Supporting Information

Exploring noncovalent protease inhibitors for the treatment of SARS and SARS-like coronaviruses

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Table S1. Data collection and refinement statistics

	BtSCoV-Rf1.2004 PLpro/**GRL0617**	BtSCoV-Rf1.2004 PLpro/**37**
Data collection		
Space group	P 2_1 2_1 2	P 6_4 2 2
Wavelength (Å)	1.0	1.0
Cell dimensions		
a, *b*, *c* (Å)	67.4, 67.2, 165.3	176.3, 176.3, 79.8
α, β, γ (°)	90, 90, 90	90, 90, 120
Resolution (Å)	50.00 – 3.15 (3.20 – 3.15)	50.00 – 2.90 (2.95 – 2.90)
R_{pim}*(%)*	9.1 (52.8)	4.9 (27.3)
R_{merge}(%)	25.0 (131.7)	17.9 (97.9)
$cc_{1/2}$	0.756 (0.602)	0.982 (0.762)
$I/\sigma I$	11.6 (1.2)	15.5 (1.5)
Completeness (%)	100.0 (100.0)	99.5 (99.3)
Redundancy	4.4 (3.9)	7.4 (6.4)
Refinement		
Resolution (Å)	45.72 – 3.16 (3.28 – 3.16)	38.62 – 2.89 (3.00 – 2.89)
No. reflections	13391	16525
R_{work}(%)/ R_{free}(%)	23.05/25.90	20.09/23.97
No. atoms		
Protein	4875	2507
Ligand/ion	50	37
Water	49	25
B-factors (Å^2)		
Protein	70.9	66.8
Ligand/ion	48.5	89.6
Water	42.0	60.8
R.m.s deviations		
Bond lengths (Å)	0.002	0.002
Bond angles (°)	0.47	0.48

*Highest resolution shell is shown in parenthesis.

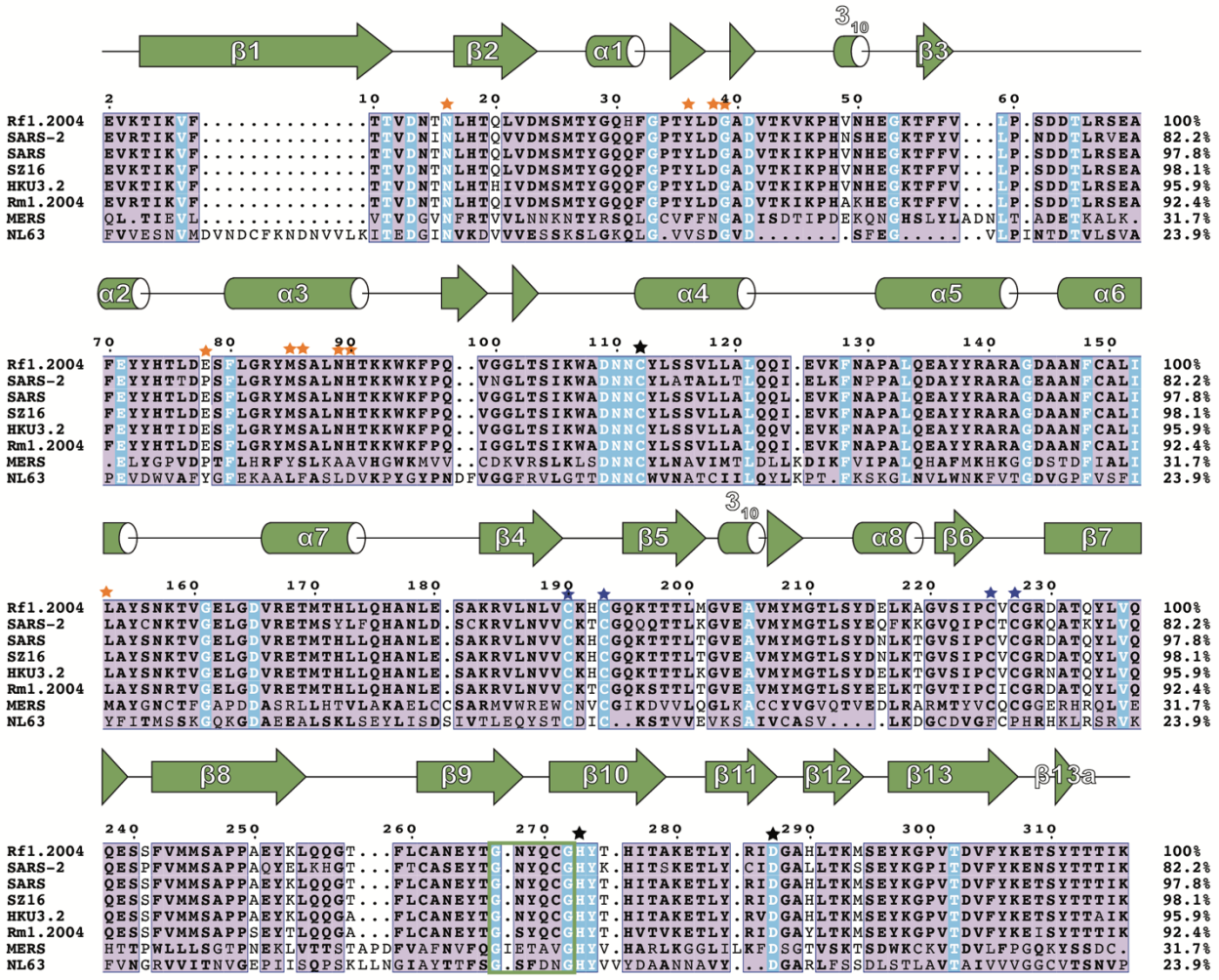


Figure S1. Sequence alignment of PLPs from SARS family coronaviruses.

The PLpro or PLP from BtSCoV-Rf1.2004 (accession number ABD75321.1), SARS-CoV-2 (accession number MN908947.3), SARS-CoV-1 (accession number P0C6U8), SZ16 (accession number AY304488.1), HKU3.2 (accession number AAZ41328.1), Rm1.2004 (accession number ABD75330.1), MERS-CoV (accession number AFS88944), and NL63 (accession number P0C6U6.1). The secondary structure shown is the predicted by DSSP for BtSCoV-Rf1.2004 PLpro. Similarity and alignment calculations were performed using ClustalW. Residue positions that are fully conserved are marked in blue, with those being highly conserved marked in purple. Residues that form the catalytic triad are marked with black stars, while residues forming the zinc finger motif are marked with blue stars. Residues forming interactions between the Ubl domain and thumb domain of PLpros are marked in orange. The BL2 loop is boxed in green.

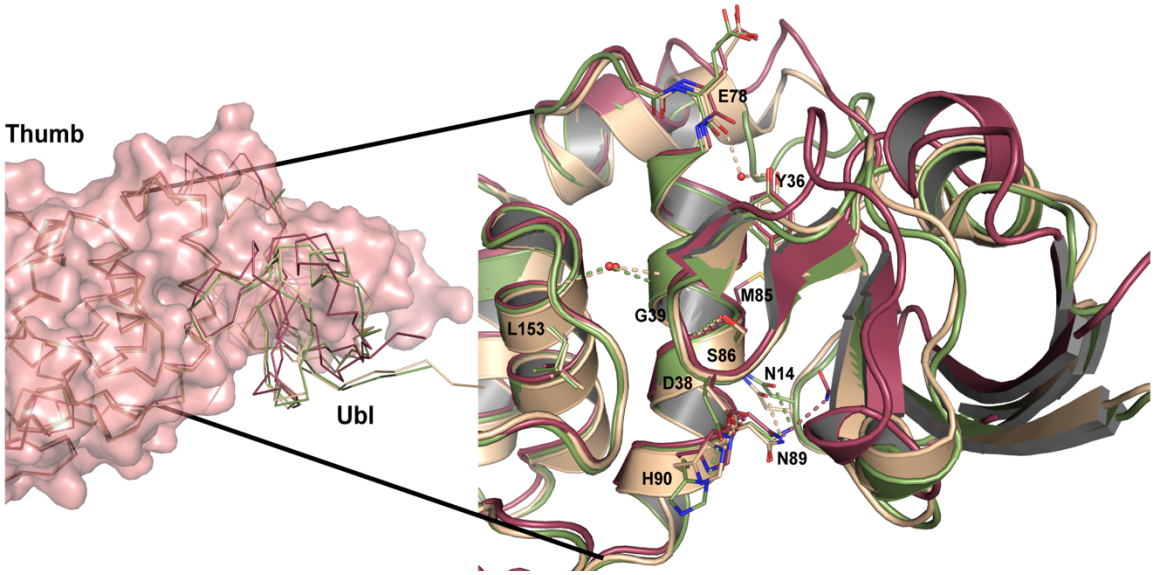


Figure S2. Tucked conformation of PLpro Ubl domains. Variation in position of Ubl domains from SARS-CoV-1 PLpro bound to **GRL0617** (pink surface: PDB 3E9S) compared with SARS-CoV-1 PLpro in complex with mouse ISG15 (tan ribbon/cartoon: PDB 5TL7), BtSCoV-Rf1.2004 PLpro bound to **GRL0617** (green ribbon/cartoon), and BtSCoV-Rf1.2004 PLpro bound to **37** (raspberry ribbon/cartoon).

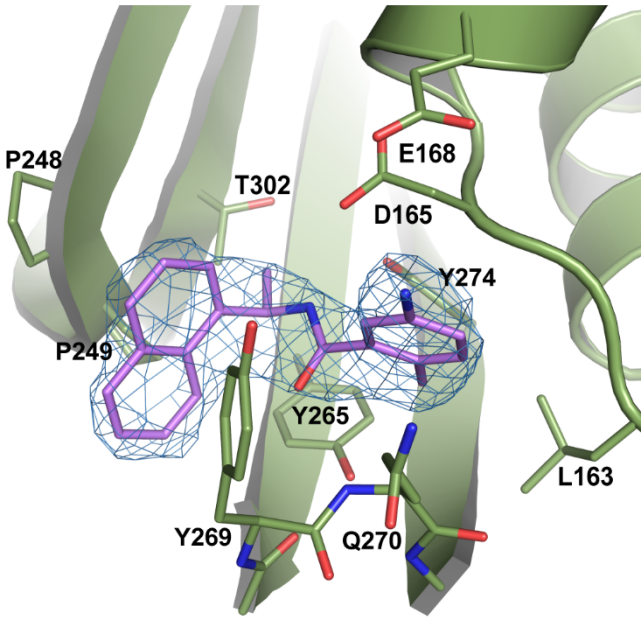


Figure S3. GRL0617 density in the P3/P4 pocket. Inhibitor binding pocket of BtSCoV-Rf1.2004 PLpro (green) in complex with **GRL0617** (purple). A $2F_o$-F_c electron density map is shown contoured at 1σ (blue mesh).

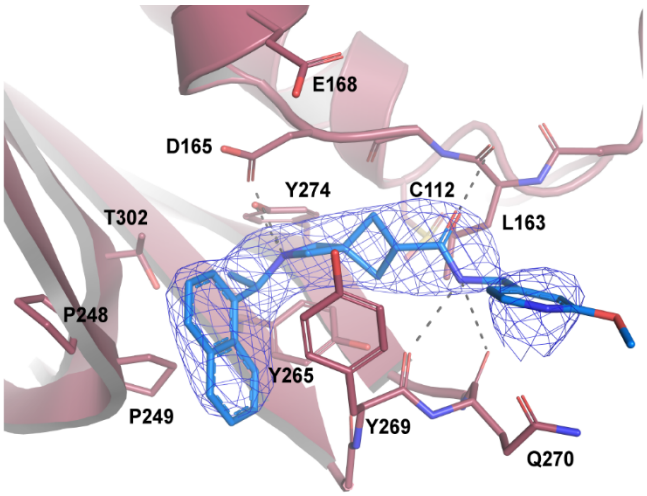


Figure S4. 37 density in the P3/P4 pocket. Inhibitor binding pocket of BtSCoV-Rf1.2004 PLpro (raspberry) in complex with **37** (blue). A $2F_o$-F_c electron density map is shown contoured at 1σ (blue mesh).

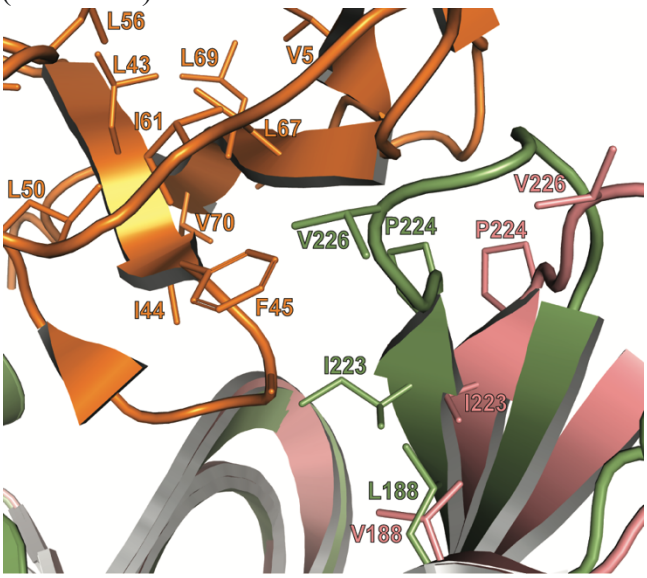


Figure S5. Hydrophobic interactions between Ub and PLpro finger domains.

Close up view of the hydrophobic residues within the finger domain portion of the proximal Ub binding pocket of BtSCoV-Rf1.2004 PLpro (green) and SARS-CoV-1 PLpro (pink). BtSCoV-Rf1.2004 PLpro is overlaid with a structure (PDB 5E6J) of SARS-CoV-1 bound to K48 linked di-Ub (orange).

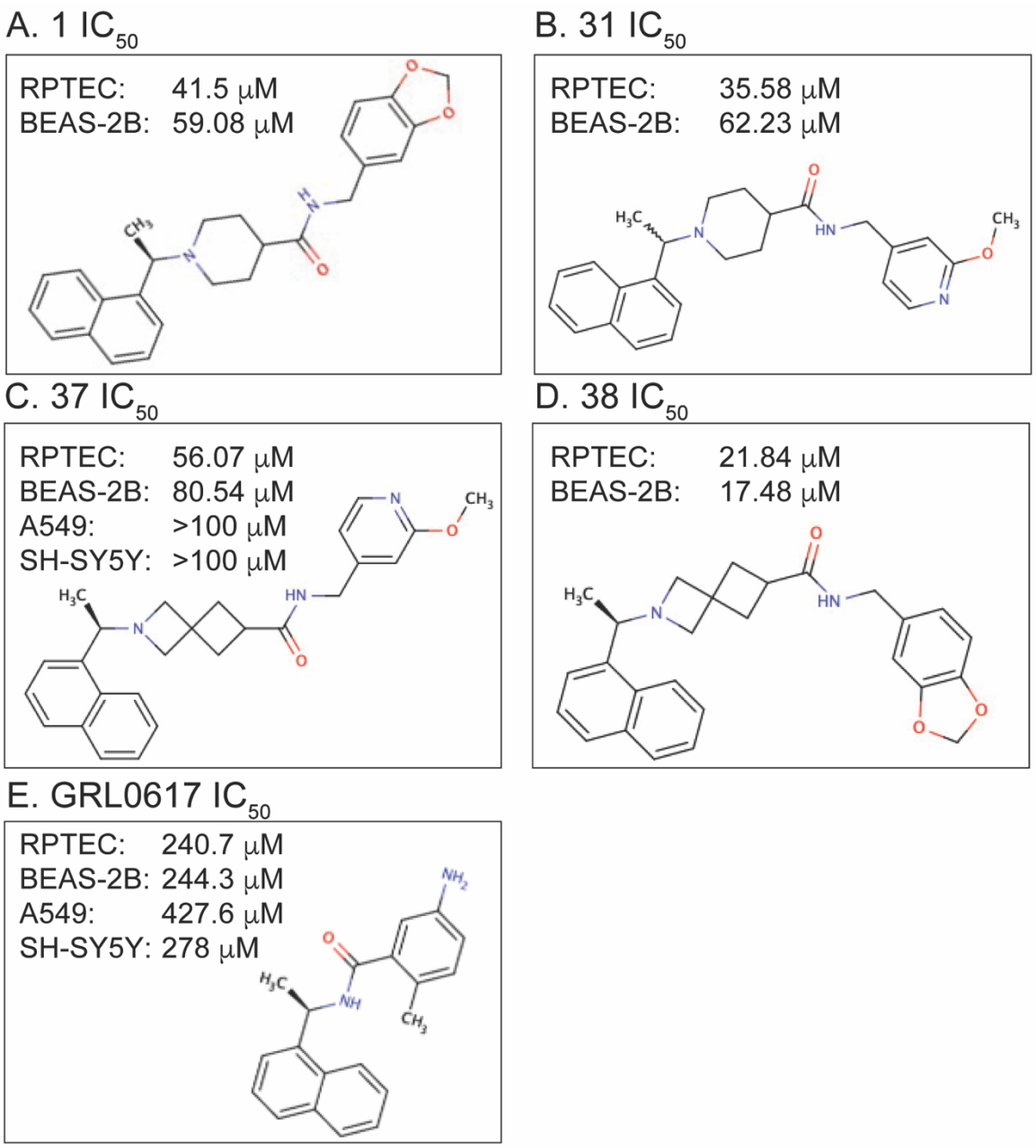


Figure S6: Structure-activity relationship between PLpro inhibitors and their off-target toxicity. (A) **37**, (B) **38**, (C) **31**, (D) **1**, and (E) **GRL0617** structures were matched with the respective IC_{50}s in multiple human cell lines.

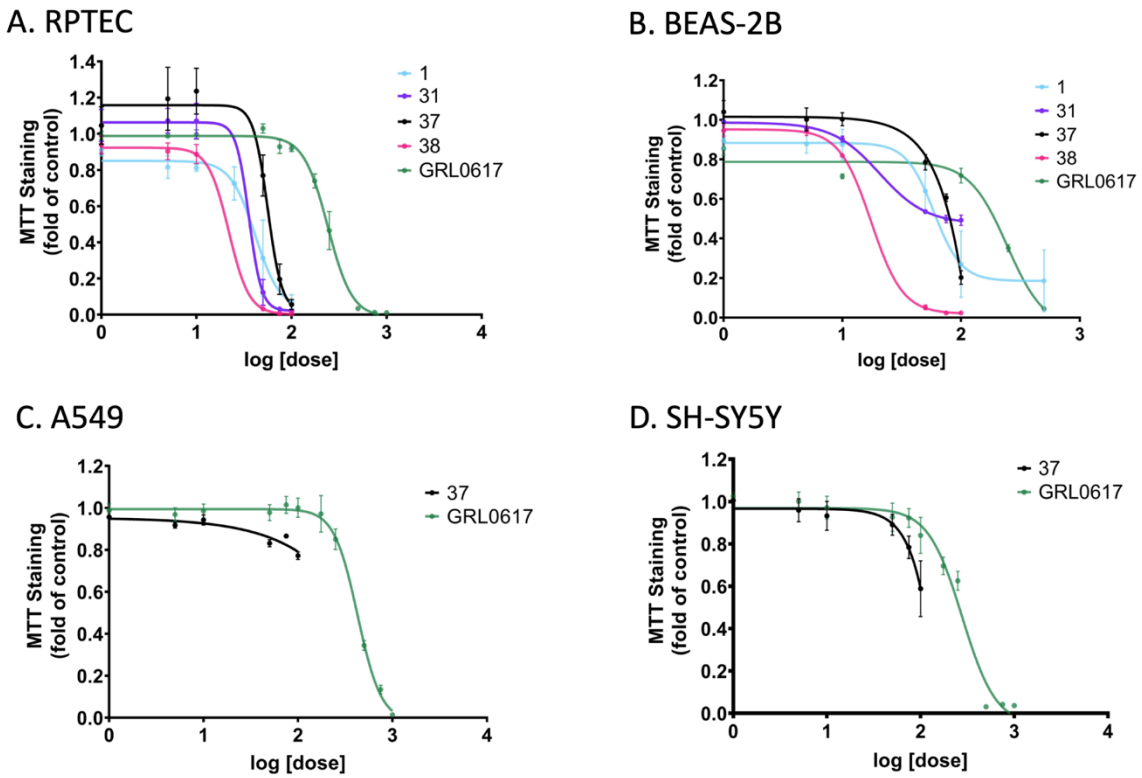


Figure S7. Cell viability of multiple human cell lines upon 48 hr exposure to PLpro inhibitors. MTT linear regression curves of (A) RPTEC, (B) BEAS-2B, (C) A549, and (D) SH-SY5Y cells upon 48 hr exposure to **37**, **38**, **31**, **1**, or **GRL0617**.

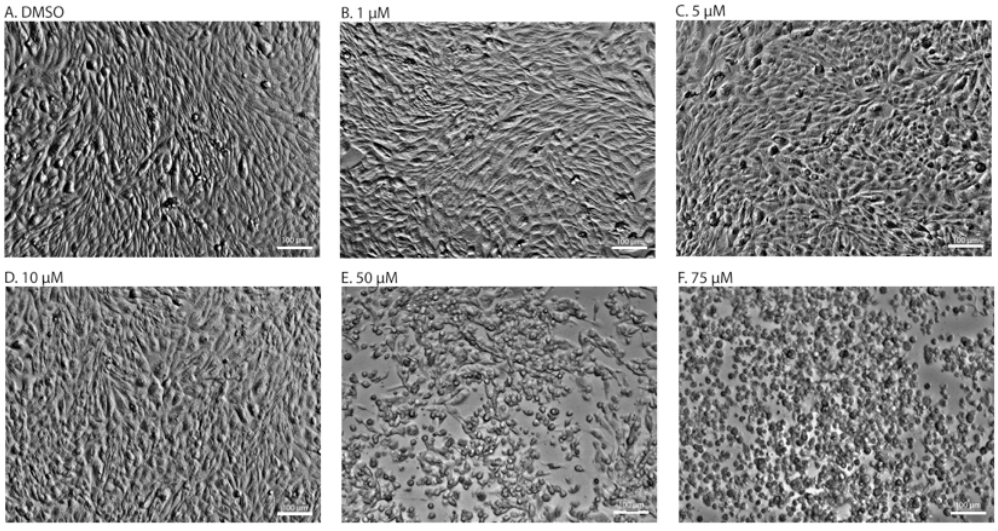


Figure S8. Cellular morphology of RPTECs upon 48 hr 37 exposure. RPTECs were exposed to (A) DMSO or (B) 1 mM, (C) 5 mM, (D) 10 mM, (E) 50 mM, or (F) 75 mM **37** for 48 hr. Scale bar: 100 mm.

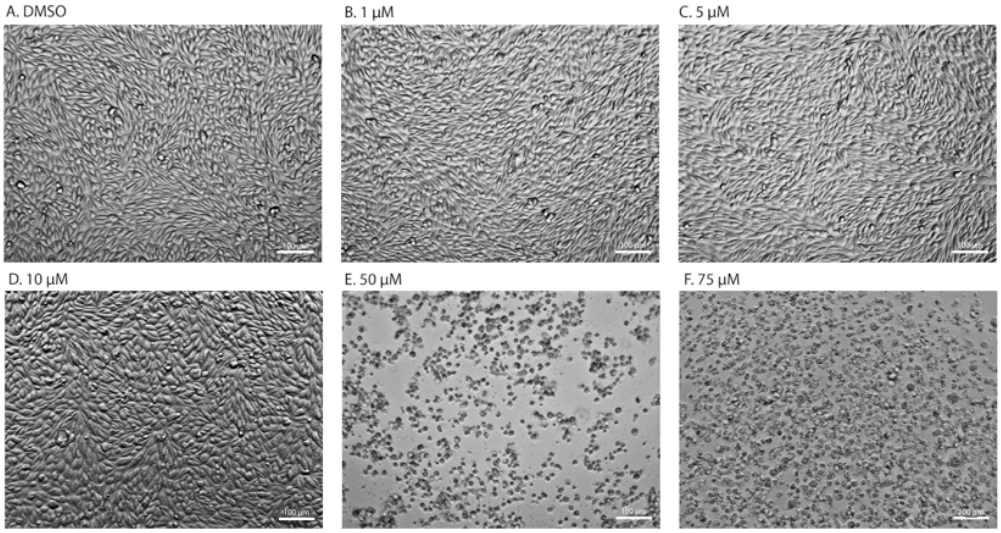


Figure S9. Cellular morphology of RPTECs upon 48 hr 38 exposure. RPTECs were exposed to (A) DMSO or (B) 1 mM, (C) 5 mM, (D) 10 mM, (E) 50 mM, or (F) 75 mM **38** for 48 hr. Scale bar: 100 mm.

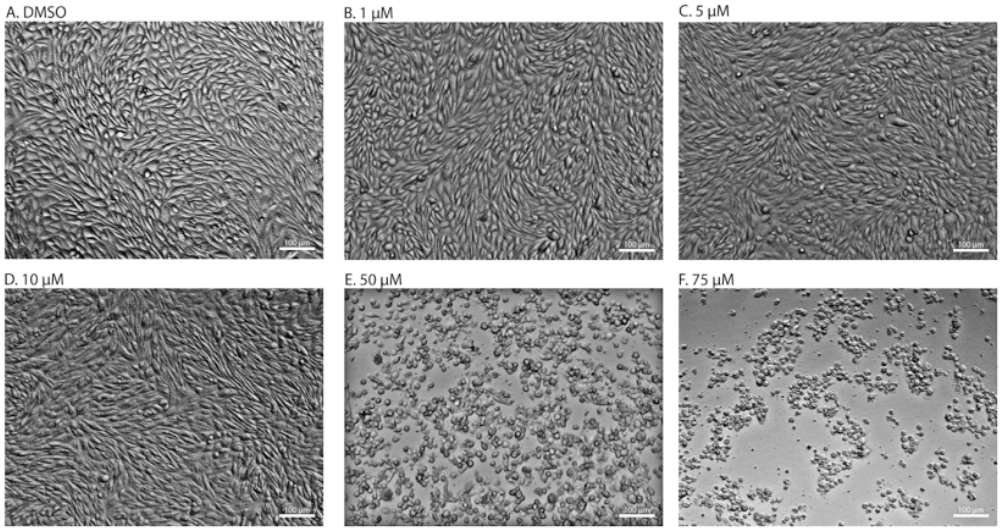


Figure S10. Cellular morphology of RPTECs upon 48 hr 31 exposure. RPTECs were exposed to (A) DMSO or (B) 1 mM, (C) 5 mM, (D) 10 mM, (E) 50 mM, or (F) 75 mM **31** for 48 hr. Scale bar: 100 mm.

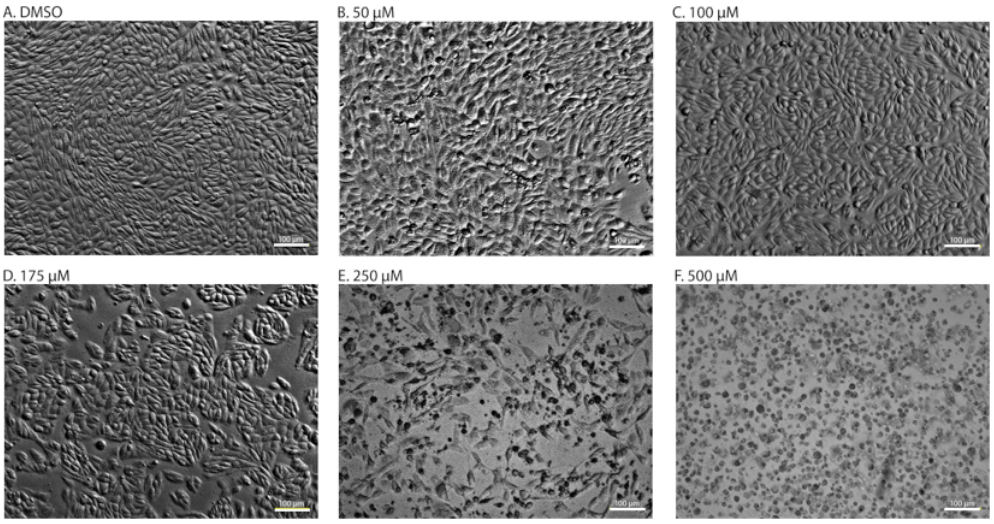


Figure S11. Cellular morphology of RPTECs upon 48 hr GRL0617 exposure. RPTECs were exposed to (A) DMSO or (B) 50 mM, (C) 100 mM, (D) 175 mM, (E) 250 mM, or (F) 500 mM **GRL0617** for 48 hr. Scale bar: 100 mm.

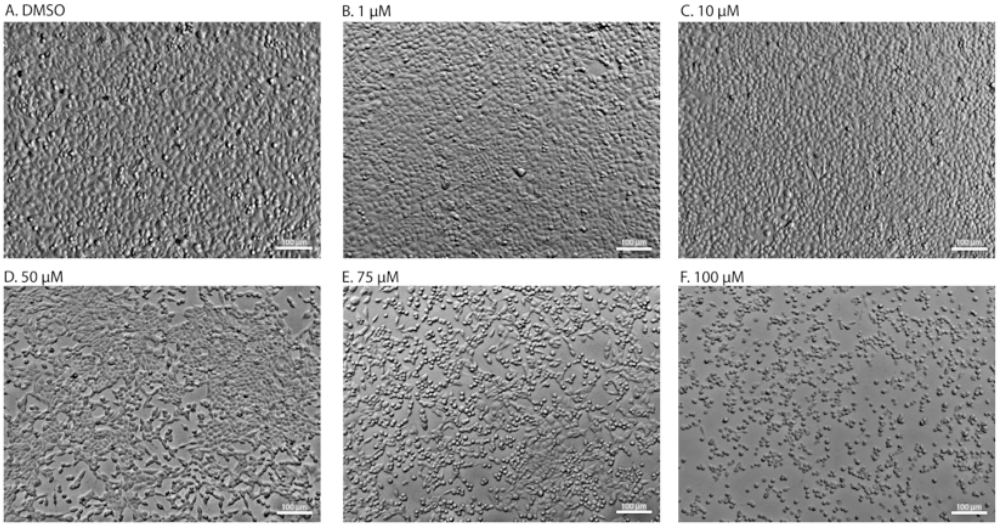


Figure S12. Cellular morphology of BEAS-2Bs upon 48 hr 37 exposure. BEAS-2Bs were exposed to (A) DMSO or (B) 1 mM, (C) 10 mM, (D) 50 mM, (E) 75 mM, or (F) 100 mM **37** for 48 hr. Scale bar: 100 mm.

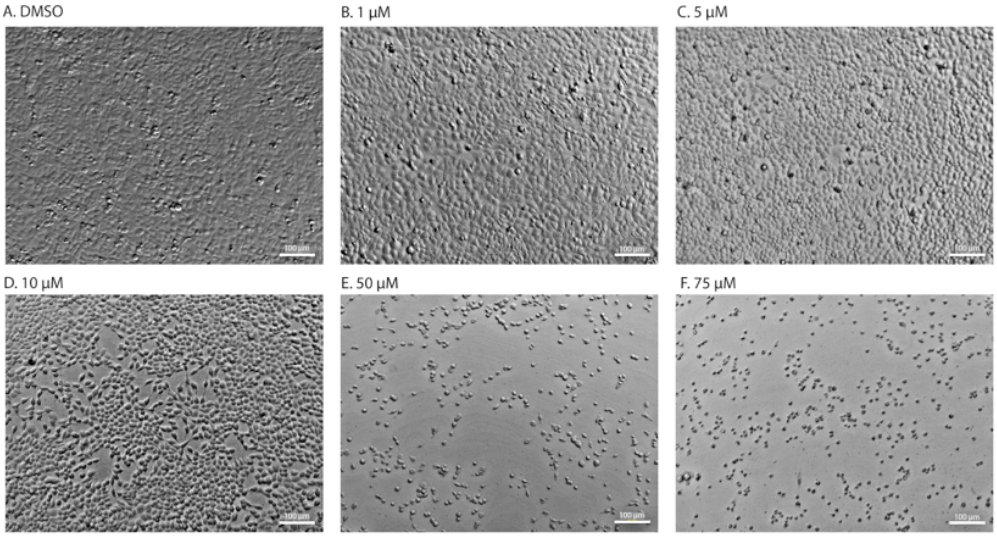


Figure S13. Cellular morphology of BEAS-2Bs upon 48 hr 38 exposure. BEAS-2Bs were exposed to (A) DMSO or (B) 1 mM, (C) 5 mM, (D) 10 mM, (E) 50 mM, or (F) 75 mM **38** for 48 hr. Scale bar: 100 mm.

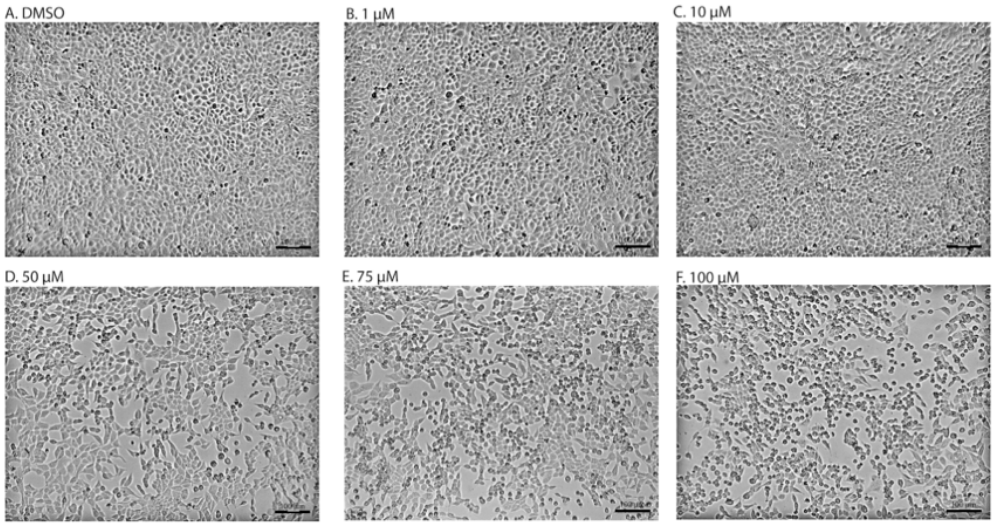


Figure S14. Cellular morphology of BEAS-2Bs upon 48 hr 31 exposure. BEAS-2Bs were exposed to (A) DMSO or (B) 1 mM, (C) 10 mM, (D) 50 mM, (E) 75 mM, or (F) 100 mM **31** for 48 hr. Scale bar: 100 mm.

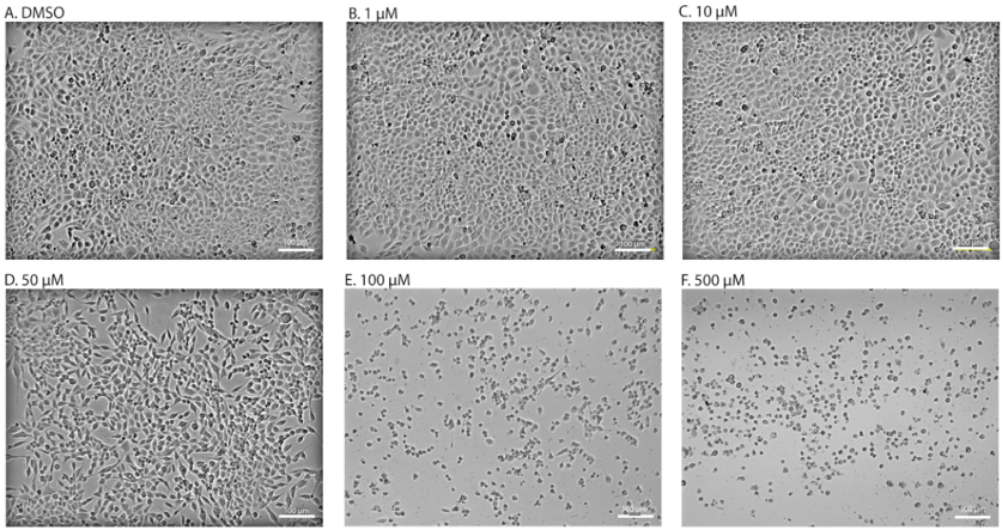


Figure S15. Cellular morphology of BEAS-2Bs upon 48 hr 1 exposure. BEAS-2Bs were exposed to (A) DMSO or (B) 1 mM, (C) 10 mM, (D) 50 mM, (E) 100 mM, or (F) 500 mM **1** for 48 hr. Scale bar: 100 mm.

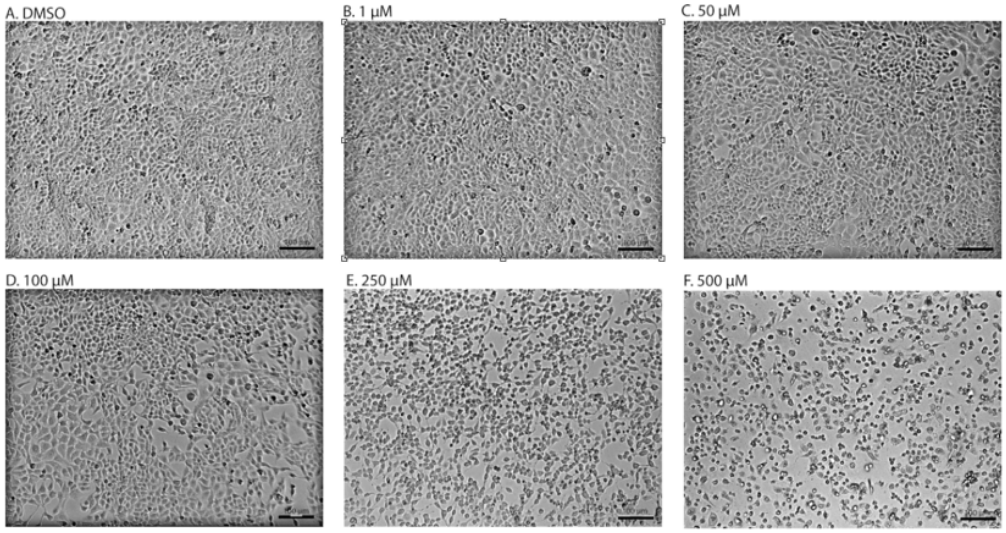


Figure S16. Cellular morphology of BEAS-2Bs upon 48 hr GRL0617 exposure. BEAS-2Bs were exposed to (A) DMSO or (B) 1 mM, (C) 50 mM, (D) 100 mM, (E) 250 mM, or (F) 500 mM **GRL0617** for 48 hr. Scale bar: 100 mm.

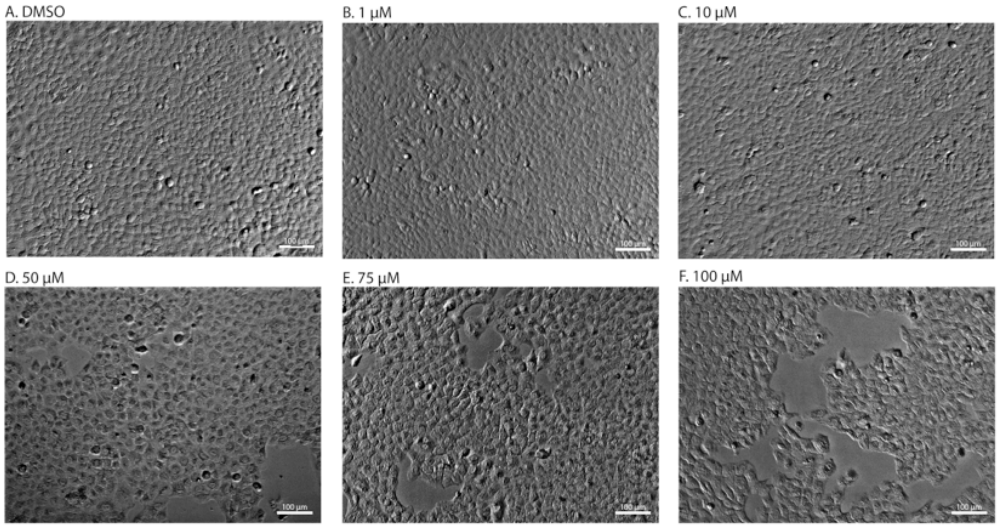


Figure S17. Cellular morphology of A549s upon 48 hr 37 exposure. A549s were exposed to (A) DMSO or (B) 1 mM, (C) 10 mM, (D) 50 mM, (E) 75 mM, or (F) 100 mM **37** for 48 hr. Scale bar: 100 mm.

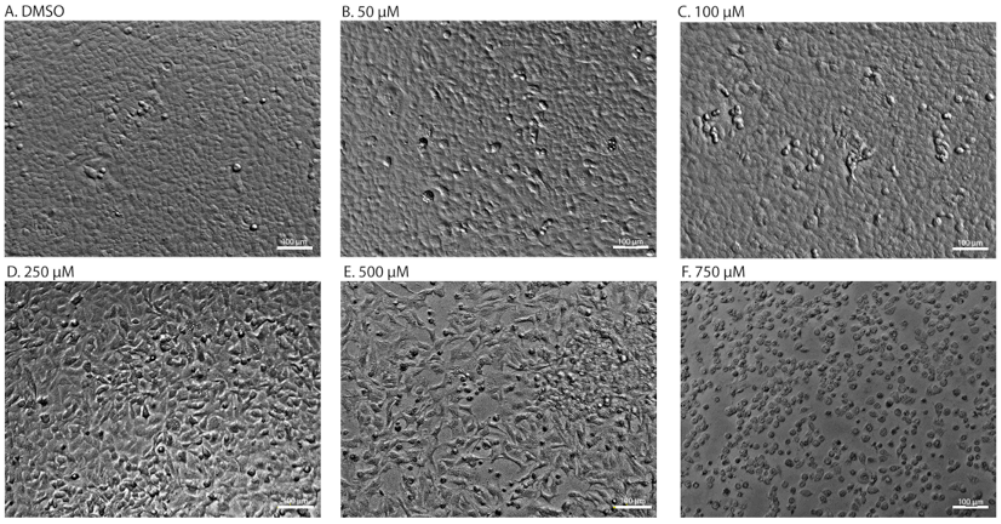


Figure S18. Cellular morphology of A549s upon 48 hr GRL0617 exposure. A549s were exposed to (A) DMSO or (B) 50 mM, (C) 100 mM, (D) 250 mM, (E) 500 mM, or (F) 750 mM **GRL0617** for 48 hr. Scale bar: 100 mm.

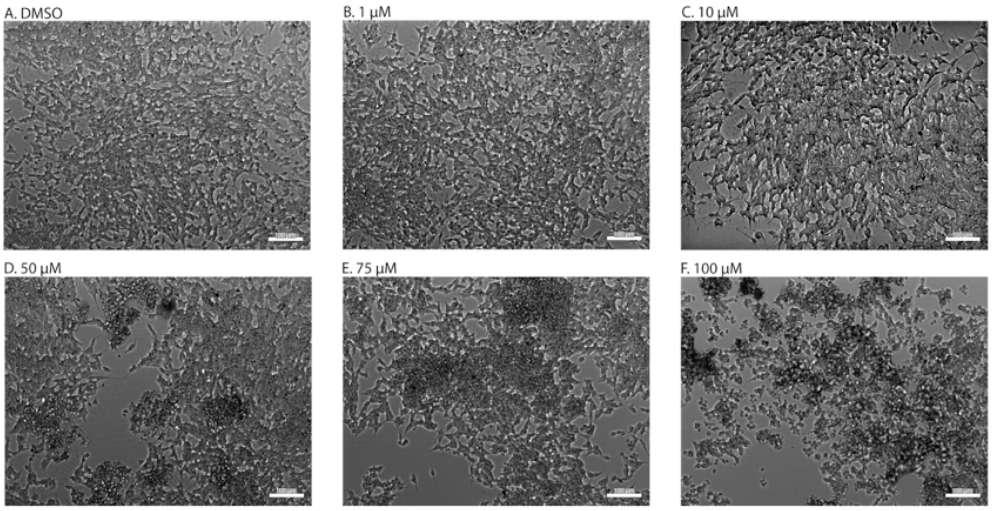


Figure S19. Cellular morphology of SH-SY5Ys upon 48 hr 37 exposure. A549s were exposed to (A) DMSO or (B) 1 mM, (C) 10 mM, (D) 50 mM, (E) 75 mM, or (F) 100 mM **37** for 48 hr. Scale bar: 100 mm.

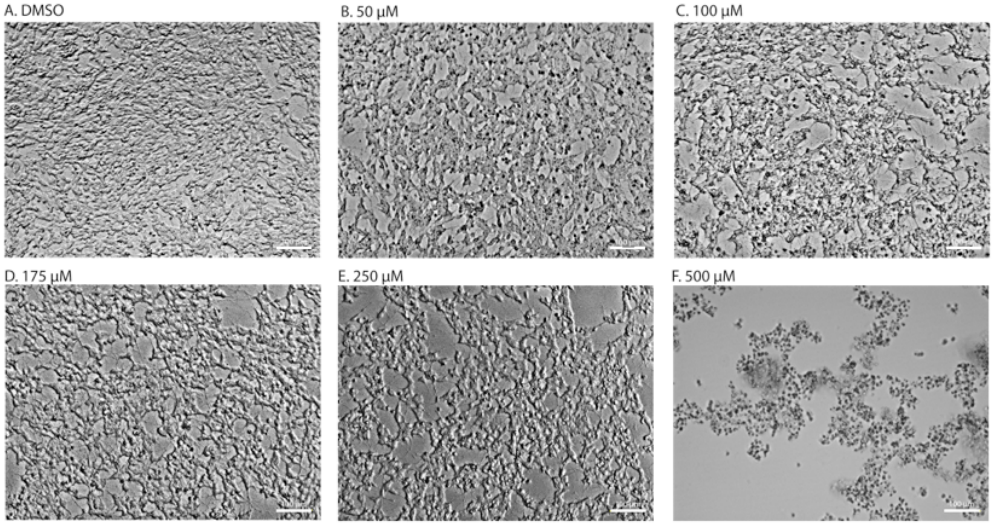
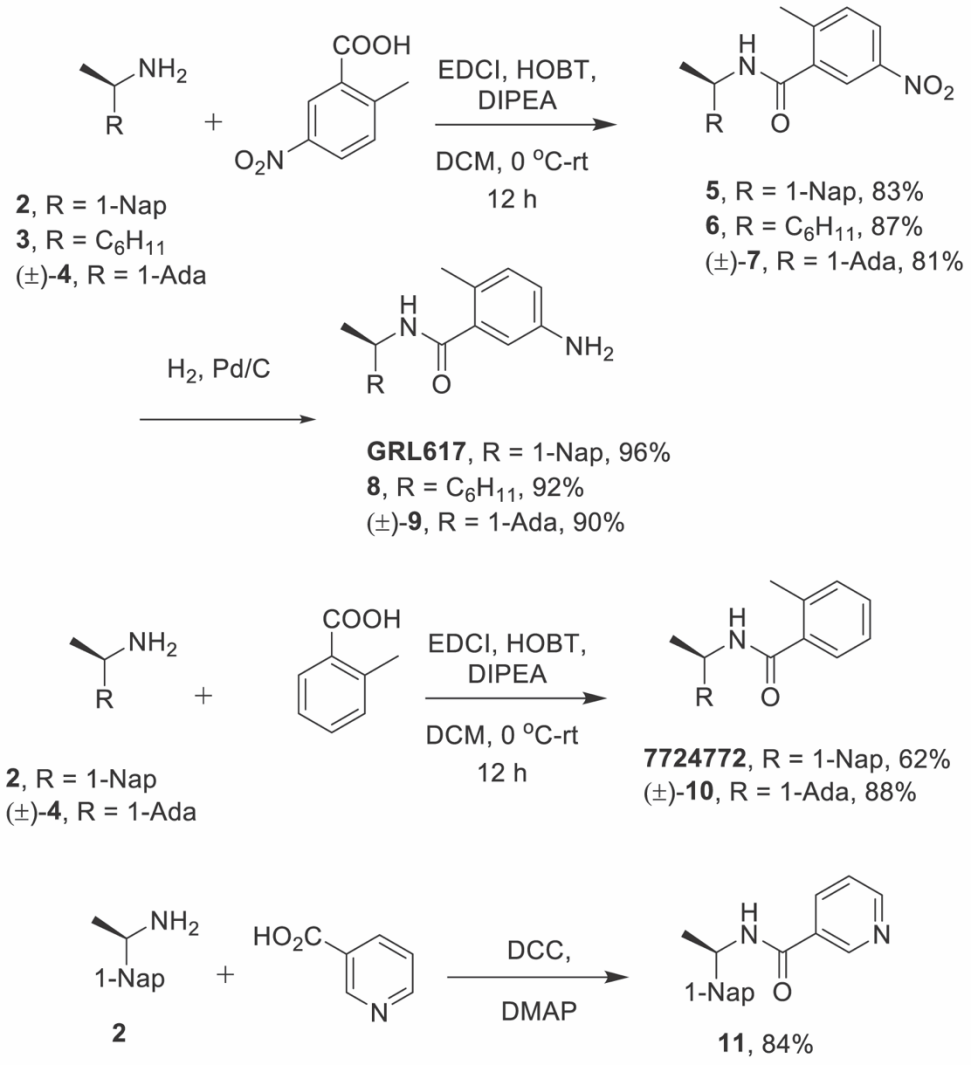


Figure S20. Cellular morphology of SH-SY5Ys upon 48 hr GRL0617 exposure. RPTECs were exposed to (A) DMSO or (B) 50 mM, (C) 100 mM, (D) 175 mM, (E) 250 mM, or (F) 500 mM **GRL0617** for 48 hr. Scale bar: 100 mm.

SCHEMES

We began with a brief exploration of the hydrophobic easter part of the binding domain by the synthesis of analogs of series I compounds in which the naphthalene unit was exchanged for a cyclohexyl or 1-adamantanyl moiety. We first prepared an authentic sample of **GRL0617** coupling *R*-1-(1-naphthyl)ethylamine **2** with 2-methyl-5-nitrobenzoic acid followed by hydrogenolytic reduction of the intermediate nitroarene **5**. Carbodiimide coupling of *R*-1-cyclohexylethylamine **3** with 2-methyl-5-nitrobenzoic acid gave the amide **6**, which was reduced with hydrogen over palladium on charcoal to afford **8**. Similarly, (±)-1-(1-adamantanyl)ethylamine **4** was condensed with 2-methyl-5-nitrobenzoic acid to give **7**, hydrogenolysis of which afforded **9**. 2-Methylbenzoic acid also was coupled *R*-1-(1-naphthyl)ethylamine **2** and (±)-1-(1-adamantanyl)ethylamine **4** to give an authentic sample of (±)-**7724772**[1] and **10**. A further analog, **11** of **GRL0617** in which the 5-amino-2-methylbenzamide moiety was replaced by a nicotinamide group was also prepared at this time through carbodiimide coupling (Scheme S1).

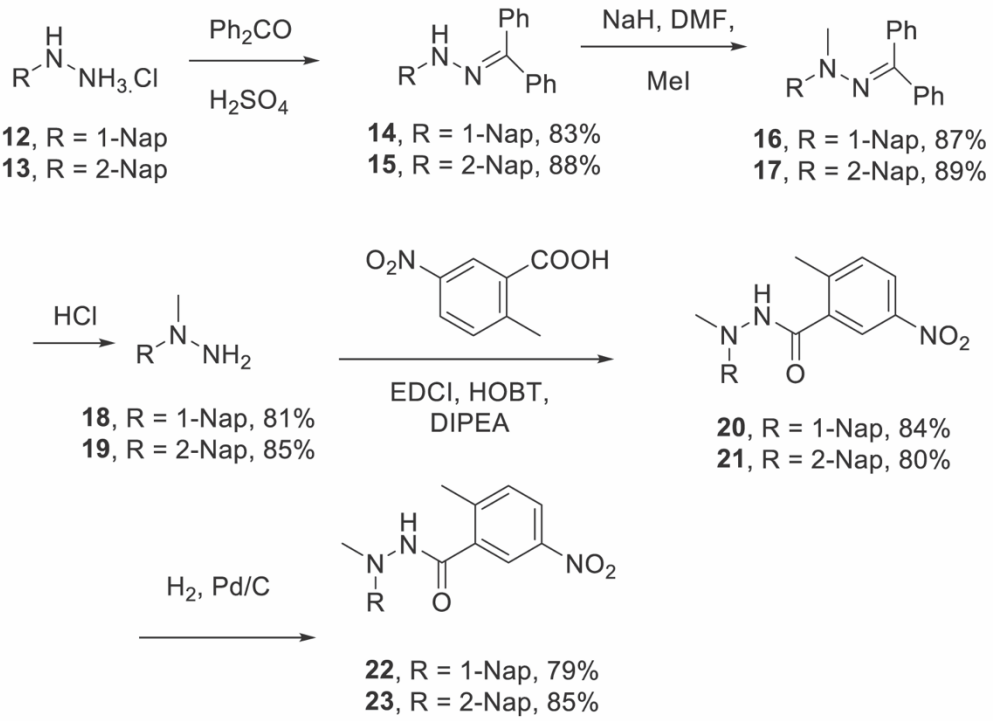
Scheme S1. Synthesis of Compounds GRL0617, 8, 9, 7724772, 10 and 11.



Remaining with series I, we next investigated the influence of absolute configuration at the stereogenic center in the amide portion of **GRL0617** by replacing the *R*-configured CHMe with an NMe moiety in the form of the hydrazide **22** (Scheme S2). For good measure, we also accessed the regioisomer **23** by analogous means. The substitution of the *R*-configured CHMe by an NMe moiety in both **22** and **23** draws on analogy with our recent work with trisubstituted hydroxylamines[2, 3], according to which we consider the *N*-methyl hydrazide moiety as an isostere of either enantiomer of the parent compound owing to the pyramidal yet rapidly inverting nature

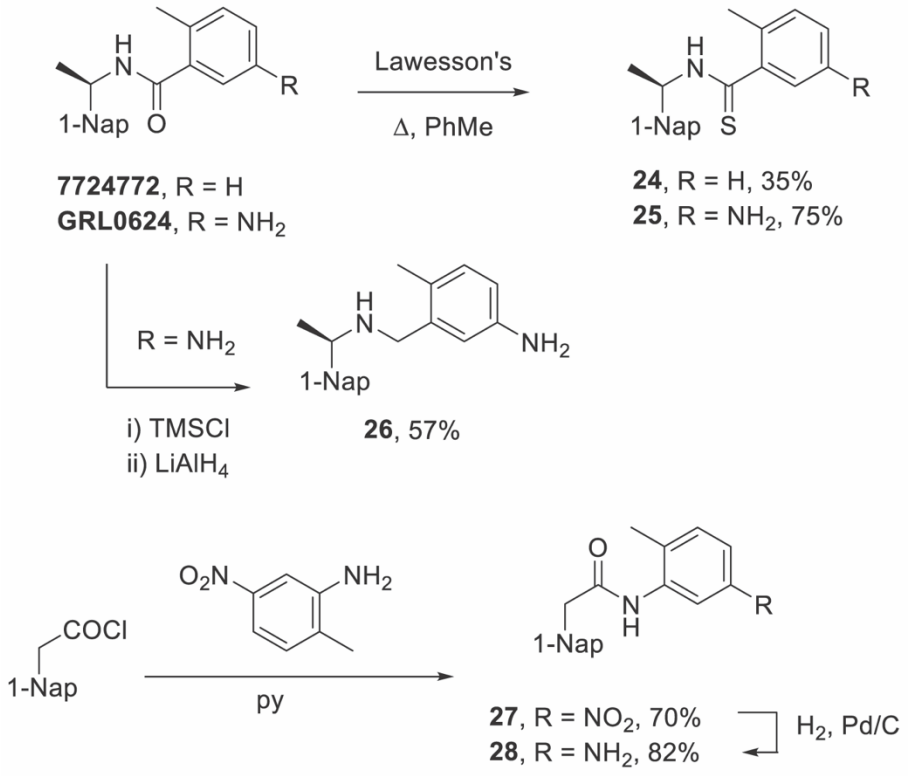
of the hydrazide nitrogen atom. The 1- and 2-naphthylhydrazines **12** and **13** required for these syntheses were accessed by a literature method[4].

Scheme S2. Preparation of the Regioisomeric Hydrazides 22 and 23.



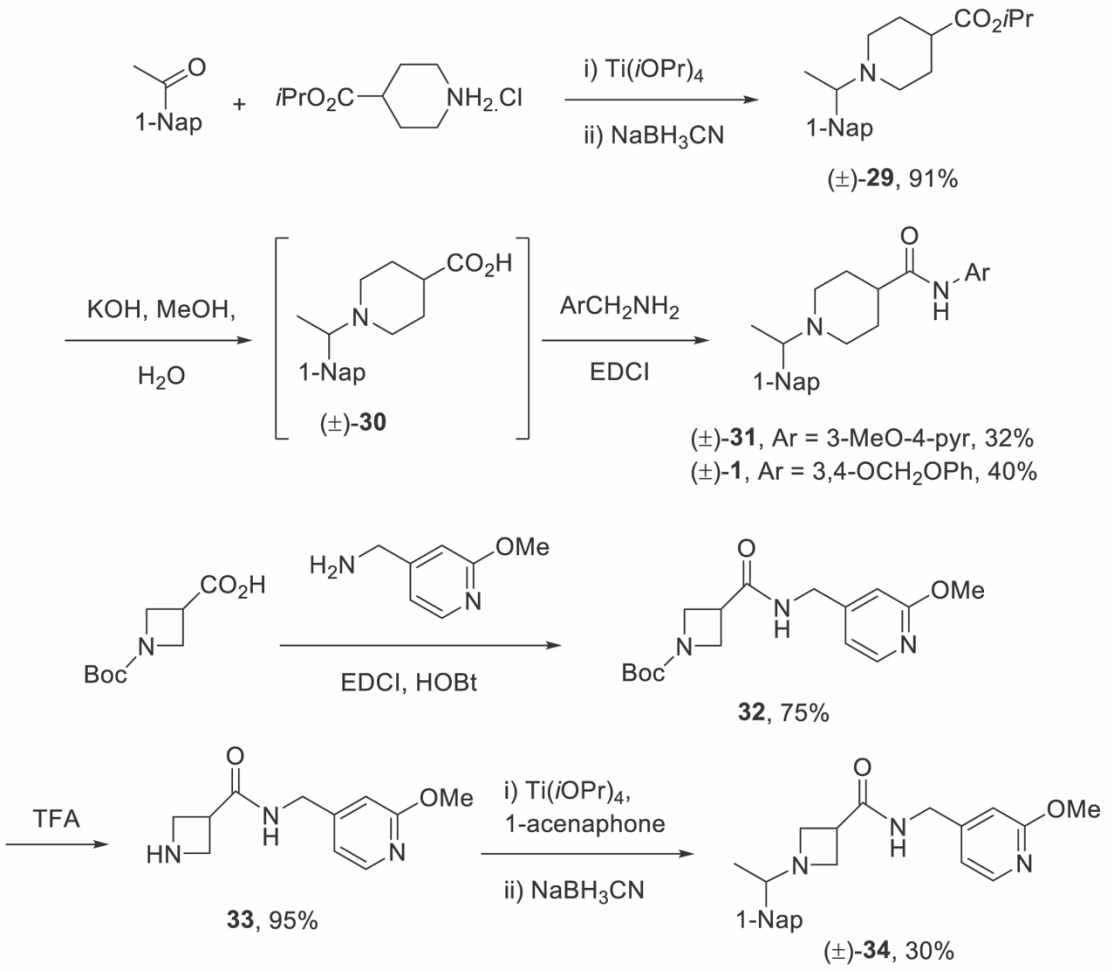
Remaining with series I, we prepared thioamides **24** and **25** by treatment of the parent amides with Lawesson's reagent, and reduced the amide in **GRL0617**, by silylation and subsequent treatment with lithium aluminum hydride,[5] to the corresponding amine **26**. Finally, in this series, we prepared the inverted amide **28** by condensation of 1-naphthylacetyl chloride with 2-methyl-5-nitroaniline giving **27**, followed by hydrogenolysis (Scheme S3).

Scheme S3. Preparation of 24, 25, 26, 27, and 28.



Turning to the series II compounds, reductive amination of 1-acetonaphthone isopropyl piperidine-4-carboxylate[6] by condensation in the presence of titanium tetraisopropoxide followed by sodium cyanoborohydride reduction gave the racemic amine **29**[7]. Saponification then afforded the corresponding acid **30**, which was condensed with (2-methoxy-4-pyridyl)methylamine and 3,4-methylenedioxybenzylamine to give **31** and **1**, respectively (Scheme S4). An analog of **31** in which the 4-piperidine carboxamide moiety was replaced by a 3-azetidinecarboxamide was prepared by related approach in which *N*-(tert-butyloxycabonyl)azetidine-3-carboxylic acid[8] was condensed with (2-methoxy-4-pyridyl)methylamine to give the amide **32**, followed by removal of the carbamate and ultimate reductive amination with 1-acetonaphthone giving **34** (Scheme S4).

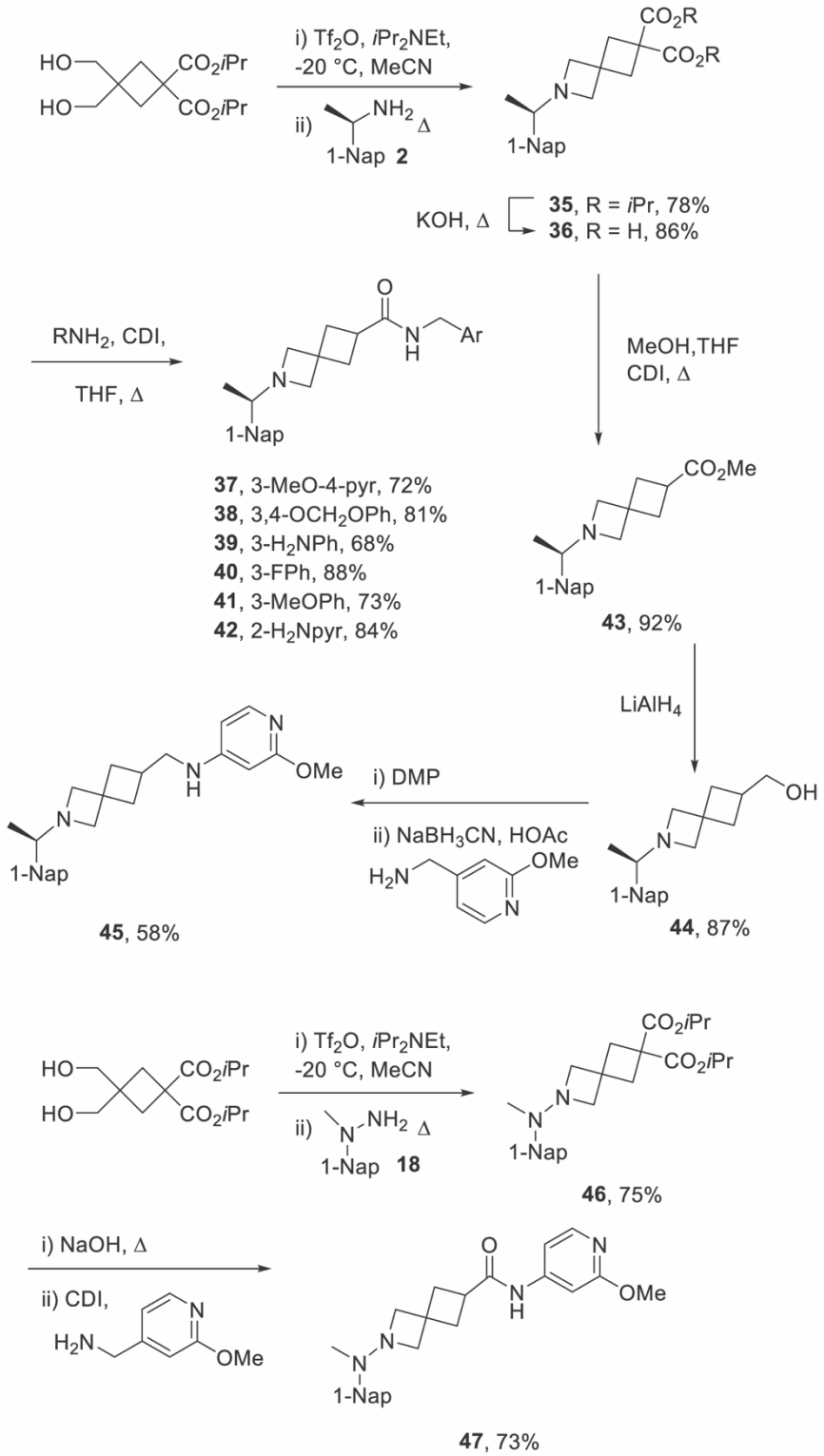
Scheme S4. Preparation of 1, 29, 31, and 34.



We next turned to the preparation of series II analogs in which the central piperidine ring was replaced by a spiroazetidine moiety. To this end diisopropyl 3,3-di(hydroxymethyl)cyclobutane-1,1-dicarboxylate[9] was activated with triflic anhydride in the presence of Hunig's base before addition of 1-(1*R*-naphthyl)ethylamine **2** and heating to 70 °C to afford the spiroazetidine **35**. Saponification then gave the dicarboxylic acid **36**, which was coupled to an assortment of benzylic amines with carbonyl diimidazole in THF at reflux[10] to afford **37**, **38**, **39**, **40**, **41**, and **42**. Heating of the dicarboxylic acid **36** with carbonyl diimidazole in a mixture of methanol and THF at reflux afforded the ester **43**, which was reduced with lithium aluminum hydride to afford alcohol **44**. Oxidation of this alcohol with the Dess-Martin periodinane then

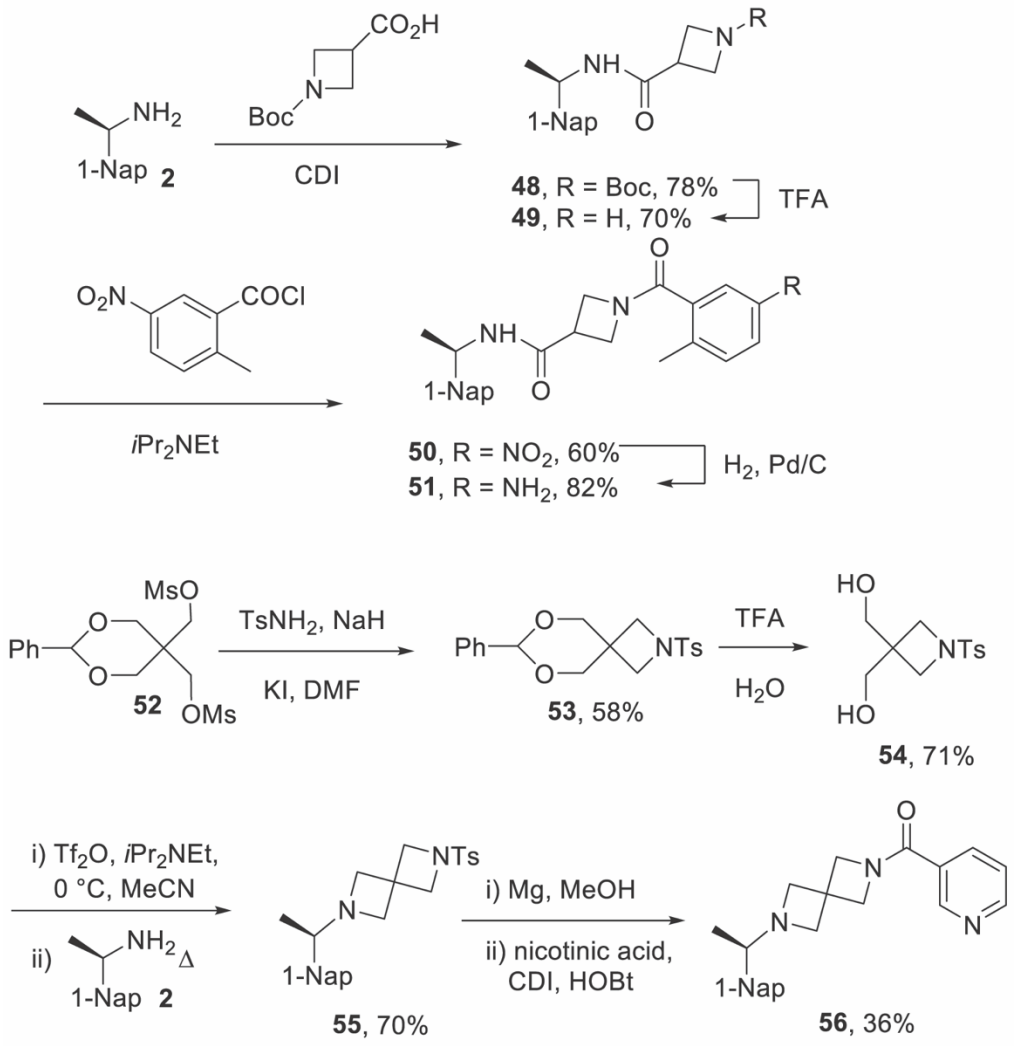
gave an aldehyde, which was coupled to 2-methyoxy-4-pyridylmethylamine under standard reductive amination conditions affording the diamine **45**. Finally, we returned to the *N*-methyl hydrazide concept and prepared an analog **47**, of **37** in which the chiral CHMe unit was replaced by the NMe moiety, using a minor variation on the general route to the spiroazetidines (Scheme S5)[11, 12].

Scheme S5. Preparation of Spiroazetidine Derivatives 37-42, 45, and 47.



Returning to the theme of inverted amides and hybrid structures encompassing aspects of both the series I and II compounds, we first prepared **51** based on the azetidine core by standard means. In a similar vein, starting with the pentaerythritol derivative 2-phenyl-1,3-dioxane-5,5-diylbis(methylene) dimethanesulfonate **52**[13] we prepared the spirodiazetidine **55**, and coupled it to nicotinic acid affording **56** (Scheme S6).

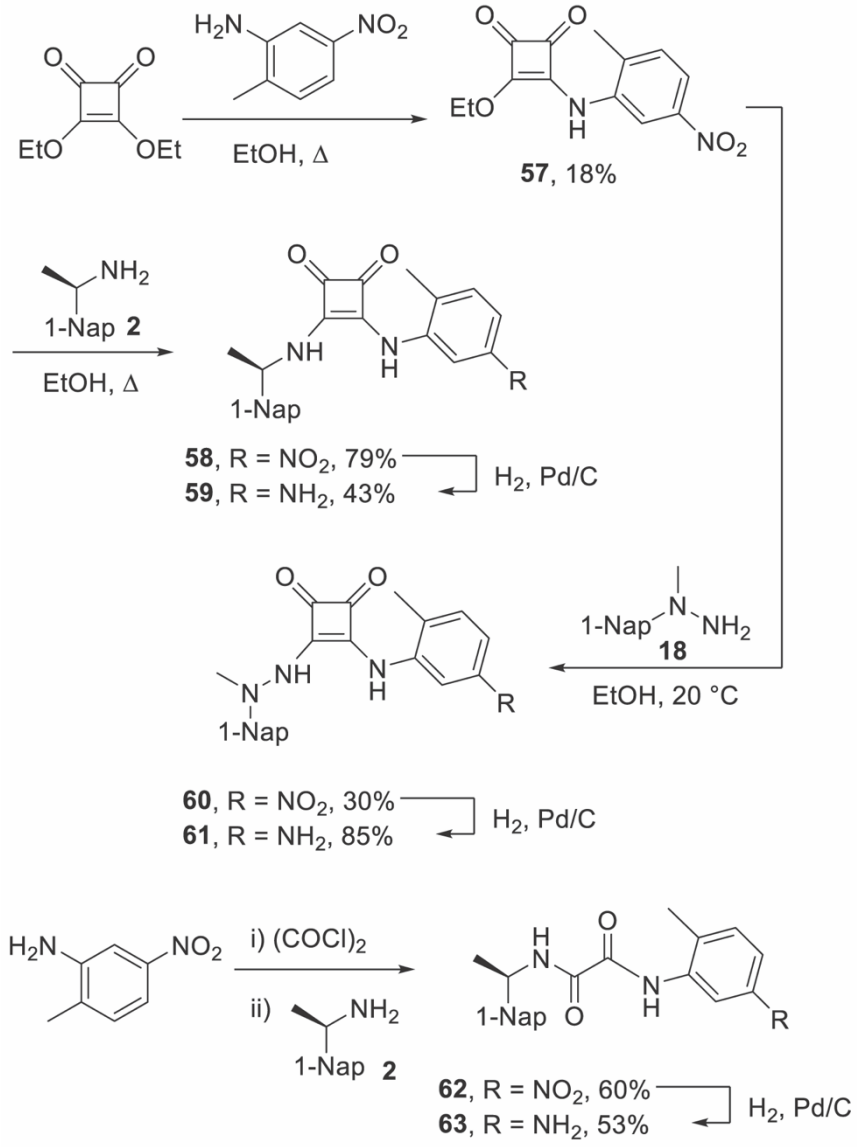
Scheme S6. Preparation of Azetidine 51 and Spirodiazetidine 56.



To further probe the structural requirements in the central portion of the binding pocket we turned to a brief exploration of squaramides[14, 15] and oxalamides[16]. To this end diethyl squarate

was heated with 2-methyl-5-nitroaniline in ethanol with microwave irradiation to give **57** as a yellow solid, albeit only in 18% yield. Subsequent heating of **57** with 1*R*-(1-naphthyl)methylamine, again in ethanol with microwave heating afforded **58** in 79% yield, which was subjected to hydrogenolysis over palladium on charcoal to afford the desired **59** in 43% yield (Scheme S7). Stirring of the half-squaramide **57** with 1-(1-naphthyl)methylhydrazine **18** in ethanol at 20 °C afforded the hydrazide **60** in 30%, and was followed by hydrogenolysis, which gave **61** in 85% yield (Scheme S7). An unsymmetrical oxalamide **62** was prepared in 60% yield by briefly stirring 2-methyl-5-nitroaniline with an excess of oxalyl chloride and potassium carbonate in dichloromethane at room temperature, followed by concentration to dryness and subsequent exposure to 1*R*-(1-naphthyl)ethylamine. Hydrogenolysis then gave the target compound **63** in 53% isolated yield (Scheme S7).

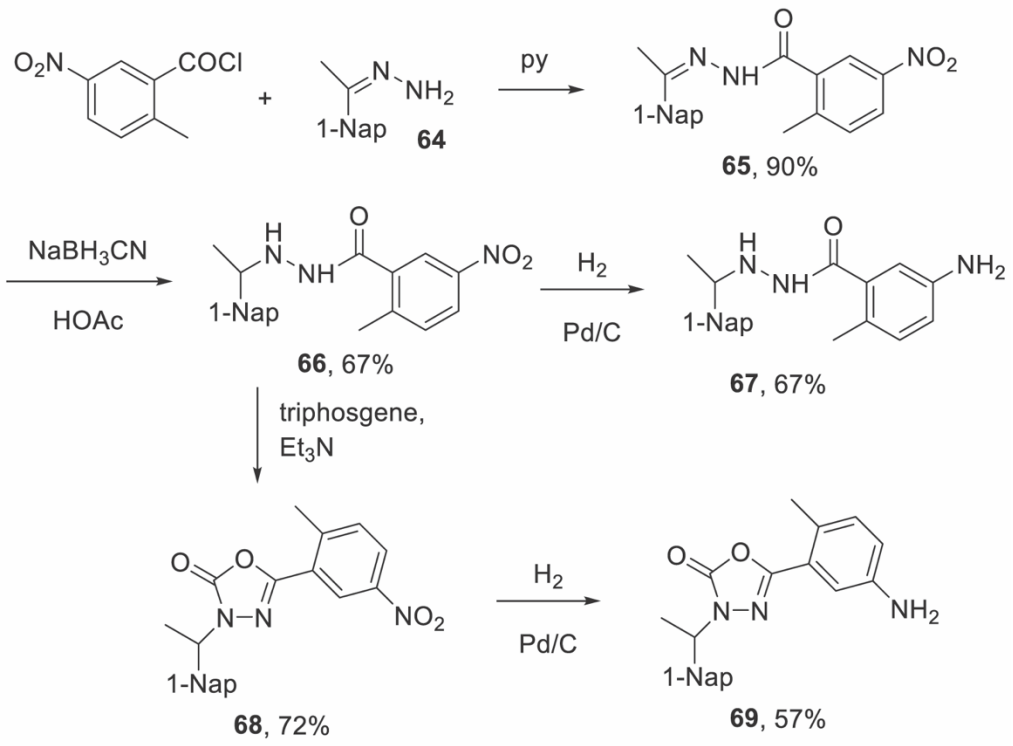
Scheme S7. Preparation of Squaramides 59 and 61, and Oxalamide 63.



To complete our investigation of the structural requirements of the central portion of the binding pocket, taking note of the broad utility of oxadiazoles as molecular scaffolds[17], we prepared the oxazdiazole **69**. The synthesis began with acylation of 1-acenaphthone hydrazone **64** with 2-methyl-5-nitrobenzoyl chloride to give the acyl hydrazone **65**, which was reduced to the corresponding acyl hydrazide **66** with sodium cyanoborohydride. Hydrogenolysis of this substance over palladium on carbon gave hydrazide **67**, itself suitable for screening, whereas

cyclodehydration to the oxadiazolone **68** was achieved with triphosgene, leaving only hydrogenolysis of the nitro group to complete the synthesis of **69** (Scheme S8).

Scheme S8. Synthesis of Hydrazide 67 and Oxadiazolone 69.

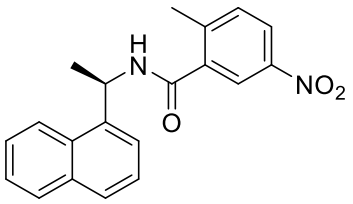


General Experimental. All reactions were conducted in oven dried glassware capped with a rubber septa under an argon atmosphere unless otherwise stated. All organic solutions were concentrated under reduced pressure on a rotary evaporator and water bath. Flash-column chromatography was performed using silica gel (Fischer Silica Gel Sorbent (230 -400 Mesh, Grade 60)) or COMBIFLASH® NextGen system, unless otherwise stated. Thin-layer chromatography (TLC) was carried out with 250 μm glass back silica (XHL) plates with fluorescent indicator (254 nm). TLC plates were visualized by exposure to ultraviolet light (UV) and/or submersion in ceric ammonium molybdate (CAM) or *p*-anisaldehyde solution in ethanol followed by heating on a hot plate (120 °C, 10-15 s).

Instrumentation. Nuclear magnetic resonance (NMR) spectra of all compounds were obtained in either $CDCl_3$ (δ 7.26 and 77.16 ppm, respectively), CD_3OD (δ 3.31 and 49.00 ppm, respectively) or DMSO-d_6 (δ 2.50 and 39.52 ppm, respectively) using a 500 MHz, EZC500 JEOL instrument. The chemical shifts (δ) are calculated with respect to residual solvent peak and are given in ppm. Multiplicities are abbreviated as follows: s (singlet), m (multiplet), br (broad), d (doublet), t (triplet), q (quarter). High resolution mass spectra were obtained on a ThermoFisher Orbitrap Q-Exactive using electrospray ionization (ESI). Specific rotations were recorded in $CHCl_3$, at 589 nm on a digital polarimeter with a path length of 10 cm. Melting points of crystalline compounds were determined on a Barstead Electrothermal 9100. UHPLC traces of final compounds were obtained using a ThermoFisher Vanquish UHPLC with PDA detector and an Acclaim 120 ^{18}C 4.6 x 50 mm column. For compounds that were insufficiently detectable *via* UV, a TIC trace has been included.

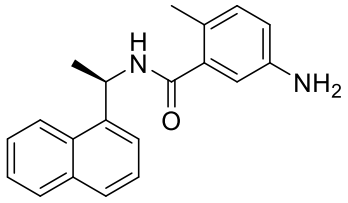
Synthesis and Characterization of Compounds

(*R*)-2-Methyl-5-nitro-*N*-(1'-(naphthalene-1'-yl)ethyl)benzamide (5)[18]



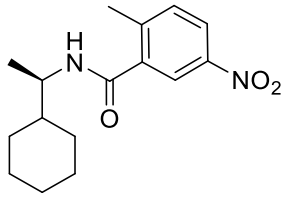
To a stirred solution of nitrotoluic acid (0.232 g, 1.2 mmol), *N*-(3-dimethylaminopropyl)-*N*-ethylcarbodiimide hydrochloride (0.205 g, 1.5 mmol) in DCM (3 mL) was added a solution of (*R*)-1-(1-naphthyl)ethylamine **1** (0.2 g, 1.1 mmol) and diisopropylethylamine (1.11 mL, 6.4 mmol) in DCM (2 mL) at 0 °C. The reaction mixture was quenched with water (20 mL) and extracted with DCM (2 x 15 mL). The organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluent: 30:70 EtOAc:hexanes) to funish the title benzamide (**5**) (0.323 g, 83%) as a white solid. $[\alpha]^{20}_D$ -49.7 (*c* = l, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.21 (d, *J* = 8.4 Hz, 1H), 8.14 (d, *J* = 2.4 Hz, 1H), 8.11 (dd, *J* = 8.3, 2.4 Hz, 1H), 7.90 (dd, *J* = 8.3, 1.4 Hz, 1H), 7.84 (d, *J* = 8.3 Hz, 1H), 7.64 – 7.57 (m, 2H), 7.54 (ddd, *J* = 7.9, 6.7, 1.2 Hz, 1H), 7.48 (dd, *J* = 8.1, 7.2 Hz, 1H), 7.35 (d, *J* = 8.4 Hz, 1H), 6.20 – 6.05 (m, 2H), 2.53 (s, 3H), 1.84 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.5, 145.8, 144.2, 137.3, 137.3, 134.0, 131.9, 131.0, 128.9, 128.8, 126.7, 126.1, 125.2, 124.4, 123.1, 122.7, 121.6, 45.2, 20.5, 20.0. HRMS (ESI) (*m*/*z*): $[M+Na]^+$ Calcd for $[C_{20}H_{18}N_2O_3Na]^+$ 357.1209; Found 357.1205.

(*R*)-2-Methyl-5-nitro-*N*-(1'-(naphthalene-1'-yl)ethyl)benzamide (GRL0617)[18]



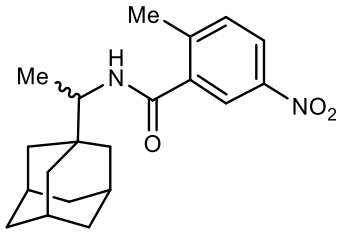
To a stirred solution of (*R*)-2-Methyl-5-nitro-*N*-(1'-(naphthalene-1'-yl)ethyl)benzamide (**5**) (0.070 g, 0.20 mmol) in 4 mL MeOH:EtOAc (1:1) was treated with Pd/C (10% wt) (7 mg). The vessel was purged with H_2 (3X), after which, H_2 was allowed to continuously flow into the stirred vessel for 15 h. After such time, the solvent was evaporated, and the residue dissolved in DCM (5 mL) and filtered over Celite ®, the filtrate was then concentrated and purified by silica gel column chromatography (eluent: 40:60 EtOAc:hexanes) to afford the title compound (**GRL0617**) (0.061 g, 96%) as a white solid. $[\alpha]^{20}_{D}$ -62.3 (*c* = l, $CHCl_3$); ^{1}H NMR (500 MHz, CD_3OD) δ 8.29 (d, *J* = 8.5 Hz, 1H), 7.93 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.84 (d, *J* = 8.2 Hz, 1H), 7.67 (d, *J* = 7.1 Hz, 1H), 7.61 (ddd, *J* = 8.5, 6.8, 1.5 Hz, 1H), 7.57 – 7.49 (m, 2H), 7.03 – 6.94 (m, 1H), 6.83-6.61 (m, 2H), 6.07 (q, *J* = 6.9 Hz, 1H), 2.25 (s, 3H), 1.73 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (126 MHz, CD_3OD) δ 171.2, 145.0, 139.0, 137.1, 134.1, 131.0, 130.9, 128.5, 127.6, 125.9, 125.3, 125.0, 124.1, 123.0, 122.3, 116.6, 113.7, 44.8, 20.0, 17.2. HRMS (ESI) (*m*/*z*): $[M+H]^+$ Calcd for $[C_{20}H_{21}N_2O]^+$ 305.1648; Found 305.1636.

(*R*)-*N*-[1-(1-Cyclohexyl)ethyl] 2-methyl-5-nitro-benzamide (6).



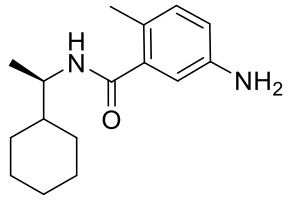
A stirred solution of 2-methyl-5-nitrobenzoic acid (0.39 g, 2.1 mmol), *N*-(3-dimethylaminopropyl)-*N*-ethylcarbodiimide hydrochloride (EDCI) (0.489 g, 2.5 mmol), and 1-hydroxybenzotriazole hydrate (HOBT) (0.344 g, 2.5 mmol) in DCM (3 mL) was treated with a solution of (*R*)-cyclohexylethylamine **3** (0.25 g, 1.9 mmol) and diisopropylethylamine (1.87 mL, 10.8 mmol) in DCM (2 mL) at 0 °C and stirred for 12 h at room temperature. The reaction mixture was quenched with water (20 mL) and extracted with DCM (2 x 15 mL). The organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eleuent: 30:70 EtOAC:hexanes) to furnish the title benzamide (**6**) (0.495 g, 87%) as a white solid. $[\alpha]^{20}_D$ -21.4 (*c* = 2.2, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.56 – 7.82 (m, 2H), 7.38 (d, *J* = 8.3 Hz, 1H), 5.68 (d, *J* = 9.1 Hz, 1H), 4.35 – 3.84 (m, 1H), 2.53 (d, *J* = 1.7 Hz, 3H), 1.88 – 1.72 (m, 4H), 1.72 – 1.52 (m, 1H), 1.52 – 1.32 (m, *J* = 5.7, 3.0 Hz, 1H), 1.32 – 1.24 (m, 2H), 1.22 (dd, *J* = 6.7, 1.8 Hz, 3H), 1.19 – 1.00 (m, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.2, 146.0, 144.3, 138.2, 132.1, 124.4, 121.7, 50.4, 43.2, 29.4, 29.3, 26.5, 26.3 (2C), 20.2, 18.2. HRMS (ESI) (*m*/*z*): $[M+H]^+$ Calcd for $[C_{16}H_{23}N_2O_3Na]^+$ 291.1697; Found 291.1703.

(±)-*N*-[1'-(Adamantan-1'-yl)ethyl]-2-methyl-5-nitrobenzamide (7).



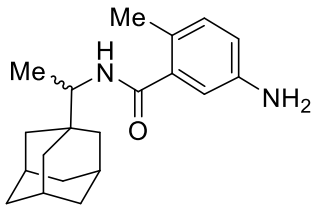
To a stirred solution of 2-methyl-5-nitrobenzoic acid (168 mg, 0.93 mmol), EDCI (194 mg, 1.16 mmol), and HOBT (156 mg, 1.16 mmol) in anhydrous DCM/DMF (1:1) (3 mL) at 0 °C was added (±)-1-(1-adamantyl)ethylamine hydrochloride **4** (200 mg, 0.93 mmol) followed by diisopropylethylamine (647 μL, 3.72 mmol). The reaction mixture was allowed to reach room temperature over a period of 10 min, and stirred for 12 h. After such time, the reaction mixture was quenched *via* addition of H_2O (4 mL) and the aqueous layer was re-extracted with DCM (10 mL, 3X). The organic layers were combined, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue obtained was purified by flash column chromatography on silica (eluent: 5:95 – 20:80 EtOAc:hexanes) to afford the title compound (**7**) (259 mg, 81 %) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.18 – 8.11 (m, 2H), 7.39 (d, J = 8.3 Hz, 1H), 5.64 (d, J = 9.9 Hz, 1H), 3.92 (m, 1H), 2.54 (s, 3H), 2.02 (p, J = 3.1 Hz, 3H), 1.73 (dt, J = 12.5, 2.7 Hz, 3H), 1.68 – 1.58 (m, 6H), 1.54 (dq, J = 11.9, 2.5 Hz, 3H), 1.16 (d, J = 6.9 Hz, 3H).^{13}C NMR (126 MHz, $CDCl_3$): δ 167.3, 146.1, 144.2, 138.4, 132.1, 124.5, 121.7, 53.9, 38.7 (3C), 37.1 (3C), 36.0, 28.4 (3C), 20.3, 14.9. HRMS (ESI) *m*/*z*: $[M+H]^+$ Calcd for $[C_{20}H_{27}O_3N_2]^+$ 343.2016; Found 343.2011.

(*R*)-*N*-[1-(1-Cyclohexyl)ethyl] 5-amino-2-methylbenzamide (8).



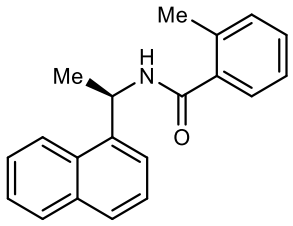
A stirred solution of (*R*)-*N*-[1-(1-cyclohexyl)ethyl] 2-methyl-5-nitro-benzamide **6** (0.440 g, 1.5 mmol) in 50 mL (33.8 M) MeOH:EtOAc (1:1) was hydrogenated over 10% Pd(C) (28 mg). The vessel was purged with H_2 (3X), after which, H_2 was allowed to continuously flow into the stirred vessel for 12 h. Upon completion, the reaction mixture was filtered on Celite ® and the filtrate was concentrated. The residue was purified by chromatography over silica (eluent: 30:70 EtOAc:hexanes) to afford the title amide (**8**) (0.364 g, 92%) as a white solid. $[\alpha]^{20}_{D}$ -22.1 (*c* = l, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.98 (d, *J* = 8.1 Hz, 1H), 6.68 (d, *J* = 2.5 Hz, 1H), 6.64 (dd, *J* = 8.1, 2.6 Hz, 1H), 5.51 (d, *J* = 9.3 Hz, 1H), 4.04 (dp, *J* = 9.2, 6.7 Hz, 1H), 2.31 (s, 3H), 1.88 – 1.70 (m, 4H), 1.70 – 1.63 (m, 1H), 1.39 (m, 1H), 1.30 – 1.17 (m, 2H) 1.18-1.16 (d, *J* = 4.4 Hz, 3H), 1.13 – 0.96 (m, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.7, 144.2, 138.0, 131.9, 125.3, 116.7, 113.6, 49.8, 43.3, 29.3, 29.2, 26.6, 26.3 (2C), 18.9, 18.3. HRMS (ESI) (*m*/*z*): $[M+H]^+$ Calcd for $[C_{16}H_{25}N_2O]^+$ 261.1961; Found: 261.1953.

(±)-*N*-(1'-(Adamantan-1'-yl)ethyl)-5-amino-2-methylbenzamide (9).



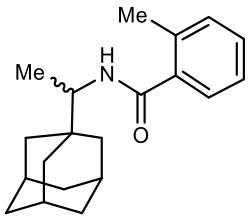
To a stirred solution of (±)-*N*-(1-adamantan-1-yl)ethyl)-2-methyl-5-nitrobenzamide **7** (60 mg, 0.175 mmol) in dioxane (3 mL) was added Pd/C (10% wt) (6 mg, 0.056 mmol). The vessel was purged with H_2 (3X), after which, H_2 was allowed to continuously flow into the stirred vessel for 12 h. After such time, the reaction mixture was filtered over Celite and washed with MeOH (10 mL). The filtrate was concentrated *in vacuo* and the residue obtained was subjected to flash column chromatography on silica (eluent: 10:90 MeOH:DCM – 100:0 MeOH:DCM) to afford the title compound (**9**) (49 mg, 90%) as a grey solid. ^{1}H NMR (500 MHz, CD_3OD): δ 7.92 – 7.84 (m, 1H), 6.96 (d, J = 7.9 Hz, 1H), 6.73 – 6.66 (m, 2H), 3.81 (m, 1H), 2.25 (s, 3H), 2.00 (m, 3H), 1.77 (m, 3H), 1.74 – 1.66 (m, 3H), 1.65 (br s, 6H), 1.11 (d, J = 7.0 Hz, 3H). ^{13}C NMR (126 MHz, CD_3OD): δ 173.3, 146.4, 139.2, 132.2, 125.2, 117.8, 115.0, 54.8, 39.7 (3C), 38.2 (3C), 37.5, 29.9 (3C), 18.8, 14.4. HRMS (ESI) *m*/*z*: $[M+H]^+$ Calcd for $[C_{20}H_{29}ON_2]^+$ 313.2274; Found 313.2268.

(*R*)-2-Methyl-*N*-(1'-(naphthalene-1'-yl)ethyl)benzamide (7724772)[18]



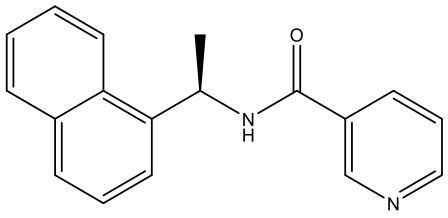
A stirred solution of *o*-toluic acid (49 mg, 0.36 mmol), *N*-(3-dimethylaminopropyl)-*N*'-ethylcarboiimide hydrochloride (EDCI) (87.3 mg, 0.45 mmol), hydroxybenzotriazole (HOBT) (62 mg, 0.45 mmol) in anhydrous DCM (1 mL) at 0 °C was treated with *(R)*-1-(1-naphthyl)ethylamine (60 mg, 0.36 mmol) and then gradually brought to r.t. over a period of 10 min and stirred for 16 h. After such time, the reaction mixture was quenched with H_2O (2 mL) and the aqueous layer re-extracted with EtOAc (5 mL, 3X). The organic layers were combined and dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue obtained was purified by flash column chromatography on silica (eluent: 15:85 EtOAc:hexanes) to afford the title compound (**7724772**) (64 mg, 62%) as a white solid, with spectral data in accord with that previously reported in the literature.[18] ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.24 (d, *J* = 8.5 Hz, 1H), 7.87 (d, *J* = 10 Hz, 1H), 7.81 (d, *J* = 8.2 Hz, 1H), 7.61 – 7.54 (m, 2H), 7.54 – 7.48 (m, 1H), 7.45 (t, *J* = 7.7 Hz, 1H), 7.27 (s, 2H), 7.17 (d, *J* = 7.5 Hz, 1H), 7.11 (t, *J* = 7.5 Hz, 1H), 6.13 (p, *J* = 7.0 Hz, 1H), 5.93 (d, *J* = 8.2 Hz, 1H), 2.43 (s, 3H), 1.79 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): 169.1, 138.2, 136.6, 136.2, 134.1, 131.4, 131.1, 129.9, 129.0, 128.7, 126.8, 126.7, 126.1, 125.8, 125.3, 123.7, 122.7, 45.0, 20.7, 19.9. HRMS (ESI) *m/z*: $[M+H]^+$ Calcd for $[C_{20}H_{20}NO]^+$ 290.1539; Found 290.1528.

(±)-*N*-(1'-(Adamantan-1'-yl)ethyl)-2-methylbenzamide (10).



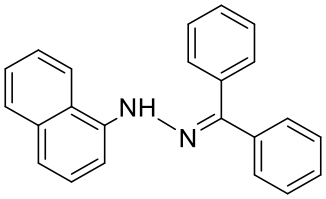
To a stirred solution of *o*-toluic acid (35 mg, 0.23 mmol), EDCI (45 mg, 0.29 mmol), HOBT (39 mg, 0.29 mmol) in anhydrous DCM/DMF (1:1) (1 mL) at 0 °C was added (±)-1-(1-adamantyl)ethylamine hydrochloride **4** (50 mg, 0.23 mmol) followed by diisopropylethylamine (160 µL, 0.92 mmol). The reaction mixture was allowed to reach room temperature over a period of 10 min, and stirred for 12 h. After such time, the reaction mixture was quenched *via* addition of H_2O (3 mL) and the aqueous layer was re-extracted with DCM (5 mL, 3X). The organic layers were combined, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue obtained was purified by flash column chromatography on silica (eluent: 20:80 EtOAc:hexanes) to afford the title compound (**10**) (60 mg, 88%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.35 (dd, J = 7.3, 1.5 Hz, 1H), 7.30 (td, J = 7.4, 1.4 Hz, 1H), 7.24 – 7.17 (m, 2H), 5.57 (d, J = 9.9 Hz, 1H), 3.93 (dq, J = 10.0, 6.9 Hz, 1H), 2.46 (s, 3H), 2.01 (p, J = 3.1 Hz, 3H), 1.73 (m, 3H), 1.64 (m, 6H), 1.55 (m, 3H), 1.13 (m, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 169.7, 137.5, 136.0, 131.1, 129.8, 126.6, 125.9, 53.4, 38.7 (3C), 37.2 (3C), 36.1, 28.5 (3C), 20.0, 14.9. HRMS (ESI) *m*/*z*: $[M+H]^+$ Calcd for $[C_{20}H_{28}ON]^+$ 298.2165; Found 298.2157.

(*R*)-*N*-(1-(Naphthalen-1-yl)ethyl) nicotinamide (11).



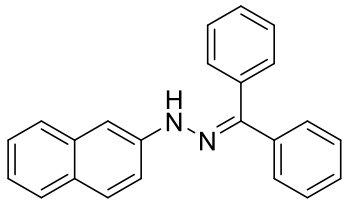
A solution of DCC (0.253 g, 1.23 mmol) in CH_2Cl_2 (4.2 mL) was added to a stirred solution of nicotinic acid (0.102 g, 0.83 mmol), DMAP (24 mg, 0.20 mmol), and (*R*)-(+)-1-(1-naphthyl)ethylamine (0.20 mL, 1.25 mmol) in CH_2Cl_2 (4.0 mL) and stirred for 7.5 h. The reaction mixture was then diluted with ethyl acetate and washed with 1 N HCl. Following concentration of the aqueous layer the resulting yellow oil was dissolved in ethyl acetate, washed with 10% NH_4OH solution and brine, and dried with Na_2SO_4 before concentration under vacuum. The resulting solid was recrystallized from CH_2Cl_2 and hexanes to give the title amide (**11**) (0.193 mg, 84%) as white crystals. $[\alpha]_D^{23}$ = -19.0 (*c* = 0.4, $CHCl_3$), m.p. = 155 ^oC, ^1H NMR (500 MHz, $CDCl_3$) δ 8.91 – 8.87 (m, 1H), 8.64 – 8.59 (m, 1H), 8.12 (d, *J* = 8.4 Hz, 1H), 8.06 (dt, *J* = 8.0, 2.0 Hz, 1H), 7.85 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.79 (d, *J* = 8.2 Hz, 1H), 7.57 (d, *J* = 7.2 Hz, 1H), 7.55 – 7.46 (m, 2H), 7.45 (dd, *J* = 8.2, 7.2 Hz, 1H), 7.30 (dd, *J* = 8.0, 4.8 Hz, 1H), 6.62 (d, *J* = 7.8 Hz, 1H), 6.10 (p, *J* = 7.0 Hz, 1H), 1.77 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.6, 152.0, 147.8, 137.8, 135.5, 134.1, 131.2, 130.3, 129.0, 128.8, 126.9, 126.1, 125.3, 123.6, 123.3, 122.9, 45.5, 20.7. HRMS (ESI) *m/z*: $[M+H]^+$ Calcd for $[C_{18}H_{17}N_2O]^+$ 277.1335; Found 277.1326.

Benzophenone 1-naphthylhydrazone (14).



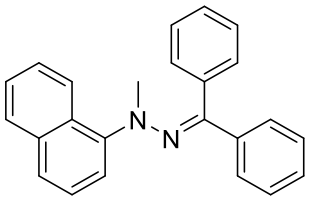
A stirred solution of benzophenone (0.94 g, 5.14 mmol) in MeOH (8 mL) was treated dropwise with concentrated H_2SO_4 (0.16 mL) at 20 °C followed by 1-napthylhydrazine hydrochloride **12**[4] (1 g, 5.14 mmol). The reaction mixture was heated to 50 °C and stirred for 4 h then was cooled at 0 °C for 20 min, and the precipitate was filtered, and washed with cold MeOH (6 mL) to afford the product as a yellow solid (**14**) (1.37 g, 83%), which was directly used for the next step without further purification. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.31 (s, 1H), 7.92 – 7.86 (m, 2H), 7.83 – 7.79 (m, 2H), 7.73 – 7.69 (m, 2H), 7.68 – 7.62 (m, 1H), 7.58 (t, J = 7.9 Hz, 1H), 7.53 (d, J = 1.7 Hz, 1H), 7.49 – 7.30 (m, 8H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 146.4, 139.3, 138.3, 134.3, 132.9, 129.9 (2C), 129.6, 129.1 (2C), 128.8, 128.4 (2C), 128.3 (2C), 126.8 (2C), 125.7, 125.1, 121.9, 120.0, 119.0, 108.2. HRMS (ESI) *m*/*z*: $[M + H]^+$ Calcd for $[C_{23}H_{19}N_2]^+$ 323.1543; Found 323.1535.

