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In Pursuit of Fluorinated Sigma Receptor Ligand Candidates Related to [^{18}F]-FPS

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Supplementary Material

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EXPERIMENTAL

General Information

All chemicals used were purchased from either Sigma Aldrich or Alfa Aesar and used without purification.

Nuclear magnetic resonance (^{1}H, ^{19}F and ^{13}C NMR) experiments were carried out using a Bruker DPX 300 (^{1}H, 300.2 MHz; ^{19}F, 282.4 MHz; ^{13}C, 75.5 MHz), a Bruker Avance III 400 MHz (^{1}H, 400.1 MHz; ^{13}C, 100.6 MHz), or Bruker Avance III Cryo 600 MHz (^{1}H, 600.2 MHz; ^{13}C, 150.9 MHz) instrument. Samples were dissolved in the stated deuterated solvents and the spectra referenced against residual non-deuterated solvent peaks: δ_H 7.26 and δ_C 77.16 for $CDCl_3$.[1] Concern has been raised over the widespread irreproducibility of ^{19}F NMR data.[2] In the current work, the data were indirectly calibrated to the chemical shift of Me_4Si by reference to the residual non-deuterated solvent signal in $CDCl_3$ for each sample and multiplying the ^{1}H SF value by 0.94094011 to obtain the SF value for the ^{19}F spectrum, according to IUPAC Recommendations 2008.[3] The resulting data were within 5 decimal places of those obtained following the absolute method described at https://www.chem.wisc.edu/~cic/nmr/Guides/Other/Xi_chem_shift_scale.pdf. In all cases, NMR multiplicities are reported as singlet (s), doublet (d), triplet (t), quartet (q), broad (br), multiplet (m), and based on first order analyses. Data are reported as chemical shifts measured in parts per million (ppm) downfield from TMS (δ), multiplicity, observed coupling constant (*J*) in Hertz (Hz), proton count, and assignment.

NOTES:

1. Systematic nomenclature has been used throughout the Experimental Section for all new compounds. However, in order to simplify comparisons and ensure accuracy of assignments,

the ^{1}H, ^{19}F and ^{13}C NMR spectra have been assigned according to a different, uniform positional numbering scheme with the piperidine ring as core, as represented throughout the text and in generic structures **57** and **58** (see Table S1). In accordance with the literature,[4 and references therein] position 2 in the piperidine ring of amide derivatives (X = O) has been assigned to the position *anti* to the X group. Analysis of multiplicities has been based on first order principles and assignment of signals has been assisted or confirmed by COSY, HSQC and/or HMBC experiments.

2. The assignment of quaternary carbon signals in the ^{13}C NMR spectra was also supported by the observation of consistent trends in the chemical shifts, as recorded in Table S1.

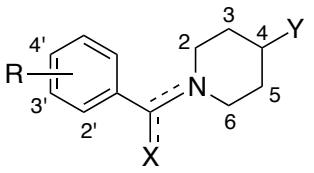
Low-resolution electrospray ionisation (ESI) mass spectra were carried out on a Waters Micromass ZQ2000 electrospray instrument. High resolution ESI-MS were carried out by Dr Sarowar Chowdhury, Bioanalytical Mass Spectrometry Facility, Mark Wainwright Analytical Centre, UNSW.

Infrared spectra were recorded on a Nicolet Avatar 320 FTIR spectrometer over the range of 4000 to 400 cm^{-1}. Spectra are reported in wavenumbers (cm^{-1}).

Column chromatography was carried out on Merck Kieselgel 60 silica gel (0.040-0.063 mm). Thin layer chromatography (TLC) was performed using Merck Kieselgel 60 F-254 precoated aluminium sheets (0.2 mm). Ratios of solvents used for chromatography were expressed as volume/volume as specified.

Elemental microanalyses were performed by staff in the Microanalytical Unit, Research School of Chemistry, The Australian National University.

Table S1. Correlation trends in the chemical shift values of selected quaternary signals that were helpful in the assignment of ^{13}C NMR spectra for compounds **25**–**30**, **36**–**38**, **40**–**45**, **47**, **49**, **51**–**54**, and **5**–**7**. ^{13}C NMR chemical shifts were referenced to literature residual solvent signal shifts.[1]



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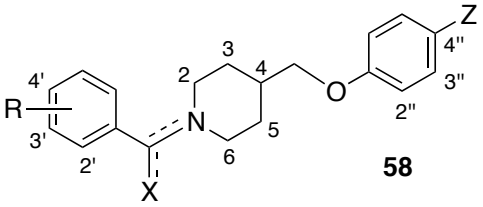

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Str	Base	X	R	Y	Z	δ_C (ppm) (major/minor isomer)			
						C1'	C4"-Z	C'-OMe	C1"-O
25	**57**	O	2'-OMe	CO_2Et	na	125.7/125.8	na	155.2/155.1	na
26	**57**	O	3'-OMe	CO_2Et	na	137.4	na	159.8	na
27	**57**	O	4'-OMe	CO_2Et	na	127.7	na	160.5	na
28	**57**	O	2'-OMe	CH_2OH	na	125.7/125.9	na	155.1	na
29	**57**	O	3'-OMe	CH_2OH	na	137.6	na	159.7	na
30	**57**	O	4'-OMe	CH_2OH	na	128.5	na	160.7	na
36	**57**	O	2'-OMe	CH_2OMs	na	125.8/126.0	na	155.3	na
37	**57**	O	3'-OMe	CH_2OMs	na	137.3	na	159.6	na
38	**57**	O	4'-OMe	CH_2OMs	na	128.1	na	160.8	na
40	**58**	O	2'-OMe	na	CHO	126.1/126.3	130.0	155.4	164.0
41	**58**	O	3'-OMe	na	CHO	137.5	130.1	159.7	163.9
42	**58**	O	4'-OMe	na	CHO	128.3	130.1	160.8	164.0
43	**58**	O	2'-OMe	na	CH_2OH	126.1/126.2	133.6	155.3	158.4
44	**58**	O	3'-OMe	na	CH_2OH	137.5	133.6	159.7	158.4
45	**58**	O	4'-OMe	na	CH_2OH	128.3	133.5	160.8	158.5
47	**58**	O	4'-OMe	na	CH_3	128.5	130.1	160.7	156.9
53	**58**	O	3'-OMe	na	$CH_2)_2$-O	136.9	130.7	159.8	158.6
54	**58**	H_2	4'-OMe	na	CH_2OH	130.2	133.2	158.93	158.85
51	**58**	O	2'-OMe	na	CH_2Cl	126.2/126.4	129.9	155.4	159.2
52	**58**	O	3'-OMe	na	CH_2Cl	137.7	130.0	159.8	159.1
49	**58**	O	4'-OMe	na	CH_2Cl	128.3	130.0	160.8	159.1
5	**58**	O	2'-OMe	na	CH_2F	126.3/126.4	128.5	155.5	159.6
6	**58**	O	3'-OMe	na	CH_2F	137.7	128.6	159.8	159.6
7	**58**	O	4'-OMe	na	CH_2F	128.4	128.6	160.8	159.9

Reaction of 4-hydroxybenzyl alcohol 8 with KF under Appel reaction conditions[5]

Following the method of Bandgar *et al*.,[5] 4-hydroxybenzyl alcohol **8** (0.64 g, 5.2 mmol) was added to a mixture of KF (0.61 g, 10.5 mmol), PPh_3 (3.38 g, 12.9 mmol) in a solution of CCl_4 (1 mL) and DMF (4 mL). The mixture was stirred at r.t. for 30 min, then the mixture extracted with pentane (2 × 5 mL). The combined organic layers were dried over Na_2SO_4 and the solvent evaporated *in vacuo* to yield the crude product (0.60 g, 93% mass recovery). The crude material was analysed by ESI mass spectrometry and ^{1}H and ^{18}F NMR spectroscopy.

Reductive N-methoxybenzylation of 4-hydroxymethylpiperidine 14

General procedure: 4-Hydroxymethylpiperidine **14** (~9 mmol; 1.0 mol equiv.) was dissolved in CH_2Cl_2 (25 mL) and methoxybenzaldehyde (1.1 mol equiv.) was added. Solid $NaBH(OAc)_3$ (~10 mmol, 1.1 mol equiv.) was added in one portion, and the mixture was stirred at ambient temperature for 19 h. The mixture was then quenched with 1 M aq. NaOH (50 mL), the organic layer separated and dried over Na_2SO_4, and the solvent evaporated under reduced pressure. The crude material was column chromatographed or dissolved in CH_2Cl_2 (50 mL) and the solution extracted with 10% aq. HCl (100 mL), the extracts basified using NaOH pellets, and the solution reextracted with CH_2Cl_2 (3 × 25 mL), to give combined extracts that were dried over Na_2SO_4 and evaporated to dryness.

(i) 4-Hydroxymethylpiperidine **14** (1.12 g, 9.7 mmol) and 2-methoxybenzaldehyde **17** (1.3 mL, 1.46 g, 10.7 mmol) with $NaBH(OAc)_3$ (2.30 g, 10.8 mmol) gave a yellow oil that was chromatographed on silica gel (MeOH:EtOAc, 1:20) to yield (1-(2-methoxybenzyl)piperidin-4-yl)methanol **18** as a yellow oil (1.02 g, 51%). ^{1}H NMR (400 MHz, $CDCl_3$; **dfr-180311** at 25 °C; 110318-dfr 3 1): δ 7.37 (dd, J = 7.4, 1.5 Hz, 1H, H6'), 7.24 (td, J = 7.9, 1.7 Hz, 1H, H4'), 6.94 (td, J = 7.4, 0.6 Hz, 1H, H5'), 6.87 (d, J = 8.2 Hz, 1H, H3'), 3.82 (s, 3H, 2'-OCH_3), 3.60 (s, 2H, 1'-CH_2N), 3.45 (d, J = 6.3, 2H, 4-CH_2OH), 2.98 (d, J = 11.7 Hz, 2H, H_{eq}2 and

$H_{eq}6$), 2.07 (ddd, J = 11.8, 11.7, 2.2 Hz, 2H, $H_{ax}2$ and $H_{ax}6$), 1.71 (br d, J = 12.7 Hz, 2H, $H_{eq}3$ and $H_{eq}5$), 1.49 (m, 1H, H4), 1.34 (dddd, J = 12.7, 12.2, 11.8, 3.6 Hz, 2H, $H_{ax}3$ and $H_{ax}5$). ^{13}C NMR (100.1 MHz, $CDCl_3$; **dfr-180311** at 25 °C; 110318-dfr 4 1): δ 159.3 (C2'), 132.4 (C6'), 129.6 (C4'), 127.1 (C1'), 121.7 (C5'), 111.9 (C3'), 69.0 (4-CH_2O), 57.6 (1'-CH_2N), 56.8 (2'-OCH_3), 54.7 (C2 and C6), 39.8 (C4), 30.0 (C3 and C5). HRMS (ESI) *m/z*: 493.3029 ($[2M+Na]^+$, 13%), 356.2213 ($[M+MeO\text{-}benzyl]^+$, 25), 258.1459 ($[M+Na+H]^+$, 38), 236.1640 ($[M+H]^+$, 100%).

(ii) 4-Hydroxymethylpiperidine **14** (1.00 g, 8.7 mmol) and 3-methoxybenzaldehyde **17** (1.3 mL, 1.45 g, 10.7 mmol) were treated with $NaBH(OAc)_3$ (2.2 g, 10.4 mmol) gave a yellow oil that was chromatographed on silica gel (MeOH:EtOAc, 1:20) to yield (1-(3-methoxybenzyl)piperidin-4-yl)methanol **19**[6] as a yellow oil (1.14 g, 56 %) (Found: C, 71.20; H, 9.11; N, 6.08%. $C_{14}H_{21}NO_2$ requires C, 71.46; H, 8.99; N, 5.95%). ^{1}H NMR (400 MHz, $CDCl_3$; **dfr-210211** at 25 °C; 110221-dfr 3 1): δ 7.22 (dd, J = 8.4, 7.7 Hz, 1H, H5'), 6.91 (dd, J = 8.0, 1.7 Hz, 1H, H2'), 6.90 (d, J = 7.7 Hz, 1H, H6'), 6.79 (dd, J = 8.4, 1.7 Hz, 1H, H4'), 3.80 (s, 3H, 3'-OCH_3), 3.49 (s, 2H, 1'-CH_2N), 3.47 (d, J = 6.4 Hz, 2H, 4-CH_2OH), 2.92 (br d, J = 11.6 Hz, 2H, $H_{eq}2$ and $H_{eq}6$), 2.45 (br s, 1H, OH), 1.98 (ddd, J = 11.8, 11.6, 2.2 Hz, 2H, $H_{ax}2$ and $H_{ax}6$), 1.70 (br d, J = 12.7 Hz, 2H, $H_{eq}3$ and $H_{eq}5$), 1.49 (m, 1H, H4), 1.31 (dddd, J = 12.7, ~12.0, 11.8, 3.8 Hz, 2H, $H_{ax}3'$ and $H_{ax}5'$). ^{13}C NMR (100.1 MHz, $CDCl_3$; **dfr-210211** at 25 °C; 110221-dfr 4 1): δ 161.0 (C3'), 141.0 (C1'), 130.6 (C5'), 123.1 (C6'), 116.2 (C2'), 114.0 (C4'), 69.1 (4-CH_2O), 64.7 (1'-CH_2N), 56.6 (3'-OCH_3), 54.8 (C2 and C6), 39.9 (C4), 30.0 (C3 and C5). MS (ESI) *m/z*: 547.22 ($[2M+2K]^+$, 3%), 471.31 ($[2M+H]^+$, 6), 258.30 ($[M+Na+H]^+$, 4), 237.24 ($[M+2H]^+$, 16), 236.34 ($[M+H]^+$, 100).

(iii) 4-Hydroxymethylpiperidine **14** (1.12 g, 9.7 mmol) and 4-methoxybenzaldehyde **17** (1.3 mL, 10.7 mmol) with $NaBH(OAc)_3$ (2.30 g, 10.8 mmol) gave a yellow oil (1.93 g) that

contained aldehyde, and after acid/base extraction yielded (1-(4-methoxybenzyl)piperidin-4-yl)methanol **20**[7,8] as white needles (1.65 g, 74%) m.p. 52-55 °C (Found: C, 71.51; H, 8.99; N, 5.72%. $C_{14}H_{21}NO_2$ requires C, 71.46; H, 9.12; N, 5.95%). IR (Nujol): 3110, 1609, 1515, 1299, 1183, 1074, 1039, 970, 851, 723 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$; **dfr-161110** at 25 °C; 101116-dfr 5 1): δ 7.21 (d, J 8.4 Hz, 2H, H2' and H6'), 6.83 (d, J = 8.4 Hz, 2H, H3' and H5'), 3.77 (s, 3H, 4'-OCH_3), 3.43 (s, 2H, 1'-CH_2N), 3.41 (d, J 6.8 Hz, 2H, 4-CH_2OH), 3.15 (br s, 1H, OH), 2.88 (br d, J 11.2 Hz, 2H, H_{eq}2 and H_{eq}6), 1.92 (ddd, J 12.0, 11.2, 2.0 Hz, 2H, H_{ax}2 and H_{ax}6), 1.68 (br d, J 11.2 Hz, 2H, H_{eq}3 and H_{eq}5), 1.44 (m, 1H, H4), 1.25 (dddd, J = 12.4, 12.0, 11.6, 3.6 Hz, 2H, H_{ax}3' and H_{ax}5'). ^{13}C NMR (100.1 MHz, $CDCl_3$; **dfr-161110** at 25 °C; 101116-dfr 6 1): δ 158.7 (C4'), 130.7 (C2' and C6'), 129.8 (C1'), 113.6 (C3' and C5'), 67.4 (4-CH_2OH), 62.7 (1'-CH_2N), 55.2 (4'-OCH_3), 53.2 (C2 and C6), 38.5 (C4), 28.7 (C3 and C5). MS (ESI) m/z: 493.56 ($[2M+Na]^+$, 7%), 258.50 ($[M+Na]^+$, 20), 236.47 ($[M+H]^+$, 100).

Treatment of (1-(4-methoxybenzyl)piperidin-4-yl)methanol 20 with $(CF_3SO_2)_2O$

(i) In pyridine. Following the method of Lee *et al.*,[9] aminoalcohol **20** (0.21 g, 0.89 mmol) was dissolved in pyridine (5.0 mL) and the solution stirred in ice for 15 min, then trifluoromethanesulfonic anhydride (0.22 mL, 1.31 mmol) added dropwise. The temperature of the mixture was raised to r.t. and the mixture stirred for 1 h. The mixture was diluted with water, and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed sequentially with water (3 × 15 mL), sat. aq. $NaHCO_3$ solution (3 × 20 mL), and brine (3 × 20 mL). The organic layers were then dried over Na_2SO_4, filtered, and evaporated to dryness *in vacuo* to yield a brown oil (0.33 g, 60% based on the expected triflate **31** or **32**). The mixture was analysed by ^{1}H NMR spectroscopy (AP 110314-ahp 1 1) and the main features described in the Results and Discussion.

(ii) In dichloromethane with no added base. Aminoalcohol **20** (0.40, 1.71 mmol) was dissolved in CH_2Cl_2 (10 mL) and stirred at 0 °C for 15 min before trifluoromethanesulfonic anhydride (0.60 mL, 3.57 mmol) was added dropwise. The temperature of the mixture was then raised to r.t., and stirring continued for 1 h. The mixture was then quenched with water, and the organic layer washed with sat. aq. $NaHCO_3$ solution (3 × 10 mL) and brine (3 × 20 mL). The organic layer was dried over Na_2SO_4 and evaporated *in vacuo* to yield a brown oil (0.59 g, 94% based on the expected triflate **31** or **32**). The mixture was analysed by ^{1}H (AP 110328-ahp 1 2) and ^{19}F (AP 110328-ahp 3 2) NMR spectroscopy, and subsequently after further D_2O exchange (AP 110404-ahp 1 2), then the main features described in the Results and Discussion.

(iii) In dichloromethane with Hunig's base. Aminoalcohol **20** (0.47 g, 2.00 mmol) and *N*,*N*-diisopropylethylamine (0.67 mL, 4.00 mmol) were dissolved together in CH_2Cl_2 (10 mL) and stirred at 0°C for 15 min. Trifluoromethanesulfonic anhydride (0.67 mL, 4.15 mmol) was added dropwise and the temperature of the mixture was raised to r.t., and the mixture stirred for a further 1 h. The mixture was then quenched in water, and the organic layer washed with sat. aq. $NaHCO_3$ solution (3 × 10 mL) and brine (3 × 20 mL). The organic layer was dried over Na_2SO_4 and evaporated to dryness *in vacuo* to yield an oil (0.71 g, 96 % based on the expected triflate **31** or **32**). The product was analysed by ^{1}H NMR spectroscopy (AP 110520-ahp 1 2) and the main features described in the Results and Discussion.

Treatment of (1-(3-methoxybenzyl)piperidin-4-yl)methanol 19 with $(CH_3SO_2)_2O$

4-Hydroxymethyl-1-(3-methoxybenzyl)piperidine **33** (0.40, 1.71 mmol) was dissolved in CH_2Cl_2 (10 mL), and the solution stirred at 0°C for 15 min. Methanesulfonic anhydride (0.60 mL, 3.57 mmol) in CH_2Cl_2 (10 mL) was added dropwise and the temperature of the mixture raised to r.t. and stirring continued for another 1 h. The mixture was quenched with water,

and the organic layer washed with sat. aq. $NaHCO_3$ solution (3 × 10 mL) and brine (3 × 20 mL). The organic layer was then dried over Na_2SO_4 and evaporated to dryness *in vacuo* to yield a brown oil (0.59 g, 94 %, based on the anticipated norbornanium methanesulfonate **35**). The mixture was analysed by NMR spectroscopy (AP 110526-ahp 1 2) and mass spectrometry and the outcome described in the Results and Discussion.

Treatment of aminotriflate 31/32 with sodium 4-(hydroxymethyl)phenolate

A solution of aq. NaOH (0.1 M, 100 mL) was titrated into an aq. solution of 4-hydroxymethylphenol (0.12 g, 1.0 mmol) in water (20 mL) containing phenolphthalein indicator until the endpoint (colour change from clear to pink; ~100 mL). The slightly basic solution was then added to a portion of the supposed triflate **31** or **32** (0.37 g, 1.0 mmol) from the preparation above and the mixture stirred at reflux for 24 h. The mixture was then extracted with EtOAc (3 × 25 mL). The combined organic layers were dried over Na_2SO_4 and the solvent removed *in vacuo* to yield the crude mixture as a brown oil (0.29 g). The ^{1}H NMR spectrum of the crude product was then analysed to show aminoalcohol **20** as the only piperidine-derived material admixed with other purely aromatic residues.

Methoxybenzoylation of ethyl isonipecotate 21

General procedure: Triethylamine (1.74 mL, 1.26 g, 12.5 mmol) was added in one portion to a solution of ethyl isonipecotate **21** (1.73 mL, 1.76 g, 11.2 mmol) in dry CH_2Cl_2 (10 mL) and the mixture stirred at 0 ºC for 10 min under nitrogen. The appropriate acid chloride (1.35 mL, 1.55 g, 9.1 mmol) was introduced dropwise *via* syringe. The reaction mixture was stirred for 30 min, allowed to warm to r.t. and then stirred overnight. The mixture was diluted with CH_2Cl_2 (50 mL) and washed with 1 N HCl (2 × 25 mL) and water (25 mL). The organic layer was dried over Na_2SO_4, evaporated to dryness under reduced pressure, and the residue flash

chromatographed on silica gel (MeOH/CH_2Cl_2, 1:25) and the major component isolated and characterised.

(i) *Ethyl 1-(2-methoxybenzoyl)piperidine-4-carboxylate* ***25***

Yellow oil (1.60 g, 60%). R_f 0.71 (EtOAc). FTIR (neat) ν_{max} 2930, 2857, 1722, 1622, 1432, 1372, 1311, 1263, 1248, 1177, 1112, 1038, 860 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$; **RJ-01-43** at 25 °C; 140605-rsj 1 2; 52:48 mixture of isomers): δ (major) 7.338 (ddd, *J* 8.4, 7.5, 1.7 Hz, 1H, H4'), 7.199 (ddd, *J* 7.5, 1.7 Hz, 1H, H6'), 6.974 (dd, *J* 7.5, 7.5 Hz, 1H, H5'), 6.915 (dd, *J* 8.4, 0.8 Hz, 1H, H3'), 4.587 (ddd, *J* 13.4, 4.1, 4.1 Hz, 1H, $H_{eq}6$), 4.142 (q, *J* 7.1 Hz, 2H, 4-$CO_2CH_2CH_3$), 3.817 (s, 3H, 2'-OCH_3), 3.489 (dm, *J* 13.5 Hz, 1H, $H_{eq}2$), 3.064 (ddd, *J* 13.5, 11.4, 3.1 Hz, 1H, $H_{ax}2$), 3.016 (ddd, *J* 13.3, 10.8, 2.9 Hz, 1H, $H_{ax}6$), 2.554 (tt, *J* 10.8, 4.1 Hz, 1H, H4), 2.017 (dm, *J* 13.1 Hz, 1H, $H_{eq}5$), 1.182 (dm, *J* 13.4 Hz, 1H, $H_{eq}3$), 1.710 (dddd, *J* 13.1, 10.8, 10.8, 4.1 Hz, 1H, $H_{ax}5$), 1.566 (dddd, *J* 13.1, 11.4, 10.8, 4.2 Hz, 1H, $H_{ax}3$), 1.252 (t, *J* 7.1 Hz, 3H, 4-$CO_2CH_2CH_3$). δ (minor) 7.338 (ddd, *J* 8.4, 7.5, 1.7 Hz, 1H, H4'), 7.229 (ddd, *J* 7.5, 1.7 Hz, 1H, H6'), 6.974 (dd, *J* 7.5, 7.5 Hz, 1H, H5'), 6.915 (dd, *J* 8.4, 0.8 Hz, 1H, H3'), 4.592 (ddd, *J* 13.6, 4.1, 4.1 Hz, 1H, $H_{eq}6$), 4.154 (q, *J* 7.1 Hz, 2H, 4-$CO_2CH_2CH_3$), 3.829 (s, 3H, 2'-OCH_3), 3.489 (dm, *J* 13.5 Hz, 1H, $H_{eq}2$), 2.992 (ddd, *J* 13.6, 11.0, 3.7 Hz, 1H, $H_{ax}6$), 2.970 (ddd, *J* 13.5, 10.4, 3.7 Hz, 1H, $H_{ax}6$), 2.538 (tt, *J* 10.7, 4.4 Hz, 1H, H4), 2.017 (dm, *J* 13.1 Hz, 1H, $H_{eq}5$), 1.182 (dm, *J* 13.4 Hz, 1H, $H_{eq}3$), 1.781 (dddd, *J* 13.1, 11.0, 10.7, 4.1 Hz, 1H, $H_{ax}5$), 1.566 (dddd, *J* 13.1, 11.0, 10.8, 4.2 Hz, 1H, $H_{ax}3$), 1.263 (t, *J* 7.1 Hz, 3H, 4-$CO_2CH_2CH_3$). ^{13}C NMR (75 MHz, $CDCl_3$; **RJ-01-43** at 25 °C; 140605-rsj 2 2; 52:48 mixture of isomers): δ (major) 174.11 (4-$CO_2CH_2CH_3$), 167.68 (1'-C(O)N), 155.15 (C2'), 130.22 (C4'), 127.54 (C6'), 125.70 (C1'), 120.76 (C5'), 110.81 (C3'), 60.425 (4-$CO_2CH_2CH_3$), 55.42 (2'-OCH_3), 46.31 (C2), 40.94 (C4), 40.73 (C6), 28.28 (C3), 27.76 (C5), 14.06 (4-$CO_2CH_2CH_3$). δ (minor) 174.19 (4-$CO_2CH_2CH_3$), 167.52 (1'-C(O)N), 155.13 (C2'), 130.16

(C4'), 127.68 (C6'), 125.82 (C1'), 120.72 (C5'), 110.73 (C3'), 60.420 (4-$CO_2CH_2CH_3$), 55.35 (2'-OCH_3), 45.79 (C2), 40.94 (C4), 40.66 (C6), 28.28 (C3), 27.82 (C5), 14.06 (4-$CO_2CH_2CH_3$). HRMS (ESI, +ve) *m/z*: 314.1356 $[M + Na]^+$. $C_{16}H_{21}O_4Na$ requires 314.1363.

(ii) *Ethyl 1-(3-methoxybenzoyl)piperidine-4-carboxylate* ***26***

White solid (2.56 g, 97%) mp 57–59 °C, R_f 0.77 (EtOAc). FTIR (neat) ν_{max}: 3066, 2989, 2863, 1721, 1625, 1581, 1425, 1311, 1264, 1248, 1175, 1037, 946, 860, 814 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$; **RJ-01-45-m** at 25 °C; 140609-rsj 1 2): δ 7.29 (m, 1H, H5'), 6.92 (m, 2H, H4' and H6'), 6.91 (m, H2'), 4.50 (4.35-4.65) (br s, 1H, $H_{eq}6$), 4.14 (q, *J* 7.1, 2H, 4-$CO_2CH_2CH_3$), 3.80 (s, 3H, 3'-OCH_3), 3.74 (3.60-3.90) (br s, 1H, $H_{eq}2$), 3.02 (m, 2H, $H_{ax}2$ and $H_{ax}6$), 2.55 (tt, *J* 10.8, 4.1 Hz, 1H, H4), 1.98 (1.88-2.13) (br s, 1H, $H_{eq}5$), 1.85 (1.73-1.96) (br s, 1H, $H_{eq}3$), 1.71 (1.50-1.85) (br s, 2H, $H_{ax}3$ and $H_{ax}5$), 1.24 (t, *J* 7.1, 3H, 4-$CO_2CH_2CH_3$). ^{13}C NMR (75 MHz, $CDCl_3$; **RJ-01-45-m** at 25 °C; 140609-rsj 2 2): δ 174.3 (4-$CO_2CH_2CH_3$), 170.2 (1'-C(O)N), 159.8 (C3'), 137.4 (C1'), 129.7 (C5'), 118.9 (C6'), 115.6 (C4'), 112.3 (C2'), 60.8 (4-$CO_2CH_2CH_3$), 55.5 (2'-OCH_3), 47.0 (br, C2), 41.6 (br, C6), 41.2 (C4), 28.4 (br, C3), 28.0 (br, C5), 14.3 (4-$CO_2CH_2CH_3$). HRMS (ESI, +ve) *m/z*: 314.1353 $[M + Na]^+$. $C_{16}H_{21}O_4Na$ requires 314.1363 $[M + Na]^+$.

(iii) *Ethyl 1-(4-methoxybenzoyl)piperidine-4-carboxylate* ***27***

Yellow oil (1.89 g, 71%), R_f 0.74 (EtOAc). FTIR (neat) ν_{max}: 3262, 2933, 2857, 2008, 1879, 1832, 1758, 1722, 1624, 1509, 1485, 1424, 1300, 1241, 1170, 1107, 1027, 935, 838, 684 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$; **RJ-01-08** at –20 °C): δ 7.36 (d, *J* 8.8 Hz, 2H, H2' and H6'), 6.89 (d, *J* 8.9 Hz, 2H, H3' and H5'), 4.56 (ddd, *J* 13.3, 4.0, 3.2 Hz, 1H, $H_{eq}6$), 4.12 (q, *J* 7.2 Hz, 2H, 4-$CO_2CH_2CH_3$), 3.84 (ddd, *J* 13.3, 4.1, 3.4 Hz, 1H, $H_{eq}2$), 3.82 (s, 3H, 4'-OCH_3), 3.06 (ddd, *J* 13.3, 11.2, 2.7 Hz, 1H, $H_{ax}2$), 2.90 (ddd, *J* 13.3, 11.4, 2.6 Hz, 1H, $H_{ax}6$), 2.56 (tt, *J* 11.2, 3.9 Hz, 1H, H4), 2.03 (dddd, *J* 13.6, 3.9, 3.2, 2.6 Hz, 1H, $H_{eq}5$), 1.86 (dddd, *J* 13.4,

3.9, 3.4, 2.7 Hz, 1H, $H_{eq}3$), 1.72 (dddd, *J* 13.6, 11.4, 11.2, 4.0 Hz, 1H, $H_{ax}5$), 1.65 (dddd, *J* 13.4, 11.2, 11.2, 4.1 Hz, 1H, $H_{ax}3$), 1.24 (t, *J* 7.2 Hz, 3H, 4-$CO_2CH_2CH_3$). ^{13}C NMR (100 MHz, $CDCl_3$; **RJ-01-08** at –20 °C): δ 174.5 (4-$CO_2CH_2CH_3$), 170.5 (1'-C(O)N), 160.5 (C4'), 129.0 (C2' and C6'), 127.7 (C1'), 113.6 (C3' and C5'), 60.9 (4-$CO_2CH_2CH_3$), 55.4 (4'-OCH_3), 47.3 (C2), 41.7 (C6), 41.1 (C4), 28.5 (C3), 27.9 (C5), 14.2 (4-$CO_2CH_2CH_3$). HRMS (ESI, +ve) *m/z*: 314.1363 $[M + Na]^+$. $C_{16}H_{21}O_4Na$ requires 314.1363 $[M + Na]^+$.

Treatment of amidoesters 25-27 with $NaBH_4$

General procedure: Sodium borohydride (0.39 g, 10.3 mmol) was added to a solution of the amidoester (0.50 g, 1.7 mmol) in dry THF (4 mL) under nitrogen and the reaction mixture warmed to reflux. MeOH (1 mL) was added dropwise and the reaction mixture was refluxed overnight. Upon cooling to r.t., the mixture was quenched with 1N HCl and concentrated under reduced pressure. The residue was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were washed with brine (2 x 10 mL), dried over Na_2SO_4 and the solvent was removed under reduced pressure. The oily residue was flash chromatographed on silica gel using a gradient of MeOH/CH_2Cl_2 (1:25 to 1:15) to yield amidoalcohols **28-30**.

(i) *4-(Hydroxymethyl)piperidin-1-yl)(2-methoxyphenyl)methanone* ***28***

White solid (0.19 g, 44%) mp 135–137 °C, R_f 0.29 (EtOAc). FTIR (neat) ν_{max}: 3360, 2907, 2847, 1591, 1438, 1365, 1186, 878, 767 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$; **RJ-01-61** at 10 °C; 170607-rsj 2 2; 54:46 mixture of isomers): δ (major isomer) 7.296 (ddd, *J* 8.3, 7.4, 1.7 Hz, 1H, H4'), 7.164 (dd, *J* 7.4, 1.7 Hz, 1H, H6'), 6.925 (ddd, *J* 7.4, 7.4, 0.8 Hz, 1H, H5'), 6.857 (d, *J* 8.3 Hz, 1H, H3'), 4.698 (ddd, *J* 13.1, 4.4, 2.2 Hz, 1H, $H_{eq}6$), 3.763 (s, 3H, 2'-OCH_3), 3.414 (ddd, *J* 13.4, 4.4, ~2 Hz, 1H, $H_{eq}2$), 3.352 (dd, *J* 14.0, 10.7 Hz, 1H, 4-C*H*aHbOH), 3.342 (dd, *J* 14.0, 10.7 Hz, 1H, 4-CHa*H*bOH), 3.19 (br s, 1H, 4-CH_2OH), 2.923 (ddd, *J* 13.2, 12.8, 2.6 Hz, 1H, $H_{ax}2$), 2.682 (ddd, *J* 13.1, 12.7, 2.9 Hz, 1H, $H_{ax}6$), 1.731 (dm,

J 13.4 Hz, 1H, $H_{eq}5$), 1.61 (br m, 1H, H4), 1.551 (dm, *J* 13.1 Hz, 1H, $H_{eq}3$), 1.110 (dddd, *J* 13.4, 12.7, 12.2, 4.4 Hz, 1H, $H_{ax}5$), 0.937 (dddd, *J* 13.1, 12.8, 12.2, 4.4 Hz, 1H, $H_{ax}3$). δ (minor isomer) 7.287 (ddd, *J* 8.3, 7.4, 1.7 Hz, 1H, H4'), 7.130 (dd, *J* 7.4, 1.7 Hz, 1H, H6'), 6.921 (ddd, *J* 7.4, 7.4, 0.8 Hz, 1H, H5'), 6.857 (d, *J* 8.3 Hz, 1H, H3'), 4.698 (ddd, *J* 13.1, 4.4, 2.2 Hz, 1H, $H_{eq}6$), 3.758 (s, 3H, 2'-OCH_3), 3.414 (ddd, *J* 13.4, 4.4, ~2 Hz, 1H, $H_{eq}2$), 3.324 (dd, *J* 13.4, 10.7 Hz, 1H, 4-C*H*aHbOH), 3.314 (dd, *J* 13.4, 10.7 Hz, 1H, 4-CHa*H*bOH), 3.19 (br s, 1H, 4-CH_2O*H*), 2.816 (ddd, *J* 13.2, 12.7, 2.5 Hz, 1H, $H_{ax}2$), 2.650 (ddd, *J* 13.1, 12.6, 3.0 Hz, 1H, $H_{ax}6$), 1.731 (dm, *J* 13.4 Hz, 1H, $H_{eq}5$), 1.61 (br m, 1H, H4), 1.594 (dm, *J* 13.1 Hz, 1H, $H_{eq}3$), 1.163 (dddd, *J* 13.4, 12.7, 12.2, 4.3 Hz, 1H, $H_{ax}5$), 0.937 (m, 1H, $H_{ax}3$). ^{13}C NMR (150 MHz, $CDCl_3$; **RJ-01-61** at 10 °C; 170607-rsj 8 2; 54:46 mixture of isomers): δ (major) 167.86 (1'-C(O)N), 155.09 (C2'), 130.31 (C4'), 127.51 (C6'), 125.72 (C1'), 120.77 (C5'), 110.75 (C3'), 66.81 (4-*C*H_2OH), 55.49 (2'-OCH_3), 46.66 (C2), 41.52 (C6), 38.72 (C4), 29.14 (C3), 28.43 (C5). δ (minor) 167.69 (1'-C(O)N), 155.11 (C2'), 130.20 (C4'), 127.70 (C6'), 125.87 (C1'), 120.75 (C5'), 110.63 (C3'), 66.91 (4-*C*H_2OH), 55.35 (2'-OCH_3), 47.33 (C2), 41.57 (C6), 38.72 (C4), 29.21 (C3), 28.37 (C5). HRMS (ESI, +ve) *m/z*: 272.1250 $[M+Na]^+$. $C_{14}H_{19}NO_3Na$ requires 272.1257 $[M + Na]^+$.

(ii) *4–(Hydroxymethyl)piperidin–1–yl)(3–methoxyphenyl)methanone* ***29***

White solid (0.21 g, 49%) mp 79–81 °C, R_f 0.34 (EtOAc). FTIR (neat) ν_{max}: 3378, 3151, 3009, 2912, 2907, 2859, 2306, 1598, 1451, 1298, 1255, 1110, 1037, 854, 790, 725 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$; single isomer at 25 °C; RJ-01-59-2 140619-rsj 4 2): δ 7.28 (dddd, *J* 8.1, 7.1, 1.0, 0.8 Hz, 1H, H5'), 6.92 (m, 1H, H4'), 6.91 (m, 1H, H6'), 6.90 (m, 1H, H2'), 4.69 (very br d, *J* 9.9 Hz, 1H, Heq6), 3.79 (s, 3H, OCH_3), 3.75 (very br d, *J* 10.4 Hz, 1H, Heq2), 3.45 (br d, *J* 5.5 Hz, 2H, 4-C*H*$_2$OH), 2.95 (br dd, *J* 10.4, 9.8 Hz, 1H, Hax2), 2.73 (br dd, *J* 9.9, 9.4 Hz, 1H, Hax6), 2.30 (2.05-2.55) (br s, 1H, 4-CH_2O*H*), 1.80 (1.65-1.90) (br s, 1H,

Heq5), 1.74 (1.60-1.82) (br s, 1H, Heq3), 1.72 (m, 1H, H4), 1.18 (1.10-1.35) (br s, 1H, Hax5), 1.15 (1.00-1.25) (br s, 1H, Hax3). ^{1}H NMR (300 MHz, $CDCl_3$; RJ-01-59-2 at –10 °C; 140701-rsj 2 2): δ 7.27 (dddd, *J* 8.1, 7.3, 0.6, 0.4 Hz, 1H, H5'), 6.90 (m, 1H, H4'), 6.89 (m, 1H, H6'), 6.86 (m, 1H, H2'), 4.66 (dm, $J_{Heq,Hax}$ 13.2 Hz, 1H, Heq6), 3.77 (s, 3H, OCH_3), 3.71 (dm, $J_{Heq,Hax}$ 13.4 Hz, 1H, Heq2), 3.37 (m, 2H, 4-CH_2OH), 3.17 (t, *J* 4.4 Hz, 1H, 4-CH_2O*H*), 2.92 (ddd, $J_{Hax2,Heq2}$ 13.4, $J_{Hax2,Hax3}$ 12.8, $J_{Hax2,Heq3}$ 3.0 Hz, 1H, Hax2), 2.68 (ddd, $J_{Hax6,Heq6}$ 13.2, $J_{Hax6,Hax5}$ 12.6, $J_{Hax6,Heq5}$ 3.1 Hz, 1H, Hax6), 1.77 (dm, $J_{Heq,Hax}$ 13.2 Hz, 1H, Heq5), 1.65 (m, 1H, H4), 1.63 (dm, $J_{Heq,Hax}$ 12.4 Hz, 1H, Heq3), 1.17 (ddd, $J_{Hax5,Heq5}$ 13.2, $J_{Hax5,Hax6}$ 12.6, $J_{Hax5,H4}$ 11.9, $J_{Hax5,Heq6}$ 3.1 Hz, 1H, Hax5), 1.06 (ddd, $J_{Hax3,Hax2}$ 12.8, $J_{Hax3,H4}$ 12.8, $J_{Hax3,Heq3}$ 12.4, $J_{Hax3,Heq2}$ 3.0 Hz, 1H, Hax3). ^{13}C NMR (75 MHz, $CDCl_3$; **RJ-01-59-2** at 25 °C; 140619-rsj 2 2): δ 170.2 (1'-C(O)N), 159.7 (C3'), 137.6 (C1'), 129.6 (C5'), 118.9 (C6'), 115.4 (C4'), 112.3 (C2'), 67.1 (4-*C*H_2OH), 55.4 (3'-OCH_3), 47.8 (br, C2), 42.2 (br, C6), 38.9 (C4), 29.5 (br, C3), 28.5 (br, C5). HRMS (ESI, +ve) *m/z*: 272.1256 $[M+Na]^+$. $C_{14}H_{19}NO_3Na$ requires 272.1257 $[M + Na]^+$.

(iii) *4–(Hydroxymethyl)piperidin–1–yl)(4–methoxyphenyl)methanone* ***30***

White solid (0.26 g, 60%) mp 118–120 °C, R_f 0.31 (EtOAc). FTIR (neat) ν_{max}: 3373, 3000, 2907, 2907, 2321, 2090, 1601, 1438, 1301, 1249, 1167, 1112, 1028, 956, 931 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$; **RJ-01-22** at 25 °C; 140506-rsj 1 2): δ 7.35 (d, *J* 8.7 Hz, 2H, H2' and H6'), 6.89 (d, *J* 8.7 Hz, 2H, H3' and H5'), 4.2-4.9 (very br s, 1H, H_{eq}6), 3.7-4.2 (very br s, 1H, H_{eq}2), 3.81 (s, 3H, 4'-OCH_3), 3.25 (d, *J* 5.9 Hz, 2H, 4-CH_2OH), 1.9-2.2 (br s, 1H, 4-CH_2O*H*), 2.6-3.2 (br s, 2H, H_{ax}2 and H_{ax}6), 1.77 (m, 1H, H_{eq}5), 1.75 (m, 1H, H4), 1.72 (m, 1H, H_{eq}3), 1.24 (m, 1H, H_{ax}5), 1.20 (m, 1H, H_{ax}3). ^{1}H NMR (400 MHz, $CDCl_3$; **RJ-01-22** at –20 °C; 170412-rsj 3 2): δ 7.34 (d, *J* 8.7 Hz, 2H, H2' and H6'), 6.88 (d, *J* 8.7 Hz, 2H, H3' and H5'), 4.67 (br d, *J* 13.0 Hz, 1H, H_{eq}6), 3.85 (br d, *J* 13.0 Hz, 1H, H_{eq}2), 3.81 (s, 3H, 4'-OCH_3), 3.42

(br s, 2H, 4-C*H*$_2$OH), 3.10 (br s, 1H, 4-CH$_2$O*H*), 2.97 (ddd, *J* 13.2, 13.0, 2.2 Hz, 1H, H$_{ax}$2), 2.70 (ddd, *J* 13.0, 12.9, 2.6 Hz, 1H, H$_{ax}$6), 1.80 (br d, *J* 13.0 Hz, 1H, H$_{eq}$5), 1.70 (m, 1H, H4), 1.68 (br d, *J* 13.2 Hz, 1H, H$_{eq}$3), 1.20 (dddd, *J* 13.0, 13.0, 12.5, 4.4 Hz, 1H, H$_{ax}$5), 1.11 (dddd, *J* 13.2, 13.0, 12.5, 3.8 Hz, 1H, H$_{ax}$3). ^{13}C NMR (75 MHz, CDCl$_3$; **RJ-01-22** at 25 °C; 140506-rsj 2 2): δ 170.5 (1'-C(O)N), 160.7 (C4'), 129.0 (C2' and C6'), 128.5 (C1'), 113.8 (C3' and C5'), 67.3 (4-*C*H$_2$OH), 55.4 (4'-OCH$_3$), ~47.8 (very br, C2), ~43.3 (very br, C6), 39.0 (C4), 29.1 (br, C3), 29.0 (br, C5). HRMS (ESI, +ve) *m*/*z*: 272.1256 [M+Na]$^+$. C$_{14}$H$_{19}$NO$_3$Na requires 272.1257 [M + Na]$^+$.

