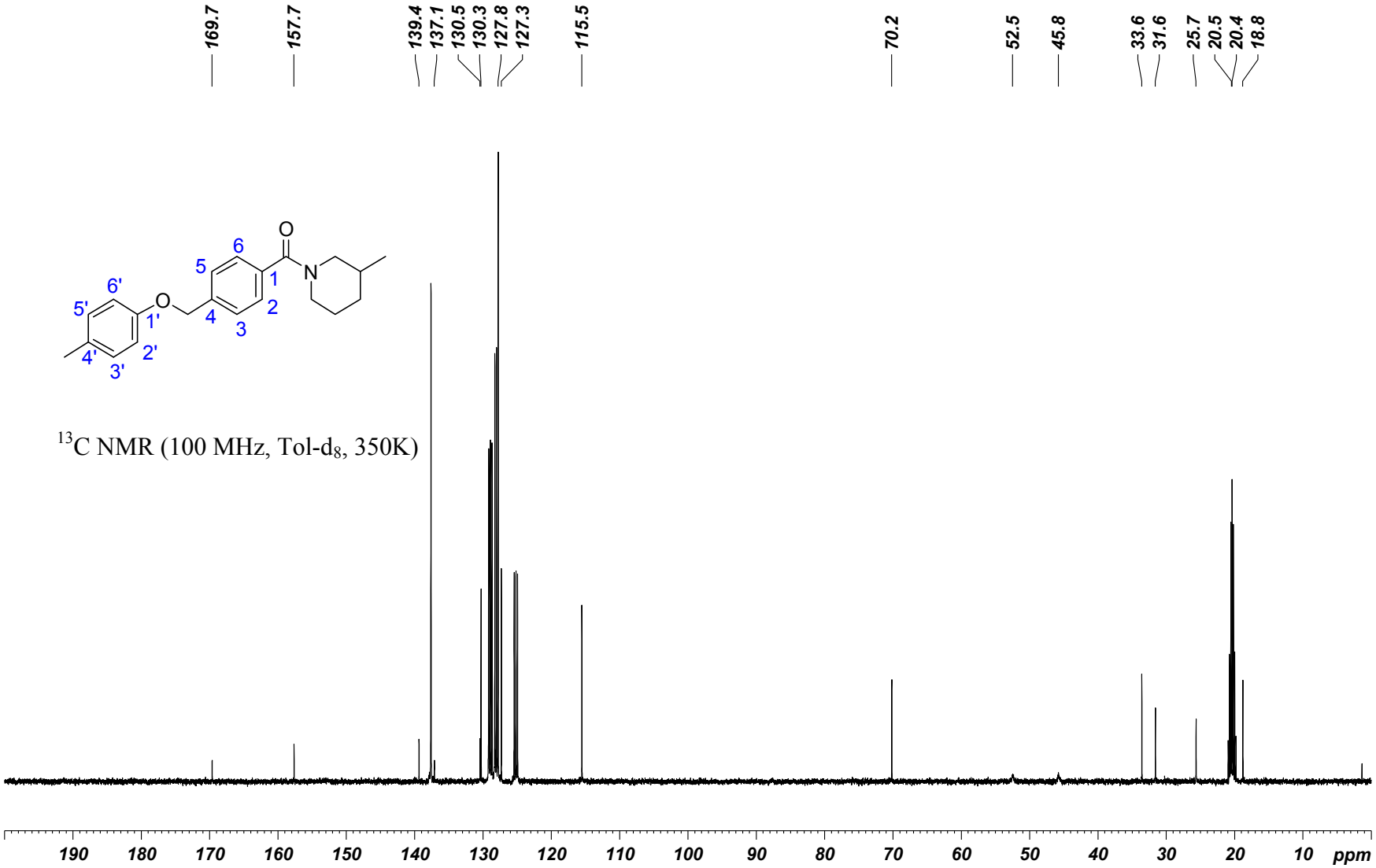


(3-Methylpiperidin-1-yl)(4-((*p*-tolyloxy)methyl)phenyl)methanone; S54.



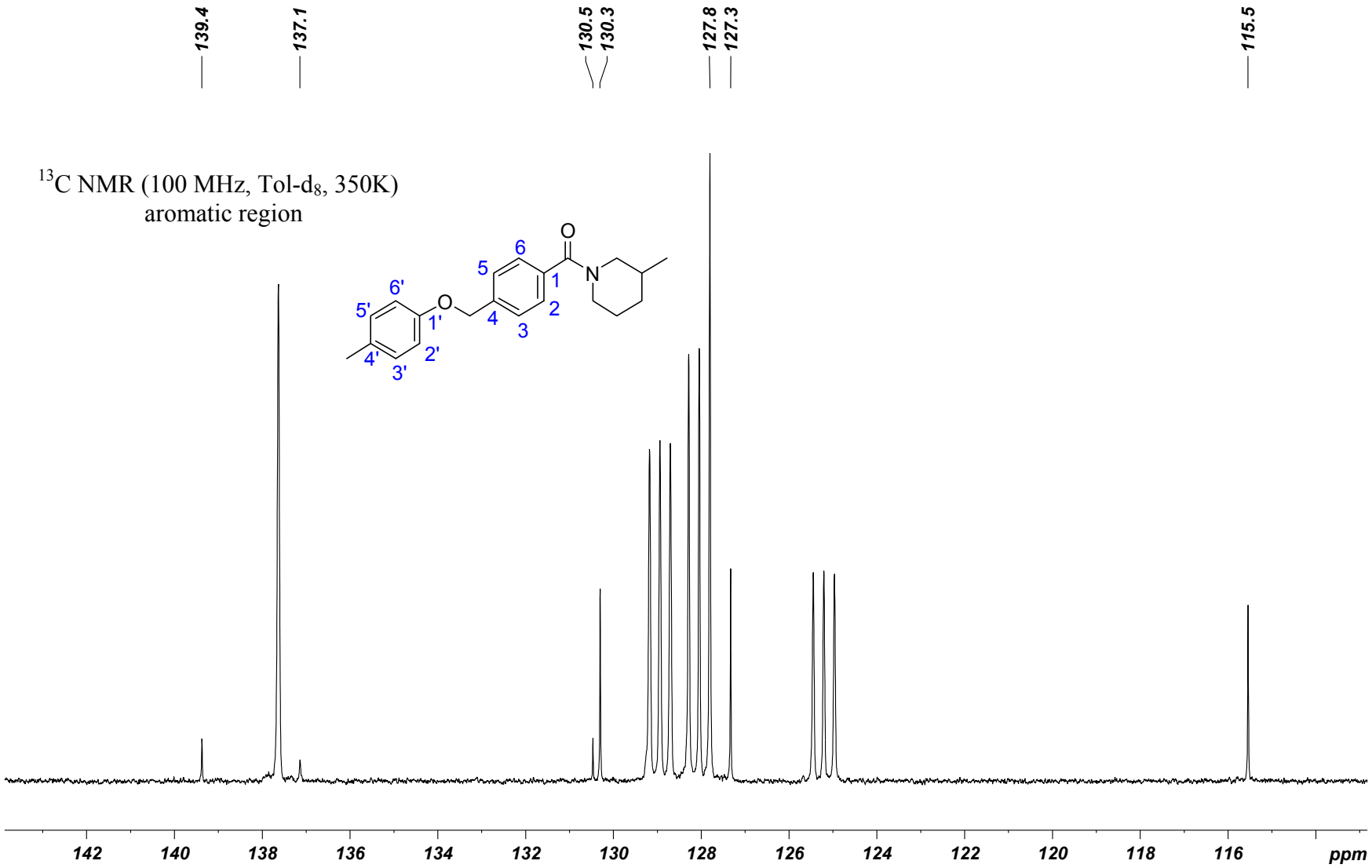
^{1}H NMR (400 MHz, Tol-d_8, 350K)

(3-Methylpiperidin-1-yl)(4-((*p*-tolyloxy)methyl)phenyl)methanone; S54.

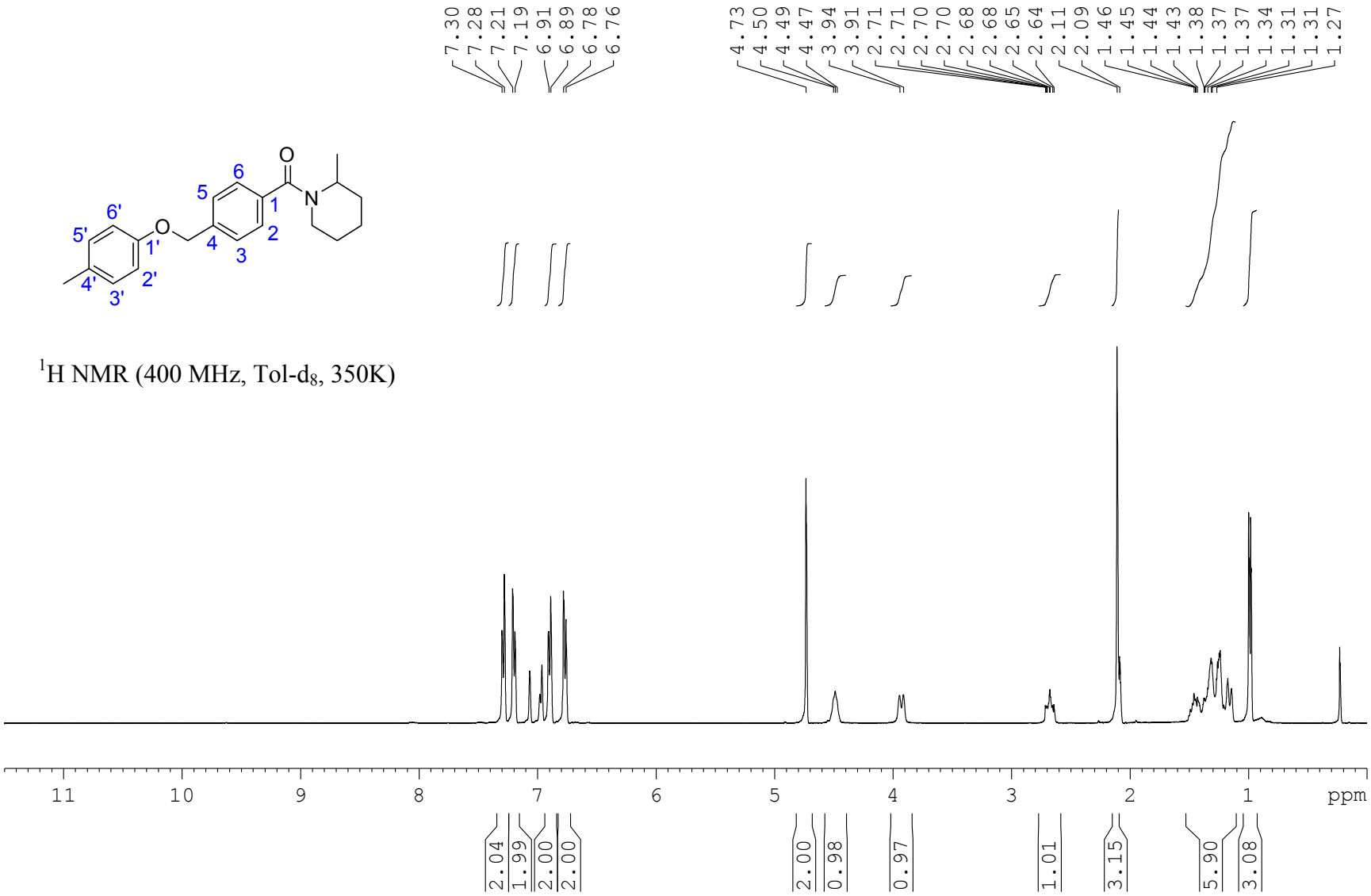


^{13}C NMR (100 MHz, Tol-d_8, 350K)

(3-Methylpiperidin-1-yl)(4-((*p*-tolyloxy)methyl)phenyl)methanone; S54.

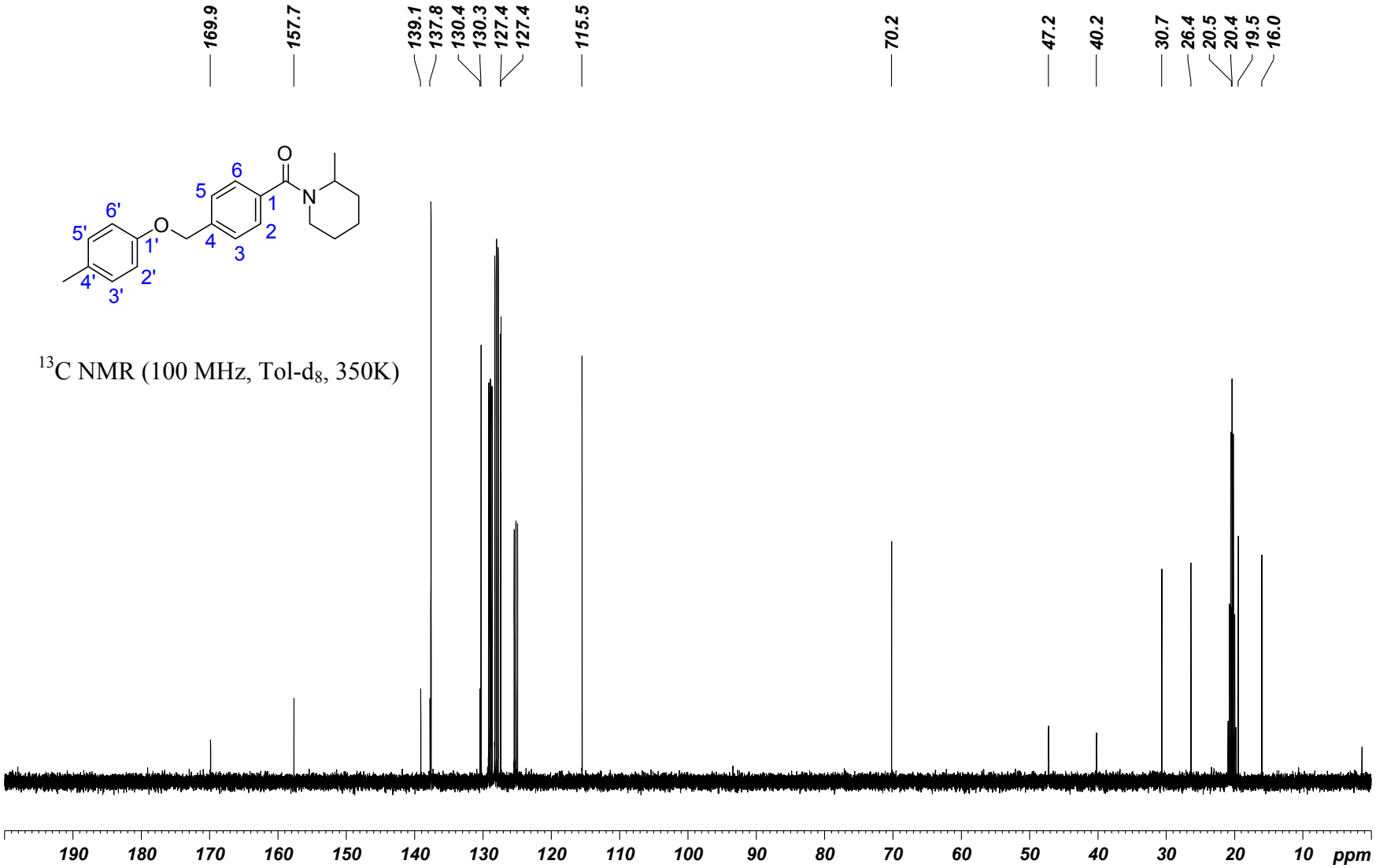


(2-Methylpiperidin-1-yl)(4-((*p*-tolyloxy)methyl)phenyl)methanone; 14.



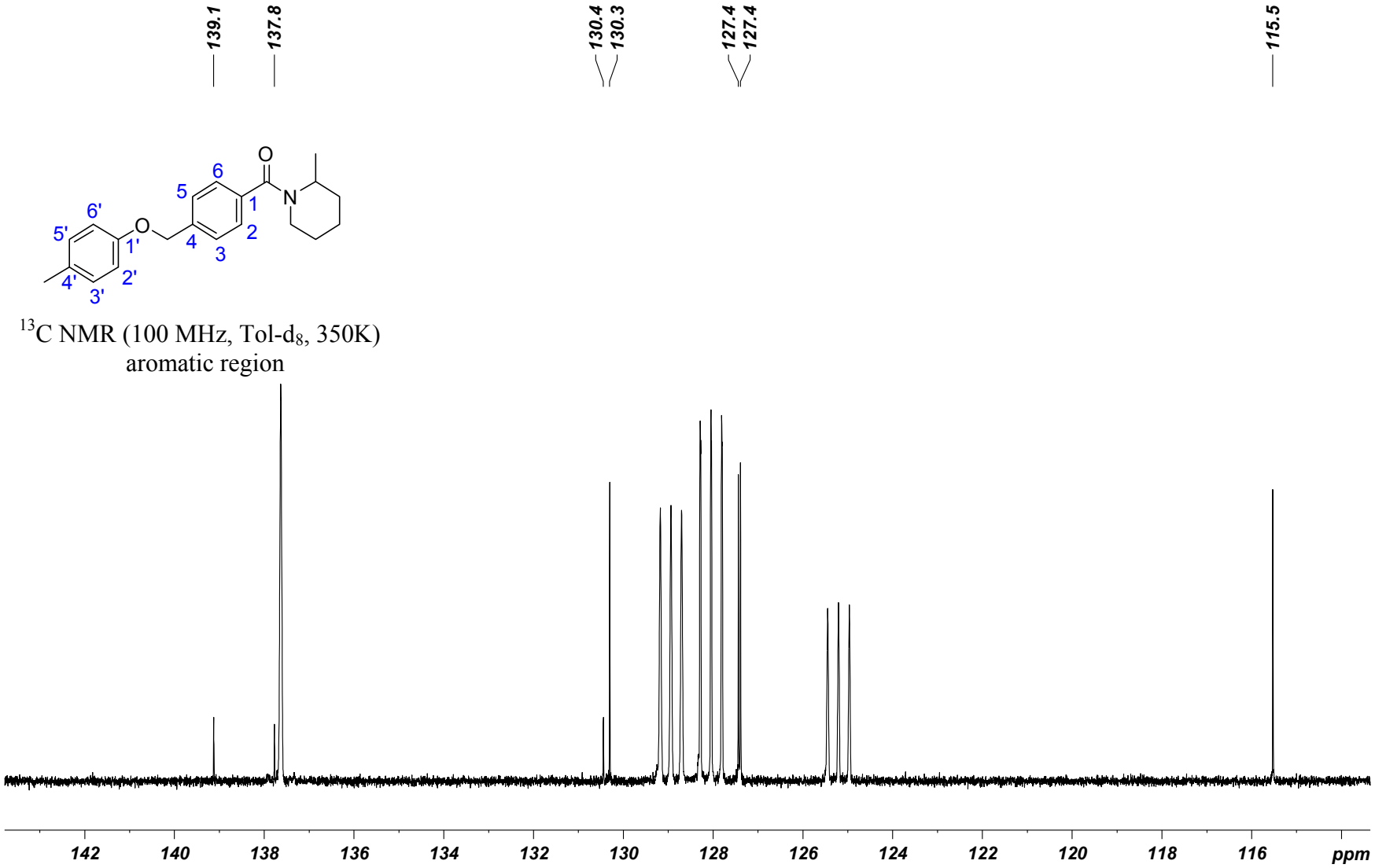
^{1}H NMR (400 MHz, Tol-d_8, 350K)

(2-Methylpiperidin-1-yl)(4-((*p*-tolyloxy)methyl)phenyl)methanone; 14.



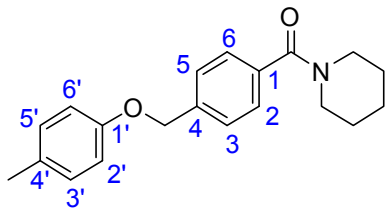
^{13}C NMR (100 MHz, Tol-d_8, 350K)

(2-Methylpiperidin-1-yl)(4-((*p*-tolyloxy)methyl)phenyl)methanone; 14.



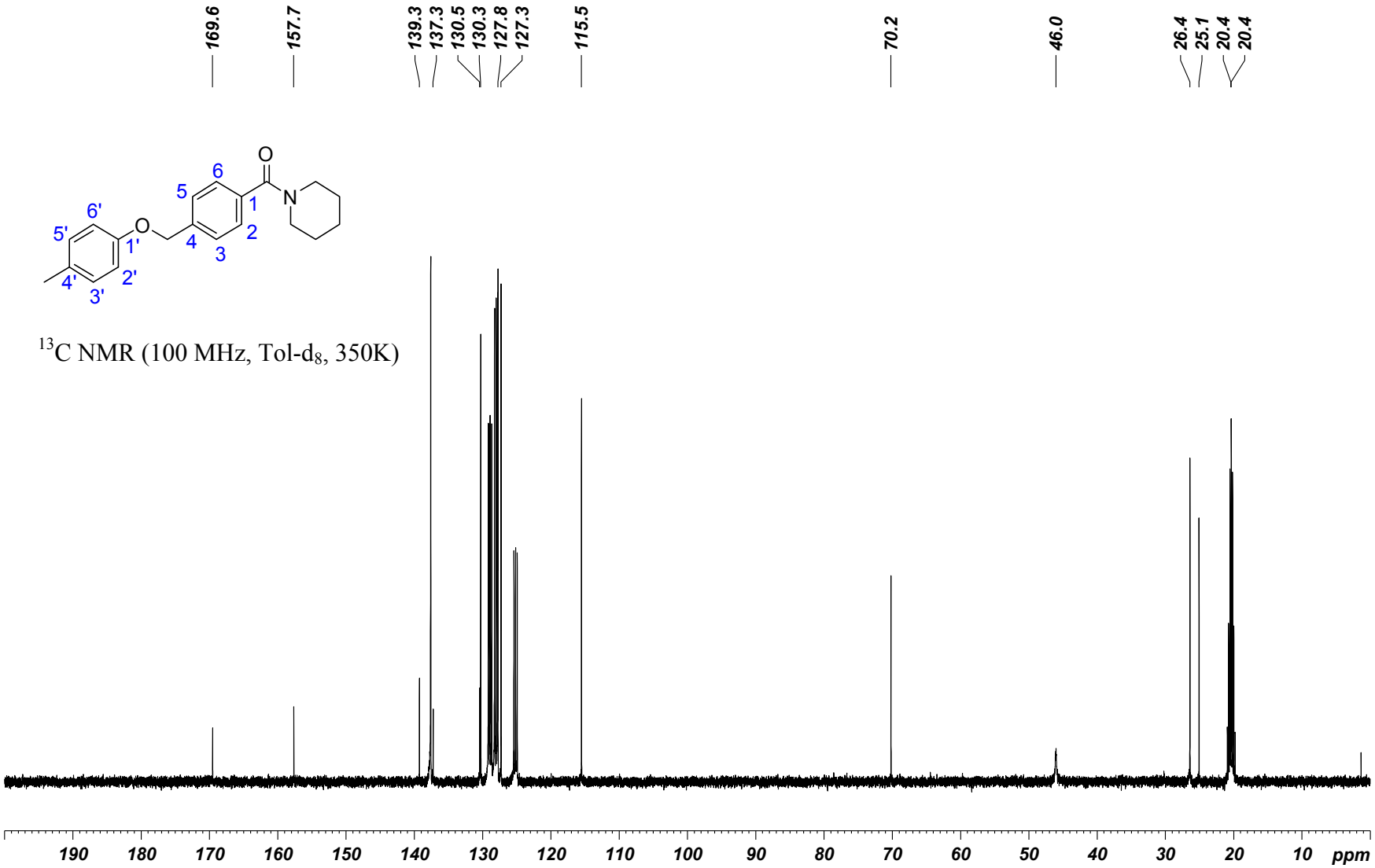
^{13}C NMR (100 MHz, Tol-d$_8$, 350K)
aromatic region

Piperidin-1-yl(4-((*p*-tolyloxy)methyl)phenyl)methanone; S55.

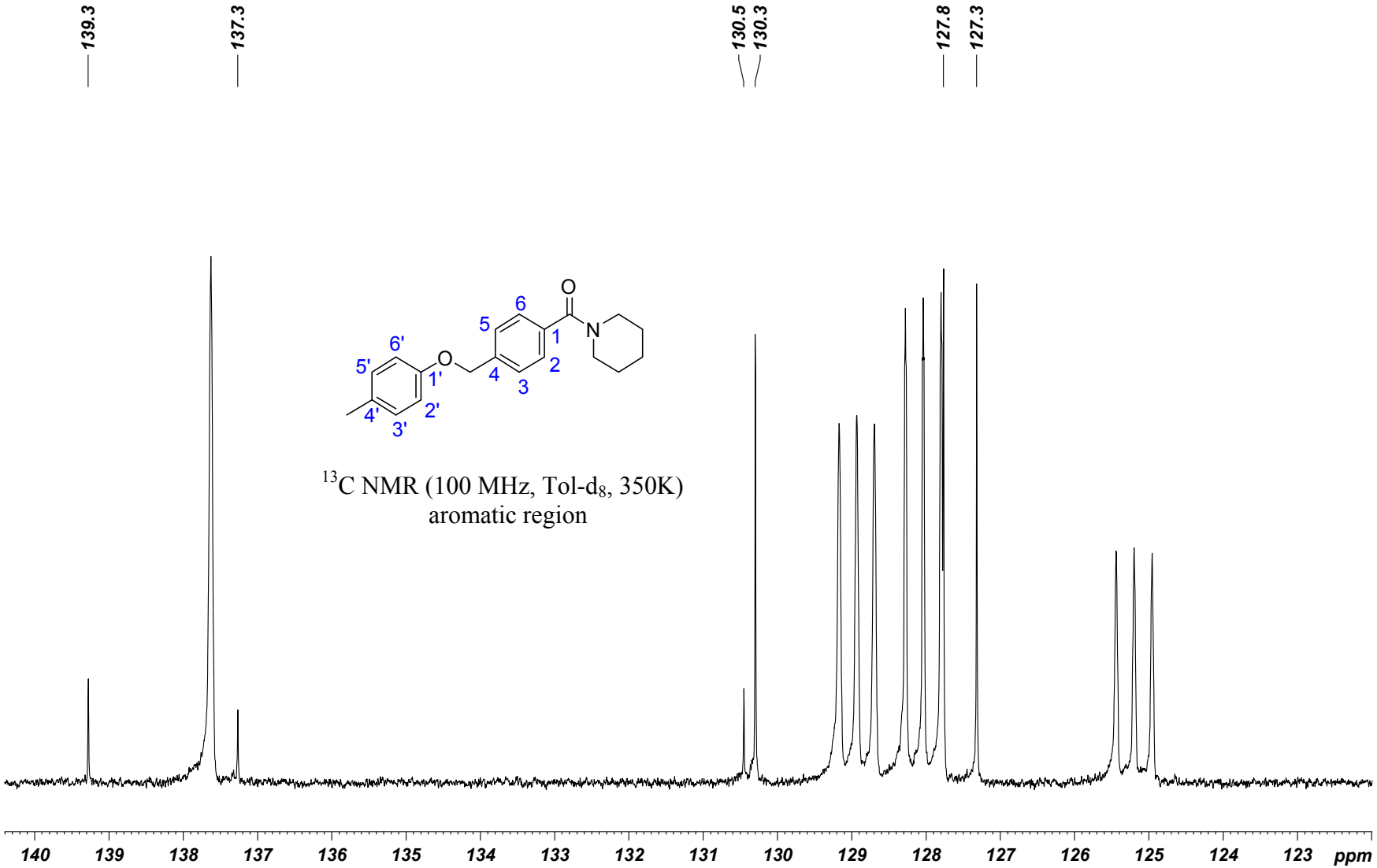


^{1}H NMR (400 MHz, Tol-d_8, 350K)

Piperidin-1-yl(4-((*p*-tolyloxy)methyl)phenyl)methanone; S55.

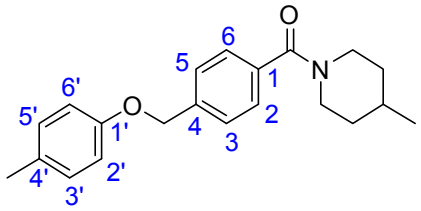


Piperidin-1-yl(4-((*p*-tolyloxy)methyl)phenyl)methanone; S55.



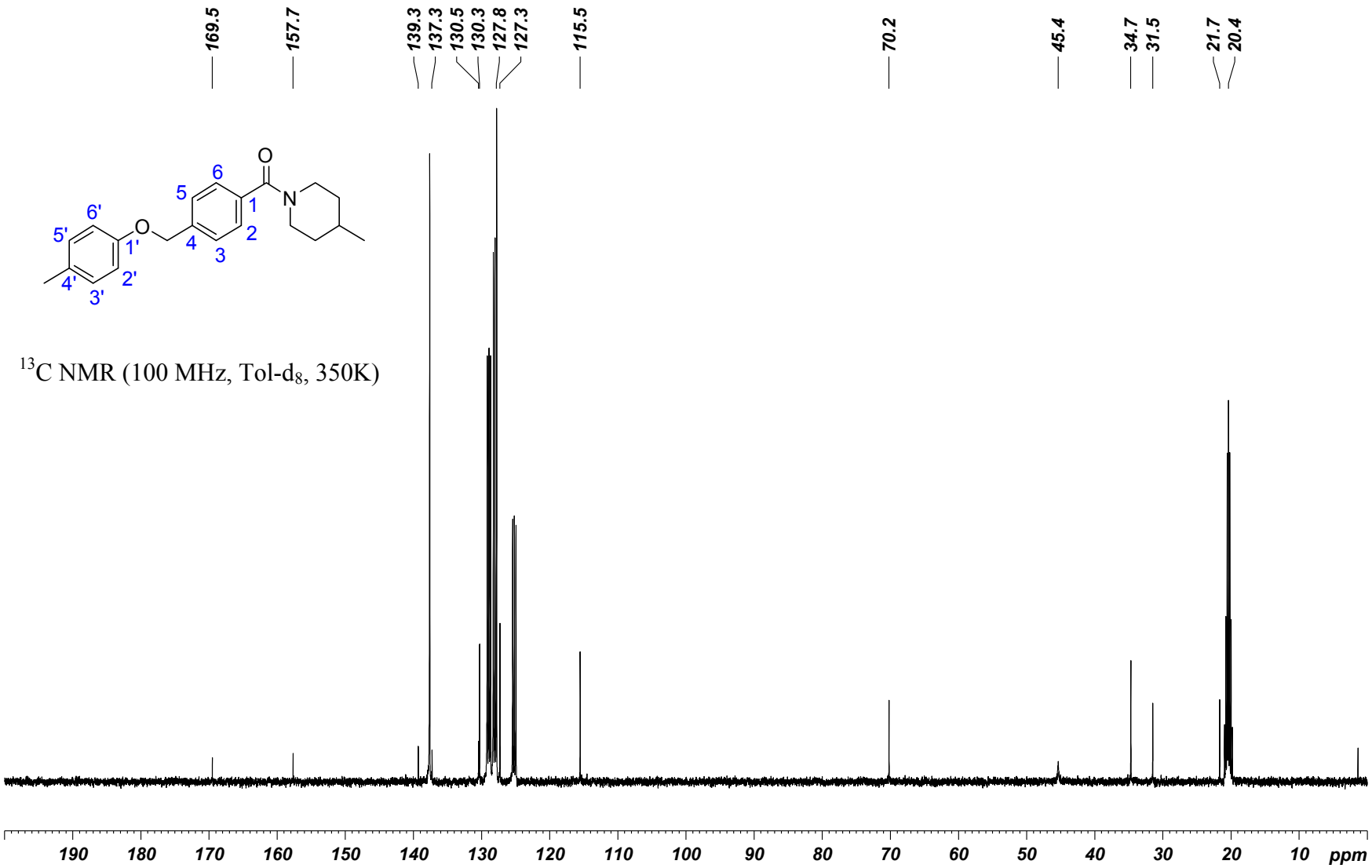
^{13}C NMR (100 MHz, Tol-d_8, 350K)
aromatic region

(4-Methylpiperidin-1-yl)(4-((*p*-tolyloxy)methyl)phenyl)methanone; 19.



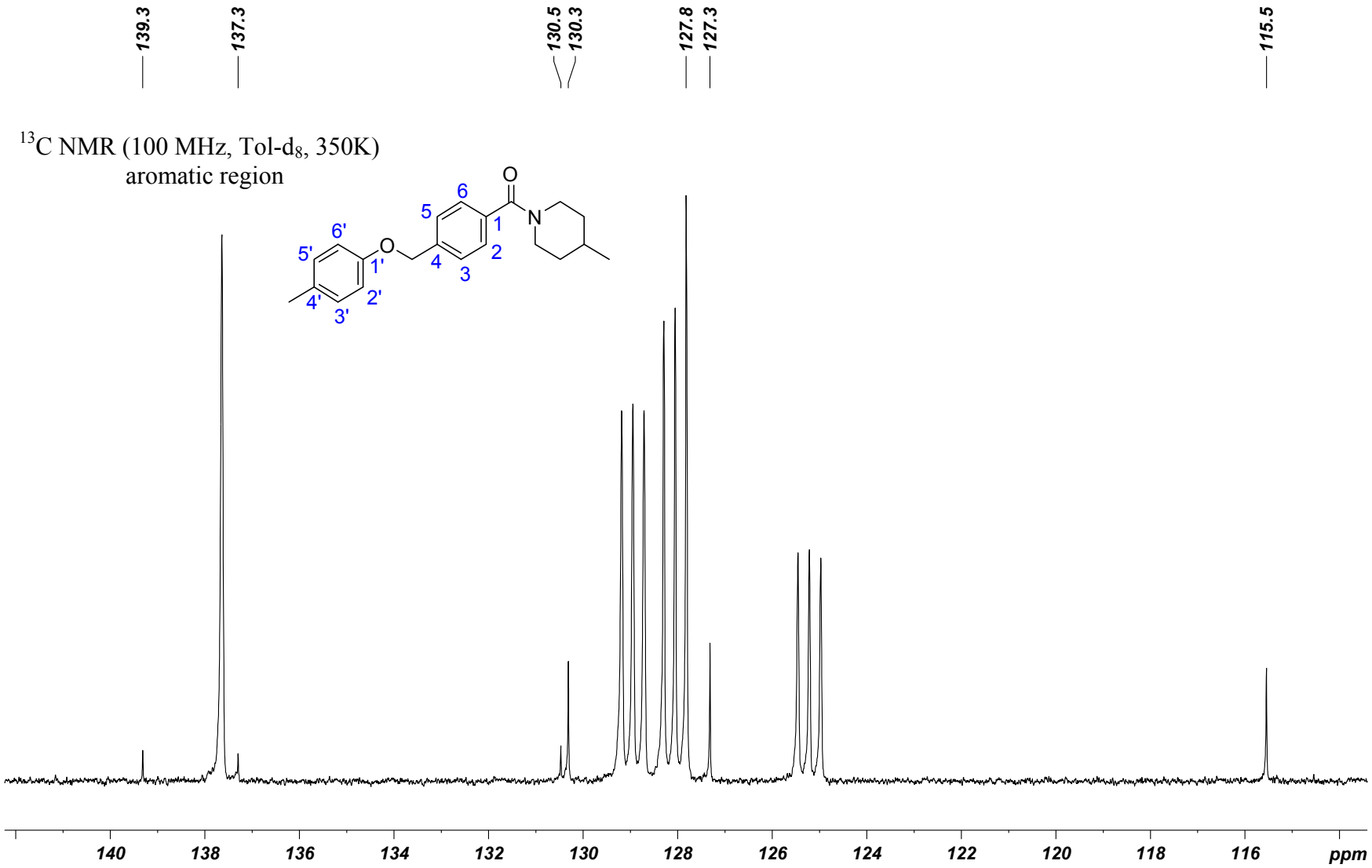
^{1}H NMR (400 MHz, Tol-d_8, 350K)

(4-Methylpiperidin-1-yl)(4-((*p*-tolyloxy)methyl)phenyl)methanone; 19.

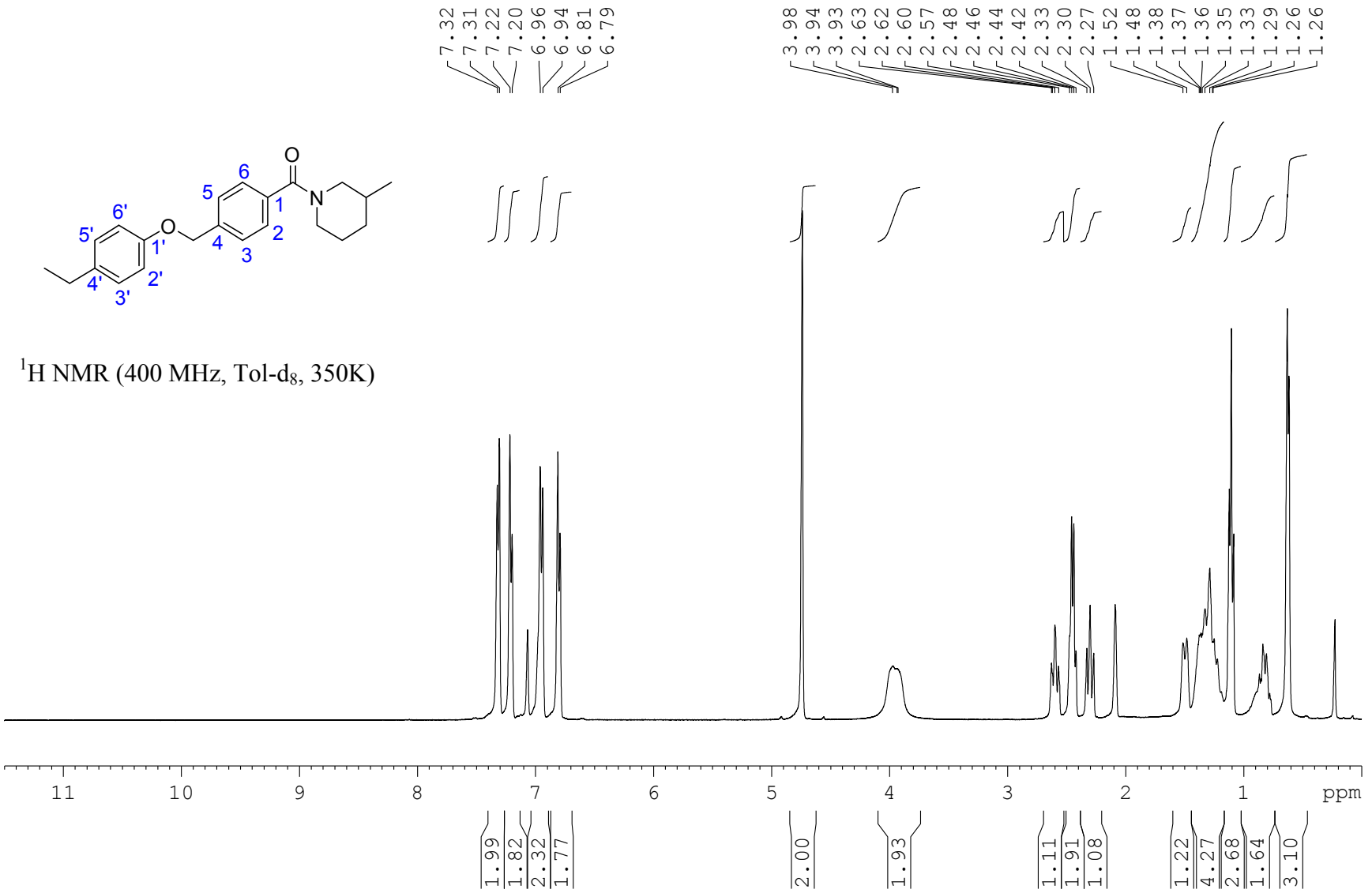


^{13}C NMR (100 MHz, Tol-d_8, 350K)

(4-Methylpiperidin-1-yl)(4-((*p*-tolyloxy)methyl)phenyl)methanone; 19.

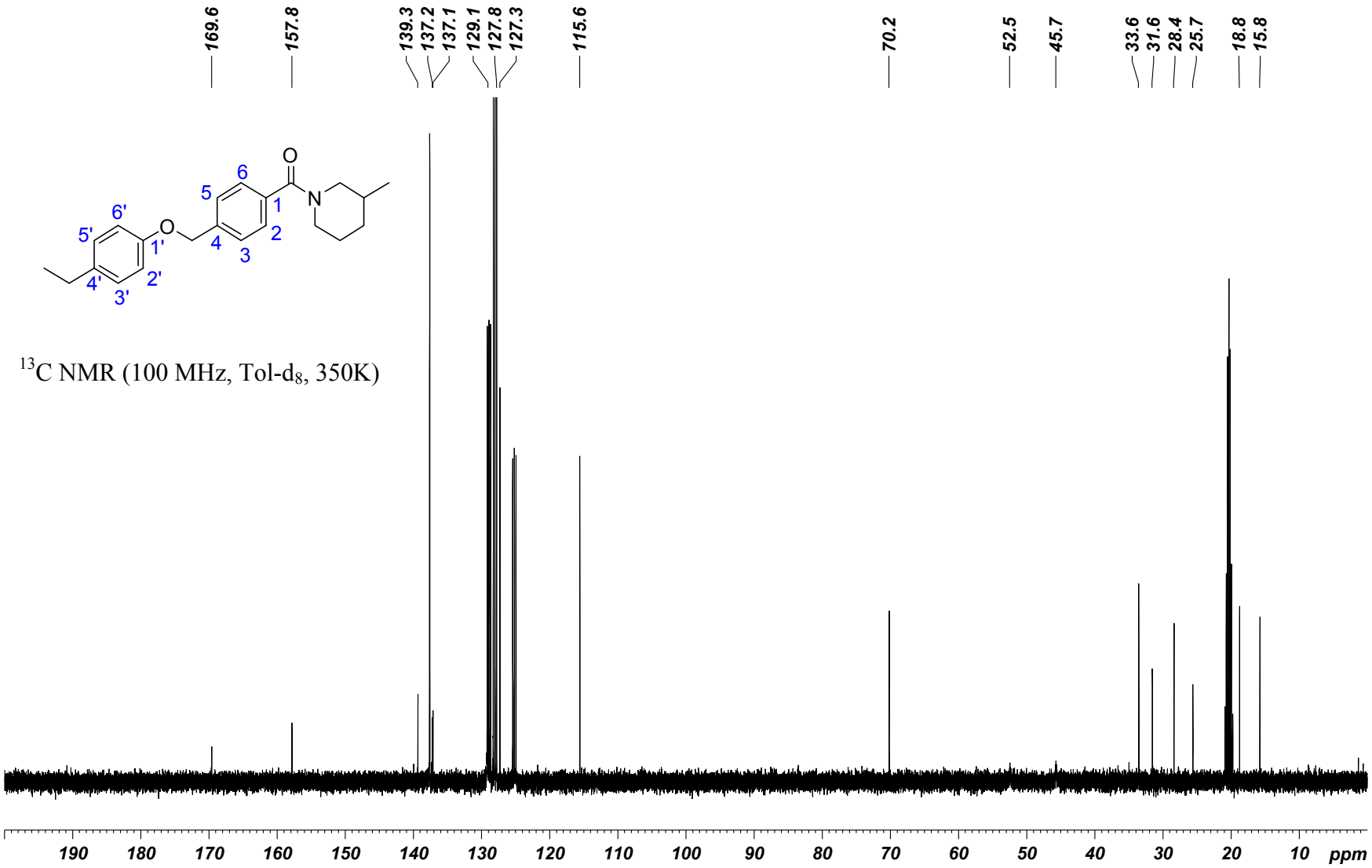


(4-((4-Ethylphenoxy)methyl)phenyl)(3-methylpiperidin-1-yl)methanone; S56.



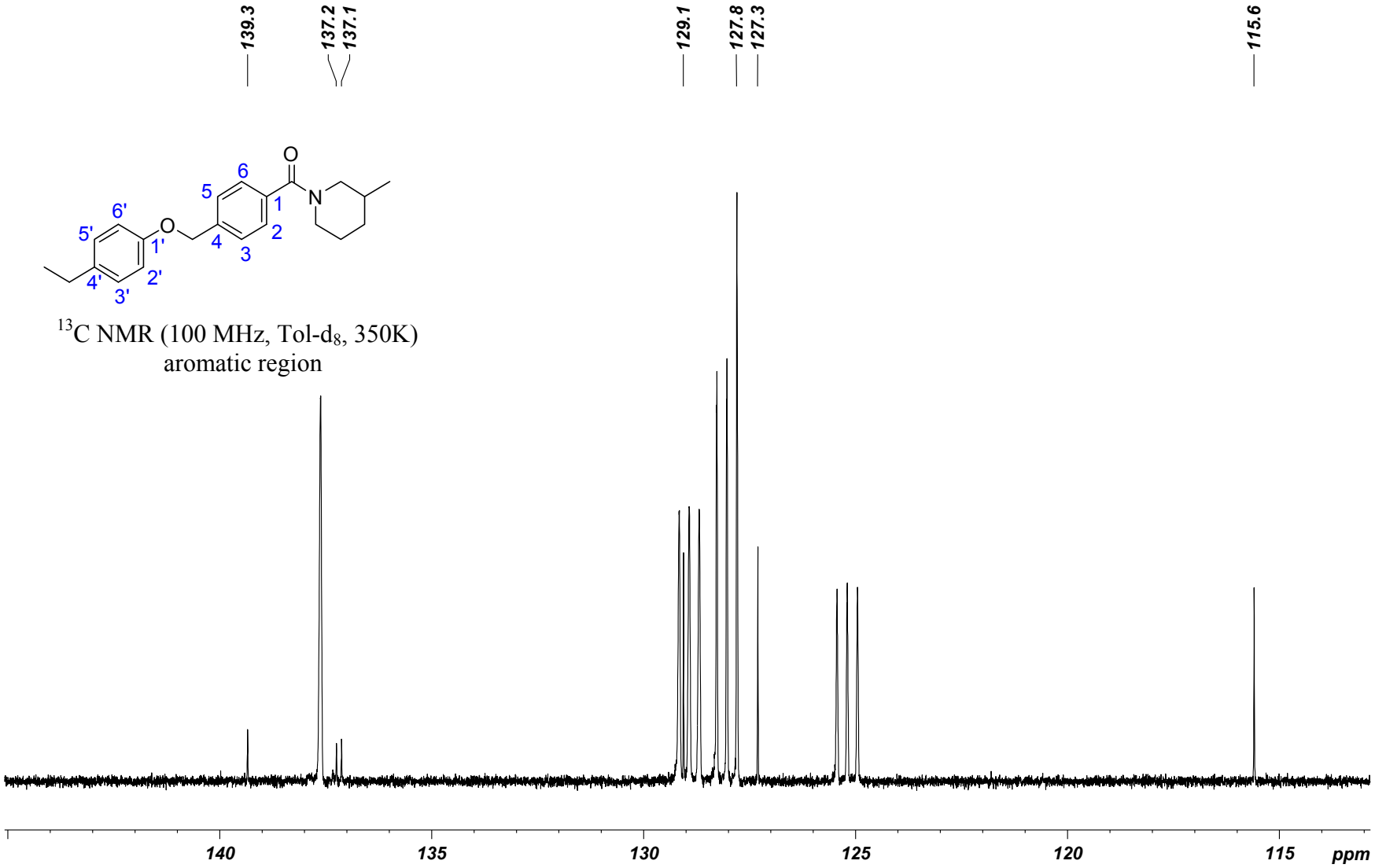
^{1}H NMR (400 MHz, Tol-d_8, 350K)

(4-((4-Ethylphenoxy)methyl)phenyl)(3-methylpiperidin-1-yl)methanone; S56.



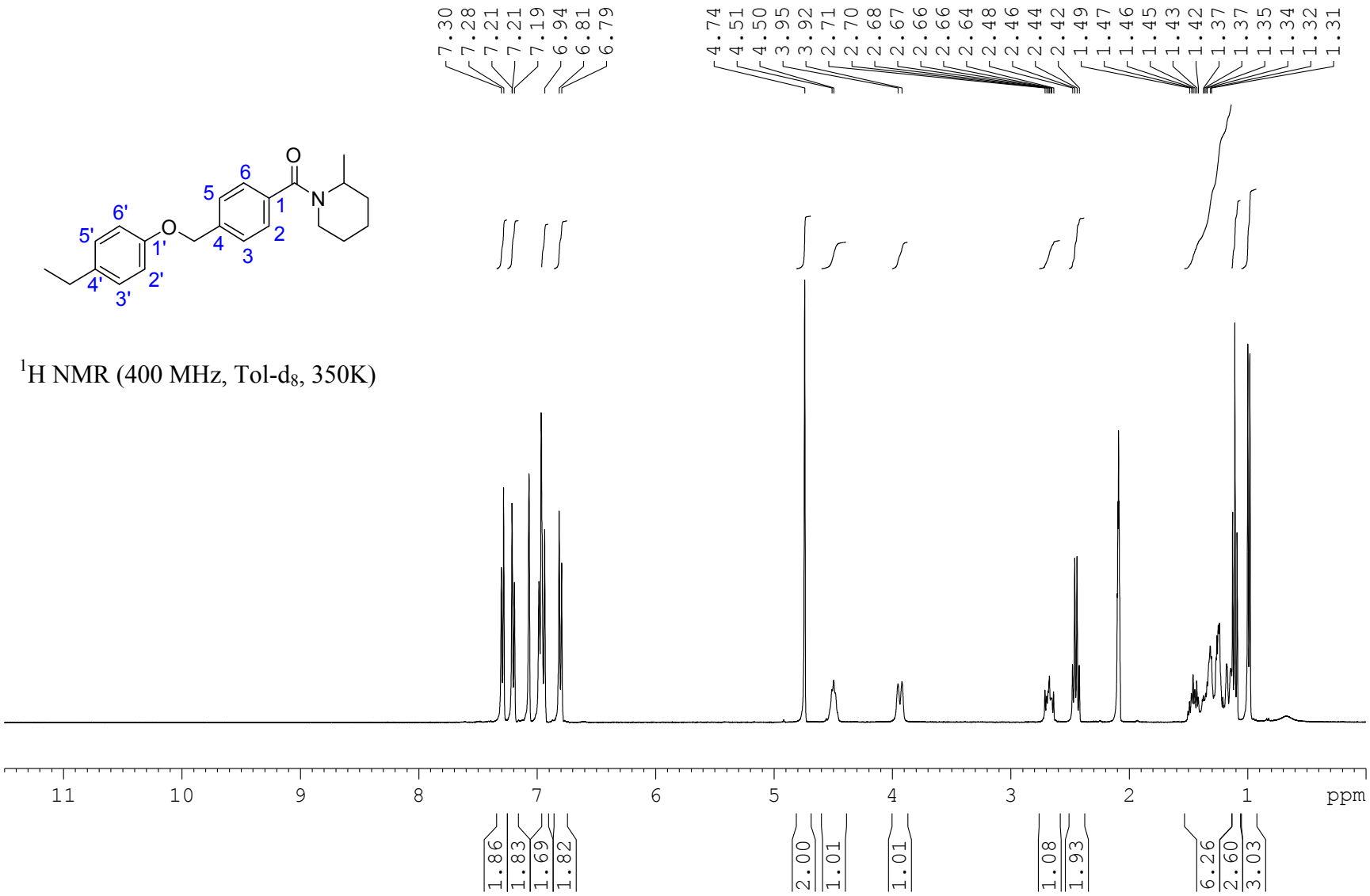
^{13}C NMR (100 MHz, Tol-d_8, 350K)

(4-((4-Ethylphenoxy)methyl)phenyl)(3-methylpiperidin-1-yl)methanone; S56.



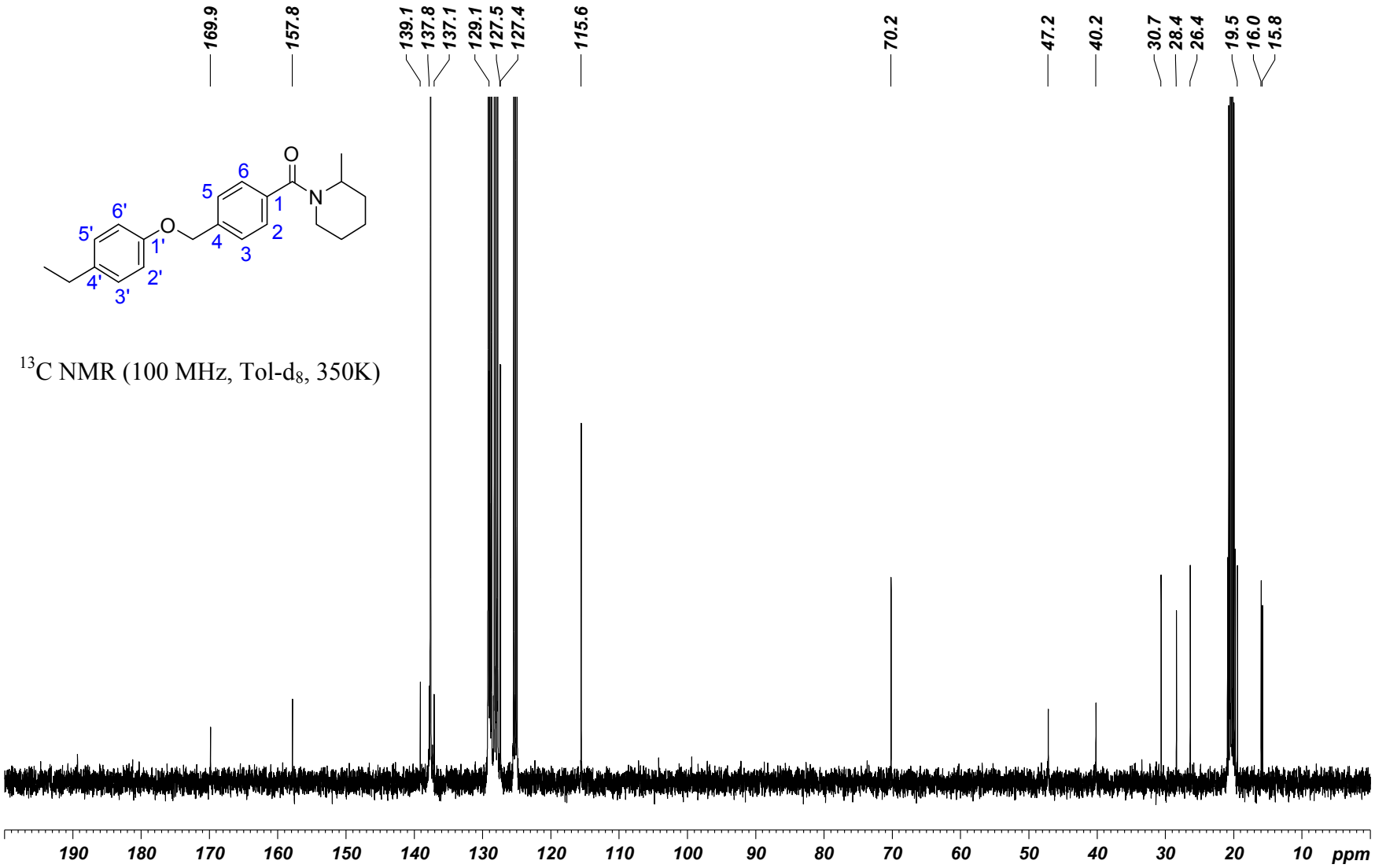
^{13}C NMR (100 MHz, Tol-d$_8$, 350K)
aromatic region

(4-((4-Ethylphenoxy)methyl)phenyl)(2-methylpiperidin-1-yl)methanone; S57.



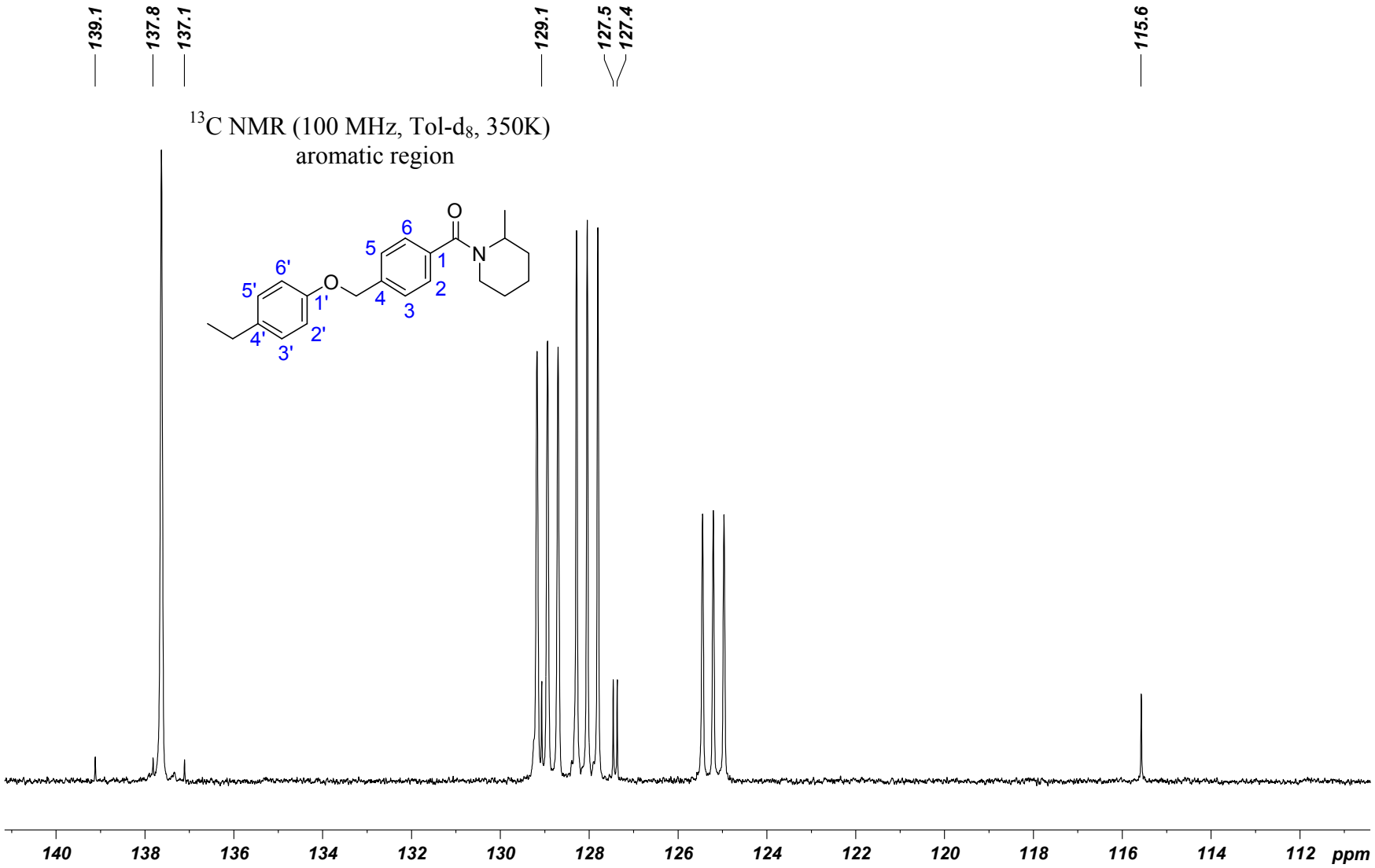
^{1}H NMR (400 MHz, Tol-d_8, 350K)

(4-((4-Ethylphenoxy)methyl)phenyl)(2-methylpiperidin-1-yl)methanone; S57.

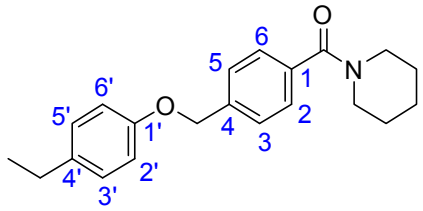


^{13}C NMR (100 MHz, Tol-d_8, 350K)

(4-((4-Ethylphenoxy)methyl)phenyl)(2-methylpiperidin-1-yl)methanone; S57.

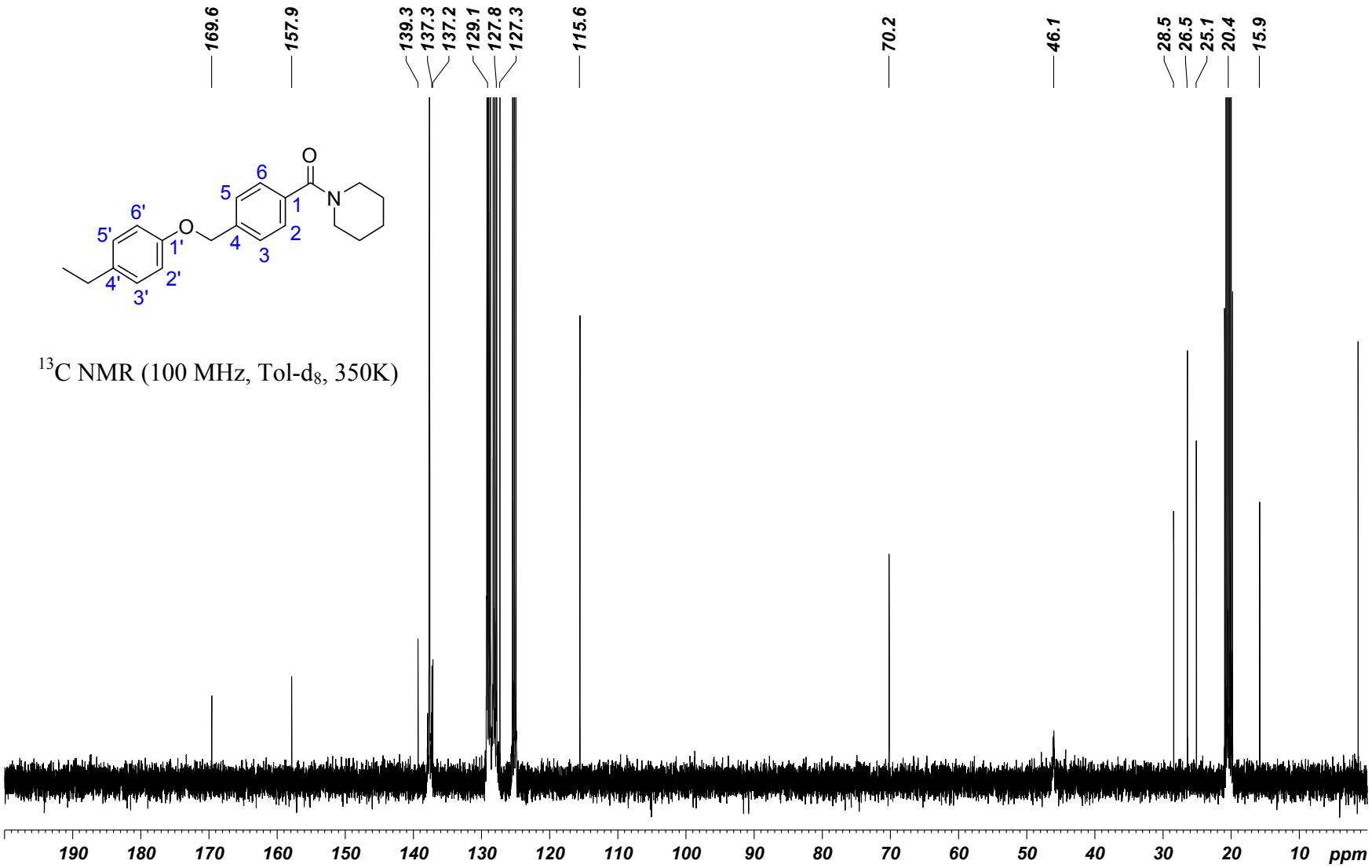


(4-((4-Ethylphenoxy)methyl)phenyl)(piperidin-1-yl)methanone; S58.