Benzophenone 2-naphthylhydrazone (15).



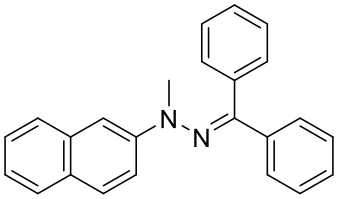
A stirred solution of benzophenone (0.94 g, 5.14 mmol) in MeOH (8 mL) was treated dropwise with concentrated H_2SO_4 (0.16 mL) at 20 °C, followed by 2-napthylhydrazine hydrochloride **13** [4] (1 g, 5.14 mmol). The reaction mixture was heated to 50 °C and stirred for 6 h then was cooled on an ice bath for 20 min. The precipitate was filtered, washed with cold MeOH (6 mL) and dried to give the title product as a pale pink solid (**15**) (1.46 g, 88%), which was directly used for the next step without further purification. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75 – 7.68 (m, 3H), 7.68 – 7.63 (m, 3H), 7.63 – 7.58 (m, 2H), 7.57 – 7.51 (m, 1H), 7.45 (d, J = 2.2 Hz, 1H), 7.42 – 7.35 (m, 4H), 7.35 – 7.22 (m, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 144.9, 142.4, 138.4, 134.9, 132.9, 129.9 (2C), 129.4, 129.3 (2C), 129.2, 129.1, 128.4 (2C), 128.3, 127.9, 126.7 (2C), 126.6, 126.5, 123.0, 115.7, 107.2. HRMS (ESI) *m*/*z*: $[M + H]^+$ Calcd for $[C_{23}H_{19}N_2]^+$ 323.1543; Found 323.1533.

Benzophenone *N*-methyl-(1-naphthyl)hydrazone (16).



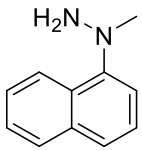
A stirred solution of benzophenone 1-naphthylhydrazone **14** (2 g, 6.20 mmol) in anhydrous DMF (12 mL) was slowly treated with NaH (0.04 g, 9.30 mmol) at 0 °C, and then stirred at 0 °C for 0.5 h, before methyl iodide (0.58 mL, 9.30 mmol) was added dropwise over 5 min and the resulting mixture was warmed to 20 °C and stirred for 3 h. The reaction mixture was cooled to 0 °C before it was quenched with water (20 mL) and extracted with ethyl acetate (3×20 mL), and the combined organic phase washed with 1N HCl (30 mL), saturated aqueous $NaHCO_3$ (30 mL), and brine (30 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was subjected to flash chromatography (eluent: 0:100 - 10:90 EtOAc:hexanes) to give the title product (**16**) (1.82 g, 87%) as a light orange solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.99 – 7.91 (m, 1H), 7.71 – 7.67 (m, 1H), 7.64 – 7.59 (m, 2H), 7.47 (m, 2H), 7.41 – 7.36 (m, 2H), 7.35 – 7.32 (m, 3H), 7.31 – 7.22 (m, 1H), 7.09 – 7.04 (m, 2H), 7.03 – 6.99 (m, 2H), 6.98 – 6.93 (m, 1H), 3.26 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.9, 150.8, 139.6, 137.2, 134.4, 128.96, 128.89 (2C), 128.8, 128.2 (2C), 127.98, 127.8 (2C), 127.6 (2C), 127.4, 125.7 (2C), 125.3, 124.9, 123.9, 120.4, 48.7. HRMS (ESI) *m*/*z*: $[M + Na]^+$ Calcd for $[C_{24}H_{20}N_2Na]^+$ 359.1524; Found 359.1530.

Benzophenone *N*-methyl-(2-naphthyl)hydrazone (17).



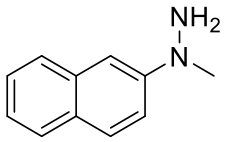
A stirred solution of benzophenone 2-naphthylhydrazone **15** (6.49 g, 20.1 mmol) in 40.3 mL of dry DMF was slowly treated with NaH (1.21 g, 30.2 mmol) at 0 °C, and then stirred at this temperature for 0.5 h. Then methyl iodide (1.88 ml, 30.19 mmol, 1.5 equiv.) was added dropwise over 5 min and the resulting mixture was warmed to 20 °C and stirred for 3 h. The reaction mixture was cooled to 0 °C and quenched with water (100 mL). The mixture was extracted with ethyl acetate (3×100 mL) and the combined organic phase was washed with 1N HCl, saturated aqueous $NaHCO_3$, brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by flash column chromatography (eluent: 0:100 - 10:90 EtOAc:hexanes) to yield the title product (**17**) (6 g, 89%) as an orange solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81 – 7.71 (m, 3H), 7.71 – 7.61 (m, 3H), 7.47 – 7.37 (m, 9H), 7.30 (m, 2H), 3.03 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.9, 148.2, 139.6, 137.4, 134.6, 129.4, 129.3 (2C), 128.8, 128.7 (2C), 128.6 (2C), 128.5 (2C), 128.2 (2C), 127.7, 126.9, 126.3, 123.1, 117.4, 108.7, 41.6. HRMS (ESI) *m*/*z*: $[M + Na]^+$ Calcd for $[C_{24}H_{20}N_2Na]^+$ 359.1524; Found 359.1536.

***N*-Methyl-*N*-(1-naphthyl)hydrazine (18).**



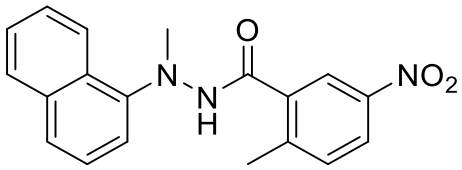
A solution of benzophenone *N*-methyl-(1-naphthyl)hydrazone **16** (2 g, 5.94 mmol) in THF (60 mL) was treated with 6 M HCl (18.2 mL, 109 mmol) and stirred at room temperature for 10 h before concentration *in vacuo*. The residue was washed with diethyl ether (2× 20 mL) and the solid was dried under reduced pressure. The solid was dissolved in water (30 mL) with vigorous stirring and the pH was carefully adjusted to 7 with 20% aqueous NaOH. The cloudy mixture was extracted with diethyl ether (2× 20 mL) and the combined organic phase was dried over Na_2SO_4, and concentrated under reduced pressure to give the title product (**18**) (829 mg, 81%) as a dark brown oil.^{1}H NMR (500 MHz, CD_3OD) δ 8.26 (d, *J* = 8.9 Hz, 1H), 7.92 (d, *J* = 9.7 Hz, 1H), 7.85 (d, *J* = 8.0 Hz, 1H), 7.63 – 7.58 (m, 2H), 7.55 (m, 2H) 3.20 (s, 3H). ^{13}C NMR (126 MHz, CD_3OD) δ 145.7, 136.1, 129.7, 129.5, 129.0, 128.1, 128.0, 126.5, 123.4, 117.6, 46.3. HRMS (ESI) *m*/*z*: $[M + H]^+$ Calcd for $[C_{11}H_{13}N_2]^+$ 173.1079; Found 173.1070.

***N*-Methyl-*N*-(2-naphthyl)hydrazine (19).**



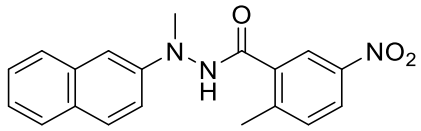
To a solution of benzophenone *N*-methyl-(2-naphthyl)hydrazone **17** (1.27 g, 3.77 mmol) in THF (38 mL) was added 6 M HCl (18.2 mL, 109 mmol). The resulting mixture was stirred at 20 °C for 12 h and then concentrated *in vacuo*. The residue was washed with diethyl ether (2×20 mL) and the solid was dried under reduced pressure and then was dissolved in water (20 mL) with vigorous stirring and carefully neutralized with 20% aqueous NaOH, after which the mixture was extracted three times with diethyl ether. The combined organic phase was dried over Na_2SO_4 and concentrated to give the product (553 mg, 85%) as a dark brown oil.^{1}H NMR (500 MHz, CD_3OD) δ 7.91 (d, J = 9.0 Hz, 1H), 7.83 (m, 2H), 7.53 – 7.47 (m, 2H), 7.43 (m, 1H), 7.39 (dd, J = 9.1, 2.5 Hz, 1H), 3.28 (s, 3H). ^{13}C NMR (126 MHz, CD_3OD) δ 145.5, 133.7, 130.9, 129.6, 127.4, 127.3, 126.9, 125.5, 118.3, 113.2, 42.8. HRMS (ESI) *m*/*z*: $[M + H]^+$ Calcd for $[C_{11}H_{13}N_2]^+$ 173.1079; Found 173.1085.

***N*'-Methyl-*N*'-(naphthalen-1-yl) 2-methyl-5-nitrobenzhydrazide (20).**



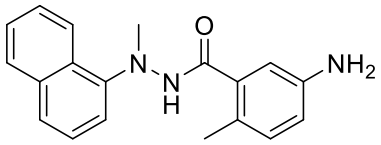
To a mixture of *N*-methyl-*N*-(1-naphthyl)hydrazine **18** (70 mg, 0.41 mmol) and anhydrous dichloromethane (2.3 mL), were added 2-methyl-5-nitrobenzoic acid (110 mg, 0.61 mmol), 1-ethyl-3-[3-dimethylaminopropyl]carbodiimide hydrochloride (95 mg, 0.61 mmol) and diisopropylethylamine (0.14 mL, 0.81 mmol). The reaction mixture was stirred at 20 °C for 3 h before it was washed with 1N HCl (2×2 mL), saturated aqueous $NaHCO_3$ (2× 2 mL), brine (2 mL), dried over Na_2SO_4, filtered, concentrated and then purified by flash chromatography (eluent: 0:100- 50:50 EtOAc:hexanes) to give the title product (**20**) (114 mg, 84%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.30 (dd, *J* = 6.3, 3.5 Hz, 1H), 8.01 (d, *J* = 2.5 Hz, 1H), 7.80 (dd, *J* = 6.2, 3.3 Hz, 1H), 7.65 (s, 1H), 7.61 (d, *J* = 8.5 Hz, 1H), 7.48 (dd, *J* = 6.4, 3.3 Hz, 2H), 7.36 (d, *J* = 7.7 Hz, 1H), 7.28 (d, *J* = 7.3 Hz, 1H), 7.26 – 7.22 (m, 1H), 7.18 – 7.12 (m, 1H), 3.28 (s, 3H), 2.43 (s, 3H).^{13}C NMR (126 MHz, $CDCl_3$) δ 165.6, 145.7, 145.6, 144.8, 135.5, 134.7, 132.0, 131.2, 128.3, 126.5, 126.2, 125.9, 125.2, 124.8, 123.8, 122.0, 114.8, 43.0, 20.0. HRMS (ESI) *m/z*: $[M+Na]^+$ Calcd for $[C_{19}H_{17}N_3O_3Na]^+$ 358.1168; Found 358.1160.

***N*'-Methyl-*N*'-(naphthalen-2-yl) 2-methyl-5-nitrobenzhydrazide (21).**



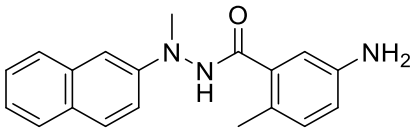
To a stirred mixture of *N*-methyl-*N*-(2-naphthyl)hydrazine **19** (100 mg, 0.58 mmol) and dry dichloromethane (3 mL), were added 2-methyl-5-nitrobenzoic acid (158 mg, 0.87 mmol), 1-ethyl-3-[3-dimethylaminopropyl]carbodiimide hydrochloride (135 mg, 0.87 mmol) and diisopropylethylamine (0.20 ml, 1.16 mmol). The reaction mixture was stirred at 20 °C for 4 h before it was washed with 1N HCl (2×2 mL), saturated aqueous $NaHCO_3$ (2×2 mL), brine (2 mL), dried over Na_2SO_4, filtered, concentrated and then subjected to flash column chromatographic purification (eluent: 0:100 - 50:50 EtOAc:hexanes) to give the title product (**21**) (156 mg, 80%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.50 (s, 1H), 8.08 (d, *J* = 2.4 Hz, 1H), 7.93 (dd, *J* = 8.4, 2.5 Hz, 1H), 7.64 (d, *J* = 8.1 Hz, 1H), 7.55 (dd, *J* = 8.6, 6.6 Hz, 2H), 7.36 (ddd, *J* = 8.2, 6.7, 1.3 Hz, 1H), 7.26 (ddd, *J* = 8.0, 6.7, 1.3 Hz, 1H), 7.12 (d, *J* = 8.4 Hz, 1H), 6.96 (dd, *J* = 9.0, 2.5 Hz, 1H), 3.09 (s, 3H), 2.32 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.9, 146.7, 145.6, 144.9, 134.3, 132.1, 129.1, 128.5, 127.6, 126.8, 126.6, 124.9, 123.6, 122.0, 115.8, 107.7, 60.5, 40.6, 20.0. HRMS (ESI) *m*/*z*: $[M + Na]^+$ Calcd for $[C_{19}H_{17}N_3O_3Na]^+$ 358.1168; Found 358.1156.

***N*'-Methyl-*N*'-(naphthalen-1-yl) 5-amino-2-methylbenzhydrazide (22).**



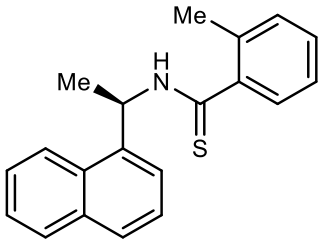
A stirred solution of *N*'-methyl-*N*'-(naphthalen-1-yl) 2-methyl-5-nitrobenzhydrazide **20** (110 mg, 0.33 mmol) in 1,4-dioxane (3.3 mL) was treated with Pd/C (17.42 mg, 0.02 mmol, 0.05 equiv) and stirred at 20 °C under hydrogen (1 atm) for 5 h. The reaction mixture was filtered, and the filtrate was evaporated to give a residue, which was purified by silica gel column chromatography (eluent: 20:80 - 60:40 EtOAc:hexanes) to yield the title product (**22**) (79.1 mg, 79%) as a white solid. ^{1}H NMR (500 MHz, CD_3OD) δ 7.70 (d, *J* = 9.0 Hz, 1H), 7.70 – 7.70 (m, 2H), 7.40 (m, 1H), 7.30 – 7.20 (m, 2H), 7.20 (d, *J* = 2.5 Hz, 1H), 7.00 (d, *J* = 8.2 Hz, 1H), 6.90 (d, *J* = 2.5 Hz, 1H), 6.70 (dd, *J* = 8.1, 2.5 Hz, 1H), 3.30 (s, 3H), 2.30 (s, 3H). ^{13}C NMR (126 MHz, CD_3OD) δ 171.4, 147.5, 145.4, 134.7, 134.6, 131.4, 128.7, 128.6, 127.1, 126.4, 126.1, 124.7, 122.9, 117.3, 116.0, 113.9, 107.4, 39.8, 17.5. HRMS (ESI) *m*/*z*: $[M + H]^+$ Calcd for $[C_{19}H_{20}N_3O]^+$ 306.1601; Found 306.1610.

***N*'-Methyl-*N*'-(naphthalen-2-yl) 5-amino-2-methylbenzhydrazide (23).**



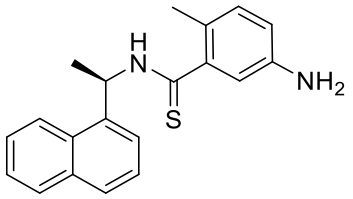
A stirred solution of *N*'-methyl-*N*'-(naphthalen-2-yl) 2-methyl-5-nitrobenzhydrazide **21** (50 mg, 0.15 mmol) in 1,4-dioxane (1.5 mL) was treated with Pd/C (7.93 mg, 0.01 mmol) then was stirred at 20 °C under hydrogen (1 atm) for 5 h. Then the mixture was filtered and the fitrate was evaporated. The residue was purified by silica gel column chromatography (eluent: 20:80 - 60:40 EtOAc:hexanes) to give the title product (**23**) (38.7 mg, 85%) as a white solid. ^{1}H NMR (500 MHz, CD_3OD) δ 8.37 (d, *J* = 8.2, 1H), 7.83 – 7.80 (m, 1H), 7.62 (dt, *J* = 7.8, 1.1 Hz, 1H), 7.51 – 7.44 (m, 2H), 7.43 – 7.35 (m, 2H), 6.92 (d, *J* = 8.2 Hz, 1H), 6.66 (dd, *J* = 8.1, 2.5 Hz, 1H), 6.58 (d, *J* = 2.5 Hz, 1H), 3.24 (s, 3H), 2.20 (s, 3H). ^{13}C NMR (126 MHz, CD_3OD) δ 170.2, 146.3, 145.2, 134.9, 134.8, 131.1, 128.6, 127.9, 125.8, 125.3, 125.0, 124.8, 124.7, 123.7, 117.1, 114.5, 113.9, 42.1, 17.2. HRMS (ESI) *m*/*z*: $[M + H]^+$ Calcd for $[C_{19}H_{20}N_3O]^+$ 306.1601; Found 306.1615.

(*R*)-2-Methyl-*N*-(1'-(naphthalene-1'-yl)ethyl)benzothioamide (24).



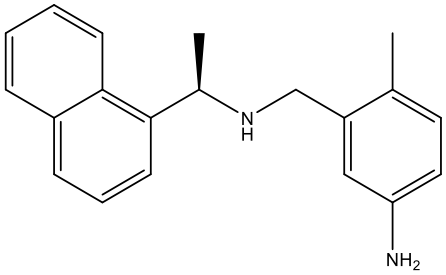
To a stirred solution of (*R*)-2-methyl-*N*-(1-(naphthalene-1-yl)ethyl)benzamide (**7724772**) (29 mg, 0.1 mmol) in anhydrous toluene (0.5 mL) was added Lawesson's reagent (49 mg, 0.12 mmol) under an argon atmosphere. The solution was gradually brought to reflux and stirred for 2 h. After such time, the solvent was removed *in vacuo* and the residue obtained was subjected to flash column chromatography on silica (eluent: 20:80 EtOAc:hexanes) affording the title compound (**24**) (12.2 mg, 35%) as a white solid.$[\alpha]_D^{21}$ = -44.0 ° (c = 1.0, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.21 (d, *J* = 8.5 Hz, 1H), 7.88 (dd, *J* = 8.1, 1.4 Hz, 1H), 7.84 (d, *J* = 8.2 Hz, 1H), 7.65 – 7.57 (m, 2H), 7.54 (dd, *J* = 8.1, 6.8 Hz, 1H), 7.46 (dd, *J* = 8.2, 7.2 Hz, 1H), 7.38 – 7.32 (m, 1H), 7.20 – 7.13 (m, 2H), 7.13 – 7.06 (m, 2H), 6.66 – 6.57 (m, 1H), 2.31 (s, 3H), 1.89 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): 199.9, 143.9, 136.4, 134.1, 133.2, 131.7, 130.9, 129.3, 129.01, 128.98, 127.1, 126.4 (2C), 126.0, 125.3, 123.8, 123.4, 50.7, 19.5, 17.8. HRMS (ESI) *m*/*z*: $[M+H]^+$ Calcd for $[C_{20}H_{20}NS]^+$ 306.1311; Found 306.1309.

(*R*)-*N*-[1-(1-Naphthyl)ethyl] 5-amino-2-methylthiobenzamide (**25**).



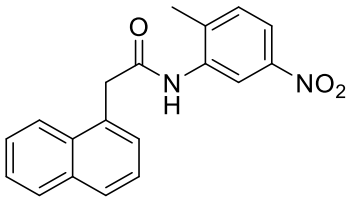
A mixture of (*R*)-*N*-[1-(1-naphthyl)ethyl] 5-amino-2-methylbenzamide (**GRL0617**) (0.035 g, 0.11 mmol) and Lawesson's reagent (0.046 g, 0.11 mmol) were dissolved in 2 mL toluene and heated to 80 °C with stirring for 2 h. The solvents were evaporated under reduced pressure and the residue dissolved in EtOAc (5 mL) and washed with water (10 x 2 mL). The organic layer was separated, dried over Na_2SO_4, filtered, and concentrated. The residue was subjected to column chromatography over silica gel (eluent: 30:70 EtOAc:hexanes) to afford the title thiobenzamide (**25**) (0.027 g, 75 %) as a brown solid. $[\alpha]^{20}_D$ +66.8 (*c* = l, $CHCl_3$); ^{1}H NMR (500 MHz, CD_3OD) δ 8.33 (d, *J* = 8.5 Hz, 1H), 7.94 (d, *J* = 8.4 Hz, 1H), 7.87 (d, *J* = 8.2 Hz, 1H), 7.67 (d, *J* = 7.2 Hz, 1H), 7.64 – 7.59 (m, 1H), 7.59 – 7.48 (m, 2H), 6.91 (d, *J* = 8.1 Hz, 1H), 6.68 – 6.57 (m, 3H), 2.15 (s, 3H), 1.81 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (126 MHz, CD_3OD) δ 201.4, 146.3, 146.0, 138.7, 135.4, 133.0, 132.0, 129.9, 129.4, 127.4, 126.9, 126.4, 124.9, 124.6, 123.4, 117.1, 115.0, 51.9, 19.1, 18.5; HRMS (ESI) (*m*/*z*): Calcd for $[C_{20}H_{21}N_2S]^+$ [M+H]+, 321.1420; Found 321.1406.

(*R*)-4-Methyl-3-(((1-(naphthalen-1-yl)ethyl)amino)methyl)aniline (26).



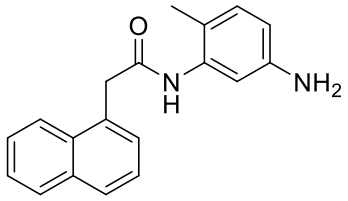
TMSCl (0.04 mL, 0.32 mmol) was added to a stirred solution of (*R*)-5-amino-2-methyl-*N*-(1-(naphthalen-1-yl)ethyl)benzamide (**GRL0617**) (41.6 mg, 0.14 mmol) in THF (1.5 mL) at 0 °C. After 20 min $LiAlH_4$ (24.9 mg, 0.66 mmol) was added and the reaction mixture was heated to reflux for 16 h. The reaction mixture was then diluted with ethyl acetate, washed with 1N NaOH and brine, dried over Na_2SO_4, filtered, and concentrated. The crude product was adsorbed on Celite® and purified over silica gel (eleuent: 0:100 - 10:90 MeOH:DCM) to give the title amine (**26**) (22.6 mg, 57%) as a yellow film. $[\alpha]_D^{23}$ = -12.28 (*c* = 0.9, $CHCl_3$), ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.18 (dd, *J* = 7.7, 2.0 Hz, 1H), 7.89 (dd, *J* = 7.0, 2.7 Hz, 1H), 7.80 – 7.74 (m, 2H), 7.55 – 7.45 (m, 3H), 6.93 (d, *J* = 7.9 Hz, 1H), 6.69 (d, *J* = 2.5 Hz, 1H), 6.51 (dd, *J* = 7.9, 2.6 Hz, 1H), 4.72 (q, *J* = 6.6 Hz, 1H), 3.66 (d, *J* = 13.2 Hz, 1H), 3.62 (d, *J* = 13.2 Hz, 1H), 2.15 (s, 3H), 1.54 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 144.5, 141.2, 139.5, 134.1, 131.5, 131.1, 129.1, 127.3, 126.2, 125.9, 125.8, 125.4, 123.2, 123.0, 115.9, 113.8, 53.5, 49.8, 23.8, 18.1. HRMS (ESI) *m/z*: $[M+H]^+$ Calcd for $[C_{20}H_{23}N_2]^+$ 291.1856; Found 291.1854.

***N*-(2-Methyl-5-nitrophenyl)-2-(naphthalen-1-yl)acetamide (27).**



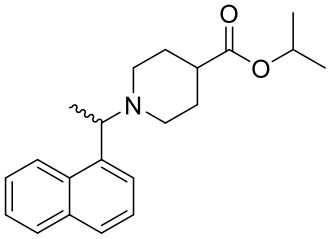
2-Methyl-5-nitroaniline (3.0 g, 19.7 mmol) was dissolved in pyridine (4 mL) and anhydrous CH_2Cl_2 (4 mL) and reaction mixture was cooled down to 0 °C before 2-(naphthalen-1-yl)acetyl chloride[19] (3.6 mL, 21.7 mmol) was added dropwise. The reaction mixture then was allowed to warm up to 20 °C and was stirred for 20 min before MeOH (10 mL) was added and the precipitate was filtered off. The precipitate was washed with MeOH (30 mL) and suspended hot EtOH (30 mL) giving a slightly yellow suspension. The white precipitate was filtered off, washed with EtOH (3×30 mL) and dried *in vacuo* to give the title compound (**27**) as a white solid (4.5 g, 70%). ^{1}H NMR (500 MHz, DMSO-*d*6) δ 9.89 (s, 1H), 8.46 (d, *J* = 2.5 Hz, 1H), 8.17 (d, *J* = 8.3 Hz, 1H), 8.02 – 7.77 (m, 3H), 7.61 – 7.25 (m, 5H), 4.28 (s, 2H), 2.35 (s, 3H). ^{13}C NMR (126 MHz, DMSO-*d*6) δ 169.8, 145.7, 138.9, 137.2, 133.4, 132.2, 132.0, 131.4, 128.5, 127.3, 126.1, 125.7, 125.6, 124.1 (2C), 119.3, 118.3, 40.1, 18.1. HRMS (ESI) *m*/*z*: $[M+Na]^+$ Calcd for $[C_{19}H_{16}N_2NaO_3]^+$ 343.1059; Found 343.1044.

***N*-(5-Amino-2-methylphenyl)-2-(naphthalen-1-yl)acetamide (28).**



N-(2-Methyl-5-nitrophenyl)-2-(naphthalen-1-yl)acetamide **27** (100 mg, 0.31 mmol) was dissolved in 1,4-dioxane (6 mL) and Pd/C (10% wt) (19.9 mg, 0.037 mmol) was added. The reaction mixture then was stirred for 4 h under H_2 (balloon) at 20 °C. After such time, the reaction mixture was filtered on Celite and the filter cake was washed with Et_2O (3×20 mL). The filtrate was concentrated to dryness and the crude product was purified by flash column chromatography over silica gel (eluent: 0:100 - 30:70 acetone:hexanes) to give the title compound (**28**) as a white solid (75 mg, 82 %). ^{1}H NMR (500 MHz, DMSO-*d*6) δ 9.31 (s, 1H), 8.20 (d, *J* = 8.2 Hz, 1H), 7.94 (d, *J* = 7.5 Hz, 1H), 7.84 (d, *J* = 8.0 Hz, 1H), 7.60 – 7.45 (m, 5H), 6.80 (d, *J* = 8.0 Hz, 1H), 6.68 (d, *J* = 2.5 Hz, 1H), 6.30 (dd, *J* = 8.0, 2.5 Hz, 1H), 4.83 (s, 2H), 4.13 (s, 2H), 1.99 (s, 3H). ^{13}C NMR (126 MHz, DMSO-*d*6) δ 168.7, 146.7, 136.5, 133.4, 132.9, 132.0, 130.3, 128.4, 127.8, 127.1, 126.0, 125.7, 125.5, 124.3, 118.3, 111.3, 110.9, 40.3, 16.8. HRMS (ESI) *m*/*z*: $[M+Na]^+$ Calcd for $[C_{19}H_{19}N_2NaO]^+$ 313.1317; Found 313.1300.

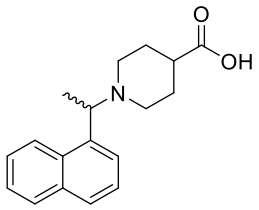
(±)-Isopropyl 1-(1-(naphthalen-1-yl)ethyl)piperidine-4-carboxylate (29).



Isopropyl piperidine-4-carboxylate hydrochloride[6] (2.07 g, 10 mmol) was added into the solution of acetonaphthone (1.70 g, 10 mmol) in anhydrous tetrahydrofuran (THF) (300 mL) under argon atmosphere. Then titanium (IV) isopropoxide (3.55 g, 12.5 mmol) was added into the reaction mixture. The reaction mixture was stirred for 12 h at room temperature, cooled down to -78 °C, and sodium cyanoborohydride (1.35 g, 20 mmol) was added. The temperature was slowly raised to room temperature, and the reaction mixture was stirred for another 24 h. The solvent was removed under reduced pressure to obtain a yellowish viscous crude product. The desired product (**29**) was obtained as a colorless liquid (2.18 g, 67%) after the silica gel column purification (eluent: 0:100 - 15:85 EtOAc:hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) ^{1}H NMR δ 8.44 (d, *J* = 7.2 Hz, 1H), 7.87 – 7.81 (m, 1H), 7.73 (d, *J* = 8.1 Hz, 1H), 7.57 (d, *J* = 7.2 Hz, 1H), 7.50 – 7.39 (m, 3H), 4.99 (hept, *J* = 6.3 Hz, 1H), 4.09 (q, *J* = 6.8 Hz, 1H), 3.17 – 3.09 (m, 1H), 2.82 (m, 1H), 2.23 (tt, *J* = 11.2, 4.1 Hz, 1H), 2.13 – 2.01 (m, 2H), 1.95 – 1.86 (m, 1H), 1.81 – 1.64 (m, 3H), 1.46 (d, *J* = 6.7 Hz, 3H), 1.20 (d, *J* = 6.4 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.1, 141.0, 134.2, 131.8,

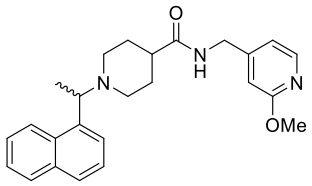
128.8, 127.4, 125.5, 125.5, 125.4, 124.6, 124.4, 67.4, 61.7, 51.6, 49.3, 41.7, 28.7 (2C), 21.9 (2C), 18.8. HRMS (ESI) *m/z*: $[M+H]^+$ Calcd for $[C_{21}H_{28}NO_2]^+$ 326.2115; Found 326.2111.

(±)-1-(1-(Naphthalen-1-yl)ethyl)piperidine-4-carboxylic acid (30).



Isopropyl 1-(1-(naphthalen-1-yl)ethyl)piperidine-4-carboxylate **29** (0.325 g, 1 mmol) was dissolved in methanol (5 mL) and aqueous KOH (2 mL, 5N), and refluxed at 70 ºC for 3 hours with continuous stirring. The solvent was evaporated under reduced pressure to obtain white solid, which was slurried with methanol (10 mL) for 15 minutes, after which the suspension was filtered and the filtrate dried over anhydrous sodium sulfate and concentrated under the reduced pressure to afford a white solid. The solid was dissolved in water (2 mL), and the pH of the solution was adjusted to four with concentrated hydrochloric acid. The precipitate formed at pH four was collected and dried to obtain of the desired product (**30**) (0.261 g, 85%) as a white solid. The compound was used in the subsequent step without further purification.

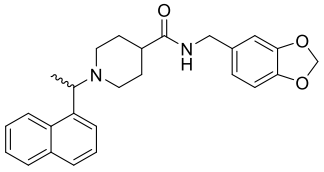
(±)-*N*-((2-Methoxypyridin-4-yl)methyl)-1-(1-(naphthalen-1-yl)ethyl)piperidine-4-carboxamide (31).



1-(1-(Naphthalen-1-yl)ethyl)piperidine-4-carboxylic acid **30** (0.141 g, 0.5 mmol) and (2-methoxypyridin-4-yl)methanamine (0.069 g, 0.5 mmol) was dissolved in anhydrous THF (3 mL) and dimethylformamide (DMF) (1 mL). Then reaction mixture was cooled to the 0 ^{o}C and 1-ethyl-3-(-3-dimethylaminopropyl) carbodiimide hydrochloride (0.115 g, 0.6 mmol) was added. The temperature was raised to room temperature and the reaction mixture was stirred for 12 h. After completion, the solvent was removed under reduced pressure to give a yellowish white solid, which was dissolved in dichloromethane (10 mL) and washed with water (5 mL), saturated sodium bicarbonate (5 mL), and then water (5 mL) and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure to obtain a white solid. The solid was subjected to silica gel column chromatography (eluent: 0:100 - 5:95 MeOH:DCM) to afford the title compound (**31**) (0.065 g, 32%) as white solid. Spectral data are in accord with that previously reported in the literature.[20] ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.43 (m, 1H), 8.06 (d, J = 5.2 Hz, 1H), 7.84 (m, 1H), 7.73 (d, J = 8.1 Hz, 1H), 7.56 (d, J = 7.0 Hz, 1H), 7.49-7.40 (m, 3H), 6.70 (dd, J = 5.4, 1.6 Hz,

1H), 6.56 (d, *J* = 1.3 Hz, 1H), 6.03 (br t, *J* = 6.0 Hz, 1H), 4.35 (d, *J* = 6.0 Hz, 2H), 4.10 (q, *J* =6.7 Hz, 1H), 3.90 (s, 3H), 3.21 (m, 1H), 2.88 (m, 1H), 2.14 (m, 1H), 2.08-1.98 (m, 2H), 1.88 (dd, *J* = 13.1, 3.4 Hz, 1H), 1.79 (td, *J* = 12.2, 3.9 Hz, 1H), 1.72 (m, 2H), 1.46 (d, *J* =6.6 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.5, 164.7, 150.5, 147.2, 140.8, 134.2, 131.8, 128.8, 127.5, 125.6, 125.5, 125.4, 124.6, 124.4, 115.7, 108.9, 61.7, 53.5, 51.9, 49.2, 43.7, 42.1, 29.8, 29.5, 18.6.

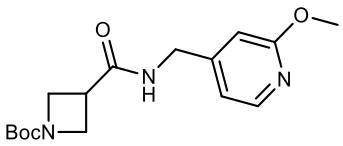
(±)-*N*-(Benzo[*d*][1,3]dioxol-5-ylmethyl)-1-(1-(naphthalen-1-yl)ethyl)piperidine-4-carboxamide (1).



1-(1-(Naphthalen-1-yl)ethyl)piperidine-4-carboxylic acid **30** (0.0705 g, 0.25 mmol) and 1,3-benzodioxole-5-methylamine (0.057 g, 0.375 mmol) was dissolved in anhydrous THF (2 mL) and DMF (1 mL). Then the reaction mixture was cooled to 0 ^{o}C and 1-ethyl-3-(-3-dimethylaminopropyl) carbodiimide hydrochloride (0.071 g, 0.375 mmol) was added. The temperature was raised to room temperature and the reaction mixture was stirred for 12 h. After completion, the solvent was removed under reduced pressure to obtain a yellowish white solid, which was dissolved in dichloromethane (5 mL) and washed with water (2.5 mL), saturated sodium bicarbonate (2.5 mL), and then water (2.5 mL) and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure to afford a white solid. The white solid was subject silica gel column chromatography (eluent: 0:100 - 5:95 MeOH:DCM) to afford the title compound (**1**) (0.042 g, 40%) as a white solid. Spectral data are in accord with that previously reported in the literature.[21] ^{1}H NMR (500 MHz, CD_3OD) δ 8.42 (d, *J* =8.1 Hz, 1H), 7.84 (dd, *J* = 7.6, 1.9 Hz, 1H), 7.74 (d, *J* = 8.1 Hz, 1H), 7.58 (dd, *J* = 7.1, 1.2 Hz, 1H), 7.49-7.41 (m, 3H), 6.72

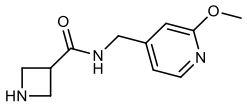
(m, 3H), 5.88 (s, 2H), 4.22-4.18 (m, 3H), 3.26 (m, 1H), 2.86 (m, 1H), 2.18 (m, 1H), 2.12-2.01 (m, 2H), 2.19 (m, 2H), 1.73-1.61 (m, 2H), 1.47 (d, J =6.6 Hz, 3H). ^{13}C NMR (126 MHz, CD_3OD) δ 178.0, 149.2, 148.1, 141.3, 135.6, 134.1, 133.1, 129.8, 128.5, 126.6, 126.4, 126.3, 125.6, 125.1, 121.8, 109.0, 102.3, 62.3, 52.6, 50.7, 44.4, 43.7, 30.1 (2C), 19.1.

***tert*-Butyl-3-(((2'-methoxypyridin-4'-yl)methyl)carbamoyl)azetidine-1-carboxylate (32).**



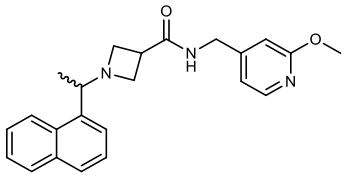
To a stirred solution of 1-(*tert*-butoxycarbonyl)azetidine-3-carboxylic acid (500 mg, 2.5 mmol), EDCI (485 mg, 3.13 mmol) and HOBT (422 mg, 3.13 mmol) in anhydrous DCM (10 mL) was added (2-methoxypyridin-4-yl)methanamine (345 mg, 2.5 mmol) followed by DIPEA (1.7 mL, 9.75 mmol) at 0 °C. The reaction mixture was gradually brought up to r.t. over a period of 15 min, and stirred for 16 h. After such time, the reaction mixture was quenched *via* addition of H_2O (20 mL) and the aqueous layer re-extracted with DCM (20 mL, 3X). The organic layers were combined, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue obtained was subjected to flash column chromatography on silica (eluent: 5:95 MeOH:DCM) to afford the title compound (**32**) (610 mg, 75%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.09 (d, J = 5.3 Hz, 1H), 6.75 (dd, J = 5.2, 1.7 Hz, 1H), 6.59 (s, 1H), 5.91 (s, 1H), 4.41 (d, J = 6.0 Hz, 2H), 4.15 – 4.08 (m, 2H), 4.07 (q, J = 9.8, 8.4 Hz, 2H), 3.91 (d, J = 1.4 Hz, 3H), 3.21 (dddd, J = 14.6, 8.3, 6.1, 1.3 Hz, 1H), 1.42 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 172.3, 164.6, 156.3, 150.3, 146.9, 115.7, 108.8, 79.9, 53.4, 51.6 (2C), 42.2, 32.9, 28.3 (3C). HRMS (ESI) *m*/*z*: $[M+H]^+$ Calcd for $[C_{16}H_{24}O_4N_4]^+$ 322.1761; Found 322.1748.

***N*-((2'-Methoxypyridin-4'-yl)methyl)azetidine-3-carboxamide (33).**



To a stirred solution of *tert*-butyl-3-(((2-methoxypyridin-4-yl)methyl)carbamoyl)azetidine-1-carboxylate **32** (610 mg, 1.9 mmol) in anhydrous DCM (2.83 mL) was added TFA (2.83 mL, 37 mmol) dropwise at r.t. The solution was stirred for 45 min, after such time, the reaction mixture was washed with $NaHCO_3$ (15 mL, 1X) and the organic layers concentrated *in vacuo*. The solution was then co-concentrated with toluene (20 mL, 3X) to afford the title compound (**33**) (400 mg, 95%) as a yellow oil. ^{1}H NMR (500 MHz, CD_3OD): δ 8.11 (dd, *J* = 5.8, 1.3 Hz, 1H), 7.07 (dt, *J* = 5.9, 1.5 Hz, 1H), 6.99 (s, 1H), 4.47 (s, 2H), 4.27 – 4.17 (m, 4H), 4.00 (d, *J* = 1.4 Hz, 3H), 3.78 – 3.67 (m, 1H). ^{13}C NMR (126 MHz, CD_3OD): δ 172.6, 164.7, 157.1, 144.7, 117.4, 109.7, 56.0, 49.6 (2C), 43.4, 37.0 . HRMS (ESI) *m*/*z*: $[M+H]^+$ Calcd for $[C_{11}H_{16}O_2N_3]^+$ 222.1237; Found 222.1229.

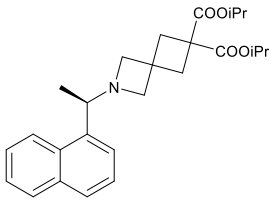
(±)-*N*-((2'-Methoxypyridin-4'-yl)methyl)-1-(1''-(naphthalene-1''-yl)ethyl)azetidine-3-carboxamide (34).



To a stirred solution of 1-acetonaphthone (230 mg, 1.5 mmol) in anhydrous THF (5 mL) was added *N*-((2'-methoxypyridin-4'-yl)methyl)azetidine-3-caboxamide **33** (400 mg, 1.8 mmol), followed by $Ti(O^iPr)_4$ (532 µL, 1.8 mmol) at r.t. The reaction mixture was stirred for 1 h, after which, it was cooled down to -78 °C, and $NaCNBH_3$ (762 mg, 3.6 mmol) was added portion-wise. The mixture was stirred for 15 min at -78 °C, after which, it was slowly brought to r.t. over 20 min and stirred for an additional 1 h. After such time, the mixture was quenched *via* addition of H_2O (5 mL) and diluted with EtOAc (10 mL). The aqueous layer was re-extracted with EtOAc (10 mL, 3X). The organic layers were combined and dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue obtained was subjected to flash column chromatography on silica (eluent: 98:2 EtOAc:Et_3N) to afford the title compound (**34**) (169 mg, 30%) as a white foam. ^1H NMR (500 MHz, CD_3OD): δ 8.22 (d, *J* = 8.4 Hz, 1H), 7.99 (d, *J* = 5.4 Hz, 1H), 7.88 – 7.75 (m, 1H), 7.71 (d, *J* = 8.2 Hz, 1H), 7.55 (dd, *J* = 7.3, 1.3 Hz, 1H), 7.48 (ddd, *J* = 8.6, 6.8, 1.6 Hz, 1H), 7.46 – 7.37 (m, 2H), 6.80 (dd, *J* = 5.2, 1.4 Hz, 1H), 6.69 – 6.61 (m, 1H), 4.30 (dd, *J* = 8.9, 3.2 Hz, 3H), 3.83

(s, 3H), 3.66 (td, *J* = 7.6, 1.7 Hz, 1H), 3.47 – 3.37 (m, 2H), 3.35 – 3.19 (m, 1H), 3.14 (t, *J* = 7.4 Hz, 1H), 1.29 (d, *J* = 6.5 Hz, 3H). ^{13}C NMR (126 MHz, CD_3OD): 174.9, 166.1, 152.8, 147.8, 139.5, 135.5, 132.6, 129.9, 128.6, 126.9, 126.6 (2C), 124.6, 124.1, 116.9, 109.6, 64.9, 57.0, 56.7, 54.1, 42.9, 35.3, 20.5. HRMS (ESI) *m*/*z*: $[M+H]^+$ Calcd for $[C_{23}H_{26}O_2N_3]^+$ 376.2019; Found 376.2003.

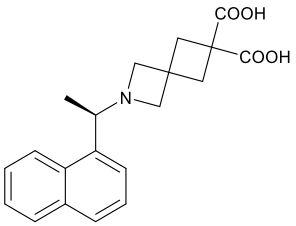
Diisopropyl (*R*)-2-(1-(naphthalen-1-yl)ethyl)-2-azaspiro[3.3]heptane-6,6-dicarboxylate (35).



Diisopropyl 3,3-bis(hydroxymethyl)cyclobutane-1,1-dicarboxylate[9] (0.5 g, 1.73 mmol) was dissolved in dry CH_3CN (4 mL) and the solution was cooled to -20 °C. Triflic anhydride (0.62 mL, 3.64 mmol) was added in a dropwise manner while keeping temperature below -10 °C. DIPEA (0.76 mL, 4.34 mmol) was then added slowly over 15 mins to the reaction mixture. After formation of the bistriflate (by mass spectral analysis), additional DIPEA (0.76 mL, 4.34 mmol) was added in a dropwise manner followed by (*R*)-(+)-1-(1-naphthyl)ethylamine (0.28 mL, 1.73 mmol), and the resulting mixture was heated to 70 °C for 2 h. After completion, the reaction mixture was cooled to room temperature and diluted with 25 mL of toluene and washed with 3 times with 20 mL of water. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a crude residue which was purified by silica gel column chromatography (eluent: 1:2 EtOAc:hexanes) to furnish the title compound (**35**) (0.58 g, 78%) as a colorless syrup. $[\alpha]_D^{22}$ = +25.5 (c = 1.0, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.18 (d, *J* = 8.2 Hz, 1H), 7.83 (dd, *J* = 8.1, 1.6 Hz, 1H), 7.70 (d, *J* = 8.2 Hz, 1H), 7.62 (d, *J* = 7.1 Hz, 1H), 7.52 – 7.38 (m, 3H), 5.02 (hept, *J* = 6.3 Hz, 2H), 4.02 (q, *J* = 6.5 Hz, 1H), 3.24 (q, *J* = 7.7 Hz, 4H), 2.67 (qd, *J* = 11.5, 1.8 Hz, 4H),

1.30 (d, J = 6.5 Hz, 3H), 1.21 (d, J = 2.4 Hz, 6H), 1.20 (d, J = 2.4 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.2, 139.2, 134.0, 131.2, 129.0, 127.2, 125.8, 125.7, 125.2, 123.9, 123.3, 68.8, 65.8 (2C), 64.7, 49.1, 39.5 (2C), 32.7, 21.6 (6C), 20.6. HRMS (ESI) m/z: $[M + H]^+$ Calcd for $[C_{26}H_{34}NO_4]^+$ 424.2482; Found 424.2473.

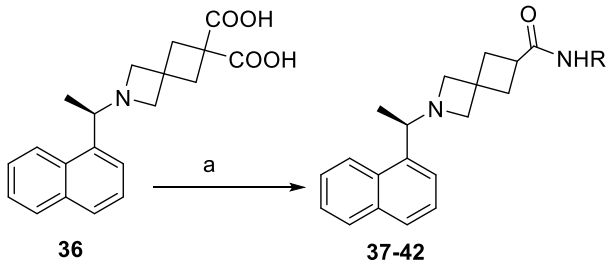
(*R*)-2-(1-(Naphthalen-1-yl)ethyl)-2-azaspiro[3.3]heptane-6,6-dicarboxylic acid (36).



To a solution of diisopropyl (*R*)-2-(1-(naphthalen-1-yl)ethyl)-2-azaspiro[3.3]heptane-6,6-dicarboxylate **35** (0.50g, 1.15 mmol) in ethanol (5 mL), a solution of NaOH (47mg, 3.90 mmol) in ethanol (1 mL) was added. The resulting mixture was refluxed for 2 h and cooled down to room temperature. A white salt formed and was filtered, washed with EtOH (2×10 mL) and dried under high vacuum to afford the disodium salt of **35**, which was dissolved in water (5 mL) and stirred for 10 min until homogeneity was achieved. The resulting solution was acidified with 2N HCl to pH = 2, leading to the formation of a slurry, which was cooled to 0 °C and stirred for 1 h. The so-obtained solid was filtered and washed with MeOH (2×10 mL) and dried under high vacuum to furnish the title compound (**36**) (0.34 g, 86%) as a white solid. $[\alpha]_D^{22}$ = +28.7 (c = 0.7, DMSO). ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.21 (d, J = 8.2 Hz, 1H), 7.88 (dd, J = 7.7, 1.8 Hz, 1H), 7.75 (d, J = 8.0 Hz, 1H), 7.61 (d, J = 7.0 Hz, 1H), 7.57 – 7.41 (m, 3H), 4.48 (q, J = 6.6 Hz, 1H), 4.32 (d, J = 9.9 Hz, 1H), 4.25 (d, J = 9.7 Hz, 1H), 2.50 (d, J = 12.5 Hz, 1H), 2.37 (d, J = 12.5 Hz, 1H), 2.29 (dd, J = 15.4, 8.9 Hz, 2H), 2.03 – 1.87 (m, 2H), 1.35 (d, J = 6.6 Hz, 3H); ^{13}C NMR (126 MHz,

DMSO-D_6) δ 172.0, 171.1, 141.7, 134.0, 131.4, 129.2, 127.3, 126.3, 126.2, 125.9, 123.6, 123.3, 75.9, 54.2, 50.5, 49.2, 38.3, 34.8, 34.7, 24.2. HRMS (ESI) *m*/*z*: $[M + H]^+$ Calcd for $[C_{20}H_{22}NO_4]^+$ 340.1543; Found 340.1528.

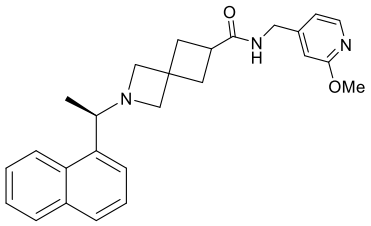
General procedure for synthesis of amides from (*R*)-2-(1-(Naphthalen-1-yl)ethyl)-2-azaspiro[3.3]heptane-6,6-dicarboxylic acid 36.



[a]Reagents and conditions: (a) RNH_2, carbonyl diimidazole, THF, rt to reflux

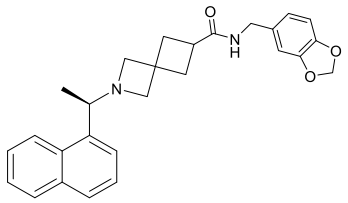
To a stirred suspension of the diacid **36** (50 mg, 0.147 mmol) in dry THF (2 mL). was added 1.1'-carbonyl diimidazole (26 mg, 0.22 mmol) in two portions. The resulting mixture was stirred at rt for 2 h under an argon atmosphere. The amine (0.16 mmol) was added in one portion and the mixture refluxed (70 ^oC) for 0.5 h. The reaction mixture was cooled down to room temperature and the solvent was removed *in vacuo* to give a crude residue, which was dissolved in 20 mL of ethyl acetate and washed with saturated $NaHCO_3$ solution (10 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a crude residue which was purified by silica gel column chromatography (eluent: 1:99 - 10:90 MeOH:DCM) to afford the desired amide (**37**-**42**).

***N*-((2-Methoxypyridin-4-yl)methyl) (*R*)-2-(1-(naphthalen-1-yl)ethyl)-2-azaspiro[3.3]heptane-6-carboxamide (37).**



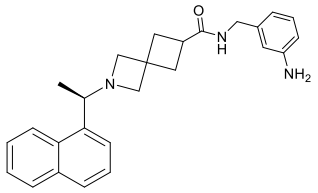
This colorless oil (**37**) was prepared according to the general procedure (44 mg, 72%); $[\alpha]_D^{22}$ = +8.9 (c = 0.5, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.15 (d, *J* = 8.1 Hz, 1H), 8.06 (d, *J* = 5.3 Hz, 1H), 7.84 (dd, *J* = 8.1, 1.6 Hz, 1H), 7.71 (d, *J* = 8.2 Hz, 1H), 7.64 (d, *J* = 7.2 Hz, 1H), 7.53 – 7.41 (m, 3H), 6.72 (dd, *J* = 5.4, 1.5 Hz, 1H), 6.56 (s, 1H), 5.76 (t, *J* = 6.0 Hz, 1H), 4.35 (d, *J* = 6.0 Hz, 2H), 4.04 (q, *J* = 6.3 Hz, 1H), 3.89 (s, 3H), 3.38 – 3.19 (m, 4H), 2.85 (p, *J* = 8.1 Hz, 1H), 2.49 – 2.41 (m, 2H), 2.40 – 2.29 (m, 2H), 1.33 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.6, 164.7, 150.2, 147.2, 139.1, 134.0, 131.2, 129.0, 127.2, 125.8, 125.7, 125.2, 123.9, 123.2, 115.7, 109.0, 66.1, 65.2, 64.7, 53.5, 42.3, 36.2, 35.8, 35.0, 34.5, 20.6. HRMS (ESI) *m*/*z*: $[M + H]^+$ Calcd for $[C_{26}H_{30}N_3O_2]^+$ 416.2332; Found 416.2317.

***N*-(Benzo[d][1,3]dioxol-5-ylmethyl) (*R*)-2-(1-(naphthalen-1-yl)ethyl)-2-azaspiro[3.3]heptane-6-carboxamide (38).**



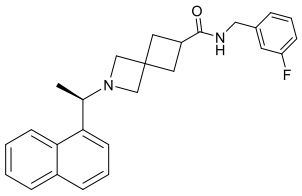
This colorless syrup (**38**) was prepared according to the general procedure (51 mg, 81%); $[\alpha]_D^{22}$ = +9.7 (c = 0.7, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 8.17 (d, *J* = 8.4 Hz, 1H), 7.83 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.71 (d, *J* = 8.1 Hz, 1H), 7.62 (d, *J* = 7.1 Hz, 1H), 7.55 – 7.38 (m, 3H), 6.80 – 6.68 (m, 2H), 6.68 (dd, *J* = 7.9, 1.7 Hz, 1H), 5.90 (s, 2H), 5.67 (t, *J* = 5.7 Hz, 1H), δ 4.28 (d, *J* = 5.7 Hz, 1H), 4.03 (q, *J* = 6.5 Hz, 1H), 3.25 (dd, *J* = 15.6, 7.6 Hz, 2H), 3.18 (t, *J* = 7.0 Hz, 2H), 2.79 (p, *J* = 8.3 Hz, 1H), 2.42 (dt, *J* = 11.6, 8.0 Hz, 2H), 2.38 – 2.21 (m, 2H), 1.31 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.3, 148.0, 147.0, 139.2, 134.0, 132.3, 131.2, 129.0, 127.2, 125.8, 125.7, 125.2, 123.9, 123.3, 121.1, 108.4, 108.3, 101.1, 66.2, 65.2, 64.7, 43.5, 36.2, 35.9, 35.1, 34.4, 20.6. HRMS (ESI) *m*/*z*: $[M + H]^+$ Calcd for $[C_{27}H_{29}N_2O_3]^+$ 429.2172; Found 429.2167.

***N*-(3-Aminobenzyl) (*R*)-2-(1-(naphthalen-1-yl)ethyl)-2-azaspiro[3.3]heptane-6-carboxamide (39).**



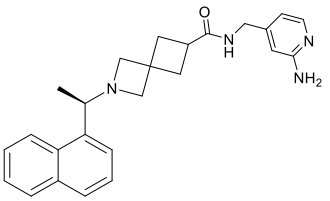
This colorless syrup (**39**) was prepared according to the general procedure (40 mg, 68%); $[\alpha]_D^{22}$ = +24.5 (c = 0.4, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 8.19 (d, *J* = 8.5 Hz, 1H), 7.84 (d, *J* = 8.0 Hz, 1H), 7.71 (d, *J* = 8.2 Hz, 1H), 7.63 (d, *J* = 7.2 Hz, 1H), 7.46 (dq, *J* = 21.2, 7.3 Hz, 3H), 7.07 (t, *J* = 7.6 Hz, 1H), 6.60 (d, *J* = 7.6 Hz, 1H), 6.54 (d, *J* = 8.2 Hz, 2H), 5.72 (t, *J* = 5.8 Hz, 1H), 4.28 (d, *J* = 5.7 Hz, 2H), 4.03 (q, *J* = 6.5 Hz, 1H), 3.65 (s, 2H), 3.36 – 3.07 (m, 4H), 2.79 (p, *J* = 8.3 Hz, 1H), 2.43 (dt, *J* = 14.2, 7.2 Hz, 2H), 2.38 – 2.21 (m, 2H), 1.31 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.4, 146.9, 139.6, 139.3, 134.0, 131.2, 129.7, 129.0, 127.2, 125.8, 125.7, 125.2, 123.9, 123.3, 117.8, 114.4, 114.3, 66.2, 65.2, 64.7, 43.7, 36.3, 35.9, 35.1, 34.4, 20.7. HRMS (ESI) *m*/*z*: $[M + H]^+$ Calcd for $[C_{26}H_{30}N_3O]^+$ 400.2383; Found 400.2372.

***N*-(3-Fluorobenzyl) (*R*)-2-(1-(naphthalen-1-yl)ethyl)-2-azaspiro[3.3]heptane-6-carboxamide (40).**



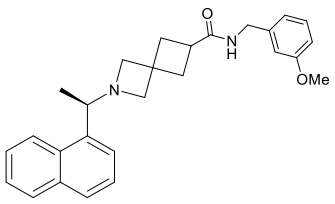
This colorless syrup (**40**) was prepared according to the general procedure (52 mg, 88%); $[\alpha]_D^{22}$ = +7.4 (c = 0.6, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 8.15 (d, *J* = 8.3 Hz, 1H), 7.84 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.72 (d, *J* = 8.2 Hz, 1H), 7.65 (d, *J* = 7.1 Hz, 1H), 7.57 – 7.39 (m, 3H), 7.31 – 7.20 (m, 1H), 7.00 (d, *J* = 7.7 Hz, 1H), 6.98 – 6.87 (m, 2H), 5.70 (t, *J* = 6.0 Hz, 1H), 4.39 (d, *J* = 5.8 Hz, 2H), 4.11 (s, 1H), 3.30 (dd, *J* = 33.5, 7.9 Hz, 4H), 2.83 (p, *J* = 8.2 Hz, 1H), 2.45 (dt, *J* = 11.7, 7.2 Hz, 2H), 2.42 – 2.25 (m, 2H), 1.34 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.4, 163.0 (d, *J* = 247.2), 141.07, 141.01, 134.0, 131.1, 130.3 (d, *J* = 8.3), 129.0, 127.4, 125.8 (2C), 125.3, 124.0, 123.2 (d, *J* = 2.7), 123.1, 114.6 (d, *J* = 19.8), 114.4 (d, *J* = 19.6), 65.9, 65.1, 64.4, 43.1, 36.2, 35.8, 35.0, 34.5, 20.4. HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $[C_{26}H_{28}N_2OF]^+$ 403.2180; Found 403.2169.

***N*-((2-Aminopyridin-4-yl)methyl) (*R*)-2-(1-(naphthalen-1-yl)ethyl)-2-azaspiro[3.3]heptane-6-carboxamide (41).**



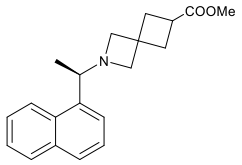
This white foam (**41**) was prepared according to the general procedure (43 mg, 73%); $[\alpha]_D^{22}$ = +13.0 (c = 0.7, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 8.18 (s, 1H), 7.98 (d, *J* = 5.6 Hz, 1H), 7.88 – 7.80 (m, 1H), 7.71 (d, *J* = 8.0 Hz, 1H), 7.61 (d, *J* = 7.2 Hz, 1H), 7.53 – 7.38 (m, 3H), 6.53 – 6.46 (m, 1H), 6.34 (s, 1H), 5.62 (t, *J* = 5.9 Hz, 1H), 4.38 (s, 2H), 4.29 (d, *J* = 6.0 Hz, 2H), 4.03 (q, *J* = 6.5 Hz, 1H), 3.34 – 3.15 (m, 4H), 2.85 (p, *J* = 8.4 Hz, 1H), 2.51 – 2.24 (m, 4H), 1.30 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.6, 158.8, 149.2, 148.6, 139.2, 134.0, 131.2, 129.0, 127.2, 125.7, 125.7 , 125.2, 123.9, 123.2, 113.0, 106.8, 66.1, 65.2, 64.7, 42.5, 36.3, 35.9, 35.1, 34.5, 20.6. HRMS (ESI) *m*/*z*: $[M + H]^+$ Calcd for $[C_{25}H_{29}N_4O]^+$ 401.2335; Found 401.2320.

***N*-(3-Methoxybenzyl) (*R*)-2-(1-(naphthalen-1-yl)ethyl)-2-azaspiro[3.3]heptane-6-carboxamide (42).**



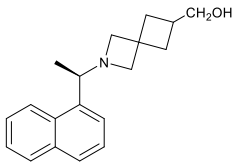
This colorless syrup (**42**) was prepared according to the general procedure (51 mg, 84%); $[\alpha]_D^{22}$ = +5.3 (c = 1.0, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 8.17 (d, *J* = 8.1 Hz, 1H), 7.84 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.71 (d, *J* = 8.1 Hz, 1H), 7.62 (d, *J* = 7.1 Hz, 1H), 7.53 – 7.38 (m, 3H), 7.22 (t, *J* = 7.8 Hz, 1H), δ 6.84 – 6.77 (m, 3H), 5.62 (t, *J* = 5.8 Hz, 1H), 4.37 (d, *J* = 5.7 Hz, 2H), 4.04 (q, *J* = 6.6 Hz, 1H), 3.77 (s, 3H), 3.27 (dd, *J* = 15.6, 7.7 Hz, 2H), 3.22 – 3.14 (m, 2H), 2.81 (p, *J* = 8.3 Hz, 1H), 2.45 (dt, *J* = 11.6, 7.6 Hz, 2H), 2.39 – 2.24 (m, 2H), 1.31 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.3, 159.9, 140.0, 139.2, 134.0, 131.2, 129.8, 129.0, 127.2, 125.8, 125.7, 125.2, 123.9, 123.2, 120.0, 113.4, 113.0, 66.1, 65.2, 64.7, 55.3, 43.6, 36.3, 35.9, 35.1, 34.4, 20.6 . HRMS (ESI) *m*/*z*: $[M + H]^+$ Calcd for $[C_{27}H_{31}N_2O_2]^+$ 415.2380; Found 415.2373.

Methyl (*R*)-2-(1-(naphthalen-1-yl)ethyl)-2-azaspiro[3.3]heptane-6-carboxylate (43).



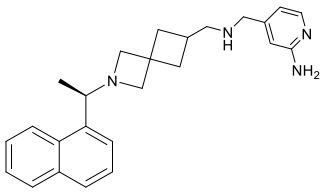
To a stirred suspension of (*R*)-2-(1-(naphthalen-1-yl)ethyl)-2-azaspiro[3.3]heptane-6,6-dicarboxylic acid **36** (0.50g, 1.47 mmol) in dry THF (5 mL). was added 1.1'-carbonyl diimidazole (0.36g, 2.21 mmol) in two portions. The resulting mixture was stirred at rt for 2h under an argon atmosphere. Dry MeOH (2 mL) was added in one portion and the mixture refluxed (70 ^{o}C) for 0.5 h. The reaction mixture was cooled down to room temperature and solvent was removed *in vacuo* to give a crude residue. This residue was dissolved in 20 mL of ethyl acetate and washed with saturated $NaHCO_3$ solution (10 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a residue which was purified by neutral alumina column chromatography (eluent: 5:95 - 10:90 EtOAc:hexanes) to furnish the title compound (**43**) (0.42 g, 92%) as a colorless syrup; $[\alpha]_D^{22}$ = +36.8 (c = 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.19 (d, *J* = 8.4 Hz, 1H), 7.84 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.72 (d, *J* = 8.1 Hz, 1H), 7.64 (d, *J* = 7.1 Hz, 1H), 7.54 – 7.40 (m, 3H), 4.03 (q, *J* = 6.5 Hz, 1H), 3.65 (s, 3H), 3.27 (d, *J* = 7.4 Hz, 1H), 3.26 – 3.16 (m, 3H), 2.98 (p, *J* = 8.4 Hz, 1H), 2.48 – 2.30 (m, 4H), 1.32 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.8, 139.3, 134.0, 131.2, 129.0, 127.2, 125.8, 125.7, 125.2, 123.9, 123.3, 66.1, 65.4, 64.7, 51.7, 36.2, 35.9, 34.7, 33.3, 20.7. HRMS (ESI) *m*/*z*: $[M + H]^+$ Calcd for $[C_{20}H_{24}NO_2]^+$ 310.1801; Found 310.1796.

(*R*)-2-(1-(Naphthalen-1-yl)ethyl)-2-azaspiro[3.3]heptane-6-methanol (44).



To a suspension of LAH (27.6 mg, 0.73 mmol) in THF (1 mL) was added a solution of **43** (150 mg, 0.49 mmol) in THF (1 mL) in a dropwise manner at 0 °C under an argon atmosphere. The reaction was then brought to rt, stirred until completion (monitored by TLC and mass spectral analysis), then quenched with ice cold water and diluted with CH_2Cl_2 (15 mL). The organic layer was separated, collected, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a residue which was purified by neutral alumina column chromatography (eluent: 20:80 - 30:70 EtOAc:Hexanes) to furnish the title compound (**44**) (0.12 g, 87%) as white solid. $[\alpha]_D^{22}$ = +32.1 (c = 0.6, DMSO); ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.23 (d, J = 8.7 Hz, 1H), 7.90 – 7.83 (m, 1H), 7.73 (d, J = 8.1 Hz, 1H), 7.55 (d, J = 7.1 Hz, 1H), 7.45 (m, 3H), 4.38 (t, J = 5.3 Hz, 1H), 3.96 (q, J = 6.6 Hz, 1H), 3.27 – 3.23 (m, 2H), 3.12 – 3.03 (m, 2H), 3.03 – 2.95 (m, 2H), 2.15 (h, J = 6.9, 6.4 Hz, 1H), 2.07 – 1.99 (m, 2H), 1.82 – 1.72 (m, 2H), 1.16 (d, J = 6.4 Hz, 3H); ^{13}C NMR (126 MHz, DMSO-D_6) δ 140.0, 134.0, 131.2, 129.2, 127.3, 126.2, 126.2, 125.8, 124.3, 123.8, 66.4, 66.0, 65.5, 40.3, 35.5 (2C), 34.6, 32.3, 21.1. HRMS (ESI) *m*/*z*: [M + H] Calcd for $[C_{19}H_{24}NO]^+$ 282.1852; Found 282.1845.

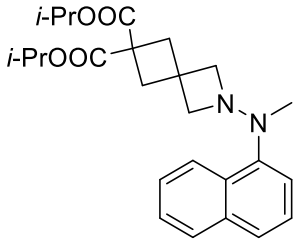
(*R*)-*N*-((2-Methoxypyridin-4-yl)methyl)-2-(1-(naphthalen-1-yl)ethyl)-2-azaspiro[3.3]heptane-6-methanamine (45).



A stirred solution of (*R*)-2-(1-(naphthalen-1-yl)ethyl)-2-azaspiro[3.3]heptane-6-methanol **44** (0.11g, 0.39 mmol) in CH_2Cl_2 (3 mL) was treated with Dess Martin Periodinane (0.33 g, 0.78 mmol), and then stirred at rt for 2 h. After complete conversion, the reaction mixture was diluted with 5 mL CH_2Cl_2, 5 mL of sat. aqueous $NaHCO_3$, 5 mL of aqueous sodium thiosulfate and stirred for 0.5 h at room temperature. The organic layer was separated, collected, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a residue which was used immediately for the next reaction without purification. The above residue was dissolved in dry MeOH (2 mL), treated with (2-methoxypyridin-4-yl)methanamine (0.14 mL, 0.8 mmol), and stirred at room temperature for 2 h. $NaCNBH_3$ (74.2 mg, 1.18 mmol) and AcOH (0.09 mL, 1.57 mmol) were then added and the mixture was stirred overnight at room temperature under an argon atmosphere. The reaction was quenched with 2 mL Et_3N, and the volatiles evaporated under high vacuum to give a residue, which was dissolved in CH_2Cl_2 (20 mL), and diluted with saturated aqueous $NaHCO_3$. The organic layer was separated, collected, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a residue, which was purified by silica gel column chromatography (eluent: 5:95 - 10:90 MeOH:DCM) to furnish the title compound (**45**) (91 mg, 58%) as a colorless syrup; $[\alpha]_D^{22}$ = +10 (c = 0.4, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.20 – 8.13 (m, 1H), 8.07 (d, *J* = 5.2 Hz, 1H), 7.87 – 7.82 (m, 1H), 7.72 (d, *J* = 8.2 Hz, 1H), 7.60 (d, *J* = 7.0 Hz, 1H), 7.45 (m, 3H), 6.87 (dd, *J* = 5.3, 1.3 Hz, 1H), 6.73 (s, 1H), 4.52 (q, *J* = 6.6 Hz, 1H), 3.93 (s, 3H), 3.61 (s,

2H), 2.83 – 2.73 (m, 3H), 2.71 (d, J = 9.4 Hz, 1H), 2.47 (d, J = 11.7 Hz, 1H), 2.37 (d, J = 11.8 Hz, 1H), 2.30 – 2.24 (m, 1H), 1.89 (s, 1H), 1.71 (dt, J = 10.9, 7.1 Hz, 2H), 1.57 (dt, J = 22.9, 7.9 Hz, 2H), 1.45 (d, J = 6.6 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.6, 151.7, 146.6, 141.3, 134.0, 131.4, 129.0, 127.2, 125.7, 125.7, 125.3, 123.1, 122.9, 117.3, 110.3, 60.2, 59.9, 56.4, 55.1, 54.3, 53.4, 42.9, 35.6, 35.4, 30.2, 23.6. HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $[C_{26}H_{32}N_3O]^+$ 402.2539; Found 402.2530.

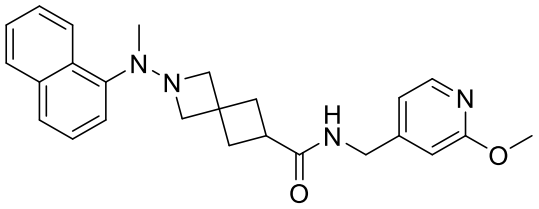
Diisopropyl *N*-[(naphthalen-1-yl)methylamino]-2-azaspiro[3.3]heptane-6,6-dicarboxylate (46).



To a stirred mixture of diisopropyl 3,3-bis(hydroxymethyl)cyclobutane-1,1-dicarboxylate[9] (167 mg, 0.58 mmol) and acetonitrile (1 mL) at -20 °C, was carefully added trifluoromethanesulfonic

anhydride (0.2 mL, 1.22 mmol) while maintaining the temperature below -10 °C. DIPEA (0.25 mL, 1.45 mmol) was then added slowly to the reaction mixture over 10 min. After formation of the bistriflate was complete (by mass spectral analysis), a second aliquot of DIPEA (0.25 mL, 1.45 mmol) was added dropwise followed by addition of *N*-methyl-*N*-(1-naphthyl)hydrazine **18** (100 mg, 0.58 mmol) and heating of the resulting mixture to 70 °C for 2 h. The reaction mixture was cooled to room temperature and diluted with ethyl acetate (6 mL), washed with water (3×5 mL) and brine (3 mL). The combined organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude residue was purified by silica gel column chromatography (0 to 3% methanol/dichloromethane) to yield the title product (**46**) (185 mg, 75%) as a brown foam. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.34 (br s, 1H), 8.00 (m, 2H), 7.79 (t, *J* = 7.8 Hz, 1H), 7.62 (t, *J* = 7.6 Hz, 1H), 7.54 (t, *J* = 8.1 Hz, 1H), 7.37 (t, *J* = 8.2 Hz, 1H), 5.05 (d, *J* = 11.7 Hz, 1H), 4.94 (h, 6.3 Hz, 2H), 4.71 (d, *J* = 11.7 Hz, 1H), 4.08 (s, 3H), 3.85 (dd, *J* = 12.3, 7.0 Hz, 1H), 3.36 (dd, *J* = 12.3, 9.7 Hz, 1H), 2.98 – 2.87 (m, 2H), 2.15 (d, *J* = 12.4 Hz, 2H), 1.19 – 1.10 (m, 9H), 1.07 (d, *J* = 6.3 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.5, 170.4, 140.2, 135.9, 133.1, 130.6, 129.0, 127.2, 124.8, 123.6, 122.4, 122.0, 120.5, 119.4, 79.5, 69.6, 58.4, 57.1, 47.8, 42.0, 39.0, 38.0, 21.5, 21.4, 21.4 . HRMS (ESI) *m*/*z*: $[M + H]^+$ Calcd for $[C_{25}H_{33}N_2O_4]^+$ 425.2435; Found 425.2445.

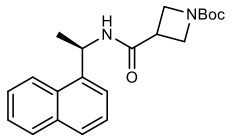
***N*-[(2-Methoxypyridin-4-yl)methyl] *N'*-[(naphthalen-1-yl)methylamino]-2-azaspiro[3.3]heptane-6-carboxamide (47).**



Diisopropyl *N*-[(naphthalen-1-yl)methylamino]-2-azaspiro[3.3]heptane-6,6-dicarboxylate **46** (60 mg, 0.14 mmol) and methanol (0.2 mL), and 2 M aqueous NaOH (0.6 mL) were stirred at 20 °C for 12 h. The reaction mixture was then acidified by 3 N HCl to pH 3 and then extracted with diethyl ether (4×1 mL). The combined organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude mixture was dissolved in dry THF (1.6 mL) and treated with 1,1′-carbonyl diimidazole (30.5 mg, 0.19 mmol) in two portions. The resulting mixture was stirred at 20 °C for 2 h, then was treated with (2-methoxypyridin-4-yl)methylamine (16.2 µL, 0.13 mmol) and the temperature increased to 70 °C for 0.5 h. After cooling to 20 °C the mixture was concentrated *in vacuo*, dissolved in ethyl acetate (2 mL), washed with saturated aqueous $NaHCO_3$ (1 mL), dried over Na_2SO_4, filtered, concentrated under reduced pressure to give a residue, which was purified by column chromatography on neutral alumina (eluent: 50:50 - 100:0 EtOAc:hexanes) to furnish the title product (**47**) (43 mg, 73%, over 2 steps) as a colorless syrup. ^{1}H NMR (500 MHz, CD_3OD) δ 8.63 (br s, 1H), 8.37 (d, *J* = 7.9 Hz, 1H), 8.14 (d, *J* = 8.2 Hz, 1H), 8.10 (d, *J* = 11.9 Hz, 1H), 8.00 (dd, *J* = 5.4, 3.3 Hz, 1H), 7.79 (q, *J* = 7.3 Hz, 1H), 7.72 – 7.65 (m, 2H), 7.62 (td, *J* = 8.1, 3.3 Hz, 1H), 7.03 (s, 1H), 6.81 (t, *J* = 5.1 Hz, 1H), 6.63 (s, 1H), 5.03 (d, *J* = 11.4 Hz, 1H), 4.62 (t, *J* = 11.5 Hz, 1H), 4.31 (s, 2H), 3.95 – 3.83 (m, 6H), 3.78 (dd, *J* = 17.7, 12.5 Hz, 1H), 3.48 (dd, *J* = 21.5, 12.5 Hz, 1H), 3.22 – 3.08 (m, 1H), 2.73 (td, *J* = 10.0, 9.1, 5.3 Hz, 1H), 2.68 – 2.59 (m, 1H), 2.41 – 1.99 (m, 2H). ^{13}C NMR (126 MHz, CD_3OD) δ 175.5, 164.8, 151.5,

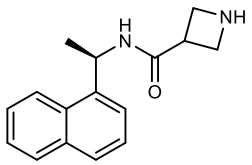
146.5, 142.4, 136.1, 132.7, 130.0, 128.2, 126.9, 124.6, 123.0, 121.7, 119.9, 115.5, 108.3, 80.4, 80.3, 58.0, 57.6, 52.7, 41.6 , 35.6, 33.6, 33.2. HRMS (ESI) *m*/z: $[M + H]^+$ Calcd for $[C_{25}H_{29}N_4O_2]^+$ 417.2285; Found 417.2292.

***tert*-Butyl (*R*)-3-[(1'-(Naphthalen-1'-yl)ethyl]carbamoyl)azetidine-1-carboxylate(48).[8]**



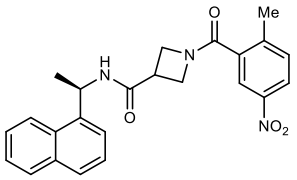
A stirred solution of 1-(*tert*-butoxycarbonyl)azetidine-3-carboxylic acid[8] (1.57 g, 7.8 mmol) in anhydrous DCM (15 mL) was treated with 1,1'-carbonyl diimidazole (2.53 g, 15.6 mmol) and stirred for 1 h at r.t. After such time, *(R)*-1-(1-naphthyl)ethylamine (3.75 mL, 23.4 mmol) was added and stirring continued for 1 h at r.t. The reaction mixture was then filtered and the filtrate diluted with EtOAc (60 mL) and subsequently quenched *via* addition of H_2O (30 mL). The layers were separated and the aqueous layer re-extracted with EtOAc (20 mL, 3X). The organic layers were combined and dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue obtained was subjected to flash column chromatography on silica (eluent: 40:60 EtOAc:Hexanes) to afford the title compound (**48**) (2.15 g, 78%) as a yellow oil. $[\alpha]_D^{21}$ = +46.0 ° (c = 1.0, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$, T = 313K): δ 8.07 (d, *J* = 8.5 Hz, 1H), 7.87 (d, *J* = 8.1 Hz, 1H), 7.81 (d, *J* = 8.0 Hz, 1H), 7.57 – 7.44 (overlapping m, 4H), 5.97 (p, *J* = 7.0 Hz, 1H), 5.66 (br d, *J* = 8.0 Hz, 1H), 4.14 (br t, *J* = 7.2 Hz, 1H), 4.06 (br t, *J* = 7.3 Hz, 1H), 4.01 (t, *J* = 8.5 Hz, 1H), 3.96 (t, *J* = 8.5 Hz, 1H), 3.09 (m, 1H), 1.69 (d, *J* =6.7 Hz, 3H), 1.43 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$, T = 313K): δ 170.5, 156.3, 138.0, 134.2, 131.3, 129.0, 128.8, 126.9, 126.2, 125.3, 123.4, 122.8, 79.9, 51.9 (2C), 45.1, 33.7, 28.5 (3C), 20.8. HRMS (ESI) *m*/*z*: $[M+Na]^+$ Calcd for $[C_{21}H_{26}O_3N_2Na]^+$ 377.1836; Found 377.1832.

(*R*)-*N*-(1'-(Naphthalene-1'-yl)ethyl)azetidine-3-carboxamide (49).



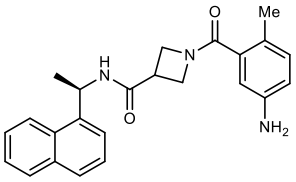
A stirred solution of *tert*-butyl (*R*)-3-[(1-(naphthalen-1-yl)ethyl]carbamoyl)azetidine-1-carboxylate **48** (2.1 g, 5.9 mmol) in anhydrous DCM (9 mL) was treated with trifluoroacetic acid (TFA) (9 mL, 118 mmol) and stirred at r.t. for 45 min. After such time, the reaction mixture was washed with $NaHCO_3$ (15 mL, 1X) and the organic layers concentrated *in vacuo*. The solution was then co-concentrated with toluene (20 mL, 3X) to afford the title compound (**49**) (1.05 g, 70%) as a white solid. $[\alpha]_D^{21}$ = +32.0 ° (c = 1.0, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.74 (s, 1H), 7.90 (dd, *J* = 8.5, 3.2 Hz, 1H), 7.78 (dd, *J* = 8.2, 3.1 Hz, 1H), 7.72 (dd, *J* = 8.4, 3.2 Hz, 1H), 7.51 – 7.34 (m, 4H), 7.23 (dd, *J* = 7.3, 3.4 Hz, 1H), 5.65 (dt, *J* = 9.6, 6.3 Hz, 1H), 4.21 (s, 1H), 4.07 (s, 1H), 3.82 (m, 2H), 3.64 (q, *J* = 8.2 Hz, 1H), 1.55 (dd, *J* = 7.3, 3.8 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 169.9, 138.0, 133.9, 130.4, 129.3, 128.5, 126.9, 126.2, 125.7, 122.3 (2C), 48.9, 46.4, 35.9, 27.7, 21.1. HRMS (ESI) *m*/*z*: $[M+H]^+$ Calcd for $[C_{16}H_{19}ON_2]^+$ 255.1492; Found 255.1488.

(*R*)-1'-(2'-Methyl-5'-nitrobenzoyl)-*N*-(1''-(naphthalene-1''-yl)ethyl)azetidine-3-carboxamide (50).



A stirred solution of (*R*)-*N*-(1'-(naphthalene-1'-yl)ethyl)azetidine-3-carboxamide **49** (700 mg, 2.75 mmol) in anhydrous DCM (8 mL) was treated with DIPEA (1.9 mL, 10 mmol) at 0 °C and stirred for 10 min. After such time, 2-methyl-5-nitrobenzoyl chloride (547 mg, 2.75 mmol) was added portion-wise and the solution was stirred for 20 min. After such time, the reaction mixture was filtered and the solids washed with DCM (10 mL, 3X). The filtrate was then concentrated *in vacuo* and the residue obtained was subjected to flash column chromatography on silica (1:9 MeOH:DCM) to afford the title compound (**50**) (688 mg, 60%) as an orange solid. $[\alpha]_D^{21}$ = +69.0 ° (c = 1.0, $CHCl_3$). ^{1}H NMR (500 MHz, CD_3OD): δ 8.21 – 8.13 (m, 2H), 8.07 (dd, *J* = 12.1, 8.4 Hz, 1H), 7.83 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.76 (m, 1H), 7.54-7.38 (m, 5H), 5.83 (qd, *J* = 7.0, 2.3 Hz, 1H), 4.37 (m, 1.5 H), 4.14 (dd, *J* = 5 Hz, 0.5H), 4.10 (d, *J* = 7.2 Hz, 1H), 4.04 (t, *J* = 8.8 Hz, 0.5 H), 3.94 (dd, *J* = 9.0, 5.6 Hz, 0.5 H), 3.45 (dddd, *J* = 11.6, 8.6, 5.6, 3.6 Hz, 1H), 2.44 (s, 3H), 1.58 (dd, *J* = 11.7, 6.9 Hz, 3H).* ^{13}C NMR (126 MHz, CD_3OD): δ 172.7, 170.6, 147.5, 144.9, 140.0, 135.9 , 135.5, 133.2, 132.2, 129.9, 129.1, 127.3, 126.8, 126.4, 125.5, 124.0, 123.5, 122.8, 54.8, 52.3, 46.2, 34.1, 21.3, 19.5.* HRMS (ESI) *m*/*z*: $[M+Na]^+$ Calcd for $[C_{24}H_{23}O_4N_3Na]^+$ 440.1581; Found 440.1571. *As a result of the dynamic conformational assembly about the azetidine ring due to pyramidalization, doubling of ^{13}C resonances and splitting of azetidine protons was observed. Where doubling of ^{13}C resonances appear, one signal is reported.[22, 23]

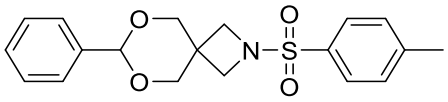
(*R*)-1'-(5'-Amino-2'-methylbenzoyl)-*N*-(1''-(naphthalene-1''-yl)ethyl)azetidine-3-caboxamide (51).



To a stirred solution of (*R*)-1'-(2'-methyl-5'-nitrobenzoyl)-*N*-(1''-(naphthalene-1''-yl)ethyl)azetidine-3-carboxamide **50** (120 mg, 0.29 mmol) in dioxane (6 mL) was added Pd/C (10% wt) (12 mg, 0.11 mmol). The vessel was purged with H_2 (3X), after which, H_2 was allowed to continuously flow into the stirred vessel for 12 h. After such time, the reaction mixture was filtered over Celite and washed with MeOH (10 mL). The filtrate was concentrated *in vacuo* and the residue obtained was subjected to flash column chromatography on silica (eluent: 10:90 MeOH:DCM – 100:0 MeOH:DCM) to afford the title compound (**51**) (92 mg, 82%) as a pink solid. $[\alpha]_D^{21}$ = +60.0 ° (c = 1.0, $CHCl_3$). ^{1}H NMR (500 MHz, CD_3OD): δ 8.07 (t, *J* = 10.0 Hz, 1H), 7.91 – 7.83 (m, 1H), 7.78 (dd, *J* = 11.3, 8.2 Hz, 1H), 7.56-7.39 (m, 4H), 6.97 (t, *J* = 8.8 Hz, 1H), 6.68 (tt, *J* = 8.1, 2.4 Hz, 1H), 6.59 (dd, *J* = 16.6, 2.3 Hz, 1H), 5.83 (q, *J* = 7.0 Hz, 1H), 4.23 (m, 1.5H), 4.11 (t, *J* = 6.2 Hz, 1H), 4.04 (t, *J* = 8.9 Hz, 0.5H), 3.95 (d, *J* = 7.2 Hz, 1H), 3.40 (q, *J* = 7.5, 6.7 Hz, 1H), 2.18 (dd, *J* = 12.4, 2.0 Hz, 3H), 1.62 – 1.55 (m, 3H).* ^{13}C NMR (126 MHz, CD_3OD): δ 173.9, 172.8, 146.9, 140.1, 135.5, 134.8, 132.6, 132.2, 129.9, 129.0, 127.3, 126.8, 126.4, 124.9, 124.0, 123.5, 118.2, 114.1, 54.8, 52.0 , 46.2, 33.9, 21.4, 18.2.* HRMS (ESI) *m*/*z*: $[M+H]^+$ Calcd for $[C_{24}H_{26}O_2N_3]^+$ 388.2019; Found 388.2015.

*As a result of the dynamic conformational assembly about the azetidine ring due to pyramidalization, doubling of ^{13}C resonances and splitting of azetidine protons was observed. Where doubling of ^{13}C resonances appear, one signal is reported.[22, 23]

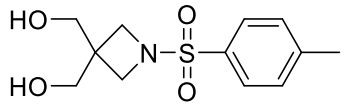
7-Phenyl-2-tosyl-6,8-dioxa-2-azaspiro[3.5]nonane (53).



A stirred suspension of NaH (60 % dispersion in mineral oil) (262 mg, 6.57 mmol) in anhydrous DMF (20 mL) was treated with KI (43.6 mg, 0.263 mmol) followed portion-wise by $TsNH_2$ (495 mg, 2.89 mmol) and then was stirred for 0.5 h at 20 °C. 2-Phenyl-1,3-dioxane-5,5-diyl)bis(methylene) dimethanesulfonate **52**[13] (1g, 2.63 mmol) was then added and the reaction mixture stirred overnight (16 h) at 140 °C. After cooling to room temperature, the reaction then was quenched with brine (20 mL) and the reaction mixture was extracted with Et_2O (3×30 mL). The combined organic layers were washed with brine (60 mL), dried over $MgSO_4$ and concentrated to dryness. The crude product was purified by flash column chromatography over silica gel (eluent: 0:100 - 30:70 EtOAc:hexanes) to give the title compound (**53**) as a white solid (550 mg, 58 %).^{1}H NMR (500 MHz, DMSO-*d*6) δ 7.76 (d, *J* = 8.2 Hz, 2H), 7.52 (d, *J* = 8.0 Hz, 2H), 7.33 (s, 5H), 5.38 (s, 1H), 3.74 (d, *J* = 8.8 Hz, 4H), 3.66 (d, *J* = 11.2 Hz, 2H), 3.36 (s, 2H)[1], 2.44 (s, 3H). ^{13}C NMR (126 MHz, DMSO-*d*6) δ 144.8, 138.4, 131.3, 130.6 (2C), 129.3 (2C), 128.8, 128.5 (2C), 126.6 (2C) , 100.7, 72.5, 60.2, 53.8, 40.6, 32.1, 21.6. HRMS (ESI) *m*/*z*: $[M+Na]^+$ Calcd for $[C_{19}H_{21}NNaO_4S]^+$ 382.1089; Found 382.1072.

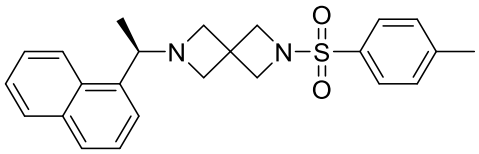
[1] Peak overlaps with residual signal of DMSO-*d6*

(1-Tosylazetidine-3,3-diyl)dimethanol (54).



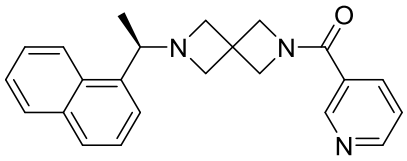
7-Phenyl-2-tosyl-6,8-dioxa-2-azaspiro[3.5]nonane **53** (500 mg, 1.39 mmol) was dissolved in CH_2Cl_2 (20 mL) and the reaction mixture was cooled down to 0 °C before TFA (90% aq. solution) (4 mL) was added and the reaction mixture was stirred for 1.5 h at 0 °C. After completion of the reaction, detected by LCMS, the reaction mixture was concentrated to dryness and the crude product was purified by flash column chromatography over silica gel (eluent: 0:100 - 30:70 EtOAc:hexanes, then 0:100 - 20:80 MeOH:DCM) to give the title compound (**54**) as a colorless syrup (270 mg, 71 %). ^{1}H NMR (500 MHz, CD_3OD) δ 7.77 – 7.71 (m, 1H), 7.71 – 7.65 (m, 1H), 7.43 (d, J = 8.0 Hz, 1H), 7.30 (d, J = 8.1 Hz, 1H), 3.53 (s, 5H), 3.42 (s, 3H), 2.46 (s, 3H).^{13}C NMR (126 MHz, CD_3OD) δ 144.4, 131.6, 129.7 (2C), 128.3 (2C), 62.8 , 54.2, 39.7, 35.7, 30.4, 20.3. HRMS (ESI) *m*/*z*: $[M+Na]^+$ Calcd for $[C_{12}H_{17}NNaO_4S]^+$ 294.0776; Found 294.0763.

(*R*)-2-(1-(Naphthalen-1-yl)ethyl)-6-tosyl-2,6-diazaspiro[3.3]heptane (55).



(1-Tosylazetidine-3,3-diyl)dimethanol **54** (250 mg, 0.921 mmol) was dissolved in anhydrous MeCN (3 mL) and the reaction mixture was cooled down to 0 °C with stirring. Subsequently, Tf_2O (324 µL, 1.93 mmol) was added followed drop-wise by DIPEA (400 µL, 2,39 mmol). After formation of the ditriflate (15 min), detected by LCMS, further DIPEA (400 µL, 2,39 mmol) was added drop-wise followed by slow addition of (*R*)-1-(naphthalen-1-yl)ethan-1-amine (147 µL, 0.921 mmol). The reaction mixture then was stirred for 10 min at 0 °C and then refluxed for 3 h. After completion, detected by LCMS, the reaction mixture was quenched with sat. aq. $NaHCO_3$ (10 mL) and extracted with EtOAc (3×20 mL). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$ and concentrated to dryness. The crude product was purified by flash column chromatography over silica gel (eluent: 0:100 - 30:70 EtOAc:hexanes) to give the title compound (**55**) as white solid (260 mg 70 %). $[\alpha]_D^{20\text{-}22}$ – 9.6 (*c* 7.5, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83 (dd, J = 7.8, 1.8 Hz, 1H), 7.78 – 7.62 (m, 3H), 7.54 – 7.37 (m, 4H), 7.32 (d, J = 8.0 Hz, 2H), 7.28 – 7.22 (m, 1H), 7.19 – 7.09 (m, 1H), 4.03 (m, 1H), 3.84 (s, 4H), 3.18 (s, 4H), 2.40 (s, 3H), 1.28 (d, J = 6.5 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 144.2, 133.9, 131.2, 130.9, 129.9, 129.7, 128.9, 128.3, 128.2, 127.5, 125.8, 125.6, 125.3, 125.2, 123.8, 122.9, 62.9 (2C), 60.3 (2C), 56.0, 32.0, 21.5, 20.1. HRMS (ESI) *m*/*z*: $[M+H]^+$ Calcd for $[C_{24}H_{27}N_2O_2S]^+$ 407.1788; Found 407.1775.

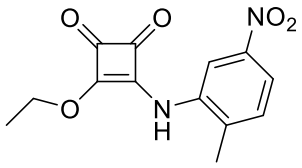
(*R*)-(6-(1-(Naphthalen-1-yl)ethyl)-2,6-diazaspiro[3.3]heptan-2-yl)(pyridin-3-yl)methanone (56).



A stirred solution of (*R*)-2-(1-(naphthalen-1-yl)ethyl)-6-tosyl-2,6-diazaspiro[3.3]heptane **55** (110 mg, 0.271 mmol) in MeOH (10 mL) was treated with Mg turnings (52.5 mg, 2.17 mmol) and sonicated (40 kHz) for 1.5 h at 20 °C. After completion, detected by LCMS, the reaction mixture was diluted with Et_2O (20 mL) and filtered on Celite ®. The filter cake was additionally washed with Et_2O (3×20 mL), and the filtrate was dried over $MgSO_4$ and concentrated to dryness. The residue (80 mg, 0.317 mmol) was taken up in anhydrous CH_2Cl_2 (2 mL) and added at 0 °C to a stirred solution of nicotinic acid (39 mg, 0.317 mmol), EDCI (76 mg, 0.396 mmol) and HOBt (53.5 mg, 0.396 mmol) in anhydrous CH_2Cl_2 (4 mL), followed by addition of DIPEA (220 µL, 1.26 mmol). The reaction mixture then was allowed to warm up to 20 °C and was stirred for 16 h before it was quenched with H_2O (5 mL) and extracted with CH_2Cl_2 (3×10 mL). The combined organic layers were dried over $MgSO_4$ and concentrated to dryness. The crude material was purified by flash column chromatography over silica gel (eluent: 0:100 - 30:70 EtOAc:hexanes then 0:100 - 10:90 MeOH:DCM) to give the title compound (**56**) as a colorless syrup (35 mg, 36 %, over 2 steps).$[\alpha]_D^{20\text{-}22}$ + 4.5 (*c* = 5, MeOH). ^{1}H NMR (500 MHz, CD_3OD): δ 8.80 (dd, *J* = 2.2, 0.9 Hz, 1H), 8.66 (dd, *J* = 4.9, 1.6 Hz, 1H), 8.24 – 8.18 (m, 1H), 8.08 (dt, *J* = 7.9, 1.9 Hz, 1H), 7.86 (dd, *J* = 8.2, 1.5 Hz, 1H), 7.75 (d, *J* = 8.1 Hz, 1H), 7.59 – 7.41 (m, 5H), 4.52 – 4.44 (m, 2H), 4.26 (d, *J* = 13.9 Hz, 2H), 3.49 – 3.39 (m, 4H), 2.01 (s, 1H), 1.36 – 1.27 (m, 3H). ^{13}C NMR (126 MHz, CD_3OD): δ 179.0, 167.8, 151.1, 148.1, 138.2, 136.1, 134.2, 131.2, 129.4, 128.7, 127.3,

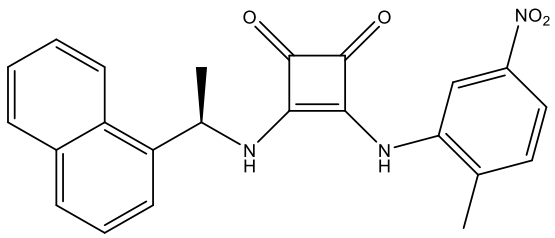
125.7, 125.3, 125.2, 123.8, 122.7, 62.8, 62.7, 58.8 (2C), 32.9, 22.9, 19.4. HRMS (ESI) *m*/*z*: $[M+H]^+$ Calcd for $[C_{23}H_{24}N_3O]^+$ 358.1914; Found 358.1902.

3-Ethoxy-4-((2-methyl-5-nitrophenyl)amino)cyclobut-3-ene-1,2-dione (57).



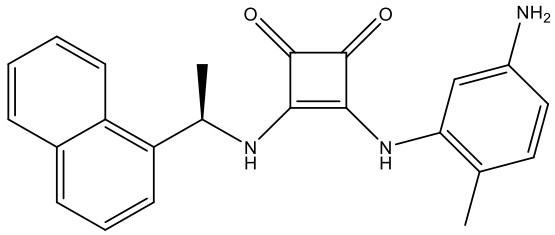
A solution of diethyl squarate (2.05 mL, 13.8 mmol) and 2-methyl-5-nitroaniline (2.00 g, 13.14 mmol) in ethanol was heated under microwave irradiation to 120 °C for 4 h. The reaction mixture was then concentrated under vacuum, suspended in ether, and filtered. The precipitate was washed with MeCN and the filtrate was concentrated to give the title compound (**57**) (0.647 g, 18%) as a yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.23 – 8.16 (m, 2H), 7.95 (dd, *J* = 8.3, 2.3 Hz, 1H), 7.37 (d, *J* = 8.3 Hz, 1H), 4.89 (q, *J* = 7.0 Hz, 2H), 2.49 (s, 3H), 1.50 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 188.8, 184.8, 179.0, 168.5, 147.0, 136.1 (2C), 131.7, 120.0, 116.1, 71.1, 18.2, 15.8. HRMS (ESI): *m/z*: $[M+H]^+$ Calcd for $[C_{13}H_{13}N_2O_5]^+$ 277.0814; Found 277.0811.

(*R*)-3-((2-methyl-5-nitrophenyl)amino)-4-((1-(naphthalen-1-yl)ethyl)amino)cyclobut-3-ene-1,2-dione (58).



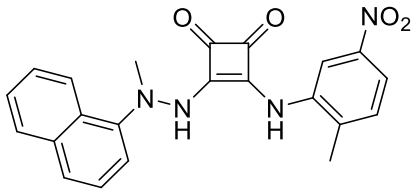
A solution of 3-ethoxy-4-((2-methyl-5-nitrophenyl)amino)cyclobut-3-ene-1,2-dione **57** (0.304 g, 1.10 mmol) and (*R*)-(+)-1-(1-naphthyl)ethylamine (0.19 mL, 1.2 mmol) in ethanol (3 mL) was heated under microwave irradiation to 50 °C for 15 min. The reaction mixture was concentrated and adsorbed on Celite® followed by purification over silica gel eluting (eluent: 100% EtOAc) to give the title compound (**58**) (0.348 g, 79%) as a yellow solid. $[\alpha]_D^{23}$ = -140.3 (*c* = 1.0, $CHCl_3$), ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.78 (s, 1H), 8.56 (d, *J* = 7.8 Hz, 1H), 8.24 (d, *J* = 2.3 Hz, 1H), 7.97 (d, *J* = 8.5 Hz, 1H), 7.74 (dd, *J* = 8.1, 1.4 Hz, 1H), 7.64 (d, *J* = 8.2 Hz, 1H), 7.57 (dd, *J* = 8.3, 2.3 Hz, 1H), 7.48 – 7.41 (m, 2H), 7.38 (t, *J* = 7.4 Hz, 1H), 7.28 (t, *J* = 7.7 Hz, 1H), 6.98 (d, *J* = 8.3 Hz, 1H), 6.04 (p, *J* = 6.9 Hz, 1H), 2.05 (s, 3H), 1.70 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 182.6, 181.3, 170.9, 162.4, 146.7, 137.5, 137.0, 135.0, 134.0, 131.1, 130.2, 129.1, 128.8, 126.6, 125.9, 125.5, 123.0, 122.7, 118.4, 115.3, 51.0, 23.1, 18.1. HRMS (ESI) *m/z*: $[M+Na]^+$ Calcd for $[C_{23}H_{19}N_3O_4Na]^+$ 424.1268; Found 424.1261.

(*R*)-3-((5-amino-2-methylphenyl)amino)-4-((1-(naphthalen-1-yl)ethyl)amino)cyclobut-3-ene-1,2-dione (59).



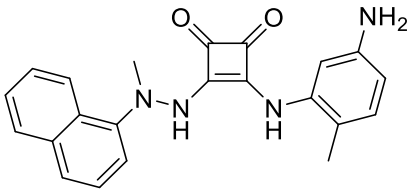
Palladium on carbon (10 wt%, 2 mg) was added to a solution of *N*-((2-methyl-5-nitrophenyl)) *N*'-(*R*)-((1-(naphthalen-1-yl)ethyl))squaramide **58** (20 mg, 0.05 mmol) in 1,4-dioxane (1 mL) and the reaction mixture was stirred under H_2 at atmospheric pressure for 2 h followed by addition of 10% aqueous acetic acid (1.0 mL). After an additional 0.5 h stirring, palladium on carbon (10 wt%, 6.6 mg) was added and the reaction mixture was stirred for 1 h before it was filtered and concentrated under vacuum. The crude residue was then dry loaded on Celite® and purified over silica gel (eluent: 0:100 - 10:90 MeOH:DCM) to give the title compound (**59**) (7.9 mg, 43%) as a brown solid. $[\alpha]_D^{23}$ = -88.29 (*c* = 0.3, $CHCl_3$), ^{1}H NMR (500 MHz, CD_3OD): δ 8.14 (br s, 1H), 7.89 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.82 (d, *J* = 8.2 Hz, 1H), 7.61 – 7.53 (m, 2H), 7.51 – 7.47 (m, 2H), 6.85 (d, *J* = 8.1 Hz, 1H), 6.74 (br s, 1H), 6.41 (dd, *J* = 8.1, 2.3 Hz, 1H), 6.24 (br s, 1H), 2.09 (s, 3H), 1.76 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (126 MHz, CD_3OD): δ 184.1, 181.5, 168.3, 164.8, 146.4, 138.1, 136.5, 134.3, 130.9 , 130.6, 128.7, 128.3, 126.4, 125.7, 125.2, 122.6, 122.3, 117.5, 112.3, 108.7, 49.8, 22.0, 15.5. HRMS (ESI) *m/z*: $[M+H]^+$ Calcd for $[C_{23}H_{22}N_3O_2]^+$ 372.1707; Found 372.1700.

3-[*N*'-(Naphthalen-1-yl)-*N*'-methylhydrazinyl]-4-[(2-methyl-5-nitrophenyl)amino]cyclobut-3-ene-1,2-dione (60).



