SUPPLEMENTARY MATERIAL for

Synthesis and biological evaluation of aminothiazoles against *Histoplasma capsulatum* and *Cryptococcus neoformans*

Keisuke Ishita,[1] Stavros Stephanopoulos,[2] Ahmed Khalil,[1#] Xiaolin Cheng,[1] Werner Tjarks,[1] Chad Rappleye[2*]

[1]*Division of Medicinal Chemistry and Pharmacognosy, College of Pharmacy, The Ohio State University;* [2]*Department of Microbiology, The Ohio State University*

*Corresponding Author: Chad Rappleye: 484 West 12th Avenue, Columbus, OH 43210, USA; Tel.: 614-247-2718; Fax: 614-292-8120; E-mail address: rappleye.1@osu.edu

[#]Permanent address: Chemistry Department, Faculty of Science, Zagazig University, Zagazig, Egypt; Current address: Chemistry Department, College of Science, King Faisal University, Al-Hofuf 31982, Al-Ahssa, KSA.

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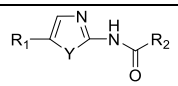
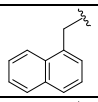
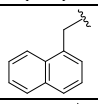
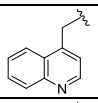
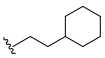
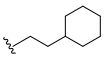
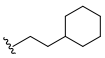
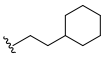
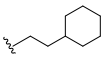
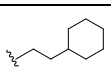
S.1. Abbreviations

ACD, advanced chemistry development; ATCC, American type culture collection; DMAP, 4-dimethylaminopyridine; DCM, dichloromethane; DMF, dimethylformamide; DMSO, dimethyl sulfoxide; EDCI, 1-ethyl-3-(-3-dimethylaminopropyl) carbodiimide; FBS, fetal bovine serum; HEPES, 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid; HMM, *Histoplasma*-macrophage media; HR-ESI, high resolution–electrospray ionization; LDA lithium diisopropyl amide; LTQ, linear trap quadrupole; MIC, minimal inhibitory concentration; MOPS, 3-(N-morpholino)propanesulfonic acid; Q-TOF, quadrupole time of flight; RFP, red fluorescence protein; RP-8, reversed-phase 8; RPMI, Roswell Park Memorial Institute; SD, standard deviation; TFA, trifluoroacetic acid, THF, tetrahydrofuran; TLC, thin layer chromatography; YPD, yeast extract peptone dextrose.

S.2. Antifungal activities of 41F5-derived antifungal compounds having an ionizable aromatic ring at the 5-position or an ionizable core structure at pH 5 and pH 7

Data shown in Tables 3-5 of the main manuscript are from assays carried out in Roswell Park Memorial Institute (RPMI) media buffered with 25 mM 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid (HEPES) to pH 7. Table S1 shows data for compounds containing nitrogen-containing ionizable groups, such as quinoline (**28a/b**), pyridine (**29a/b**, **31**, **32a/b**) and imidazole (**40**), that were obtained from experiments carried out in RPMI at pH 7 in comparison with experiments carried out in RPMI that was buffered with 25 mM 3-(N-morpholino)propanesulfonic acid (MOPS) to pH 5 in order to explore possible effects of charge and water solubility on activity. With the exception of **28a**, the tested compounds were, if at all, somewhat more active at pH 7 as compared to pH 5 (**28b**, **29a/b**, **32a**, **40**).

Table S.1. Activity of 2-aminoazoles having an ionizable aromatic ring at the 5-position or as a core structure

	pH				*H. capsulatum*		*C. neoformans* (H99 strain)	
		Y	R_1	R_2	IC_{50} (μM) [±SD]	MIC (μM)	IC_{50} (μM) [±SD]	MIC (μM)
41F5	7	S			0.48 [±0.01]	1.25	0.67 [±0.06]	1.25
41F5	5	S			6.75 [±0.69]	10.00	3.04 [±0.62]	5.00
28a	7	S			> 20	> 40	> 20	> 40
28a	5	S			15.67 [±1.17]	40.00	> 20	> 40
28b	7	S			3.05 [±0.25]	10.00	3.24 [±0.42]	10.00
28b	5	S			16.78 [±1.60]	40.00	4.29 [±0.18]	10.00
29a	7	S			8.09 [±0.70]	20.00	> 20	> 40
29a	5	S			> 20	> 40	> 20	> 40
29b	7	S			18.30 [±1.06]	40.00	7.17 [±0.84]	20.00
29b	5	S			> 20	> 40	15.57 [±5.94]	> 40
31	7	S			> 20	> 40	> 20	> 40
31	5	S			> 20	> 40	> 20	> 40
32a	7	S			7.67 [±0.25]	20.00	> 20	> 40
32a	5	S			11.08 [±2.72]	40.00	> 20	> 40
32b	7	S			> 20	> 40	> 20	> 40
32b	5	S			> 20	> 40	> 20	> 40
40	7	NH			8.11 [±0.33]	20.00	> 20	> 40
40	5	NH			> 20	> 40	> 20	> 40

SD: Standard deviation

S.3. Aqueous solubility of 41F5-derived antifungal compounds having an ionizable aromatic ring at the 5-position or an ionizable core structure at pH 5 and pH 7 (see S.4.4.)

Aqueous solubilities and pKa values of compounds **28a/b**, **29a/b**, **31**, **32a/b**, **40** were calculated with ACD/Percepta software (Version 14.1.0, Advanced Chemistry Development, Inc.,Toronto, ON, Canada) (Table S2). The calculated pKa values of thiazoles with a pyridine/quinoline group range from 4.7 to 5.4 whereas that of imidazole-containing compound **40** is 7. The calculated pKa values of the amide hydrogen atom were approximately 10 for **28a/b**, **29a/b**, **31**, **32a/b** and 17 for **40**. Except for **28a**, which has a 4-quinoline and a cyclohexylethylamide group at the 5- and 2-position, respectively, the water solubilities of all compounds were increased by factors ranging from 15 to 7850 at pH 5 and from 10 to 190 at pH 7 as compared to that of 41F5. In general, it appears that a cyclohexylethylamide group at the 2-position has a negative effect on water solubility, as cyclohexylamide-substituted compounds **28b**, **29b** and **32b** have higher aqueous solubility at both pHs 5 and 7 as compared to their cyclohexylethylamide-substituted counterparts **28a**, **29a** and **32a**.

Table S.2. pKa values and aqueous solubilities of 41F5 and 2-aminoazoles with ionizable groups

Cmpd.	pKa of pyridine, quinoline or imidazole	Aqueous solubility at pH 5 [mg/mL]	Aqueous solubility at pH 7 [mg/mL]	Ratio of solubility at pH 5 over pH 7
41F5	n.a.	0.004	0.004	1.0
28a	5.0	0.005	0.003	1.7
28b	5.0	0.13	0.07	1.9
29a	4.7	0.06	0.04	1.5
29b	4.7	0.48	0.34	1.4
31	4.9	0.59	0.34	1.7
32a	5.4	0.14	0.04	3.5
32b	5.4	1.19	0.35	3.4
40	7.0	31.4	0.76	41.3

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S.4. Experimental section

S.4.1. General synthetic procedures

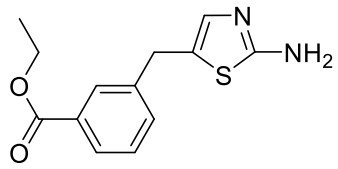
^{1}H and ^{13}C NMR spectra were obtained on a Bruker AVIII400HD NMR spectrometer, a Bruker DRX400 NMR spectrometer or a Bruker AV300 NMR spectrometer at The Ohio State University College of Pharmacy. Chemical shifts (δ) are reported in ppm from non-deuterated chloroform, non-deuterated methanol, non-deuterated acetone, and non-deuterated dimethylsulfoxide. Coupling constants are reported in Hz. ^{13}C NMR spectra are fully decoupled. Melting points were obtained on a Thomas Hoover "UNI-MELT" capillary melting apparatus and are uncorrected. High-resolution mass spectra were obtained at The Ohio State University College of Pharmacy on a Waters Micromass Q-TOF micro mass spectrometer or a Thermo LTQ Orbitrap mass spectrometer.

Silica gel 60 (0.063–0.200 mm) used for gravity column chromatography, was purchased from Dynamic Adsorbents Inc. (Norcross, GA). LiChroprep® RP-8 silica gel (0.040–0.063 mm), used for gravity reverse-phase column chromatography, was purchased from EM Science (Gibbstown, NJ). Reagent-grade solvents were used for silica gel column chromatography. Precoated glass-backed TLC plates with silica gel 60 F254 (0.25-mm layer thickness) from Dynamic Adsorbents (Norcross, GA) were used for TLC. Precoated glass-backed TLC plates with RP-8 silica gel F254 (0.25-mm layer thickness) from Alltech (Deerfield, IL) were used for RP-8 TLC. General compound visualization for TLC was performed with short ultraviolet light (254 nm).

Chemicals and anhydrous solvents for reactions were purchased from standard vendors and were used as such. Unless specified otherwise, all reactions were performed under argon atmosphere.

Key starting materials **1**, **3**, **5**, **7p**, **8**, **11**, (1*R/S*, 4*R/S*)-4-(methoxycarbonyl)cyclohexane-1-carboxylic acid, (1*R*, 4*R*)-4-(methoxycarbonyl)cyclohexane-1-carboxylic acid, (1*R*, 2*S*)-2-(methoxycarbonyl)cyclohexane-1-carboxylic acid, **39**, and 5-benzyl-1*H*-imidazol-2-amine hydrochloride were purchased from standard vendors. Compounds **2**,[1] **7o**,[2] **9**,[3] and **37**[4] are reported compounds and were synthesized according to published procedures. Compounds **6o**,[2] **10**,[3] and **12**[5] are reported compounds that were synthesized according to modified protocols.

S.4.2. Preparation of precursors and target compounds



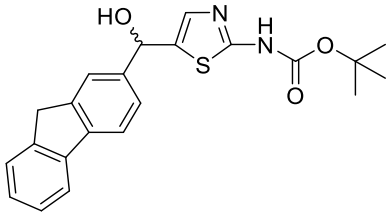
S.4.2.1. Ethyl 3-(2-aminothiazol-5-ylmethyl)benzoate (4)

Compound **4** was synthesized from **3** by adapting a published procedure.[1] A solution of sodium nitrite (0.9 g, 12.9 mmol) in water (15 mL) was added dropwise to a solution of ethyl 3-aminobenzoate (2.0 g, 12.1 mmol) in 18% aqueous HCl (15 mL) at –5 ºC. Following stirring at 0 ºC for 30 min, the reaction mixture was carefully neutralized with $NaHCO_3$ and subsequently added to an ice-cold suspension of acrolein (2.0 mL, 36 mmol), $CuCl_2$ x $2H_2O$ (600 mg, 3.5 mmol), and CaO (200 mg, 3.5 mmol) in acetone (30 mL). The solution was stirred at room temperature for 2 h. Acetone was removed by evaporation and the resulting mixture extracted with DCM, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was dissolved in ethanol (40 mL) and thiourea (1.1 g, 14.6 mmol) was added. The mixture was refluxed for 24 h. Following cooling to room temperature, $NaHCO_3$ was added, the resulting mixture filtered, and the filtrate evaporated. The residue was purified by silica gel column chromatography.

Yield = 1.10 g (22%, brown oil). R_f = 0.31 (DCM/methanol, 9:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (s, 2H), 7.39 – 7.28 (m, 2H), 6.74 (s, 1H), 5.54 (s, 2H), 4.33 (q, *J* = 7.1 Hz, 2H), 3.94 (s, 2H), 1.35 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.3, 166.5, 140.1, 135.6, 132.8, 130.7, 129.4, 128.6, 127.8, 126.5, 61.0, 33.1, 14.3. MS (HR-ESI) for $C_{13}H_{15}N_2O_2S$ ($[M+H]^+$), calcd: *m/z* 263.08487, found: *m/z* 263.08450.

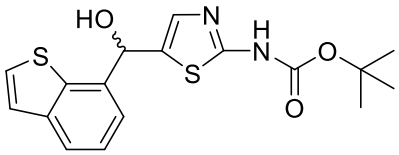
S.4.2.2. General procedure for the synthesis of 6a-o

To a stirred solution of **5** (1 equiv.) in THF (~20 mL) was added dropwise a 2.0 M solution of lithium diisopropylamide (LDA) in THF/heptane/ethylbenzene (2.2 equiv.) at -78 ºC. The reaction mixture was stirred for 30 min at 0 ºC followed by dropwise addition of aldehyde (1.2 equiv.). The solution was stirred for 16 h at room temperature, quenched by a saturated aqueous solution of NH_4Cl and extracted with ethyl acetate. The organic phase was dried with $MgSO_4$, evaporated, and the residue was purified by silica gel column chromatography.



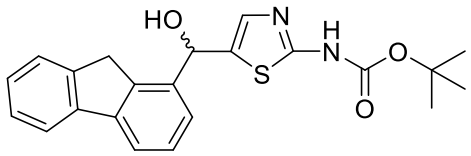
S.4.2.2.1. *tert*-Butyl {5-[hydroxy(fluoren-2-yl)methyl]thiazol-2-yl}carbamate (6a).

Starting material = **5** (2.00 g, 10.0 mmol). Yield = 1.04 g (26%, yellow solid). R_f = 0.08 (DCM/acetone, 10:1). ^{1}H NMR (400 MHz, CD_3COCD_3) δ 10.97 (br s, 1H), 7.85 (m, 2H), 7.71 (s, 1H), 7.57 (m, 1H), 7.51 (m, 1H), 7.37 (m, 1H), 7.30 (td, *J* = 7.4, 1.1 Hz, 1H), 7.12 (d, *J* = 0.8 Hz, 1H), 6.12 (d, *J* = 3.8 Hz, 1H), 5.19 (d, *J* = 4.1 Hz, 1H), 3.92 (s, 2H), 1.46 (s, 9H). ^{13}C NMR (100 MHz, CD_3COCD_3) δ 161.4, 153.5, 144.42, 144.35, 144.0, 142.3, 141.9, 138.2, 135.0, 127.62, 127.56, 126.0, 125.9, 123.7, 120.7, 120.5, 82.0, 70.7, 37.4, 28.3. mp 182 ºC (dec.). MS (HR-ESI) for $C_{22}H_{23}N_2O_3S$ ($[M+H]^+$), calcd: *m/z* 395.14239, found: *m/z* 395.14236.



S.4.2.2.2. *tert*-Butyl {5-[hydroxy(benzothiophen-7-yl)methyl]thiazol-2-yl}carbamate (6b).

Starting material = **5** (256 mg, 1.28 mmol). Yield = 135 mg (29%, light-yellow solid). R_f = 0.16 (DCM/acetone, 10:1). ^{1}H NMR (400 MHz, CD_3COCD_3) δ 11.45 (br s, 1H), 7.83 (d, *J* = 7.9 Hz, 1H), 7.61 (t, *J* = 6.5 Hz, 2H), 7.43 (t, *J* = 6.8 Hz, 2H), 7.20 (s, 1H), 6.34 (d, *J* = 3.2 Hz, 1H), 5.53 (d, *J* = 3.7 Hz, 1H), 1.44 (s, 9H). ^{13}C NMR (100 MHz, CD_3COCD_3) δ 161.7, 153.5, 141.7, 139.0, 137.3, 135.7, 135.5, 128.1, 125.2, 124.7, 123.9, 122.0, 82.0, 69.9, 28.3. mp 173-174 ºC. MS (HR-ESI) for $C_{17}H_{19}N_2O_3S_2$ ($[M+H]^+$), calcd: *m/z* 363.08316, found: *m/z* 363.08298.

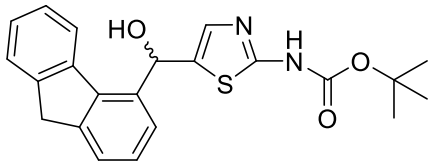


S.4.2.2.3. *tert*-Butyl {5-[hydroxy(fluoren-1-yl)methyl]thiazol-2-yl}carbamate (6c).

Starting material = **5** (124 mg, 0.62 mmol). Yield = 32 mg (13%, light-yellow solid). R_f = 0.14 (DCM/acetone, 10:1). ^{1}H NMR (400 MHz, CD_3COCD_3) δ 11.70 (br s, 1H), 7.84 (dd, *J* = 12.5,

7.6 Hz, 2H), 7.61 (d, *J* = 7.6 Hz, 1H), 7.54 (d, *J* = 7.4 Hz, 1H), 7.46 (t, *J* = 7.6 Hz, 1H), 7.35 (t, *J* = 7.3 Hz, 1H), 7.28 (t, *J* = 7.4 Hz, 1H), 7.12 (s, 1H), 6.30 (s, 1H), 3.97 – 3.78 (m, 2H), 1.40 (s, 9H). ^{13}C NMR (100 MHz, CD_3COCD_3) δ161.9, 153.4, 144.0, 142.8, 142.2, 141.1, 140.9, 136.3, 135.0, 128.2, 127.7, 127.5, 125.8, 124.8, 120.7, 120.0, 82.0, 68.6, 36.1, 28.2. mp 128-129 ºC. MS (HR-ESI) for $C_{22}H_{23}N_2O_3S$ ([M+H]$^+$), calcd: *m/z* 395.14239, found: *m/z* 395.14218.

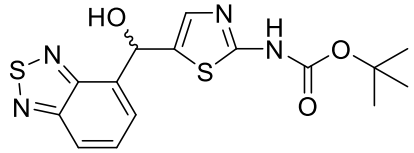
*See **S.4.2.15** for information on the synthesis of 1-fluorenecarbaldehyde (**III**), which was used as the aldehyde component in the synthesis of **6c**.*



S.4.2.2.4. *tert*-Butyl {5-[hydroxy(fluoren-4-yl)methyl]thiazol-2-yl}carbamate (6d).

Starting material = **5** (156 mg, 0.78 mmol). Yield = 114 mg (37%, yellow solid). R_f = 0.11 (DCM/acetone, 10:1). ^{1}H NMR (400 MHz, CD_3COCD_3) δ 11.64 (br s, 1H), 7.86 (d, *J* = 6.7 Hz, 1H), 7.77 (d, *J* = 7.7 Hz, 1H), 7.57 (d, *J* = 7.3 Hz, 2H), 7.39 (t, *J* = 7.6 Hz, 1H), 7.27 (p, *J* = 7.2 Hz, 2H), 6.87 (s, 1H), 6.76 (s, 1H), 5.37 (s, 1H), 3.95 (s, 2H), 1.34 (s, 9H). ^{13}C NMR (100 MHz, CD_3COCD_3) δ 161.9, 153.4, 144.9, 144.8, 141.8, 139.5, 138.9, 135.9, 135.7, 127.5, 127.5, 127.2, 125.7, 125.6, 125.2, 125.1, 81.9, 67.6, 37.6, 28.2. mp 256 ºC (dec.). MS (HR-ESI) for $C_{22}H_{23}N_2O_3S$ ([M+H]$^+$), calcd: *m/z* 395.14239, found: *m/z* 395.14255.

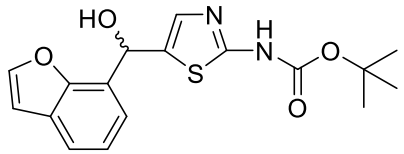
*See **S.4.2.15.** for information on the synthesis of 4-fluorenecarbaldehyde (**VI**), which was used as the aldehyde component in the synthesis of **6d**.*



S.4.2.2.5. *tert*-Butyl {5-[hydroxy(2,1,3-benzothiazol-4-yl)methyl]thiazol-2-yl}carbamate (6e).

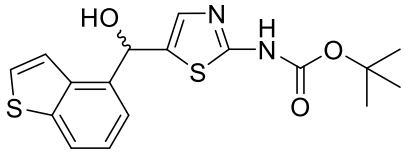
Starting material = **5** (1.02 g, 5.08 mmol). Yield = 974 mg (53%, orange solid). R_f = 0.25 (DCM/methanol, 20:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.23 (br s, 1H), 7.84 (dd, *J* = 8.6, 0.8 Hz, 1H), 7.69 (d, *J* = 6.8 Hz, 1H), 7.52 (dd, *J* = 8.8, 6.9 Hz, 1H), 7.04 (s, 1H), 6.59 (s, 1H), 4.50 (br s, 1H), 1.38 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.0, 155.0, 152.8, 152.4, 135.1, 134.2, 133.5,

129.4, 125.6, 120.9, 81.8, 67.4, 28.1. mp 177-180 ºC. MS (HR-ESI) for $C_{15}H_{16}N_4O_3S_2Na$ ($[M+Na]^+$), calcd: *m/z* 387.05560, found: *m/z* 387.05719.



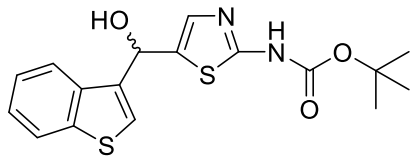
S.4.2.2.6. *tert*-Butyl {5-[hydroxy(benzofuran-7-yl)methyl]thiazol-2-yl}carbamate (6f).

Starting material = **5** (286 mg, 1.43 mmol). Yield = 400 mg (81%, yellowish white solid). R_f = 0.15 (DCM/methanol, 40:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.99 (br s, 1H), 7.62 (d, *J* = 2.2 Hz, 1H), 7.58 (dd, *J* = 7.8, 1.1 Hz, 1H), 7.47 (d, *J* = 7.4 Hz, 1H), 7.31 – 7.27 (m, 1H), 7.08 (d, *J* = 0.5 Hz, 1H), 6.80 (d, *J* = 2.2 Hz, 1H), 6.48 (s, 1H), 2.98 (br s, 1H), 1.45 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.2, 152.9, 151.7, 145.1, 134.3, 133.9, 128.0, 126.3, 123.3, 121.6, 121.3, 106.9, 82.0, 66.6, 28.3. mp 167-169 ºC. MS (HR-ESI) for $C_{17}H_{19}N_2O_4S$ ($[M+H]^+$), calcd: *m/z* 347.10600, found: *m/z* 347.10593.



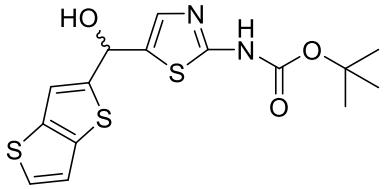
S.4.2.2.7. *tert*-Butyl {5-[hydroxy(benzothiophen-4-yl)methyl]thiazol-2-yl}carbamate (6g).

Starting material = **5** (1.12 g, 5.60 mmol). Yield = 1.16 g (57%, off-white solid). R_f = 0.17 (DCM/methanol, 40:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.08 (br s, 1H), 7.83 (d, *J* = 8.1 Hz, 1H), 7.54 (d, *J* = 7.3 Hz, 1H), 7.42 (s, 2H), 7.34 (t, *J* = 7.3 Hz, 1H), 6.89 (d, *J* = 0.7 Hz, 1H), 6.37 (s, 1H), 2.92 (br s, 1H), 1.35 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.2, 152.8, 140.8, 136.8, 136.7, 134.7, 134.1, 129.2, 128.4, 127.1, 125.4, 124.4, 122.7, 121.8, 121.7, 82.0, 77.2, 69.4, 28.2. mp 191 ºC (dec.). MS (HR-ESI) for $C_{17}H_{19}N_2O_3S_2$ ($[M+H]^+$), calcd: *m/z* 363.08316, found: *m/z* 363.08304.



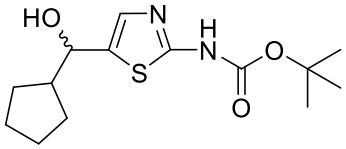
S.4.2.2.8. *tert*-Butyl {5-[hydroxy(benzothiophen-3-yl)methyl]thiazol-2-yl}carbamate (6h).

Starting material = **5** (1.12 g, 5.60 mmol). Yield = 1.10 g (54%, yellow amorphous solid). R_f = 0.13 (DCM/acetone, 10:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.14 (br s, 1H), 7.84 – 7.80 (m, 1H), 7.71 – 7.66 (m, 1H), 7.54 (d, *J* = 0.5 Hz, 1H), 7.33 – 7.27 (m, 2H), 7.08 – 7.04 (m, 1H), 6.32 – 6.27 (m, 1H), 3.11 (br s, 1H), 1.37 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.3, 152.9, 141.1, 137.3, 136.7, 134.7, 133.3, 124.7, 124.3, 123.8, 123.0, 122.5, 82.0, 66.2, 28.2. MS (HR-ESI) for $C_{17}H_{19}N_2O_3S_2$ ([M+H]$^+$), calcd: *m/z* 363.08316, found: *m/z* 363.08304.



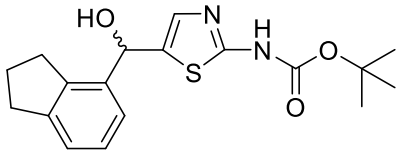
S.4.2.2.9. *tert*-Butyl (5-{hydroxy[thieno(3,2-b)thiophen-2-yl]methyl}thiazol-2-yl)carbamate (6i).

Starting material = **5** (1.08 g, 5.40 mmol). Yield = 186 mg (9%, orange amorphous solid). R_f = 0.13 (DCM/acetone, 10:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.69 (br s, 1H), 7.35 (d, *J* = 5.2 Hz, 1H), 7.26 – 7.20 (m, 3H), 6.26 (s, 1H), 2.87 (br s, 1H), 1.48 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.4, 152.8, 148.4, 139.1, 138.6, 134.8, 133.8, 127.4, 119.7, 117.4, 82.4, 67.4, 28.3. MS (HR-ESI) for $C_{15}H_{17}N_2O_3S_3$ ([M+H]$^+$), calcd: *m/z* 369.03958, found: *m/z* 369.03897.



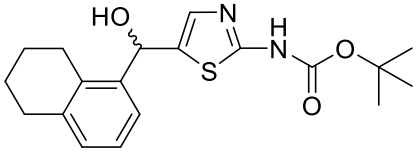
S.4.2.2.10. *tert*-Butyl {5-[hydroxy(cyclopentyl)methyl]thiazol-2-yl}carbamate (6j).

Starting material = **5** (1.85 g, 9.26 mmol). Yield = 1.62 g (59%, white solid). R_f = 0.15 (DCM/methanol, 40:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.16 (br s, 1H), 7.18 (s, 1H), 4.58 (d, *J* = 8.5 Hz, 1H), 2.45 (br s, 1H), 2.25 (sext, *J* = 8.0 Hz, 1H), 1.95 – 1.86 (m, 1H), 1.65 – 1.46 (m, 15H), 1.23 – 1.13 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.7, 153.0, 135.0, 133.4, 82.0, 72.8, 47.7, 29.7, 28.4, 25.8, 25.6. mp 167-168 ºC. MS (HR-ESI) for $C_{14}H_{23}N_2O_3S$ ([M+H]$^+$), calcd: *m/z* 299.14239, found: *m/z* 299.14240.



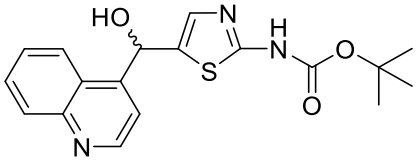
S.4.2.2.11. *tert*-Butyl {5-[hydroxy(indan-4-yl)methyl]thiazol-2-yl}carbamate (6k).

Starting material = **5** (627 mg, 3.13 mmol). Yield = 573 mg (53%, dark orange amorphous solid). R_f = 0.12 (DCM/methanol, 50:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.19 (br s, 1H), 7.41 – 7.34 (m, 1H), 7.20 – 7.14 (m, 2H), 6.95 (s, 1H), 5.99 (s, 1H), 2.93 – 2.81 (m, 3H), 2.78 – 2.68 (m, 1H), 2.03 (quin, J = 7.4 Hz, 2H), 1.46 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.3, 152.9, 144.7, 141.0, 138.1, 134.2, 134.1, 126.8, 124.0, 122.8, 81.8, 68.3, 32.7, 30.9, 28.2, 25.0. MS (HR-ESI) for $C_{18}H_{23}N_2O_3S$ ([M+H]$^+$), calcd: m/z 347.14239, found: m/z 347.14252.



S.4.2.2.12. *tert*-Butyl {5-[hydroxy(tetralin-5-yl)methyl]thiazol-2-yl}carbamate (6l).

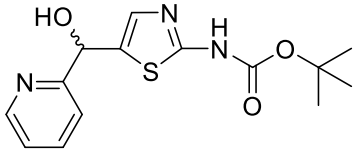
Starting material = **5** (1.14 g, 5.67 mmol). Yield = 1.09 g (53%, white solid). R_f = 0.12 (DCM/methanol, 50:1). ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.89 (br s, 1H), 7.48 (d, J = 7.6 Hz, 1H), 7.16 (t, J = 7.6 Hz, 1H), 7.06 – 7.00 (m, 1H), 6.96 (s, 1H), 6.12 (s, 1H), 2.84 – 2.69 (m, 3H), 2.58 – 2.45 (m, 1H), 2.36 (br s, 1H), 1.81 – 1.69 (m, 4H), 1.45 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.2, 152.8, 140.4, 137.7, 134.8, 134.2, 133.7, 129.4, 125.9, 122.9, 82.0, 66.6, 30.2, 28.3, 25.7, 23.2, 22.7. mp 208 ºC (dec.). MS (HR-ESI) for $C_{19}H_{25}N_2O_3S$ ([M+H]$^+$), calcd: m/z 361.15804, found: m/z 361.15845.



S.4.2.2.13. *tert*-Butyl {5-[hydroxy(quinolin-4-yl)methyl]thiazol-2-yl}carbamate (6m).

Starting material = **5** (1.06 g, 5.30 mmol). Yield = 503 mg (27%, off-white solid). R_f = 0.13 (DCM/methanol, 25:1). ^{1}H NMR (400 MHz, CD_3SOCD_3) δ 11.38 (br s, 1H), 8.96 (d, J = 4.4 Hz, 1H), 8.20 (d, J = 8.2 Hz, 1H), 8.04 (d, J = 8.2 Hz, 1H), 7.79 (d, J = 4.4 Hz, 1H), 7.76 – 7.69 (m,

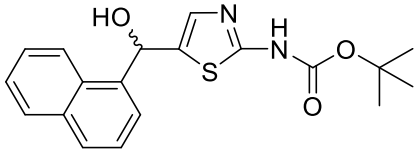
1H), 7.61 – 7.53 (m, 1H), 7.29 (s, 1H), 6.69 (d, *J* = 3.9 Hz, 1H), 6.52 (d, *J* = 4.2 Hz, 1H), 1.40 (s, 9H). ^{13}C NMR (100 MHz, CD_3SOCD_3) δ 159.6, 152.7, 150.6, 149.2, 147.8, 135.4, 134.6, 129.7, 129.1, 126.5, 124.8, 124.1, 117.6, 81.1, 64.7, 27.8. mp 201 ºC (dec.). MS (HR-ESI) for $C_{18}H_{20}N_3O_3S$ ([M+H]$^+$), calcd: *m/z* 358.12199, found: *m/z* 358.12198.



S.4.2.2.14. *tert*-Butyl {5-[hydroxy(pyridin-2-yl)methyl]thiazol-2-yl}carbamate (6n).

Deviation from standard procedure (vide supra): Following quenching of the reaction with a saturated aqueous solution of NH_4Cl, the resulting mixture was filtered, evaporated and the residue dissolved in methanol. Silica gel was added followed by evaporation. The residue was applied on top of silica gel column for chromatographic purification.

Starting material = **5** (2.00 g, 10.0 mmol). Yield = 993 mg (32%, orange solid). R_f = 0.25 (DCM/methanol, 15:1). ^{1}H NMR (400 MHz, CD_3OD) δ 8.49 (d, *J* = 4.3 Hz, 1H), 7.89 (td, *J* = 7.8, 1.6 Hz, 1H), 7.69 (d, *J* = 7.9 Hz, 1H), 7.38 – 7.30 (m, 1H), 7.14 (s, 1H), 5.98 (s, 1H), 1.51 (s, 9H). ^{13}C NMR (100 MHz, CD_3OD) δ 163.3, 162.7, 154.3, 149.4, 139.1, 135.9, 135.8, 124.3, 121.8, 82.9, 71.6, 28.4. mp 98 ºC (dec.). MS (HR-ESI) for $C_{14}H_{18}N_3O_3S$ ([M+H]$^+$), calcd: *m/z* 308.10634, found: *m/z* 308.10614.

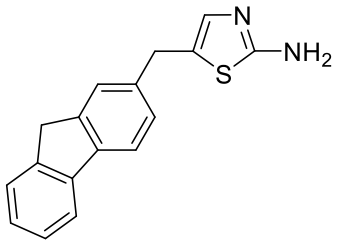


S.4.2.2.15. *tert*-Butyl {5-[hydroxy(naphthalen-1-yl)methyl]thiazol-2-yl}carbamate (6o).

Starting material = **5** (300 mg, 1.50 mmol). Yield = 280 mg (52%, yellow solid). R_f = 0.14 (DCM/acetone, 10:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.76 (br s, 1H), 7.99 – 7.94 (m, 1H), 7.87 – 7.78 (m, 3H), 7.51 – 7.41 (m, 3H), 6.92 (s, 1H), 6.65 (s, 1H), 2.68 (br s, 1H), 1.32 (s, 9H).^{13}C NMR (100 MHz, $CDCl_3$) δ 162.1, 152.8, 137.7, 134.8, 134.4, 134.0, 130.2, 129.0, 129.0, 126.5, 125.9, 125.5, 123.8, 123.6, 82.1, 67.8, 28.2. The ^{1}H and ^{13}C NMR spectroscopic data match those previously reported.[2]

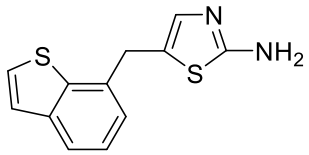
S.4.2.3. General procedure for the synthesis of compounds 7a-l

These compounds were prepared by adapting a published procedure.[2] A mixture of compounds **6a–l**, triethylsilane (8 equiv.), and trifluoroacetic acid (14 equiv.) in DCM (~20 mL) was stirred overnight at room temperature. The reaction mixture was treated with a saturated aqueous solution of $NaHCO_3$. The product was extracted with DCM, dried over $MgSO_4$, filtered and evaporated. The residue was purified by silica gel column chromatography.



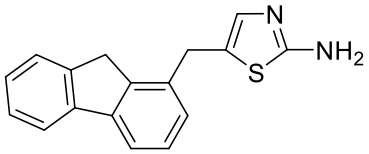
S.4.2.3.1. 5-(2-Fluorenylmethyl)-2-thiazolamine (7a).

Starting material = **6a** (1.00 g, 2.53 mmol). Yield = 533 mg (76%, yellow solid). R_f = 0.25 (DCM/methanol, 15:1). ^{1}H NMR (400 MHz, CD_3COCD_3) δ 7.87 – 7.74 (m, 2H), 7.55 (d, J = 7.4 Hz, 1H), 7.45 (s, 1H), 7.35 (t, J = 7.7 Hz, 1H), 7.31 – 7.23 (m, 2H), 6.78 (s, 1H), 6.09 (br s, 2H), 4.03 (s, 2H), 3.88 (s, 2H). ^{13}C NMR (100 MHz, CD_3COCD_3) δ 168.9, 144.6, 144.2, 142.4, 140.9, 140.4, 136.6, 127.9, 127.6, 127.5, 127.4, 125.9, 125.9, 120.6, 120.5, 37.3, 33.9. mp 197-198 ºC. MS (HR-ESI) for $C_{17}H_{15}N_2S$ ($[M+H]^+$), calcd: m/z 279.09505, found: m/z 279.09491.



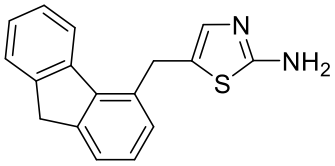
S.4.2.3.2. 5-(7-Benzothiophenylmethyl)-2-thiazolamine (7b).

Starting material = **6b** (120.6 mg, 0.33 mmol). Yield = 60 mg (74%, light yellow solid). R_f = 0.27 (DCM/methanol, 15:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, J = 7.5 Hz, 1H), 7.45 – 7.41 (m, 1H), 7.39 – 7.31 (m, 2H), 7.22 – 7.17 (m, 1H), 6.93 (s, 1H), 4.89 (s, 2H), 4.23 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.5, 140.2, 139.2, 136.9, 134.0, 126.2, 125.9, 124.8, 124.6, 123.9, 122.5, 32.7. mp 137-140 ºC. MS (HR-ESI) for $C_{12}H_{11}N_2S_2$ ($[M+H]^+$), calcd: m/z 247.03582, found: m/z 247.03569.



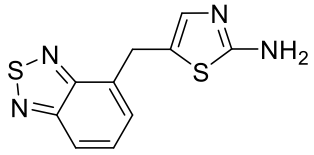
S.4.2.3.3. 5-(1-Fluorenylmethyl)-2-thiazolamine (7c).

Starting material = **6c** (29.0 mg, 74 μmol). Yield = 16 mg (77%, yellow solid). R_f = 0.20 (DCM/methanol, 15:1). ^{1}H NMR (400 MHz, CD_3COCD_3) δ 7.86 (d, *J* = 7.5 Hz, 1H), 7.76 (d, *J* = 7.6 Hz, 1H), 7.59 (d, *J* = 7.5 Hz, 1H), 7.41 – 7.28 (m, 3H), 7.23 – 7.17 (m, 1H), 6.80 (s, 1H), 6.09 (br s, 2H), 4.12 (s, 2H), 3.88 (s, 2H). ^{13}C NMR (100 MHz, CD_3COCD_3) δ 168.6, 143.9, 142.7, 142.5, 137.8, 137.0, 128.3, 127.8, 127.6, 127.6, 125.9, 120.8, 119.1, 36.0, 31.5. mp 186 ºC (dec.). MS (HR-ESI) for $C_{17}H_{15}N_2S$ ($[M+H]^+$), calcd: *m/z* 279.09505, found: *m/z* 279.09503.



S.4.2.3.4. 5-(4-Fluorenylmethyl)-2-thiazolamine (7d).

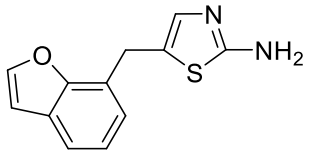
Starting material = **6d** (66.9 mg, 0.17 mmol). Yield = 35 mg (73%, white solid). R_f = 0.18 (DCM/methanol, 15:1). ^{1}H NMR (400 MHz, CD_3COCD_3) δ 7.94 (d, *J* = 7.7 Hz, 1H), 7.59 (d, *J* = 7.3 Hz, 1H), 7.49 (d, *J* = 7.1 Hz, 1H), 7.39 – 7.22 (m, 4H), 6.65 (s, 1H), 6.05 (br s, 2H), 4.43 (d, *J* = 1.4 Hz, 2H), 3.94 (s, 2H). ^{13}C NMR (100 MHz, CD_3COCD_3) δ 168.6, 145.1, 144.7, 142.4, 140.1, 136.9, 135.8, 129.3, 127.6, 127.5, 127.2, 125.8, 125.8, 124.4, 124.3, 37.6, 32.0. mp 217-218 ºC. MS (HR-ESI) for $C_{17}H_{15}N_2S$ ($[M+H]^+$), calcd: *m/z* 279.09505, found: *m/z* 279.09477.



S.4.2.3.5. 5-(2,1,3-Benzothiadiazol-4-ylmethyl)-2-thiazolamine (7e).

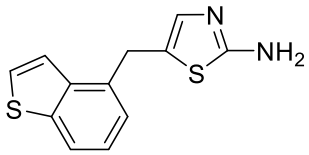
Starting material = **6e** (97.2 mg, 0.27 mmol). Yield = 44 mg (66%, yellowish white solid). R_f = 0.28 (DCM/methanol, 20:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, *J* = 8.8 Hz, 1H), 7.53 (dd, *J* = 8.8, 6.8 Hz, 1H), 7.38 (dd, *J* = 6.8, 0.9 Hz, 1H), 6.94 (s, 1H), 4.80 (br s, 2H), 4.50 (s, 2H). ^{13}C

NMR (100 MHz, $CDCl_3$) δ 167.3, 155.2, 154.4, 136.8, 133.4, 129.7, 127.7, 125.9, 120.2, 29.4. mp 154-157 ºC. MS (HR-ESI) for $C_{10}H_9N_4S_2$ ([M+H]$^+$), calcd: *m/z* 249.02631, found: *m/z* 249.02652.



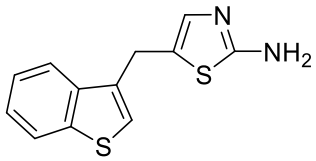
S.4.2.3.6. 5-(7-Benzofuranylmethyl)-2-thiazolamine (7f).

Starting material = **6f** (300 mg, 0.87 mmol). Yield = 142 mg (71%, yellowish white solid). R_f = 0.27 (DCM/methanol, 20:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (d, *J* = 2.2 Hz, 1H), 7.49 (dd, *J* = 7.7, 0.9 Hz, 1H), 7.21 – 7.09 (m, 2H), 6.86 (s, 1H), 6.77 (d, *J* = 2.2 Hz, 1H), 4.91 (br s, 2H), 4.25 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.5, 153.1, 144.9, 136.0, 127.5, 126.5, 124.2, 123.7, 123.1, 119.9, 106.9, 27.2. mp 100-101 ºC. MS (HR-ESI) for $C_{12}H_{11}N_2OS$ ([M+H]$^+$), calcd: *m/z* 231.05866, found: *m/z* 231.05812.



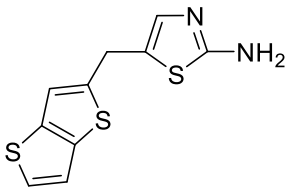
S.4.2.3.7. 5-(4-Benzothiophenylmethyl)-2-thiazolamine (7g).

Starting material = **6g** (1.10 g, 3.04 mmol). Yield = 392 mg (52%, yellowish white solid). R_f = 0.08 (DCM/acetone, 10:1). ^{1}H NMR (400 MHz, CD_3COCD_3) δ 7.85 (d, *J* = 8.0 Hz, 1H), 7.64 (d, *J* = 5.7 Hz, 1H), 7.59 (dd, *J* = 5.6, 0.8 Hz, 1H), 7.31 (t, *J* = 7.6 Hz, 1H), 7.28 – 7.23 (m, 1H), 6.80 (t, *J* = 1.1 Hz, 1H), 6.15 (br s, 2H), 4.32 (s, 2H). ^{13}C NMR (100 MHz, CD_3COCD_3) δ 168.8, 141.0, 139.4, 136.8, 136.3, 127.3, 126.6, 125.3, 125.0, 122.7, 121.7, 32.0. mp 153-154 ºC. MS (HR-ESI) for $C_{12}H_{11}N_2S_2$ ([M+H]$^+$), calcd: *m/z* 247.03582, found: *m/z* 247.03549.

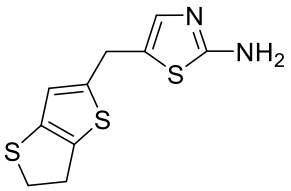


S.4.2.3.8. 5-(3-Benzothiophenylmethyl)-2-thiazolamine (7h).

Starting material = **6h** (1.03 g, 2.84 mmol). Yield = 361 mg (52%, white solid). R_f = 0.08 (DCM/acetone, 10:1). ^{1}H NMR (400 MHz, CD_3COCD_3) δ 7.97 – 7.90 (m, 1H), 7.90 – 7.83 (m, 1H), 7.43 – 7.33 (m, 3H), 6.84 (s, 1H), 6.09 (br s, 2H), 4.24 (s, 2H). ^{13}C NMR (100 MHz, CD_3COCD_3) δ 168.6, 141.4, 139.4, 137.1, 136.0, 125.5, 125.2, 124.8, 123.9, 123.6, 122.8, 26.9. mp 176-177 °C. MS (HR-ESI) for $C_{12}H_{11}N_2S_2$ ([M+H]$^+$), calcd: *m/z* 247.03582, found: *m/z* 247.03500.



7i



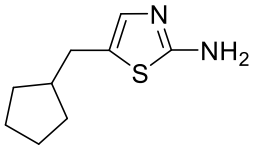
7i'

S.4.2.3.9. 5-[2-Thieno(3,2-b)thiophenylmethyl]-2-thiazolamine (7i).

Starting material = **6i** (166 mg, 0.45 mmol). Yield = 16 mg (14%, white solid). R_f = 0.12 (DCM/acetone, 5:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (d, *J* = 5.1 Hz, 1H), 7.18 (d, *J* = 5.1 Hz, 1H), 7.05 (s, 1H), 6.90 (s, 1H), 6.85 (s, 0.22H)[a], 6.79 (d, *J* = 3.5 Hz, 0.21H)[a], 6.57 (s, 0.19H)[a], 4.89 (br s, 2H), 4.22 (s, 2H)[b], 4.07 (s, 0.38H)[a,b], 3.72 (t, *J* = 7.9 Hz, 0.42H)[a], 3.13 (t, *J* = 7.9 Hz, 0.39H)[a]. MS (HR-ESI) for $C_{10}H_9N_2S_3$ ([**7i**+H]$^+$), calcd: *m/z* 252.99224, found: *m/z* 252.99196. MS (HR-ESI) for $C_{10}H_{11}N_2S_3$ ([**7i'**+H]$^+$), calcd: *m/z* 255.00789, found: *m/z* 255.00740.

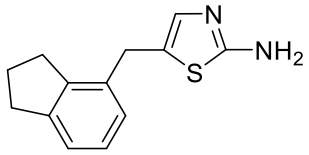
[a] *It appears that these signals arise from the partially reduced compound,* ***7i'***.

[b] *The purity of* ***7i*** *is approximately 84% based on the integration of the two signals.*



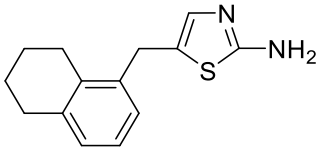
S.4.2.3.10. 5-(Cyclopentylmethyl)-2-thiazolamine (7j).

Starting material = **6j** (1.50 g, 5.03 mmol). Yield = 807 mg (88%, yellow solid). R_f = 0.23 (DCM/methanol, 20:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.70 (s, 1H), 4.92 (br s, 2H), 2.60 (d, *J* = 7.3 Hz, 2H), 2.00 (hept, *J* = 7.6 Hz, 1H), 1.82 – 1.71 (m, 2H), 1.66 – 1.46 (m, 4H), 1.23 – 1.12 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.7, 134.8, 129.1, 41.7, 33.4, 32.5, 25.2. mp 86-88 °C. MS (HR-ESI) for $C_9H_{15}N_2S$ ([M+H]$^+$), calcd: *m/z* 183.09505, found: *m/z* 183.09445.



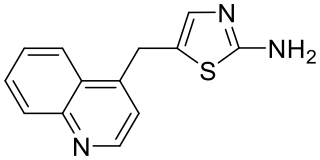
S.4.2.3.11. 5-(4-Indanylmethyl)-2-thiazolamine (7k).

Starting material = **6k** (1.50 g, 5.03 mmol). Yield = 140 mg (45%, white solid). R_f = 0.31 (DCM/methanol, 20:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16 – 7.07 (m, 2H), 7.02 – 6.95 (m, 1H), 6.74 (s, 1H), 4.84 (br s, 2H), 3.91 (s, 2H), 2.92 (t, J = 7.5 Hz, 2H), 2.86 (t, J = 7.4 Hz, 2H), 2.06 (p, J = 7.5 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.1, 144.8, 142.8, 135.6, 127.9, 126.7, 126.2, 123.0, 33.1, 31.4, 31.2, 24.9. mp 113-115 ºC. MS (HR-ESI) for $C_{13}H_{15}N_2S$ ($[M+H]^+$), calcd: m/z 231.09505, found: m/z 231.09439.



S.4.2.3.12. 5-(5-Tetralinylmethyl)-2-thiazolamine (7l).

Starting material = **6l** (1.06 g, 2.94 mmol). Yield = 608 mg (85%, off-white solid). R_f = 0.15 (DCM/acetone, 5:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.11 – 7.03 (m, 1H), 7.03 – 6.97 (m, 2H), 6.69 (s, 1H), 4.98 (br s, 2H), 3.89 (s, 2H), 2.79 (t, J = 6.0 Hz, 2H), 2.70 (t, J = 6.2 Hz, 2H), 1.87 – 1.71 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.2, 137.8, 135.6, 135.3, 128.2, 127.7, 126.6, 125.5, 30.7, 30.2, 26.2, 23.4, 22.9. mp 148-150 ºC. MS (HR-ESI) for $C_{14}H_{17}N_2S$ ($[M+H]^+$), calcd: m/z 245.11070, found: m/z 245.11023.

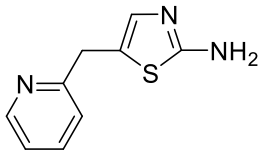


S.4.2.4. 5-(4-Quinolinylmethyl)-2-thiazolamine (7m).

Compound **7m** was synthesized by adapting a published procedure.[6] To a solution of **6m** (400 mg, 1.12 mmol) in acetic acid (5 mL) was added dropwise a 57% aqueous solution of hydrogen iodide (0.89 mL, 6.72 mmol) at 100 ºC. The reaction mixture was stirred at the same temperature

for 4 h, neutralized with 3N NaOH aqueous solution at room temperature, and extracted with ethyl acetate. The organic phase was dried over $MgSO_4$, filtered, and evaporated. The residue was purified by silica gel column chromatography.

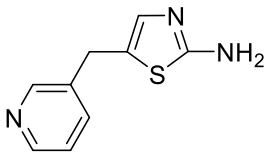
Yield = 27.2 mg (10%, orange solid). R_f = 0.11 (Ethyl acetate/methanol, 10:1). ^{1}H NMR (400 MHz, CD_3OD) δ 8.76 (d, *J* = 4.5 Hz, 1H), 8.23 (d, *J* = 8.3 Hz, 1H), 8.05 (d, *J* = 8.4 Hz, 1H), 7.78 (t, *J* = 8.2 Hz, 1H), 7.65 (t, *J* = 7.6 Hz, 1H), 7.42 (d, *J* = 4.5 Hz, 1H), 6.77 (s, 1H), 4.50 (s, 2H). ^{13}C NMR (100 MHz, CD_3OD) δ 171.4, 151.1, 148.8, 148.7, 136.6, 131.0, 129.8, 128.5, 128.2, 125.1, 124.5, 122.4, 30.4. mp 167 ºC (dec.). MS (HR-ESI) for $C_{13}H_{12}N_3S$ ($[M+H]^+$), calcd: *m/z* 242.07464, found: *m/z* 242.07465.



S.4.2.5. 5-(2-Pyridinylmethyl)-2-thiazolamine (7n).

Compound **7n** was synthesized by adapting a published procedure.[6] To a solution of **6n** (700 mg, 2.28 mmol) in acetic acid (5 mL) was added dropwise a 57% aqueous solution of hydrogen iodide (1.80 mL, 13.68 mmol) at 100 ºC. The reaction mixture was stirred at the same temperature for 4 h, neutralized with 3N NaOH aqueous solution at room temperature, and extracted with ethyl acetate. The organic phase was dried over $MgSO_4$, filtered, and evaporated. The residue was purified by neutral alumina column chromatography.

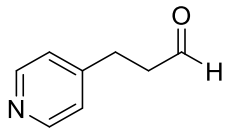
Yield = 188 mg (43%, dark green solid). R_f = 0.18 (Ethyl acetate/methanol, 40:1, neutral alumina TLC). ^{1}H NMR (400 MHz, CD_3OD) δ 8.45 (d, *J* = 4.9 Hz, 1H), 7.78 (td, *J* = 7.7, 1.7 Hz, 1H), 7.35 (d, *J* = 7.9 Hz, 1H), 7.32 – 7.24 (m, 1H), 6.74 (s, 1H), 4.10 (s, 2H). ^{13}C NMR (100 MHz, CD_3OD) δ 171.6, 160.8, 149.7, 139.1, 136.0, 124.9, 124.5, 123.4, 36.2. mp 144-145 ºC. MS (HR-ESI) for $C_9H_{10}N_3S$ ($[M+H]^+$), calcd: *m/z* 192.05899, found: *m/z* 192.05898.



S.4.2.6. 5-(3-Pyridinylmethyl)-2-thiazolamine (10).

Compound **10** was synthesized by modifying a published procedure.[3] A mixture of **9** (1.67 g, 12.35 mmol), dimethyl sulfoxide (1.75 mL, 24.70 mmol), *tert*-butyl bromide (5.55 mL, 49.40 mmol) in acetonitrile (20 mL) was stirred at 65 ºC for 16 h. The reaction mixture was evaporated and the residue dissolved in anhydrous ethanol (30 mL). Thiourea (1.03 g, 13.59 mmol) was added and the mixture was refluxed for 16 h. The solution was evaporated and the residue was purified by reverse-phase (RP-8) silica gel column chromatography.

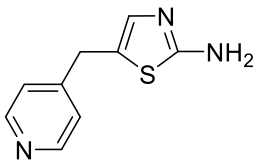
Yield = 343 mg (15%, yellow solid). R_f = 0.26 (Methanol/H_2O, 2:1, RP-8 TLC). ^{1}H NMR (400 MHz, CD_3SOCD_3) δ 8.43 (m, 2H), 7.61 (dt, *J* = 7.9, 2.0 Hz, 1H), 7.32 (ddd, *J* = 7.7, 4.7, 0.9 Hz, 1H), 6.76 (s, 2H), 6.72 (s, 1H), 3.93 (s, 2H). ^{13}C NMR (100 MHz, CD_3SOCD_3) δ 168.2, 149.4, 147.7, 136.1, 135.9, 135.8, 123.7, 123.6, 29.6. MS (HR-ESI) for $C_9H_{10}N_3S$ ($[M+H]^+$), calcd: *m/z* 192.05899, found: *m/z* 192.05891. The ^{1}H NMR spectroscopic data match those previously published.[3]



S.4.2.7. 4-Pyridinepropanal (12).

Compound **12** was synthesized by adapting a published procedure.[3] A mixture of **11** (1.00 g, 7.29 mmol), Dess-Martin periodinane (3.40 g, 8.02 mmol), and 4Å molecular sieves (5 g) was stirred in DCM (40 mL) at room temperature for 16 h. The reaction mixture was filtered and the product purified by silica gel column chromatography.

Yield = 432 mg (44%, red liquid). R_f = 0.19 (DCM/acetone, 5:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.81 (s, 1H), 8.49 (d, *J* = 6.0 Hz, 2H), 7.13 (d, *J* = 5.9 Hz, 2H), 2.94 (t, *J* = 7.3 Hz, 2H), 2.82 (t, *J* = 7.3 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.4, 149.8, 149.7, 123.9, 44.0, 27.3. The ^{1}H NMR spectroscopic data match those previously reported.[5]



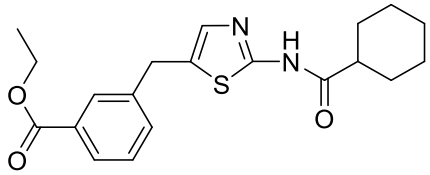
S.4.2.8. 5-(4-Pyridinylmethyl)-2-thiazolamine (13).

Compound **13** was prepared by adapting a method described for the synthesis of compound **10**.[3] A mixture of **12** (426 mg, 3.15 mmol), dimethyl sulfoxide (448 mL, 6.30 mmol), *tert*-butyl bromide (1.42 mL, 12.60 mmol) in acetonitrile (10 mL) was stirred at 65ºC for 16 h. The reaction mixture was evaporated and the residue dissolved in anhydrous ethanol (20 mL). Thiourea (264 mg, 3.47 mmol) was added and the mixture was refluxed for 16 h. The solution was evaporated and the residue was purified by reverse-phase (RP-8) silica gel column chromatography.

Yield = 79 mg (13%, off-white solid). R_f = 0.21 (Methanol/H_2O, 2:1, RP-8 TLC).^{1}H NMR (400 MHz, CD_3OD) δ 8.43 (m, 2H), 7.31 (d, *J* = 5.9 Hz, 2H), 6.78 (s, 1H), 4.01 (s, 2H). ^{13}C NMR (100 MHz, CD_3OD) δ 171.7, 152.2, 150.1, 136.6, 125.3, 124.5, 33.1. mp 163–164 ºC. MS (HR-ESI) for $C_9H_{10}N_3S$ ($[M+H]^+$), calcd: *m/z* 192.05899, found: *m/z* 192.05898.

S.4.2.9. General procedure for the synthesis of compounds 14-27, 30a and 30b

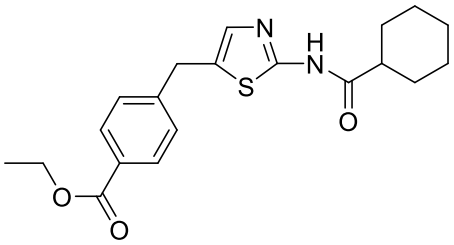
These compounds were prepared by adapting a published procedure.[2] To a mixture of **2**, **4**, **7a-n**, **7p** and acid chloride (1.1 equiv.) in THF (20 mL) was added triethylamine (3 equiv.). The reaction mixture was stirred at room temperature for 15 min and quenched with distilled water. Following addition of a 0.1 N HCl aqueous solution, the product was extracted with DCM. The organic phase was washed with a saturated aqueous solution of $NaHCO_3$, dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by silica gel column chromatography.



S.4.2.9.1. *N*-[5-(3-Ethoxycarbonylbenzyl)thiazol-2-yl]cyclohexanecarboxamide (14).

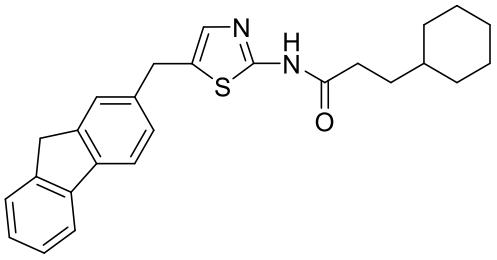
Starting material = **4** (250 mg, 0.95 mmol). Yield = 85 mg (31%, white solid). ^{1}H NMR (400 MHz, $CDCl_3$) δ 13.48 (br s, 1H), 7.99 (d, *J* = 7.4 Hz, 1H), 7.89 (s, 1H), 7.42 (dt, *J* = 15.2, 7.4 Hz, 2H), 7.31 (s, 1H), 4.38 (q, *J* = 7.1 Hz, 2H), 4.13 (s, 2H), 2.60 (t, *J* = 11.2 Hz, 1H), 2.02 (d, *J* = 11.7 Hz, 2H), 1.80 (d, *J* = 12.9 Hz, 2H), 1.68 (d, *J* = 12.2 Hz, 1H), 1.53 (q, *J* = 11.5 Hz, 2H), 1.45 – 1.20 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.9, 166.0, 136.9, 132.9, 131.8, 131.7,

129.7, 129.5, 129.2, 122.2, 61.4, 44.9, 32.8, 28.8, 25.5, 25.2, 14.5. mp 155-158 ºC. MS (HR-ESI) for $C_{20}H_{25}O_3N_2S$ ([M+H]$^+$), calcd: *m/z* 373.15804, found: *m/z* 373.15805.



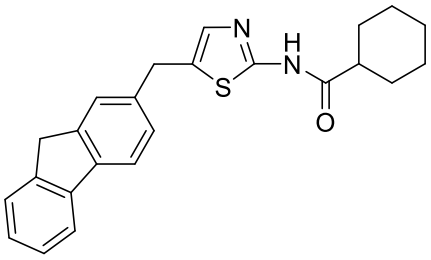
S.4.2.9.2. *N*-[5-(4-Ethoxycarbonylbenzyl)thiazol-2-yl]cyclohexanecarboxamide (15).

Starting material = **2** (250 mg, 0.95 mmol). Yield = 110 mg (34%, white solid). ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.07 (br s, 1H), 7.99 (d, *J* = 8.0 Hz, 2H), 7.32 (d, *J* = 7.9 Hz, 2H), 6.98 (s, 1H), 4.36 (q, *J* = 7.0 Hz, 2H), 4.12 (s, 2H), 2.34 (t, *J* = 11.6 Hz, 1H), 1.86 (d, *J* = 12.5 Hz, 2H), 1.79 (d, *J* = 12.6 Hz, 2H), 1.65 (d, *J* = 11.6 Hz, 1H), 1.53 (q, *J* = 12.1 Hz, 2H), 1.38 (t, *J* = 7.1 Hz, 3H), 1.29 – 1.07 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.3, 166.4, 159.6, 144.3, 133.4, 131.1, 130.2, 129.3, 128.8, 61.1, 45.0, 33.1, 29.2, 25.7, 25.6, 14.5. mp 169-171 ºC. MS (HR-ESI) for $C_{20}H_{25}O_3N_2S$ ([M+H]$^+$), calcd: *m/z* 373.15804, found: *m/z* 373.15811.



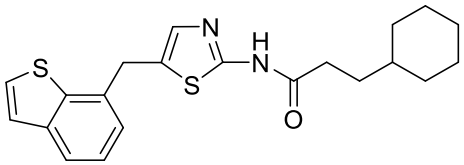
S.4.2.9.3. *N*-[5-(2-Fluorenylmethyl)thiazol-2-yl]-3-cyclohexanepropanamide (16a).

Starting material = **7a** (140 mg, 0.50 mmol). Yield = 170 mg (82%, off-white solid). R_f = 0.22 (DCM/acetone, 40:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.46 (s, 1H), 7.88 (dd, *J* = 16.2, 7.6 Hz, 2H), 7.67 (d, *J* = 7.4 Hz, 1H), 7.56 (s, 1H), 7.51 (t, *J* = 7.4 Hz, 1H), 7.46 – 7.37 (m, 2H), 7.26 (s, 1H), 4.29 (s, 2H), 4.01 (s, 2H), 2.63 (t, *J* = 7.7 Hz, 2H), 1.86 – 1.70 (m, 7H), 1.44 – 1.19 (m, 4H), 1.10 – 0.93 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.6, 159.4, 144.0, 143.3, 141.5, 140.6, 138.0, 133.0, 132.4, 127.2, 126.9, 126.7, 125.3, 125.1, 120.1, 119.9, 37.3, 36.9, 33.8, 33.3, 33.1, 32.5, 26.6, 26.3. mp 188-190 ºC. MS (HR-ESI) for $C_{26}H_{29}N_2OS$ ([M+H]$^+$), calcd: *m/z* 417.19951, found: *m/z* 417.19940.



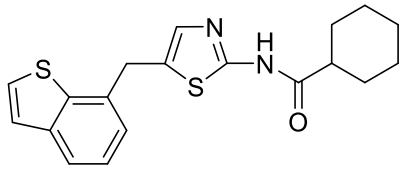
S.4.2.9.4. *N*-[5-(2-Fluorenylmethyl)thiazol-2-yl]cyclohexanecarboxamide (16b).

Starting material = **7a** (140 mg, 0.50 mmol). Yield = 171 mg (88%, light yellow solid). R_f = 0.20 (DCM/acetone, 40:1). ^{1}H NMR (400 MHz, CD_3SOCD_3) δ 11.87 (s, 1H), 7.83 (dd, *J* = 11.6, 7.7 Hz, 2H), 7.55 (d, *J* = 7.3 Hz, 1H), 7.45 (s, 1H), 7.36 (t, *J* = 7.3 Hz, 1H), 7.31 – 7.22 (m, 3H), 4.13 (s, 2H), 3.88 (s, 2H), 2.48 – 2.37 (m, 1H), 1.72 (t, *J* = 14.0 Hz, 4H), 1.61 (d, *J* = 8.9 Hz, 1H), 1.35 (q, *J* = 11.0, 10.3 Hz, 2H), 1.28 – 1.07 (m, 3H). ^{13}C NMR (100 MHz, CD_3SOCD_3) δ 174.0, 157.1, 143.5, 143.0, 140.9, 139.5, 139.2, 134.5, 131.2, 127.1, 126.7, 126.6, 125.1, 125.1, 120.0, 119.9, 43.3, 36.3, 32.1, 28.8, 25.3, 25.0. mp 222-224 ºC. MS (HR-ESI) for $C_{24}H_{25}N_2OS$ ($[M+H]^+$), calcd: *m/z* 389.16821, found: *m/z* 389.16818.



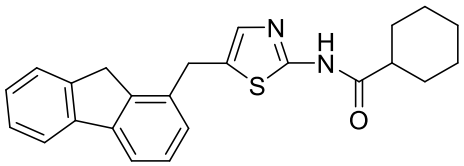
S.4.2.9.5. *N*-[5-(7-Benzothiophenylmethyl)thiazol-2-yl]-3-cyclohexanepropanamide (17a).

Starting material = **7b** (23 mg, 93 μmol). Yield = 30 mg (84%, white solid). R_f = 0.36 (DCM/acetone, 40:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.26 (br s, 1H), 7.77 – 7.70 (m, 1H), 7.43 – 7.40 (m, 1H), 7.38 – 7.32 (m, 2H), 7.24 – 7.19 (m, 2H), 4.34 (s, 2H), 2.47 (t, *J* = 7.7 Hz, 2H), 1.74 – 1.64 (m, 5H), 1.63 – 1.57 (m, 2H), 1.25 – 1.08 (m, 4H), 0.88 (q, *J* = 11.5 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.6, 159.5, 140.3, 139.2, 133.8, 133.4, 129.9, 126.1, 124.9, 124.7, 124.2, 122.7, 37.3, 33.8, 33.1, 32.5, 32.4, 26.6, 26.3. mp 190-192 ºC. MS (HR-ESI) for $C_{21}H_{25}N_2OS_2$ ($[M+H]^+$), calcd: *m/z* 385.14028, found: *m/z* 385.14020.



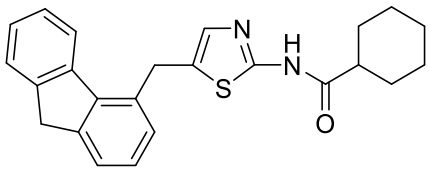
S.4.2.9.6. *N*-[5-(7-Benzothiophenylmethyl)thiazol-2-yl]cyclohexanecarboxamide (17b).

Starting material = **7b** (23 mg, 93 μmol). Yield = 25 mg (77%, white solid). R_f = 0.34 (DCM/acetone, 40:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.27 (br s, 1H), 7.76 – 7.71 (m, 1H), 7.41 (d, *J* = 5.4 Hz, 1H), 7.38 – 7.31 (m, 2H), 7.24 (d, *J* = 7.2 Hz, 1H), 7.10 (s, 1H), 4.34 (s, 2H), 2.31 (tt, *J* = 11.7, 3.5 Hz, 1H), 1.87 – 1.79 (m, 2H), 1.73 (dt, *J* = 13.3, 3.4 Hz, 2H), 1.66 – 1.60 (m, 1H), 1.51 (qd, *J* = 12.6, 3.4 Hz, 2H), 1.23 – 1.02 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.4, 159.6, 140.4, 139.3, 133.8, 133.4, 129.9, 126.1, 124.9, 124.7, 124.4, 122.7, 44.9, 32.4, 29.2, 25.7, 25.6. mp 164-165 ºC. MS (HR-ESI) for $C_{19}H_{21}N_2OS_2$ ($[M+H]^+$), calcd: *m/z* 357.10898, found: *m/z* 357.10895.



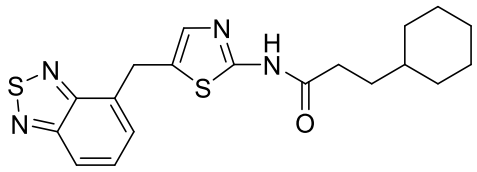
S.4.2.9.7. *N*-[5-(1-Fluorenylmethyl)thiazol-2-yl]cyclohexanecarboxamide (18).

Starting material = **7c** (12 mg, 43 μmol). Yield = 10 mg (58%, white solid). R_f = 0.13 (DCM/acetone, 40:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.90 (br s, 1H), 7.77 (d, *J* = 7.5 Hz, 1H), 7.70 (d, *J* = 7.5 Hz, 1H), 7.50 (d, *J* = 7.4 Hz, 1H), 7.36 (t, *J* = 7.5 Hz, 2H), 7.32 – 7.27 (m, 1H), 7.19 (d, *J* = 7.5 Hz, 1H), 6.96 (s, 1H), 4.19 (s, 2H), 3.81 (s, 2H), 2.33 – 2.23 (m, 1H), 1.86 – 1.78 (m, 2H), 1.72 – 1.64 (m, 2H), 1.56 – 1.41 (m, 3H), 1.17 – 0.97 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.3, 159.2, 142.8, 142.4, 141.8, 135.3, 132.8, 131.2, 127.8, 127.4, 127.0, 126.9, 125.1, 120.1, 118.9, 44.9, 35.6, 30.9, 29.2, 25.6. mp 205-206 ºC. MS (HR-ESI) for $C_{24}H_{25}N_2OS$ ($[M+H]^+$), calcd: *m/z* 389.16821, found: *m/z* 389.16818.



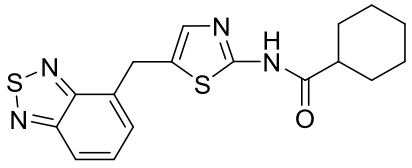
S.4.2.9.8. *N*-[5-(4-Fluorenylmethyl)thiazol-2-yl]cyclohexanecarboxamide (19).

Starting material = **7d** (18 mg, 65 μmol). Yield = 16 mg (65%, white solid). R_f = 0.32 (DCM/acetone, 30:1). ^{1}H NMR (400 MHz, CD_3SOCD_3) δ 11.84 (s, 1H), 7.88 (d, *J* = 7.5 Hz, 1H), 7.60 (d, *J* = 7.1 Hz, 1H), 7.52 (d, *J* = 7.2 Hz, 1H), 7.38 – 7.22 (m, 4H), 7.17 (s, 1H), 4.52 (s, 2H), 3.95 (s, 2H), 2.45 – 2.34 (m, 1H), 1.70 (t, *J* = 11.4 Hz, 4H), 1.60 (d, *J* = 8.8 Hz, 1H), 1.37 – 1.08 (m, 5H). ^{13}C NMR (100 MHz, CD_3SOCD_3) δ 173.9, 156.8, 144.1, 143.6, 140.8, 138.7, 134.5, 134.5, 130.1, 128.6, 126.9, 126.8, 126.4, 125.1, 123.7, 123.2, 43.2, 36.6, 30.5, 28.8, 25.3, 25.0. mp 204-206 ºC. MS (HR-ESI) for $C_{24}H_{25}N_2OS$ ([M+H]$^+$), calcd: *m/z* 389.16821, found: *m/z* 389.16824.



S.4.2.9.9. *N*-[5-(2,1,3-Benzothiadiazol-4-ylmethyl)thiazol-2-yl]-3-cyclohexanepropanamide (20a).

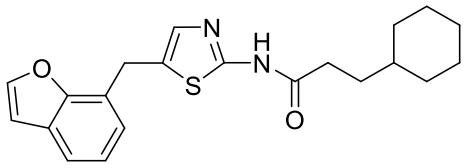
Starting material = **7e** (18 mg, 72 μmol). Yield = 19 mg (66%, white solid). R_f = 0.25 (DCM/methanol, 40:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.14 (br s, 1H), 7.89 (d, *J* = 8.8 Hz, 1H), 7.56 – 7.47 (m, 1H), 7.40 (d, *J* = 6.7 Hz, 1H), 7.28 – 7.25 (m, 1H), 4.60 (s, 2H), 2.48 (t, *J* = 7.6 Hz, 2H), 1.75 – 1.57 (m, 7H), 1.32 – 1.10 (m, 4H), 0.88 (q, *J* = 11.2, 10.4 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.6, 159.3, 155.2, 154.3, 134.0, 133.0, 129.9, 129.6, 127.9, 120.4, 37.3, 33.8, 33.2, 32.5, 29.2, 26.6, 26.3. mp 186-188 ºC. MS (HR-ESI) for $C_{19}H_{23}N_4OS_2$ ([M+H]$^+$), calcd: *m/z* 387.13078, found: *m/z* 387.12994.



S.4.2.9.10. *N*-[5-(2,1,3-Benzothiadiazol-4-ylmethyl)thiazol-2-yl]cyclohexanecarboxamide (20b).

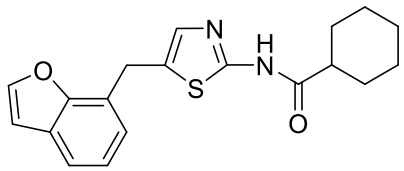
Starting material = **7e** (18 mg, 72 μmol). Yield = 18 mg (68%, white solid). R_f = 0.25 (DCM/methanol, 40:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.14 (br s, 1H), 7.89 (dd, *J* = 8.9, 1.0 Hz, 1H), 7.53 (dd, *J* = 8.8, 6.8 Hz, 1H), 7.42 (dd, *J* = 6.8, 1.1 Hz, 1H), 7.20 (s, 1H), 4.60 (s, 2H), 2.35

(tt, J = 11.7, 3.5 Hz, 1H), 1.90 – 1.74 (m, 4H), 1.71 – 1.65 (m, 1H), 1.58 – 1.46 (m, 2H), 1.29 – 1.08 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.4, 159.4, 155.2, 154.3, 133.8, 132.9, 130.0, 129.6, 128.0, 120.4, 44.9, 29.2, 29.2, 25.7, 25.6. mp 182-184 ºC. MS (HR-ESI) for $C_{17}H_{19}N_4OS_2$ ([M+H]$^+$), calcd: m/z 359.09948, found: m/z 359.09811.



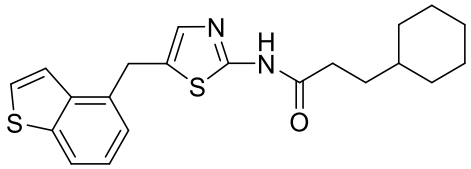
S.4.2.9.11. *N*-[5-(7-Benzofuranylmethyl)thiazol-2-yl]-3-cyclohexanepropanamide (21a).

Starting material = **7f** (57 mg, 0.25 mmol). Yield = 64 mg (69%, white solid). R_f = 0.25 (DCM/methanol, 50:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.35 (br s, 1H), 7.62 (d, J = 2.2 Hz, 1H), 7.49 (dd, J = 7.3, 1.6 Hz, 1H), 7.21 – 7.12 (m, 3H), 6.77 (d, J = 2.2 Hz, 1H), 4.37 (s, 2H), 2.52 – 2.42 (m, 2H), 1.72 – 1.57 (m, 7H), 1.26 – 1.09 (m, 4H), 0.93 – 0.84 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.6, 159.4, 153.1, 145.0, 133.4, 130.8, 127.6, 124.3, 123.2, 123.2, 120.1, 107.0, 37.3, 33.8, 33.1, 32.5, 27.0, 26.6, 26.3. mp 152-154 ºC. MS (HR-ESI) for $C_{21}H_{25}N_2O_2S$ ([M+H]$^+$), calcd: m/z 369.16313, found: m/z 369.16266.