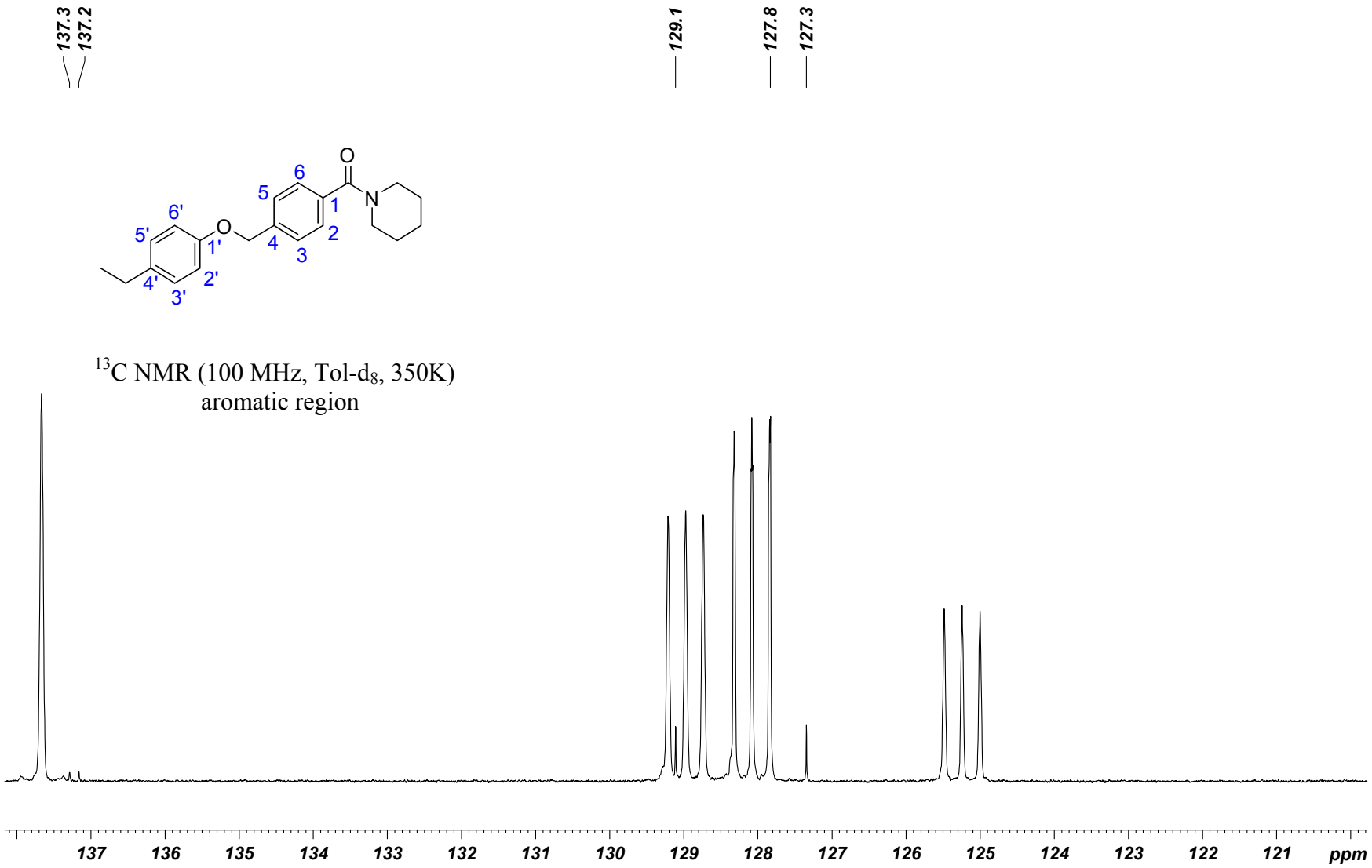
^{1}H NMR (400 MHz, Tol-d_8, 350K)

(4-((4-Ethylphenoxy)methyl)phenyl)(piperidin-1-yl)methanone; S58.

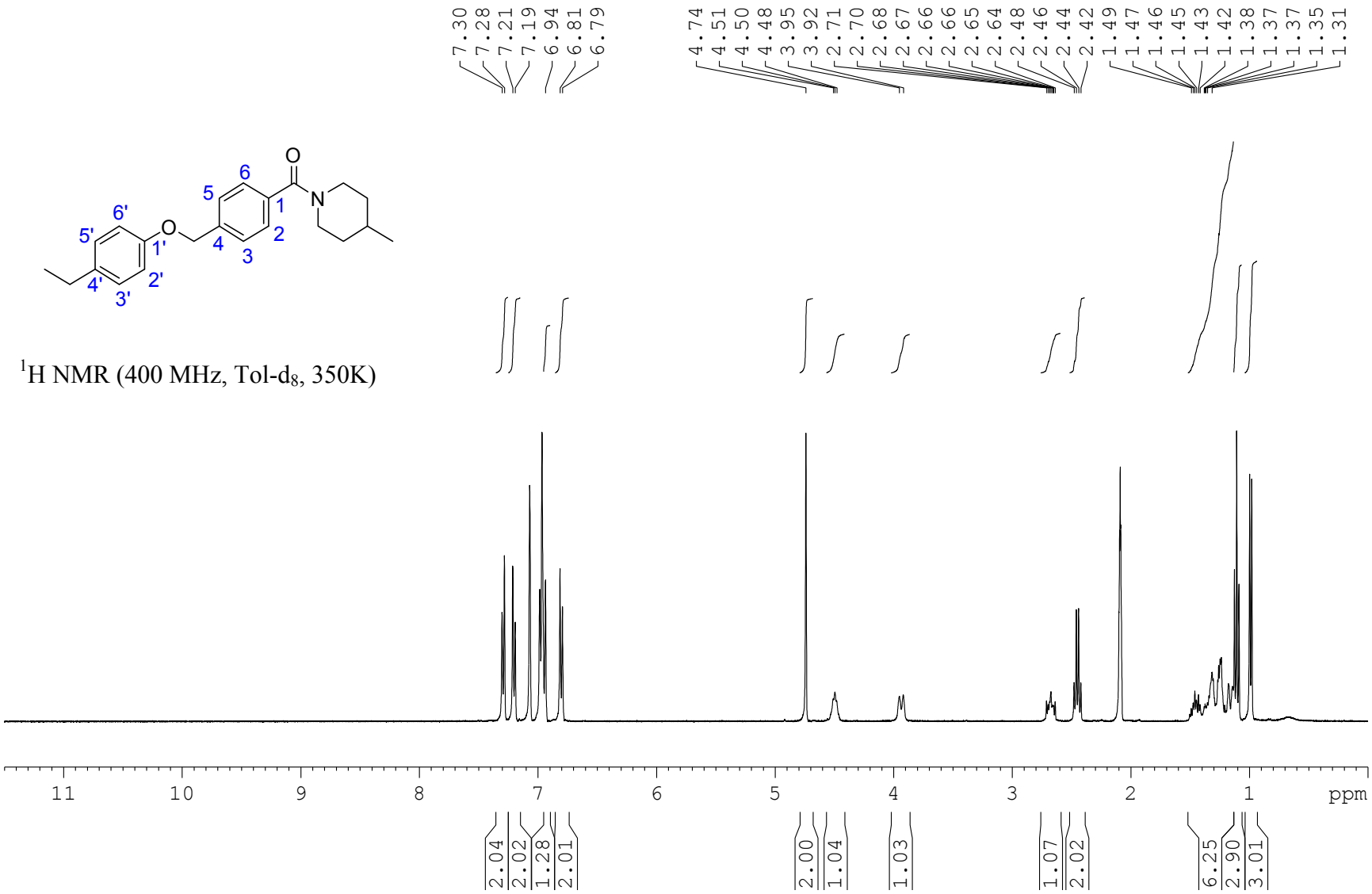


^{13}C NMR (100 MHz, Tol-d_8, 350K)

(4-((4-Ethylphenoxy)methyl)phenyl)(piperidin-1-yl)methanone; S58.

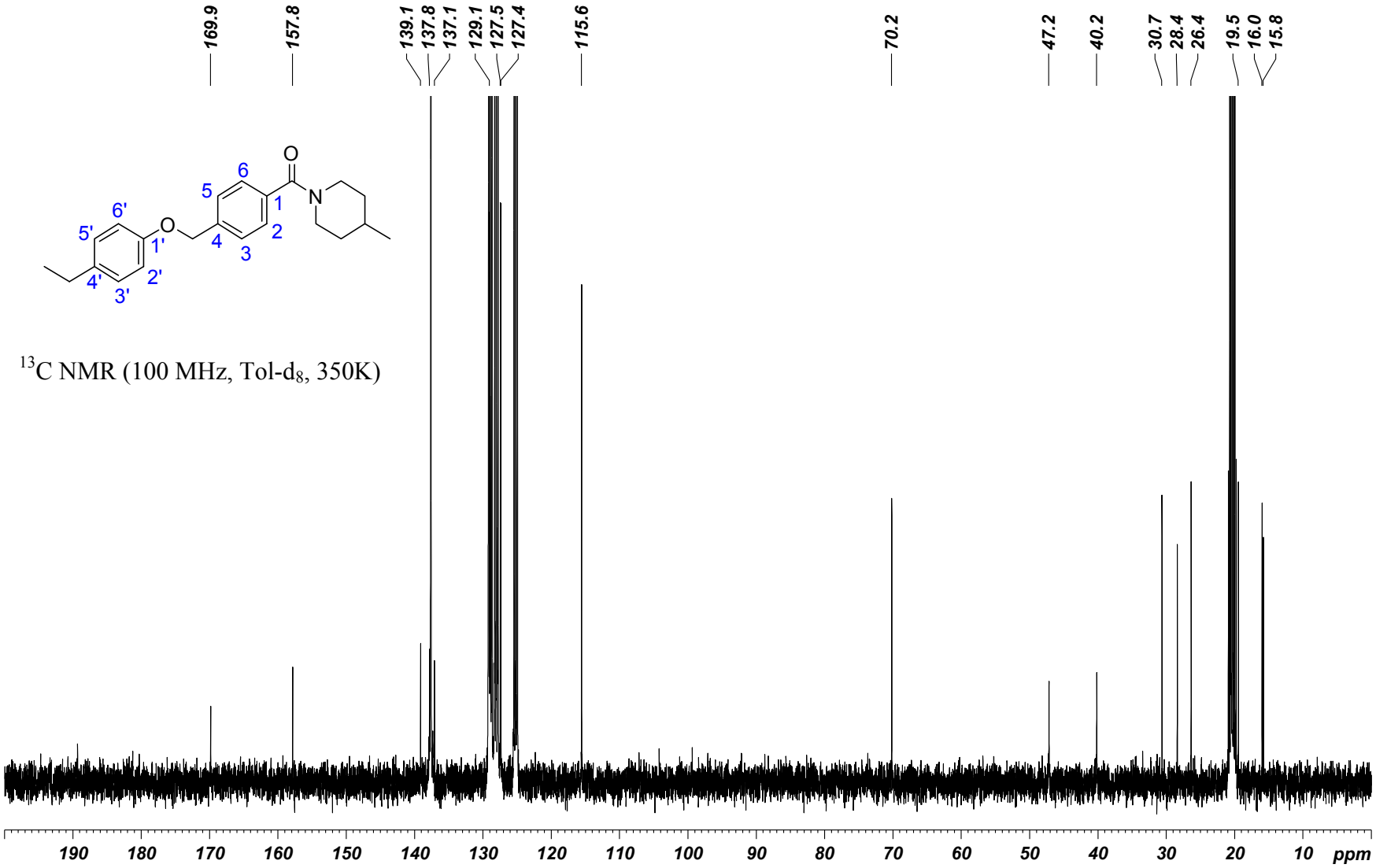


(4-((4-Ethylphenoxy)methyl)phenyl)(4-methylpiperidin-1-yl)methanone; 20.



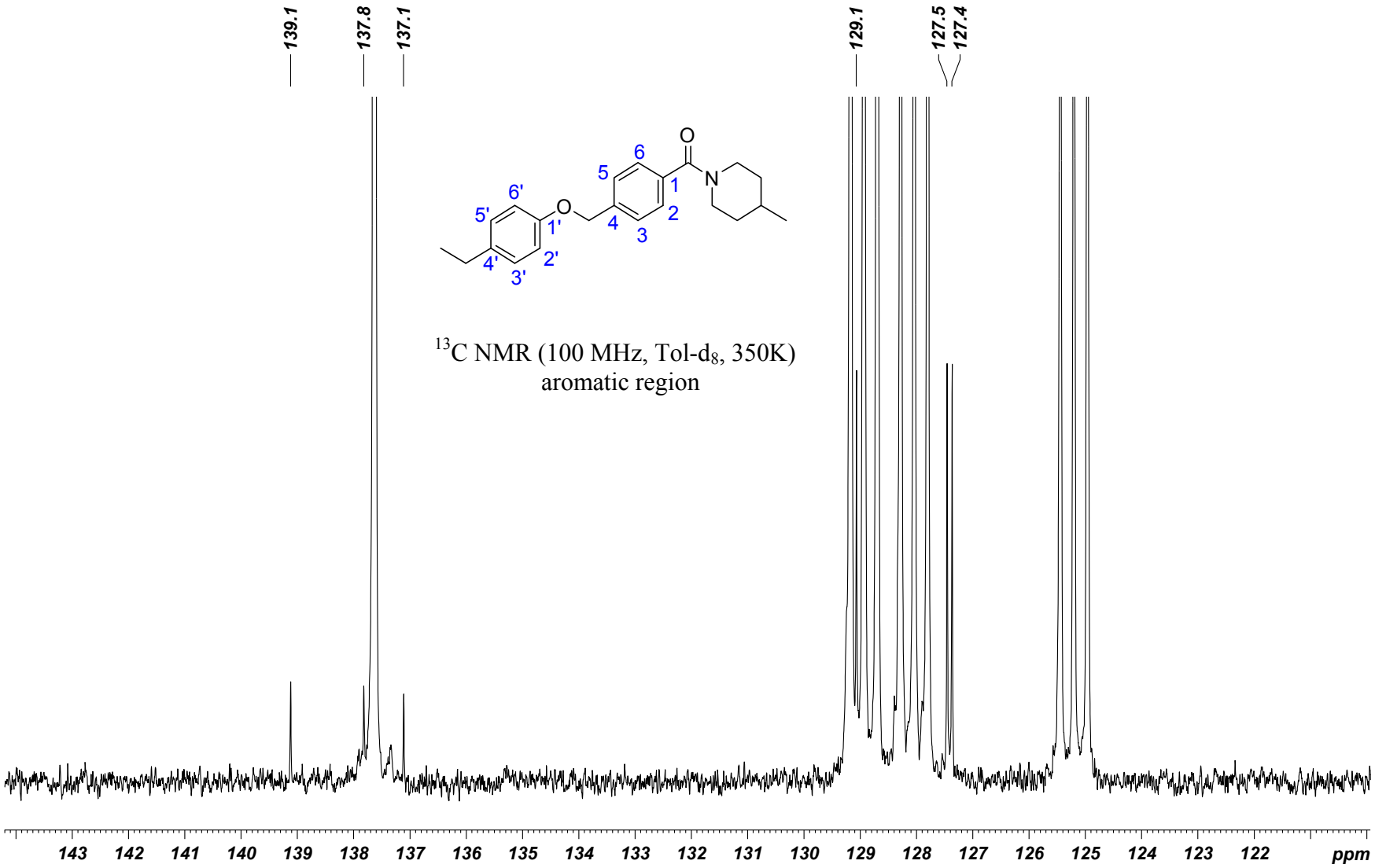
^{1}H NMR (400 MHz, Tol-d_8, 350K)

(4-((4-Ethylphenoxy)methyl)phenyl)(4-methylpiperidin-1-yl)methanone; 20.



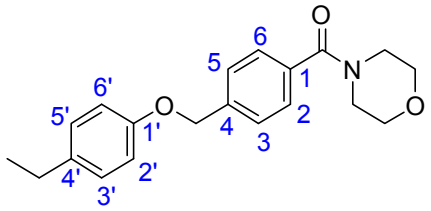
^{13}C NMR (100 MHz, Tol-d_8, 350K)

(4-((4-Ethylphenoxy)methyl)phenyl)(4-methylpiperidin-1-yl)methanone; 20.



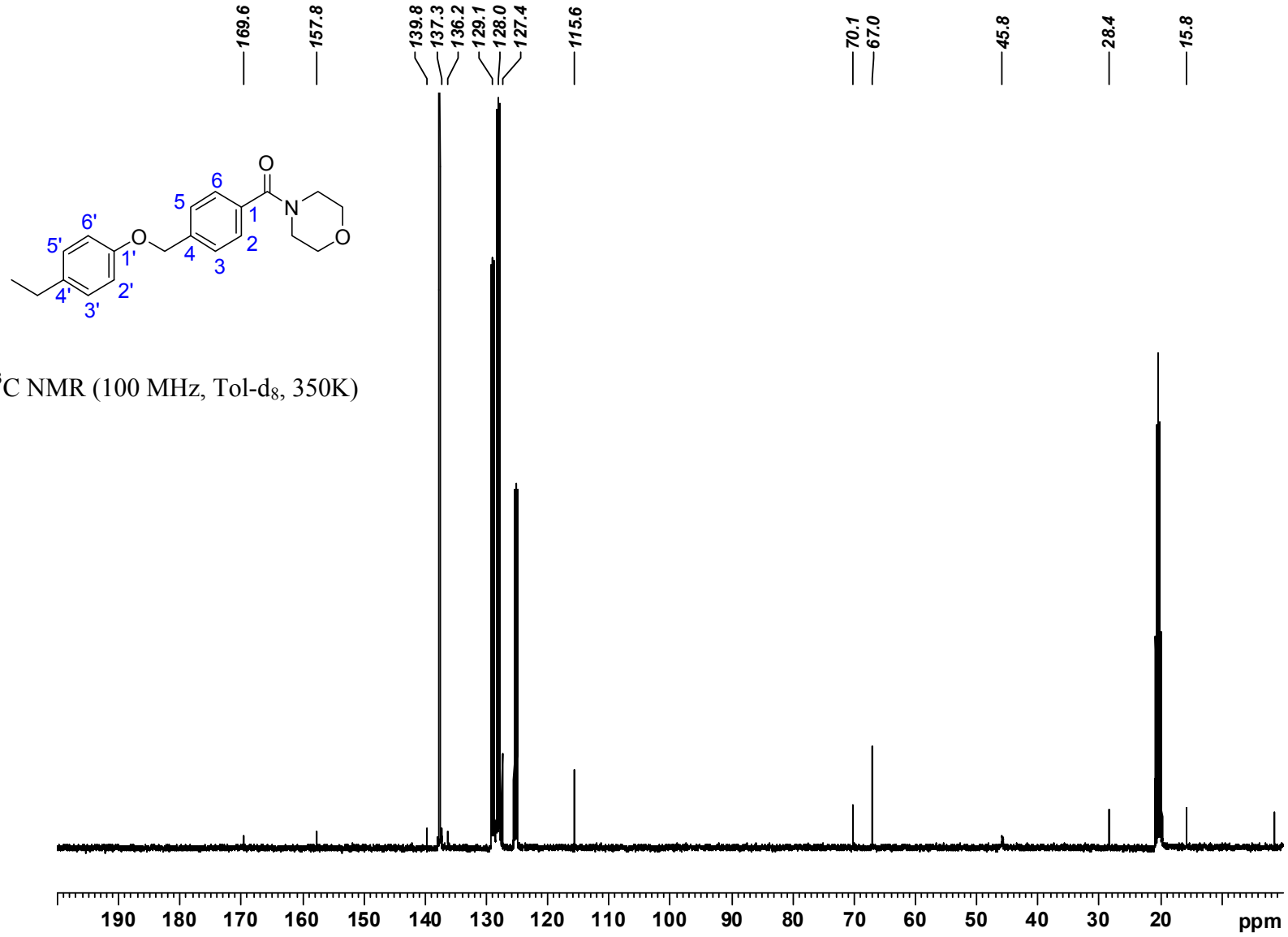
^{13}C NMR (100 MHz, Tol-d_8, 350K)
aromatic region

(4-((4-Ethylphenoxy)methyl)phenyl)(morpholino)methanone, 25.



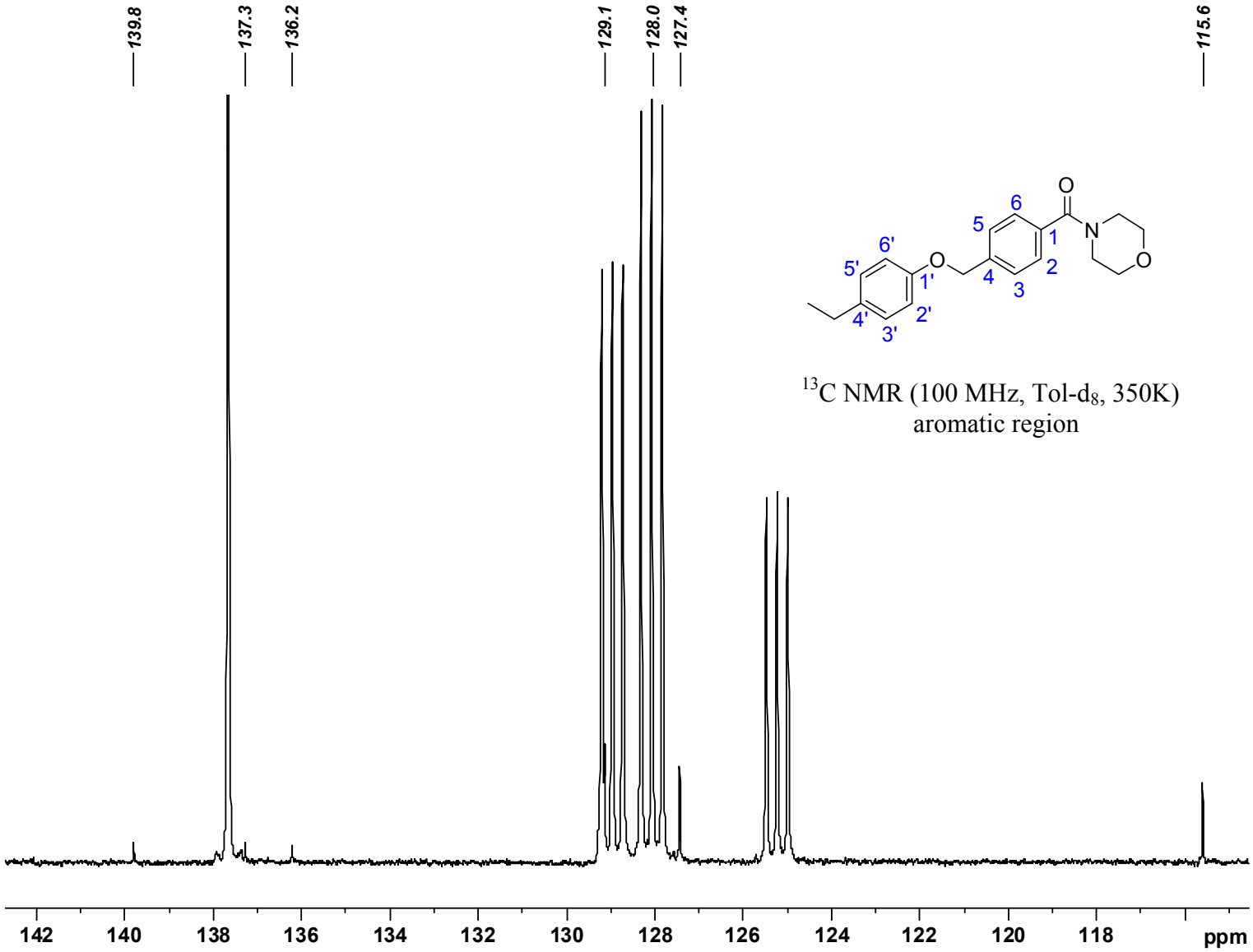
^{1}H NMR (400 MHz, Tol-d_8, 350K)

(4-((4-Ethylphenoxy)methyl)phenyl)(morpholino)methanone, 25.

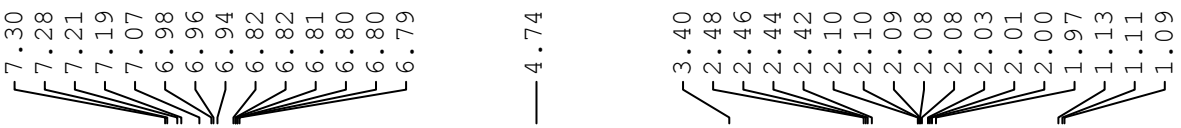


^{13}C NMR (100 MHz, Tol-d_8, 350K)

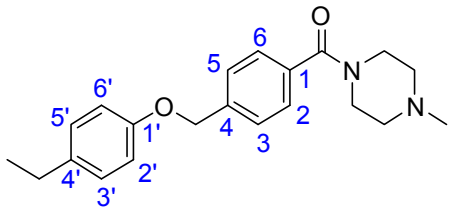
(4-((4-Ethylphenoxy)methyl)phenyl)(morpholino)methanone, 25.



^{13}C NMR (100 MHz, Tol-d_8, 350K)
aromatic region

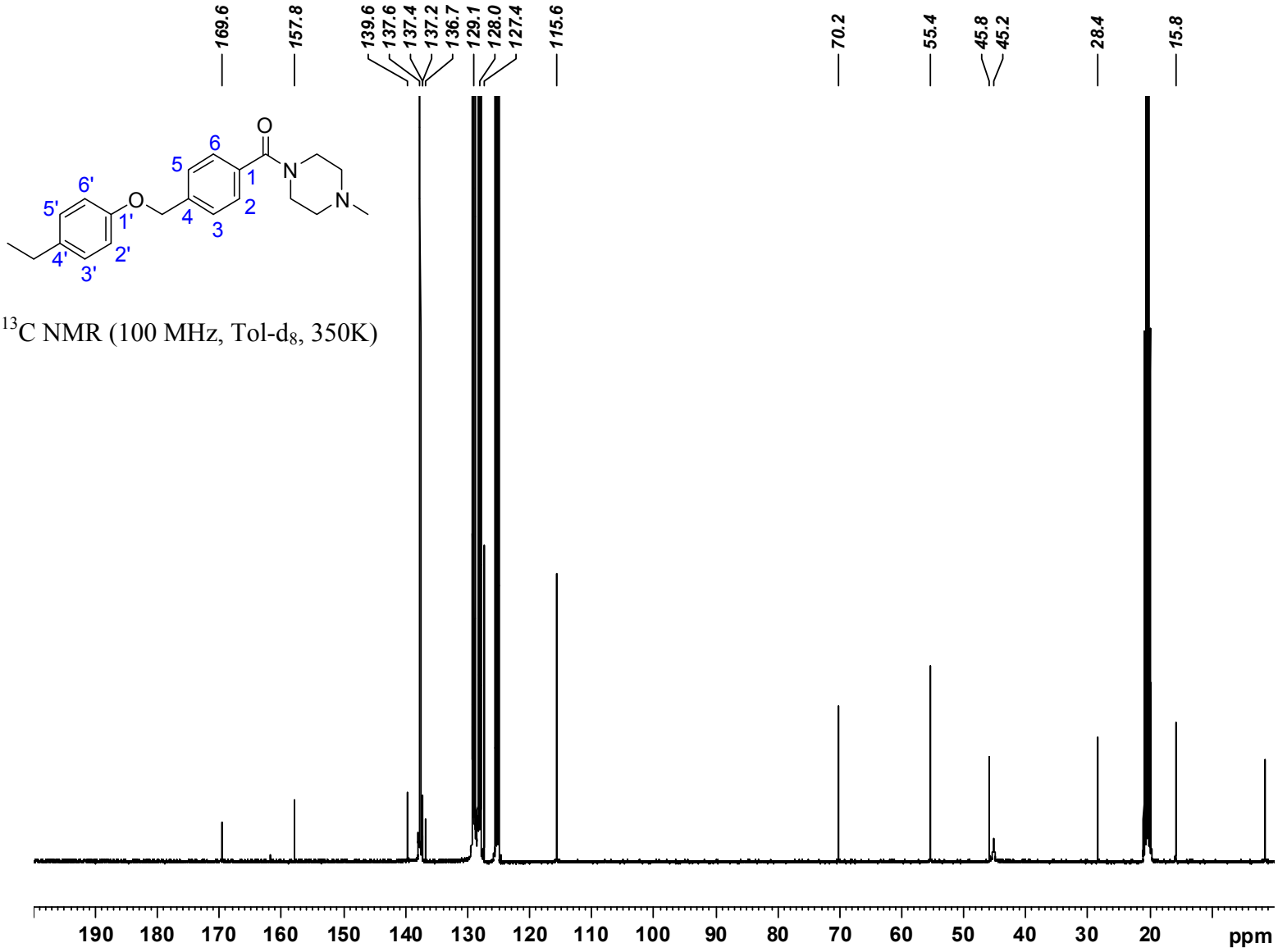


(4-((4-Ethylphenoxy)methyl)phenyl)(4-methylpiperazin-1-yl)methanone, 29.



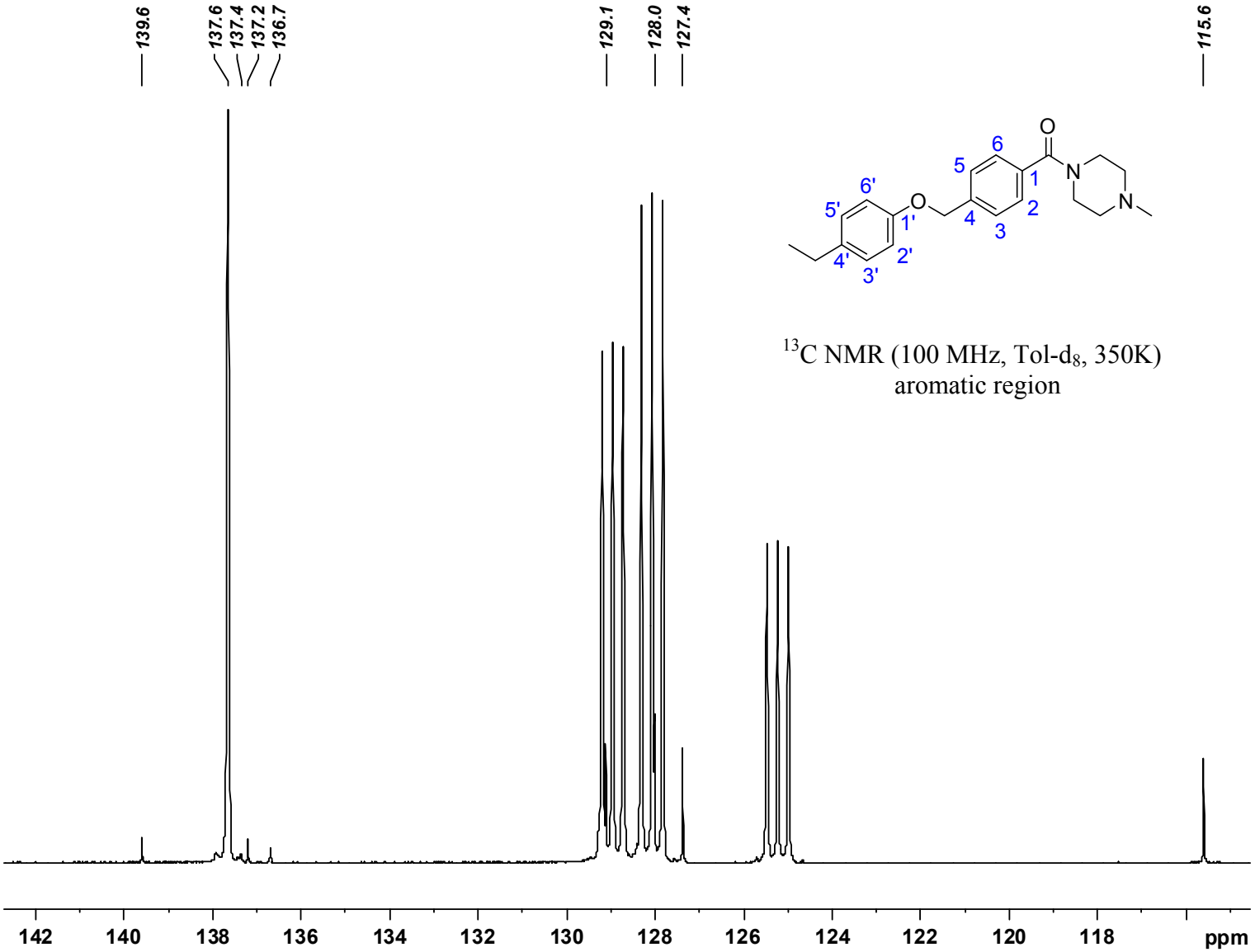
^{1}H NMR (400 MHz, Tol-d_8, 350K)

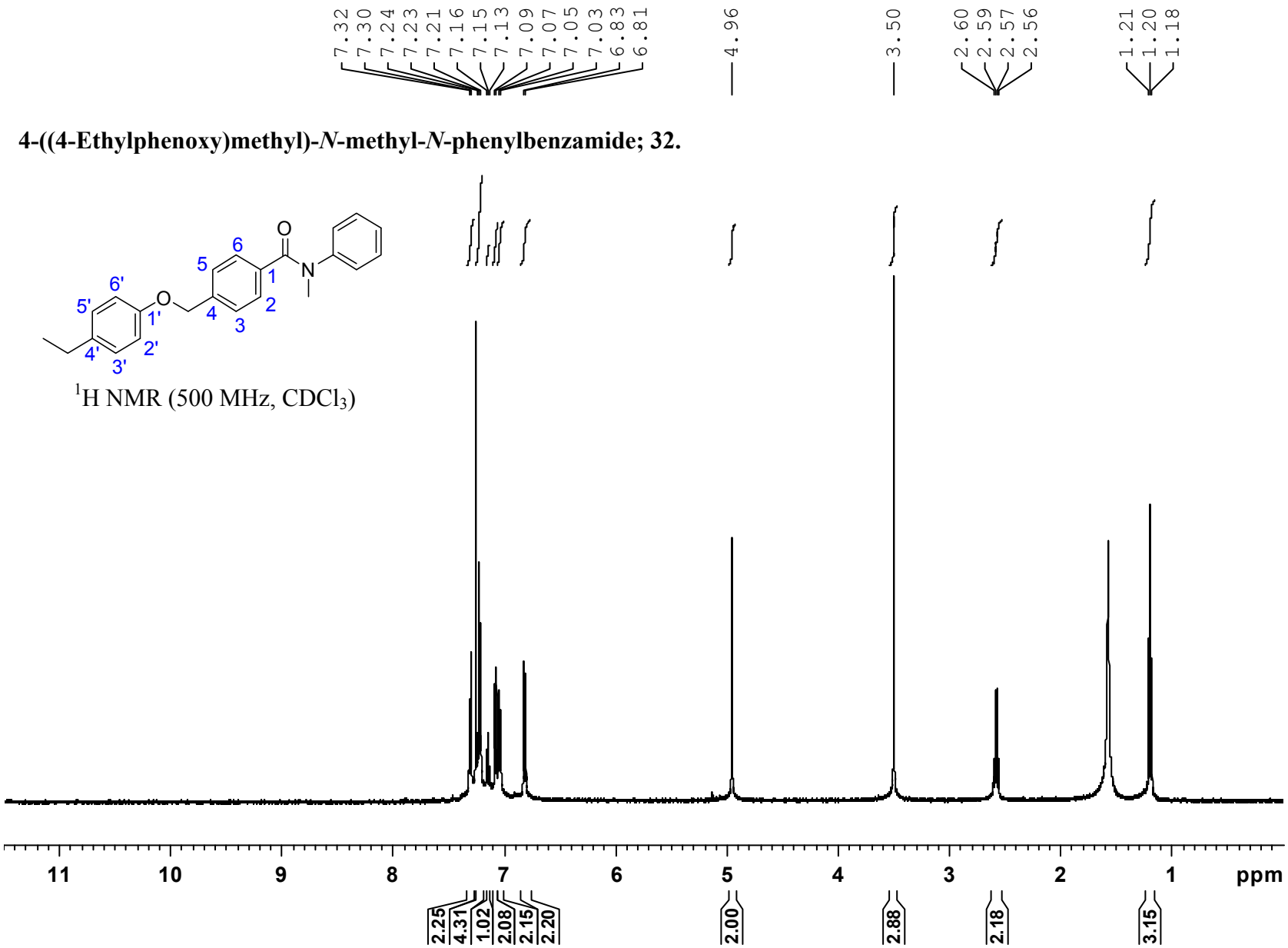
(4-((4-Ethylphenoxy)methyl)phenyl)(4-methylpiperazin-1-yl)methanone, 29.



^{13}C NMR (100 MHz, Tol-d_8, 350K)

(4-((4-Ethylphenoxy)methyl)phenyl)(4-methylpiperazin-1-yl)methanone, 29.

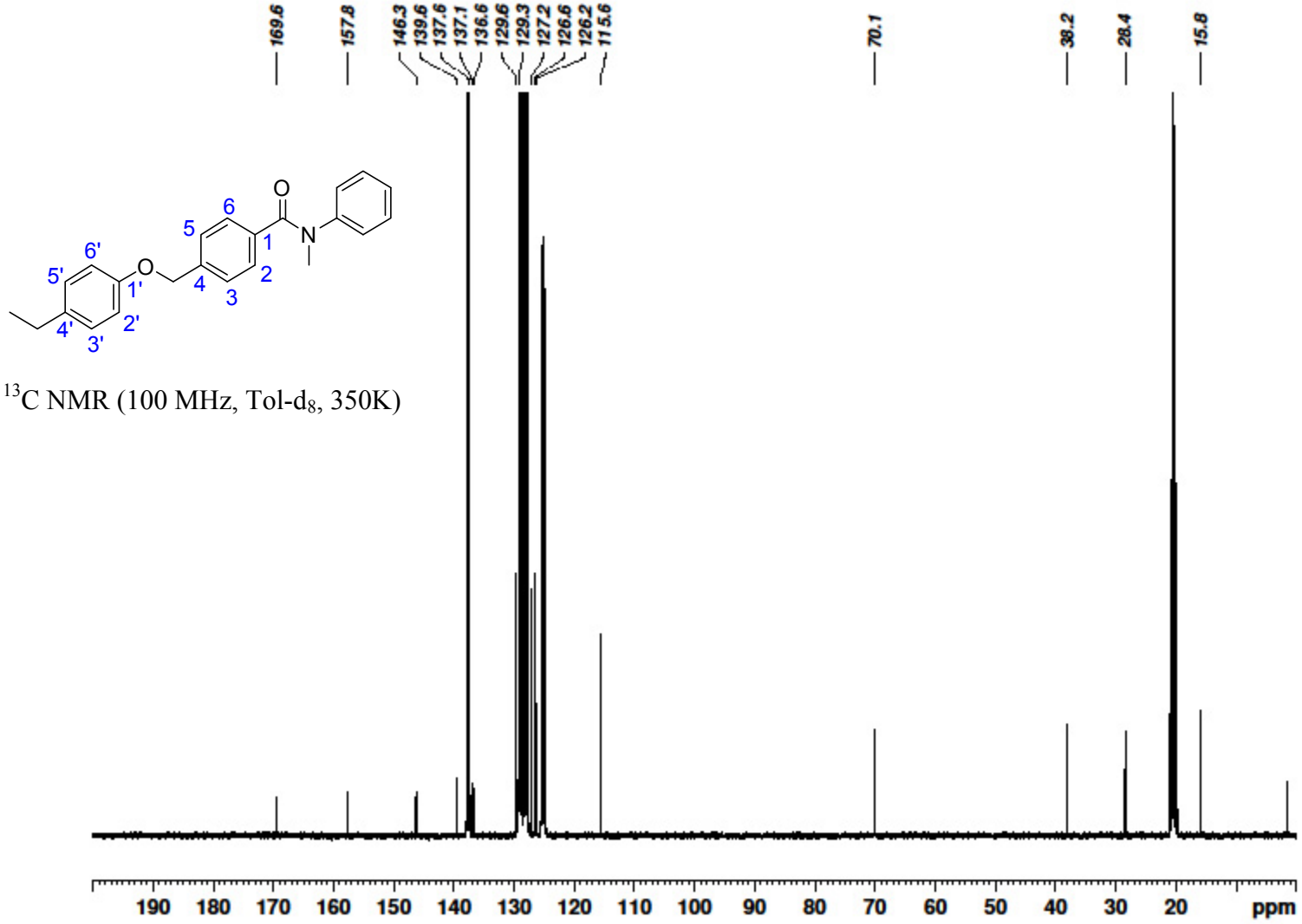




4-((4-Ethylphenoxy)methyl)-*N*-methyl-*N*-phenylbenzamide; 32.

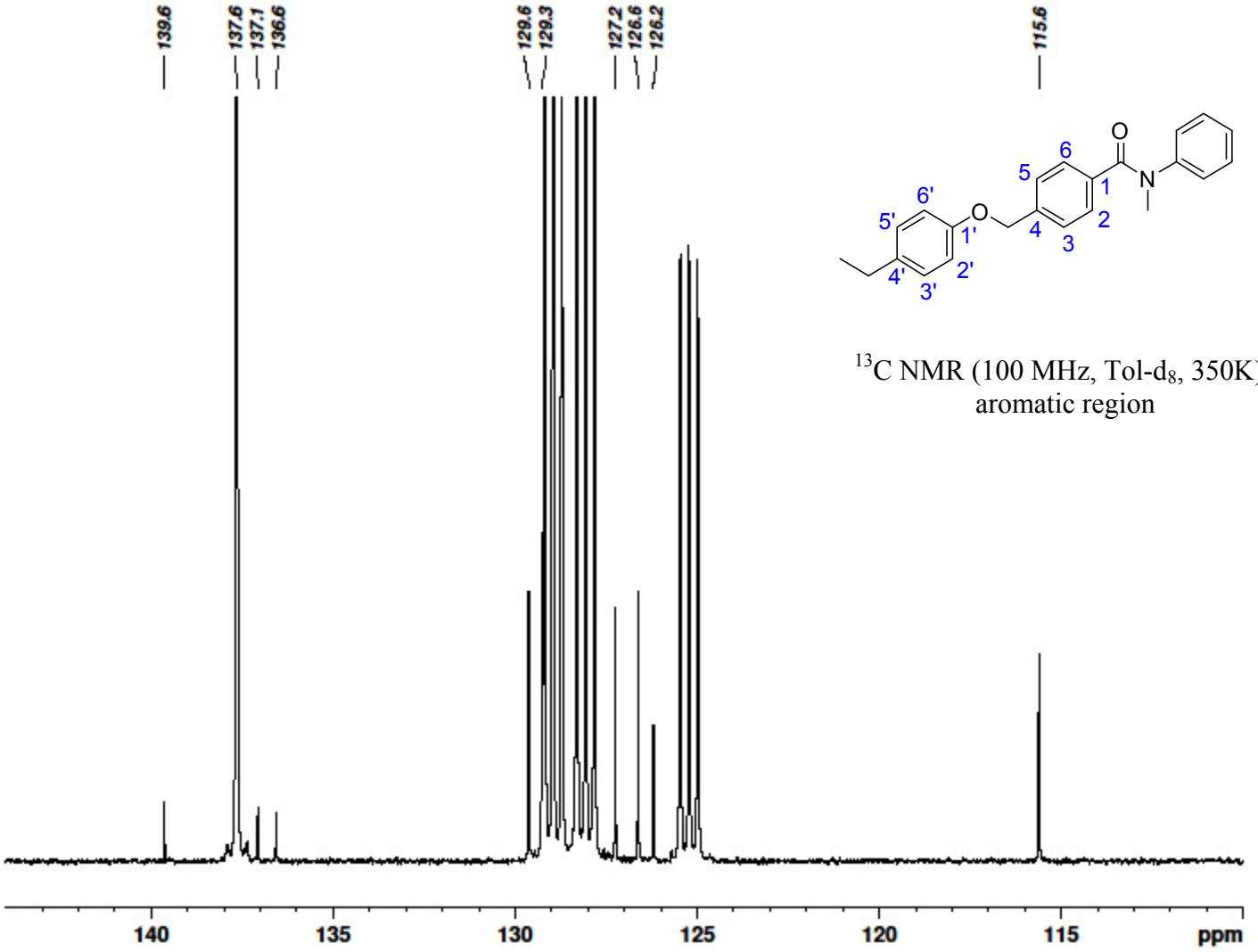
^{1}H NMR (500 MHz, $CDCl_3$)

4-((4-Ethylphenoxy)methyl)-*N*-methyl-*N*-phenylbenzamide; 32.



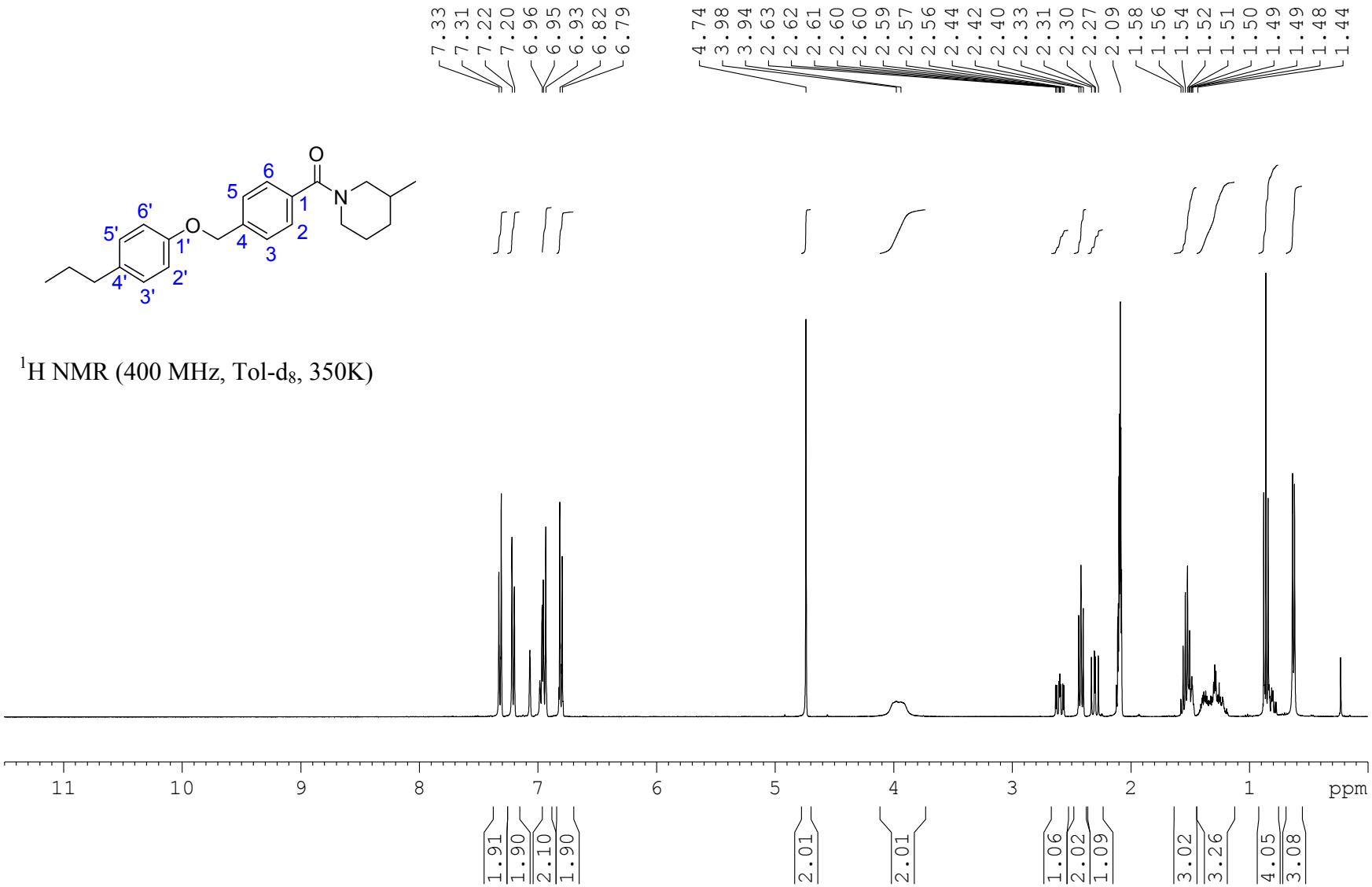
^{13}C NMR (100 MHz, Tol-d_8, 350K)

4-((4-Ethylphenoxy)methyl)-*N*-methyl-*N*-phenylbenzamide; 32.



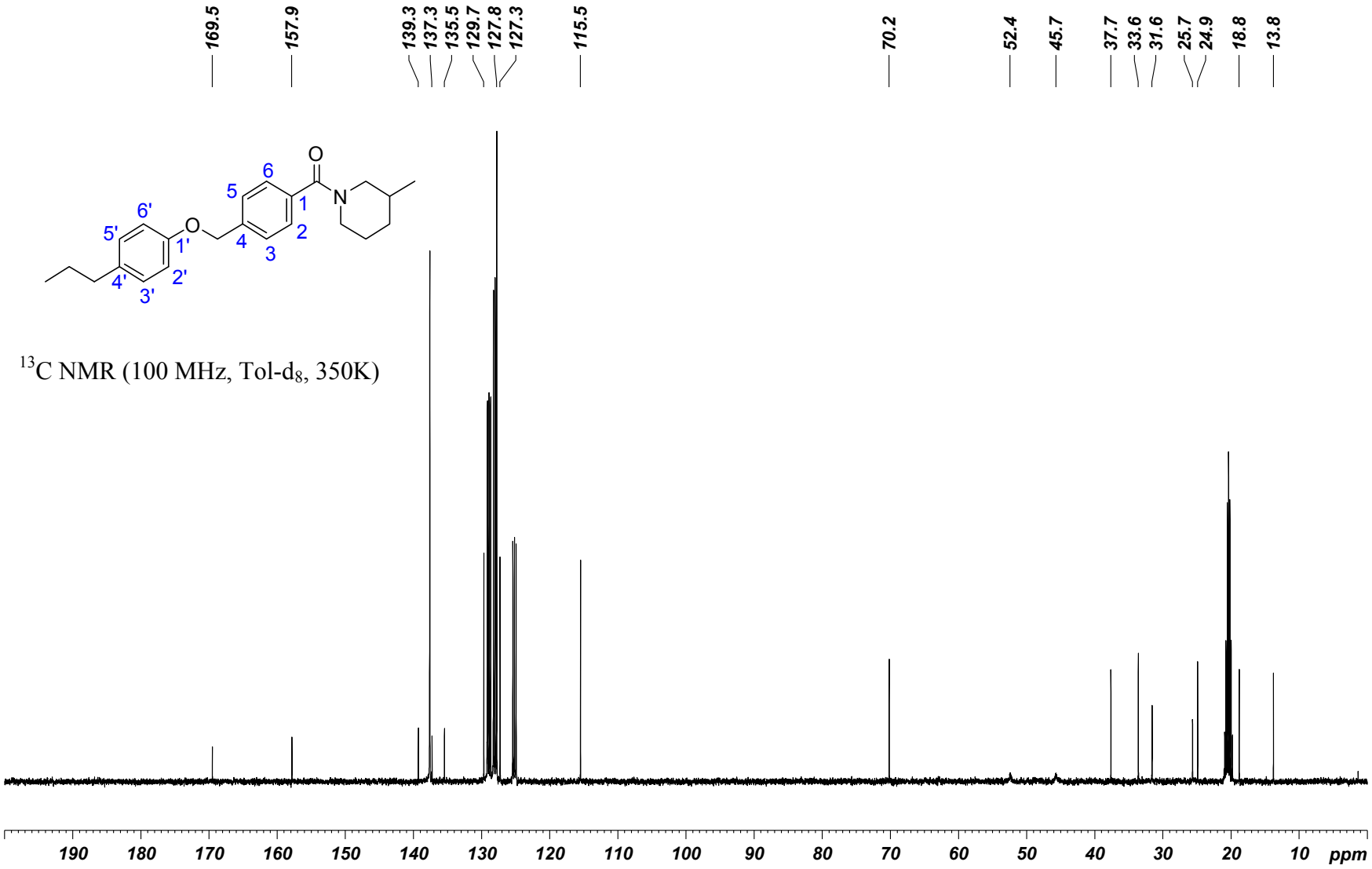
^{13}C NMR (100 MHz, Tol-d_8, 350K)
aromatic region

(3-Methylpiperidin-1-yl)(4-((4-propylphenoxy)methyl)phenyl)methanone; 12.



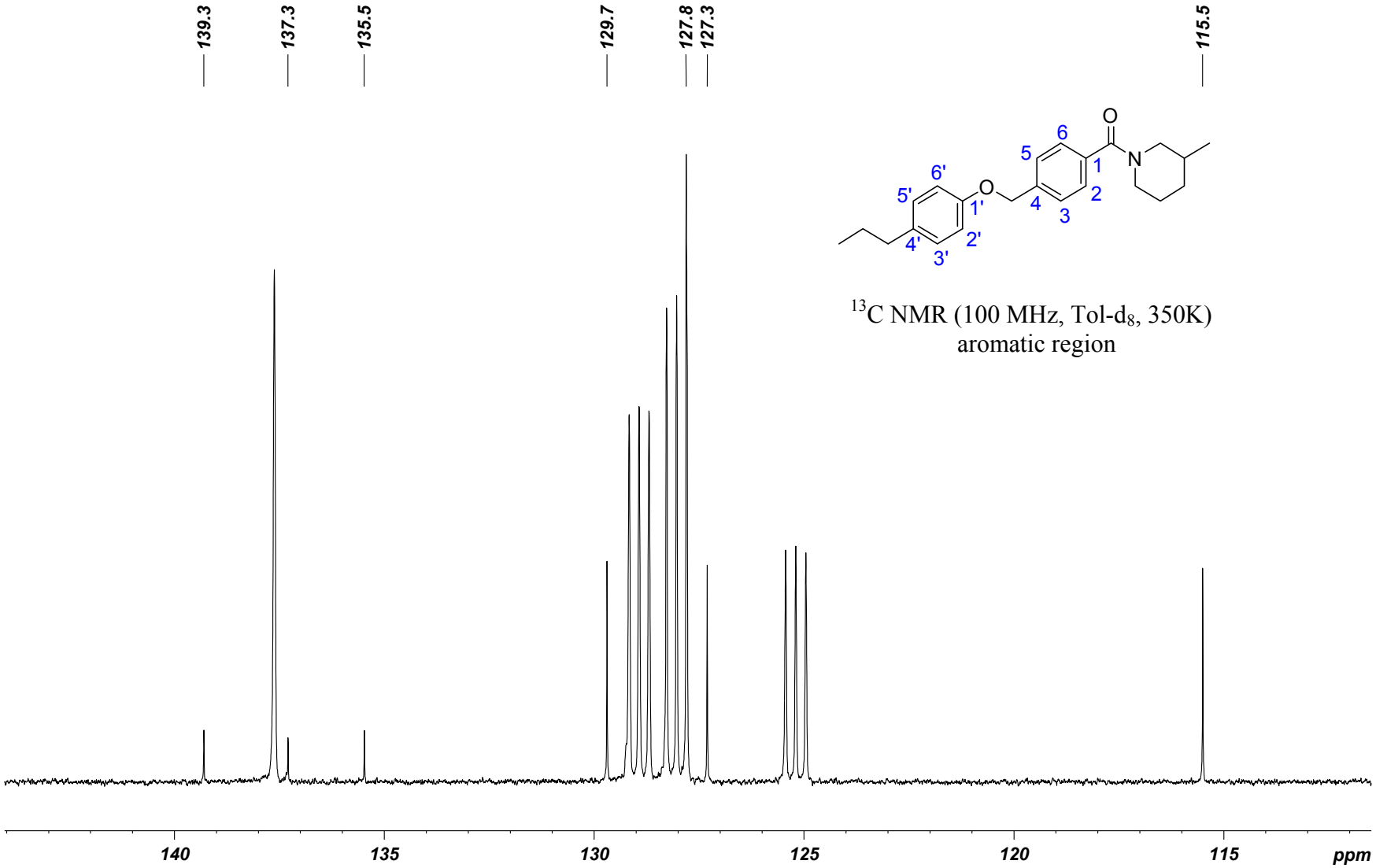
^{1}H NMR (400 MHz, Tol-d_8, 350K)

(3-Methylpiperidin-1-yl)(4-((4-propylphenoxy)methyl)phenyl)methanone; 12.



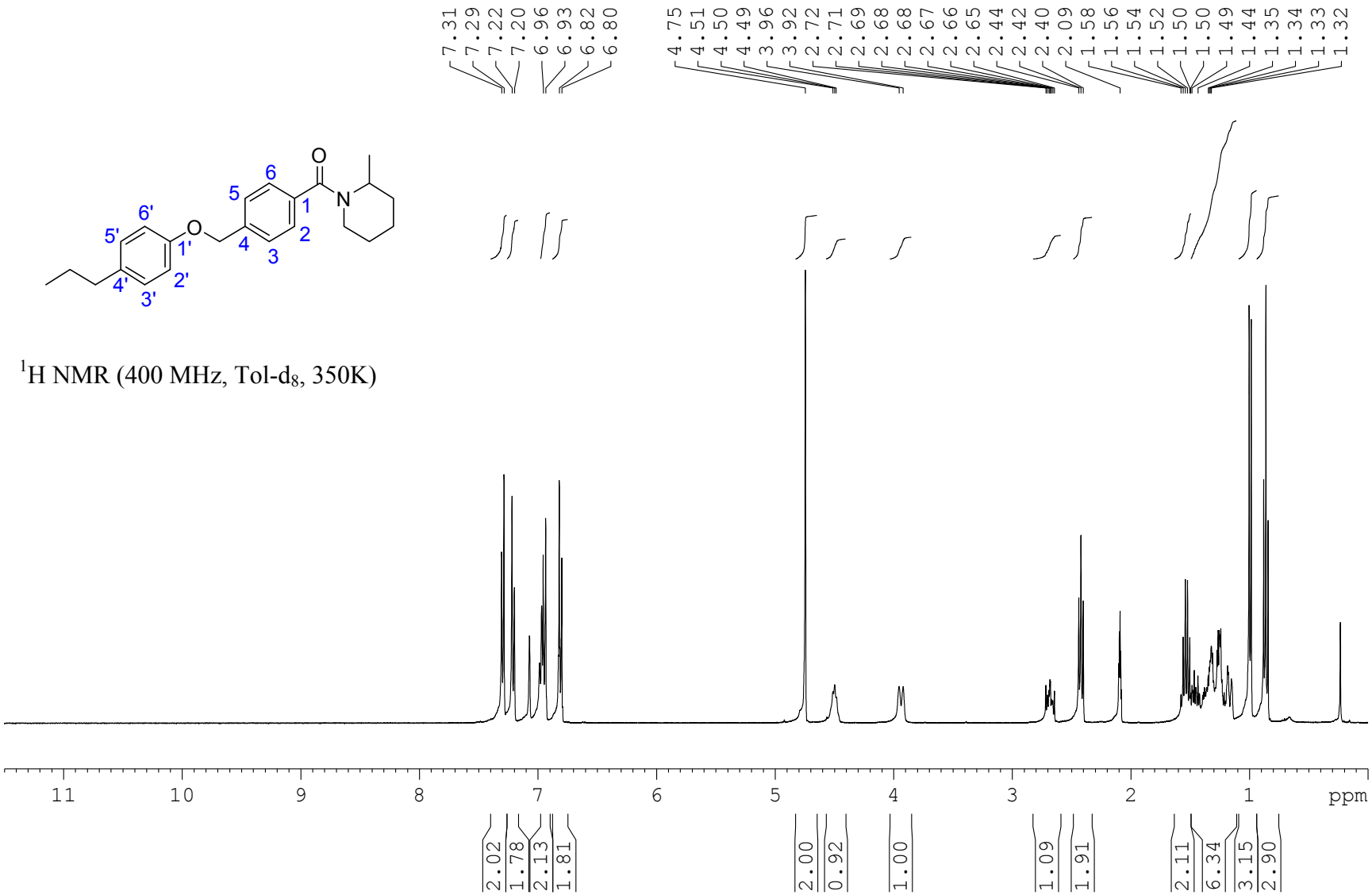
^{13}C NMR (100 MHz, Tol-d_8, 350K)

(3-Methylpiperidin-1-yl)(4-((4-propylphenoxy)methyl)phenyl)methanone; 12.



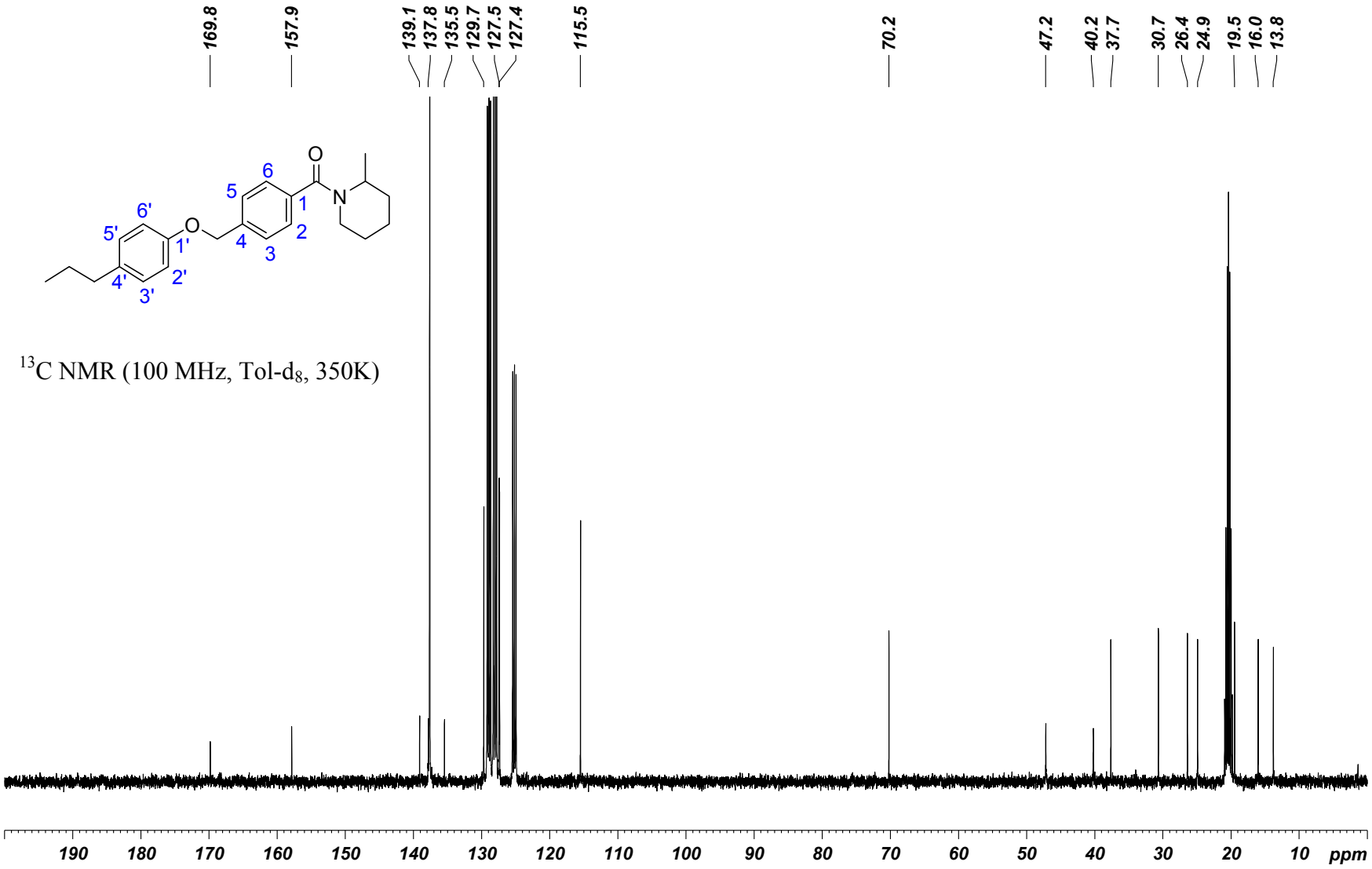
^{13}C NMR (100 MHz, Tol-d_8, 350K)
aromatic region

(2-Methylpiperidin-1-yl)(4-((4-propylphenoxy)methyl)phenyl)methanone; 15.