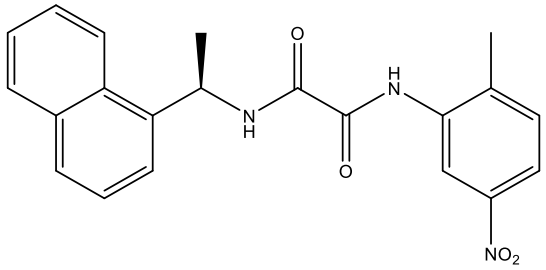
N-Methyl-*N*-(1-naphthyl)hydrazine **18** (90 mg, 0.52 mmol) and 3-ethoxy-4-((2-methyl-5-nitrophenyl)amino)cyclobut-3-ene-1,2-dione **57** (173 mg, 0.63 mmol) were taken up in ethanol (1.7 mL) and stirred at 20 °C for 16 h. The reaction mixture was concentrated and purified by silica gel column chromatography (eluent: 20:80 - 60:40 EtOAc:hexanes) to yield the title product (**60**) (63.1 mg, 30%) as a dark brown syrup. ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.64 (s, 1H), 8.45 (s, 1H), 8.08 (d, J = 7.9 Hz, 1H), 7.89 (d, J = 7.9 Hz, 1H), 7.73 (m, 2H), 7.52 (m, 4H), 7.14 (d, J = 8.3 Hz, 1H), 3.40 (s, 3H), 1.90 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 183.6, 179.2, 167.0, 147.3, 146.5, 136.7, 134.9, 134.4, 131.1 (2C), 129.5, 127.0, 126.6, 126.5 (2C), 126.2, 121.6, 119.1, 116.1, 115.9, 48.3, 17.7. HRMS (ESI) *m*/*z*: $[M + Na]^+$ Calcd for $[C_{22}H_{18}N_4O_4Na]^+$ 425.1226; Found 425.1230.

3-[*N*'-(Naphthalen-1-yl)-*N*'-methylhydrazinyl]-4-[(5-amino-2-methylphenyl)amino]cyclobut-3-ene-1,2-dione (61).



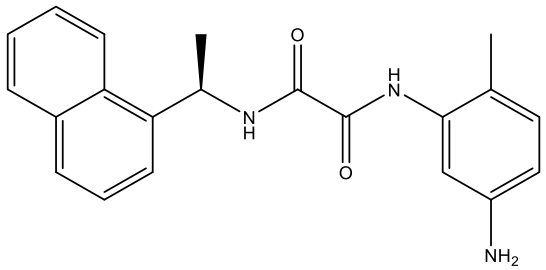
To a stirred solution of 3-[*N*'-(naphthalen-1-yl)-*N*'-methylhydrazinyl]-4-[(2-methyl-5-nitrophenyl)amino]cyclobut-3-ene-1,2-dione **60** (47.7 mg, 0.12 mmol) in a 1:1 mixture of 1,4-dioxane (1.2 mL) and 10% aqueous acetic acid (0.6 mL) was added Pd/C (6.31 mg, 0.01 mmol). The resulting mixture was stirred at 20 °C under hydrogen (1 atm) for 5 h, then was filtered and the filtrate concentrated to give a residue, which was purified by silica gel column chromatography (20 - 60% ethyl acetate/hexane) to furnish the title product (**61**) (38.4 mg, 85%) as an off-white solid. ^{1}H NMR (500 MHz, $CDCl_3$ + CD_3OD): δ 8.00 (br s, 1H), 7.83 (d, J = 9.5 Hz, 1H), 7.66 (d, J = 8.0 Hz, 1H), 7.47 (m, 2H), 7.43 (d, J = 7.9 Hz, 1H), 7.39 (t, J = 7.7 Hz, 1H), 7.02 (br s, 1H), 6.77 (d, J = 8.3 Hz, 1H), 6.33 (dd, J = 8.3, 2.3 Hz, 1H), 3.27 (s, 3H), 1.78 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$ + CD_3OD) δ 182.4, 166.7, 146.2, 136.3, 134.9, 131.3 (2C), 129.1, 126.9 (2C), 126.5 (2C), 126.5 (2C), 125.6 (2C), 122.1, 115.0, 112.2, 107.9, 47.7, 16.4. HRMS (ESI) *m*/*z*: $[M + H]^+$ Calcd for $[C_{22}H_{20}N_4O_2]^+$ 373.1659; Found 373.1680.

***N*^{1}-(2-Methyl-5-nitrophenyl) *N*^{2}-(*R*)-(1-(naphthalen-1-yl)ethyl)oxalamide (62).**



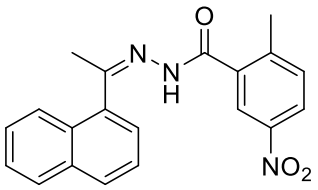
A solution of 2-methyl-5-nitroaniline (101 mg, 0.66 mmol) in CH_2Cl_2 (3 mL) was added to a stirred solution of oxalyl chloride (0.17 mL, 1.98 mmol) and K_2CO_3 (0.273 g, 1.98 mmol) in CH_2Cl_2 (3 mL) at 0 °C. After 10 min the reaction mixture was concentrated under vacuum and dissolved in CH_2Cl_2 (12 mL) followed by addition of (*R*)-(+)-1-(1-naphthyl)ethylamine (0.11 mL, 0.69 mmol) at 0 °C. The reaction mixture was stirred for 15 min then diluted with EtOAc and washed with 1N HCl and brine. The organic layer was dried with Na_2SO_4, filtered, and concentrated. The crude residue was adsorbed on Celite® and purified over silica gel (eluent: 70:30 - 100:0 DCM:hexanes) to give the title compound (**62**) (0.151 g, 60%) as a white solid. $[\alpha]_D^{23}$ = -59.71 (*c* = 0.07, $CHCl_3$), ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.42 (s, 1H), 8.99 (d, *J* = 2.4 Hz, 1H), 8.07 (d, *J* = 8.5 Hz, 1H), 7.95 (dd, *J* = 8.4, 2.4 Hz, 1H), 7.90 – 7.85 (m, 2H), 7.82 (d, *J* = 8.2 Hz, 1H), 7.59 – 7.54 (m, 2H), 7.53 – 7.44 (m, 2H), 7.34 (d, *J* = 8.4 Hz, 1H), 5.93 (qd, *J* = 6.9, 6.9, 1.6 Hz, 1H), 2.42 (s, 3H), 1.77 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.5, 157.7, 147.1, 137.1, 135.4, 135.2, 134.1, 131.2, 130.8, 129.2, 128.9, 126.8, 126.1, 125.4, 122.8, 122.8, 120.2, 115.9, 46.0, 21.1, 17.8. HRMS (ESI) *m/z*: $[M+Na]^+$ Calcd for $[C_{21}H_{19}N_3O_4Na]^+$ 400.1269; Found 400.1263.

***N*^{1}-(5-Amino-2-methylphenyl) *N*^{2}-(*R*)-(1-(naphthalen-1-yl)ethyl)oxalamide (63).**



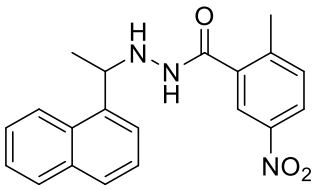
Palladium on carbon (10 wt%, 5.2 mg) was added to a solution of *N*^{1}-(2-methyl-5-nitrophenyl) *N*^{2}-(*R*)-(1-(naphthalen-1-yl)ethyl)oxalamide **62** (33.7 mg, 0.09 mmol) in 1,4-dioxane (2 mL) and the reaction mixture was stirred under H_2 for 1 h followed by addition of further palladium on carbon (11 mg). After an additional 1 h of stirring glacial AcOH (0.25 mL) was added and the reaction mixture was stirred for 9 h before filtration and concentration under vacuum. The residue was adsorbed on Celite® and purified over silica gel (eluent: 25:75 - 100:0 EtOAc:hexanes) to give the title compound (**63**) (16.3 mg, 53%) as a yellow film. $[\alpha]_D^{23}$ = -40.34 (*c* = 0.7, $CHCl_3$), ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.27 (s, 1H), 8.09 (d, *J* = 8.4 Hz, 1H), 7.92 (d, *J* = 8.5 Hz, 1H), 7.87 (dd, *J* = 8.1, 1.4 Hz, 1H), 7.81 (d, *J* = 8.2 Hz, 1H), 7.59 – 7.53 (m, 2H), 7.52 – 7.48 (m, 2H), 7.46 (dd, *J* = 8.2, 7.2 Hz, 1H), 6.95 (d, *J* = 8.1 Hz, 1H), 6.42 (dd, *J* = 8.1, 2.4 Hz, 1H), 5.92 (dq, *J* = 8.5, 6.9 Hz, 1H), 2.22 (s, 3H), 1.74 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.3, 157.2, 145.3, 137.4, 135.2, 134.1, 131.2, 130.9, 129.1, 128.7, 126.8, 126.0, 125.4, 122.9, 122.8, 117.7, 112.4, 107.8, 45.8, 21.1, 16.5. HRMS (ESI) *m/z*: $[M+Na]^+$ Calcd for $[C_{21}H_{21}N_3O_2Na]^+$ 370.1526; Found 370.1518.

(*E/Z*)-2-Methyl-*N′*-(1-(naphthalen-1-yl)ethylidene)-5-nitrobenzohydrazide (65).



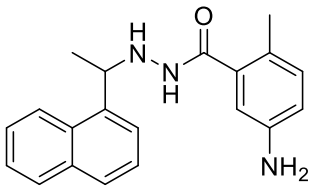
(*E/Z*)-(1-(Naphthalen-1-yl)ethylidene)hydrazine **64**[24] (4 g, 21.71 mmol) was dissolved in pyridine (3 mL) and anhydrous CH_2Cl_2 (2 mL) and cooled down to 0 °C before 2-methyl-5-nitrobenzoyl chloride (4.77 g, 23.88 mmol) in anhydrous CH_2Cl_2 (4 mL) was added dropwise. The reaction mixture then was allowed to warm up to 20 °C and was stirred for 15 min before it was filtered and the white precipitate was washed with cold CH_2Cl_2 (3×10 mL) and hexanes (3×10 mL) to give a mixture of (*E/Z*)-isomers of the title compound (**65**) as a white solid (6.8 g, 90 %). Hydrazide (**65**) was obtained as a 1:1 ratio of *E/Z* isomers. ^{1}H NMR (500 MHz, DMSO-*d6*) δ 11.38 (s, 1H), 11.13 (s, 1H), 8.37 (d, *J* = 2.5 Hz, 1H), 8.30 – 8.25(m, 2H), 8.21 (d, *J* = 2.5 Hz, 1H), 8.08 (dd, *J* = 8.5, 2.5 Hz, 1H), 8.03 – 7.96 (m, 2H), 7.92 – 7.81 (m, 3H), 7.67 – 7.53 (m, 5H), 7.51 – 7.39 (m, 4H), 7.23 (td, *J* = 6.8, 3.3 Hz, 1H), 2.55 (s, 3H), 2.46 (s, 6H), 2.38 (s, 3H). ^{13}C NMR (126 MHz, DMSO-*d6*) δ 170.1, 163.7, 157.7, 152.0, 145.3, 145.2, 144.5, 142.5, 138.2, 137.5, 136.7, 133.4, 133.3, 131.9 , 131.3, 130.0, 129.6, 129.0 (2C), 128.4, 128.3, 126.6 (2C), 126.1, 126.0, 125.93, 125.88, 125.6, 125.3, 125.2, 125.1, 124.3, 123.30, 122.8, 121.8, 19.7, 19.67, 19.2, 18.8. HRMS (ESI) *m*/*z*: $[M+H]^+$ Calcd for $[C_{20}H_{18}N_3O_3]^+$ 348.1343; Found 348.1337.

2-Methyl-*N′*-(1-(naphthalen-1-yl)ethyl)-5-nitrobenzohydrazide (66).



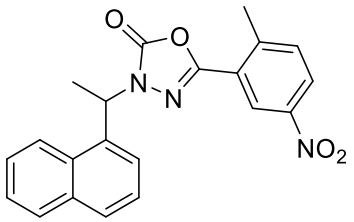
(*E/Z*)-2-Methyl-N'-(1-(naphthalen-1-yl)ethylidene)-5-nitrobenzohydrazide **65** (2.3 g, 6.62 mmol) was suspended in MeOH—THF (1 : 1, (v/v)) (20 mL) and $NaBH_3CN$ (428 mg, 6.81 mmol, 1.03 eq.) was added followed by drop-wise addition of glacial AcOH (570 µL, 9.97 mmol) until pH 4—5. The reaction mixture was stirred 16 h at 20 °C (completion was detected by LCMS) and then quenched with 1M aq. NaOH (60 mL) and extracted with Et_2O (3×80 mL). The combined organic layers were dried over $MgSO_4$ and concentrated to dryness. The crude product was purified by flash column chromatography over silica gel (eluent: 0:100 - 30:70 EtOAc:hexanes) to give the title compound (**66**) as a yellowish solid (1.55 g, 67%). ^{1}H NMR (500 MHz, DMSO-*d*6) δ 9.95 (s, 1H), 8.32 (t, *J* = 4.2 Hz, 1H), 8.13 (dd, *J* = 8.4, 2.5 Hz, 1H), 7.96 – 7.90 (m, 2H), 7.85 – 7.78 (m, 2H), 7.58 – 7.48 (m, 3H), 7.46 (d, *J* = 8.4 Hz, 1H), 5.58 (br s, 1H), 5.13 (q, *J* = 6.6 Hz, 1H), 2.25 (s, 3H), 1.49 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR (126 MHz, DMSO-*d*6) δ 166.8, 145.7, 144.7, 139.8, 137.0 , 134.0, 132.4, 131.6, 129.2, 127.8, 126.5, 126.1, 126.0, 124.6, 124.3, 123.7, 122.6, 54.8, 21.5, 19.7. HRMS-ESI: m/z $[M+Na]^+$ calcd. for $[C_{20}H_{19}N_3NaO_3]^+$ 372.1324, found 372.1308.

5-Amino-2-methyl-N'-(1-(naphthalen-1-yl)ethyl)benzohydrazide (67).



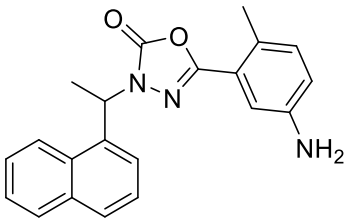
2-Methyl-*N′*-(1-(naphthalen-1-yl)ethyl)-5-nitrobenzohydrazide **66** (150 mg, 0.429 mmol) was dissolved in 1,4-dioxane (4 mL) and Pd/C (10% wt) (27.4 mg, 0.025) was added. The reaction mixture then was stirred for 4 h under H_2 (balloon) at 20 °C. After completion, detected by LCMS, the reaction mixture was filtered through Celite and the filter cake was additionally washed with Et_2O (3×15 mL). The filtrate was concentrated to dryness and the crude product was purified by flash column chromatography over silica gel (eluent: 0:100 - 30:70 EtOAc:hexanes) to give the title compound (**67**) as a yellowish resin (69 mg, 51 %). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.31 (d, *J* = 8.3 Hz, 1H), 7.86 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.79 – 7.69 (m, 2H), 7.52 – 7.41 (m, 3H), 7.16 (s, 1H), 6.84 (d, *J* = 8.1 Hz, 1H), 6.47 (dd, *J* = 8.1, 2.5 Hz, 1H), 6.28 (d, *J* = 2.5 Hz, 1H), 5.15 (m, 1H), 3.39 (br, 1H), 2.11 (s, 3H), 1.56 (d, *J* = 6.6 Hz, 3H), 1.24 (br, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.7, 143.9, 138.9, 134.7, 134.0 (2C), 131.7, 131.6, 128.9, 127.9, 126.1, 125.7, 125.6, 123.8, 123.3, 117.0, 113.7, 55.8, 20.9, 18.4. HRMS (ESI): *m*/*z*: $[M+Na]^+$ Calcd for $[C_{20}H_{21}N_3NaO]^+$ 342.1577; Found 342.1558.

5-(2-Methyl-5-nitrophenyl)-3-(1-(naphthalen-1-yl)ethyl)-1,3,4-oxadiazol-2(3*H*)-one (68).



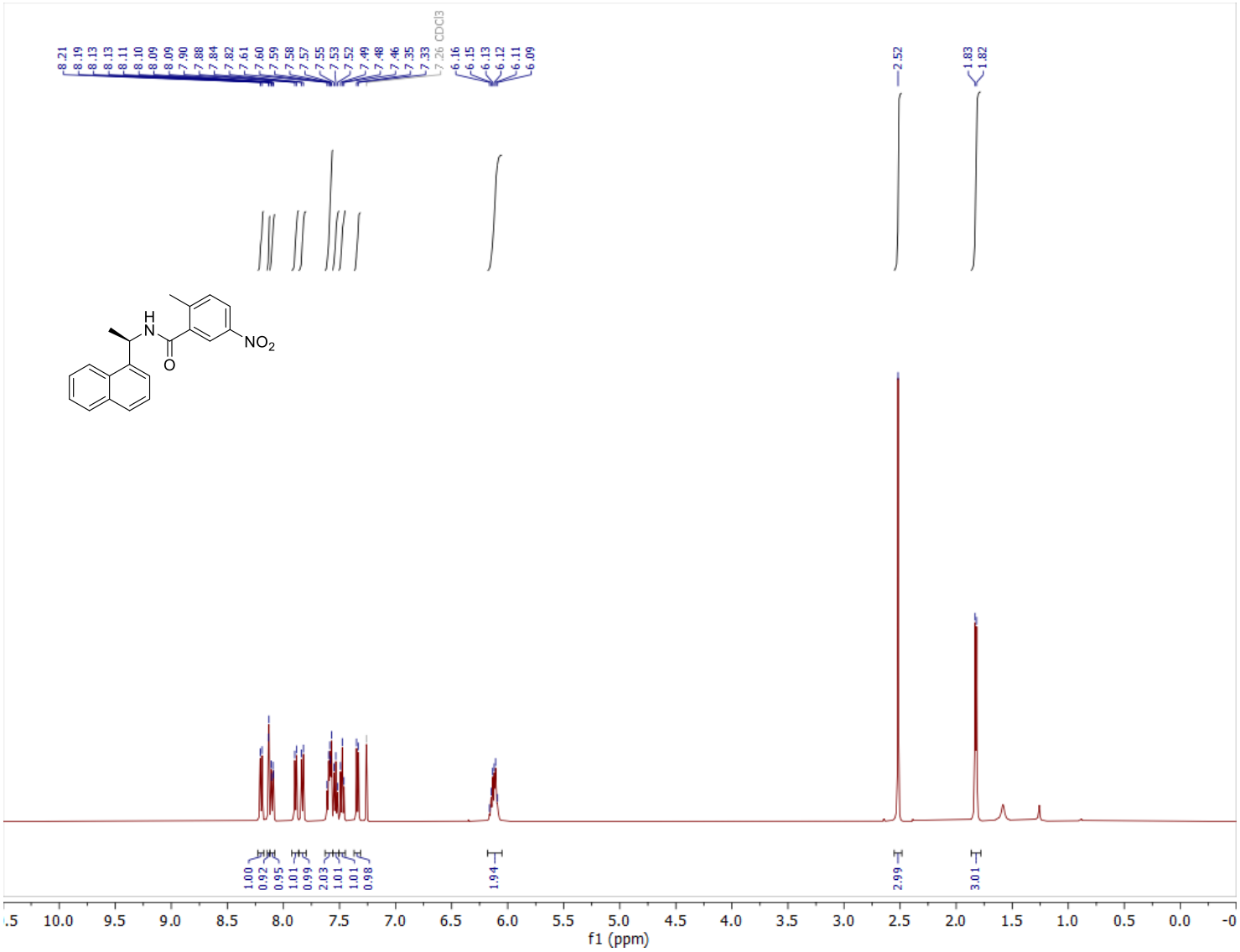
To a stirred solution of triphosgene (135.9 mg, 0.457 mmol) in anhydrous CH_2Cl_2 (6 mL) at 0 °C was added 2-methyl-*N*'-(1-(naphthalen-1-yl)ethyl)-5-nitrobenzohydrazide **66** (400 mg, 1.14 mmol) in anhydrous CH_2Cl_2 (6 mL) and then, dropwise, NEt_3 (160 µL, 1.14 mmol). After warming to 20 °C the reaction mixture was stirred for 4 h. The reaction then was quenched with H_2O (20 mL), and the reaction mixture was extracted with CH_2Cl_2 (3×30 mL). The combined organic layers were dried over $MgSO_4$ and concentrated to dryness. The crude product was purified by flash column chromatography over silica gel (eluent: 5:95 - 25:75 EtOAc:hexanes) to give the title compound (**68**) as a yellow foam (310 mg, 72%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.61 (d, *J* = 2.5 Hz, 1H), 8.29 (d, *J* = 8.6 Hz, 1H), 8.16 (dd, *J* = 8.6, 2.5 Hz, 1H), 7.91 – 7.83 (m, 2H), 7.79 – 7.74 (m, 1H), 7.65 – 7.58 (m, 1H), 7.56 – 7.49 (m, 2H), 7.42 (d, *J* = 8.4 Hz, 1H), 6.28 (q, *J* = 7.0 Hz, 1H), 2.66 (s, 3H), 2.02 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 152.0, 151.7, 146.3, 144.8, 134.7, 133.8, 132.8, 130.7, 129.1, 129.0, 127.0, 125.9, 125.1, 125.0, 124.3, 123.8, 122.8, 122.5, 50.8, 22.2, 19.2 . HRMS (ESI) *m/z*: $[M+Na]^+$ Calcd for $[C_{21}H_{17}N_3NaO_4]^+$ 398.1113; Found 398.1097.

5-(5-Amino-2-methylphenyl)-3-(1-(naphthalen-1-yl)ethyl)-1,3,4-oxadiazol-2(3*H*)-one (69).

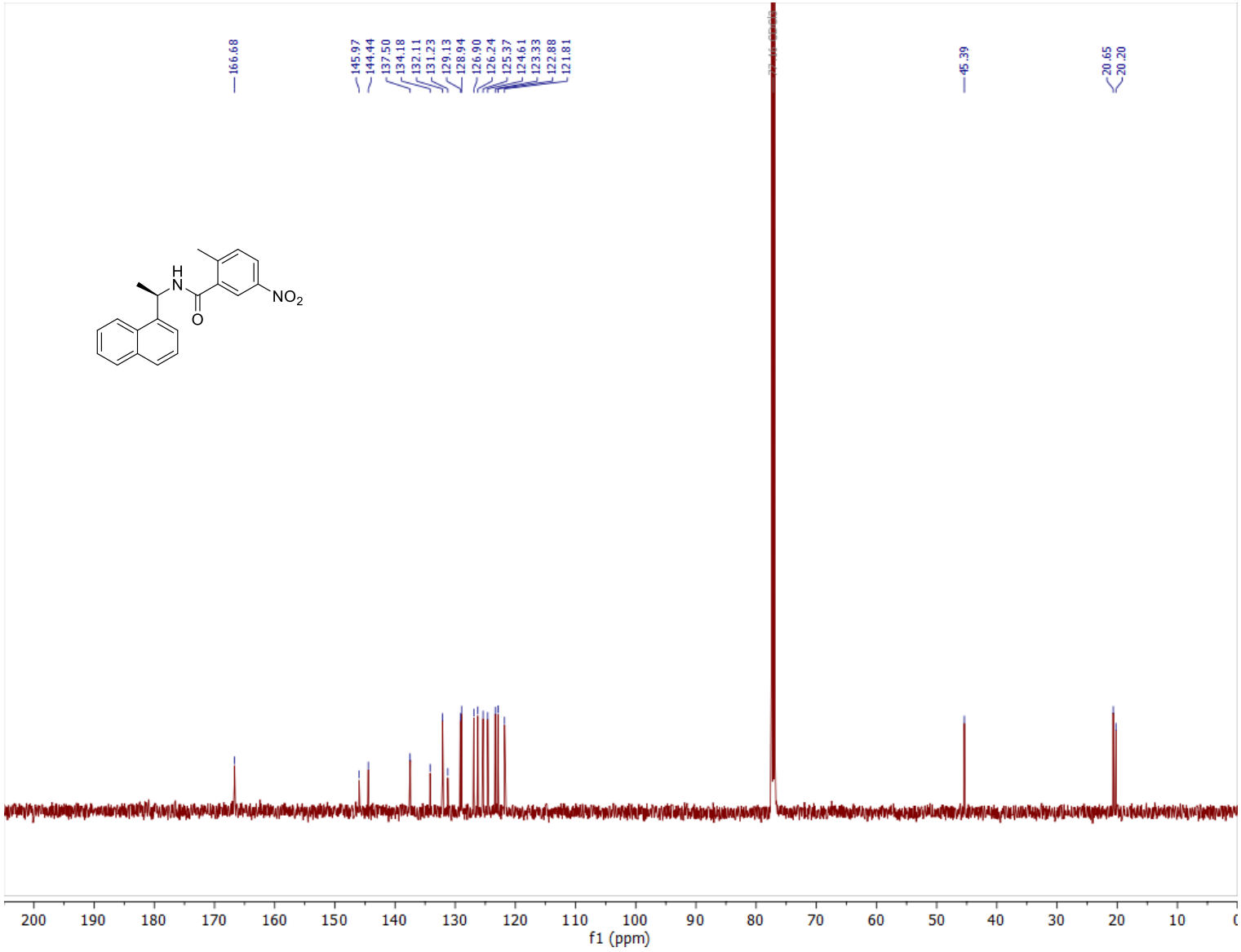


5-(2-Methyl-5-nitrophenyl)-3-(1-(naphthalen-1-yl)ethyl)-1,3,4-oxadiazol-2(3*H*)-one **68** (132 mg, 0.35 mmol) was dissolved in 1,4-dioxane (4 mL) and Pd/C (10% wt) (22.4 mg, 0.021 mmol) was added. The reaction mixture was stirred for 4 h under H_2 (balloon) at 20 °C. After such time, the reaction mixture was filtered through Celite and the filter cake was additionally washed with Et_2O (3×15 mL). The filtrate was concentrated to dryness and crude product was purified by flash column chromatography over silica gel (eluent: 0:100 - 30:70 EtOAc:hexanes) to give the title compound (**69**) as a yellow syrup (70 mg, 57 %). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.27 (d, J = 8.6 Hz, 1H), 7.89 – 7.79 (m, 2H), 7.76 – 7.70 (m, 1H), 7.59 (ddd, J = 8.6, 6.8, 1.4 Hz, 1H), 7.55 – 7.44 (m, 2H), 7.06 (d, J = 2.6 Hz, 1H), 7.01 (d, J = 8.2 Hz, 1H), 6.66 (dd, J = 8.1, 2.5 Hz, 1H), 6.21 (q, J = 7.0 Hz, 1H), 3.21 (s, 2H), 2.41 (s, 3H), 1.96 (d, J = 7.0 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 153.8 , 152.8, 144.3, 135.37, 133.8, 132.6, 130.8, 129.0, 128.9, 127.5, 126.9, 125.9, 125.2, 124.3, 123.1, 122.8, 117.9, 114.0, 50.6, 20.9, 19.4. HRMS (ESI) *m*/*z*: $[M+H]^+$ Calcd for $[C_{21}H_{19}N_3O_2]^+$ 346.1550; Found 346.1532.

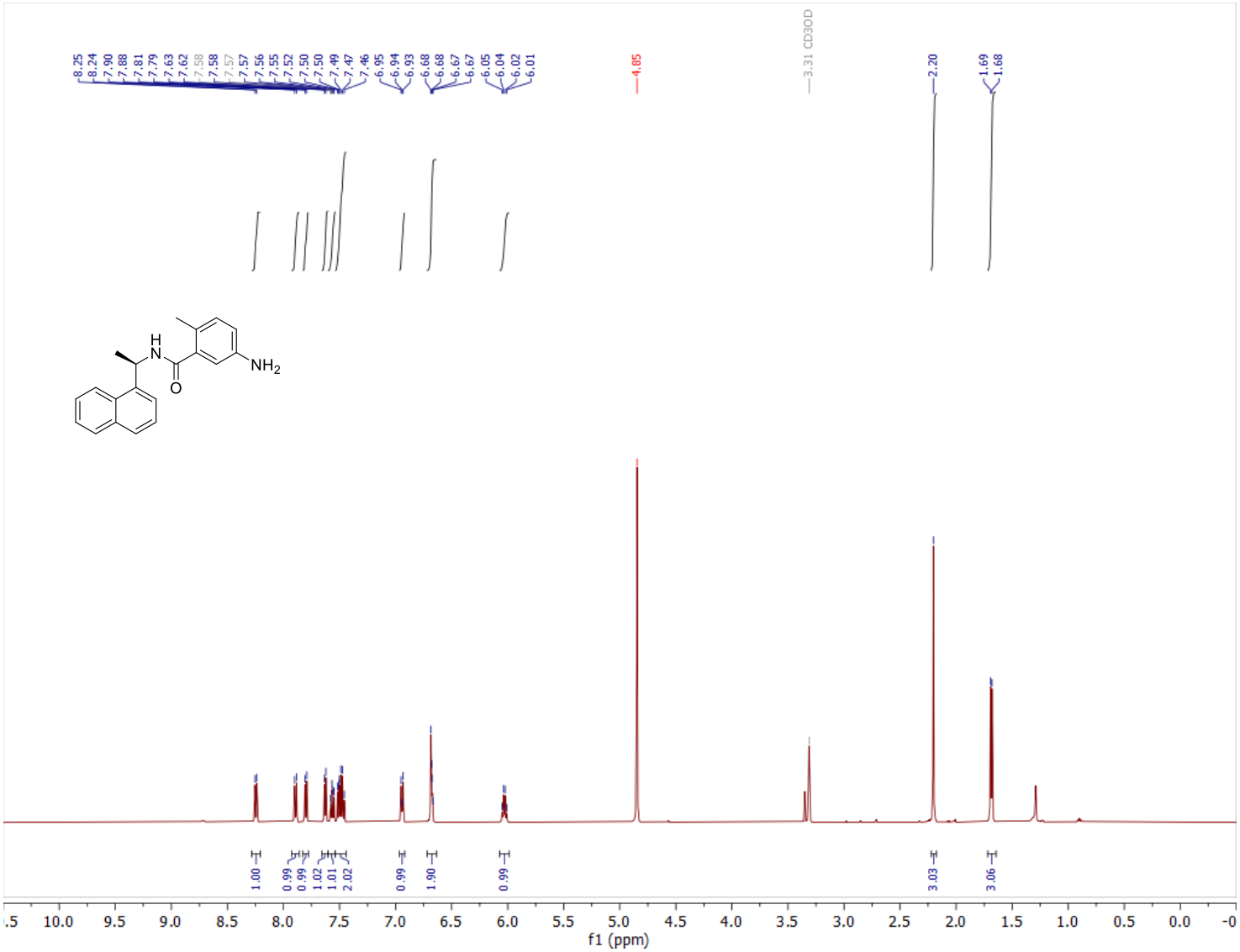
^{1}H NMR (500 MHz, $CDCl_3$) spectrum of (*R*)-2-Methyl-5-nitro-*N*-(1'-(naphthalene-1'-yl)ethyl)benzamide (5).



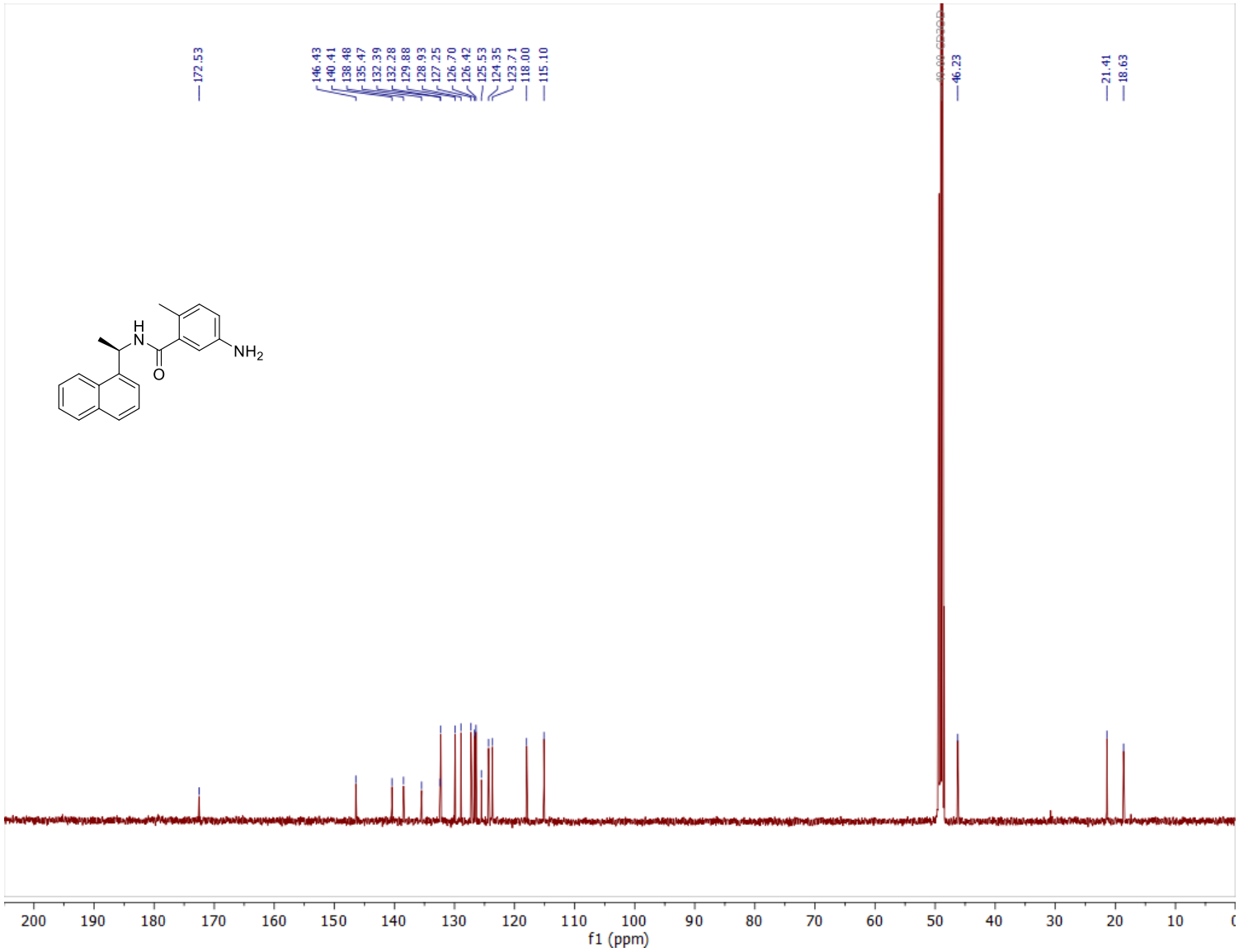
^{13}C NMR (126 MHz, $CDCl_3$) spectrum of (*R*)-2-Methyl-5-nitro-*N*-(1'-(naphthalene-1'-yl)ethyl)benzamide (5).



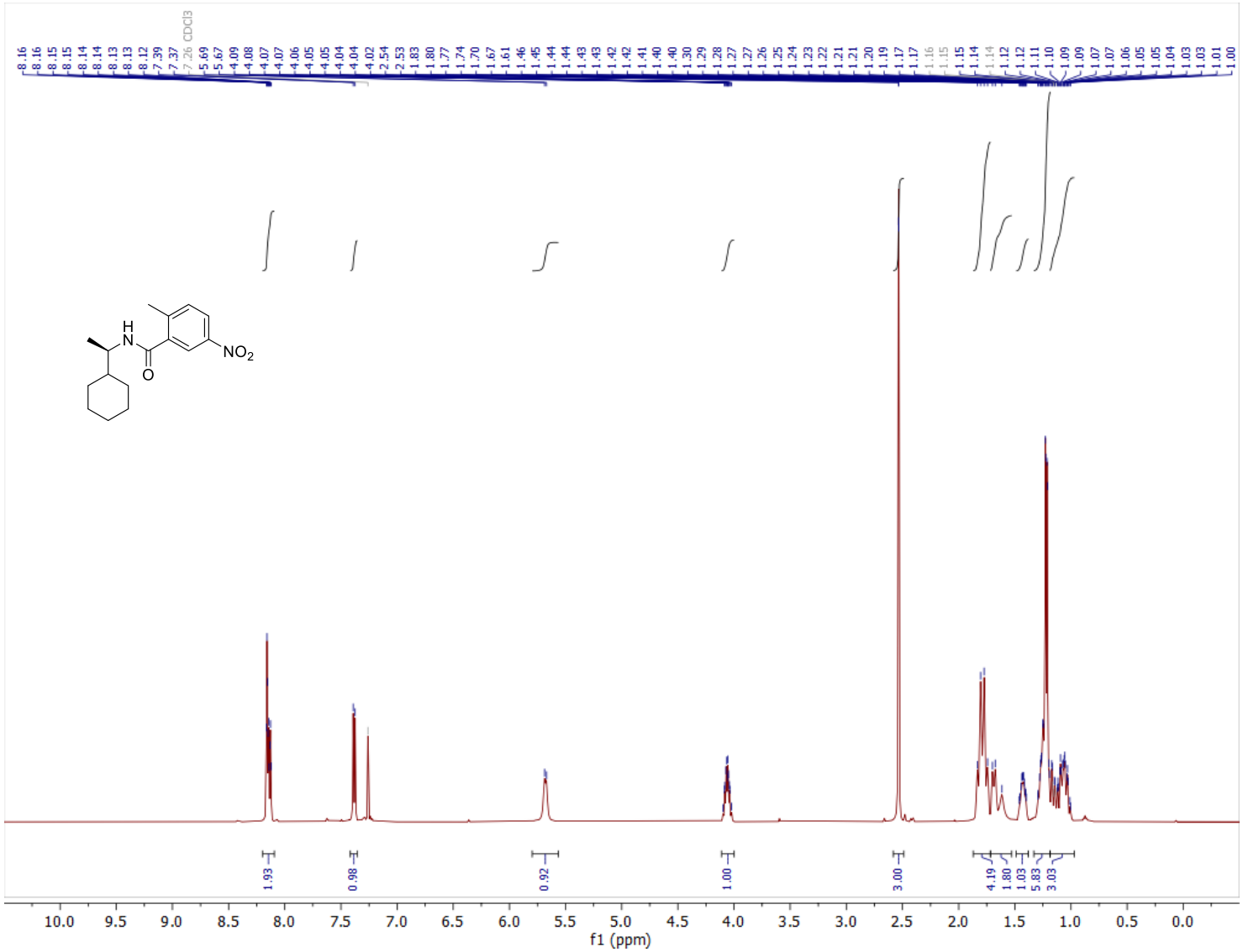
^{1}H NMR (500 MHz, $CDCl_3$) spectrum of (*R*)-2-Methyl-5-nitro-*N*-(1'-(naphthalene-1'-yl)ethyl)benzamide (GRL0617).



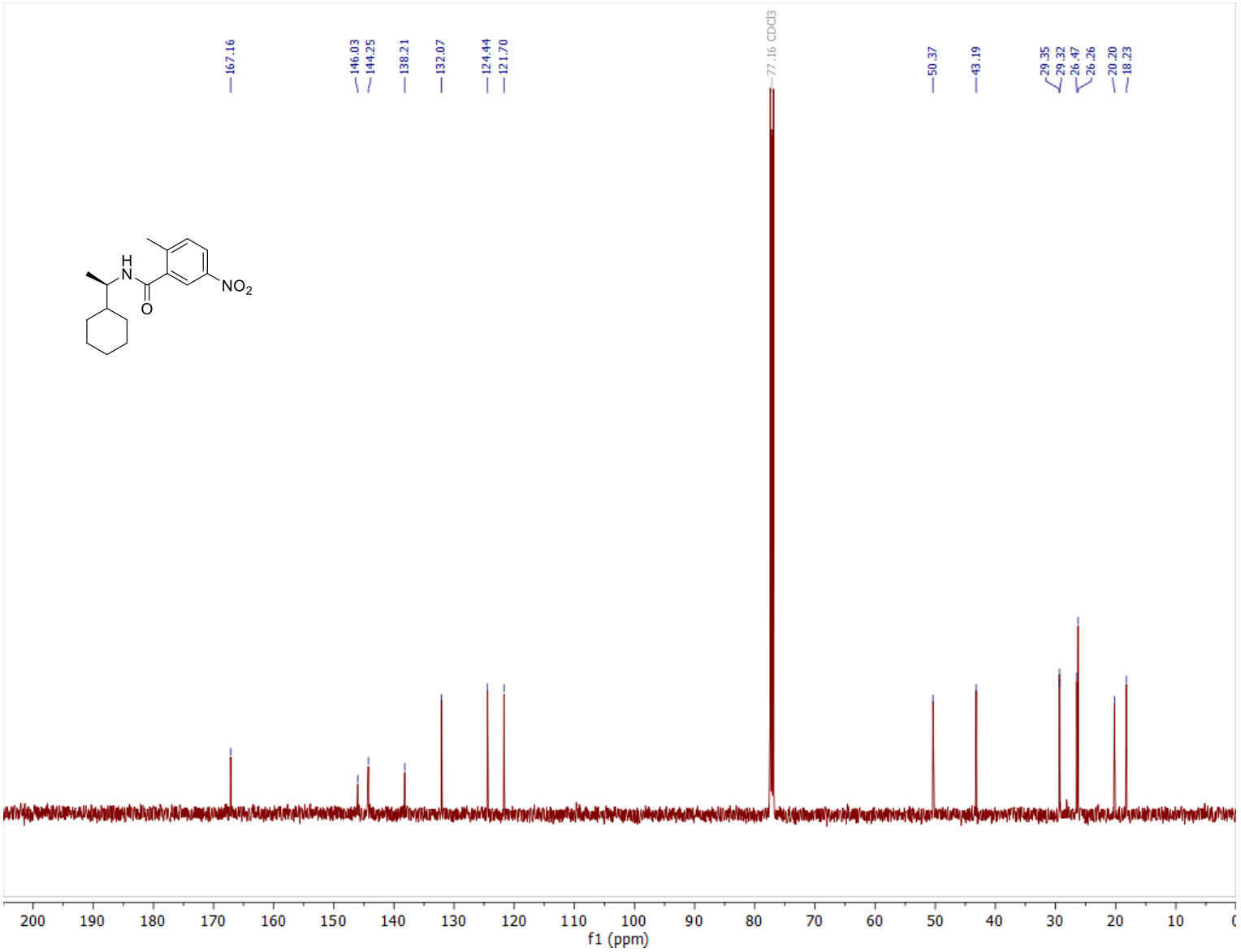
^{13}C NMR (126 MHz, $CDCl_3$) spectrum of (*R*)-2-Methyl-5-nitro-*N*-(1'-(naphthalene-1'-yl)ethyl)benzamide (GRL0617).



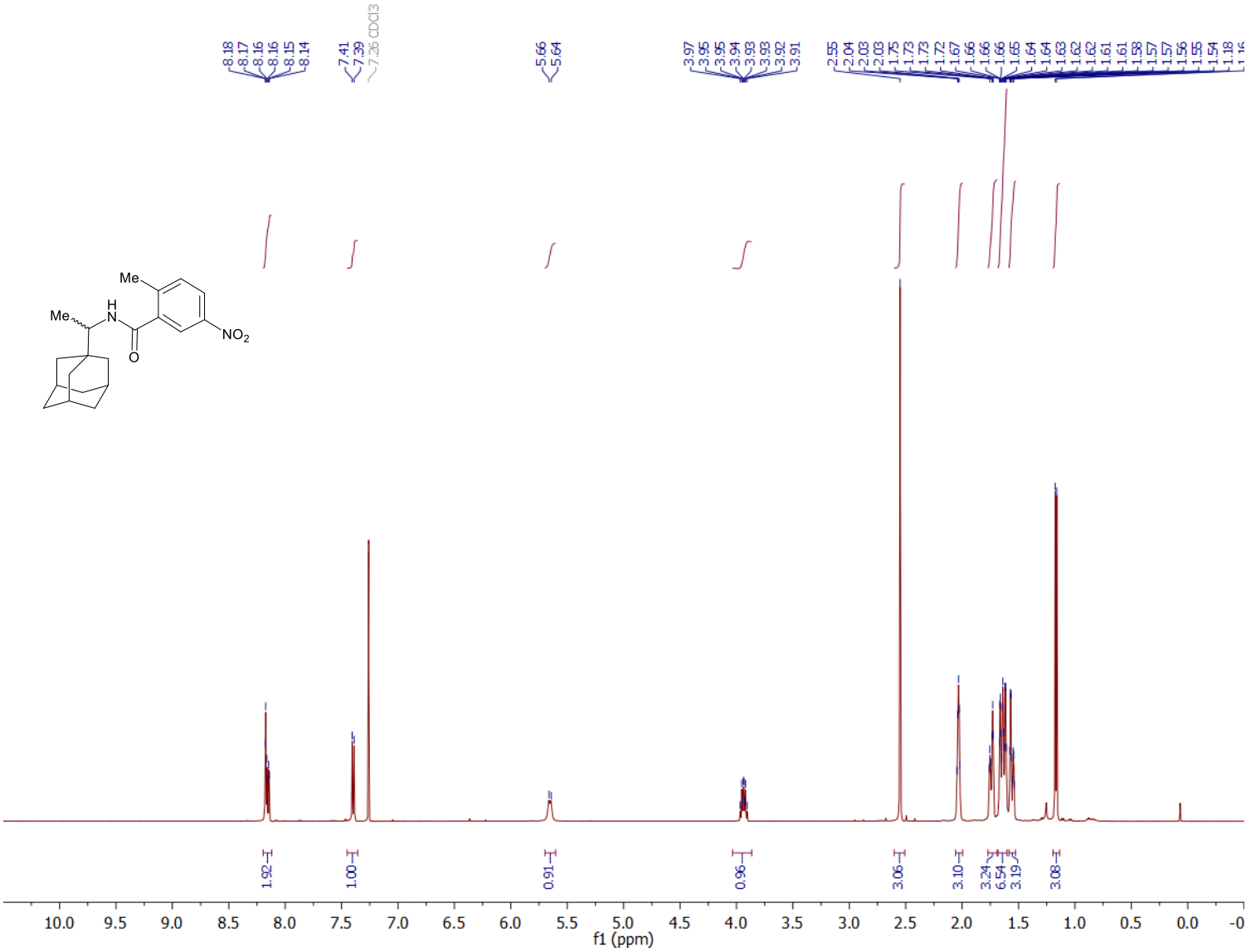
^{1}H NMR (500 MHz, $CDCl_3$) spectrum of (*R*)-*N*-[1-(1-Cyclohexyl)ethyl] 2-methyl-5-nitro-benzamide (6).



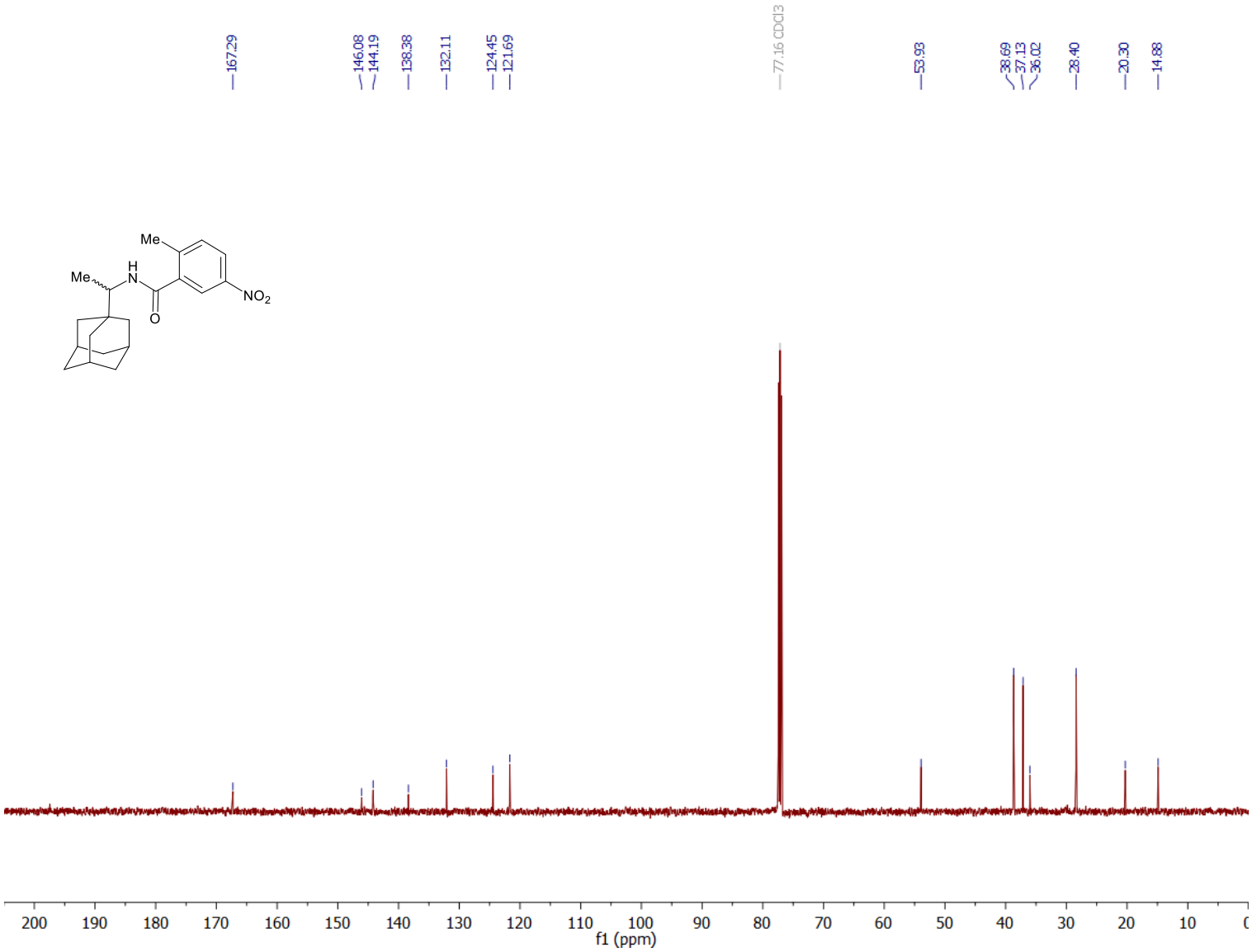
^{13}C NMR (126 MHz, $CDCl_3$) spectrum of (*R*)-*N*-[1-(1-Cyclohexyl)ethyl] 2-methyl-5-nitro-benzamide (6).



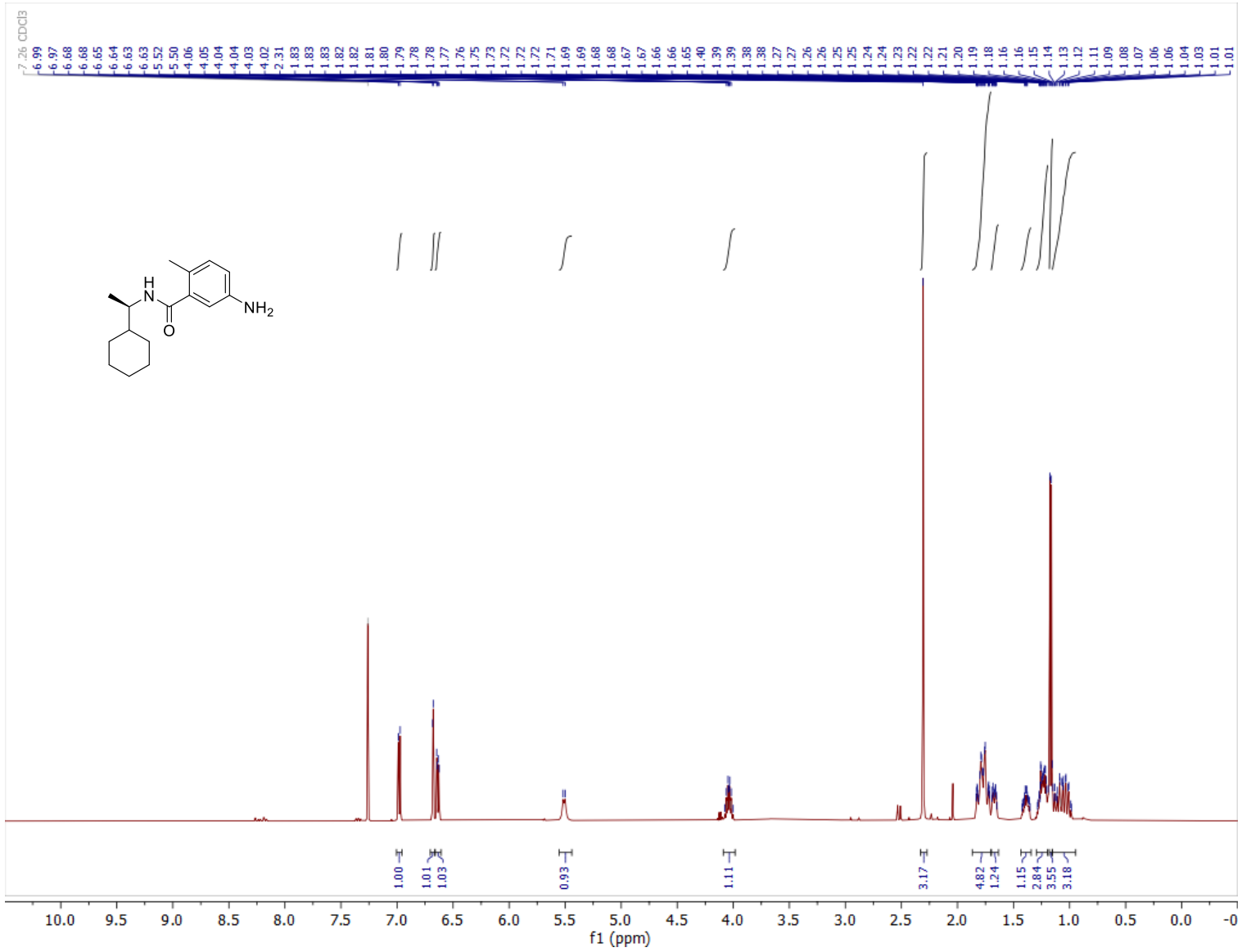
^{1}H NMR (500 MHz, $CDCl_3$) spectrum of (±)- *N*-(1'-(adamantan-1'-yl)ethyl)-2-methyl-5-nitrobenzamide (7).



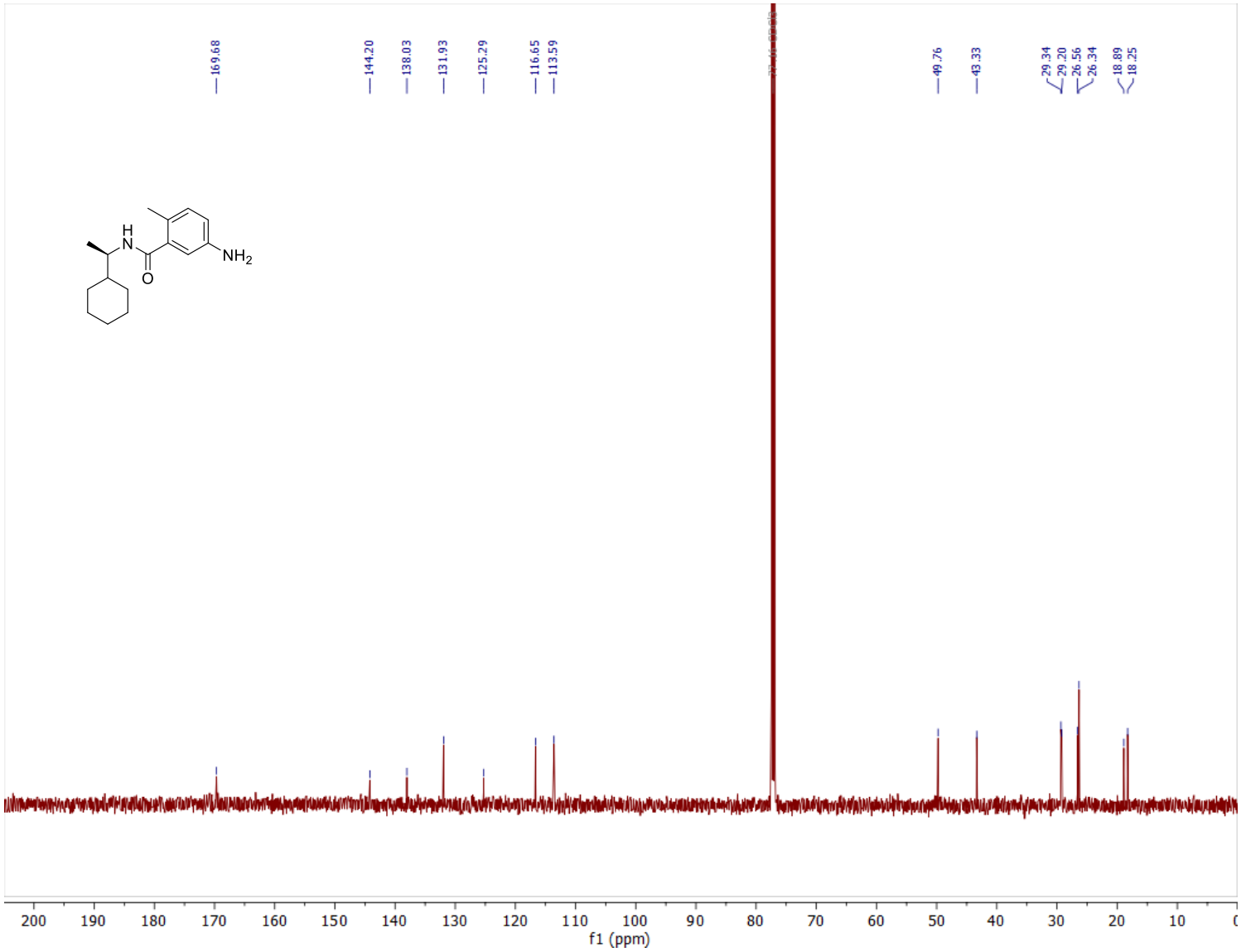
^{13}C NMR (126 MHz, $CDCl_3$) spectrum of (±) *N*-(1'-(adamantan-1'-yl)ethyl)-2-methyl-5-nitrobenzamide (7).



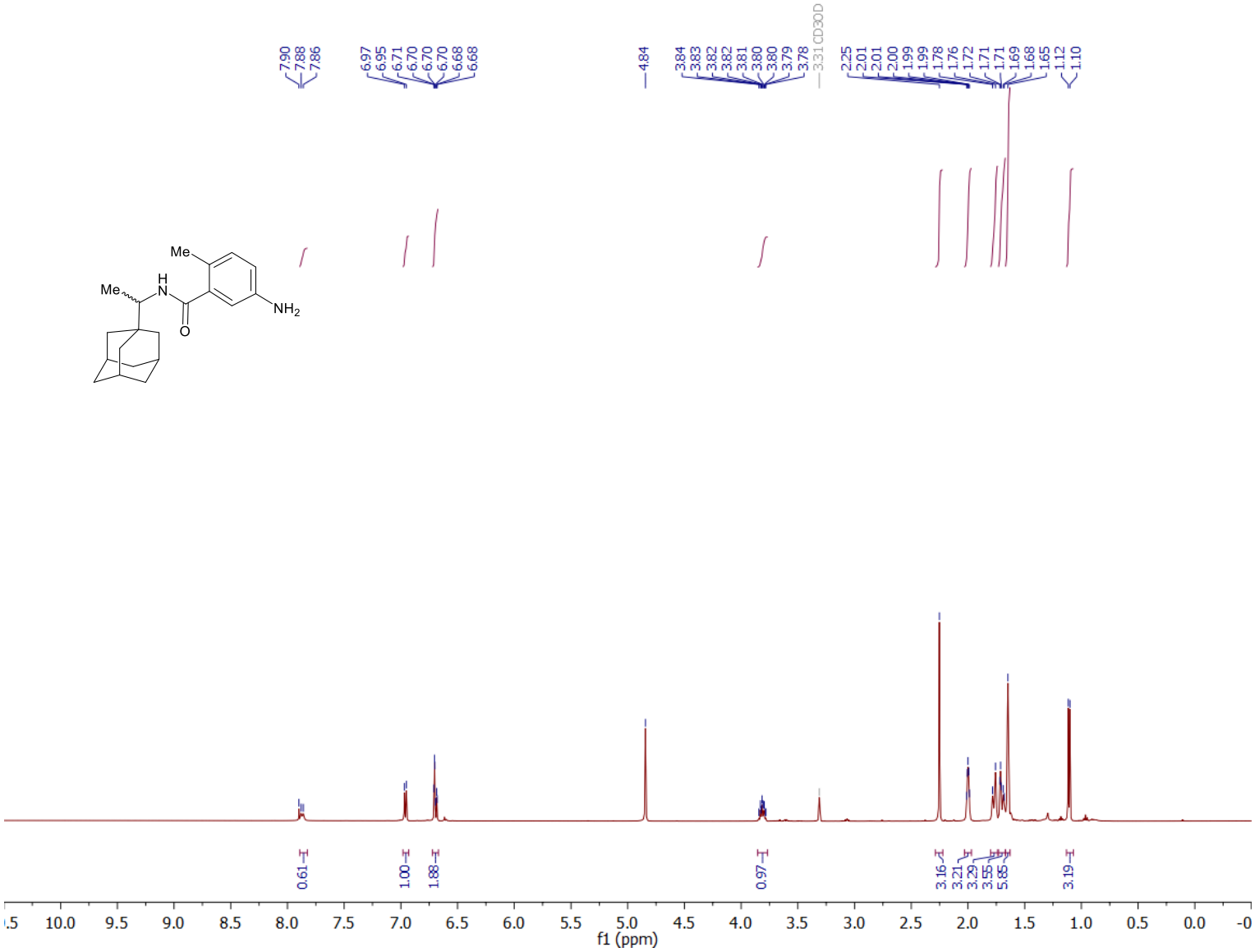
^{1}H NMR (500 MHz, $CDCl_3$) spectrum of (*R*)-*N*-[1-(1-Cyclohexyl)ethyl] 5-amino-2-methylbenzamide (8).



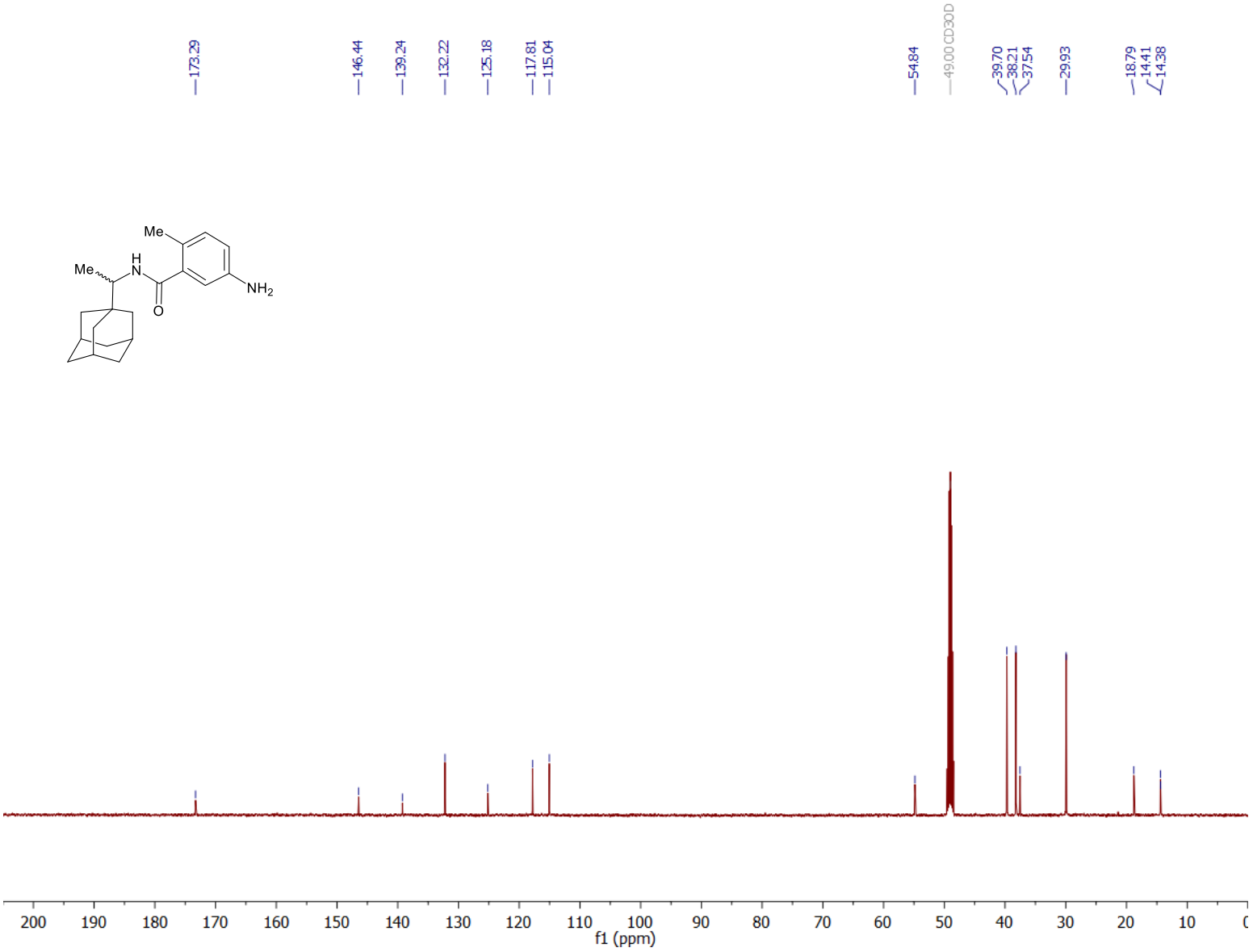
^{13}C NMR (126 MHz, $CDCl_3$) spectrum of (*R*)-*N*-[1-(1-Cyclohexyl)ethyl] 5-amino-2-methylbenzamide (8).



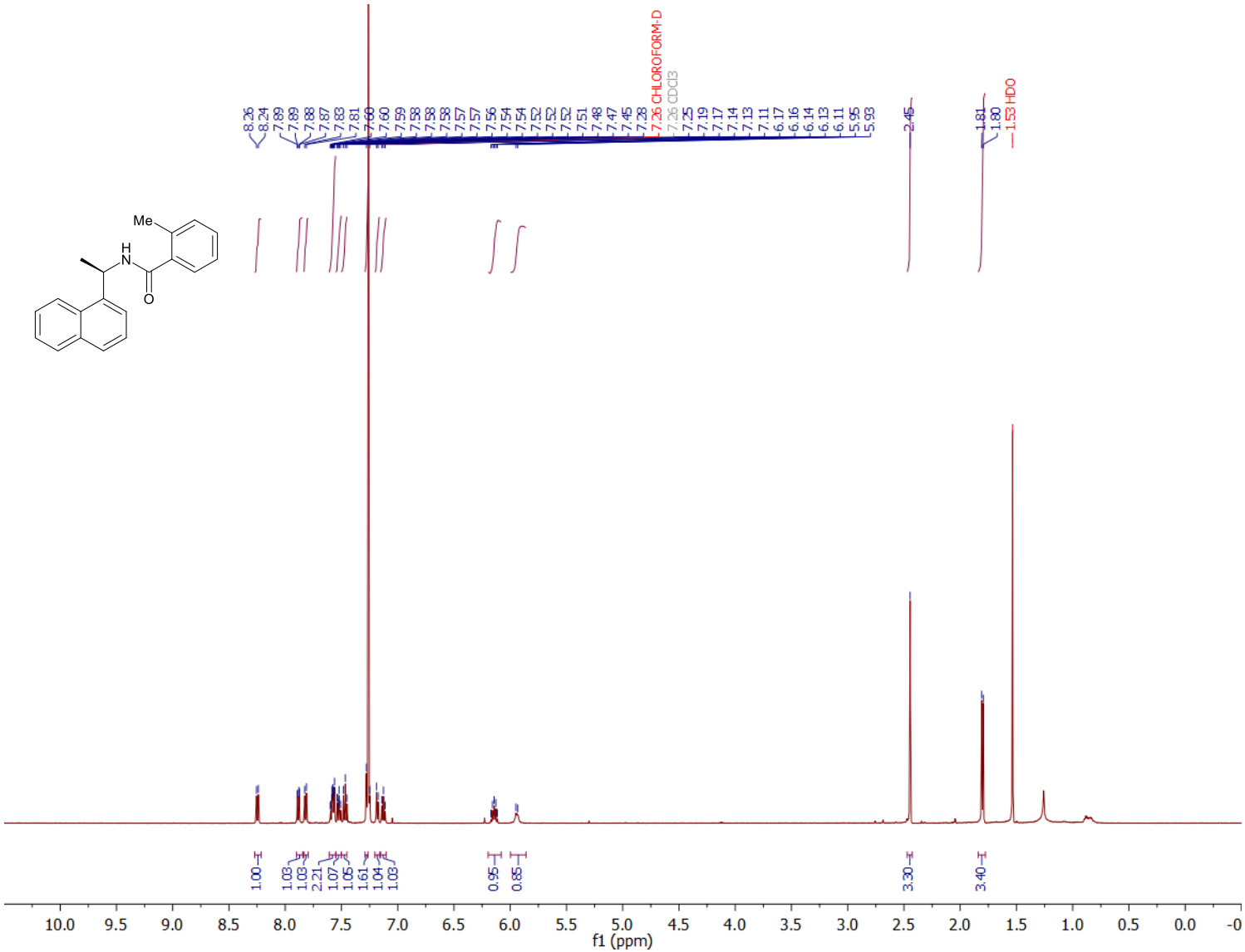
^{1}H NMR (500 MHz, CD_3OD) spectrum of (±)-*N*-(1'-(adamantan-1'-yl)ethyl)-5-amino-2-methylbenzamide (9).



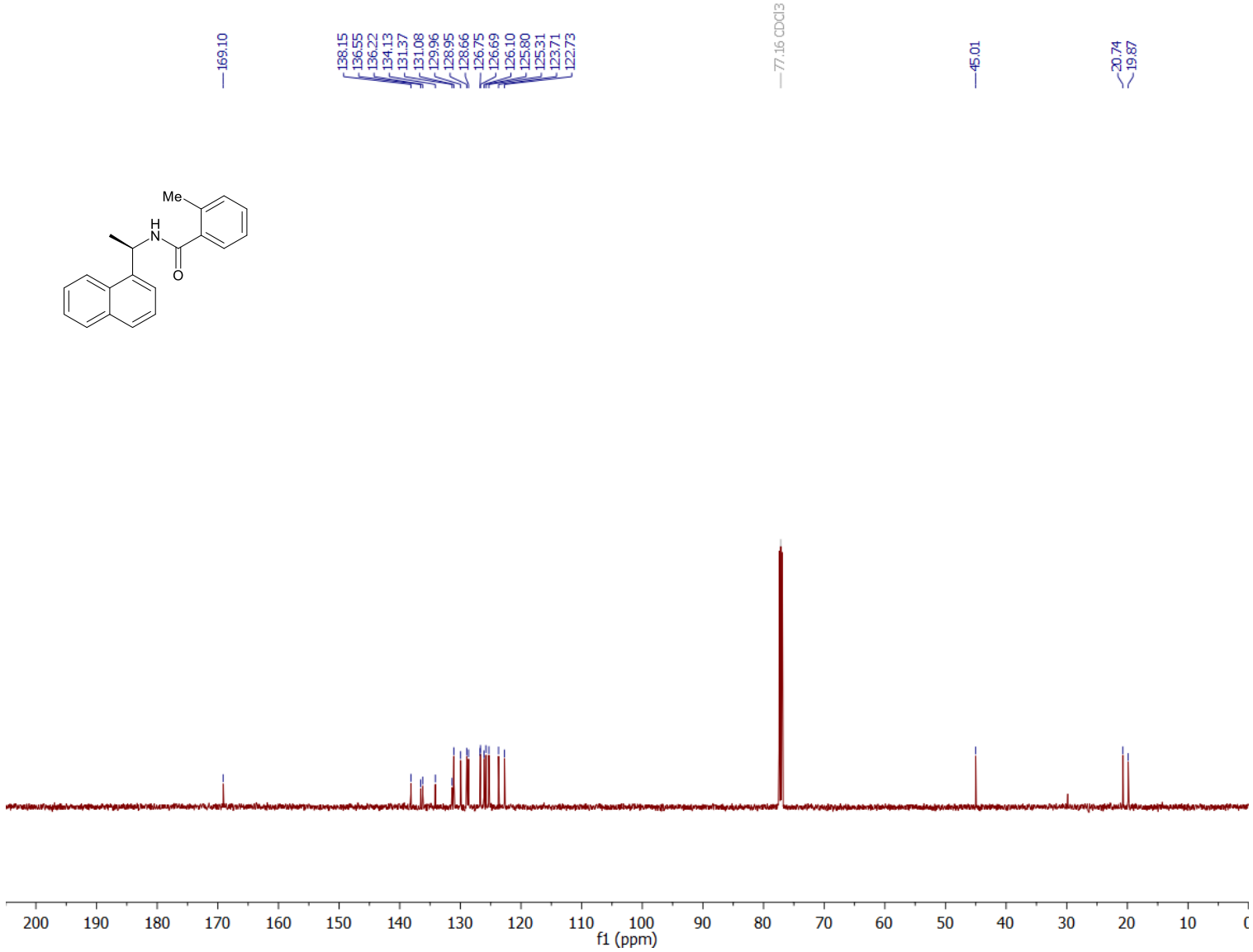
^{13}C NMR (126 MHz, CD_3OD) spectrum of (±)-*N*-(1'-(adamantan-1'-yl)ethyl)-5-amino-2-methylbenzamide (9).



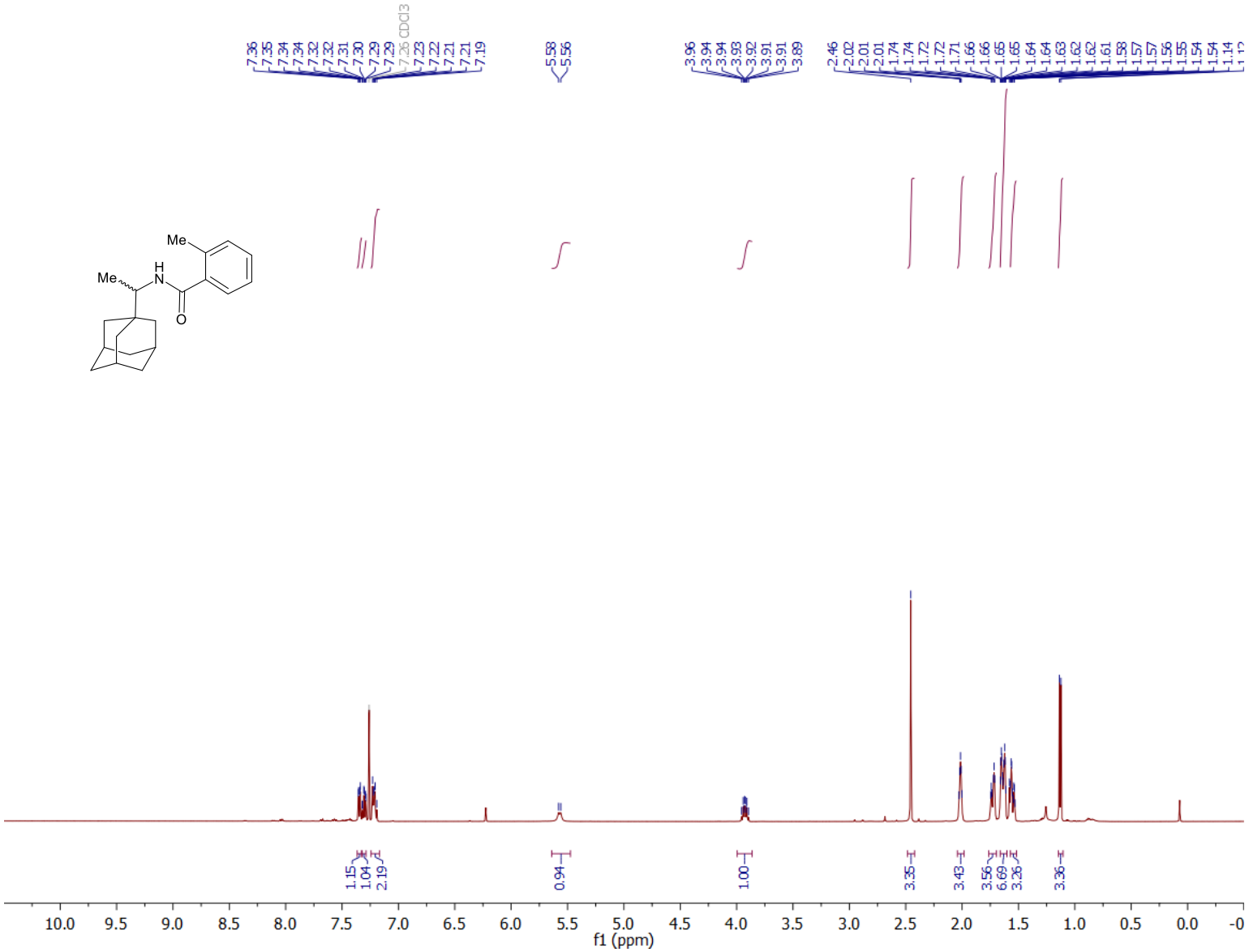
^{1}H NMR (500 MHz, $CDCl_3$) spectrum of (*R*)-2-methyl-*N*-(1'-(naphthalene-1'-yl)ethyl)benzamide (7724772).



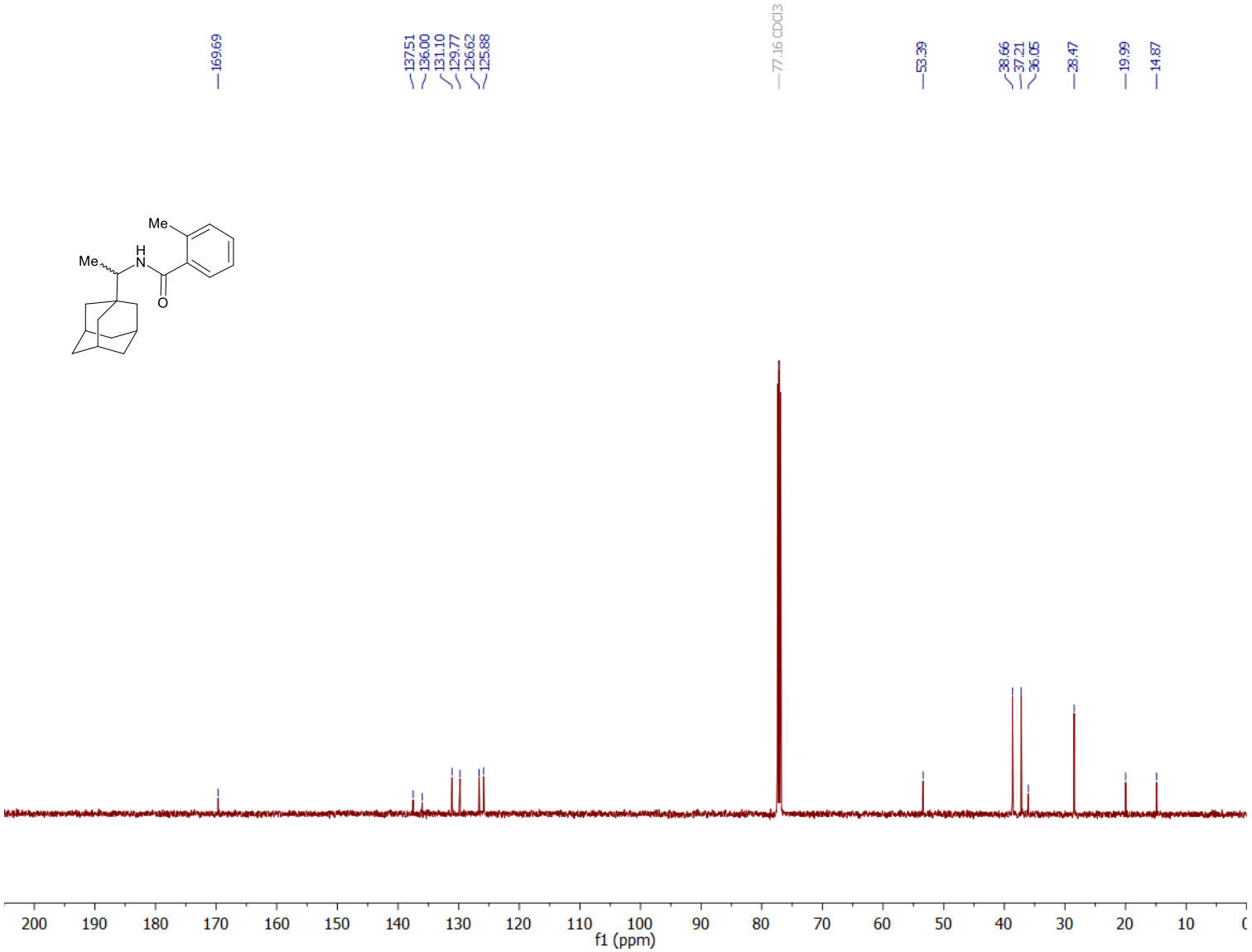
^{13}C NMR (126 MHz, $CDCl_3$) spectrum of (*R*)-2-methyl-*N*-(1'-(naphthalene-1'-yl)ethyl)benzamide (7724772).



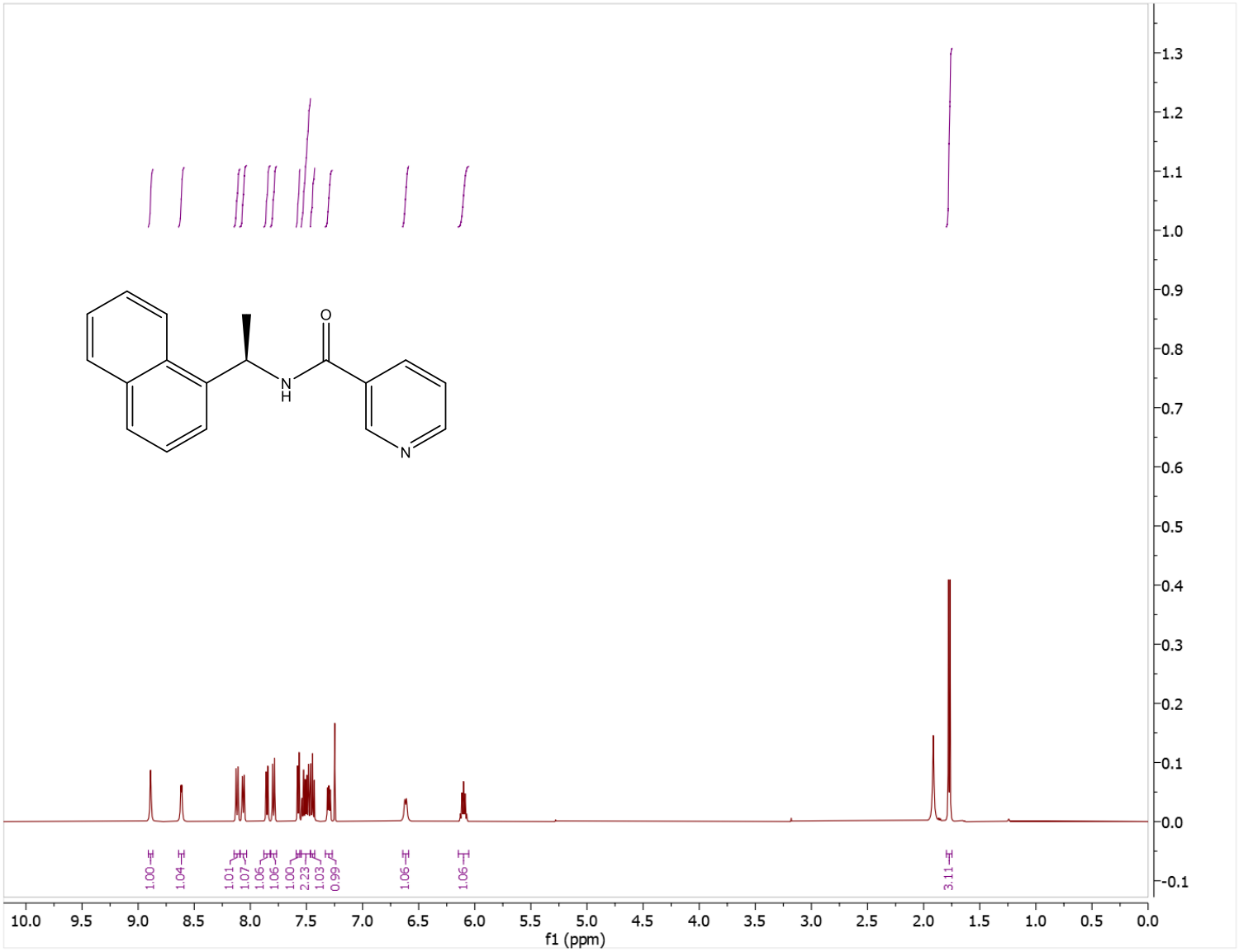
^{1}H NMR (500 MHz, $CDCl_3$) spectrum of *N*-(1'-(adamantan-1'-yl)ethyl)-2-methylbenzamide (10).



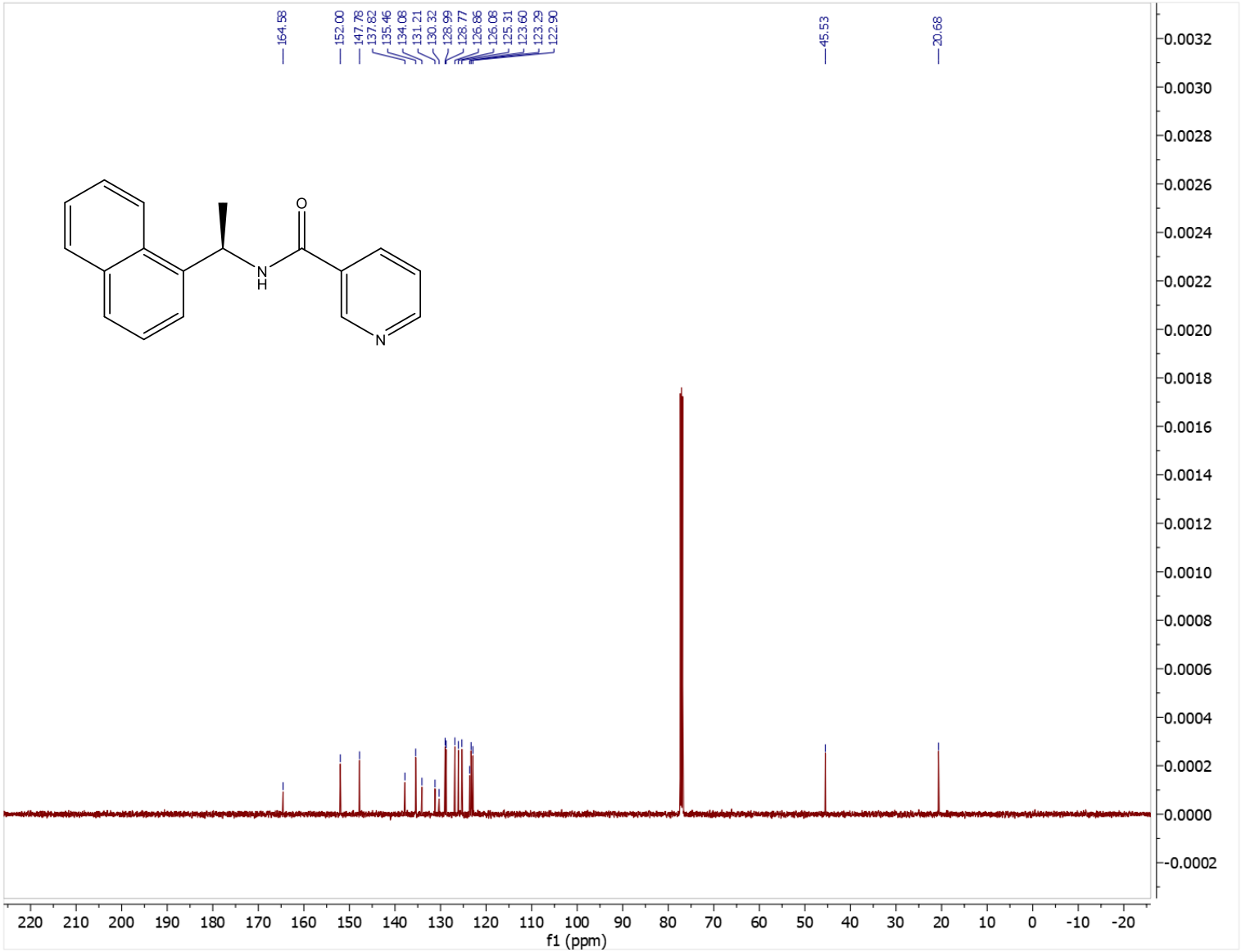
^{13}C NMR (126 MHz, $CDCl_3$) spectrum of *N*-(1'-(adamantan-1'-yl)ethyl)-2-methylbenzamide (10).



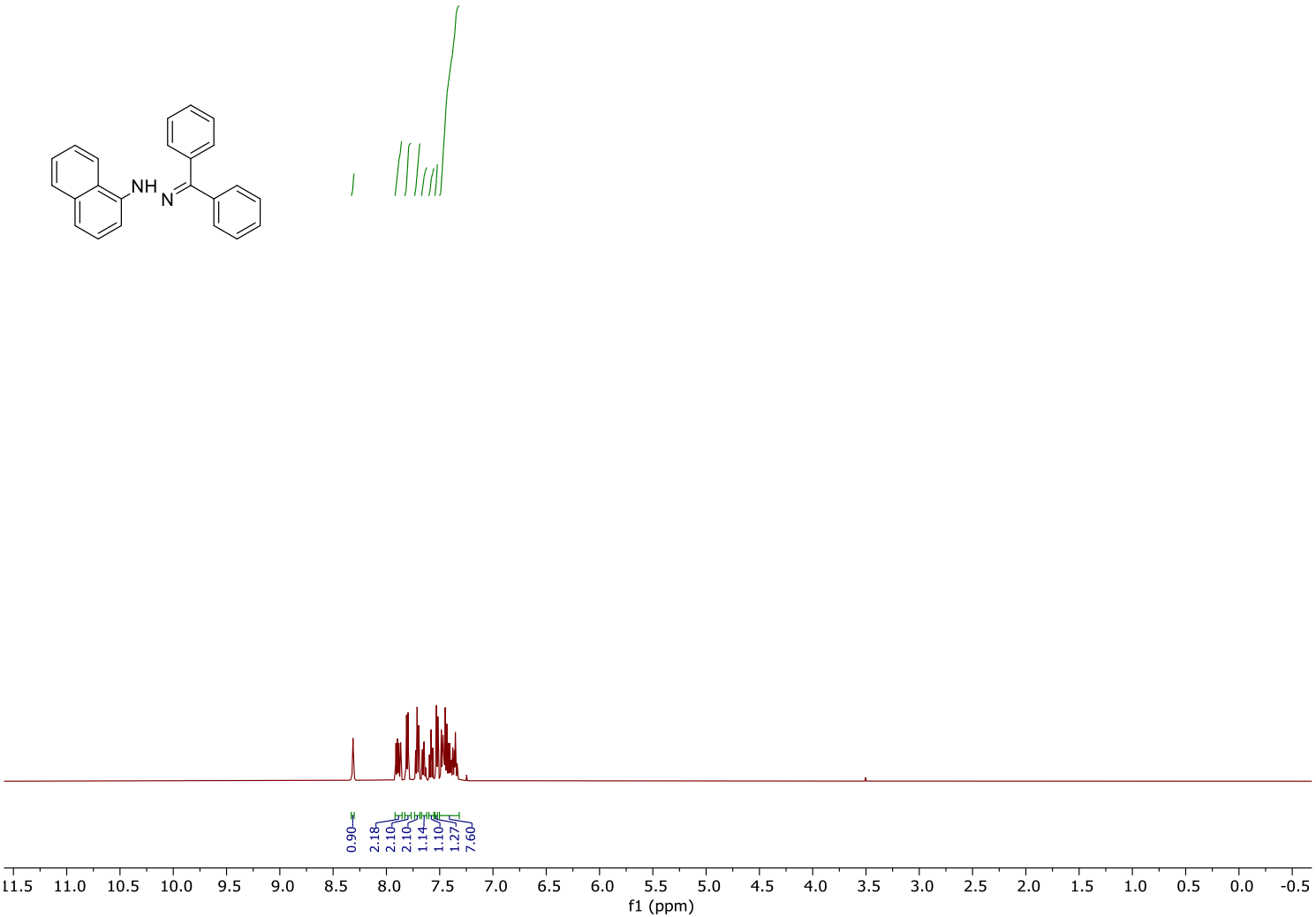
^{1}H NMR (500 MHz, $CDCl_3$) spectrum of (*R*)-*N*-(1-(naphthalen-1-yl)ethyl)nicotinamide (11).



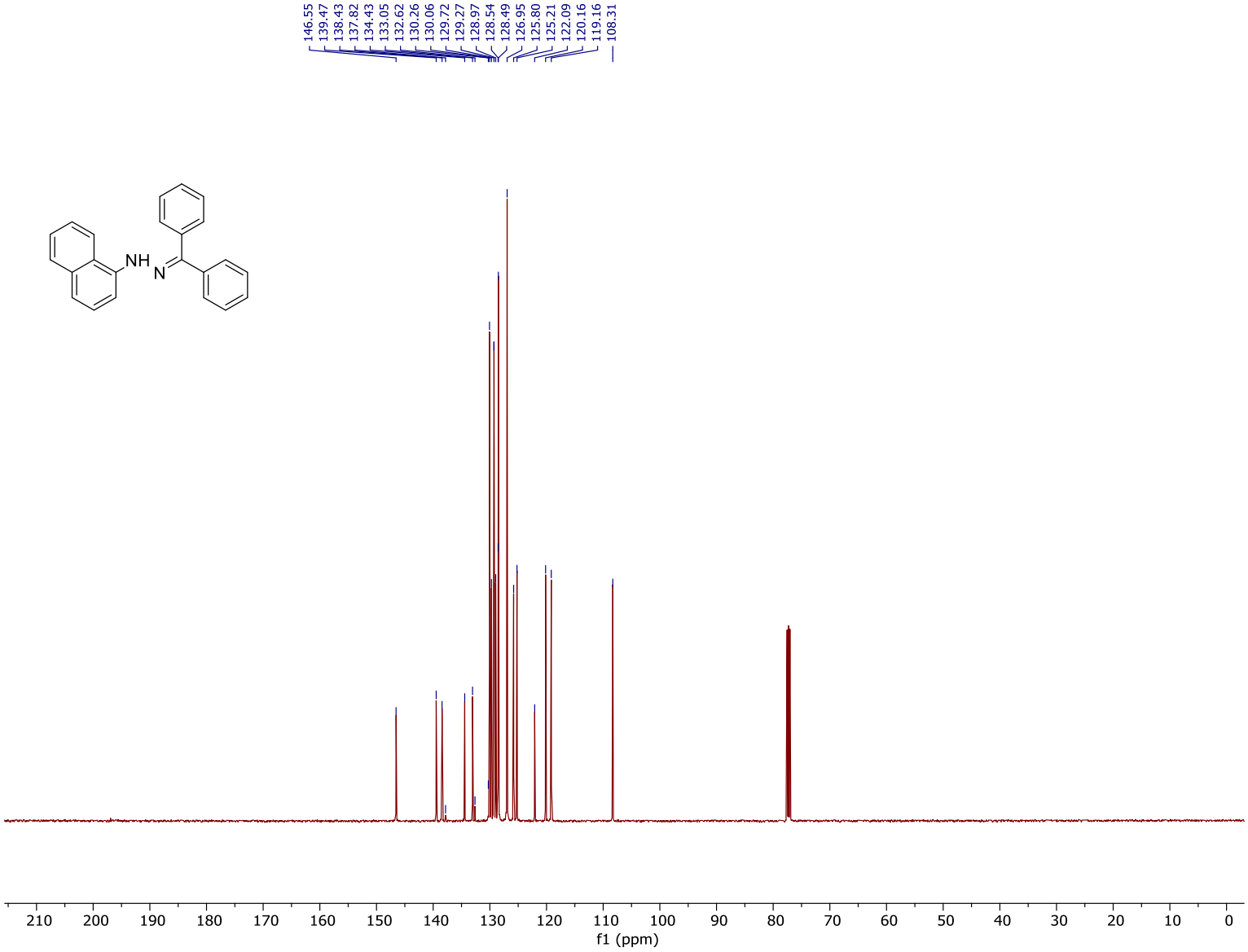
^{13}C NMR (126 MHz, $CDCl_3$) spectrum of (*R*)-*N*-(1-(naphthalen-1-yl)ethyl)nicotinamide (11).



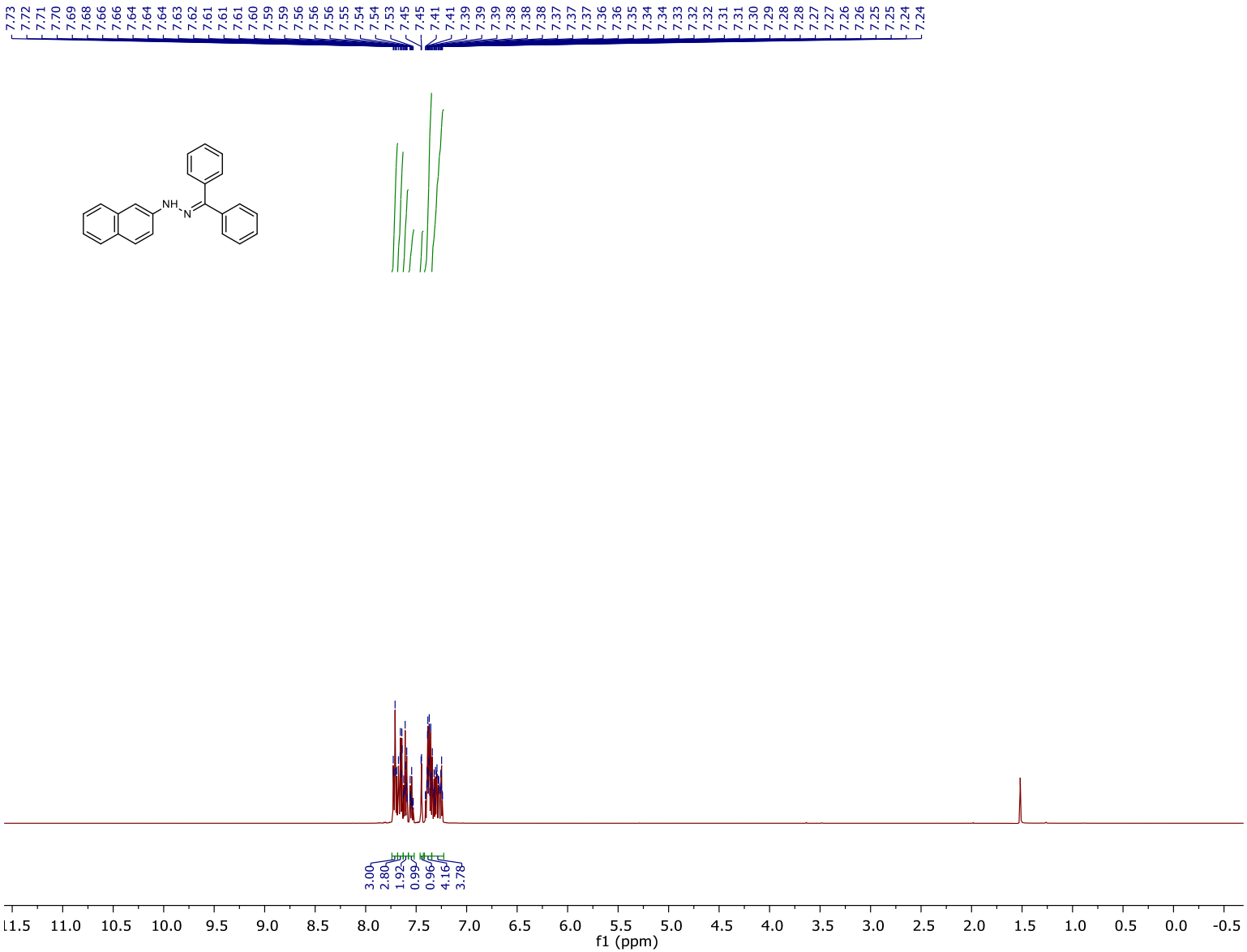
^{1}H NMR (500 MHz, $CDCl_3$) spectrum of benzophenone 1-naphthylhydrazone (14).