Treatment of amidoester 27 with LiAlH$_4$

(i) Lithium aluminiumhydride (0.12 g, 3.2 mmol) was added in one portion to a stirred solution of amidoester **27** (0.15 g, 0.52 mmol) in dry THF (10 mL) under nitrogen at –20 °C. Stirring was continued at the same temperature for 45 min then the mixture quenched with sat. aq. NH$_4$Cl (10 mL). The mixture was extracted with CH$_2$Cl$_2$ (3 x 10 mL) and the combined extracts washed with water (2 x 10 mL), dried over Na$_2$SO$_4$ and evaporated to dryness under reduced pressure. The oily residue was flash chromatographed over silica gel using a gradient of 2:1 EtOAc/*n*-hexane to pure EtOAc to yield 4–(hydroxymethyl)piperidin–1–yl)(4–methoxyphenyl)methanone **30** (0.11 g, 88%) with identical spectroscopic properties to those of the product derived through reduction with NaBH$_4$.

(ii) Treatment of amidoester **27** (0.94 g) under the same conditions as in (i) except that reaction time was increased to 2 h gave (1-(4-methoxybenzyl)piperidin-4-yl)methanol **20** as a white solid (0.56 g, 74%) mp 44–45 °C, R$_f$ 0.15 (EtOAc) with identical spectroscopic properties to those of the product derived through reductive alkylation of 4-hydroxymethylpiperidine **14**, namely FTIR (neat) ν_{max}: 3106, 2806, 1607, 1511, 1438, 1326, 1298, 1240, 1180, 1102, 1035, 967, 819 cm^{-1}. ^{1}H NMR (300 MHz, CDCl$_3$; **RJ-01-75** at 25

°C; 150120-rsj 13 2): δ 7.21 (d, *J* 8.4 Hz, 2H, H2' and H6'), 6.83 (d, *J* 8.4 Hz, 2H, H3' and H5'), 3.78 (s, 3H, 4'-OCH_3), 3.44 (d, *J* 6.5 Hz, 2H, 4-CH_2OH), 3.43 (s, 2H, 1'-CH_2N), 2.88 (br d, *J* 11.2 Hz, 2H, H_{eq}2 and H_{eq}6), 2.47 (br s, 1H, OH), 1.92 (ddd, *J* 12.0, 11.2, 2.0 Hz, 2H, H_{ax}2 and H_{ax}6), 1.68 (br d, *J* 11.2 Hz, 2H, H_{eq}3 and H_{eq}5), 1.44 (m, 1H, H4), 1.25 (dddd, *J* 12.4, 12.0, 11.6, 3.6 Hz, 2H, H_{ax}3' and H_{ax}5'). ^{13}C NMR (100.1 MHz, $CDCl_3$): δ 158.7 (C4'), 130.7 (C2' and C6'), 129.8 (C1'), 115.6 (C3' and C5'), 67.4 (4-CH_2OH), 62.7 (1'-CH_2N), 55.2 (4'-OCH_3), 53.2 (C2 and C6), 38.55 (C4), 28.7 (C3 and C5). ^{13}C NMR (75 MHz, $CDCl_3$; **RJ-01-75** at 25 °C; 150120-rsj 14 2): δ 158.7 (C4'), 130.6 (C2' and C6'), 130.2 (C1'), 113.6 (C3' and C5'), 67.7 (4-CH_2OH), 62.9 (1'-CH_2N), 55.3 (4'-OCH_3), 53.3 (C2 and C6), 38.6 (C4), 28.8 (C3 and C5). HRMS (ESI, +ve) *m/z*: 236.1629 $[M+H]^+$. $C_{14}H_{22}NO_2$ requires 236.1645 $[M + H]^+$.

Reaction of amidoalcohols 28-30 with CH_3SO_2Cl

General procedure: Methanesulfonyl chloride (0.23 mL, 0.34 g, 3.0 mmol) was added to a solution of alcohol **28-30** (0.50 g, 2.0 mmol) in pyridine (5 mL). The mixture was stirred overnight at r.t. and then concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 (25 mL) and the solution washed successively with 15% aq. HCl (2 x 10 mL) and distilled water (10 mL), dried over $MgSO_4$ and evaporated to dryness. The crude product was column chromatographed on silica gel using MeOH/CH_2Cl_2 as eluent to give amido mesylate esters **36-38**.

(i) *(1-(2-Methoxybenzoyl)piperidin-4-yl)methyl methanesulfonate* ***36***

White solid (0.52 g, 80%) mp 72–74 °C, R_f 0.42 (EtOAc). FTIR (neat) ν_{max}: 3020, 2918, 1616, 1467, 1327, 1244, 1167, 1017, 904, 850 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$; 52:48 mixture at 25 °C; RJ-01-70; 150120-rsj 2 2): δ (major) 7.310 (ddd, *J* 8.4, 7.4, 1.7 Hz, 1H, H4'), 7.199 (dd, *J* 7.5, 1.7 Hz, 1H, H6'), 6.982 (dd, *J* 7.5, 7.4 Hz, 1H, H5'), 6.883 (dd, *J* 8.4

Hz, 1H, H6'), 4.798 (dm, *J* 13.1 Hz, 1H, Heq6), 4.069 (dd, *J* 10.6, 6.4 Hz, 1H, 4–C*H*$_a$H$_b$OSO$_2$CH$_3$), 4.037 (dd, *J* 10.6, 6.5 Hz, 1H, 4–CH$_a$*H*$_b$OSO$_2$CH$_3$), 3.788 (s, 3H, OCH**$_3$**), 3.498 (dm, *J* 13.6 Hz, 1H, Heq2), 2.996 (ddd, $J_{Hax2,Heq2}$ 13.6, $J_{Hax2,Hax3}$ 12.4, $J_{Hax2,Heq3}$ 2.8 Hz, 1H, Hax2), 2.973 (s, 3H, 4–CH$_a$H$_b$OSO$_2$C*H*$_3$), 2.756 (ddd, $J_{Hax6,Heq6}$ 13.1, $J_{Hax6,Hax5}$ 12.9, $J_{Hax6,Heq5}$ 2.9 Hz, 1H, Hax6), 1.977 (m, 1H, H4), 1.833 (br d, $J_{Heq5,Hax5}$ 12.9 Hz, 1H, Heq5), 1.658 (br d, $J_{Heq3,Hax3}$ 12.9 Hz, 1H, Heq3), 1.349 (dddd, $J_{Hax5,Heq5}$ 12.9, $J_{Hax5,Hax6}$ 12.9, $J_{Hax5,Hax4}$ 12.4, $J_{Hax5,Heq6}$ 4.5 Hz, 1H, Hax5), 1.111 (dddd, $J_{Hax3,Heq3}$ 12.9, $J_{Hax3,Hax2}$ 12.4, $J_{Hax3,Hax4}$ 12.2, $J_{Hax3,Heq2}$ 4.1 Hz, 1H, Hax3). δ (minor) 7.316 (ddd, *J* 8.4, 7.4, 1.7 Hz, 1H, H4'), 7.159 (dd, *J* 7.5, 1.7 Hz, 1H, H6'), 6.982 (dd, *J* 7.5, 7.4 Hz, 1H, H5'), 6.883 (d, *J* 8.4 Hz, 1H, H6'), 4.798 (dm, *J* 13.1 Hz, 1H, Heq6), 4.076 (dd, *J* 10.6, 6.4 Hz, 1H, 4–C*H*$_a$H$_b$OSO$_2$CH$_3$), 4.034 (dd, *J* 10.6, 6.5 Hz, 1H, 4–CH$_a$*H*$_b$OSO$_2$CH$_3$), 3.798 (s, 3H, OCH**$_3$**), 3.498 (dm, $J_{Heq2,Hax2}$ 13.6 Hz, 1H, Heq2), 2.981 (s, 3H, 4–CH$_a$H$_b$OSO$_2$C*H*$_3$), 2.844 (ddd, $J_{Hax2,Heq2}$ 13.6, $J_{Hax2,Hax3}$ 12.3, $J_{Hax2,Heq3}$ 2.8 Hz, 1H, Hax2), 2.713 (ddd, $J_{Hax6,Heq6}$ 13.1, $J_{Hax6,Hax5}$ 12.8, $J_{Hax6,Heq5}$ 2.9 Hz, 1H, Hax6), 1.977 (m, 1H, H4), 1.833 (br d, $J_{Heq5,Hax5}$ 12.9 Hz, 1H, Heq5), 1.658 (br d, $J_{Heq3,Hax3}$ 12.9 Hz, 1H, Heq3), 1.314 (m, 1H, Hax3), 1.298 (m, 1H, Hax5). ^{13}C NMR (75 MHz, $CDCl_3$; 52:48 mixture at 25 °C; RJ-01-70; 150120-rsj 2 2): δ (major) 167.86 (1'-C(O)N), 155.29 (C2'), 130.44 (C4'), 127.69 (C6'), 125.82 (C1'), 120.94 (C5'), 110.97 (C3'), 73.21 (4-*C*H$_2$OAr), 55.59 (OCH$_3$), 46.77 (C2), 41.08 (C6), 37.34 (4-CH$_2$OSO$_2$*C*H$_3$), 36.13 (C4), 28.85 (C3), 28.03 (C5). δ (minor) 167.66 (1'-C(O)N), 155.29 (C2'), 130.31 (C4'), 127.84 (C6'), 126.00 (C1'), 120.94 (C5'), 110.90 (C3'), 73.30 (4-*C*H$_2$OAr), 55.50 (OCH$_3$), 46.07 (C2), 40.99 (C6), 37.34 (4-CH$_2$OSO$_2$*C*H$_3$), 36.13 (C4), 28.85 (C3), 28.03 (C5). HRMS (ESI, +ve) *m/z*: 350.1028 $[M+Na]^+$. $C_{15}H_{21}NO_5SNa$ requires 350.1033 $[M + Na]^+$.

(ii) *(1-(3-Methoxybenzoyl)piperidin-4-yl)methyl methanesulfonate* ***37***

White solid (0.54 g, 83%) mp 62–63 °C, R_f 0.45 (EtOAc). FTIR (neat) ν_{max}: 3008, 2917, 2857, 2320, 1616, 1454, 1339, 1290, 1258, 1169, 1107, 973 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$; near equal isomers at 25 °C; RJ-01-72; 150120-rsj 5 1): δ 7.29 (dddd, *J* 7.4, 6.9, 1.7, 0.8 Hz, 1H, H5'), 6.892 (m, 1H, H4'), 6.891 (m, 1H, H6'), 6.87 (m, 1H, H2'), 4.69 (4.40-4.85) (br s, 1H, Heq6), 4.04 (d, *J* 6.4 Hz, 2H, 4-C*H*$_2$OSO$_2$CH$_3$), 3.79 (3.52-4.00) (br s, 1H, Heq2), 3.771(minor) / 3.770(major) (2xs, 3H total, OCH$_3$), 2.968(major) / 2.966(minor) (2xs, 3H total, 4-CH$_2$OSO$_2$C*H*$_3$), 2.95 (2.83-3.10) (br s, 1H, Hax2), 2.76 (2.60-2.90) (br s, 1H, Hax6), 2.00 (m, 1H, H4), 1.76 (1.57-1.85) (br s, 2H, Heq3 and Heq5), 1.26 (1.07-1.42) (br s, 2H, Hax3 and Hax5). ^{13}C NMR (75 MHz, $CDCl_3$; apparent single isomer at 25 °C; RJ-01-72; 150120-rsj 6 2): δ 170.06 (1'-C(O)N), 159.61 (C3'), 137.27 (C1'), 129.60 (C5'), 118.78 (C6'), 115.37 (C4'), 112.23 (C2'), 73.10 (4-*C*H$_2$OSO$_2$CH$_3$), 55.33 (OCH$_3$), 47.12 (br, C2), 41.61 (br, C6), 37.27 (4-CH$_2$OSO$_2$*C*H$_3$), 36.05 (C4), 29.91 (br, C3), 28.00 (br, C5). HRMS (ESI, +ve) *m/z*: 350.1033 [M+Na]$^+$. $C_{15}H_{21}NO_5SNa$ requires 350.1033 [M + Na]$^+$.

(iii) *(1-(4-Methoxybenzoyl)piperidin-4-yl)methyl methanesulfonate* ***38***

White solid (0.53 g, 81%) mp 91–93 °C, R_f 0.63 (EtOAc). FTIR (neat) ν_{max}: 3005, 2931, 2863, 2307, 1607, 1514, 1436, 1335, 1296, 1249, 1167, 1121, 1110, 949 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$; single isomer at 25 °C; RJ-01-29-1; 140516-rsj 1 2): δ 7.34 (d, *J* 8.8 Hz, 2H, H2' and H6'), 6.88 (d, *J* 8.8 Hz, 2H, H3' and H5'), 4.48 (4.00-5.00) (br s, 1H, Heq6), 4.07 (d, *J* 6.4 Hz, 2H, 4-C*H*$_2$OSO$_2$CH$_3$), 3.80 (s, 3H, OCH$_3$), 3.72 (3.20-4.30) (br s, 1H, Heq2), 2.99 (s, 3H, 4-CH$_2$OSO$_2$C*H*$_3$), 2.87 (2.70-3.05) (br s, 2H, Hax2 and Hax6), 2.02 (m, 1H, H4), 1.78 (br d, *J* 12.5 Hz, 2H, Heq3 and Heq5), 1.28 (dddd, *J* 12.5, 12.0, 10.5, 4.1 Hz, 2H, Hax3 or Hax5). ^{13}C NMR (75 MHz, $CDCl_3$; single isomer at 25 °C; RJ-01-29/2; 140516-rsj 2 2): δ 170.5 (1'-C(O)N), 160.8 (C4'), 129.0 (C2' and C6'), 128.1 (C1'), 113.8 (C3' and C5'), 73.2 (4-*C*H$_2$OSO$_2$CH$_3$), 55.4 (OCH$_3$), 46.6 (very br and weak, C2), 42.4 (very br and weak, C6), 37.4

(4-$CH_2OSO_2CH_3$), 36.2 (C4), 28.5 (br, C3 and C5). HRMS (ESI, +ve) *m/z*: 350.1030 $[M+Na]^+$. $C_{15}H_{21}NO_5SNa$ requires 350.1033 $[M + Na]^+$.

Reaction of amidoalcohol mesylates 36-38 with 4-hydroxybenzaldehyde 39

General procedure: Mesylate ester (1.25 g, 3.82 mmol) was added with stirring to a mixture of 4-hydroxybenzaldehyde **7** (0.50 g, 4.10 mmol) and K_2CO_3 (2.30 g, 16.7 mmol) in dry DMF (40 mL) under nitrogen. The reaction mixture was heated to 70 °C overnight, after which time it was cooled to r.t., poured into distilled water (100 mL) and extracted with CH_2Cl_2 (3 x 100 mL). The combined extracts were washed with distilled water (3 x 100 mL), dried over Na_2SO_4 and the solvent removed under reduced pressure to give a white solid that was flash chromatographed over silica gel using a gradient of 1:2 EtOAc/*n*–hexane to 100% EtOAc.

(i) *4-((1-(2-Methoxybenzoyl)piperidin-4-yl)methoxy)benzaldehyde* ***40***

Colourless gum (0.90 g, 67%), R_f 0.57 (EtOAc). FTIR (neat) ν_{max}: 2996, 2933, 2861, 1672, 1594, 1508, 1431, 1292, 1245, 1155, 1121, 1015, 985, 832, 753 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$; 52:48 mixture at 25 °C; RJ-02-41; 150323-rsj 1 2): δ (major) 9.855 (s, 1H, 4"-CHO), 7.806 (dd, *J* 8.8, 2.1 Hz, 1H, H3" and H5"), 7.325 (ddd, *J* 8.1, 7.7, 1.8 Hz, 1H, H4'), 7.235 (dd, *J* 7.4, 1.7 Hz, 1H, H6'), 6.964 (dd, *J* 8.8, 2.1 Hz, 2H, H2" and H6"), 6.962 (ddd, *J* 7.4, 7.4, 1.0 Hz, 1H, H5'), 6.894 (dd, *J* 8.4, 0.9 Hz, 1H, H3'), 4.846 (dddd, $J_{Heq6,Hax6}$ 13.3, $J_{Heq6,Hax5}$ 4.2, $J_{Heq6,Heq2}$ 2.5, $J_{Heq6,Heq5}$ 2.0 Hz, 1H, Heq6), 3.928 (dd, $J_{Ha,Hb}$ 9.2 Hz, $J_{Ha,H4}$ 6.1 Hz, 1H, 4–C$H_a$$H_b$OAr), 3.867 (dd, $J_{Hb,Ha}$ 9.2 Hz, $J_{Hb,H4}$ 6.5 Hz, 1H, 4–C$H_a$$H_b$OAr), 3.807 (s, 3H, OCH_3), 3.538 (dddd, $J_{Heq2,Hax2}$ 13.6, $J_{Heq2,Hax3}$ 4.5, $J_{Heq2,Heq3}$ 2.8, $J_{Heq2,Heq6}$ 2.5 Hz, 1H, Heq2), 3.055 (dddd, $J_{Hax2,Heq2}$ 13.6, $J_{Hax2,Hax3}$ 12.5, $J_{Hax2,Heq3}$ 2.8 Hz, 1H, Hax2), 2.816 (ddd, $J_{Hax6,Heq6}$ 13.3, $J_{Hax6,Hax5}$ 12.4, $J_{Hax6,Heq5}$ 3.0 Hz, 1H, Hax6), 2.079 (m, 1H, H4), 1.932 (dm, $J_{Heq5,Hax5}$ 13.0, 1H, Heq5), 1.746 (dm, $J_{Heq3,Hax3}$ 13.0, 1H, Heq3), 1.385 (m, 1H, Hax5),

1.197 (dddd, $J_{Hax5,Heq5}$ 13.0, $J_{Hax3,Hax2}$ 12.5, $J_{Hax3,Hax4}$ 12.4, $J_{Hax3,Heq2}$ 4.3 Hz, 1H, Hax3). δ (minor) 9.855 (s, 1H, 4"-CHO), 7.806 (dd, *J* 8.8, 2.1 Hz, 1H, H3" and H5"), 7.319 (ddd, *J* 8.1, 7.7, 1.8 Hz, 1H, H4'), 7.191 (dd, *J* 7.4, 1.7 Hz, 1H, H6'), 6.964 (dd, *J* 8.8, 2.1 Hz, 2H, H2" and H6"), 6.962 (ddd, *J* 7.4, 7.4, 1.0 Hz, 1H, H5'), 6.894 (dd, *J* 8.4, 0.9 Hz, 1H, H3'), 4.846 (dddd, $J_{Heq6,Hax6}$ 13.3, $J_{Heq6,Hax5}$ 4.2, $J_{Heq6,Heq2}$ 2.5, $J_{Heq6,Heq5}$ 2.0 Hz, 1H, Heq6), 3.928 (dd, $J_{Ha,Hb}$ 9.2 Hz, $J_{Ha,H4}$ 6.1 Hz, 1H, 4–CH_aH$_b$OAr), 3.858 (dd, $J_{Ha,Hb}$ 9.2 Hz, $J_{Hb,H4}$ 6.2 Hz, 1H, 4–CH$_a$$H_b$OAr), 3.811 (s, 3H, OCH$_3$), 3.538 (dddd, $J_{Heq2,Hax2}$ 13.6, $J_{Heq2,Hax3}$ 4.5, $J_{Heq2,Heq3}$ 2.8, $J_{Heq2,Heq6}$ 2.5 Hz, 1H, Heq2), 2.945 (ddd, $J_{Hax2,Heq2}$ 13.6, $J_{Hax2,Hax3}$ 12.5, $J_{Hax2,Heq3}$ 2.8 Hz, 1H, Hax2), 2.773 (ddd, $J_{Hax6,Heq6}$ 13.3, $J_{Hax6,Hax5}$ 12.4, $J_{Hax6,Heq5}$ 3.0 Hz, 1H, Hax6), 2.079 (m, 1H, H4), 1.932 (m, 1H, Heq5), 1.778 (dm, $J_{Heq3,Hax3}$ 13.0 Hz, 1H, Heq3), 1.428 (m, 1H, Hax5), 1.385 (m, 1H, Hax3). ^{13}C NMR (75 MHz, $CDCl_3$; 52:48 mixture at 25 °C; RJ-02-41; 150323-rsj 2 2): δ (major) 190.81 (4"-CHO), 167.91 (1'-C(O)N), 163.97 (C1"), 155.36 (C2'), 132.05 (C3" and C5"), 130.39 (C4'), 130.04 (C4"), 127.72 (C6'), 126.07 (C1'), 120.94 (C5'), 114.77 (C2" and C6"), 111.01 (C3'), 72.42 (4-*C*H$_2$OAr), 64.76 (4"-CH$_2$OH), 55.64 (OCH$_3$), 46.45 (C2), 41.36 (C6), 36.30 (C4), 29.47 (C3), 28.59 (C5). δ (minor) 190.81 (4"-CHO), 167.69 (1'-C(O)N), 164.00 (C1"), 155.36 (C2'), 132.05 (C3" and C5"), 130.26 (C4'), 130.04 (C4"), 128.62 (C3" and C5"), 127.92 (C6'), 126.25 (C1'), 120.99 (C5'), 114.77 (C2" and C6"), 110.91 (C3'), 72.48 (4-*C*H$_2$OAr), 64.76 (4"-CH$_2$OH), 55.54 (OCH$_3$), 47.14 (C2), 41.43 (C6), 36.30 (C4), 29.52 (C3), 28.66 (C5). HRMS (ESI, +ve) *m/z*: 376.1513 $[M+Na]^+$. $C_{21}H_{23}NO_4Na$ requires 376.1519 $[M + Na]^+$.

(ii) *4-((1-(3-Methoxybenzoyl)piperidin-4-yl)methoxy)benzaldehyde* ***41***

Colourless gum (0.93 g, 69%), R_f 0.63 (EtOAc). FTIR (neat) ν_{max}: 2933, 2858, 2730, 1692, 1600, 1437, 1293, 1249, 1162, 1106, 979, 829, 813, 749 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$; single isomer at 25 °C; RJ-02-42; 150323-rsj 6 2): δ 9.86 (s, 4"-CHO), 7.81 (d, *J* 8.7 Hz, 1H, H3" and H5"), 7.28 (dd, *J* 8.9, 7.2 Hz, 1H, H5'), 6.97 (d, *J* 8.7 Hz, 2H, H2" and H6"), 6.94 (d, *J*

8.9 Hz, 1H, H6'), 6.92 (d, *J* 7.2 Hz, 1H, H4'), 6.92 (m, 1H, H2'), 4.76 (4.65-4.85) (br s, 1H, Heq6), 3.90 (br d, J 4.6 Hz, 2H, 4–CH_2OAr), 3.82 (3.70-3.95) (br s, 1H, Heq2), 3.80 (s, 3H, OCH_3), 3.01 (2.85-3.20) (br s, 1H, Hax2), 2.81 (2.60-3.10) (br s, 1H, Hax6), 2.10 (m, 1H, H4), 1.87 (1.65-2.10) (br, 2H, Heq3 and Heq5), 1.36 (1.15-1.60) (br s, 2H, Hax3 and Hax5). ^{13}C NMR (75 MHz, $CDCl_3$; single isomer at 25 °C; RJ-02-42; 150323-rsj 7 2): δ 190.798 (4"-CHO), 170.2 (1'-C(O)N), 163.9 (C1"), 159.7 (C3'), 137.5 (C1'), 132.0 (C3" and C5"), 130.1 (C4"), 129.6 (C5'), 118.9 (C6'), 115.4 (C4'), 114.8 (C2" and C6"), 112.3 (C2'), 72.3 (4-*C*H_2OAr), 55.4 (OCH_3), 47.6 (br, C2), 42.0 (br, C6), 36.3 (C4), 29.6 (br, C3), 28.6 (br, C5). HRMS (ESI, +ve) *m/z*: 376.1513 $[M+Na]^+$. $C_{21}H_{23}NO_4Na$ requires 376.1519 $[M + Na]^+$.

(iii) *4-((1-(4-Methoxybenzoyl)piperidin-4-yl)methoxy)benzaldehyde* ***42***

White solid (0.99 g, 73%) mp 116–118 °C, R_f 0.60 (EtOAc). FTIR (neat) ν_{max}: 2936, 2865, 1674, 1593, 1508, 1428, 1293, 1253, 1156, 1110, 1014, 822 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$; single isomer at 25 °C; RJ-01-47-1; 140604-rsj 12 2): δ 9.87 (s, 4"-CHO), 7.82 (d, *J* 8.8 Hz, 1H, H3" and H5"), 7.38 (m, 2H, H2' and H6'), 6.98 (d, *J* 8.8 Hz, 2H, H2" and H6"), 6.90 (d, *J* 8.8 Hz, 2H, H3' and H5'), 4.62 (4.28-5.10) (br s, 1H, Heq6), 3.91 (d, *J* 6.2 Hz, 2H, 4–C*H*$_2$OAr), 3.86 (3.50-4.40) (br s, 1H, Heq2), 3.82 (s, 3H, OCH_3), 2.94 (2.76-3.10) (br s, 2H, Hax2 and Hax6), 2.12 (m, 1H, H4), 1.89 (br d, *J* 12.0 Hz, 2H, Heq3 and Heq5), 1.38 (br ddd, *J* 12.0, 11.7, 10.7 Hz, 2H, Hax3 and Hax5). ^{13}C NMR (75 MHz, $CDCl_3$; single isomer at 25 °C; RJ-01-47-1; 140604-rsj 13 2): δ 190.9 (4"-CHO), 170.5 (1'-C(O)N), 164.0 (C1"), 160.8 (C4'), 132.1 (C3" and C5"), 130.1 (C4"), 129.1 (C2' and C6'), 128.3 (C1'), 114.8 (C2" and C6"), 113.8 (C3' and C5'), 72.5 (4-*C*H_2OAr), 55.5 (OCH_3), 47.8 (very br and weak, C2), 43.4 (very br and weak, C6), 36.4 (C4), 29.2 (br, C3 and C5). HRMS (ESI, +ve) *m/z*: 376.1512 $[M+Na]^+$. $C_{21}H_{23}NO_4Na$ requires 376.1519 $[M + Na]^+$.

Reduction of aldehydes 40-42 with $NaBH_4$

General procedure: A cold solution of $NaBH_4$ (0.16 g, 4.23 mmol) in dry MeOH (3 mL) was added to a solution of the aldehyde (0.28 g, 0.79 mmol) in dry MeOH (3 mL). The reaction mixture was refluxed for 2h under nitrogen then cooled to r.t., quenched with 1N HCl (5 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The combined extracts were washed with distilled water (2 x 10 mL), dried over Na_2SO_4 and the solvent removed under reduced pressure. The residue was flash chromatographed over silica gel using a gradient of 1:1 EtOAc/*n*–hexane to 100% EtOAc.

(i) *(4-((4-(Hydroxymethyl)phenoxy)methyl)piperidine-1-yl)(2-methoxyphenyl)methanone* ***43***

White solid (0.18 g, 65%) mp 122–124°C, R_f 0.56 (EtOAc). FTIR (neat) ν_{max}: 3372, 2941, 2857, 1602, 1491, 1472, 1287, 1237, 1171, 1117, 1023, 985, 825, 750 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$; 52:48 mixture at 25 °C; RJ-02-43; 150323-rsj 11 2): δ (major) 7.331 (ddd, *J* 8.4, 7.7, 1.7 Hz, 1H, H4'), 7.242 (d, *J* 8.6 Hz, 1H, H3" and H5"), 7.229 (dd, *J* 7.4, 1.7 Hz, 1H, H6'), 6.966 (ddd, *J* 7.7, 7.4, 0.8 Hz, 1H, H5'), 6.895 (dd, *J* 8.4, 0.8 Hz, 1H, H6'), 6.834 (d, *J* 8.6 Hz, 2H, H2" and H6"), 4.813 (dm, *J* 13.3 Hz, 1H, Heq6), 4.554 (s, 2H, 4"-CH_2OH), 3.843 (dd, $J_{Ha,Hb}$ 9.2, $J_{Ha,H4}$ 6.2 Hz, 1H, 4–C$H_a$$H_b$OAr), 3.807 (s, 3H, OCH_3), 3.774 (dd, $J_{Hb,Ha}$ 9.2, $J_{Hb,H4}$ 6.2 Hz, 1H, 4–C$H_a$$H_b$OAr), 3.522 (dm, *J* 13.5 Hz, 1H, Heq2), 3.041 (ddd, $J_{Hax2,Heq2}$ 13.5, $J_{Hax2,Hax3}$ 12.9, $J_{Hax2,Heq3}$ 2.8 Hz, 1H, Hax2), 2.764 (ddd, $J_{Hax6,Heq6}$ 13.3, $J_{Hax6,Hax5}$ 12.6, $J_{Hax6,Heq5}$ 3.0 Hz, 1H, Hax6), 2.372 (br s, 1H, OH), 2.032 (m, 1H, H4), 1.925 (m, 1H, Heq5), 1.744 (m, 1H, Heq3), 1.420 (m, 1H, Hax5), 1.196 (dddd, $J_{Hax3,Heq3}$ ~12.8 (*ex* COSY), $J_{Hax3,Hax2}$ 12.6, $J_{Hax3,Hax4}$ 12.3, $J_{Hax3,Heq2}$ 4.2 Hz, 1H, Hax3). δ (minor) 7.322 (ddd, *J* 8.4, 7.7, 1.7 Hz, 1H, H4'), 7.249 (d, *J* 8.6 Hz, 1H, H3" and H5"), 7.186 (dd, *J* 7.4, 1.7 Hz, 1H, H6'), 6.966 (ddd, *J* 7.7, 7.4, 0.8 Hz, 1H, H5'), 6.895 (dd, *J* 8.4, 0.8 Hz, 1H, H6'), 6.845 (d, *J* 8.6 Hz, 2H, H2" and H6"), 4.813 (dm, $J_{Heq6,Hax6}$ 13.3 Hz, 1H, Heq6), 4.554 (s, 2H, 4"-CH_2OH), 3.843

(dd, $J_{Ha,Hb}$ 9.2, $J_{Ha,H4}$ 6.2 Hz, 1H, 4–C*H*$_a$H$_b$OAr), 3.807 (s, 3H, OCH**3**), 3.768 (dd, $J_{Hb,Ha}$ 9.2, $J_{Hb,H4}$ 6.6 Hz, 1H, 4–CH$_a$*H*$_b$OAr), 3.522 (dm, $J_{Heq2,Hax2}$ 13.5 Hz, 1H, Heq2), 2.930 (ddd, $J_{Hax2,Heq2}$ 13.5, $J_{Hax2,Hax3}$ 12.9, $J_{Hax2,Heq3}$ 2.8 Hz, 1H, Hax2), 2.802 (ddd, $J_{Hax6,Heq6}$ 13.3, $J_{Hax6,Hax5}$ 12.6, $J_{Hax6,Heq5}$ 3.0 Hz, 1H, Hax6), 2.372 (br s, 1H, OH), 2.032 (m, 1H, H4), 1.925 (m, 1H, Heq5), 1.781 (m, 1H, Heq3), 1.420 (m, 1H, Hax5), 1.370 (m, 1H, Hax3). ^{13}C NMR (75 MHz, $CDCl_3$; 52:48 mixture at 25 °C; RJ-02-43; 150323-rsj 12 2): δ (major) 167.96 (1'-C(O)N), 158.43 (C1"), 155.34 (C2'), 133.56 (C4"), 130.36 (C4'), 128.62 (C3" and C5"), 127.73 (C6'), 126.06 (C1'), 120.92 (C5'), 114.46 (C2" and C6"), 111.00 (C3'), 72.21 (4-*C*H$_2$OAr), 64.76 (4"-CH$_2$OH), 55.63 (OCH_3), 47.57 (C2), 41.48 (C6), 36.37 (C4), 29.56 (C3), 28.74 (C5). δ (minor) 167.75 (1'-C(O)N), 158.43 (C1"), 155.34 (C2'), 133.56 (C4"), 130.24 (C4'), 128.62 (C3" and C5"), 127.91 (C6'), 126.23 (C1'), 120.92 (C5'), 114.46 (C2" and C6"), 110.88 (C3'), 72.21 (4-*C*H$_2$OAr), 64.76 (4"-CH$_2$OH), 55.51 (OCH_3), 47.25 (C2), 41.55 (C6), 36.37 (C4), 29.60 (C3), 28.66 (C5). HRMS (ESI, +ve) *m/z*: 378.1674 $[M+Na]^+$. $C_{21}H_{25}NO_4Na$ requires 378.1676 $[M + Na]^+$.

(ii) *(4-((4-(Hydroxymethyl)phenoxy)methyl)piperidin-1-yl)(3-methoxyphenyl)methanone* ***44***

White solid (0.20 g, 72%) mp 91–93 °C, R_f 0.63 (EtOAc). FTIR (neat) ν_{max}: 3427, 3290, 3002, 2914, 2862, 1603, 1510, 1452, 1286, 1240, 1172, 1106, 1017, 970, 916, 823 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$; single isomer at 25 °C; RJ-02-44; 150323-rsj 16 1): δ 7.29 (m, 1H, H5'), 7.25 (d, *J* 8.7 Hz, 1H, H3" and H5"), 6.93 (m, 2H, H4' and H6'), 6.92 (m, 1H, H2'), 6.84 (d, *J* 8.7 Hz, 2H, H2" and H6"), 4.65-4.82 (br s, 1H, Heq6), 4.56 (s, 2H, 4"-C*H*$_2$OH), 3.70-4.00 (m, 3H, 4–C*H*$_2$OAr and Heq2), 3.80 (s, 3H, OCH**3**), 2.90-3.12 (m, 1H, Hax2), 2.70-2.90 (m, 1H, Hax6), 2.3-2.5 (br m, 1H, OH), 2.08 (br m, 1H, H4), 1.75-2.00 (m, 2H, Heq3 and Heq5), 1.28-1.50 (m, 2H, Hax3 and Hax5). ^{13}C NMR (75 MHz, $CDCl_3$; single isomer at 25 °C; RJ-02-44; 150323-rsj 17 1): δ 170.2 (1'-C(O)N), 159.7 (C3'), 158.4 (C1"), 137.5 (C1'),

133.6 (C4"), 129.6 (C5'), 128.6 (C3" and C5"), 118.9 (C6'), 115.4 (C4'), 114.5 (C2" and C6"), 112.6 (C2'), 72.1 (4-*C*H$_2$OAr), 64.8 (4"-CH$_2$OH), 55.4 (OCH$_3$), 47.7 (br, C2), 42.1 (br, C6), 36.4 (C4), 29.7 (br, C3), 28.7 (br, C5). HRMS (ESI, +ve) *m/z*: 378.1673 $[M+Na]^+$. $C_{21}H_{25}NO_4Na$ requires 378.1676 $[M + Na]^+$.

(iii) *(4-((4-(Hydroxymethyl)phenoxy)methyl)piperidin-1-yl)(4-methoxyphenyl)methanone* ***45***

White solid (0.23 g, 83%) mp 76–78 °C, R_f 0.57 (EtOAc). FTIR (neat) ν_{max}: 3333, 2920, 2857, 1590, 1508, 1440, 1392, 1300, 1238, 1170, 1112, 1030, 988, 834 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$; single isomer at 25 °C; RJ-01-86-1; 140819-rsj 5 2): δ 7.37 (d, *J* 8.8 Hz, 2H, H2' and H6'), 7.27 (d, *J* 8.7 Hz, 2H, H3" and H5"), 6.90 (d, *J* 8.8 Hz, 2H, H3' and H5'), 6.86 (d, *J* 8.7 Hz, 2H, H2" and H6"), 4.59 (s, 2H, –C*H*$_2$OH), 3.3-5.3 (br s, 2H, Heq2 and Heq6), 3.82 (d, *J* 6.2 Hz, 2H, 4–C*H*$_2$OAr), 3.82 (s, 3H, OCH$_3$), 2.92 (br t, *J* ~10.3 Hz, 2H, Hax2 and Hax6), 2.08 (br m, 1H, H4), 2.06 (br m, 1H, OH), 1.88 (br d, *J* 12.7 Hz, 2H, Heq3 and Heq5), 1.35 (br m, 2H, Hax3 and Hax5). ^{13}C NMR (75 MHz, $CDCl_3$; single isomer at 25 °C; RJ-01-86-1; 140819-rsj 6 2): δ 170.5 (1'-C(O)N), 160.8 (C4'), 158.6 (C1"), 133.5 (C4"), 129.1 (C2' and C6'), 128.7 (C3" and C5"), 128.3 (C1'), 114.6 (C2" and C6"), 113.8 (C3' and C5'), 72.2 (4-*C*H$_2$OAr), 65.0 (4"-CH$_2$OH), 55.5 (OCH$_3$), 41.7-43.5 (very br, C2 and C6), 36.5 (C4), 29.4 (br, C3 and C5). HRMS (ESI, +ve) *m/z*: 378.1676 $[M+Na]^+$. $C_{21}H_{25}NO_4Na$ requires 378.1676 $[M + Na]^+$.

Reaction of mesylate 38 with 4-hydroxybenzyl alcohol 8 and 4-methylphenol (*p*-cresol) 46

General procedure: Mesylate **38** (0.33 g, 1.01 mmol) was added with stirring to a mixture of *p*-hydroxybenzyl alcohol **8** (0.19 g, 1.53 mmol) or *p*-cresol **46** (0.19 g, 1.76 mmol) and KOH (0.34 g, 6.0 mmol) in dry DMF (10 mL) under nitrogen. The reaction mixture was heated to 70 °C overnight then cooled to r.t., poured into distilled water (25 mL) and the mixture

extracted with CH_2Cl_2 (3 x 25 mL). The combined extracts were washed with distilled water (2 x 25 mL), dried over Na_2SO_4, and the solvent was removed under reduced pressure to give a white solid that was flash chromatographed over silica gel using 1:1 EtOAc/*n*–hexane to afforded the desired product.

(i) *(4-((4-(Hydroxymethyl)phenoxy)methyl)piperidin-1-yl)(4-methoxyphenyl)methanone* ***45***

White solid (0.23 g, 60%) with identical spectroscopic properties to those of the product from reduction of aldehyde **42**.

(ii) *(4-Methoxyphenyl)(4-((4-tolyloxy)methyl)piperidin-1-yl)methanone* ***47***

p-Cresol yielded the product as a white solid (0.28 g, 82%) mp 122–123 °C, R_f 0.66 (EtOAc). FTIR (neat) ν_{max}: 3017, 2910, 2863, 1608, 1507, 1429, 1394, 1286, 1240, 1172, 1108, 1026, 917, 826 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$; single isomer at 25 °C; RJ-01-105; 141011-rsj 7 2): δ 7.39 (d, *J* 8.8 Hz, 2H, H2' and H6'), 7.08 (d, *J* 8.6 Hz, 2H, H3" and H5"), 6.91 (d, *J* 8.8 Hz, 2H, H3' and H5'), 6.79 (d, *J* 8.6 Hz, 2H, H2" and H6"), 4.62 (4.20-5.20) (br s, 2H, Heq6), 3.99 (3.40-4.50) (br s, 2H, Heq2), 3.83 (s, 3H, OCH_3), 3.81 (d, *J* 6.3 Hz, 2H, 4–CH_2OAr), 2.93 (2.80-3.07) (br s, 2H, Hax2 and Hax6), 2.28 (s, 3H, 4"-CH_3), 2.07 (m, 1H, H4), 1.89 (br d, *J* 12.4 Hz, 2H, Heq3 and Heq5), 1.36 (br ddd, *J* 12.4, 12.1, 11.8 Hz, 2H, Hax3 and Hax5). ^{13}C NMR (75 MHz, $CDCl_3$; single isomer at 25 °C; RJ-01-105; 141011-rsj 8 2): δ 170.5 (1'-C(O)N), 160.7 (C4'), 156.9 (C1"), 130.1 (C4"), 130.0 (C3" and C5"), 129.0 (C2' and C6'), 128.5 (C1'), 114.4 (C2" and C6"), 113.8 (C3' and C5'), 72.3 (4-*C*H_2OAr), 55.4 (OCH_3), 46.8 (br and very weak, C2), 42.7 (br and very weak, C6), 36.6 (C4), 29.3 (br, C3 and C5), 20.6 (4"-CH_3). HRMS (ESI, +ve) *m/z*: 362.2743 $[M+Na]^+$. $C_{21}H_{25}NO_3Na$ requires 362.2717 $[M + Na]^+$.

Treatment of amidoalcohols 43–45 with CH_3SO_2Cl

General procedure: The amidoalcohols **43-45** (0.50 g, 2 mmol) were dissolved separately with Et_3N (3.1 mmol) in dry CH_2Cl_2 (5 mL) and the solution cooled in a bath at –20 °C. Methanesulfonyl chloride (0.23 mL, 3 mmol) was added dropwise and the mixture allowed to warm to r.t. then stirred overnight. The reaction mixture was concentrated under reduced pressure, the residue dissolved in CH_2Cl_2 (25 mL), and the solution washed with 15% aq. HCl (2 x 10 mL) and distilled water (10 mL), dried over anhydrous Na_2SO_4 and evaporated to dryness. Flash chromatography on a silica gel column packed in 10:90 EtOAc/*n*-hexane containing 0.5% v/v Et_3N and eluted with 1:2 EtOAc/*n*-hexane afforded the unexpected amidochlorides **51**, **52** and **49**, respectively.