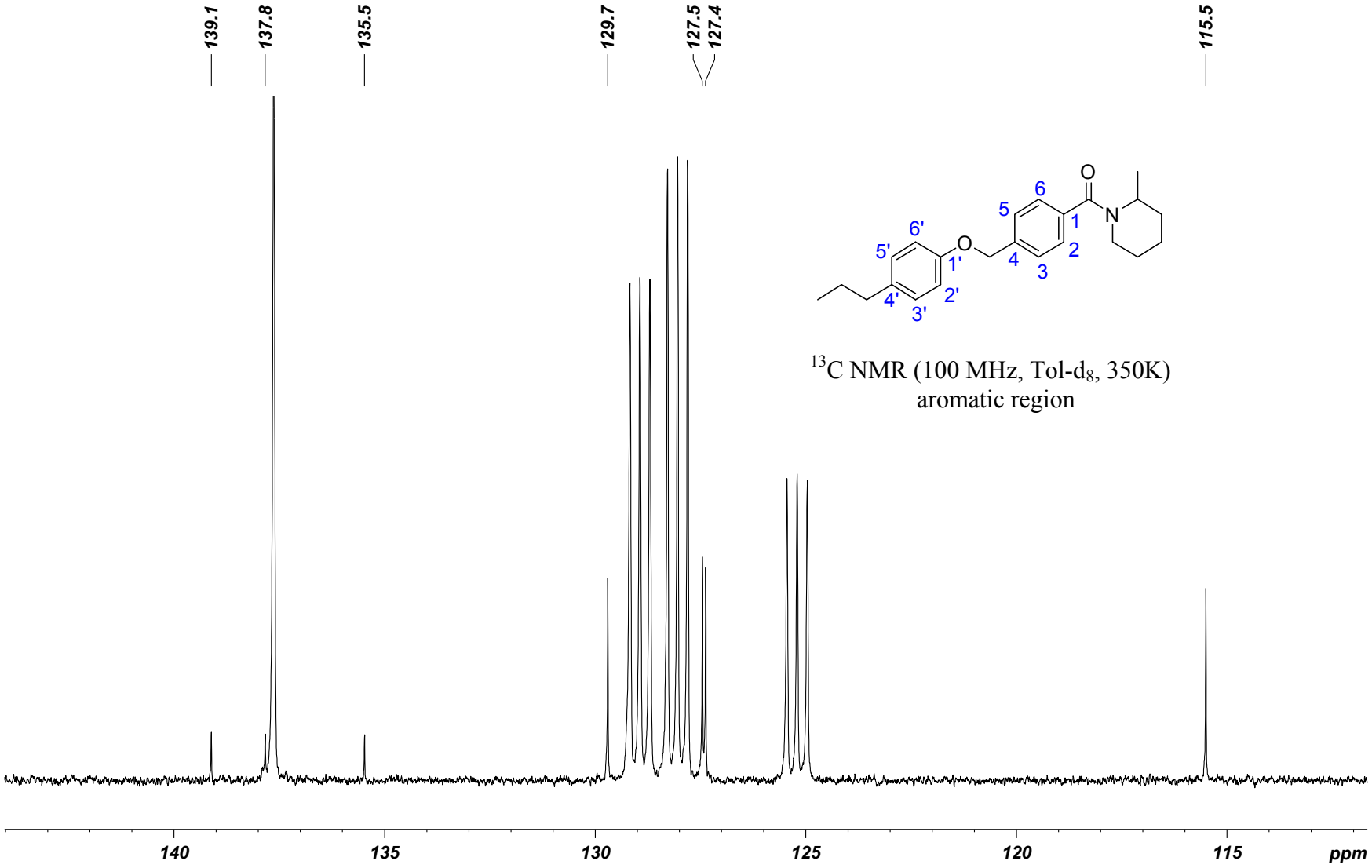
^{1}H NMR (400 MHz, Tol-d_8, 350K)

(2-Methylpiperidin-1-yl)(4-((4-propylphenoxy)methyl)phenyl)methanone; 15.



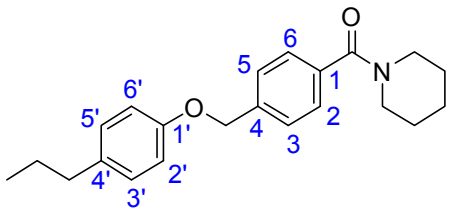
^{13}C NMR (100 MHz, Tol-d_8, 350K)

(2-Methylpiperidin-1-yl)(4-((4-propylphenoxy)methyl)phenyl)methanone; 15.



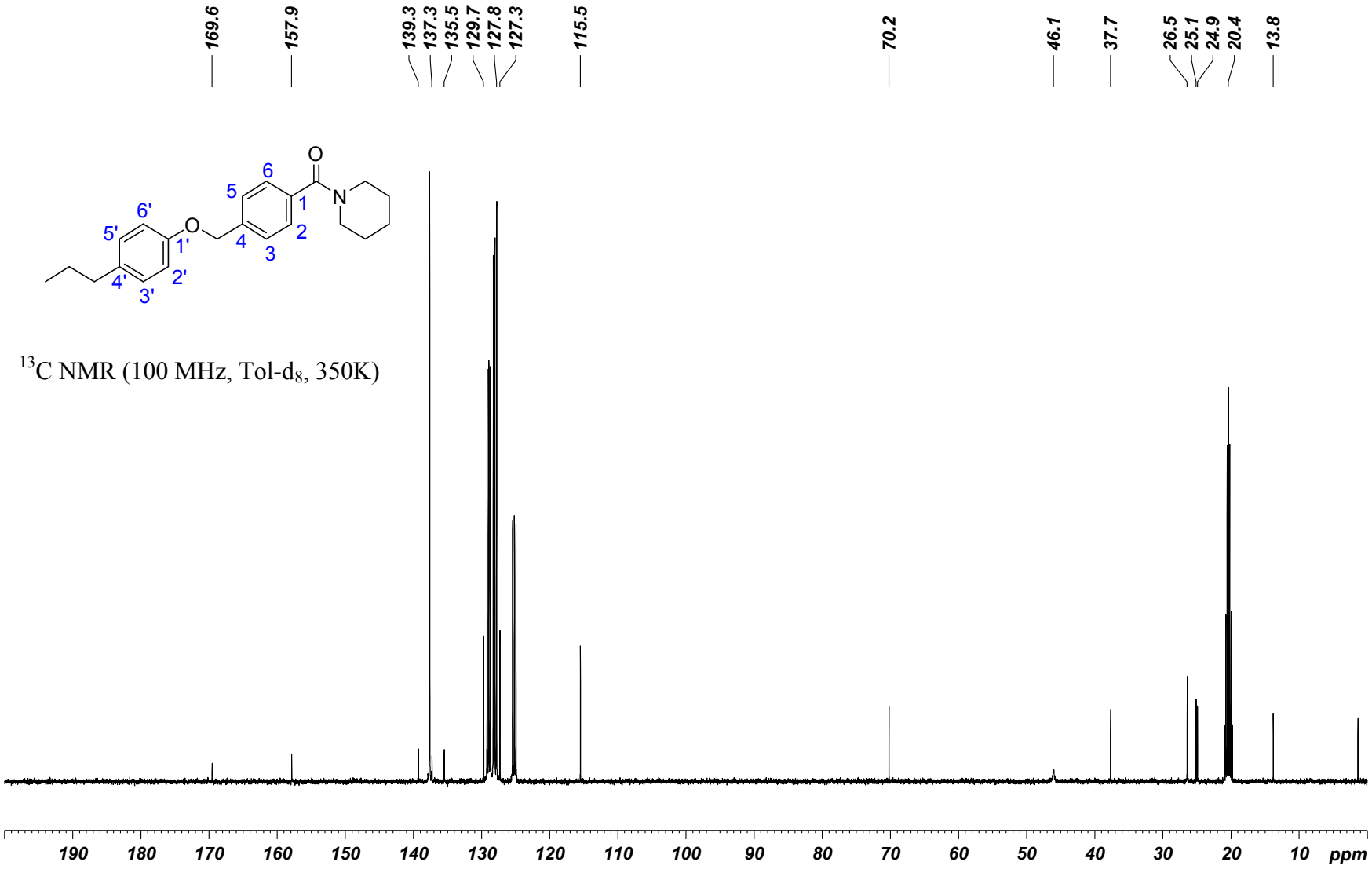
^{13}C NMR (100 MHz, Tol-d_8, 350K)
aromatic region

Piperidin-1-yl(4-((4-propylphenoxy)methyl)phenyl)methanone; S59.



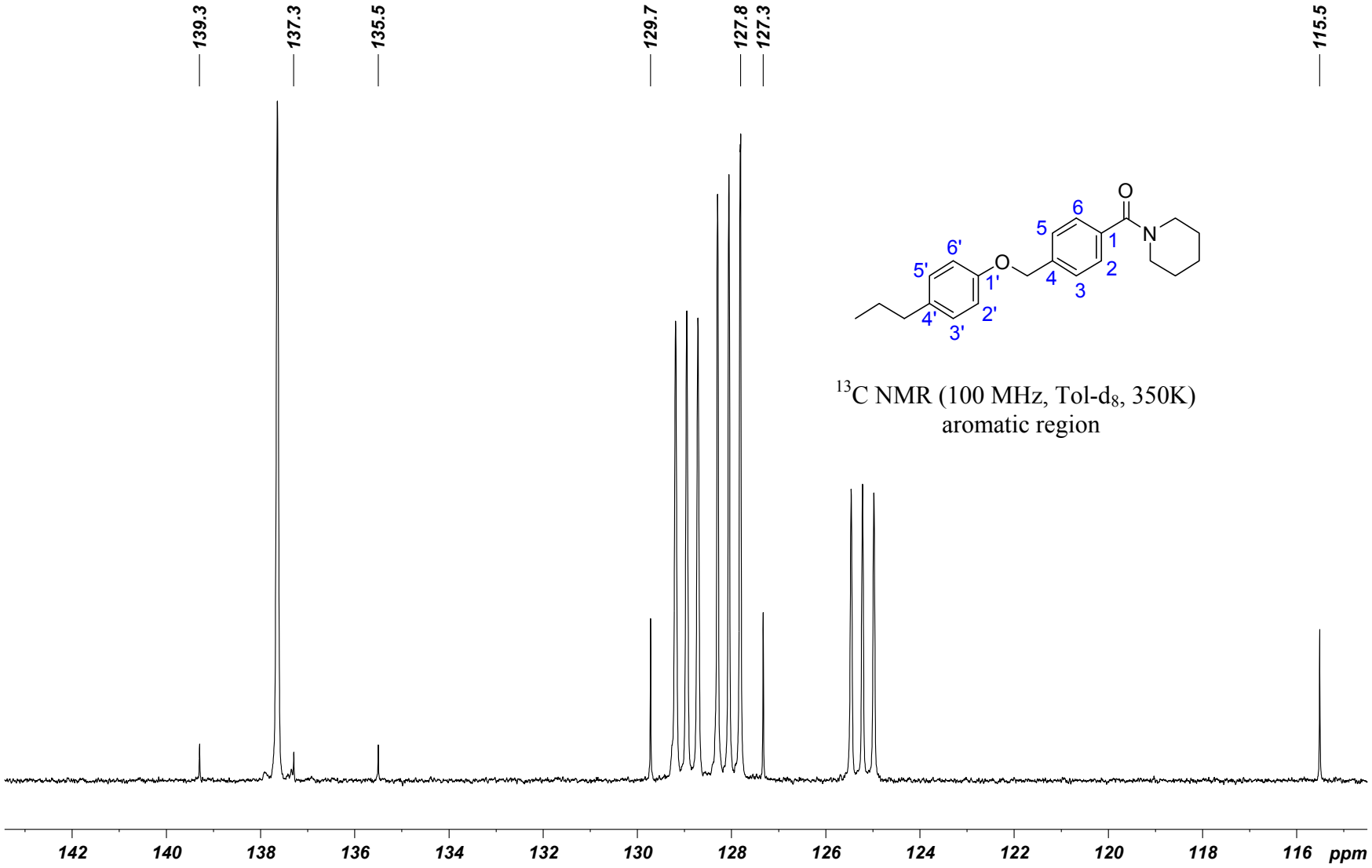
^{1}H NMR (400 MHz, Tol-d_8, 350K)

Piperidin-1-yl(4-((4-propylphenoxy)methyl)phenyl)methanone; S59.



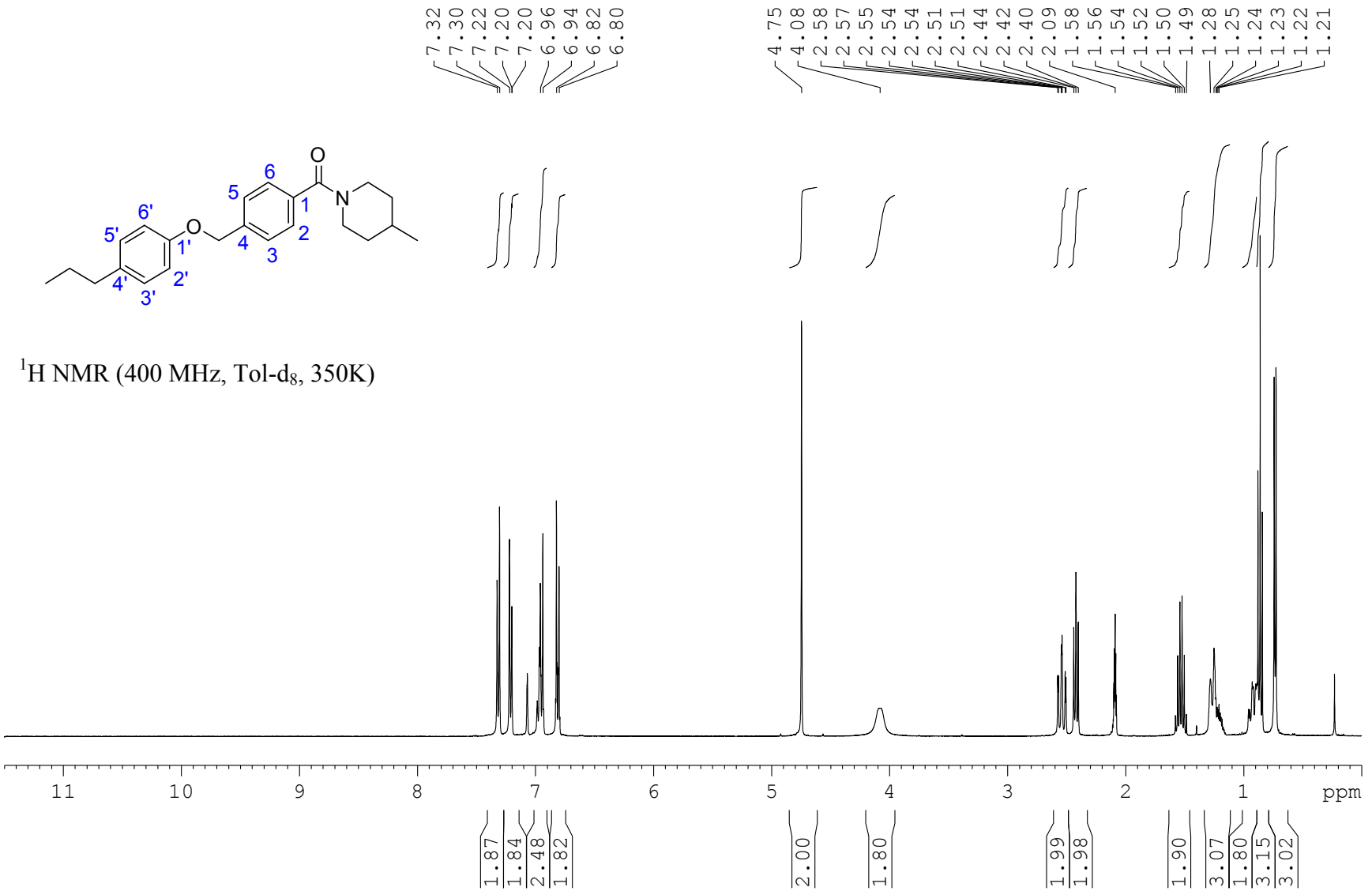
^{13}C NMR (100 MHz, Tol-d_8, 350K)

Piperidin-1-yl(4-((4-propylphenoxy)methyl)phenyl)methanone; S59.

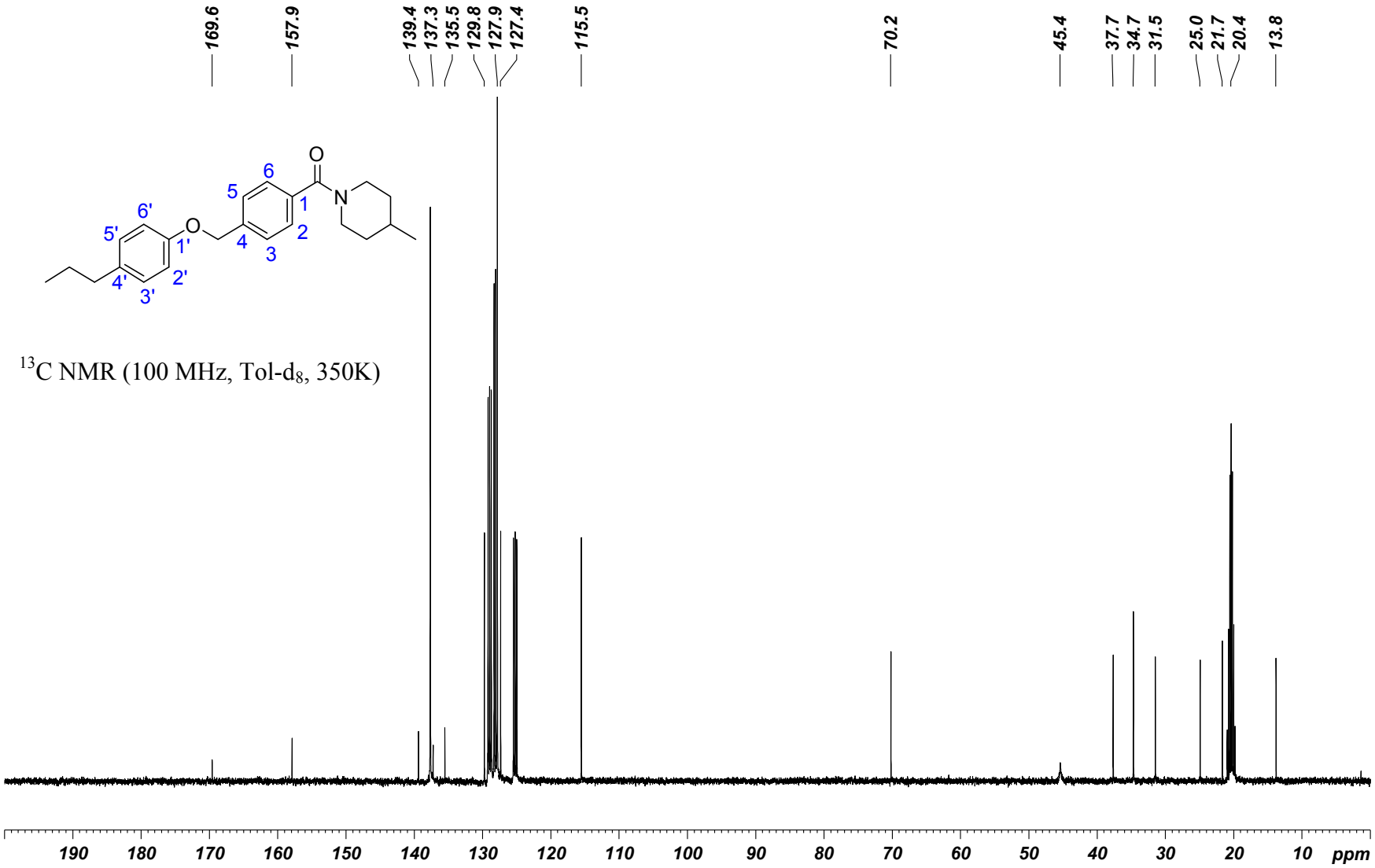


^{13}C NMR (100 MHz, Tol-d$_8$, 350K)
aromatic region

(4-Methylpiperidin-1-yl)(4-((4-propylphenoxy)methyl)phenyl)methanone; S60.

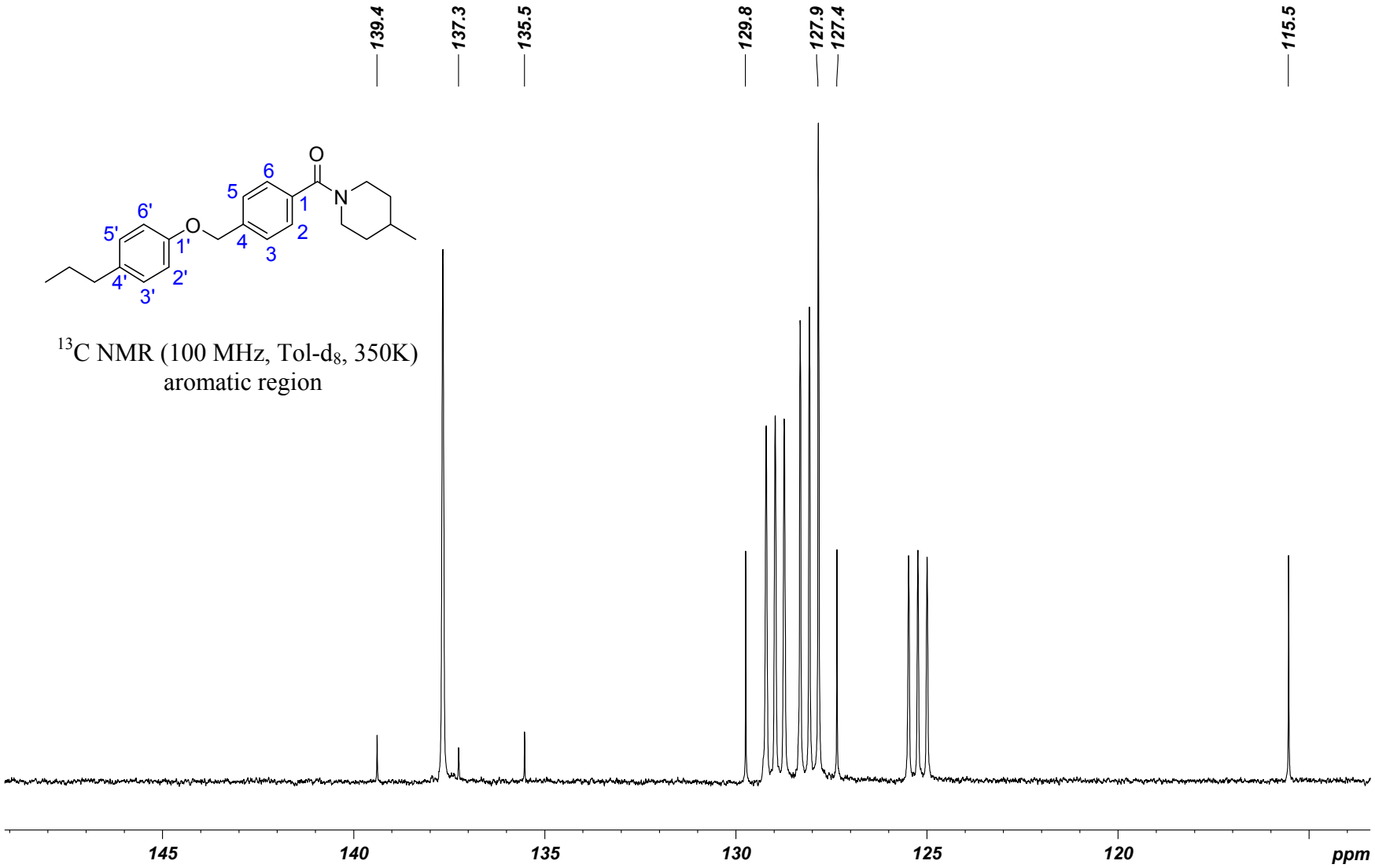


(4-Methylpiperidin-1-yl)(4-((4-propylphenoxy)methyl)phenyl)methanone; S60.

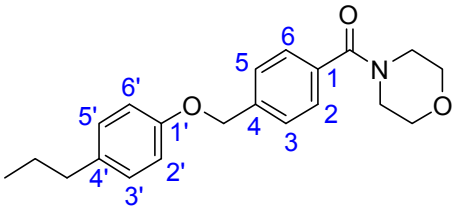


^{13}C NMR (100 MHz, Tol-d_8, 350K)

(4-Methylpiperidin-1-yl)(4-((4-propylphenoxy)methyl)phenyl)methanone; S60.

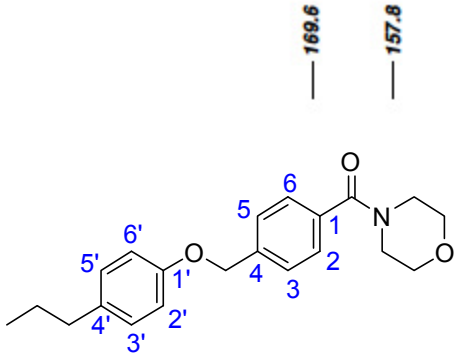


Morpholino(4-((4-propylphenoxy)methyl)phenyl)methanone, 26.



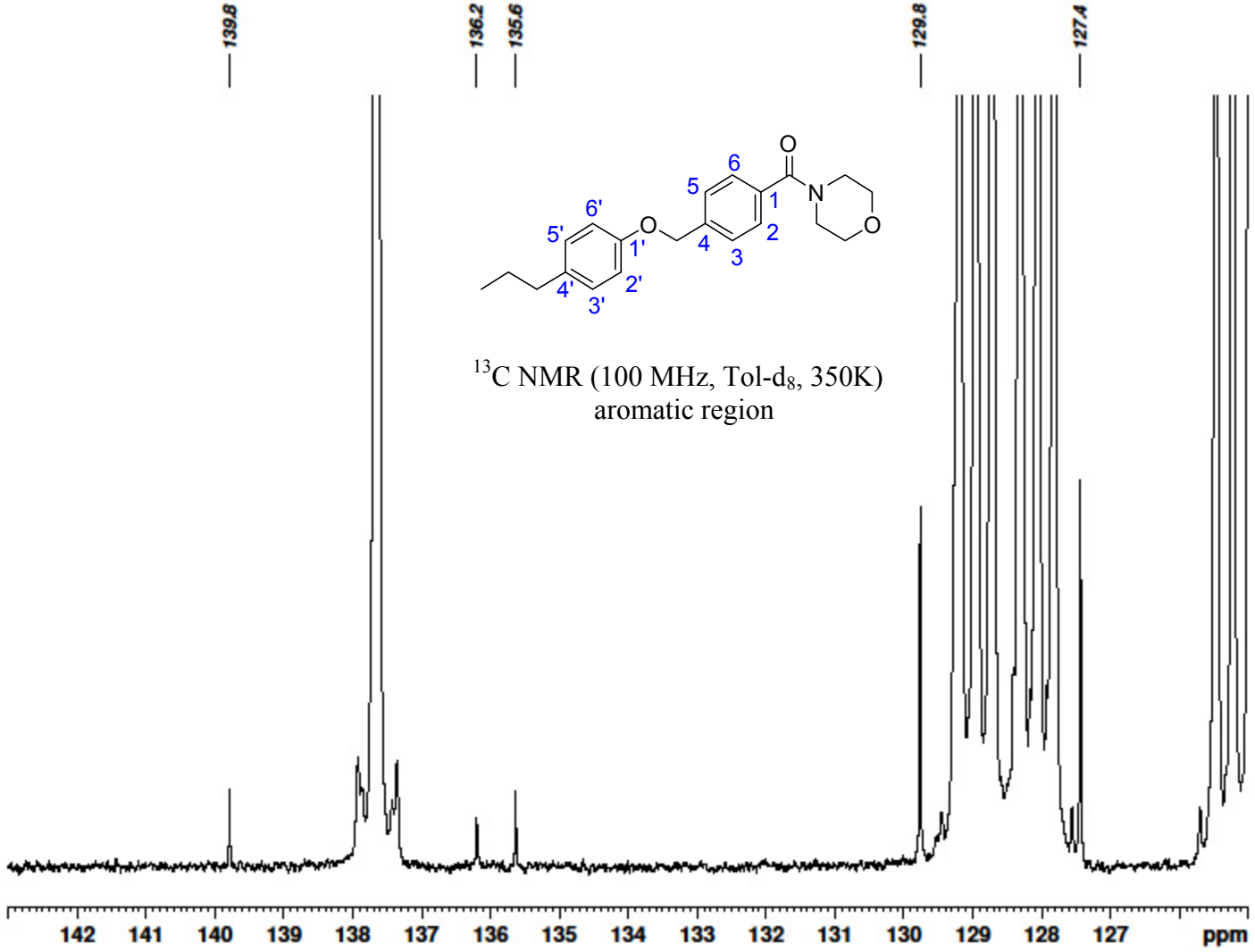
^{1}H NMR (400 MHz, Tol-d_8, 350K)

Morpholino(4-((4-propylphenoxy)methyl)phenyl)methanone, 26.



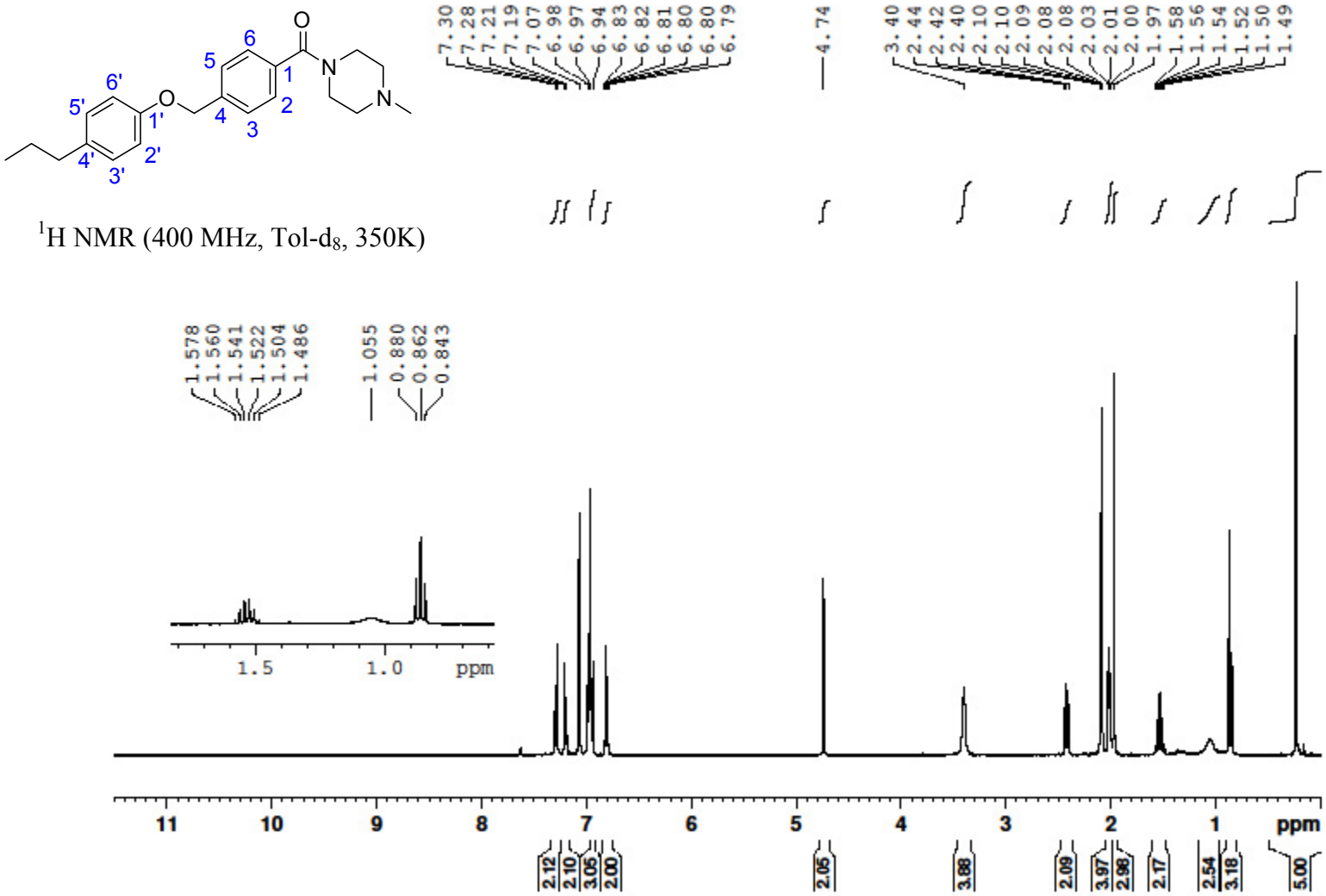
^{13}C NMR (100 MHz, Tol-d_8, 350K)

Morpholino(4-((4-propylphenoxy)methyl)phenyl)methanone, 26.



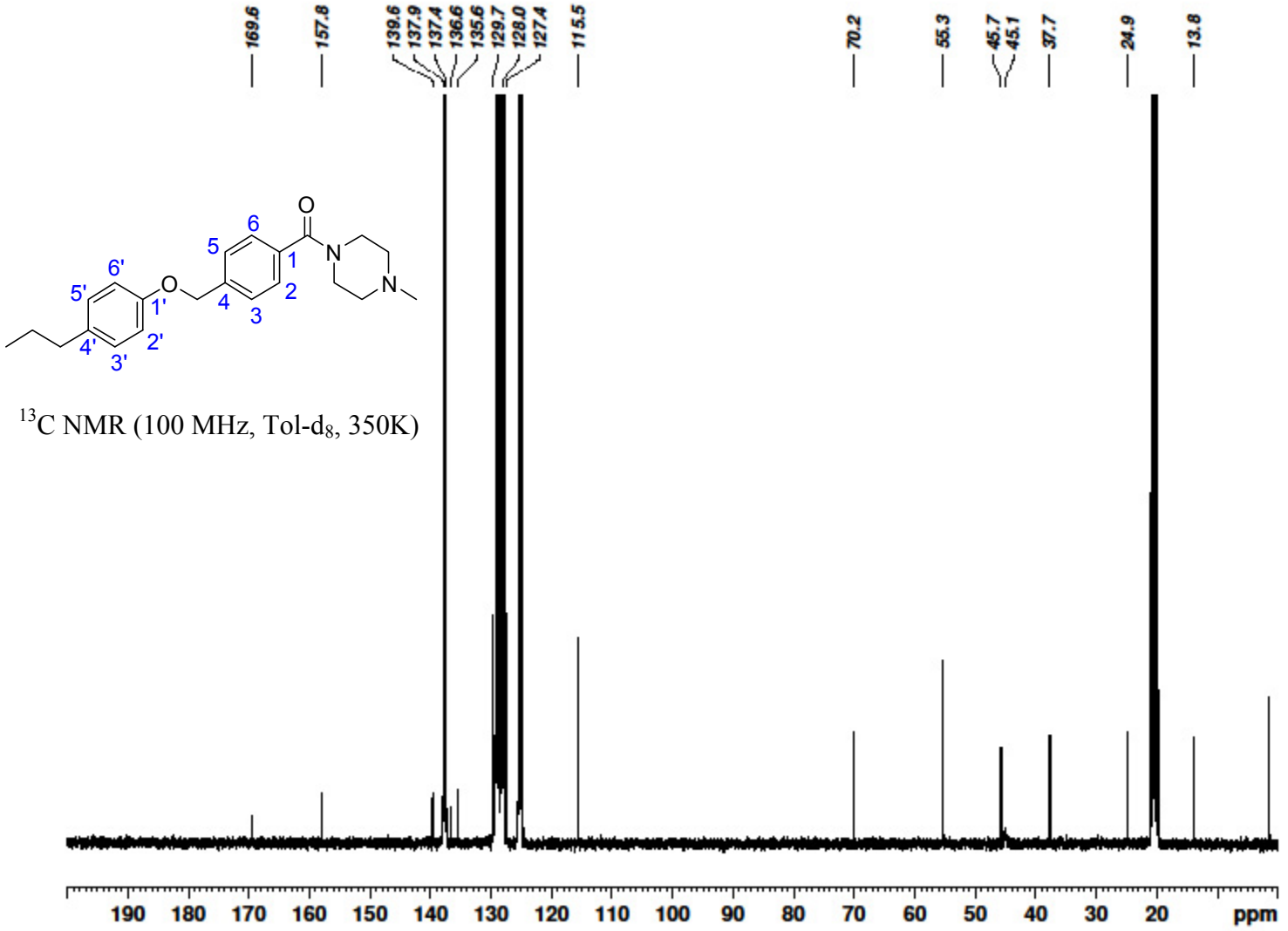
^{13}C NMR (100 MHz, Tol-d_8, 350K)
aromatic region

(4-Methylpiperazin-1-yl)(4-((4-propylphenoxy)methyl)phenyl)methanone, S61.



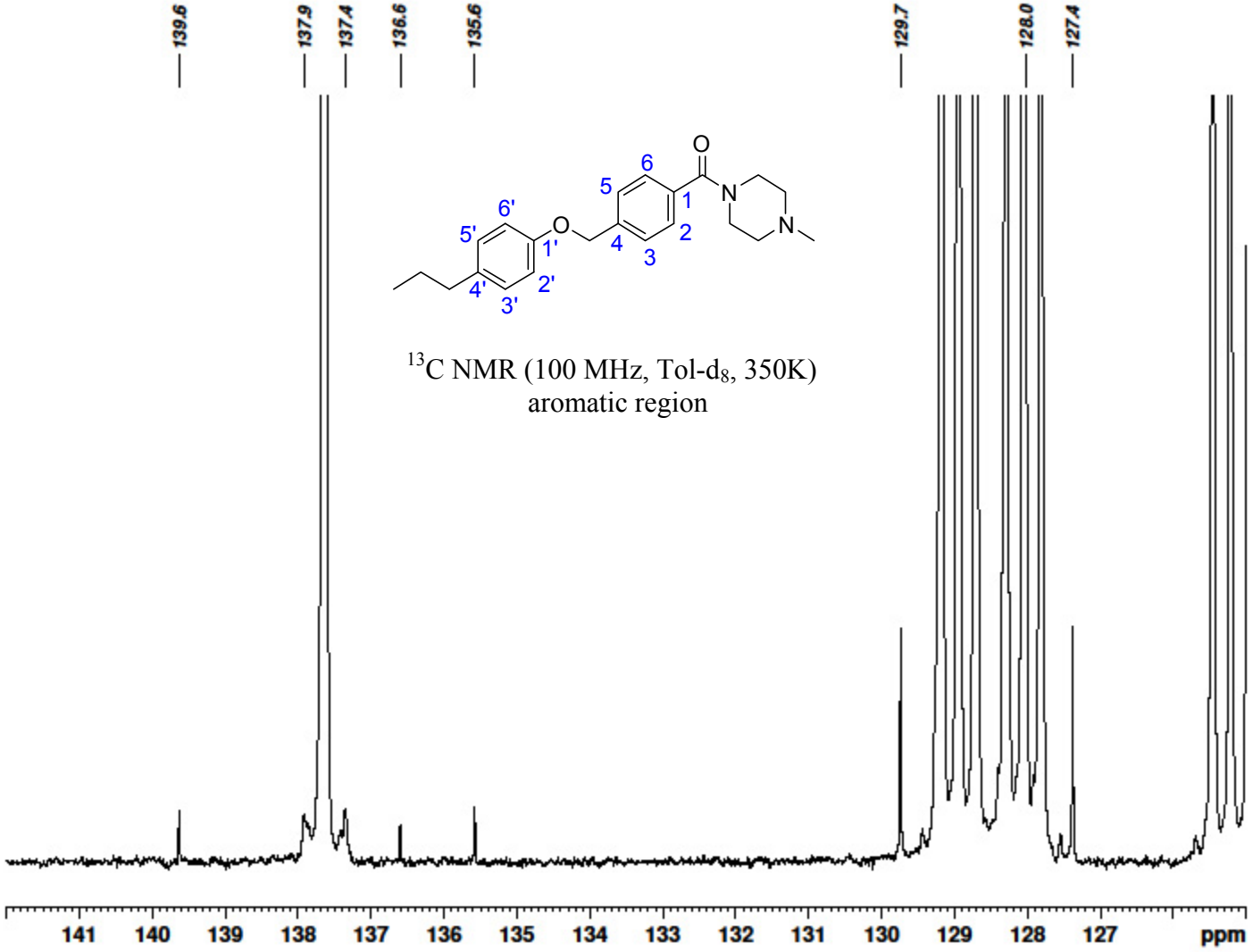
^{1}H NMR (400 MHz, Tol-d_8, 350K)

(4-Methylpiperazin-1-yl)(4-((4-propylphenoxy)methyl)phenyl)methanone, S61.



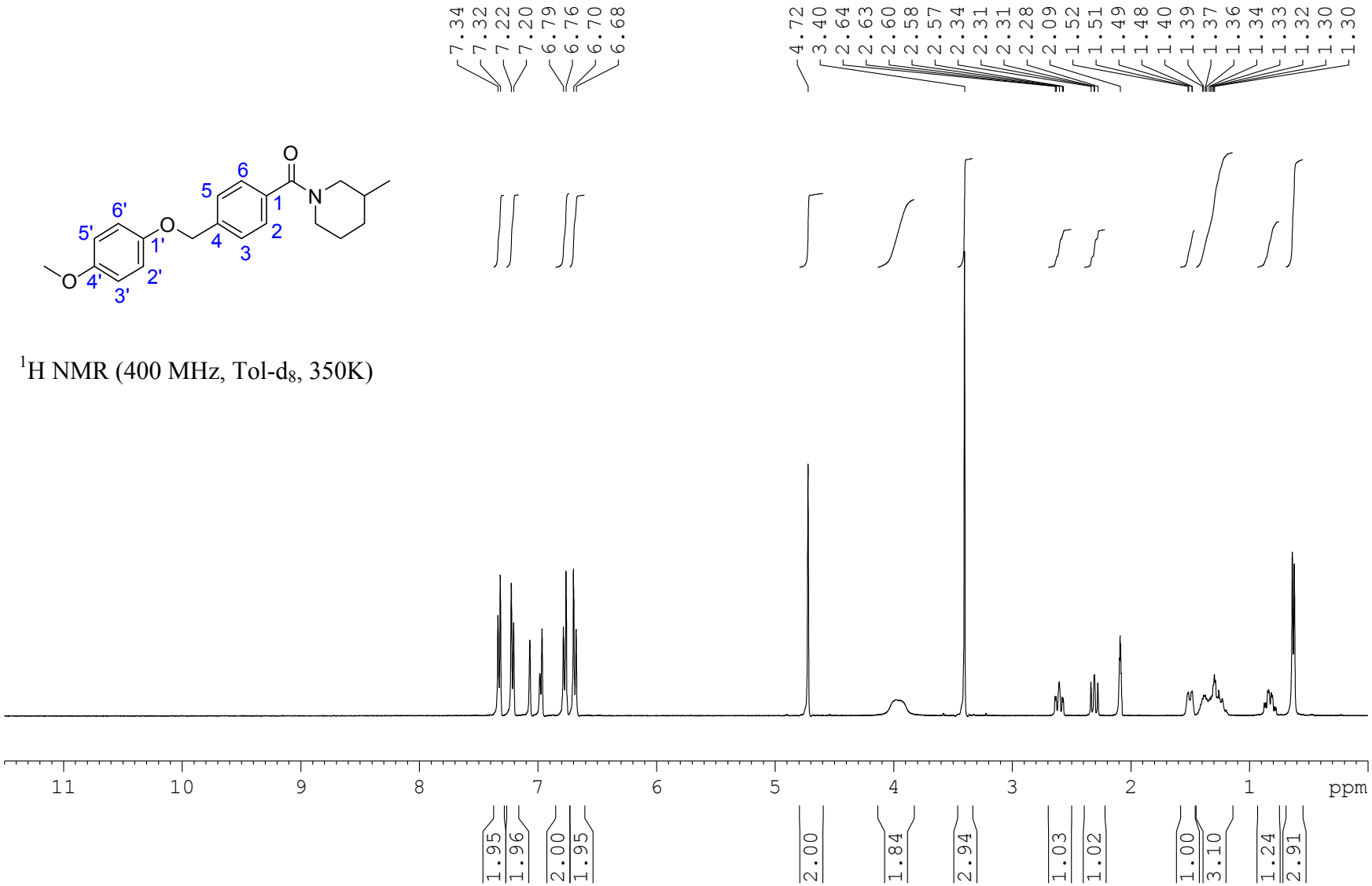
^{13}C NMR (100 MHz, Tol-d_8, 350K)

(4-Methylpiperazin-1-yl)(4-((4-propylphenoxy)methyl)phenyl)methanone, S61.



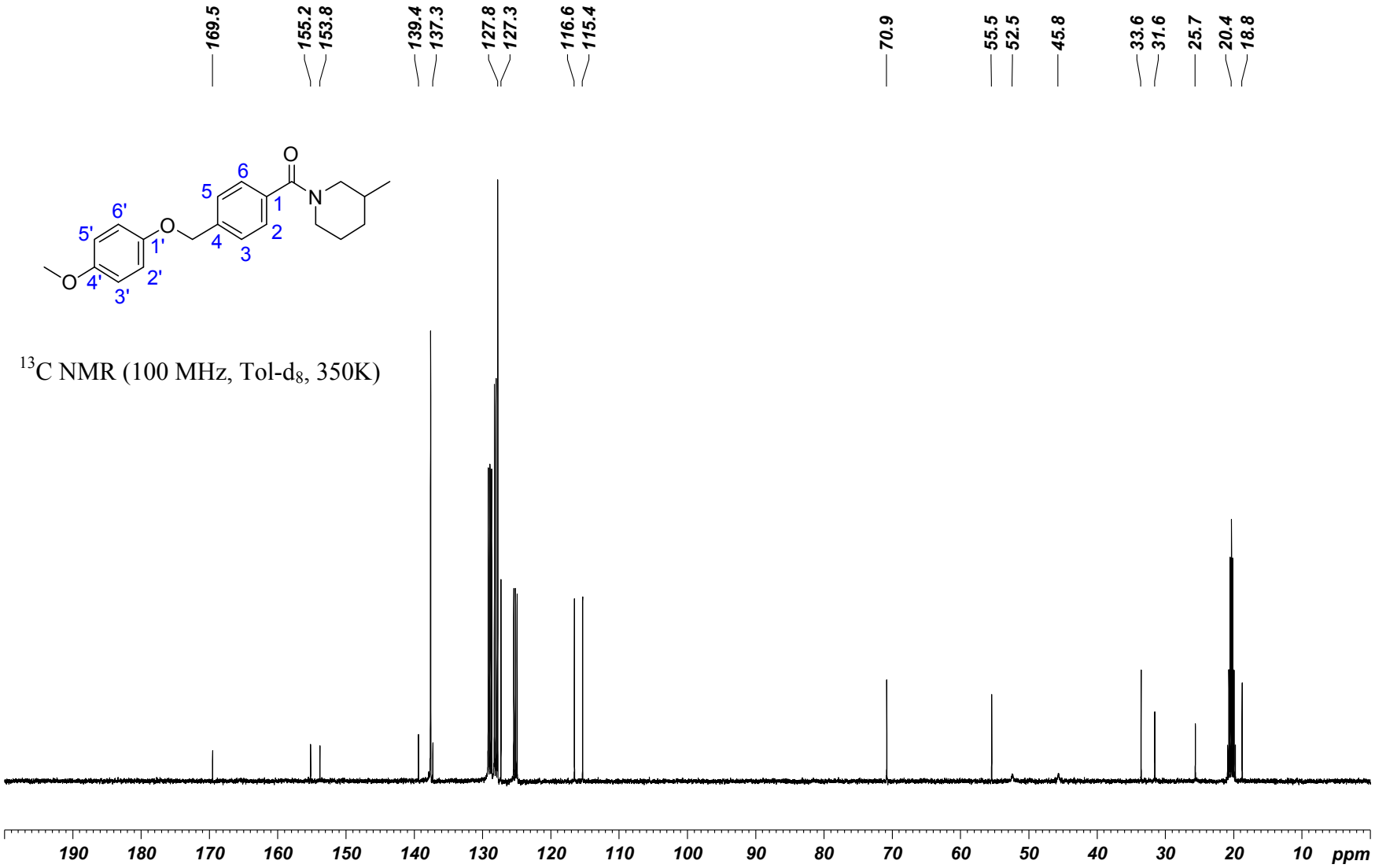
^{13}C NMR (100 MHz, Tol-d_8, 350K)
aromatic region

(4-((4-Methoxyphenoxy)methyl)phenyl)(3-methylpiperidin-1-yl)methanone; 11.



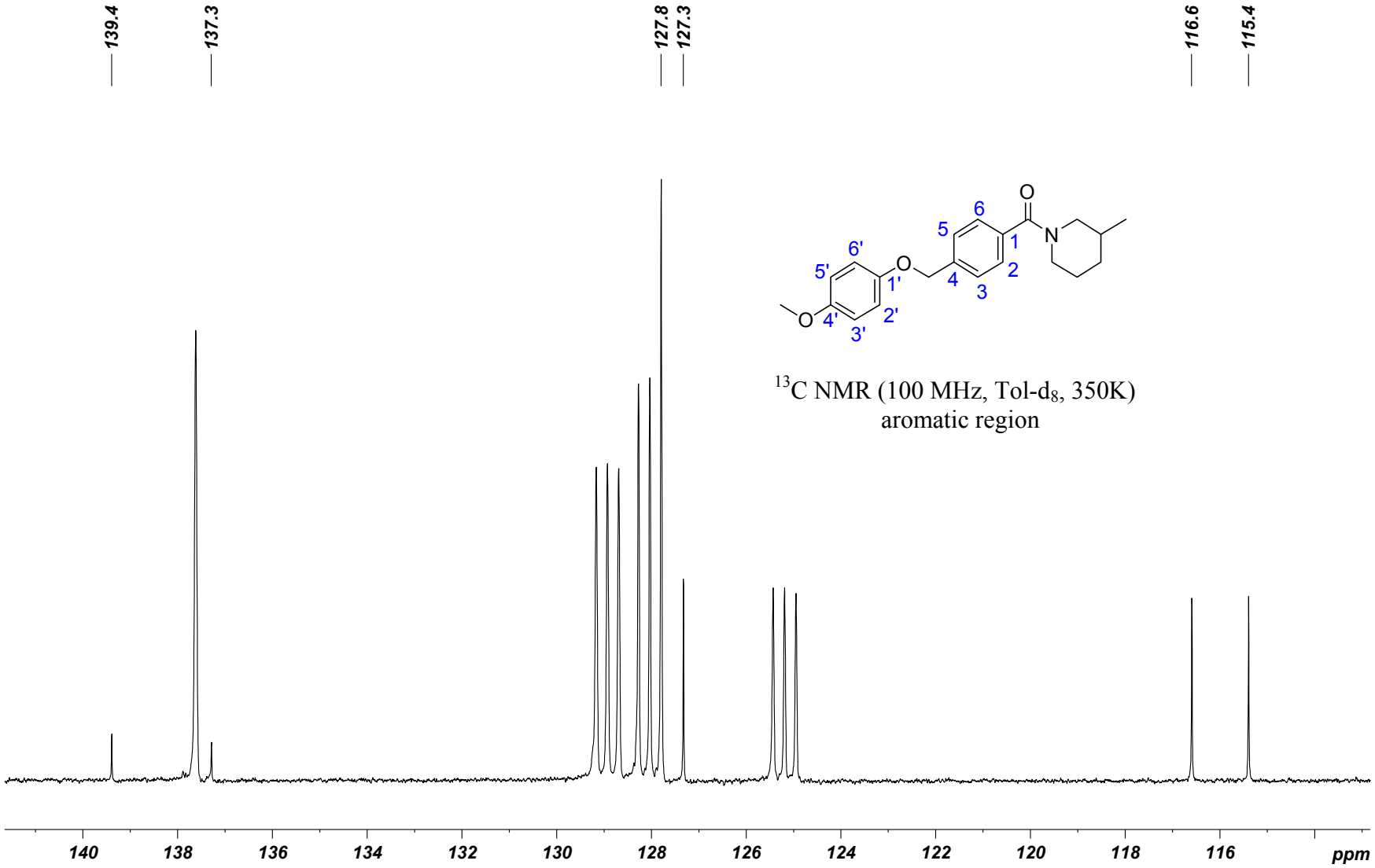
^{1}H NMR (400 MHz, Tol-d_8, 350K)

(4-((4-Methoxyphenoxy)methyl)phenyl)(3-methylpiperidin-1-yl)methanone; 11.

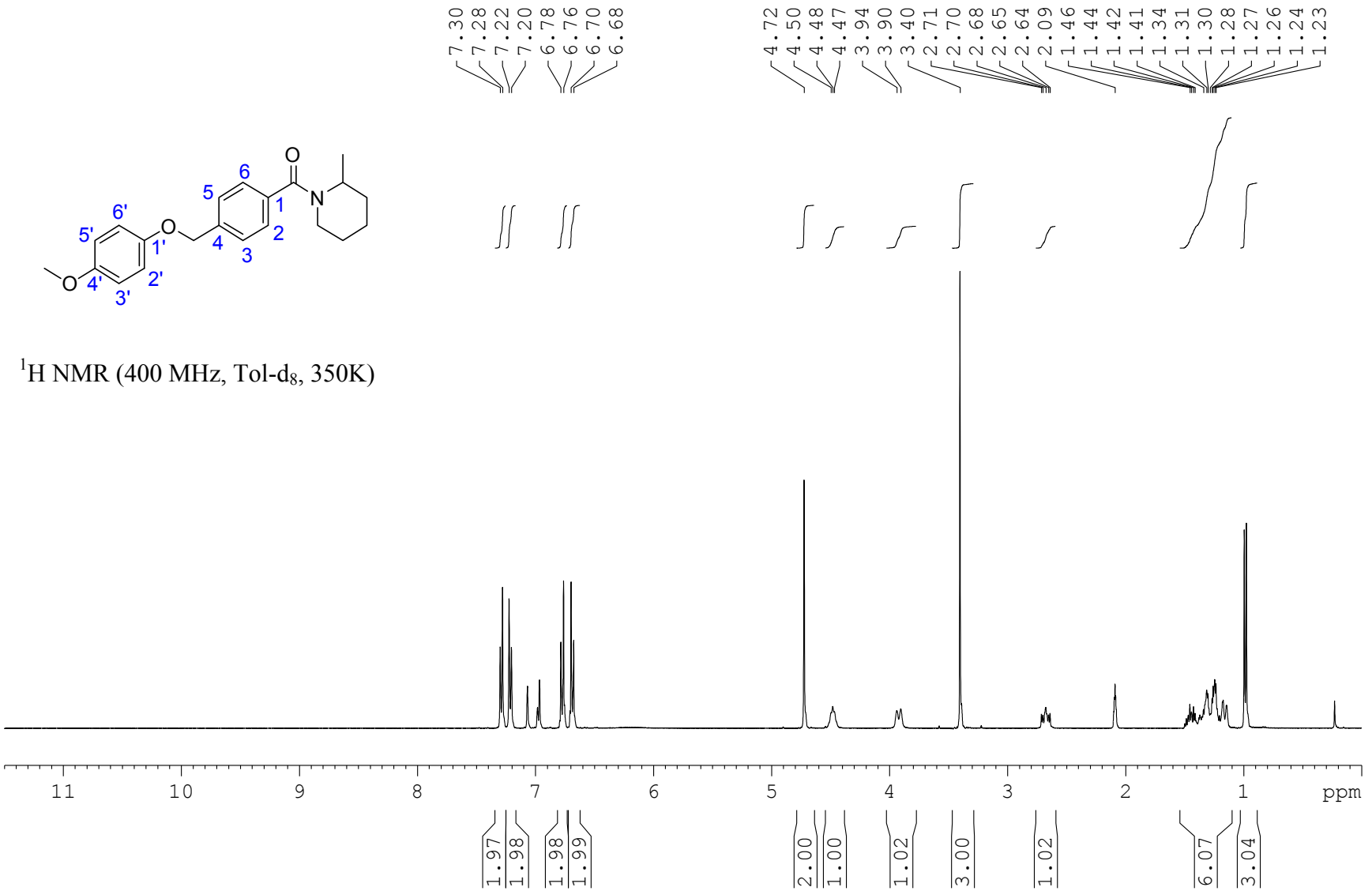


^{13}C NMR (100 MHz, Tol-d_8, 350K)

(4-((4-Methoxyphenoxy)methyl)phenyl)(3-methylpiperidin-1-yl)methanone; 11.

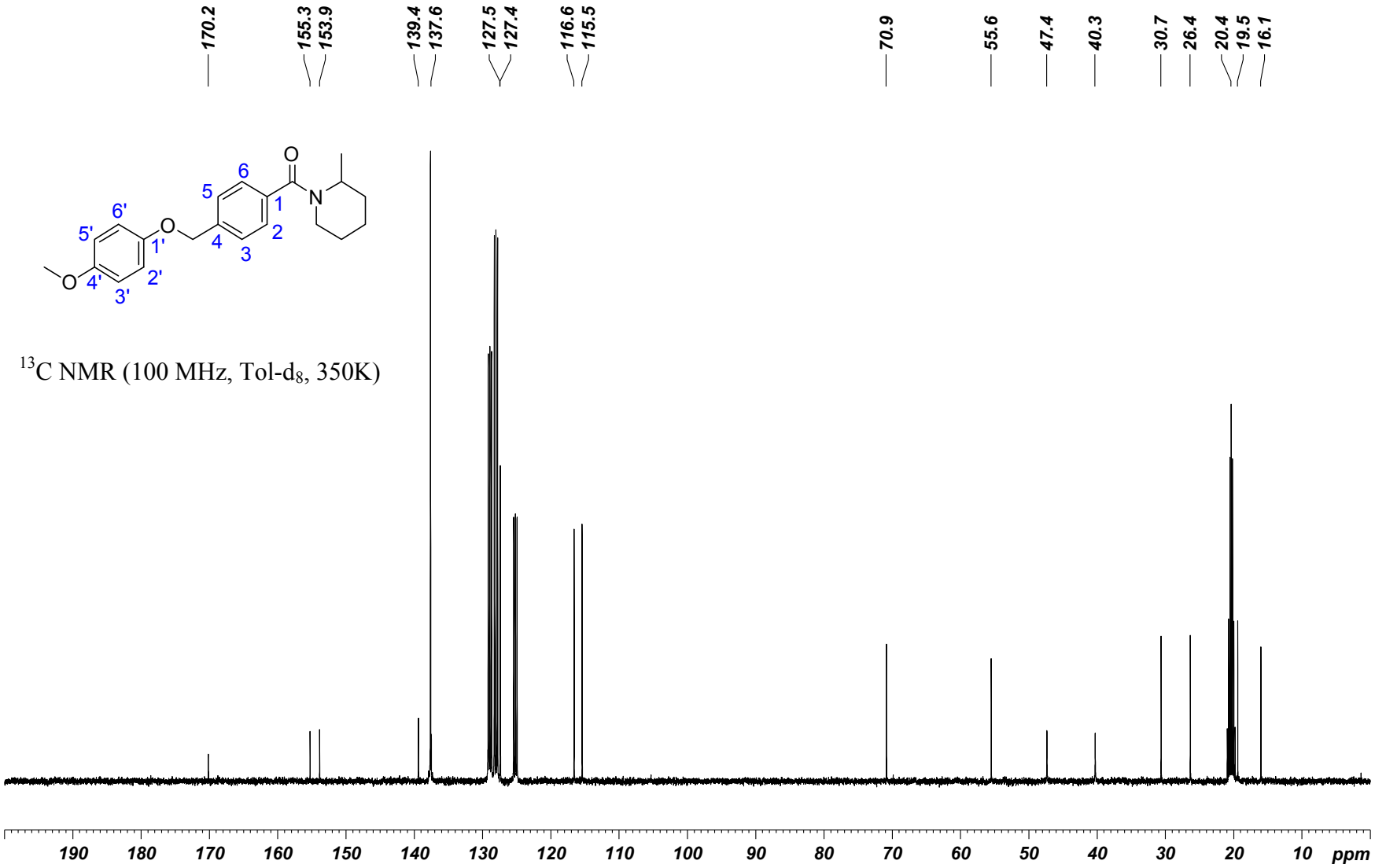


(4-((4-Methoxyphenoxy)methyl)phenyl)(2-methylpiperidin-1-yl)methanone; 16.



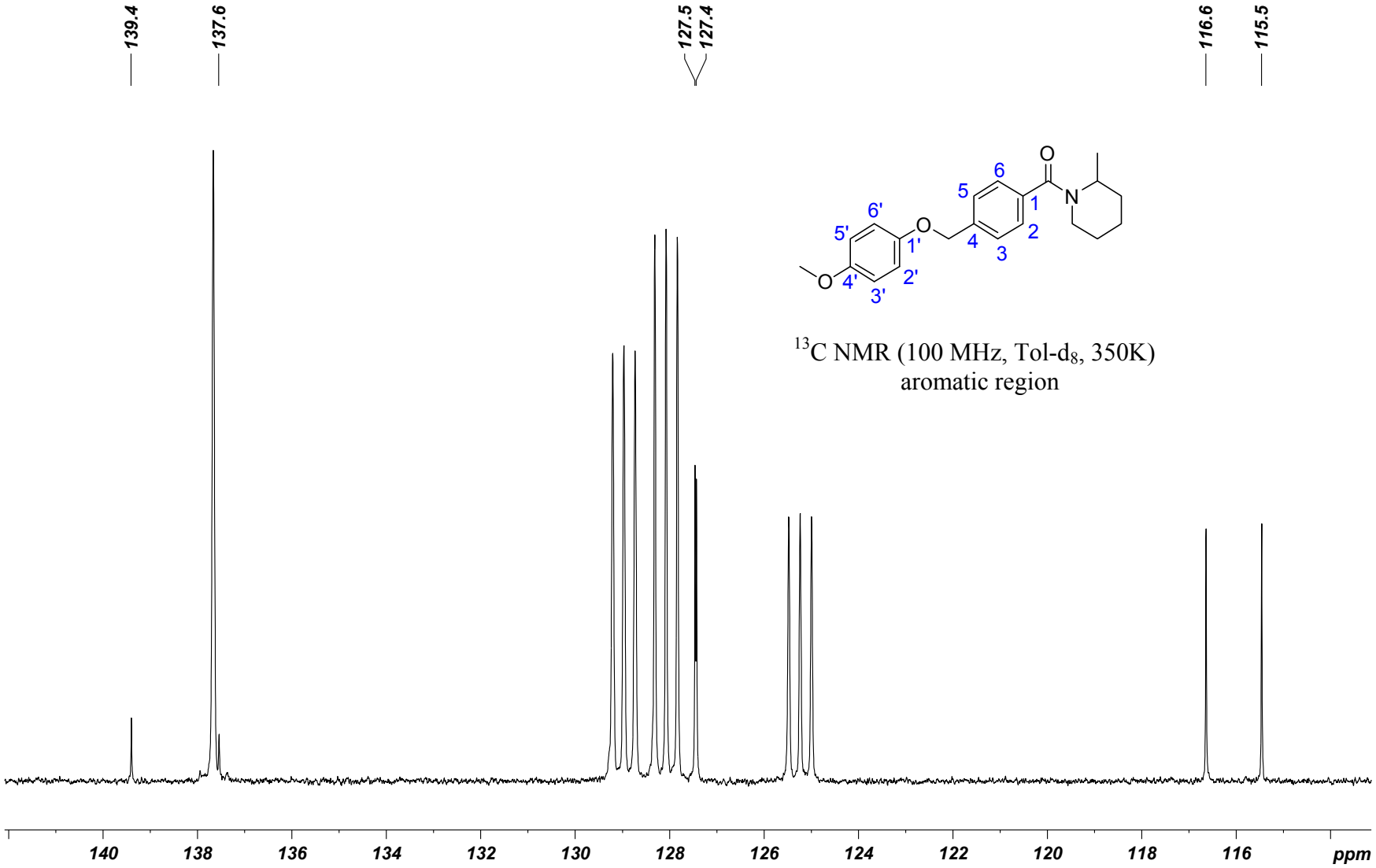
^{1}H NMR (400 MHz, Tol-d_8, 350K)

(4-((4-Methoxyphenoxy)methyl)phenyl)(2-methylpiperidin-1-yl)methanone; 16.