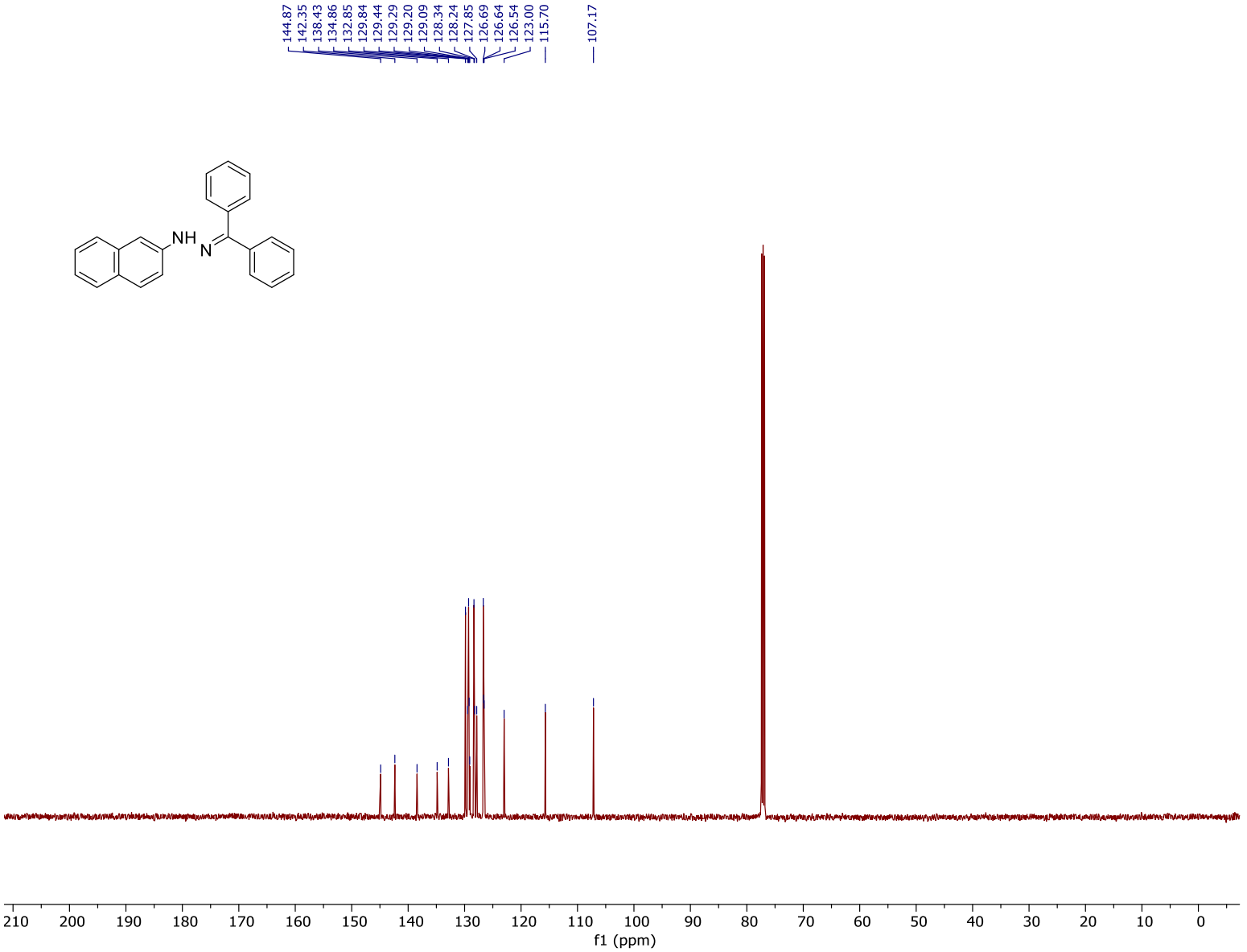
^{13}C NMR (126 MHz, $CDCl_3$) spectrum of benzophenone 1-naphthylhydrazone (14).



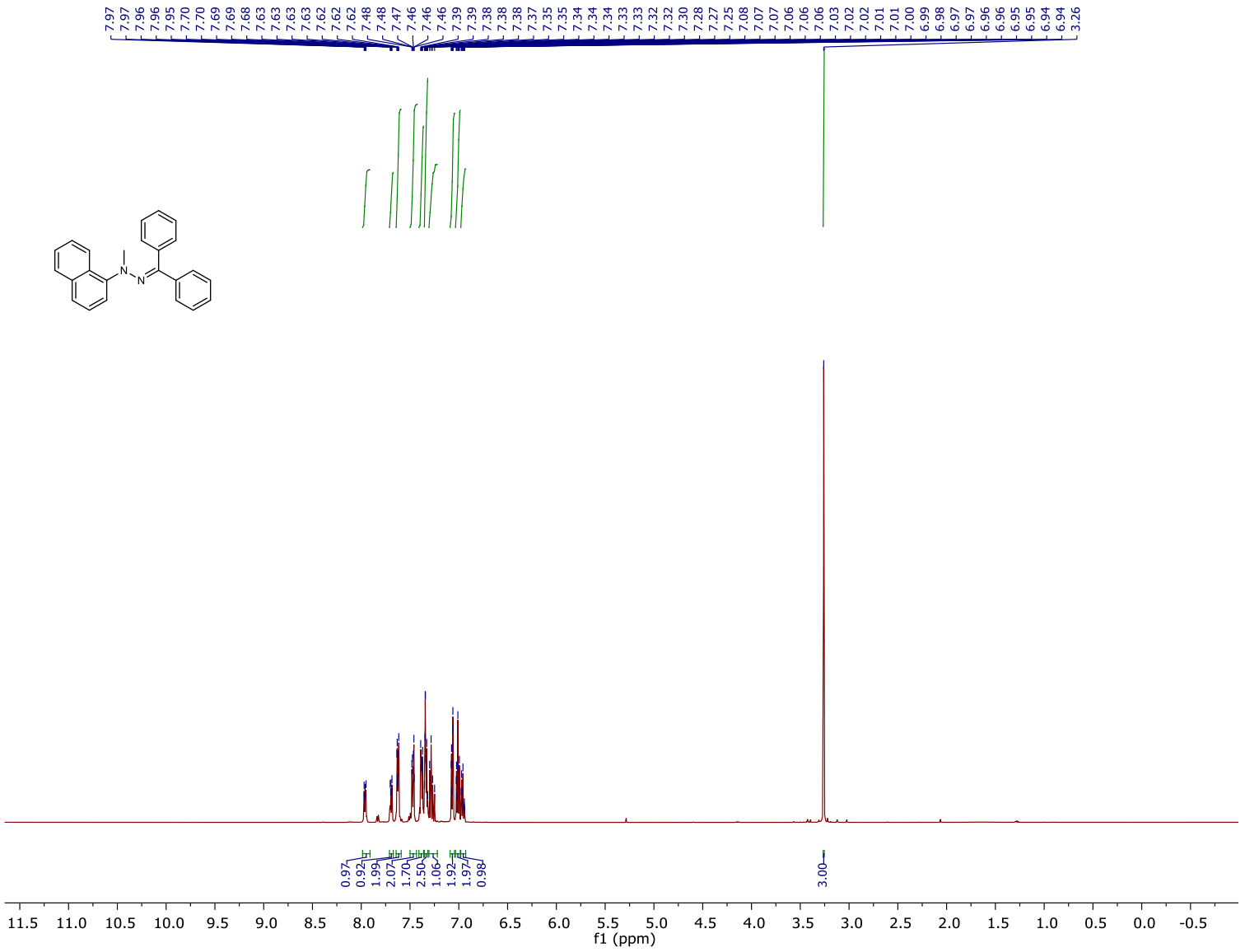
^{1}H NMR (500 MHz, $CDCl_3$) spectrum of benzophenone 2-naphthylhydrazone (15).



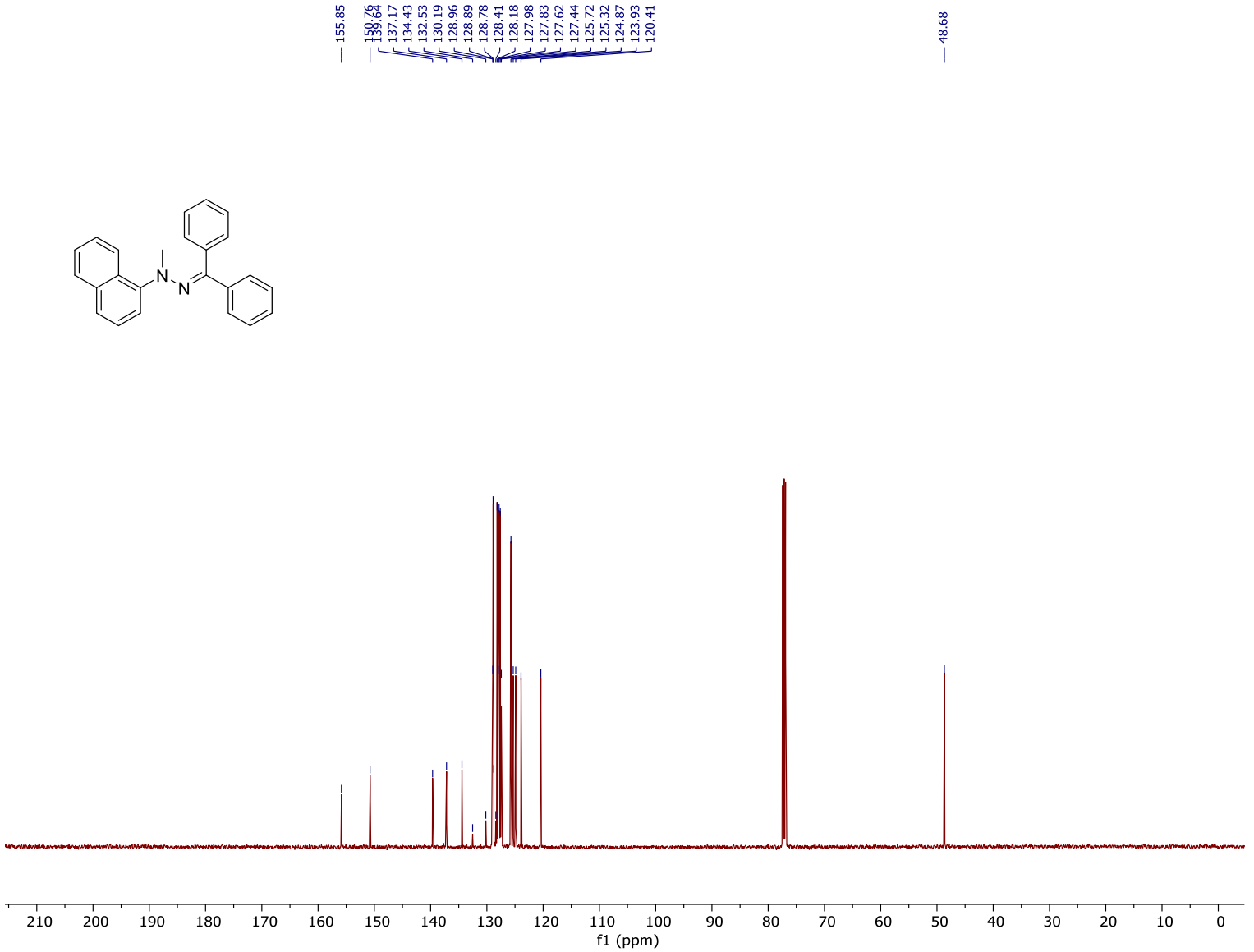
^{13}C NMR (126 MHz, $CDCl_3$) spectrum of benzophenone 2-naphthylhydrazone (15).



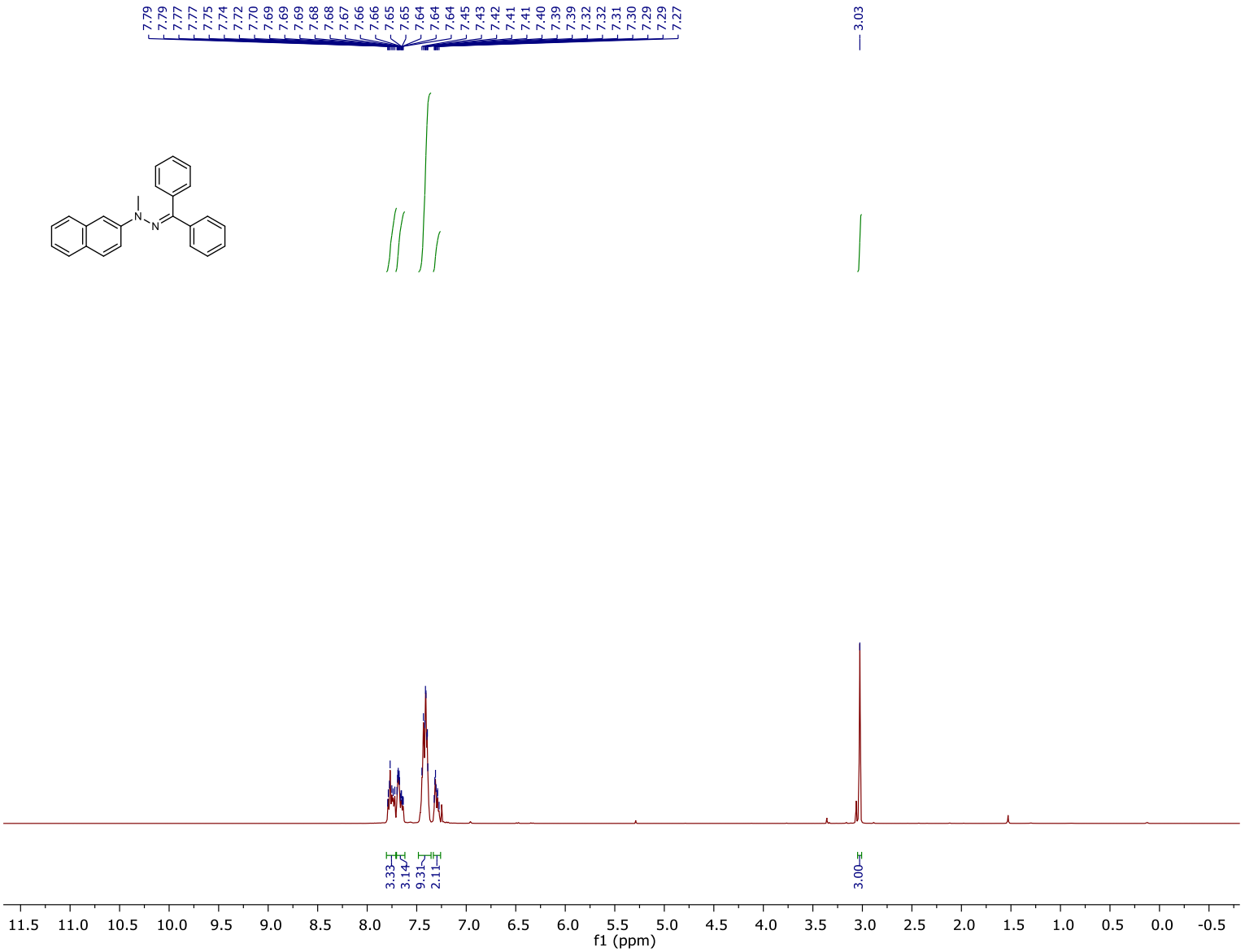
^{1}H NMR (500 MHz, $CDCl_3$) spectrum of benzophenone *N*-methyl-(1-naphthyl)hydrazone (16).



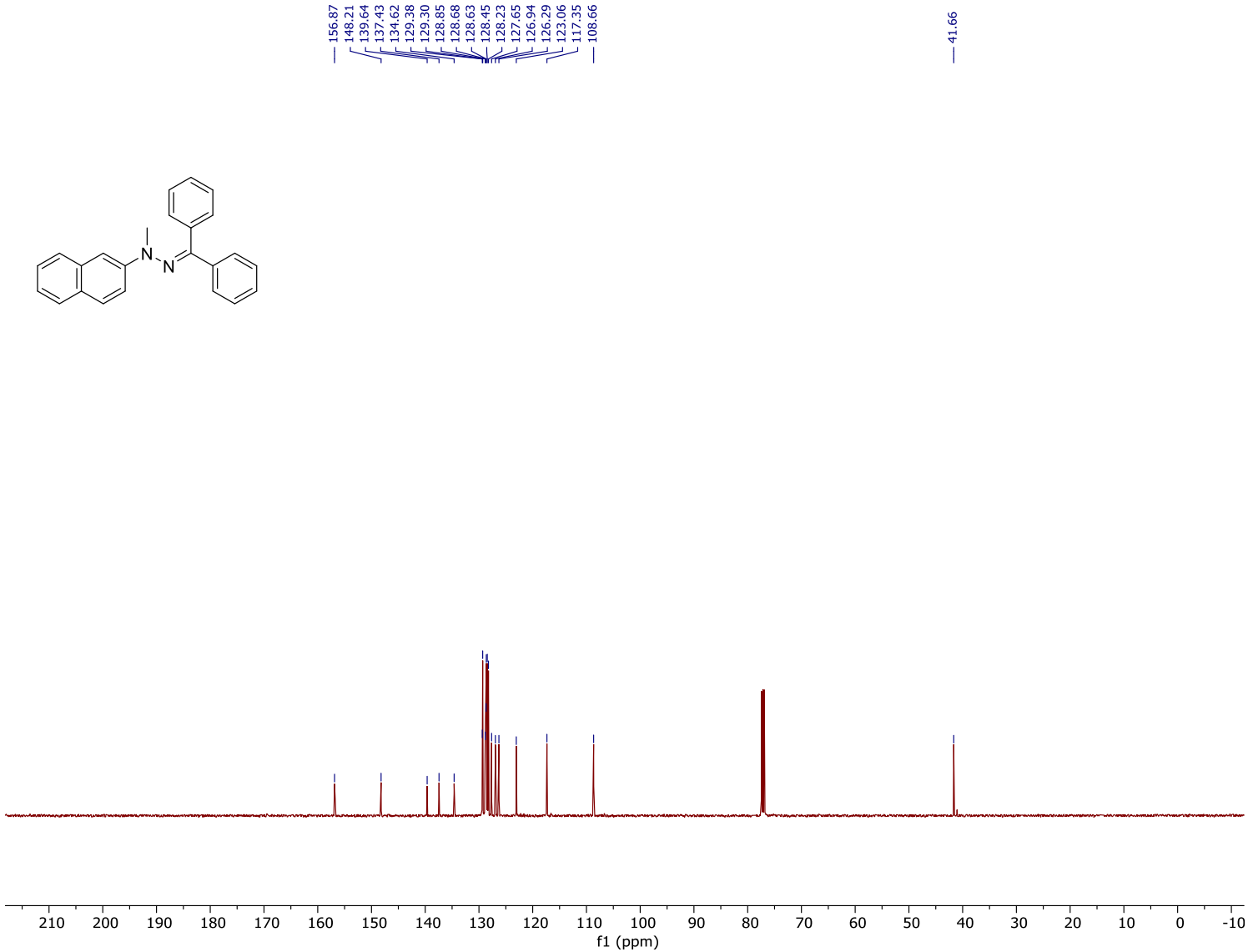
^{13}C NMR (126 MHz, $CDCl_3$) spectrum of benzophenone *N*-methyl-(1-naphthyl)hydrazone (16).



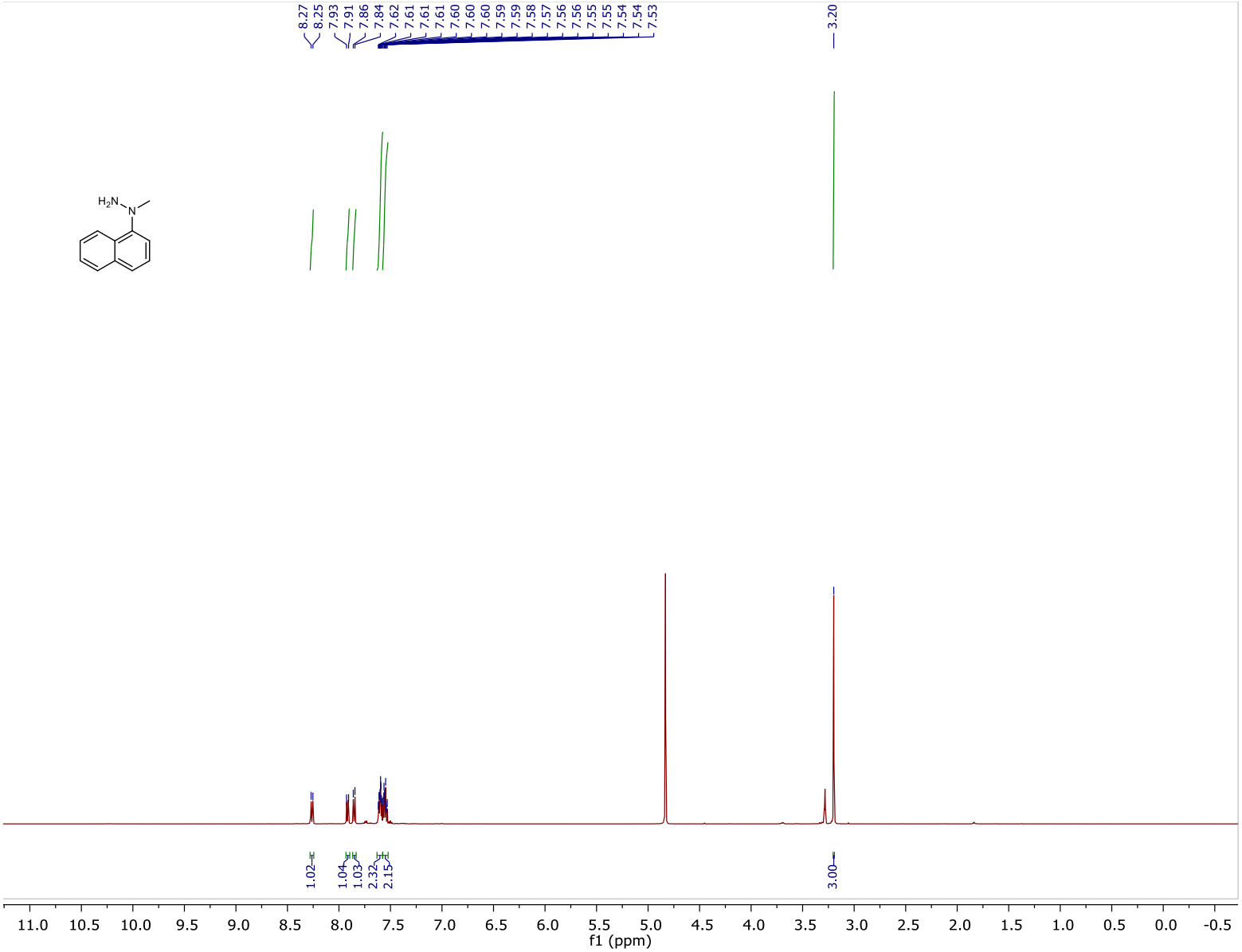
^{1}H NMR (500 MHz, $CDCl_3$) spectrum of benzophenone *N*-methyl-(2-naphthyl)hydrazone (17).



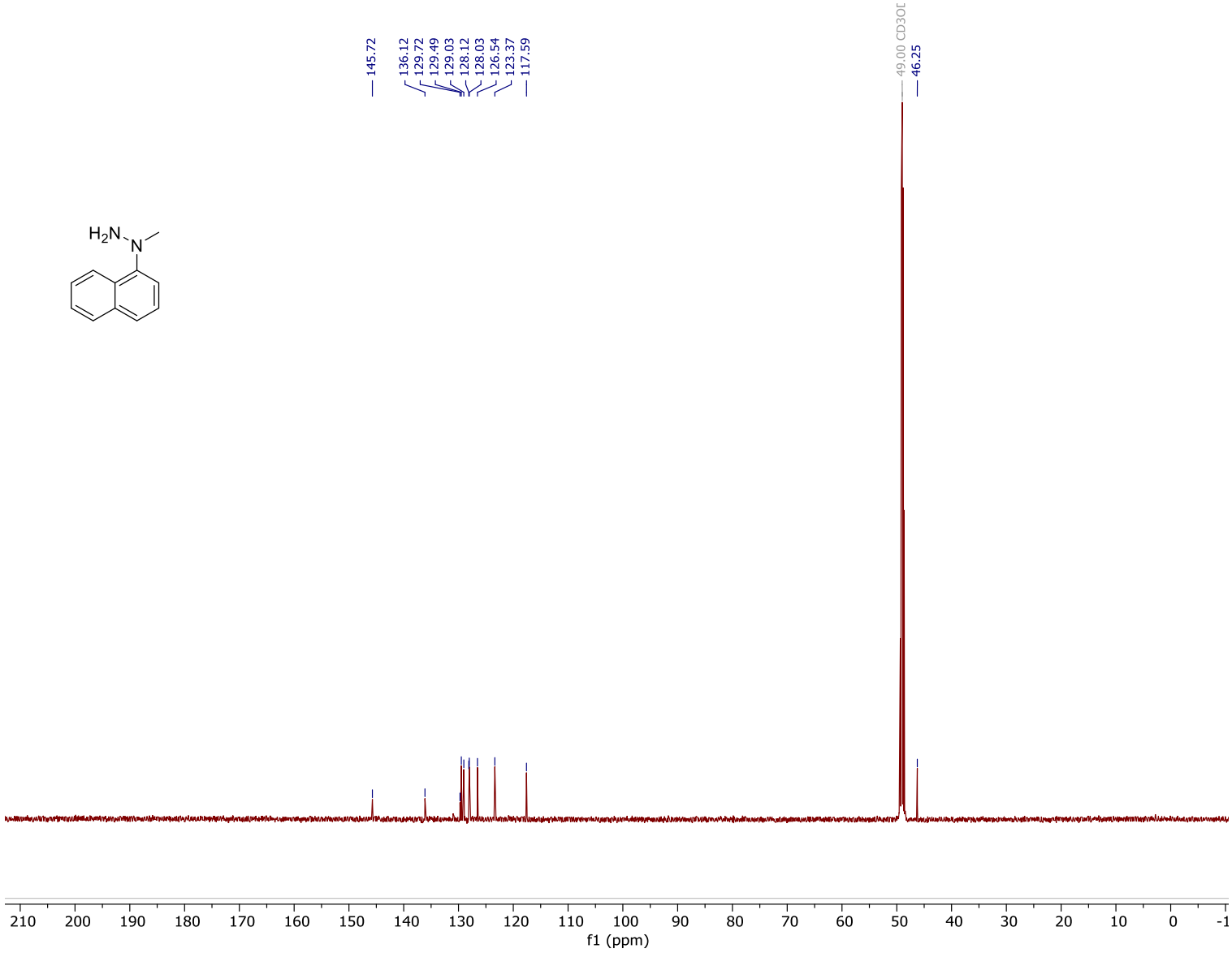
^{13}C NMR (126 MHz, $CDCl_3$) spectrum of benzophenone *N*-methyl-(2-naphthyl)hydrazine (17).



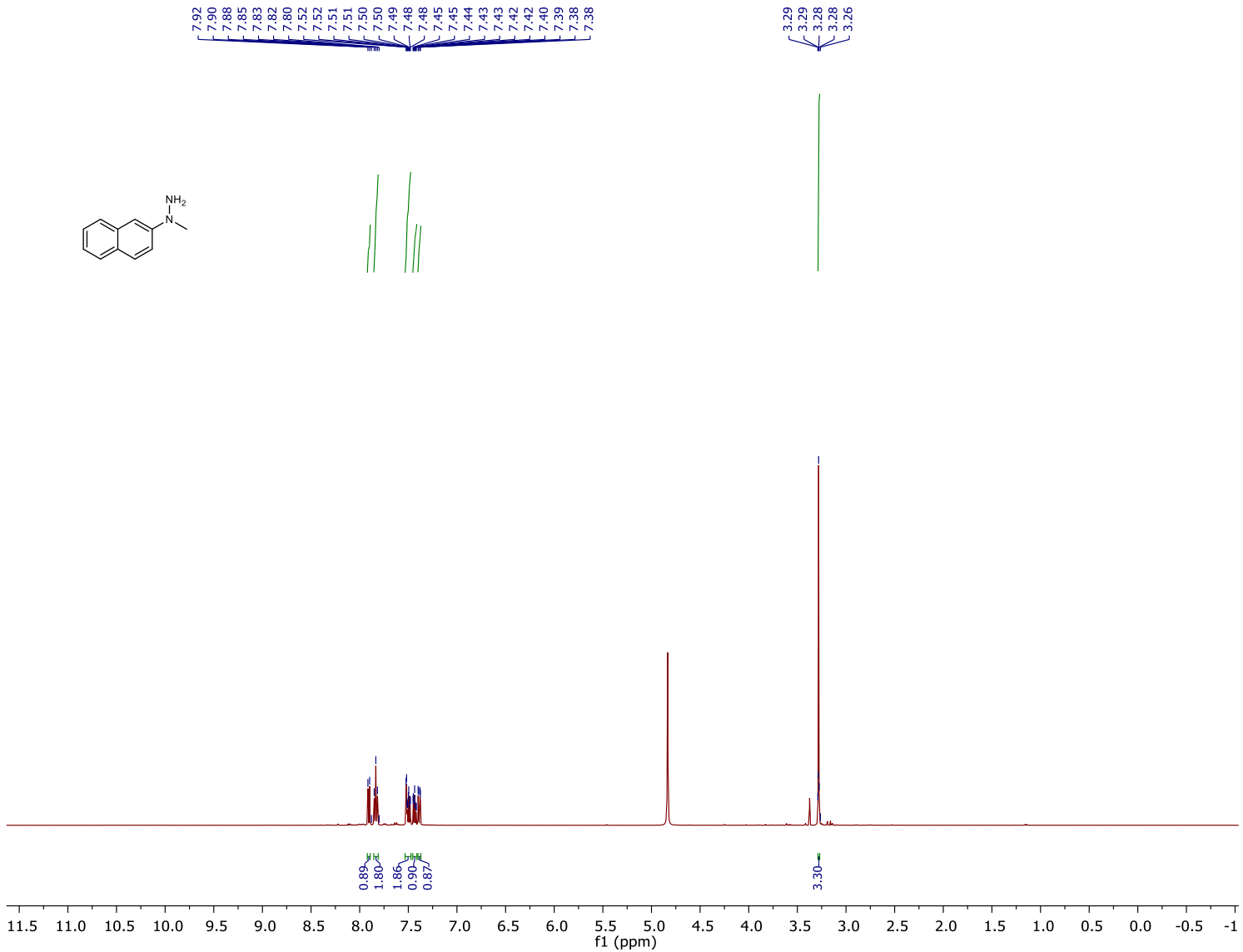
^{1}H NMR (500 MHz, CD_3OD) spectrum of *N*-Methyl-*N*-(1-naphthyl)hydrazine (18).



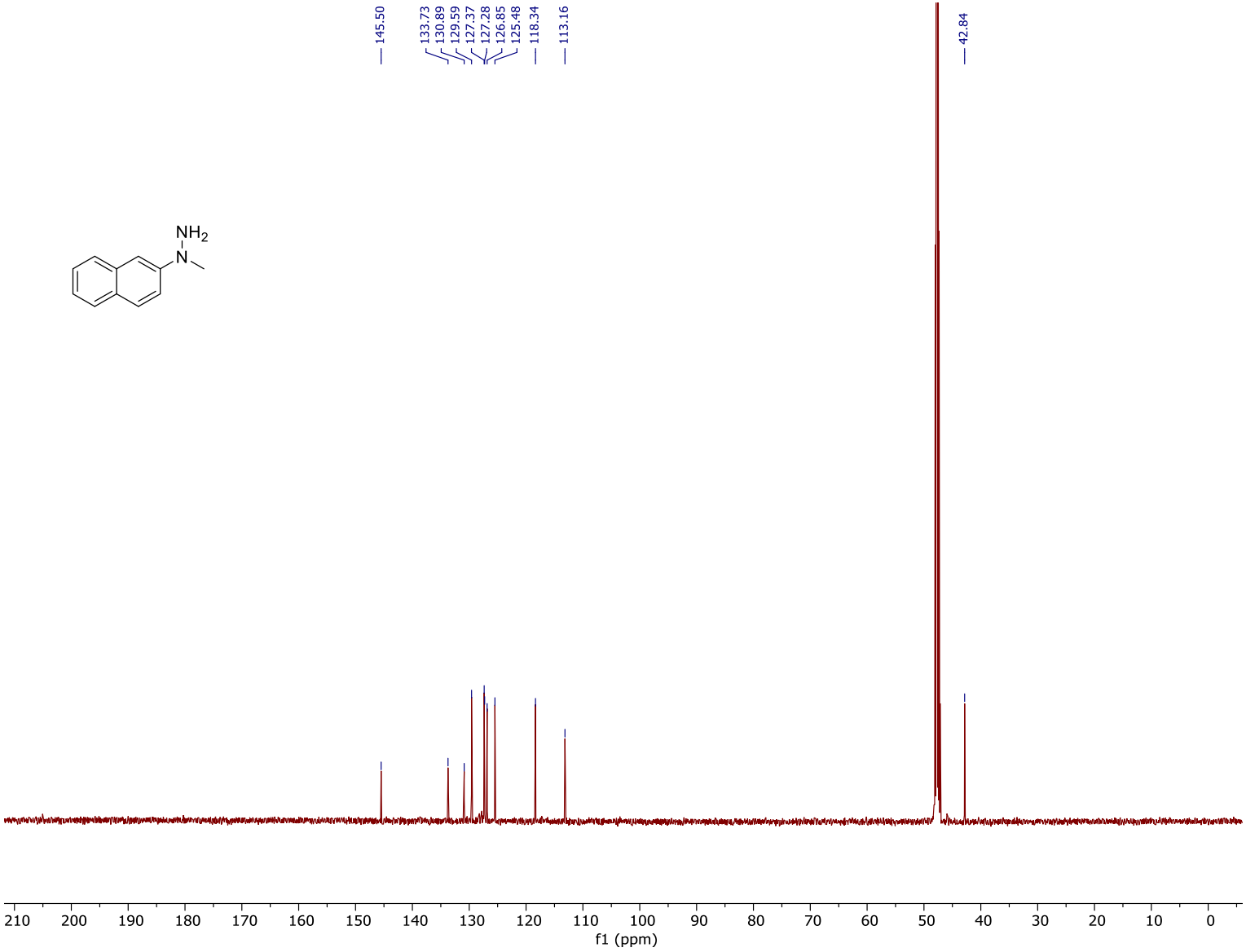
^{13}C NMR (126 MHz, CD_3OD) spectrum of *N*-Methyl-*N*-(1-naphthyl)hydrazine (18).



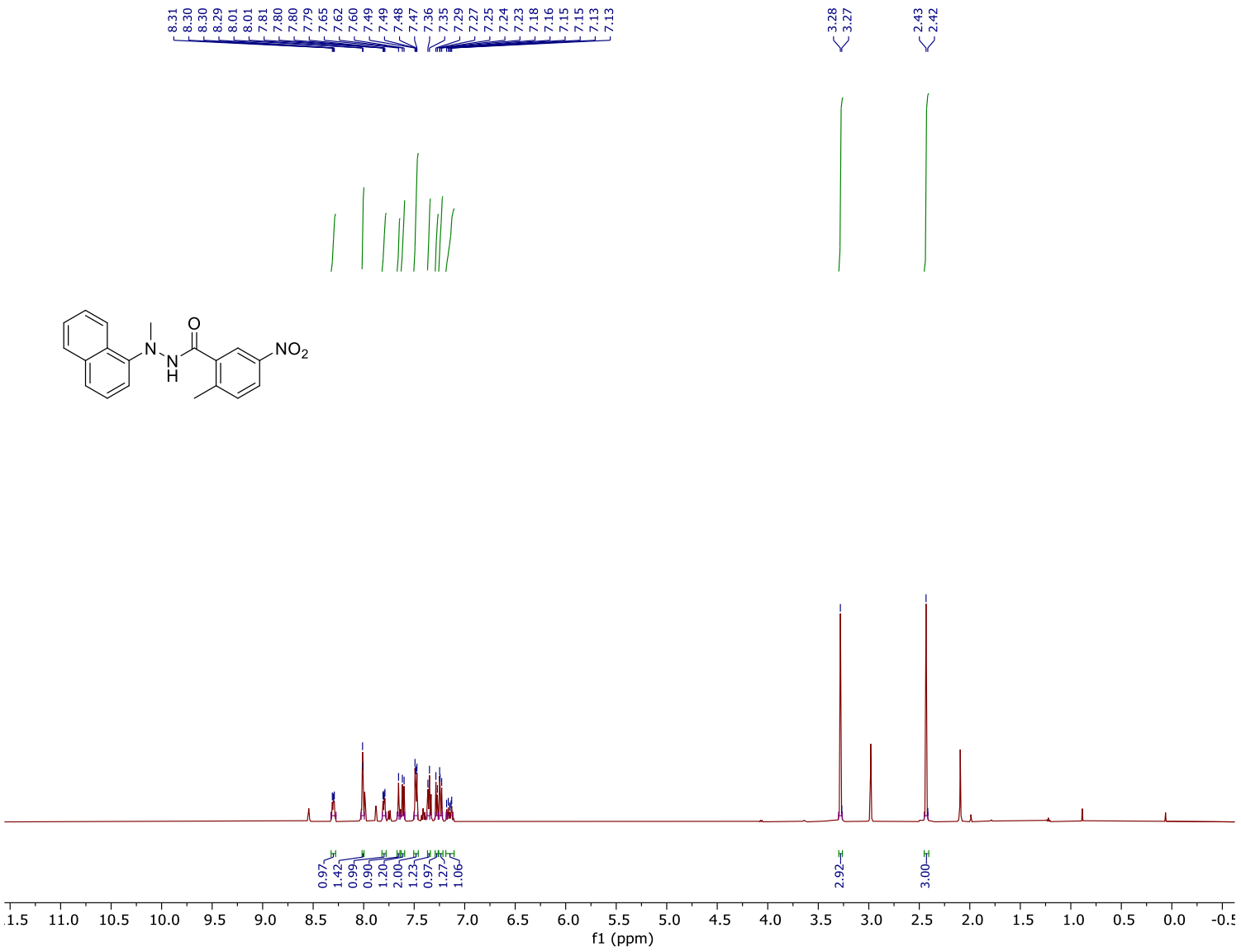
^{1}H NMR (500 MHz, CD_3OD) spectrum of *N*-Methyl-*N*-(2-naphthyl)hydrazine (19).



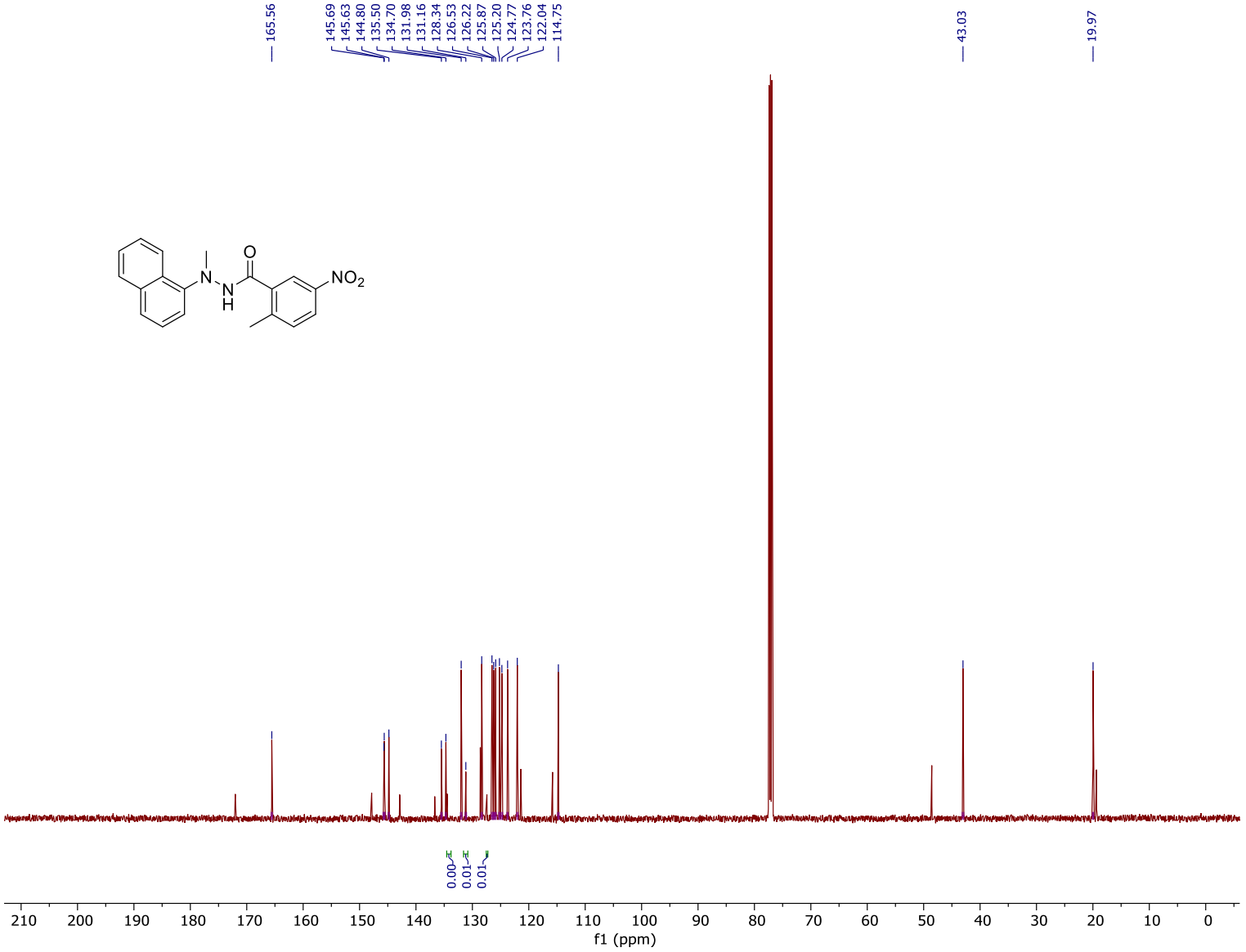
^{13}C NMR (126 MHz, CD_3OD) spectrum of *N*-Methyl-*N*-(2-naphthyl)hydrazine (19).



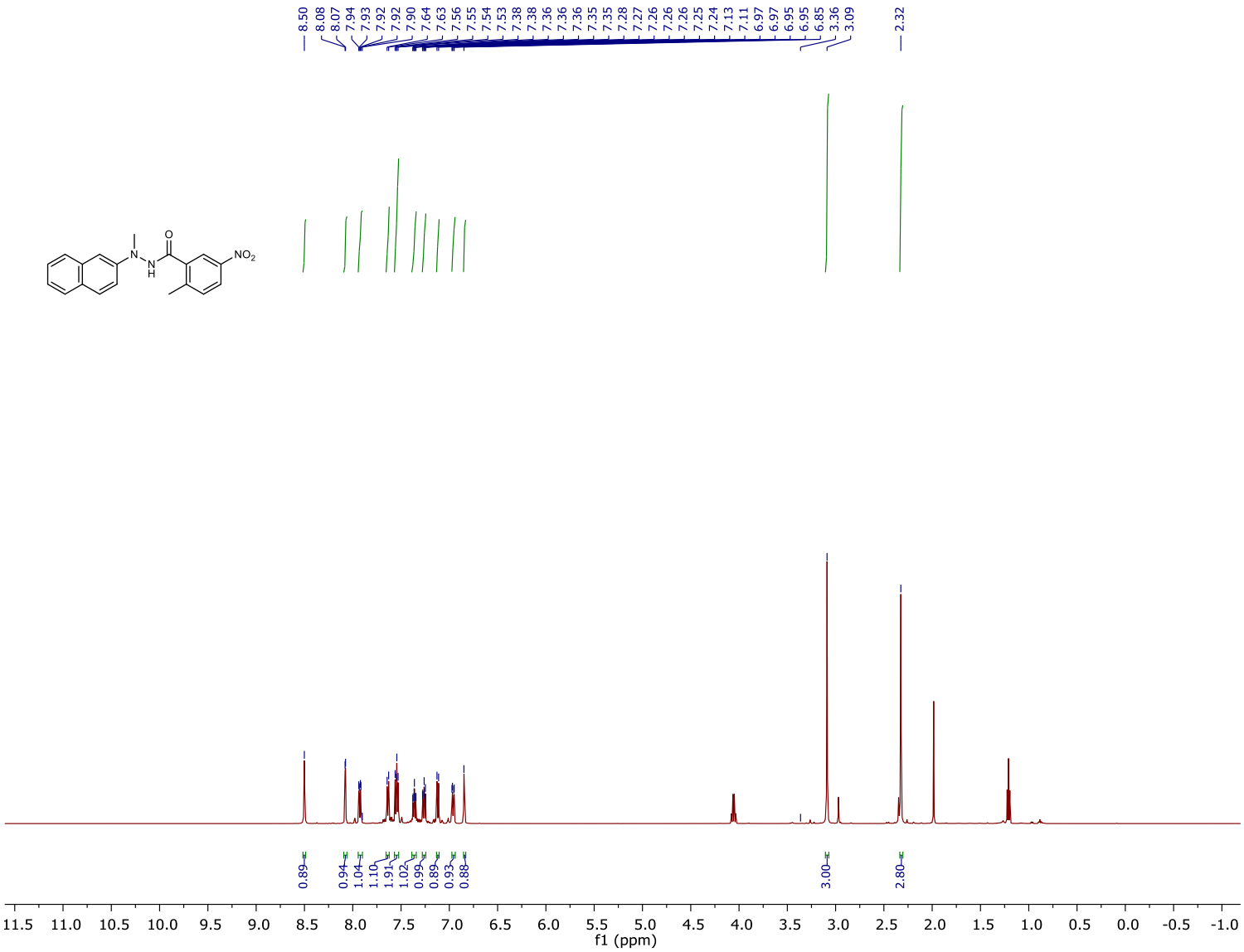
^{1}H NMR (500 MHz, $CDCl_3$) spectrum of *N*'-Methyl-*N*'-(naphthalen-1-yl) 2-methyl-5-nitrobenzhydrazide (20).



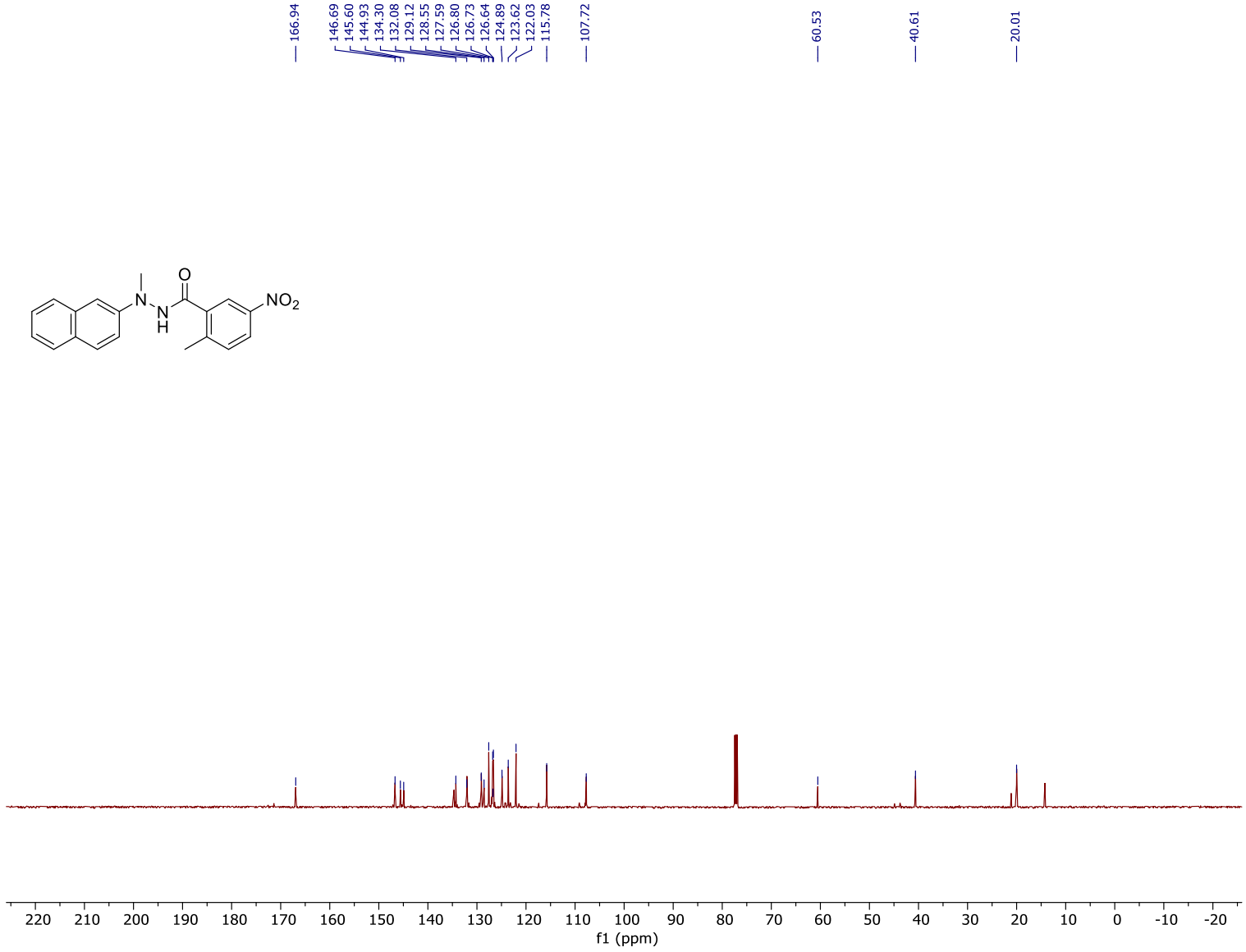
^{13}C NMR (126 MHz, $CDCl_3$) spectrum of *N*'-Methyl-*N*'-(naphthalen-1-yl) 2-methyl-5-nitrobenzhydrazide (20).



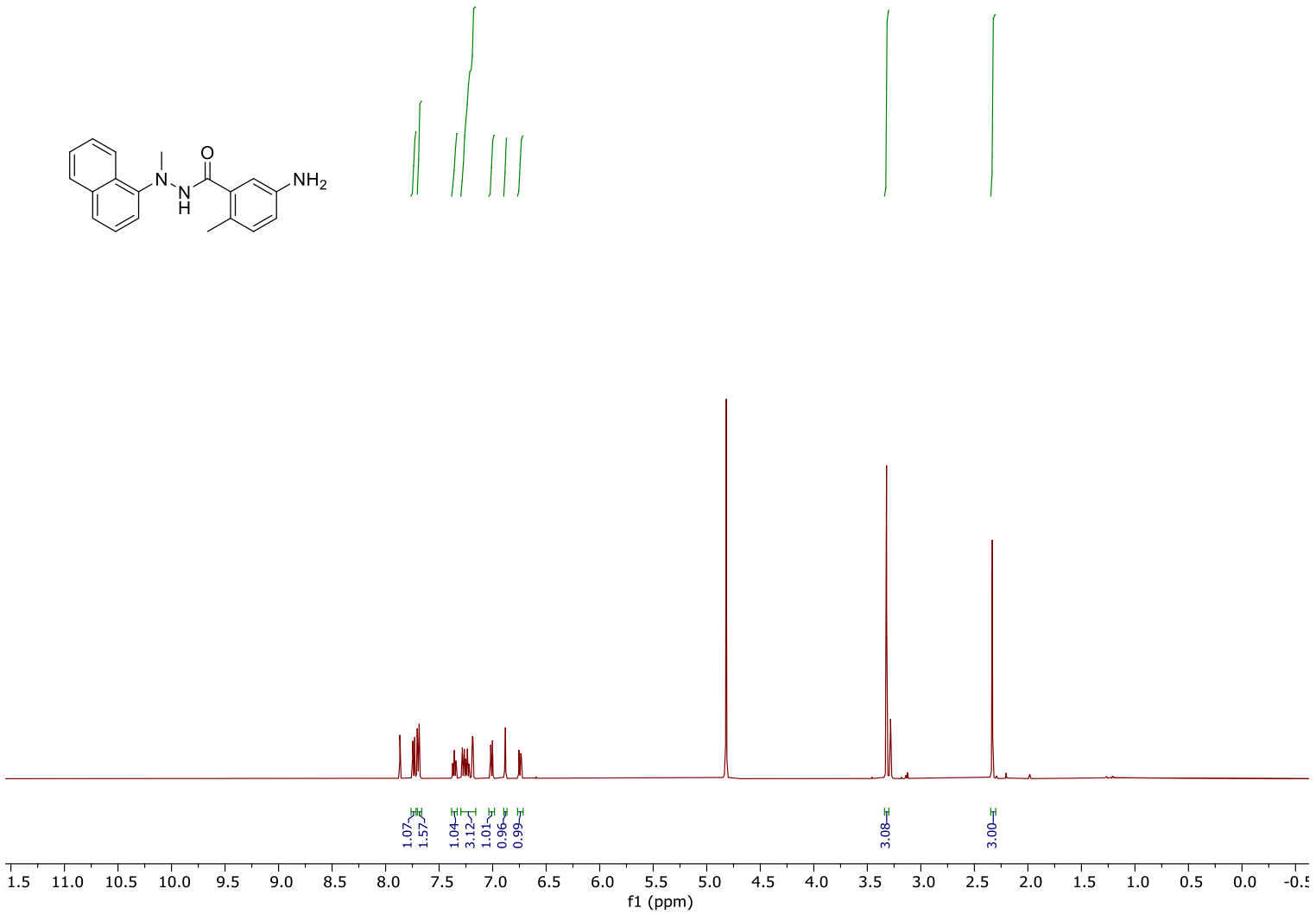
^{1}H NMR (500 MHz, $CDCl_3$) spectrum of *N*'-Methyl-*N*'-(naphthalen-2-yl) 2-methyl-5-nitrobenzhydrazide (21).



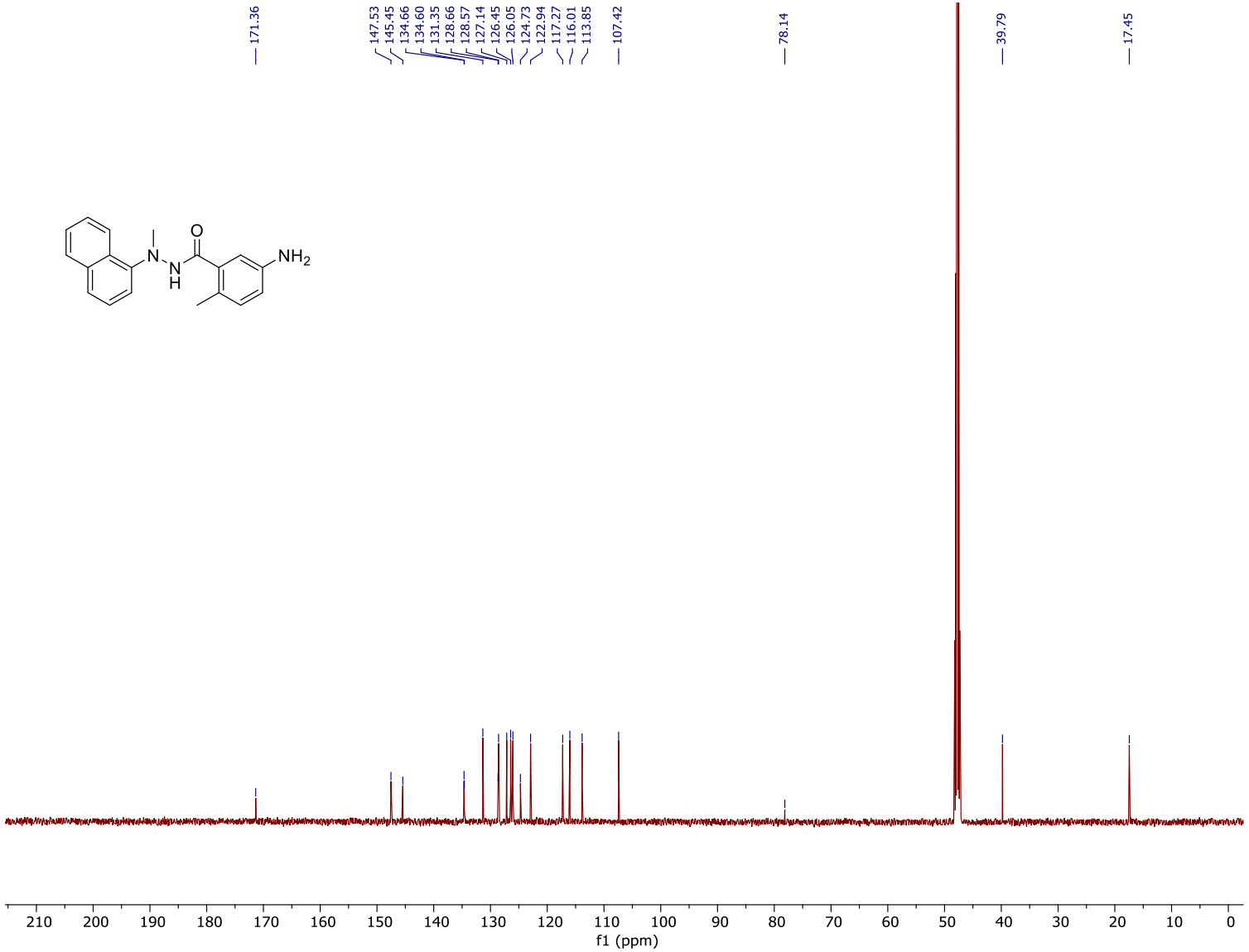
^{13}C NMR (126 MHz, $CDCl_3$) spectrum of *N*'-Methyl-*N*'-(naphthalen-2-yl) 2-methyl-5-nitrobenzhydrazide (21).



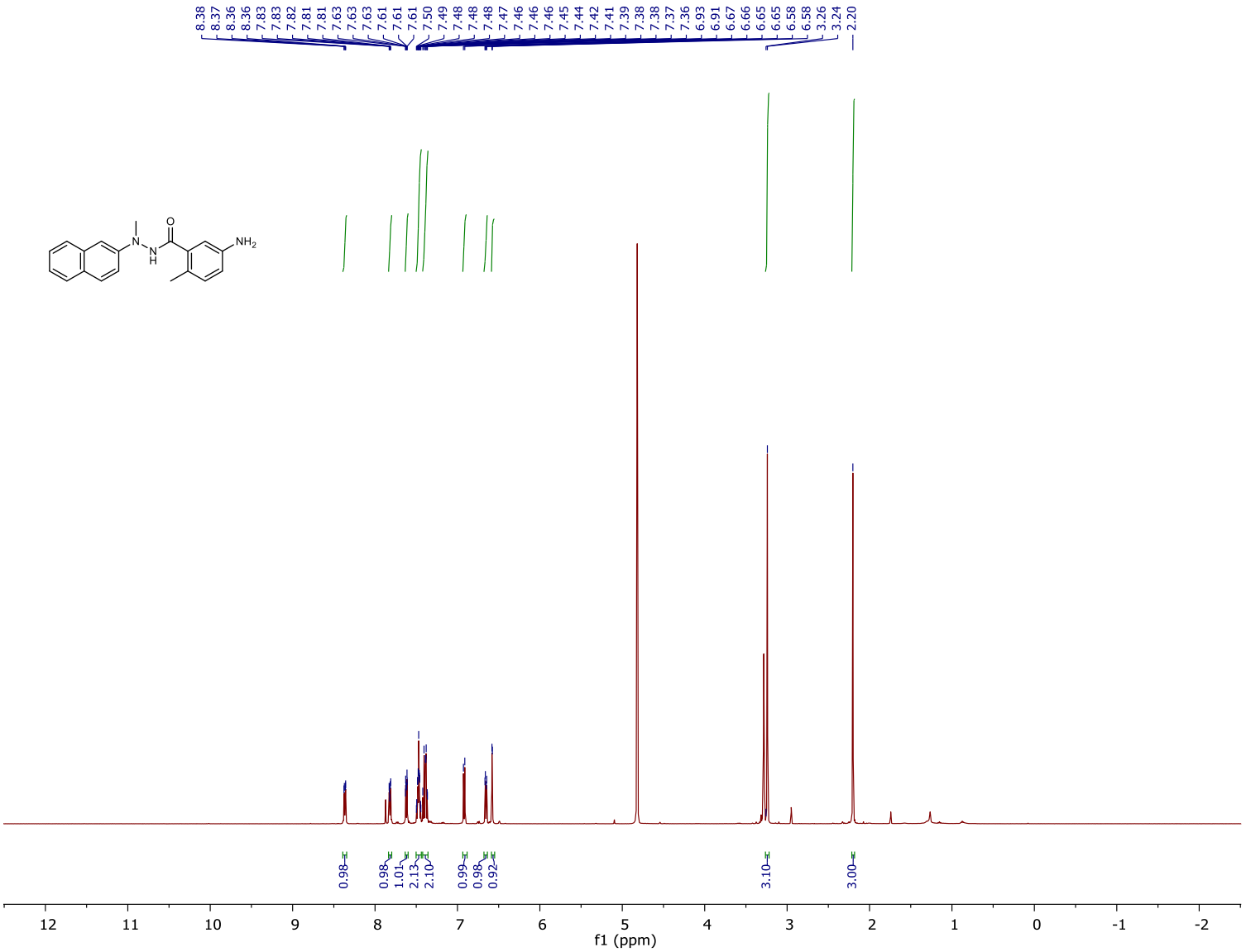
^{1}H NMR (500 MHz, CD_3OD) spectrum of *N*'-Methyl-*N*'-(naphthalen-1-yl) 5-amino-2-methylbenzhydrazide (22).



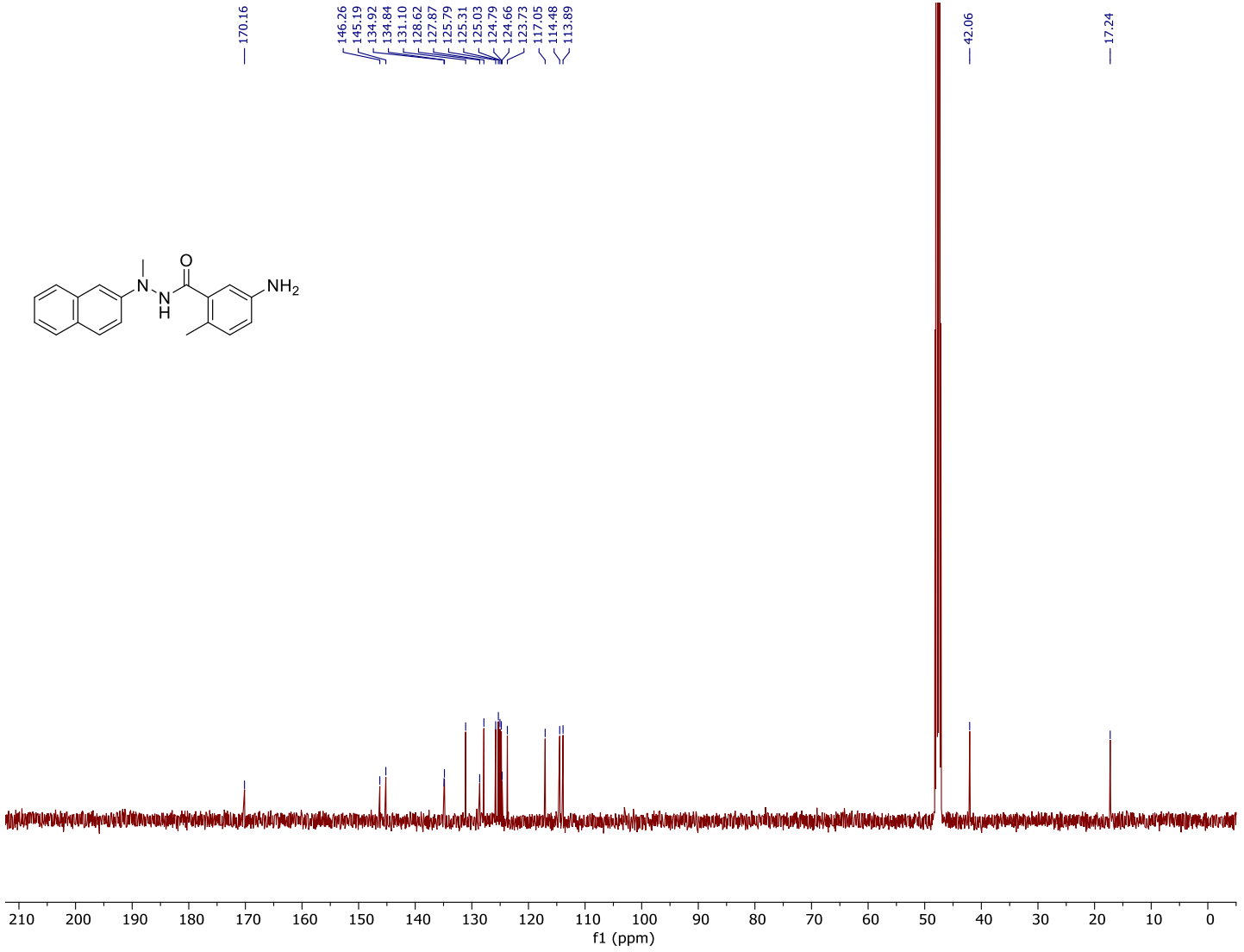
^{13}C NMR (126 MHz, CD_3OD) spectrum of *N*'-Methyl-*N*'-(naphthalen-1-yl) 5-amino-2-methylbenzhydrazide (22).



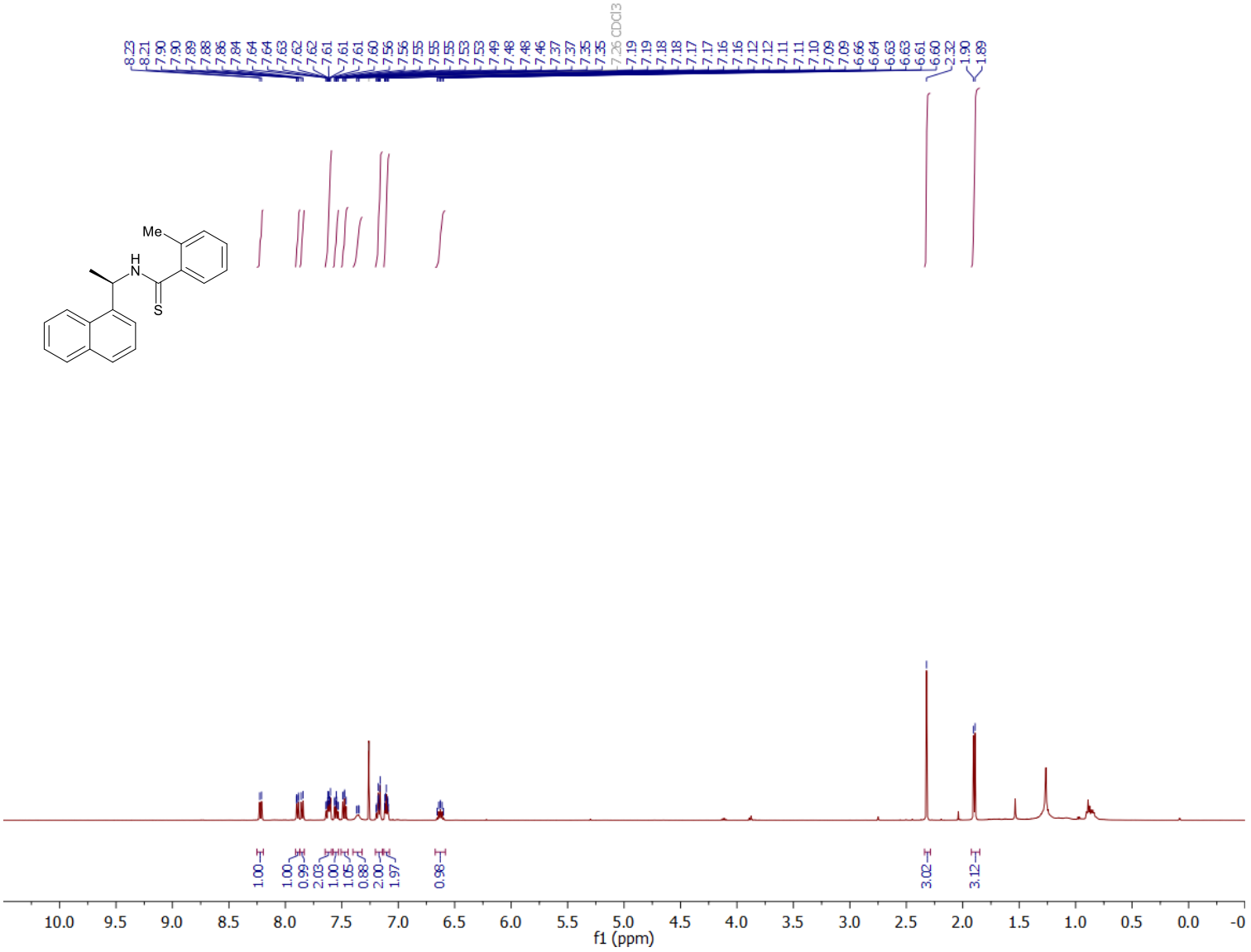
^{1}H NMR (500 MHz, CD_3OD) spectrum of *N*'-Methyl-*N*'-(naphthalen-2-yl) 5-amino-2-methylbenzhydrazide (23).



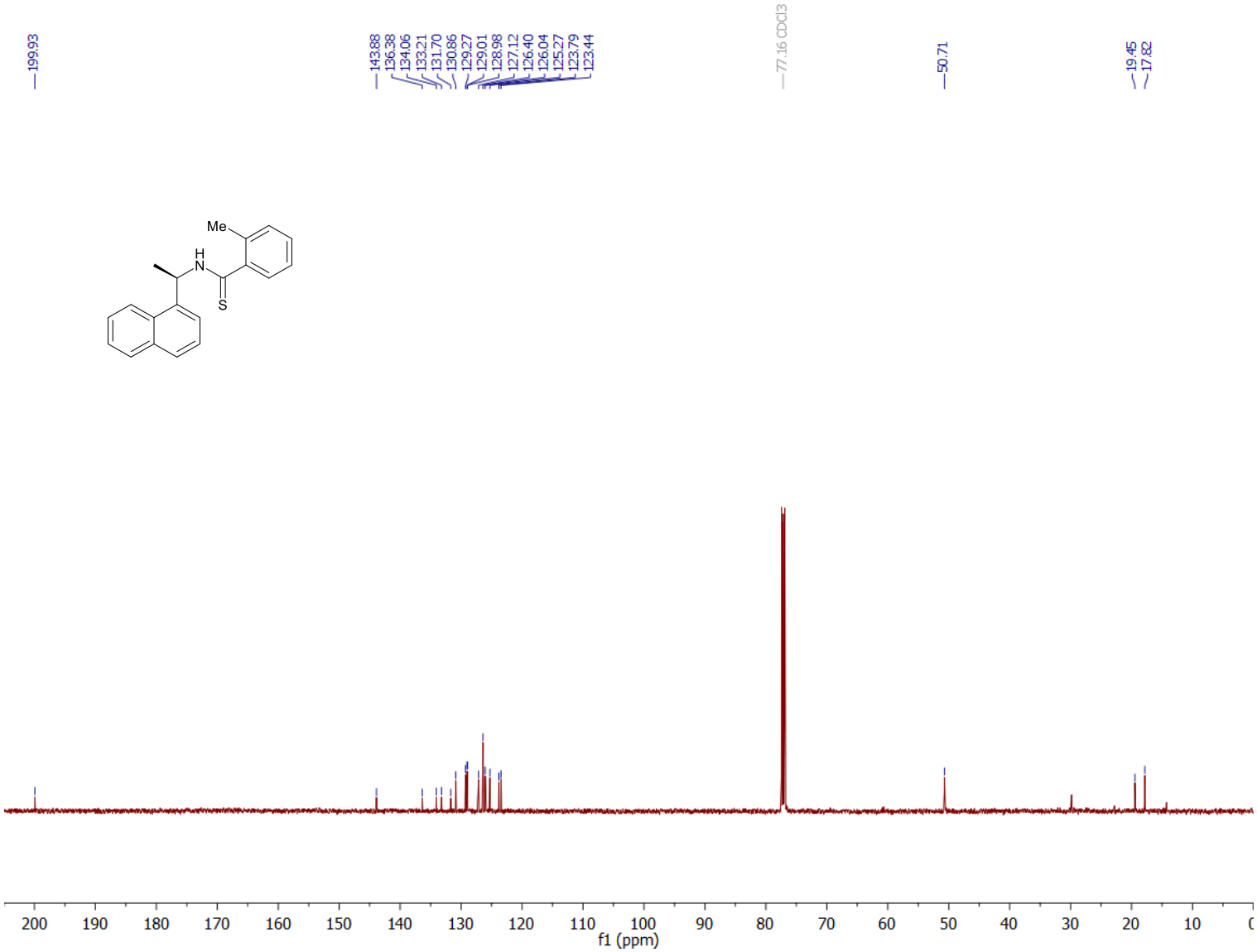
^{13}C NMR (126 MHz, CD_3OD) spectrum of *N*'-Methyl-*N*'-(naphthalen-2-yl) 5-amino-2-methylbenzhydrazide (23).



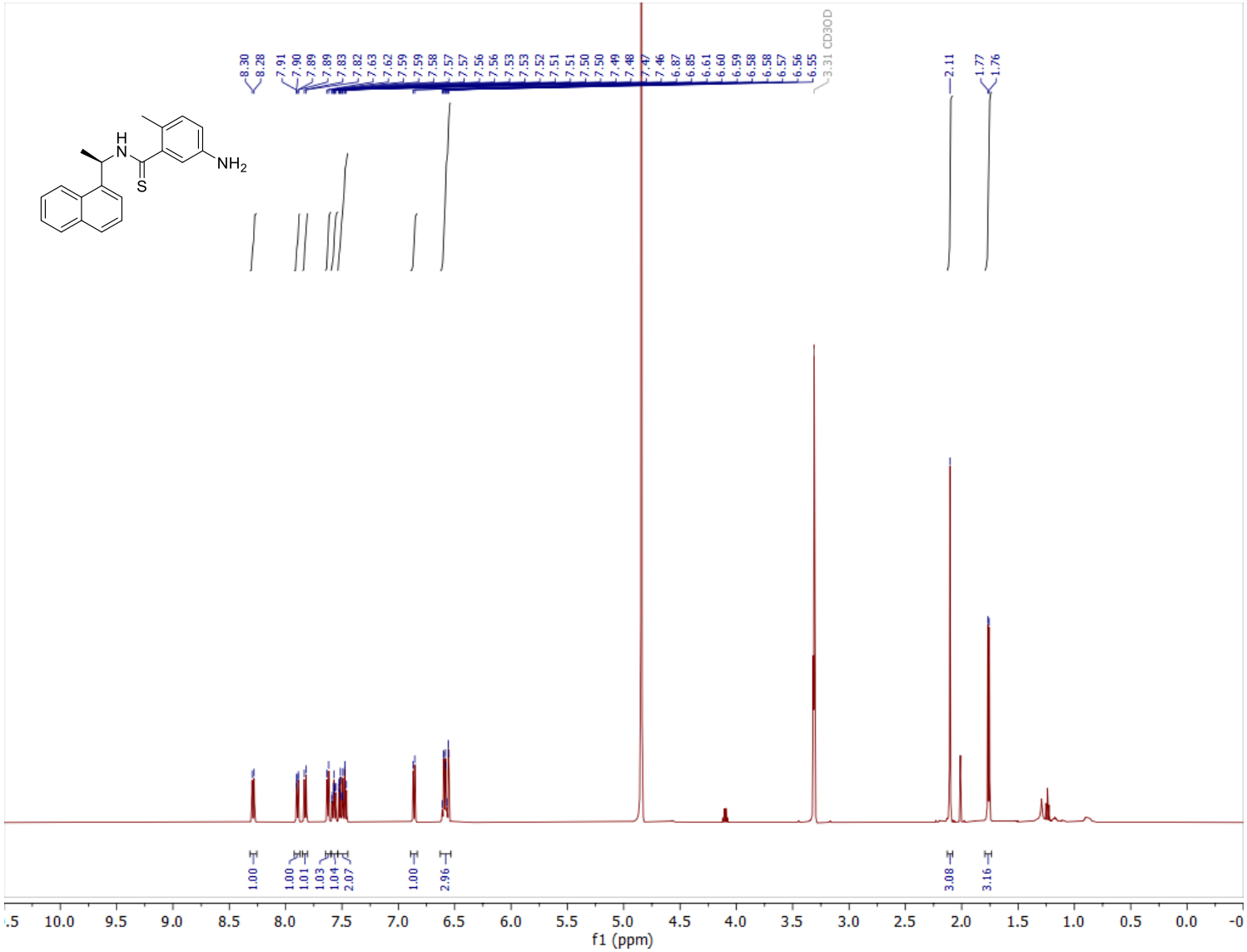
^{1}H NMR (500 MHz, $CDCl_3$) spectrum of (*R*)-2-methyl-*N*-(1'-(naphthalene-1'-yl)ethyl)benzothioamide (24).



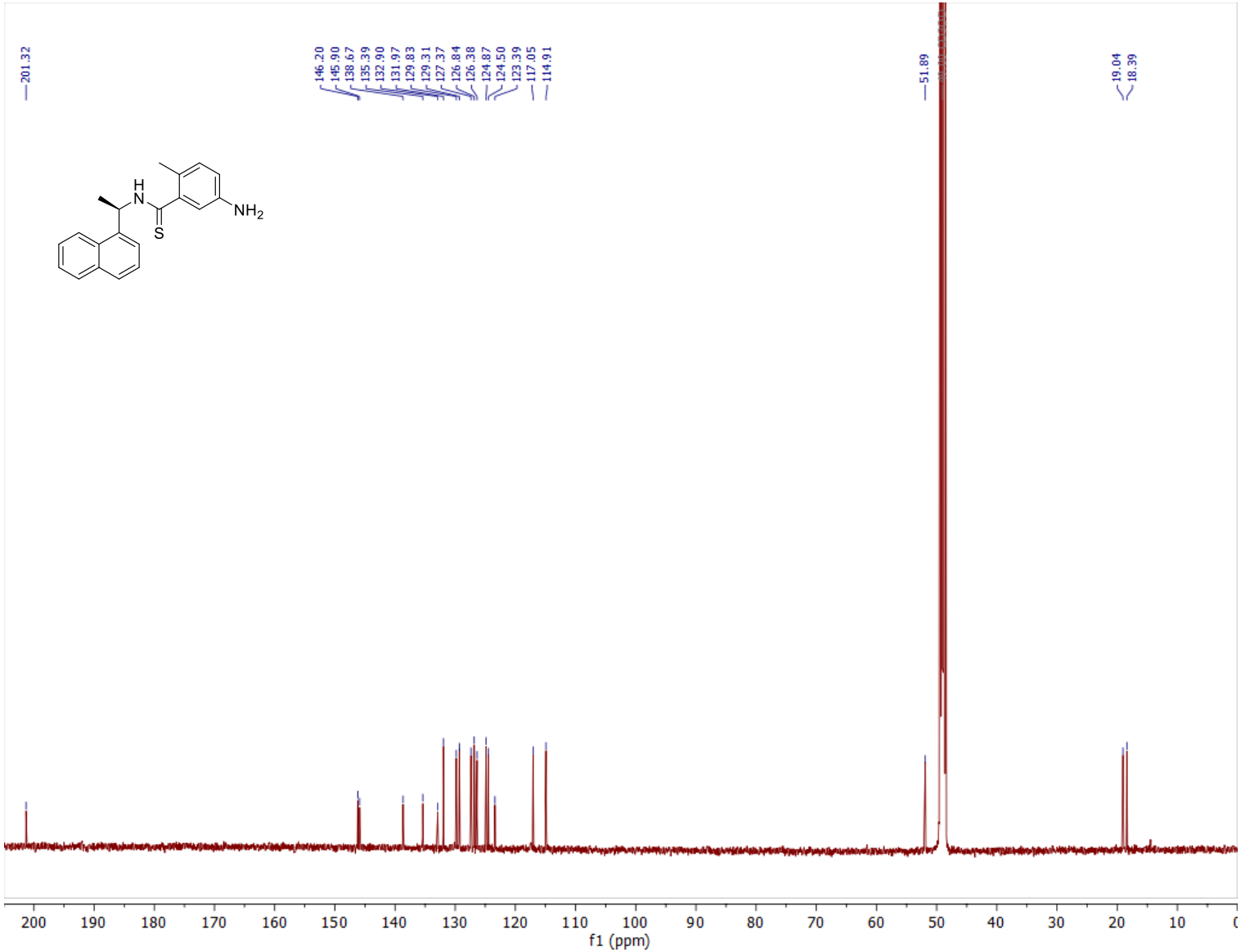
^{13}C NMR (126 MHz, $CDCl_3$) spectrum of (*R*)-2-methyl-*N*-(1'-(naphthalene-1'-yl)ethyl)benzothioamide (24).



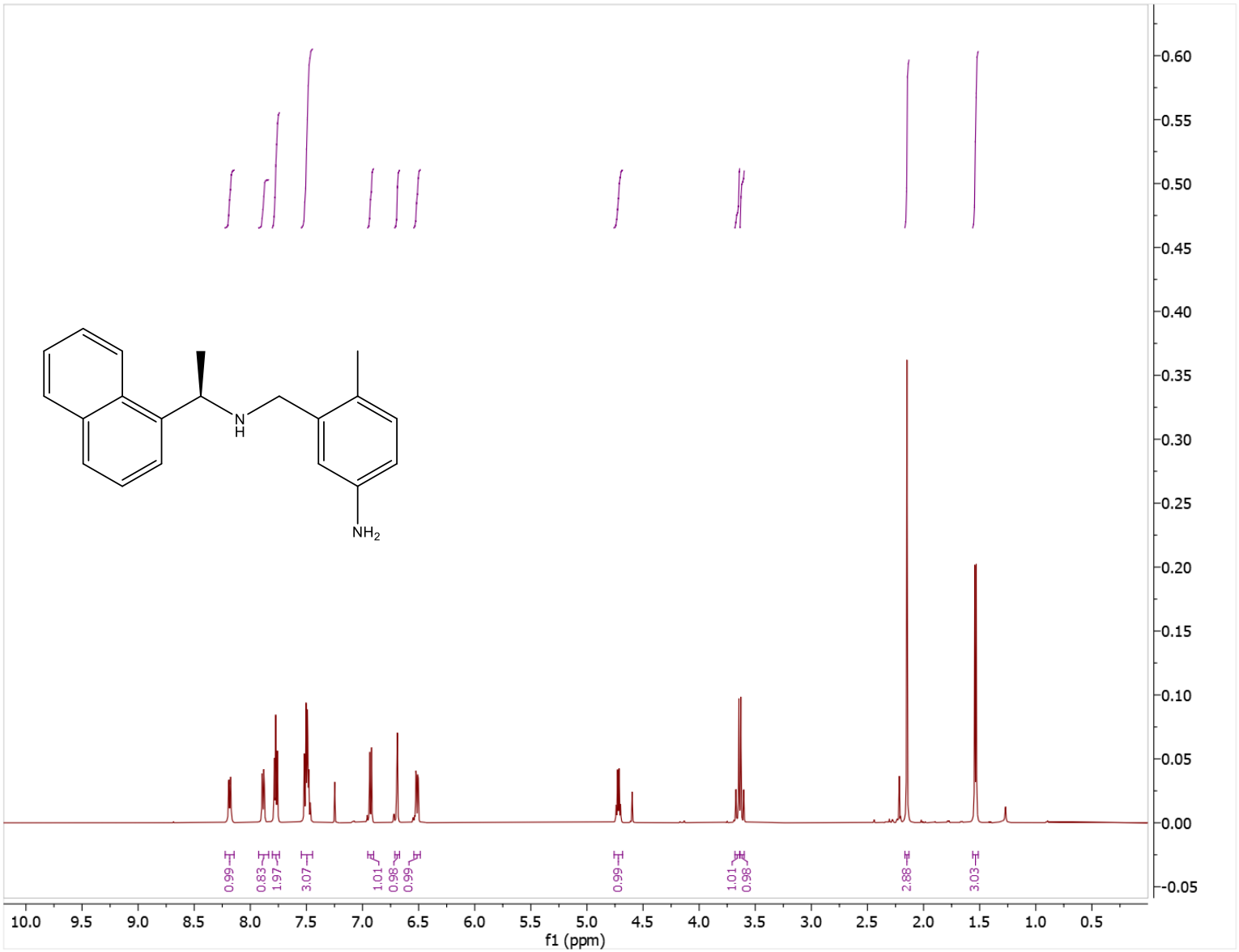
^{1}H NMR (500 MHz, $CDCl_3$) spectrum of (*R*)-*N*-[1-(1-Naphthyl)ethyl] 5-amino-2-methylthiobenzamide (25).



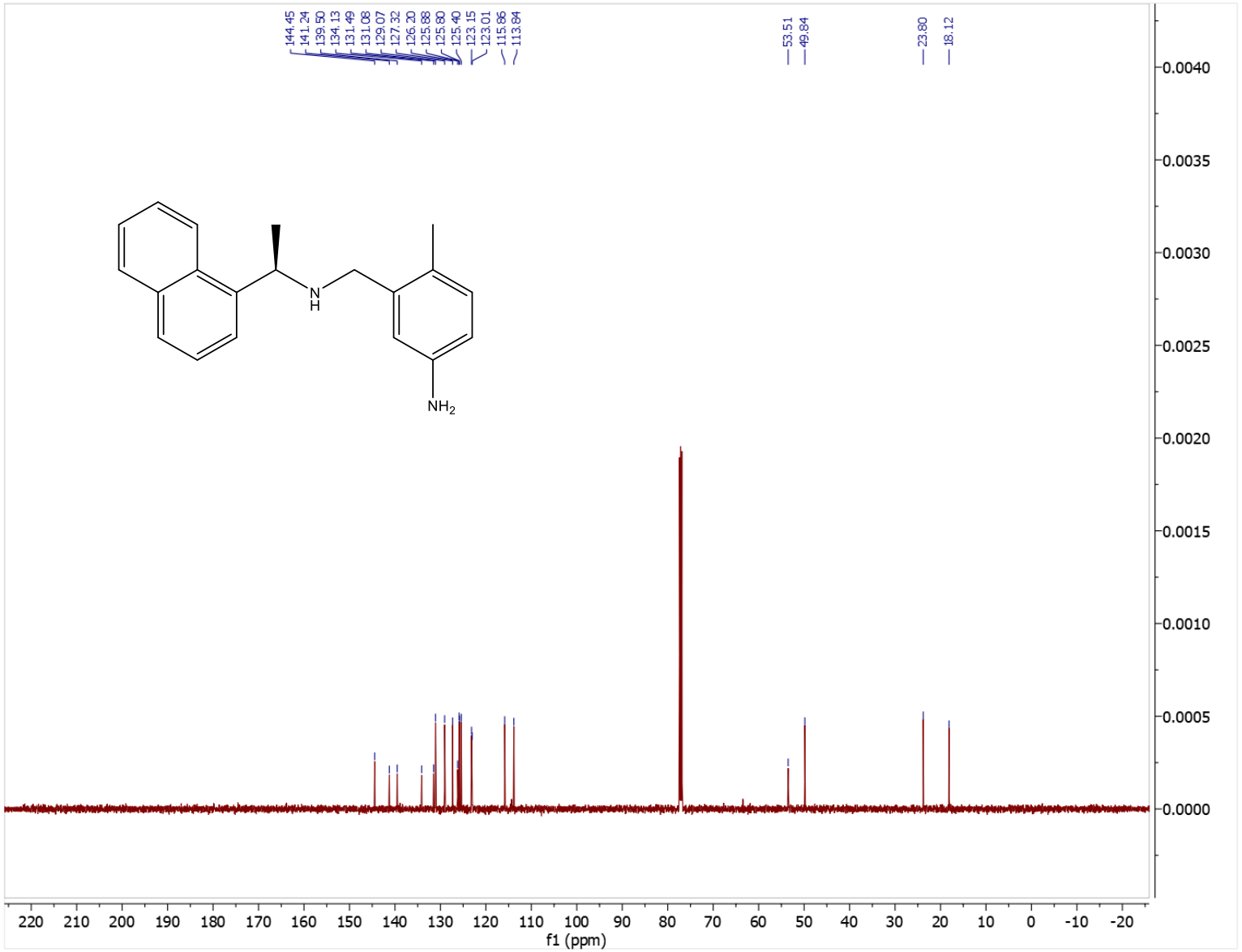
^{13}C NMR (126 MHz, $CDCl_3$) spectrum of (*R*)-*N*-[1-(1-Naphthyl)ethyl] 5-amino-2-methylthiobenzamide (25).



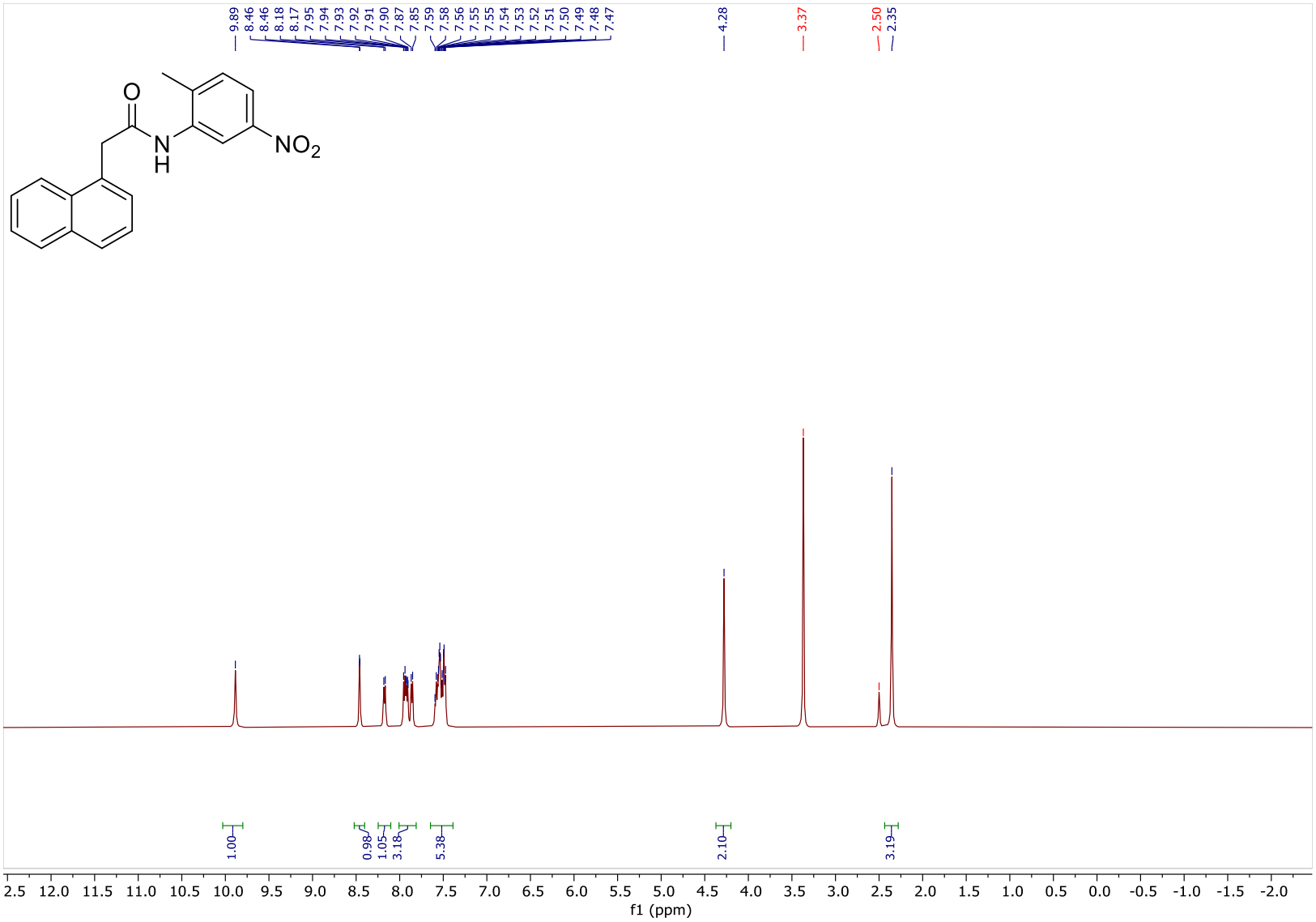
^{1}H NMR (500 MHz, $CDCl_3$) spectrum of (*R*)-4-methyl-3-(((1-(naphthalen-1-yl)ethyl)amino)methyl)aniline (26).



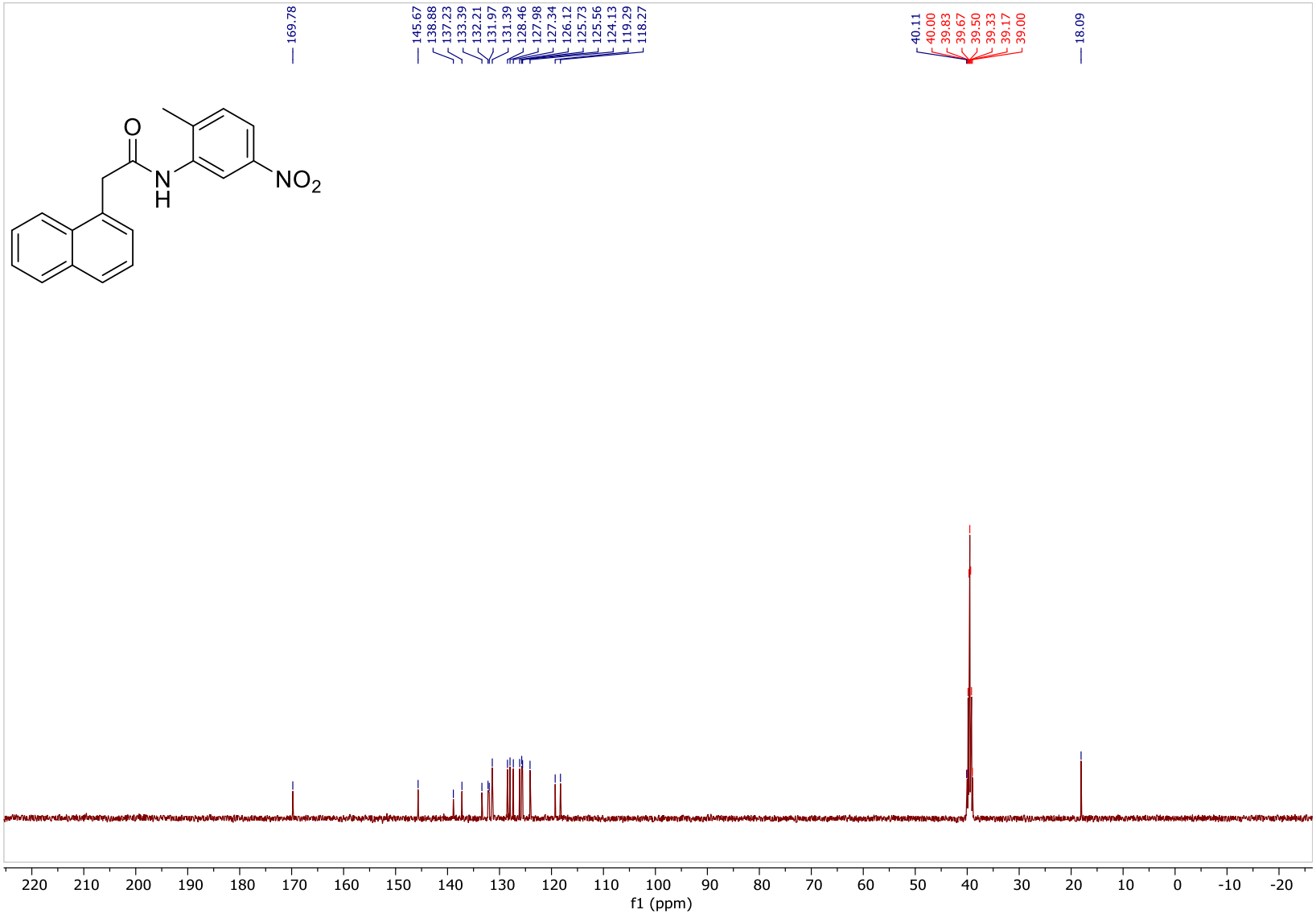
^{13}C NMR (126 MHz, $CDCl_3$) spectrum of (*R*)-4-methyl-3-(((1-(naphthalen-1-yl)ethyl)amino)methyl)aniline (26).



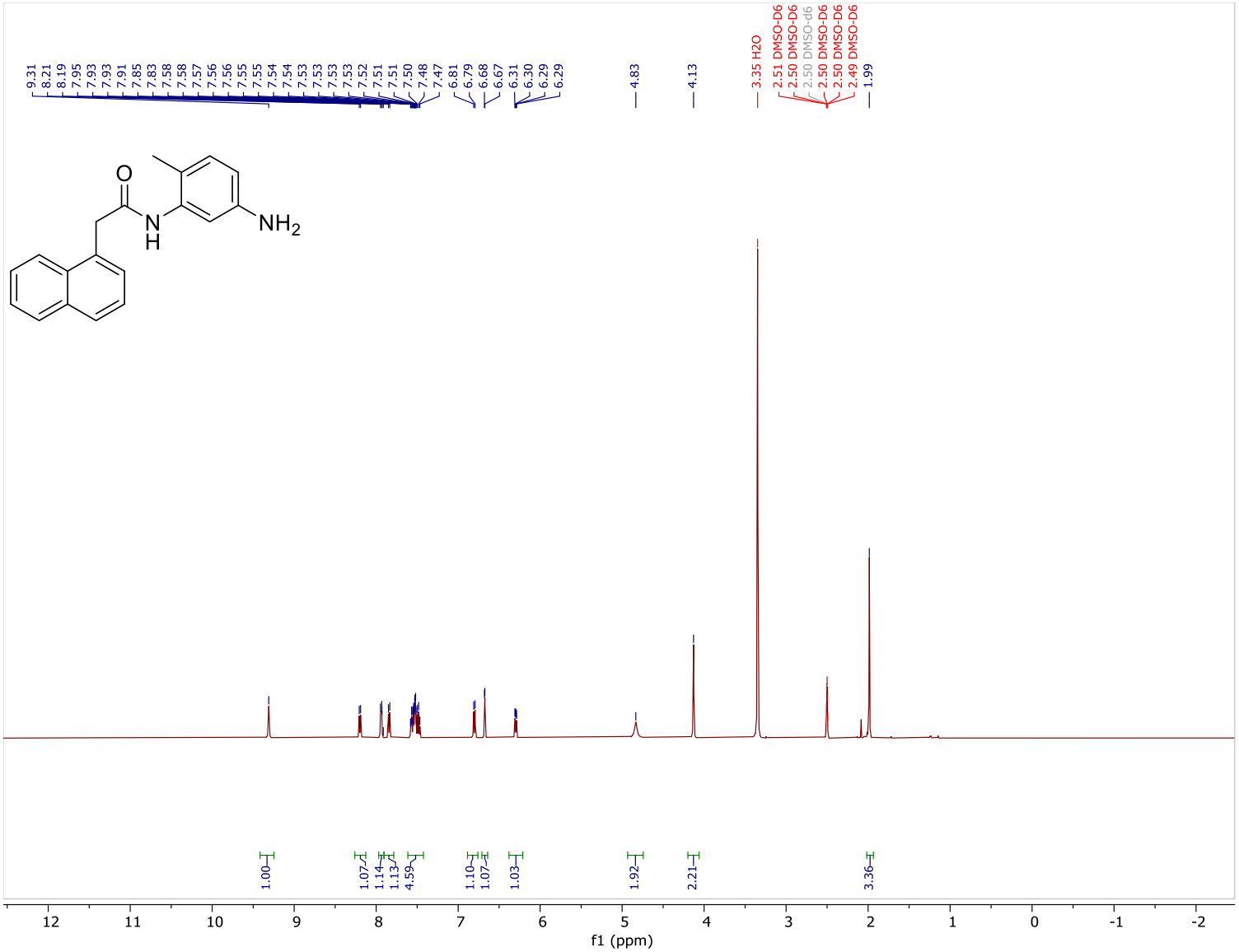
^{1}H NMR (500 MHz, DMSO-*d6*) spectrum of N-(2-methyl-5-nitrophenyl)-2-(naphthalen-1-yl)acetamide (27).