(i) *(4-((4-(Chloromethyl)phenoxy)methyl)piperidin-1-yl)(2-methoxyphenyl)methanone **51***

White gum (0.39 g, 74%), R_f 0.82 (EtOAc). FTIR (neat) ν_{max}: 2932, 2856, 1627, 1511, 1466, 1294, 1245, 1176, 1099, 1025, 833 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$; 52:48 mixture at 25 °C; RJ-02-88-1; 150714-rsj 1 2): δ (major) 7.344 (ddd, *J* 8.4, 7.6, 1.7 Hz, 1H, H4'), 7.297 (d, *J* 8.7 Hz, 1H, H3" and H5"), 7.252 (dd, *J* 7.4, 1.7 Hz, 1H, H6'), 6.982 (ddd, *J* 7.6, 7.4, 0.9 Hz, 1H, H5'), 6.910 (dd, *J* 8.4, 0.9 Hz, 1H, H3'), 6.850 (d, *J* 8.7 Hz, 2H, H2" and H6"), 4.842 (dm, $J_{Heq6,Hax6}$ 13.3 Hz, 1H, Heq6), 4.560 (s, 2H, 4"-CH_2Cl), 3.867 (dd, $J_{Ha,Hb}$ 9.2, $J_{Ha,H4}$ 6.4 Hz, 1H, 4–CH_aH$_b$OAr), 3.828 (s, 3H, OCH_3), 3.793 (dd, $J_{Hb,Ha}$ 9.2, $J_{Hb,H4}$ 6.4 Hz, 1H, 4–CH$_a$$H_b$OAr), 3.541 (dm, $J_{Heq2,Hax2}$ 13.0 Hz, 1H, Heq2), 3.056 (ddd, $J_{Hax2,Heq2}$ 13.0, $J_{Hax2,Hax3}$ 12.9, $J_{Hax2,Heq3}$ 2.8 Hz, 1H, Hax2), 2.786 (ddd, $J_{Hax6,Heq6}$ 13.3, $J_{Hax6,Hax5}$ 12.6, $J_{Hax6,Heq5}$ 3.0 Hz, 1H, Hax6), 2.053 (m, 1H, H4), 1.954 (m, 1H, Heq5), 1.755 (m, 1H, Heq3), 1.447 (m, 1H, Hax5), 1.194 (dddd, $J_{Hax3,Heq3}$ ~12.8 (*ex* COSY), $J_{Hax3,Hax2}$ 12.6, $J_{Hax3,Hax4}$ 12.3, $J_{Hax3,Heq2}$ 4.2 Hz, 1H, Hax3). δ (minor) 7.337 (ddd, *J* 8.4, 7.6, 1.7 Hz, 1H, H4'), 7.303 (d, *J* 8.7 Hz, 1H, H3" and H5"), 7.210 (dd, *J* 7.4, 1.7 Hz, 1H, H6'), 6.982 (ddd, *J* 7.6, 7.4, 0.9 Hz, 1H, H5'), 6.910

(dd, *J* 8.4, 0.9 Hz, 1H, H3'), 6.860 (d, *J* 8.7 Hz, 2H, H2" and H6"), 4.842 (dm, $J_{Heq6,Hax6}$ 13.3 Hz, 1H, Heq6), 4.560 (s, 2H, 4"-C*H*$_2$Cl), 3.867 (dd, $J_{Ha,Hb}$ 9.2, $J_{Ha,H4}$ 6.4 Hz, 1H, 4–C*H*$_a$H$_b$OAr), 3.828 (s, 3H, OCH$_3$), 3.787 (dd, $J_{Hb,Ha}$ 9.2, $J_{Hb,H4}$ 6.5 Hz, 1H, 4–CH$_a$*H*$_b$OAr), 3.541 (dm, $J_{Heq2,Hax2}$ 13.0 Hz, 1H, Heq2), 2.948 (ddd, $J_{Hax2,Heq2}$ 13.0, $J_{Hax2,Hax3}$ 12.9, $J_{Hax2,Heq3}$ 2.8 Hz, 1H, Hax2), 2.826 (ddd, $J_{Hax6,Heq6}$ 13.3, $J_{Hax6,Hax5}$ 12.6, $J_{Hax6,Heq5}$ 3.0 Hz, 1H, Hax6), 2.053 (m, 1H, H4), 1.925 (m, 1H, Heq5), 1.800 (m, 1H, Heq3), 1.447 (m, 1H, Hax5), 1.378 (m, 1H, Hax3). ^{13}C NMR (75 MHz, CDCl$_3$; 52:48 mixture at 25 °C; RJ-02-88-1; 150714-rsj 2 2): δ (major) 167.98 (1'-C(O)N), 159.16 (C1"), 155.44 (C2'), 130.28 (C4'), 130.21 (C3" and C5"), 129.95 (C4"), 127.82 (C6'), 126.39 (C1'), 121.04 (C5'), 114.75 (C2" and C6"), 111.07 (C3'), 72.29 (4-*C*H$_2$OAr), 55.71 (OCH$_3$), 47.60 (C2), 46.38 (4"-CH$_2$Cl), 41.51 (C6), 36.46 (C4), 29.71 (C3), 28.72 (C5). δ (minor) 167.76 (1'-C(O)N), 159.14 (C1"), 155.44 (C2'), 130.40 (C4'), 130.21 (C3" and C5"), 129.95 (C4"), 128.00 (C6'), 126.23 (C1'), 121.02 (C5'), 114.75 (C2" and C6"), 110.94 (C3'), 72.32 (4-*C*H$_2$OAr), 55.59 (OCH$_3$), 47.29 (C2), 46.38 (4"-CH$_2$Cl), 41.59 (C6), 36.46 (C4), 29.65 (C3), 28.82 (C5). HRMS (ESI, +ve) *m/z*: 396.1328 [M+Na]$^+$ C$_{21}$H$_{24}$ClNO$_3$Na requires 396.1337.

(ii) *(4-((4-(Chloromethyl)phenoxy)methyl)piperidin-1-yl)(3-methoxyphenyl)methanone* ***52***

White gum (0.43 g, 82%), R$_f$ 0.78 (EtOAc). FTIR (neat) ν_{max}: 3014, 2911, 2864, 1621, 1511, 1429, 1290, 1239, 1169, 1110, 1033, 973, 931, 827 cm^{-1}. ^{1}H NMR (300 MHz, CDCl$_3$; single isomer at 25 °C; RJ-02-95-1; 150714-rsj 5 2): δ 7.31 (dd, *J* 9.1, 7.2 Hz, 1H, H5'), 7.302 (d, *J* 8.8 Hz, 1H, H3" and H5"), 6.95 (m, 1H, H6'), 6.938 (m, 1H, H2'), 6.937 (m, 1H, H4'), 6.87 (d, *J* 8.8 Hz, 2H, H2" and H6"), 4.64-4.92 (br s, 1H, Heq6), 4.56 (s, 2H, 4"-C*H*$_2$Cl), 3.83 (d, *J* 5.9 Hz, 2H, 4–C*H*$_2$OAr), 3.70-3.95 (br s, Heq2), 3.82 (s, 3H, OCH$_3$), 2.38-3.18 (br s, 1H, Hax2), 2.65-3.00 (br s, 1H, Hax6), 2.09 (m, 1H, H4), 1.72-2.01 (br s, 2H, Heq3 and Heq5), 1.12-1.57 (br s, 2H, Hax3 and Hax5). ^{13}C NMR (75 MHz, CDCl$_3$; single isomer at 25 °C; RJ-

02-95-1; 150714-rsj 6 2): δ 170.2 (1'-C(O)N), 159.8 (C3'), 159.1 (C1''), 137.7 (C1'), 130.2 (C3'' and C5''), 130.0 (C4''), 129.7 (C5'), 119.0 (C6'), 115.5 (C4'), 114.8 (C2'' and C6''), 112.4 (C2'), 72.2 (4-*C*H$_2$OAr), 55.5 (OCH$_3$), 47.7 (br, C2), 46.4 (4''-CH$_2$Cl), 42.3 (br, C6), 36.5 (C4), 29.9 (br, C3), 28.8 (br, C5). HRMS (ESI, +ve) *m/z*: 396.1331 [M+Na]$^+$. $C_{21}H_{24}ClNO_3Na$ requires 396.1337 [M + Na]$^+$.

On one occasion, attempted chromatography of a crude sample of amidochloride **52** (0.28 g) on silica gel gave *(((((oxybis(methylene))bis(4,1-phenylene))bis(oxy))bis(methylene))bis(piperidine-4,1-diyl))bis((3-methoxyphenyl)methanone)* ***56*** as a yellow gum (0.23 g, 83% mass recovery). R_f 0.46 (EtOAc). FTIR (neat) ν_{max}: 3344, 2915, 2854, 1607, 1508, 1430, 1319, 1272, 1237, 1172, 1108, 1033, 987, 958, 788 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$; single isomer at 25 °C; RJ-02-96-1-2; 150714-rsj 21 2): δ 7.32 (dd, *J* 8.2, 8.1 Hz, 1H, H5'), 7.27 (d, *J* 8.7 Hz, 2H, H3'' and H5''), 6.95 (dm, *J* 8.2 Hz, 1H, H4'), 6.94 (dm, *J* 8.1 Hz, 1H, H6'), 6.93 (m, 1H, H2'), 6.86 (d, *J* 8.7 Hz, 2H, H2'' and H6''), 4.72 (4.60-4.86) (br s, 1H, Heq6), 4.45 (s, 2H, 4''-C*H*$_2$O), 3.82 (3.70-3.95) (m, 3H, 4–C*H*$_2$OAr and Heq2), 3.82 (s, 3H, OCH$_3$), 3.05 (2.90-3.15) (br s, 1H, Hax2), 2.85 (2.70-2.98) (br s, 1H, Hax6), 2.08 (m, 1H, H4), 1.89 (1.70-2.02) (br s, 2H, Heq3 and Heq5), 1.36 (1.15-1.57) (br s, 2H, Hax3 and Hax5). ^{13}C NMR (75 MHz, $CDCl_3$; single isomer at 25 °C; RJ-02-96-1-2; 150714-rsj 22 2): δ 170.5 (1'-C(O)N), 159.8 (C3'), 158.6 (C1''), 136.9 (C1'), 130.7 (C4''), 129.8 (C5'), 129.6 (C3'' and C5''), 119.0 (C6'), 115.8 (C4'), 114.5 (C2'' and C6''), 112.3 (C2'), 72.1 (4-*C*H$_2$OAr), 71.6 (4''-CH$_2$O), 55.5 (OCH$_3$), 47.9 (br, C2), 42.4 (br, C6), 36.4 (C4), 29.8 (br, C3), 28.7 (br, C5). HRMS (ESI, +ve) *m/z*: 715.3347 [M+Na]$^+$. $C_{42}H_{48}N_2O_7Na$ requires 715.3354 [M + Na]$^+$.

(iii) *(4-((4-(Chloromethyl)phenoxy)methyl)piperidin-1-yl)(4-methoxyphenyl)methanone* ***49***

White solid (0.40 g, 76 %) m.p. 118-120 °C, R_f 0.82 (EtOAc). FTIR (neat) ν_{max}: 3010, 2917, 2865, 1606, 1509, 1429, 1396, 1290, 1241, 1173, 1109, 1024, 973, 829 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$; single isomer at 25 °C; RJ-01-chloride; 150120-rsj 17 2): δ 7.39 (d, *J* 8.68 Hz, 2H, H2' and H6'), 7.30 (d, *J* 8.71 Hz, 2H, H3" and H5"), 6.91 (d, *J* 8.68 Hz, 2H, H3' and H5'), 6.86 (d, *J* 8.71 Hz, 2H, H2" and H6"), 4.56 (s, 2H, –C*H*$_2$Cl), 4.00-4.65 (br s, 2H, Heq2 and Heq6), 3.834 (d, *J* 6.1 Hz, 2H, 4–C*H*$_2$OAr), 3.830 (s, 3H, OCH_3), 2.94 (br t, *J* 11.6 Hz, 2H, Hax2 and Hax6), 2.09 (m, 1H, H4), 1.89 (br d, *J* 12.4 Hz, 2H, Heq3 and Heq5), 1.37 (dddd, *J* 12.6, 12.4, 11.6, 3.8 Hz, 2H, Hax3 and Hax5). ^{13}C NMR (75 MHz, $CDCl_3$; single isomer at 25 °C; RJ-01-chloride; 150120-rsj 18 2): δ 170.6 (1'-C(O)N), 160.8 (C4'), 159.1 (C1"), 130.2 (C3" and C5"), 130.0 (C4"), 129.1 (C2' and C6'), 128.3 (C1'), 114.8 (C2" and C6"), 113.8 (C3' and C5'), 72.2 (4-*C*H$_2$OAr), 55.5 (OCH_3), 42-49 (br, C2 and C6), 46.4 (4"-CH_2Cl), 36.5 (C4), 29.3 (br, C3 and C5). HRMS (ESI, +ve) *m/z*: 374.1510 $[M+H]^+$. $C_{21}H_{25}ClNO_3$ requires 374.1517 $[M + Na]^+$.

Treatment of amidochlorides 51, 52 and 49 with *n*-Bu$_4$NF (TBAF)

A solution of tetra-*n*-butylammonium fluoride (TBAF) in THF (1.5 mL of 1.0 M; 0.36 g, 1.5 mmol,) was added a stirred solution of amidochloride (0.100 g, 0.27 mmol) in dry THF (5.0 mL) under N_2. The reaction mixture was heated to reflux for 30 min and then cooled to r.t. and the solvent evaporated under reduced pressure. The residue was dissolved in EtOAc (10 mL), the solution washed with distilled water (3 × 5 mL) then dried over Na_2SO_4 and evaporated to dryness under reduced pressure to give a white residue. The residue was flash chromatographed on a silica gel column packed in using 0.5% TEA in 10:90 EtOAc/*n*-hexane containing 0.5% v/v Et_3N and eluted with 1:2 EtOAc/*n*-hexane to afford the desired amidofluoride.

(i) *4-((4-(Fluoromethyl)phenoxy)methyl)piperidin-1-yl)(2-methoxyphenyl)methanone* ***5***

White gum (0.092 g, 90%), R_f 0.82 (EtOAc). FTIR (neat) ν_{max}: 2938, 2359, 1628, 1513, 1467, 1372, 1294, 1247, 1176, 1123, 1025, 967, 765 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$; 53:47 mixture at 25 °C; RJ-02-93-1; 150714-rsj 9 2): δ (major) 7.338 (ddd, *J* 9.0, 8.6, 1.8 Hz, 1H, H4'), 7.319 (dd, $J_{H,H}$ 9.2 Hz, $J_{H,F}$ 2.2 Hz, 2H, H3" and H5"), 7.248 (dd, *J* 7.5, 1.7 Hz, 1H, H6'), 6.982 (ddd, *J* 7.5, 7.4, 1.0 Hz, 1H, H5'), 6.911 (dd, *J* 8.3, 0.8 Hz, 1H, H3'), 6.892 (dd, $J_{H,H}$ 8.8 Hz, $J_{H,F}$ 2.4 Hz, 2H, H2" and H6"), 5.291 (d, $J_{H,F}$ 48.6 Hz, 2H, 4"-CH_2F), 4.856 (dm, $J_{Heq6,Hax6}$ 13.0 Hz, 1H, Heq6), 3.877 (dd, $J_{Ha,Hb}$ 9.2, $J_{Ha,H4}$ 6.4 Hz, 1H, 4–CH_aH$_b$OAr), 3.830 (s, 3H, OCH$_3$), 3.810 (dd, $J_{Hb,Ha}$ 9.2, $J_{Hb,H4}$ 6.4 Hz, 1H, 4–CH$_a$$H_b$OAr), 3.544 (dddd, $J_{Heq2,Hax2}$ 13.2, $J_{Heq2,Hax3}$ 4.5, $J_{Heq2,Heq6}$ 2.5, $J_{Heq2,Heq3}$ 2.0 Hz, 1H, Heq2), 3.058 (ddd, $J_{Hax2,Heq2}$ 13.2, $J_{Hax2,Hax3}$ 12.7, $J_{Hax2,Heq3}$ 2.8 Hz, 1H, Hax2), 2.830 (ddd, $J_{Hax6,Heq6}$ 13.1, $J_{Hax6,Hax5}$ 12.2, $J_{Hax6,Heq5}$ 3.1 Hz, 1H, Hax6), 2.061 (m, 1H, H4), 1.933 (br d, $J_{Heq5,Hax5}$ 11.9 Hz, 1H, Heq5), 1.763 (br d, $J_{Heq3,Hax3}$ 11.6 Hz, 1H, Heq3), 1.387 (m, 1H, Hax5), 1.200 (dddd, $J_{Hax3,Heq3}$ 12.2, $J_{Hax3,Hax2}$ 12.0, $J_{Hax3,Hax4}$ 11.5, $J_{Hax3,Heq2}$ 4.2 Hz, 1H, Hax3). δ (minor) 7.338 (ddd, *J* 9.0, 8.6, 1.8 Hz, 1H, H4'), 7.319 (dd, $J_{H,H}$ 9.2 Hz, $J_{H,F}$ 2.2 Hz, 2H, H3" and H5"), 7.211 (dd, *J* 7.4, 1.7 Hz, 1H, H6'), 6.982 (ddd, *J* 7.5, 7.4, 1.0 Hz, 1H, H5'), 6.911 (dd, *J* 8.3, 0.8 Hz, 1H, H3'), 6.892 (dd, $J_{H,H}$ 8.8 Hz, $J_{H,F}$ 2.4 Hz, 2H, H2" and H6"), 5.291 (d, $J_{H,F}$ 48.6 Hz, 2H, 4"-CH_2F), 4.856 (dm, $J_{Heq6,Hax6}$ 13.0 Hz, 1H, Heq6), 3.877 (dd, $J_{Ha,Hb}$ 9.2, $J_{Ha,H4}$ 6.4 Hz, 1H, 4–CH_aH$_b$OAr), 3.830 (s, 3H, OCH$_3$), 3.804 (dd, $J_{Hb,Ha}$ 9.2, $J_{Hb,H4}$ 6.4 Hz, 1H, 4–CH$_a$$H_b$OAr), 3.544 (dddd, $J_{Heq2,Hax2}$ 13.2, $J_{Heq2,Hax3}$ 4.5, $J_{Heq2,Heq6}$ 2.5, $J_{Heq2,Heq3}$ 2.0 Hz, 1H, Heq2), 2.954 (ddd, $J_{Hax2,Heq2}$ 12.5, $J_{Hax2,Hax3}$ 12.2, $J_{Hax2,Heq3}$ 3.1 Hz, 1H, Hax2), 2.789 (ddd, $J_{Hax6,Heq6}$ 13.1, $J_{Hax6,Hax5}$ 12.6, $J_{Hax6,Heq5}$ 3.1 Hz, 1H, Hax6), 2.061 (m, 1H, H4), 1.954 (br d, *J* 12.0 Hz, 1H, Heq5), 1.800 (br d, *J* 12.1 Hz, 1H, Heq3), 1.454 (dddd, $J_{Hax5,Heq5}$ 12.2, $J_{Hax5,Hax6}$ 12.0, $J_{Hax5,Hax4}$ 11.5, $J_{Hax5,Heq6}$ 4.2 Hz, 1H, Hax5), 1.387 (m, 1H, Hax3). ^{13}C NMR (75 MHz, $CDCl_3$; 53:47 mixture at 25 °C; RJ-02-93-1; 150714-rsj 10 2): δ (major) 167.76 (1'-C(O)N),

159.63 (d, $J_{C,F}$ 3.5 Hz, C1"), 155.45 (C2'), 130.40 (C4'), 130.00 (d, $J_{C,F}$ 5.0 Hz, C3" and C5"), 128.54 (d, $J_{C,F}$ 17.4 Hz, C4"), 127.82 (C6'), 126.25 (C1'), 121.01 (C5'), 114.63 (d, $J_{C,F}$ 1.9 Hz, C2" and C6"), 110.95 (C3'), 84.62 (d, $J_{C,F}$ 164.5 Hz, 4"-*C*H_2F), 72.28 (4-*C*H_2OAr), 55.71 (OCH_3), 46.60 (C2), 41.58 (C6), 36.48 (C4), 29.72 (C3), 28.74 (C5). δ (minor) 168.00 (1'-C(O)N), 159.63 (d, $J_{C,F}$ 3.5 Hz, C1"), 155.45 (C2'), 130.28 (C4'), 130.00 (d, $J_{C,F}$ 5.0 Hz, C3" and C5"), 128.54 (d, $J_{C,F}$ 17.4 Hz, C4"), 128.01 (C6'), 126.43 (C1'), 121.06 (C5'), 114.63 (d, $J_{C,F}$ 1.9 Hz, C2" and C6"), 111.08 (C3'), 84.62 (d, $J_{C,F}$ 164.5 Hz, 4"-*C*H_2F), 72.32 (4-*C*H_2OAr), 55.60 (OCH_3), 47.28 (C2), 41.53 (C6), 36.48 (C4), 29.66 (C3), 28.82 (C5). ^{19}F NMR (282 MHz, $CDCl_3$; 52:48 mixture by integration at 25 °C; RJ-02-93-1; 150714-rsj 13/14 2): δ (minor) −199.30 (t, $^2J_{F,H}$ 48.6 Hz, 1F, –CH_2F); δ (major) −199.36 (t, $^2J_{F,H}$ 48.6 Hz, 1F, –CH_2F). HRMS (ESI, +ve) *m/z*: 380.1624 $[M+Na]^+$. $C_{21}H_{24}FNO_3Na$ requires 380.1632 $[M + Na]^+$.

(ii) *4-((4-(Fluoromethyl)phenoxy)methyl)piperidin-1-yl)(3-methoxyphenyl)methanone* ***6***

White gum (0.075 g, 74%), R_f 0.82 (EtOAc). FTIR (neat) ν_{max}: 3049, 2994, 2933, 1626, 1599, 1512, 1319, 1290, 1245, 1176, 1115, 1029, 973, 958, 821, 794 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$; single isomer at 25 °C; RJ-02-96-1; 150714-rsj 15 2): δ 7.32 (dd, $J_{H,H}$ 8.8 Hz, $J_{H,F}$ 2.3 Hz, 2H, H3" and H5"), 7.31 (dd, *J* 9.1, 7.4 Hz, 1H, H5'), 6.96 (dd, *J* 8.3, 1.0 Hz, 1H, H6'), 6.940 (dd, *J* 7.7, 2.1 Hz, 1H, H4'), 6.939 (m, 1H, H2'), 6.89 (dd, $J_{H,H}$ 8.8 Hz, $J_{H,F}$ 1.0 Hz, 2H, H2" and H6"), 5.29 (d, $J_{H,F}$ 48.6 Hz, 2H, 4"–CH_2F), 4.78 (4.65-4.90) (br s, 1H, Heq6), 3.84 (3.78-3.94) (m, 2H, 4–CH_2OAr), 3.82 (s, 3H, OCH_3), 3.80 (3.67-3.07) (br s, 1H, Heq2), 3.03 (2.90-3.15) (br s, 1H, Hax2), 2.83 (2.65-3.00) (br s, 1H, Hax6), 2.10 (m, 1H, H4), 1.92 (1.74-1.94) (br s, 1H, Heq3), 1.87 (1.74-1.94) (br s, 1H, Heq5), 1.37 (1.15-1.55) (br s, 2H, Hax3 and Hax5). ^{13}C NMR (75 MHz, $CDCl_3$; single isomer at 25 °C; RJ-02-96-1; 150714-rsj 16 2): δ 170.2 (1'-C(O)N), 159.8 (C3'), 159.6 (d, $J_{C,F}$ 3.3 Hz, C1"), 137.7 (C1'),

130.0 (d, $J_{C,F}$ 4.9 Hz, C3" and C5"), 129.7 (C5'), 128.6 (d, $J_{C,F}$ 17.4 Hz, C4"), 119.0 (C6'), 115.5 (C4'), 114.6 (d, $J_{C,F}$ 1.9 Hz, C2" and C6"), 112.4 (C2'), 84.6 (d, $J_{C,F}$ 164.5 Hz, 4"-CH_2F), 72.2 (4-*C*H_2OAr), 55.5 (OCH_3), 47.8 (very br, C2), 42.2 (very br, C6), 36.5 (C4), 29.8 (br, C3), 28.7 (br, C5). ^{19}F NMR (282 MHz, $CDCl_3$; single isomer at 25 °C; RJ-02-96-1; 150714-rsj 19/20 2): δ −199.39 (t, $^2J_{F,H}$ 48.8 Hz, 1F, –CH_2F). HRMS (ESI, +ve) *m/z*: 380.1625 $[M+Na]^+$. $C_{21}H_{24}FNO_3Na$ requires 380.1632 $[M + Na]^+$.

(iii) *4-((4-(Fluoromethyl)phenoxy)methyl)piperidin-1-yl)(4-methoxyphenyl)methanone* ***7***

White solid (0.076 g, 75%) mp 115–117°C, R_f 0.81 (EtOAc). FTIR (neat) ν_{max}: 3020, 2915, 2865, 1609, 1510, 1430, 1373, 1290, 1243 1117, 1109, 1025, 966, 834, 704 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$; single isomer at 25 °C; RJ-02-38-1; 150309-rsj 1 2): δ 7.39 (d, *J* 8.8 Hz, 2H, H2' and H6'), 7.32 (dd, $J_{H,H}$ 8.7 Hz, $J_{H,F}$ 2.2 Hz, 2H, H3" and H5"), 6.91 (d, *J* 8.8 Hz, 2H, H3' and H5'), 6.90 (dd, $J_{H,H}$ 8.7 Hz, $J_{H,F}$ 1.0 Hz, 2H, H2" and H6"), 5.29 (d, $J_{H,F}$ 48.6 Hz, 2H, 4"–C*H*$_2$F), 4.65 (4.35-5.00) (br s, 2H, Heq6), 4.08 (3.80-4.35) (br s, 2H, Heq2), 3.85 (d, *J* 6.4 Hz, 2H, 4–C*H*$_2$OAr), 3.83 (s, 3H, OCH_3), 2.93 (2.80-3.10) (br s, 2H, Hax2 and Hax6), 2.09 (m, 1H, H4), 1.89 (br d, *J* 12.8 Hz, 2H, Heq3 and Heq5), 1.39 (br ddd, *J* 12.4, 10.8, 10.3 Hz, 2H, Hax3 and Hax5). ^{13}C NMR (75 MHz, $CDCl_3$; single isomer at 25 °C; RJ-02-38-1; 150309-rsj 2 2): δ 170.5 (1'-C(O)N), 160.8 (C4'), 159.9 (d, $J_{C,F}$ 3.4 Hz, C1"), 130.0 (d, $J_{C,F}$ 4.9 Hz, C3" and C5"), 129.1 (C2' and C6'), 128.6 (d, $J_{C,F}$ 17.3 Hz, C4"), 128.4 (C1'), 114.6 (d, $J_{C,F}$ 2.0 Hz, C2" and C6"), 113.8 (C3' and C5'), 84.6 (d, $J_{C,F}$ 164.5 Hz, 4"-CH_2F), 72.3 (4-*C*H_2OAr), 55.5 (OCH_3), 45.6 (very br, C2), 40.8 (very br, C6), 36.5 (C4), 29.3 (br, C3), 28.3 (br, C5). ^{19}F NMR (282 MHz, $CDCl_3$; single isomer at 25 °C; RJ-02-38-1; 150309-rsj 3/6 2): δ −199.36 (t, $^2J_{F,H}$ 48.6 Hz, 1F, –CH_2F). HRMS (ESI, +ve) *m/z*: 380.1624 $[M+Na]^+$ $C_{21}H_{24}FNO_3Na$ requires 380.1632 $[M + Na]^+$.

Free radical fluorination[10] of ibuprofen methyl ester and of compound 47

(i) Following the method of Groves *et al.*,[10] ibuprofen methyl ester (35 mg, 0.16 mmol) and AgF (62 mg, 0.5 mmol) were added to an oven-dried Schlenk flask containing Mn(Salen)Cl (20 mg, 0.3 mmol). The flask was capped with a rubber septum and the flask connected to the Schlenk line to evacuate and refill with nitrogen, a cycle that was replicated three times. Degassed MeCN (2.0 mL) was then added *via* syringe through the septum followed by adding of Et_3N•3HF (12 µL). The flask was placed in a pre-heated oil bath at 60 °C, PhIO (32 mg, 0.15 mmol) was added in portions over 3 h to the stirred mixture at the same temperature and the mixture left for a further 30 min. The reaction mixture was allowed to cool to r.t., diluted with CH_2Cl_2 (2 mL), the solution filtered, and the residue washed with fresh CH_2Cl_2 (3 × 2 mL). The combined solution and washings were evaporated to dryness to give the crude product as a pale-yellow syrup. Analysis of the syrup by ^{1}H NMR spectroscopy revealed a 94:6 mixture (based on integration of signals at δ 2.45 (d, *J* 7.2 Hz, 2H) and 5.09 (dd, $^2J_{H,F}$ 47.0, $^2J_{H,F}$ 6.8 Hz, 1H)) of unreacted ibuprofen methyl ester and of its monofluoro derivative, respectively. The latter was observed, particularly in the ^{19}F NMR spectrum, as an equimolar mixture of diastereomers with the following diagnostic signals: ^{1}H NMR (300 MHz, $CDCl_3$; RJ-02-107 crude; 150803-rsj 5 2): δ 7.30 (d, *J* 8.3 Hz, 2H), 7.25 (d, *J* 8.3 Hz, 2H), 5.09 (dd, $^2J_{H,F}$ 47.0, $^2J_{H,F}$ 6.8 Hz, 1H), 3.74 (q, *J* 7.2 Hz, 1H), 3.67 (s, 3H), 2.10 (ddh, $^3J_{H,F}$ 16.8, $^3J_{H,H}$ 6.8, $^3J_{H,H}$ 6.8 Hz, 1H), 1.51 (d, *J* 7.2 Hz, 3H), 1.028/1.025 (2xd, *J* 6.6/6.7 Hz, total 3H), 0.86 (d, *J* 6.8 Hz, 3H). ^{19}F NMR (282 MHz, $CDCl_3$; RJ-02-107 crude; 150803-rsj 6/7 2) δ −179.64 (dd, $^2J_{F,H}$ 47.0, $^3J_{F,H}$ 16.9 Hz), −179.62 (dd, $^2J_{F,H}$ 46.9, $^3J_{F,H}$ 17.0 Hz). The observation of diastereoisomers was not mentioned in the report by Groves *et al.*,[10] but was supported by data and tangentially mentioned in Supporting Information in an earlier reported synthesis of the same compound by Fasan *et al.*.[11]

(ii) Identical treatment of compound **47** to that described for ibuprofen methyl ester in part (i), gave, with identical workup and chromatography on silica gel, a fraction with largely unreacted tolylamido compound **47**, admixed with ~4% of the desired amidofluoride **7**, as evidenced by NMR signals at (300 MHz, $CDCl_3$; RJ-02-40-2; 150306-rsj 4 2) δ_H 5.30 (d, $^2J_{F,H}$ 48.5 Hz, 2H, 4"-CH_2F), δ_H 7.32 (dd, $^3J_{H,H}$ 8.86 Hz, $^4J_{H,F}$ 2.10 Hz, 2H, H3" and H5"), and (282 MHz, $CDCl_3$; RJ-02-40-2; 150306-rsj 6 2) δ_F –199.4 (tt, $^2J_{F,H}$ 49.5 Hz, $^4J_{F,H}$ 2.7 Hz, 4'-CH_2F).

Treatment of amidofluoride 7 with $LiAlH_4$

(i) A solution of amidofluoride **7** (0.025 g, 0.07 mmol) in dry THF (3 mL) was added dropwise to a stirred solution of lithium aluminiumhydride (0.20 mL of 1.0 M THF solution, 0.20 mmol) under nitrogen in a bath at –20 °C. The reaction mixture was stirred at bath temperature for 30 min, warmed to 0 °C then sat. aq. NH_4Cl solution (5 mL) added. The mixture was extracted with EtOAc (3 x 10 mL), the combined extracts washed with water (3 x 5 mL), dried over Na_2SO_4, and evaporated under reduced pressure. The oily residue was analysed by NMR spectroscopy to reveal complete consumption of compound **7** and 54% yield of an 11:50:39 mixture of what appeared by ^{1}H NMR spectroscopy to be 4-methoxybenzaldehyde, 4-methoxybenzyl alcohol and 4-((4"-fluoromethylphenoxy)methyl)piperidine **54**, respectively; spectra were described in Section 2.3 of the main text.

(ii) The reaction in part (i) was repeated but with addition of the lithium aluminiumhydride solution to the amidofluoride **7** solution and the reaction prolonged at –20 °C for 50 min. Reaction workup gave by ^{1}H NMR spectroscopic analysis a 3:15:11:71 mixture of what appeared to be 4-methoxybenzaldehyde, 4-methoxybenzyl alcohol, aminofluoride **54** and the desired aminoalcohol **56**, respectively, in 77% yield; spectra are discussed in the main text.

The crude product was flash chromatographed on a column packed with silica gel in 10:90 EtOAc/*n*-hexane containing 0.5% Et_3N. Elution with a 1:2 EtOAc/*n*-hexane to 100% EtOAc gradient eventually afforded only *(4-((1-(4-methoxybenzyl)piperidin-4-yl)methoxy)phenyl)methanol* **56** as a white solid (0.23 g) m.p. 76–78 °C, R_f 0.14 (EtOAc). FTIR (neat) ν_{max}: 2916, 2854, 2359, 1610, 1509, 1463, 1240, 1172, 1100, 1032, 814, 754 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$; RJ-03-06-1; 150929-rsj 13 2): δ 7.27 (d, *J* 8.7 Hz, 2H, H3" and H5"), 7.24 (d, *J* 8.6 Hz, 2H, H2' and H6'), 6.859 (d, *J* 8.6 Hz, 2H, H2" and H6"), 6.856 (d, *J* 8.8 Hz, 2H, H3' and H5'), 4.61 (s, 2H, 4"–CH_2OH), 3.90 (s, 3H, OCH_3), 3.79 (d, *J* 6.2 Hz, 2H, 4–CH_2OAr), 3.47 (s, 2H, 1'-CH_2N), 2.93 (dm, *J* 11.5 Hz, 2H, Heq2 and Heq6), 1.99 (dd, *J* 11.5, 11.0 Hz, 2H, Hax2 and Hax6), 1.81 (br d, *J* 12.1 Hz, 2H, Heq3 and Heq5), 1.80 (m, 1H, H4), 1.71 (1.55-1.80) (br s, 1H, OH), 1.40 (m, 2H, Hax3 and Hax5). ^{13}C NMR (75 MHz, $CDCl_3$; RJ-03-06-1 at 25 °C; 150930-rsj 13 2): δ 158.9 (C4'), 158.9 (C1"), 133.2 (C4"), 130.6 (C2' and C6'), 130.2 (br, C1'), 128.8 (C3" and C5"), 114.7 (C2" and C6"), 113.7 (C3' and C5'), 72.9 (4-*C*H_2OAr), 65.2 (4"-CH_2OH), 62.9 (1'-CH_2N), 55.4 (OCH_3), 53.3 (C2 and C6), 36.0 (C4), 29.1 (C3 and C5). HRMS (ESI, +ve) *m/z*: 342.2060 $[M+H]^+$. $C_{21}H_{28}NO_3$ requires 342.2064 $[M + H]^+$.

References

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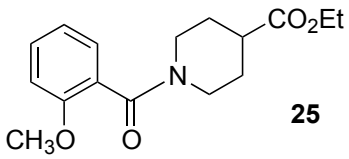
Copies of ^{1}H and ^{13}C NMR Spectra (see following)

Ethyl 1-(2-methoxybenzoyl)piperidine-4-carboxylate **25**

^{1}H NMR at 25 °C



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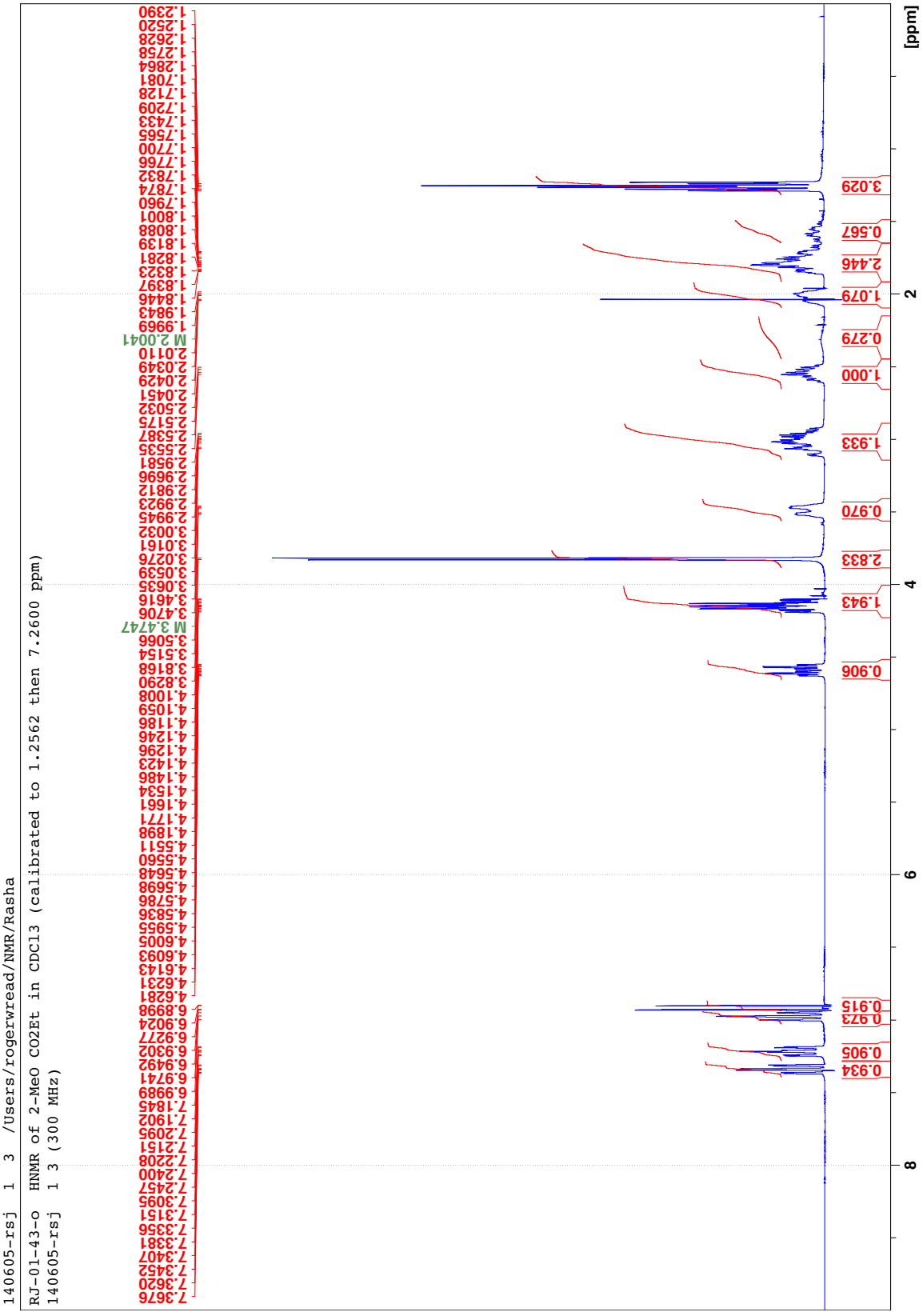
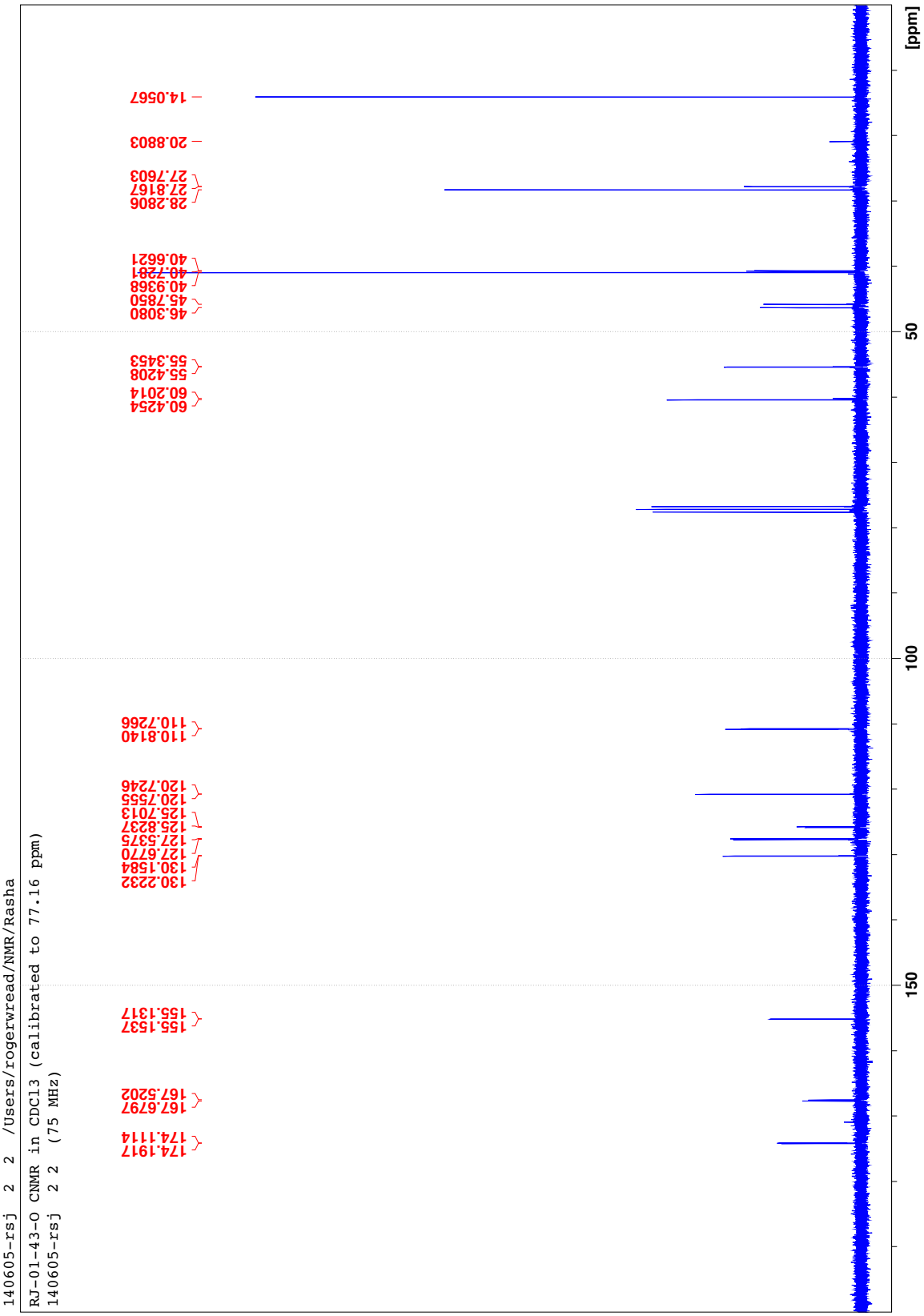
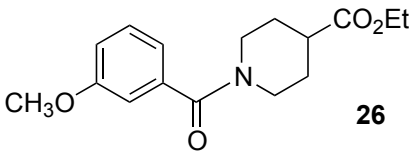