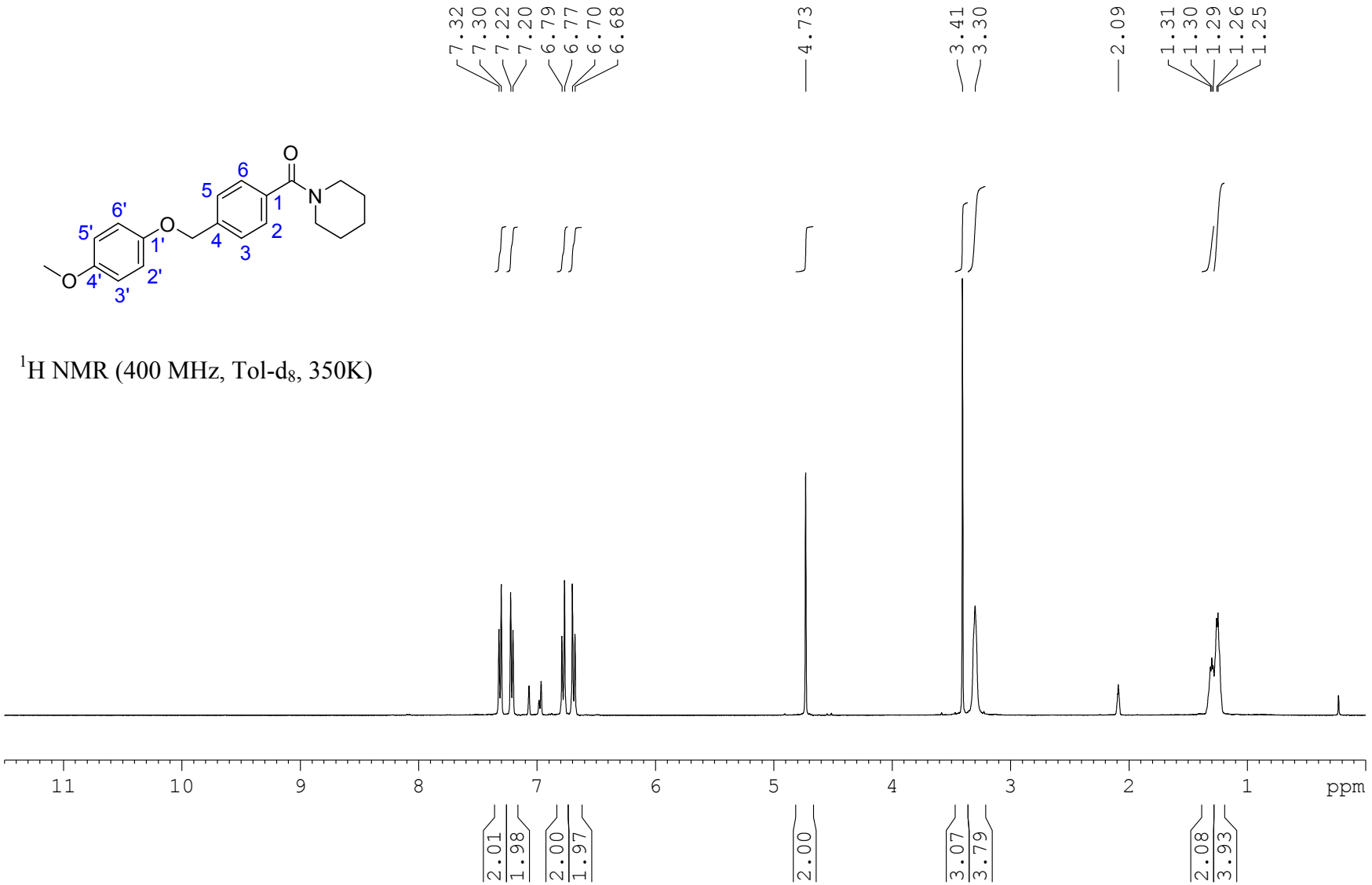
^{13}C NMR (100 MHz, Tol-d_8, 350K)

(4-((4-Methoxyphenoxy)methyl)phenyl)(2-methylpiperidin-1-yl)methanone; 16.



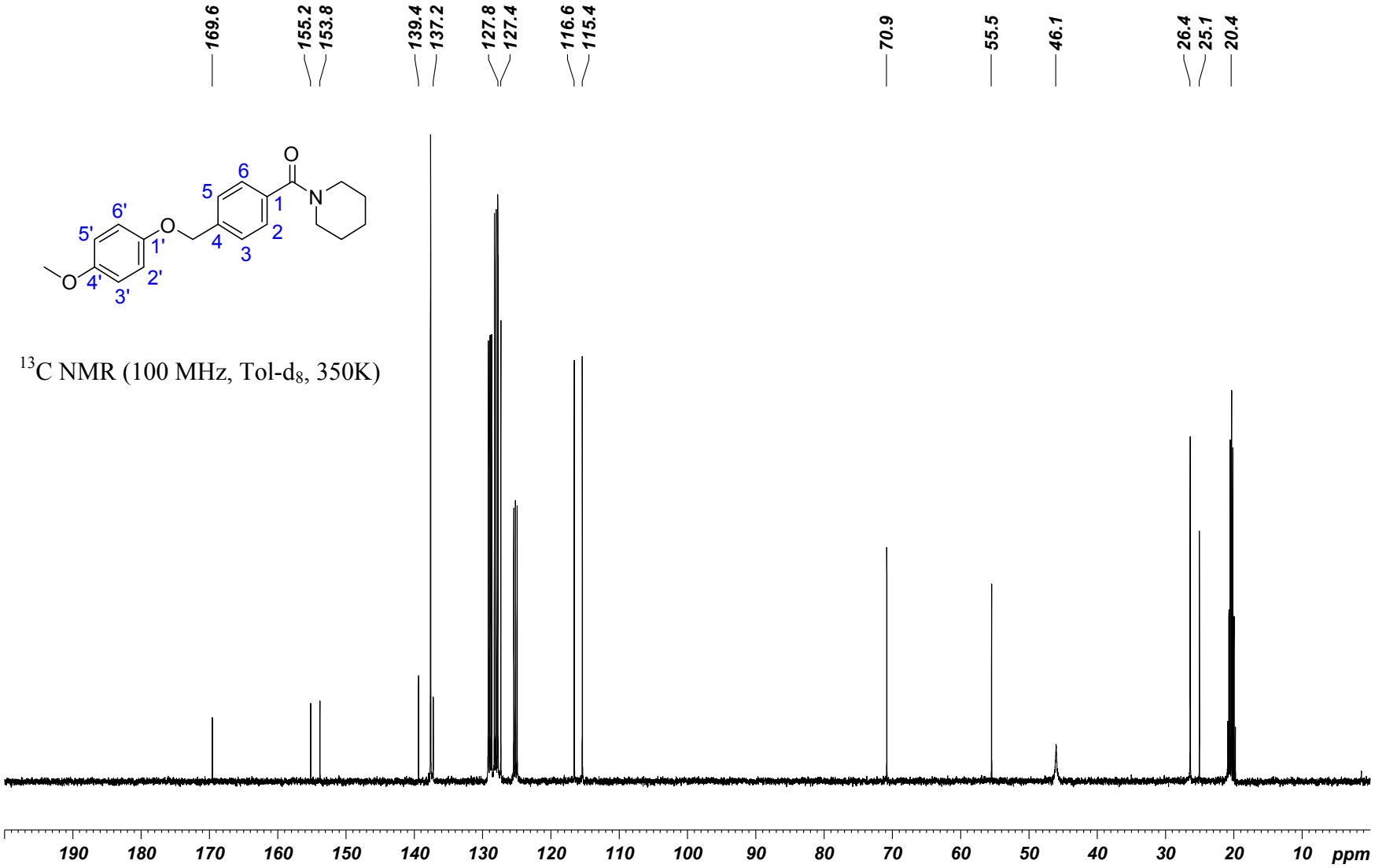
^{13}C NMR (100 MHz, Tol-d$_8$, 350K)
aromatic region

(4-((4-Methoxyphenoxy)methyl)phenyl)(piperidin-1-yl)methanone; S62.



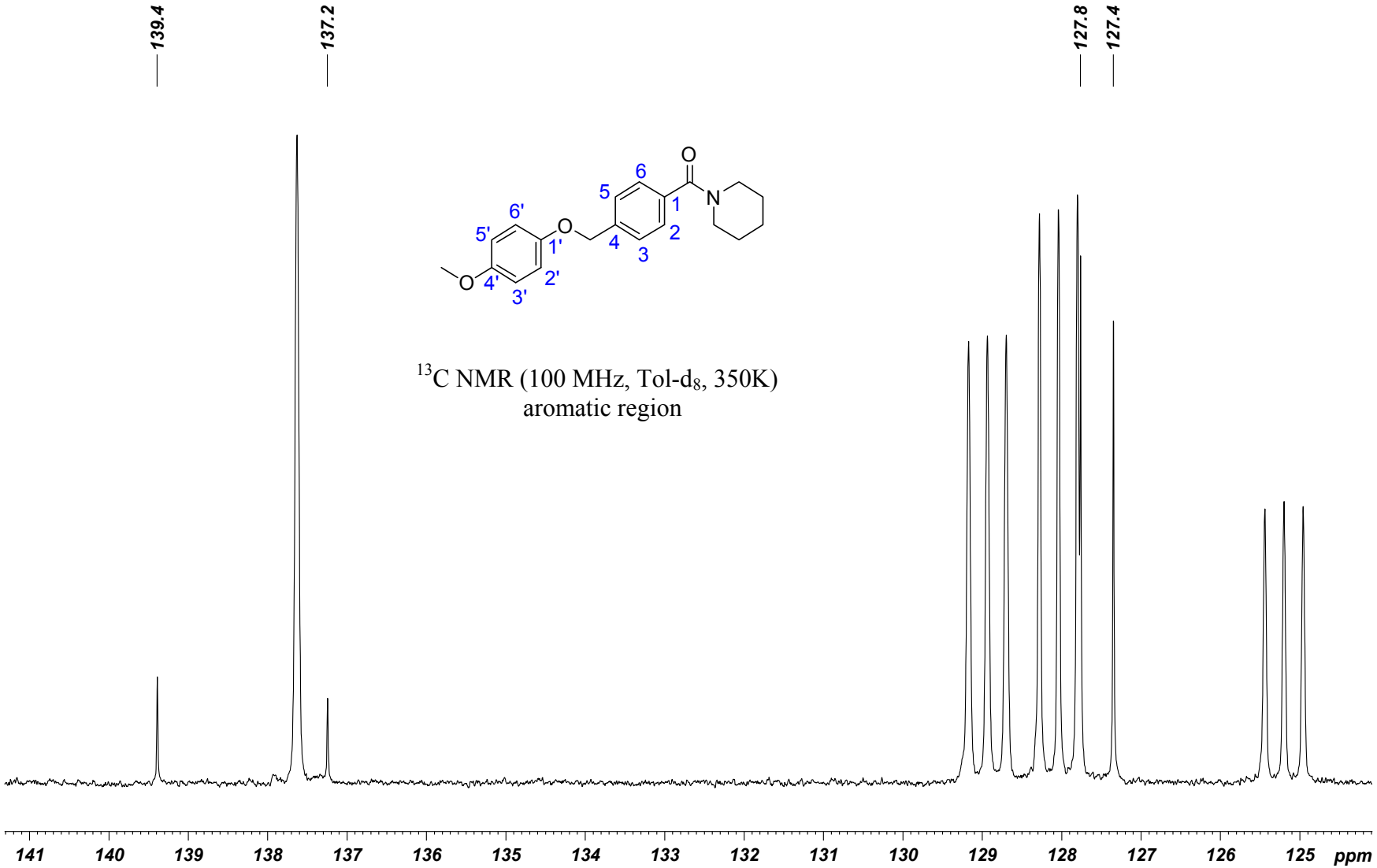
^{1}H NMR (400 MHz, Tol-d_8, 350K)

(4-((4-Methoxyphenoxy)methyl)phenyl)(piperidin-1-yl)methanone; S62.



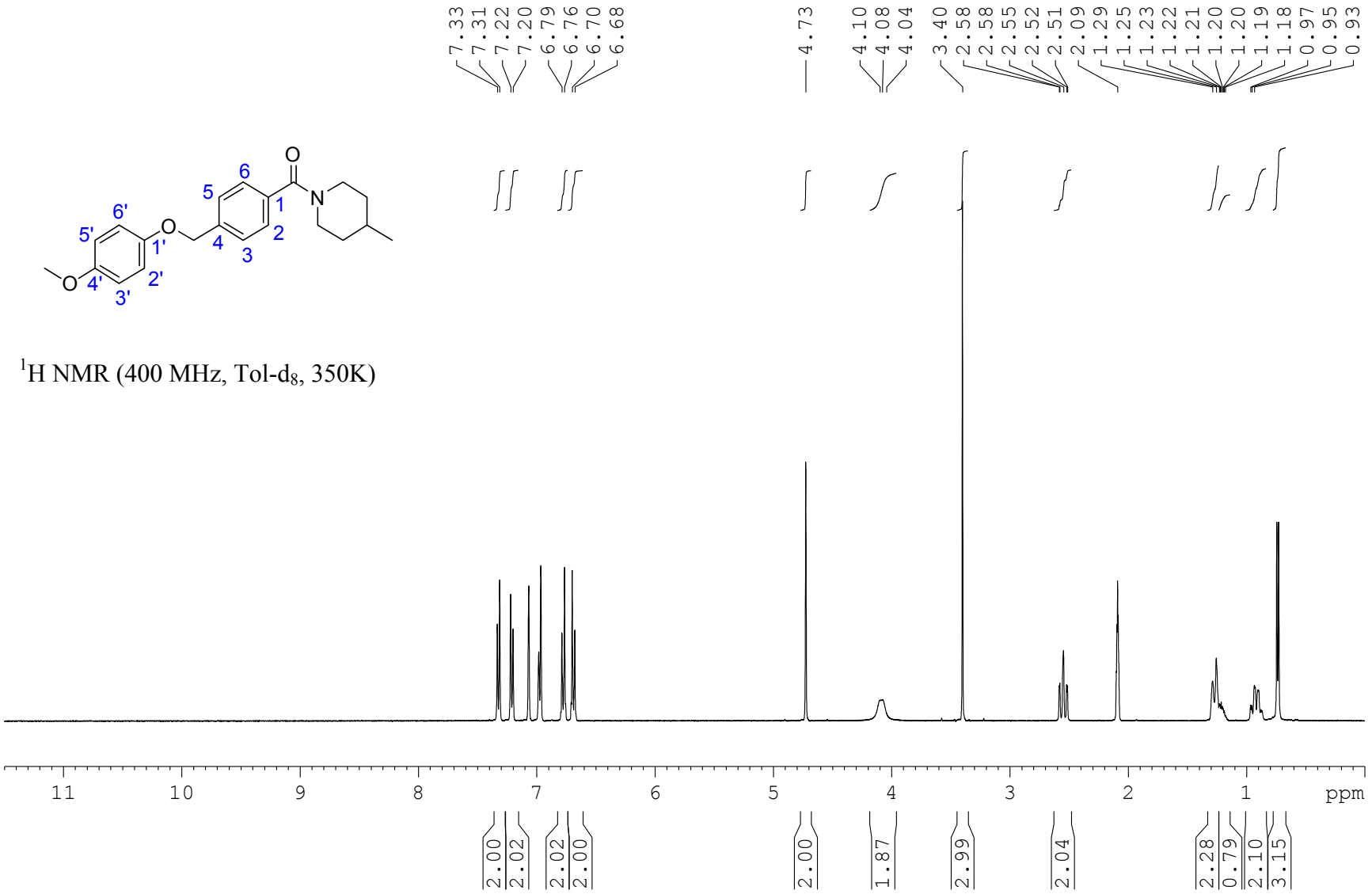
^{13}C NMR (100 MHz, Tol-d_8, 350K)

(4-((4-Methoxyphenoxy)methyl)phenyl)(piperidin-1-yl)methanone; S62.



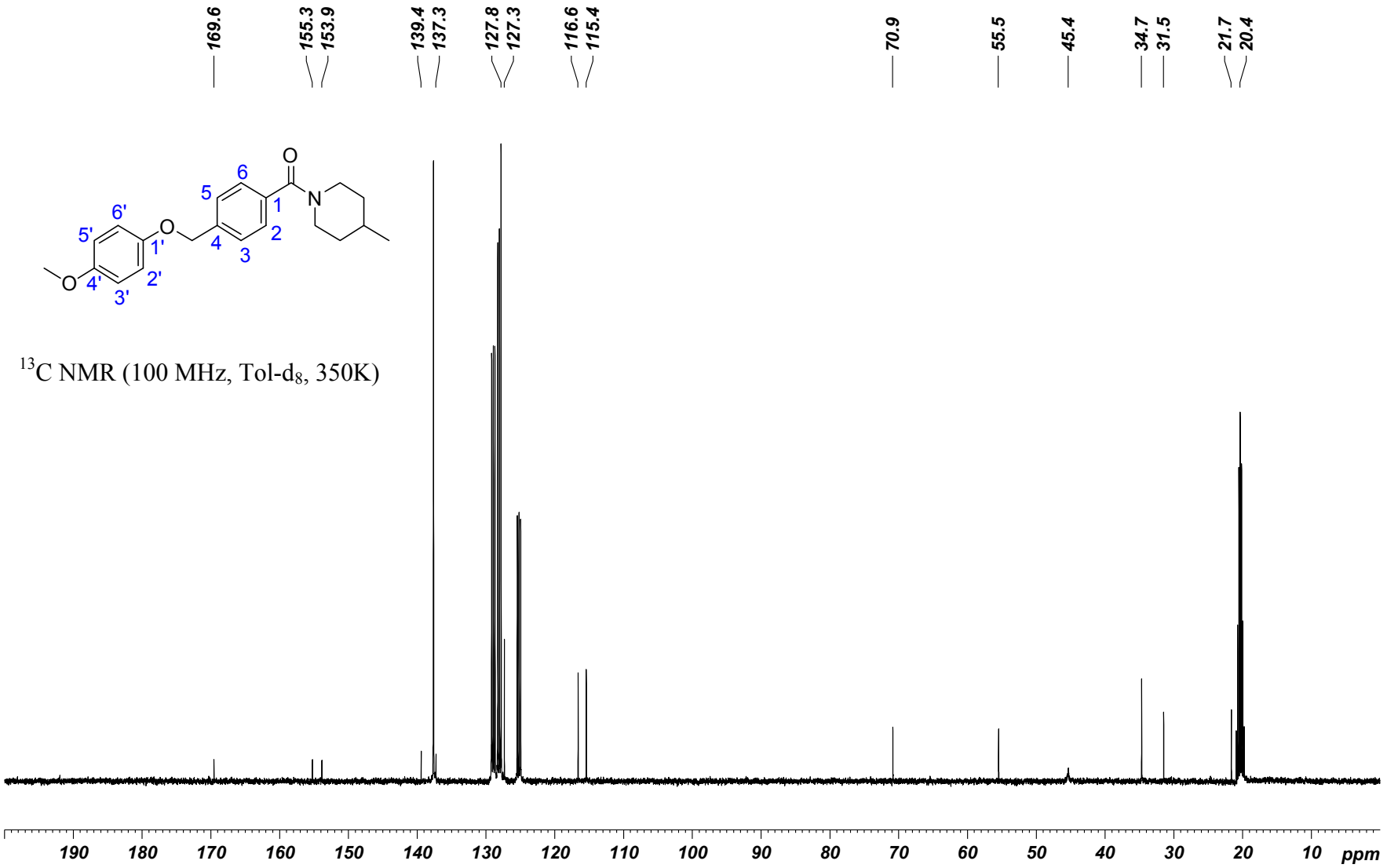
^{13}C NMR (100 MHz, Tol-d_8, 350K)
aromatic region

(4-((4-Methoxyphenoxy)methyl)phenyl)(4-methylpiperidin-1-yl)methanone; 21.



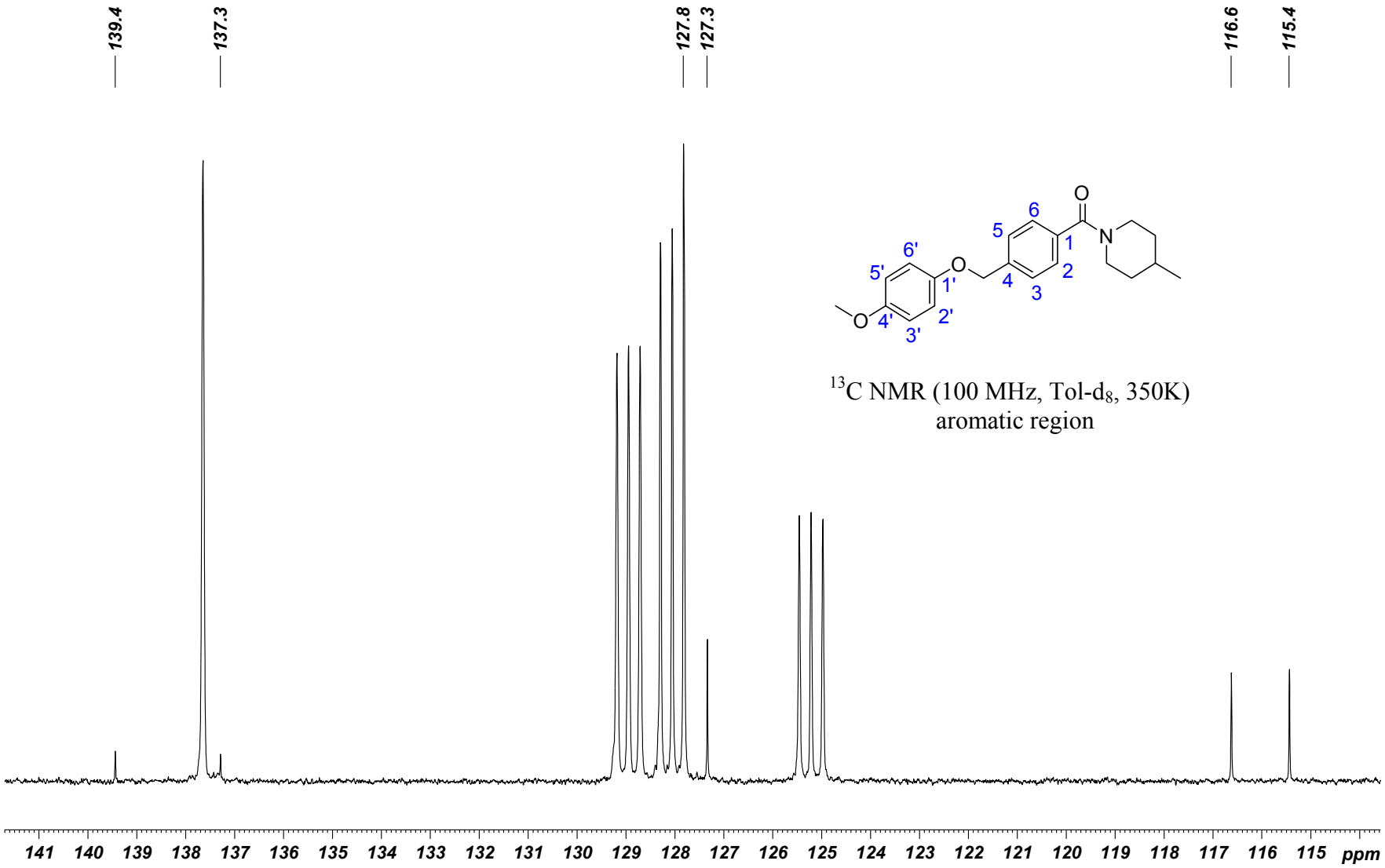
^{1}H NMR (400 MHz, Tol-d_8, 350K)

(4-((4-Methoxyphenoxy)methyl)phenyl)(4-methylpiperidin-1-yl)methanone; 21.



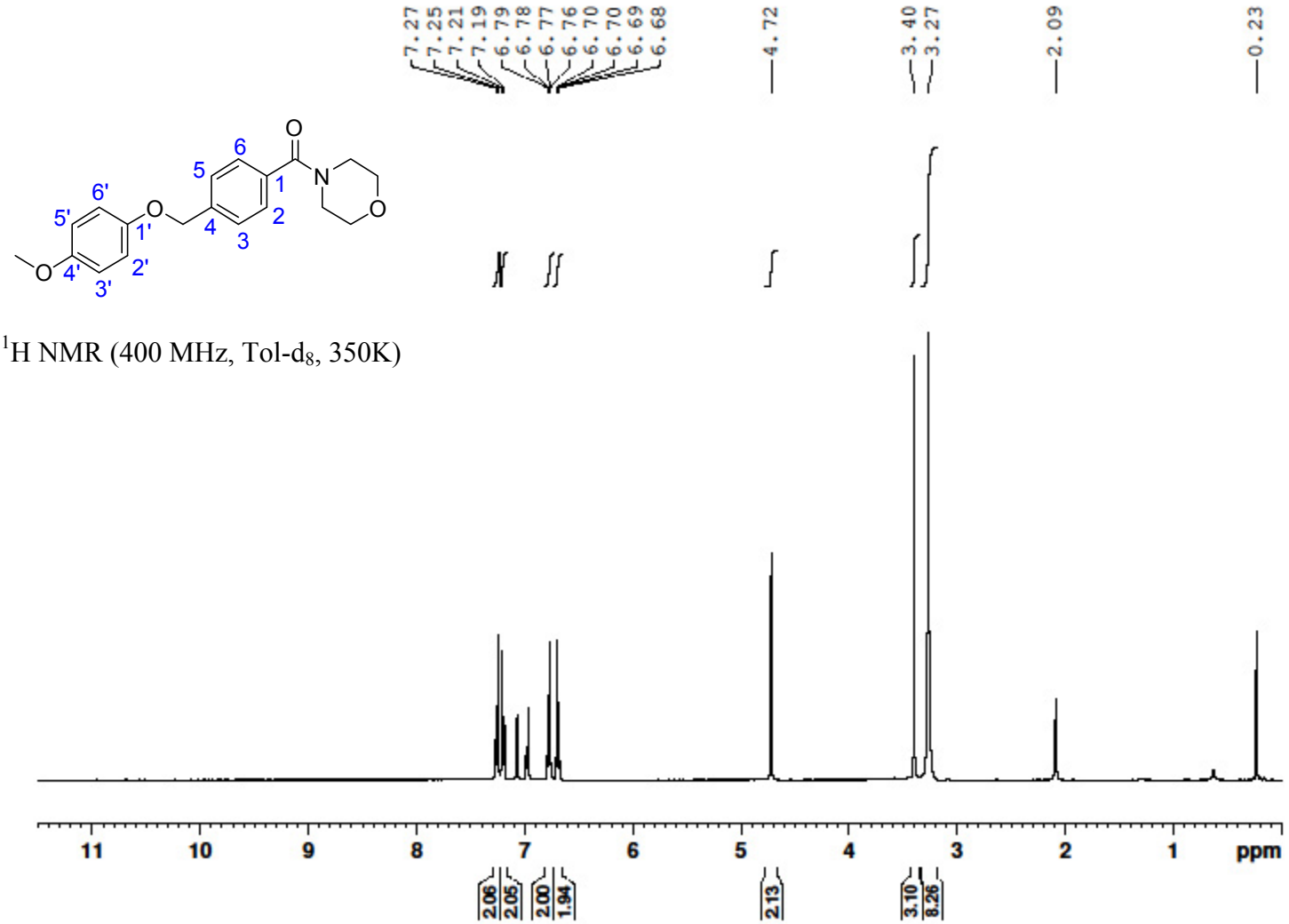
^{13}C NMR (100 MHz, Tol-d_8, 350K)

(4-((4-Methoxyphenoxy)methyl)phenyl)(4-methylpiperidin-1-yl)methanone; 21.



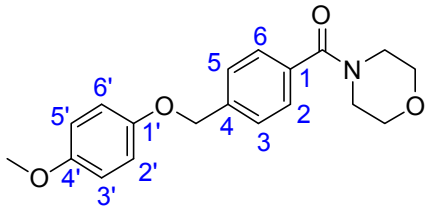
^{13}C NMR (100 MHz, Tol-d_8, 350K)
aromatic region

(4-((4-Methoxyphenoxy)methyl)phenyl)(morpholino)methanone; S63.



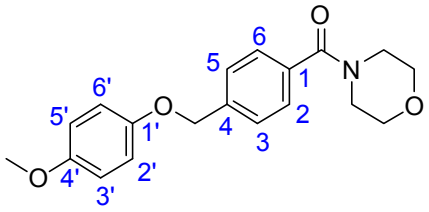
^{1}H NMR (400 MHz, Tol-d_8, 350K)

(4-((4-Methoxyphenoxy)methyl)phenyl)(morpholino)methanone; S63.



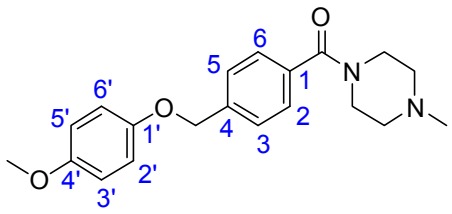
^{13}C NMR (100 MHz, Tol-d_8, 350K)

(4-((4-Methoxyphenoxy)methyl)phenyl)(morpholino)methanone; S63.



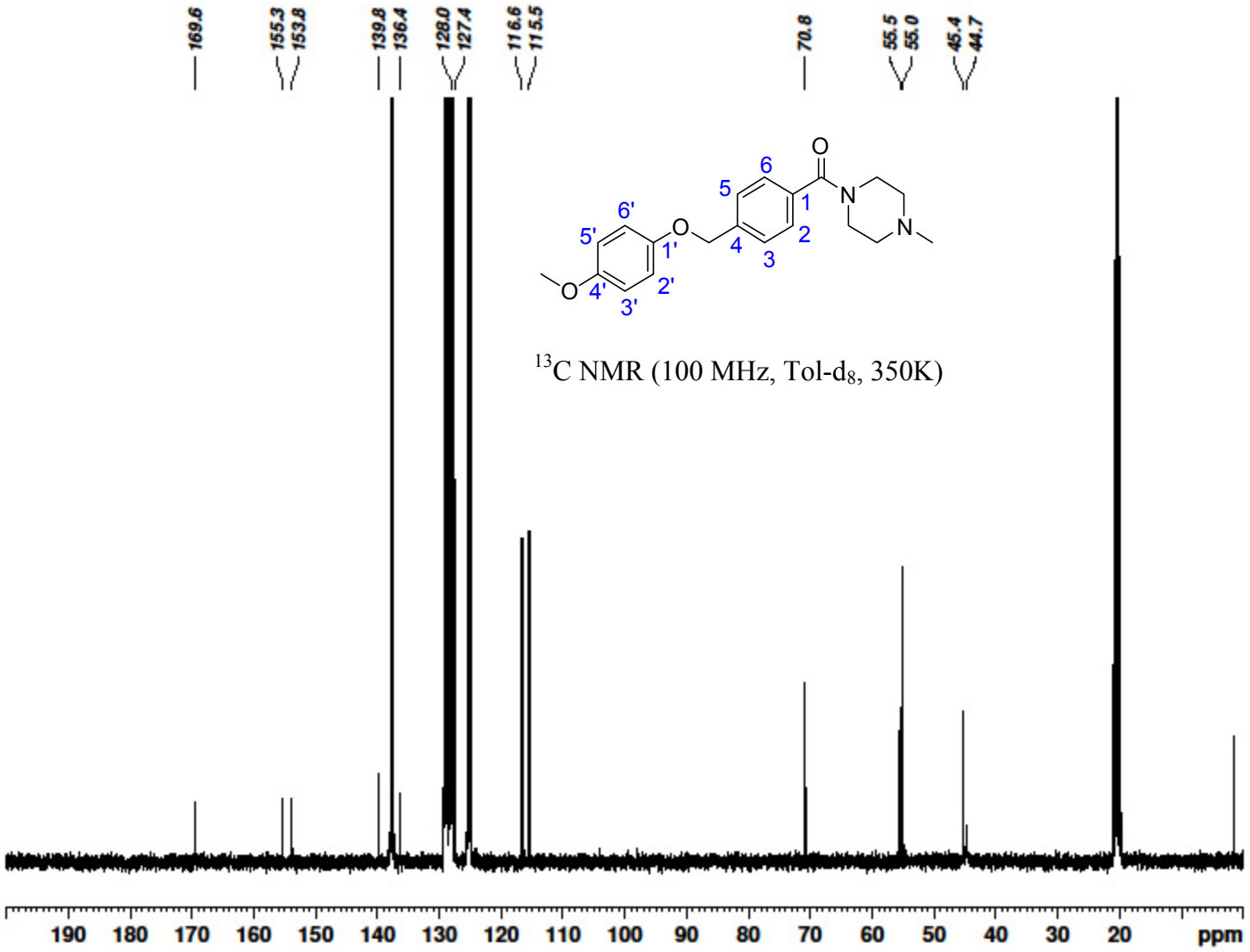
^{13}C NMR (100 MHz, Tol-d_8, 350K)
aromatic region

(4-((4-Methoxyphenoxy)methyl)phenyl)(4-methylpiperazin-1-yl)methanone; 30.



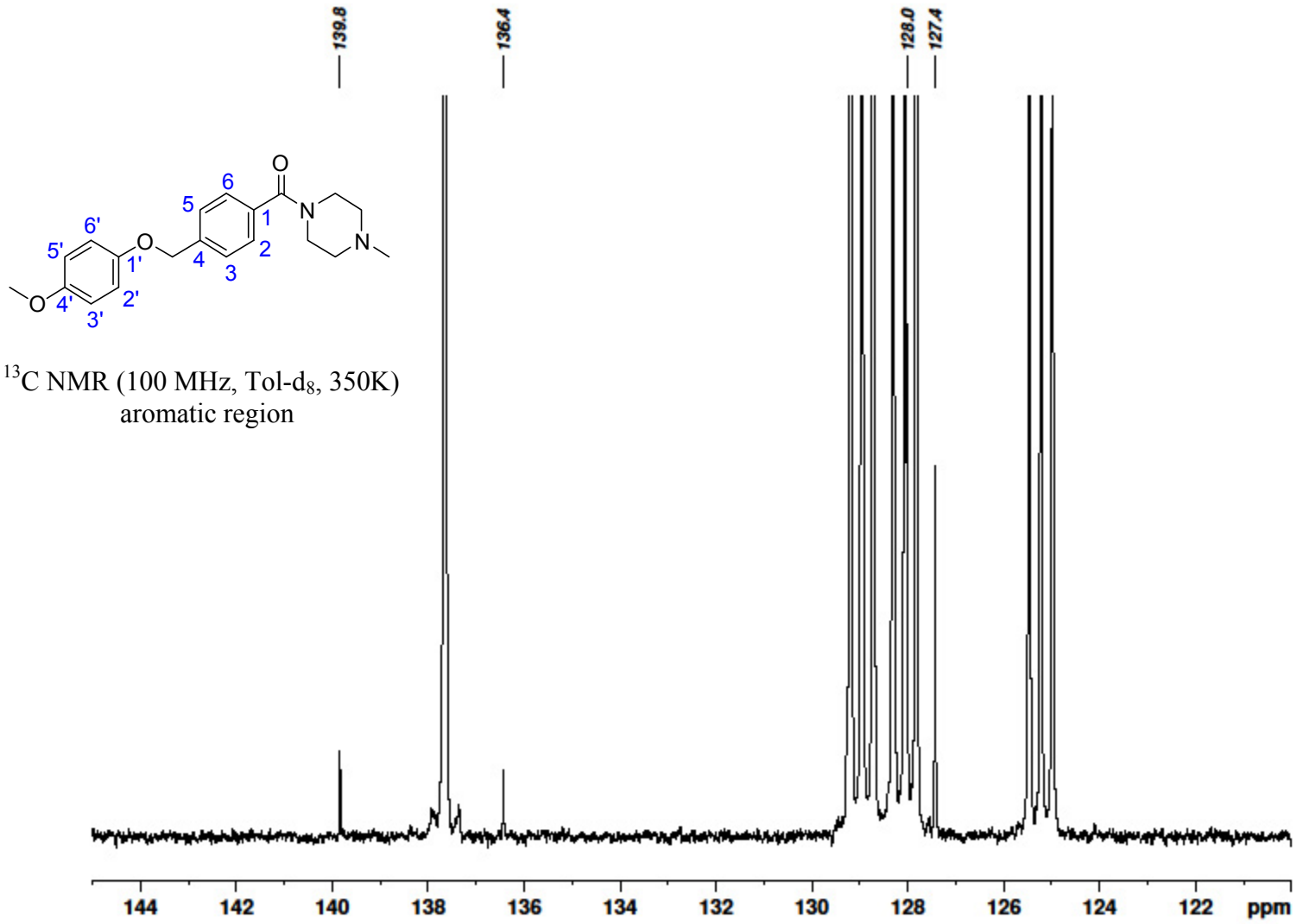
^{1}H NMR (400 MHz, Tol-d_8, 350K)

(4-((4-Methoxyphenoxy)methyl)phenyl)(4-methylpiperazin-1-yl)methanone; 30.



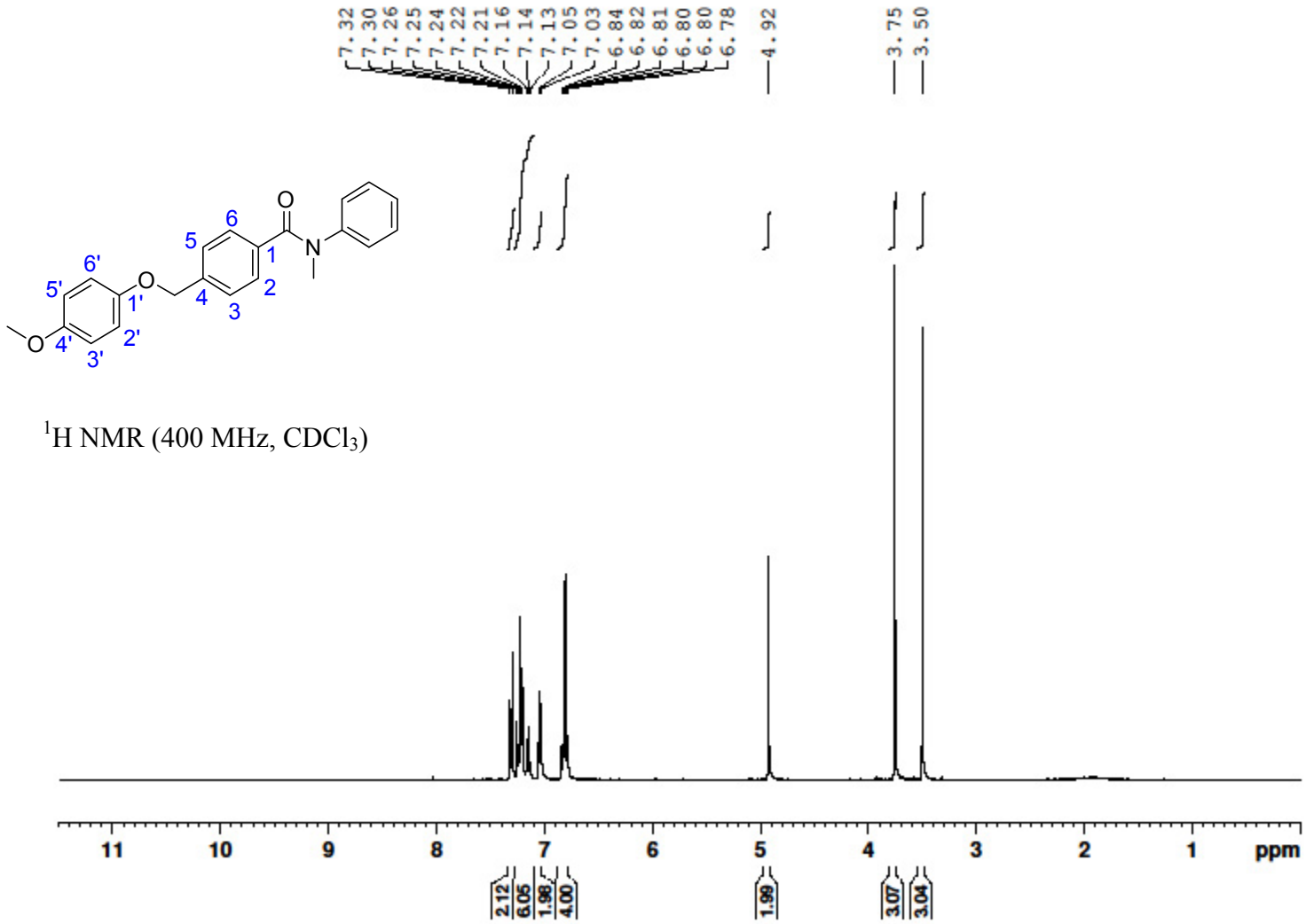
^{13}C NMR (100 MHz, Tol-d_8, 350K)

(4-((4-Methoxyphenoxy)methyl)phenyl)(4-methylpiperazin-1-yl)methanone; 30.



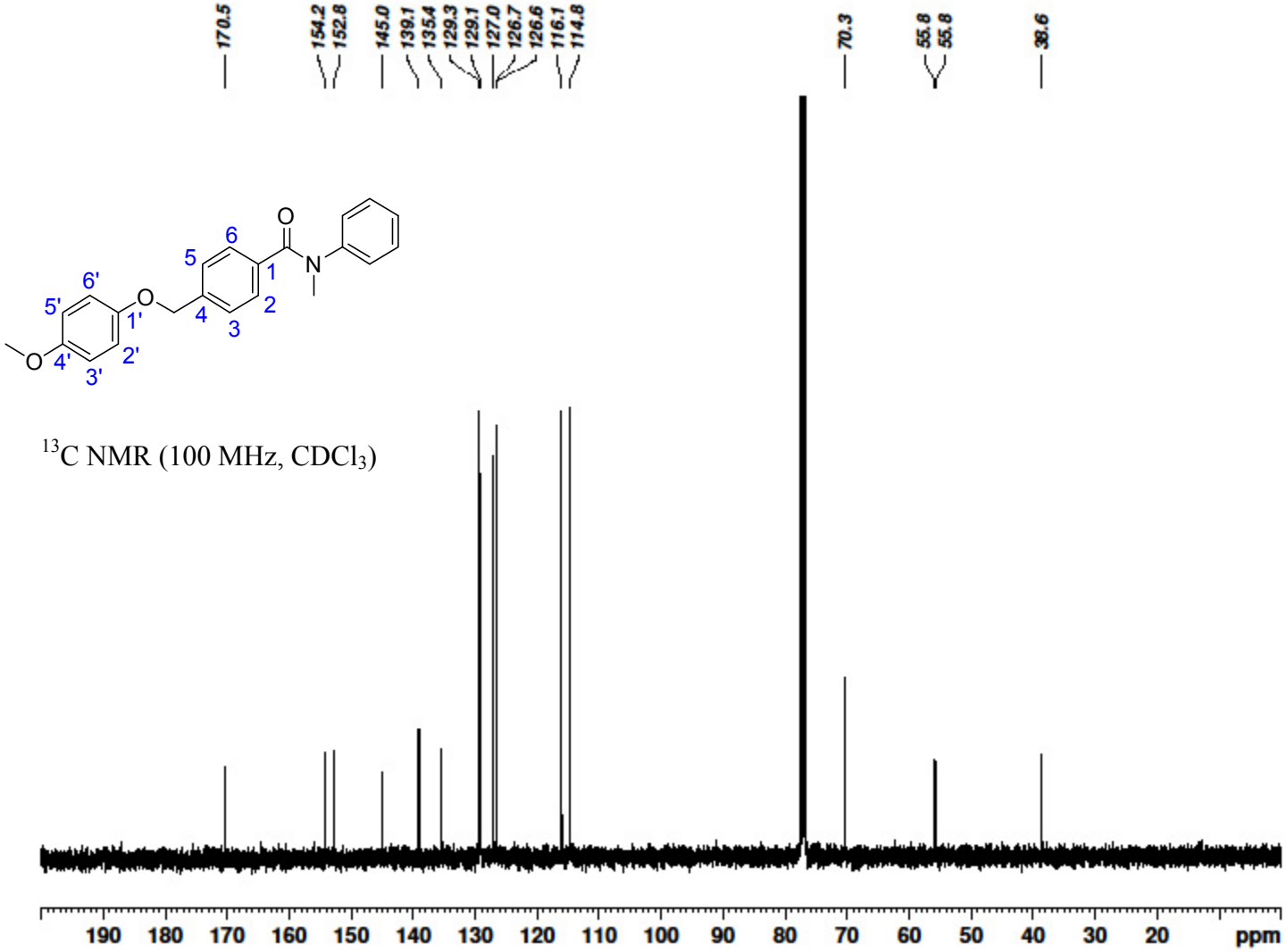
^{13}C NMR (100 MHz, Tol-d_8, 350K)
aromatic region

4-((4-Methoxyphenoxy)methyl)-*N*-methyl-*N*-phenylbenzamide; 30.

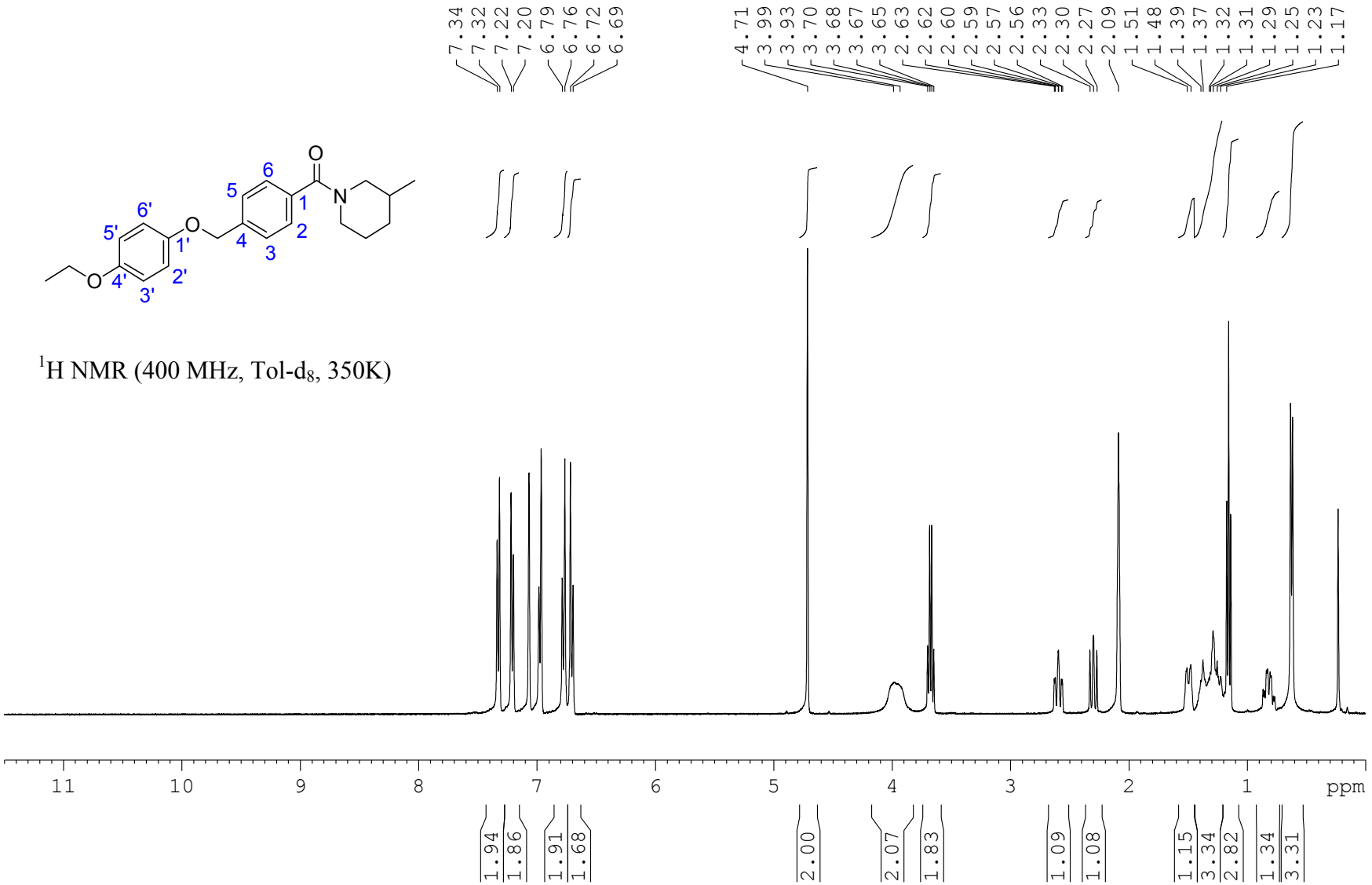


^{1}H NMR (400 MHz, $CDCl_3$)

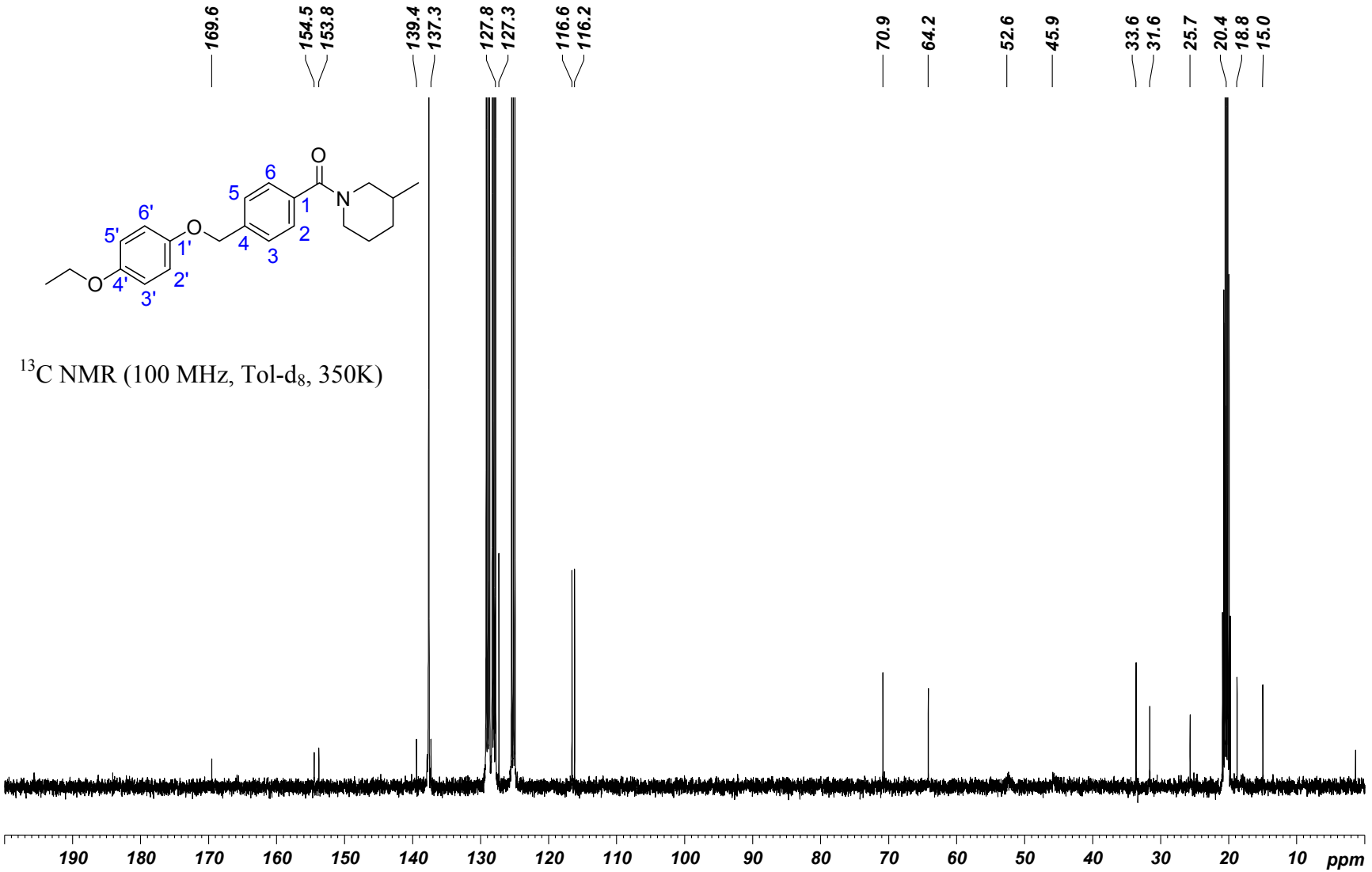
4-((4-Methoxyphenoxy)methyl)-*N*-methyl-*N*-phenylbenzamide; 30.



(4-((4-Ethoxyphenoxy)methyl)phenyl)(3-methylpiperidin-1-yl)methanone; 1.

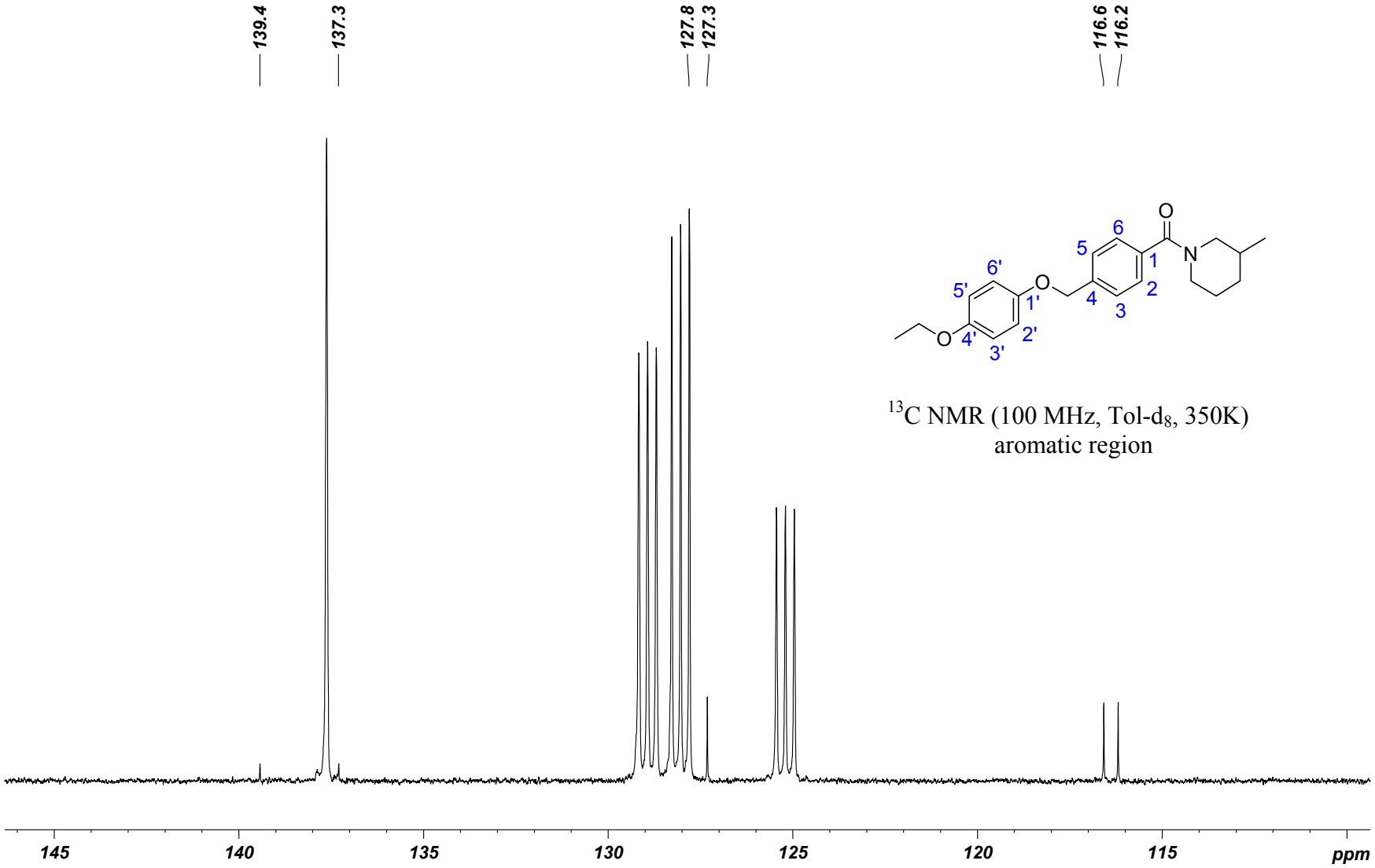


(4-((4-Ethoxyphenoxy)methyl)phenyl)(3-methylpiperidin-1-yl)methanone; 1.



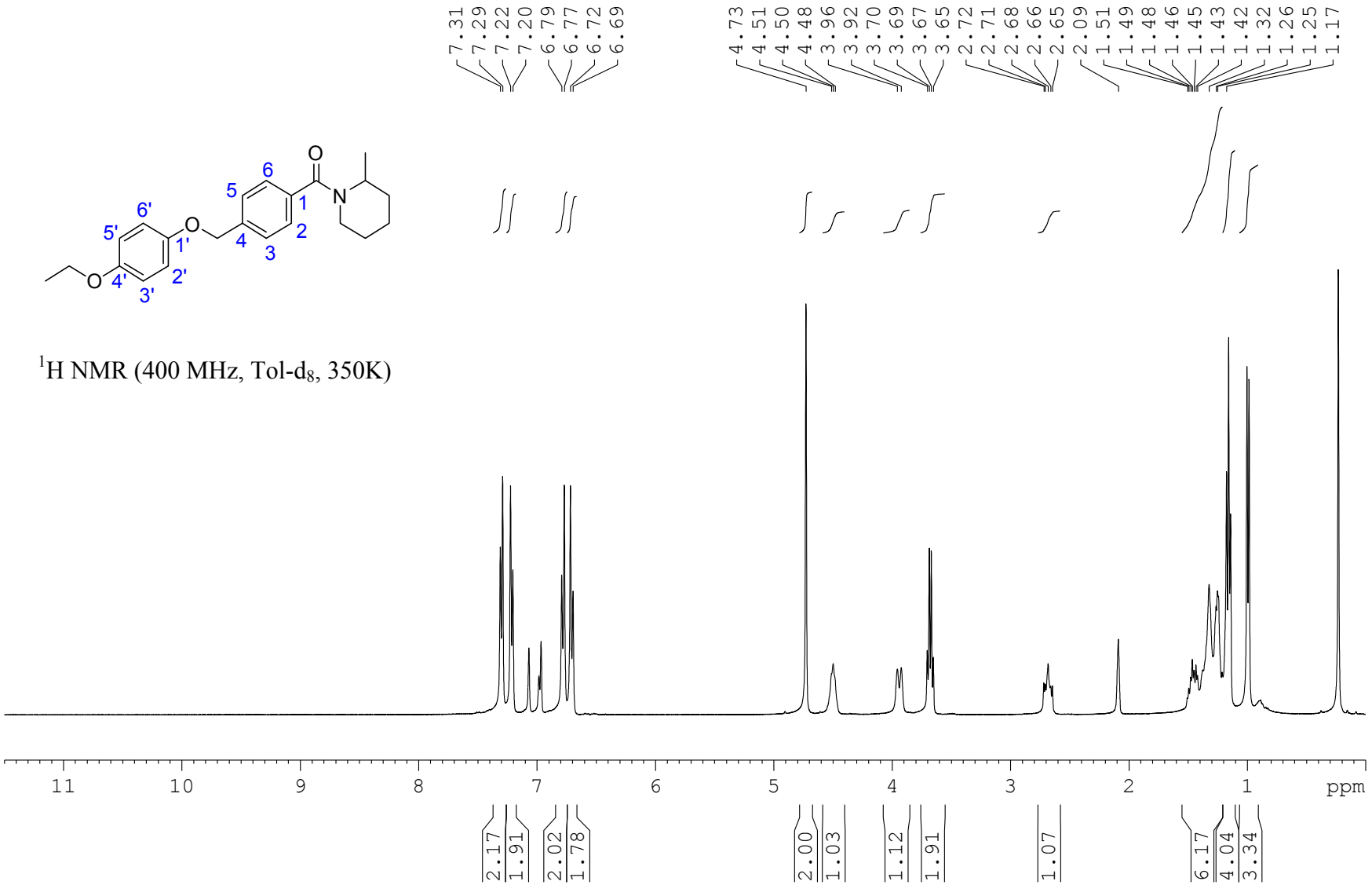
^{13}C NMR (100 MHz, Tol-d_8, 350K)

(4-((4-Ethoxyphenoxy)methyl)phenyl)(3-methylpiperidin-1-yl)methanone; 1.