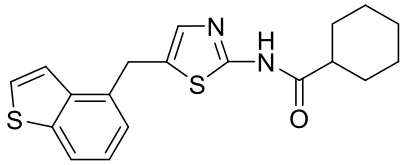


S.4.2.9.12. *N*-[5-(7-Benzofuranylmethyl)thiazol-2-yl]cyclohexanecarboxamide (21b).

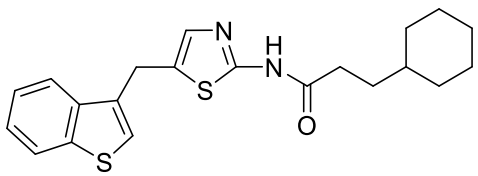
Starting material = **7f** (57 mg, 0.25 mmol). Yield = 50 mg (59%, white solid). R_f = 0.25 (DCM/methanol, 50:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.13 (br s, 1H), 7.61 (d, J = 2.2 Hz, 1H), 7.49 (dd, J = 6.9, 2.1 Hz, 1H), 7.21 – 7.13 (m, 2H), 7.06 (s, 1H), 6.77 (d, J = 2.2 Hz, 1H), 4.36 (s, 2H), 2.32 (tt, J = 11.7, 3.4 Hz, 1H), 1.88 – 1.81 (m, 2H), 1.78 – 1.72 (m, 2H), 1.68 – 1.62 (m, 1H), 1.51 (qd, J = 12.6, 3.1 Hz, 2H), 1.24 – 1.04 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.3, 159.4, 153.2, 145.0, 133.3, 130.9, 127.7, 124.6, 123.3, 123.1, 120.2, 107.0, 44.9, 29.2, 27.0, 25.7, 25.6. mp 173-174 ºC. MS (HR-ESI) for $C_{19}H_{21}N_2O_2S$ ([M+H]$^+$), calcd: m/z 341.13183, found: m/z 341.13168.



S.4.2.9.13. *N*-[5-(4-Benzothiophenylmethyl)thiazol-2-yl]-3-cyclohexanepropanamide (22a). Starting material = **7g** (104 mg, 0.42 mmol). Yield = 219 mg (80%, white solid). R_f = 0.28 (DCM/acetone, 40:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.05 (br s, 1H), 7.80 (d, *J* = 8.0 Hz, 1H), 7.45 (d, *J* = 5.6 Hz, 1H), 7.40 (dd, *J* = 5.6, 0.8 Hz, 1H), 7.29 (t, *J* = 7.4 Hz, 1H), 7.22 (d, *J* = 7.1 Hz, 1H), 7.05 (s, 1H), 4.40 (s, 2H), 2.48 – 2.38 (m, 2H), 1.72 – 1.62 (m, 5H), 1.58 (q, *J* = 6.7 Hz, 2H), 1.25 – 1.09 (m, 4H), 0.86 (qd, *J* = 12.8, 12.0, 3.4 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.5, 159.2, 140.5, 138.4, 133.9, 133.2, 131.5, 126.8, 124.6, 124.5, 121.6, 121.5, 37.3, 33.8, 33.1, 32.5, 31.4, 26.6, 26.3. mp 173-174 ºC. MS (HR-ESI) for $C_{21}H_{25}N_2OS_2$ ($[M+H]^+$), calcd: *m/z* 385.14028, found: *m/z* 385.13928.

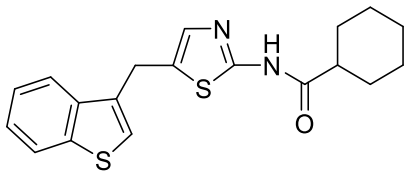


S.4.2.9.14. *N*-[5-(4-Benzothiophenylmethyl)thiazol-2-yl]cyclohexanecarboxamide (22b). Starting material = **7g** (104 mg, 0.42 mmol). Yield = 228 mg (90%, white solid). R_f = 0.28 (DCM/acetone, 40:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.34 (br s, 1H), 7.80 (d, *J* = 8.0 Hz, 1H), 7.44 (d, *J* = 5.5 Hz, 1H), 7.38 (dd, *J* = 5.6, 0.7 Hz, 1H), 7.30 (t, *J* = 7.6 Hz, 1H), 7.24 (d, *J* = 6.7 Hz, 1H), 6.89 (s, 1H), 4.39 (s, 2H), 2.24 (tt, *J* = 11.7, 3.4 Hz, 1H), 1.82 – 1.74 (m, 2H), 1.69 (dt, *J* = 13.3, 3.1 Hz, 2H), 1.65 – 1.57 (m, 1H), 1.48 (qd, *J* = 12.9, 3.4 Hz, 2H), 1.18 (qt, *J* = 12.9, 3.4 Hz, 1H), 0.93 (qt, *J* = 12.9, 3.3 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.4, 159.4, 140.6, 138.5, 133.7, 133.1, 131.4, 126.9, 124.8, 124.6, 121.6, 121.6, 44.9, 31.4, 29.2, 25.7, 25.6. mp 178-179 ºC. MS (HR-ESI) for $C_{19}H_{21}N_2OS_2$ ($[M+H]^+$), calcd: *m/z* 357.10898, found: *m/z* 357.10846.



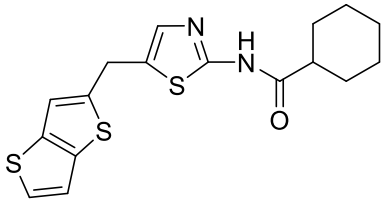
S.4.2.9.15. *N*-[5-(3-Benzothiophenylmethyl)thiazol-2-yl]-3-cyclohexanepropanamide (23a).

Starting material = **7h** (176 mg, 0.71 mmol). Yield = 142 mg (87%, white solid). R_f = 0.21 (DCM/acetone, 40:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.09 (br s, 1H), 7.89 – 7.83 (m, 1H), 7.75 – 7.69 (m, 1H), 7.39 – 7.32 (m, 2H), 7.21 (s, 1H), 7.14 (s, 1H), 4.31 (s, 2H), 2.45 (t, *J* = 7.5 Hz, 2H), 1.72 – 1.56 (m, 7H), 1.27 – 1.08 (m, 4H), 0.94 – 0.82 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.6, 159.2, 140.8, 138.2, 133.7, 133.5, 130.3, 124.6, 124.3, 123.7, 123.1, 121.7, 37.3, 33.8, 33.1, 32.5, 26.6, 26.3, 26.3. mp 168-169 ºC. MS (HR-ESI) for $C_{21}H_{25}N_2OS_2$ ([M+H]$^+$), calcd: *m/z* 385.14028, found: *m/z* 385.13992.



S.4.2.9.16. *N*-[5-(3-Benzothiophenylmethyl)thiazol-2-yl]cyclohexanecarboxamide (23b).

Starting material = **7h** (176 mg, 0.71 mmol). Yield = 114 mg (76%, white solid). R_f = 0.21 (DCM/acetone, 40:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.12 (br s, 1H), 7.89 – 7.83 (m, 1H), 7.74 – 7.68 (m, 1H), 7.38 – 7.32 (m, 2H), 7.24 (s, 1H), 7.01 (s, 1H), 4.31 (s, 2H), 2.28 (tt, *J* = 11.7, 3.4 Hz, 1H), 1.86 – 1.79 (m, 2H), 1.70 (dt, *J* = 13.3, 3.2 Hz, 2H), 1.64 – 1.57 (m, 1H), 1.50 (qd, *J* = 12.8, 3.4 Hz, 2H), 1.18 (qt, *J* = 12.8, 3.4 Hz, 1H), 0.99 (qt, *J* = 13.0, 3.4 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.4, 159.4, 140.8, 138.3, 133.4, 133.3, 130.3, 124.7, 124.3, 123.9, 123.1, 121.8, 44.9, 29.2, 26.3, 25.7, 25.6. mp 209-210 ºC. MS (HR-ESI) for $C_{19}H_{21}N_2OS_2$ ([M+H]$^+$), calcd: *m/z* 357.10898, found: *m/z* 357.10864.



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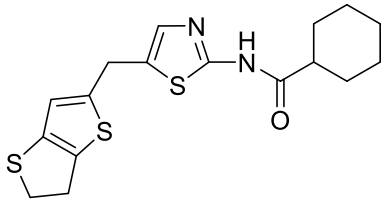


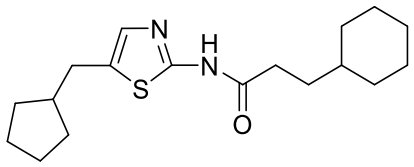
24'

S.4.2.9.17. *N*-{5-[2-Thieno(3,2-b)thiophenylmethyl]thiazol-2-yl}cyclohexanecarboxamide (24).

Starting material = **7i** (13 mg, 52 μmol). Yield = 13 mg (68%, yellowish white solid). R_f = 0.17 (DCM/acetone, 40:1). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 11.84 (s, 1H), 7.31 (d, *J* = 5.2 Hz, 1H), 7.19 – 7.14 (m, 2H), 7.09 (s, 1H), 4.34 (s, 2H)[a], 4.19 (s, 0.15H)[a,b], 3.71 (t, *J* = 8.0 Hz, 0.16H)[b], 3.12 (t, *J* = 8.0 Hz, 0.17H)[b], 2.38 (tt, *J* = 11.7, 3.5 Hz, 1H), 1.89 (d, *J* = 13.6 Hz, 2H), 1.83 – 1.74 (m, 2H), 1.65 – 1.49 (m, 3H), 1.24 – 1.15 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.3, 159.5, 144.1, 138.8, 138.5, 133.6, 130.9, 126.5, 119.5, 118.1, 45.0, 29.3, 28.6, 25.7. MS (HR-ESI) for $C_{17}H_{19}N_2OS_3$ ([**24**+H]$^+$), calcd: *m/z* 363.06540, found: *m/z* 363.06458. MS (HR-ESI) for $C_{17}H_{21}N_2OS_3$ ([**24'**+H]$^+$), calcd: *m/z* 365.08105, found: *m/z* 363.07922.

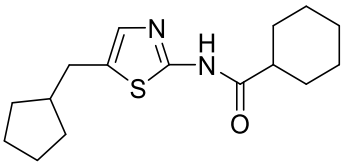
[a] *The purity of **24** is approximately 93% based on the integration of the two signals (see **S.6.17.1.**).*

[b] *It appears that these signals arise from the partially reduced compound, **24'** (see **S.6.17.1.**).*



S.4.2.9.18. *N*-[5-(Cyclopentylmethyl)thiazol-2-yl]-3-cyclohexanepropanamide (25a).

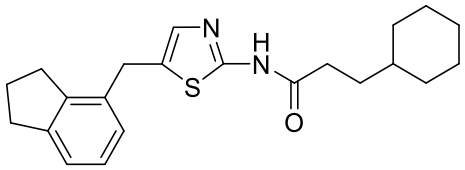
Starting material = **7j** (100 mg, 0.55 mmol). Yield = 146 mg (83%, white solid). R_f = 0.29 (DCM/acetone, 40:1). ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.43 (br s, 1H), 7.06 (s, 1H), 2.74 (d, *J* = 7.3 Hz, 2H), 2.51 (t, *J* = 7.8 Hz, 2H), 2.12 (hept, *J* = 7.6 Hz, 1H), 1.86 – 1.49 (m, 14H), 1.38 – 1.28 (m, 1H), 1.23 – 1.07 (m, 4H), 0.99 – 0.85 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.6, 158.8, 132.7, 132.5, 41.7, 37.5, 33.9, 33.2, 33.0, 32.6, 32.6, 26.6, 26.3, 25.3. mp 177-179 ºC. MS (HR-ESI) for $C_{18}H_{29}N_2OS$ ([M+H]$^+$), calcd: *m/z* 321.19951, found: *m/z* 321.20102.



S.4.2.9.19. *N*-[5-(Cyclopentylmethyl)thiazol-2-yl]cyclohexanecarboxamide (25b).

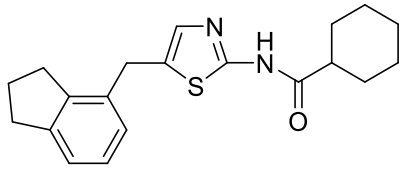
Starting material = **7j** (100 mg, 0.55 mmol). Yield = 135 mg (84%, white solid). R_f = 0.29 (DCM/acetone, 40:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.28 (br s, 1H), 7.06 (s, 1H), 2.75 (d, *J* = 7.3 Hz, 2H), 2.45 (tt, *J* = 11.7, 3.6 Hz, 1H), 2.11 (hept, *J* = 7.7 Hz, 1H), 1.98 – 1.90 (m, 2H),

1.89 – 1.76 (m, 4H), 1.75 – 1.70 (m, 1H), 1.67 – 1.49 (m, 6H), 1.35 (m, 1H), 1.30 – 1.16 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.4, 158.9, 132.8, 132.4, 44.9, 41.8, 33.0, 32.6, 29.3, 25.8, 25.8, 25.2. mp 170-171 ºC. MS (HR-ESI) for $C_{16}H_{25}N_2OS$ ($[M+H]^+$), calcd: *m/z* 293.16821, found: *m/z* 293.16962.



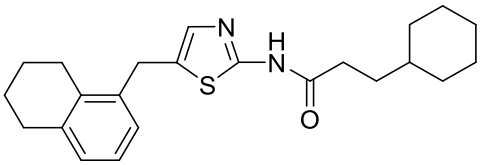
S.4.2.9.20. *N*-[5-(4-Indanylmethyl)thiazol-2-yl]-3-cyclohexanepropanamide (26a).

Starting material = **7k** (64 mg, 0.28 mmol). Yield = 92 mg (89%, white solid). R_f = 0.25 (DCM/acetone, 50:1). ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.45 (br s, 1H), 7.17 – 6.97 (m, 4H), 4.04 (s, 2H), 2.90 (dt, *J* = 15.5, 7.4 Hz, 4H), 2.53 – 2.42 (m, 2H), 2.07 (p, *J* = 7.5 Hz, 2H), 1.77 – 1.57 (m, 7H), 1.29 – 1.11 (m, 4H), 0.90 (q, *J* = 11.5 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.6, 159.4, 144.9, 142.6, 135.0, 132.8, 131.7, 126.9, 126.4, 123.2, 37.4, 33.8, 33.2, 33.1, 32.5, 31.3, 31.0, 26.6, 26.3, 24.9. mp 149-150 ºC. MS (HR-ESI) for $C_{22}H_{29}N_2OS$ ($[M+H]^+$), calcd: *m/z* 369.19951, found: *m/z* 369.20047.



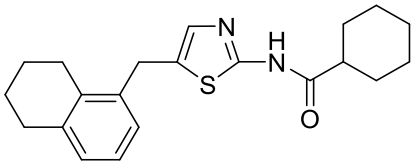
S.4.2.9.21. *N*-[5-(4-Indanylmethyl)thiazol-2-yl]cyclohexanecarboxamide (26b).

Starting material = **7k** (64 mg, 0.28 mmol). Yield = 89 mg (93%, white solid). R_f = 0.25 (DCM/acetone, 50:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.50 (br s, 1H), 7.12 (q, *J* = 7.5 Hz, 2H), 7.02 (d, *J* = 6.7 Hz, 1H), 6.93 (s, 1H), 4.03 (s, 2H), 2.93 (t, *J* = 7.5 Hz, 2H), 2.87 (t, *J* = 7.4 Hz, 2H), 2.35 (tt, *J* = 11.7, 3.4 Hz, 1H), 2.06 (p, *J* = 7.5 Hz, 2H), 1.86 (d, *J* = 11.8 Hz, 2H), 1.82 – 1.75 (m, 2H), 1.71 – 1.63 (m, 1H), 1.54 (qd, *J* = 12.7, 3.1 Hz, 2H), 1.30 – 1.06 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.4, 159.5, 144.9, 142.7, 134.8, 132.7, 131.7, 126.9, 126.6, 123.2, 44.9, 33.1, 31.3, 31.0, 29.2, 25.7, 24.9. mp 178-179 ºC. MS (HR-ESI) for $C_{20}H_{25}N_2OS$ ($[M+H]^+$), calcd: *m/z* 341.16821, found: *m/z* 341.16922.



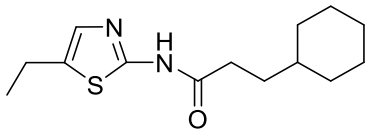
S.4.2.9.22. *N*-[(5-Tetralinylmethyl)thiazol-2-yl]-3-cyclohexanepropanamide (27a).

Starting material = **7l** (100 mg, 0.41 mmol). Yield = 128 mg (82%, white solid). R_f = 0.22 (DCM/acetone, 50:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.12 (br s, 1H), 7.10 – 6.95 (m, 4H), 4.01 (s, 2H), 2.78 (t, *J* = 6.0 Hz, 2H), 2.68 (t, *J* = 6.1 Hz, 2H), 2.50 – 2.41 (m, 2H), 1.84 – 1.57 (m, 11H), 1.30 – 1.11 (m, 4H), 0.96 – 0.83 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.5, 159.1, 138.0, 137.3, 135.2, 133.0, 131.9, 128.5, 126.9, 125.7, 37.3, 33.8, 33.2, 32.5, 30.4, 30.2, 26.6, 26.3, 26.3, 23.4, 22.9. mp 148-150 ºC. MS (HR-ESI) for $C_{23}H_{31}N_2OS$ ($[M+H]^+$), calcd: *m/z* 383.21516, found: *m/z* 383.21423.



S.4.2.9.23. *N*-[(5-Tetralinylmethyl)thiazol-2-yl]cyclohexanecarboxamide (27b).

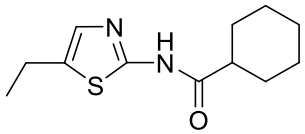
Starting material = **7l** (100 mg, 0.41 mmol). Yield = 132 mg (91%, white solid). R_f = 0.22 (DCM/acetone, 50:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.55 (br s, 1H), 7.11 – 6.97 (m, 3H), 6.86 (s, 1H), 4.01 (s, 2H), 2.78 (t, *J* = 5.8 Hz, 2H), 2.69 (t, *J* = 5.9 Hz, 2H), 2.33 (tt, *J* = 11.7, 3.4 Hz, 1H), 1.89 – 1.81 (m, 2H), 1.81 – 1.71 (m, 6H), 1.65 (d, *J* = 12.8 Hz, 1H), 1.53 (qd, *J* = 12.8, 3.2 Hz, 2H), 1.29 – 1.17 (m, 1H), 1.08 (qt, *J* = 13.1, 3.1 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.4, 159.4, 138.0, 137.1, 135.2, 132.8, 131.8, 128.4, 127.1, 125.7, 44.9, 30.4, 30.2, 29.2, 26.2, 25.7, 23.4, 22.9. mp 209-210 ºC. MS (HR-ESI) for $C_{21}H_{27}N_2OS$ ($[M+H]^+$), calcd: *m/z* 355.18386, found: *m/z* 355.18338.



S.4.2.9.24. *N*-(5-Ethylthiazol-2-yl)-3-cyclohexanepropanamide (30a).

Starting material = **7p** (100 mg, 0.78 mmol). Yield = 171 mg (82%, white solid). R_f = 0.23 (DCM/methanol, 60:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.42 (br s, 1H), 7.06 (s, 1H), 2.79 (q, *J* =

7.5 Hz, 2H), 2.51 (t, *J* = 7.7 Hz, 2H), 1.77 – 1.61 (m, 7H), 1.31 (t, *J* = 7.5 Hz, 4H), 1.26 – 1.08 (m, 3H), 0.99 – 0.87 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.6, 158.6, 134.9, 131.5, 37.5, 33.9, 33.2, 32.6, 26.6, 26.3, 20.4, 15.7. mp 137-138 ºC. MS (HR-ESI) for $C_{14}H_{23}N_2OS$ ($[M+H]^+$), calcd: *m/z* 267.15256, found: *m/z* 267.15250.

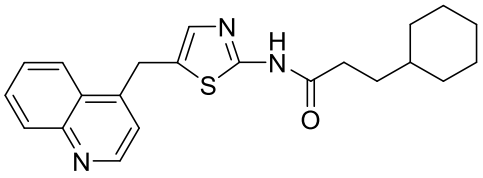


S.4.2.9.25. *N*-(5-Ethylthiazol-2-yl)cyclohexanecarboxamide (30b).

Starting material = **7p** (100 mg, 0.78 mmol). Yield = 162 mg (87%, white solid). R_f = 0.23 (DCM/methanol, 60:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.33 (br s, 1H), 7.07 (s, 1H), 2.80 (qd, *J* = 7.5, 1.1 Hz, 2H), 2.45 (tt, *J* = 11.7, 3.5 Hz, 1H), 1.96 – 1.83 (m, 4H), 1.75 – 1.69 (m, 1H), 1.66 – 1.54 (m, 2H), 1.36 – 1.24 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.4, 158.8, 134.9, 131.4, 44.9, 29.3, 25.8, 25.7, 20.4, 15.9. mp 124-125 ºC. MS (HR-ESI) for $C_{12}H_{19}N_2OS$ ($[M+H]^+$), calcd: *m/z* 239.12126, found: *m/z* 239.12144.

S.4.2.10. General procedure for the synthesis of 28a, 28b, 29a, 29b, 31, 32a and 32b

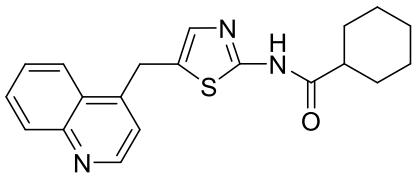
These compounds were prepared by adapting a published procedure.[2] To a mixture of **7m**, **7n**, **10** and **13** in anhydrous THF (20 mL) was added acid chloride (1.1 equiv.). The reaction mixture was stirred at room temperature for 15 min and diluted with ethyl acetate. Following addition of a 1 N NaOH (20 mL), the product was extracted with ethyl acetate. The organic phase was dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography.



S.4.2.10.1. *N*-[5-(4-Quinolinylmethyl)thiazol-2-yl]-3-cyclohexanepropanamide (28a).

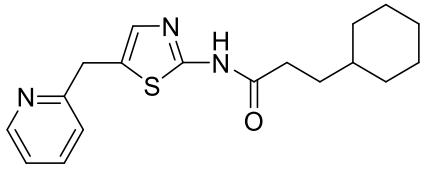
Starting material = **7m** (11 mg, 46 μmol). Yield = 10 mg (60%, white solid). R_f = 0.43 (Ethyl acetate/methanol, 60:1). ^{1}H NMR (400 MHz, CD_3OD) δ 8.78 (d, *J* = 4.5 Hz, 1H), 8.27 – 8.21 (m, 1H), 8.09 – 8.02 (m, 1H), 7.82 – 7.74 (m, 1H), 7.68 – 7.61 (m, 1H), 7.44 (d, *J* = 4.5 Hz, 1H),

7.21 (s, 1H), 4.65 (s, 2H), 2.47 – 2.40 (m, 2H), 1.76 – 1.62 (m, 5H), 1.54 (q, J = 6.9 Hz, 2H), 1.26 – 1.16 (m, 4H), 0.95 – 0.88 (m, 2H). ^{13}C NMR (100 MHz, CD_3OD) δ 173.9, 159.3, 151.1, 148.9, 148.5, 136.5, 131.0, 130.7, 129.9, 128.4, 128.3, 125.1, 122.6, 38.6, 34.1, 34.1, 33.8, 30.0, 27.6, 27.3. mp 170-172 ºC. MS (HR-ESI) for $C_{22}H_{26}N_3OS$ ([M+H]$^+$), calcd: m/z 380.17911, found: m/z 380.18045.



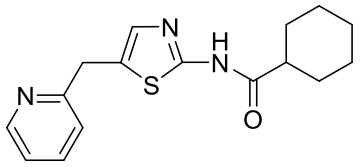
S.4.2.10.2. *N*-[5-(4-Quinolinylmethyl)thiazol-2-yl]cyclohexanecarboxamide (28b).

Starting material = **7m** (11 mg, 46 μmol). Yield = 10 mg (64%, white solid). R_f = 0.41 (Ethyl acetate/methanol, 60:1). ^{1}H NMR (400 MHz, CD_3OD) δ 8.78 (d, J = 4.5 Hz, 1H), 8.27 – 8.22 (m, 1H), 8.08 – 8.03 (m, 1H), 7.81 – 7.75 (m, 1H), 7.68 – 7.62 (m, 1H), 7.44 (d, J = 4.5 Hz, 1H), 7.21 (s, 1H), 4.65 (s, 2H), 2.43 (tt, J = 11.7, 3.3 Hz, 1H), 1.87 – 1.76 (m, 4H), 1.73 – 1.66 (m, 1H), 1.52 – 1.42 (m, 2H), 1.37 – 1.31 (m, 2H), 1.26 – 1.22 (m, 1H). ^{13}C NMR (100 MHz, CD_3OD) δ 176.6, 151.1, 148.9, 148.5, 136.5, 131.0, 130.7, 129.9, 128.4, 128.3, 125.1, 122.6, 45.7, 30.4, 30.0, 26.8, 26.6. mp 199-202 ºC. MS (HR-ESI) for $C_{20}H_{22}N_3OS$ ([M+H]$^+$), calcd: m/z 352.14781, found: m/z 352.14926.



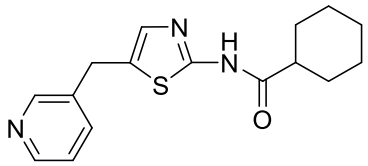
S.4.2.10.3. *N*-[5-(2-Pyridinylmethyl)thiazol-2-yl]-3-cyclohexanepropanamide (29a).

Starting material = **7n** (40 mg, 0.21 mmol). Yield = 46 mg (67%, yellowish white solid). R_f = 0.29 (DCM/methanol, 15:1). ^{1}H NMR (400 MHz, CD_3OD) δ 8.47 (d, J = 4.1 Hz, 1H), 7.79 (td, J = 7.7, 1.7 Hz, 1H), 7.38 (d, J = 7.8 Hz, 1H), 7.34 – 7.25 (m, 1H), 7.21 (s, 1H), 4.25 (s, 2H), 2.51 – 2.40 (m, 2H), 1.79 – 1.63 (m, 5H), 1.56 (q, J = 7.1 Hz, 2H), 1.30 – 1.14 (m, 4H), 0.92 (q, J = 10.6, 9.4 Hz, 2H). ^{13}C NMR (100 MHz, CD_3OD) δ 173.8, 160.6, 159.5, 149.9, 139.2, 136.0, 130.9, 124.6, 123.5, 38.6, 35.8, 34.2, 34.1, 33.8, 27.6, 27.4. mp 128-129 ºC. MS (HR-ESI) for $C_{18}H_{24}N_3OS$ ([M+H]$^+$), calcd: m/z 330.16346, found: m/z 330.16394.



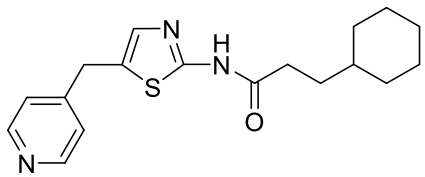
S.4.2.10.4. *N*-[5-(2-Pyridinylmethyl)thiazol-2-yl]cyclohexanecarboxamide (29b).

Starting material = **7n** (40 mg, 0.21 mmol). Yield = 33 mg (52%, off-white solid). R_f = 0.29 (DCM/methanol, 15:1). ^{1}H NMR (400 MHz, CD_3OD) δ 8.52 – 8.42 (m, 1H), 7.79 (td, *J* = 7.7, 1.7 Hz, 1H), 7.37 (d, *J* = 7.8 Hz, 1H), 7.34 – 7.26 (m, 1H), 7.20 (s, 1H), 4.25 (s, 2H), 2.49 – 2.40 (m, 1H), 1.83 (t, *J* = 13.8 Hz, 4H), 1.71 (d, *J* = 12.0 Hz, 1H), 1.48 (q, *J* = 11.2, 10.1 Hz, 2H), 1.42 – 1.23 (m, 3H). ^{13}C NMR (100 MHz, CD_3OD) δ 176.5, 160.6, 159.6, 149.9, 139.1, 136.0, 130.9, 124.6, 123.5, 45.7, 35.8, 30.4, 26.8, 26.6. mp 148-150 ºC. MS (HR-ESI) for $C_{16}H_{20}N_3OS$ ($[M+H]^+$), calcd: *m/z* 302.13216, found: *m/z* 302.13263.



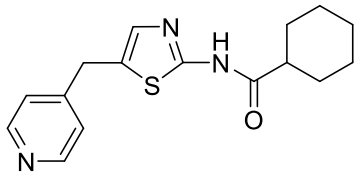
S.4.2.10.5. *N*-[5-(3-Pyridinylmethyl)thiazol-2-yl]cyclohexanecarboxamide (31).

Starting material = **10** (50 mg, 0.26 mmol). Yield = 50 mg (64%, off-white solid). R_f = 0.25 (DCM/methanol, 15:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.90 (br s, 1H), 8.59 – 8.45 (m, 2H), 7.57 (d, *J* = 7.8 Hz, 1H), 7.26 – 7.21 (m, 1H), 7.04 (s, 1H), 4.10 (s, 2H), 2.36 (tt, *J* = 11.5, 3.2 Hz, 1H), 1.93 – 1.85 (m, 2H), 1.85 – 1.76 (m, 2H), 1.73 – 1.65 (m, 1H), 1.55 (q, *J* = 12.3 Hz, 2H), 1.27 – 1.16 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.3, 159.6, 149.9, 148.4, 136.2, 134.9, 133.7, 130.7, 123.7, 45.0, 30.4, 29.2, 25.7, 25.6. mp 165-167 ºC. MS (HR-ESI) for $C_{16}H_{20}N_3OS$ ($[M+H]^+$), calcd: *m/z* 302.13216, found: *m/z* 302.13208.



S.4.2.10.6. *N*-[5-(4-Pyridinylmethyl)thiazol-2-yl]-3-cyclohexanepropanamide (32a).

Starting material = **13** (28 mg, 0.15 mmol). Yield = 17 mg (34%, white solid). R_f = 0.19 (DCM/methanol, 15:1). ^{1}H NMR (400 MHz, CD_3OD) δ 8.45 (d, *J* = 5.8 Hz, 2H), 7.35 (d, *J* = 5.9 Hz, 2H), 7.23 (s, 1H), 4.17 (s, 2H), 2.51 – 2.40 (m, 2H), 1.78 – 1.62 (m, 5H), 1.56 (q, *J* = 7.2 Hz, 2H), 1.28 – 1.14 (m, 4H), 0.93 (q, *J* = 10.9, 9.8 Hz, 2H). ^{13}C NMR (100 MHz, CD_3OD) δ 173.9, 159.6, 152.0, 150.2, 136.5, 130.6, 125.5, 38.6, 34.2, 34.1, 33.8, 32.6, 27.6, 27.4. mp 121-124 ºC. MS (HR-ESI) for $C_{18}H_{24}N_3OS$ ($[M+H]^+$), calcd: *m/z* 330.16346, found: *m/z* 330.16345.

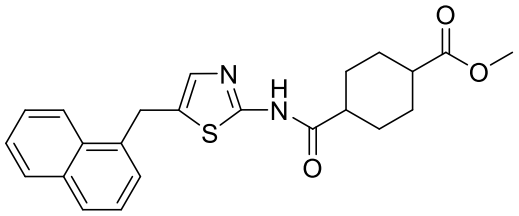


S.4.2.10.7. *N*-[5-(4-Pyridinylmethyl)thiazol-2-yl]cyclohexanecarboxamide (32b).

Starting material = **13** (28 mg, 0.15 mmol). Yield = 16 mg (35%, yellowish white solid). R_f = 0.19 (DCM/methanol, 15:1). ^{1}H NMR (400 MHz, CD_3OD) δ 8.45 (d, *J* = 5.8 Hz, 2H), 7.34 (d, *J* = 5.7 Hz, 2H), 7.23 (s, 1H), 4.17 (s, 2H), 2.52 – 2.38 (m, 1H), 1.83 (t, *J* = 14.6 Hz, 4H), 1.71 (d, *J* = 11.0 Hz, 1H), 1.49 (q, *J* = 11.4, 10.5 Hz, 2H), 1.40 – 1.32 (m, 2H), 1.28 – 1.22 (m, 1H). ^{13}C NMR (100 MHz, CD_3OD) δ 176.5, 159.7, 152.0, 150.2, 136.5, 130.6, 125.4, 45.7, 32.6, 30.4, 26.8, 26.6. mp 135-140 ºC. MS (HR-ESI) for $C_{16}H_{20}N_3OS$ ($[M+H]^+$), calcd: *m/z* 302.13216, found: *m/z* 302.13217.

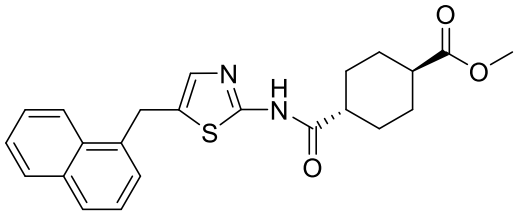
S.4.2.11. General procedure for the synthesis of 33a-c

Compounds **33a-c** were prepared by adapting a published procedure.[2] To a mixture of **7o** (140 mg, 0.58 mmol), methoxycarbonyl cyclohexane carboxylic acid (140 mg, 0.75 mmol), DMAP (32 mg, 0.26 mmol) in DCM/DMF (2 mL, 3:1) were added EDCI (182 mL, 1.04 mmol) and triethylamine (145 mL, 1.04 mmol). The reaction mixture was stirred at room temperature for 16 h, diluted with ethyl acetate, washed with brine, 0.2 N HCl aqueous solution, and a saturated aqueous solution of $NaHCO_3$. The organic phase was dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography.



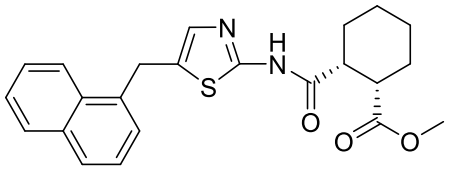
S.4.2.11.1. *N*-[5-(1-Naphthalenylmethyl)thiazol-2-yl]-4-(methoxycarbonyl)-cyclohexanecarboxamide (33a).

Yield = 23 mg (10%, yellowish white solid). R_f = 0.30 (DCM/acetone, 15:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.23 (br s, 1H), 8.01 – 7.91 (m, 1H), 7.90 – 7.81 (m, 1H), 7.82 – 7.76 (m, 1H), 7.51 – 7.39 (m, 4H), 6.75 (s, 1H), 2.40 (p, J = 4.5 Hz, 1H), 2.28 – 2.18 (m, 1H), 2.02 – 1.92 (m, 2H), 1.75 – 1.62 (m, 2H), 1.62 – 1.52 (m, 2H), 1.13 – 1.02 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.9, 173.6, 159.2, 134.8, 134.2, 133.1, 131.8, 131.7, 128.9, 128.0, 127.3, 126.5, 126.0, 125.8, 123.9, 51.8, 43.0, 39.5, 30.6, 26.0, 25.9. mp 197-198 ºC. MS (HR-ESI) for $C_{23}H_{25}N_2O_3S$ ($[M+H]^+$), calcd: m/z 409.15804, found: m/z 409.15805.



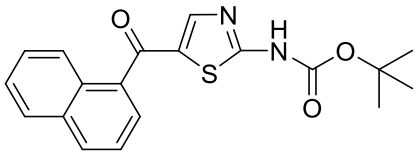
S.4.2.11.2. *N*-[5-(1-Naphthalenylmethyl)thiazol-2-yl]-*trans*-4-(methoxycarbonyl)-cyclohexanecarboxamide (33b).

Yield = 39 mg (16%, yellowish white solid). R_f = 0.30 (DCM/acetone, 15:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.38 (br s, 1H), 8.01 – 7.97 (m, 1H), 7.87 – 7.81 (m, 1H), 7.79 – 7.74 (m, 1H), 7.51 – 7.40 (m, 4H), 6.93 (s, 1H), 4.52 (s, 2H), 3.74 (s, 3H), 2.33 – 2.22 (m, 2H), 2.08 – 1.99 (m, 2H), 1.95 – 1.87 (m, 2H), 1.56 (qd, *J* = 13.4, 3.4 Hz, 2H), 1.32 – 1.19 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.7, 173.6, 159.1, 134.9, 134.1, 132.9, 132.3, 131.6, 129.0, 128.0, 127.0, 126.4, 125.9, 125.7, 123.7, 51.8, 43.9, 42.3, 30.5, 28.3, 28.0. mp 182-185 ºC. MS (HR-ESI) for $C_{23}H_{25}N_2O_3S$ ([M+H]$^+$), calcd: *m/z* 409.15804, found: *m/z* 409.15802.



S.4.2.11.3. *N*-[5-(1-Naphthalenylmethyl)thiazol-2-yl]-(1R,2S)-2-(methoxycarbonyl)-cyclohexanecarboxamide (33c).

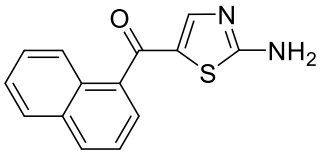
Yield = 22 mg (9%, yellow glassy solid). R_f = 0.30 (DCM/acetone, 15:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.50 (br s, 1H), 8.02 – 7.96 (m, 1H), 7.89 – 7.83 (m, 1H), 7.78 (dd, *J* = 7.2, 2.0 Hz, 1H), 7.51 – 7.38 (m, 4H), 6.95 (s, 1H), 4.50 (s, 2H), 3.60 (s, 3H), 2.88 – 2.79 (m, 1H), 2.68 (dt, *J* = 8.5, 4.0 Hz, 1H), 2.14 – 1.94 (m, 2H), 1.69 – 1.45 (m, 4H), 1.38 – 1.26 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.2, 172.1, 158.7, 135.1, 134.1, 133.6, 131.8, 131.7, 128.9, 128.0, 127.1, 126.4, 125.9, 125.7, 123.9, 51.9, 43.3, 42.7, 30.6, 27.2, 26.1, 23.8, 23.1. MS (HR-ESI) for $C_{23}H_{25}N_2O_3S$ ([M+H]$^+$), calcd: *m/z* 409.15804, found: *m/z* 409.15823.



S.4.2.12. *tert*-Butyl [5-(1-naphthoyl)thiazol-2-yl]carbamate (34).

A mixture of **6o** (571 mg, 1.6 mmol) and Dess-Martin periodinane (2.04 g, 4.8 mmol) in DCM (10 mL) was stirred for 16 h at room temperature. A saturated aqueous solution (30 mL) of $NaHCO_3$ was added and the mixture extracted with DCM. The organic layer was dried over $MgSO_4$, filtered, and evaporated. The residue was purified by silica gel column chromatography.

Yield = 303 mg (54%, yellow solid). R_f = 0.14 (DCM). ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.50 (br s, 1H), 8.17 – 8.12 (m, 1H), 7.99 (d, *J* = 8.3 Hz, 1H), 7.93 – 7.88 (m, 1H), 7.72 (dd, *J* = 7.0, 1.0 Hz, 1H), 7.65 (s, 1H), 7.57 – 7.47 (m, 3H), 1.36 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.0, 168.0, 146.8, 136.2, 133.9, 131.4, 130.5, 128.5, 127.5, 126.8, 126.7, 125.5, 124.4, 83.1, 28.1. mp 188 ºC (dec.). MS (HR-ESI) for $C_{19}H_{19}N_2O_3S$ ([M+H]$^+$), calcd: *m/z* 355.11109, found: *m/z* 355.11102.

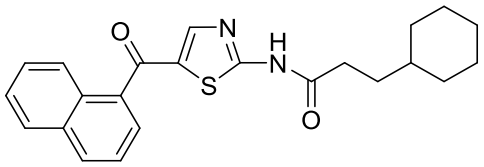


S.4.2.13. 5-(1-Naphthoyl)-2-thiazolamine (35).

A mixture of **34** (303 mg, 0.86 mmol) and trifluoroacetic acid (0.92 ml, 12 mmol) in DCM (5 mL) was stirred for 16 h at room temperature. The solution was treated with a saturated aqueous solution of $NaHCO_3$ and the product was extracted with DCM. The organic layer was dried over $MgSO_4$, filtered, and evaporated. The residue was purified by silica gel column chromatography. Yield = 179 mg (82%, white solid). R_f = 0.32 (DCM/acetone, 5:1). ^{1}H NMR (400 MHz, CD_3COCD_3) δ 8.14 – 8.04 (m, 2H), 8.02 – 7.96 (m, 1H), 7.74 (dd, *J* = 7.0, 1.1 Hz, 1H), 7.62 – 7.44 (m, 5H), 7.37 (s, 1H). ^{13}C NMR (100 MHz, CD_3COCD_3) δ 188.1, 176.2, 152.1, 137.5, 134.8, 131.4, 131.1, 129.2, 127.7, 127.3, 127.2, 126.2, 125.5. mp 190-191 ºC. MS (HR-ESI) for $C_{14}H_{11}N_2OS$ ([M+H]$^+$), calcd: *m/z* 255.05866, found: *m/z* 255.05812.

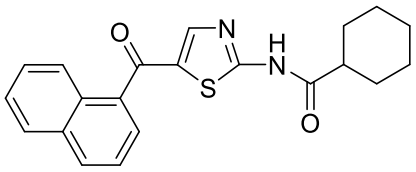
S.4.2.14. General procedure for the synthesis of compounds 36a, 36b, 38a and 38b

Compounds **36a**, **36b**, **38a** and **38b** were prepared using the method described for the synthesis of compounds **14-27**, **30a and 30b** (*vide supra*).



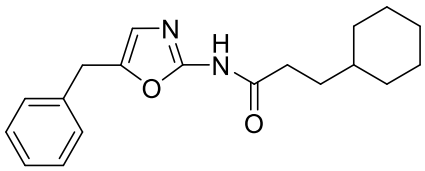
S.4.2.14.1. *N*-[5-(1-Naphthoyl)thiazol-2-yl]-3-cyclohexanepropanamide (36a).

Starting material = **35** (79 mg, 0.31 mmol). Yield = 65 mg (53%, white solid). R_f = 0.36 (DCM/acetone, 50:1). ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.84 (br s, 1H), 8.24 – 8.15 (m, 1H), 8.03 (d, *J* = 8.3 Hz, 1H), 7.92 (d, *J* = 9.5 Hz, 1H), 7.78 – 7.71 (m, 2H), 7.60 – 7.49 (m, 3H), 2.51 – 2.39 (m, 2H), 1.68 – 1.49 (m, 7H), 1.19 – 1.00 (m, 4H), 0.86 – 0.74 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 189.2, 171.9, 165.4, 145.5, 136.0, 134.6, 134.0, 131.9, 130.5, 128.6, 127.7, 127.1, 126.9, 125.4, 124.4, 37.3, 34.1, 33.0, 32.3, 26.5, 26.1. mp 198-200 ºC. MS (HR-ESI) for $C_{23}H_{25}N_2O_2S$ ($[M+H]^+$), calcd: *m/z* 393.16313, found: *m/z* 393.16183.



S.4.2.14.2. *N*-[5-(1-Naphthoyl)thiazol-2-yl]cyclohexanecarboxamide (36b).

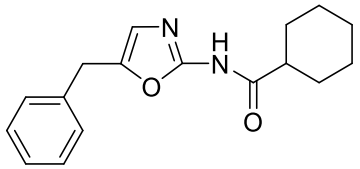
Starting material = **35** (79 mg, 0.31 mmol). Yield = 86 mg (76%, white solid). R_f = 0.36 (DCM/acetone, 50:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.15 (br s, 1H), 8.13 (d, *J* = 9.1 Hz, 1H), 8.01 (d, *J* = 8.2 Hz, 1H), 7.91 (d, *J* = 9.4 Hz, 1H), 7.74 – 7.66 (m, 2H), 7.58 – 7.47 (m, 3H), 2.26 (tt, *J* = 11.7, 3.3 Hz, 1H), 1.83 (d, *J* = 11.8 Hz, 2H), 1.66 (dt, *J* = 13.3, 3.0 Hz, 2H), 1.57 – 1.44 (m, 3H), 1.16 (qt, *J* = 12.8, 3.4 Hz, 1H), 0.85 (qt, *J* = 13.0, 3.2 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.3, 174.6, 165.9, 145.9, 136.2, 134.4, 133.9, 131.6, 130.4, 128.5, 127.6, 126.9, 126.7, 125.4, 124.4, 45.2, 29.0, 25.5, 25.4. mp 218-219 ºC. MS (HR-ESI) for $C_{21}H_{21}N_2O_2S$ ($[M+H]^+$), calcd: *m/z* 365.13183, found: *m/z* 365.13068.



S.4.2.14.3. *N*-[5-(Phenylmethyl)oxazol-2-yl]-3-cyclohexanepropanamide (38a).

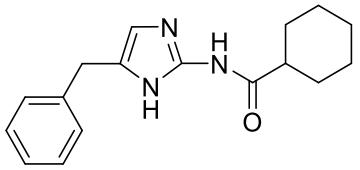
Starting material = **37** (69 mg, 0.40 mmol). Yield = 10 mg (8%, yellow glassy solid). R_f = 0.18 (DCM/acetone, 10:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.29 (m, 2H), 7.28 – 7.24 (m, 3H), 6.48 (s, 1H), 3.97 (s, 2H), 2.46 (s, 2H), 1.74 – 1.64 (m, 5H), 1.58 (q, *J* = 6.8 Hz, 2H), 1.24 – 1.08 (m, 4H), 0.88 (q, *J* = 11.5 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.7, 153.6, 148.3, 136.3,

128.9, 128.9, 127.2, 121.3, 37.4, 33.2, 32.4, 32.2, 26.6, 26.3. MS (HR-ESI) for $C_{19}H_{25}N_2O_2$ ([M+H]$^+$), calcd: *m/z* 313.19105, found: *m/z* 313.19006.



S.4.2.14.4. *N*-[5-(Phenylmethyl)oxazol-2-yl]cyclohexanecarboxamide (38b).

Starting material = **37** (69 mg, 0.40 mmol). Yield = 31 mg (27%, yellow glassy solid). R_f = 0.18 (DCM/acetone, 10:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.51 (br s, 1H), 7.34 – 7.28 (m, 2H), 7.26 – 7.21 (m, 3H), 6.47 (s, 1H), 3.97 (s, 2H), 2.34 (s, 1H), 1.88 (d, *J* = 12.9 Hz, 2H), 1.84 – 1.75 (m, 2H), 1.70 – 1.63 (m, 1H), 1.57 – 1.46 (m, 2H), 1.24 – 1.16 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.2, 148.4, 136.4, 128.8, 128.8, 127.1, 120.9, 32.2, 29.8, 29.2, 25.7, 25.7. MS (HR-ESI) for $C_{17}H_{21}N_2O_2$ ([M+H]$^+$), calcd: *m/z* 285.15975, found: *m/z* 285.15927.



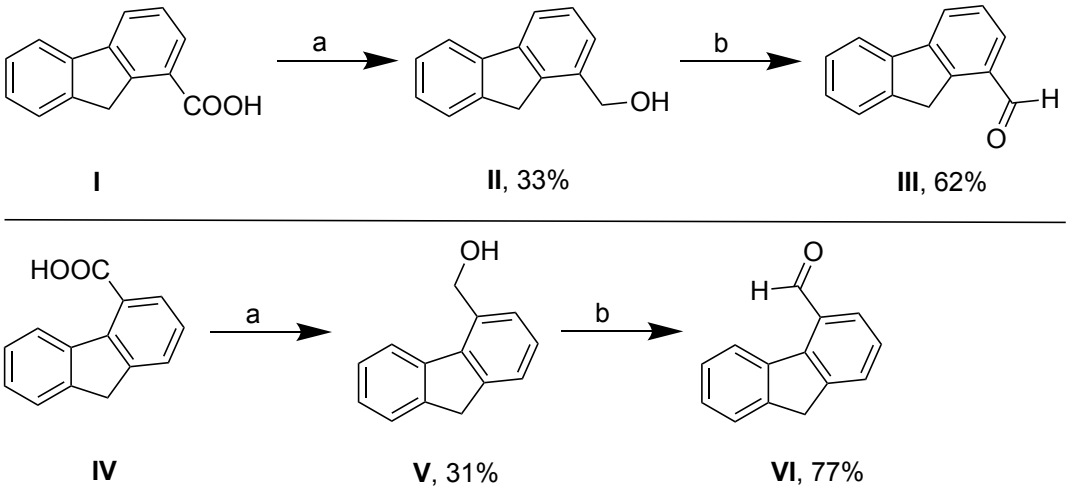
S.4.2.14.5. *N*-(5-Benzyl-1*H*-imidazol-2-yl)cyclohexanecarboxmide (40).

Compound **40** was synthesized by adapting a published procedure.[7] A mixture of **39** (100 mg, 0.48 mmol), 1-hydroxybenzotriazole hydrate (65 mg, 0.48 mmol), EDCI hydrochloride (92 mg, 0.48 mmol), and triethylamine (134 mL, 0.96 mmol) in acetonitrile (10 mL) was stirred at room temperature for 10 min. To this solution was added 5-benzyl-1*H*-imidazol-2-amine hydrochloride (100 mg, 0.48 mmol) and the reaction mixture was stirred at 80 ºC for 16 h. The solution was evaporated and the residue was purified by silica gel column chromatography.

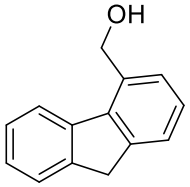
Yield = 88 mg (65%, off white solid). R_f = 0.25 (DCM/methanol, 20:1). ^{1}H NMR (400 MHz, CD_3COCD_3) δ 11.72 (br s, 1H), 7.31 – 7.24 (m, 4H), 7.22 – 7.16 (m, 1H), 6.52 (s, 1H), 3.94 (s, 2H), 2.48 (tt, *J* = 11.6, 3.5 Hz, 1H), 1.90 – 1.82 (m, 2H), 1.80 – 1.73 (m, 2H), 1.70 – 1.63 (m, 1H), 1.50 (qd, *J* = 12.3, 2.9 Hz, 2H), 1.36 – 1.22 (m, 3H). ^{13}C NMR (100 MHz, CD_3COCD_3) δ 175.7, 143.4, 141.0, 129.5, 129.1, 126.9, 45.4, 33.5, 26.5, 26.2. mp 154-155 ºC. MS (HR-ESI) for $C_{17}H_{22}N_3O$ ([M+H]$^+$), calcd: *m/z* 284.17574, found: *m/z* 284.17569.

S.4.2.15. Preparation of fluorenyl aldehydes

Fluorenyl aldehydes **III** and **VI** were synthesized because the former was not available from standard vendors and the latter had not been described previously. Fluorene-1-carboxylic acid (**I**) and fluorene-4-carboxylic acid (**IV**) were purchased from standard vendors. Compounds **II**[8] and **III**[8] are reported compounds, which were synthesized according to published procedures. Compound **III** was used for the synthesis of **6c** (see S.4.2.2.3).



Scheme S.1. Preparation of fluorene derivatives **II**, **III**, **V** and **VI** from commercially available compounds **I** and **IV**. Reaction conditions: a) Lithium aluminum hydride, THF, 0 ^{o}C to r.t., 1 h; b) Pyridinium dichromate, silica gel, DCM, r.t., 16 h

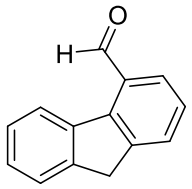


S.4.2.15.1. 4-Hydroxymethylfluorene (V).

Compound **V** was prepared by adapting a published procedure.[8] To fluorene-4-carboxylic acid (**IV**) (1.0 g, 4.8 mmol) in anhydrous THF (30 mL) was added a 1 M solution of lithium aluminum hydride in THF (24.0 mL, 24.0 mmol) at 0 ºC. The reaction mixture was stirred at room temperature for 16 h and quenched with ice-cold water. The solution was evaporated and

the residue extracted with ether. The organic phase was dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography.

Yield = 289 mg (31%, pale yellow solid). R_f = 0.43 (DCM). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, *J* = 7.7 Hz, 1H), 7.58 (d, *J* = 7.3 Hz, 1H), 7.52 (d, *J* = 7.3 Hz, 1H), 7.46 – 7.28 (m, 4H), 5.12 (s, 2H), 3.93 (s, 2H), 1.75 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.4, 143.8, 141.3, 139.6, 135.2, 127.2, 126.7, 126.7, 126.7, 125.0, 124.7, 123.7, 64.2, 37.3. mp 127-129 ºC. MS (HR-ESI) for $C_{14}H_{12}O$ ($[M+H]^+$), calcd: *m/z* 219.07804, found: *m/z* 219.07808.



S.4.2.15.2. 4-Fluorenecarbaldehyde (VI).

Compound **VI** was prepared by adapting a published procedure.[8] A mixture of **V** (268.7 mg, 1.37 mmol), pyridinium dichromate (617 mg, 1.64 mmol), silica gel (3 g) in DCM (20 mL) was stirred at room temperature for 16 h. The solution was filtered and the filtrate evaporated. The residue was purified by silica gel column chromatography.

Yield = 206 mg (77%, off white solid). R_f = 0.62 (Toluene). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.64 (s, 1H), 8.61 – 8.52 (m, 1H), 7.89 (d, *J* = 7.6 Hz, 1H), 7.75 (d, *J* = 7.4 Hz, 1H), 7.64 – 7.56 (m, 1H), 7.48 – 7.37 (m, 3H), 3.94 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.1, 145.3, 144.5, 142.5, 140.5, 132.6, 130.9, 130.4, 128.1, 127.3, 126.5, 125.9, 125.1, 37.2. mp 84-85 ºC. MS (HR-ESI) for $C_{14}H_{11}O$ ($[M+H]^+$), calcd: *m/z* 195.08044, found: *m/z* 195.08028.

Compound **VI** was used for the synthesis of **6d** (see S.4.2.2.4).

S.4.3 Biological assays

S.4.3.1 *In vitro* antifungal activity against *H. capsulatum* and *C. neoformans* yeasts

The *H. capsulatum* strain used in this study was the wild-type strain G217B (ATCC 26032). *Histoplasma* cells were maintained as yeasts by growth in Histoplasma-macrophage media (HMM)[9] at 37 ºC in 95% air/5% CO_2. The *Cryptococcus* strains used were the wild-type serotype A strain H99, the wild-type serotype D strain B3501, or the fluconazole-resistant strains TES9 and MRL862 (kindly provided by J. Kwon-Chung).[10] *Cryptococcus* yeasts were cultured in YPD medium at 37 ºC for routine maintenance.

For IC_{50} determination, *Histoplasma* or *Cryptococcus* yeasts were cultured in 96-well microtiter plates with a two-fold dilution series of each compound from 40 μM to 0.078 μM in 100 μL of RPMI buffered to pH 7.0 with 25 mM HEPES. *Histoplasma* and *Cryptococcus* yeasts were pre-grown in HMM or YPD media, respectively, until exponential-phase growth and the density determined by hemacytometer counts. *Histoplasma* and *Cryptococcus* yeasts were subsequently diluted into RPMI and added to wells containing compounds to a final density of 5 x 10^5 or 2 x 10^3 per well, respectively. Plates were incubated at 37 ^oC and agitated twice daily for improved aeration. Yeast growth was monitored by absorbance at 595 nm over 5 days (*Histoplasma*) or 4 days (*Cryptococcus*) using a Synergy2 plate reader (BioTek). The turbidity in each well was normalized to control wells lacking the antifungal compound but with an equivalent amount of DMSO solvent. Relative turbidity measurements at 4 days (*Histoplasma*) or 3 days (*Cryptococcus*) were used for non-linear regression analysis (4 parameters) and IC_{50} determination. Compounds with an initial IC_{50} < 20 μM were evaluated in assays. MICs were determined as the concentrations that inhibited yeast growth to 10% or less than the growth of yeasts in the absence of any compounds.

For evaluation of pH effects on compound potency, dose-response assays were conducted with select compounds on *Histoplasma* or *Cryptococcus* yeasts in RPMI at pH 7.0 (buffered with 25 mM HEPES) or pH 5.0 (buffered with 25 mM MOPS).

S.4.3.2 *In vitro* toxicity to macrophages

Cytotoxicity was evaluated using the murine phagocyte cell line P388D1 (ATCC #CCL-46) for compounds with IC_{50}s for yeasts < 20 μM. P388D1 cells were maintained at 37 ºC under 5% CO_2 / 95% air in Ham's F-12 medium supplemented with 10% fetal bovine serum

(FBS) and 2 mM L-glutamine. For dose-response evaluations, P388D1 cells were seeded into wells of a 96-well microtiter plate at 5×10^3 cells per well and allowed to adhere overnight. Antifungal compounds were subsequently added to cells in a concentration range from 80 μM to 0.3 μM. After 72 hours, P388D1 cell viability was determined by addition of 0.1 mM resazurin to wells and measurement of the metabolic conversion to resorufin, which was quantified by fluorescence (530/25 nm excitation, 590/35 nm emission wavelengths) using a Synergy2 plate reader (BioTek) over time. Kinetics of fluorescence were obtained and the resorufin fluorescence at time points before saturation used for the dose-response data. Assays were performed on three biological replicates and the resorufin fluorescence from macrophages treated with compounds normalized to the resorufin fluorescence from untreated macrophages. The dose-response data were used for non-linear regression analysis and IC_{50} determination.

S.4.3.3. Evaluation of compound toxicity against intramacrophage *Histoplasma* yeasts

Efficacy of compounds was measured on *Histoplasma* yeasts within macrophages using a red-fluorescence protein (RFP) expressing *Histoplasma* strain[11] to monitor intramacrophage yeast proliferation by fluorescence. LacZ-expressing P388D1 macrophages[12] were seeded into 96-well microtiter plates at $3x10^4$ cells per well and allowed to adhere for 3 hours. RFP-expressing *Histoplasma* yeasts were added to macrophages at an MOI of 1:2 (yeasts:macrophages) and allowed to infect the cells for 3 hours at 37 ^oC in 5% CO_2 / 95% air, after which the culture media was replaced with fresh F-12 + 10% serum to remove any remaining extracellular yeasts. Infected macrophages were incubated at 37 ^oC overnight. The following day, the culture media was removed and replaced with media containing a concentration gradient of aminothiazole compounds. Infected macrophages were cultured for an additional 6 days and intracellular yeast RFP fluorescence measured daily using a Synergy2 plate reader (530/25 nm excitation, 590/35 emission wavelengths; BioTek). Relative RFP fluorescence at 4 days between compound-treated infected macrophages and untreated-infected macrophages was used for non-linear regression of the dose-response data. Macrophage survival after 7 days of infection was quantified by removal of culture supernatants, lysis of the macrophages with 0.5% Triton X-100, 2 mM $MgCl_2$, and measurement of the remaining macrophage β-galactosidase activity by addition of *o*-nitrophenyl-β-D-galactopyranoside.[11] β-Galactosidase activity (absorbance at 420 nm) was measured during the linear range of the assay (e.g., 30

minutes) and corrected for absorbance at 600 nm. Relative macrophage survival was determined by comparison to uninfected macrophages treated with equivalent concentrations of aminothiazole compounds. Assays were conducted in triplicate and the data used to generate the dose-response curves and non-linear regression.

S.4.4. Computational analyses of drug properties 28a/b, 29a/b, 31, 32a/b, 40 (see S.3.).

ACD/Percepta software (version 14.1.0) from Advanced Chemistry Development, Inc. (Toronto, ON, Canada) was used. Detailed parameters are described below:

- Module used: LogS
- pKa - Predicted using ACD/pKa Classic with the following trainable libraries: No libraries were selected.
- Intrinsic Solubility - User defined value (**28a**, **28b**, **29a**, **32a** and **36b**) or predicted using ACD/LogS0 GALAS with the following trainable libraries: LogS0 v. 1.2.trn (41F5, **29b**, **31**, **32b** and **40**).

S.5. References

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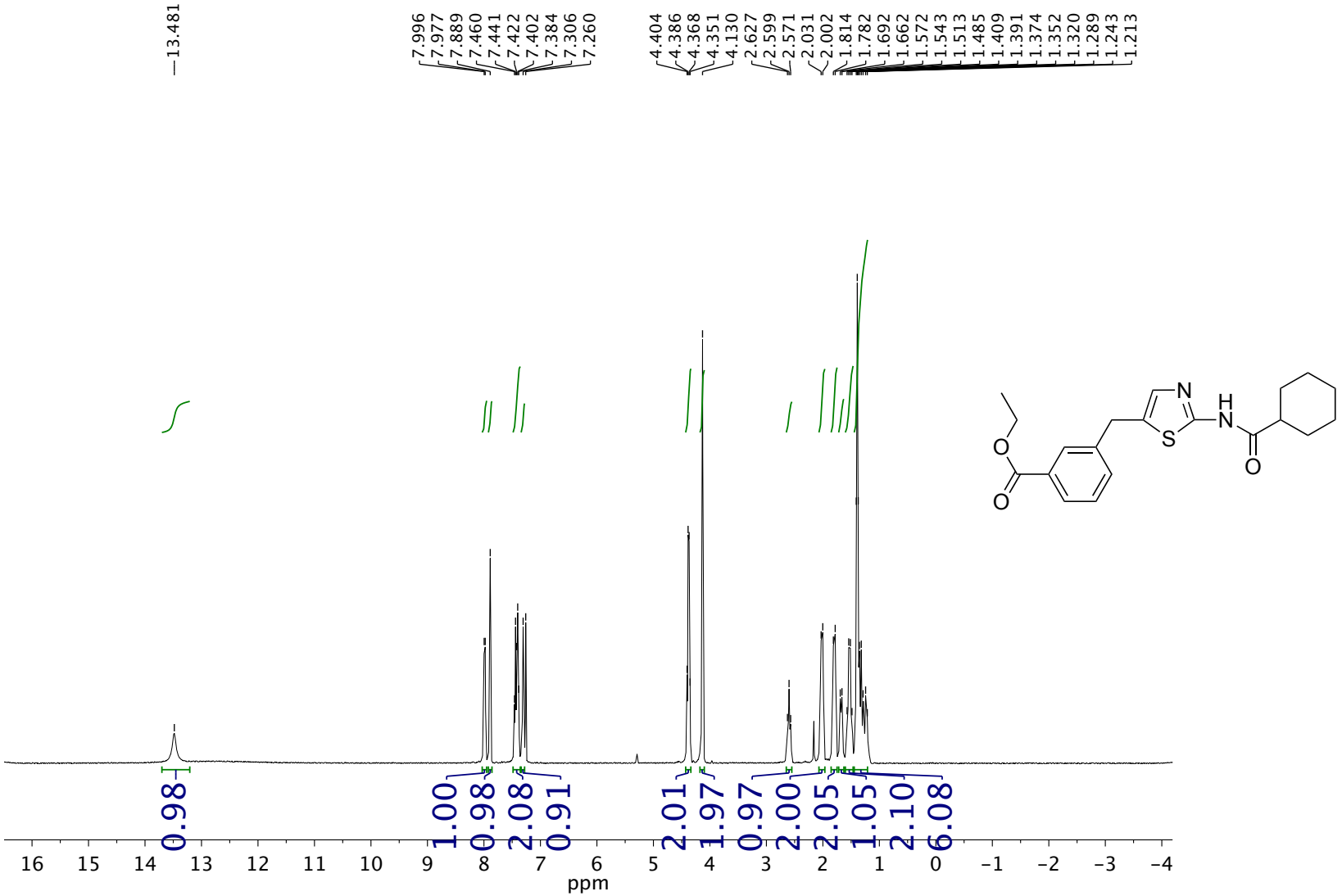
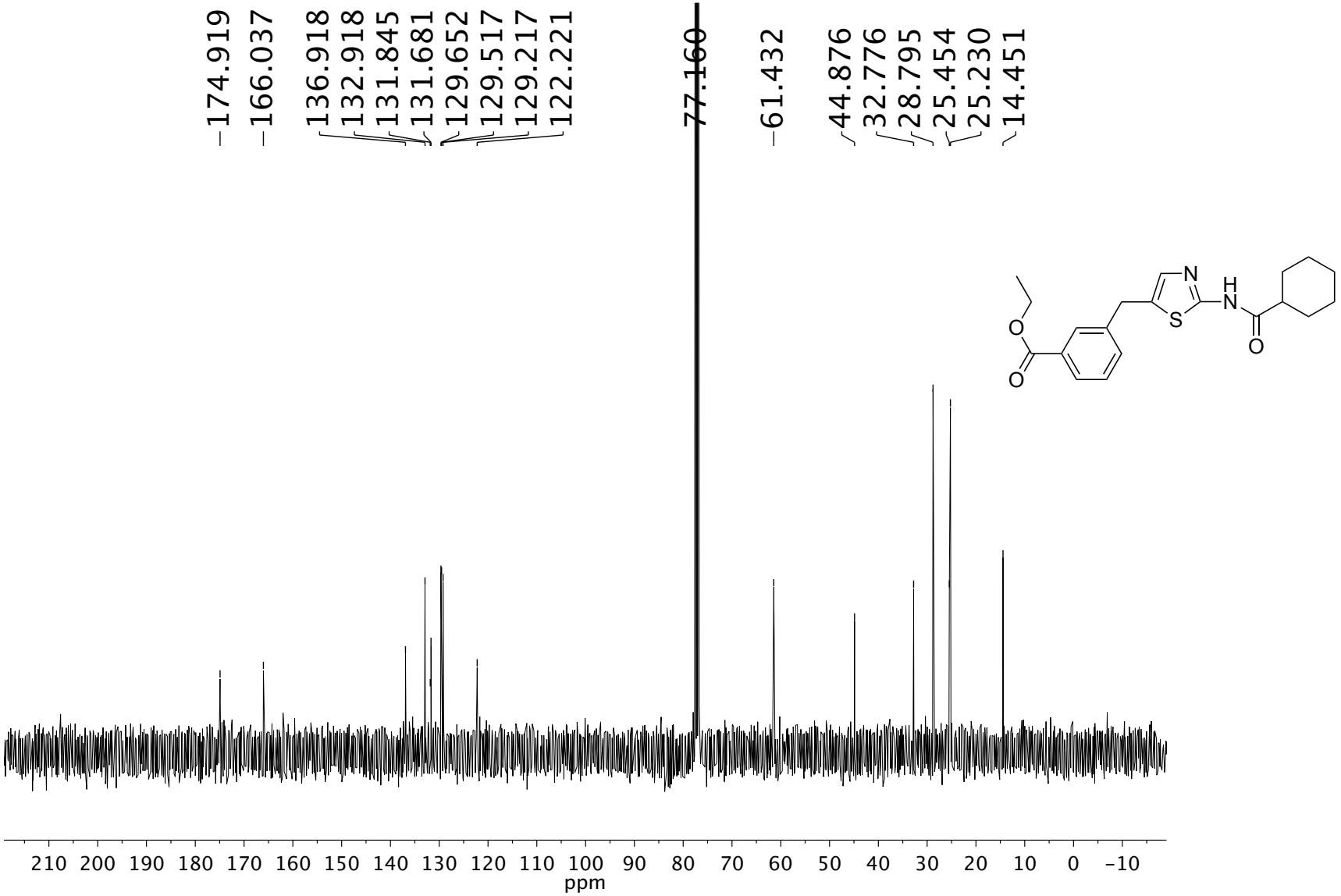
S.6. NMR and MS spectra of target compounds

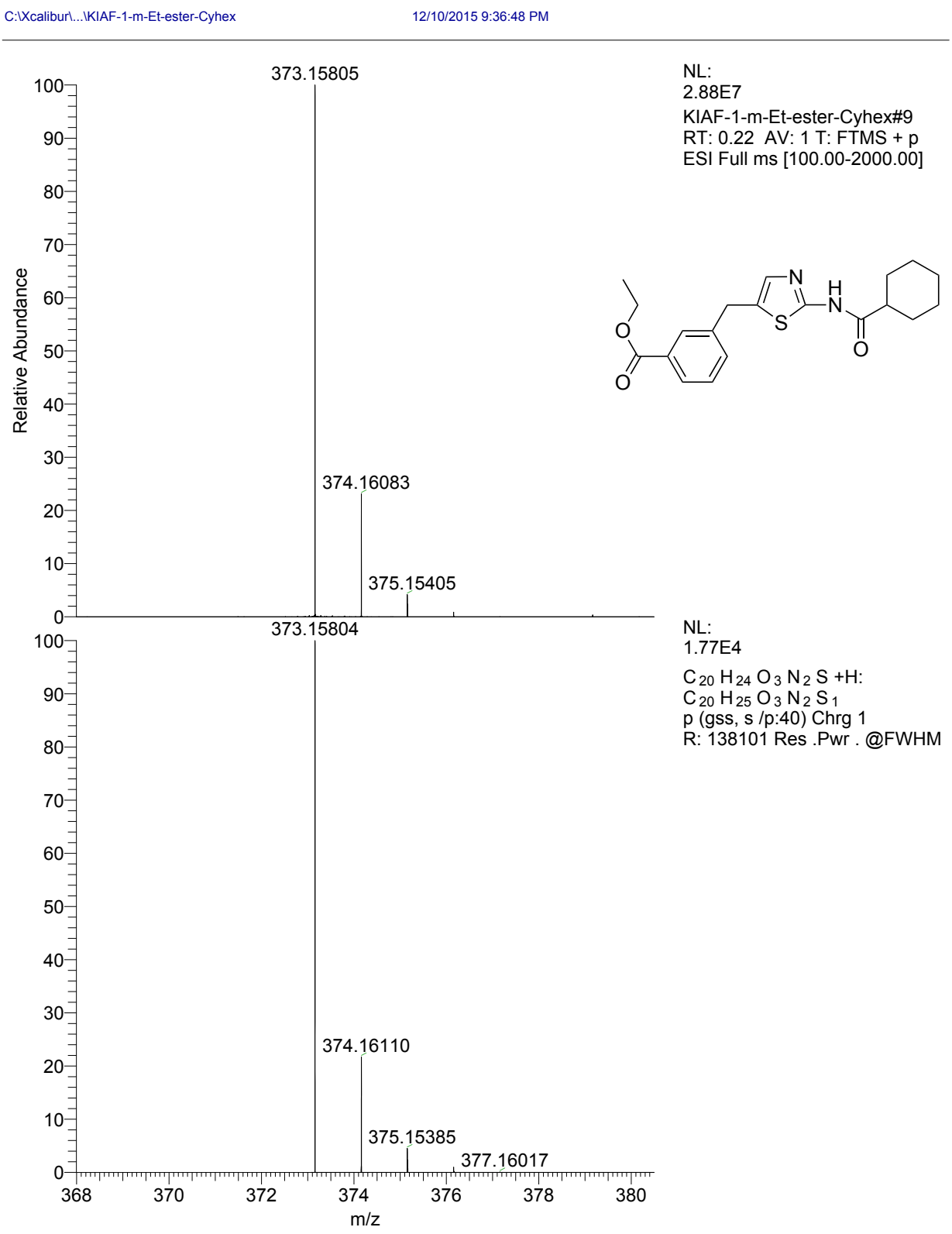
S.6.1.1. *N*-[5-(3-Ethoxycarbonylbenzyl)thiazol-2-yl]cyclohexanecarboxamide (14). ^{1}H NMR (400 MHz, $CDCl_3$)



S.6.1.2. *N*-[5-(3-Ethoxycarbonylbenzyl)thiazol-2-yl]cyclohexanecarboxamide (14). ^{13}C NMR (100 MHz, $CDCl_3$)



S.6.1.3. *N*-[5-(3-Ethoxycarbonylbenzyl)thiazol-2-yl]cyclohexanecarboxamide (14). HR-ESI-MS



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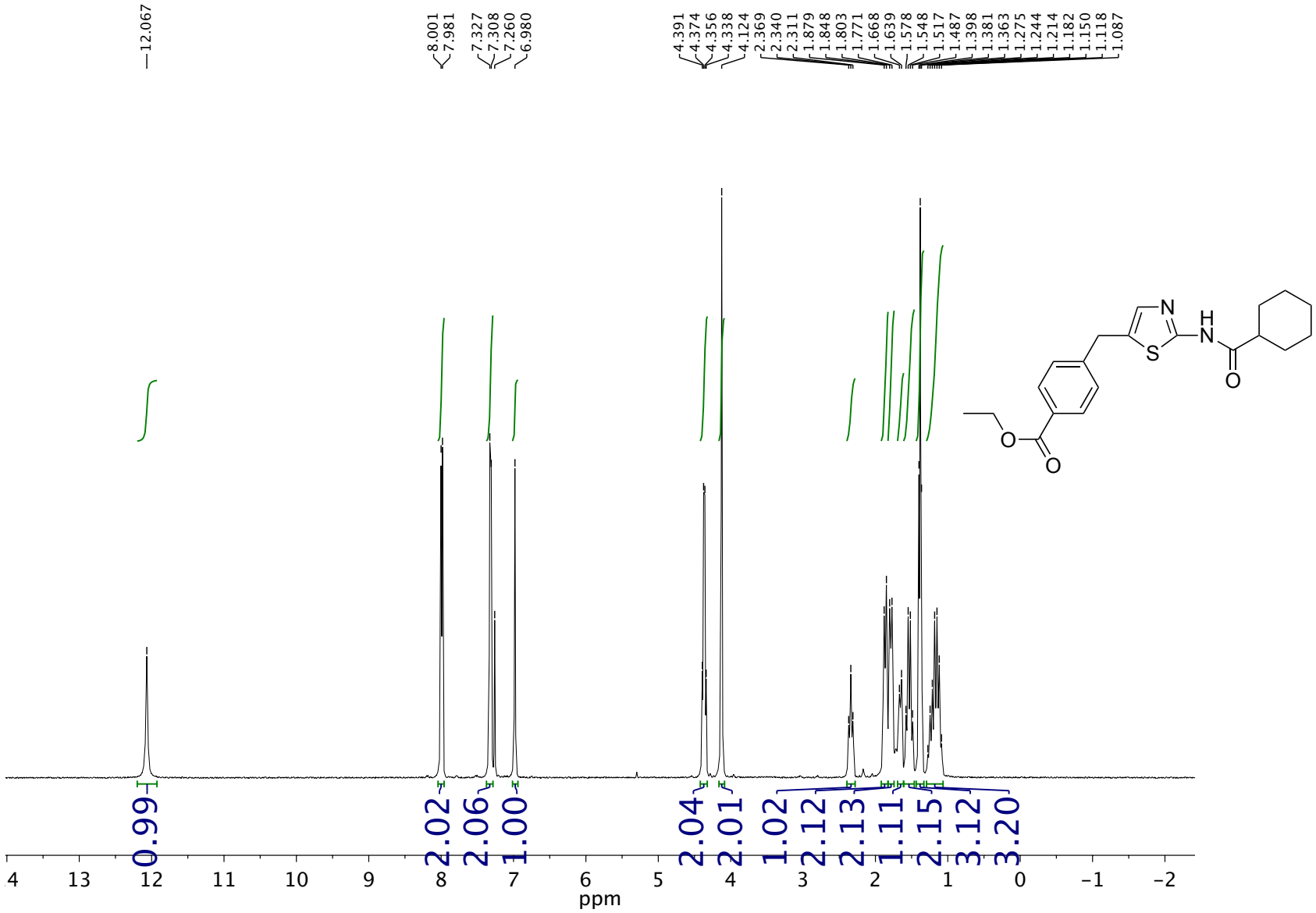