^{13}C NMR at 25 °C



Ethyl 1-(3-methoxybenzoyl)piperidine-4-carboxylate **26**

^{1}H NMR at 25 °C



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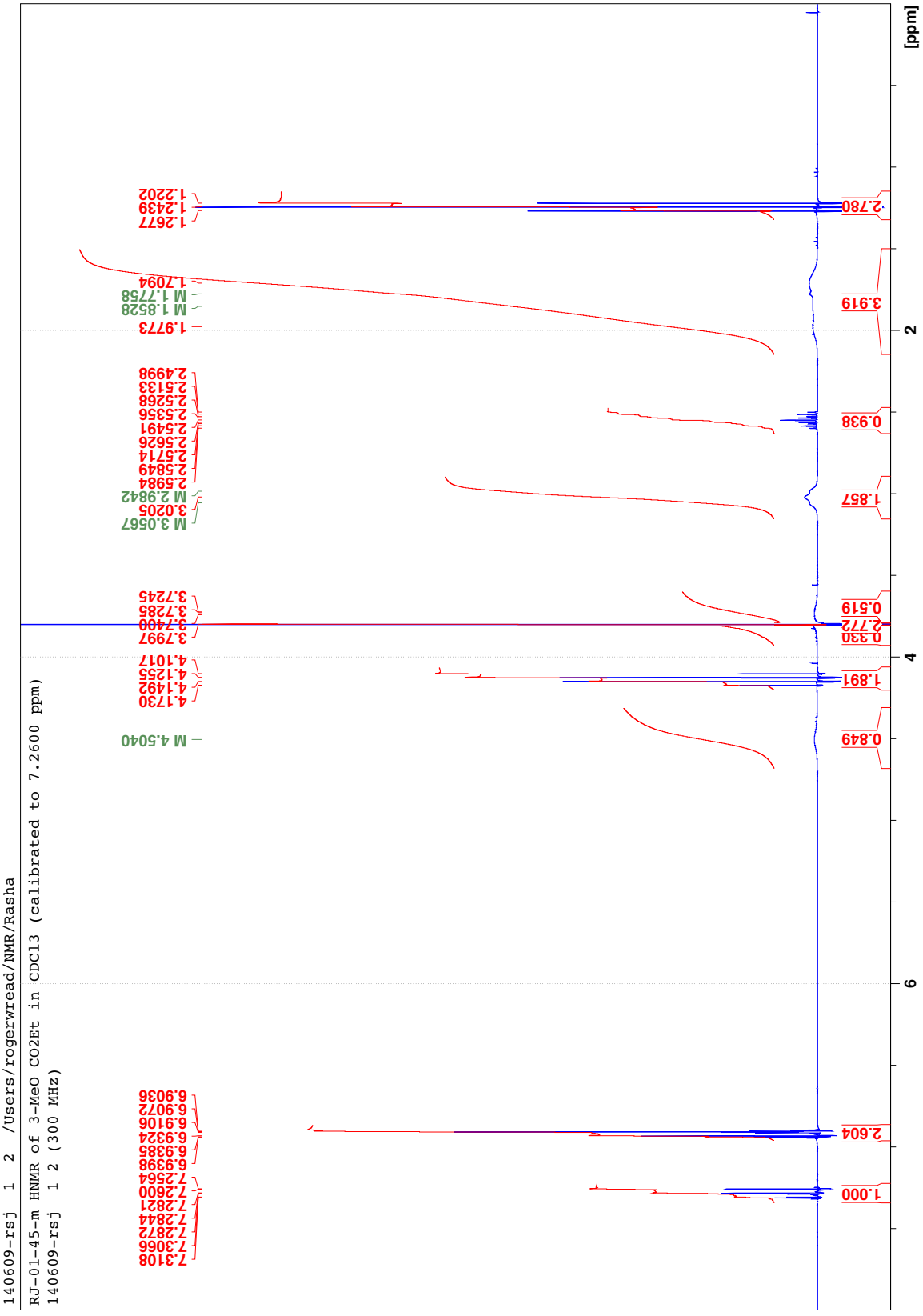
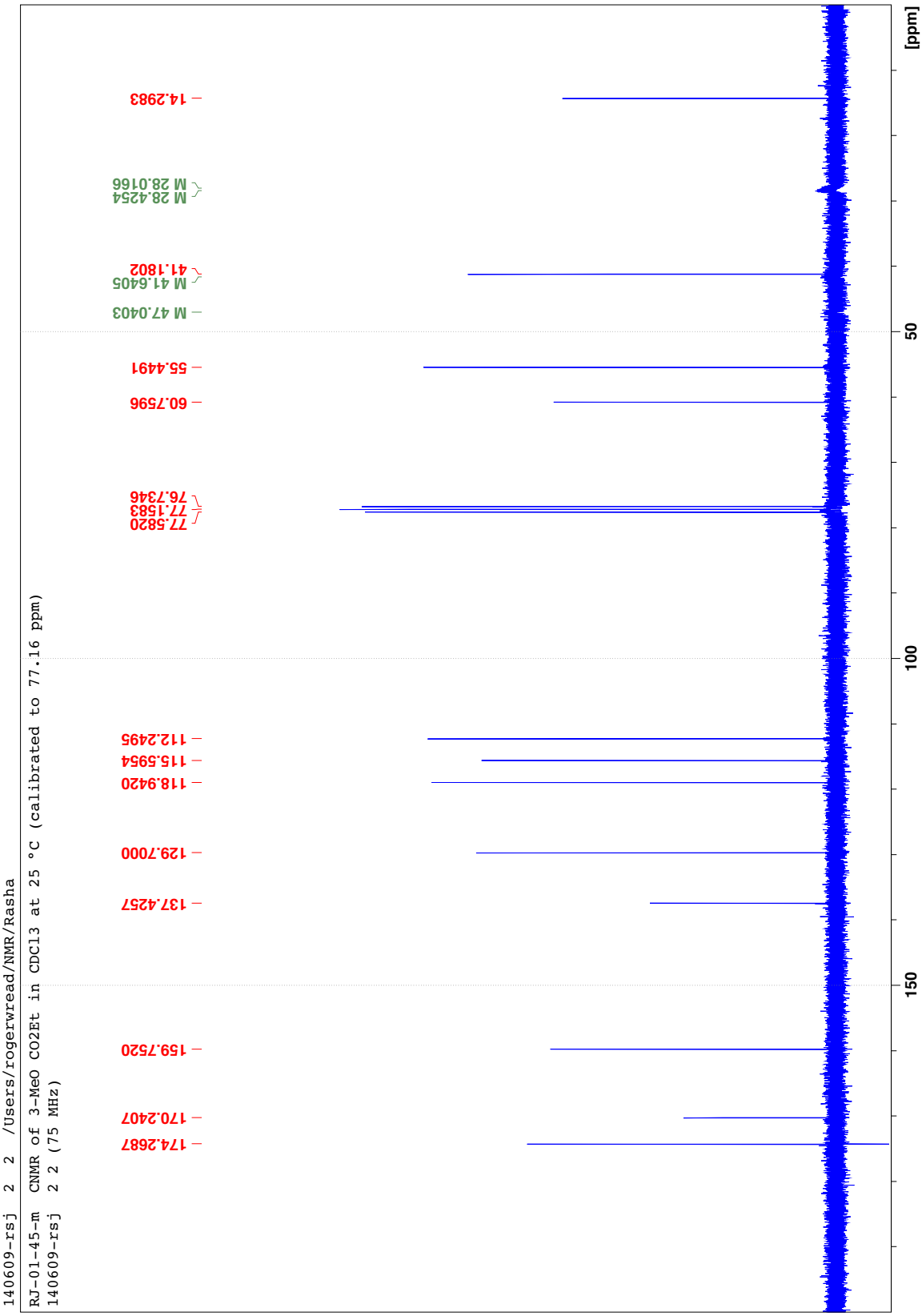
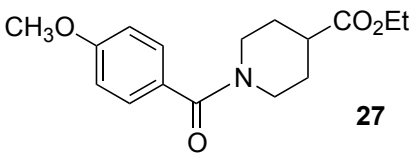


^{13}C NMR at 25 °C

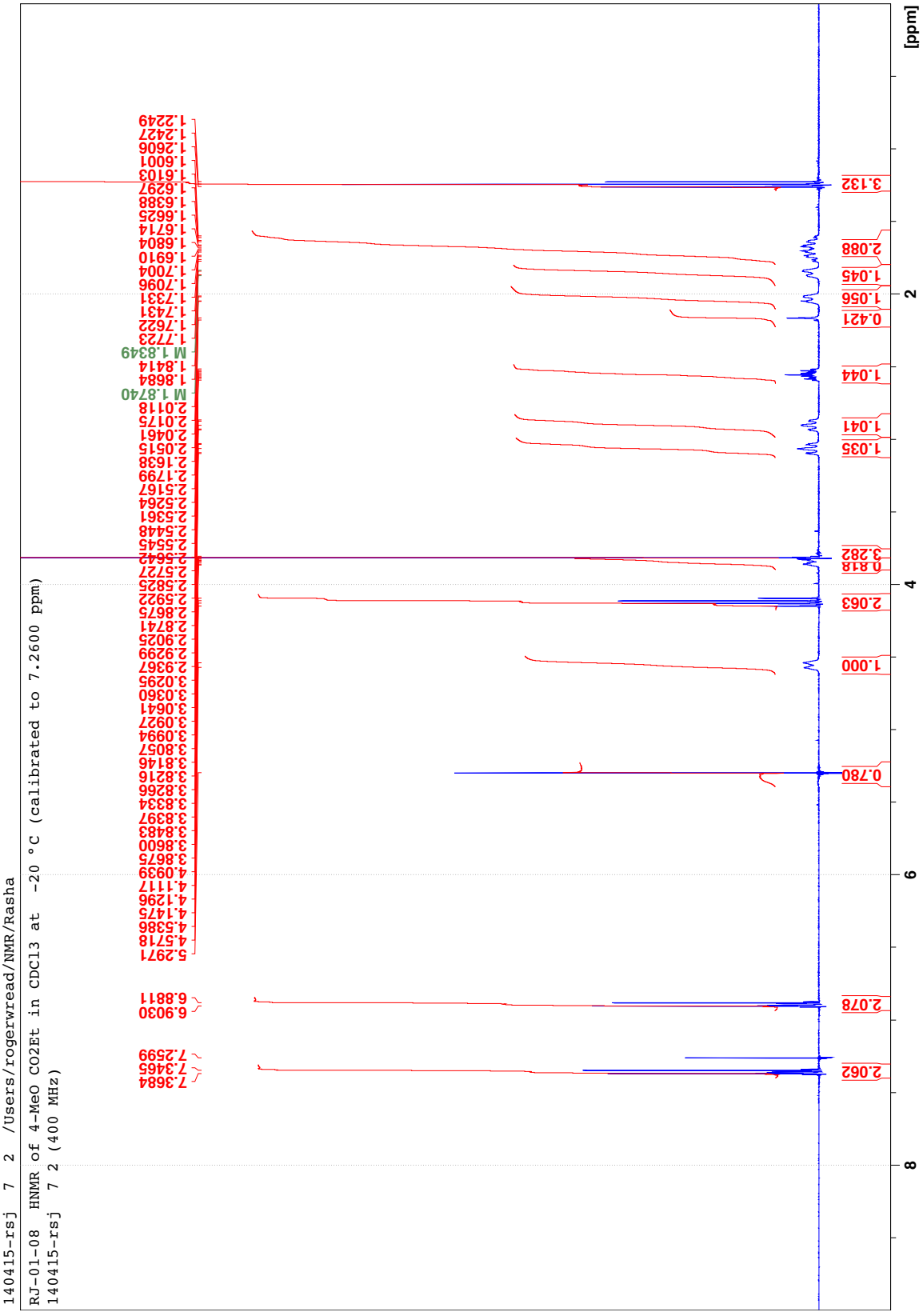


Ethyl 1-(4-methoxybenzoyl)piperidine-4-carboxylate **27**

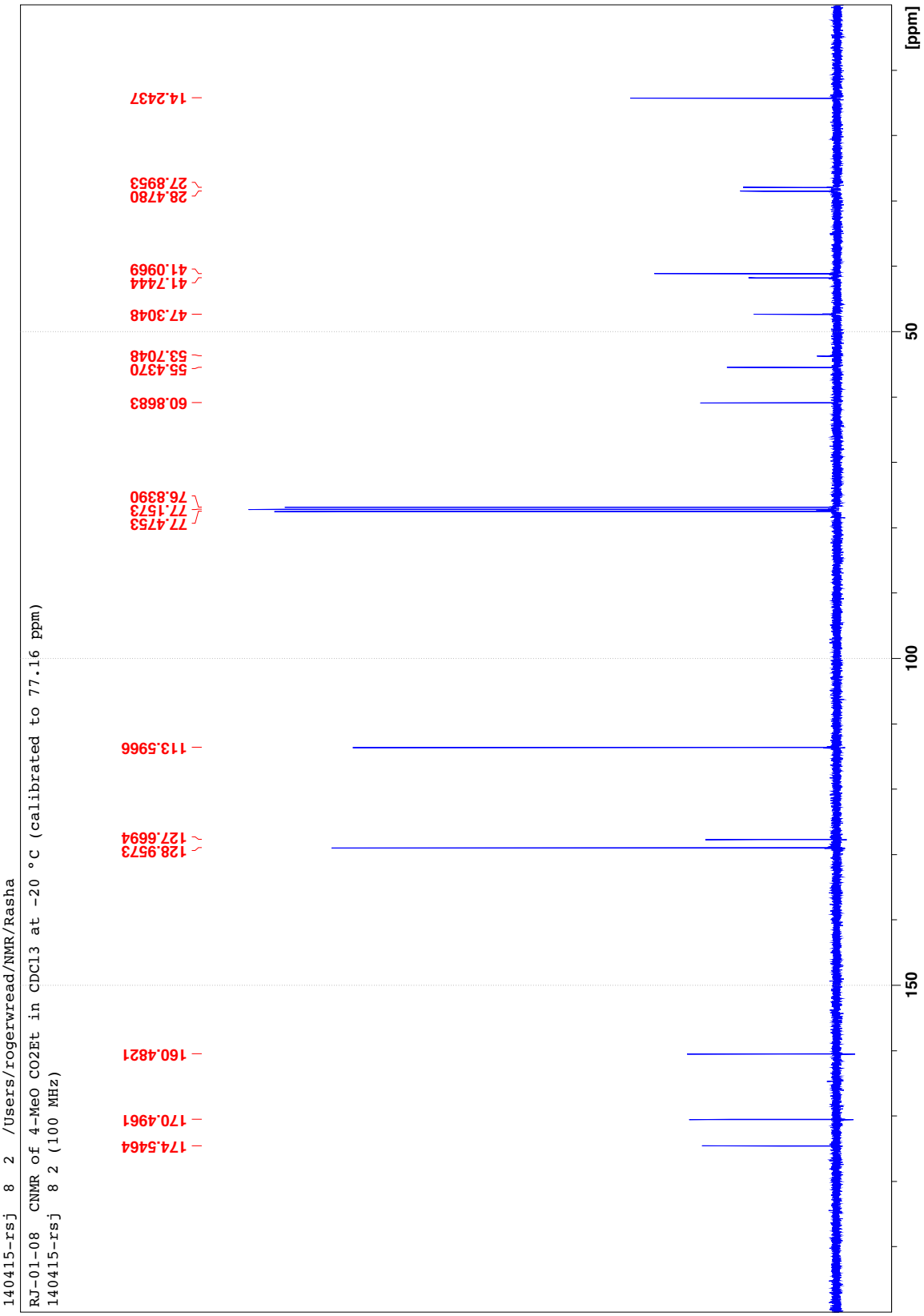


27

^{1}H NMR at –20 °C

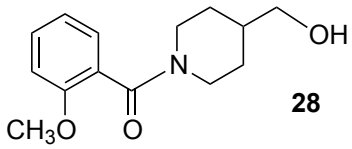


^{13}C NMR at –20 °C



4-(Hydroxymethyl)piperidin-1-yl)(2-methoxyphenyl)methanone **28**

^{1}H NMR (600 MHz) at 10 °C



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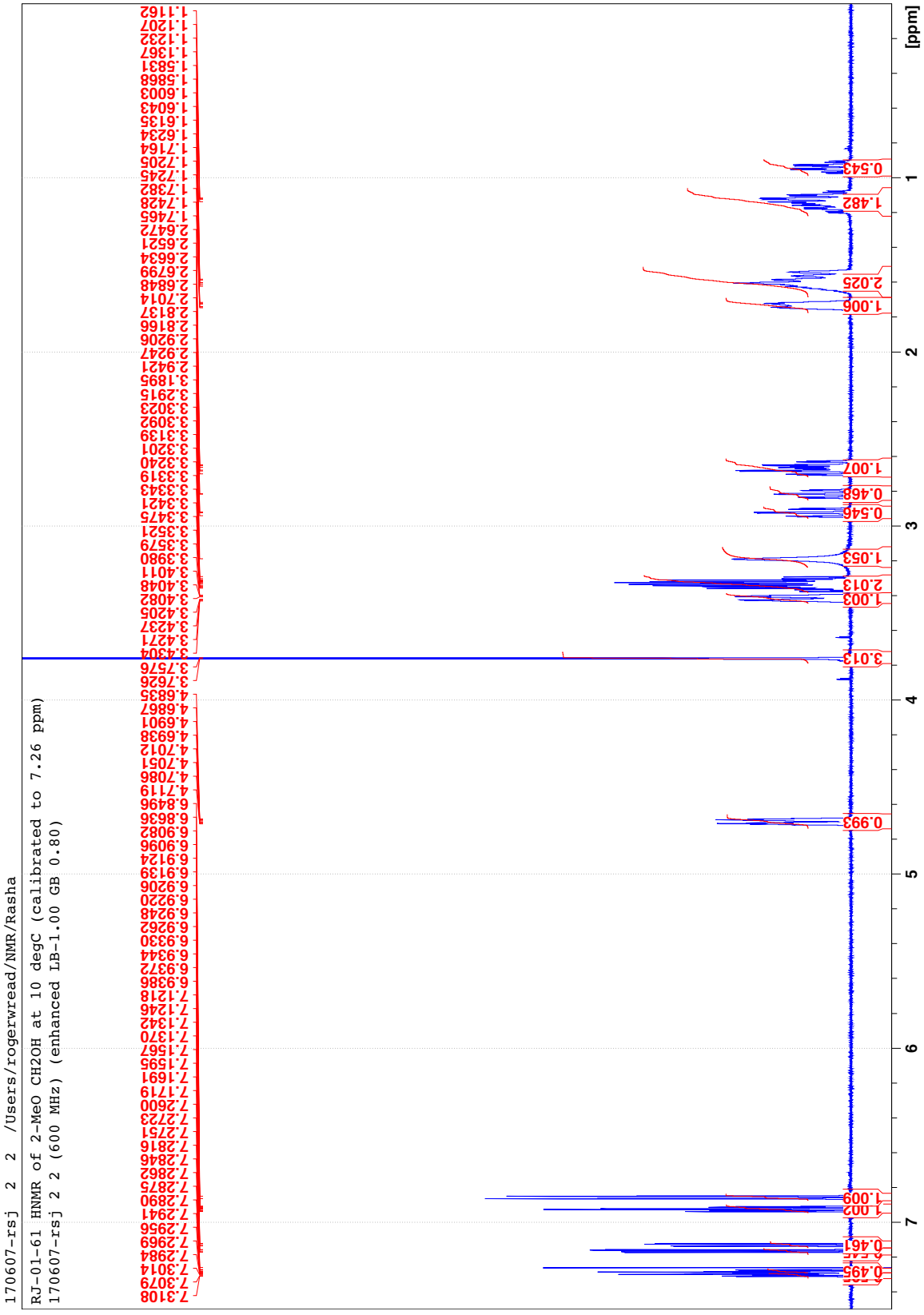
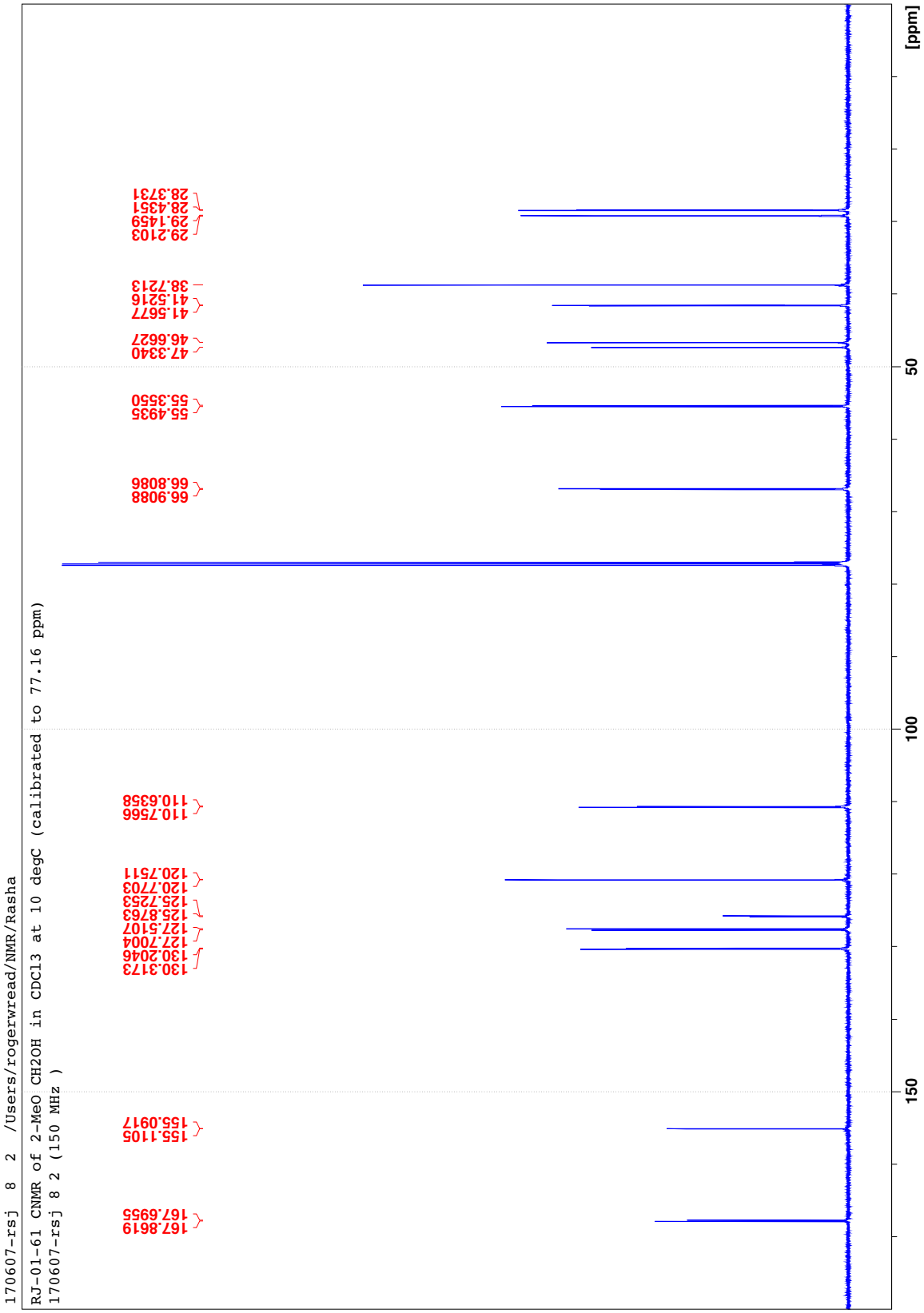
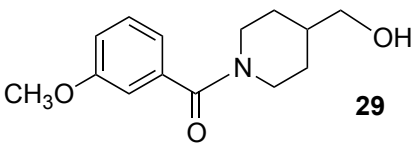


^{13}C NMR (150 MHz) at 10 °C



4-(Hydroxymethyl)piperidin-1-yl)(3-methoxyphenyl)methanone **29**

^{1}H NMR at 25 °C



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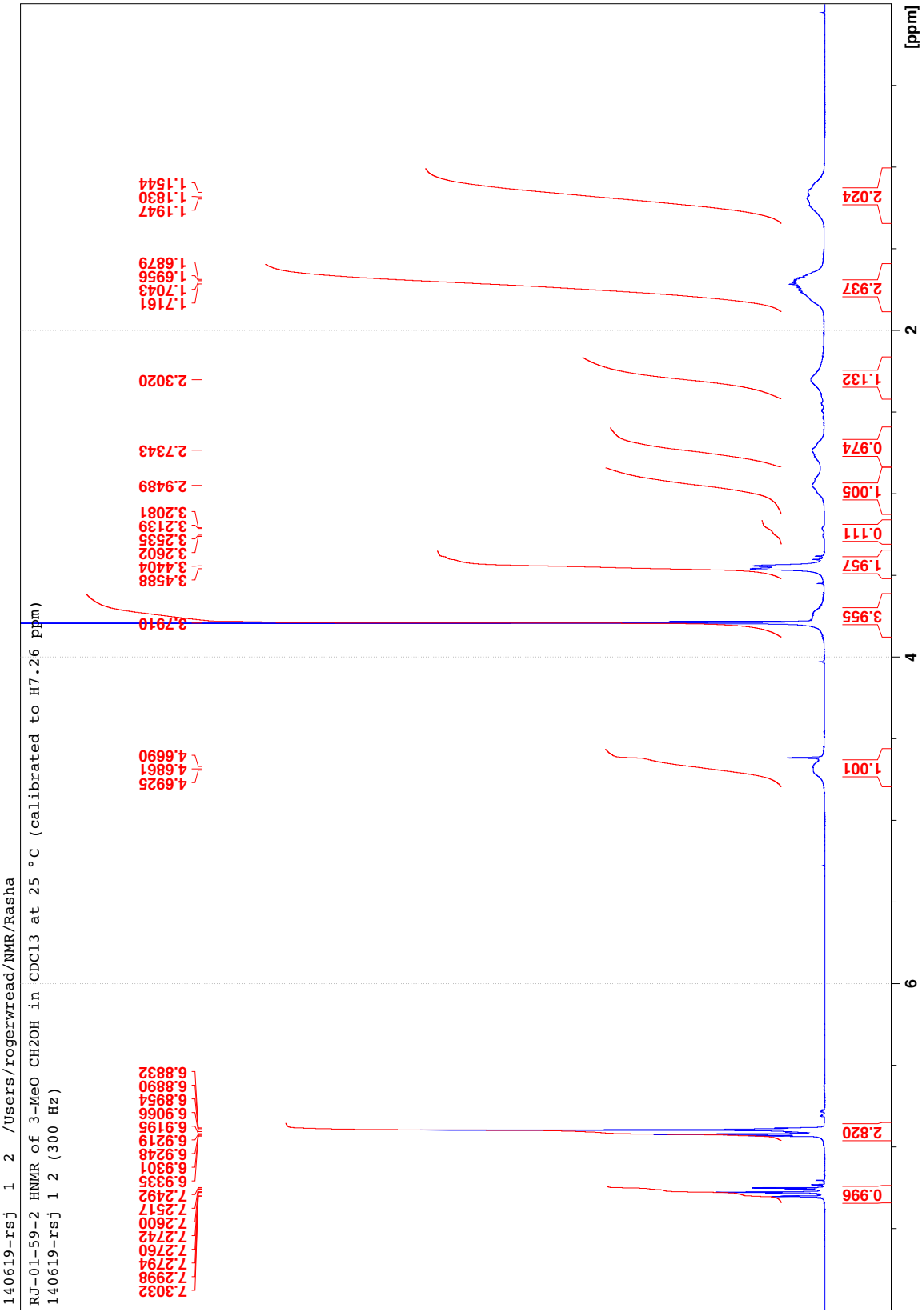
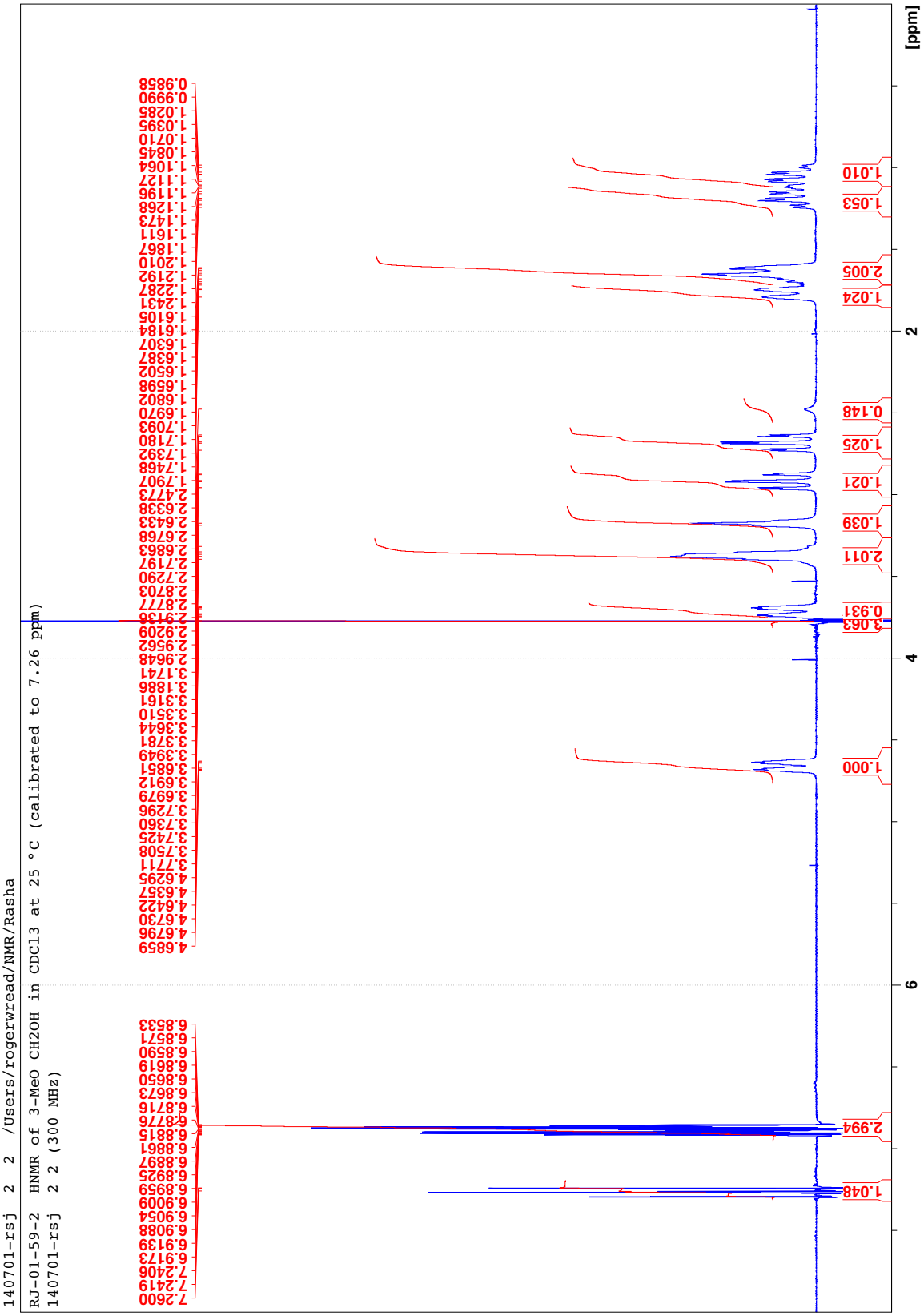
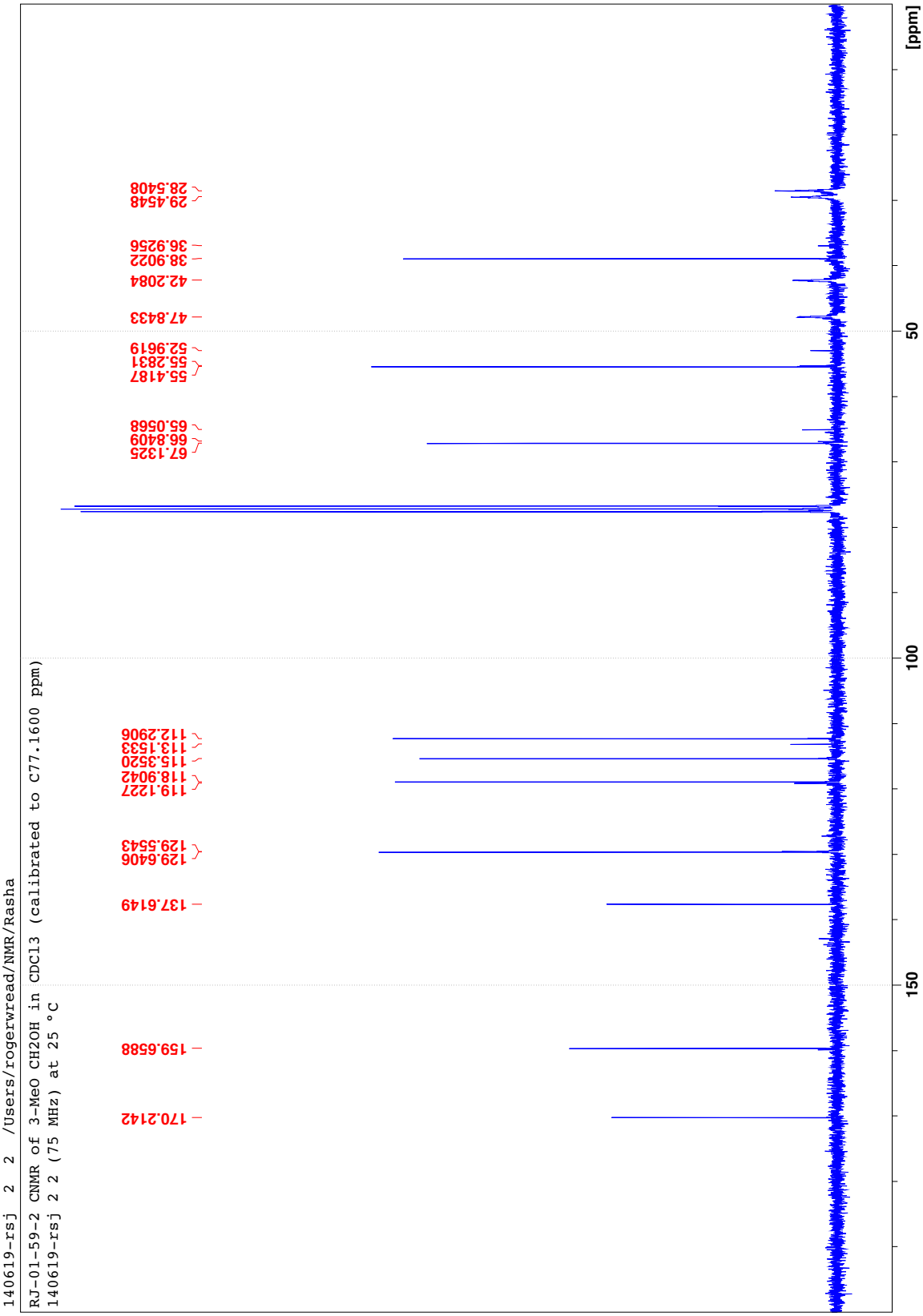


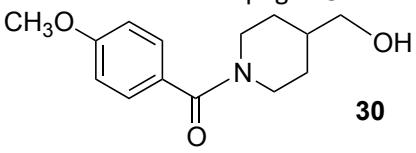
^{1}H NMR at –10 °C


140701-rsj 2 2 /Users/rogerwread/NMR/Rasha
RJ-01-59-2 HNMR of 3-MeO CH2OH in CDCl3 at 25 °C (calibrated to 7.26 ppm)
140701-rsj 2 2 (300 MHz)
[ppm]
2
4
6
1.010
1.053
2.005
1.024
0.148
1.025
1.021
1.039
2.011
0.931
3.063
1.000
2.994
1.048