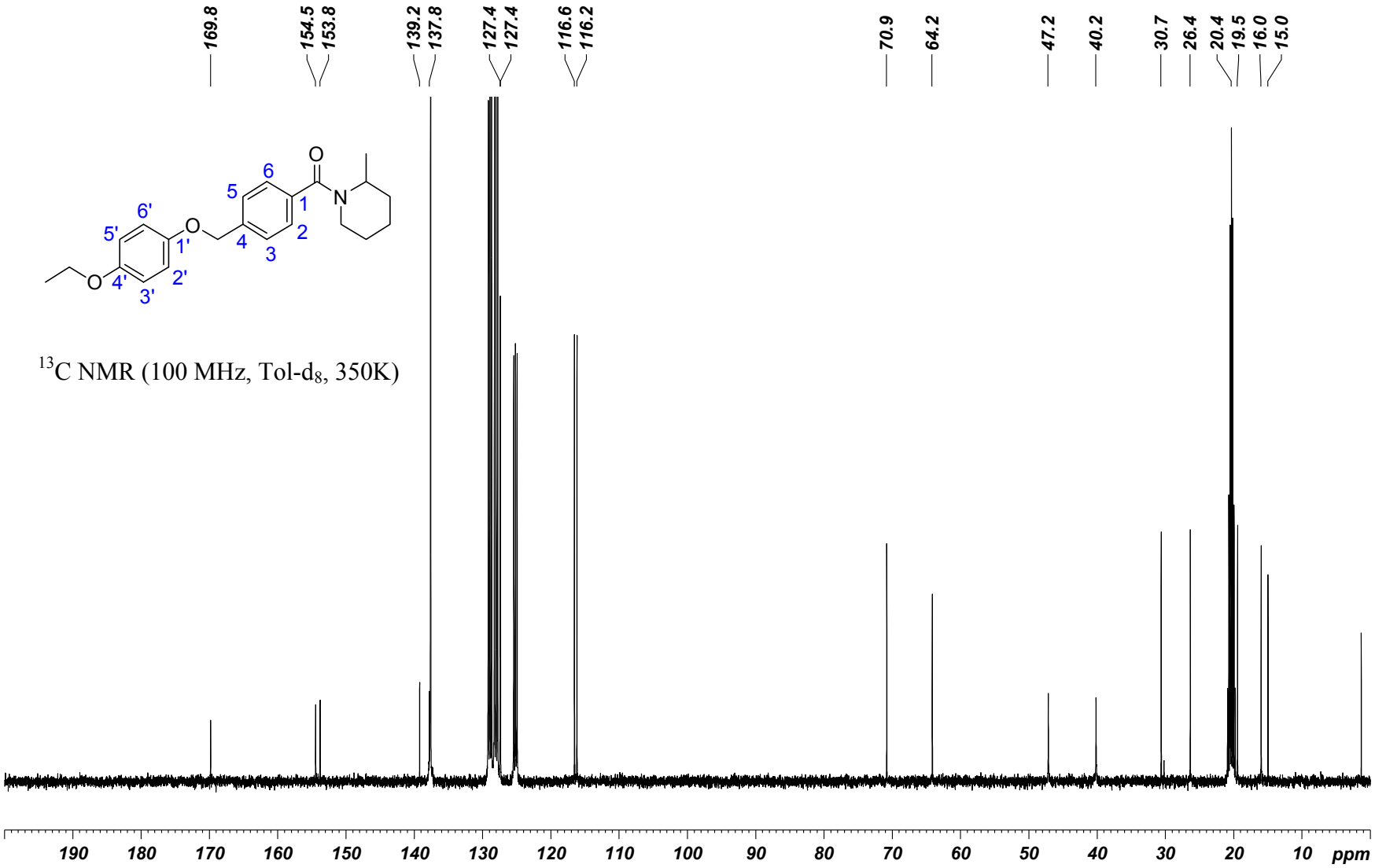


^{13}C NMR (100 MHz, Tol-d_8, 350K)
aromatic region

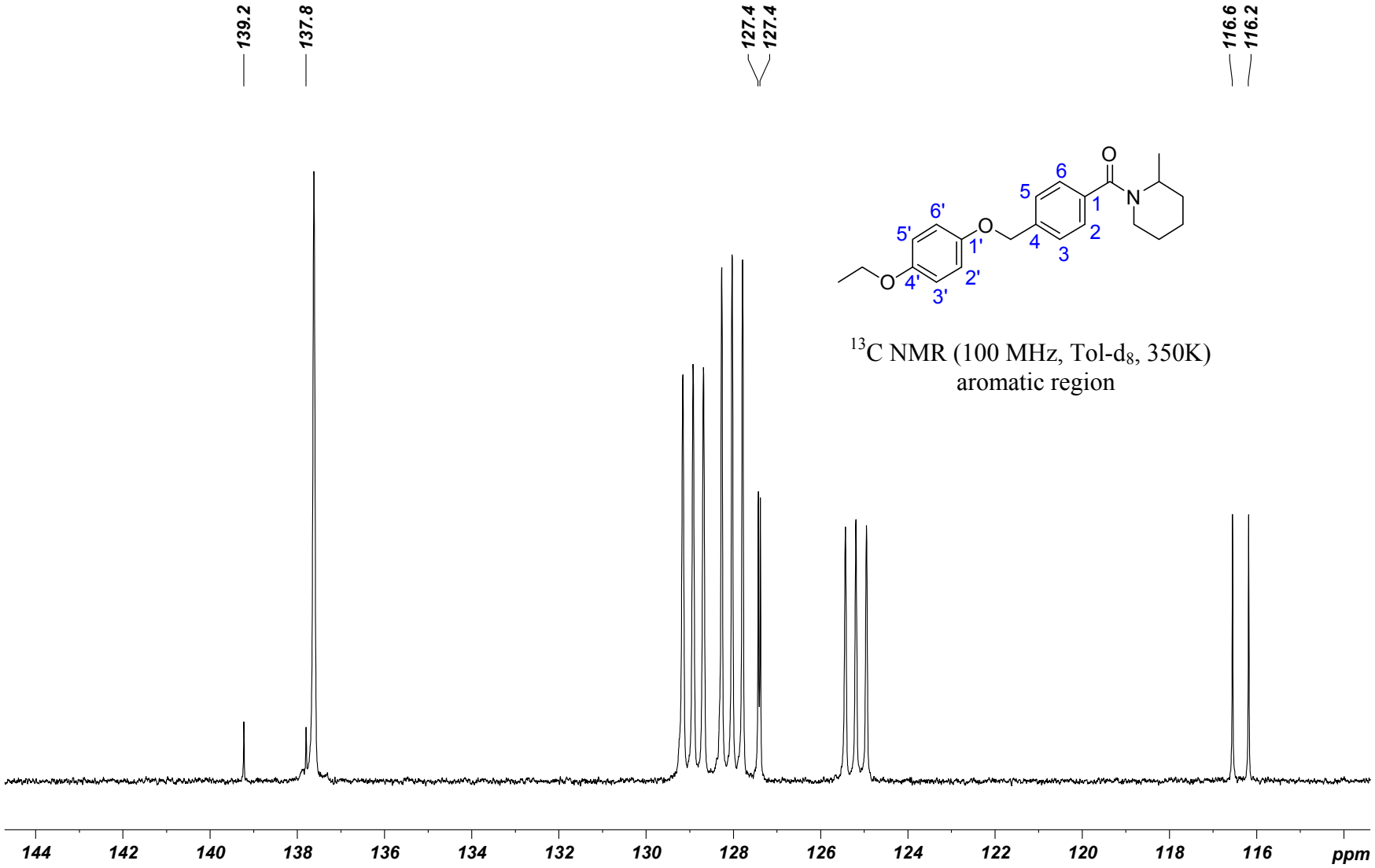
(4-((4-Ethoxyphenoxy)methyl)phenyl)(2-methylpiperidin-1-yl)methanone; 17.



(4-((4-Ethoxyphenoxy)methyl)phenyl)(2-methylpiperidin-1-yl)methanone; 17.

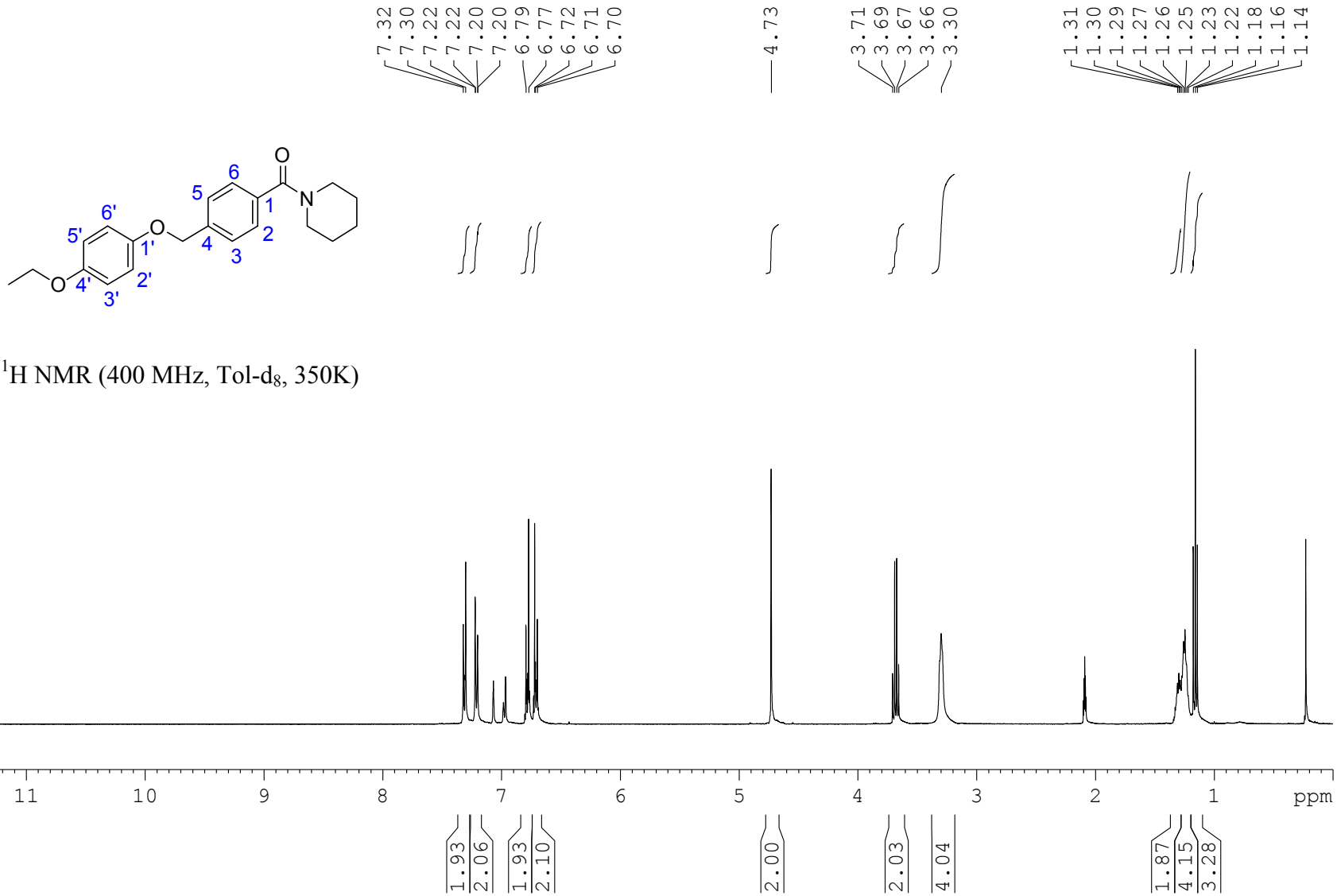


(4-((4-Ethoxyphenoxy)methyl)phenyl)(2-methylpiperidin-1-yl)methanone; 17.



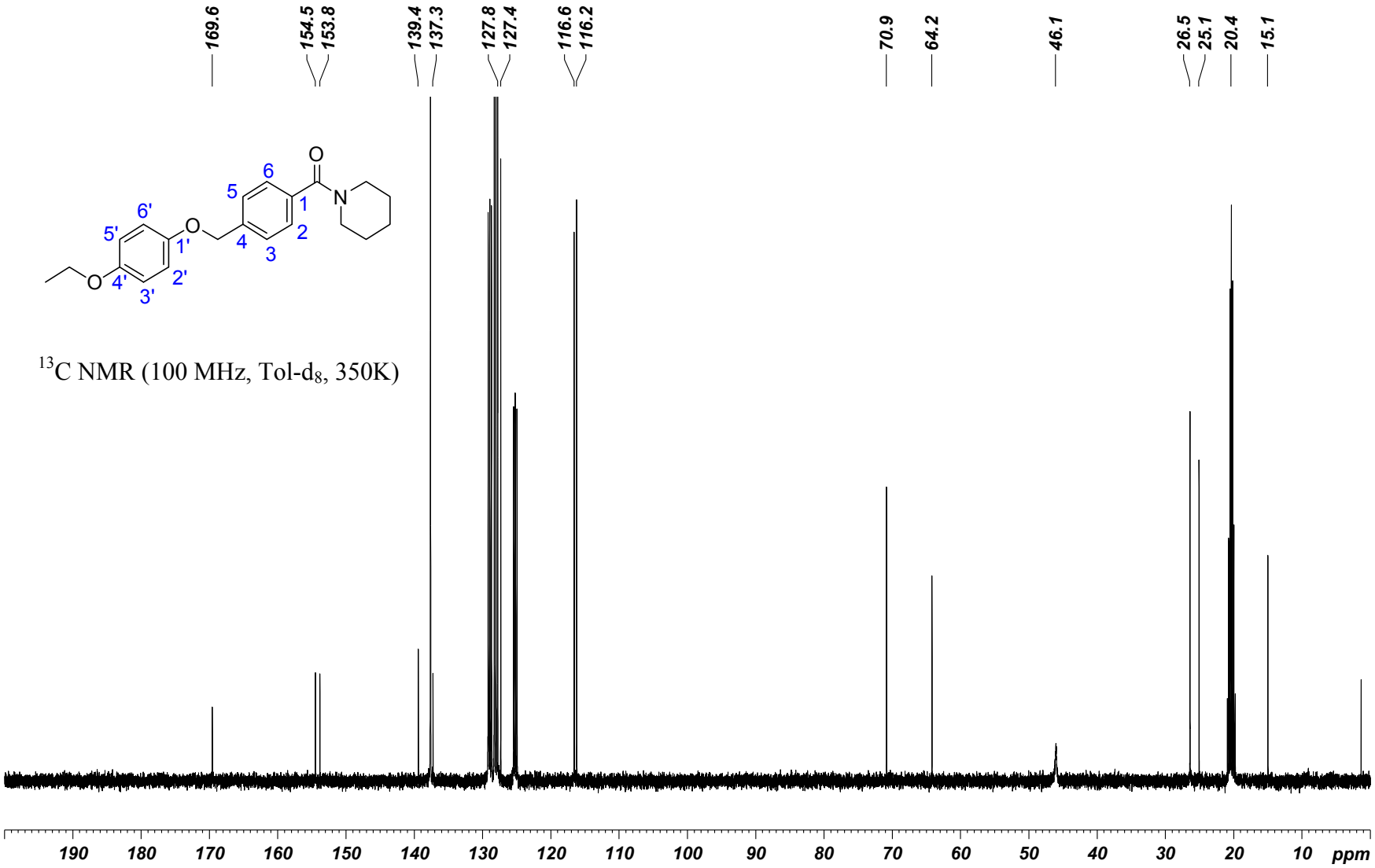
^{13}C NMR (100 MHz, Tol-d_8, 350K)
aromatic region

(4-((4-Ethoxyphenoxy)methyl)phenyl)(piperidin-1-yl)methanone; 23.

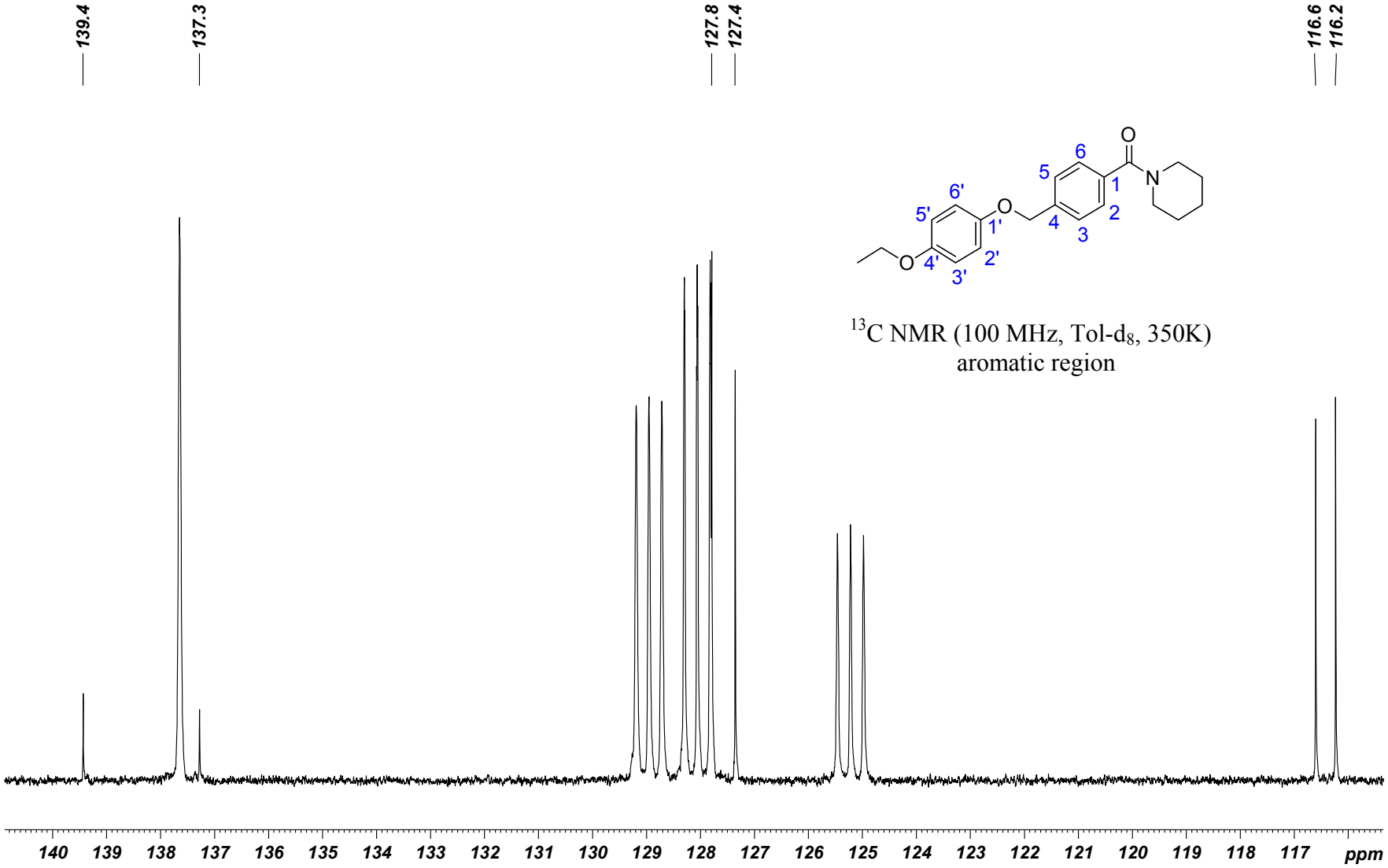


^{1}H NMR (400 MHz, Tol-d_8, 350K)

(4-((4-Ethoxyphenoxy)methyl)phenyl)(piperidin-1-yl)methanone; 23.

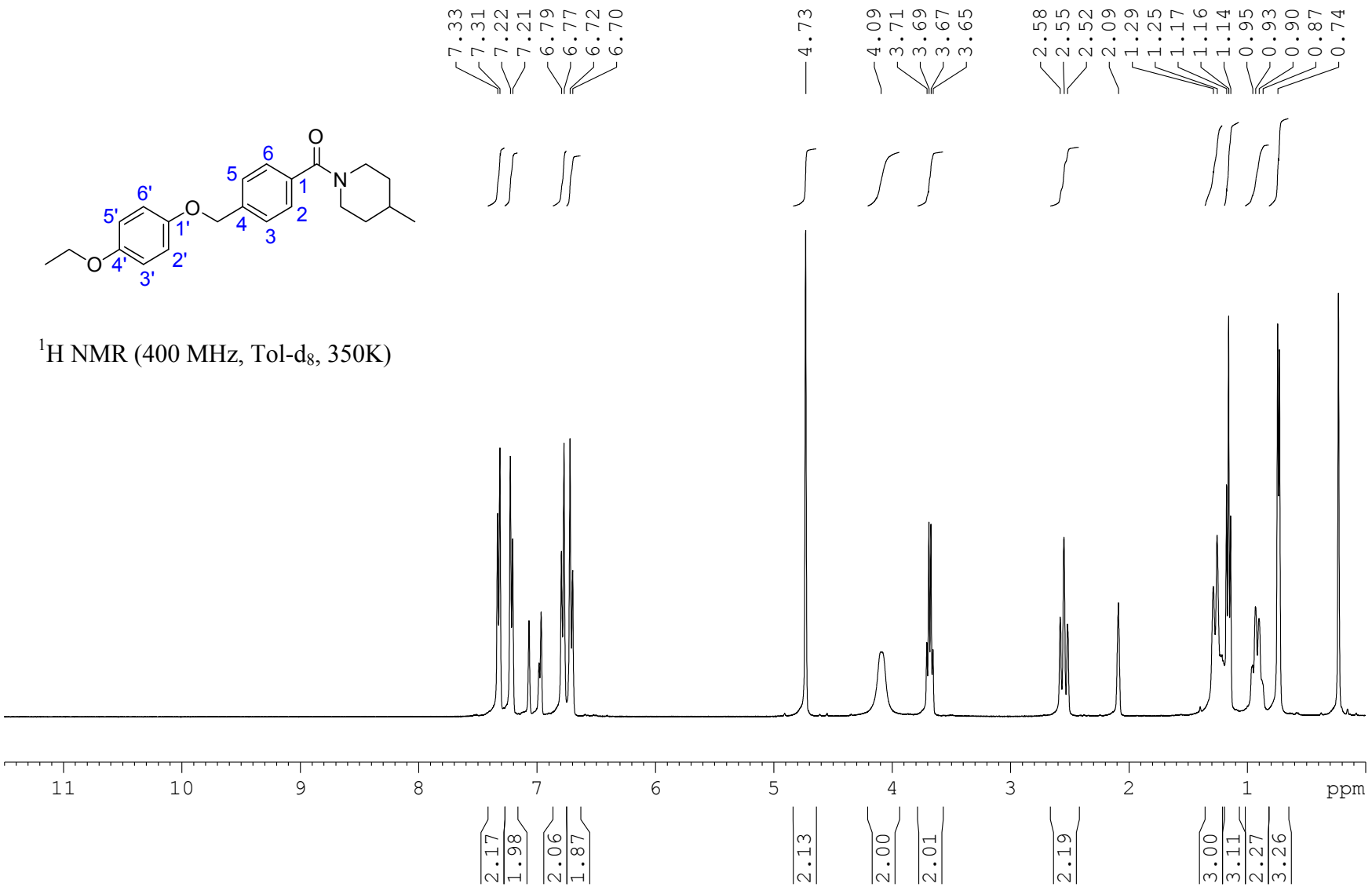


(4-((4-Ethoxyphenoxy)methyl)phenyl)(piperidin-1-yl)methanone; 23.



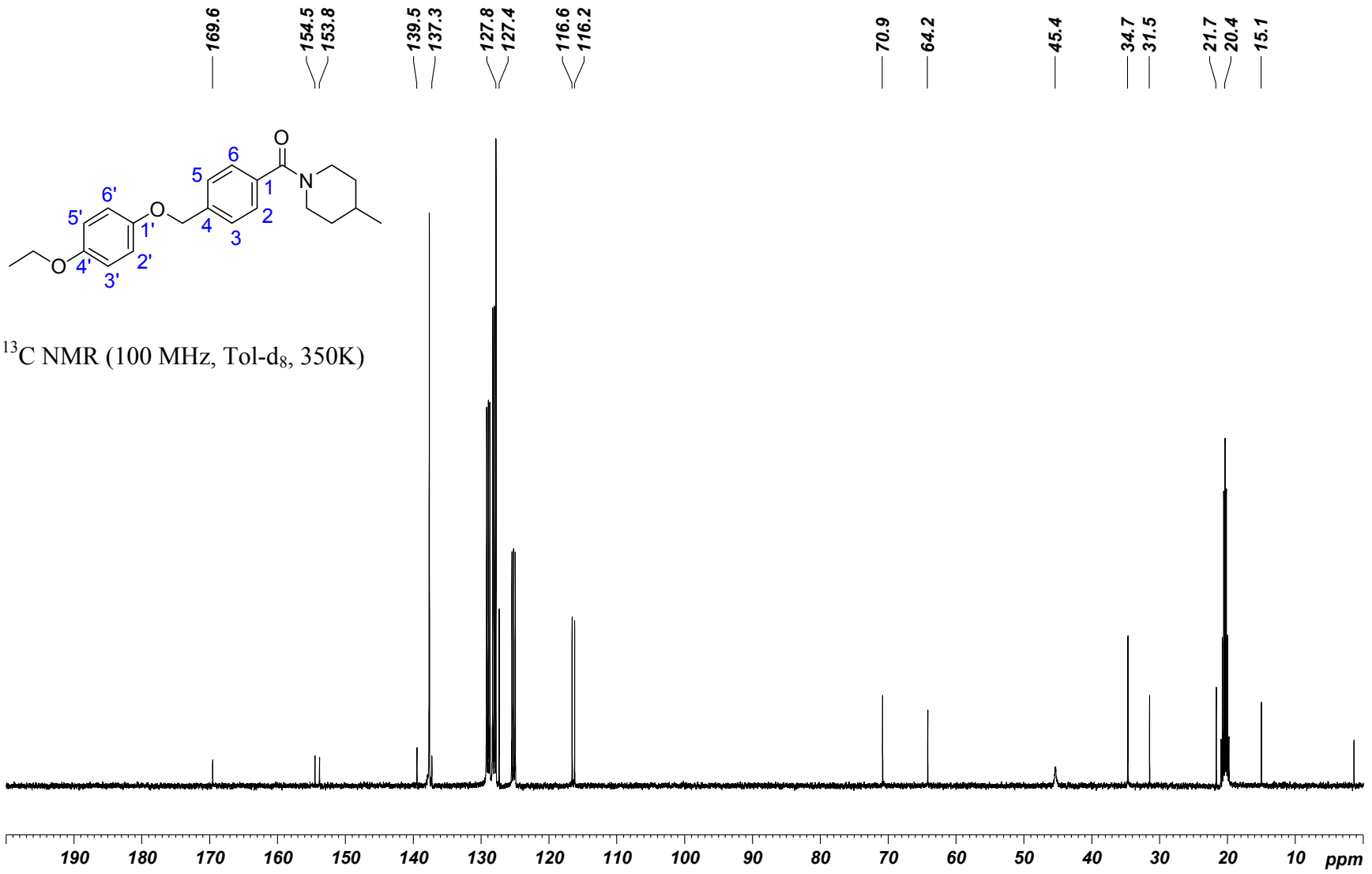
^{13}C NMR (100 MHz, Tol-d_8, 350K)
aromatic region

(4-((4-Ethoxyphenoxy)methyl)phenyl)(4-methylpiperidin-1-yl)methanone; 22.



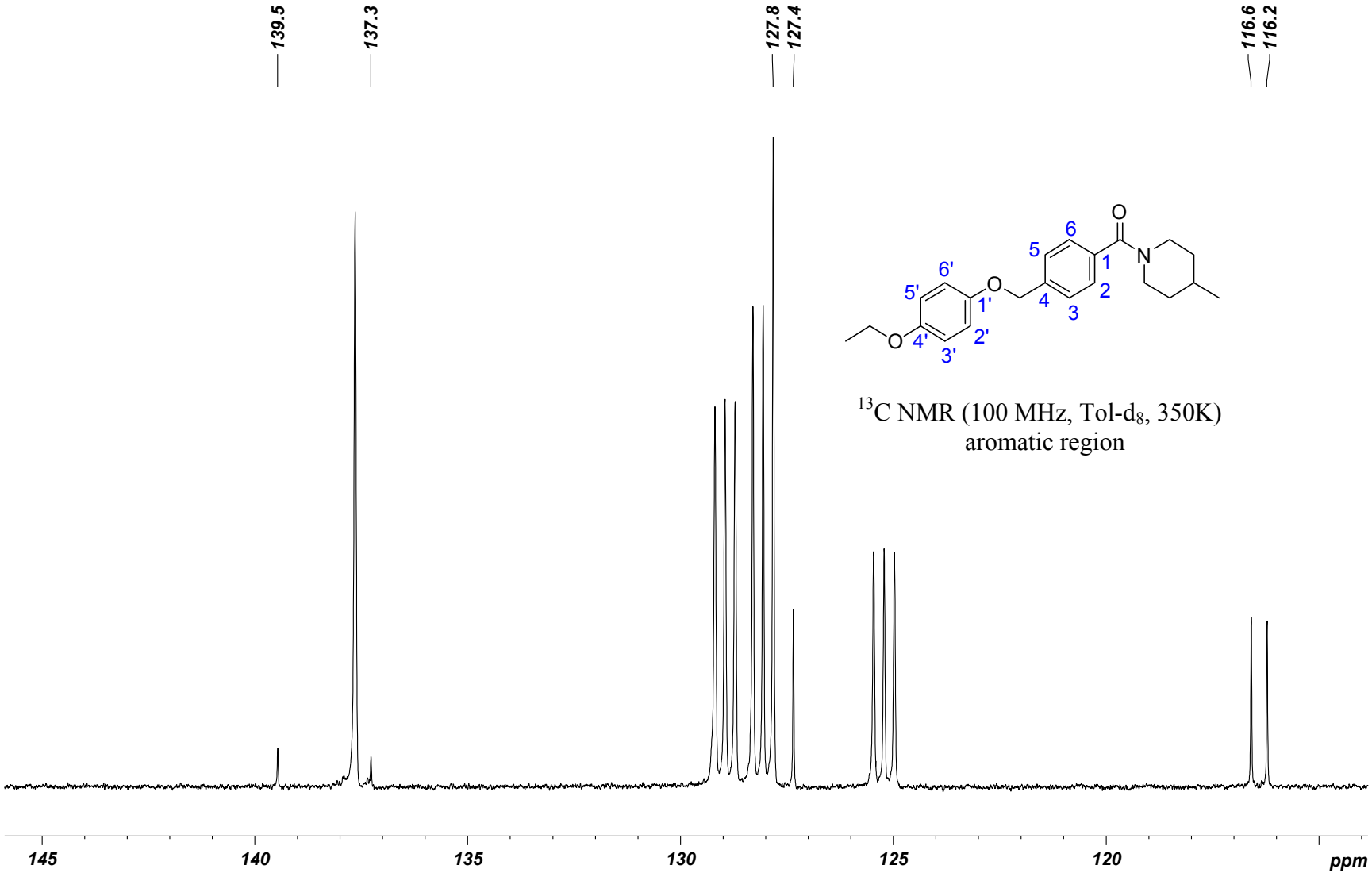
^{1}H NMR (400 MHz, Tol-d_8, 350K)

(4-((4-Ethoxyphenoxy)methyl)phenyl)(4-methylpiperidin-1-yl)methanone; 22.



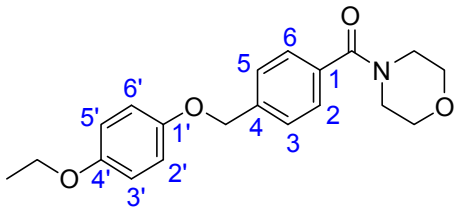
^{13}C NMR (100 MHz, Tol-d_8, 350K)

(4-((4-Ethoxyphenoxy)methyl)phenyl)(4-methylpiperidin-1-yl)methanone; 22.



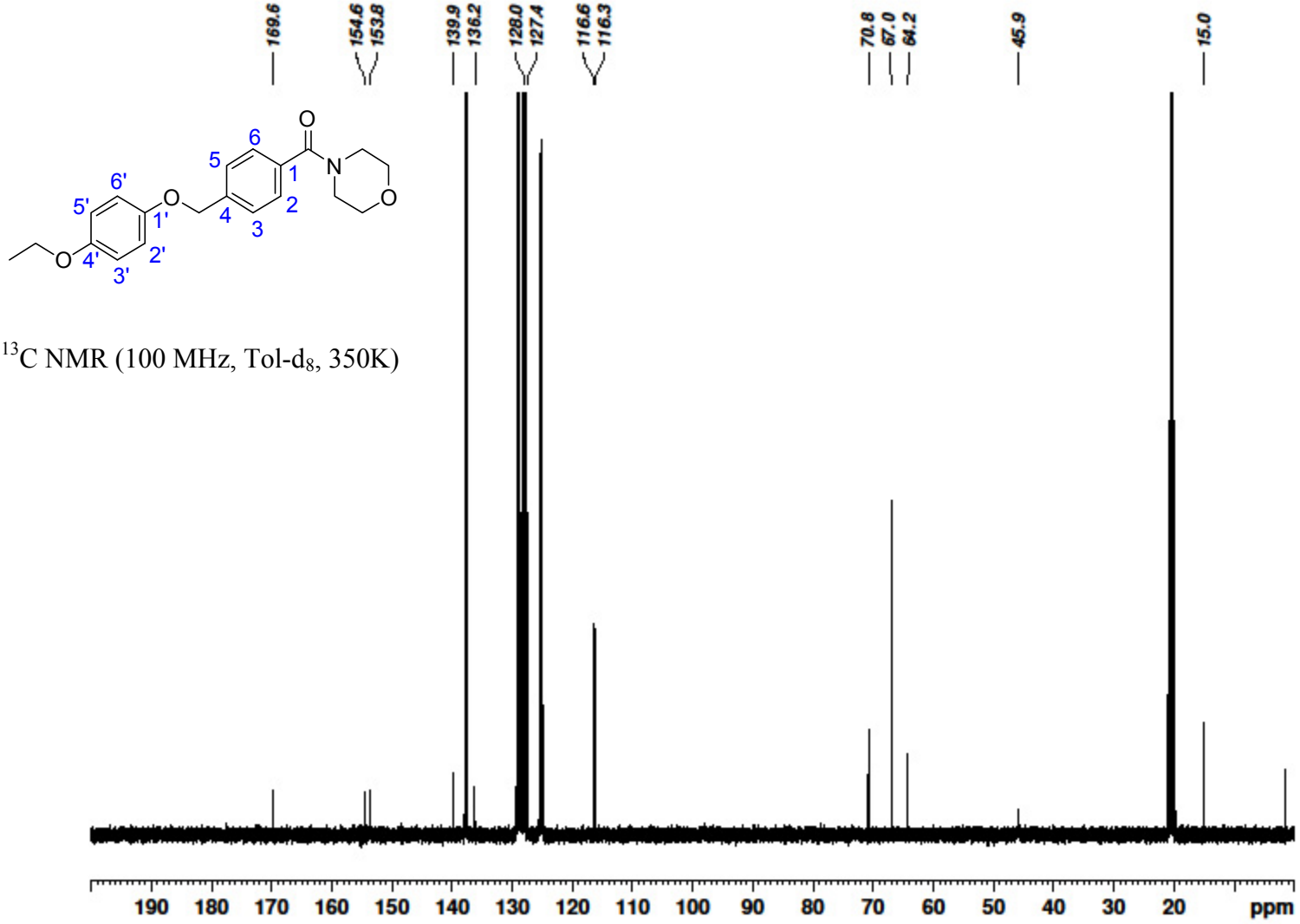
^{13}C NMR (100 MHz, Tol-d_8, 350K)
aromatic region

(4-((4-Ethoxyphenoxy)methyl)phenyl)(morpholino)methanone, 27.



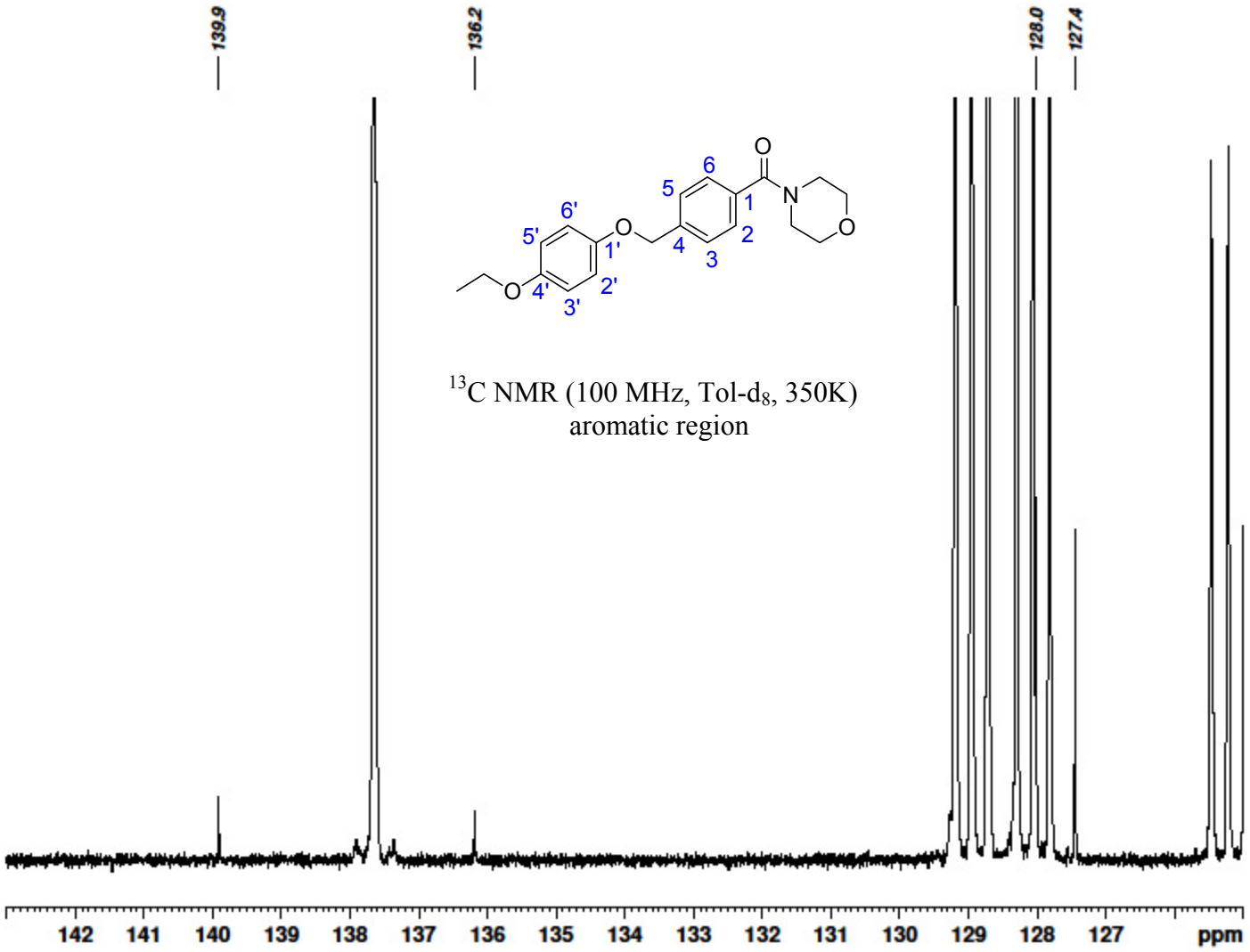
^{1}H NMR (400 MHz, Tol-d_8, 350K)

(4-((4-Ethoxyphenoxy)methyl)phenyl)(morpholino)methanone, 27.



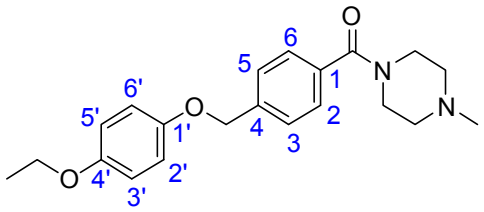
^{13}C NMR (100 MHz, Tol-d_8, 350K)

(4-((4-Ethoxyphenoxy)methyl)phenyl)(morpholino)methanone, 27.



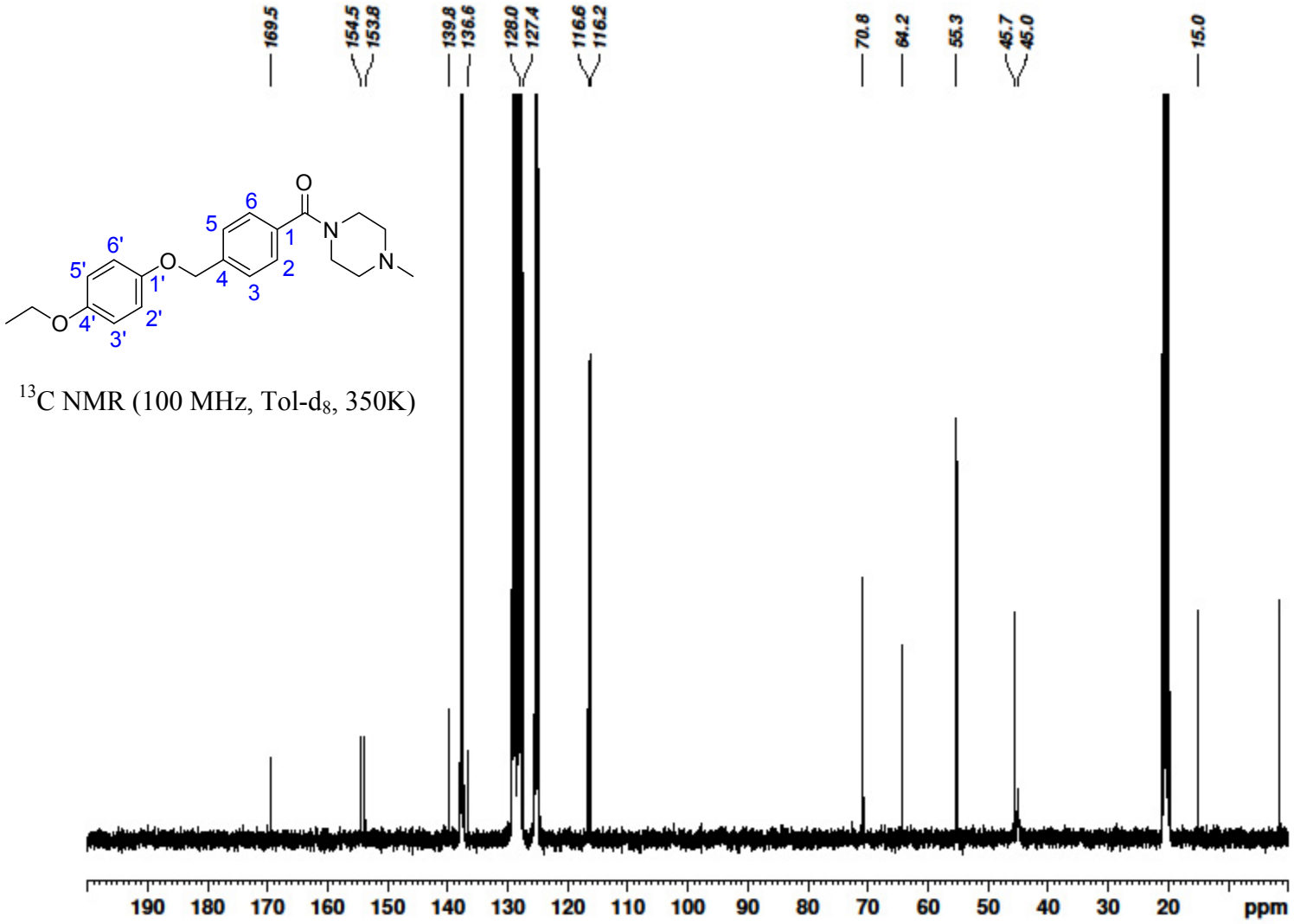
^{13}C NMR (100 MHz, Tol-d_8, 350K)
aromatic region

(4-((4-Ethoxyphenoxy)methyl)phenyl)(4-methylpiperazin-1-yl)methanone, 31.



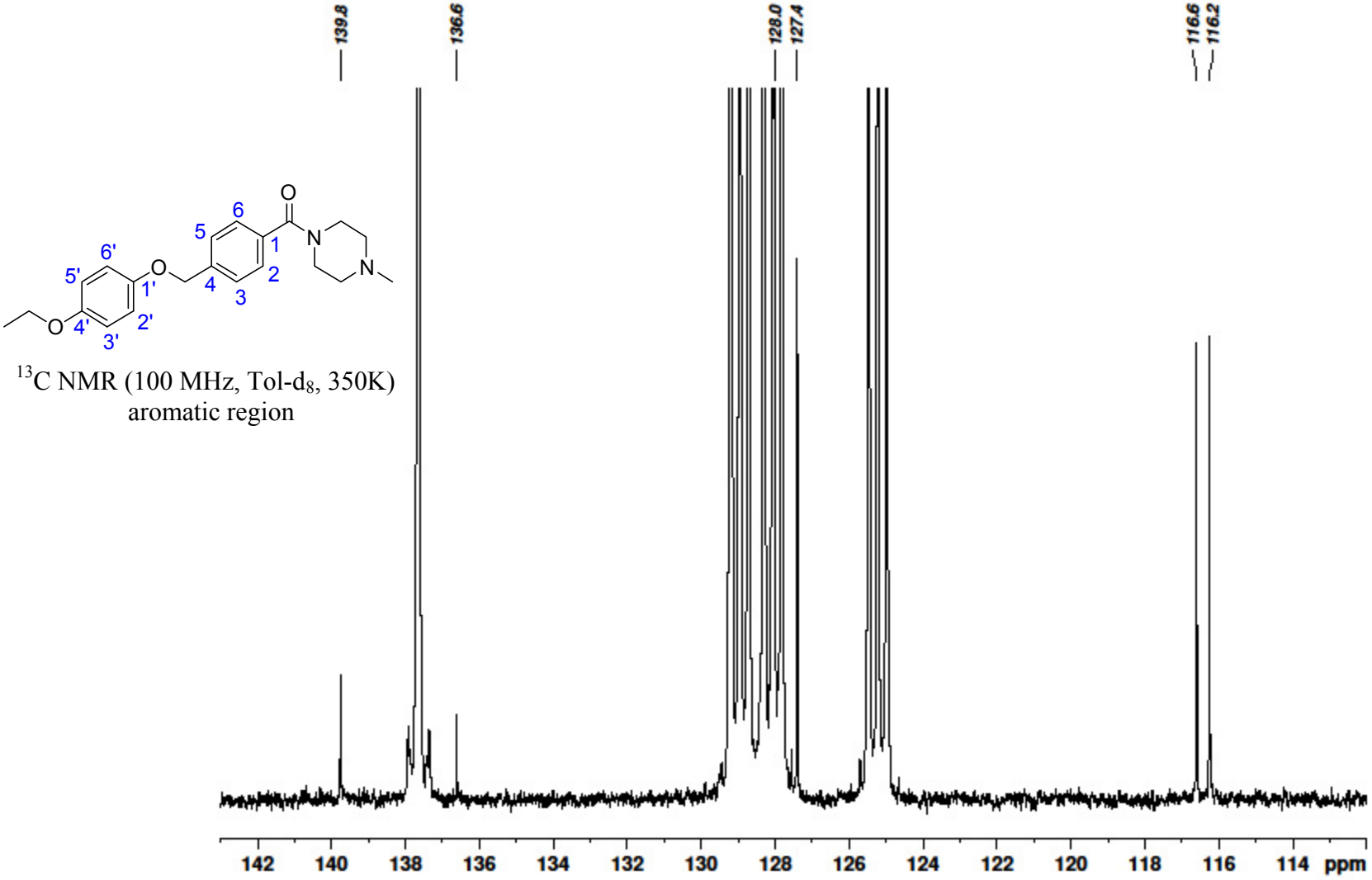
^{1}H NMR (400 MHz, Tol-d_8, 350K)

(4-((4-Ethoxyphenoxy)methyl)phenyl)(4-methylpiperazin-1-yl)methanone, 31.



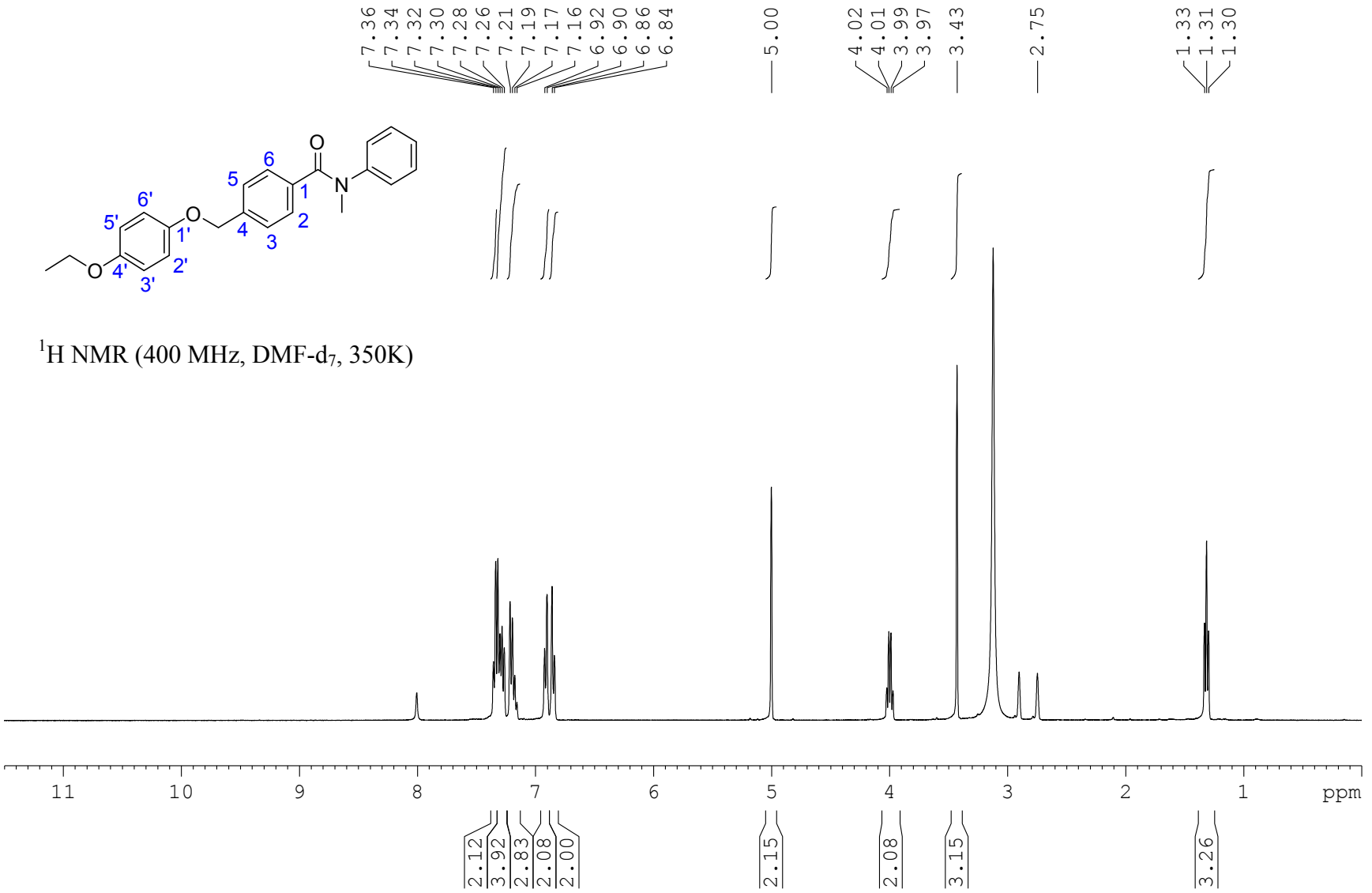
^{13}C NMR (100 MHz, Tol-d_8, 350K)

(4-((4-Ethoxyphenoxy)methyl)phenyl)(4-methylpiperazin-1-yl)methanone, 31.



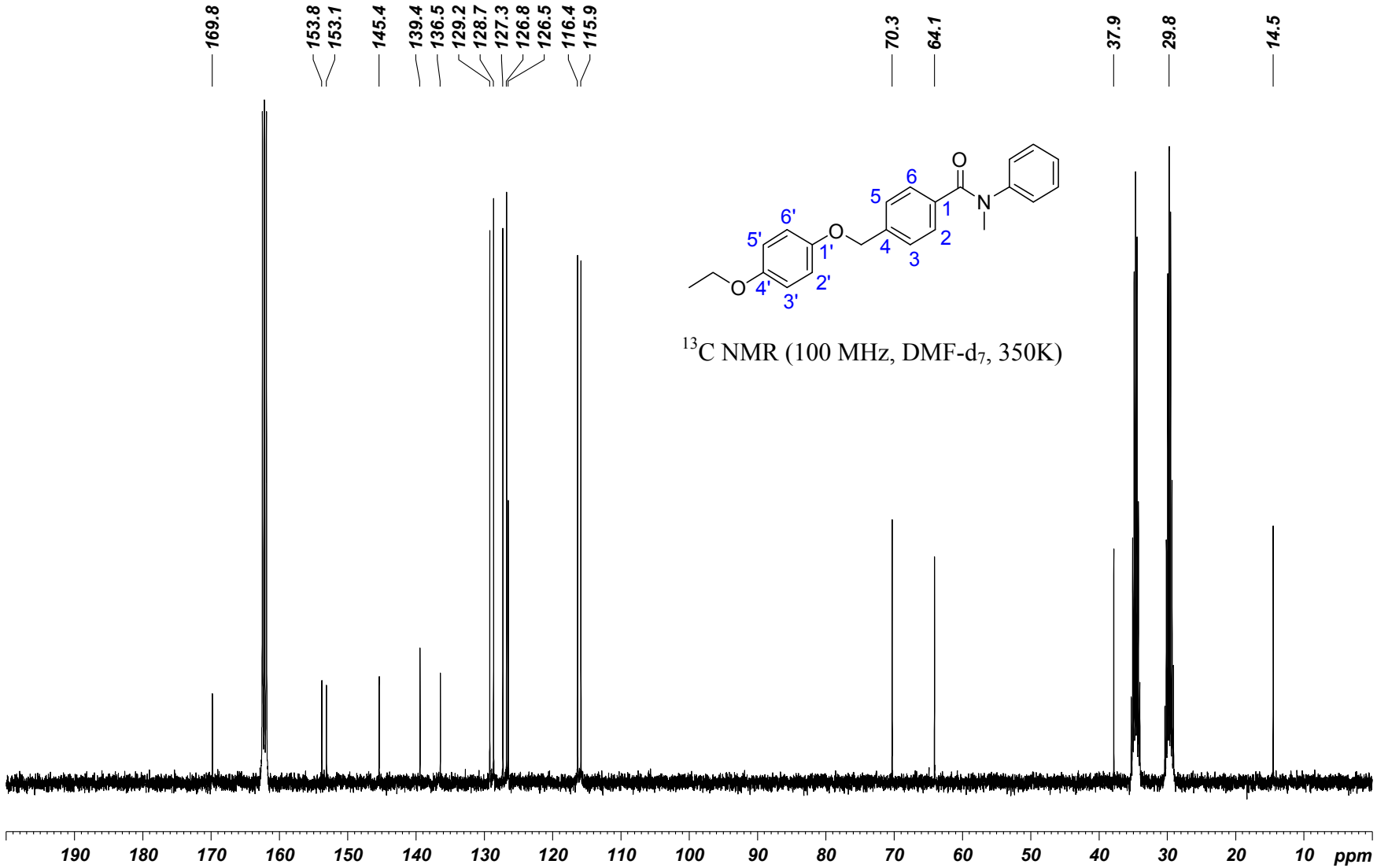
^{13}C NMR (100 MHz, Tol-d_8, 350K)
aromatic region

4-((4-Ethoxyphenoxy)methyl)-*N*-methyl-*N*-phenylbenzamide; 34.



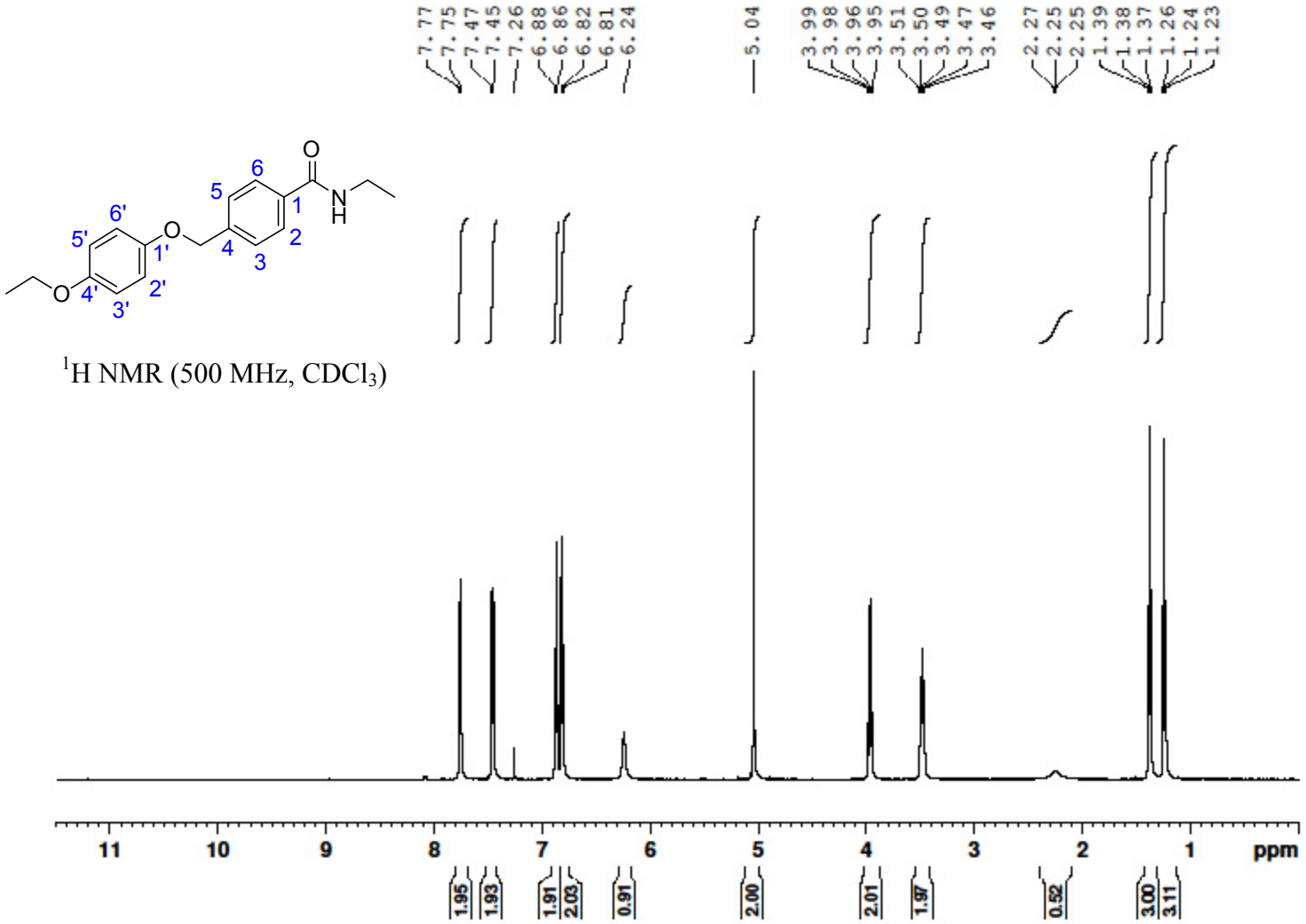
^{1}H NMR (400 MHz, DMF-d_7, 350K)

4-((4-Ethoxyphenoxy)methyl)-*N*-methyl-*N*-phenylbenzamide; 34.



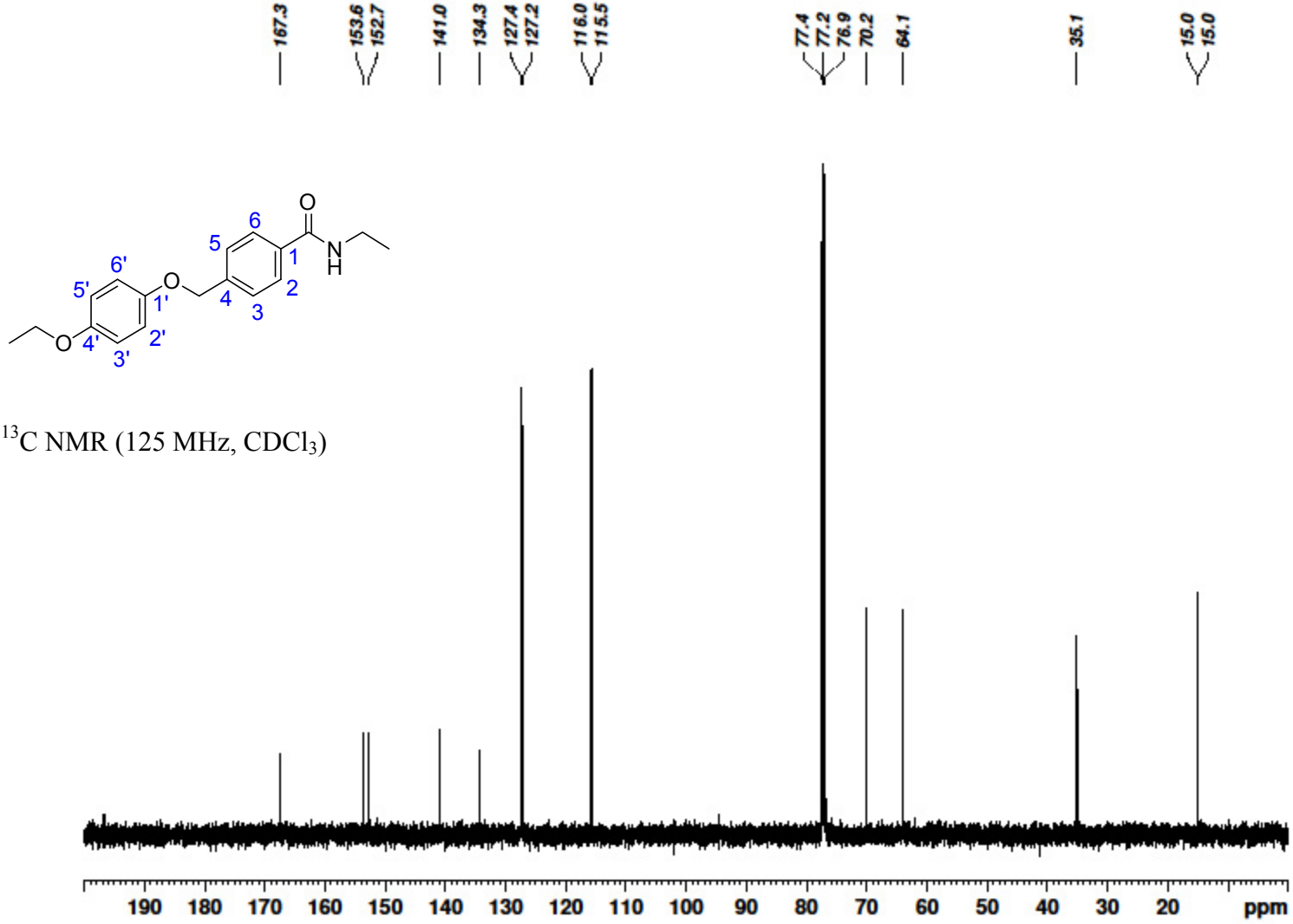
^{13}C NMR (100 MHz, DMF-d_7, 350K)

4-((4-Ethoxyphenoxy)methyl)-*N*-ethylbenzamide; S64.



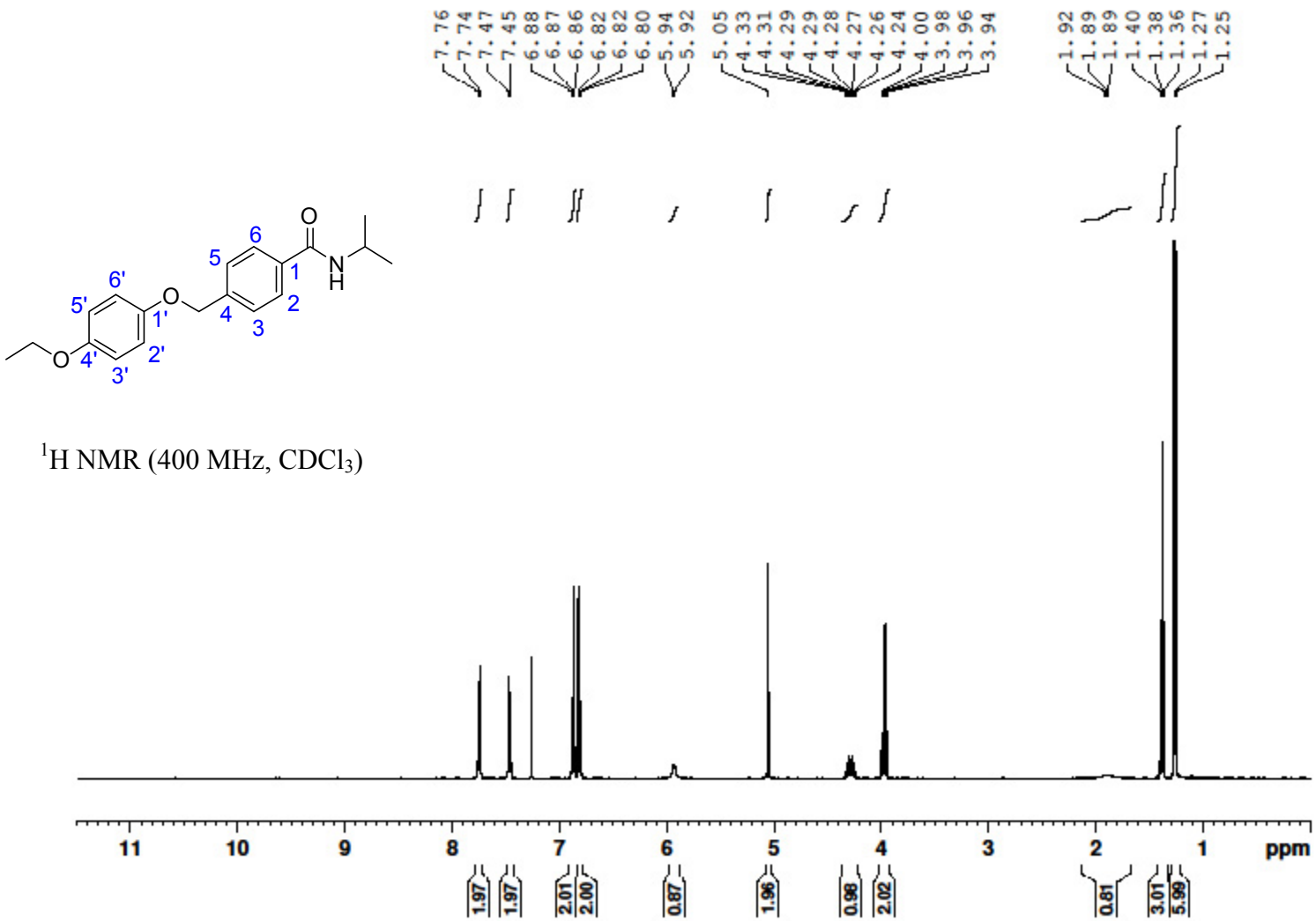
^{1}H NMR (500 MHz, $CDCl_3$)

4-((4-Ethoxyphenoxy)methyl)-*N*-ethylbenzamide; S64.