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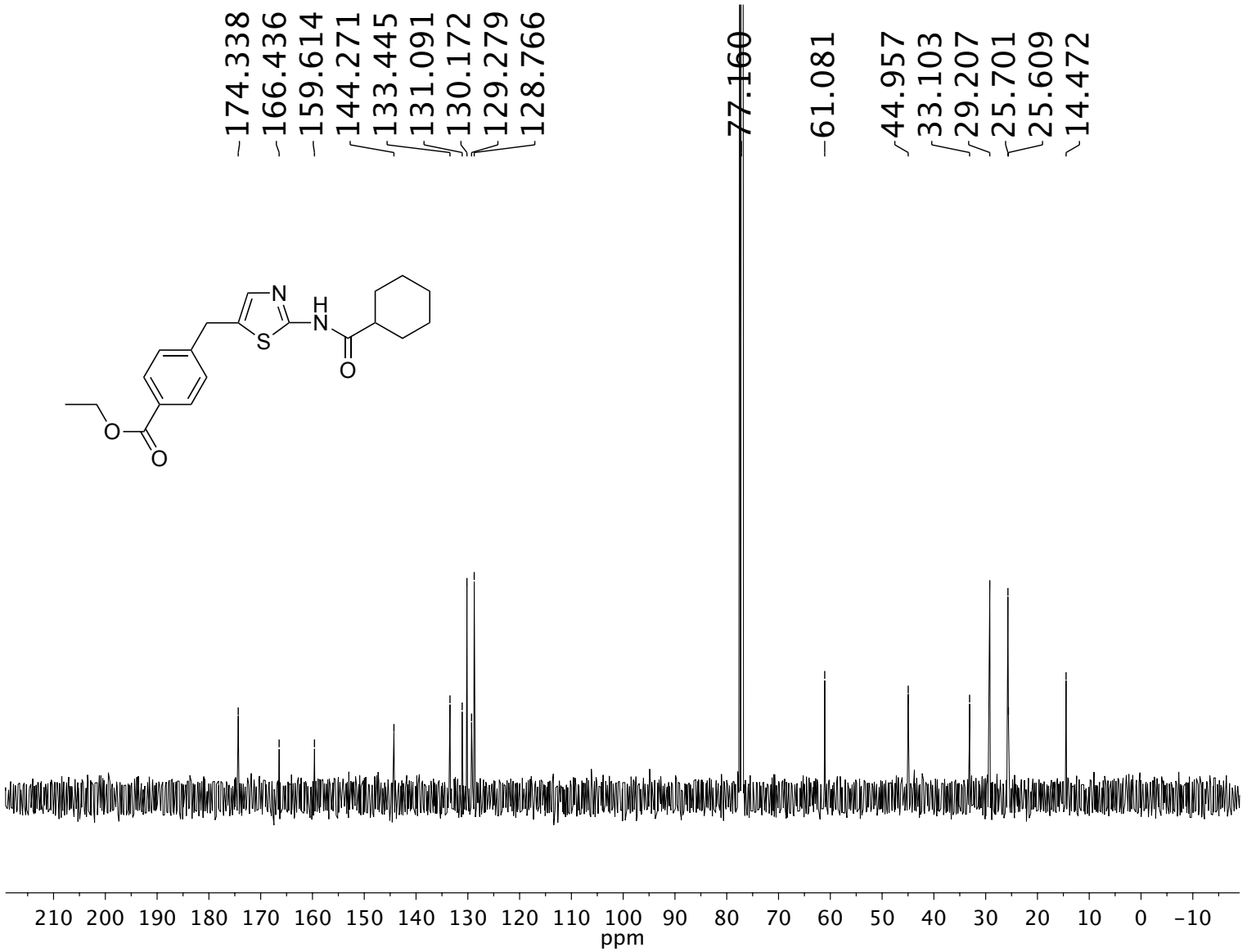

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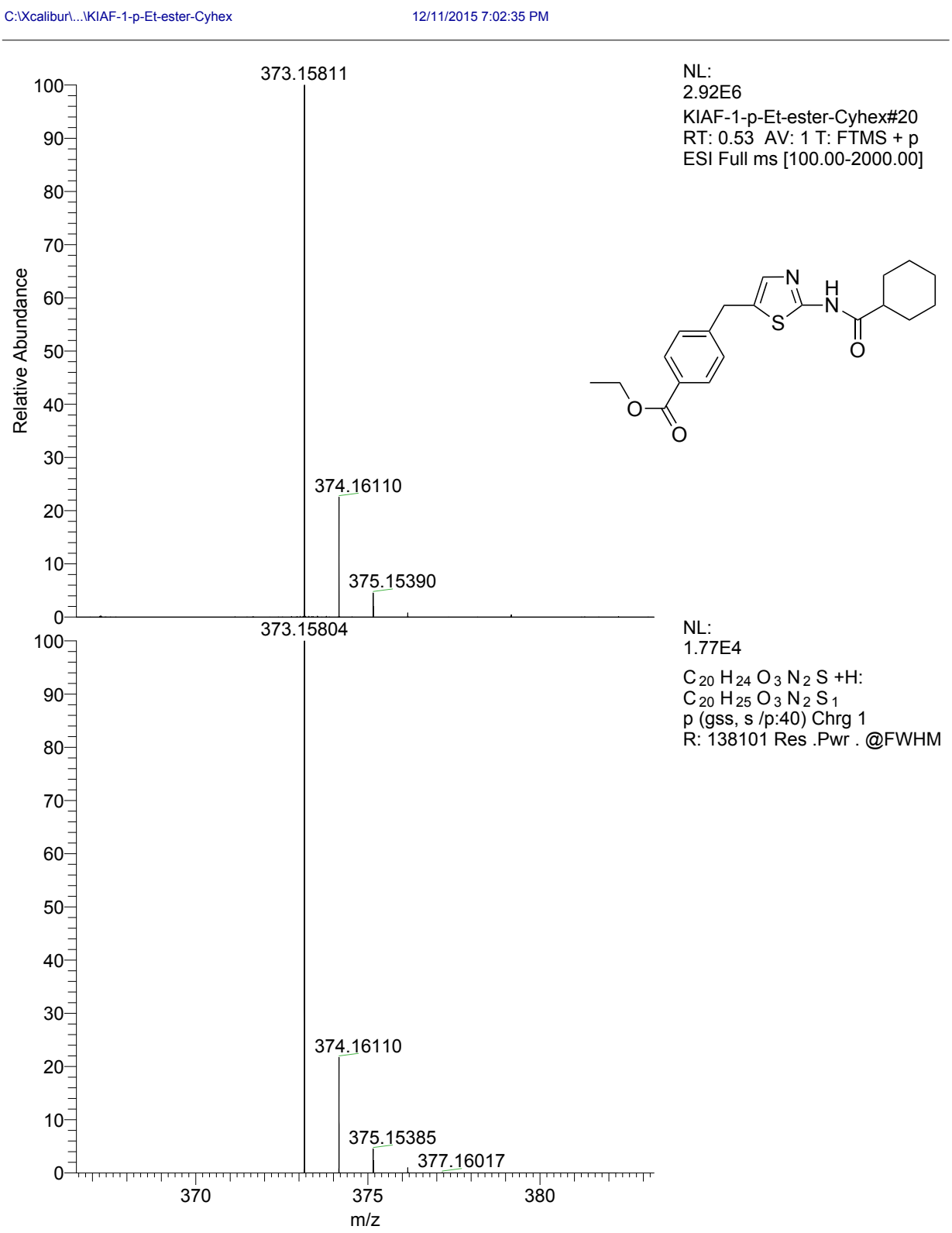
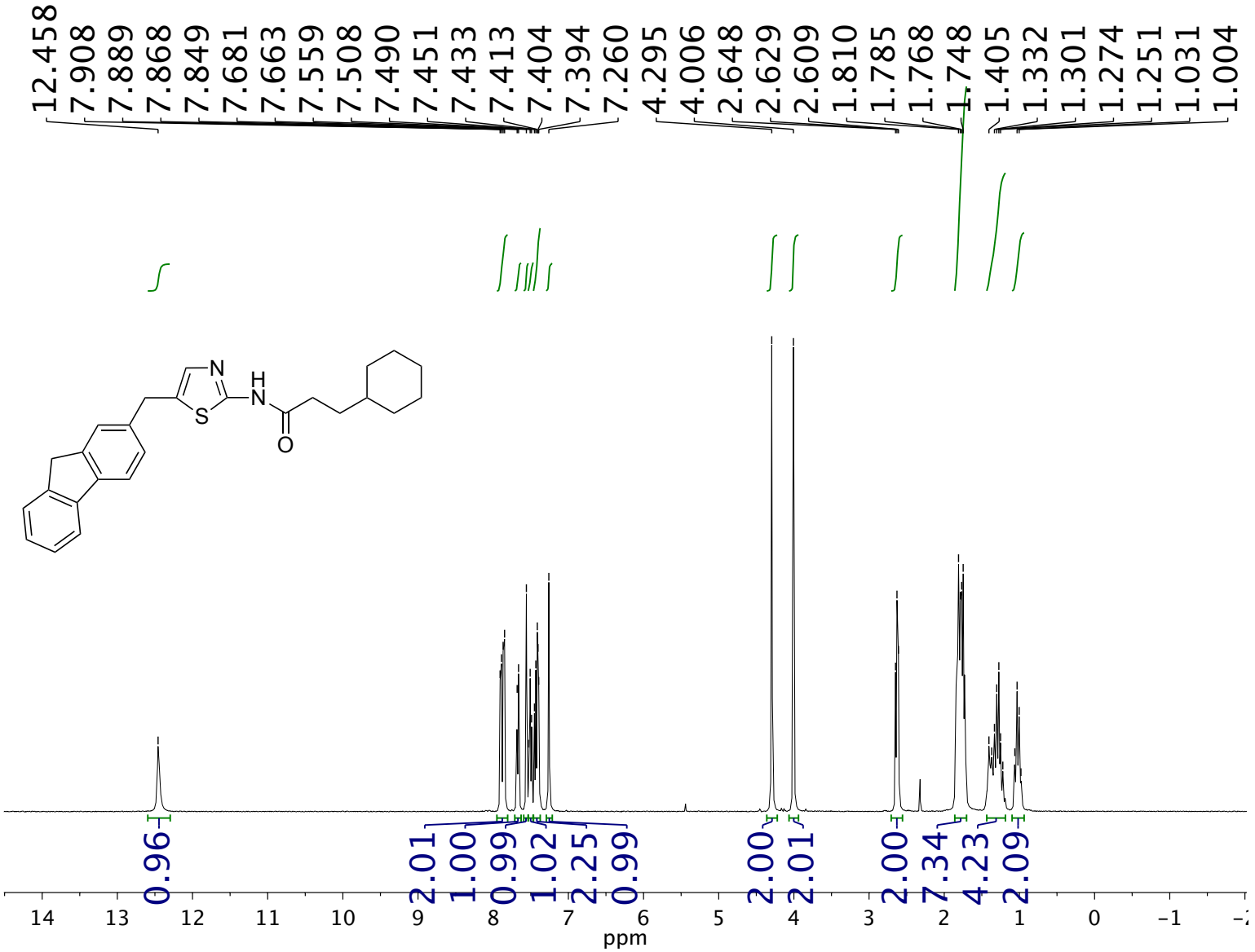


S.6.3.1. *N*-[5-(2-Fluorenylmethyl)thiazol-2-yl]-3-cyclohexanepropanamide (16a). ^{1}H NMR (400 MHz, $CDCl_3$)



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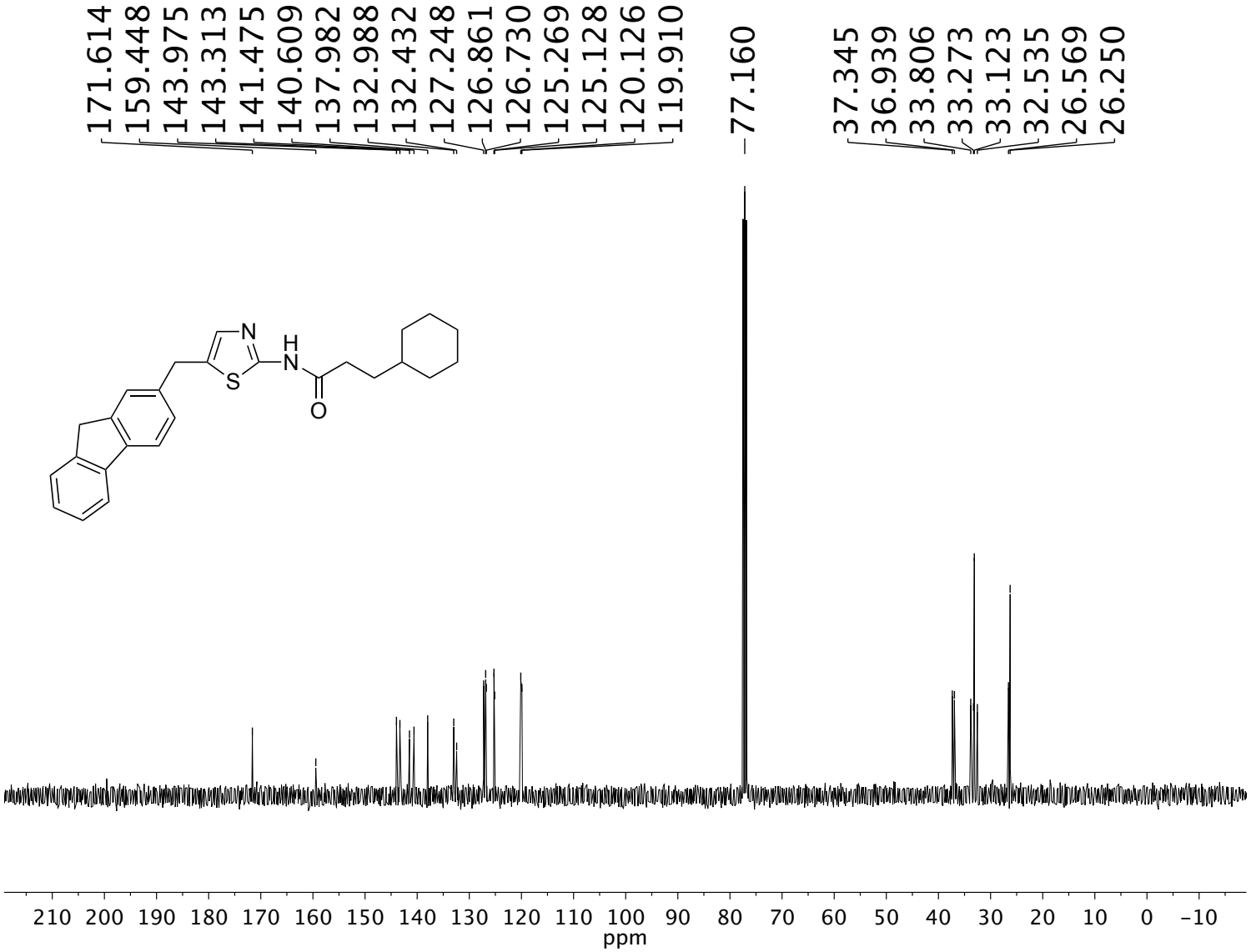
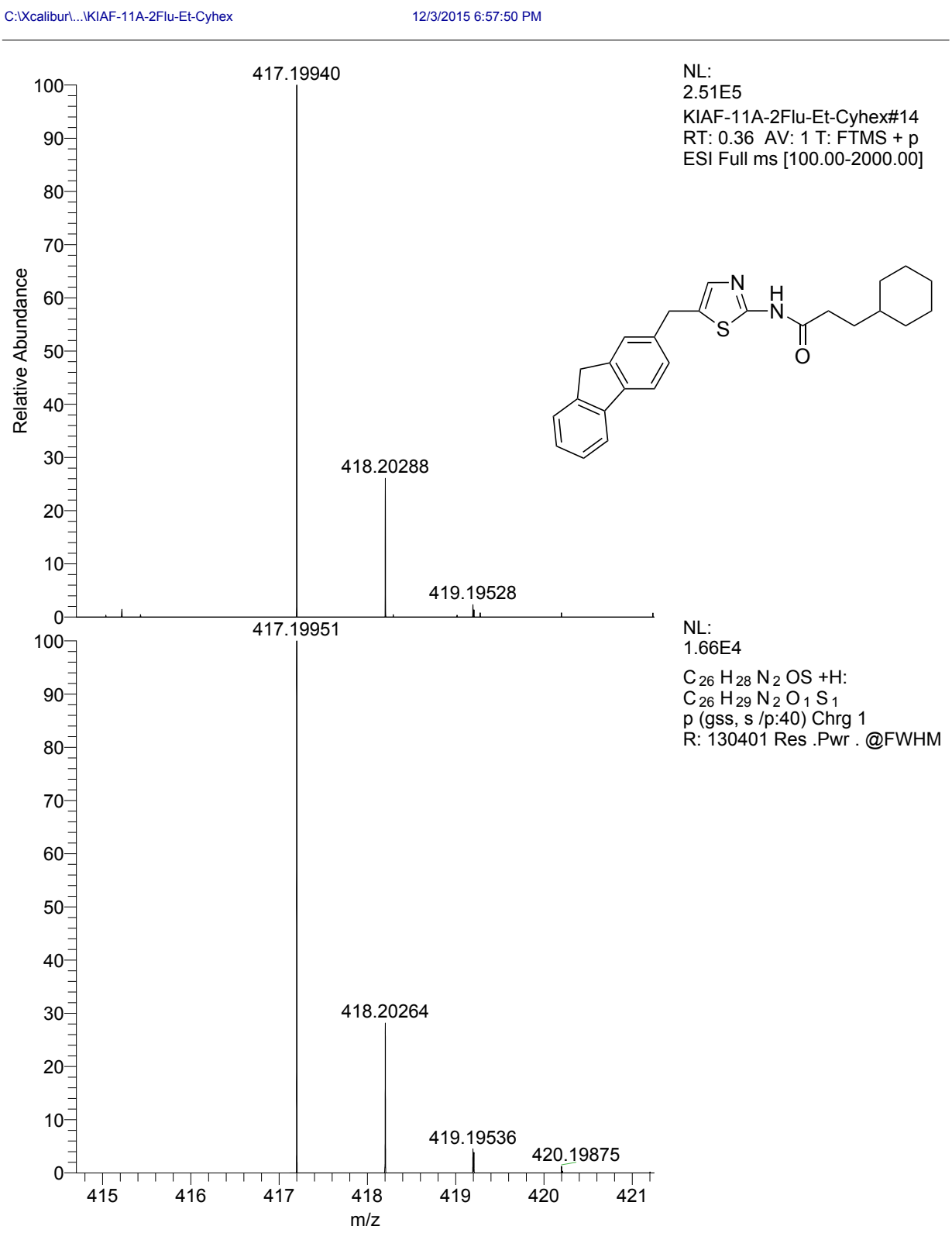


S.6.3.3. *N*-[5-(2-Fluorenylmethyl)thiazol-2-yl]-3-cyclohexanepropanamide (16a). HR-ESI-MS



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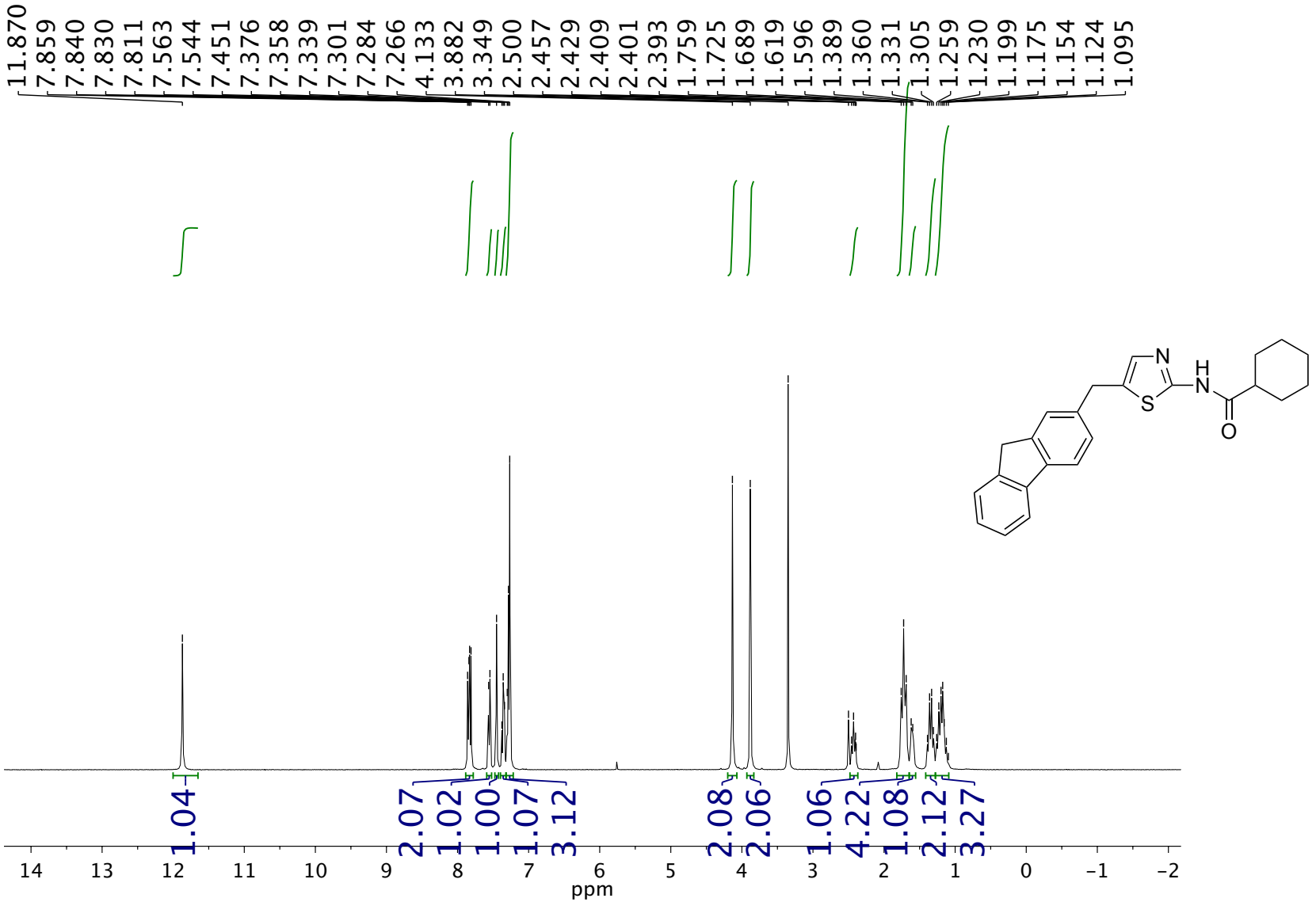

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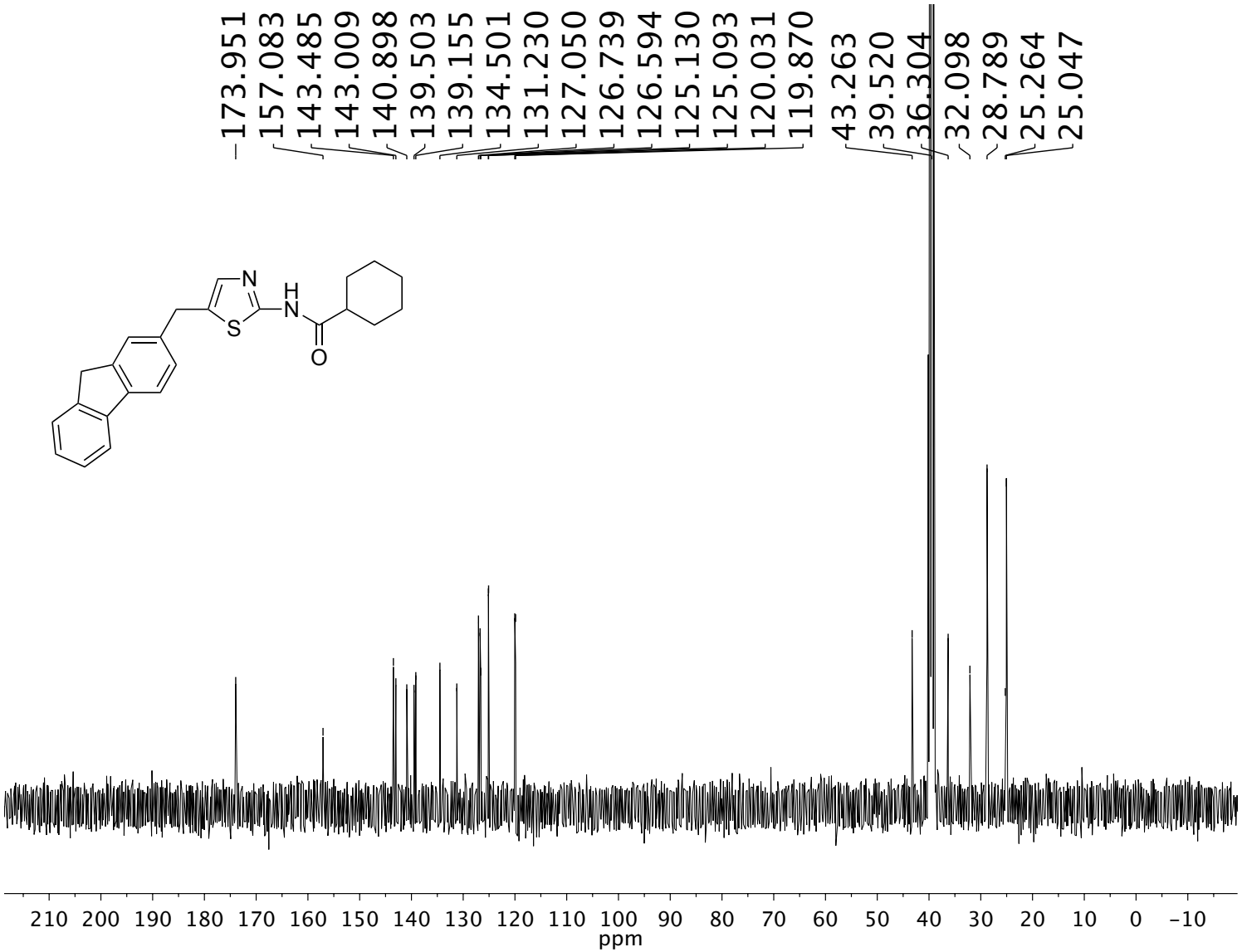

S.6.4.3. *N*-[5-(2-Fluorenylmethyl)thiazol-2-yl]cyclohexanecarboxamide (16b). HR-ESI-MS

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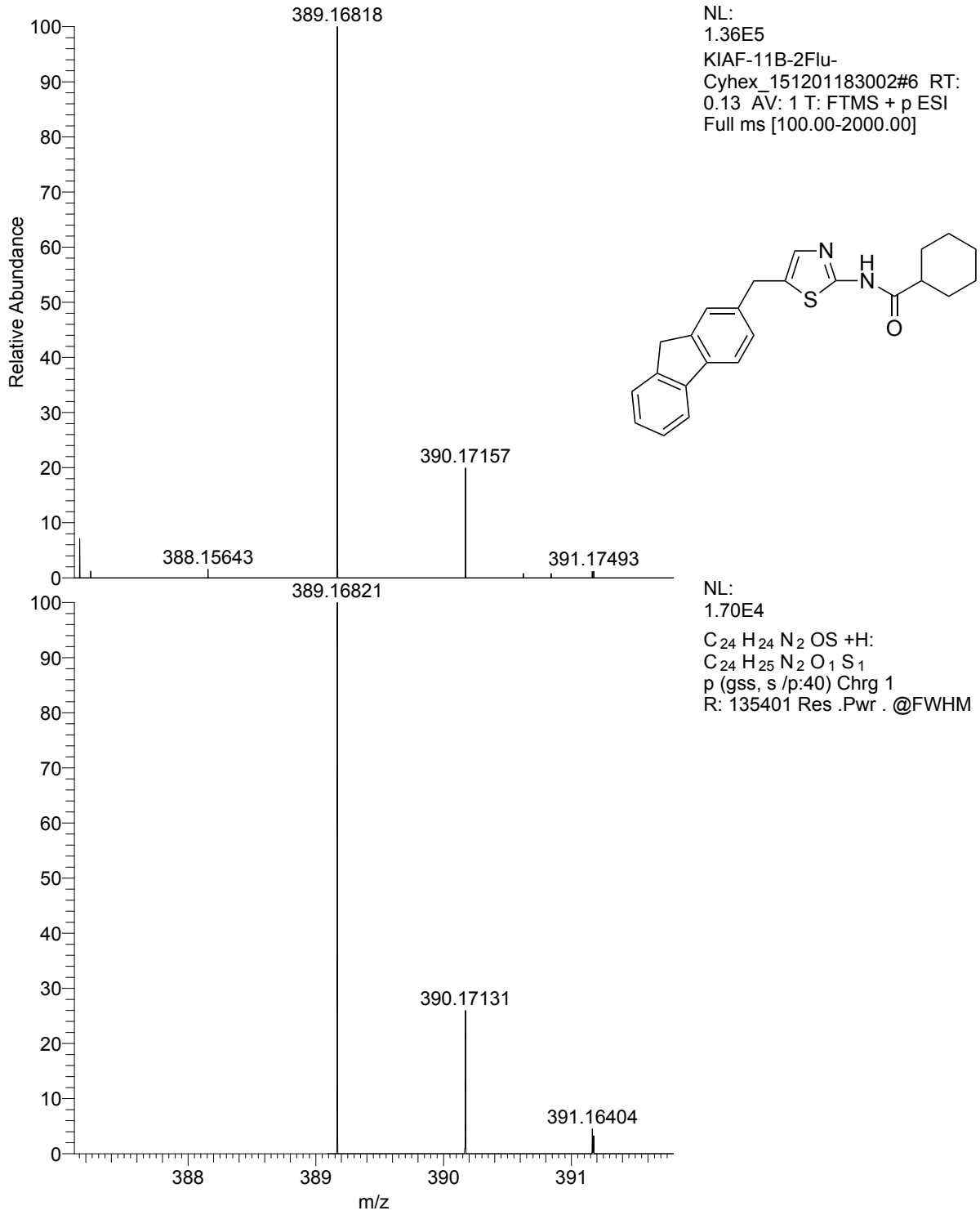
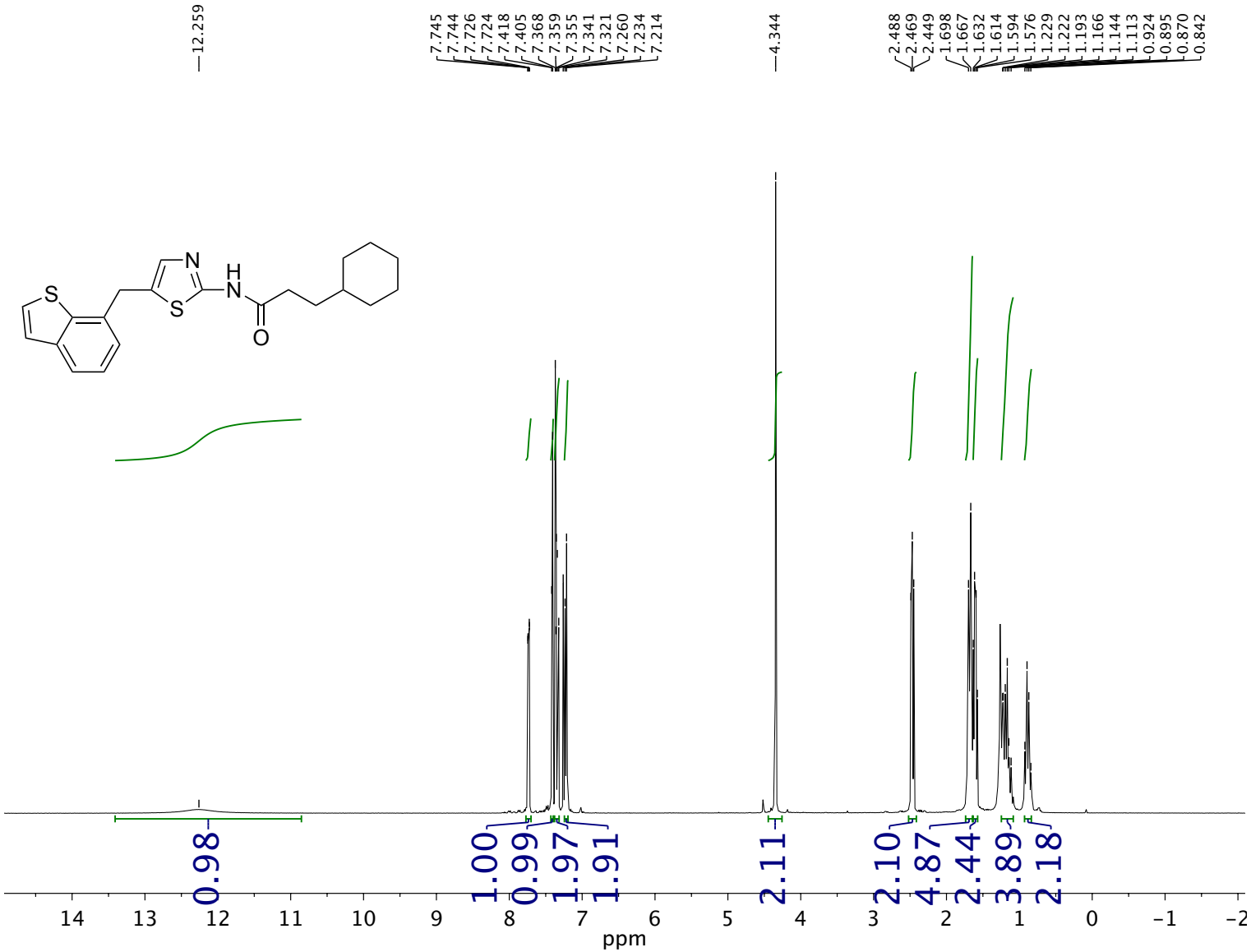
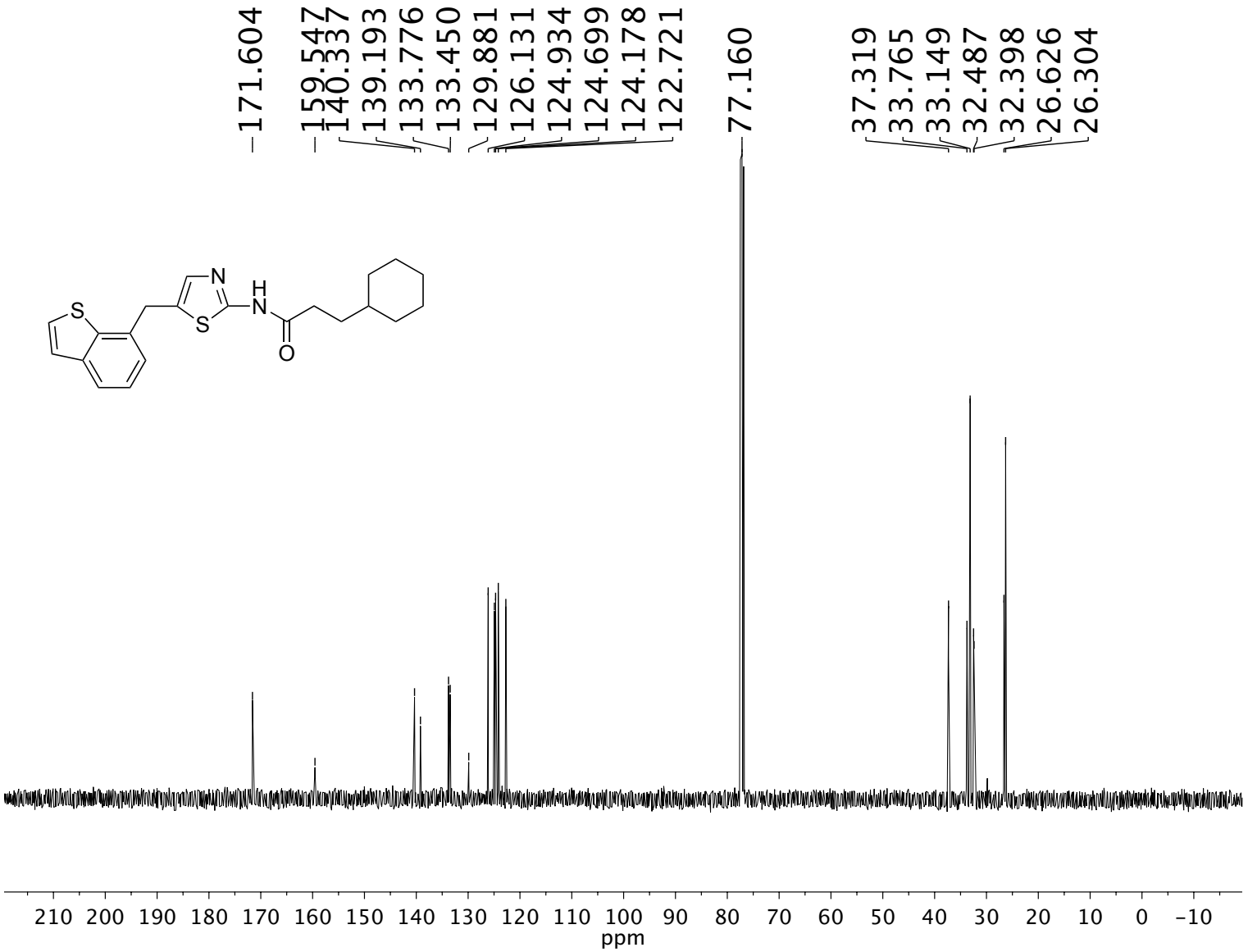


S.6.5.1. *N*-[5-(7-Benzothiophenylmethyl)thiazol-2-yl]-3-cyclohexanepropanamide (17a). ^{1}H NMR (400 MHz, $CDCl_3$)

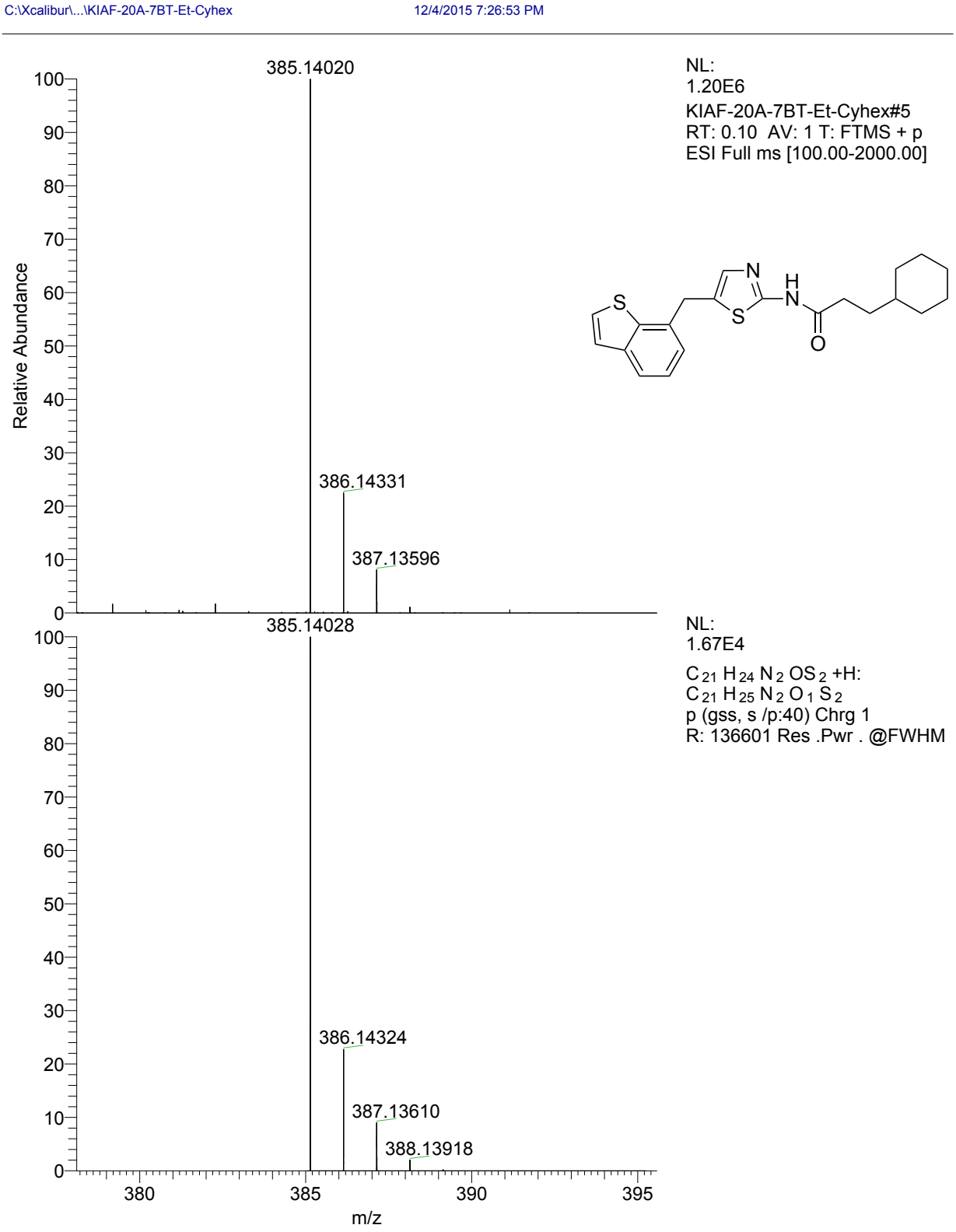


S.6.5.2. *N*-[5-(7-Benzothiophenylmethyl)thiazol-2-yl]-3-cyclohexanepropanamide (17a). ^{13}C NMR (100 MHz, $CDCl_3$)



S.6.5..3. *N*-[5-(7-Benzothiophenylmethyl)thiazol-2-yl]-3-cyclohexanepropanamide (17a).

HR-ESI-MS



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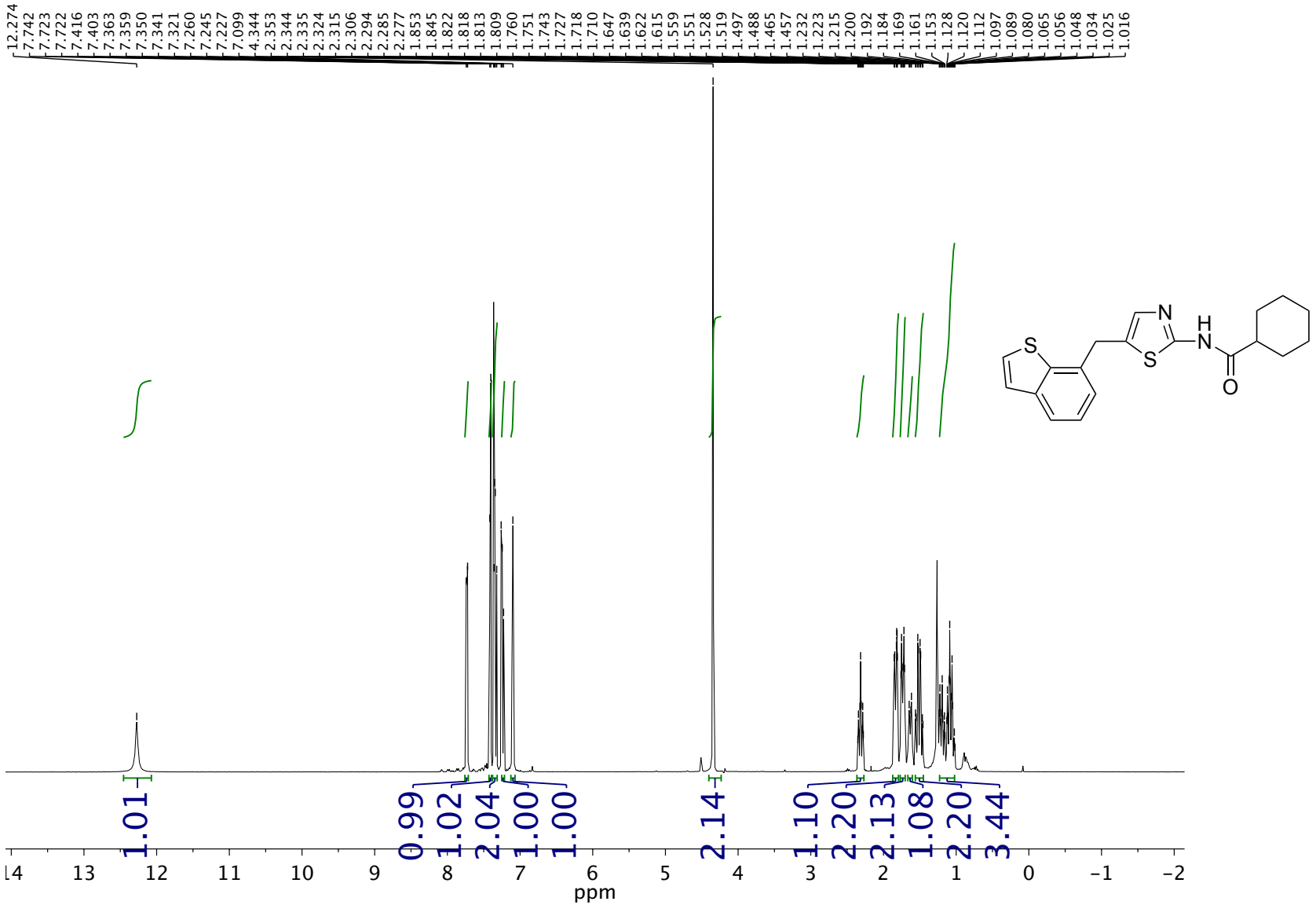

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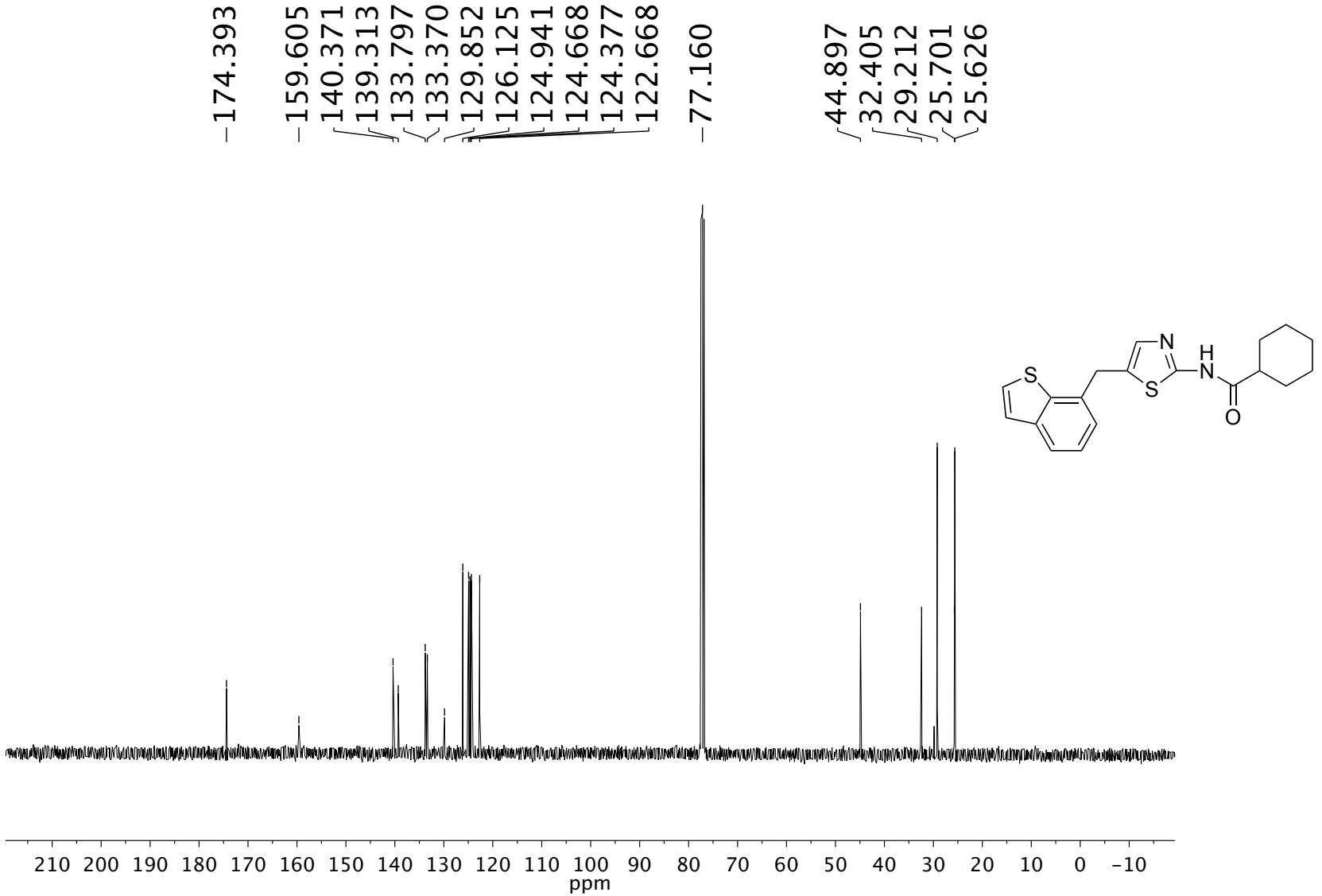

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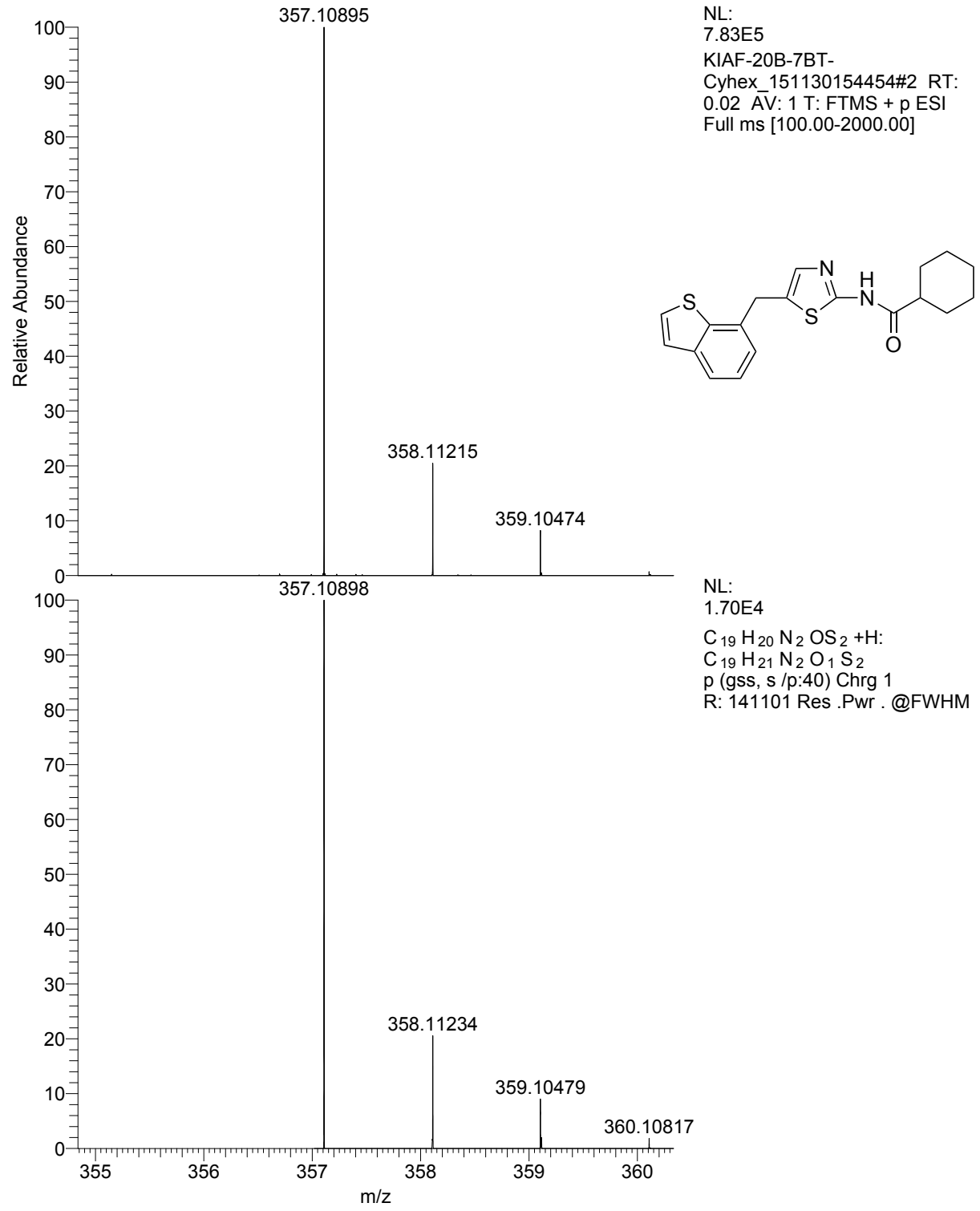
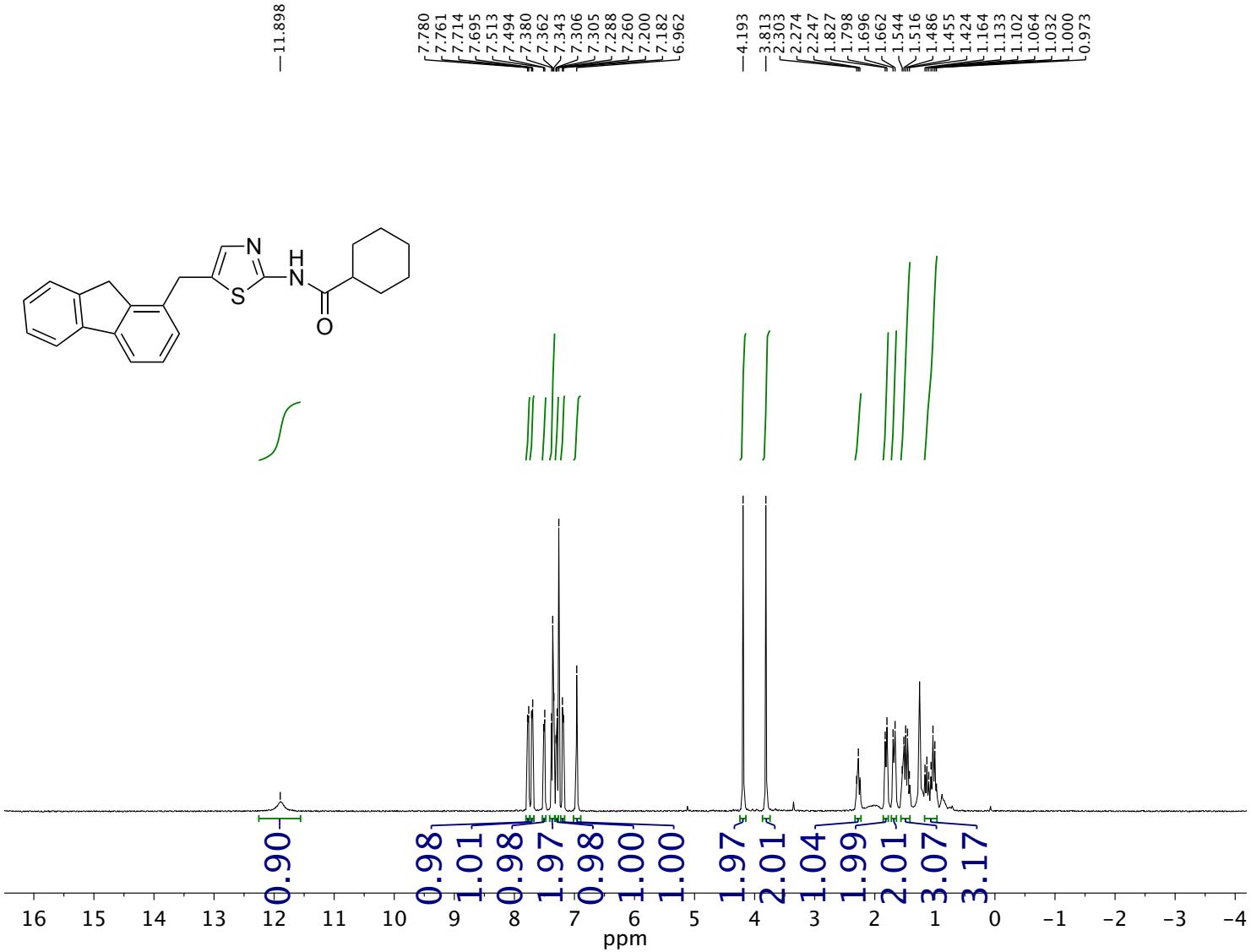


S.6.7.1. *N*-[5-(1-Fluorenylmethyl)thiazol-2-yl]cyclohexanecarboxamide (18). ^{1}H NMR (400 MHz, $CDCl_3$)



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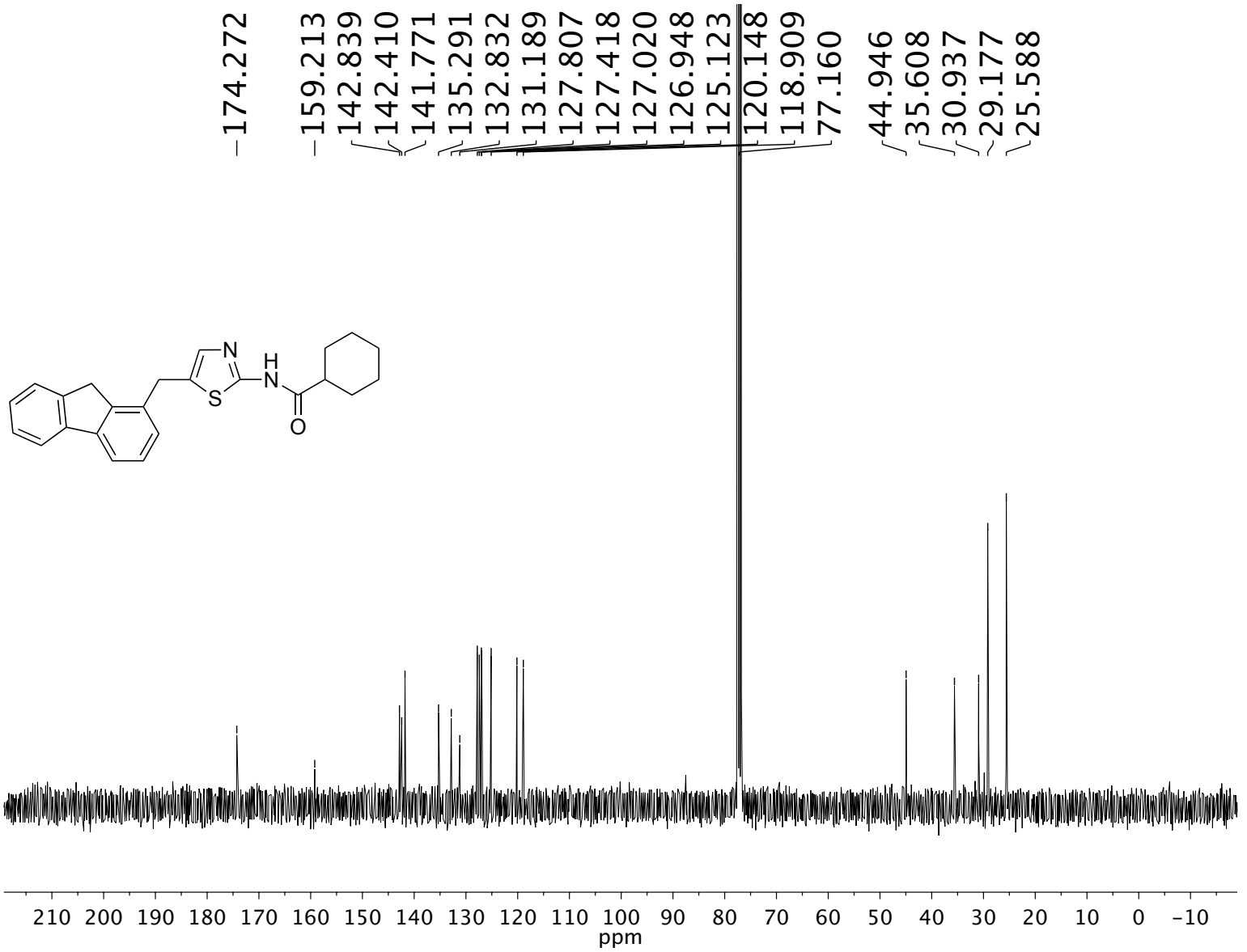

S.6.7.3. *N*-[5-(1-Fluorenylmethyl)thiazol-2-yl]cyclohexanecarboxamide (18). HR-ESI-MS

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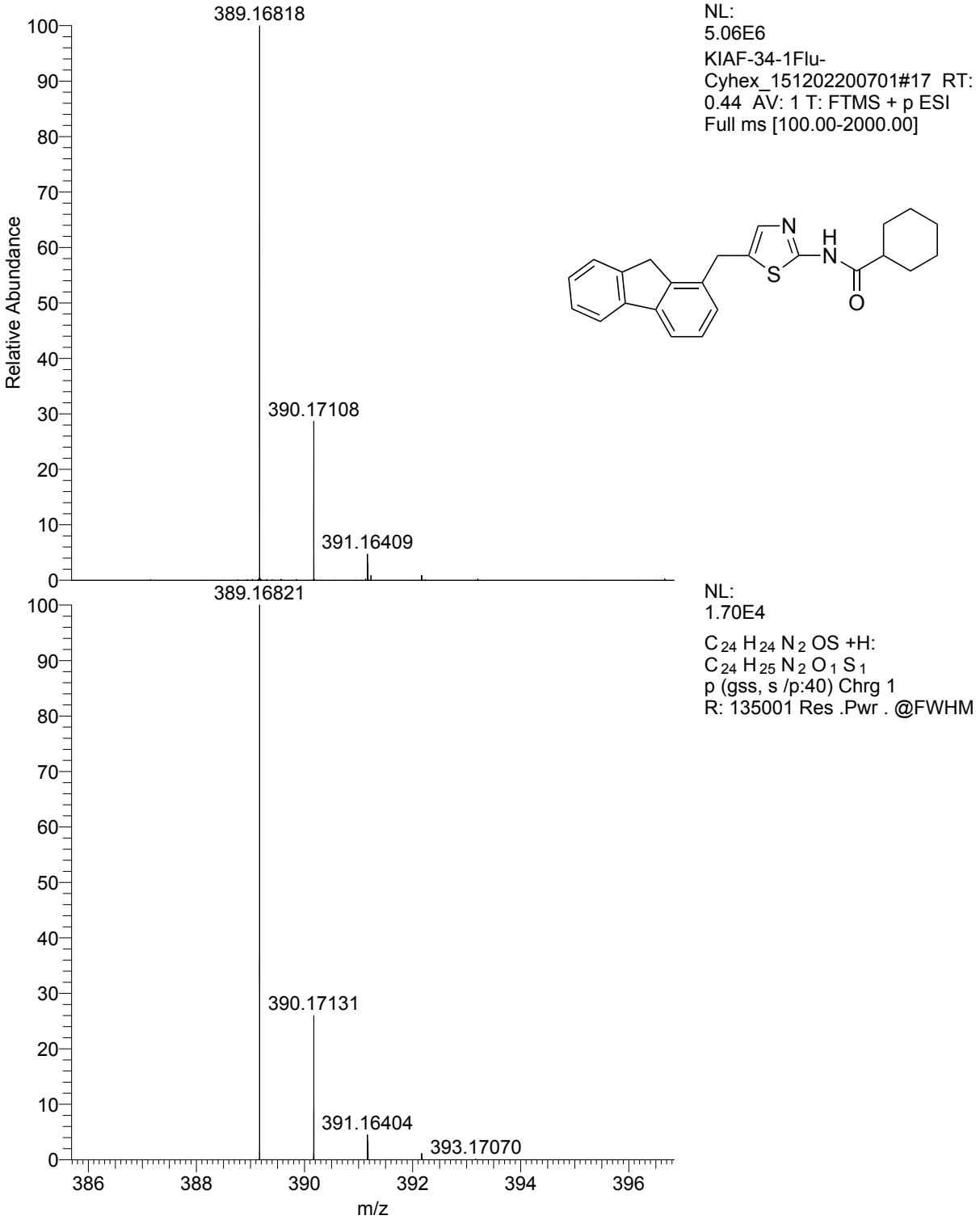
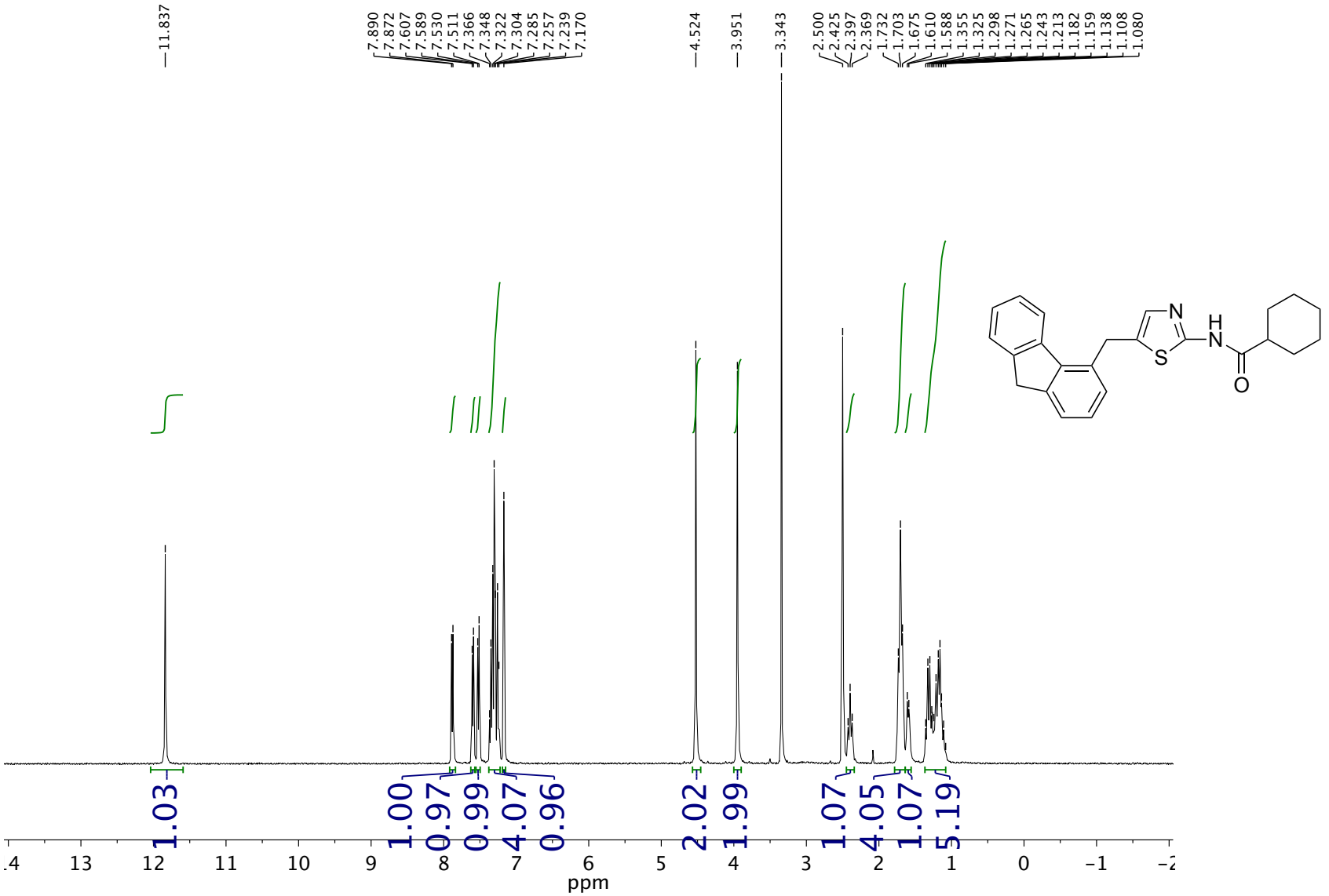


S.6.8.1. *N*-[5-(4-Fluorenylmethyl)thiazol-2-yl]cyclohexanecarboxamide (19). ^{1}H NMR (400 MHz, CD_3SOCD_3)



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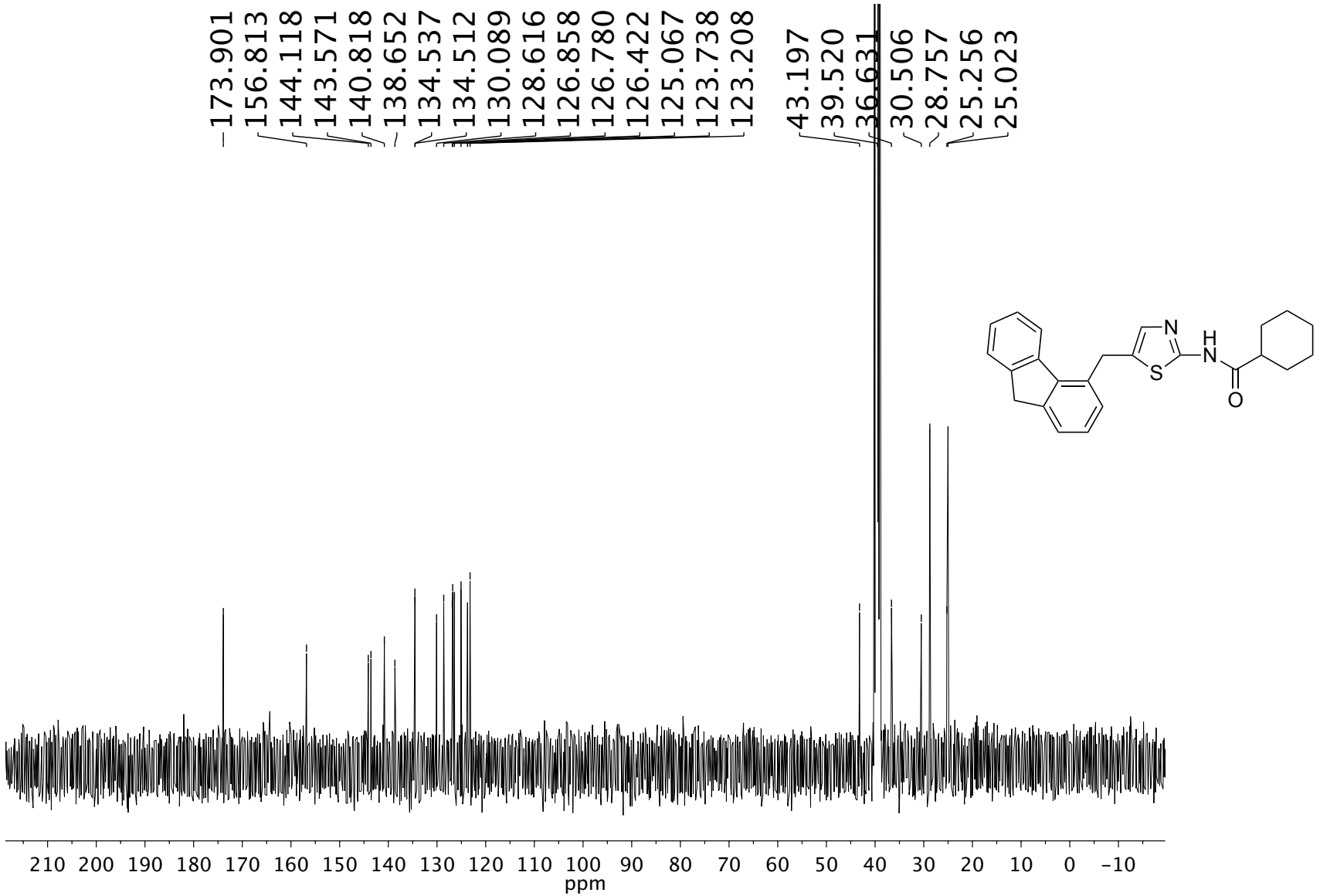

S.6.8.3. *N*-[5-(4-Fluorenylmethyl)thiazol-2-yl]cyclohexanecarboxamide (19). HR-ESI-MS

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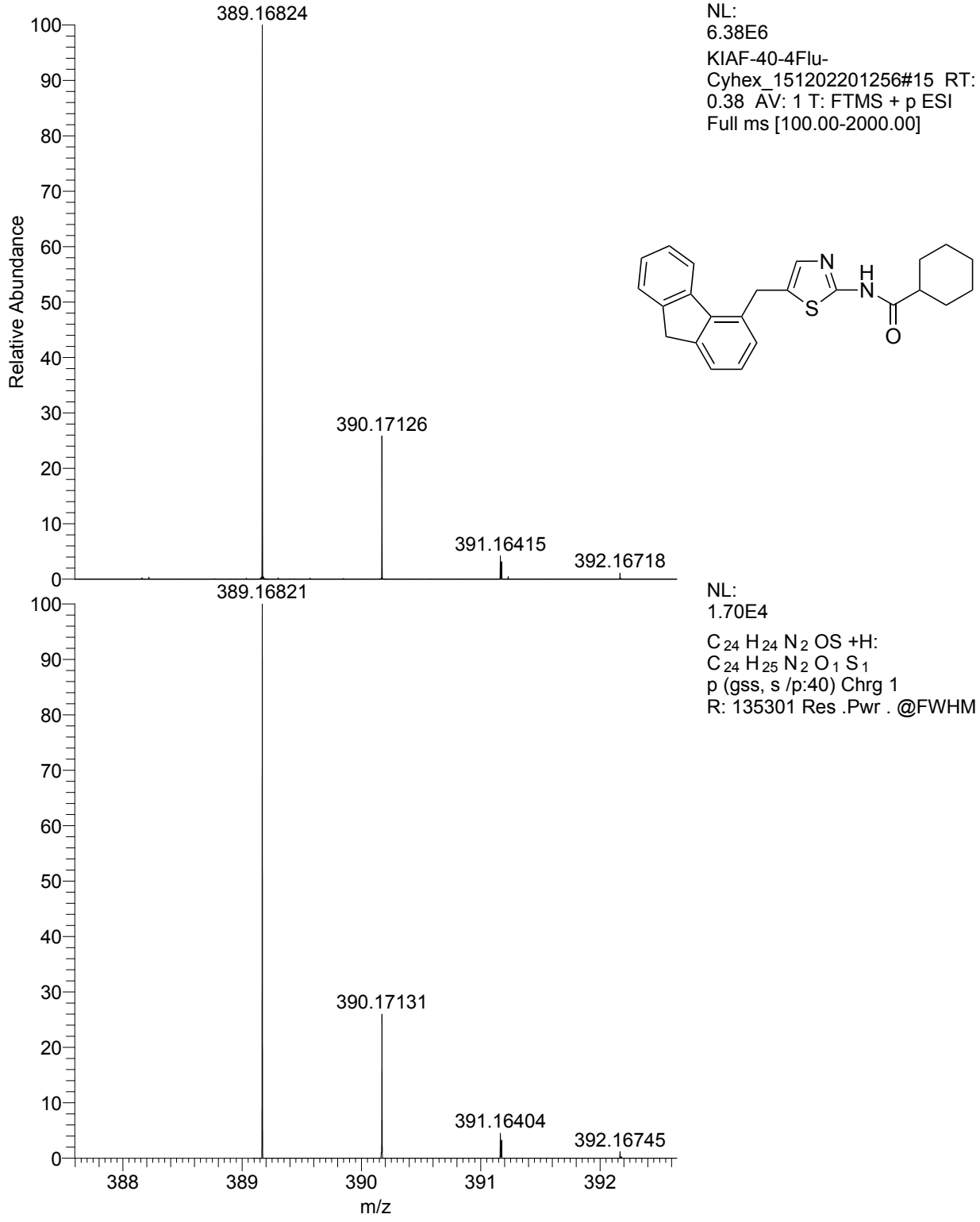
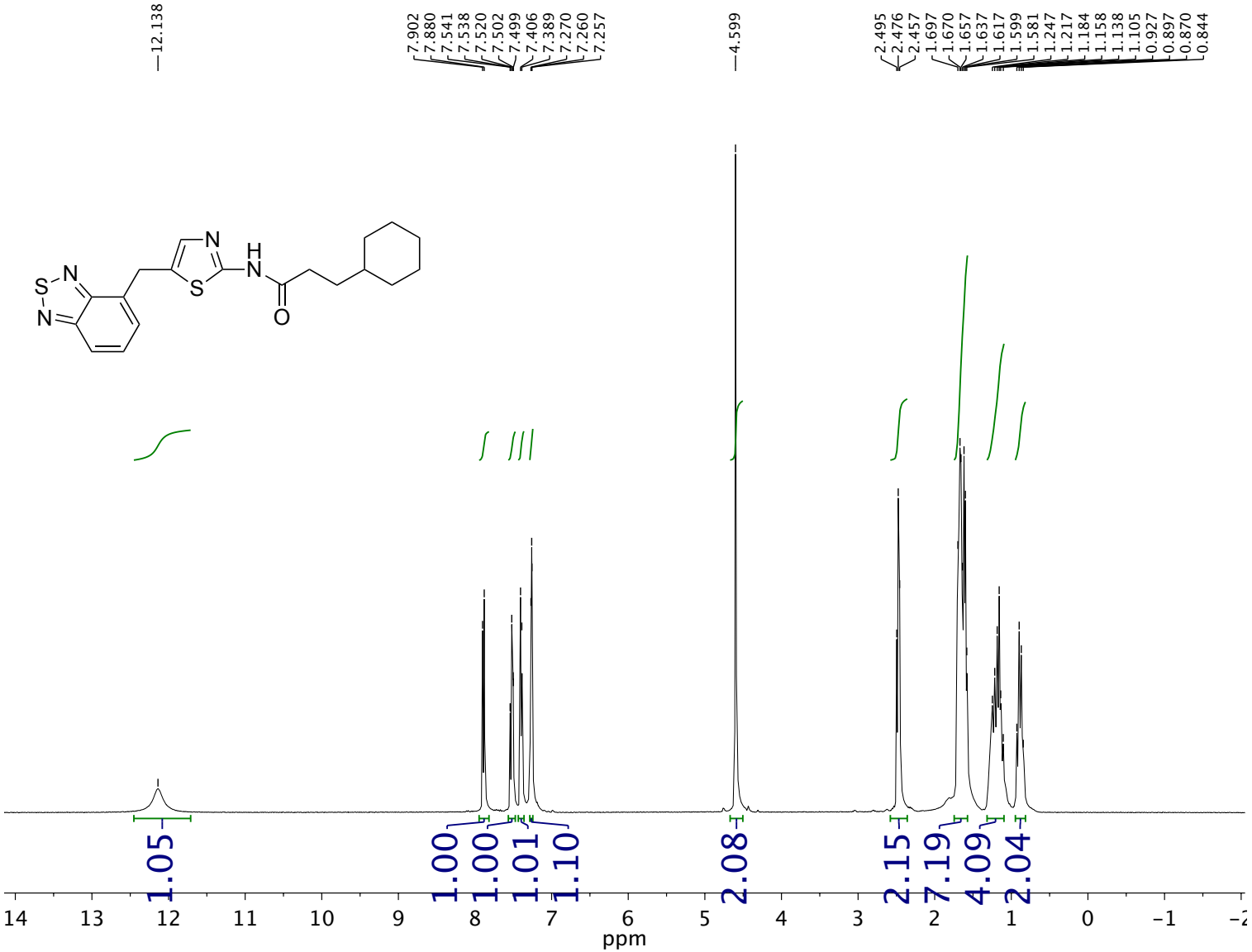
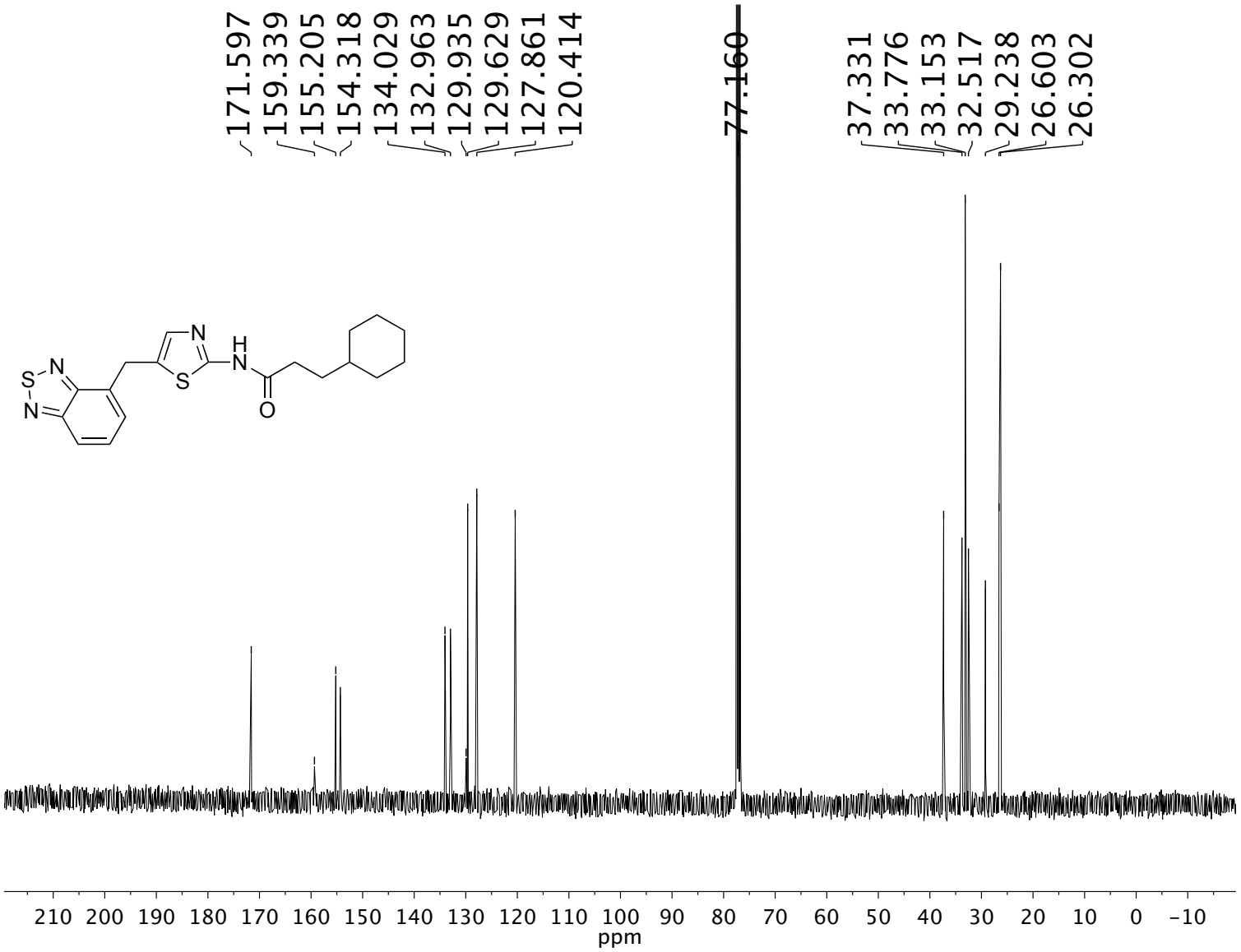


S.6.9.1. *N*-[5-(2,1,3-Benzothiadiazol-4-ylmethyl)thiazol-2-yl]-3-cyclohexanepropanamide (20a). ^{1}H NMR (400 MHz, $CDCl_3$)



S.6.9.2. *N*-[5-(2,1,3-Benzothiadiazol-4-ylmethyl)thiazol-2-yl]-3-cyclohexanepropanamide (20a). ^{13}C NMR (100 MHz, $CDCl_3$)



S.6.9.3. *N*-[5-(2,1,3-Benzothiadiazol-4-ylmethyl)thiazol-2-yl]-3-cyclohexanepropanamide (20a).