^{13}C NMR at 25 °C

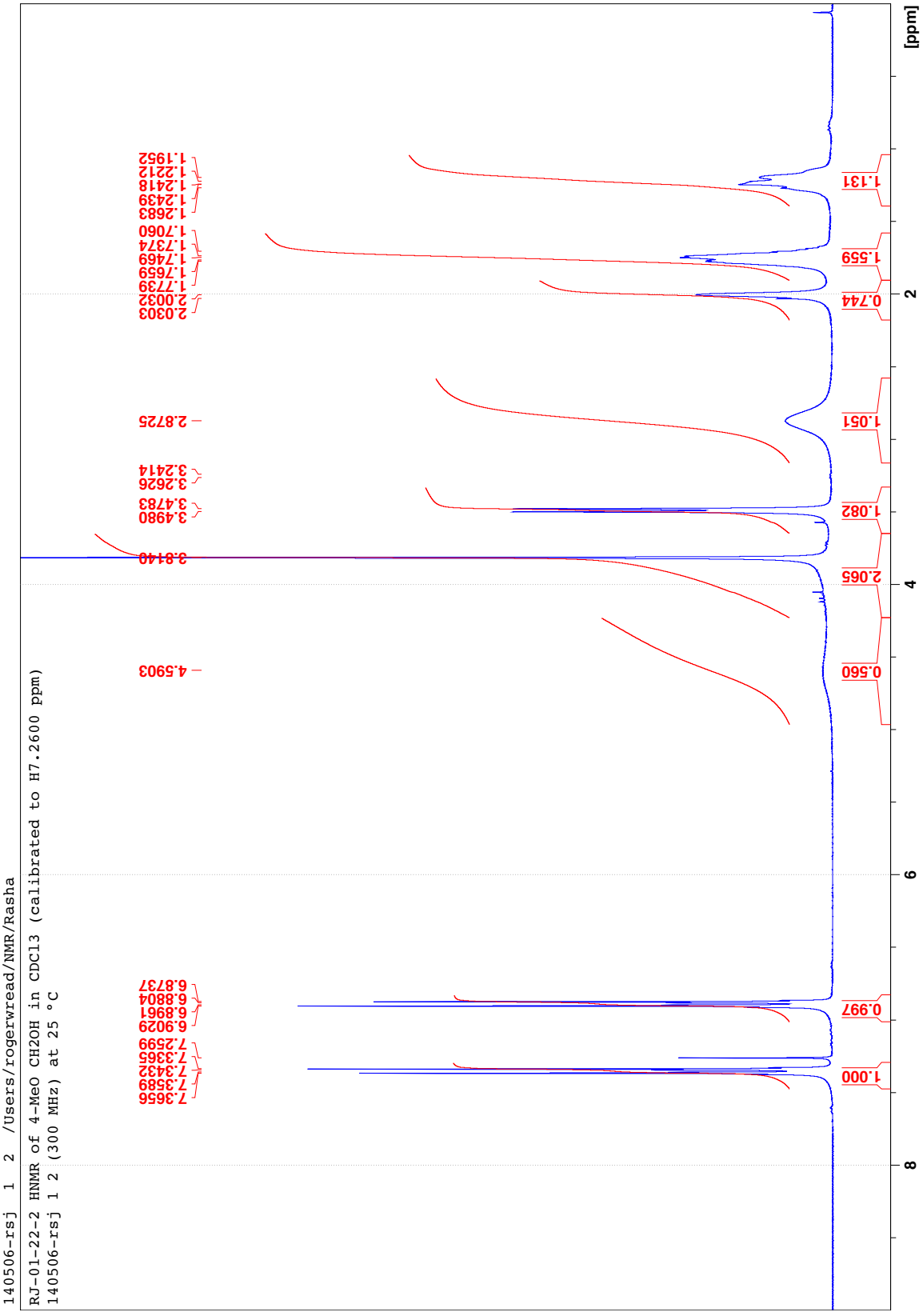


4-(Hydroxymethyl)piperidin-1-yl)(4-methoxyphenyl)methanone **30**

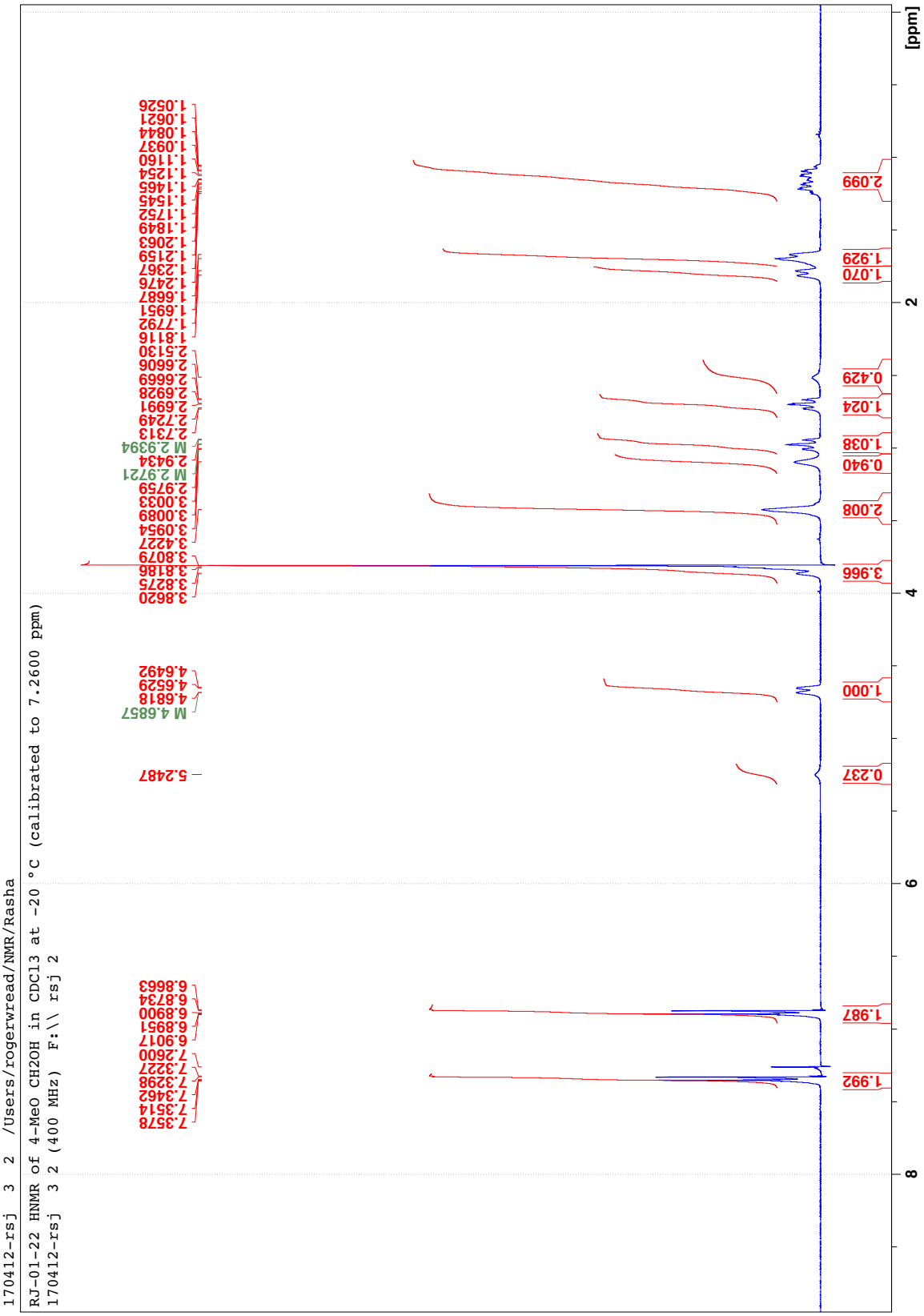


30

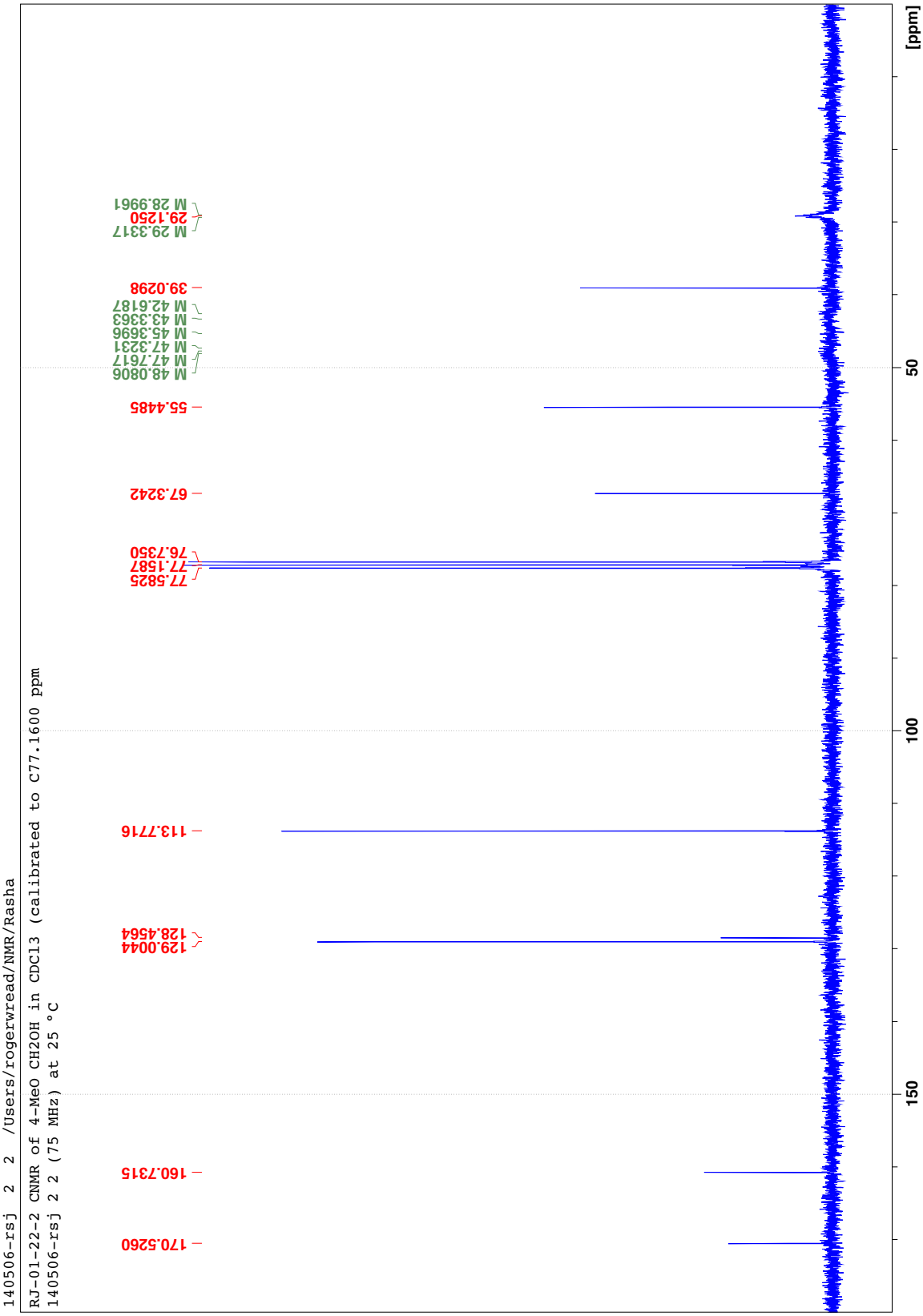
^{1}H NMR (300 MHz) at 25 °C



^{1}H NMR (400 MHz) at –20 °C

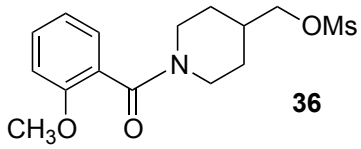


^{13}C NMR (75 MHz) at 25 °C

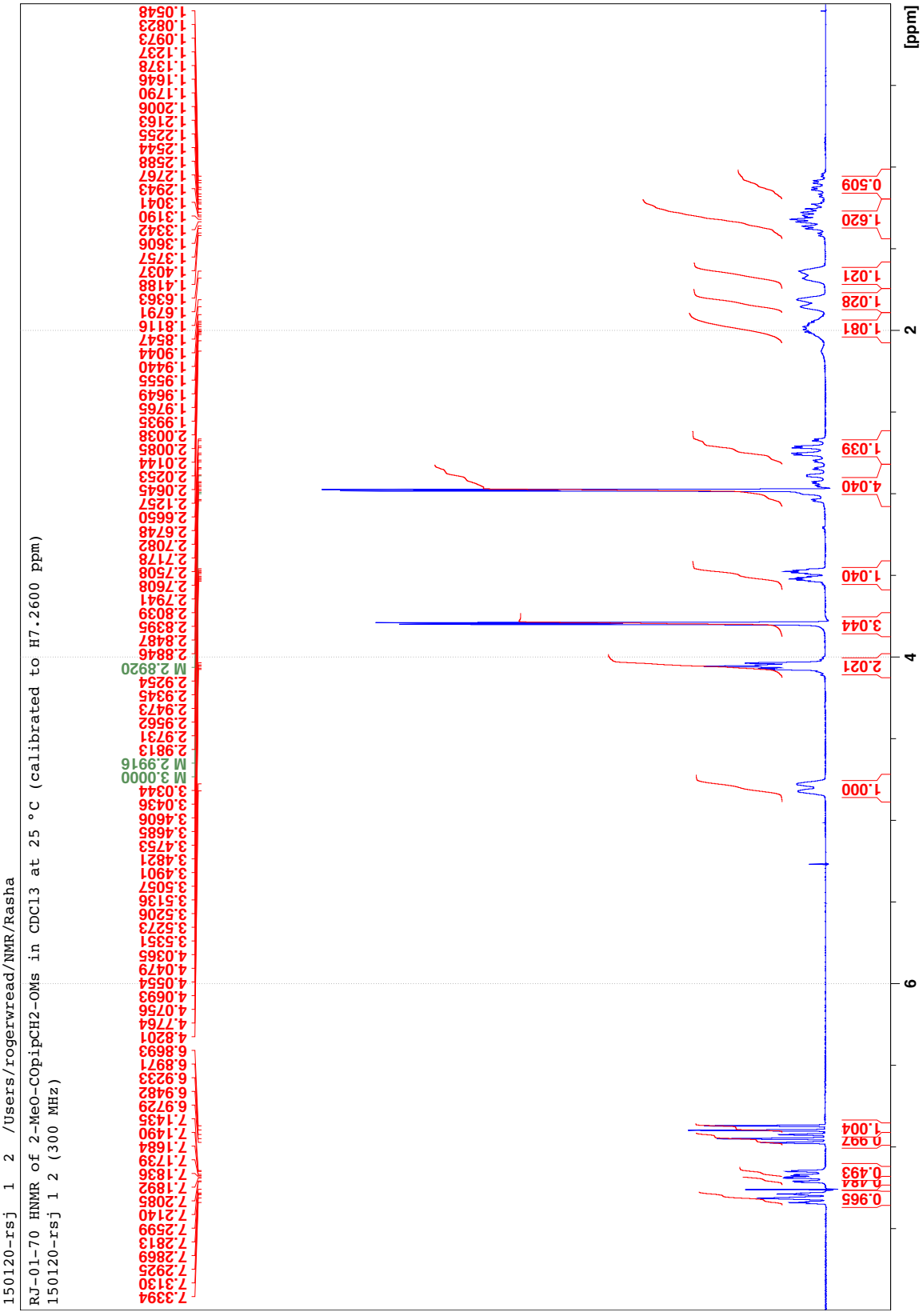


(1-(2-Methoxybenzoyl)piperidin-4-yl)methyl methanesulfonate **36**

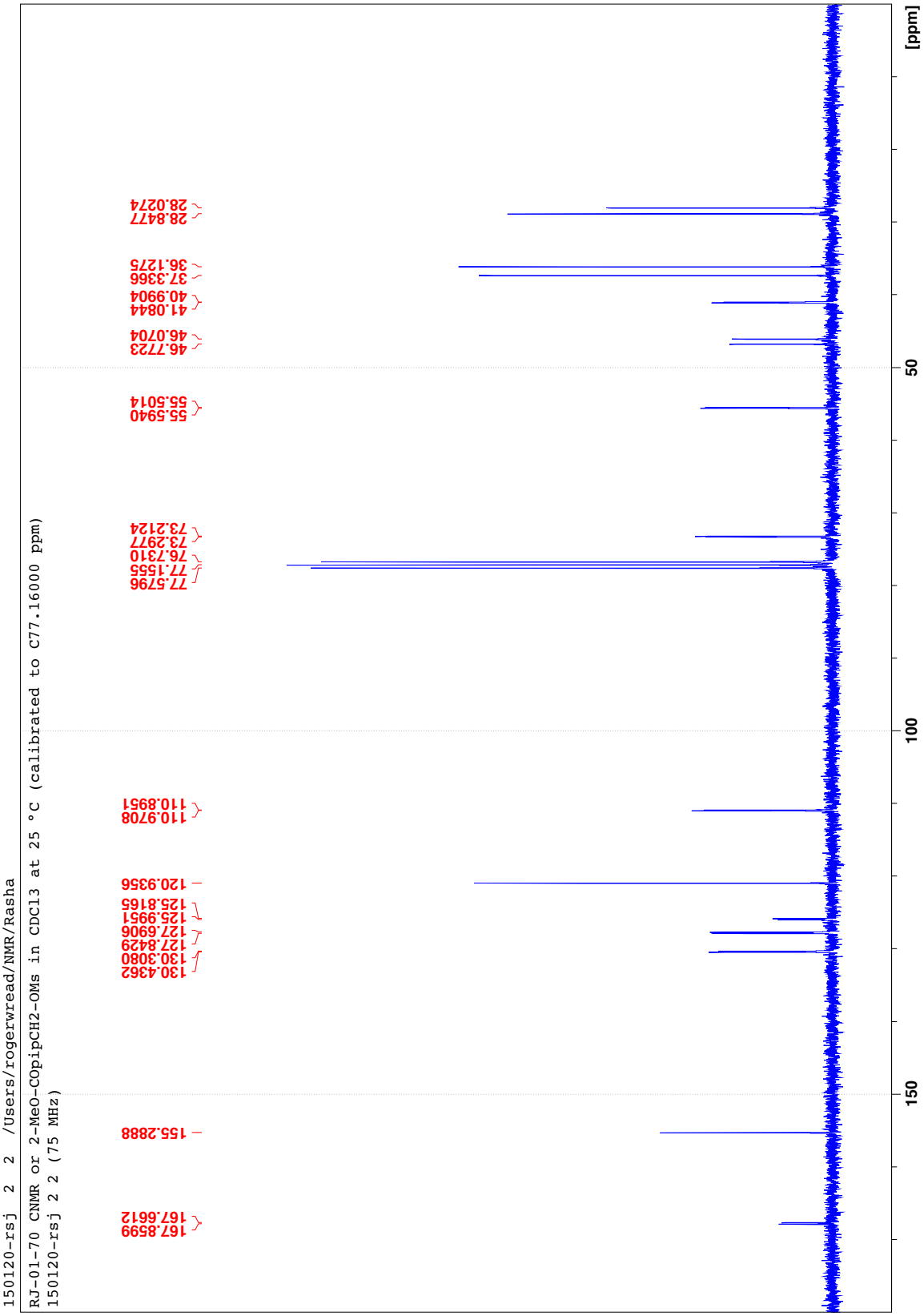
^{1}H NMR at 25 °C



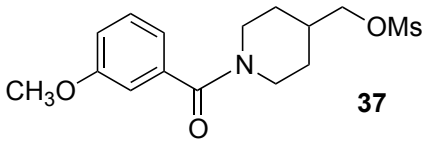
36



^{13}C NMR at 25 °C

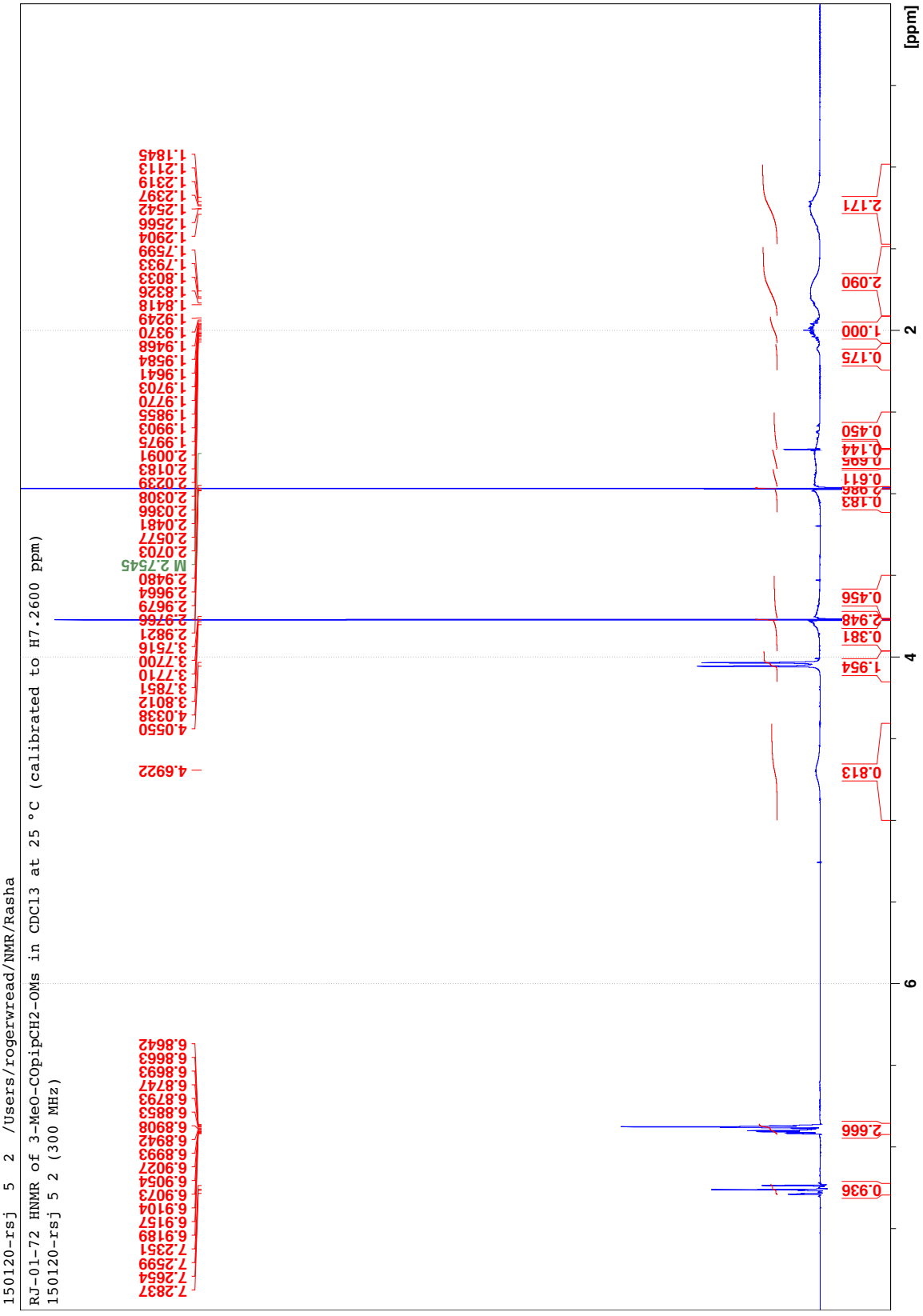


(1-(3-Methoxybenzoyl)piperidin-4-yl)methyl methanesulfonate **37**

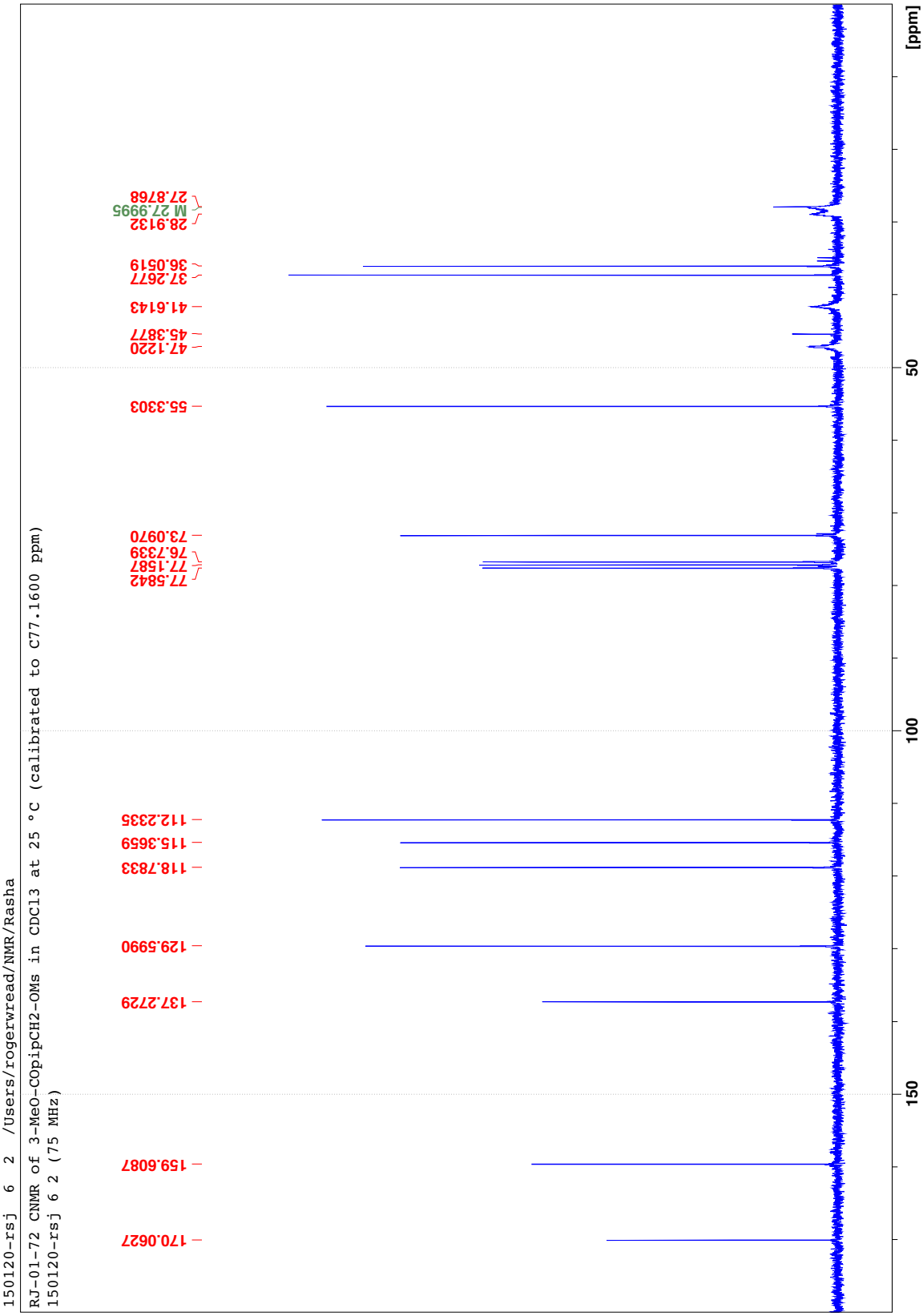


37

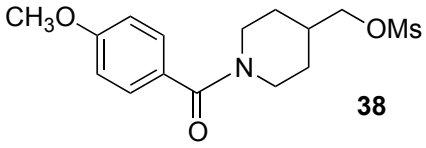
^{1}H NMR at 25 °C



^{13}C NMR at 25 °C

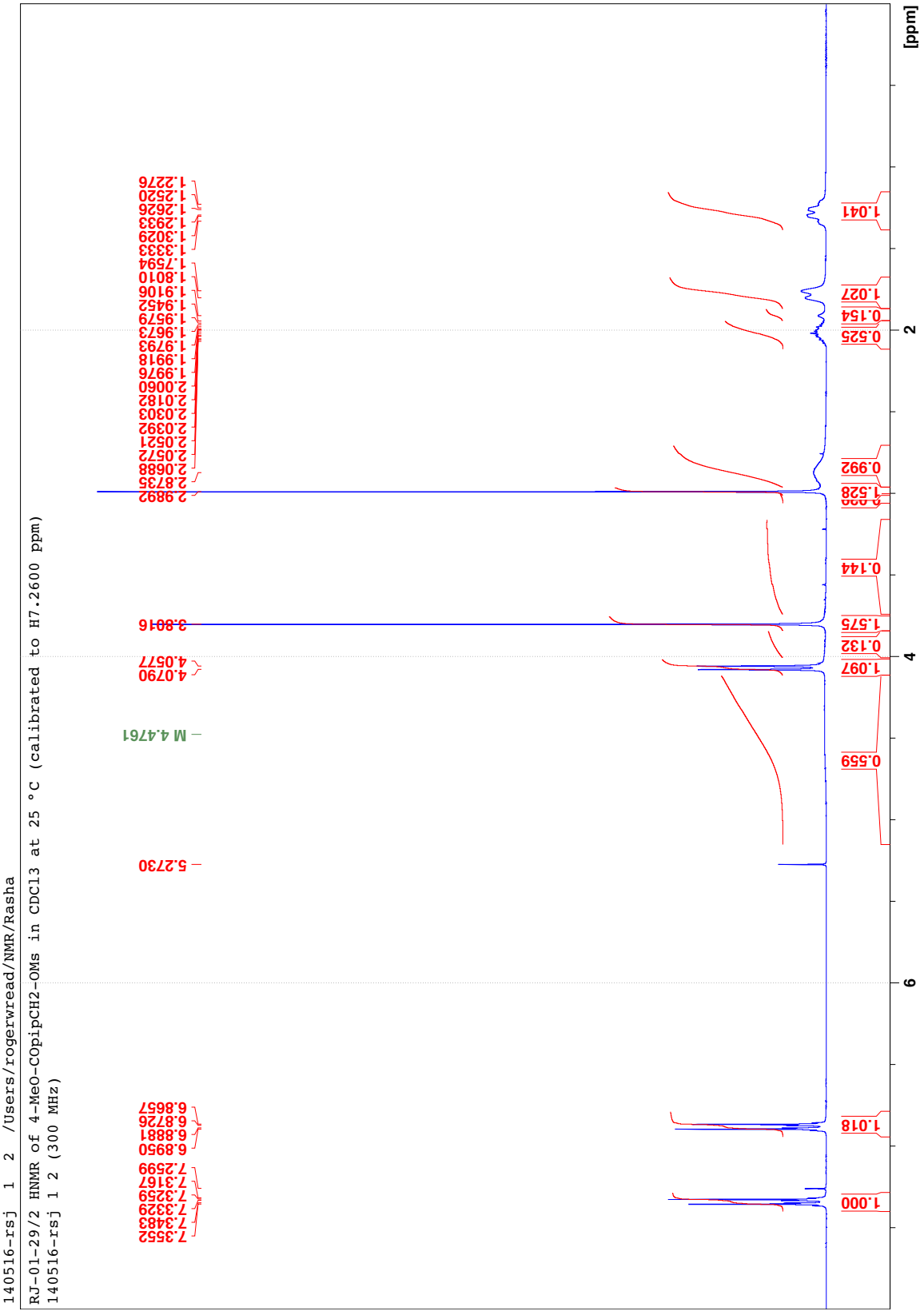


(1-(4-Methoxybenzoyl)piperidin-4-yl)methyl methanesulfonate **38**

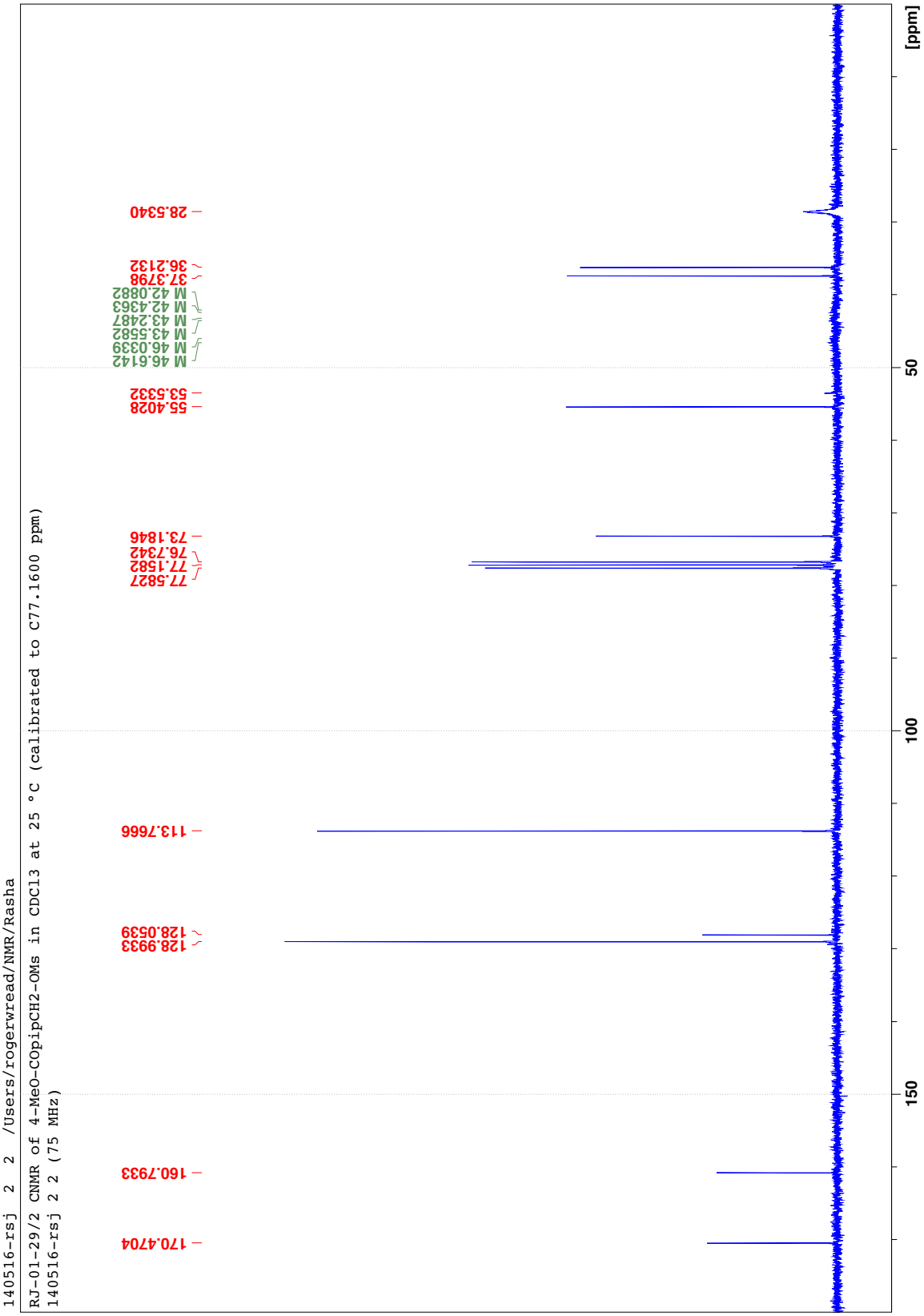


38

^{1}H NMR at 25 °C

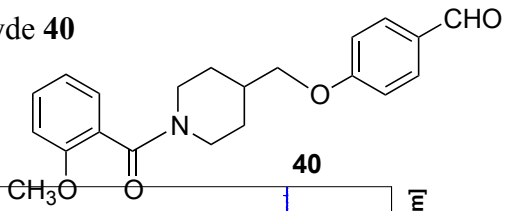


^{13}C NMR at 25 °C



4-((1-(2-Methoxybenzoyl)piperidin-4-yl)methoxy)benzaldehyde **40**

^{1}H NMR at 25 °C



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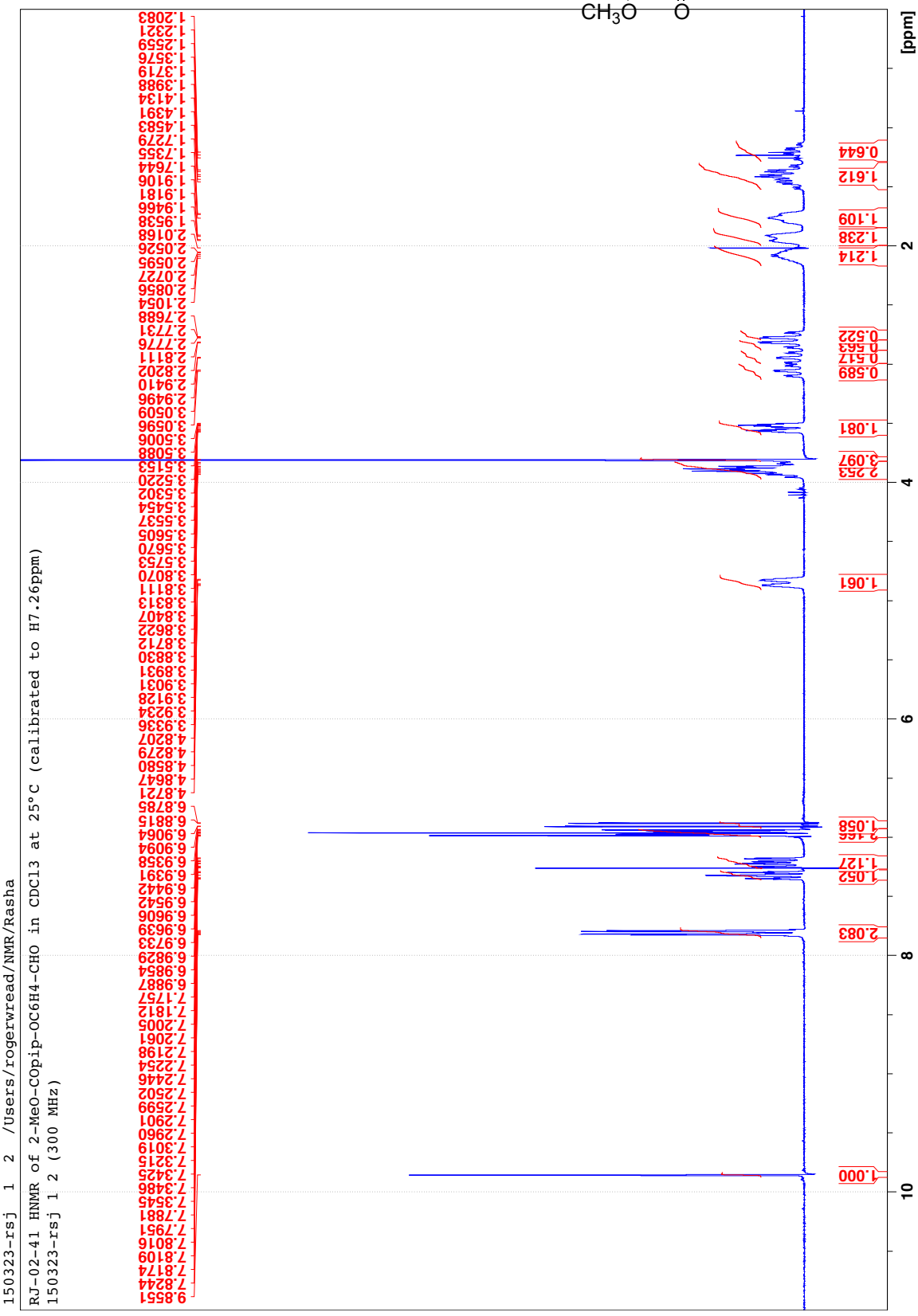
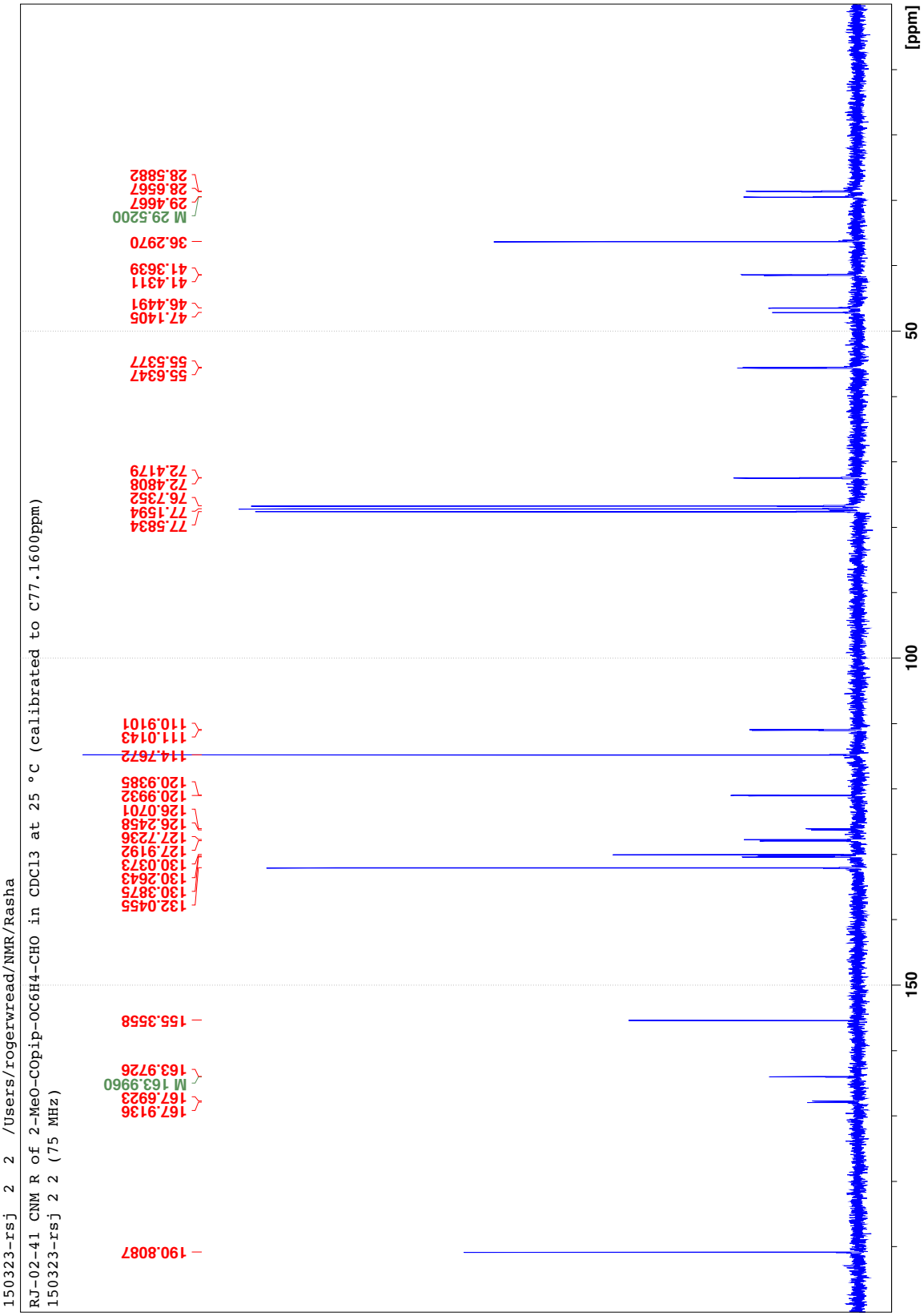
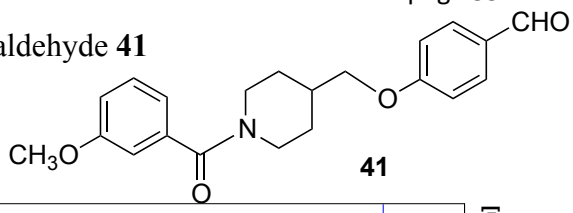


^{13}C NMR at 25 °C



4-((1-(3-Methoxybenzoyl)piperidin-4-yl)methoxy)benzaldehyde **41**

^{1}H NMR at 25 °C



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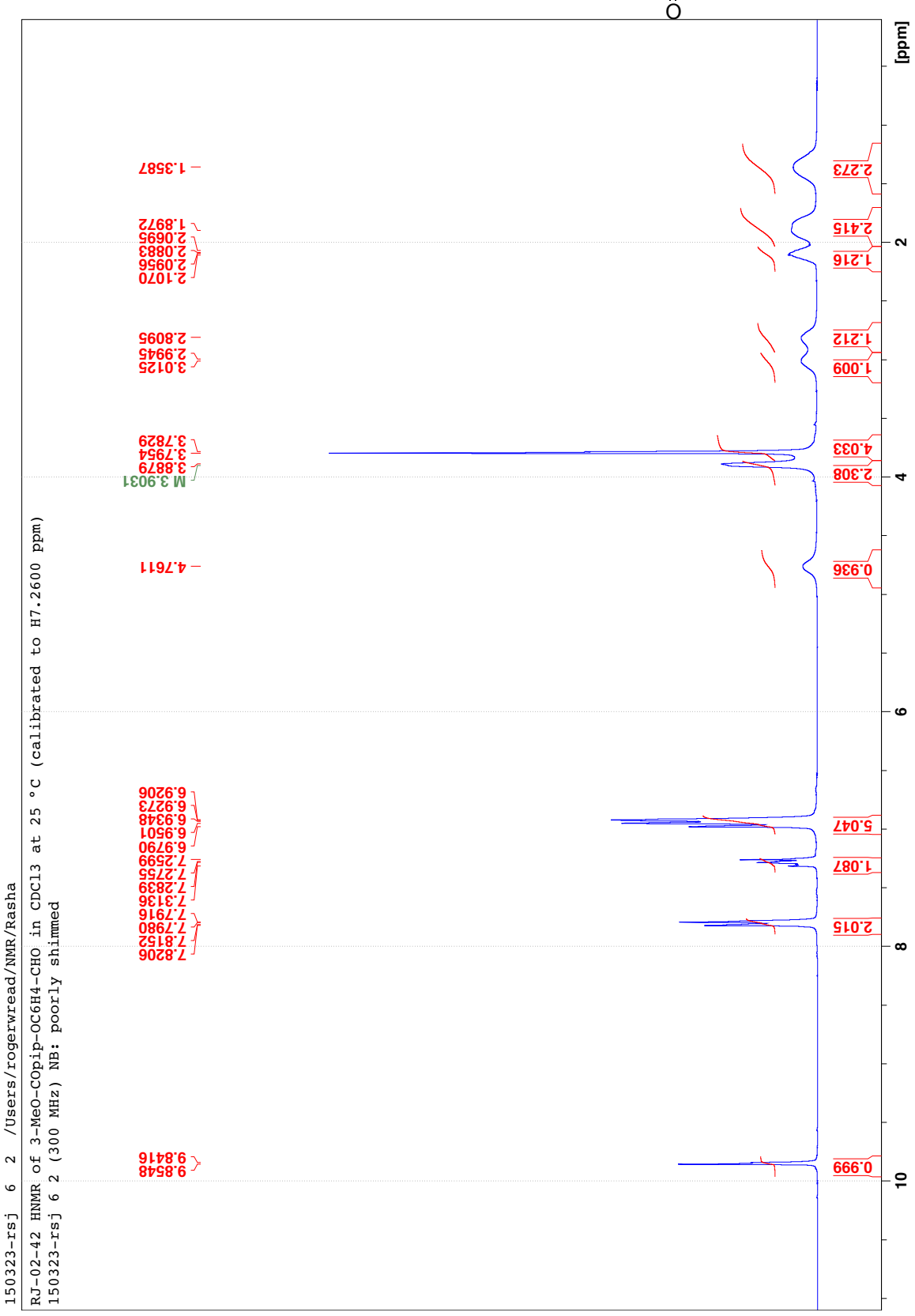
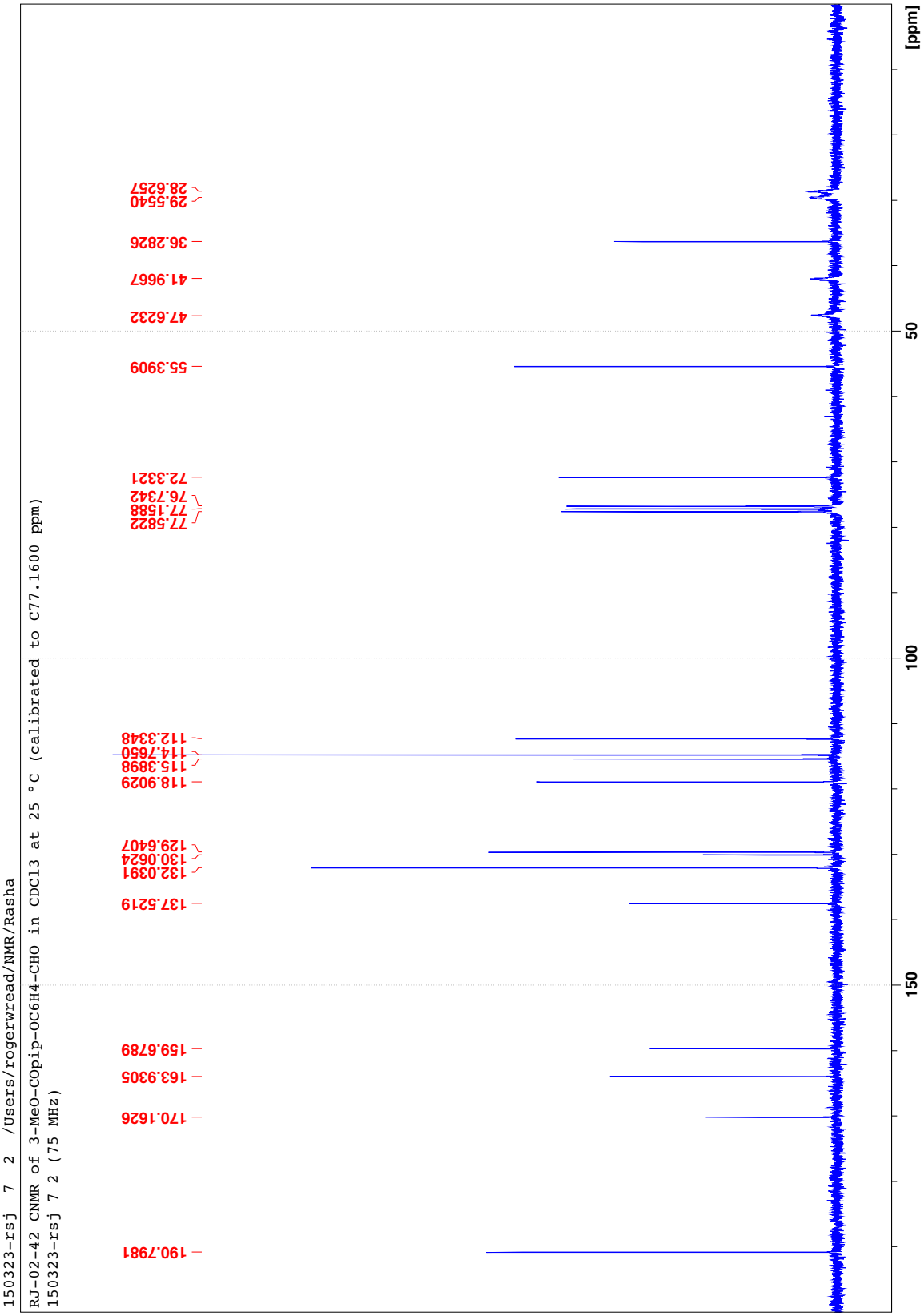
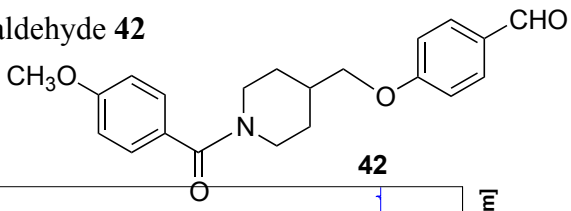


^{13}C NMR at 25 °C



4-((1-(4-Methoxybenzoyl)piperidin-4-yl)methoxy)benzaldehyde **42**

^{1}H NMR at 25 °C



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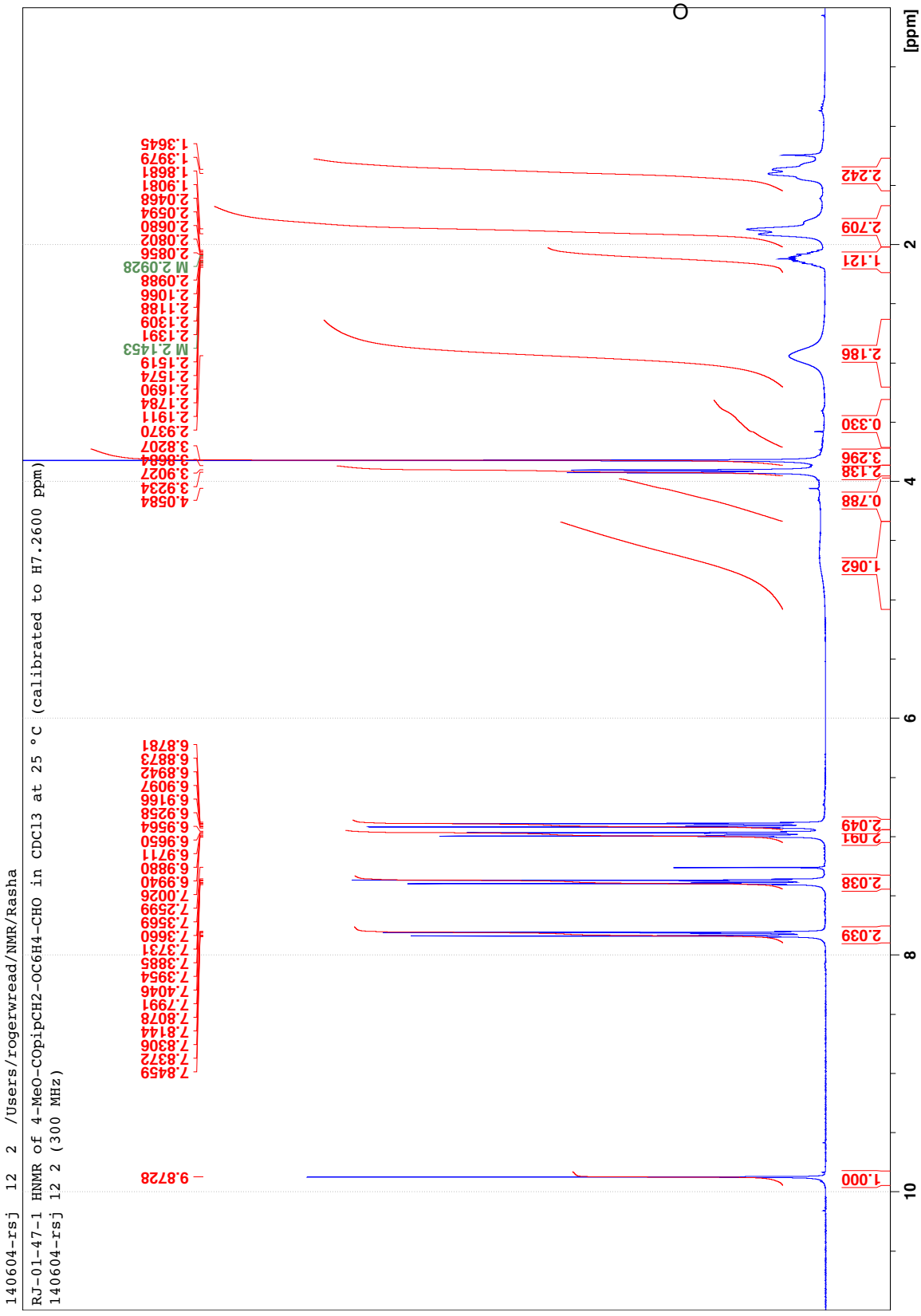