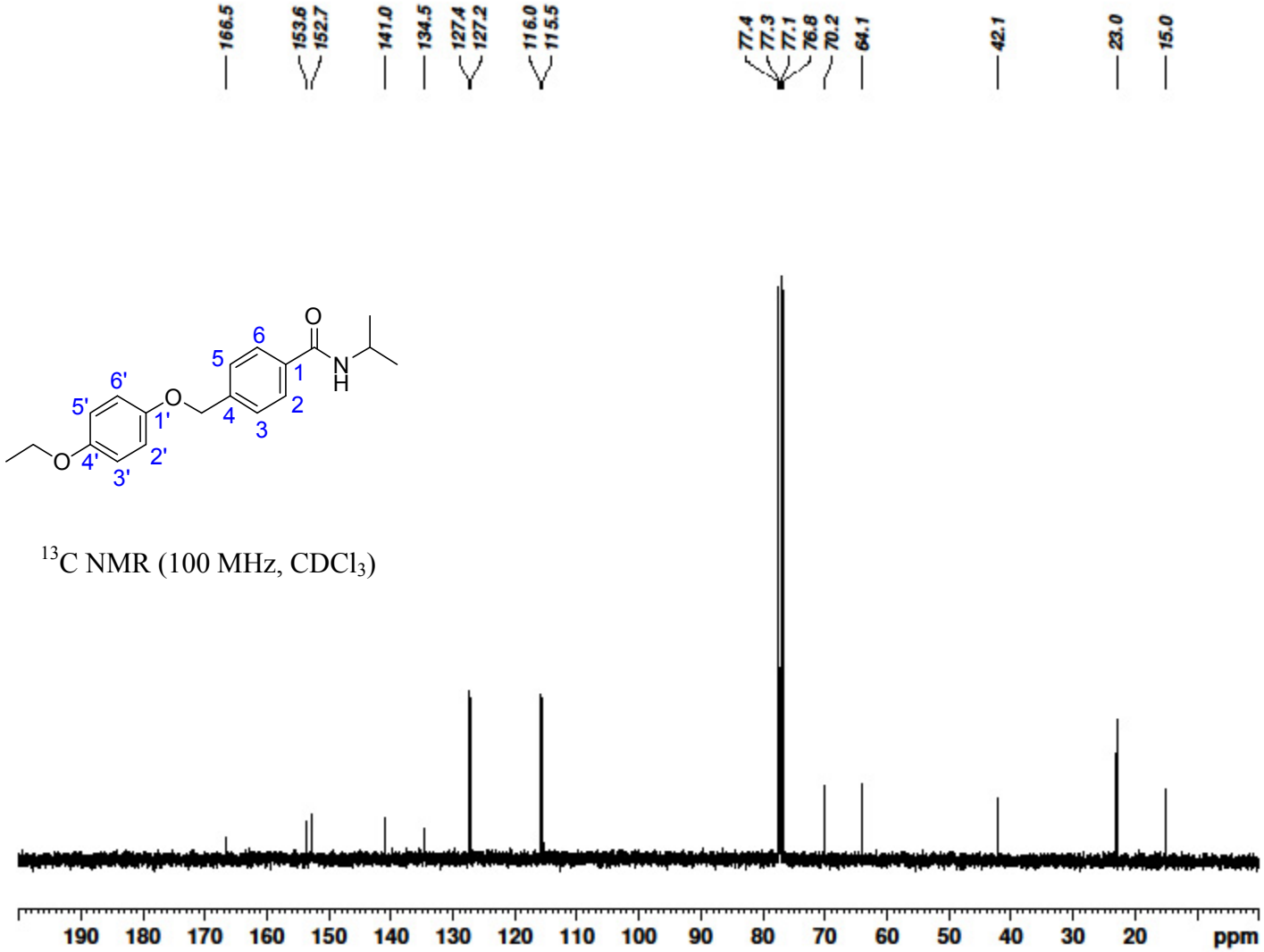
^{13}C NMR (125 MHz, $CDCl_3$)

4-((4-Ethoxyphenoxy)methyl)-*N*-isopropylbenzamide; 36.



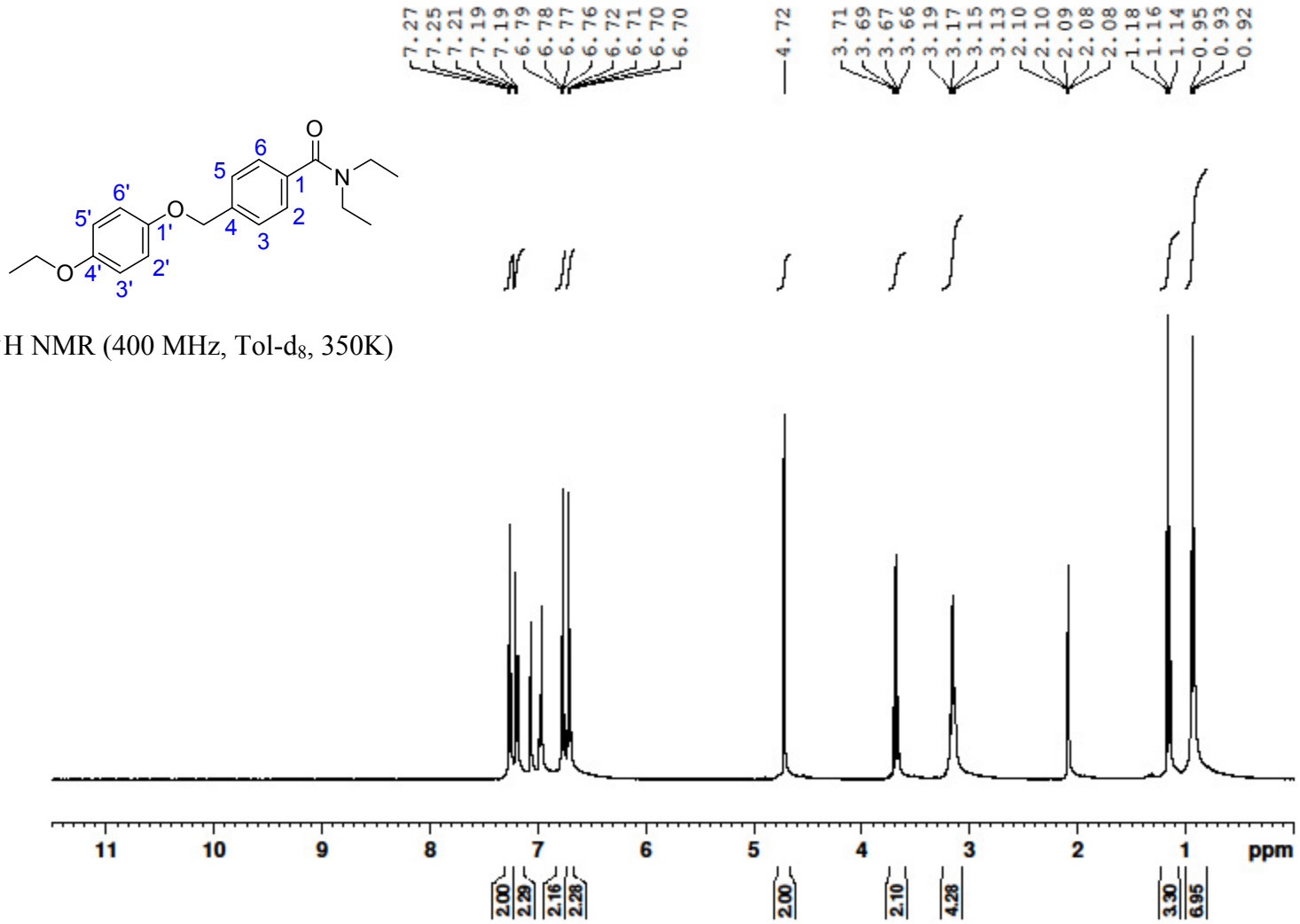
^{1}H NMR (400 MHz, $CDCl_3$)

4-((4-Ethoxyphenoxy)methyl)-*N*-isopropylbenzamide; 36.



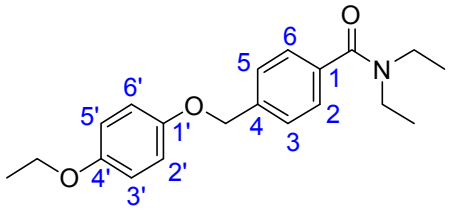
^{13}C NMR (100 MHz, $CDCl_3$)

4-((4-Ethoxyphenoxy)methyl)-*N*,*N*-diethylbenzamide; S65.



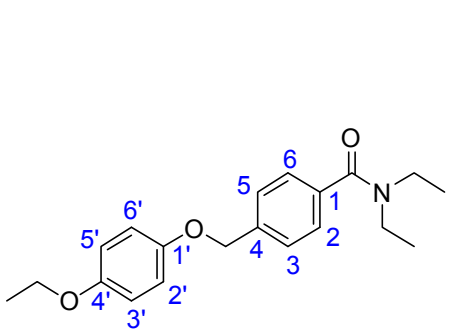
^{1}H NMR (400 MHz, Tol-d_8, 350K)

4-((4-Ethoxyphenoxy)methyl)-*N*,*N*-diethylbenzamide; S65.



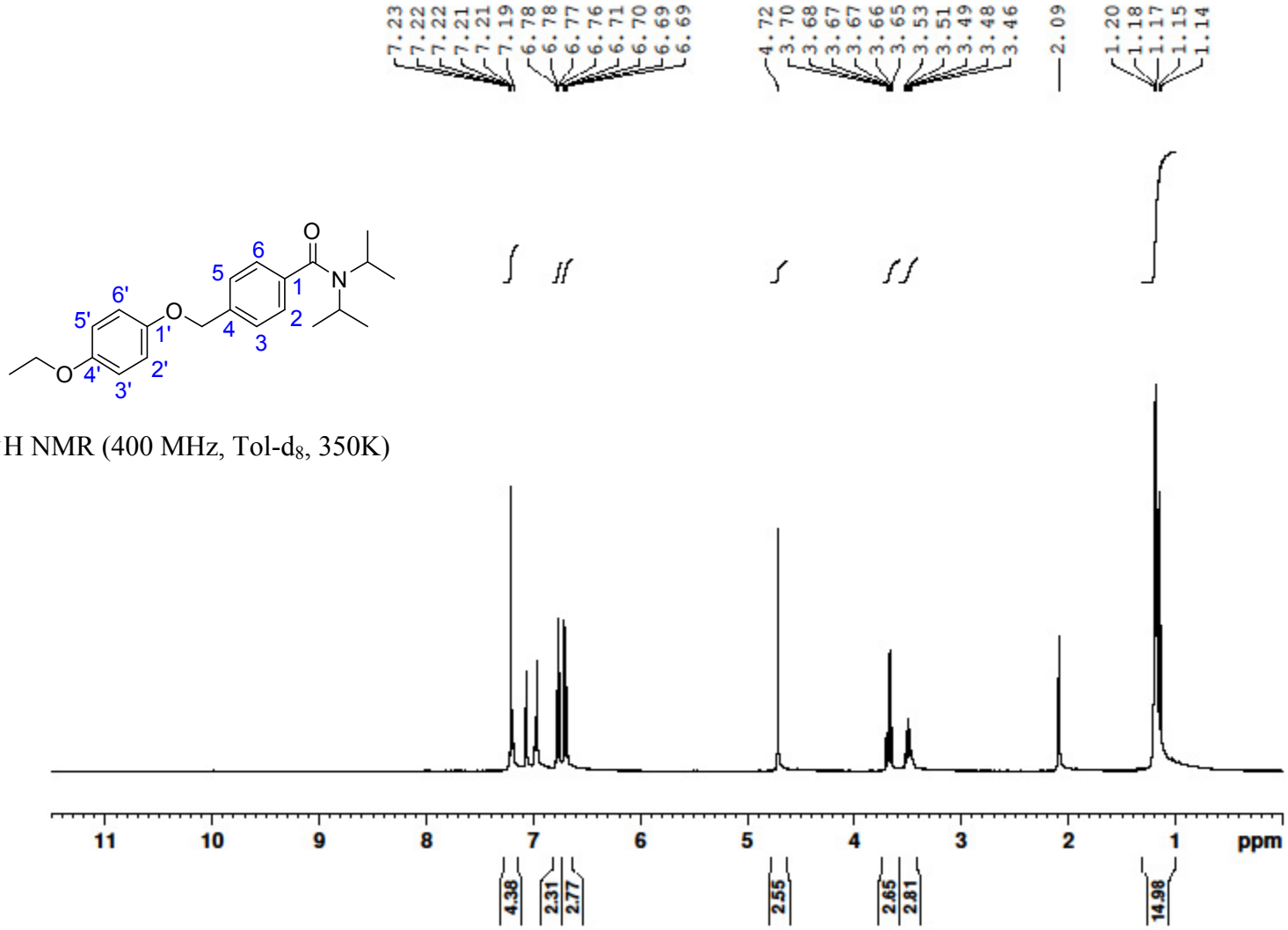
^{13}C NMR (100 MHz, Tol-d_8, 350K)

4-((4-Ethoxyphenoxy)methyl)-*N*,*N*-diethylbenzamide; S65.



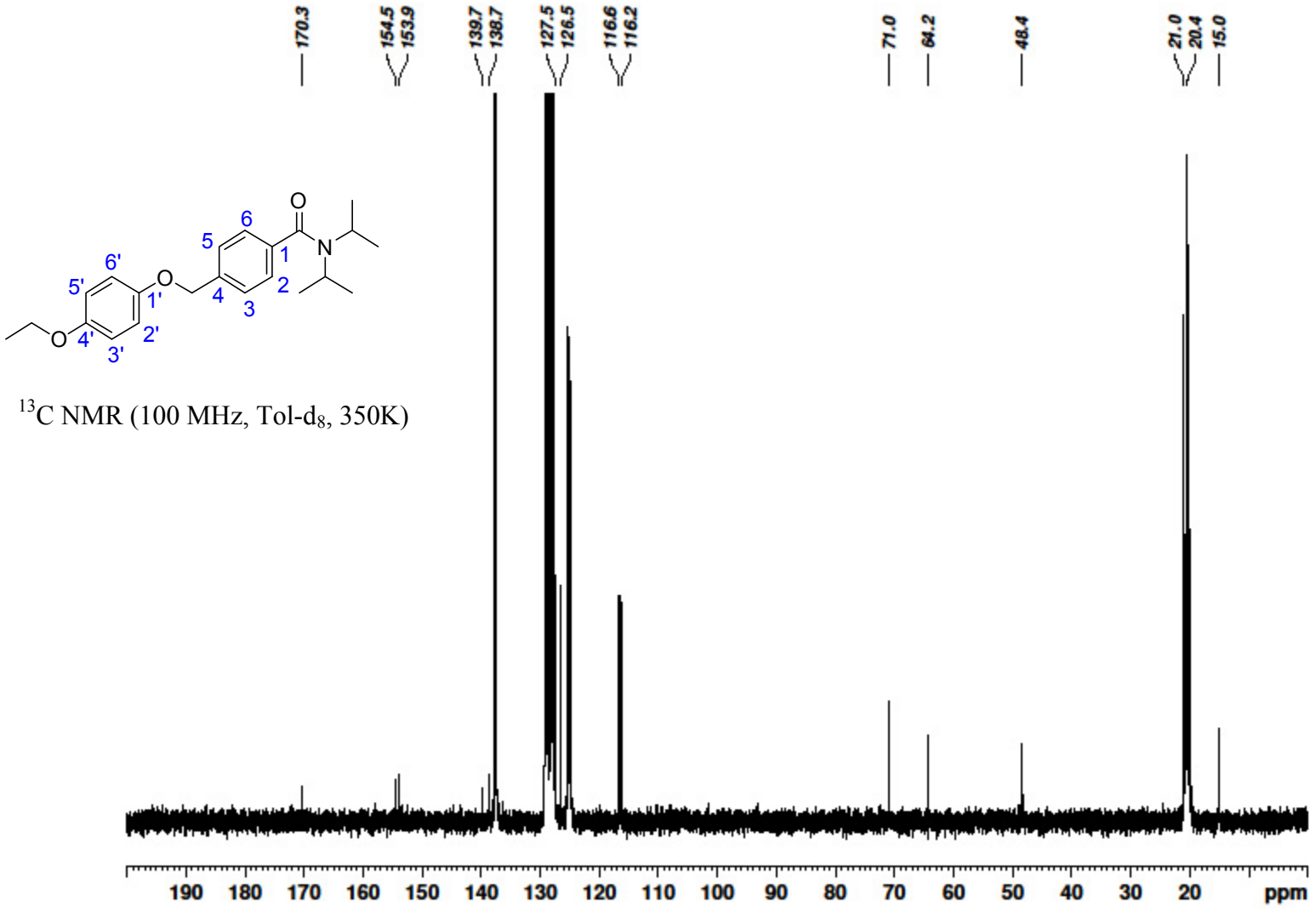
^{13}C NMR (100 MHz, Tol-d$_8$, 350K)
aromatic region

4-((4-Ethoxyphenoxy)methyl)-*N*,*N*-diisopropylbenzamide; 37.



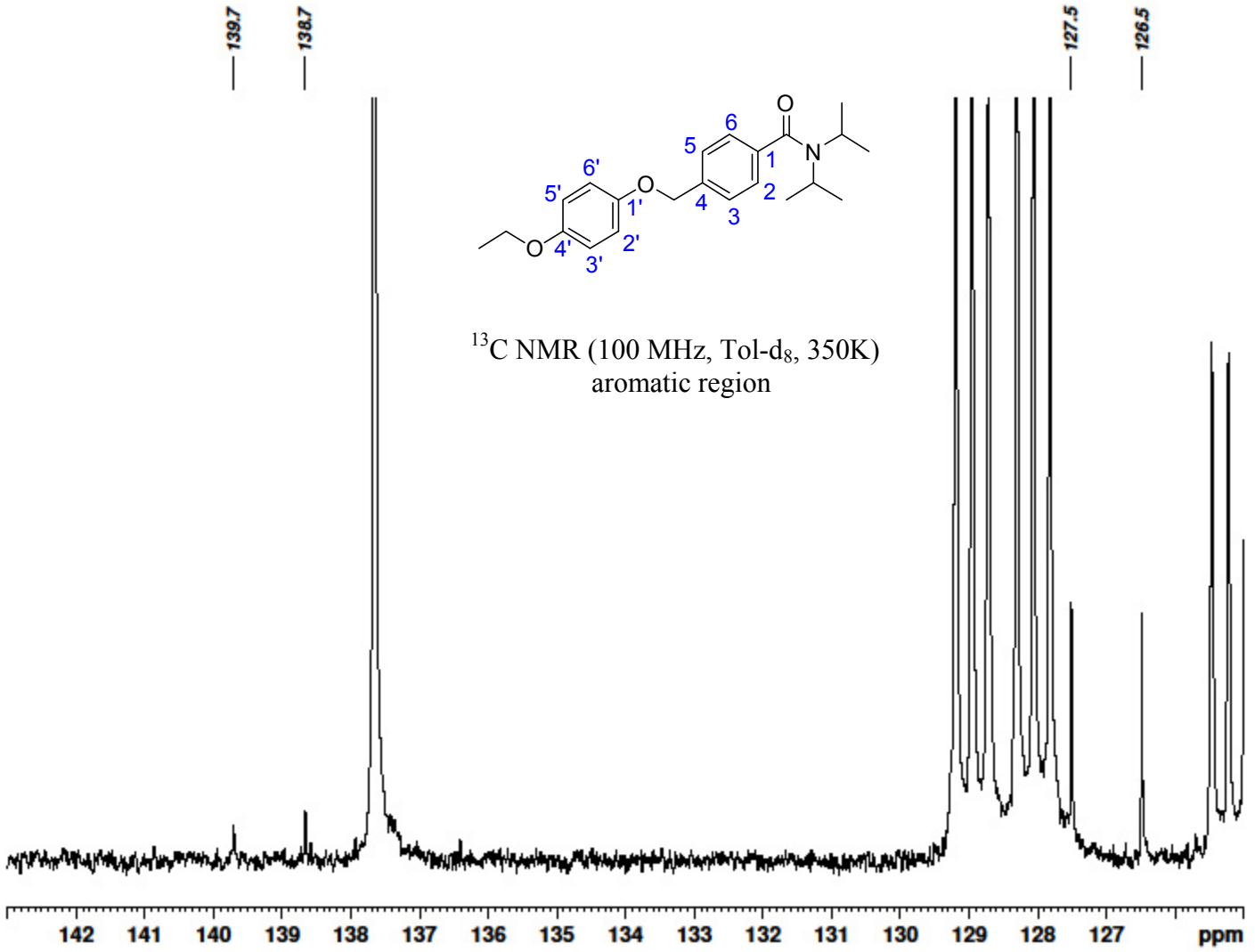
^{1}H NMR (400 MHz, Tol-d_8, 350K)

4-((4-Ethoxyphenoxy)methyl)-*N*,*N*-diisopropylbenzamide; 37.

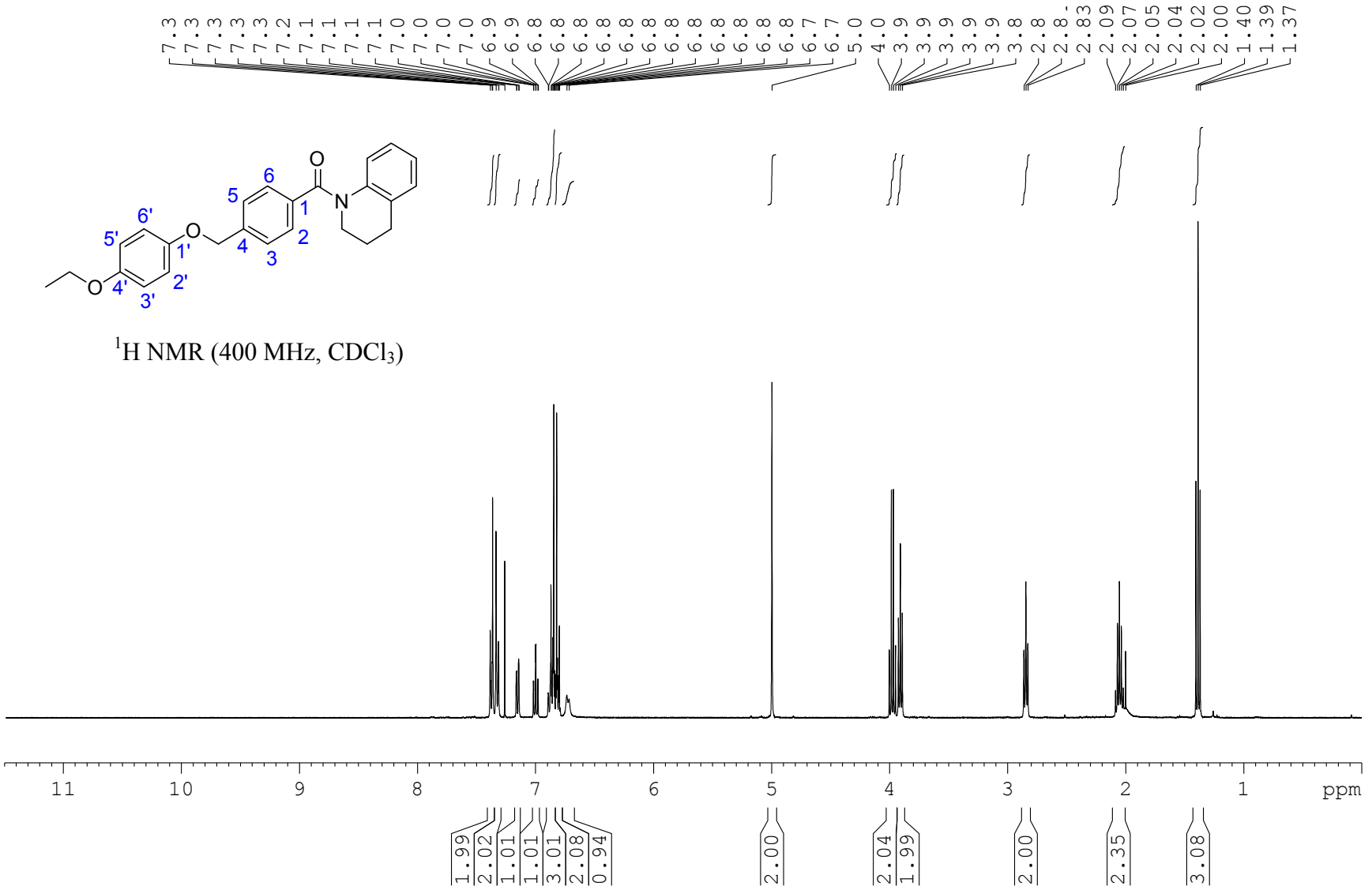


^{13}C NMR (100 MHz, Tol-d_8, 350K)

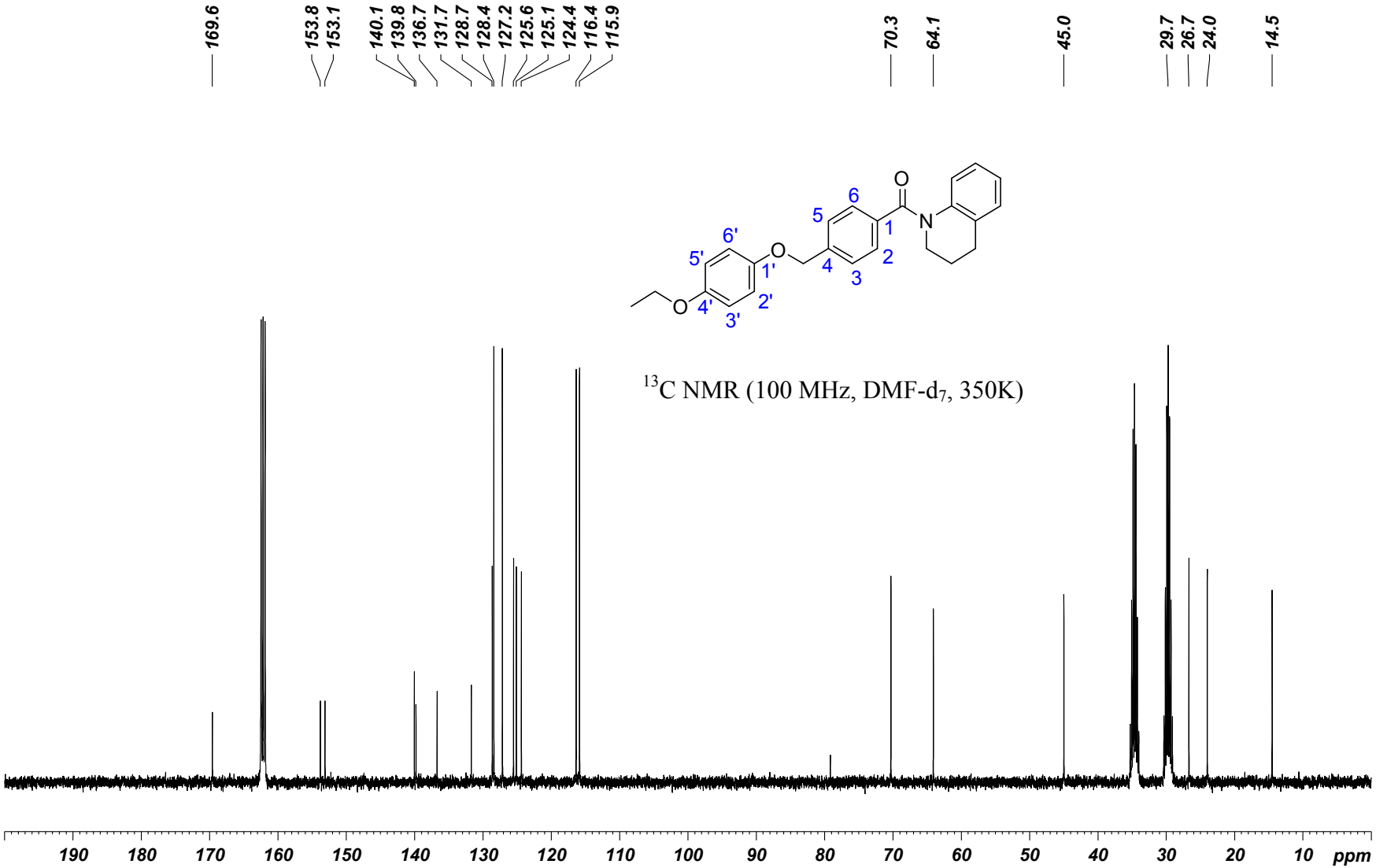
4-((4-Ethoxyphenoxy)methyl)-*N*,*N*-diisopropylbenzamide; 37.



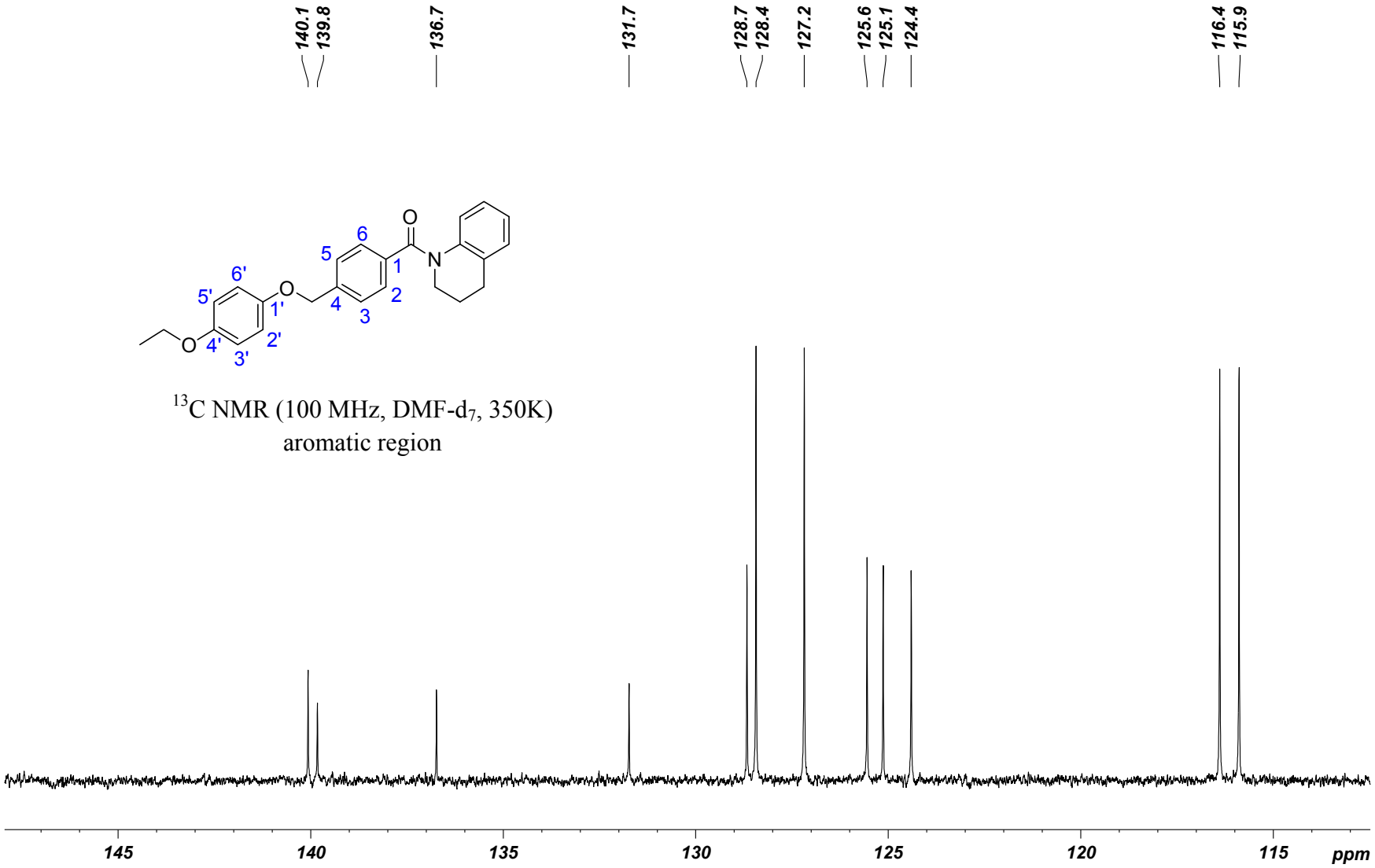
(3,4-Dihydroquinolin-1(2*H*)-yl)(4-((4-ethoxyphenoxy)methyl)phenyl)methanone; S66.



(3,4-Dihydroquinolin-1(2*H*)-yl)(4-((4-ethoxyphenoxy)methyl)phenyl)methanone; S66.

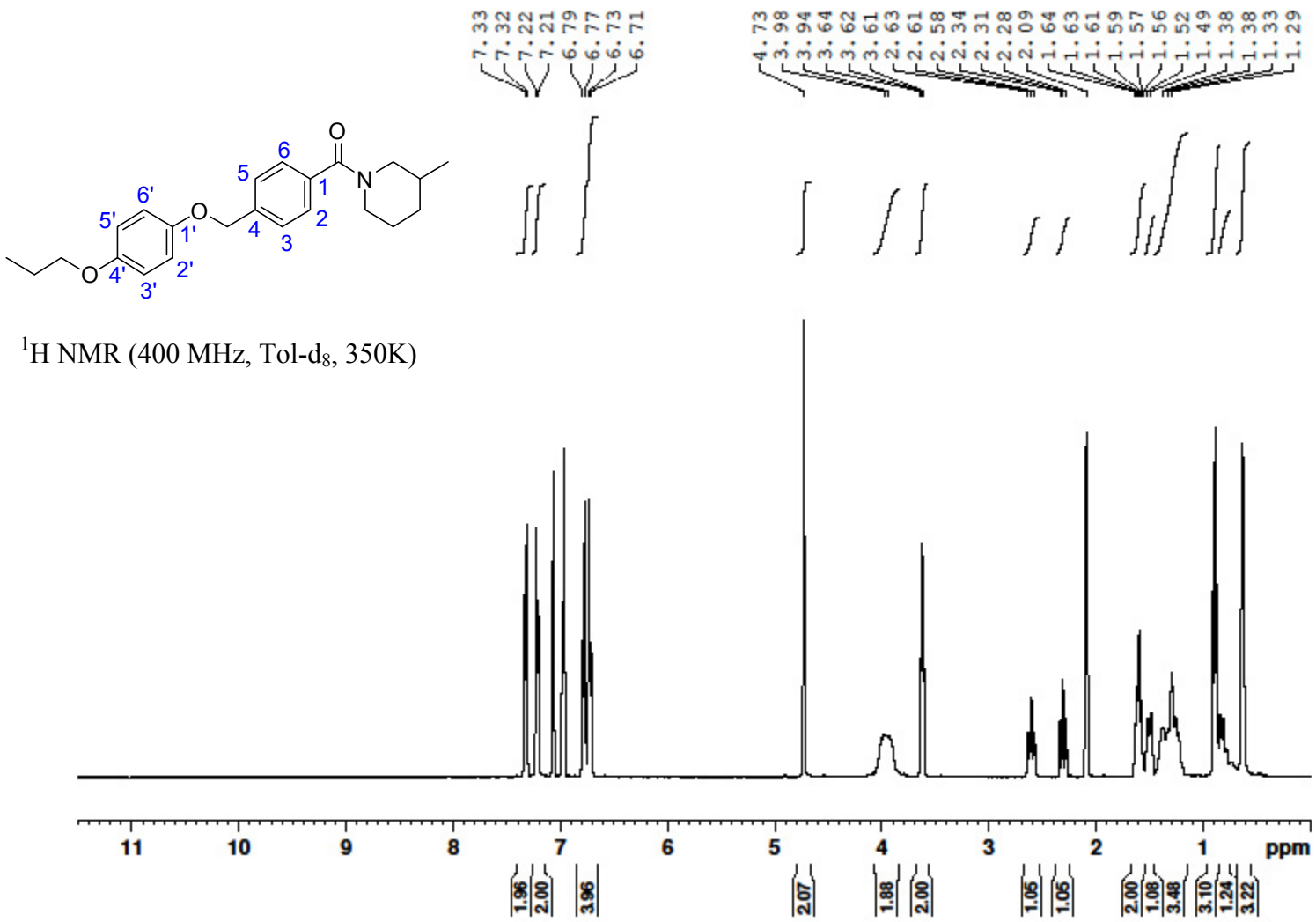


(3,4-Dihydroquinolin-1(2*H*)-yl)(4-((4-ethoxyphenoxy)methyl)phenyl)methanone; S66.



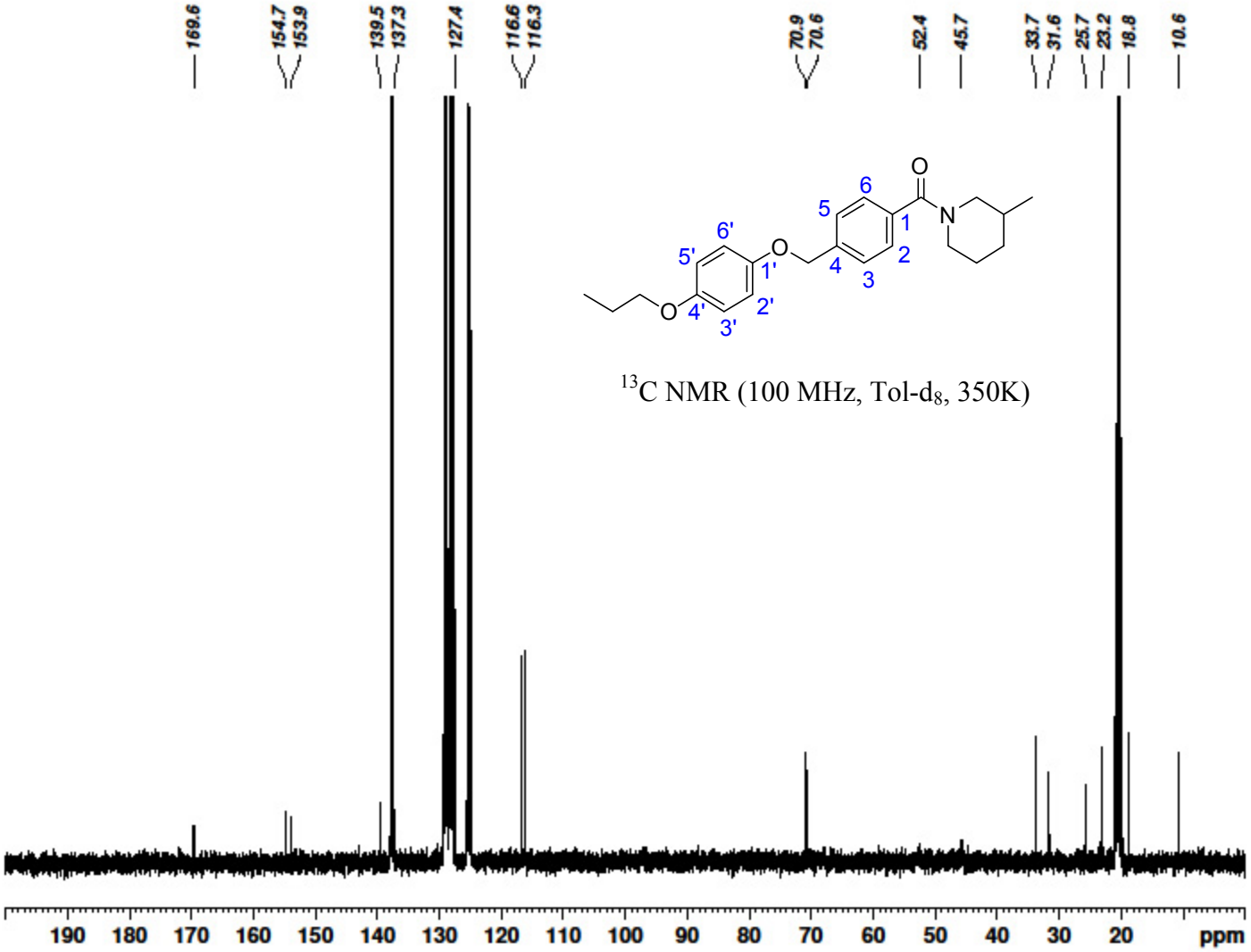
^{13}C NMR (100 MHz, DMF-d_7, 350K)
aromatic region

(3-Methylpiperidin-1-yl)(4-((4-propoxyphenoxy)methyl)phenyl)methanone; S67.



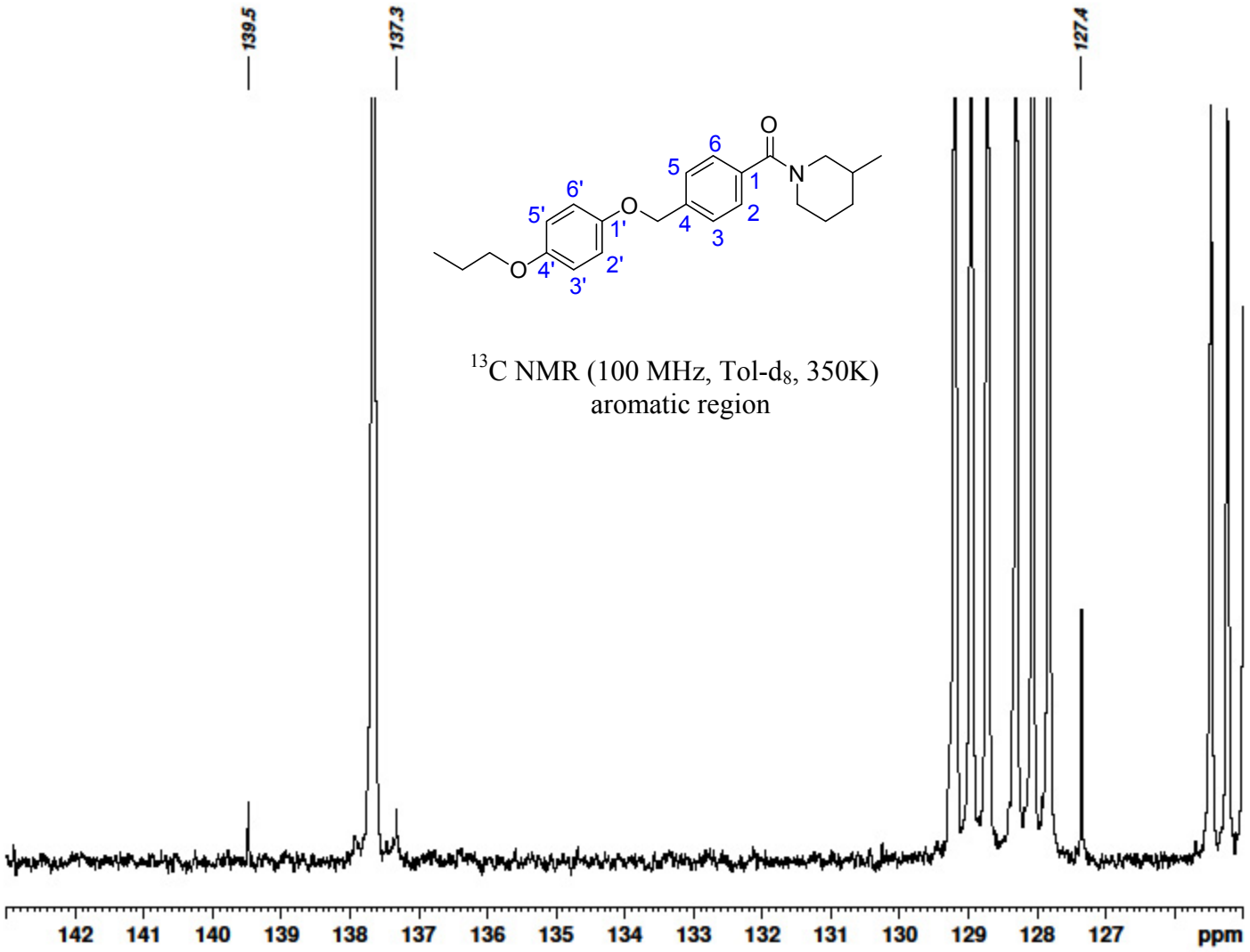
^{1}H NMR (400 MHz, Tol-d_8, 350K)

(3-Methylpiperidin-1-yl)(4-((4-propoxyphenoxy)methyl)phenyl)methanone; S67.



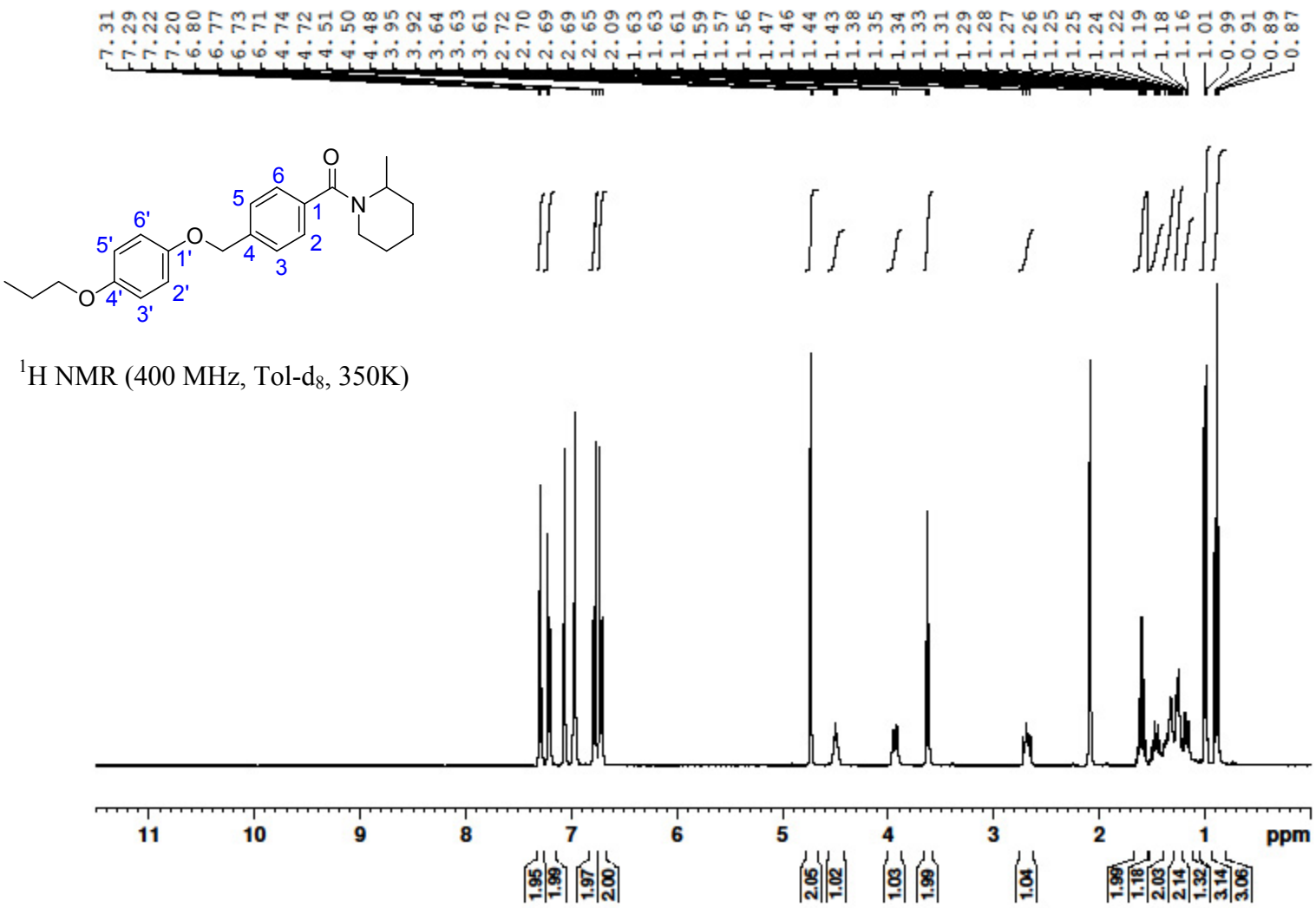
^{13}C NMR (100 MHz, Tol-d_8, 350K)

(3-Methylpiperidin-1-yl)(4-((4-propoxyphenoxy)methyl)phenyl)methanone; S67.



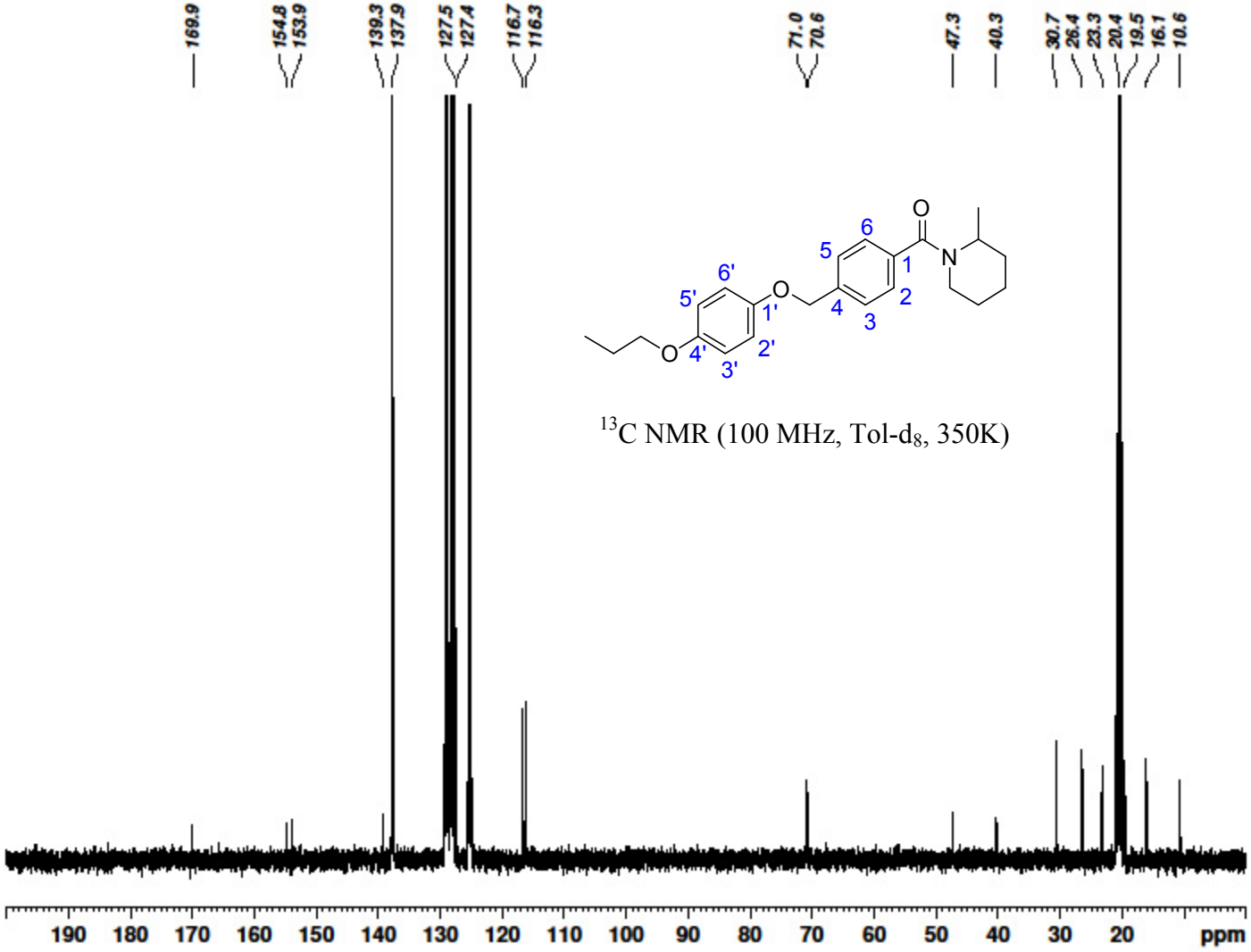
^{13}C NMR (100 MHz, Tol-d$_8$, 350K)
aromatic region

(2-Methylpiperidin-1-yl)(4-((4-propoxyphenoxy)methyl)phenyl)methanone; S68.



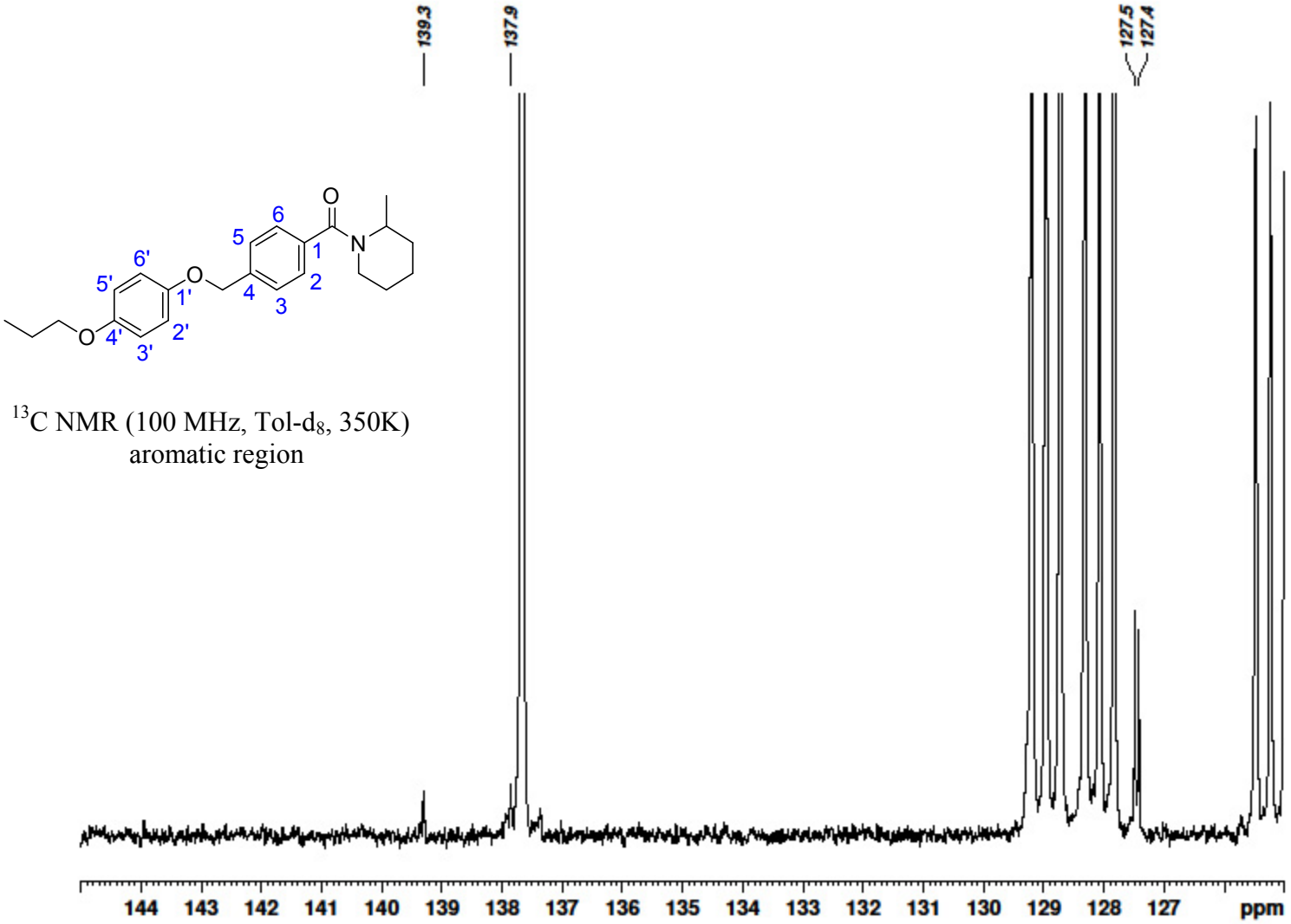
^{1}H NMR (400 MHz, Tol-d_8, 350K)

(2-Methylpiperidin-1-yl)(4-((4-propoxyphenoxy)methyl)phenyl)methanone; S68.



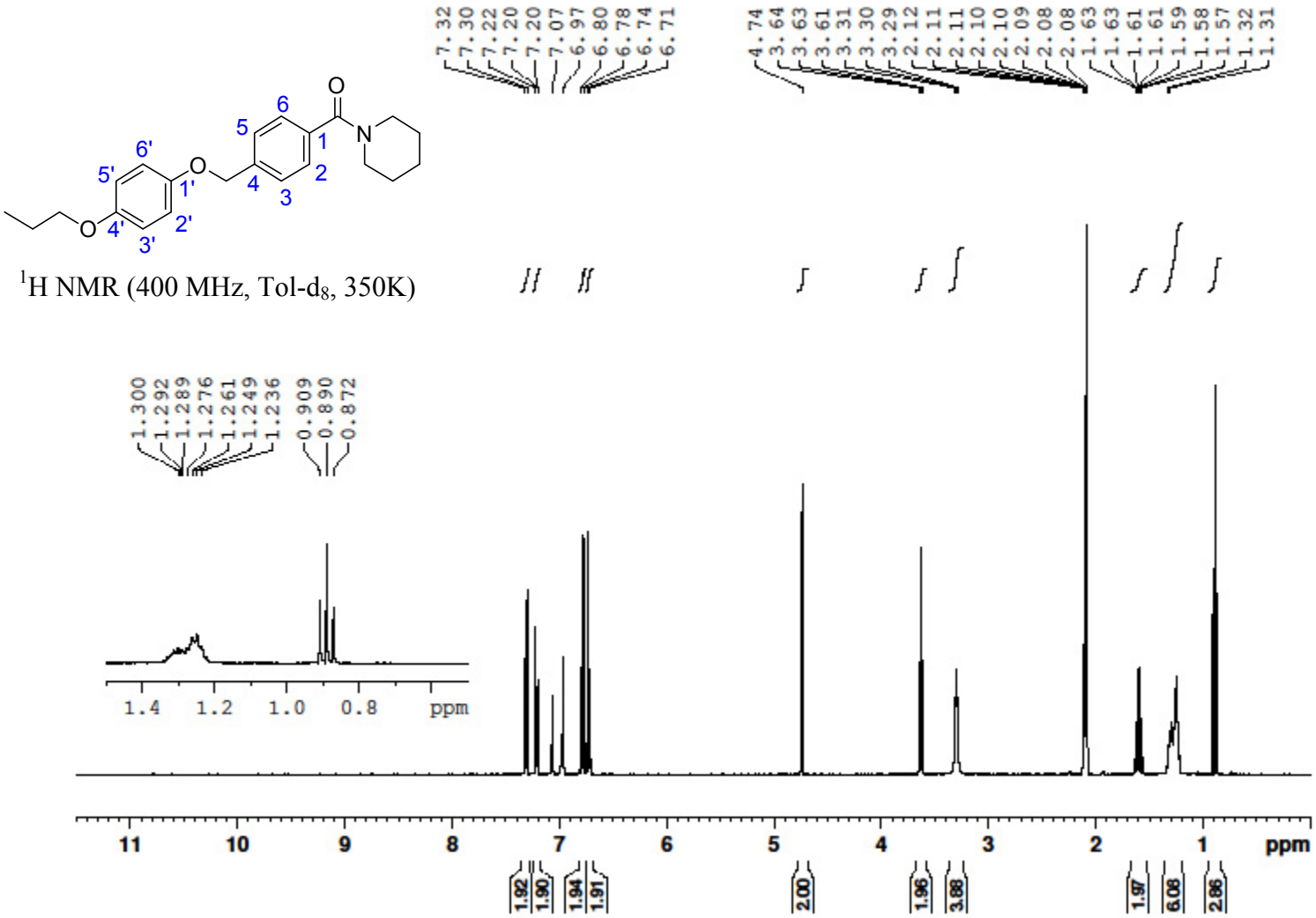
^{13}C NMR (100 MHz, Tol-d_8, 350K)

(2-Methylpiperidin-1-yl)(4-((4-propoxyphenoxy)methyl)phenyl)methanone; S68.



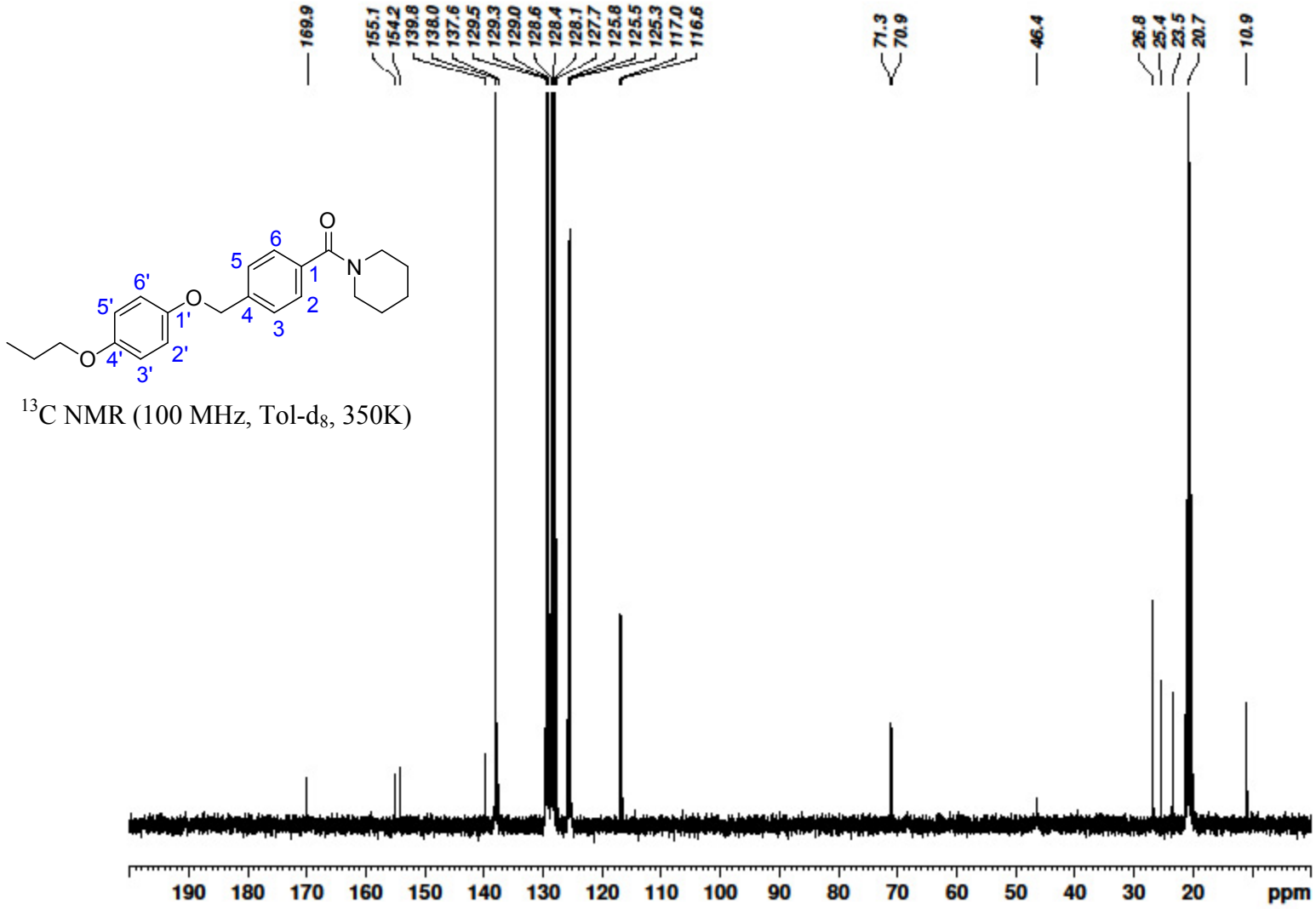
^{13}C NMR (100 MHz, Tol-d_8, 350K)
aromatic region

Piperidin-1-yl(4-((4-propoxyphenoxy)methyl)phenyl)methanone; S69.