HR-ESI-MS

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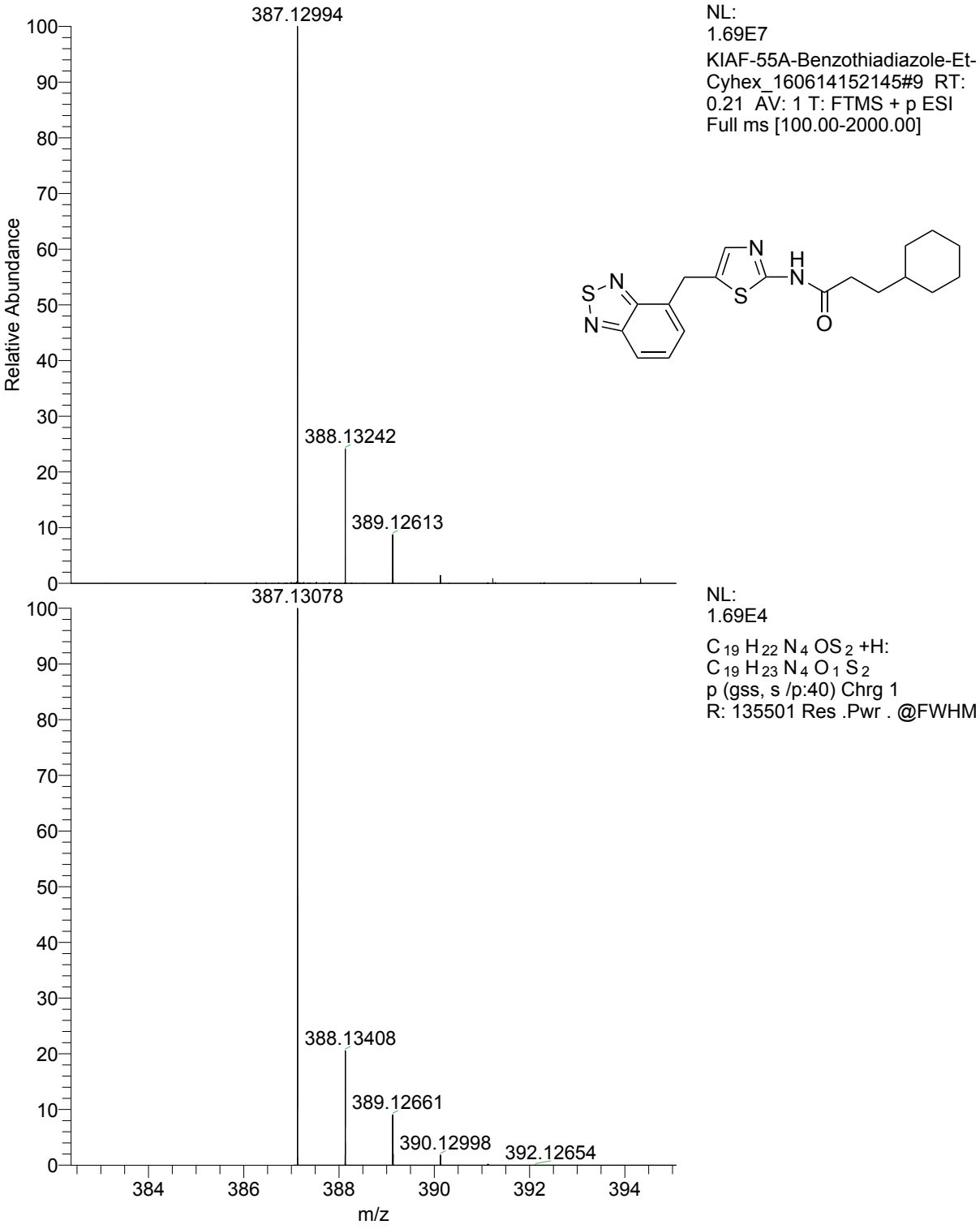
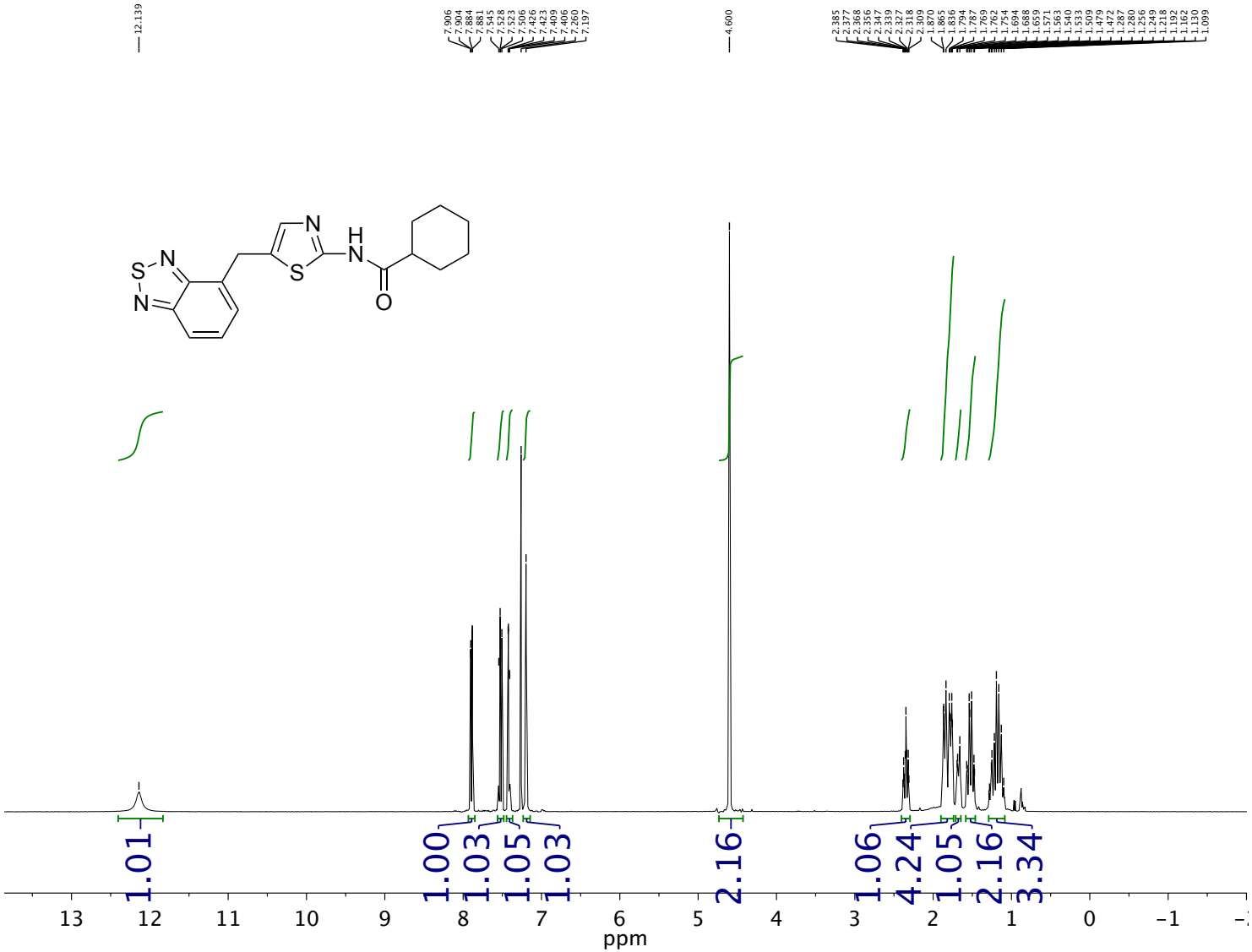
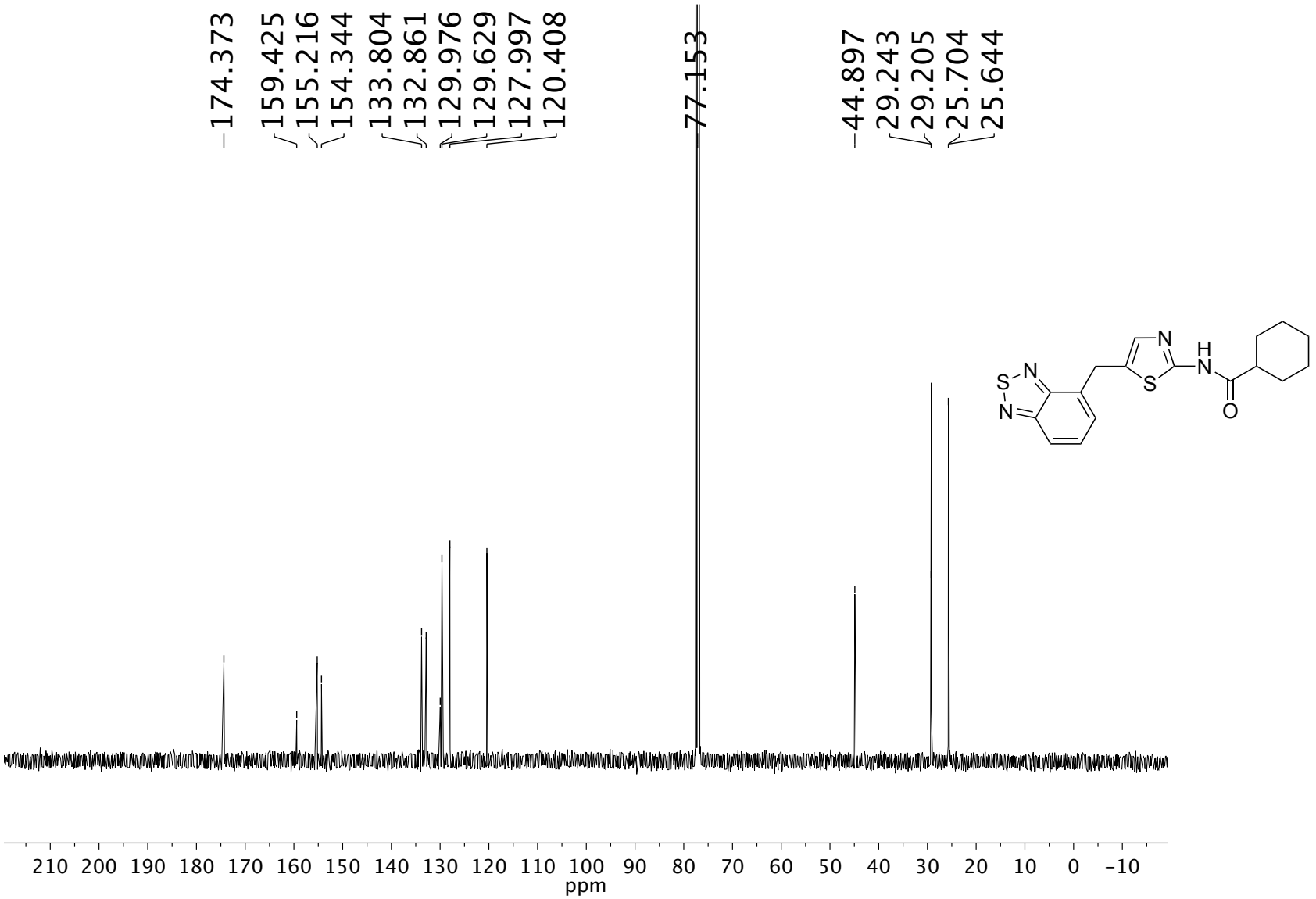


S.6.10.1. *N*-[5-(2,1,3-Benzothiadiazol-4-ylmethyl)thiazol-2-yl]cyclohexanecarboxamide (20b). ^{1}H NMR (400 MHz, $CDCl_3$)



S.6.10.2. *N*-[5-(2,1,3-Benzothiadiazol-4-ylmethyl)thiazol-2-yl]cyclohexanecarboxamide (20b). ^{13}C NMR (100 MHz, $CDCl_3$)



S.6.10.3. *N*-[5-(2,1,3-Benzothiadiazol-4-ylmethyl)thiazol-2-yl]cyclohexanecarboxamide (20b).

HR-ESI-MS

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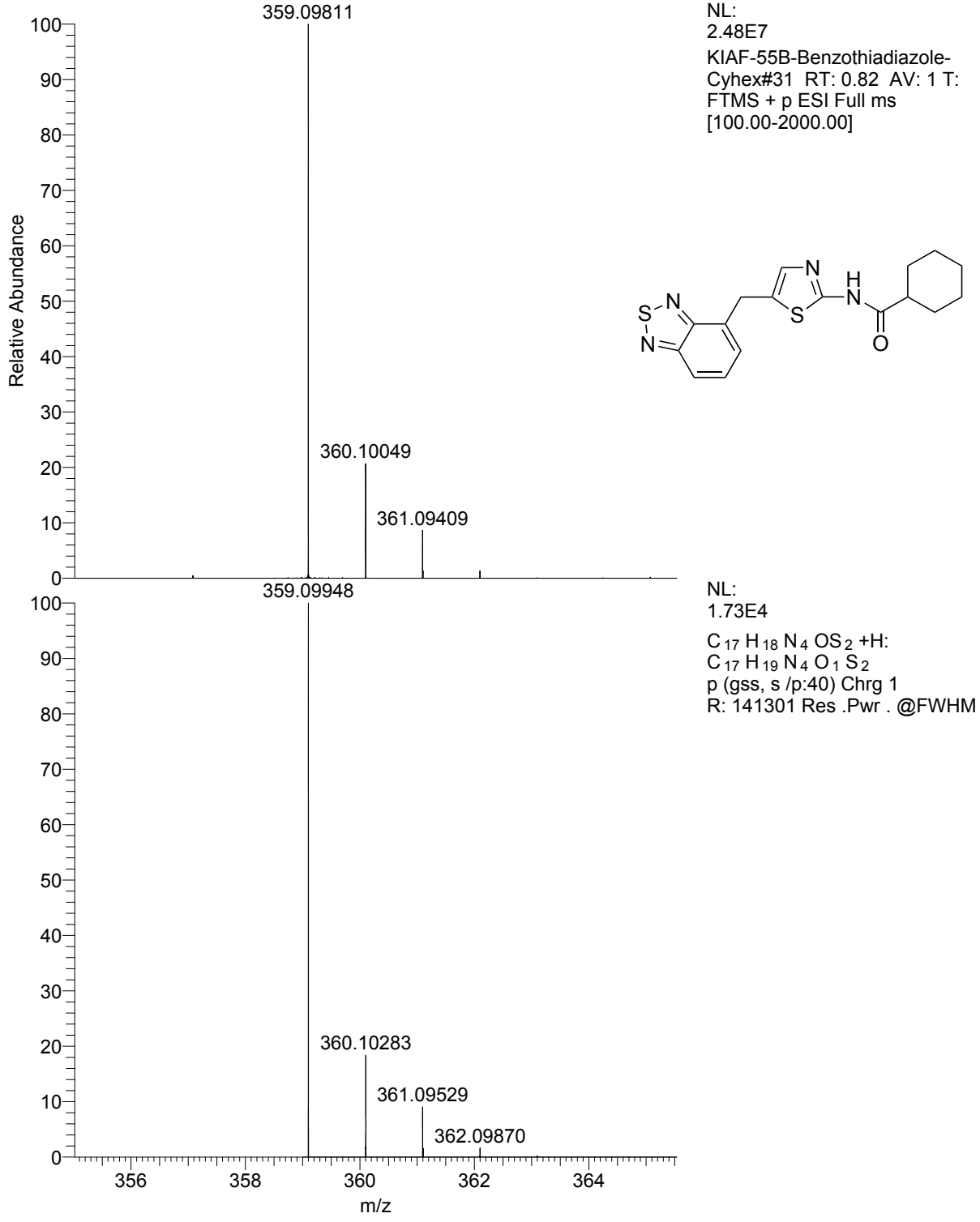
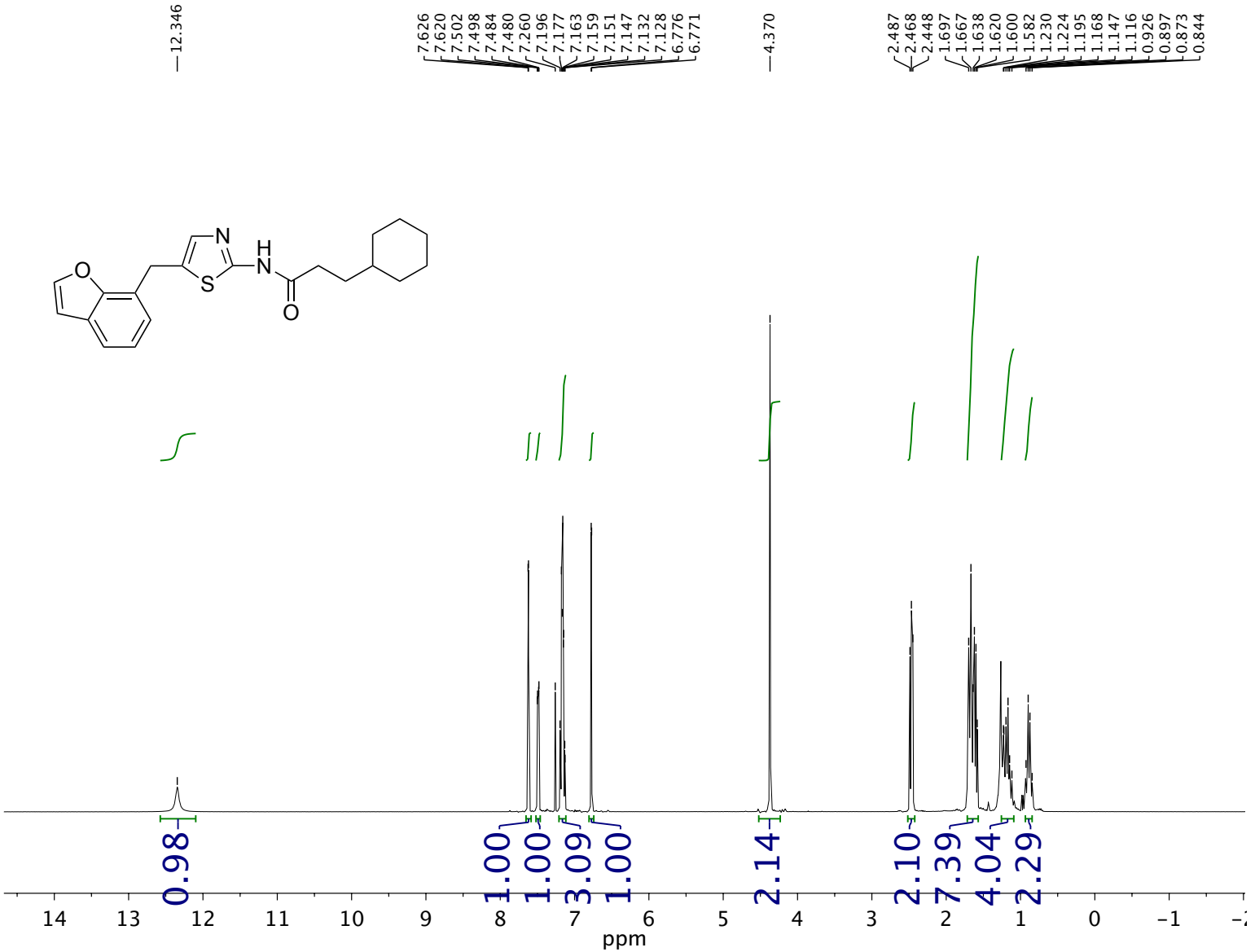
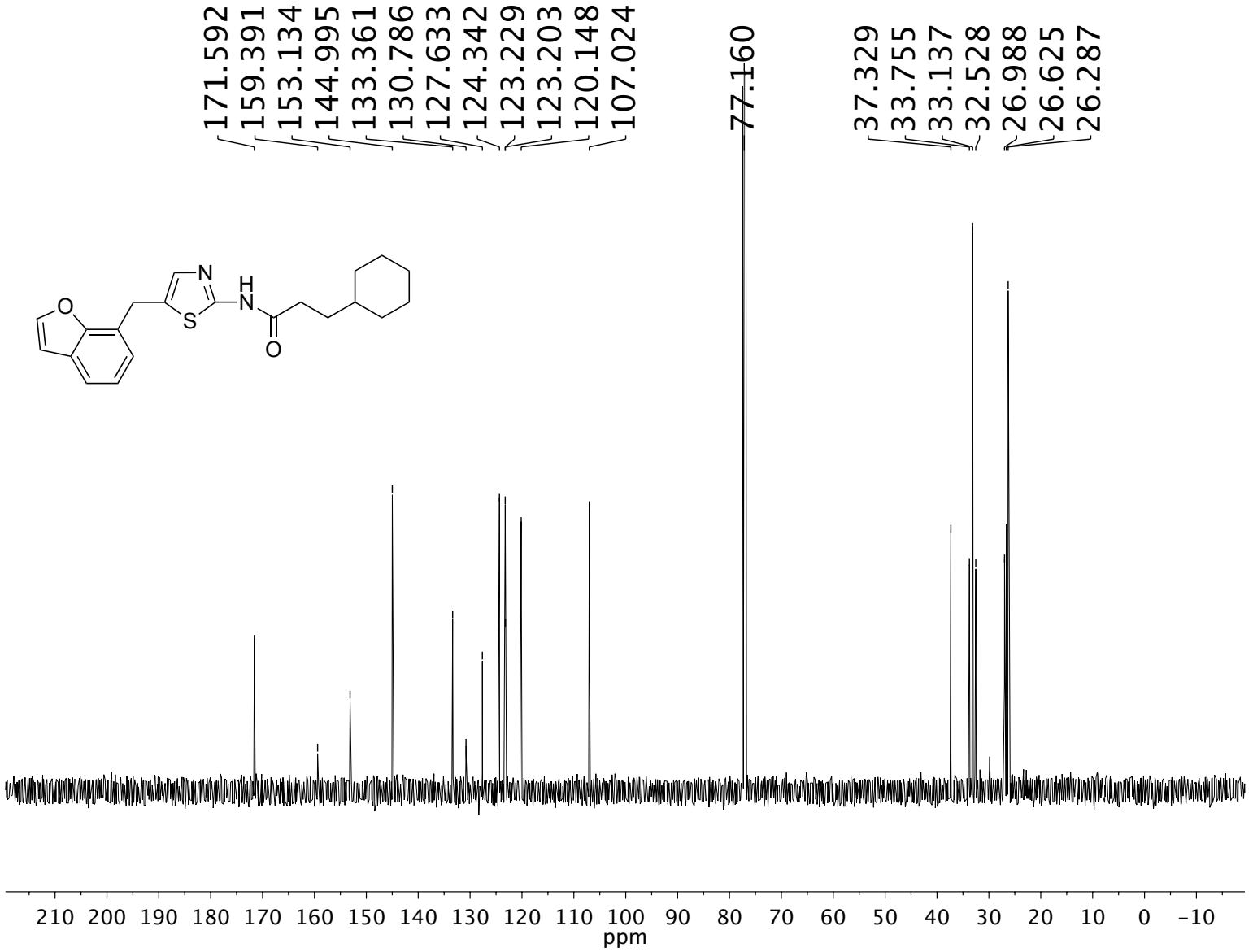


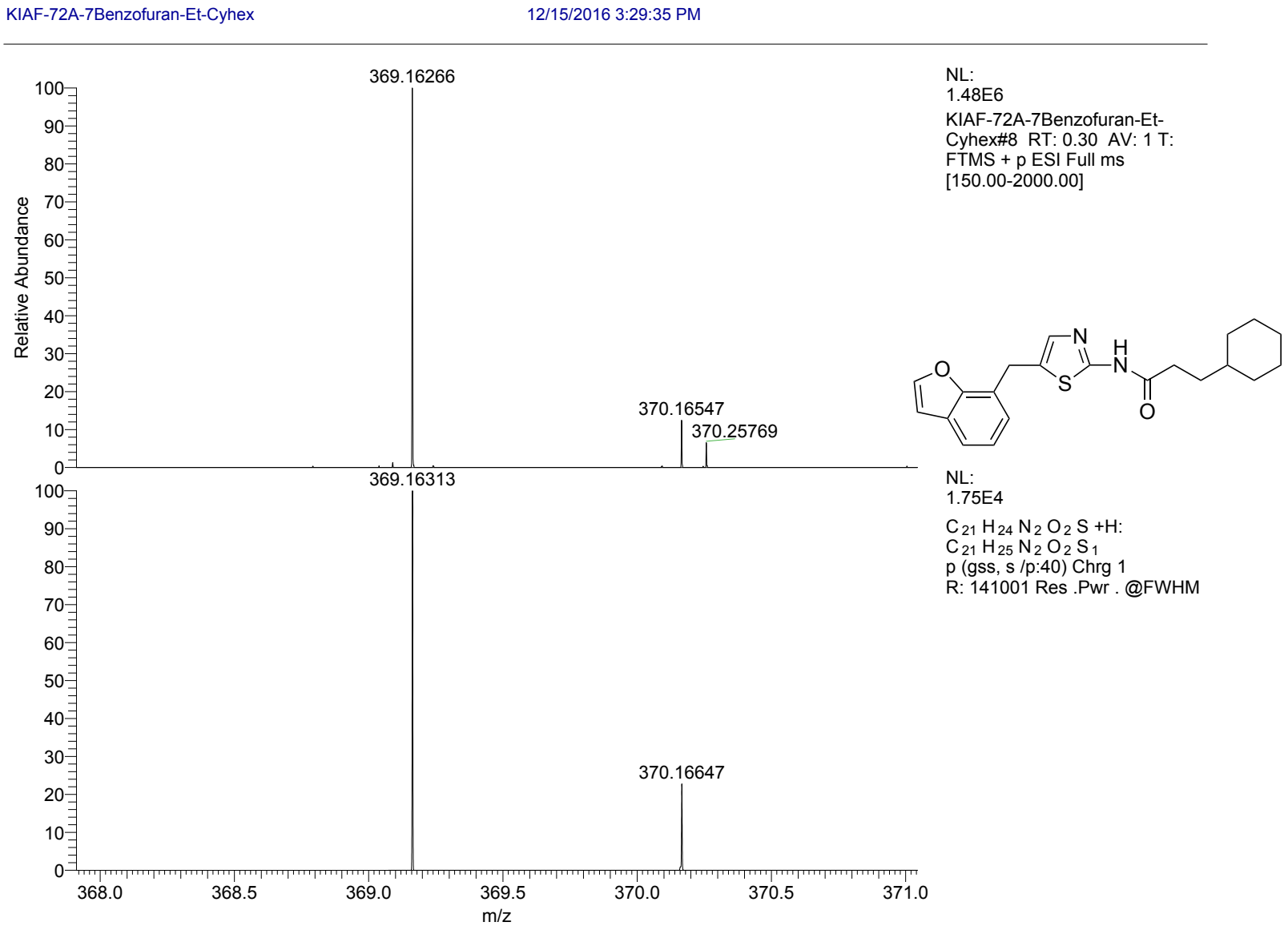
S.6.11.1. *N*-[5-(7-Benzofuranylmethyl)thiazol-2-yl]-3-cyclohexanepropanamide (21a). ^{1}H NMR (400 MHz, $CDCl_3$)



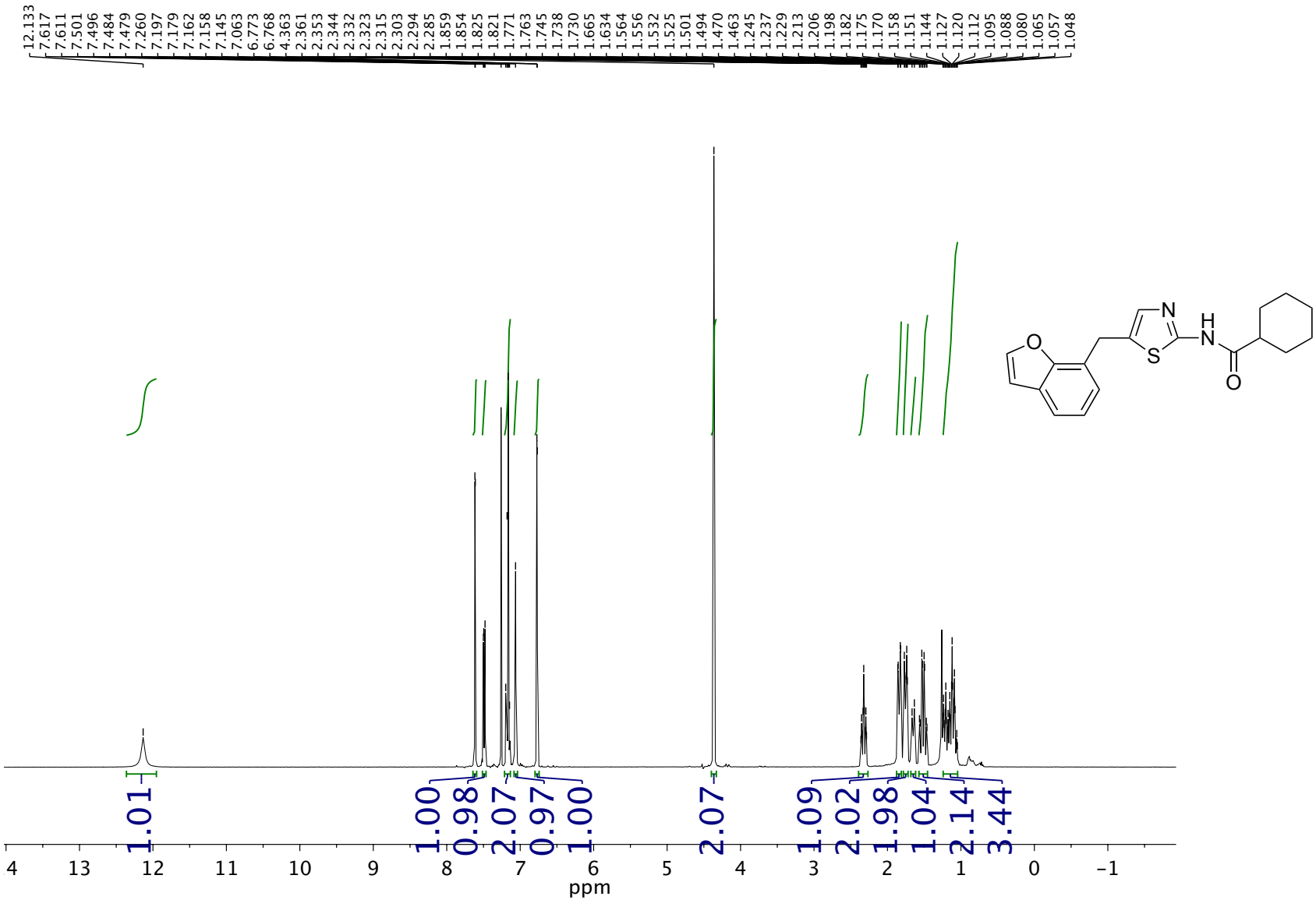
S.6.11.2. *N*-[5-(7-Benzofuranylmethyl)thiazol-2-yl]-3-cyclohexanepropanamide (21a). ^{13}C NMR (100 MHz, $CDCl_3$)



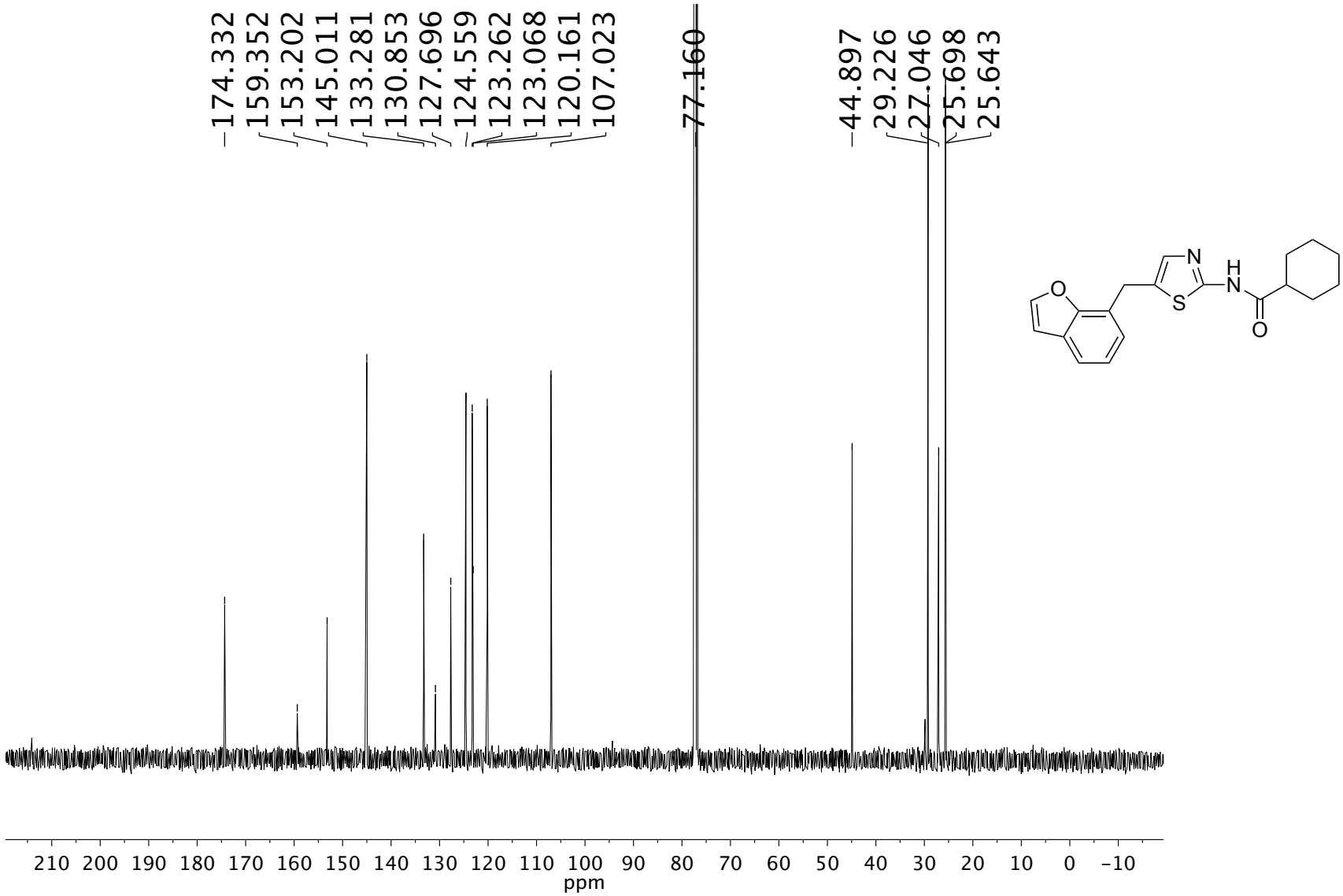
S.6.11.3. *N*-[5-(7-Benzofuranylmethyl)thiazol-2-yl]-3-cyclohexanepropanamide (21a). HR-ESI-MS



S.6.12.1. *N*-[5-(7-Benzofuranylmethyl)thiazol-2-yl]cyclohexanecarboxamide (21b). ^{1}H NMR (400 MHz, $CDCl_3$)

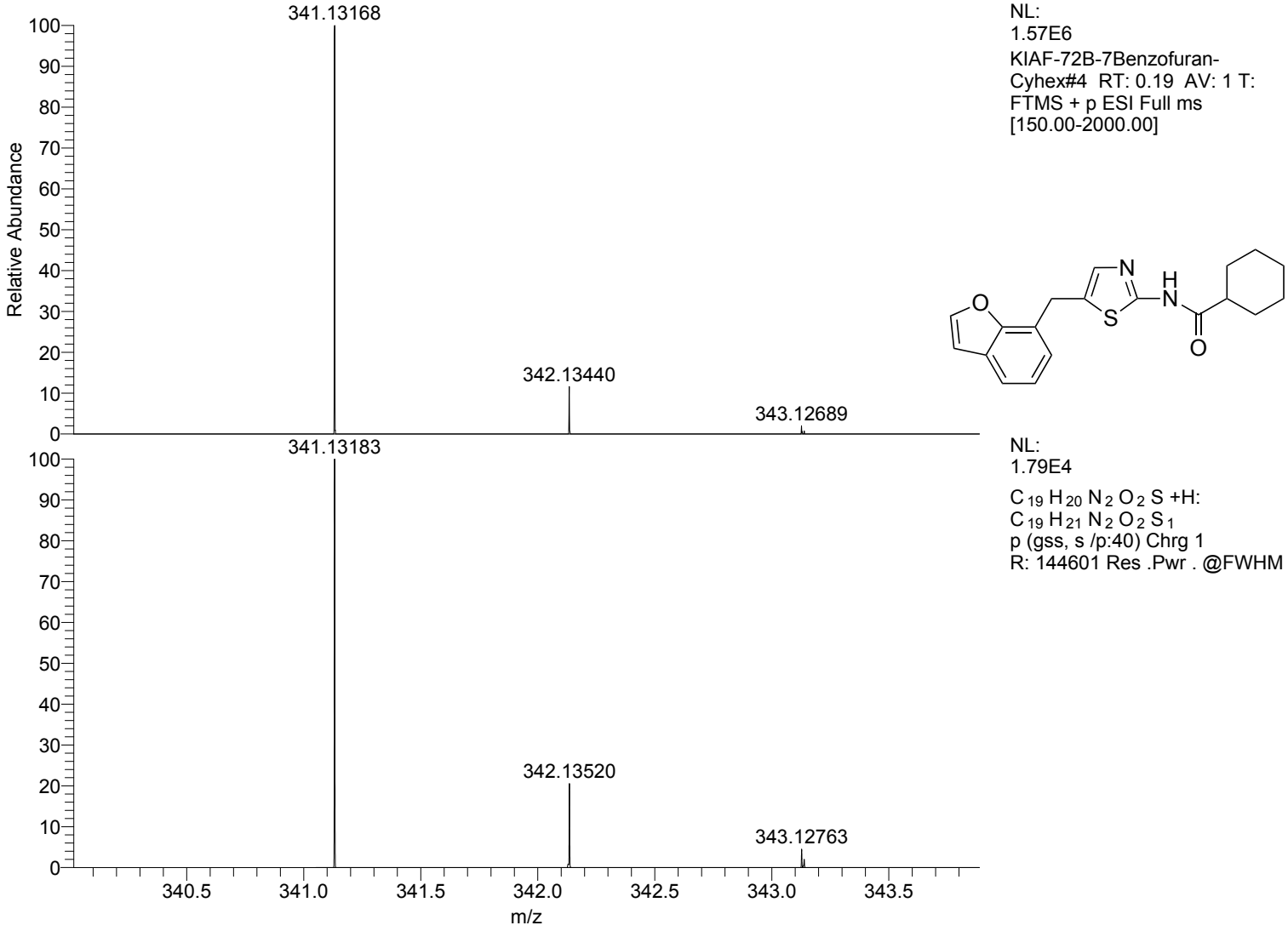


S.6.12.2. *N*-[5-(7-Benzofuranylmethyl)thiazol-2-yl]cyclohexanecarboxamide (21b). ^{13}C NMR (100 MHz, $CDCl_3$)

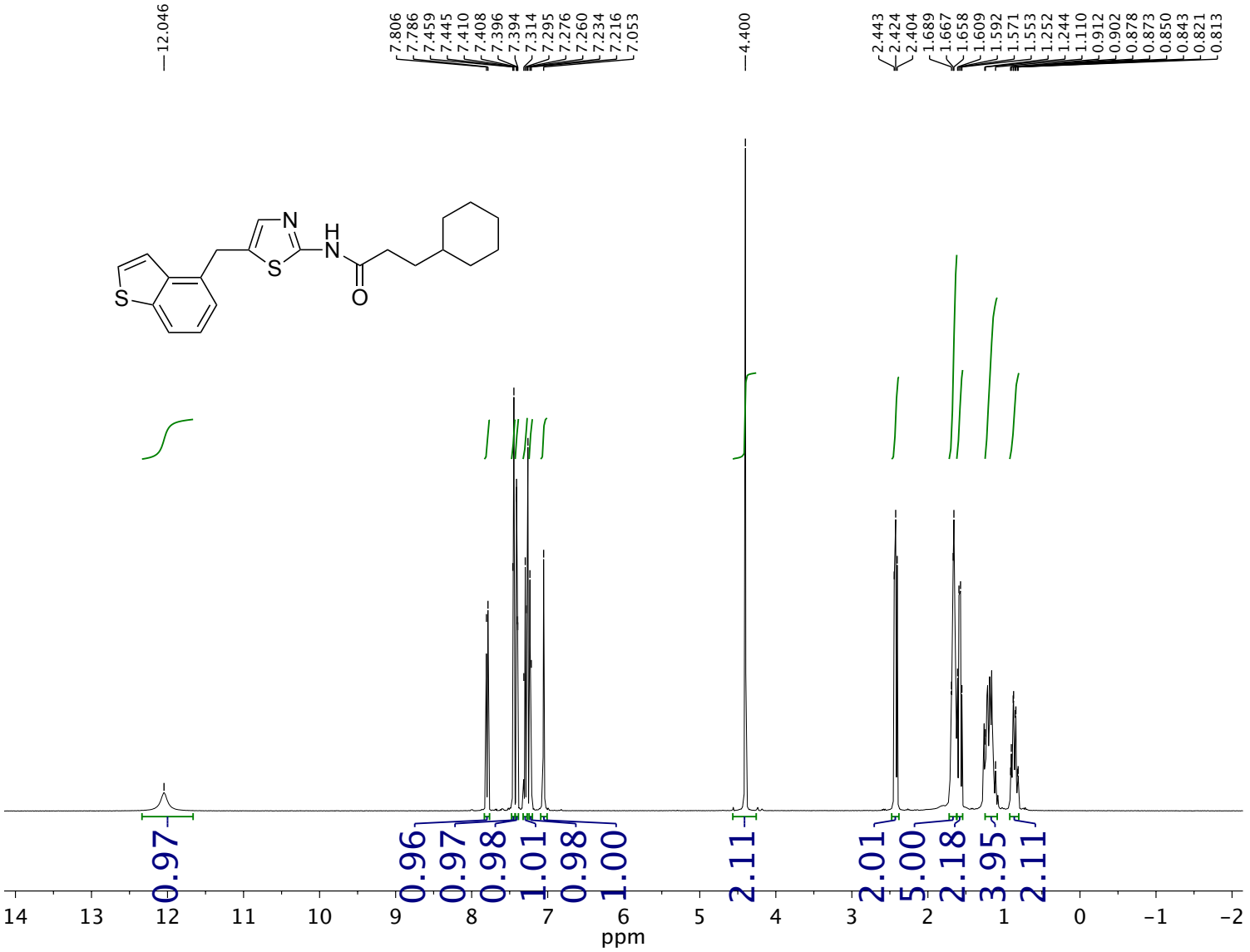


S.6.12.3. *N*-[5-(7-Benzofuranylmethyl)thiazol-2-yl]cyclohexanecarboxamide (21b). HR-ESI-MS

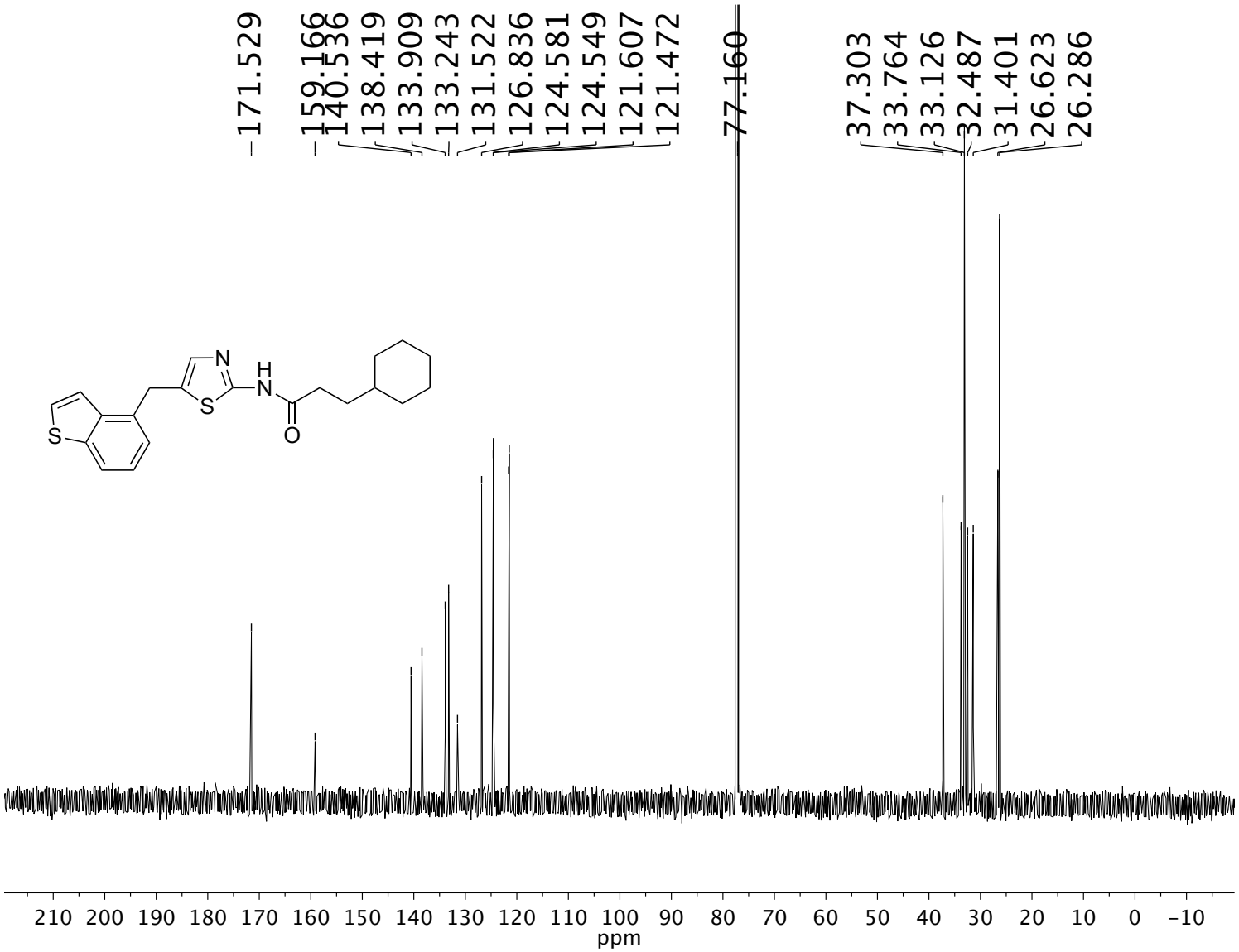
KIAF-72B-7Benzofuran-Cyhex 12/15/2016 3:33:09 PM



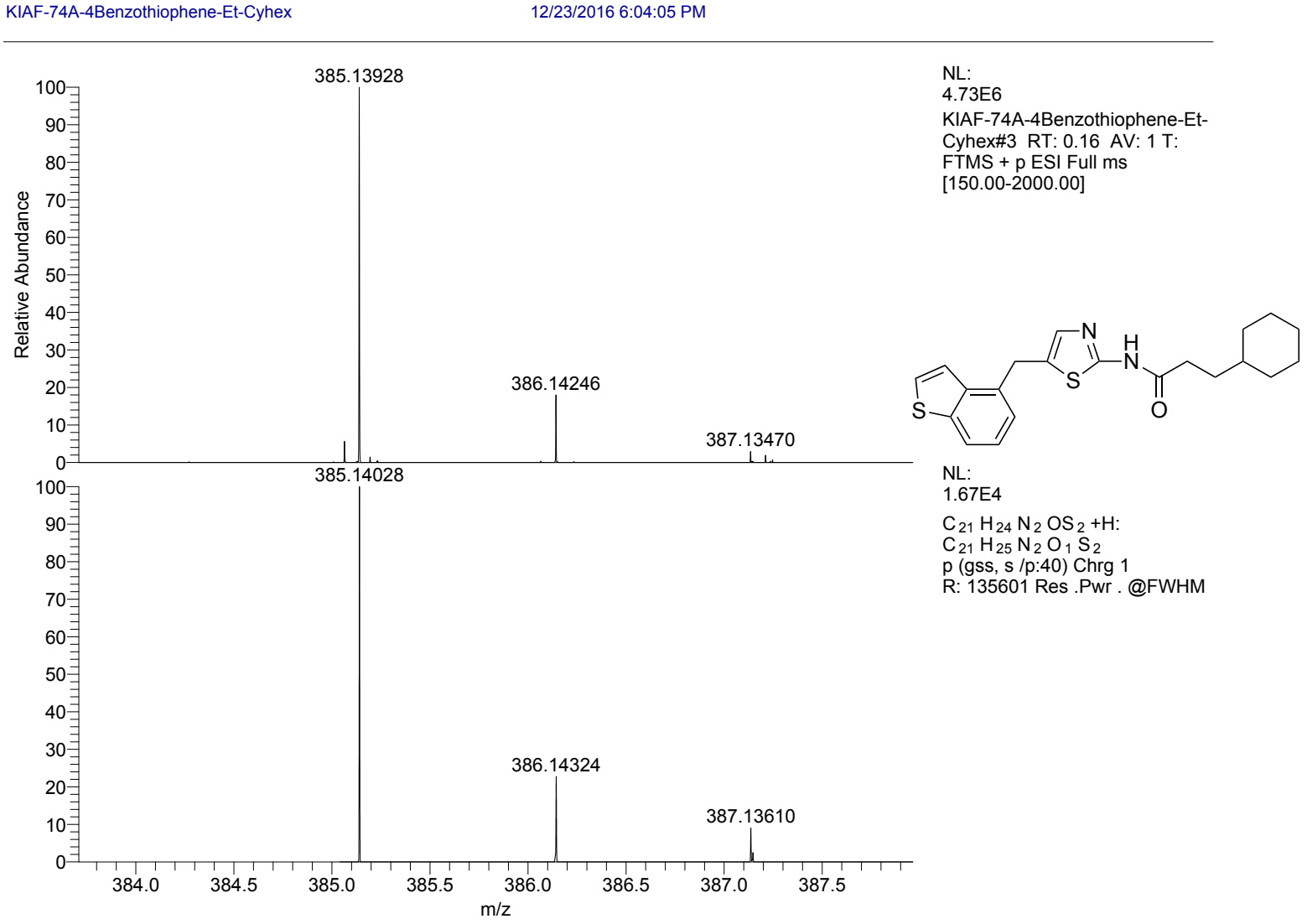
S.6.13.1. *N*-[5-(4-Benzothiophenylmethyl)thiazol-2-yl]-3-cyclohexanepropanamide (22a). ^{1}H NMR (400 MHz, $CDCl_3$)



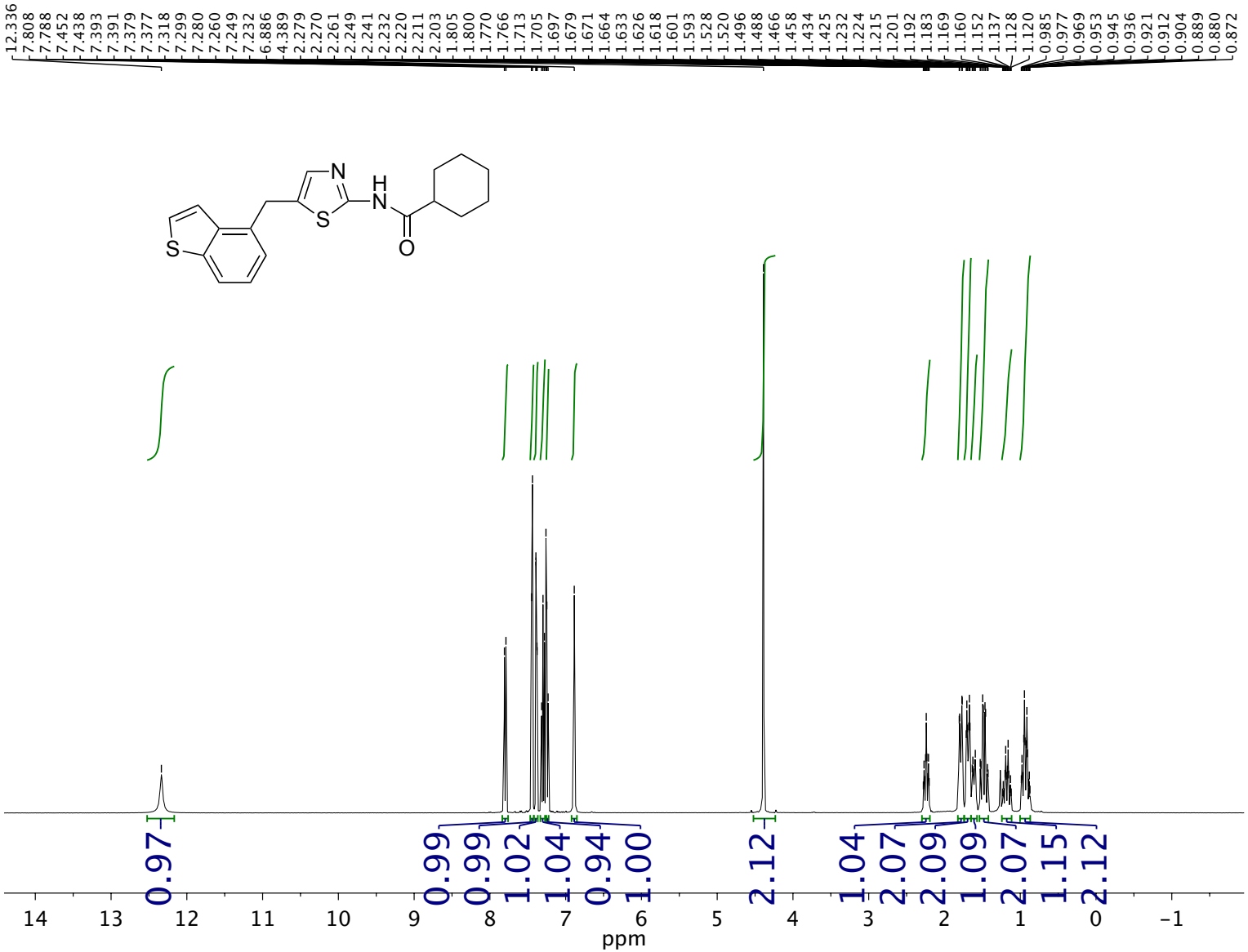
S.6.13.2. *N*-[5-(4-Benzothiophenylmethyl)thiazol-2-yl]-3-cyclohexanepropanamide (22a). ^{13}C NMR (100 MHz, $CDCl_3$)



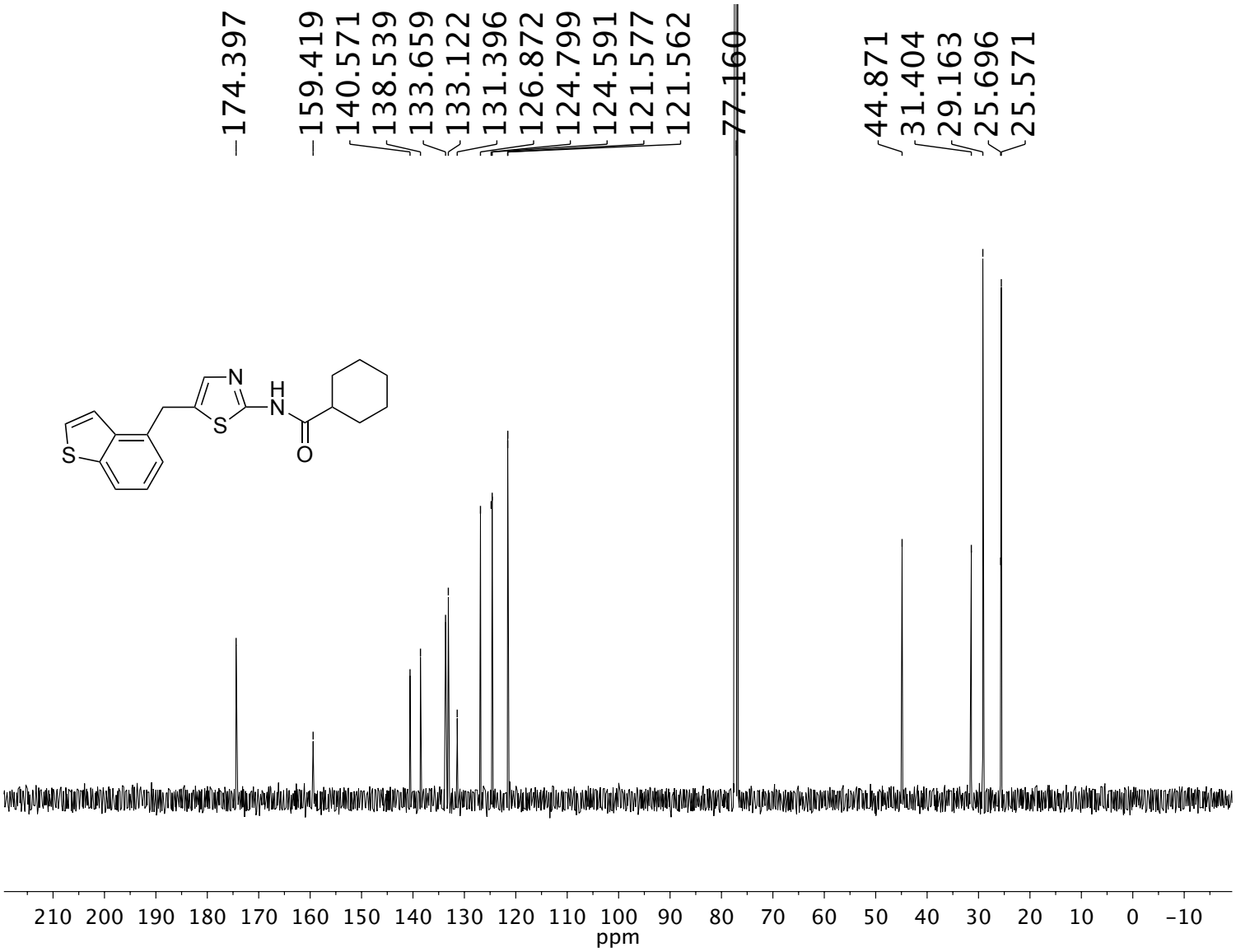
S.6.13.3. *N*-[5-(4-Benzothiophenylmethyl)thiazol-2-yl]-3-cyclohexanepropanamide (22a). HR-ESI-MS



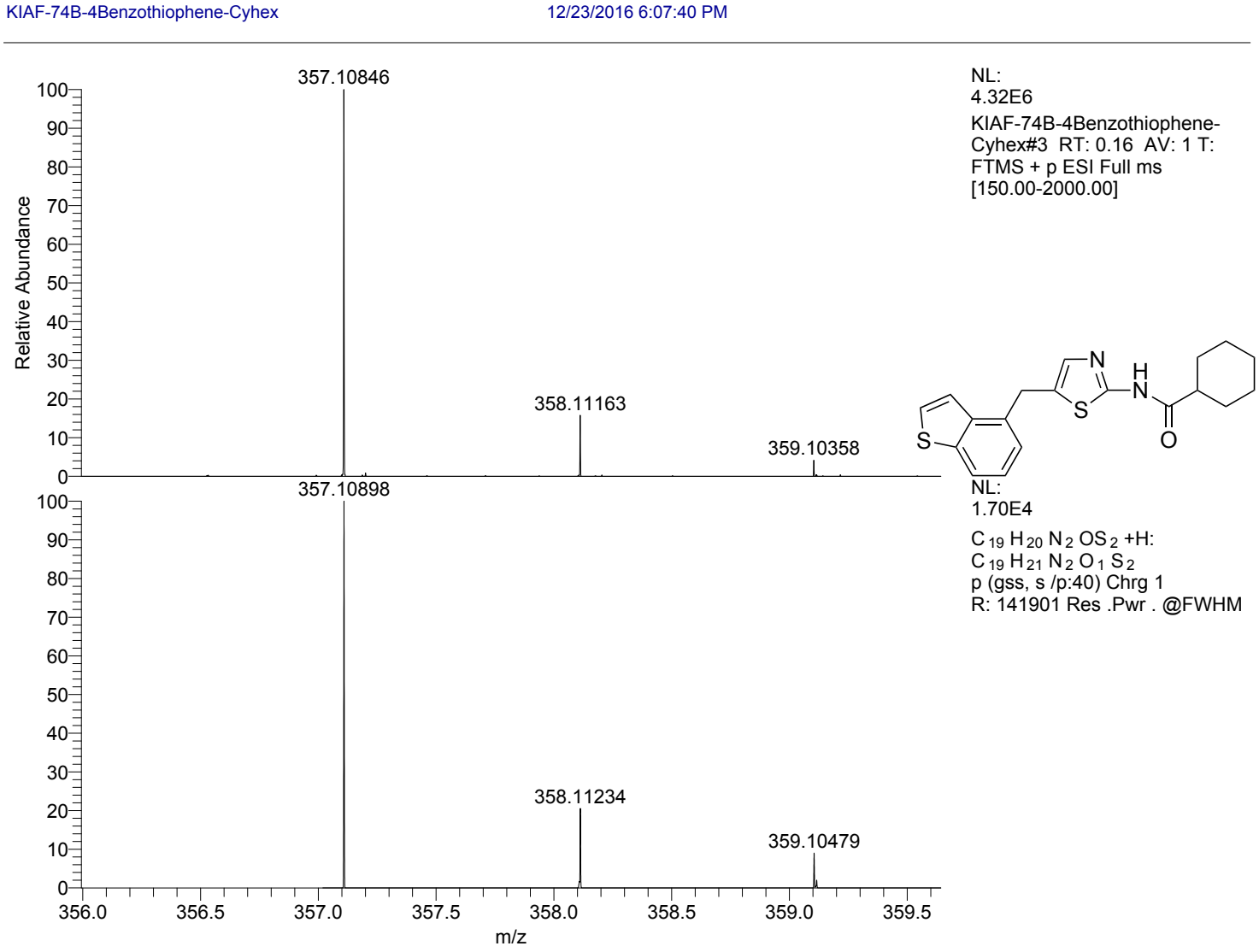
S.6.14.1. *N*-[5-(4-Benzothiophenylmethyl)thiazol-2-yl]cyclohexanecarboxamide (22b). ^{1}H NMR (400 MHz, $CDCl_3$)



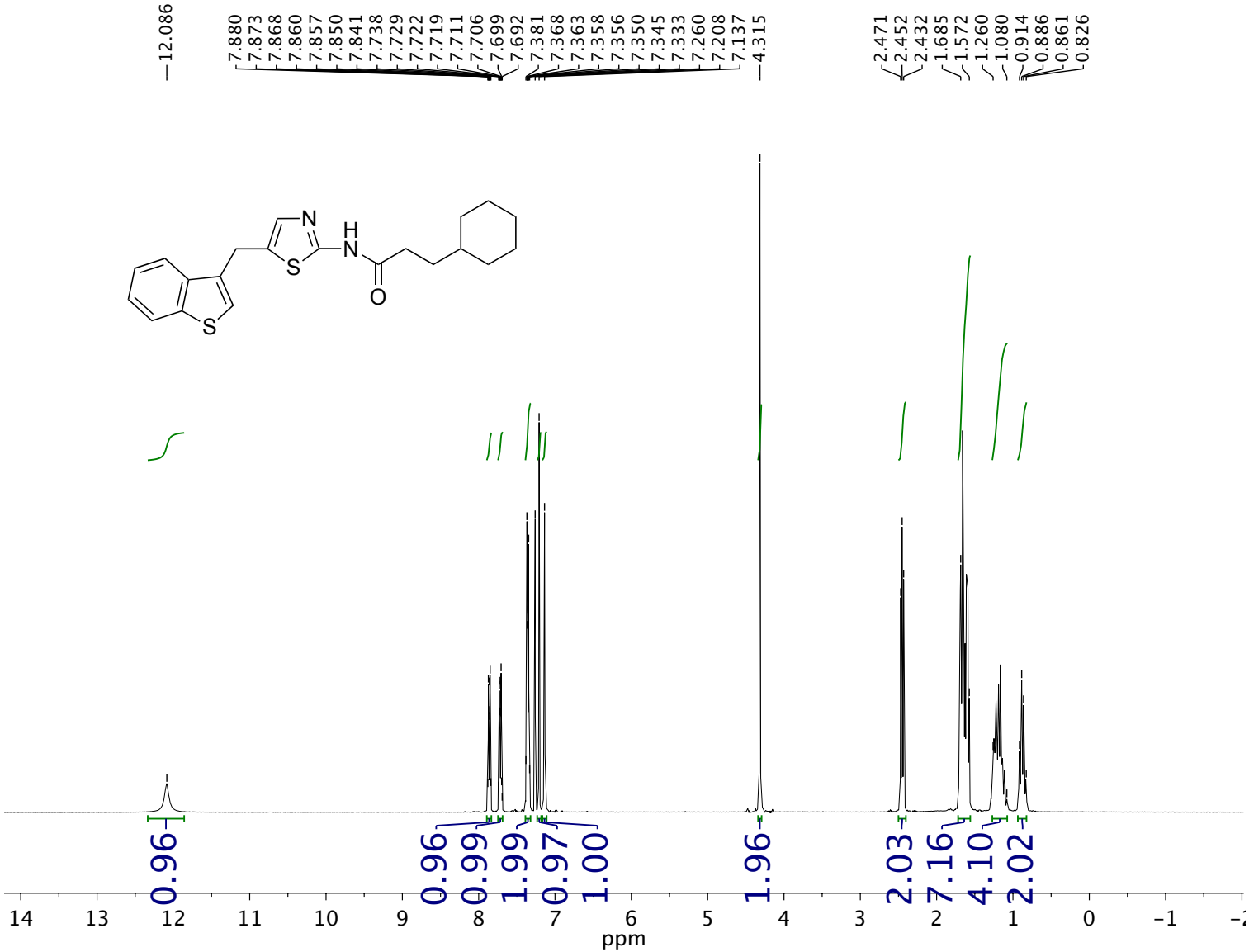
S.6.14.2. *N*-[5-(4-Benzothiophenylmethyl)thiazol-2-yl]cyclohexanecarboxamide (22b). ^{13}C NMR (100 MHz, $CDCl_3$)