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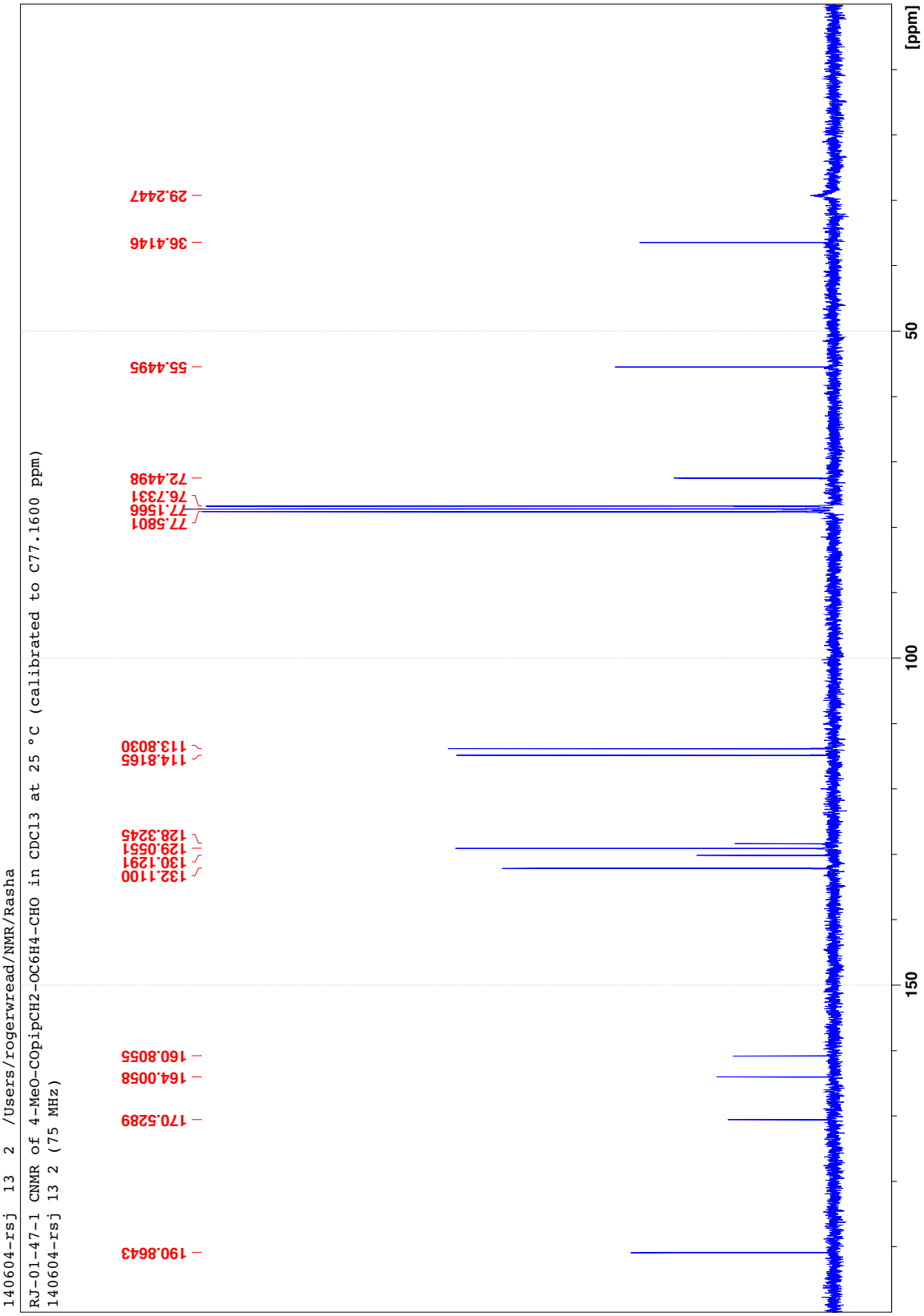
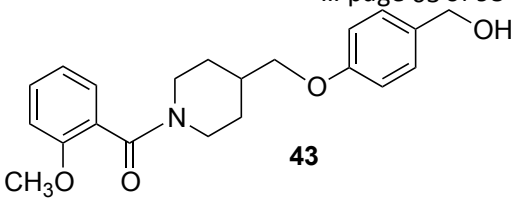


(4-((4-(Hydroxymethyl)phenoxy)methyl)piperidin-1-yl)(2-methoxyphenyl)methanone **43**

^{1}H NMR at 25 °C



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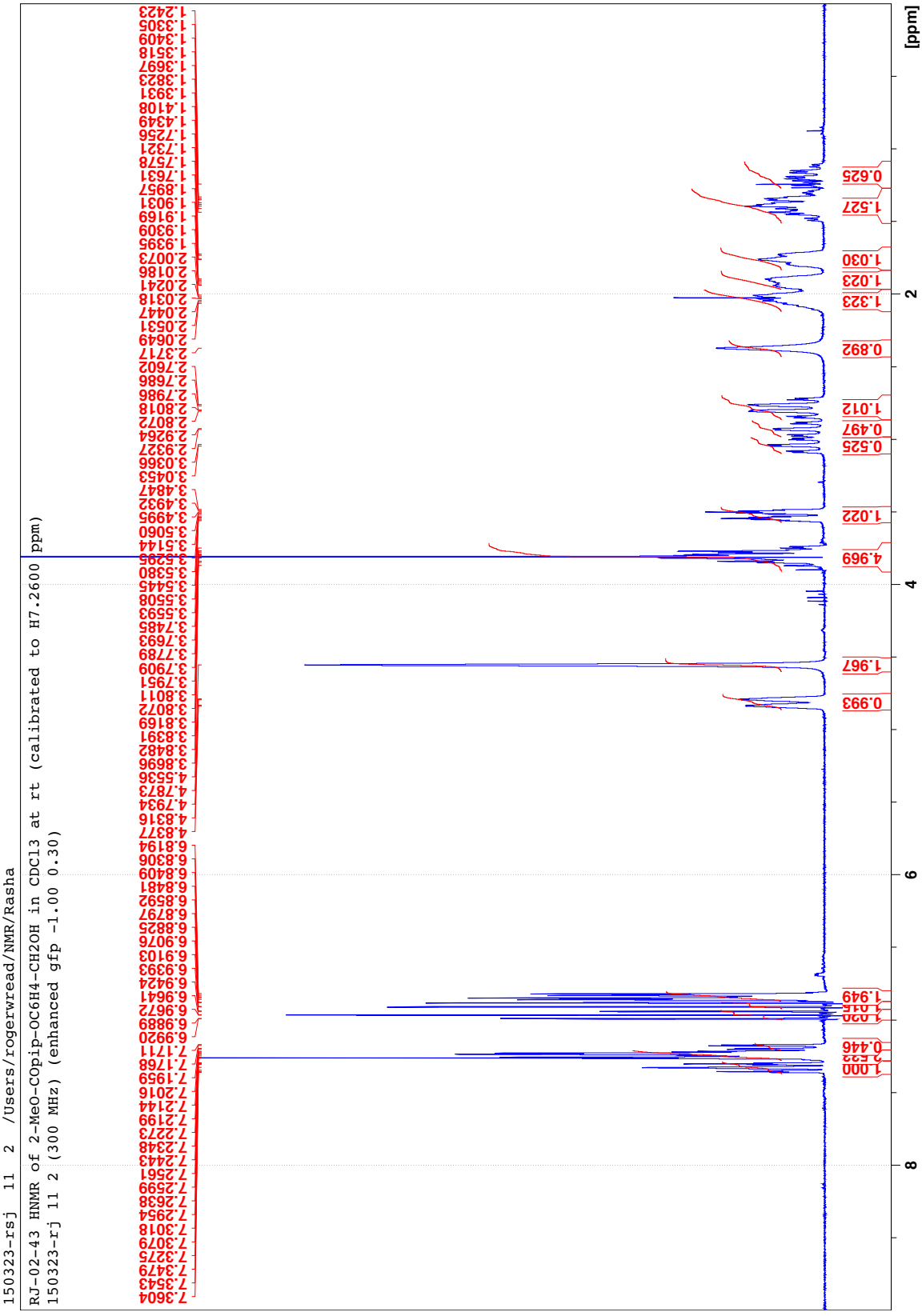
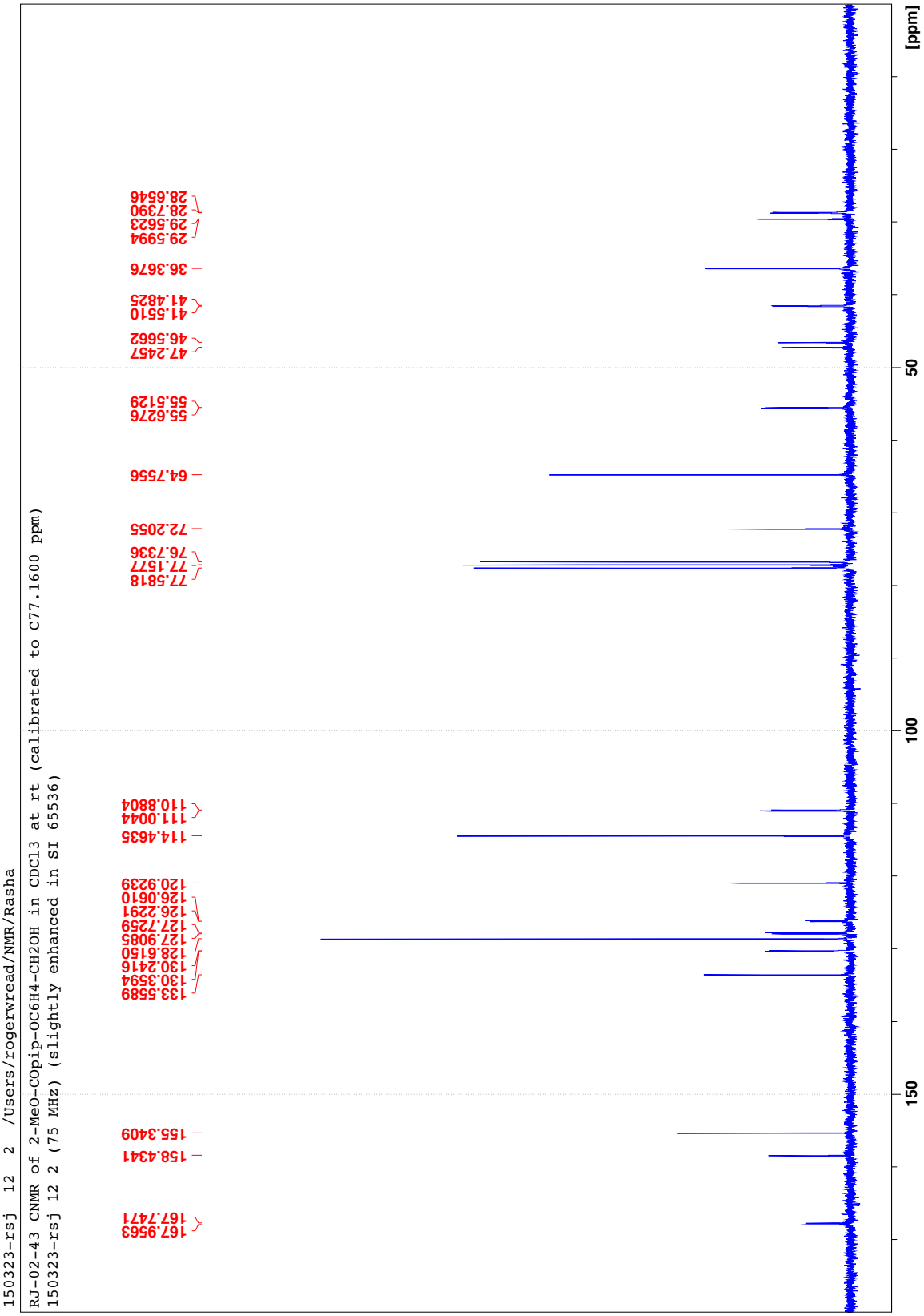
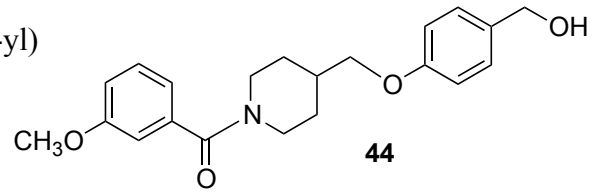


^{13}C NMR at 25 °C



(4-((4-(Hydroxymethyl)phenoxy)methy)piperidin-4-1-yl)
(3-methoxyphenyl)methanone **44**
^{1}H NMR at 25 °C



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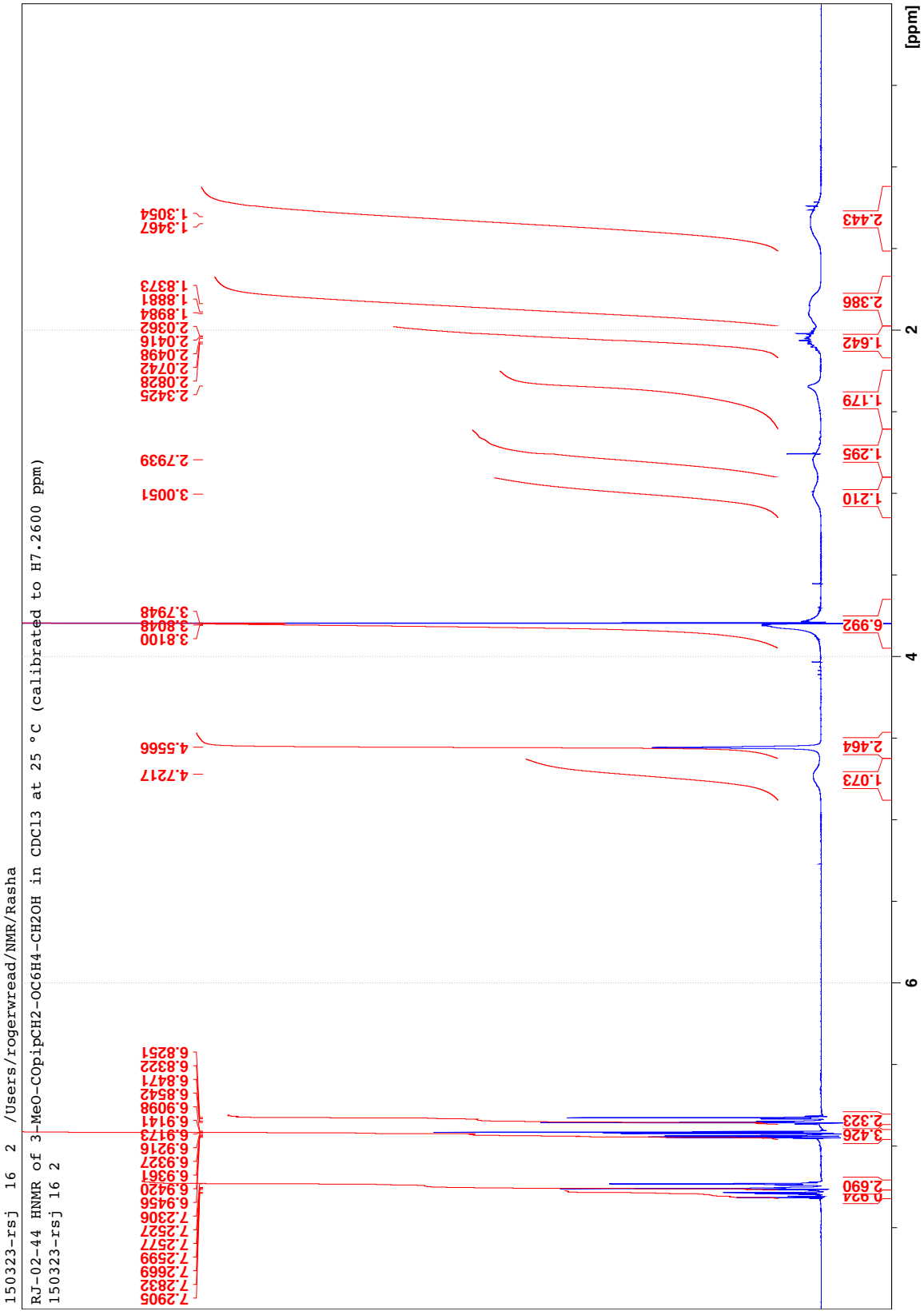
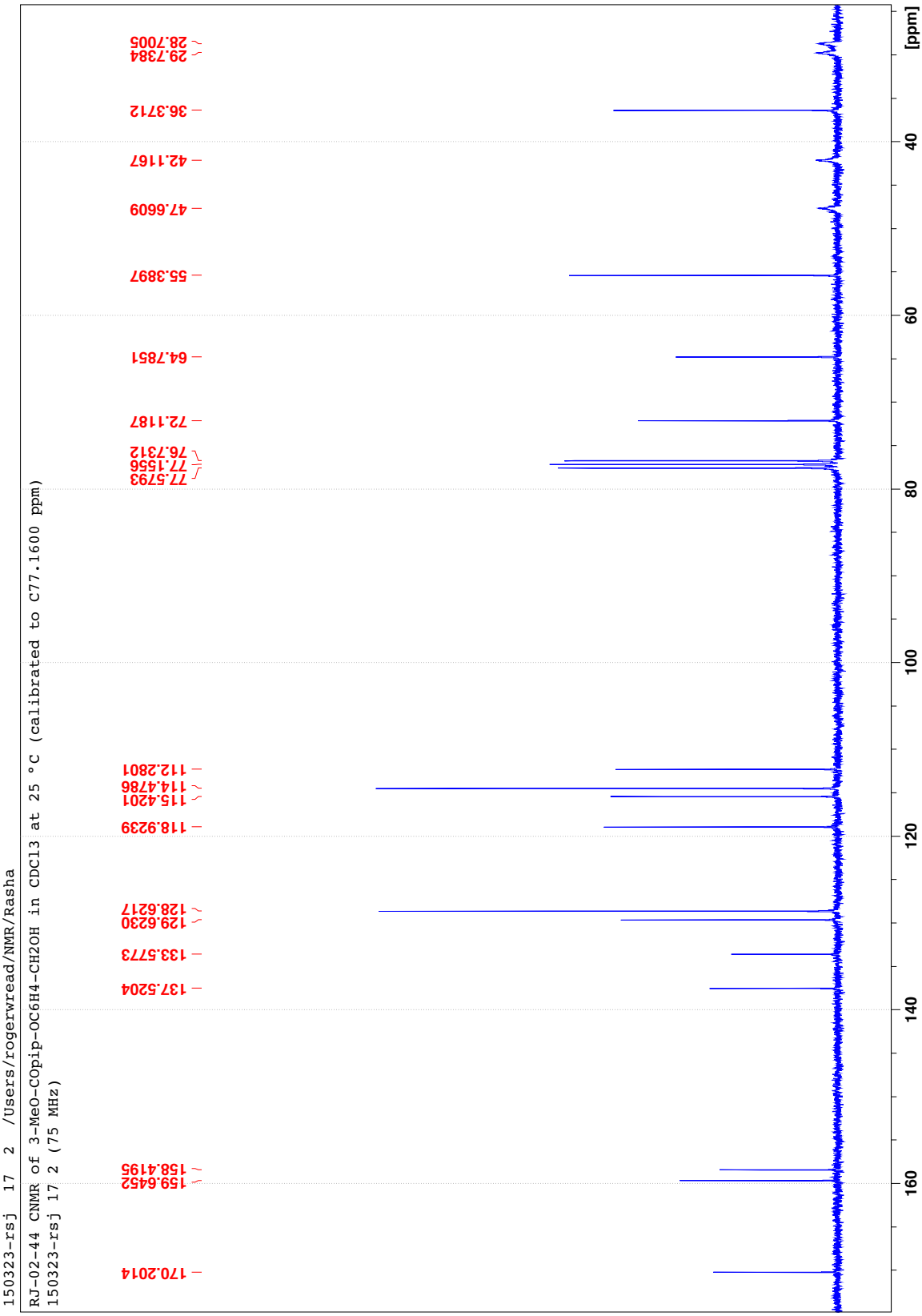
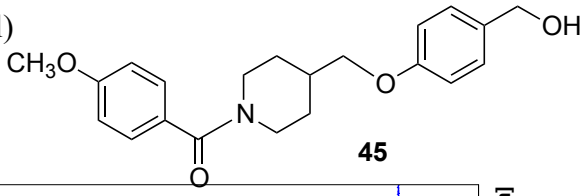


^{13}C NMR at 25 °C



(4-((4-(Hydroxymethyl)phenoxy)methyl)piperidin-1-yl)
(4-methoxyphenyl)methanone **45**
^{1}H NMR at 25 °C



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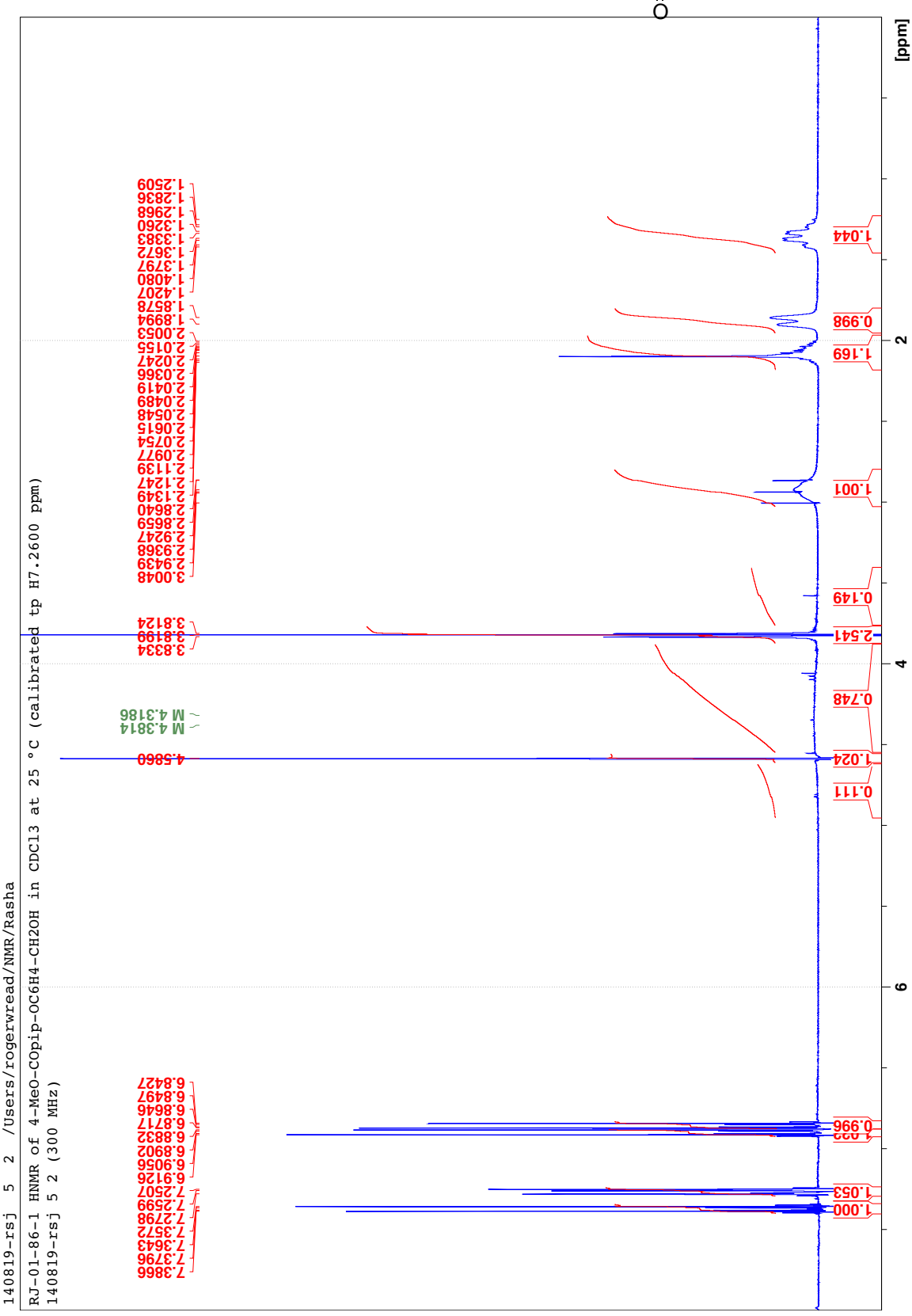
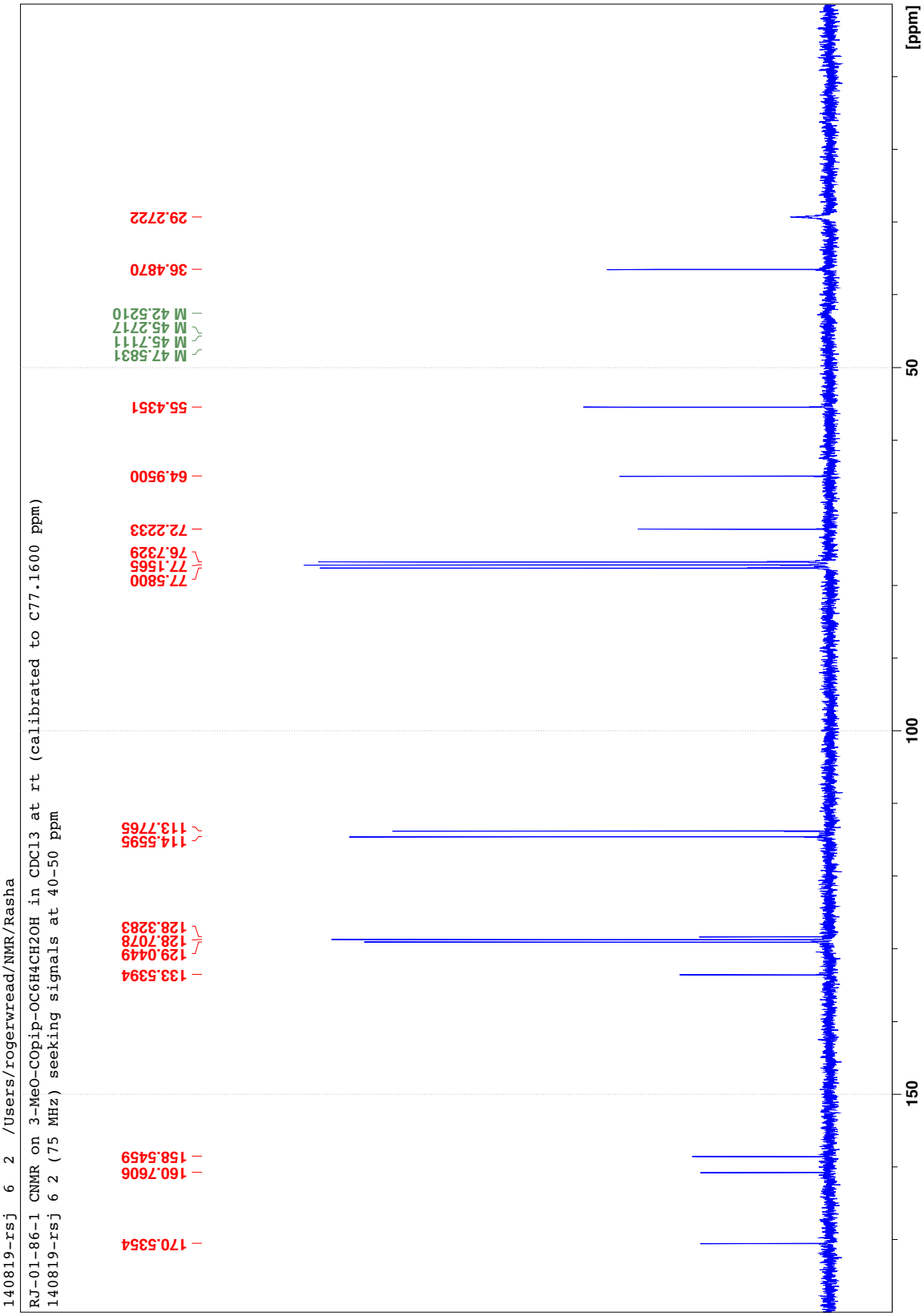
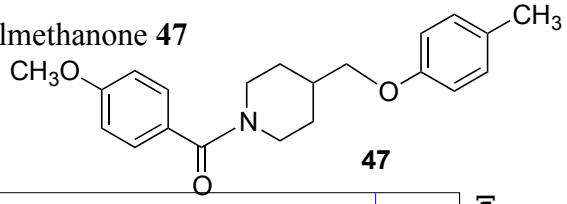


^{13}C NMR at 25 °C

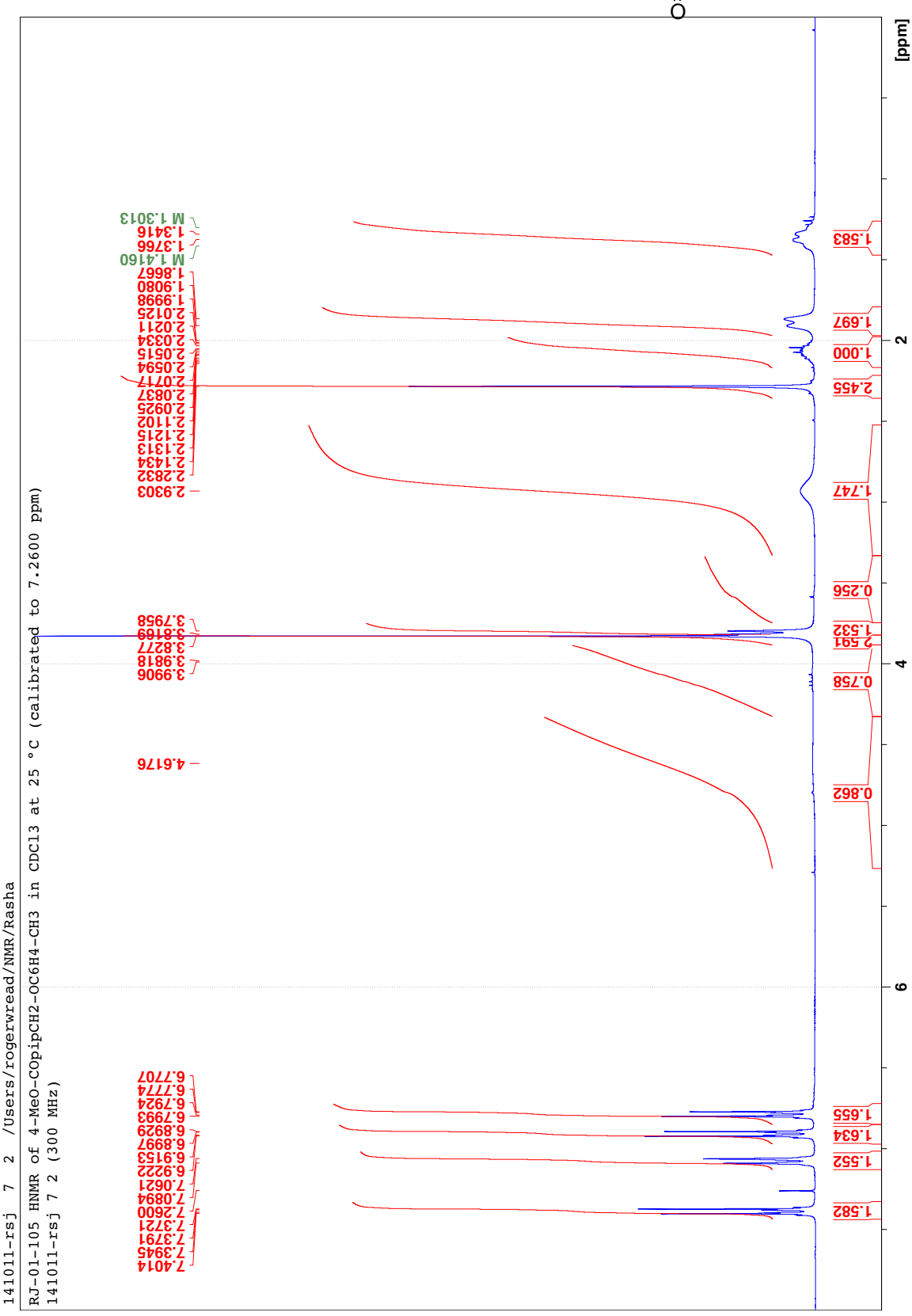


(4-Methoxyphenyl)(4-((4-tolyloxy)methyl)piperidin-1-ylmethanone **47**

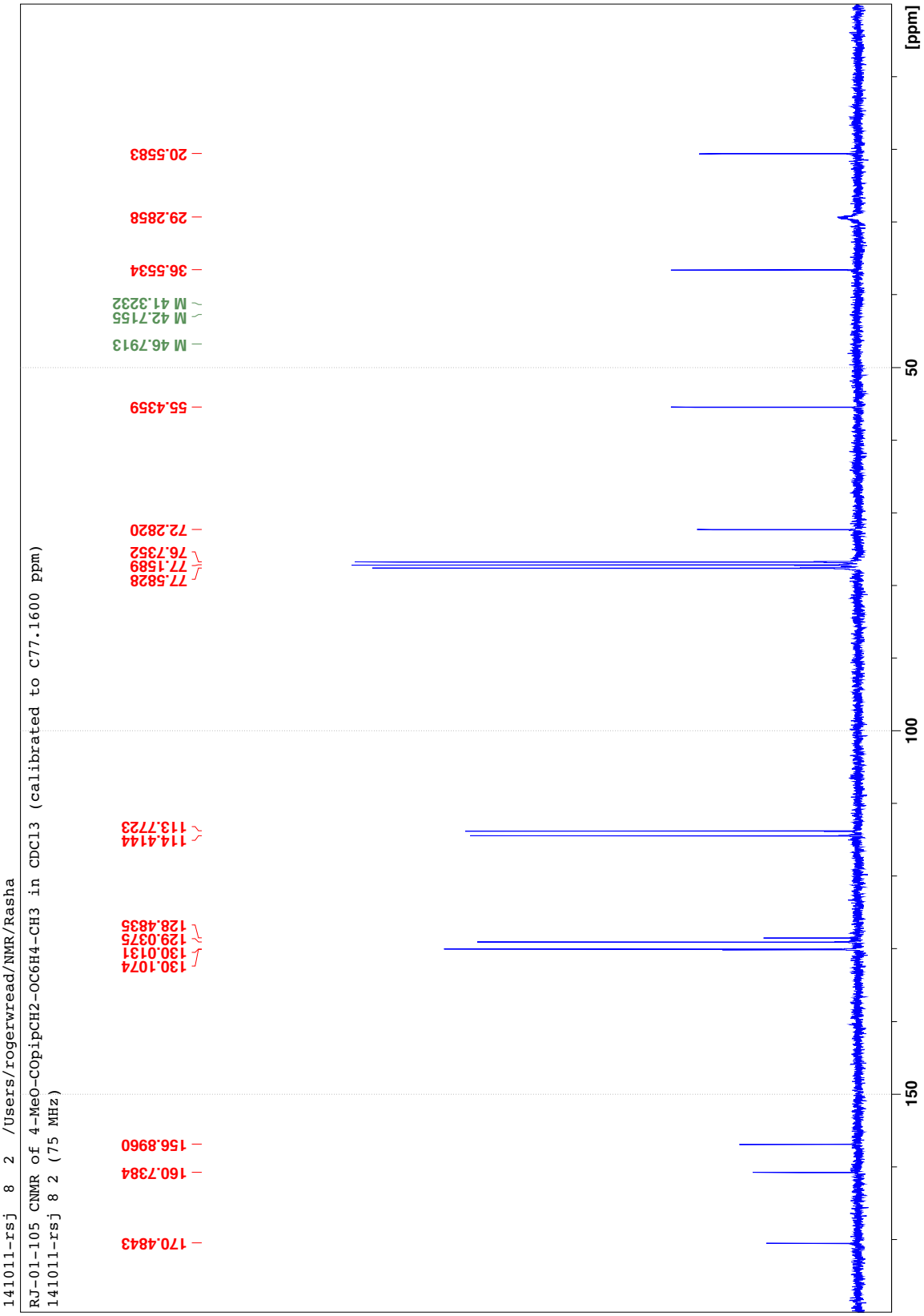
^{1}H NMR at 25 °C



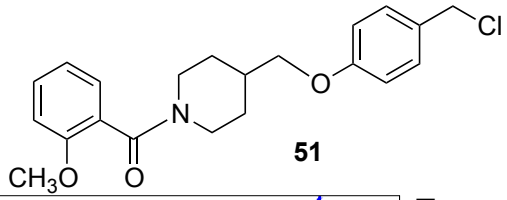
47



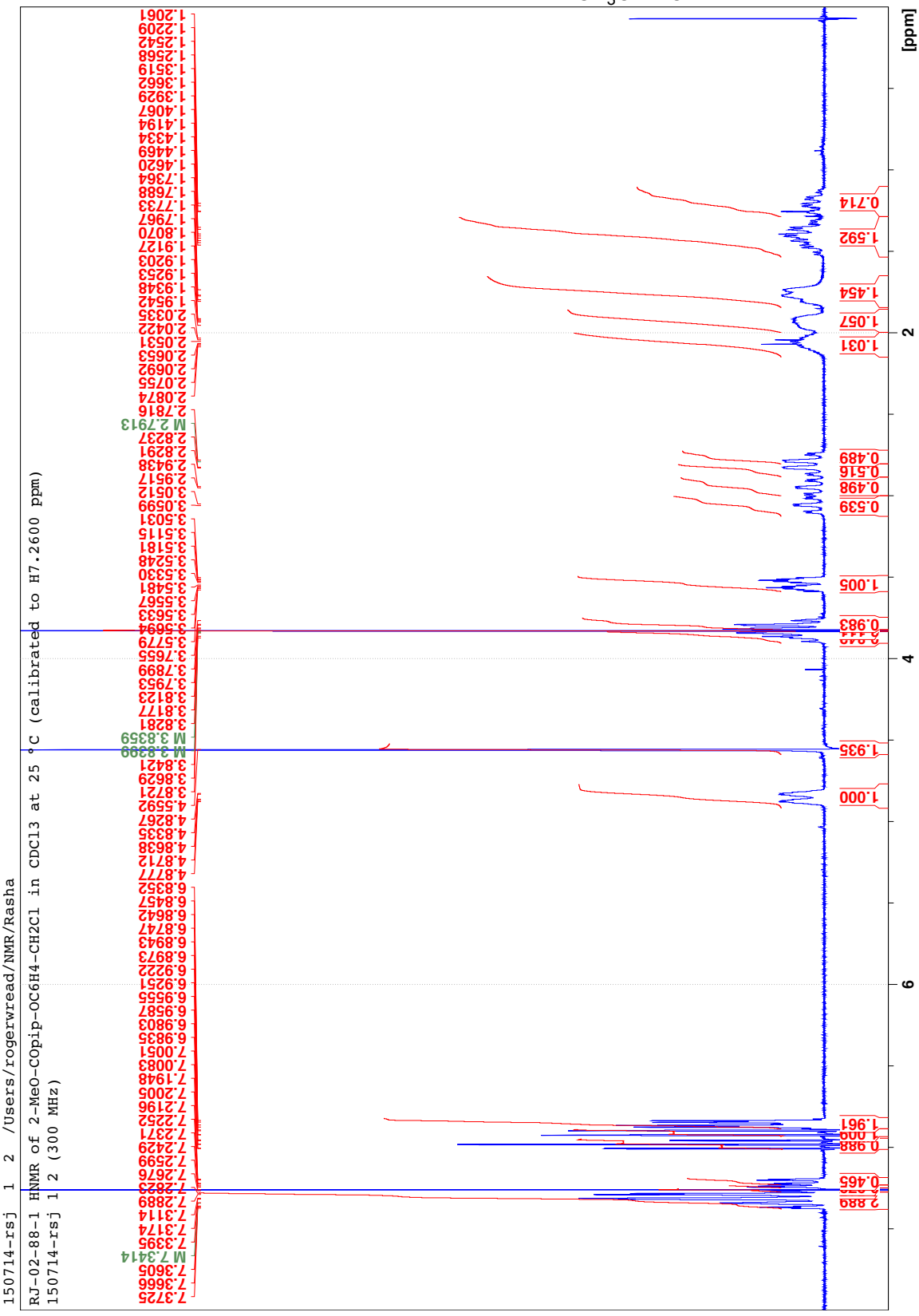
^{13}C NMR at 25 °C



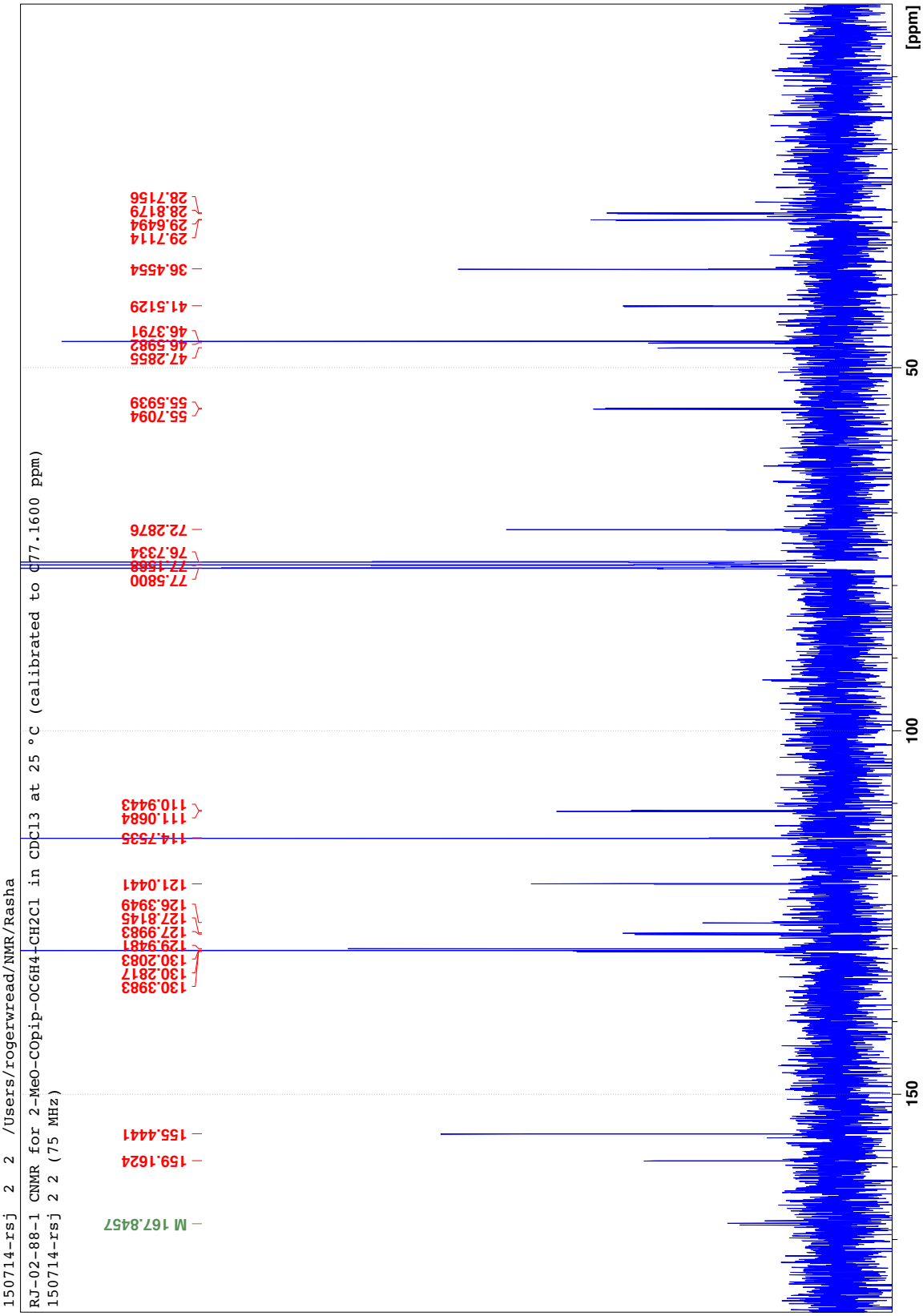
(4-((4-(Chloromethyl)phenoxy)methyl)piperidin-1-yl)(2-methoxyphenyl)methanone **51**
^{1}H NMR at 25 °C