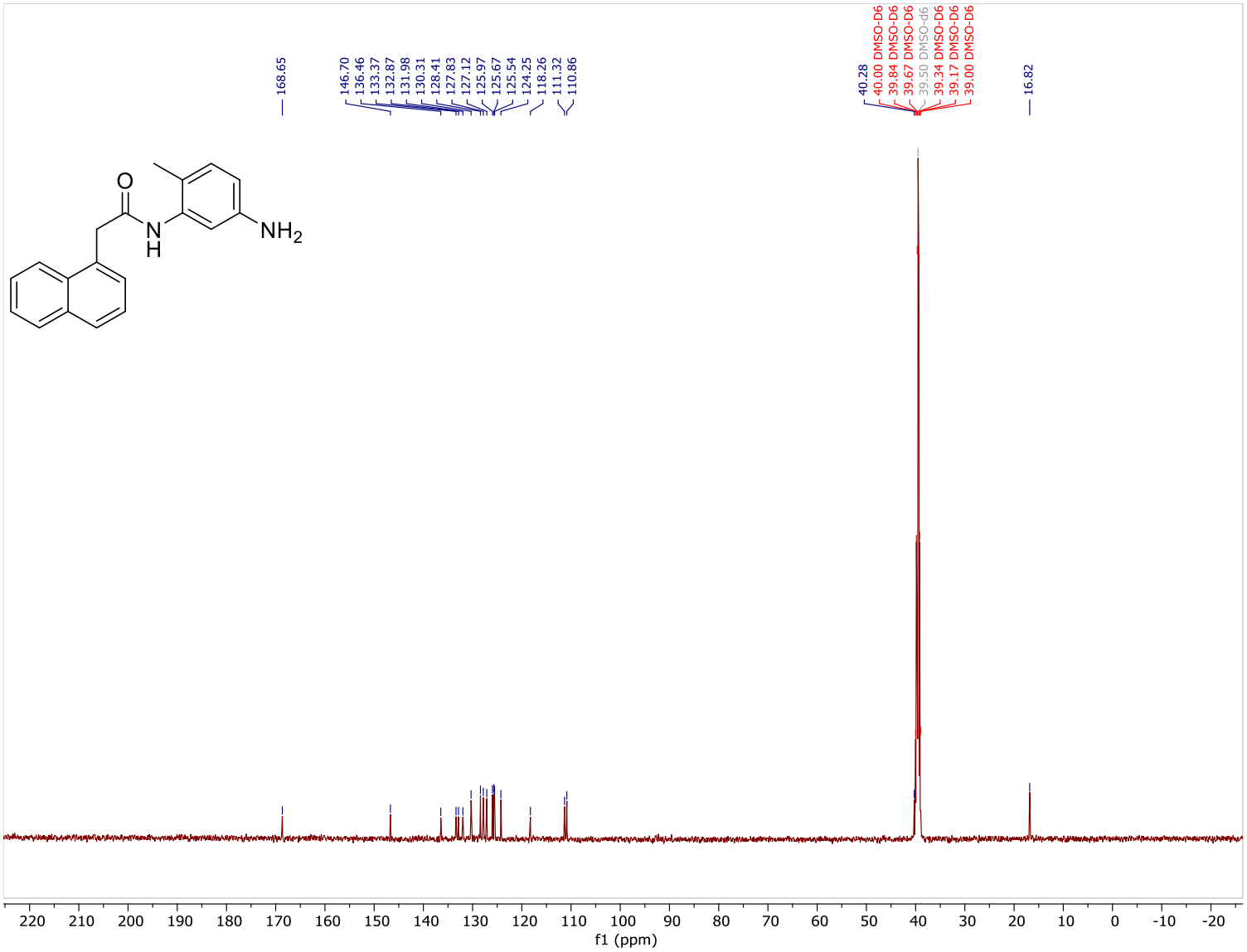
^{13}C NMR (126 MHz, DMSO-*d6*) spectrum of N-(2-methyl-5-nitrophenyl)-2-(naphthalen-1-yl)acetamide (27).



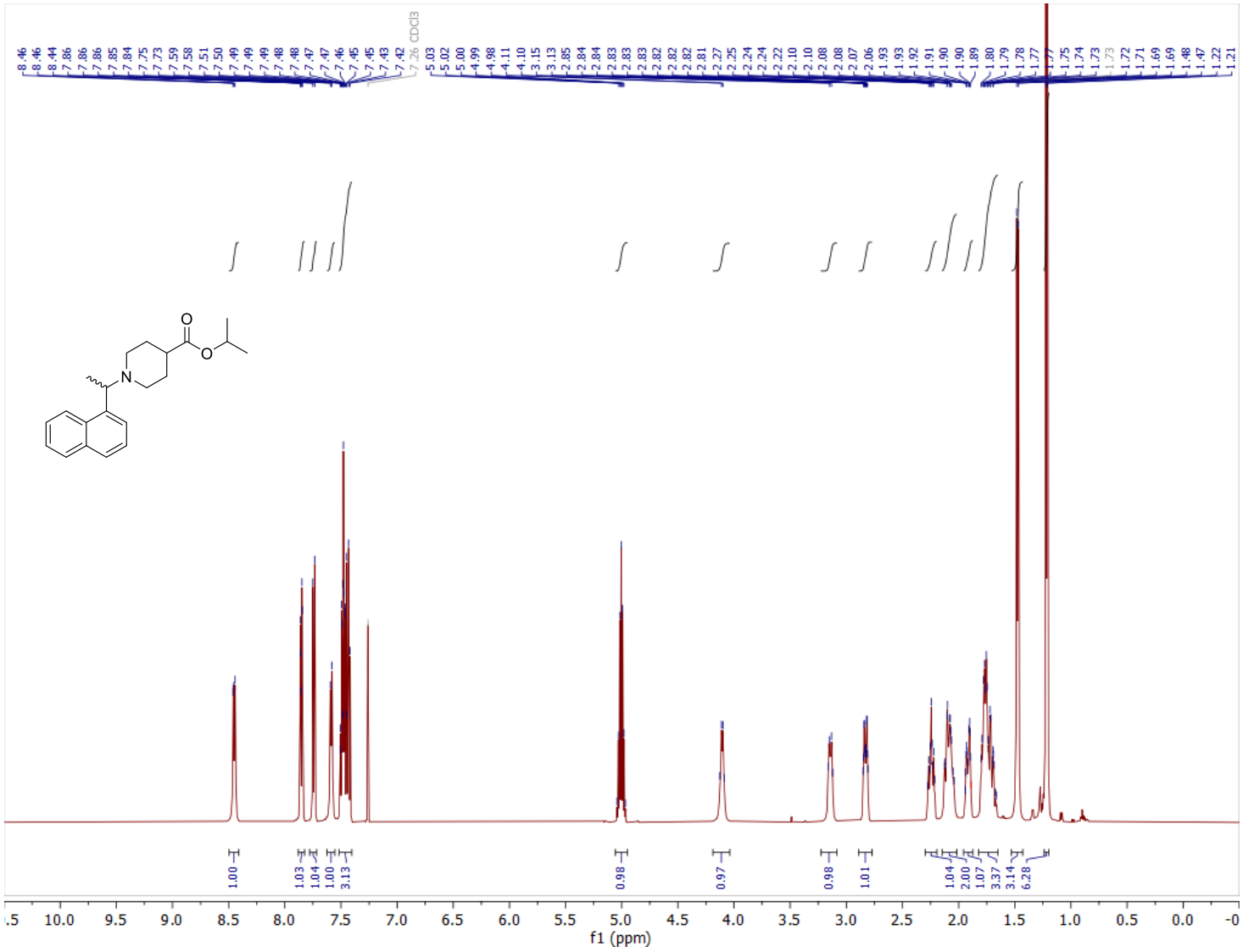
^{1}H NMR (500 MHz, DMSO-*d6*) spectrum of N-(5-amino-2-methylphenyl)-2-(naphthalen-1-yl)acetamide (28).



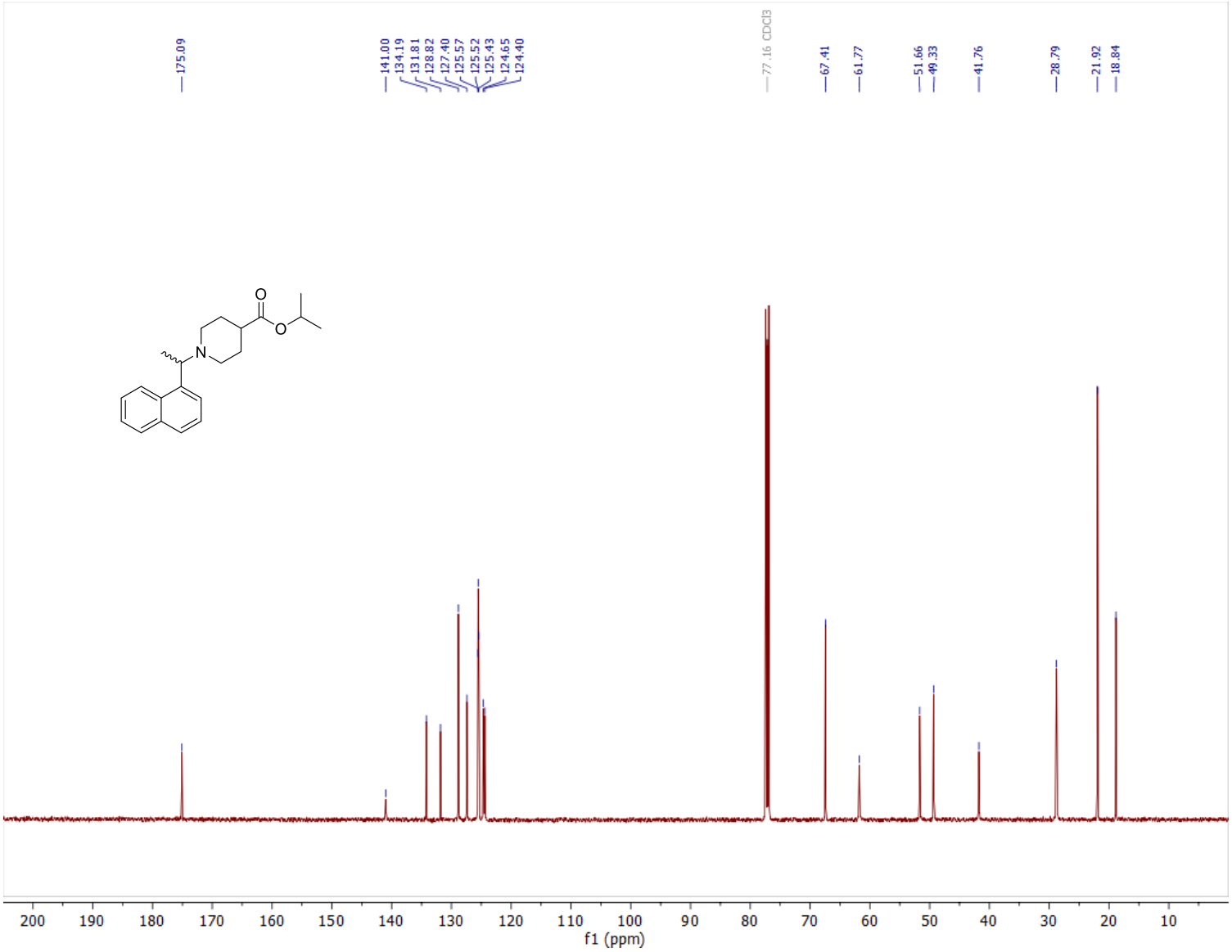
^{13}C NMR (126 MHz, DMSO-*d6*) spectrum of N-(5-amino-2-methylphenyl)-2-(naphthalen-1-yl)acetamide (28).



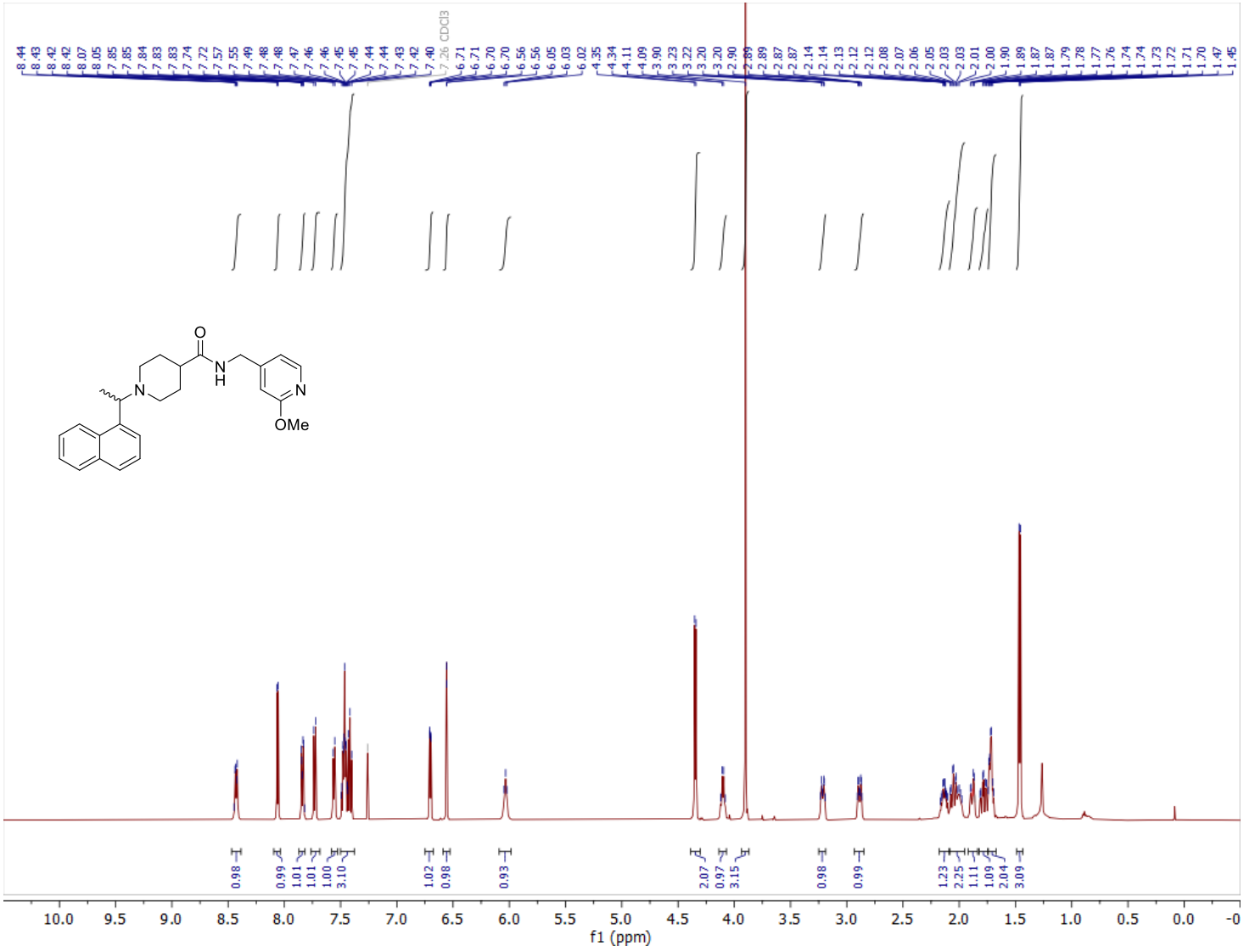
^{1}H NMR (500 MHz, $CDCl_3$) spectrum of (±)-Isopropyl 1-(1-(naphthalen-1-yl)ethyl)piperidine-4-carboxylate (29).



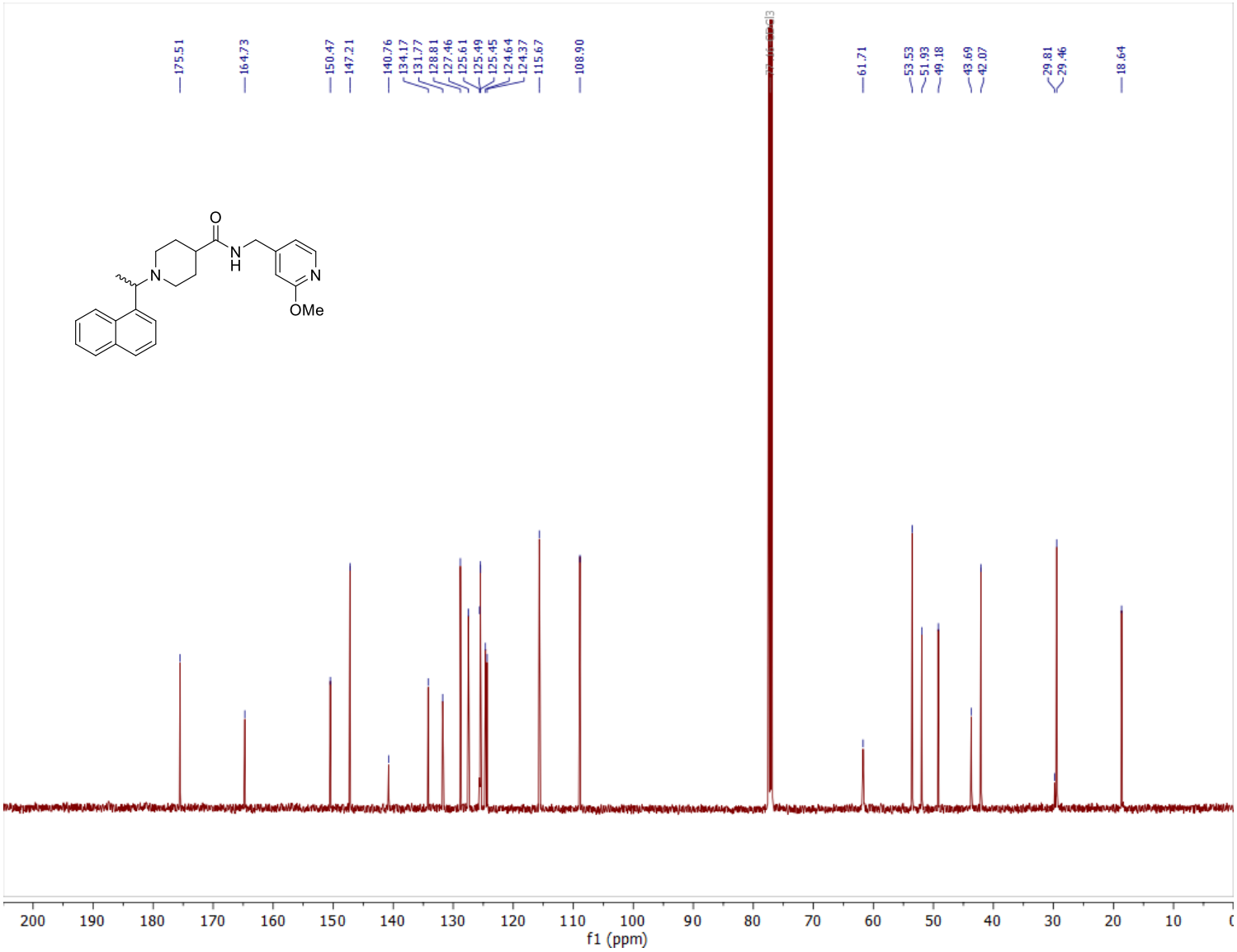
^{13}C NMR (126 MHz, $CDCl_3$) spectrum of (±)-Isopropyl 1-(1-(naphthalen-1-yl)ethyl)piperidine-4-carboxylate (29).



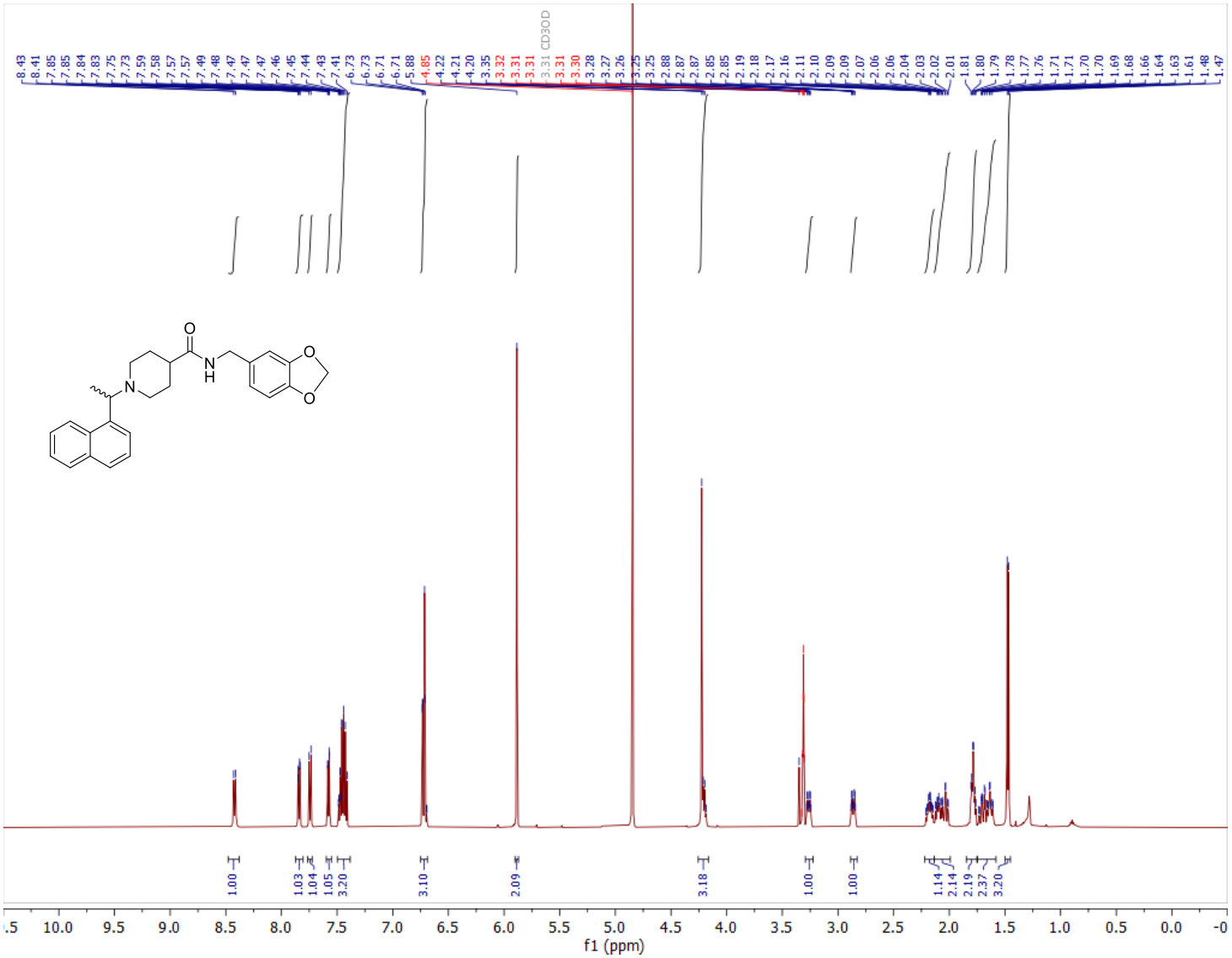
^{1}H NMR (500 MHz, $CDCl_3$) spectrum of (±)-*N*-((2-Methoxypyridin-4-yl)methyl)-1-(1-(naphthalen-1-yl)ethyl)piperidine-4-carboxamide (31).



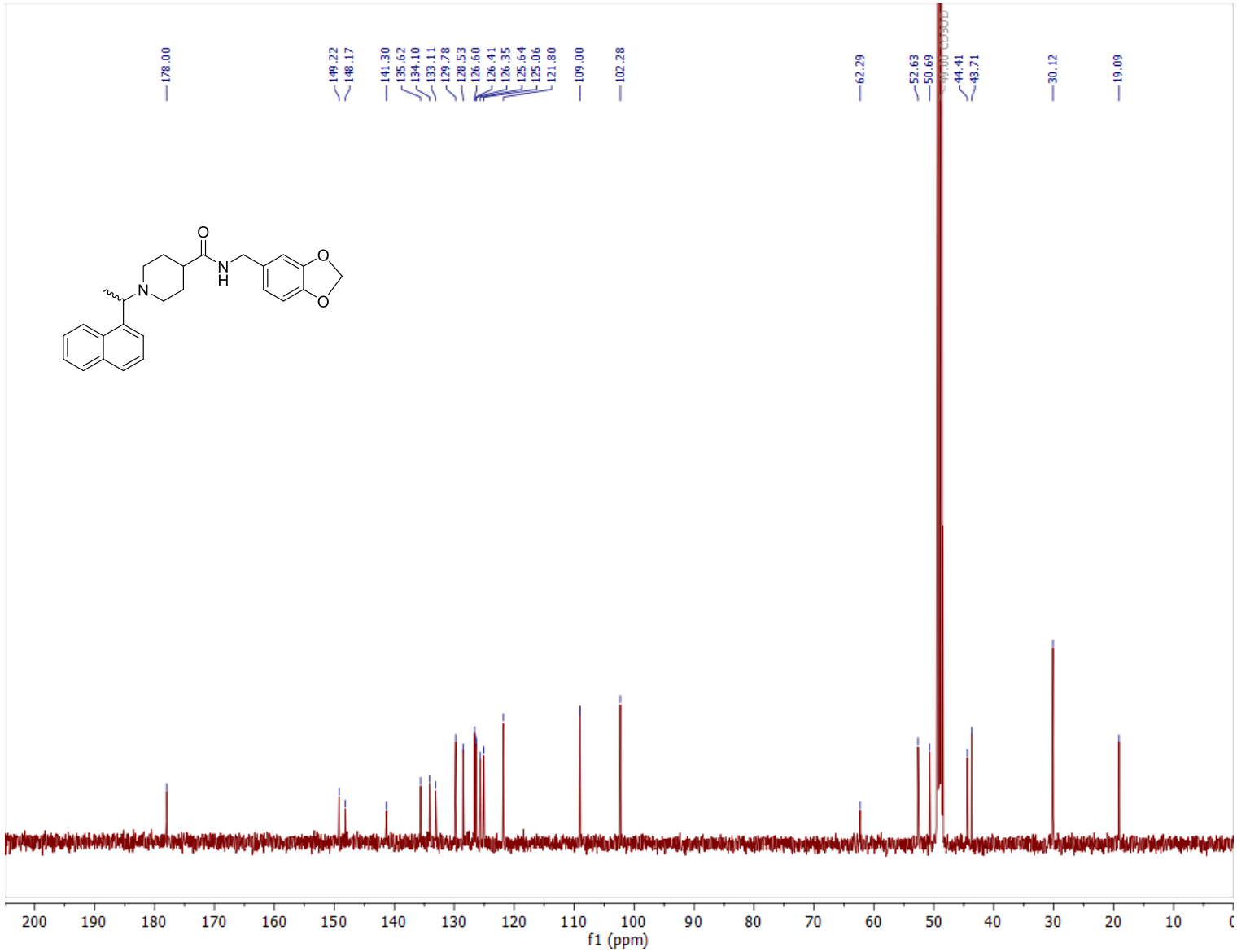
^{13}C NMR (126 MHz, $CDCl_3$) spectrum of (±)-*N*-((2-Methoxypyridin-4-yl)methyl)-1-(1-(naphthalen-1-yl)ethyl)piperidine-4-carboxamide (31).



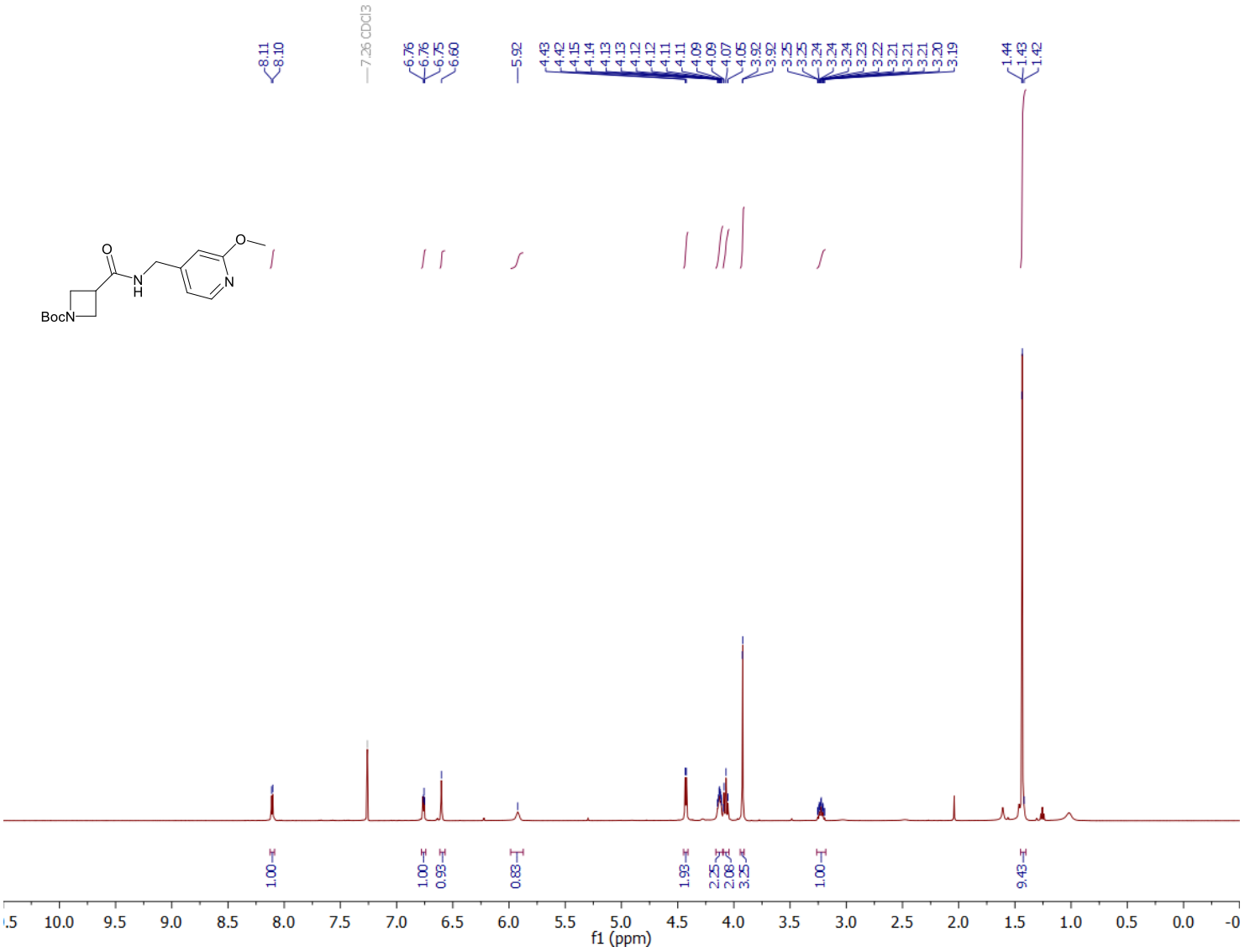
^{1}H NMR (500 MHz, $CDCl_3$) spectrum of (±)-*N*-(Benzo[*d*][1,3]dioxol-5-ylmethyl)-1-(1-(naphthalen-1-yl)ethyl)piperidine-4-carboxamide (1).



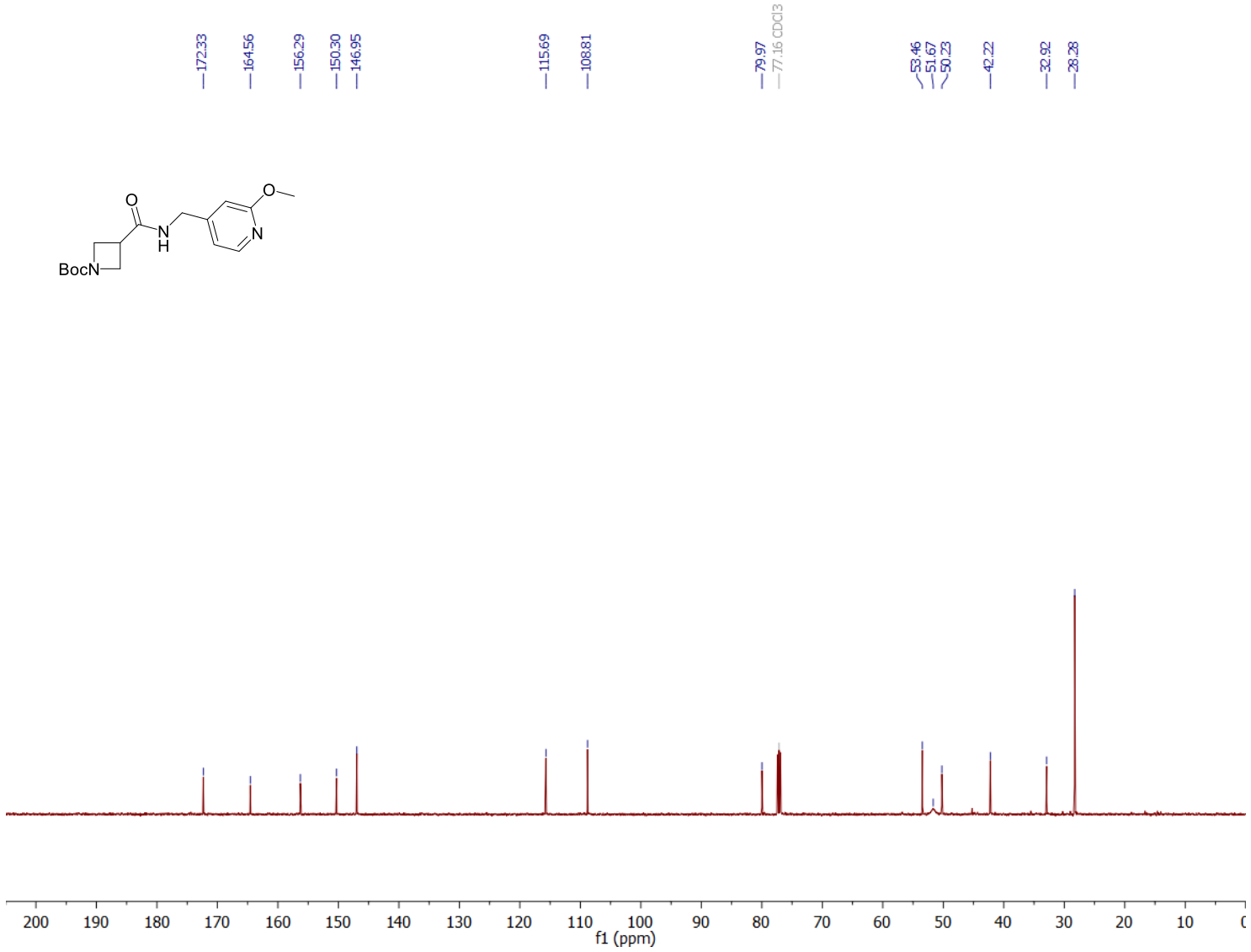
^{13}C NMR (126 MHz, $CDCl_3$) spectrum of (±)-*N*-(Benzo[*d*][1,3]dioxol-5-ylmethyl)-1-(1-(naphthalen-1-yl)ethyl)piperidine-4-carboxamide (1).



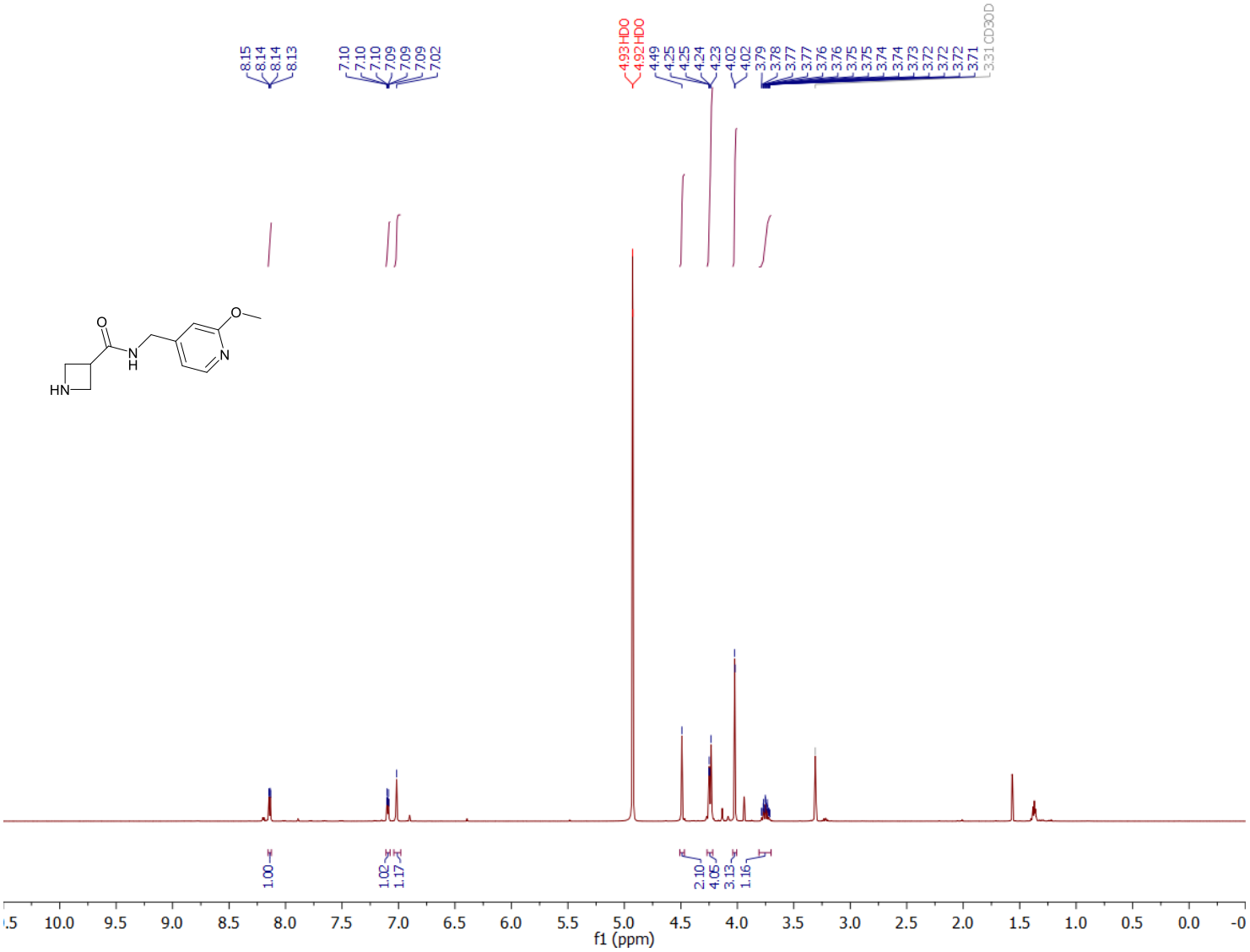
^{1}H NMR (500 MHz, $CDCl_3$) spectrum of *tert*-butyl-3-(((2'-methoxypyridin-4'-yl)methyl)carbamoyl)azetidine-1-carboxylate (32).



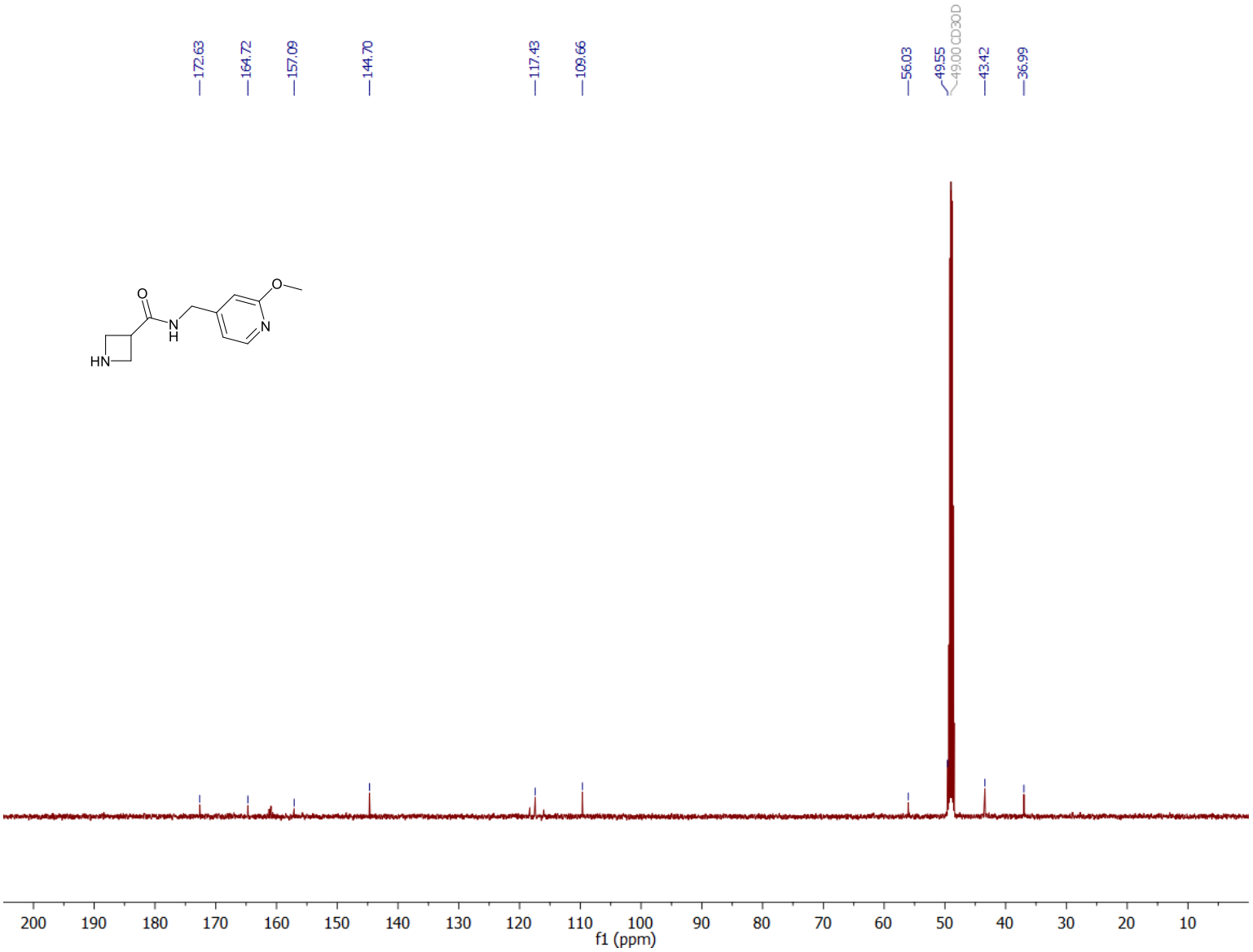
^{13}C NMR (126 MHz, $CDCl_3$) spectrum of *tert*-butyl-3-(((2'-methoxypyridin-4'-yl)methyl)carbamoyl)azetidine-1-carboxylate (32).



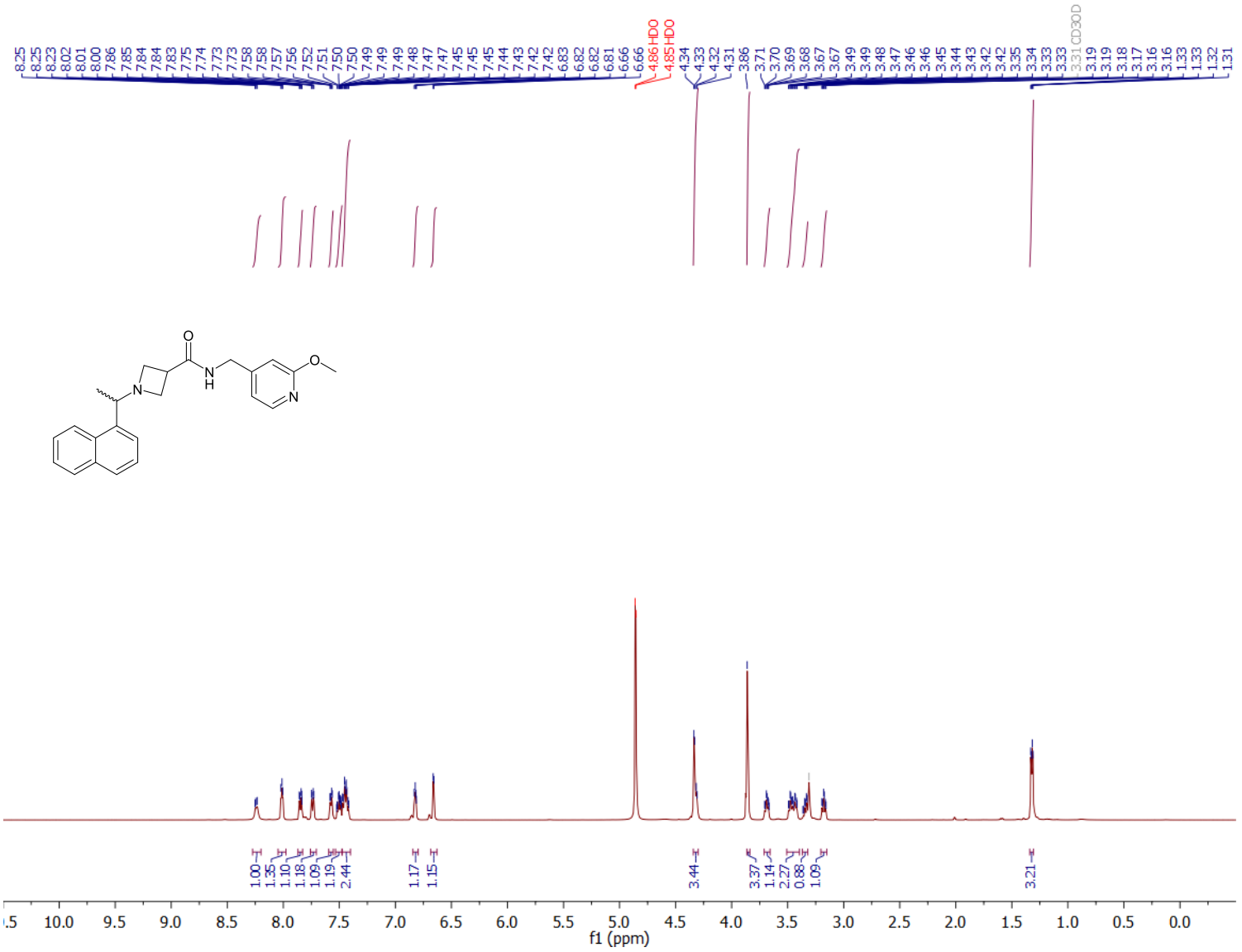
^{1}H NMR (500 MHz, CD_3OD) spectrum of *N*-((2'-methoxypyridin-4'-yl)methyl)azetidine-3-caboxamide (33).



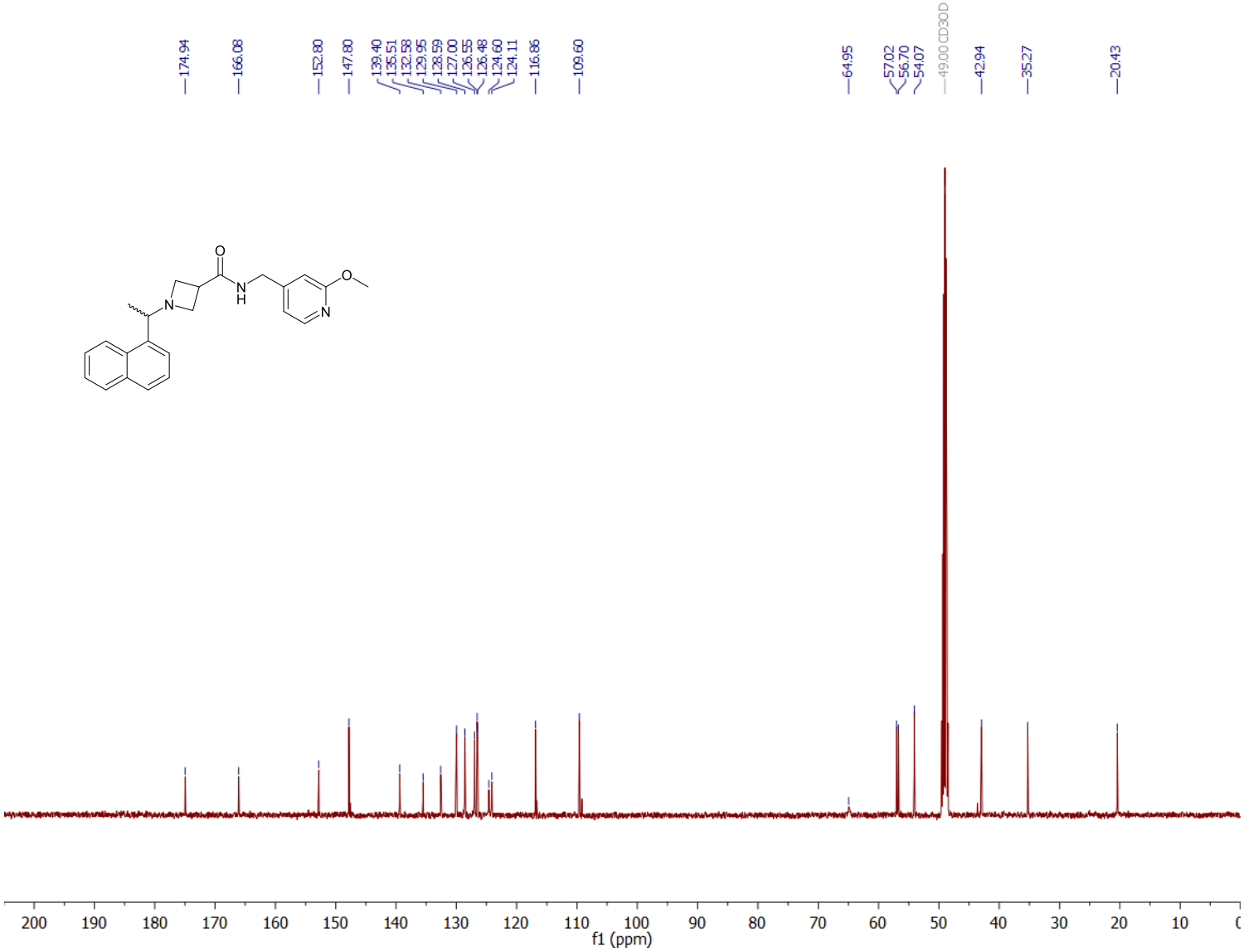
^{13}C NMR (126 MHz, CD_3OD) spectrum of *N*-((2'-methoxypyridin-4'-yl)methyl)azetidine-3-caboxamide (33).



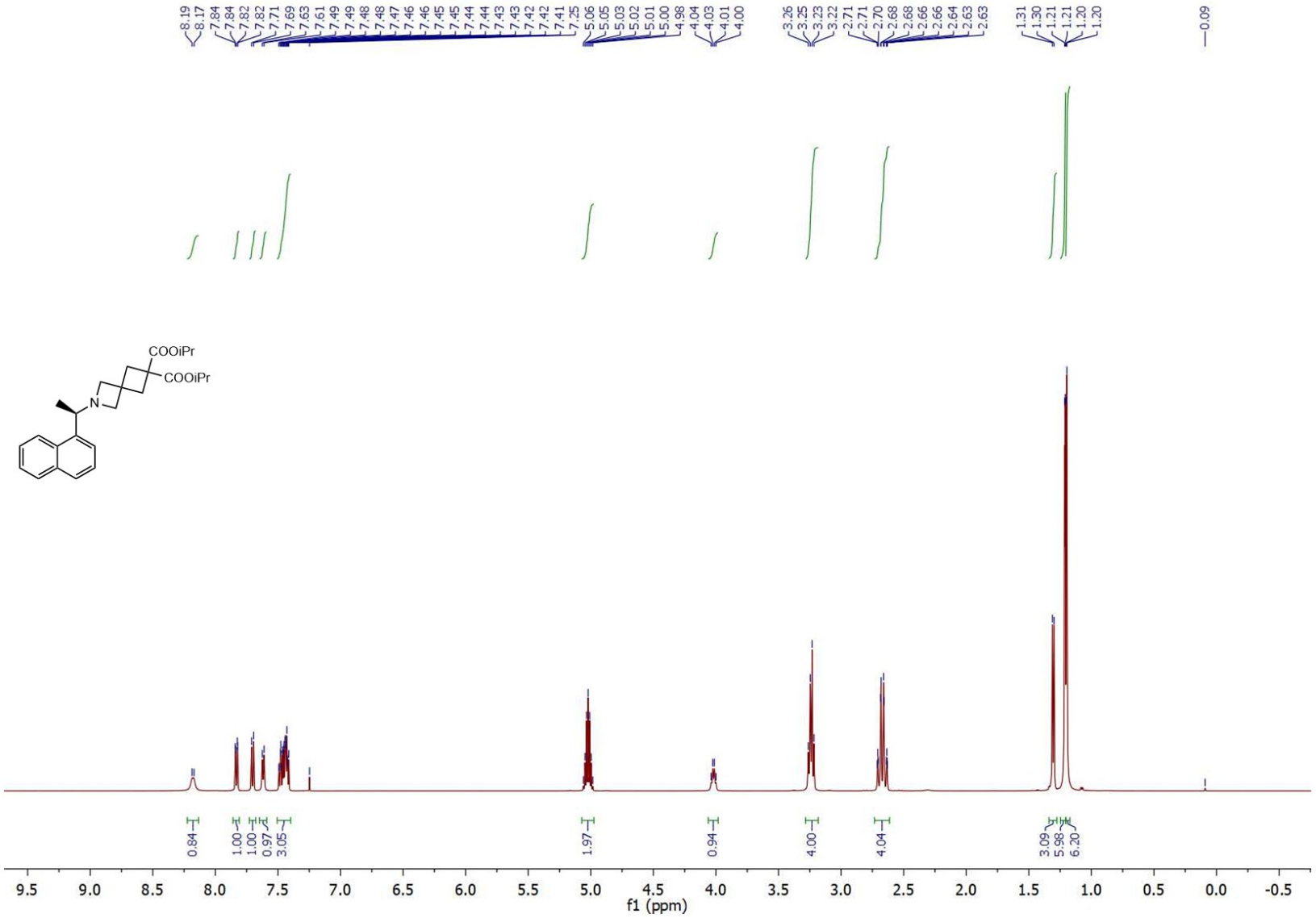
^{1}H NMR (500 MHz, CD_3OD) spectrum of (±)-*N*-((2'-methoxypyridin-4'-yl)methyl)-1-(1''-(naphthalene-1''-yl)ethyl)azetidine-3-caboxamide (34).



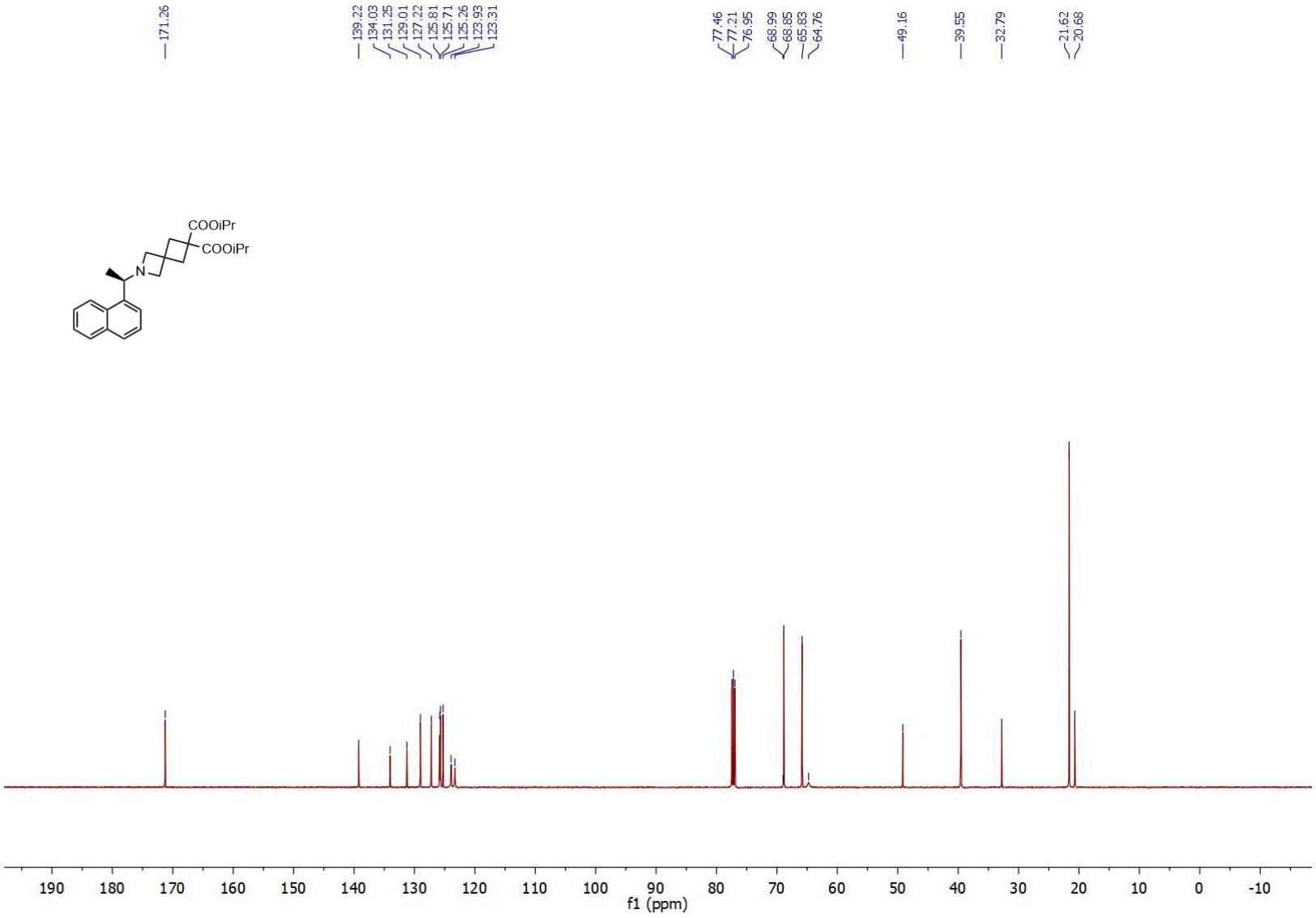
^{13}C NMR (126 MHz, CD_3OD) spectrum of (±)-*N*-((2'-methoxypyridin-4'-yl)methyl)-1-(1''-(naphthalene-1''-yl)ethyl)azetidine-3-caboxamide (34).



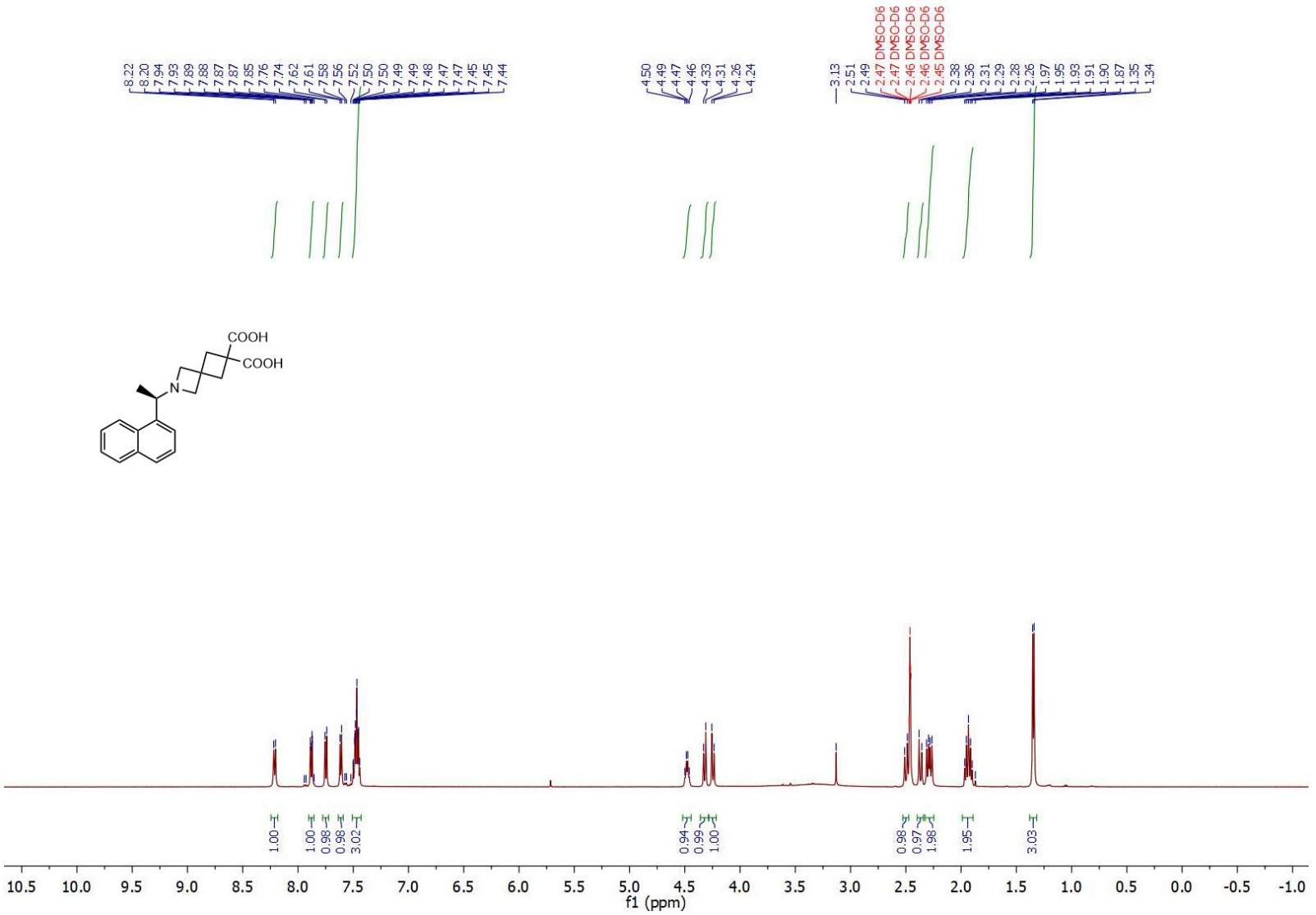
^{1}H NMR (500 MHz, $CDCl_3$) spectrum of diisopropyl (*R*)-2-(1-(naphthalen-1-yl)ethyl)-2-azaspiro[3.3]heptane-6,6-dicarboxylate (35).



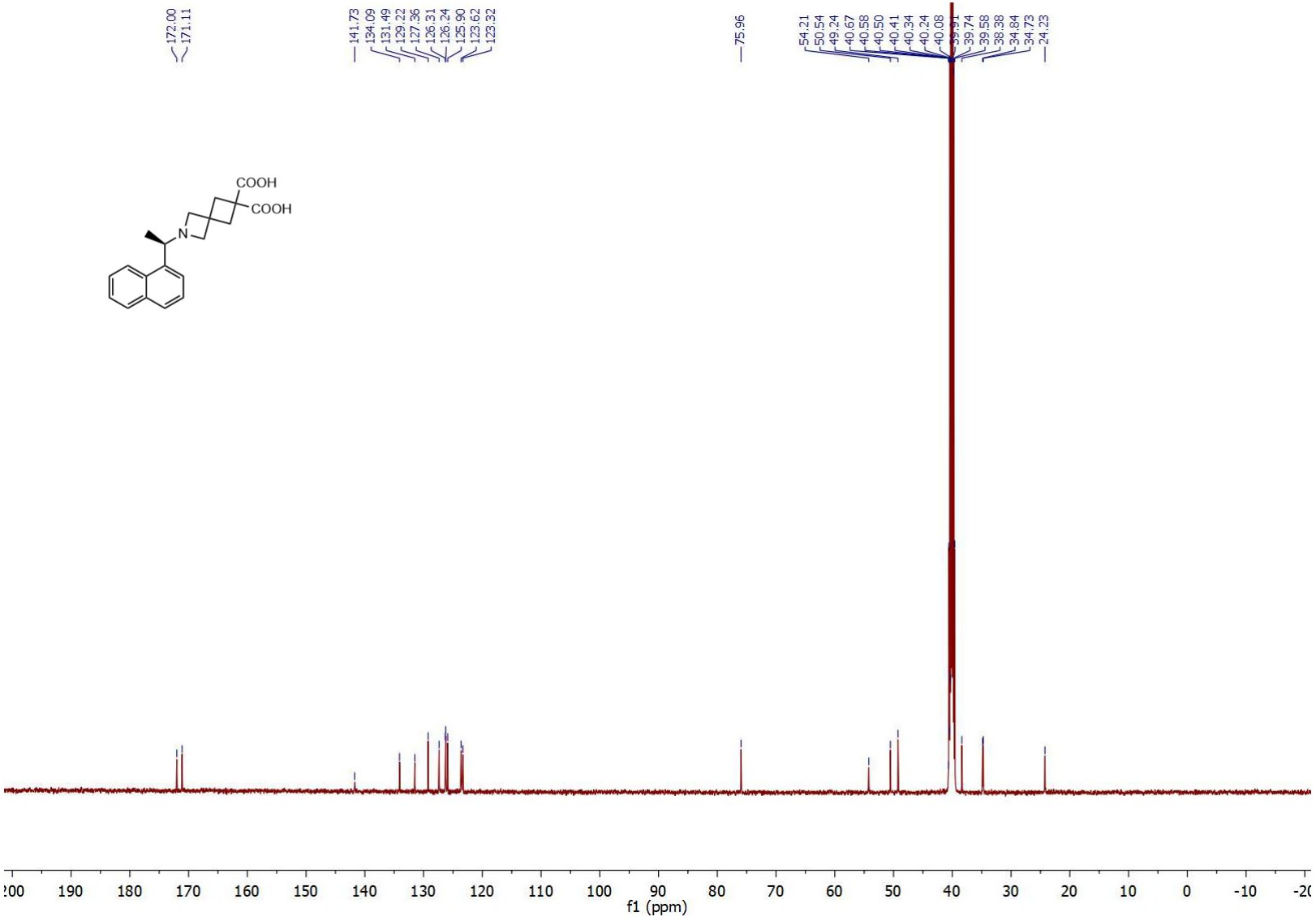
^{13}C NMR (126 MHz, $CDCl_3$) spectrum of diisopropyl (*R*)-2-(1-(naphthalen-1-yl)ethyl)-2-azaspiro[3.3]heptane-6,6-dicarboxylate (35).



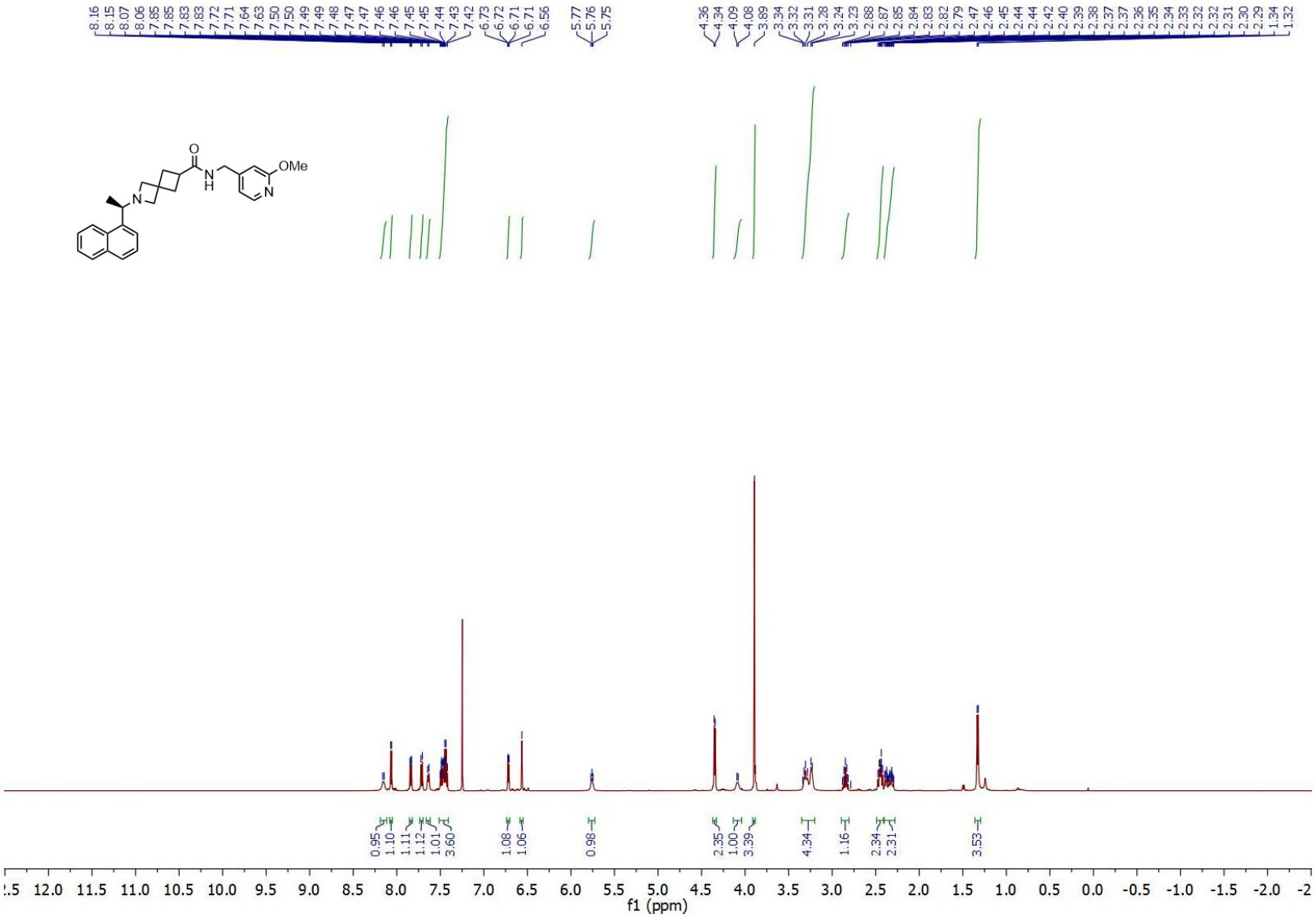
^{1}H NMR (500 MHz, $CDCl_3$) spectrum of (*R*)-2-(1-(naphthalen-1-yl)ethyl)-2-azaspiro[3.3]heptane-6,6-dicarboxylic acid (36).



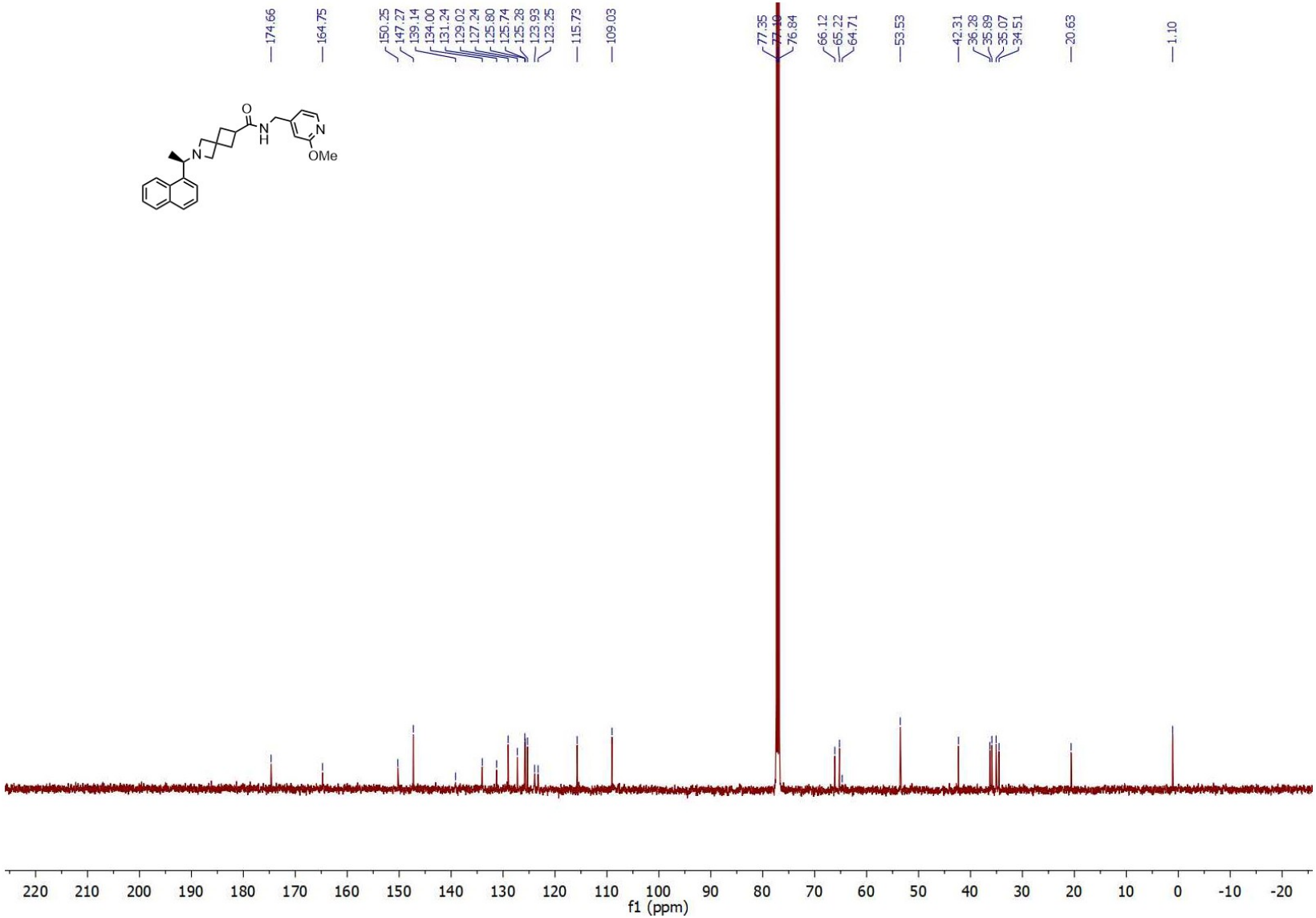
^{13}C NMR (126 MHz, $CDCl_3$) spectrum of (*R*)-2-(1-(naphthalen-1-yl)ethyl)-2-azaspiro[3.3]heptane-6,6-dicarboxylic acid (36).



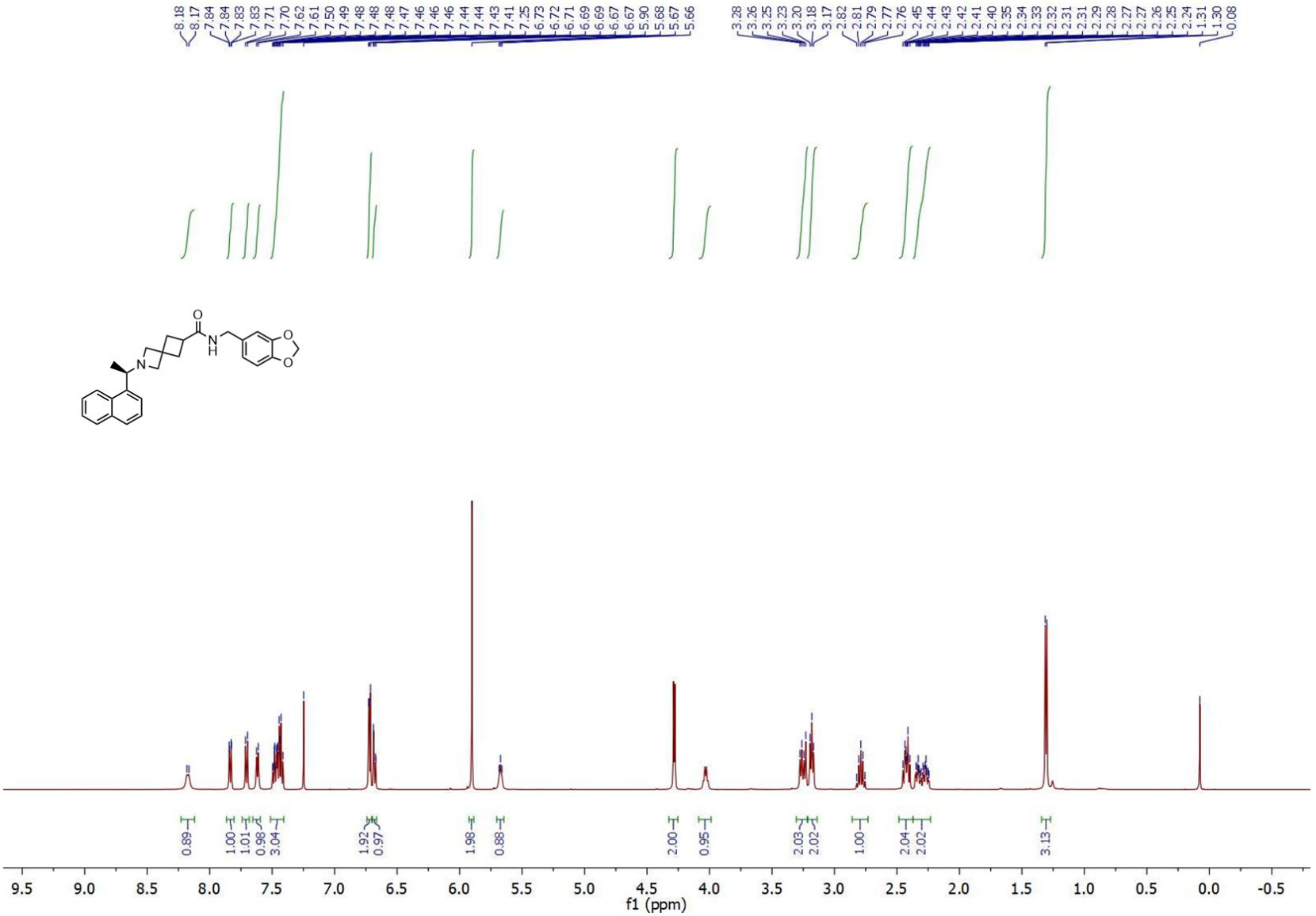
^{1}H NMR (500 MHz, $CDCl_3$) spectrum of (*R*)-*N*-((2-methoxypyridin-4-yl)methyl)-2-(1-(naphthalen-1-yl)ethyl)-2-azaspiro[3.3]heptane-6-carboxamide (37).



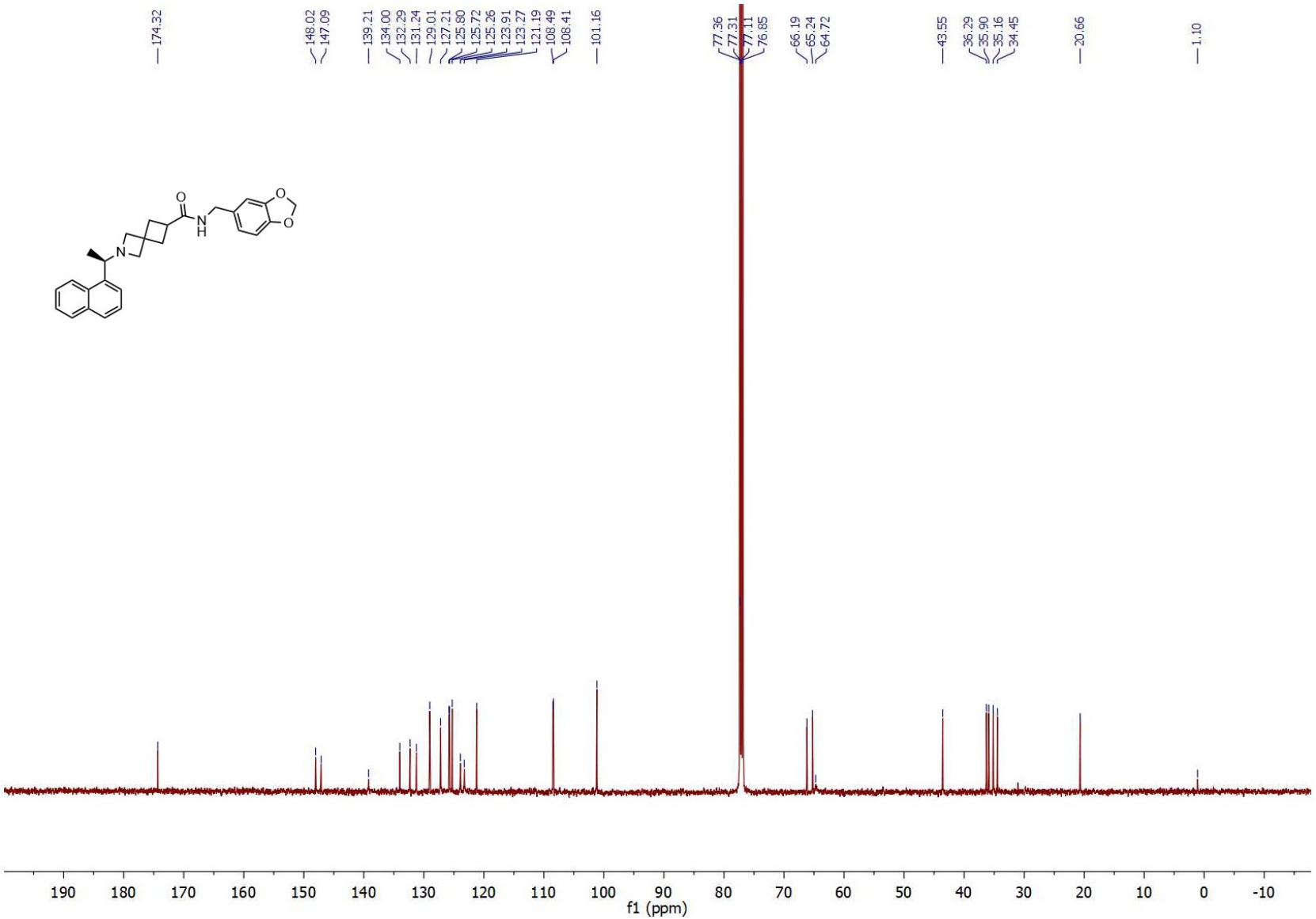
^{13}C NMR (126 MHz, $CDCl_3$) spectrum of (*R*)-*N*-((2-methoxypyridin-4-yl)methyl)-2-(1-(naphthalen-1-yl)ethyl)-2-azaspiro[3.3]heptane-6-carboxamide (37).



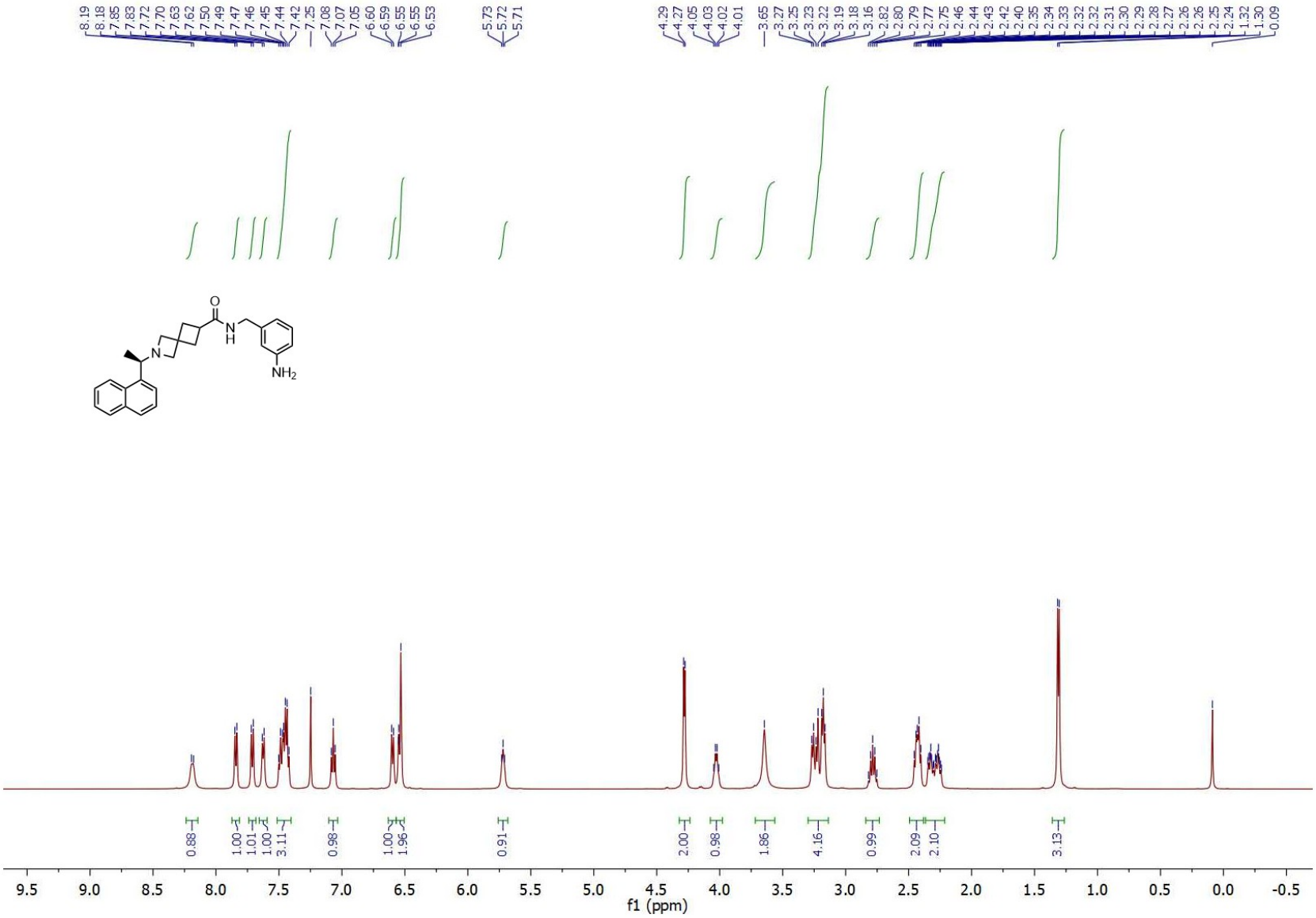
^{1}H NMR (500 MHz, $CDCl_3$) spectrum of (*R*)-*N*-(Benzo[d][1,3]dioxol-5-ylmethyl)-2-(1-(naphthalen-1-yl)ethyl)-2-azaspiro[3.3]heptane-6-carboxamide (38).



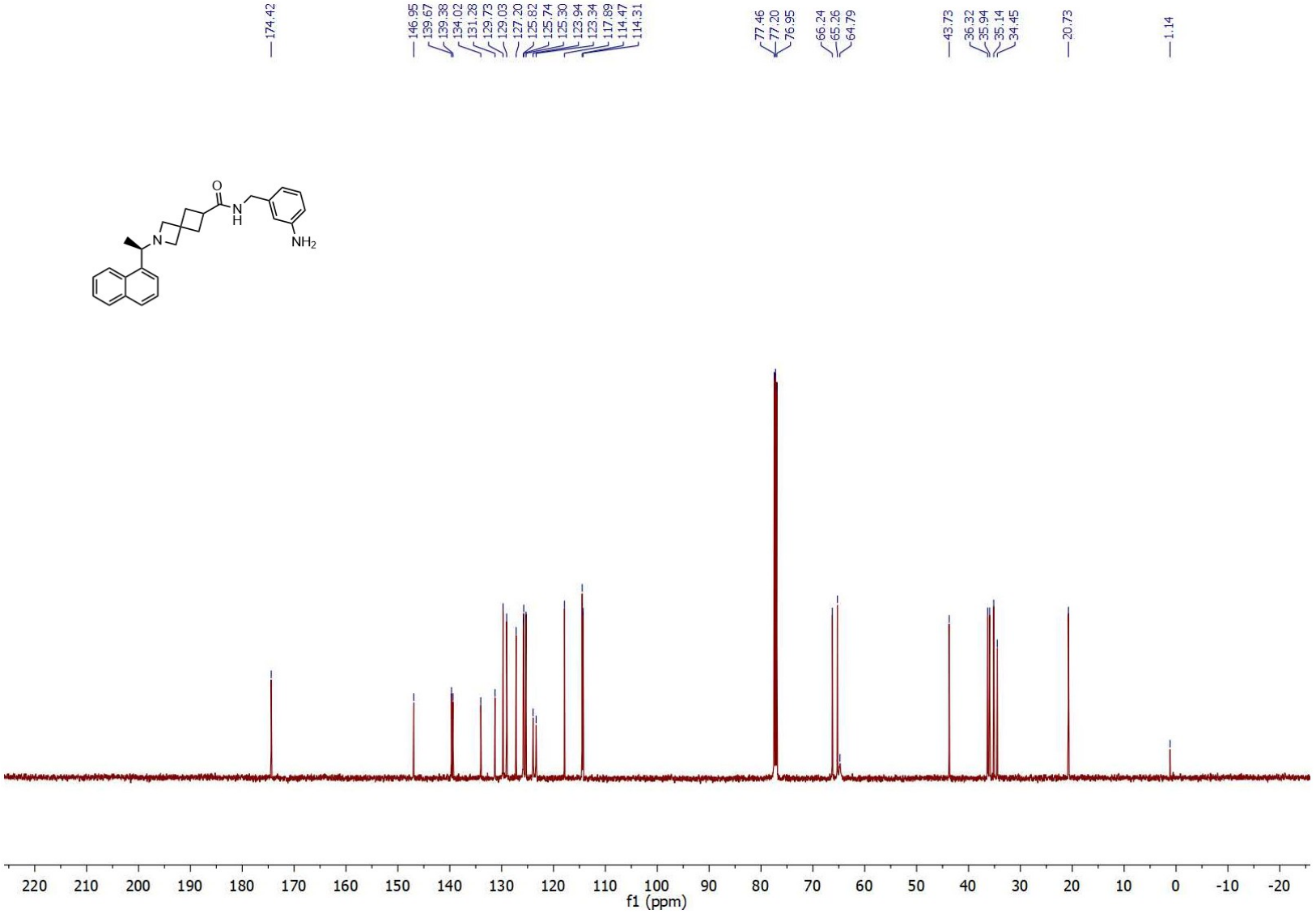
^{13}C NMR (126 MHz, $CDCl_3$) spectrum of (*R*)-*N*-(Benzo[d][1,3]dioxol-5-ylmethyl)-2-(1-(naphthalen-1-yl)ethyl)-2-azaspiro[3.3]heptane-6-carboxamide (38).



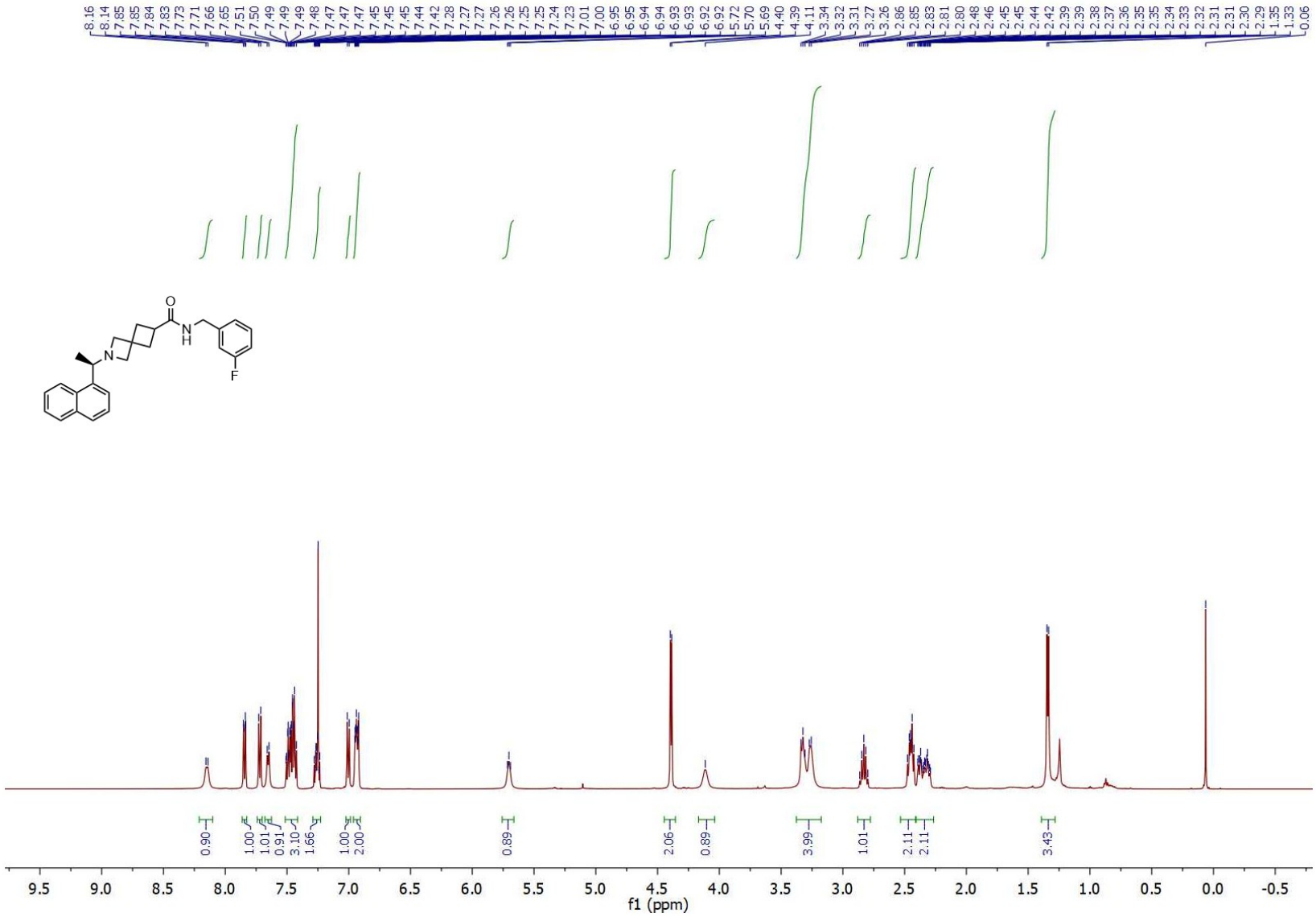
^{1}H NMR (500 MHz, $CDCl_3$) spectrum of (*R*)-*N*-(3-Aminobenzyl)-2-(1-(naphthalen-1-yl)ethyl)-2-azaspiro[3.3]heptane-6-carboxamide (39).



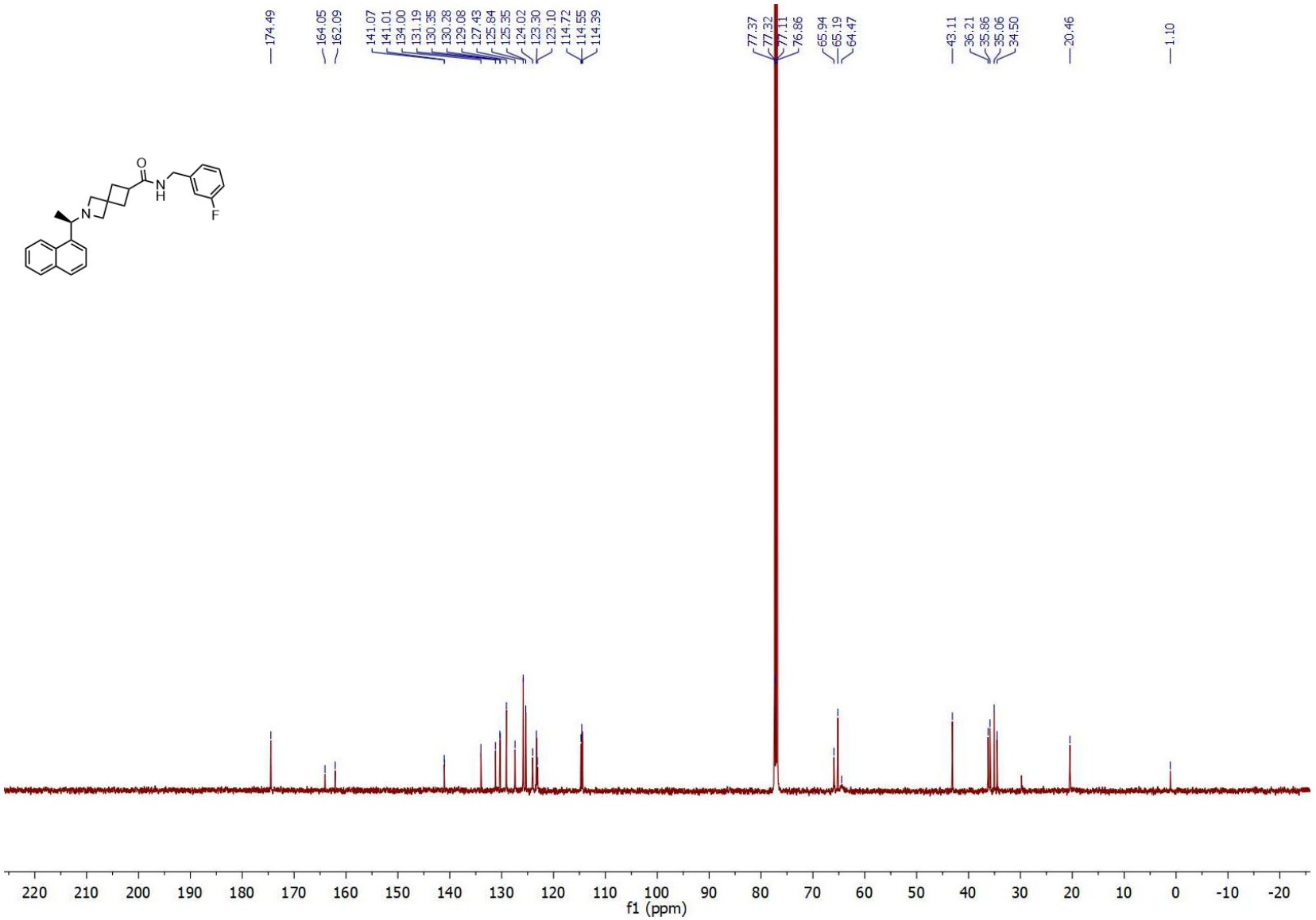
^{13}C NMR (126 MHz, $CDCl_3$) spectrum of (*R*)-*N*-(3-Aminobenzyl)-2-(1-(naphthalen-1-yl)ethyl)-2-azaspiro[3.3]heptane-6-carboxamide (39)..



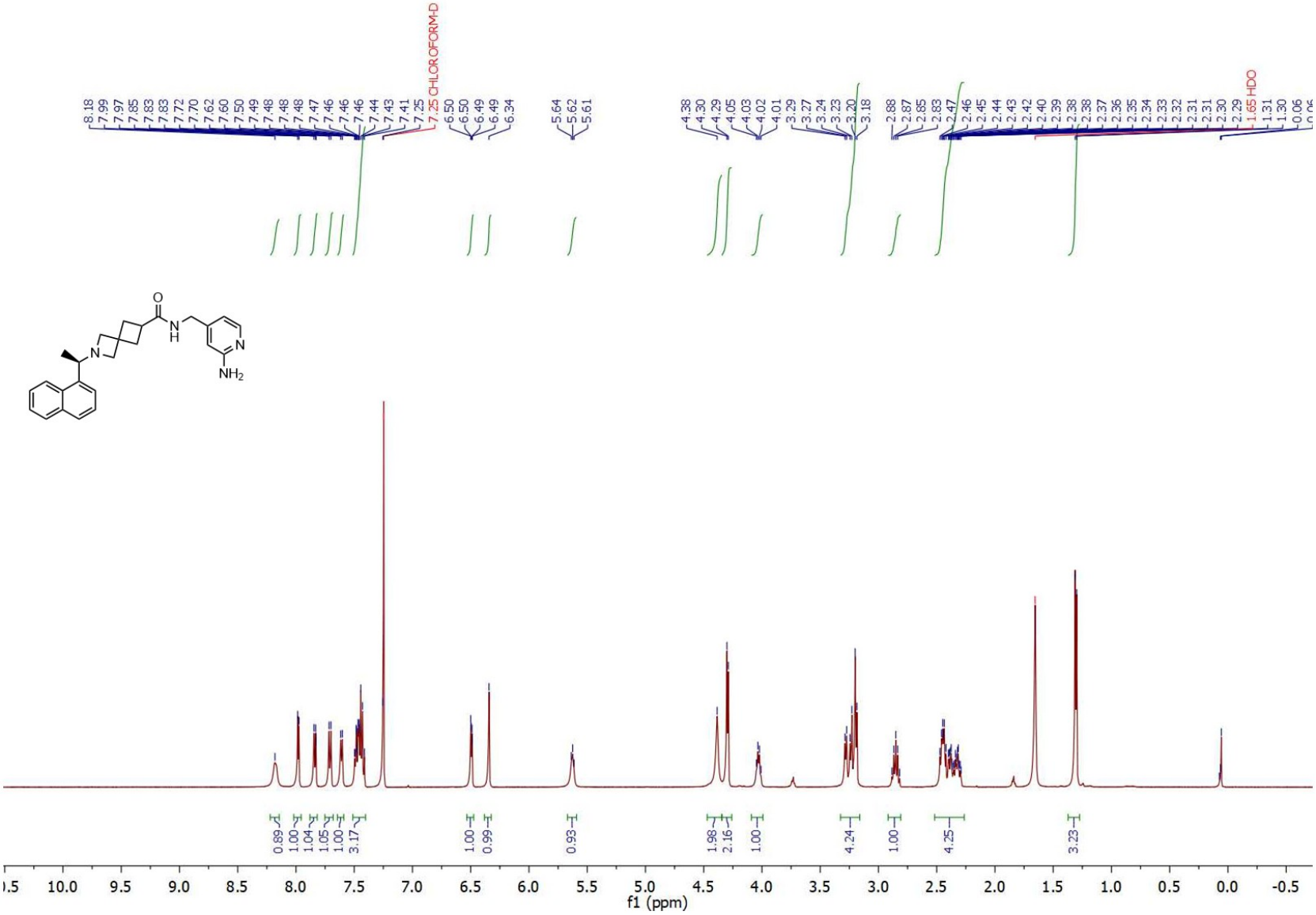
^{1}H NMR (500 MHz, $CDCl_3$) spectrum of (*R*)-*N*-(3-Fluorobenzyl)-2-(1-(naphthalen-1-yl)ethyl)-2-azaspiro[3.3]heptane-6-carboxamide (40).