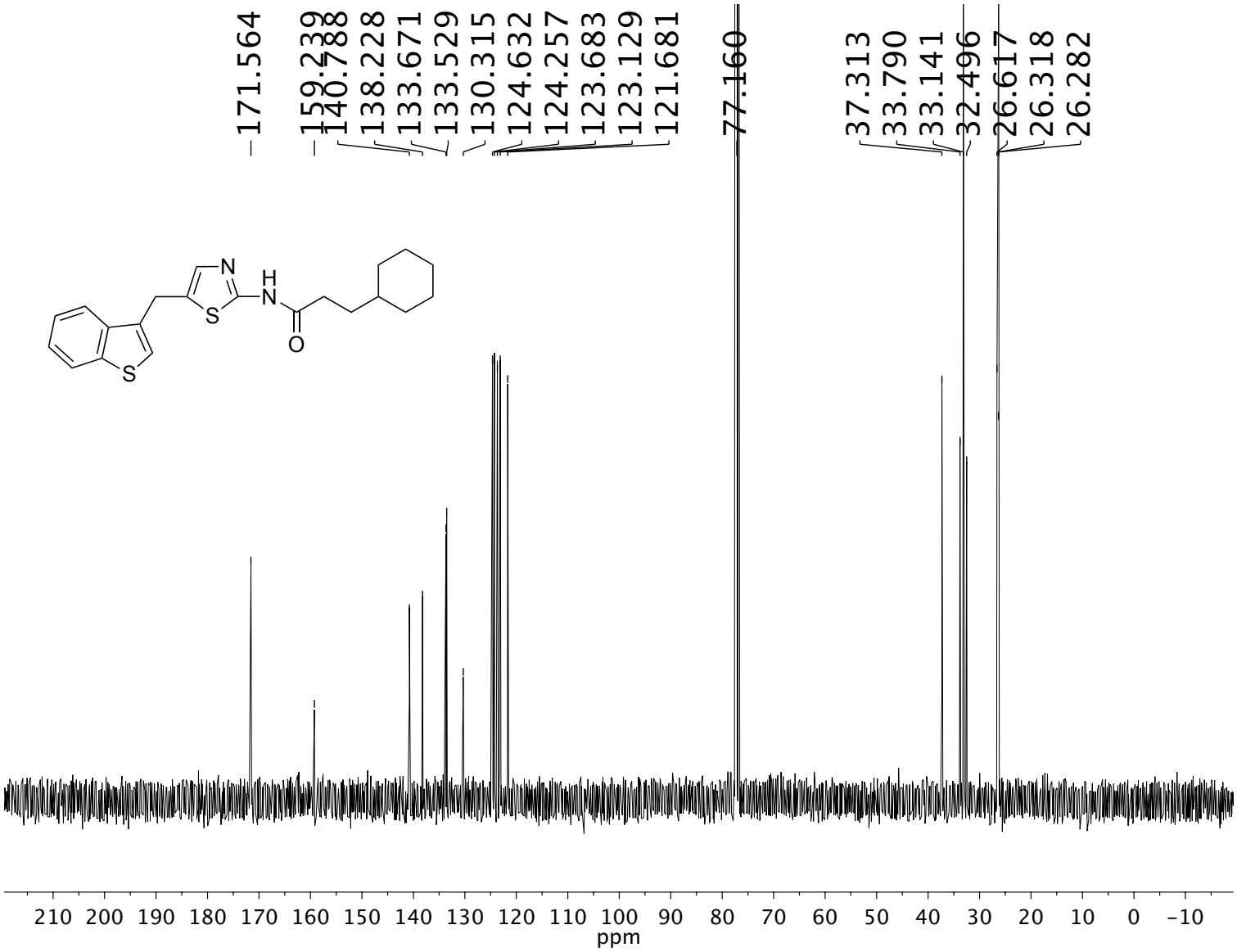
S.6.14.3. *N*-[5-(4-Benzothiophenylmethyl)thiazol-2-yl]cyclohexanecarboxamide (22b). HR-ESI-MS



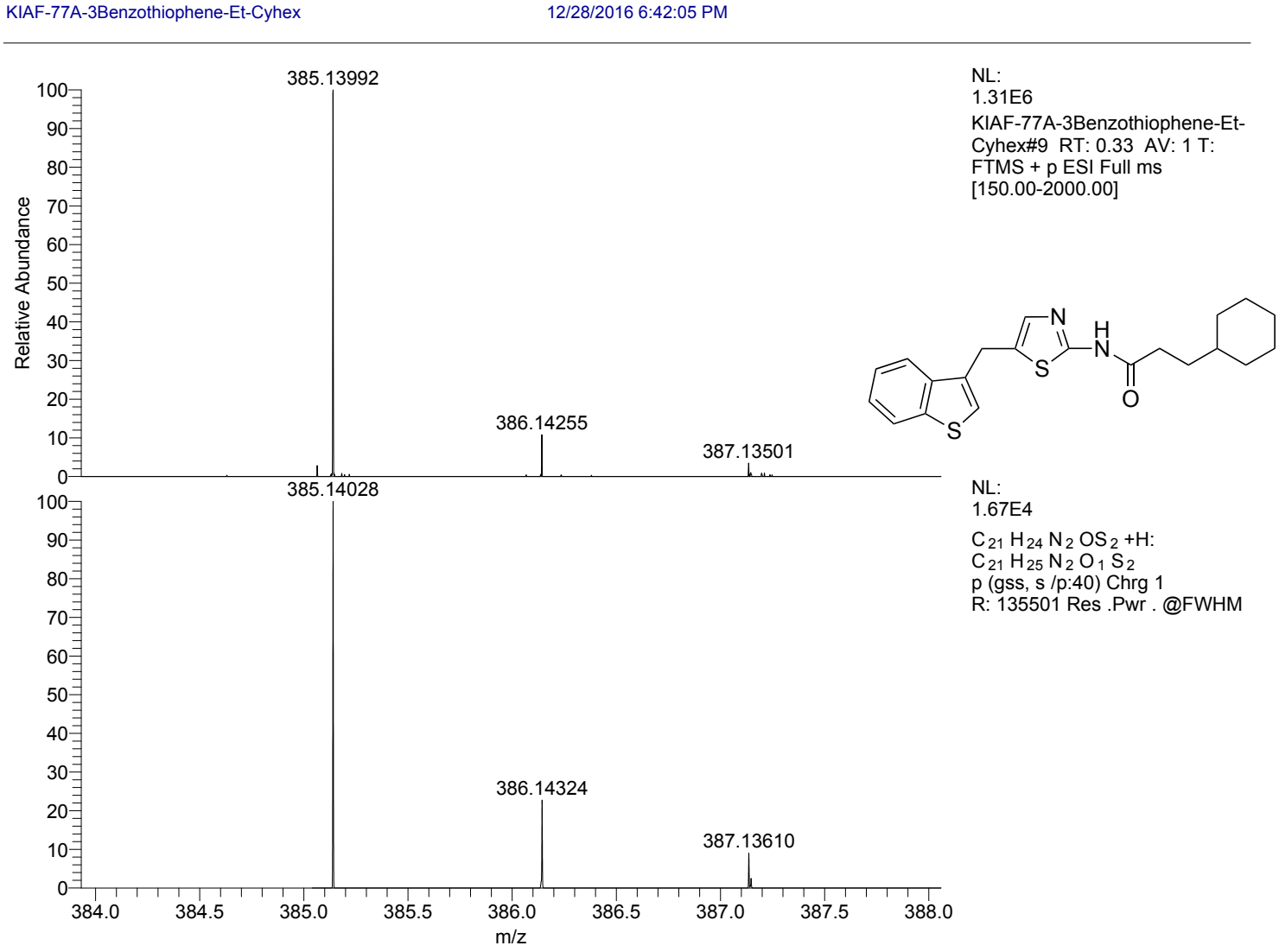
S.6.15.1. *N*-[5-(3-Benzothiophenylmethyl)thiazol-2-yl]-3-cyclohexanepropanamide (23a). ^{1}H NMR (400 MHz, $CDCl_3$)



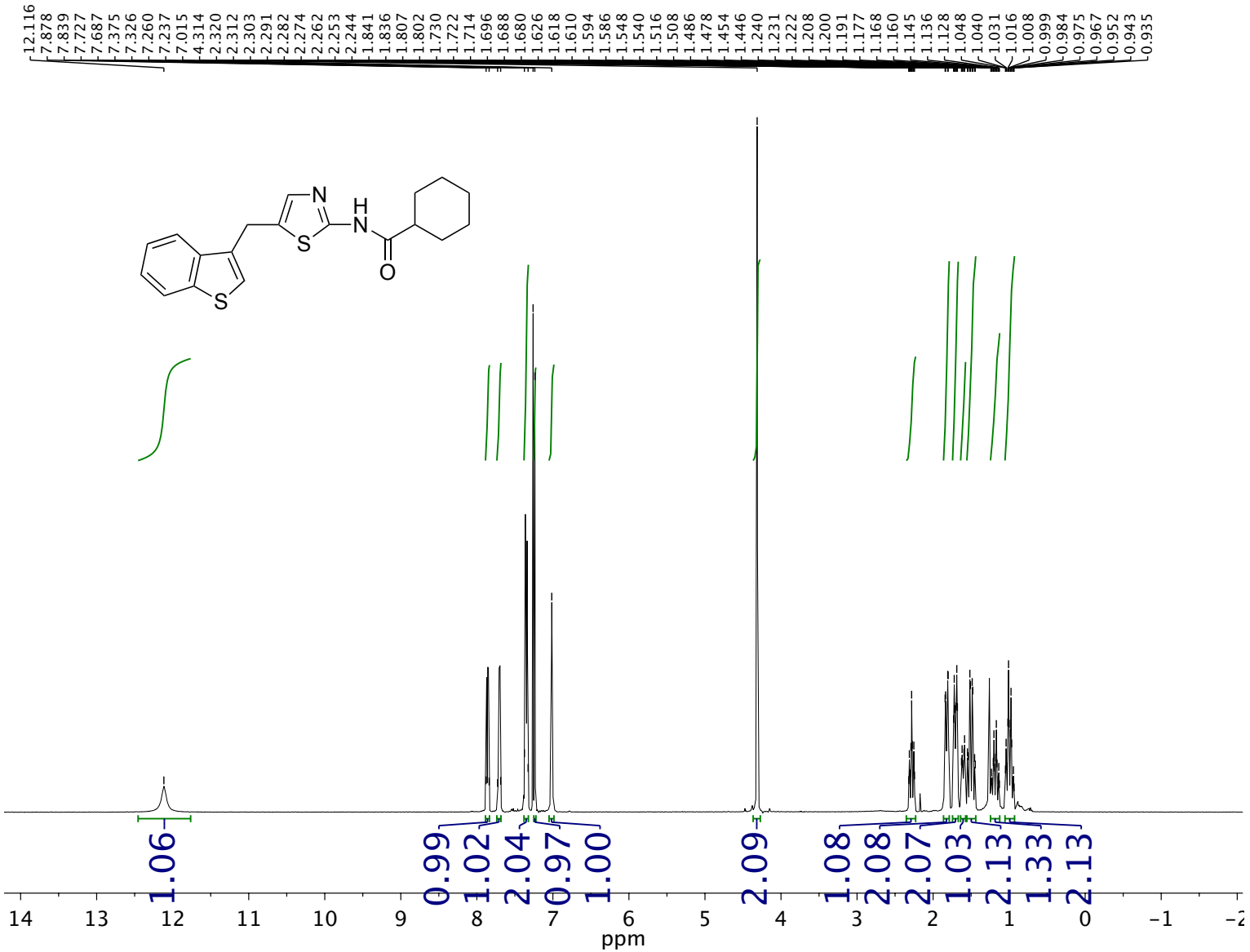
S.6.15.2. *N*-[5-(3-Benzothiophenylmethyl)thiazol-2-yl]-3-cyclohexanepropanamide (23a). ^{13}C NMR (100 MHz, $CDCl_3$)



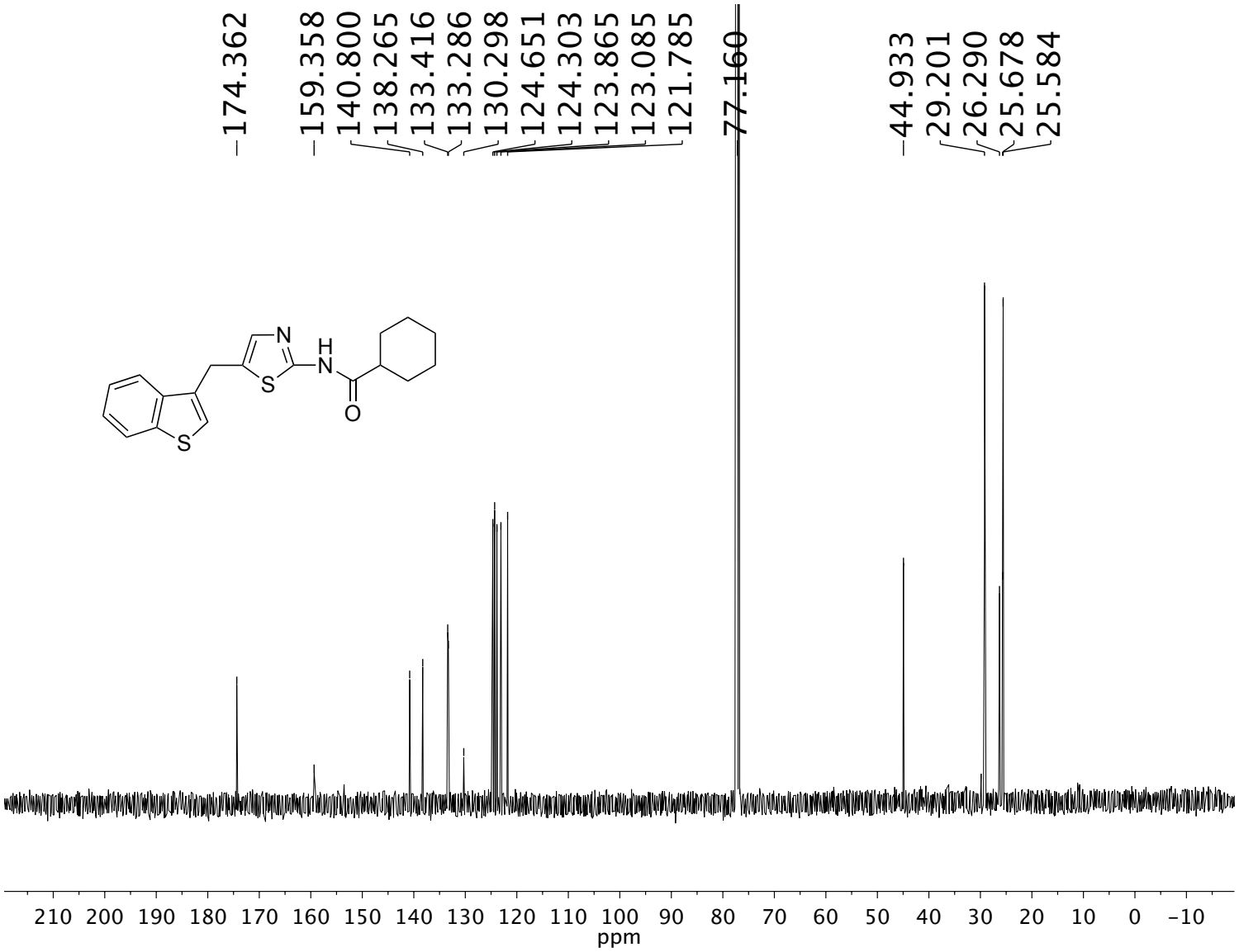
S.6.15.3. *N*-[5-(3-Benzothiophenylmethyl)thiazol-2-yl]-3-cyclohexanepropanamide (23a). HR-ESI-MS



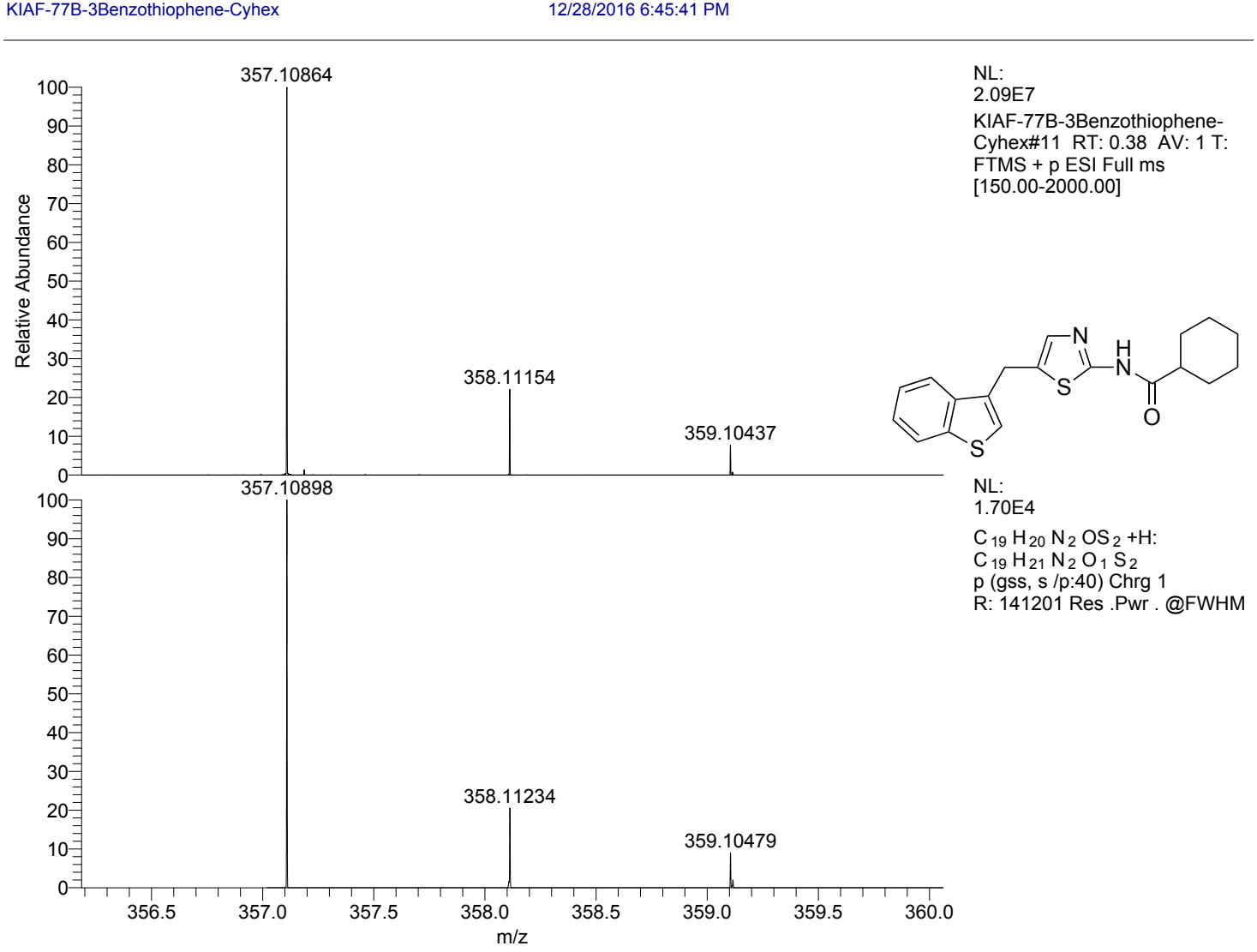
S.6.16.1. *N*-[5-(3-Benzothiophenylmethyl)thiazol-2-yl]cyclohexanecarboxamide (23b). ^{1}H NMR (400 MHz, $CDCl_3$)



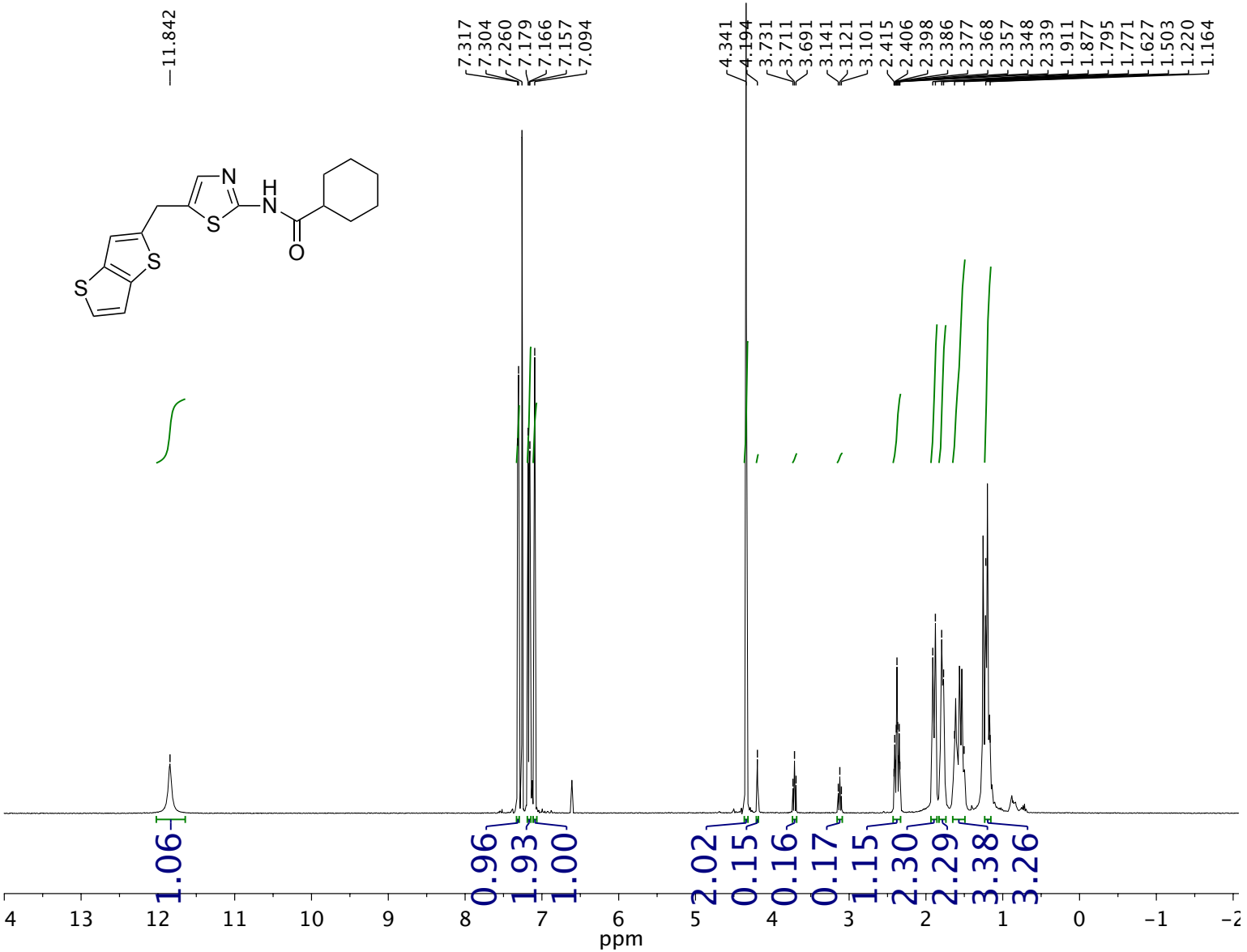
S.6.16.2. *N*-[5-(3-Benzothiophenylmethyl)thiazol-2-yl]cyclohexanecarboxamide (23b). ^{13}C NMR (100 MHz, $CDCl_3$)



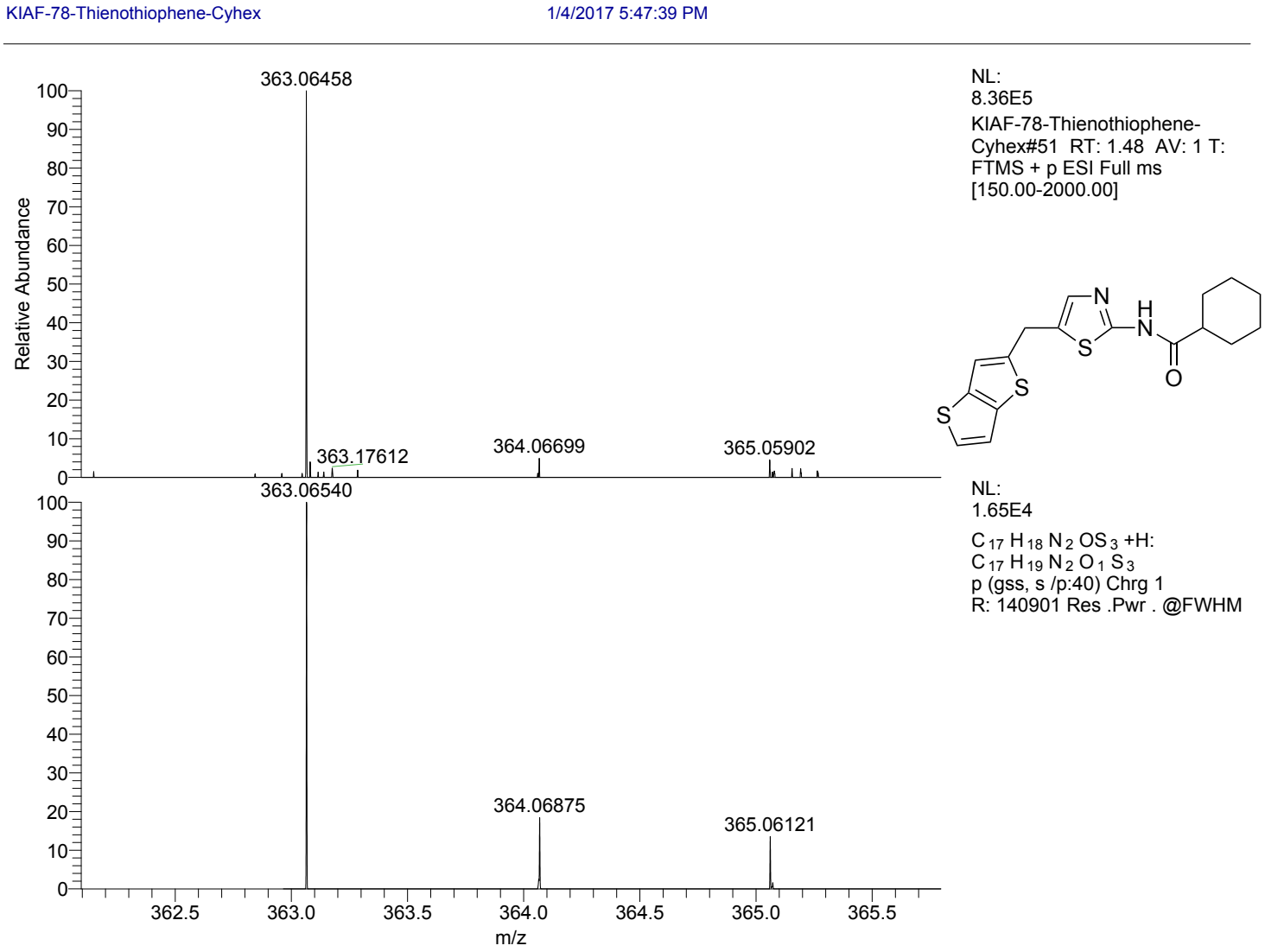
S.6.16.3. *N*-[5-(3-Benzothiophenylmethyl)thiazol-2-yl]cyclohexanecarboxamide (23b). HR-ESI-MS



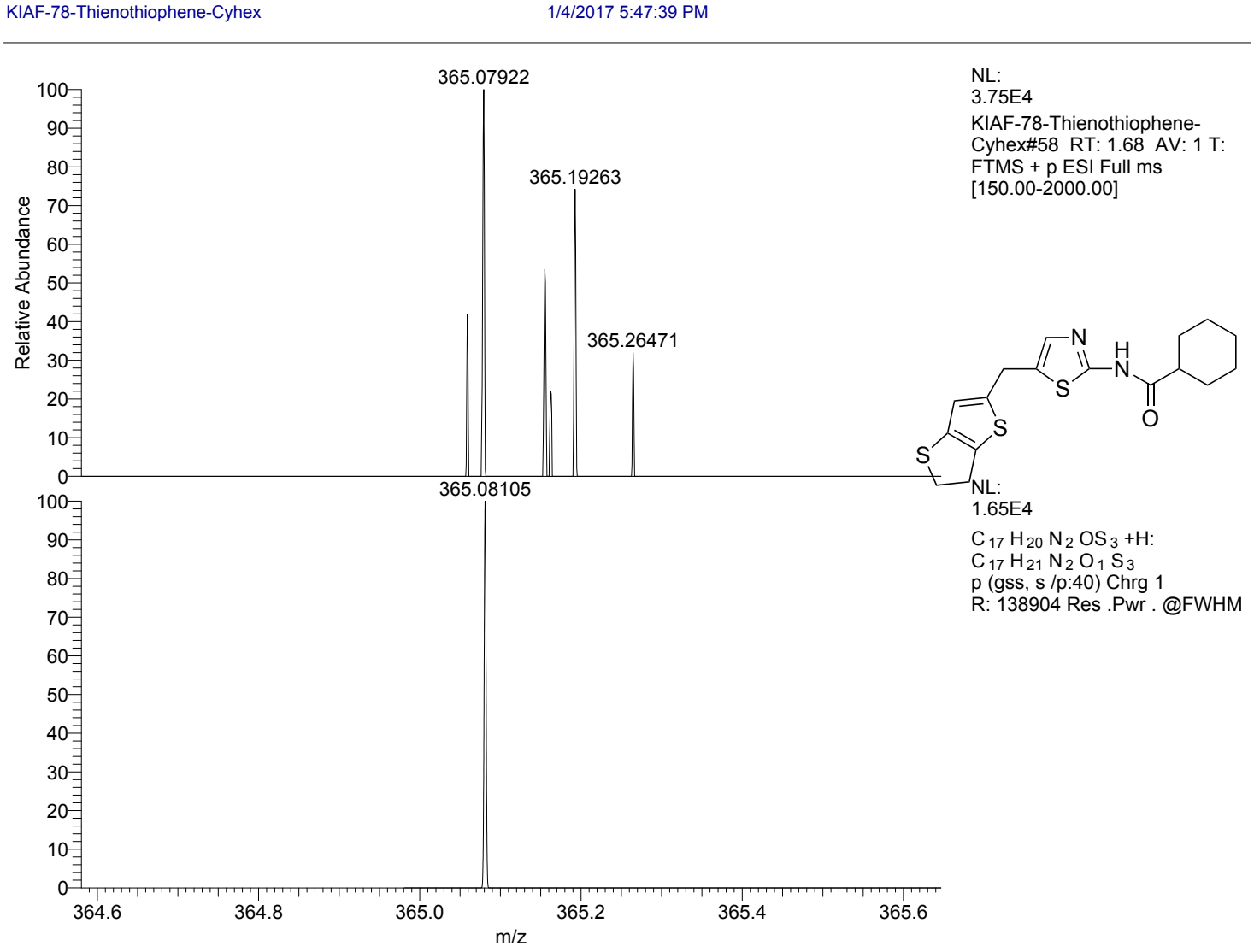
S.6.17.1. *N*-{5-[2-Thieno(3,2-b)thiophenylmethyl]thiazol-2-yl}cyclohexanecarboxamide (24). ^{1}H NMR (400 MHz, $CDCl_3$)



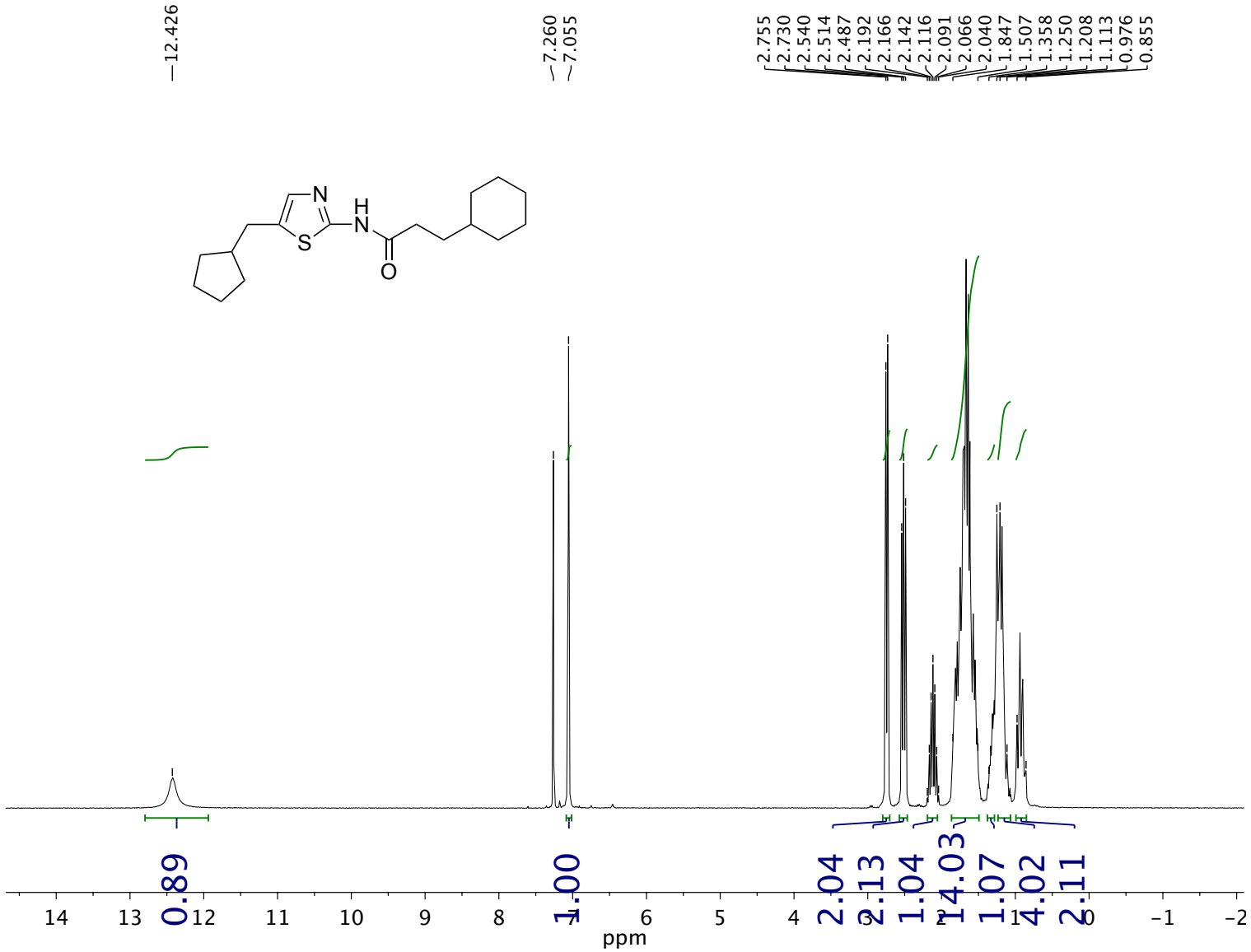
S.6.17.2. *N*-{5-[2-Thieno(3,2-b)thiophenylmethyl]thiazol-2-yl}cyclohexanecarboxamide (24). HR-ESI-MS



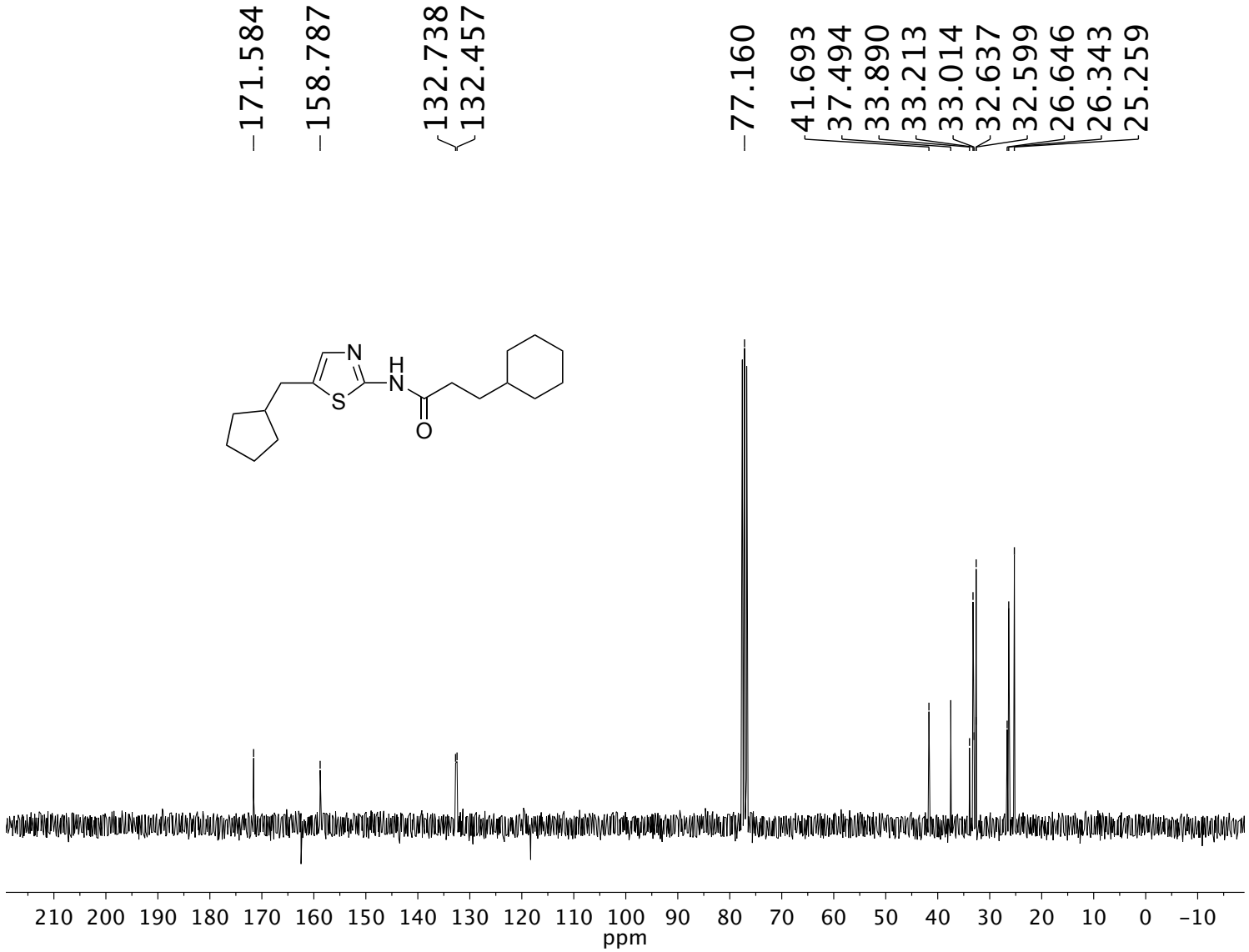
S.6.17.3. Reduced form (24') of *N*-{5-[2-Thieno(3,2-b)thiophenylmethyl]thiazol-2-yl}cyclohexanecarboxamide (24). HR-ESI-MS



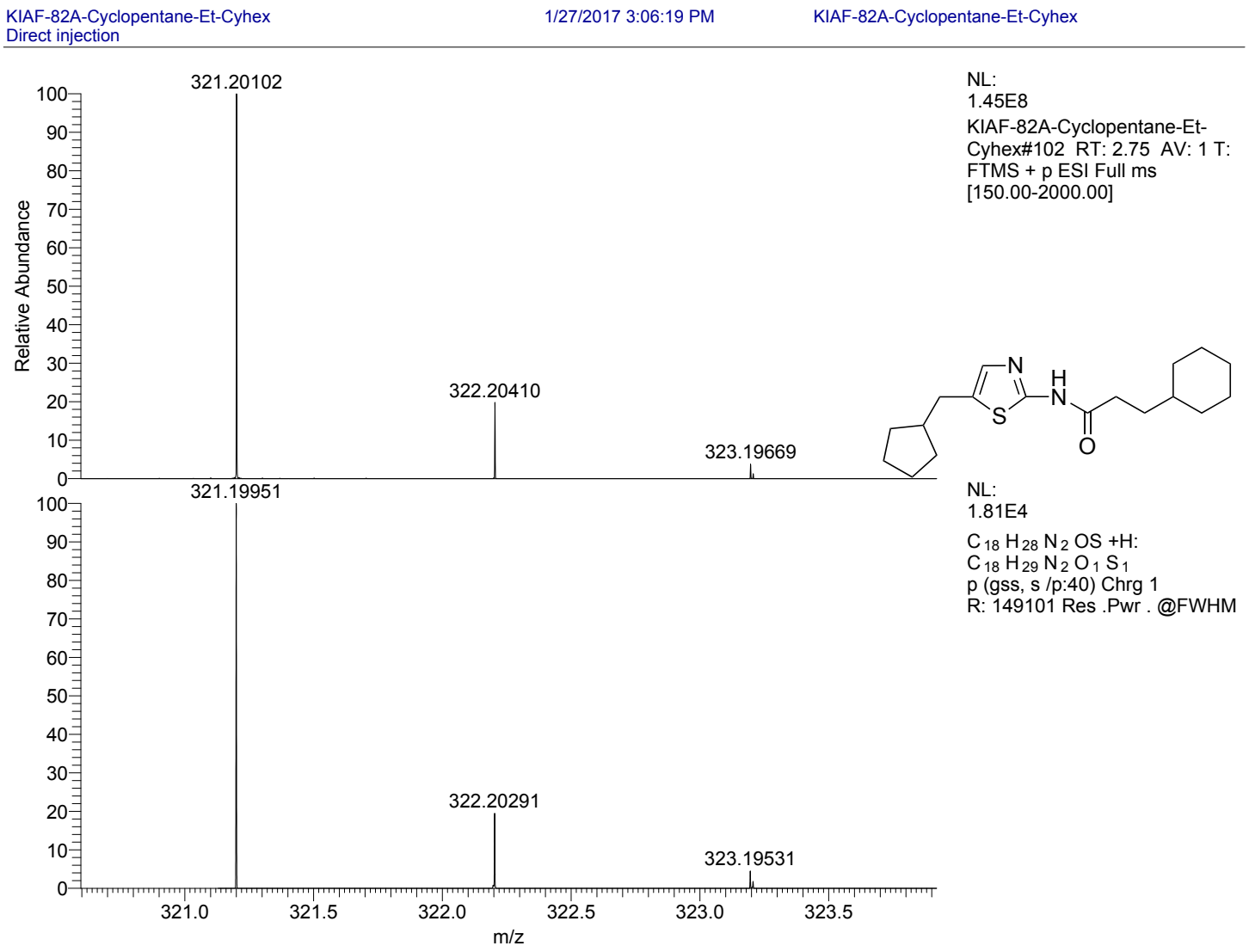
S.6.18.1. *N*-[5-(Cyclopentylmethyl)thiazol-2-yl]-3-cyclohexanepropanamide (25a). ^{1}H NMR (300 MHz, $CDCl_3$)



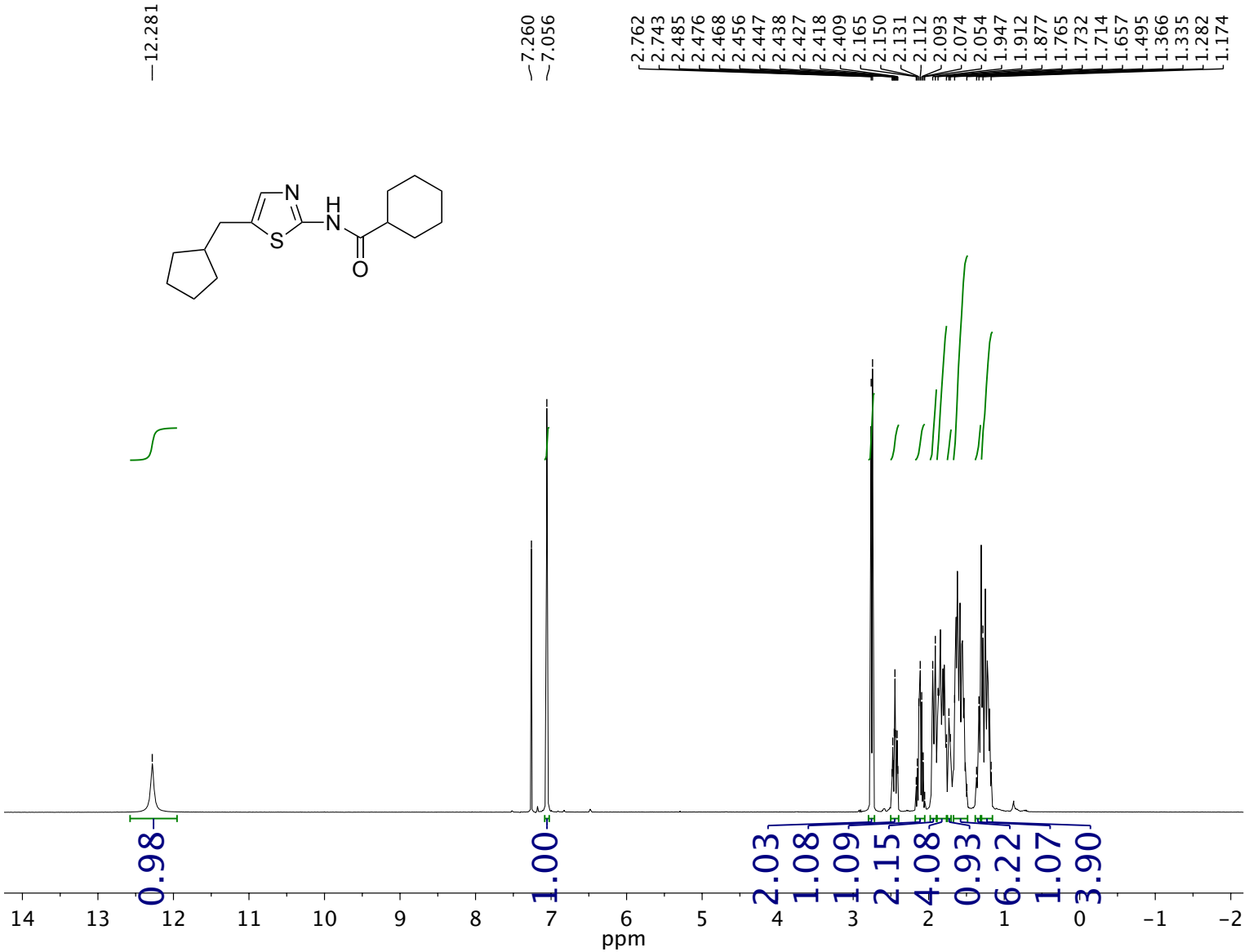
S.6.18.2. *N*-[5-(Cyclopentylmethyl)thiazol-2-yl]-3-cyclohexanepropanamide (25a). ^{13}C NMR (75 MHz, $CDCl_3$)



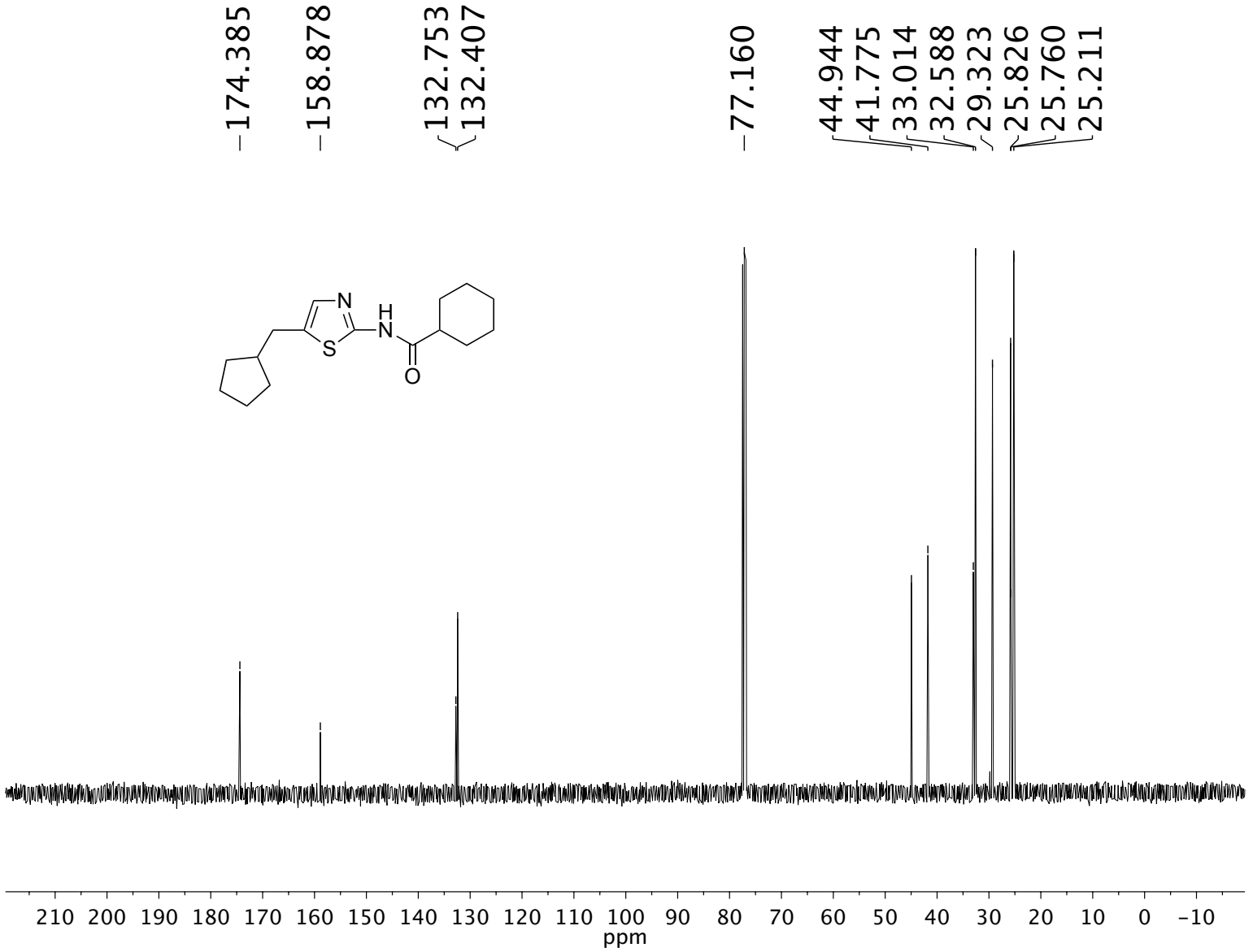
S.6.18.3. *N*-[5-(Cyclopentylmethyl)thiazol-2-yl]-3-cyclohexanepropanamide (25a). HR-ESI-MS



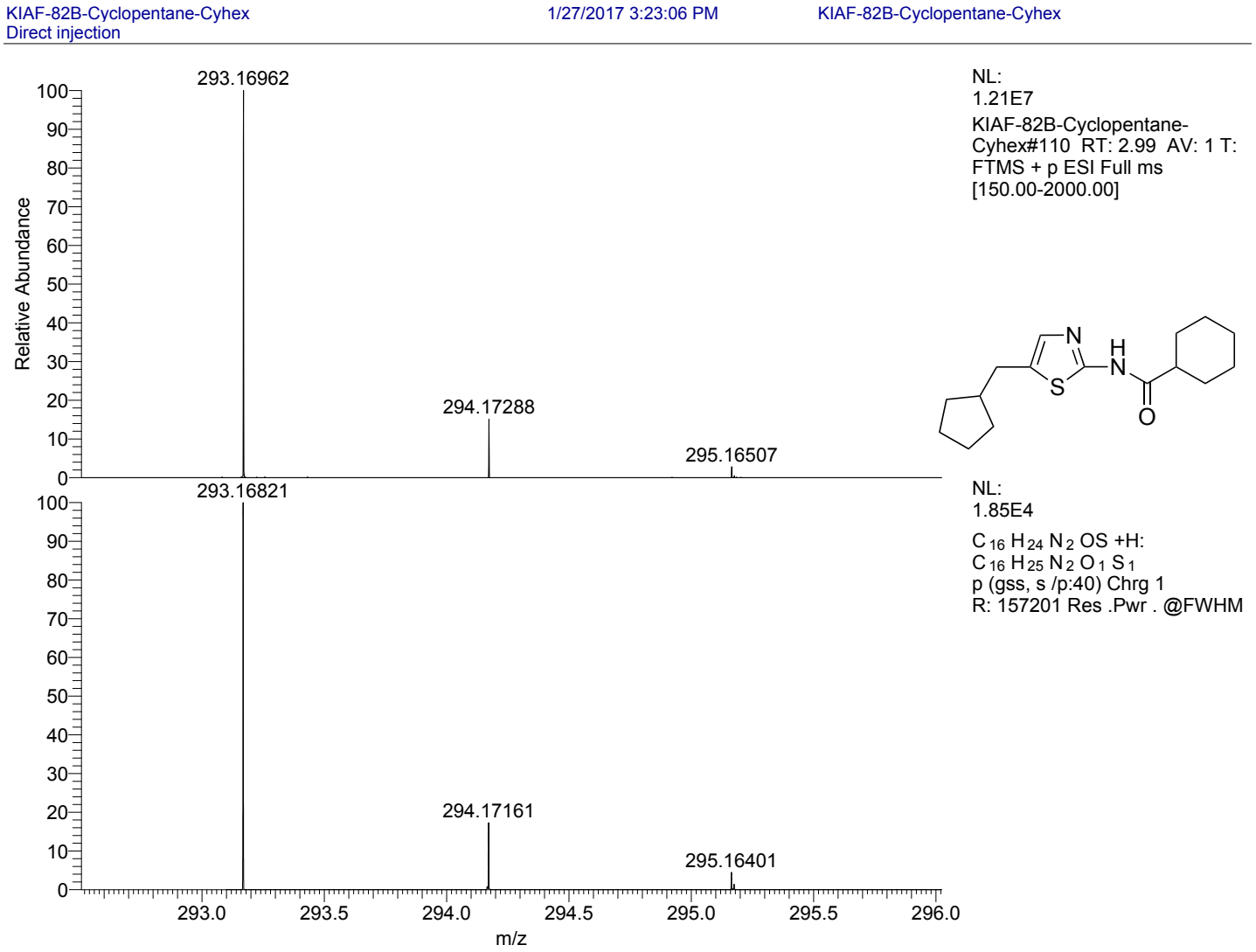
S.6.19.1. *N*-[5-(Cyclopentylmethyl)thiazol-2-yl]cyclohexanecarboxamide (25b). ^{1}H NMR (400 MHz, $CDCl_3$)



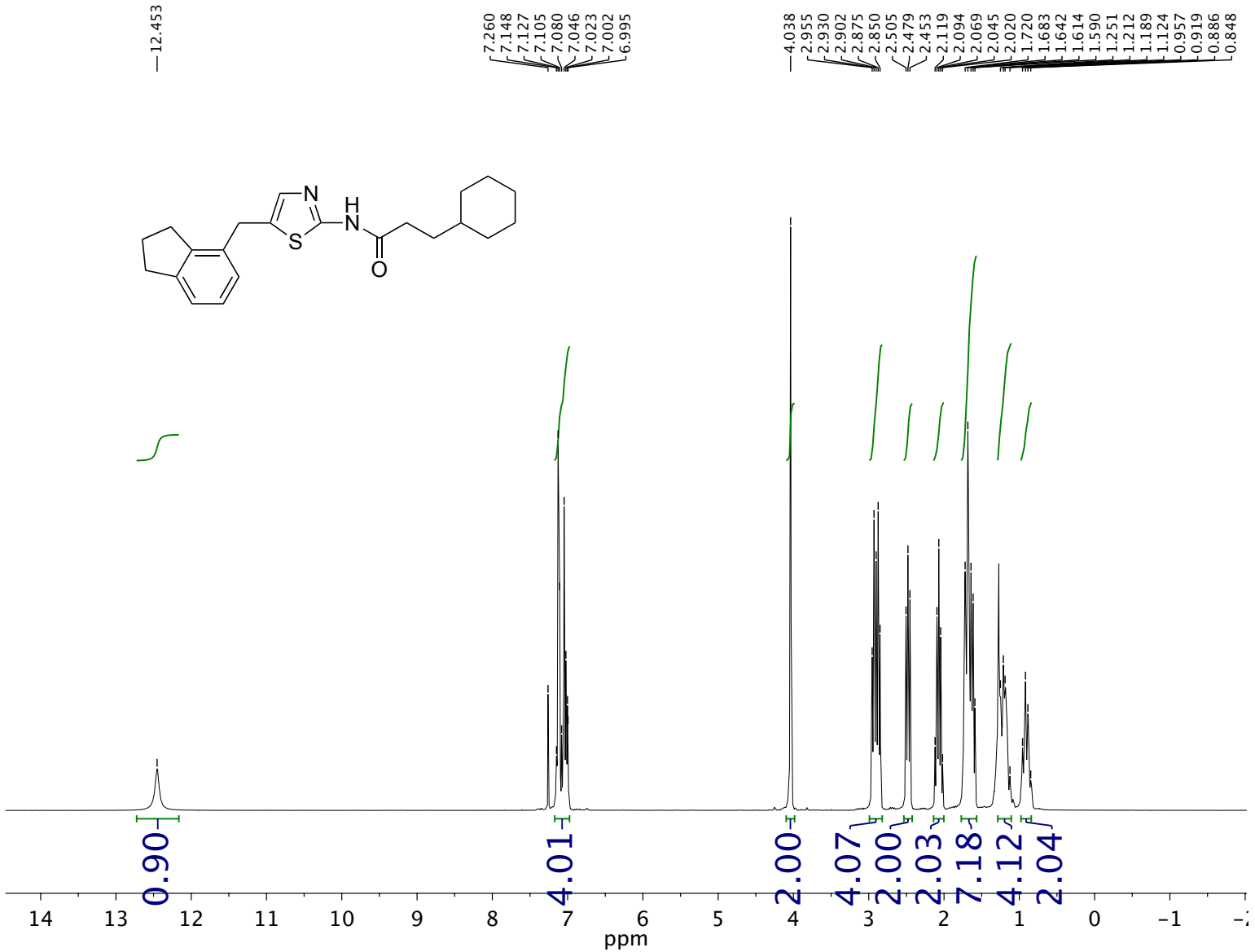
S.6.19.2. *N*-[5-(Cyclopentylmethyl)thiazol-2-yl]cyclohexanecarboxamide (25b). ^{13}C NMR (100 MHz, $CDCl_3$)



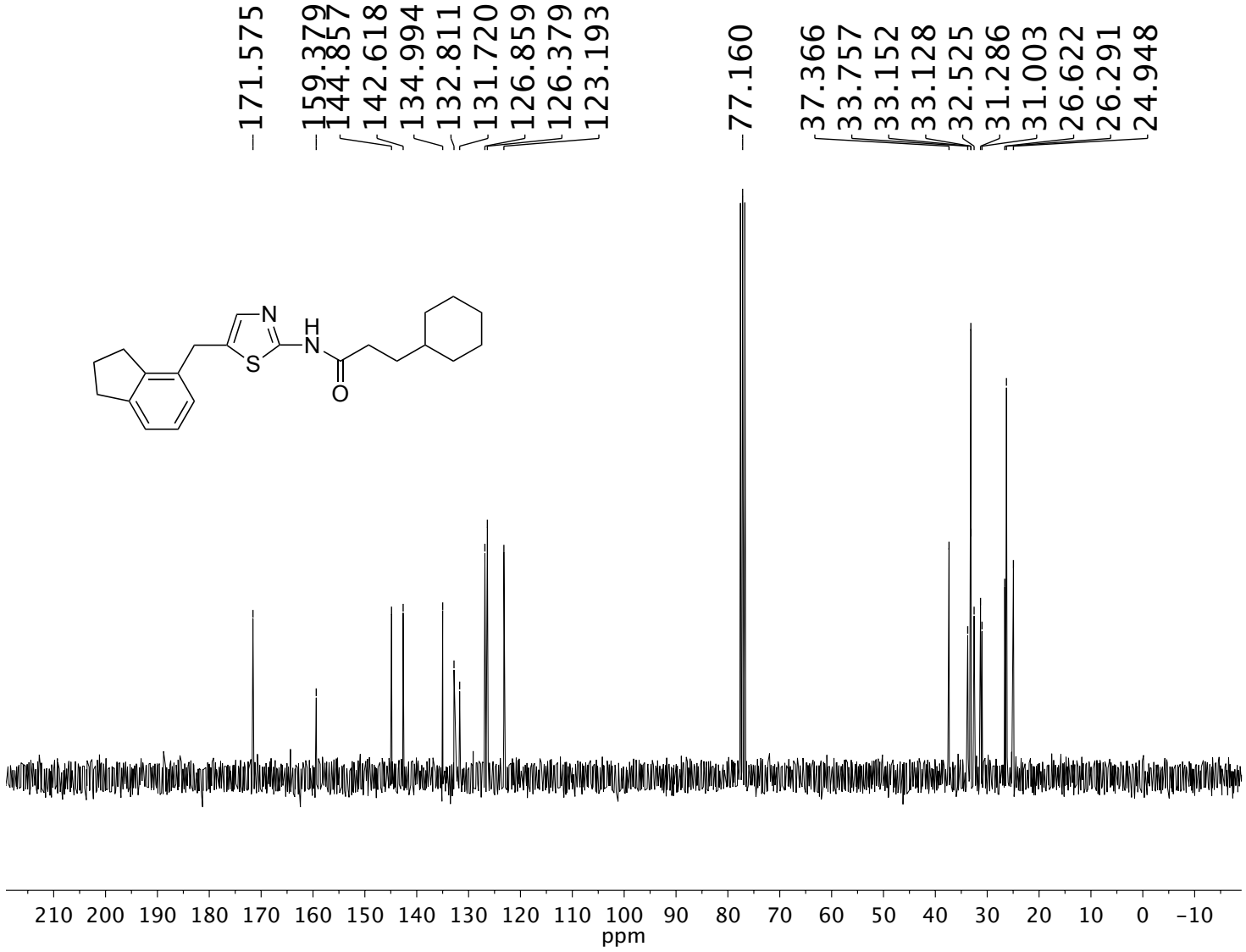
S.6.19.3. *N*-[5-(Cyclopentylmethyl)thiazol-2-yl]cyclohexanecarboxamide (25b). HR-ESI-MS



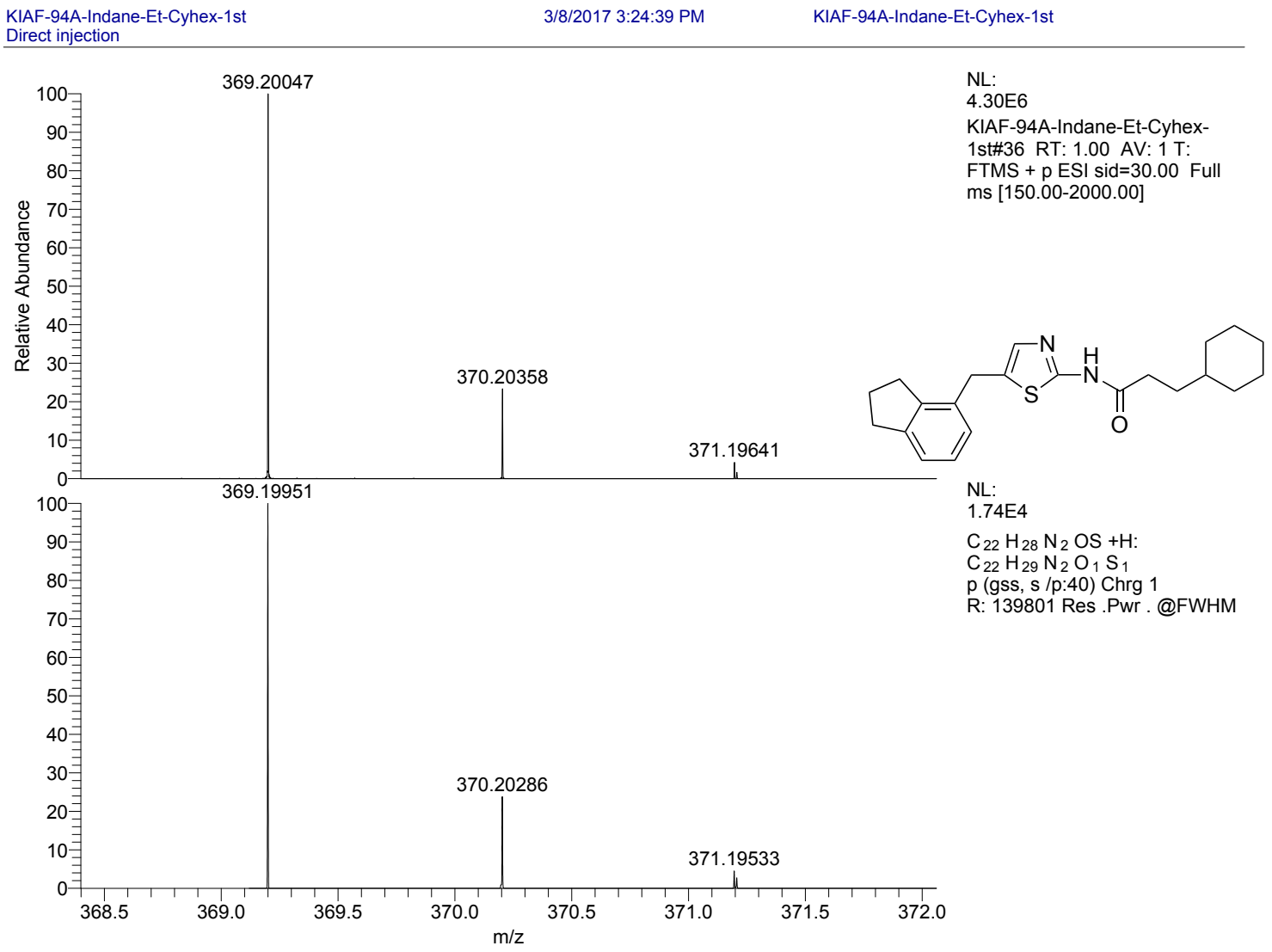
S.6.20.1. *N*-[5-(4-Indanylmethyl)thiazol-2-yl]-3-cyclohexanepropanamide (26a). ^{1}H NMR (300 MHz, $CDCl_3$)



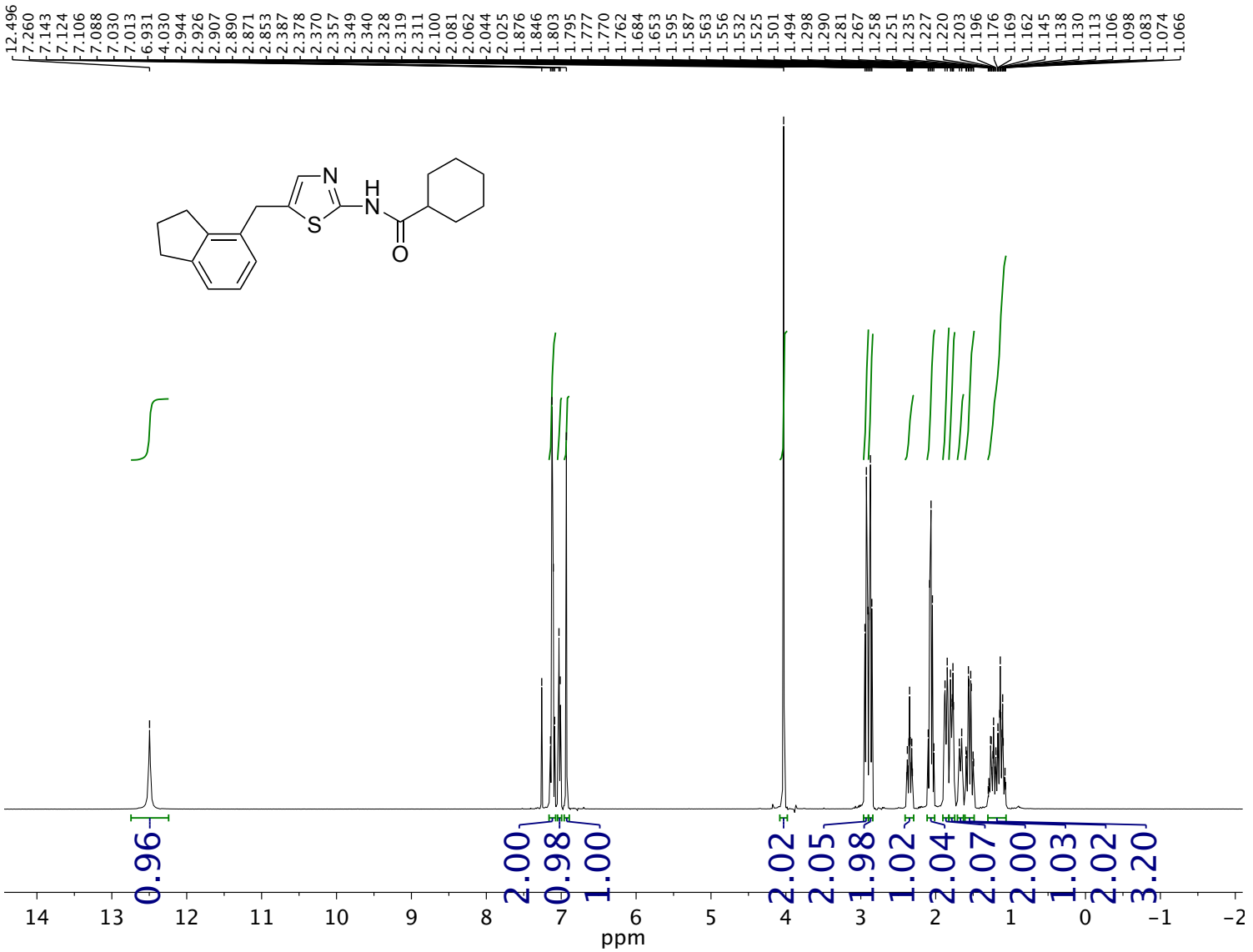
S.6.20.2. *N*-[5-(4-Indanylmethyl)thiazol-2-yl]-3-cyclohexanepropanamide (26a). ^{13}C NMR (75 MHz, $CDCl_3$)



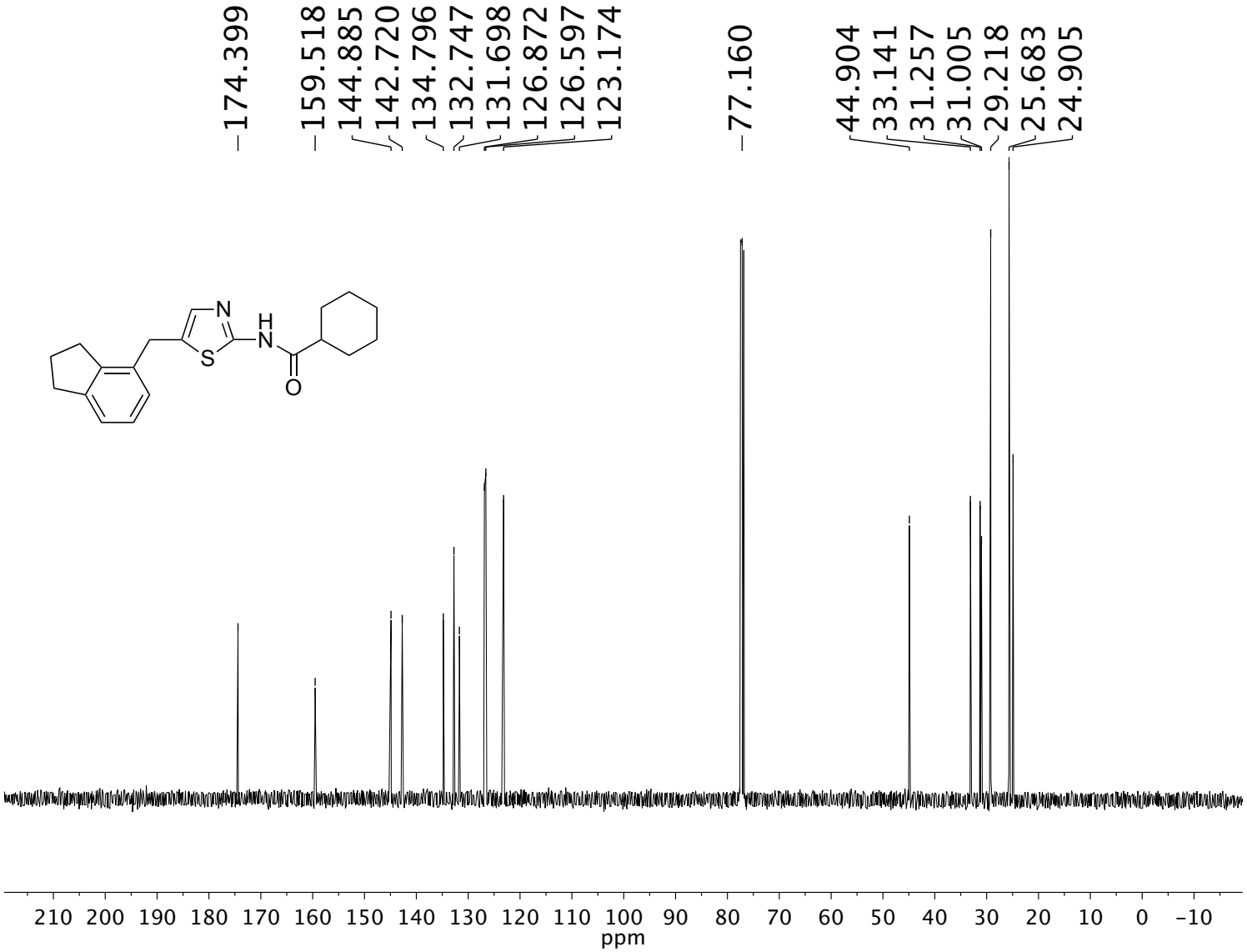
S.6.20.3. *N*-[5-(4-Indanylmethyl)thiazol-2-yl]-3-cyclohexanepropanamide (26a). HR-ESI-MS