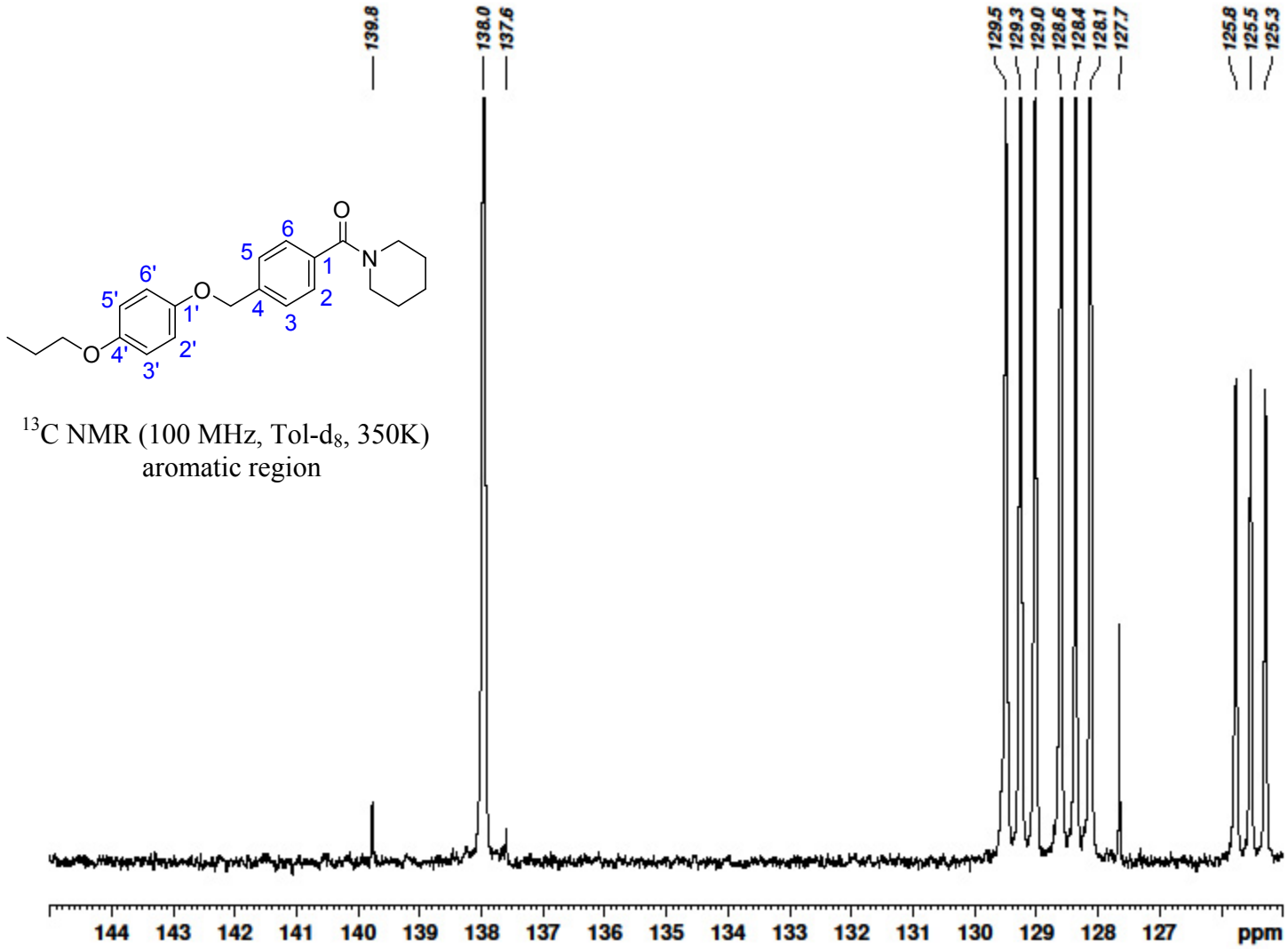
^{1}H NMR (400 MHz, Tol-d_8, 350K)

Piperidin-1-yl(4-((4-propoxyphenoxy)methyl)phenyl)methanone; S69.



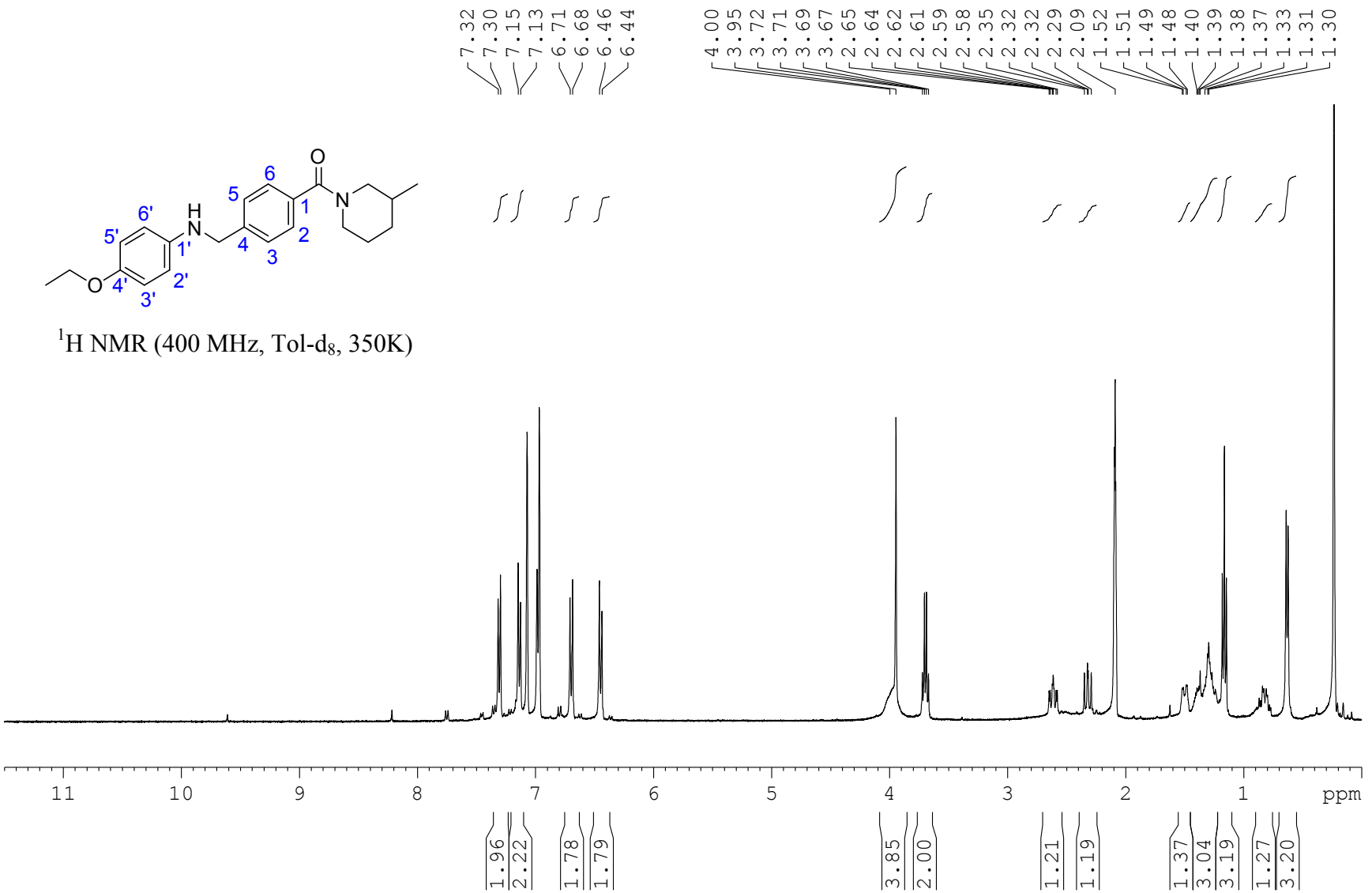
^{13}C NMR (100 MHz, Tol-d$_8$, 350K)

Piperidin-1-yl(4-((4-propoxyphenoxy)methyl)phenyl)methanone; S69.



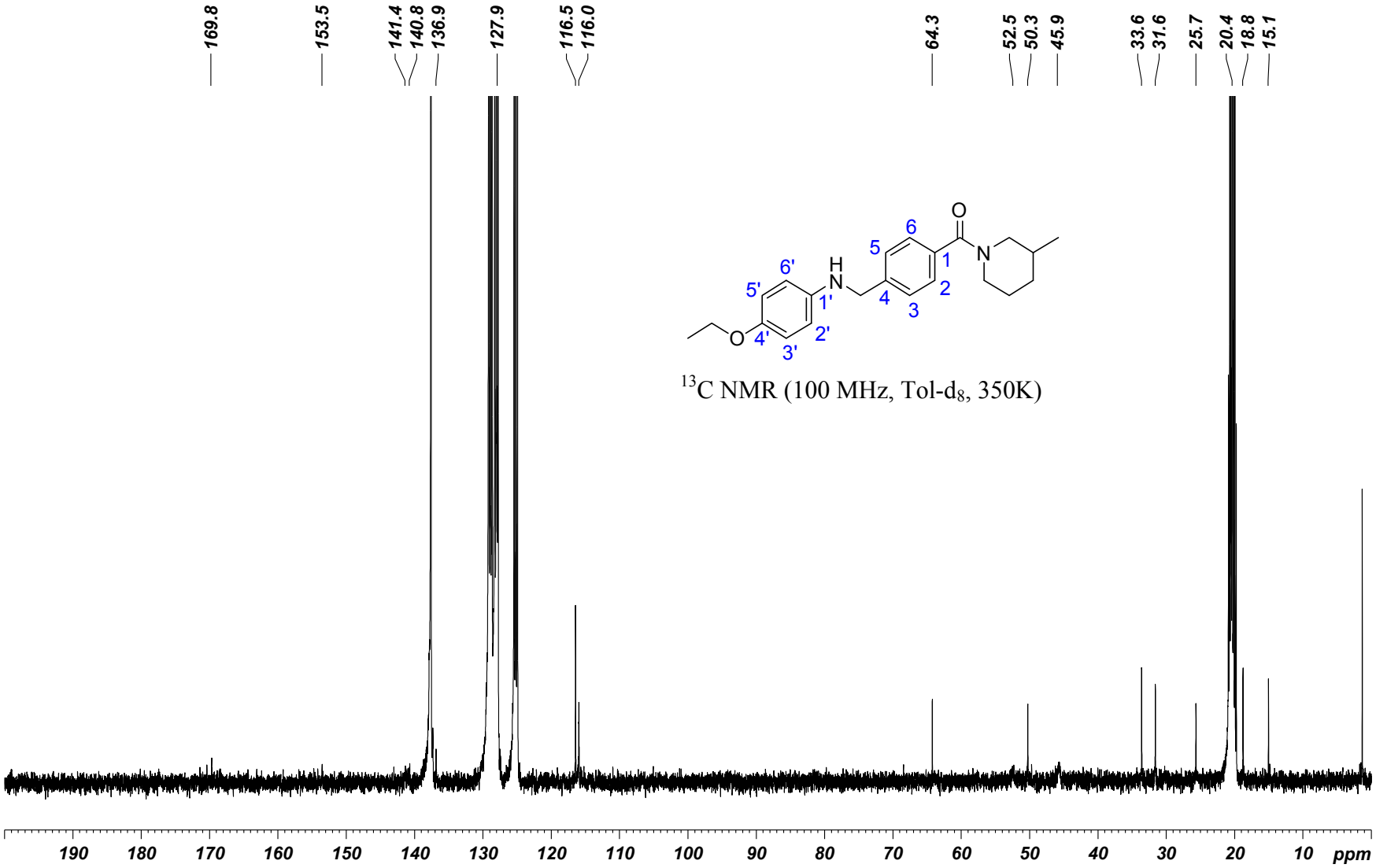
^{13}C NMR (100 MHz, Tol-d_8, 350K)
aromatic region

(4-(((4-Ethoxyphenyl)amino)methyl)phenyl)(3-methylpiperidin-1-yl)methanone; 13.



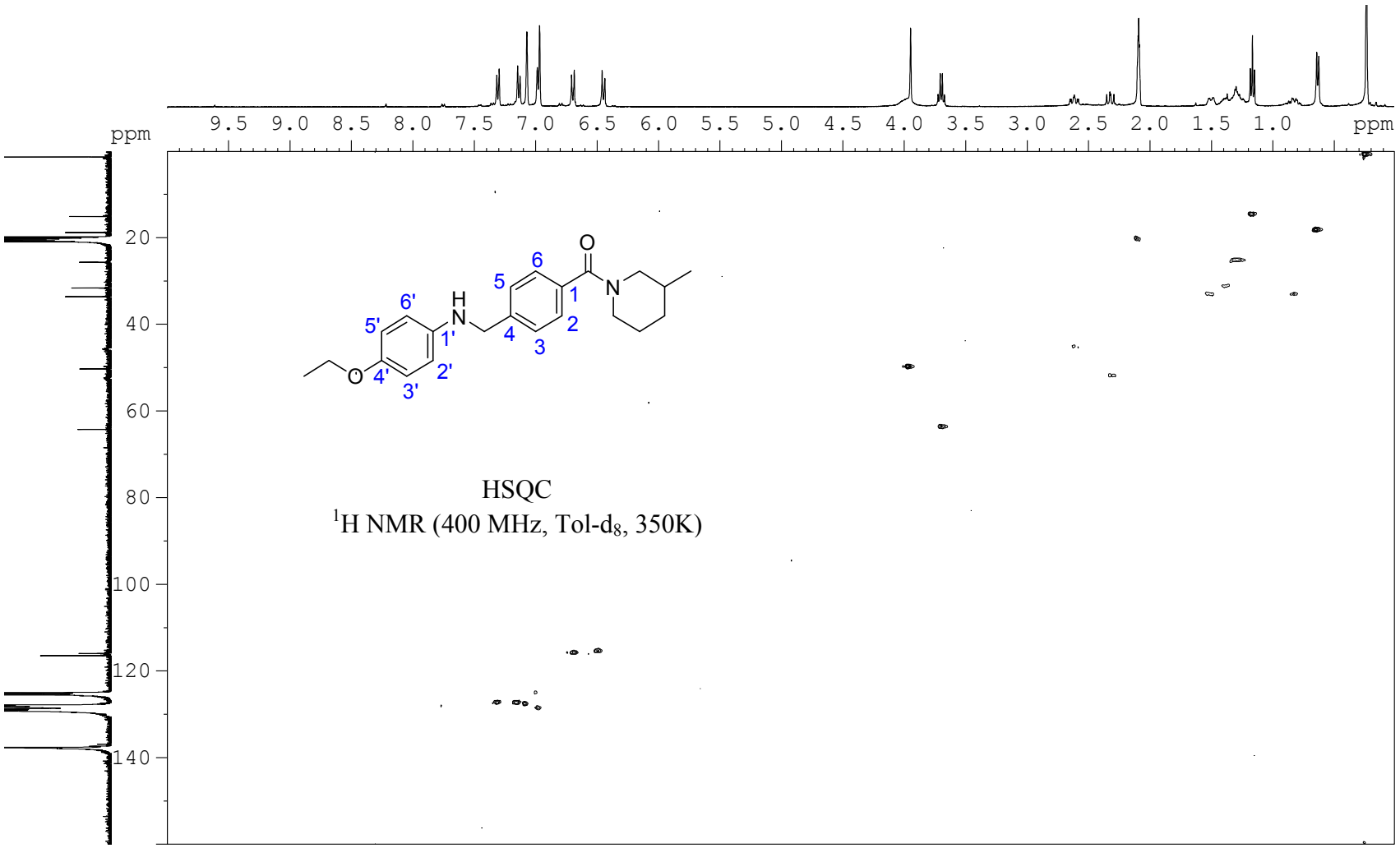
^{1}H NMR (400 MHz, Tol-d_8, 350K)

(4-(((4-Ethoxyphenyl)amino)methyl)phenyl)(3-methylpiperidin-1-yl)methanone; 13.

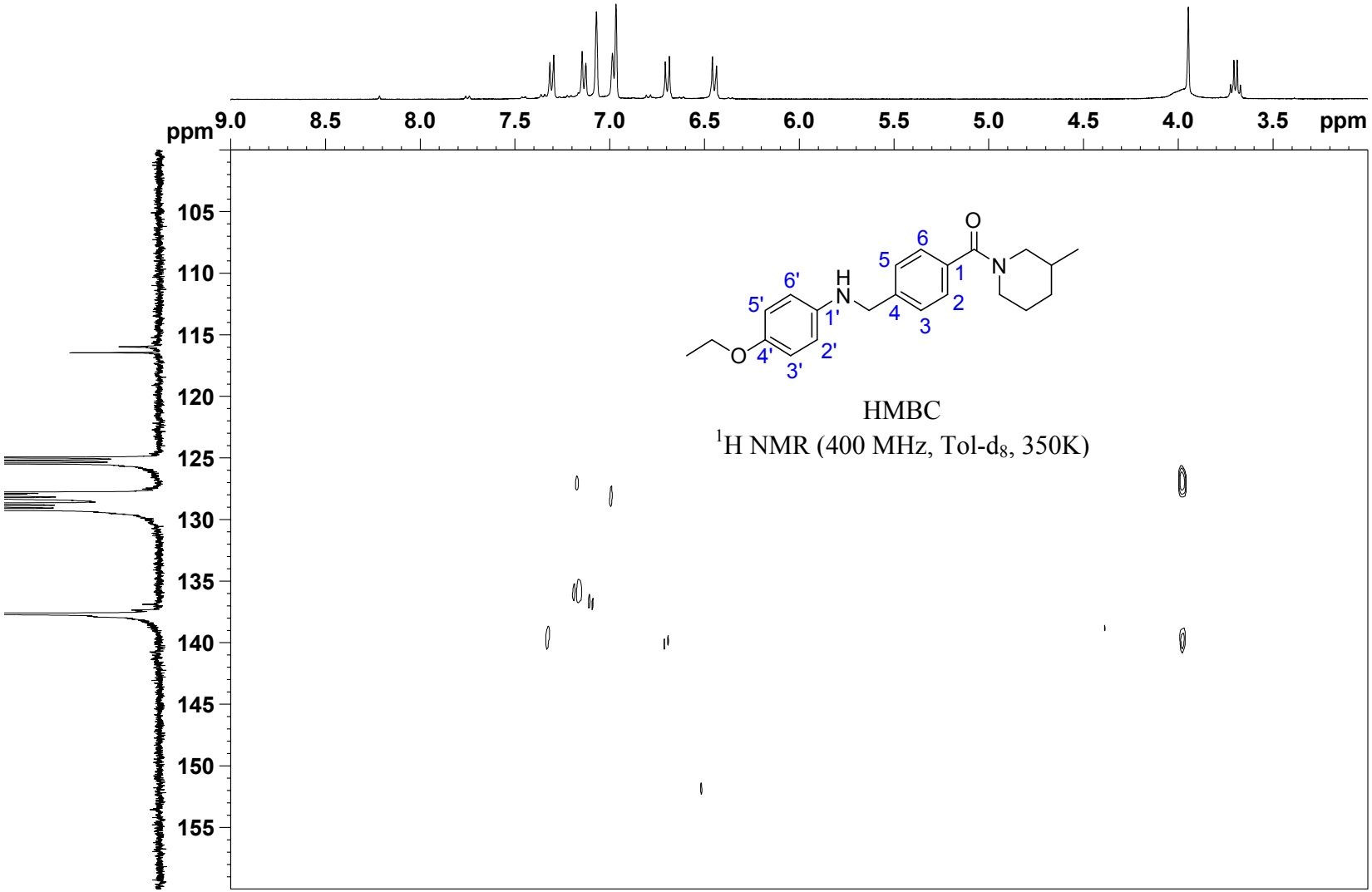


^{13}C NMR (100 MHz, Tol-d_8, 350K)

(4-(((4-Ethoxyphenyl)amino)methyl)phenyl)(3-methylpiperidin-1-yl)methanone; 13.



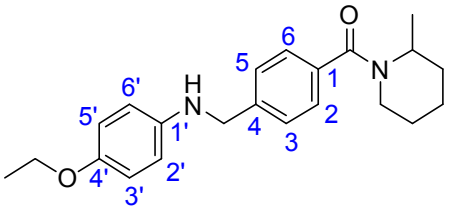
(4-(((4-Ethoxyphenyl)amino)methyl)phenyl)(3-methylpiperidin-1-yl)methanone; 13.



HMBC

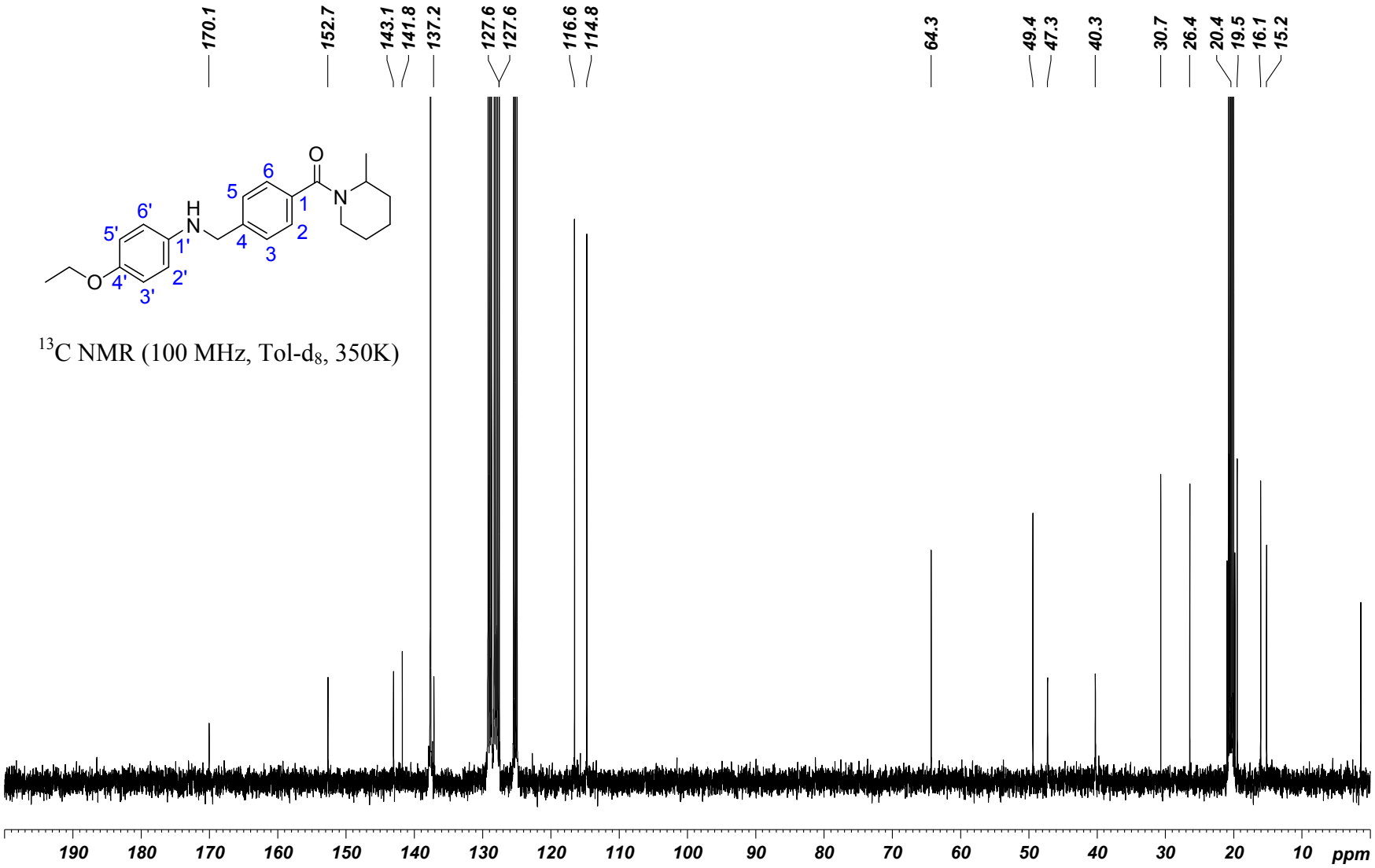
^{1}H NMR (400 MHz, Tol-d_8, 350K)

(4-(((4-Ethoxyphenyl)amino)methyl)phenyl)(2-methylpiperidin-1-yl)methanone; 18.



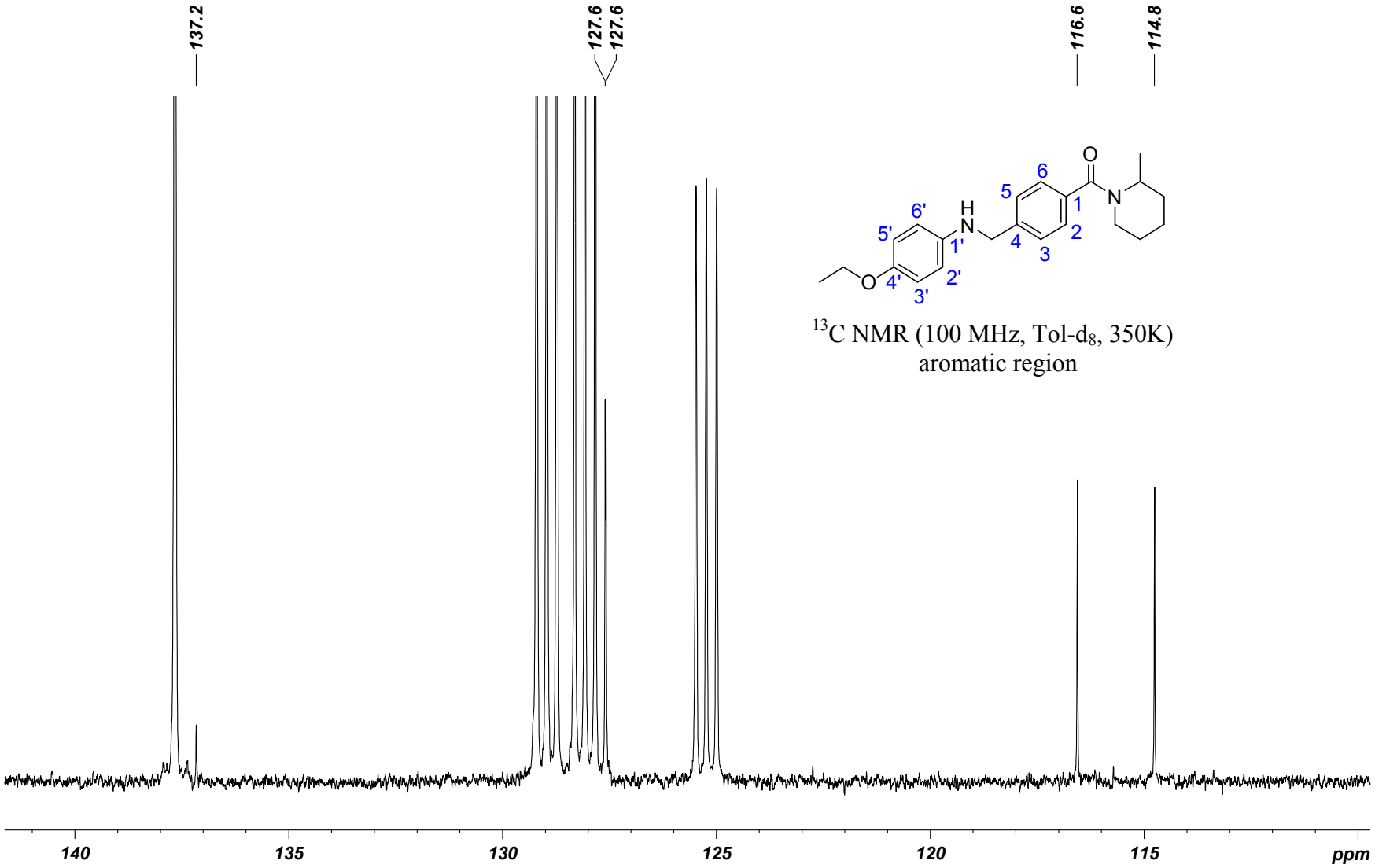
^{1}H NMR (400 MHz, Tol-d_8, 350K)

(4-(((4-Ethoxyphenyl)amino)methyl)phenyl)(2-methylpiperidin-1-yl)methanone; 18.



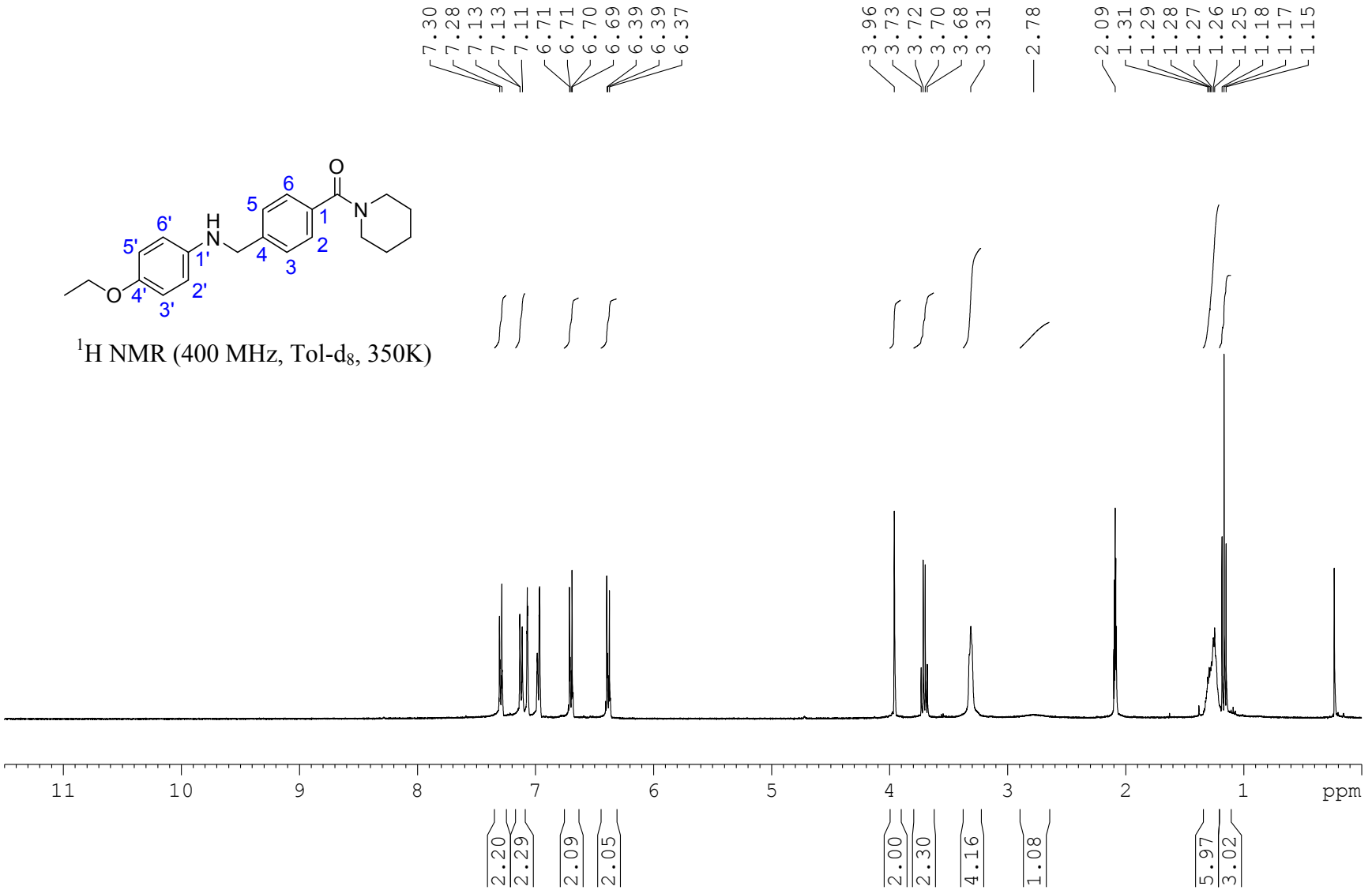
^{13}C NMR (100 MHz, Tol-d_8, 350K)

(4-(((4-Ethoxyphenyl)amino)methyl)phenyl)(2-methylpiperidin-1-yl)methanone; 18.



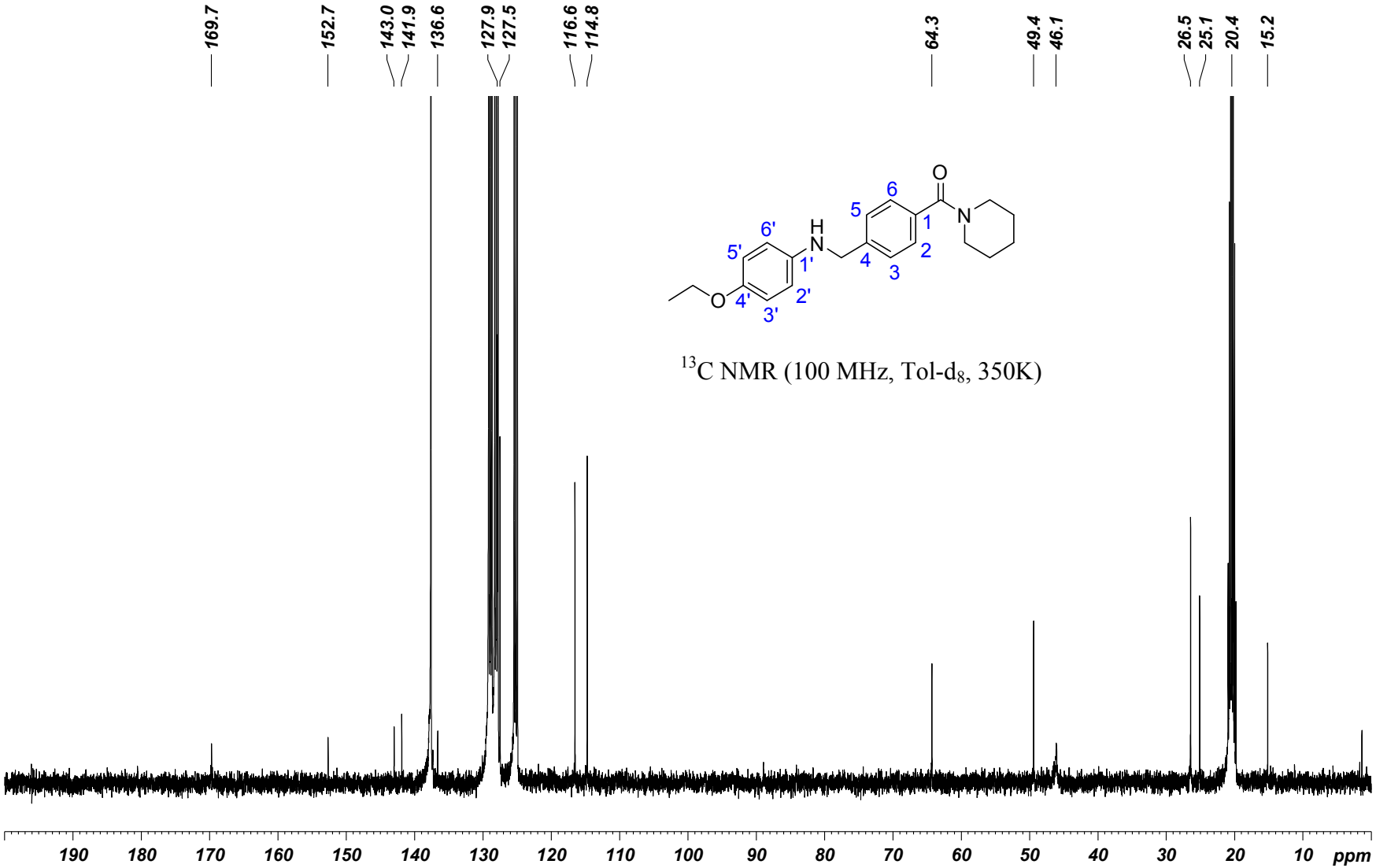
^{13}C NMR (100 MHz, Tol-d$_8$, 350K)
aromatic region

(4-(((4-Ethoxyphenyl)amino)methyl)phenyl)(piperidin-1-yl)methanone; 24.



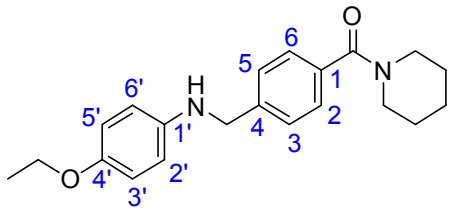
^{1}H NMR (400 MHz, Tol-d_8, 350K)

(4-(((4-Ethoxyphenyl)amino)methyl)phenyl)(piperidin-1-yl)methanone; 24.



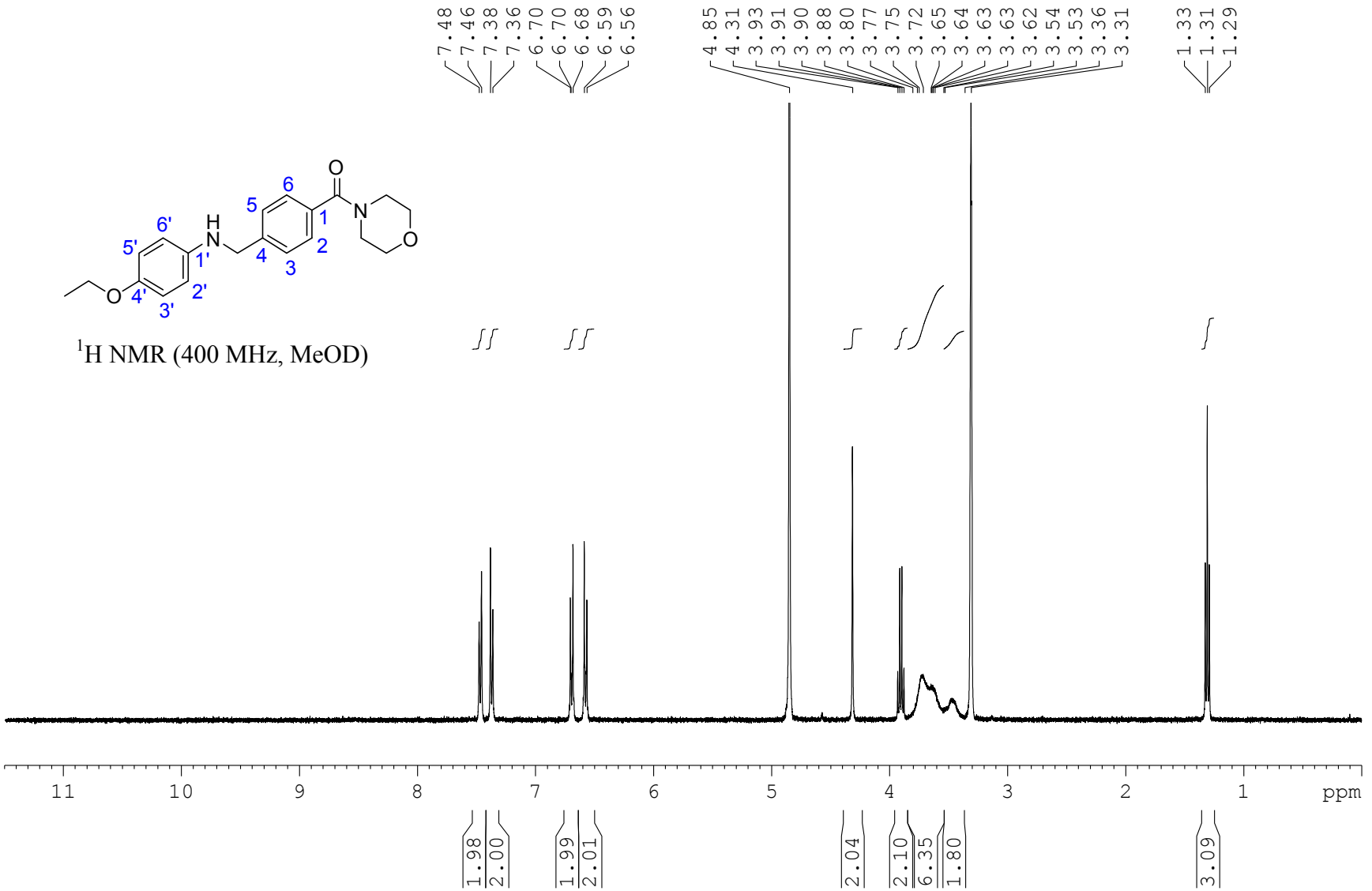
^{13}C NMR (100 MHz, Tol-d_8, 350K)

(4-(((4-Ethoxyphenyl)amino)methyl)phenyl)(piperidin-1-yl)methanone; 24.

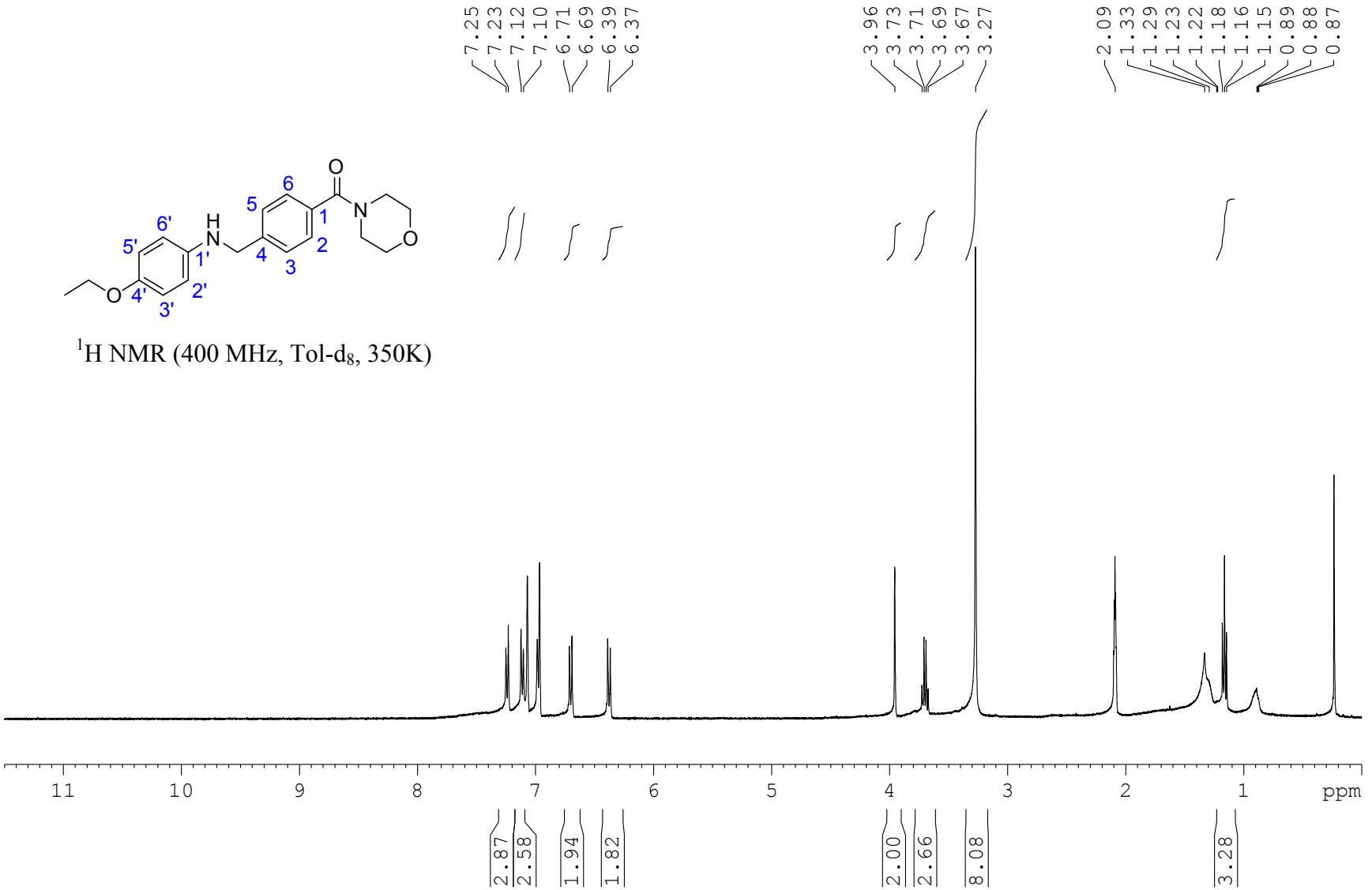


^{13}C NMR (100 MHz, Tol-d_8, 350K)
aromatic region

(4-(((4-Ethoxyphenyl)amino)methyl)phenyl)(morpholino)methanone; 28.

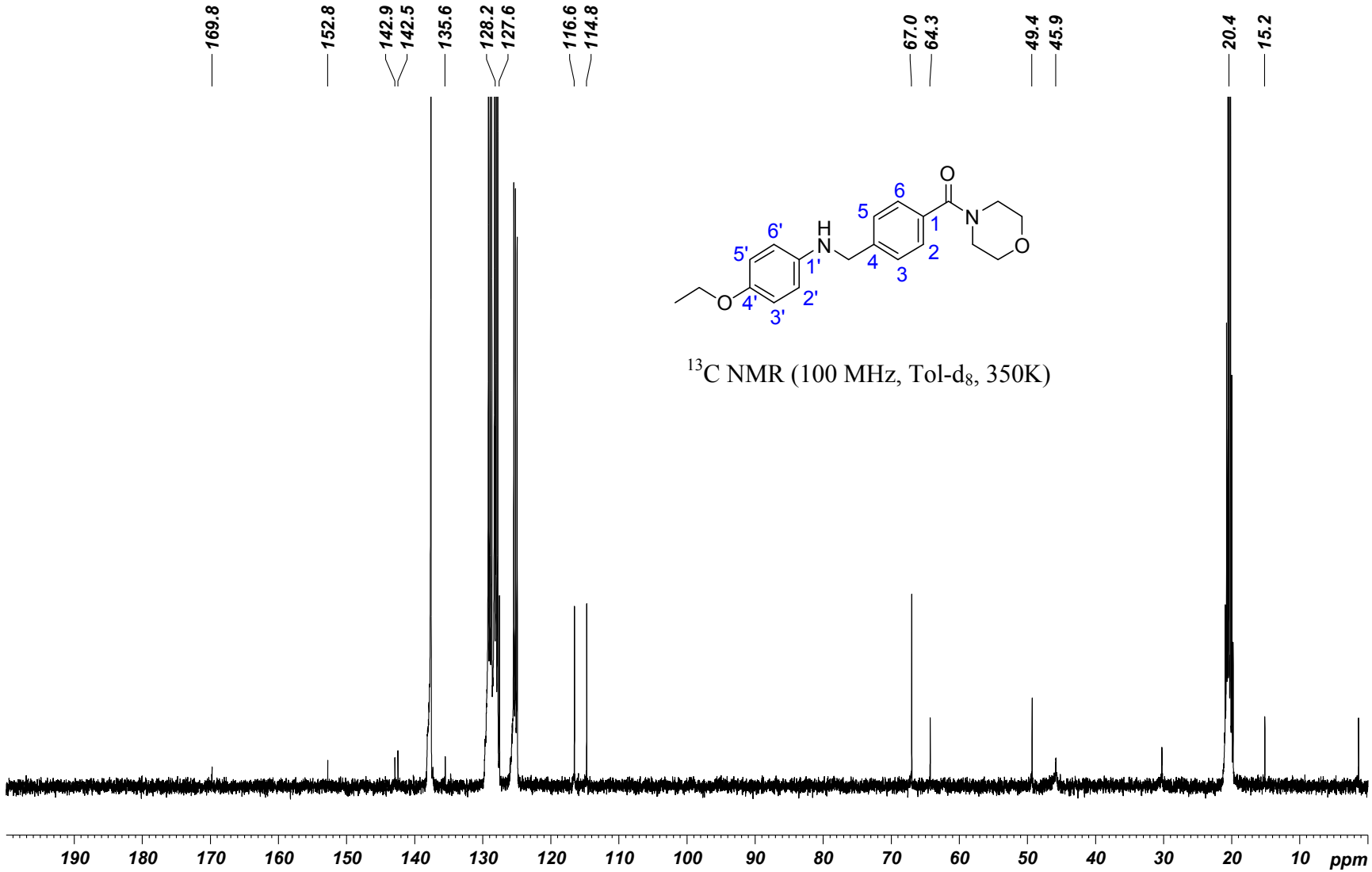


(4-(((4-Ethoxyphenyl)amino)methyl)phenyl)(morpholino)methanone; 28.



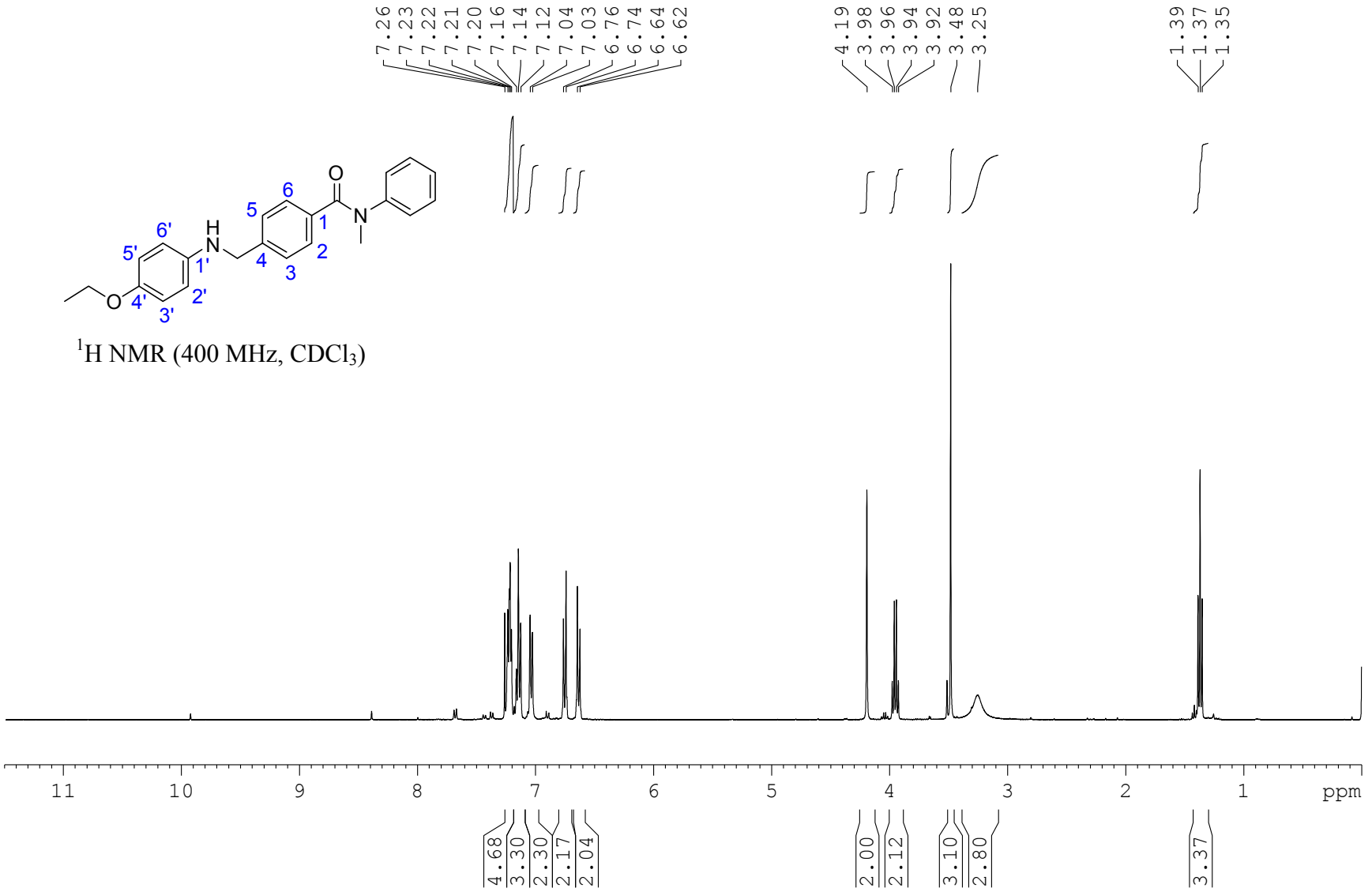
^{1}H NMR (400 MHz, Tol-d_8, 350K)

(4-(((4-Ethoxyphenyl)amino)methyl)phenyl)(morpholino)methanone; 28.



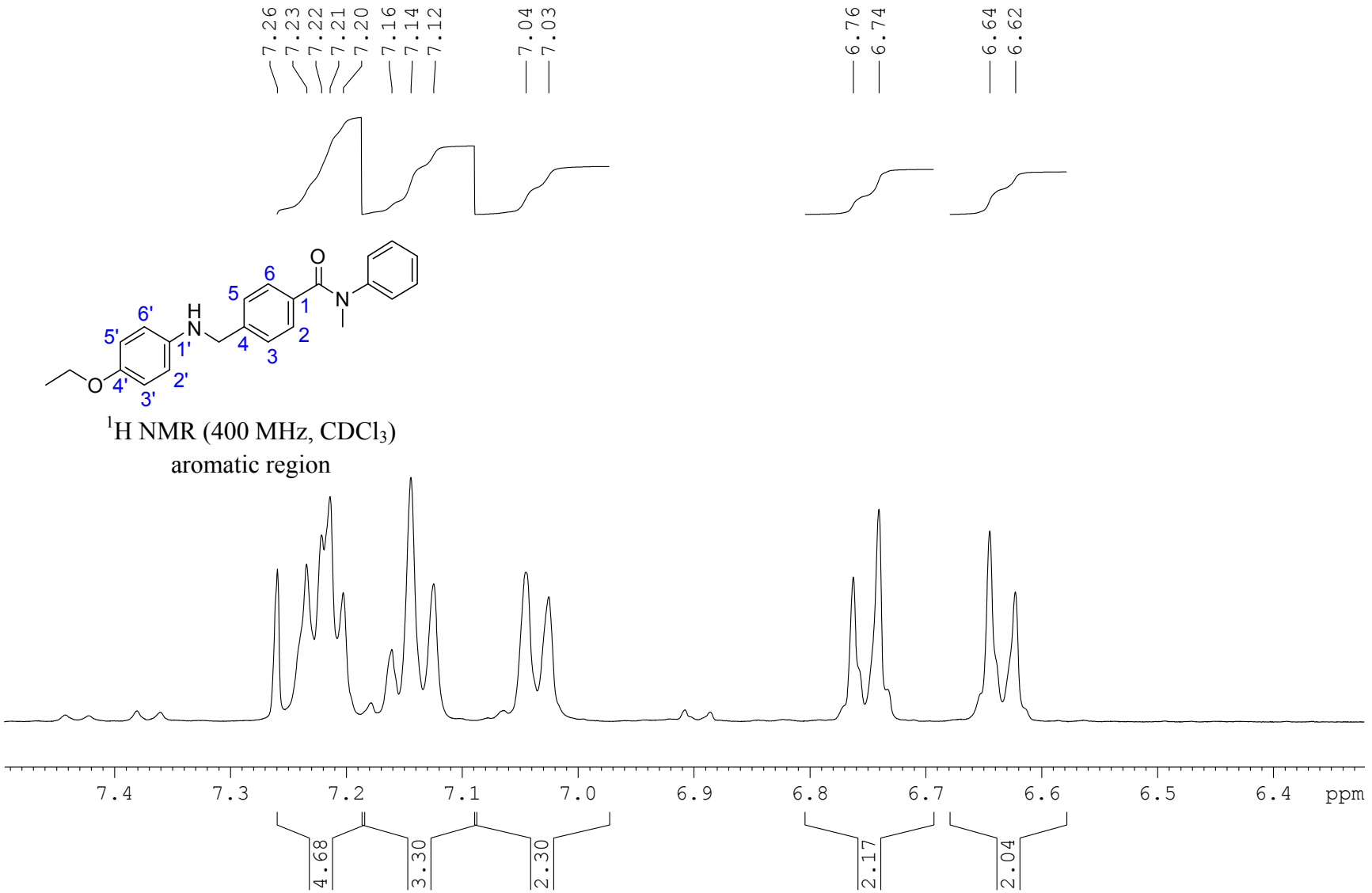
^{13}C NMR (100 MHz, Tol-d_8, 350K)

4-(((4-Ethoxyphenyl)amino)methyl)-*N*-methyl-*N*-phenylbenzamide; 35.

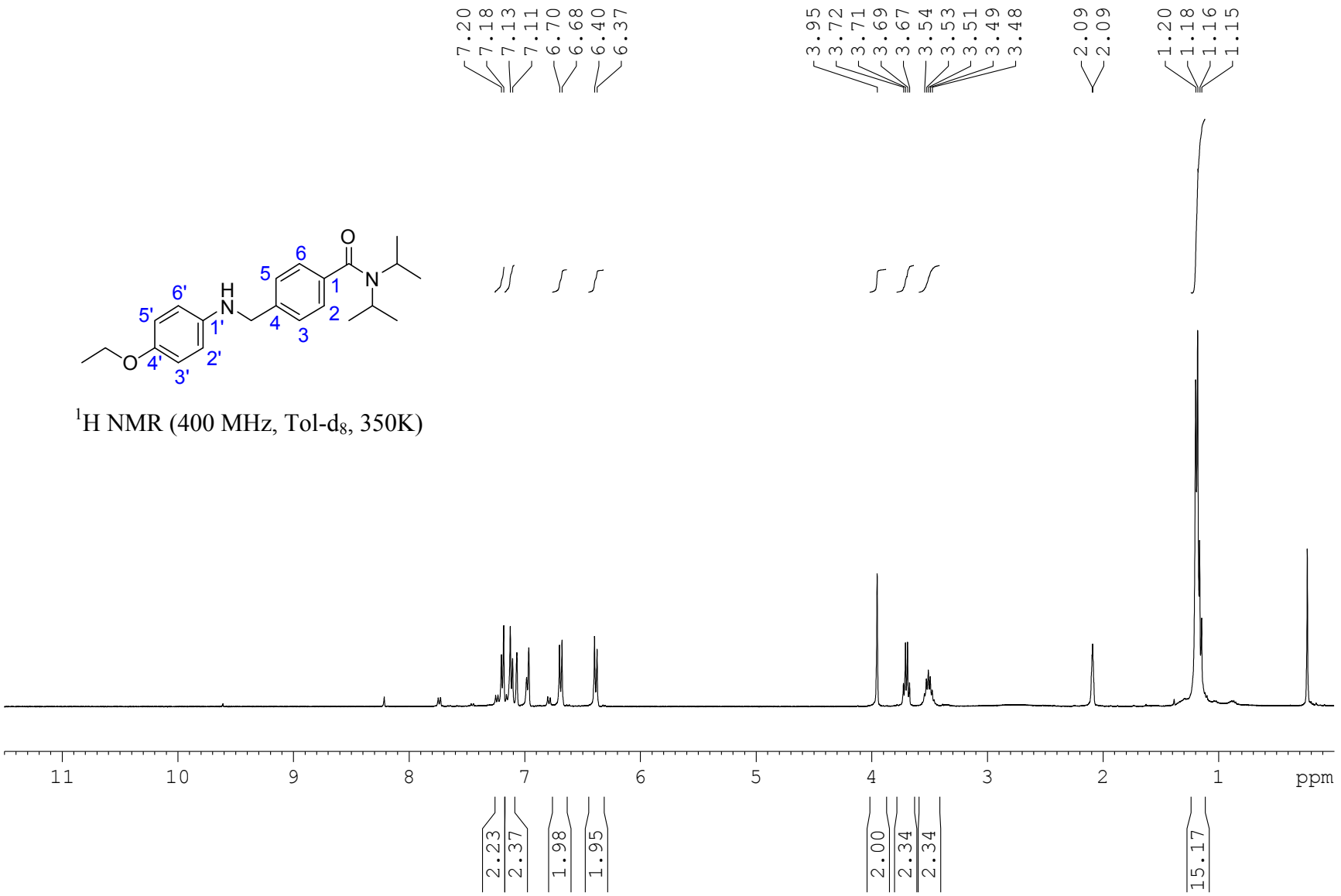


^{1}H NMR (400 MHz, $CDCl_3$)

4-(((4-Ethoxyphenyl)amino)methyl)-*N*-methyl-*N*-phenylbenzamide; 35.

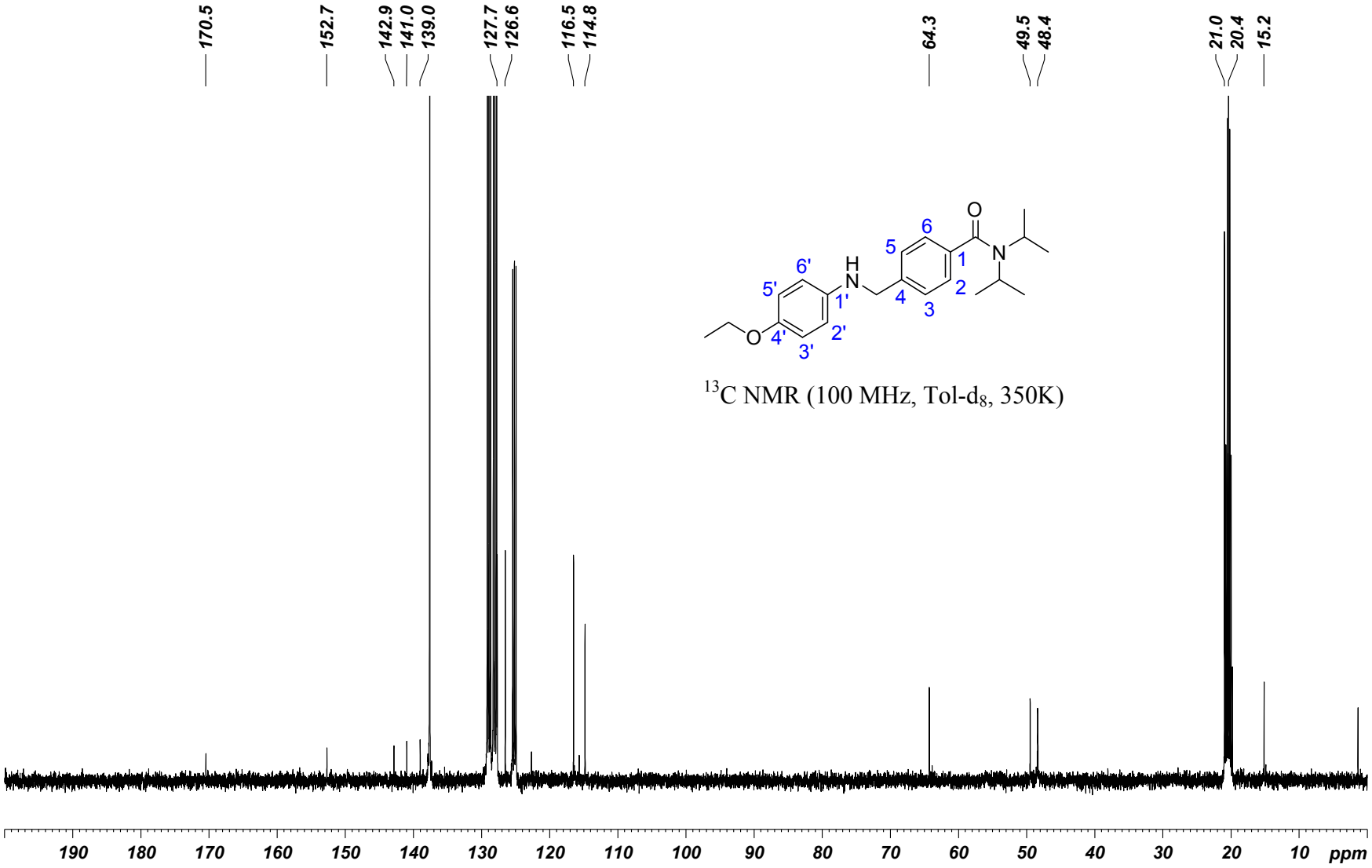


4-(((4-Ethoxyphenyl)amino)methyl)-*N*,*N*-diisopropylbenzamide; 38.