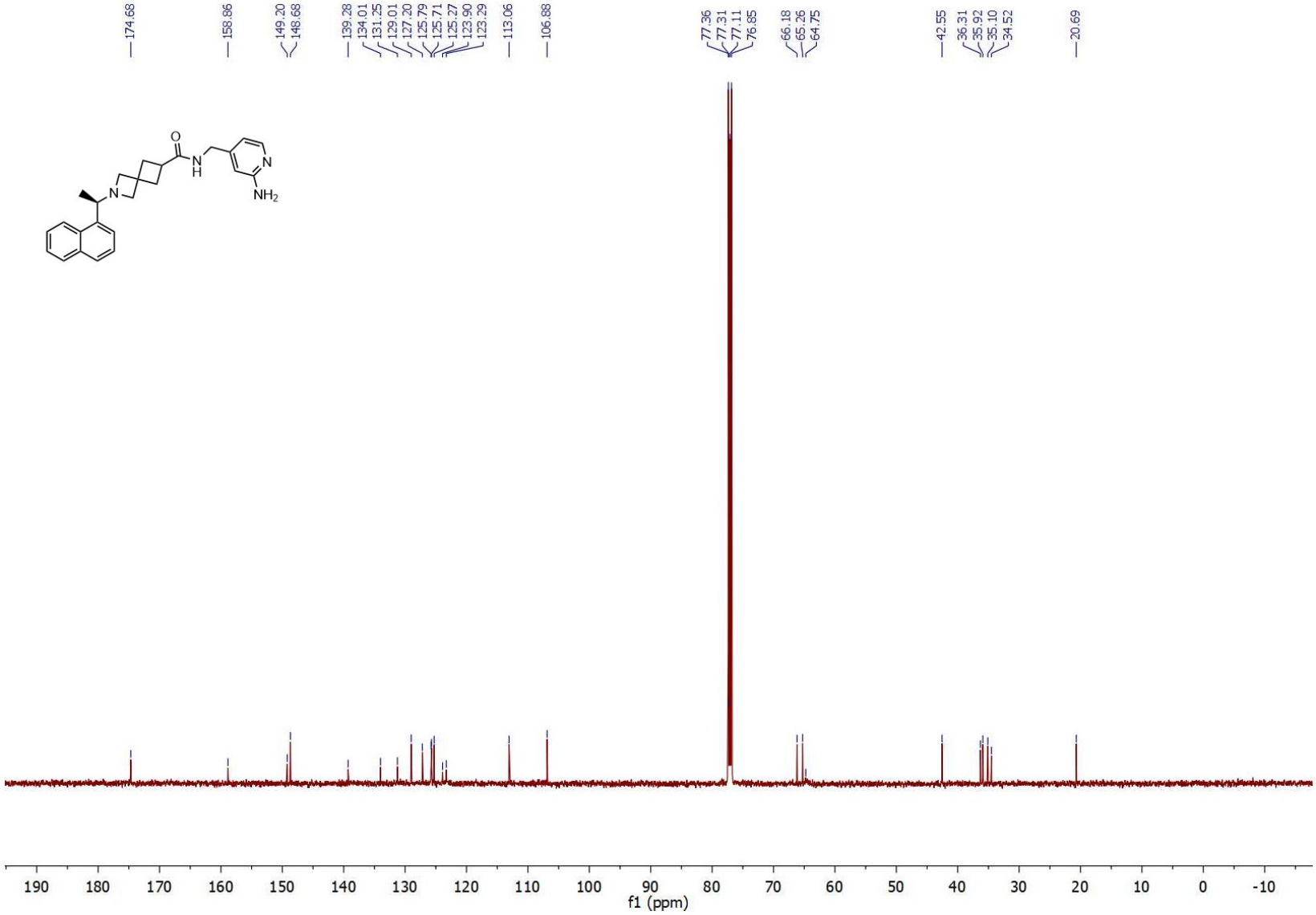
^{13}C NMR (126 MHz, $CDCl_3$) spectrum of (*R*)-*N*-(3-Fluorobenzyl)-2-(1-(naphthalen-1-yl)ethyl)-2-azaspiro[3.3]heptane-6-carboxamide (40).



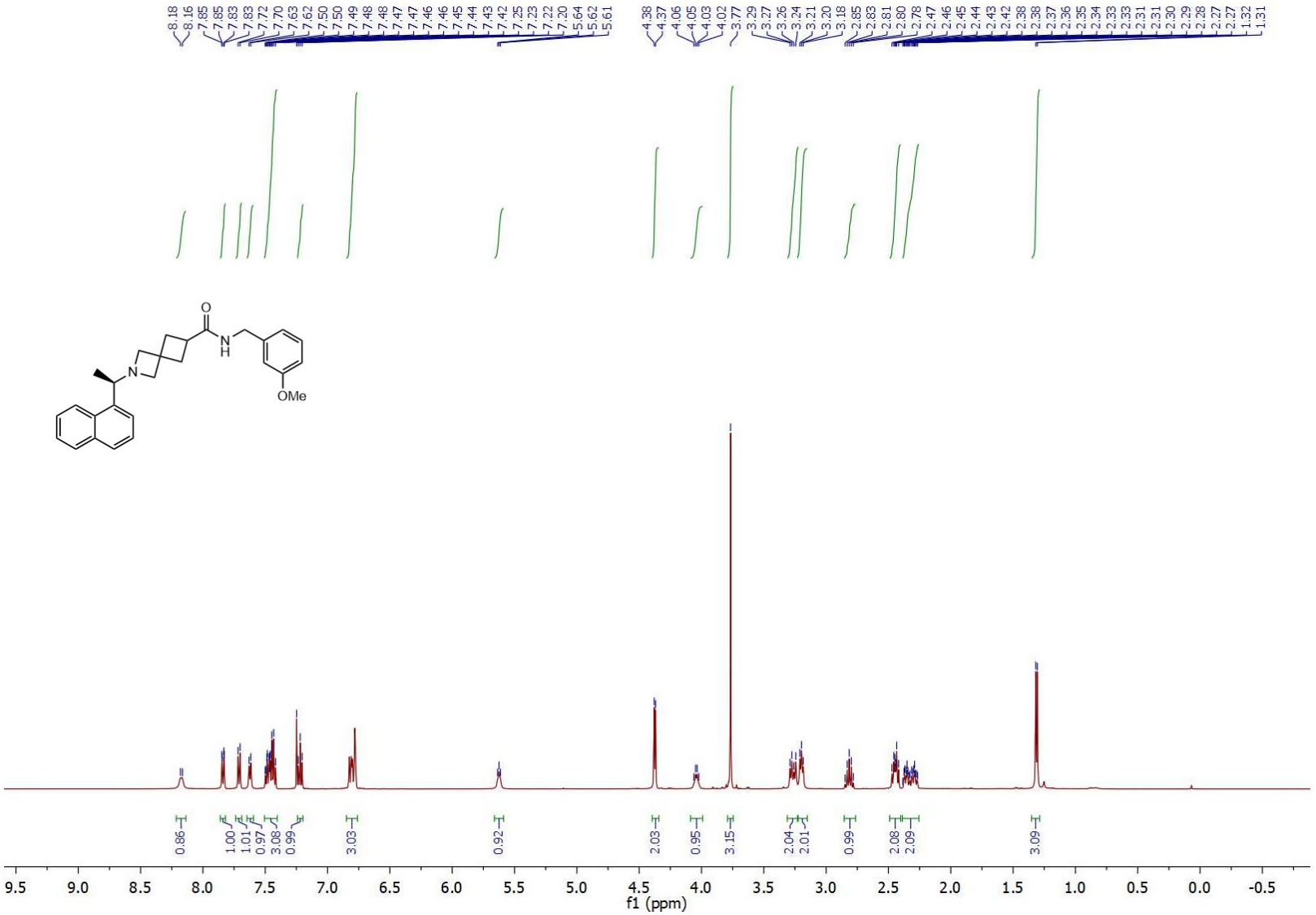
^{1}H NMR (500 MHz, $CDCl_3$) spectrum of (*R*)-*N*-((2-Aminopyridin-4-yl)methyl)-2-(1-(naphthalen-1-yl)ethyl)-2-azaspiro[3.3]heptane-6-carboxamide (41).



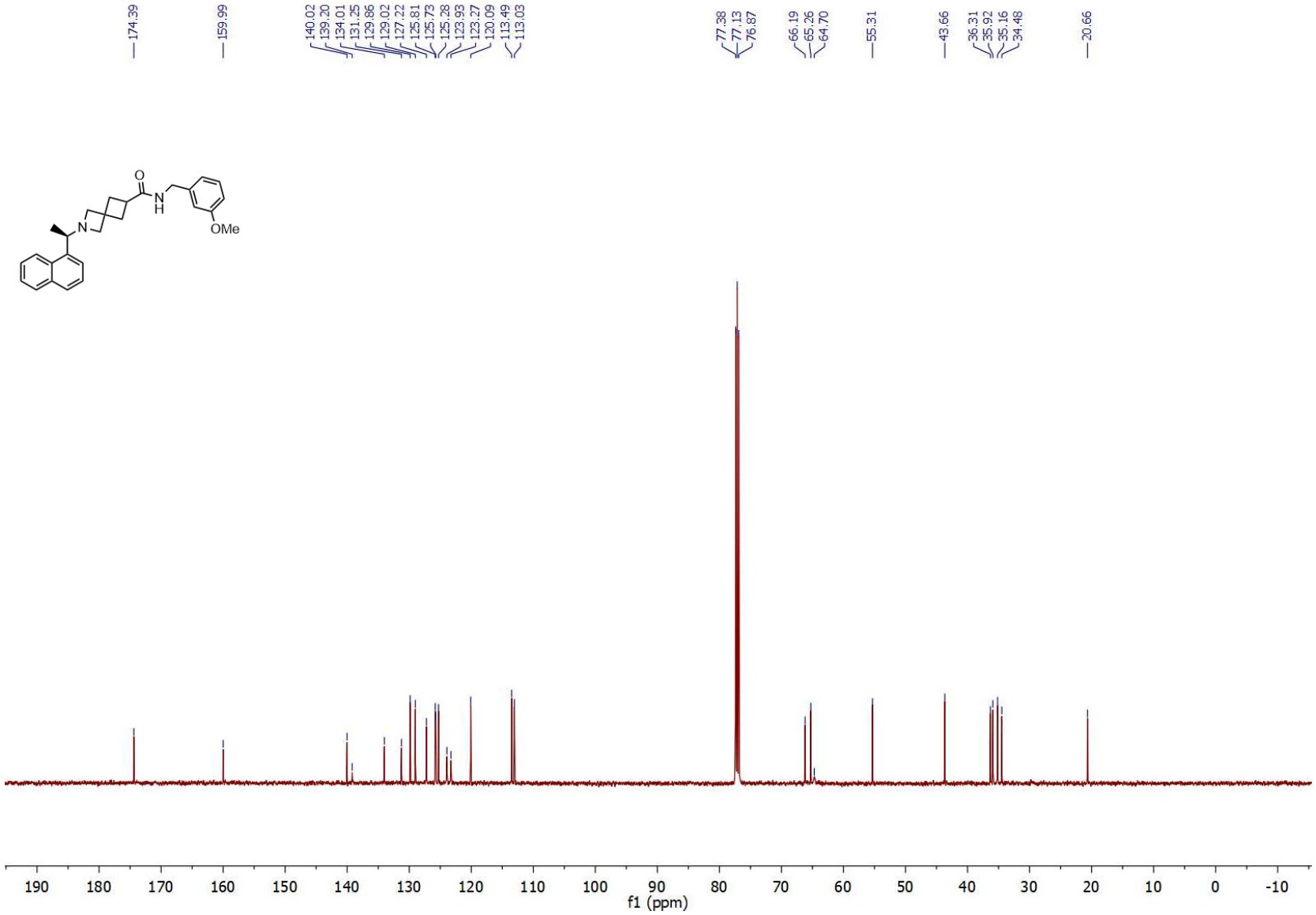
^{13}C NMR (126 MHz, $CDCl_3$) spectrum of (*R*)-*N*-((2-Aminopyridin-4-yl)methyl)-2-(1-(naphthalen-1-yl)ethyl)-2-azaspiro[3.3]heptane-6-carboxamide (41).



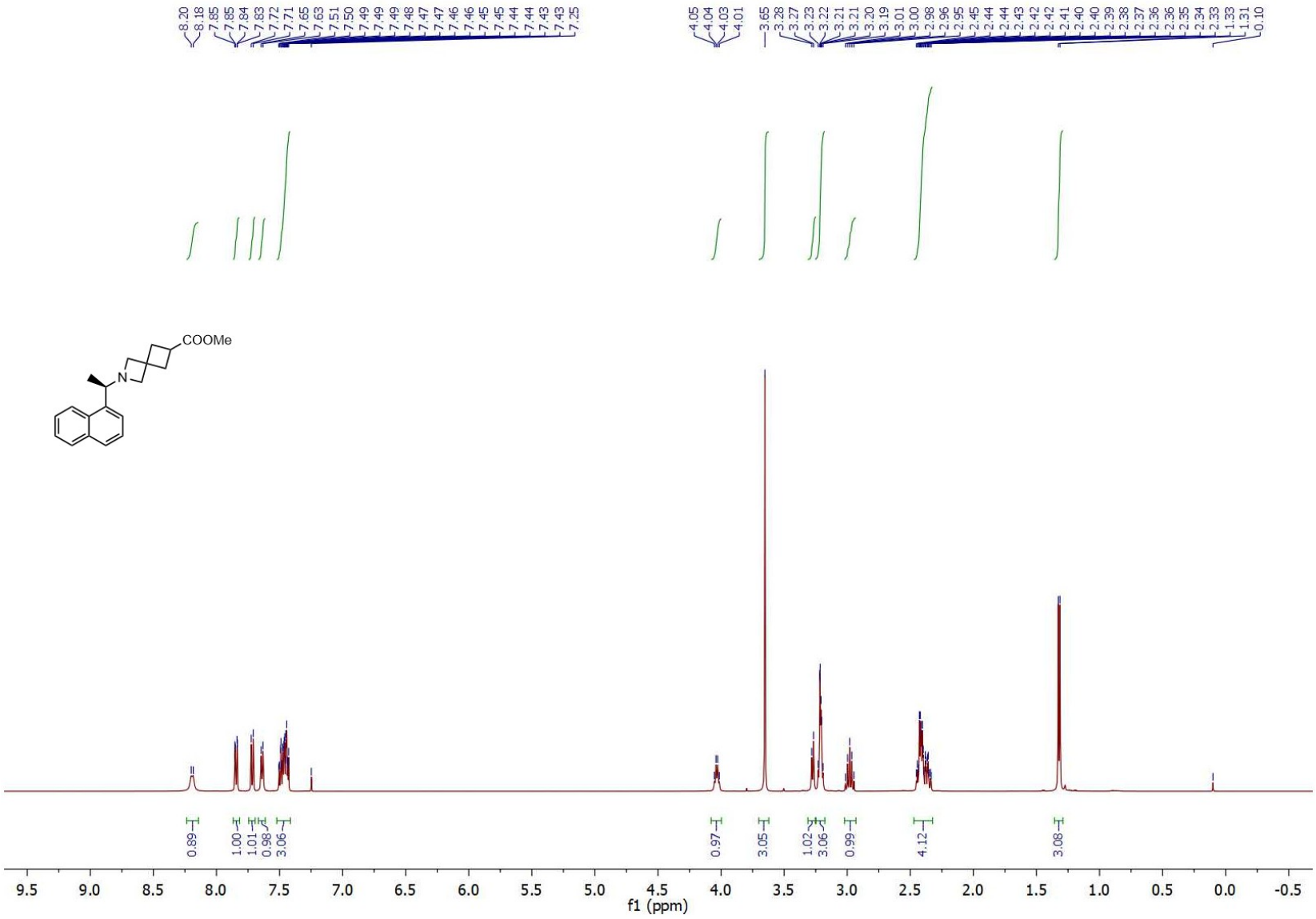
^{1}H NMR (500 MHz, $CDCl_3$) spectrum of (*R*)-*N*-(3-Methoxybenzyl)-2-(1-(naphthalen-1-yl)ethyl)-2-azaspiro[3.3]heptane-6-carboxamide (42)



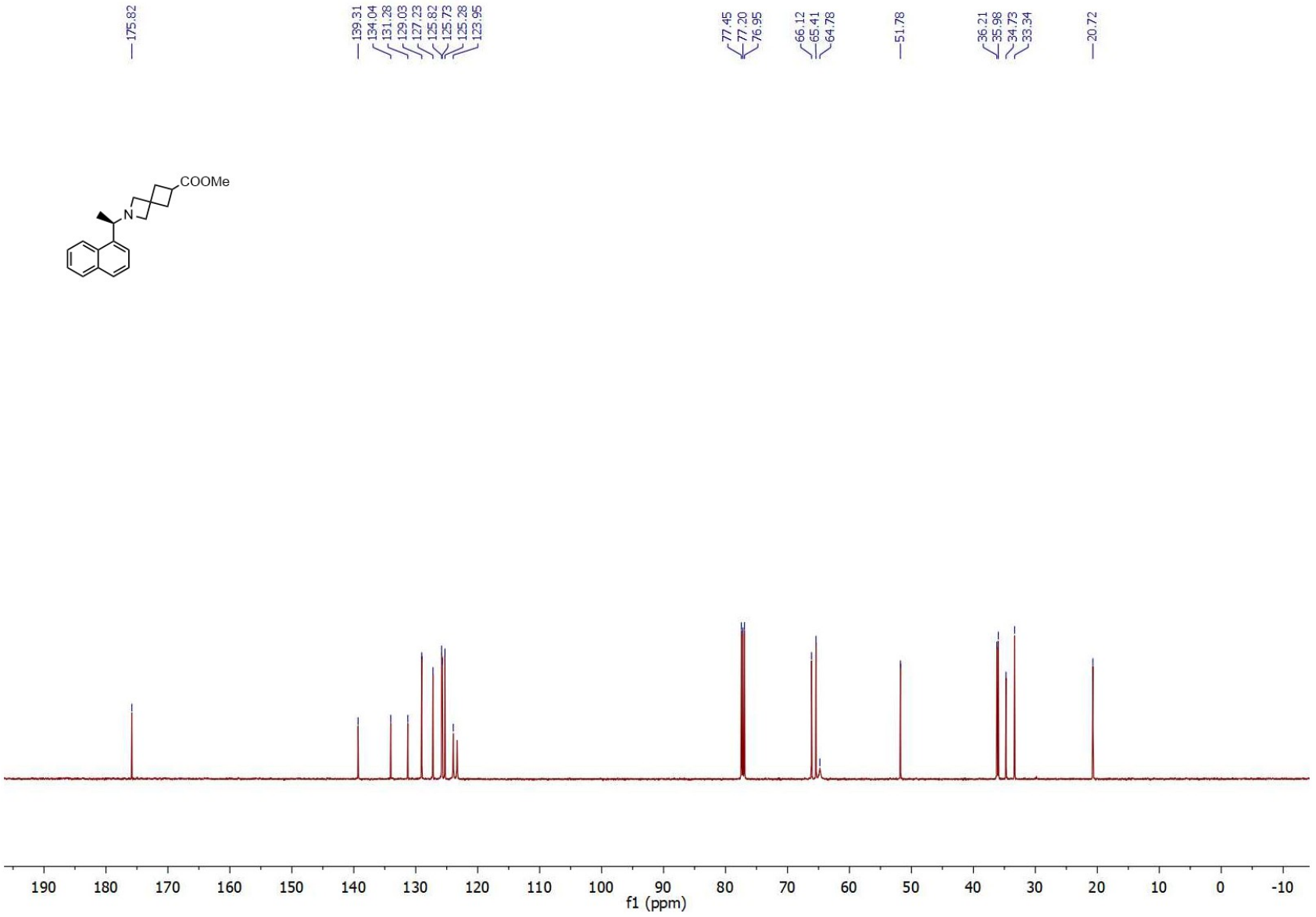
^{13}C NMR (126 MHz, $CDCl_3$) spectrum of (*R*)-*N*-(3-Methoxybenzyl)-2-(1-(naphthalen-1-yl)ethyl)-2-azaspiro[3.3]heptane-6-carboxamide (42).



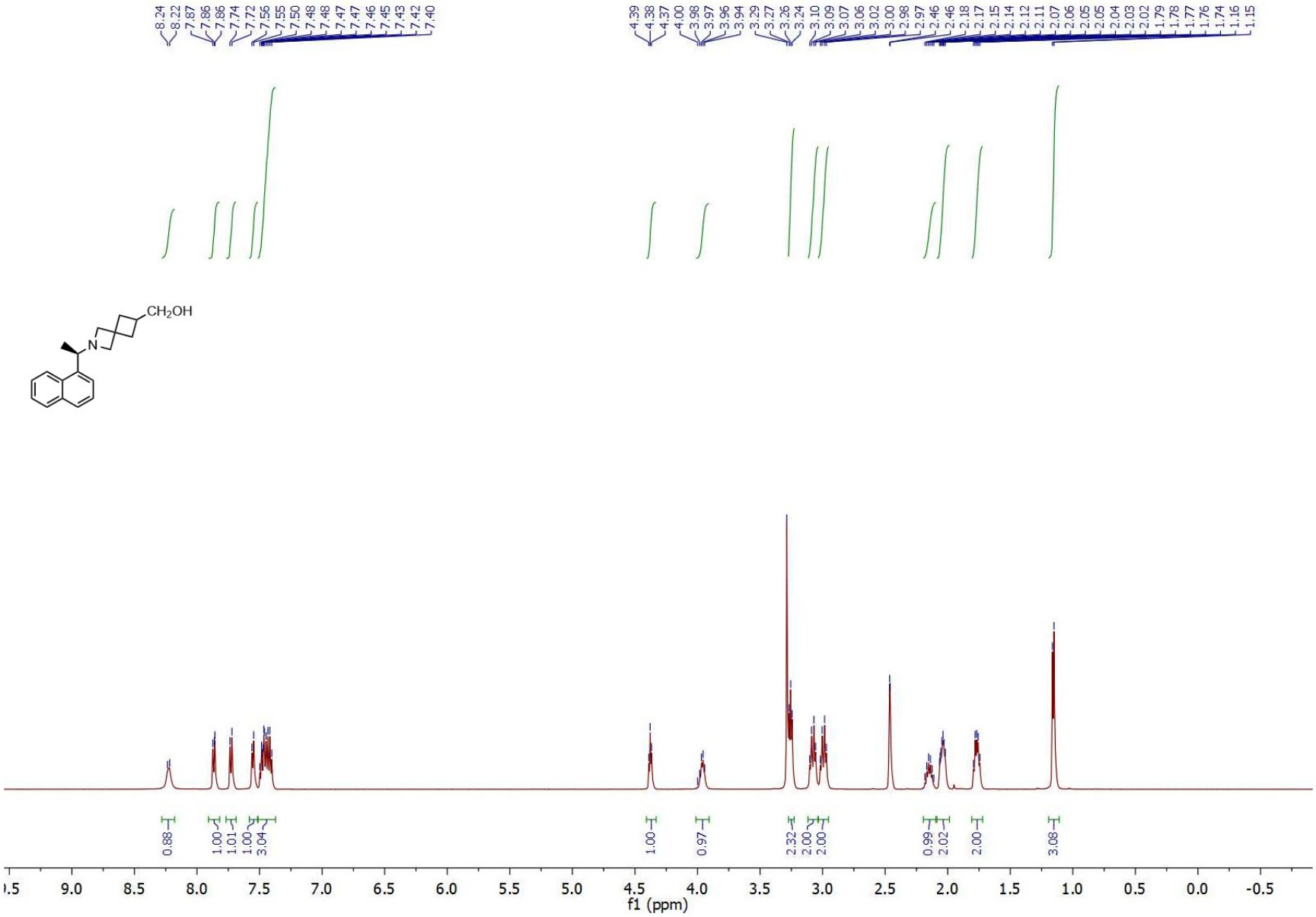
^{1}H NMR (500 MHz, $CDCl_3$) spectrum of Methyl (*R*)-2-(1-(naphthalen-1-yl)ethyl)-2-azaspiro[3.3]heptane-6-carboxylate (43).



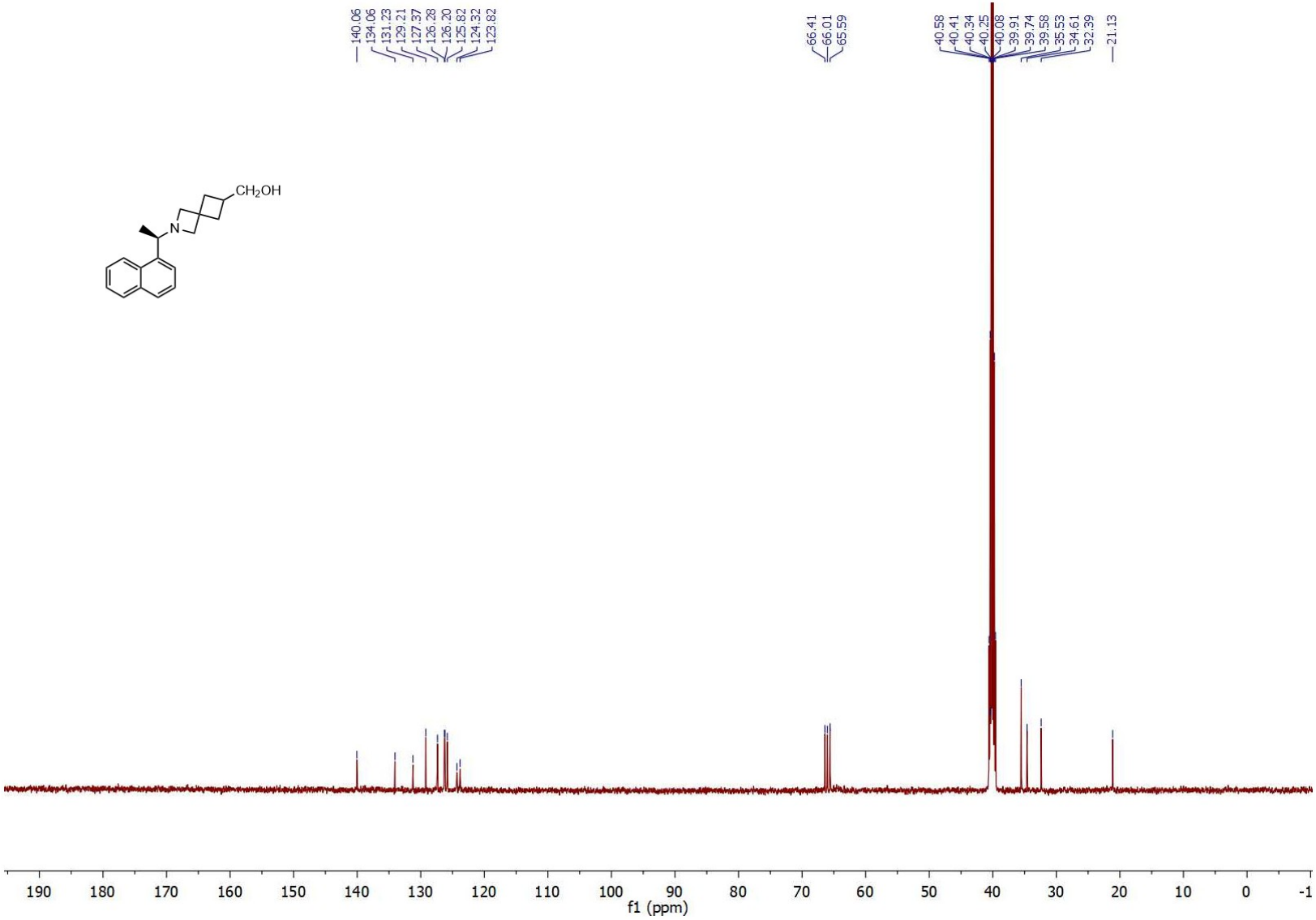
^{13}C NMR (126 MHz, $CDCl_3$) spectrum of Methyl (*R*)-2-(1-(naphthalen-1-yl)ethyl)-2-azaspiro[3.3]heptane-6-carboxylate (43).



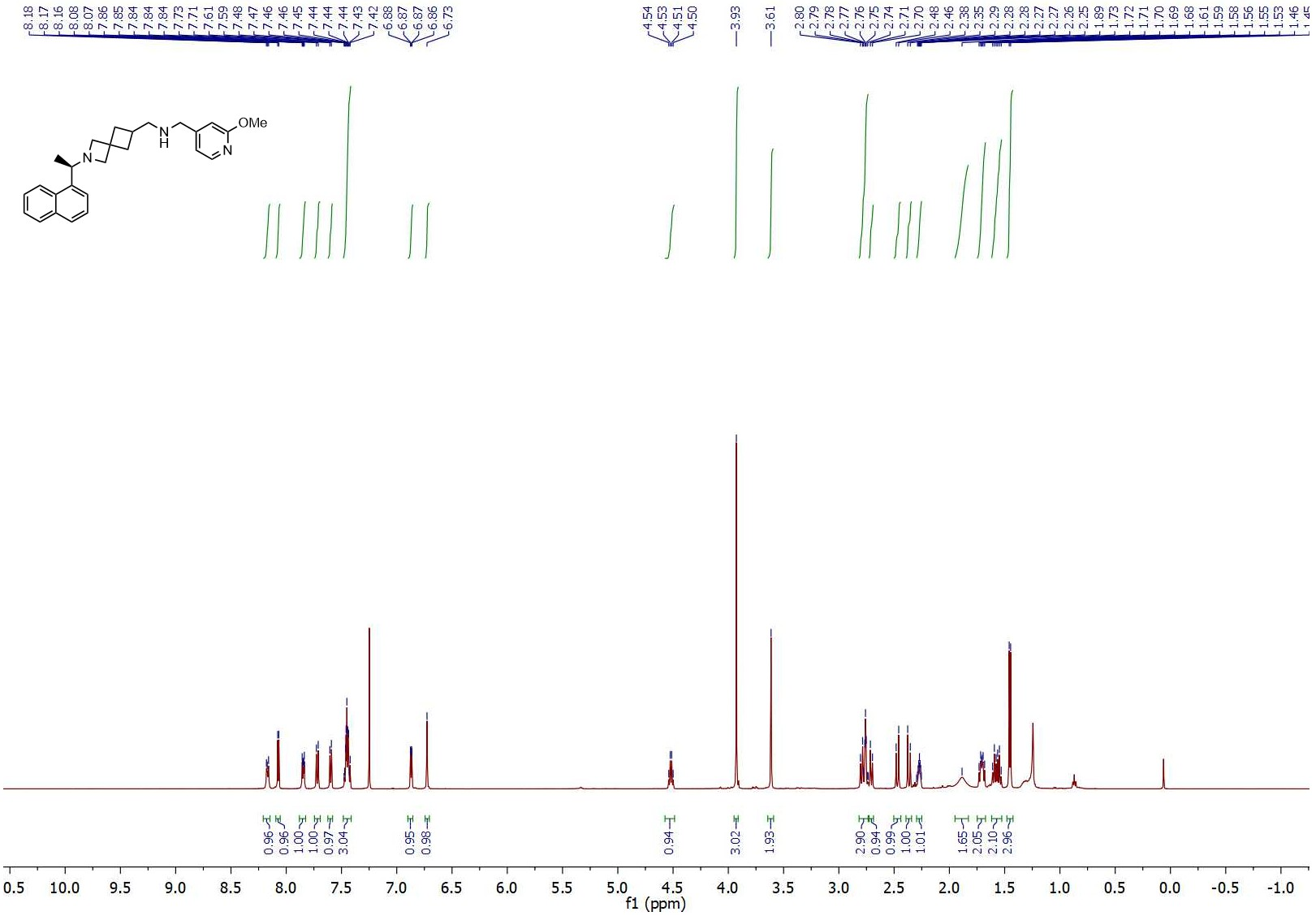
^{1}H NMR (500 MHz, $CDCl_3$) spectrum of (*R*)-2-(1-(naphthalen-1-yl)ethyl)-2-azaspiro[3.3]heptane-6-methanol (44).



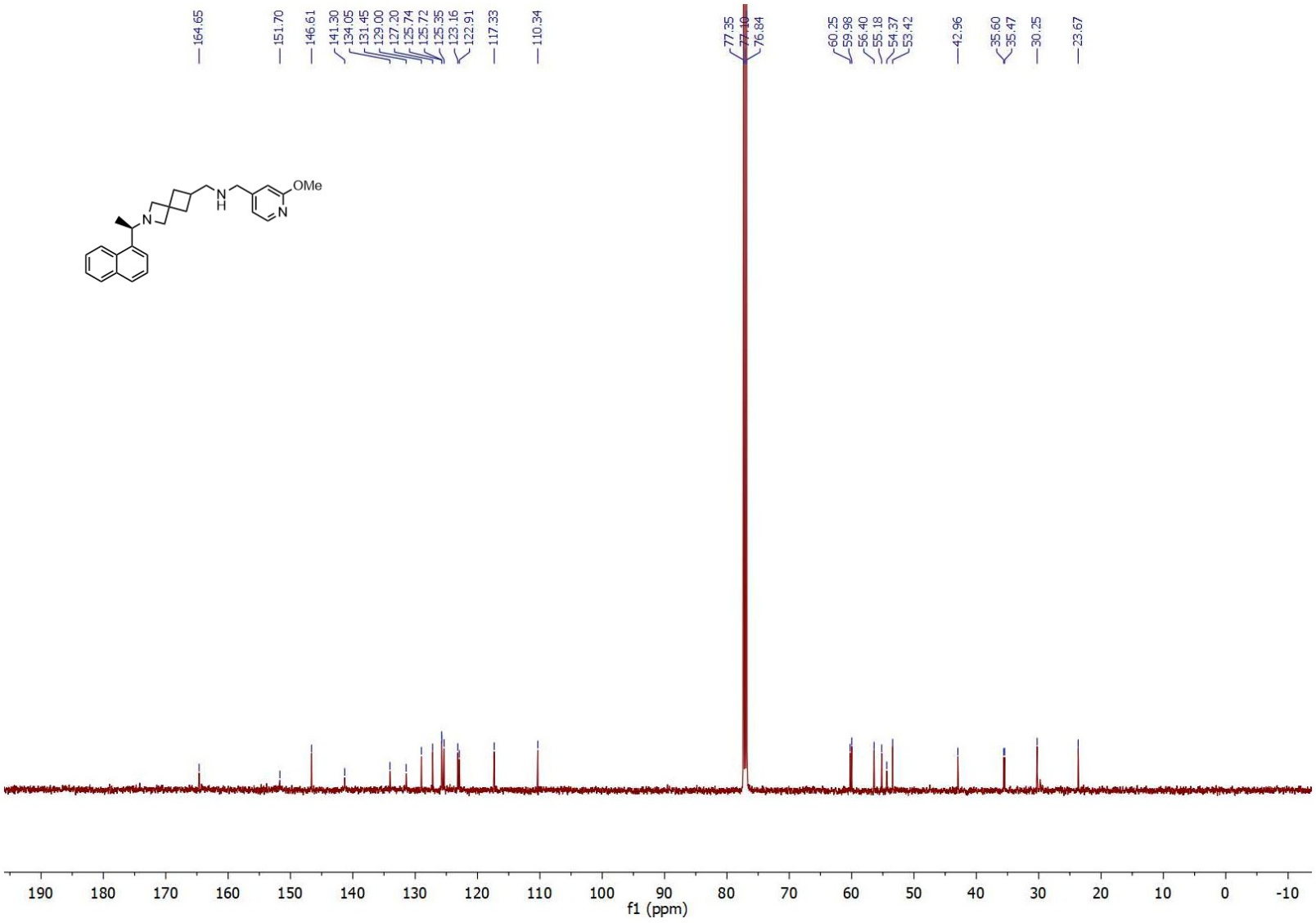
^{13}C NMR (126 MHz, $CDCl_3$) spectrum of (*R*)-2-(1-(naphthalen-1-yl)ethyl)-2-azaspiro[3.3]heptane-6-methanol (44).



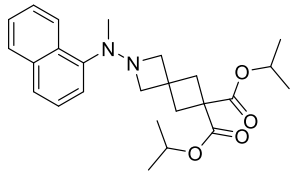
^{1}H NMR (500 MHz, $CDCl_3$) spectrum of (*R*)-*N*-((2-methoxypyridin-4-yl)methyl)-2-(1-(naphthalen-1-yl)ethyl)-2-azaspiro[3.3]heptane-6-methanamine (45).

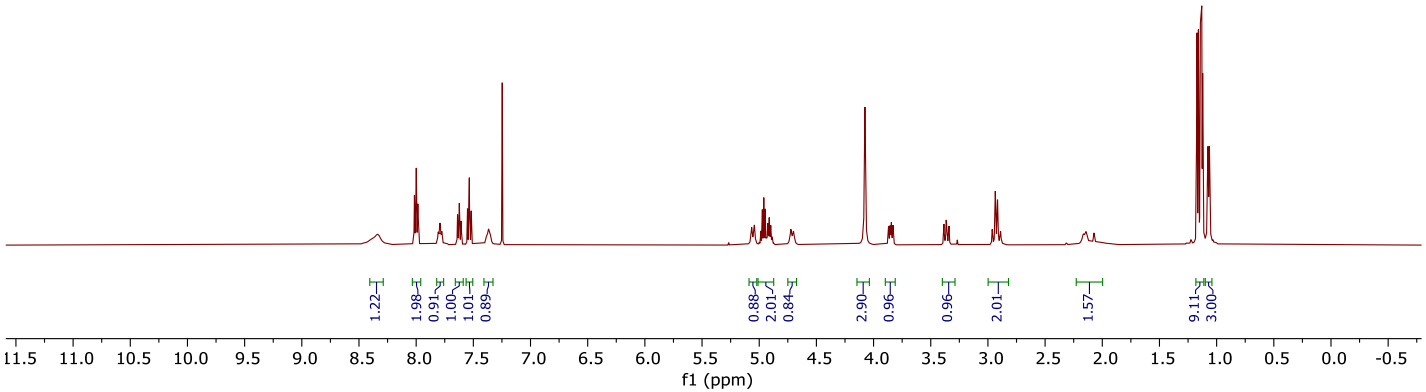


^{13}C NMR (126 MHz, $CDCl_3$) spectrum of (*R*)-*N*-((2-methoxypyridin-4-yl)methyl)-2-(1-(naphthalen-1-yl)ethyl)-2-azaspiro[3.3]heptane-6-methanamine (45).

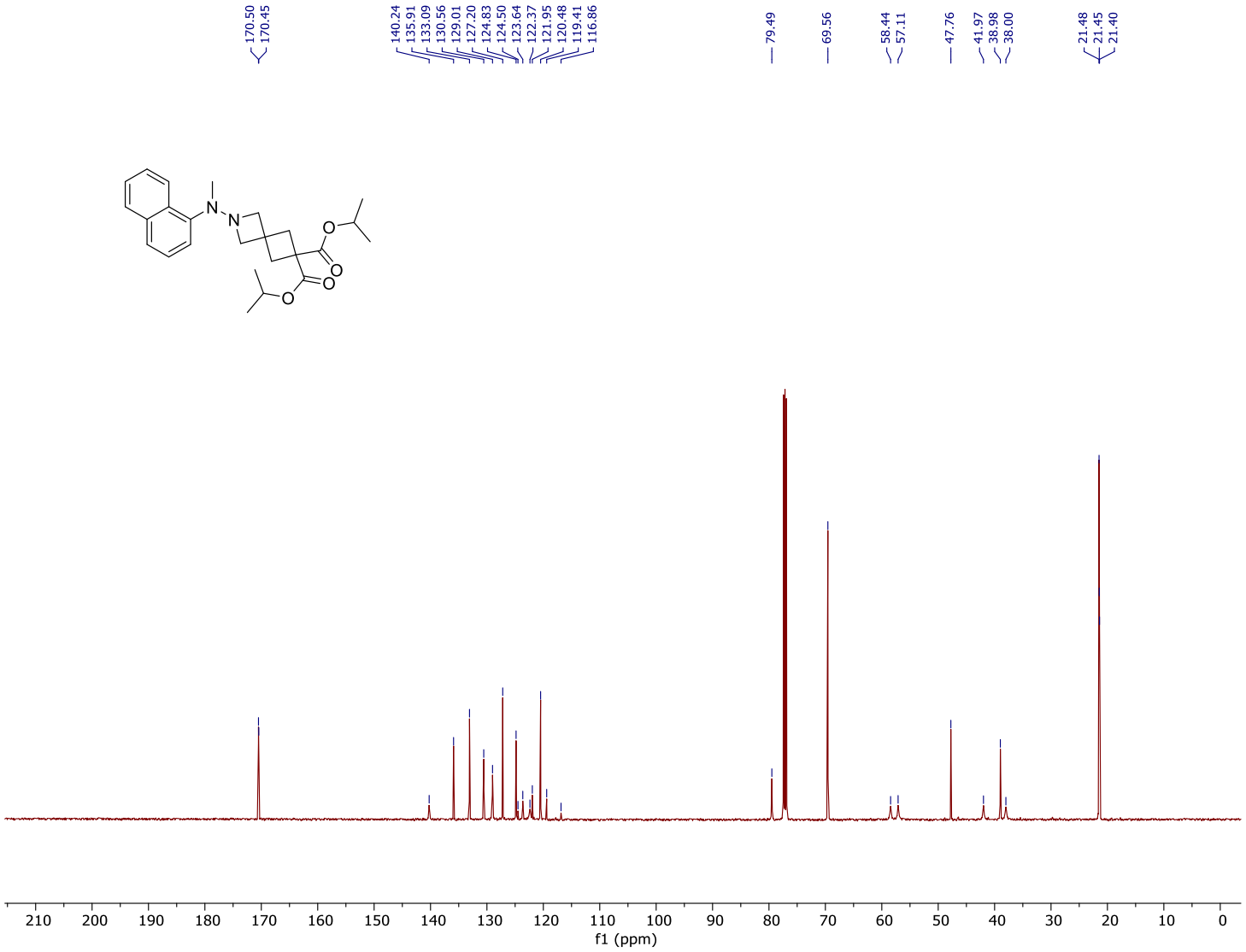


^{1}H NMR (500 MHz, $CDCl_3$) spectrum of diisopropyl *N*-[(naphthalen-1-yl)methylamino]-2-azaspiro[3.3]heptane-6,6-dicarboxylate (46).

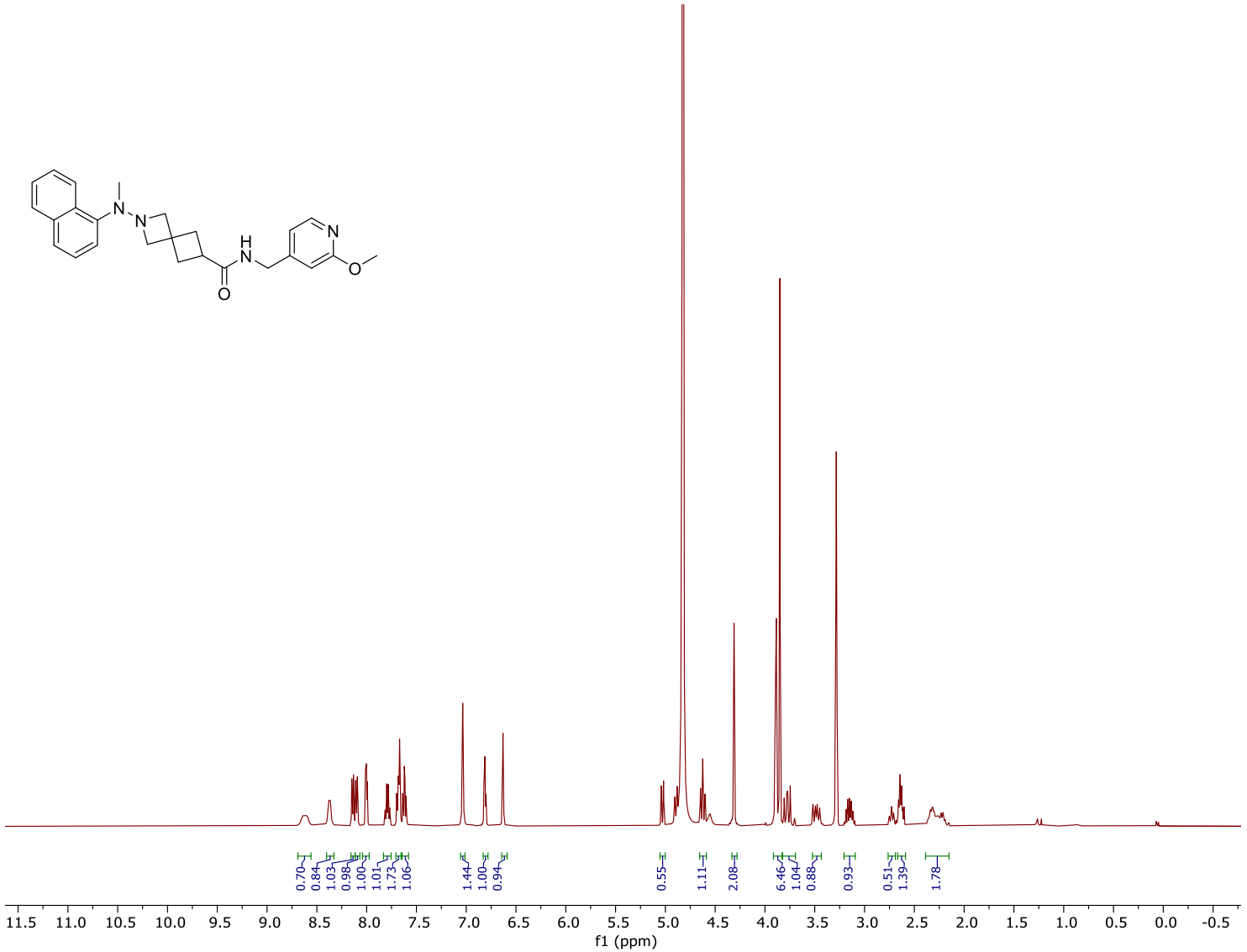




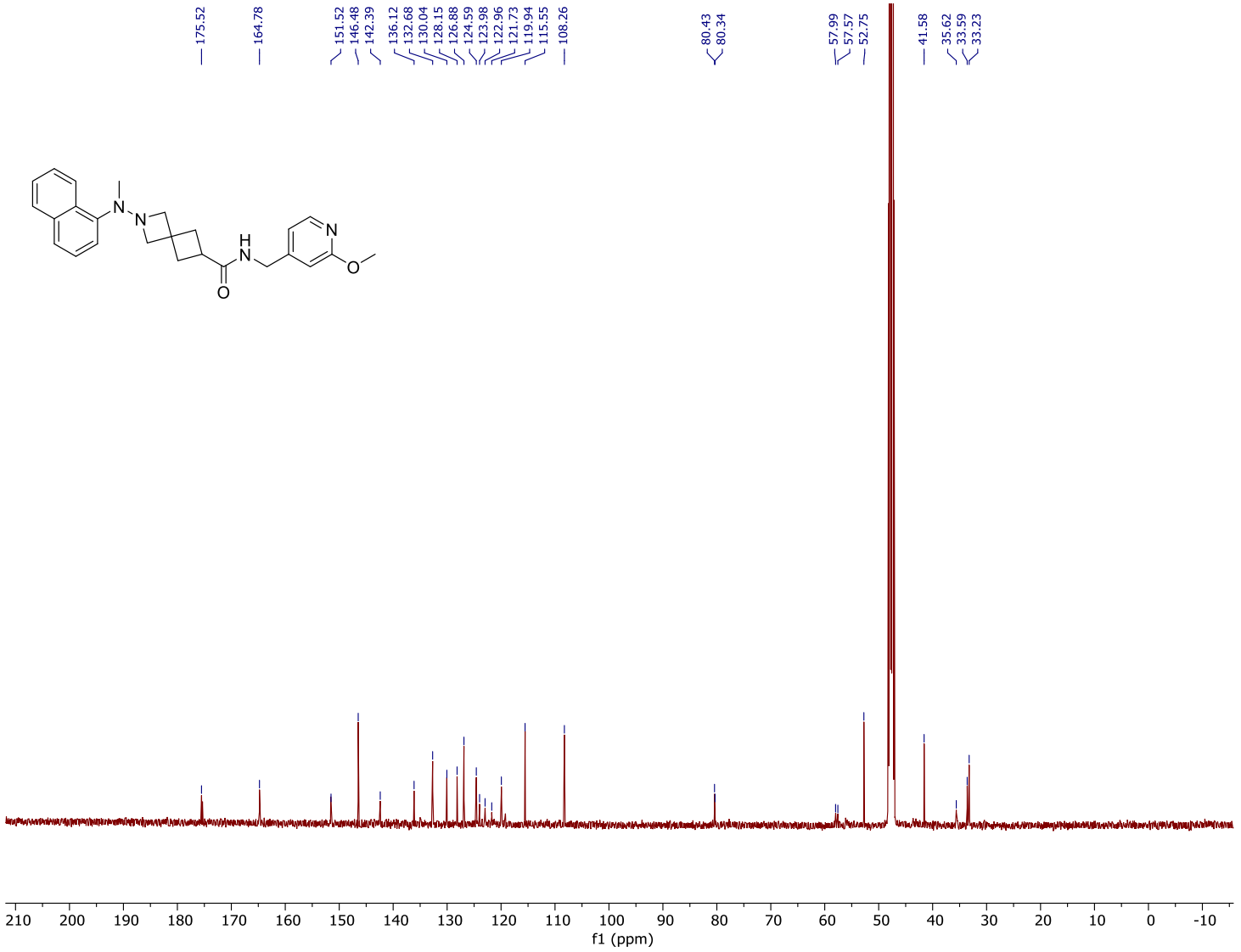
^{13}C NMR (126 MHz, $CDCl_3$) spectrum of diisopropyl *N*-[(naphthalen-1-yl)methylamino]-2-azaspiro[3.3]heptane-6,6-dicarboxylate (46).



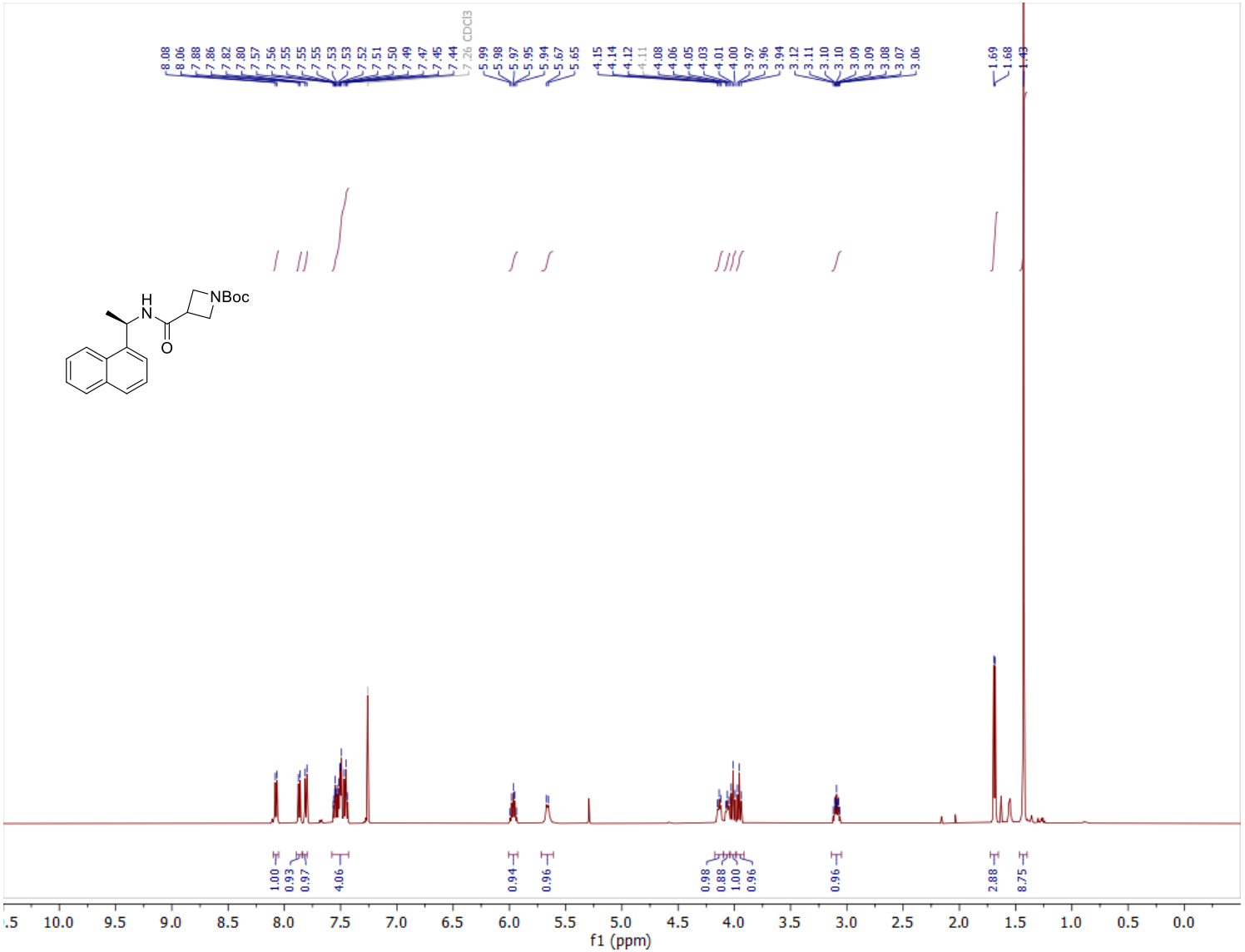
^{1}H NMR (500 MHz, CD_3OD) spectrum of *N*-[(2-Methoxypyridin-4-yl)methyl] *N'*-[(naphthalen-1-yl)methylamino]-2-azaspiro[3.3]heptane-6-carboxamide (47).



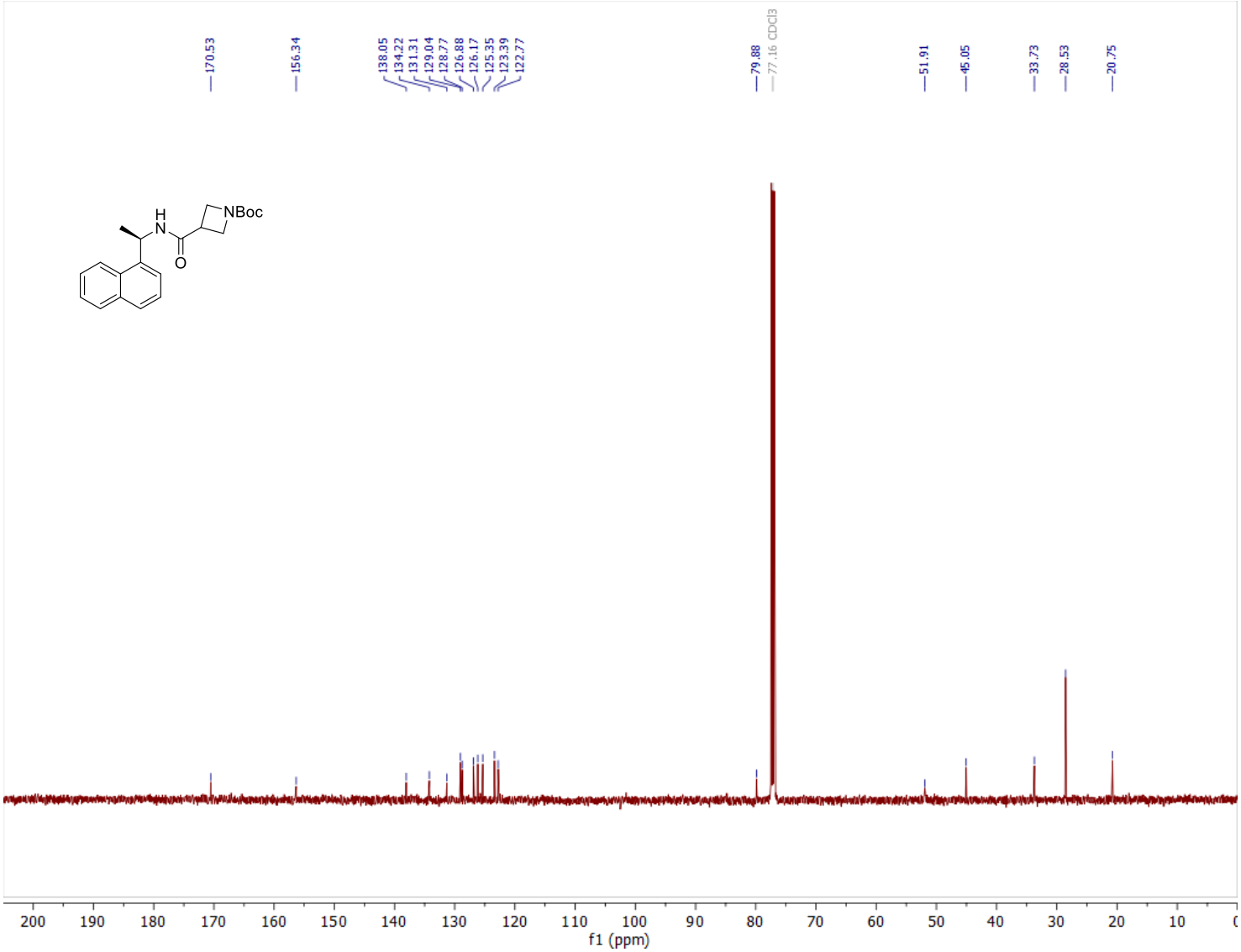
^{13}C NMR (126 MHz, CD_3OD) spectrum of *N*-((2-methoxypyridin-4-yl)methyl)-2-(methyl(naphthalen-1-yl)amino)-2-azaspiro[3.3]heptane-6-carboxamide (47).



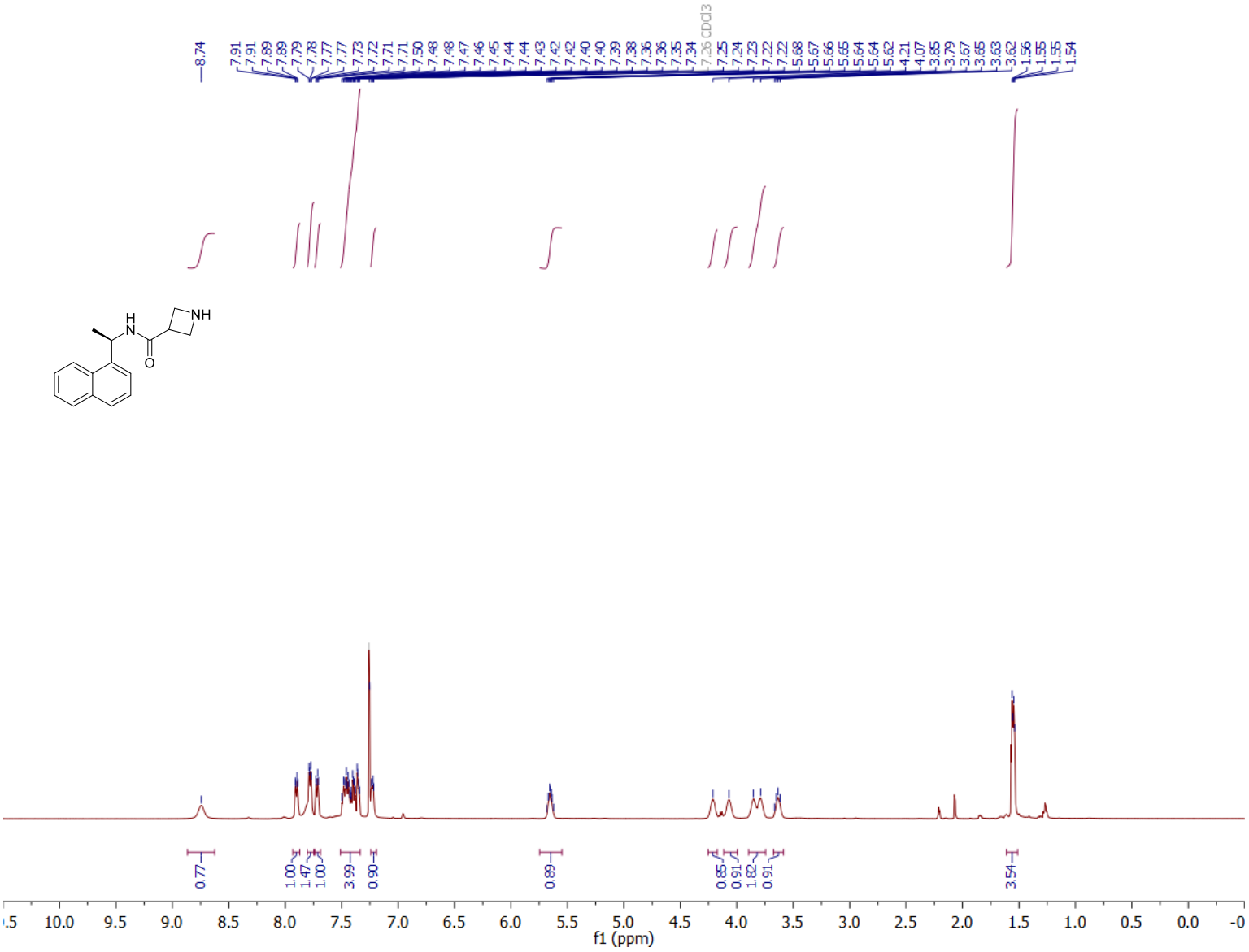
^{1}H NMR (500 MHz, $CDCl_3$, T = 313K) spectrum of *tert*-butyl (*R*)-3-((1'-(naphthalen-1'-yl)ethyl)carbamoyl)azetidine-1-carboxylate (48).



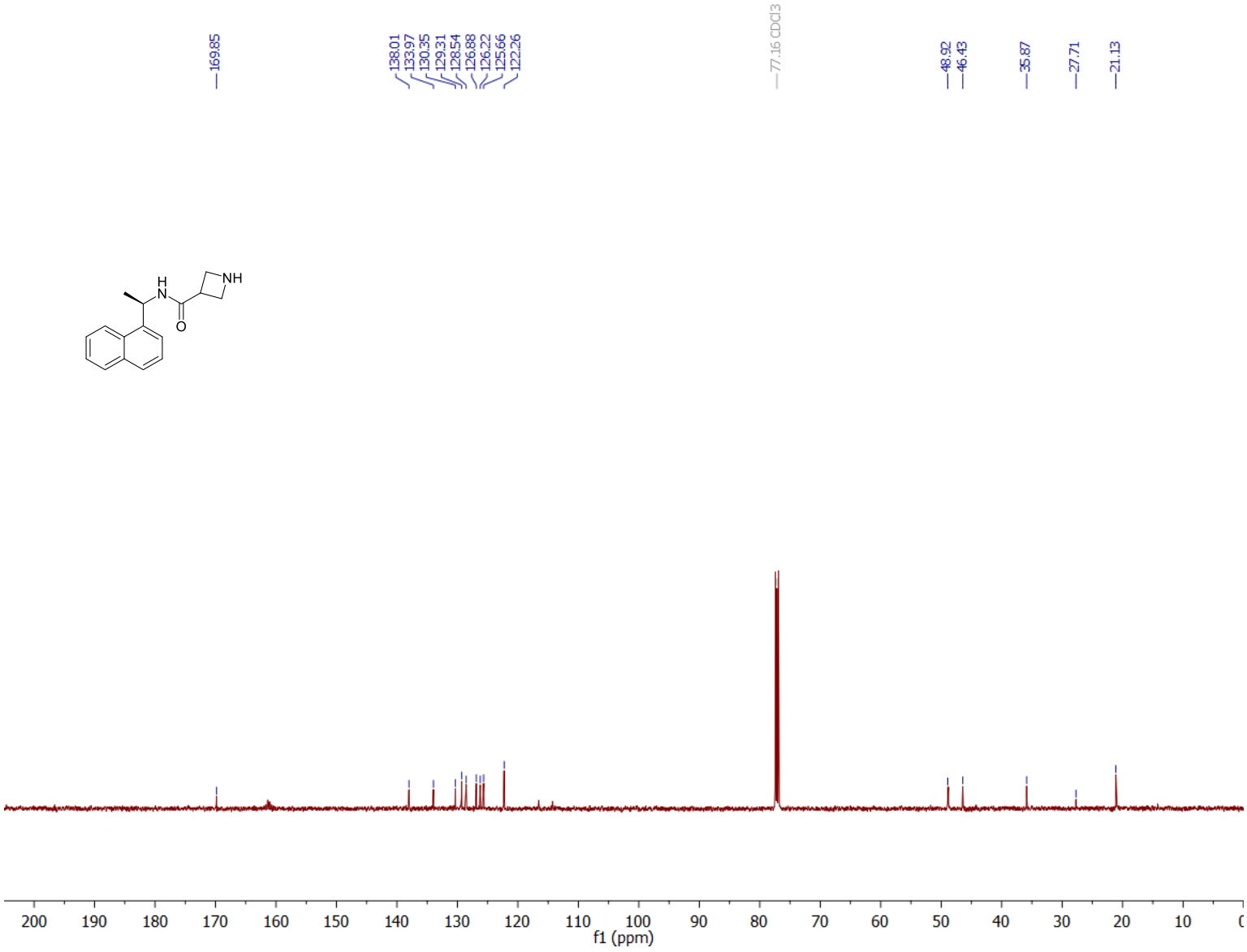
^{13}C NMR (126 MHz, $CDCl_3$,T = 313K) spectrum of *tert*-butyl (*R*)-3-((1'-(naphthalen-1'-yl)ethyl)carbamoyl)azetidine-1-carboxylate (48).



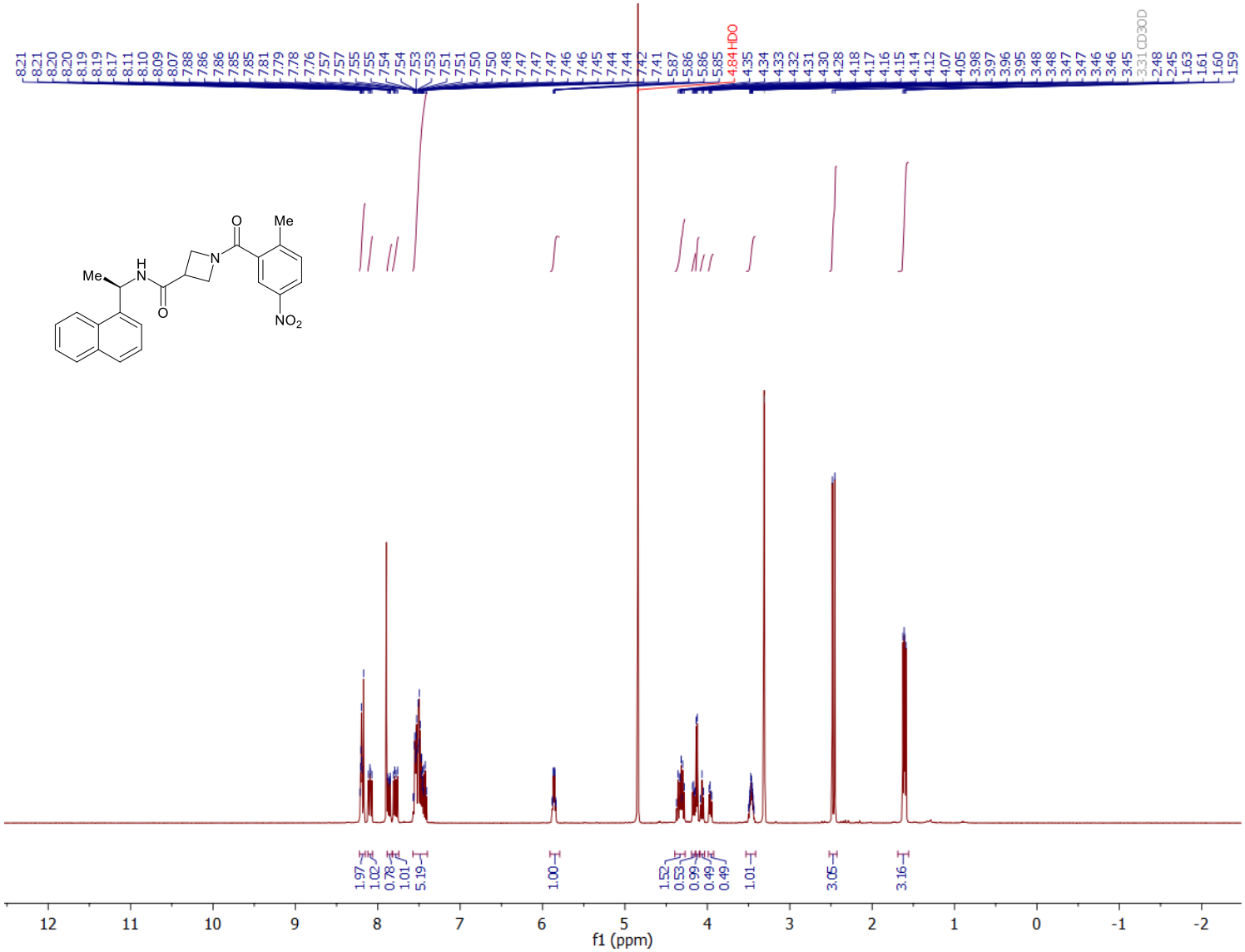
^{1}H NMR (500 MHz, $CDCl_3$) spectrum of (*R*)-*N*-(1'-(naphthalene-1'-yl)ethyl)azetidine-3-carboxamide (49).



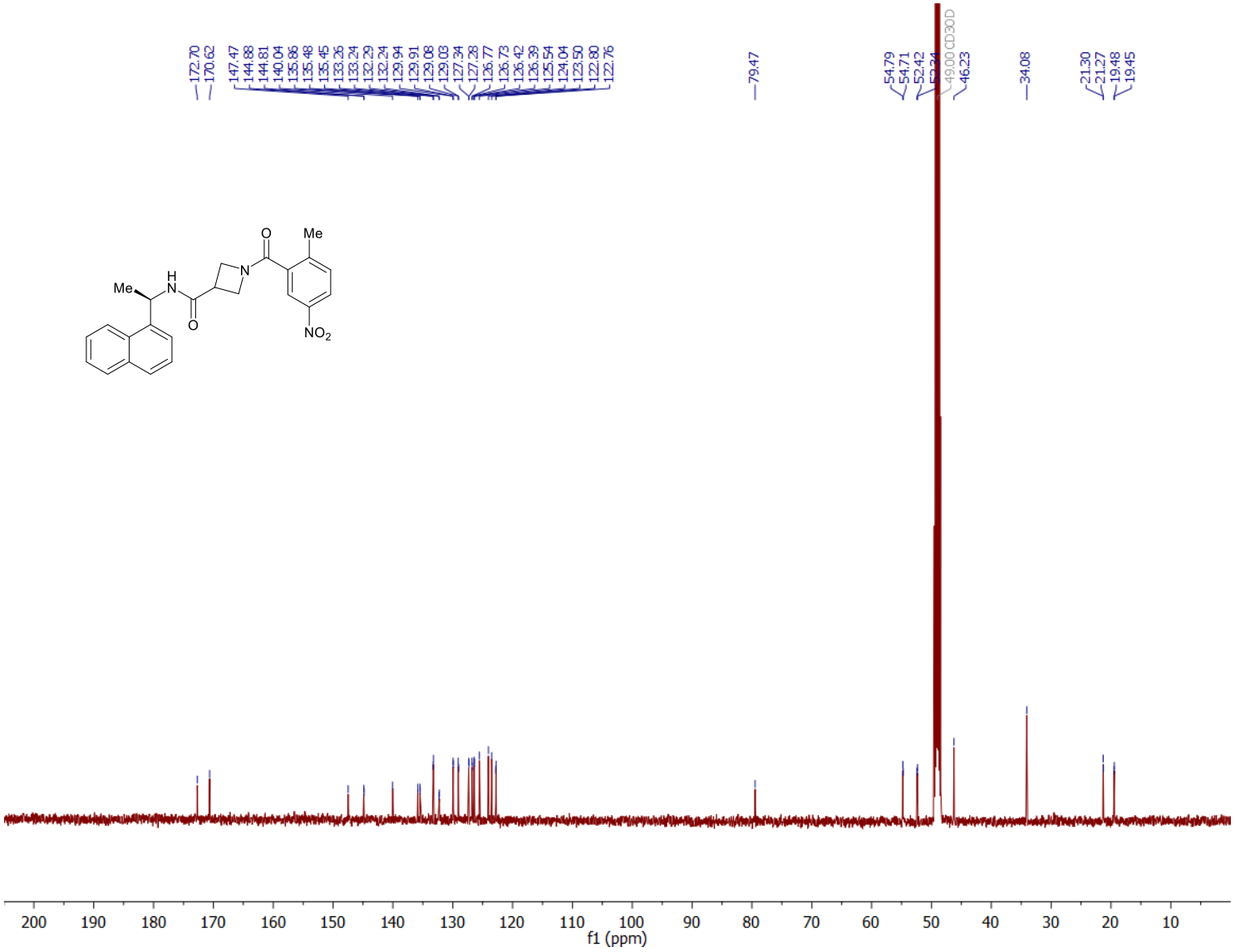
^{13}C NMR (126 MHz, $CDCl_3$) spectrum of (*R*)-*N*-(1'-(naphthalene-1'-yl)ethyl)azetidine-3-carboxamide (49).



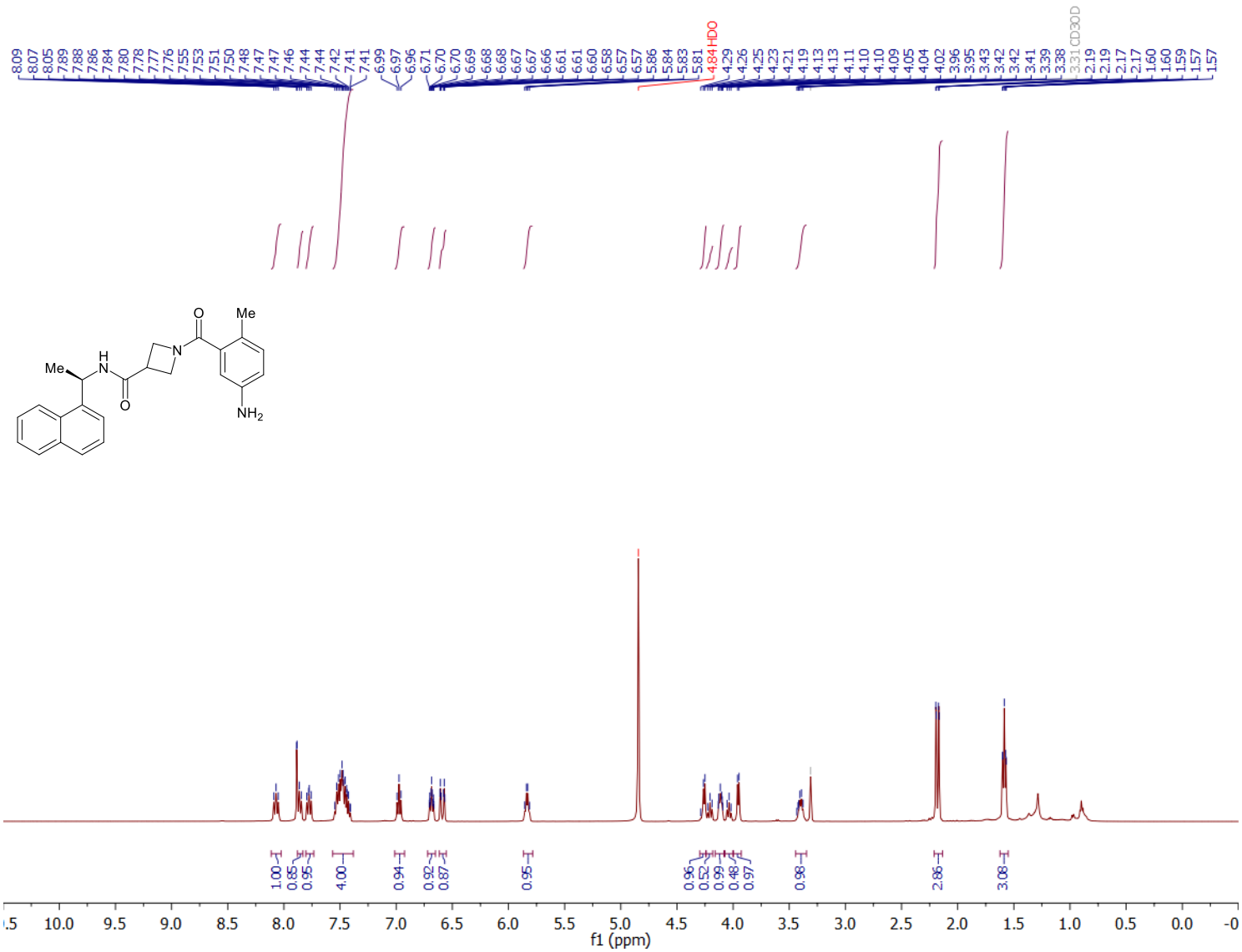
^{1}H NMR (500 MHz, CD_3OD) spectrum of (*R*)-1'-(2'-methyl-5'-nitrobenzoyl)-*N*-(1''-(naphthalene-1''-yl)ethyl)azetidine-3-carboxamide (50).



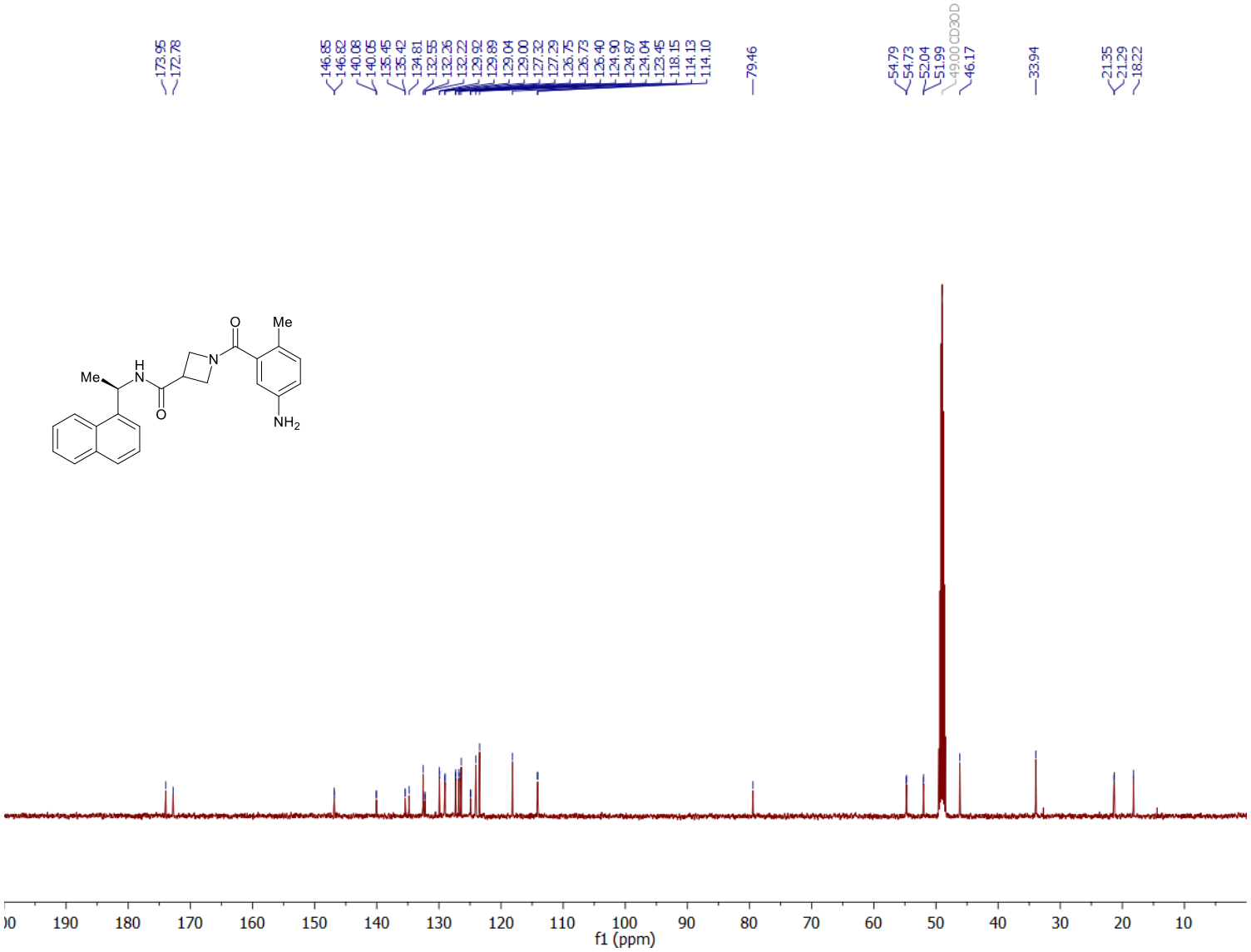
^{13}C NMR (126 MHz, CD_3OD) spectrum of (*R*)-1'-(2'-methyl-5'-nitrobenzoyl)-*N*-(1''-(naphthalene-1''-yl)ethyl)azetidine-3-carboxamide (50).



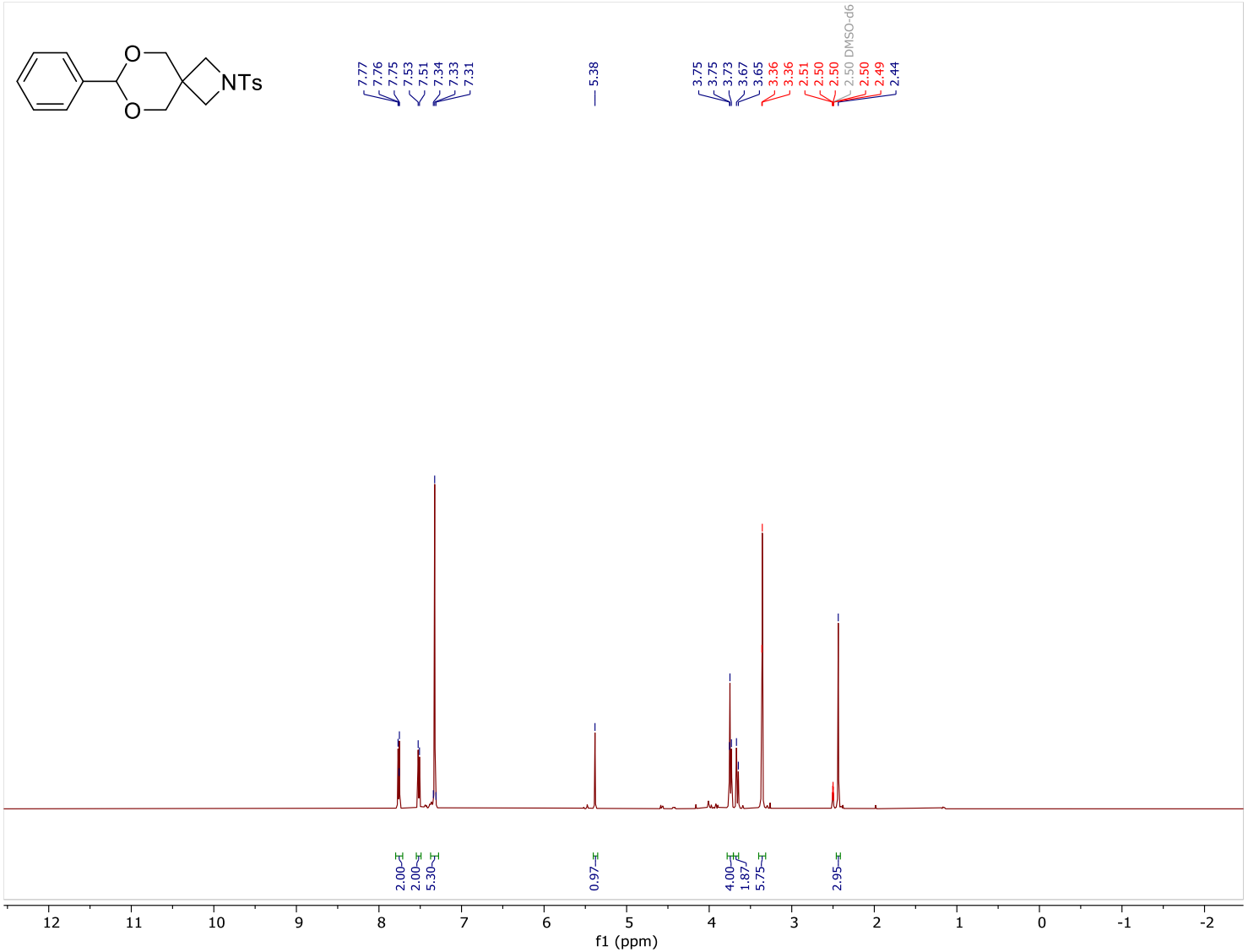
^{1}H NMR (500 MHz, CD_3OD) spectrum of (*R*)-1'-(5'-amino-2'-methylbenzoyl)-*N*-(1''-(naphthalene-1''-yl)ethyl)azetidine-3-caboxamide (51).



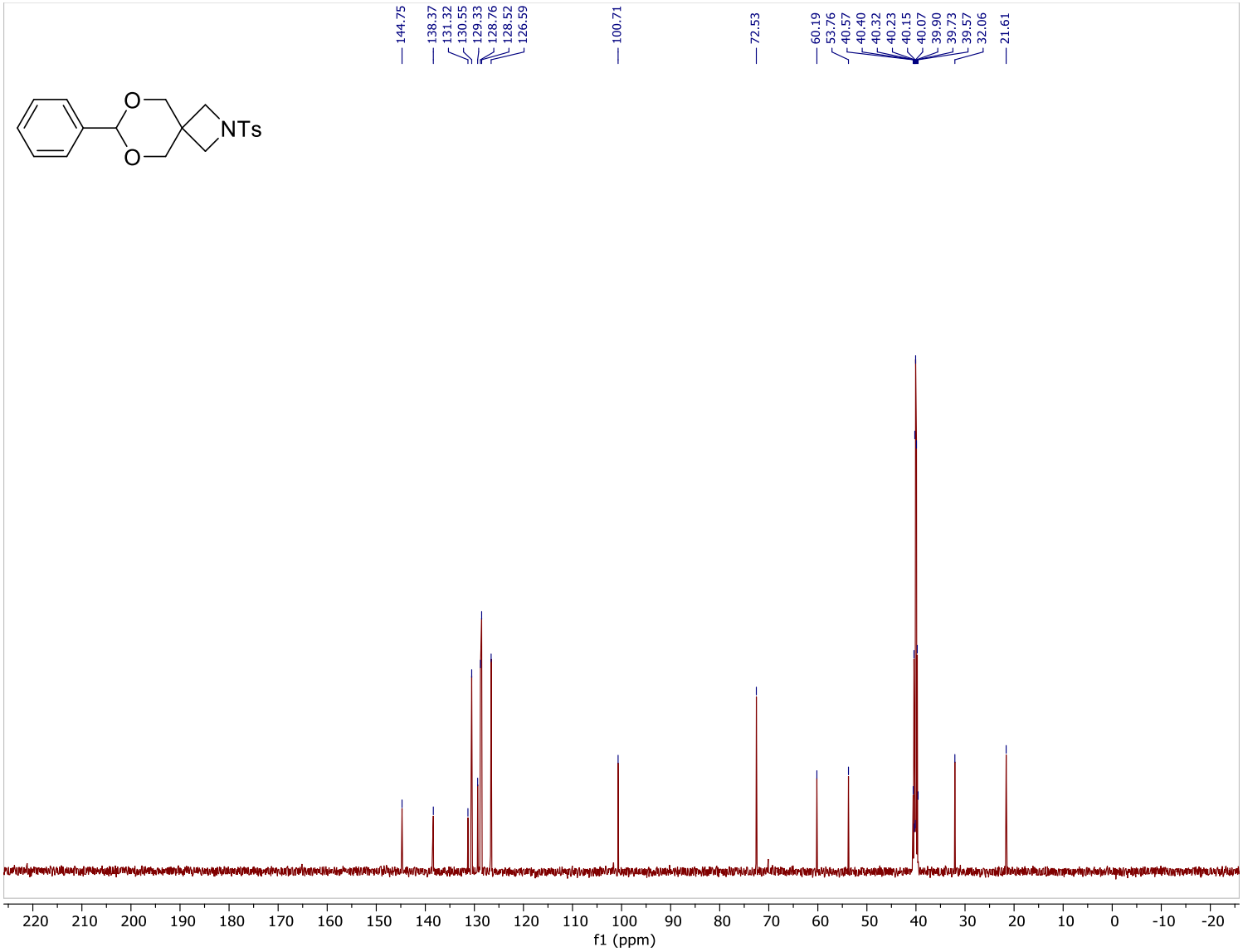
^{13}C NMR (126 MHz, CD_3OD) spectrum of (*R*)-1'-(5'-amino-2'-methylbenzoyl)-*N*-(1''-(naphthalene-1''-yl)ethyl)azetidine-3-caboxamide (51).



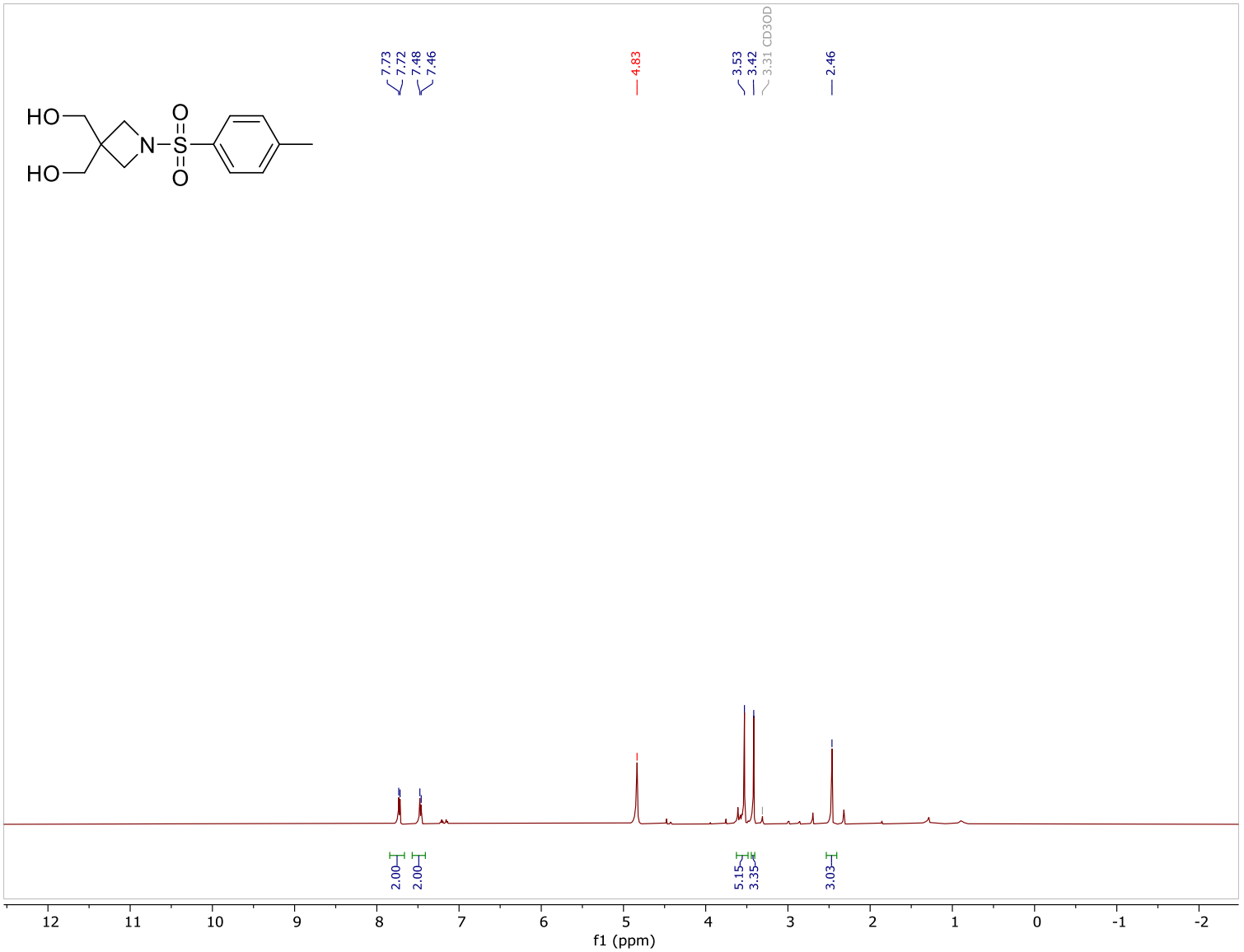
^{1}H NMR (500 MHz, DMSO-*d6*) spectrum of 7-phenyl-2-tosyl-6,8-dioxa-2-azaspiro[3.5]nonane (53).



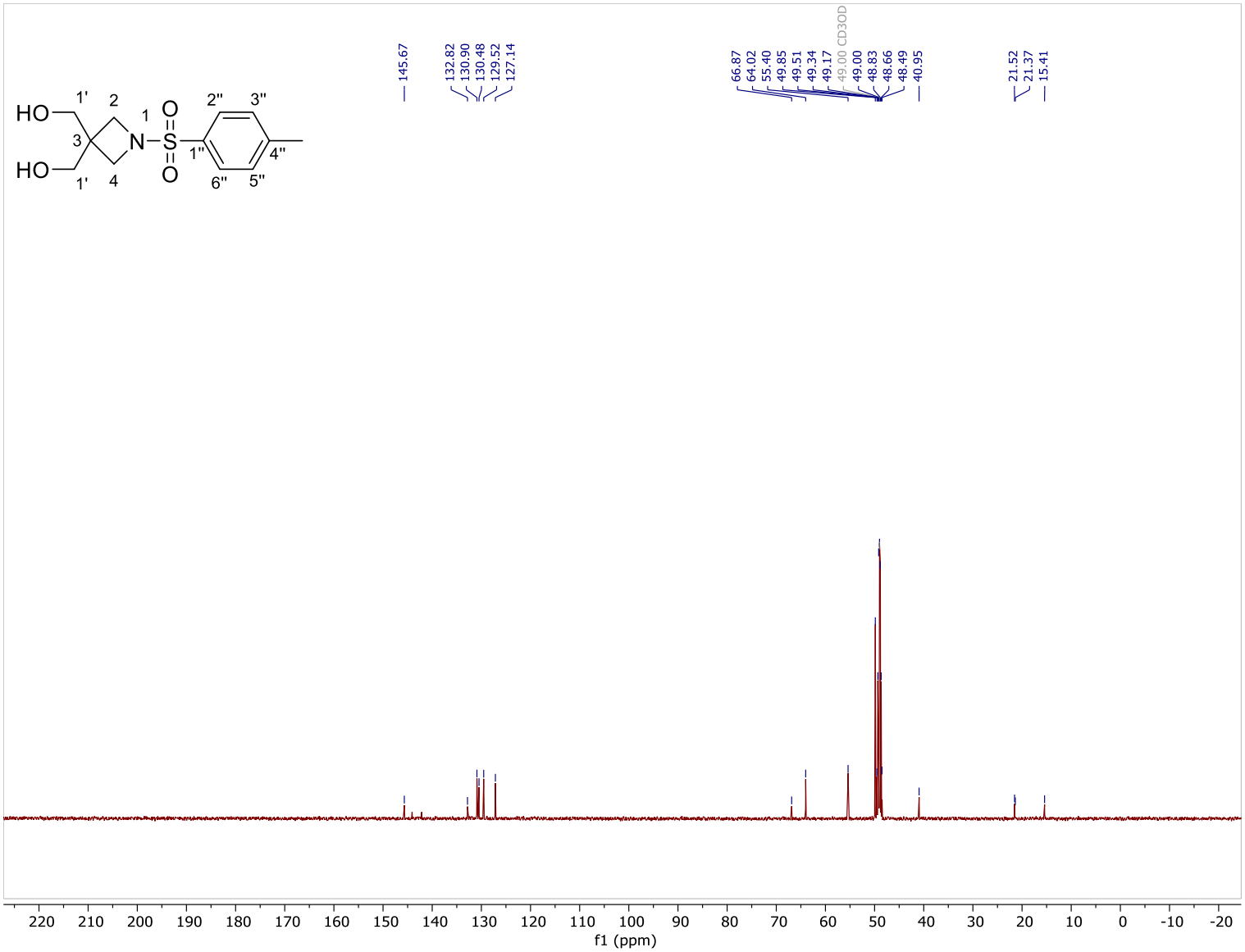
^{13}C NMR (126 MHz, DMSO-*d6*) spectrum of 7-phenyl-2-tosyl-6,8-dioxa-2-azaspiro[3.5]nonane (53).



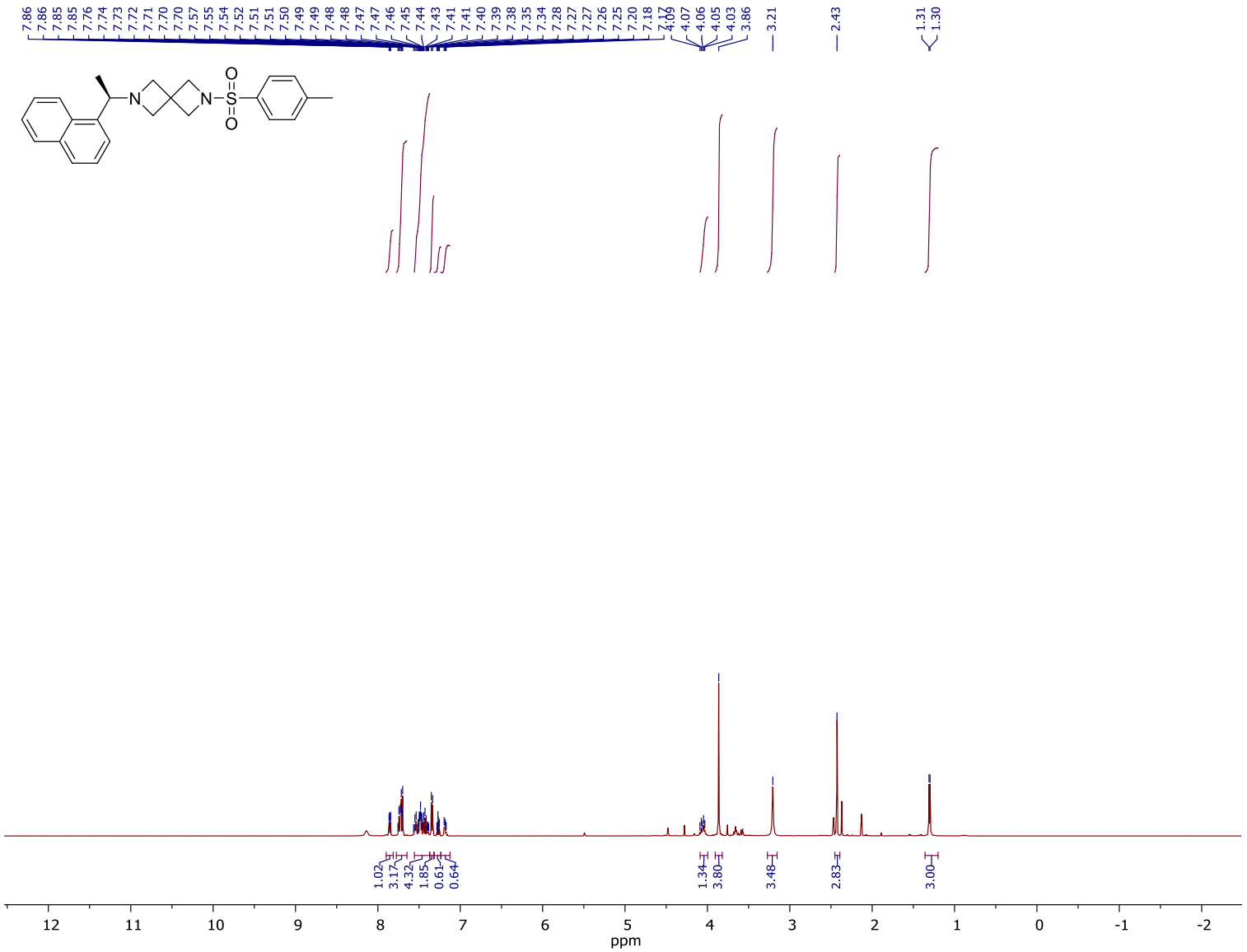
^{1}H NMR (500 MHz, CD_3OD) spectrum of (1-tosylazetidine-3,3-diyl)dimethanol (54).