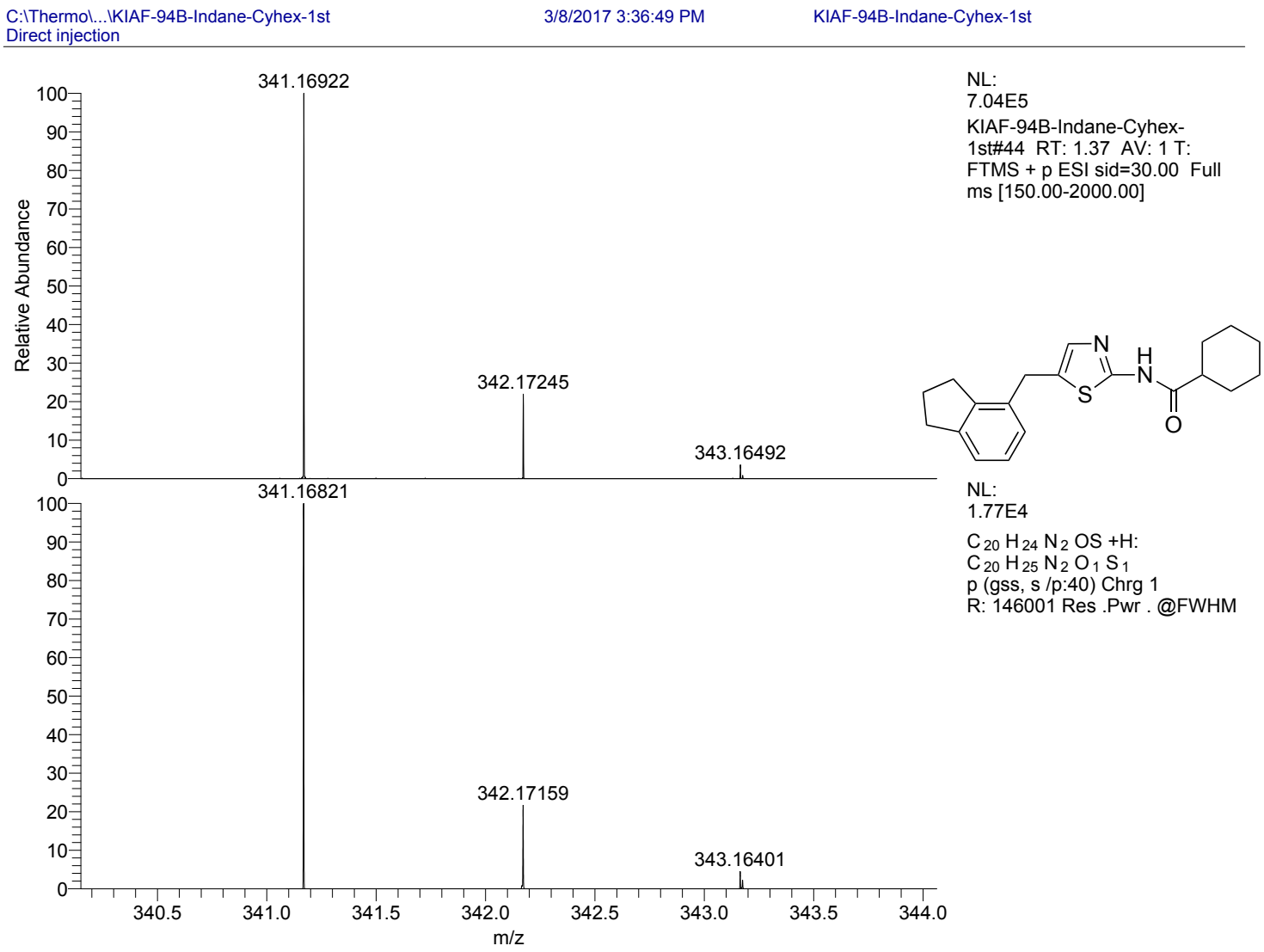
S.6.21.1. *N*-[5-(4-Indanylmethyl)thiazol-2-yl]cyclohexanecarboxamide (26b). ^{1}H NMR (400 MHz, $CDCl_3$)



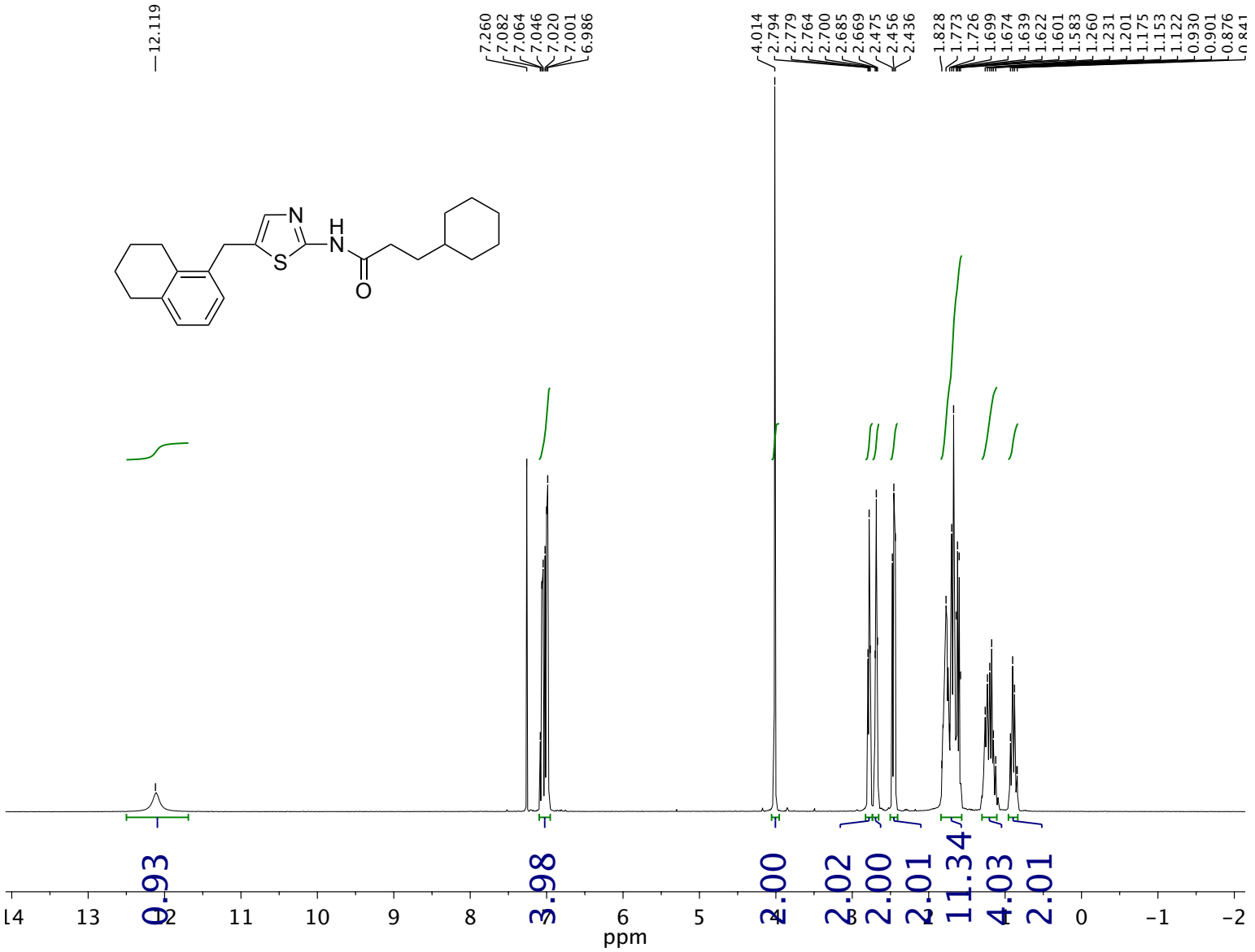
S.6.21.2. *N*-[5-(4-Indanylmethyl)thiazol-2-yl]cyclohexanecarboxamide (26b). ^{13}C NMR (100 MHz, $CDCl_3$)



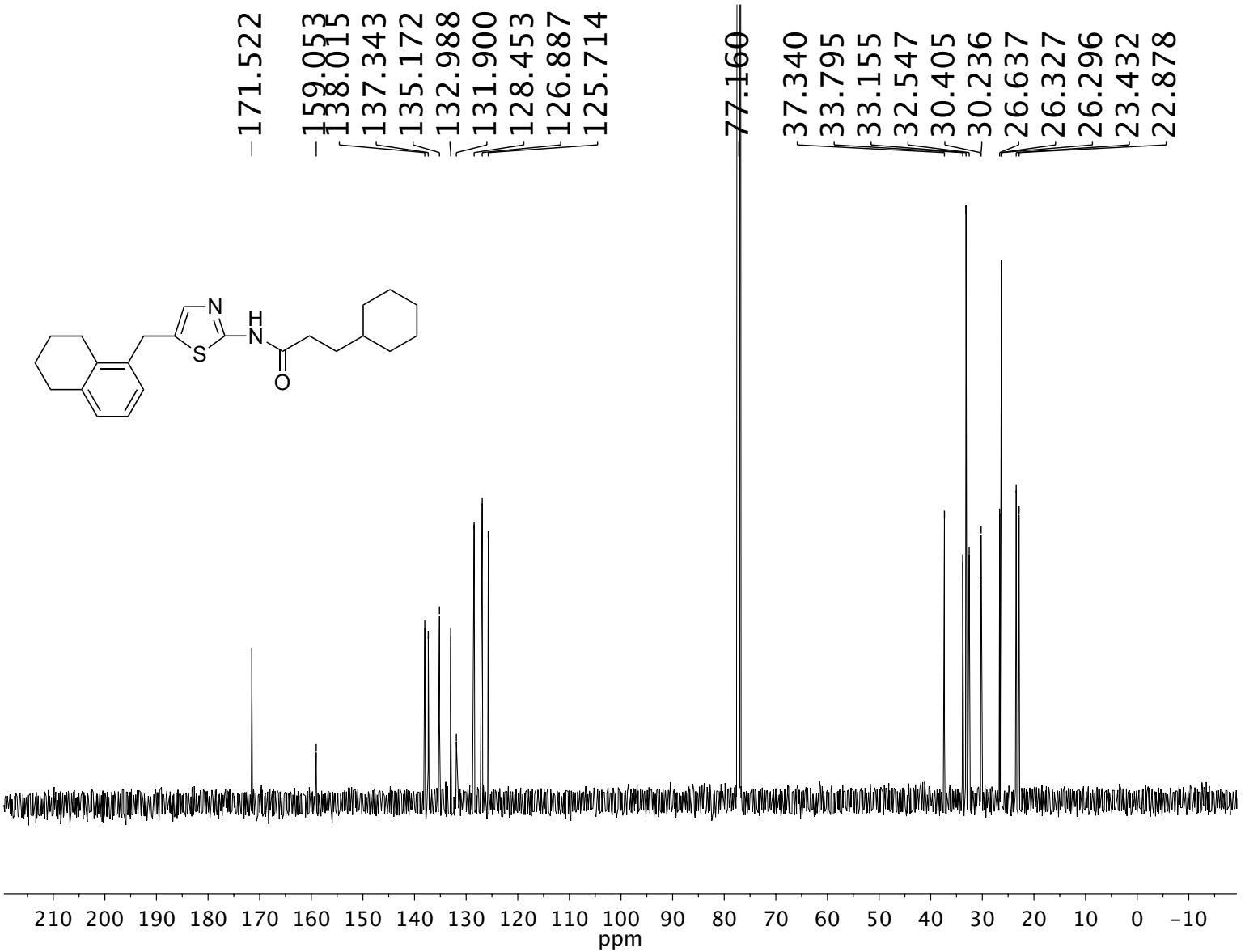
S.6.21.3. *N*-[5-(4-Indanylmethyl)thiazol-2-yl]cyclohexanecarboxamide (26b). HR-ESI-MS



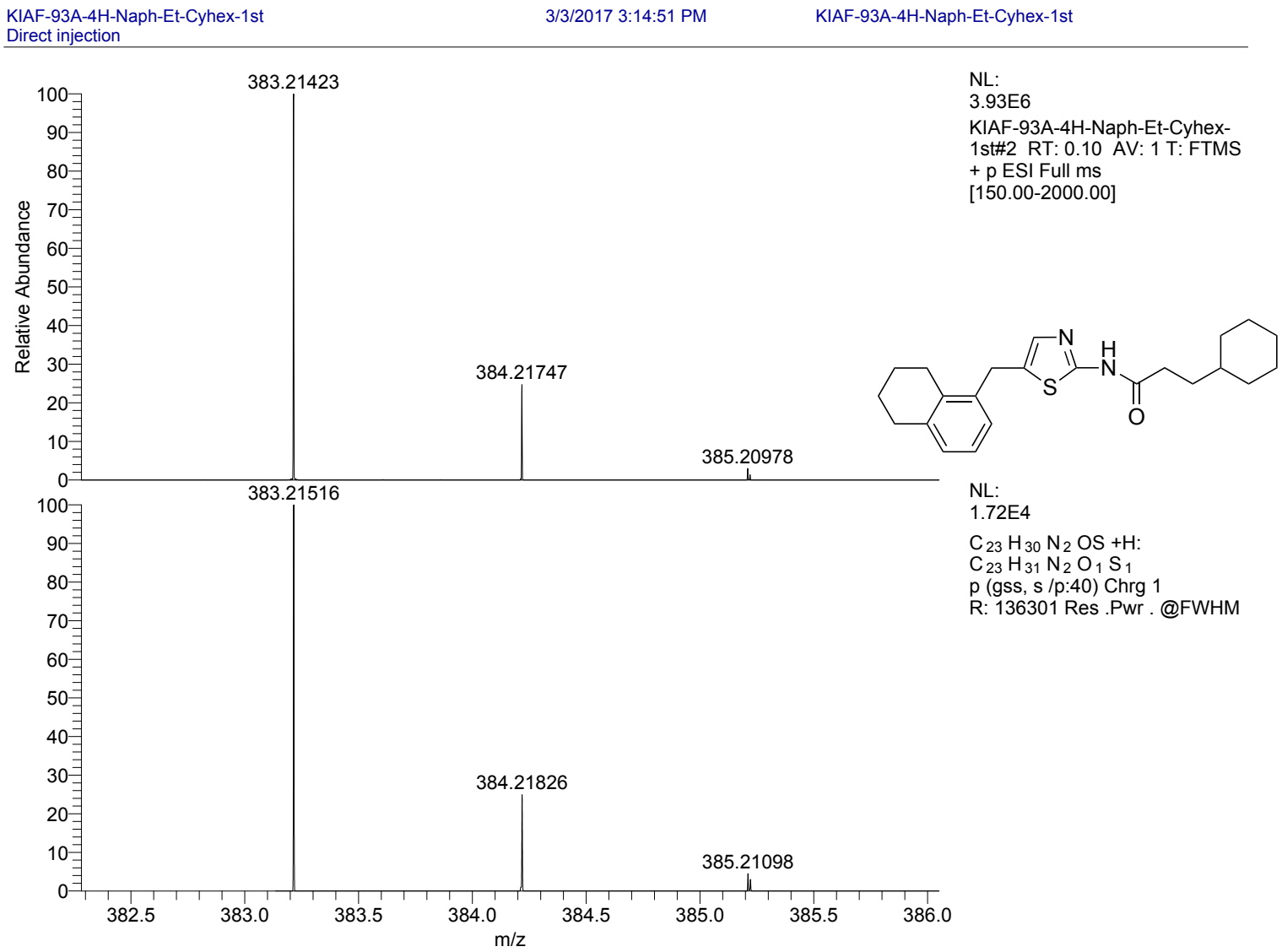
S.6.22.1. *N*-[(5-Tetralinylmethyl)thiazol-2-yl]-3-cyclohexanepropanamide (27a). ^{1}H NMR (400 MHz, $CDCl_3$)



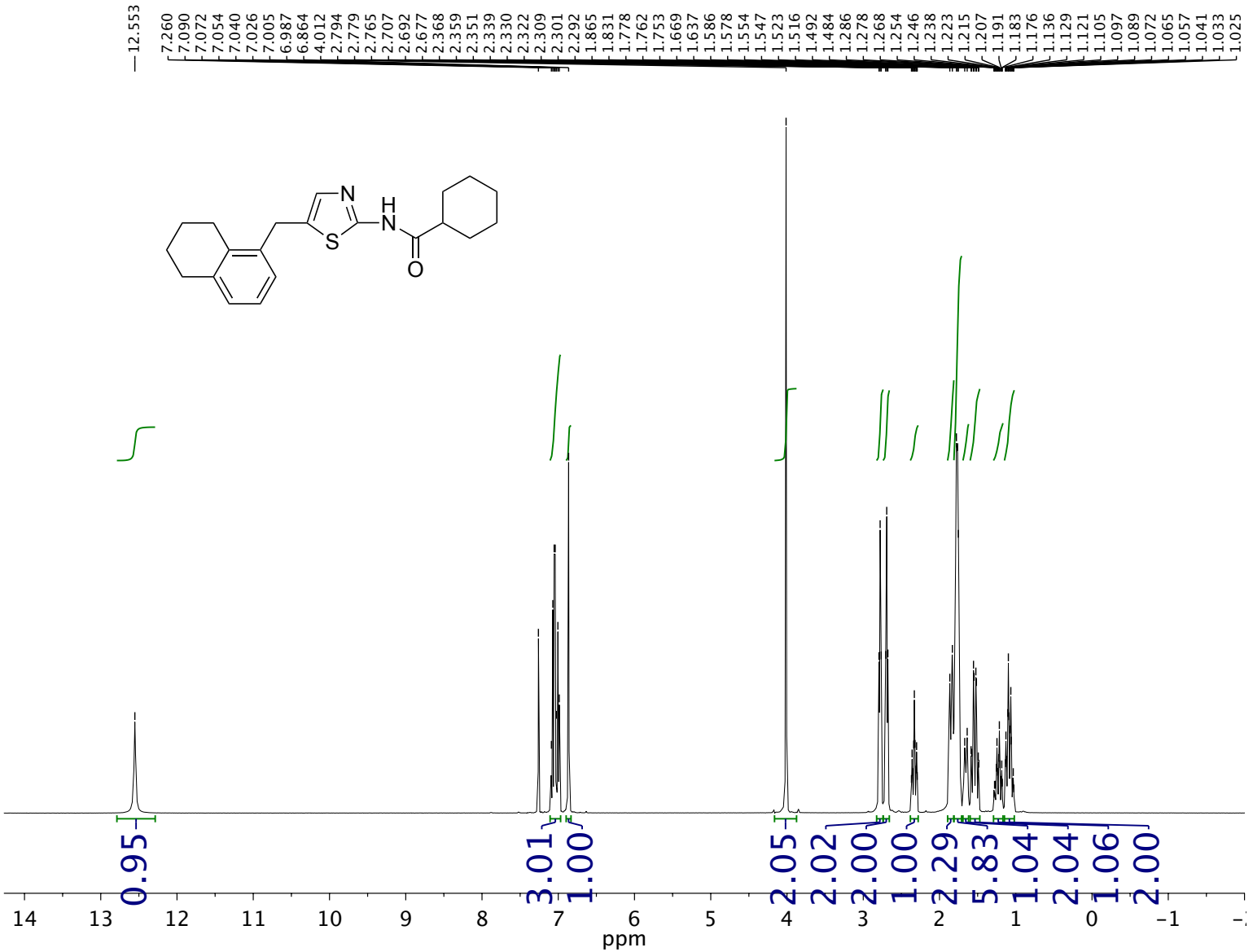
S.6.22.2. *N*-[(5-Tetralinylmethyl)thiazol-2-yl]-3-cyclohexanepropanamide (27a). ^{13}C NMR (100 MHz, $CDCl_3$)



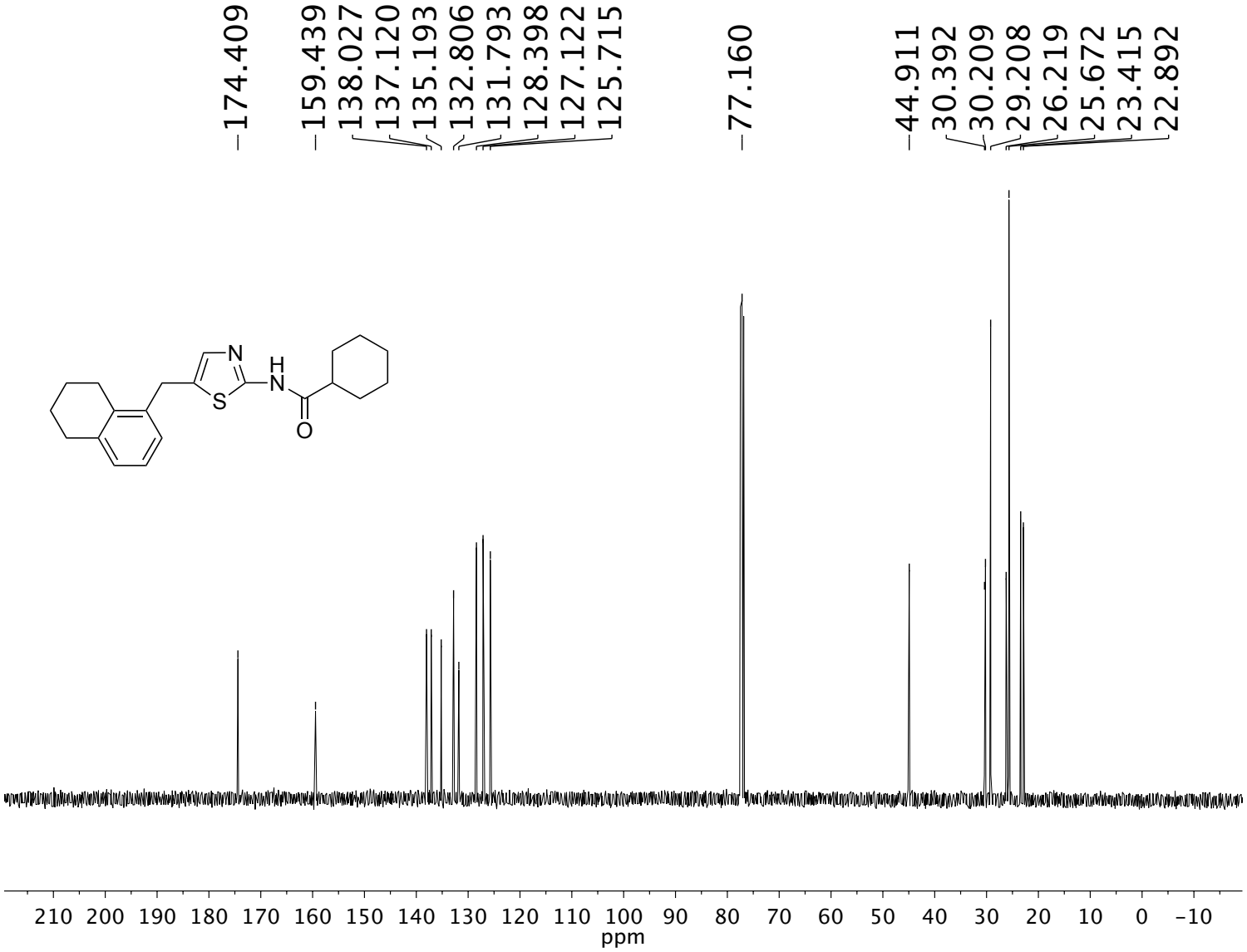
S.6.22.3. *N*-[(5-Tetralinylmethyl)thiazol-2-yl]-3-cyclohexanepropanamide (27a). HR-ESI-MS



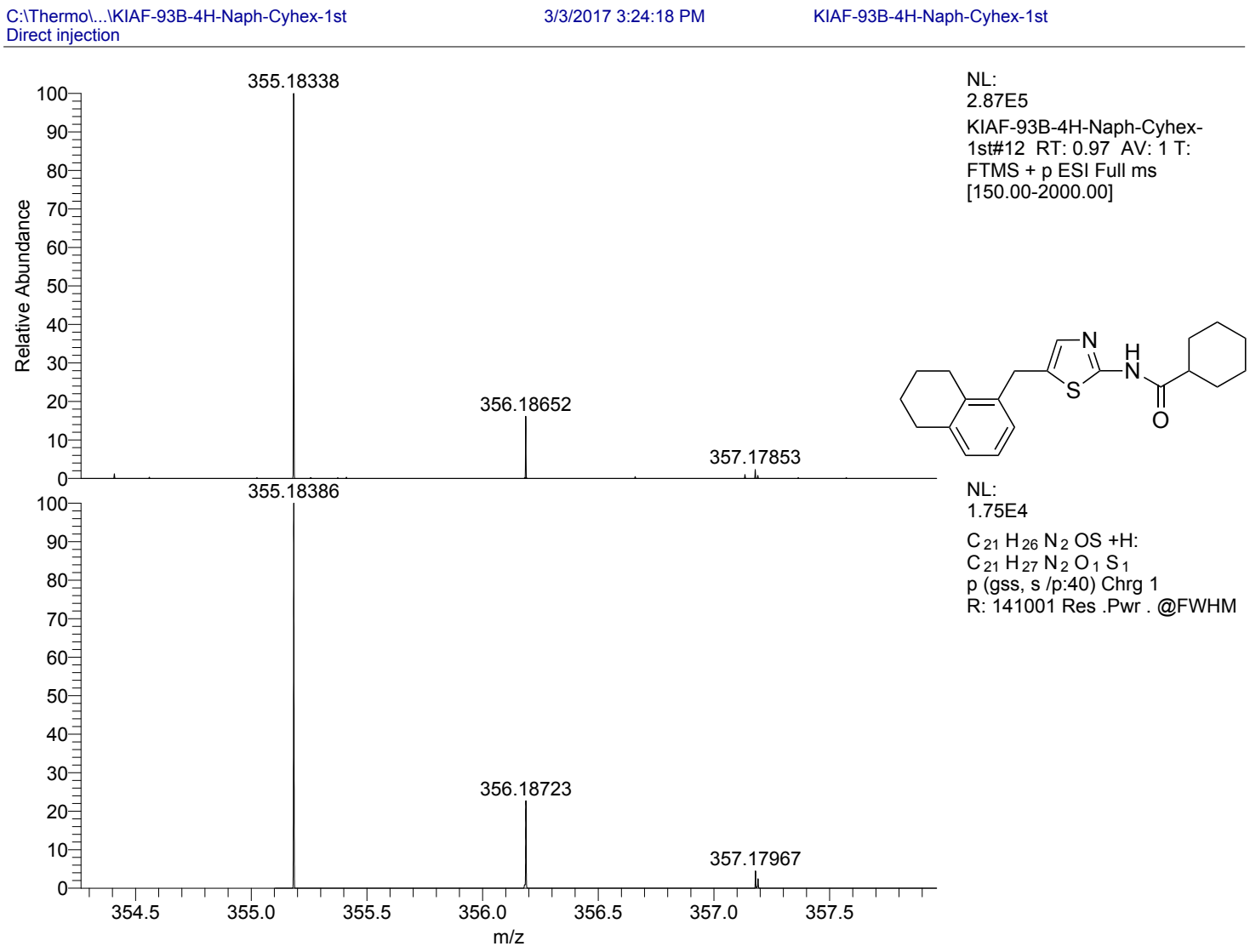
S.6.23.1. *N*-[(5-Tetralinylmethyl)thiazol-2-yl]cyclohexanecarboxamide (27b). ^{1}H NMR (400 MHz, $CDCl_3$)



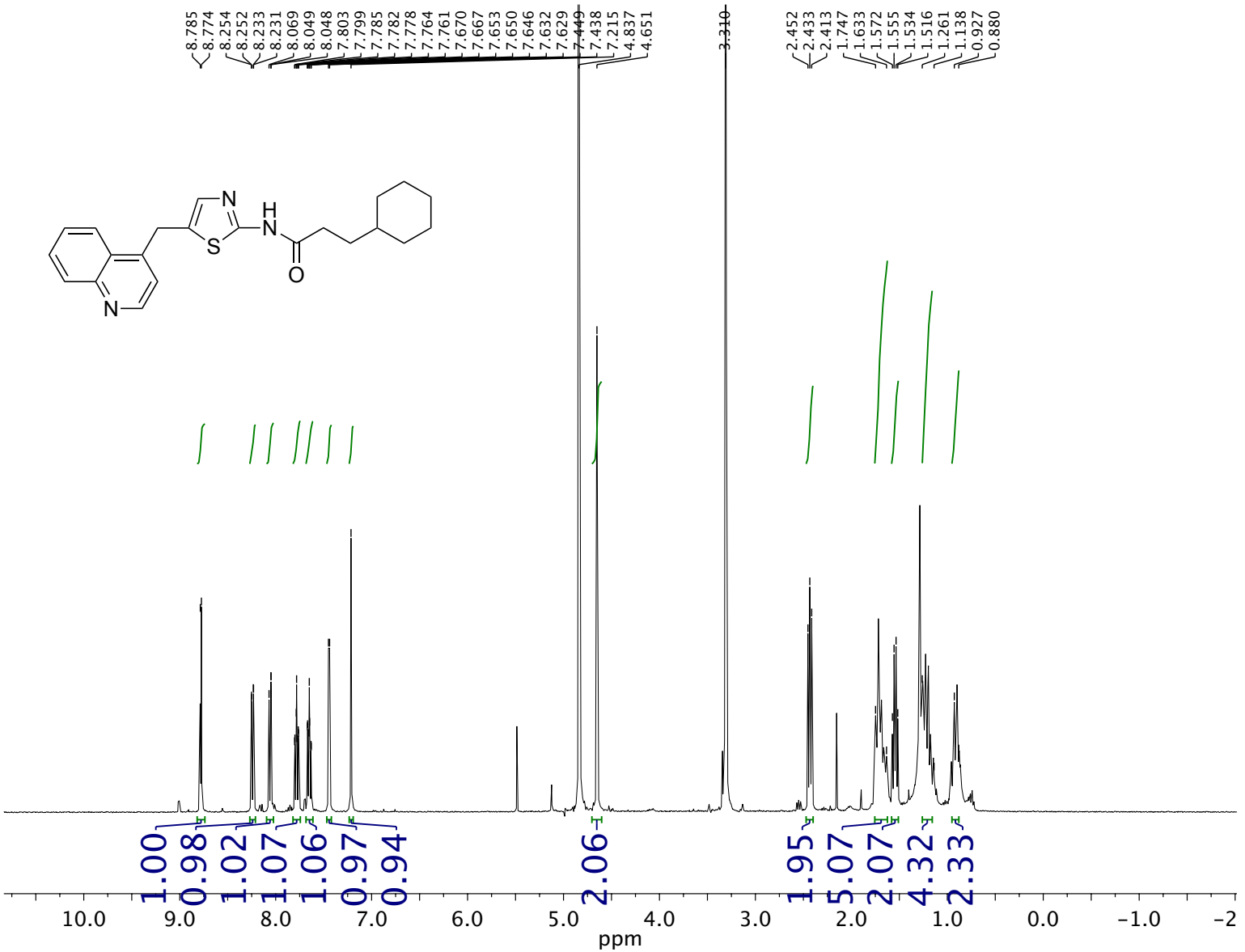
S.6.23.2. *N*-[(5-Tetralinylmethyl)thiazol-2-yl]cyclohexanecarboxamide (27b). ^{13}C NMR (100 MHz, $CDCl_3$)



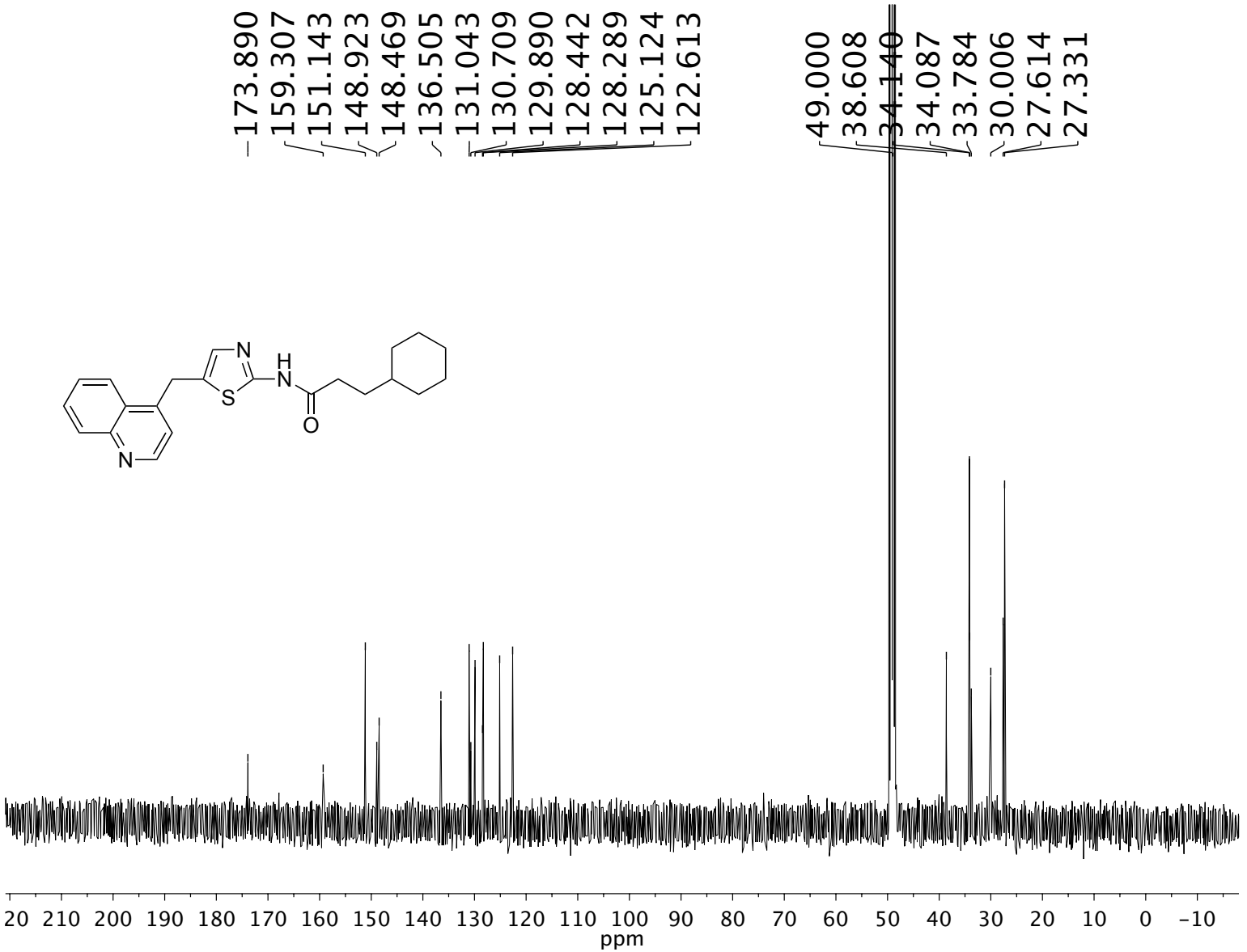
S.6.23.3. *N*-[(5-Tetralinylmethyl)thiazol-2-yl]cyclohexanecarboxamide (27b). HR-ESI-MS



S.6.24.1. *N*-[5-(4-Quinolinylmethyl)thiazol-2-yl]-3-cyclohexanepropanamide (28a). ^{1}H NMR (400 MHz, CD_3OD)



S.6.24.2. *N*-[5-(4-Quinolinylmethyl)thiazol-2-yl]-3-cyclohexanepropanamide (28a). ^{13}C NMR (100 MHz, CD_3OD)



S.6.24.3. *N*-[5-(4-Quinolinylmethyl)thiazol-2-yl]-3-cyclohexanepropanamide (28a). HR-ESI-MS

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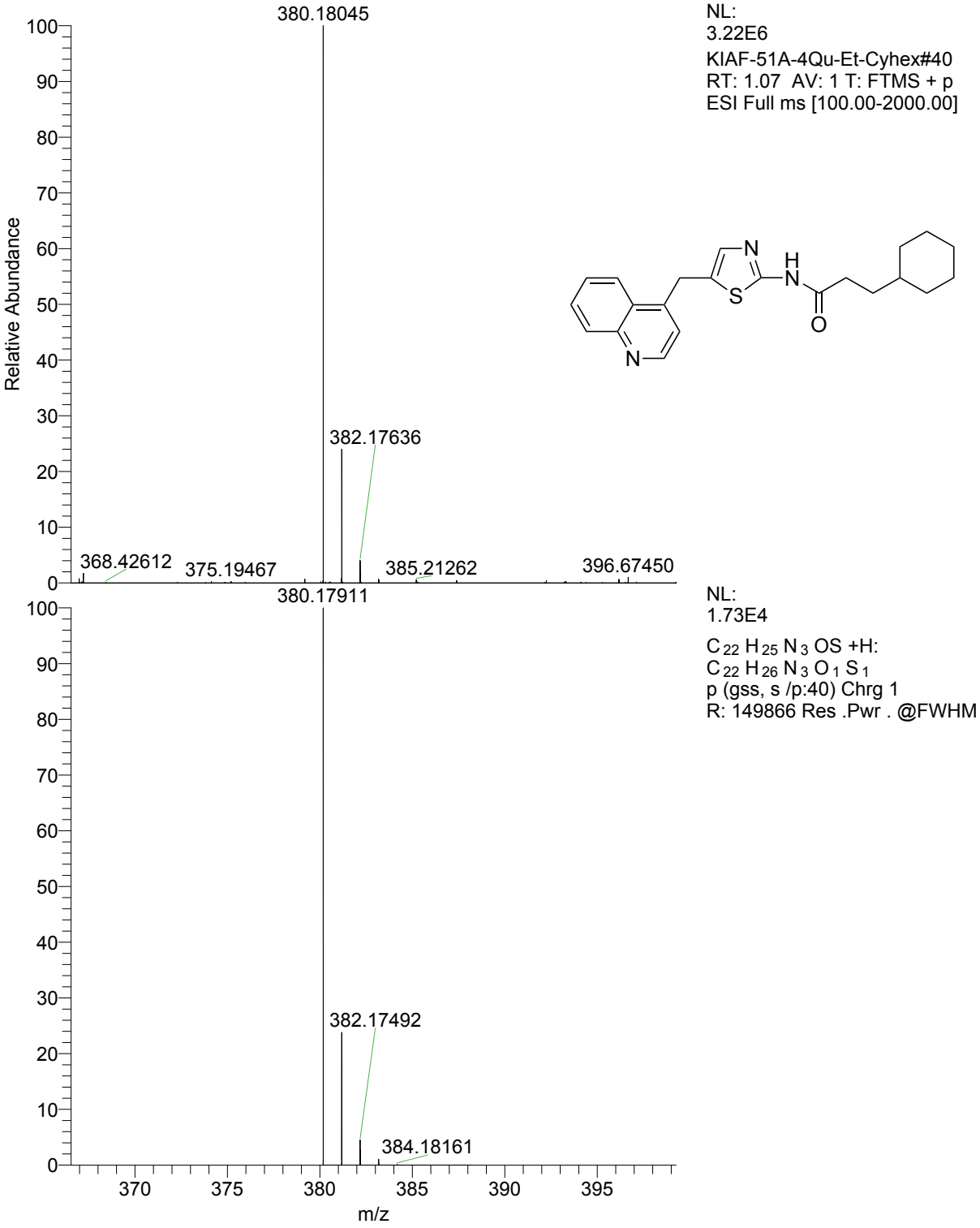
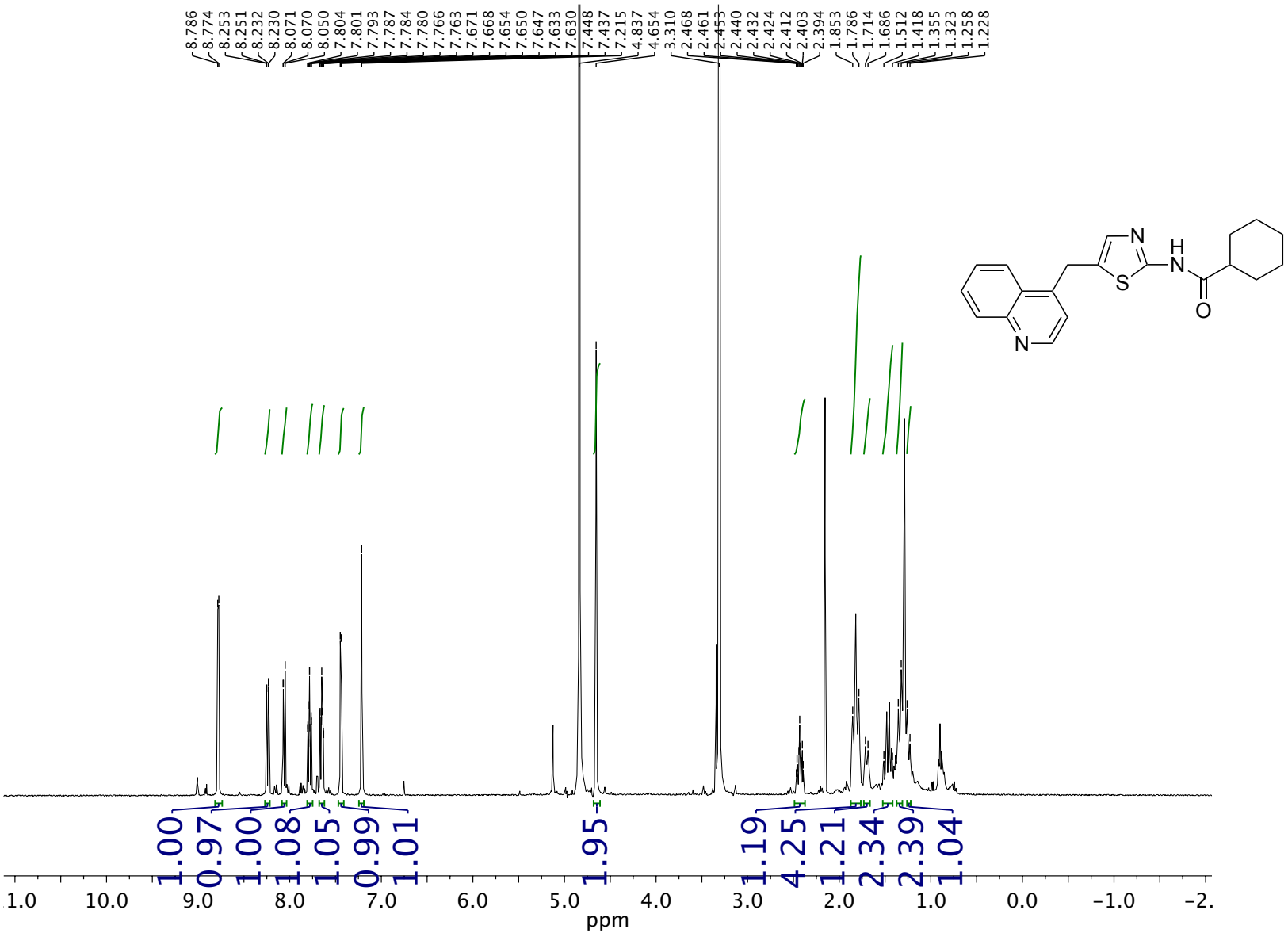
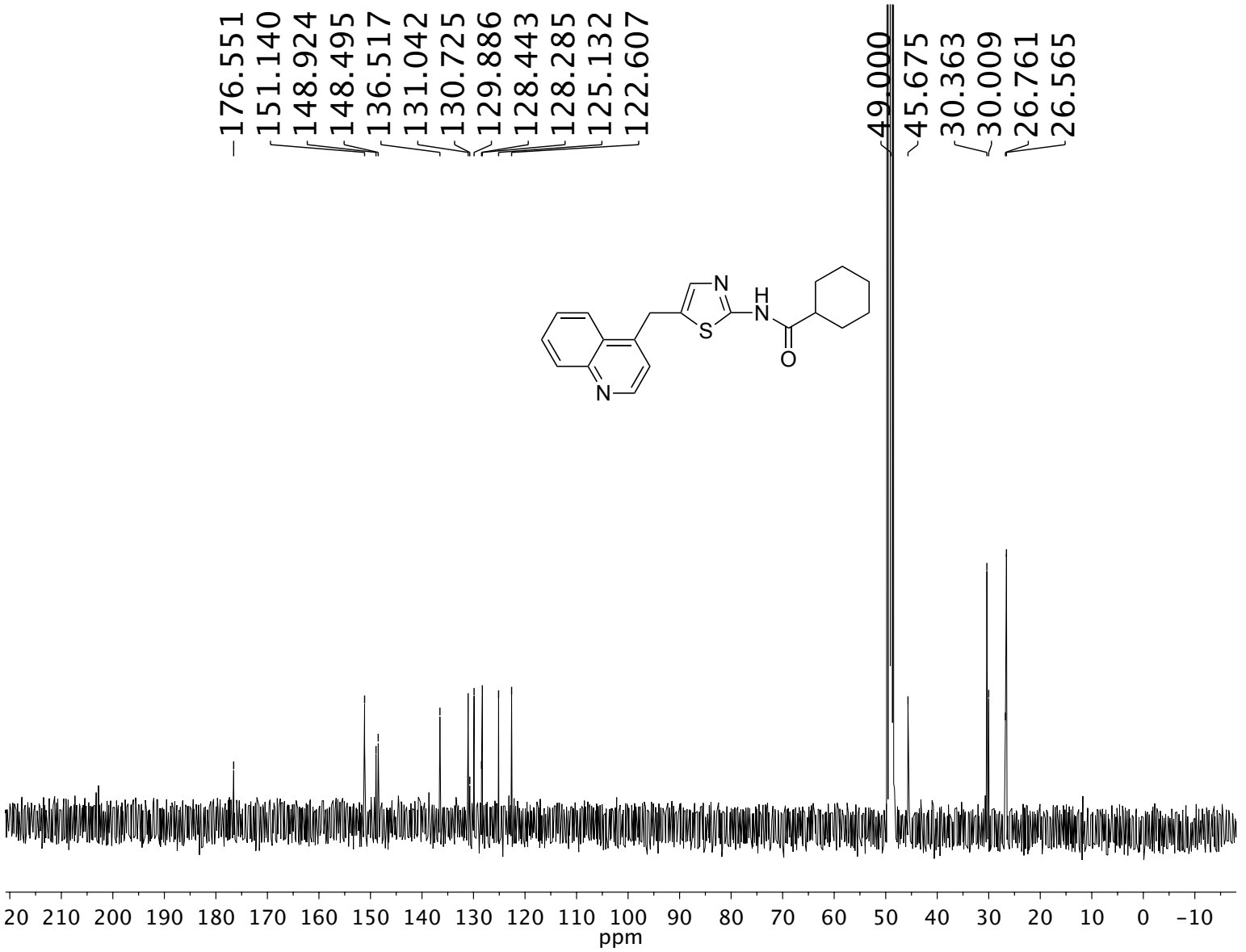


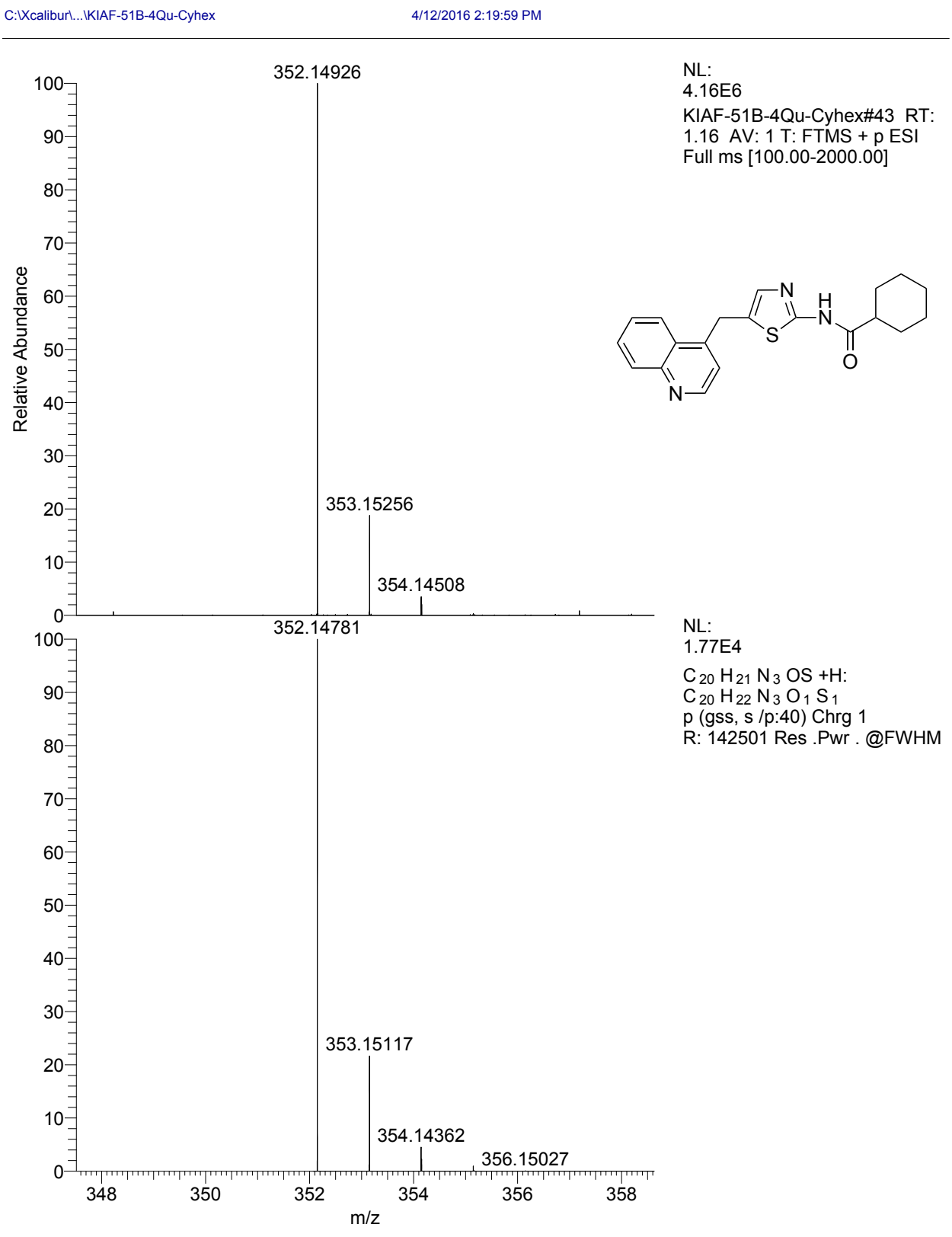
S.6.25.1. *N*-[5-(4-Quinolinylmethyl)thiazol-2-yl]cyclohexanecarboxamide (28b). ^{1}H NMR (400 MHz, CD_3OD)



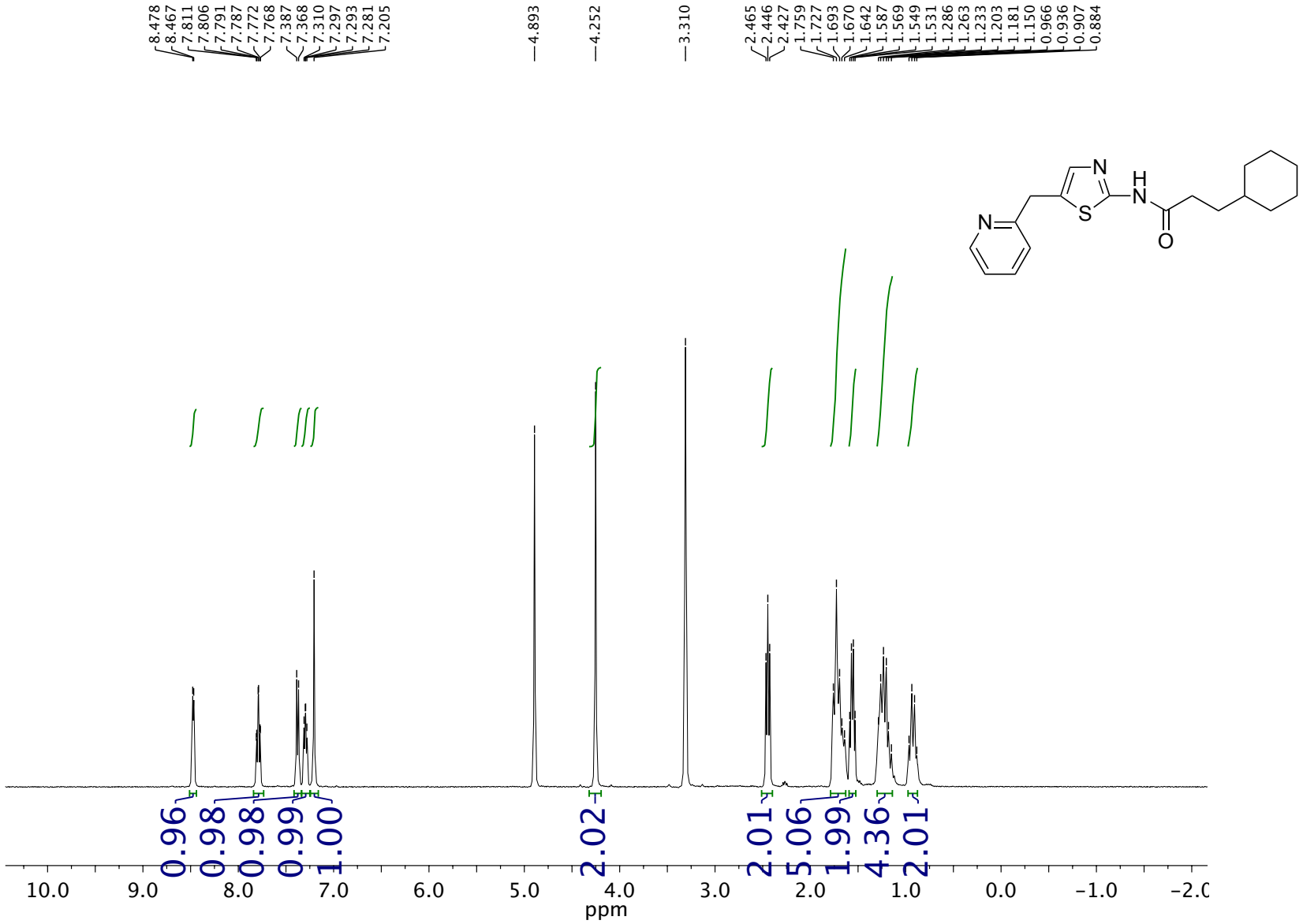
S.6.25.2. *N*-[5-(4-Quinolinylmethyl)thiazol-2-yl]cyclohexanecarboxamide (28b). ^{13}C NMR (100 MHz, CD_3OD)



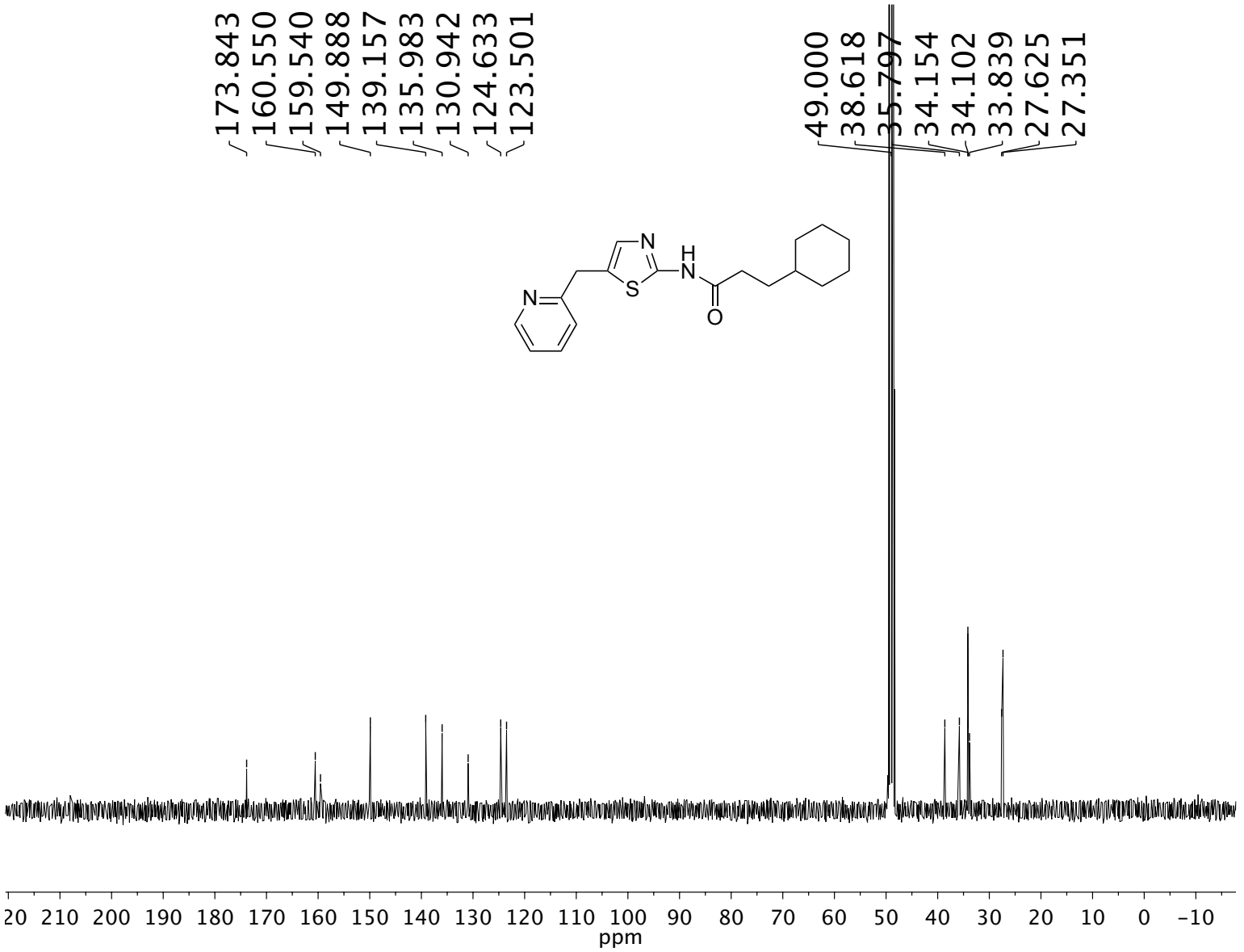
S.6.25.3. *N*-[5-(4-Quinolinylmethyl)thiazol-2-yl]cyclohexanecarboxamide (28b). HR-ESI-MS



S.6.26.1. *N*-[5-(2-Pyridinylmethyl)thiazol-2-yl]-3-cyclohexanepropanamide (29a). ^{1}H NMR (400 MHz, CD_3OD)



S.6.26.2. *N*-[5-(2-Pyridinylmethyl)thiazol-2-yl]-3-cyclohexanepropanamide (29a). ^{13}C NMR (100 MHz, CD_3OD)



S.6.26.3. *N*-[5-(2-Pyridinylmethyl)thiazol-2-yl]-3-cyclohexanepropanamide (29a). HR-ESI-MS

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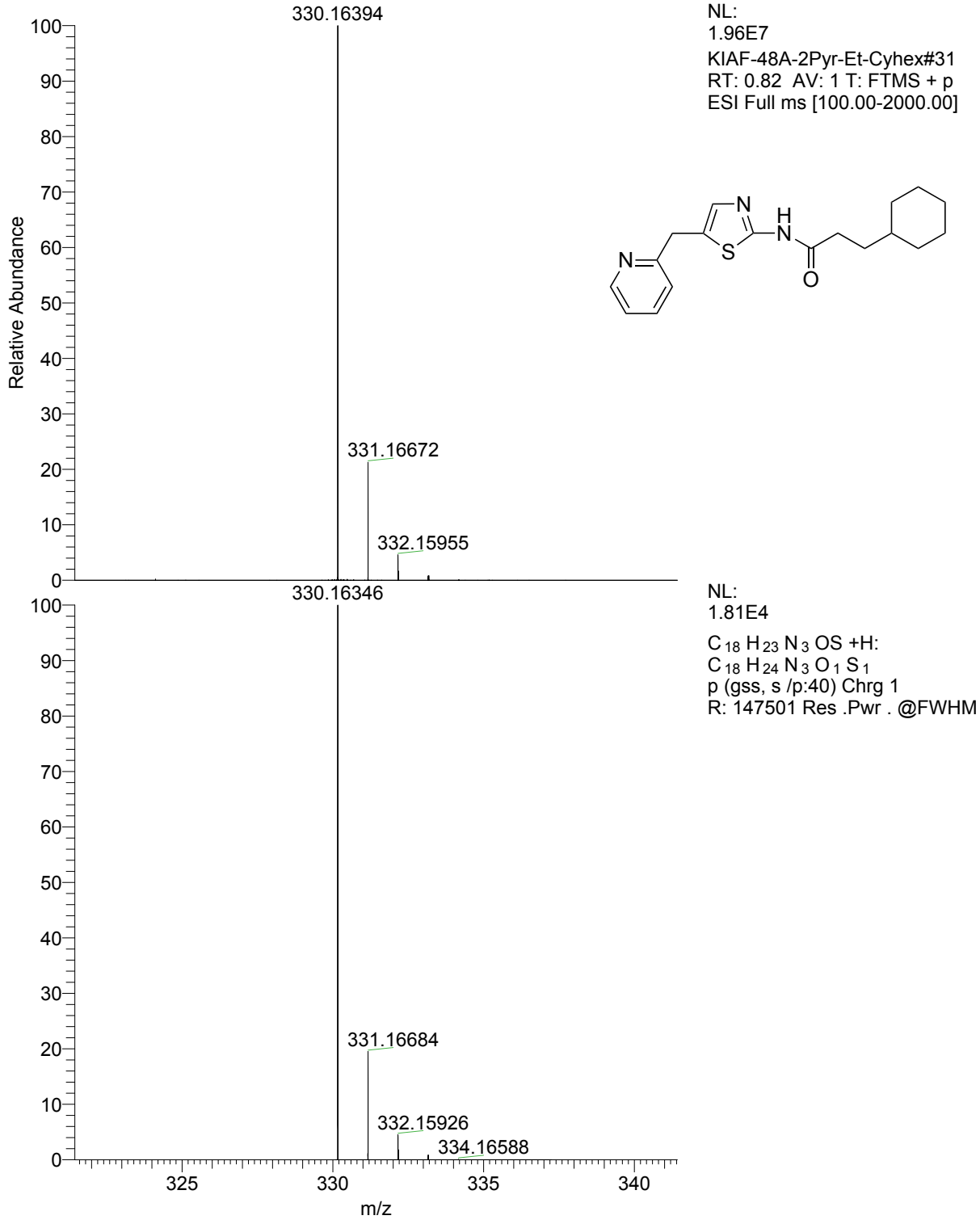
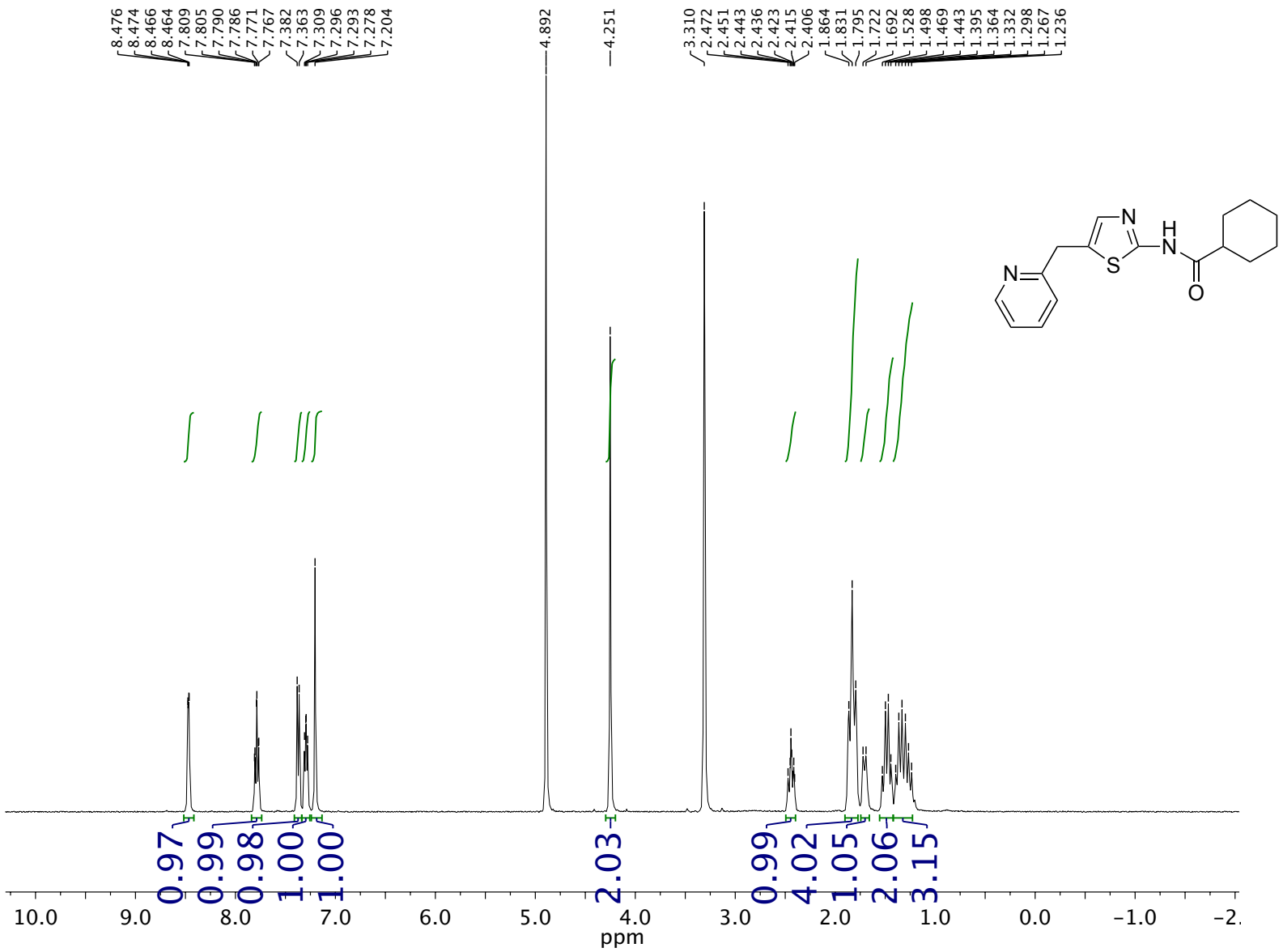
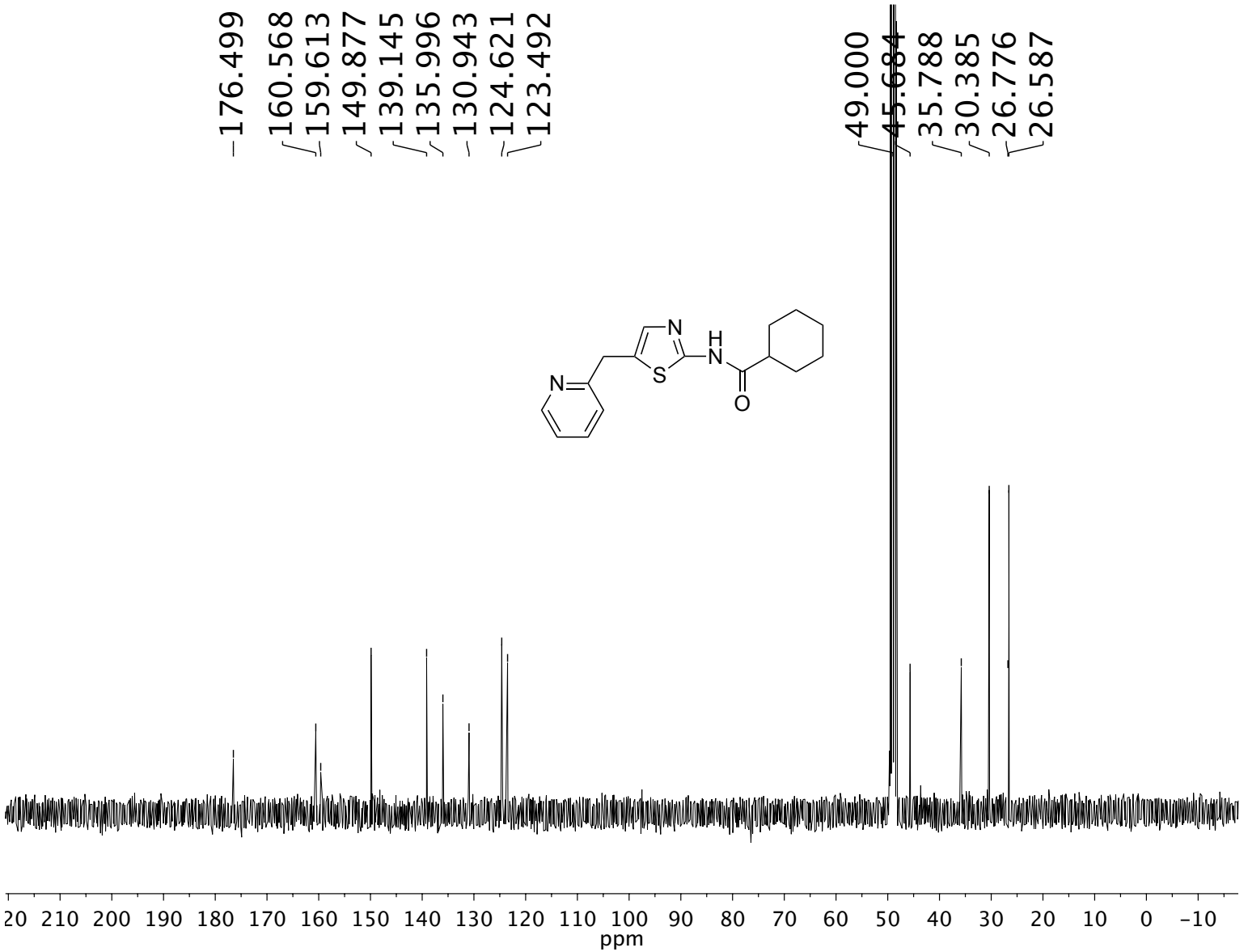


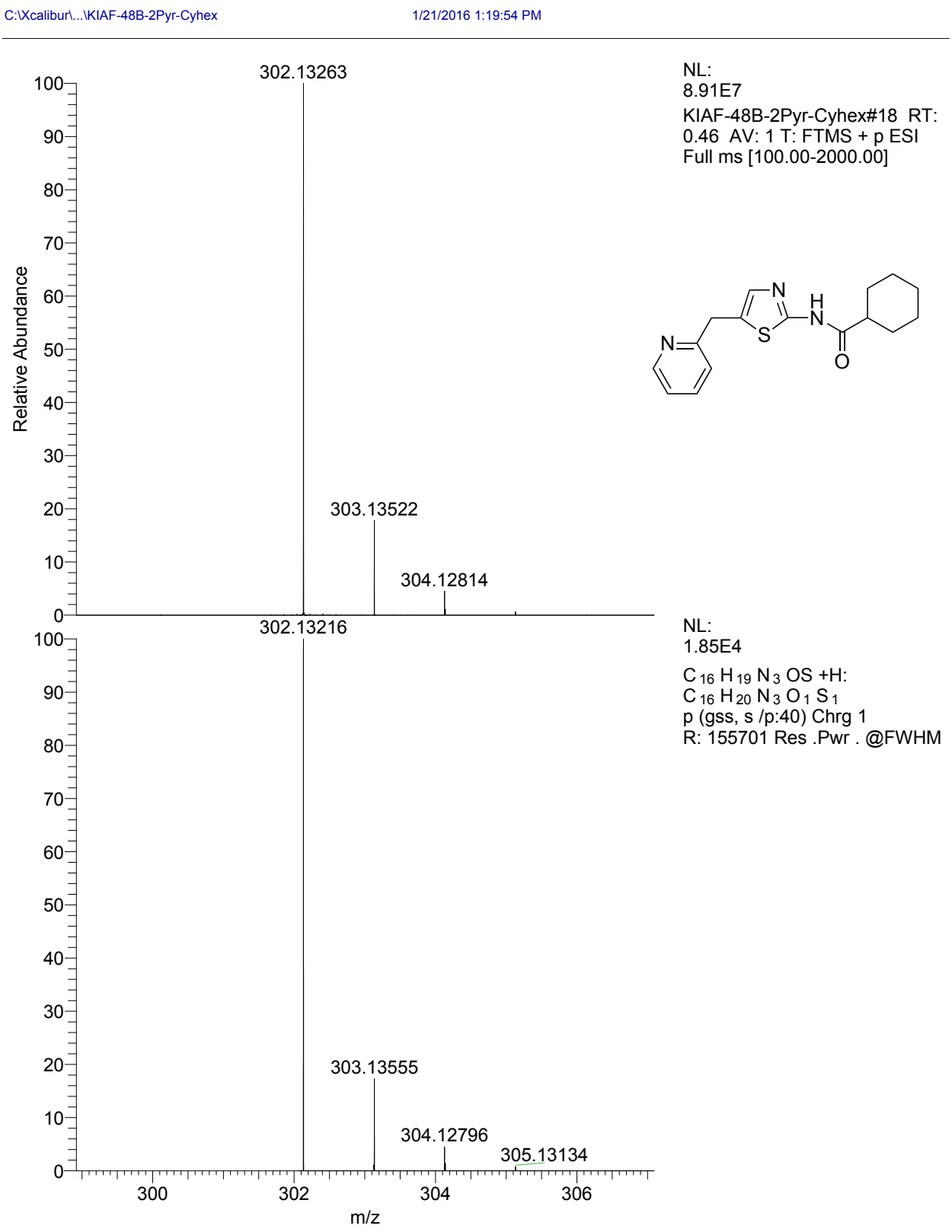
S.6.27.1. *N*-[5-(2-Pyridinylmethyl)thiazol-2-yl]cyclohexanecarboxamide (29b). ^{1}H NMR (400 MHz, CD_3OD)