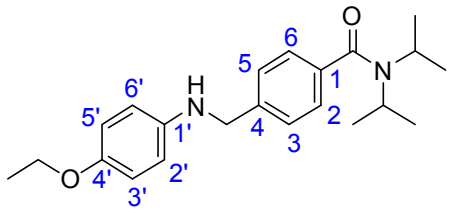
^{1}H NMR (400 MHz, Tol-d_8, 350K)

4-(((4-Ethoxyphenyl)amino)methyl)-*N*,*N*-diisopropylbenzamide; 38.



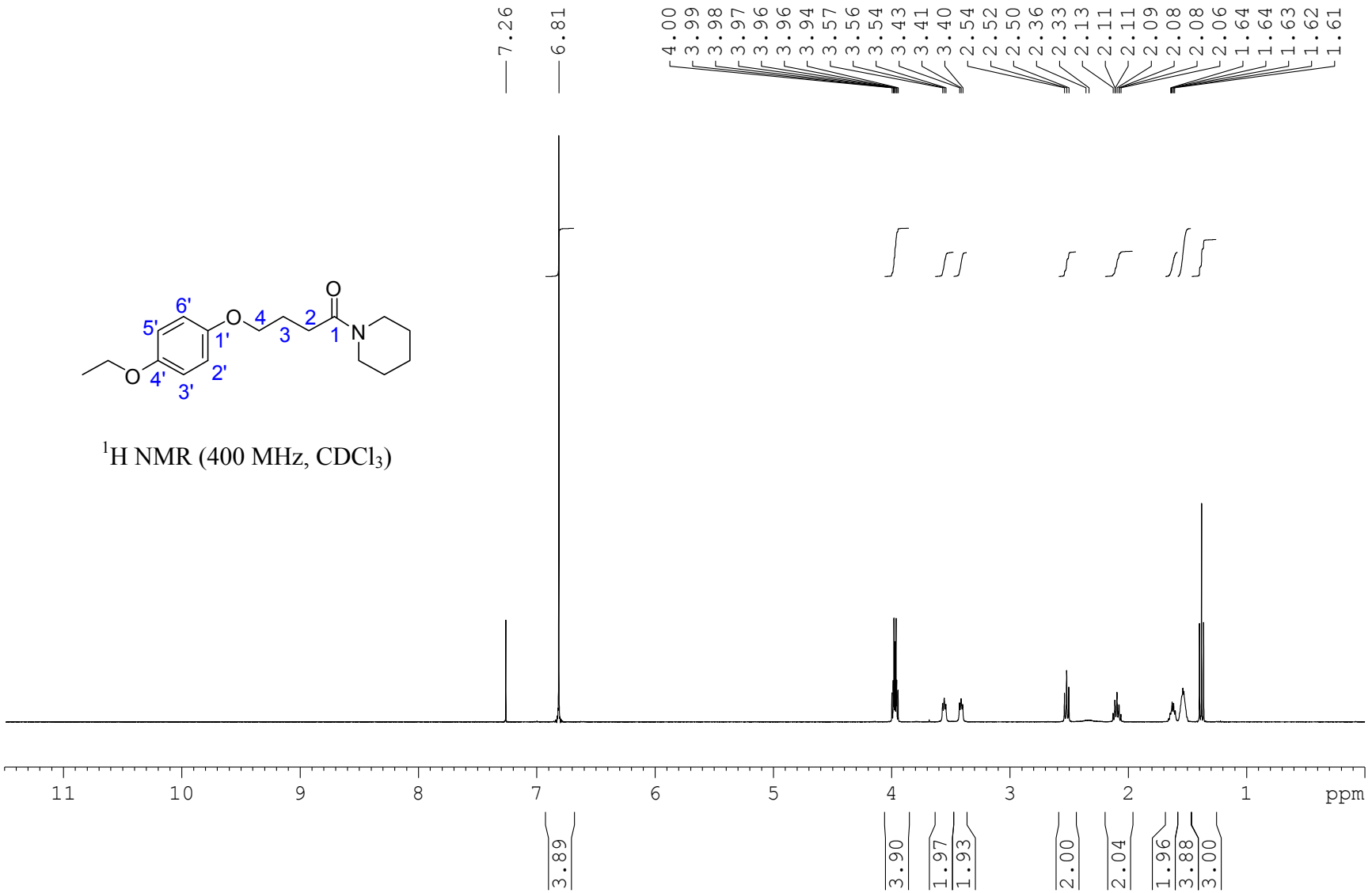
^{13}C NMR (100 MHz, Tol-d_8, 350K)

4-(((4-Ethoxyphenyl)amino)methyl)-*N*,*N*-diisopropylbenzamide; 38.



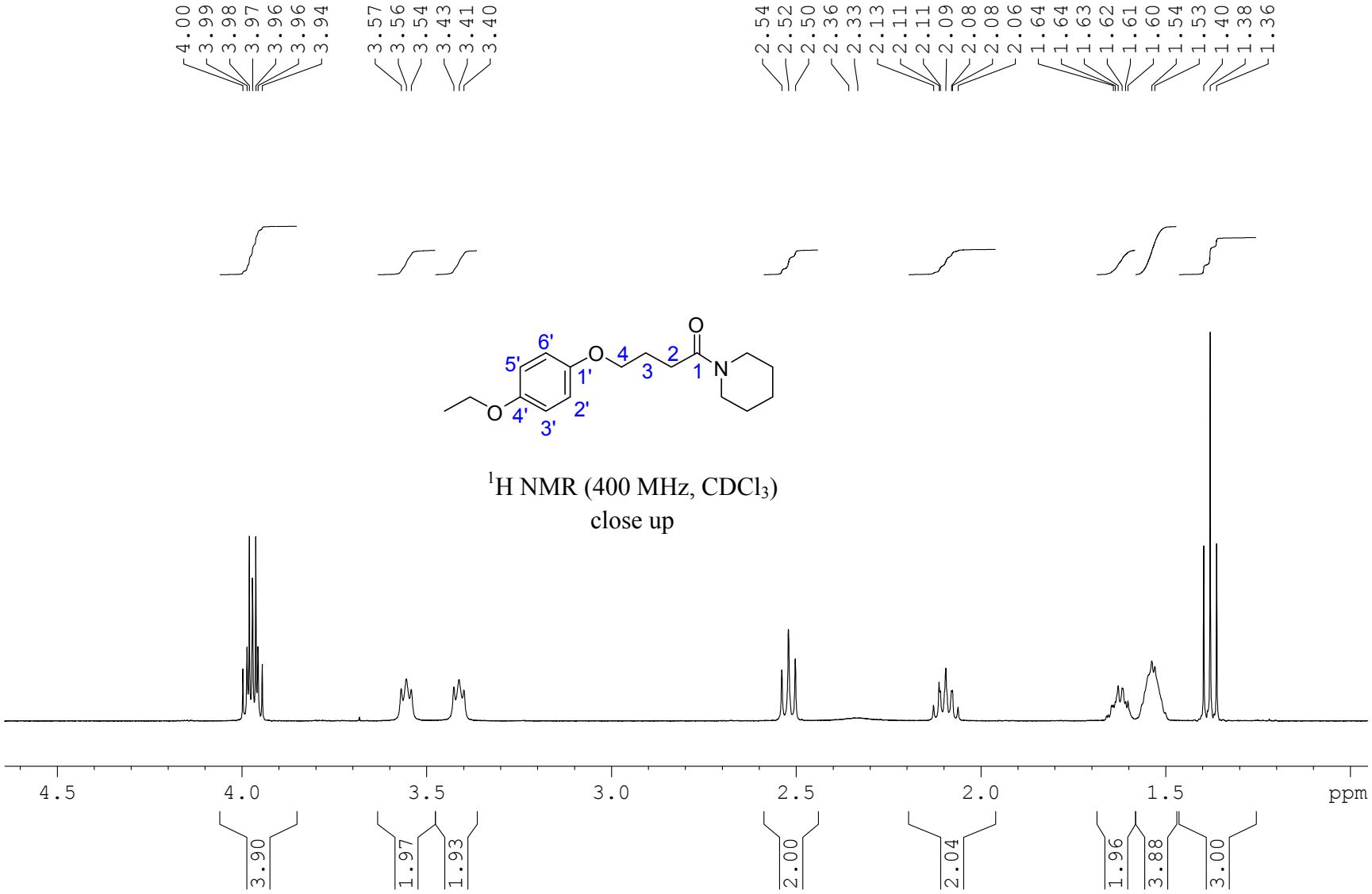
^{13}C NMR (100 MHz, Tol-d$_8$, 350K)
aromatic region

4-(4-Ethoxyphenoxy)-1-(piperidin-1-yl)butan-1-one; S79.



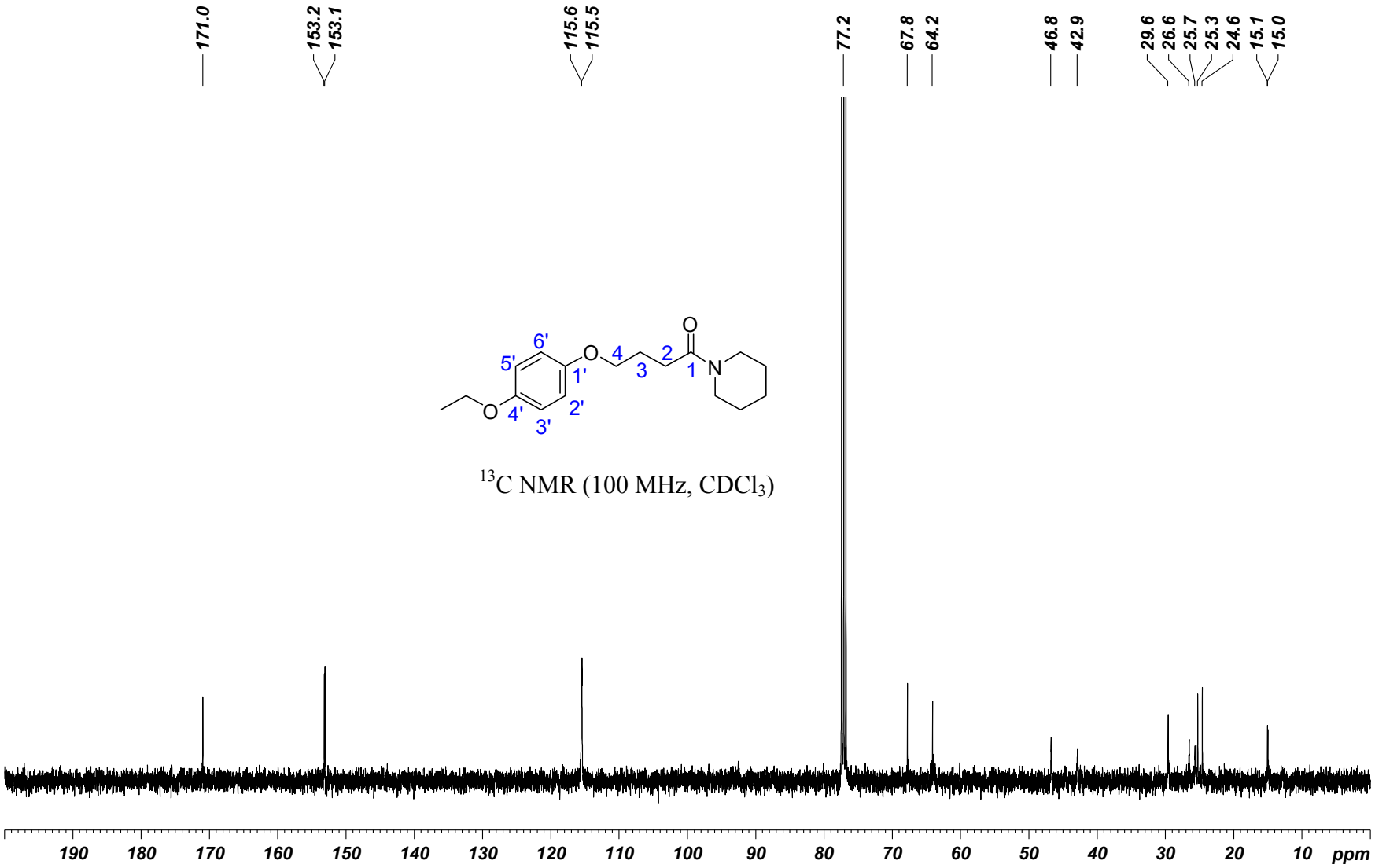
^{1}H NMR (400 MHz, $CDCl_3$)

4-(4-Ethoxyphenoxy)-1-(piperidin-1-yl)butan-1-one; S79.



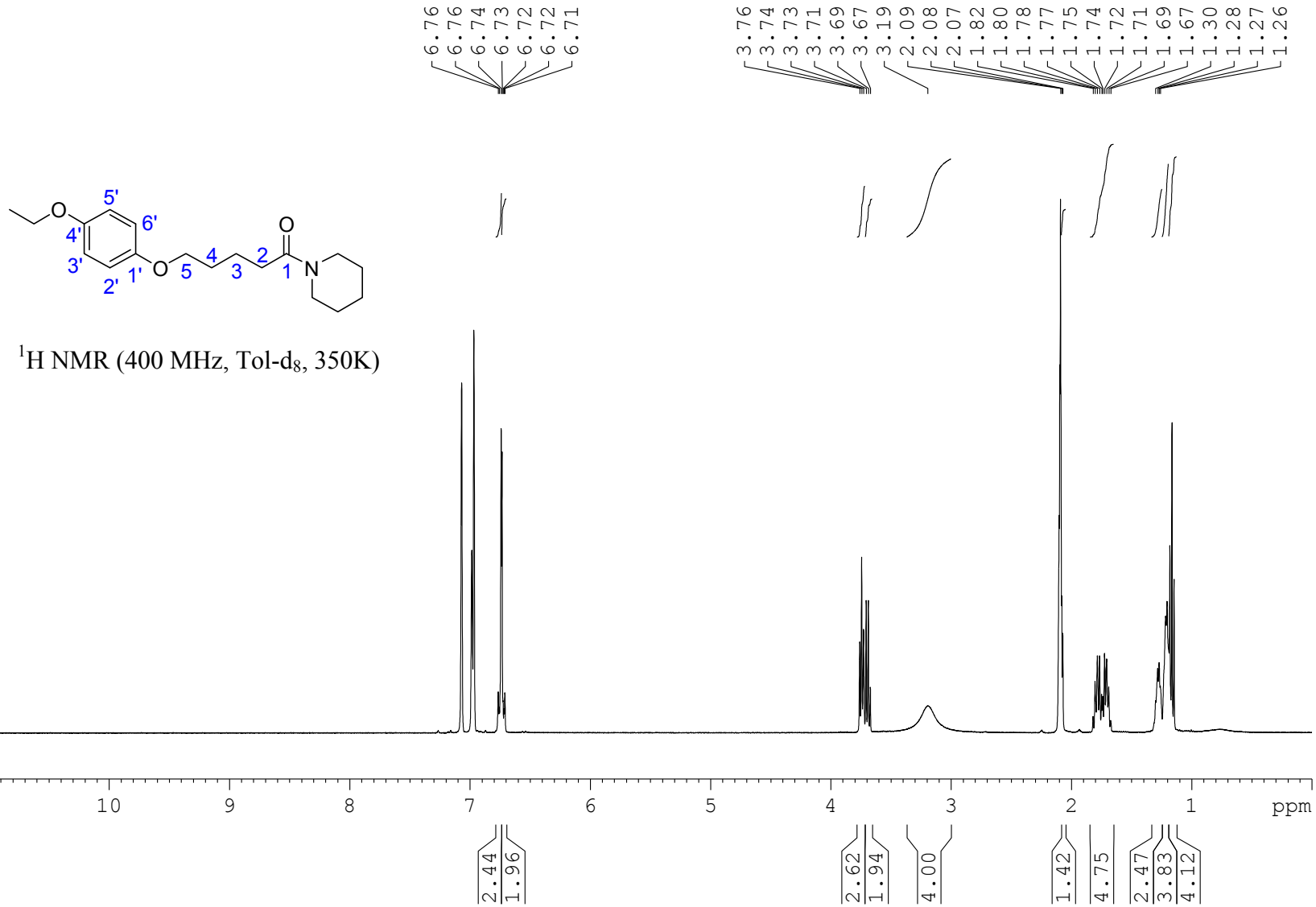
^{1}H NMR (400 MHz, $CDCl_3$)
close up

4-(4-Ethoxyphenoxy)-1-(piperidin-1-yl)butan-1-one; S79.



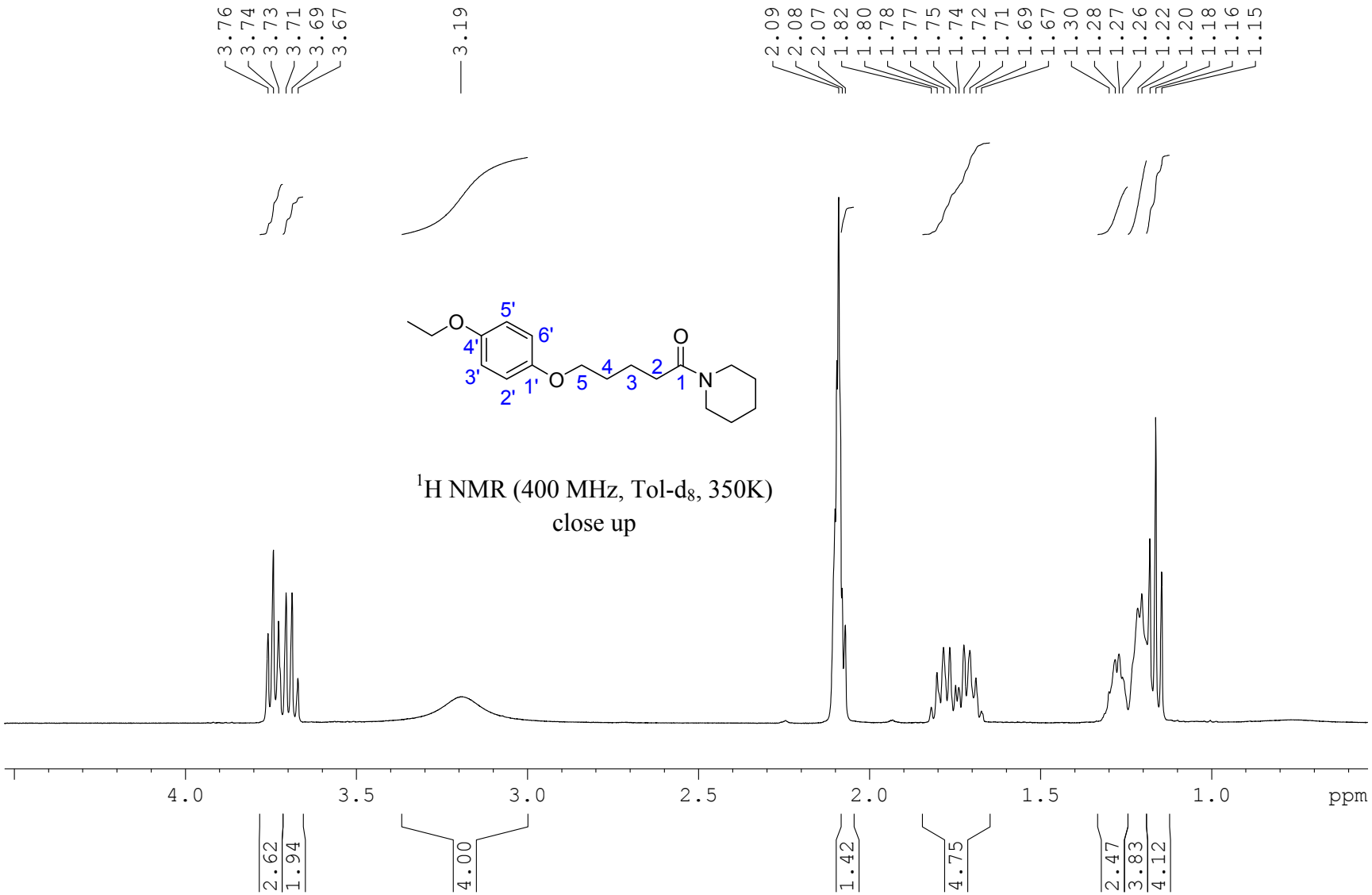
^{13}C NMR (100 MHz, $CDCl_3$)

5-(4-Ethoxyphenoxy)-1-(piperidin-1-yl)pentan-1-one; S80.



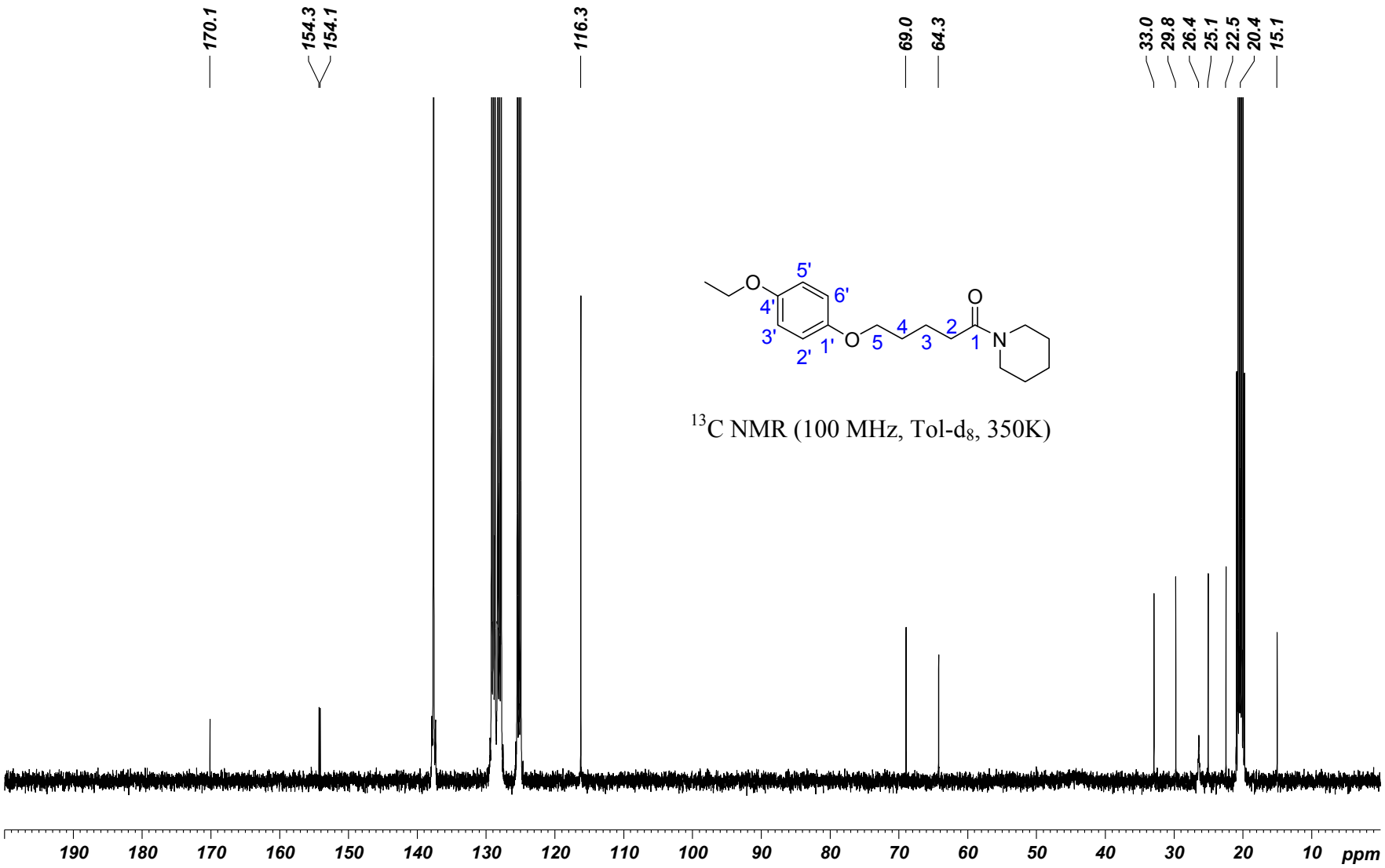
^{1}H NMR (400 MHz, Tol-d_8, 350K)

5-(4-Ethoxyphenoxy)-1-(piperidin-1-yl)pentan-1-one; S80.



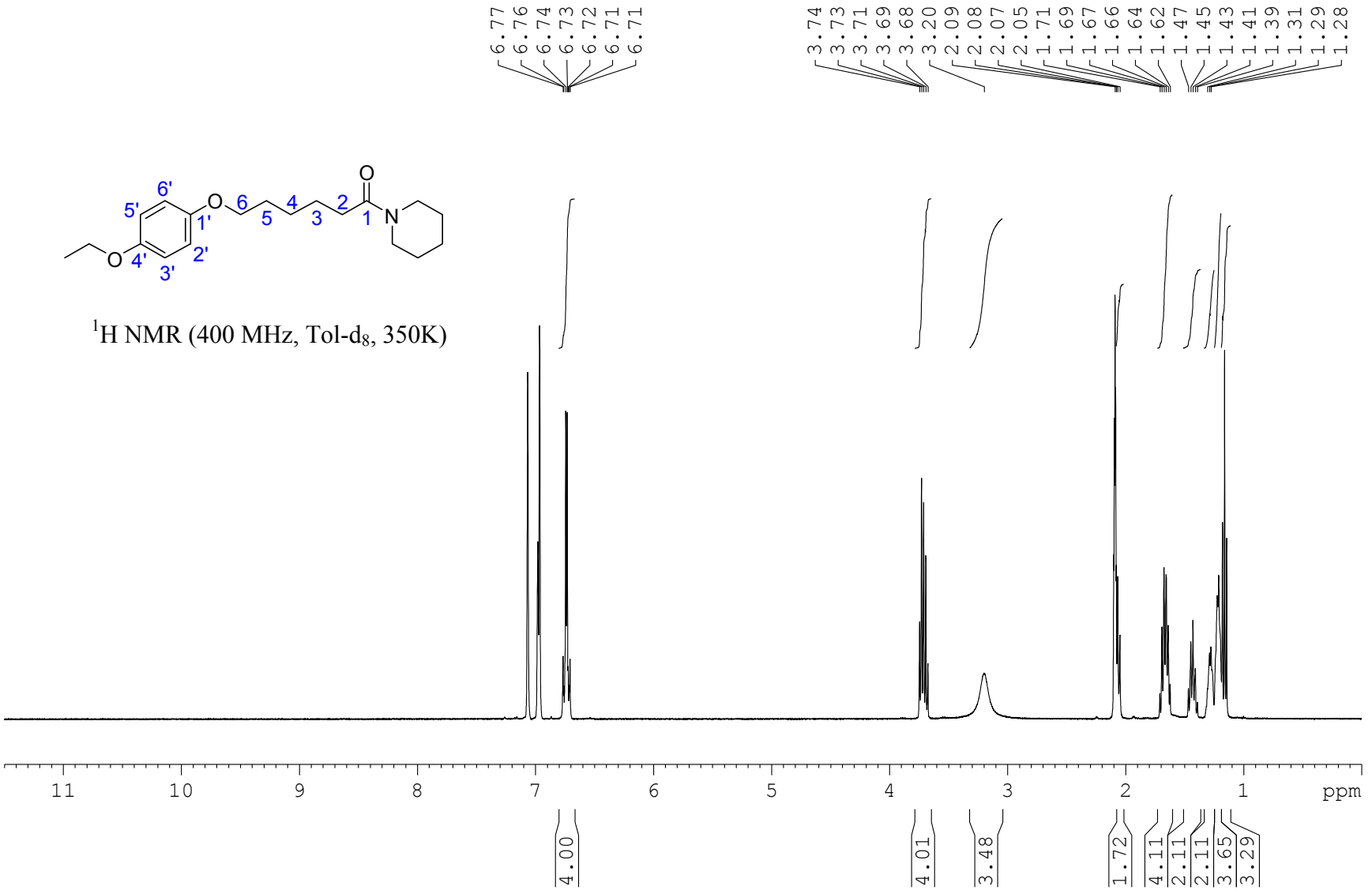
^{1}H NMR (400 MHz, Tol-d_8, 350K)
close up

5-(4-Ethoxyphenoxy)-1-(piperidin-1-yl)pentan-1-one; S80.

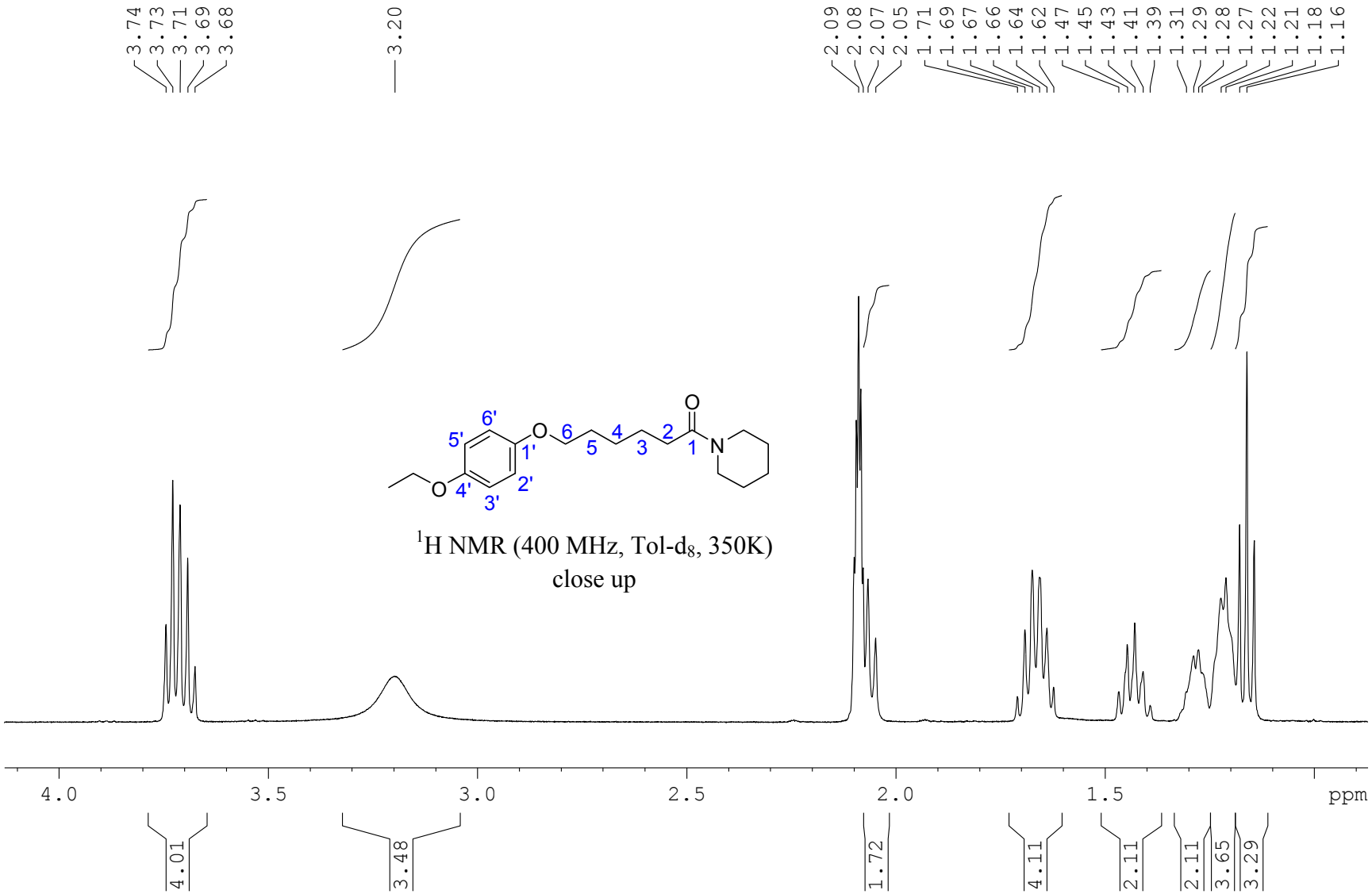


^{13}C NMR (100 MHz, Tol-d_8, 350K)

6-(4-Ethoxyphenoxy)-1-(piperidin-1-yl)hexan-1-one; 39.

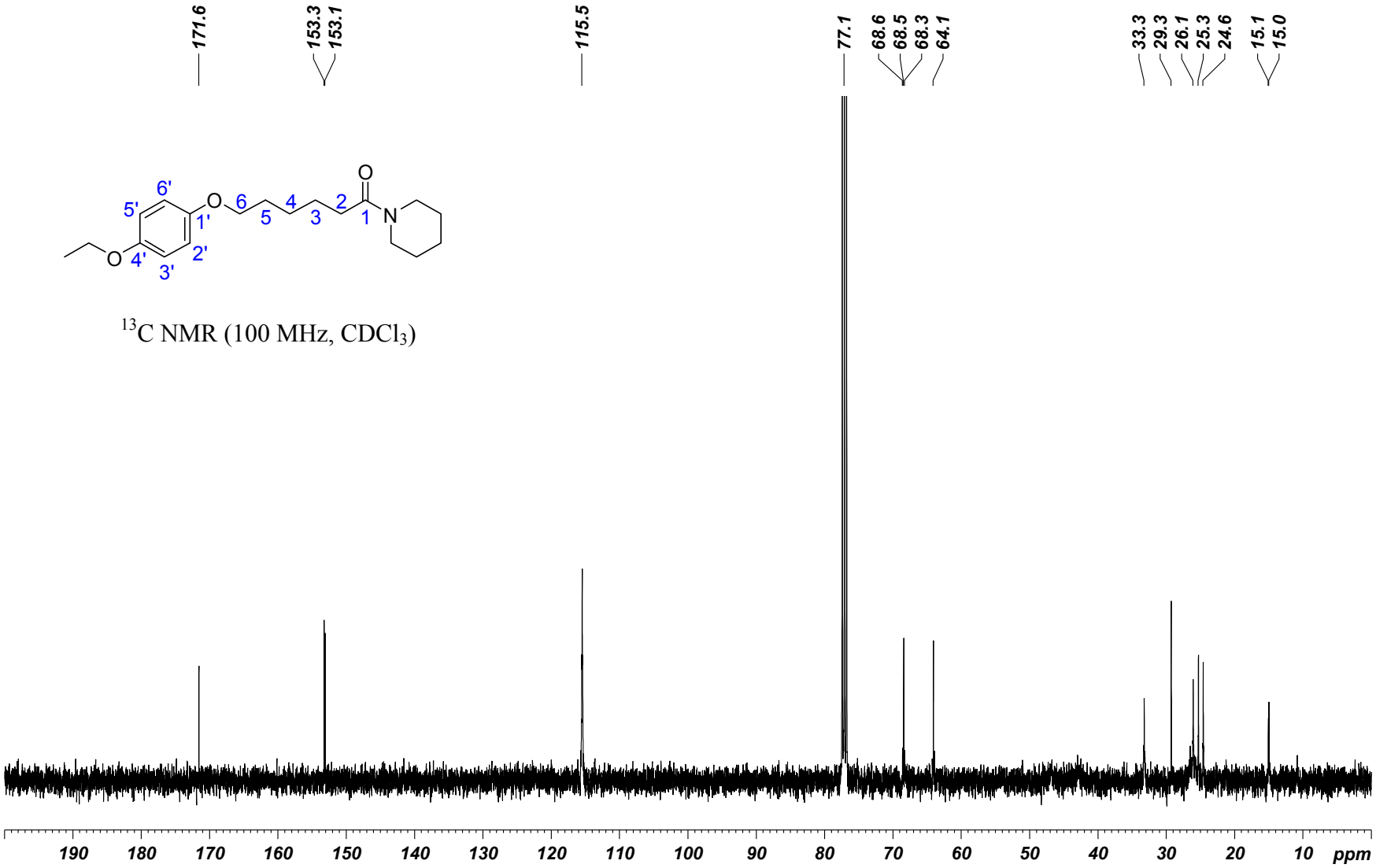


6-(4-Ethoxyphenoxy)-1-(piperidin-1-yl)hexan-1-one; 39.



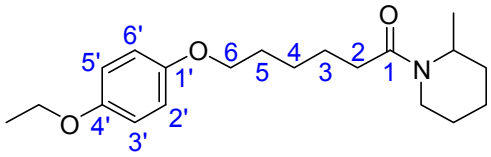
^{1}H NMR (400 MHz, Tol-d_8, 350K)
close up

6-(4-Ethoxyphenoxy)-1-(piperidin-1-yl)hexan-1-one; 39.



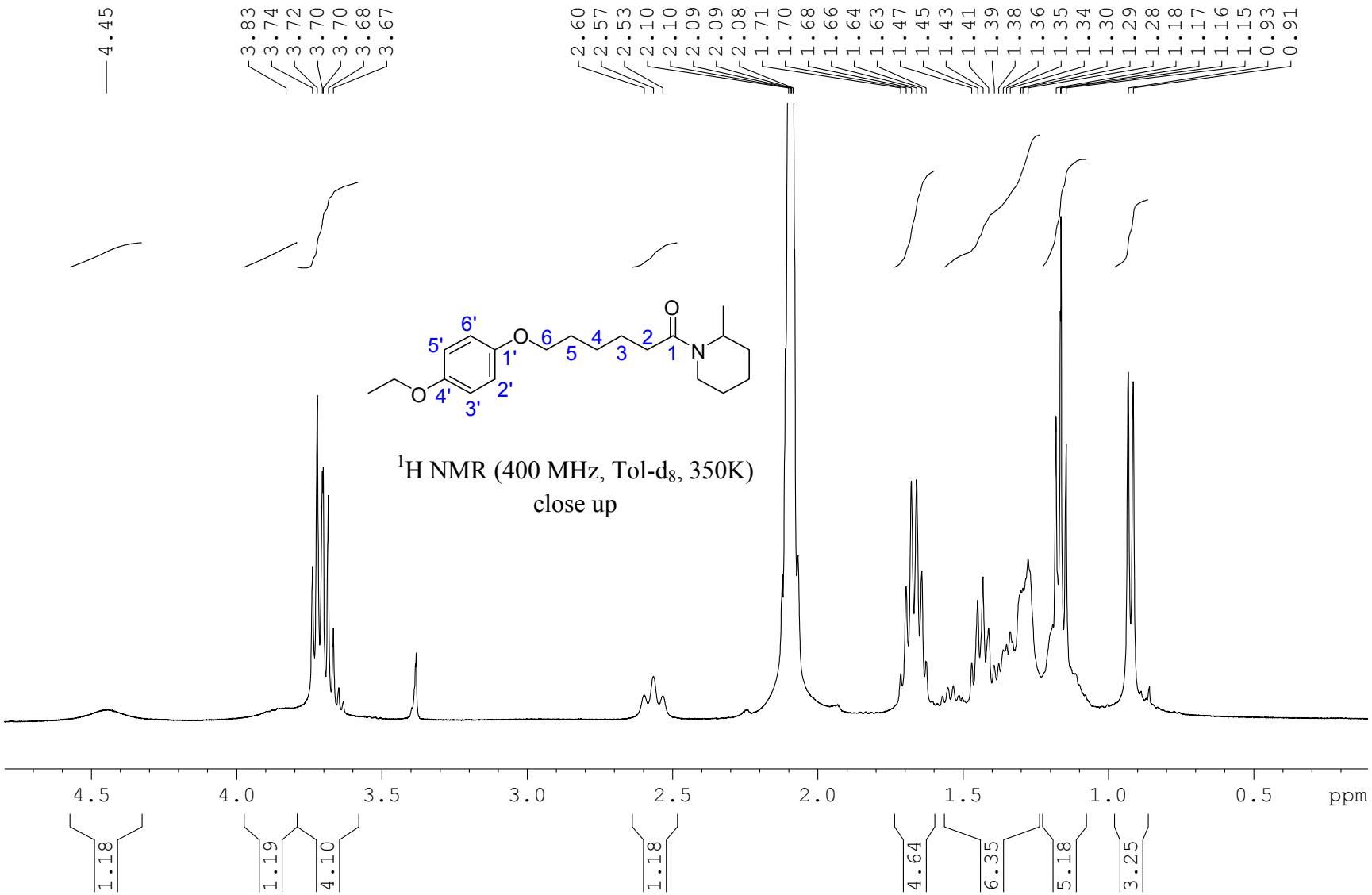
^{13}C NMR (100 MHz, $CDCl_3$)

6-(4-Ethoxyphenoxy)-1-(2-methylpiperidin-1-yl)hexan-1-one; 40.

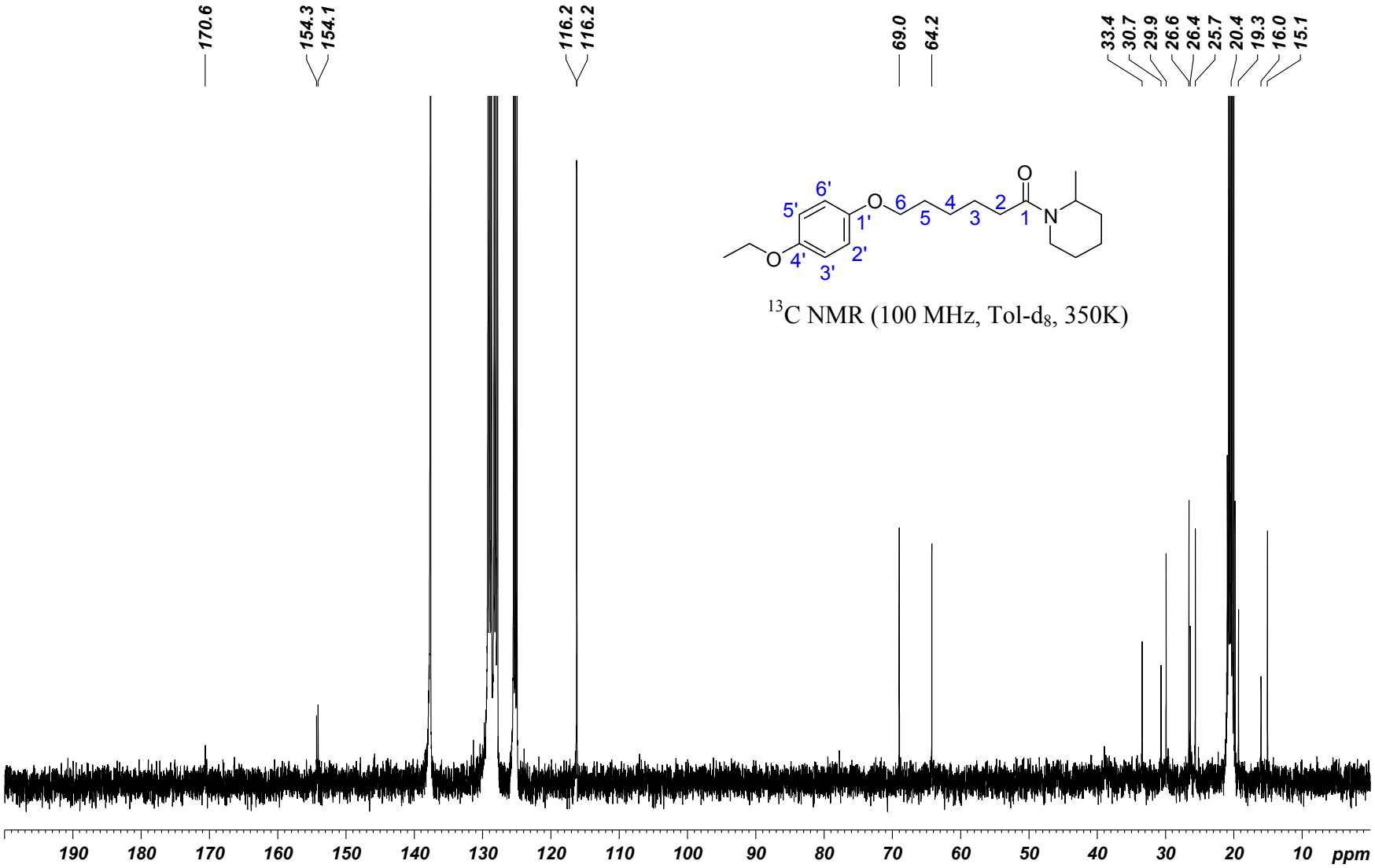


^{1}H NMR (400 MHz, Tol-d$_{8}$, 350K)

6-(4-Ethoxyphenoxy)-1-(2-methylpiperidin-1-yl)hexan-1-one; 40.

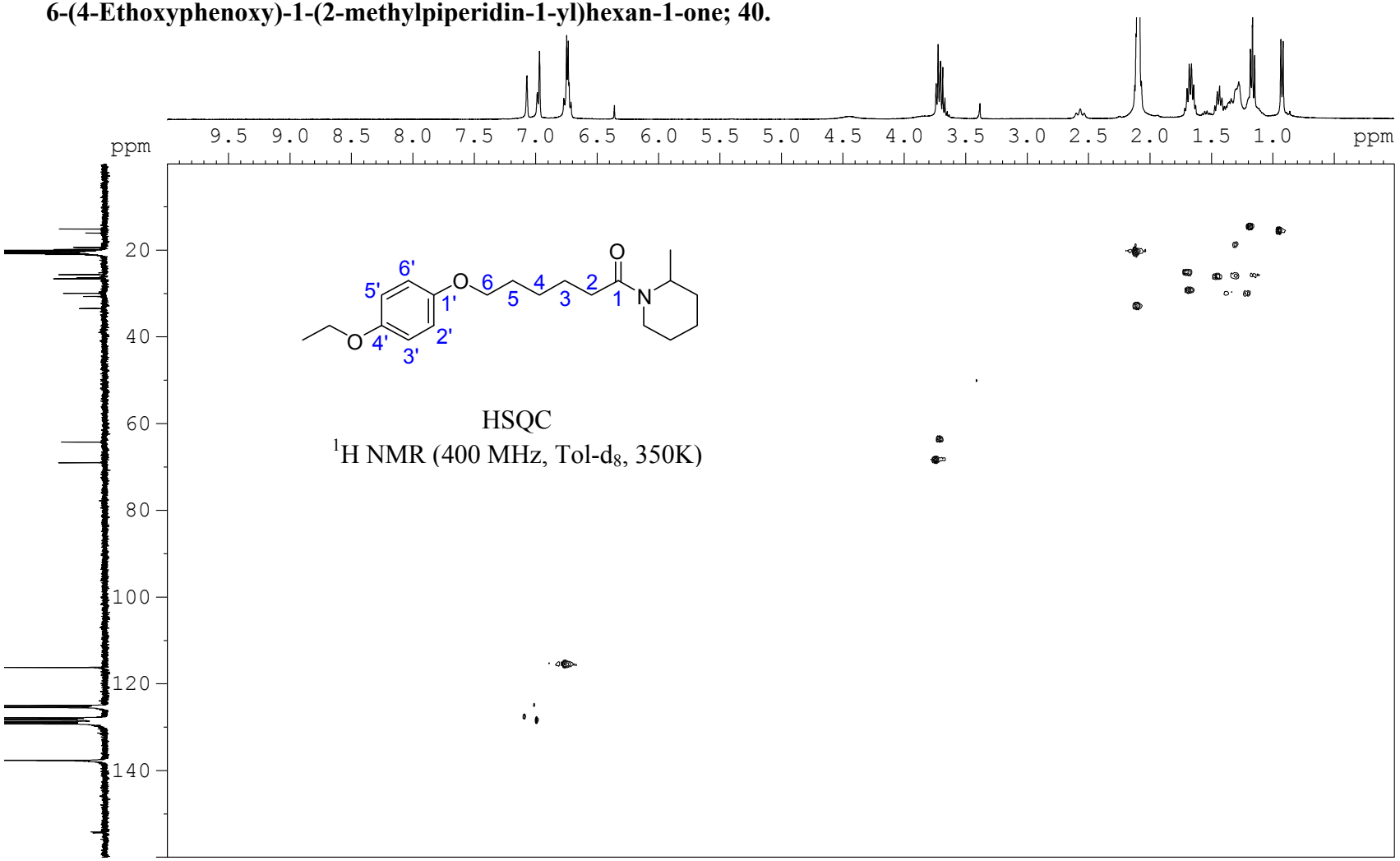


6-(4-Ethoxyphenoxy)-1-(2-methylpiperidin-1-yl)hexan-1-one; 40.

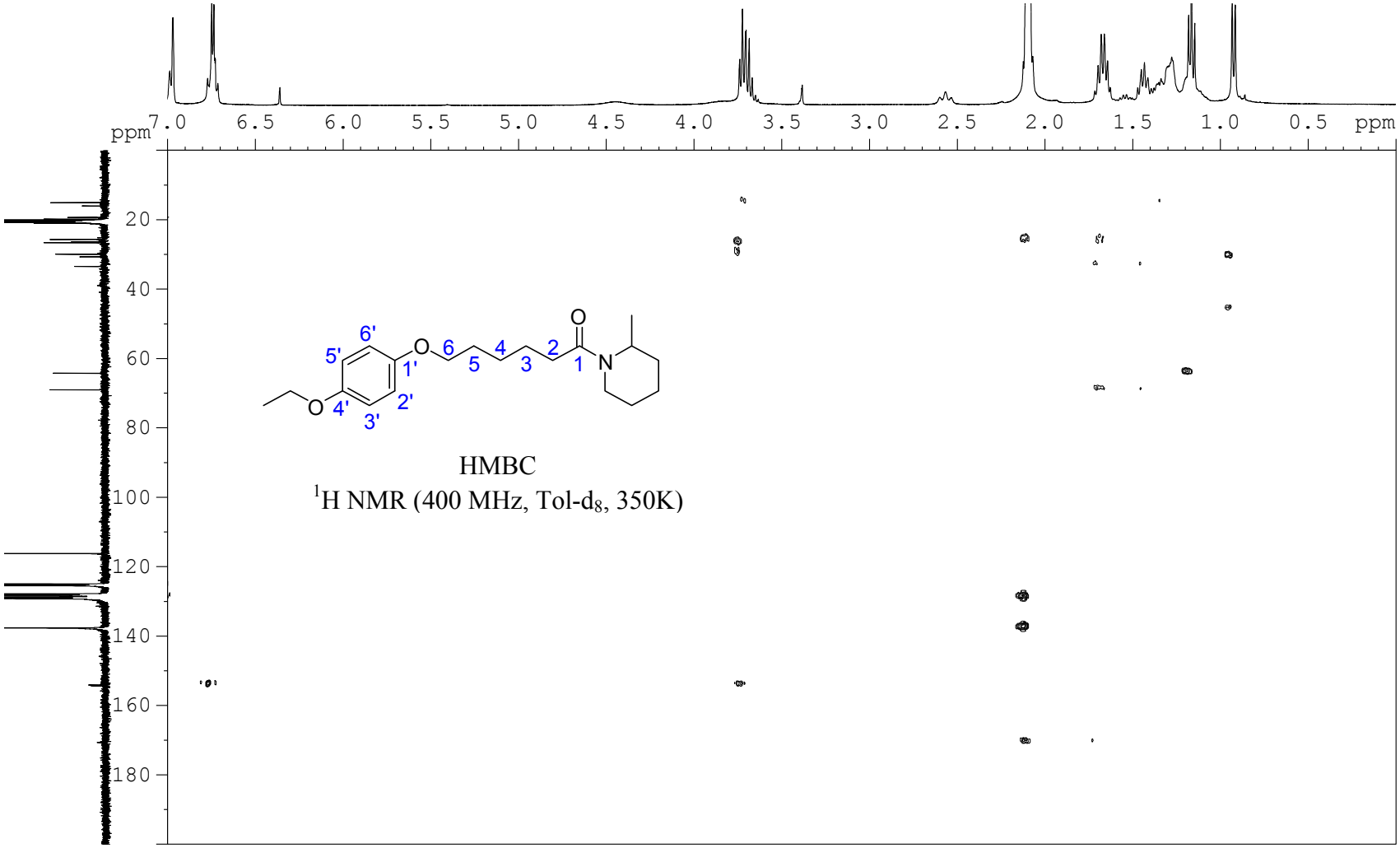


^{13}C NMR (100 MHz, Tol-d_8, 350K)

6-(4-Ethoxyphenoxy)-1-(2-methylpiperidin-1-yl)hexan-1-one; 40.



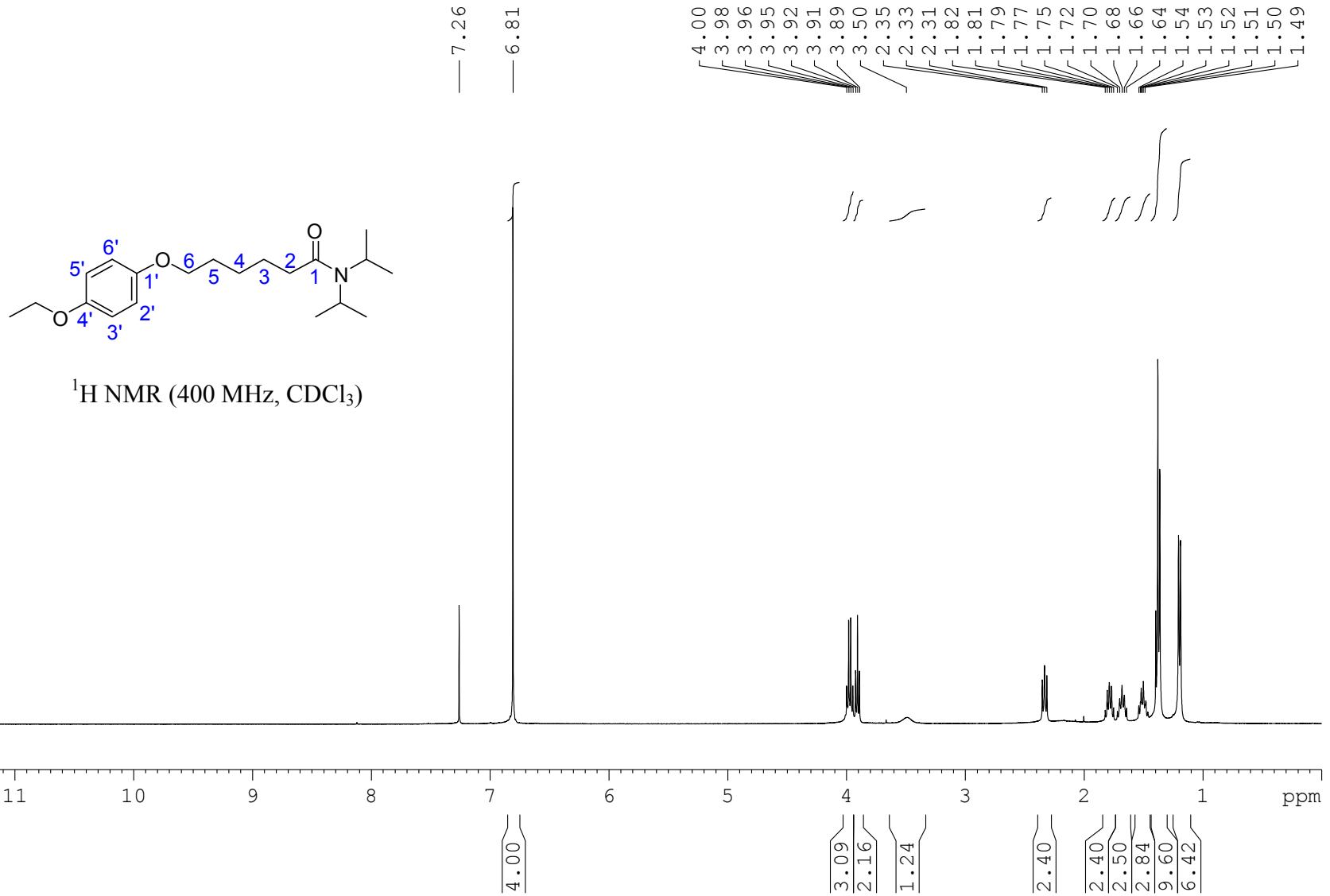
6-(4-Ethoxyphenoxy)-1-(2-methylpiperidin-1-yl)hexan-1-one; 40.



HMBC

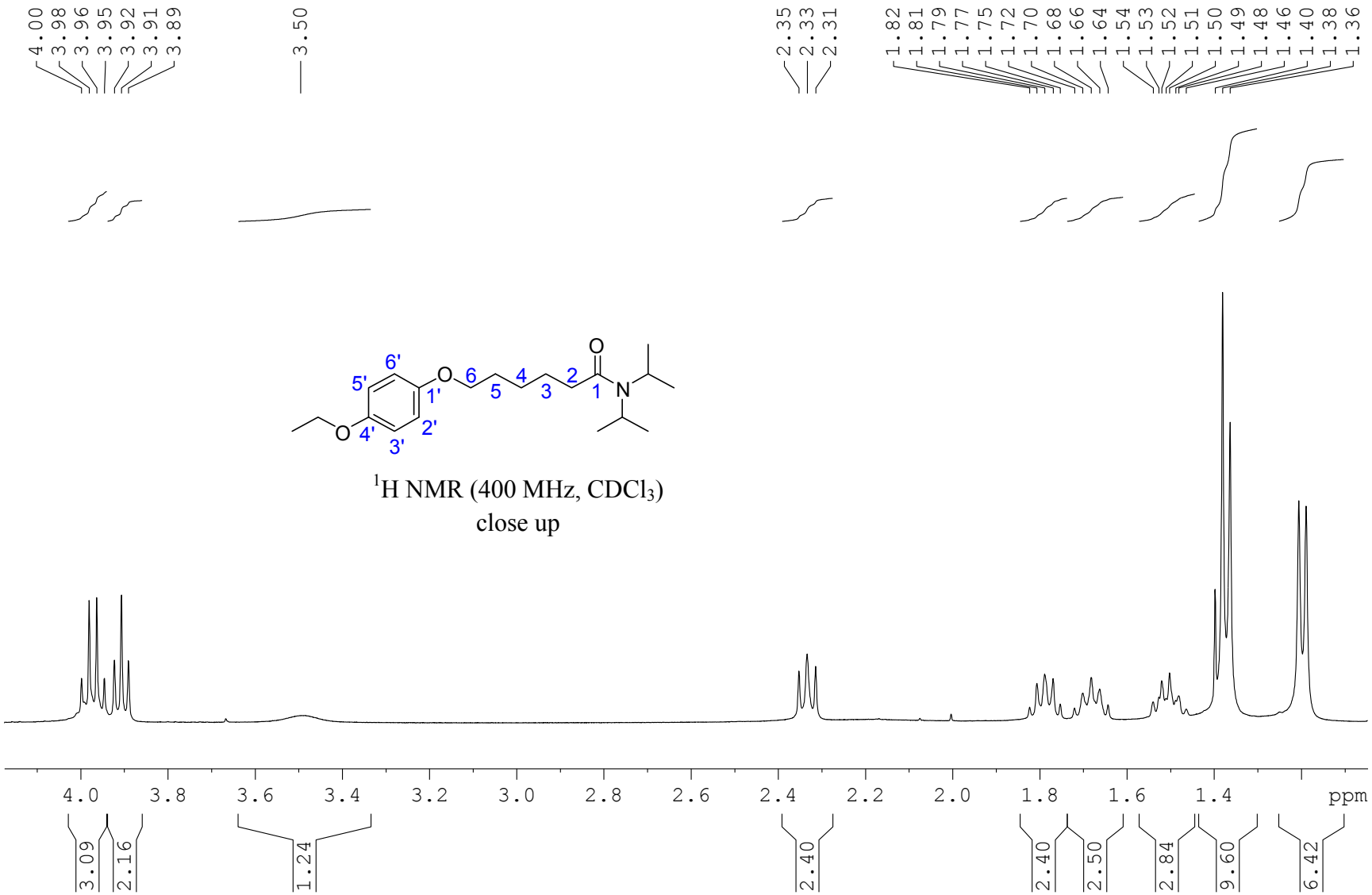
^{1}H NMR (400 MHz, Tol-d_8, 350K)

6-(4-Ethoxyphenoxy)-*N*,*N*-diisopropylhexanamide; 41.



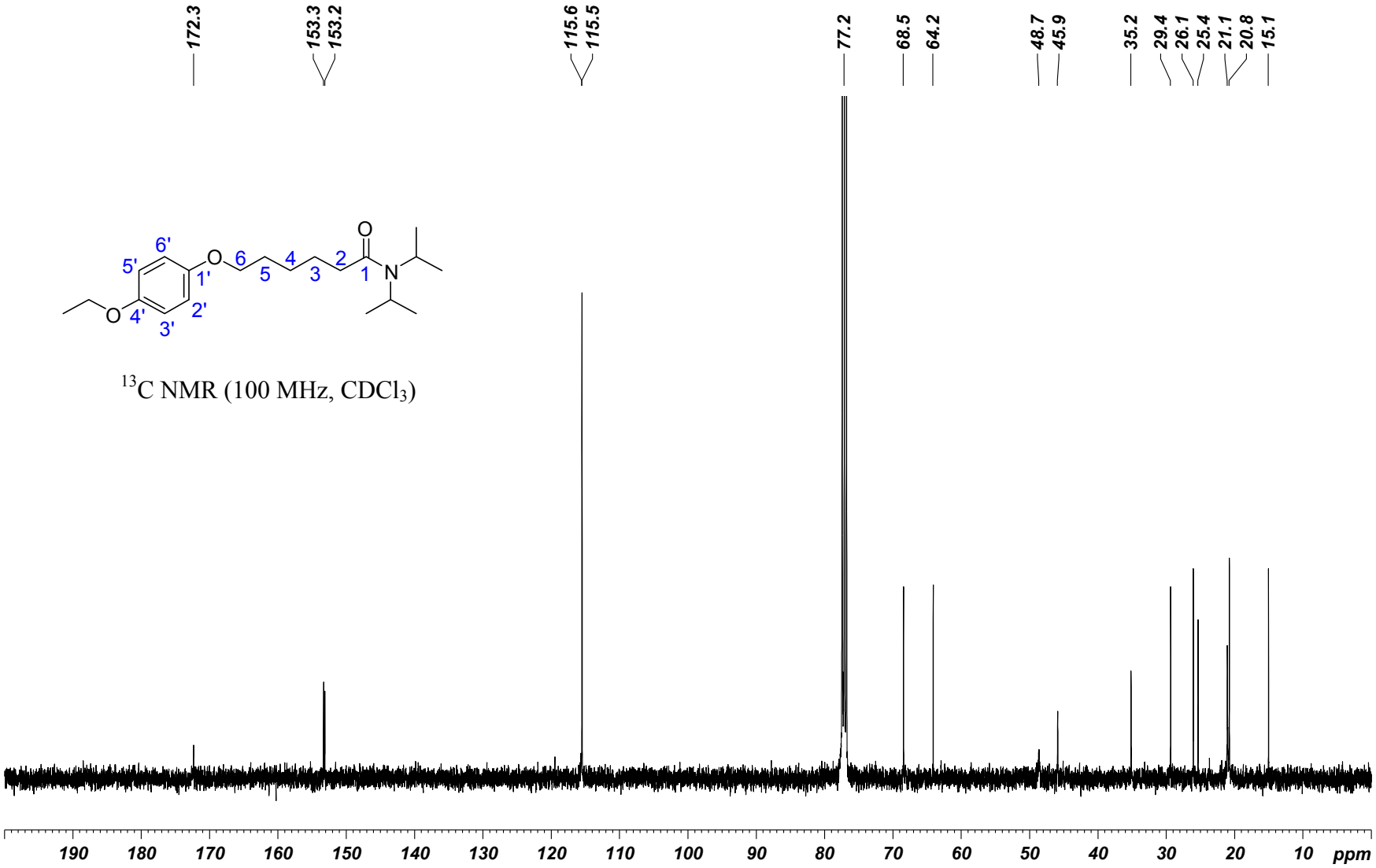
^{1}H NMR (400 MHz, $CDCl_3$)

6-(4-Ethoxyphenoxy)-*N*,*N*-diisopropylhexanamide; 41.



^{1}H NMR (400 MHz, $CDCl_3$)
close up

6-(4-Ethoxyphenoxy)-*N*,*N*-diisopropylhexanamide; 41.



^{13}C NMR (100 MHz, $CDCl_3$)