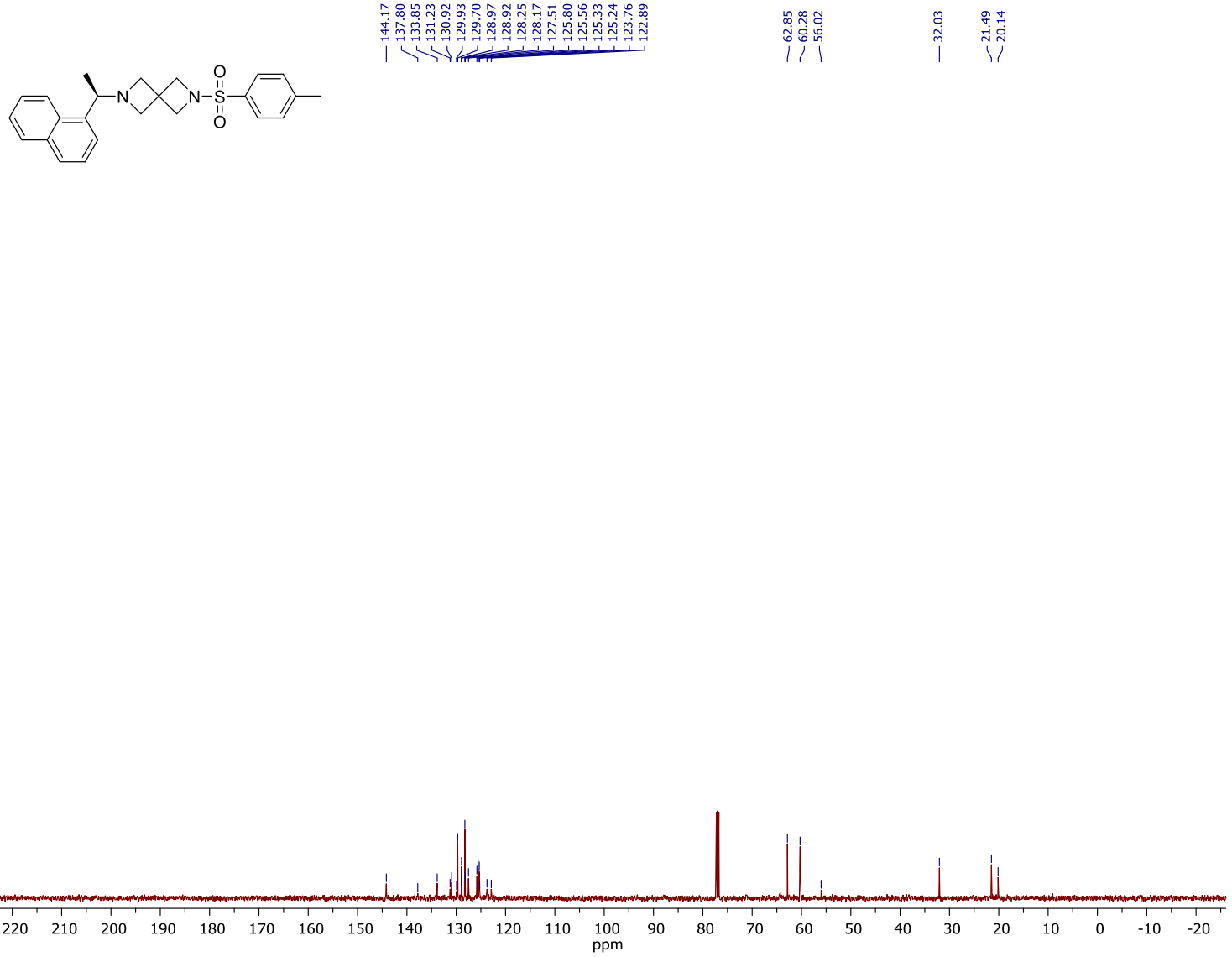
^{13}C NMR (126 MHz, CD_3OD) spectrum of (1-tosylazetidine-3,3-diyl)dimethanol (54).



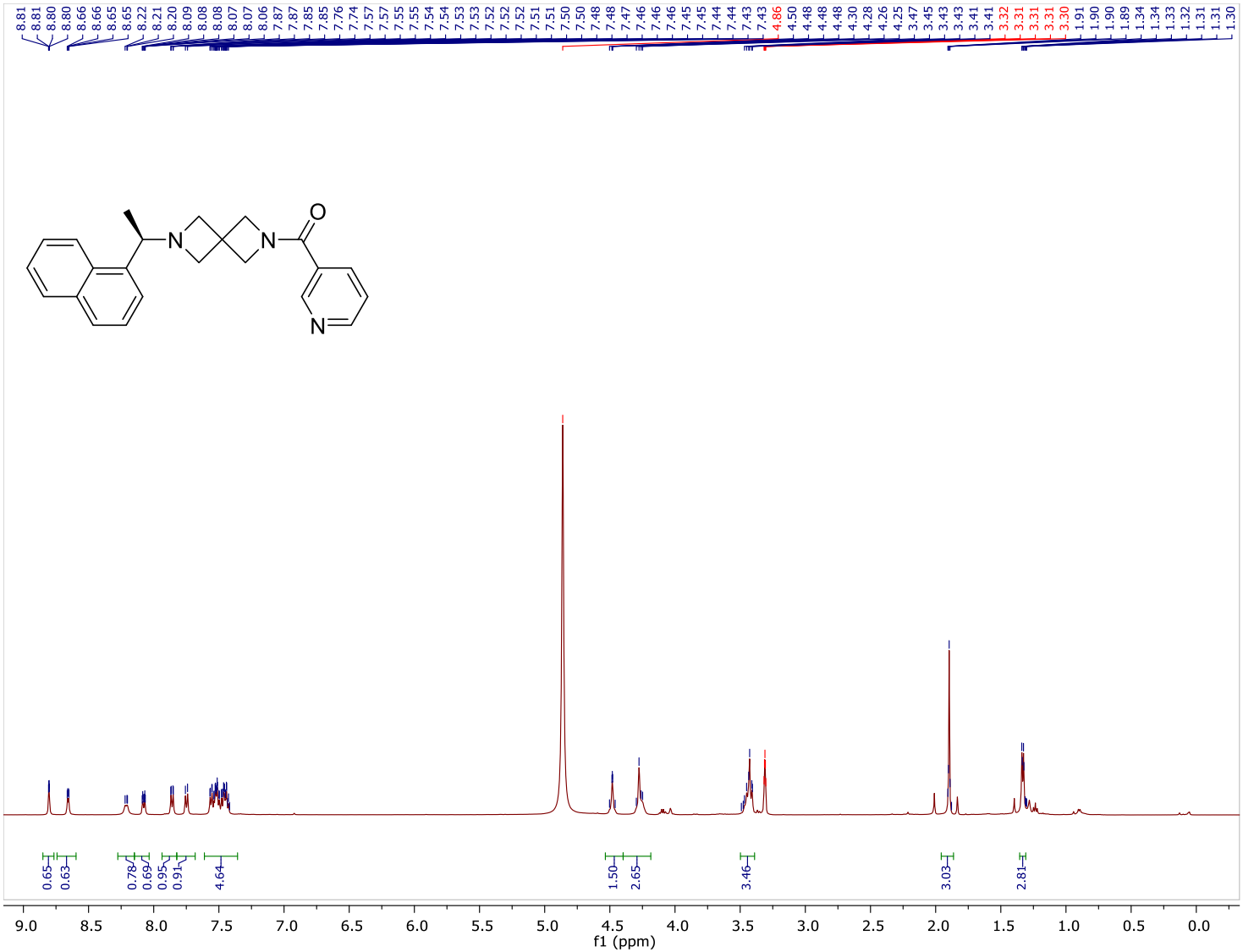
^{1}H NMR (500 MHz, $CDCl_3$) (*R*)-2-(1-(Naphthalen-1-yl)ethyl)-6-tosyl-2,6-diazaspiro[3.3]heptane (55).



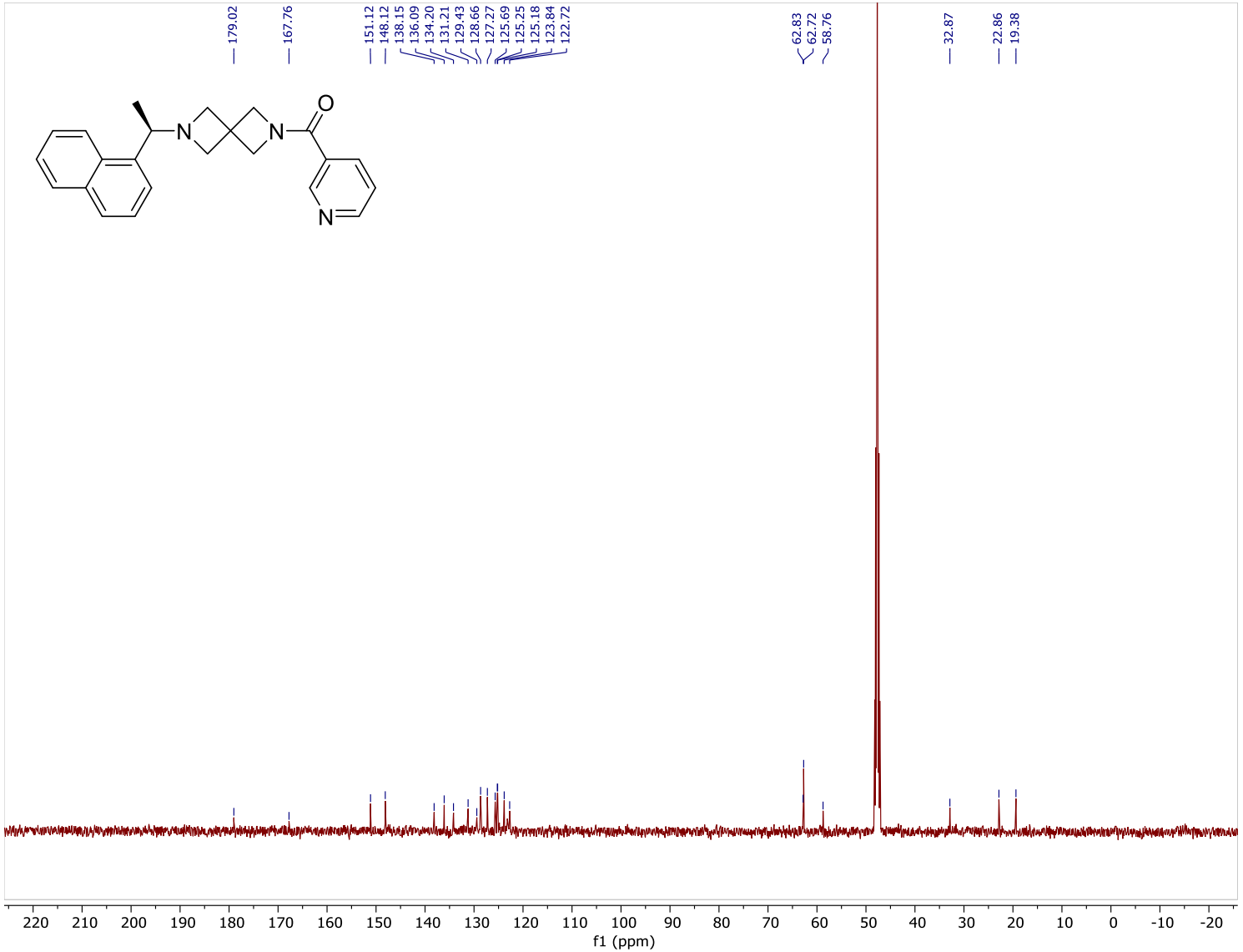
^{13}C NMR (126 MHz, $CDCl_3$) (*R*)-2-(1-(Naphthalen-1-yl)ethyl)-6-tosyl-2,6-diazaspiro[3.3]heptane (55).



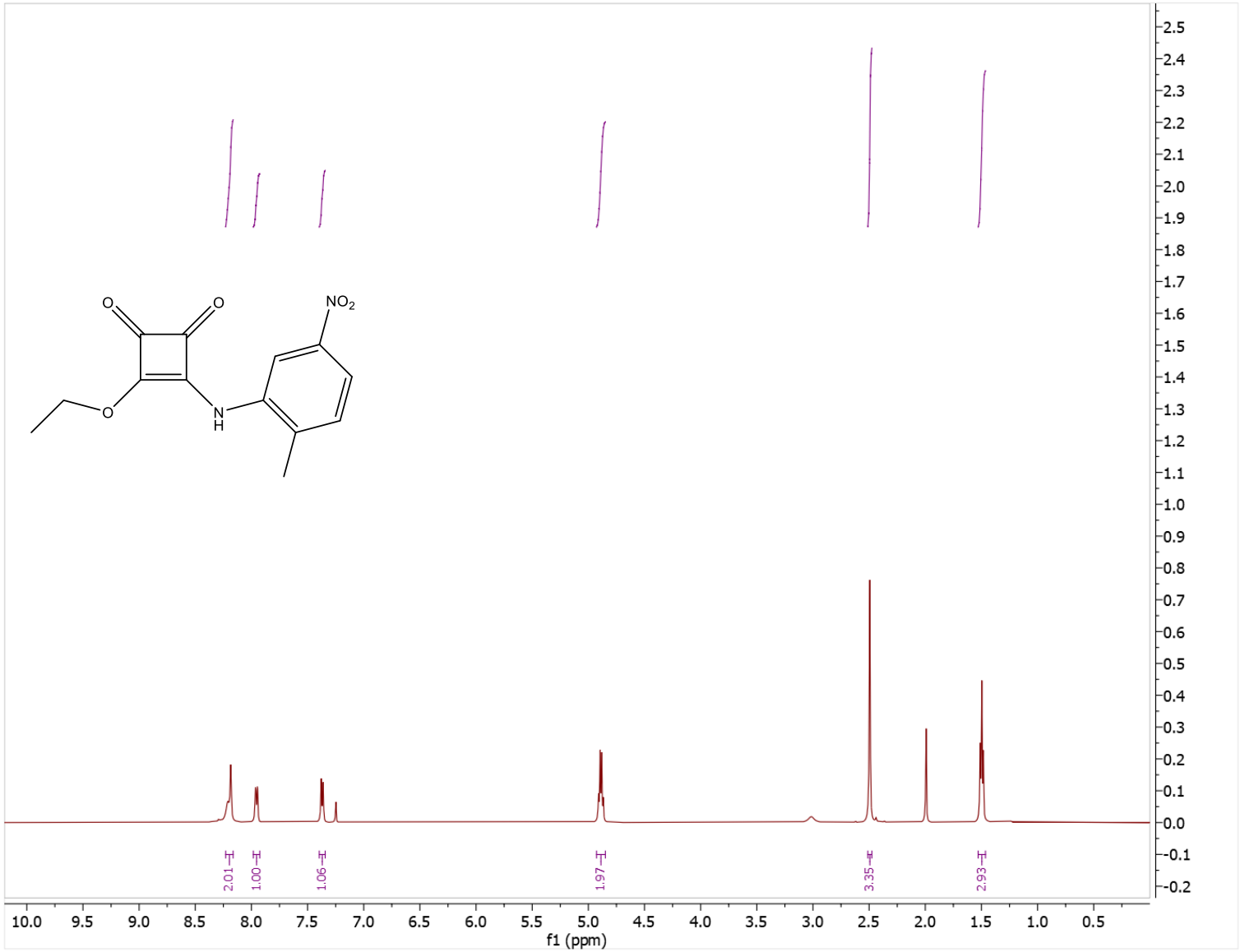
^{1}H NMR (500 MHz, CD_3OD) spectrum of (R)-(6-(1-(naphthalen-1-yl)ethyl)-2,6-diazaspiro[3.3]heptan-2-yl)(pyridin-3-yl)methanone (56).



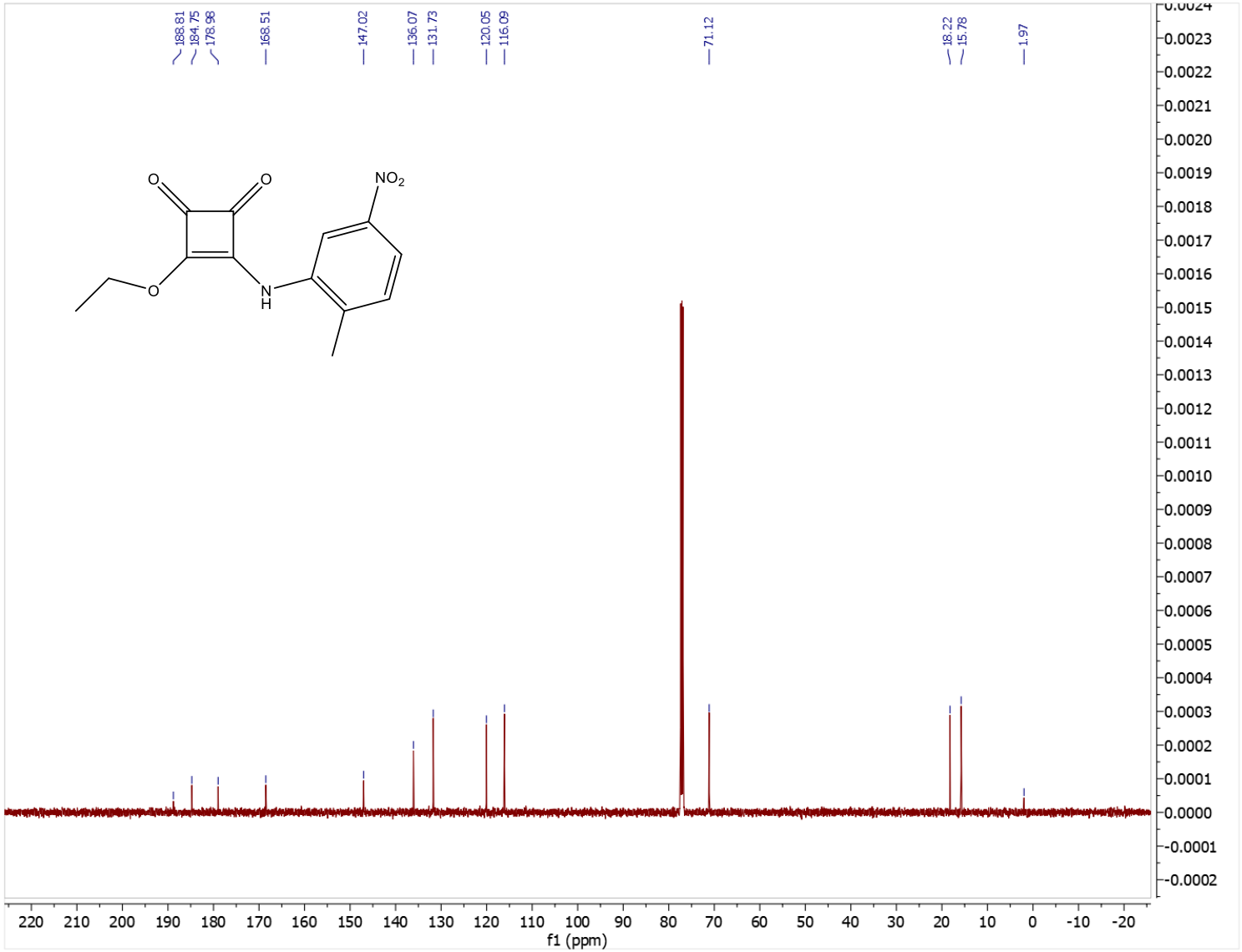
^{13}C NMR (126 MHz, CD_3OD) spectrum of (R)-(6-(1-(naphthalen-1-yl)ethyl)-2,6-diazaspiro[3.3]heptan-2-yl)(pyridin-3-yl)methanone (56).



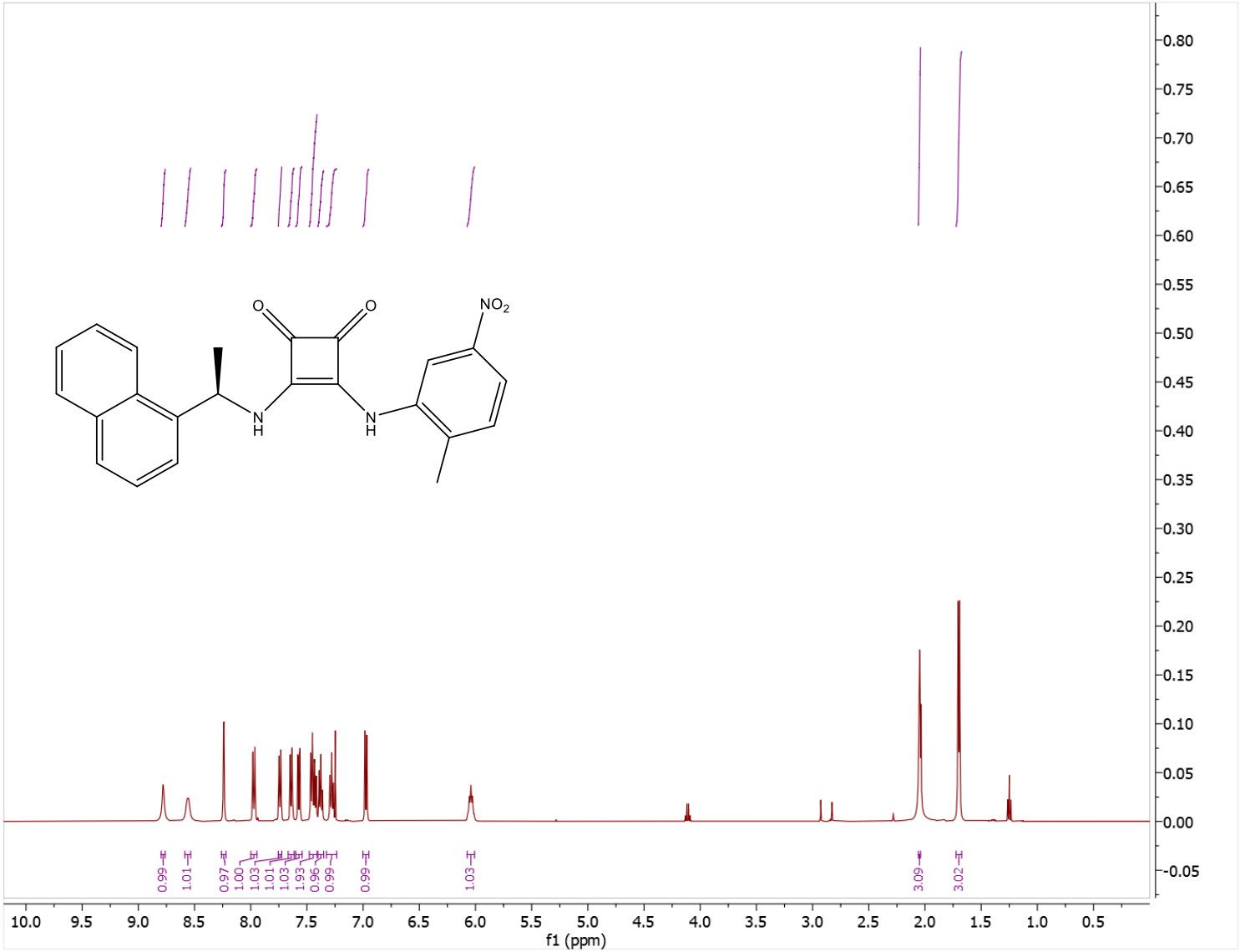
^{1}H NMR (500 MHz, $CDCl_3$) spectrum of 3-ethoxy-4-((2-methyl-5-nitrophenyl)amino)cyclobut-3-ene-1,2-dione (57).



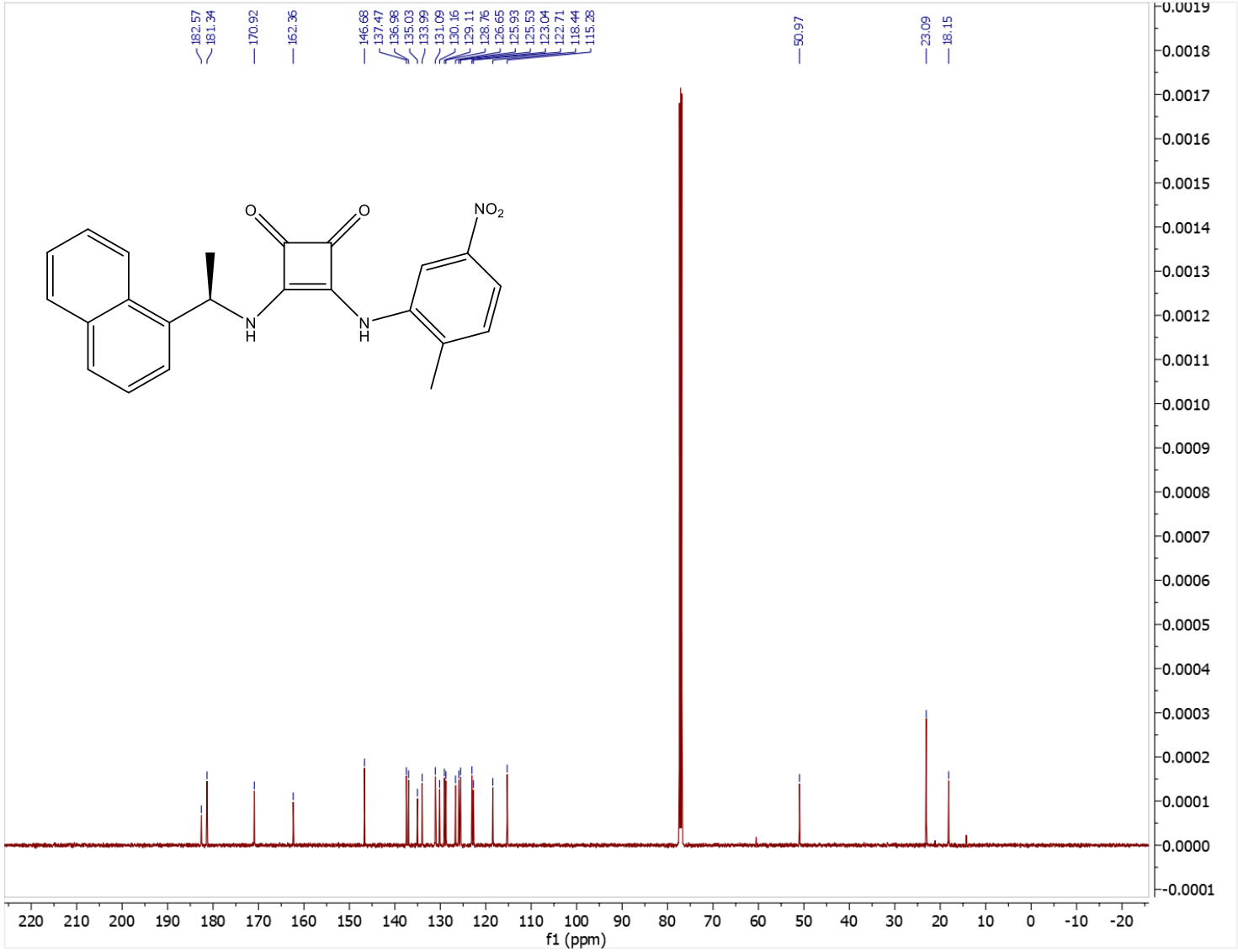
^{13}C NMR (126 MHz, $CDCl_3$) spectrum of 3-ethoxy-4-((2-methyl-5-nitrophenyl)amino)cyclobut-3-ene-1,2-dione (57).



^{1}H NMR (500 MHz, $CDCl_3$) spectrum of (*R*)-3-((2-methyl-5-nitrophenyl)amino)-4-((1-(naphthalen-1-yl)ethyl)amino)cyclobut-3-ene-1,2-dione (58).

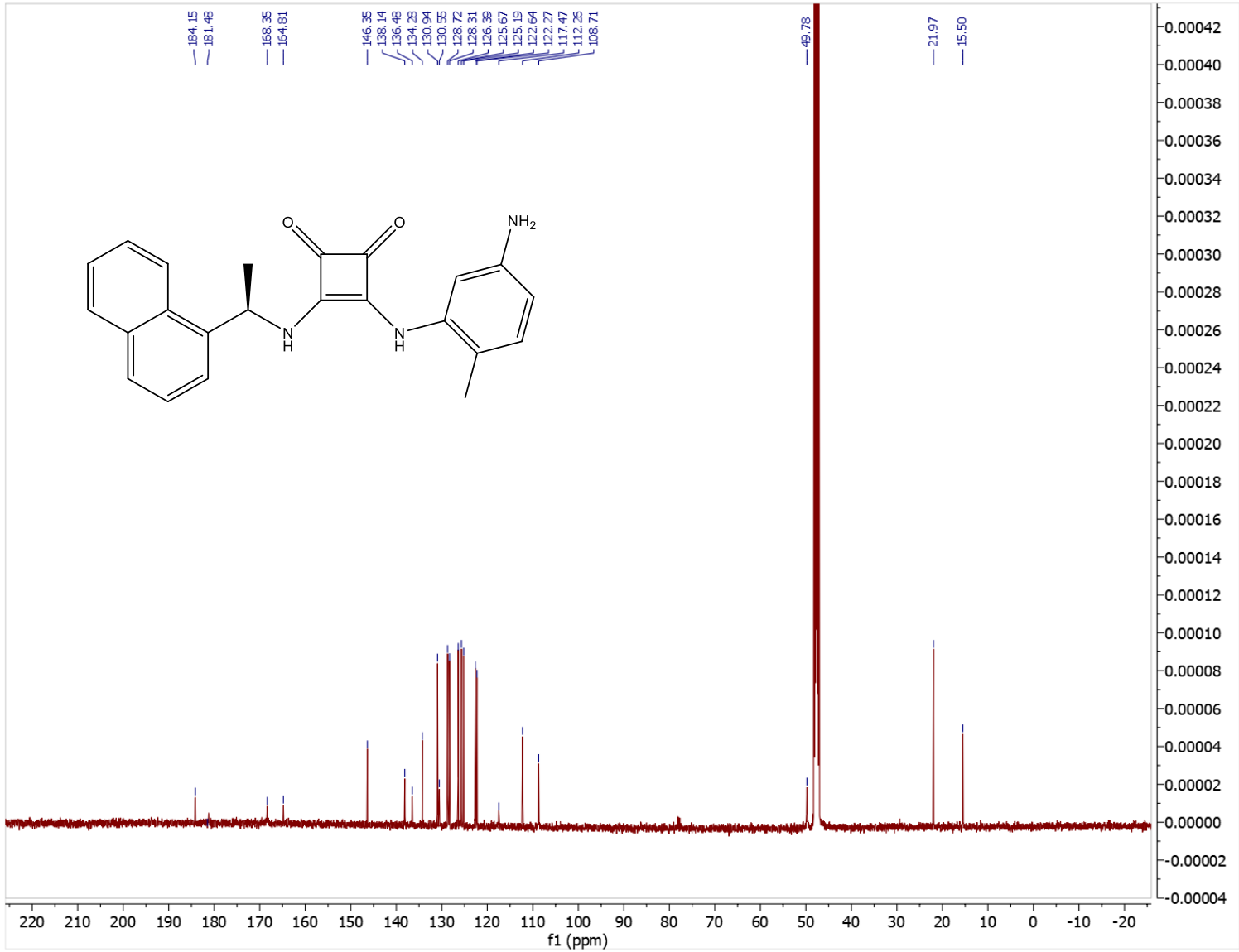


^{13}C NMR (126 MHz, $CDCl_3$) spectrum of (*R*)-3-((2-methyl-5-nitrophenyl)amino)-4-((1-(naphthalen-1-yl)ethyl)amino)cyclobut-3-ene-1,2-dione (58).

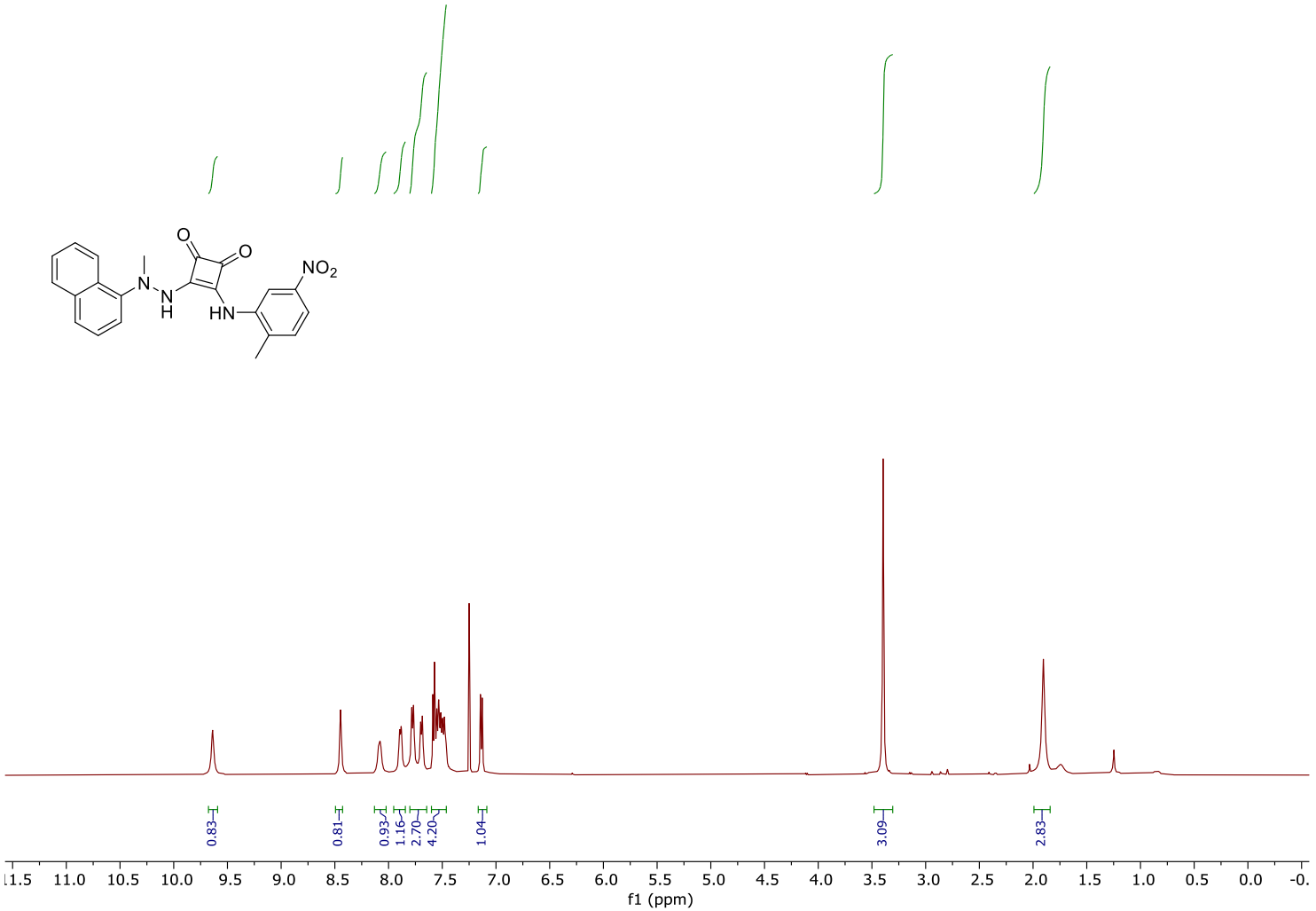


^{1}H NMR (500 MHz, CD_3OD) spectrum of (*R*)-3-((5-amino-2-methylphenyl)amino)-4-((1-(naphthalen-1-yl)ethyl)amino)cyclobut-3-ene-1,2-dione (59).

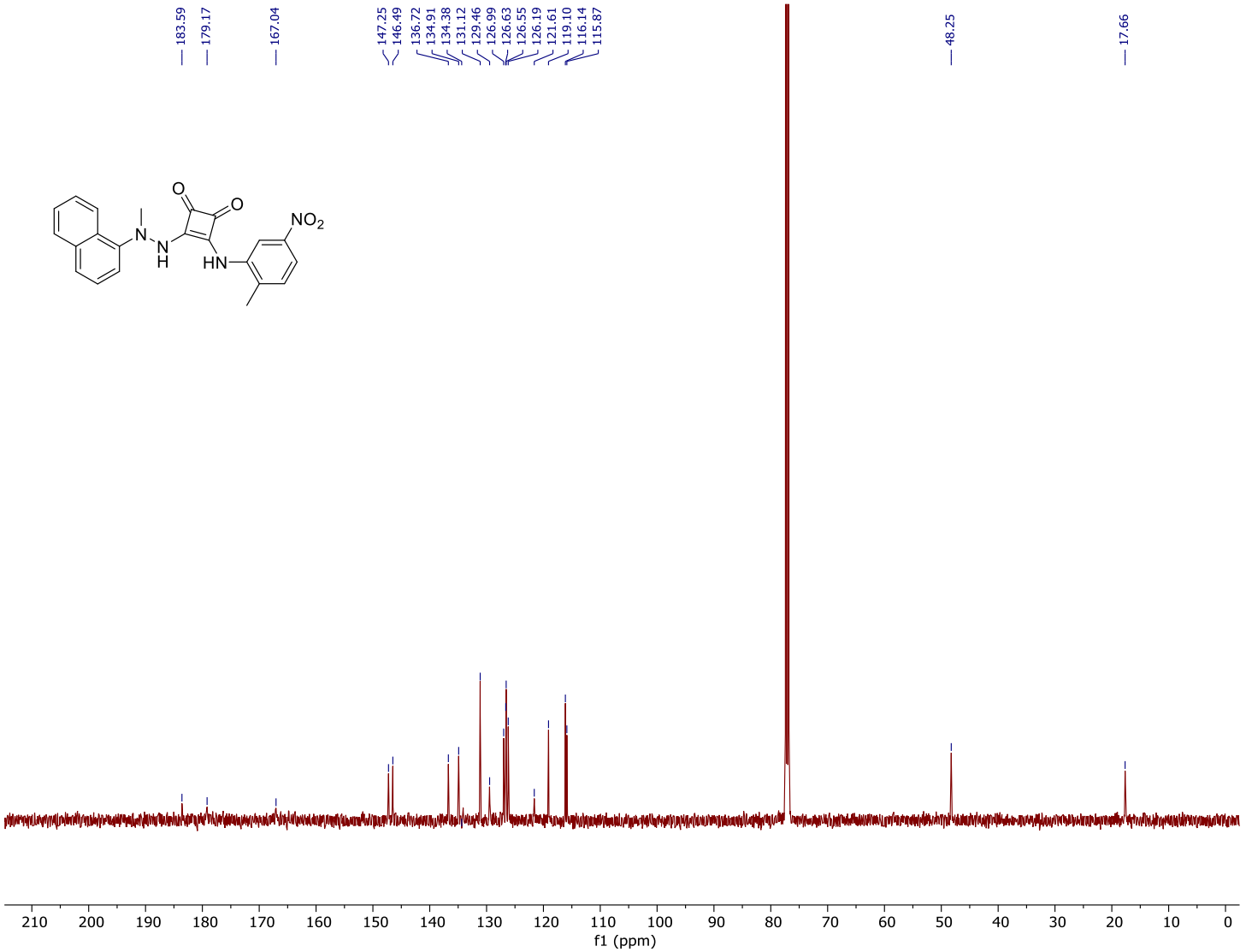
^{13}C NMR (126 MHz, CD_3OD) spectrum of (*R*)-3-((5-amino-2-methylphenyl)amino)-4-((1-(naphthalen-1-yl)ethyl)amino)cyclobut-3-ene-1,2-dione (59).



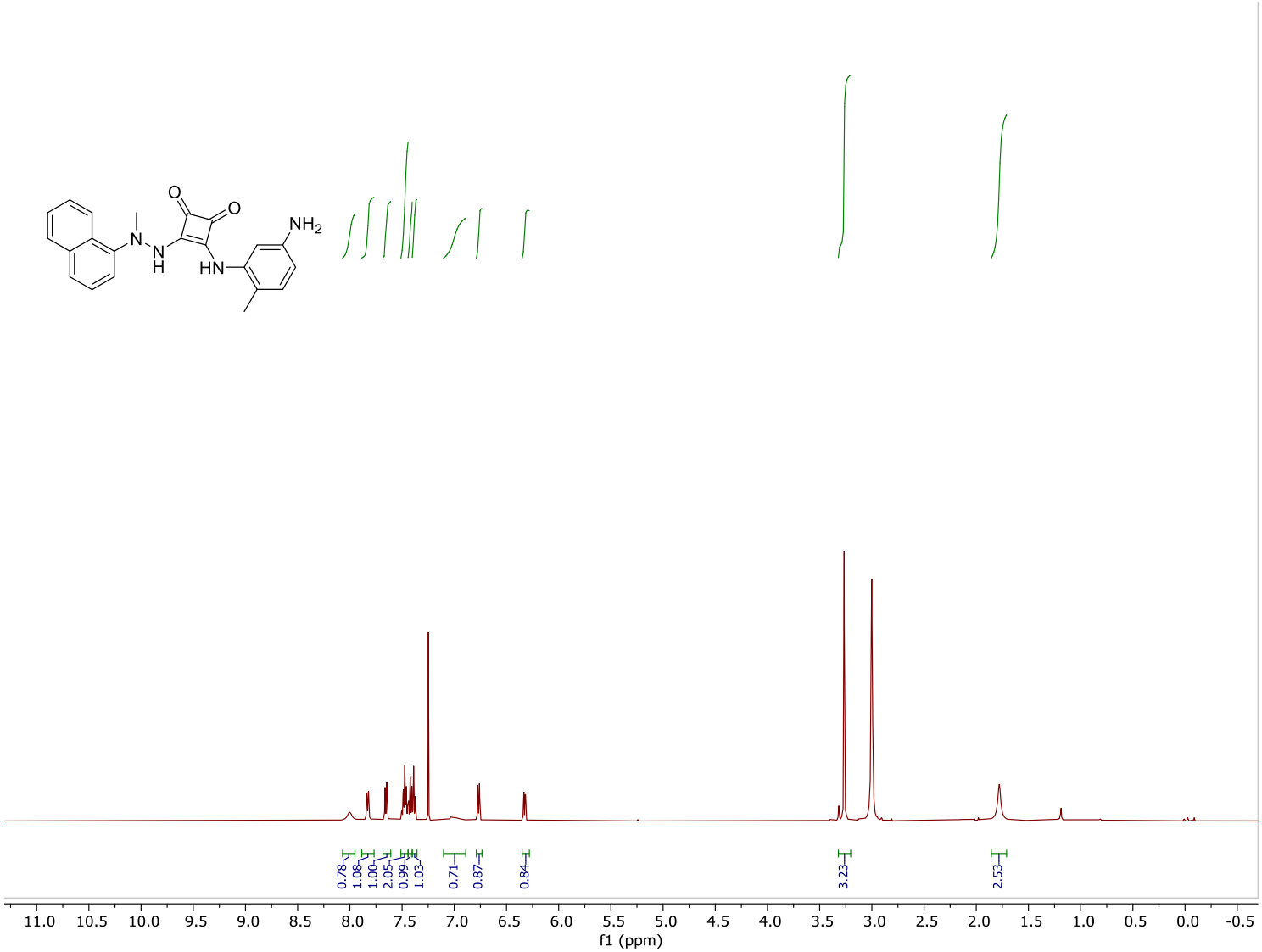
^{1}H NMR (500 MHz, $CDCl_3$) spectrum of 3-[*N*'-(Naphthalen-1-yl)-*N*'-methylhydrazinyl]-4-[(2-methyl-5-nitrophenyl)amino]cyclobut-3-ene-1,2-dione (60).



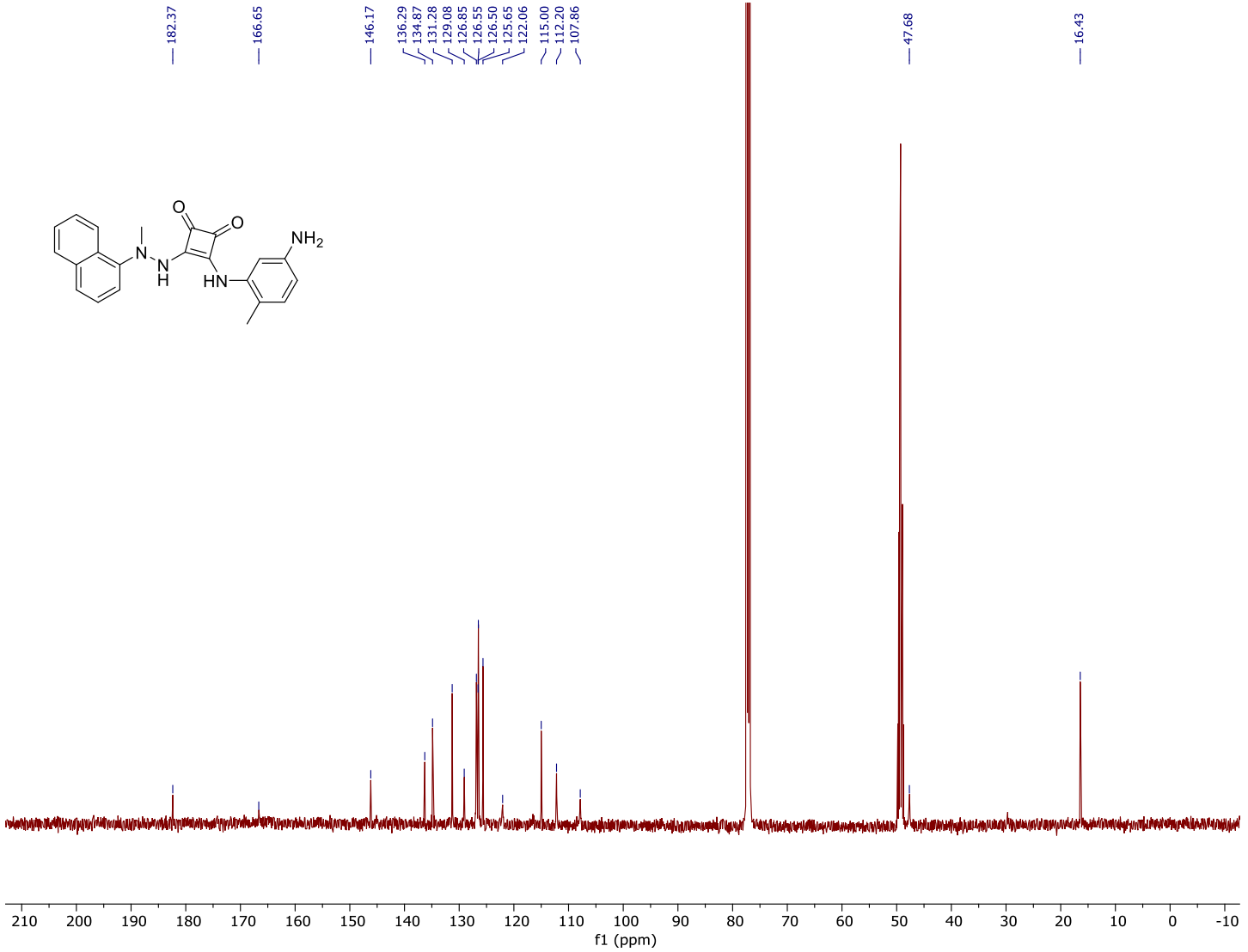
^{13}C NMR (126 MHz, $CDCl_3$) spectrum of 3-[*N*'-(Naphthalen-1-yl)-*N*'-methylhydrazinyl]-4-[(2-methyl-5-nitrophenyl)amino]cyclobut-3-ene-1,2-dione (60).



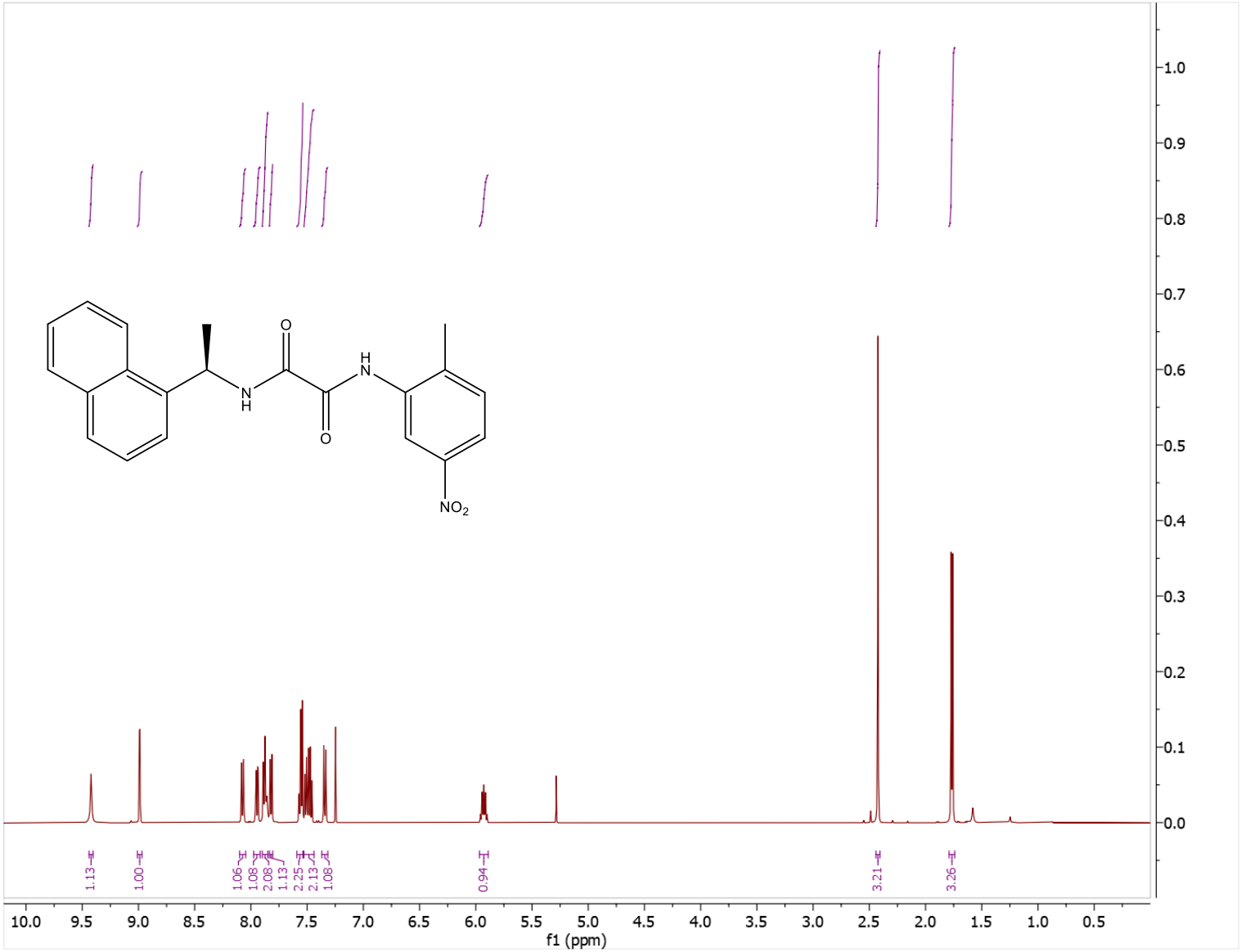
^{1}H NMR (500 MHz, $CDCl_3$ + CD_3OD) spectrum of 3-[*N*'-(Naphthalen-1-yl)-*N*'-methylhydrazinyl]-4-[(5-amino-2-methylphenyl)amino]cyclobut-3-ene-1,2-dione (61).



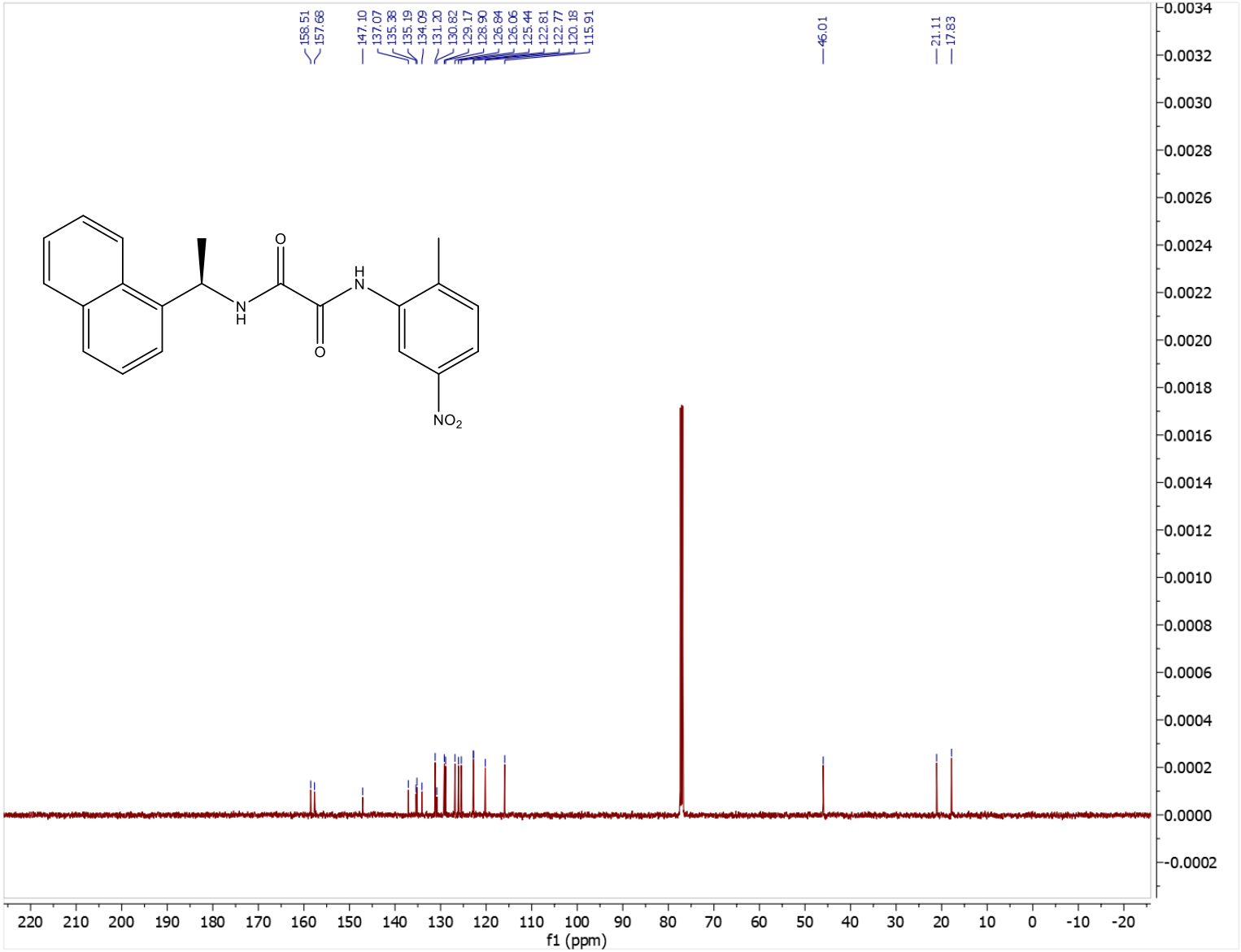
^{13}C NMR (126 MHz, $CDCl_3$ + CD_3OD) spectrum of 3-[*N*'-(Naphthalen-1-yl)-*N*'-methylhydrazinyl]-4-[(5-amino-2-methylphenyl)amino]cyclobut-3-ene-1,2-dione (61).



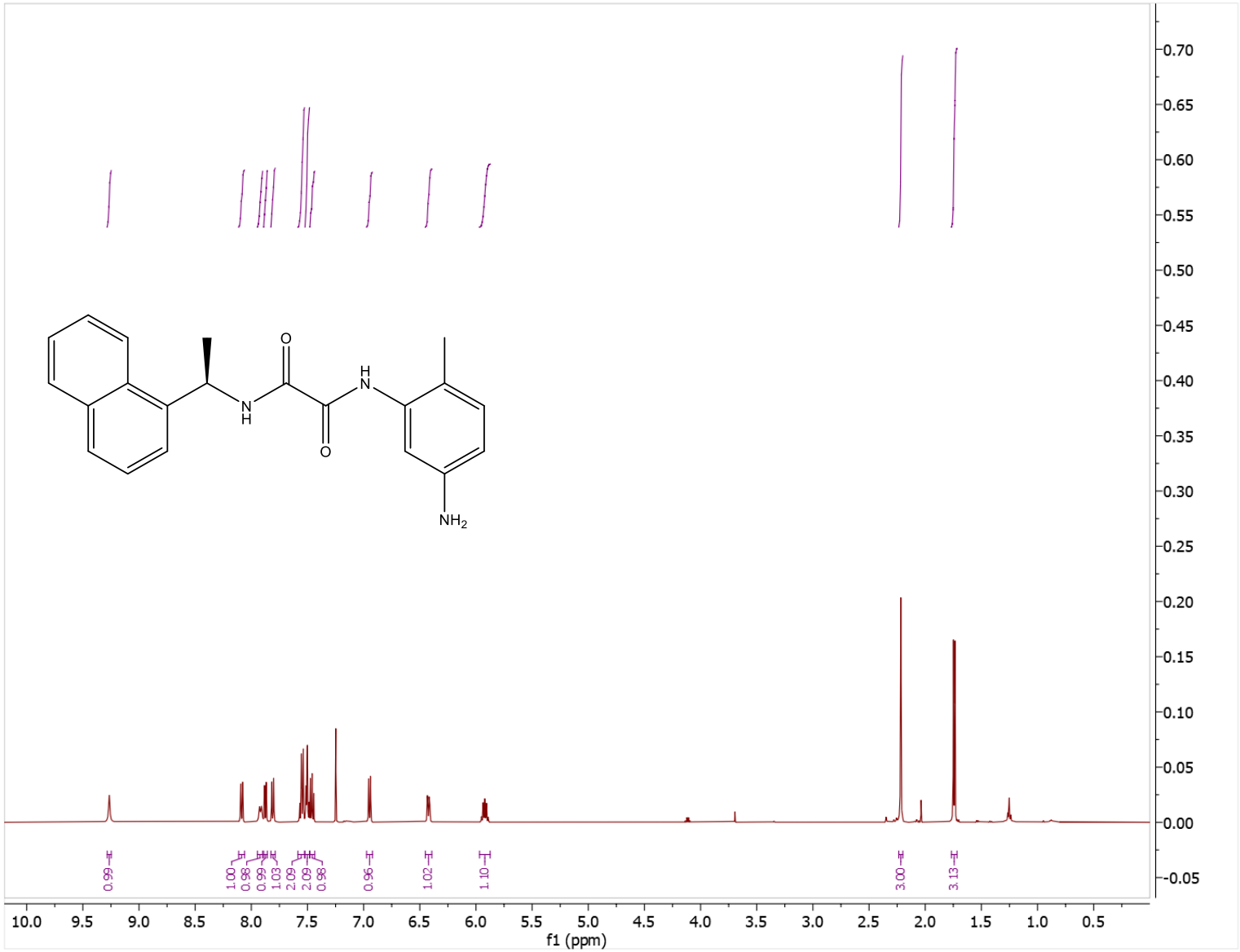
^{1}H NMR (500 MHz, $CDCl_3$) spectrum of (*R*)-N^1-(2-methyl-5-nitrophenyl)-N^2-(1-(naphthalen-1-yl)ethyl)oxalamide (62).



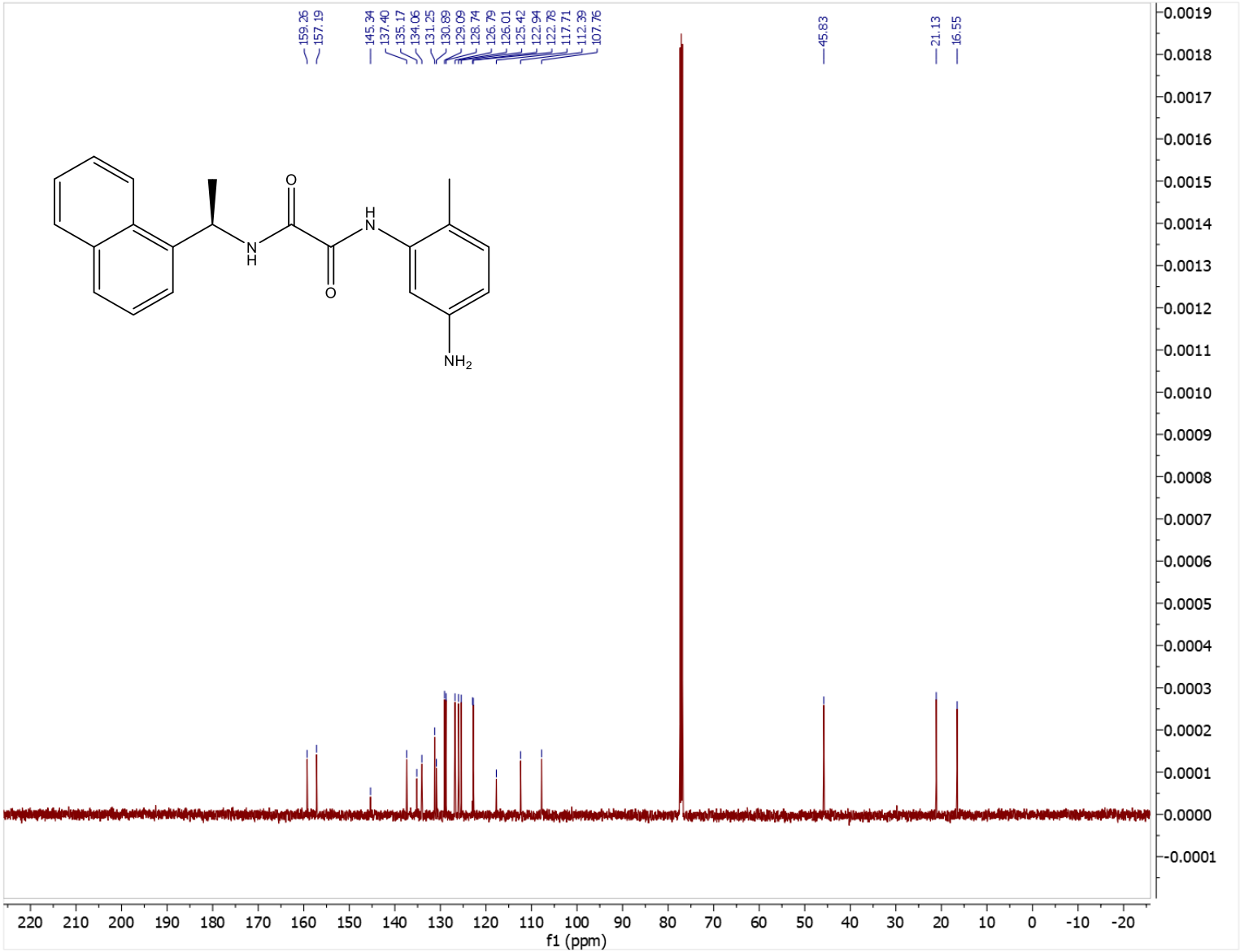
^{13}C NMR (126 MHz, $CDCl_3$) spectrum of (*R*)-*N*^{1}-(2-methyl-5-nitrophenyl)-*N*^{2}-(1-(naphthalen-1-yl)ethyl)oxalamide (62).



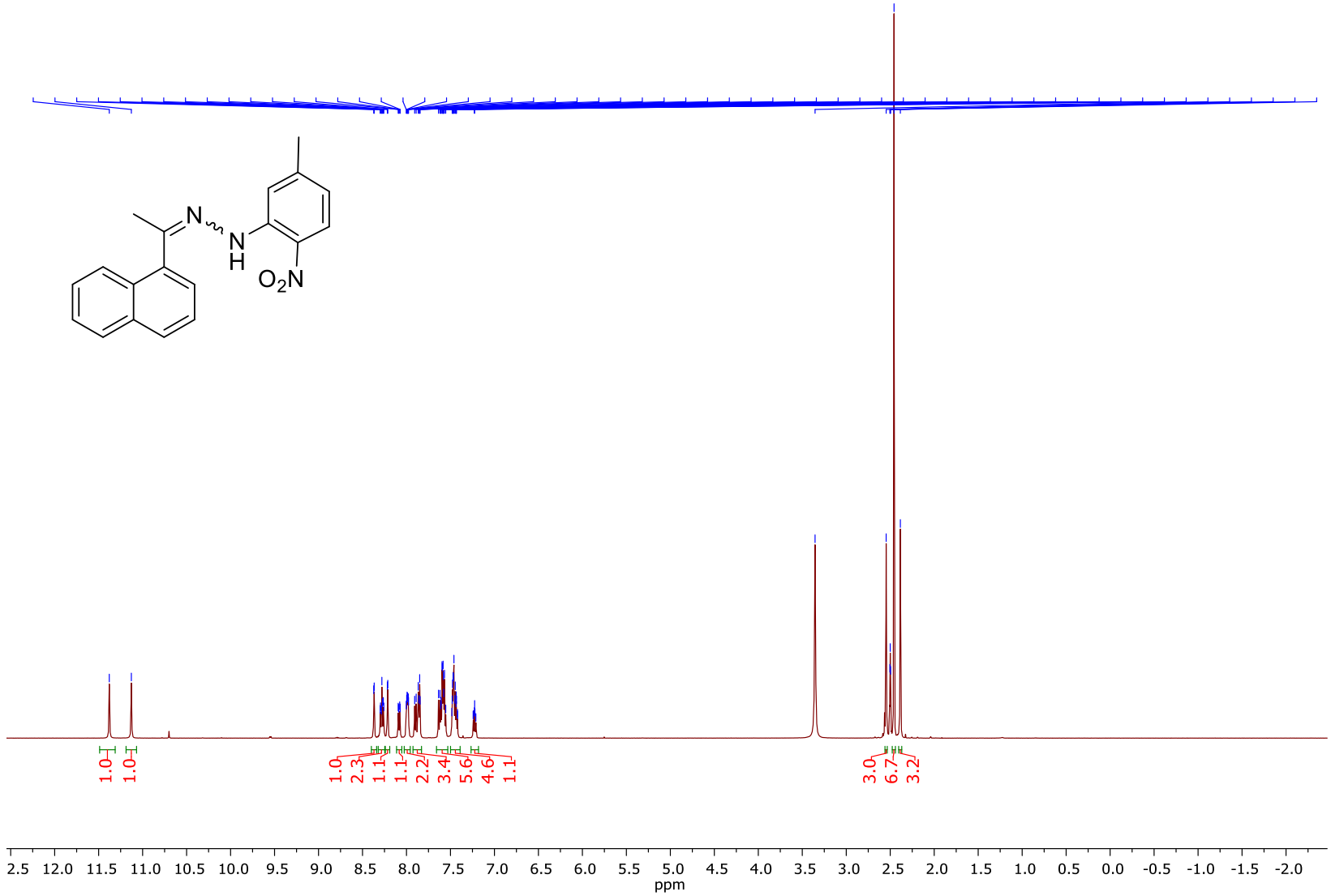
^{1}H NMR (500 MHz, $CDCl_3$) spectrum of (*R*)-N^1-(5-amino-2-methylphenyl)-N^2-(1-(naphthalen-1-yl)ethyl)oxalamide (63).



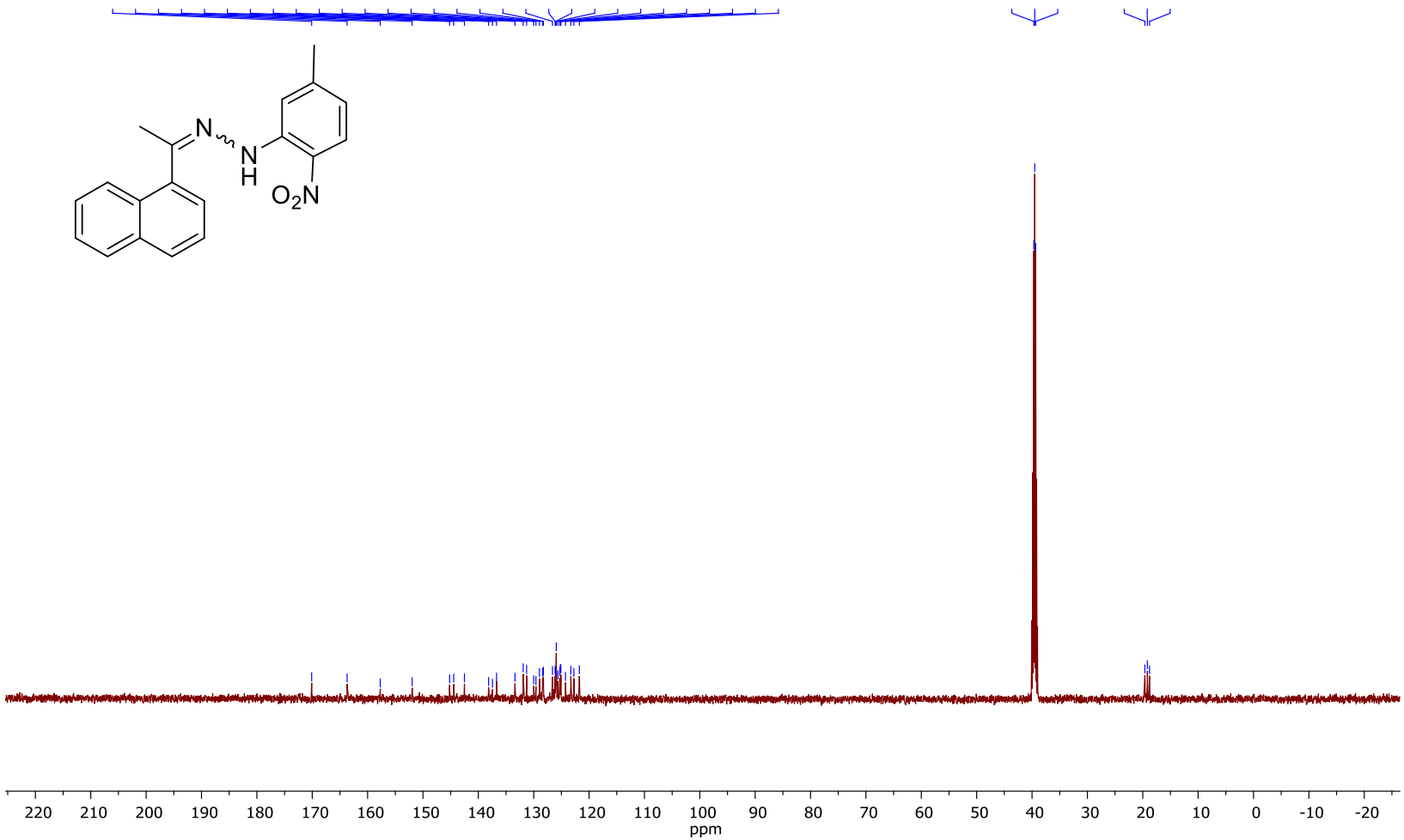
^{13}C NMR (126 MHz, $CDCl_3$) spectrum of (*R*)-*N*^{1}-(5-amino-2-methylphenyl)-*N*^{2}-(1-(naphthalen-1-yl)ethyl)oxalamide (63).



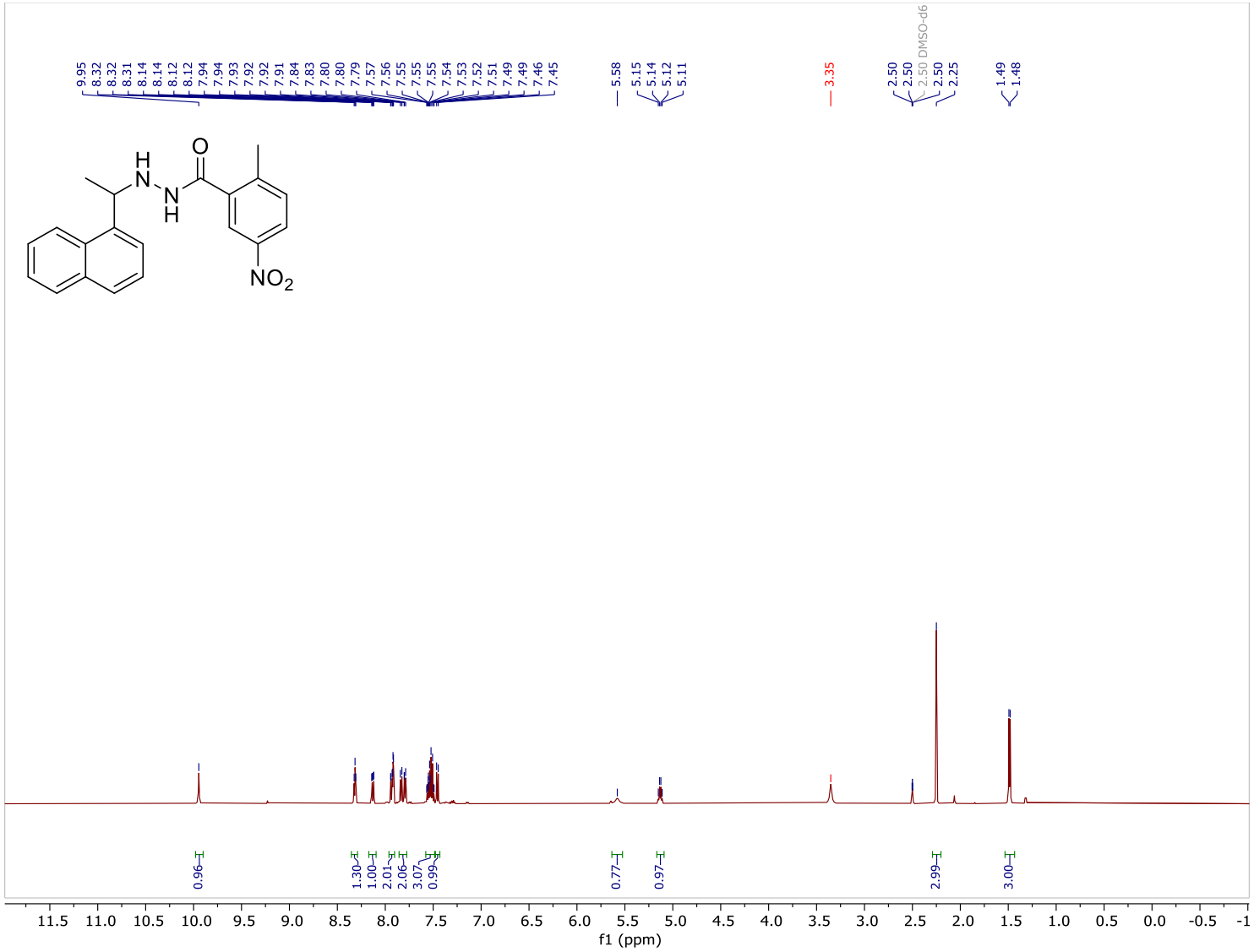
^{1}H (500 MHz, DMSO-*d6*) spectrum of (*Z*)-2-methyl-*N*′-(1-(naphthalen-1-yl)ethylidene)-5-nitrobenzohydrazide (65).



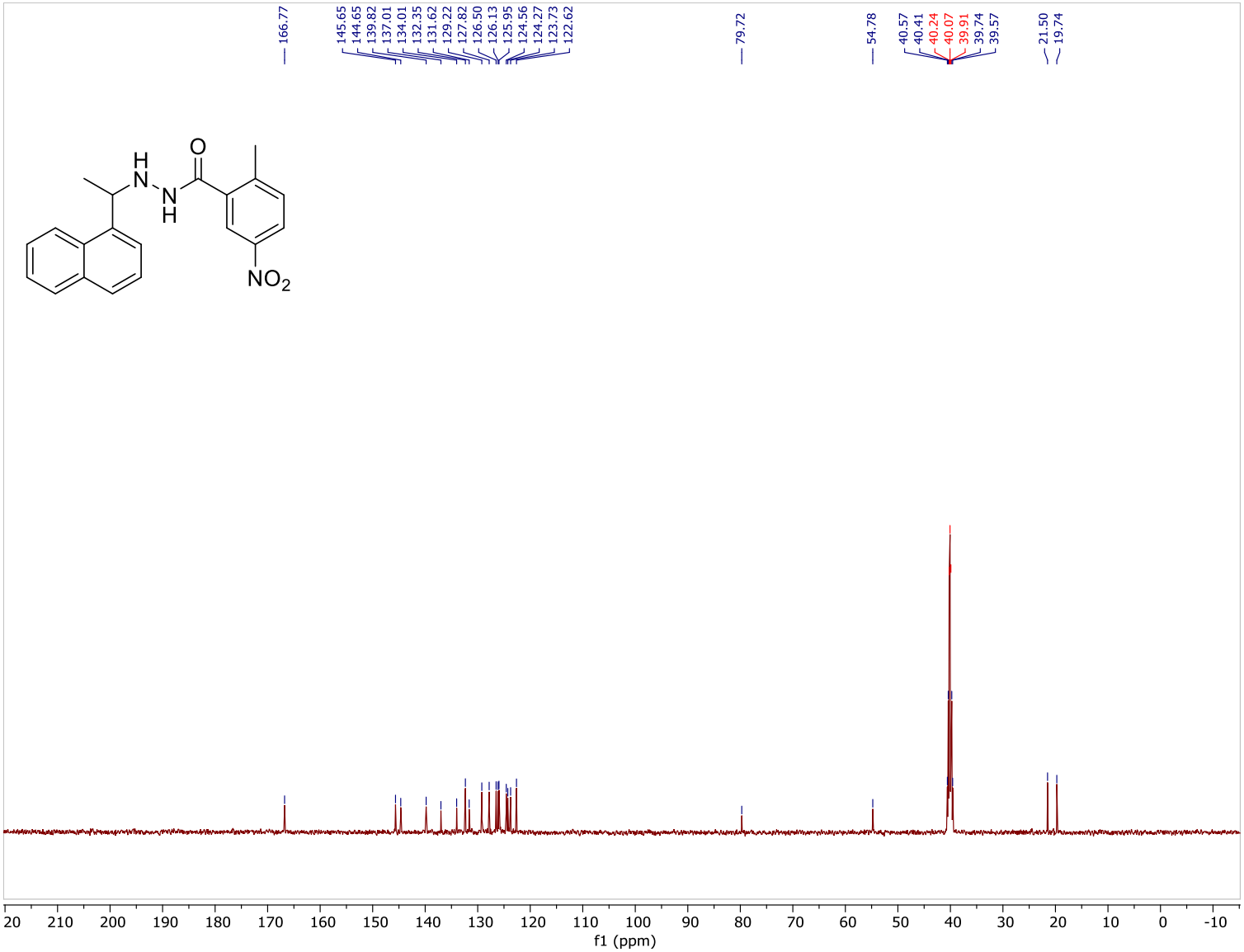
^{13}C (126 MHz, DMSO-*d6*) spectrum of (*Z*)-2-methyl-*N'*-(1-(naphthalen-1-yl)ethylidene)-5-nitrobenzohydrazide (65).



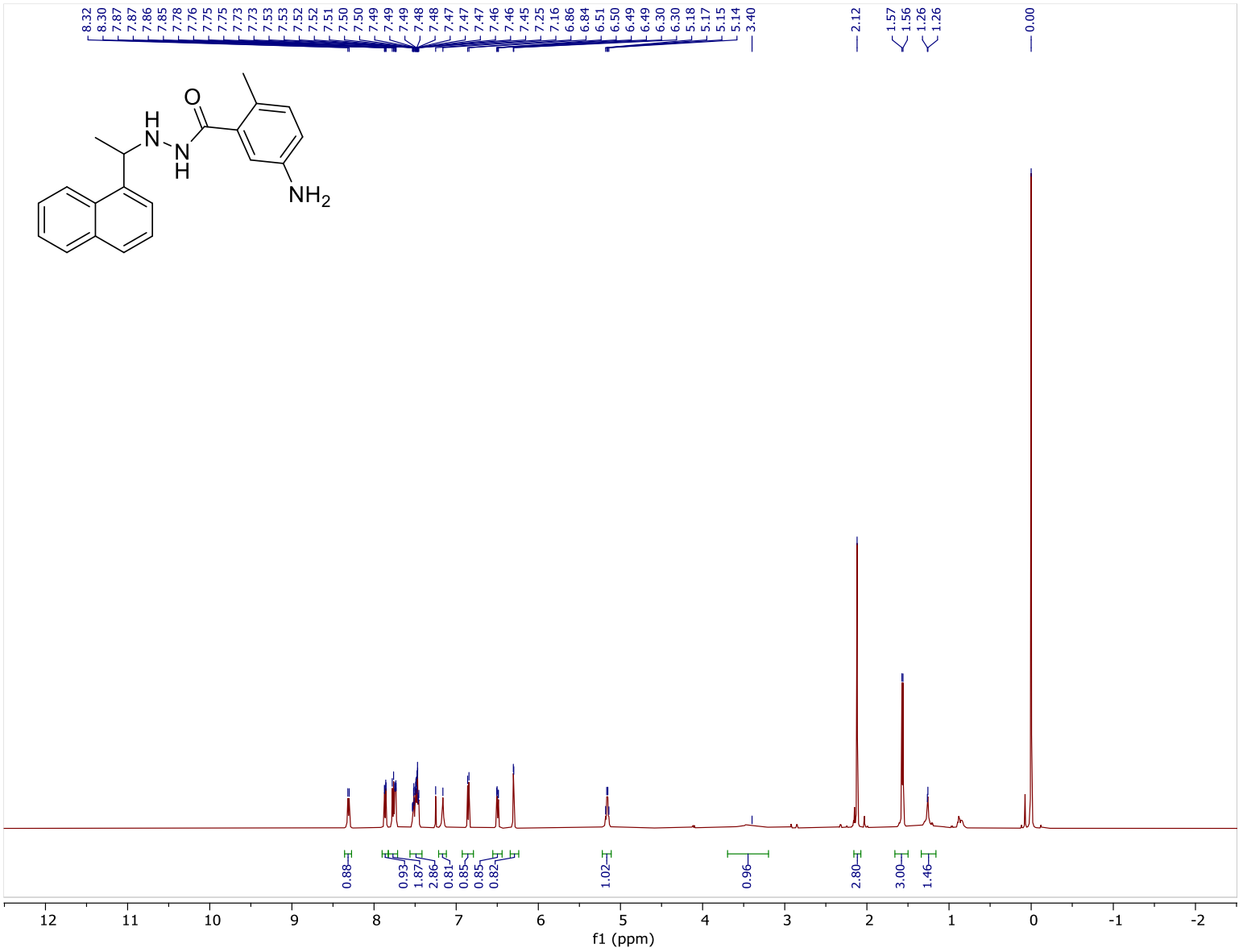
^{1}H NMR (500 MHz, DMSO-*d6*) spectrum of 5-amino-2-methyl-N'-(1-(naphthalen-1-yl)ethyl)benzohydrazide (66).



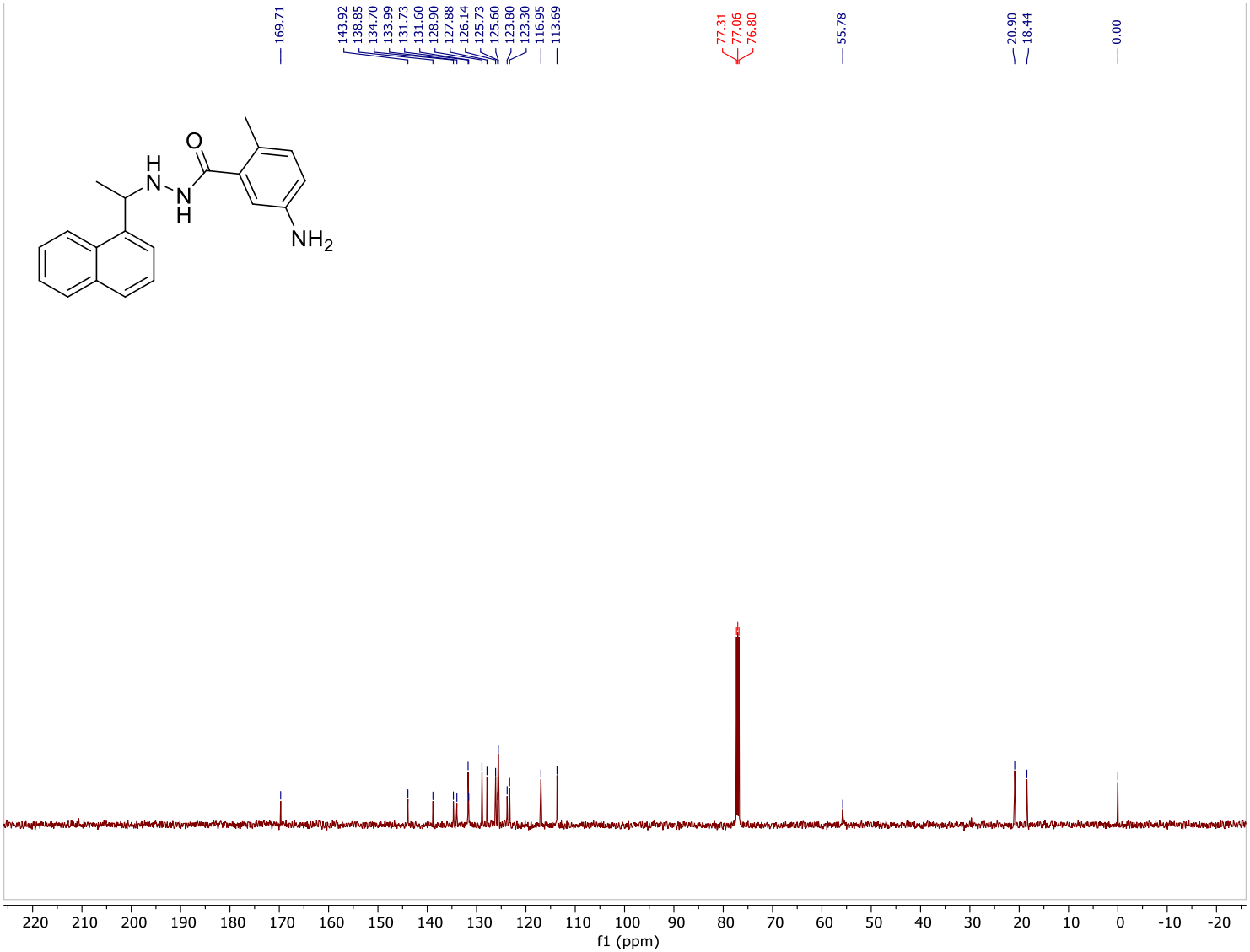
^{13}C NMR (126 MHz, DMSO-*d6*) spectrum of 5-amino-2-methyl-N'-(1-(naphthalen-1-yl)ethyl)benzohydrazide (66).



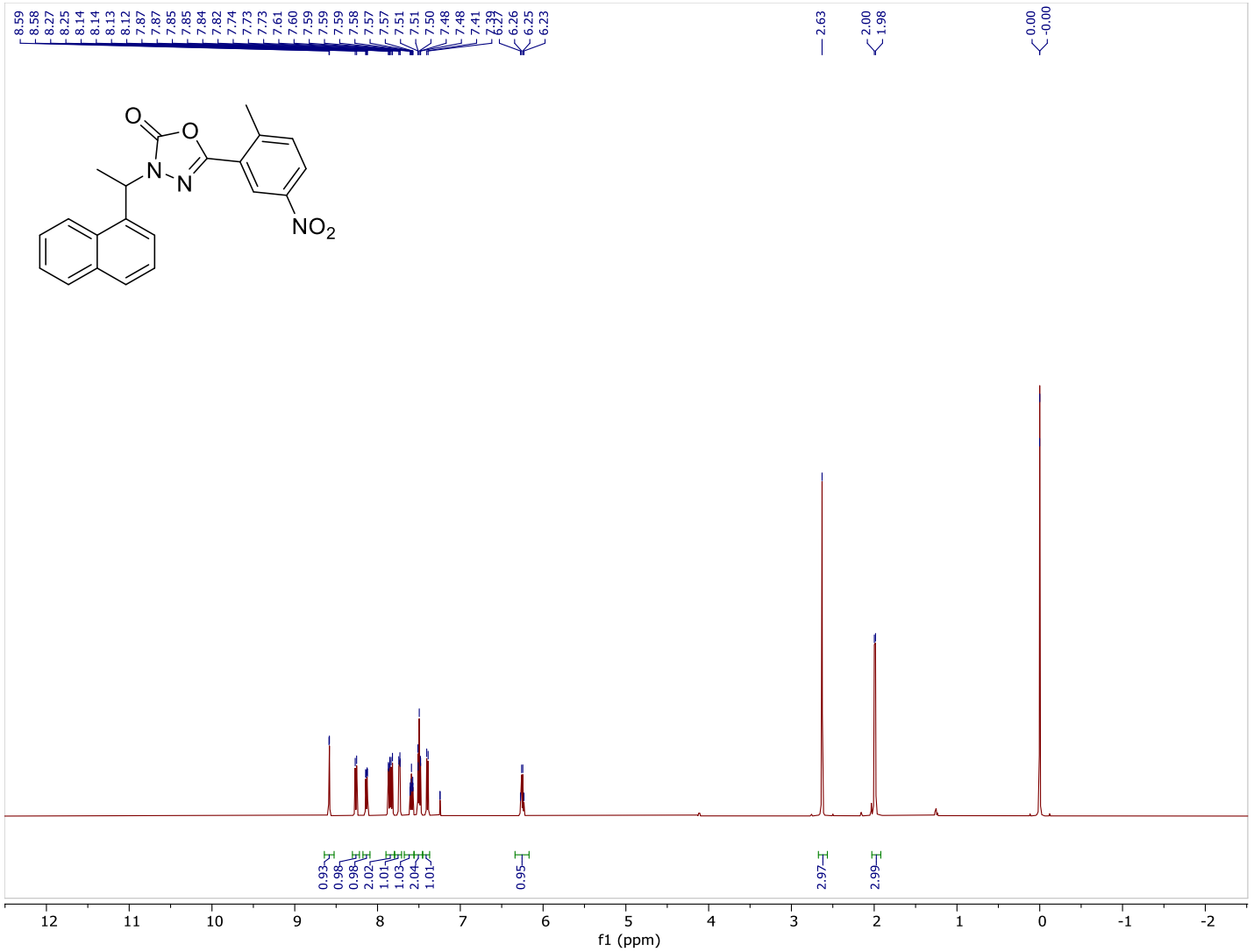
^{1}H NMR (500 MHz, $CDCl_3$ + 1% (v/v) TMS) spectrum of 5-amino-2-methyl-N'-(1-(naphthalen-1-yl)ethyl)benzohydrazide (67).



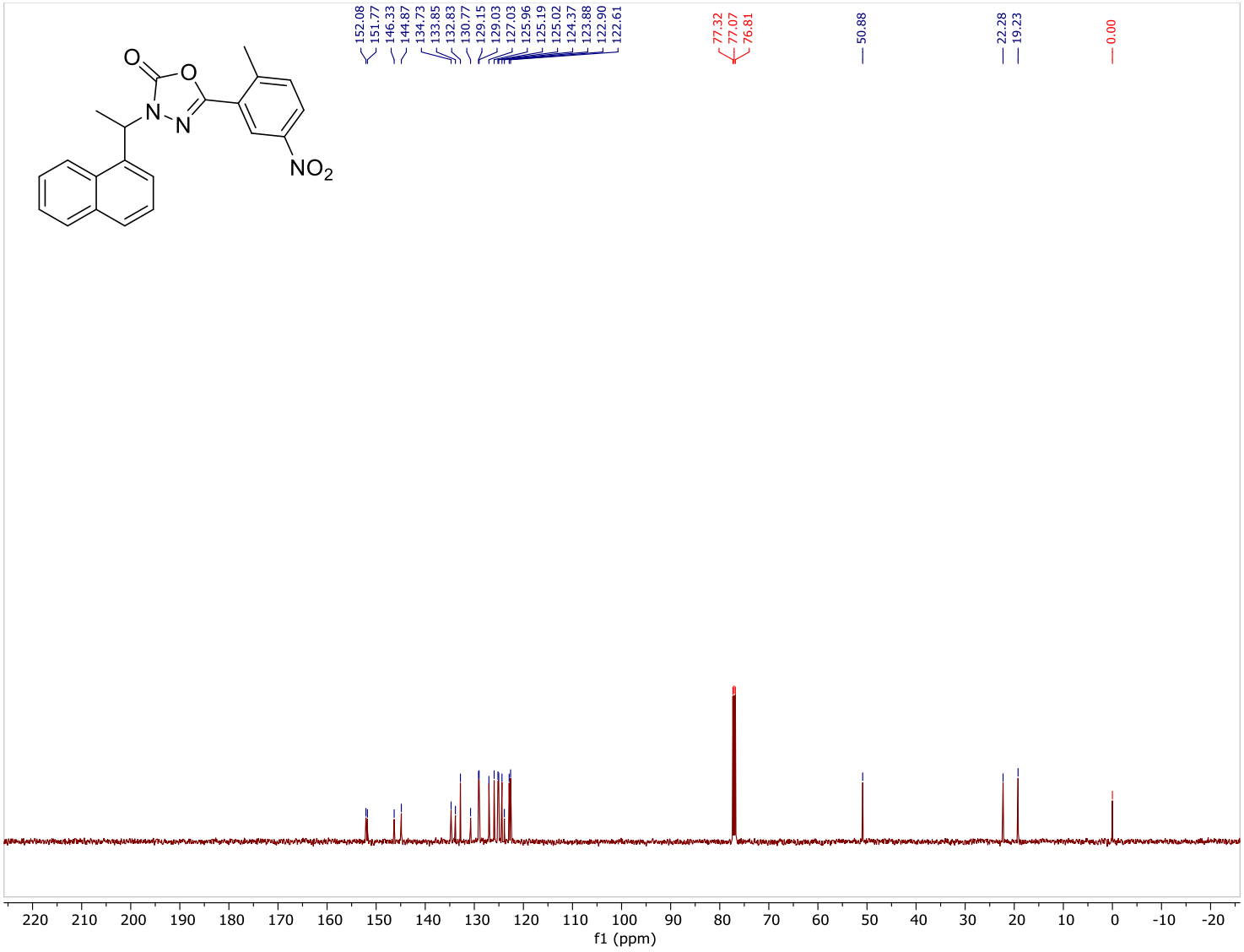
^{13}C NMR (126 MHz, $CDCl_3$ + 1% (v/v) TMS) spectrum of 5-amino-2-methyl-N'-(1-(naphthalen-1-yl)ethyl)benzohydrazide (67).



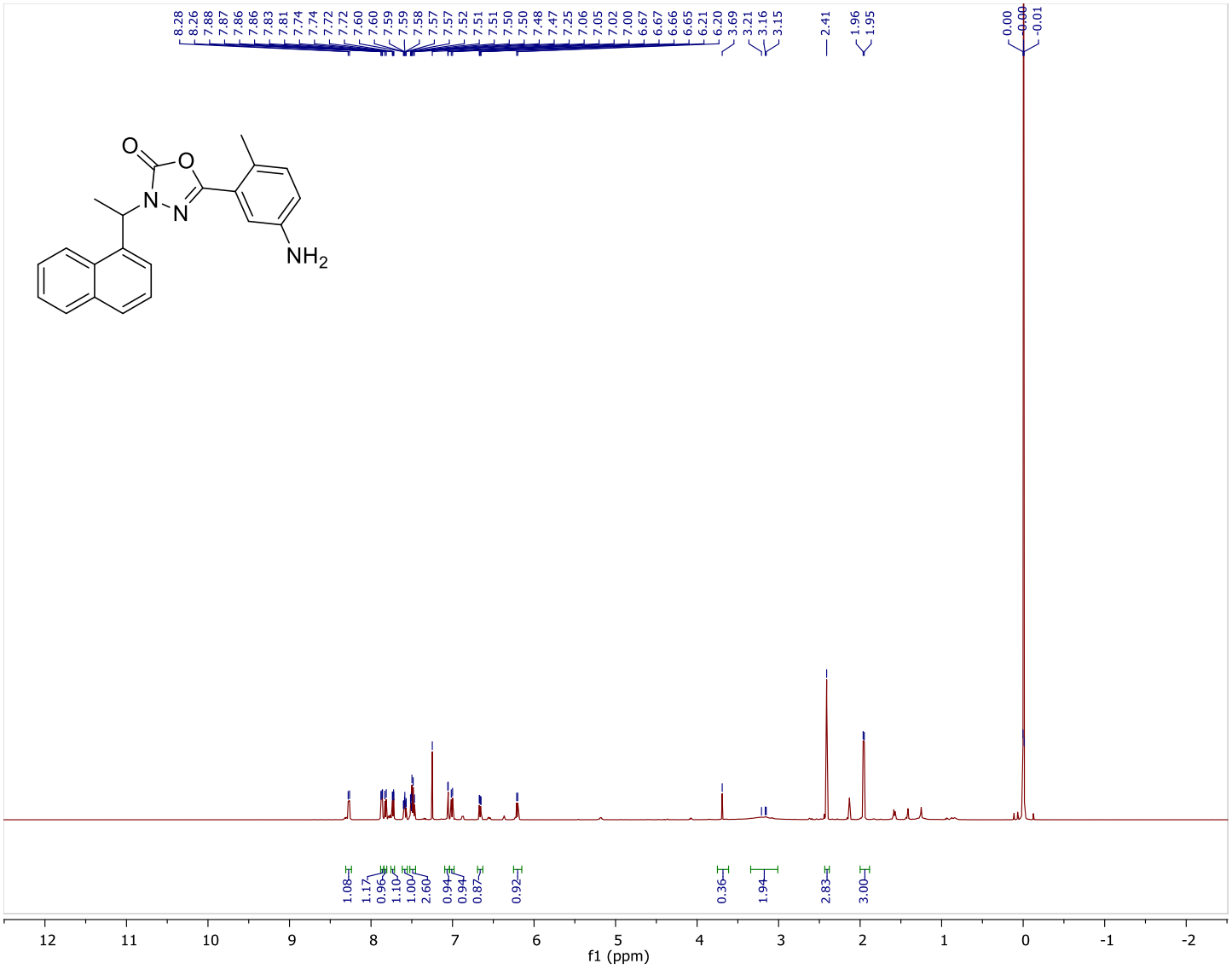
^{1}H NMR (500 MHz, $CDCl_3$ + 1% (v/v) TMS) spectrum of 5-(2-methyl-5-nitrophenyl)-3-(1-(naphthalen-1-yl)ethyl)-1,3,4-oxadiazol-2(3H)-one (68).