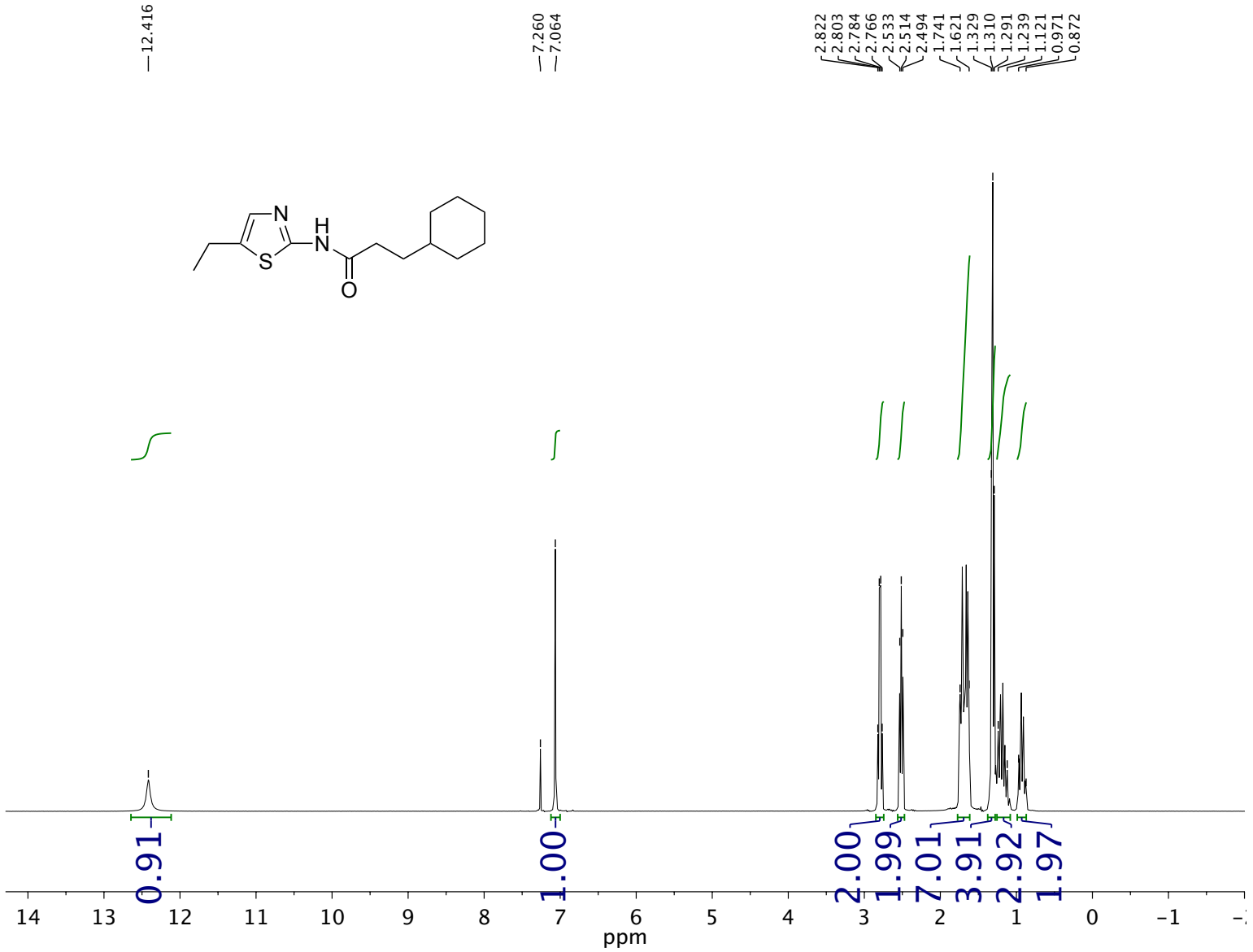
S.6.27.2. *N*-[5-(2-Pyridinylmethyl)thiazol-2-yl]cyclohexanecarboxamide (29b). ^{13}C NMR (100 MHz, CD_3OD)



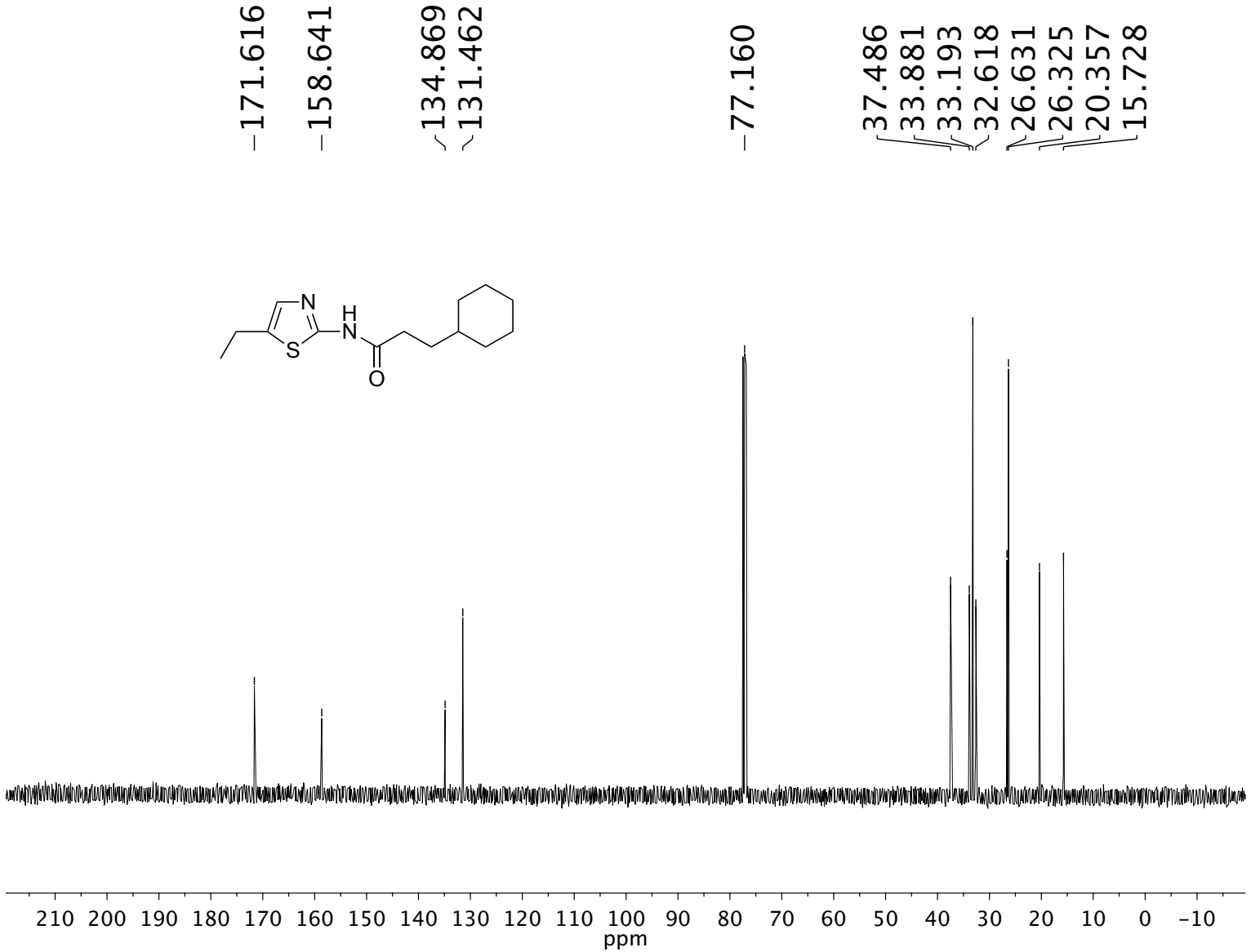
S.6.27.3. *N*-[5-(2-Pyridinylmethyl)thiazol-2-yl]cyclohexanecarboxamide (29b). HR-ESI-MS



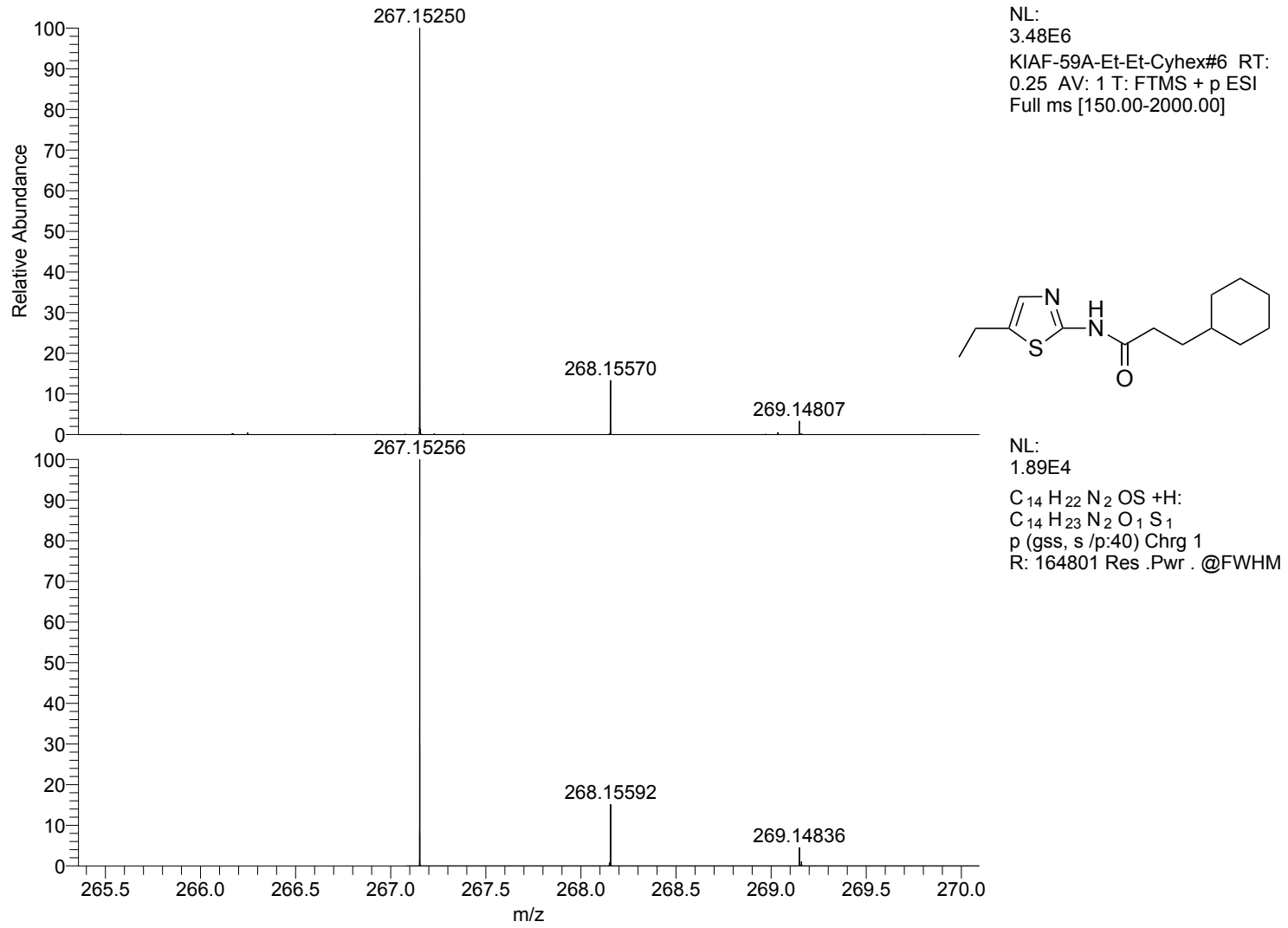
S.6.28.1. *N*-(5-Ethylthiazol-2-yl)-3-cyclohexanepropanamide (30a). ^{1}H NMR (400 MHz, $CDCl_3$)



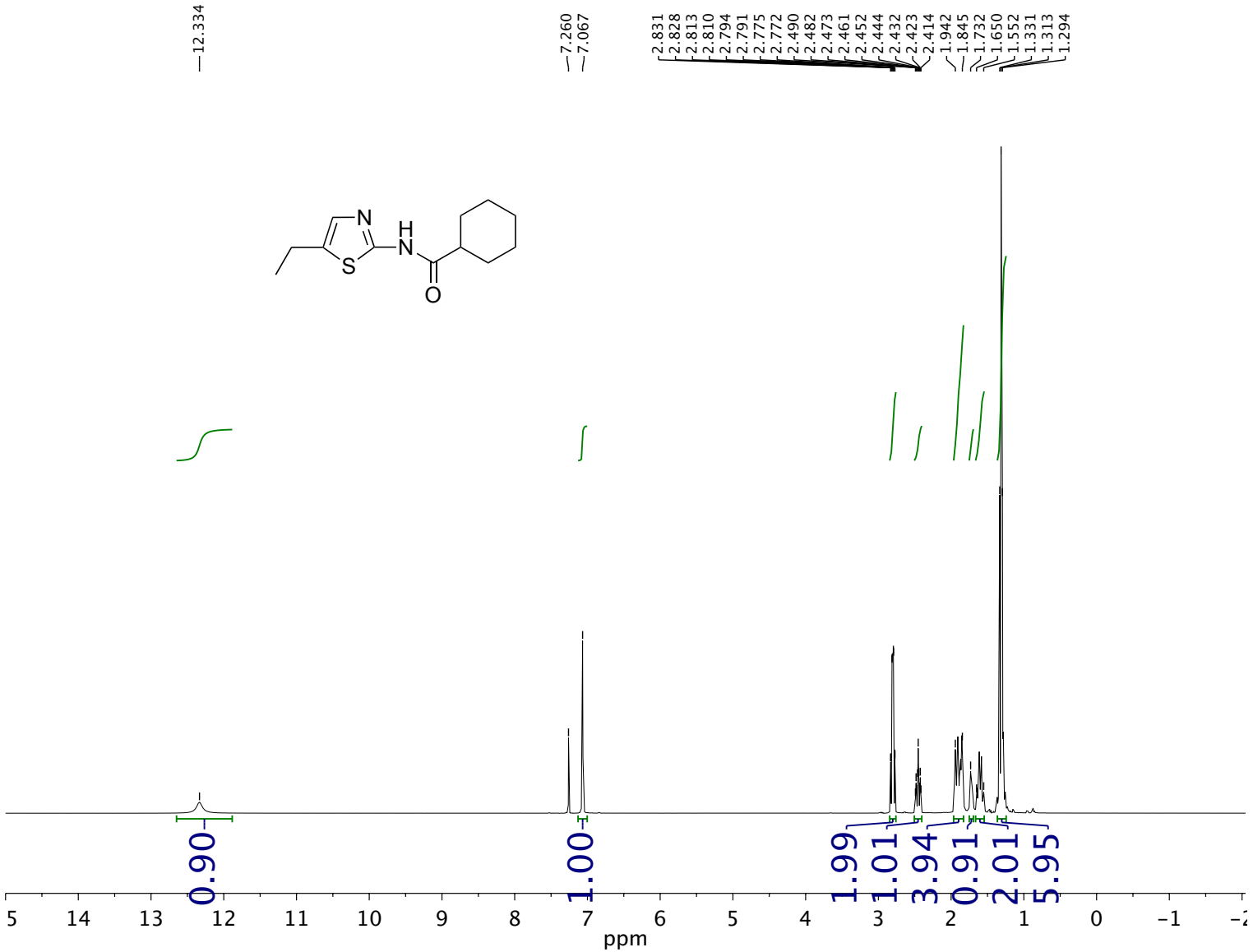
S.6.28.2. *N*-(5-Ethylthiazol-2-yl)-3-cyclohexanepropanamide (30a). ^{13}C NMR (100 MHz, $CDCl_3$)



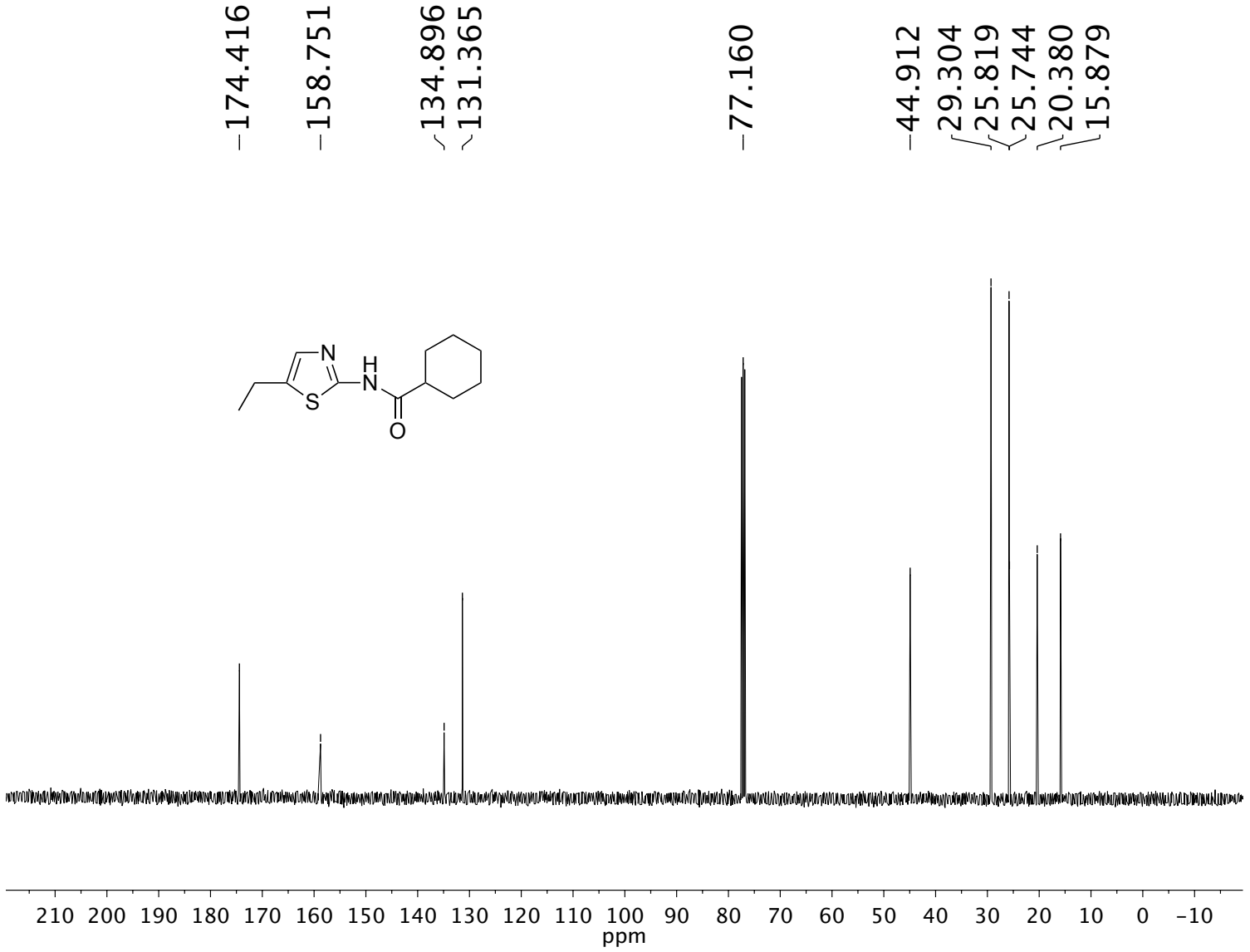
S.6.28.3. *N*-(5-Ethylthiazol-2-yl)-3-cyclohexanepropanamide (30a). HR-ESI-MS



S.6.29.1. *N*-(5-Ethylthiazol-2-yl)cyclohexanecarboxamide (30b). ^{1}H NMR (400 MHz, $CDCl_3$)



S.6.29.2. *N*-(5-Ethylthiazol-2-yl)cyclohexanecarboxamide (30b). ^{13}C NMR (100 MHz, $CDCl_3$)



S.6.29.3. *N*-(5-Ethylthiazol-2-yl)cyclohexanecarboxamide (30b). HR-ESI-MS

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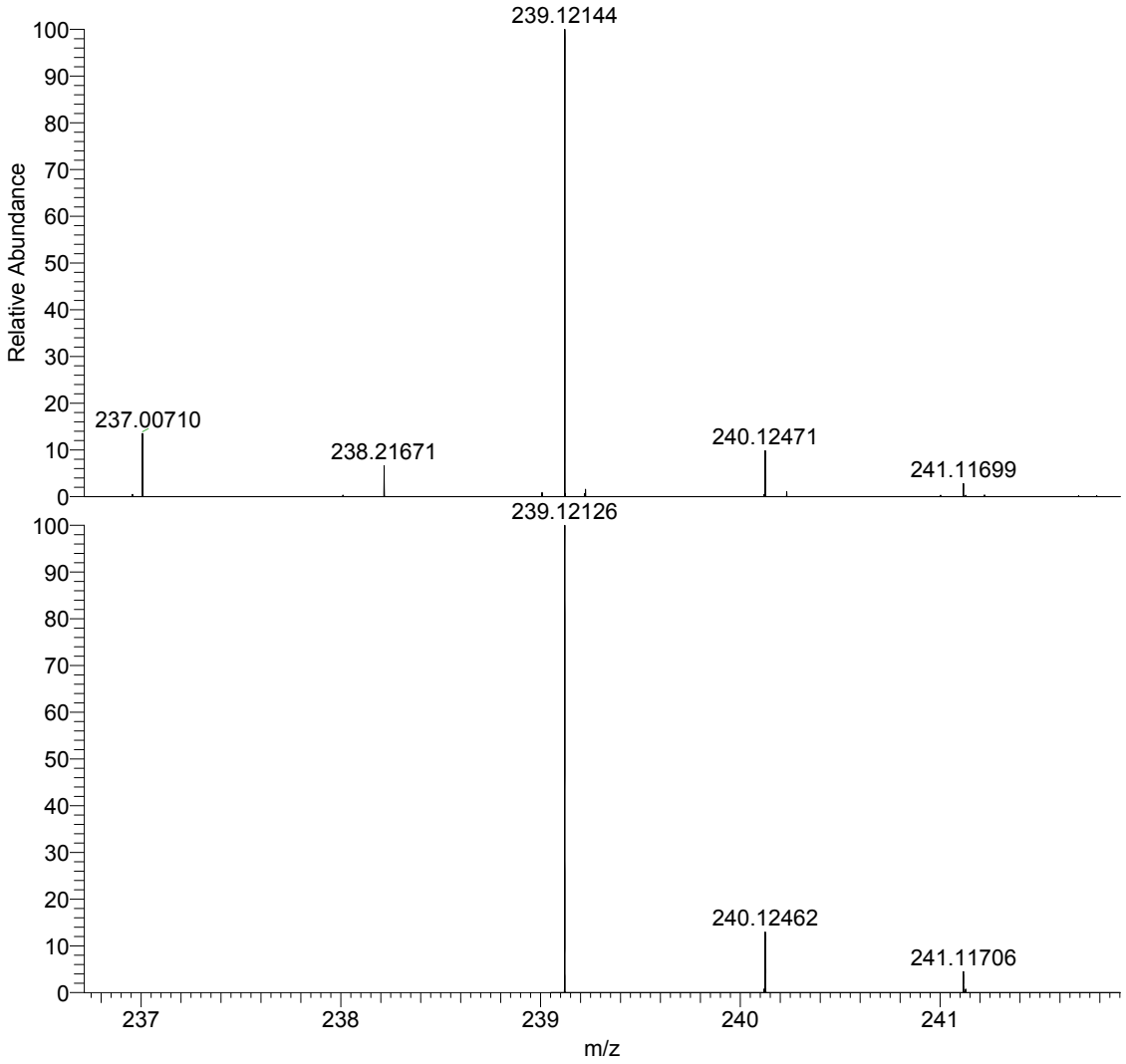

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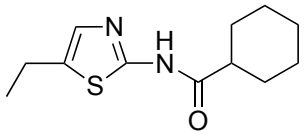
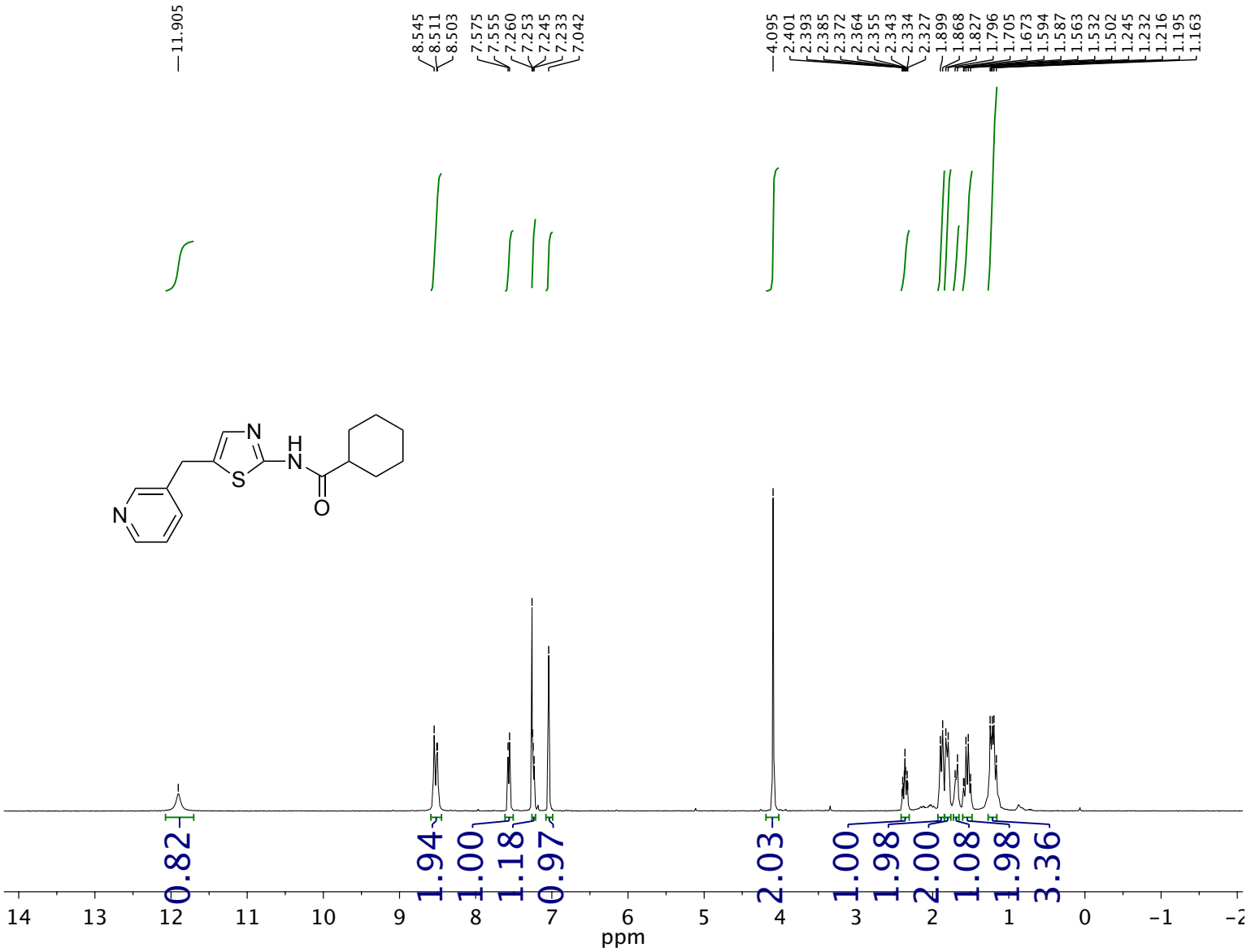
KIAF-59B-Et-Cyhex#7 RT:
0.28 AV: 1 T: FTMS + p ESI
Full ms [150.00-2000.00]

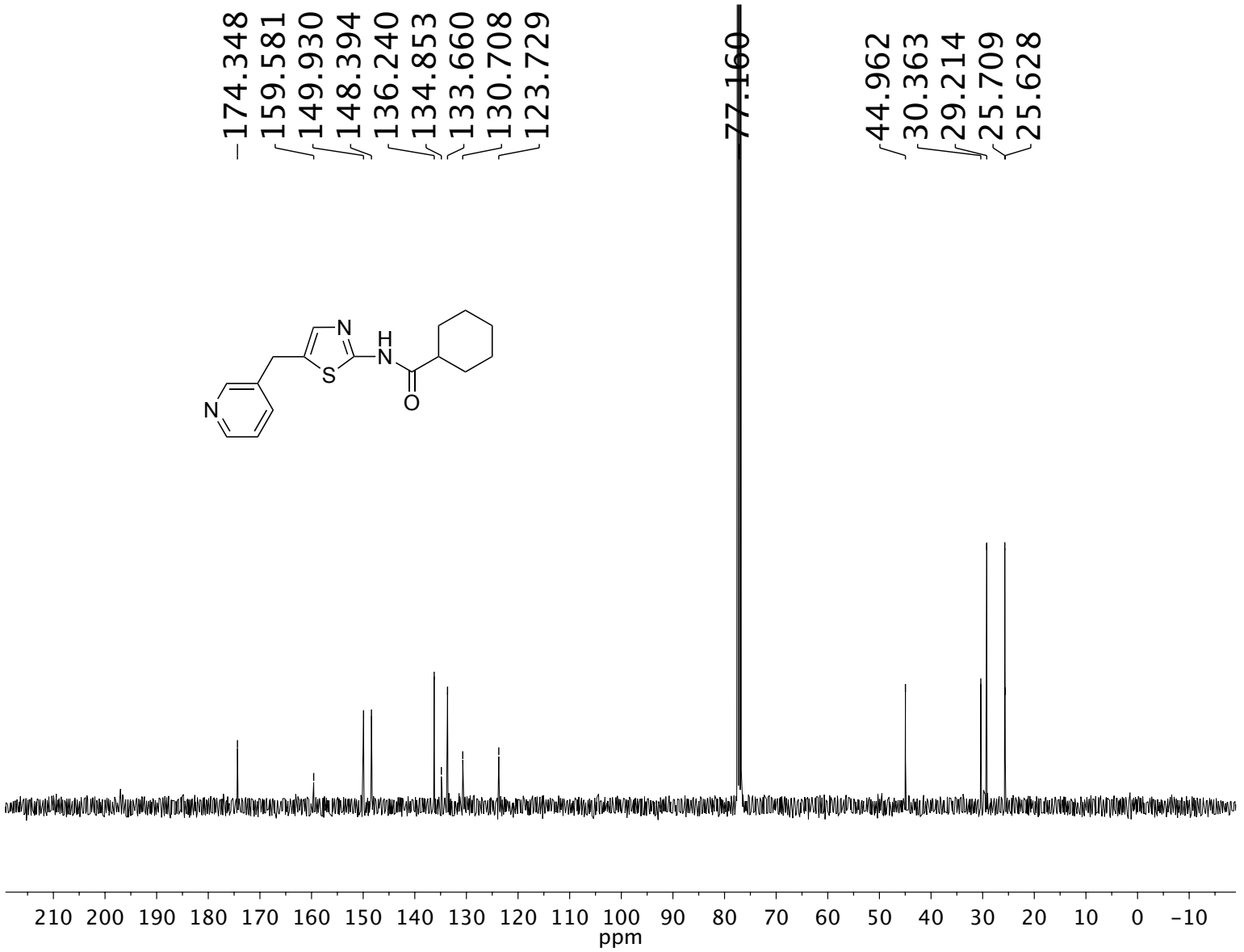


NL:
1.93E4
$C_{12}H_{18}N_2OS$ +H:
$C_{12}H_{19}N_2O_1S_1$
p (gss, s /p:40) Chrg 1
R: 172801 Res .Pwr . @FWHM

S.6.30.1. *N*-[5-(3-Pyridinylmethyl)thiazol-2-yl]cyclohexanecarboxamide (31). ^{1}H NMR (400 MHz, $CDCl_3$)



S.6.30.2. *N*-[5-(3-Pyridinylmethyl)thiazol-2-yl]cyclohexanecarboxamide (31). ^{13}C NMR (100 MHz, $CDCl_3$)



S.6.30.3. *N*-[5-(3-Pyridinylmethyl)thiazol-2-yl]cyclohexanecarboxamide (31). HR-ESI-MS

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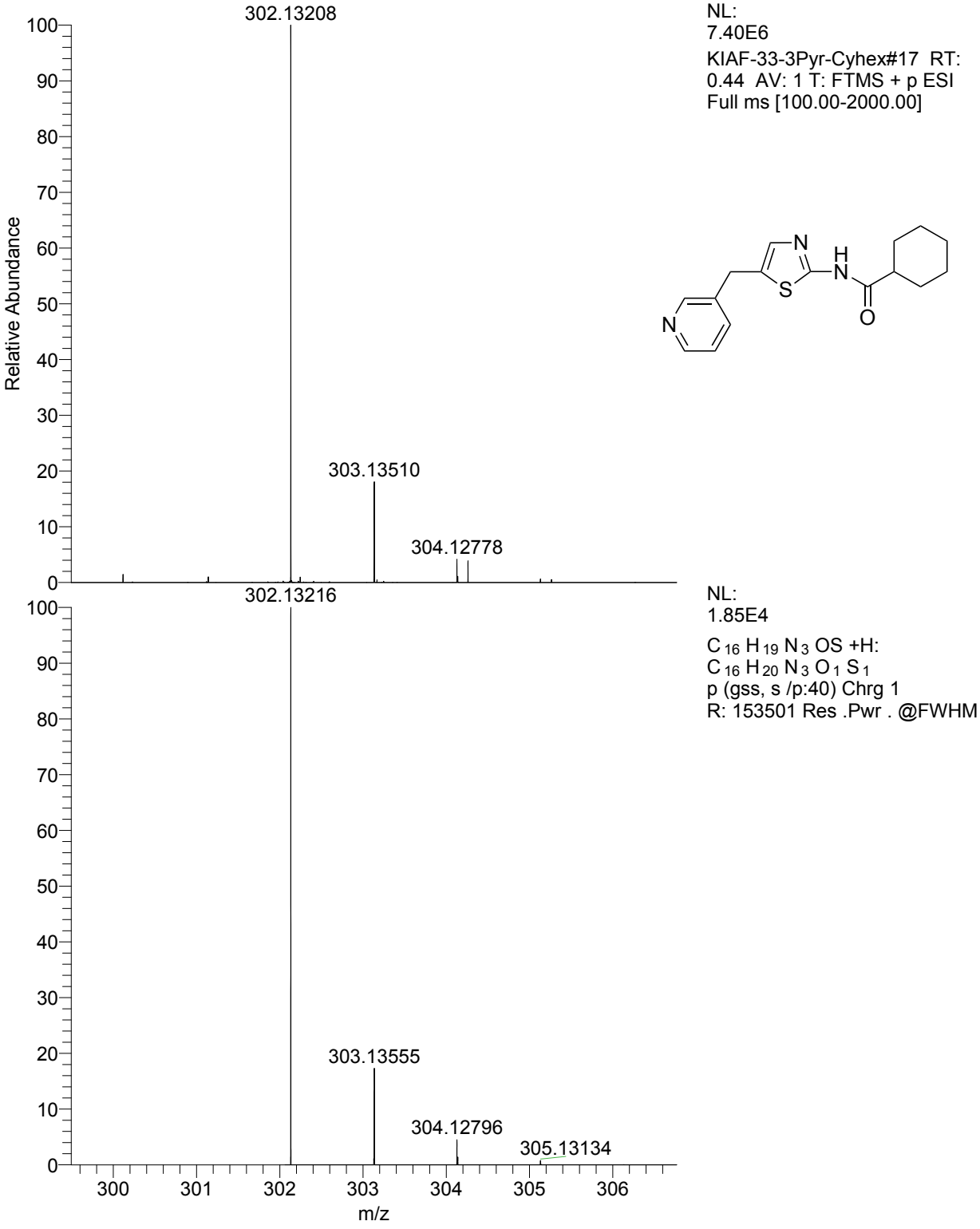
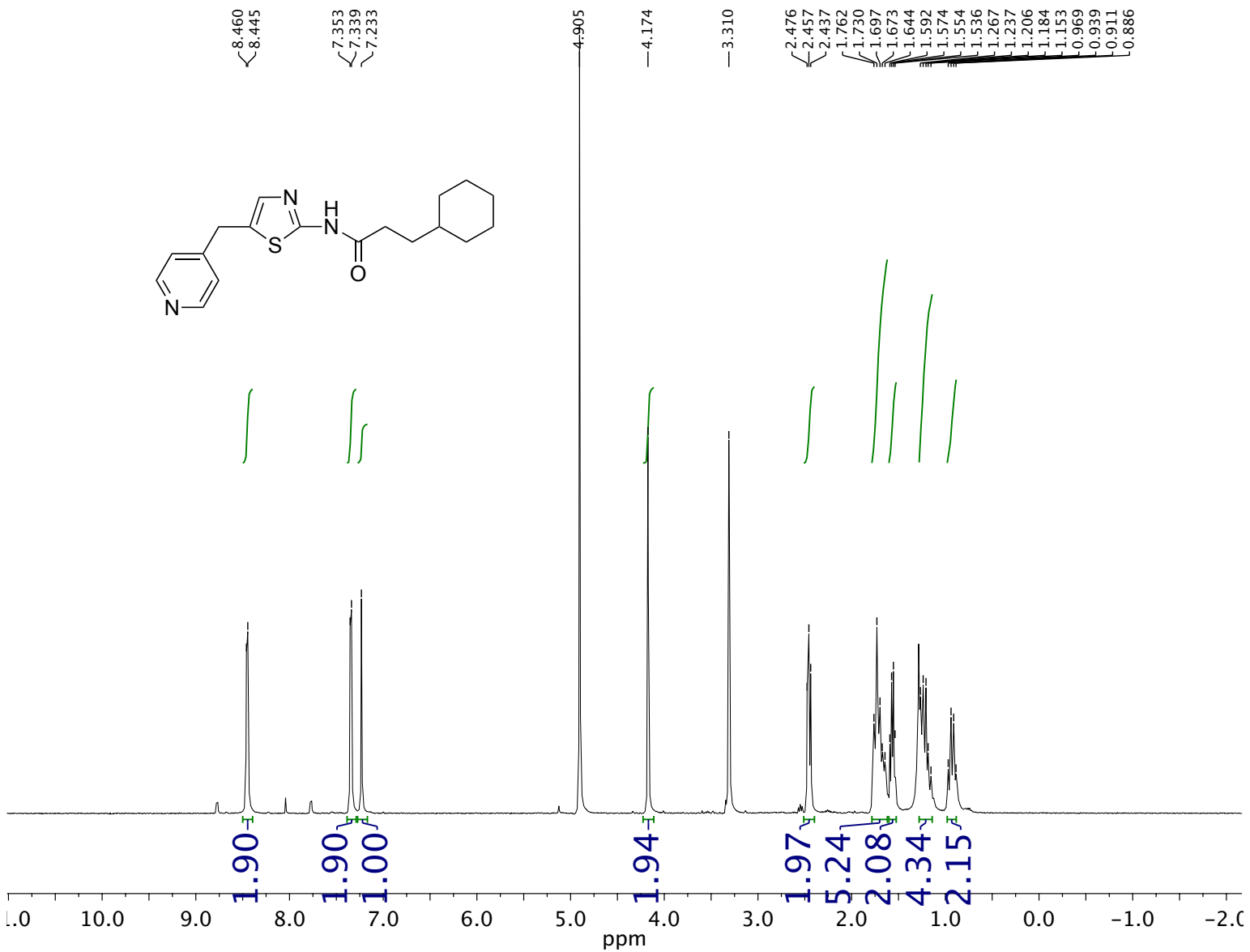
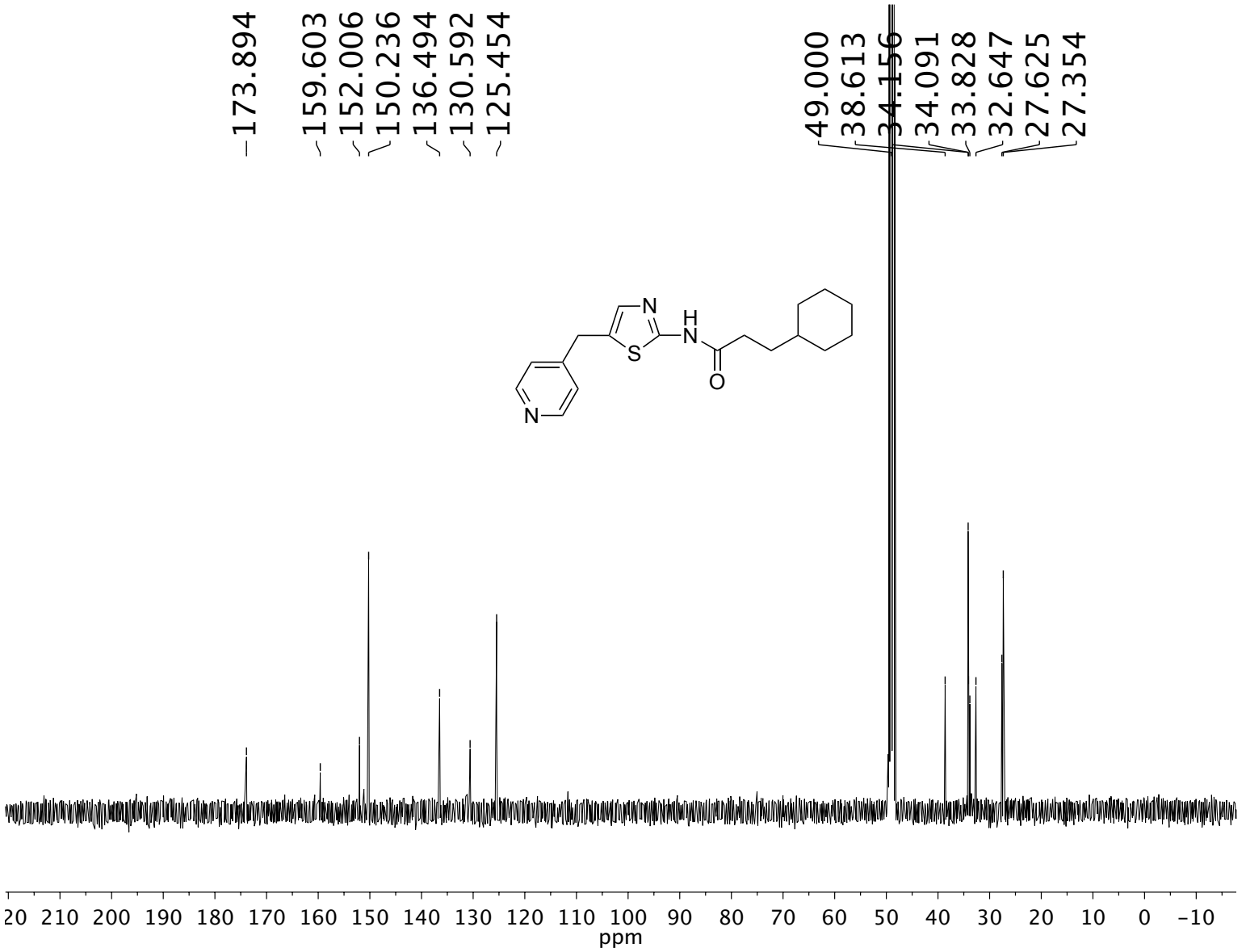


S.6.31.1. *N*-[5-(4-Pyridinylmethyl)thiazol-2-yl]-3-cyclohexanepropanamide (32a). ^{1}H NMR (400 MHz, CD_3OD)

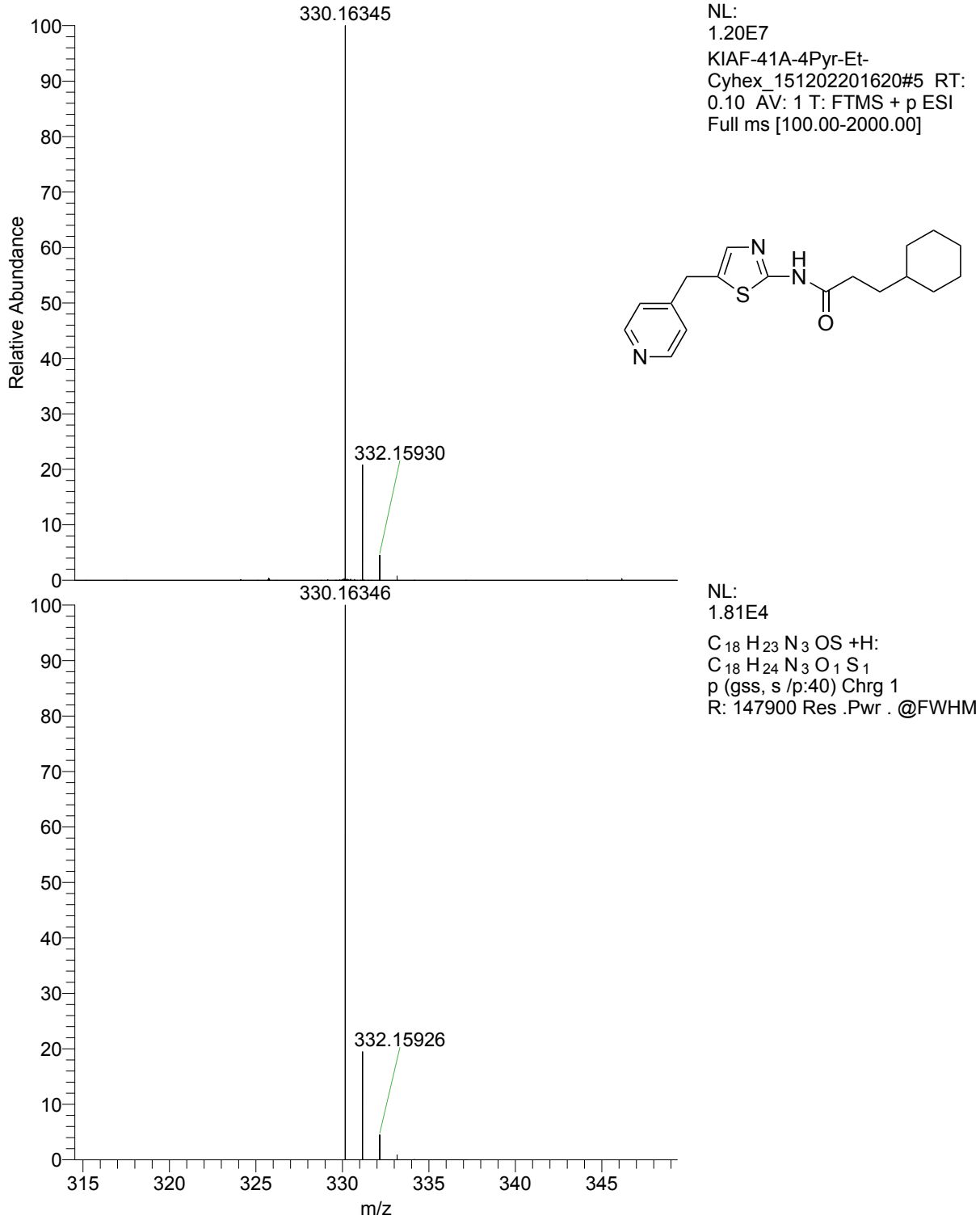


S.6.31.2. *N*-[5-(4-Pyridinylmethyl)thiazol-2-yl]-3-cyclohexanepropanamide (32a). ^{13}C NMR (100 MHz, CD_3OD)

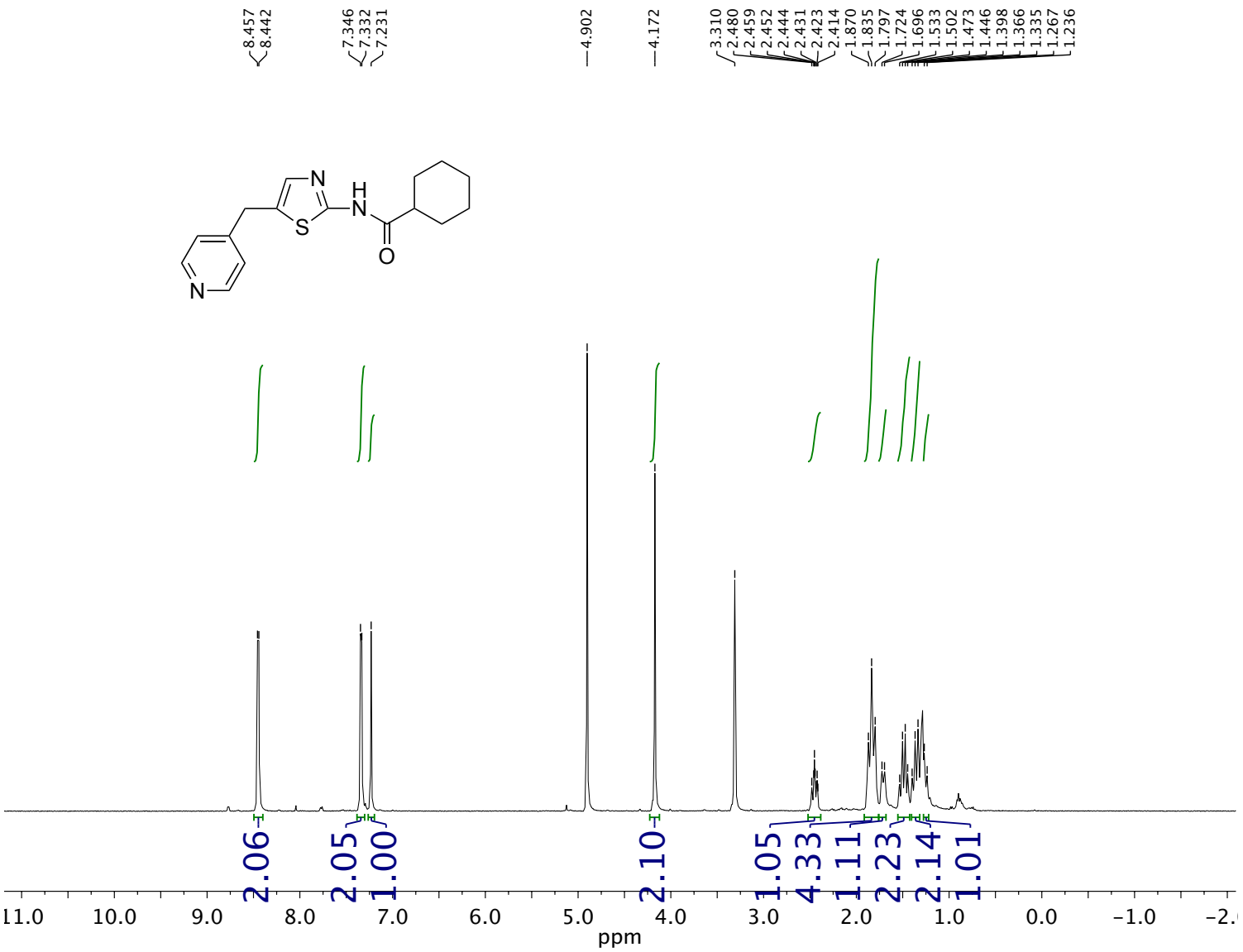


S.6.31.3. *N*-[5-(4-Pyridinylmethyl)thiazol-2-yl]-3-cyclohexanepropanamide (32a). HR-ESI-MS

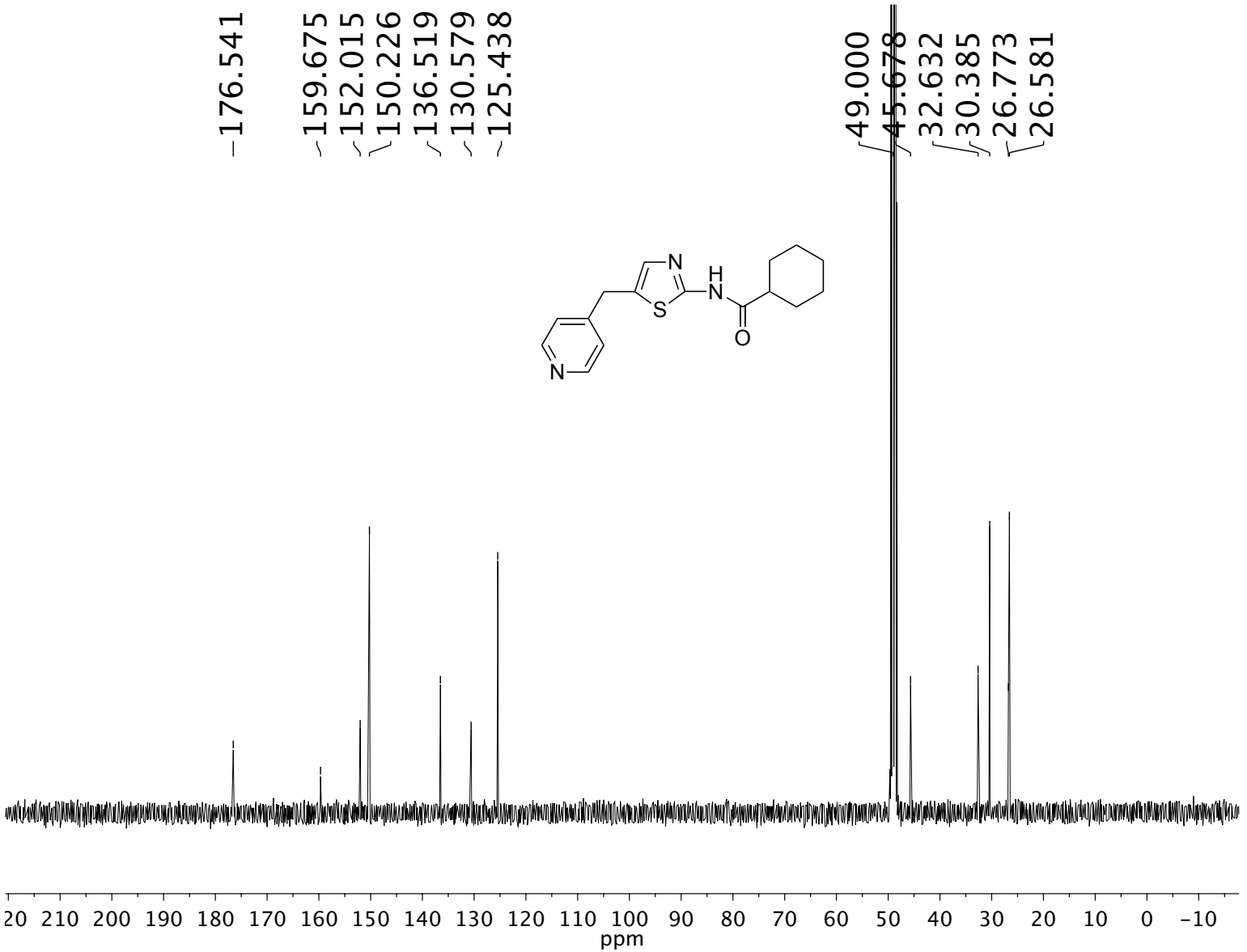
KIAF-41A-4Pyr-Et-Cyhex_151202201620 12/2/2015 8:16:20 PM



S.6.32.1. *N*-[5-(4-Pyridinylmethyl)thiazol-2-yl]cyclohexanecarboxamide (32b). ^{1}H NMR (400 MHz, CD_3OD)



S.6.32.2. *N*-[5-(4-Pyridinylmethyl)thiazol-2-yl]cyclohexanecarboxamide (32b). ^{13}C NMR (100 MHz, CD_3OD)



S.6.32.3. *N*-[5-(4-Pyridinylmethyl)thiazol-2-yl]cyclohexanecarboxamide (32b). HR-ESI-MS

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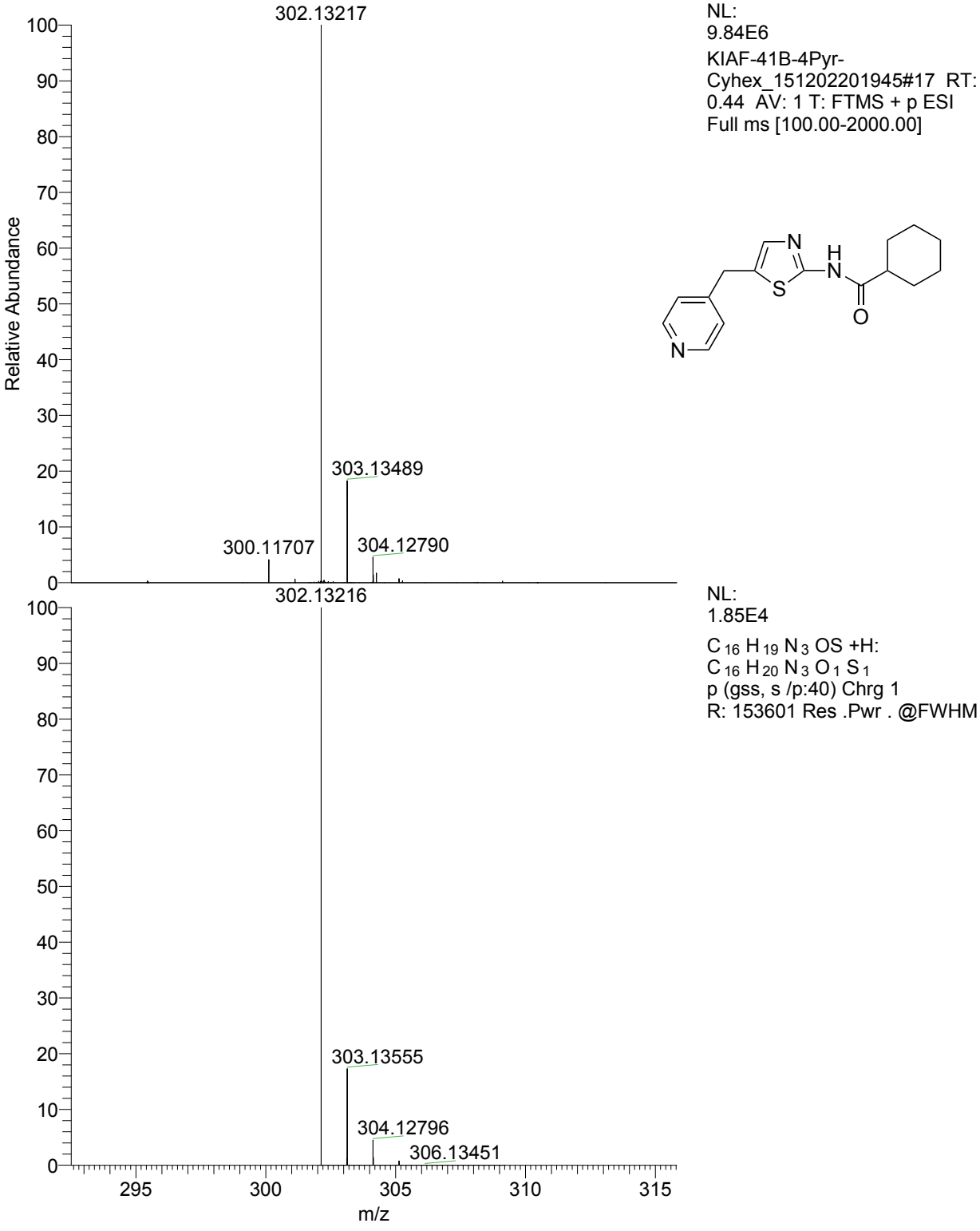
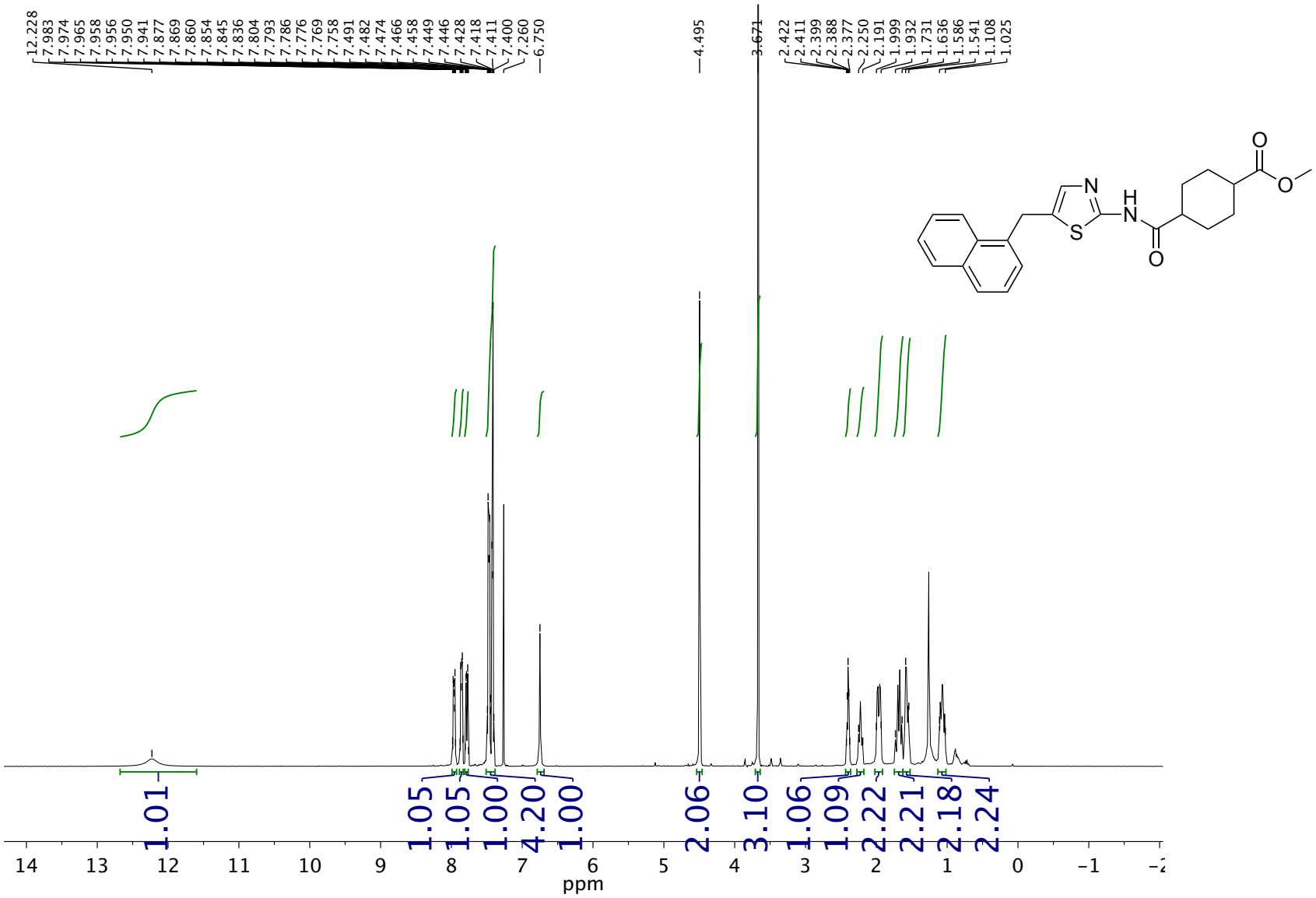
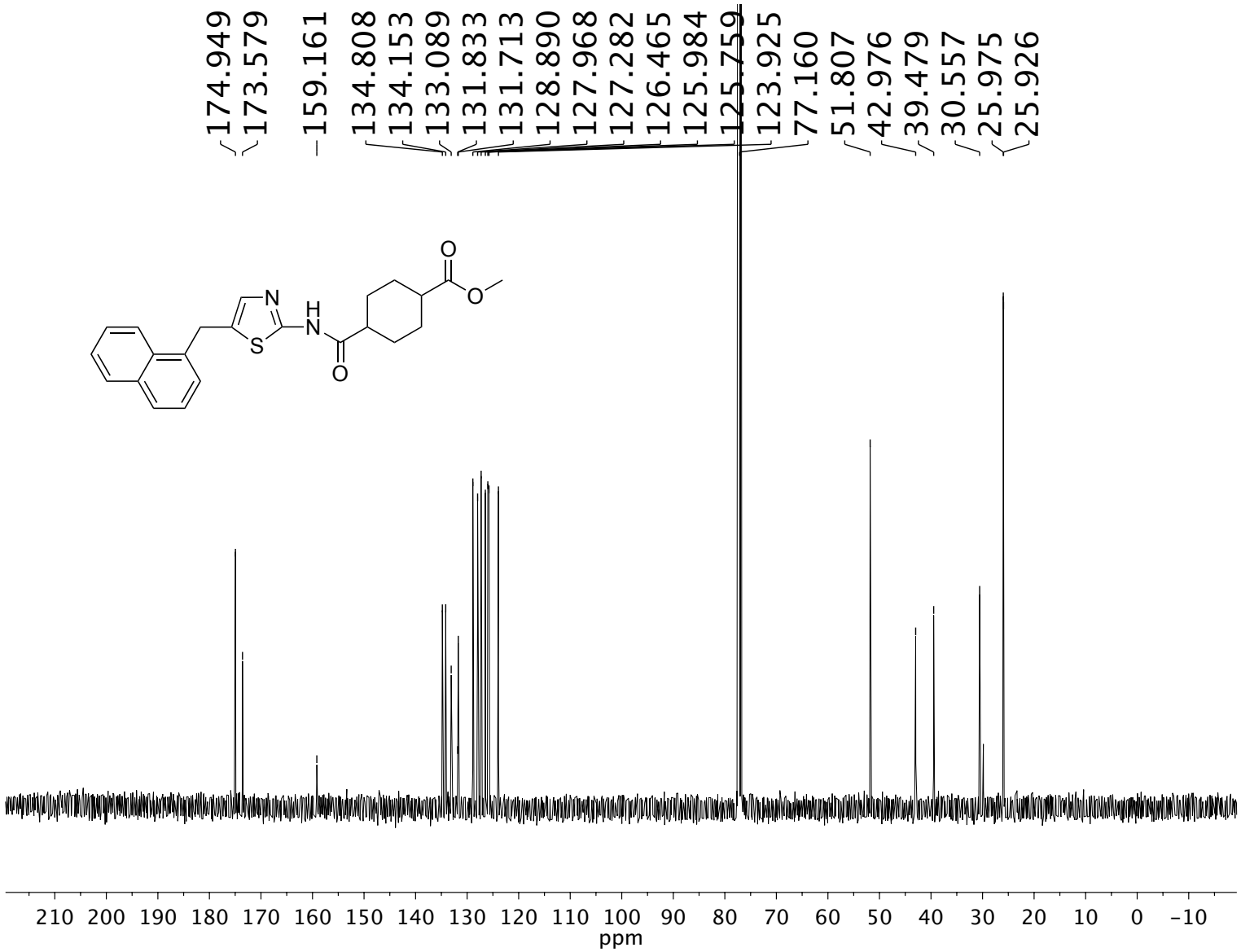


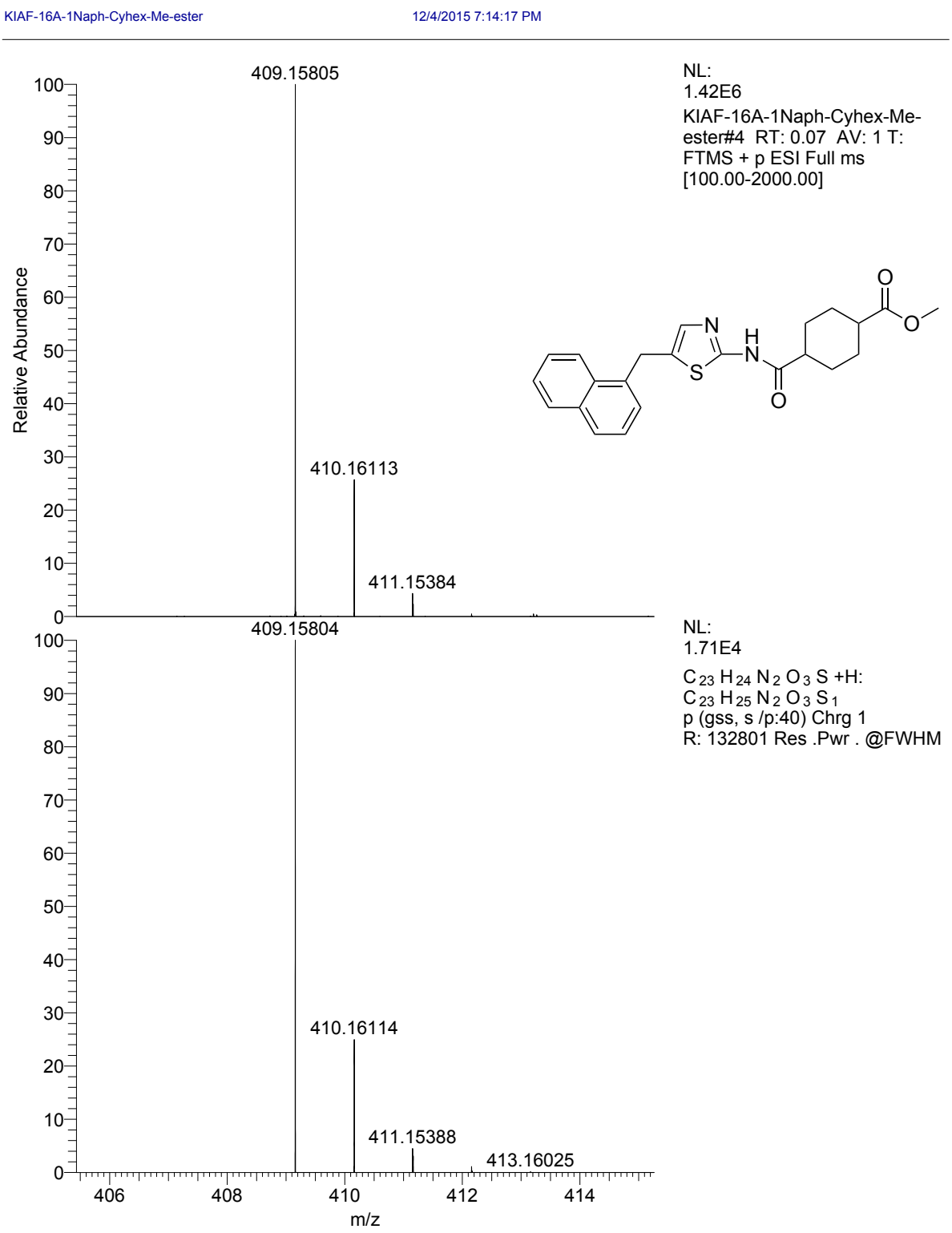
S.6.33.1. *N*-[5-(1-Naphthalenylmethyl)thiazol-2-yl]-4-(methoxycarbonyl)cyclohexanecarboxamide (33a). ^{1}H NMR (400 MHz, $CDCl_3$)



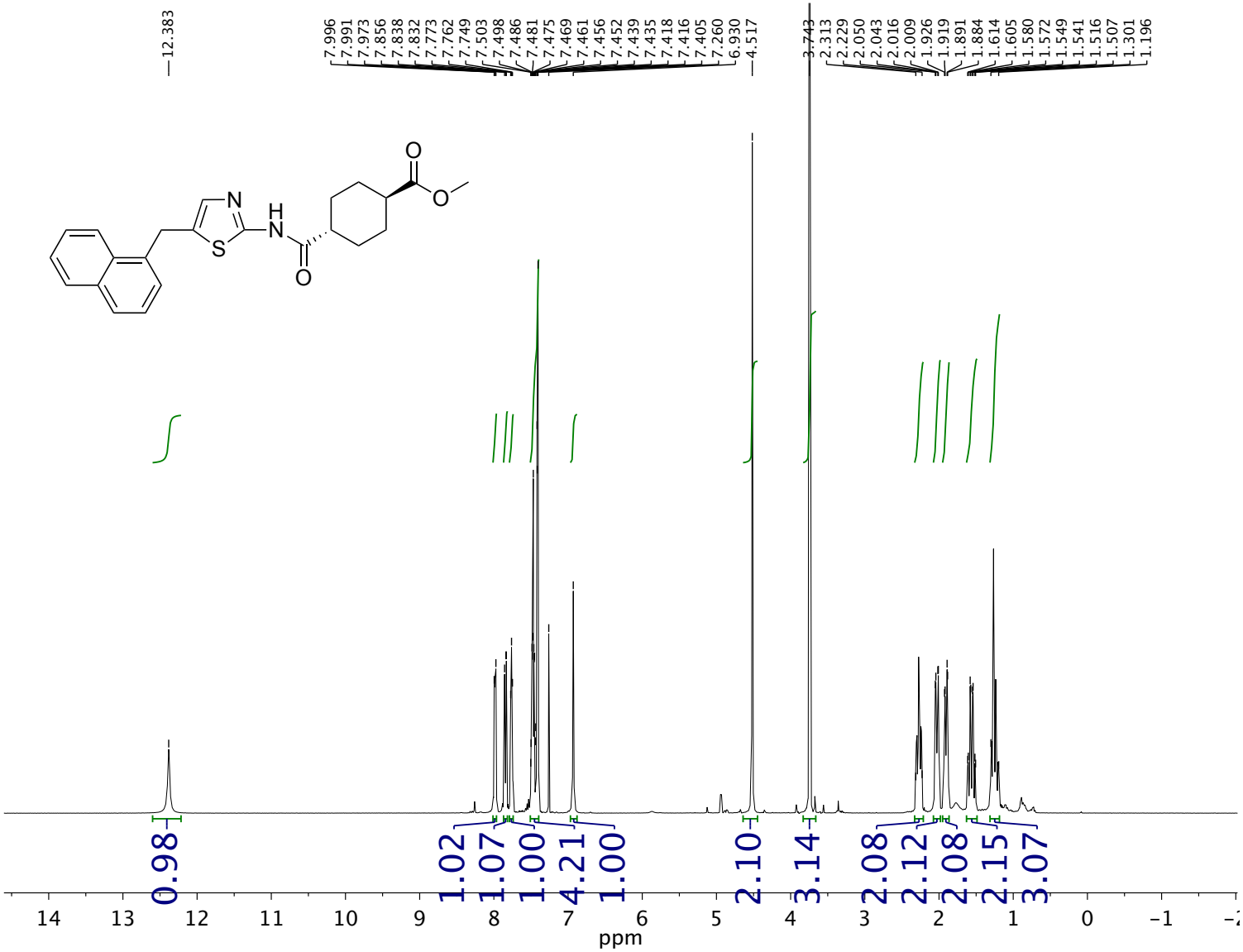
S.6.33.2. *N*-[5-(1-Naphthalenylmethyl)thiazol-2-yl]-4-(methoxycarbonyl)cyclohexanecarboxamide (33a). ^{13}C NMR (100 MHz, $CDCl_3$)