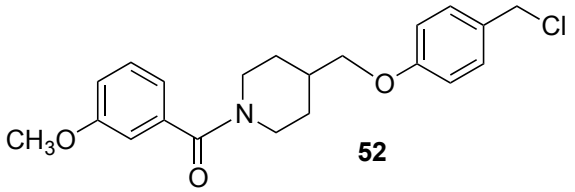
51



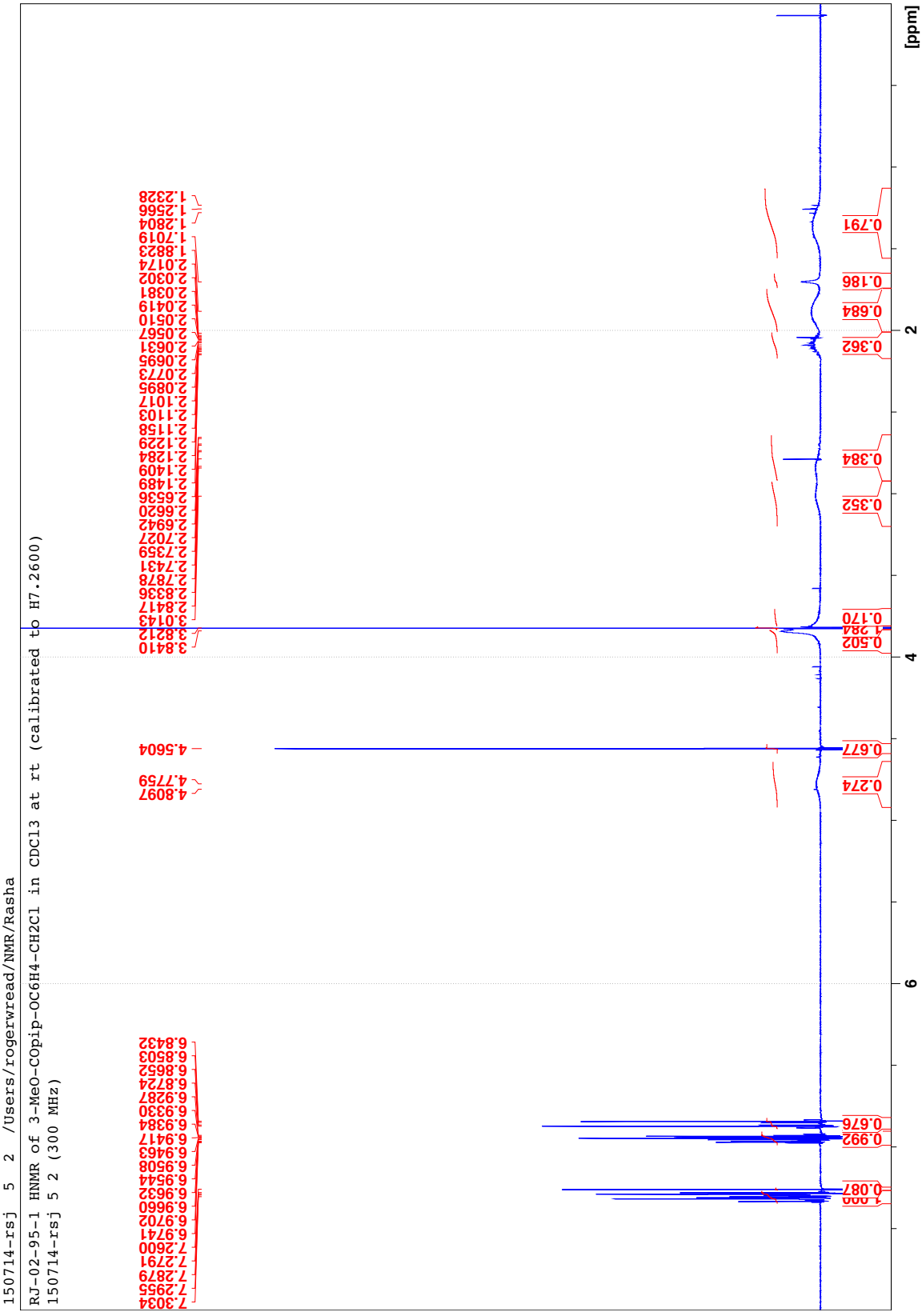
^{13}C NMR at 25 °C



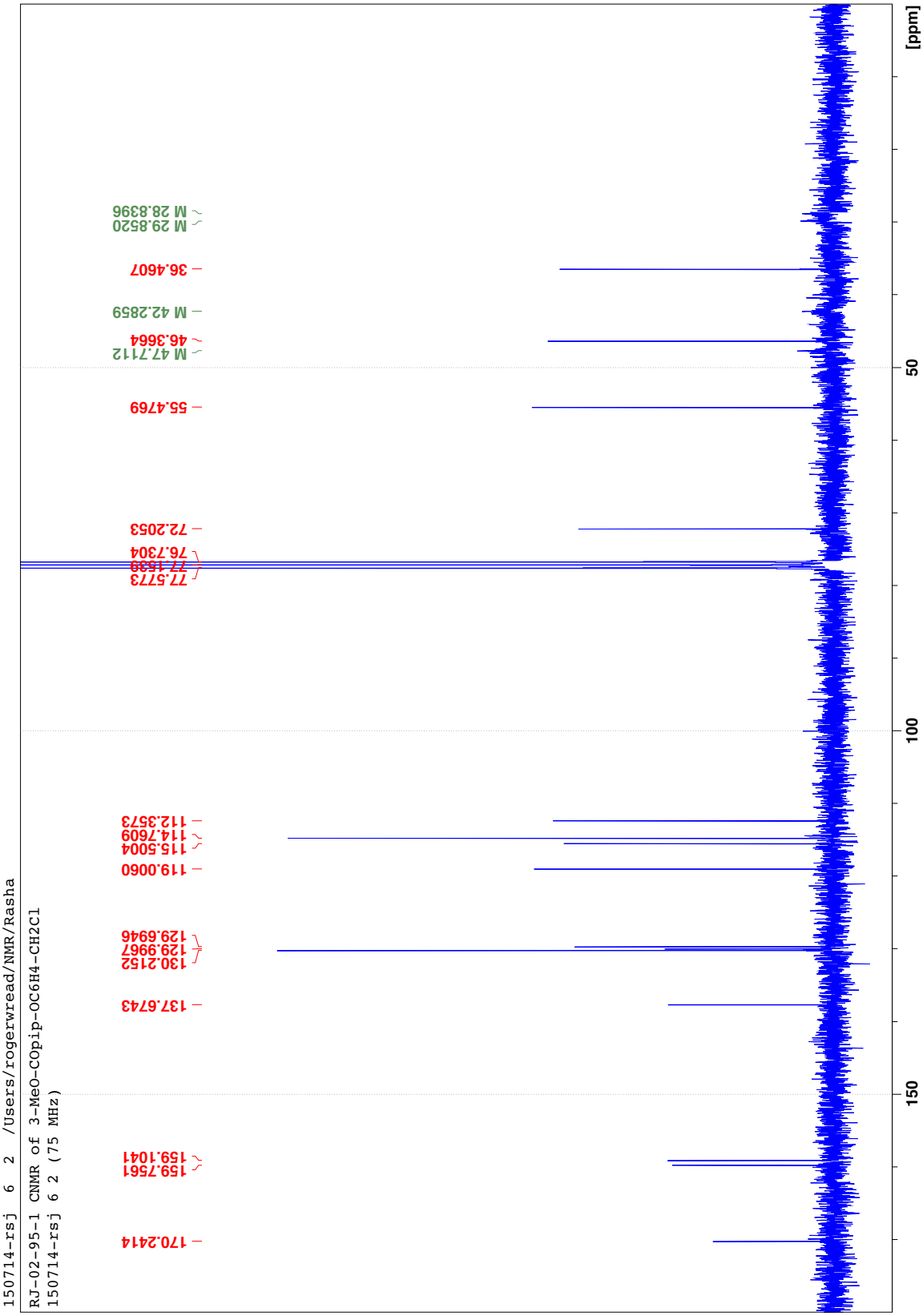
(4-((4-(Chloromethyl)phenoxy)methyl)piperidin-1-yl)(3-methoxyphenyl)methanone **52**
^{1}H NMR at 25 °C



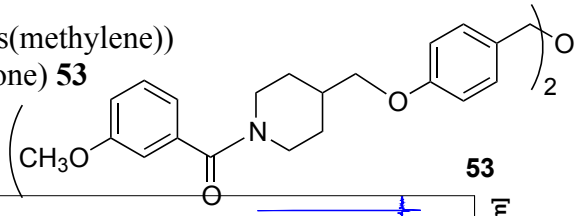
52



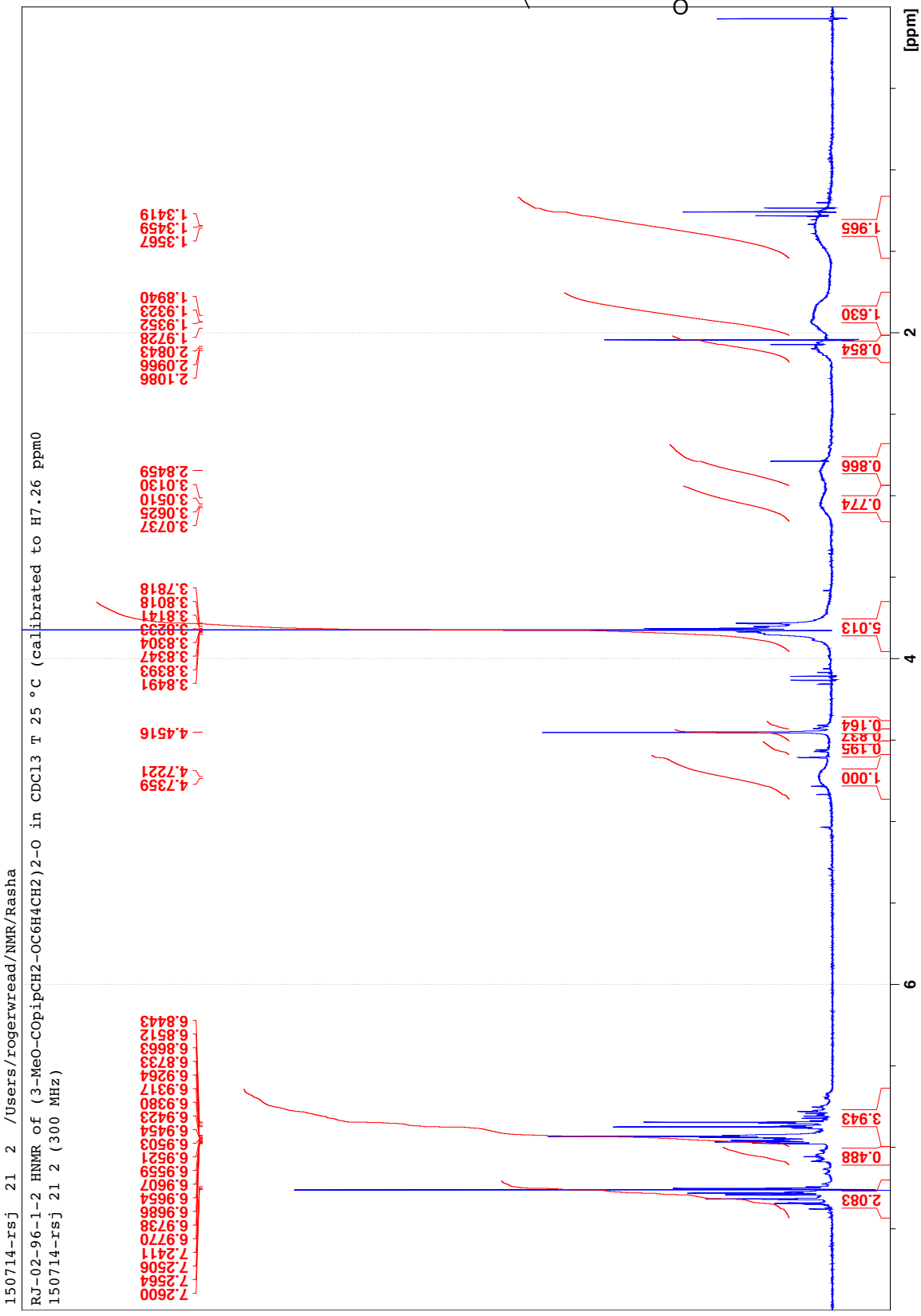
^{13}C NMR at 25 °C



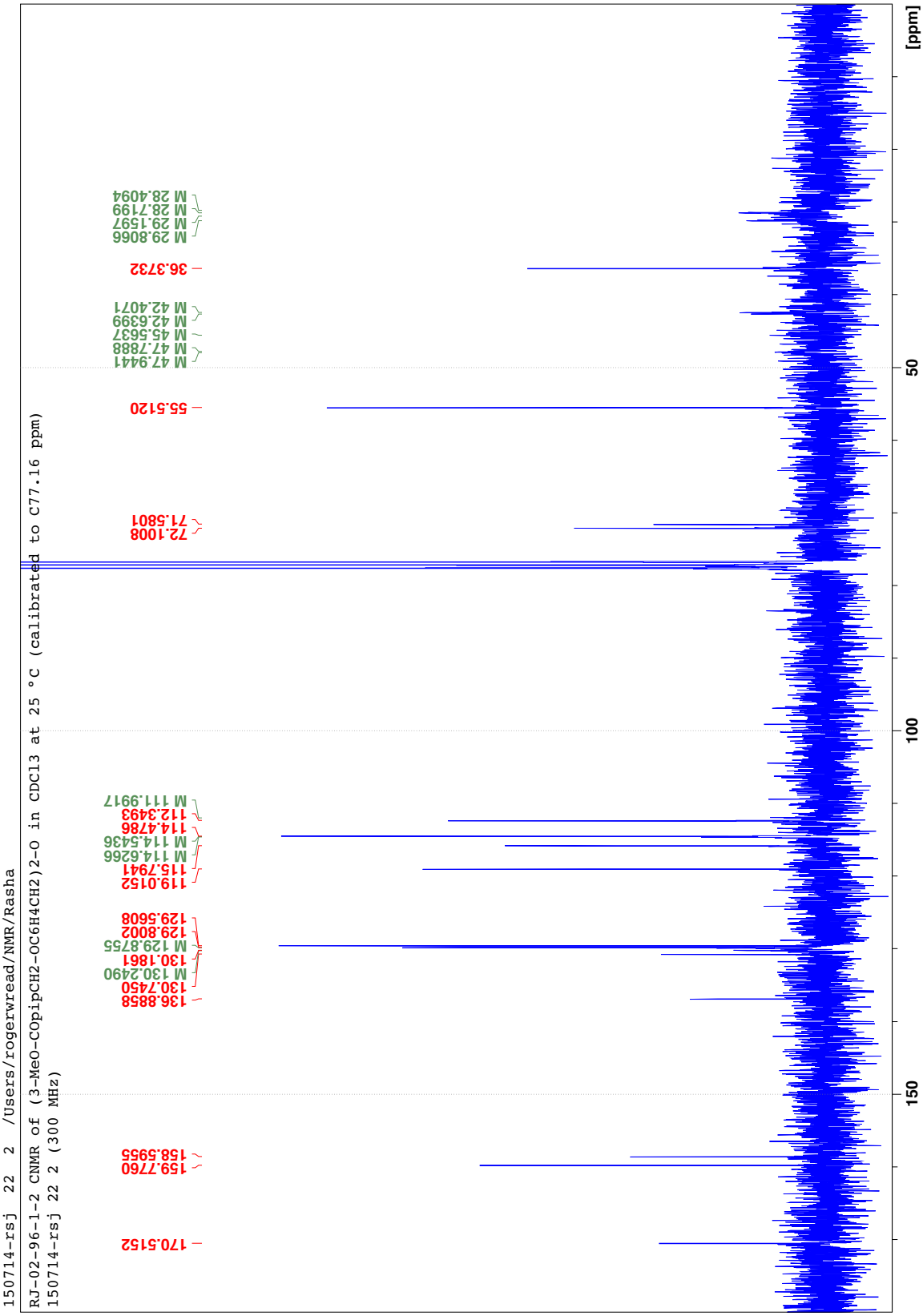
((((((Oxybis(methylene))bis(4,1-phenylene))bis(oxy))bis(methylene))
bis(piperidine-4,1-diyl))bis((3-methoxyphenyl)methanone) **53**
^{1}H NMR at 25 °C



53

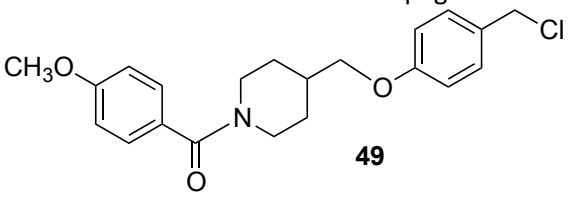


^{13}C NMR at 25 °C

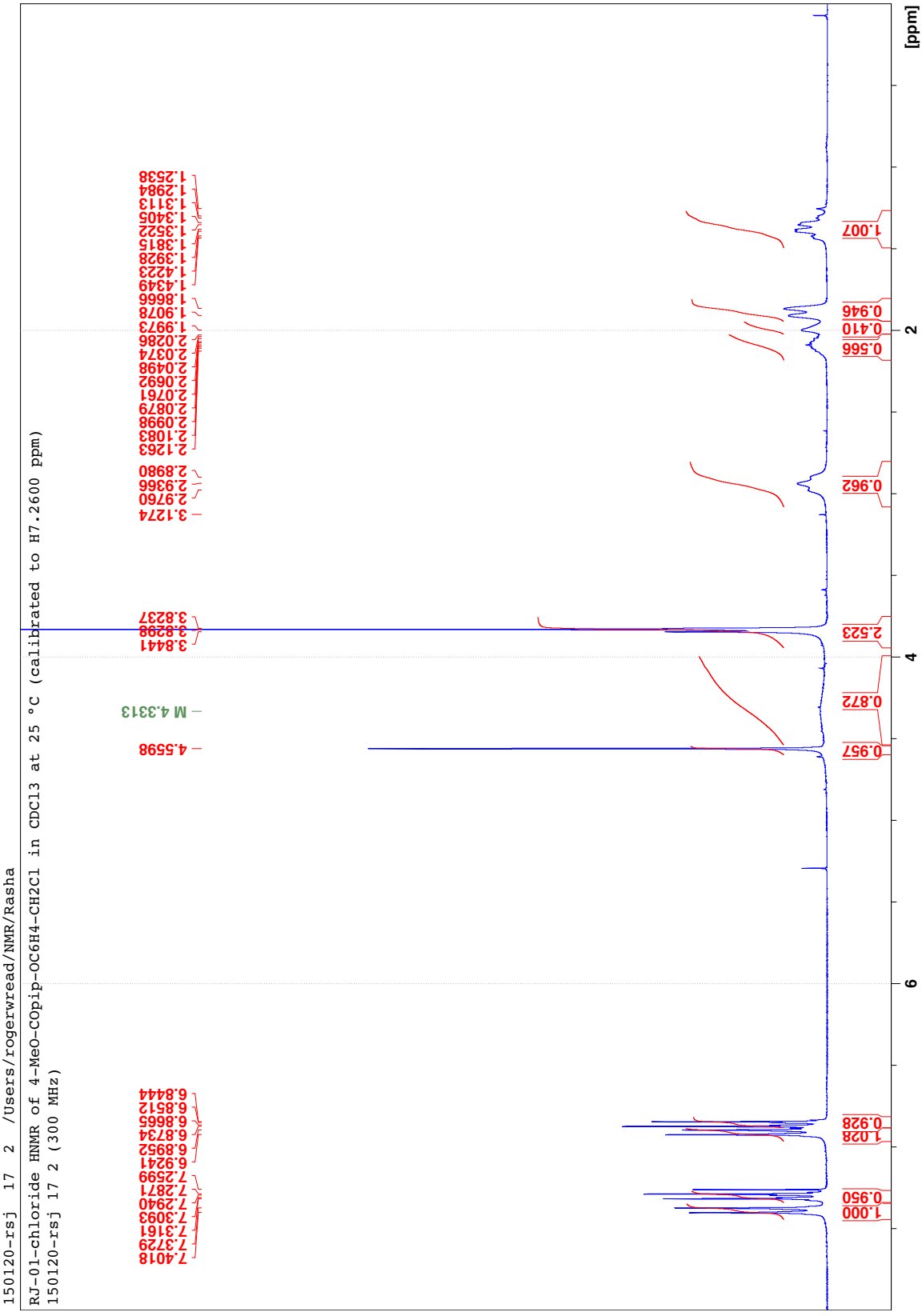


(4-((4-(Chloromethyl)phenoxy)methyl)piperidin-1-yl)(4-methoxyphenyl)methanone **49**

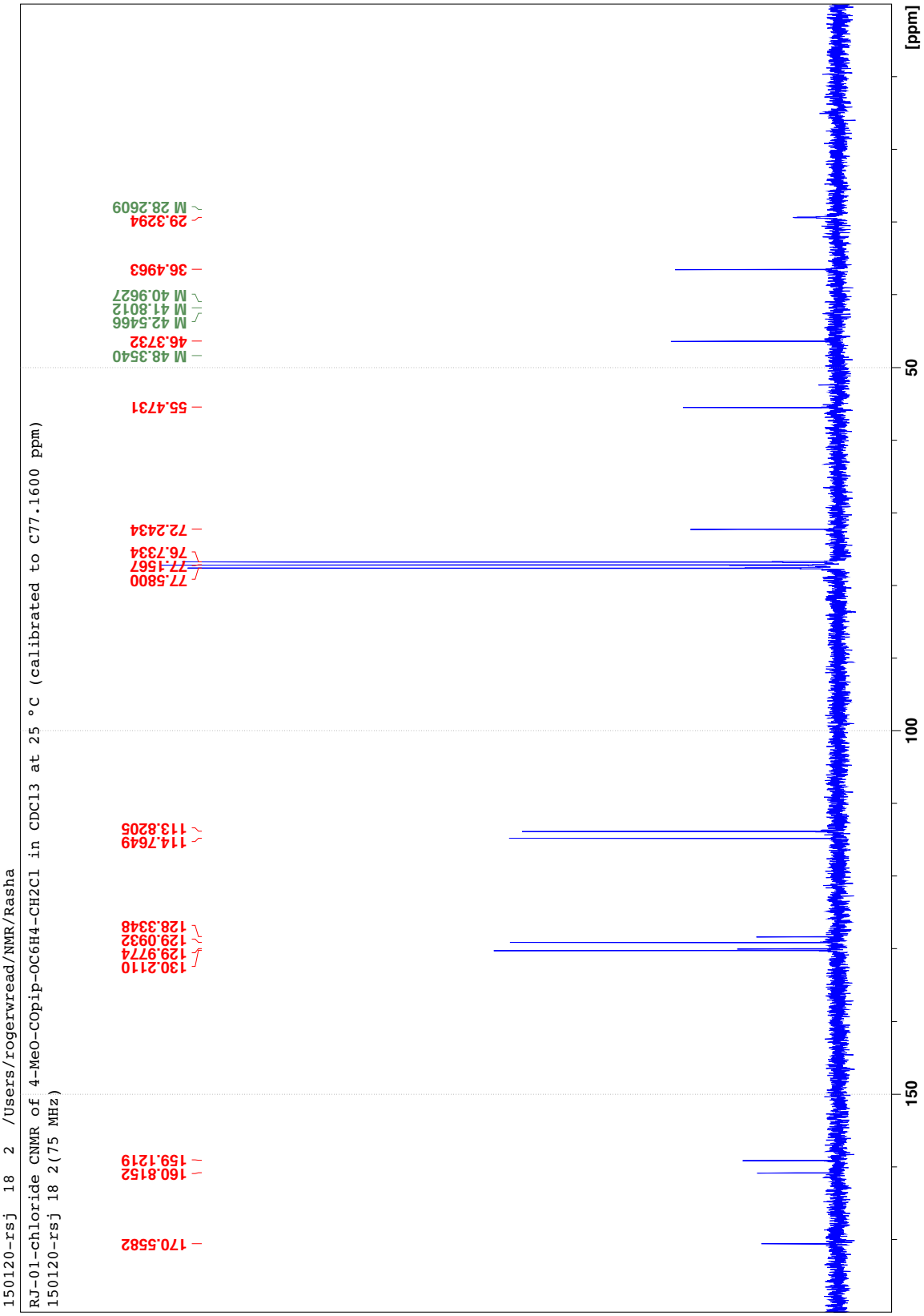
^{1}H NMR at 25 °C



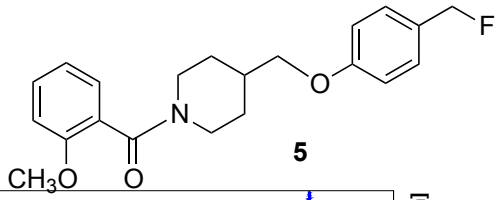
49



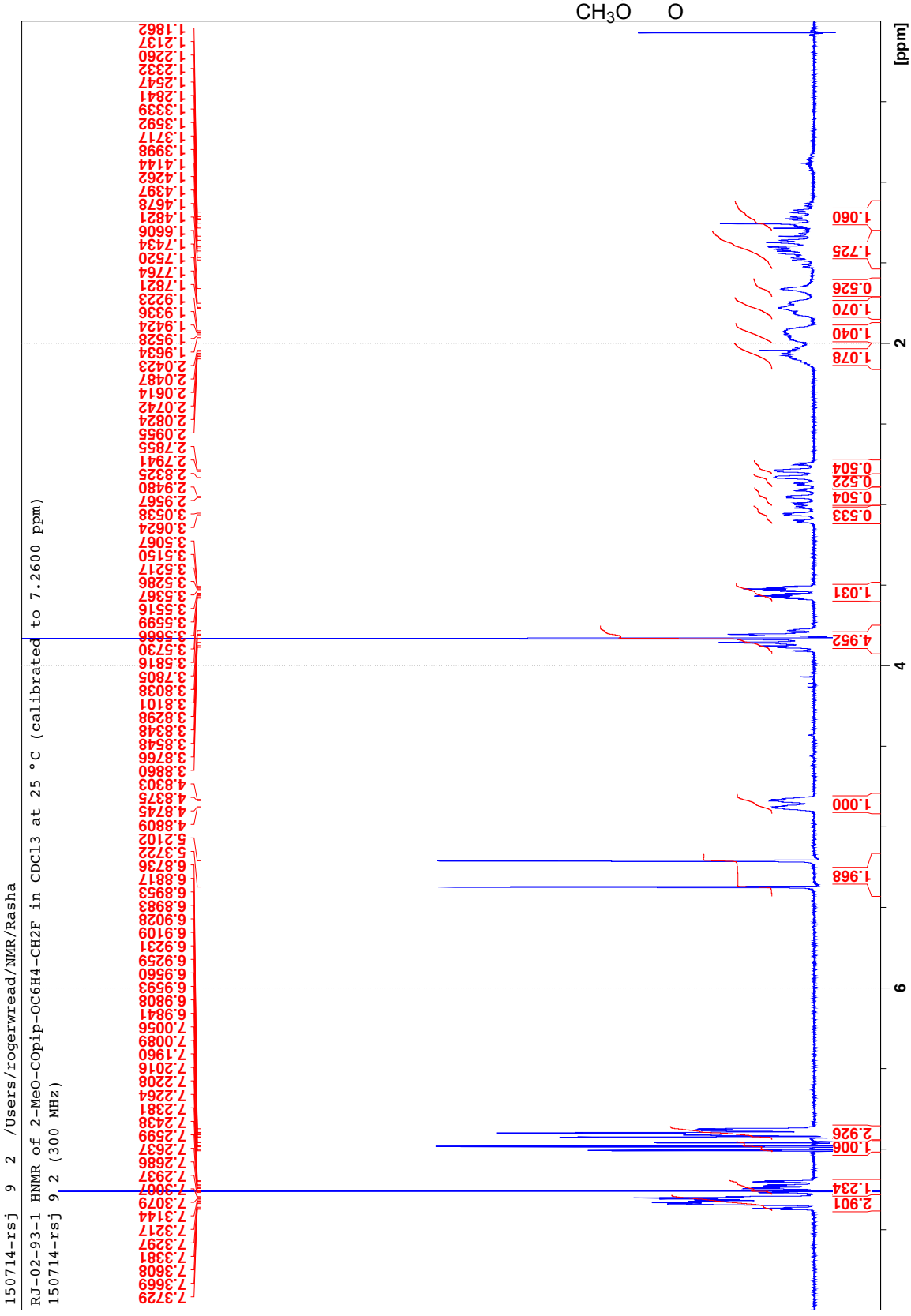
^{13}C NMR at 25 °C



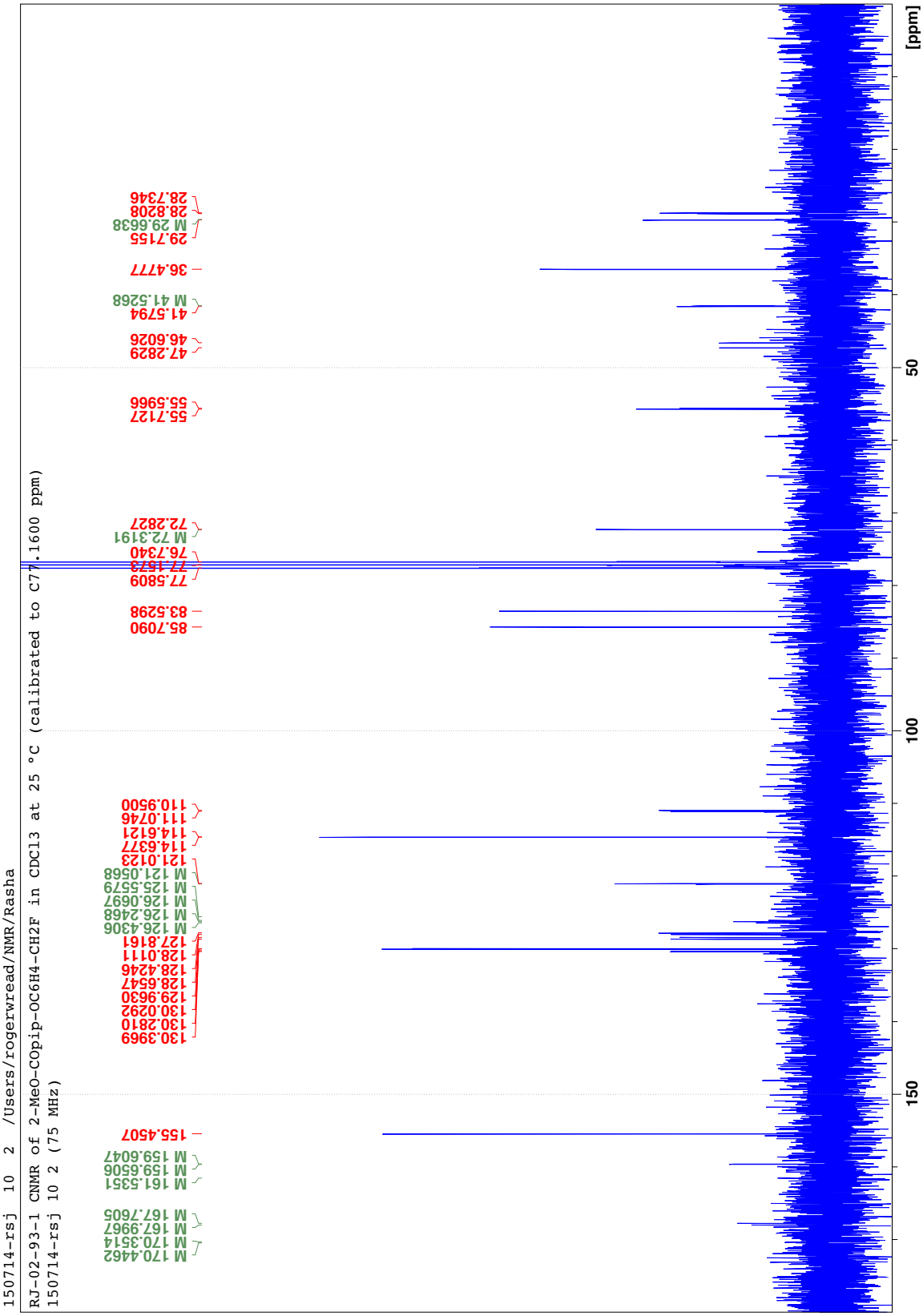
(4-((4-(Fluoromethyl)phenoxy)methyl)piperidin-1-yl)
(2-methoxyphenyl)methanone **5**
^{1}H NMR at 25 °C



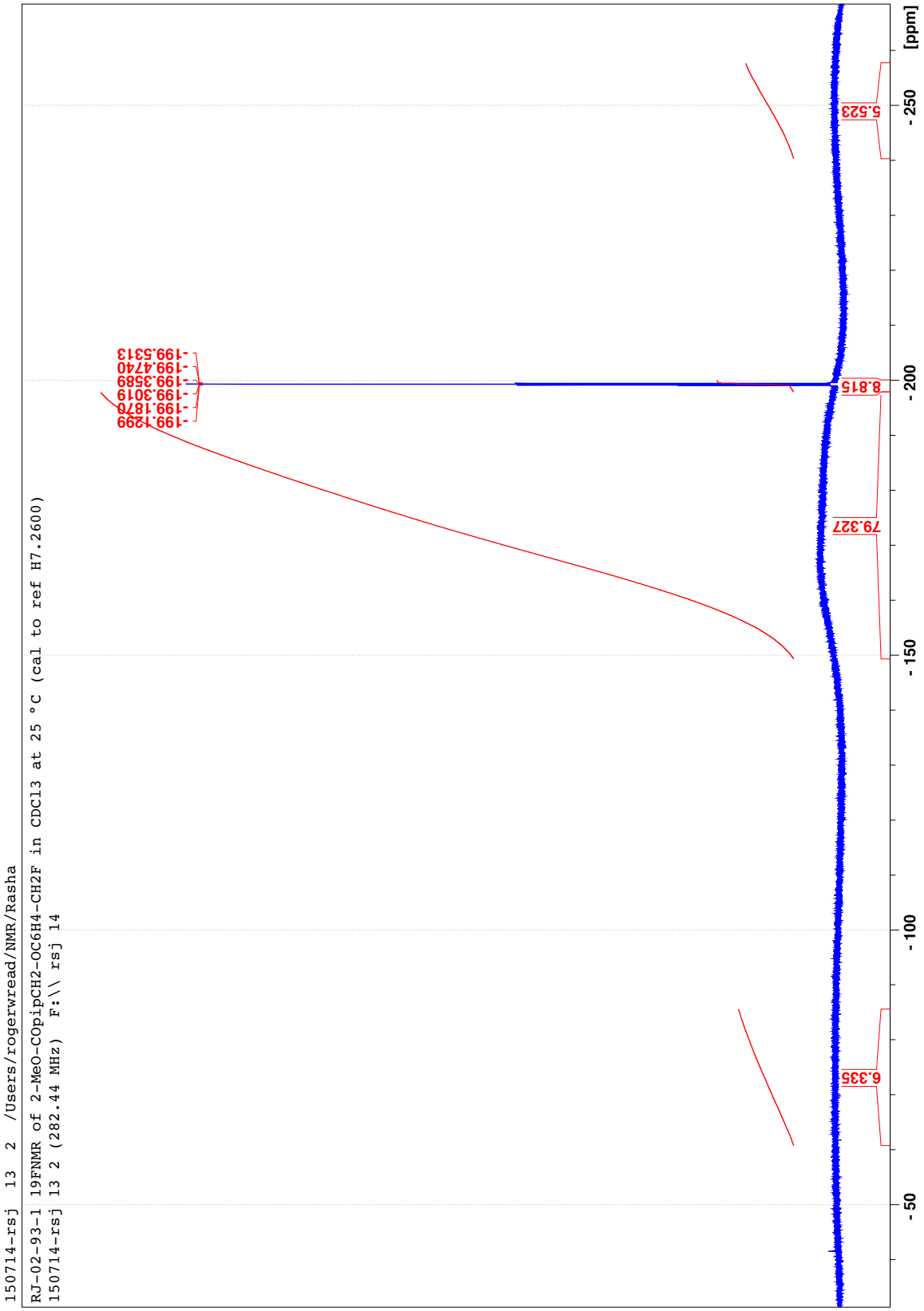
5



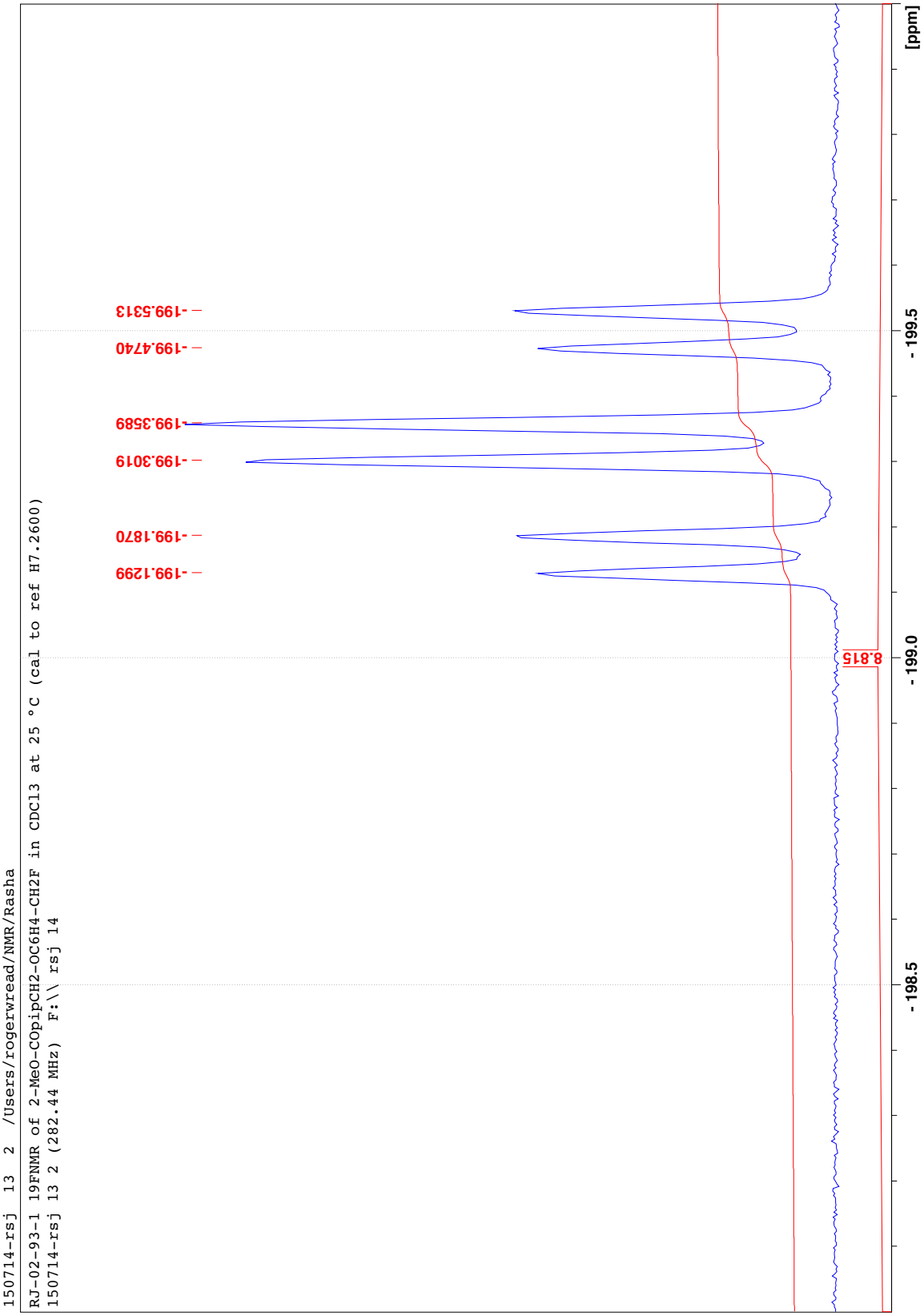
^{13}C NMR at 25 °C



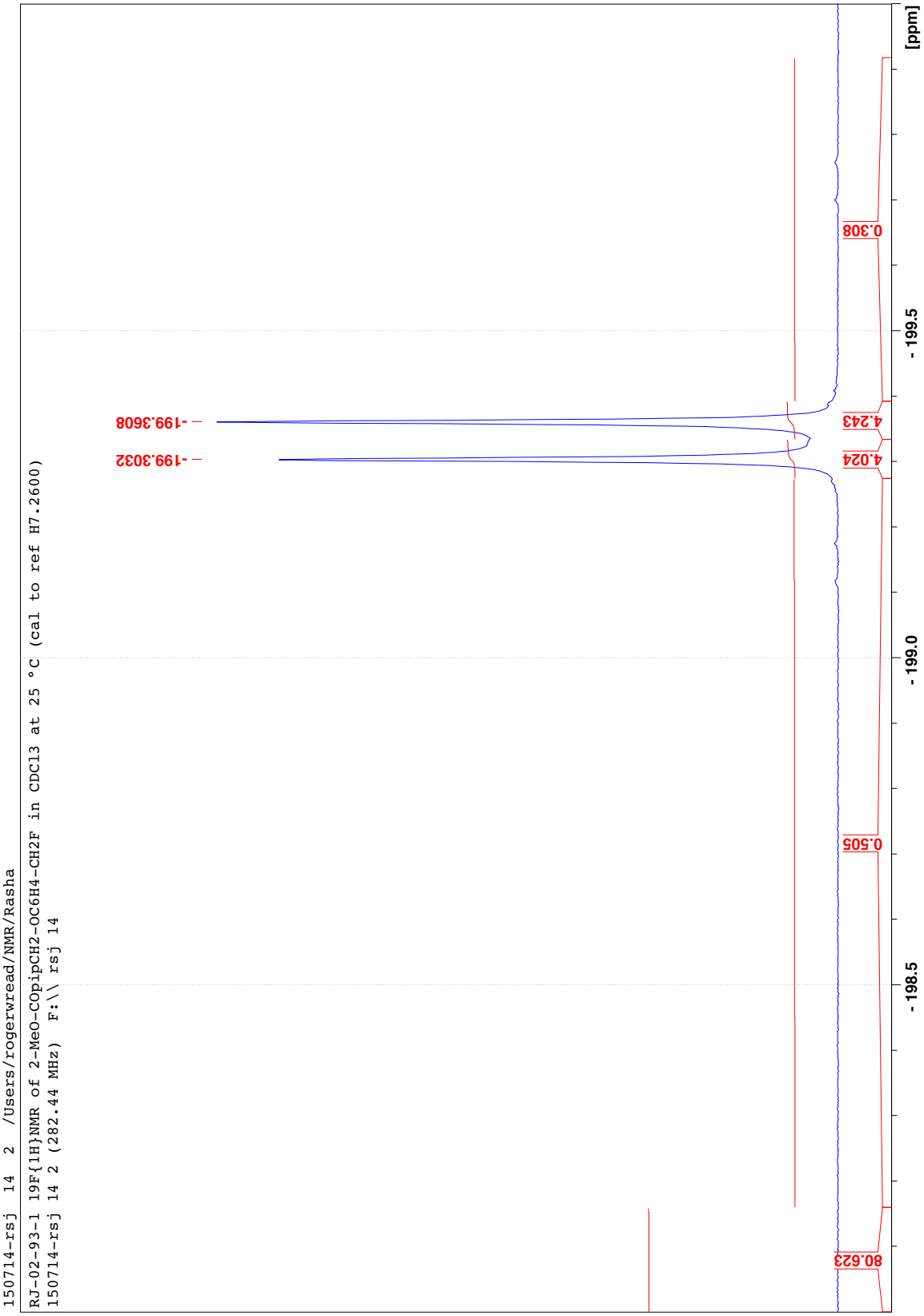
^{19}F NMR at 25 °C



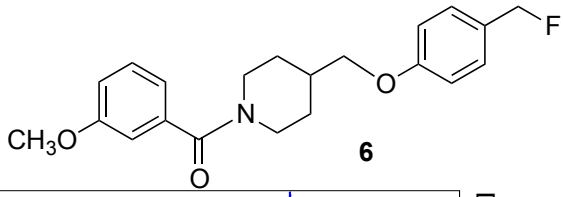
^{19}F NMR at 25 °C (–200 to –198 ppm)