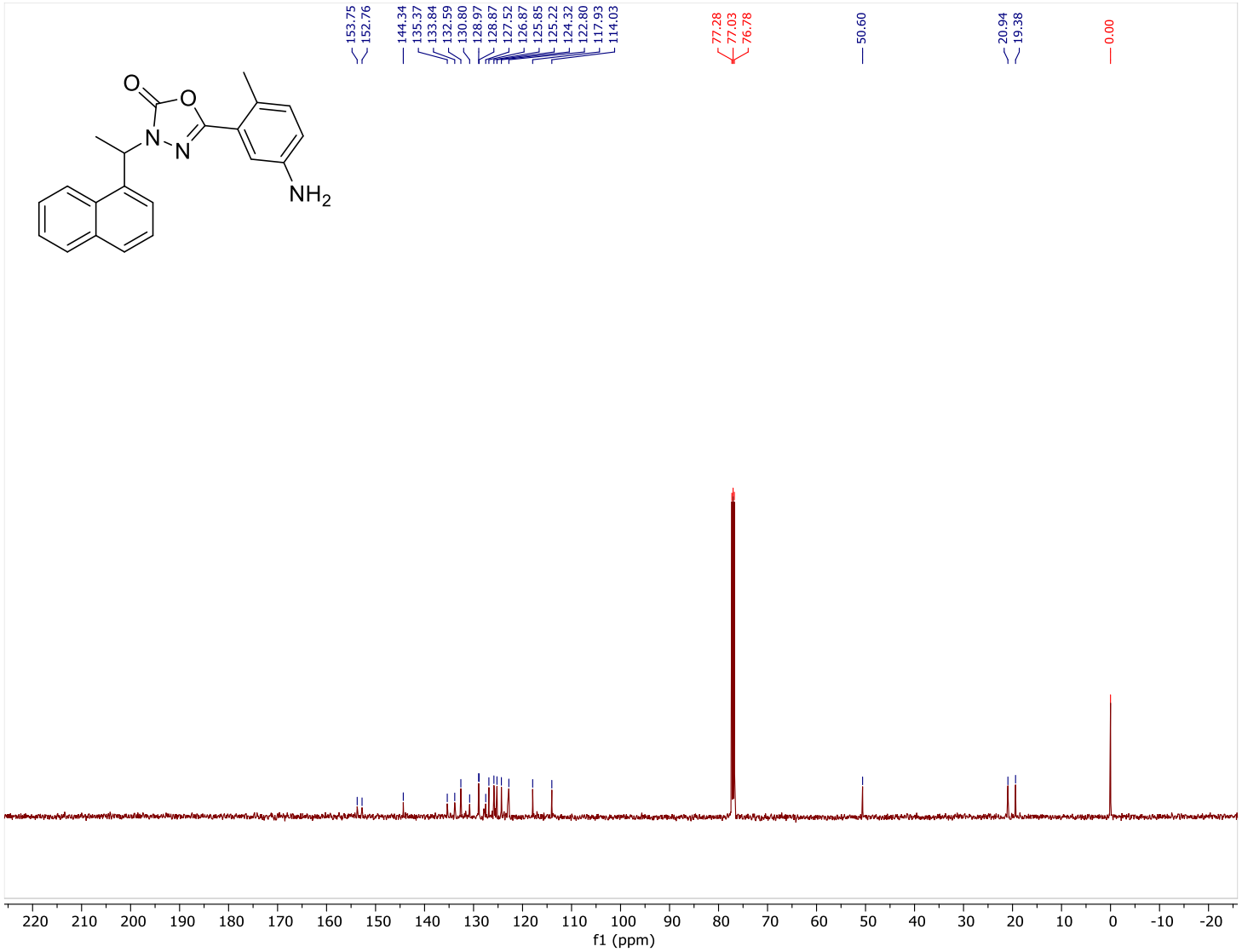
^{13}C NMR (126 MHz, $CDCl_3$ + 1% (v/v) TMS) spectrum of 5-(2-methyl-5-nitrophenyl)-3-(1-(naphthalen-1-yl)ethyl)-1,3,4-oxadiazol-2(3H)-one (68).



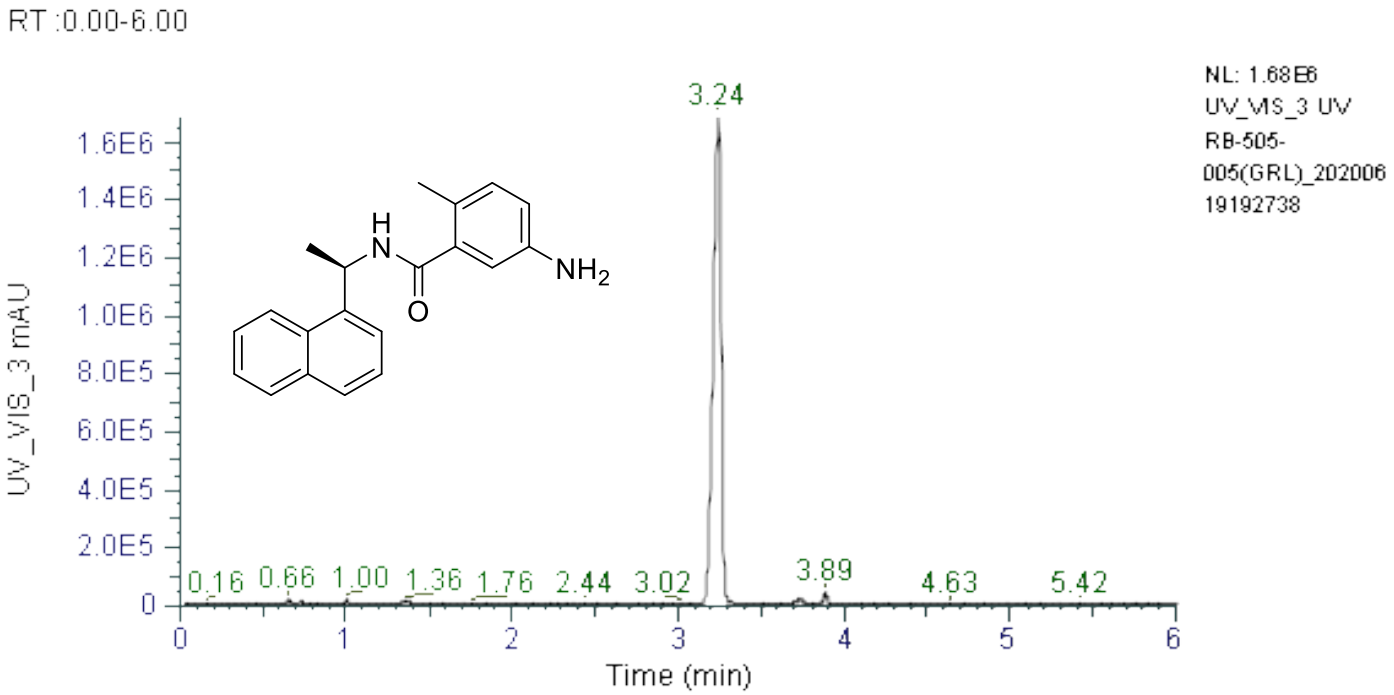
^{1}H NMR (500 MHz, $CDCl_3$ + 1% (v/v) TMS) spectrum of 5-(5-amino-2-methylphenyl)-3-(1-(naphthalen-1-yl)ethyl)-1,3,4-oxadiazol-2(3H)-one (69).



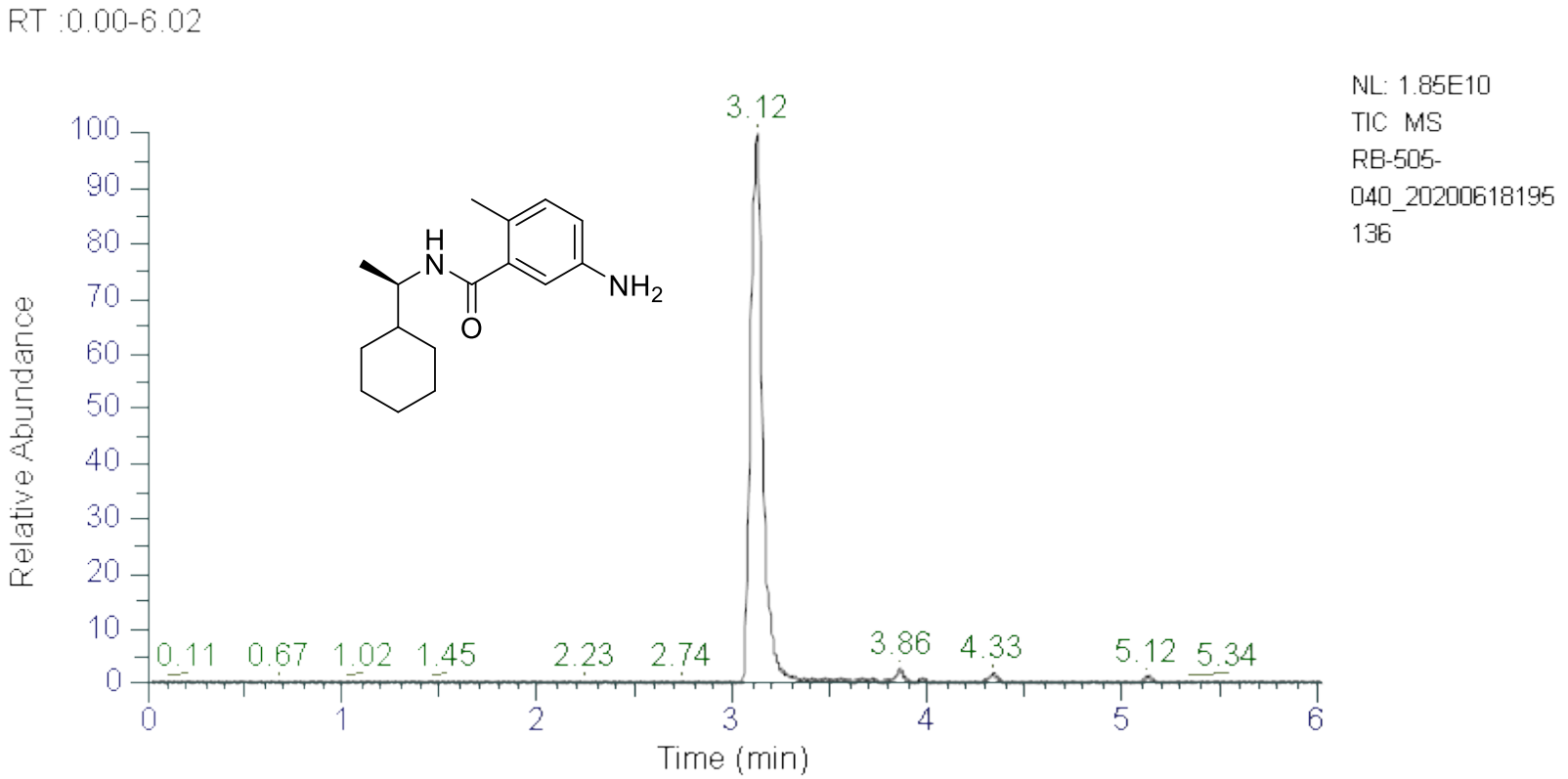
^{13}C NMR (126 MHz, $CDCl_3$ + 1% (v/v) TMS) spectrum of 5-(5-amino-2-methylphenyl)-3-(1-(naphthalen-1-yl)ethyl)-1,3,4-oxadiazol-2(3H)-one (69).



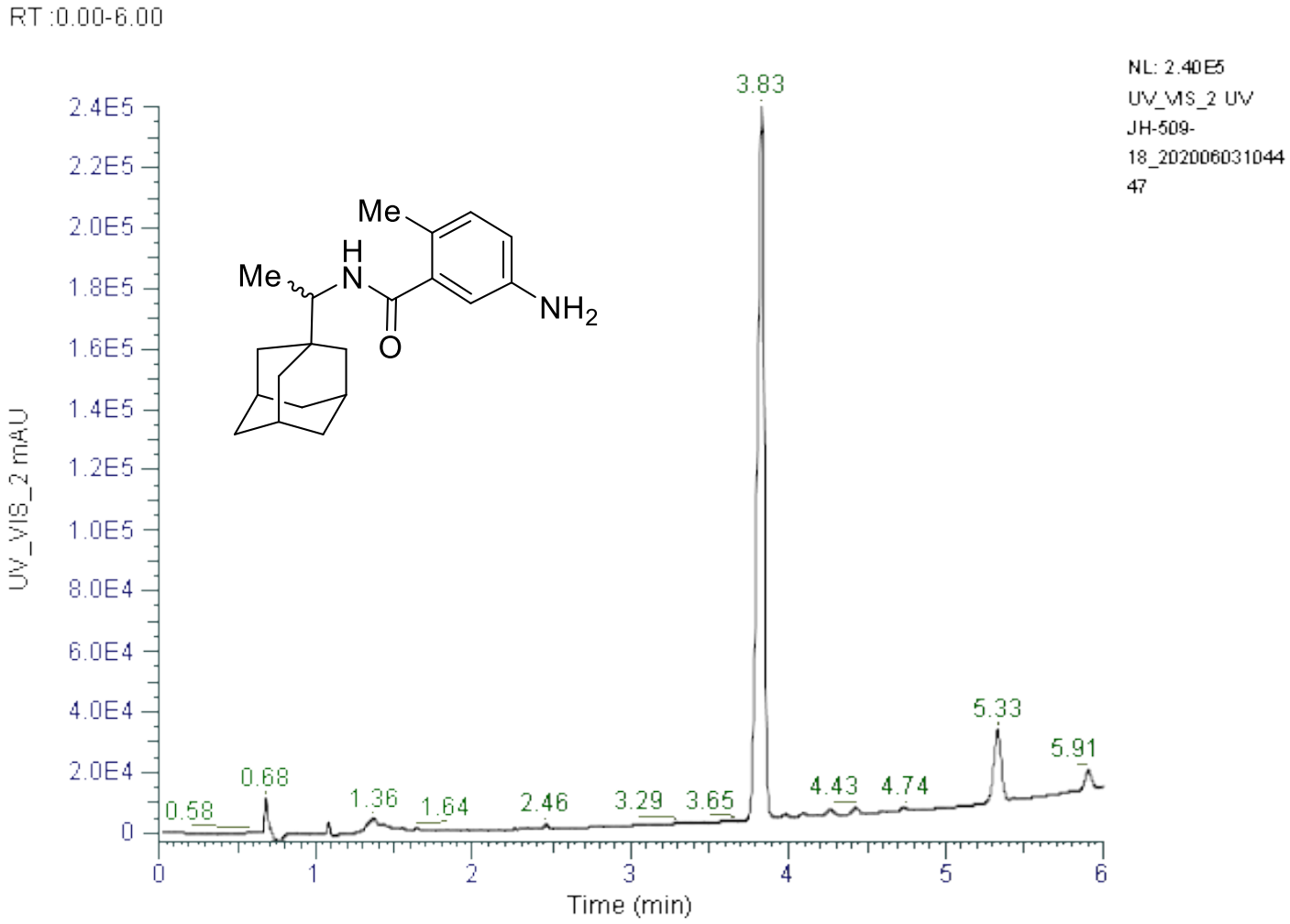
UHPLC trace of (*R*)-2-methyl-5amino-*N*-(1'-(naphthalene-1'-yl)ethyl)benzamide (GRL0617)



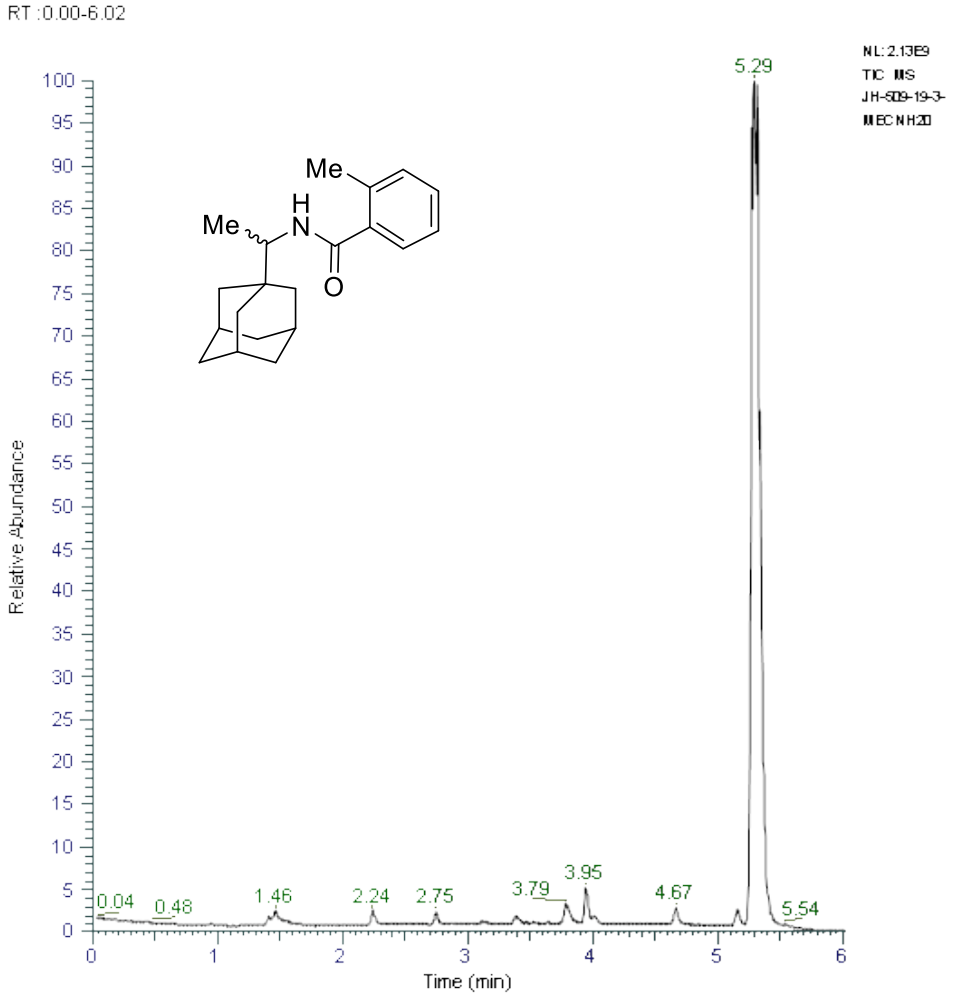
UHPLC trace of (*R*)-*N*-[1-(1-Cyclohexyl)ethyl] 5-amino-2-methylbenzamide (8).



UHPLC trace of (±)-*N*-(1'-(adamantan-1'-yl)ethyl)-5-amino-2-methylbenzamide (9).

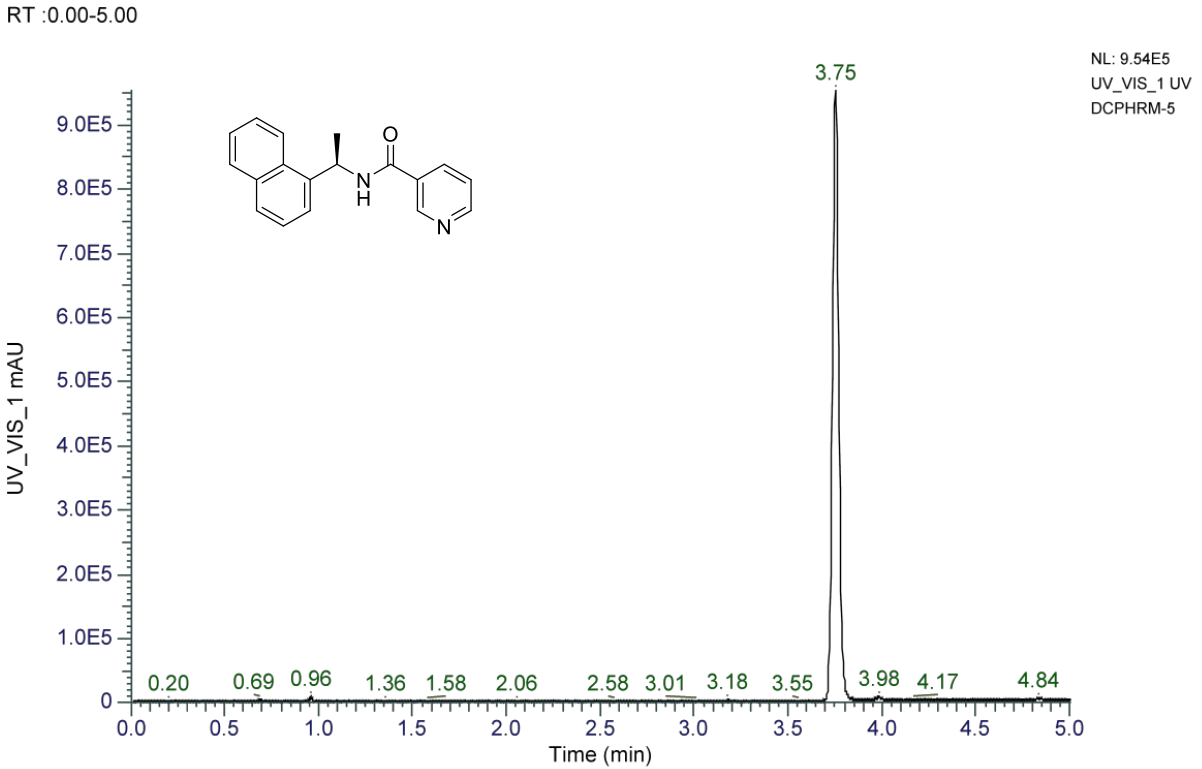


UHPLC trace of (±)-*N*-(1'-(adamantan-1'-yl)ethyl)-2-methylbenzamide (10).*

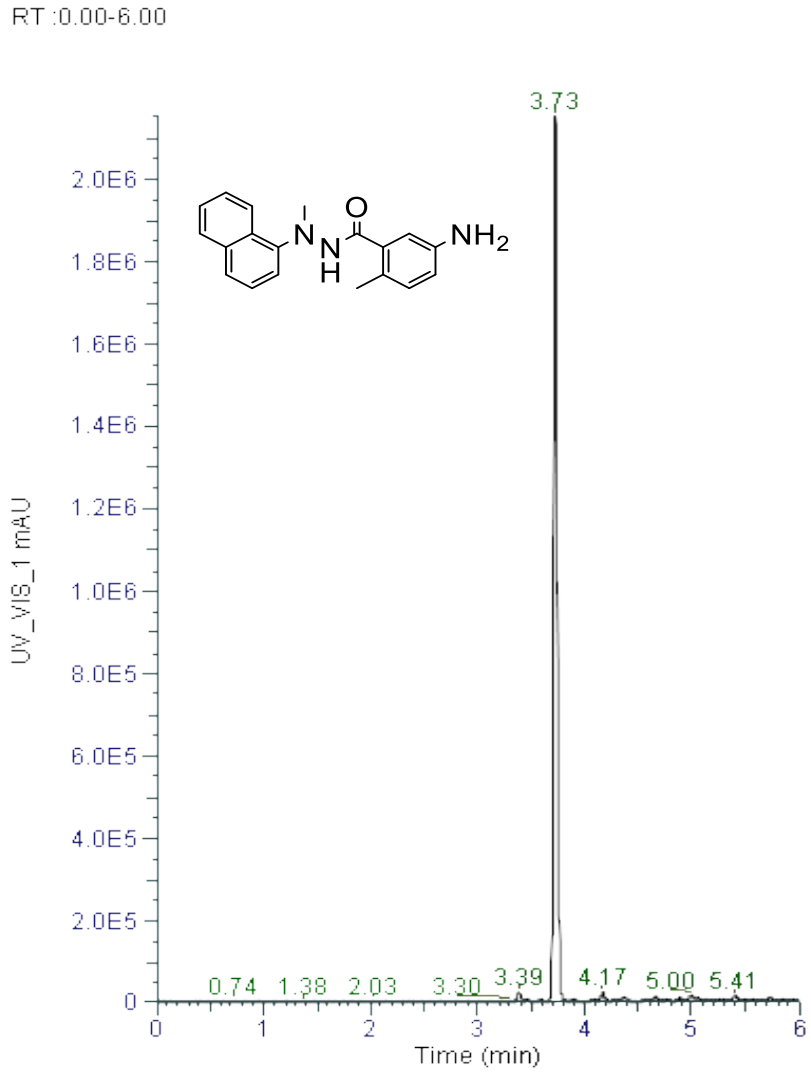


*Compound was insufficiently detectable *via* UV, therefore a TIC has been included.

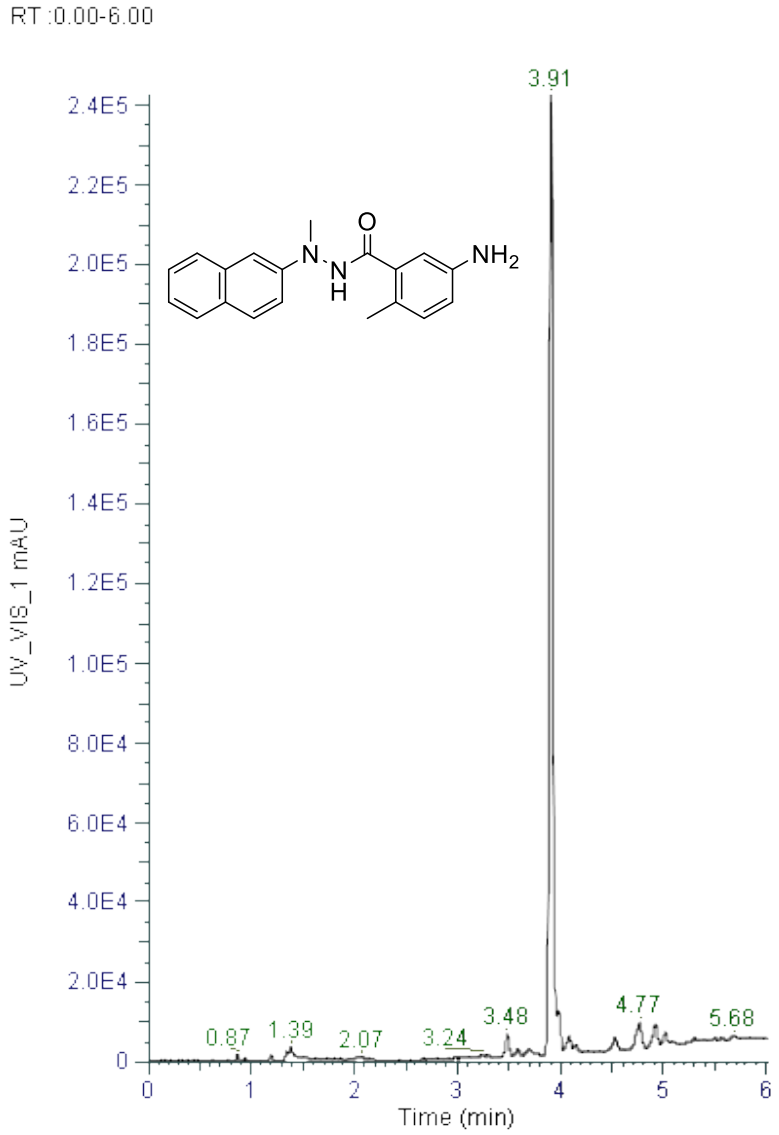
UHPLC trace of (*R*)-*N*-(1-(naphthalen-1-yl)ethyl)nicotinamide (11).



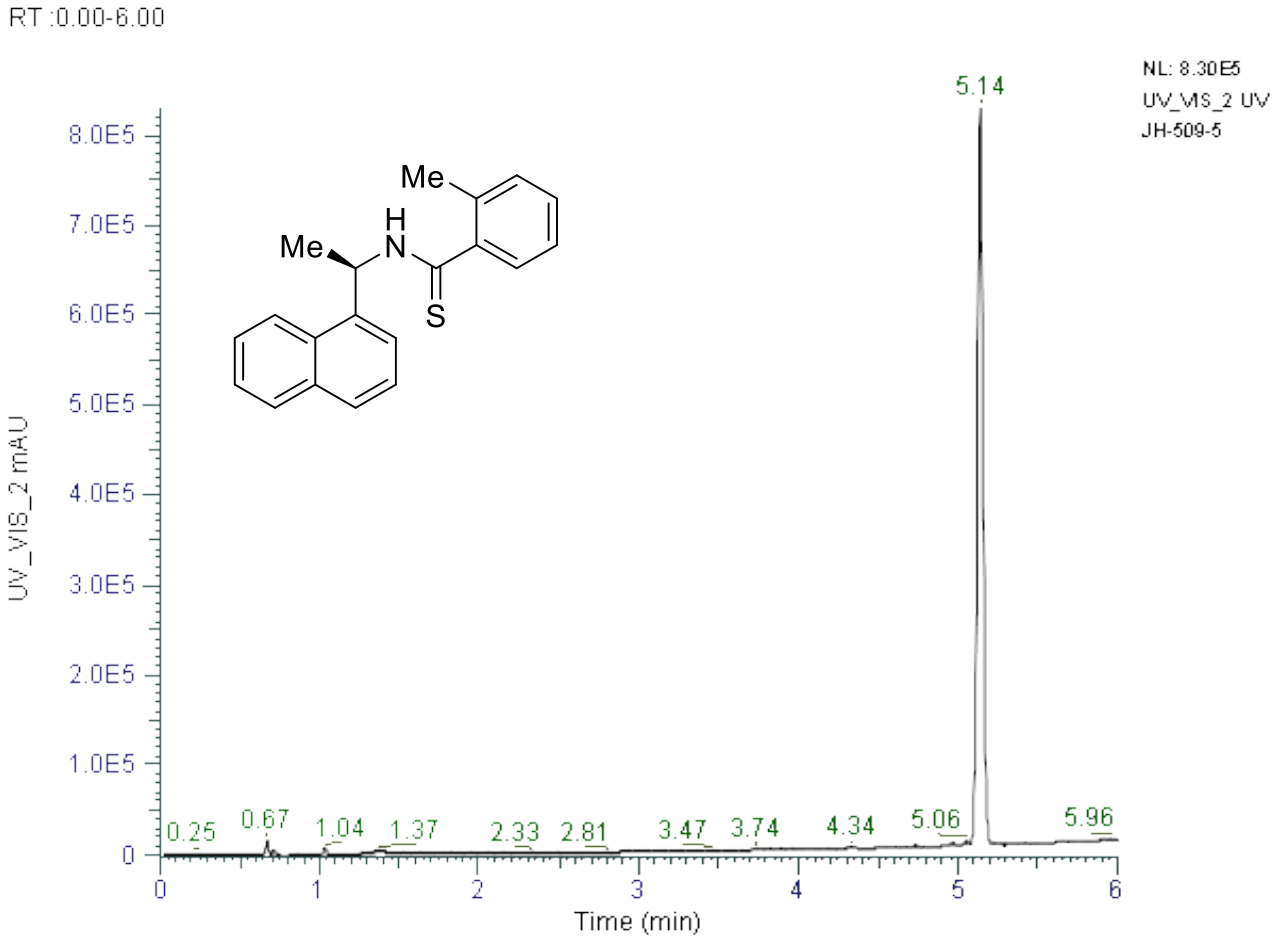
UHPLC trace of *N*'-Methyl-*N*'-(naphthalen-1-yl) 5-amino-2-methylbenzhydrazide (22).



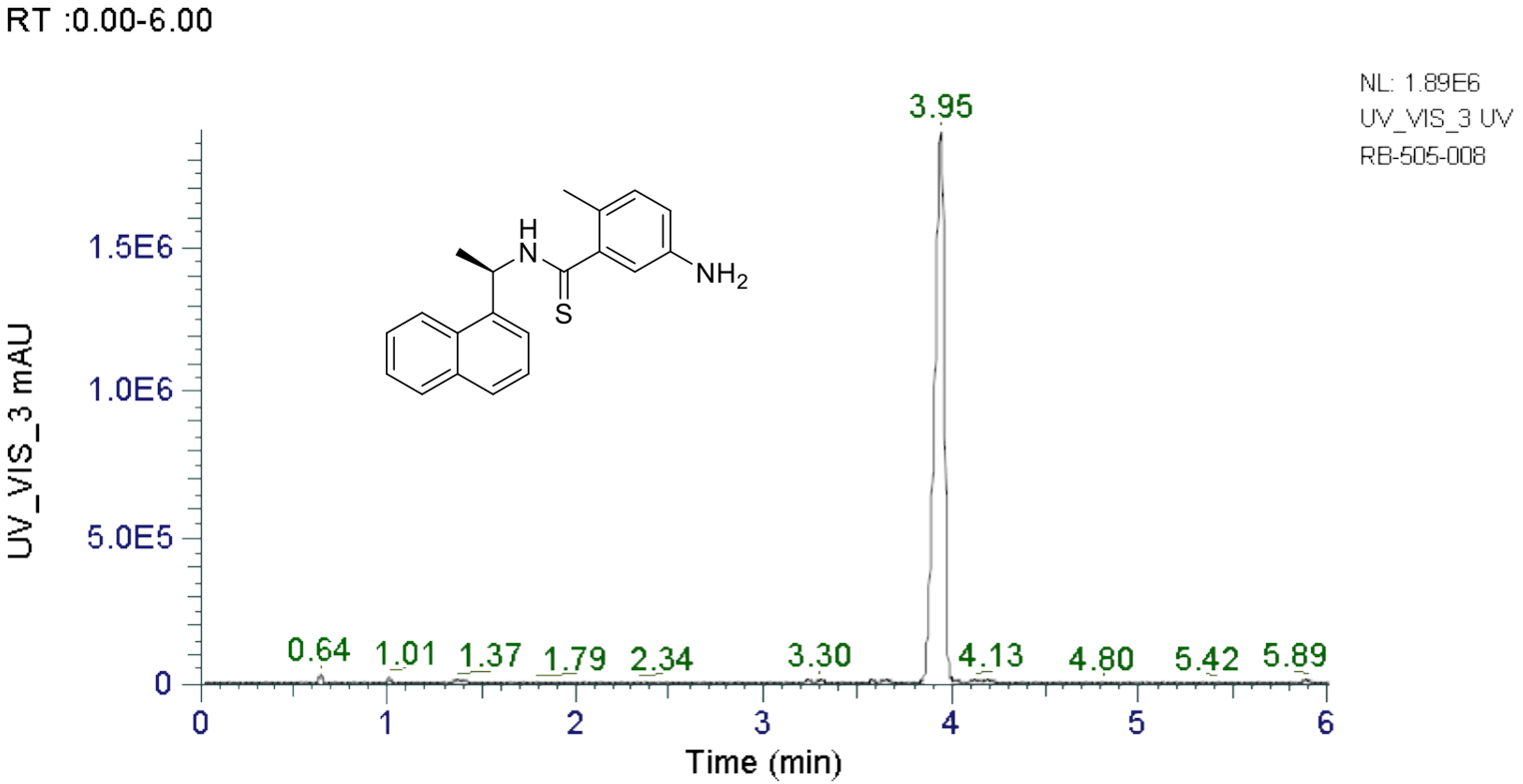
UHPLC trace of *N*'-Methyl-*N*'-(naphthalen-2-yl) 5-amino-2-methylbenzhydrazide (23).



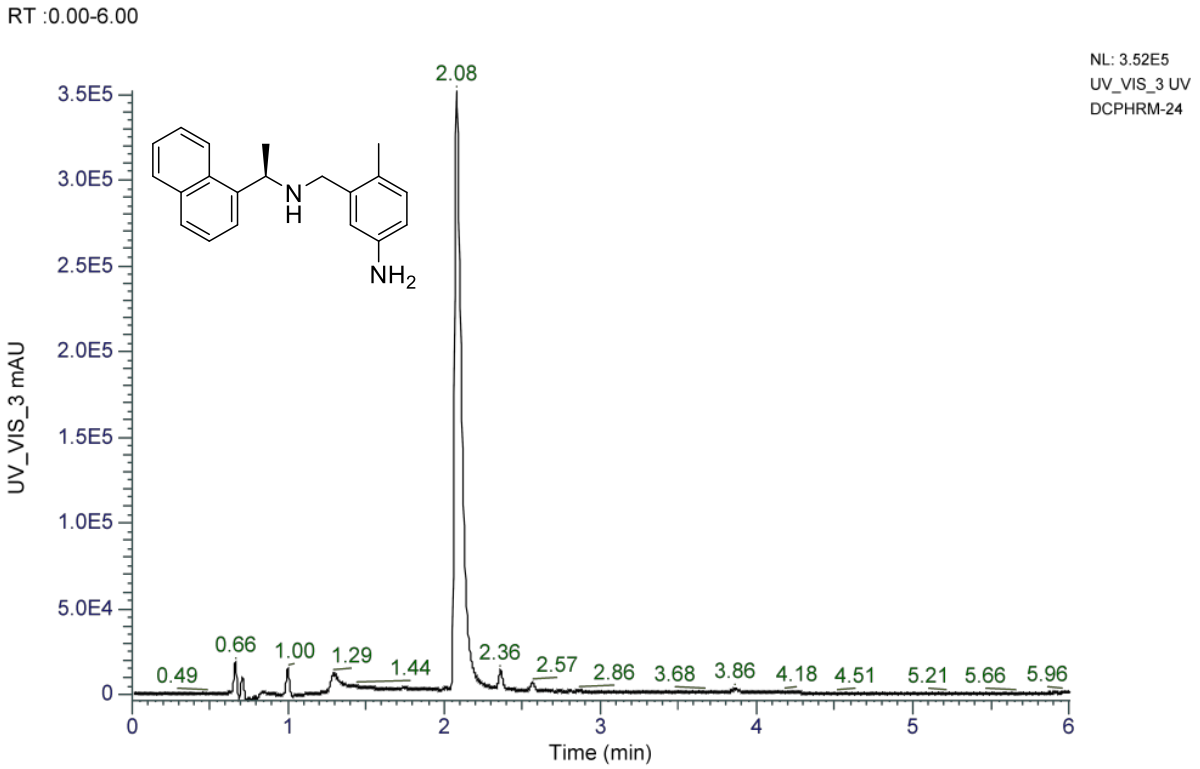
UHPLC trace of (*R*)-2-methyl-*N*-(1'-(naphthalene-1'-yl)ethyl)benzothioamide (24).



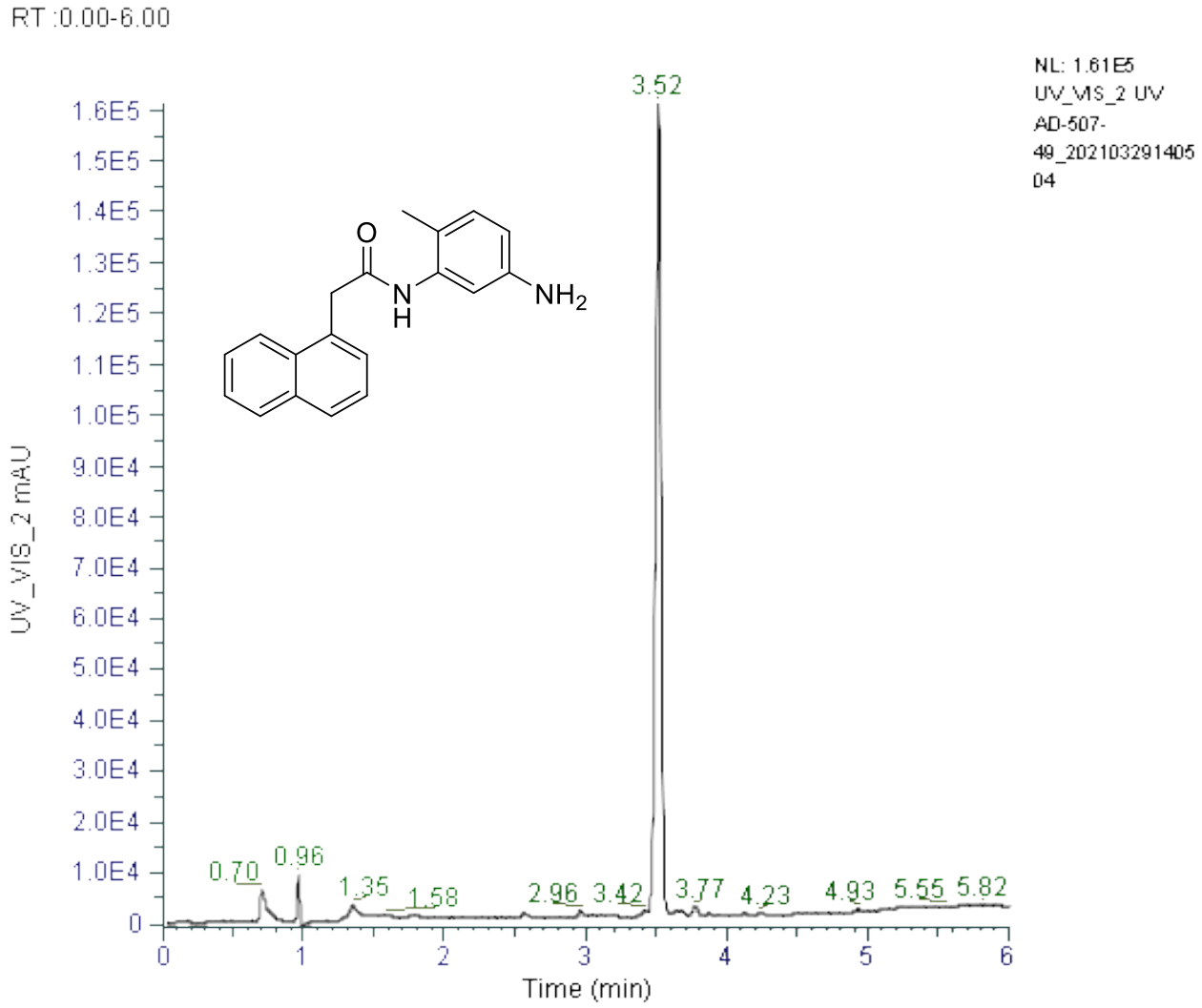
UHPLC trace of (*R*)-*N*-[1-(1-Naphthyl)ethyl] 5-amino-2-methylthiobenzamide (25).



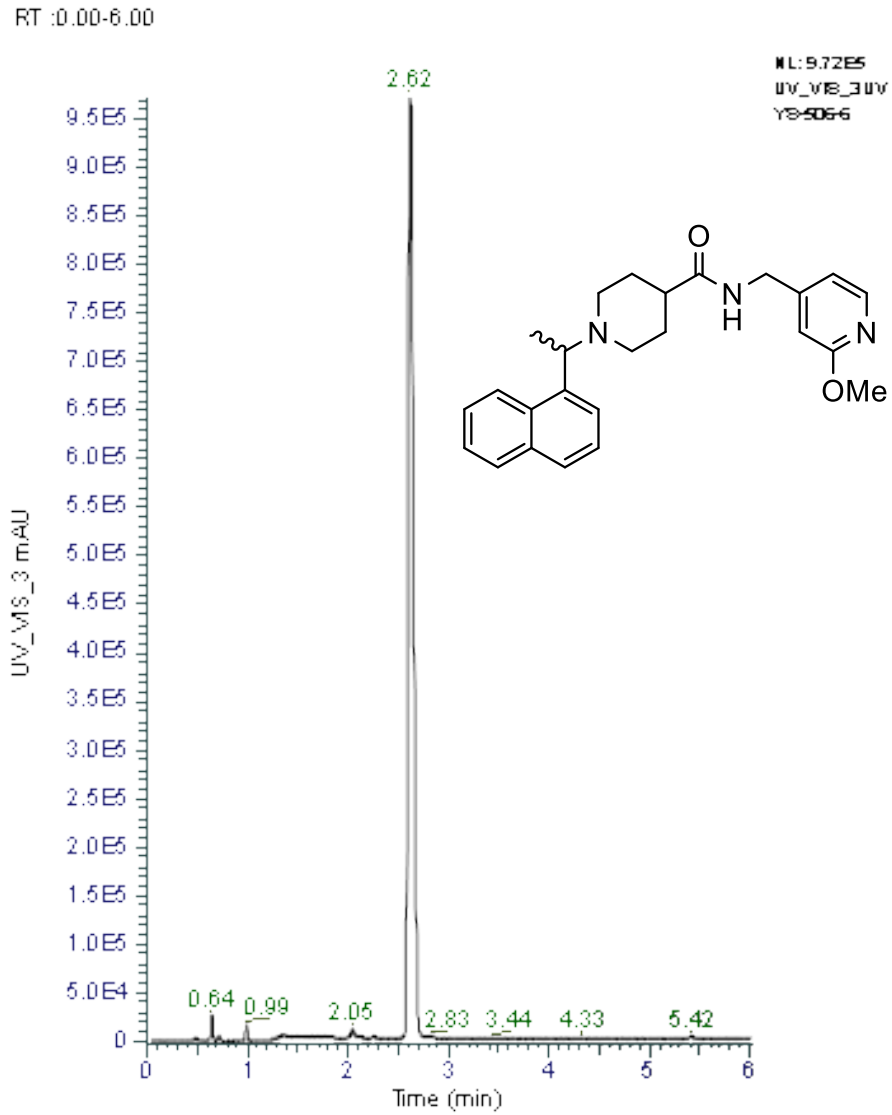
UHPLC trace of (*R*)-4-methyl-3-(((1-(naphthalen-1-yl)ethyl)amino)methyl)aniline (26).



UHPLC trace of N-(5-amino-2-methylphenyl)-2-(naphthalen-1-yl)acetamide (28).



UHPLC trace of (±)-*N*-((2-methoxypyridin-4-yl)methyl)-1-(1-(naphthalen-1-yl)ethyl)piperidine-4-carboxamide (31).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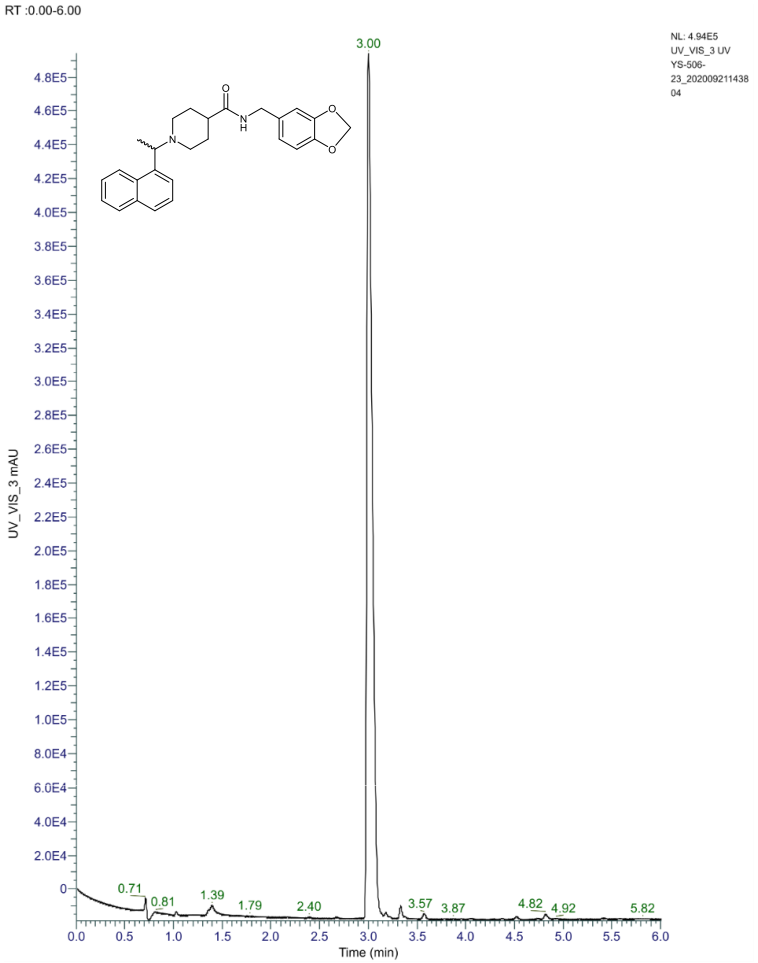
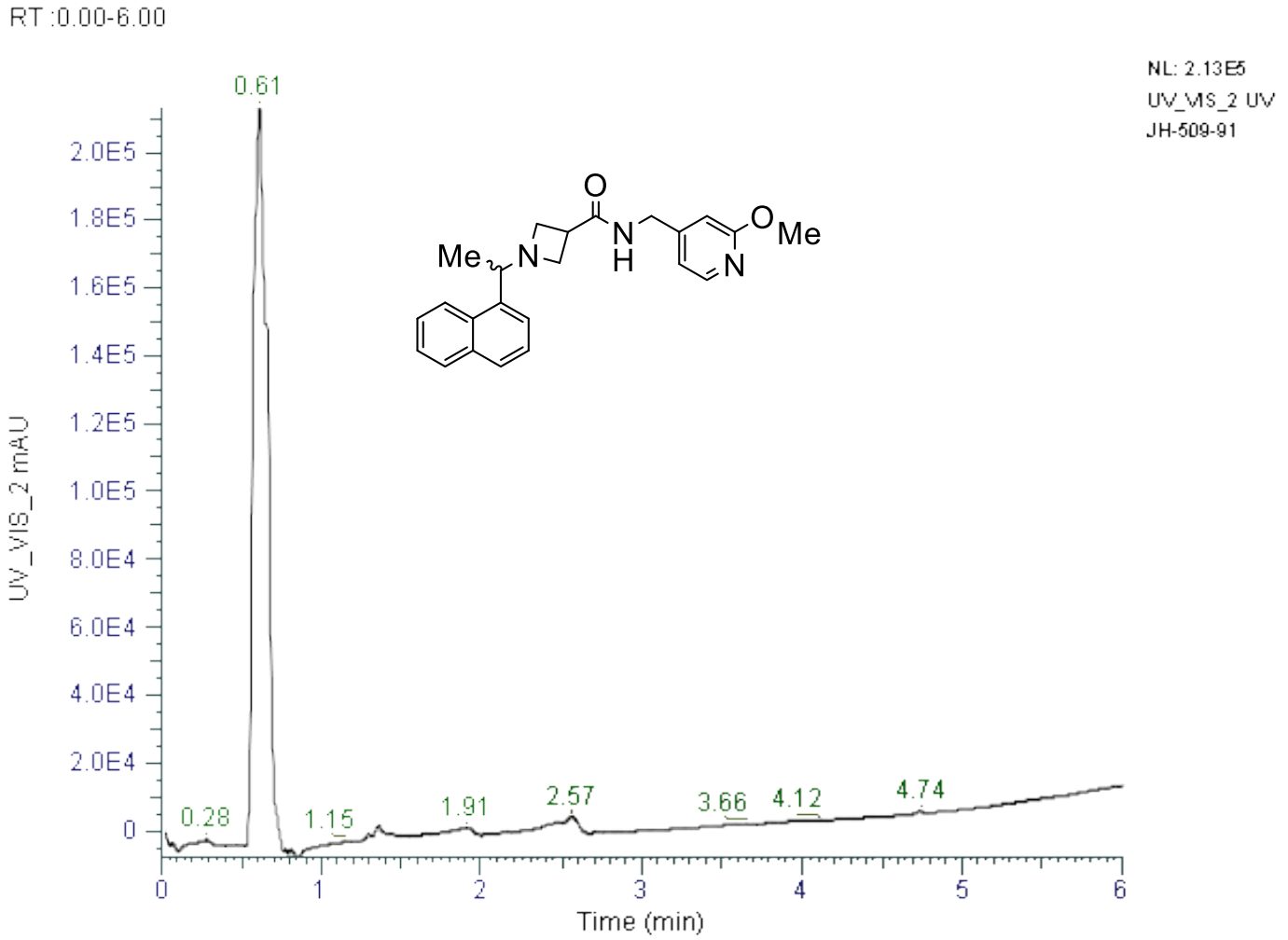
NL:9.72E5
UV_VIS_3 UV
YS-506-6
2.62
9.5E5
9.0E5
8.5E5
8.0E5
7.5E5
7.0E5
6.5E5
6.0E5
5.5E5
5.0E5
4.5E5
4.0E5
3.5E5
3.0E5
2.5E5
2.0E5
1.5E5
1.0E5
5.0E4
0
UV_VIS_3 mAU
0.64
0.99
2.05
2.83
3.44
4.33
5.42
0
1
2
3
4
5
6
Time (min)
O
N
H
N
N
OMe

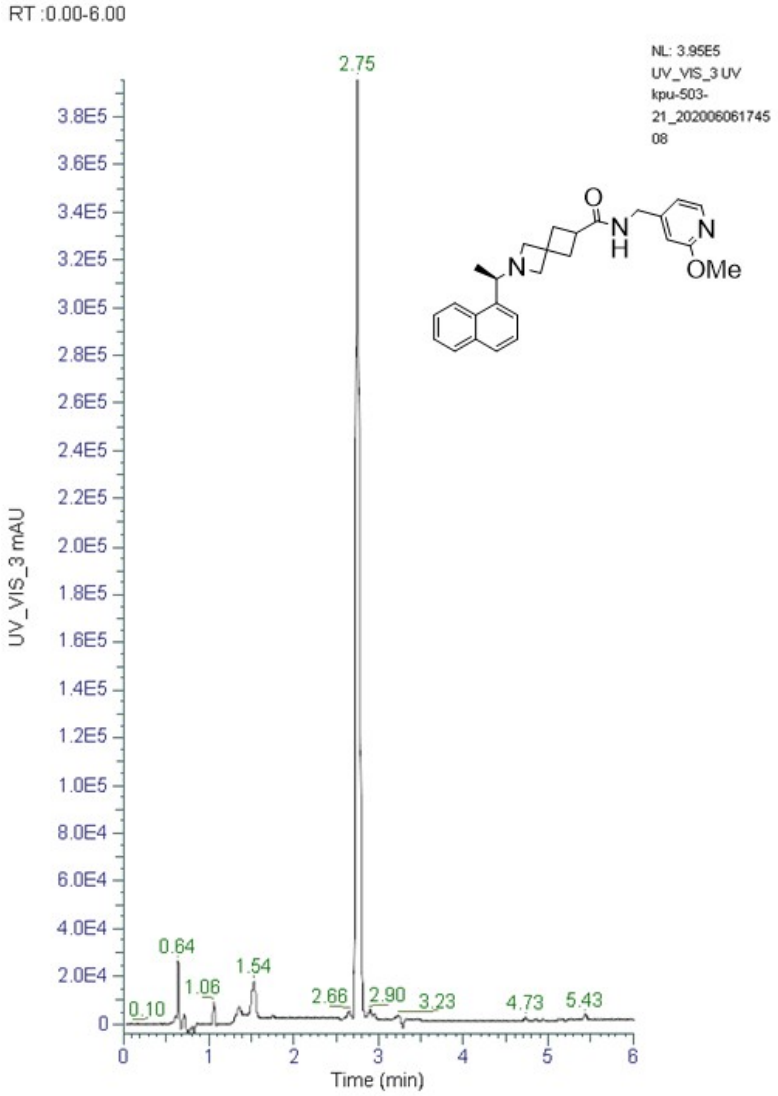
UHPLC trace of (±)-*N*-(Benzo[*d*][1,3]dioxol-5-ylmethyl)-1-(1-(naphthalen-1-yl)ethyl)piperidine-4-carboxamide (1).



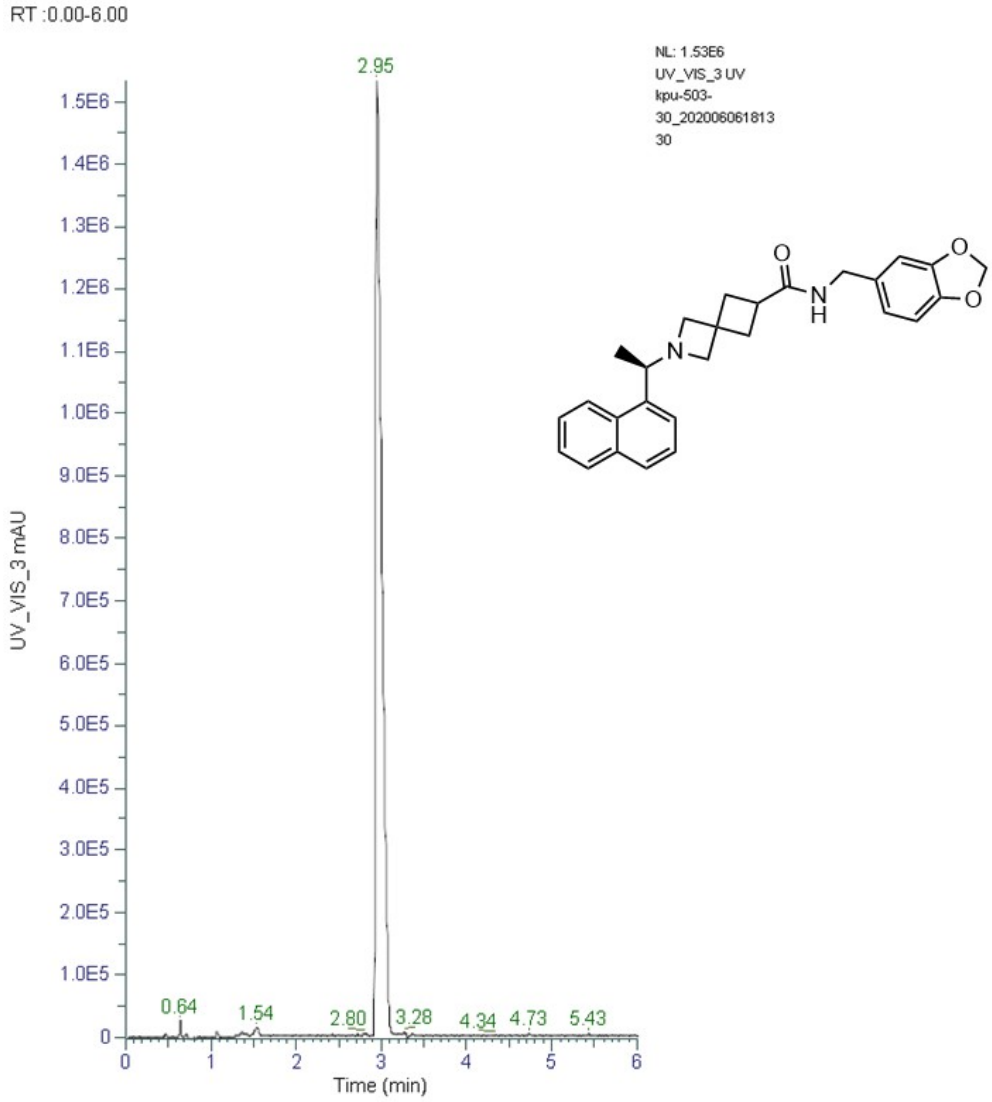
UHPLC trace of (±)-*N*-((2'-methoxypyridin-4'-yl)methyl)-1-(1''-(naphthalene-1''-yl)ethyl)azetidine-3-caboxamide (34).



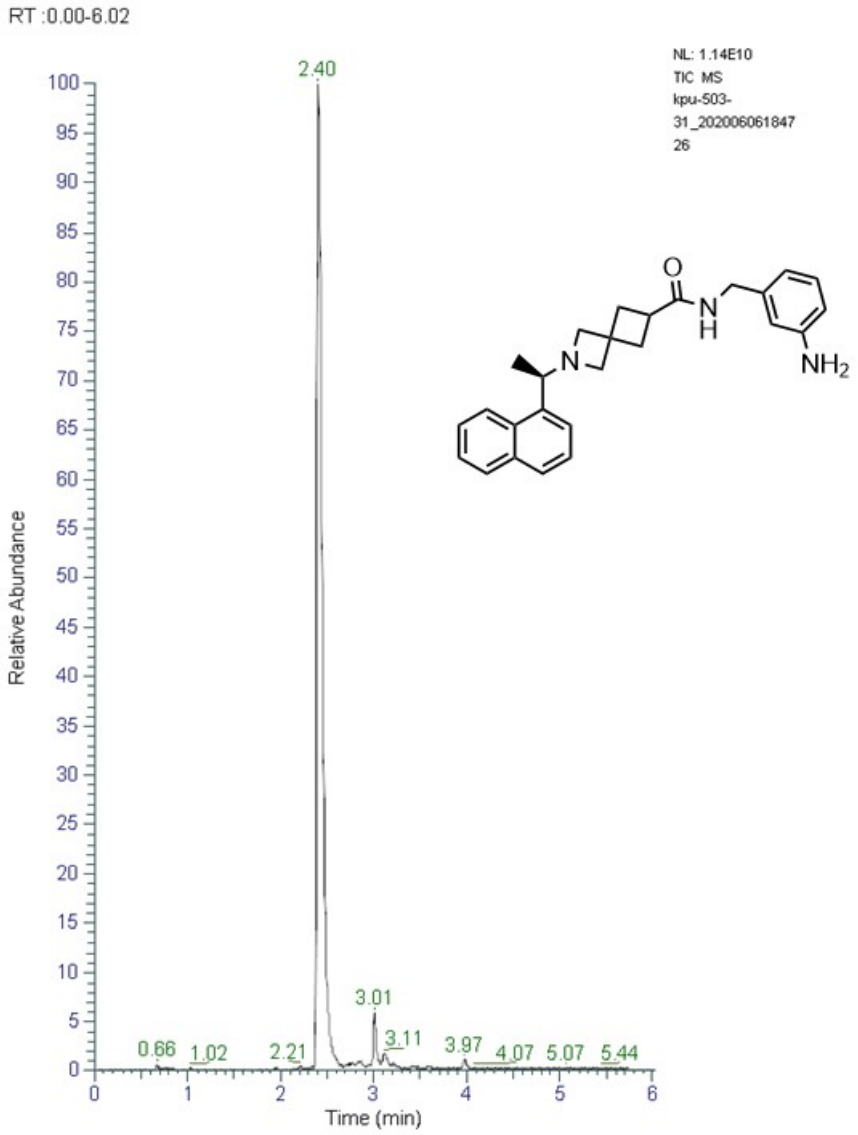
UHPLC trace of (*R*)-*N*-((2-methoxypyridin-4-yl)methyl)-2-(1-(naphthalen-1-yl)ethyl)-2-azaspiro[3.3]heptane-6-carboxamide (37).



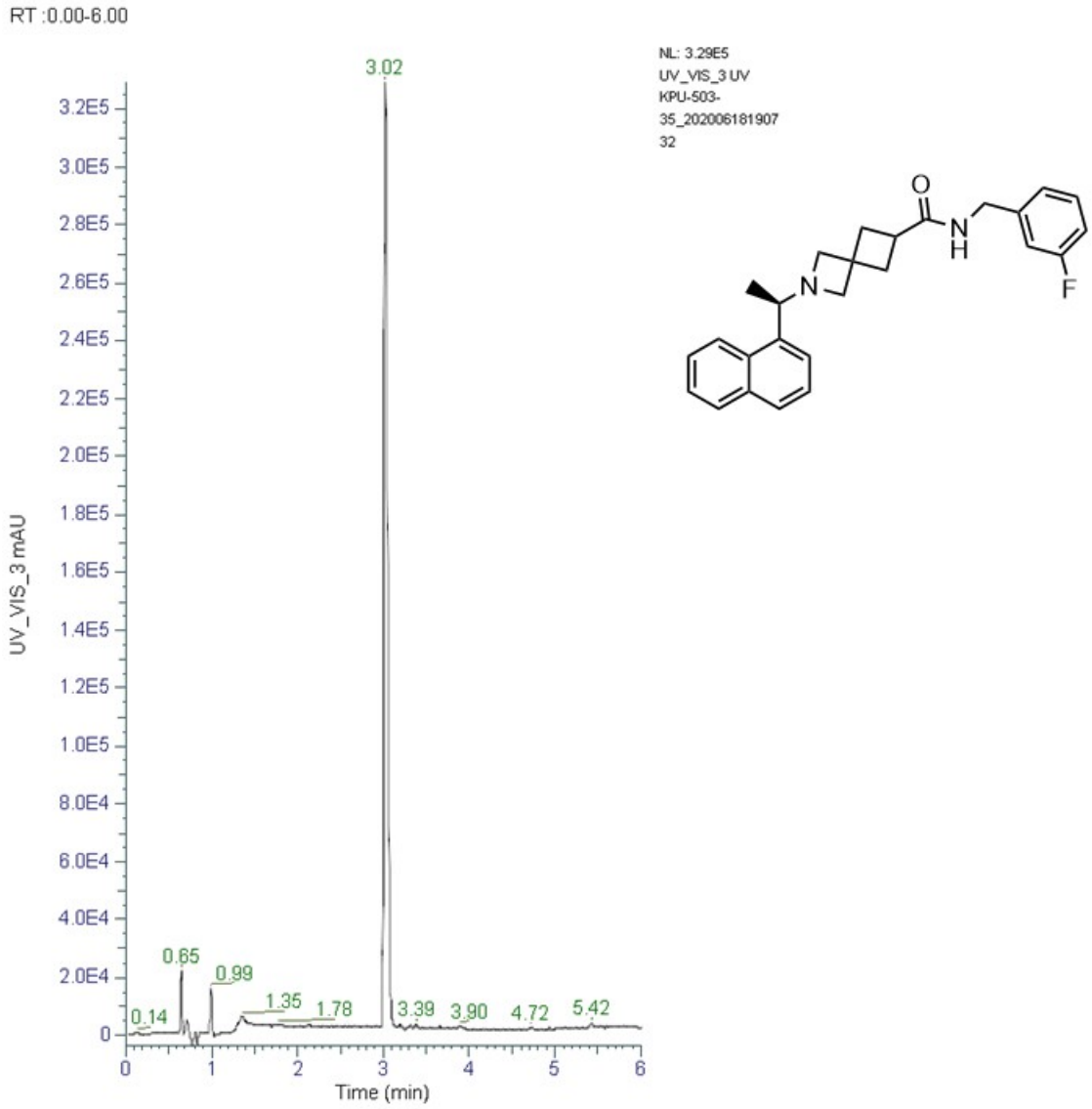
UHPLC trace of (*R*)-*N*-(Benzo[d][1,3]dioxol-5-ylmethyl)-2-(1-(naphthalen-1-yl)ethyl)-2-azaspiro[3.3]heptane-6-carboxamide (38).



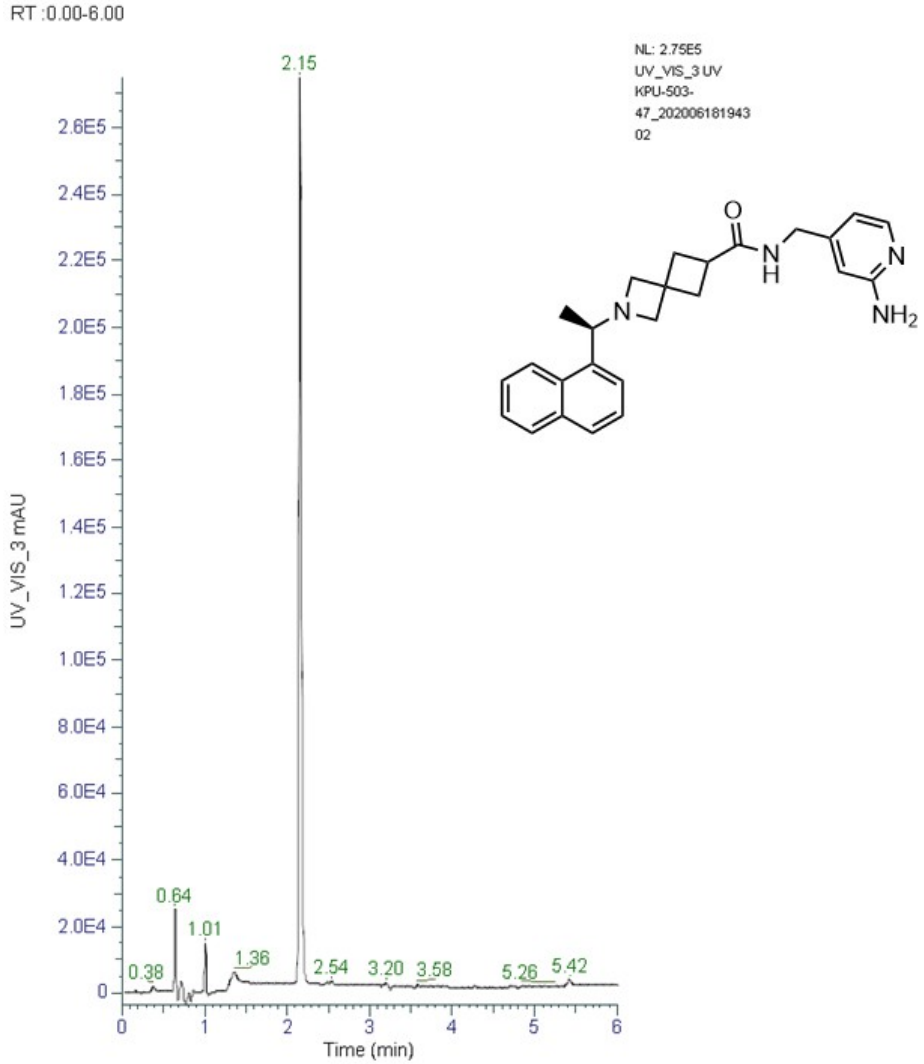
UHPLC trace of (*R*)-*N*-(3-Aminobenzyl)-2-(1-(naphthalen-1-yl)ethyl)-2-azaspiro[3.3]heptane-6-carboxamide (39)..



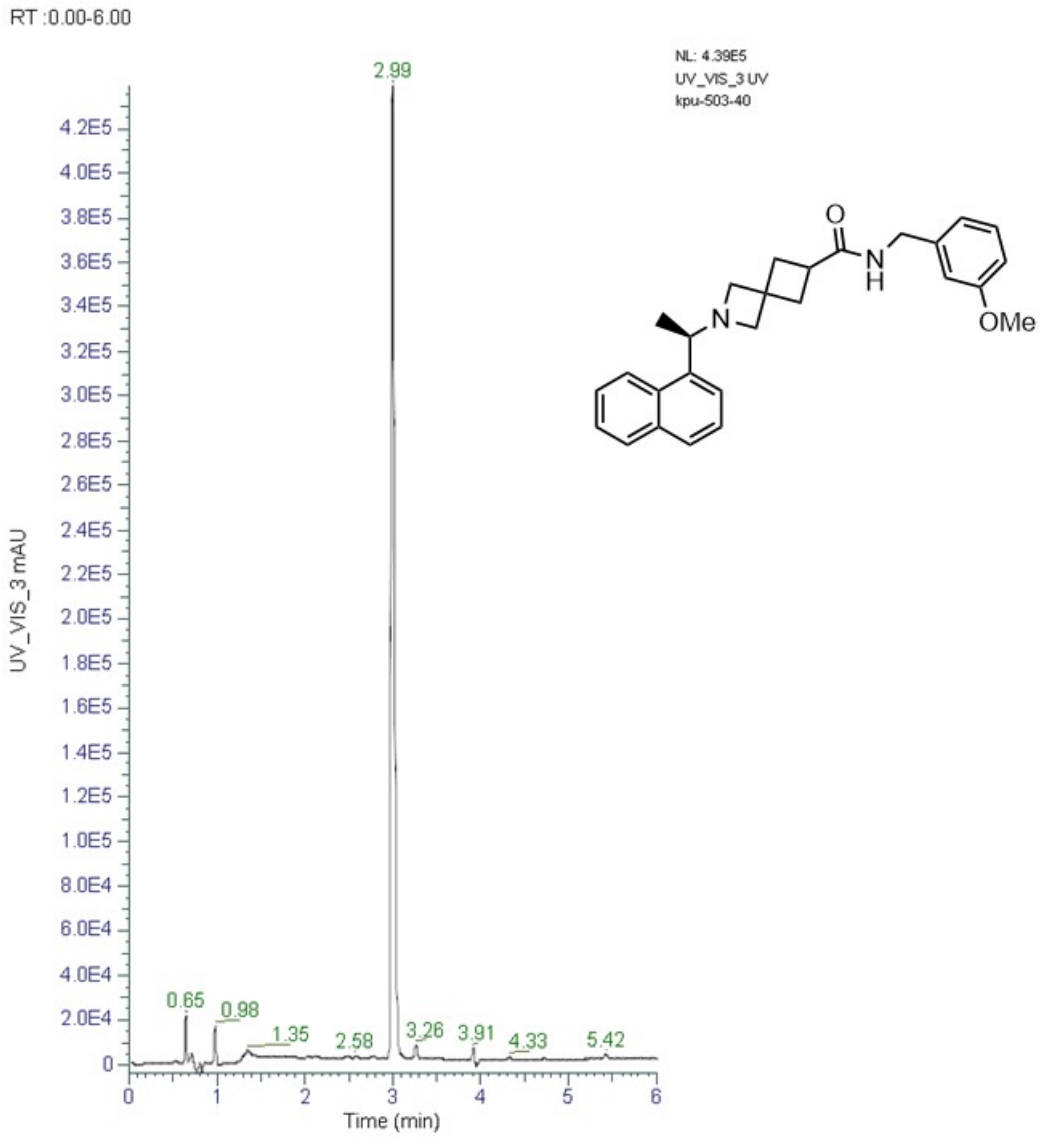
UHPLC trace of (*R*)-*N*-(3-Fluorobenzyl)-2-(1-(naphthalen-1-yl)ethyl)-2-azaspiro[3.3]heptane-6-carboxamide (40).



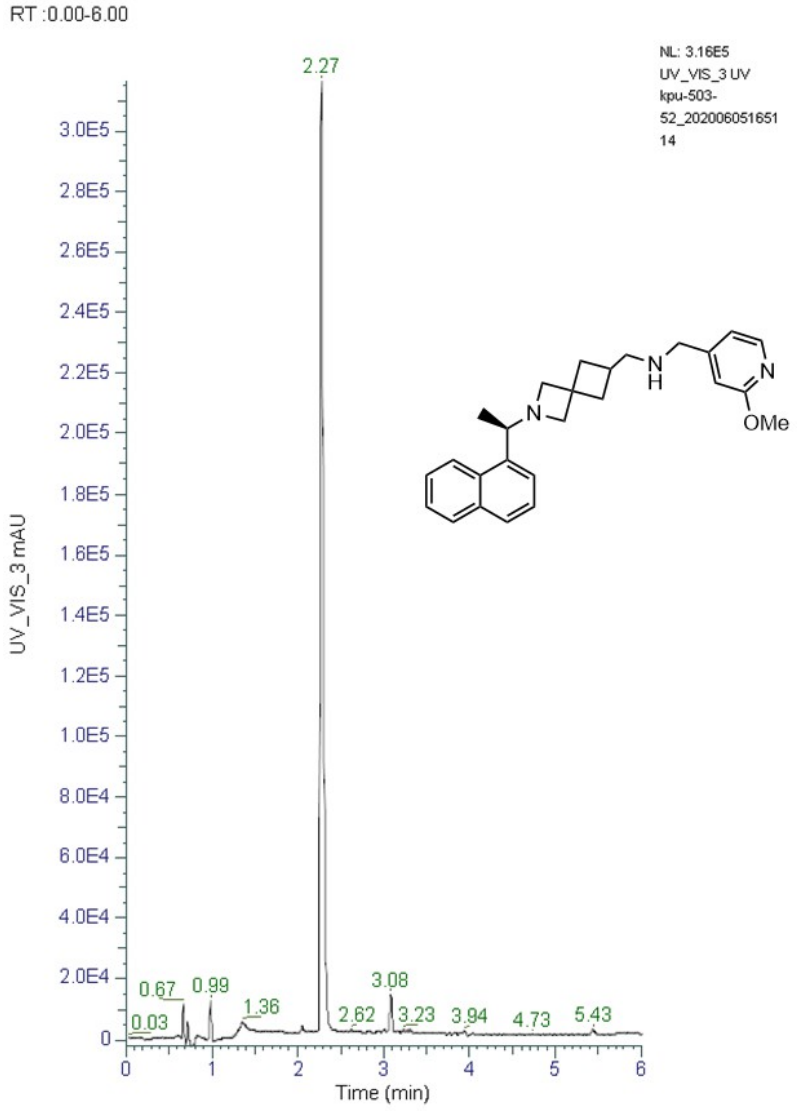
UHPLC trace of (*R*)-*N*-((2-Aminopyridin-4-yl)methyl)-2-(1-(naphthalen-1-yl)ethyl)-2-azaspiro[3.3]heptane-6-carboxamide (41).



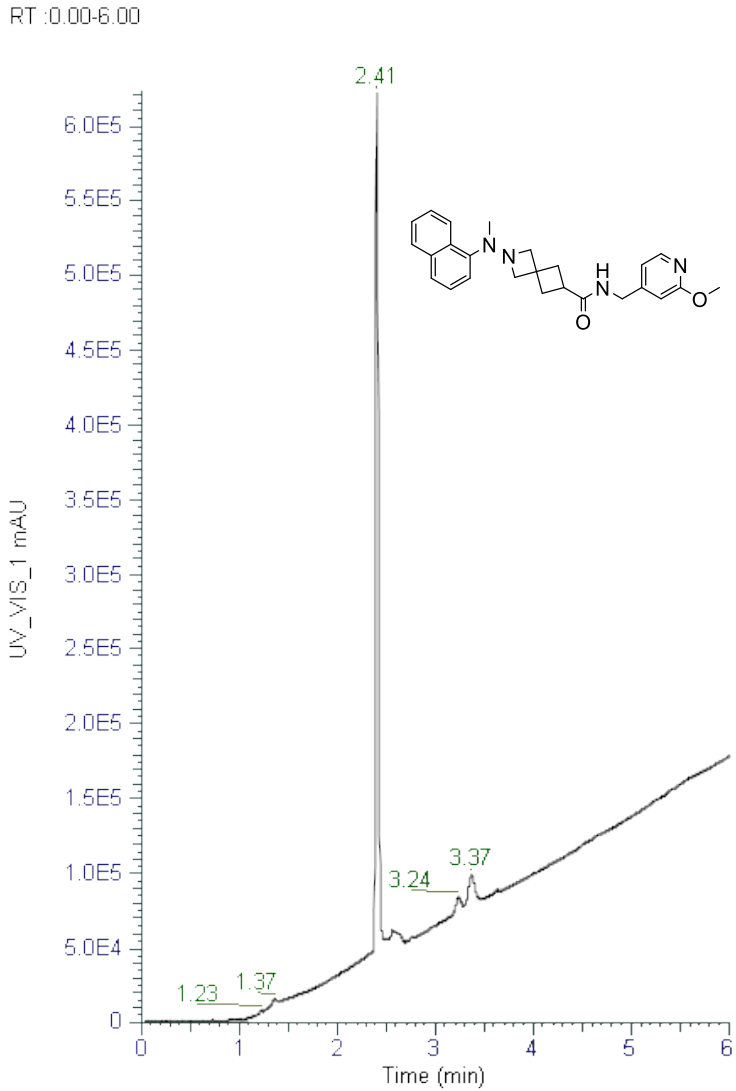
UHPLC trace of (*R*)-*N*-(3-Methoxybenzyl)-2-(1-(naphthalen-1-yl)ethyl)-2-azaspiro[3.3]heptane-6-carboxamide (42).



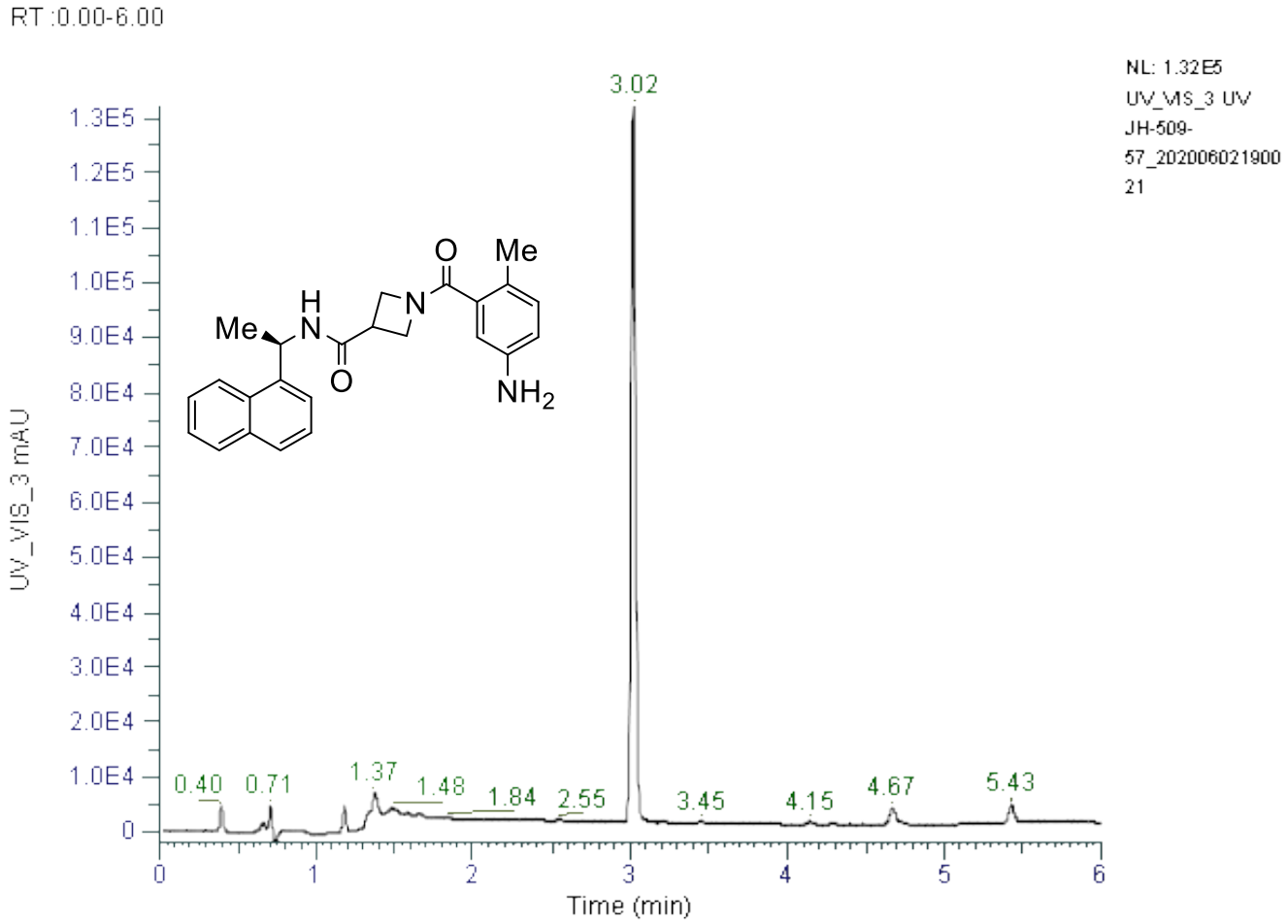
UHPLC trace of (*R*)-*N*-((2-methoxypyridin-4-yl)methyl)-2-(1-(naphthalen-1-yl)ethyl)-2-azaspiro[3.3]heptane-6-methanamine (45).



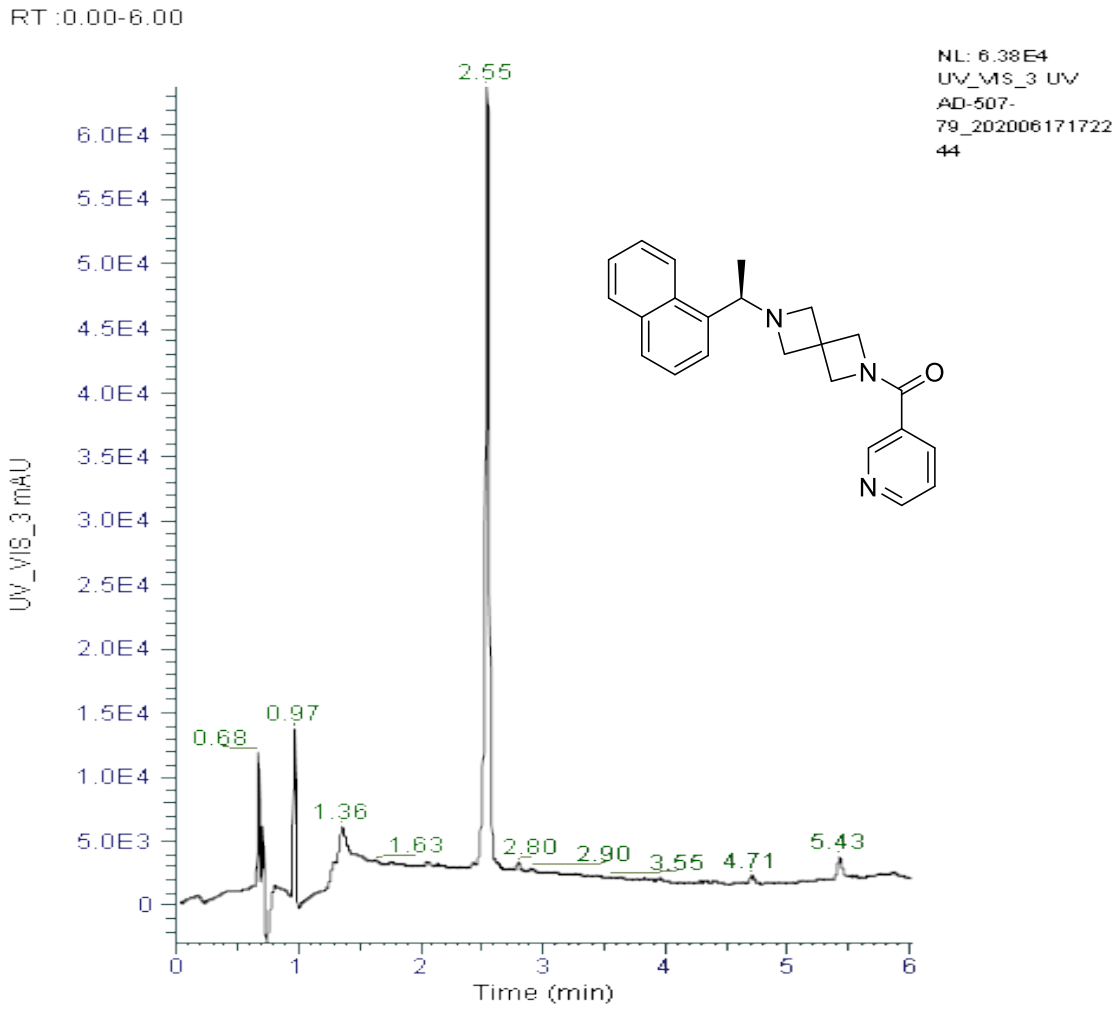
UHPLC trace of *N*-[(2-Methoxypyridin-4-yl)methyl] *N'*-[(naphthalen-1-yl)methylamino]-2-azaspiro[3.3]heptane-6-carboxamide (47).



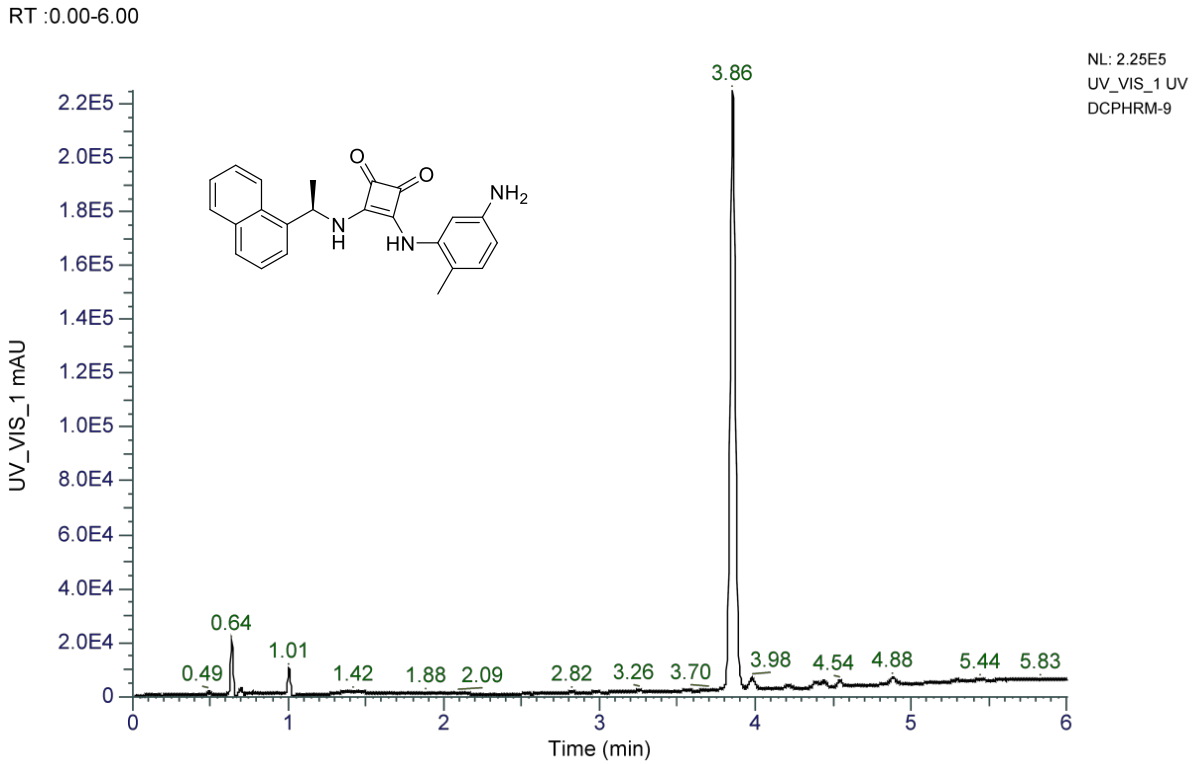
UHPLC trace of (*R*)-1'-(5'-amino-2'-methylbenzoyl)-*N*-(1''-(naphthalene-1''-yl)ethyl)azetidine-3-caboxamide (51).



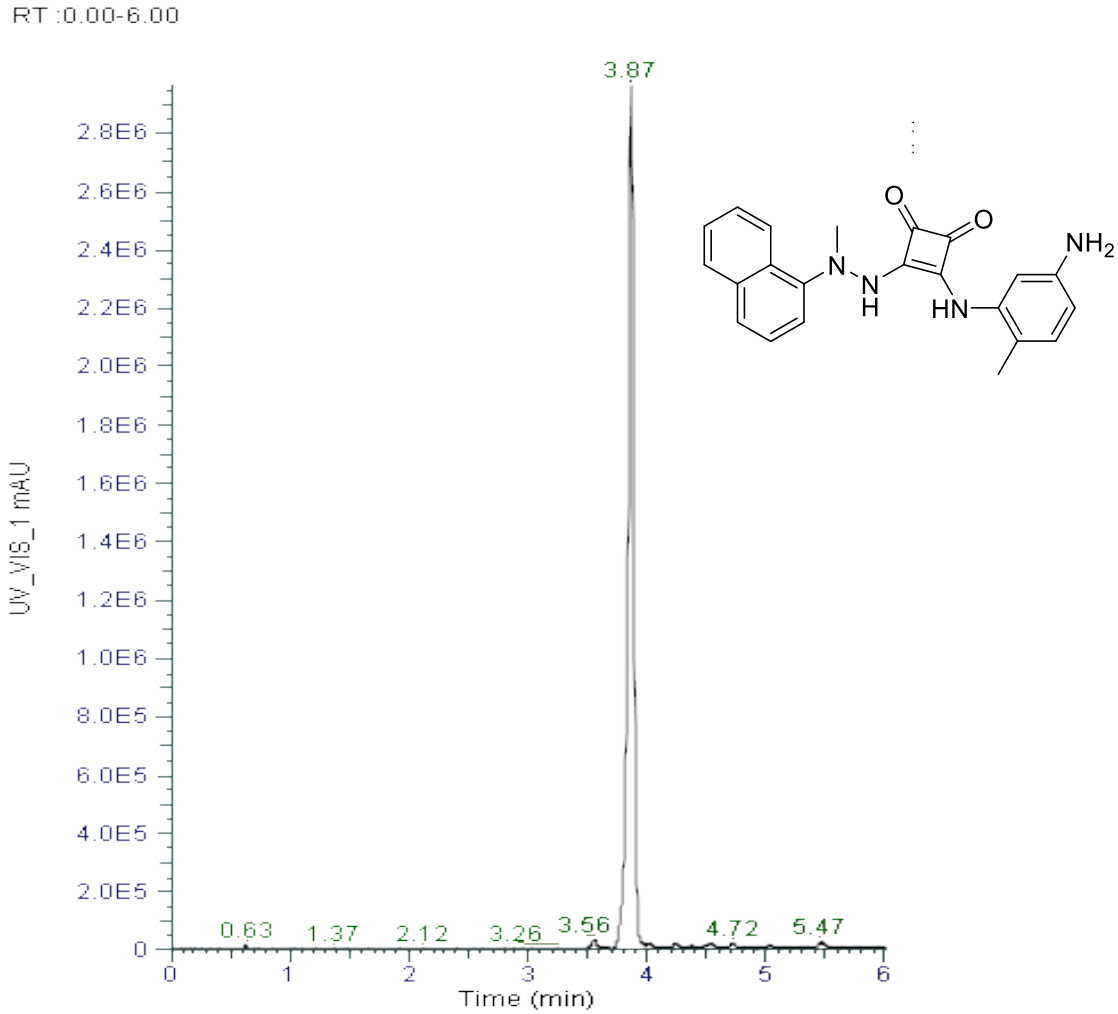
UHPLC trace of (R)-(6-(1-(naphthalen-1-yl)ethyl)-2,6-diazaspiro[3.3]heptan-2-yl)(pyridin-3-yl)methanone (56).



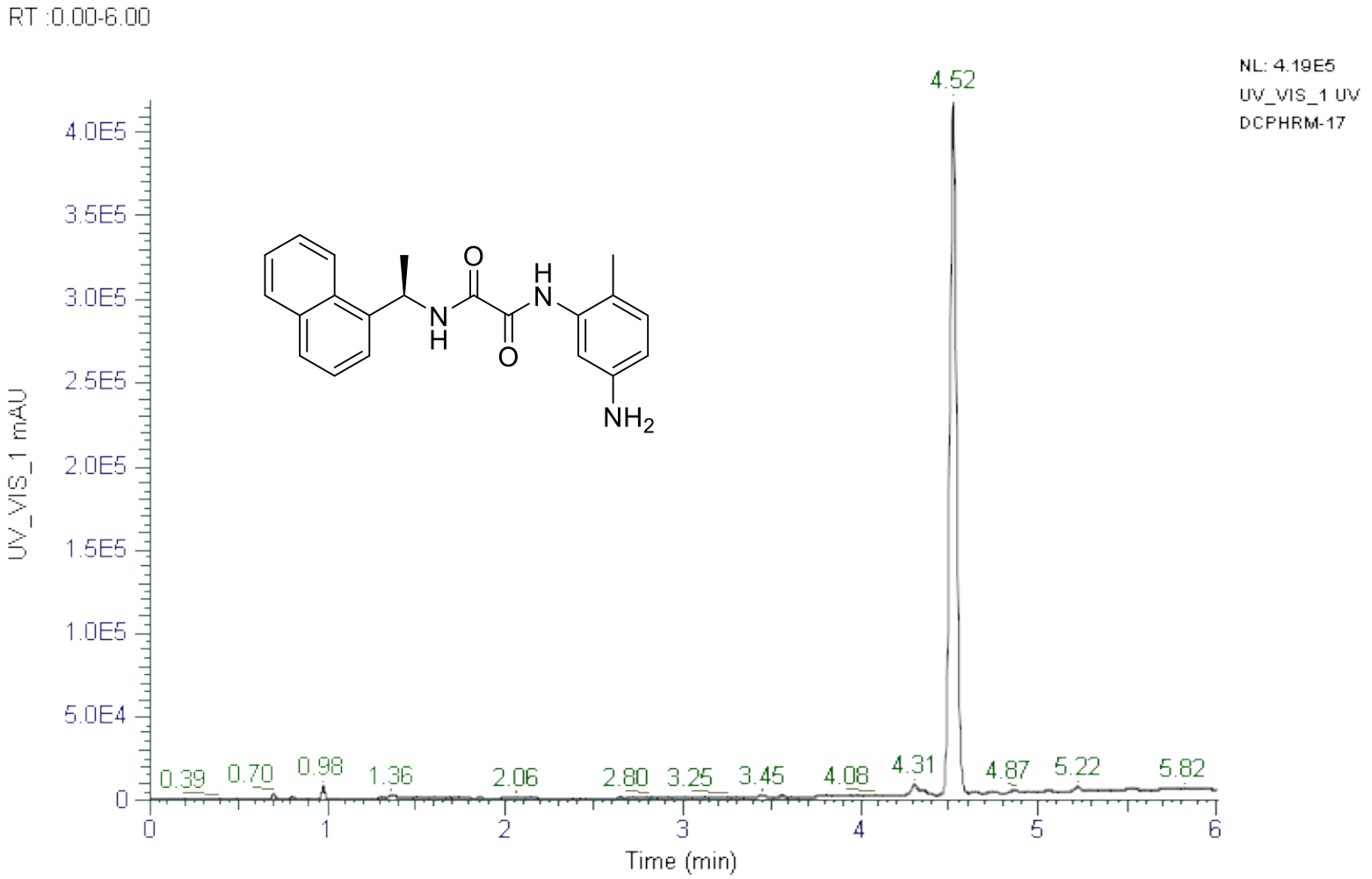
UHPLC trace of (*R*)-3-((5-amino-2-methylphenyl)amino)-4-((1-(naphthalen-1-yl)ethyl)amino)cyclobut-3-ene-1,2-dione (59).



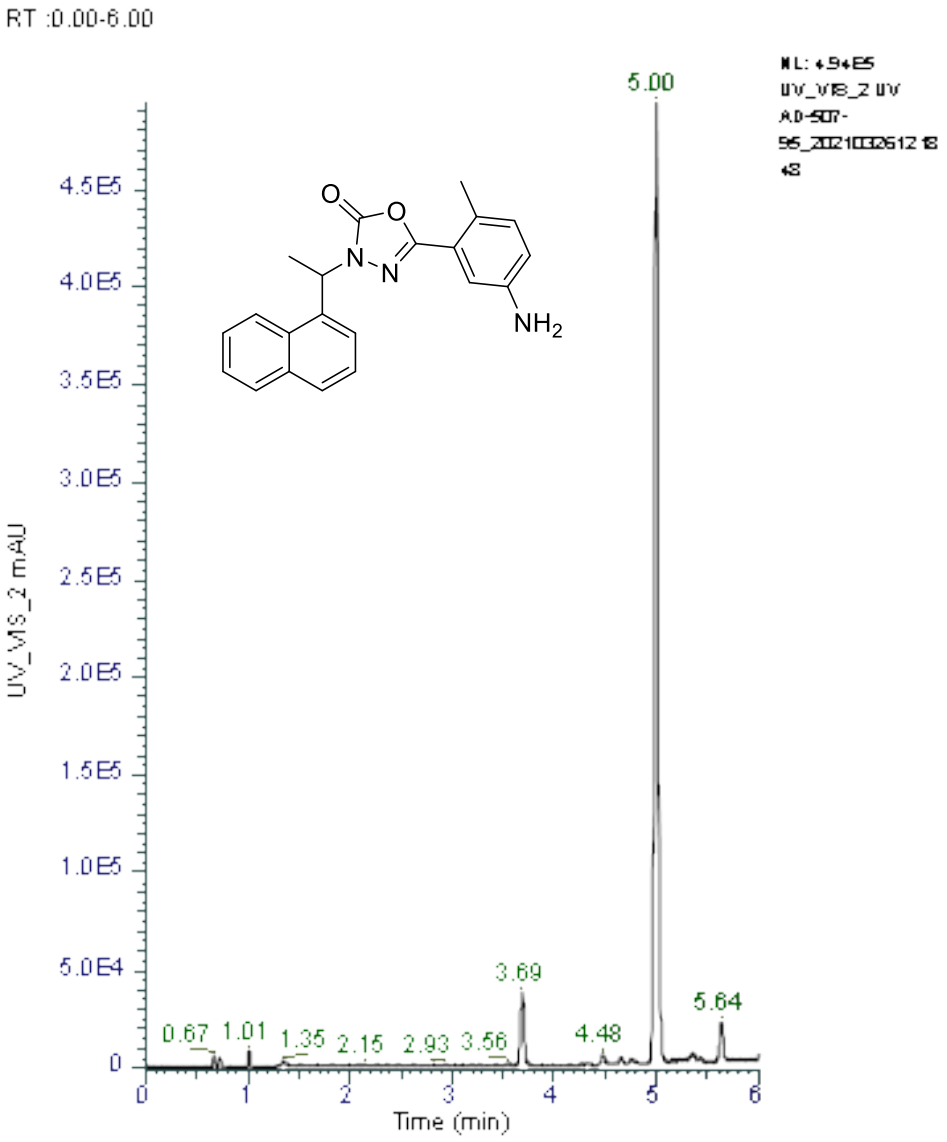
UHPLC trace of 3-[*N*'-(Naphthalen-1-yl)-*N*'-methylhydrazinyl]-4-[(5-amino-2-methylphenyl)amino]cyclobut-3-ene-1,2-dione (61).



UHPLC trace of (*R*)-*N*^{1}-(5-amino-2-methylphenyl)-*N*^{2}-(1-(naphthalen-1-yl)ethyl)oxalamide (63).



UHPLC trace of 5-(5-amino-2-methylphenyl)-3-(1-(naphthalen-1-yl)ethyl)-1,3,4-oxadiazol-2(3H)-one (69).


RT :0.00-6.00
5.00
4.5E5
4.0E5
3.5E5
3.0E5
2.5E5
2.0E5
1.5E5
1.0E5
5.0E4
0
UV_VIS_2 mAU
3.69
5.64
0.67
1.01
1.35
2.15
2.93
3.56
4.48
0
1
2
3
4
5
6
Time (min)
O
O
N
N
NH2

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