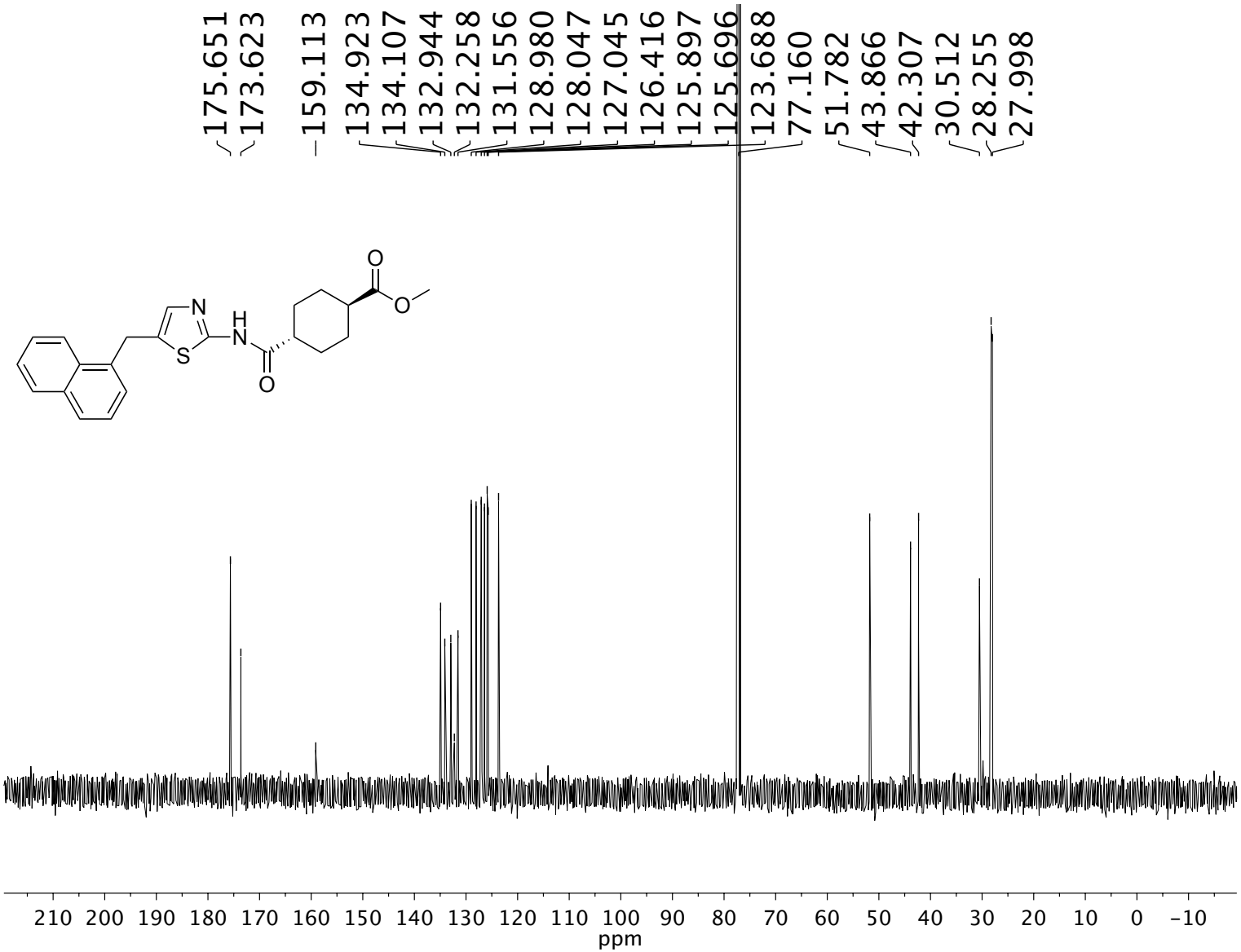
S.6.33.3. *N*-[5-(1-Naphthalenylmethyl)thiazol-2-yl]-4-(methoxycarbonyl)cyclohexanecarboxamide (33a). HR-ESI-MS



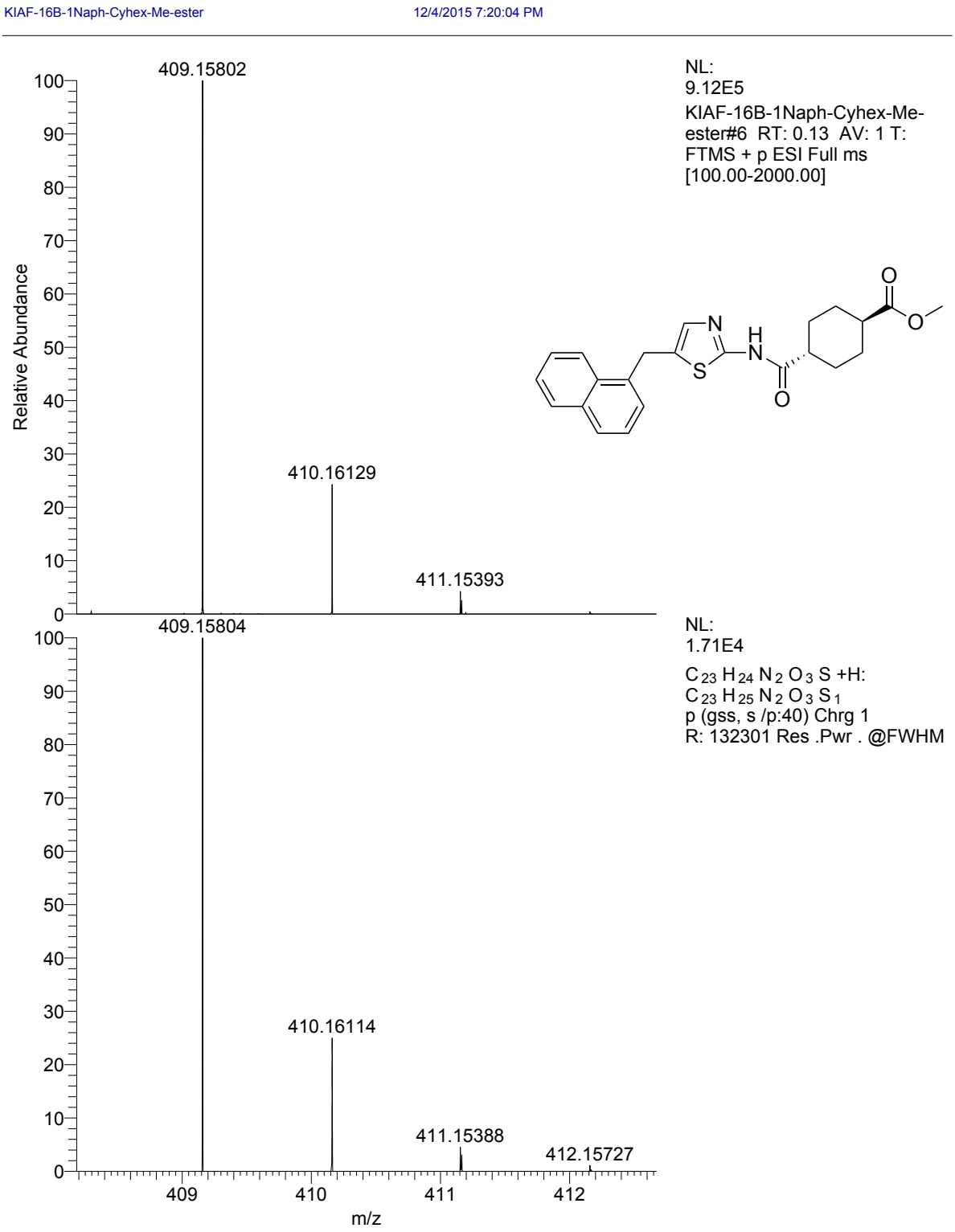
S.6.34.1. *N*-[5-(1-Naphthalenylmethyl)thiazol-2-yl]-*trans*-4-(methoxycarbonyl)cyclohexanecarboxamide (33b). ^{1}H NMR (400 MHz, $CDCl_3$)



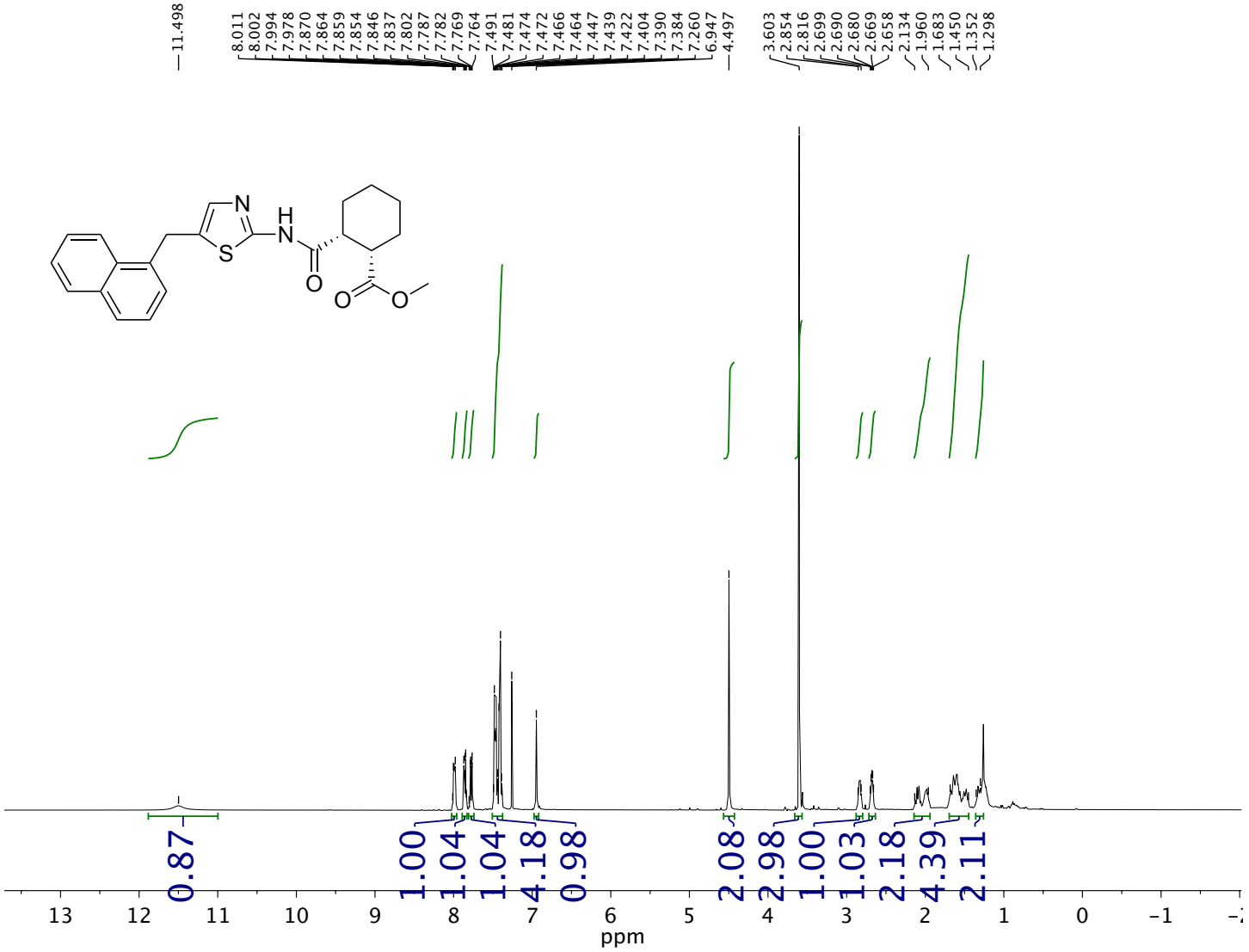
S.6.34.2. *N*-[5-(1-Naphthalenylmethyl)thiazol-2-yl]-*trans*-4-(methoxycarbonyl)cyclohexanecarboxamide (33b). ^{13}C NMR (100 MHz, $CDCl_3$)



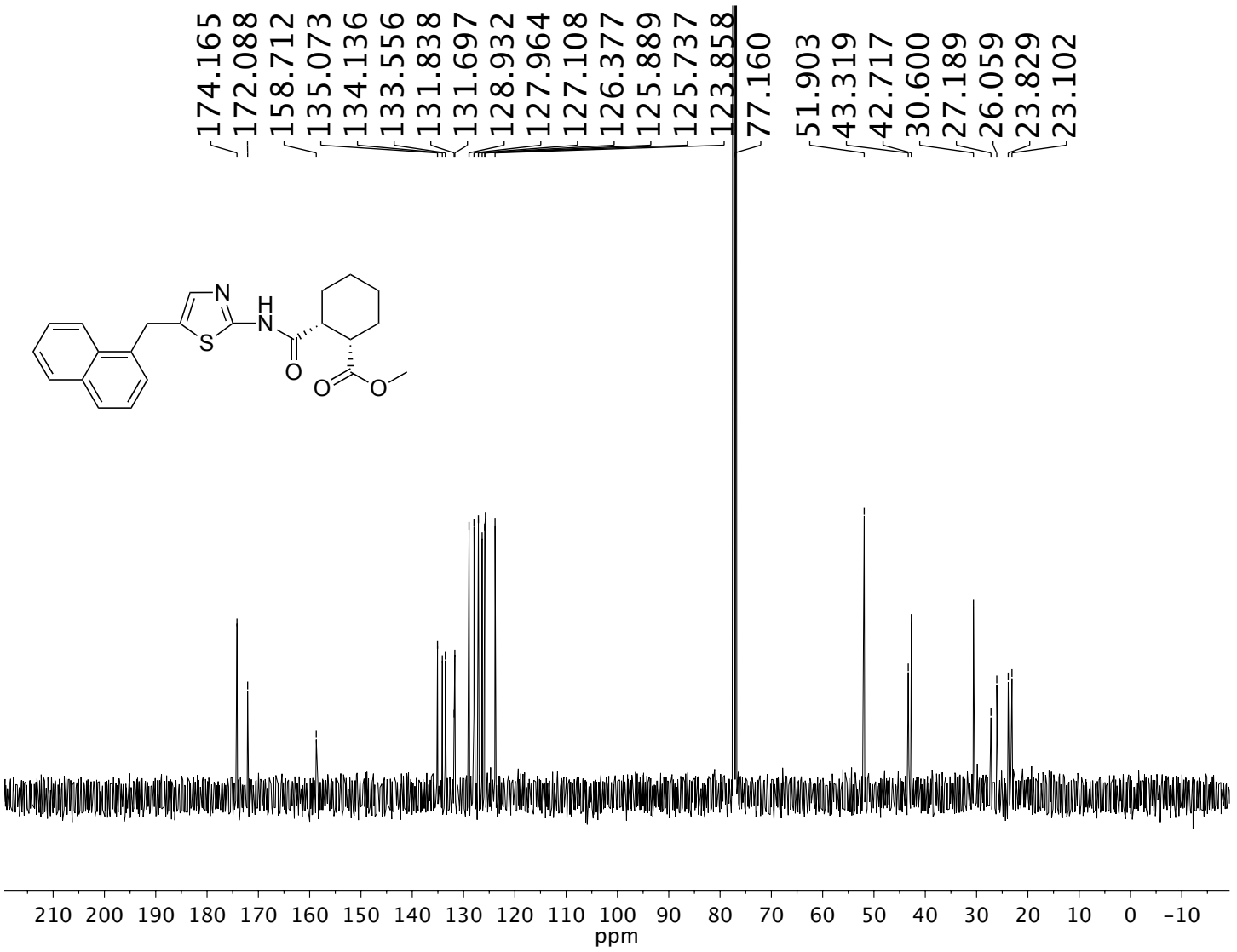
S.6.34.3.*N*-[5-(1-Naphthalenylmethyl)thiazol-2-yl]-*trans*-4-(methoxycarbonyl)cyclohexanecarboxamide (33b). HR-ESI-MS



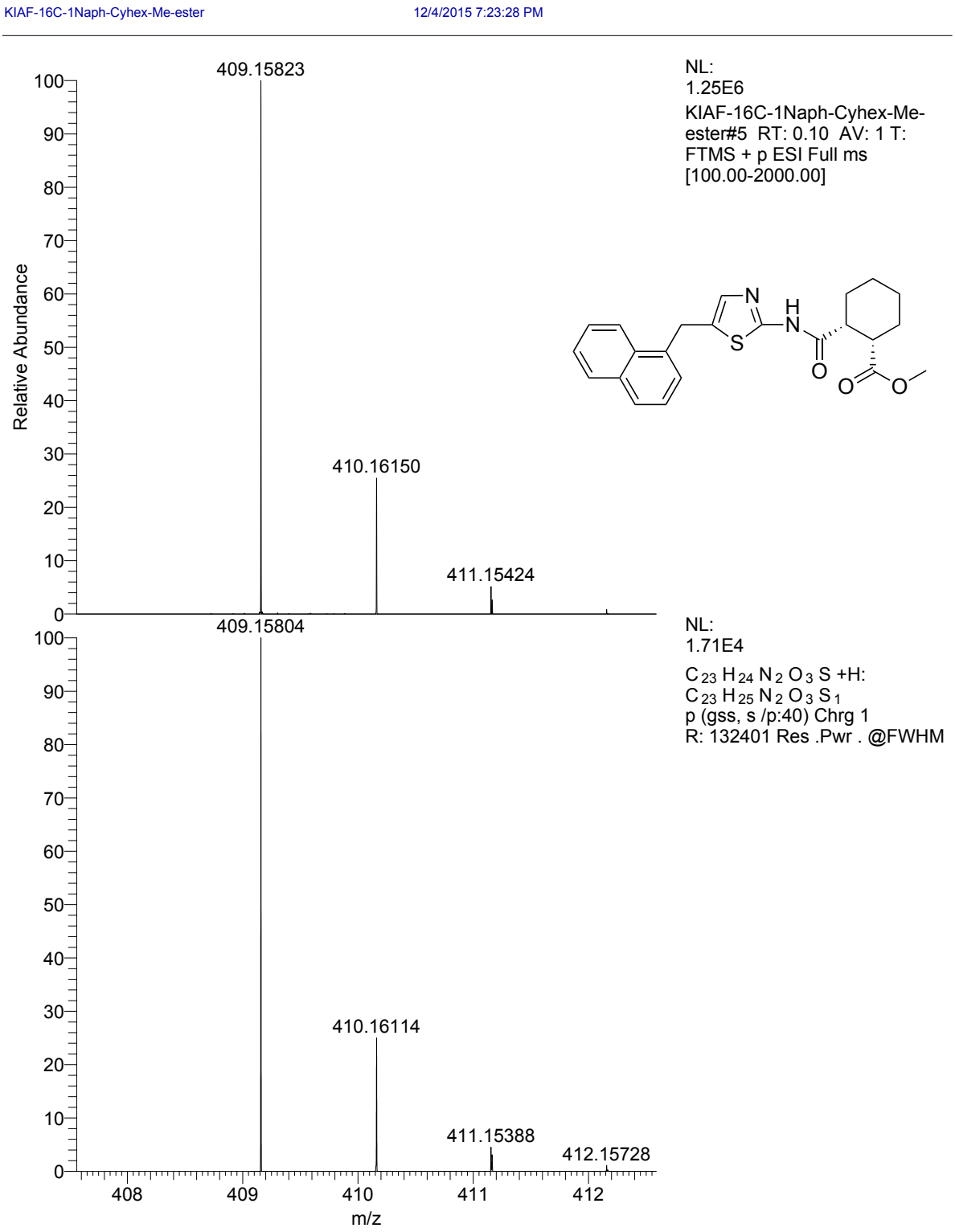
S.6.35.1. *N*-[5-(1-Naphthalenylmethyl)thiazol-2-yl]-(1R,2S)-2-(methoxycarbonyl)cyclohexanecarboxamide (33c). ^{1}H NMR (400 MHz, $CDCl_3$)



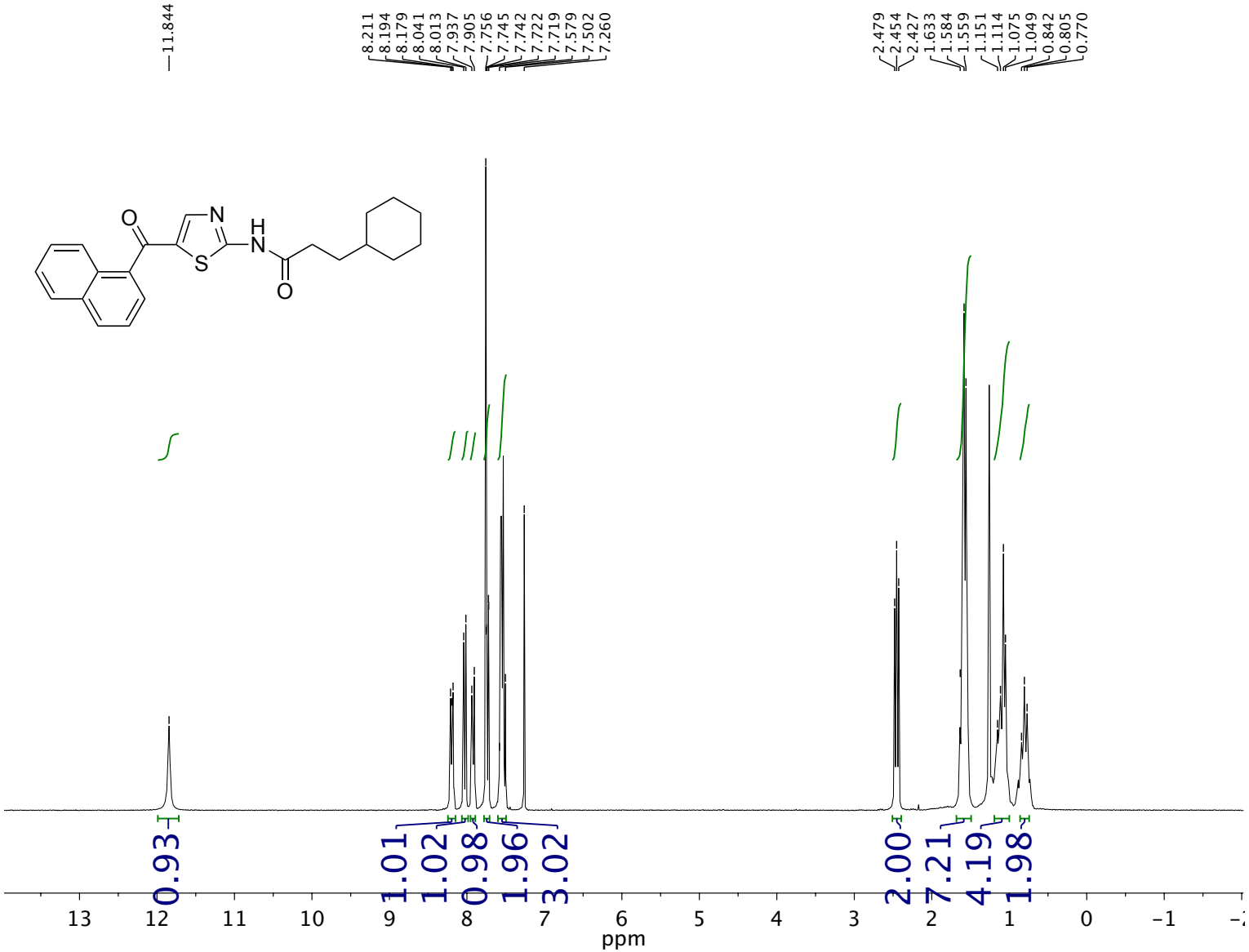
S.6.35.2. *N*-[5-(1-Naphthalenylmethyl)thiazol-2-yl]-(1R,2S)-2-(methoxycarbonyl)cyclohexanecarboxamide (33c). ^{13}C NMR (100 MHz, $CDCl_3$)



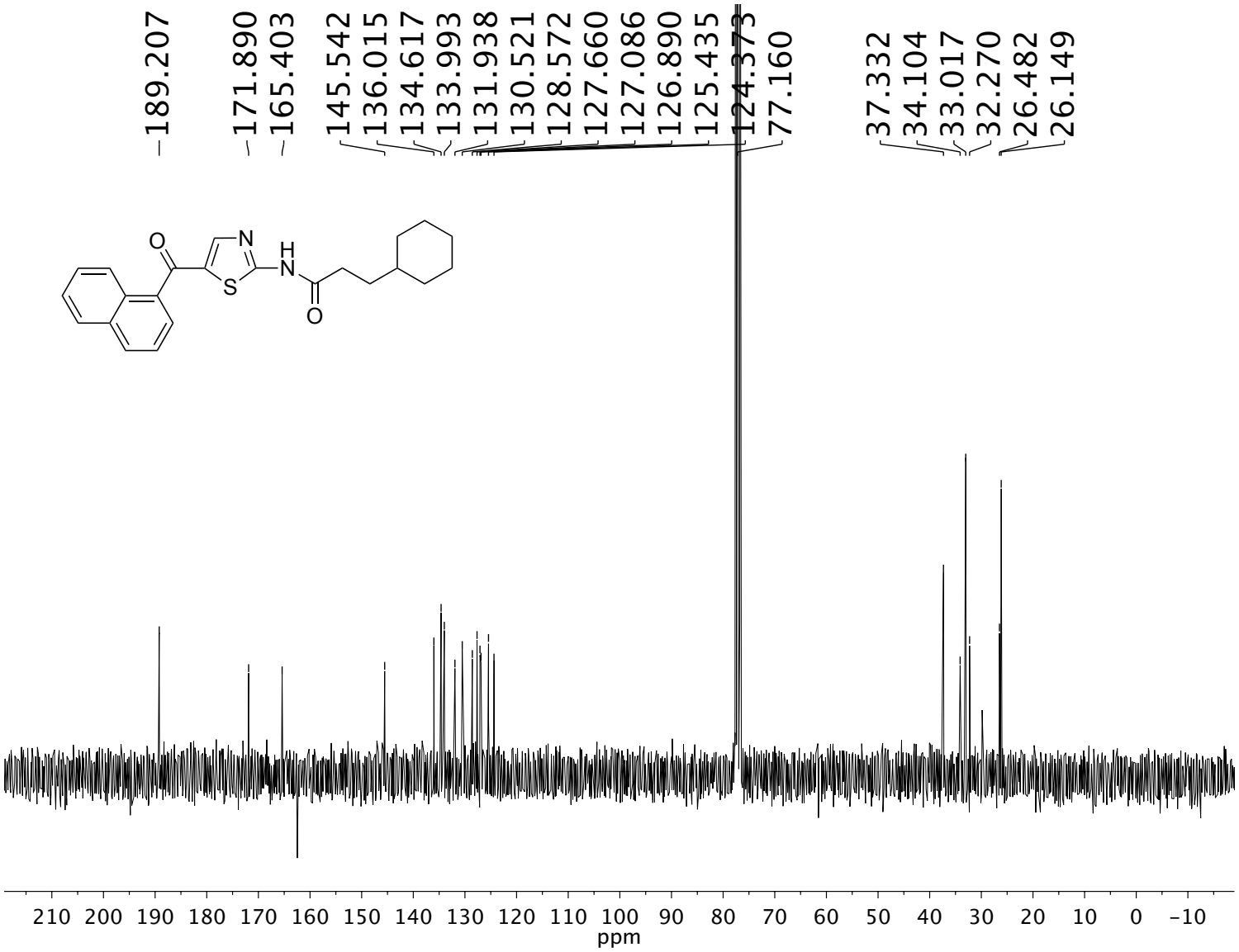
S.6.35.3.*N*-[5-(1-Naphthalenylmethyl)thiazol-2-yl]-(1R,2S)-2-(methoxycarbonyl)cyclohexanecarboxamide (33c). HR-ESI-MS



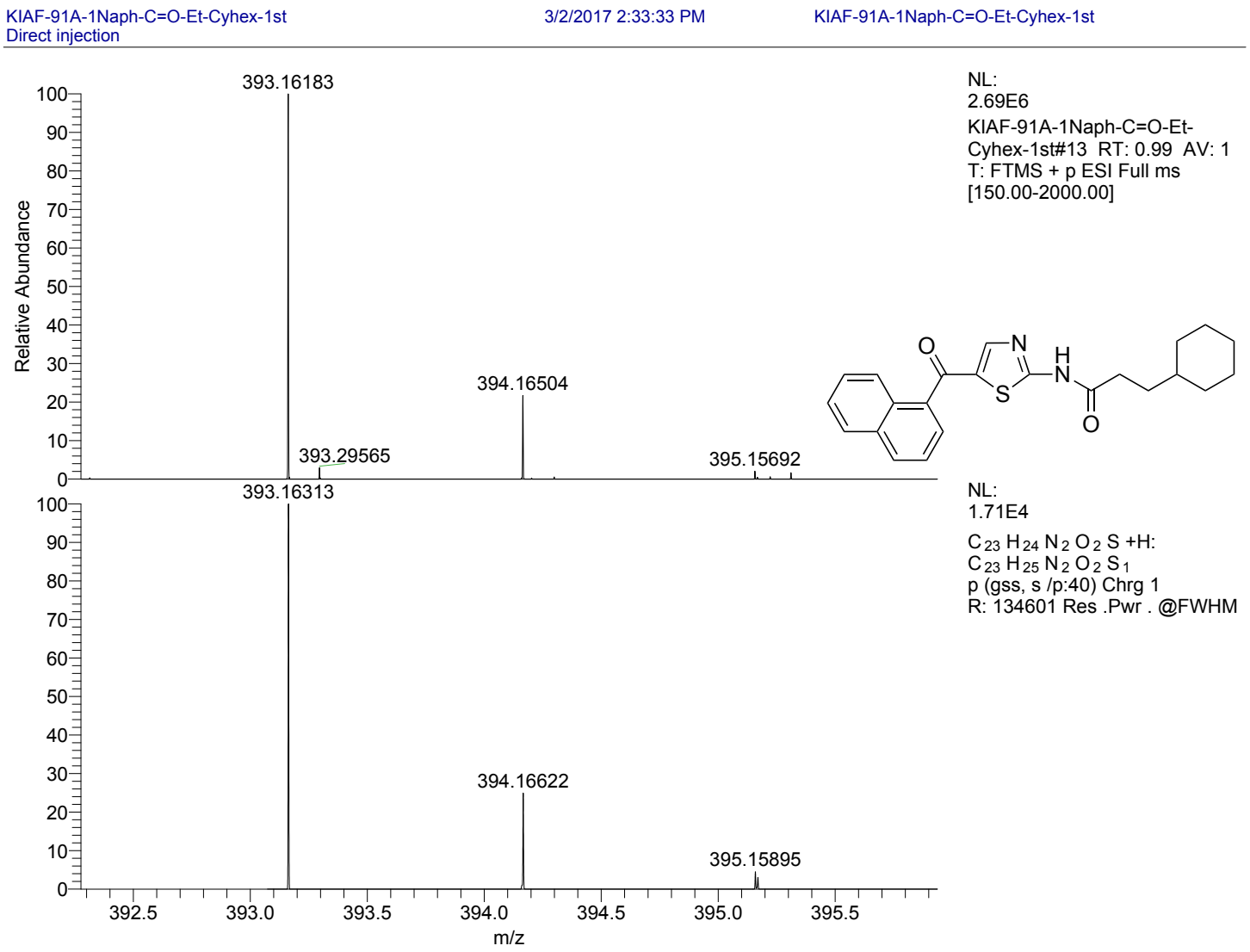
S.6.36.1. *N*-[5-(1-Naphthoyl)thiazol-2-yl]-3-cyclohexanepropanamide (36a). ^{1}H NMR (300 MHz, $CDCl_3$)



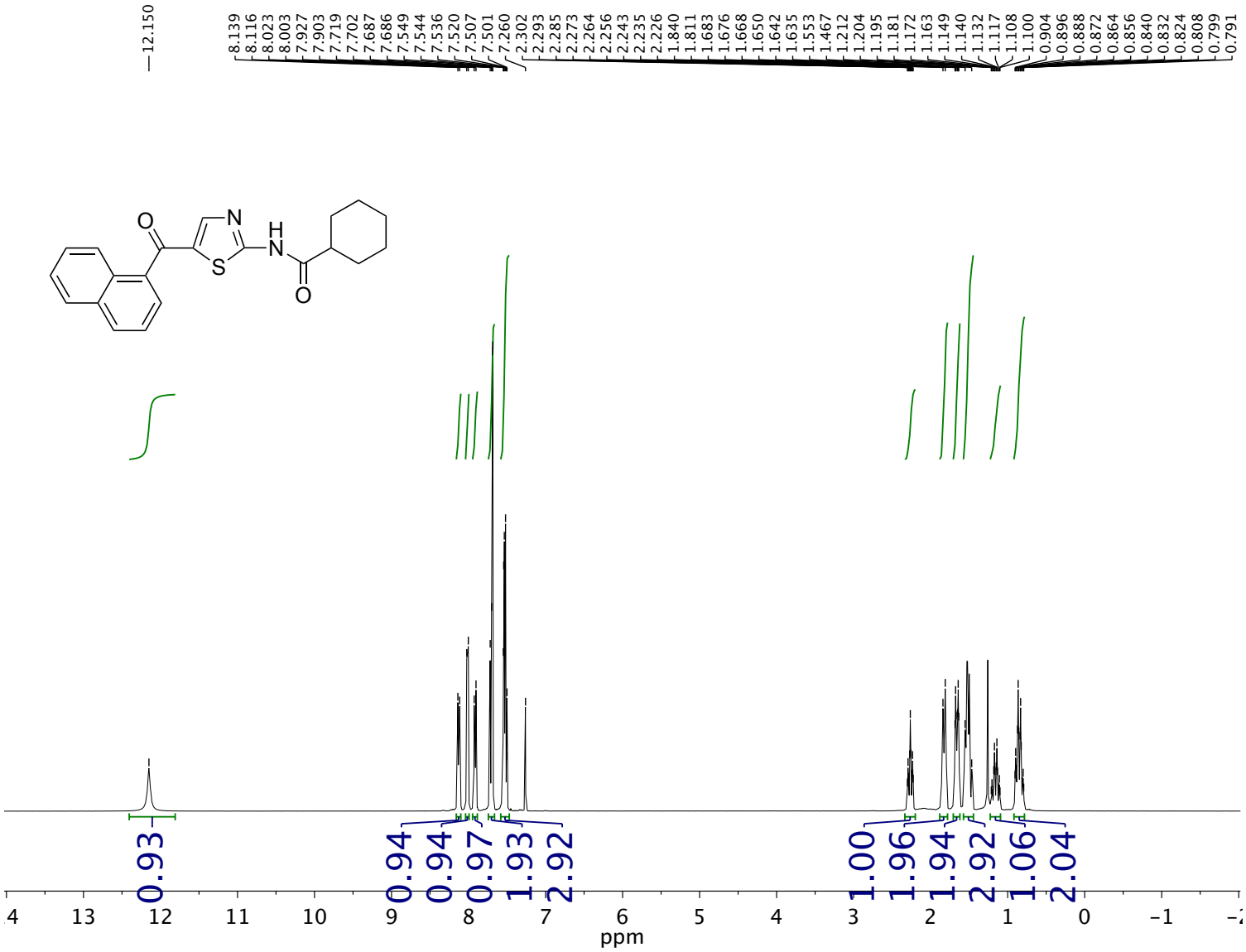
S.6.36.2. *N*-[5-(1-Naphthoyl)thiazol-2-yl]-3-cyclohexanepropanamide (36a). ^{13}C NMR (75 MHz, $CDCl_3$)



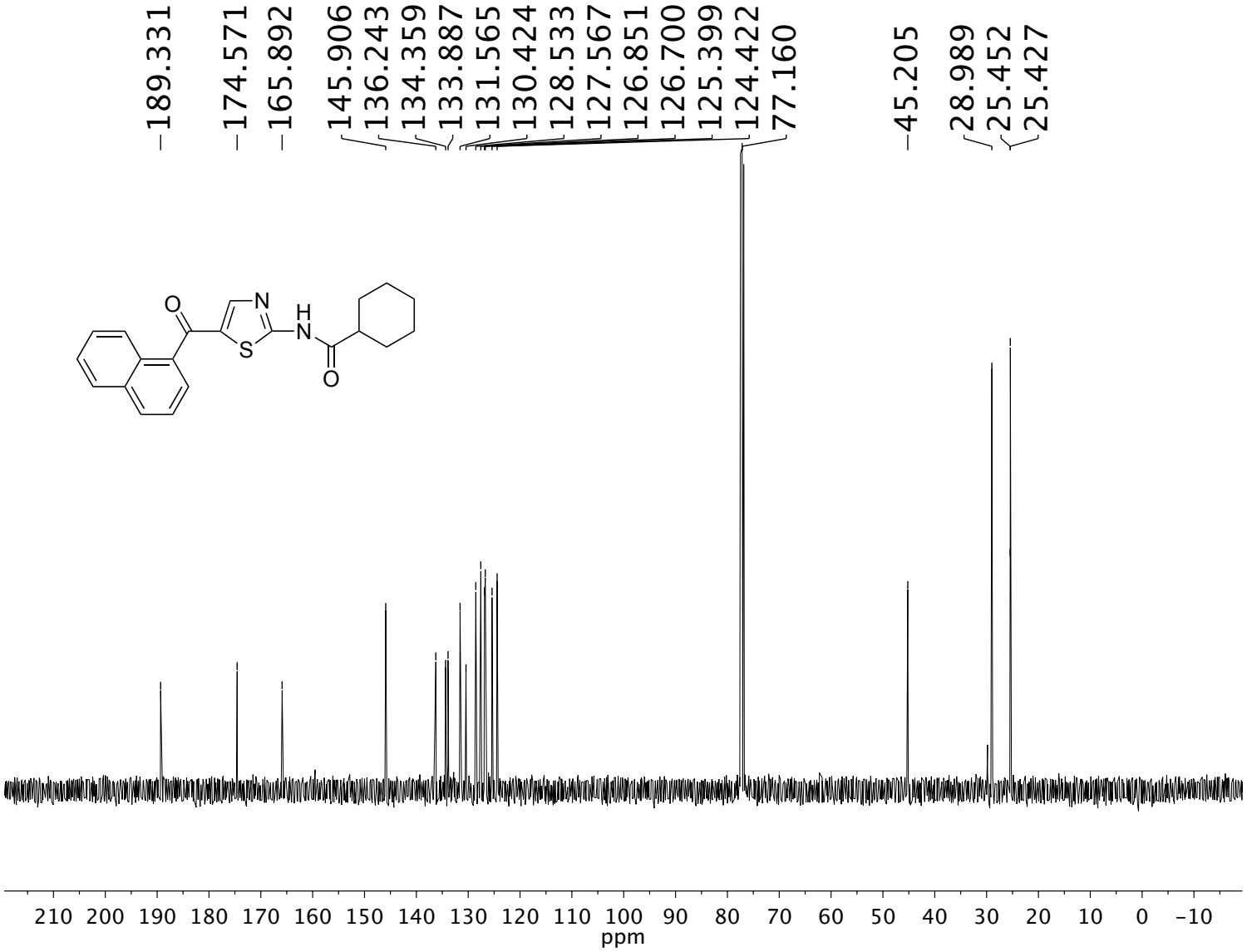
S.6.36.3. *N*-[5-(1-Naphthoyl)thiazol-2-yl]-3-cyclohexanepropanamide (36a). HR-ESI-MS



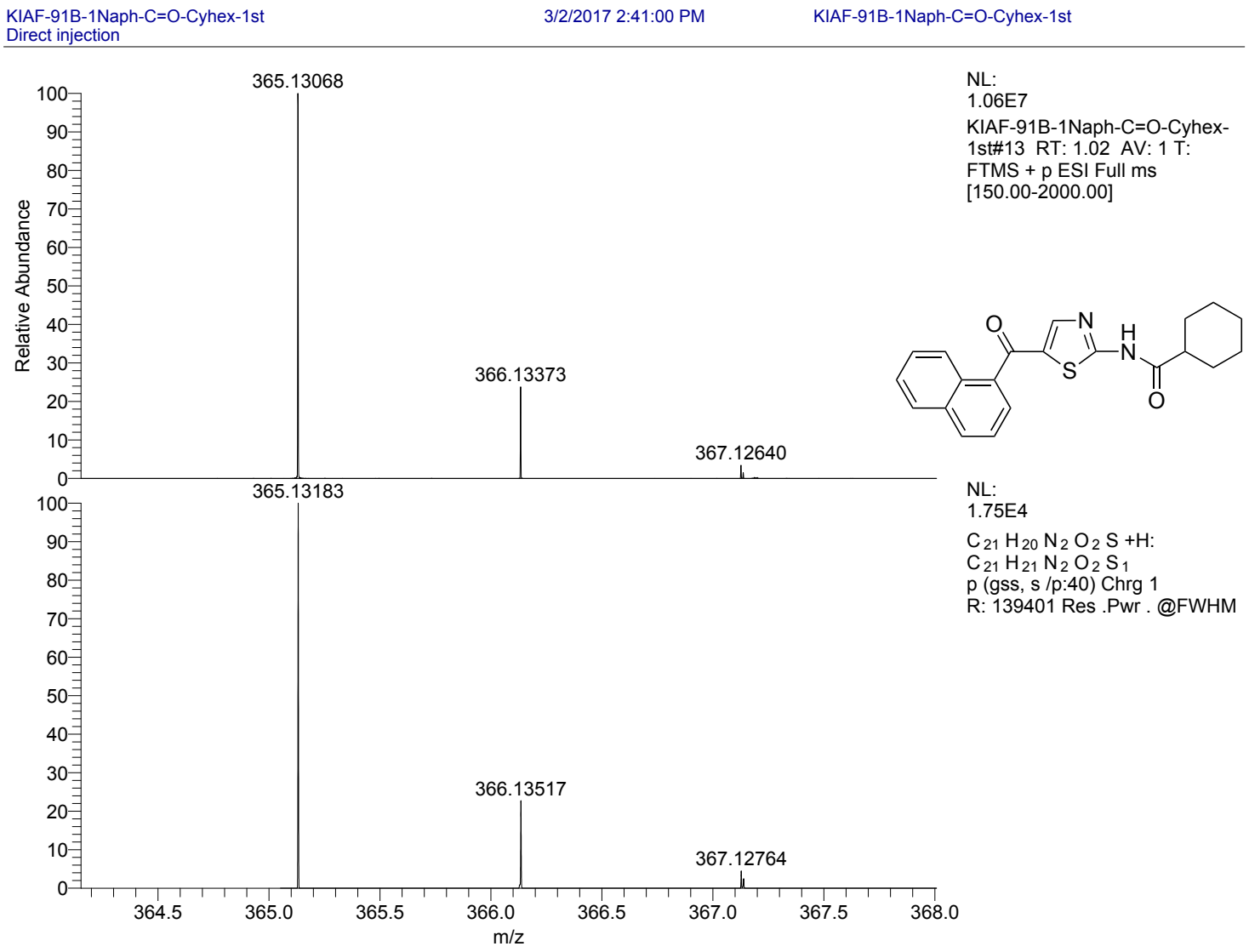
S.6.37.1. *N*-[5-(1-Naphthoyl)thiazol-2-yl]cyclohexanecarboxamide (36b). ^{1}H NMR (400 MHz, $CDCl_3$)



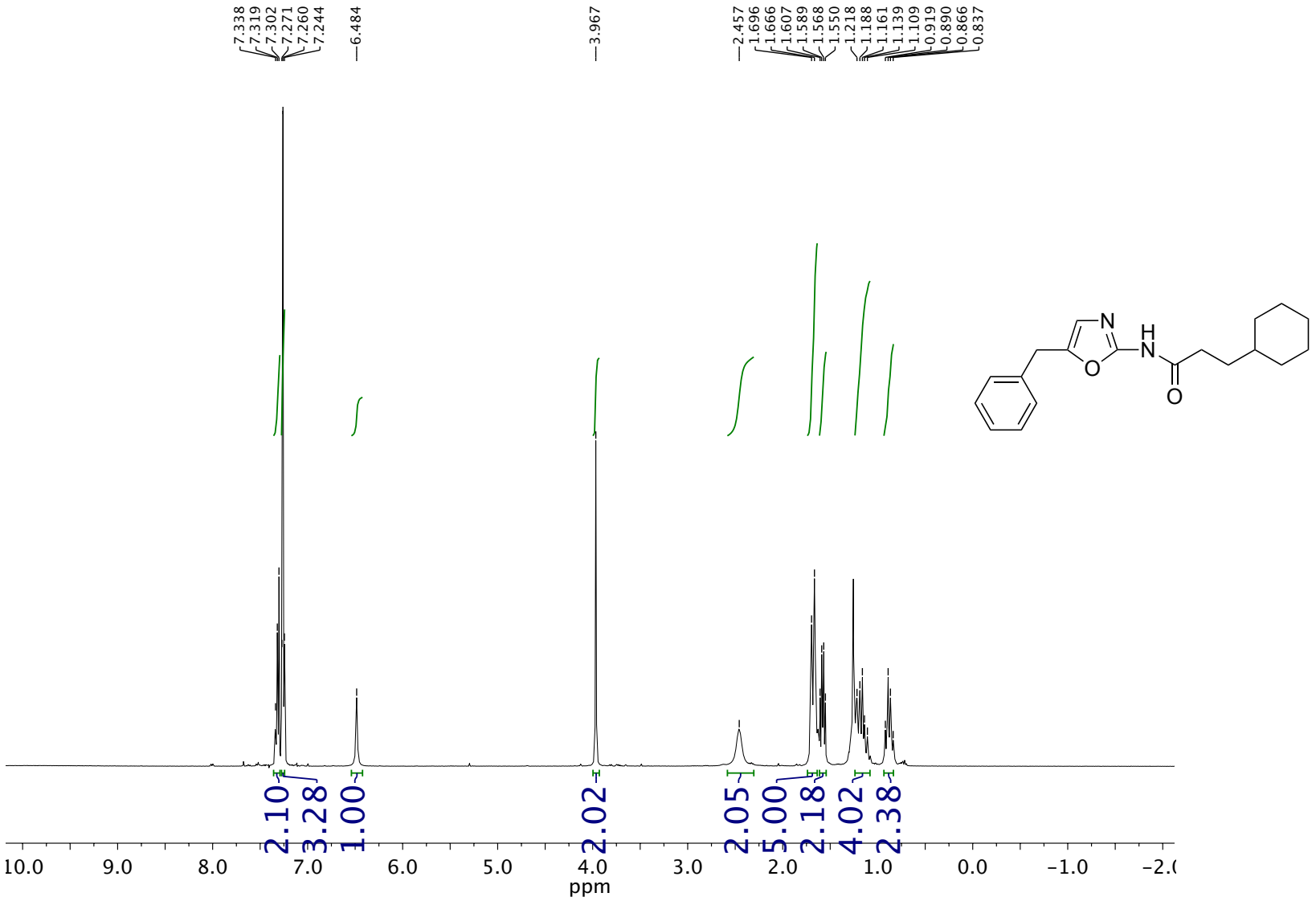
S.6.37.2. *N*-[5-(1-Naphthoyl)thiazol-2-yl]cyclohexanecarboxamide (36b). ^{13}C NMR (100 MHz, $CDCl_3$)



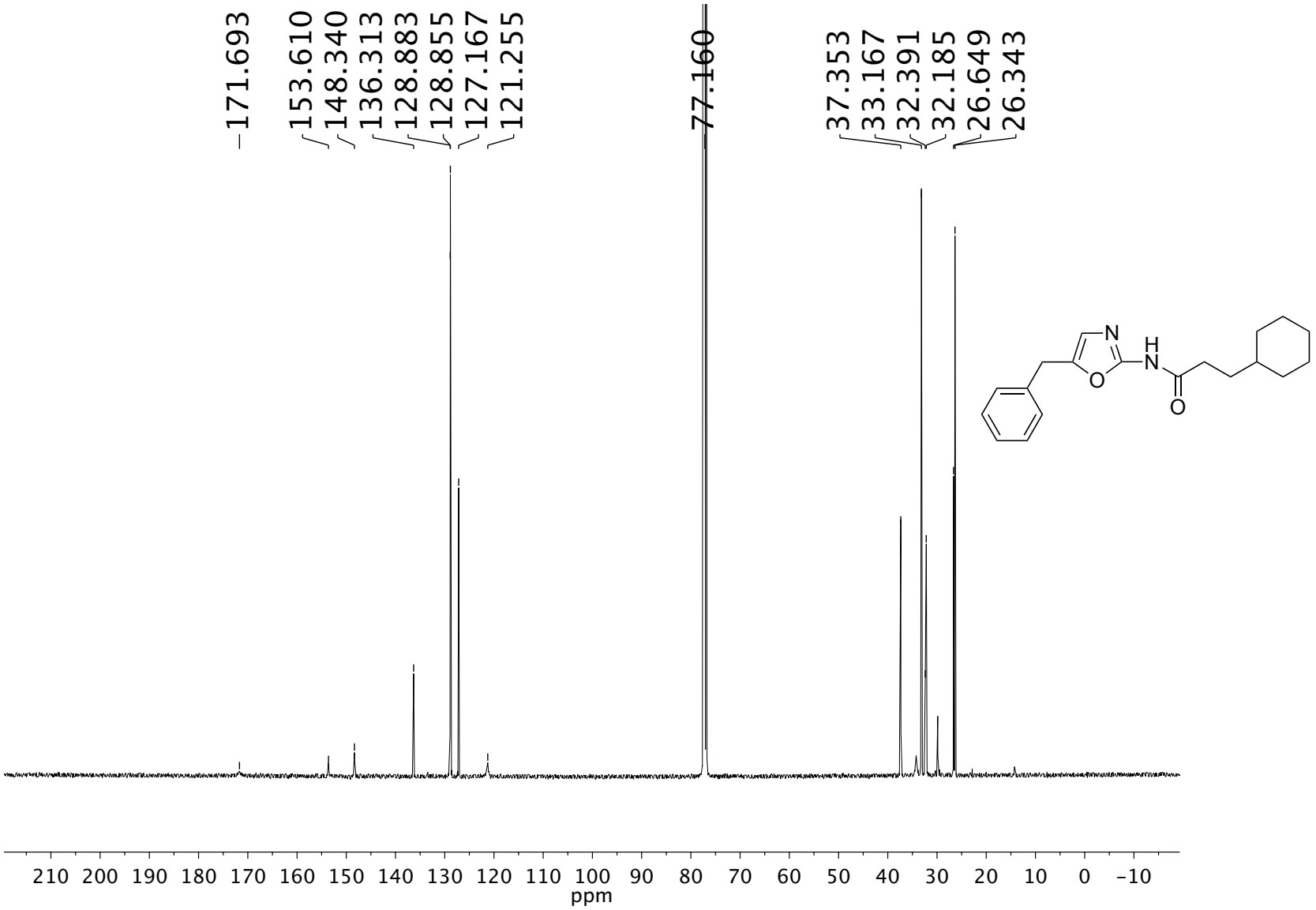
S.6.37.3. *N*-[5-(1-Naphthoyl)thiazol-2-yl]cyclohexanecarboxamide (36b). HR-ESI-MS



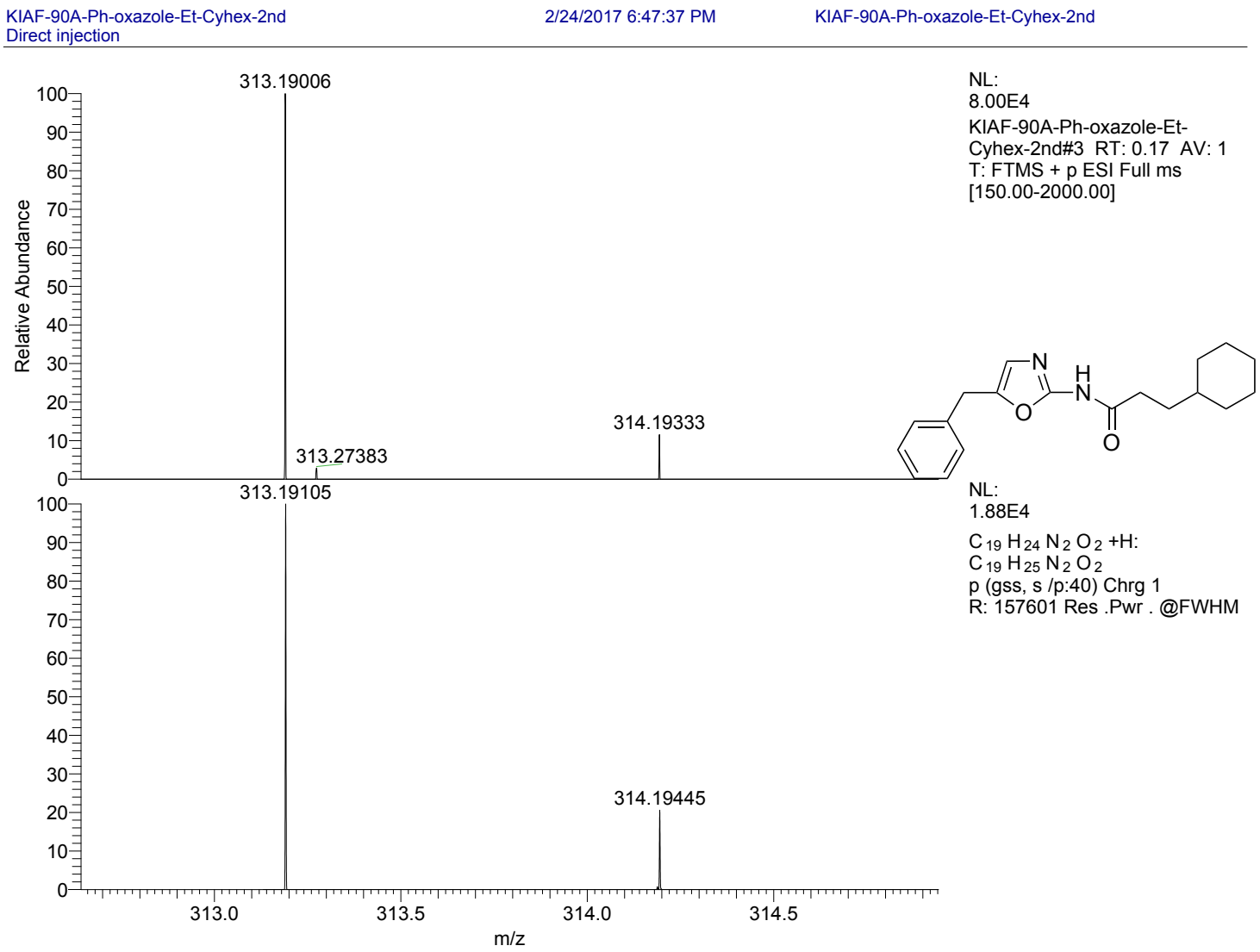
S.6.38.1. *N*-[5-(Phenylmethyl)oxazol-2-yl]-3-cyclohexanepropanamide (38a). ^{1}H NMR (400 MHz, $CDCl_3$)



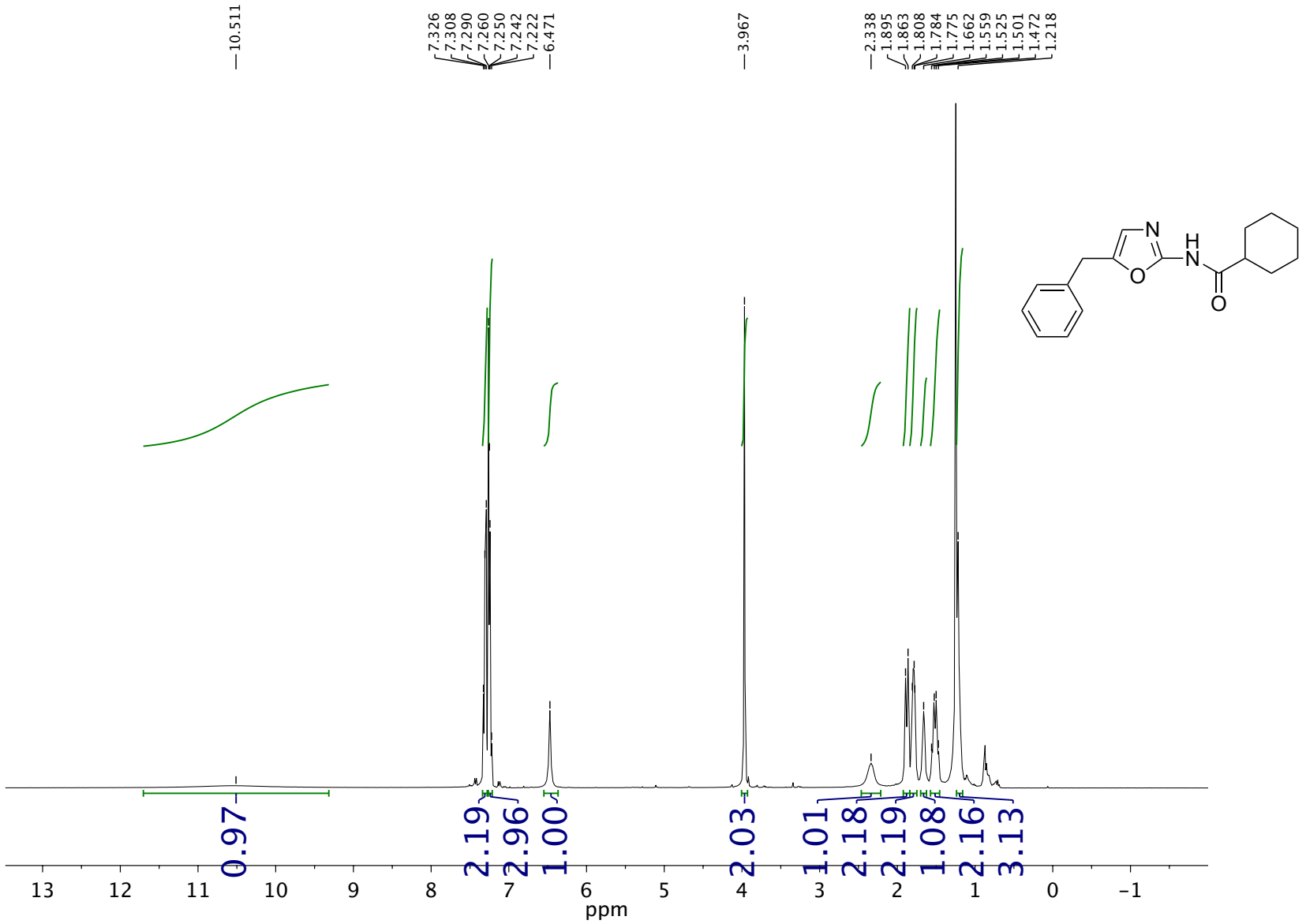
S.6.38.2. *N*-[5-(Phenylmethyl)oxazol-2-yl]-3-cyclohexanepropanamide (38a). ^{13}C NMR (100 MHz, $CDCl_3$)



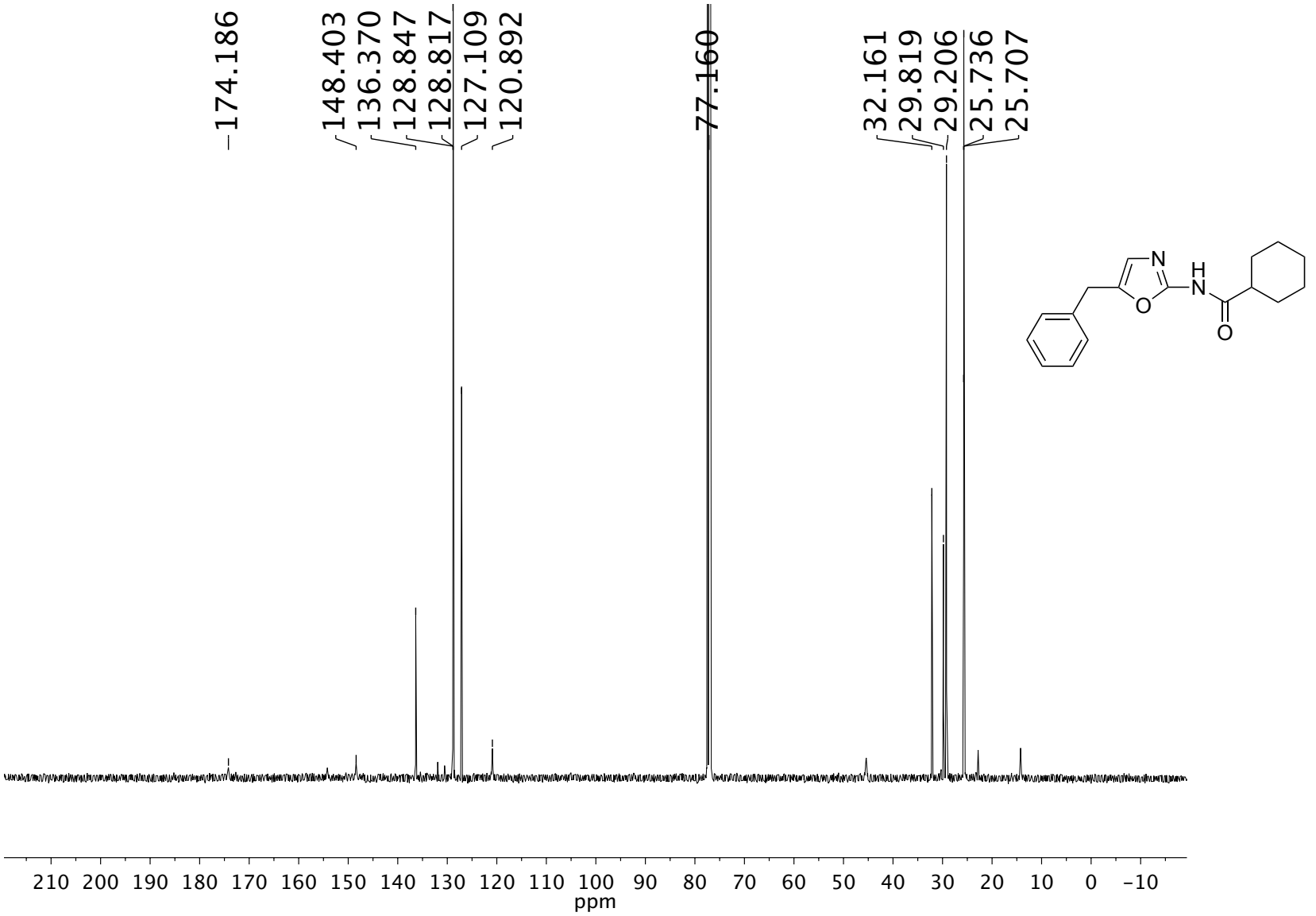
S.6.38.3. *N*-[5-(Phenylmethyl)oxazol-2-yl]-3-cyclohexanepropanamide (38a). HR-ESI-MS



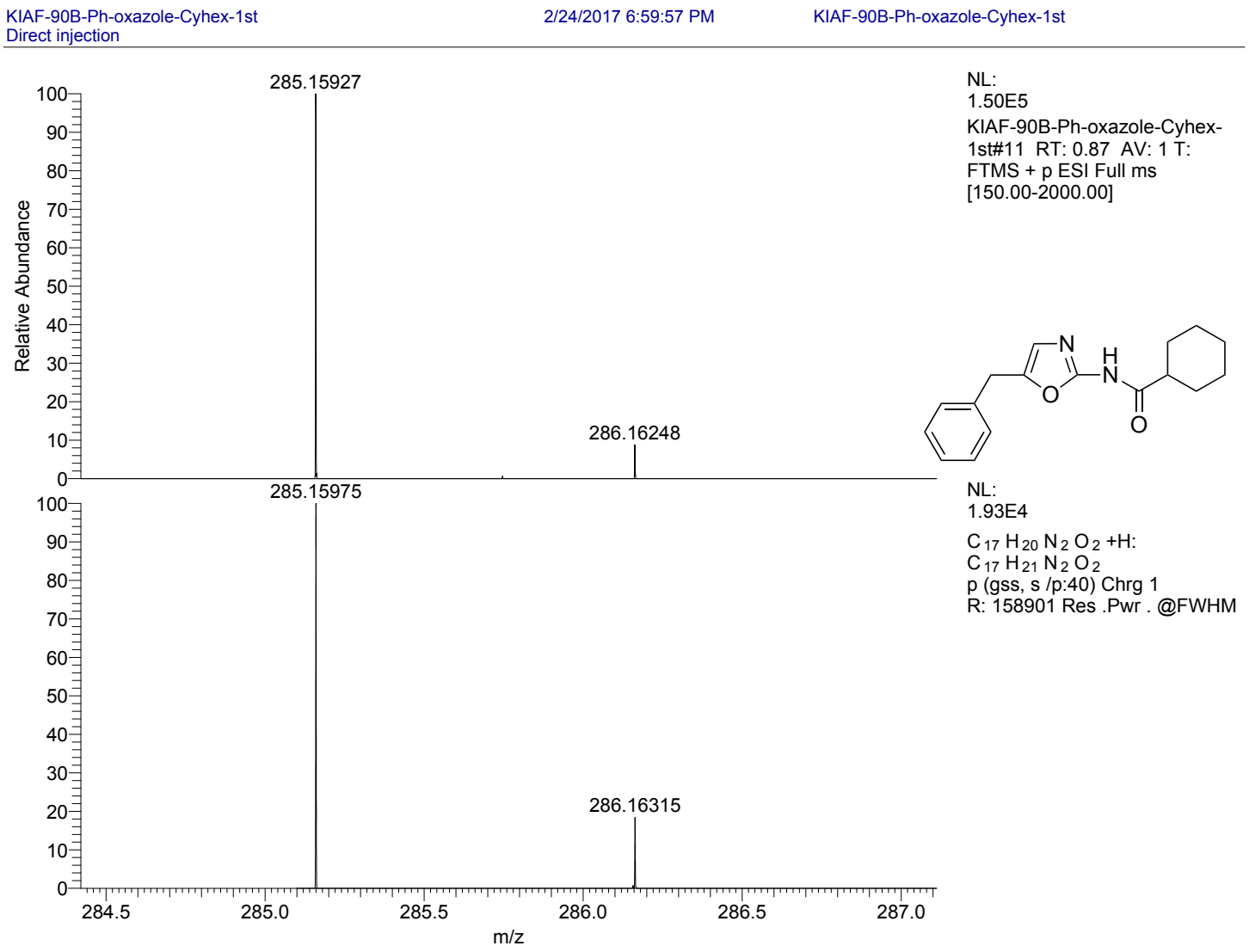
S.6.39.1. *N*-[5-(Phenylmethyl)oxazol-2-yl]cyclohexanecarboxamide (38b). ^{1}H NMR (400 MHz, $CDCl_3$)



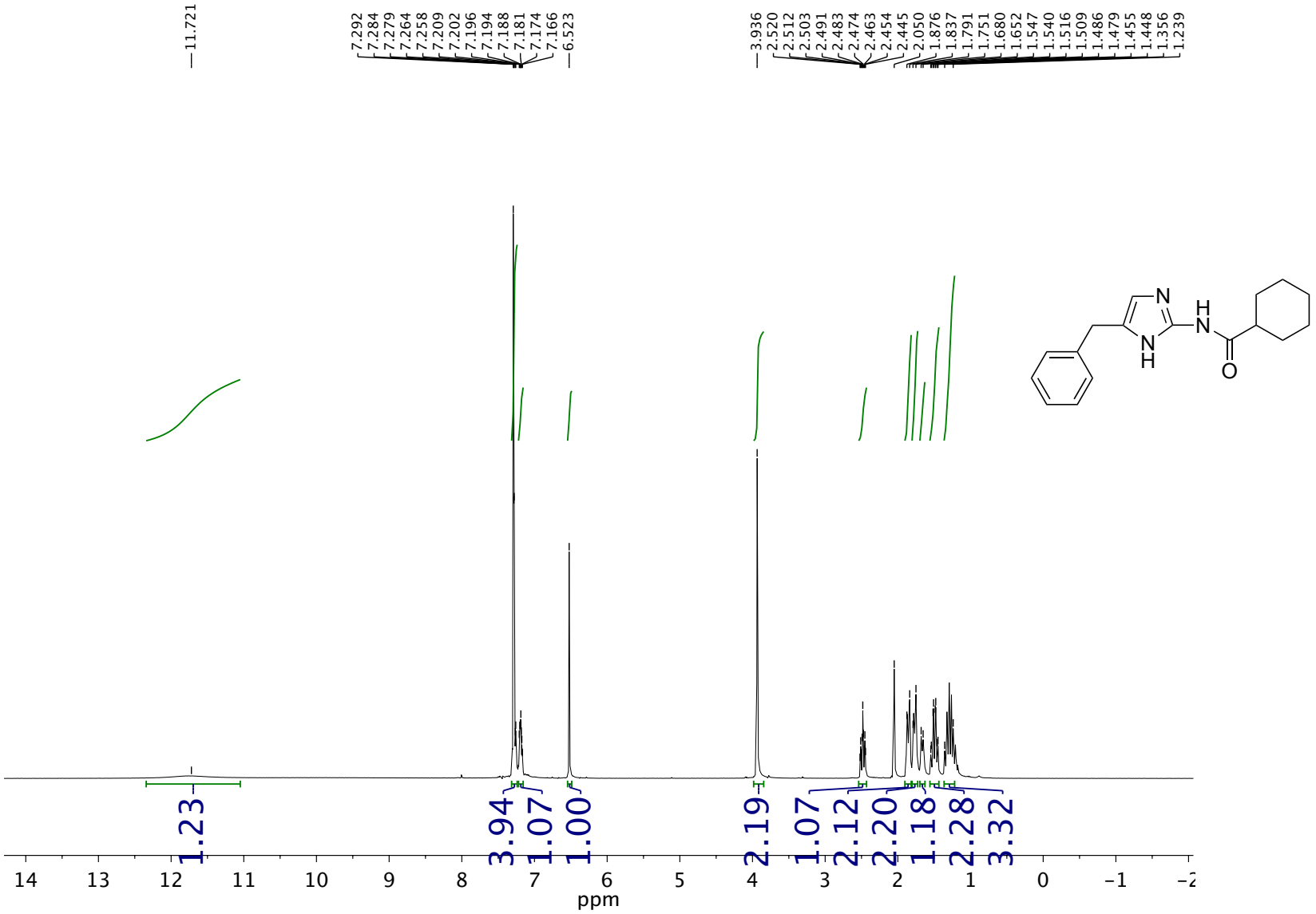
S.6.39.2. *N*-[5-(Phenylmethyl)oxazol-2-yl]cyclohexanecarboxamide (38b). ^{13}C NMR (100 MHz, $CDCl_3$)



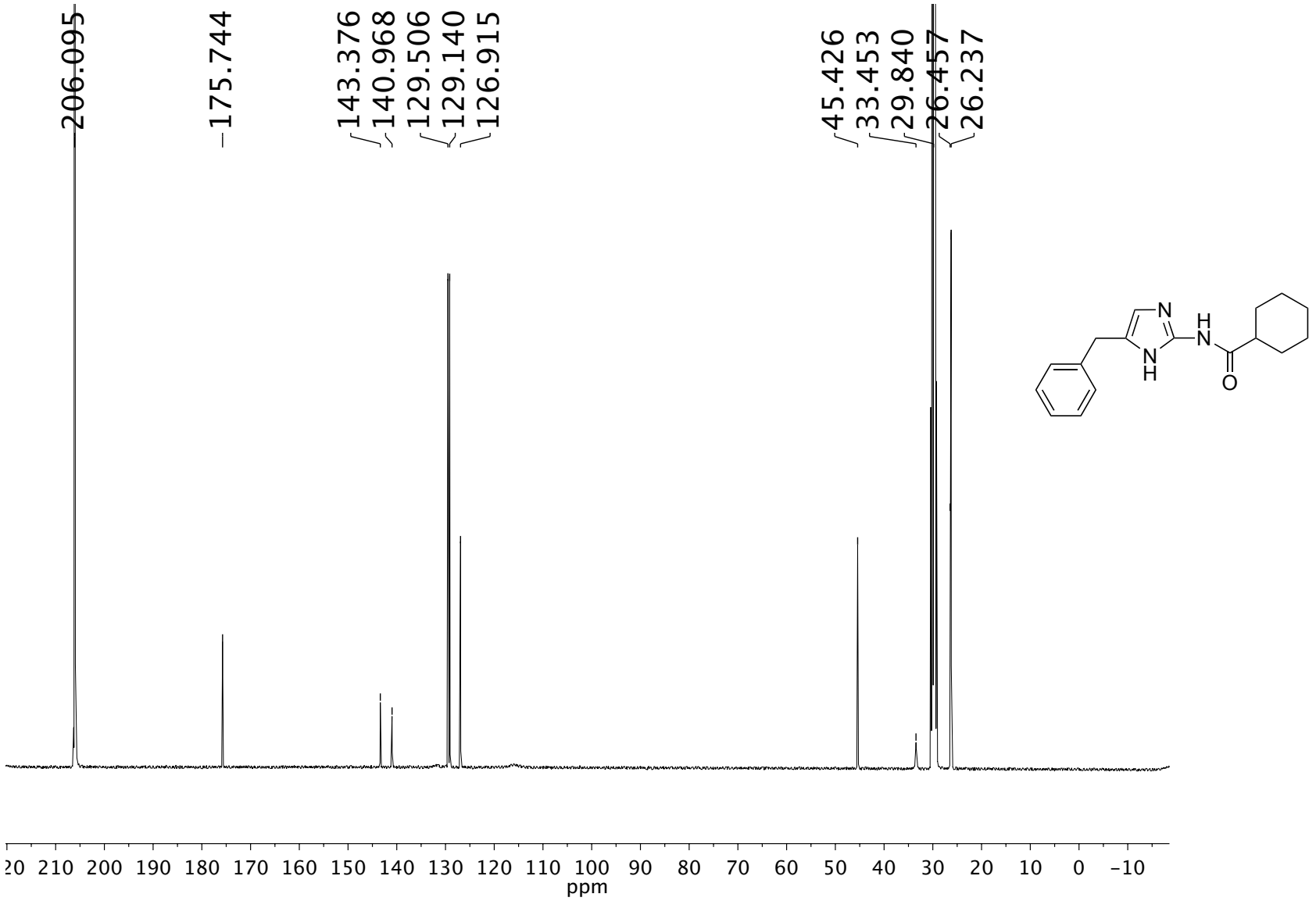
S.6.39.3. *N*-[5-(Phenylmethyl)oxazol-2-yl]cyclohexanecarboxamide (38b). HR-ESI-MS



S.6.40.1. *N*-(5-Benzyl-1*H*-imidazol-2-yl)cyclohexanecarboxmide (40). ^{1}H NMR (400 MHz, CD_3COCD_3)



S.6.40.2. *N*-(5-Benzyl-1*H*-imidazol-2-yl)cyclohexanecarboxmide (40). ^{13}C NMR (100 MHz, CD_3COCD_3)



S.6.40.3. *N*-(5-Benzyl-1*H*-imidazol-2-yl)cyclohexanecarboxmide (40). HR-ESI-MS