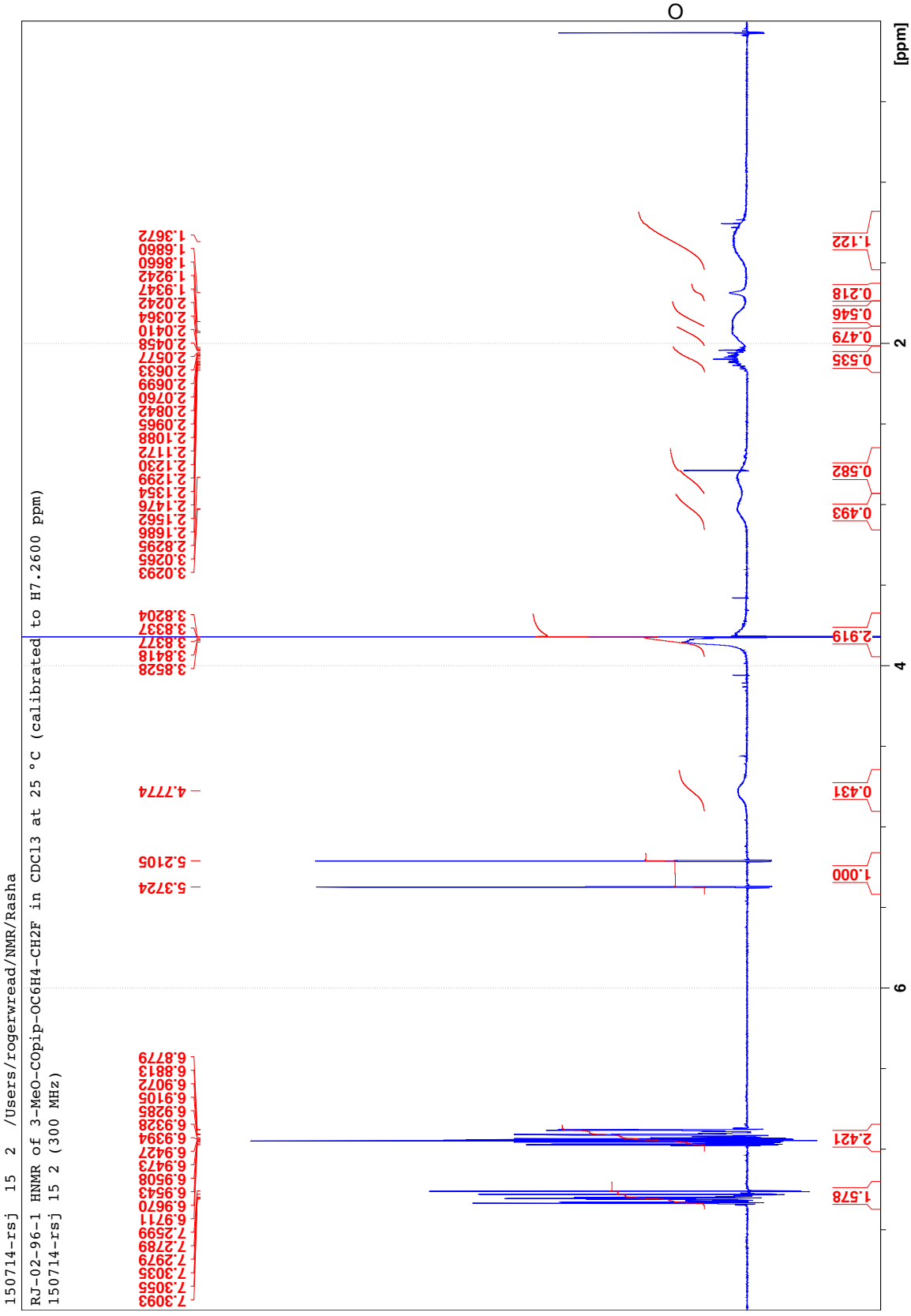
$^{19}F\{^{1}H\}$ NMR at 25 °C (–200 to –198 ppm)



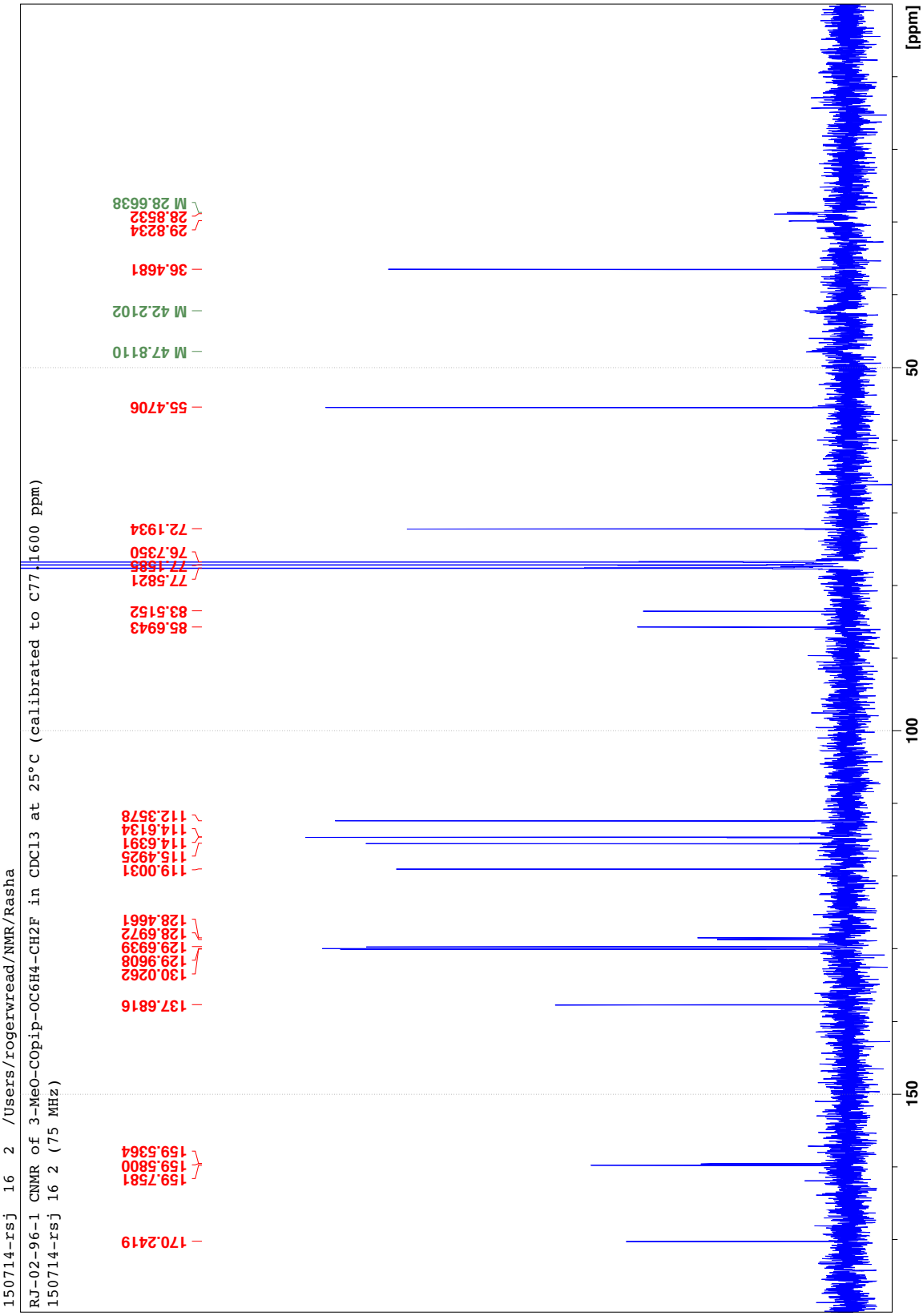
(4-((4-(Fluoromethyl)phenoxy)methyl)piperidin-1-yl)
(3-methoxyphenyl)methanone **6**
^{1}H NMR at 25 °C



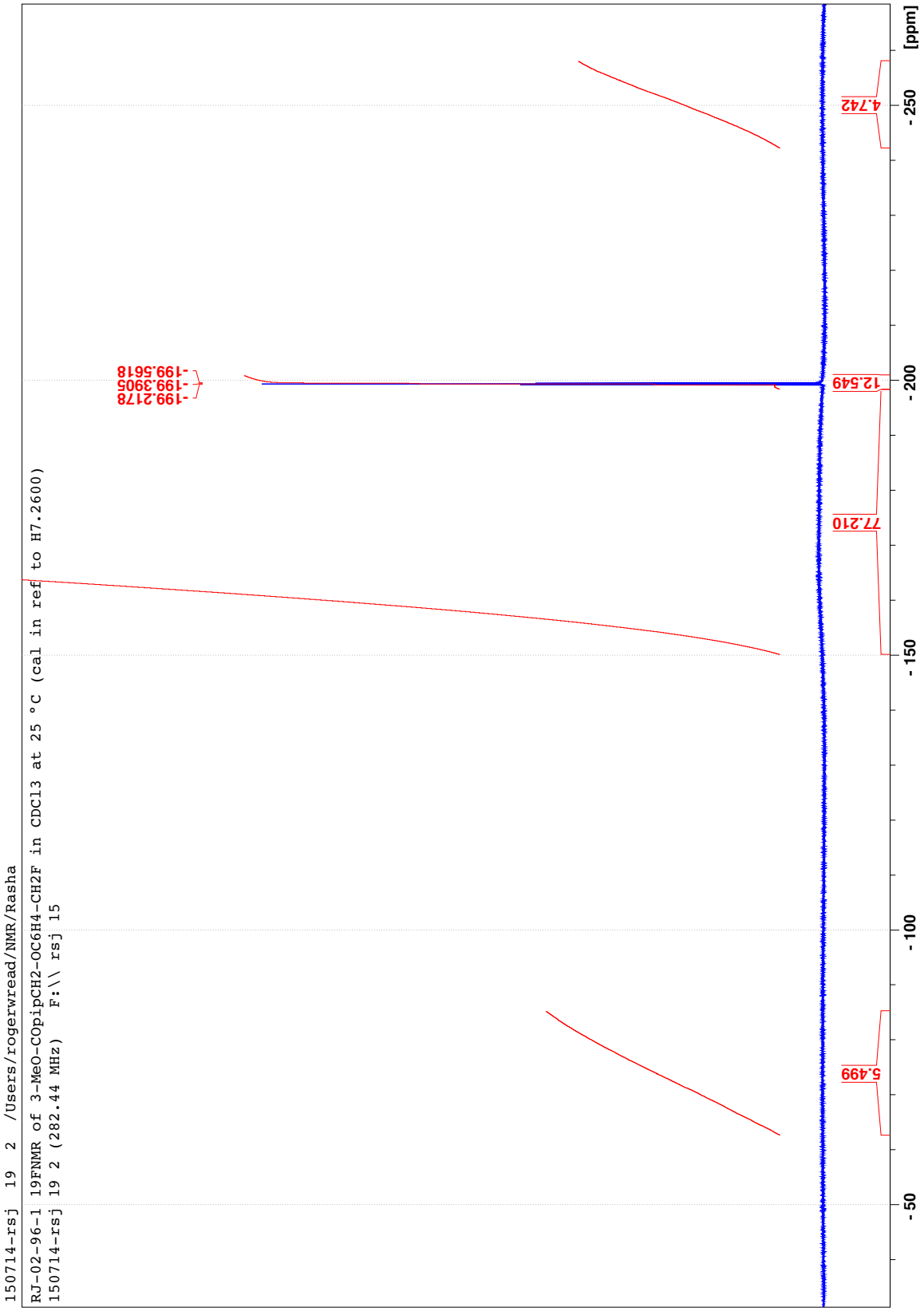
6



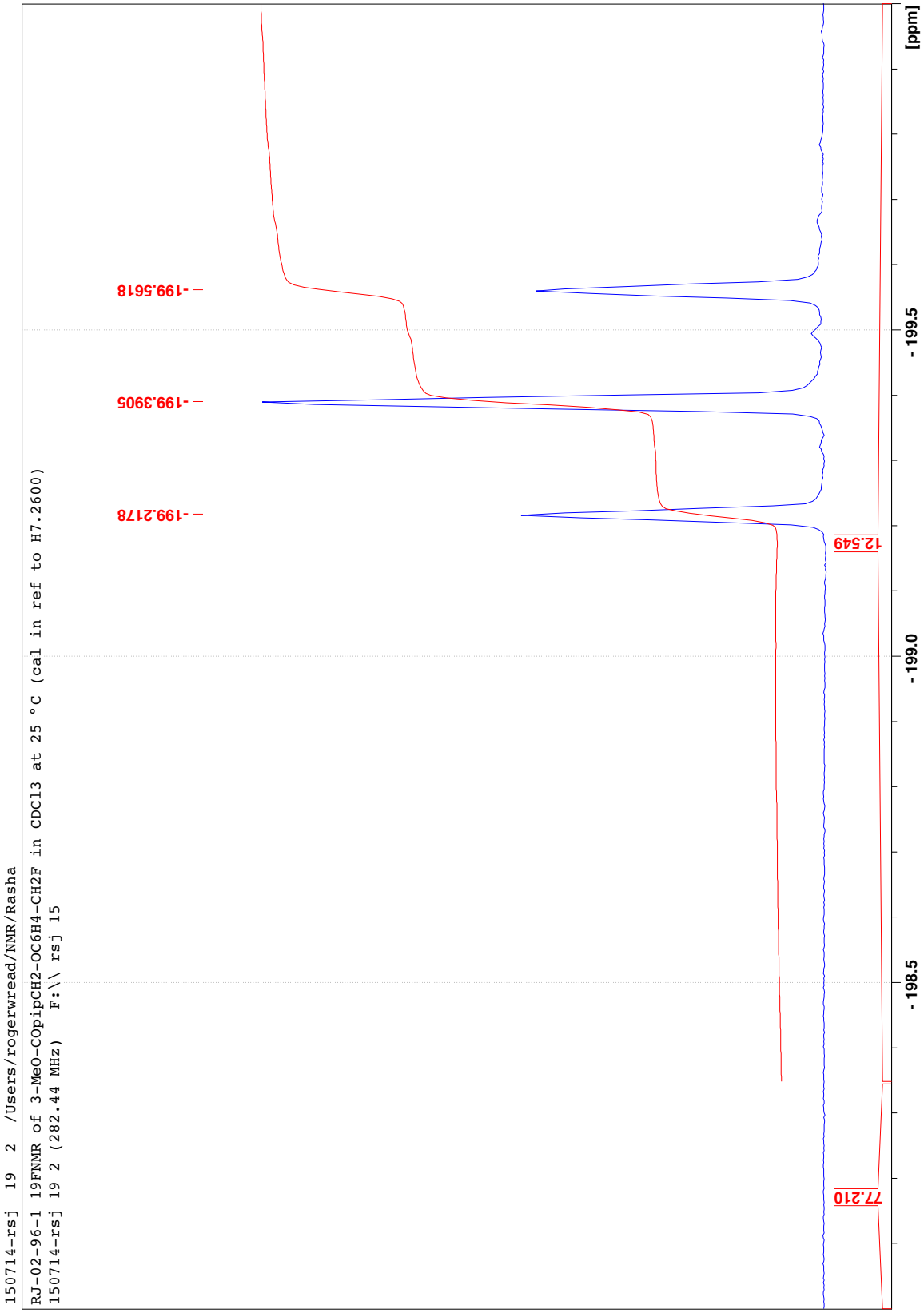
^{13}C NMR at 25 °C



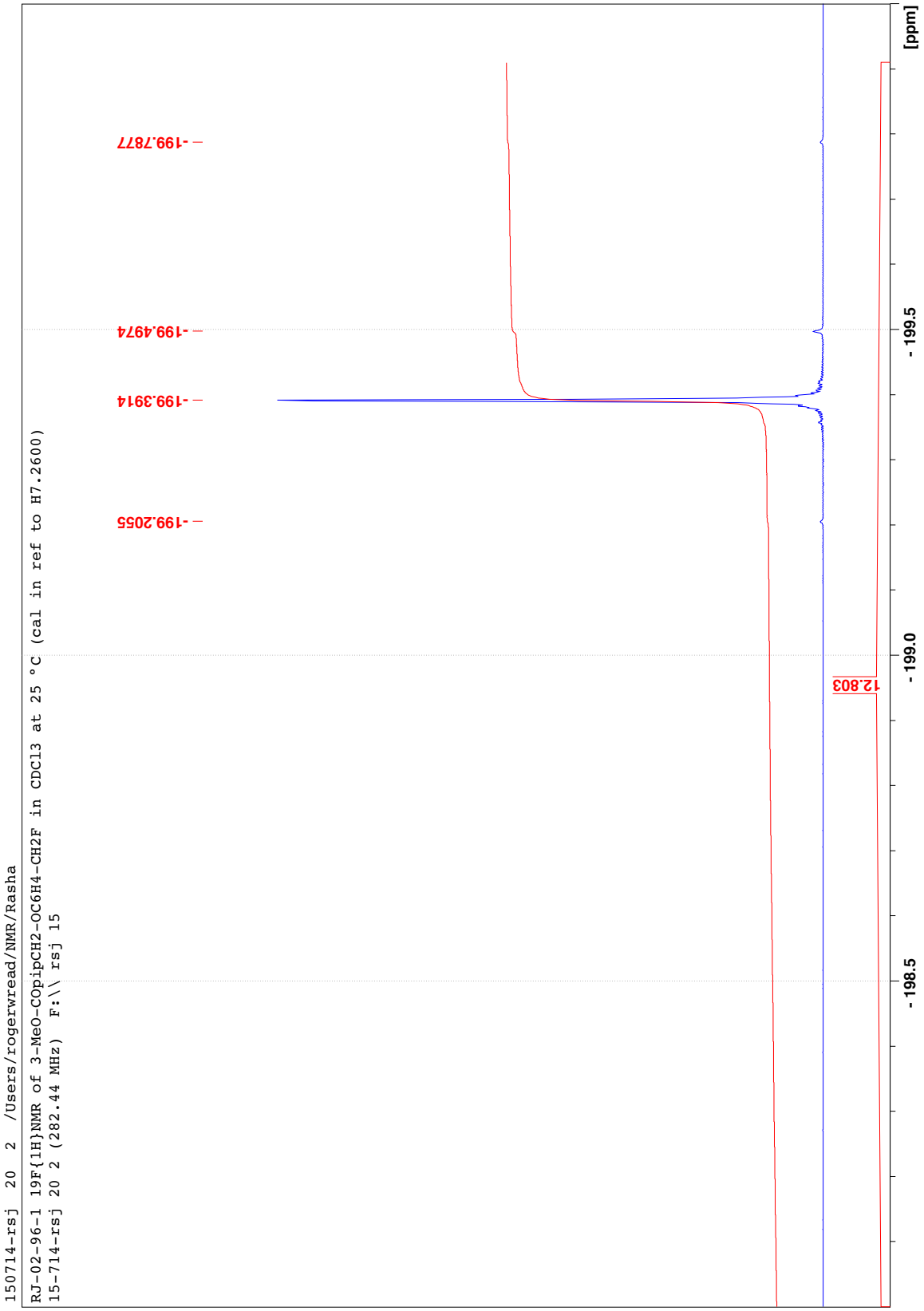
^{19}F NMR at 25 °C



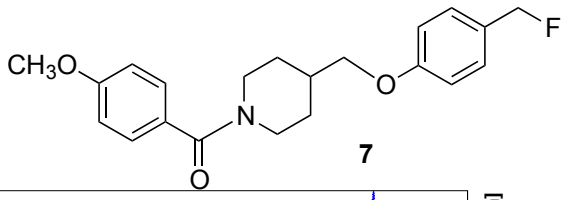
^{19}F NMR at 25 °C (–200 to –198 ppm)



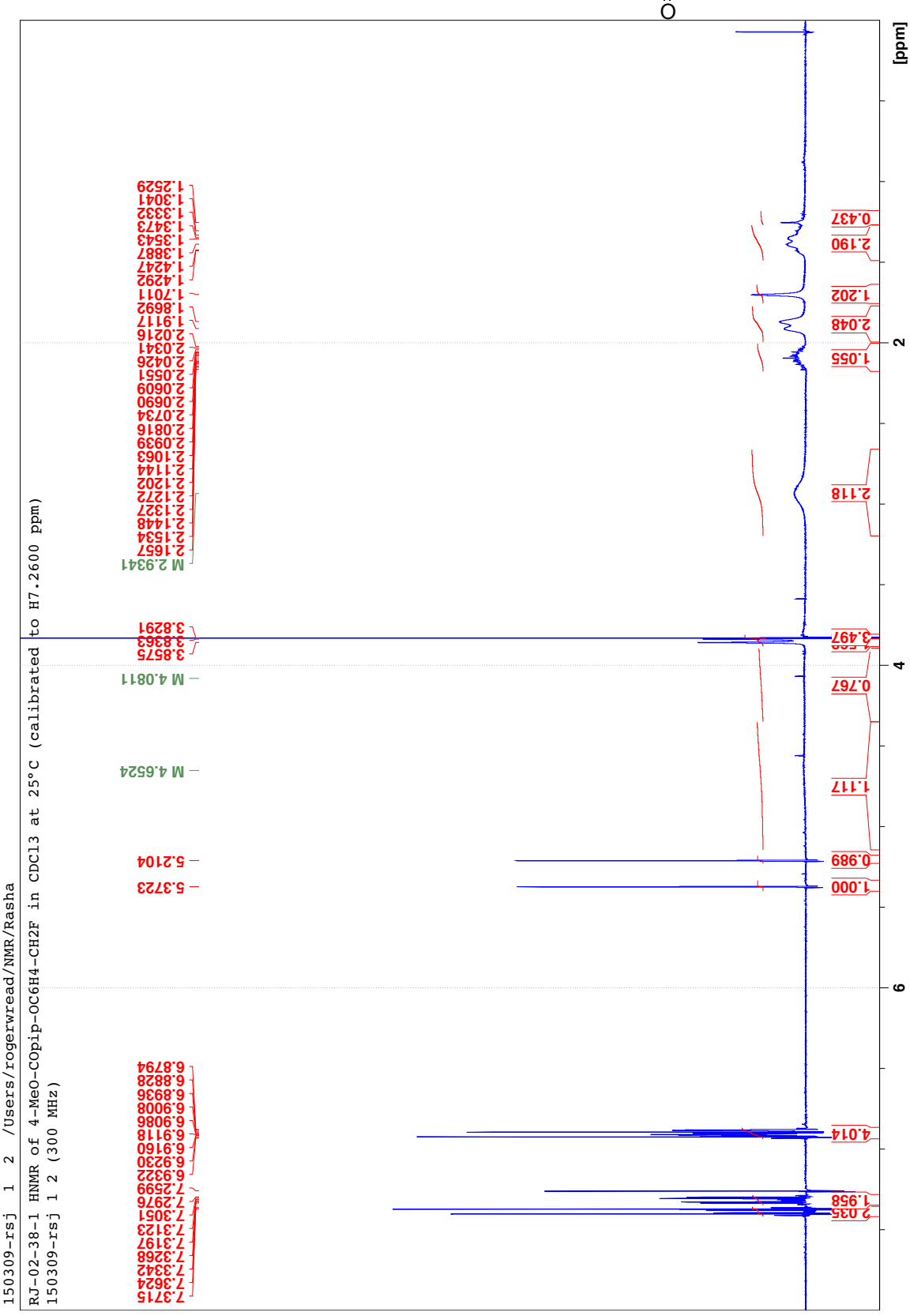
$^{19}F\{^{1}H\}$ NMR at 25 °C (–200 to –198 ppm)



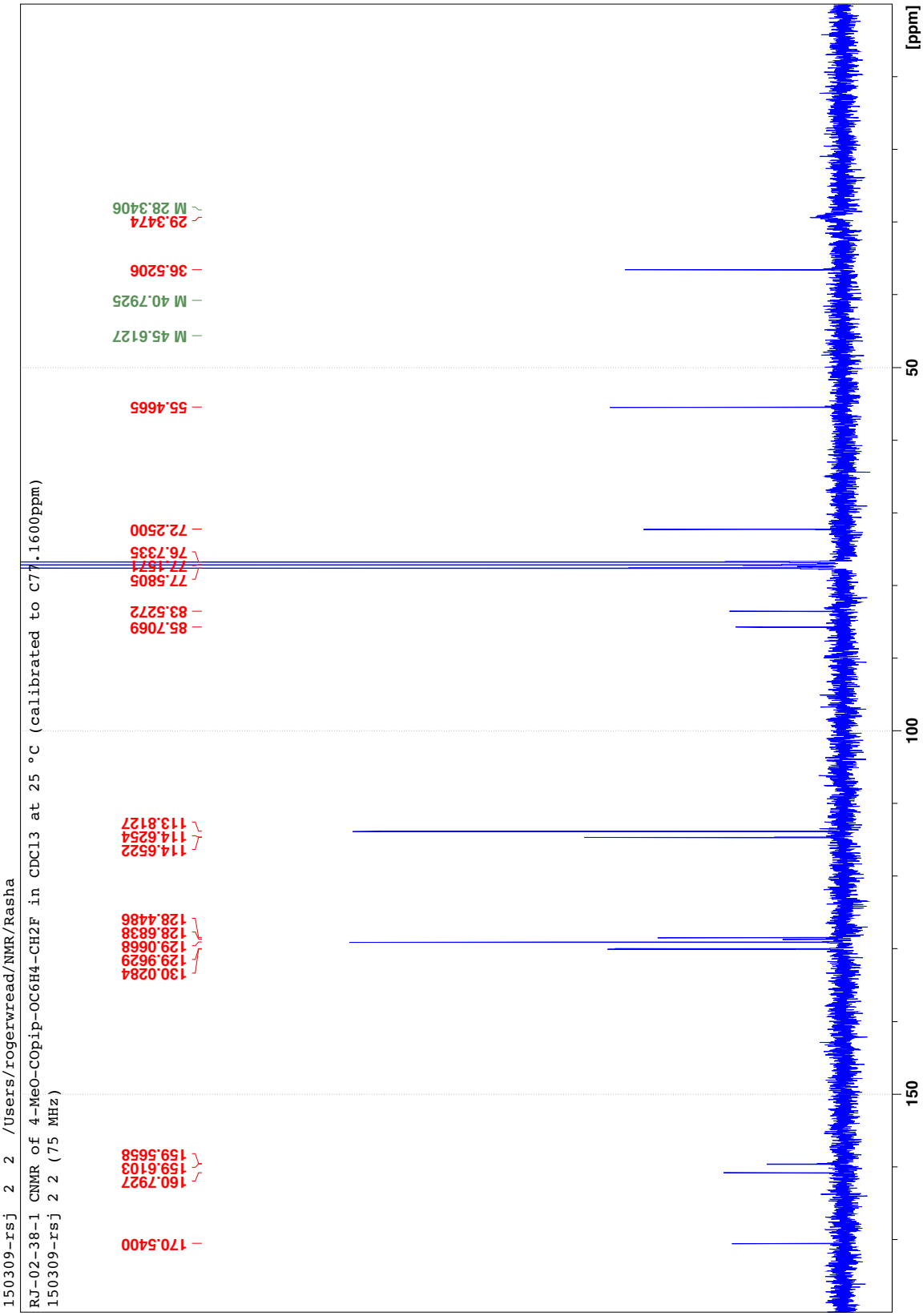
(4-((4-(Fluoromethyl)phenoxy)methyl)piperidin-1-yl)
(4-methoxyphenyl)methanone **7**
^{1}H NMR at 25 °C



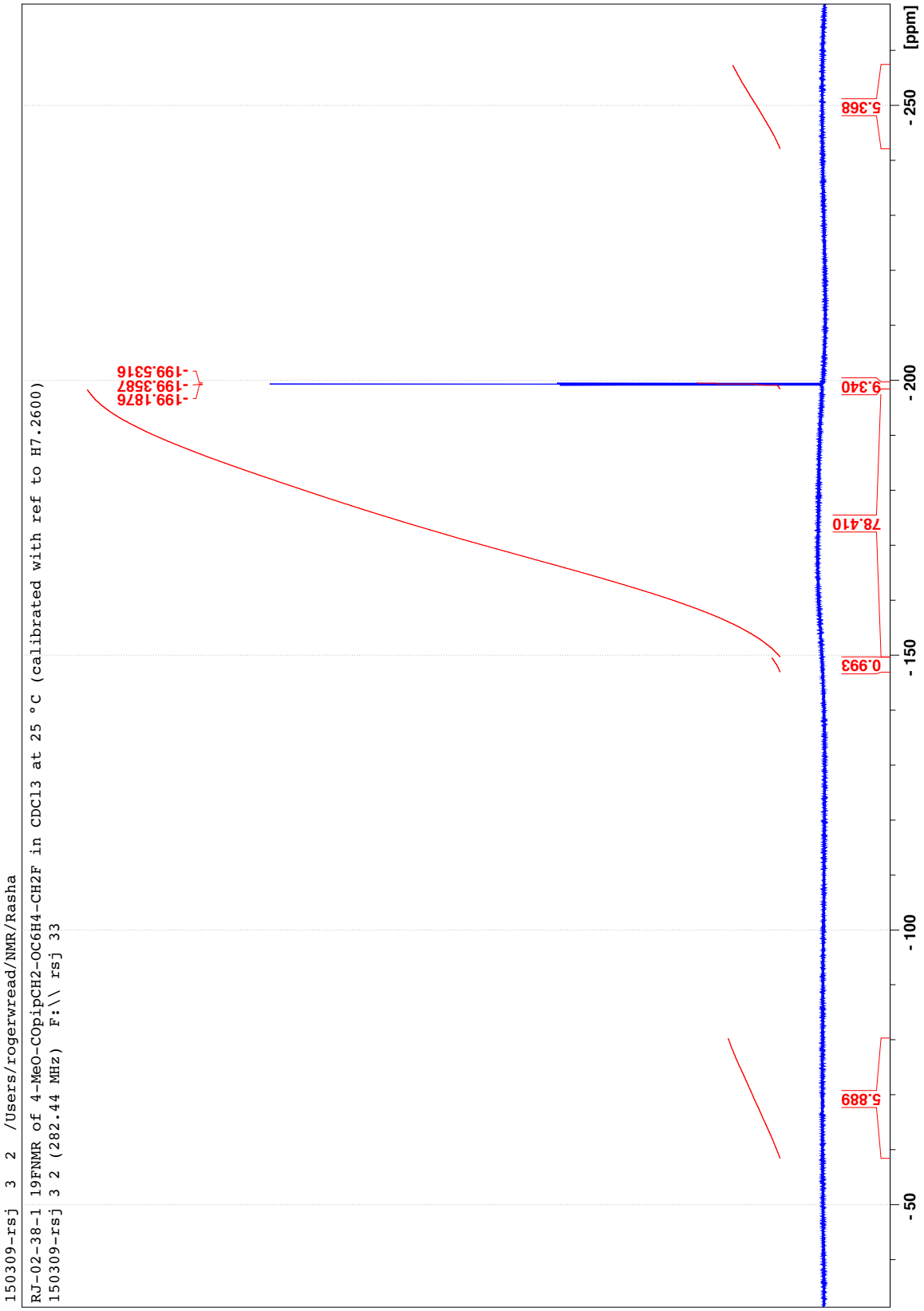
7



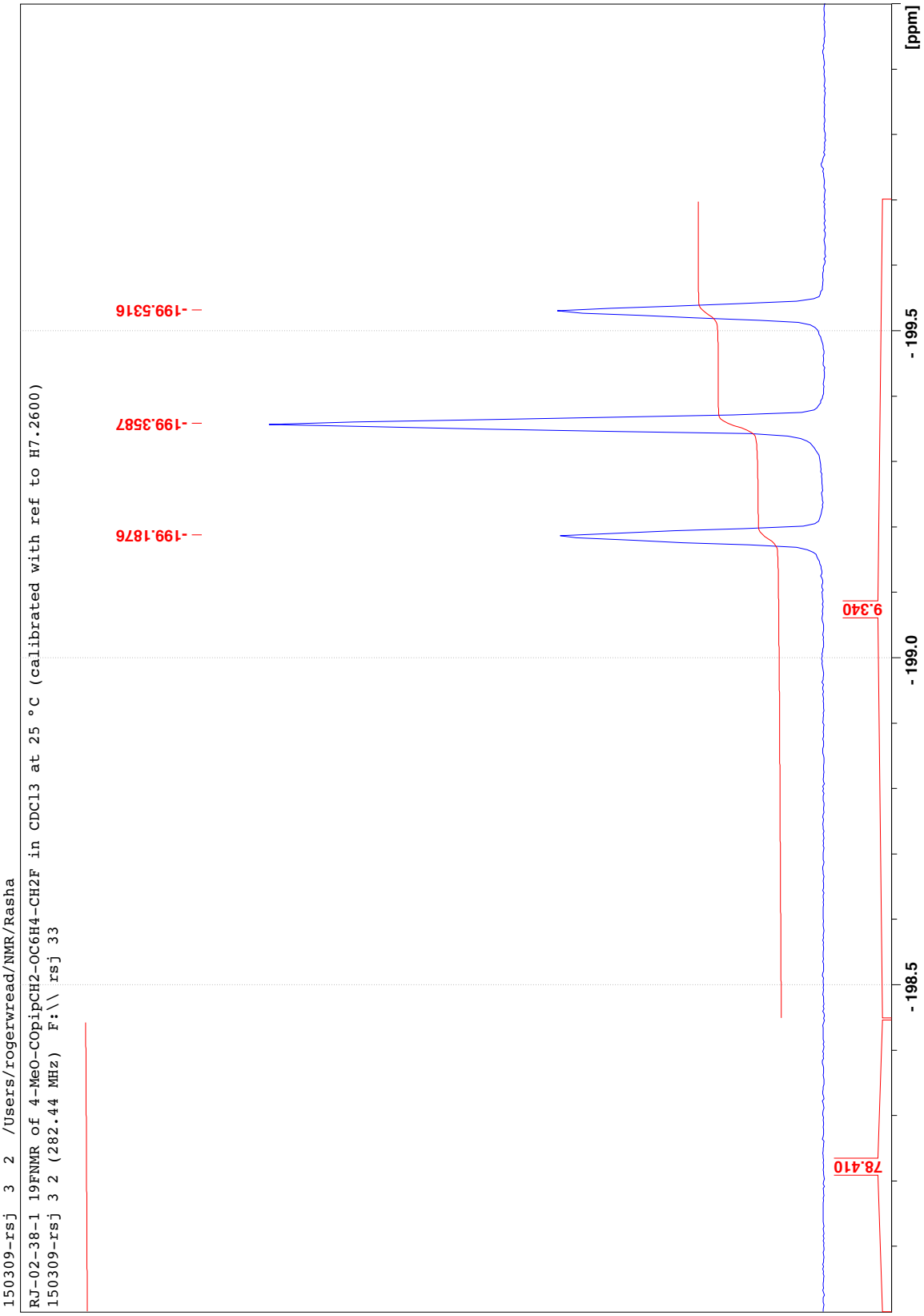
^{13}C NMR at 25 °C



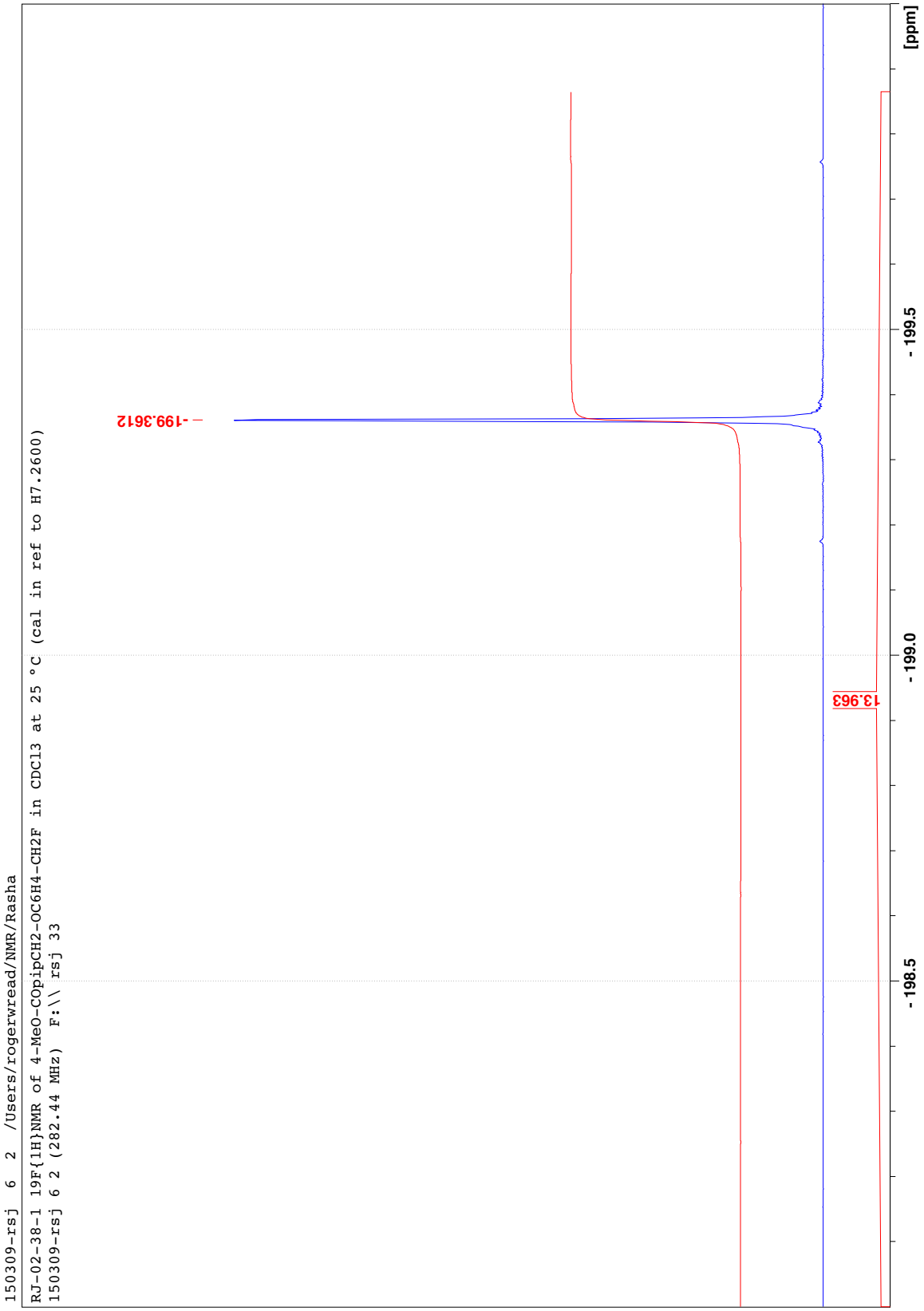
^{19}F NMR at 25 °C



^{19}F NMR at 25 °C (–200 to –198 ppm)

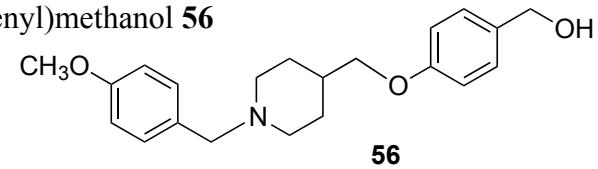


$^{19}F\{^{1}H\}$ NMR at 25 °C (–200 to –198 ppm)

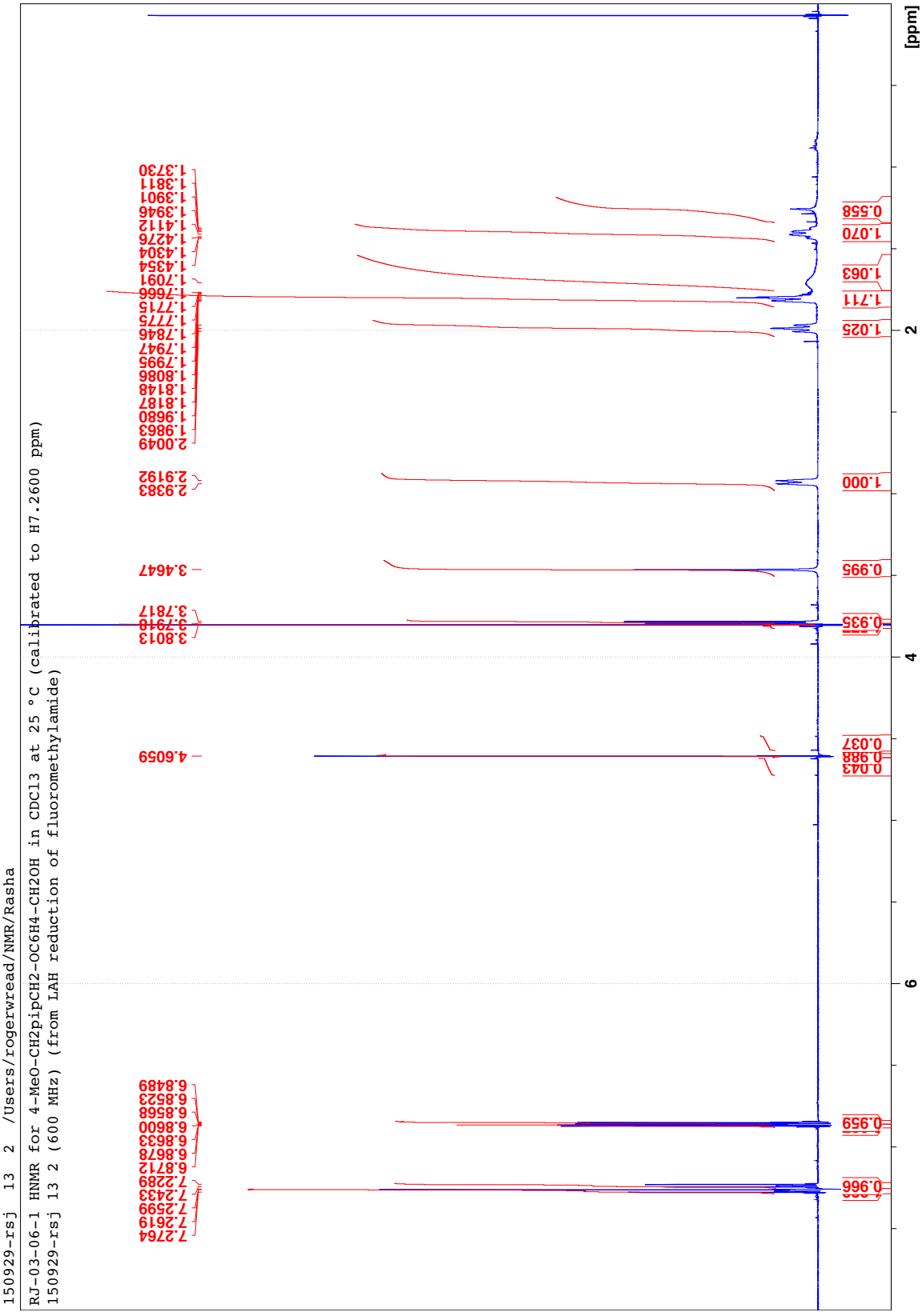


(4-((1-(4-Methoxybenzyl)piperidin-4-yl)methoxy)phenyl)methanol **56**

^{1}H NMR at 25 °C



56



^{13}C NMR at 25 °C